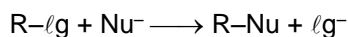




# Organic Reaction Mechanisms-III

## Nucleophilic substitution reaction ( $S_N$ ) :

Replacement (displacement) of an atom or group by an other atom or group in a molecule is known as substitution reaction. If substitution reaction is brought about by a nucleophile then it is known as nucleophilic substitution reaction. Generally substitution takes place at  $sp^3$  carbon.



Types of nucleophilic substitution reaction :

(I)  $S_N1$       (II)  $S_N2$       (III)  $S_Ni$

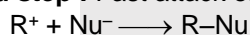
## Section (A) : Unimolecular nucleophilic substitution reaction ( $S_N1$ )

Nucleophilic substitution which involves two step process

- (a) **First step** : Slow step which involves ionisation (to form carbocation)

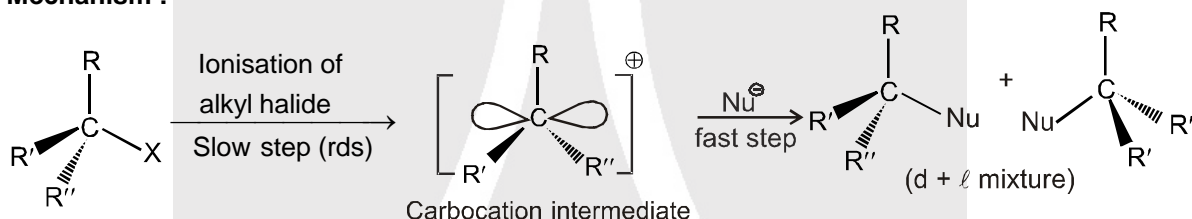


- (b) **Second step** : Fast attack of nucleophile on carbocation results into product.



### (1) $S_N1$ Reaction of Alkyl halide

Mechanism :



Characteristics of  $S_N1$  reactions :

1. It is unimolecular, two step process.
2. Carbocation intermediate is formed, so rearrangement is possible in  $S_N1$  reaction.
3. It is first order reaction.

4. **Kinetics of the reaction**      Rate  $\propto$  [Alkyl halide]

Rate of  $S_N1$  reaction is independent of concentration and reactivity of nucleophile.

5. **Energetics of the  $S_N1$  reaction :**

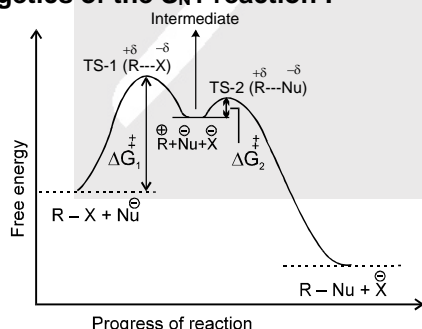


Figure : Free energy diagram for the  $S_N1$  reaction.

6. **Factors affecting the rate of  $S_N1$  reaction :**

(i) **The structure of the substrate** : The rds of the  $S_N1$  reaction is ionization step, a carbocation is formed in this step. This ionisation is strongly endothermic process, rate of  $S_N1$  reaction depends strongly on carbocation stability because carbocation is the intermediate of  $S_N1$  reaction which determines the energy of activation of the reaction.

Reactivity of  $S_N1 \propto$  stability of carbocation.

$S_N1$  reactivity :  $3^\circ > 2^\circ > 1^\circ > CH_3-X$



**(ii) Concentration and reactivity of the nucleophile :** The rate of  $S_N1$  reaction is unaffected by the concentration and nature of the nucleophile.

Weak and neutral nucleophile favours  $S_N1$  reaction.

Mostly solvents (protic) itself functions as nucleophiles in  $S_N1$  reaction, so  $S_N1$  reaction is termed as solvolysis reaction.

water  $\rightarrow$  hydrolysis

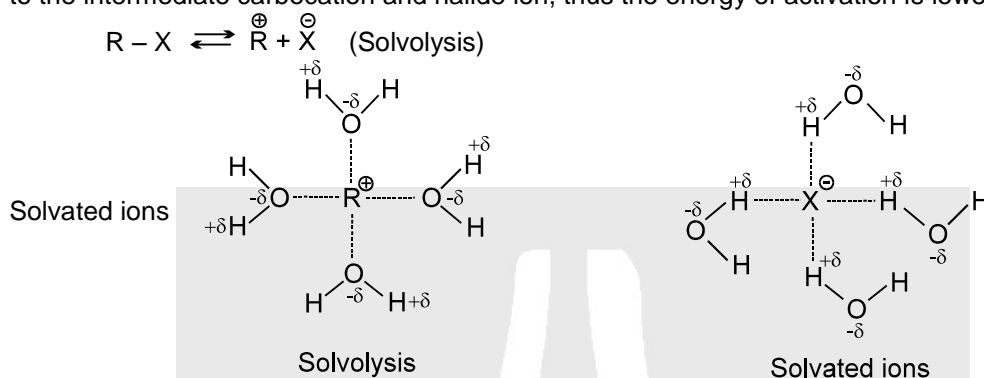
$C_2H_5OH \rightarrow$  ethanolysis

$CH_3COOH \rightarrow$  acetolysis

$NH_3 \rightarrow$  ammonolysis

**(iii) Effect of the solvent :** (Ionising ability of the solvent)

The use of a polar protic solvent will greatly increase the rate of ionisation of an alkyl halide in any  $S_N1$  reaction because it solvate cations and anions so effectively and stabilises the transition state leading to the intermediate carbocation and halide ion, thus the energy of activation is lower.



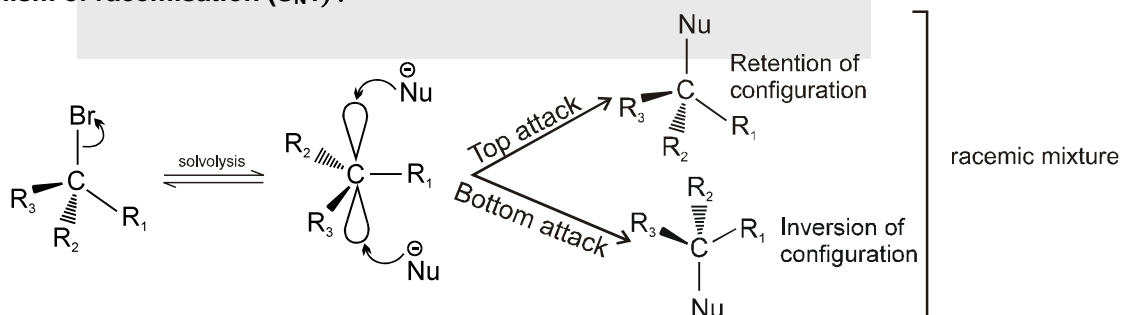
**Table :** Dielectric constants ( $\epsilon$ ) and ionisation rate of t-Butylchloride in few common solvents

Solvent	$\epsilon$	Relative rate
$H_2O$	80	8000
$CH_3OH$	33	1000
$C_2H_5OH$	24	200
$(CH_3)_2CO$	21	1
$CH_3CO_2H$	6	—

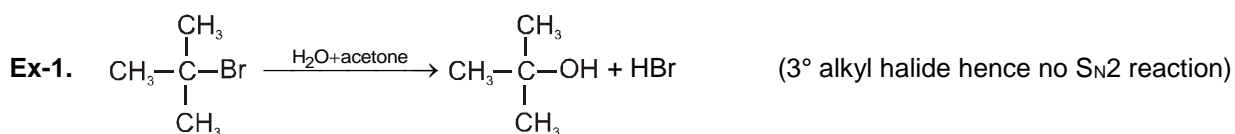
**(iv) The nature of the leaving group :** In the  $S_N1$  reaction the leaving group begins to acquire a negative charge as the transition state is reached. Stabilisation of this developing negative charge at the leaving group stabilises the transition state and this lowers the free energy of activation and thereby increases the rate of reaction. Leaving ability of halogen is  $F^- < Cl^- < Br^- < I^-$

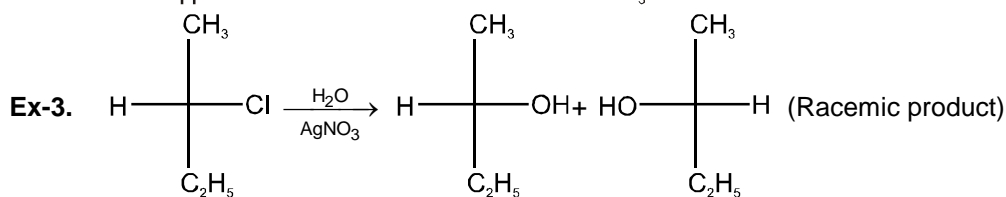
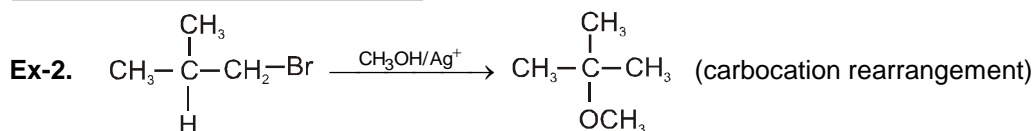
**7. Stereochemistry of  $S_N1$  reactions :** In the  $S_N1$  mechanism, the carbocation intermediate is  $sp^2$  hybridized and planar. A nucleophile can attack on the carbocation from either face, if reactant is chiral then attack of nucleophile from both faces gives enantiomers as the product, which is called racemisation.

**Mechanism of racemisation ( $S_N1$ ) :**



**Reagents for alkyl halide are :**  $H_2O$ ,  $RCOOH$ ,  $ROH$  &  $RSH$





## (2) S<sub>N</sub>1 Reaction of Alcohols

### (i) Reaction with hydrogen halides

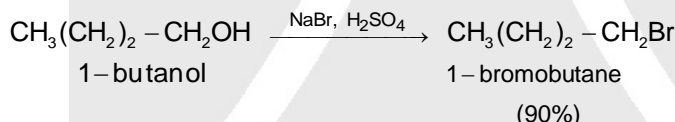
A common method is to treat the alcohol with a hydrohalic acid, usually HI or HBr. These acids are used to convert alcohols into the corresponding alkyl halides.

(i) In acidic solution, an alcohol is in equilibrium with its protonated form. Protonation converts the hydroxy group from a poor leaving group (OH)<sup>−</sup> into a good leaving group (H<sub>2</sub>O). If the alcohol is protonated all the usual substitution and elimination reactions are feasible, depending on the structure (1°, 2°, 3°) of the alcohol.

(ii) Halides are anions of strong acids, so they are weak bases. Solutions of HBr and HI contain nucleophilic Br<sup>−</sup> and I<sup>−</sup> ions.

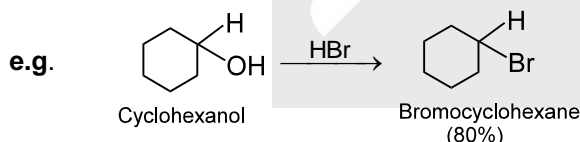
(iii) Concentrated hydrobromic acid rapidly converts t-Butyl alcohol to t-Butyl bromide. The strong acid protonates the hydroxyl group, converting it into a good leaving group. The hindered tertiary carbon atom cannot undergo S<sub>N</sub>2 displacement, but it can ionise to a tertiary carbocation. Attack by bromide ion gives the alkyl bromide. The mechanism is similar to S<sub>N</sub>1 mechanism.

(iv) 1-Butanol reacts with sodium bromide in concentrated sulfuric acid to give 1-Bromobutane by an S<sub>N</sub>2 displacement.



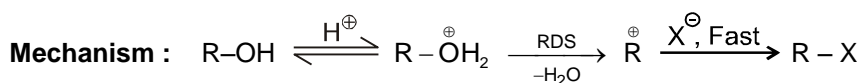
Protonation converts the hydroxy group to a good leaving group, but ionization to a primary carbocation is unfavourable. The protonated unbranched primary alcohol is well suited for the S<sub>N</sub>2 displacement.

(v) Secondary alcohols also react with HBr to form alkyl bromides usually by the S<sub>N</sub>1 mechanism.



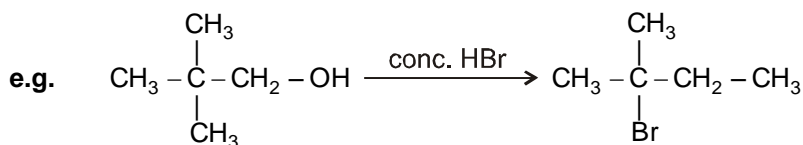
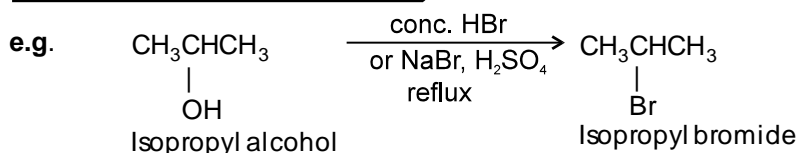
(vi) HCl (Hydrochloric acid) reacts with alcohols in much the same way that as the hydrobromic acid.

(vii) Chloride ion is a weaker nucleophile than bromide ion because it is smaller and less polarizable. Lewis acid, such as ZnCl<sub>2</sub>, is sometimes necessary to promote the reaction of HCl with primary and secondary alcohols.



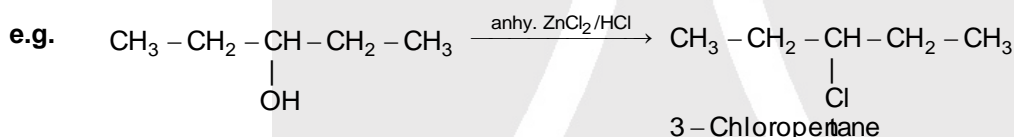
**Reactivity of HX :** **HI > HBr > HCl**

**Reactivity of ROH :** **3° > 2° > 1°**



### Lucas Reagent

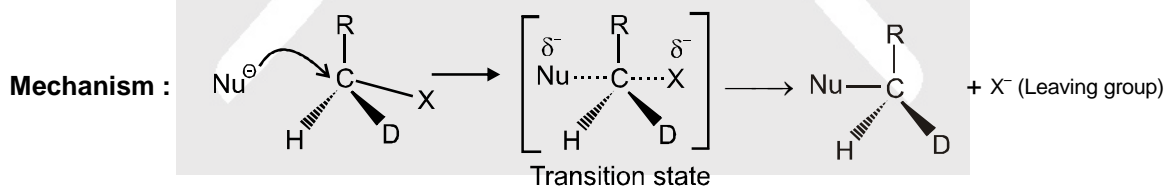
- A mixture of concentrated hydrochloric acid and anhydrous zinc chloride is called the Lucas reagent.
- Whether an alcohol is primary, secondary or tertiary is identified by the Lucas test, which is based upon the difference in reactivity of the three classes of alcohol towards hydrogen halides.
- Alcohol (of not more than six carbons in their molecule) are soluble in the Lucas reagent. The corresponding alkyl chlorides are insoluble.
- Formation of a chloride from an alcohol is indicated by the cloudiness that appears when the chloride separates from the solution hence, the time required for cloudiness to appear is a measure of the reactivity of the alcohol.
- A tertiary alcohol reacts immediately with the Lucas reagent, a secondary alcohol reacts within five minutes and a primary alcohol does not react appreciably at room temperature.



## Section (B) : Bimolecular nucleophilic substitution reaction (S<sub>N</sub>2)

Nucleophilic substitution in which incoming group replaces leaving group in one step only.

### (1) S<sub>N</sub>2 Reaction of Alkyl halide :



#### Characteristic of S<sub>N</sub>2

- It is bimolecular, one step concerted process
- It is second order reaction because in the rds both species are involved

**3. Kinetics of the reaction :**

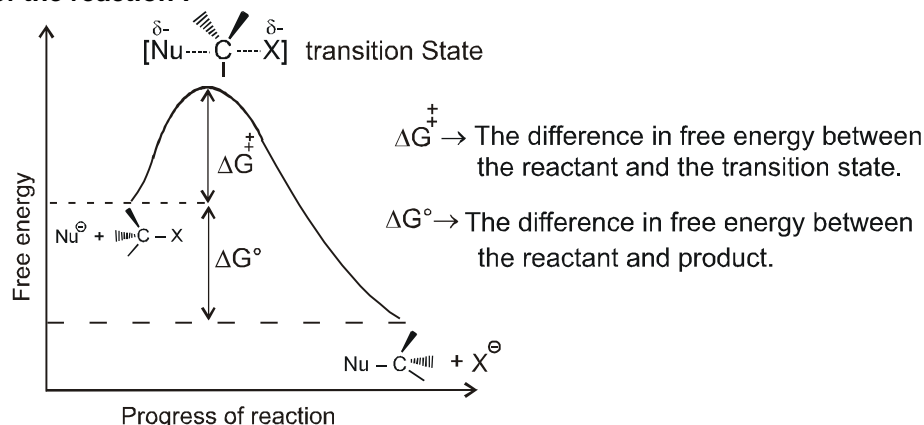
$$\text{rate} \propto [\text{alkyl halide}] [\text{nucleophile}]$$

$$\text{rate} = k[\text{alkyl halide}] [\text{nucleophile}]$$

If the concentration of alkyl halide in the reaction mixture is doubled, the rate of the nucleophilic substitution reaction is double. If the concentration of nucleophile is doubled the rate of reaction is also double. If the concentration of both are doubled then the rate of the reaction quadruples.



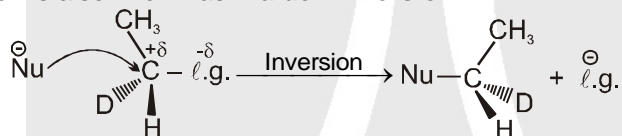
#### 4. Energetics of the reaction :



**Figure : A free energy diagrams for  $S_N2$  reaction**

5. No intermediates are formed in the  $S_N2$  reaction, the reaction proceed through the formation of an unstable arrangement of atoms or groups called transition state.

6. **The stereochemistry of  $S_N2$  reaction :** As we seen earlier, in an  $S_N2$  mechanism the nucleophile attacks from the back side, that is from the side directly opposite to the leaving group. This mode of attack causes an inversion of configuration at the carbon atom that is the target of nucleophilic attack. This inversion is also known as **Walden inversion**.



7. **Factor's affecting the rate of  $S_N2$  reaction :** Number of factors affect the relative rate of  $S_N2$  reaction, the most important factors are

(i) **Effect of the structure of the substrate :**

**$S_N2$  reactivity  $CH_3 > 1^\circ > 2^\circ \gg 3^\circ$  (unreactive)**

The important reason behind this order of reactivity is a steric effect. Very large and bulky groups can often hinder the formation of the required transition state and crowding raises the energy of the transition state and slow down the rate of reaction.

**Table :** Relative rate of reaction of alkyl halides by  $S_N2$  mechanism.

Substituent	Compound	Relative rate
Methyl	$CH_3X$	30
$1^\circ$	$CH_3CH_2X$	1
$2^\circ$	$(CH_3)_2CHX$	0.02
Neopentyl	$(CH_3)_3CCH_2X$	0.00001
$3^\circ$	$(CH_3)_3CX$	$\sim 0$

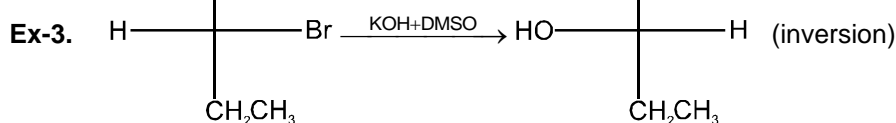
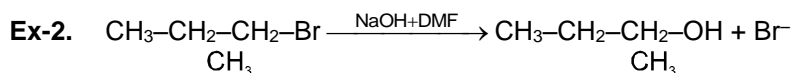
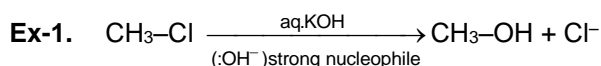
(ii) **Concentration and reactivity of the nucleophile :**

- As nucleophilicity of nucleophile increases rate of  $S_N2$  increases.
- Anionic nucleophiles mostly give  $S_N2$  reaction
- A stronger nucleophile attacks upon  $\alpha$ -carbon with faster rate than the rate of departing of leaving group.

(iii) **The effect of the solvent :** Polar aprotic solvent have crowded positive centre, so they do not solvate the anion appreciably therefore the rate of  $S_N2$  reactions increased when they are carried out in polar aprotic solvent.

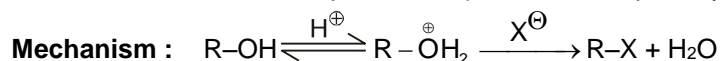
(iv) **The nature of the leaving group :** Weaker bases are good leaving groups. A good leaving group always stabilise the transition state and lowers its free energy of activation and there by increases the rate of the reaction. Order of leaving ability of halide ion  $F^- < Cl^- < Br^- < I^-$

**Reagents for alkyl halide are :**  $OH^-$ ,  $SH^-$ ,  $I^-$ ,  $CN^-$ ,  $NH_3$  ..... (strong anionic nucleophiles)



## (2) S<sub>N</sub>2 Reaction of Alcohol :

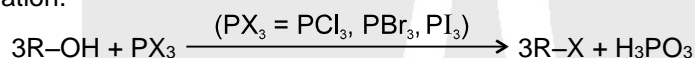
(i) **Reaction with HX :** The protonated β unbranched primary alcohol is well suited for the S<sub>N</sub>2 reaction.



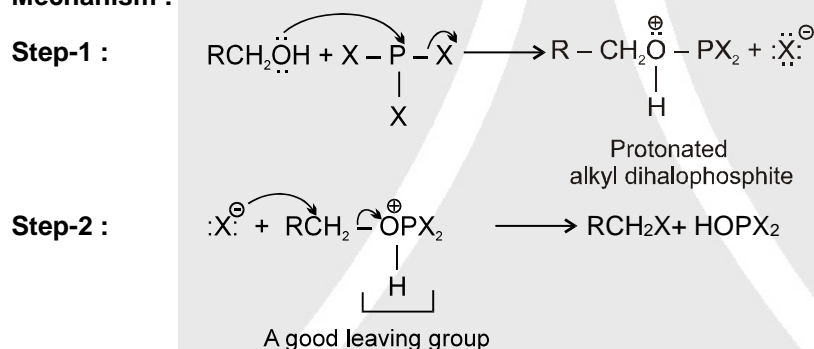
## (ii) Reaction with phosphorus trihalides

Several phosphorus halides are useful for converting alcohols to alkyl halides. PBr<sub>3</sub>, PCl<sub>3</sub>, & PCl<sub>5</sub> work well and are commercially available.

Phosphorus halides produce good yields of most primary and secondary alkyl halides, but none works well with tertiary alcohols. The two phosphorus halides used most often are PBr<sub>3</sub> and the P<sub>4</sub>/I<sub>2</sub> combination.



**Mechanism :**

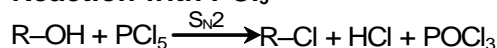


### Remarks

The mechanism for the reaction involves attack of the alcohol group on the phosphorus atom, displacing a halide ion and forming a protonated alkyl dihalophosphite

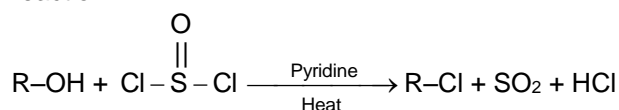
In second step a halide ion acts as nucleophile to displace HOPX<sub>2</sub>, a good leaving group due to the electronegative atoms bonded to the phosphorus.

## (iii) Reaction with PCl<sub>5</sub>



## (iv) Reaction with thionyl chloride in presence of pyridine

Thionyl chloride (SOCl<sub>2</sub>) is often the best reagent for converting an alcohol to an alkyl chloride. The by products (gaseous SO<sub>2</sub> and HCl) leave the reaction mixture and ensure that there can be no reverse reaction.



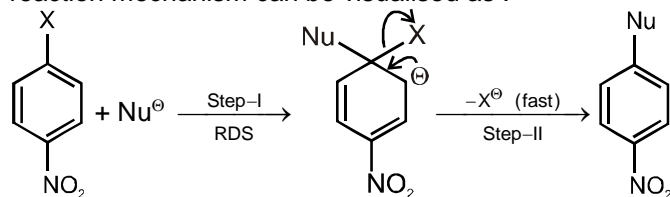




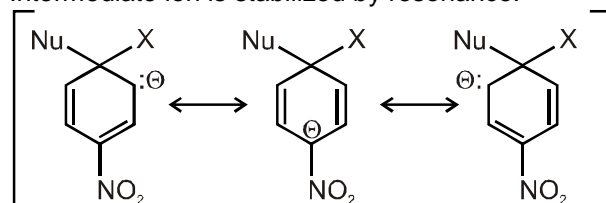


## Section (C) : Bimolecular aromatic nucleophilic substitution reaction ( $S_N2$ Ar)

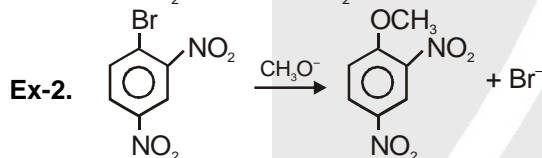
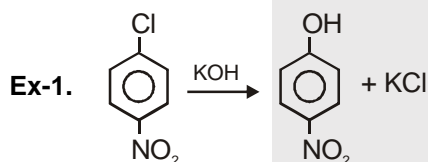
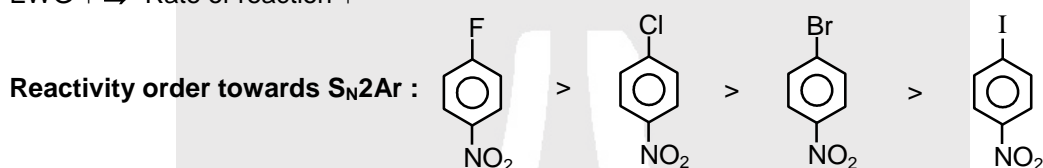
This is the characteristic reaction of arylhalides with ortho or para electron withdrawing substituent. The reaction mechanism can be visualised as :



Intermediate ion is stabilized by resonance.



EWG  $\uparrow \Rightarrow$  Rate of reaction  $\uparrow$



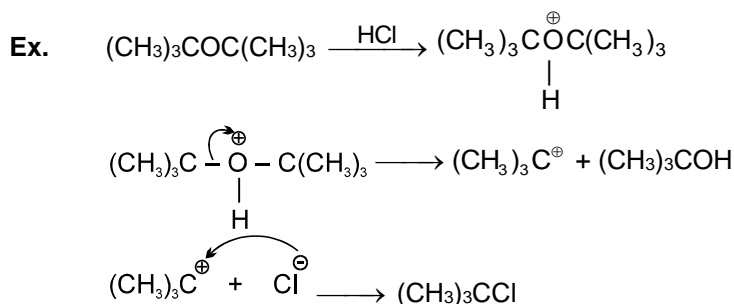
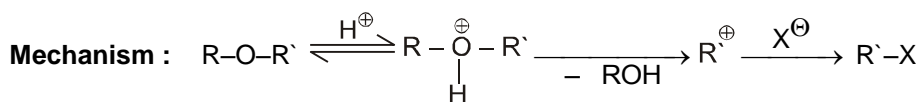
## Section (D) : Nucleophilic substitution reaction of Ethers & Epoxides

### (1) $S_N1$ Reaction of Ethers

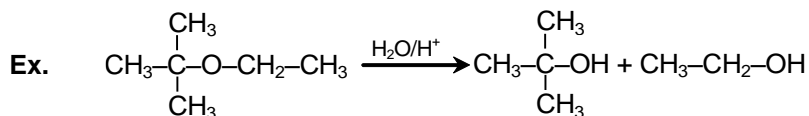
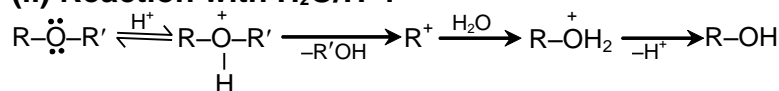
#### (i) Reaction with HX :

Ethers are unreactive towards most bases, but they can react under acidic conditions. A protonated ether can undergo substitution or elimination with the expulsion of an alcohol. Ethers react with conc. HBr and HI because these reagents are sufficiently acidic to protonate the ether, while bromide iodide are good nucleophiles for the substitution.

If R or R' is  $3^\circ$  then mechanism will be  $S_N1$  otherwise  $S_N2$ .

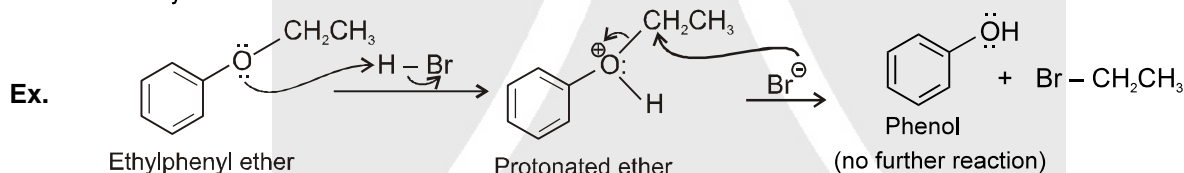
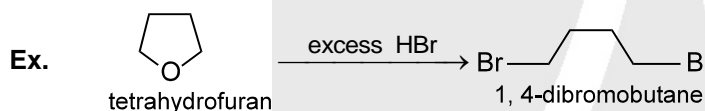
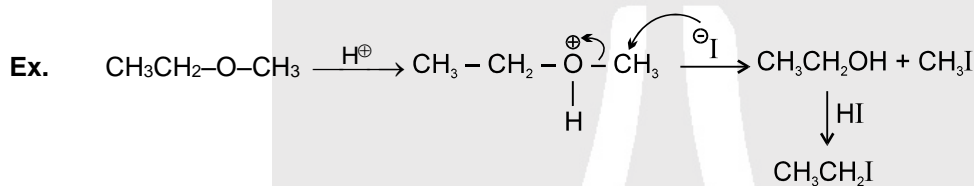
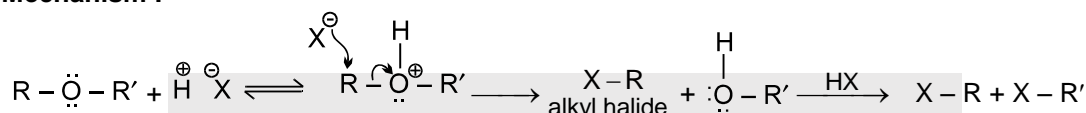
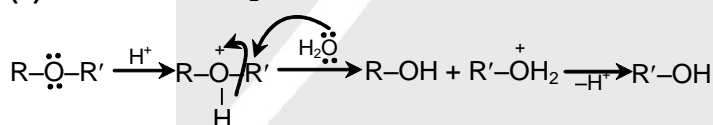




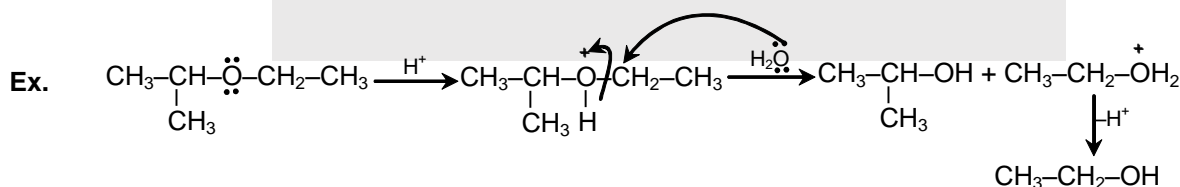
**(ii) Reaction with  $\text{H}_2\text{O}/\text{H}^+$  :****(2)  $\text{S}_\text{N}2$  Reaction of Ethers****(i) Reaction with  $\text{HX}$  :**

A protonated ether can undergo substitution reaction. Ether react with conc. HBr and HI because these reagents are sufficiently acidic to protonate the ether. If R or R' is  $3^\circ$  then mechanism will be  $\text{S}_\text{N}1$  otherwise  $\text{S}_\text{N}2$ .

**Mechanism :**

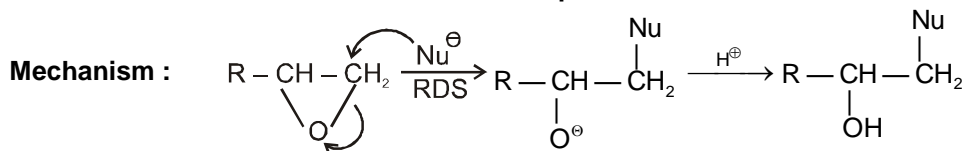
**(ii) Reaction with  $\text{H}_2\text{O}/\text{H}^+$  :**

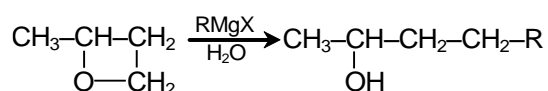
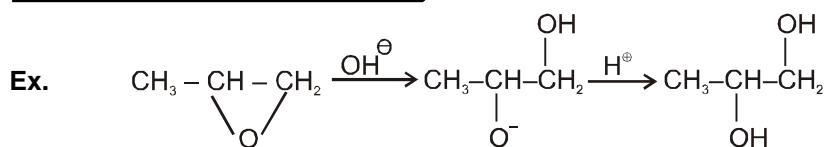
(Steric crowding  $\text{R} > \text{R}'$ )

**(3) Nucleophilic substitution reaction of Epoxide :**

Epoxides are much more reactive than ether because of angle strain in three membered ring therefore epoxide readily undergo nucleophilic substitution reaction.

In basic medium mechanism is  $\text{S}_\text{N}2$ . Nucleophile attacks on less hindered carbon.





In acidic medium mechanism is  $\text{S}_{\text{N}}1$  type. Nucleophile attacks on more substituted carbon.

