

## PREFACE

In a bid to standardize higher education in the country, the University Grants Commission (UGC) has introduced Choice Based Credit System (CBCS) based on five types of courses viz. *core, discipline specific, generic elective, ability and skill enhancement* for graduate students of all programmes at Honours level. This brings in the semester pattern, which finds efficacy in sync with credit system, credit transfer, comprehensive continuous assessments and a graded pattern of evaluation. The objective is to offer learners ample flexibility to choose from a wide gamut of courses, as also to provide them lateral mobility between various educational institutions in the country where they can carry their acquired credits. I am happy to note that the University has been recently accredited by National Assessment and Accreditation Council of India (NAAC) with grade "A".

UGC (Open and Distance Learning Programmes and Online Programmes) Regulations, 2020 have mandated compliance with CBCS for U. G. programmes for all the HEIs in this mode. Welcoming this paradigm shift in higher education, Netaji Subhas Open University (NSOU) has resolved to adopt CBCS from the academic session 2021-22 at the Under Graduate Degree Programme level. The present syllabus, framed in the spirit of syllabi recommended by UGC, lays due stress on all aspects envisaged in the curricular framework of the apex body on higher education. It will be imparted to learners over the six semesters of the Programme.

Self Learning Materials (SLMs) are the mainstay of Student Support Services (SSS) of an Open University. From a logistic point of view, NSOU has embarked upon CBCS presently with SLMs in English/Bengali. Eventually, the English version SLMs will be translated into Bengali too, for the benefit of learners. As always, all of our teaching faculties contributed in this process. In addition to this we have also requisitioned the services of best academics in each domain in preparation of the new SLMs. I am sure they will be of commendable academic support. We look forward to proactive feedback from all stakeholders who will participate in the teaching-learning based on these study materials. It has been a very challenging task well executed, and I congratulate all concerned in the preparation of these SLMs.

I wish the venture a grand success.

**Professor (Dr.) Subha Sankar Sarkar**  
Vice-Chancellor



**Netaji Subhas Open University**  
**Under Graduate Degree Programme**  
**Choice Based Credit System (CBCS)**  
**Subject : HONOURS IN CHEMISTRY (HCH)**  
**Course Title : Organic Chemistry-II**  
**Course Code : CC-CH-08**

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Open University**

**UG : Chemistry  
(HCH)**

**Course Code : CC-CH-08**

**Course Title : Organic Chemistry-II**

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## **Unit - 1 □ Substitution and Elimination Reactions**

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### **Structure**

#### **1.0 Objective**

#### **1.1 Introduction**

#### **1.2 Free-radical substitution Reaction**

##### **1.2.1 Hologenation of alkanes Mechanism and stereochemical features**

##### **1.2.2 Reactivity selective principle in the light of Hammond's postulate**

#### **1.3 Nucleophilic substitution Reactions**

##### **1.3.1 Substitution at $sp^3$ centre Mechanisms**

##### **1.3.2 Relative rates and stereochemical features**

##### **1.3.3 Effects of solvent substrate structure, Leaving group and nucleophiles**

##### **1.3.4 Substitutions involving NGP**

##### **1.3.5 Role of crown ethers and phase transfer catalysts**

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##### **1.4.2 $E_2$ Reactions**

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##### **1.5.2 Reactivity, regioselectivity (saytzeff/Hofmann) and stereoselectivity**

##### **1.5.3 Comparison between substitution and elimination**

## 1.6 Importance of Bredt's rule relating to the formation of C = C

## 1.7 Summary

## 1.8 Additional Problems

# 1.0 Objective

By studying this units we will learn about—

- The methods of formations of alkynes, halides, alcohols, alkenes, alkynes.
- The mechanisms of formation of the products.
- The conditions and different factors of the reactions.
- How to apply the conditions to increase the yield of the products.

## 1.1 Introduction

A substitution reaction is one in which one atom or group replaces another. Substitution reactions occur by free radical or ionic mechanisms.

Example of substitution reaction occurring by free radical mechanism is halogenation of alkanes in which a halogen atom replaces one (or more) of the hydrogen atoms of alkanes  $RH + X_2 \rightarrow RX + H X$ .

Example of substitution reaction occurring by ionic mechanism is the base catalysed hydrolysis of alkyl halides (RX).  $RX + \overset{\ominus}{O}H + X^{\ominus}$

Here one nucleophile  $\overset{\ominus}{O}H$  replaces another negative group  $X^{\ominus}$  (called nucleofuge) so it is called Nucleophilic substitution reaction.

## 1.2 Free-radical substitution Reaction

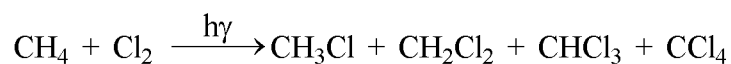
Free-radicals are formed by the homolytic bond dissociation of co-valent bond. These are odd electron species and are extremely reactive



### 1.2.1 Halogenation of alkanes. Mechanism and stereochemical features :

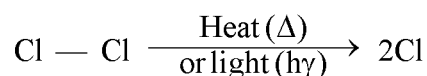
Methane, ethane and other alkanes react with the first three members of the halogen family fluorine, chlorine and bromine replacing hydrogen atom. Fluorination is difficult to carry out as fluorine is very much reactive and possibility of explosion exists. So fluoro compounds are prepared by other methods.

Direct chlorination or bromination of alkanes can be carried out. In alkanes the hydrogen atoms are successively replaced by halogen atoms giving mixture of haloalkanes e.g.



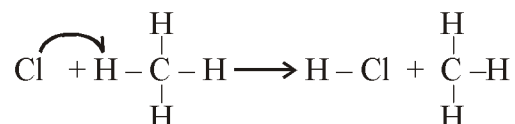
Mechanism

**Step-1** is the fragmentation of chlorine molecule by heat or light to chlorine free-radicals.

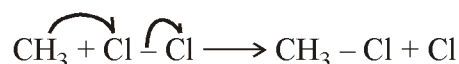


This is the initiation step.

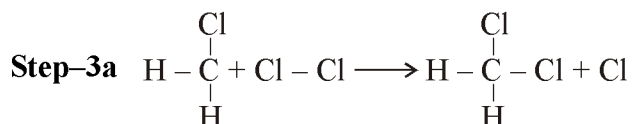
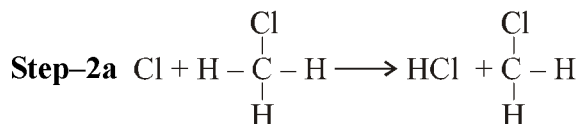
**Step-2** The abstraction of hydrogen atom from methane molecule by a chlorine radical forming methyl radical and HCl.



**Step-3** This highly reactive methyl radical abstracts a chlorine atom from chlorine molecule forming methyl chloride and a chlorine radical. It can attack another methane molecule and carry on repetition of step-2 and step-3 to form other  $\text{CH}_3\text{Cl}$  molecules.

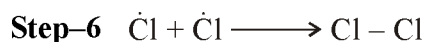
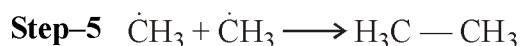
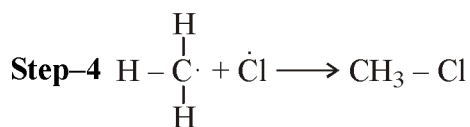


The chlorine radical can also attack  $\text{CH}_3\text{Cl}$  forming  $\text{CH}_2\text{Cl}$  and so on and ultimately to  $\text{CCl}_4$



Similarity  $\text{CHCl}_3$  and  $\text{CCl}_4$  are also formed. This type of sequential stepwise mechanism in which each step generates the reactive intermediate that causes the next step to occur is called a chain mechanism. Step-1 is the chain initiation step and step-2 and step-3 are chain propagation step. Single-barbed arrow ( $\curvearrowright$ ) shows the movement of one electron only.

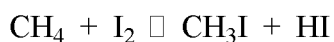
How chain termination occurs? Plausible chain termination steps are —



The last step occurs least frequently.

**Evidence :** The observation that the light promoted reaction is highly efficient and the presence of a relatively few atoms of chlorine at any given moment can produce thousand molecules of methyl chloride supports this chain mechanism.

Iodine is less reactive and iodination is reversible but it may be carried out in the presence of an oxidising agent such as  $\text{HIO}_3$ ,  $\text{HNO}_3$ ,  $\text{HgO}$  etc. Which destroys the  $\text{HI}$  formed and drives the reaction to the right e.g.



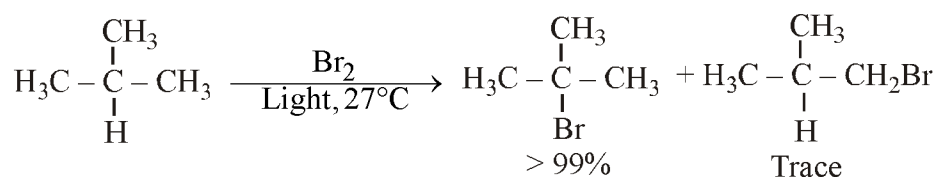
Iodides are more conveniently prepared by treating the chloro or bromo derivatives with  $\text{NaI}$  in methanol or acetone solution e.g.  $\text{RCl} + \text{NaI} \xrightarrow{\text{Acetone}} \text{RI} + \text{NaCl}$ . The reaction is possible as  $\text{NaI}$  is soluble in methanol or acetone where as

NaCl or NaBr are not.

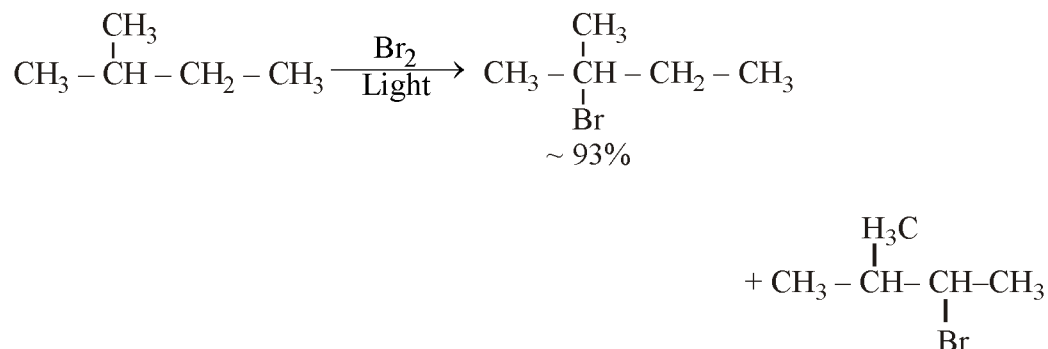
This reaction is known as the Finkelstein or conant– Finkelstein reaction.

### 1.2.2 Reactivity selectivity Principle in the light of Hammond's Postulate

Bromine is less reactive but more selective than chlorine when it attacks an alkane. The reaction of isobutane and bromine gives almost exclusively replacement of the tertiary hydrogen.



Similarly,



This is due to less reactivity of Bromine and hence more selective.

#### Hammond Postulate

According to the postulate by G. S. Hammond "the structure of the transition state of an endothermic step of a reaction resembles the products of that step more than it does the reactants. For an exothermic step the structure of the transition state is more like the reactants than the products. This principle can be better understood by a potential energy versus reaction co-ordinate

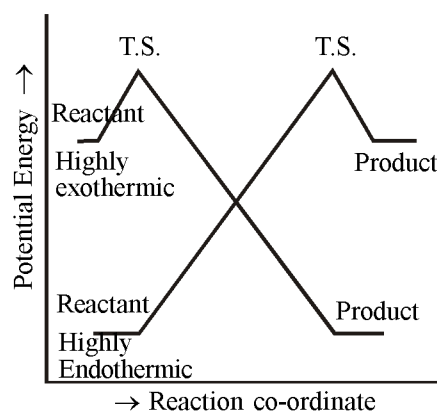


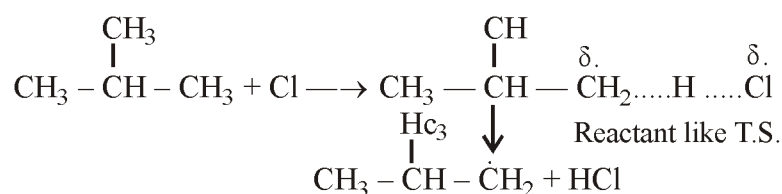
Fig. 1



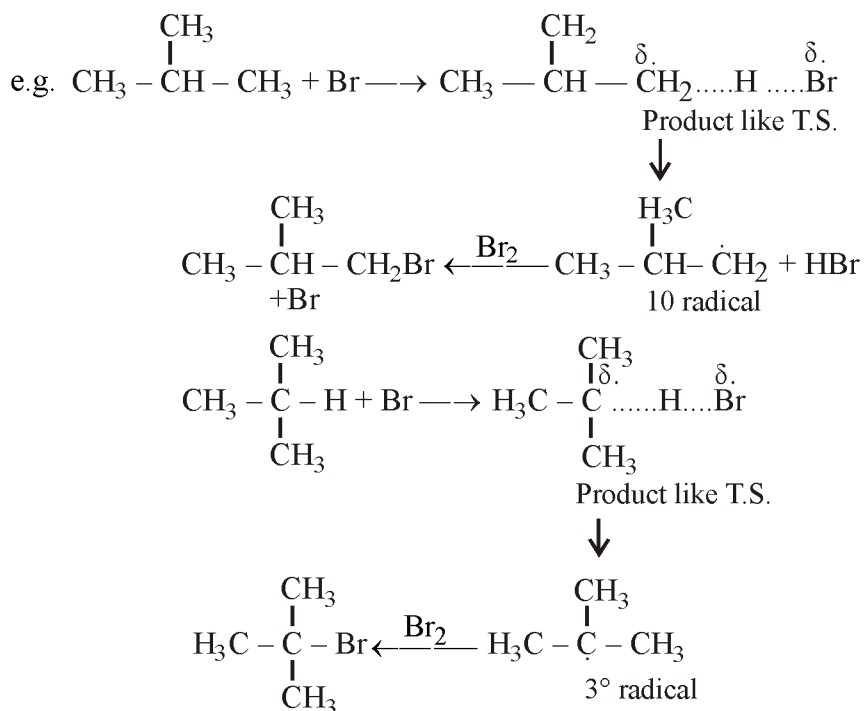
diagram as shown in Fig.1.

In the highly exothermic step the energy levels of the reactants and the transition state are close to each other.

In an exothermic reaction the T.S. lies close to the reactants along the reaction co-ordinate. This means that the bond-breaking has not proceeded very far when the transition state (TS) is reached. This has been shown in the following example of chlorination of isobutane where relatively little carbon-hydrogen bond breaking has developed in the T.S.



The T.S. of highly endothermic step, on the other hand lie close to the product along the reaction co-ordinate. In this case the bond has broken to a considerable extent by the time the T.S. is reached.



Abstraction of 3° hydrogen takes place much faster as tertiary radical is more stable than primary radical.

Bromine discriminates effectively between primary and tertiary hydrogens.

**Problem–1 :** When methane is chlorinated, among the products traces of chloroethane are found. How is it formed ? Of what significance is its formation?

**Problem–2 :** How can you prepare  $\text{CH}_3\text{Cl}$  exclusively by chlorination?

**Problem–3 :** Carbon tetrachloride is formed exclusively by using large excess of chlorine. Explain.

### **Stereo chemical Feature**

Halogenation of alkanes proceed through free-radical mechanism as discussed earlier. Now free radicals generally contain  $\text{sp}^2$  hybridised carbon which is planar. Hence if the product is an optically active halide always racemisation occurs i.e. the product is a 50 : 50 mixture of (+) and (–) form.

**Problem–4 :** Bromination of 2-methyl butane gives predominance of one product. What is it?

**Problem–5 :** Chlorination of 2-Methylbutane gives a mixture of monochloro product in the following proportions : 1-chloro-2-Methyl butane (30%), 2-Chloro-2-methylbutane (22%), 2-chloro-3-methylbutane (33%) and 1-Chloro-3 methylbutane (15%). Show how each of these products is formed?

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## **1.3 Nucleophilic substitution Reactions**

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In a reaction where a nucleophile, a species with an unshared pair of electrons reacts with an alkyl halide/called the substrate, replacing the halogen atom as halide ion is called a Nucleophilic substitution reaction. The halide ion or the atom that is replaced is called the leaving group or the nucleofuge. Because the substitution is initiated by a nucleophile it is called Nucleophilic substitution.

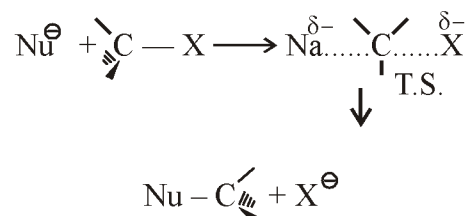
### Examples

1.  $\text{OH}^\ominus + \text{CH}_3 - \text{Cl} \longrightarrow \text{CH}_3\text{OH} + \text{Cl}^\ominus$
2.  $\text{CH}_3\text{O}^\ominus + \text{CH}_3\text{CH}_2\text{Br} \longrightarrow \text{CH}_3\text{CH}_2\text{OCH}_3 + \text{Br}^\ominus$
3.  $\text{CN}^\ominus + \text{RX} \longrightarrow \text{RCN} + \text{X}^\ominus$
4.  $\text{Q}'\text{OH} + \text{RX} \longrightarrow \text{R}'\text{OR} + \text{HX}$
5.  $\text{Q}'\text{SH}' + \text{RX} \longrightarrow \text{R}'\text{SR} + \text{HX}$

### 1.3.1 Substitution at $\text{sp}^3$ Centre Mechanisms (with evidence)

In nucleophilic substitution reactions the substrate is generally alkyl halide where the central carbon atom is  $\text{sp}^3$  hybridised. Substitutions occurring in this  $\text{sp}^3$  carbon are mainly of three types  $\text{SN}_1$ ,  $\text{SN}_2$ , and  $\text{SN}_i$ . Besides two other types of substitution reactions are observed namely  $\text{SN}_2'$  and  $\text{SN}_1'$ .

#### Mechanism of $\text{SN}_2$ Reaction



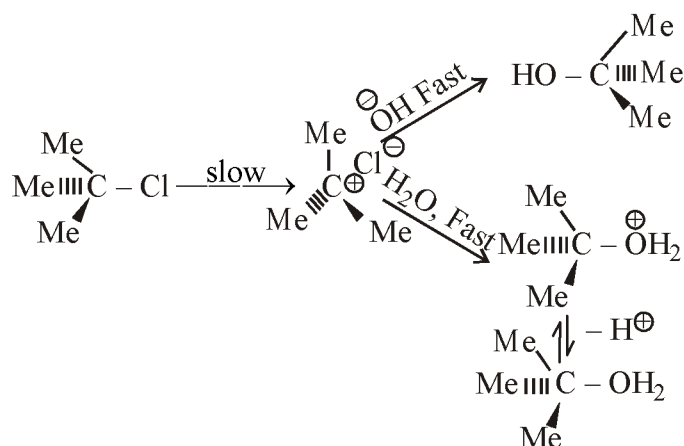
Here in the formation of the transition state both nucleophile and the alkyl halide (substrate) are involved. Hence the term bimolecular. This type of mechanism has been designated by Ingold as  $\text{SN}_2$  : Substitution Nucleophilic bimolecular.

**Evidence :** When methyl chloride reacts with aqueous NaOH, experiments have shown that the rate depends on the concentrations of both methyl chloride and hydroxide ion. When one doubles the concentration of NaCl keeping the concentration of hydroxide ion constant, the rate of the reaction doubles. When the concentration of hydroxide ion is doubled keeping the concentration of NaCl constant the rate of the reaction also doubles. And, finally when the concentrations of both NaCl and hydroxide ion are doubled the rate of the reaction increases four times. In all these experiments temperature remains same.

### Mechanism of SN1 reaction

When tert butyl chloride reacts with aqueous sodium hydroxide the mechanism and kinetic results are quite different. Here the first slow rate determining step is ionisation of the alkyl halide to form the carbocation followed by the attack of the nucleophile to give the product. As in the rate determining step only the alkyl halide molecule is involved it is called SN<sup>1</sup> reaction.

#### Mechanism :



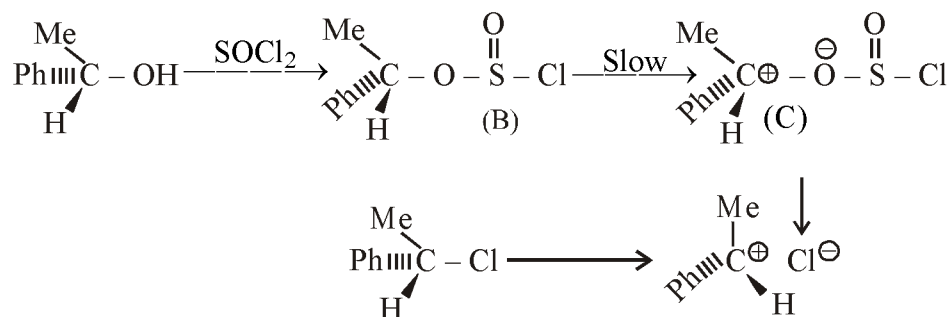
Here the solvent also acts as the nucleophile. The reaction is then called solvolysis.

**Evidence :** It is observed experimentally that rate of formation of tert-butyl alcohol is dependent on the concentration of tert butyl chloride, but is independent of the concentration of hydroxide ion. Doubling the concentration of tert-butyl chloride the rate of the reaction increases twice. But increasing the concentration of hydroxide ion the rate of the reaction does not change appreciably. It essentially establishes the fact, the ionisation of alkyl halide is the rate determining step to form the ion pair (A) followed by the non rate limiting attack by the nucleophile  $\text{OH}^{\ominus}$  or by solvent, the latter often predominates as the solvent is present in much high concentration. So the reaction is called solvolysis.

### SNi Reaction

Hughes and Ingold et. al have shown that optically active  $\alpha$ -phenyl ethanol reacts with thionyl chloride ( $\text{SOCl}_2$ ) to give  $\alpha$ -phenyl ethyl chloride of same configuration. This is called SNi or substitution Nucleophilic internal reaction.

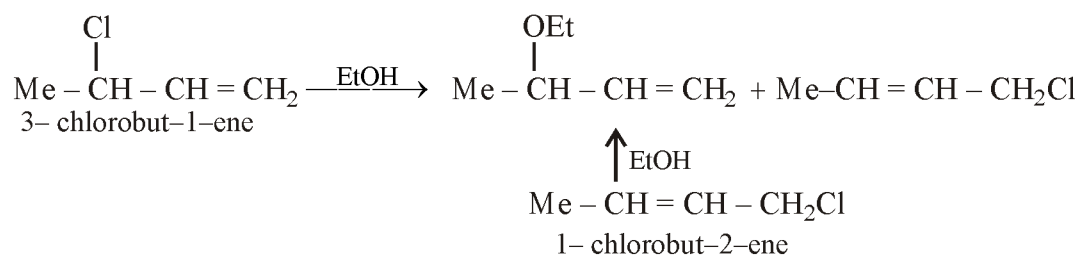
#### Mechanism :



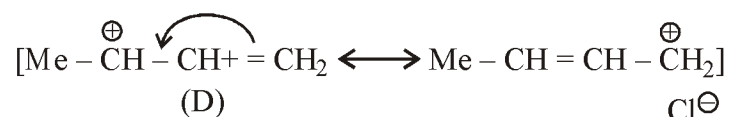
**Evidence :** Carrying out the reaction under milder conditions allows the isolation of an alkyl chlorosulphite, (B) and this can be shown to be a true intermediate. The chlorosulphite is formed with retention of configuration, the R–O bond not being broken during the reaction. The rate at which the alkyl chlorosulphite intermediate (B) breaks down to the product is found to increase, with increasing polarity of the solvent, and also with increasing stability of the carbocation  $\text{R}^{\oplus}$ . Hence, it is established that a ion pair  $\text{R}^{\oplus} \text{OSOCl}^{\ominus}$  (C) is almost certainly involved. The intimate ion pair (C) within a solvent cage is then attacked by  $\text{Cl}^{\ominus}$  ion on the same side of  $\text{R}^{\oplus}$  from which  $\text{OSOCl}^{\ominus}$  has departed with retention of configuration.

### SN1' and SN2' Reactions

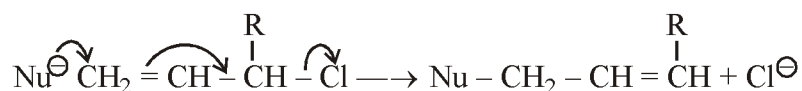
In the SN1 solvolysis of 3-chlorobut-1-ene in EtOH not one but a mixture of two isomeric ethers are obtained and the same mixture is also obtained from the similar solvolysis (where solvent is the nucleophile) of 1-chlorobut-2-ene. It is the example of SN1' reaction.



This clearly indicates the formation of the following same delocalised allylic cation (D) as an ion pair intermediate from each halide capable of undergoing subsequent rapid nucleophilic attack by EtOH at either C<sub>1</sub> or C<sub>3</sub>.



But when  $\text{OEt}^{\ominus}$  is present in fairly high concentration SN<sup>2</sup> type reaction occurs giving only one either. Here  $\text{OEt}^{\ominus}$  acts as the nucleophile in preference to EtOH. Then it is called Allylic rearrangement.



Such reactions are referred to as SN<sup>2</sup>'.

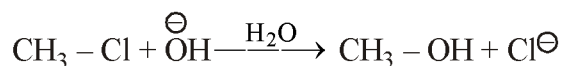
### Problem-6

Show how you might use a nucleophilic substitution reaction of propyl bromide to synthesise each of the following compounds.

- (a) CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>OH, (b) CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>I, (c) CH<sub>3</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>  
 (d) CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub> - S - CH<sub>3</sub>

### 1.3.2 Relative rates and stereochemical features

**SN<sup>2</sup> reaction :** The rate equation for this type of reaction is first order with respect to each reactant and second order overall.



$$\text{Rate} \propto [\text{CH}_3\text{Cl}] [\text{OH}^{\ominus}]$$

$$\text{Rate} = K [\text{CH}_3\text{Cl}] [\text{OH}^{\ominus}]$$

Hence the transition state for this reaction involves both  $\text{CH}_3\text{Cl}$  and  $\text{OH}^-$  as shown in the mechanism and the reaction is bimolecular. Fig-2 shows the potential energy diagram of the reaction of  $\text{MeCl}$  with  $\text{OH}^-$  ion.

Here  $\Delta E$  is the activation energy of the reaction which amounts to 26 K cal/mol and  $\Delta H^\circ$  is the enthalpy change or heat evolved in the reaction which amounts to  $-18$  K.Cal / mole as the reaction is exothermic.

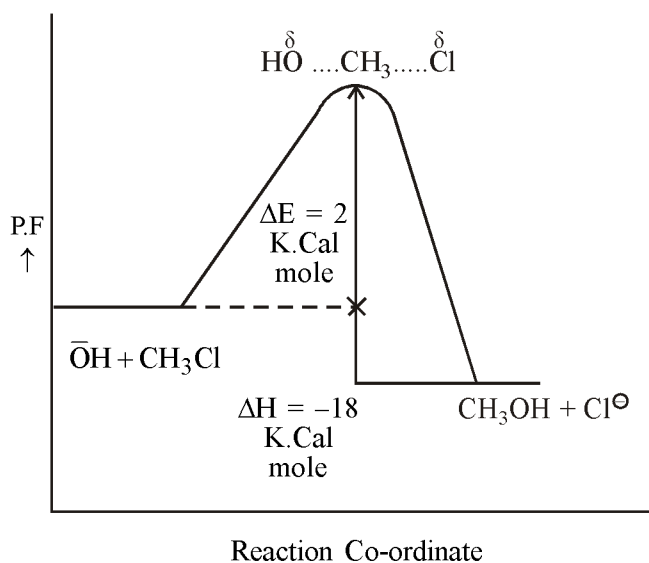
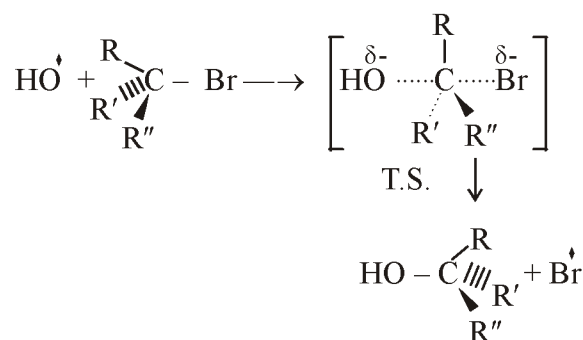


Fig-2

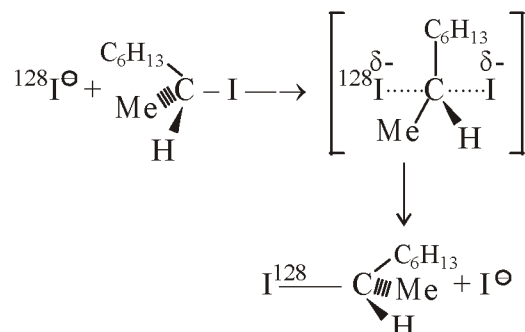
### Stereo Chemistry

If a chiral halide undergoes  $\text{SN}^2$  reaction always inversion of configuration occurs as shown below :



### Evidence in support of inversion

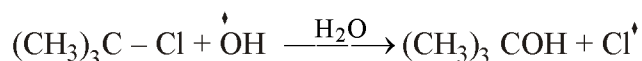
To establish inversion occurring in  $\text{SN}^2$  substitution an ingenious experiment was carried out. An optically active alkyl halide undergoes the reaction by the same radioactive halide ion as nucleophile e.g. radioactive  $^{128}\text{I}^-$  reacts with (+) 2-iodooctane.



It was observed that optical activity of the solution declines to zero indicating racemisation. This happens as the (+) iodide has been converted to (-) iodide by  $\text{SN}^2$  reaction causing inversion. And as soon as 50% (+) iodide has been transformed to 50% (-) iodide the over all mixture will be 50 : 50 mixture of (+) iodide and (-) causing racemisation. The observed rate of racemisation is thus twice the rate of inversion and the optical activity becomes zero. It proves  $\text{SN}^1$  reaction causes inversion.

### **$\text{SN}^1$ Reaction**

The rate equation for this reaction is first order with respect to tert-butyl chloride and first order over all.



$$\text{Rate} \propto [(\text{CH}_3)_3\text{C} - \text{Cl}]$$

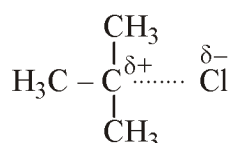
$$\text{Rate} = K [(\text{CH}_3)_3\text{C} - \text{Cl}]$$

As the nucleophile  $\overset{\ominus}{\text{O}}\text{H}$  is not involved in the slow rate determining step and the rate is dependent only on concentration change of alkyl halide, it is called substitution Nucleophilic unimolecular or  $\text{SN}^1$  reaction.

Potential energy diagram of  $\text{SN}^1$  reaction is shown below. It is a two step reaction. First step is the formation of the carbocation intermediate and second step is the attack by nucleophile or solvent molecule to this carbocation to give the product. Hence it has two transition states  $\text{Ts}_1$  and  $\text{Ts}_2$ .



Between these two  $Ts_1$  is more important where the carbon chlorine bond of tert butyl chloride is largely broken and ions are beginning to develop.



The solvent water molecules stabilizes the ions by solvation.

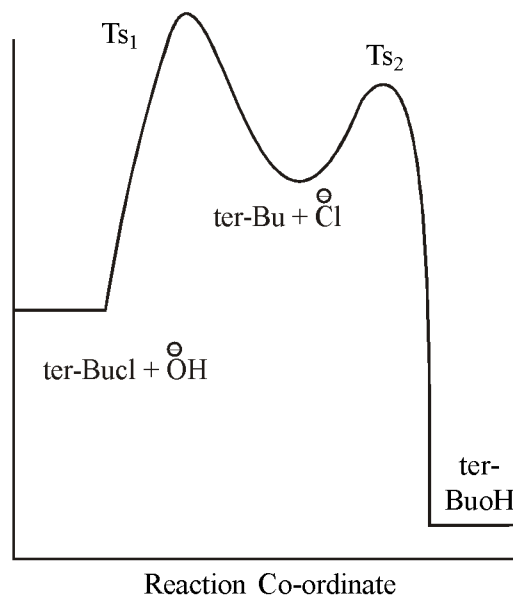


Fig-3

### Stereo Chemistry

The carbocation is formed in the rate determining step of a  $SN^1$  reaction. As the carbocation is planar the nucleophile can attack it from either side leading to 50 : 50 mixture of the product causing racemisation. Hence the product is optically inactive ( $\pm$ ) mixture.

In practice sometimes racemisation is accompanied by some extent of inversion. The more stable the carbocation, the greater the proportion of racemisation. The more nucleophilic the solvent, the greater is the proportion of inversion.

### $SNi$ Reaction :

The reaction has been shown to follow a second order rate equation.

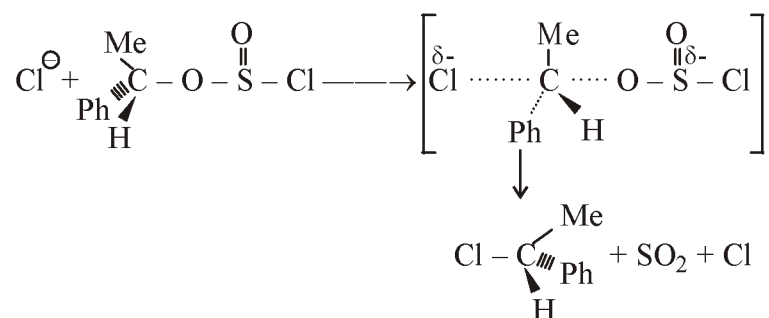
Rate =  $K$   $[\text{KOH}]$   $[\text{SOCl}_2]$  but does not proceed through simple  $SN^2$  mode. So here no inversion of configuration occurs in the product.

### Stereo Chemistry

$SNi$  reaction is always accompanied by retention of configuration of the product as shown in the mechanism.

It is interesting that if the  $\text{SOCl}_2$  reaction of  $\text{ROH}$  is carried out in the presence of pyridine, the product  $\text{RCl}$  is found to have undergone inversion of configuration. This occurs because the  $\text{HCl}$  produced during the formation of  $\text{ROSOCl}$  is converted

by pyridine into  $C_6H_5NHCl^\ominus$  and  $Cl^\ominus$  being an effective nucleophile attacks ROSOCl from the back, like normal  $SN^2$  reaction with inversion of configuration.



### 1.3.3 Effects of solvent, substrate structure leaving group and nucleophiles

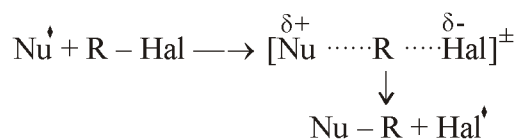
(i) **Solvents** : Changing the solvent in a particular reaction changes the rate and sometimes mechanistic pathway also. Thus by increasing the polarity of the solvent the rate of hydrolysis of alkyl halide by  $SN^1$  pathway increase considerably. e.g. the rate of solvolysis of tertiary halide,  $Me_3CBr$  is found to be  $3 \times 10^4$  times faster, in 50% aqueous ethanol than in ethanol above.

**Reason** : In  $SN^1$  mode charge is developed and concentrated in the T.S. compared to the starting material.  $R - Hal \longrightarrow [R^\delta+ - Hal^\delta-]^\ddagger \longrightarrow R^\square Hal^\dagger$  The energy require to effect such a process decreases with increase in polarity of the solvent. Polar solvent stabilises the ion pair by solvation than the starting material. Hence, the rate of the reaction is increased by  $SN^1$  mode.

The solvent plays an important role in  $SN^1$  way, is supported by the fact that the  $SN^1$  type of reactions are extremely uncommon in the gas phase.

For  $SN^2$  mode, increasing solvent polarity decreases the reaction rate slightly.

**Reason** : No new charge develops in the T.S. instead the existing charge is dispersed compared with the starting material.

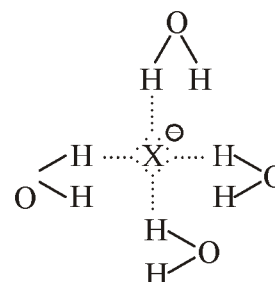


Hence, solvation of the T.S. is less effective than that of the nucleophile. So the rate is slightly decreased.

A very prominent effect on the rate of  $\text{SN}^2$  reactions is observed when the solvent is changed from a polar protic to a polar aprotic solvent.

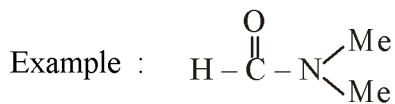
What is protic solvent?

A molecule of a solvent that contains hydrogen atom attached to a strongly electro negative element (oxygen) is called a protic solvent e.g.  $\text{H}_2\text{O}$ ,  $\text{EtOH}$ , molecules of protic solvents stabilise the nucleophile by forming hydrogen bonds as shown below. A small nucleophile e.g.  $\text{F}^\ominus$  is more strongly solvated than a larger ion as the charge is concentrated in a small volume. So to participate in the reaction the solvent molecules must be removed first, to make the nucleophile ( $\text{F}^\ominus$ ) free. On the other hand, the large ion is solvated by weak hydrogen bonds for the spreading of charge and the solvent molecules can be easily removed to make the nucleophile free. So the order of nucleophilicity of halide ions in alcohol or water is  $\text{I}^\ominus > \text{Br}^\ominus > \text{Cl}^\ominus > \text{F}^\ominus >$ .

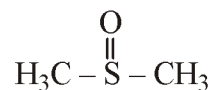


What is polar aprotic solvent?

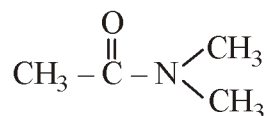
Aprotic solvents are those which do not have hydrogen atom that is attached to a strong electronegative element.



Dimethylformamide (DMF)



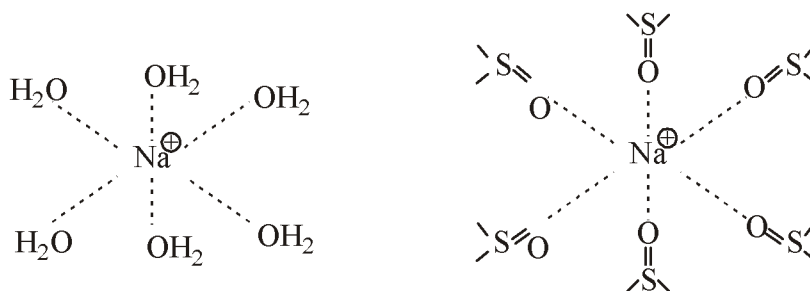
Dimethylsulfoxide (DMSO)



Dimethylacetamide  
(DMA)

Hexamethylphosphoric triamide  
(HMPT)

All of these solvents solvate cat ions making the anions free. Hence, the anions act as effective nucleophiles.



$\text{Na}^+$  ion solvated by  $\text{H}_2\text{O}$  molecules and  $\text{DMSO}$  molecules.

Thus, in  $\text{DMSO}$  the order of nucleophilicity of halide ions is in the order of the charge density of  $\text{F}^- > \text{Cl}^- > \text{Br}^- > \text{I}^-$ . The rates of  $\text{S}_\text{N}2$  reactions are increased considerably in polar aprotic solvent.

**Example :** The rate of reaction of  $\text{MeI}$  with  $\text{NaN}_3$  at  $0^\circ\text{C}$  is increased  $4.5 \times 10^4$  times by changing the solvent from  $\text{MeOH}$  to  $\text{DMF}$  with almost of same polarity. The largely unsolvated ion  $\text{N}_3^-$  in  $\text{DMF}$  is a more powerful nucleophile than the solvated  $\text{N}_3^-$  ion in  $\text{MeOH}$ . So the rate increases.

Increase in solvent polarity and ion solvating ability may change the reaction mode from  $\text{S}_\text{N}2 \longrightarrow \text{S}_\text{N}1$ .

Transfer from hydrogen to polar aprotic solvents change the reaction mode from  $\text{S}_\text{N}1 \longrightarrow \text{S}_\text{N}2$  by increasing the nucleophilicity of the attacking nucleophile.

**(ii) Structure of the Substrate**

Simple alkyl halides show the following general order of reactivity in  $\text{S}_\text{N}2$  reaction Methyl  $>$  Primary  $>$  Secondary  $>$  Tertiary. Measurement of the rates of hydrolysis with dilute, aqueous

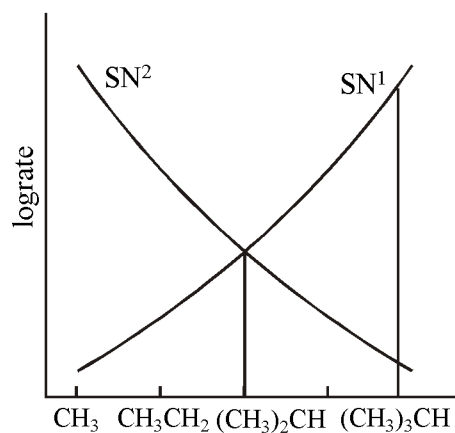
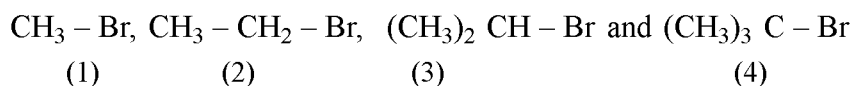


Fig-3(a)

ethanolic NaOH solution gives the plot given below for



The bromo-methane (1) and bromoethane (2) are found to follow  $\text{SN}^2$  mode. 2-Bromo propane (3) a mixed second and first order reaction. (i.e. mixture of  $\text{SN}^1$  and  $\text{SN}^2$ , the relative proportion of the two depending on the initial  $[\text{OH}^-]$  the higher the initial concentration the greater the  $\text{SN}^2$  proportion) while 2-bromo - 2 methyl propane (4) is found to follow  $\text{SN}^1$  mode.

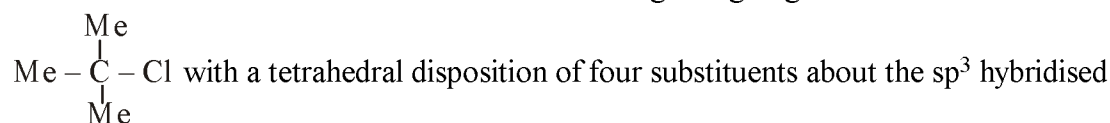
The relative rates of  $\text{SN}^2$  mode of the alkyl halides are as follows :

Relative $\text{SN}^2$ rate	$\text{CH}_3\text{Cl}$	$\text{CH}_2\text{CH}_2\text{Cl}$	$(\text{CH}_3)_2\text{CHCl}$	$(\text{CH}_3)_3\text{CCl}$
	1	$2.7 \times 10^{-2}$	$4.9 \times 10^{-4}$	$2.2 \times 10^{-5}$

**Explanation :** For  $\text{SN}^2$  attack, the greater inductive effect of an increasing number of methyl groups on going for (1) to (4) make the carbon atom bearing the bromine atom less positively polarised and less readily attacked by  $\text{OH}^-$ . Hence the  $\text{SN}^2$  reaction rate decreases from (1)  $\longrightarrow$  (4). Besides the more crowded the T.S. relative to the starting materials the higher the energy will be and slower will be the  $\text{SN}^2$  reaction rate as observed from (1) to (4).

For  $\text{SN}^1$  attack the rate depends on the stability of the carbocation formed as the intermediate ion pair. The carbocation stability increases by inductive and hyperconjugative effect as we go from primary to tertiary halides. Thus tertiary carbocation is most stable and rate of  $\text{SN}^1$  attack increases from (1) to (4).

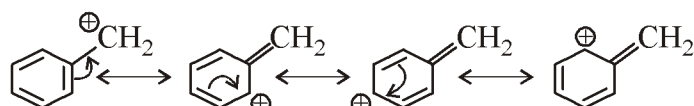
In steric terms there is a relief of crowding on going from the initial halide



carbon atom, to the carbocations  $\text{H}_3\text{C} - \begin{array}{c} \text{CH}_3 \\ | \\ \text{C} \\ | \\ \text{CH}_3 \end{array} - \text{Cl}$  with a planar disposition of three substituents about the  $\text{sp}^2$  hybridised carbon atom. The three substituents are as far apart from each other as they can get in the planar carbocation and relative relief of crowding will increase as the substituents increase in size ( $\text{H} \rightarrow \text{Me} \rightarrow \text{Me}_3\text{C}$ ). The  $\text{SN}^1$  reaction rate will thus increase by electronic and steric ground from (1) to (4).

### Hydrolysis of benzyl chloride ( $C_6H_5CH_2Cl$ ) :

Hydrolysis of 50% aqueous acetone of benzyl chloride gives a mixture of  $SN^1$  and  $SN^2$  reaction but in water shifts to  $SN^1$  mode completely. Here  $SN^1$  mode is preferred as benzyl cation is stabilised by delocalisation of positive charge e.g.



$SN^2$  attack on  $-CH_2$  in benzyl chloride is found to proceed at very much at the same rate as on that in  $MeCH_2Cl$  for the steric crowding in the T.S. by the bulky  $C_6H_5 - gr$  is compensated by a small stability imparting in the T.S. by the electronic effect of the phenyl group.

### Hydrolysis of Allyl halides

Carbocation stabilisation occurs in the hydrolysis of allyl halides, e.g. 3-chloropropene.

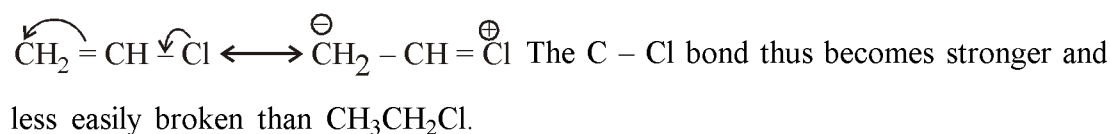


Hence,  $SN^1$  attack is promoted in allyl halides at much greater rate than  $CH_3CH_2CH_2Cl$  and  $C_6H_5CH_2CH_2Cl$  in which such carbocation stabilisation does not occur.

$SN^2$  attack is also increased compared to  $CH_3CH_2CH_2Cl$  because of the electronic effect of the double bond.

By contrast, vinyl halides such as  $CH_2 = CHCl$ , chloroethane is very unreactive towards nucleophilic substitution.

**Reason :** Here the chlorine atom is attached to a  $SP^2$  hybridised carbon, with the result that the electron pair of chlorine atom is drawn closer to carbon atom e.g.

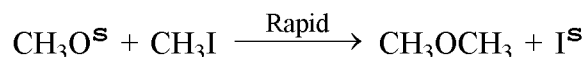


Thus less tendency to ionisation ( $\text{SN}^1$ ) and less positive carbon for  $\text{OH}^\ominus$  attack ( $\text{SN}^2$ ), the p-electrons of the double bond also inhibit the approach of an attacking nucleophile. The double bond would not help to stabilise either the  $\text{SN}^2$  T.S. or the carbocation involved in  $\text{SN}^1$  pathway very much the same considerations apply to halobenzenes. Hence vinyl halide and halobenzenes are resistant towards nucleophilic substitution.

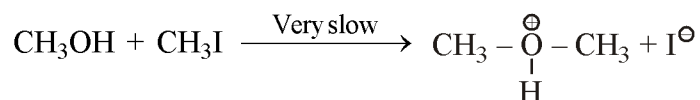
### (iii) Nucleophiles

Nucleophile does not participate in the rate limiting step of an  $\text{SN}^1$  reaction. So the rate of  $\text{SN}^1$  reaction is unaffected by the change in concentration or the strength of a nucleophile.

The rates of  $\text{SN}^2$  reaction depend on both the concentration and the nature of the attacking nucleophile. Increasing the concentration of the nucleophile increases the rate of  $\text{SN}^2$  reaction. The rate of  $\text{SN}^2$  reaction depends on the strength of the nucleophile also e.g. methoxide ion is a strong nucleophile and reacts relatively rapidly with MeI to produce dimethyl ether.



Methanol on the other hand, is a weak nucleophile, under the same conditions it reacts very slowly with MeI.



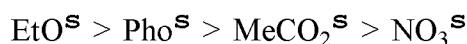
A nucleophile with a negative charge is always more powerful than its conjugate acid. So  $^\ominus\text{OCH}_3$  more powerful than  $\text{CH}_3\text{OH}$ .

Nucleophiles are expected to co-relate with its basicity, as both involve the availability of electron pairs and the ease with which they are donated. The difference between basicity and nucleophilicity are

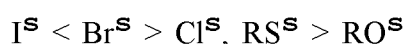
- Basicity involves electron pair donation to hydrogen, whereas nucleophilicity involves electron pair donation to another atom very often carbon.
- Basicity involves a thermodynamic equilibrium whereas nucleophilicity usually involves a kinetic condition.

(c) Basicity is little affected by steric influences. Whereas nucleophilicity is markedly affected by steric influences.

If the attacking atom is the same nucleophilicity runs parallel to basicity i.e. the stronger the base the more powerful the nucleophile.

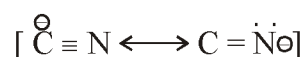
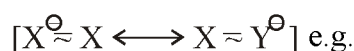


Nucleophilicity is affected by the size of the attacking atom. Thus we find

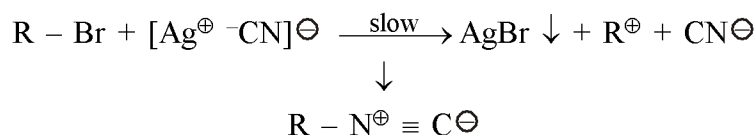


As the atom increases in size nuclear force of attraction to the peripheral electrons decreases with the result that they become more polarizable. Also the larger the nucleophilic ion or group the less is its solvation energy, i.e. the more readily is it converted into the effective, largely non-solvated nucleophile. Combination these factors makes the large, highly polarizable, weakly solvated iodide ion,  $\text{I}^{\ominus}$ , a very good nucleophile whereas  $\text{F}^{\ominus}$ , being small, difficultly polarizable strongly solvated is a weak nucleophile in a protic solvent. But for polar non protic solvent  $\text{I}^{\ominus}$  is weaker nucleophile. Thus  $\text{Br}^{\ominus}$  is a better nucleophile than  $\text{I}^{\ominus}$  in acetone.

**Ambident nucleophile :** Nucleophiles which have more than one generally two suitable atoms through which they can attack the substrate are ambident nucleophiles.

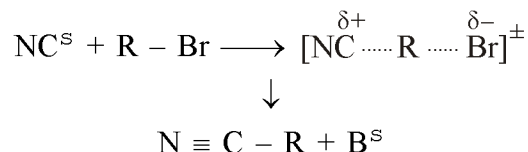


It is found in  $\text{SN}^1$  reactions attack takes place on  $\text{R}^{\oplus}$  through the atom having higher electron density i.e. through nitrogen atom of cyanide grp.  $\text{SN}^1$  attack can be promoted by the use of silver salt of the anion e.g.  $\text{AgCN}$ . Here  $\text{Ag}^+$  promotes  $\text{R}^{\oplus}$  formation by precipitating by  $\text{CN}^{\ominus}$ .



In the absence of  $\text{Ag}^{\oplus}$  with  $\text{NaCN}$  the reaction takes  $\text{SN}^2$  mode by the attack with the more polarisable atom of the nucleophile.





Similarly, Nitrite ion  $[\text{NO}_2]^{\text{S}}$  is found to result in the formation of alkyl nitrites,  $\text{R} - \text{O} - \text{N} = \text{O}$ , under  $\text{SN}^1$  reaction conditions with  $\text{AgNO}_2$ . The attack takes place with more electro-negative oxygen atom of higher electron density forming  $\text{RONO}$ . Nitro alkane,  $\text{RNO}_2$  is formed under  $\text{SN}^2$  condition with  $\text{NaNO}_2$  when the attack takes place by the more polarisable N atom.

#### (iv) Leaving group

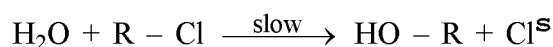
The rate of both  $\text{SN}^1$  and  $\text{SN}^2$  reactions are changed by changing the leaving group as breaking the bond to the leaving group is involved in the slow, rate limiting step of both.

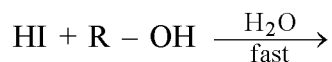
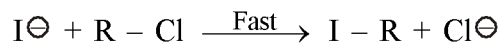
The effectivity of the leaving group is influenced by the following factors

- the strength of the  $\text{R} - \text{Y}$  bond.
- the polarisability of this bond.
- the stability of  $\text{Y}^{\text{S}}$ .
- the degree of stabilisation, through solvation, of the forming  $\text{Y}^{\text{S}}$  in the T.S. for either  $\text{SN}^1$  or  $\text{SN}^2$ .

The order of reactivity of the halogens as leaving group is  $\text{I}^{\text{S}} > \text{Br}^{\text{S}} > \text{Cl}^{\text{S}} > \text{F}^{\text{S}}$ . It indicates that factors (a) and (b) are more important than (c) and (d).  $\text{Y}^{\text{S}}$  acts as a better leaving group when it is the conjugate base of a strong acid  $\text{H} - \text{Y}$ . Thus the anions of strong oxygen acids such as p-toluene sulphonic acid p-Me  $\text{C}_6\text{H}_4\text{SO}_3^{\text{S}}$  (tosylate) or trifluoro sulphonic acid  $\text{CF}_3\text{SO}_3$  (triflate) are good leaving group showing the importance of the factors (c) and (d).

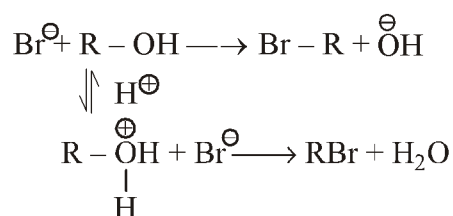
High polarisability of  $\text{I}^{\text{S}}$  makes it both a good entering group and a good leaving group. This property of  $\text{I}^{\text{S}}$  makes it nucleophilic catalysts and used to promote otherwise slow displacement reaction. e.g.





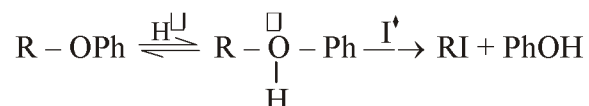
Displacement of some groups are sometimes very much difficult to carryout. In those cases modification of the potential leaving group is made e.g. by protonation.

Thus  $\overset{\ominus}{O}H$  cannot be displaced readily by  $Br^{\ominus}$  but is displaced comfortably if protonated first :



Here weakly basic  $H_2O$  is a better leaving group than the strongly basic  $\overset{\ominus}{O}H$ .

Cleavage of ethers by HI is another example of this type of modification by protonation.



Here  $I^{\ominus}$  acts as a strong nucleophile.

**Problem-7 :** Classify the following solvents as being protic or aprotic : Formic

acid,  $H - \overset{O}{\parallel} - OH$ ; Acetone  $CH_3 - \overset{O}{\parallel} - CH_3$ , Acetonitrile  $CH_3 - C \equiv N$ , Formamide

$H - \overset{O}{\parallel} - NH_2$ , Sulfur dioxide,  $SO_2$ , Ammonia  $NH_3$ ; Trimethyl amine,  $N(CH_3)_3$ , ethylene glycol,  $HOCH_2CH_2OH$ .

**Problem-8 :** The reaction of propyl formide and NaCN occurs faster in which solvent dimethyl formamide (DMF) or in Ethanol. Explain your answer.

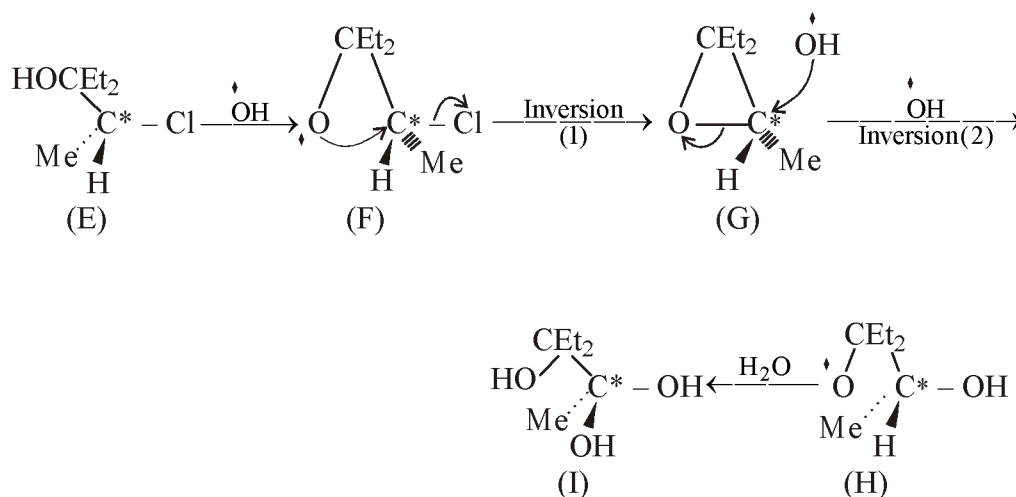
**Problem–9 :** Which of the following would be a stronger nucleophile in a protic solvent (a) the amide ion or  $\text{NH}_3$  (b)  $\text{RS}^-$  or  $\text{RSH}$  (c)  $\text{PH}_3$  or  $\text{NH}_3$  ?

**Problem–10 :** When ter butyl chloride undergoes solvolysis in a mixture of methanol and  $\text{H}_2\text{O}$  the rate increases when the percentage of water in the mixture is increased. Explain. Provide an explanation, the rate of the  $\text{SN}^2$  reaction of ethyl chloride with  $\text{KI}$  in  $\text{MeOH}$  and water decreases when the % of water in the mixture is increased.

### 1.3.4 Substitution involving Neighbouring group (NGP) :

There are some examples of nucleophilic substitution where retention of configuration occurs. The common features of this type of reaction is there is an atom or group with lone pair of electrons close to the carbon undergoing attack. The neighbouring group can attack the carbon atom from the back side preventing attack by the nucleophile from the back. Thus the attack by the nucleophile takes place from the front side leading to retention of configuration. Thus neighbouring group guides the reaction termed as neighbouring group participation.

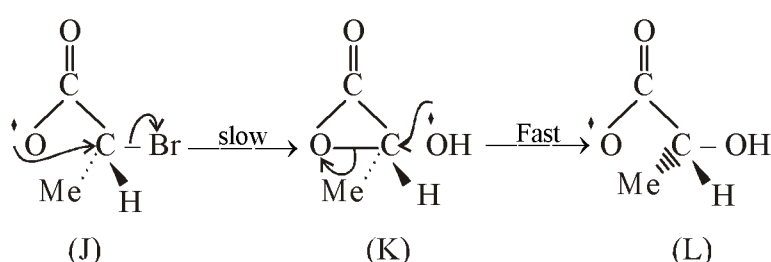
#### Example–1



Initial attack of the base to the compound (E) yields the alkoxide ion. Internal attack by  $\text{O}^-$  of (F) takes place from the back side leading to inversion of configuration of  $\text{C}^*$  in the epoxide (G). The  $\text{C}^*$  carbon atom undergoes a second

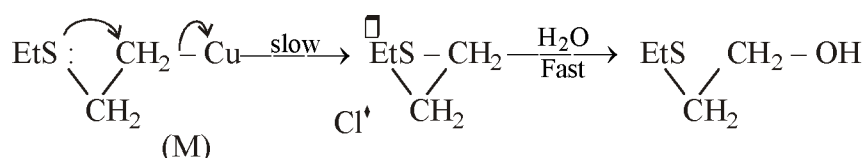
backside attack by  $\text{OH}^-$  with second inversion of configuration of  $\text{C}^*$ . Finally the second alkoxide anion (H) abstracts a proton from the solvent to yield the 1, 2 diol (I), with the same configuration as (E). This apparent retention of configuration has, however, brought about by two successive inversions.

### Example-2

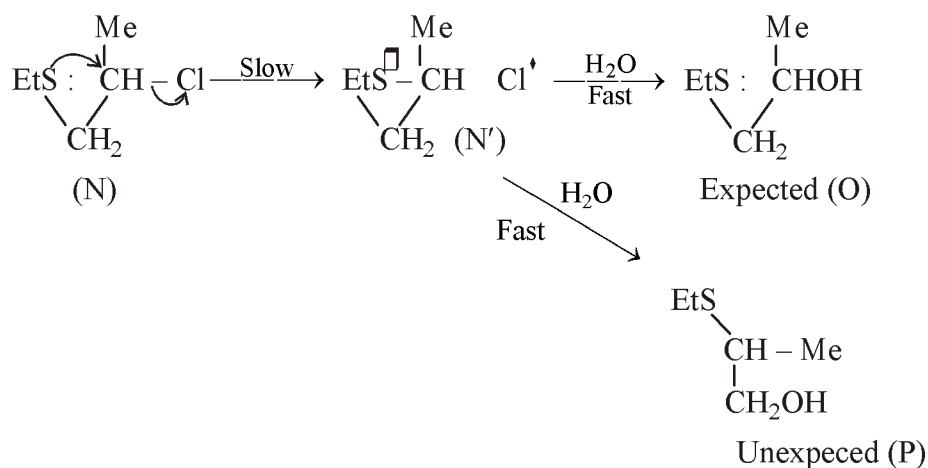


In hydrolysis of the 2-Bromopropanoate anion (J) at low  $[\text{OH}^-]$  concentration proceeds through retention of configuration to give the product (L). Here also  $\text{O}^-$  acts as the neighbouring group.

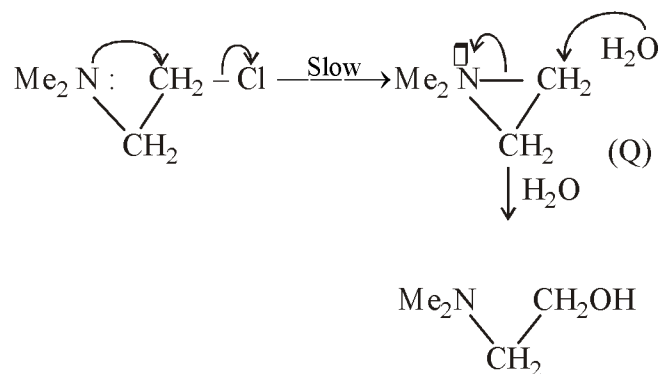
### Example-3



Neighbouring group effect is also observed with atoms other than oxygen e.g. S and N. (M) undergoes hydrolysis  $10^4$  times, faster than  $\text{EtOCH}_2\text{CH}_2\text{Cl}$  which suggests the involvement of  $\text{s}^-$  as a neighbouring group. Hydrolysis of  $\text{EtOCH}_2\text{CH}_2\text{Cl}$  proceeds by normal  $\text{S}_\text{N}2$  as oxygen being more electronegative does not donate an electron pair like (F) or (J). Thus ordinary  $\text{S}_\text{N}2$  attack makes the reaction much slower.

**Example-4**

The involvement of cyclic sulphonium salt (N') is demonstrated by the hydrolysis of (N) which yields two products (O) and (P). The unexpected one (P) is obtained in greater proportion indicates the participation of unsymmetrical intermediate (N') through the internal nucleophilic attack by lone pair of S atom.

**Example-5**

N<sup>+</sup> can act as a neighbouring group in similar circumstances but the rate of the reaction is much slower. Reason besides this slow rate is the greater stability of (Q) which is a cyclic immonium intermediate. Such cyclic species are formed during the hydrolysis of mustard gas S (CH<sub>2</sub>CH<sub>2</sub>Cl)<sub>2</sub> and the related nitrogen mustards, such as, Me<sub>2</sub>N (CH<sub>2</sub>CH<sub>2</sub>Cl)<sub>2</sub>. The cyclic immonium salts derived from nitrogen mustards are powerful neurotoxins.

### 1.3.5 Role of crown ethers and phase transfer Catalysts

We found that  $\text{SN}^2$  reactions take place much more rapidly in polar aprotic solvents such as Dimethyl sulfoxide (DMSO) or Dimethyl formamide (DMF).

**Advantage :** In these polar aprotic solvents the nucleophile is not solvated and becomes highly reactive. As a result reactions which take many hours or days are often over in few minutes.

**Disadvantage :** 1. These solvents have very high boiling points. Hence, they are often difficult to remove after the reactions is over.

2. Purification of these solvents is also time consuming, and they are expensive.

3. At high temperature some of these polar aprotic solvents decompose.

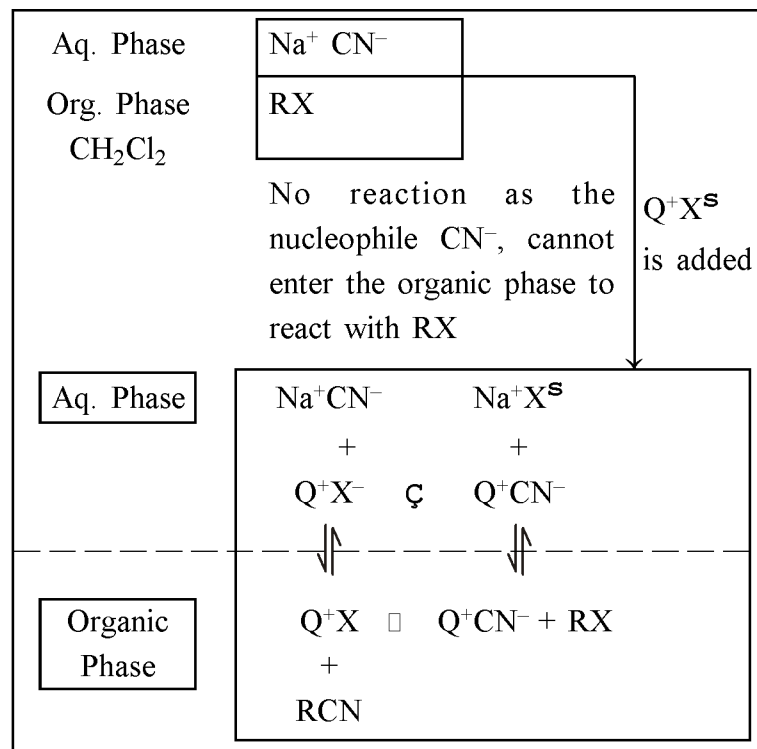
So the ideal solvent for  $\text{SN}^2$  reaction would be a nonpolar aprotic solvent such as hydrocarbon or chlorinated hydrocarbon. They have low boiling points, cheap and relatively stable. But these solvents are seldom used for their inability to dissolve ionic compounds. This problem has been overcome by the use of phase transfer catalyst. How a phase-transfer catalyst acts?

In phase-transfer catalysis we use two immiscible phases that are in contact often an aqueous phase containing an ionic reactant and an organic phase ( $\text{C}_6\text{H}_6$ ,  $\text{CHCl}_3$  etc.) containing the organic substrate. Normally in this condition the reaction does not occur because of the inability of the reagents to come together. Phase transfer catalysts solve this problem by transferring the ionic reactant to the organic phase. As the medium is aprotic  $\text{SN}^2$  reaction occurs rapidly.

**Example-1** The phase transfer catalyst,  $\text{Q}^+\text{X}^-$ , is usually quaternary ammonium halide ( $\text{R}_4\text{N}^+\text{X}^-$ ) such as tetrabutyl ammonium halide  $(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2)_4 \text{N}^+\text{X}^-$ .

The phase transfer catalyst causes the transfer of the nucleophile as an ion pair  $[\text{Q}^+\text{CN}^-]$  into the organic phase. This transfer apparently takes place because the cation ( $\text{Q}^+$ ) of the ion pair, with its 4 alkyl groups, resembles a hydrocarbon in spite of its positive charge. It is lipophilic and prefers a nonpolar environment to an aqueous one.

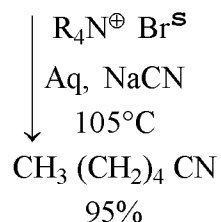
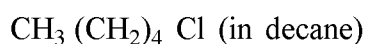
In the organic phase the nucleophile of the ion pair ( $\text{CN}^-$ ) reacts with the organic substrate  $\text{RX}$ . The cation ( $\text{Q}^+$ ) then migrates back into the aqueous phase to complete



the cycle. This process continues until all of the nucleophile or the organic substrate has reacted. Here the phase transfer catalyst transports the  $\text{CN}^-$  ion as  $(\text{Q}^+\text{CN}^-)$  into the organic phase where reaction  $\text{CN}^{\text{S}} + \text{RX} \longrightarrow \text{RCN} + \text{X}^{\text{S}}$  takes place.

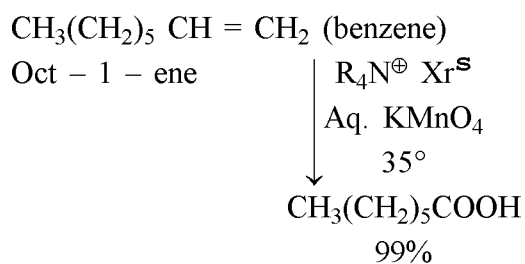
### Example–2

The reaction between 1-chlorooctane (in decane) and NaCN in water is completed in less than two hours in presence of phase transfer catalyst  $\text{R}_4\text{N}^{\oplus} \text{Br}^{\text{S}}$  at  $105^\circ\text{C}$  giving 95% yield.



**Example-3**

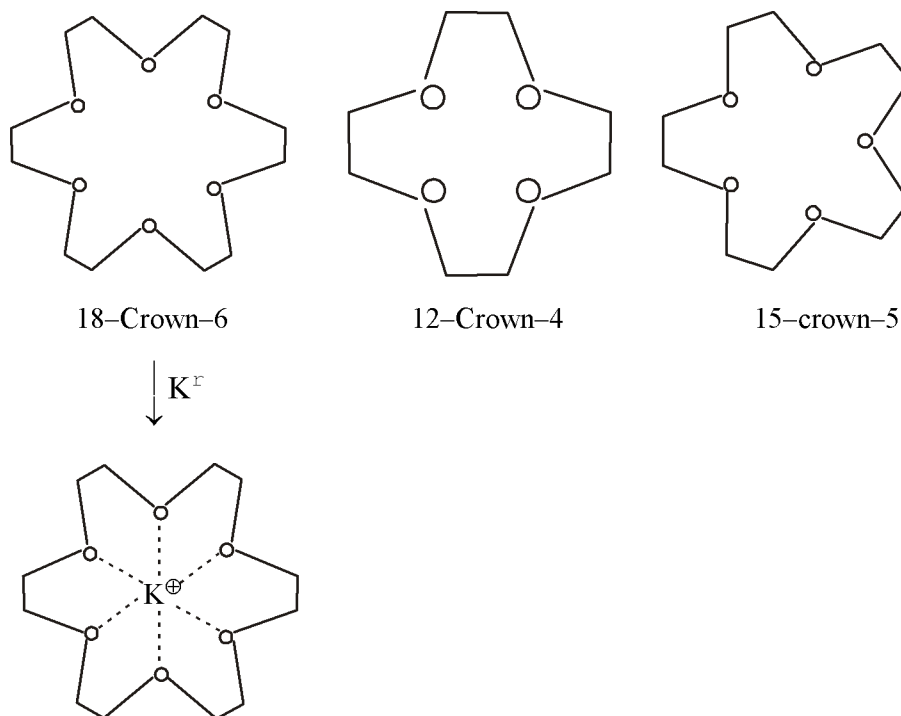
Phase transfer catalysis can be extended to other types of reactions also oxidations of alkenes dissolved in benzene can be achieved in excellent yield using  $\text{KMnO}_4$  (in water) when a phase transfer catalyst is present.

**Crown Ethers**

Compounds called crown ethers are also phase transfer catalysts and are able to transport ionic compounds into an organic phase.

**What are crown ethers?**

Crown ethers are cyclic polymers of ethylene glycol such as 18-crown-6 etc. having the structures as shown below.





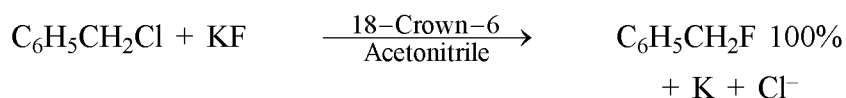
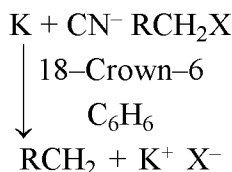
### Naming of crown ethers

Crown ethers are named as x – crown — y where x is the total number of atoms in the ring and y is the number of oxygens. The relationship between crown ether and the ion that it transports is called a host guest relationship. The crown ether acts as the host and the co-ordinated cation is the guest.

### Action as phase transfer Catalyst

When crown ethers co-ordinate with a metal cation they convert the metal ion into a species with a hydrocarbon like exterior. 18-crown-6 can co-ordinate effectively with potassium ion. The crown ether has a hole in the middle with a diameter of  $2.7\text{\AA}$ . Now the diameter of  $\text{K}^+$  is  $2.66\text{\AA}$ . Hence, just fits in the hole of 18-crown-6 where it is held by unshared pairs of electrons on the six oxygen atoms. This  $\text{K}^{\oplus}$  is bound very tightly. Crown ether is not a solvent but it holds  $\text{K}^{\oplus}$  by the same forces that a solvent uses. The forces are much stronger here salts such as KF, KCN and  $\text{CH}_3\text{COOK}$  can be transferred into aprotic solvents by using catalytic amounts of 18-crown-6.

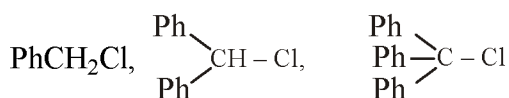
### Examples



**Problem-11** When  $\text{CH}_3$  groups of t-butyl chloride are replaced with  $\text{CO}_3$  groups the rate of  $\text{SN}^1$  solvolysis is decreased by  $\approx 10\%$  per D-atom. Explain

### Problem-12

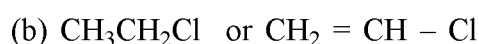
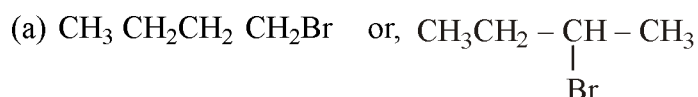
Let us consider the hydrolysis of the following compounds :



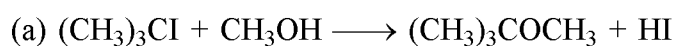
When the following results are observed. :  $\text{PhCH}_2\text{Cl}$  in 50% aqueous  $\text{CH}_3\text{CH}_2\text{OH}$  follows a mixed kinetics but in water follows the first order kinetics.

$(\text{Ph})_2\text{CHCl}$  and  $\text{Ph}_3\text{CCl}$  follow first order kinetics. Explain.

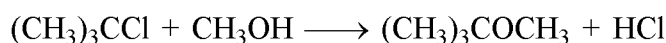
**Problem–13** Which alkyl halide would you expect to react more rapidly by  $\text{SN}^2$  mechanism? Explain your answer.



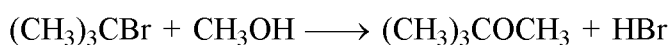
**Problem–14** Which  $\text{SN}^1$  reaction would you expect more rapidly? Explain your answer.



or



or



### Summary

- Two mechanisms for nucleophilic substitution reactions occur :  $\text{SN}^2$  and  $\text{SN}^1$ . The  $\text{SN}^2$  reaction is characterized by :
  - Second — order Kinetics.
  - Complete stereochemical inversion occurs if the substrate contains asymmetric carbon.
  - No rearrangement occurs.
  - The reactivity sequence for halides is  $1^\circ > 2^\circ > 3^\circ$ . Unhindered alkyl halides favour this pathway.
  - A strong nucleophile and a high concentration of nucleophile favours  $\text{SN}^2$  reaction.

A polar aprotic solvent e.g. DMF,  $\text{CH}_3\text{COCH}_3$  favours  $\text{SN}^2$  reaction. The  $\text{SN}^1$  reaction is characterised by

- First order kinetics.

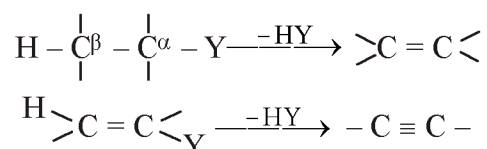
- (b) Racemisation of the optically active substrate occurs.
  - (c) Rearrangement takes place.
  - (d) The reactivity sequence is  $3^\circ > 2^\circ > 1^\circ > \text{CH}_3 - \text{L}$ .
  - (e) Highly polar solvent that can form relatively stable carbocations favours this reaction.
  - (f) Weak nucleophiles support  $\text{SN}^1$  reactions.
  - (g) Sometimes in  $\text{SN}^1$  substitution solvent molecule acts as nucleophile when the reaction is called solvolyses
2. Besides  $\text{SN}^1$  and  $\text{SN}^2$  other substitution reactions discussed are  $\text{SN}^1$ ,  $\text{SN}^{1'}$  and  $\text{SN}^{2'}$ .
- (a)  $\alpha$ -phenyl ethanol reacts with  $\text{SOCl}_2$  to give  $\alpha$ -phenyl ethyl chloride of same configuration. It is called  $\text{SN}^1$  substitution or substitution nucleophilic internal reaction.
  - (b) It is always accompanied by retention of configuration but in presence of pyridine inversion occurs.
  - (c)  $\text{SN}^1$  solvolysis in EtOH of 3-chlorobut 1-ene gives two isomeric ethers which are also obtained from the similar solvolysis of 1-chlorobut -2-ene. It is  $\text{SN}^{1'}$  reaction.
- But when  $\overset{\text{S}}{\text{O}}\text{Et}$  is present in fairly high concentration in preference to EtOH the reaction becomes  $\text{SN}^2$  and gives only one ether. Then the reaction is termed as  $\text{SN}^{2'}$ .
3. The rates of  $\text{SN}^1$  and  $\text{SN}^2$  reactions depend on the (a) structure of substrate, (b) concentration and reactivity of the nucleophile (c) the nature of the solvent and (d) the nature of the leaving group.
- (a) The order of reactivity of alkyl halides towards  $\text{SN}^2$  reaction is methyl > primary > secondary > Tertiary. For  $\text{SN}^1$  reaction the rate is reversed. i.e. tertiary > Secondary > Primary > Methyl. Benzyl chloride and allyl chloride undergo hydrolysis preferentially by  $\text{SN}^1$  mode for the stability of benzyl and allyl carbocation.
  - (b)  $\text{SN}^1$  reactions are unaffected by the concentration and strength of the

nucleophile as in  $\text{SN}^1$  reaction the nucleophile is not involved in the rate limiting step. The rate of  $\text{SN}^2$  reaction depend both on concentration and nature of the nucleophile. The rate of  $\text{SN}^2$  reaction increases with increase in concentration of the nucleophile. If the attacking atom is same nucleophilicity runs parallel to basicity i.e. the stronger the base the more powerful the nucleophile. e.g.  $\text{EtO}^{\ominus} > \text{PhO}^{\ominus} > \text{MeCO}_2^{\ominus} > \text{NO}_3^{\ominus}$ . The larger the size of the atom stronger is the nucleophile e.g.  $\text{I}^{\ominus} > \text{Br}^{\ominus} > \text{Cl}^{\ominus}$ ,  $\text{RS}^{\ominus} > \text{RO}^{\ominus}$ .  $\text{CN}^{\ominus}$  and  $[\text{NO}_2]^{\ominus}$  are ambident nucleophile i.e. the attack can occur by both the atoms Nitrogen and carbon for cyanide and nitrogen and oxygen for nitrites giving different products.

- (c) Increasing the polarity of the solvent rate of  $\text{SN}^1$  reaction increases.  $\text{SN}^2$  reactions are favoured in polar aprotic solvent. In polar aprotic solvent the nucleophile is not solvated and free to attack. Hence, the rate of  $\text{SN}^2$  reaction is increased Examples of polar aprotic solvents are DMF, DMSO, Acetone etc.
- (d) The nature of the leaving group affects both  $\text{SN}^1$  and  $\text{SN}^2$  reactions. For halides the order of reactivity of leaving groups are  $\text{I}^{\ominus} > \text{Br}^{\ominus} > \text{Cl}^{\ominus} > \text{F}^{\ominus}$ . The anions of strong acids are better leaving groups e.g. anion of P-toluene-sulphonic acid  $\text{P-Me C}_6\text{H}_4\text{SO}_3^{\ominus}$ . High Polarizability of  $\text{I}^{\ominus}$  makes it both a good entering group and a good leaving group. This property makes  $\text{I}^{\ominus}$  as a nucleophilic catalyst. Modification of potential leaving group can readily remove the groups which are otherwise difficult to remove e.g. protonation of  $-\text{OH}$  group can remove it as  $\text{H}_2\text{O}$  easily.
4. The atom or group with lone pair of electrons close to the carbon undergoing attack is called the neighbouring group. It also participates in substitution reaction with retention of configuration. However, here retention occurs by two successive inversions  $\text{O}^{\ominus}$ ,  $\text{S}^{\ominus}$ ,  $\text{N}^{\ominus}$  acts as neighbouring group.
5. For some disadvantages of using polar aprotic solvent for other high boiling points and difficulty to remove, non polar aprotic solvents e.g. hydrocarbon are used in many  $\text{SN}^2$  reactions. Those solvents cannot dissolve ionic reactants. So catalyst is used called phase transfer catalysts that brings the ionic reactant to the organic phase e.g. quaternary ammonium salts and crown ethers which are cyclic polymers of ethylene glycol.

## 1.4 Elimination Reactions

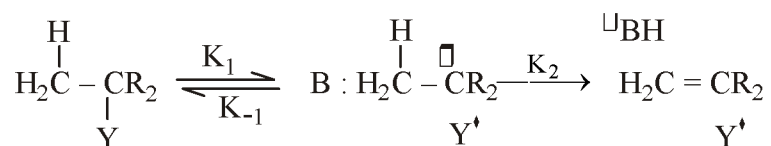
Elimination reactions involve the removal of two atoms or groups from the adjacent carbon atoms of a molecule. Generally, one of them being a proton and the other a nucleophile, Y : or Y<sup>S</sup>. There by a multiple bond is formed as shown below.



The atom from which Y is lost is designated as  $\alpha$ -carbon and that losing H – as the  $\beta$ -carbon. Initially this eliminations are termed as  $\alpha$ ,  $\beta$  – elimination reactions. But now  $\alpha$  is commonly omitted and the reaction are termed as  $\beta$ -eliminations. Elimination reactions are of four types viz, E<sub>1</sub>, E<sub>2</sub>, E<sub>1</sub>CB and E<sub>i</sub>.

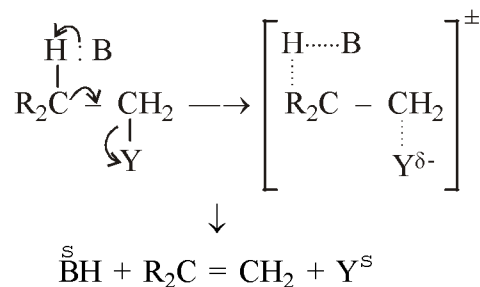
### 1.4.1 E<sub>1</sub> Mechanism

In this type of reactions first the C – Y bond breaks to form a carbocationic intermediate which is the slow rate determining step. From this intermediate H<sup>⊕</sup> is abstracted by a base to form the alkene. It is referred to as E<sub>1</sub> or elimination unimolecular as the alkyl halide is only involved in the rate determining step. The process is compared to SN<sup>1</sup> as both involve carbocation intermediate.



### 1.4.2 E<sub>2</sub> Mechanism

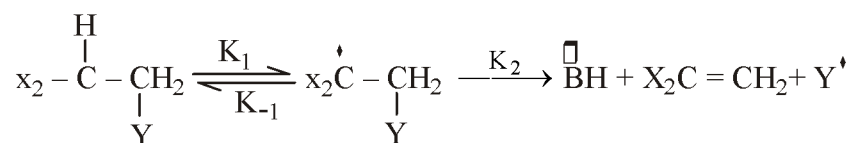
In this type of reactions C – H and C – Y bonds break simultaneously in our step, through a single transition state. e.g.



This is referred to as E<sub>2</sub> mechanism i.e. elimination bimolecular as in the rate determining step both alkyl halide and the base is involved. It is comparable to S<sub>N</sub><sup>2</sup> and a concerted one step reaction.

### 1.4.3 E<sub>1</sub>CB Mechanism

In this type of reactions H – C bond breaks first to form a carbonionic intermediate followed by breaking of C – Y bond.

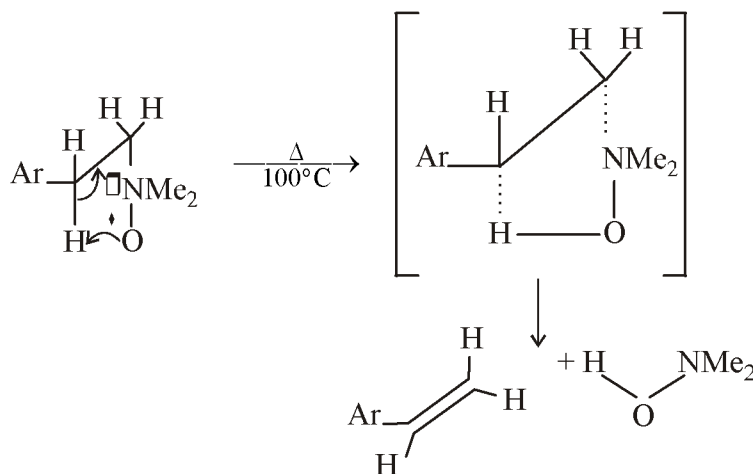


This is referred to as E<sub>1</sub>CB mechanism i.e. elimination unimolecular with respects to conjugate base.

### 1.4.4 Pyrolytic Syn Elimination E<sub>i</sub>

There are a number of organic compounds e.g. esters (acetates, xanthates) amine oxides and halides which undergo pyrolytic syn elimination of HY either in inert solvents or in the absence of solvent and in some cases in the gas phase. The rate law is Rate = K [Substrate] is found to be indistinguishable from E<sub>1</sub>. But syn stereoselectivity of these reactions distinguish it from E<sub>1</sub>. The formation of syn product indicates the reaction proceeds via a cyclic transition state forming us product.

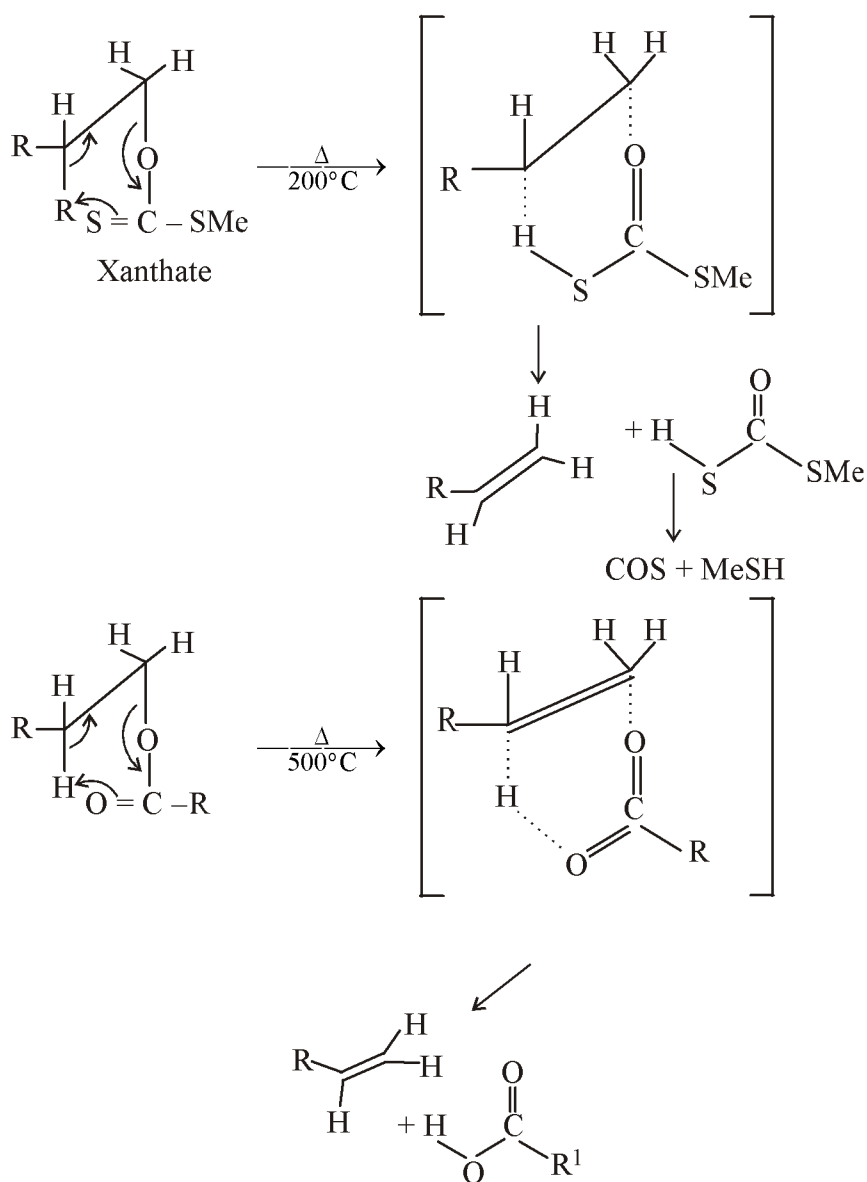
**Example–1. Cope reaction :** It has the greatest synthetic utility as the alkene is formed from the amine oxide at comparatively low temperature.



The leaving group H and NMe<sub>2</sub>O must assume a syn-periplanar conformation.

**Example-2. Chugaev Reaction :**

The pyrolysis of xanthates and of carboxylic esters proceed via six membered cyclic transition states causing E<sub>i</sub> elimination.



In this reaction the T.S. is six membered and are more flexible than the five

membered T.S. of cope reaction. So here the syn stereo selectivity is lower than that of cope reaction. Both reactions require higher temperature than cope reaction.

## 1.5 The formation and alkenes and alkynes

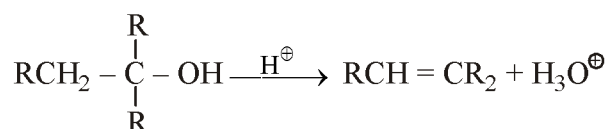
The most common methods for the formation of alkenes and alkynes are :

- (i) Base catalysed dehydro halogenation of alkyl halides :

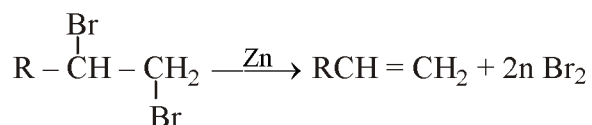


It can follow E<sub>1</sub>, E<sub>2</sub> or E<sub>1</sub>CB mechanism depending on the structure of the alkyl halide.

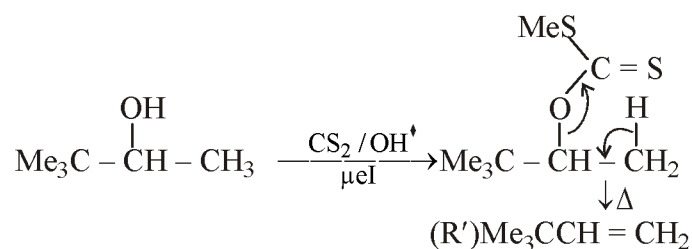
- (ii) Acid catalysed dehydration of alcohols :



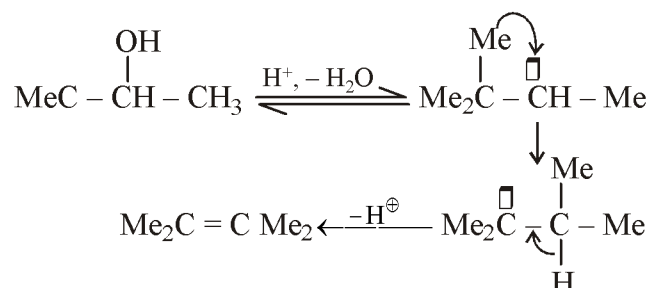
- (iii) Dehalogenation of 1, 2 dihalides



- (iv) Chugaev reaction of pyrolysis of xanthates is used for preparation of less substituted alkenes. e.g. the compound (Q') is converted to xanthate and subjected to chugaev reaction the unrearranged terminal alkene (R') is formed as the major product. But the usual acid catalysed dehydration gives the thermodynamically more stable rearranged alkene







### 1.5.1 Discussions of mechanisms and Evidence

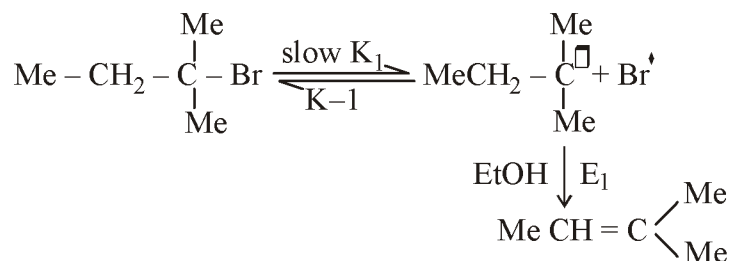
**E<sub>2</sub> Mechanism** By far the commonest elimination mechanism is the one step concerted E<sub>2</sub> pathway. e.g. the base catalysed elimination of H<sup>+</sup> from the halide RCH<sub>2</sub>CH<sub>2</sub>Br. The rate law is

$$\text{Rate} = K [\text{RCH}_2\text{CH}_2\text{Br}] [\text{B}]$$

As B is often a nucleophile as well as a base elimination is frequently accompanied by one step concerted S<sub>N</sub><sup>2</sup>.

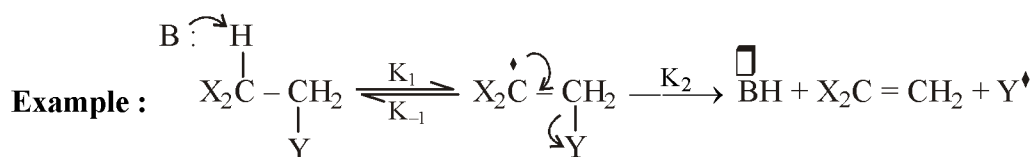
**Evidence :** That C – H bond fission occurs in the rate determining step is proved by the fact that when H is replaced by D atom the rate of the reaction is decreased i.e. primary kinetic isotope effect is observed. It is an experimental evidence in support of the concerted mechanism in E<sub>2</sub> elimination.

**E<sub>1</sub> Mechanism :** In E<sub>1</sub> mechanism the formation of the carbocation by the breaking of C – Y bond is the slow rate determining step. Hence the rate law observed with Me CH<sub>2</sub> C Me<sub>2</sub> Br is Rate = K [Me CH<sub>2</sub> C Me<sub>2</sub> Br] as in this step the base or the solvent molecule for the removal of proton is not involved.



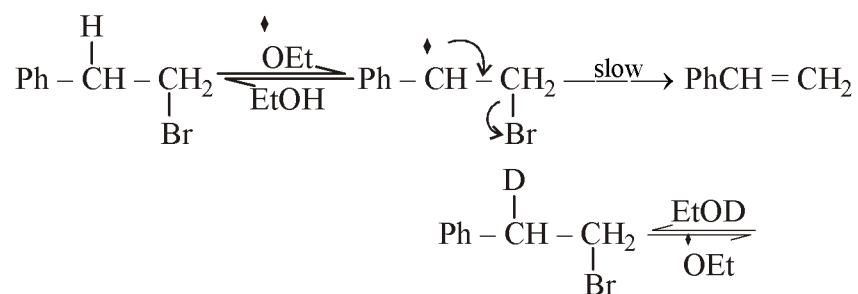
**Evidence :** By adding  $\overset{\ominus}{\text{O}}\text{Et}$  with EtOH the rate of the reaction does not change significantly. It proves that  $\text{E}_2$  mechanism is not operating and  $\text{E}_1$  reaction is followed. Because in  $\text{E}_1$  mechanism the base is not involved in the rate determining step which is ionisation of the alkyl halide by breaking C – X bond.

**$\text{E}_1$  CB mechanism :**



In this pathway the formation of carbanion intermediate (1) is fast and reversible while subsequent loss of  $\text{Y}^\ominus$  is slow and rate determining step i.e.  $\text{K}_{-1} > \text{K}_2$ , so the rate law will be  $\text{Rate} = \text{K} [\text{RY}] [\text{B}]$  and will be kinetically distinguishable from  $\text{E}_2$ .

**Evidence :** To establish whether  $\text{E}_1\text{CB}$  mechanism is operating, an experiment is carried out with  $\text{PhCH}_2\text{CH}_2\text{Br}$  in  $\text{NaOEt}$  in EtOH. It can undergo dehydrobromination by  $\text{E}_1\text{CB}$  mechanism as the hydrogen atom attached to the carbon atom adjacent to Ph group is acidic and can form carbanion.



The reaction was carried out in  $\overset{\ominus}{\text{O}}\text{Et}$  and EtOD and no deuterium was found in recovered starting material or in product alkene. Hence, it is proved that  $\text{E}_1\text{CB}$  mechanism is not operating. On the other hand, it follows concerted  $\text{E}_2$  Path way.

### 1.5.2 Reactivity, Regioselectivity, Stereo-selectivity of elimination reactions

#### Factors affecting E<sub>2</sub> reaction

- (a) **Strength of base** : The stronger the base the faster is E<sub>2</sub> reactions. Hence,  $\overset{\ominus}{\text{N}}\text{H}_2 > \overset{\ominus}{\text{R}}\text{O} > \overset{\ominus}{\text{O}}\text{H}$ . The conjugate base of a weak acid is a strong base.
- (b) **Nature of the solvent** : The preferred solvent for E<sub>2</sub> reaction is bipolar aprotic one e.g. DMF (HCONMe<sub>2</sub>) or DMSO (Me<sub>2</sub>S + O<sup>⊖</sup>). Such a change of solvent may result in a mechanistic shift of pathway from E<sub>1</sub> to E<sub>2</sub> for same substrate/base pairs.
- (c) **Nature of this leaving group** : The stronger the C – Y bond the lesser is the rate of elimination reaction.

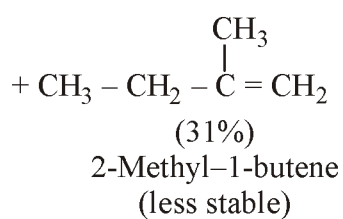
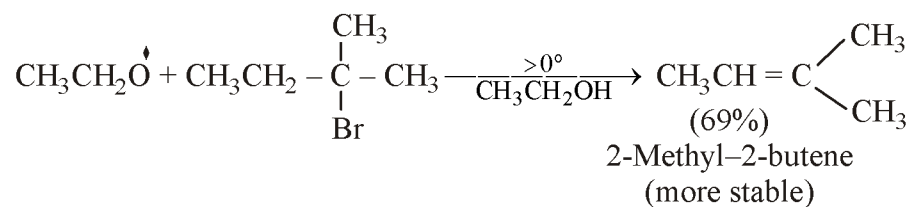
**Example** : The elimination rate of PhCH<sub>2</sub>CH<sub>2</sub> Hal with  $\overset{\ominus}{\text{O}}\text{Et}/\text{EtOH}$  is

PhCH <sub>2</sub> CH <sub>2</sub> F	PhCH <sub>2</sub> CH <sub>2</sub> Cl	PhCH <sub>2</sub> CH <sub>2</sub> Br	PhCH <sub>2</sub> CH <sub>2</sub> I
Set-rate :	1	70	4.2 × 10 <sup>3</sup>
			2.7 × 10 <sup>4</sup>

The more stable is Y<sup>⊖</sup> ion the faster is the rate of elimination reaction. The conjugate base of a strong acid is more stable than that of a weak acid. Thus tosylate (p-toluene sulphonyl gr – p - Me C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub><sup>⊖</sup>) is a very much better leaving group than  $\overset{\ominus}{\text{O}}\text{H}$  reflecting the fact that p-MeC<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H is much stronger acid than H<sub>2</sub>O. Here solvent also plays important role. Y<sup>⊖</sup> can be stabilised by hydrogen bonding by the protic solvent. So change of solvent change the sequence of relative leaving group ability.

- (d) **Structure of the product** : The more is the thermodynamic stability of the resultant alkene the less is the activation energy leading to the T.S. for its formation and faster is the elimination reaction. Thus increasing the alkyl substitution at α or β-carbon atoms or introduction of Ph group that can become conjugated with the developing double bond the rate of E<sub>2</sub> reaction increases.

**Example** : 2-Bromo – 2-methyl butane on E<sub>2</sub> reaction by ethoxide or hydroxide in ethanol or H<sub>2</sub>O produces the more stable 2-Methyl–2–butene as the major product.



It is reflected in the PE, diagram of the reaction.

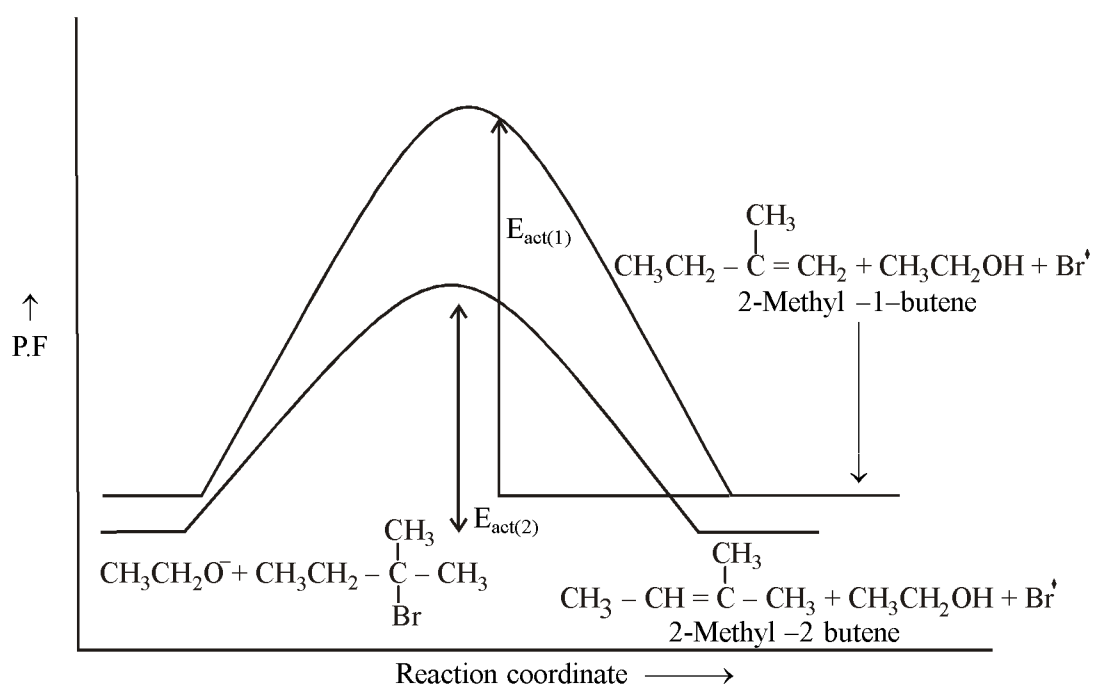
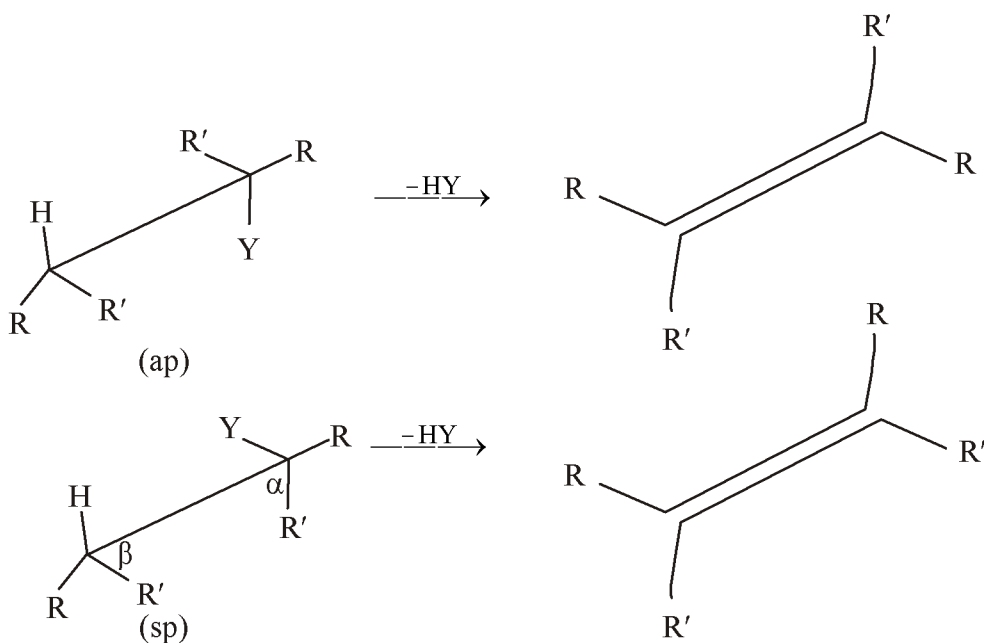


Fig-4

$E_{\text{act}(2)}$  leading to the formation of the more stable alkene is less than the  $E_{\text{act}(1)}$  leading to the formation of less stable alkene.

### Stereo Chemistry of E<sub>2</sub> elimination

In acyclic molecules elimination can take place from one or the other of the two limiting conformations the anti-periplanar (ap) or the syn-periplanar (sp).



The elimination taking place from a conformation in which H, C<sup>β</sup>, C<sup>α</sup> and Y are in the same plane is preferred. As in this conformation the P orbitals that are developing an c<sup>β</sup> and c<sup>α</sup> by the ions H<sup>⊕</sup> and X<sup>⊖</sup> will be parallel to each other causing maximum overlap in burning the bound. It is energetically advantageous as for the attacking atom of the base B to lie in this common plane also.

Now the question arises which planar conformation is preferred (ap) or (sp)?

#### Support in favour of elimination from anti periplanar conformation (ap).

(a) The “staggered” (ap) conformation is of lower energy than that of higher energy “eclipsed” conformation” (sp). It is also observed in the energy of the respective transition states.

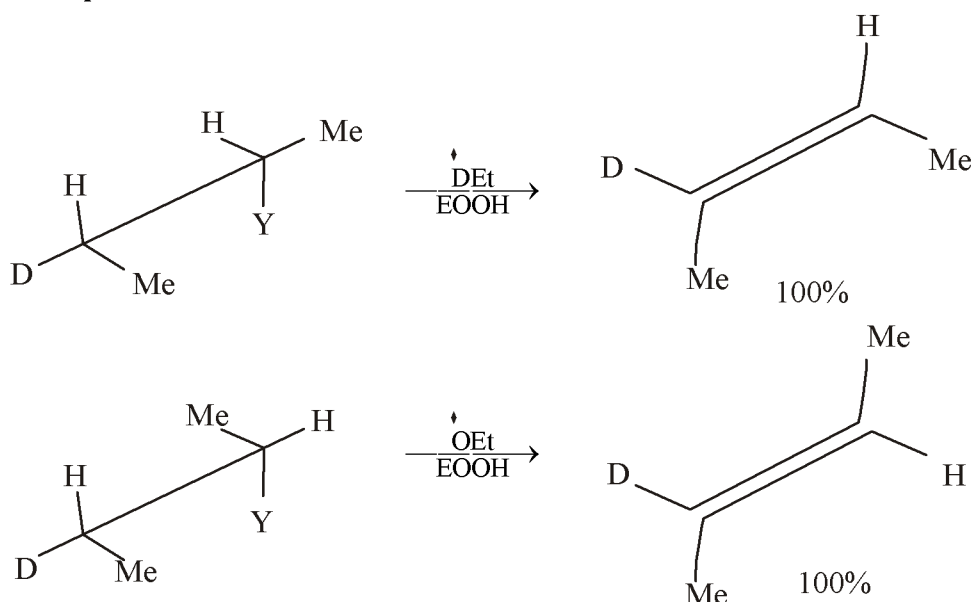
(b) The attacking base ‘B’ and the leaving group Y<sup>⊖</sup>, would be as far apart from each other as possible in the anti periplanar T.S. (ap).

(c) The electron pair of the C – H bond will attack the  $\alpha$ -carbon atom from the back side from which the electron pair of the initial C – Y bond will be departing.

From all these facts the “anti elimination” (opposite side) of H and Y is preferred. Either than syn (“same side”) elimination of H and Y.

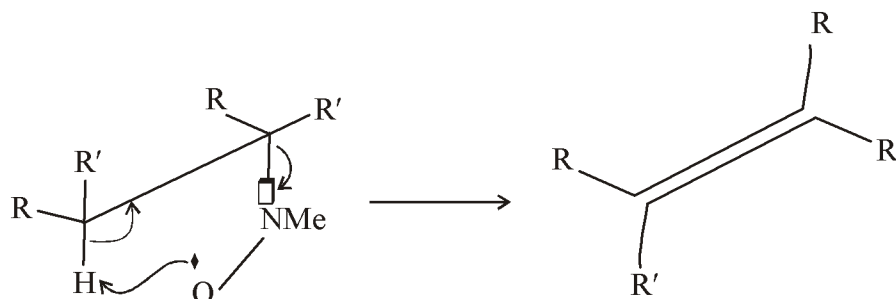
If the original compound is chiral anti elimination gives rise to trans alkene. It proves the stereo selectivity of  $E_2$  elimination reaction.

### Example



This 100% stereo selectivity is observed when  $Y = \text{Br}, \text{Ts}$  or  $\overset{\text{S}}{\text{N}}\text{Me}_3$

**Exception :** For longer chain  $\overset{\text{S}}{\text{N}}\text{R}_3$ , syn elimination of the  $\beta$  – H via a cyclic T.S. is observed e.g. in the following quaternary ammonium hydroxide is n pair

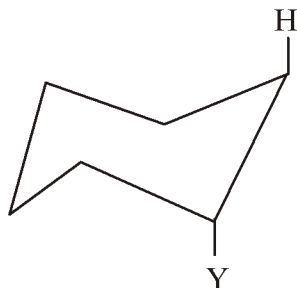


However, in cyclic compounds syn elimination occurs for the rigidity of ring,

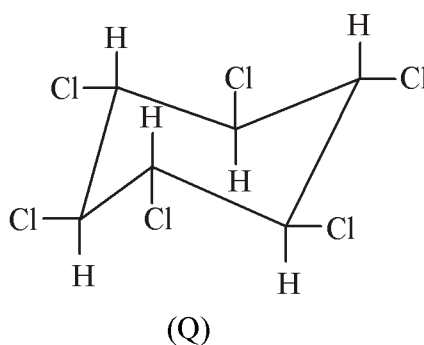
structure with the exception of cyclohexane ring. Cyclohexane can be flipped to maintain the elimination group in trans-diaxial conformation. The proportion of elimination in different rings are shown below :

Ring size	% SYN Elimination
Cyclobutyl	90
Cyclopentyl	46
Cyclohexyl	4
Cycloheptyl	37

The marked ANTI stereoselectivity observed with cyclohexyl systems is due to the trans diaxial conformation of the eliminating groups as shown below.



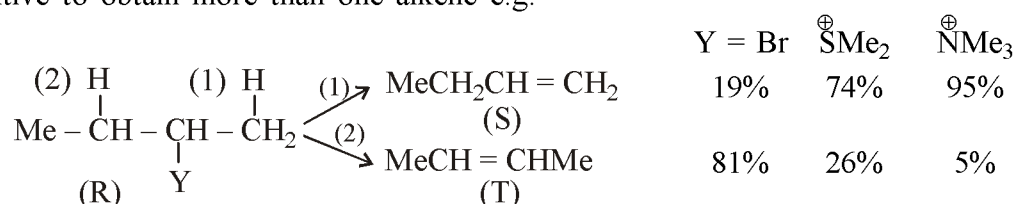
In the geometrical isomers of hexa chlorocyclohexane,  $C_6H_6Cl_6$ , one is found to undergo elimination of HCl at a rate slower by a factor of  $7 - 24 \times 10^3$ , than any of the others. It is found to be (Q) as shown below.



In this isomers H and Cl cannot assume the above trans-diaxial conformation so the rate of elimination is slow.

### Orientation in E<sub>2</sub>

In substrates where there are alternative β-hydrogen atoms available, it is positive to obtain more than one alkene e.g.

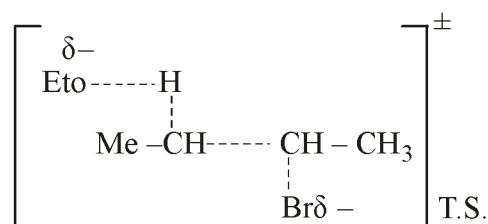


To predict which alkene is the major product two empirical rules are present. They are summarised as follows :

(a) Hofmann (1851 working on  $RN^+Me_3$  compounds i.e.  $Y = N^+Me_3$ ) stated that alkene will predominate which has least alkyl substituents to the double bond i.e. (s) above. This is Hofmann's rule.

(b) Saytzev (1875 : working on  $RB_2$  compounds i. e.  $y = Br$ ) stated "that alkene will predominate which has most alky substituents on the double landed carbon atoms". i.e. (T) above. This is Saytzev's rule : Hence it is clear that the composition of the alkene mixture is dependant on the nature of the leaving grp Y.

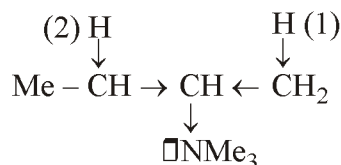
Saytzev elumination occurs when Y is neutral (e.g. with  $Y = OTs$  etc as well as Br) and leads to the more stable i.e. more substituted alkene. Hence it is reasonable to assume that the reaction proceeds via an alkene like transition state. Alkyl substituents there by stabilises or decreases the energy of the transition state in the single step of E<sub>2</sub> pathway.



So why a +vely charged Y should deverge the reaction in the other direction?

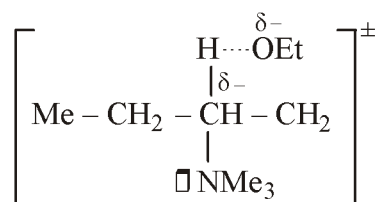
A Y group such as  $N^+Me_3$  will exert a powerful electron withdrawing inductive effect on both β carbon atoms and also on the hydrogen atoms attached to them and makes them acidic.





The acidity of H<sup>⊖</sup> is less than that of H<sup>⊕</sup> as the electron-donating inductive effect of the Me group. Thus, in this case the relative proton acidity is the controlling factor and not the stability of alkenes.

The T.S. has now carbonion like character and the more stable carbons is the less substitute one. So the transition state of lower energy will be as shown below.

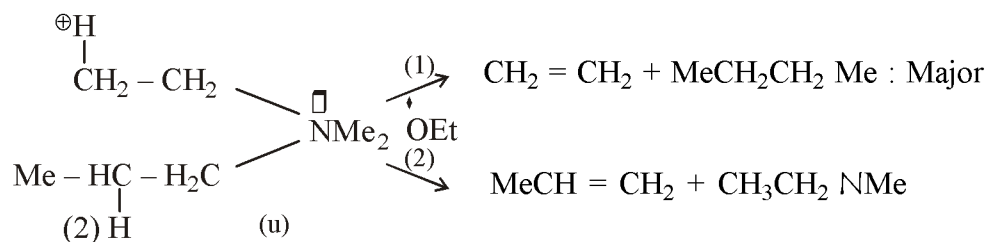


It is interesting to note when Y is F, Hofmann product is the major one. Thus EtCH<sub>2</sub>CH(F)CH<sub>3</sub> gives 85% EtCH<sub>2</sub>CH = CH<sub>2</sub>. This “unexpected” result is observed due to extremely powerful electron withdrawing effect of F and that F<sup>S</sup> is a very poor leaving group.

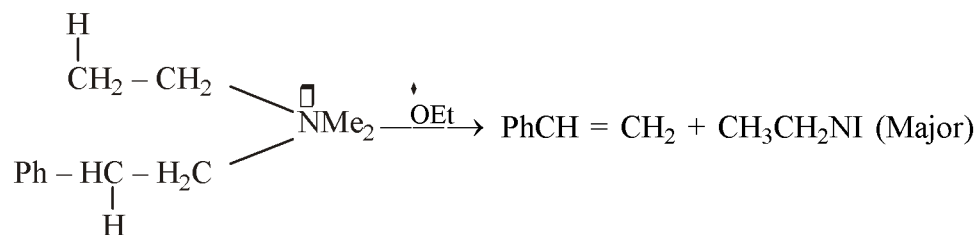
### Evidence in support of carbonion character of the T.S. in Hofmann elimination

Increasing the strength of the base yield of Hofmann product increases.

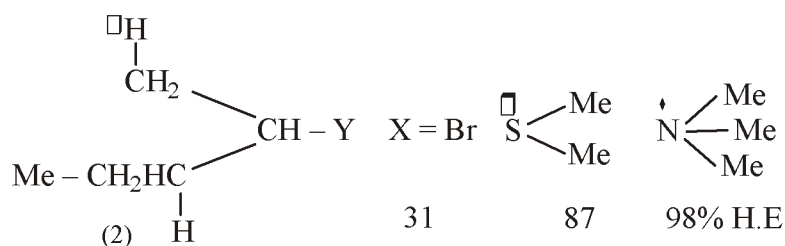
β – substituents that would help to stabilise a developing –ve charges promote formation of Hofmann product. But substituents such as C = C promote the formation of that alkene where the double bond is in conjugated with them e.g. in (u) there are alternative potential RNMe<sub>2</sub> leaving groups. The least substituted alkene is formed preferentially.



But if Me is changed with Ph group the more substituted alkene is the major product as the Ph grp is in conjugation with the double bond and the carbonion like T.S. also gets stability by the Ph ring.

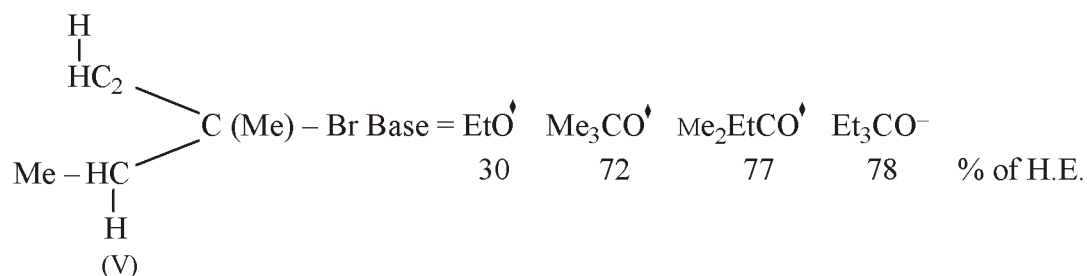


Branching in Y to increase its size leads to an increase in Hofmann product for a particular substrate e.g.



For a particular Y or base the branching in the alkyl group of the substrate increases the proportion of H.E. product.

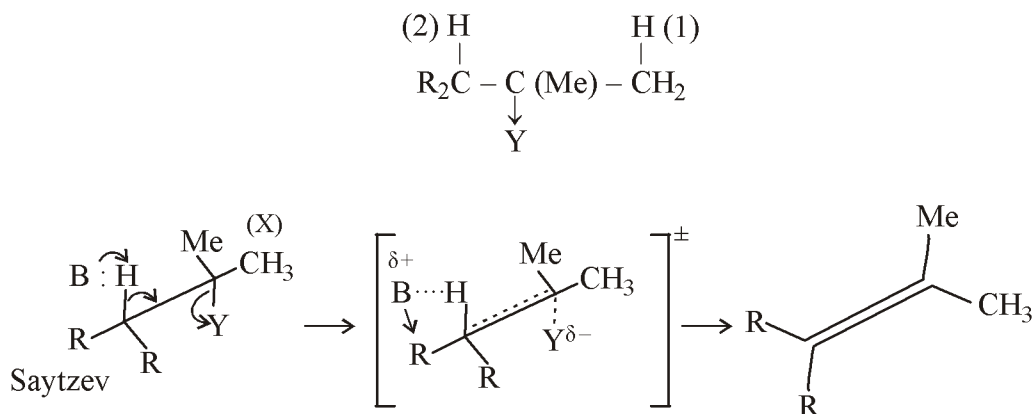
Increase in the branching if the base also increases H.E. even for bromide (V) where Saytzev elimination is normally expected.



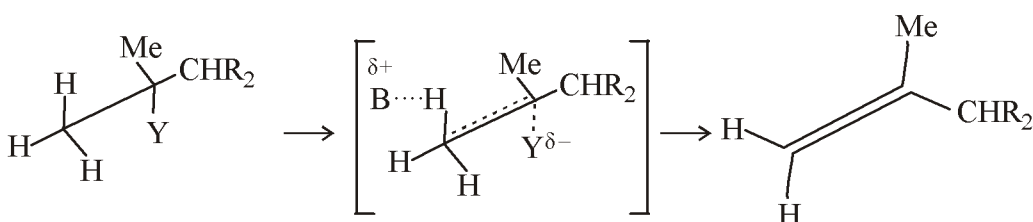
### Explanation of several steric effects

The several steric effects are explained by the fact that steric crowding increases

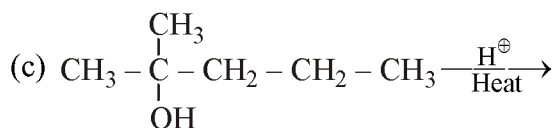
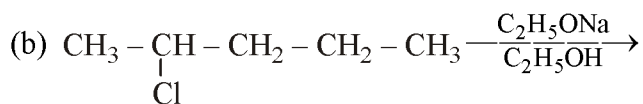
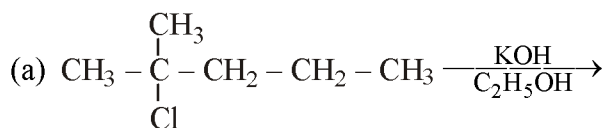
the energy of the T.S. leading to Saytzev elimination by removal of proton (2) to a greater extent than that of the T.S. of Hofmann elimination that involves removal of proton 1 in X.



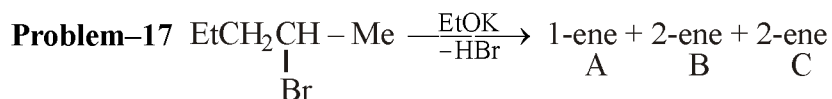
### Hofmann



**Problem-15** Write structural formulae of the products of the following reactions. If more than one product is possible tell which one would be the major product?



**Problem–16** Dehydrohalogenation of isopropyl bromide which requires several hours of refluxing in alcoholic KOH, is brought about in less than a minute at room temp, by  $t\text{Buo}^- - \text{K}^+$  in DMSO. Suggest a possible explanation.



What are A, B, C and which one is the major product? (Assume the mechanism is  $E_2$ )

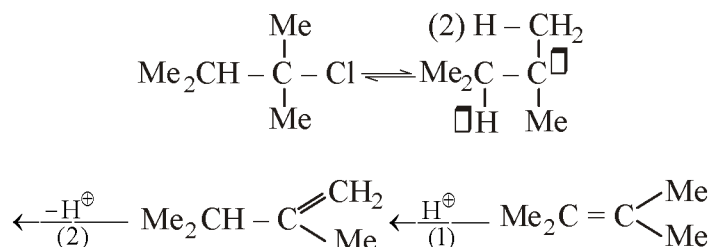
**Problem–18** Compare the  $E_2$  reaction rates of  $\text{CD}_3\text{CHClCD}_3$  and  $\text{CH}_3\text{CHClCH}_3$  in  $\text{NaOCH}_3$  in  $\text{CH}_3\text{OH}$ .

**The factors that influence the rate of  $\text{SN}^1$  reaction also favours  $E_1$  reactions**

(a) The structure of the substrates : The greater the alkyl group in the substrate the more stable is the carbocation. Hence less energy is required to break the C – Y bond i.e. for the formation of the carbocation. Thus rate of  $E_1$  reaction is increases so the order of rate of  $E_1$  reactions for halides are primary < Secondary < tertiary.

Branching at the  $\beta$ -carbon atom also favours  $E_1$  elimination.

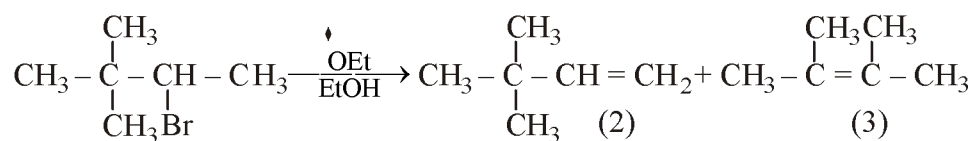
**Example :**  $\text{MeCH}_2\text{CMe}_2\text{Cl}$  gives 34% alkene while  $\text{Me}_2\text{CHCMe}_2\text{Cl}$  yields 62%. This is probably due to the fact that the halide  $\text{Me}_2\text{CH} - \text{C}(\text{Me})_2 - \text{Cl}$  gives thermodynamically more stable alkene. As in this case there is the possibility of formation of two alkenes the major controlling factor is stability of alkene following Saytzev elimination and the major product is the more substituted alkene generated from the carbocationic intermediate.



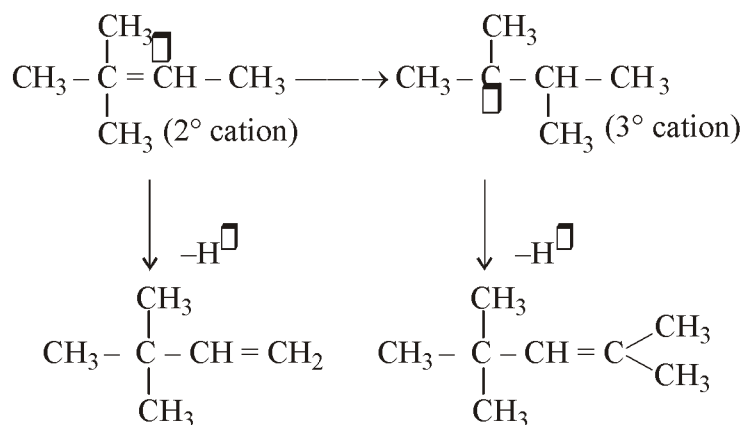
Here in the product mixture the more substituted alkene (1) is the major product (82%).

E<sub>1</sub> elimination undergoes rearrangement of the carbocation giving unexpected alkenes.

**Example :** 3, 3-dimethyl – 2-butyl bromide on dehydrohalogenation gives 3, 3-dimethyl but – 1-ene (2) and 2, 3- dimethyl but – 2 – ene (3)



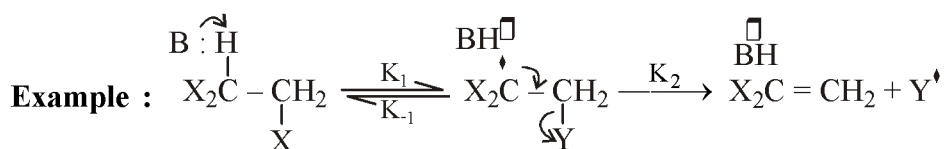
The unexpected product (3) arises by rearrangement of the carbocation (4)



Here a secondary carbocation rearranges to a tertiary cation which is more stable. Rearrangement of cation always converts a less stable carbocation to a more stable one. This is called 1, 2 shift as here –CH<sub>3</sub> grp migrates from carbon to its neighbouring carbon atom.

A good ionising or ion-solvating medium favours E<sub>1</sub> elimination.

E<sub>1</sub>CB Elimination unimolecular with respect to conjugate base.

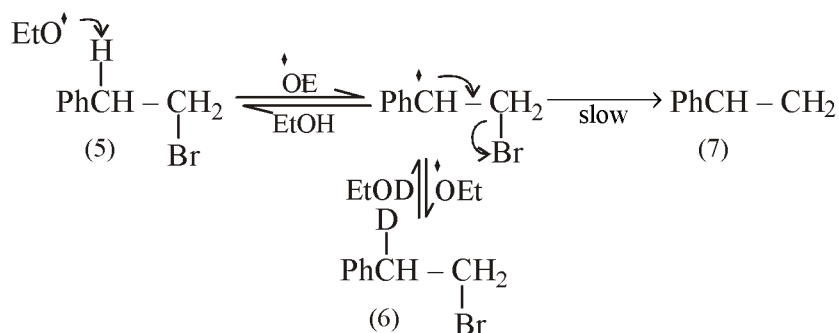


In this pathway the formation of carbanion intermediate (4) is fast and reversible

while subsequent loss of  $X^s$  is slow and rate determining step i.e.  $K_{-1} > K_a$ . So the rate law will be  $\text{Rate} = K[\text{RY}][\text{B}]$  and will be kinetically indistinguishable from  $E_2$ .

### Distinction of $E_2$ and $E_1\text{CB}$ by isotope labelling Experiment

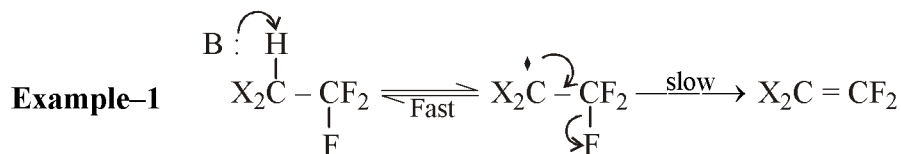
$\text{PhCH}_2\text{CH}_2\text{Br}$  (5) contains Ph group with  $\beta$ -carbon atom. So  $\beta$ -H atoms are acidic and can form carbonions which is stabilised by delocalisation.



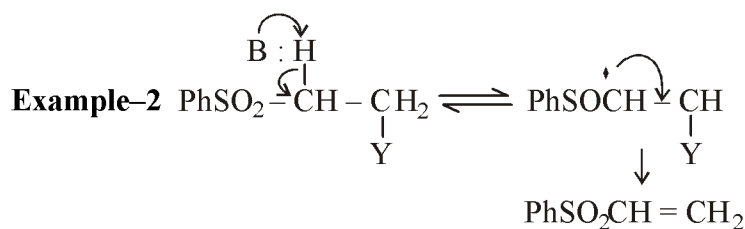
The reaction was carried out with  $\overset{\text{S}}{\text{OEt}}$  and EtOD and no deuterium was found in recovered (5) or in the alkene (Y). It essentially ruled out the formation of (6) and proves the reaction is not proceeding by  $E_1\text{CB}$  route.

The characteristics of the substrate for  $E_1\text{CB}$  (a) electronegative atoms must be present on the  $\beta$ -carbon to make the  $\beta$ -H more acidic. (b) Stabilisation of the carbonion formed by the loss of proton must be done by the substituent at  $\beta$ -carbon atom. (c) a poor leaving group.

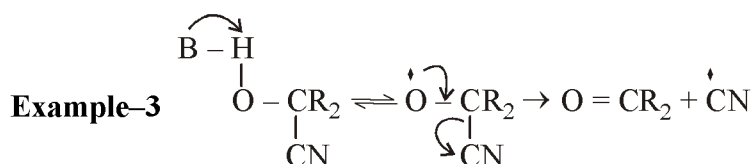
### Examples for $E_1\text{CB}$ Pathway



Here F is the poor leaving group and X halogen atoms stabilise carbonion.



The leaving group abilities of different Y group in E<sub>1</sub>CB reaction is



### 1.5.3 Elimination versus substitution

#### E<sub>1</sub> versus SN<sup>1</sup>

E<sub>1</sub> elimination are normally accompanied by SN<sup>1</sup> substitution as both pass through the same common carbocationic intermediate though they are converted into products via different T.S. s in a fast; non rate limiting step. It is usually difficult to influence the relative partition between SN<sup>1</sup> and E<sub>1</sub> because the difference in energies of activation for either reaction of carbocation (loss of proton or combination with a molecule of the solvent) is very small.

In most unimolecular reactions the SN<sup>1</sup> reaction is favored over the E<sub>1</sub> reaction, especially at lower temperature.

In general, substitution reactions of tertiary halides are not very useful synthetic methods. Such halides undergo eliminations much easily.

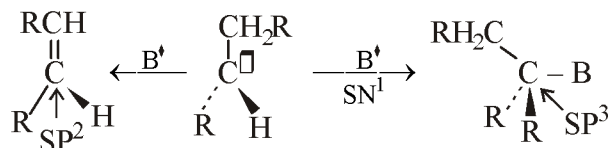
Increasing the temperature of the reaction favours E<sub>1</sub> pathway at the expense of SN<sup>1</sup>. If the elimination product is desired, however it is more convenient to add a strong base forcing the reaction to follow E<sub>2</sub> pathway.

**Example :** Thus E<sub>1</sub>/SN<sup>1</sup> solvolysis of Me<sub>3</sub> CBr and Et Me<sub>2</sub> CBr in EtOH of 25° was found of yield 19% and 36% of alkene respectively. While introduction of 2M EtO<sup>S</sup> with EtOH shifts the mechanism to some extent to E<sub>2</sub>/SN<sup>2</sup> with the yield of alkene 93% and 99% respectively.

**Conclusion :** For a given substrate the E<sub>2</sub>/SN<sup>2</sup> ratio is substantially higher than E<sub>1</sub>/SN<sup>1</sup> ratio.

In E<sub>1</sub>/SN<sup>1</sup> increasing branching in R – Y leads to an increase in proportion or elimination. This arises for the increase in stability of the alkene due to more substitution and the carbocationic T.S. is also more stable for greater substitution.

A steric factor also operates to favour elimination. In  $E_1$  path way  $SP^2$  carbocation is formed from  $SP^3$  carbon substrate. On elimination the product alkene contains  $sp^2$  carbon ( $\approx 120^\circ$  bond angles) but becomes  $SP^3$  hybridised ( $\approx 109^\circ$  bond angle) on substitution.



Crowding strain is thus reintroduced in the T.S. for substitution. So with increase in branching of R grp the proportion of  $E_1$  increases.

Also the peripheral hydrogen is more accessible than the hindered carbocationic carbon. So the proportion of elimination also increases with increase in size of the base.

Increasing the concentration of base e.g. concentrated alkali rather than dilute potash favours elimination.

### $SN^2$ versus $E^2$

Substitution by  $SN^2$  pathway often compete with  $E_2$  reaction. When a nucleophile (base) attacks a  $\beta$  hydrogen, elimination occurs. When a nucleophile attacks the carbon bearing the leaving group substitution occurs.

**The structure of the substrate** is very important for elimination reaction. The proportion of elimination for alkyl halides is Primary < Secondary < tertiary.

Thus with  $\text{EtO}^{\ominus}$  is EtOH on alkyl bromides we find primary  $\rightarrow$  10% alkene secondary  $\rightarrow$  60% and tertiary  $\rightarrow$  99% alkene.

This is not only due to increasing rate of elimination but also due to decreasing rate of substitution.

Substituents such as C = C or Ph also favour elimination over substitution as the developing double bond is stabilised by conjugation with these groups. Thus  $\text{CH}_3\text{CH}_2\text{Br}$  yields 1% alkene but  $\text{PhCH}_2\text{CH}_2\text{Br}$  yields  $\approx$  99% alkene.

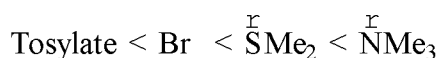
**Size of the attacking base or nucleophile**  $\text{Me}_3\text{CO}$  is a better base than  $\text{OEt}^{\ominus}$  for carrying out elimination reaction. Thus the bulkier the base faster is the elimination



reaction because the steric effects are involved in the differential stabilisation of the T.S. for  $E_2$  with respect to the T.S. for  $SN_2$ .

### Nature of the leaving group

$E_2/SN^2$  ratio is dependent on the nature of the leaving group Y as C – Y bond breaking is involved increasing in each alternative T.S. The order of elimination reaction is shown below for the leaving groups.



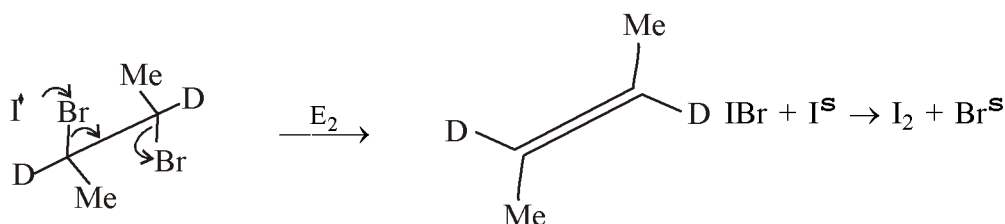
Finally the attacking base for  $E_2$  should be such that it should be a strong base but a poor nucleophile e.g.  $\text{Et}_3\text{N}$ , pyridine are often used to promote elimination. Branching in  $\text{Et}_3\text{N}$  hinders the nucleophilic attack to carbon but not our attack on a peripheral hydrogen.

The use of a base of high b.p is also advantageous.

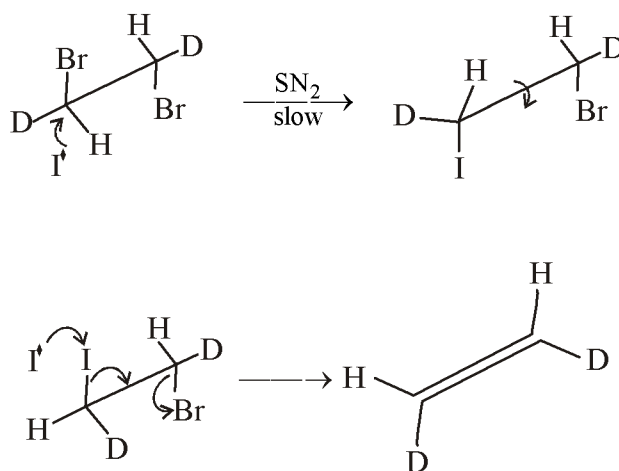
Finally, elimination whether  $E_1$  or  $E_2$  is favoured with respect to substitution by rise in temperature of this is probably due to elimination leading to increase in the number of particles whereas substitution does not. Thus elimination has more the entropy and free energy of activation  $\Delta G^\ddagger$  becomes more –ve by the relation  $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$ . Hence this +ve value of entropy outweighs the  $\Delta H^\ddagger$  term as the temperature rises.

Other 1, 2 – Eliminations. Examples are known that involve the departure of atom other than hydrogen from  $\beta$ -carbon atom e.g. debrominations. This can be induced by  $\text{I}^{\text{S}}$  or Zn metal or  $\text{Fe}^{3+}$  ion. The reaction with  $\text{I}^{\text{S}}$  in acetone is found to follow the rate law  $\text{Rate} = K [1, 2 = \text{debromide}] [\text{I}^{\text{S}}]$  which is comparable with simple  $E_2$  pathway.

**Stereoselectivity** : Anti stereoselectivity is observed in acyclic systems when either or both the bromine atoms are attached to secondary or tertiary carbon atoms e.g.

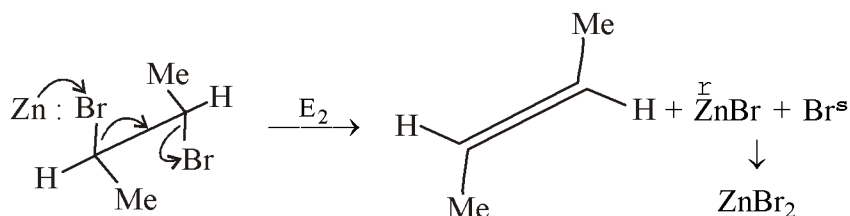


When either or both the bromine atoms are attached to primary carbon atoms, however, the overall reaction is found to proceed stereoselectively SYN. This result is obtained by a combination of  $\text{S}_{\text{N}}^2$  and  $\text{E}_2$  mechanism. First  $\text{S}_{\text{N}}^2$  displacement of  $\text{Br}^{\text{S}}$  takes place by  $\text{I}^{\text{S}}$  with inversion of configuration. It is followed by stereoselective ANTI elimination producing SYN alkene. e.g.

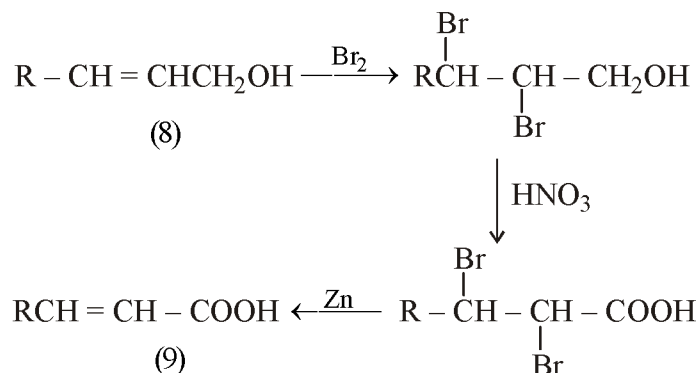


**Evidence :** In support of the  $\text{E}_2$  elimination step the evidence is that changing the alkyl substituents on  $\text{C}_{\alpha}$  or  $\text{C}_{\beta}$  the rate of elimination increases for greater stability of alkenes. Metals such as Zn has long been used for dehalogenation. Here reaction takes place on the surface of the metal and the solvent removes the metal halides renewing the active surface.

**Stereoselectivity :** High degree of ANTI stereoselectivity is observed like  $\text{E}_2$  pathway strict ANTI stereoselectivity is however, departed from with longer chain 1, 2-dibromides. i.e. above  $\text{C}_4$ . The reaction may also be induced by Mg.



**Use :** Bromination/debromination is sometimes used for “Protecting” double bonds e.g. the oxidation of 8 → 9 cannot be carried out directly as the double bond would be attacked oxidatively at the same time.



Eliminations have also been carried out on a number of compounds of the form Hal CH<sub>2</sub>CH<sub>2</sub>Y where Y = OH, OR, OCOR, NH<sub>2</sub>ClO. These eliminations require more drastic conditions. Metals and metal cations are effective of these compound than I<sup>S</sup>.

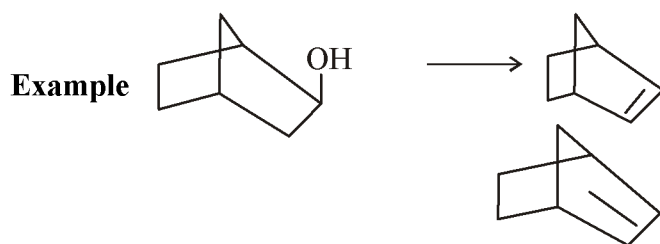
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## 1.6 Bredt's rule

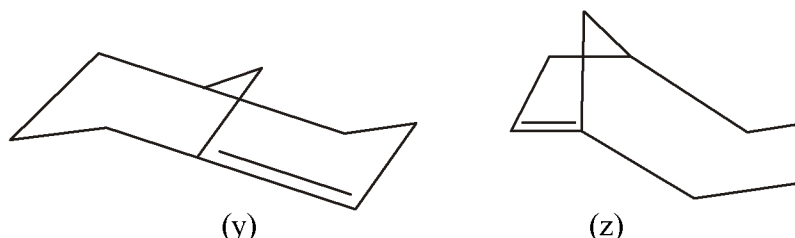
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For cyclic systems Saytzev or Hofmann eliminations need same special requirements of the system e.g. in cyclohexane derivatives trans-diaxial conformation is the essential condition for elimination.

Another such limitation arises for fused ring system. In bridged bicyclic compounds double bonds at the bridgehead are impossible in small systems. This is the basis of Bredt's rule. It states that elimination to give a double bond in a bridged bicyclic system always leads away from the bridgehead. This rule is not applicable when the ring is large enough.



Bicyclo [3.3.1] non – 1 – ene (y) or Bicyclo [4.2.1] non – 1 (8) ene (z) are stable compound.



### Problem–19

Account for the fact that in bimolecular substitution and elimination reaction with strongly basic sodium ethoxide,  $C_2H_5ONa$ , the proportion of substitution and elimination products are obtained from the following alkyl bromides all primary : ethyl 99% substitution and 1% elimination : n-propyl 91% substitution 9% elimination, isobutyl 40% substitution, 60% elimination.

### Problem–20

The reaction of tertiarybutyl chloride in water to yield ter-butyl alcohol (chiefly) is not appreciably effected by dissolving NaF in DMSO instead isobutylene is formed rapidly. Explain this observation.

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## 1.7 Summary

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- Like substitution the major types of elimination reactions are  $E_1$  and  $E_2$ .
- Two other types are  $E_1CB$  and  $E_i$  i.e. elimination unimolecular with respect to conjugate base and elimination internal.
- **Characteristics of  $E_1$  elimination**
  - (a) Follows first order kinetics and formation of carbocation is the r.d.s. and the rate is independent of the nature of the base which is involved in the non rate limiting fast step.
  - (b) The greater the alkyl group in the substrate the more stable is the carbocation and faster is  $E_1$  elimination so the rate of  $E_1$  in alkyl halides Primary < Secondary < tertiary.
  - (c) In  $E_1$  elimination rearrangement of carbocations occur giving unexpected alkene. A polar solvent favours  $E_1$  elimination.

● **Characteristics of E<sub>1</sub> CB**

- Unimolecular with respect to conjugate base i.e. loss of leaving group is the slow rate determining step and abstraction of proton is the fast step.
- The rate law is indistinguishable from E<sub>2</sub> but the mechanism is established by isotope labelling experiment.
- Electronegative atoms must be present on the p-carbon to make the βH more acidic.
- A poor leaving group must be present with the substrate.
- Substituent to stabilise the carbonian must be present with the β-carbon.

● **Characteristics of E<sub>i</sub> reaction**

- Elimination internal occurs for amine oxides, Xanthates or acetates in the presence of inert solvent or in the absence of solvent by application of heat only without any reagent.
- It follows a first order kinetics and is indistinguishable from E<sub>1</sub>. But syn stereoselectivity of the product distinguishes it from E<sub>1</sub>.
- It has got some synthetic utility as gives unrearranged alkene.

● **Characteristics of E<sub>2</sub> reactions**

- Most common type of elimination reaction. C – H and C – Y bond breaking take place in a single, concerted pathway.
- Follows 2nd order kinetics.
- Stronger the base faster the E<sub>2</sub> reaction. Hence the rate is  $\overset{\ominus}{\text{N}}\text{H}_2 > \text{RO}^\ominus > \overset{\ominus}{\text{O}}\text{H}$ .
- Bipolar aprotic solvent like DMF, DMSO favour E<sub>2</sub> reaction as β the base ion is free to abstract the proton with no solvation through hydrogen bonding.
- The stronger is the C – Y bond slower is the E<sub>2</sub> reaction.
- The more stable is Y<sup>⊖</sup> faster is E<sub>2</sub> reaction, conjugate base of a strong acid is more stable.
- The more stable is the product alkene the faster is E<sub>2</sub> reaction.

- (h) Elimination occurs in antiperiplanar conformation.
- (i) When there is the possibility of formation of more than one alkene two empirical rules are followed to predict the major product.

For alkyl halides RBr Saytzeff's rule is followed indicating the thermodynamical more stable alkene as the major product.

For  $\text{RNMe}_3$  or  $\text{RSM}_2$  Hofmann's rule is obeyed indicating the less stable alkene as the major product. Here acidity of the  $\beta$ -H controls the reaction.

- (j) In bridged bicyclic systems Bredt's rule is followed and double bond cannot exist on the bridge head of small rings.
- (k) Dehalogenation from geminal dihalides take place either by I, or by metal Zn or metal ions  $\text{Fe}^{3+}$ . Here also anti stereo selectivity is maintained we can summarize the most important reaction pathways according to the substrate in the following way.

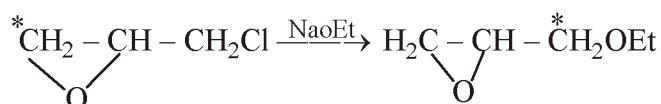
$\text{CH}_3\text{X}$ Methyl	$\text{RCH}_2\text{X}$ (1°)	$\begin{array}{c} \text{R} \\   \\ \text{R}-\text{CH}-\text{X} \end{array}$ (2°)	$\begin{array}{c} \text{R} \\   \\ \text{R}-\text{C}-\text{X} \\   \\ \text{R} \end{array}$ (3°)
Bimolecular	reaction only $\rightarrow$		$\text{SN}^1/\text{E}^1$ or $\text{E}_2 \rightarrow$
Gives $\text{SN}^2$ reactions	Gives mainly $\text{SN}^2$ except with a hindered strong base and then gives mainly $\text{E}_2$	gives mainly $\text{SN}^2$ with weak base and mainly $\text{E}_2$ with strong base	No $\text{SN}^2$ reaction. In solvolysis gives $\text{SN}^1/\text{E}^1$ and at lower temp $\text{SN}^1$ predominated when a strong base is used $\text{E}_2$ predominated

### Model Questions

1. Although ethyl bromide and isobutyl bromide are both primary halides, ethyl bromide undergoes  $\text{SN}^2$  reaction more than ten times faster than isobutyl bromide. When each compound is treated with a strong base/nucleophile ( $\text{CH}_3\text{CH}_2\text{O}^-$ ), isobutyl bromide gives a better yield of elimination, products than substitution products where as with ethyl

bromide this behaviour is reversed. What factor accounts for these results?

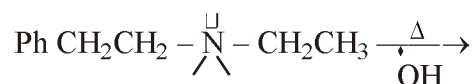
- The hydrolysis of methyl bromide takes place much faster in the presence of NaI Explain.
- Account for the fact  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$  reacts with .01 (M) NaCN in ethanol to yield primarily  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CN}$  where as under the same conditions,  $(\text{CH}_3)_3\text{CCl}$  reacts to give primarily  $(\text{CH}_3)_3\text{COCH}_2\text{CH}_3$ .
- Arrange the following compounds in order of reactivity toward dehydrohalogenation by strong base.
  - 2-Bromo-2-methylbutane, 1-Bromopentane, 2-Bromopentane, 3-Bromopentane.
- When neopentyl alcohol,  $(\text{CH}_3)_3\text{CCH}_2\text{OH}$  is heated with acid, it is slowly converted into an 85 : 15 mixture of two alkenes of formula  $\text{C}_5\text{H}_{10}$ . What are these alkenes and how are they formed, which one is the major product and why?
- Discuss the reaction  $\text{ClCH}_2\text{CHCl}_2 \xrightarrow{\text{OH}^-} \text{CH}_2 = \text{CCl}_2$ .
- Account for the fact that in DMSO the order of reactivity of halide ions with MeBr is  $\text{F}^- > \text{Cl}^- > \text{Br}^- > \text{I}^-$  which is opposite to that observed in MeOH.
- What is meant by nucleophilicity? Arrange the following anions in order of increasing nucleophilicity. Give reasons.  $\text{R}_2\text{N}^-$ ,  $\text{RO}^-$ ,  $\text{F}^-$ ,  $\text{R}_3\text{C}^-$
- How would you prove experimentally that inversion of configuration at the saturated carbon atom during  $\text{S}_\text{N}2$  reaction.
- Provide the explanation for the following transformation.



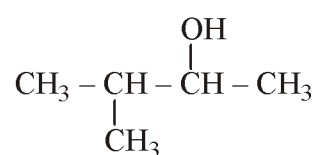
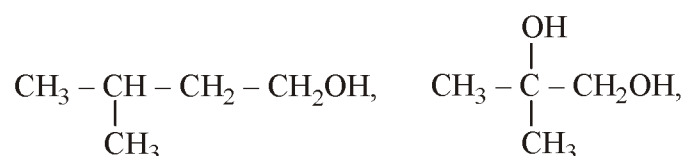
- Predict the product and explain the stereochemical course of the following reaction.



12. Give the product (s) of the following reaction. Explain.



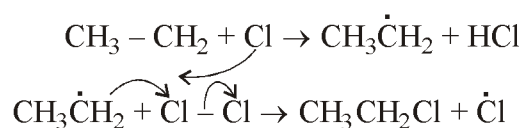
13. Write the structure of 18-carbon -6 and its role in the reaction of  $\text{CH}_3(\text{CH}_2)_6\text{CH}_2\text{Br}$  with KF in warm benzene.
14. Arrange the following alcohols in order of their reactivity toward acid catalysed dehydration and explain.



**Answers :**

**Problems-1 :** Ethane is formed by combination of two  $\text{CH}_3$  radical formed from chlorination of methane  $\dot{\text{C}}\text{H}_3 + \dot{\text{C}}\text{H}_3 \rightarrow \text{H}_3\text{C} - \text{CH}_3$

The reaction of Cl with ethane forms  $\text{C}_2\text{H}_5\text{Cl}$ .

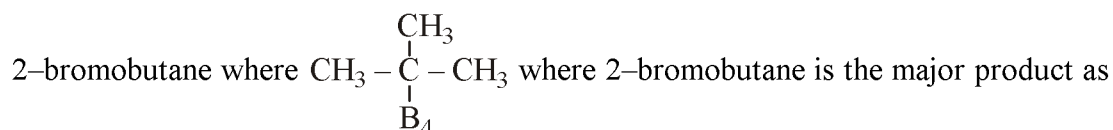
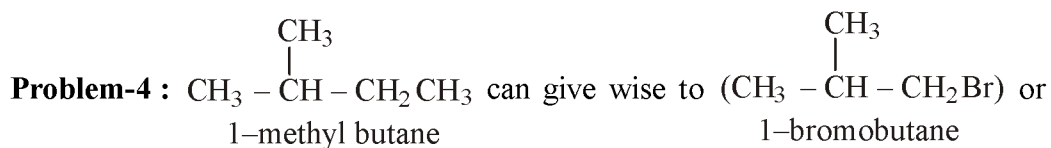


Its formation signifies the ethane formation is one of the termination steps of the chain reaction of chlorination of methane.

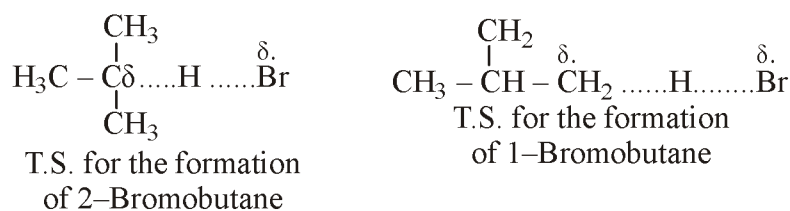
**Problem-2 :** By using a **large excess of methane** in the reaction mixture so that the chlorine atoms will attack the methane molecule only minimizing the attack of chlorine to  $\text{CH}_3\text{Cl}$  or  $\text{CH}_2\text{Cl}$  the after the reaction is over the unreacted excess methane can be recovered or recycled.

**Problem-3 :** By using large excess of chlorine the chain reaction will continue and the end product  $\text{CCl}_4$  is formed. Show the chain propagation steps from that.

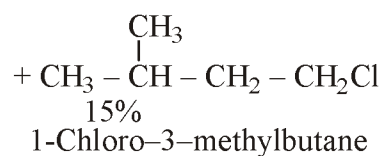
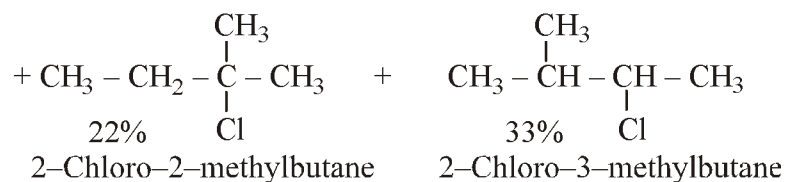
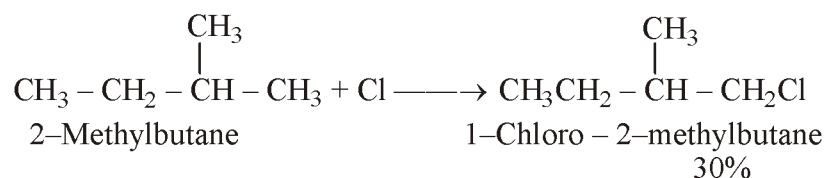


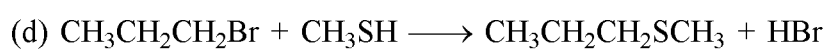
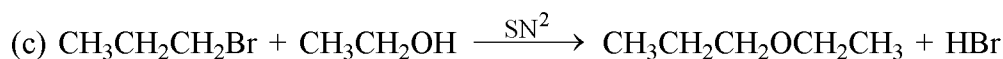
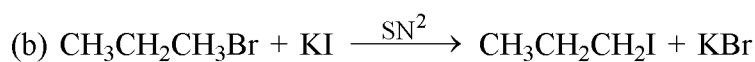
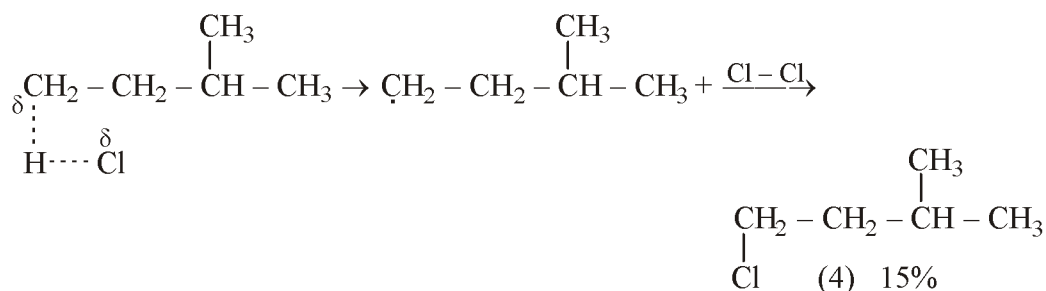
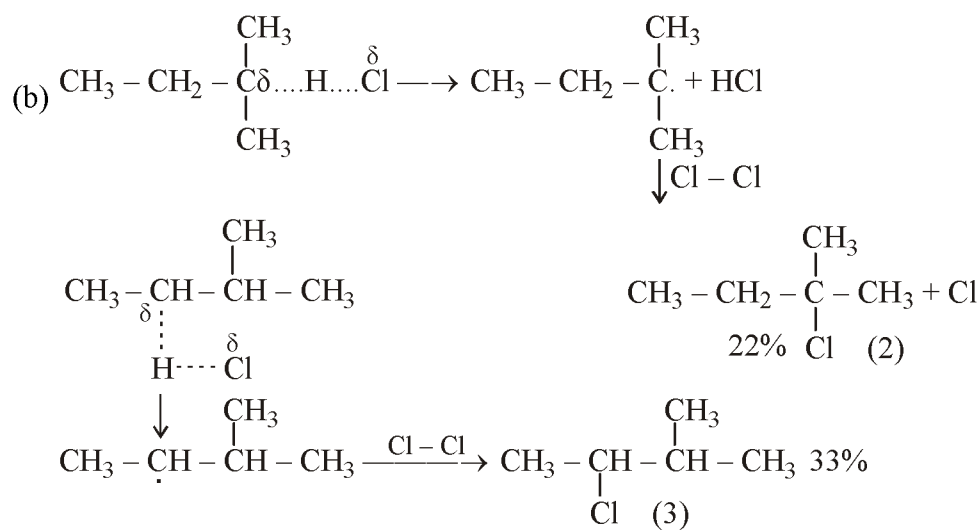
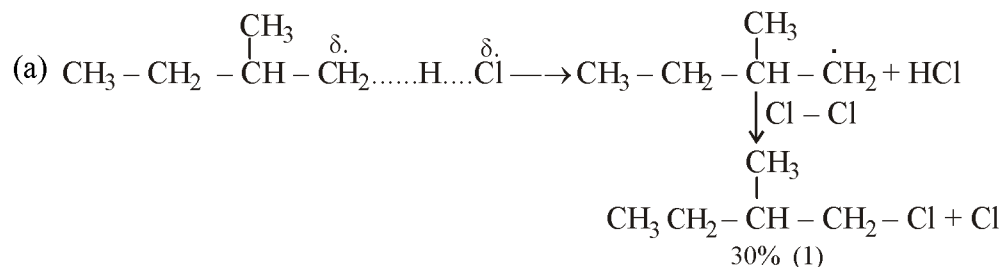


the TS resembles a stable  $3^\circ$  radical than that of 1-bromobutane which resembles a less stable  $1^\circ$  radical.



**Problem-5 :**

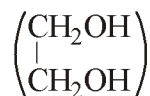




**Problem-7 :** Formic acid — Protic, Acetone — Aprotic, Acetonitrile aprotic,  
 (HCOOH) (CH<sub>3</sub>COCH<sub>3</sub>) (CH<sub>3</sub>CN)

Formamide Protic, Sulfur dioxide — Aprotic, Ammonia — protic,  
 (HCONH<sub>2</sub>) (SO<sub>2</sub>) (NH<sub>3</sub>)

Trimethyl ammine (CH<sub>3</sub>)<sub>3</sub>N — Aprotic, Ethylene Glycol — Protic



**Problem-8 :** In DMF the reaction is faster as it is a polar aprotic solvent and does not solvate the nucleophile CN<sup>⊖</sup>. Hence SN<sup>2</sup> reactions is faster with the free nucleophile.

**Problem-9 :** (a)  $\overset{\ominus}{\text{N}}\text{H}_2$  is stronger than NH<sub>3</sub> as charged ions.

(b) Similarly RS<sup>⊖</sup> will be stronger than RSH.

(c) PH<sub>3</sub> than NH<sub>3</sub>. As the solvation is greater for NH<sub>3</sub> as N is more electro – ve than P.

**Problem-10 :** Tert-butyl chloride undergoes SN<sup>1</sup> solvolysis. Stability of carbocation increases with increasing solvation. H<sub>2</sub>O solvates the cation more than methanol. Hence increases water the rate of SN<sup>1</sup> solvolysis increases.

When the % of water in the SN<sup>2</sup> substitution of C<sub>2</sub>H<sub>5</sub>Cl with KI in MeOH is increased the solvation of nucleophile I<sup>⊖</sup> occurs to a much greater extent as a result it is not free of attack the central carbon atom. So the rate of the reaction decreases.

**Problem-11 :** In SN<sup>1</sup> solvolysis of  $\text{CH}_3 - \overset{\text{Cl}}{\underset{\text{H}_3\text{C}}{\text{C}}} - \text{CH}_3$  the first step is ionisation to

from the tertiary carbocation  $\text{H}_3\text{C} - \overset{\oplus}{\underset{\text{H}_3\text{C}}{\text{C}}} - \text{CH}_3$ . It is stabilised by the hyperconjugation

of the H<sub>3</sub>C grps one of the hyper conjugative structures is  $\text{H}^{\oplus} - \text{CH}_2 = \overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}}$ . In this

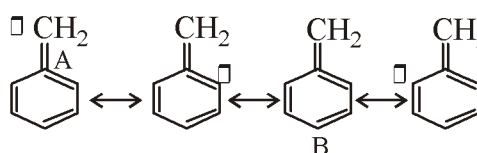
way 9 hyper conjugative structures are formed. In  $\begin{matrix} \text{CD}_3 \\ \text{D}_3\text{C} \end{matrix} \overset{\oplus}{\underset{\text{D}_3\text{C}}{\text{C}}} - \text{Cl}$  the carbocation is

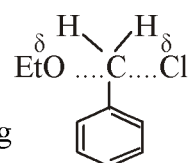
$\begin{array}{c} \text{D}_3\text{C} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{D}_3\text{C} \\ | \\ \text{D}_3\text{C} \end{array}$  and the hyper conjugative structure is  $\begin{array}{c} \text{D}_2\text{C} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{D}_3\text{C} \\ | \\ \text{D}_3\text{C} \end{array}$ . This hyper conjugative

structure is less readily formed than that of  $\begin{array}{c} \text{H}_2\text{C} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{H}_3\text{C} \end{array} - \text{CH}_3$  as C – D bond is stronger

than C – H bond. Hence this hyperconjugative stability decreases and the stability of the carbocation decreases. Hence the first ionisation step which is the rate determining step requires greater activation energy and the reaction rate decreases for  $(\text{CD}_3)_3\text{CCl}$ .

**Problem-12 :** In  $\text{PhCH}_2\text{Cl}$  the carbocation  $\text{Ph}\overset{\ominus}{\text{C}}\text{H}_2$  is stabilised by resonance in

the Ph ring . So,  $\text{SN}^1$  solvolysis is observed in

water. In this comp. the  $\text{SN}^2$  T.S. is also stabilised by the Ph ring . So

$\text{SN}^2$  reaction occurs in aq ethanol where the nucleophile  $\text{EtOH}$  is stronger than  $\text{H}_2\text{O}$ . In  $\text{Ph}_2\text{CHCl}$  or  $\text{Ph}_3\text{CCl}$  the carbocation is very much stable by resonance through 2 or 3 Ph groups. So  $\text{SN}^1$  reaction is much more favoured.  $\text{SN}^2$  is also hindered by steric crowding.

**Problem-13 :** (a)  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}$  will undergo faster  $\text{SN}^2$  reaction as a primary bromide.

(b)  $\text{CH}_3\text{CH}_2\text{Cl}$  will undergo faster  $\text{SN}^2$  reaction as in  $\text{CH}_2 = \overset{\ominus}{\text{C}}\text{H} - \overset{\ominus}{\text{C}}\text{H} - \overset{\ominus}{\text{C}}\text{H}_2 \leftrightarrow \overset{\ominus}{\text{C}}\text{H}_2 - \overset{\ominus}{\text{C}}\text{H} = \overset{\ominus}{\text{C}}\text{H} - \overset{\ominus}{\text{C}}\text{H}_2$  the nucleophilicity of central carbon decreases by resonance.

**Problem-14 :** (a)  $(\text{CH}_3)_3\text{CCl}$  will undergo faster  $\text{SN}^1$  reaction as  $\text{I}^\ominus$  is a better leaving group than  $\text{Cl}^\ominus$  and C – Cl bond is more stronger. So the breaking of C – Cl bond requires greater activation energy.

(b)  $\text{SN}^1$  reaction in water will be faster than in  $\text{CH}_3\text{OH}$  as the solvent of

carbocation will be greater in water. Hence the carbocation is more water in water than in MeOH. So the activation energy for the formation of this carbocation for the formation of the carbocation is less and the rate of the reaction is faster.

**Problem-15 :** (a) (i)  $\text{CH}_2 = \overset{\text{CH}_3}{\text{C}} - \text{CH}_2\text{CH}_2\text{CH}_3$  and (ii)  $\text{CH}_3 - \overset{\text{CH}_3}{\text{C}} = \text{CH} - \text{CH}_2\text{CH}_3$

(ii) is the major product : as more substituted alkene according to Saytzeff's rule.

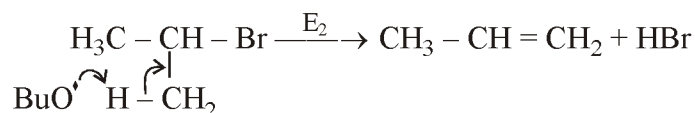
(b) (i)  $\text{CH}_2 = \text{CH} - \text{CH}_2\text{CH}_2\text{CH}_3$ , (ii)  $\text{CH}_3\text{CH} = \text{CHCH}_2\text{CH}_3$

(iii)  $\text{CH}_3\text{CH}(\text{OEt}) - \text{CH}_2\text{CH}_2\text{CH}_3$ . At low temperature (iii) will be the major product. At high

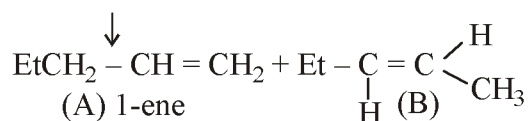
temperature (ii).

(c) (i)  $\text{CH}_3 - \overset{\text{CH}_3}{\text{C}} = \text{CHCH}_2\text{CH}_3$  (ii)  $\text{CH}_2 = \overset{\text{CH}_3}{\text{C}} = \text{CH}_2\text{CH}_2\text{CH}_3$  (i) will be the major product.

**Problem-16 :** DMSO is a polar aprotic solvent where  $\text{BuO}^-$  is free and not solvated. Hence can readily abstract proton from



**Problem-17 :**  $\text{EtCH}(\text{H}) - \underset{\text{Br}}{\text{CH}}(\text{H}) - \text{CH}_2(\text{H})$



(B) will predominate as trans alkene where +  $\text{Et} - \underset{\text{H}}{\text{C}} = \underset{\text{H}}{\text{C}} - \text{CH}_3$  steric interaction (C)

is less and also more substituted one.

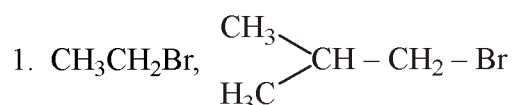
**Problem-18 :**  $\text{CD}_3\text{CHCl}$  undergoes  $\text{E}_2$  reaction at a slower rate than  $\text{CH}_3\text{CH}$  (a)  $\text{CH}_3$  as C-D bond is stronger than C-H bond and in  $\text{E}_2$  T.S. the C-D bond breaking is required in the r.d.s.

**Problem-19 :** With increase in size of the primary alkyl group from ethyl to isobutyl halide the steric strain increases for larger size of the alkyl group. So the proportion of substitution decreases and E<sub>2</sub> elimination increases as the stability of alkenes increase for greater substitution.

**Problem-20 :** Tertiary butyl chloride  $\text{H}_3\text{C} - \overset{\text{H}_3\text{C}}{\underset{\text{H}_3\text{C}}{\text{C}}} - \text{Cl}$  undergoes SN<sup>1</sup> solvolysis

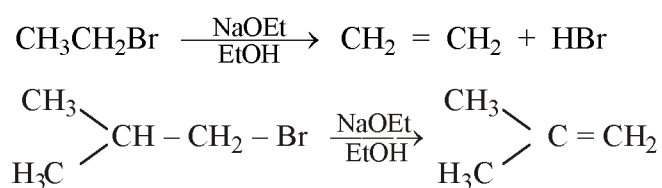
in water. Its rate is independent on the nucleophile as the C – Cl bond breaking is the r.d.s. But E<sub>2</sub> elimination rate is increased as F<sup>S</sup> acts as a stronger base in DMSO than in water as not solvated and is involved in the r.d.s. So the rate of E<sub>2</sub> elimination increases.

**Answer Model Questions :**



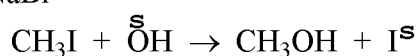
$\text{CH}_3\text{CH}_2\text{Br}$ , gives faster SN<sup>2</sup> as no steric crowding is present in the T.S.. But in isopropyl bromide isopropyl gr exists a steric effect due to its bulk. So the SN<sup>2</sup> T.S. is more crowded and is of high energy. So the rate is decreased.

During elimination E<sub>2</sub> isobutyl bromide gives better elimination as gives more substituted alkene.



More substituted alkene generally substitution is more favoured than elimination. So for ethyl chloride through the strength of the base is increased it will act as a strong nucleophile also and SN<sup>2</sup> substitution is favoured. Also here elimination (E<sub>2</sub>) gives rise to less stable alkene so less favoured.

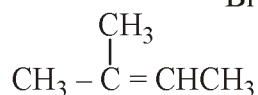
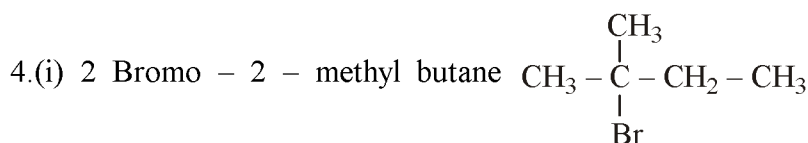
2. Here the 1st step is substitution (SN<sup>2</sup>) of Br by I<sup>S</sup>CH<sub>3</sub>Br + NaI → CH<sub>3</sub>I + NaBr



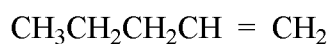
$I^-$  is a stronger nucleophile and a better leaving grp. So NaI acts as catalyst.

3.  $CH_3CH_2CH_2CH_2Cl$  reacts with  $0.1(M)$  NaCN in EtOH by  $SN^2$  mode giving  $CH_3CH_2CH_2CH_2CN$  where  $CN^-$  acts as the nucleophile.

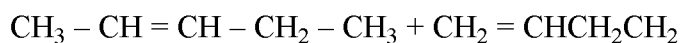
But  $(CH_3)_3C-Cl$  undergoes  $SN^1$  solvolysis as the solvent ethanol is present in much greater amount. Hence the product is  $(CH_3)_3COCH_2CH_3$ .



(ii)  $CH_3CH_2CH_2CH_2CH_2Br$  - Bromopentane.



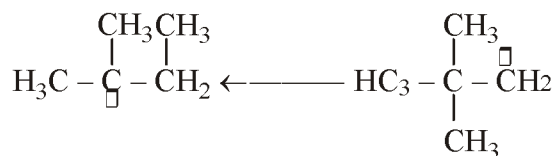
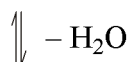
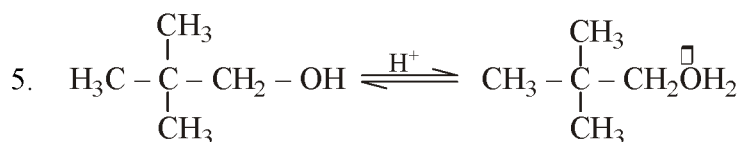
(iii)  $CH_3-\underset{\underset{Br}{|}}{CH}-CH_2CH_2-CH_3$  - 2-Bromopentane

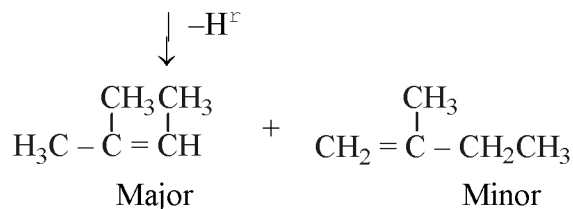


(iv)  $CH_3-CH_2-\underset{\underset{Br}{|}}{CH}-CH_2CH_3$  - 3-Bromopentane

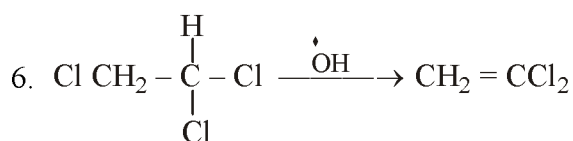


(i) gives most substituted alkene. So the reaction is fastest. (iv) and (iii) gives the same alkene and (ii) gives the least stable alkene. Hence the order.

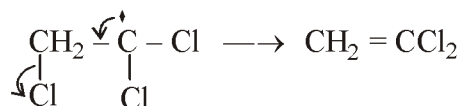




More substituted alkene formed from tertiary carbocation obtained by Me migration from primary carbocation. This is neopentyl rearrangement.



This is an example of E<sub>1</sub> CB reaction. Due to the presence of two chlorine atoms the marked H is acidic and abstracted by OH to form the conjugate base which loses a Cl<sup>s</sup> ion to form the alkene.



7. In DMSO the reactivity of halide ions depend on their electro negativities i.e. on the greater conc<sup>n</sup> of negative charge on the atom as the solvation of nucleophile is about in DMSO. Hence the order is F<sup>s</sup> > Cl<sup>s</sup> > Br<sup>s</sup> > I<sup>s</sup>. But in MeOH the greater the conc<sup>n</sup>. of -ve charge the more is the solvation and the vely charged ion is not free to act as nucleophile. This solvation is maximum for F<sup>s</sup> and minimum for I<sup>s</sup>. Hence in MeOH the order of reactivity is I<sup>s</sup> > Br<sup>s</sup> > Cl<sup>s</sup> > F<sup>s</sup>.

8. Nucleophilicity is the donation of electron pair to an atom very often carbon other than hydrogen by a negatively chaged atom or group or by a neutral molecule having love pair of electrons. Nucleophilicity involves kinetic situation and not thermodynamic equilibrium and is affected by steric factors.

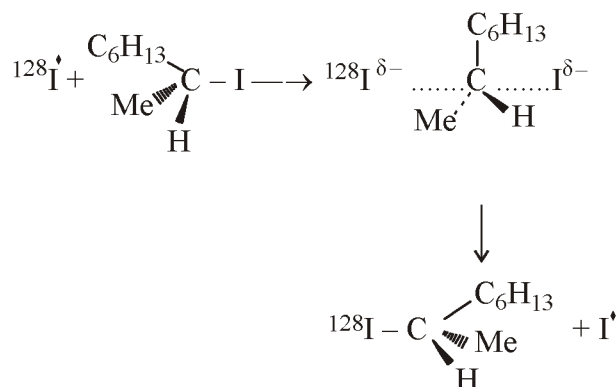


**Reason :** As we go from the left to right in a periodic table nucleophilicity decreases. The reason behind this order is the decrease in polarizability and increase in charge density on a small atom i.e. greater electro negativity. Increase in charge

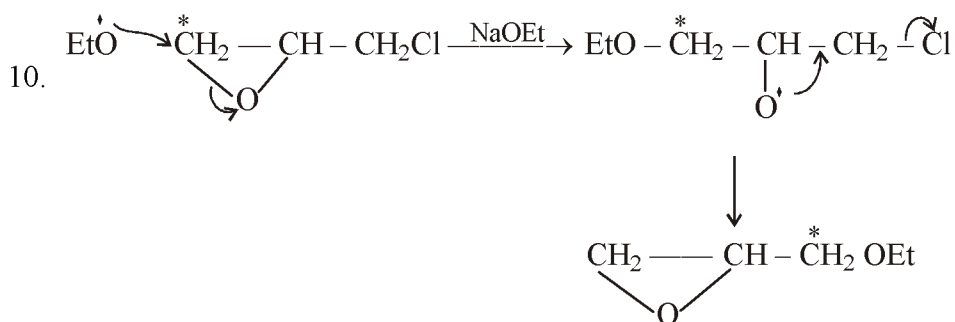


density causes greater solvation and the nucleophile is not free to react. So  $F^-$  is the weakest nucleophile.

9. The  $S_N2$  displacement reaction is accompanied by inversion of configuration is proved by an experiment where (+) 2-iodooctane undergoes  $S_N2$  displacement by radioactive  $^{128}I^-$  ion as nucleophile.

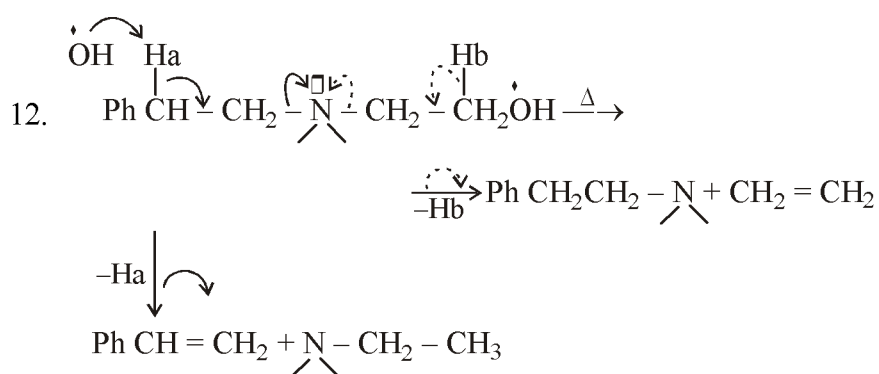
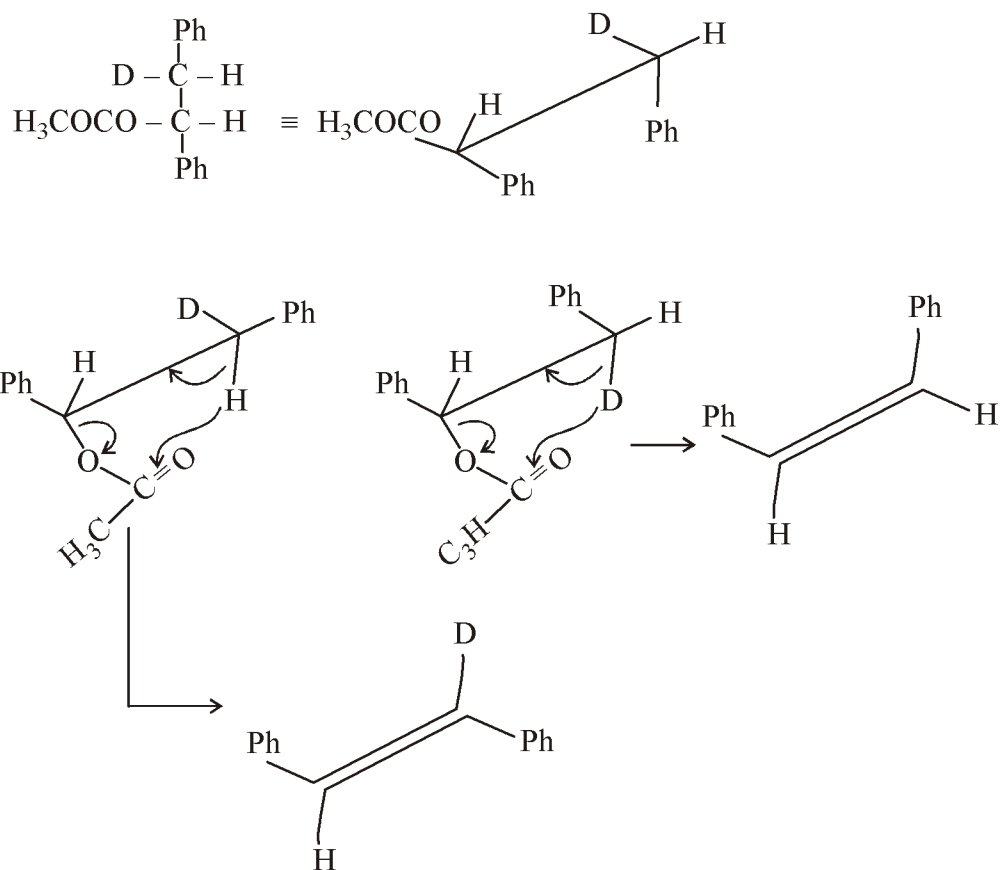


The displacement was monitored by observing the change in distribution of  $^{128}I$  between NaI and 2-Iodo octane. The reaction is found to be 2nd order. And the optical activity gradually comes to zero. It occurs as when due (+) molecule has converted to the (-) isomer this (-) combines with a (+) isomer forming the inactive ( $\pm$ ) racemate. In this way when 50% (+) isomer is converted to 50% (-) isomer, the overall mixture is  $\pm$  mixture and optical activity will be zero. As this is experimentally found by a polarimeter it is proved that  $S_N2$  reaction causes inversion of configuration.

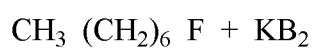
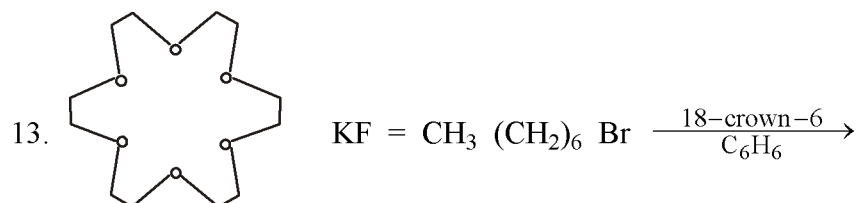


This is an example of NGP by oxygen.

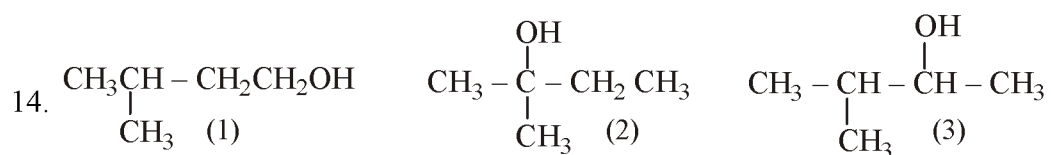
11. This is an example of pyrolytic syn elimination of an ester.



This is Hofmann elimination.  $H_a$  is more acidic than  $H_b$ . So  $H_a$  will be eliminated and the major product will be  $\text{Ph CH} = \text{CH}_2$  not ethylene though less substituted.



18-crown -6 Here 18-crown - 6 is the phase transfer catalyst.



Ans.  $2 > 3 > 1$ .

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## **Unit - 2 □ Aromatic Substitution : Electrophilic**

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### **Structure**

#### **2.0 Objectives**

#### **2.1 Introduction**

#### **2.2 Electrophilic aromatic substitution**

##### **2.2.1 Mechanisms and evidences in favour of it**

##### **2.2.2 Orientation and reactivity**

#### **2.3 Reactions (Different electrophilic substitution reactions are discussed)**

##### **2.3.1 Nitration**

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##### **2.3.5 Friedel–Crafts reaction**

#### **2.4 Reactions involving one carbon electrophiles**

##### **2.4.1 Chloromethylation reaction**

##### **2.4.2 Gattermann — Koch reaction**

##### **2.4.3 Gattermann reaction**

##### **2.4.4 Houben Hoesch Reaction**

##### **2.4.5 Vilsmeier – Haack Reaction**

##### **2.4.6 Reimer-Tiemann Reaction**

##### **2.4.7 Kolbe Schmitt Reaction**

#### **2.5 Ipso substitution**

#### **2.6 Nucleophilic aromatic substitution**

##### **2.6.1 Bimolecular mechanism and its evidence**

#### **2.7 SN1 mechanism**

#### **2.8 Cine substitution (Elimination Addition mechanism)**

##### **2.8.1 Structure of Benzyne**

## 2.9 Summary

## 2.10 Model Questions

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## 2.0 Objectives

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Electrophilic and Nucleophilic substitution reactions lead to the introduction of various substituent in benzene ring.

Variety of aromatic compounds viz. Halobenzene, Nitro benzene, benzene sulphonic acids etc. can be synthesised by these substitution reactions which are difficult to prepare otherwise.

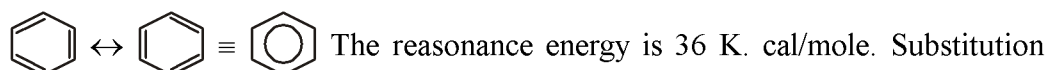
By knowing the mechanisms of the reactions variations can be done by changing the conditions or reagents of the reaction giving different products.

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## 2.1 Introduction

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Aromatic compounds are cyclic, planar, stable compounds containing a total no. of  $(4n + 2)$   $\pi$  electrons (following Huckels rule) in a delocalized condition. Benzene is an aromatic compound with  $6\pi$  electrons in delocalized state where  $n = 1$  in Huckels rule. Its unusual stability comes from resonance between the Kekulé structures with extensive delocalisation of  $\pi$  electrons



of hydrogen atom by some other atom or group does not destroy the aromatic sextet system of benzene and stability of substituted benzene remains almost same. Addition reaction destroys the aromatic sextet system and the resonance energy is lost. So benzene undergoes substitution reactions and not addition reactions generally though it contains 3 double bonds.

Substitution reactions in benzene are mostly ionic in character and are of two types (i) electrophilic substitution (ii) Nucleophilic substitution.

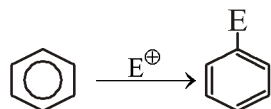
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## 2.2 Electrophilic aromatic substitution

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Benzene ring is considered to be electron rich due to the presence of six pi ( $\pi$ )

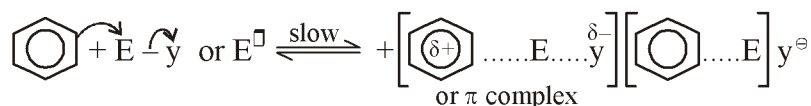
electrons. Therefore, electrophilic reagents ( $E^+$ ) are easily attracted by benzene molecule giving rise to substituted product.



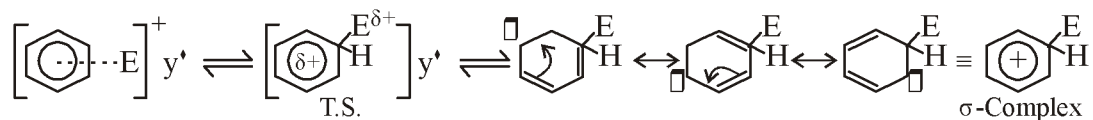
$E^+$  is electrophilic reagent common electrophilic are  $NO_2^+$ ,  $CH_3^+$ ,  $Cl^+$ ,  $CH_3CO^+$  etc.

### 2.2.1 Mechanism

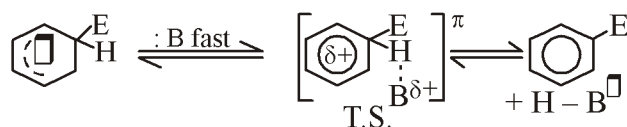
In the initial step the electrophile approaches perpendicularly and polarises the  $\pi$  bond of benzene ring. Again under the influence of the  $\pi$  charge polarisation occurs in the reactant. Due to this difference in polarisation the reactant attaches itself with the substrate by an electrostatic force and forms a charge transfer complex. It is called a  $\pi$  complex.



In the second step the electrophile forms a  $\sigma$ -bond with the carbon atom of the aromatic ring. The intermediate stabilises the +ve charge formed due to  $\sigma$  bond formation by delocalisation in the ring. Also the group already present in the aromatic ring affects the delocalisation. This carbocation is called  $\sigma$ -complex or wheland Intermediate.



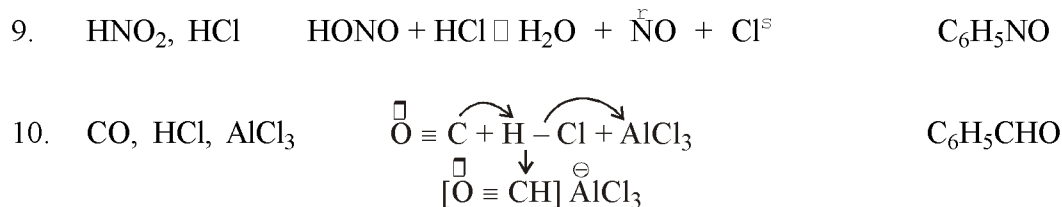
In the next step  $H^+$  or other electrofugal leaving group is eliminated giving the substituted product. The lewis base present in the medium takes up  $H^+$ .



Formation of the  $\sigma$  complex is the rate determining step where both reactant and substrate are present. This reactivity path way is termed as bimolecular electrophilic substitution aromatic or SE2 Ar reaction.

### Examples

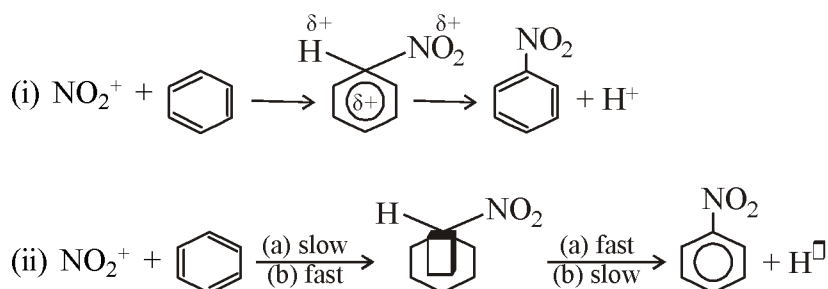
Regent used	Formation of Active electrophile	The product from benzene
1. D-Cl, AlCl <sub>3</sub>	$D-Cl + AlCl_3 \rightleftharpoons D\overset{\ominus}{C}l-\overset{\oplus}{Al}Cl_3$	C <sub>6</sub> H <sub>5</sub> D C <sub>6</sub> H <sub>4</sub> D <sub>2</sub> C <sub>6</sub> H <sub>3</sub> D <sub>3</sub> electro
2. R-Cl, AlCl <sub>3</sub>	$R-Cl + AlCl_3 \rightleftharpoons R^{\oplus} [AlCl_4]^{-}$	C <sub>6</sub> H <sub>5</sub> R
3. R-OH, BF <sub>3</sub>	$R-OH + BF_3 \rightleftharpoons R-\overset{\ominus}{O}-\overset{\oplus}{B}F_3$ $\begin{array}{c}   \\ H \\ \updownarrow \\ R^{\oplus} [HOBF_3]^{-} \end{array}$	C <sub>6</sub> H <sub>5</sub> R
4. Br <sub>2</sub> , I <sub>2</sub>	$Br_2 + I_2 \rightarrow IBr$ $Br-Br + I-Br \rightarrow \overset{\oplus}{Br} [Br I Br]^{-}$	C <sub>6</sub> H <sub>5</sub> Br
5. conc. HNO <sub>3</sub>	HONO <sub>2</sub> + 2H <sub>2</sub> SO <sub>4</sub>	
conc. H <sub>2</sub> SO <sub>4</sub>	$\downarrow$ $H_3O^{\oplus} + 2HSO_4^{-} + NO_2$	C <sub>6</sub> H <sub>5</sub> NO <sub>2</sub>
6. H <sub>2</sub> S <sub>2</sub> O <sub>7</sub>	$HO-SO_2-\overset{\ominus}{O}-SO_2-OH$ $\updownarrow$ $HO\overset{\oplus}{S}O_2 + HSO_4^{\ominus}$	C <sub>6</sub> H <sub>5</sub> SO <sub>3</sub> H
7. Cl <sub>2</sub> , Fe	$2Fe + 3Cl_2 \rightarrow 2FeCl_3$ $Cl-Cl + FeCl_3$ $\begin{array}{c} \delta^+ \quad \downarrow \quad \delta^- \\ Cl \cdots Cl - FeCl_3 \end{array}$	C <sub>6</sub> H <sub>5</sub> Cl
8. RCOCl, AlCl <sub>3</sub>	$RCOCl, AlCl_3$ $\updownarrow$ $AlCl_4^{\ominus} + RCO^{\oplus}$	C <sub>6</sub> H <sub>5</sub> COR



### Evidence

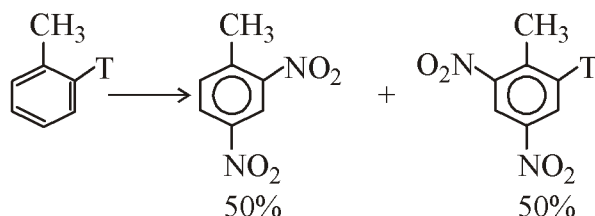
During the nitration of benzene with mixed acid (conc. Nitric and conc.  $\text{H}_2\text{SO}_4$ ) the attacking species is the nitronium ion and this reaction can be a second order reaction and the rate equation is  $\text{Rate} = K [\text{Substrate}] [\text{NO}_2^+]$ . Two possible mechanisms can be suggested in accordance with second order Kinetics :

(i) Synchronous formation of the C – N bond and breaking of C – H bond; (ii) addition of the nitronium ion to the nucleus, followed by the repulsion of a proton. In this two step mechanism, either (a) the addition of the nitronium ion or (b) the proton repulsion may be the r.d.s.



### Problem-1

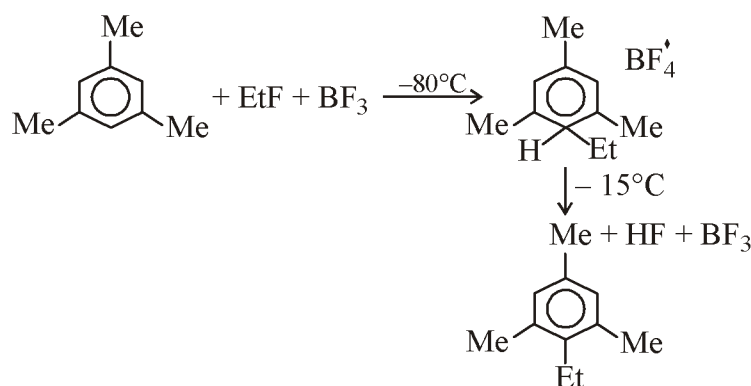
To distinguish between these two possibilities Melander (1949, 1950) examined the nitration of toluene containing tritium instead of hydrogen atom in the 2-position and showed that the 2, 4 dinitrotoluene contains 50% of the original tritium content.





Thus the rates of substitutions at 2-H and 2-T positions are equal. Hence it is proved since the rate has not been changed by labelling H with T, the expulsion of proton is not involved in the r.d.s. Hence the possibility (i) is ruled out and the nitration occurs by the two step process (ii).

**Proof-2.** Also the intermediate  $\sigma$  complex is isolated when mesitylene is treated with a mixture of ethyl fluoride and boron trifluoride ( $\text{BF}_3$ ) at  $-80^\circ\text{C}$ , the  $\sigma$  complex is an orange solid (m.p.  $-15^\circ$ ) which when the temperature is allowed to rise at  $15^\circ\text{C}$ , decomposes to form the ethyl substituted product which is obtained in the normal way.



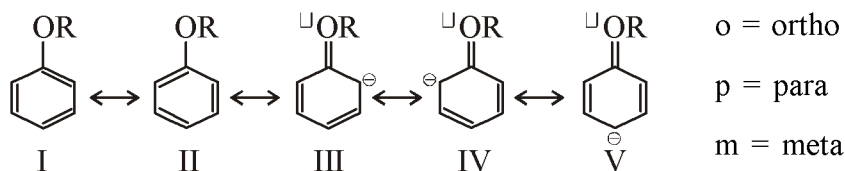
In some electrophilic aromatic substitution when the electrophile is highly reactive formation of  $\pi$ -complex becomes the rate determining step. The existence of  $\pi$ -complex is proved by dissolving toluene in  $\text{HCl}$  at  $-70^\circ\text{C}$  to form a 1 : 1 complex which is electrically conducting 20 DCL is used similar results are obtained. But both on decomposition gives the starting material indicate that these are not  $\sigma$ -complex. On the other hand benzene dissolves in  $\text{D}_2\text{SO}_4$  gives hexadentate benzene. In this case  $\sigma$  complexes must have been formed as inter mediates.

## 2.2.2 Orientation and Reactivity

There are two ways of studying the relative reactivities of positions in substituted benzenes. (a) based on charge distribution. (b) the stabilities of the intermediate carbocation i.e. a complex. In both approaches the substituted products are kinetically controlled not thermodynamically controlled.

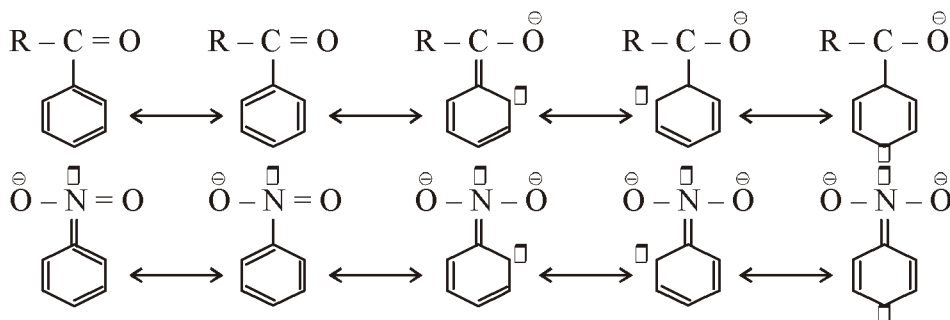
### Orientation based on charge distribution

The charge distribution in a monosubstituted benzene depends on the polar effects (I and/ or R) of the group. When the group present in the ring is OH, OR, NH<sub>2</sub> etc. the product of further substitution is mainly O-P. The common property of this type of group is the “key atom” must contain at least one lone pair of electrons. The resonance effect gives rise to increased electron densities in the O-P position e.g.



(I) and (II) are the normal structures, (III) and (IV) are O-quinonoid and (V) is the p-quinonoid structure. C<sub>6</sub>H<sub>5</sub>OR is a resonance hybrid of all these V structures. Hence the C<sub>6</sub>H<sub>5</sub>OR molecule has electron rich centres at two O-positions and one P-position. Thus the electrophilic reagents attack these O and P position and the activation energy leading to the attack at O and P positions is less than that of meta. Hence further electrophilic substitution occurs at these O and P-positions.

When the group present in the ring is NO<sub>2</sub>, CO<sub>2</sub>H, COR, SO<sub>3</sub>H etc, the product of further substitution is mainly meta (m). These groups attract the electrons away from the ring and the ring gets small + ve charges at O and P positions. Hence the m - position is comparatively electron rich and the activation energy leading to the attack of the electrophile at m position is less than that of O and P. Hence these group are m orienting.



Further more, since all m-orienting groups contain at least one strongly electron attracting atom, the inductive effect of this atom will also help to withdraw electrons from the O-, P- positions. Hence the substituent group presents is associated with deactivation of the ring i.e. further substitution is made more difficult by the presence of m-orienting group.

The electron attracting power (-I effect) of an atom cannot decide whether the substituent atom or group will be O-, P- or m- orienting; i. e. OH, NH<sub>2</sub>, have a strong -I effect and therefore tend to withdraw electrons from the ring i.e. the -I effect tends to promote m- substitution but these are O, P- orienting groups. As the key atom of these groups contain lone pair the +R effect is possible and it is stronger than the -I effect, the above groups become O-P- orienting (with activation of the ring).

### Examples

#### 1. Orientation in chlorobenzene

Chlorine has -I effect and +R effect as the C - Cl dipole is in the C → Cl direction. Here -I effect is greater than +R effect. On this basis chlorine would be expected to be m-directing with deactivation of the ring. In practice it has been O-, P- directing with deactivation e.g. nitration of chloro benzene gives O- and P- substituted products, but the reaction is slower than that for benzene itself. The O-P- orientation with deactivation is characteristic of aryl halides, styrene, cinnamic acid and benzyl chloride. When in a ring both O-, P- orienting and m- orienting groups are present the orientation of the third is controlled by the O-, P- group and not by m- as the +M and +E effect of O-, P- orienting group are more prominent.

#### 2. Orientation in aniline NH<sub>2</sub> is a O-, P- orienting group

Bromination of aniline gives 2, 4, 6-tribromoaniline; nitration with dilute HNO<sub>3</sub> produces a mixture of O- and P- nitroaniline. But nitration with 98% H<sub>2</sub>SO<sub>4</sub> gives 38% P-substitution, the rest being m-isomer. Here  $\overset{+}{N}H_3$  is formed in 98% H<sub>2</sub>SO<sub>4</sub> which has -M effect so the m-isomer is formed.

#### 3. Orientation of other groups

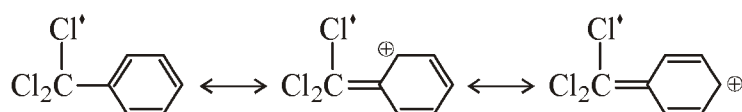
The carbonyl (-COOH) group is m-orienting, but the carboxylate ion is O-P orienting. This is due to the negative charge on each oxygen atom of carboxylate ion

electron repelling properties (+I) in contrast to the carboxyl group which is electron attracting (-I).



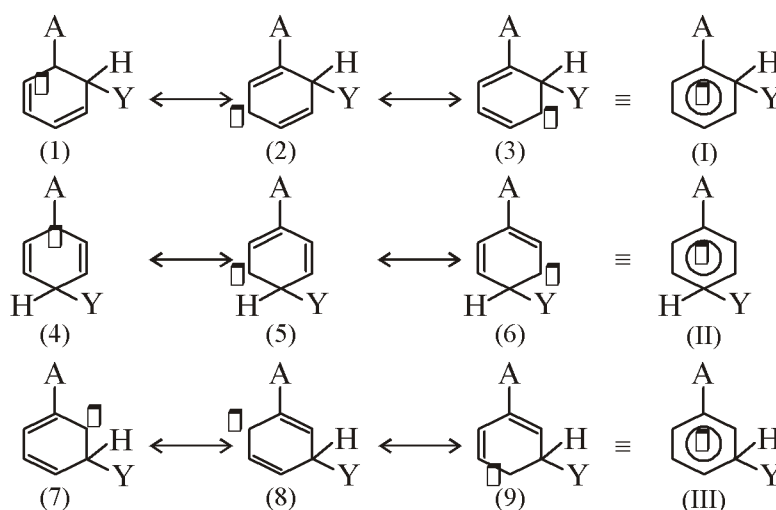
The polar effect of alkyl benzenes is particularly interesting. Because alkyl groups are electron-repelling (+I), the O- P- positions become points of high electron density and consequently alkyl groups are O-, P- orienting. Since the order of the inductive effect of alkyl gr is Methyl < ethyl < propyl < isopropyl < t-butyl then the activating effect of an R gr, if entirely due to +I effect, would be in the same order. Actually, in the number of cases the order is the reverse.

Explanation for this is hyperconjugation which is greatest in Me gr and least in t-butyl gr. Hyperconjugation is also responsible for the m-orienting power of the CCl<sub>3</sub> grp. as well as by the -I effect.



### Orientation based on $\sigma$ -complex stability

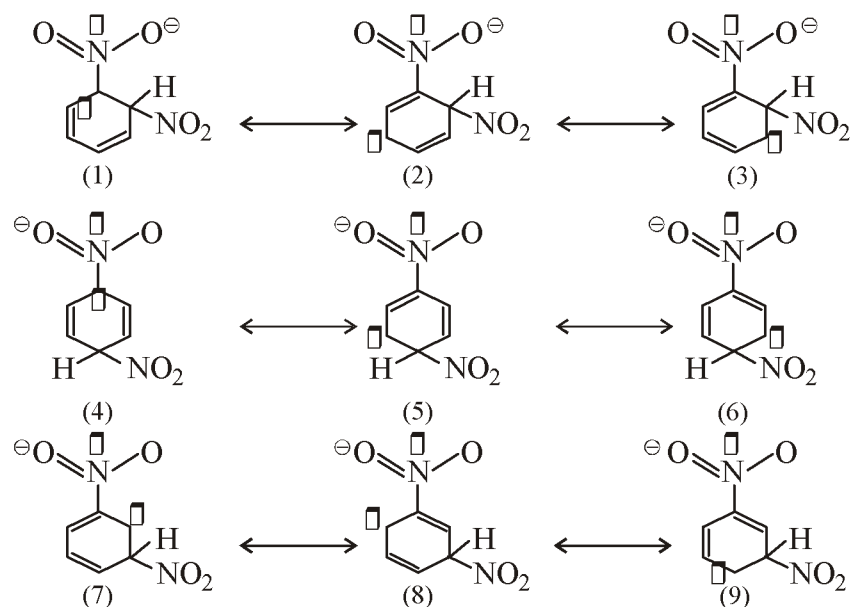
If A is the substituent and y the entering group, then the various carbocations for O-, P- and m- substitutions are as follows.



If A has a + I effect (e.g. Me) or is an electron donating group (e.g. OH) then the +ve charge in structures (1) and (4) will tend to be neutralised and consequently the  $\sigma$  complexes I and II stability by resonance. There is no such resonance stability for the  $\sigma$ -complex (III) consequently A is O-, P- orienting. If A has -I effect (e.g.  $\text{NR}_3^+$ ) or an electron withdrawing group (e.g.  $\text{NO}_2$ ) the  $\sigma$  complex (III) is more stable than (I) and (II) and consequently A will be m-orienting.

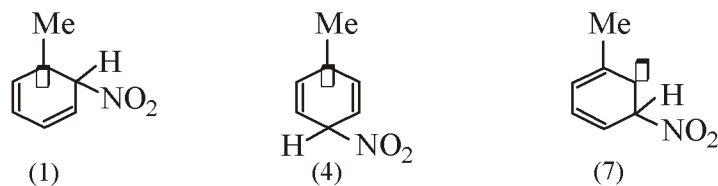
### Examples :

#### (i) Nitration of Nitrobenzene



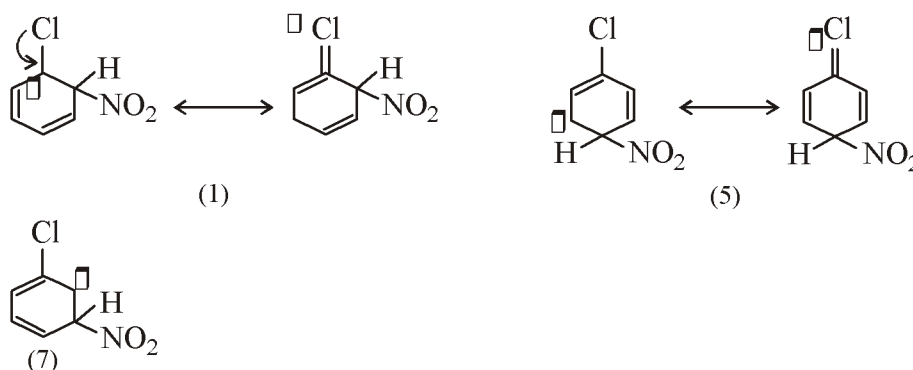
In O- and P- substitutions structures (1) and (4) contains positive charge on adjacent carbon atoms of +ve by charged N-atom so are unstable. But in the resonance hybrid of m- substitution no such structure is present. So m- substitution is forward.

#### (ii) Nitration of toluene



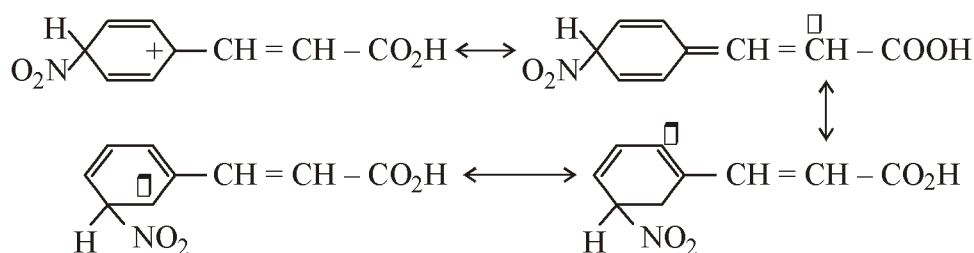
In structures 1 and 4 the +ve charge is stabilised by the +I effect of the Me grp due to partial neutralisation of the +ve charge on C of C–Me and spreading the +ve charge to Me carbon. No such stabilisation occurs in the m-ion. So O, P-substitution is favoured.

### (iii) Nitration of chlorobenzene



For O- and P- substitution +R effect involving the lone pairs of chlorine atom stabilises the  $\sigma$  complex. But it is not possible for the m-ion. So O, P- substitution is favoured. But as here  $-I > R$  the ring is deactivated.

### (iv) Nitration of cinnamic acid

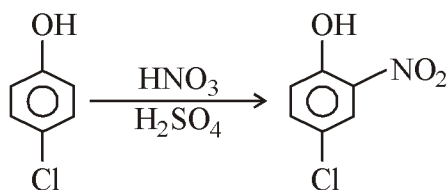


Only in the O- and P-  $\sigma$ - complex the +ve charge spread to the side chain. There by stabilising the  $\sigma$  complex for O- and P- substitution. So the product is O-, P- substituted not m- as in m- substitution the spreading of the charge to the side chain is not possible.

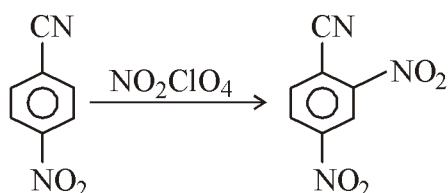
### Orientation of Polysubstitution in benzene

(a) The electronic effects of different groups present in the benzene ring

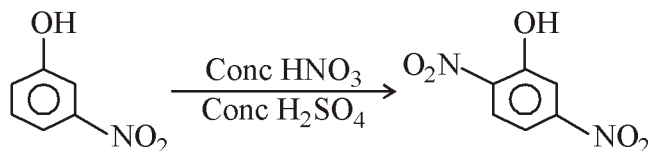
determine the polarisability of the ring and directs the third incoming group e.g. In para chloro phenol the  $-OH$  gr is more electron repelling and the entering electrophile goes O to  $-OH$  gr



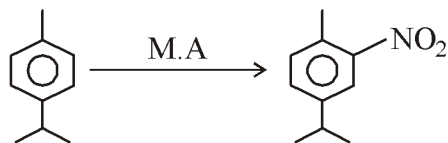
(b) If both groups are electron attracting the one which is more electron attracting guides the incoming electrophile to the m-position. e.g.



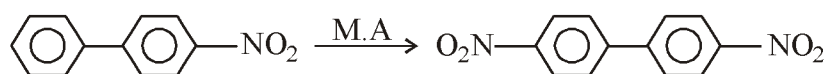
(c) If one is electron attracting and other is electron repelling the electron repelling group guides the entering electrophile.



(d) Steric crowding also affects electrophilic substitution e.g.



(e) If two aromatic rings are present in the molecule the ring which is more active guides  $SE_2$  Ar reach e.g.

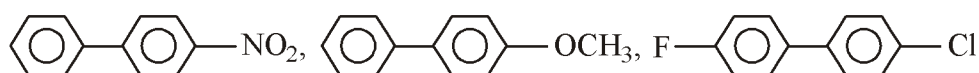


**Problem-1.**  $C_6H_6$  with anhydrous  $DCl$  in ether at  $-72^\circ C$  forms a complex. At ordinary temperature this complex decomposes again to form  $C_6H_6$  and  $D-Cl$ . But if this experiment is performed in presence of  $AlCl_3$  at ordinary temperature  $C_6H_6$  increases in molecular weight. Explain

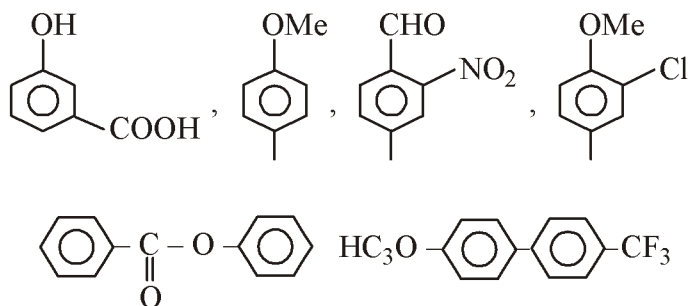
**Problem-2.** Arrange according to the order of nitration—phenol, chlorobenzene, fluorobenzene, Toluene.

**Problem-3.** Write the structure of the mono nitro derivative of the following compounds (i)  $C_6H_5COOH$ , (ii)  $C_6H_5CH = CHCOOH$  (iii) Dimethylaniline, (iv) Benzonitrile (v) Methoxybenzene (vi)  $C_6H_5CD_3$

**Problem-4.** Which aromatic ring will undergo faster  $SE_2$  Ar reaction.  $C_6H_5O-COC_6H_5$ ,  $C_6H_5NHCOC_6H_5$



**Problem-5.** Write down the major mononitro product of the following compounds.



### Potential energy diagram of electrophilic substitution reaction in benzene

The two step electrophilic substitution reaction consists of the first rate determining slow step for the formation of arenium ion or  $\sigma$  complex which gives rise to the product. This  $\sigma$  complex is the intermediate and not a transition state.

The reaction leading from benzene to the  $\sigma$  complex is highly endothermic because the benzene ring loses its stabilisation energy. It is shown in  $TS_1$  the bond between the electrophile and one carbon of benzene is only partially formed. The  $\sigma$  complex being the intermediate lies in the energy valley between the two transition



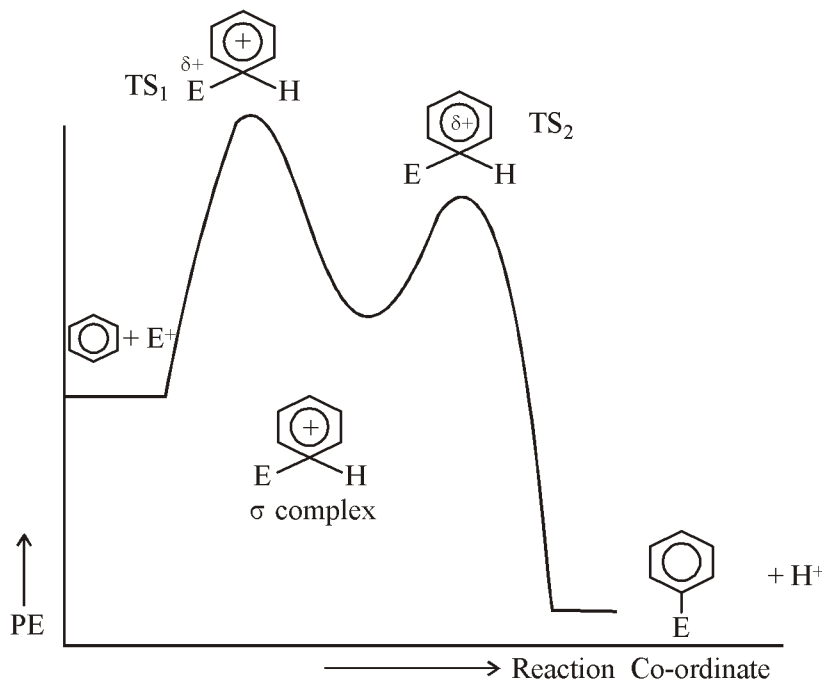


Fig-5

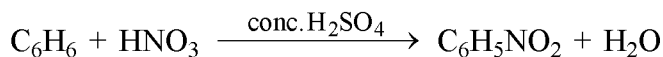
states. The reaction leading from the  $\sigma$  complex to the product is highly exothermic as the benzene ring regains its stabilisation energy. In T-S<sub>2</sub> the bond between H and the ring carbon is partially broken.

## 2.3 Reactions (Different electrophilic substitution reactions are discussed)

### 2.3.1 Nitration

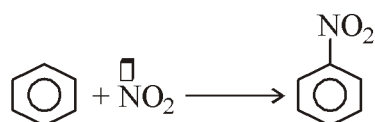
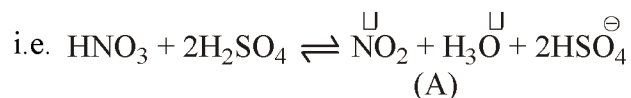
Nitration is the most widely studied aromatic electrophilic substitution reaction.

**Reagent :** The reaction is carried out by “classical” nitrating mixture using conc. nitric acid and conc. sulphuric acid.



**Mechanism :** The electrophile for nitration is



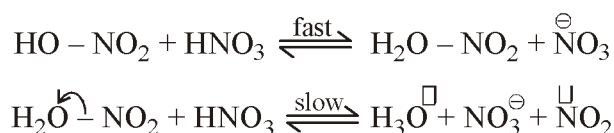


**Evidence :** The presence of  $\overset{\oplus}{\text{NO}}_2$  the nitronium ion in this solution and a number of salts has been confirmed spectroscopically.

Salt  $\overset{\oplus}{\text{NO}}_2\text{ClO}_4^\ominus$  and  $\overset{\oplus}{\text{NO}}_2\text{BF}_4^\ominus$  are actually isolated indicating the existence of  $\overset{\oplus}{\text{NO}}_2$ .

The solution of nitric acid in pure sulphuric acid shows an almost four fold molecular freezing point depression (actually i.e. 3.82) which is due to formation of four coin in equation (A). The slight short fall of  $i$  from 4 is probably due to incomplete protonation of  $\text{H}_2\text{O}$  under these conditions.

The role of  $\text{H}_2\text{SO}_4$  is to function as a highly acid medium. It is established by the fact that other strong acids e.g.  $\text{HClO}_4$ ,  $\text{HF}$  with  $\text{BF}_3$  are also effective for nitration. The poor rate of nitric acid in the nitration of benzene is due to the fact that it contains little  $\overset{\oplus}{\text{NO}}_2$  by the two stage process

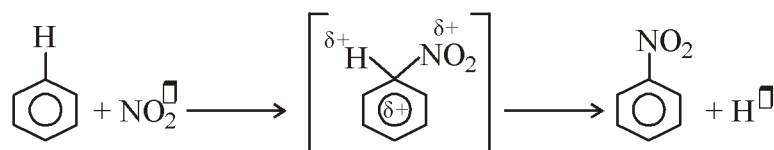


### Rate equation

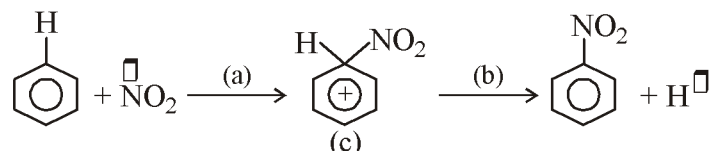
Many nitration reactions with nitrating mixture follow the idealised 2nd order rate equation of the form

$$\text{Rate} = K [\text{Ar} - \text{H}] [\overset{\oplus}{\text{NO}}_2]$$

The above rate equation is compatible with at least three potential path ways for nitration : one-step, concerted pathway that involves a single transition state (B).



Here C – NO<sup>2</sup> bond formation and C – H bond breaking occur simultaneously or two step pathways involving  $\sigma$ -complex.



Here either step (a) is the rate determining step or step (b) is the slow rate determining step.

### Evidence or rate determining step

If the C – H bond is broken in a rate limiting step, the reaction will exhibit a primary kinetic isotope effect if C<sub>6</sub>H<sub>6</sub> is replaced by C<sub>6</sub>D<sub>6</sub>. The comparison is made with C<sub>6</sub>H<sub>5</sub>NO<sub>2</sub> and C<sub>6</sub>D<sub>5</sub>NO<sub>2</sub> which does not show primary kinetic isotope effect i.e. rate of the reaction remains unaltered. Hence it is proved that C – H bond breaking is not the rate determining step. So the concerted mechanism is ruled out and the two step mechanism where formation of the  $\sigma$  complex is the rate determining step is accepted. The potential energy diagram for 2 step nitration is shown below.

### Nitration of phenol

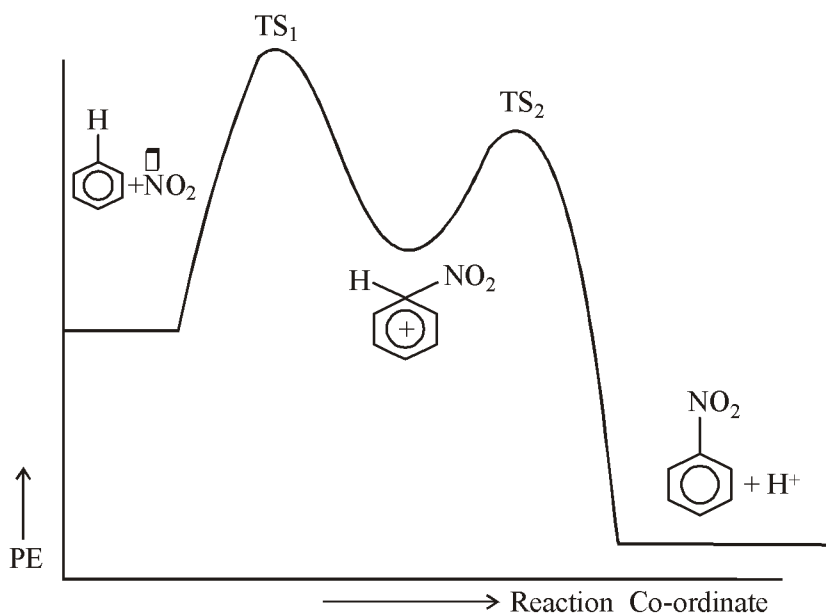
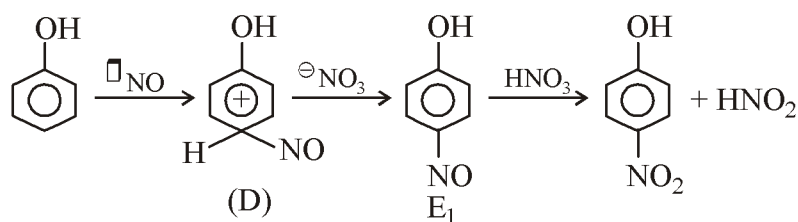


Fig-6

Highly reactive aromatic compounds such as phenol, are found to undergo ready

nitration even in dil  $\text{HNO}_3$  and at a much more rapid rate than the normal nitration with nitrating mixture. This happens due to the formation of  $\overset{\text{r}}{\text{N}}\text{O}$  species nitrosonium ion in dil  $\text{HNO}_3$  effecting nitrosation.



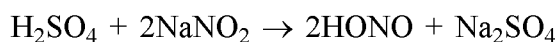
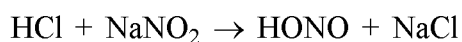
The nitrosophenol ( $\text{E}_1$ ) is isolated and is oxidised rapidly to nitrophenol by  $\text{HNO}_3$  producing more nitrous acid. The process is progressively speeded up. No nitrous acid need to be initially present in the nitric acid as dil nitric acid.

Oxidises phenol and itself is reduced to  $\text{HNO}_2$  which carries the reaction. Here also the  $\sigma$  complex (d) formation is the rate determining step.

### 2.3.2 Nitrosation

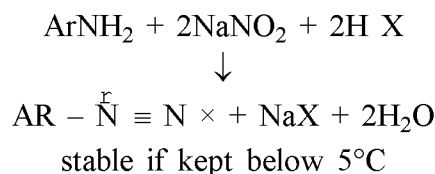
It is the method of introduction of  $\overset{\text{r}}{\text{N}}\text{O}$  group in a ring or in side chain.

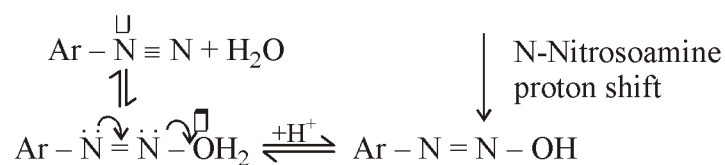
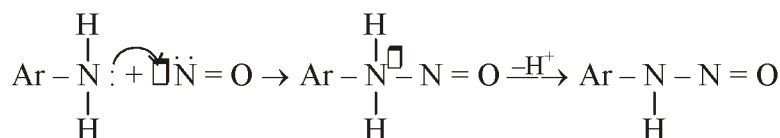
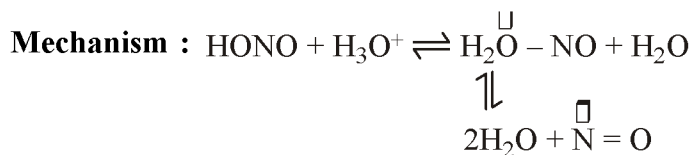
**Reagent :** Nitrous acid formed in situ by treating  $\text{NaNO}_2$  with an aqueous solution of strong acid



Amines react with nitrous acid giving different products.

1. Reaction of primary arylamines with nitrous acid—Primary aromatic amines react with  $\text{HNO}_2$  to give arene diazoumin salts.

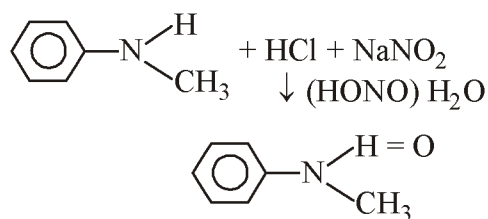




This reaction has considerable synthetic importance because the diazo group  $-\overset{\text{U}}{\text{N}} \equiv \text{N}$  can be replaced by a variety of groups.

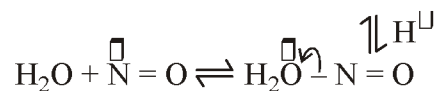
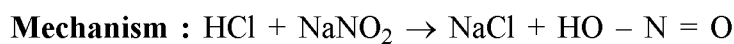
### Reaction of secondary aromatic amines with nitrous acid

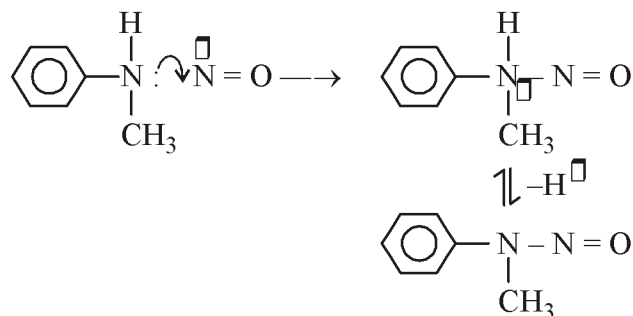
Secondary aromatic amines react with nitrous acid to form N-nitrosoamines. Which separate as only yellow liquids.



N-Nitroso - N - methylaniline

A yellow product.

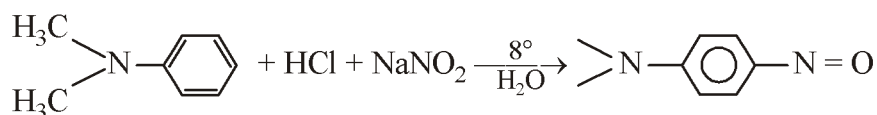




N-Nitrosoamines are very powerful carcinogenous. They may be present in many foods, especially in cooked meats that have been cured with  $\text{NaNO}_2$ .

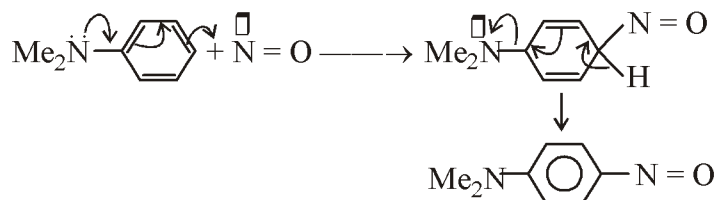
### Reactions of tertiary amines with $\text{HNO}_2$

Tertiary aromatic amines react with nitrous acid to form C-Nitroso aromatic compounds, Nitration takes place exclusively of para position if it is free, if not, at the ortho position.



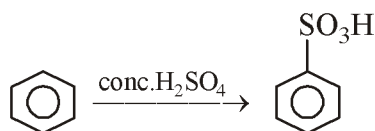
P-Nitroso - N, N - demethyl  
aniline (80 - 90%)

**Mechanism :** The  $\overset{\ominus}{\text{N}}\text{O}$  is formed by HCl and  $\text{NaNO}_2$  as shown in the previous case. Then it reacts with N, N-dimethyl aniline.

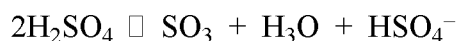


### 2.3.3 Sulphonation

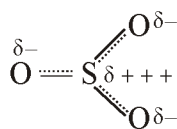
Benzene with conc.  $\text{H}_2\text{SO}_4$  or by oleum or by  $\text{SO}_3$  in inert solvents forms benzene sulphonic acid. It is called sulphonation reaction.



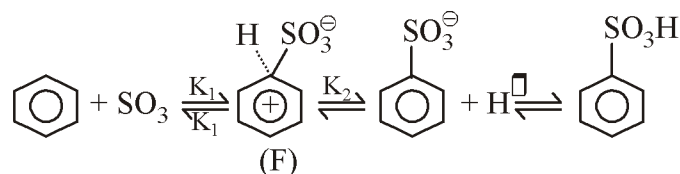
**Mechanism :** The mechanism has less exposed. The nature of the electrophile depends on the conditions but it is probably always  $\text{SO}_3$  either free or linked to a carrier; e.g.  $\text{H}_2\text{SO}_4$ .  $\text{SO}_3$  ( $\text{H}_2\text{S}_2\text{O}_7$ ) in sulphuric acid. As small concentration of  $\text{SO}_3$  is developed in  $\text{H}_2\text{SO}_4$  itself through the equilibrium.



Attack takes place through S as this is highly positively polarised i.e. electron-deficient :



Sulphonation is a reversible process.



In oleum, the  $\sigma$  complex is believed to undergo protonation of the  $\text{SO}_3^{\ominus}$  before undergoing C – H fission to yield the  $\text{SO}_3\text{H}$  analogue.

**Kinetics :** Sulphonation exhibits primary kinetic isotope effect. It apparently appears that C – H bond breaking is the rate limiting step. But actually that is not true. It can be proved by the potential energy diagram of sulphonation of benzene and deuterated benzene. Reversibility means the  $\sigma$ -complex can lose  $\text{SO}_3$  to form the reactant or can break the C – H or C – D bond to give the product.

In sulphonation the energy hump on either side of carbocation (F) is roughly same. So some ions (F) go towards the product and some to the starting material showing the reversibility of the reaction. When the hydrogen atom is labelled by deuterium the barrier to the left towards the starting material is same but towards the

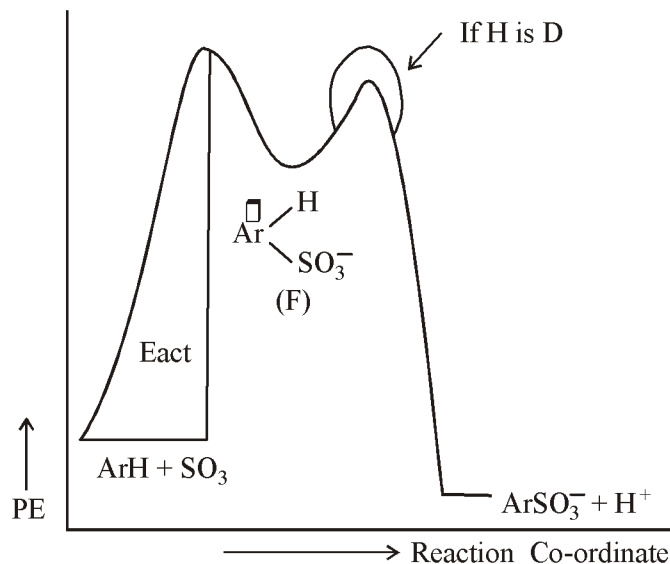
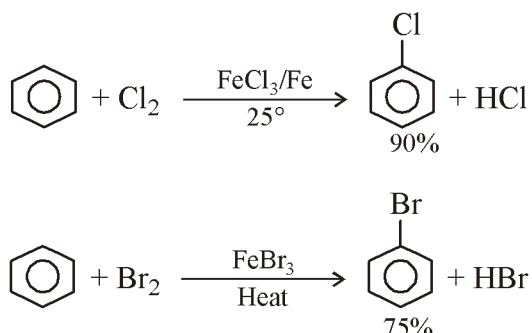


Fig-7

product the barrier is higher and the rate of formation of the product is slow. Hence sulphonation shows primary kinetic isotope effect though C – H bond breaking is not the rate determining step. The reversibility of sulphonation is used to introduce –SO<sub>3</sub>H group for its directive influence and then to eliminate readily to form different compounds.

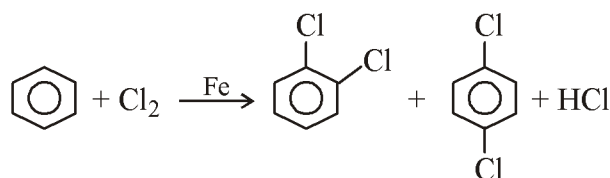
### 2.3.4 Halogenation

Benzene reacts with chlorine or bromine at low temperature in the presence of halogen carrier e.g. FeCl<sub>3</sub>, FeBr<sub>3</sub> or Fe etc. which are Lewis acids to form chloro or Bromo benzene.

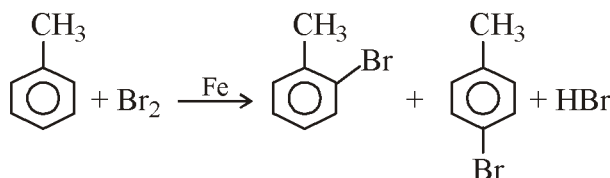


with two moles of chlorine mixture of O-dichloro and P-dichloro benzenes are obtained where P isomer is the major one.

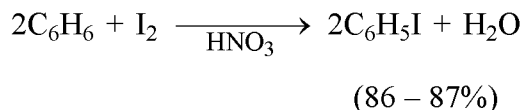




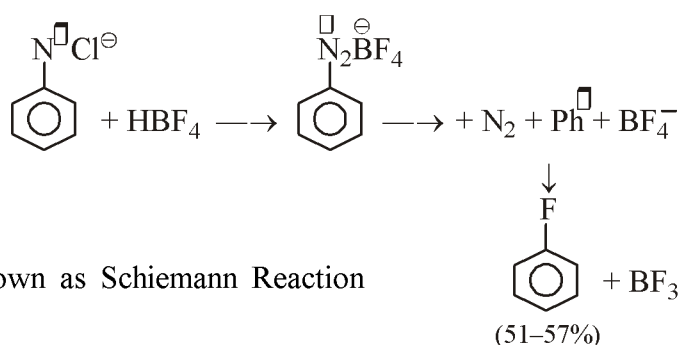
When toluene is brominated in the presence of iron (using 1 molecule of bromine), a mixture of O- and P- bromotoluenes are obtained.



As iodine is very much unreacting direct iodination causes some difficulty. So iodination is carried out in presence of an oxidizing agent e.g.  $\text{HNO}_3$ ,  $\text{HgO}$  etc the yield of iodo compound is usually very good.



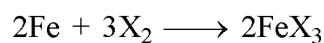
Fluoro compounds are best prepared from diazonium salt

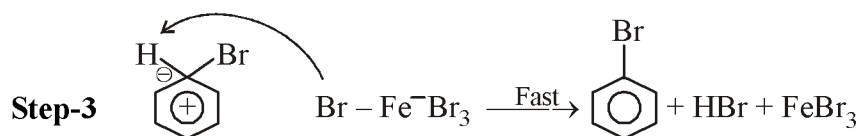
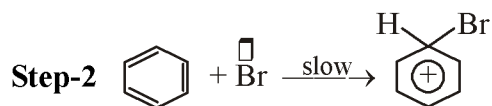


This is known as Schiemann Reaction

### Mechanism

The Lewis acids are usually generated in the reaction mixture by adding iron which reacts with halogens.

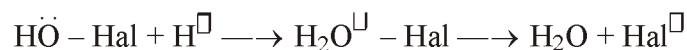




The function of Lewis acid is in step-1 to produce the active electrophile  $\text{Br}^{\oplus}$ . In step-2  $\text{Br}^{\oplus}$  attacks  $\text{C}_6\text{H}_6$  to form the  $\sigma$ -complex. Then finally in step-3 the  $\sigma$ -complex transfers a proton to  $\text{FeBr}_4^{-}$ . This results in the formation of bromobenzene and HBr, regenerating the catalyst  $\text{FeBr}_3$ .

The mechanism of chlorination is analogous to bromination where  $\text{FeCl}_3$  acts as the Lewis acid.

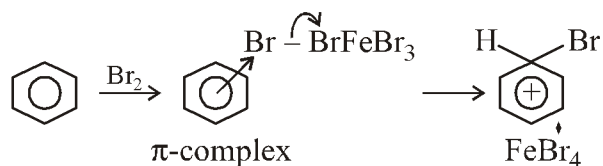
Halogenation can also be carried out by interhalogen compounds  $\overset{\delta+}{\text{Br}}-\overset{\delta-}{\text{Cl}}$ ,  $\overset{\delta+}{\text{I}}-\overset{\delta-}{\text{Cl}}$  etc. Halogenation can be effected by hypohalous acids also  $\overset{\delta-}{\text{HO}}-\overset{\delta+}{\text{Hal}}$  also. But the reaction is much slower as  $\overset{\ominus}{\text{O}}\text{H}$  is a poorer leaving group. In presence of strong acid  $\text{HO}-\text{Hal}$  becomes a very powerful halogenating agent due to the formation of a highly polarised complex.



### Kinetics

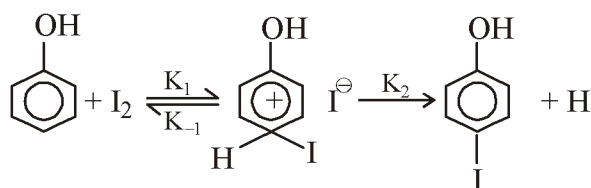
The Rate equation is found to be  $\text{Rate} = K [\text{Ar}-\text{H}] [\text{X}_2] [\text{Lewis acid}]$

Here the formation of  $\sigma$ -complex is the rate determining step. But the  $\sigma$ -complex is formed from a  $\pi$ -complex which includes the halogen atom and the Lewis acid. Hence the rate equation is as shown.



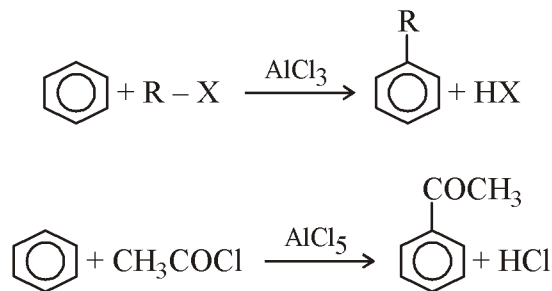
### Evidence

Kinetic isotope effects have not been observed for chlorination and only rarely for bromination. Hence it is proved that formation of  $\sigma$ -complex is the rate determining step. Iodination only behaves differently and shows kinetic isotope effect. This is due to the fact that as it is reversible, the loss of I occurs at a faster rate than loss of H from  $\sigma$ -complex i.e.  $K_{-1} > K_2$ .



### 2.3.5 Friedel Crafts Reaction

In 1877 a French chemist, Charles Friedel and his American collaboration James M. Crafts discovered new methods for the preparation of alkyl benzenes (Ar R) and Acyl benzenes ArCOR. These reactions are now called Friedel Crafts Alkylation and acylation reactions.

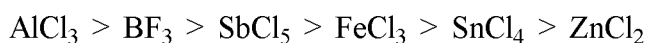


**Reagents :** The aromatic compounds used for Friedel Crafts reaction are usually hydrocarbons, aryl chlorides or bromides, mono and polyhydric phenols or their ethers.

The alkylating agents may be alkyl halides, aliphatic alcohols, alkenes, ethers, alkyl esters of organic inorganic acids. The acylating agents may be acid chlorides or anhydrides acids or esters. For a given alkyl group the order is  $RF > RCl > RBr_2 > RI$ . For a given halogen atom the order is  $3^\circ > 2^\circ > 1^\circ$ .

Two types of catalysts are used

(i) Metal halides (Lewis Acids); their general order of reactivity is shown below



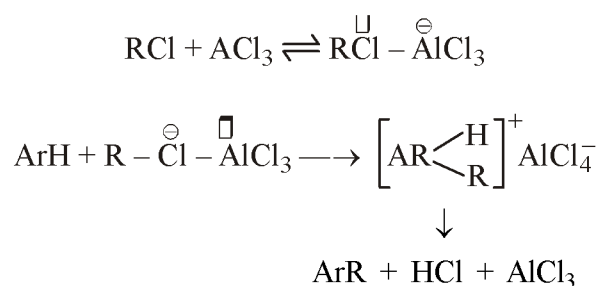
(ii) Proton acid catalysts : HF, H<sub>2</sub>SO<sub>4</sub>, H<sub>3</sub>PO<sub>4</sub>, AlCl<sub>3</sub> is the most widely used catalyst. It is used with an alkylating or acylating agent. In the case of alkene as alkylating agent a small amount of halogen acid must be present, BF<sub>3</sub> is used as catalyst for alkenes and alcohols.

Solvents are generally used in Friedel-Crafts reaction but if the substrate is liquid, it should be used in excess. Two common solvents are nitrobenzene and carbondisulphide. Nitrobenzene is inert towards Friedel Crafts reaction. So is used as a solvent.

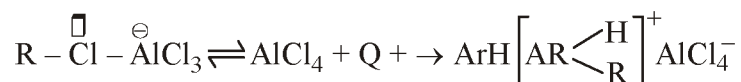
### Mechanism

Two possible mechanisms operate with alkyl halides, one involving an alkyl halide-Lewis acid complex (Bimolecular mechanism) and the other involving alkyl carbocation (unimolecular mechanism)

(i) Alkyl halides from 1 : 1 adducts with Lewis acids reacts with the aromatic compound if the alkyl group is straight chain type.

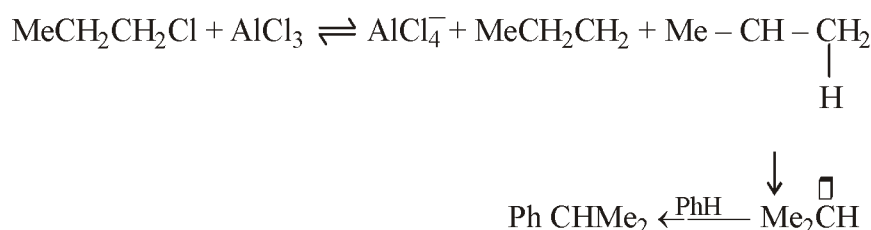


(ii) On the other hand, due to the relative stability of 2° and 3° carbocation the adducts with 2° and 3° halides ionise and this carbocation is the active species.



The mechanisms account for the fact that n-alkyl groups can be introduced without rearrangement at low temp. but when carbocation is formed rearrangement

occurs by  $H^{\ominus}$  shift or  $CH_3^{\ominus}$  shift e.g. at higher temperatures, n-propyl chloride gives isopropyl benzene.

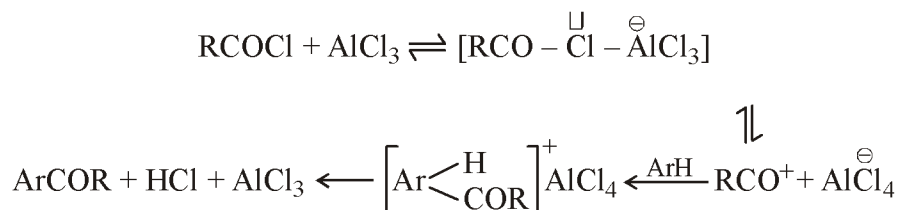


In the same way isobutyl chloride gives t-butyl benzene.

These two mechanisms are the extremes,  $\text{MeX}$  behaving as the adduct and  $\text{ter-RX}$  as the carbocation. For branched alkyl halide carbocation route is increasingly favoured. Many reactions proceed by dual mechanisms.

### Friedel Crafts

**Acylation :** For many reactions involving acyl chlorides there is evidence to show that the reaction proceeds through the intermediate formation of an acyl cation.

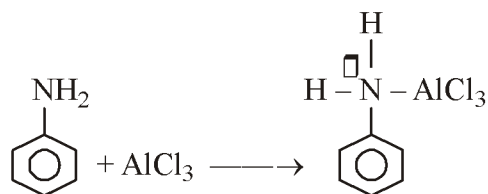


There is also evidence that the adduct  $\text{RCOClAlCl}_3$  can be the active species.

### Limitations of Friedel Crafts reactions :

Several restrictions limit the usefulness of Friedel-Crafts reaction.

1. Rearrangement of straight chain carbocation occurs.
2. The reaction does not occur when a powerful electron withdrawing group is present on the aromatic ring or when the ring bears an  $-\text{NH}_2$ ,  $-\text{NHR}$  or  $-\text{NR}_2$  group. This is applicable to alkylations and acylations. The amino groups are changed into powerful electron withdrawing groups by the Lewis acid's used to catalyze Friedel-Crafts reaction. e.g.



Does not undergo  
Friedel Crafts reaction

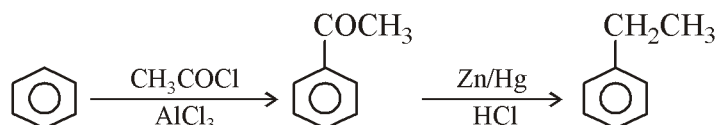
3. Aryl or vinyl halides cannot be used as the halide component do not form carbocations readily.

4. Polyalkylations often occur Alkyl groups are electron releasing groups and once one is introduced into the benzene ring it activates the ring toward further substitution.

This is not the problem for Friedel-Crafts acylation. The RCO (acyl gr) deactivates the ring and inhibits further substitution causing monoacylation.

But during the preparation of toluene, O-xylene and P-xylene

are also formed Ethyl benzene is formed not by direct Friedel-Crafts alkylation with  $\text{CH}_3\text{CH}_2\text{Cl}$  instead it is prepared by Fr. crafts acylation followed by clemensons reduction to convert CO to  $\text{CH}_2$  group.



### Problem-1

Show how an acylium ion could be formed from an acid anhydride.

### Problem-2

What would be the major monochloro product (or products) formed when each of the following compounds react with chlorine in the presence of ferric chloride?

(a) Ethyl benzene,  $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_3$ .

(b) (Trifluoromethyl) benzene  $C_6H_5CF_3$ .

(c) Trimethylphenylammonium chloride,  $C_6H_5N^+(CH_3)_3 Cl^-$

(d) Methyl benzoate.

### Problem-3

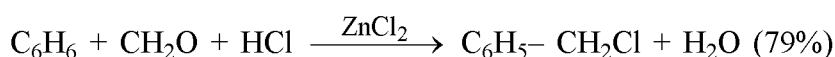
Acetanilide is less reactive toward electrophilic substitution than aniline explain.

## 2.4 Reactions involving one carbon electrophiles

### 2.4.1 Chloromethylation reaction

This is the process where by a hydrogen atom generally of an aromatic ring is replaced by a chloromethyl group,  $(CH_2Cl)$ .

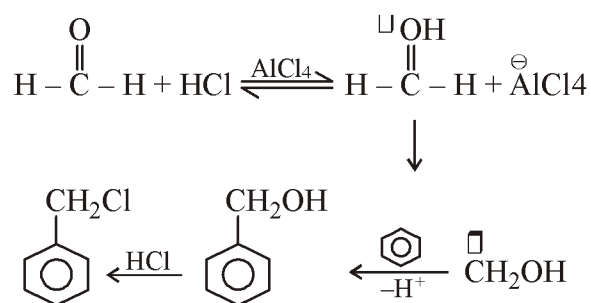
**Reagents :** The reaction is carried out by heating the aromatic compound with formaldehyde or paraformaldehyde and HCl acid in the presence of  $ZnCl_2$  as catalyst. e.g. benzyl chloride from benzene



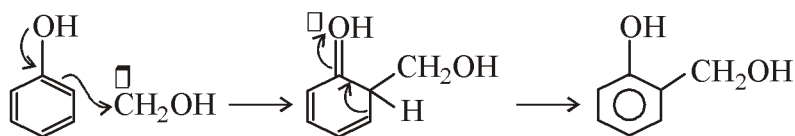
chloromethyl ether and dichloromethyl ether may be used instead of formaldehyde or paraformaldehyde and they do not require any catalyst.

The catalyst used with formaldehyde are  $ZnCl_2$ ,  $AlCl_3$ ,  $SnCl_4$ ,  $CH_3COOH$  and  $H_2SO_4$ .

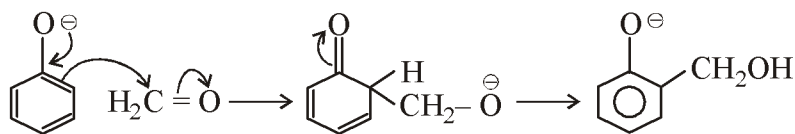
### Mechanism



The presence of halogen atom in the ring reduces the yield of the chloromethylated product. The presence of nitro group also retards the reaction and the presence of two nitro groups inhibits the reaction completely. Nitro benzene gives little chloromethylated product but m-dinitrobenzene gives none. Ketones of type ArCOAR give very poor yield and the ketone of the type ArCOAr do not react at all. Phenols are very much reactive and gives polymer.

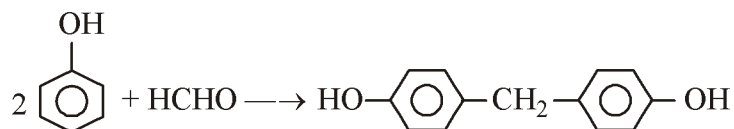
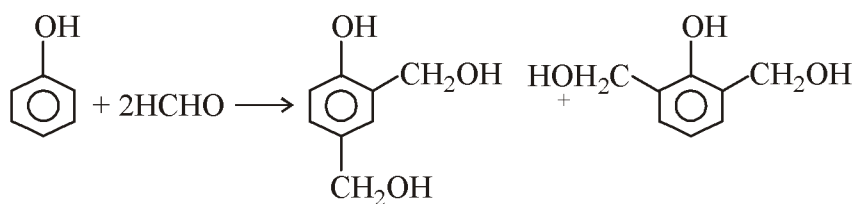


Acid catalysis



Base catalysis

when larger quantity of formaldehyde are used dihydroxy methylphenol of P, P<sup>1</sup> - dihydroxydiphenyl methane are obtained.



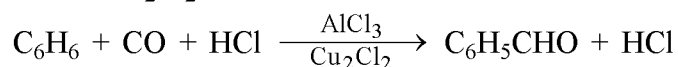
These condensations are the basis of formation of phenol of formaldehyde resins Bakelites.



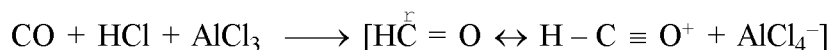
### 2.4.2 Gattermann Koch reaction

In this method CHO or formyl grp is introduced in benzene ring.

**Reagents and method :** Benzaldehyde is synthesised by refluxing a mixture of carbon monoxide (CO) and hydrogen chloride (HCl) through a solution of nitrobenzene or ether containing benzene and a catalyst consisting of aluminium chloride  $\text{AlCl}_3$  and a small amount of  $\text{Cu}_2\text{Cl}_2$ .



**Mechanism :** The mechanism is not quite certain, but it appears likely that the formyl cation is the active species



It also appears likely that the cuprous chloride forms a complex with a carbon monoxide, thereby increasing its local concentration when there are substituents in the ring e.g. a methyl group, the aldehyde group is introduced into the p-position only. The Gattermann-Koch aldehyde synthesis is not applicable to phenols and their ethers or when the substituent is strongly deactivating e.g. nitrobenzene.

### 2.4.3 Gattermann reaction

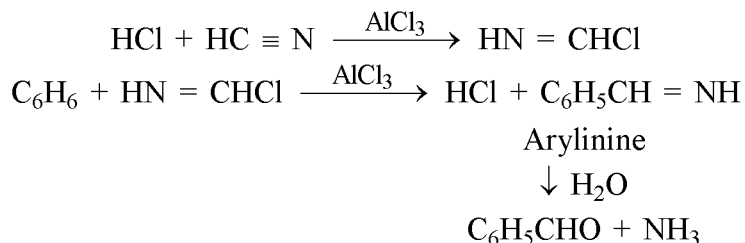
It is also a method of synthesis of benzaldehyde i.e. introduction of  $-\text{CHO}$  group in the benzene nucleus.

#### Reagents and method

When benzene is treated with a mixture of hydrogen cyanide and hydrogen chloride in the presence of aluminium chloride followed by the decomposition of the complex with water, benzaldehyde is produced in low yield.



#### Mechanism

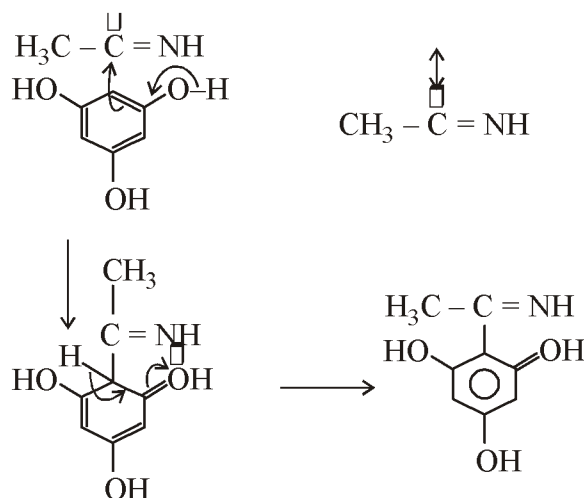
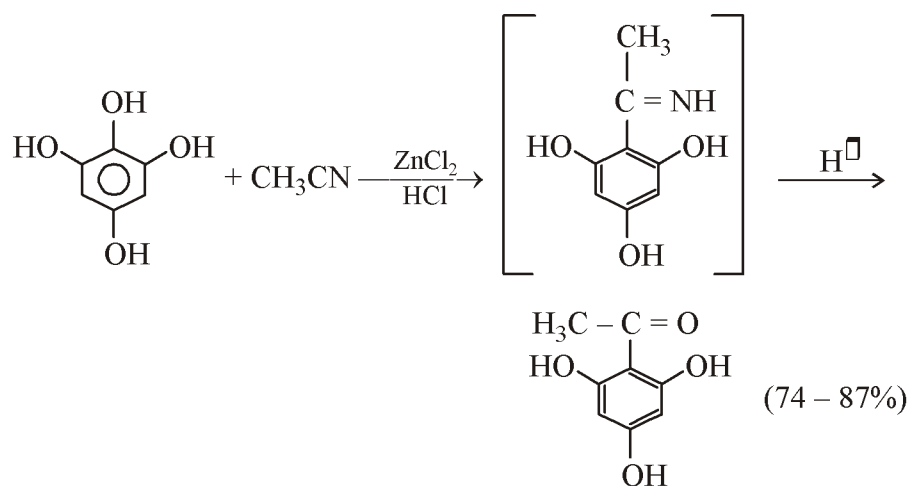


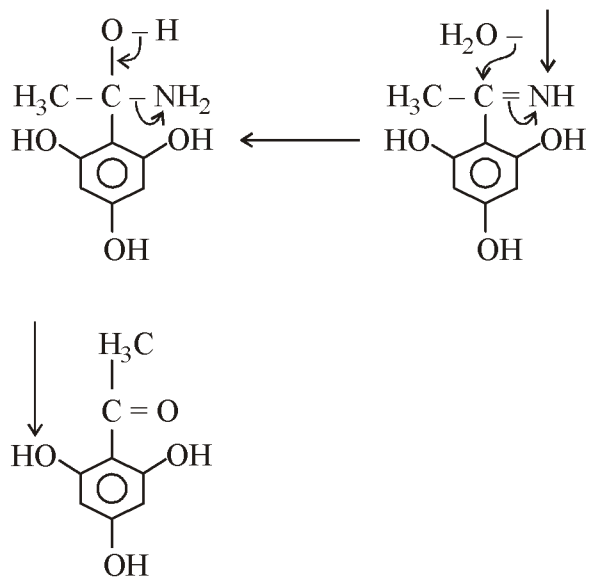
The gattermann reaction is applicable to phenols and phenolic ethers but not to nitrobenzene.

### 2.4.4 Hauben Hoesch Reaction

Phenolic Ketones are prepared by this method.

**Reagents and Method :** Condensation of alkyl cyanide with polyhydric phenols, forms phenolic ketones particularly m-compounds in the presence of zinc chloride and HCl e.g. phloroglucinol condenses with  $\text{CH}_3\text{CN}$  to form phloroacetophenone.





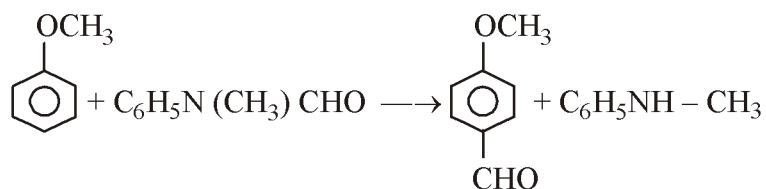
This is an extension of Gattermann synthesis. It is not applicable to phenol itself.

### 2.4.5 Vilsmeier – Haack Reaction

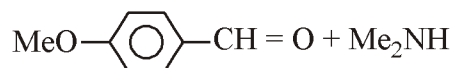
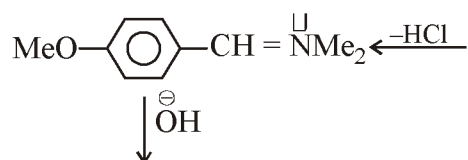
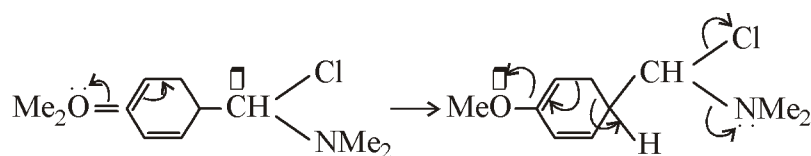
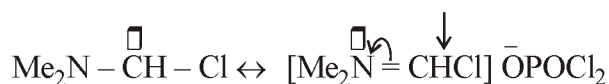
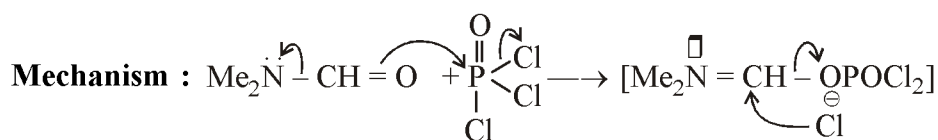
The activated aromatic compounds can be formylated by this reaction.

#### Reagents and Method

The aromatic compounds particularly phenolic ethers can be formylated by means of N-methyl formanilide at the O- and P- position. It does not work with hydrocarbons except anthracene where -CHO grp enters at a position. The formylation is carried out by treating the compound with N-methylformanilide and phosphoryl chloride followed by treatment with aqueous CH<sub>3</sub>COONa and steam distillation.



N, N-Di methylformanilide is often used instead of N-methylformanilide.

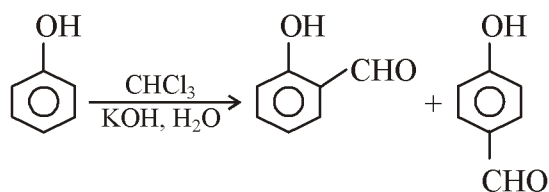


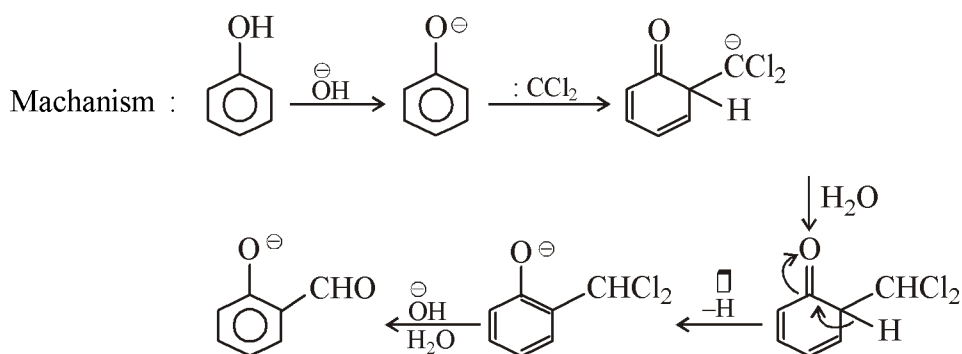
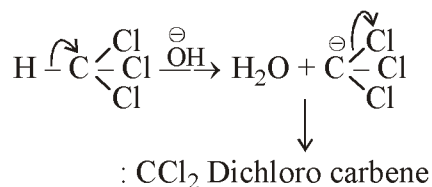
### 2.4.6 Reimer-Tiemann Reaction

Phenols give rise to O-Hydroxybenzaldehyde and P-Hydroxybenzaldehyde by this reaction.

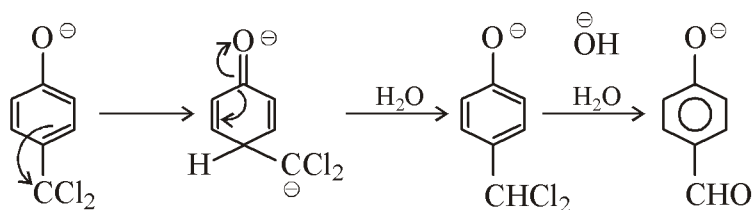
#### Reagents and Method

This reaction is carried out by refluxing an alkaline solution of phenol with chloroform at 60°C, distilling the excess of chloroform, acidifying the residual liquid with H<sub>2</sub>SO<sub>4</sub> and then steam distilling it. Unchanged phenol and O-hydroxybenzaldehyde distil over, leaving behind p-Hydroxybenzaldehyde.

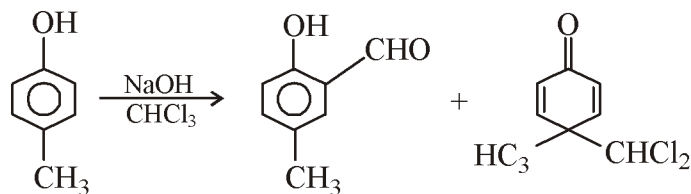




also the attack at P-position occurs

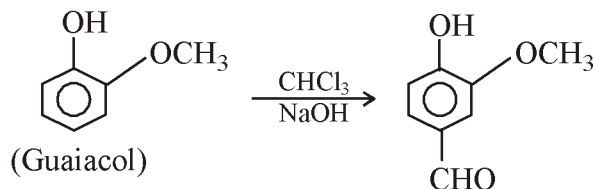


Phenols with blocked P-position give cyclohexadrenones conducting the dichloro methyl grp.

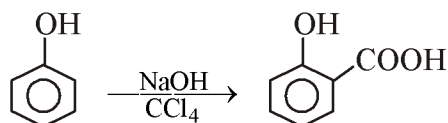


The dichloro compound can be isolated. It is not hydrolysed in aqueous basic medium for its insolubility.

In the Reimer-Tiemann reaction the O-isomer predominates. But if O-positions is occupied, the aldehyde group tends to go to the p-position. e.g. Guaiacol forms vanillin.



With alkaline solution of phenol and  $\text{CCl}_4$  salicylic acid is produced by this reaction.

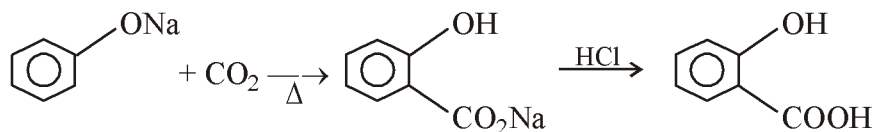


### 2.4.7 Kolbe Schmitt Reaction

The industrial preparation of salicylic acid is carried out by this reaction.

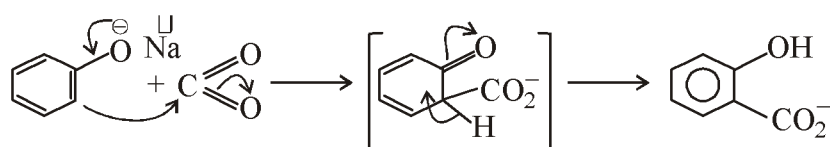
#### Reagent and Method

Sodium phenoxide and  $\text{CO}_2$  are heated at  $120\text{--}140^\circ\text{C}$  under pressure.

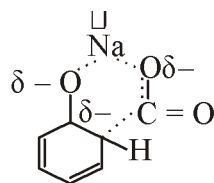


A small amount of P-derivative is formed at the same time, and if the temp, rises above  $140^\circ\text{C}$ , the P-isomer is the main product.

**Mechanism :** Here the electrophile is  $\text{CO}_2$



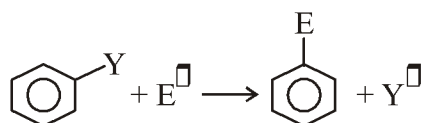
Here only a trace of P-isomer is obtained when the alkali used is  $\text{NaOH}$ . But if the reaction is carried out on potassium phenoxide the salt of P-acid becomes the major product. It has been proposed that the preferential O-attack with sodium phenoxide may result from stabilisation of the T.S. through chelation by  $\text{Na}^+$  in the ion pair.



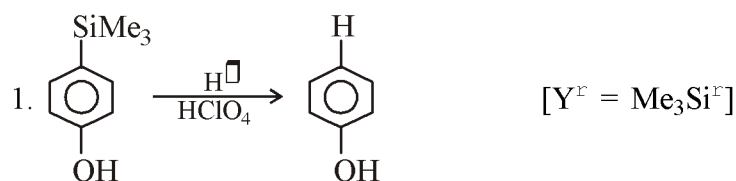
The  $K^r$  cation is larger and less effective to stabilize the complex so the attack is more effective at P-position.

## 2.5 Ipso substitution

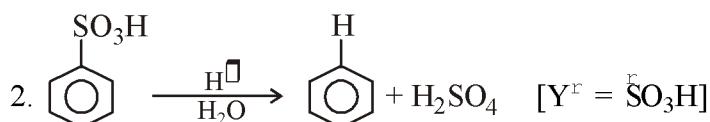
If an electrophile replaces an electrofuge other than hydrogen it is called Ipso substitution. The groups other than  $H^+$  that are replaced are  $\overset{\ominus}{S}O_3H$ ,  $\overset{\oplus}{C}OOH$ ,  $R^r$  etc.



**Examples :** A number of such reactions are known where the attacking electrophile is  $H^r$ .

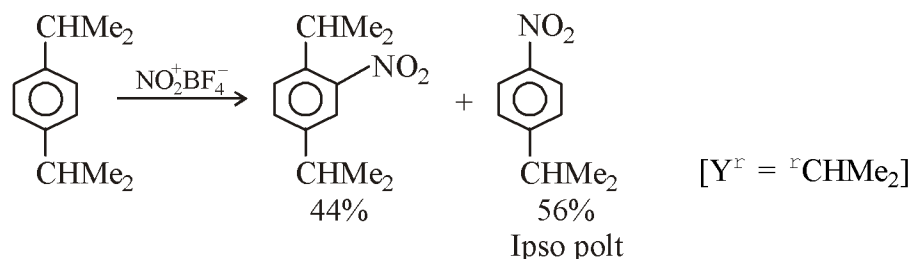


It is called protodesilylation.



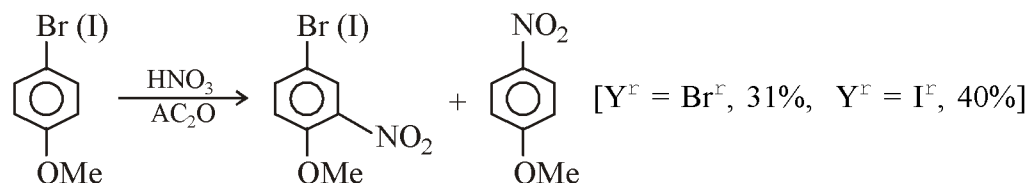
Hence sulphonation is a reversible process.

3. Secondary or tertiary alkyl substituents can be removed for the stability of carbocations.



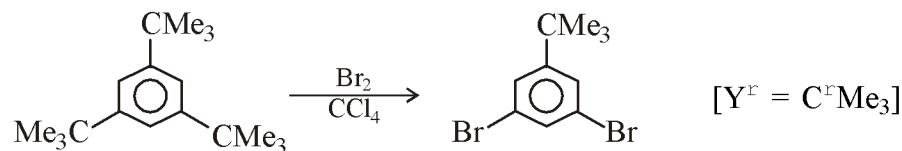
This is Nitrodealkylation

4. Halogen atoms can also be displaced which is called nitrodehalogenation.



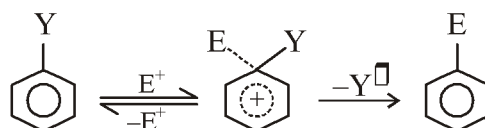
Analogous nitrodechlorination is not observed, owing to the greater resistance to the formation of  $\text{Cl}^\text{r}$ , compared with  $\text{Br}^\text{r}$  and  $\text{I}^\text{r}$ .

5. Bromodealkylation.



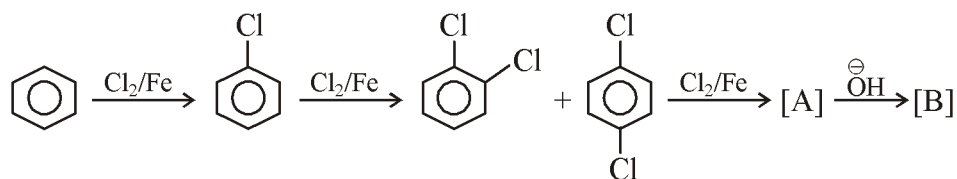
Hence, during preparation of a compound by electrophilic substitution possibility of Ipso substitution for more heavily substituted benzene derivatives must be considered.

**Mechanism :**



Here the electrophile  $\text{E}^\text{r}$  displaces the electrofuge  $\text{Y}^\text{r}$ . Electrophile may be  $\text{H}^\text{r}$  also making the reaction reversible.

**Problem-9.** Identify [A] and [B] in the following conversions and explain the formation of [B] from [A]

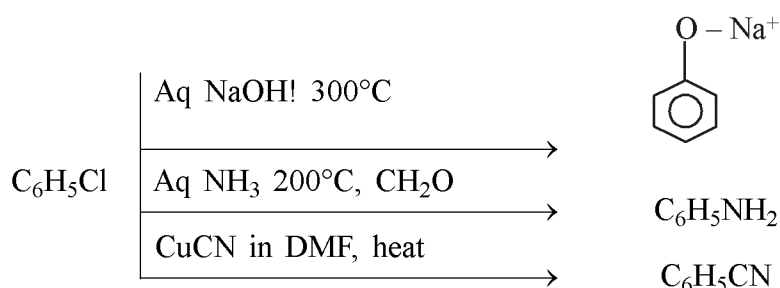




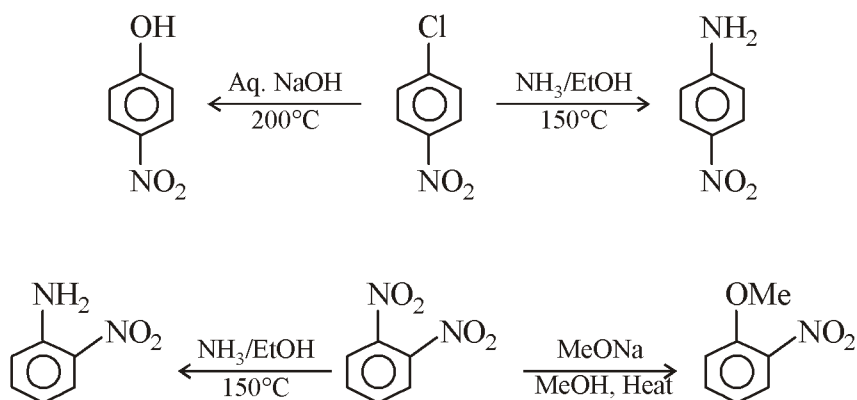
**Problem-10.** What happens when Resorcinol is treated with  $\text{POCl}_3/\text{DDIF}$  followed by acidification.

## 2.6 Nucleophilic Substitution

Aromatic  $\pi$ -cloud is inert towards nucleophiles. Aryl halides undergo nucleophilic substitution with difficulty. vigorous conditions are generally required e.g.

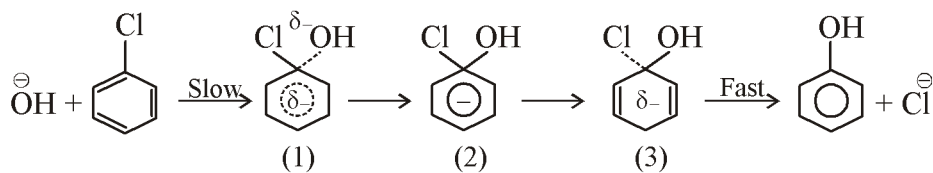


On the other hand when a powerful electron withdrawing groups is present O- and/ or P- to the halogen atom, replacement of the latter by nucleophilic reagents is more facilitated. This is activated nucleophile substitution, and also includes the replacement of various groups such as  $\text{NO}_2$ , OMe, H, e.g.

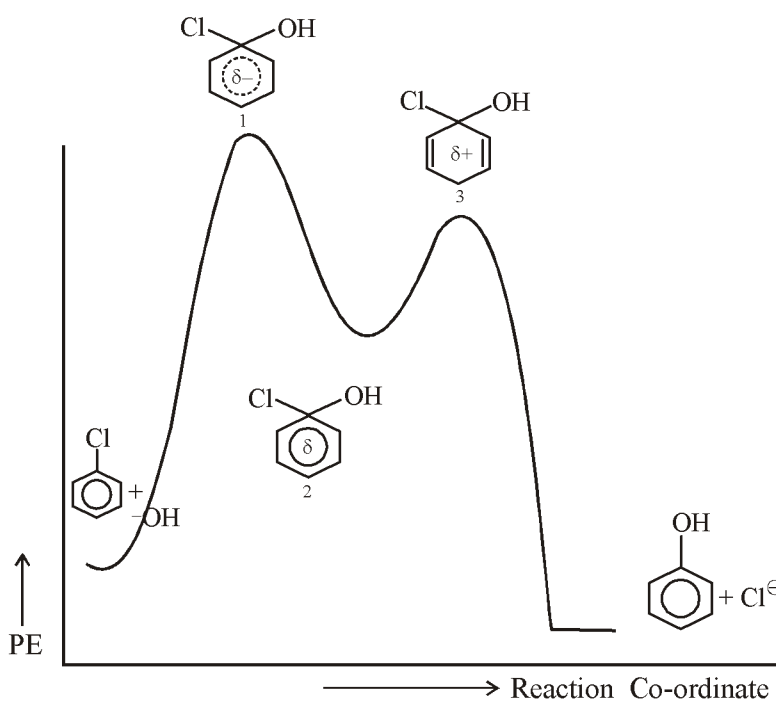


### 2.6.1 Bimolecular mechanism and its evidence

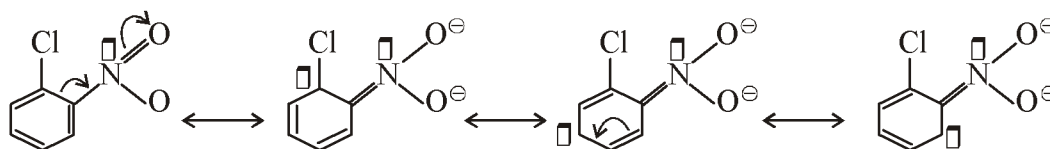
The mechanism was suggested bimolecular like electrophilic aromatic substitution via an intermediate  $\sigma$ -complex the benzenonium carbanion.



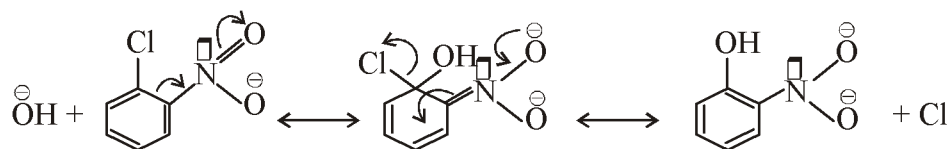
The energy profile is similar that for electrophilic substitution.



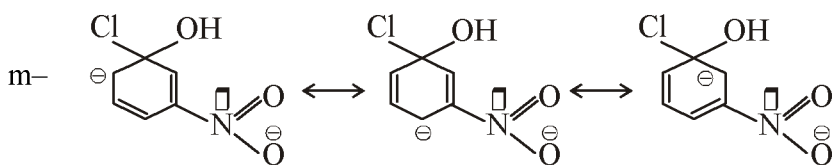
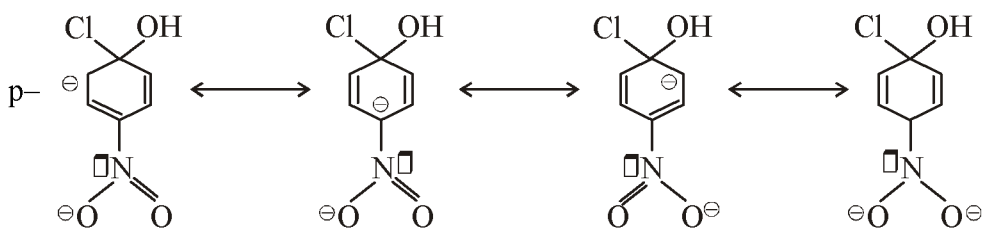
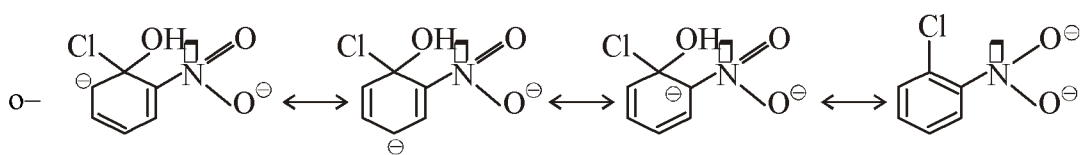
In case of activated nucleophilic substitution considered or the charge distributions. e.g. the carbon of C - Cl or O-chlorobenzene carries a small positive charge.



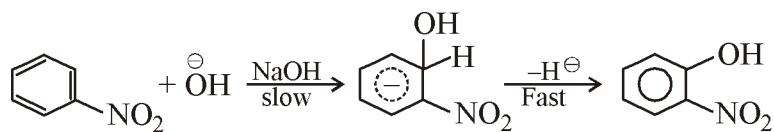
Because of this positive charge nucleophile attacks this carbon.



Now the stability of carbonious are considered for ortho para and meta substitution.



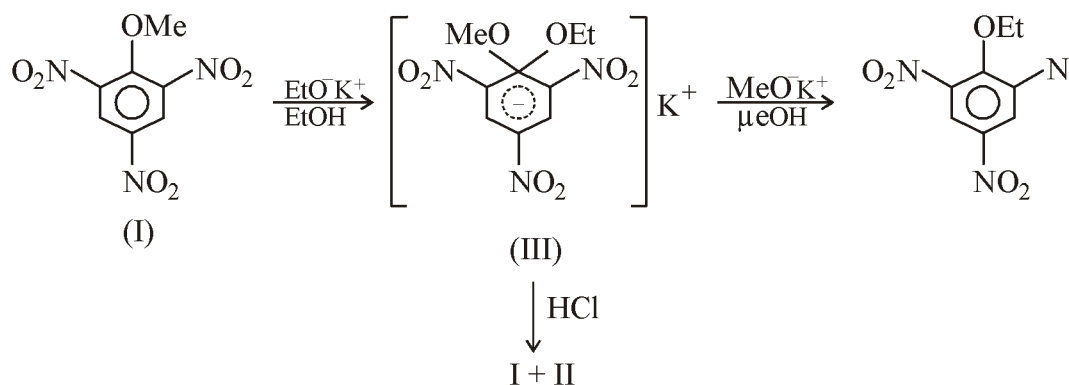
After examination of the canonical forms it is observed that in o- and p- substitutions there are structures where the charge involves extended conjugation upto the electronegative oxygen atom. These are the most stable canonical forms. No such structures are found in m- carbanion. Hence the electron withdrawing groups activate o- and p- substitution, but not m- substitution of hydrogen by a nucleophile in benzene is difficult but occurs in presence of nitro group in o- and p- position e.g.



Removal of H' is more difficult than X<sup>S</sup> or  $\overset{\ominus}{O}\mu e$ . Hence an oxidizing agent is needed. Nitro benzene itself acts as an oxidizing agent.

### Evidence of this mechanism

The intermediate carbonion is isolated for some cases indicating that the reaction follows this mechanism. Thus Meisenheimer (1902) showed that the adduct (III), a Meisenheimer compound (complex, or salt), formed from 2, 4, 6 trinitroanisole (I) and potassium ethoxide is identical with that obtained from 2, 4, 6-trinitrophenetole, (II) an potassium methoxide. The same mixture of (1) and (II) is obtained from each adduct on acidification.



Also IR, UV, and NMR, X-ray analysis support the formation of III.

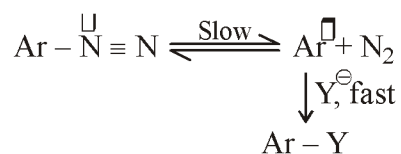
The grp activating o- and p- positions are CN, CoMe,  $\text{SO}_2\text{Me}$ , etc.

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## 2.7 SN<sup>1</sup> Mechanism

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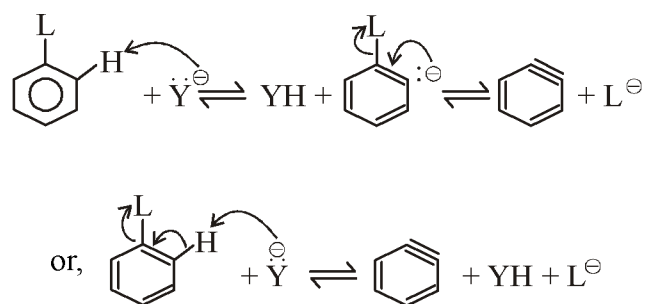
The nucleophilic substitution occurs by SN<sup>1</sup> mode when the leaving group is a strong one. In that case the C – L (L = leaving group) bond gets polarised and the heterolytic cleavage of C – L bond has lower activation energy. So SN<sup>1</sup><sub>AR</sub> reaction occurs. e.g.



But other nucleofuge does not give this type of reaction.

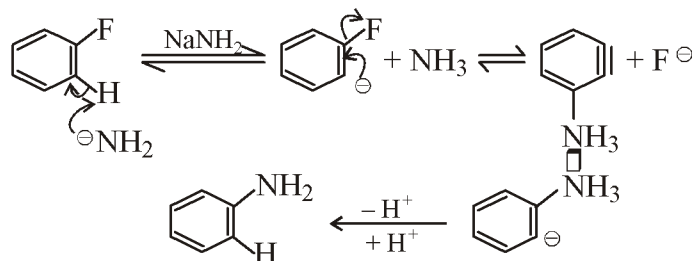
## 2.8 Elimination addition mechanism-cine substitution

If the electron attracting group is absent bimolecular aromatic nucleophilic substitution reaction requires high temp and high P. But the substituent already present in the ring makes the ortho hydrogen acidic by its electron withdrawing  $-I$  effect and the nucleophile acts as a base for its greater charge density. So a parallel path way occurs known as elimination addition reaction. Reaction of this types are called cine substitution.

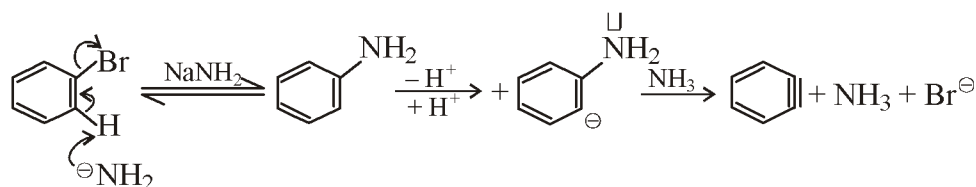


This reaction proceeds through the formation of 1, 2 dehydrobenzene known as benzyne.

If the  $\text{C-L}$  bond is strong the reaction follows stepwise  $\text{E}_1\text{CB}$  type of elimination but if  $-I$  effect of  $\text{L}$  is less and  $\text{C-L}$  bond is weak it follows the concerted  $\text{E}_2$  type elimination e.g. with fluorobenzene the reaction is stepwise with  $\text{NaNH}_2$ .



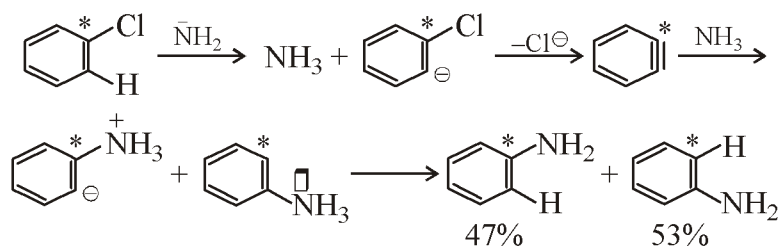
But with Bromo or iodobenzene it is concerted.



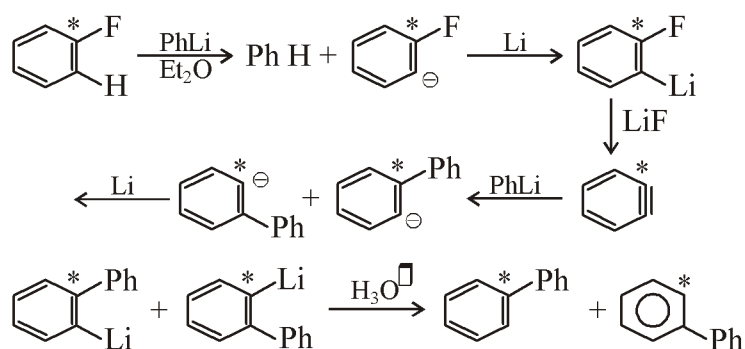
This benzyne undergoes stepwise addition to give the product.

### Evidence for the mechanism

When chlorobenzene labelled with  $^{14}\text{C}$  at the carbon of the C – Cl group is treated with potassium in liq.  $\text{NH}_3$  the amino group  $\text{NH}_2$  enters partly at the labelled carbon atom and partly at the ortho carbon atom.



In the same way when labelled fluorobenzene is treated with phenyl lithium in ether solution followed by acidification at the end of the reaction, the phenyl group enters partly at the labelled carbon atom and partly at the ortho carbon atom.

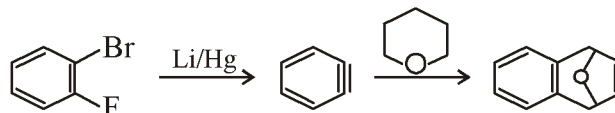


This experiment proves the formation of benzyne intermediate.

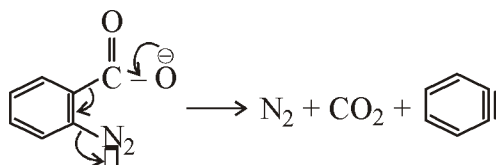
Other experimental work also support this mechanism.

(i) Benzene intermediate has been detected by trapping experiment e.g. in the

presence of furan, o-bromo-o-fluorobenzene reacts with Lithium amalgam to form 1,4-ethoxy-1,4-dihydronaphthalene. This is Diels-Alder reaction and one of the most important and useful reactions of benzyne.



(ii) Benzyne has been detected by flash photolysis and mass spectrometry in the decomposition of benzene diazotium o-carboxylate.



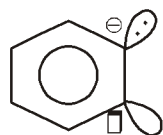
(iii) O-deuterobenzene reacts more slowly than the protium analogue. Thus there is a kinetic isotope effect and therefore the formation of benzyne is the r.d.s.

### 2.8.1 Structure of benzyne

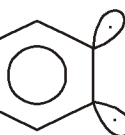
The orbital structure of benzyne is shown below.

The orbitals formed after the removal of H or L are not parallel; instead, they are projected along C-H or C-L bonds. So the sidewise overlap or bonding interaction is negligible, and this  $\pi$  bond is very weak. So it is readily broken and addition occurs.

Benzenes are of two types: singlet or triplet.



Singlet



Triplet

**Problem-11.** Give the mechanism of formations of three isomeric toluidines by the reaction of m-chlorotoluene with  $\text{NaNH}_2$  and  $\text{Liq NH}_3$ .

**Problem-12.** Predict the probable products when m di nitrobenzene is based with caustic soda in the presence of potassium ferricyanide.

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## 2.9 Summary

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- Electrophilic aromatic substitution – Benzene ring being electron rich due to the presence of  $\pi$ -electron cloud above and below the ring is readily attacked by electrophiles (+ vely charged species) and substitutes Hydrogen atom giving substituted benzene derivaties. It is known as electrophilic aromatic substitution.
- Mechanism indicates the formation of  $\pi$ -complex than  $\sigma$ -complex followed by C – H bond breaking giving the product. Formation of  $\sigma$ -complex is the rate determining step.
- The substituent already present in the ring guides the position of the second substituent. If the substituent present in the ring has +I effect the entering group occupies ortho or para position e.g. –OH, –OR, –NH<sub>2</sub>, –CH<sub>3</sub>, –Cl etc. Here the key atom must contain at least one lone pair of electrons. Groups with –I effect are motor orienting e.g. NO<sub>2</sub>, –CF<sub>3</sub>,  $\overset{\ominus}{\text{N}}\text{R}_3$ ,  $\overset{\ominus}{\text{S}}\text{R}_2$ , –COOH, –COR.
- Orientation is decided either by charge distribution or by  $\sigma$ -complex stability.
- The electronic effects of different groups present in the ring directs the third incoming group. The position of the third incoming group is determined by the strength of the group already present.
- Nitration is the most common electrophilic substitution reaction and is carried out by nitrating, mixture conc. HNO<sub>3</sub> and conc. H<sub>2</sub>SO<sub>4</sub>. Nitrosation is carried out by nitrous acid which is formed in situ by NaNO<sub>2</sub> and HCl. Does not show primary kinetic isotope effect.
- Sulphuration is carried out by heating with conc. H<sub>2</sub>SO<sub>4</sub> but it is a everseble reaction and shows primary kinetic isotope effect.
- Chlorimation and bromination occur in presence of halogen carriers FeCl<sub>3</sub> or FeBr<sub>3</sub> or Fe. Iodonation is a reversible reaction and is carried out in



presence of an oxidizing agent e.g.  $\text{HNO}_3$ ,  $\text{H}_2\text{O}_2$  etc. Fluoro compounds are prepared from diazonium salts.

- Friedel-Crafts reaction is used to prepare alkyl benzene and acyl benzene. Alkylation is done with alkyl halides, alcohols or alkenes in presence of a Lewis acid catalyst e.g.  $\text{AlCl}_3$ ,  $\text{BF}_3$ ,  $\text{FeCl}_3$ ,  $\text{ZnCl}_2$  etc in an inert solvent like nitrobenzene or  $\text{CS}_2$ .
- Carbomethylation is a reaction where a one carbon containing electrophile  $-\text{CH}_2\text{Cl}$  enters in benzene ring. The reagent is formaldehyde,  $\text{HCl}$  in presence of  $\text{ZnCl}_2$  catalys.
- Gattermann–Koch and Gattermann reaction are the method of preparation of aromatic aldehydes where  $-\text{CHO}$  group enters in the ring. Gattermann Koch reaction is carried out in presence of  $\text{CO}$  and  $\text{HCl}$  in presence of catalyst. In Gattermann reaction carbon monoxide is replaced by  $\text{HCN}$  and other reagents are same.
- Phenolic Ketones are prepared by Houben Hoesch reaction. Polyhydric phenols are treated with methyl cyanide,  $\text{HCl}$  in presence of  $\text{ZnCl}_2$  catalyst.
- In Vilsmeier Haack reaction activated aromatic compounds can be formulated by  $N$ -methylformamide and phosphoryl chloride followed by treatment with sodium acetate and steam distillation.
- Ortho hydroxy and para hydroxy benzaldehydes are prepared from phenols by Reimer Tiemann reaction with  $\text{CHCl}_3$  and  $\text{NaOH}$ .
- Industrial preparation of salicylic acid is carried out by Kolbe Schindt reaction where sodium phenoxide and  $\text{CO}_2$  are heated at  $120\text{--}140^\circ\text{C}$  with potassium phenoxide the major product is  $p$ -hydroxybenzoic acid.
- If an electrophile replaces an electrofuge other than hydrogen it is called  $\text{I}_p\text{S}_o$  substitution. The groups replaced are  $\text{SO}_3\text{H}$ ,  $\text{COOH}$ ,  $\text{R}$  etc.
- Nucleophilic substitution in aromatic ring requires drastic condition as the  $\pi$ -cloud hinders the attack of nucleophile which is a negatively charged atom or group or neutral molecule with lone pair of electrons.
- When an electron withdrawing group is present  $o$ - or  $p$ - to the leaving

group, nucleophilic substitution is facilitated in aromatic compounds. So it is called activated nucleophilic substitution.

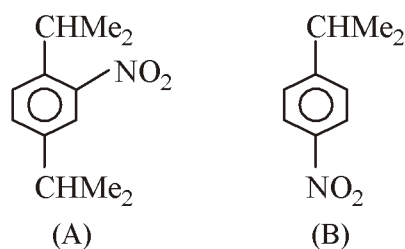
- It occurs generally by a bimolecular mechanism through the formation of an intermediate anion i.e. the  $\sigma$ -complex. The energy profile diagram is similar to that of an electrophilic substitution.
- The effect of the activating group is decided by the negative charge density or by the carbonion stability.
- The isolation of Meisluheimer complex and identification of this salt by UV, IR, NMR and X-ray analysis support the bi-molecular mechanism.
- Where the leaving group is diazo ( $\overset{\ominus}{\text{N}} \equiv \text{N}$ )  $\text{SN}^1$  mode of reaction occurs.
- Elimination addition mechanism or line substitution occurs when no activating group is present in the ring. Here the  $-I$  effect of the leaving group makes O- hydrogen acidic and the nucleophile acts as a base.
- Cine substitution involves the formation of benzyne intermediate. The formation of benzyne is proved by isotope labelling experiment and by trapping experiment.
- Benzyne is not acetylenic in the true sense. Here the second  $\pi$ -bond is formed by the sidewise overlap of two vacant  $\text{Sp}^2$  hybrid orbitals. So the overlap is poor and the  $\pi$ -bond is weak. So benzyne is very reactive species.

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## 2.10 Model Questions

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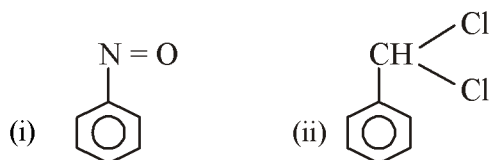
1. Nitration of P- diisopropyl benzene gives two products A and B, the latter being formed in major amount. Explain the observation.



2. Nitration of phenol in dil  $\text{HNO}_3$  turns out to be more efficient in presence of a cut amount of  $\text{NaNO}_2$ . Explain.
3. Nitration of cinnamic acid afford. P-Nitrocinnamic acid. Explain.
4. How would you carry out the following transformation? Give mechanism.



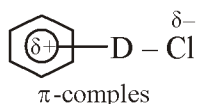
5. Predict the product when the amine (A) is treated with a strong base give the mechanism of the reaction. What experiment do you prepare to carry out to confirm the mechanism.
6. Both O bromoanisole and m-bromoanisole give the same product on treatment with  $\text{KNH}_2/\text{Liq. NH}_3$ . Explain the observation with appropriate mechanism.
7. Predict the favoured position of electrophilic substitution of the following compounds and justify your answer.



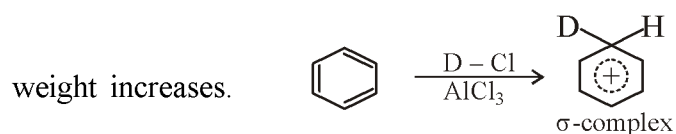
8. What are  $\pi$  and  $\sigma$ -complex in aromatic substitution ?
9. When benzene reacts with neopentyl chloride,  $(\text{CH}_3)_3\text{C CH}_2\text{Cl}$ , in the presence of aluminium chloride, the major product is 2-methyl 2-phenyl butane, not neopcutyl benzene. Explain the result.
10. Predict the major product of the following reactions.
  - (a) Sulfonation of P-methylacetophenone.
  - (b) Nitration of m - dichlorobenzene
  - (c) Nitration of 1, 3-dimethoxybenze
  - (d) Nitration of D- $\text{HO}_3\text{SC}_6\text{H}_4\text{OH}$ .

### Answers

**Problem-1.** The complex formed first is the  $\pi$ -complex. Hence it decomposes to  $C_6H_6$  and  $DCl$ .



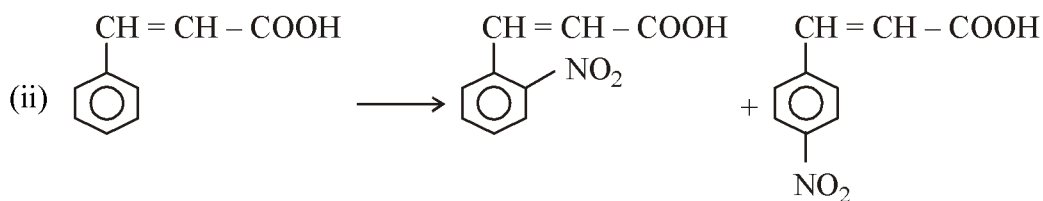
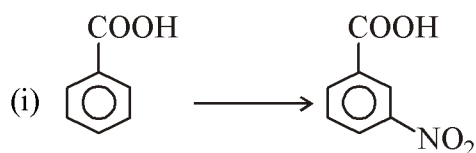
But in presence of  $AlCl_3$  at ordinary temp.  $C_6H_6$  forms  $\sigma$ -complex. So molecular



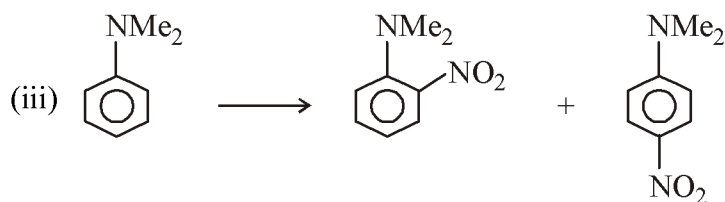
**Problem-2.** Phenol > Toluene > Fluoro benzene > Chlorobenzene.

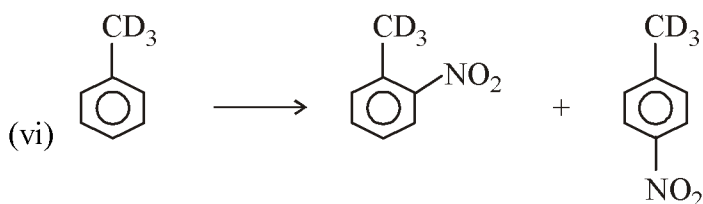
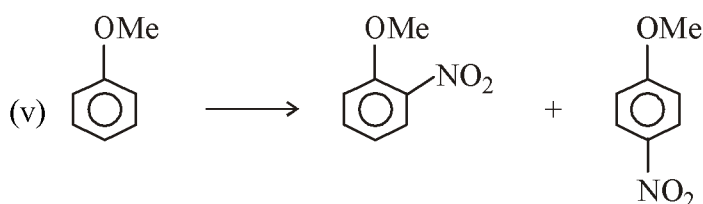
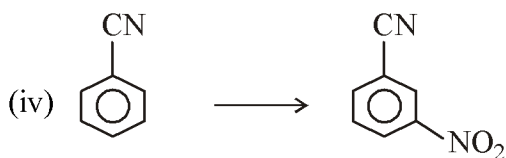
In all the compounds the products are O-, P- substituted product. Fluorobenzene has greater rate than chlorobenzene as far smaller size of fluorine and 2-p orbital of F overlaps with 2P orbital. So its back donation is greater than chlorine. Hence the rate increases.

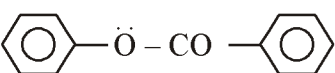
**Problem-3.**

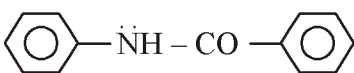


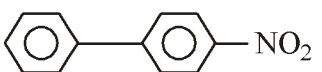
See Text for Major reason

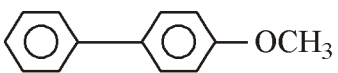


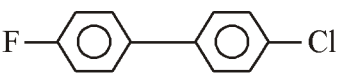


**Problem-4.**  The ring attached to oxygen will undergo faster reaction as the lone pair of oxygen activates the ring.

 Here also the ring attached to NH group is activated by the lone pair of nitrogen. So undergoes faster reaction.

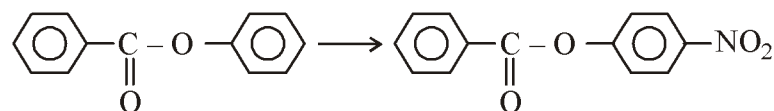
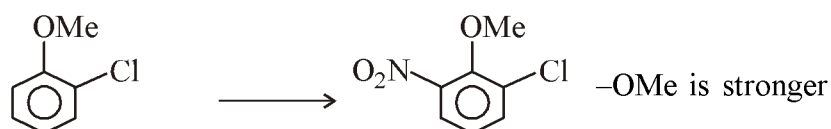
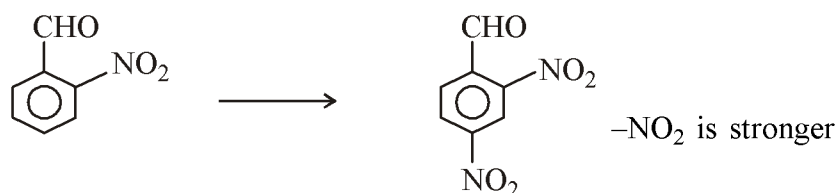
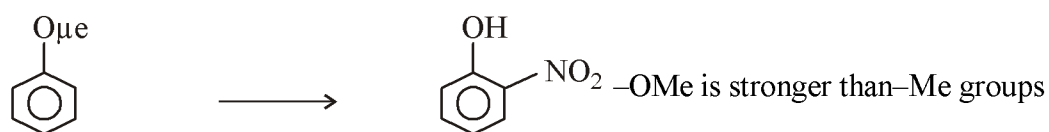
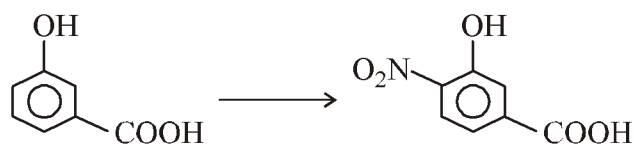
 Nitro group deactivates the ring by electron withdrawing effect. So the former ring will undergo faster reaction.

 The ring attached to  $-OCH_3$  group will undergo faster reaction as  $OCH_3$  activates like ring by +R effect.

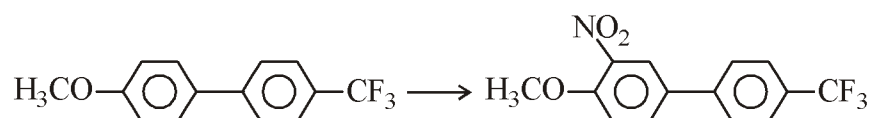
 The ring attached to F undergoes faster reaction as the back donation or +R effect of F is greater than that of Cl as the lone pair of F is 2P orbital. So the overlap of F - 2P and 1 - 2P takes place much more readily.

**Problem-5.**

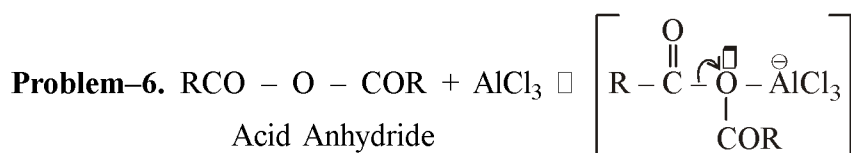
-OH gr will direct

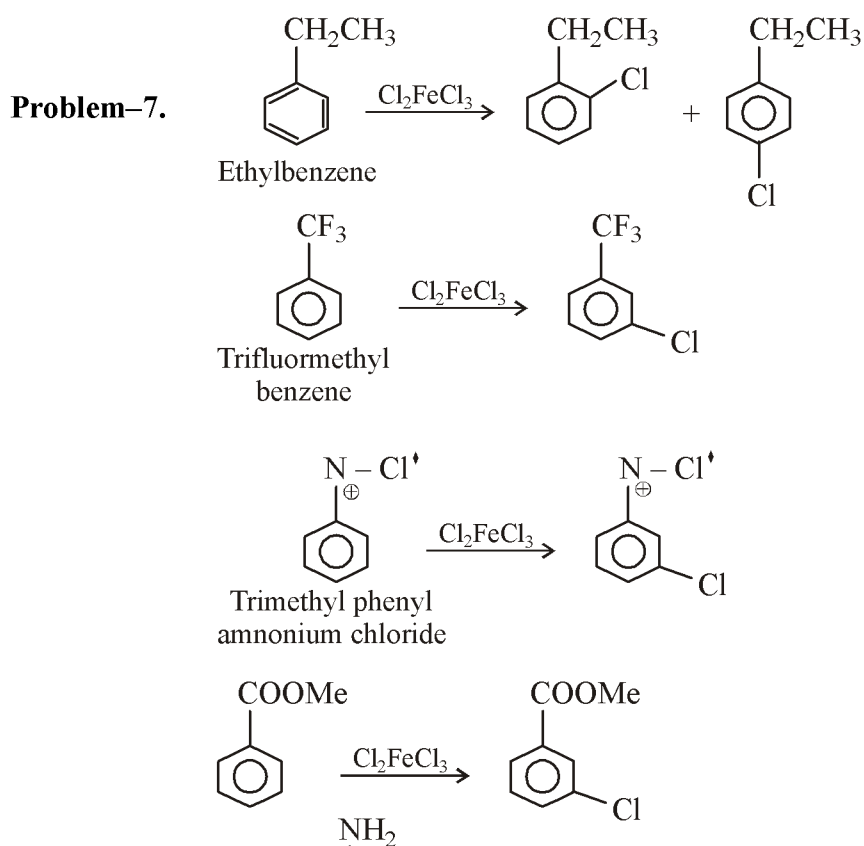
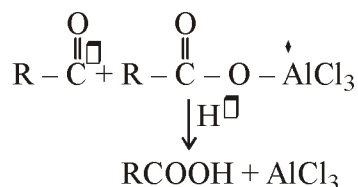



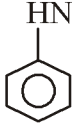
the lone pair of oxygen activates the ring.

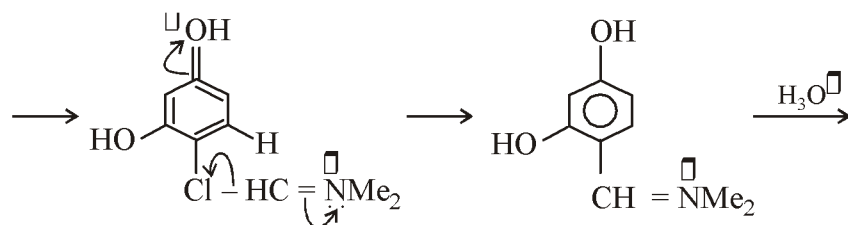
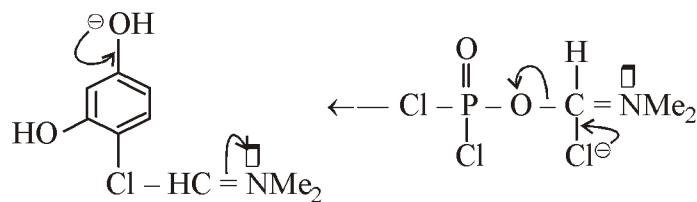
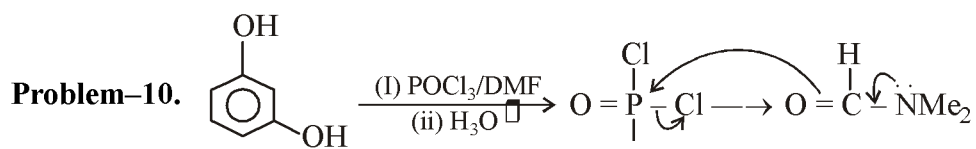
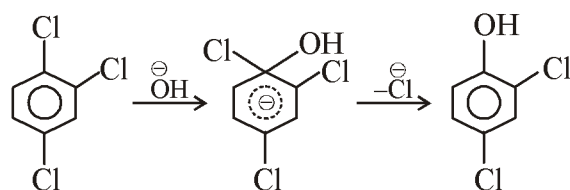
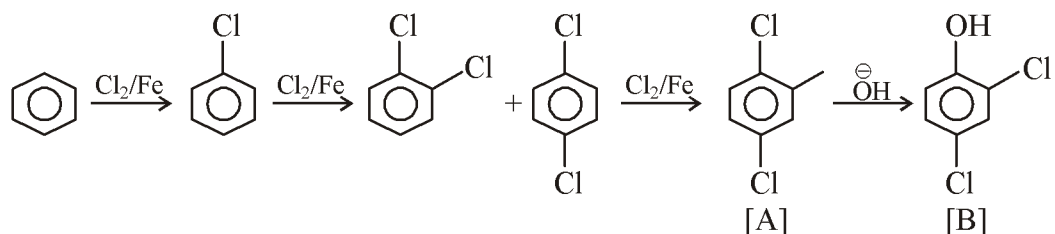


-OCH<sub>3</sub> is more powerful O- P- orienting grp than -CF<sub>3</sub> which is electron withdrawing.

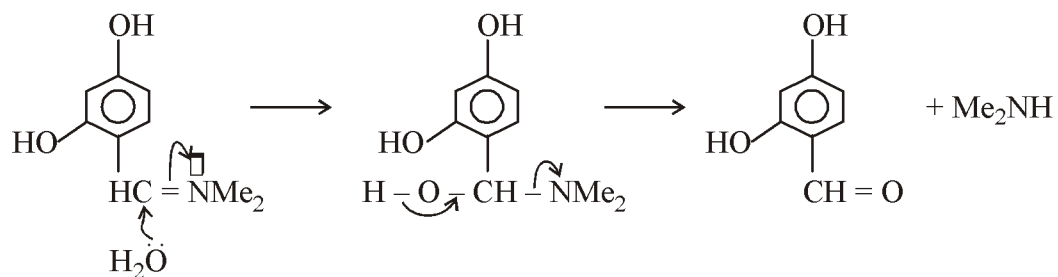
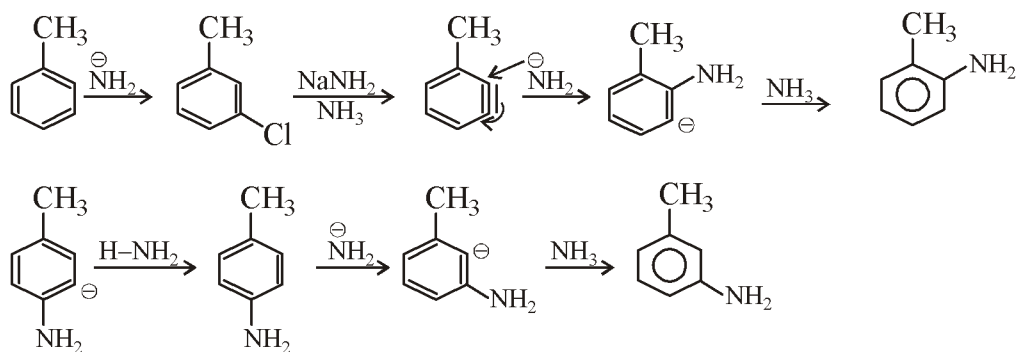




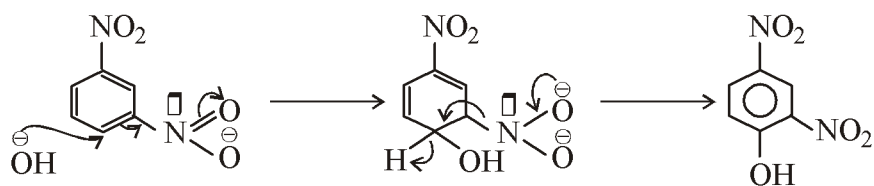
**Problem-8.** In Aniline  the lone pair on nitrogen atom is totally involved in activating the benzene ring by +R effect. But in acetanilide  the lone pair of Nitrogen atom is drawn by the electron withdrawing carbonyl group and partly involved in activating aromatic ring. So the rate of electrophilic substitution is less for acetanilide than aniline.

**Problem-9.**

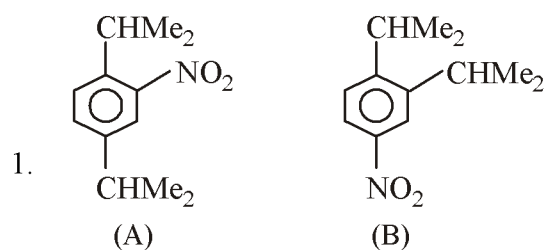


**Problem-11.**

Thus the three isomeric toluidines o-, m- and p- are formed.

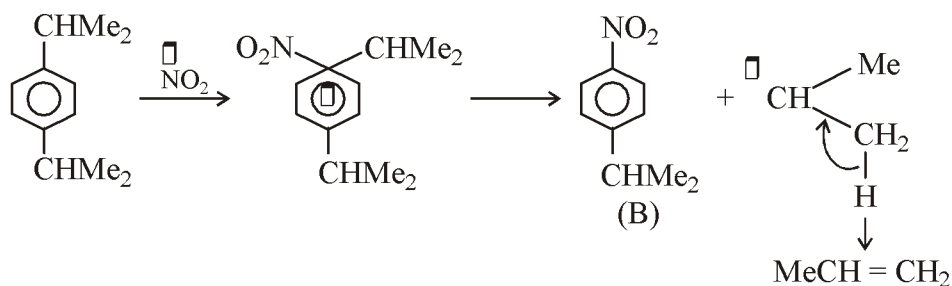
**Problem-12.**

Here potassium ferricyanide acts as the oxidizing agent.

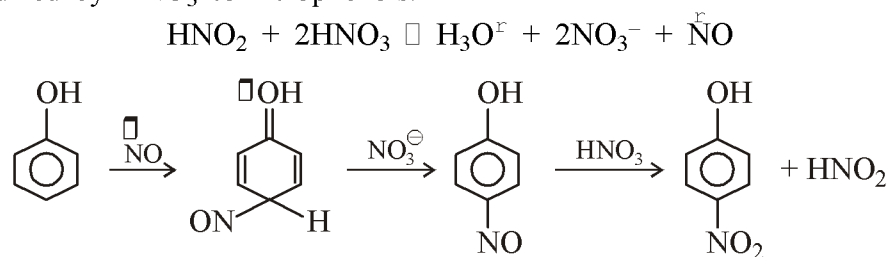
**Answer of Model Questions**

(A) is formed by normal nitration of diisopropyl benzene as  $-\text{CHMe}_2$  group is O-, P- orienting. As P-position is blocked the substitution occurs at ortho.

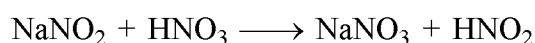
(B) is formed by IPSO substitution



2. Nitration of phenol in dil.  $\text{HNO}_3$  gives first o and p nitrosophenols by nitrosation with little amount of  $\text{HNO}_2$  present in Nitric acid. These nitrosophenols are oxidized by  $\text{HNO}_3$  to nitrophenols.

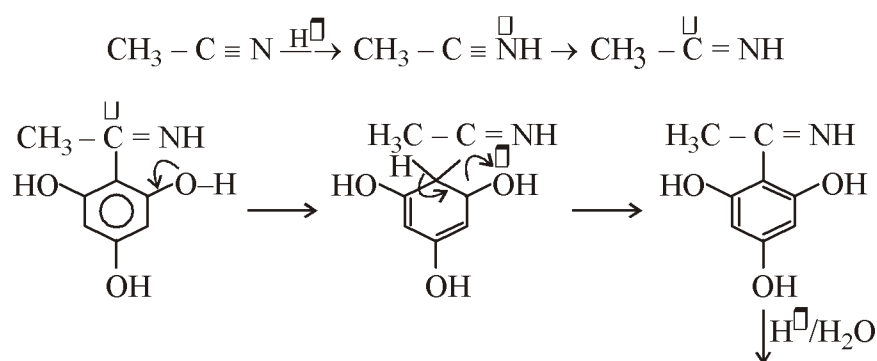


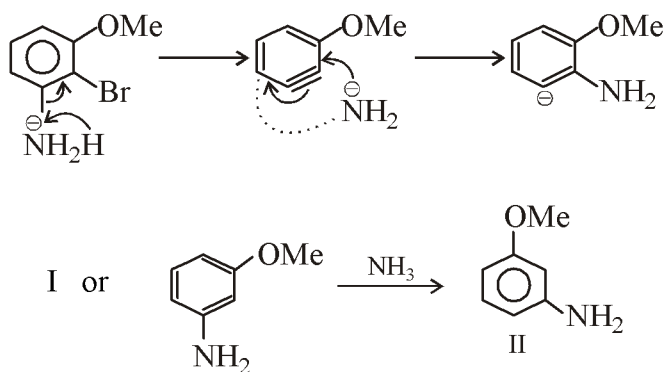
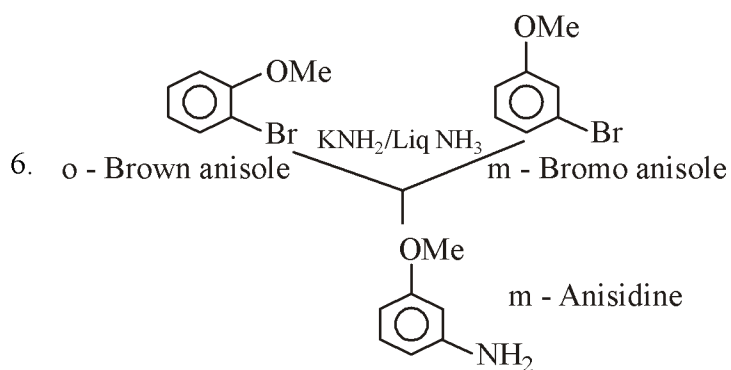
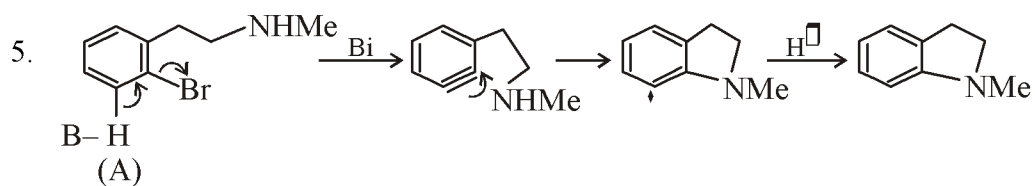
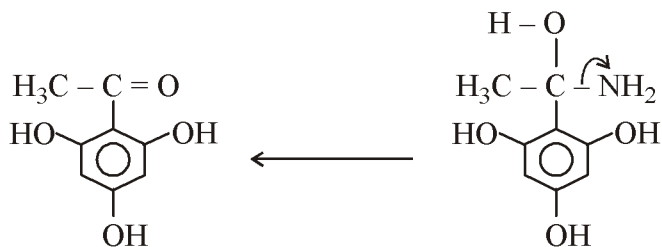
Now if small amount of  $\text{NaNO}_2$  is added initially  $\text{HNO}_2$  will be produced and the reaction will be accelerated for greater concentration of  $\overset{\cdot}{\text{N}}\text{O}$ .



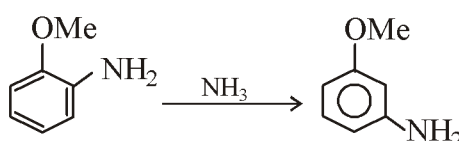
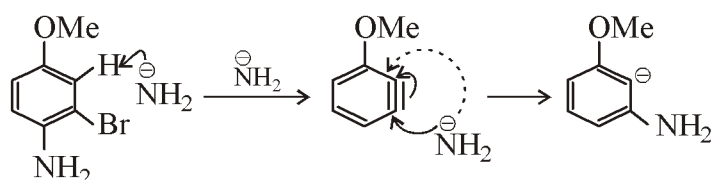
3. See text.

4. This is Honben-Hoesch reaction.

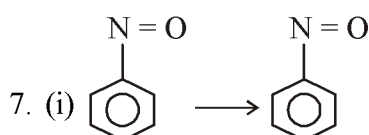




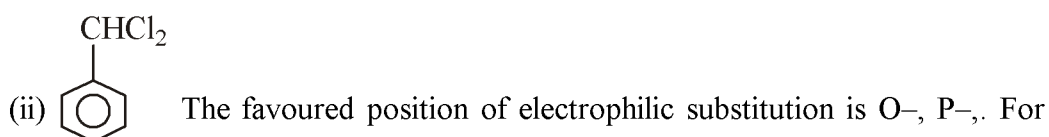
The  $-I$  effect of the OMe group stabilises the carbanion II. Hence the product is *m*-anisidine.



Here also the anion II is stable. Hence on protonation the product is m-anisidine. So both o and m Bromoanisole give the same product m-anisidine.

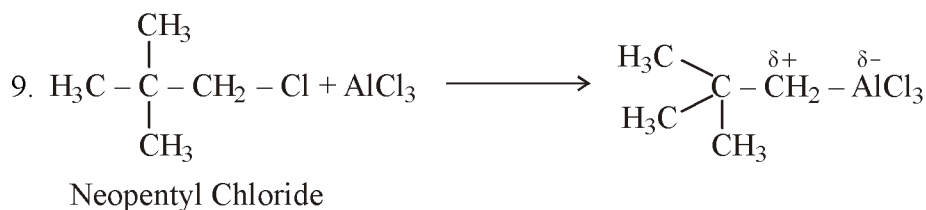


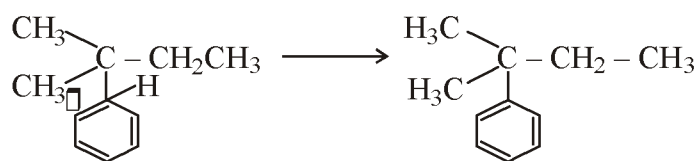
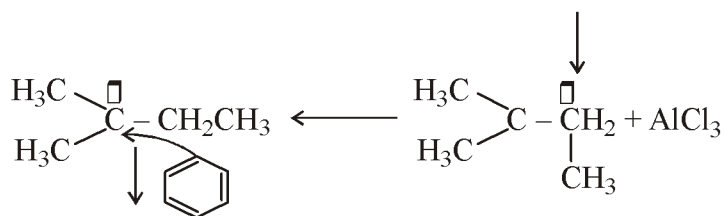
The favoured position of electrophilic substitution is meta as  $\text{N}=\text{O}$  is an electron withdrawing group and makes o- and p- positions electron deficient. Hence m- position is comparatively electron rich easily electrophilic substitution at m- position.



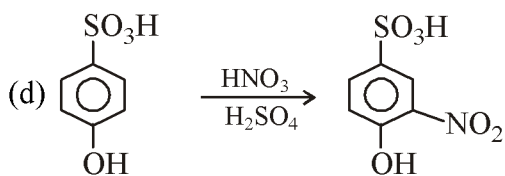
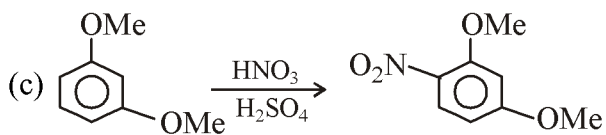
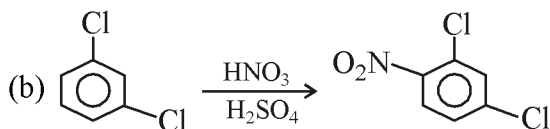
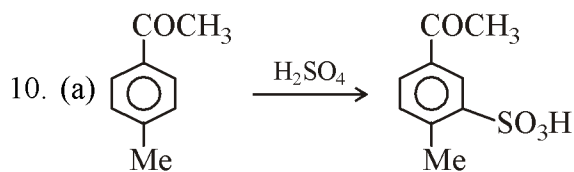
hyperconjugation of  $-\text{CHCl}_2$  grp the O-, and P- positions are electron rich. Hence electrophilic substitution occurs at O- and P- positions. Again P- is favoured position as no steric interaction occurs.

8. See Text.





2-Methyl-2- Phenylebutane



**Reference**

1. Organic Chemistry Vol. 1. by IL Finar
2. Organic Chemistry by T. W. Graham Solomons.
3. Organic Chemistry by Morison Boyd.
4. A guide of Mechanism in Organic Chemistry by Peter Sykes.

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## **Unit - 3 □ Carbonyl and Related Compounds**

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### **Structure**

#### **3.1 Objective**

#### **3.2 Introduction**

#### **3.3 Carbonyl Compounds**

##### **3.3.1 Structures of Carbonyl Groups**

##### **3.3.2 Physical properties of Carbonyl Compounds**

##### **3.3.3 Reactivity of Carbonyl Compounds**

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#### **3.6.2 Cannizzaro Reaction**

#### **3.6.3 Tishchenko Reaction**

#### **3.6.4 Wittig Reaction**

#### **3.6.5 Corey-Chaykovsky Reaction**

#### **3.6.6 Rupe Rearrangement**

#### **3.6.7 Clemmensen Reduction**

#### **3.6.8 Wolff-Kishner Reduction**

#### **3.6.9 Reduction of LiAlH<sub>4</sub>**

#### **3.6.10 Reduction by NaBH<sub>4</sub>**

#### **3.6.11 Meerwin-Ponndorf-Verley (MPV) Reduction**

#### **3.6.12 Opener Oxidation**

#### **3.6.13 Bouveault-Blanc reduction**

#### **3.6.14 Acyloin Condensation**

### **3.7 Exploitation of acidity of $\alpha$ -H of C = O**

#### **3.7.1 Acidities of Hydrogens on the $\alpha$ -Carbon of Carbonyl Compounds**

#### **3.7.2 Kinetic vs. Thermodynamic Enolates**

#### **3.7.3 $\alpha$ -Halogenation of Carbonyl Compounds**

#### **3.7.4 Haloform Reaction**

#### **3.7.5 Hell Volhard Zelinsky (H.V.Z.) Reaction**

#### **3.7.6 SeO<sub>2</sub> Oxidation**

#### **3.7.7 Aldol Condensation Reaction**

#### **3.7.8 Claisen Schmidt Reaction**

#### **3.7.9 Knoevenagel Condensation**



- 3.7.10 Dieckmann Condensation**
- 3.7.11 Mannich Reaction**
- 3.7.12 Perkin Reaction**
- 3.7.13 Favorskii Rearrangement**
- 3.7.14 Knoevenagel Condensation**
- 3.7.15 Claisen Condensation**
- 3.7.16 Michael Reaction**
- 3.8 Green Chemistry**
  - 3.8.1 The Need of Green Chemistry**
  - 3.8.2 Twelve Principle of Green Chemistry**
  - 3.8.3 Green Reactions**
    - 3.8.3.1 Aldol Condensation**
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- 3.9 Ester Hydrolysis**
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  - 3.9.3 A<sub>AC</sub>1 Mechanism**
  - 3.9.4 B<sub>AL</sub>1 Mechanism**
  - 3.9.5 A<sub>AL</sub>1 Mechanism**
- 3.10 Summary**
- 3.11 Additional Problems in Carbonyl Chemistry**
- 3.12 Reference Books**

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### 3.1 Objective

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After going through this Unit a learner will be able to :

- recognize the general structures of different carbonyl base functionally such as carboxylic acids, acyl halides, acid anhydrides, esters, amides, and nitriles, and be able to assign names of simple members of these compound families.
- identify and write the general mechanism for nucleophilic substitution reaction to the different carbonyl compounds like ketone, aldehyde, ester, amide, acyl halides, and esters by the proper name reactions. The learner will enable themselves to judge the relative reactivity of carbonyl compounds in this study.
- identify and write the mechanism for the acid and base catalysed condensation reaction of a carbonyl group.
- know the 3R (reduce, reused, recycle) principal in green chemistry in any chemical reaction.
- identify and write the mechanism for the acid-catalyzed hydrolysis of an ester.
- face unknown problem involving and synthetic transformation.

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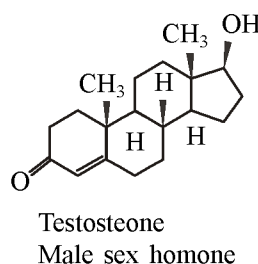
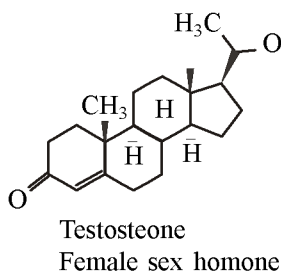
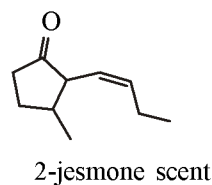
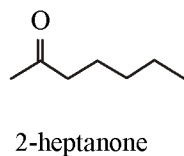
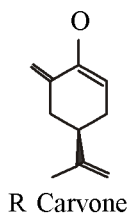
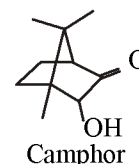
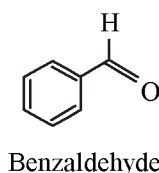
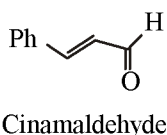
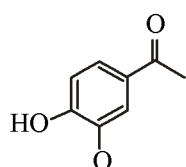
### 3.2 Introduction

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Chemistry is the centre of science among all branches of scientific study. Organic chemistry is the key area of drug discovery in human civilization. Aldehydes and ketones are the backbone of organic chemistry. Since most of naturally occurring substrate contain an aldehyde or ketone functional group they are shown in the following figures.

For example, carvone is found as its levorotatory (R)-enantiomer is spearmint oil, whereas, caraway seed contain the dextrorotatory (S)-enantiomer. In this case the change of the stereochemistry causes a drastic change in the perceived scent.

Aldehydes and ketones are known for their sweet and sometimes pungent odors. The odor from vanilla extract comes from the molecule vanillin. Likewise, benzaldehyde provides a strong scent of almonds. Because of their pleasant fragrances aldehyde and ketone containing molecules are often found in perfumes. However, not all of the fragrances are pleasing. In particular, 2-Heptanone provides part of the sharp scent from blue cheeses and (R)-Muscone is part of the musky smell from the Himalayan musk deer. Lastly, ketones show up in many important hormones such as progesterone (a female sex hormone) and testosterone (a male sex hormone). Notice how subtle differences in structure can cause drastic changes in biological activity. The ketone functionality also shows up in the anti-inflammatory steroid, Cortisone.




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### 3.3 Carbonyl Compounds

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Carbonyl Compounds are the organic compounds containing carbon-oxygen double bond ( $\text{>C=O}$ ).  $\text{>C=O}$  is the most important functional group of organic chemistry. Carbonyl compounds in which carbonyl group is bonded to a carbon and

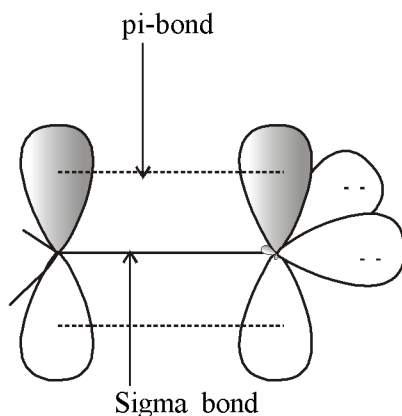
hydrogen are known as aldehydes. Carbonyl compounds in which carbonyl group is bonded to carbon atoms are known as ketons.

Carbonyl group ( $C = O$ ) has following property :

1. The group has planer geometry.
2. It is a polar group and can function as an acid as well as a base
3. Depending on the nature of carbonyl compound, it can behave as enantiotopic face or diastereotopic.
4. Carbonyl compounds with  $\alpha$ -H atoms exhibit kinetic acidity to generate stable carbanion in presence of strong base.

### 3.3.1 Structures of Carbonyl groups

One of the double between carbon and oxygen in  $C = O$  group is a stable sigma bond (sigma bond formed by developing between  $sp^2$  hybridise orbital of carbon and  $sp^2$  hybridised orbital of oxygen. The other bond is a weak pi bond ( $\pi$ -bond) formed by the overlapping of 2p orbitals on carbon and oxygen. Since both the carbon and oxygen atom of group are  $sp^2$  hybridised. The structure of  $C = O$  group if planner.

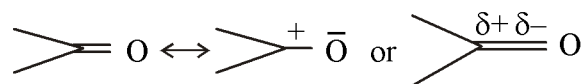


Structure of carbonyl group

Fig-9

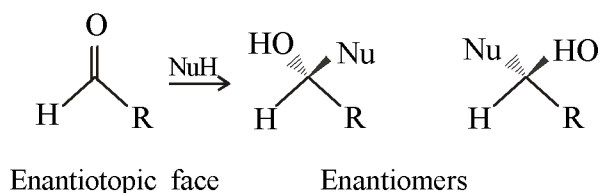
Oxygen is more electronegative than carbon and that is why bonded electron pairs are always near to the oxygen atom. This makes the  $C = O$  group to assume polar character. This is why the dipole moment of  $C = O$  group is found to be high

(2.3-2.8D). The actual structure of carbonyl group is considered to be a resonance hybrid.



It is to be noted that in C = O group carbon atom is always electron deficient centre and therefore undergoes ready nucleophilic attack. In these reactions carbonyl carbon of C = O accepts a pair of electrons from the nucleophile to form a covalent bond. In this respect C = O group behaves as an acid (electron acceptor). On the other hand, lone pair of electrons on oxygen atom of C = O group can accept a cation like H<sup>+</sup> acidic medium. In this case carbonyl group functions as a base (electron donor).

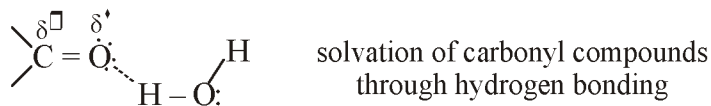
Carbonyl group in aldehydes and unsymmetrical ketones are enantiotopic and undergoes nucleophilic addition reaction to form equimolecular amounts of enantiomers. Carbonyl group of symmetrical ketone is not enantiotopic.



### 3.3.2 Physical properties of carbonyl compounds

The polarity of the carbonyl group is manifest in the physical properties of carbonyl compounds. Boiling points for the lower members of a series of aldehydes and ketones are 50-80° C higher than for hydrocarbons of the same molecular weight. The boiling point increases with increasing number of carbon atom. This is because there are more electrons, hence more temporary dipoles can be set up. More energy is required to overcome these forces. Methanal and ethanal are gases at room temperature, while others are liquids.

Carbonyl compounds are soluble in water molecules. This is because they are able to form hydrogen bond with water molecules. The solubility decreases with increasing number of carbon atoms. This is because the long hydrocarbon chain disrupts the hydrogen bonding.



### 3.3.3 Reactivity of carbonyl compounds

The reactivity of the carbonyl bond is primarily due to the difference in electronegativity between carbon and oxygen, which leads to a considerable contribution of the dipolar resonance form with oxygen negative and carbon positive. The polarity of the carbonyl bond facilitates addition of nucleophile, water and other polar reagents relative to addition of the same reagents to alkene double bonds. The polar C = O group also activates neighboring atoms for other types of chemical reactions. Of particular importance is its role in causing -OH protons of carboxylic acids, as well as the  $\alpha$ -C-H protons of aldehydes, ketones, and other carbonyl compounds, to be acidic.

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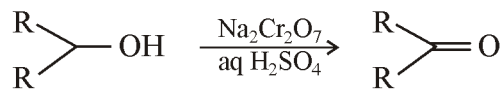
## 3.4 Preparation of carbonyl compounds

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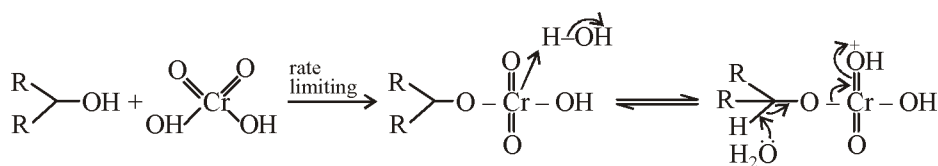
There are so many methods for the Preparation of carbonyl compounds. We will discuss about few methods among them.

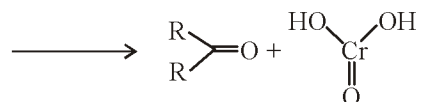
### 3.4.1 Oxidation of Alcohols

Carbonyl compounds may be prepared by the oxidation of alcohols in the presence of acid dichromate. The reaction probably proceeds via the rate limiting formation of a chromate ester followed by decomposition of the ester to give the products.

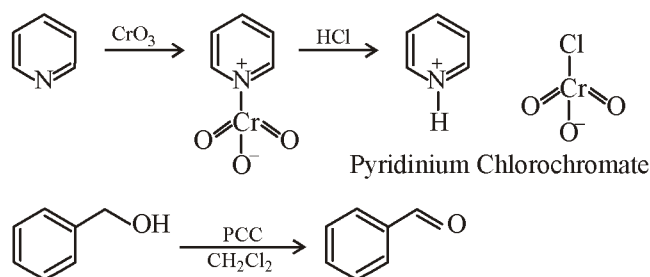


Mechanism :



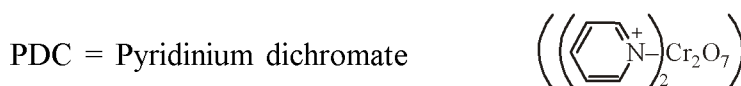
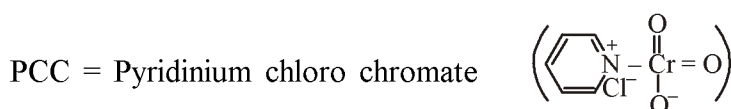


In case of primary alcohol, this process may lead to oxidation of the alcohol to carboxylic acid. This problem is overcome by attenuating the oxidizing power of chromic acid based reagents to generate a milder oxidizing agent. The two most popular oxidizing agents for oxidizing primary alcohols to aldehydes are **pyridinium chlorochromate** (PCC) and **pyridinium dichromate** (PDC). These reagents are prepared by the treatment of chromic acid with pyridine. Chromic acid does not used for the oxidation tertiary alcohol to aldehyde.



Q. What is PDC?

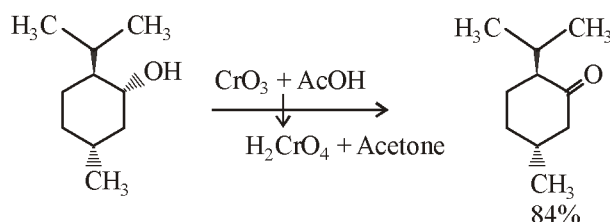
This is the modified oxidising agent for oxidation of alcohol to ketone for better yield. Pyridinium dichromate, PDC can be obtained by gradual addition of a solution of chromic anhydride (CrO<sub>3</sub>) in water to pyridine in ice cold conditions. For the conversion of alcohol to ketone Collins reagent is needed as excess amount. But in PDC and PCC method equivalent amount of reagent is used.



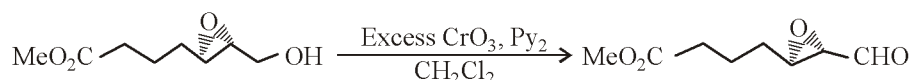
**Advantage of PDC :**

1. Yield of oxidation product is very high
2. No oxidation product will be obtain
3. Equivalent amount of reagent for the oxidation.

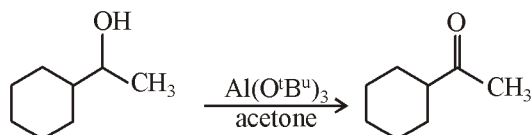
**Jones Reagent :** Jones reagent is a solution prepared by dissolving chromium trioxide in aqueous sulfuric acid or acetic acid. To effect a Jones oxidation, this acidic mixture is then added to an acetone solution of the substrate. Jones reagent is strong and oxidizes primary alcohol to carboxylic acids.



**Collins Reagent :** Collins reagent is the complex of chromium (VI) oxide with pyridine in dichloromethane. This metal-pyridine complex, a red solid, is used to oxidize primary alcohols to the aldehyde.



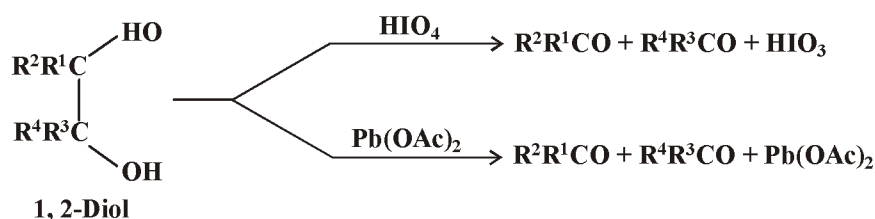
The ketones may also be generated from the secondary alcohols using aluminium t-butoxide in the presence of acetone. The secondary alcohol is refluxed with the reagent in an excess of acetone. This reagent is particularly helpful in oxidation of unsaturated alcohol as only the alcoholic OH is oxidized.

**Oxidation of 1, 2-diols :**

The vicinal glycols prepared by alkene hydroxylation (reaction with osmium tetroxide or permanganate) are cleaved to aldehydes and ketones in high yield by the

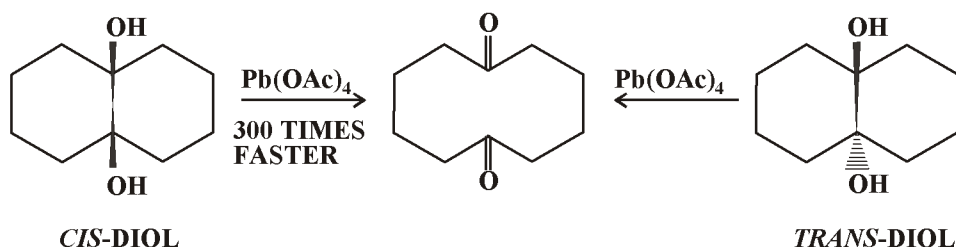


action of lead tetraacetate  $[\text{Pb}(\text{OAc})_4]$  or periodic acid  $[\text{HIO}_4]$ . This oxidative cleavage of a carbon-carbon single bond provides a two-step, high-yield alternative to ozonolysis, that is often preferred for small scale work involving precious compounds. As a rule, glycols react more rapidly than trans-glycols, and there is evidence for the intermediacy of heterocyclic intermediates, although their formation is not necessary for reaction to occur.

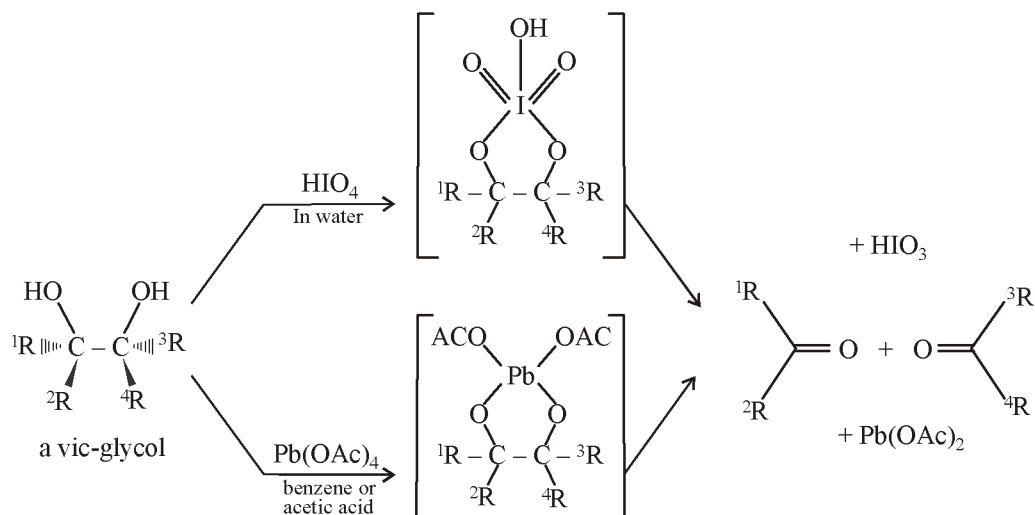


#### Characteristics :

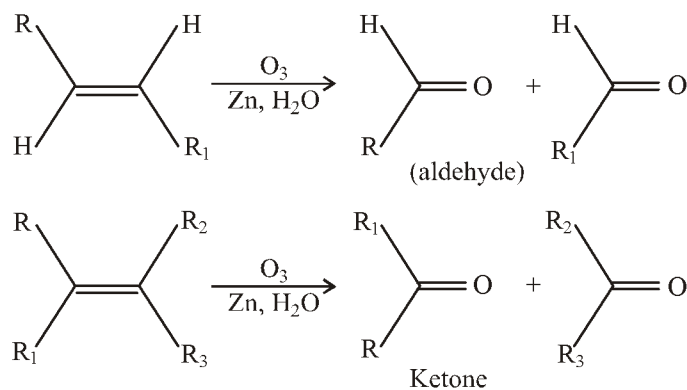
- Oxidation of 1, 2-glycols occurs more rapidly with syn-diol than with the corresponding anti-isomers and this fact indicates the formation of cyclic intermediates.



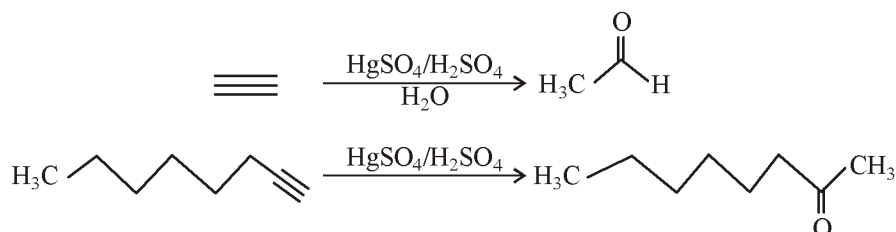
- The fact that anti-isomers are oxidized suggest that the reaction proceeds through a non-cyclic intermediate for these compounds. This could be the non-cyclic ester formed in the first step.
- These oxidations are also subject to steric hindrance, e.g., glycol is oxidised much faster than pinacol by periodic acid.
- The alcohol reacts to form a cyclic intermediate. The intermediate then undergoes a rearrangement of the electrons, cleaving the C – C bond and forming two C = O bonds.

**Mechanism :****3.4.2 Oxidative Cleavage of Alkene :**

Both aldehydes and ketones may be formed by ozonolysis of suitable alkene. The ozonolysis of alkenes of the type  $RCH = CHR_1$  leads to the formation of aldehydes while the tetrasubstituted alkenes will give ketones as product.

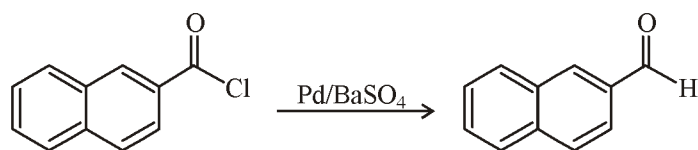
**3.4.3 Hydration of Alkynes :**

The hydration of alkynes by the mercuration-demercuration procedure can be utilized to prepare acetaldehyde and ketones. The hydration of acetylene gives acetaldehyde while the hydration of any other alkyne leads to formation of ketones.



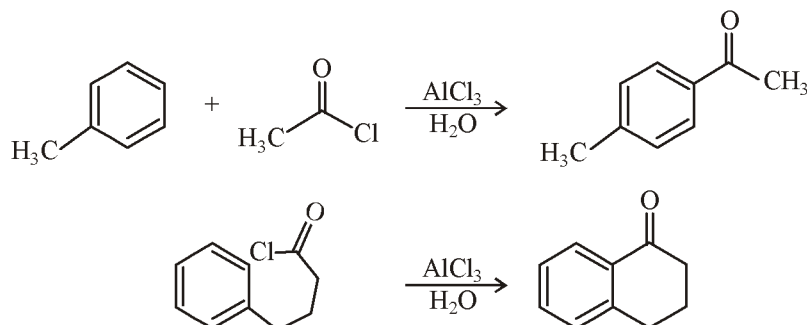
### 3.4.4 Rosenmund reduction :

Aldehydes can be prepared by the reduction of acid chloride with hydrogen in xylene using a palladium catalyst suspended on barium sulphate is called Rosenmund reduction. This process demonstrates the control of chemoselectivity by poisoning of the catalyst. The role of barium sulphate is to prevent the reaction from proceeding further to alcohol.



### 3.4.5 Acylation of Arenes :

Friedel Craft acylation may be used to prepare alkyl aryl ketones or diaryl ketones. In this process, an arene is usually treated with an acid halide or acid anhydride in the presence of a Lewis acid catalyst. This reaction is an example of aromatic electrophilic substitution.



## 3.5 Addition to carbonyl (C = O) compounds

Since the carbonyl group is extremely polar across the carbon-oxygen double bond, this makes it susceptible to addition reactions like the ones that occur in the pi bond of alkenes, especially by nucleophilic electrophilic attack. There are so many examples of addition to carbonyl (C = O) group of carbonyl compounds. We will discuss about few among them.

### 3.5.1 Bürgi-Dunitz Trajectory for the nucleophile attack on aldehyde and ketone

HOMO-LUMO interaction is the main key step for the attack of nucleophiles on carbonyl carbon. Not only nucleophile always attack carbonyl group at but they always approach from a perpendicular angle. The nucleophile attack not from a direction perpendicular to the plane of the carbonyl group but at about  $107^\circ$  to the C = O bond. This approach route is known as **Bürgi-Dunitz Trajectory**. The angle of attack by nucleophile as a result of a compromise between maximum orbital overlap of HOMO with the LUMI of C = O  $\pi^*$  and minimum repulsion of HOMO, by electron density in the carbonyl carbon.

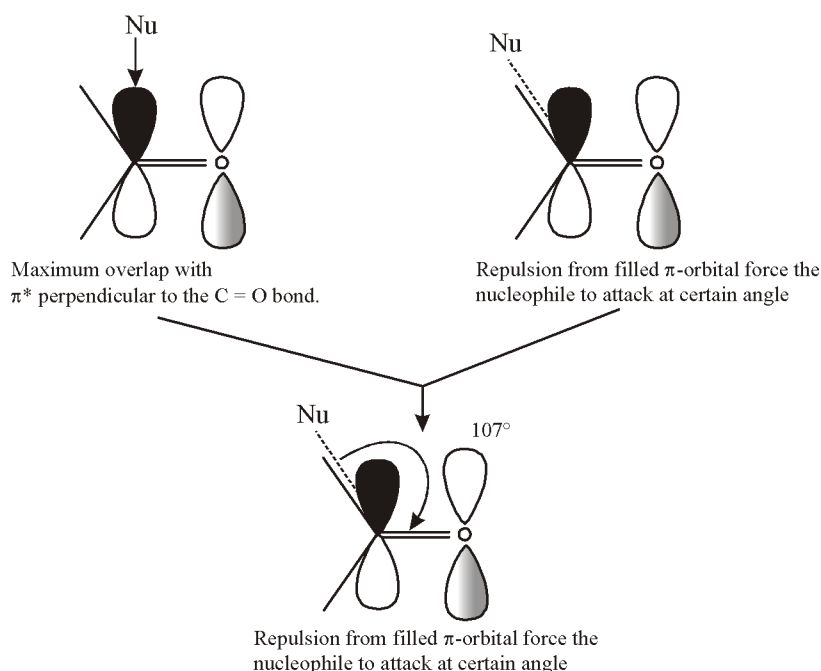
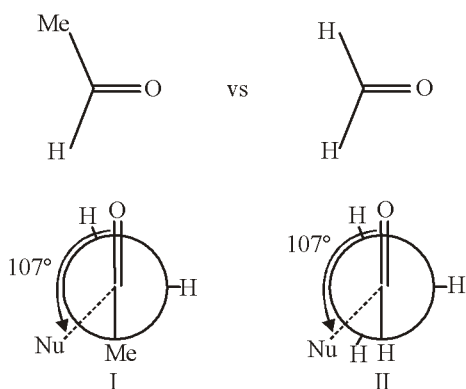


Fig-10

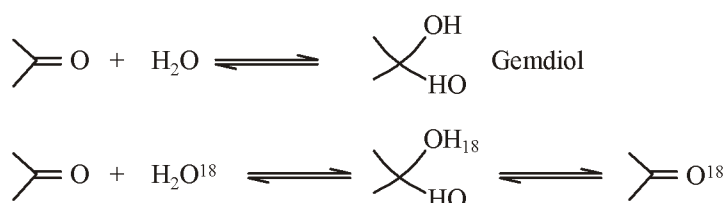


In case of one I during attack of nucleophile at the carbonyl carbon steric interaction take place due to the presence of ‘-CH<sub>3</sub>’ group. So attack of nucleophile is less favorable. But in case of II such type of interaction does not take place and hence attack of nucleophile is more favourable.

Burgi Dantiz Trajectory is greatly reducing the rate of addition of nucleophile to the carbonyl carbon. This trajectory produces steric hindrance with the incoming nucleophile and substituent of carbonyl group. In case of aldehyde, the addition reaction is less bulky than acetone. Therefore, acetaldehyde is more reactive than acetone.

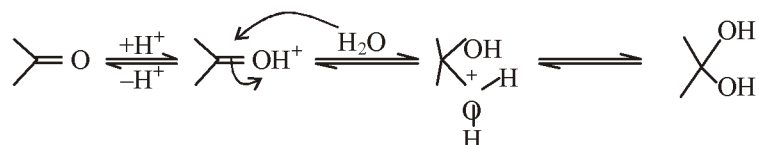
### 3.5.2 Hydration of carbonyl compounds

Gemdiol is formed by the reaction with carbonyl compound and water. This is very unstable intermediate and readily eliminates water to give carbonyl compound. This reaction can be understood by using H<sub>2</sub>O<sup>18</sup> isotope. After sometime, we get the carbonyl compound containing O<sup>18</sup> isotope. This indicates that there has equilibrium between gemdiol and carbonyl compound.

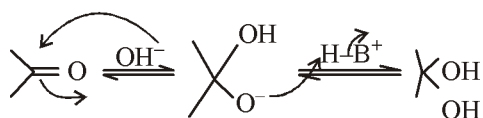


Gamdiol can be prepared by using acid catalyst. The mechanism is shown below.

- Acid catalyst hydration :

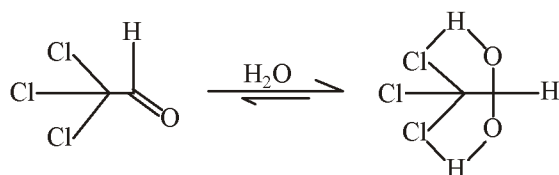


- Base catalyst hydration :

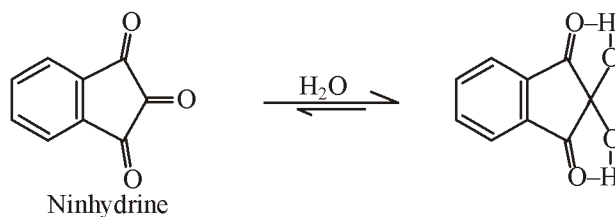


**Q.1. “Chloral is very unstable in ketone form, it readily undergoes to gemdiol under treatment of water”—Explain.**

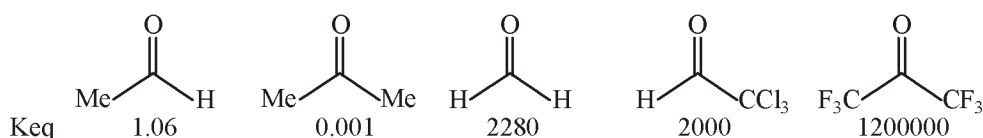
**Ans.** Chloral is very unstable in ketone form due to the +ve charge on carbon atom of carbonyl group and three electron withdrawing Cl atoms on  $\alpha$ -carbon of carbonyl group create a greater partial +ve charge on that carbon atom. This two partial +ve charge repel each other on the adjacent position. To minimize the repulsion it readily reacts with water to form gemdiol intermediate. This gemdiol is stabilised by the intramolecular H-bonding effect between  $-\text{OH}$  and Cl groups.



Ninhydrin is also stabilised by the intra molecular H-bonding effect between  $\text{C}=\text{O}$  and  $-\text{OH}$  group.



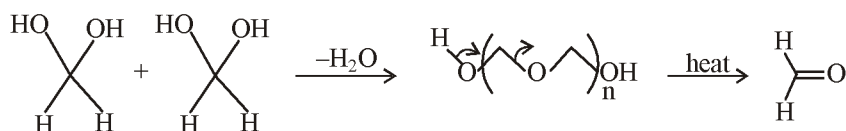
**Q. 2. Compare the rate of hydration reaction in the following carbonyl compound.**



Trifluoroacetone mostly exists in the gem-diol form. This is due to the stronger intramolecular H-bonding effect and good electrophilicity of the carbonyl group are major driving force to form the gemdiol compound. The rate of addition of nucleophiles to carbonyl carbon is comparatively lower in chloral due to lower electrophilicity of carbonyl group than trifluoro acetone.

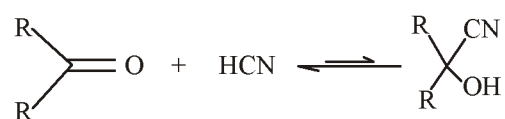
The gemdiol mostly exists in formaldehyde. Formaldehyde (HCHO) is an extremely reactive aldehyde and it has no substituent to hindered attack, it is so reactive that it is rather prone to polarization. It is quite happy to move from  $sp^2$  to  $sp^3$  hybridisation because there is very little increased steric hindrance between two H atoms as the bond angle changes from  $120^\circ$  to  $109^\circ 28'$ . That is why our aqueous solution of HCHO contain essentially no HCHO group rather it is completely hydrated.

- HCHO always exist in polymeric form not as in monomeric form



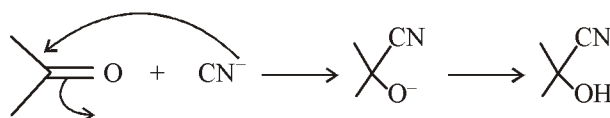
### 3.5.3 HCN addition to carbonyl compounds

Carbonyl compound reacts with HCN to form cyanohydrin compound but the equilibrium is present in this reaction is left hand side. This is due to the sufficient  $\text{CN}^-$  is not produced from HCN to attack the carbonyl carbon. Hence to shift the equilibrium in the right hand side the base is used as the catalyst.

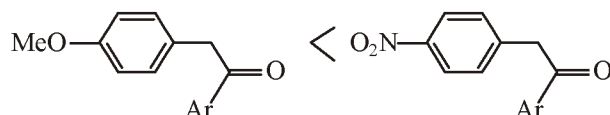




In presence of base

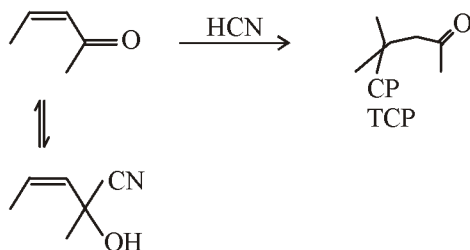


The rate of cyanohydrin formation depends on the electron density of carbonyl carbon atom. With increasing the electrophilicity of carbonyl carbon the rate of cyanohydrin formation increases.



The rate of cyanohydrin formation :

- In case of  $\alpha, \beta$  unsaturated carbonyl compound 1, 4 addition is more favorable than 1, 2 addition.



1, 4 addition product is favorable because—

1. Soft-Soft combination is possible in 1, 4 addition.
2. The carbonyl carbon addition is reversible addition.
3. Since greater electronegativity of oxygen atom, the concentration of electron on oxygen atom is fat whereas the electron density of the  $\beta$ -carbon atom is thin. Therefore the  $CN^-$  can easily attack on the  $\beta$ -carbon atom.



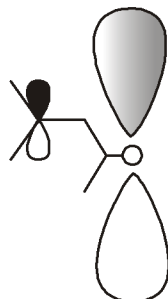


Fig-10 (a)

Q. Why conjugate addition product is most stable?

In conjugate addition product, we get C-C sigma bond losing C = C  $\pi$ -bond, but keeping the C = O  $\pi$  = bond. With direct addition, we still gain C-C bond, but loss of C = O  $\pi$ -bond and give the C = C  $\pi$ -bond. We know that C = O  $\pi$  bond is more energetically favorable than C = C  $\pi$ -bond. So, the conjugate addition product is more stable.

**Conjugate addition to the  $\alpha$ ,  $\beta$  unsaturated carbonyl carbon :**

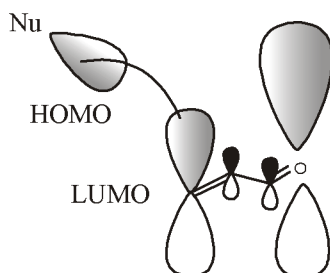


Fig-10 (b)

In the LUMO the large orbital co-efficient is on the  $\beta$ -carbon of the  $\alpha$ - $\beta$  unsaturated system. Therefore, the nucleophile attack occur on the  $\beta$ -carbon atom. The second large orbital co-efficient on the C = O 'C' atom. So some case 1, 2 addition also favour.

● **Hard Soft nucleophile :**

Hard nucleophile :  $F^-$ ,  $OH^-$ ,  $RO^-$ ,  $ROH$ ,  $NH_3$ ,  $RMgBr$  and  $RLi$

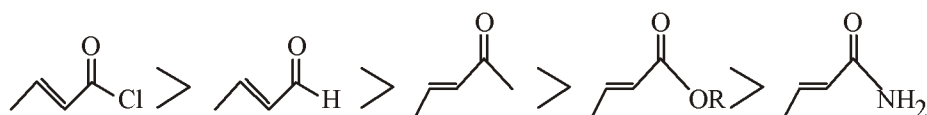
Borderline nucleophile :  $N_3^-$ ,  $CN^-$ ,  $RNH_2$

Soft nucleophile :  $I^-$ ,  $RS^-$ ,  $RSe^-$ ,  $S^-$



$\alpha$ ,  $\beta$  unsaturated carbonyl compound is unusual, it has two electrophile sides. One of which is hard and one is soft. The carbonyl group has high partial charge on the carbonyl carbon and will tend to react with hard  $\text{Nu}^-$  carbon atom such as organo Li. and  $\text{RMgX}$  (Grignard reagent), that have a high partial charge on  $\text{Nu}^-$  carbon atom. Conversely, the  $\beta$ -carbon of the  $\alpha$ ,  $\beta$ -unsaturated carbonyl system does not have a partial positive charge but it is the site of the largest co-efficient in the LUMO. This make  $\beta$ -carbon a soft  $\text{E}^+$  and likely to react well with soft  $\text{Nu}^-$  such as thiols.

- Proportion of direct addition of carbonyl compound :

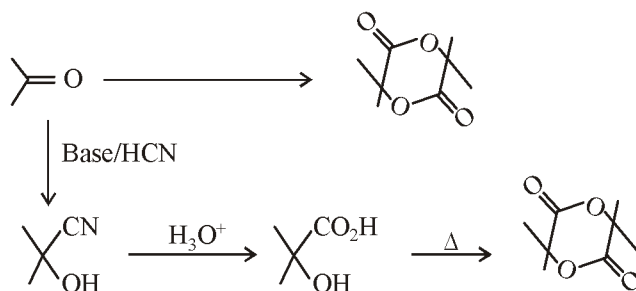


- Cyanohydrin formation is also possible in presence of  $\text{Me}_3\text{SiCN}$ , as  $\text{CN}^-$  source.

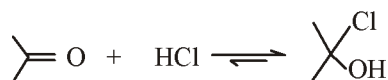


- In presence of  $\text{Me}_3\text{SiCN}$ ,  $\alpha$ ,  $\beta$  unsaturated carbonyl compound gives 1, 2 addition product which is more favorable than 1, 4 addition.

#### Conversion :



#### 3.4.5 HCl addition to Carbonyl :



### Q. Why equilibrium go to the left hand side ?

Enthalpy (H) : (H – Cl) = 103 Kcal/mole, (CH<sub>3</sub> – Cl) = 85 Kcal/mole, (H – Cl) – (CH<sub>3</sub> – Cl) = 18 Kcal/mole

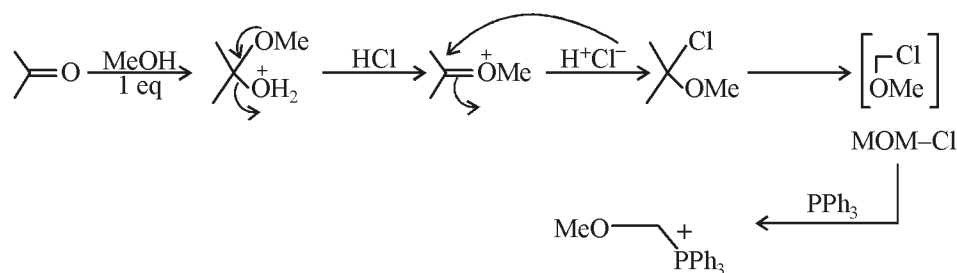
Since  $\Delta H = +ve$  i.e. the reaction is endothermic in nature. Therefore, the reaction undergoes backward direction.

$$\Delta G = \Delta H - T\Delta S, \Delta S = -ve, \Delta H = +ve \Delta G > 0.$$

### Utility :

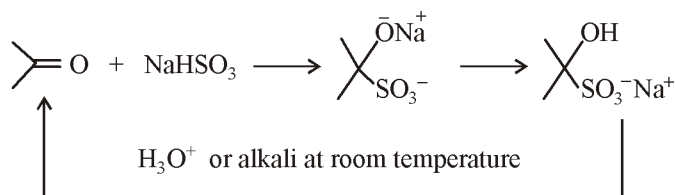
The utility of HCl addition of the carbonyl carbon is the preparation of Methoxymethyl chloride which is used in Wittig reaction.

The above reagent are easily prepared by HCl addition to the hemiacetal form

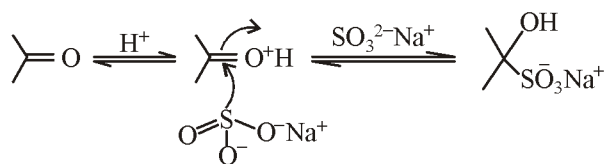


Wittig reagent : This is very useful for the homologation of carbonyl carbon.

### 3.5.5 Bisulphite addition

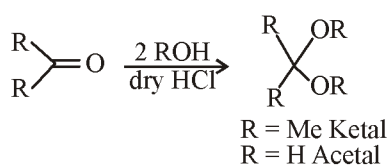


### Mechanism :

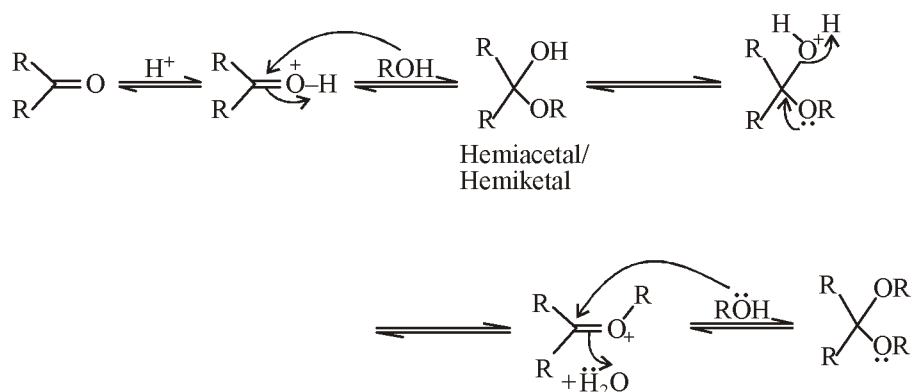


This reaction is very useful for the preparation of pure carbonyl compound. The impure carbonyl compound reacts with  $\text{NaHSO}_3$  to give bisulphite addition product as their salt. So this compound undergoes precipitation and after filtration the impurity is easily removed. The bisulphite addition product converted to pure carbonyl compound by the treatment of  $\text{H}_3\text{O}^+$  or alkali at room temperature.

### 3.5.6 Addition of Alcohol to carbonyl compounds

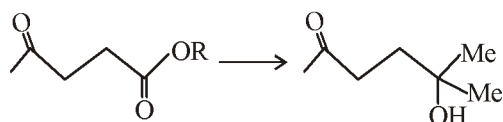


#### Mechanism :



**Utility :** This reaction broadly used in protection chemistry.

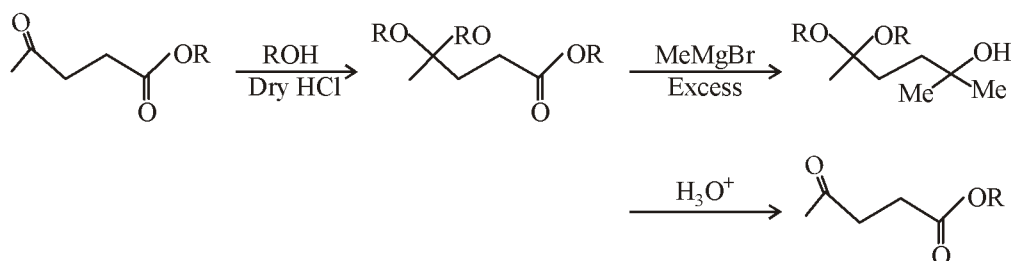
**Q. Why protection technique is used?**



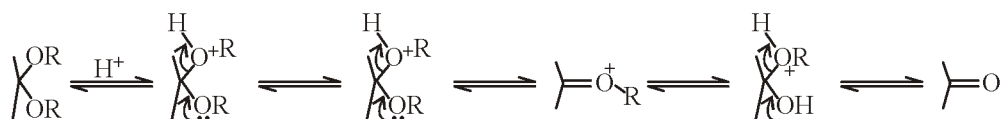
In synthetic purpose some reaction is needed for a particular functional group in presence of other similar type functional group. When a compound contains more than one similar type functional then protection technique is used for specific reaction in one functional group.

### Q. What is chemoselectivity?

When a molecule contains more than similar types functional groups but specifically allow reacting one functional group. This type of selectivity is known as chemo selectivity.

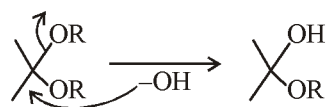


### Deprotection of Acetal or ketal :



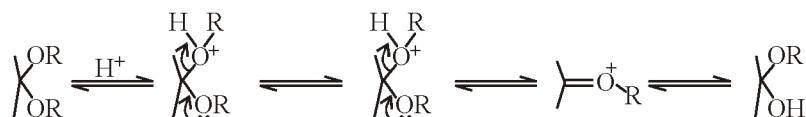
**Q. Acetal and ketal are stable in base medium but they are not stable in acid medium. Explain**

In basic medium,



SN<sub>2</sub> attack is not occur

In acid medium,

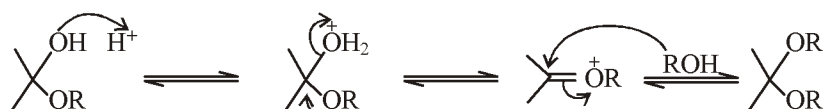


In presence of basic medium, –OR group is not cleaved by OH<sup>-</sup> due to its bad leaving aptitude. But in acid medium, after protonation of –OR group the charge

species  $\text{RO}^+\text{H}$  has greater leaving aptitude and readily cleavage by  $\text{H}_2\text{O}$  molecule to give hemiacetal form and consequently it gives carbonyl compound.

**Q. Why acid catalysed acetal/ketal formation will occur but base catalysed did not?**

**Acid catalysed acetal/ketal :**



**Base catalysed acetal/ketal :**



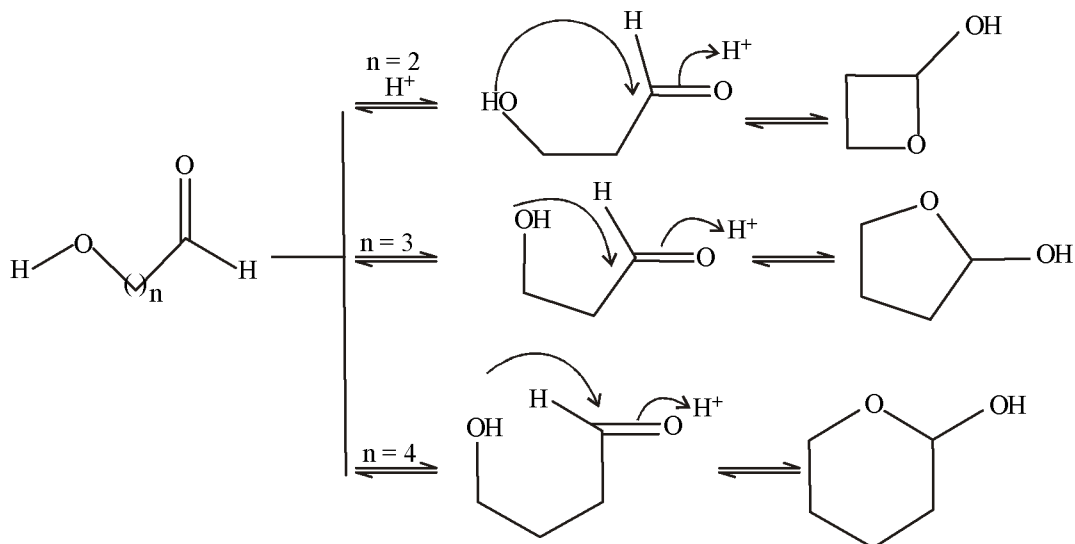
Acid catalyzed hemiacetal/ketal formation occur for the following reason–

1. The addition of another alcohol to unstable oxonium ion is very favorable as alcohol molecule shifted the weak  $\pi$  electron.
2. After the hemiacetal or hemiketal, the protonated form of hydroxyl group produces good leaving group aptitude by which it influences to added another alcohol molecule.

The base catalysed acetal or ketal formation does not take place for the following reasons :

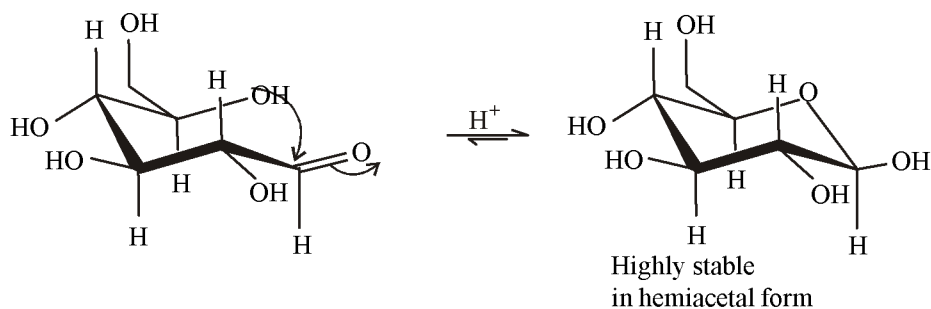
After the formation of hemiacetal or ketal the  $\text{RO}^-$  ion can't attack to the back side leaving group as it produces more steric interaction. Again, the  $\text{RO}^-$  can't break the more stronger C-O  $\sigma$ -bond as  $\text{OH}^-$  has lower leaving aptitude.

**Q. Stabilization of aldehyde in hemiacetal form :**

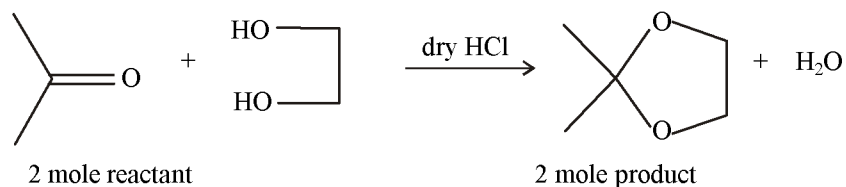
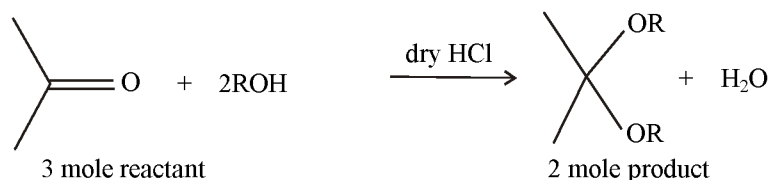


The hemiacetal formation can be stabilized with increase in the number of 'n'. The size of the ring as well as the release of the angle strain increases with increasing the no. of 'n'. This is the main driving force for the stability of hemiacetal formation.

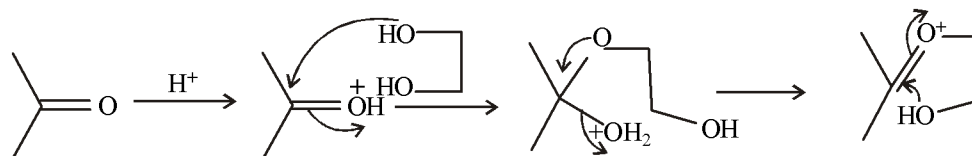
Hence the rate of hemiacetal formations are  $k_1 > k_2 > k_3$



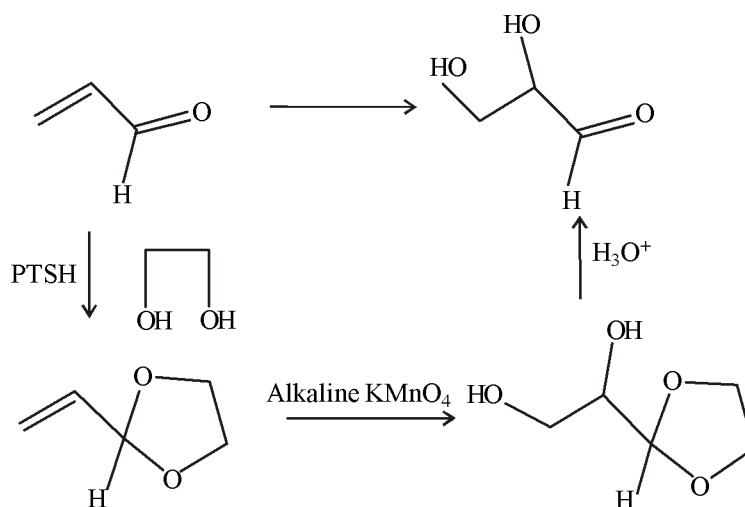
**Q. Protection of carbonyl compound by 1, 2-diol is more favorable than the simple alcohol. Explain**



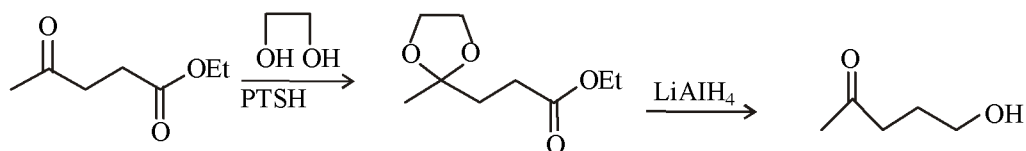
**Mechanism :**



The cyclic acetal or ketal formation is entropically more favorable than acyclic acetal/ketal. Since in the first reaction three mole reactant molecule give two mole products where as in the second reaction 2 mole reactants give two mole products.

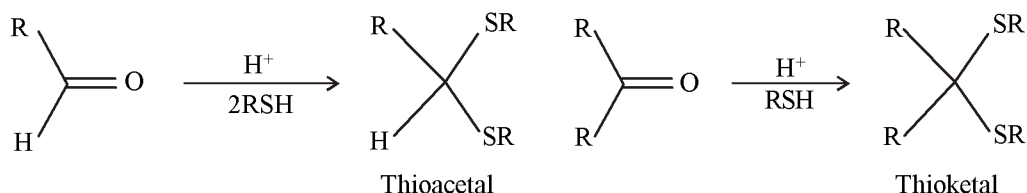






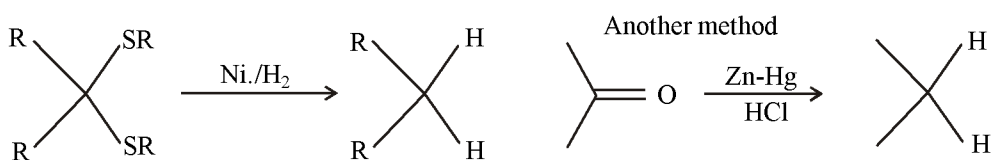
### 3.5.7 Protection of aldehyde and ketone by thiol group

The reaction of aldehyde or ketone with thiol in presence of dry HCl, we get thio acetal and thio ketal derivatives.



The rate formation of thioacetal/thioketal is greater than simple acetal ketal formation. This is due to the higher nucleophilicity of 'S' atom.

Thio acetal and ketal are very useful for the protection group chemistry. Since, it is stable in base medium as well as in acid medium where as simple acetal or ketal are unstable in acid medium. Therefore, those substrates which are acid sensitive that substrate can apply thioacetal and ketal protection group chemistry.



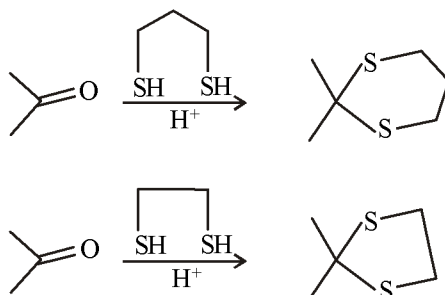
Metal hydrogenation, i.e. thioacetals and thioketals can be reduced by metal to get alkane derivatives.



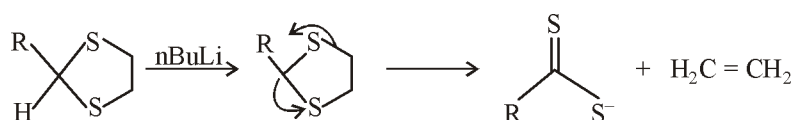
This is one of the deoxygenation techniques for the carbonyl group.

Similar to that of cyclic acetal/ketal, we can easily prepare cyclic thioacetal/thioketal by using 1, 3 dithiol as the reagent.

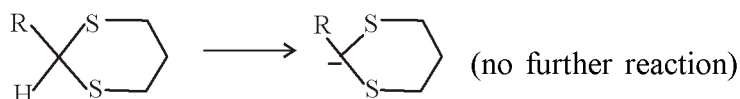
**\*Why 1, 2 di thiol is not used as the protecting group?**



If we use 1, 2 dithiol as the protecting group then the following reaction takes place in strong base medium–

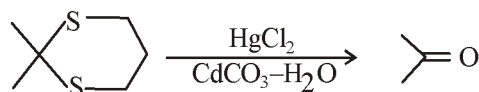


1, 2 cyclic thioacetal is very unstable in strong base medium due to it becomes alkene by the cleavage of  $\sigma$ -bonds. But when the carbonyl carbon is treated with 1, 3 dithiol, we get cyclic thioacetal cyclic thioketal. They are stable in strong base medium.

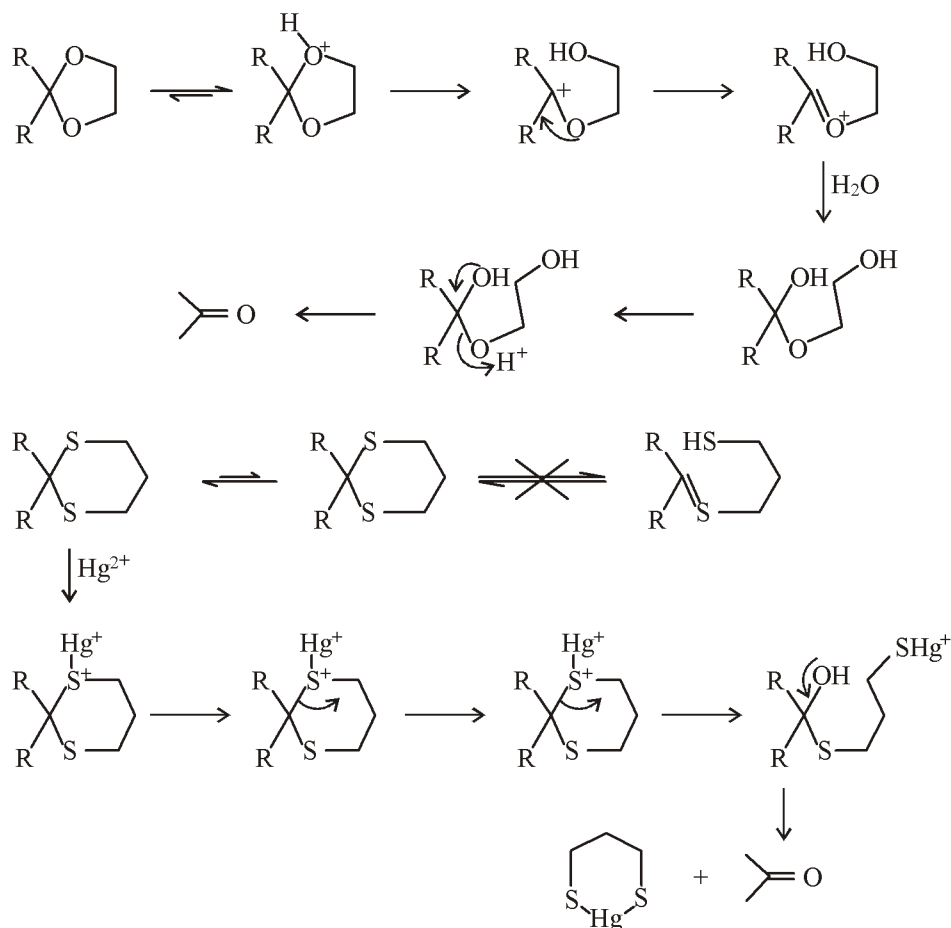


### Deprotection of thioacetal and thioketal :

The cyclic thioacetal and thioketal can be deprotected by the treatment of  $\text{HgCl}_2/\text{CdCO}_3\text{-H}_2\text{O}$ .



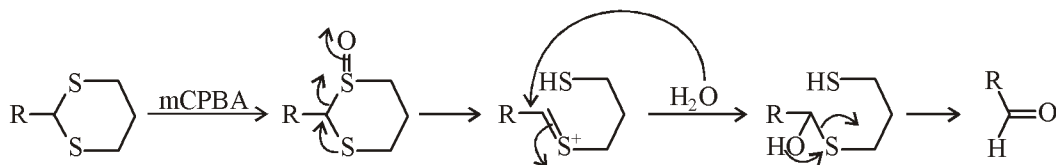
**Q. Acetal and ketal is deprotected under acid catalyst where as thioacetal and thioketal are stable under acid condition, it become de-protected in presence of  $\text{HgCl}_2/\text{CdCO}_3\text{-H}_2\text{O}$  condition.–Explain.**



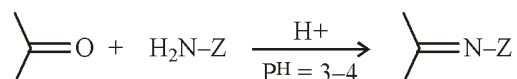
- Thioacetal and thioketal react with  $\text{H}^+$  ion to produce an intermediate which is very unstable as it is formed by soft-hard combination.
- This intermediate does not undergo forward reaction due to the produced carbocation is not stabilized by orbital mismatching overlap between the 2p orbital of carbon with 3p orbital of S atom.

Hence, the deprotection of thioacetal/ketal are not possible under acid catalyst

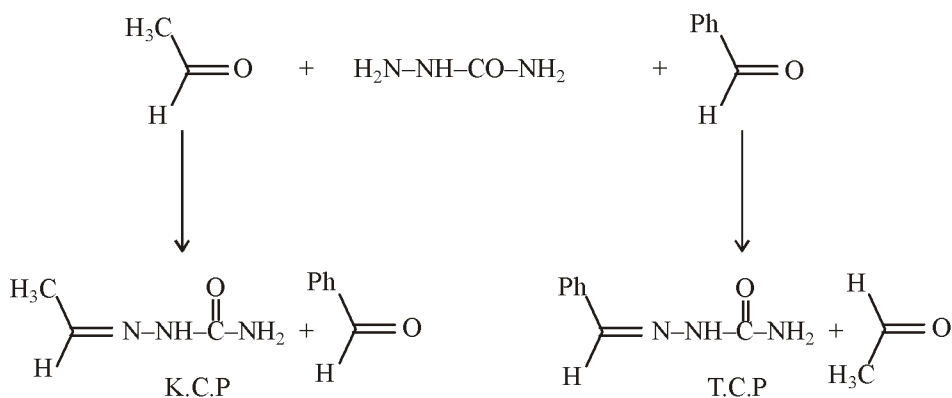
But thioacetal and thioketal are deprotected under  $\text{HgCl}_2/\text{CdCO}_3\text{-H}_2\text{O}$  medium. This is due to stable intermediate is formed in forward direction by soft – soft combination. Again after de-protection, it produces cyclic stable Hg-containing compound.

**Alternating de-protecting agents :****3.5.8 Addition of nitrogen-based nucleophiles (Z-NH<sub>2</sub>)**

Carbonyl compound react with amine compound in presence acid catalyst to give β-hydroxy amine compound at first, then it eliminates water to form imine compound.



**Q. When one mole acetaldehyde, one mole of benzaldehyde and one mole semicarbazide react at low temperature, give semicarbazone derivative of aldehyde but at high temperature give semi carbazone derivative of benzaldehyde. Explain—**



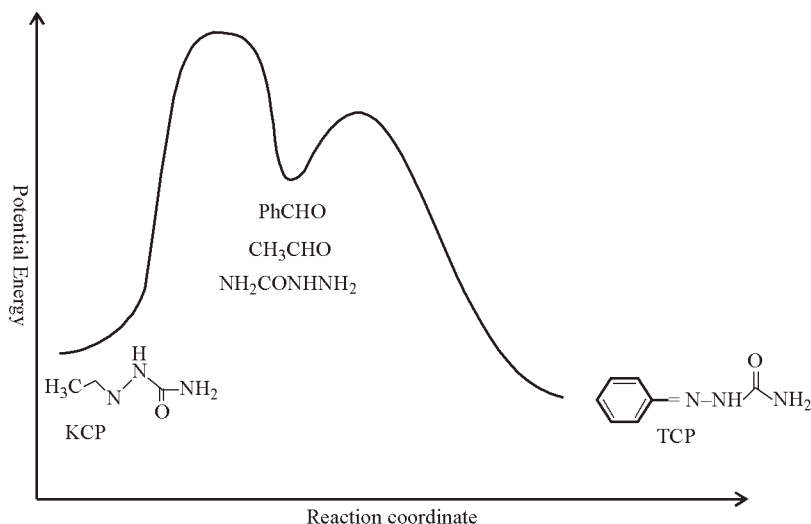
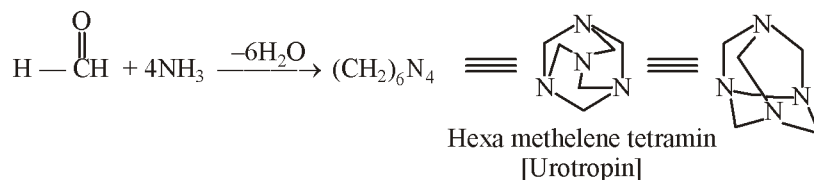


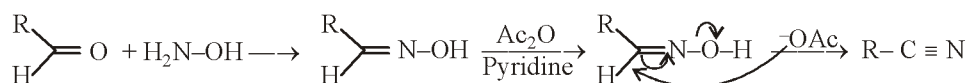
Fig-11

At low temperature, the reaction will take place for those substrate, which is more reactive. Therefore, among acetaldehyde and benzaldehyde, the benzaldehyde is less reactive due to +R effect of phenyl ring reduces the electrophilicity of carbonyl group. So in the low temperature condition semicarbazone of acetaldehyde is produced. But at high temperature, the reaction will take place for that substrate which leads to the more stable product. This is due to the semicarbazone derivative of benzaldehyde is stabilised by long conjugation with phenyl ring. Hence, the former case gives KCP and latter give TCP.

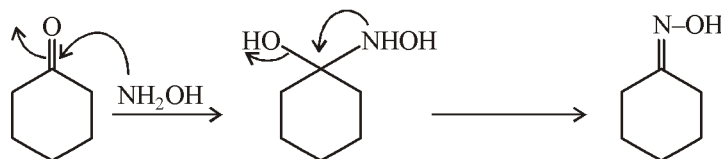
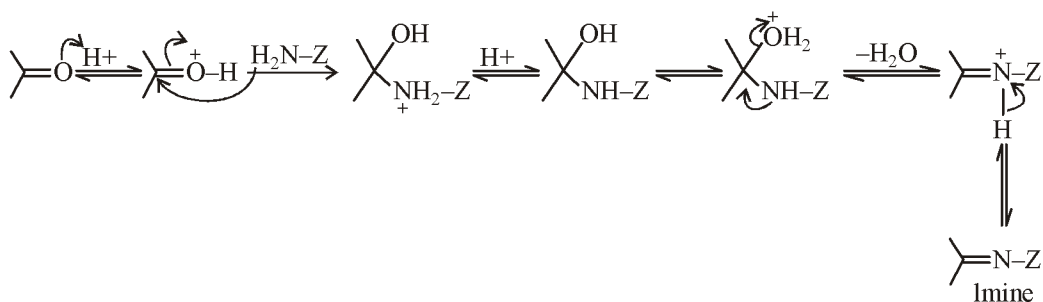
Group Z	NH <sub>2</sub> -Z	Product
-H	Amonia	Imine $\text{>C=N-H}$
-OH	Hydroxyl amine	Oxime $\text{>C=N-OH}$
-NH <sub>2</sub>	Hydrazine	$\text{>C=N-NHPh}$
-NH-NH <sub>2</sub>	Phenyl hydrazine	Phenyl hydrazone
-Brady's reagent	2,4 dinitro phenyl hydrazine	2,4 dinitrophenyl hydrazone
-NH-CO-NH <sub>2</sub>	Semicarbazide	Semicarbazone

**Urotropine :****How will you convert :**

Carbonyl compound to Cyanide compound



- Mechanism of imine formation :

**Q. Why optimum pH is required for imine formation?**

1. In the first step of imine formation, reactivity of carbonyl compound increase by the protonation of oxygen atom. If the pH is high, the reactivity of carbonyl is not so high to be attacked by amine group.

2. In the second step of imine formation, if the pH is lower then protonation

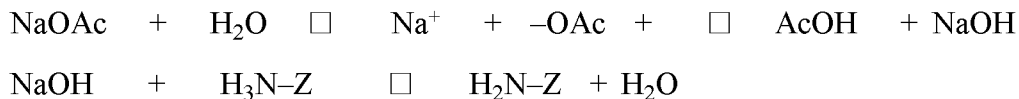
takes place by the lone pair of amine group. Hence, it can't attack to the electrophilic carbonyl carbon atom.

Therefore, optimum pH is required for imine formation. The pH is maintained during the imine formation between 3-4.

**Q. Phenyl hydrazine hydrochloride does not react with carbonyl compound but it does in presence of NaOAc. Explain**

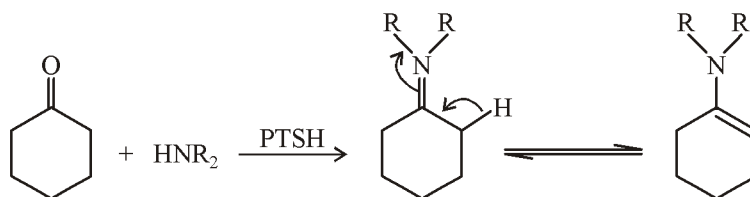
Most of the imine derivatives are present in the laboratory as their amine salt of hydrochloric acid. This is due to the lone pair on N-atom has greater tendency of oxidized by the air. To avoid this oxidation amine is used in the laboratory as their hydrochloric salt. Since the lone pair of nitrogen atom captures the proton (from HCl). So it can not attack to the carbonyl carbon to the i.e. the nucleophilicity of amine derivative is lost by the protonation.

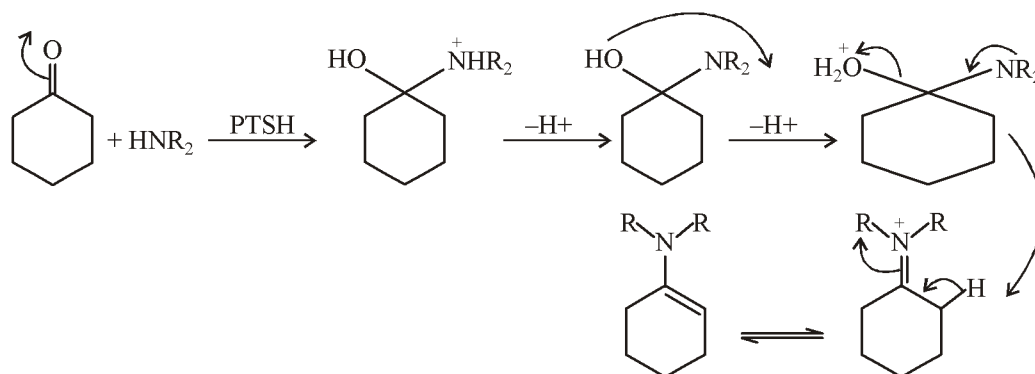
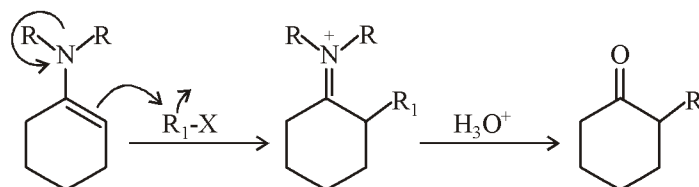
To regain their nucleophilicity NaOAc is used which captures the proton and free the amine compound, react with carbonyl compound to give amine compound.



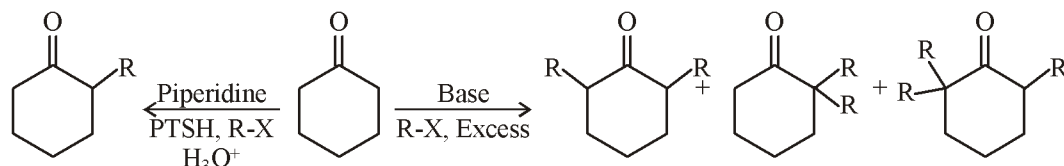
**Stock Enamine Synthesis :**

2° amine react with carbonyl compound in presence of PTSH to give iminium salt which undergoes isomerisation form enamine derivative. From this we can introduce electrophile at  $\alpha$ -position of carbonyl group.

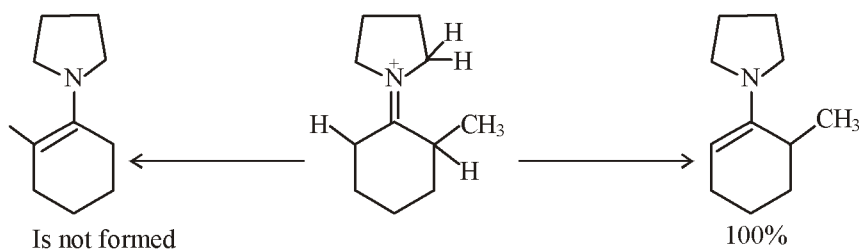


**Mechanism :****• Advantages of enamine synthesis :**

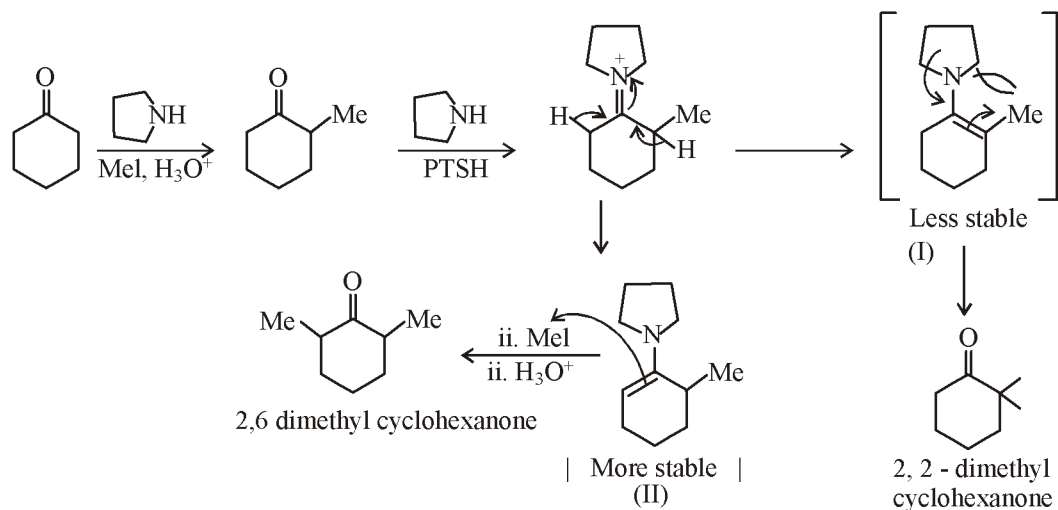
The advantage of stock enamine synthesis over base catalyzed alkylation is that the poly alkylation can take place. In base catalyzed reaction selectivity is less where as in enamine synthesis, we mostly get monoalkylation product and selectivity is very high.



In case of unsymmetrical ketone, enamine is form at less hindered side. The strong steric interaction unstabilized enamine at the more substituted end.



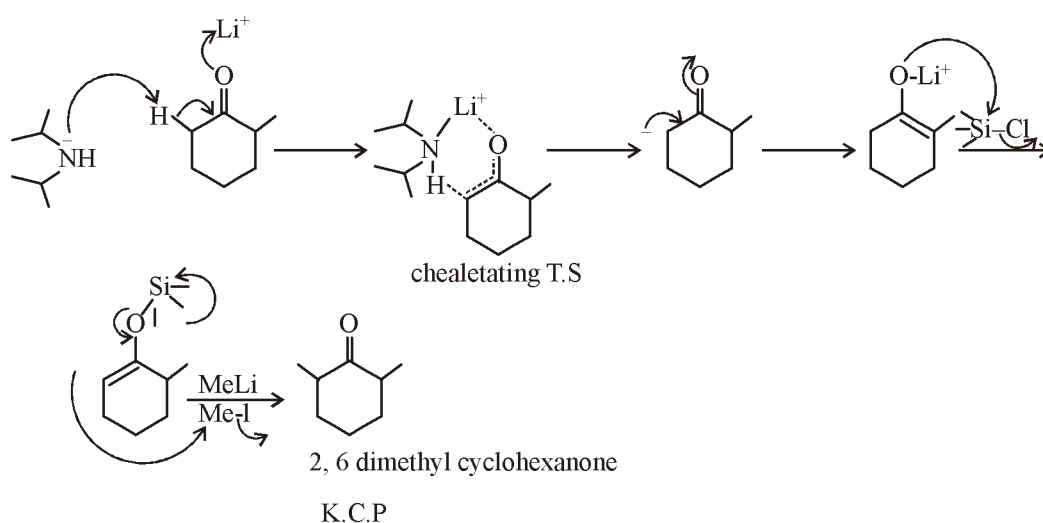


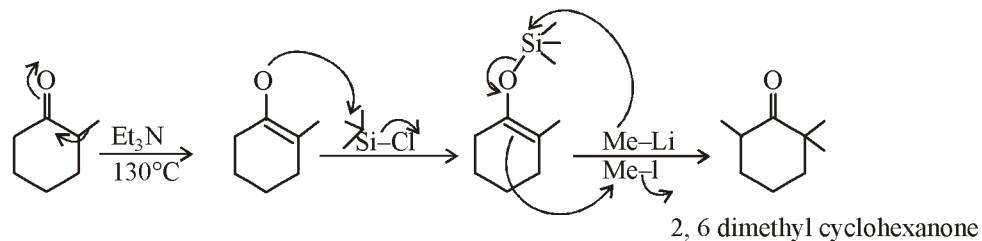


2, 2 dimethyl cyclohexanone does not prepare by stock enamine synthesis because the lone pair on the "N" atom of intermediate I is not conjugated with the more substituted end for steric interaction where as the lone pair on "N" atom of intermediate II is conjugated with the olefin is sterically nonhindered. Hence 2, 6 dimethyl cyclohexanone is prepare by stock enamine synthesis.

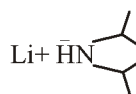
### Avoiding Stock Enamine Synthesis :

#### Silyl protection :

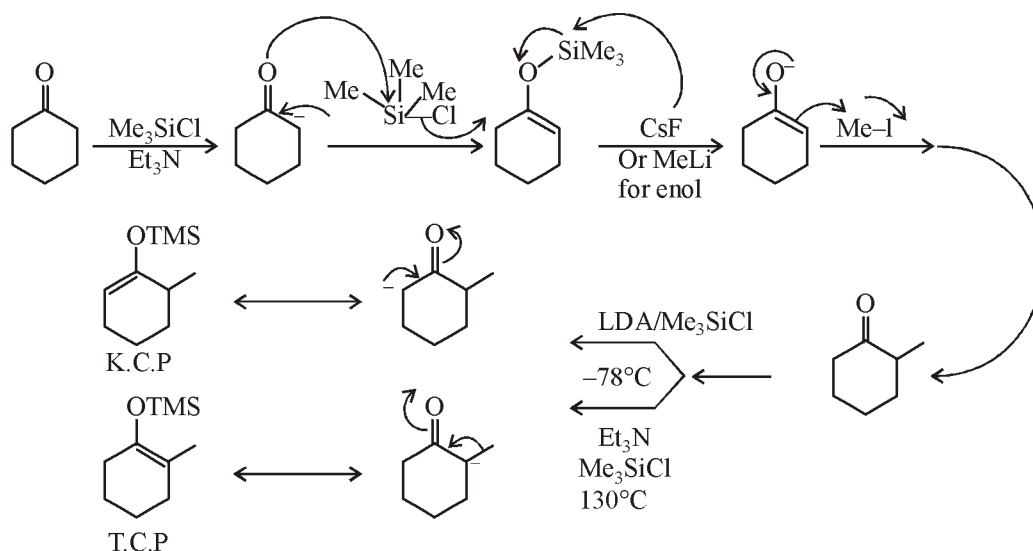




L.D.A : Lithium diisopropyl amide



**Mechanism :**



### 3.6 Reactions of carbonyl (C = O) compounds

Now we will discuss some named reaction of carbonyl compounds.

#### 3.6.1 Benzoin Condensation :

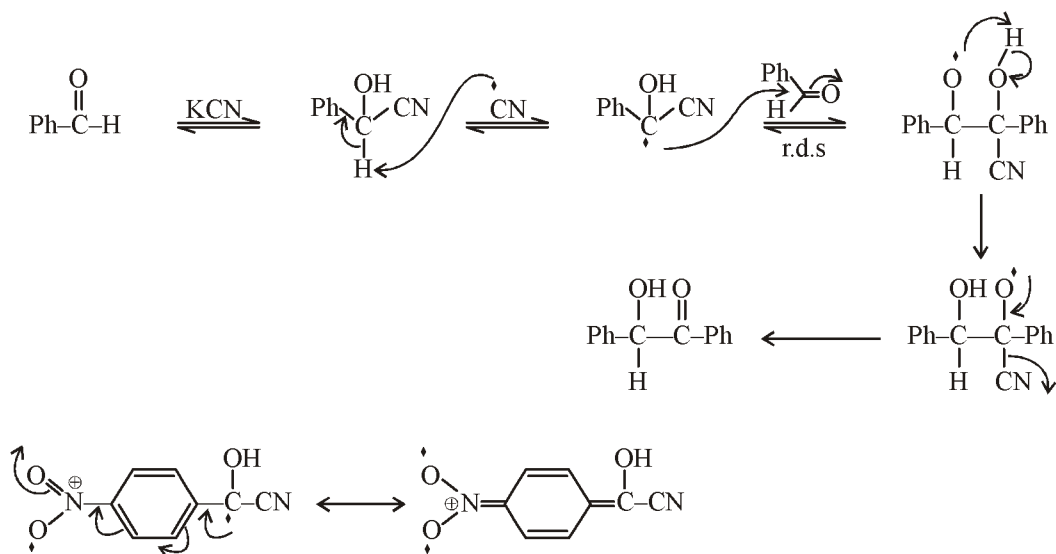
Aromatic aldehyde reacts with KCN/EtOH to give Benzoin as the product.

**Reaction :**



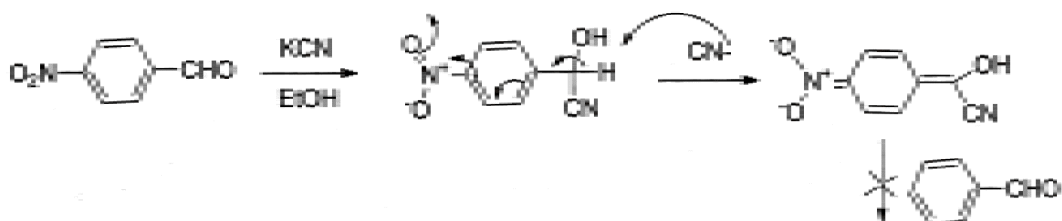


### Mechanism



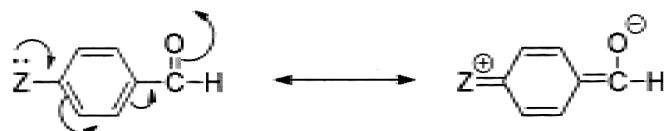
### Q. Why p-nitro benzaldehyde does not give benzoin condensation reaction?

When electron withdrawing group is present in the phenyl ring then Benzoin condensation does not occur. This is due to the negative charge on the carbon atom is stabilised by the electron withdrawing group. So, carbanion can't attack to the another aldehyde group to give the Benzoin condensation product.

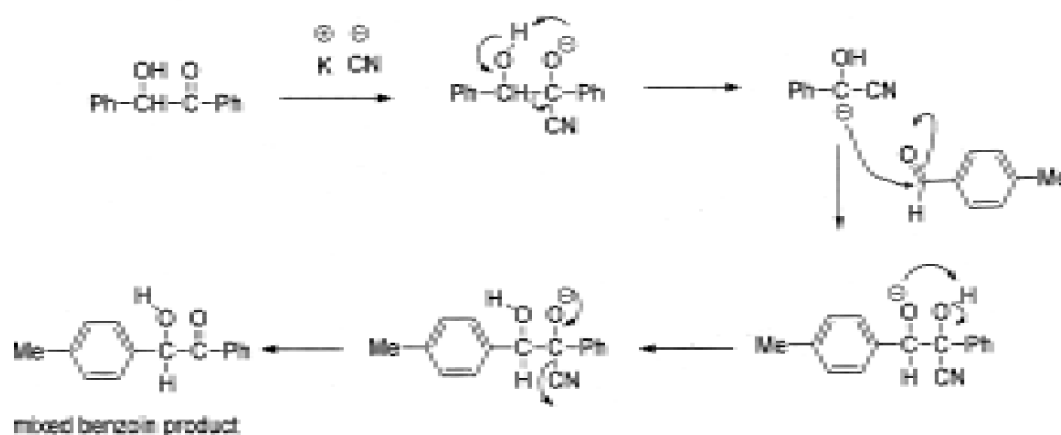


No reaction

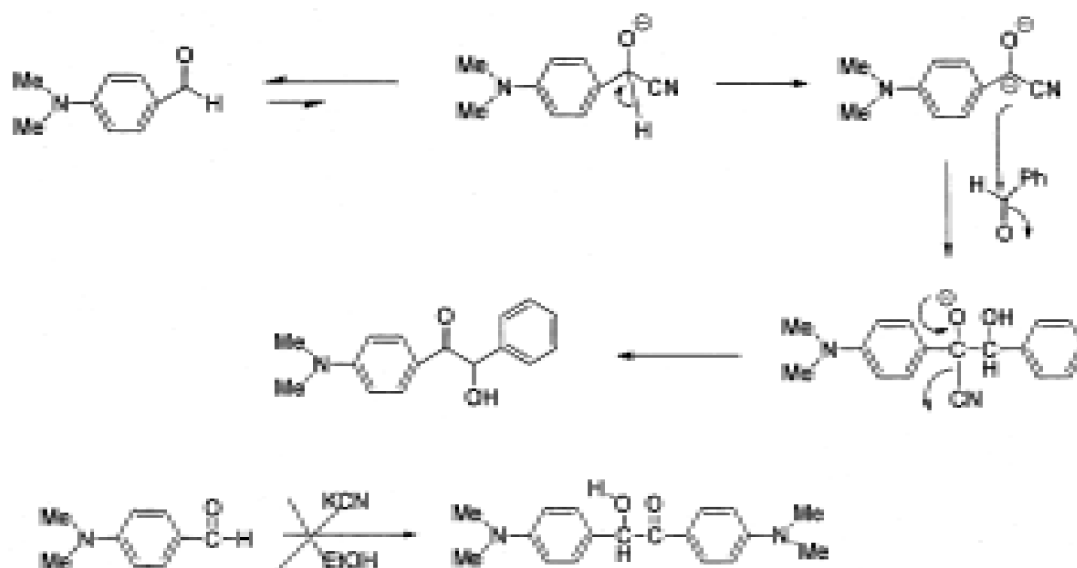
Again, electron donating substituent on aryl group reduces the electrophilicity of carbonyl carbon. So CN<sup>-</sup> can't attack to the aldehyde group. Therefore, the electron donating substituent on the phenyl ring does not give Benzoin condensation product.

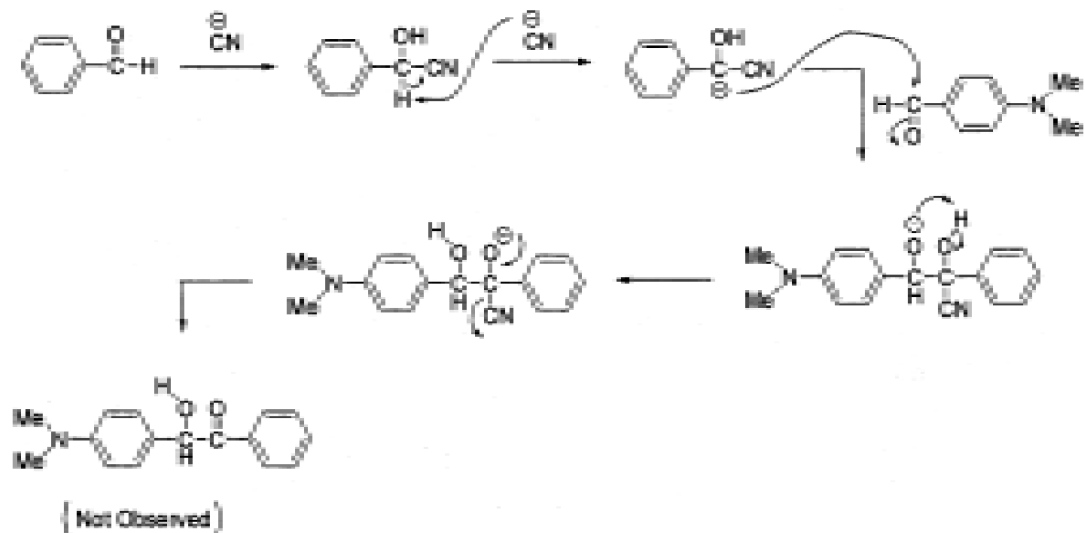


Q. If benzoin is treated with KCN p-methyl benzaldehyde, we get mixed benzoin as the major product. Explain.



Q. N,N—di methyl benzaldehyde does not give benzoin condensation product but in presence of benzaldehyde does. Explain—

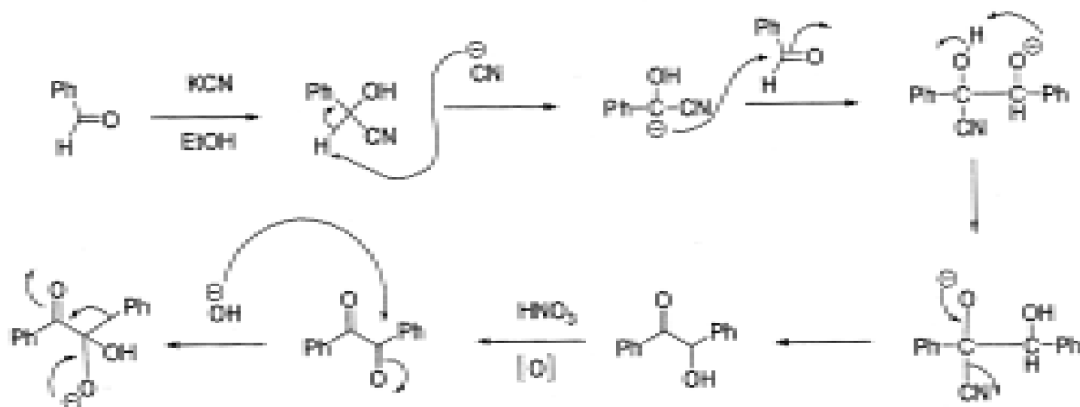


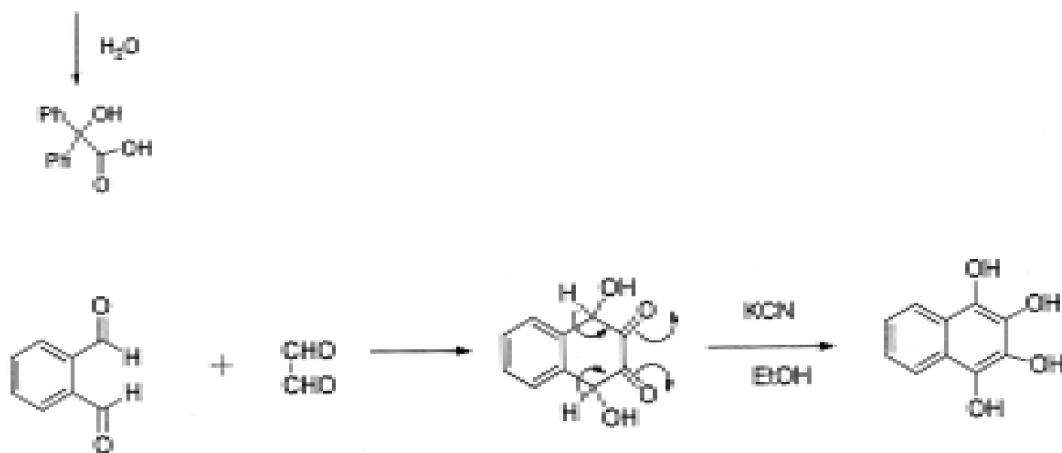


**Ans.** At first CN-attack to the N, N- di methyl benzaldehyde produces cyanohydrin as the product but equilibrium go in the left hand side. But the addition of benzaldehyde, the nucleophilic attack from the anion of A (cyanohydrin derivative) to the benzaldehyde occur readily, as equilibrium go in the right hand side. Hence mixed benzoin condensation product is formed.

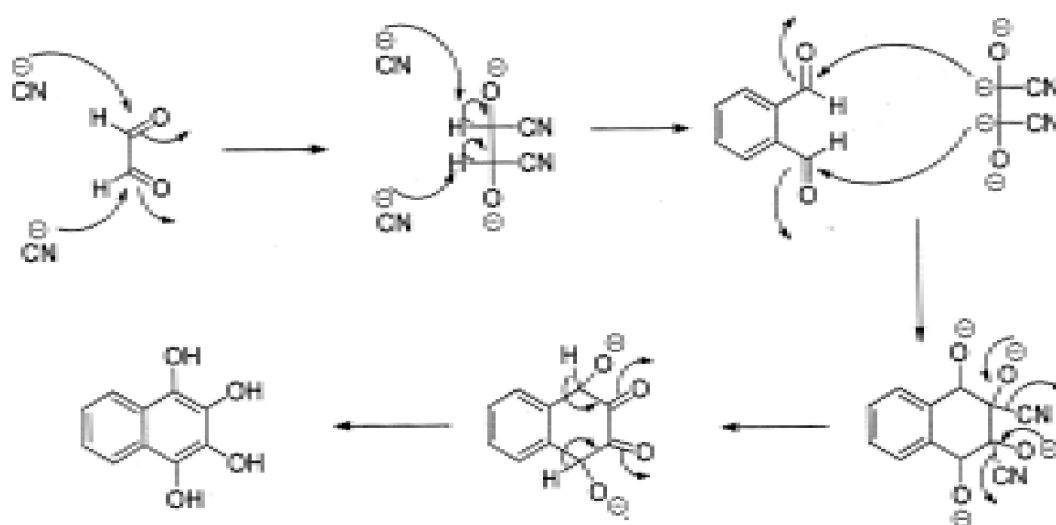


### Mechanism



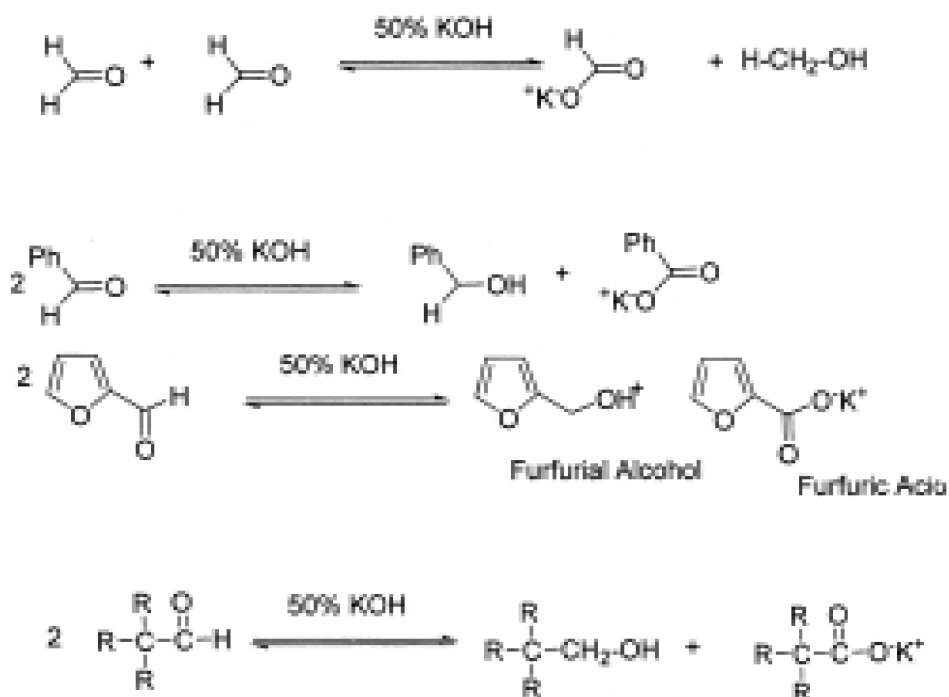


### Mechanism

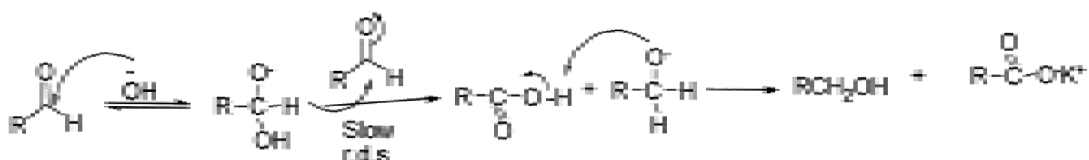


### 3.6.2 Cannizzaro Reaction

In concentrate alkali (50% NaOH or KOH), the aldehyde or ketone with no  $\alpha$ -hydrogen atom undergo oxidation and reduction to give corresponding acid and alcohol. This reduction is known as Cannizzaro reaction.



### Mechanism of cannizzaro reaction :

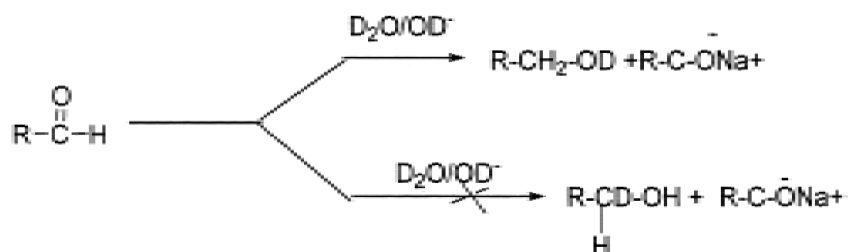


$$\text{Rate} = [\text{substrate}]^2 [\text{OH}^-]$$

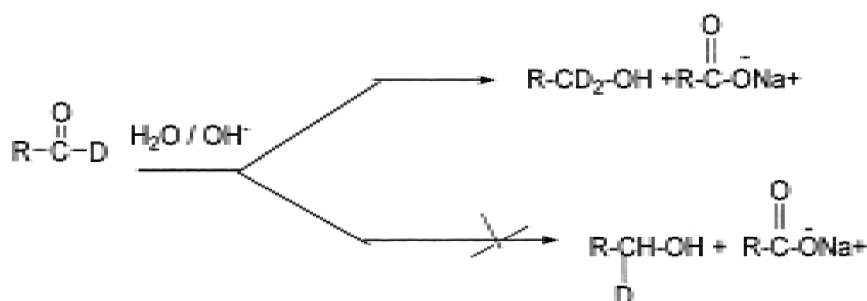
Here hydride ion is transferred from dianion intermediate to aldehyde group.

### Evidence for the mechanism :

1. If we start from the reaction from  $\text{D}_2\text{O} / \text{DO}^-$ . Then we get  $\text{R}-\text{CH}_2-\text{OD}$  as the alcohol product. So, no  $\text{C}-\text{D}$  bond is formed during the reaction. Therefore this indicates  $\text{H}^-$  ion must come from another molecule of aldehyde not from the solvent molecule.

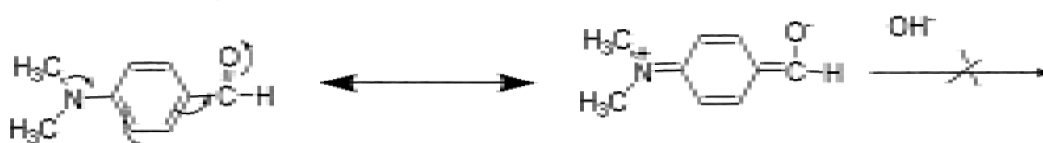


2. Again if we start with RCO<sub>2</sub>D then we get R-CD<sub>2</sub>-OH where the product contains C-D bond. This indicates that deuterium comes from the substrate molecule.

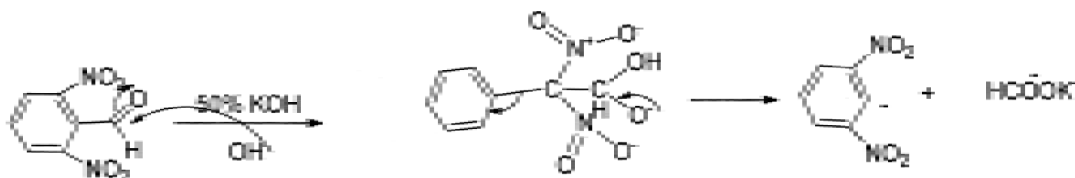


### Exception cannizzaro Reaction :

1. The substrate does not give cannizzaro reaction in which absent of  $\alpha$ -hydrogen atom. Such as N, N dimethyl *p*-amino benzaldehyde does not give cannizzaro reaction. This is due to the higher electron donating group reduces the electrophilicity of aldehyde group. Hence,  $\text{OH}^-$  can't attack to the carbonyl group.



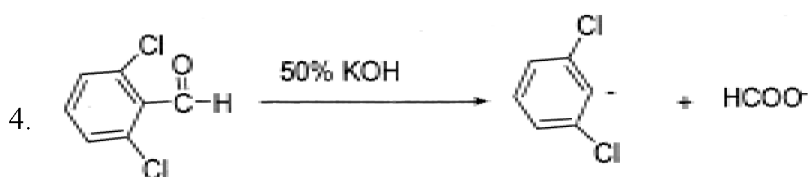
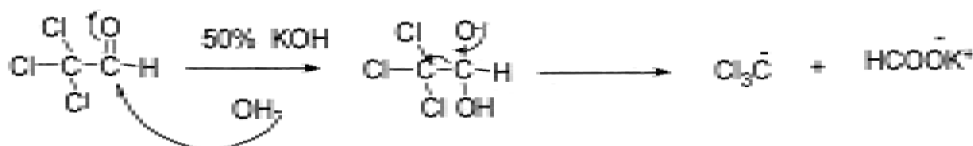
2. If the aldehyde group is hindered then Cannizzaro reaction does not take place.



Here,  $\text{H}^-$  ion is transferred to aldehyde group due to the hindrances of  $-\text{NO}_2$  group and strong electron withdrawing group stabilised the  $(-)$  ve charges.

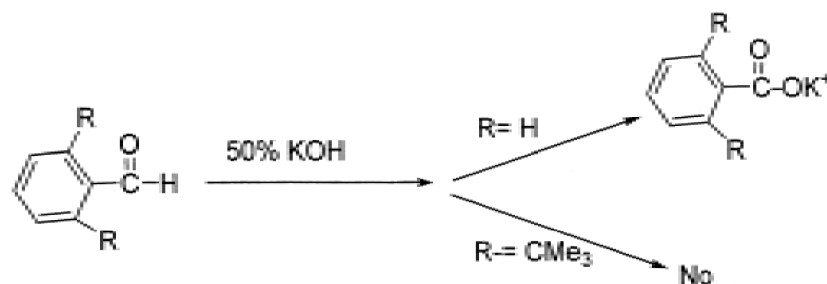


3. Chloral does not undergo cannizzaro reaction due to after the attack of  $\text{OH}^-$ , the hydride migration does not take place as the better leaving aptitude of  $\text{CCl}_3$  group.

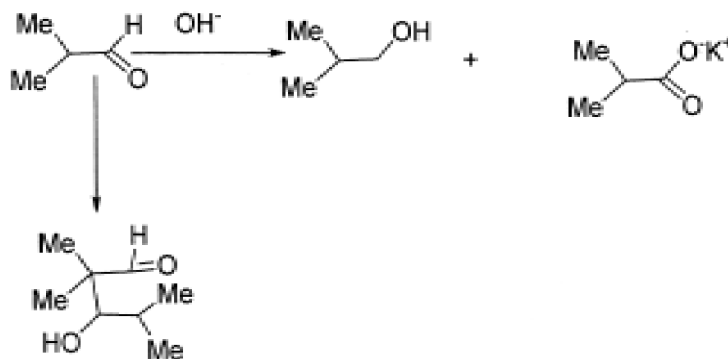


Here the  $-$  charge is stabilised by the stronger  $-I$  effect of  $-\text{Cl}$  group.

5. Aromatic aldehyde with bulky substituent at *o*-position does not undergo cannizzaro reaction.

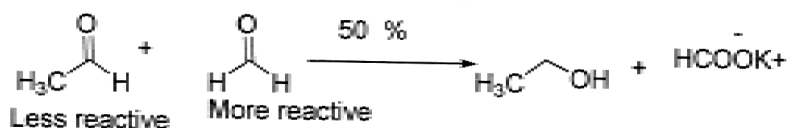


6.  $\alpha$ -hydrogen containing aldehyde group undergo cannizzaro reaction rather than aldol condensation.

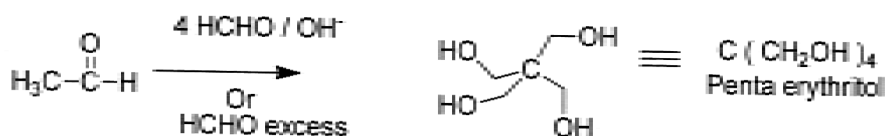
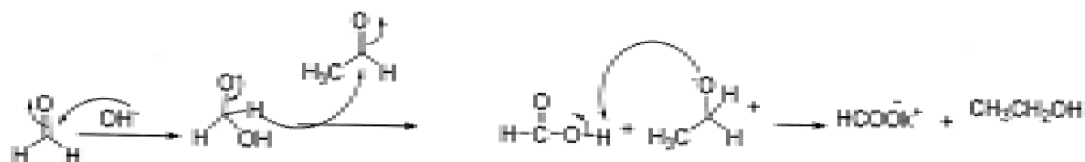


**Cross cannizzaro Reaction :**

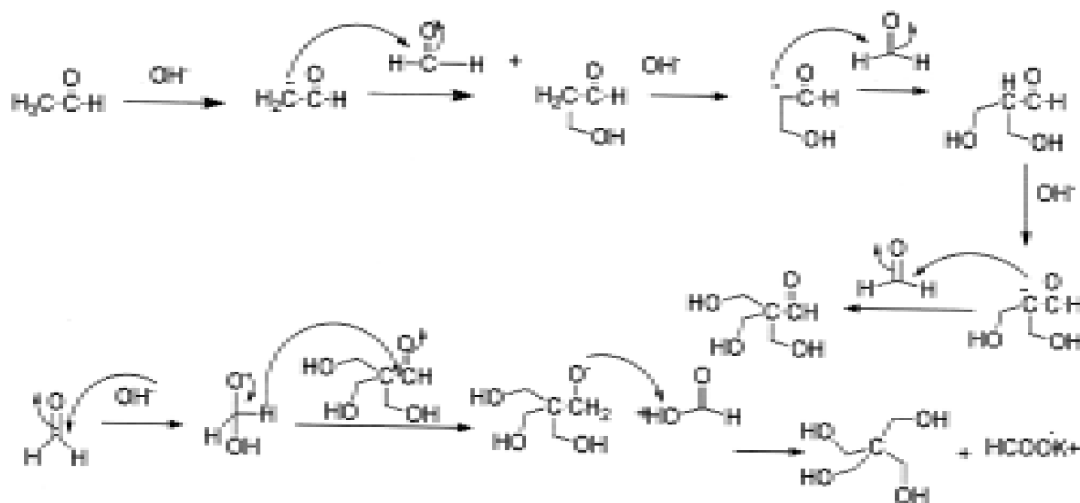
In cross cannizzaro reaction, two different aldehydes with no  $\alpha$ -H atom undergoes disproportionation reaction. The formation of the product depends upon the rate of the reaction. At first, higher reactive aldehyde group is attacked by the  $\text{OH}^-$  to give the intermediate and then  $\text{H}^-$  is transferred from it to less reactive aldehyde group and it is converted to alcohol.

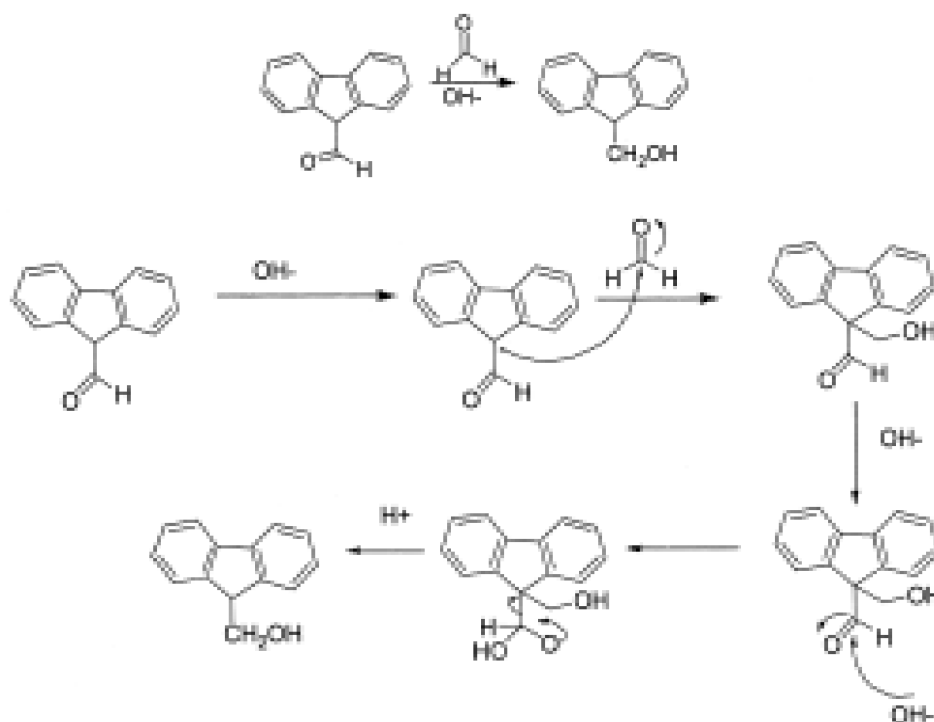


**Mechanism :**



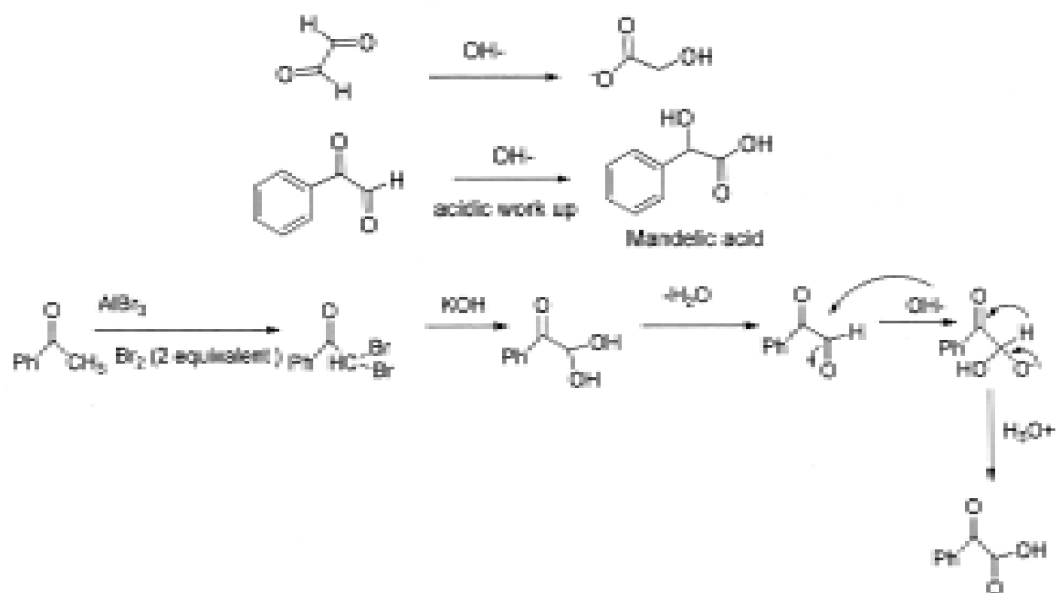
**Mechanism :**



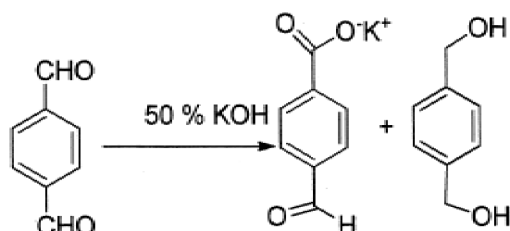


### Intramolecular Cannizzaro Reaction :

If a molecule contain two aldehyde group in same molecule with no  $\alpha$ -H atom, then this compound undergoes disproportionation reaction and give alcohol and acid.



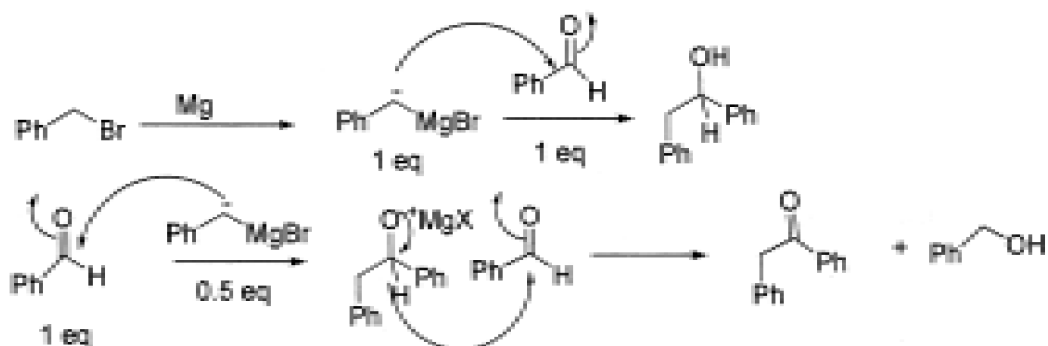
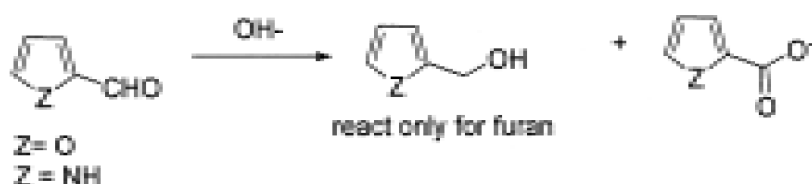
**Intramolecular**  $H^-$  transfer take place as the distance between two working group is short.



Inter molecularcannizaro reaction take place  
distance of two working group is long

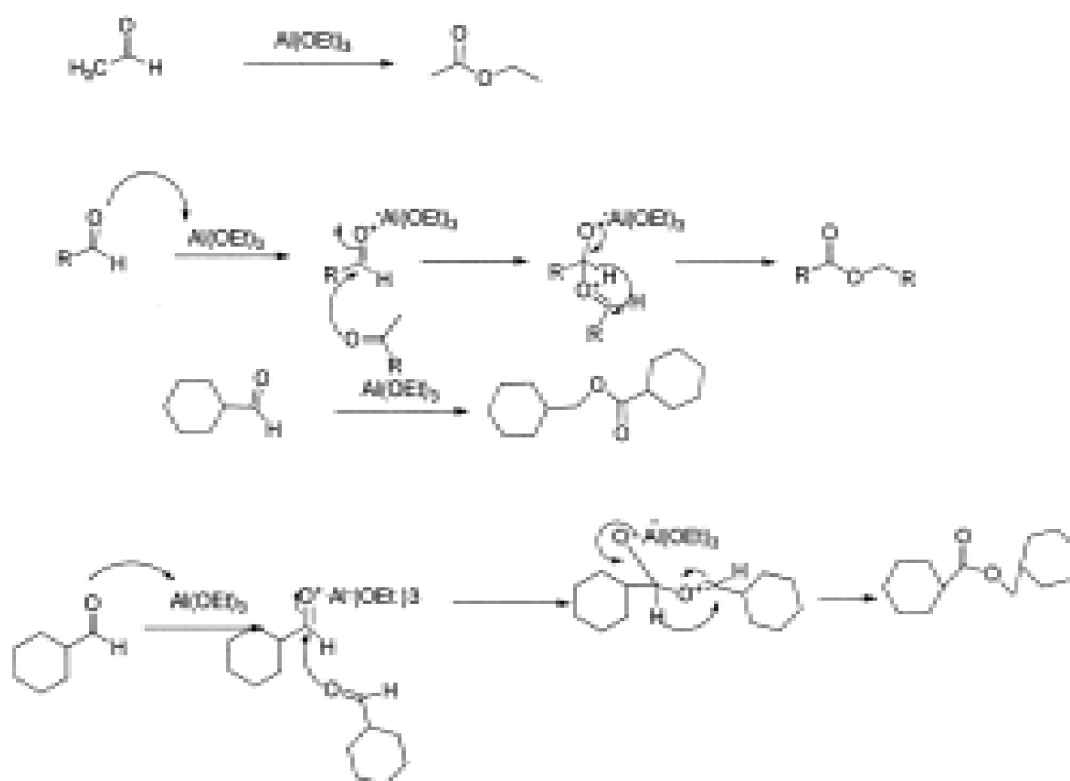
Pyrrole 2-aldehyde does not give cannizzaro reaction. This is due to electron donating power of N atom reduces the electrophilicity of aldehyde group through resonance effect. Hence,  $OH^-$  group can't easily attack carbonyl carbon and does not give corresponding alcohol and acid.

Furan 2-aldehyde give cannizzaro reaction. This is due to more electronegative "O" atom reduces the electron donating power and hence here resonance is less reactive. Since the hydroxyl group easily attack carbonyl carbon and give corresponding acid and alcohol.



### 3.6.3 Tishchenko Reaction :

This is special type of cannizzaro reaction. In this reaction the  $\alpha$ -H containing aldehyde undergo disproportionation reaction in presence of  $(\text{AlOEt})_3$  to give corresponding alcohol and acid which immediately converted to their corresponding ester.



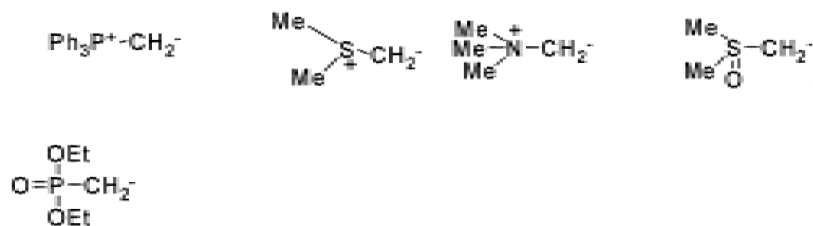
### 3.6.4 Wittig Reaction :

The Wittig reaction is the reaction of carbonyl carbon with ylide to give alkene compound with homologation of one carbon atom. This is very useful method for the preparation of alkene compound from the carbonyl compound.

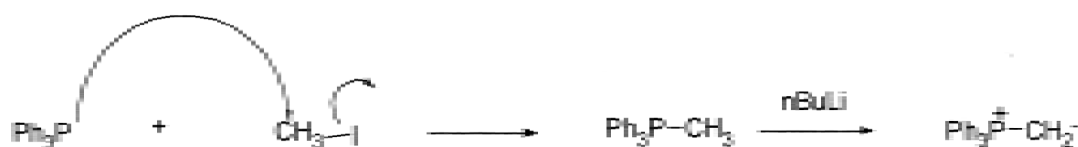


When an anionic carbon is attached covalently with the hetero atom such as N, P, S atoms which are positively charged then it is called as ylide.

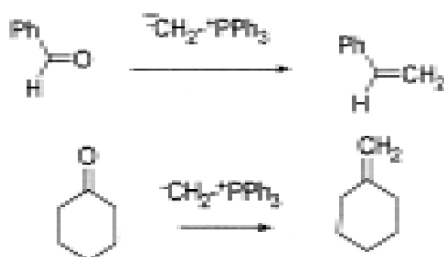
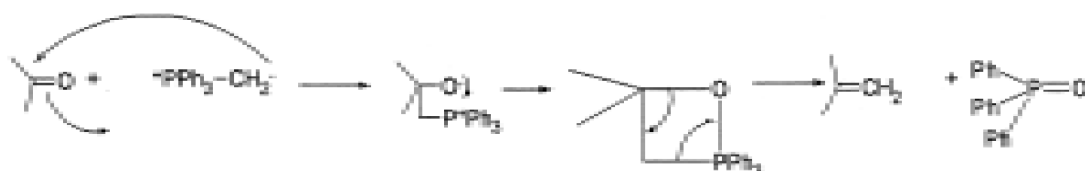
**Example :**



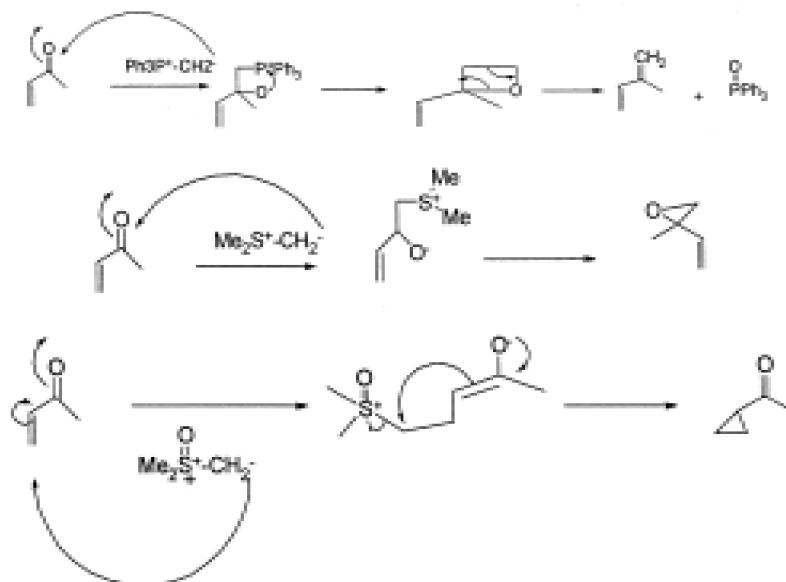
**Preparation of Ylide :**



**Mechanism :**



The driving force for the oxophosphetane cleavage is due to the formation of strong P = O bond. But in case of sulphonium ylide such type of cleavage does not occur. Here, epoxide is formed after the addition to the carbonyl compound.

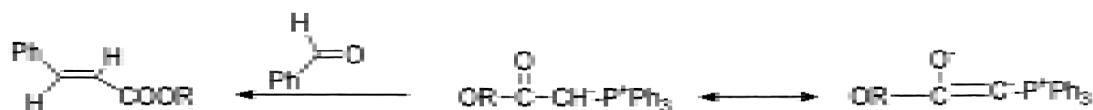


What is stabilized ylide and non stabilized ylide?

**Stabilized ylide :**

When the carbanion of ylide is stabilized by electron withdrawing group then it is called stabilized ylide.

**Example :**



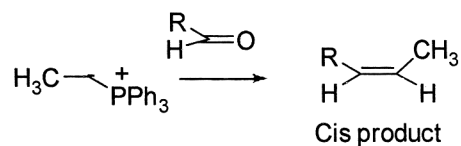
trans cinamate

Stabilised ylide always gives trans olefin product.

● **Non stabilised ylide :**

When the carbanion of ylide becomes unstable by electron donating group then it is called non stabilized ylide :

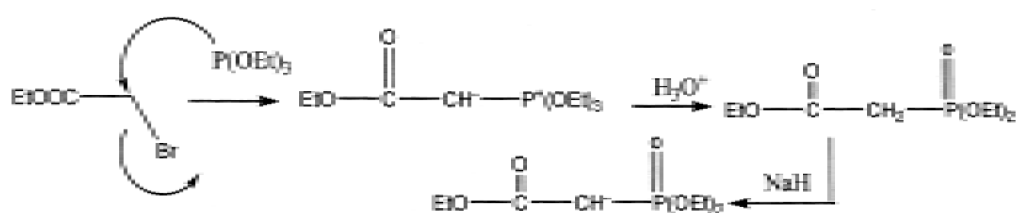
**Example :**



Non stabilized ylide gives cis olefin product

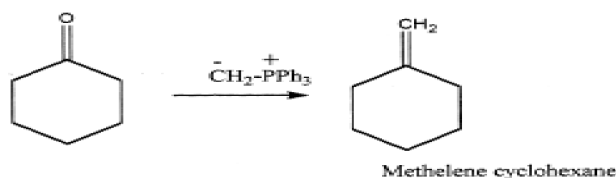
In case of stabilized ylide the – ve charge on “C” atom is delocalized by electron withdrawing group. Therefore, the nucleophilicity of this carbon atom is reduced and hence reluctant to attack on carbonyl carbon.

To avoid this problem modified ylide is used as their phosphonium salt.

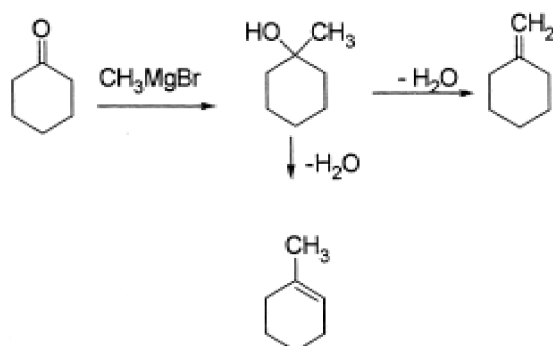


#### Utility :

In witting reaction the new double bond is produced from carbonyl compound and this double bond is fixed in their position.

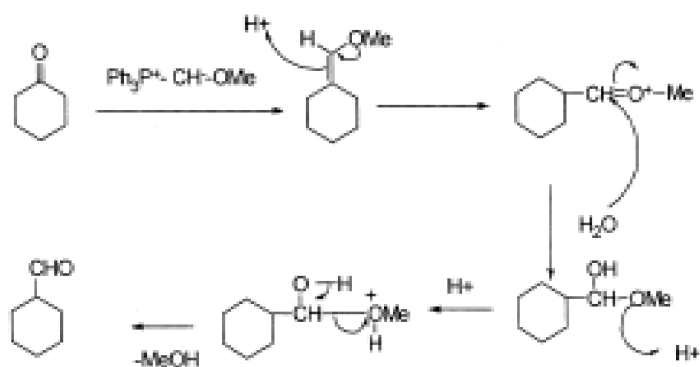
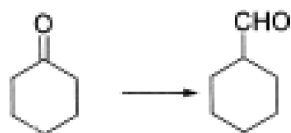


But in Grignard reaction the new double bond can be formed by elimination of water in both side of carbonyl group.





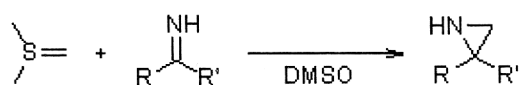
How will you convert :



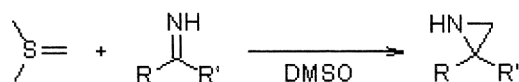
### 3.6.5 Corey-Chaykovsky reaction :

The Corey-Chaykovsky reaction or sometimes known as Johnson-Corey-Chaykovsky reaction is employed in modern organic synthesis to prepare three membered rings like epoxides (oxiranes), aziridines and thiiranes. This is the reaction of sulfur ylides with carbonyl compounds such as ketones or the related imines leads to the corresponding epoxides or aziridines.

#### Corey-Chaykovsky Epoxidation



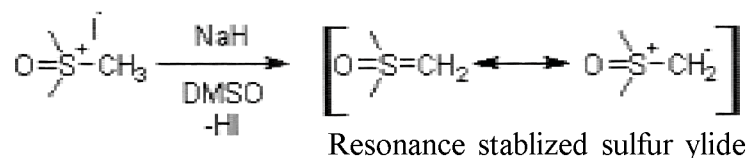
#### Corey-Chaykovsky Aziridination



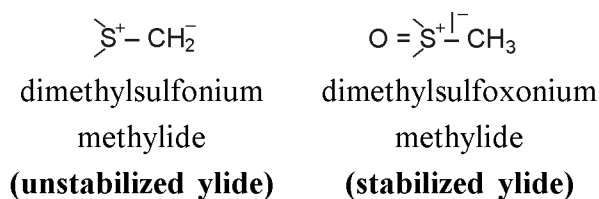
#### Sulfur Ylides :

The sulfur ylides are generated in situ by the deprotonation of sulfonium halides with strong base like  $\text{NaH}$  in solvents like DMSO. E.g. The corey ylide,

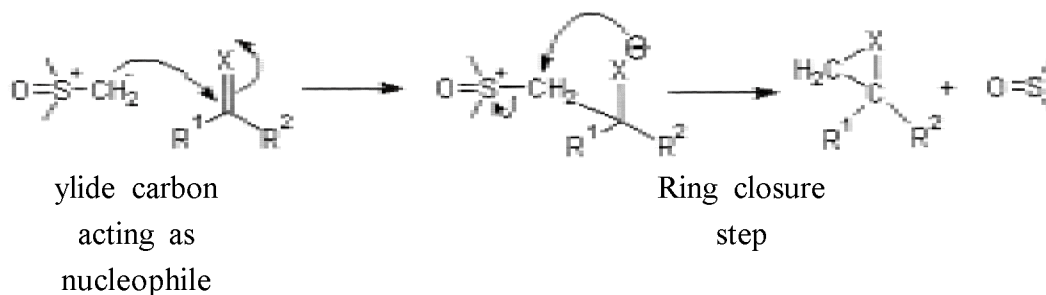
dimethylsulfoxonium methylide can be generated easily by treating trimethylsulfoxonium iodide with NaH in DMSO.



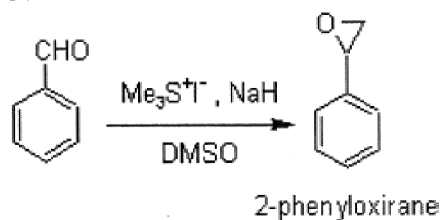
The sulfur ylides are stabilized when electron withdrawing groups are attached to it. Usually the groups like phenyl, carbonyl, ester etc., stabilize the ylide. Whereas the electron releasing group like alkyl tend to destabilize the ylides, E.g. the dimethylsulfoxonium methylide ( ) is more stable than dimethylsulfoxonium methylide due to presence of S = O group. Sometimes the course of the reaction is influenced by the stability of the sulfur ylides.



**Mechanism :**

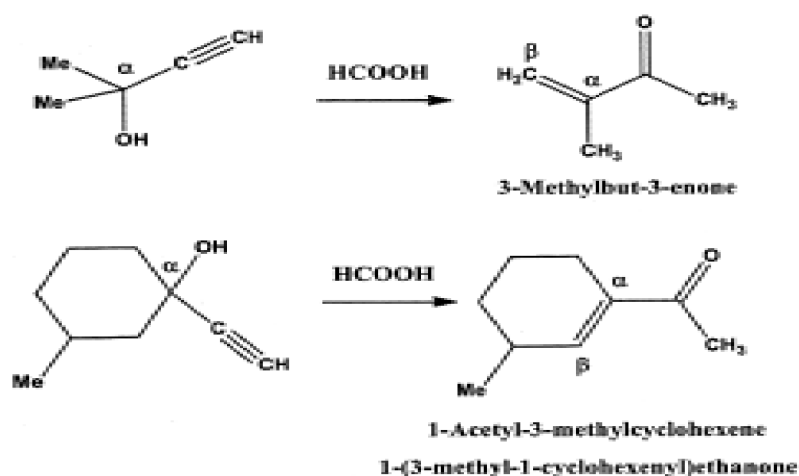


For an example, benzaldehyde can be converted to 2-phenyloxirane by treating it with dimethylsulfoxonium methylide, which generated it situ from trimethylsulfoxonium iodide and NaH in DMSO.

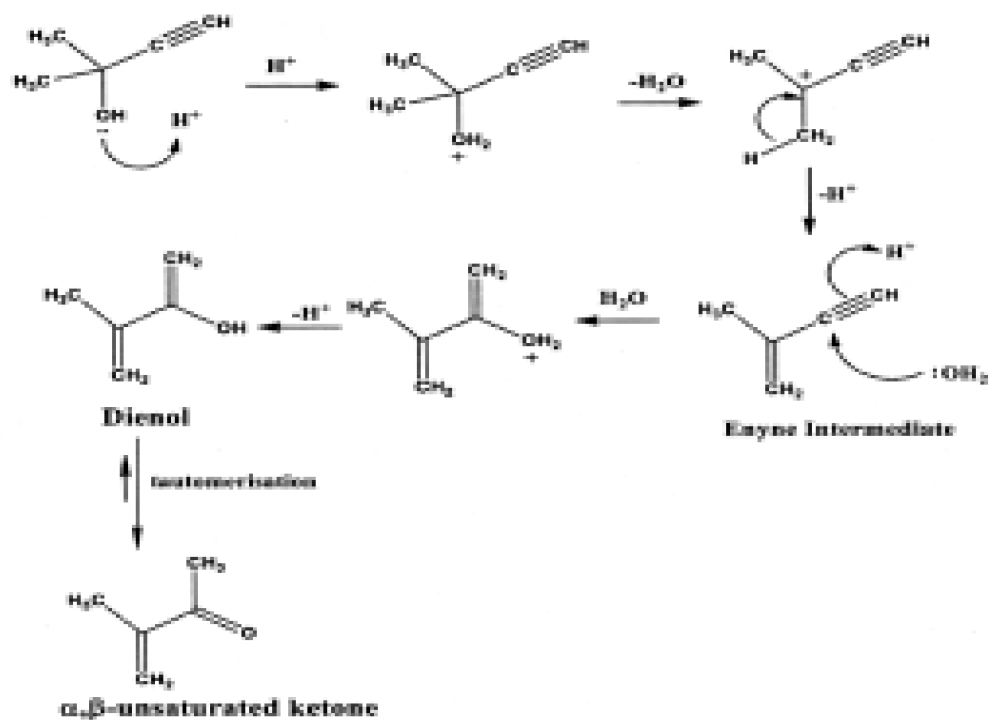


### 3.6.6 Rupe rearrangement

The acid catalysed thermal transformation of tertiary  $\alpha$ -cetylenic alcohols into the corresponding  $\alpha,\beta$ -unsaturated ketones is generally known as the Rupe rearrangement. The acid catalyst normally used is formic acid.

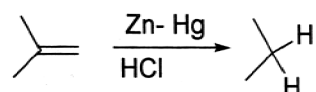


**Mechanism :** An enyne intermediate is formed during the reaction. The mechanism begins with the protonation of alcohol followed by the loss of the water molecule to form the corresponding carbocation. Subsequent loss of a proton from the  $\beta$ -position with respect to the alkyne to form an enyne. This is then followed by protonation, nucleophilic attack by water and tautomeric change to yield  $\alpha,\beta$ -unsaturated ketones.

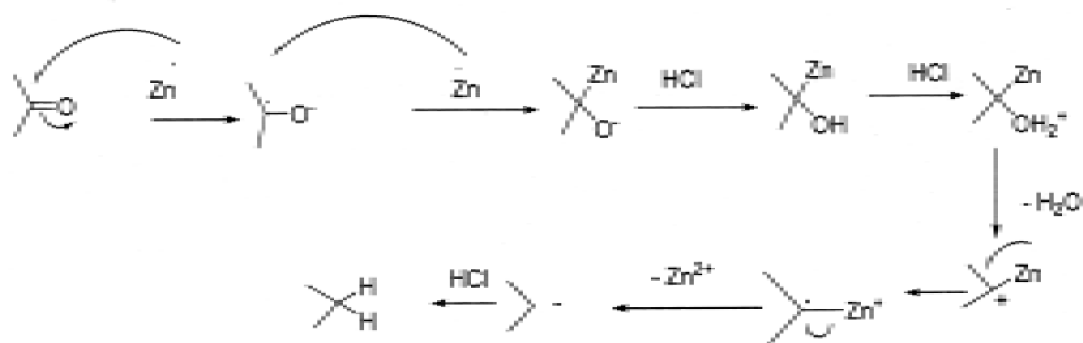


### 3.6.7 Clemmensen Reduction :

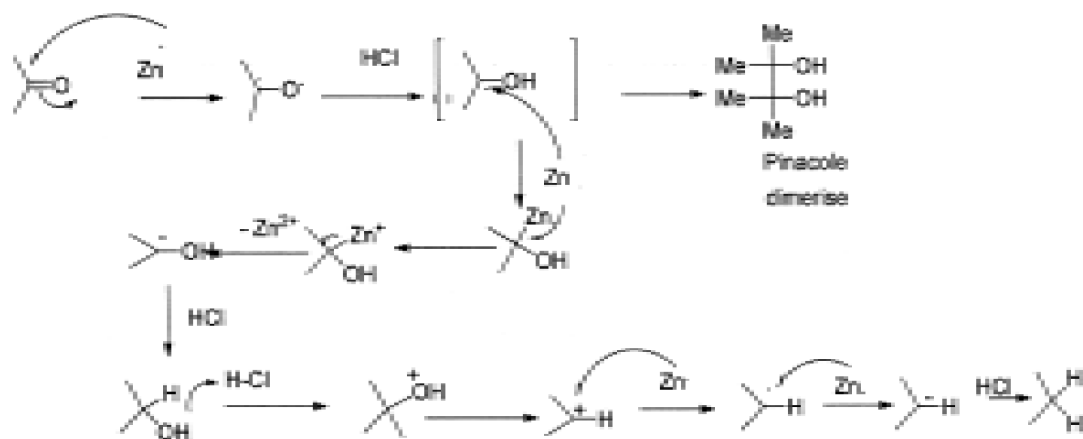
The reagent is used for this reaction is Zn-Hg/HCl



Mechanism :

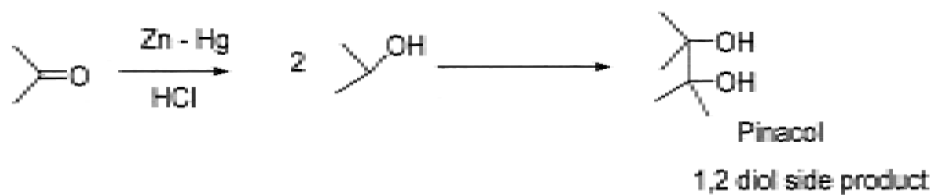


Another pathway :

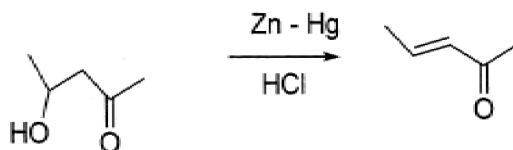


Disadvantages :

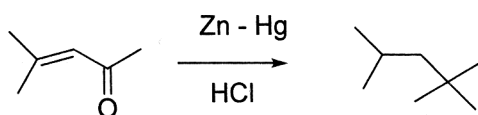
1. During the course of the reaction a side product is formed i.e., diol.



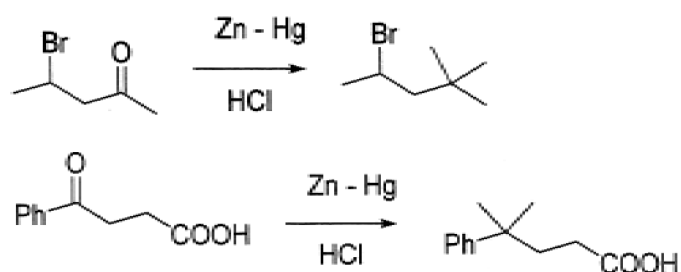
2. Deoxygenation does not take place in presence of acid sensitive function group.



3. For  $\alpha, \beta$  unsaturated ketone we get,

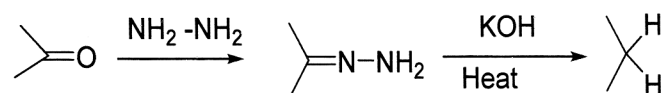


Utility :

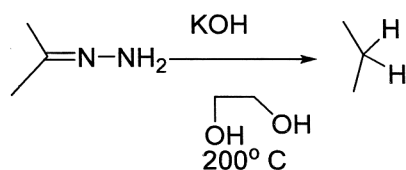


Clemmensen reduction is used for those substrates which are base sensitive. When substrate does not undergo Wolff-Kishner reduction then this substrate can be reduced by Clemmensen reduction.

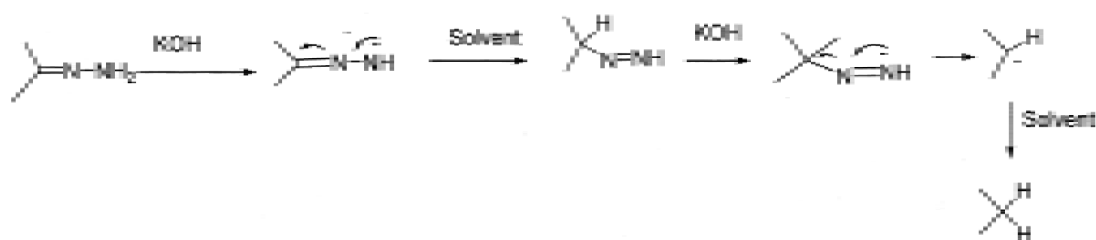
### 3.6.8 Wolff-Kishner Reduction :



In this reaction hydrazone compound is treated with strong base in sealed tube to give alkane compound. High boiling point ethylene glycol is used as the alternative solvent instead of sealed tube.

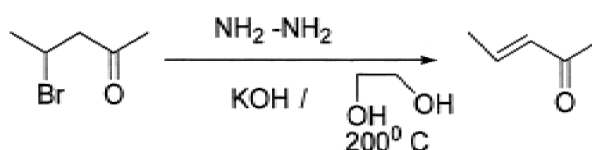


**Mechanism :**

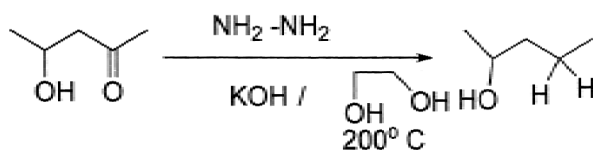


**Limitation :**

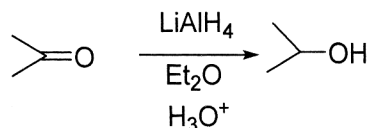
If a compound contains base sensitive functional group then deoxygenation does not take place under Wolff-Kishner condition.

**Advantages :**

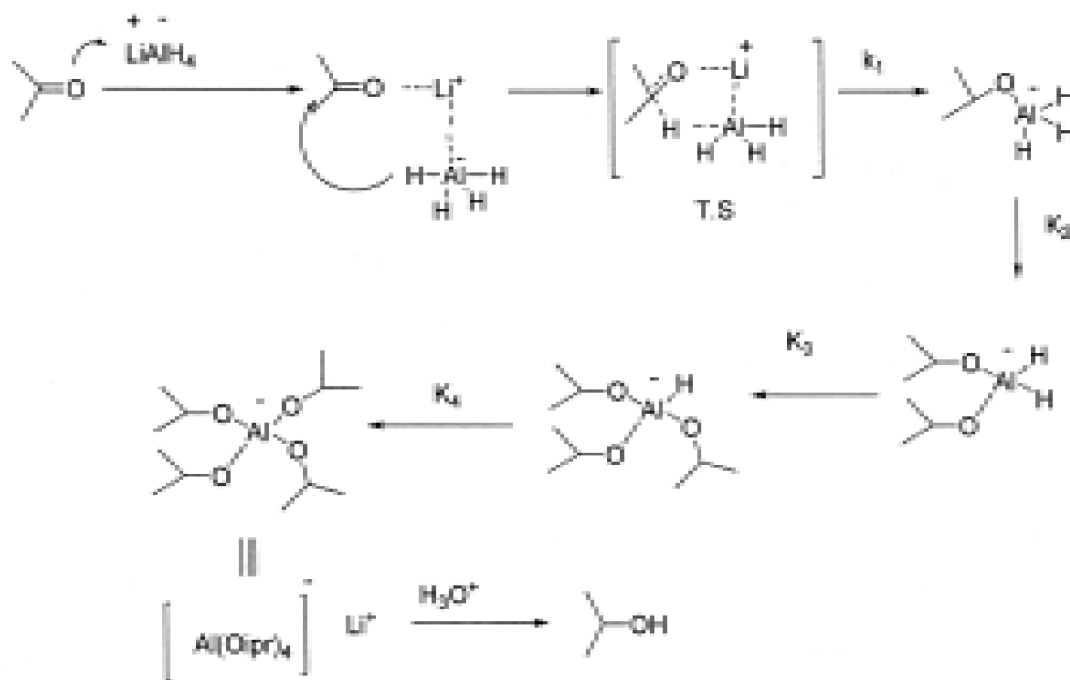
If a compound contains acid sensitive functional groups then deoxygenation is tolerated under Wolff-Kishner Condition.

**3.6.9 Reduction by LiAlH<sub>4</sub> :**

LiAlH<sub>4</sub> reduces the various functional groups to their corresponding reduced products. Since LiAlH<sub>4</sub> reduces various functional groups. Therefore, this reagent has lower selectivity for functional reduction. Condition for the reduction of carbonyl by LiAlH<sub>4</sub> :

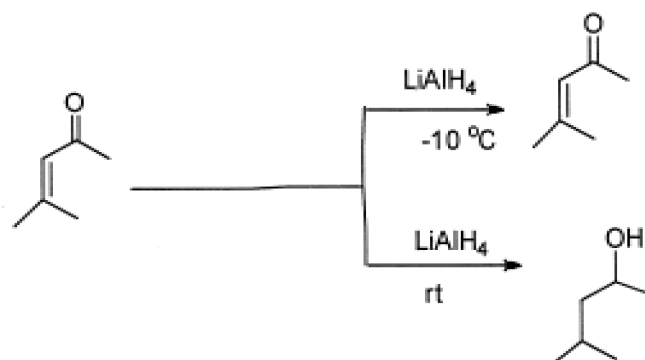
**Q. Why dry ether is used for the reduction of carbonyl group?**

This is due to the Li<sup>+</sup> violently reacts with water and damages the LiAlH<sub>4</sub>. Therefore, dry ether is used.

**Mechanism :**

The rate of addition to carbonyl group by the hydride ion is  $K_1 > K_2 > K_3 > K_4$ , due to steric interaction.

**Q.  $\text{LiAlH}_4$  can't reduce simple olefin double bond but it can reduce the ethylinic bond of  $\alpha, \beta$ -unsaturated carbonyl compound. Explain**



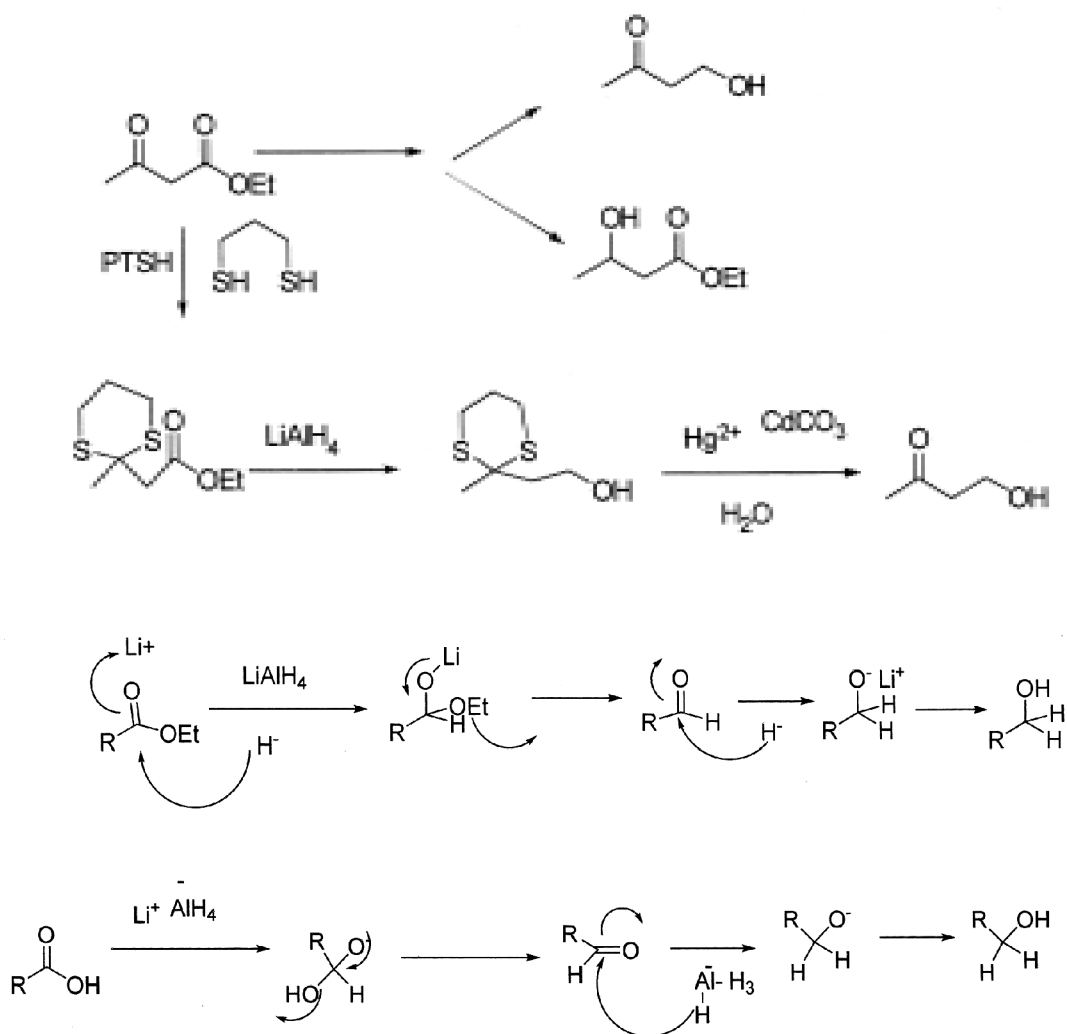
$\text{LiAlH}_4$  can't reduce isolated olefin or alkyne system. This is due to  $\text{H}^-$  is nucleophilic species and ethylinic double bond is also electron rich species. So there



has greater repulsion when they come closer to each other. But  $\alpha\beta$ , unsaturated carbonyl compound is reduced by  $\text{LiAlH}_4$  as polarization is developed in double bond by carbonyl group.

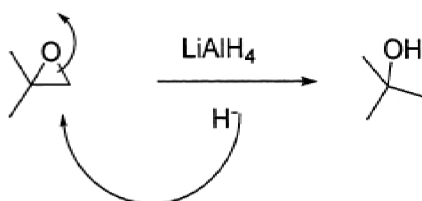
**Q. What is the role of  $\text{Li}^+$  in  $\text{LiAlH}_4$  reduction?**

$\text{Li}^+$  is a hard acid. So it readily co-ordinates with carbonyl oxygen and increases the polarity of  $\text{C}=\text{O}$ . Hence, carbonyl carbon become much higher electrophilic in nature than the non-coordinated carbonyl group. Hence  $\text{H}^-$  easily attack to the carbonyl carbon and reduces to alcohol.

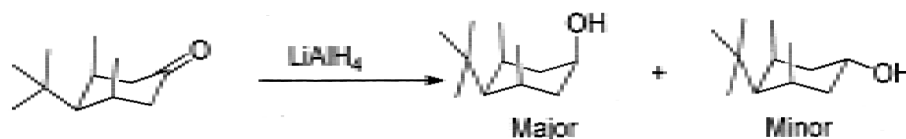


**Epoxide cleavage by  $\text{LiAlH}_4$  :**

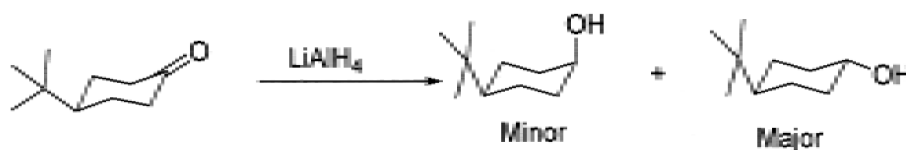
Here,  $\text{S}_{\text{N}}2$  attack is favoured and  $\text{H}^-$  attacks at the less hindered side.



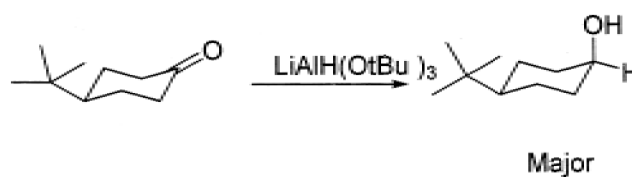
In case of a hindered substrate,  $\text{H}^-$  attacks to those sides in which it is less hindered. Here the equatorial side is less hindered than the axial side. Hence, we get axial alcohol as the major product. The reaction is known as steric development control (S.D.C).

**If the cyclohexanone is non-hindered :**

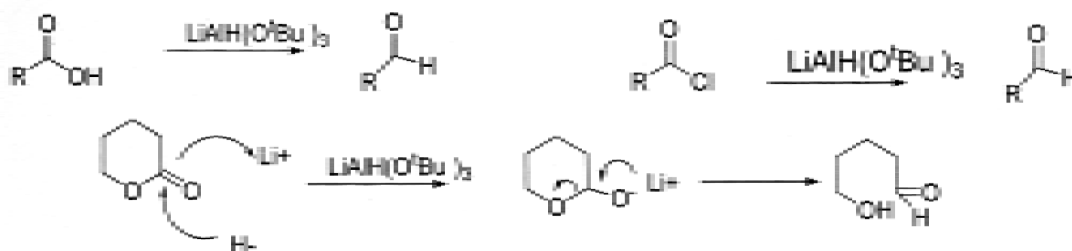
In case of a non-hindered cyclohexanone system,  $\text{H}^-$  attacks to those side where the product becomes stabilized. Here the axial alcohol is less stable than the equatorial alcohol. So axial attack is more favourable. This reaction is known as product development control (P.D.C).

**Hindered hydride donor :**

$[\text{LiAl}(\text{O}^t\text{Bu})_3\text{AlH}]$  = Lithium tritertiary butoxide aluminium hydride.



If the  $\text{H}^-$  donor is hindered in nature then  $\text{H}^-$  attacks the cyclohexanone from the less hindered side; i.e. equatorial side. So we get axial product as prominent product.



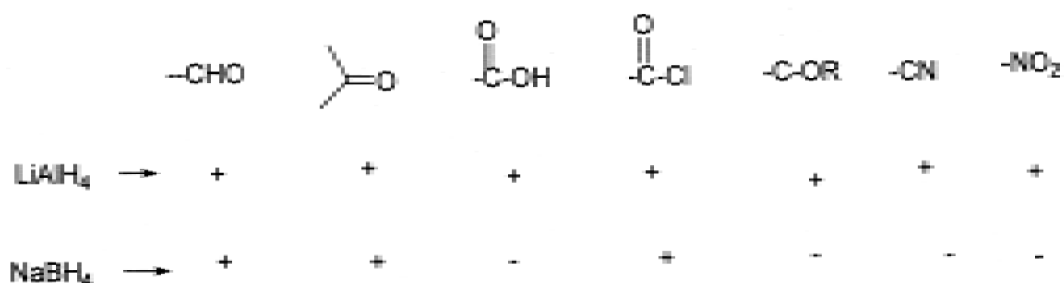
### 3.6.10 Reduction of $\text{Na}^+\text{BH}_4^-$ :

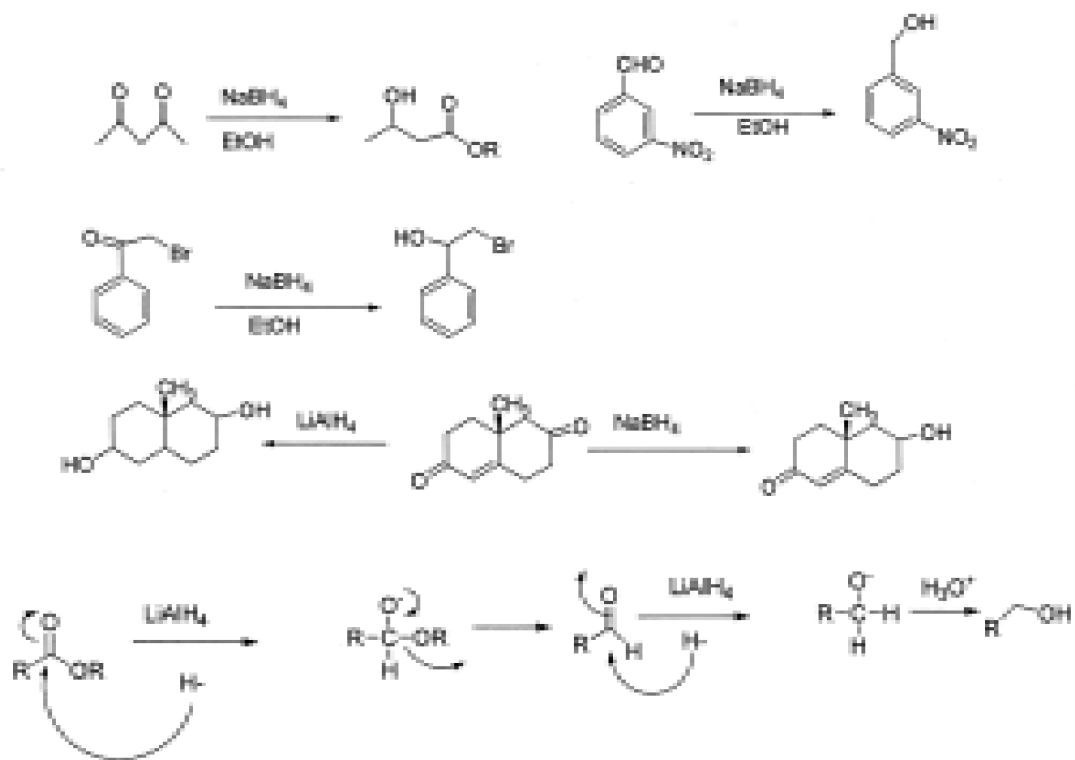
**Q. Why  $\text{NaBH}_4$  reduction take place in polar solvent ?**

$\text{Na}^+$  is a soft metal comparatively to that of  $\text{Li}^+$ . In  $\text{LiAlH}_4$ ,  $\text{Li}^+$  coordinates to the oxygen atom of carbonyl group and increase the electrophilicity of carbonyl carbon. But in  $\text{NaBH}_4$ ,  $\text{Na}^+$  can't coordinate to the oxygen atom as the size of the  $\text{Na}^+$  is greater than  $\text{Li}^+$ . So it does not increase the electrophilicity of carbonyl carbon.

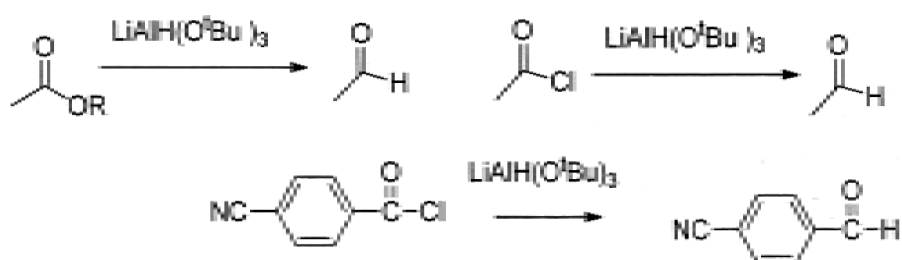
But in polar solvent, oxygen atom takes part in H-bonding with the solvent molecule. This H-bonding effect increase the electrophilicity of carbonyl carbon and  $\text{H}^-$  can reaily attack to the carbonyl carbon to give alcohol as the product. Therefore, to increase the electrophilicity of carbonyl carbon polar solvent is used in  $\text{NaBH}_4$  reduction.

**Comparision of  $\text{NaBH}_4$  reduction/ $\text{LiAlH}_4$  reduction**



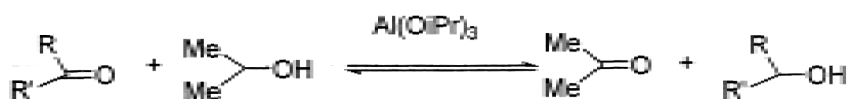
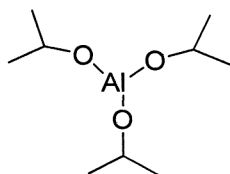


$\text{LiAlH}_4$  has no selectivity to reduce the ester group of alcohol. If we want the conversion of ester to aldehyde then only one hydride is needed. For this purpose, we use  $\text{LiAlH}(\text{O}^t\text{Bu})_3$ .

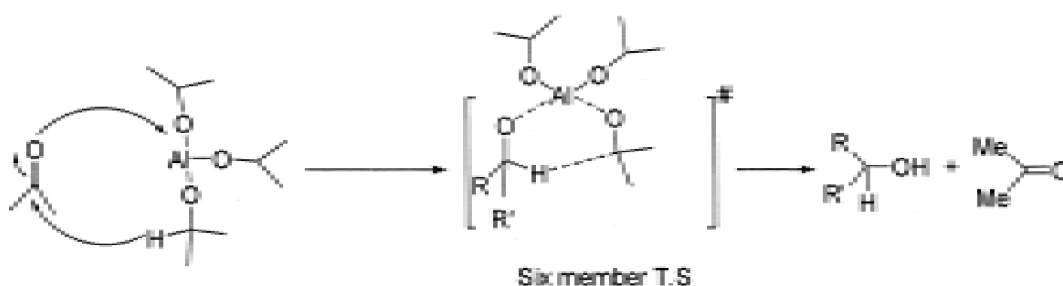


### 3.6.11 Meerwin Ponndrof Verley (MPV) Reduction

This method is used for the selective reduction of carbonyl group. The reagent for this reduction is Aluminium triisopropoxide  $[\text{Al}(\text{O}^i\text{Pr})_3]$ .

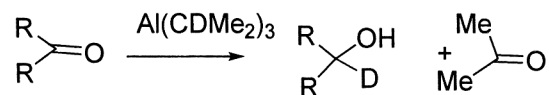


#### Mechanism :



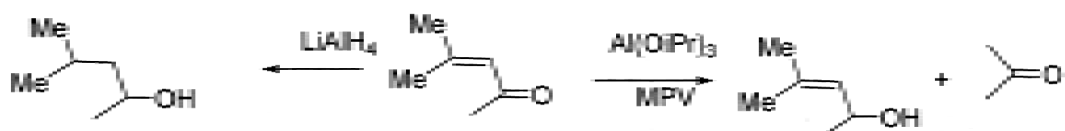
#### Evidence :

If the hydride donor aluminum isopropoxide contains Deuterium then we get the reduced product with deuterium. So, hydride transfer takes place through a six-membered cyclic T.S.

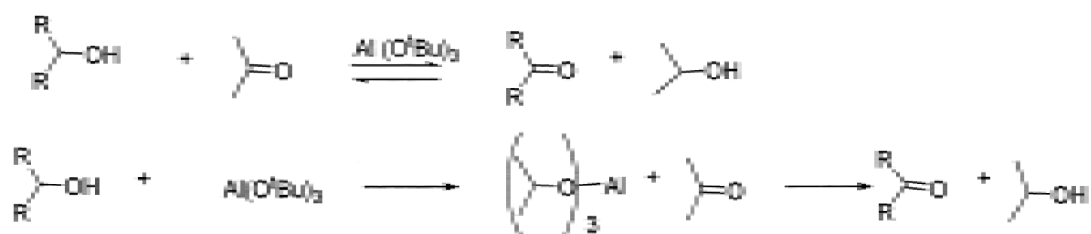


#### 3. Limitation :

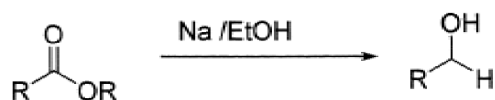
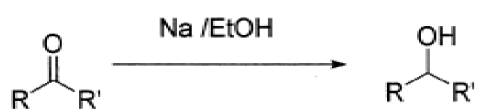
MPV reduction method can't be used for the reduction of  $-\text{NO}_2$ ,  $-\text{CN}$ ,  $-\text{COOR}$ ,  $-\text{C}=\text{C}-$ , and  $-\text{C}=\text{C}$  etc.

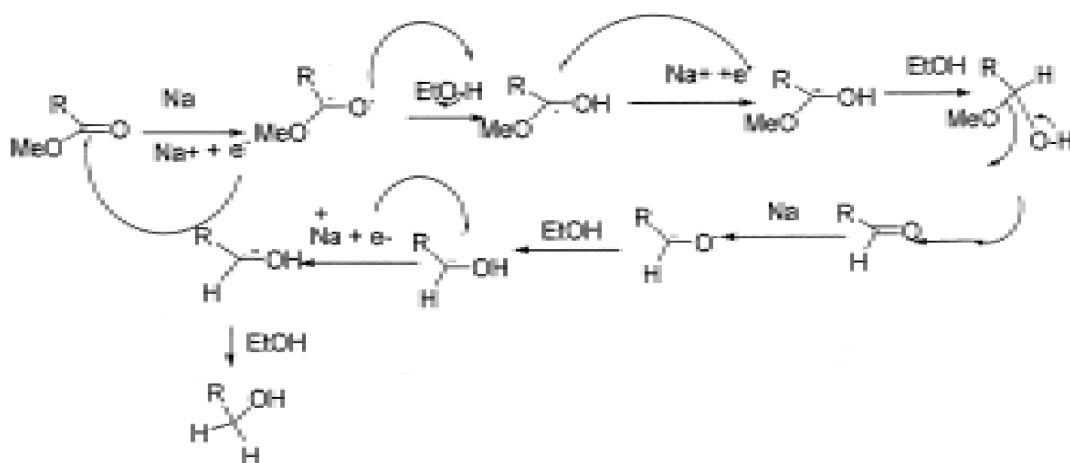
**4. Reaction :****3.6.12 Oppenauer Oxidation :**

The reverse of MPV reduction is known as the oppenauer oxidation. Here 2° alcohol is converted to ketone in presence to tertiary butoxide in acetone.

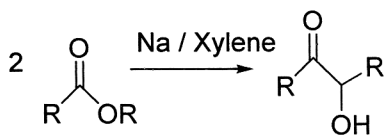
**3.6.13 Bouveault-Blanc reduction :**

This method is used for the carbonyl or ester group by Na/EtOH reagent

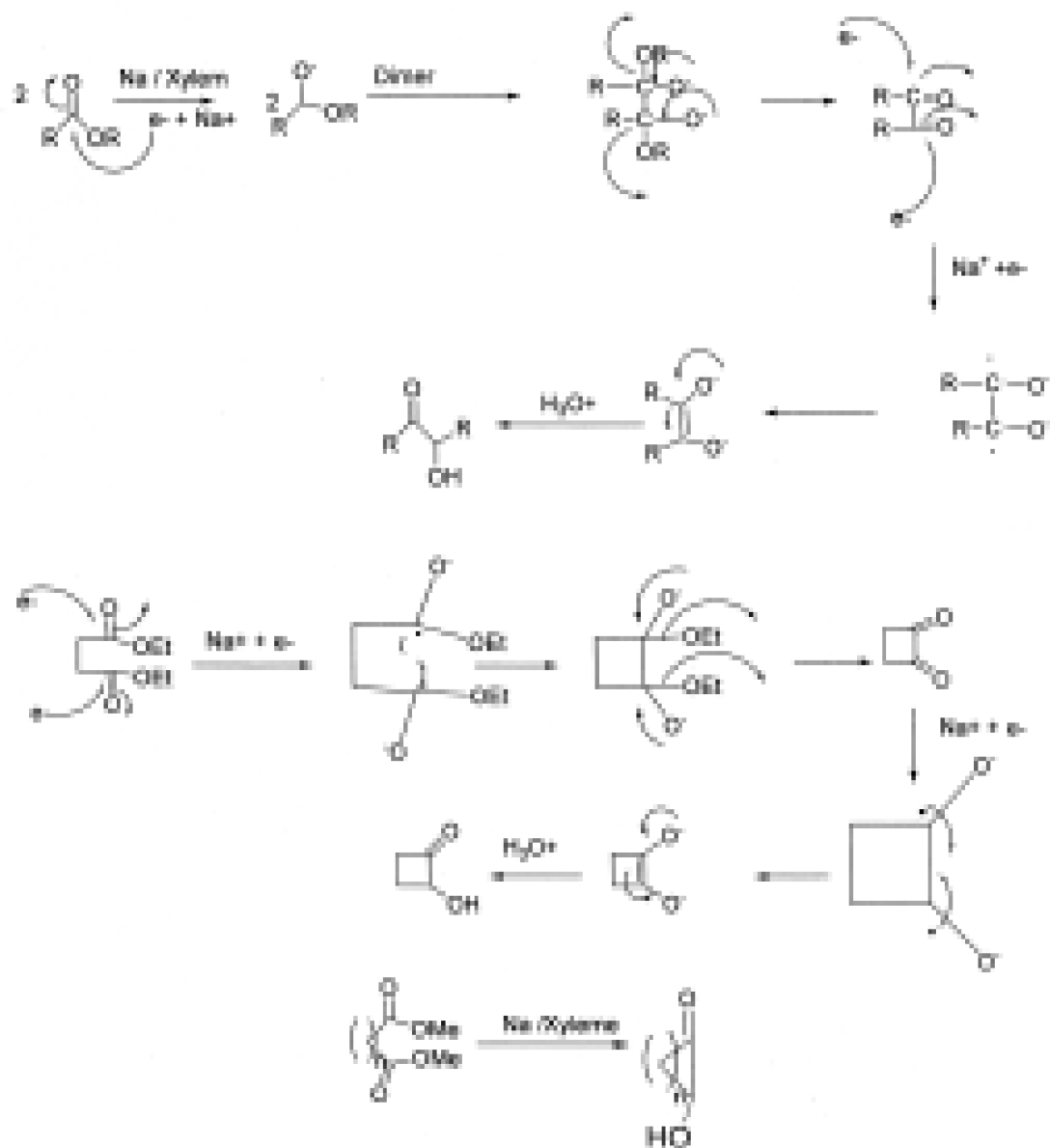


**Mechanism :****3.6.14 Acyloin Condensation :**

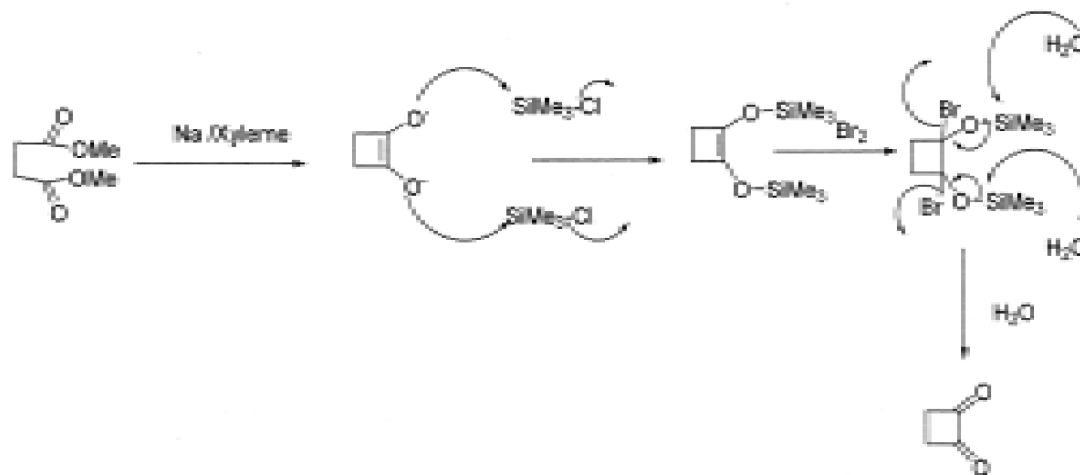
If the reduction is performed in nonpolar solvent then there has no chance of protonation. In Na/xylene medium, the dimerisation of ester takes place to form 2-hydroxy ketone derivatives.



**Mechanism :**





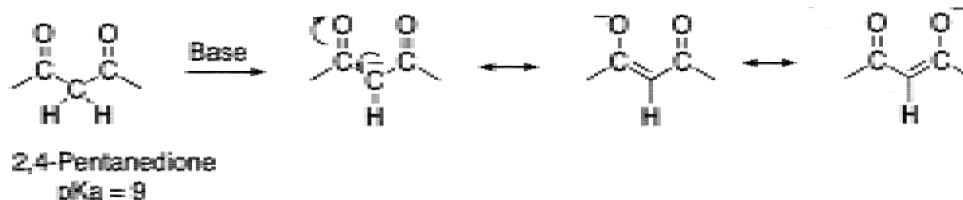


### 3.7 Exploitation of acidity of $\alpha$ -H of $\text{C}=\text{O}$

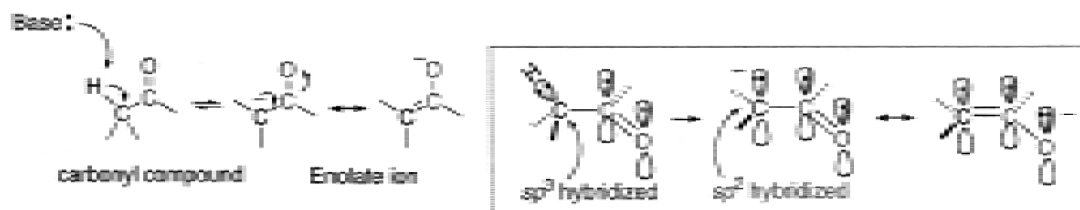
Alkyl hydrogen atoms bonded to a carbon atom is  $\alpha$  (alpha)-position relative to a carbonyl group display unusual acidity. This property leads to show various interesting properties of a carbonyl compound which are discussed below.

#### 3.7.1 Acidities of hydrogens on the $\alpha$ -Carbon of Carbonyl Compounds

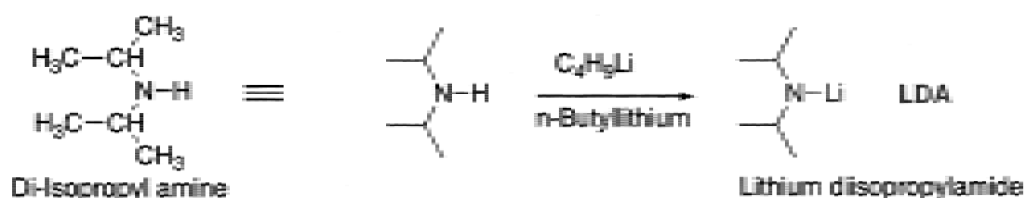
The C-H bond on the  $\alpha$ -carbon of carbonyl compounds (aldehydes, ketones, acids, and acid derivatives) have modest acidity ( $\text{pK}_a$  17-30) depending on the functional group. The carbonyl group is an electron-withdrawing group and is able to acidify the hydrogen on the alpha carbon. When two electron-withdrawing groups flank a methylene group, its acidity is increased. E.g. the methylene group in 1,3-dicarbonyl compounds is highly acidic.



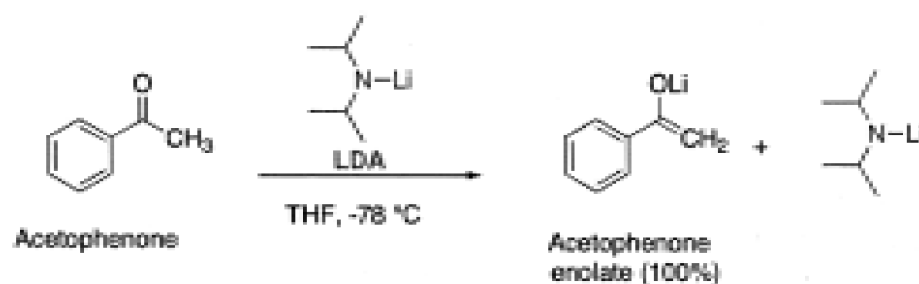
Strong bases will deprotonate the  $sp^3$  hydrogen on the alpha carbon generating an enolate ion. In the enolate ion the alpha carbon is  $sp^2$  hybridized. This anion is stabilized by delocalization of the negative charge into the carbonyl group placing the charge on the oxygen atom.



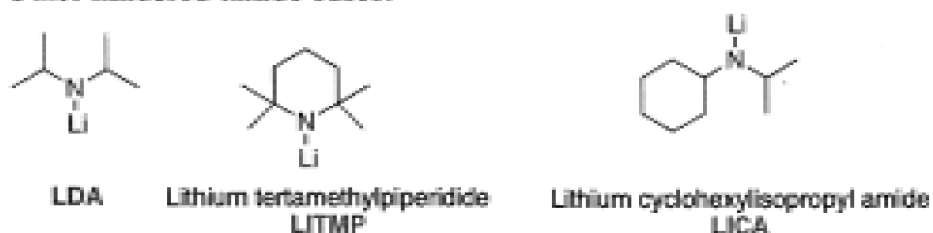
Thus the alpha C–H bonds in carbonyl compounds can be deprotonated using a strong base. This base needs to be non nucleophilic (i.e. it will not add to the carbonyl group). Amide bases (reagents derived from amines and a base) are typically used for deprotonation.



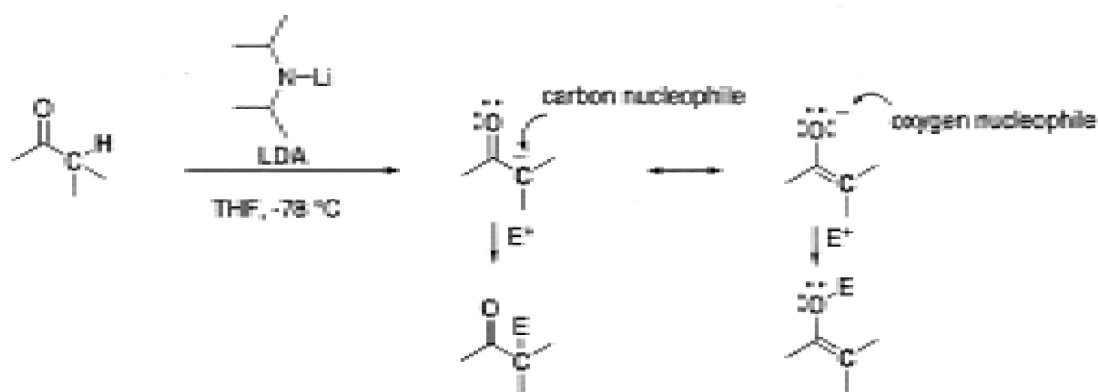
Lithium diisopropylamide (LDA) is an excellent non-nucleophilic base (the nitrogen is hindered because of the two bulky isopropyl groups). It is a strong base (pKa of diisopropylamine is  $\sim 40$ ). It is soluble in most common organic solvents. Furthermore, reactions can be carried out at  $-78^\circ C$ . LDA will completely deprotonate carbonyl compounds.



Other hindered amide bases.



Enolates are electron rich intermediates. They are ambident nucleophiles. They are nucleophilic on the alpha carbon and the carbonyl oxygen. The enolates react with electrophiles.



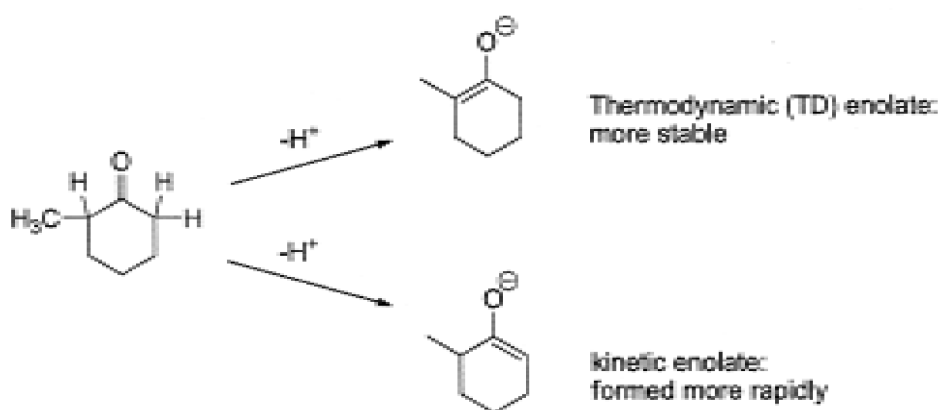
There are a variety of reactions one can do with enolate ion. There are a large number of electrophiles, which can be used with enolates.

### 3.7.2 Kinetic vs. Thermodynamic Enolates :

An asymmetric ketone with hydrogens at both  $\alpha$ -carbons can form two regioisomeric enolates. If the two  $\alpha$ -carbons differ in their degree of substitution, it may be possible to control which of the two regioisomers predominates.

Removal of a proton from the more substituted (and more hindered)  $\alpha$ -carbon gives the enolate with the more substituted C = C double bond. This enolate is the more thermodynamically stable, and is referred to as the thermodynamic enolate. Compare this with Zaitsev's rule, which predicts that reactions that form alkenes favour the production of the more substituted alkene.

Removal of a proton from the less substituted (and less hindered)  $\alpha$ -carbon gives the enolate with the less substituted C = C double bond is referred to as the kinetic enolate. This enolate is less stable than the thermodynamic enolate, but it is formed more rapidly because the hydrogen being removed is more sterically accessible.

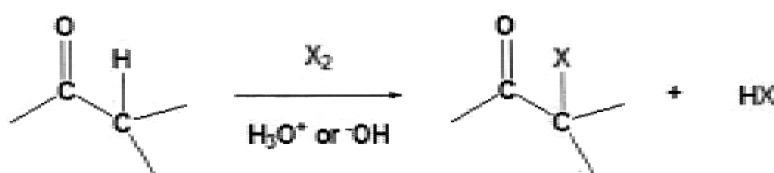


In reactions where one product is kinetically favoured and another thermodynamically favoured, the kinetic result is favoured by low temperatures and an irreversible reaction. However, if the reaction is reversible, the kinetic product can revert back to starting material and react again, possibly forming the thermodynamic product. Higher temperatures would then increase the rate at which the two products interconvert.

It may be remembered that **strong, hindered base** like LDA, at **low temperatures**, typically will favour formation of the **kinetic enolate**. **Weaker bases** such as alkoxides or amines, and **at higher temperatures**, favour formation of the **thermodynamic enolate**.

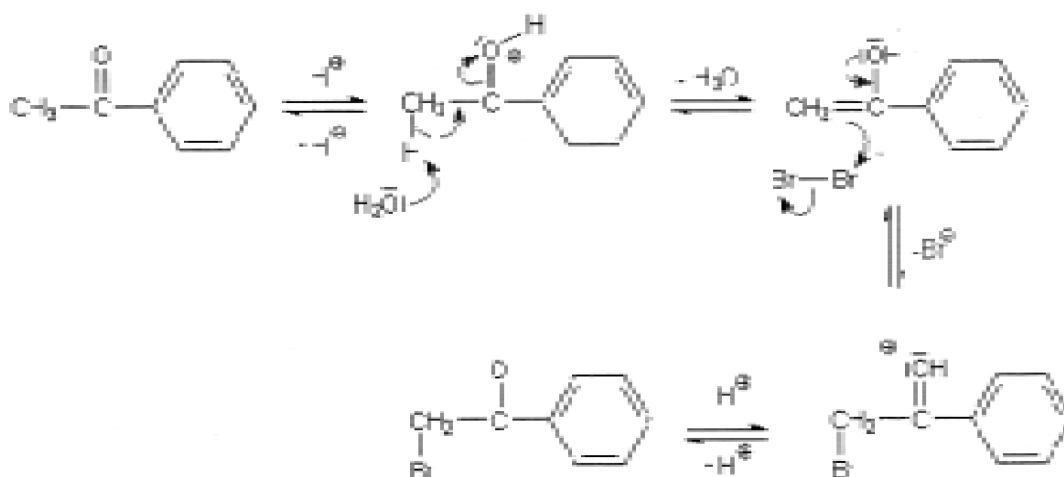
### 3.7.3 $\alpha$ -Halogenation of carbonyl Compounds :

Carbonyl Compounds can form enolates in basic condition and enols in acidic condition. If enolizable carbonyl compounds are treated with iodine, bromine, or chlorine, halogenation of the  $\alpha$ -carbon occurs. Halogenation yields different products depending on whether the reaction conditions are acidic or basic.



**(a) Acid-catalyzed  $\alpha$ -halogenation :**

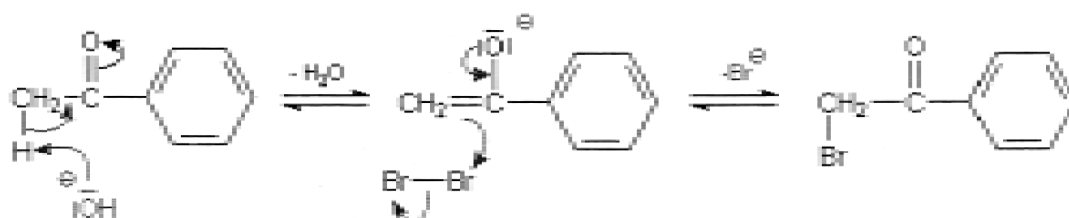
Acid-catalyzed  $\alpha$ -halogenation leads to the exchange of only one  $\alpha$ -hydrogen for a halogen even if the  $\alpha$ -carbon carries additional hydrogens. In the initial reaction step, the enol nucleophilically attacks the halogen molecule. As a result, the halogen molecule is heterolytically cleaved and a single bond between the  $\alpha$ -carbon and a halogen atom is formed. That is, the reaction step yields a halide anion, as well as a protonated and, thus, positively charged  $\alpha$ -halocarbonyl compound. Deprotonation results in the formation of the  $\alpha$ -halocarbonyl compound. Under acidic conditions, the enol is continually supplied through keto-enol tautomerism. The reaction rate does not depend on the halogen's concentration.



In the reaction product, the  $\alpha$ -halocarbonyl compound, the electron density of the carbonyl carbon is reduced by the electron-withdrawing effect of the halogen. As a result, protonation of the carbonyl carbon and, thus, enolization is considerably retarded. Consequently, under acidic conditions, the reaction rate of a second halogenation is much lower than that of the first halogenation. Therefore, halogenation of carbonyl compounds under acidic conditions yields monohalogenated  $\alpha$ -halocarbonyl compounds.

**(b) Base-catalyzed  $\alpha$ -halogenation :**

If halogenation is carried out under basic conditions with a halogen excess, all  $\alpha$ -hydrogens are exchanged for a halogen atom.

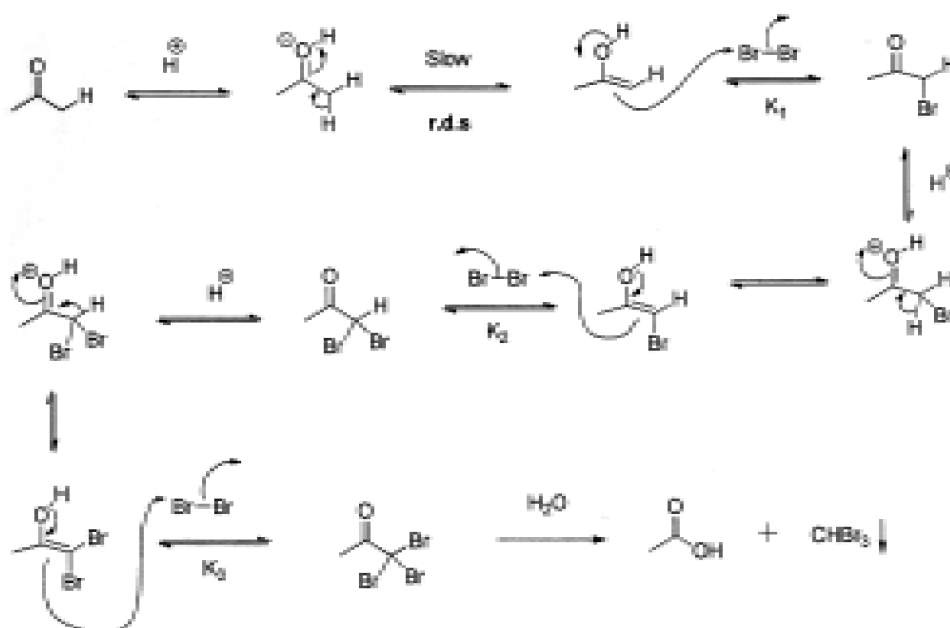


Under basic conditions, the halogen atom's electron-withdrawing effect promotes a second  $\alpha$ -deprotonation and, thus, the enolization, as the  $\alpha$ -hydrogen acidity has increased. As a result, all  $\alpha$ -hydrogens are exchanged for a halogen atom under basic conditions. It is difficult to stop the base promoted reaction after a single substitution, so acidic conditions are used when a monohalo product is required.

### 3.7.4 Haloform Reaction :

Haloform reaction takes place in presence halogen molecule such as ( $\text{X} = \text{Cl}, \text{Br}, \text{I}$ ) and acid or base. In case of acid catalysed haloform, the reaction goes through enolization intermediate. But in case of base catalysed haloform reaction, the reaction goes through carbanion intermediate.

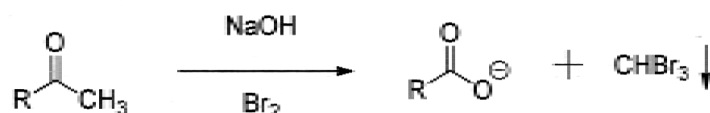
#### Acid catalysed haloform reaction :



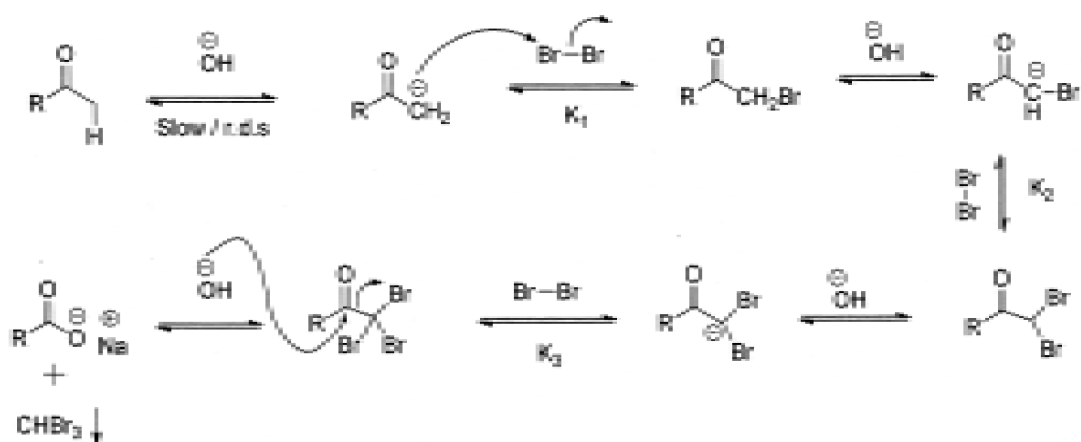
**Q. In acid catalysed haloform reaction the rate of introduction of  $\text{Br}_2$  molecule has the order  $K_1 > K_2 > K_3$ . Explain**

On acid catalysed haloform reaction, the rate of enol formation gradually decreases with increasing the halogen atom on the  $\alpha$  carbon atom. This is due to after introduction one halogen atom on the  $\alpha$ -carbon atom, the  $-I$  effect of halogen atom creates a partial +ve charge on the  $\alpha$ -carbon atom. This +ve charge is repelled by the partial positive charge on the carbonyl carbon. Again with increasing the halogen, the  $\alpha$ -carbon atom becomes more sterically hindered. Hence, the rate of proton capture for enolate formation becomes reduced.

**Base catalysed haloform reaction :**



**Mechanism**



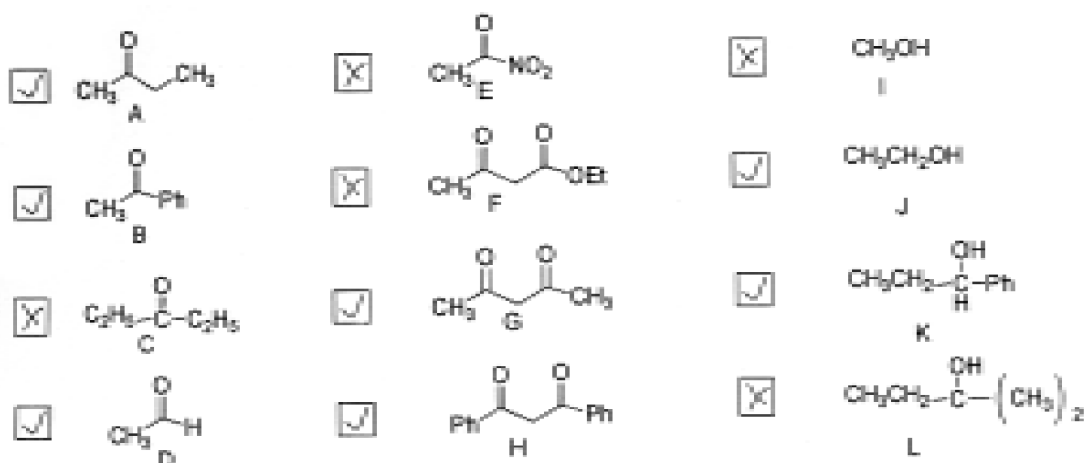
**Q. In case of base catalysed haloform reaction the rate of introduction of  $\text{Br}_2$  molecule has the order  $K_1 < K_2 < K_3$ . Explain.**

In base catalysed haloform reaction, hydrogen abstraction is the r.d.s. Again the rate of introduction of halogen atom in presence of base increases with increasing the halogen atom on  $\alpha$ -carbon atom. This is due to with increasing the halogen atom, the  $\alpha$ -carbon proton becomes more acidic as the halogen atom has  $-I$  effect. So the rate of halogenations can be explained.

In acid catalysed haloform reaction, the rate determined step is the formation of enolate intermediate and in base catalysed haloform reaction, the rate determined step is proton abstraction. So, in both acid and base catalysed haloform reaction the introduction of  $\text{Br}_2$  molecule to the  $\alpha$ -position of carbonyl group doesn't effect the rate of reaction. So, in haloform reaction the order of  $\text{Br}_2$  molecule is Zero in rate equation. So we can write—

$$\text{Rate} = [\text{substrate}] \cdot [\text{H}^+ / \text{OH}^-] \cdot [\text{X}_2]^0$$

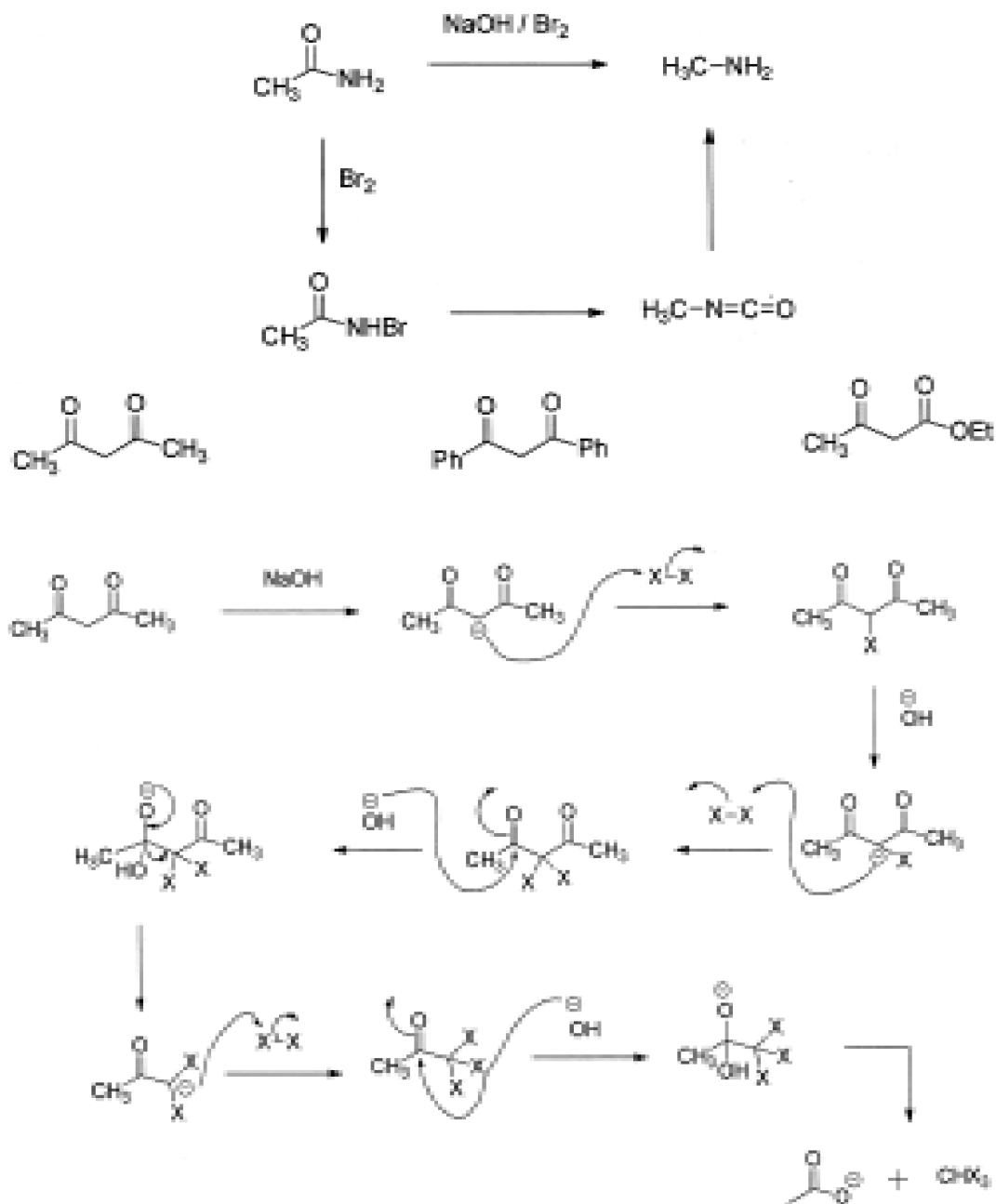
**Q. Which of the following compounds undergoes haloform reaction?**



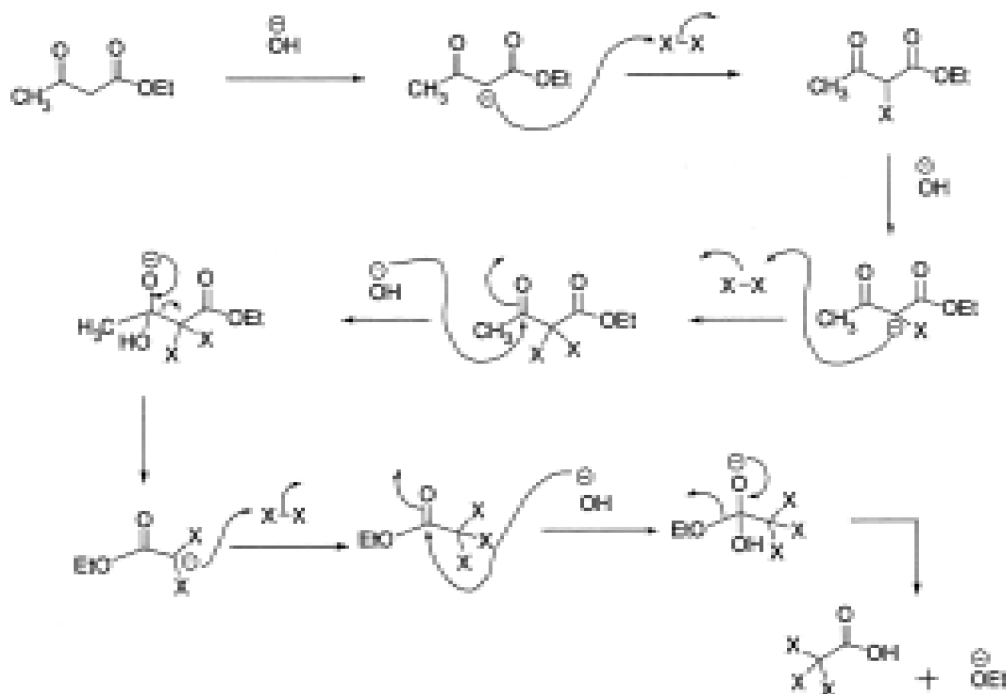
**Hint :** Structure A, B, D, E; the above compounds have keto-methyl group ( $\text{CH}_3\text{-CO-}$ ). So they undergo haloform reaction in presence of  $\text{NaOH}/\text{X}_2$ . Structure C compound does not has ketomethyl group. So it does not respond haloform reaction. In case of acetic acid, acidic carboxyl proton is removed first instead of a carbon proton in base medium. After deprotonation of carboxyl group, the deprotonation of a carbon does not occur due to the cross conjugation factor.

Again in case of acetamide, the proton abstraction take place from the *N*-atom than  $\alpha$ -carbon atom. Again in case of amide the  $\text{Br}_2$  molecule, introduction take place at the *N*-atom through the lone pair of *N*-atom and degradation product is produced instead of haloform product.

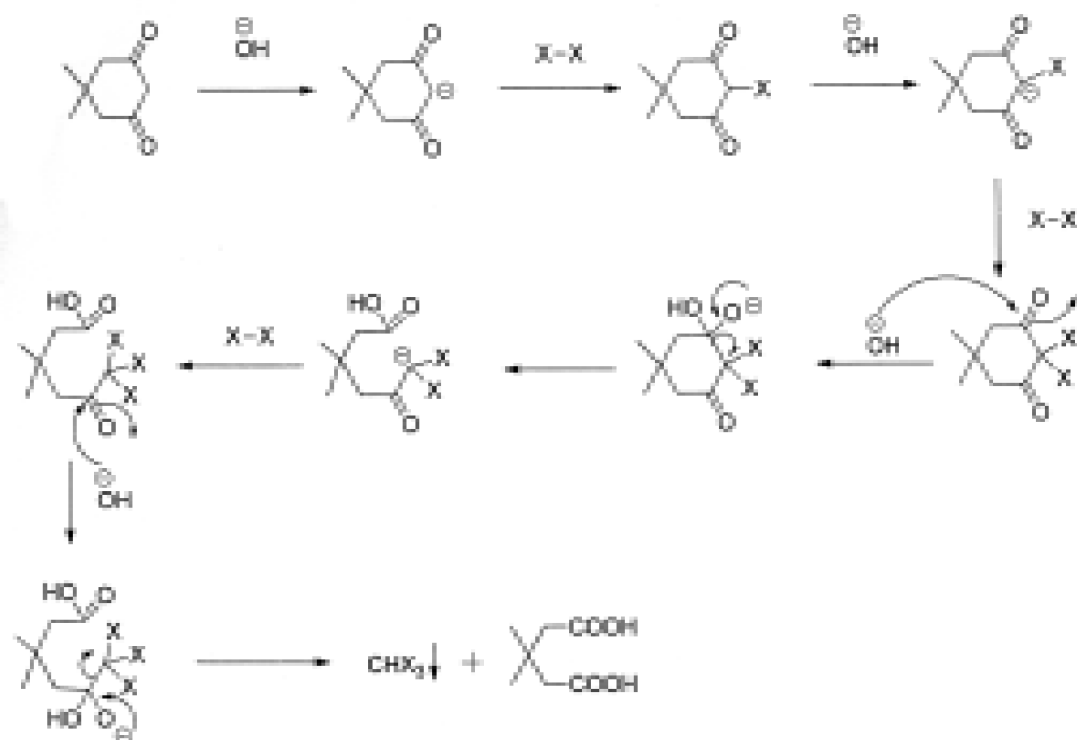




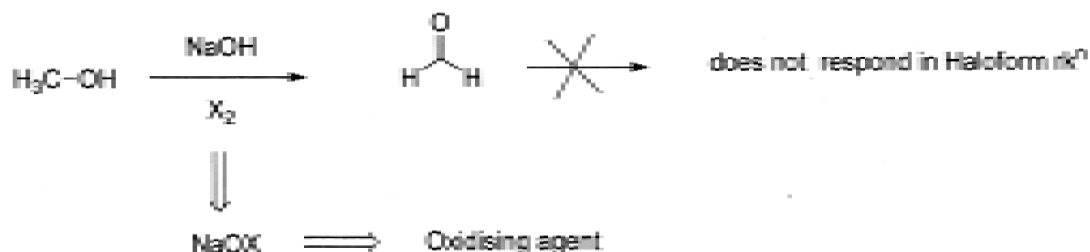
In case of acetyl acetone, the methylene proton is more acidic than methyl proton. So in presence of base this methylene proton is first deprotonated to give carbanion and two  $\text{Br}_2$  molecules are introduced at this carbon atom in consequent manner. Hence after basic cleavage produce haloform as the final product.



Here  $-\text{CX}_3$  has lower leaving aptitude than  $-\text{OEt}$ . So after of  $\text{OH}^-$  it removes  $\text{EtO}^-$  rather than  $\text{CX}_3$ .

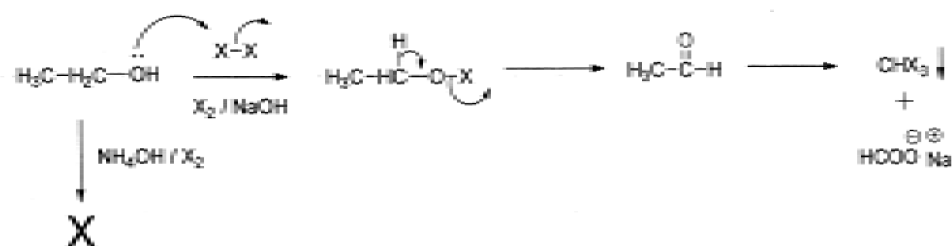


**MeOH** does not respond haloform test as it after oxidation gives formaldehyde which does not have any keto-methyl group.

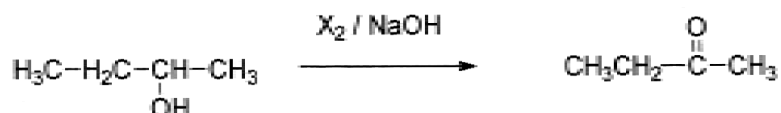


### Q. Why ethanol gives haloform reaction?

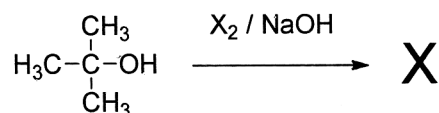
In case of ethanol,  $\text{X}_2/\text{NaOH}$  gives  $\text{NaOX}$  which acts as oxidising agent. It oxidises ethanol to acetaldehyde. Acetaldehyde has ketomethyl group. So it gives haloform test.



But it does not undergo oxidation in presence of  $\text{NH}_4\text{OH}$  (weak base). So in this condition it does not undergo haloform reaction.



Since after oxidation it has keto-methyl group, so it responds haloform test.

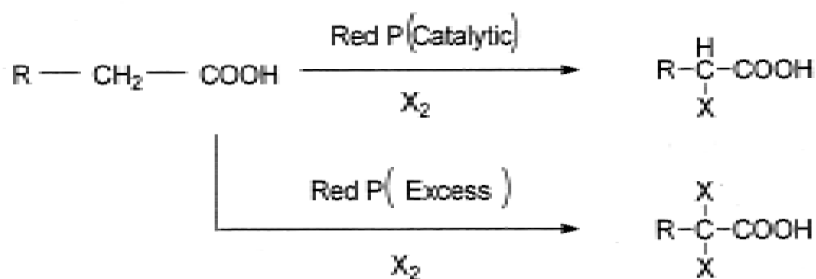


It does not undergo haloform reaction as  $3^\circ$  alcohol does not undergo oxidation.

### 3.7.5 Hell Volhard Zelinsky (H.V.Z.) Reaction :

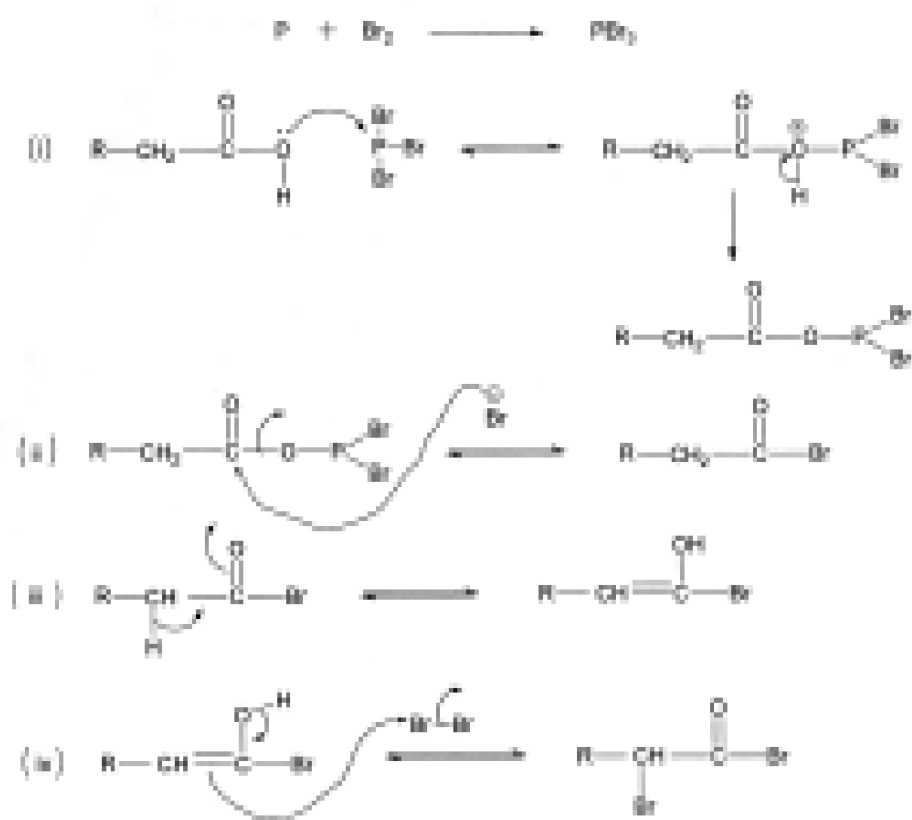
H.V.Z. (Hell Volhard Zelinsky) is used for the  $\alpha$  halogenation of carboxylic acid in presence red phosphorous and  $\text{Br}_2$  molecule. This reaction is used for the detection

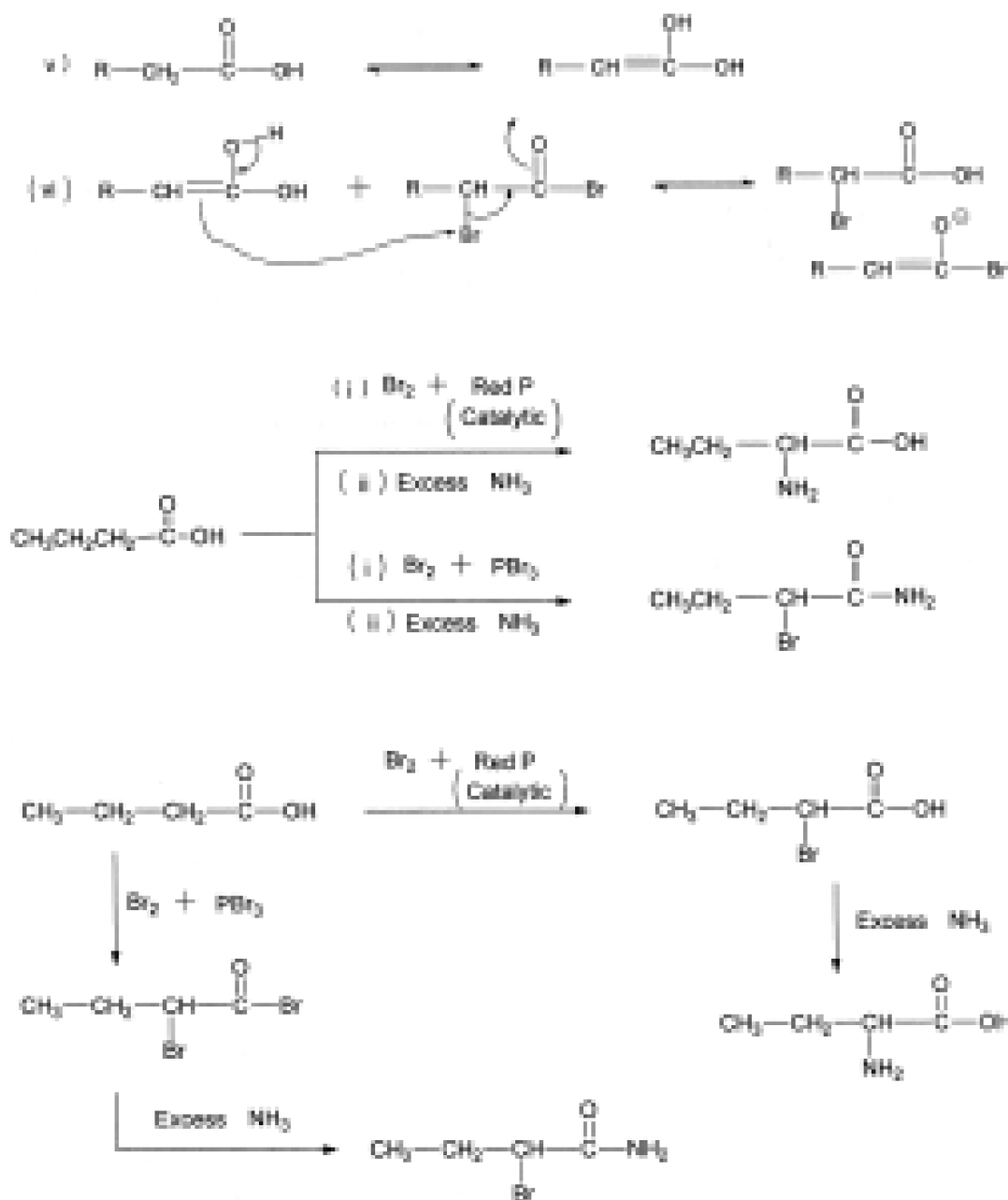
of the number  $\alpha$ -hydrogen atom with respect to carboxylic acid. If catalytic amount of red phosphorous is used then  $\alpha$  hydrogen atom is substituted but in presence of excess P all the  $\alpha$ -hydrogen atoms are eliminated.



In presence of  $\text{Br}_2$  molecule only  $\alpha$ -hydrogen atom is eliminated but in presence of  $\text{Cl}_2$  molecule  $\alpha$ -H, as well as  $\beta$ -H,  $\delta$ -H atoms are also eliminated.

### Mechanism





**In H.V.Z. reaction catalytic amount of P is used along with halogen. Explain.**

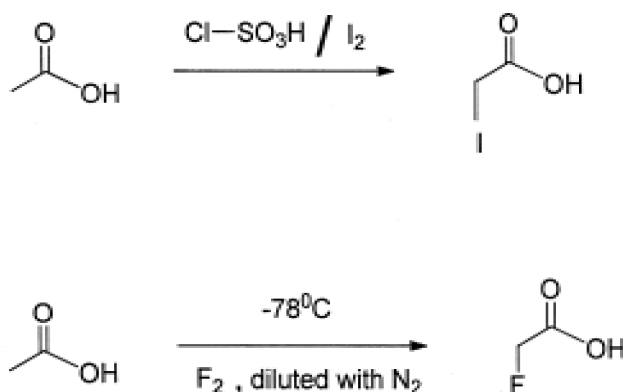
At first, P react with halogen to produce  $PX_3$ . Then this  $PX_3$  react with acid to form acid halide. This acid halide undergoes equilibrium reaction with acid produces  $\alpha$ -halo carboxylic acid and acid halide as the side /bi-product. This acid halide

further react with halogen produces a reacting species which is the active reagent for  $\alpha$ -halogenation of acid. Hence, from this reaction sequence, we see that “P” is used in only initial state. Therefore P is used as catalytic amount.

**Problem :**  $\alpha$ -iodo acid are not normally prepared by direct iodination of carboxylic acid under condition of H.V.Z reaction. So, how would you correct octadecanoic acid to its two iodo derivative by an efficient sequence reaction.

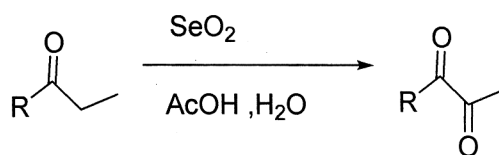
**Ans.** Phosphorous in presence of iodine produces  $PI_3$ , which is very much unstable due to larger size of I-atom. Hence, first step in H.V.Z reaction does not forward. Therefore,  $\alpha$ -iodo acid does not prepared.

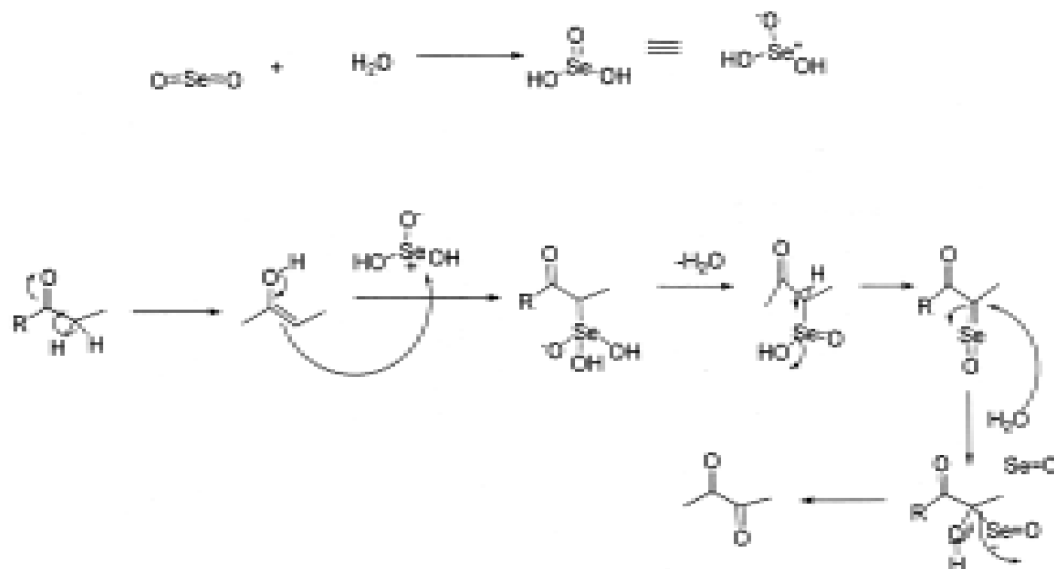
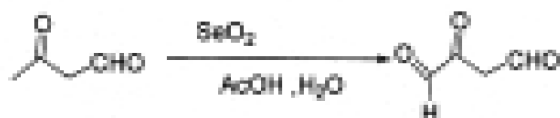
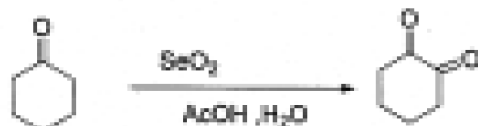
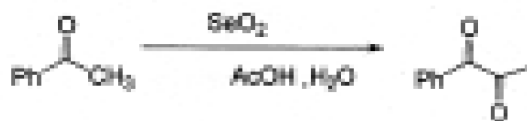
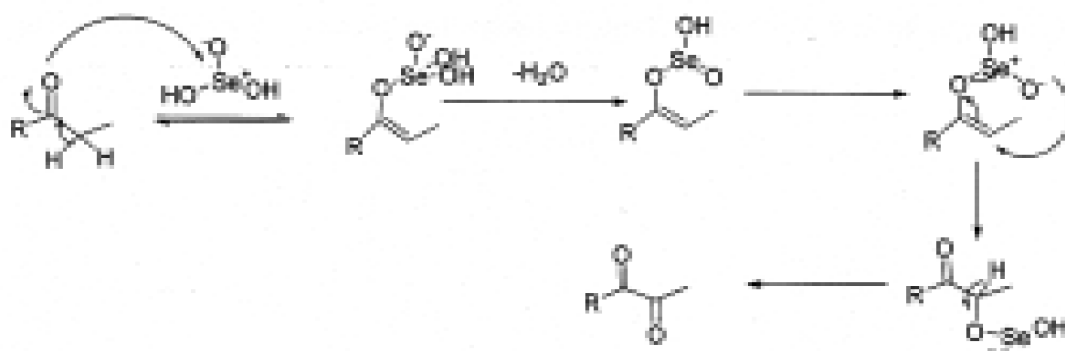
If chloro sulphonic acid ( $Cl-SO_3H$ ) is used as a catalyst in presence “I”  $\alpha$ -iodo acid can be prepared.



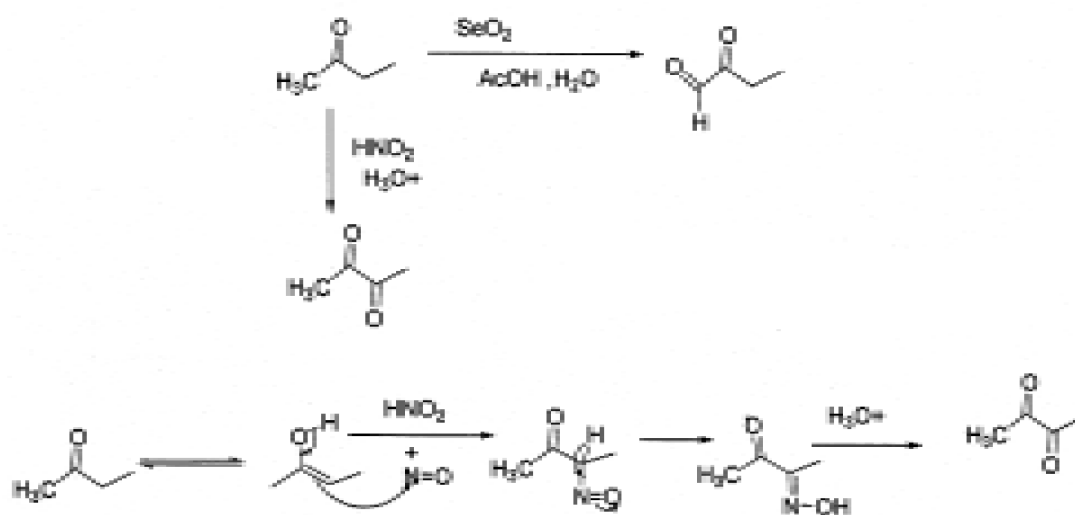
### 3.7.6 $SeO_2$ Oxidation :

$SeO_2$  is used for the oxidation of carbonyl compound to di-carbonyl compound at  $\alpha$ -position.

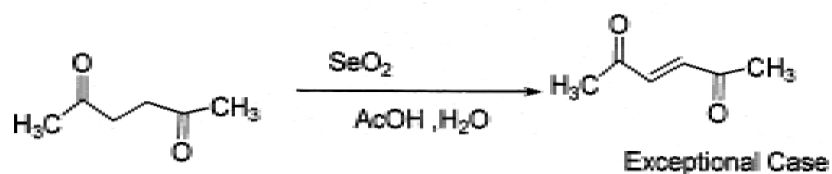


**Mechanism :****Alternative Method :**

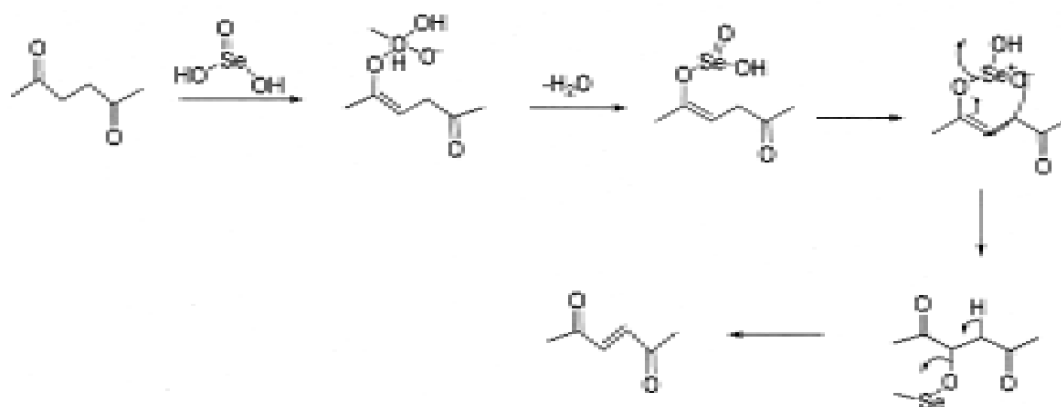
## Selectivity of oxidation



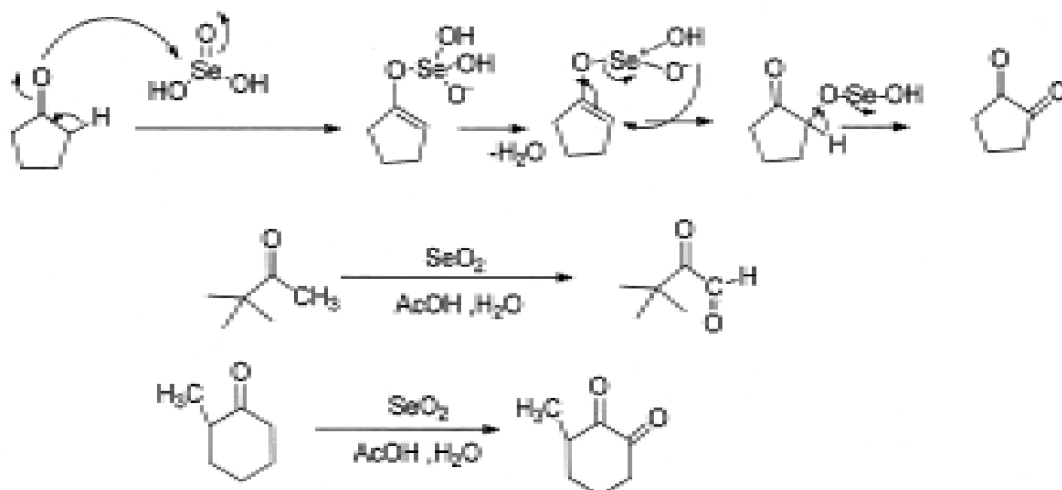
The reaction goes through most stable enolate form.



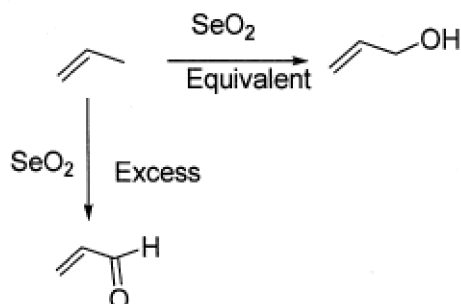
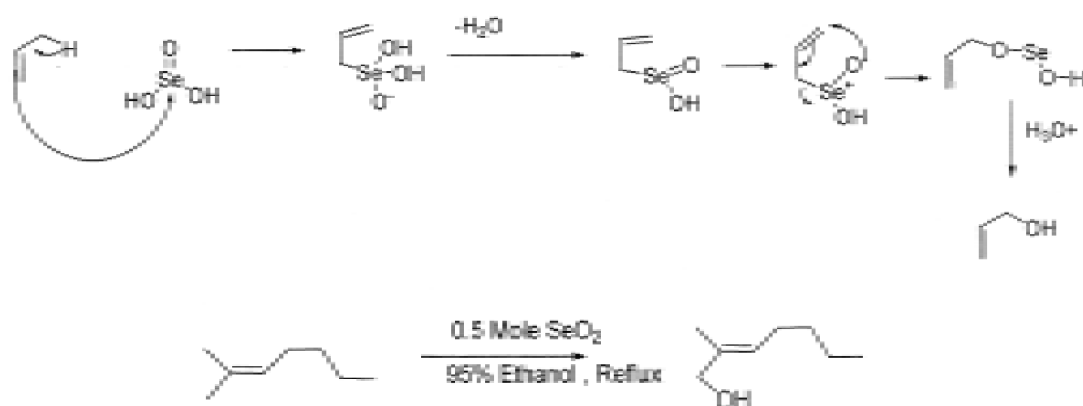
## Abnormal Mechanism :





**Problem :**

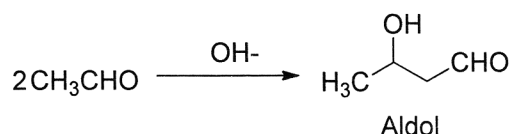
SeO<sub>2</sub> oxidizes alkene system to form allylic alcohol under equivalent condition. Alkene is form  $\alpha, \beta$  unsaturated aldehyde (ketone) in the presence of excess SeO<sub>2</sub>.

**Mechanism :**

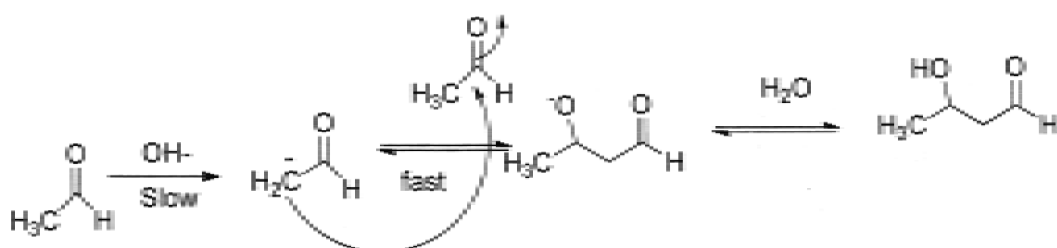
SeO<sub>2</sub> Always oxidises alkene to allylic alcohol at less substituted end.

### 3.7.7 Aldol condensation reaction

The treatment of aldehyde and ketone with  $\alpha$ -H atom in presence of base or acid to form  $\beta$ -hydroxy aldehyde or ketone, is known as Aldol reaction and the removal of water from aldol product is called as aldol condensation reaction. Simply two mole acetaldehydes undergo condensation reaction to form aldol product.

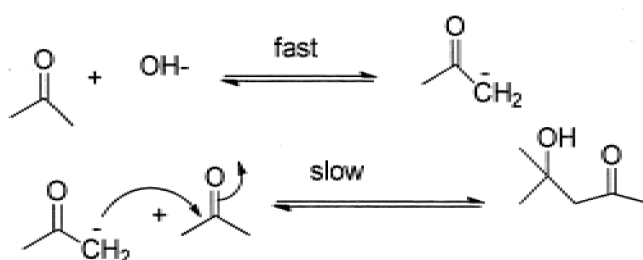


#### Mechanism :



The rate of condensation is different for aldehyde and ketone. The carbanion formation rate determined step in case of aldehyde.

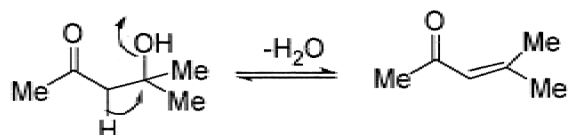
$$\text{Rate} = [\text{CH}_3\text{CHO}][\text{OH}^-] \text{ for aldehyde}$$



But in case of ketone the phenomenon become opposite. This is due to the acetone is less reactive than acetaldehyde. So the rate of carbanion attack to the another ketone molecule become slow. Therefore in case of ketone, the second step becomes r.d.s.

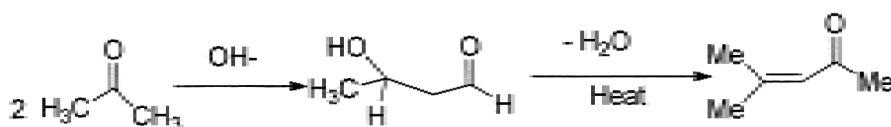
$$\text{Rate} = [\text{CH}_3\text{COCH}_3]^2 [\text{OH}^-] \text{ For ketone}$$

All the steps in aldol condensation are reversible in nature. So the aldol product is formed in lesser amount (2%). To increase the yield the product **soxhlet** apparatus is used for the removal of water from aldol product.

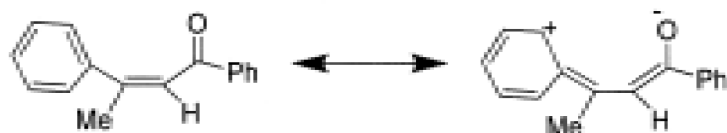
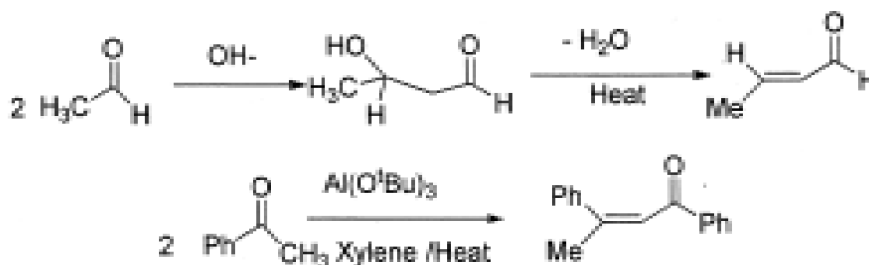


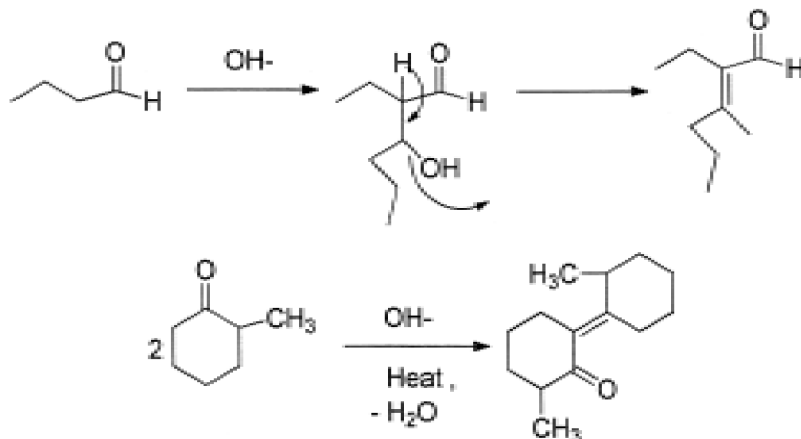
If removal of water takes place from this system then the aldol condensation product becomes much higher amount.

How can you convert : Acetone to Mesityl oxide.



Acetaldehyde to Crotonaldehyde



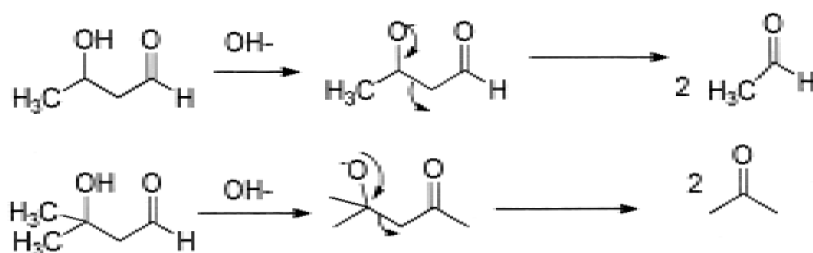


**Q. Acetaldehyde when treated with  $\text{NaOD}/\text{D}_2\text{O}$  we get no D/H on recovered aldehyde after incomplete reaction but in case of ketone D/H exchange take place. Explain**

Carbonyl group is reactive than aldehyde group. So after carbanion formation in case of aldehyde it readily attacks to the aldehyde group to give  $\beta$ -hydroxy aldehyde product. But in case ketone the condensation reaction is very slow. So, it undergoes D/H exchange in presence of  $\text{NaOD}/\text{D}_2\text{O}$ .

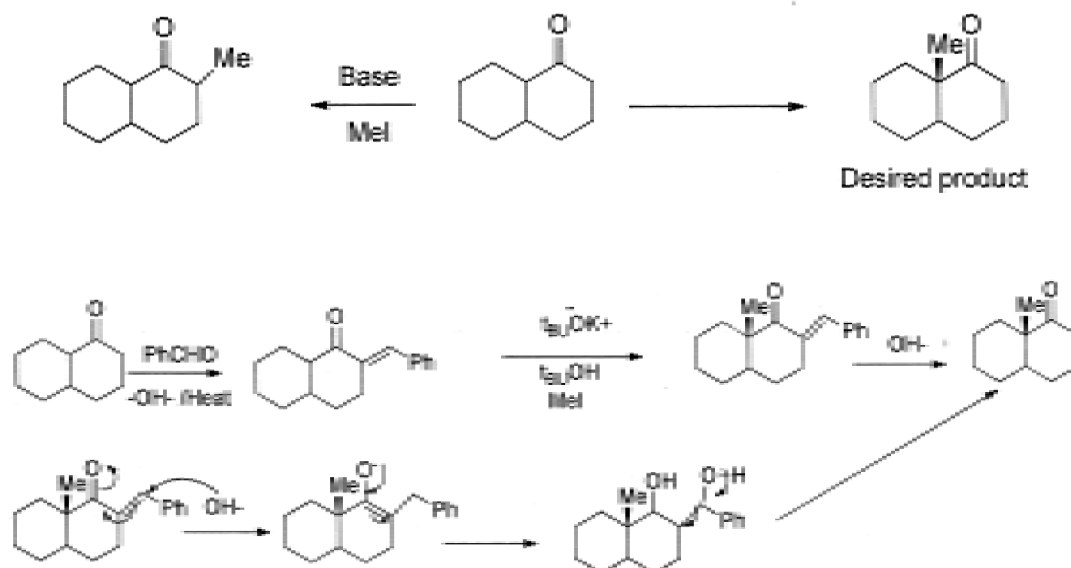
**Q. Proof that aldol condensation reaction is reversible reaction.**

Upon treatment of excess base the aldol product give two mole aldehyde / ketone. This indicates that aldol condensation is reversible in nature.

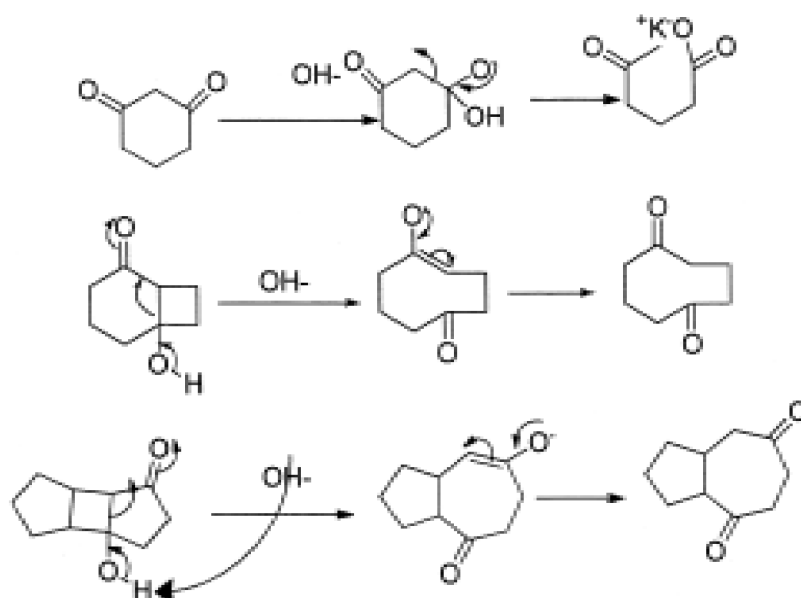


This reaction is known as reverse aldol condensation reaction.

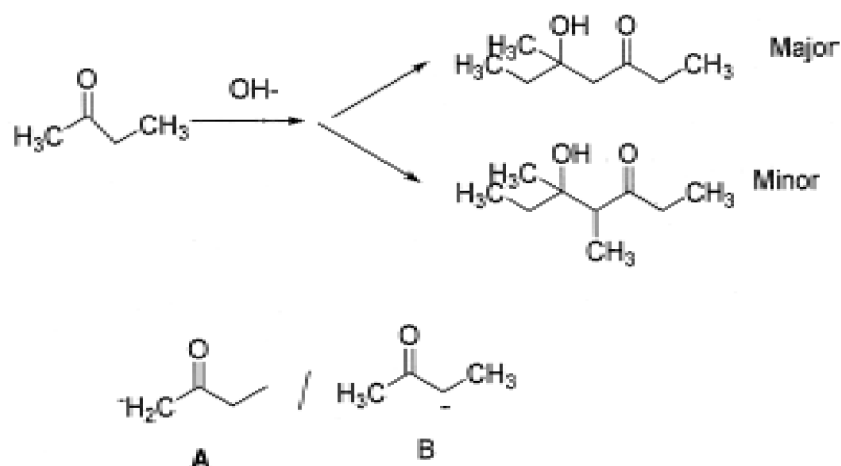
### Utility of reverse aldol reaction :



This is the utility of reverse aldol condensation reaction. The ring can be ruptured by reverse aldol condensation reaction.



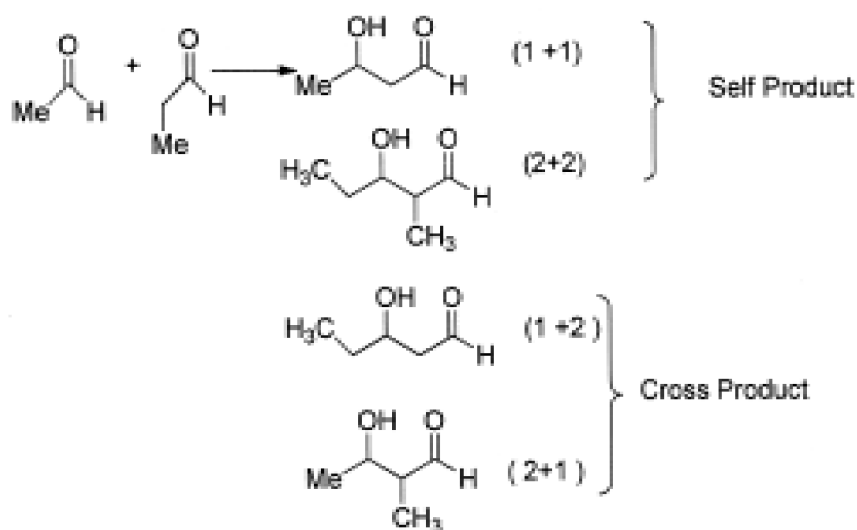
### Aldol condensation reaction for unsymmetrical ketone



In presence of base two types of carbanions are produced. Among them B carbanion is unstabilised by the +I effect. Therefore, A product is formed as major amount. Again B carbanion attack to the ketone compound is more hindered than A carbanion.

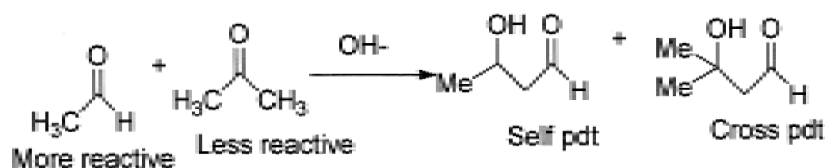
### Mixed Aldol condensation

Two different aldehyde or ketone with  $\alpha$ -H atom undergo aldol condensation to give different type alcohol product.



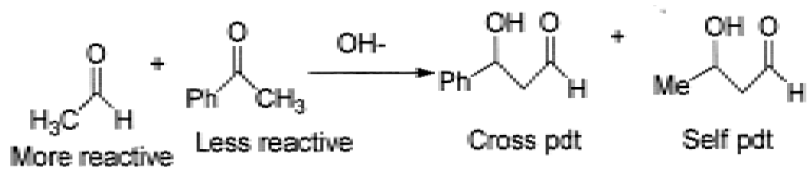
In this reaction, we get four types of products. To avoid this problem some condition are needed.

1. If we take one reactive and another less reactive substrate then we get two products with significant amount.

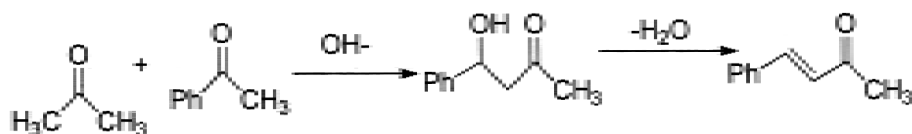


Hence we get two products instead of four products. This is due to the lower reactivity carbonyl carbon in acetone.

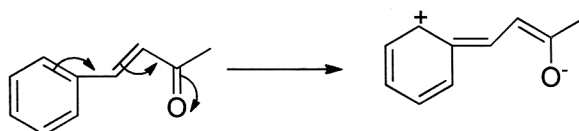
2. If we take a substrate with no  $\alpha$ -H atom such as benzaldehyde then there has no chance for the formation of self aldol. Again if we take more reactive substrate with  $\alpha$ -H atom then the cross products becomes reduce to give two products.



3. If we take one substrate which does not contain  $\alpha$ -H atom and another less reactive substrate with  $\alpha$ -H atom then there has lower possibility of self-condensation. Consequently only cross aldol product will be formed.



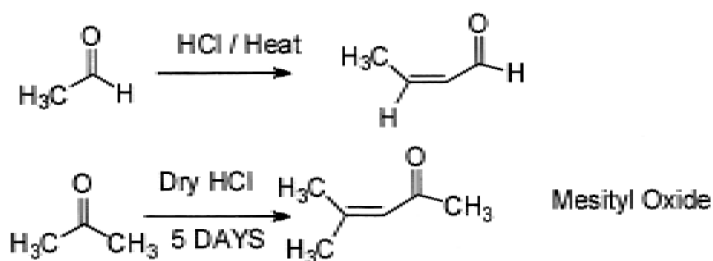
Thus product is also stabilised by conjugation with benzen ring.



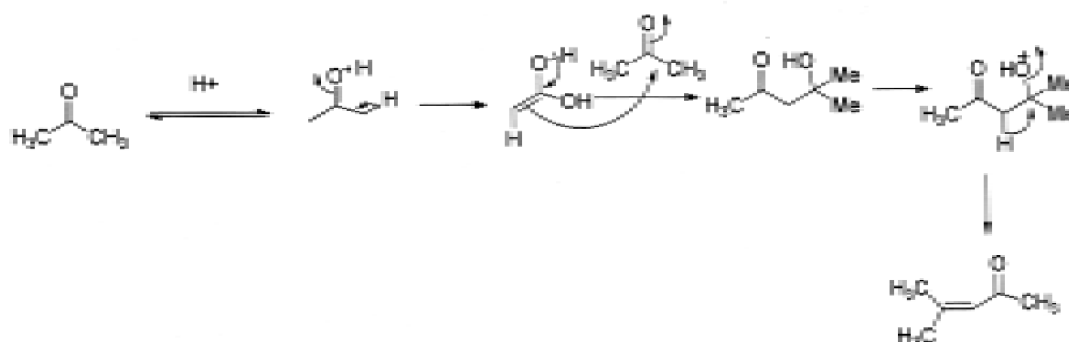
If we start from two mole benzaldehydes and one mole acetone then we get Dibenzylideneacetone (DBA) after aldol condensation reaction.

### Acid Catalysed Aldol Condensation

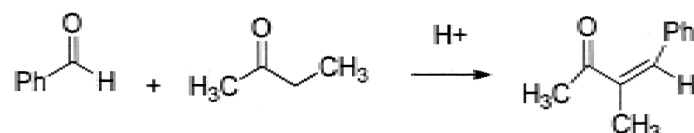
In presence of acid, aldehyde and ketone undergo condensation reaction to give  $\alpha, \beta$  unsaturated aldehyde and ketone compound.



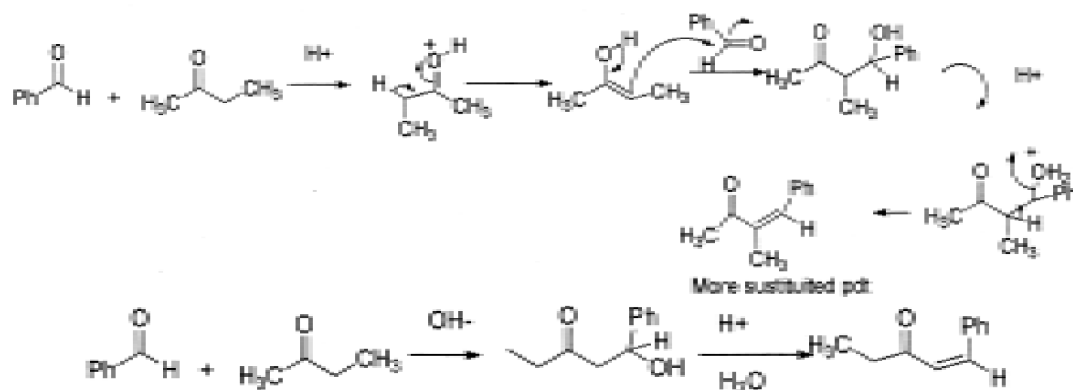
#### Mechanism :



#### For unsymmetrical substrate :

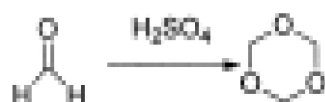


#### Mechanism :

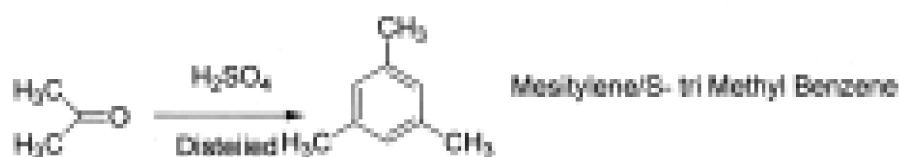
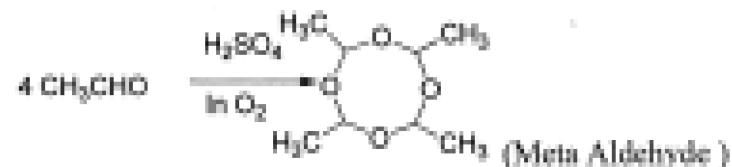
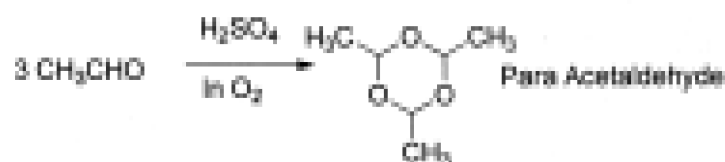


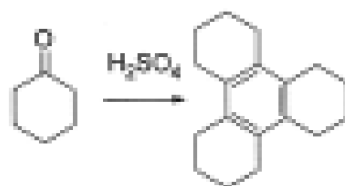
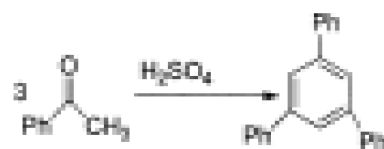
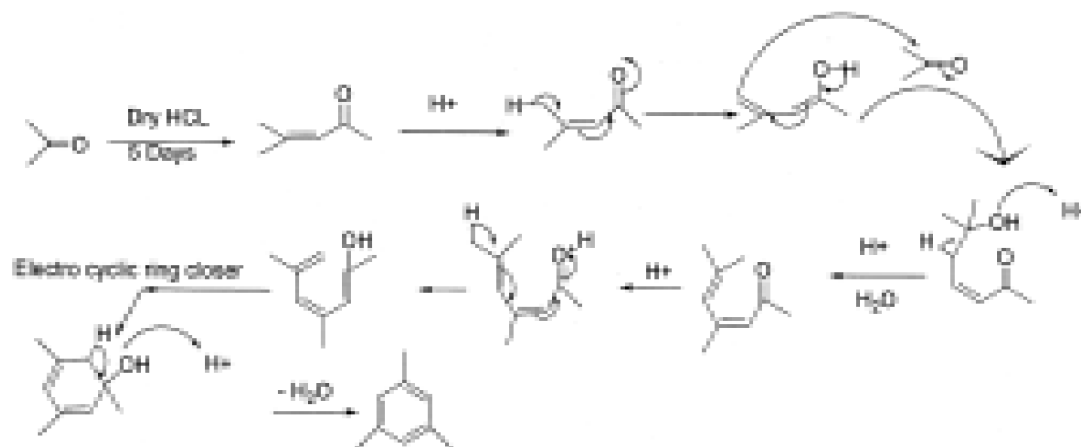


In acid medium the reaction goes through more stable enol intermediate. But in base medium the reaction goes through more stable anionic intermediate.

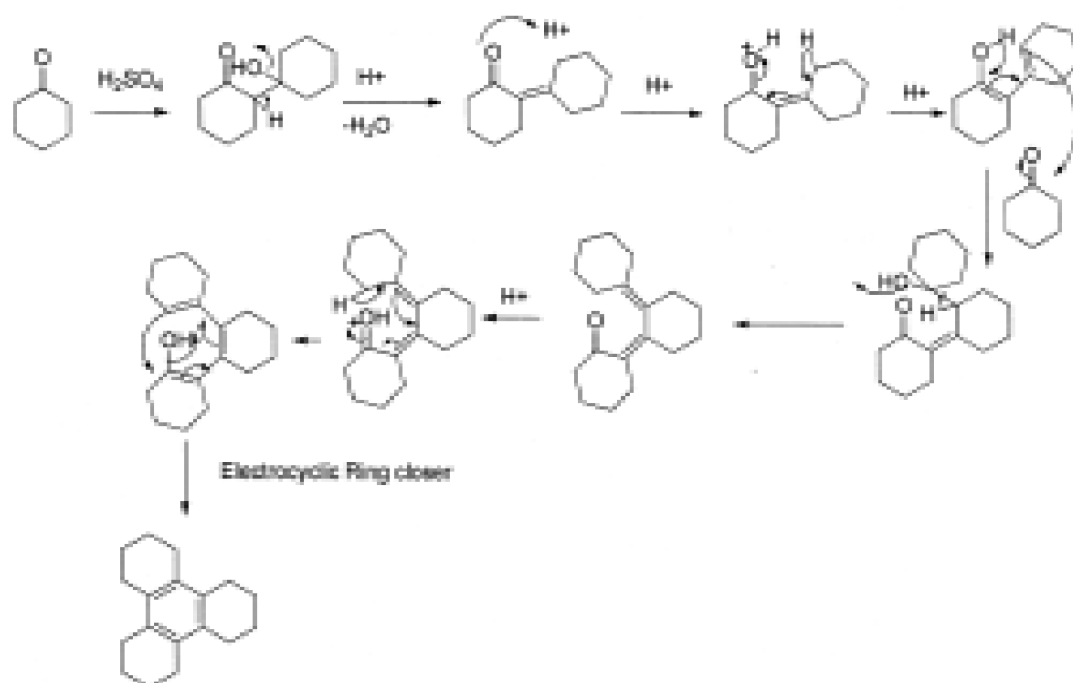


Trioxane (para formaldehyde)

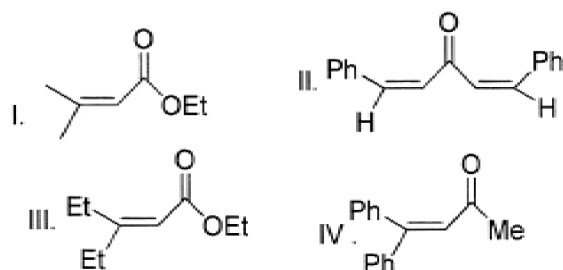




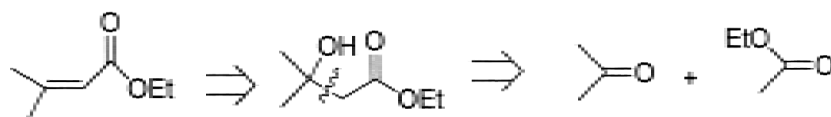
### Mechanism :



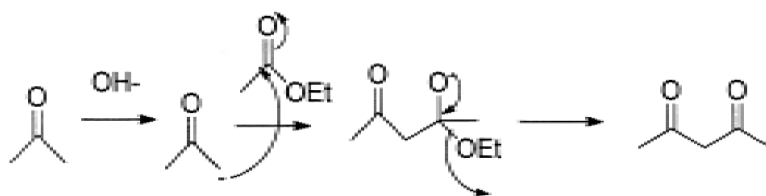
**Q. Work backward and identify the starting material of following product to be derived by aldol condensation and comment on the feasibility of the reaction.**



**Reaction :**

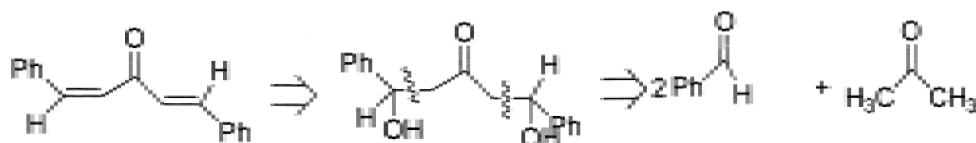


The given substrate does not produced by aldol condensation reaction where acetone and ethyl acetate are the starting material. This product can be obtained when carb anion is produced from ethyl acetate. But this is not possible when acetone and ethyl acetate are present as substrate under basic condition. This is due to methyl proton of acetone is more acidic than the methyl proton of ethyl acetate. Therefore, we get acetyl acetone instead of given product, i.e this above reaction is not feasible by aldol condensation reaction.

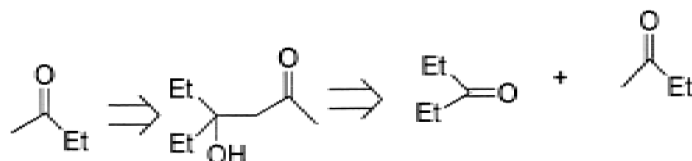


Again it produces self-product due to higher leaving aptitude of -OEt group.

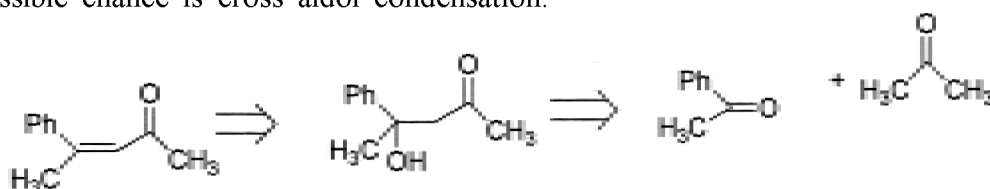
**Reaction :**



This reaction is feasible through aldol condensation. As acetone is less reactive in nature. So, there have no chance for self-condensation. Only one possible chance is cross aldol condensation. After product formation the product is stabilised through large conjugation.



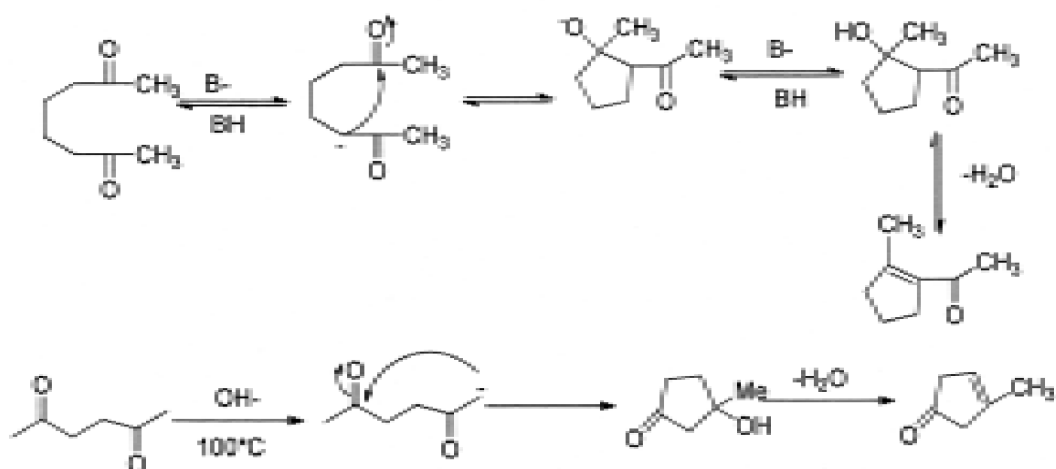
The reaction is feasible under aldol condensation reaction. This is due to the lower reactivity of carbonyl group reduces the self-condensation product. So, the possible chance is cross aldol condensation.



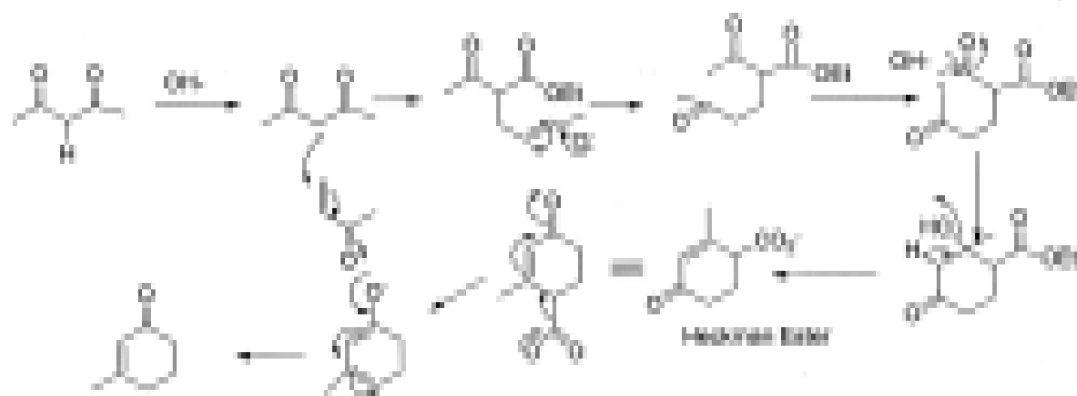
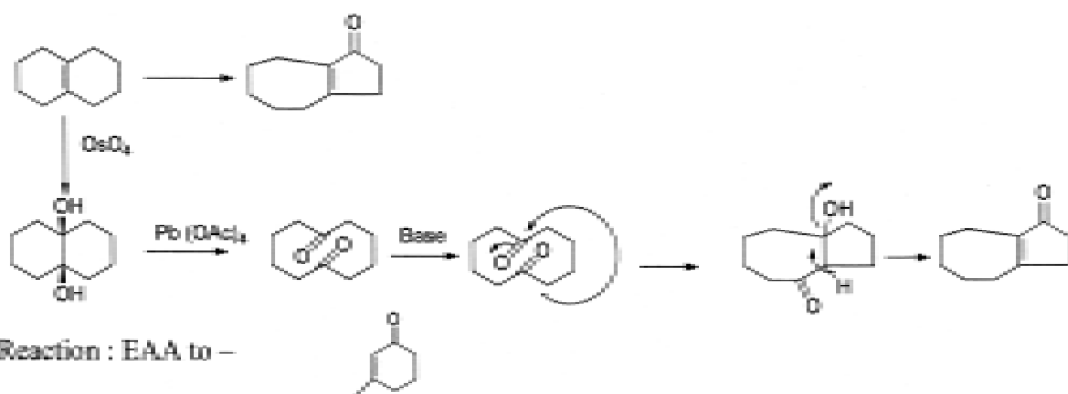
This reaction is not feasible because both acetophenone and acetone is less reactive towards cross aldol condensation.

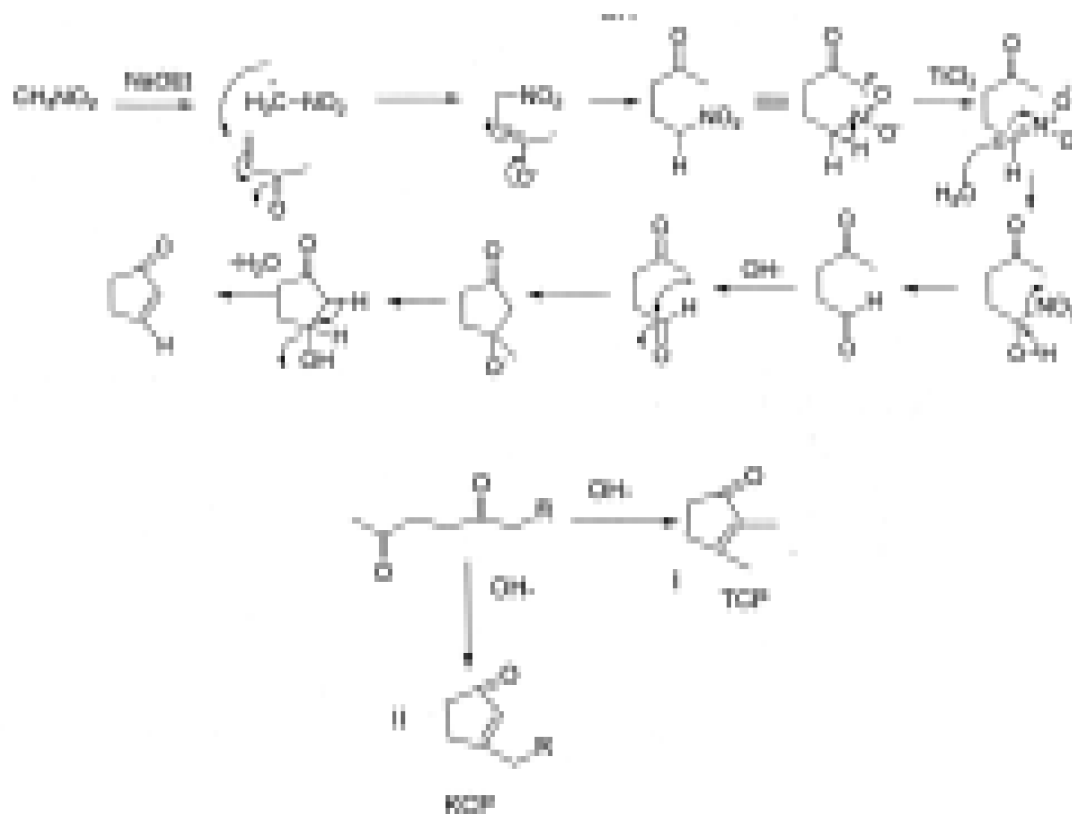
### Intra molecular Aldol Condensation :

Intramolecular aldol reaction is an important pathway for the synthesis of cyclic compounds. However, only five membered and six membered rings may be easily achieved by intra molecular aldol reaction.

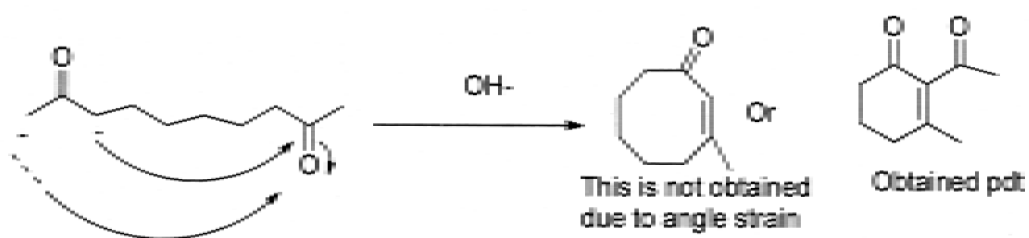


These products are formed according to Bayer strain theory.

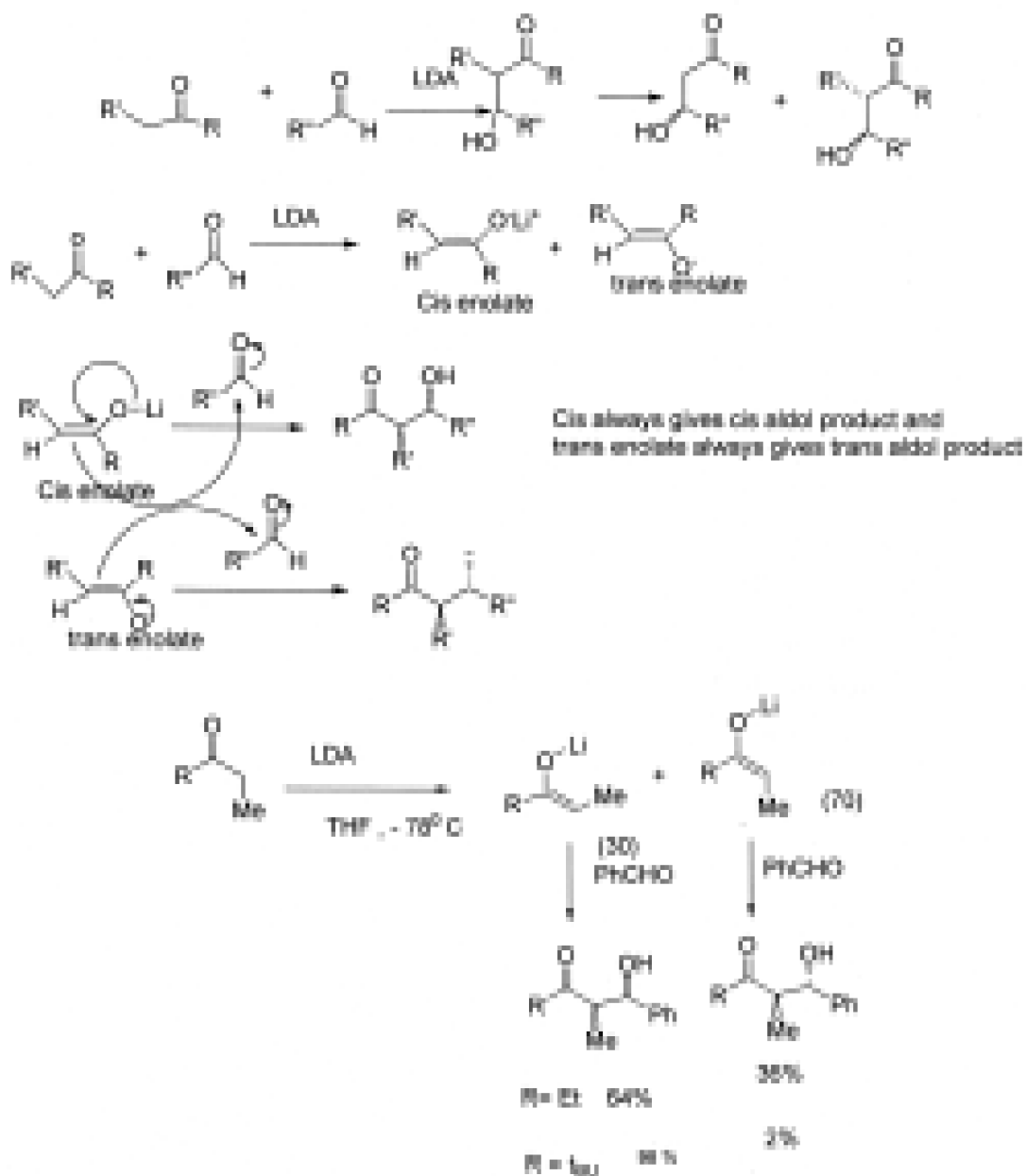




So, it is difficult to see much different between the two routes. We might have argued that product II is form through better enolisation route than product I. But this is wrong because the reaction is not under kinetic rather under thermodynamic control. The product I, differ by the number of substituent, product I is more stable.

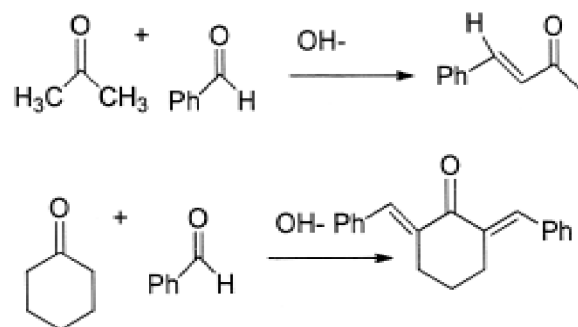


### Diastereoselectivity of aldol Reaction



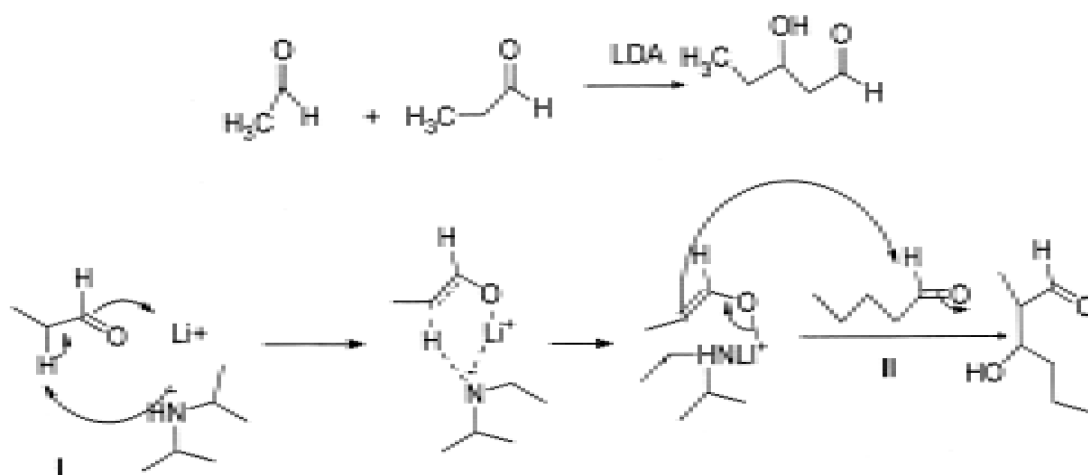
### 3.7.8 Claisen Schmidt Reaction :

The cross aldol condensation of aromatic aldehyde with aliphatic aldehyde / ketone to give more stable conjugated carbonyl compound and this reaction is known as Claisen Schmidt reaction.



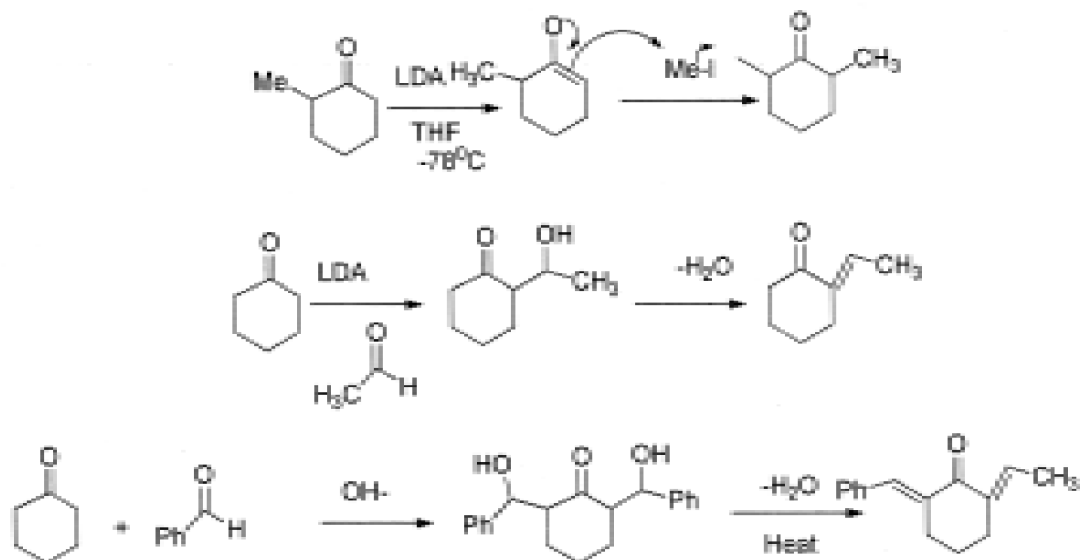
### L.D.A. Method

LDA is the more advance method in organic chemistry where we get desired cross aldol product in significant amount. LDA means lithium diisopropyl amide.



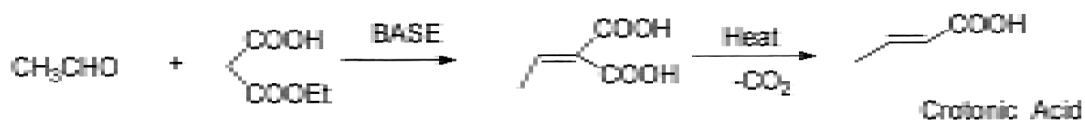
To obtain the demand cross aldol product the reactant I is first taken in the reaction vessel to generate enolate ion by LDA.  $\text{Li}^+$  in LDA is readily co-ordinate with carbonyl group and form lithium enolate. The formation of Li-enolate is so fast that there has no chance of self-condensation product. After Li-enolate formation pentanal (II) is added drop by drop by slow addition pump to the lithium enolate of aldehyde and give desired cross aldol product. There has no chance of self-condensation of pantanal due to the concentration of substrate is very lower in reaction vessel.



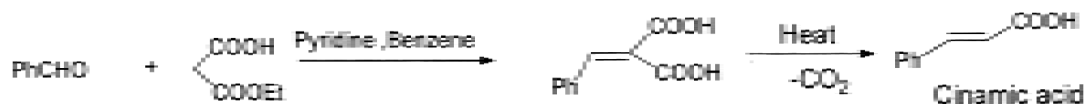


### 3.7.9 Knoevenagel Condensation :

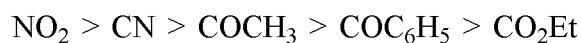
Base catalysed condensation between an aldehyde or ketone, with any compound having an active methylene group (specially malonic ester) is called Knoevenagel Condensation.



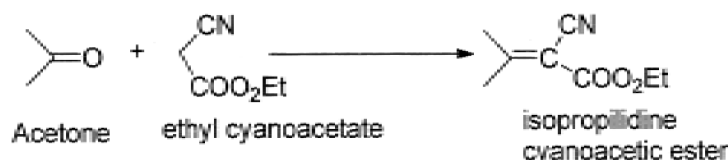
The base used in the above condensation is a weak base like ammonia or amine (primary or secondary). However, when condensation is carried out in presence of pyridine as a base, decarboxylation usually occurs during the condensation. This is known as **Doebner modification**.



The effectiveness of various activating groups in the active methylene compounds is found to be in the order

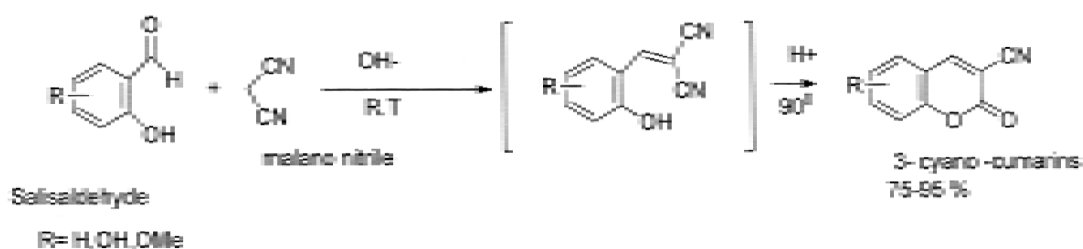


Ketone does not undergo Knoevenagel condensation with malonic ester but can react with more active cyanoacetic acid or its ester. For example, acetone forms isopropylidene cyanoacetic ester when condensed with ethyl cyanoacetate.



### Knoevenagel reaction in water

The Knoevenagel reaction has been carried out between aldehydes and acetonitrile in water. Thus salicylaldehydes react with malononitrile in heterogeneous aqueous alkaline medium at room temperature to give O-hydroxybenzylidene malonitrile which are converted by acidification and heating to give 3-cyanocoumarins in good yield.



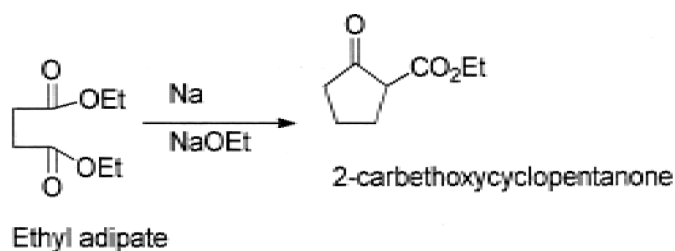
### Knoevenagel Reaction in solid state

Knoevenagel reaction has been carried out in dry media. The method consists in adding solid inorganic support to a solution of aromatic aldehyde and diethyl malonate in acetone. The adsorbed material was mixed properly, dried in air (beaker) and placed in an alumina bath inside the microwave oven for 2-3 min. at medium power level (600w) intermittently, at 0.5 min. intervals at 102°C. The product was isolated by extraction of the reaction mixture with alcohol.

### 3.7.10 Dieckmann condensation :

Diester of C6 and C7 dibasic acids undergo an intramolecular Claisen condensation in presence of base to give good yields of cyclic β-ketoesters. This is known as Dieckmann condensation. It is of considerable value in the synthesis of

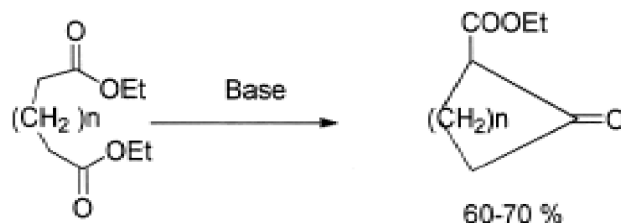
cyclic compounds. For example, ethyl esters of adipic acid and pimelic acids give 2-carbethoxycyclopentanone and 2-carbethoxycyclohexanone respectively.



Dieckmann condensation best proceeds with esters having 6, 7 or 8 carbon atoms and gives stable rings with 5, 6, 7 carbons.

#### Dieckmann Condensation in Solid State

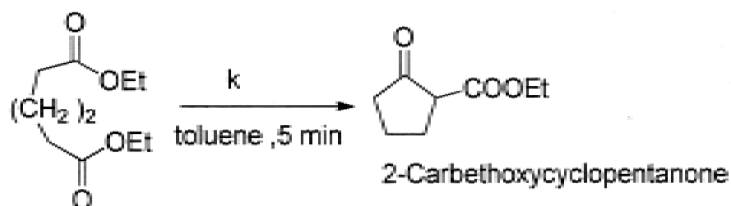
Dieckmann condensation of diesters has been carried out in solid state in the absence of any solvent in presence of a base (Na /NaOEt). The reaction products are obtained by direct distillation of the powdered reaction mixture, which was neutralised with *p*-TSOH. H<sub>2</sub>O



Diethyl adipate  $n = 2$   
diethyl pimelate  $n = 3$

#### Dieckmann Condensation under Sonication

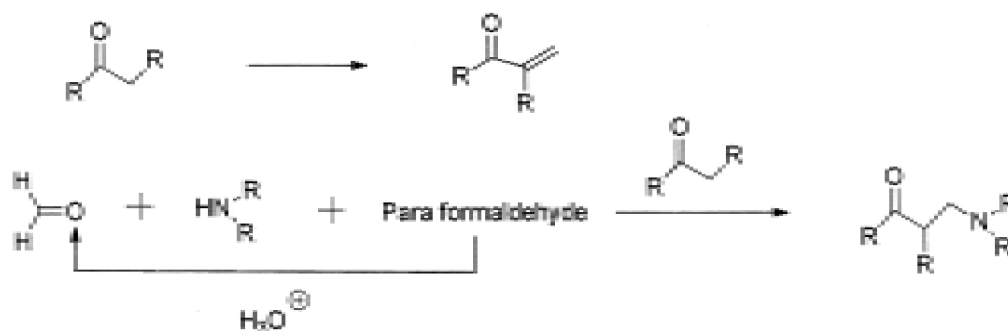
It is found that Dieckmann proceeded very well on sonication in a short time. On sonication potassium is easily transfer to a silver blue suspension in toluene. The ultrasonically dispersed potassium is extremely helpful in Dieckmann condensation.



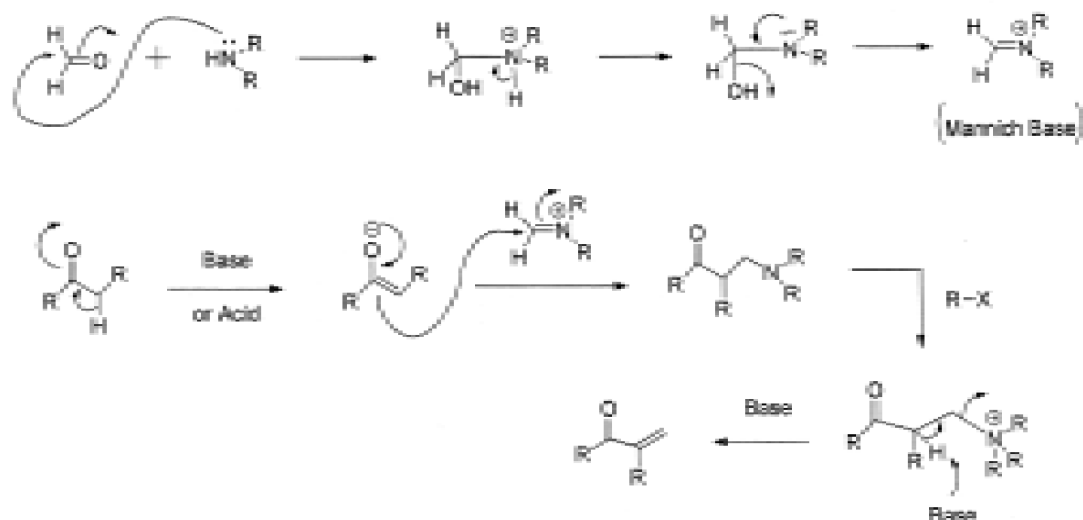
In the above condensation base like 'BuOK, <sup>t</sup>BuONa, EtOK or EtONa could be used.

### 3.7.11 Mannich Reaction :

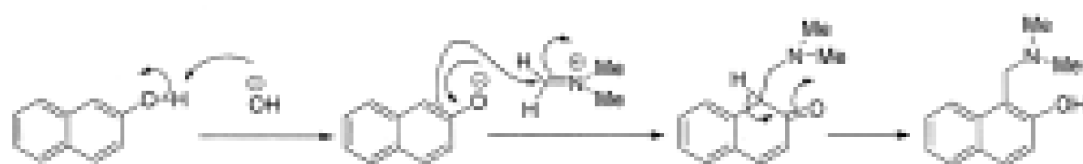
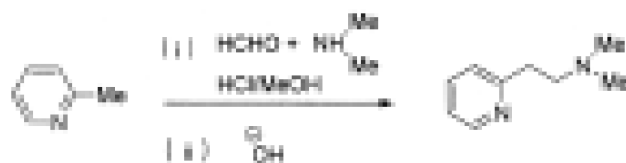
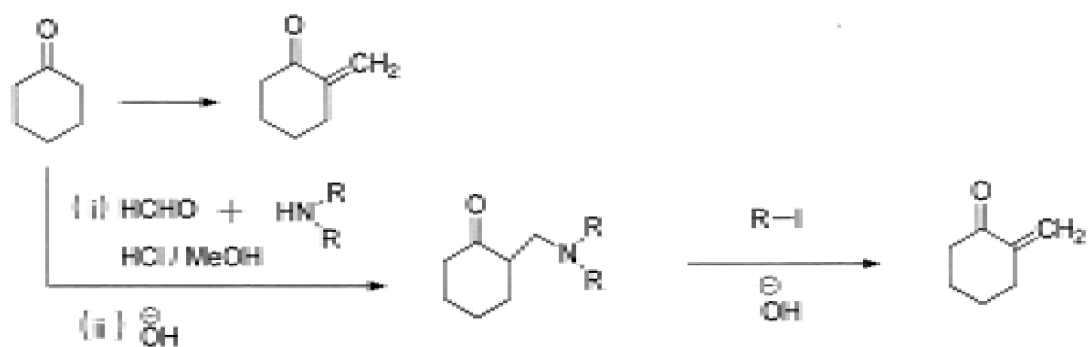
The utility of Mannich reaction is the preparation of unsaturated carbonyl group from ketone compound. Enolisable hydrogen atom containing aldehyde and ketone undergo reaction in presence of formaldehyde, 2° amine. At first 2° amine reacts with formaldehyde to give Mannich base. This base reacts with enolisable ketone to give αβ bita unsaturated carbonyl compound.



#### Mechanism

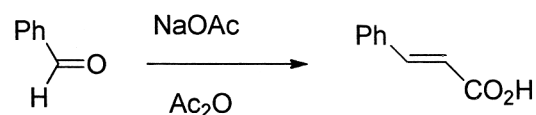


How will you convert

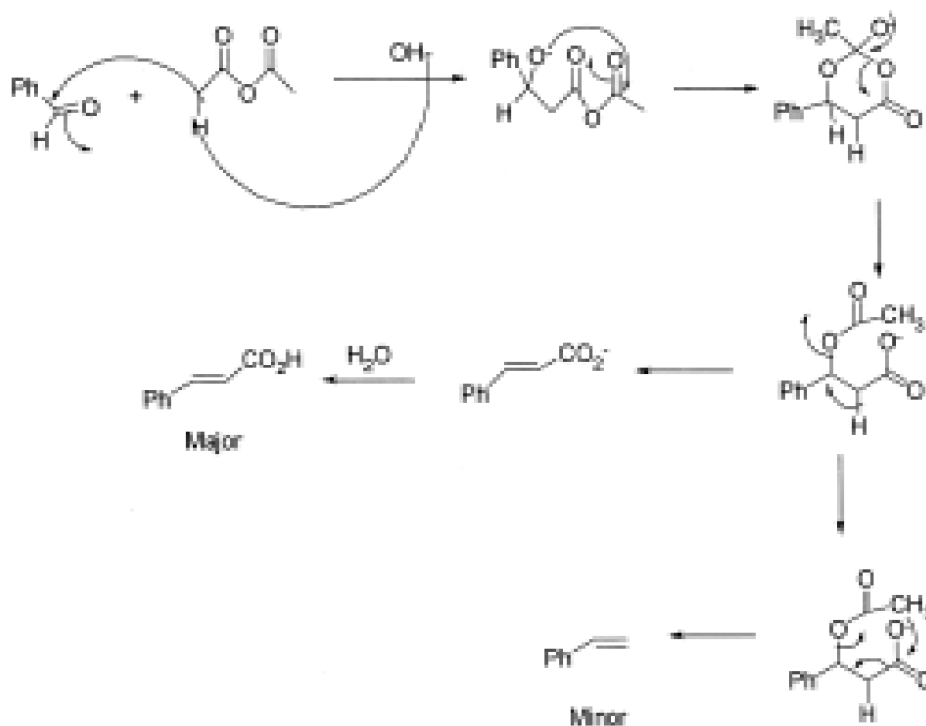


### 3.7.12 Perkin Reaction :

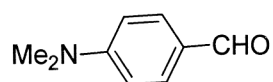
In Perkin reaction aromatic aldehyde reacts with sodium acetate and its corresponding anhydride to give  $\alpha, \beta$  unsaturated acid through condensation reaction.



#### Mechanism :

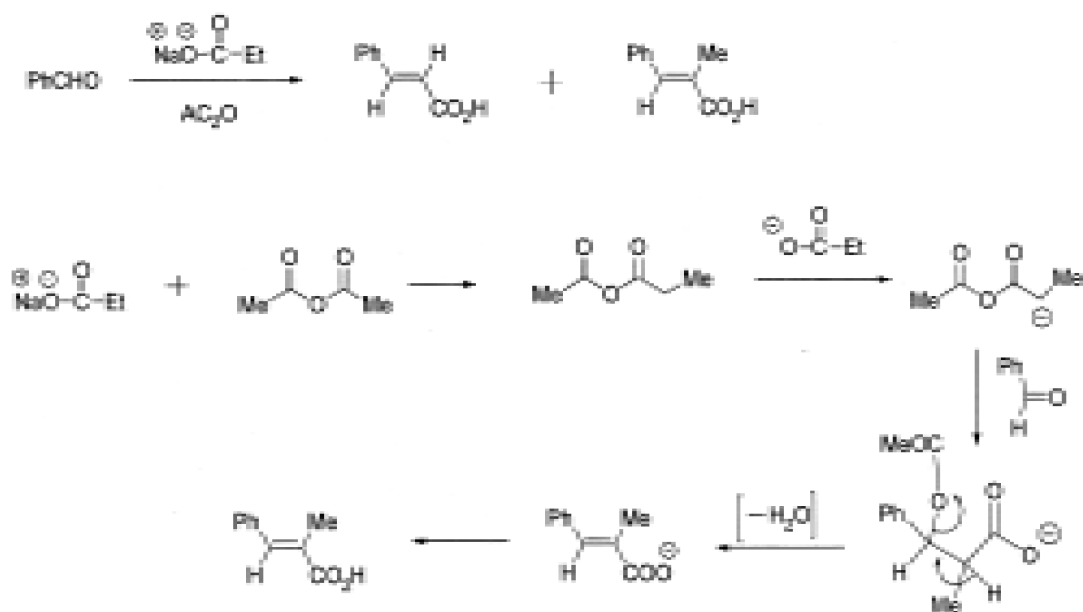


In presence of electron withdrawing group in phenyl ring, the reaction rate is increase. Therefore *p*-nitro benzaldehyde in presence of  $\text{NaOAc}/\text{Ac}_2\text{O}$  gives *p*-nitro cinamic acid in higher rate. Again in presence of electron donating group in phenyl ring, the reaction rate become slower due to the electrophilicity of carbonyl get reduced.



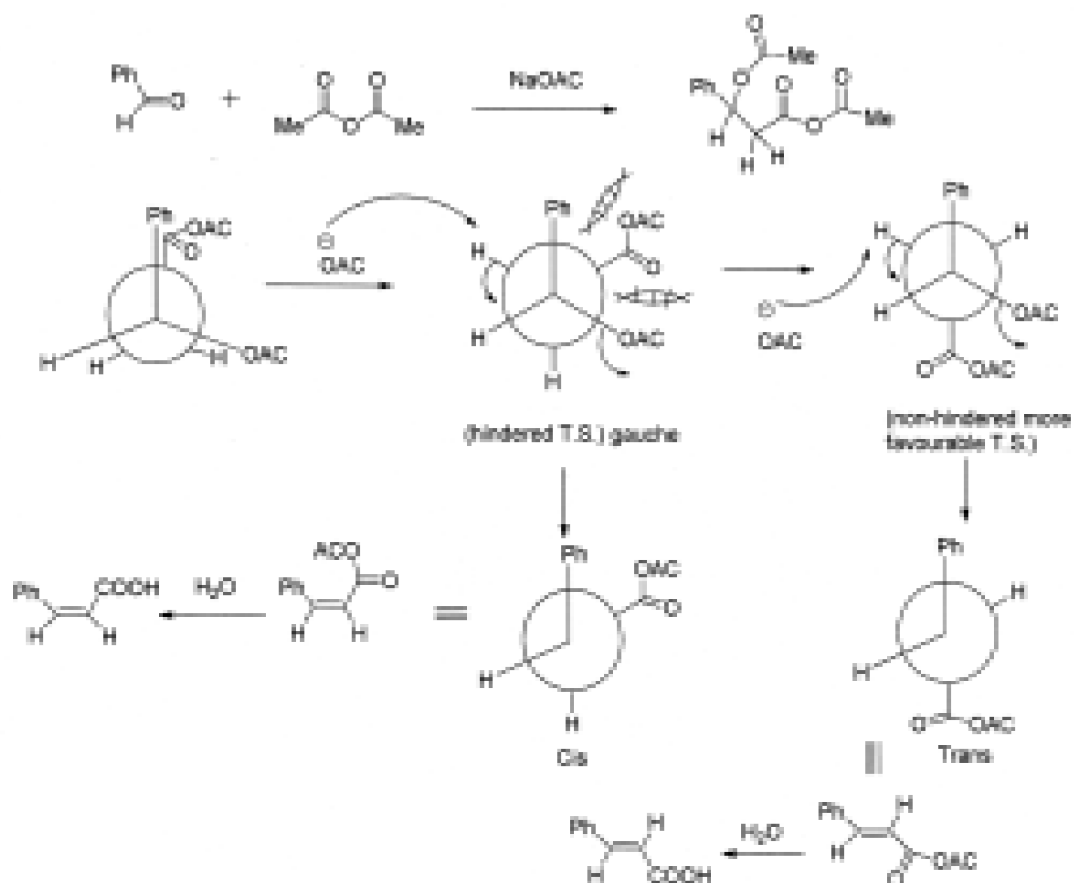
**Q. Why in Perkin reaction base and its corresponding anhydride is used ?**

If we use NaOCOEt instead of NaOAc in presence of Ac<sub>2</sub>O then we get a mixture of Perkin condensation product. This is due to the destruction of anhydride in presence of NaOCOEt. It should be noted that in Perkin reaction, the anhydride and the sodium salt should be form the same carboxylic acid; otherwise a mixture of  $\alpha,\beta$  unsaturated acids should be formed. This is because of the fact that when one carboxylic acid and sodium salt of another acid are taken following side reaction produces a second set of reagents leading to the formation of another product. If sodium salt and anhydride of the same acid is used then side reaction produces the same original set of reagents and consequently only one product is obtained



To avoid this mixture of product, we always use an anhydride and their corresponding salt in Perkin reaction.

**Q. Why we always get trans cinamic acid rather than cis-cinamic acid?**

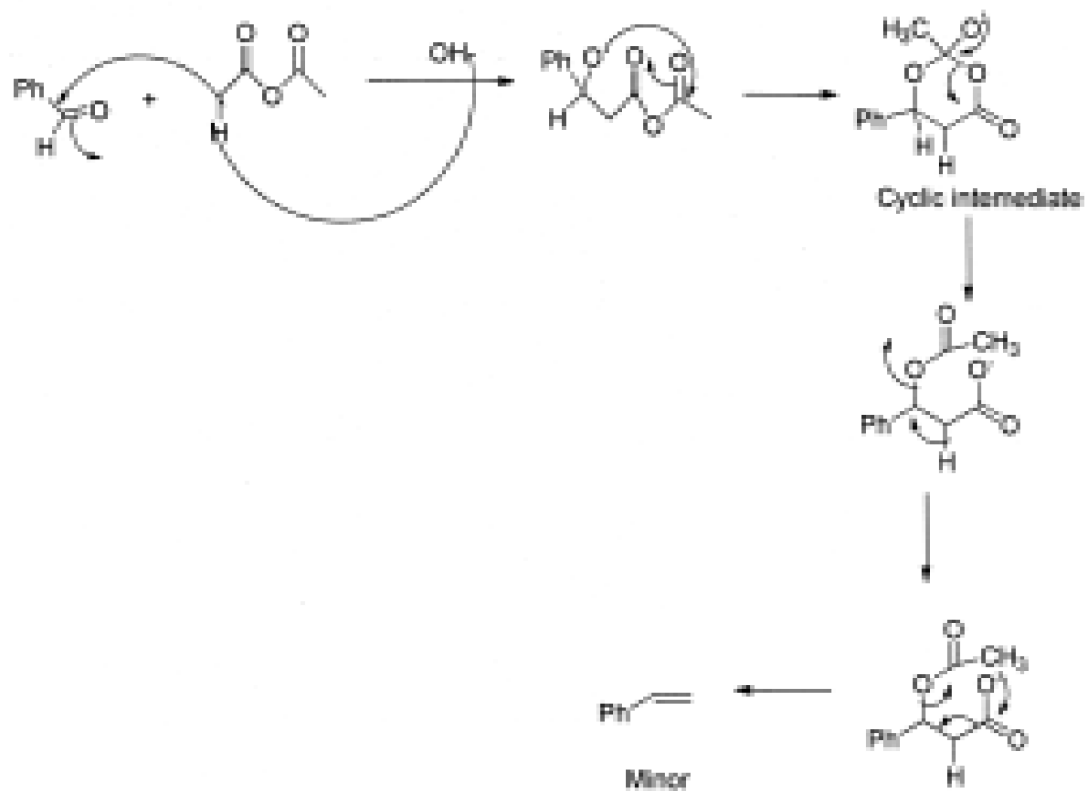


We get trans-cinamic acid rather than cis-cinamic acid as the transition state for cis acid is more sterically hindered than trans acid.

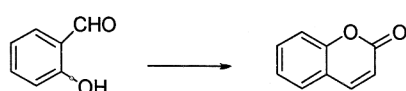
**Q. During Perkin reaction between Benzaldehyde and Acetic anhydride in presence Sodium acetate, some amount of styrene is formed along with cinamic acid . How can you account for this on the basis of the mechanism of Perkin reaction?**

During Perkin reaction a cyclic intermediate is supposed to be formed. Styrene can be formed from this intermediate. This is shown below —

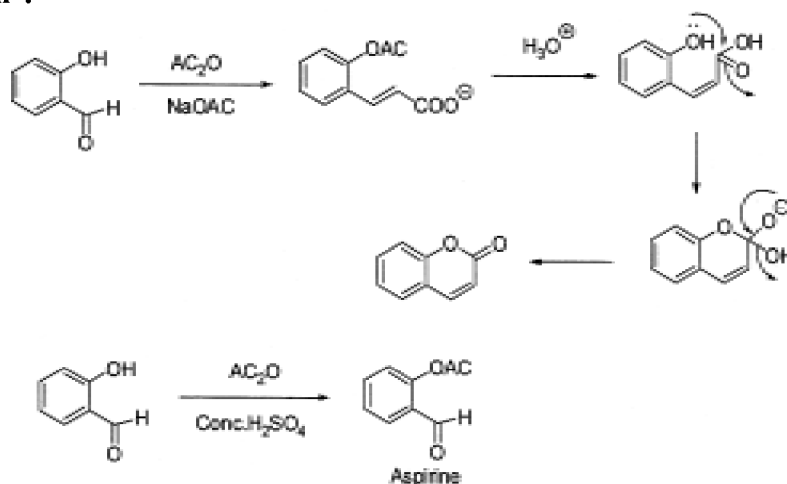




**Problem :** Transform the following

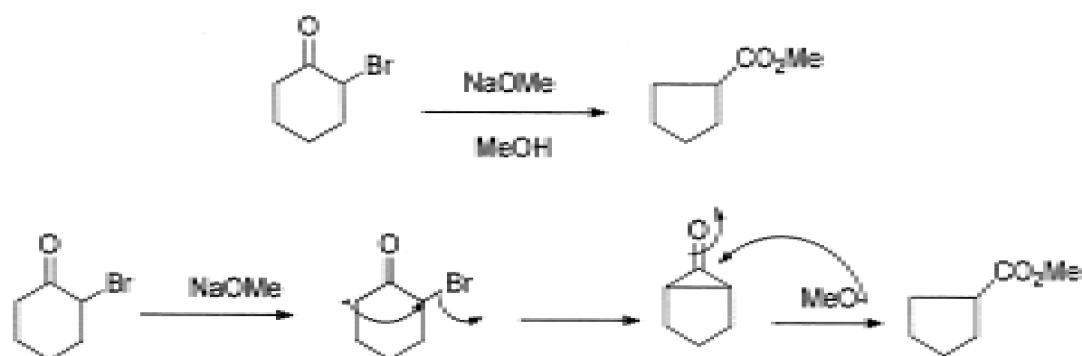


**Mechanism :**



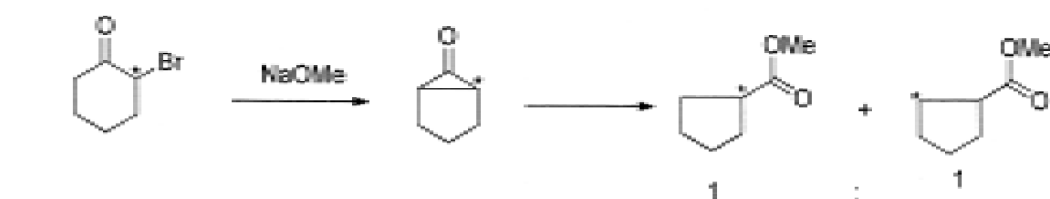
### 3.7.13 Favorskii rearrangement :

**The Favorskii rearrangement**, named for the Russian chemist Alexei Yevgrafovich Favorskii, is most principally a rearrangement of cyclopropanones and  $\alpha$ -halo ketones which leads to carboxylic acid derivatives. In the case of cyclic  $\alpha$ -halo ketones, the Favorskii rearrangement constitutes a ring contraction. This rearrangement takes place in the presence of a base, sometimes hydroxide, to yield a carboxylic acid but most of the time either an alkoxide base or an amine to yield an ester or an amide, respectively.  $\alpha,\alpha'$ -Dihaloketones eliminate HX under the reaction conditions to give  $\alpha,\beta$ -unsaturated carbonyl compounds.



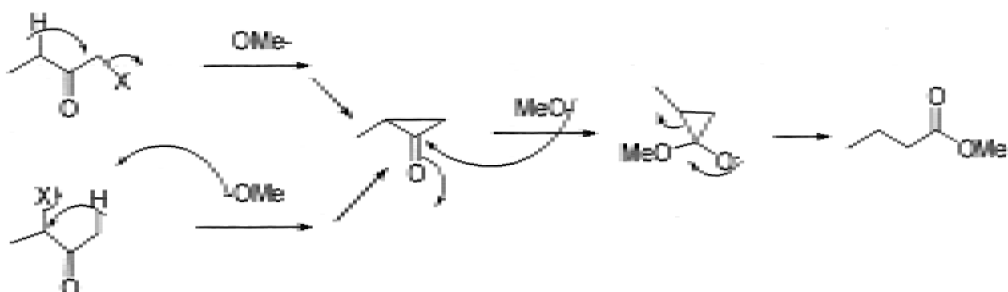
#### Evidence for mechanism :

Isotoping labeling experiment predict that the rearrangement occur via symmetrical intermediate where cyclopropanone intermediate undergoes cleavage to give the product.

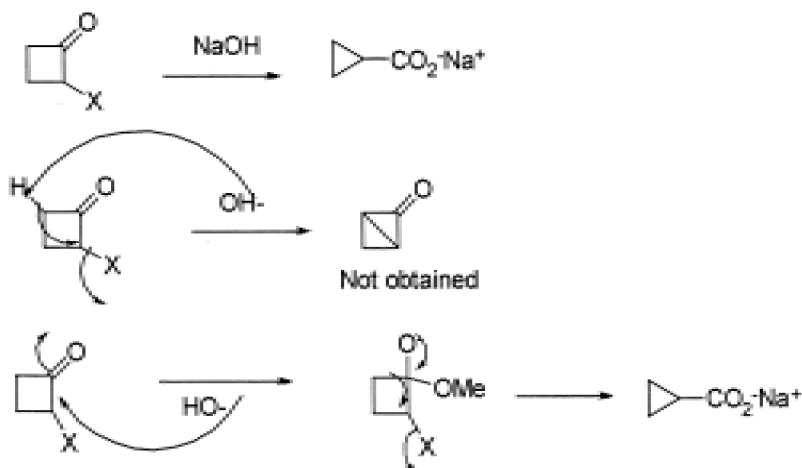


Q.



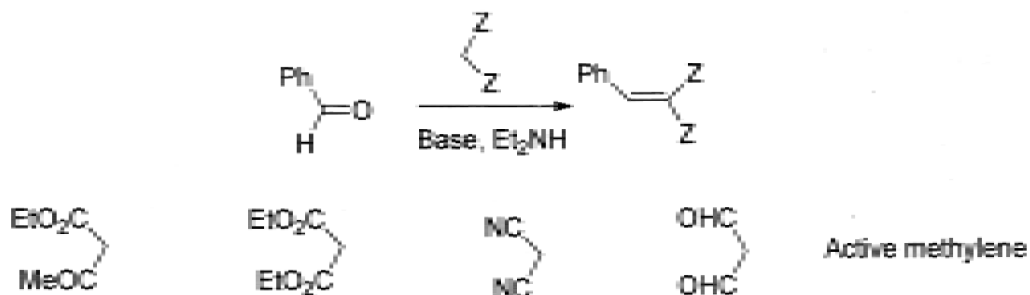


**Q. Draw the mechanism of the following transformation**



### 3.7.14 Knoevenagel Condensation

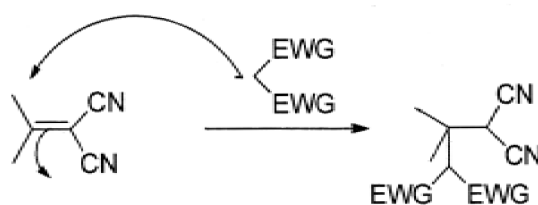
The base catalysed condensation reaction of aldehyde and ketone in presence of active methylene compound is known as Knoevenagel condensation. The product formed in this reaction is  $\alpha, \beta$  unsaturated ester.



The base used in Knoevenagel condensation is mainly 2° amine such as  $\text{Et}_2\text{NH}$ , piperidine. The active methylene compound is nitromethane, ethyl acetate, acetyl acetone, diethyl malonate. Knoevenagel condensation is more favorable in case of aldehyde compound rather than the ketone compound as ketone has  $\alpha\text{-H}$  atom. So it undergoes self condensation between them.

**Q. Why excess methylene compound is not used in Knoevenagel condensation?**

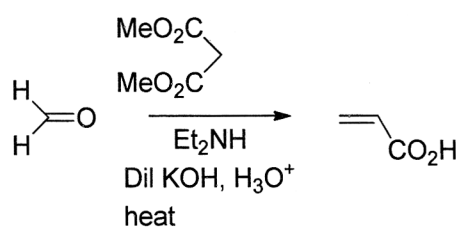
If excess active methylene compound is used in Knoevenagel condensation then the de protonated form of active methylene compound undergoes 1,4 addition. As a result Knoevenagel condensation product is destroyed. This type of 1,4 addition called Michael addition.



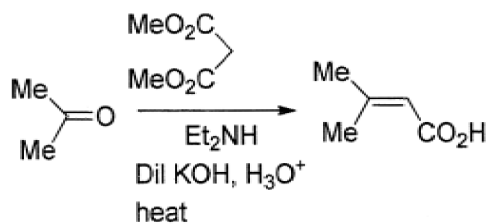
To avoid this problem, always equivalent amount active methylene compound is used in this condensation.

**Q. How will you convert ?**

Formaldehyde to Acrylic Acid ( $\text{CH}_2=\text{CHCO}_2\text{H}$ )

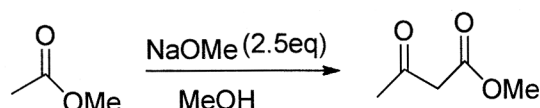


Acetone -to  $\beta$ ,  $\beta$ -dimethyl acrylic acid

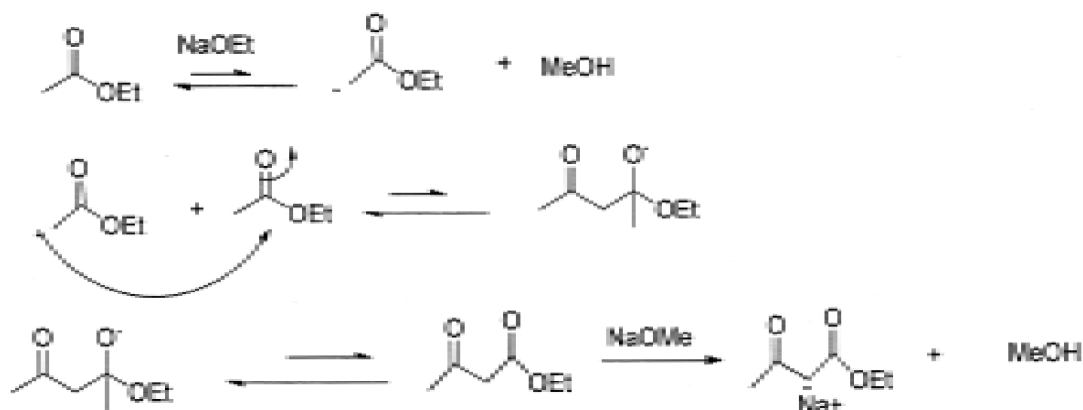


### 3.7.15 Claisen Condensation

$\alpha$ -H atom containing ester compound undergoes condensation reaction in presence of NaOEt/EtOH to give 1,3 di carbonyl compound. Such as ethyl acetate reacts itself in presence of excess NaOEt/EtOH to form ethyl acetoacetate.



**Mechanism :**

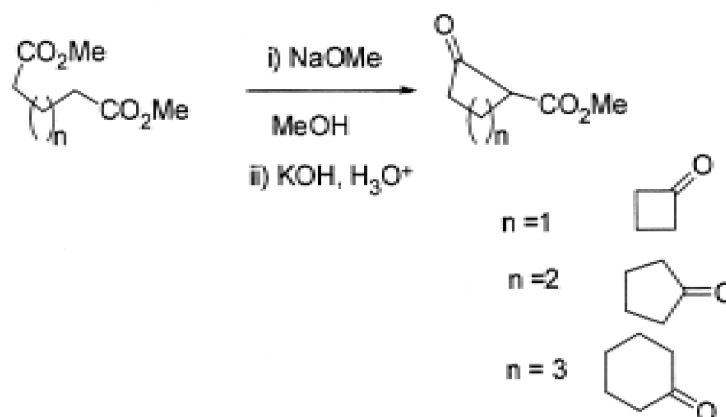


**Q. Why excess base ( EtOH/ NaOMe) is used in claisen Condensation reaction ?**

In the first of claisen condensation equilibrium goes in the backward direction due to ethyle acetate is less acidic than ethanol. So, the de-protected form of ethyl acetate is lower than deprotected form of ethanol. So the equilibrium goes in the back ward direction.

But after formation of ethyl acetoacetate, the active methylene proton is more acidic than that of ethanol. Therefore, when we used excess amount of NaOEt /EtOH then equilibrium goes in the right side by deprotonation of EtOH. Claisen condensation takes place in forward direction.

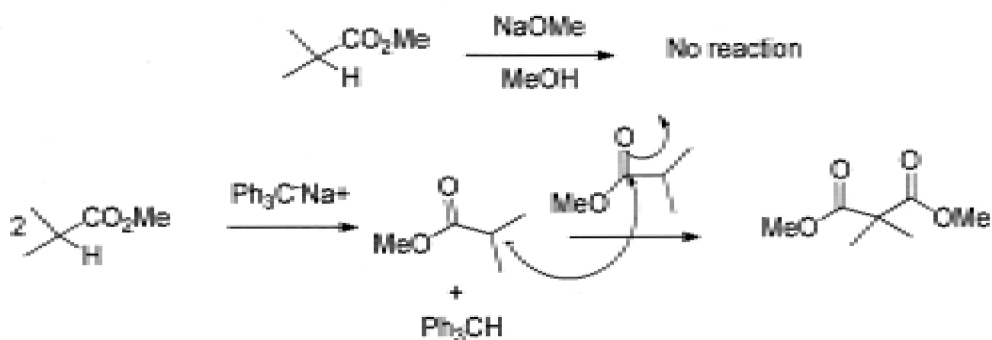
### Intramolecular Claisen condensation (Dieckman Cyclisation)



**Q. Why does not undergo claisen condensation reaction in presence in presence of NaOEt/ EtOH but it does in presence of  $\text{Ph}_3\text{CNa}^+$  .**

This compound does not undergo Claisen in presence of NaOEt / EtOH as the methylene H-atom is absent in this  $\beta$ -keto ester compound. So the equilibrium goes in the backward direction.

But in presence of  $\text{Ph}_3\text{C}^- \text{Na}^+$ , a strong base which equilibrates the first equilibrium in the right side . As a result Claisen condensation takes place.



**Q. What is the high dilution technic that is used in claisen condensation? How does it affect the nature of product ?**

Concentration of the reacting ester can control the nature of final product in claisen condensation. For example when the concentration of di ethyl succinate is

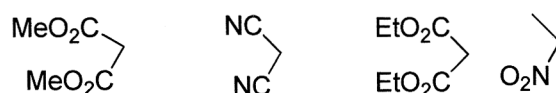
high, then base catalysed intermolecular claisen condensation reaction take place as the inter molecular reaction sites are closer. However when the concentration of ester is low, intramolecular claisen condensation (Dick man reaction) occur to give a cyclic compound.

### 3.7.16 Michael Reaction

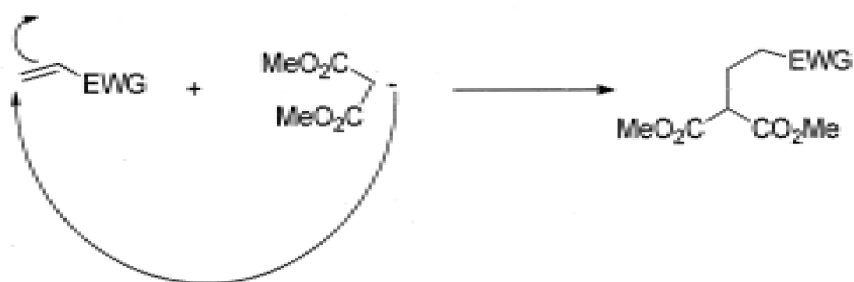
$\alpha, \beta$  unsaturated carbonyl compound reacts with active methylene compound in presence of base such as NaOEt/EtOH to give di carbonyl compound.

$\alpha, \beta$  unsaturated carbonyl compound called as Micheal acceptor and active methylene compound is called as Micheal donor.

**Michael donor :**

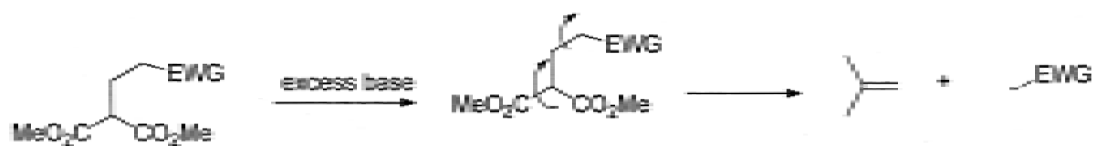


**Michael Acceptor :**

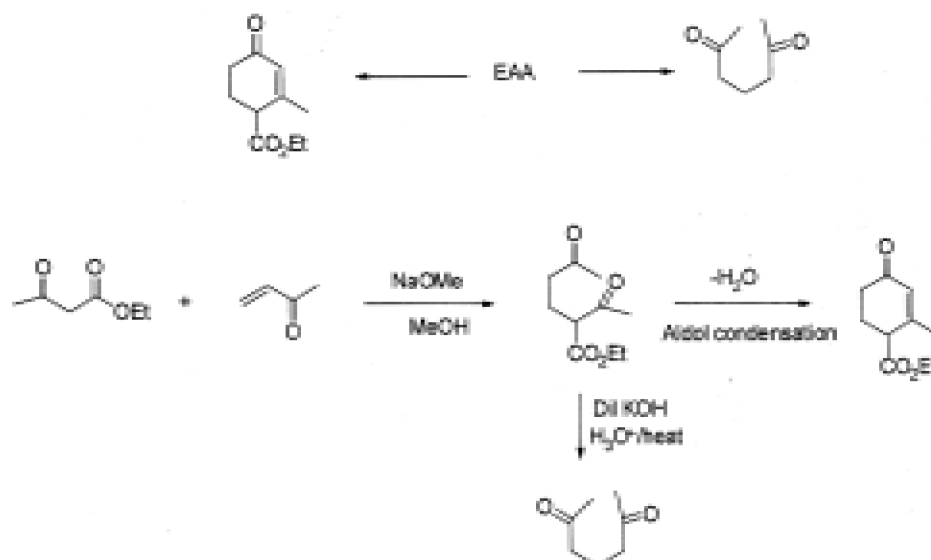


**Q. Why excess base does not used in Michael addition reactionn reaction ?**

If we use excess base then the Michael product undergoes cleavage and this type of reaction known as Michael *retrogression*.



Conversion :



Michael addition followed by aldol condensation is known as Robinson annulations.

### 3.8 Green Chemistry

Green chemistry is defined as environmentally benign chemical synthesis. It focuses on a process (where carried out in industry or chemical laboratory) that reduces the use and generation of hazardous substances or products. Strict laws have been passed by various governments particularly in advance countries like USA to strictly follow the procedure for various synthesis so as to reduce or eliminate products (or by products) that are responsible for the pollution of environment. The chemist all over the globe are motivated not only for the environmentally benign synthesis of new products but also to develop green synthesis for existing chemicals. This has been possible by replacement of the organic solvents, which are hazardous by water or eliminate the solvent together.

There is absolutely no doubt that green chemistry has brought medical revolution (e.g. synthesis of drug etc). The world food supply has increased many fold due to the discovery of hybrid varieties of improved method of farming, better seed, and use of agro chemicals like fertilizer, insecticides and herbicides etc. Also the quality of



life has also improved due to the discovery of dyes, plastics, cosmetics and other materials. All these developments increased the average life expectancy from 1900 to 75 years in 1900s. However, the ill effects of all development become pronounced. The most important effect is the release of hazardous by products of chemical industries and the release of agro chemicals in the atmosphere, land and water bodies; all these are responsible for polluting the environment including atmosphere, land and water bodies. Due to all these green chemistry assumed special importance.

### 3.8.1 The Need of Green Chemistry :

It has already been started that various scientific developments in the 20<sup>th</sup> century brought about various benefits to mankind, but all this was responsible for a number of environmental problems at local and global levels. It is of course, important to formulate guidelines and pass strict rule for the practicing chemist. But the most important is to bring about changes at grass root level. And this can be achieved by bringing about necessary changes in the chemistry curriculum in the colleges and universities and also in the secondary schools. A concerted and pervasive effort is needed to reach the widest the audience. Bringing green chemistry to the class room and laboratory will have the desired effects in educating the learners at various levels about green chemistry.

### 3.8.2 Twelve Principle of Green Chemistry

**Green chemistry** deals with environmentally benign chemical synthesis with a view to devise pathway for prevention of pollution. According to Paul T Anastas the following twelve basic principles of green chemistry have been formulated.

**1. It is better to prevent waste than to treat or clean up waste after it is formed.**

It is best to carry out synthesis by following a pathway so that formation of waste (by products) is minimum or absent. It must be kept in mind that in most of the cases, the cost involved in the treatment and disposal of the waste add to the overall cost of production. The unreacted starting materials (which may or may not be hazardous) form parts of waste. The basic principle “prevention is better than cure” should be followed. The waste if discharge in the atmosphere, sea, or land not only causes pollution but also requires expenditure for cleaning up.

**2. Synthetic materials should be designed to maximize the incorporation of all materials used in the process into the final product.**

It has so far been believed that if the yield in a particular reaction is about 90%, it is considered to be good. The percent yield is calculated by  $\% \text{ yield} = \text{Actual yield of product} / \text{Theoretical yield of product of product} \times 100$ .

The above calculation implies that if one mole of a starting material produces one mole of the product, the yield is 100%. However, such a synthesis may generate significant amount of waste or by products which is not visible in the above calculation. Such a synthesis, even though is 100% (by above calculation) is not considered to a green synthesis. For example, reaction like Grignard reaction and Wittig reaction may proceed with 100% yield but they do not like into account the large amount of by product obtained.

A reaction or synthesis is to be considered green if there is maximum incorporation of starting materials or reagents in the final product. One should take into account the percentage atom utilization, which is determined by the following equation  $\% \text{ atom utilization} = \text{MW of desired product} / (\text{MW of desired product} + \text{MW of waste products}) \times 100$ .

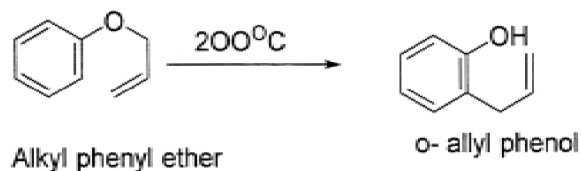
This concept of economy was developed by B.M Trostin a consideration of how much of the reactants up in final the product the same concept was also determined by R.A Sheldon as given below —

$\% \text{ atom economy} = \text{FW of atoms utilized} / \text{FW of the reactants used in the reaction} \times 100$ .

The most common reaction we generally come across in organic synthesis are rearrangement, addition, substitution and elimination reaction. Let us find out quick of the above reaction is more atom economical.

**Rearrangement reactions :**

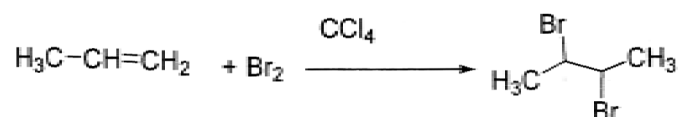
This reaction involve rearrangement of atoms that make up a molecule. For example, allyl phenyl ether on heating on heating 200°C gives O allyl phenol.



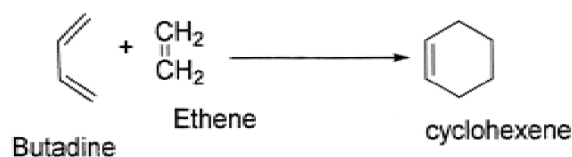
The rearrangement reaction (in fact all rearrangement reaction) is 100% atom economical reaction, since all the reactants are incorporated into the product.

### Addition Reaction :

Consider the bromination of propene

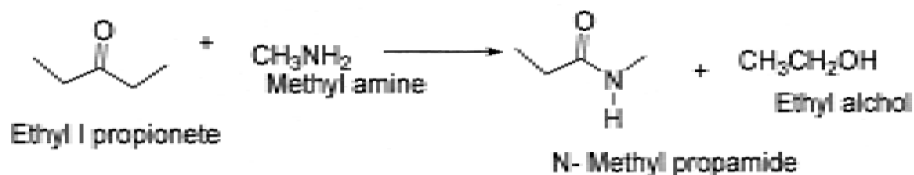


Here also all the elements of reactants (propene and bromine) are incorporated into the final product (1,2 di bromopropane). So this reaction is also 100% atom economical reaction.



### Substitution Reaction :

In substitution reactions, one atom (or group of atoms) is replaced by another atom (or group of atoms). The atom or group that is replaced is not utilised in the final product. So the substitution reactions are less atom economical than rearrangement or addition reactions. Let us consider the reaction of ethyl propionate with methyl amine.



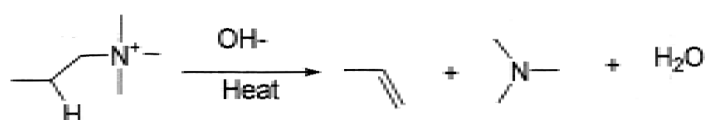
In the above reaction, the leaving group ( $-\text{OC}_2\text{H}_5$ ) is not incorporated in the formed amide and also, one hydrogen atom of amine is not utilized. The remaining atoms of the reactants are incorporated into the final product.

The total of atomic weights of atom in reactants that are utilized is 87.106 g/mole, while the total molecular weight including the reagent used is 133.189 g/mole. Thus a molecular weight of 46.069 g/mole remain unutilized in the reaction.

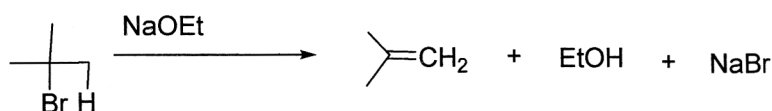
**Therefore the** atom economy (%) =  $(87.106/133.189) \times 100 = 65.40\%$

### Elimination reactions :

In an elimination reaction, two atoms or groups of atoms are lost from the reaction from the reactant to form a pi bond. Consider the following Hofmann elimination reaction



The above elimination reaction is not very atom economical. The percentage of atom economy is 35.30 % and is the least atom economical of all above reactions. Consider the another elimination reaction involving dehydrogenation of 2-bromo 2-methyl propane with base to give 2-methyl propene.



The above dehydrogenation reaction ( an elimination reaction ) also not very atom economical. The percentage atom economy is 27% which is even less than the Hofmann elimination reaction.

### 3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and environment.

One of the most important principle of green chemistry is to prevent or at least minimize the formation of hazardous product which may be toxic and or environmentally harmful. In case hazardous product are formed their effect on the workers must be minimize by the use of protective clothing, respirator etc. This, of course, will add to the cost of production. At times, it is found that the controls may fail and there may be more risk involved. Green chemistry, in fact, offers a scientific option to deal with such situations.

**4. Chemical products should be design to preserve efficacy of function while reducing toxicity.**

It is extremely important that the chemicals synthesized or developed (e.g, dyes, paints cosmetics, pharmaceuticals etc.) should be safe to use. A typical example of unsafe drug is thalidomide (introduced in 1961) for reducing the effects of nausea and vomiting during pregnancy (morning sickness). The children born to women talking thalidomide suffered birth defects. Subsequently, the use of thalidomide was banned, the drug withdrawn and strict regulations passed for testing all new drug. With the advantage of technology, the designed and production of safer chemicals has become possible. In fact, it is possible to manipulate the molecular structure to achieve this goal.

**5. The use of auxiliary substances (solvents, separation agents etc.) should be made unnecessary whenever possible and, when used, innocuous.**

A number of solvents like methylene chloride, chloroform, perchloroethylene, carbon tetrachloride, benzene and other aromatic hydrocarbons have been used (in a large number of reactions) due to their excellent solvent properties. However, the halogenated solvents (mentioned above) have been identified as suspected human carcinogens. Also, benzene and other aromatic are believe to promote cancer in humans and other animals. The solvent selected for particular reaction should not cause any environment pollution and health hazard. The use of liquid carbon dioxide should be explored. If possible, the reaction should be carried out in aqueous phase or without the use of solvent in solid phase.

A lot of concern has been expressed about the use of solvents which have direct hazardous effect on the environment. One such example is chlorofluorocarbon (CFCs) which have been widely used as cleaning agents, blowing agents and as refrigerants. These CFCs are responsible for depleting the ozone layer, which in turn has disastrous on human survival. Even the volatile organic compounds (VOCs) like carbon tetrachloride, methylene chloride, chloroform etc. which have been used as solvents in a number of applications have been disastrous effect in the atmosphere. In view of all these effects, regulations have been made under the clear air act in some of

the advanced countries like USA to control many classes chemical used as solvents. As far as possible the pathway for a reaction should be such that there is no need for separation or purification. By this procedure, the energy requirement is kept to a minimum.

**6. Energy requirement should be recognized for their environmental and economic impacts and should be minimized.**

In chemical synthesis, the requirement of energy should be kept to a minimum. For example, if the starting materials and reagents are soluble in a particular solvent, the reaction mixture has to be heated to reflux for completing the reaction. In such cases, the time required for completion of the reaction should be minimum, so that least amount of energy is required. The use of catalyst has the great advantage of lowering the requirement of energy of a reaction.

In case the final product is not pure, it has to be purified by distillation, recrystallization or ultrafiltration. All these steps require energy the process should be designed in such a way that there is no need for separation or purification.

It is possible, the energy to a reaction can be supplied photochemically, by using microwave or sanitation.

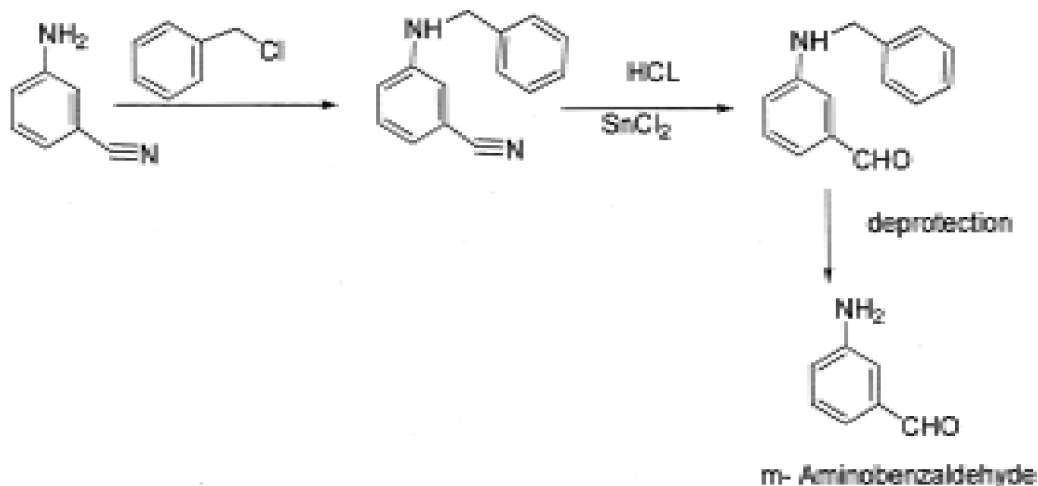
**7. A raw material or feedstock should be renewable rather than depleting, whenever technically and economically practicable.**

The starting material can be obtained from renewable or non-renewable material. For example, petrochemicals are mostly obtained petroleum oil, which is non-renewable source since its formation take million of years from animal and vegetable remains. The starting material which can be obtained from agriculture or biological process are refer to as renewable starting materials; however, these can not be obtained in continuous supply due to factor like failure of crops etc.

Substances like carbon dioxide (generated from natural sources or synthetic routes) and methane gas (obtained from natural sources such as marsh gas, natural gas etc.) are available in abundance; there are consider as renewable starting materials.

**8. Unnecessary derivatization (blocking group, protection /deprotection, temporary modification of physical /chemical process) should be avoided whenever possible.**

A commonly used technique in organic synthesis is the use of protecting or blocking group. These groups are used to protect a sensitive moiety from the conditions of the reaction, which may make the reaction to go in an unwanted way if it is left unprotected. A typical example of this type of transformation would be protection of amine by making benzyl ether in order to carry out a transformation of another group present in the molecule. After the reaction is complete, the NH<sub>2</sub> group can be regenerated through cleavage of benzyl ether.



Derivation of this type is quite common in the synthesis of fine chemicals, pharmaceuticals, pesticides and certain dyes. In the above example, benzyl chloride (a known hazard) needs to be handled with care and used in the preparation of desired material and then generated as waste upon deprotection.

In the above procedure, the protecting group is not incorporated into the final product, their use makes a reaction less atom economical. Thus, as far as possible the use of protecting groups be avoided. Though atom economy is a valuable criteria in evaluating a particular synthesis as : green “other aspect of efficiency must be considered.

**9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.**

In some reactions the reactants (A and B) react to form a product (C), in which all the atoms contained within A and B are incorporated in the product (C). In such cases stoichiometric reactions are equally environmentally benign from the point of material usage any other type of reactions. However if one of the starting material (A and B) is a limiting reagent; in such case even if the yield is 100%, some un reacted starting material will be left over as waste. In other cases, if the reagents A and B do not give 100% yield of the product (C), both the excess of unreacted reagents will form part of waste. It is found that due to the reason mentioned above, catalysts, where available offer distinct advantages over typical stoichiometric reagents. The catalyst facilitates the transformations without being consumed or without being incorporated into the final product. Catalyst are selective in their action in that the degree of reaction that takes place is controlled, e.g., mono addition vs multiple addition; also the stoichiometry is controlled (e.g., R vs S enantiomer). By using catalysts, both starting material utilization is enhanced and formation of waste reduced. An additional advantage of the use of catalyst is that the activation energy of a reaction is reduced and so the temperature necessary for the reaction is also lowered. This results in saving the energy.

It should be understood that in stoichiometric process the product obtained is one mole for every mole of reagent used. However a catalyst will carry out thousands of transformations before being exhausted. Following are given some of the applications of the use of catalysts. Oxidation of toluene with  $\text{KMnCO}_4$  in presence of crown ether gives much better yields

**10. Chemical products should be so designed that at the end of their function they do not persist in the environment and break down into innocuous degradation products**

It is of utmost importance that the products that are synthesised should be biodegradable; they should not be “persistent chemicals” or “persistent bio-accumulators; such chemicals (which are non-biodegradable) remain in the same form in the environment or are taken up by various plants and animal



species and accumulate in their systems; this is detrimental to the concerned species. The problem of non bio-degradability is generally associated with pesticides, and plastics and a host of other organic molecules.

Most of the pesticides in use are organohalogen based compounds. These pesticides in use are based compounds. These pesticides though effective tend to bio-accumulate in plants and animals. The pesticide DDT was one of the first pesticide which bio-accumulated in plants and animals. Whenever a chemical is being designed, it should be made sure that it will be biodegradable. It is now possible to place functional groups and other features in the molecule which will facilitate its degradation. Functional groups which are susceptible to hydrolysis, photolysis or other cleavage have been used to ensure that products will be biodegradable. It is equally important to make sure that the degradation products should not possess any toxicity and be detrimental to the environment. Plastics are known to remain persistent and are not biodegradable. The waste plastics were mostly used for landfills etc. However, it has now been possible to make plastics (particularly for garbage bags etc. which are biodegradable).

**11. Analytical methodologies need to be further developed to allow for real-time, in process monitoring and control prior to the formation of hazardous substances.**

Analytical methodologies and technology have been developed which allow the prevention and minimization of generation of hazardous substances monitors, and analytical techniques to assess the hazardous that are present be monitored for generation of hazardous by products and side reactions. These procedures can prevent any accident which may occur in chemical plants.

**12. Substances and forms of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.**

The occurrence of accidents in chemicals industry must be avoided. The accidents in Bhopal (India) and Seveso (Italy) and many others have resulted in the loss of thousands of lives.

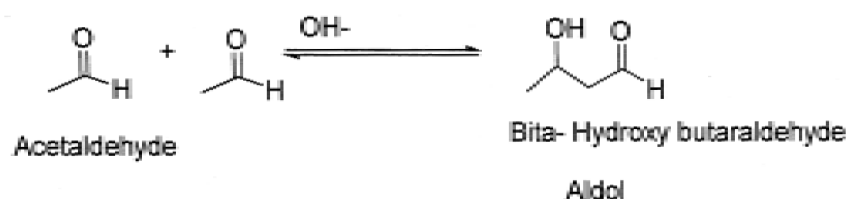
At times it is possible to increase accident potential inadvertently in an

attempt to minimize the generation of waste in order to prevent pollution. It has been noticed that in an attempt to recycle solvents from a process (in order to be economical and also prevent escape of solvent to the atmosphere) increase the potential for a chemical accident or fire. In fact, a process must balance the accident prevention with a desire for preventing pollution. A possible course is not to use volatile solvents instead solids or low vapor pressure substance can be used.

### 3.8.3 Green Reactions

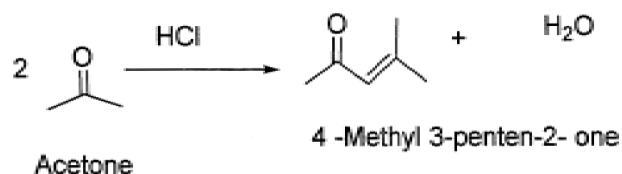
#### 3.8.3.1 Aldol condensation :

Self condensation of aldehydes (having  $\alpha$  hydrogen atom) on warming with dilute alkali to give  $\beta$ -hydroxyaldehydes (known as aldols) is called aldol condensation. A typical example is the reaction of acetaldehyde with dilute alkali.



#### (i) Acid-Catalysed Aldol Condensation

In aldol condensation cited above the condensation takes place in presence of a base. However, aldol condensation can also be brought about with acid catalysts. For example treatment of acetone with hydrogen chloride gives the aldol condensation product *via*, 4-methyl 3-penten-2-one. In general, in acid catalysed aldol reactions there is simultaneous dehydration of the initially formed aldol.

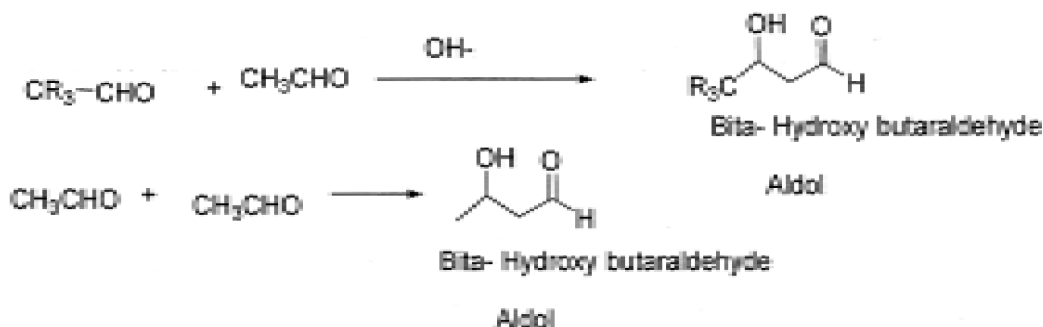


#### (ii) Crossed Aldol Condensation

An aldol condensation that uses two different carbonyl compounds is called a crossed aldol condensation. In such a situation the following three situations may be there :

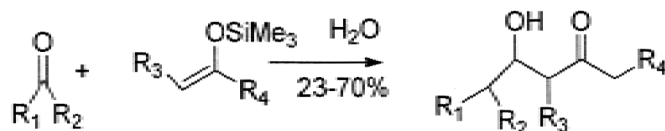
### Crossed aldol condensation between two different aldehydes.

In case, both the aldehyde have  $\alpha$ -hydrogen (s), both can form carbanions and so a mixture of four products are formed. Such a reaction has no synthetic utility. If, on the other hand one of the aldehyde has no  $\alpha$ -hydrogen then in such case two products are formed as shown below :



### (iii) Aldol Condensation of Silyl Enol Ethers in Aqueous Media

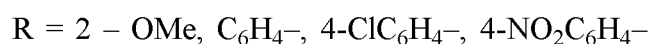
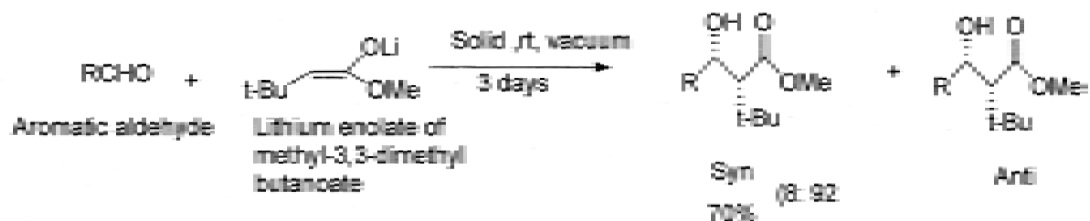
The aldol condensation of silylenol ethers with benzaldehydes, catalysed by titanium tetrachloride was first reported in 1937. However, these reactions are carried out in hydrous solvents. It has now been possible to perform aldol condensation of silylenol ethers with aldehydes in aqueous phase.



The aqueous phase reaction was carried out without any catalyst, but it took several days for completion, since water serves as a weak Lewis acid. The addition of stronger Lewis acid (e.g., ytterbium triflate) greatly improved the yield and the rate.

### (iv) Aldol Condensation in Solid Phase

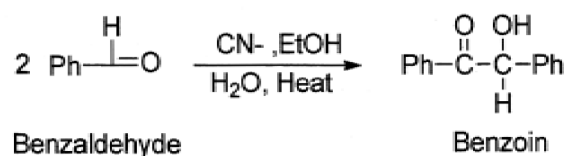
The aldol condensation of lithium enolate of methyl 3, 3-dimethyl butanoate with aromatic aldehyde gives 8 : 92 mixture of the syn and anti products in 70% yields.



The above reaction is carried out by mixing freshly ground mixture of starting materials in vacuum for 3 days at room temperature. In the absence of any solvent, some aldol condensation proceed more efficiently and stereoselectively. In this procedure the appropriate aldehyde and ketone and NaOH are grounded in a pestle and mortar at room temperature for 5 minute, the product obtained is corresponding chalcone. In this case, the initially formed aldol dehydrates easily.

### 3.8.3.2 Benzoin Condensation

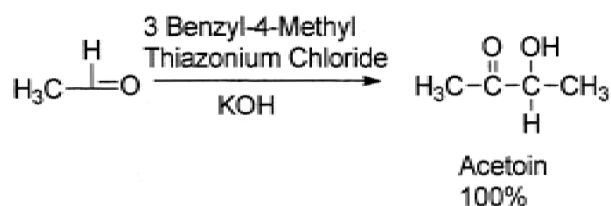
Aromatic aldehydes (having no  $\alpha$  hydrogen) on treatment with sodium or potassium cyanide undergo self condensation to give  $\alpha$ -hydroxy ketone (benzoin). This is known as benzoin condensation.



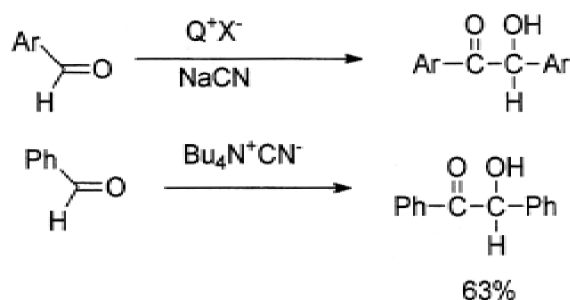
Benzoin condensation does not take place with aliphatic aldehydes under these conditions.

### Benzoin condensation under catalytic conditions

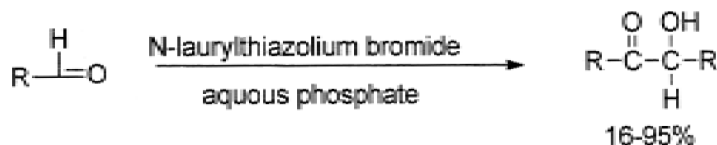
It has found that even aliphatic aldehydes like acetaldehyde undergo benzoin condensation with solid potassium hydroxide and using 3-benzy 1-4-methylthiazolium chloride as a catalyst. Thus acetaldehyde yields acetoin in quantitative yield.



It is found that aromatic aldehydes reacted in a few minutes under the above conditions; where as aliphatic aldehydes required 5-10 hour. Benzoin condensations of aromatic aldehydes with aqueous sodium cyanide are catalysed by quaternary ammonium salts.



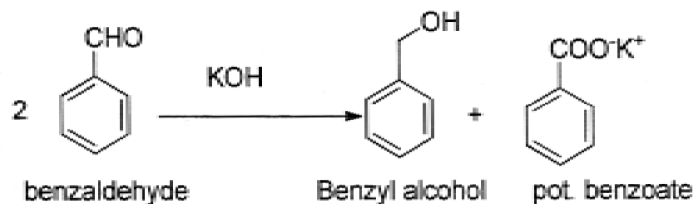
In a similar way, acyloin condensations with aromatic or aliphatic aldehydes proceed remarkably well using N-laurylthiazolium bromide as catalyst with an aqueous phosphate solution.



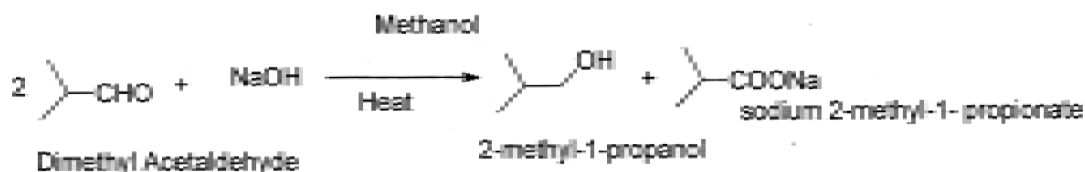
It was found by Breslow that the benzoin condensation in aqueous media using inorganic salts (e.g., LiCl) is about 200 times faster than in ethanol without any salt. The benzoin condensation was also accelerated by the addition of  $\gamma$ -cyclodextrin, whereas addition of  $\beta$ -cyclodextrin inhibited the condensation.

### 3.8.3.3 Cannizzaro Reaction

Aldehyde without  $\alpha$ -hydrogen(s) on treatment with concentrated aqueous alkali undergoes self oxidation and reduction to give an alcohol and the salt of the corresponding carboxylic acid.

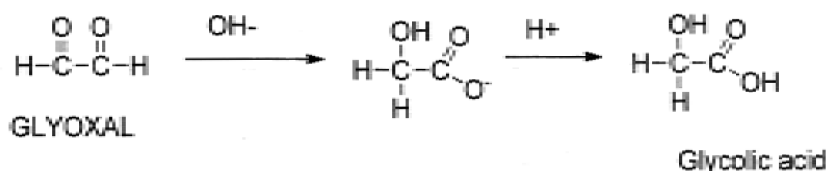


This disproportionate or self oxidation and reduction of aromatic aldehydes, devoid of  $\alpha$ -hydrogen is known as cannizzaro reaction.



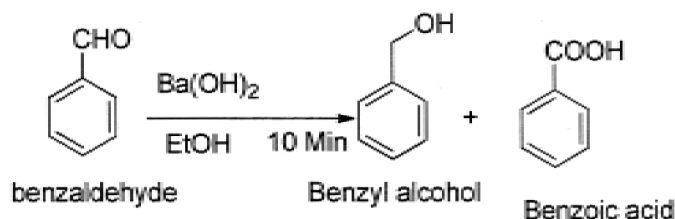
### (i) Intramolecular cannizzaro reaction

Certain compounds, which contain two carbonyl groups undergo internal cannizzaro reaction. For example, glyoxal on treatment with base gives glycolic acid.



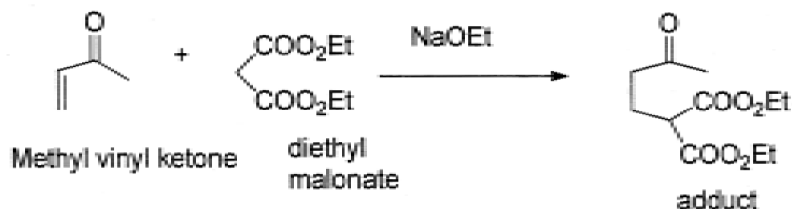
### (ii) Cannizzaro reaction Under Sonication

The cannizzaro reaction under heterogeneous conditions catalysed by barium hydroxide is considerably accelerated by sonication. The yield is 100% after 10 min., whereas no reaction is observed during this period without ultrasound.



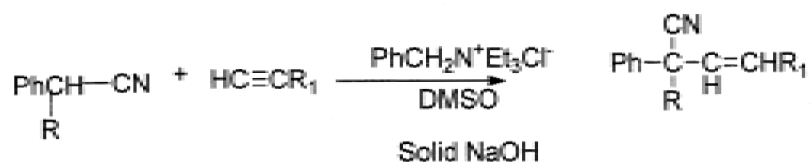
### 3.8.3.4 Michael Addition

The base catalysed addition reaction between  $\alpha$ ,  $\beta$  unsaturated carbonyl compounds (e.g., cinnamaldehyde,  $\text{PhCH}=\text{CH}-\text{CHO}$ ; benzylidene acetone  $\text{PhCH}=\text{CHCOCH}_3$ , mesityloxide,  $(\text{CH}_3)_2\text{C}=\text{CHCOCH}_3$ ) etc. and a compound with active methylene group (e.g., malonic ester, acetoacetic ester, cyanoacetic esters, nitroparafins) is known as Michael addition. The base usually employed is sodium ethoxide or a secondary amine (usually piperidine). Thus, methyl vinyl ketone reacts with diethyl malonate in presence of sodium ethoxide to give the addition product.



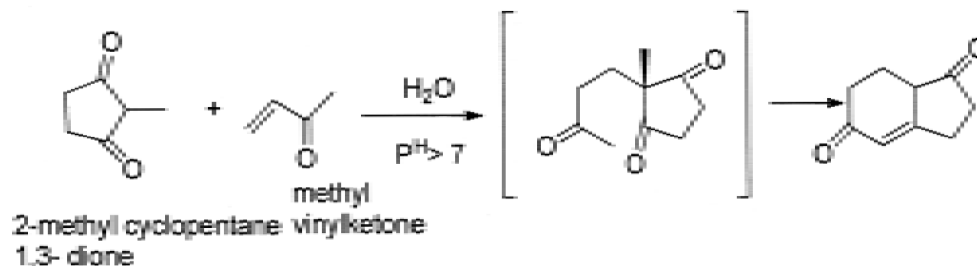
### (i) Michael addition under PTC conditions

The Michael addition of active nitriles to acetylenes can be catalysed by the addition of quaternary ammonium chloride.



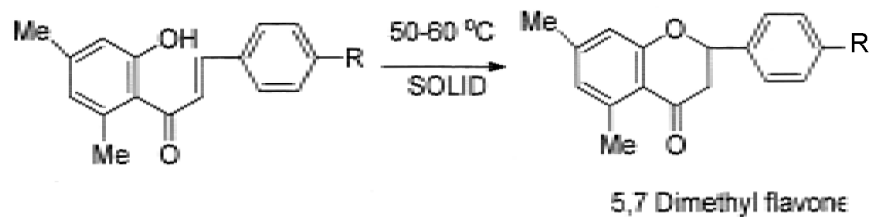
### (ii) Michael Addition in Aqueous medium

Michael addition in aqueous phase was first reported in 1970s. 2-methylcyclopentane-1,3-dione on reaction with methyl vinyl ketone in water gave an adduct with the use of a basic catalyst ( $\text{pH} > 7$ ). The adduct further cyclises to give fused ring systems (Scheme-8)



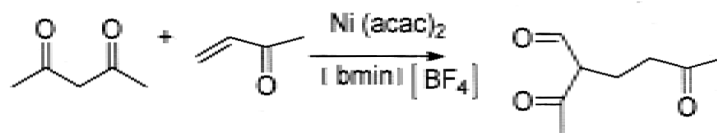
### (iii) Michael addition in solid state

A number of 2'-hydroxy-4',6'-dimethylchalcones undergo a solid state intramolecular Michael type addition to yield the corresponding flavones.



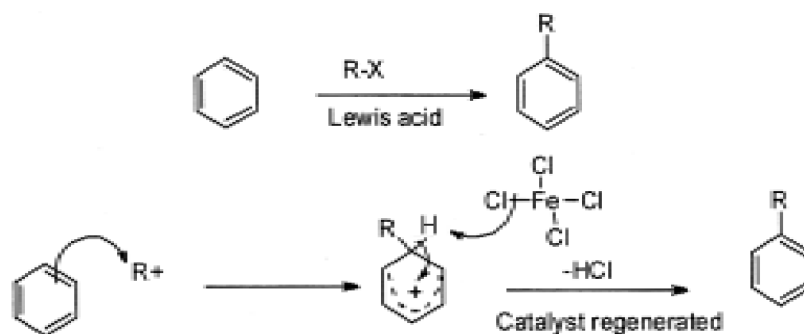
#### (iv) Michael Addition in Ionic Liquids

Michael addition reactions of acetyl acetone to methyl vinyl ketone in presence of catalyst  $\text{Ni}(\text{acac})_2$  in ionic liquid  $[\text{bmin}]^+[\text{BF}_4]^-$  provides excellent in terms of activity, high selectivity and recyclable catalytic system.



#### 3.8.5 Friedel Crafts Reaction

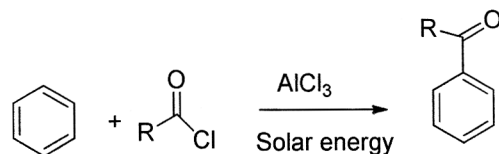
Friedel-Crafts alkylation involves the alkylation of an aromatic ring with an alkyl halide using a strong Lewis acid, such as aluminum chloride, ferric chloride, or other  $\text{MX}_n$  reagent, as catalyst.



#### (i) Friedel-Crafts Acylation Using Solar Irradiation :

In recent decades, scientists have attempted to make more environmentally friendly chemical synthesis procedures. One area of environmental concern is the amount of electricity required to complete an experiment. An effective means for minimizing the amount of electricity needed to drive chemical reactions to completion is proposed through the use of solar parabolic reflectors. The proposed solar reflectors are assembled by covering unused satellite dishes with Mylar tape, giving the satellite dish reflective properties when the dish is directed at the sun. The ability to use the solar reflector as the sole heat source for organic synthesis reactions is being considered. Comparative studies will be conducted using electrical supplies to compare the solar reflectors ability to generate heat to drive the chemical reactions to completion. The synthesis of isobutyrophenone, which is synthesized through a Friedel-Crafts acylation of benzene, has been attempted using the solar reflector.





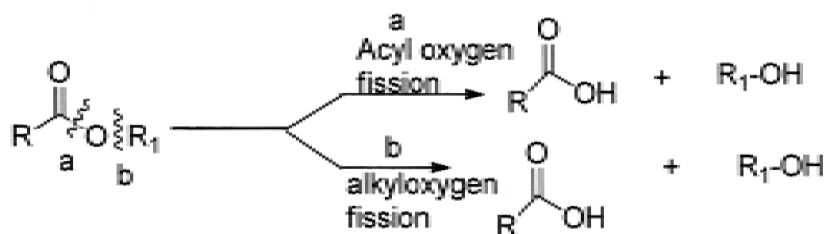
### Water as a solvent for Friedel-Crafts reactions under catalytic systems

The emerging scenario of green and sustainable chemistry in synthesis developed the catalytic process using water as a solvent due to its versatility, unique and superior properties over organic and other solvents. The catalysts efficiently stimulate the nucleophilic substitutions in the presence of water, thus facilitate the reaction. Catalysts are preferred due to their high atom economy. Certainly, a number of synergistic and potential catalysts or promoters ranging from homogeneous catalysts such as Lewis and Bronsted acids to heterogeneous catalysts such as zeolites, metalloenzymes, mesoporous oxides which have been utilized for the Friedel-Crafts carbon-carbon bond forming reactions in water or aqueous mixtures.

## 3.9 Ester Hydrolysis

Ester undergoes hydrolysis in presence of acid or base to give their corresponding acid and alcohol. When ester undergoes hydrolysis in presence of base then it gives sodium salt of acid. The salt of long chain fatty acid is called soap. So the hydrolysis of ester in presence of is called saponification. (Saponification is a Latin word, it means soap)

Ester can be hydrolysed by the cleavage of acyl and alkyl oxygen fission.



Type of mechanism	Hydrolysis	Esterrification
$B_{AC}^1$		
$B_{AC}^2$	Very common	—
$A_{AC}^1$	Special case	Special case
$A_{AC}^2$	Very common	Very common
$B_{AL}^1$	Special case	—
$B_{AL}^2$	Rare	
$A_{AL}^1$	Very common for t-alcohol	Very common for t-alcohol
$A_{AL}^2$		

AC = acyl oxygen fission, AL = Alkyl oxygen fission

B = base catalysed, A = Acid catalysed

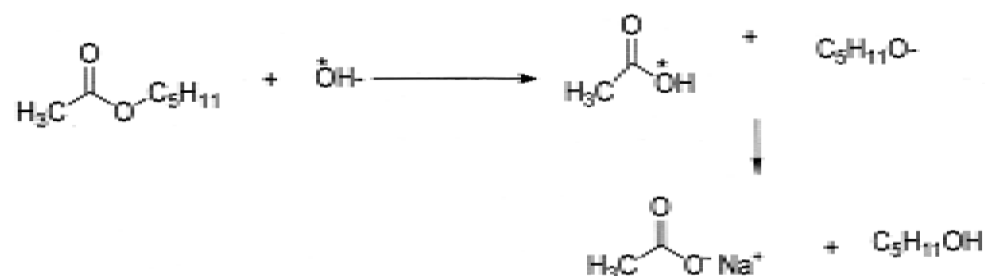
Number 1 and 2 represents the number of molecule take part in the r.d.s

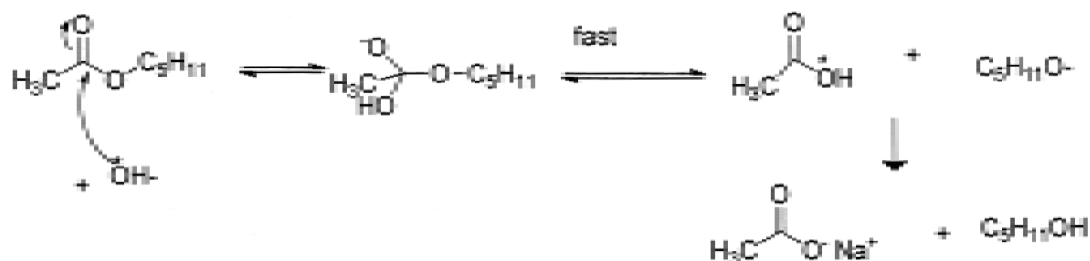
$B_{AC}^1$  = Base catalysed acyl oxygen fission unimolecular

$B_{AC}^2$  = Base catalysed acyl oxygen fission bimolecular

### 3.9.1 $B_{AC}^2$ Mechanism :

#### $B_{AC}^2$ Mechanism



**Mechanism :**

$$\text{Rate} \propto [\text{Substrate}] \cdot [\text{OH}^-]$$

**Evidence for this mechanism :**

1. If we use  $\text{H}_2\text{O}^{18}$  with marked O-atom then we get acid with marked oxygen atom and alcohol without marked oxygen atom. This is possible only when the acyl oxygen fission takes place rather than alkyl oxygen fission.
2. If alkoxide group is taken as chiral then after acyl oxygen fission leads to retention of configuration atom.

**The electronic factor also supports the acyl oxygen fission :**

If the nucleophile attacks to the carbonyl group of ester then the reaction rate increases with increasing – I effect as the  $\alpha$ -carbon of carbonyl group. Hence, with increasing the electronegativity of carbonyl carbon  $\text{OH}^-$  easily attacks to the centre and the reaction rate increases. This indicates that acyl oxygen fission takes place rather than alkyl oxygen fission.

**–I Effect of Ester :**

$\text{MeCO}_2\text{Me}$	$\text{ClCH}_2\text{CO}_2\text{Me}$	$\text{Cl}_2\text{CHCO}_2\text{Me}$
<b>1</b>	<b>761</b>	<b>16000</b>

**Steric factor :**

When nucleophile attacks to the carbonyl carbon of ester group then  $\text{Sp}^2$  carbon inter converted to  $\text{Sp}^3$  carbon atom. Therefore, steric intereaction will occur in the T.S rather than the ground state. So with increasing the  $\alpha$ -substituent on  $\alpha$ -carbon of carbonyl group, the hydrolysis rate becomes dimmish .This is observed in the spherical case. Hence acyl oxygen fission will take place in  $\text{B}_{\text{AC}}2$  mechanism of ester hydrolysis.

**Steric effect of ester :**

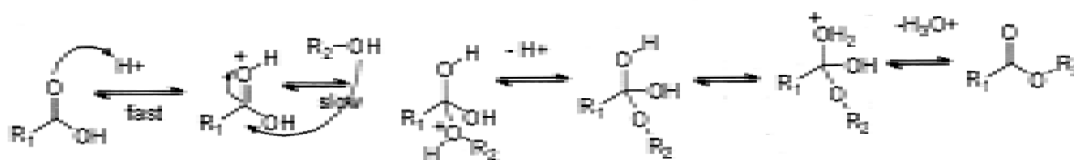
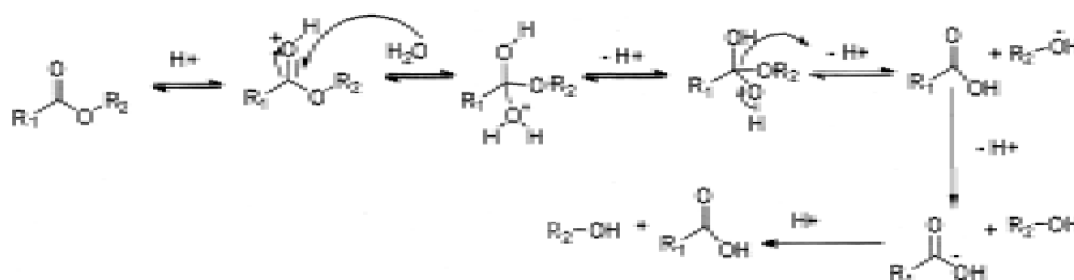
1

0.47

0.10

**3.9.2 A<sub>AC</sub>2 Mechanism :**

Ester is formed in presence of acid and ester is hydrolysed in presence of acid. Therefore formation of ester and hydrolysis of ester is reversible in nature.

**Ester formation :****Ester Hydrolysis :****Evidence for this mechanism :**

1. If we use the H<sub>2</sub>O<sup>18</sup> then the acid part contains marked oxygen atom and alcohol part contains unmarked oxygen atom. Hence acyl oxygen fission will take place.
2. If we increase the steric interaction on the α carbon of ester group by alkyl substitutions, then the rate of hydrolysis become slower. This is also indicates that acyl oxygen fission will occur.

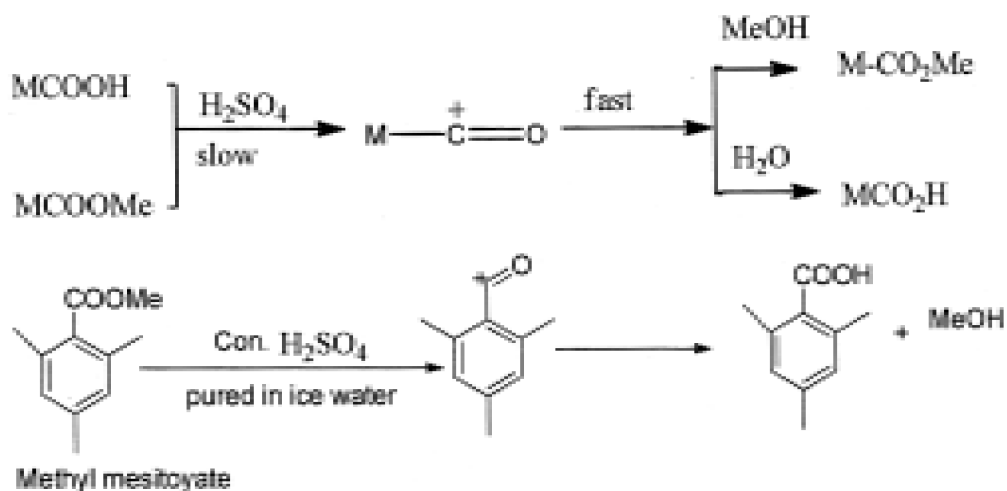
**3.9.3 A<sub>AC</sub>1 Mechanism :**

When methyl benzoate treated with concentrated H<sub>2</sub>SO<sub>4</sub> following by poured in ice water then it does not undergo hydrolysis. But methyl mesitoate undergoes

hydrolysis in that condition to give their corresponding acid and alcohol. This indicates that have an another path way for acid catalyted hydrolysis. Here in presence of con,  $H_2SO_4$  it gives acylium cation is then attacked by water molecule to give the alcohol.

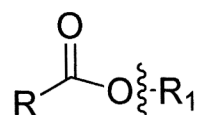


Here Vant Hoff factor (i) = 4

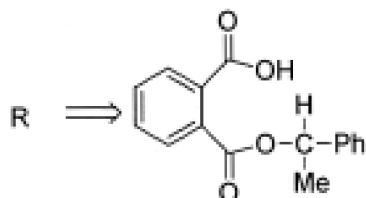
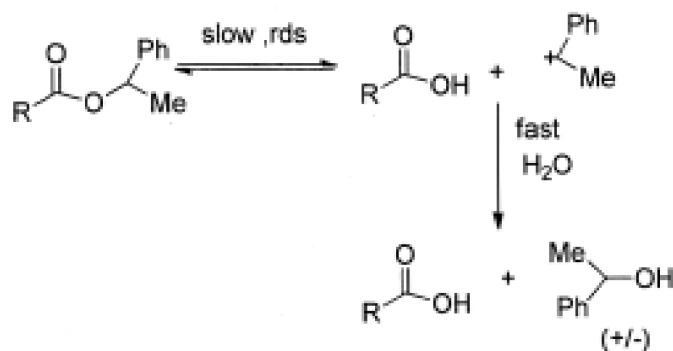


The four fold freezing point depression indicates; four ions are produced in hydrolysis mixture. This is possible if acylium carbocation is produced during hydrolysis by unimolecular mechanism.

### 3.9.4 B<sub>AL</sub>1 Mechanism :



This mechanism is observed when the alkyl group in alkoxy ester is stabilized by resonance. This stabilization factor leads to the cleavage of alkyl oxygen bond of ester. If alkyl oxygen fission will occur then the carbocation is formed which gives the racemic alcohol. Again acyl oxygen fission occurs then we get the chiral alcohol with retention of configuration.

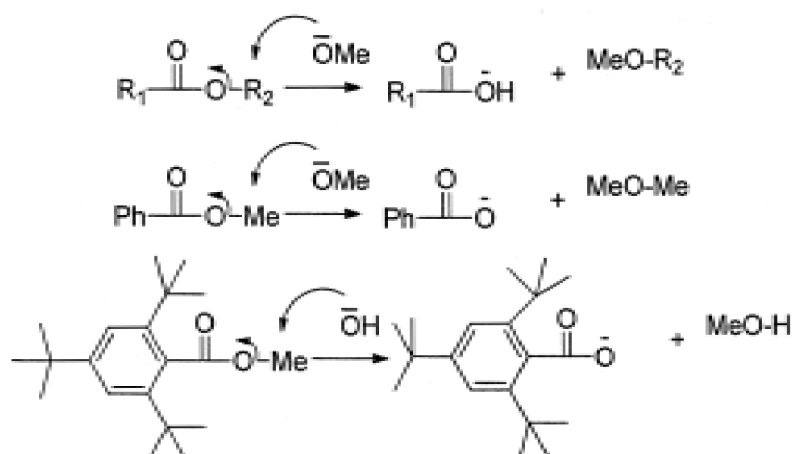


Alpha Phenyl -ethyl Hydrogen phthalate

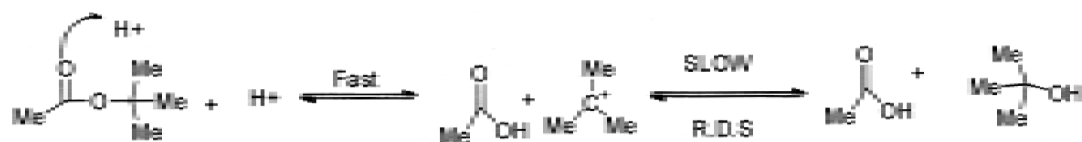
Since in practical case, we get racemic alcohol as the product, so alkyl oxygen fission will occur.

#### The condition for this mechanism :

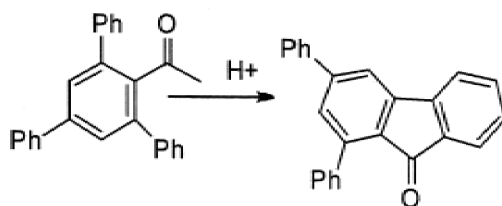
1. Low concentration of hydroxide ion
2. High power of ionising solvent, i.e polar solvent.

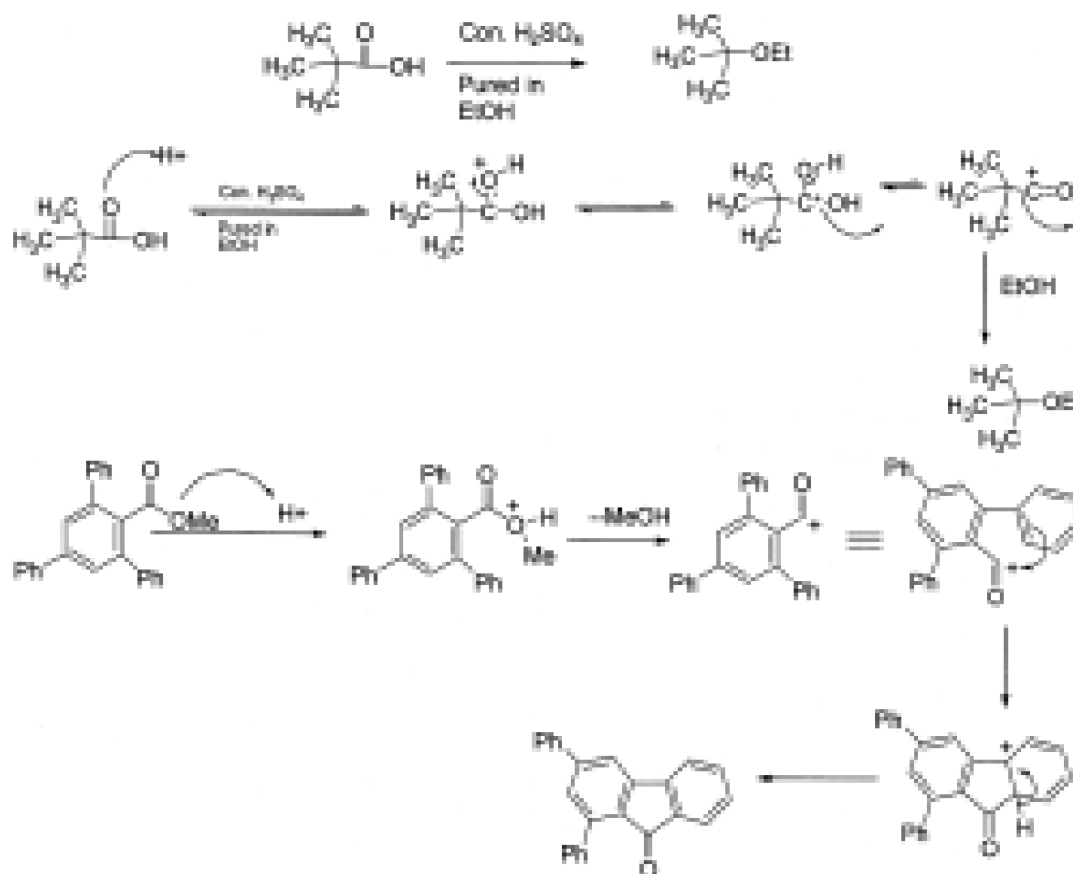
**B<sub>AL</sub>2 Mechanism:****3.9.5 A<sub>AL</sub>1 Mechanism :**

When the alkyl group is stabilized then thus type of cleavage will occur.



This reaction goes through A<sub>AL</sub>1 mechanism.



**Mechanism :****3.10 Summary**

In conclusion, this module generates an elaborate description carbonyl chemistry (including name reaction of carbonyl chemistry), green chemistry (including green principal of any chemical transformation) and ester hydrolysis (detailed mechanism). This unit describes

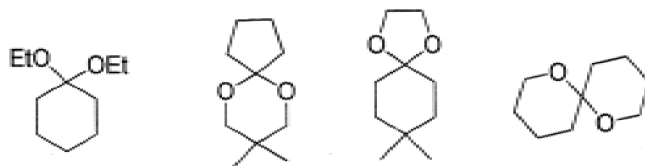
- I. Nucleophilic addition of carbonyl (e.g H<sub>2</sub>O, ROM, HCN, HCl, amine etc)
- II. Condensation reaction of aldehyde/Ketone
- III. Name reactions of carbonyl chemistry
- IV. Green principle of organic transformation
- V. Detailed mechanism of ester hydrolysis.



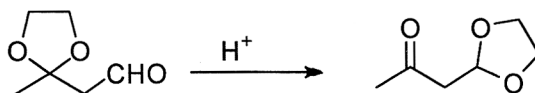
**Glossary / Keywords:** Carbonyl Group, Nucleophilic addition, Name reaction, Green chemistry, Ester hydrolysis

### 3.11 Additional Problem

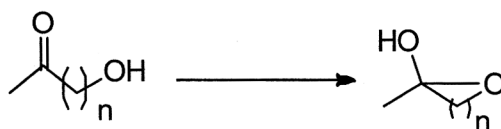
1. Find out the starting materials for each of the following substrate



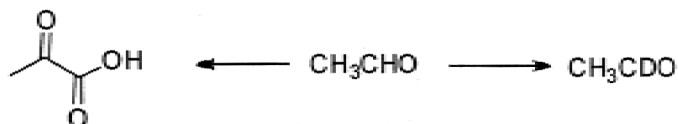
2. Write down mechanism of the following transformation



3. Give the stability of the following hemiacetal formation reaction

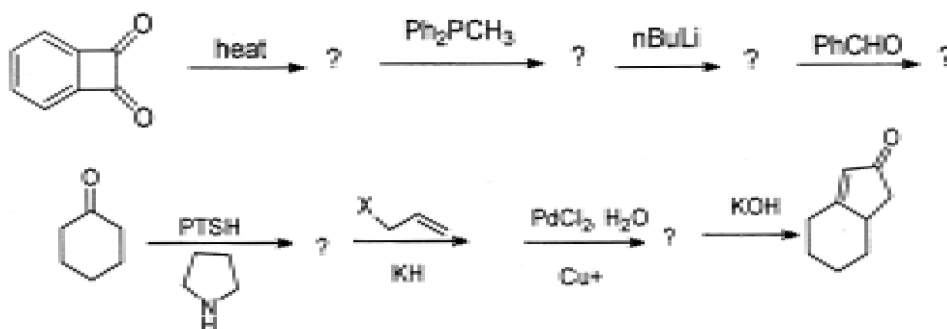


4. Find out the conversion

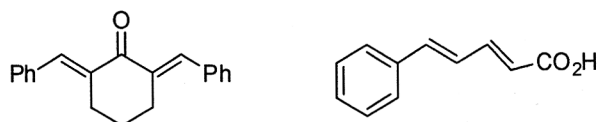


5. What is stabilized and non stabilized ylide in Wittig reaction? Predict the product when stabilized ylide treated with benzaldehyde

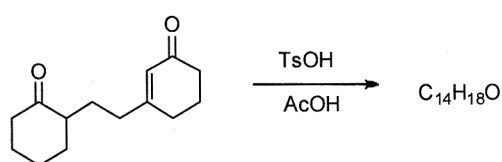
6. Fill in the following scheme



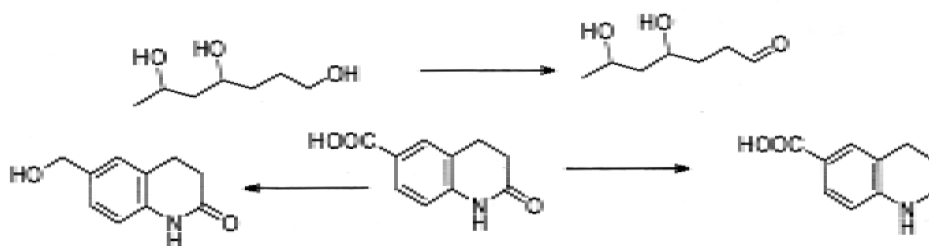
7. How will you synthesis following compounds using aldol condensation reaction?



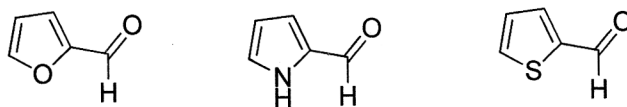
8. Predict which enone product would be formed in this intramolecular aldol reaction.



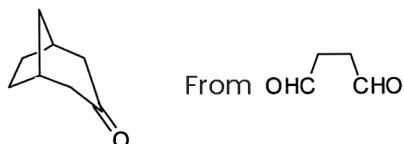
9. What is chemoselective reaction? Find out proper reagent for the following transformation.



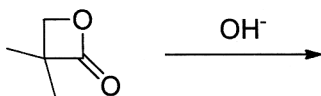
10. Compare the reactivity of cannizaro reaction of the following substrate



11. Give the structure of Manich salt? Using this reaction how will you synthesis following substrate



12. In Perkin reaction a side product is formed along with Cinamic acid. Write the structure of the side product.
13. Define atom economy and step economy. Show that substitution reaction is more atom economic than elimination reaction.
14. Give the brief mechanism of following ester in hydrolysis



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### 3.12 Reference Books

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1. Clayden J., Greeves N., Warren S. & Wothers P. "Organic Chemistry"
2. Sykes, P. "Mechanism in Organic Chemistry" (6th ed.)
3. Warren, S. "Chemistry of the Carbonyl Group"
4. W. Carruthers "Modern methods of Organic Chemistry"

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## Unit - 4 □ Organometallic Compounds

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### Structure

#### 4.1 Objective

#### 4.2 Introduction

#### 4.3 The Grignard reagents

##### 4.3.1 Reactions of the Grignard Reagents

##### 4.3.2 Synthetic uses of the Grignard reagents

##### 4.3.3 Abnormal behavior of Grignard reagents

#### 4.4 Metal Alkyls

#### 4.5 The Reformasky reaction

#### 4.6 Blaise reaction

#### 4.7 Organocopper reagents

#### 4.8 Corey-House reaction

#### 4.9 Summary

#### 4.10 Problems in organometallic chemistry

#### 4.11 Reference Books

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### 4.1 Objective

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- Students make idea about how organic compound form bond with the inorganic metal. Hence, Organometallic chemistry is a hybrid discipline; it utilizes principles of both organic and inorganic chemistry.
- The students are able to learn the different reactivity of Grignard reagent towards various functional groups such as nucleophilic addition of ketone, aldehyde, ester, amide, acyl halides, and esters.
- Students furnish idea about organolithium reagents and also emphasis different reactivity nature of organomagnesium and organolithium reagents.

- Identify and be able to write the mechanism for the Organometallic reaction.
- Be able to face unknown problem involving any synthetic transformation.

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## 4.2 Introduction

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*Organometallic*” compounds are those compounds which contain a metal-carbon bond (R-M). Organometallic compounds of Li, Mg (Grignard reagents) are amongst some of the most important organic reagents. Many other metals have been utilised, for example Na, Cu, Pd and Zn. Organometallic compounds creates a nucleophilic carbon atoms which can react with electrophilic carbon to form a new carbon-carbon bond. This is very important for the synthesis of complex molecules from simple starting materials. The polarity of organometallic compound represented by  $R-M = R^{-}M^{+}$ . The most important reactions is this chapter are the reactions of Grignard reagents (RMgX), organolithiums (RLi), and with the carbonyl groups in aldehydes, ketones and esters to give alcohols. However, we will also look at some useful reactions involving Cu and Zn.

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## 4.3 The Grignard reagents

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The alkylmagnesium halides, R-Mg-X, introduced by Grignard in 1900, are extremely valuable in organic synthesis. Franfois-Auguste-Victor Grignard got nobel prize in 1912 for his great innovation. A Grignard reagent is generally prepared by reaction between magnesium (1 atom ) and alkyl halaid (1 atom) in dry, alcohol free ether.



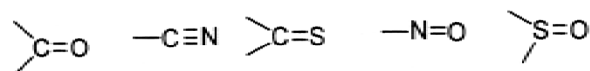
The ethereal solution of Grignard reagent is generally used in all reactions. Other solvents besides ether may be used e.g., tertiary amines, tetrahydrofuran and diethyl ether of ethylene glycol. Tetrahydrofuran is being used increasingly as a solvent, since it has been that it increases the reactivity of organic halides towards magnesium. Thus, Normat (1953) has prepared Grignard reagent of vinyl halides and aryl chlorides in THF. In many cases where the preparation of Grignard reagent is difficult, the addition some methyl iodide may result in the formation of the Desired

Grignard reagent; this is preferred to as the entrainment method. However the best entrainment technique is to ethylene dibromaide (3 moles or more) and to use magnesium in excess (6 moles or more).

The ease with which and alkyl halide forms a Grignard reagent depends on a number of factors. It has been found that for a given alkyl group the ease of formation is alkyl iodide > bromide > chloride. It has also been found that the formation of a Grignard reagent becomes increasingly difficult as the number of carbon atoms in the alkyl group increases, i.e., the ease of formation is  $\text{CH}_3\text{X} > \text{C}_2\text{H}_5\text{X} > \text{C}_3\text{H}_7\text{X}$ .... . Since tertiary alkyl iodides readily eliminates hydrogen iodide with the formation of an alkene, tertiary alkyl chlorides are used. Also, in the preparation of the Grignard reagent, a common side reaction is coupling between two R groups to give R-R.

#### 4.3.1 Reactions of the Grignard Reagents

Addition of the Grignard reagent to a compound containing a multiple bond group e, g



Addition of the R group of  $\text{RMgX}$  occurs at the less electronegative and that of the  $\text{MgX}$  at the more electronegative atom. This is understandable on the basis that R and  $\text{MgX}$  are the respectively the negative and positive ends of the dipole in  $\text{RMgX}$ .

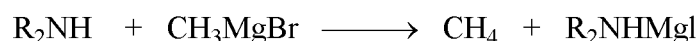
#### **Double decomposition with compounds containing an active hydrogen atom or a reactive hydrogen atom.**

As we have seen, an active hydrogen atom is one joined to oxygen, nitrogen or sulphur. When such compound react with a Grignard reagent, the alkyl group is converted into alkane.



Since reactions with compounds containing active hydrogen atom results in quantitative yield of hydrocarbon, this type of reaction is valuable for the determination

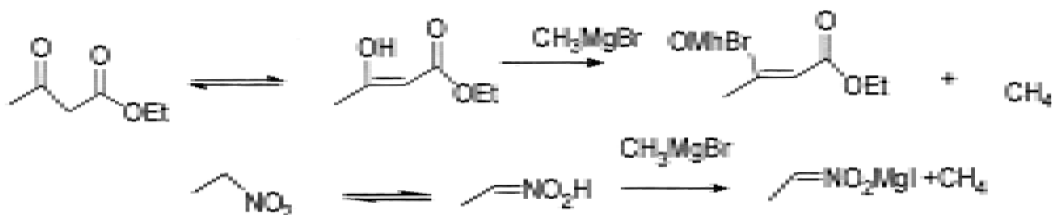
of the number of active hydrogen atom in a compound. The procedure is known as the Zerewitinoff active hydrogen determination (1907), and methyl magnesium iodide is normally used as the Grignard reagent. The methane which is liberated is measured (by volume), one molecule of methane being equivalent to active hydrogen atom.



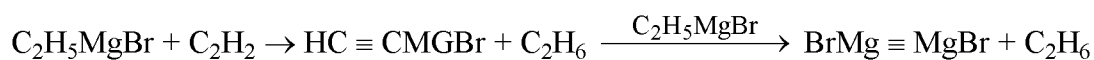
Only one hydrogen atom in a primary amine reacts at room temperature. At a sufficiently high temperature, the active hydrogen atom in the magnesium derivative of the primary amine will react with a further molecule of methylmagnesium iodide.



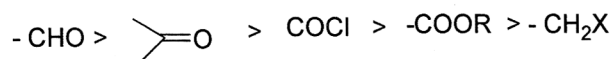
- The enolic form of a compound, since it contains an active hydrogen atom, reacts with a Grignard reagent. e.g., acetoacetic ester and nitroethene.



The acetylene molecule has active hydrogen atoms in both side of triple bond and they are immediately eliminated to produce ethane as the by product.



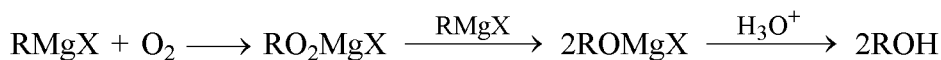
The different reactivity of Grignard reagent with the functional groups are



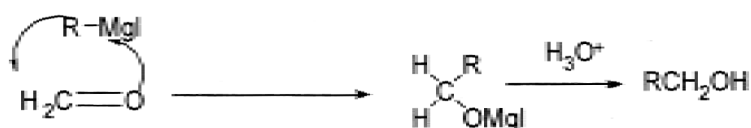
### 4.3.2 Synthetic uses of the Grignard reagents

#### Primary Alcohols :

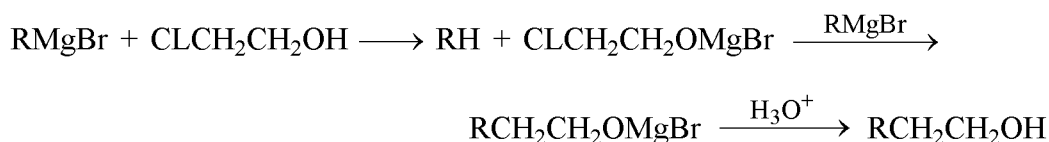
A Grignard reagent may be used to synthesise an alcohol by treating it with oxygen and decomposing the product with acid.



This method is little used in practice since an alkyl halide may be converted into the corresponding alcohol by simpler means. The method, however, is useful for converting aryl halide into phenols.



A primary alcohol containing two carbon atoms more than Grignard alkyl group can be prepared by adding one molecule of ethylene and chlorhydrin to two molecules of Grignard reagent.



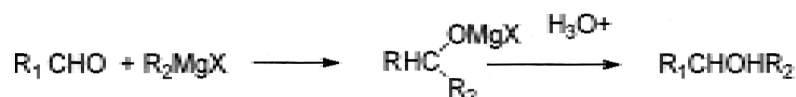
Two molecule of Grignard reagent is not required if ethylene oxide used instead of ethylene chlorohydrins.



Similarly, a primary alcohol containing three more carbon atoms can be prepared from the Grignard reagent by using trimethylene oxide.

### Secondary alcohol :

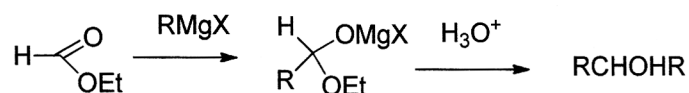
When a Grignard reagent is treated with any aldehyde other than formal aldehyde, a secondary alcohol is formed.



It can be seen that the secondary alcohol  $\text{R}_1\text{CHOHR}_2$ , is obtained whether we start with  $\text{R}_1\text{CHO}$  and  $\text{R}_2\text{MgX}$  or  $\text{R}_2\text{CHO}$  and  $\text{R}_1\text{MgX}$  which pair we use is generally a matter of their relative accessibility.

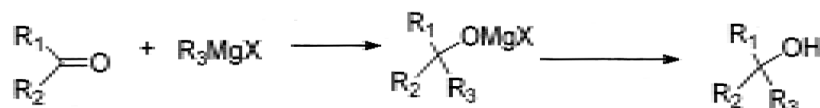


Secondary alcohols may also be prepared by interaction of a Grignard reagent and ethyl formate.



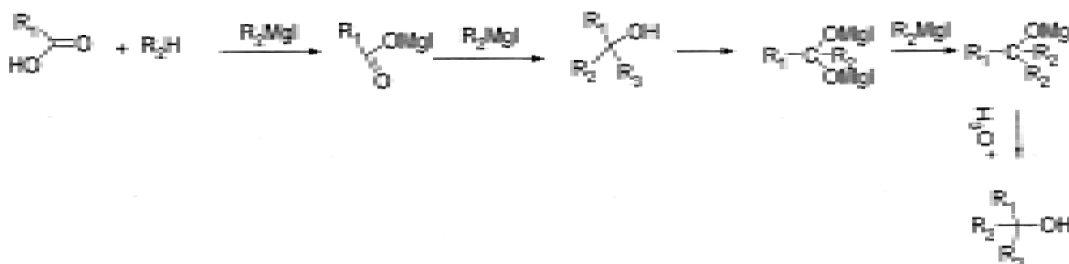
### Tertiary alcohols :

A tertiary alcohol may be prepared by the action of a Grignard on a ketone.



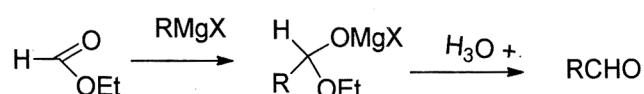
By this means a tertiary alcohol with three difficult alkyl groups may be prepared, and the starting materials may be any of the following pairs of compounds:  $\text{R}_1\text{COR}_2$  and  $\text{R}_3\text{MgX}$ ;  $\text{R}_1\text{COR}_3$  and  $\text{R}_1\text{MgX}$ . It may be noted here that because t-alcohols are readily dehydrated to alkenes by acids, the complex is often broken up with aqueous ammonium chloride or buffered acid solution.

- Tertiary alcohol may also be prepared by using acid a slight excess of Grignard reagent i.e. more than 3 molecules.

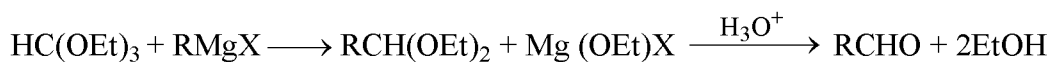


### Aldehydes :

An aldehyde may be prepared by the reaction between a Grignard reagent and ethyl formate. If the Grignard reagent is in excess, a secondary alcohol is formed. Hence to avoid this as much as possible, the Grignard reagent is added to the ester:



If ethyl orthoformate is used instead of ethyl formate, a better yield of aldehyde is obtained, since the formation of secondary alcohol is prevented by the formation of an acetal.



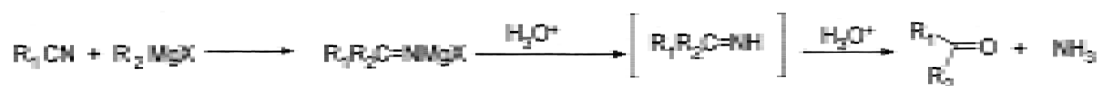
Aldehyde may also be prepared by the reaction between a Grignard reagent and hydrogen cyanide or formamide.

### Ketones :

These are not usually prepared by reaction between a Grignard reagent and any ester rather than formic ester. They may be prepared, however, as ketals by using any orthoester other than ortho formic ester.

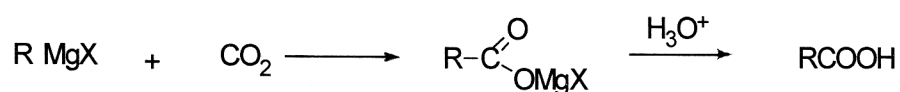


Ketones may also be prepared by addition an alkyl cyanide to a Grignard reagent :



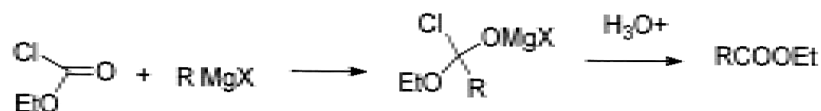
### Acid :

When a Grignard reagent is treated with solid carbon dioxide and the complex decomposed with dilute acid, a mono carboxylic acid is obtained.



### Esters :

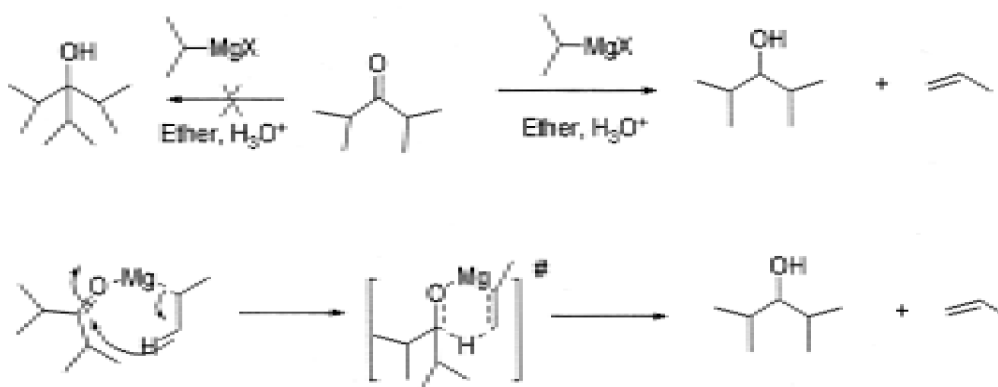
When a Grignard reagent reacts with ethyl chloroformate ester is formed and to avoid the reaction with carboxyl group, the Grignard reagent is added to ester.



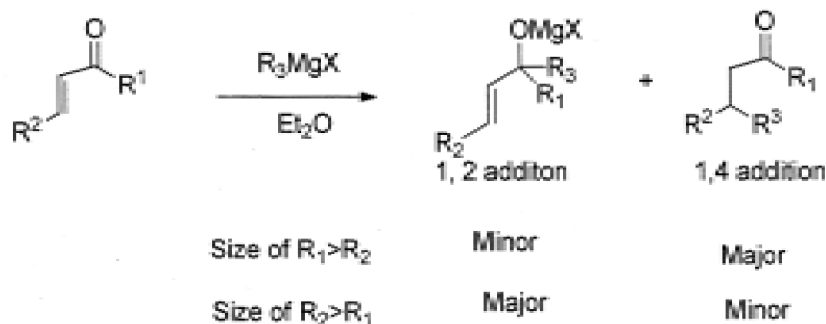
### 4.3.3 Abnormal behavior of Grignard reagents

In certain cases a Grignard reagent does not react with compounds containing a functional group which is normally capable of reaction. Generally, branching of the carbon chain near the functional group prevents reaction; the cause is probably the steric effect, e.g., methylmagnesium bromide or iodide does not react with hexamethyl acetone,  $(\text{CH}_3)_3\text{CCOC}(\text{CH}_3)_3$ . It has also been found that if the Grignard reagent contains a large alkyl group, reaction may be prevented; e.g., isopropyl methyl ketone reacts with methylmagnesium iodide but not with *t*-butyl-magnesium chloride. In other cases, abnormal reaction may take place, e.g., when isopropyl-magnesium bromide is added to di-isopropyl ketone, the expected tertiary alcohol is not formed; instead, the secondary alcohol, di-isopropyl carbinol, is obtained, resulting from the reduction of the ketone.

This abnormal reaction may be explained by the transfer of a hydride ion from the Grignard reagent *via* a cyclic transition state.

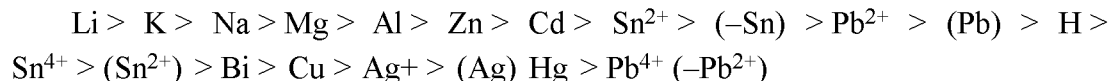


$\alpha$ ,  $\beta$  unsaturated carbonyl compounds react with a Grignard reagent in the 1, 2 or 1, 4 positions. The predominant factor in deciding the course of addition is steric hindrance and when  $\text{R}_1$  is more hindered than  $\text{R}_2$  then 1, 4 addition is the major product. In the reverse situation 1, 2 addition is the predominant product. On the other hand, 1, 4 addition can be made to predominate by carrying out the reaction in the presence of chloride, cupric acetate, etc.



#### 4.4 Metal Alkyls

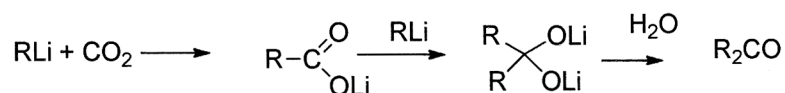
Alkyl derivatives of practically all the metals have been prepared; they are named as the alkyl metal, e.g.,  $(\text{CH}_3)_2\text{Hg}$ , dimethylmercury,  $(\text{C}_2\text{H}_5)_4\text{Pb}$ , Tetra ethyl lead. Since metal displacement reaction depend on the standard electrode potential of the metals concerned, it is useful to refer to the electrochemical series (i.e.; the arrangement of metals in order of their standard electrode potentials):



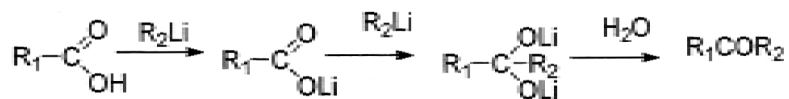
When alkyl lithium compounds are prepared in solution, hydrocarbon solvent are generally used. The use of ether encourages Wurtz reaction, and more important, lithium alkyls attacks ether. This reaction probably proceeds via metalation :



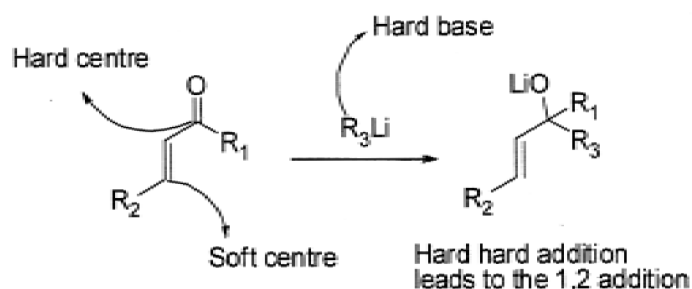
From the practical point of view, lithium compounds are the most satisfactory to use in organic synthesis, since they are very easily prepared and dissolve in organic solvent. Generally speaking the lithium compounds behave like the Grignard reagent, but the lithium compounds are usually more reactive and yield of product is often better. Because of their sensitivity to oxygen and water, reaction with alkyls are best carried out in an atmosphere of dinitrogen. Some reaction of lithium compounds are as follows. With carbon dioxide a good yield of ketone is obtained.



A ketone is also the when carboxylic acid is used as starting material.



**Lithium compound also react with cyanide** to give ketones, and with aldehyde and ketone to give alcohol in better yields than with Grignard reagent.

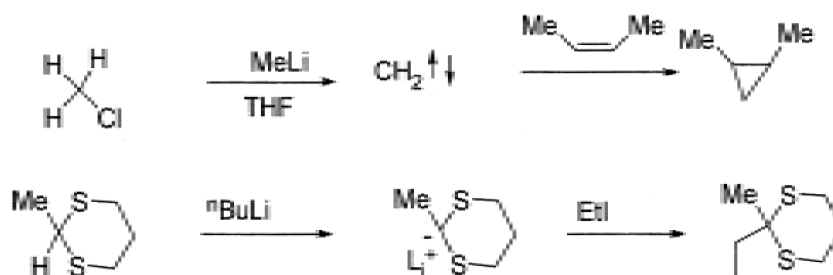


Thus organo lithium compounds are less susceptible to steric hindrance than Grignard reagent. This is also illustrated by the fact that addition organolithium compound to  $\alpha, \beta$  unsaturated carbonyl compound is usually almost exclusively 1, 2. The main difference between the two reagent is that lithium compound add to an ethylinic compound. Where as Grignard reagent do not. e.g.

Here steric hindrance overcome the 1, 2 addition with alkyl lithium and Grignard reagent lead to the hydride transfer to the ketone.

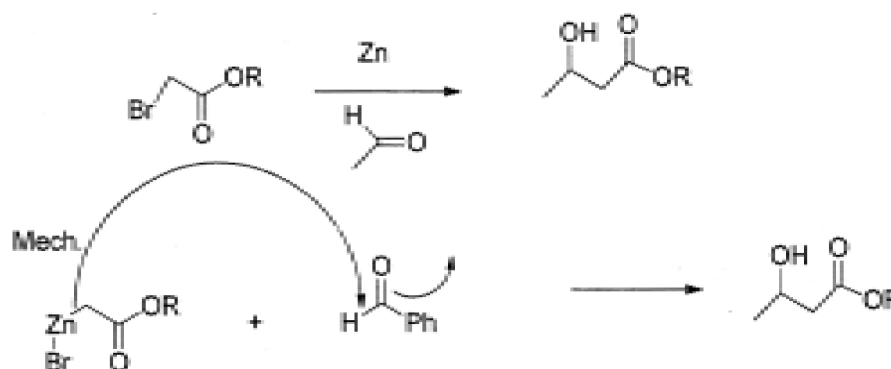


Apart from the synthetic uses described above, organolithium compounds are used in the preparation of carbene, Umpolung synthesis etc.

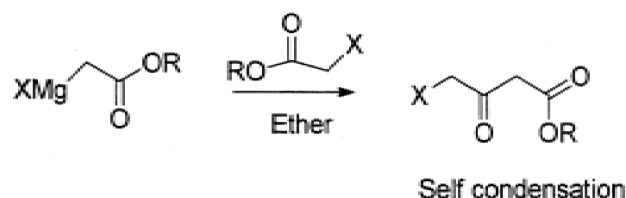


## 4.5 The Reformsky reaction

The reformsky reaction is the reaction between an  $\alpha$ -bromo acid ester and a carbonyl compound, in presence of zinc to form  $\beta$ -hydroxy ester.



The intermediate organozinc bromides have been isolated. The use of zinc instead of magnesium in the reformsky reaction is based on the fact that the Grignard reagent formed immediately attacks the ester group of a second molecule.

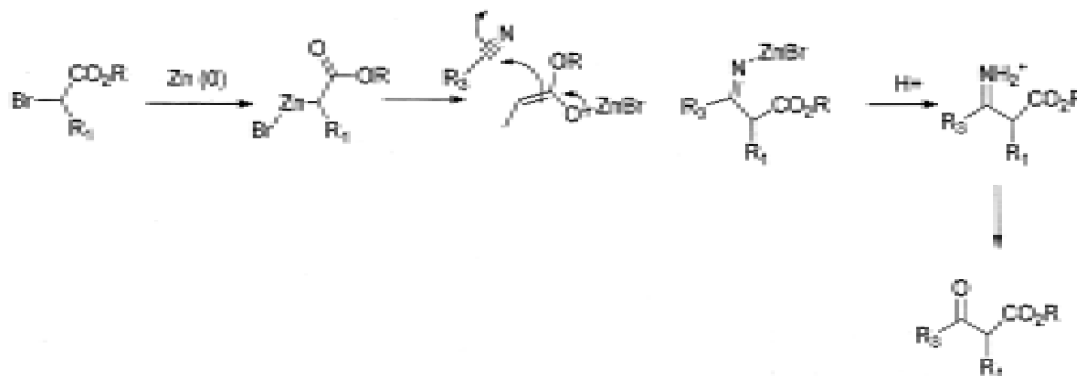


A difficulty with Refortmsky reaction is the conversion of the  $\beta$ -hydroxyl ester into the corresponding acid; in general, hydrolysis lead to the  $\alpha$ ,  $\beta$ -unsaturated ester and acid. However, Read et al. have shown that by refluxing the adduct (Zn + carbonyl compound + ester ) in benzene, and then followed by acid, good yields of hydroxyl acid are obtained.

## 4.6 Blaise reaction

The Blaise reaction is an organic reaction that forms a  $\beta$ -ketoester from the reaction of zinc metal with a  $\alpha$ -bromoester and a nitrile. The reaction was first

reported by Edmond Blaise (1872-1939) in 1901. The final intermediate is a metalloimine, which is then hydrolyzed to give the desired  $\beta$ -ketoester

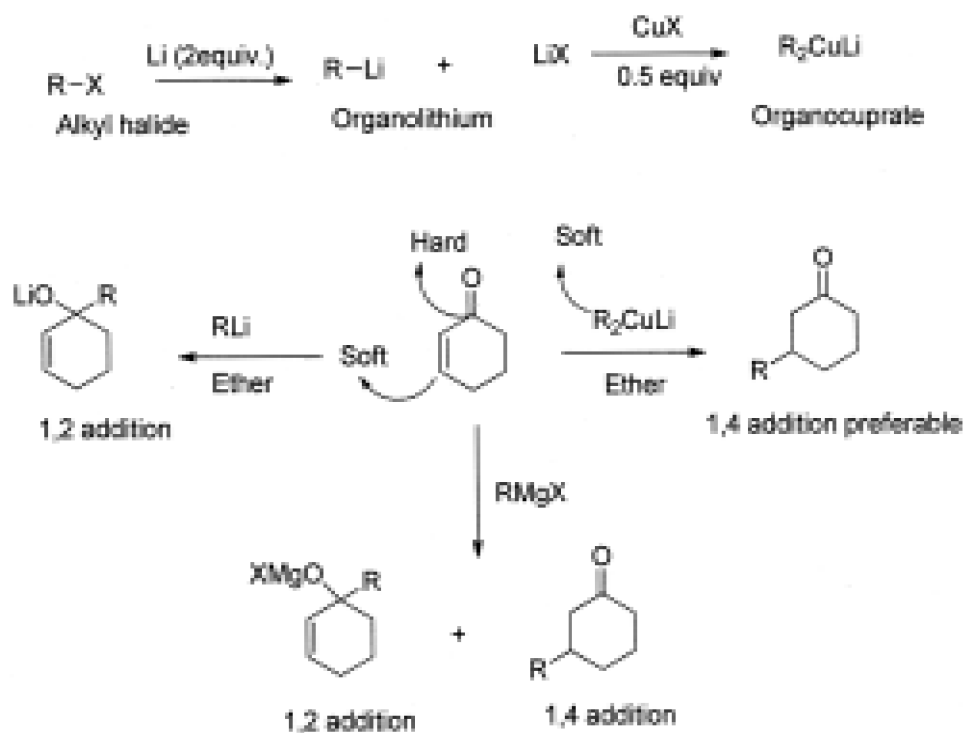



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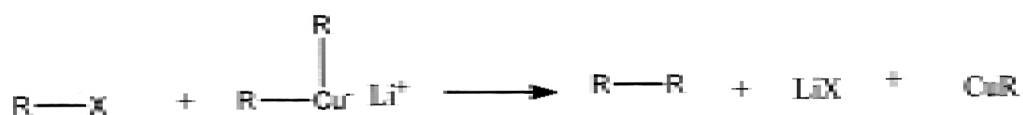
## 4.7 Organocopper reagents

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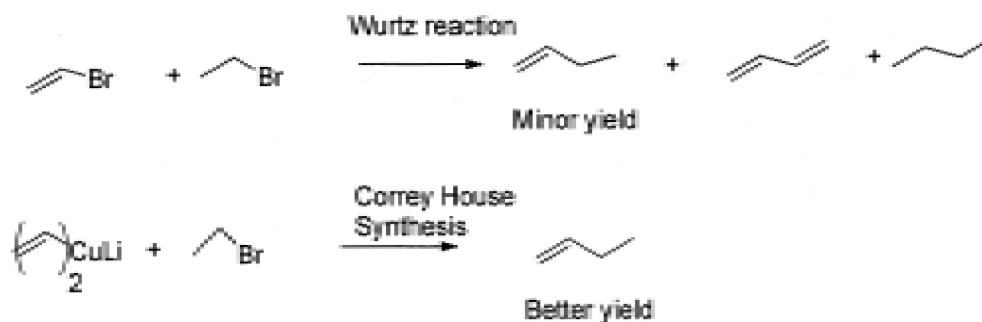
A **Gilman reagent** is a lithium and copper (diorganocopper) reagent compound,  $\text{R}_2\text{CuLi}$ , where R is an alkyl or aryl. These reagents are useful because, unlike related Grignard reagents and organolithium reagents, they react with organic halides to replace the halide group with an R group (**the Corey-House reaction**). Such displacement reactions allow for the synthesis of complex products from simple building blocks.



#### 4.8 Corey-House reaction



This reaction is more useful over Wurtz reaction where unsymmetrical alkane is formed with better yields.





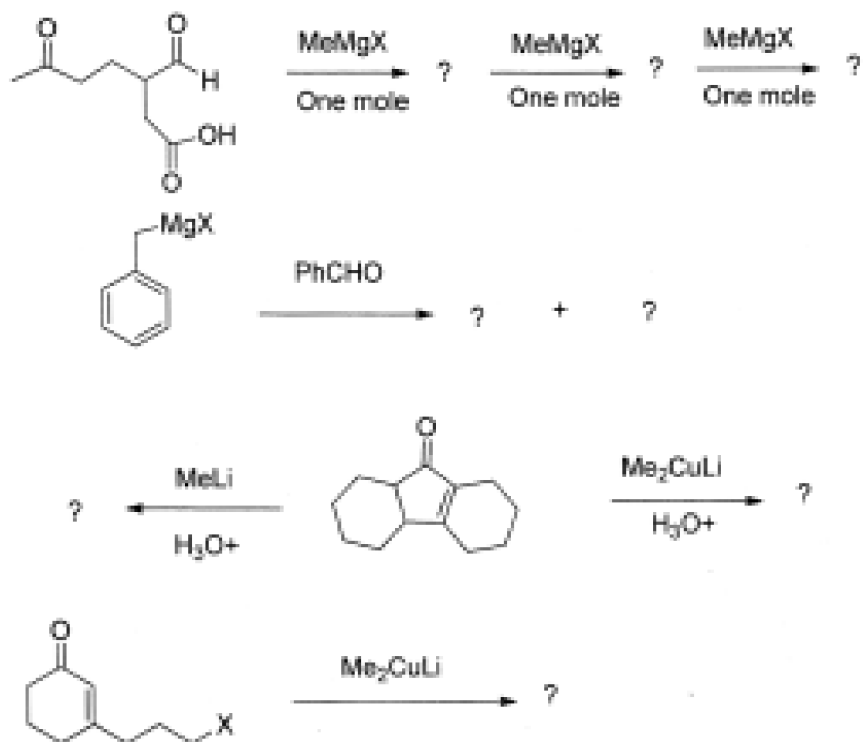
## 4.9 Summary

This module generates elaborate description organometallic chemistry. It gives us idea about the chemoselective addition of Grignard, organolithium & organocopper reagents. This module describes

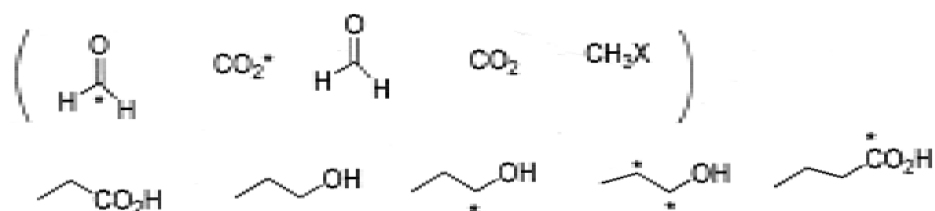
- I. Nucleophilic addition of Grignard reagents
- II. Comparison reactivity of Grignard reagent with organolithium and organocopper reagent
- III. Describe the reformsky reaction
- IV. Describe the Blaise reaction

## 4.10 Problems in organometallic chemistry

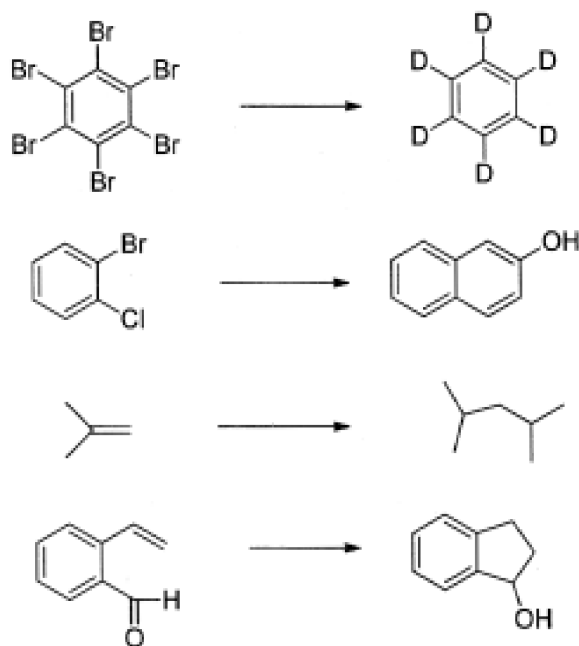
1. Fill in the following scheme :



2. Synthesize following compounds using the following reagents (involving Grignard reaction)



3. Find out following transformation using organometallic reaction



4. Why iodine is added during the preparation Grignard reagent from alkyl halide.

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#### 4.11 Reference Books

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1. Clayden J., Greeves N., Warren S. & Wothers P. "Organic Chemistry"
2. IL Finar Volume 1 "Organic Chemistry"

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## **Unit - 5 □ Chemistry of alkanes and alkenes**

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### **Structure**

#### **5.1 Objectives**

#### **5.2 Introduction**

#### **5.3 Reactivity of Alkene**

#### **5.4 Regioselectivity of Electrophilic Addition Reactions**

#### **5.5 Reaction of alkenes**

##### **5.5.1 Hydrogenations : Addition of Hydrogen to an Alkene**

##### **5.5.2 Halogenations : Addition of Halogens to an alkene**

##### **5.5.3 Hydrohalogenation : Addition of hydrogen halide to an alkene**

##### **5.5.4 Hydration : Addition of Water and Alcohols to alkenes**

##### **5.5.5 Oxymercuration-demercuration : Oxymercuration-Reduction Reaction**

##### **5.5.6 Hydroboration-oxidation : Addition of Borane**

##### **5.5.7 Epoxidation : Oxidation of Alkenes with Peroxyacids**

##### **5.5.8 Syn and Anti-dihydroxylation**

##### **5.5.9 Ozonolysis : Oxidative Cleavage of Alkenes**

##### **5.5.10 Addition of singlet and triplet carbenes : Formation of three cyclopropanes**

##### **5.5.11 Electrophilic addition to conjugated dienes**

##### **5.5.12 Free Radical addition : Anti-Markovnikov addition (peroxide effect)**

##### **5.5.13 Birch reduction of benzenoid aromatics : Dissolving metal reductions**

##### **5.5.14 Halo-lactonization : Halo-alkoxylation**

##### **5.5.15 Inter conversion of E and Z alkenes**

#### **5.6. The Structure of Alkynes**

#### **5.7 Reactivity of Alkynes**

## 5.8 Reactions of alkynes

### 5.8.1 Hydrogenation: Addition of Hydrogen

### 5.8.2 Hydrohalogenation of alkyne

### 5.8.3 Halogenations of alkyne

### 5.8.4 Hydration : Addition of Water

### 5.8.5 Addition of Borane : Hydroboration-Oxidation

### 5.8.6 Acidity of Terminal alkynes : Hydrogen bonded to an sp- carbon

### 5.8.7 Interconversion of terminal and non-terminal alkynes.

## 5.9 Summary

## 5.10 Additional Problems

## 5.11 Reference books

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## 5.1 Objectives

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In this unit, we will discuss about the reactivity and reactions of alkene and alkynes with various reagents. The basic ideas and method of preparation of alkenes and alkynes are not discussed here as you have already gone through in your earlier courses.

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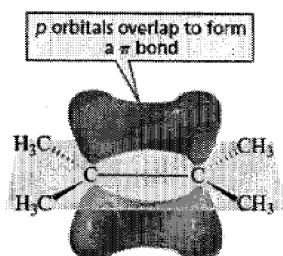
## 5.2 Introduction

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Alkenes are molecules containing a C = C double bond. They are also sometimes referred to as olefins or as unsaturated compounds. They called unsaturated because the C atoms in a C = C double bond don't have as many hydrogens bonded to them as an alkane does. Molecules with one double bond are called monounsaturated. Molecules with multiple double bonds are called polyunsaturated. In contrast, alkane molecules with no double bonds are saturated. When we discuss the chemical reactions of alkenes, we will see that the primary site of reaction is the double bond and the most common type of reaction is the addition of atoms to the double bond to make a saturated molecule.

### 5.3 Reactivity of Alkene

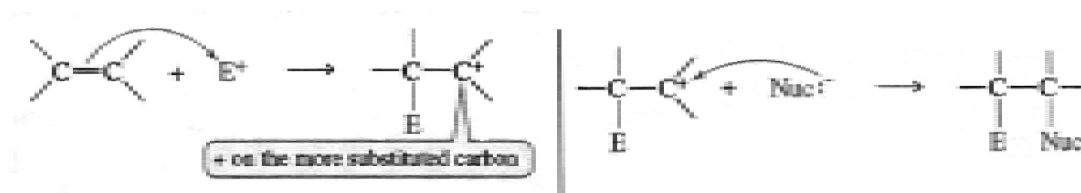
The characteristic feature of alkene structure is a carbon-carbon double bond. Each double-bonded carbon of an alkene has three orbitals that lie in a plane with angles of  $120^\circ$  and overlapping of these orbitals with an orbital of another atom leads to formation of a bond. Thus, one of the carbon-carbon bonds in a double bond is a  $\sigma$ -bond, formed by the overlap of an orbital of one carbon with an orbital of the other carbon. The second carbon-carbon bond in the double bond (the  $\pi$ -bond) is formed from side-to-side overlap of the remaining  $p$  orbitals of the carbons.



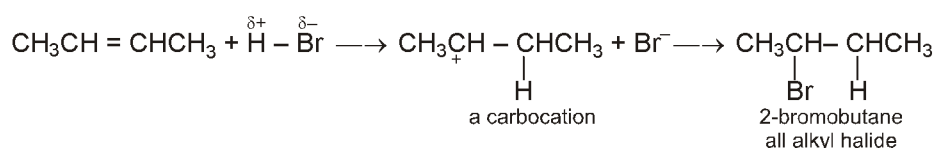
**Figure :** Electron clouds in the  $\pi$ -bond is spread further from the carbon nuclei and are more loosely held than the  $\sigma$ -bond.

**Fig-12**

The  $\pi$ -bond is weaker than the  $\sigma$ -bond, therefore, this  $\pi$ -bond is easily broken when an alkene undergoes addition reaction. It is also clear that the bond of an alkene consists of a cloud of electrons above and below the bond. As a result of this cloud of electrons, an alkene is an electron rich molecule i.e. a nucleophile. In the electrophilic addition, initially, a strong electrophile ( $E^+$ ) attracts the loosely held electrons from the  $\pi$ -bond of an alkene. Thus the electrophile ( $E^+$ ) forms a  $\sigma$ -bond to one of the carbons of the (former) double bond, while the other carbon becomes a carbocation. The carbocation (a strong electrophile) reacts with a nucleophile ( $Nuc:^-$ ) to form another  $\sigma$ -bond.

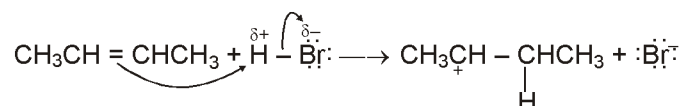


As alkenes behaves like a nucleophile, will undergo electrophilic addition reaction. So if a reagent HBr is added to an alkene, the first step, the alkene (a nucleophile) will react slowly with a proton (an electrophile) of HBr and a carbocation will be formed. In the second step of the reaction, the carbocation (an electrophile) will react rapidly with the bromide ion (a nucleophile) to form an alkyl halide.

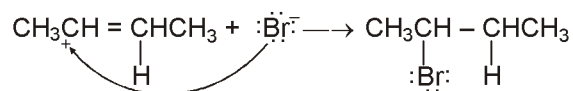


### Mechanism of the reaction :

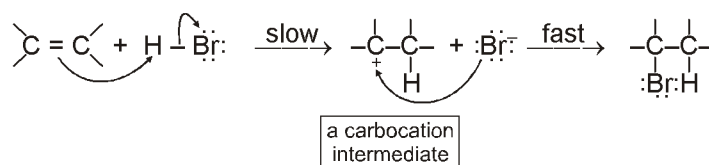
#### Step-1 :



#### Step-2 :



Because the initial step of the reaction involves the addition of an electrophile to the alkene, the reaction is known as an electrophilic addition reaction, a characteristic reactions of alkenes.

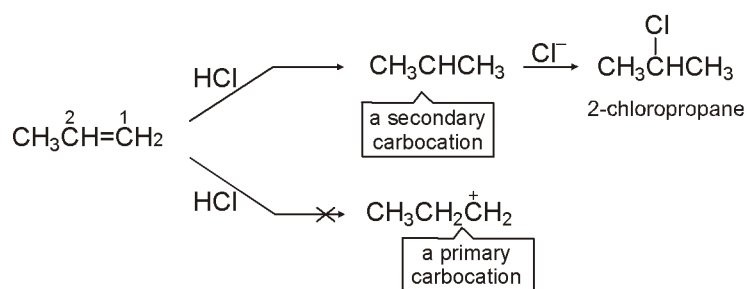


### Electrophilic Addition Reactions

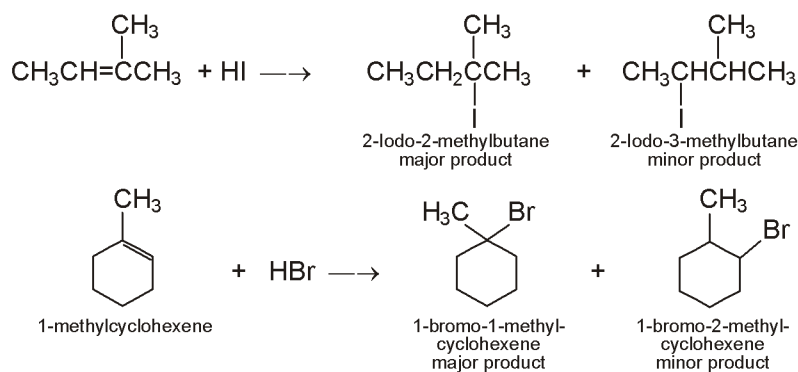
## 5.4 Regioselectivity of Electrophilic Addition Reactions

When unsymmetrical alkene undergoes an electrophilic addition reaction, the electrophile can add to two different carbons. For example, when propene reacts with HCl, the proton can add to the number-1 carbon (C-1) to form a secondary

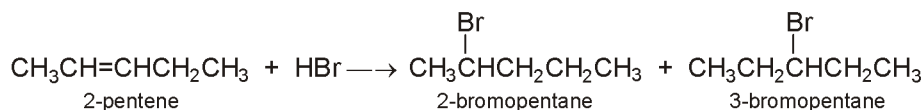
carbocation, or it can add to the number-2 carbon (C-2) to form a primary carbocation. The secondary carbocation is formed more rapidly because it is more stable than the primary carbocation. The product of the reaction, therefore, is 2-chloropropane.



The major product obtained from the addition of HI to 2-methyl-2-butene is 2-iodo-2-methylbutane; only a small amount of 2-iodo-3-methylbutane is obtained. The major product obtained from the addition of HBr to 1-methylcyclohexene is 1-bromo-1-methylcyclohexane. In both cases, the more stable tertiary carbocation is formed more rapidly than the less stable secondary carbocation, so the major product of each reaction is the one that results from forming the tertiary carbocation.



A reaction (as discussed above) in which two or more constitutional isomers could be obtained as products, but one of them predominates, is called a regioselective reaction. The addition of HBr to 2-pentene is not regioselective. Because the addition of a proton to either of the carbons produces a secondary carbocation, both carbocation intermediates have the same stability, so both will be formed equally easily. Thus, approximately equal amounts of the two alkyl halides will be formed.



We now have seen that if we want to predict the major product of an electrophilic addition reaction, we must first determine the relative stabilities of the two possible carbocation intermediates. According to the Markovnikov's rule "When a hydrogen halide adds to an unsymmetrical alkene, the addition occurs in such a manner that the halogen attaches itself to the double-bonded carbon atom of the alkene bearing the lesser number of hydrogen atoms." Alternately, Markovnikov's rule as follows "The hydrogen adds to the carbon that is bonded to the greater number of hydrogens." In the study of alkene reactions, it has been seen that not all of the reaction do follow Markovnikov's rule. Those who follow i.e. the hydrogen does add to the carbon that is bonded to the greater number of hydrogens are called Markovnikov addition reactions. Those who do not follow i.e. the hydrogen does not add to the carbon that is bonded to the greater number of hydrogens are called anti-Markovnikov addition reactions.



In the above example, the electrophile adds to C-1 rather than C-2 because of the formation of a secondary carbocation, which is more stable.

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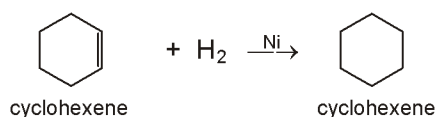
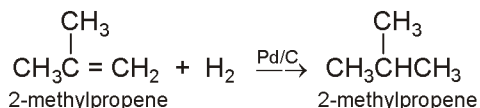
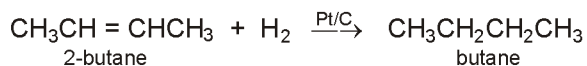
## 5.5 Reaction of alkenes

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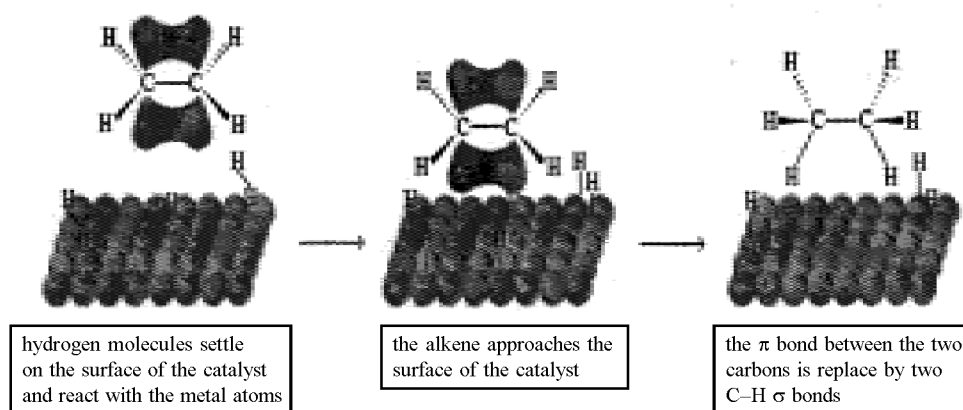
### 5.5.1 Hydrogenations : Addition of Hydrogen to an Alkene

In the presence of a metal catalyst such as platinum, palladium, or nickel, hydrogen adds to the double bond of an alkene forming an alkane. Without the catalyst, the energy barrier to the reaction would be huge because the H-H bond is so strong. The catalyst decreases the energy of activation by breaking the H-H bond. Platinum and palladium are used in a finely divided state adsorbed on charcoal (Pt/C, Pd/C). The platinum catalyst is frequently used in the form of which is known as Adams catalyst.



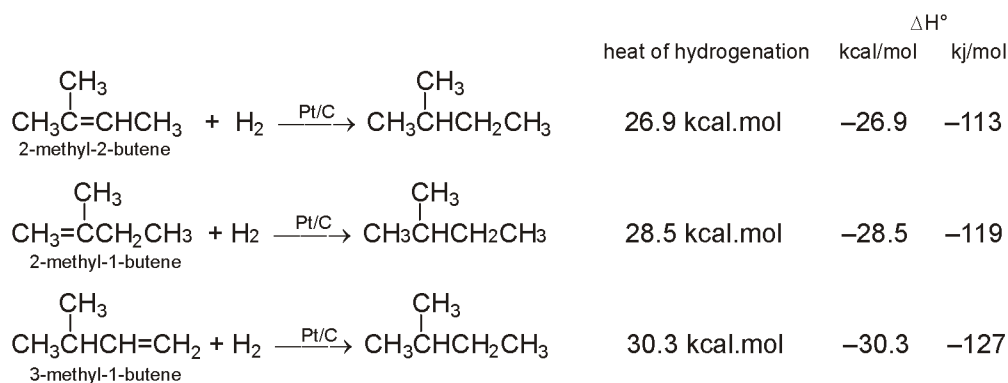


The addition of hydrogen in presence of a catalyst is called catalytic hydrogenation. The metal catalysts are insoluble in the reaction mixture and therefore are classified as heterogeneous catalysts. A heterogeneous catalyst can easily be separated from the reaction mixture by filtration. It can then be recycled, which is an important property, since metal catalysts tend to be expensive.

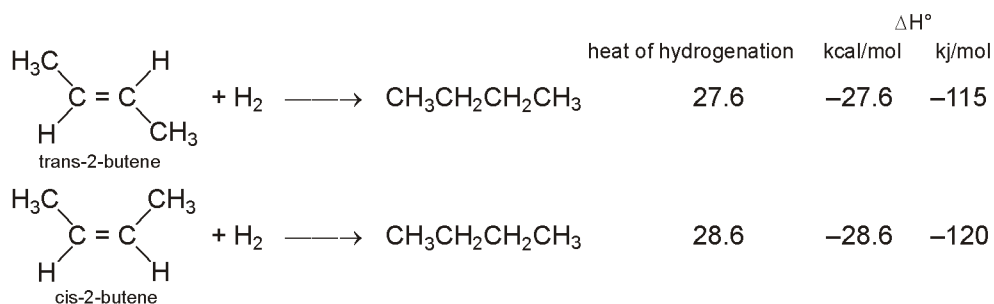


**Figure-13** : Catalytic hydrogenation reaction of an alkene

The details of the mechanism of catalytic hydrogenation are not completely understood. We know that hydrogen is adsorbed on the surface of the metal and that the alkene complexes with the metal by overlapping its own  $p$  orbitals with vacant orbitals of the metal. Breaking the  $\pi$ -bond of the alkene and the  $\sigma$ -bond of  $\text{H}_2$  and forming the C-H bonds all occur on the surface of the metal. The alkane product diffuses away from the metal surface as it is formed. The heat released in a hydrogenation reaction is called the heat of hydrogenation. It is customary to give it a positive value. Hydrogenation reactions, however, are exothermic.

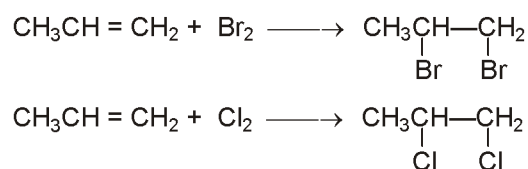


Both *trans*-2-butene and *cis*-2-butene have two alkyl groups bonded to their carbons, but *trans*-2-butene has a smaller heat of hydrogenation. This indicates that the *trans* isomer, in which the large substituents are farther apart, is more stable than the *cis* isomer, in which the large substituents are closer together.



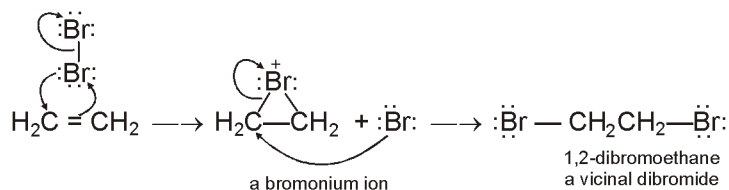
### 5.5.2 Halogenations : Addition of Halogens to an alkene

The halogens Br<sub>2</sub> and Cl<sub>2</sub> are readily adds to alkenes to form vicinal dihalides.

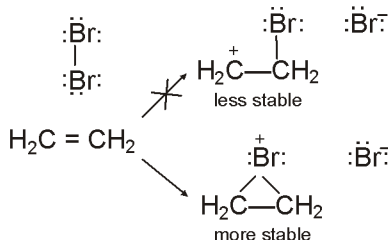


A halogen molecule (Br<sub>2</sub> or Cl<sub>2</sub>) is electrophilic; a nucleophile can react with a halogen, displacing a halide ion. When the electrons of the alkene approach a

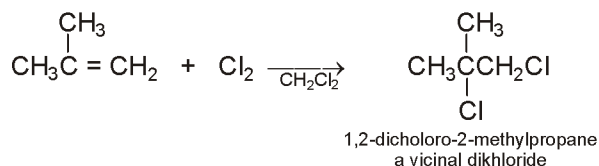
molecule of Br<sub>2</sub> [or Cl<sub>2</sub>] one of the halogen atoms accepts the electrons and releases the shared electrons to the other halogen atom. Therefore, in an electrophilic addition reaction, Br<sub>2</sub> behaves as if it were Br<sup>+</sup> and Br<sup>-</sup>, and Cl<sub>2</sub> behaves as if it were Cl<sup>+</sup> and Cl<sup>-</sup>.



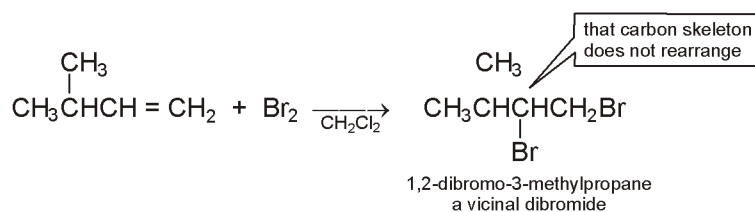
The product of the first step is not a carbocation; rather, it is a cyclic bromonium ion because bromine's electron cloud is close enough to the other carbon to engage in bond formation. The cyclic bromonium ion is more stable than the carbocation, since all the atoms (except hydrogen) in the bromonium ion have complete octets, whereas the positively charged carbon of the carbocation does not have a complete octet.



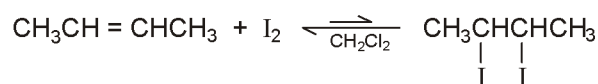
In the second step of the reaction, bromide ion attacks a carbon atom of the bromonium ion from the backside. This releases the strain in the three-membered ring and forms a vicinal dibromide. When Cl<sub>2</sub> adds to an alkene, a cyclic chloronium ion intermediate is formed. The final product of the reaction is a vicinal dichloride.



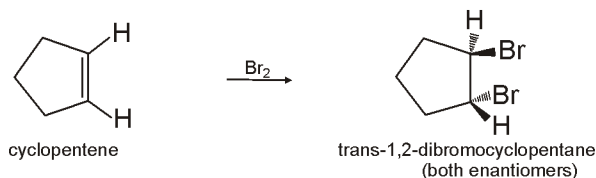
Because a carbocation is not formed when Br<sub>2</sub> or Cl<sub>2</sub> adds to an alkene, carbocation rearrangements do not occur in these reactions.



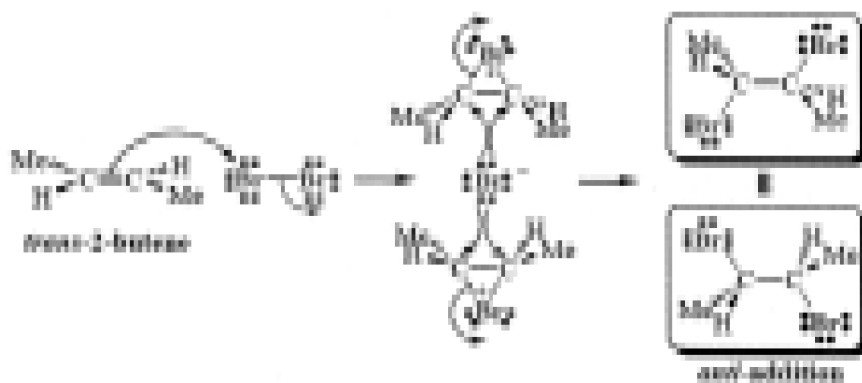
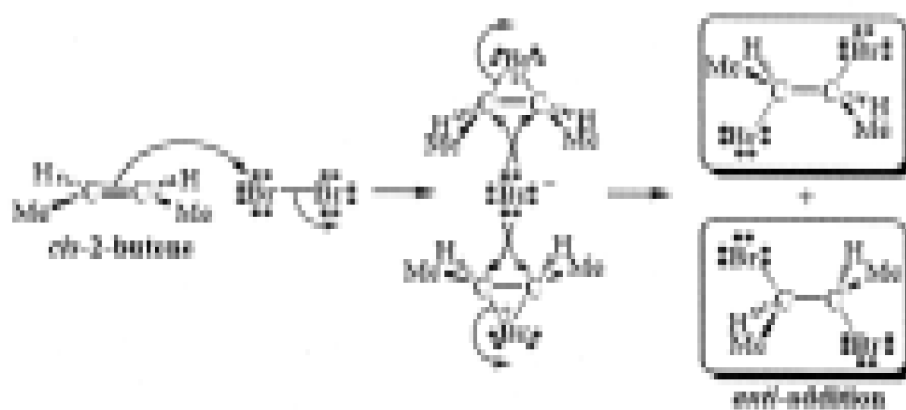
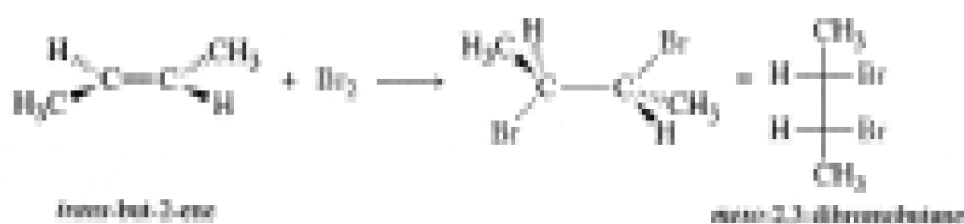
Although  $\text{F}_2$  and  $\text{I}_2$  are also halogens, but they are not used as reagents in electrophilic addition reactions. Fluorine reacts explosively with alkenes, so the electrophilic addition of  $\text{F}_2$  is not a synthetically useful reaction. The addition of  $\text{I}_2$  to an alkene is a thermodynamically unfavorable reaction. The vicinal diiodides are unstable at room temperature, decomposing back to the alkene and  $\text{I}_2$ .



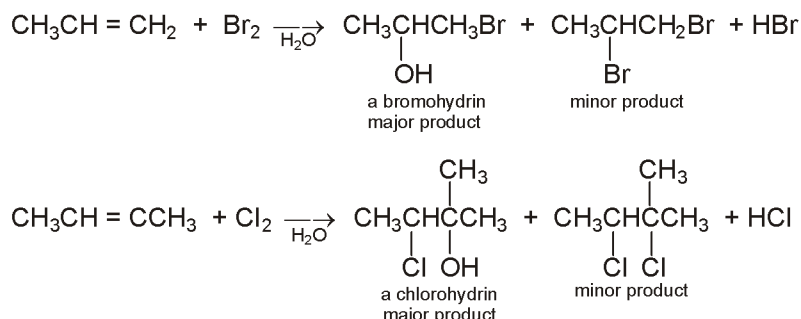
The addition of bromine to cyclopentene is a stereospecific anti addition.



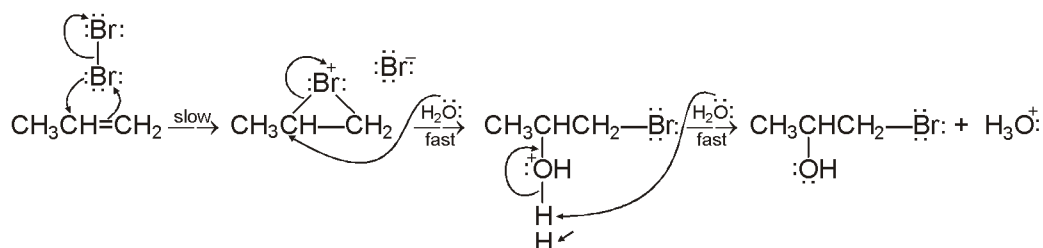
When a nucleophile attacks a halonium ion, it must do so from the back side, in a manner similar to the  $\text{S}_\text{N}2$  displacement. This back-side attack assures anti stereochemistry of addition. Halogen addition is another example of a stereospecific reaction, in which different stereoisomers of the starting material give different stereoisomers of the product.



If  $\text{H}_2\text{O}$  is present in the reaction mixture or use as a solvent, the major product of the reaction will be a vicinal halohydrin.

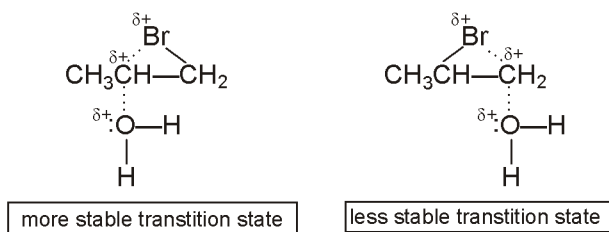


The mechanism for halohydrin formation involves the formation of a cyclic bromonium ion (or chloronium ion) in the first step of the reaction, because (Br<sup>+</sup> or Cl<sup>+</sup>) is the only electrophile in the reaction mixture. In the second step, the cyclic bromonium ion rapidly reacts with any nucleophile from the reaction mixture. Out of the two nucleophile, water and Br<sup>-</sup> in the reaction mixture, H<sub>2</sub>O concentration far exceeds that of Br<sup>-</sup> and consequently, the bromonium ion is more likely to collide with a molecule of water to form the protonated halohydrin, This protonated halohydrin loses a proton and give halohydrin.

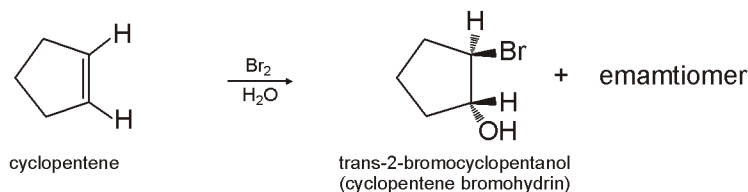


#### Mechanism of Halohydrin formation

The electrophile ends up on the carbon bonded to the greater number of hydrogens because, in the transition state for the second step of the reaction, the breaking of the C-Br bond has occurred to a greater extent than has the formation of the C-O bond. As a result, there is a partial positive charge on the carbon that is attacked by the nucleophile.

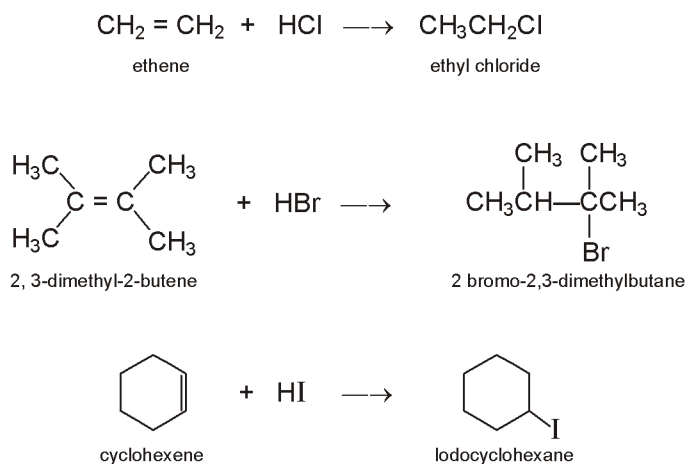


Therefore, the more stable transition state is achieved by adding the nucleophile to the most substituted carbon the one bonded to the lesser number of hydrogens because the partial positive charge will be on a secondary carbon rather than on a primary carbon. Similar to halogenations reaction, as the mechanism involves a cyclic halonium ion, the stereochemistry of addition is anti. For example, the addition of bromine-water to cyclopentene gives trans-2-bromocyclopentanol, the product of anti addition across the double bond and also follow Markovnikov's addition.



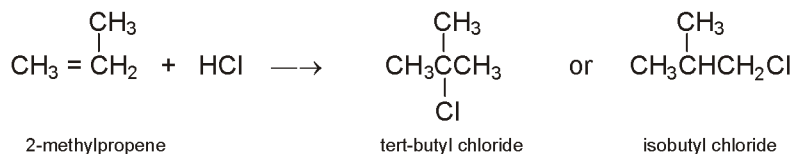
### 5.5.3 Hydrohalogenation : Addition of hydrogen halide to an alkene

If the electrophilic reagent that adds to an alkene is a hydrogen halide (HF, HCl, HBr, or HI), the product of the reaction will be an alkyl halide as discussed in the earlier section of this chapter. The order of reactivity of HX is  $\text{HI} > \text{HBr} > \text{HCl} > \text{HF}$ .

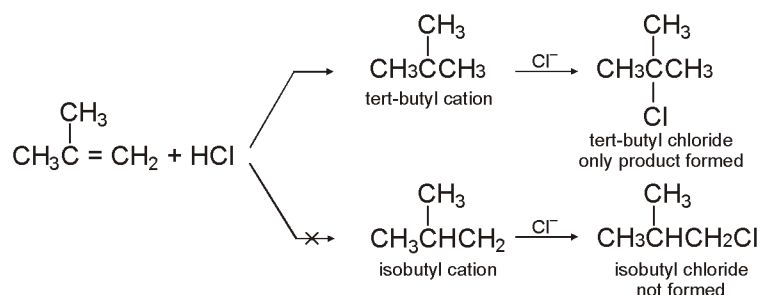


Because the alkenes in the preceding reactions have the same substituents on both of the  $\text{sp}^2$  carbons [symmetrical alkene], it is easy to determine the product of the reaction. The electrophile ( $\text{H}^+$ ) adds to one of the  $\text{sp}^2$ -carbons, and the nucleo-

phile (X<sup>-</sup>) adds to the other sp<sup>2</sup> carbon. It doesn't make any difference which sp<sup>2</sup> carbon the electrophile attaches to, because the same product will be obtained in either case. In case of unsymmetrical alkene, e.g., does the addition of HCl to 2-methylpropene produce *tert*-butyl chloride or isobutyl chloride?



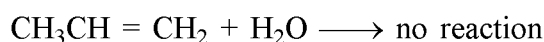
The first step of the reaction—the addition of H<sup>+</sup> to a sp<sup>2</sup>-carbon to form either the *tert*-butyl cation or the isobutyl cation is the rate-determining step. But the reaction gives *tert*-butyl chloride as only product, because out of the two carbocations, the *tert*-butyl cation is formed faster than the isobutyl cation.



### 5.5.4 Hydration: Addition of Water and Alcohols to alkenes

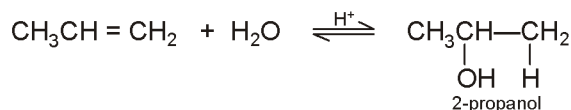
#### Addition of Water : Hydration

When water is added to an alkene, no reaction takes place, because there is no electrophile present to start a reaction by adding to the nucleophilic alkene. The O–H bonds of water are too strong or water is too weakly acidic to allow the hydrogen to act as an electrophile for this reaction.

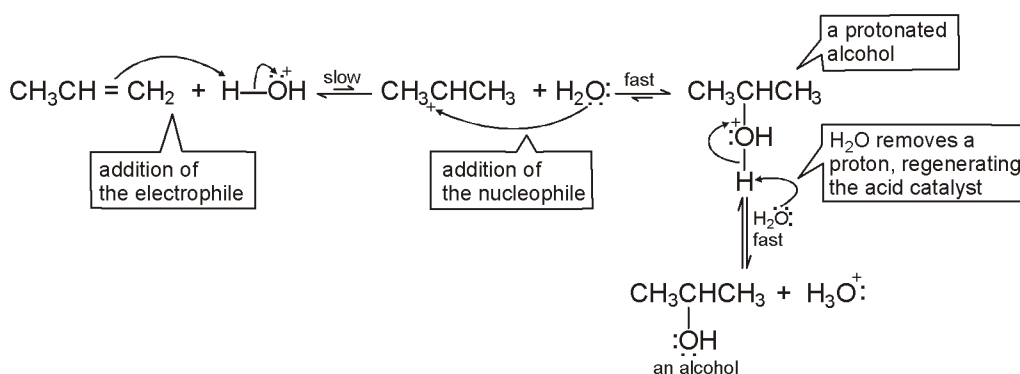


If, however, an acid (e.g., H<sub>2</sub>SO<sub>4</sub> or HCl) is added to the solution, a reaction will occur because the acid provides an electrophile and the product of the reaction is an alcohol. The addition of water to a molecule is called hydration, so we can say that an alkene will be hydrated in the presence of water and acid and follow Markovnikovs' addition.





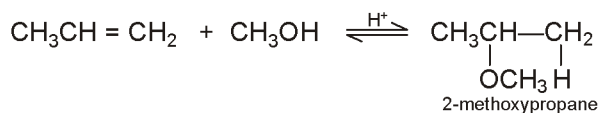
The first two steps of the mechanism for the acid-catalyzed addition of water to an alkene are essentially the same as the two steps of the mechanism for the addition of a hydrogen halide to an alkene. The electrophile adds to the carbon that is bonded to the greater number of hydrogens, and the nucleophile ( $\text{H}_2\text{O}$ ) adds to the other  $sp^2$  carbon.



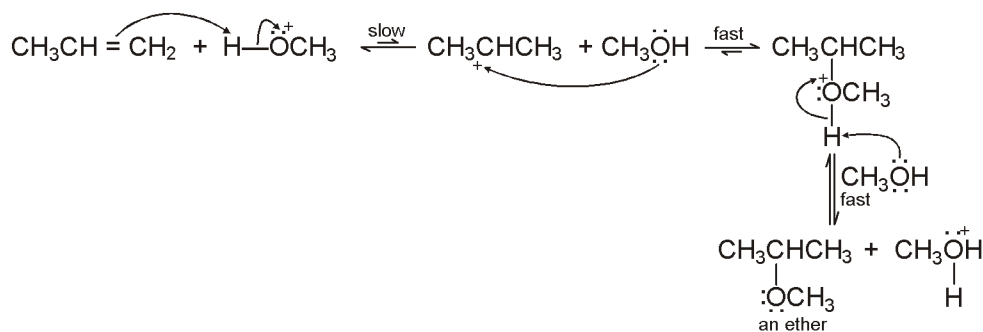
**Figure :** Mechanism of acid catalysed addition of water to an alkene

### Addition of Alcohols to an alkene : formation of ether

Alcohols react with alkenes in the same way that water does. Like the addition of water, the addition of an alcohol requires an acid catalyst and produces ether.

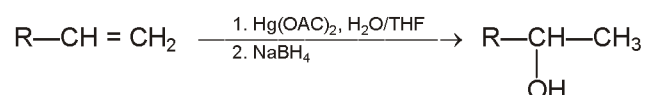


The mechanism for the acid-catalyzed addition of an alcohol is essentially the same as the mechanism for the acid-catalyzed addition of water.

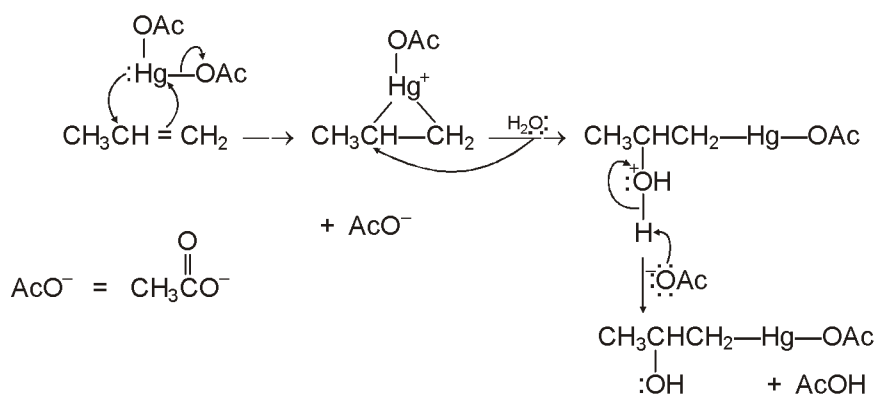


### 5.5.5. Oxymercuration-demercuration: Oxymercuration-Reduction Reaction

When water adds to an alkene in presence of an acid catalyst, it is converted into alcohols but not favourable to all alkenes. However, under normal laboratory conditions, water is added to an alkene to produce an alcohol by a procedure known as oxymercuration-reduction. The oxymercuration-reduction has advantages over acid-catalyzed addition. Firstly, it does not require acidic conditions that may be sensitive to many organic molecules. Secondly, a carbocation rearrangement is not possible as carbocations are not formed during the reaction. In oxymercuration, the alkene is treated with mercuric acetate in aqueous tetrahydrofuran (THF). When reaction with that reagent is complete, sodium borohydride is added to the reaction mixture.

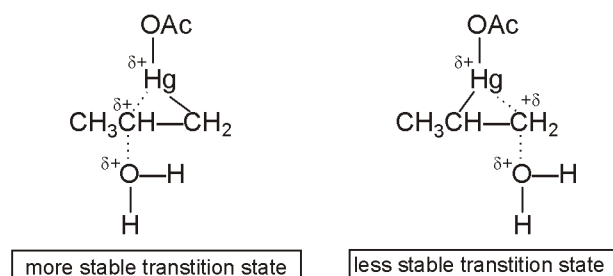


In the first step of the oxymercuration mechanism, the electrophilic mercury of mercuric acetate adds to the double bond forms a cyclic mercurinium ion rather than a carbocation. The reaction is analogous to the addition of  $\text{Br}_2$  to an alkene to form a cyclic bromonium ion.

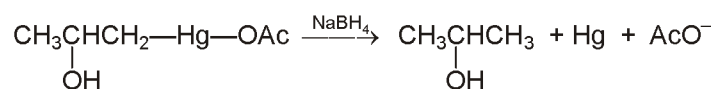


#### Mechanism of oxymercuration

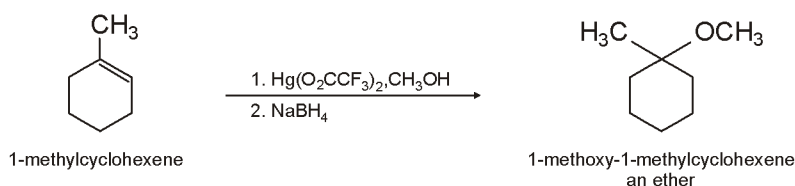
In the second step of the reaction, water attacks the more substituted carbon of the mercurinium ion—the one bonded to the lesser number of hydrogens—for the same reason that it attacks the more substituted carbon of the bromonium ion in the halohydrin reaction. That is, attacking at the more substituted carbon leads to the more stable transition state.



Sodium borohydride converts the C–Hg bond into a C–H bond. The mechanism of the reduction reaction is not fully understood, but may be passing through a radical intermediate.



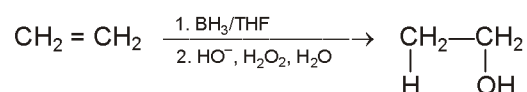
The overall reaction (oxymercuration-reduction) forms the same product that would be formed from the acid-catalyzed addition of water with Markovnikov's orientation. The hydrogen adds to the carbon bonded to the greater number of hydrogens, and OH adds to the other carbon. We have seen that alkenes react with alcohols in the presence of an acid catalyst to form ethers. Just as the addition of water works better in the presence of mercuric acetate than in the presence of a strong acid, the addition of an alcohol works better in the presence of mercuric acetate (Mercuric trifluoroacetate), and the reaction is called alkoxymercuration-reduction.



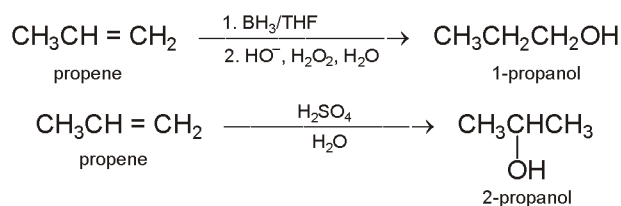
### 5.5.6. Hydroboration-oxidation : Addition of Borane

H. C. Brown discovered that diborane, dimer of borane ( $\text{B}_2\text{H}_6$ ) adds to alkenes with anti-Markovnikov orientation to form alkyboranes, which can be oxidized to give anti-Markovnikov alcohols.

Alkenes undergo electrophilic addition reactions with borane which serves as an electrophile. When the addition reaction is over, an aqueous solution of sodium hydroxide and hydrogen peroxide is added to the reaction mixture, and the resulting product is an alcohol. The addition of borane to an alkene, followed by reaction with hydroxide ion and hydrogen peroxide, is called hydroboration-oxidation.



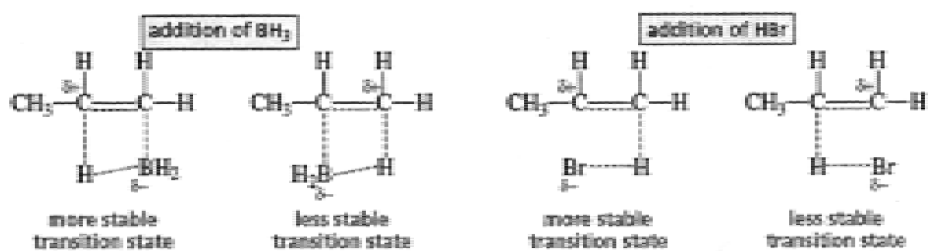
The first step in the mechanism of all alkene reactions is the same, the addition of an electrophile to the  $\text{sp}^2$  carbon that is bonded to the greater number of hydrogens.



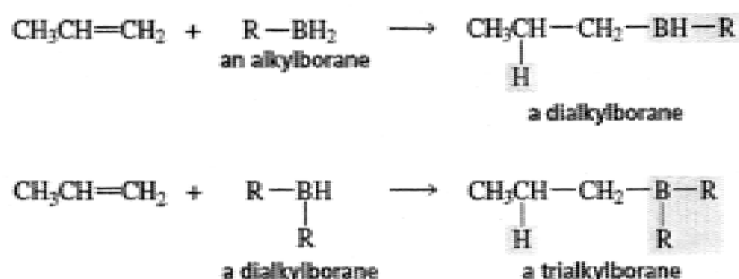
The mechanism can be discussed by taking the example of hydroboration-oxidation of propene which forms 1-propanol. The boron atom of borane is electron deficient, so borane is the electrophile that reacts with the nucleophilic alkene. As boron accepts the electrons and forms a bond with one carbon, it donates a hydride ion to the other carbon. In all the addition reactions that we have seen up to this point, the electrophile adds to the alkene in the first step and the nucleophile adds to the positively charged intermediate in the second step. In contrast, the addition of the electrophilic boron and the nucleophilic hydride ion to the alkene take place in one step. Therefore, an intermediate is not formed.



The addition of borane to an alkene is an example of a concerted reaction where all the bond-making and bond-breaking processes occur in a single step. The electrophilic boron adds to the carbon that is bonded to the greater number of hydrogens. The electrophiles that we have looked at previously (e.g.,  $\text{H}^+$ ) also added to the  $\text{sp}^2$  carbon bonded to the greater number of hydrogens, in order to form the most stable carbocation intermediate. Given that an intermediate is not formed in this concerted reaction, how can we explain the regioselectivity of the reaction. Why does boron add preferentially to the  $\text{sp}^2$  carbon bonded to the greater number of hydrogens? If we examine the two possible transition states for the addition of borane, we see that the C–B bond has formed to a greater extent than has the C–H bond. Consequently, the  $\text{sp}^2$  carbon that does not become attached to boron has a partial positive charge. The partial positive charge is on a secondary carbon if boron adds to the carbon bonded to the greater number of hydrogens. The partial positive charge is on a primary carbon if boron adds to the other  $\text{sp}^2$  carbon. So, even though a carbocation intermediate is not formed, a carbocation-like transition state is formed. Thus, the addition of borane and the addition of an electrophile such as  $\text{H}^+$  take place at the same  $\text{sp}^2$  carbon for the same reason to form the more stable carbocation or carbocation like transition state.



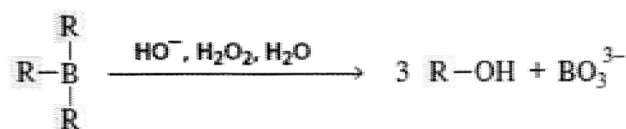
The alkylborane formed in the first step of the reaction reacts with another molecule of alkene to form a dialkylborane, which then reacts with yet another molecule of alkene to form a trialkylborane. In each of these reactions, boron adds to the carbon bonded to the greater number of hydrogens and the nucleophilic hydride ion adds to the other  $\text{sp}^2$  carbon.



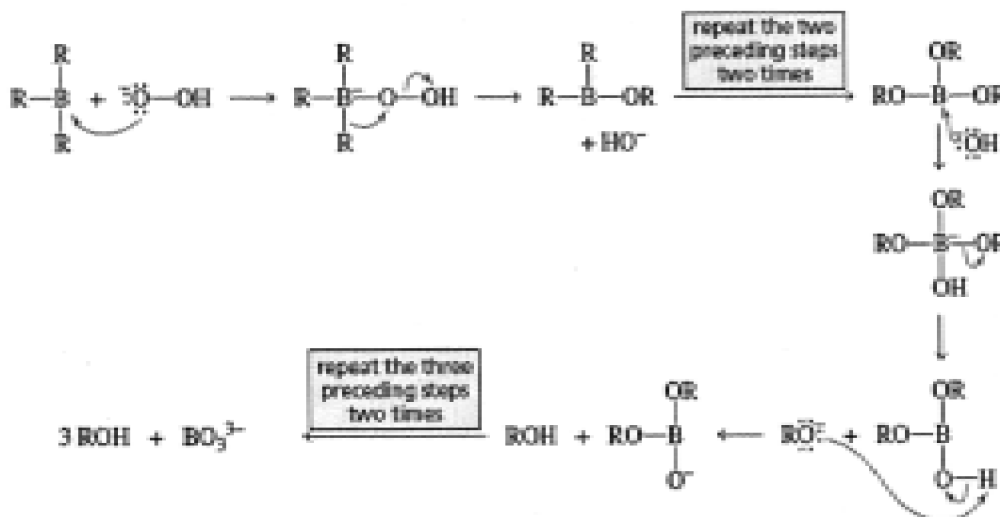
When the hydroboration reaction is over, the reaction mixture is treated with aqueous sodium hydroxide and hydrogen peroxide.



The end result is replacement of boron by an OH group. Because replacing boron by an OH group is an oxidation process, the overall reaction is called hydroboration-oxidation.

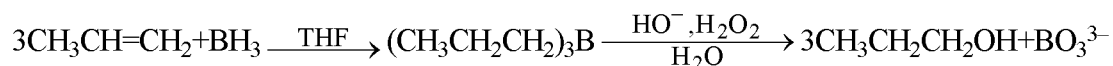


Hydroperoxide ion adds to the borane, causing the alkyl group to migrate from boron to oxygen. The alkyl group migrates with retention of configuration because it moves with its electron pair and does not alter the tetrahedral structure of the migrating carbon atom. Hydrolysis of the borate ester gives the alcohol. The mechanism of the oxidation reaction shows that a hydroperoxide ion (a Lewis base) reacts with R<sub>3</sub>B (a Lewis acid). Then, a 1,2-alkyl shift displaces a hydroxide ion. These two steps are repeated two more times. Then, hydroxide ion (a Lewis base) reacts with RO<sub>3</sub>B (a Lewis acid), and an alkoxide ion is eliminated followed by protonation of the alkoxide ion forms the alcohol. These three steps are repeated two more times.

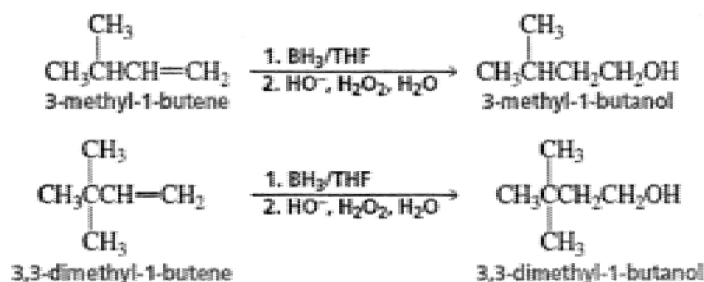


#### Mechanism of hydroboration-oxidation reaction

We have seen that, 1 mole of  $BH_3$  reacts with 3 moles of alkene to form 3 moles of alcohol. The  $OH$  ends up on the carbon that was bonded to the greater number of hydrogens because it replaces boron, which was the original electrophile in the reaction.



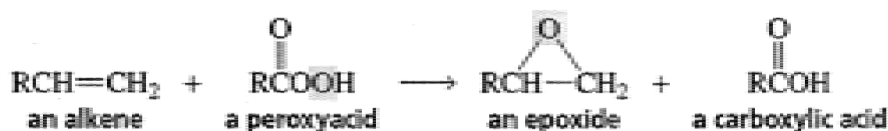
As carbocation intermediates are not formed in the hydroboration reaction, hence there is no possibility of formation carbocation rearrangement products.



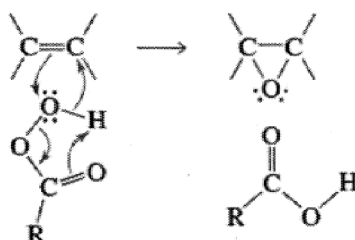
Hydroboration of alkenes is another example of a stereospecific reaction, in which different stereoisomers of the starting compound react to give different stereoisomers of the product.

### 5.5.7 Epoxidation : Oxidation of Alkenes with Peroxyacids

When an alkene is treated with peroxyacids, it is oxidized to an epoxide by the transfer of an oxygen atom from the peroxyacid to the alkene.



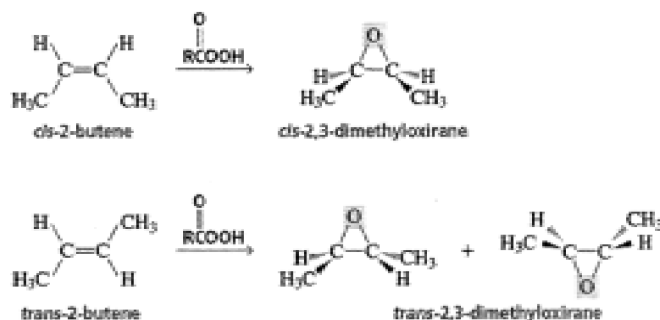
The oxygen atom of the OH group of the peroxyacid accepts a pair of electrons from the  $\pi$ -bond of the alkene, causing the weak O–O bond to break heterolytically. The electrons from the O–O bond are delocalized onto the carbonyl group. The electrons left behind as the O–H bond breaks add to the carbon of the alkene that becomes electron deficient when the  $\pi$ -bond breaks. Epoxidation of an alkene is a concerted reaction where all the bond-forming and bond-breaking processes take place in a single step.



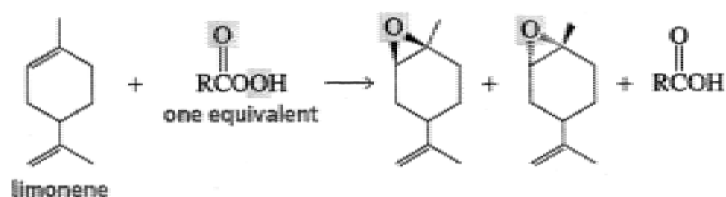
Mechanism for epoxidation of an alkene

The addition of oxygen to an alkene is a stereospecific reaction. Because the reaction is concerted, the C–C bond cannot rotate, so there is no opportunity for the relative positions of the groups bonded to the  $sp^2$  carbons of the alkene to change. The transfer of oxygen is to the same side of the double bond, the resulting oxacyclopropane ring will have the same stereochemistry as the starting alkene. Therefore, a *cis*-alkene forms a *cis*-epoxide and in a similar fashion, a *trans*-alkene forms a *trans*-epoxide.



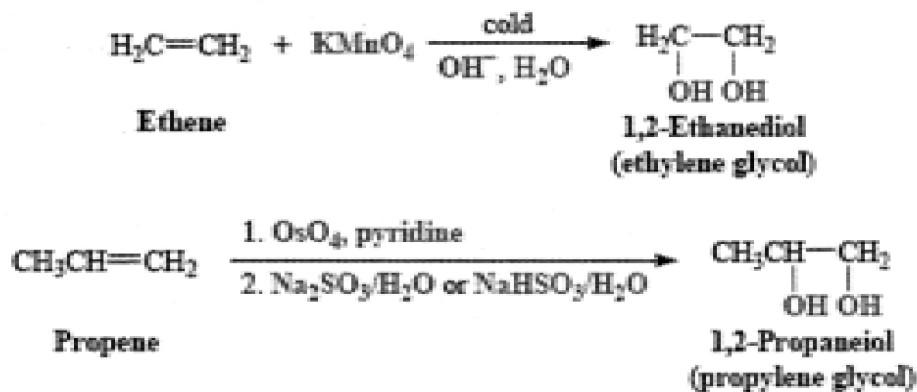


Increasing the electron density of the double bond increases the rate of epoxidation because it makes the double bond more nucleophilic. Alkyl substituents increase the electron density of the double bond. Therefore, if a diene is treated with peroxyacid, the most substituted double bond is epoxidized preferentially.

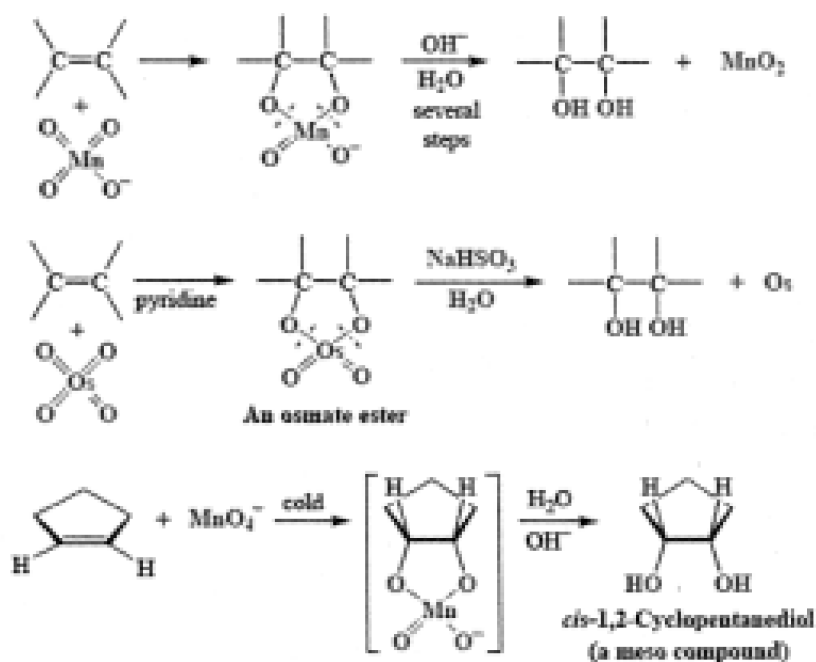


### 5.5.8 Syn and Anti-dihydroxylation

An alkene can be oxidized to a 1, 2-diol (glycol) either by potassium permanganate (KMnO<sub>4</sub>) in a cold basic solution or by osmium tetroxide (OsO<sub>4</sub>). The solution of potassium permanganate must be basic, and the oxidation must be carried out at room temperature or below. If the solution is heated or if it is acidic, the diol will be oxidized further. The OH groups are on adjacent carbons in 1, 2-diols, so 1, 2-diols are also known as vicinal diols or vicinal glycols.

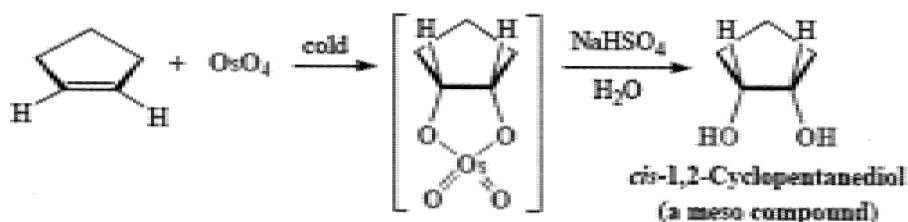


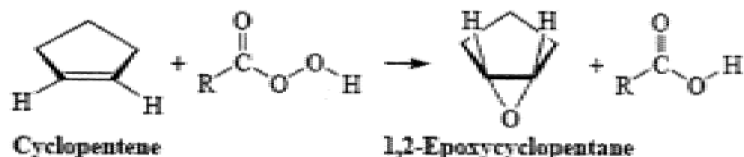
Both  $\text{KMnO}_4$  and  $\text{OsO}_4$  form a cyclic intermediate when they react with an alkene. The reactions occur because manganese and osmium are in a highly positive oxidation state and, therefore, attract electrons. Formation of the cyclic intermediate is a syn addition because both oxygens are delivered to the same side of the double bond. Therefore, the oxidation reaction is stereospecific a cis-cycloalkene forms only a cis-diol.



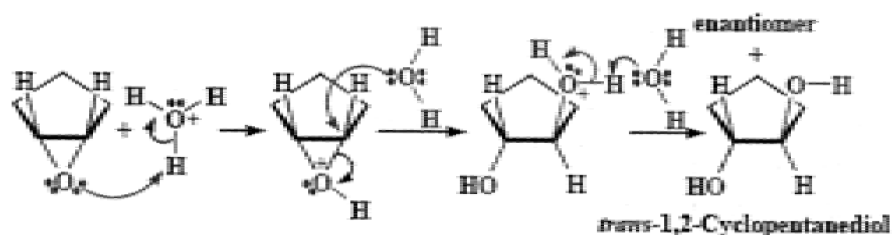
#### Mechanism of Syn-hydroxylation of an alkene

The cyclic osmate ester intermediate is hydrolyzed with hydrogen peroxide that reoxidizes osmium to osmium tetroxide. Higher yields of the diol are obtained with osmium tetroxide because the cyclic osmate intermediate is less likely to undergo side reactions.

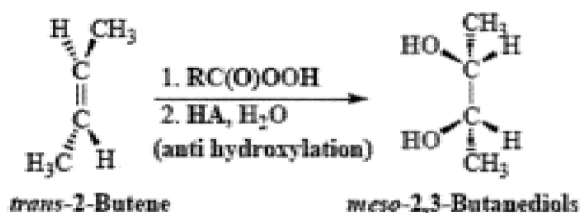
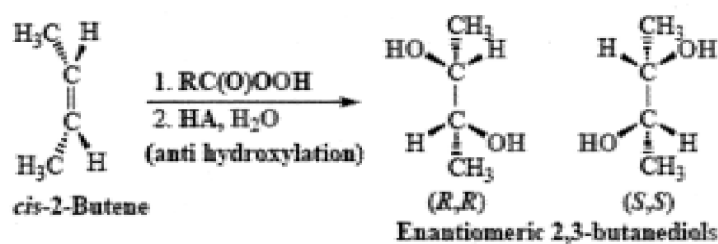


**Anti-hydroxylation via epoxides : Epoxidation followed by acid hydrolysis**

The trans-diols were obtained from the acid hydrolysis of epoxides which are in turn can be produced via epoxidation of an alkene by using a peroxy acid. The water molecule acts as a nucleophile attacks the protonated epoxides from the opposite side of the epoxide ring. The carbon atom being attacked undergoes inversion of configuration.

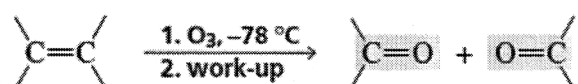


The epoxidation of an alkene followed by acid catalysed hydrolysis is a stereospecific anti-hydroxylation of the double bond. Cis-2-Butene gives the enantiomeric 2, 3-butanediols whereas trans-2-butene gives the meso products.

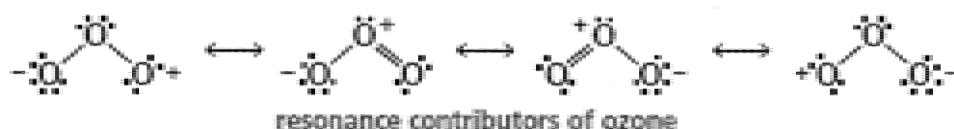


### 5.5.9 Ozonolysis : Oxidative Cleavage of Alkenes

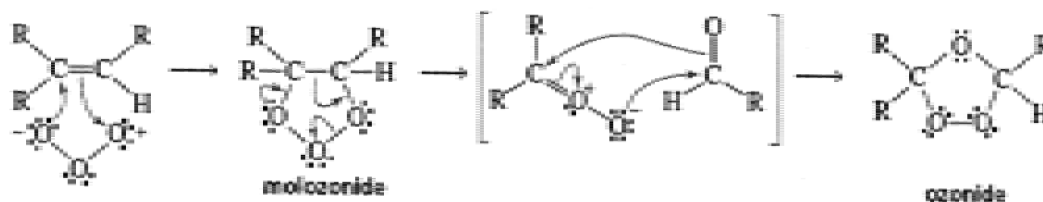
Alkenes can be directly oxidized to aldehydes and ketones by ozone. When an alkene is treated with ozone at low temperatures, the double bond breaks and the carbons that were doubly bonded to each other find themselves doubly bonded to oxygen instead. This oxidation reaction is known as ozonolysis.



Ozone is produced by passing oxygen gas through an electric discharge. The structure of ozone can be represented by the following resonance contributors :



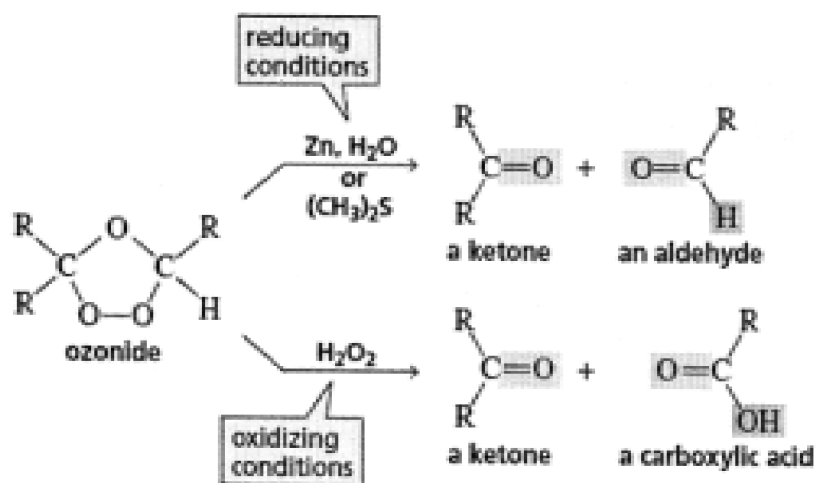
Ozone and the alkene undergo a concerted cycloaddition reaction—the oxygen atoms add to the two  $sp^2$  carbons in a single step. An electrophile adds to one of the  $sp^2$  carbons, and a nucleophile adds to the other. The electrophile is the oxygen at one end of the ozone molecule, and the nucleophile is the oxygen at the other end. The product of ozone addition to an alkene is a molozonide (1, 2, 3-trioxolane). The molozonide is unstable because it has two O-O bonds; it immediately rearranges to a more stable ozonide (1, 2, 4-trioxolane).



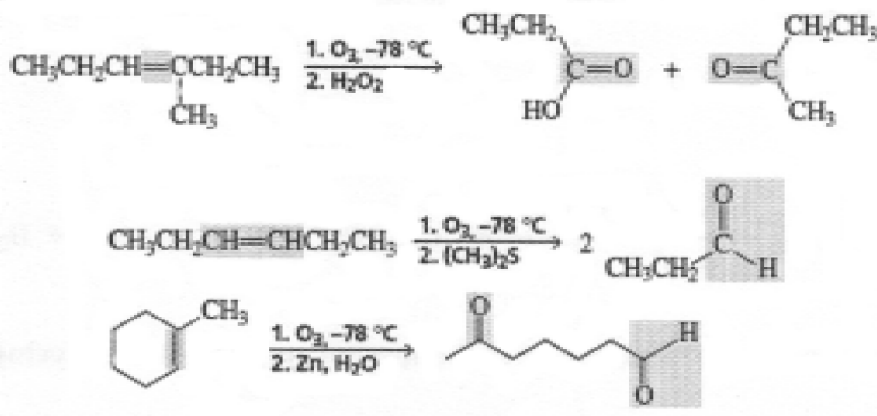
Mechanism of ozonide formation

Ozonides are explosive, so they are seldom isolated. In solution, they are easily cleaved to carbonyl compounds. If the ozonide is cleaved in the presence of a reducing agent such as zinc or dimethyl sulfide, the products will be ketones and/or aldehydes. (The product will be a ketone if the  $sp^2$  carbon of the alkene is bonded

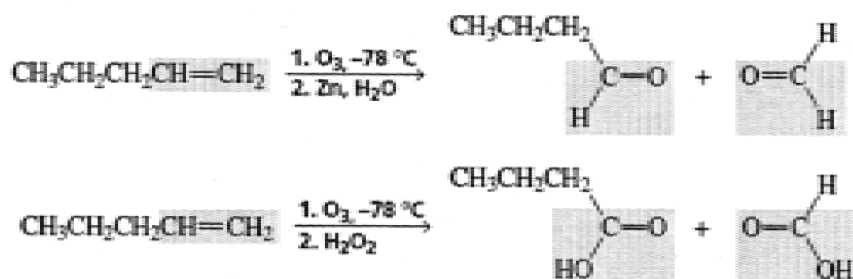
to two carbon containing substituents; the product will be an aldehyde if at least one of the substituents bonded to the  $sp^2$  carbon is a hydrogen.) The reducing agent prevents aldehydes from being oxidized to carboxylic acids. Cleaving the ozonide in the presence of zinc or dimethyl sulfide is referred to as “working up the ozonide under reducing conditions.”



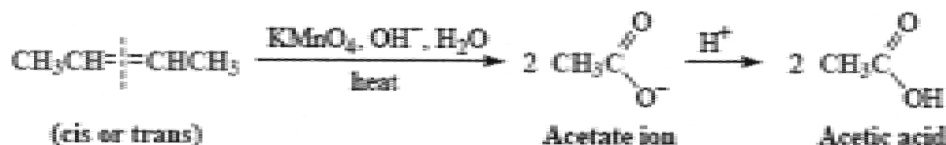
If the ozonide is cleaved in the presence of an oxidizing agent such as hydrogen peroxide the products will be ketones and/or carboxylic acids. Carboxylic acids are formed instead of aldehydes because any aldehyde that is initially formed will be immediately oxidized to a carboxylic acid by hydrogen peroxide. Cleavage in the presence of  $\text{H}_2\text{O}_2$  is referred to as “working up the ozonide under oxidizing conditions.” The following reactions are examples of the oxidative cleavage of alkenes by ozonolysis.



The one-carbon fragment obtained from the reaction of a terminal alkene with ozone will be oxidized to formaldehyde if the ozonide is worked up under reducing conditions and to formic acid if it is worked up under oxidizing conditions.

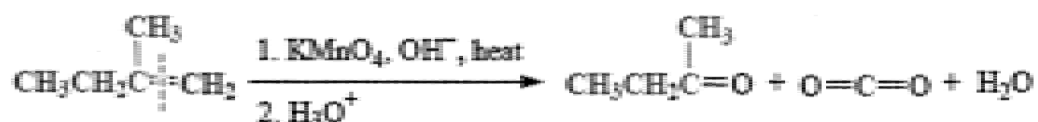


Alkene with mono substituted carbon atoms are oxidatively cleaved to carboxylic acid salts by using hot alkaline potassium permanganate. The intermediate glycol is oxidised further with the cleavage of the carbon-carbon bond.



The terminal CH<sub>2</sub>-group of 1-alkene is completely oxidised to give CO<sub>2</sub> and water in hot alkaline potassium permanganate. This type of oxidative cleavage of alkene may be used to identify the location of the double bond in the alkenes.

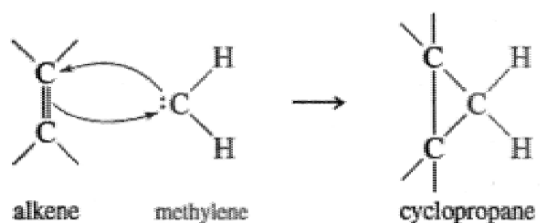
Alkenes are oxidized to 1, 2-diols by a basic solution of potassium permanganate at room temperature or below, and the 1, 2-diols can subsequently be cleaved by periodic acid to form aldehydes and/or ketones.



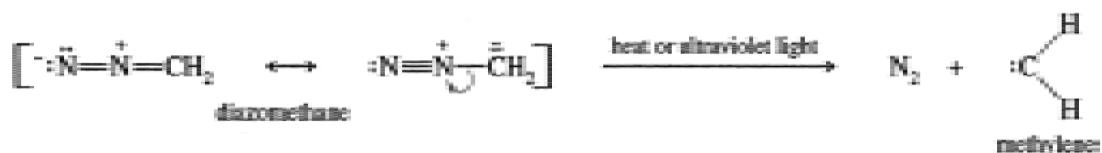
### 5.5.10 Addition of singlet and triplet carbenes: Formation of three cyclopropanes

Carbenes are neutral, reactive intermediates with a divalent carbon and a lone pair. Carbenes are potent electrophiles and react with double bonds to form

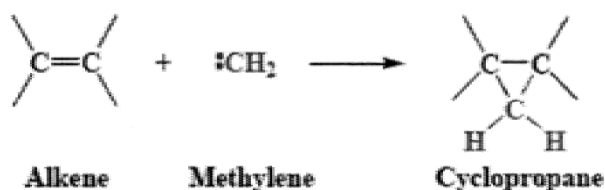
3-membered rings [cyclopropanes]. Methylene ( $:\text{CH}_2$ ) is the simplest of the carbenes, uncharged, reactive intermediates that have a carbon atom with two bonds and two nonbonding electrons.



Carbene can be generated by heating or photolysis of diazomethane which gives nitrogen gas and methylene.

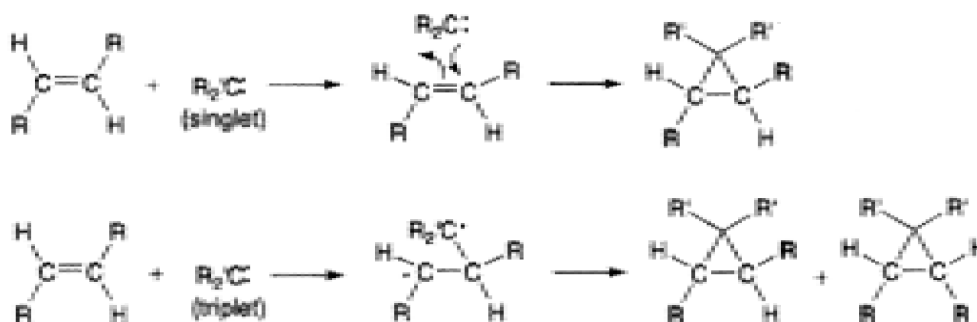


The reaction of carbenes is of great synthetic importance in the preparation of three membered ring compounds. The methylene generated from diazomethane reacts with alkenes to form cyclopropanes, but the disadvantage is that diazomethane is very toxic and explosive, and the methylene generated is so reactive that it forms many side products.



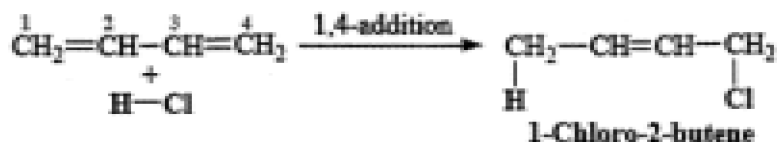
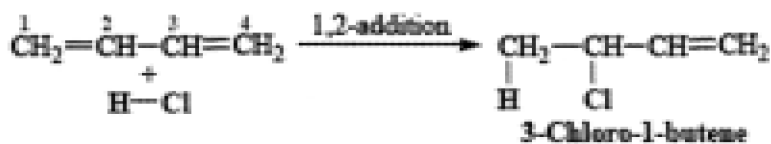
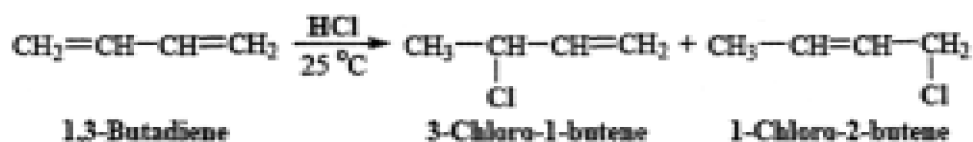
Carbenes are known as singlet and triplet according to their associated electronic spins. If spin paired it is called singlet and if unpaired is called triplet state of the carbene. Both singlet and triplet carbene shows different types of reactivity. Singlet carbene generally participates in electrophilic or nucleophilic reaction. Triplet has unpaired electron pairs and behaves as diradicals which follows a stepwise radical addition reaction. Due to these two modes of reactivity reaction of singlet methylene are stereospecific whereas triplet methylene are stereoselective. This behaviour can be used to identify the nature of the carbene. Reaction of methylene generated from

photolysis of diazomethane with *cis*-2-Butene or *trans*-2-butene each give a single diastereomer of the 1, 2-dimethylcyclopropane, *cis* from *cis* and *trans* from *trans*, which proves the methylene is singlet. If methylene is triplet is give a mixture of products.



### 5.5.11 Electrophilic addition to conjugated dienes

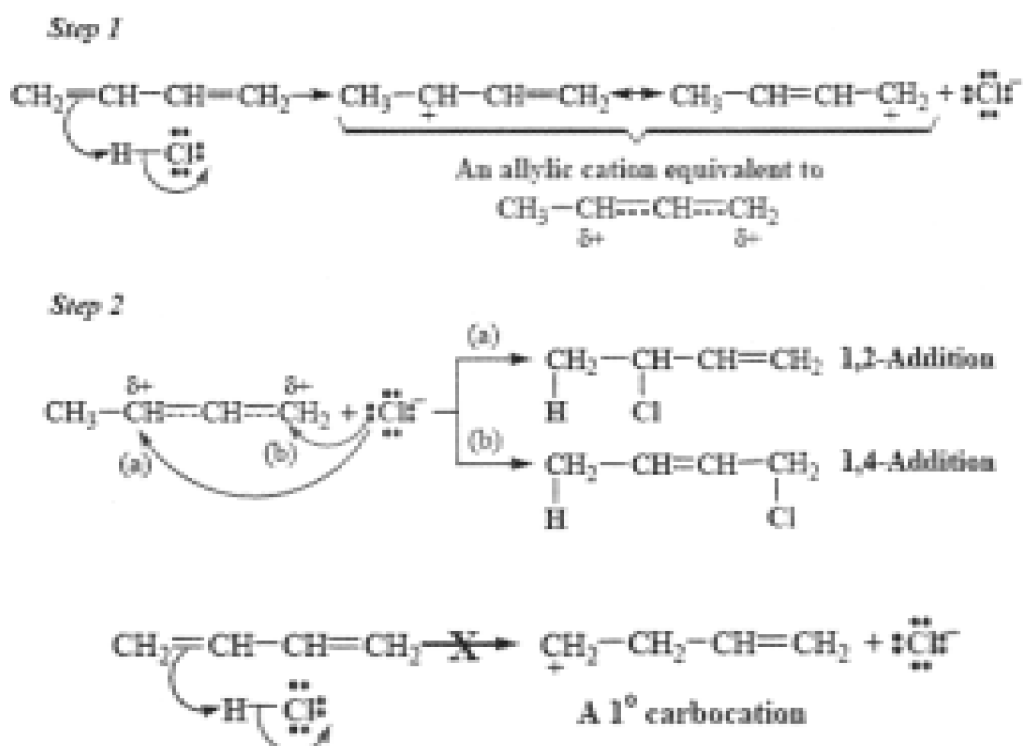
There are two types of addition possible in electrophilic addition of conjugated dienes viz-1, 2-addition and 1, 4-addition depending on the nature of the intermediate carbocation formed. 1, 3-Butadiene reacts with one molar of HCl to produce two products namely 3-chloro-1-butene and 1-chloro-2-butene by 1, 2- and 1, 4-electrophilic addition reactions.



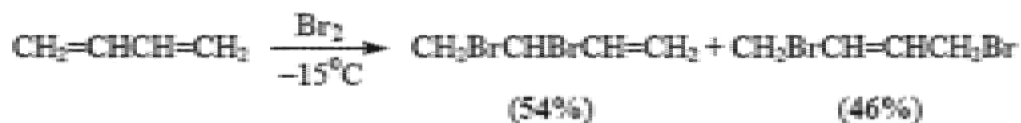
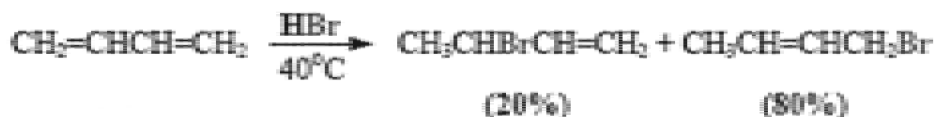


### The mechanism of addition of HCl occurs in two steps-

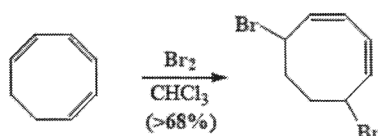
In step 1, A proton is adds to one of the terminal carbon atoms of 1, 3-Butadiene to form the more stable carbocation which is a resonance stabilised allylic cation. Addition of one of the inner carbon atom would have produced a much less primary cation which could not be stabilised by resonance. In Step-2, the nucleophile attack to the allylic cation to give 1, 2-as well as 1, 4-addition products.



1, 3-Butadiene shows 1, 4-addition product with electrophilic reagents other than HCl.

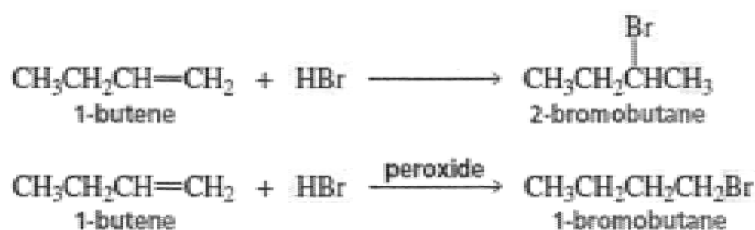


In case of conjugated trienes, it often shows 1,6-addition.



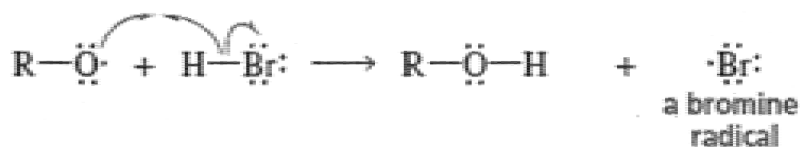
### 5.5.12. Free Radical addition : Anti-Markovnikov addition (peroxide effect)

The addition of HBr to 1-butene forms 2-bromobutane. But can we synthesize 1-bromobutane from 1-butene? The formation of 1-bromobutane requires the anti-Markovnikov addition of HBr to 1-butene. If an alkyl peroxide (ROOR) is added to the reaction mixture, the product of the addition reaction will be the desired 1-bromobutane. Thus, the presence of peroxide causes the anti-Markovnikov addition of HBr.

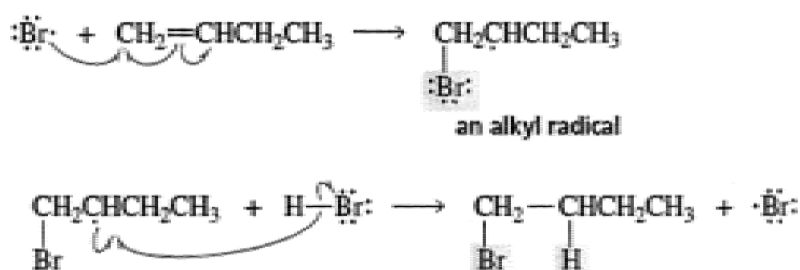


A peroxide reverses the order of addition because it changes the mechanism of the reaction in a way that causes to be the electrophile. Markovnikov's rule is not followed because it applies only when the electrophile is a hydrogen. The general rule is that the electrophile adds to the  $sp^2$  carbon bonded to the greater number of hydrogens is followed, however, because is the electrophile when HBr adds to an alkene in the presence of a peroxide.

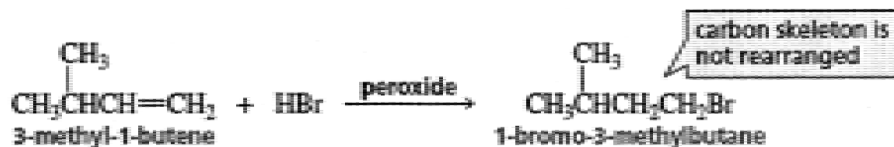
An alkyl peroxide can be used to reverse the order of addition of H and Br to an alkene. The alkyl peroxide contains a weak oxygen-oxygen single bond that is readily broken homolytically in the presence of light or heat to form radicals. A radical is a species with an unpaired electron.



The bromine radical now seeks an electron to complete its octet. Because the double bond of an alkene is electron rich, the bromine radical completes its octet by combining with one of the electrons of the bond of the alkene to form a C-Br bond. The second electron of the bond is the unpaired electron in the resulting alkyl radical. If the bromine radical adds to the carbon of 1-butene that is bonded to the greater number of hydrogens, a secondary alkyl radical is formed. If the bromine radical adds to the other carbon, a primary alkyl radical is formed. Like carbocations, radicals are stabilized by electron-donating alkyl groups, so a tertiary alkyl radical is more stable than a secondary alkyl radical, which in turn is more stable than a primary alkyl radical. The bromine radical, therefore, adds to the carbon that is bonded to the greater number of hydrogens, thereby forming the more stable (in this case) secondary radical. The alkyl radical that is formed removes a hydrogen atom from another molecule of HBr to produce a molecule of the alkyl halide product and another bromine radical. Because the first species that adds to the alkene is a radical the addition of HBr in the presence of a peroxide is called a radical addition reaction.

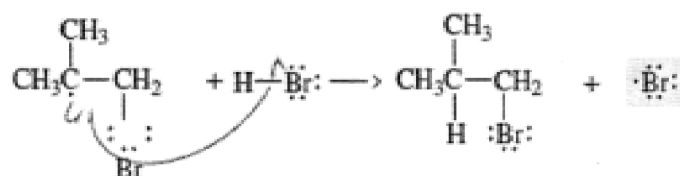
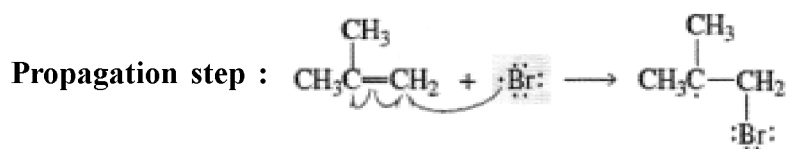
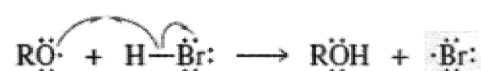
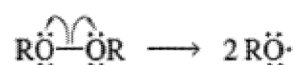


When HBr reacts with an alkene in the absence of a peroxide, the electrophile—the first species to add to the alkene—is In the presence of a peroxide, the electrophile is In both cases, the electrophile adds to the carbon that is bonded to the greater number of hydrogens, so both reactions follow the general rule for electrophilic addition reactions. The electrophile adds to the carbon that is bonded to the greater number of hydrogens. Because the addition of HBr in the presence of a peroxide forms a radical intermediate rather than a carbocation intermediate, the intermediate does not rearrange. Radicals do not rearrange as readily as carbocations.

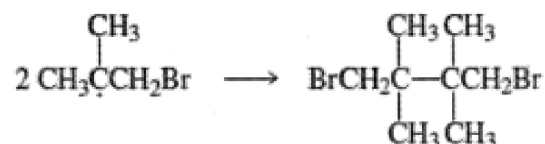
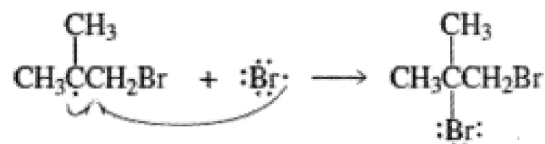
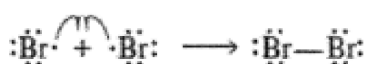


The mechanism for the addition of HBr to an alkene in the presence of peroxide involves several steps. The steps can be divided into initiation, propagation, and termination steps.

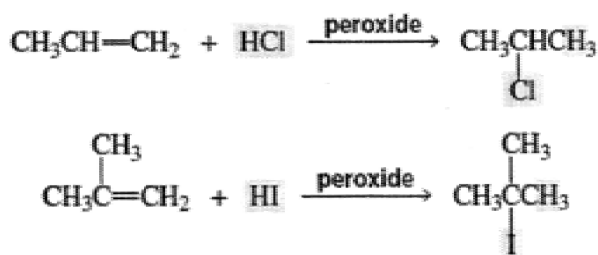
**Initiation step :**



**Termination step :**



In the initiation steps, the chain carrier, bromine radical is formed. In propagation step, the bromine radical reacts with alkene to give products and another bromine radical. The two propagation steps are repeated over and over. In a termination step, two radicals combine to produce a neutral molecule in which all the electrons are paired, thus ending the role of those radicals in the radical chain reaction. The alkyl peroxide used here, acts as a radical initiator. Without a peroxide, the preceding radical reaction would not occur. Any compound that can readily undergo homolysis can act as a radical initiator. Peroxide has no effect on the addition of HCl or HI to an alkene. In the presence of a peroxide, addition occurs just as it does in the absence of a peroxide.

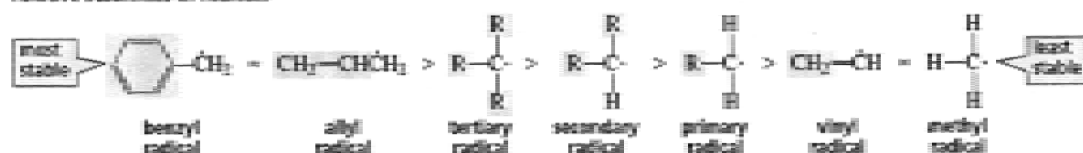


The peroxide effect observed for the addition of HBr, but not for the addition of HCl or HI can be answered if we consider the bond dissociation energies. For the radical addition of HCl, the first propagation step is exothermic and the second is endothermic. For the radical addition of HI, the first propagation step is endothermic and the second is exothermic. Only for the radical addition of HBr are both propagation steps exothermic.

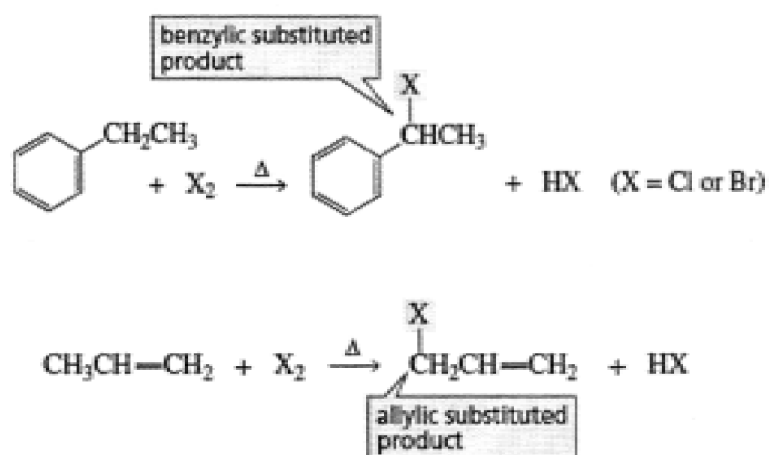
### Radical Substitution of Benzylic and Allylic Hydrogens :

Benzyl and allyl radicals are more stable than alkyl radicals because their unpaired electrons are delocalized. We have seen that electron delocalization increases the stability of a molecule.

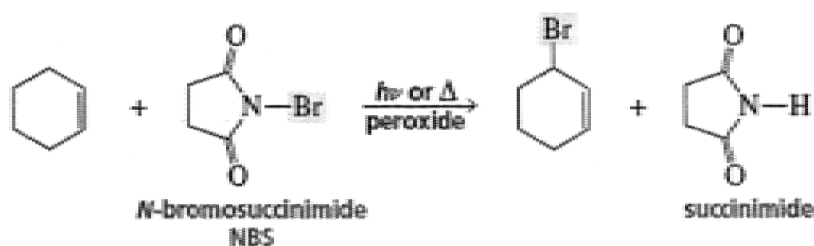
relative stabilities of radicals



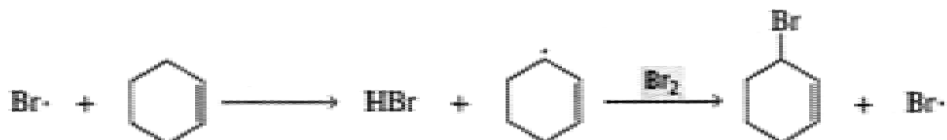
We know that the more stable the radical, the faster it can be formed. This means that a hydrogen bonded to either a benzylic carbon or an allylic carbon will be preferentially substituted in a halogenation reaction. In the reaction of alkene, bromination is highly regioselective than chlorination, so the percent of substitution at the benzylic or allylic carbon is greater for bromination.



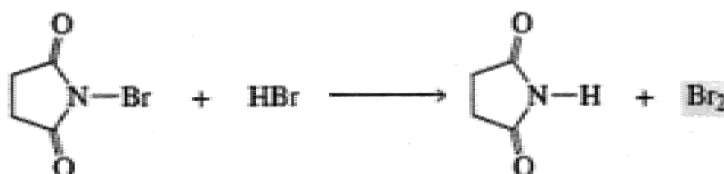
N-Bromosuccinimide (NBS) is frequently used to brominate allylic positions because it allows a radical substitution reaction to be carried out without subjecting the reactant to a relatively high concentration of Br<sub>2</sub> that could add to its double bond.



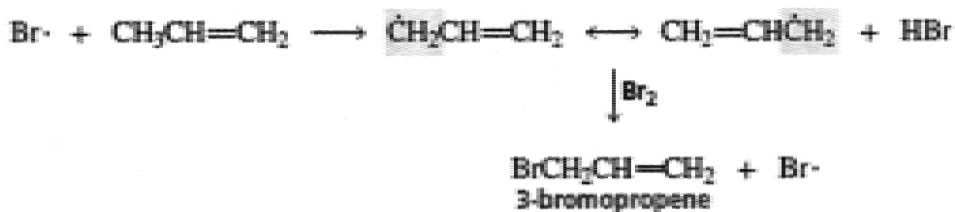
The reaction involves initial homolytic cleavage of the N-Br bond in NBS. This generates the bromine radical needed to initiate the radical reaction. Light or heat and a radical initiator such as peroxide are used to promote the reaction. The bromine radical abstracts an allylic hydrogen to form HBr and an allylic radical. The allylic radical reacts with Br<sub>2</sub> forming the allyl bromide and a chain-propagating bromine radical.



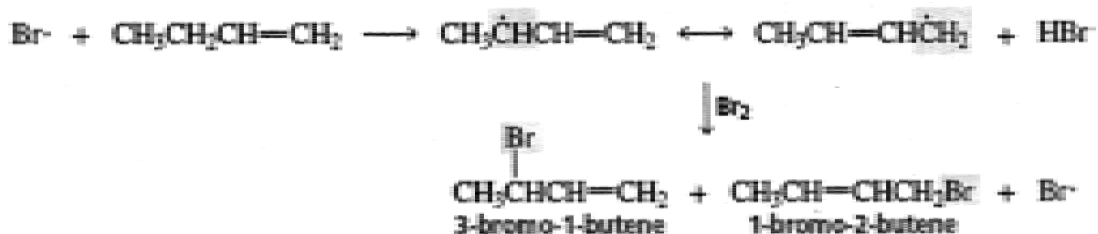
The  $\text{Br}_2$  used in the second step of the preceding reaction sequence is produced in low concentration from the reaction of NBS with HBr.



The advantage to using NBS to brominate allylic positions is that neither  $\text{Br}_2$  nor HBr is formed at a high concentration to add to the double bond. When a radical abstracts a hydrogen atom from an allylic carbon, the unpaired electron of the allylic radical is shared by two carbons. In other words, the allylic radical has two resonance contributors. In the following reaction, only one substitution product is formed, because the groups attached to the  $\text{sp}^2$  carbons are the same in both resonance contributors :



If, however, the groups attached to the two  $\text{sp}^2$  carbons of the allylic radical are not the same in both resonance contributors, two substitution products are formed.

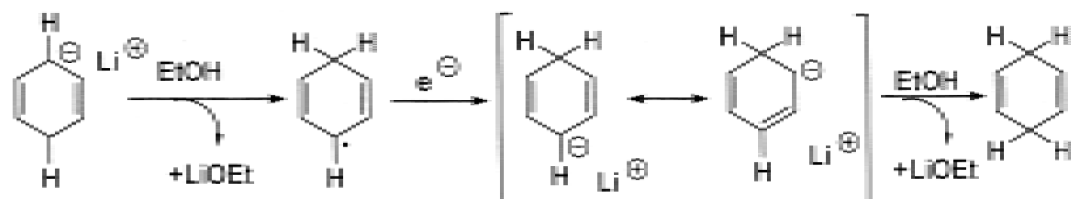


If a reactant does not have an asymmetric carbon and a radical substitution

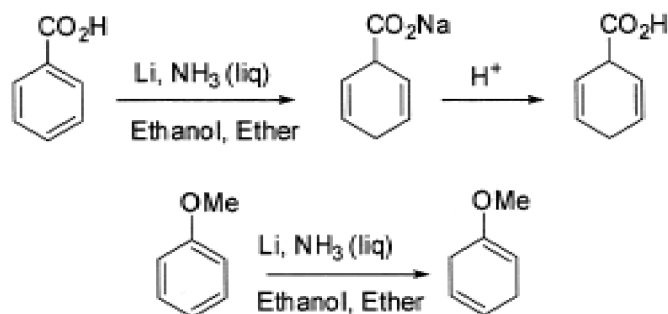




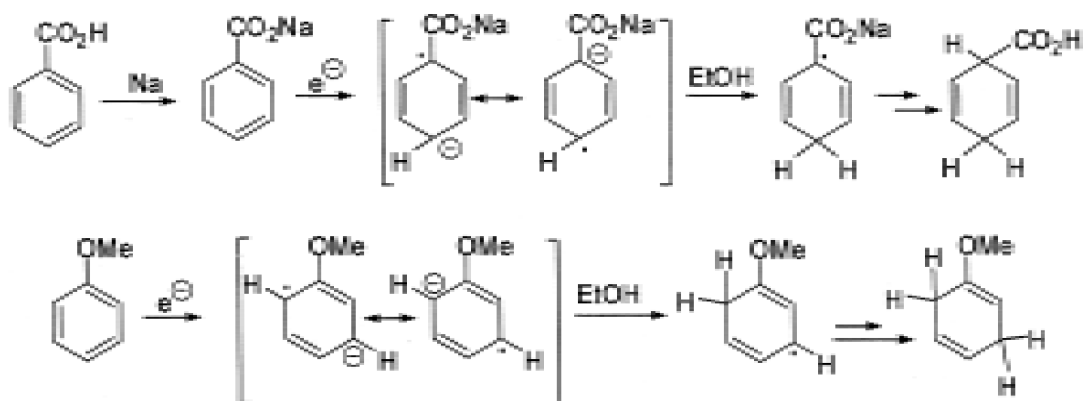
The radical anion is very basic, and it picks up a proton from the ethanol that is in the reaction mixture. The molecule is now no longer anionic, but it is still a radical. It can pick up another electron, which pairs with the radical to give an anion, which is quenched again by the proton source (ethanol).



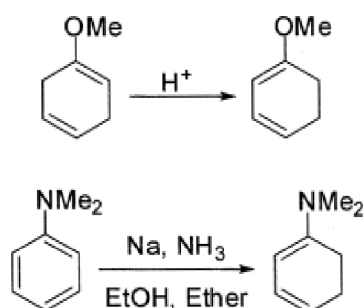
These examples serve to illustrate the general principle that electron-withdrawing groups promote ipso, para reduction while electron-donating groups promote ortho, meta reduction.



The explanation must lie in the distribution of electron density in the intermediate radical anions. Electron-withdrawing groups stabilize electron density at the ipso and para positions, and protonation occurs para, while electron-donating groups stabilize ortho and meta electron density.

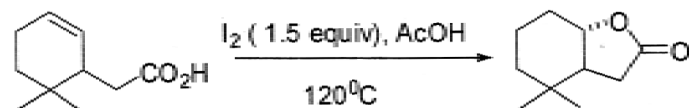


If you want the conjugated dienes as products, it is quite a simple matter to isomerize them using an acid catalyst. In fact, a small amount (about 20%) of the conjugated product is produced anyway in the reaction of anisole above. With anilines, it is impossible to stop the isomerisation taking place during the reaction, and Birch reduction always gives conjugated enamines. Birch reduction works for alkynes too, and is a good way of reducing them, to trans double bonds (the best way to reduce them to cis-alkenes is via  $H_2$  and the Lindlar catalyst) which will be discussed in the latter part of the chapter.



#### 5.5.14 Halolactonization : Halo-alkoxylation

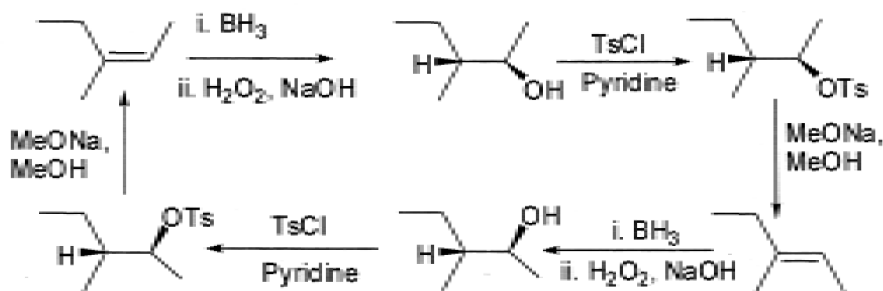
Halo-ester can be prepared by the addition of halogen atom and ester to an alkene. Alkene carboxylic acid give a tandem reaction of formation of halonium ion followed by intramolecular displacement of the carboxylic group to give a halo-lactone. This tandem addition of halogen atom and ester is called halolactonization. The most common version of this reaction where iodine is used is known as iodolactonization.



#### 5.5.15 Inter conversion of E and Z alkenes

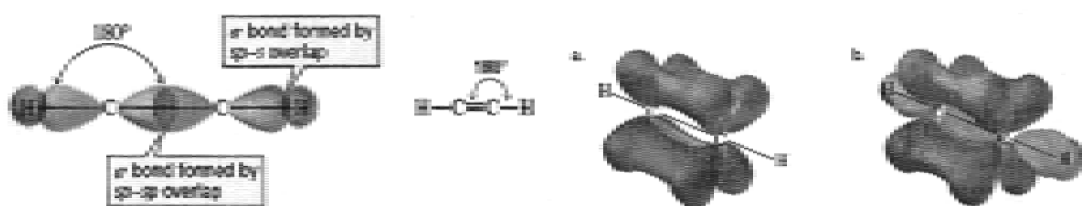
In order to interconvert the *cis* and *trans* isomers we must use a different strategy. One method is to shine light on the molecule. If UV light is used it is of the right wavelength to be absorbed by the  $C=C$  bond.

For E/Z trisubstituted alkenes capable of E<sub>2</sub> elimination the following sequence may apply. Add the elements of water in a syn, anti-Markovnikov fashion to the double bond. Remove the elements of water as p-toluenesulfonic acid via anti E<sub>2</sub> elimination.



## 5.6 The Structure of Alkynes

The alkynes are hydrocarbon which contain a carbon-carbon triple bond. Each carbon is *sp* hybridized, so each has two *sp* orbitals and two *p* orbitals. One *sp* orbital overlaps the *s* orbital of a hydrogen, and the other overlaps an *sp* orbital of the other carbon. Because the *sp* orbitals are oriented as far from each other as possible to minimize electron repulsion, ethyne is a linear molecule with bond angles of 180°.



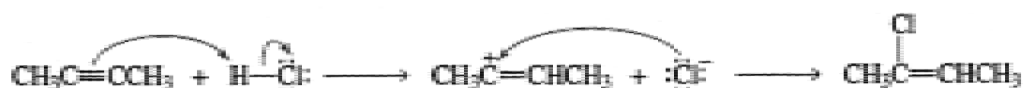
**Figure-14 :** Structure and bonding of an alkyne-(a) Each of the two bonds of a triple bond is formed by side-to-side overlap of a *p* orbital of one carbon with a parallel *p* orbital of the adjacent carbon, (b) A triple bond consists of a bond formed by *sp-sp* overlap (yellow colour) and two bonds formed by *p-p* overlap (blue and purple colour).

The two remaining *p* orbitals on each carbon are oriented at right angles to one another and to the *sp* orbitals as shown in figure above. Each of the two *p* orbitals on one carbon overlaps the parallel *p* orbital on the other carbon to form two bonds. One pair of overlapping *p* orbitals results in a cloud of electrons above and below the bond, and the other pair results in a cloud of electrons in front of and behind the

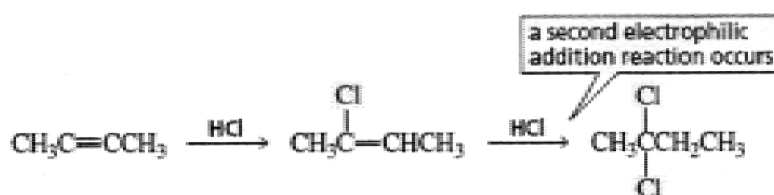
bond. A carbon-carbon triple bond is shorter and stronger than a carbon-carbon double bond, which in turn, is shorter and stronger than a carbon-carbon single bond. Similar to alkenes, alkynes are also stabilized by electron-donating alkyl groups. Internal alkynes, therefore, are more stable than terminal alkynes.

## 5.7 Reactivity of Alkynes

With a cloud of electrons completely surrounding the bond, an alkyne is an electron rich molecule. In other words, it is a nucleophile and consequently it will react with electrophiles. For example, if a reagent such as HCl is added to an alkyne, the relatively weak  $\pi$ -bond will break because the  $\pi$ -electrons are attracted to the electrophilic proton. In the second step, the positively charged carbocation intermediate reacts rapidly with the negatively charged chloride ion.



Thus alkynes, like alkenes, undergo electrophilic addition reactions and the same electrophilic reagents that add to alkenes also add to alkynes in a regioselective manner. When an electrophile adds to a terminal alkyne, it adds to the  $sp$  carbon that is bonded to the hydrogen. The addition reactions of alkynes, however, have a feature that alkenes do not have: Because the product of the addition of an electrophilic reagent to an alkyne is an alkene, a second electrophilic addition reaction can occur.

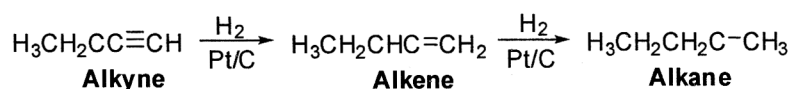


## 5.8 Reactions of alkynes

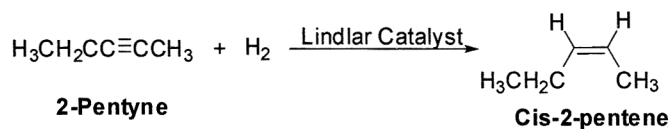
### 5.8.1 Hydrogenation : Addition of Hydrogen

Hydrogen adds to an alkyne in the presence of a metal catalyst such as

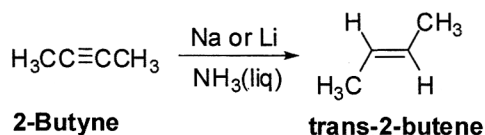
palladium, platinum, or nickel in the same manner that it adds to an alkene. It is difficult to stop the reaction at the alkene stage because hydrogen readily adds to alkenes in the presence of these efficient metal catalysts. The product of the hydrogenation reaction, therefore, is an alkane.



The reaction can be stopped at the alkene stage if a partially deactivated metal catalyst is used. The most commonly used partially deactivated metal catalyst is Lindlar catalyst, which is prepared by precipitating palladium on calcium carbonate and treating it with lead (II) acetate and quinoline. This treatment modifies the surface of the palladium, making it much more effective at catalyzing the addition of hydrogen to a triple bond than to a double bond. Because the alkyne sits on the surface of the metal catalyst and the hydrogens are delivered to the triple bond from the surface of the catalyst, only syn addition of hydrogen occurs. Syn addition of hydrogen to an internal alkyne forms a cis alkene.

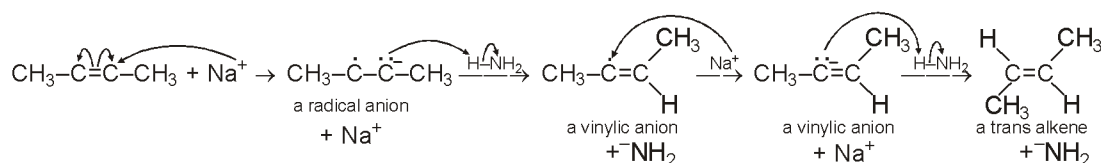


Internal alkynes can be converted into trans *alkenes* using Na (or Li) in liquid ammonia. The reaction stops at the alkene stage because Na (or Li) reacts more rapidly with triple bonds than with double bonds.

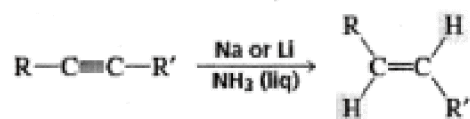
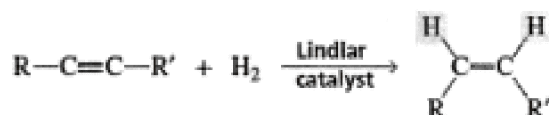
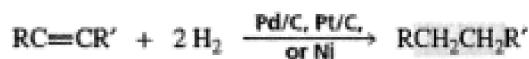
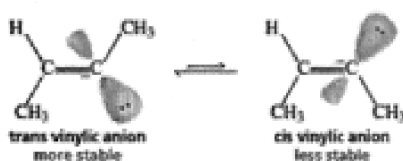


The first step in the mechanism of this reaction is transfer of the  $s$  orbital electron from Na (or Li) to an  $sp$  carbon to form a radical anion—a species with a negative charge and an unpaired electron. (Na and Li have a strong tendency to lose the single electron in their outer-shell  $s$  orbital) The radical anion is such a strong base that it can remove a proton from ammonia. This results in the formation of a vinylic radical—the unpaired electron is on a vinylic carbon. Another single-electron

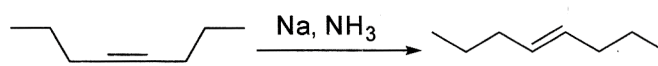
transfer from Na (or Li) to the vinylic radical forms a vinylic anion. The vinylic anion abstracts a proton from another molecule of ammonia. The product is the trans alkene.



The vinylic anion can have either the cis or the trans configuration. The cis and trans configurations are in equilibrium, but the equilibrium favors the more stable trans configuration because in this configuration the bulky alkyl groups are as far from each other as possible.

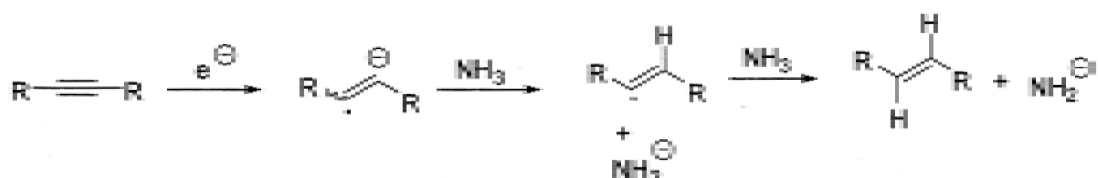


From the above three reactions of alkyne it is clear that hydrogenation reaction can give alkane, cis-alkene and trans-alkene depending on the nature of the catalysts used.



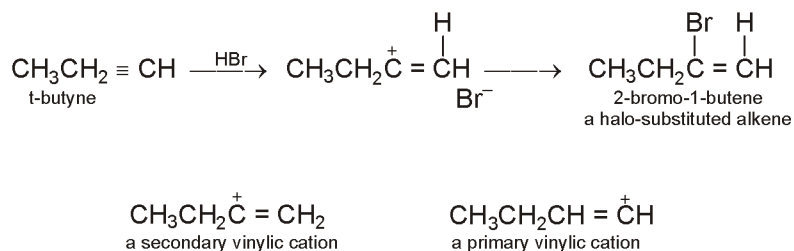
The mechanism follows the same course as the reduction of aromatic rings, but

the vinyl anion is basic enough to deprotonate ammonia, so no added proton source is required. Vinyl anions are geometrically unstable, and choose to be *E*.

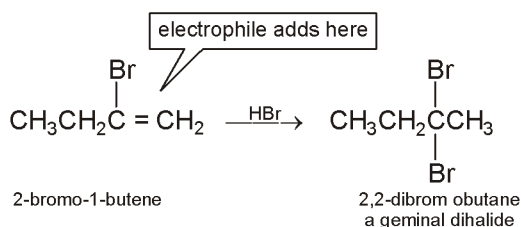


### 5.8.2 Hydrohalogenation of alkyne

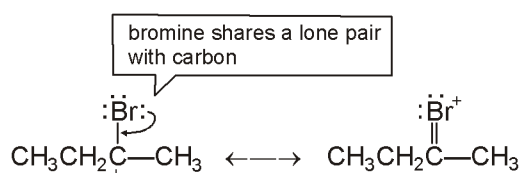
Addition of hydrogen halide to an alkyne is known as hydrohalogenation reaction. We have just seen that an alkyne is a nucleophile and that in the first step of the reaction of an alkyne with a hydrogen halide, the electrophilic reagent adds to the alkyne. If the alkyne is a terminal alkyne, it will add to the *sp* carbon bonded to the hydrogen, because the secondary vinylic cation that results is more stable than the primary vinylic cation that would be formed if it added to the other *sp* carbon.



Although the addition of a hydrogen halide to an alkyne can generally be stopped after the addition of one equivalent of hydrogen halide, a second addition reaction will take place if excess hydrogen halide is present. The product of the second addition reaction is a geminal dihalide.

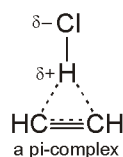


When the second equivalent of hydrogen halide adds to the double bond, the electrophile adds to the carbon bonded to the greater number of hydrogens. The carbocation that results is more stable than the carbocation that would have been formed if had added to the other carbon because bromine can share the positive charge with carbon by sharing one of its lone pairs.



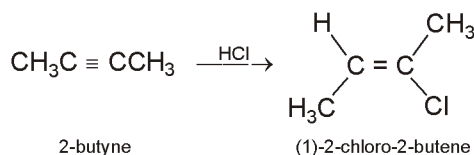
The addition of a hydrogen halide to an alkyne can be stopped after the addition of one equivalent of HBr or HCl because an alkyne is more reactive than the halo substituted alkene that is the product of the first addition reaction. The halogen substituent withdraws electrons inductively (through the bond), thereby decreasing the nucleophilic character of the double bond.

In describing the mechanism for addition of a hydrogen halide, we have shown that the intermediate is a vinylic cation. This mechanism may not be completely correct. A secondary vinylic cation is about as stable as a primary carbocation, and generally primary carbocations are too unstable to be formed. Some chemists, therefore, considered that a  $\pi$ -complex is formed in the intermediate step rather than a vinylic cation.

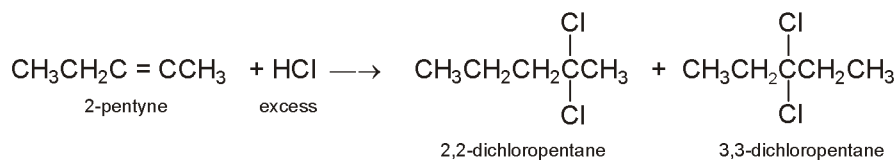


Support for the intermediate's being a  $\pi$ -complex comes from the observation that many (but not all) alkyne addition reactions are stereoselective. For example, the addition of HCl to 2-butyne forms only (*Z*)-2-chloro-2-butene, which means that only anti addition of H and Cl occurs. Clearly, the nature of the intermediate in alkyne addition reactions is not completely understood.

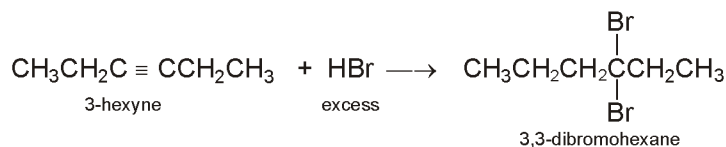




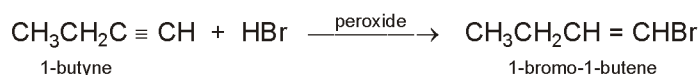
Addition of a hydrogen halide to an internal alkyne forms two geminal dihalides because the initial addition of the proton can occur with equal ease to either of the *sp* carbons.



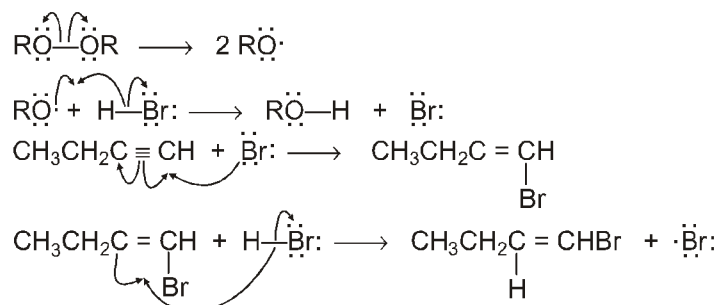
However, symmetrical internal alkyne gives only one geminal dihalide.



The peroxide effect in case of the addition of HBr to an alkyne is similar to the addition of HBr to an alkene—it reverses the order of addition because the peroxide causes to become the electrophile.



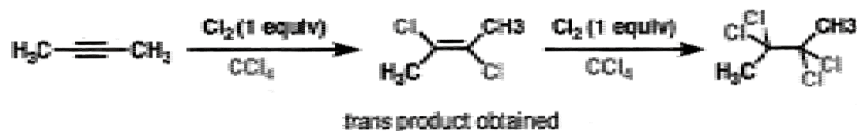
The mechanism of the reaction is the same as that for the addition of HBr to an alkene in the presence of a peroxide. That is, the peroxide is a radical initiator and creates a bromine radical (an electrophile). If the alkyne is a terminal alkyne, the bromine radical adds to the *sp* carbon bonded to the hydrogen; if it is an internal alkyne, the bromide radical can add with equal ease to either of the *sp* carbons. The resulting vinylic radical abstracts a hydrogen atom from HBr and regenerates the bromine radical. Any two radicals can combine in a termination step.



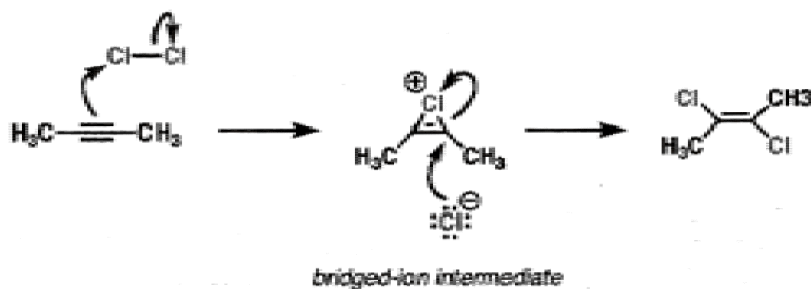
Mechanism for the addition of HBr to an alkyne in the presence of peroxide

### 5.8.3 Halogenations of alkyne

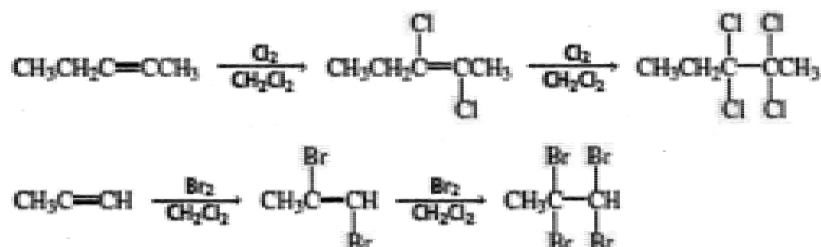
The reaction of alkynes with electrophiles such as  $\text{Cl}_2$ ,  $\text{Br}_2$ , and  $\text{I}_2$  does give very similar results to what is observed with alkenes although alkynes are not as reactive as alkenes. For example, treatment of an alkyne with 1 equivalent of  $\text{Cl}_2$  provides a dichlorinated alkene with the two chlorides opposite to each other. If a second equivalent of  $\text{Cl}_2$  is added, the tetrachloro derivative will form. A similar reaction is also observed in case of  $\text{Br}_2$  and  $\text{I}_2$  also.



Just as with alkenes, a  $\pi$ -bond from the alkyne can act as a nucleophile, attacking  $\text{Cl}_2$  and giving rise to a bridged intermediate. In the next step, chloride ion attacks the carbon from the back face, leading to the trans product. The proposed mechanism of the reaction is given below. Similar types of mechanism follow in case of the reaction with  $\text{Br}_2$  and  $\text{I}_2$  also.

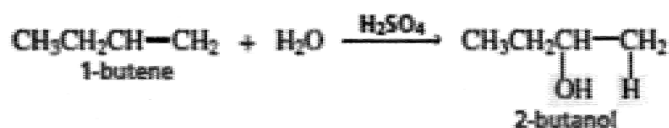


The second addition reaction of halogens  $\text{Cl}_2$  and  $\text{Br}_2$  to alkynes occurs in the presence of excess halogen.

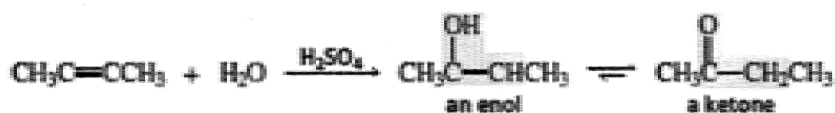


### 5.8.4 Hydration : Addition of Water

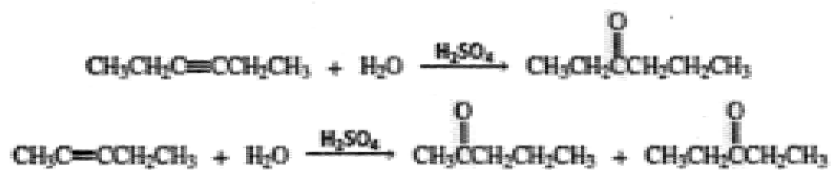
When alkenes undergo the acid-catalyzed addition of water, the product of the reaction is an alcohol.



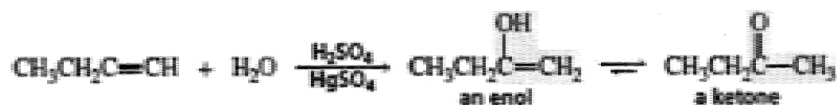
When alkynes also undergo the acid-catalyzed addition of water, the product of the reaction is an enol.



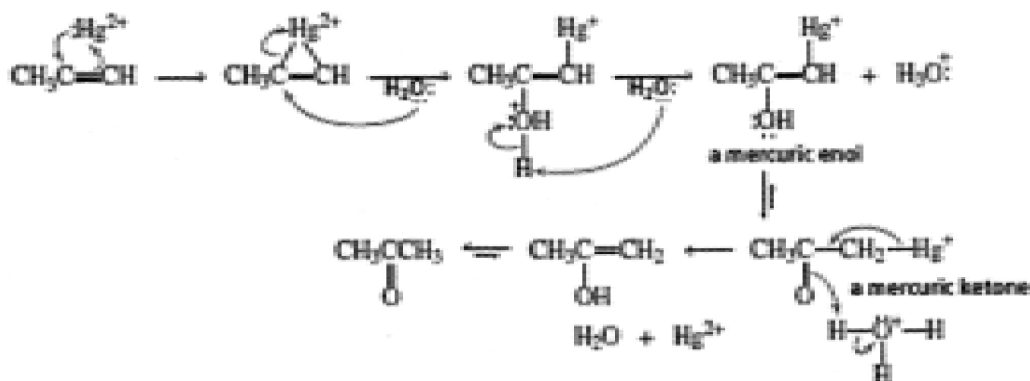
Addition of water to a symmetrical internal alkyne forms a single ketone as a product and to an unsymmetrical internal alkyne, two ketones are formed because the initial addition of the proton can occur to either of the *sp* carbons.



Terminal alkynes are less reactive than internal alkynes toward the addition of water. Terminal alkynes will add water if mercuric ion is added to the acidic mixture. The mercuric ion acts as a catalyst to increase the rate of the addition reaction.



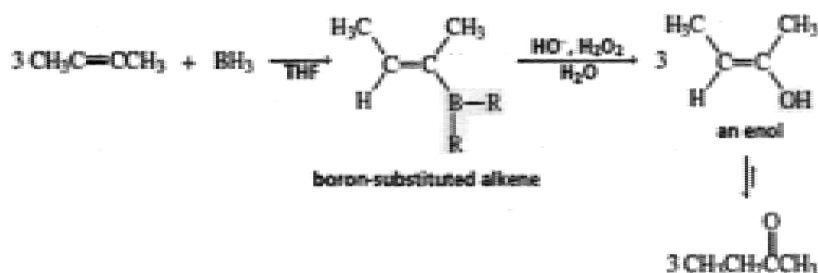
The first step in the mercuric-ion-catalyzed hydration of an alkyne is formation of a cyclic mercurinium ion similar to the cyclic bromonium and mercurinium ions formed as intermediates in electrophilic addition reactions of alkenes. In the second step of the reaction, water attacks the most substituted carbon of the cyclic intermediate. Oxygen loses a proton to form a mercuric enol, which immediately rearranges to a mercuric ketone. Loss of the mercuric ion forms an enol, which rearranges to a ketone. It is also observed that the overall addition of water follows both the general rule for electrophilic addition reactions and Markovnikov's rule. The electrophile (in the case of Markovnikov's rule) adds to the *sp* carbon bonded to the greater number of hydrogens.



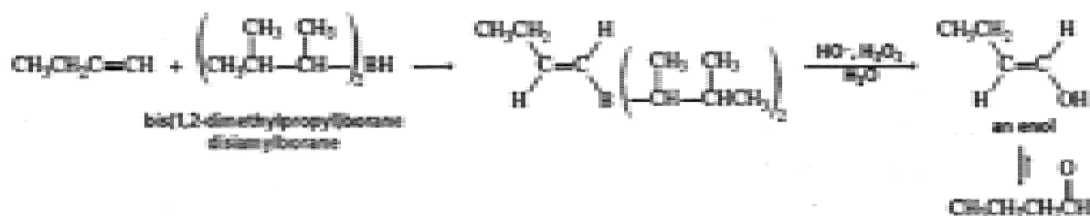
Mechanism for the  $\text{Hg}^{2+}$  ion catalysed hydration of an alkyne  
Mechanism of oxymercuration of an alkyne

### 5.8.5 Addition of Borane : Hydroboration-Oxidation

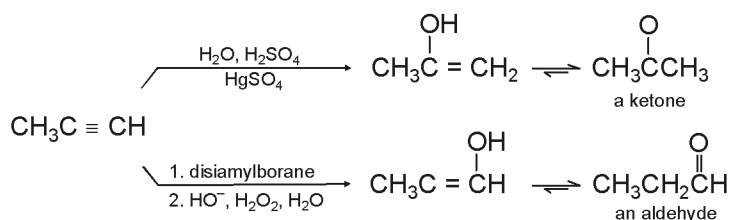
Borane adds to alkynes in the same manner it adds to alkenes. That is, one mole of reacts with three moles of alkyne to form one mole of boron-substituted alkene. When the addition reaction is over, aqueous sodium hydroxide and hydrogen peroxide are added to the reaction mixture. The end result, as in the case of alkenes, is replacement of the boron by an OH group. The enol product immediately rearranges to a ketone.



In order to obtain the enol as the product of the addition reaction, only one equivalent of can be allowed to add to the alkyne. In other words, the reaction must stop at the alkene stage. In the case of internal alkynes, the substituents on the boron substituted alkene prevent the second addition from occurring. However, there is less steric hindrance in a terminal alkyne, so it is harder to stop the addition reaction at the alkene stage. A special reagent called disiamylborane has been developed for use with terminal alkynes ("siamyl" stands for secondary iso amyl; amyl is a common name for a five-carbon fragment). The bulky alkyl groups of disiamylborane prevent a second addition to the boron-substituted alkene. So borane can be used to hydrate internal alkynes, but disiamylborane is preferred for the hydration of terminal alkynes.



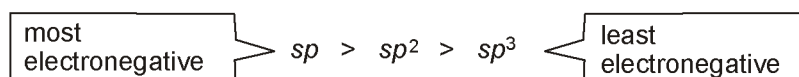
The addition of borane (or disiamylborane) to a terminal alkyne exhibits the same regioselectivity seen in borane addition to an alkene. Boron, with its electron-seeking empty orbital, adds preferentially to the *sp* carbon bonded to the hydrogen. In the second step of the hydroboration-oxidation reaction, boron is replaced by an OH group. The overall reaction is anti-Markovnikov addition because the hydrogen does not add to the *sp* carbon bonded to the greater number of hydrogens. It is to be mention that mercuric-ion catalyzed addition of water to a terminal alkyne produces a *ketone* (the carbonyl group is not on the terminal carbon), whereas hydroboration-oxidation of a terminal alkyne produces an *aldehyde* (the carbonyl group *is* on the terminal carbon).



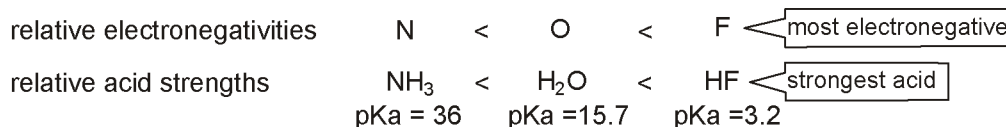
### 5.8.6 Acidity of Terminal alkynes : Hydrogen bonded to an *sp*-carbon

Carbon forms nonpolar covalent bonds with hydrogen because carbon and

hydrogen, having similar electronegativities, share their bonding electrons almost equally. However, not all carbon atoms have the same electronegativity. An  $sp$  hybridized carbon is more electronegative than an  $sp^2$  hybridized carbon, which is more electronegative than an  $sp^3$  hybridized carbon, which is just slightly more electronegative than a hydrogen.



Why does the type of hybridization affect the electronegativity of the carbon atom? Electronegativity is a measure of the ability of an atom to pull the bonding electrons toward itself. Thus, the most electronegative carbon atom will be the one with its bonding electrons closest to the nucleus. The average distance of a  $2s$  electron from the nucleus is less than the average distance of a  $2p$  electron from the nucleus. Therefore, the electrons in an  $sp$  hybrid orbital (50%  $s$  character) are closer, on average, to the nucleus than those in an  $sp^2$  hybrid orbital (33.3%  $s$  character). In turn, electrons are closer to the nucleus than  $sp^3$  electrons (25%  $s$  character). The  $sp$  hybridized carbon, therefore, is the most electronegative. The acidity of a hydrogen attached to some second-row elements depends on the electronegativity of the atom to which the hydrogen is attached. The greater the electronegativity of the atom, the greater the acidity of the hydrogen, the stronger the acid.



Because the electronegativity of carbon atoms follows the order ethyne is a stronger acid than ethene, and ethene is a stronger acid than ethane. We can compare the acidities of these compounds with the acidities of hydrogens attached to other second-row elements.

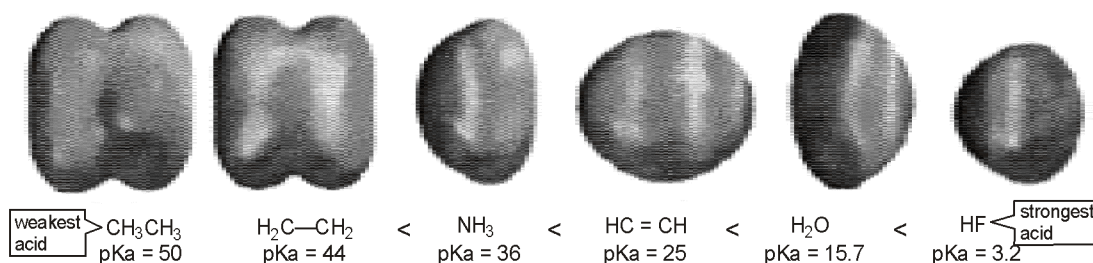
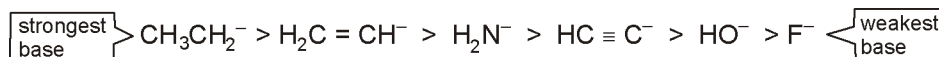


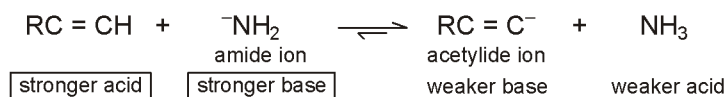
Fig-14 (a)

The corresponding conjugate bases of these compounds have the following relative base strengths because the stronger the acid, the weaker is its conjugate base.

relative base strengths

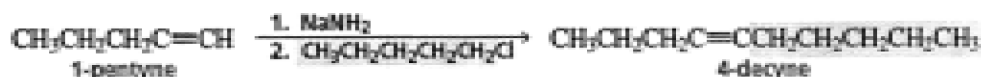
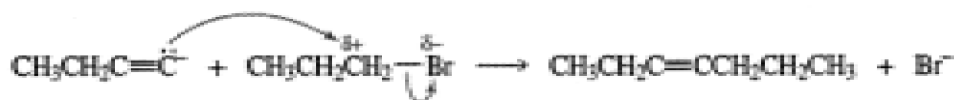


In order to remove a proton from an acid [in a reaction that strongly favors products), the base that removes the proton must be stronger than the base that is generated as a result of proton removal. In other words, you must start with a stronger base than the base that will be formed. The amide ion ( $-\text{NH}_2$ ) can remove a hydrogen bonded to an *sp* carbon of a terminal alkyne to form a carbanion called an acetylide ion, because the amide ion is a stronger base than the acetylide ion.

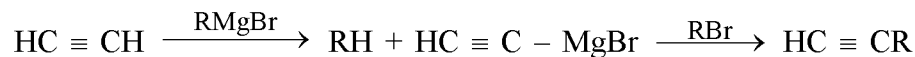


### 5.8.7 Inter-conversion of terminal and non-terminal alkynes

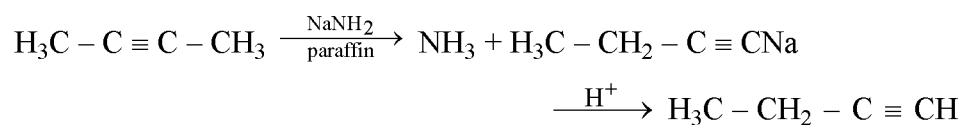
Treatment of acetylene by passing over heated sodium gives monosodium acetylide which is on treatment of alkyl halide (preferably bromide) an homologue of acetylene is produced. Simply by choosing an alkyl halide of the appropriate structure, terminal alkynes can be converted into internal alkynes of any desired chain length. Only primary alkyl halides or methyl halides should be used in this reaction.



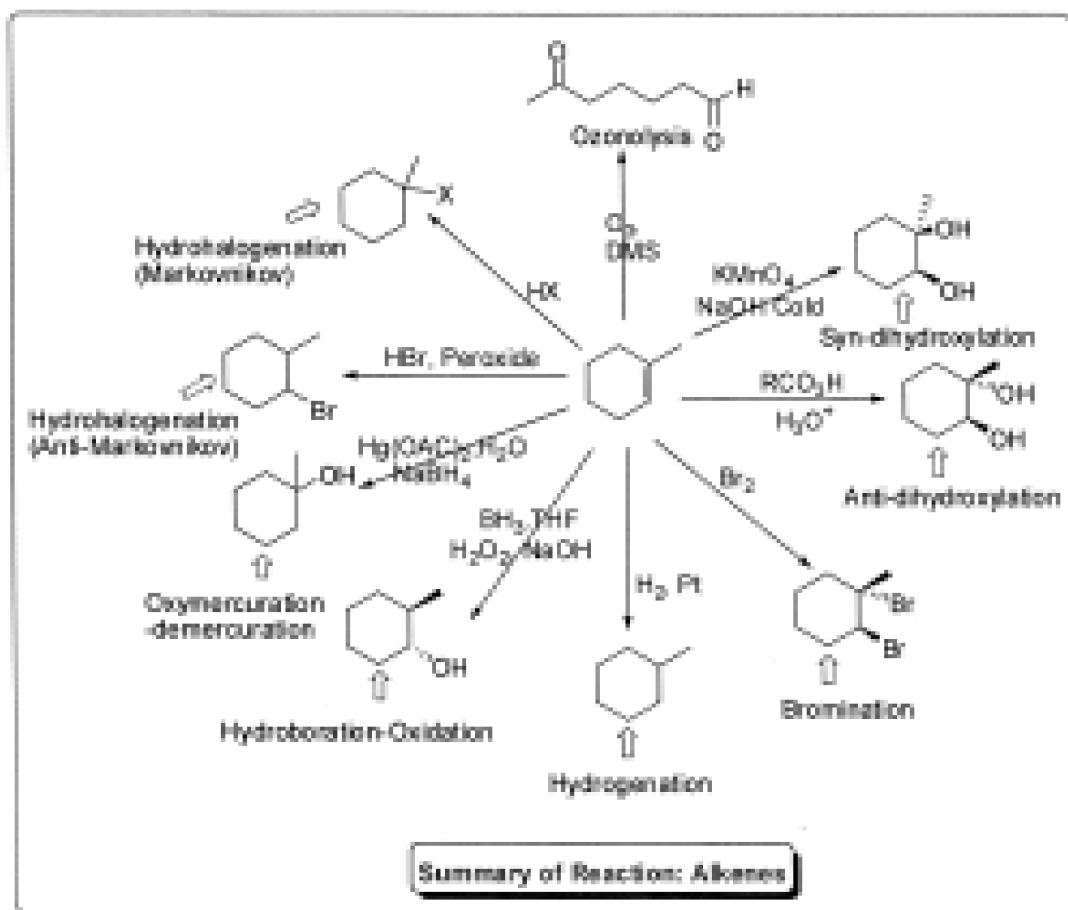
The homologues of acetylene can also be prepared by using Grignard reagents followed by the treatment of the resulting magnesium complex with an alkyl halide.



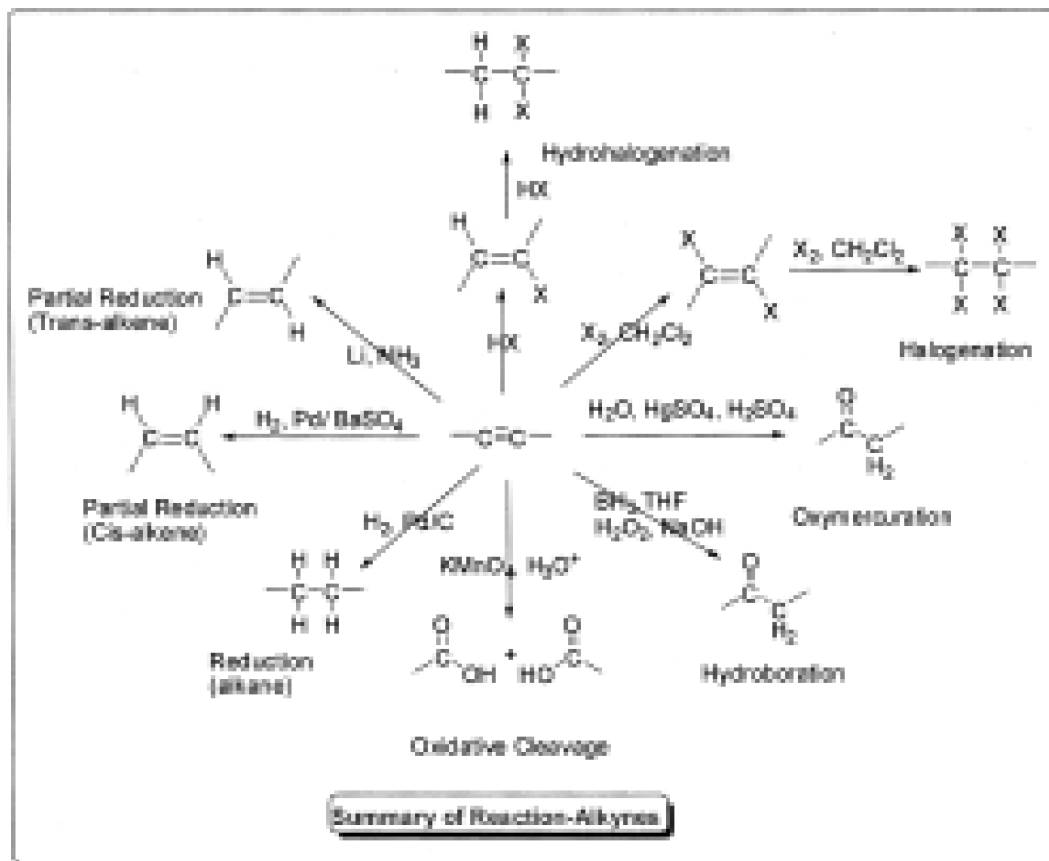
But-2-yne can be isomerised to But-1-yne when it is treated with ethanolic potassium hydroxide.



## 5.9 Summary



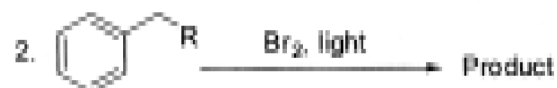
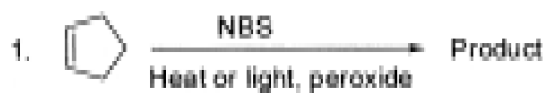


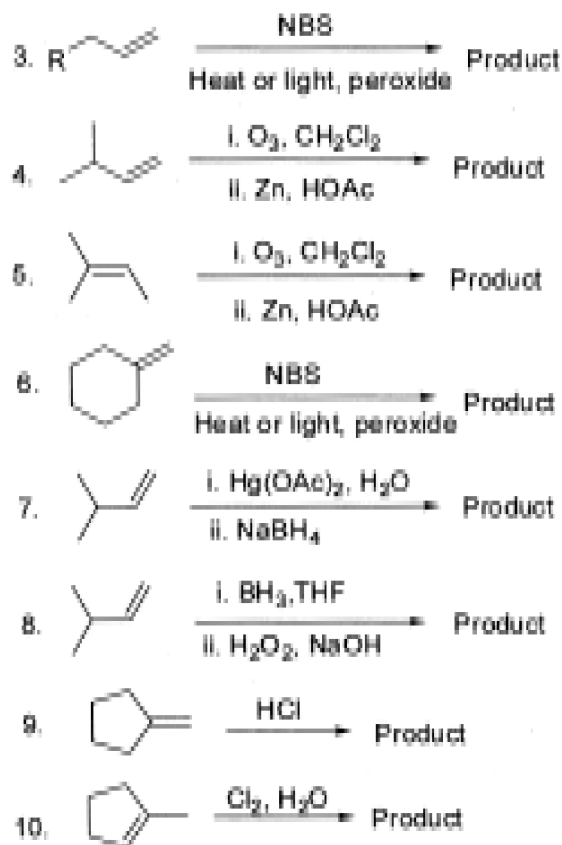


## 5.10 Model questions

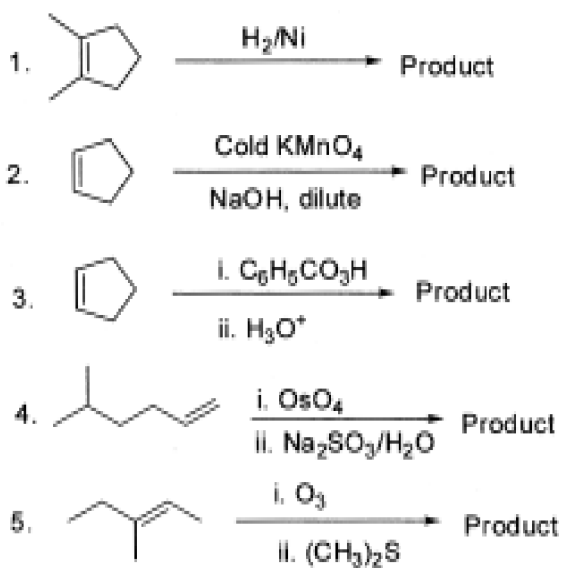
Part-A :

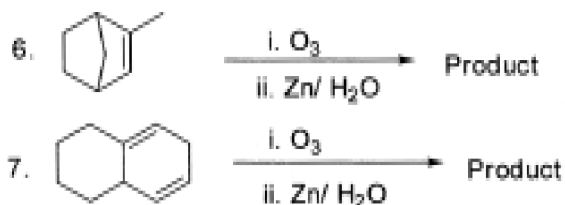
Q1. Predict the major organic product or products of the following reactions





**Q2. Predict the major product/s of the following reactions**

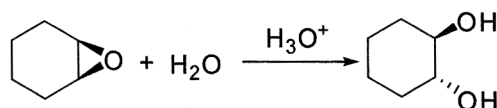




**Q3. Propose a synthetic method for preparation of compound A from compound B**



**Q4. propose a mechanism for the reaction given below-**



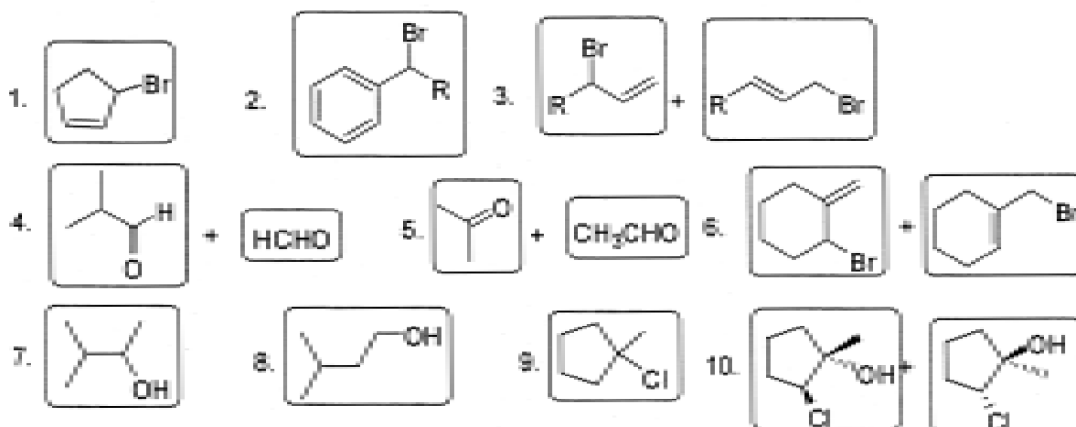
**Q5. How will you convert**

- (i) 1-Methylcyclohexene to 1-Bromo-1-methyl cyclohexane
- (ii) 1-Methylcyclohexene to 1-Bromo-2-methylcyclohexane

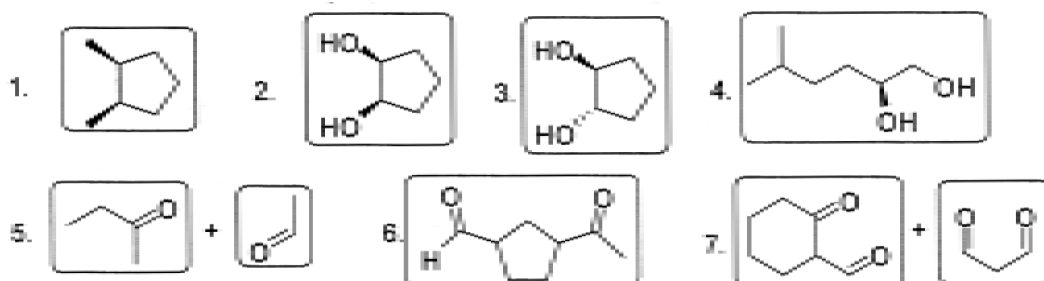
**Q6. Show the intermediate and products of the alkoxymercuration-demercuration of 1-methylcyclopentene using methanol as a solvent.**

**Q7. Explain the statement “Addition of bromine to an alkene is stereoselective and stereospecific”.**

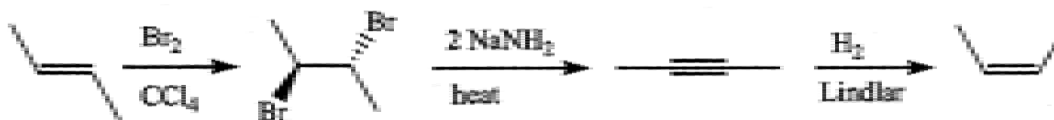
**Answer of Q1.** Predict the major organic product or products of the following reactions



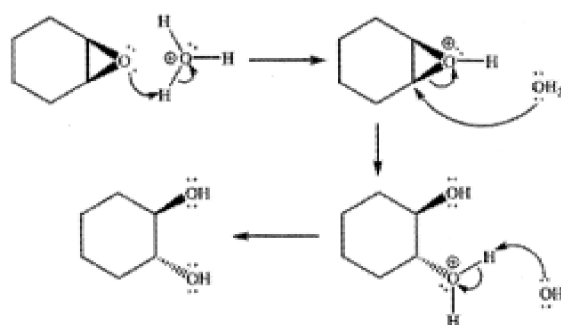
**Answer Q2.** Predict the major product/s of the following reactions



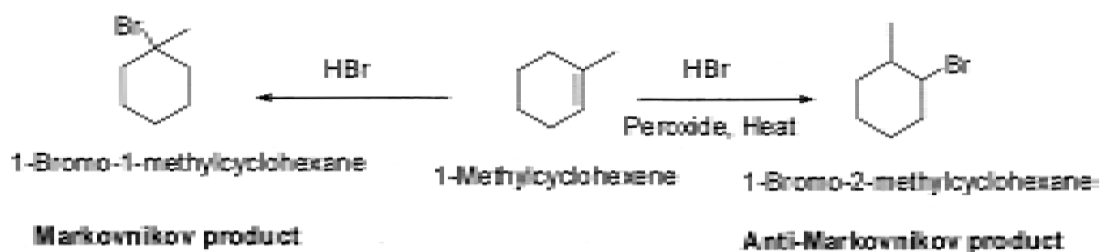
**Answer Q3.**



**Answer Q4.**

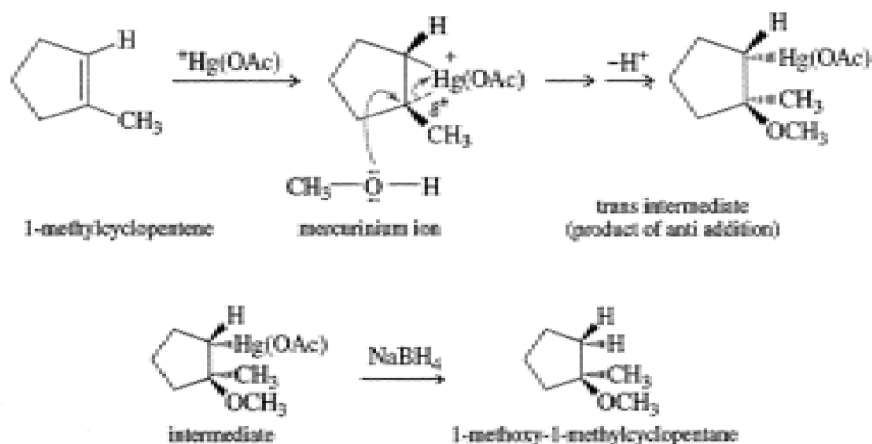


**Answer Q5.**



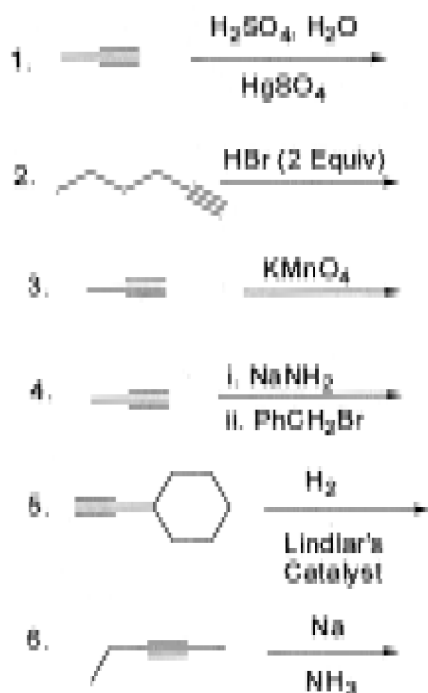
**Answer Q6.** Mercuric acetate adds to 1-methylcyclopentene give the cyclic mercurinium ion. The ion has a considerable amount of positive charge on the more

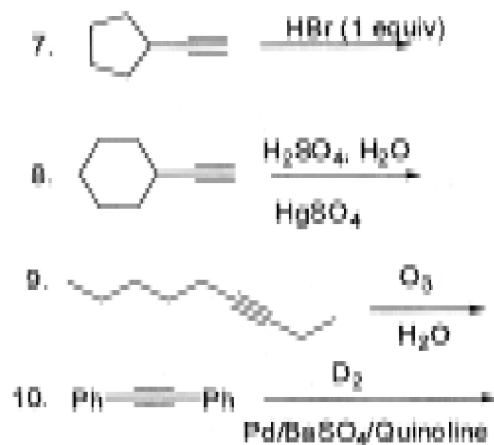
substituted tertiary carbon atom. Methanol attacks this carbon from the opposite side i.e. anti addition. Reduction of the intermediate gives the Markovnikov product, 1-methoxy-1-methylcyclopentane.



### Part-B :

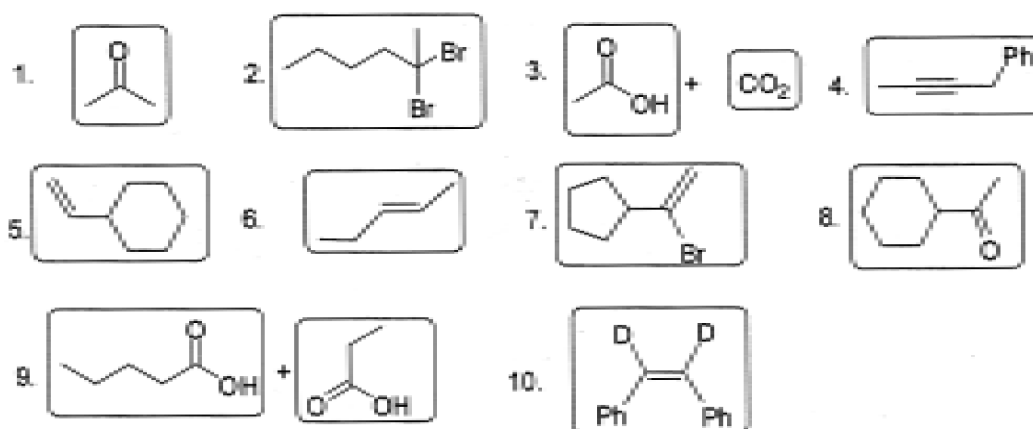
**Q1. Predict the major product of the following reactions**





**Q2.** “By using different type of hydrogenation reaction, alkyne can be converted to cis- or trans-alkene.” Justify the statement by taking suitable example.

**Answer of Q1.** Predict the major product of the following reactions



## 5.11 Reference books

- Finar, I. L. Organic Chemistry (Volume 1), Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).
- Finar, I. L. Organic Chemistry (Volume 2 : Stereochemistry and the Chemistry of Natural Products), Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).

- Norman, R.O. C., Coxon, J. M. Principles of Organic Synthesis, Third Edition, Nelson Thornes, 2003.
- Clayden, J., Greeves, N., Warren, S., Organic Chemistry, Second edition, Oxford University Press 2012.

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## **Unit - 6 □ Rearrangements**

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### **Structure**

#### **6.1 Objective**

#### **6.2 Introduction**

#### **6.3 Rearrangement of electron-deficient carbon**

##### **6.3.1 Wagner-Meerwein rearrangement**

##### **6.3.2 Pinacol Rearrangement**

##### **6.3.3 Dienone-Phenol rearrangement**

##### **6.3.4 Wolff rearrangement in Arndt-Eistert synthesis**

##### **6.3.5 Benzil-Benzilic acid rearrangement**

##### **6.3.6 Demjanov rearrangement**

##### **6.3.7 Tiffeneau-Demjanov Rearrangement**

#### **6.4 Rearrangement to electron deficient nitrogen**

##### **6.4.1 Hofmann Rearrangement**

##### **6.4.2 Curtius Rearrangement**

##### **6.4.3 Lessen Rearrangement**

##### **6.4.4 Schmidt Rearrangement**

##### **6.4.5 Beckmann Rearrangement**

#### **6.5 Rearrangement to electron-deficient oxygen**

##### **6.5.1 Baeyer-Villiger Oxidation**

##### **6.5.2 Cumene hydroperoxide-phenol rearrangement**

##### **6.5.3 Dakin Reaction**

#### **6.6 Aromatic rearrangements**

##### **6.6.1 Fries rearrangement**



- 6.6.2 Claisen rearrangement**
- 6.6.3 Hofmann-Martius rearrangement**
- 6.6.4 Fischer-Hepp rearrangement**
- 6.6.5 Bamberger rearrangement**
- 6.6.6 Orton Rearrangement**
- 6.6.7 Benzdine rearrangement**
- 6.7 Rearrangement reactions by green approach**
  - 6.7.1 Fries rearrangement**
  - 6.7.2 Claisen rearrangement**
  - 6.7.3 Beckmann rearrangement**
  - 6.7.4 Baeyer-Villiger oxidation**
- 6.8 Summary**
- 6.9 Additional Problems**
- 6.10 Reference books**

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## **6.1 Objective**

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In this unit we will learn about the following

- The mechanisms and synthetic application of rearrangement reactions involving electron deficient atoms.
- Reaction involving the rearrangement to electron-deficient carbon.
- Reaction involving the rearrangement to electron-deficient nitrogen.
- Reaction involving the rearrangement to electron-deficient oxygen.
- Reaction involving the migration of group from nitrogen to ring carbon.
- Aromatic rearrangements involving migration from oxygen to ring carbon.
- Rearrangements involving migration from nitrogen to ring carbon.

- Some rearrangement reactions involving green approach.

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## 6.2 Introduction

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Rearrangement in Organic Chemistry refers to a vast array of chemical reactions where the carbon structure of the molecule is rearranged to make way for the structural isomer of the original molecule. However, a rearrangement may refer to a multi-step reaction including migration of Hydrogen or H atoms or a larger molecular fragment forming one of its steps. Rearrangements in organic chemistry occur to give the more stable tertiary carbocation which is then attacked by the nucleophile. Here we will discuss some reactions involving molecular rearrangements.

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## 6.3 Rearrangement of electron-deficient carbon

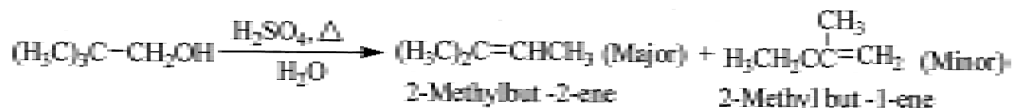
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In the first half of the nineteenth century it was generally believed that reactions of organic compounds proceeded with minimal structural change. This tenet simplified the elucidation of the numerous substitution, addition and elimination reactions that characterized the behaviour of common functional groups. However, subsequent discoveries showed that nature was not always so obliging, leaving chemists and chemistry students to grapple with the possibility of deep seated structural change occurring during certain reactions. A large number of these structural rearrangements are triggered by intermediates incorporating positively charged or electron deficient atoms, which in the case of carbon are carbocations. Two such examples, already noted, are the addition of HCl to 3, 3-dimethyl-1-butene and forced hydrolysis of neopentyl bromide. Now, we will discuss other cases of this intriguing group of transformations.

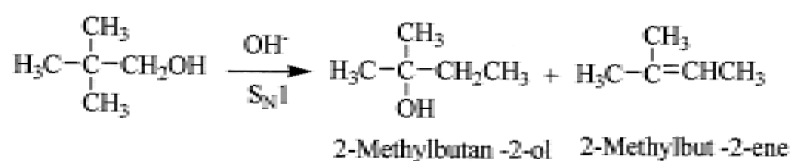
### 6.3.1 Wagner-Meerwein rearrangement

The reaction involving the change of carbon skeleton by the rearrangement of carbocation intermediate is known as Wagner-Meerwein rearrangement.

When alcohols having no  $\alpha$ -hydrogen are heated with  $\text{H}_2\text{SO}_4$ , dehydration and molecular rearrangement takes place, e.g. when neopentyl alcohol is heated with  $\text{H}_2\text{SO}_4$  mixture of alkenes are formed by the dehydration and subsequent rearrangement.

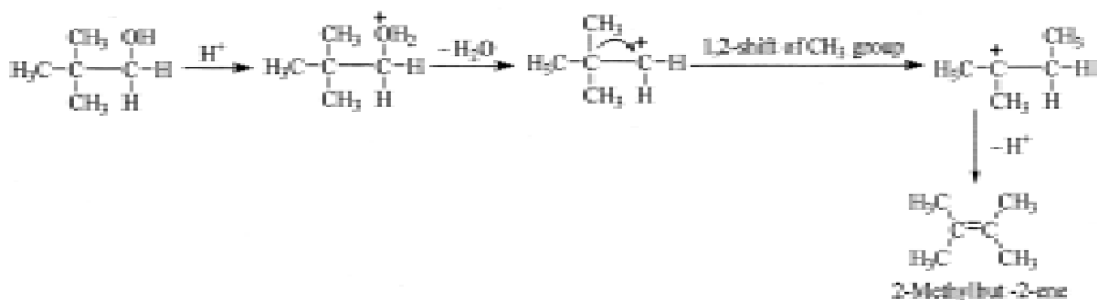


Similarly, when neopentyl bromide is hydrolysed under  $\text{S}_{\text{N}}1$  pathway it is observed that instead of expected neopentyl alcohol, 2-methyl butan-2-ol and 2-methyl but-2-ene are formed.

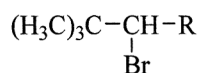


G. Wagner and H. Meerwein proposed the ionic nature of this type of reaction and explained that an initial carbocation is formed and if it is less stable then rearrangement to more stable carbocation via 1, 2-shift of an adjacent carbon-carbon bond occur immediately. This shift may be 1, 2-shift of a carbon-carbon bond of a cyclic system, an alkyl group or an aryl group.

**Mechanism :** It takes place through 1, 2-shift pathway.

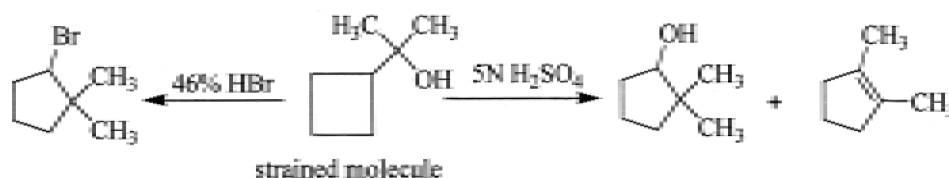


Rearrangement does not occur if the initially formed carbocation can be stabilized by other factors, e.g.



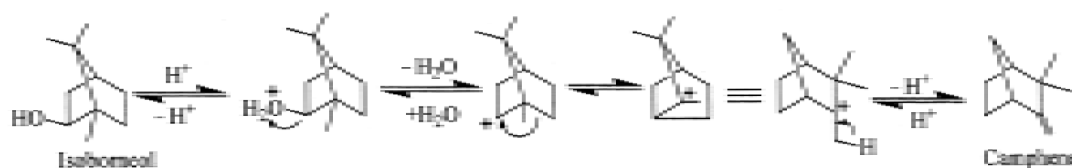
If  $\text{R} = \text{CH}_3$  rearrangement occurs with  $\text{S}_{\text{N}}1$  but if  $\text{R} = \text{Ph}$  only  $\text{S}_{\text{N}}1$  product obtained without rearrangement since benzyl carbocation is more stable than tertiary carbocation.

Stability of carbocation is not only the driving force for the molecular rearrangement. Sometimes angle strain, torsional strain or steric crowding is relieved by migration of an alkyl or aryl group to a new carbocation site.



In the above case, though a 3° carbocation is formed initially but ring expansion taken place by migration of methylene group to a 2° carbocation to relieve off the angle strain and torsional strain.

Rearrangement in the acyclic system may involve migration of ring methylene group resulting in the ring expansion and contraction.



Other examples are conversions of camphene hydrochloride to isobornyl chloride, bornyl chloride to camphene and pinene hydrochloride to bornyl chloride.

The migrating group besides being alkyl and ring methylene groups may be hydride group or aryl group. The aryl group migrates faster than alkyl group. Electron releasing group in the aryl group increases the rate of migration while electron withdrawing group decreases the rate of migration. Thus, elimination is many times faster in neophyl bromide than in neopentyl bromide.

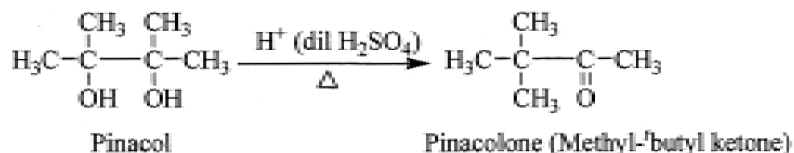
### Synthetic Application :

This rearrangement is used for ring expansion or ring contraction. They are used for commercial synthesis of camphor from  $\alpha$ -pinene and preparation of santene from camphene. This rearrangement also finds application in steroid chemistry.

### 6.3.2 Pinacol Rearrangement

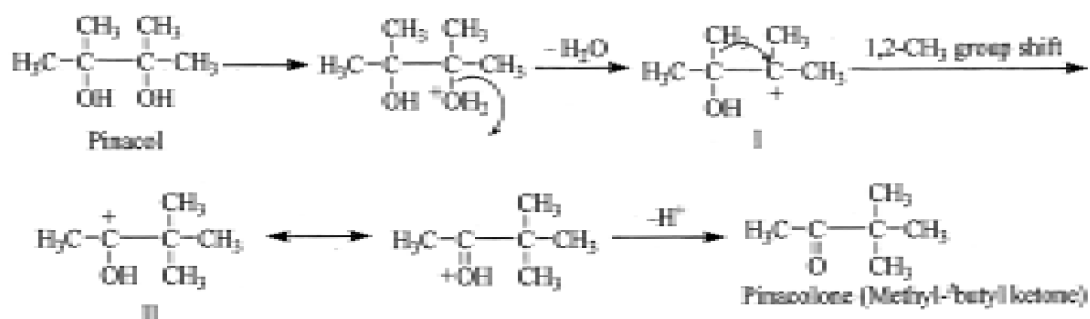
Acid catalysed rearrangement of vicinal diols (1, 2-diols) to ketones or aldehydes

with elimination of water is known as pinacol-pinacolone rearrangement. The name came from the classical example of the conversion of pinacol to pinacolone.



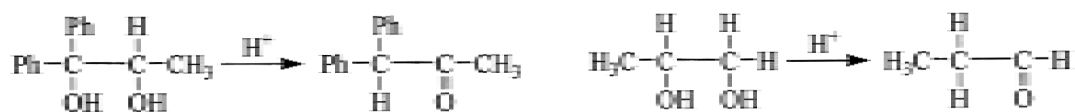
The migrating group may be alkyl, aryl, hydrogen and even ester function and the catalyst is either mineral acids (dilute  $\text{H}_2\text{SO}_4$  or  $\text{H}_3\text{PO}_4$ ) or Lewis acids ( $\text{AlCl}_3$ ,  $\text{BF}_3$ ,  $\text{ZnCl}_2$ ) or any electrophilic reagent ( $\text{PCl}_5$ ).

**Mechanism :** This is also an example of rearrangement to electron deficient carbon i.e. carbocation rearrangement where the driving force is the lone pair of oxygen atom of vicinal hydroxyl group. First step is the addition of proton from acid to the hydroxyl group and elimination of water to form carbocation (I). Next step is the stabilisation of the carbocation by Whitemore 1, 2-shift. Final step is the elimination of proton from the stable carbocation (II) to form the carbonyl compound. Due to resonance stability the carbocation (II) is more stable than carbocation (I).

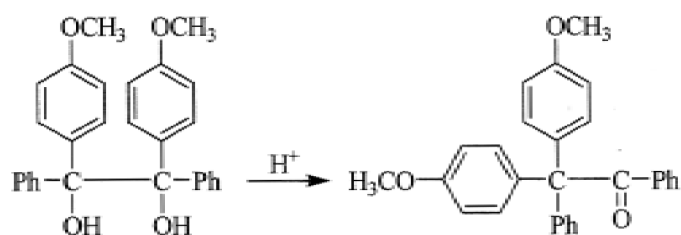


The loss of water and migration of alkyl group takes place simultaneously. The reaction is intramolecular which can be proved by (i) taking chiral migrating group and (ii) crossover experiment. When chiral migrating group is taken it retains its configuration and in crossover experiment no crossover product is formed.

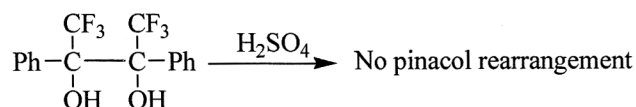
**Migratory aptitude :** Migration order in general is  $\text{H} > \text{aryl} > \text{alkyl}$ .



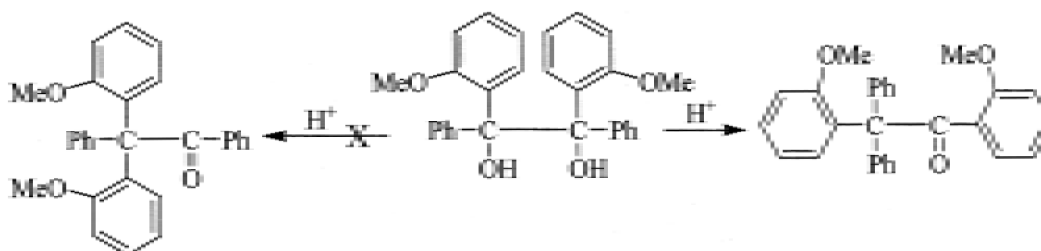
As the migrating group migrates with its electron pair, the more electron rich group might be expected to migrate. Thus, the order of migratory aptitude is p-anisyl > p-tolyl > phenyl > p-chlorophenyl, etc. The order of migration amongst the alkyl group is  $\text{Me}_3\text{C} > \text{Me}_2\text{CH} > \text{Me}$ . However, the stability of the initially formed carbocation may offset the migratory aptitude order.



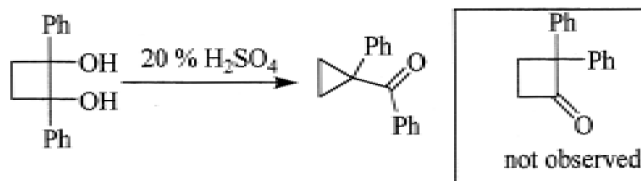
Electron withdrawing groups will retard the migration and sometimes do not undergo pinacol rearrangement. In the following example, the  $-\text{CF}_3$  group being powerful inductive electron withdrawal group inhibits positive charge formation, i.e., the resulting carbocation intermediate would be extremely unstable.



Steric factor affect the rate of migration and also plays deciding role in the product formation. p-Anisyl group migrates 1000 times faster than o-anisyl group.

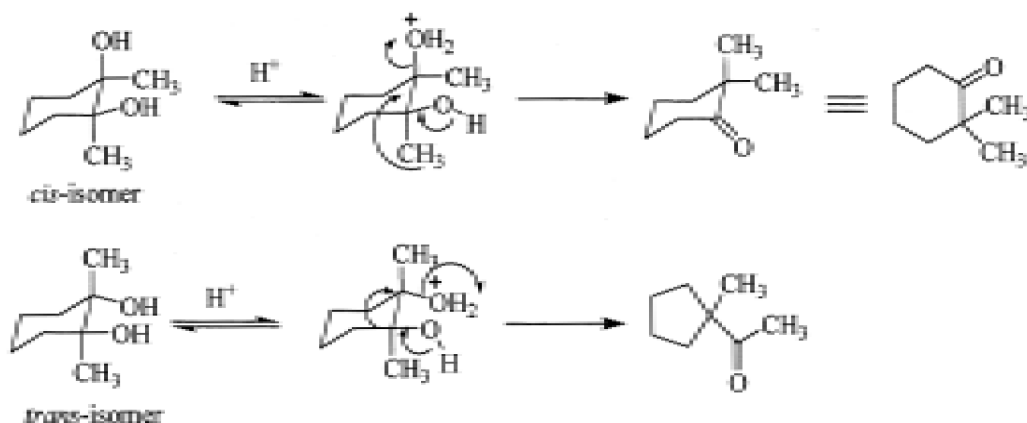


In the above case phenyl migration takes place instead of o-anisyl group though the later has greater migratory aptitude. If o-anisyl migration takes place than it would have produced large steric hindrance in the desired product.



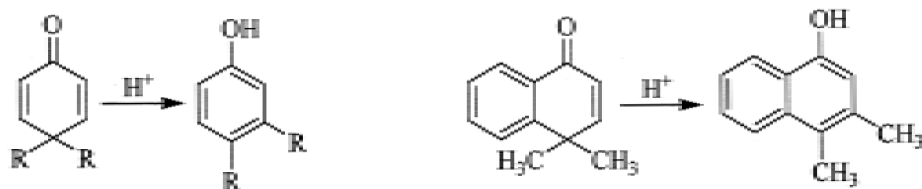
Sometimes ring strain is not the controlling factor for migration of group. In the above example, migration of ring methylene group takes place instead of phenyl group though it has higher migratory aptitude. The reason is that, the carbocation formed by phenyl group migration is as strained as its precursor, whereas the shift of a ring methylene group generates an unstrained cation stabilized by phenyl and oxygen substituents. Conjugative stabilization of the phenyl ketone and absence of  $sp^2$  hybridized carbon atoms in the small ring may also contribute to the stability of the observed product.

The most favourable stereochemistry for pinacol rearrangement is that the migrating group and the leaving group are aligned in an anti-periplanar arrangement. Thus the *cis* form of 1, 2-dimethyl cyclohexane-1, 2-diol undergoes the pinacol rearrangement easily in dilute  $H_2SO_4$  with migration of methyl group whereas the *trans* derivative undergoes rearrangement under similar condition with contraction of the ring.

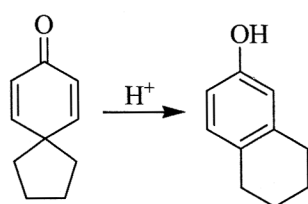


### 6.3.3 Dienone-Phenol rearrangement

When 4, 4-dialkyl cyclohexadienone is treated with acid, it is converted to phenol with shift of one of the alkyl groups to the adjacent carbon. This is known as dienone-phenol rearrangement. The term 'dienone-phenol rearrangement' was introduced by A. L. Wilds and C. Djerassi. The reaction is carried out using  $H_2SO_4$  in acetic acid or in acetic anhydride medium. This rearrangement reaction is exothermic because of formation of most stable aromatic moiety.

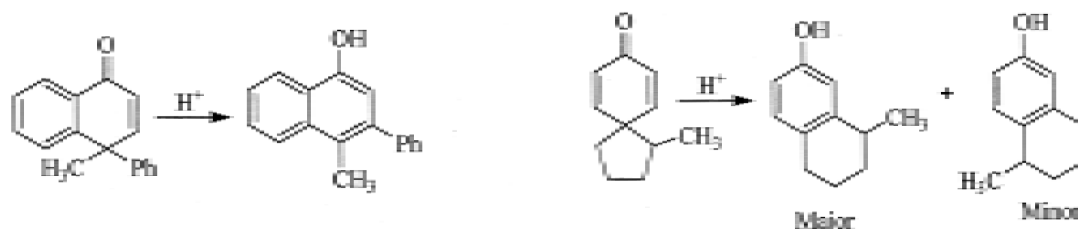


When one of the alkyl group forms a part of the cyclic system, either the alkyl group or the ring methylene group may migrate.

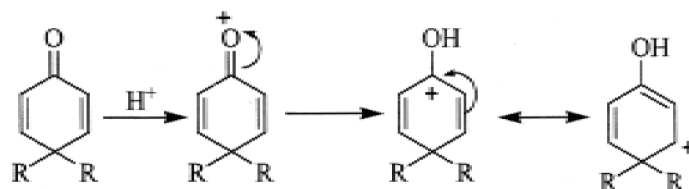


When there is a choice of migrating group, usually more electron rich group migrates.

#### Mechanism :

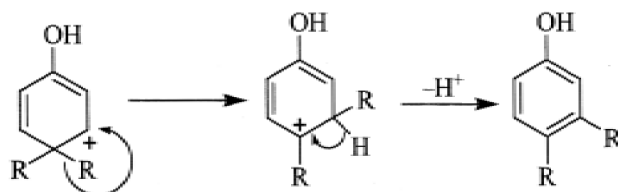


Initially proton adds to oxygen atom to generate a carbocation, which is stabilized by delocalization.



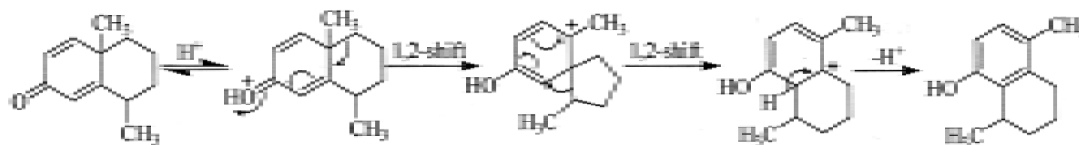
In one of the canonical structures, the positive charge is on a carbon adjacent to a highly substituted carbon. Hence, a carbocation rearrangement occurs. Subsequent loss of a proton gives the 3, 4-disubstituted phenol.



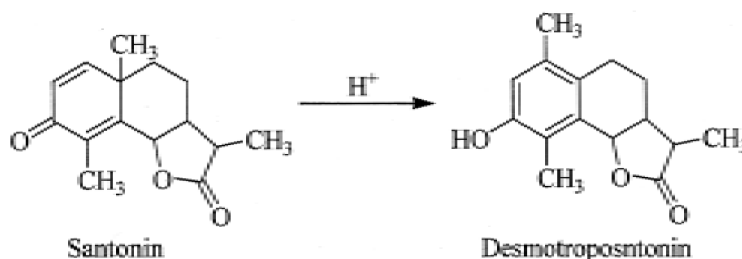


The driving force for dienone-phenol rearrangement is due to the formation of a stable aromatic moiety.

In certain cases, the formation of the product may involve two consecutive 1, 2-shift as shown below.

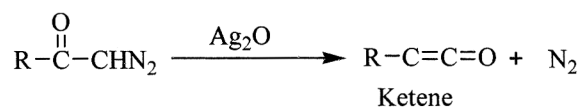


**Applications :** A good application of the reaction is the conversion of santonin to desmotroposantonin.



### 6.3.4 Wolff rearrangement in Arndt-Eistert synthesis

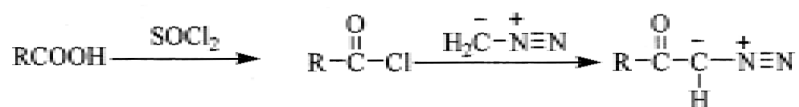
The conversion of  $\alpha$ -diazoketones into ketens is called Wolff rearrangement,  $\alpha$ -diazoketones on treatment with solid silver oxide split of nitrogen and rearrange to ketene. Freshly prepared  $\text{PhCO}_2\text{Ag}$  is also a best catalyst for this reaction. These ketenes are highly reactive and cannot be isolated. They can be converted to other products *in situ*. The rearrangement may also occur on irradiation or on heating or by transition metal catalysis.



When the reaction is carried out in presence of water, the highly reactive ketene readily reacts with water to give carboxylic acids of next higher homologue from where the  $\alpha$ -diazoketone is prepared. This reaction sequence, which first showed the synthetic potentiality of Wolff-rearrangement, was developed by Arndt and Eistert.



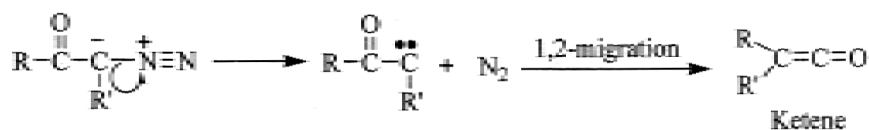
$\alpha$ -Diazoketone are normally prepared by reacting acid chloride with excess of diazomethane. This acid chloride can be prepared from corresponding acid on treatment with thionyl chloride.



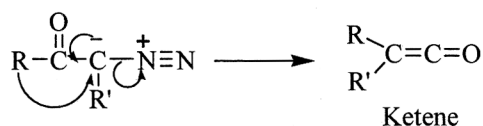
Wolff rearrangement involves the migration of an alkyl or aryl group. When the migrating group contains a stereocentre, the configuration is retained after the migration. Cyclic diazoketones undergo ring-contraction, and the method can be utilized to prepare the smaller strained ring systems.

### Mechanism :

Formation of ketene can take place either by stepwise process or by concerted process. The general consensus that has emerged is that a carbene is generated in photochemical reactions and under thermal condition the reaction can be concerted as well as stepwise. Concerted mechanism supports the retention of the configuration of the migration of a group with stereocentre.



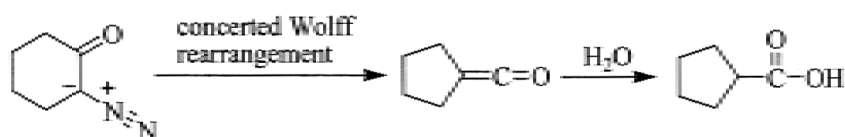
#### Stepwise mechanism or carbene mechanism



#### Concerted mechanism

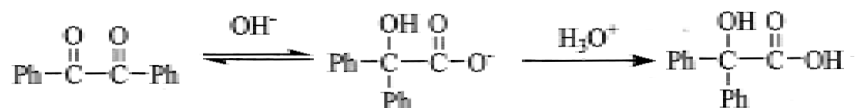
### Applications :

Arndt-Eistert homologation utilizes Wolff rearrangement in which an acid is converted to its next higher homologue. Various classes of diazoketones may be prepared to give varied types of acid derivatives for further synthetic application. Cyclic diazoketones undergo ring-contraction, and the method can be utilized to prepare the smaller strained ring systems.

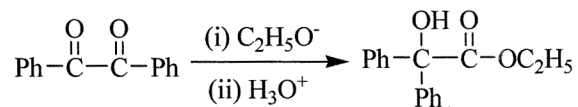


### 6.3.5 Benzil-Benzilic acid rearrangement

$\alpha$ -Diketone on treatment with strong base undergo rearrangement to give  $\alpha$ -hydroxy acids. For example, when benzil is treated with sodium hydroxide it gives sodium salt of benzilic acid which on acidification gives benzilic acid. Since the initial investigations of the reaction were carried out on benzil and the product is benzilic acid, the name of the rearrangement is given benzilic acid rearrangement.



The driving force for the reaction is the formation of carboxylate ion. Barium and thallos hydroxides are more effective than sodium or potassium hydroxides. Alkoxide ions in place of hydroxide ion give the corresponding esters.



Phenoxide ions are too weak a nucleophile to attack. The reaction takes place with both aliphatic and aromatic  $\alpha$ -diketones. Usually diaryl diketones give excellent yield but  $\alpha$ -diketones that have enolisable  $\alpha$ -protons give low yields due to competing aldol condensation reactions. When benzilic acid rearrangement is carried out with mixed  $\alpha$ -diketone having an aryl and an alkyl groups, the major product is formed by the migration of the aryl ring. When two different aryl groups are available, the major product usually results from the migration of aromatic ring having more powerful electron withdrawing group.

**Mechanism :**

In 1928 Ingold proposed the mechanism of this rearrangement shown below. This is today supported by experimental evidence.

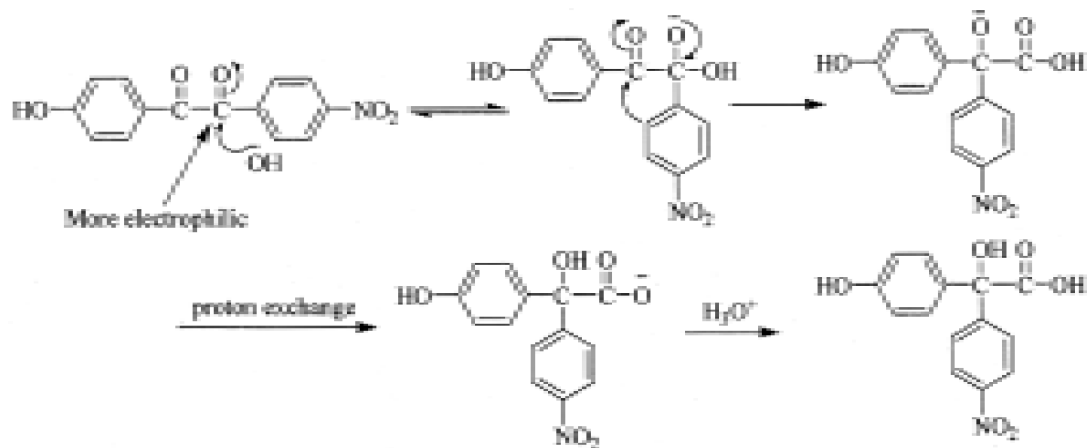


The reaction is second-order each in benzil and in base.

$$\text{Rate} \propto [\text{benzil}] [\text{OH}^-]$$

Roberts and Urey carried out the rearrangement with H<sup>18</sup>O<sup>-</sup> and found that the label was incorporated into unreacted benzil at a faster rate than the rate of rearrangement. Thus the first step must be rapid and reversible. Hence first step is not the rate determining step. When the reaction is carried out in the presence of OD<sup>-</sup>, it has been found that there is no deuterium isotope effect. This confirmed that third step is also not the rate determining step. By elimination, that leaves the migration step is the rate determining step.

An interesting aspect of this rearrangement is that aryl group with lower electron donating ability usually migrates. For example, when aryl group contains strong electron withdrawing group then its migratory aptitude increases which is in contrary to migratory aptitude of aryl group in pinacol-pinacolone rearrangement where electron releasing group migrates preferentially. The reason is that the initial attack by hydroxide or alkoxide ion takes place on that carbonyl group of the  $\alpha$ -diketone which is more electrophilic. Consequently, the resultant alkoxide ion then pushes the specific aryl group on that carbon to the adjacent carbonyl carbon resulting in a 1, 2-shift.

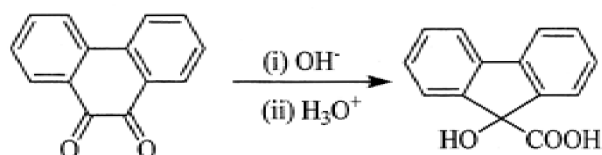


Benzilic rearrangement is analogous to intramolecular Cannizzaro reaction of glyoxal.

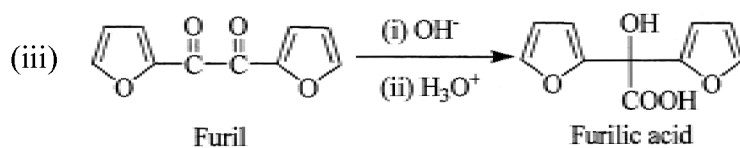
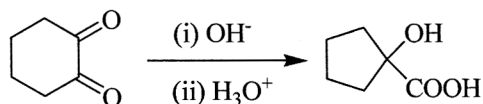
### Applications :

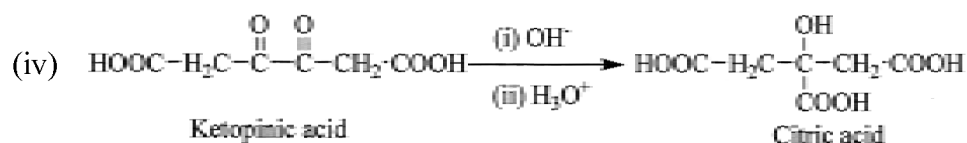
The reaction is a general one and can take place with aromatic, heterocyclic, alicyclic and aliphatic 1, 2 diketones as also 1, 2-quinones.

- (i) Cyclic 1, 2-diketones can undergo the benzilic rearrangement with ring contraction, e. g. Phenanthraquinone gives 9-hydroxyfluorene-9-carboxylic acid.



- (ii) Similarly, the acyclic cyclohexane -1, 2-dione gives 1-hydroxycyclopentane carboxylic acid.

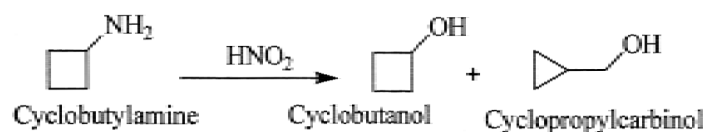




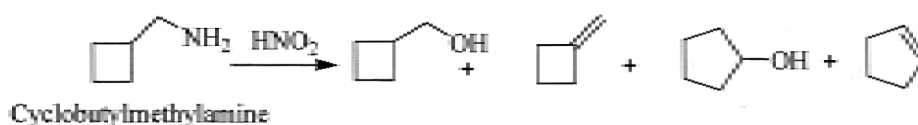
### 6.3.6 Demjanov rearrangement

When 1, 2-migration is initiated through formation of carbocation by diazotisation of primary amine, the reaction is termed Demjanov rearrangement. Actually, Demjanov rearrangement is conversion of primary amines to alcohols by reacting with  $\text{HNO}_2$ . Cyclic primary amines like aminomethylcycloalkanes usually undergo this type of reaction. Both ring expansion and ring contraction occurs in this reaction. Particularly this reaction is useful for the ring expansion of acyclic ring by one carbon atom.

When cyclobutylamine is treated with  $\text{HNO}_2$ , it gives a mixture of cyclobutanol and cyclopropylcarbinol. Cyclopropylcarbinol is formed by ring contraction.

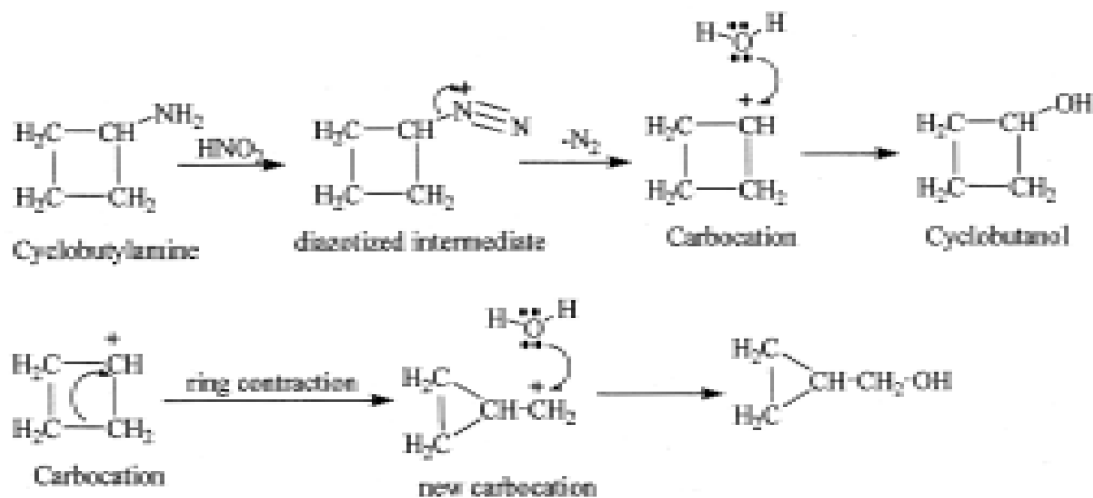


When the same reaction is carried out with cyclobutylmethyl amine, ring expansion of Demjanov rearrangement takes place. Other side products like cyclobutylcarbinol, methylenecyclobutane and cyclopentene are also formed in this reaction.

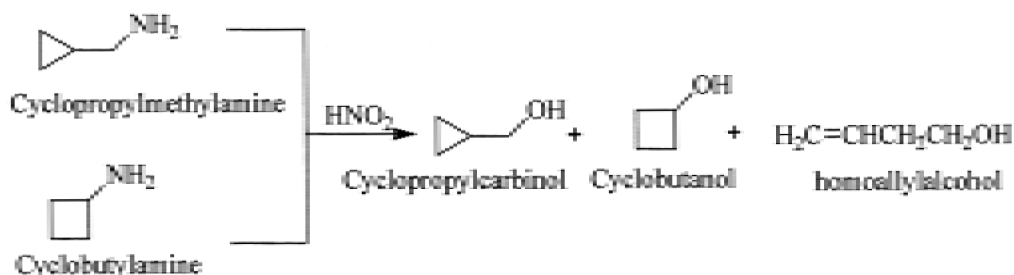


#### Mechanism :

First step is the formation of diazonium ion from the amine. Next, a carbocation is formed by the loss of nitrogen from the diazotized intermediate. This carbocation may undergo rearrangement through ring expansion as well as ring contraction.



This is to note that both cyclopropylmethylamine and cyclobutylamine give similar mixture of products when treated with nitrous acid.

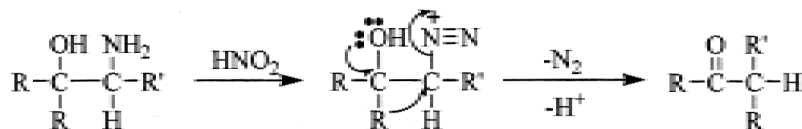


The results showed that the reaction products originate from common intermediates and can be explained on the basis of carbocation formed from each substrate molecule equilibrates rapidly with the other carbocations through which the same mixture of products are formed.

### 6.3.7 Tiffeneau-Demjanov Rearrangement

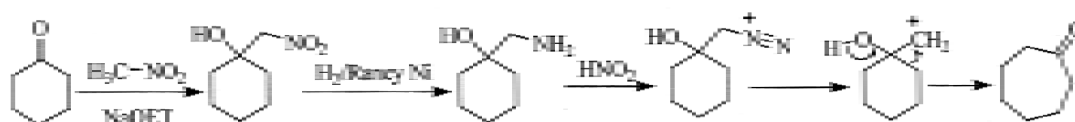
Treatment of  $\beta$ -aminoalcohol with  $\text{HNO}_2$  to synthesize carbonyl compound is known as Tiffeneau-Demjanov Rearrangement. The reaction is also known as 'Semipinacol rearrangement' and is very useful for homologating cyclic ketones by the use of nitromethane or diazomethane. This reaction is applicable to those cyclic ketones which contain three to seven carbons in the ring of the substrate.

The reaction is normally carried out under very mild conditions and that reduces the possibility of any subsequent rearrangements.

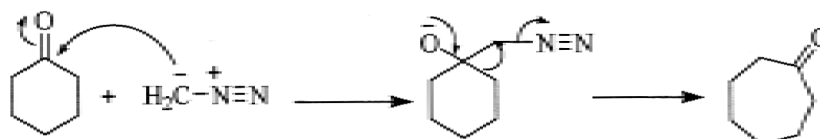


Although the mechanism has been shown to be concerted, the formation of discrete carbocation intermediate is not ruled out.

The Tiffeneau-Demjanov rearrangement is often used to transform a cyclic ketone into a homologue that is one ring size larger. Homologation of cyclic ketone with nitromethane takes place as follows.



Homologation of cyclic ketone with diazomethane takes place as follows.



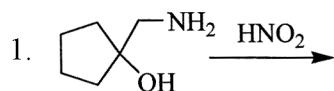
If a chiral group is present then retention of configuration occurs after rearrangement.

#### Applications :

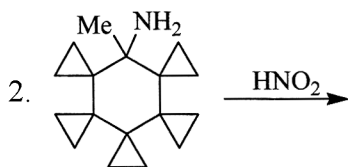
- (i) Demjanov rearrangement is useful for the formation of alcohol from amine.
- (ii) Particularly this reaction is useful for the ring expansion of acyclic ring by one carbon atom.
- (iii) Tiffeneau-Demjanov rearrangement is often used to transform a cyclic ketone into a homologue

#### Try the following Questions :

- (a) Write down the products with mechanism.





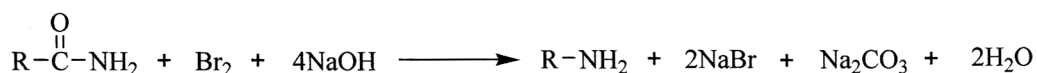


## 6.4 Rearrangement to electron deficient nitrogen

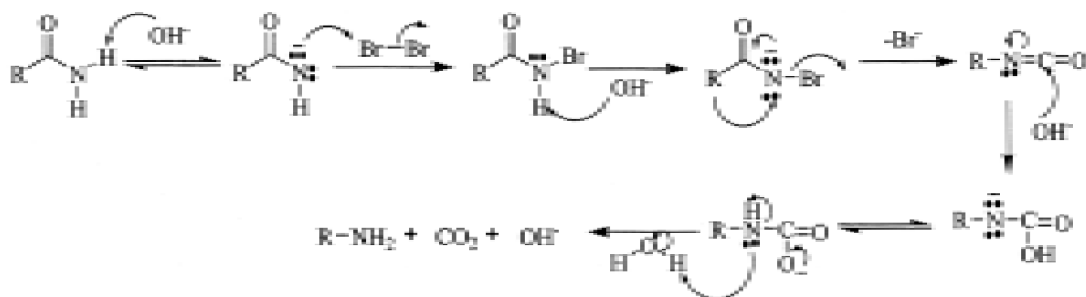
A number of rearrangements of great preparative value involve migration to nitrogen. Hofmann and Curtius rearrangements belong to this category. The driving force for these rearrangements is also an electron deficient atom but because of the trivalency of nitrogen, the course of the reaction is somewhat different from the rearrangements you have studied so far. These are discussed below.

### 6.4.1 Hofmann Rearrangement

The conversion of a primary carboxamide to the corresponding amine with one carbon less is known as Hofmann rearrangement, also known as Hofmann reaction or Hofmann degradation. The reaction is carried out under heating condition at 70-80° C in presence of alkaline hypobromite or hypochlorite. Secondary and tertiary amides do not undergo Hofmann rearrangement.



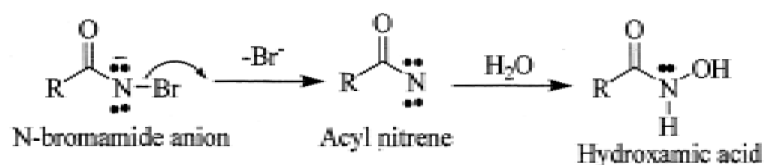
**Mechanism :**



First step is the formation of N-bromamide by the usual reaction of hypobromite

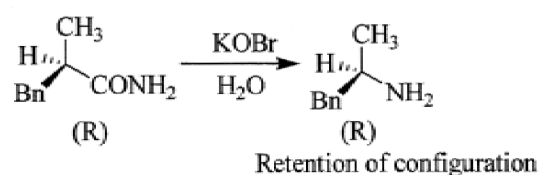
on primary amines. In the next step, N-bromamide is deprotonated by the base to the corresponding alkali salt which is quite unstable and quickly undergoes a concerted rearrangement to the isocyanate. This isocyanate then reacts with water to give carbamic acid which spontaneously eliminates carbon dioxide to yield the amine.

It was previously thought that Hofmann rearrangement occurs through a carbonylnitrene intermediate. But, carbonylnitrene, if formed, would give a hydroxamic acid by reaction with water through  $\alpha$ -addition. But such compounds have never been isolated during Hofmann rearrangement.



Hence, the loss of Br and the migration of R in N-bromamide anion is suggested to be concerted. Since no cross-over products are obtained when two different amides are rearranged, it is assumed that the rearrangement is intramolecular and the migrating group never completely separates during the migration. Had the reaction been intermolecular then there would have been cross-products.

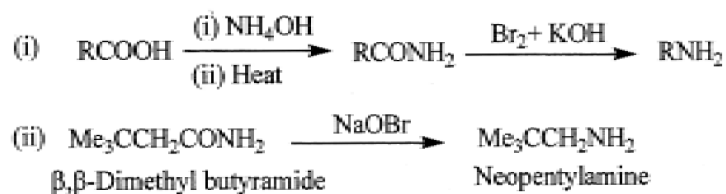
Studies of Hofmann rearrangement of optically active amides in which the chiral carbon is directly attached to the carbonyl group have shown that these reactions occur with retention of the configuration. For example, when optically active  $\alpha$ -benzylpropionamide undergoes Hofmann rearrangement,  $\alpha$ -benzylamine having the same configuration is formed.



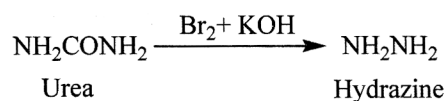
Rate of this rearrangement reaction increases when the migrating group is more electron donating and decreases when electron withdrawing.

### Applications:

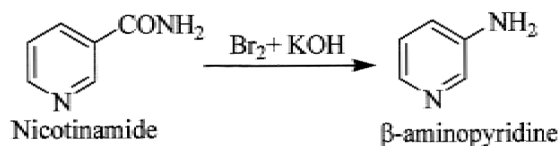
1. Formation of amines: It is very useful method for the preparation of amines.
  - (a) Acids and amides to amines.



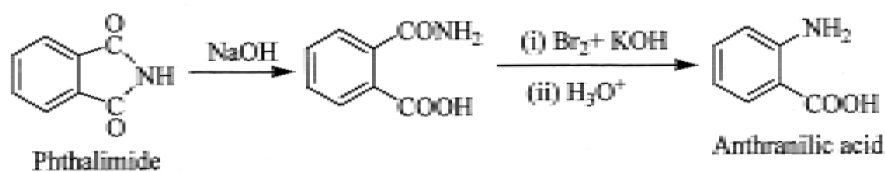
(b) Urea gives the valuable reagent hydrazine.



2. Preparation of  $\beta$ -aminopyridine from nicotinamide.

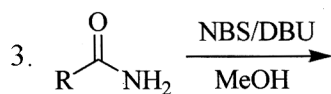
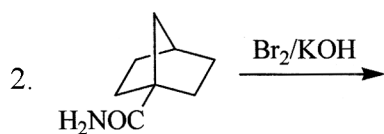
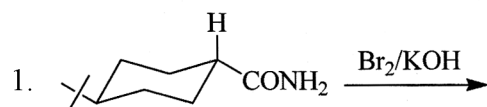


3. Synthesis of amino acids.



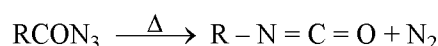
**Try the following Questions :**

Write down the products with mechanism.



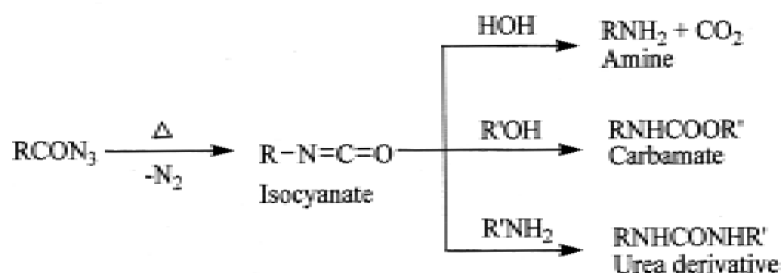
### 6.4.2 Curtius Rearrangement

The thermal or photochemical rearrangement of acyl azides to isocyanates was discovered by Curtius and it provides the means for degrading a carboxylic acid to a primary amine containing one less carbon atom. These isocyanates can be isolated if the reaction is carried out in an inert solvent (e.g. chloroform, benzene etc.)



The acyl azides are usually prepared either by the reaction of sodium azide with a reactive acylating agent or by diazotization of an acyl azide.

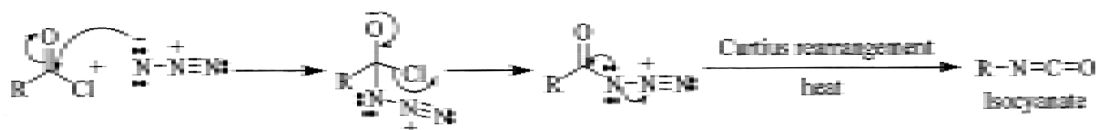
When the reaction of isocyanates is carried out with water, amines and alcohols, the isocyanates further reacts to form amines, ureas and carbamates respectively. The reaction is catalysed by both protic and Lewis acids and the reaction temperature is considerable lowered compared to uncatalysed reaction.



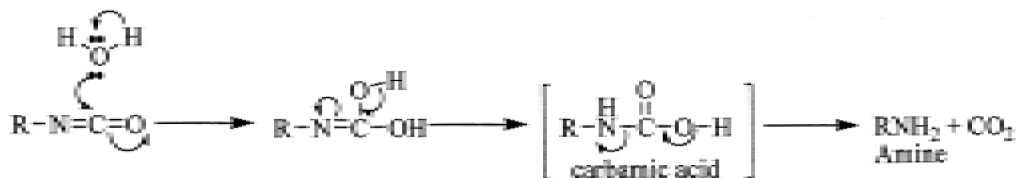
The conversion of acyl azides to isocyanates involves Curtius rearrangement while Curtius reaction involves the conversion of acids to amines, carbamates and substituted urea via Curtius rearrangement.

#### Mechanism :

The mechanism of the rearrangement is very similar to Hofmann's rearrangement to isocyanate. The driving force of the rearrangement is the electron-deficient nitrogen formed on elimination of nitrogen molecule on heating.

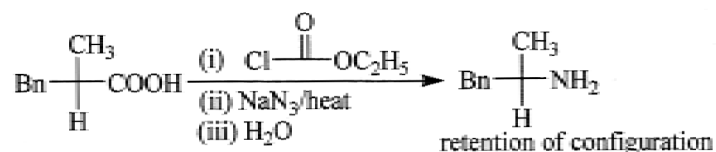


The isocyanate reacts with water to form the unstable carbamic acid which readily decomposes to a primary amine and carbon dioxide.



In the Curtius rearrangement the key step is the thermal or photochemical conversion of an acyl azide to an isocyanate. Curtius rearrangement is almost certainly concerted and does not involve the intermediacy of a nitrene. For example, neither insertion, addition nor amide products are isolated in the thermal Curtius rearrangement, which would be expected if a nitrene intermediate is involved. When Curtius rearrangement is carried out in the presence of vinyl monomers such as styrene, it does not undergo polymerization.

When Curtius rearrangement is carried out with an optically active acyl azides in which the chiral carbon is directly attached to carbonyl carbon, it is observed that reaction occurs with retention of configuration.



The essential difference between the Curtius and Hofmann rearrangement is that isocyanate can be isolable in Curtius but not in Hofmann rearrangement. In Hofmann rearrangement, base is present and the isocyanate cannot survive.

### Applications :

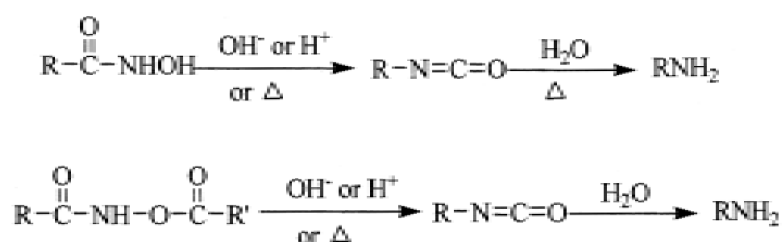
This simple one-step and mild reaction affords an important and easy preparative method for primary amines,  $\alpha$ -amino acids, aldehydes and urethane, etc.

### 6.4.3 Lessen Rearrangement

The thermal, acid or base catalysed conversion of hydroxamic acids and their O-acyl and O-royl derivatives to isocyanate is called Lossen rearrangement. As the reaction is normally carried out in water, the reaction produces the amine directly. When the nitrogen atom contains an alkyl or aryl group, however, Lossen rearrangement does not take place.

**Mechanism :**

Lossen rearrangement is intramolecular and its mechanism is closely related to Hofmann and Curtius rearrangement. The overall Lossen reaction can be shown as follows.



The reaction is facilitated by electron-supplying substituents in ‘R’ of the hydroxamic acid derivative. Isocyanate of the reaction can be isolated when reaction is carried out in benzene or in thionyl chloride. Hydroxamic acid of the reaction is generally prepared from acid chloride and hydroxylamine.

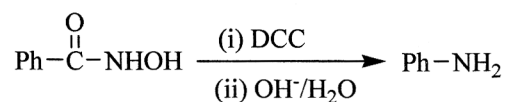
When Lossen rearrangement is carried out with an optically active hydroxamic acid, complete retention of configuration of the stereocentre is observed.

**Applications :**

This mild and simple one-step reaction affords an important and easy preparative method for primary amines,  $\alpha$ -amino acids, aldehydes and urethane, etc.

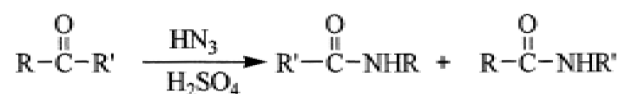
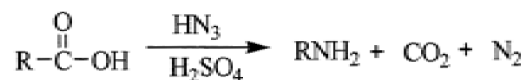
**Try the following Questions :**

1. Which one will give faster rearrangement? PhCONHOH or MeCONHOH with (i) TsCl/py and then (ii) KOH.
2. Give mechanism of the following reaction.

**6.4.4 Schmidt Rearrangement :**

The reaction of carboxylic acid with hydrazoic acid in the presence of concentrated sulphuric acid to give primary amine is known and Schmidt reaction or Schmidt rearrangement. This reaction is particularly useful for the preparation of both aliphatic and aromatic primary amines from the corresponding carboxylic acids.

The reaction can be extended to carbonyl compounds as substrate molecules. Aldehyde gives a mixture of N-alkylated formamide and nitrile. A symmetrical ketone gives single amide whereas unsymmetrical ketone gives a mixture of two isomeric amides.

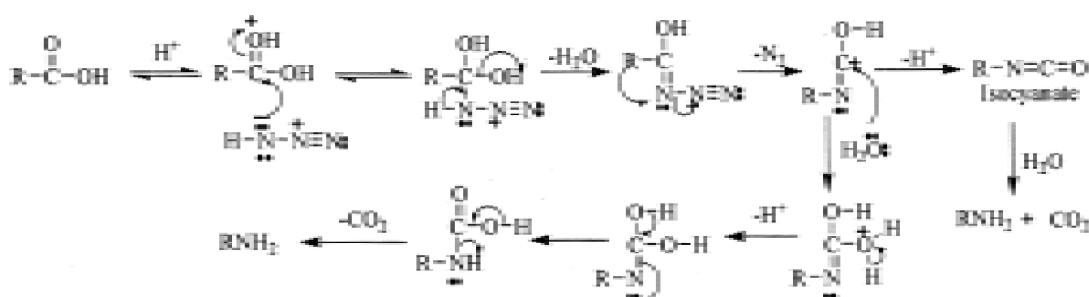


The reaction conditions are mild, the reagents are easy to get and the method is simple and does not require any specialised equipments. Hydrazoic acid is handled either as a solution in an inert solvent like  $\text{CHCl}_3$  or generated *in situ* by adding  $\text{NaN}_3$  slowly to the solution of carboxylic acid in sulphuric acid. The product amine from the carboxylic acid contains one carbon atom less than that of parent acid due to loss  $\text{CO}_2$ .

### Mechanism :

The mechanism of the rearrangement is similar to Curtius and Lossen rearrangement. The reaction works well for aliphatic carboxylic acids but less so for aromatic carboxylic acids. Dialkyl and cyclic ketones react more readily than alkyl aryl ketones. With alkyl aryl ketones, it is aryl group which migrates. Aldehydes and ketones react faster than carboxylic acids; therefore, good chemoselectivity can be achieved with keto acids. The mechanism of Schmidt reaction is shown separately for the acid and the carbonyl compounds.

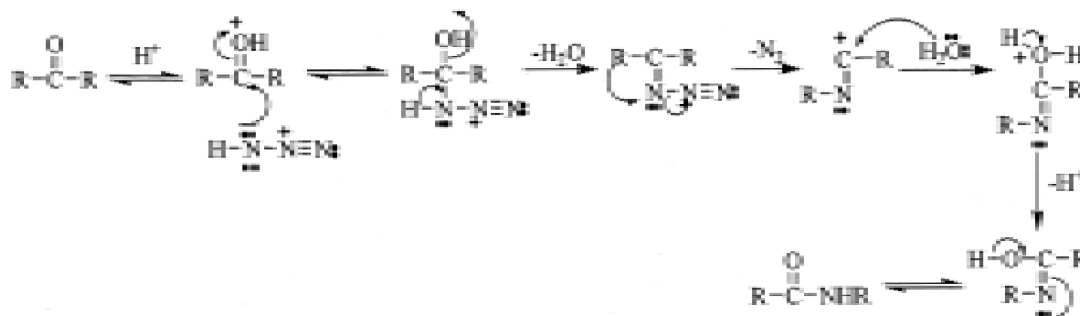
(a) Mechanism for the transformation of acid to the primary amine :



Many Scientist have argued that Schmidt reaction might have proceed through

the formation of isocyanate intermediate, as shown above, but it has never been isolated during the Schmidt rearrangement.

(b) Mechanism with Carbonyl Compound :

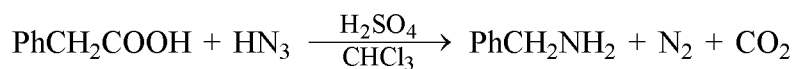


When unsymmetrical ketone is taken then a mixture of two isomeric N-substituted amides are obtained by the migration of the two different alkyl groups.

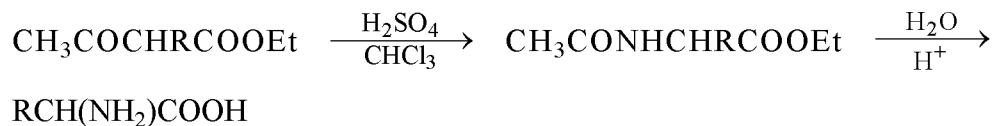
In case of Aldehyde, the main product is a nitrile with small amounts of formamide. Schmidt reaction involving cyclic ketone gives cyclic amides (lactam) through ring expansion. If an unsymmetrical cyclic ketone used then two isomeric lactams are formed.

### Applications :

- 1. Preparation of amines :** Primary amines with one carbon less are obtained in good yield directly from the acids provided the acids do not contain groups sensitive to concentrated sulphuric acid.



- 2. Preparation of  $\alpha$ -amino acids :** Ethylacetoacetate and hydrazoic acid react in the presence of sulphuric acid to give  $\alpha$ -amino acid.



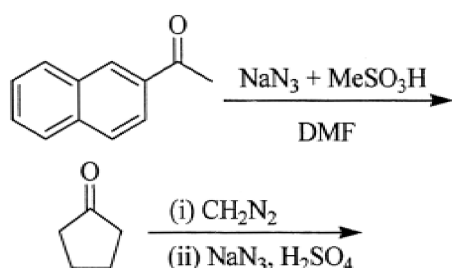
- 3. Preparation of lactams :** Cyclic ketones give lactams when react with hydrazoic acid. Cyclohexanone gives  $\epsilon$ -caprolactam.





### Try the following Questions :

Give the products with mechanism.

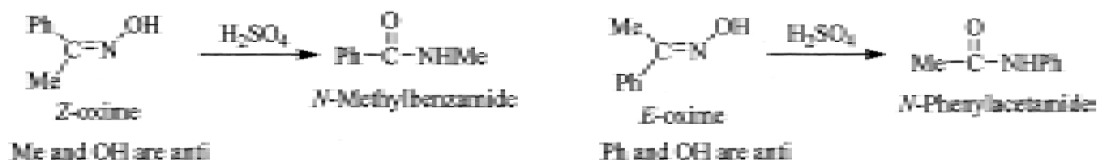


### 6.4.5 Beckmann Rearrangement :

Acid catalysed conversion of ketoximes to *N*-substituted amides is known as Beckmann rearrangement. Some aldoximes undergo the rearrangement in the presence of polyphosphoric acid but the reaction is not a general one. The reaction is catalysed by acidic reagents like  $\text{H}_2\text{SO}_4$ ,  $\text{SOCl}_2$ ,  $\text{SO}_3$ ,  $\text{PCl}_5$ ,  $\text{P}_2\text{O}_5$ ,  $\text{C}_6\text{H}_5\text{SO}_2\text{Cl}$ ,  $\text{HCl}/\text{Ac}_2\text{O}/\text{AcOH}$  etc.



The migration of the group depend not only the migratory aptitude but upon the orientation of the group in relation to the OH group. It is observed that the group *anti* to the hydroxyl group of the oxime migrates on the nitrogen atom to give the *N*-substituted amide. Therefore, it can be concluded that Beckmann rearrangement is a stereospecific reaction.

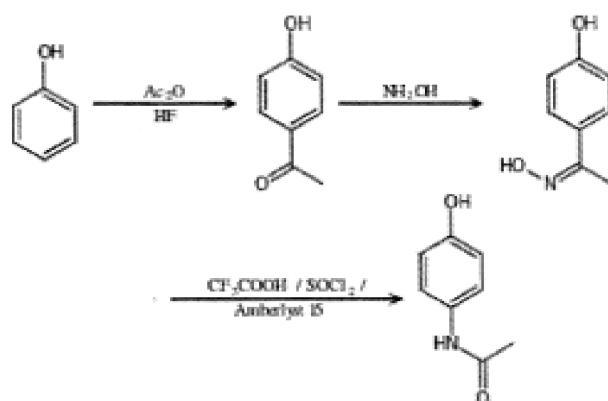


**Mechanism :**

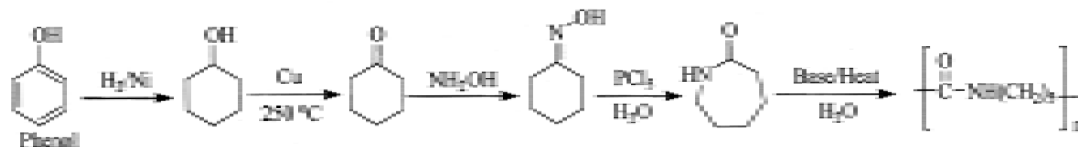
In the Beckmann rearrangement step, the oxime oxygen is protonated by acid which leads to formation of OH<sub>2</sub><sup>+</sup>, that is a much better leaving group than OH. Next, the C–C bond breaks, migrating to the nitrogen, forming a new C–N bond and displacing the water as a leaving group. This forms a free carbocation, which is then attacked by water. The positively charged oxygen is deprotonated by base to give the tautomer of the amide. Finally, protonation occurs at nitrogen, followed by deprotonation of oxygen giving the substituted amide.

**Applications :**

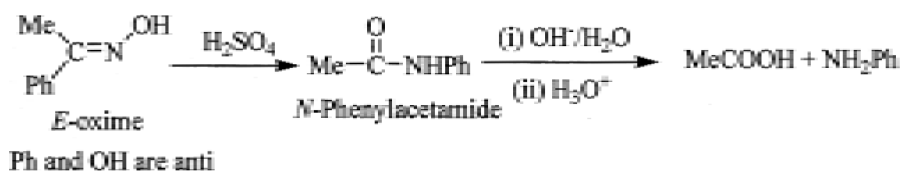
- (I) An industrial synthesis of paracetamol developed by Hoechst-Celanese involves the conversion of a methyl ketone to an acetanilide via a Beckmann rearrangement.



- (II) The Beckmann rearrangement is also used in the synthesis of DHEA, benazepril, ceforanide, elanzepine, elantrine, prazepine, enprazepine, and etazepine.
- (III) Beckmann rearrangement is also used in the synthesis of nylon-6. The industrial manufacture of nylon relies upon the alkaline polymerization of a cyclic amide known trivially as caprolactam.



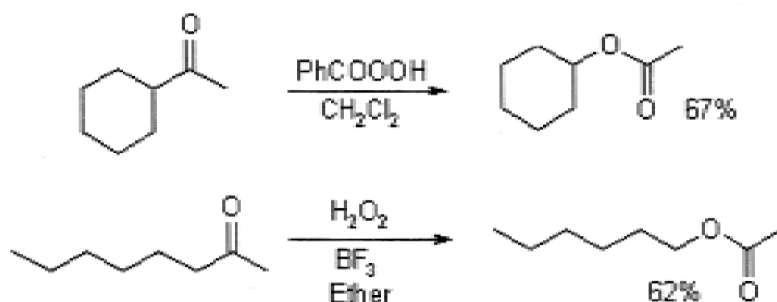
(IV) Determination of configuration of Ketoxime: Configuration of ketoxime can be assigned by studying the Beckmann rearranged product since anti group with respect to hydroxyl migrates during rearrangement. The product amide on hydrolysis yields amine. Structural analysis on which clearly suggest the configuration of the parent oxime.



## 6.5 Rearrangement to electron-deficient oxygen

### 6.5.1 Baeyer-Villiger Oxidation :

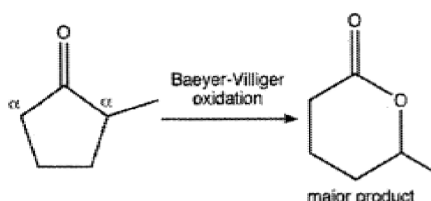
The Baeyer-Villiger Oxidation is the oxidative cleavage of a carbon-carbon bond adjacent to a carbonyl, which converts ketones to esters and cyclic ketones to lactones. In this reaction an oxygen atom is 'inserted' next to the carbonyl group. The Baeyer-Villiger can be carried out with peracids, such as MCBPA, or with hydrogen peroxide and a Lewis acid. In 1899, the Germans, A. Baeyer and V. Villiger, discovered this reaction when they treated a ketone with a peroxy-acid ( $\text{RCO}_2\text{H}$ ) and obtained an ester.



Baeyer-Villiger reactions are among the most useful of all rearrangement reactions, and the most common reagent is *m*-CPBA (*meta*-chloroperbenzoic acid)

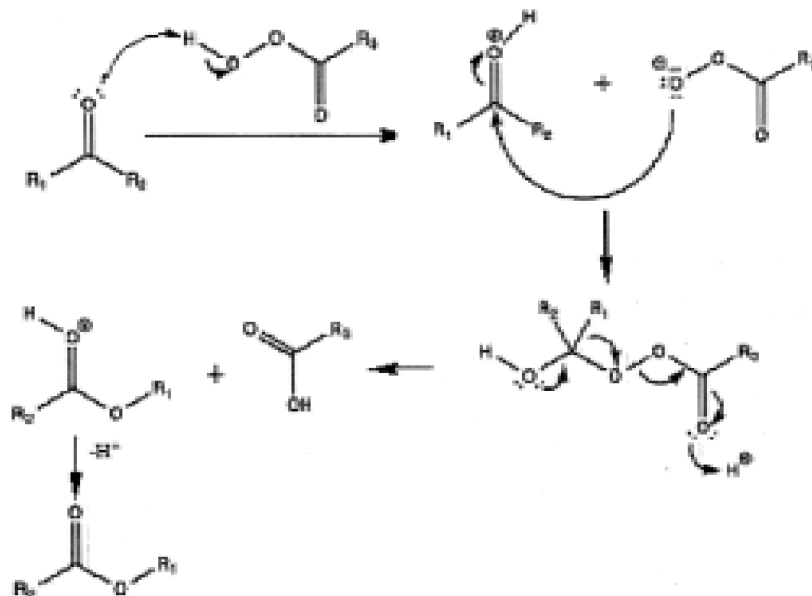
because it is commercially available. The general trend is that higher reactivity is correlated with lower  $pK_a$  (i.e. stronger acidity) of the corresponding carboxylic acid (or alcohol in the case of the peroxides). Therefore, the reactivity trend shows TFPAA > 4-nitroperbenzoic acid > mCPBA and performic acid > peracetic acid > hydrogen peroxide > tert-butyl hydroperoxide. The peroxides are much less reactive than the peroxyacids. The use of hydrogen peroxide even requires a catalyst. In addition, using organic peroxides and hydrogen peroxide tends to generate more side-reactivity due to their promiscuity

The regioselectivity of the reaction depends on the relative migratory ability of the substituents attached to the carbonyl. Substituents which are able to stabilize a positive charge migrate more readily, so that the order of preference is : *tert.* alkyl > cyclohexyl > *sec.* alkyl > phenyl > *prim.* alkyl >  $CH_3$ . In some cases, stereoelectronic or ring strain factors also affect the regiochemical outcome. When the two ligands on the carbonyl carbon in the ketone are different, Baeyer-Villiger oxidation is regioselective. Of the two alpha carbons in the ketone, the one that can stabilize a positive charge more effectively, which is the more highly substituted one, migrates from carbon to oxygen preferentially.



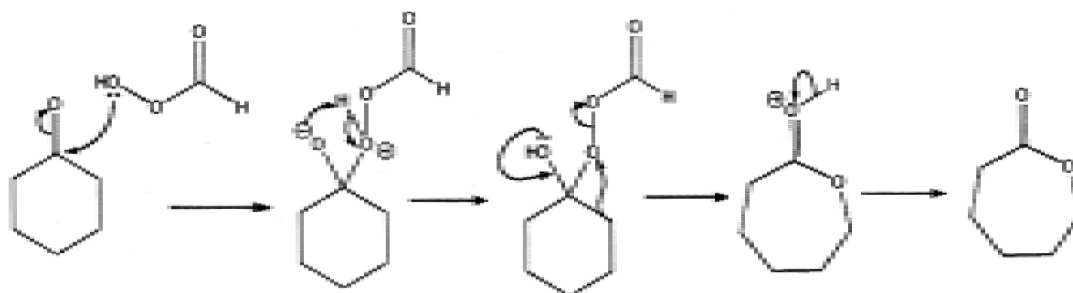
### Mechanism :

First step of the reaction mechanism is the protonation to the oxygen of the carbonyl group by peroxyacid. This makes the carbonyl group more susceptible to be attacked by the peroxyacid. Next, the peroxyacid attacks the carbon of the carbonyl group. One of the substituents on the ketone migrates to the oxygen of the peroxide group while a carboxylic acid leaves through a concerted mechanism. This migration step is thought to be the rate determining step. Finally, deprotonation of the oxocarbenium ion produces the ester.



The migration does not change the stereochemistry of the group that transfers, i.e. it is stereoretentive reaction.

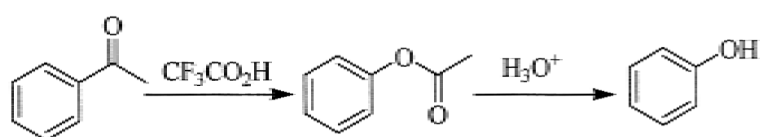
Small-ring ketones can relieve ring strain by undergoing Baeyer-Villiger reactions. Cyclohexanone on Baeyer-Villiger oxidation provides cyclic ester as follows.



There are limitations of Baeyer-Villiger oxidation. Undesirable oxidation of other functional groups occurs when Baeyer-Villiger oxidation is performed using peroxyacids and peroxides. Alkenes and amines are a few of the groups that can be oxidized. Peroxides may epoxidize alkenes faster than they take part in Baeyer-Villiger reactions, so unsaturated ketones are not often good substrates for Baeyer-Villiger reactions.

**Applications :**

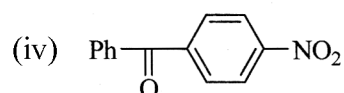
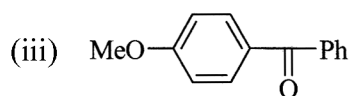
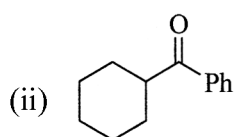
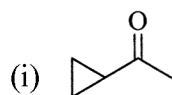
- (i) Medium and large ring lactones which are otherwise difficult to obtain can be prepared by this methodology,
- (ii) Since methyl group has a low migrating ability, the reaction provides a means of cleaving a methyl ketone to produce an alcohol or phenol on hydrolysis.



- (iii) They used the Baeyer-Villiger oxidation to make a lactone that served as a crucial building block that ultimately led to the synthesis of zoapatanol. Zoapatanol is a biologically active molecule that occurs naturally in the zeopatlé plant, which has been used in Mexico to make a tea that can induce menstruation and labor.

**Try the following Questions :**

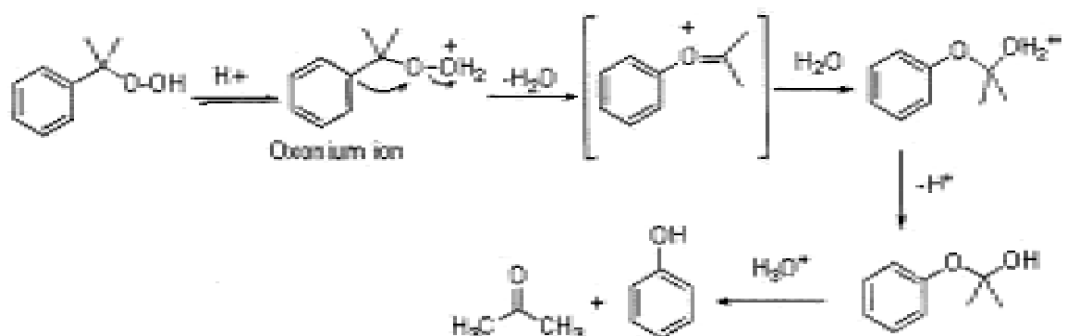
Predict the product of the following Baeyer-Villiger oxidation reaction indicating major products and show mechanism.

**6.5.2 Cumene hydroperoxide-phenol rearrangement :**

Hydroperoxide in the presence of strong acid such as  $\text{H}_2\text{SO}_4$ ,  $\text{HClO}_4$  and Lewis acids undergoes rearrangement as Baeyer-Villiger oxidation. When cumene

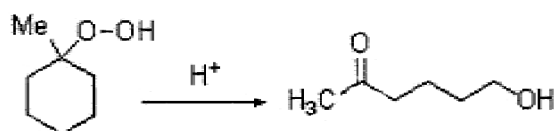
hydroperoxide in the presence of  $\text{H}_2\text{SO}_4$  undergoes rearrangement *via* hemiacetal to give phenol and acetone is called Cumene hydroperoxide-phenol rearrangement. The cumene hydroperoxide can be obtained by autooxidation of cumene. This is the commercial process used for the synthesis of phenol.

#### Mechanism :



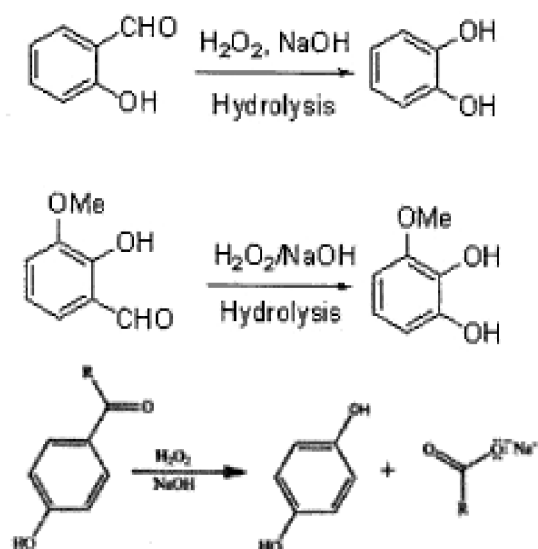
#### Applications :

Under these conditions, 1-methylcyclohexyl hydroperoxide rearranges to give 7-hydroxyhept-2-one.



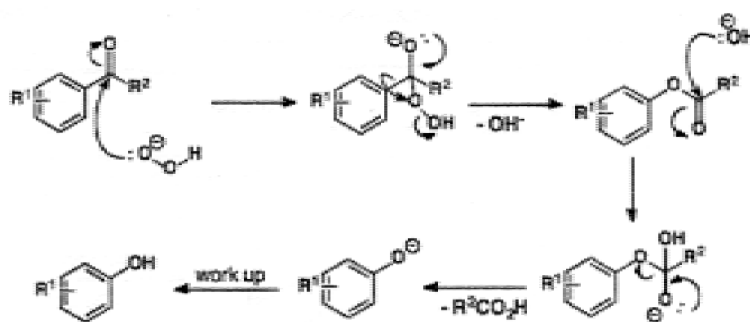
#### 6.5.3 Dakin Reaction :

The preparation of phenols from aryl aldehydes or aryl ketones involving the oxidation of corresponding aromatic compounds by hydrogen peroxide in the presence of a base and subsequent hydrolysis of the aryl formate or alkylcarboxylate intermediates is known as Dakin's reaction. The *para*- or *ortho*-substituents (such as  $\text{OH}$ ,  $\text{NH}_2$ ) on aryl aldehydes or aryl ketones have been reported to facilitate this reaction. This reaction has an application in the synthesis of phenols. This reaction is closely related to Baeyer-Villiger oxidation. This reaction is named after an English chemist Henry Drysdale Dakin.



### Mechanism :

First step of the Dakin reaction is nucleophilic addition of a hydroperoxide anion to the carbonyl carbon, forming a tetrahedral intermediate. This intermediate on subsequent [1,2]- migration of aryl group and hydroxide group elimination formed a phenyl ester. The phenyl ester so formed undergo hydrolysis by nucleophilic addition of hydroxide from solution to form a second tetrahedral intermediate which on elimination of phenoxide in give a carboxylic acid. Finally, the phenoxide extracts the acidic hydrogen from the carboxylic acid giving the required phenols.



Generally phenyl aldehydes are more active than phenyl ketones because of less electrophilic character of ketone carbonyl carbon than the aldehyde carbonyl carbon. By increasing the temperature of the reaction mixture this difference can be diminished.

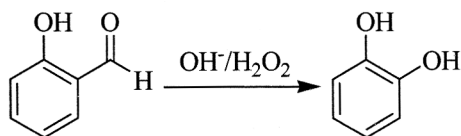


In weakly basic conditions *o*-hydroxy phenyl aldehydes and ketones oxidize faster *than* *p*-hydroxy phenyl aldehydes and ketones. In case of *o*-hydroxy compounds, when the hydroxyl group is protonated, an intramolecular hydrogen bond can form between the hydroxyl hydrogen and the carbonyl oxygen, stabilizing a resonance structure with positive charge on the carbonyl carbon, thus increasing the carbonyl carbon's electrophilicity. No such stabilization of *p*-hydroxy compounds due to H-bonding is observed. So, the carbonyl carbon is less electrophilic. Therefore, *o*-hydroxy compounds are oxidized faster than *p*-hydroxy compounds. *m*-Hydroxy compounds do not oxidize to *m*-benzenediols and carboxylates, rather, they form phenyl carboxylic acids.

Presence of electron-donating groups *ortho* or *para* to the carbonyl group increases electron density at the migrating carbon, promotes [1, 2]-aryl migration, and accelerates oxidation. Electron-donating groups *meta* to the carbonyl group does not change electron density at the migrating carbon. Electron-withdrawing groups *ortho* or *para* to the carbonyl carbon decreases electron density at the migrating carbon, inhibits [1, 2]-aryl migration, and favors hydrogen migration.

#### Applications :

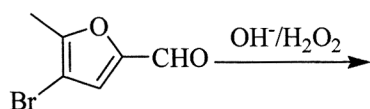
- (i) Catechol is used as the starting material for synthesis of several compounds, including the catecholamines, catecholamine derivatives, and 4-*tert*-butylcatechol, a common antioxidant and polymerization inhibitor. This catechol can be synthesized from *o*-hydroxy and *o*-alkoxy phenyl aldehydes and ketones by this methodology.
- (ii) The Dakin oxidation is most commonly used for the synthesis of benzenediols and alkoxyphenols.



- (iii) Other synthetically useful products of the Dakin oxidation include guaiacol, a precursor of several flavorants; hydroquinone, a common photograph-developing agent; and 2-*tert*-butyl-4-hydroxyanisole and 3-*tert*-butyl-4-hydroxyanisole, two antioxidants commonly used to preserve packaged food.

**Try the following Questions :**

Give the product with mechanism.



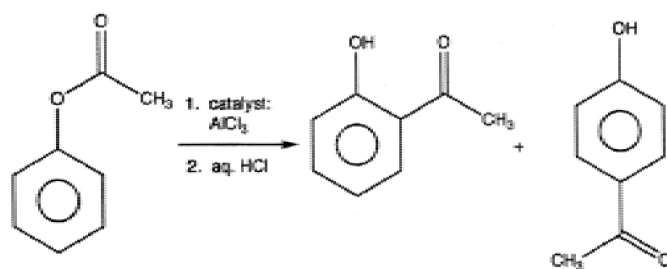
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**6.6 Aromatic rearrangements**

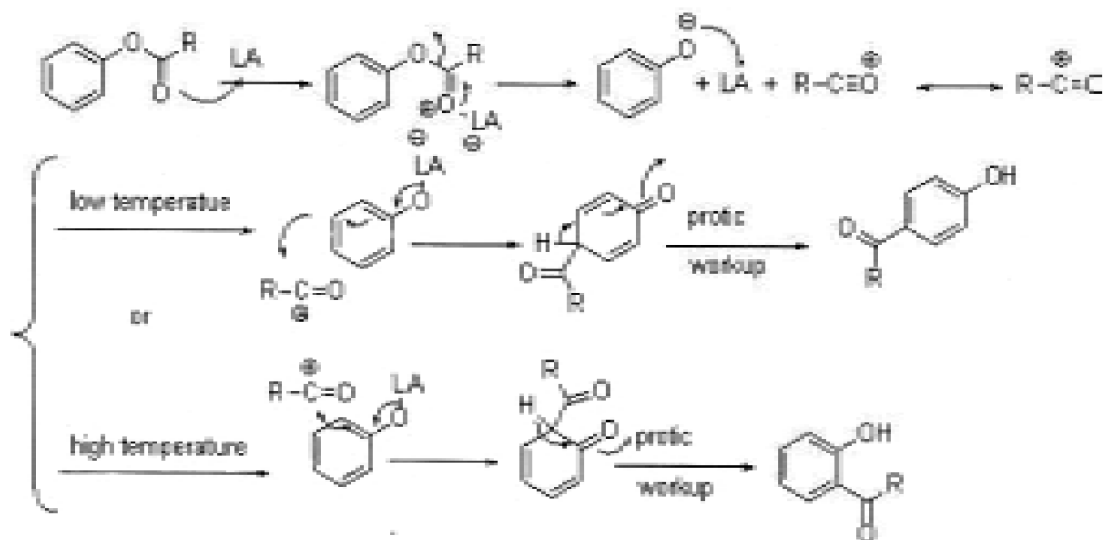
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**6.6.1 Fries rearrangement :**

The Fries rearrangement is an organic reaction used to convert a phenyl ester to an *ortho*- and *para*-hydroxy aryl ketone using a Lewis acid catalyst and Bronsted acid work-up. Generally, Lewis acids such as  $\text{HF}$ ,  $\text{AlCl}_3$ ,  $\text{BF}_3$ ,  $\text{TiCl}_4$  or  $\text{SnCl}_4$  have been used. The acids are used in excess of the stoichiometric amount, especially the Lewis acids, since they form complexes with both the starting materials and products. The reaction is *ortho* and *para* selective and one of the two products can be favoured by changing reaction conditions, such as temperature and solvent.

**Mechanism :**

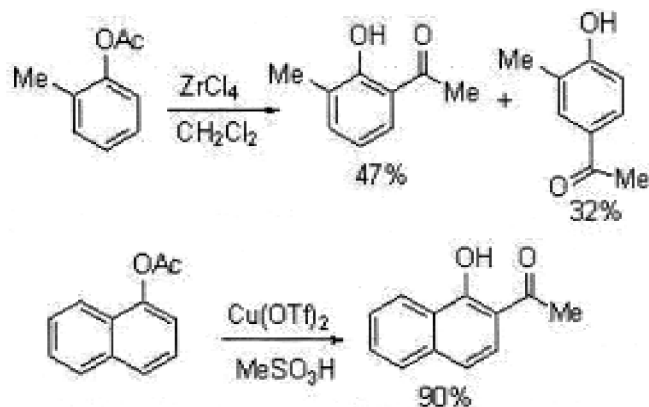
The mechanism begins with coordination of the ester to the Lewis acid, followed by a rearrangement which generates an electrophilic acylium cation. The aromatic compound then attacks the alkyl cation (both the *ortho* and *para* attack are allowed) via an electrophilic aromatic substitution ( $\text{S}_{\text{E}}\text{Ar}$ ). Deprotonation to regenerate aromaticity and Bronsted acid work-up to regenerate the Lewis acid catalyst provide the two hydroxy aryl ketone products.



Generally, at low temperature *para*-product (kinetic control) is formed and high temperature favors the formation *ortho*-product (thermodynamic control). Formation of the *ortho*-product is favoured in non-polar solvents and as the solvent polarity increases, the ratio of the *para*-product also increases. Crossover experiments proved that the reaction is intermolecular.

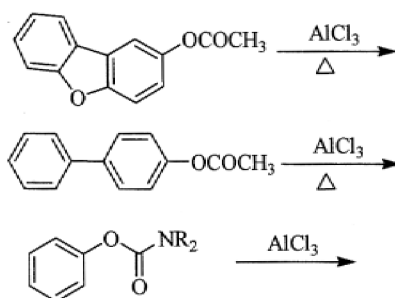
### Applications :

Hydroxyarylketones are important intermediates for several pharmaceuticals. Therefore, this reaction is of industrial importance for the synthesis of hydroxyarylketones. Friedel-Crafts acylation in presence of Phenols to form hydroxyarylketones is not possible due to formation of esters. So, Fries rearrangement is a unique pathway to synthesize hydroxyarylketones.



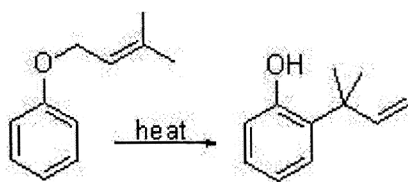
**Try the following Questions :**

Give all possible products.

**6.6.2 Claisen rearrangement :**

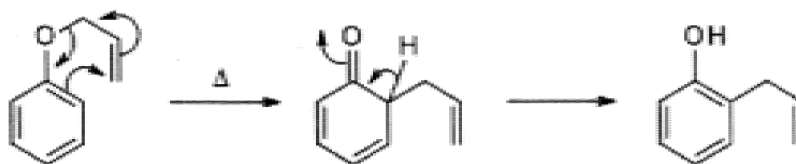
The Claisen rearrangement is an organic chemical reaction where an allyl vinyl ether or allyl aryl ether is converted into a  $\gamma, \delta$ -unsaturated carbonyl compound and ortho substituted phenols respectively. The reaction occurs in presence of heat or a Lewis acid and offers a powerful method for the formation of carbon-carbon bonds.

The Claisen rearrangement reaction was discovered by the German chemist Rainer Ludwig Claisen, in 1912. This rearrangement reaction belongs to a class of reactions termed “sigmatropic rearrangements” and it is a concerted process where bonds are forming and breaking at the same time.

**Mechanism :**

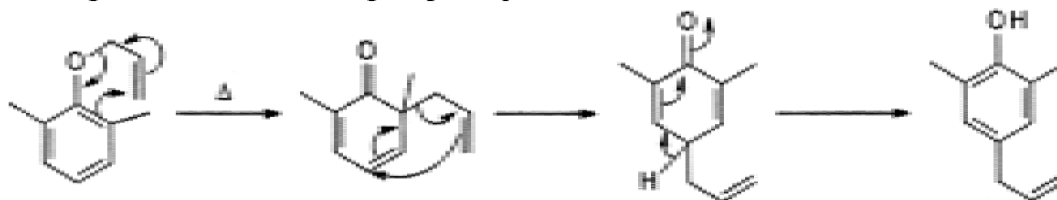
The Claisen rearrangement is an exothermic reaction. This first order reaction proceeds through a highly ordered cyclic transition state and is intramolecular. The reaction is accelerated by polar solvents. Hydrogen-bonding solvents provide the highest rate constants.

The [3,3]-sigmatropic rearrangement of the allyl phenyl ether on heating gives an intermediate. This intermediate now undergoes tautomerization to give a phenol which is substituted at the ortho position. The aromatic Claisen Rearrangement is followed by a rearomatization.



In this rearrangement, the regioselectivity is affected by the meta-substitution. When an electron withdrawing group is present at the meta-position, rearrangement occurs at the *ortho*-position, while electron donating groups direct the rearrangement to the *para*-position.

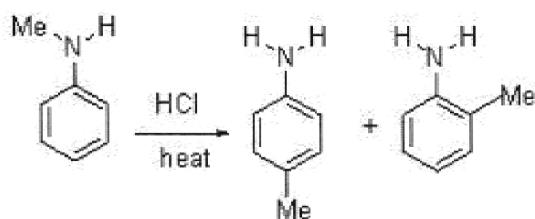
When the *ortho*-position is substituted, rearomatization cannot take place and rearrangement continues to give the *para*-product.



### 6.6.3 Hofmann-Martius rearrangement :

The Hofmann-Martius rearrangement is a rearrangement reaction where an N-alkylated aniline is converted to the corresponding *ortho* and / or *para* aryl-alkylated aniline. The reaction requires heat, and the catalyst is an acid like hydrochloric acid.

The rearrangement was discovered by Hofmann and Martius in 1871.



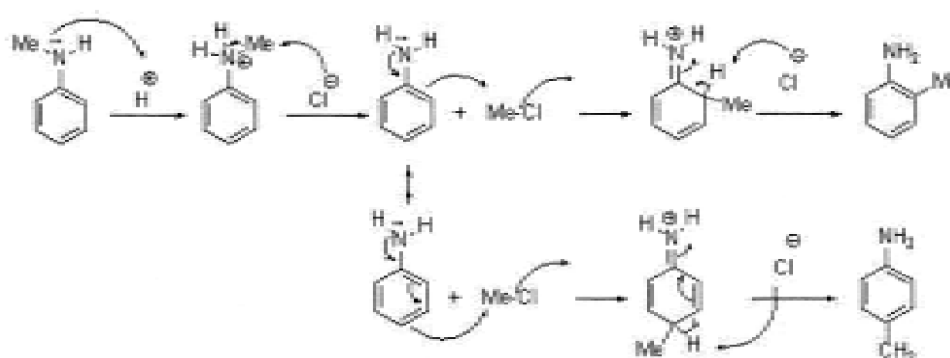
When a metal halide is used as a catalyst, the reaction is also called the Reilly-Hickinbottom rearrangement. The metal halides are cadmium chloride, cobalt chloride, and zinc chloride.

When N-alkylated aniline hydrochloride is heated at 220-335°C, various rearranged products such as xylydines, cumidines, toluidines, and multiple ring-methylated compounds are formed.

The rearrangement was regarded as intramolecular type though there are no conclusive supporting evidence was found.

### Mechanism :

The mechanism of the rearrangement was established by Reilly and Hickinbottom. Hydrochloride moiety of the aniline salt plays an important role for the reaction.



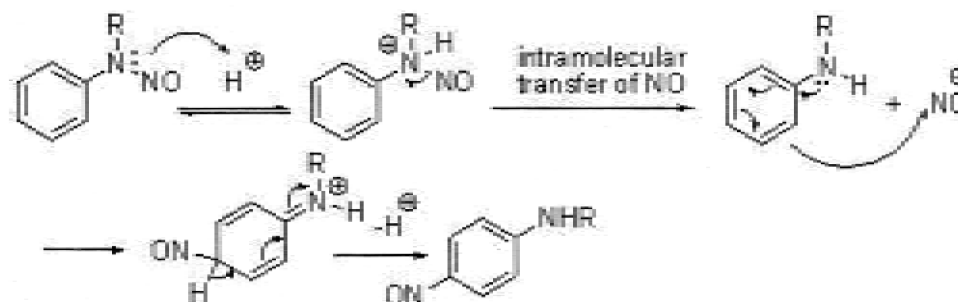
### 6.6.4 Fischer-Hepp rearrangement :

The conversion of *N*-nitroso aromatic amines into *p*-nitroso aromatic amines in the presence of HCl or HBr is generally known as the Fischer-Hepp rearrangement.

This reaction was first described by the German chemist Otto Philipp Fischer and Eduard Hepp in 1886. This rearrangement is intramolecular. It has been observed that no rearrangement occurs in the presence of urea and the rearrangement is much less effective in presence of sulfuric acid rather than HCl or HBr.

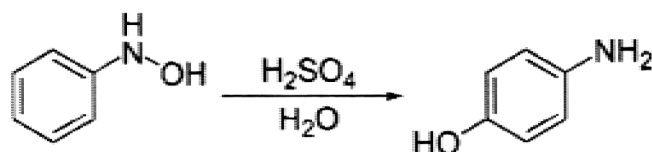
The importance of this reaction is that para-nitroso secondary anilines can be synthesized by this methodology which cannot be prepared in a direct reaction.

### Mechanism :



### 6.6.5 Bamberger rearrangement :

Rearrangement of *N*-phenylhydroxylamines to *p*-aminophenols in presence of acids is called Bamberger rearrangement. Occasionally, it is also termed the Bamberger reaction. In 1894, Bamberger reported that phenylhydroxylamine readily rearranges to *p*-aminophenol in sulfuric acid solution.

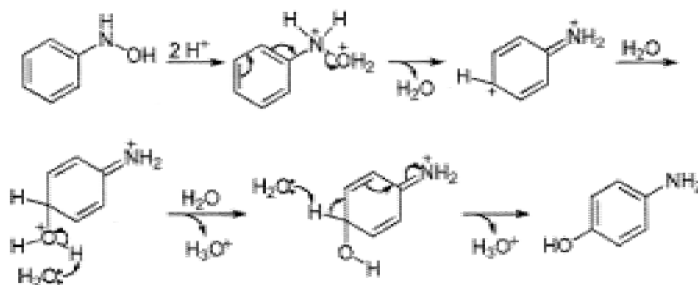


This is a convenient pathway for the synthesis of *para*-substituted anilines. Bamberger rearrangement comes under nucleophilic aromatic substitution reaction. In this substitution reaction water is the nucleophile. *p*-Aminophenol is an important intermediate for the preparation of dyestuffs, pharmaceutically active (paracetamol) compounds and plant protection agents.

It is believed that in this rearrangement the hydroxyl group is introduced into the aromatic ring via a nucleophilic attack of a hydrosulfate ion on the anilenium ion, which is generated by the heterolytic N–O bond cleavage of *O*-protonated *N*-phenylhydroxylamine. It has been found that alkoxy, halogen, phenoxy are incorporated into the aromatic ring when the rearrangement of *N*-phenylhydroxylamine is carried out in nucleophilic solvents, such as alcohols, hydrogen halides, and phenols.

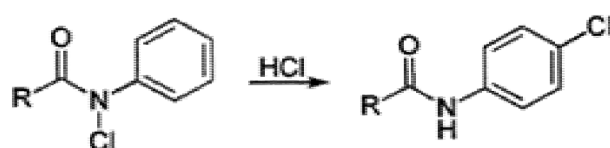
#### Mechanism :

The mechanism of the Bamberger rearrangement starts with monoprotection of *N*-phenylhydroxylamine which subsequently transformed into anilenium by releasing a water molecule, during which the aromatic ring carries a partial positive charge so that the nucleophilic attacking occurs at the *para* position.



### 6.6.6 Orton Rearrangement :

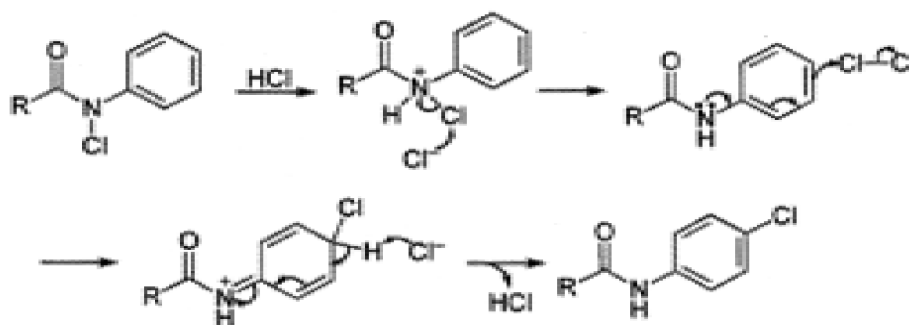
Rearrangement of *N*-chloroacetanilide in the presence of an acid (e.g. dilute HCl) in which the chlorine atom migrates to *para*-position to form *para* chloroacetanilide is known as Orton Rearrangement. Small amount of ortho product is also formed. Besides that, Orton rearrangement can also be performed by Lewis acid, such as AgBF<sub>4</sub>, as well as by light, such as irradiation from a mercury-vapour lamp even in solid state.



This reaction occurs via a multistep process in which liberation of chlorine and subsequent electrophilic substitution takes place. The Orton rearrangement is intermolecular.

#### Mechanism :

The mechanism involves the formation of chlorine and subsequent electrophilic substitution takes place to yield *para* substituted product. First step is the protonation of *N*-chloro acyl anilide, followed by halophilic substitution to form chlorine which undergoes electrophilic substitution at *para* position to give *para* chloroacetanilide.

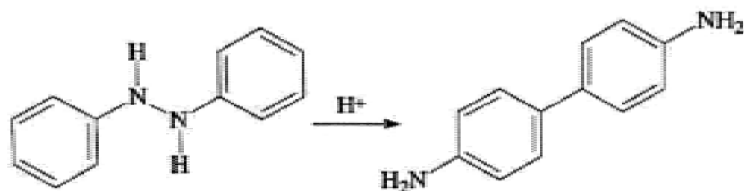


**Application :** This reaction is useful for the preparation of *para*-halo anilides.

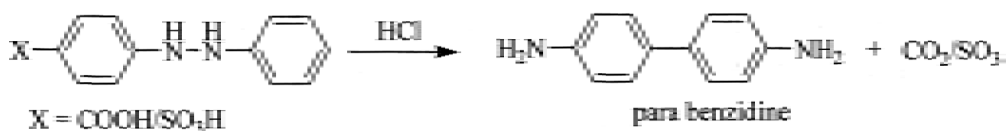
### 6.6.7 Benzidine rearrangement :

The acid catalyzed rearrangement of hydrazobenzene to benzidines is called benzidine rearrangement. When hydrazobenzene is treated with dilute HCl it rearranges to benzidine as major product. This rearrangement was discovered Pummerer.





When solid hydrazobenzene is treated with dry HCl five isomeric products are formed. Hydrazobenzene under strong heating condition disproportionates to give aniline and azobenzene. Some groups especially carboxyl and sulphonic acids are eliminated during the rearrangement and para benzidines are formed.



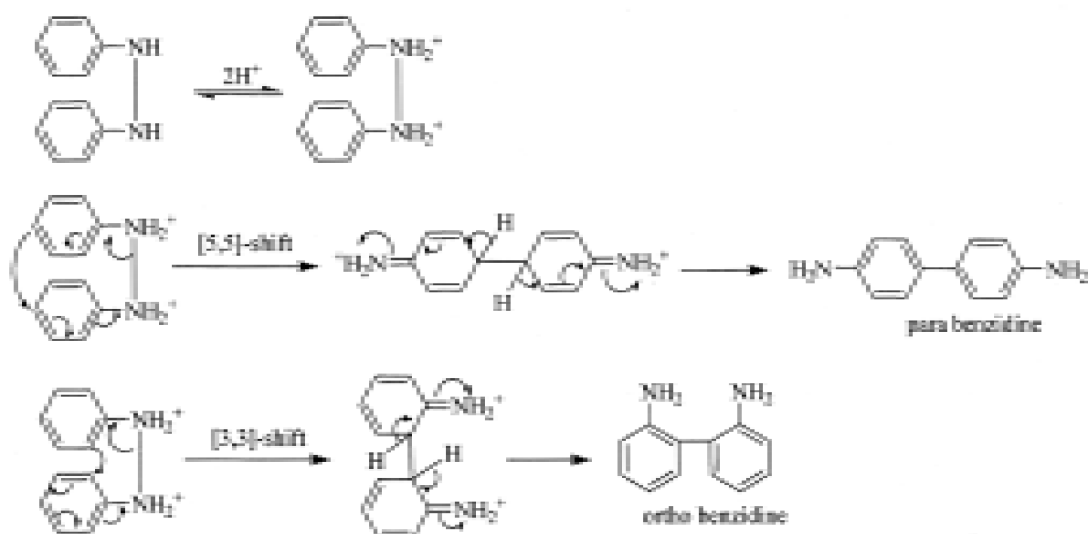
### Mechanism :

Benzidine rearrangement follows third order kinetics.

$$\text{Rate} = K[\text{PhNHNHPh}][[\text{H}^+]^2]$$

This rearrangement follows concerted pathways. The formation of new carbon-carbon bond and breaking of N-N bond are taking place in one step.

Benzidine rearrangement is thought to be pericyclic sigmatropic rearrangements which are shown as follows :



In the above sigmatropic rearrangements only [5,5] and [3,3]-shifts are 10 electrons system and the transition state of [5,5]-shift is sterically uncrowded. In this shift since largest part of the molecule is involved which is controlled by frontier orbital co-efficient and therefore [5,5]-shift is periselective. ,

The transition state of [3,3] and also all other allied rearrangements are sterically congested, strained and less periselective (since shorter chain is involved).

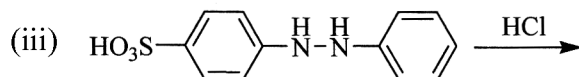
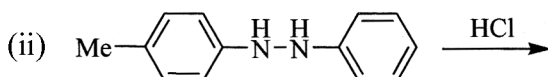
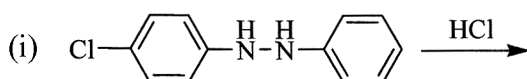
Therefore, [5,5]-shift, *i.e.*, para Benzidine is, in most cases favoured product.

Benzidine rearrangement is an intramolecular and concerted reaction and this can be experimentally verified by cross-over experiment. When a mixture of A-NH-NH-A and B-NH-NH-B is treated with HCl, the product is always H<sub>2</sub>N-A-A-NH<sub>2</sub> and H<sub>2</sub>N-B-B-NH<sub>2</sub> (normal product) and not H<sub>2</sub>N-A-B-NH<sub>2</sub> (cross-over product).

**Application:** Hydrazobenzenes can be easily obtained by the reduction of various aromatic nitro compounds using zinc and sodium hydroxide and this on rearrangement gives 4,4'-diaminobiphenyls which on functional group modification of amino group via diazotization give different biphenyl derivatives.

### Try the following Questions :

Write down the products with mechanism.




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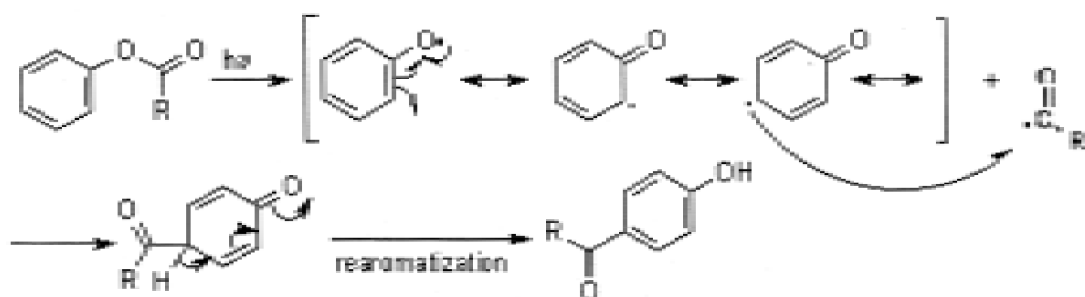
## 6.7 Rearrangement reactions by green approach

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### 6.7.1 Fries rearrangement :

The photo-initiated rearrangement of phenyl or aryl esters is generally known as the photo-Fries rearrangement or photo-Fries reaction and usually carried out in an aprotic solvent. The photo-Fries rearrangement reaction was discovered by Anderson

and Reese and involves the homolytic cleavage of a carbon-heteroatom bond, *i.e.*, C–O, C–S and C–N, of esters, thioesters and amides, respectively. The radical mechanism of the photo-Fries rearrangement is well established and it is known that this rearrangement occurs mainly through the excited singlet state. The photo-Fries rearrangement is intramolecular. This rearrangement also follows caged radical pair mechanism as evidenced from the response of CIDNP effects in the rearrangement of *p*-tolyl-*p*-chlorobenzoate that was found to be consistent with a singlet-state reaction.

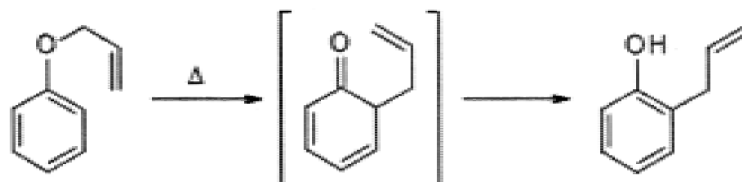


### 6.7.2 Claisen rearrangement :

The Claisen rearrangement is an example of pericyclic reaction and belongs to the category of [3,3]-sigmatropic rearrangement. This is a powerful carbon-carbon bond-forming chemical reaction and was discovered by Rainer Ludwig Claisen. The heating of an allyl vinyl ether will initiate a [3,3]-sigmatropic rearrangement to give a  $\gamma$ ,  $\delta$ -unsaturated carbonyl.



The Claisen Rearrangement of aromatic compound is accompanied with rearomatization :



All Claisen Rearrangement reactions described to date require temperatures of  $> 100^\circ\text{C}$  if uncatalyzed. To avoid high temperature some alternate processes are

designed. A few notable advantages of these processes are: (i) reasonably good yields of the products; (ii) fast reaction times; (iii) mild reaction conditions and (iv) avoidance of toxic solvents.

Microwave irradiation (MWI) has become an established tool in organic synthesis, because of the rate enhancements, higher yields and often, improved selectivity, with respect to the conventional reaction conditions. In addition, solvent-free MWI processes are also clean and efficient. Example of one-pot conversion of 1,4-bis-allyloxybenzene derivatives to 2, 3-bis-allyl-1, 4-quinone derivatives by taking advantage of the cumulative effect of the silica gel support and MWI under solvent-free conditions has been reported by Kotha et. al.

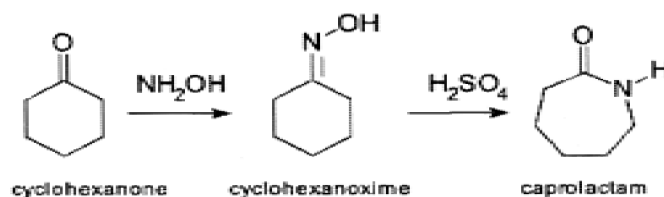
Iron (III) Chloride Catalyzed Claisen Rearrangement Reaction of Allyloxyarenes under Microwave Conditions is also reported. In this case  $\text{FeCl}_3$  catalyst is able to initiate the reaction at low temperature and induced the subsequent cyclization reaction. There are also several reports on Claisen rearrangement under environmentally benign processes like heteropolyacid supported on hexagonal mesoporous silica and solid superacid catalyst.

#### Application :

The Claisen rearrangement of allyl phenyl ethers is a fundamental reaction in organic synthesis with a variety of applications in perfumes, flavors, pharmaceuticals, agrochemicals, polymers, fine chemicals, and intermediate industries.

#### 6.7.3 Beckmann rearrangement :

The rearrangement of an oxime functional group to substituted amides is known as Beckmann rearrangement. The rearrangement is often catalyzed by acid. However, other reagents are also known to initiate the rearrangement. These are tosyl chloride, thionyl chloride, phosphorus pentachloride, phosphorus pentoxide, triethylamine, sodium hydroxide, trimethylsilyl iodide etc.



Due to the growing concern over environmental pollution, green chemistry has attracted an increasing interest on Beckmann rearrangement in recent years. Major environmental pollution is arising from the use of acids, hazardous reagents and solvents. Sometimes reaction requires high reaction temperatures and strongly acidic and dehydrating media. Thus, the reaction can lead to large amounts of by products and preclude its application to sensitive substrates. To overcome these problems greener approaches have been taken in Beckmann rearrangement.

Nano- $Fe_2O_4$  particles were used as a green and heterogeneous catalyst for Beckmann rearrangement under ultrasound irradiation and protic solvent condition in excellent yields. The advantage of this method was simple, inexpensive, easy work-up procedure, suppression of any side product.

Due to the toxicity of organic solvents and the limitations of environmentally benign solvents, the most promising approach is to perform organic reactions under solvent-free conditions. Naturally occurring organic acids are reported to be highly efficient promoters of the Beckmann rearrangement. These acids are nontoxic, and readily and cheaply available. Citric, oxalic, tartaric, malic, succinic, malonic, and fumaric acids efficiently promote the Beckmann rearrangement under solvent-free conditions and thermal and microwave irradiation. Tartaric acid was found to be the best promoter of the Beckmann rearrangement under conventional conditions as well as under microwave irradiation. Compared with conventional heating, microwave irradiation provides higher reaction rate and slightly higher yields.

The Beckmann rearrangement was reported to occur in ionic liquids at room temperature. The procedure is based on the reaction of a complex formed by 2,4,6-trichloro [1,3,5] triazine (cyanuric chloride, TCT), a very inexpensive reagent, and DMF, with a DMF solution of 1 mol equiv of the ketoxime. This method can be successfully applied on a large scale. Moreover no deoximation of the oximes to carbonyl compounds occurs.

With commonly used acid catalysts several problems such as difficulty in separation, recovery, disposal of spent catalyst, corrosion, and high toxicity, were encountered. An  $AlCl_3-ZnCl_2$  mixture supported on silica gel is found to be a new efficient medium for the Beckmann rearrangement in solvent-free conditions under microwave irradiation. When *p*-methoxy-acetophenone oxime was supported on the

catalyst and subjected to microwave irradiation in solvent-free condition for 5 min, the rearranged product was obtained in excellent yield (92%) as compared with the conventional thermal condition.

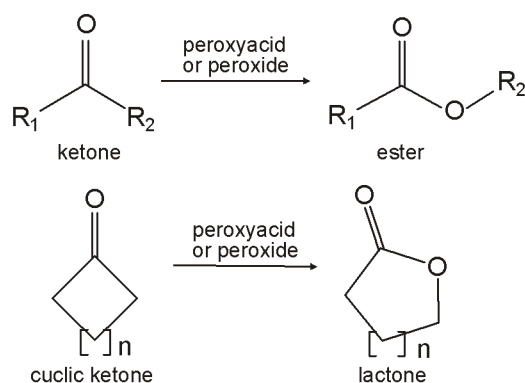
#### Application :

An industrial synthesis of paracetamol involves the conversion of a methyl ketone to an acetanilide via a Beckmann rearrangement.

The Beckmann rearrangement is also used in the synthesis of benazepril, ceforanide, elanzepine, elantrine, prazepine and enprazepine.

#### 6.7.4 Baeyer-Villiger oxidation :

Conversion of an ester from a ketone or a lactone from a cyclic ketone using peroxyacids or peroxides is known as Baeyer-Villiger oxidation. The reaction is named after Adolf von Baeyer and Victor Villiger who first reported the reaction in 1899.



Common oxidants for this reaction are expensive and/or hazardous peracids, such as *m*-chloroperbenzoic acid, or combination of aldehydes and molecular oxygen leading in both cases to the formation of the corresponding carboxylic acid as waste. To overcome these problems some alternate processes are suggested by the scientists. A few notable advantages of these processes are : (i) reasonably good yields of the products; (ii) fast reaction times; (iii) avoidance of toxic solvents. :

Over the years efforts have been made to develop catalytic systems employing hydrogen peroxide as a more environmentally friendly oxidant, being safe and relatively cheap, highly atom efficient and releasing eco-friendly water as the only byproduct.

Baeyer-Villiger oxidation of cyclic ketones with 35% hydrogen peroxide as a green oxidant mediated by monomeric Pt(II) complexes bearing alkyl diphosphines greatly benefits from the employment of water with anionic surfactants as reaction medium. Under such conditions, the reaction shows enhanced catalytic activity compared to that with organic solvents.

A new method for lactone synthesis with bis (trimethylsilyl) peroxide as the oxidant and ionic liquids as solvents is reported. It provides two possibilities for the Baeyer-Villiger reaction course. The first of these is based on simply exchanging dichloromethane, the classical solvent for Baeyer-Villiger oxidation, for the ionic liquid bmim NTf<sub>2</sub>, which results in increased product yields. Ionic liquids (ILs) have been described as one of the most promising new reaction mediums—green alternatives to volatile organic solvents. The second possibility is the elimination of the Baeyer-Villiger reaction catalyst and use of 1-butyl-3-methylimidazolium trifluoromethanesulfonate as both the solvent and catalyst. This method gives lactones in high yields with the possibility of ionic liquid recycling.

Microwave (MW) assisted reactions are currently having considerable importance in the synthesis of organic compounds. Considering the remarkable application of Baeyer-Villiger reaction in the synthesis of natural products and steroid-peptide conjugates, it is reported that Baeyer-Villiger oxidation of carbonyl compounds with special reference to steroidal ketones under MW irradiation justifying its accelerating effect.

An efficient magnetic nanocomposite catalyst (Fe<sub>3</sub>O<sub>4</sub>@GO) was synthesized and utilized as a sustainable and convenient catalyst for Baeyer-Villiger oxidation. Under solvent free conditions, hydrogen peroxide as green oxidant, Fe<sub>3</sub>O<sub>4</sub>@GO showed an efficient catalytic activity and excellent selectivity for Baeyer-Villiger oxidation at room temperature.

#### **Application :**

The Baeyer-Villiger oxidation is used to make a lactone that served as a crucial building block that ultimately led to the synthesis of zoapatanol, the transformation of the steroid dehydroepiandrosterone to anticancer agent testololactone occurs by use of a Baeyer-Villiger oxidation induced by fungus that produces Baeyer-Villiger monooxygenases.

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## 6.8 Summary

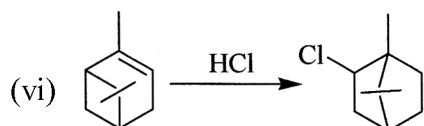
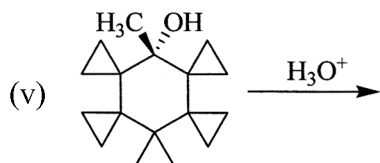
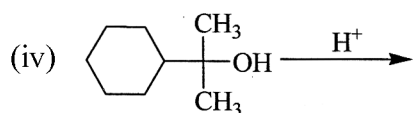
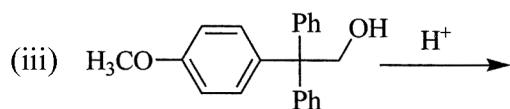
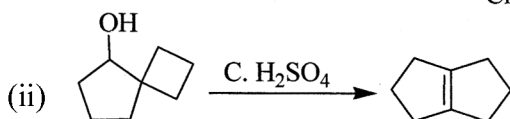
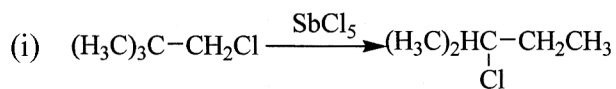
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- Molecular rearrangements in which a group shifts from one position in the molecule to a different one in the product, is an important class of reactions, 1, 2 shifts are the most common.
- In this unit we have discussed rearrangements for different types of electron deficient systems.
- The factors deciding the course of rearrangement reactions like stability of the carbocations and the migratory aptitudes of the migrating groups are important to predict the major product.
- We have discussed rearrangements involving carbocations, like Wagner-Meerwein rearrangement, Pinacol rearrangement, dienone-phenol; Wolff rearrangement in Arndt-Eistert synthesis, benzil- benzilic acid rearrangement, Demjanov rearrangement, Tiffeneau-Demjanov rearrangement.
- In rearrangements involving electron deficient nitrogen, Hofmann, Curtius Hofmann, Curtius, Lossen, Schmidt and Beckmann have been discussed along with their synthetic utility.
- Baeyer-Villiger oxidation, cumene hydroperoxide-phenol rearrangement and Dakin reaction have been taken as examples of a rearrangement involving electron deficient oxygen.
- Fries rearrangement and Claisen rearrangement are the examples of Aromatic rearrangements involving migration from oxygen to ring carbon.
- Migration from nitrogen to ring carbon involves in the case of Hofmann-Martius rearrangement, Fischer-Hepp rearrangement, N-azo to C-azo rearrangement, Bamberger rearrangement, Orton rearrangement and benzidine rearrangement.
- Rearrangement reactions by green approach have been discussed for the Fries rearrangement, Claisen rearrangement, Beckmann rearrangement and Baeyer-Villiger oxidation.

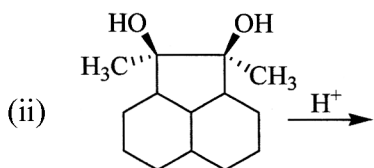
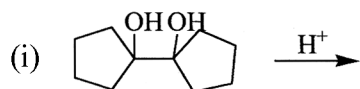


## 6.9 Additional Problems

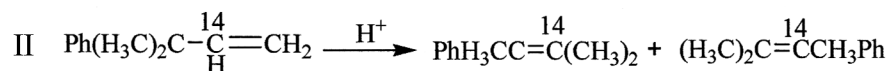
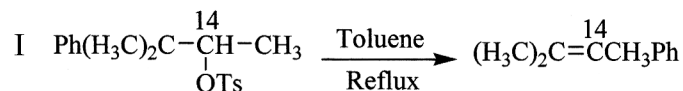
### 1. Give mechanism :



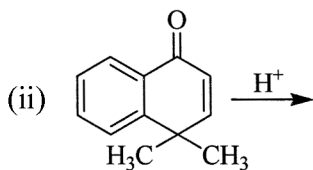
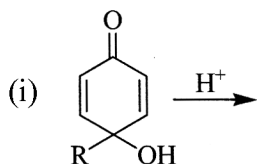
### 2. What happens in the following reactions :



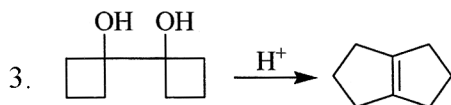
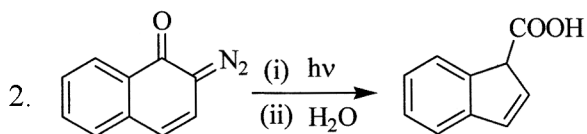
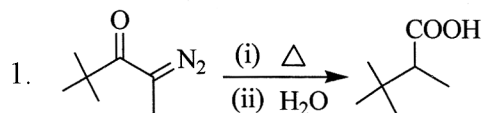
3. Explain the following rearrangement reactions where reaction I gives only one rearranged product whereas reaction II gives two rearranged products.



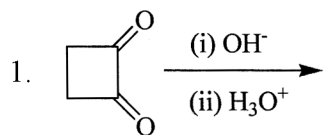
4. Give the expected products of the following reactions.

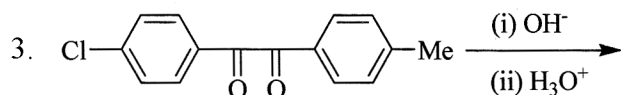
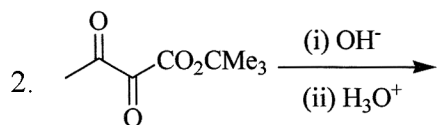


5. Give mechanism for the following reactions.

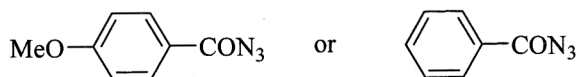


6. Predict the products with mechanism.





7. Which of the following compounds will undergo faster rearrangement?



8. Which compound will undergo the Beckmann rearrangement faster?  
Give reason in support of your answer.

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## 6.10 Reference Books

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- (i) Subrata Sengupta, Named reactions and uses of a few reagents in Organic chemistry, 1<sup>st</sup> Edition November 2010, Published by M/s Subrata Sen Gupta.
- (ii) Ratan Kr. Kar, Name Reactions and Rearrangements in Organic Chemistry, 1<sup>st</sup> Published 2016, Books and Allied (P) Ltd.
- (iii) Sanyal, S.N. (2003). Reactions, Rearrangements and Reagents (4 ed.). p. 90. ISBN 978-81-7709-605-7
- (iv) Harwood, L. M., Polar Rearrangements, Oxford Chemistry Primer, Oxford University Press.
- (v) Carruthers, W. Modern methods of Organic Synthesis, Cambridge University Press,
- (vi) Vollhardt, K. P. C.; Schore, N. E. "22". Organic Chemistry : Structure and Function (4th ed.). New York : Freeman. **2003**, p. 988. ISBN 0-7167-4374-4.
- (vii) March, J. *Advanced Organic Chemistry*, 3rd Ed.; John Wiley & Sons : Chichester, 1985; S. 499ff.

- (viii) Mundy, B. P.; Ellerd, M. G.; Favaloro Jr, F. G. *Name Reactions and Reagents in Organic Synthesis*, Wiley Interscience, New Jersey, 2005.
- (ix) Smith, M. B.; March, J. *March's Advanced Organic Chemistry* (Wiley, 2001) (ISBN 0-471-58589-0)

# NOTES

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