Chapter 4

ALIPHATIC NUCLEOPHILIC SUBSTITUTION

4.0 ALIPHATIC NUCLEOPHILIC SUBSTITUTION

Replacement (displacement) of an atom or group by any other atom or group is known as substitution reaction. If a substitution reaction is brought about by a nucleophile then it is known as nucleophilic substitution reaction. Substitution reactions at a saturated (sp^3 hybridised) carbon are amongst the most studied organic reactions. All nucleophiles are Lewis bases and contain at least an unshared pair of electrons. In nucleophilic substitutions a nucleophile attacks the substrate carbon with its unshared electrons to form a covalent bond, and the leaving group (the **nucleofuge**) departs with the electron pair of the breaking bond. Thus, like nucleophiles (entering groups), the leaving groups are also Lewis bases. In general, an aliphatic nucleophilic substitution may be depicted as follows :

$$\underset{\text{Nucleophile}}{Nu^{\ominus}} + R^2(R^3)(R^1)C{-}L \longrightarrow Nu{-}C(R^3)(R^2)(R^1) + \underset{\text{Leaving group}}{L^{\ominus}}$$

Substrate — Substitution product

Nucleophiles may be neutral or negatively charged, whereas substrates undergoing nucleophilic substitution may be neutral or positively charged. Thus, there are following four charge types for nucleophilic substitutions :

Nucleophile — Substrate — Product — Leaving group

(i) $\underset{\text{Negative}}{{}^{\ominus}OH} + \underset{\text{Neutral}}{CH_3{-}Br} \longrightarrow CH_3{-}OH + Br^{\ominus}$

(ii) $\underset{\text{Neutral}}{Me_3N} + \underset{\text{Neutral}}{Me{-}I} \longrightarrow Me_4\overset{\oplus}{N} + I^{\ominus}$

(iii) $Br^{\ominus} + \underset{\text{Positive}}{Me{-}\overset{\oplus}{O}H_2} \longrightarrow Me{-}Br + H_2O$

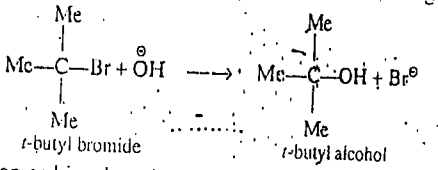
(iv) $\underset{\text{Neutral}}{H_2S} + \underset{\text{Positive}}{R{-}\overset{\oplus}{N}Me_3} \longrightarrow R{-}SH_2 + Me_3N$

A substitution reaction in which the solvent acts as a nucleophile is called solvolysis reaction or solvolysis. Depending on nucleophiles, substrates, leaving groups and reaction conditions, several mechanisms are possible for aliphatic nucleophilic substitution reactions but the most common are

SN1 and SN2 mechanisms. The reactions involving SN1 mechanism are called as SN1 reactions and those involving the SN2 mechanism are called as SN2 reactions. SN1 denotes substitution nucleophilic unimolecular, and SN2 denotes substitution nucleophilic bimolecular.

4.1 SN1 MECHANISM

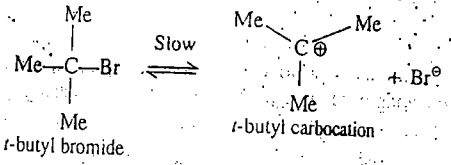
Let us take the example of alkaline hydrolysis of *t*-butyl bromide to give *t*-butyl alcohol.



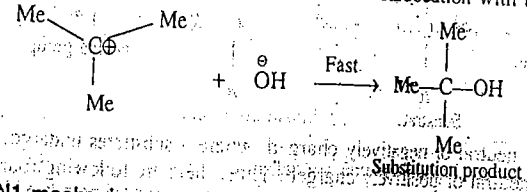
This is an SN1 reaction and involves the SN1 mechanism discussed below :

SN1 mechanism is a two-step process.

The first step is slow heterolysis of the substrate to give an intermediate carbocation. This is rate-determining step.



The second step is fast combination of the intermediate carbocation with the nucleophile.



Evidence for the SN1 mechanism

1. Kinetics : The SN1 reaction is a first order reaction following the rate law given below:

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

That is, the rate of the SN1 reaction depends only on the concentration of the substrate and it is independent of the concentration and nucleophilicity of the attacking nucleophile. Thus, kinetics is a very strong evidence for SN1 mechanism.

2. Stereochemistry : The SN1 reactions proceed with partial racemisation and some inversion.

In SN1 reactions an intermediate carbocation is formed which is planar, and the nucleophile should attack with equal facility from either side of the plane, resulting in complete racemisation. However, in practice the expected complete racemisation is rarely observed. Usually, there is 5 to 20% inversion. This may be explained by considering that the attack by a nucleophile occurs before the leaving group has completely departed from the neighbourhood of the carbocation, thus, to a certain extent the leaving group shields the front-side of the carbocation from attack. Consequently, the backside attack is preferred to some extent resulting in the inversion of configuration. The more stable the carbocation, the greater is the proportion of racemisation. This is because in such cases the leaving group gets time to leave the neighbourhood of the carbocation before the

attack by a nucelphile occurs, thus, there is almost equal facility for attack from either side of the carbocation plane leading to a greater degree of racemisation. For example, the solvolysis of (+)PhCHMeCl, which can form a stabilised benzylic carbocation, leads to 98% racemisation, while (+)C_6H_{13}CHMeCl (2-octyl chloride), where no comparable stabilisation can occur, leads to only 34% racemisation. In solvolysis reactions, the more nucleophilic the solvent, the greater is the proportion of inversion. This is due to the fast attack of the more nucleophilic solvent molecule from the backside but, not from the front-side which is shielded by the leaving group. For example, the solvolysis of (+)PhCHMeCl in mixture of 80% acetone and 20% water leads to 98% racemisation (see above), but in the more nucleophilic water alone to only 80%, *i.e.*, the greater proportion of inversion.

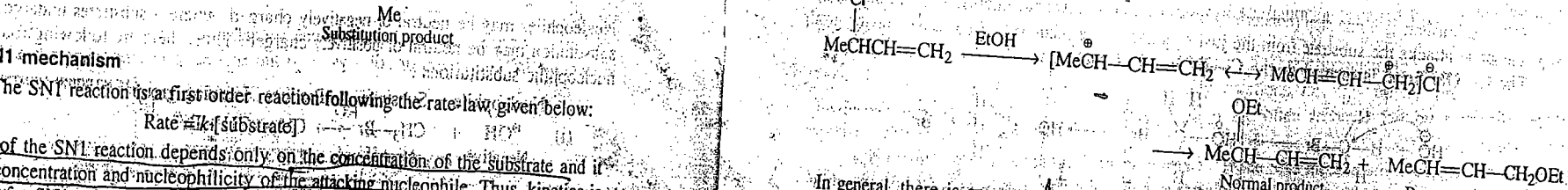
The role of ion pairs

The stereochemistry of SN1 reactions discussed above is easily understandable if the heterolysis in its rate-determining step follows the following sequence :

$$\underset{\text{I}}{R{-}X \rightleftharpoons R^{\oplus}X^{\ominus}} \rightleftharpoons \underset{\text{II}}{R^{\oplus} \parallel X^{\ominus}} \rightleftharpoons \underset{\text{III}}{R^{\oplus} + X^{\ominus}}$$

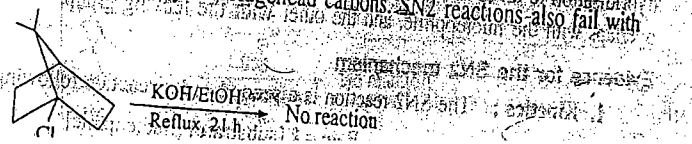
Here I is *an intimate, contact* or *tight ion pair*, II a solvent separated ion pair, and III the dissociated ions (each surrounded by solvent molecules). In I and II, $X^{\ominus}$ is called the *counterion*. The reaction in which the intimate ion pair recombines to give the original substrate is referred to as *internal return*. The reaction product can be formed by the attack of nucleophile at any stage. The *intimate ion* I is likely to lead to inversion, as the attack can take place from the backside, but not from the front-side which is shielded by $X^{\ominus}$. Attack in II is more likely from backside, leading to racemisation, whereas attack on III can take place with equal facility from either side. Thus, as we proceed from I to III the degree of racemisation increases, and proportion of inversion decreases. As the stability of $R^{\oplus}$ increases and the power of attacking nucleophile decreases, the proportion of III increases.

3. Formation of rearranged products : Rearrangement is one of the characteristic features of carbocations. Because of strong correlation between rearrangement and formation of carbocations, rearrangement is often taken as an indication of an SN1 mechanism, which are frequently accompanied by rearrangement. For example :

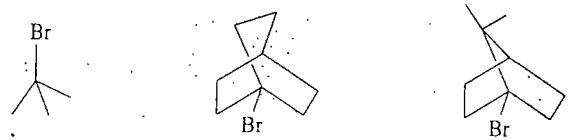


In general, there is greater number of by-products in the case of SN1 reaction as compared to the SN2 which is a one-step process involving no intermediate, hence, does not undergo rearrangement. In fact, the formation of different products from a single substrate, the reaction which follows the first order kinetics is a classic evidence that the reaction is proceeding through an intermediate.

4. No substitutions at bridgehead carbons : Substitution reactions under SN1 conditions either do not take place or proceed very slowly at bridgehead carbons. SN2 reactions also fail with



these substrates, though for different reasons (Section 4.2). SN1 reactions proceed through carbocations which must be planar. Because of rigid cage like structures of the substrates, bridgehead carbon atoms cannot assume planarity, hence, heterolysis leading to the formation of carbocation is also prevented. Consequently, bridgehead carbons are resistant towards substitution by the SN1 mechanism. For example, 1-chloroapocamphane does not react on refluxing with 30% KOH in 90% ethanol for 21 hours, although analogous open-chain systems react readily. However, if the rings are large enough, SN1 reactions should be possible, because nearly planar carbocation may be expected there. For example, [2, 2, 2]bicyclic systems undergo SN1 reactions much faster than smaller bicyclic systems, though the reaction is still slower than with analogous open-chain systems. Thus, the following rates were observed for solvolysis in 80% aqueous ethanol at 25°C :



Open chain system (*t*-butyl bromide)	[2, 2, 2]bicyclic system (*t*-bromobicyclo[2, 2, 2]octane)	[2, 2, 1]bicyclic system (1-bromo-7, 7-dimethyl bicyclo[2, 2, 1] heptane)
Rate: 1	$\approx 10^{-6}$	$\approx 10^{-14}$

4.2 SN2 MECHANISM

Let us take the example of alkaline hydrolysis of methyl bromide to give methanol.

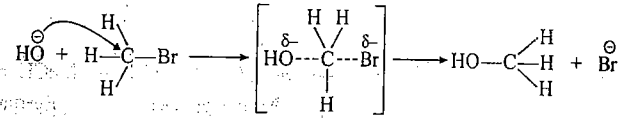
$$CH_3Br + \overset{\ominus}{O}H \longrightarrow CH_3OH + Br^{\ominus}$$

(Direct displacement)

This is an SN2 (direct displacement) reaction and proceeds through the SN2 mechanism discussed below :

SN2 mechanism is a one-step (concerted) process and involves no intermediate. In this reaction the nucleophile attacks the substrate from the just opposite (back) side (at 180°) to the leaving group.

The C—OH bond is formed as the C—Br bond is broken :



Transition state Substitution product

The energy necessary to break the C—Br bond is supplied by simultaneous formation of the C—OH bond. In the transition state (TS) the nucleophile and the leaving group are both 50% bonded to the carbon being attacked. The three nonreacting groups and the central carbon atom are approximately coplanar in the TS, *i.e.*, the central carbon atom has gone from its initial sp^3 hybridisation to an sp^2 state with an approximately perpendicular *p* orbital. One lobe of this *p* orbital overlaps with the nucleophile, and the other with the leaving group.

Evidence for the SN2 mechanism

1. Kinetics : The SN2 reaction is a second-order reaction following the rate-law given below:

$$\text{Rate} = k\,[\text{substrate}]\,[\text{nucleophile}]$$

That is, the rate of the SN2 reaction depends on both the concentration of the substrate and that of the attacking nucleophile. This rate law has been found to apply in many cases. If a large excess of nucleophile is present, *e.g.*, in solvolysis, the mechanism may still be bimolecular, although the experimentally determined kinetics will be first order :

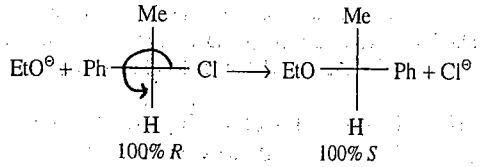
$$R = k\,[\text{substrate}]$$

Such kinetics are called *pseudo first order*. Thus, the kinetic evidence does not necessarily lead to correct conclusions in all the cases.

We have noted that the 2 in SN2 denotes bimolecular. It must be remembered that it is not always the same as second order.

As mentioned above in the case of solvolysis, the molecularity is 2 but the reaction shows the first order kinetics. The molecularity refers to the number of species (molecules, ions, etc.) that are undergoing bond-breaking and/or bond-formation in one step of the reaction, usually the rate-determining step. The molecularity is not an experimentally determined quantity, while the order of a reaction is experimentally determined. The molecularity has significance only in the light of the particular mechanism chosen for the reaction and is susceptible to re-evaluation, in the light of additional experimental information about the reaction in a way that the order cannot be.

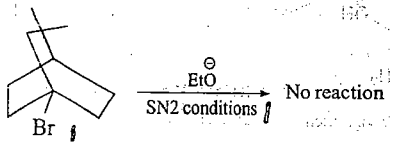
2. Stereochemistry : The SN2 reaction proceeds with inversion of configuration at the carbon at which the substitution has taken place. SN2 reaction is a stereospecifc reaction. For example :



Thus, in the SN2 reaction an enantiomerically pure reactant leads to an enantiomerically pure product with inversion of configuration. This is a very strong evidence for the SN2 mechanism because it predicts inversion of configuration in view of the attack of the nucleophile from the backside of the leaving group in a one-step process. This inversion of configuration is called *Walden inversion* (1893) and was observed long before the SN2 mechanism was proposed by Hughes and Ingold (1937).

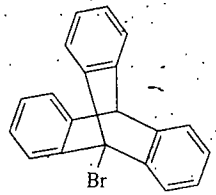
3. Formation of a single substitution product : SN2 reactions usually yield single substitution products. This is evidence that these are one-step reactions, *i.e.*, they do not proceed via reactive intermediates. This is unlike SN1 reactions which are often accompanied by rearrangement, and involve carbocation intermediate.

4. No substitution at bridgehead carbons : If the SN2 mechanism is correct, the compounds with potential leaving groups at bridgehead carbons should not be able to react by this mechanism. This is because the SN2 mechanism requires the backside attact by the nucleophile, inversion of configuration, and coplanarity of the three nonreacting groups in the TS all of which are prevented at the bridgehead carbons due to rigid cage like structures of the compounds containing the bridgehead carbons. For example, under SN2 conditions 1-bromo-3,3-dimethylbicyclo[2,2,2]octane is resistant towards reaction with ethoxide ion, whereas the open-chain analogues underwent the reactions readily.



Problem 1. *Explain why 1-bromotriptycene is inert to nucleophilic substitution by both the SN1 and SN2 mechanisms?*

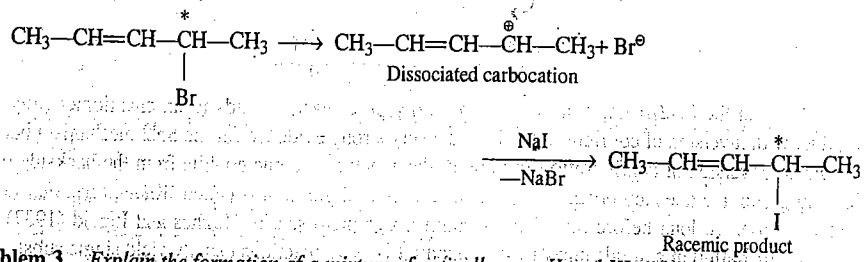
Solution : SN1 reactions proceed through carbocation intermeidate which has planar structure. Because of the following rigid cage like structure of 1-bromotriptycene, the bridgehead carbon cannot assume planarity, hence, the formation of a carbocation at the bridgehead position does not take place. Consequently, 1-bromotriptycene is inert to SN1 reactions.



SN2 reactions require the backside attack by the nucleophile, inversion of configuration, and coplanarity of the three nonreacting groups in the TS, all of these are prevented at the bridgehead due to the rigid cage like structure of 1-bromotriptycene. Thus, it is inert to nucleophilic substitution by SN2 mechanism.

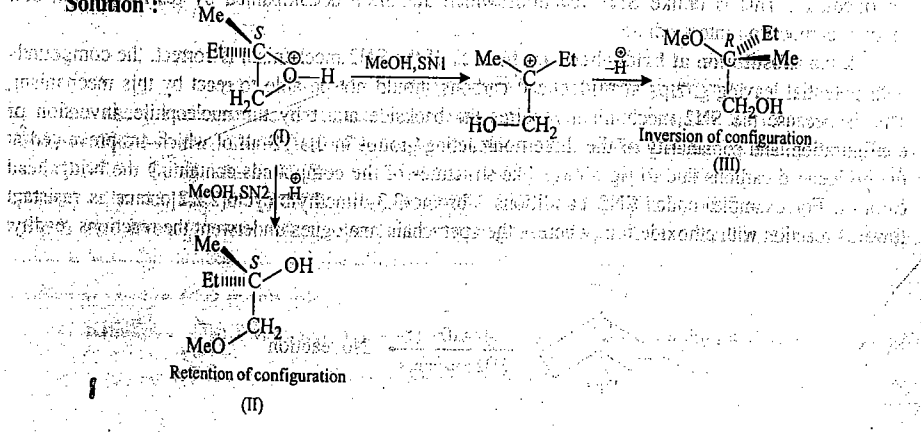
Problem 2. *(±)-4-Bromo-2-pentene forms a racemic product on treatment with sodium iodide. Explain why?*

Solution : This is due to the formation of relatively stable allylic carbocation which is attacked from either side of its plane to give a racemic product. It should be noted that there is no leaving group ($Br^{\ominus}$) in the neighbourhood of the carbocation to shield its front-side.



Problem 3. *Explain the formation of a mixture of optically pure II and III without racemisation when epoxide I reacts with acidic methanol (for structures of I-III see the solution).*

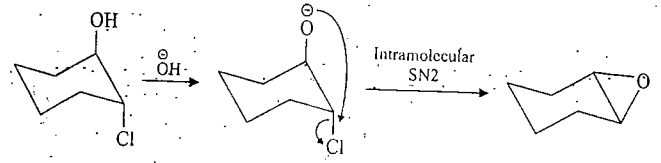
Solution :



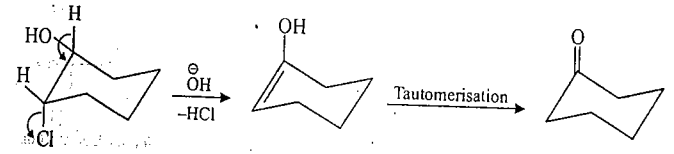
SN2 reaction occurs at the less hindered carbon of the protonated epoxide I without disturbing the chiral centre to give the product II with retention of configuration. SN1 attack occurs on the *t*-carbon of the epoxide to give III. The front-side of the involved carbocation is shielded by the leaving group (—OH), thus, the attack occurs from the backside resulting in inversion of configuration.

Problem 4. *Trans-2-chlorocyclohexanol gives epoxycyclohexane in high yield on treatment with a base, whereas the cis isomer does not react in this way. Explain why?*

Solution : In the *trans* isomer nucleophilic $—O^{\ominus}$ replaces Cl by a backside attack (intramolecular SN2) to give epoxycyclohexane in high yield.



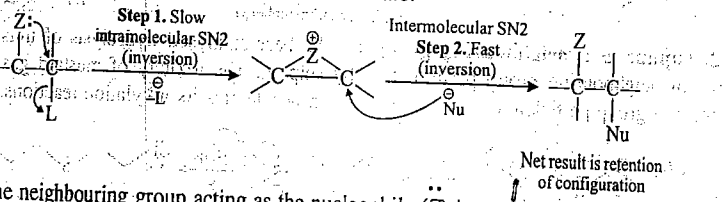
In the case of *cis* isomer, the nucleophilic $—O^{\ominus}$ is not in a favourable position for the backside attack. Here Cl and H are *trans* to each other and undergo elimination to give a vinyl alcohol which tautomerises to a ketone.



The backside attack by nucleophile is an essential requirement of SN2 without which these reactions are not possible.

4.3 NEIGHBOURING GROUP PARTICIPATION (NEIGHBOURING GROUP MECHANISM)

A number of nucleophilic substitution reactions are known which occur with complete retention (not inversion or racemisation) of configuration and with unexpectedly greater rate of reaction. In these cases usually there is an atom or group with an unshared electron pair β to the leaving group (or sometimes farther away). The mechanism operating in such cases is called *neighbouring group mechanism* or *neighbouring group participation*. It consists of two consecutive SN2 substitutions with inversion of configuration, thus, the net result is retention of configuration. In the first step of this reaction the neighbouring group acts as a nucleophile pushing out the leaving group. In the second step the external nucleophile pushes out the neighbouring group. *A common feature of all neighbouring group mechanisms is the formation of a cyclic intermediate.*



Since, the neighbouring group acting as the nucleophile (Z) is present in the same molecule and is immediately available for the attack, such reactions occur thousands times faster than comparable

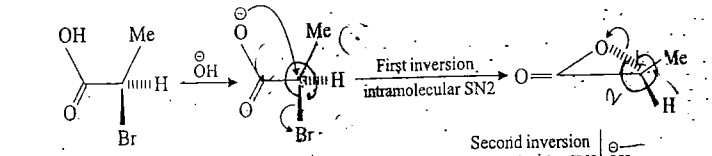
intermolecular nucleophilic substitutions. *This rate enhancement by neighbouring group participation is called anchimeric assistance and such reactions are called anchimerically assisted reactions.*

The neighbouring group mechanism follows the first-order rate law shown below :

$$\text{Rate} = k\,[\text{substrate}]$$

That is, the external nucleophile ($Nu^{\ominus}$) does not take part in the rate-determining step.

1. Oxygen as a neighbouring group : The classic example of neighbouring group participation is the alkaline hydrolysis of 2-bromopropanoate anion to lactate anion in which the carboxylate anion participates as a neighbouring group. When 2-bromopropanoic acid is treated with dilute alkali, it gives lactate anion with complete retention of configuration.

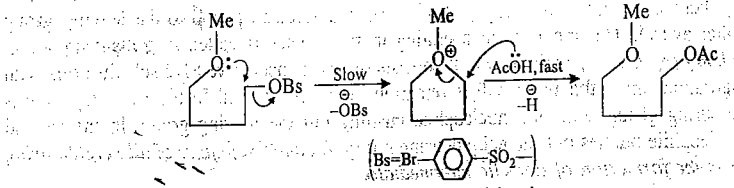


(*R*)-2-bromopropanoic acid

Net result is retention
(*R*)-Lactate anion

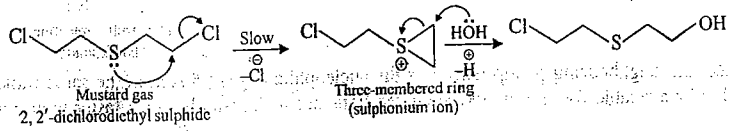
However, with concentrated sodium hydroxide (*R*)-2-bromopropanoic acid gives (*L*)-lactate anion. This reaction proceeds with inversion of configuration and is a typical SN2 reaction.

The hydroxyl group itself or via the alkoxide ion may participate as a neighbouring group. Alkoxy groups behave similar to hydroxyl groups in neighbouring group participation, *i.e.*, they show anchimeric assistance in the fromation of five-membered rings, and to far less extent in the formation of a six-membered rings. For example, the acetolysis of 4-methoxybutyl brosylate is ~ 650 times faster than that of *n*-butyl brosylate.



p-bromobenzensulphonyl

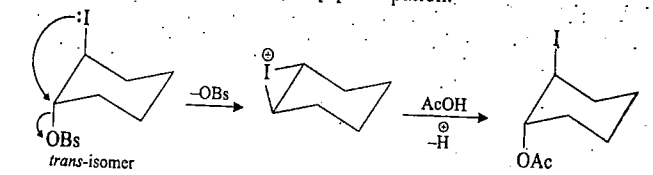
2. Suphur as a neighbouring group : The base-catalysed hydrolysis of mustard gas is an example of neighbouring group participation by sulphur. The toxicity of mustard gas is because of neighbouring group participation by sulphur, which accelerates its alkylation reactions.



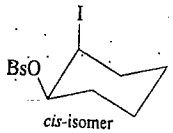
Mustard gas
2, 2′-dichlorodiethyl sulphide

Three-membered ring
(sulphonium ion)

3. Halogens as neighbouring group : A very good example of neighbouring group participation by a halogen (iodo group) is the acetolysis of *trans*-2-iodocyclohexyl brosylate which is 1.7×10^6 times faster than the acetolysis of the *cis* isomer in which the iodo group cannot attack from the backside, thus, there is no neighbouring group participation.

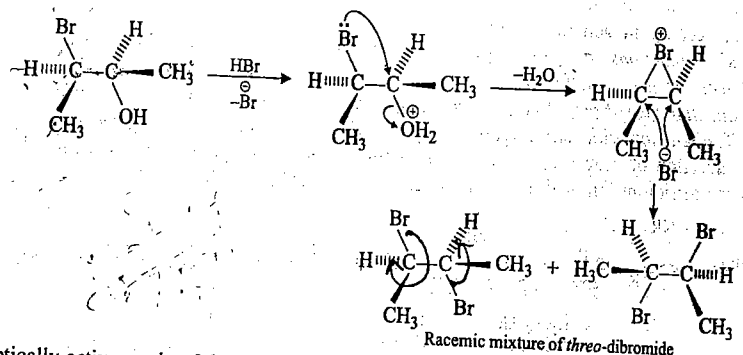


trans-isomer



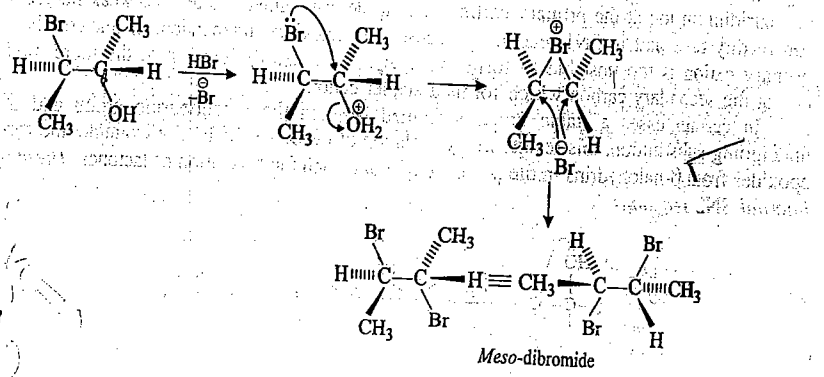
cis-isomer

Another example of participation of a halogen as a neighbouring group is that of bromine. When optically active *threo*-3-bromo-2-butanol is treated with HBr, it gives an equimolar mixture of *R,R* and *S,S* enantiomers (racemic mixture), *i.e.*, the reaction proceeds with retention of configuration indicating participation by bromine.



Racemic mixture of *threo*-dibromide

Optically active *erythro*-3-bromo-2-butanol also reacts with HBr with retention of configuration to give the *meso*-product which indicates the participation of bromine.

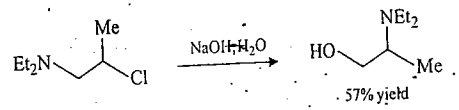


Meso-dibromide

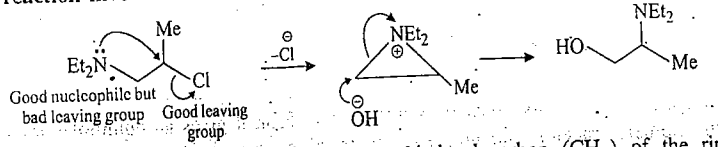
The above results can be explained by the formation of cyclic bromonium ion intermediate.

In many neighbouring group mechanisms the cyclic intermediates formed are not symmetrical. In such cases substitution and rearranged products are often formed together. Rearrangements occur when a participating group is bonded to a different atom in the product. For example, see below nitrogen as a neighbouring group.

4. Nitrogen as a neighbouring group : Let us take an example showing rearrangement during the neighbouring group participation by nitrogen atom. The following reaction gives 57% of the rearranged product.

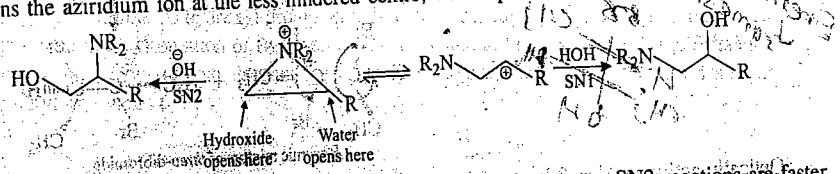


This reaction involves aziridinium ion intermediate :



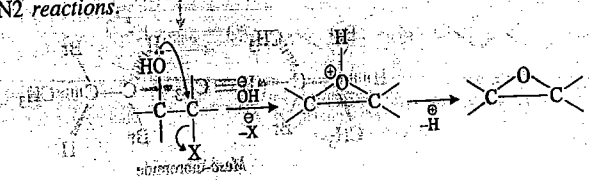
The hydroxide ion chooses to attack the less hindered carbon (CH_2) of the ring and a rearrangement results. In the above substrate substitution at secondary carbon is slow with external nucleophile, because in general, secondary alkyl halides are slow to react by SN1 or SN2, and *intramolecular reactions are usually faster than intermolecular reactions. Thus, the above rearrangement occurs. Furthermore, intramolecular reactions, including neighbouring group participation, that give three-, five-, or six-membered rings are usually faster than intermolecular reactions. The reaction with rearrangement is faster than that without rearrangement.*

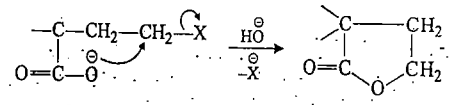
The direction of rearrangement can depend on the nucleophile : For example, hydroxide ion opens the aziridium ion at the less hindered centre; water opens the aziridinium ion at the more



hindered centre. Why? Hydroxide ion is a stronger nucleophile than water. SN2 reactions are faster at primary carbons, and they depend on the nucleophile. Thus, a stronger nucleophile (like OH) opens the aziridinium ion at the primary carbon, *i.e.*, at the less hindered site. The weak nucleophile water can readily take part in SN1 reactions because their rates are independent of nucleophile. Since the primary cation is too unstable to form, water opens the aziridinium ion at the more hindered site, *i.e.*, at the secondary carbon which forms a stabler cation.

In certain cases a stable bond is formed between the neighbouring group and the carbon undergoing substitution, this results in the isolation of cyclic products. For example, the formation of epoxides from β-halohydrins in the presence of a base, and the formation of lactones. *These are simple internal* SN2 *reactions.*





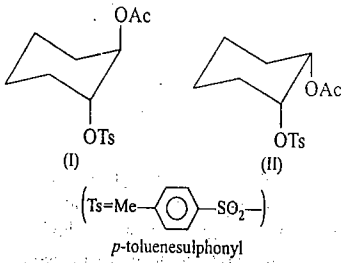
The following are some of the important neighbouring groups :

$\overset{\ominus}{COO}$ (but not COOH), OCOR, COOR, COAr, OR, OH, $\overset{\ominus}{O}$, NH_2, NH*R*, NR_2, NHCO*R*, *SH*, *SR*, $S^{\ominus}$, I, Br and Cl. The decreasing order of the effectiveness of halogens as neighbouring group is :

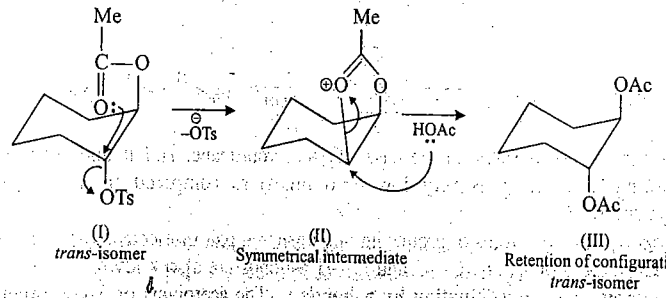
$$I > Br > Cl$$

In all of the neighbouring groups listed here, the internal nucleophilic attack is made by an atom with an unshared electron pair.

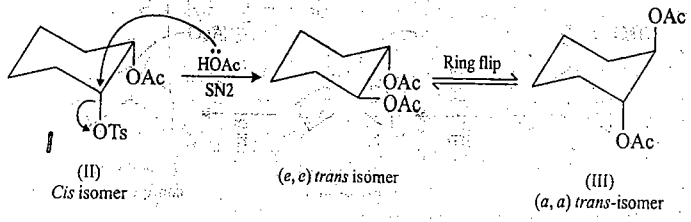
Problem 5. *Explain why the trans isomer (I) undergoes acetolysis 670 times faster than the cis isomer (II), and that the product has the same (cis) stereochemistry in both the cases?*



Solution : Acetolysis of (I) proceeds through neighbouring group participation by the AcO group resulting in the product with retention of configuration, and because of the anchimeric assistance rate of the acetolysis is very high.



On the other hand, in case of the *cis* isomer (II) the internal AcO group is not in a proper position to attack from the backside to the OTs group, hence, neighbouring group participation is not possible, and substitution takes place simply by intermolecular displacement of OTs by AcOH through SN2.



mechanism. *Just one* SN2 *step means inversion of configuration and no neighbouring participation means a slower reaction.*

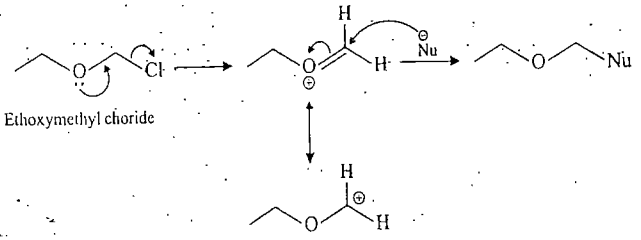
Since the configuration is retained in the case of the *trans* isomer (I), and inverted in the case of the *cis* isomer (II), the acetolysis of (I) and (II) results the same product (III) with the same stereochemistry, *i.e., trans.*

Problem 6. *Explain the following :*

(i) Ethoxymethyl chloride reacts with nucleophiles 10^6 *times faster than 1-chlorobutane.*

(ii) 2-Phenylthioethyl chloride reacts with water 600 times as fast as 1-chloropropane.

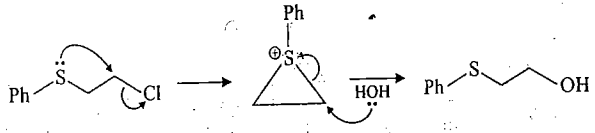
Solution : (i) Even though ethoxymethyl chloride is a primary alkyl halide, it follows SN1 mechanism as shown below. Here the heteroatom (oxygen) with unshared pair of electrons is present



on the same carbon as the leaving group and this significantly stabilises the carbocation formed resulting in the substitution by SN1 mechanism at a faster rate.

On the other hand, 1-chlorobutane, a simple primary alkyl halide without any additional rate accelerating factor undergoes SN2 reaction at a normal rate which is very low (10^6 times) than ethoxymethyl chloride.

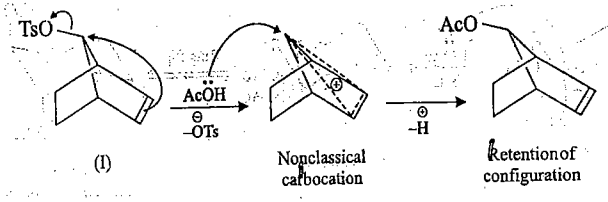
(ii) In the case of 2-phenylthioethyl chloride the rate of hydrolysis is 600 times faster than 1-chloropropane. This is because of the neighbouring group participation by a sulphide. Such type of

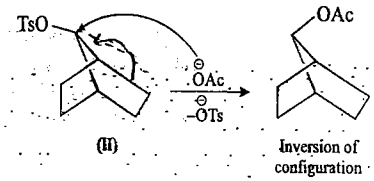


anchimeric assistance is not possible in the case of 1-chloropropane, and it undergoes simple SN2 reaction at a normal rate which is very low (600 times) as compared to that in the case of 2-phenylthioethyl chloride.

Besides properly situated atoms or groups having unshared pair of electrons, neighbouring group participation by C=C π- bonds, and C—C and C—H σ-bonds are also known.

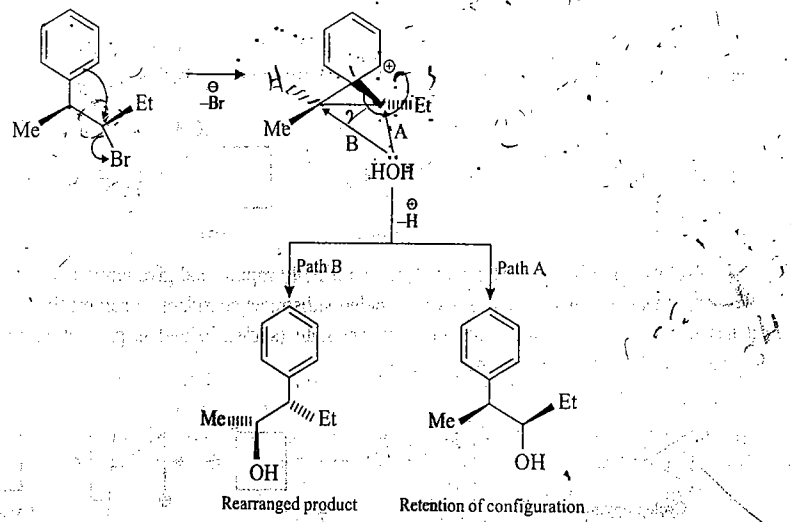
5. Neighbouring group participation by π-bonds : The acetolysis of 7-norbornenyl tosylate (I) is 10^{11} times faster than that of the saturated analogue, 7-norbornyl tosylate (II), and proceeds with retention of configuration, which gives a very strong evidence that C=C π-bond can act as a neighbouring group as shown below :



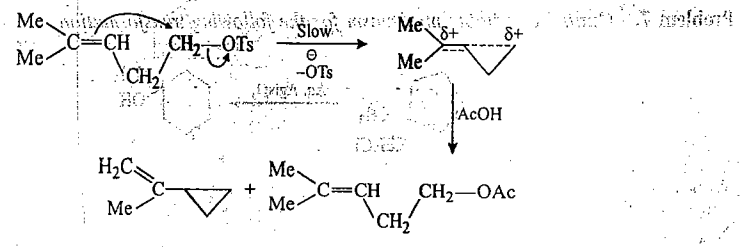


In the case of the saturated analogue (II) no such anchimeric assistance is available, thus, its acetolysis proceeds through simple SN2 reaction with inversion of configuration and at a normal rate which is very low (10^{11} times) as compared to that in the case of (I).

The neighbouring group participation by π-bonds of aromatic rings is more common than that of simple alkenes. The neighbouring group participation by an aryl group is indicated by retention of configuration and occurs through the formation of a resonance stabilised phenonium ion. As shown in the following example, the substitution takes place with retention of configuration (path A) and is accompanied by a rearranged product (path B) :

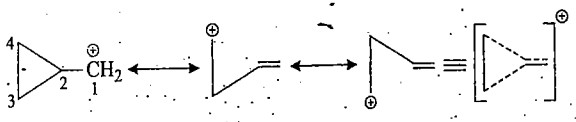


Double bonds in an open-chain system can also participate as neighbouring group, *e.g.*, the acetolysis of 4-methylpent-3-enyl tosylate proceeds abouts 1200 times faster than that of ethyl tosylate. The reaction involves a non-classical homoalkyl cation, and the products are 2-cyclopropylpropene and 4-methylpent-3-enyl acetate :



6. Neighbouring group participation by σ bonds :

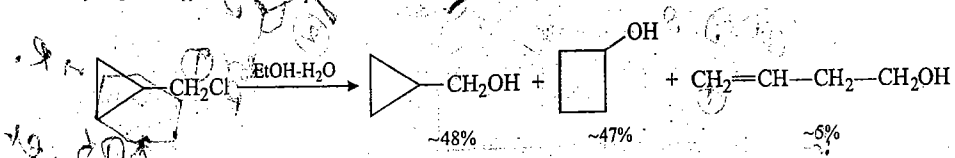
(i) Participation by C—C single (σ) bond : The cyclopropylmethyl system : In solvolysis of simple primary cyclopropylmethyl systems the rate is abnormally high because of participation by σ bonds of the ring. The ion which forms initially is an unrearranged cyclopropylmethyl cation which is symmetrically stabilised, *i.e.*, both the 2,3 and the 2,4 σ bond help to stabilise the positive charge. We know that *a cyclopropyl group stabilises an adjacent positive charge even better than phenyl group*. The cation may be represented as follows :



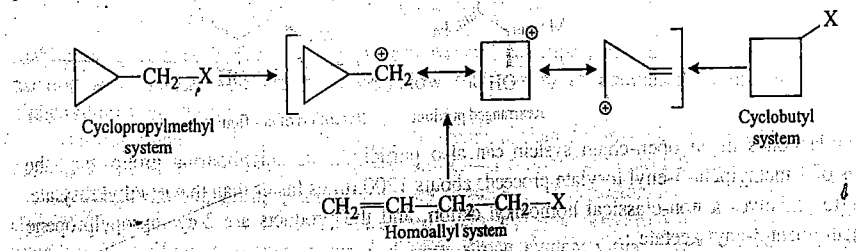
Unrearranged cyclopropylmethyl cation

The evidence that the above cation is symmetrical is that substitution of one or more methyl groups in the 3 and 4 positions increases the rate of solvolysis of cyclopropylcarbinyl 3,5-dinitrobenzoates by approximately a factor of 10 for each methyl group.

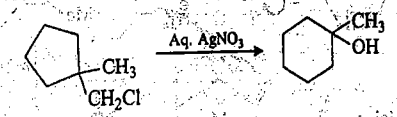
The solvolysis products of cyclopropylmethyl substrates often include not only unrearranged cyclopropylmethyl but also cyclobutyl and homoallyl compounds. For example :



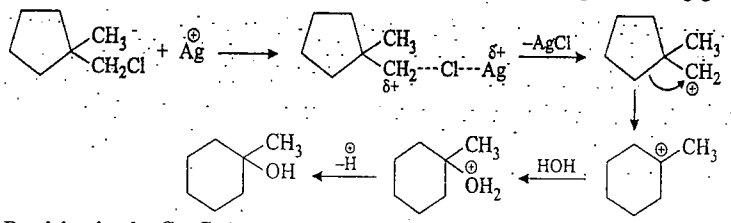
Cyclobutyl substrates also solvolyze abnormally rapidly and give similar products. Furthermore, when the reactions are carried out with labeled substrates considerable scrambling is observed. Thus, it has been suggested that a common intermediate (shown below) is present in these cases which explains the formation of all the products.



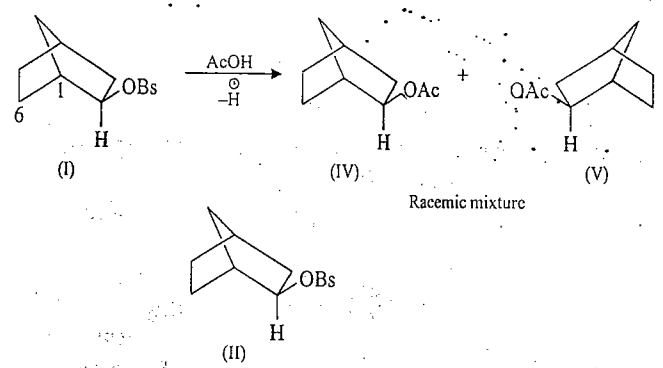
Problem 7. *Outline a suitable mechanism for the following transformation.*



Solution : $Ag^{\oplus}$ facilitates the formation of carbocation by removing the leaving group ($Cl^{\ominus}$).

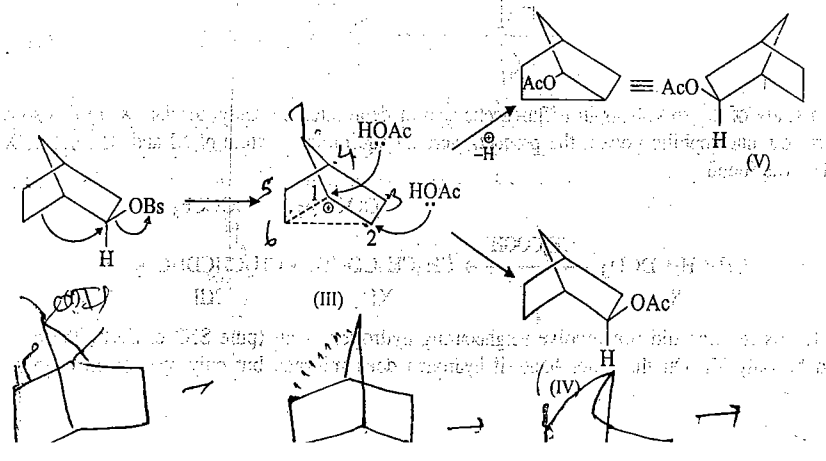


(ii) Participation by C—C single (σ) bond : The 2-norbornyl system: A good example of such participation is the acetolysis of optically active *exo*-2-norbornyl brosylate I which gave a racemic mixture of two *exo* acetates, no *endo* isomer was formed. Furthermore, I solvolyzed about 350 times faster than its *endo* isomer II. These two results (1) that solvolysis of an *exo* isomer gave only racemic *exo* isomers and (2) the high *exo*/*endo* rate ratio, were interpreted by Winstein and Trifan (1952) as an indication that the 1,6 bond assists in the departure of the leaving group and that a nonclassical intermediate III is involved.



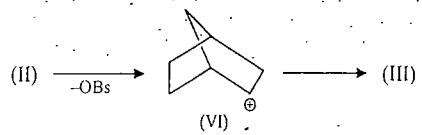
(II)

Solvolysis of the *endo* isomer (II) is not assisted by the 1,6 bond because it is not in a favourable position for backside attack. Consequently, solvolysis of II takes place at a normal rate. Therefore, much faster rate for the solvolysis of I must be caused by anchimeric assistance. The stereochemistry of the product is also explained by the intermediacy of the nonclassical carbocation III, since, in III



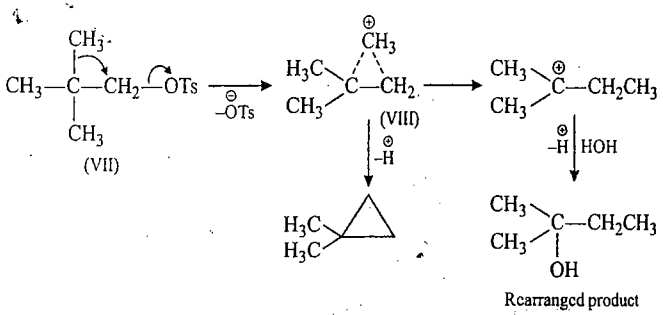
the 1,2 positions are equivalent and would be attacked by the nucleophile with equal facility but from the *exo* direction in either case.

Acetolysis of II also leads exclusively to the *exo* acetates IV and V. In this case it has been postulated that a classical ion VI is first formed and then converted to more stable III. Evidence for

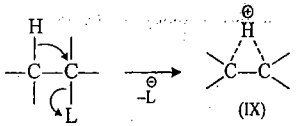


this interpretation is that the product from solvolysis of II is not racemic but contains somewhat more IV than V (corresponding to 3 to 13% inversion, depending on the solvent), suggesting that, when VI is formed, some of it goes to give IV before it is converted to III.

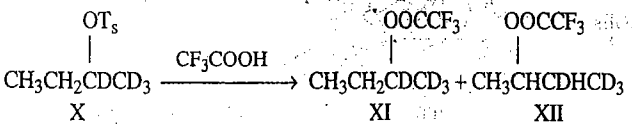
(iii) Methyl as a neighbouring group : Similar to other neopentyl systems, neopentyl tosylate VII undergoes almost exclusive rearrangement on solvolysis, and VIII must lie in the reaction path. Evidence has been presented that under some conditions the methyl group in the neopentyl system does indeed participate. Evidence that VIII is an intermediate is that small amounts of cyclopropanes (10-15%) can be isolated in these reactions. VIII is protonated cyclopropane and would give a cyclopropane on loss of a proton.



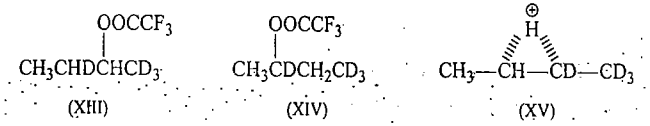
(iv) Hydrogen (C—H bond) as a neighbouring group : There is evidence that a β-hydrogen can participate through IX. Evidence that IX can be an intermediate in solvolysis reactions comes



from a study of the solvolysis in trifluroacetic acid of deuterated *sec*-butyl tosylate X. In this solvent of very low nucleophilic power, the products were an equimolar mixture of XI and XII, but no XIII or XIV was found.



If this reaction did not involve neighbouring hydrogen at all (pure SN2 or SN1), the pr t would be only XII. On the other hand, if hydrogen does migrate, but only open-chain cations e



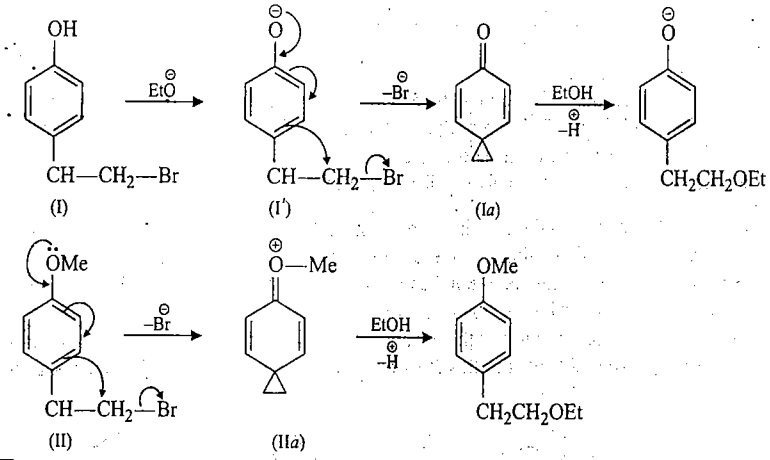
involved, then there should be an equilibrium among the following four cations leading not only to XI and XII,

$$CH_3CH_2\overset{\oplus}{C}DCD_3 \rightleftharpoons CH_3\overset{\oplus}{C}HCDHCD_3 \rightleftharpoons CH_3CD\overset{\oplus}{C}HCD_3 \rightleftharpoons CH_3\overset{\oplus}{C}DCH_2CD_3$$

but also to XII and XIV. The results are most easily compatible with the intermediacy of the bridged ion XV which can then be attacked by the solvent equally at the 2 and 3 positions.

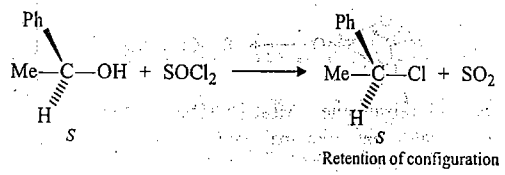
Problem 8. *Explain why ethanolysis of 2-(p-hydroxyphenyl)ethyl bromide in the presence of ethoxide ion is 10^6 times faster than that of 2-(p-methoxyphenyl)ethyl bromide.*

Solution : The oxygen atom in I′ is much more electron releasing than that in II, and so the intermediate (I*a*, which has been isolated) is much more stable than II*a*. Thus, the reaction involving the formation I*a* requires lower energy of activation than that involving the formation of II*a*. Consequently, the ethanolysis of I proceeds faster than that of II.

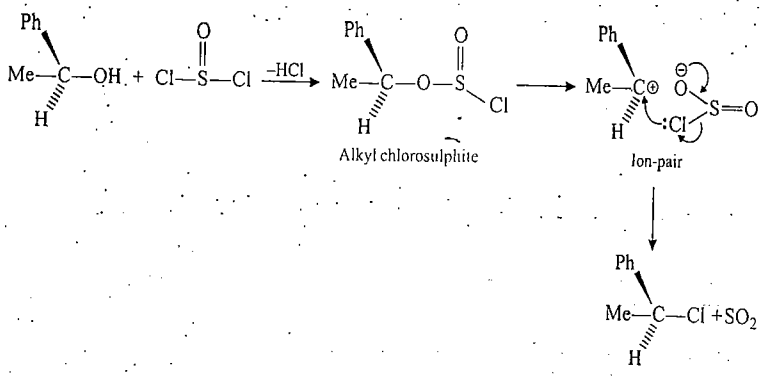


4.4 THE SNi MECHANISM

There are certain nucleophilic substitutions which proceed with retention of configuration even though no neighbouring group is involved. These reactions proceed through SNi (substitution nucleophilic internal) mechanism, and follow the second order kinetics. For example, the conversion of (*S*)-1-phenylethanol into (*S*)-1-phenylethyl chloride on treatment with thionyl chloride :



This reaction has been shown to follow the second order kinetics, but clearly cannot proceed by a simple SN2 mechanism because it would lead to inversion of configuration, whereas in the present reaction retention of configuration has been observed. Thus, the following SNi mechanism involving an ion-pair has been proposed for the above reaction :

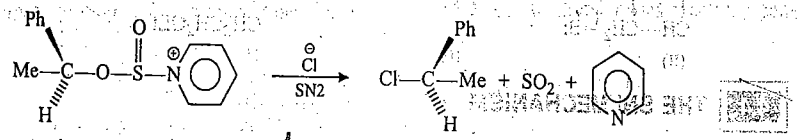


Because of the geometry of the ion-pair, the leaving group attacks from the same side as the original C—O bond with consequent retention of configuration. The above mechanism has been supported by the following facts :

(i) The true intermediate alkyl chlorosulphite has been isolated when the reaction is carried under mild conditions. The chlorosulphite is formed with retention of configuration because C—O bond is not broken during the reaction.

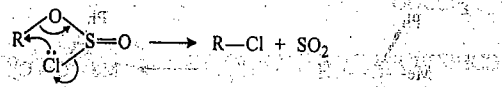
(ii) The rate of conversion of the alkyl chlorosulphite into the product increases with increasing polarity of the solvent and also with increasing stability of the carbocation ($PhCHMe^{\oplus}$). This shows that an ion-pair is almost certainly involved.

(iii) When (*S*)-1-phenylethanol and thionyl chloride react in the presence of a base, *e.g.*, pyridine, (*R*)-1-phenylethyl chloride is obtained, *i.e.*, inversion of configuration occurs. Inversion results because pyridine reacts with the alkyl chlorosulphite to give I before anything further can take place. The $Cl^{\ominus}$ freed in this reaction is an effective nucleophile which attacks from

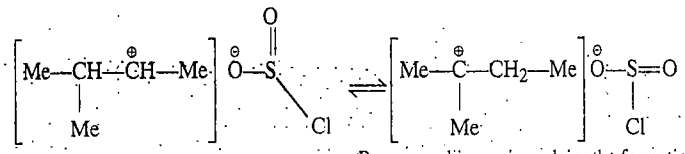


the backside of the C—O bond in a normal SN2 reaction leading to inversion of configuration.

It was previously believed that the mechanism was a one-step (concerted) process :

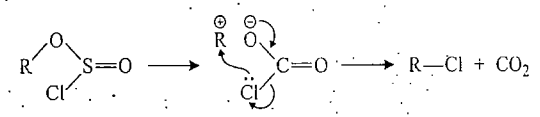


The fact that the chlorosulphite $Me_2CHCHMeOSOCl$ gives rearranged product Me_2CClCH_2Me on heating indicates that an ion-pair must be involved because there is no other way to explain the formation of the rearranged product :



Rearranged ion-pair explains the formation of the rearranged product

The SNi mechanism is relatively rare, its another example is the decomposition of ROCOCl (alkyl chloroformate) as follows:



4.5 MIXED SN1 AND SN2 MECHANISMS

Certain nucleophilic substituion reactions under a given set of conditions show all the characteristics of SN2 mechanisms; other seem to proceed by SN1 mechanism, but there are certain cases which cannot be characterized so easily. There seems to be something in between, a mechanistic borderline region where it is not clear whether the reaction is proceeding through SN1 or SN2 mechanism. Two theories have been devised for explaining these borderline cases:

1. Simultaneous SN1 and SN2 mechanisms : According to this theory borderline behaviour is caused by simultaneous occurring of both the SN1 and SN2 mechanisms in the some vessel, *i.e.*, some molecules react by the SN1, while others react by the SN2 mechanism.

2. The intermediate mechanism theory (Sneen, 1965) : This theory is very broad and applies not only to borderline cases but also to all nucleophilic substitutions at a saturated carbon. All SN1 and SN2 reactions can be accommodated by only one basic mechanism (the *ion-pair* mechanism). The substrate first ionises to an intermediate ion pair which is then converted to products :

$$RX \underset{}{\overset{k_1}{\rightleftharpoons}} R^{\oplus}X^{\ominus} \overset{k_2}{\rightleftharpoons} \text{products}$$

The difference between SN1 and SN2 mechanisms is that in the former case the formation of the ion pair (k_1) is rate-determining, whereas in SN2 mechanism its destruction (k_2) is rate-determining, *i.e.*, when $k_2 > k_1$, the mechanism is SN1, and when $k_1 > k_2$, the mechanism is SN2. The borderline behaviour is found when $k_1 = k_2$.

4.6 THE SET MECHANISM

In some nucleophilic substitution reactions where SN1 mechanism is highly probable, it has been shown, by esr detection of the intermediate, that free radicals are actually involved. In such cases a carbocation is a good electron acceptor and nucleophile is an electron donor. The mechanism involved is named as SET (single electron transfer) mechanisms, *e.g.*, the reaction between the triphenylmethyl cation and *t*-butoxide ion :

$$Ph_3C^{\oplus} + t\text{—}BuO^{\ominus} \longrightarrow Ph_3C^{\bullet} + t\text{—}BuO^{\bullet} \longrightarrow t\text{—}BuOCPh_3$$

4.7 FACTORS AFFECTING REACTIVITY IN SN REACTIONS

1. Effect of substrate structure : The rate-determining step in SN1 reactions is the formation of a carbocation. Thus, the order of reactivity of substrates in SN1 reactions is the same as the order of stability of carbocations they can form. The stabler a carbocation, the more readily it is formed.

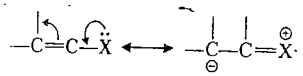
The following is decreasing order of reactivity of some substrates in SN1 reactions :

$$Ar_3CX > Ar_2CHX > R_3CX > ArCH_2X > -\overset{|}{C}=CHCH_2X > R_2CHX > RCH_2X$$

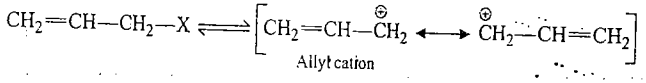
R = simple alkyl group like Me or Et; Ar = *e.g.*, Ph

The order of stability of carbocations can be explained by + I, + M and hyperconjugative effects.

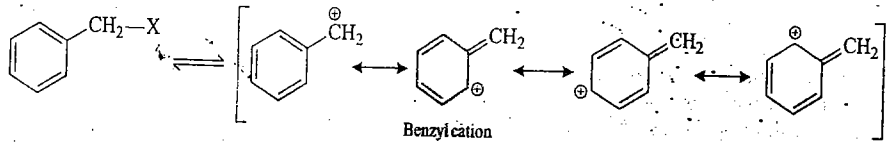
(a) Unsaturation at the α-carbon : Vinyl, acetylenic and aryl are very unreactive in SN reactions because the C—*X* bond acquires partial double bond character, *i.e.*, strengthened through resonance. Thus breaking of C—*X*, bond becomes difficult resulting in the inertness of these substrates toward SN reactions.



(b) Unsaturation at the β-carbon : SN1 reactions are highly favoured if there is unsaturation at the β-carbon. This because the resulting allyl or benzyl cations are stabilised by resonance :



Allyl cation

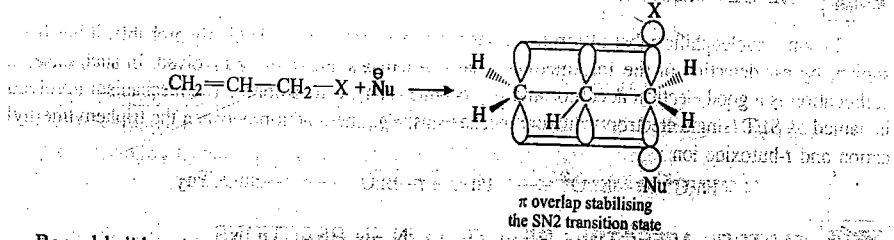


Benzyl cation

In general, SN1 rates at an allylic substrate are increased by any substituent in the 1 or 3 position which can stabilize the carbocation, *e.g.*, alkyl, aryl or halo group.

Rates of SN2 reactions for allylic and benzylic systems are also increased because of resonance in the transition state.

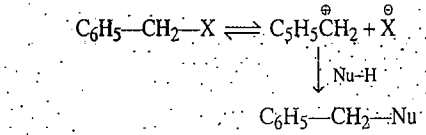
Allyl halides are more reactive than alkyl halides for SN2 reaction also. As an example, allyl bromide reacts with nucleophile by the SN2 mechanism about forty times faster than *n*-propyl bromide. This rate enhancement can be explained by allylic delocalisation of electrons in the transition state. When allyl halide undergoes SN2 reaction, the *p*-orbital that is partially bonding with the nucleophile and the leaving group overlap with the *pi* electrons of the double bond. This stabilising conjugation lowers the energy of the transition state, increasing the reaction rate.



π overlap stabilising the SN2 transition state

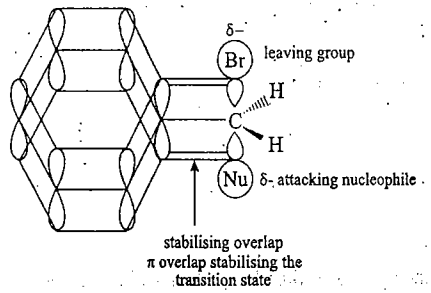
Benzyl halides give SN1 as well as SN2 reactions. In SN1 reactions benyl halide on ionisation gives benzyl carbocation which is resonance statrilised. The unsubstituted benzyl carbocation is about as stable as a seconday alkyl carbocations, and the 1-phenyl ethyl carbocation is about as stable as a tertiary alkyl carbocation.

Because benyl halides form relatively stable carbocation, they undergo SN1 reactions fairly easily.

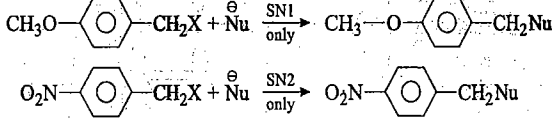


Like alkyl halides benzyl halide halides are about 100 times as reactive as primary alkyl halides in SN2 reactions.

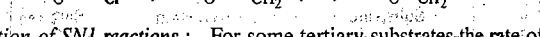
When benzyl halide undergoes SN2 reaction, the *p*-orbital that is partially bonding with the nucleophile and the leaving group overlap with the *pi* electrons in the ring. This stabilising conjugation lowers the energy of the transition state, increasing the reaction rate.



A benzyl compound having electron-donating (+*R* group) group at *ortho* or *para* or both favours SN1 reaction because electron-donating group stabilises benzyl carbocation. On the other band, benzyl compounds having electron-withdrawing group on these positions (*ortho* and/or *para*) always favours SN2 reactions. Electron-donating groups always stabilise carbocation whereas electron-withdrawing groups always stabilise the transition state.



(c) The presence of a heteroatom at the α-carbon : SN1 reactions are highly favoured if there is a heteroatom at the α-carbon because it highly stabilises the carbocation formed, *e.g.*,



(d) Steric acceleration of SN1 reactions : For some tertiary substrates the rate of SN1 reactions is greatly increased if the β-carbon is highly substituted. The formation of carbocations in such cases is facilitated because in this process the bond angle increases from 109.5° to 120° thereby reducing the non-bonded repulsive interactions (steric strain). For example, the rate constant for the solvolysis of tri (*t*-butyl) methyl chloride is 600 times larger than that of *t*-butyl chloride under identical reaction conditions.

(e) SN reactions at bridgeheads : Nucleophilic substitutions at bridgeheads are impossible or very slow as discussed in Sections 4.1 and 4.2.

(f) Alkyl groups at the α- and β-carbons in SN2 reactions : In the transition state of SN2 reactions, five atoms or groups are attached to the α-carbon. As the number and size of alkyl groups

increases on the α-and the β-carbons, the energy of transition state increases due to non-bonded repulsive interactions (steric strain), which decreases the rate of SN2 reactions. Thus, SN2 reactions are very sensitive to steric factor. For example, tertiary systems seldom react by SN2 mechanism, and neopentyl systems being primary systems react extremely slowly because of the larger size of *t*-butyl group present on the α-carbon.

The following is decreasing order of reactivity of some substrates in SN2 reactions :

$$Ar_3CX > Ar_2CHX > ArCH_2X > \underset{|}{\overset{|}{-C=CH-CH_2X}} > RCH_2X > R_2CHX > R_3CX$$

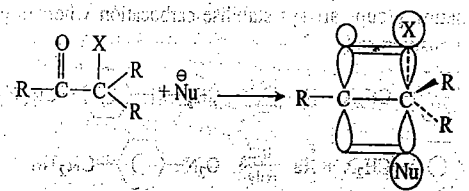
(R = simple alkyl goup like Me or Et; Ar = *e.g.*, Ph)

In general, primary alkyl substrates react by the SN2 mechanism, tertiary by the SN1 mechanism, and secondary alkyl substrates form borderline, *i.e.*, they mostly react by the SN2 and sometimes by the SN1 mechanism depending on the reaction conditions.

(g) presence of carbonyl group of α-carbon in alkyl halides in SN2 reactions : Presence of carbonyl group at α-carbon is one of the most suitable substrate for SN2 reaction. Electron-withdrawing group always decreases stability of carbocations but increases the stability of transition states.

Substrate	CH_3-X	$CH_2=CH-CH_2X$	$C_6H_5CH_2X$	CH_3-O-CH_2X	$C_6H_5-\overset{O}{\overset{\|}{C}}-CH_2X$
Relative rate for SN2 reaction	200	79	200	920	10^5

In fact primary, secondary and tertiary alkyl halides having carbonyl group at α-carbon gives SN2 reactiion. This is the only example kown in which reaction takes place at tertiary carbon. This because the carbonyl group accelerates SN2 reaction so much. The diagram of the transition state shows how the *p* orbitals on the carbonyl group are parallel to the *p*-orbital of halo group in the TS.



Stabilisation of TS by *p*-orbital of the CO group

Now we are in position to sumarise structural variations for SN1 and SN2 reactions :

	Substrate	SN1 reaction	SN2 reaction
1.	CH_3-X	no	very good
2.	$R-CH_2-X$	no	good
3.	R_2CH-X	yes	yes
4.	R_3C-X	very good	no
5.	$CH_2=CH-CH_2X$	yes	good
6.	$Ar-CH_2-X$	yes	good
7.	$R-CO-CH_2X$	no	excellent
8.	$R-O-CH_2X$	excellent	good
9.	R_2N-CH_2X	excellent	good

You must not regard this list as fixed and inflexible. The last five (no 5 to 9) types may also be either primary, secondary or tertiary. If they are primary as shown. They will favour SN2 more, but if they are tertiary, they will react by the SN1 mechanism except the tertiary α-carbonyl ($RCOCR_2X$) which will still react only, by the SN2 mechanism, if rather slowly.

2. Solvent effect : The nature of the solvent has a dominant effect on the rate of an SN reaction and the mechanism it follows. The solvent effect on the rate of SN1 reactions depends on whether the substrate is neutral or positively charged. For neutral substrates, the greater the polarity of the solvent, the faster is the reaction, because in such cases the transition state is more polar than the starting materials and so more stabilised by the polar solvent through solvation.

The interaction between a dissolved species and the solvent molecules is known as ***solvation.*** Solvation causes stabilisation by dispersing partial or full charges through hydrogen bonding, interaction through dipoles, and through electron donation.

$$R-X \longrightarrow \underset{\text{TS}}{R^{\delta+}\cdots X^{\delta-}} \longrightarrow R^{\oplus} + X^{\ominus}$$

For example, the rate of solvolysis of Me_3CBr is 3×10^4 times faster in more polar 50% aqueous ethanol than in ethanol alone. For SN2 mechanism increasing solvent polarity usually decreases reaction rate slightly. For example, in the following general SN2 reaction :

$$Nu^{\ominus} + R-X \longrightarrow \underset{\text{TS}}{[Nu^{\delta-}\cdots R\cdots X^{\delta-}]} \longrightarrow Nu-R + X^{\ominus}$$

New charge is not developed but the existing charge of the nucleophile is dispersed in the TS resulting in less charge density as compared to the starting materials, thus the stabilisation of the TS is lesser than the starting materials causing slight decrease in the reaction rate.

A very marked effect on the rate of SN2 reactions is observed on changing the solvent from polar hydroxylic (protic) to polar non-hydroxylic (aprotic). For example, water acetone, methanol, ethanol, etc. are protic solvents, and acetone, dimethyl sulphoxide, DMSO ($Me_2S=O$), dimethyl formamide, DMF ($HCONMe_2$), hexamethylphosphoric triamide, HMPT [$(Me_2N)_3P=O$], etc. are common aprotic solvents. Aprotic solvents cannot form hydrogen bonds, thus, they do not solvate anions to any appreciable extent. Anions are highly solvated by protic solvents through hydrogen bonding. Consequently, reaction rates are very fast with anionic nucleophiles in aprotic solvents because the unsolvated nucleophiles are almost "naked" to be highly reactive as nucleophiles. For example, the order of reactivity (nucleophilicity) of halide ions is as follows :

In protic solvents :

$$I^{\ominus} > Br^{\ominus} > Cl^{\ominus} > F^{\ominus}$$

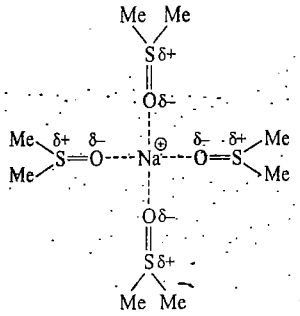
Due to smaller size $F^{\ominus}$ is highly solvated through hydrogen bonding, hence, least reactive. In aprotic solvents the order of reactivity (nucleophilicity) is:

$$F^{\ominus} > Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$$

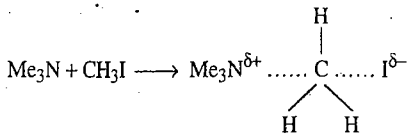
A polar aprotic solvent dissolves ionic compounds and it solvates cations by orienting the negative end of its dipole around the cation. It is unable to solvate the anion through positive end of its dipole, *e.g.*, in DMSO the two methyl groups shield its positive pole, which prevents the solvation of the anion.

Solvation of cation $Na^{\oplus}$ by DMSO, hence anion, *e.g.*, $Cl^{\ominus}$ is essentially "free".

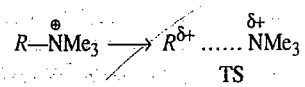
For most of reactions SN1 rates increase and SN2 rates decrease in solvents of increasing polarity, thus, it is quite possible for the same reaction to proceed by the SN1 mechanism in one solvent and the SN2 in another, *i.e.*, the solvent polarity not only affects rates of SN reactions, but may also change the mechanism of a reaction.



If the charge is increased in the TS relative to starting materials then increase in polarity will increase rates of SN reactions. If the charge is decreased or dispersed in the transition state relative to the starting material then increase in polarity will decrease rates of SN reactions. For example, in the following SN2 reaction the charge is increased in the TS, hence, polar solvents will increase its rate :



In the following SN1 reaction the charge is dispersed in the TS, hence, polar solvents will decrease its rate :



In general, the addition of an external salt affects the rates of SN1 and SN2 reactions in the same way as an increase in solvent polarity. However, there are exceptions; although the rates of SN1 reactions are usually increased by addition of salts (this is called the salt effect), addition of the leaving group ion often decreases the rate (the common-ion effect).

3. Effect of Leaving group : A leaving group which becomes a more stable species after it departs is a better leaving group. This is usually the inverse to the basicity of the leaving group, and the best leaving groups are the weakest bases. Among the halides, iodide is the best leaving group and fluoride the poorest :

$$I^{\ominus} > Br^{\ominus} > Cl^{\ominus} > F^{\ominus}$$

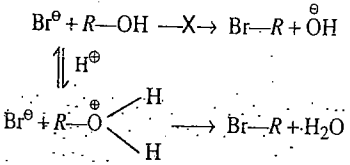
This order is just inverse of their basicity but is the same as the order of acidity of their conjugate acids :

$$HI > HBr > HCl > HF$$

Thus, the stronger the conjugate acid of the leaving group, the better is its leaving ability. Trifluoro methanesulphonic acid (CF_3SO_3H) is a strong acid (much stronger than H_2SO_4), its conjugate base, the triflate ion ($CF_3SO_3^{\ominus}$) is one of the best leaving groups known.

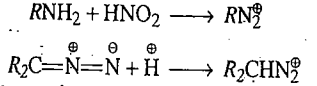
The nature of leaving group affects the rate of both SN1 and SN2 reactions, as breaking of the bond to the leaving group is involved in the rate-determining step of both. The nature of leaving group not only affects the rate of SN reactions but may also change the mechanism of a reaction.

SN reactions which are difficult or even impossible to undergo due to a poor leaving group may be carried out by converting the poor leaving group into a good leaving group. For example, OH and OR are not leaving group from ordinary alcohol and ethers but can be made better leaving groups by protonation. For example :

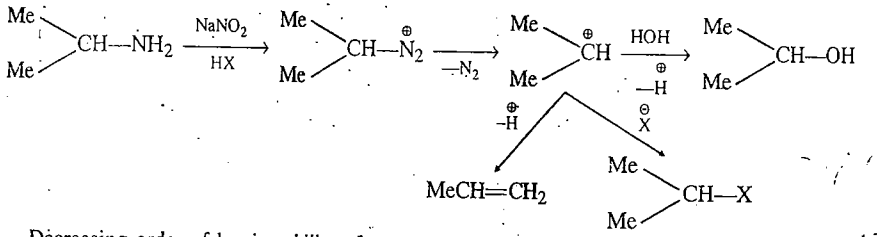


Another way of increasing leaving-group power is conversion to a reactive esters, most commonly a sulphonic esters, *e.g.*, tosylates, brosylates, triflates, etc. which are better leaving groups than halides and are frequently used.

The best leaving group is N_2 from $R—N_2^{\oplus}$, which can be generated as follows :



For example, the following HNO_2-induced deamination undergoes through SN1 mechanism with evolution of N_2.



Decreasing order of leaving ability of some groups is as follows :

$$R\overset{\oplus}{N}_2 > R\overset{\oplus}{O}R'_2 > ROSO_2C_4F_9 > ROSO_2CF_3 > ROT_s > RI > RBr > R\overset{\oplus}{O}H_2 > RCl > RF > ROH > ROR > RH$$

Here, the group attached to *R* is the leaving group.

4. Effect of the attacking nucleophile : Since the nucleophile is not involved in the rate-determining step of an SN1 reaction, its nature or concentration does not affect the rate of SN1 reaction. In an SN2 reaction the nucleophile is involved in the rate-determining step, so the nature and concentration of the nucleophile affect the rate of SN2 reaction. The stronger the nucleophile, the faster is the SN2 reaction.

The order of nucleophilicity varies and it depends on substrate, solvent, polarisability of the nucleophile, its size, etc. The following main principles govern the rate of the SN2 reaction :

(i) A negatively charged nucleophile is stronger than its conjugate acid, *e.g.*, $\overset{\ominus}{O}H$ is stronger than H_2O, $\overset{\ominus}{N}H_2$ is more powerful than NH_3.

(ii) Nucleophiles whose attacking atom is in the same period of periodic table, their nucleophilicity is roughly in order of basicity, *e.g.*,

$$\overset{\ominus}{N}H_2 > R\overset{\ominus}{O} > \overset{\ominus}{O}H > R_2NH > Ar\overset{\ominus}{O} > NH_3 > \text{pyridine} > \overset{\ominus}{F} > H_2O$$

(iii) On going down in a group of periodic table, nucleophilicity increases, although basicity decreases, *e.g.*, $\overset{\ominus}{I} > \overset{\ominus}{Br} > \overset{\ominus}{Cl} > \overset{\ominus}{F}$ (as we have seen, this order is in protic solvents). Similarly, any sulphur nucleophile is stronger than its oxygen analogue, and phosphorus nucleophile is more powerful than its nitrogen analogue. This is mainly because the smaller negatively

charged electrophiles are more solvated by the usual polar solvents. This is most important for protic polar solvents which strongly solvate through hydrogen bonding, hence, nucleophile is not so "free" to attack the substrate. However, nucleophilicity of small negatively charged nucleophiles is reversed in aprotic solvents where the solvation is not so strong, hence, the nucleophile is almost "free" to attack the substrate. For example, the order of nucleophilicity of halides in aprotic solvents (*e.g.*, DMF) is :

$$F^{\ominus} > Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$$

Thus, the free the nucleophile, the greater is the rate.

However, solvation is not the complete answer because nucleophilicity of uncharged nucleophiles also increases on going down in a group. These nucleophiles are not strongly solvated, and solvents do not greatly affect their nucleophilicity. Similarly, the order of nucleophilicity, $ArS^{\ominus} > ArO^{\ominus}$, is not affected by solvents. This can be explained on the basis of polarisability of the nuclephile. The more polarisable the nucleophile, the more easily the electron cloud is distorted, thus, large nucleophiles can actually bring a greater degree of electron density to the substrate than the small nucleophiles whose electron clouds are more tightly held.

The above cases may also be explained by hard and soft acids and bases principle (HSAB). The proton is a hard acid, but an alkyl substrate is a softer acid. According the HSAB principle the alkyl group is expected to prefer softer nucleophiles than the proton does. Thus, the larger, more polarisable (softer) nucleophiles have a greater attraction toward an alkyl carbon than toward a proton. Basicity involves electron pair donation to hydrogen, whereas nucleophilicity involves electron pair donation to carbon. Therefore, basicity and nucleophilicity are not always parallel.

There are exceptions to the above principles. For example, the *t*-butoxide ion $Me_3CO^{\ominus}$ is a stronger base than $OH^{\ominus}$ or $OEt^{\ominus}$, but a much poorer nucleophile because its large size hinders it from closely approaching a substrate.

The following overall order of nucleophilicity for SN2 mechanism (in protic solvents) was given by Edwards and Pearson (1962) :

$$RS^{\ominus} \geq ArS^{\ominus} > I^{\ominus} > CN^{\ominus} > OH^{\ominus} > N_3^{\ominus} > Br^{\ominus} > ArO^{\ominus} > Cl^{\ominus} > \text{pyridine} \geq AcO^{\ominus} > H_2O$$

Problem 9. *Explain why* $I^{\ominus}$ *is both a good leaving group and a good nucleophile? Taking its example, discuss nucleophilic catalysis.*

Solution : High polarisability of $I^{\ominus}$ makes it both a good leaving group and a good nucleophile. Thus, it is often used as a catalyst to promote a slow substitution reaction. This is known as *nucleophilic catalysis*. For example :

$$H_2O + R\text{—}Cl \xrightarrow{\text{Slow}} HO\text{—}R + HCl$$

$$I^{\ominus} + R\text{—}Cl \xrightarrow{\text{Fast}} I\text{—}R + Cl^{\ominus}$$

$$I\text{—}R \xrightarrow{HOH\ \text{fast}} HI + R\text{—}OH$$

The hydrolysis of *R*Cl is slow. When small amount of NaI is added, $I^{\ominus}$ being very good nucleophile replaces Cl from RCl fastly to give *R*—I, which undergoes hydrolysis very fast because $I^{\ominus}$ is a very good leaving group as compared to Cl. Thus, the reaction rate is highly enhanced by

$I^{\ominus}$ nucleophilic catalyst I. It is clear from the above reaction cycle that NaI is not consumed in the reaction, hence, only small amount of it is required.

4.8 NUCLEOPHILIC SUBSTITUTION AT AN ALLYLIC CARBON

Allylic substrates undergo nucleophilic substitution reactions rapidly, and are usually accompanied by a rearrangement known as an *allylic rearrangement* or an allylic shift. When allylic substrates are treated with nucleophiles under SN1 conditions, two products are usually formed the normal product and a rearranged product :

$$R\text{—}CH{=}CH\text{—}CH_2X \xrightarrow{Y^{\ominus}} \underset{\text{Normal product}}{R\text{—}CH{=}CH\text{—}CH_2Y} + \underset{\text{Rearranged product}}{R\text{—}\underset{\displaystyle Y}{\underset{|}{CH}}\text{—}CH{=}CH_2}$$

The formation of two products can be easily explained because the allyl cation is resonance hybrid of two structures:

$$R\text{—}CH{=}CH\text{—}\overset{\oplus}{C}H_2 \longleftrightarrow R\text{—}\overset{\oplus}{C}H\text{—}CH{=}CH_2$$

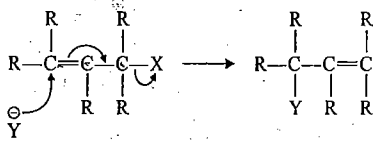
Thus, C—1 and C—2 each carry a partial positive charge, and both are attacked by $Y^{\ominus}$ (nucleophile) resulting in the formation of two products. This mechanism is called SN1′ *mechanism*. In SN1′ reactions at equilibrium more stable product (thermodynamically controlled product) is formed in greater amount, whereas if equilibrium is not reached, less stable product (kinetically controlled) is formed in greater amount. If the double bond in one isomer is in conjugation with an aromatic ring, a triple bond, another double bond or a carbonyl group, then that isomer is more stable and predominates at equilibrium, *e.g.*,

$$Ph\text{—}CH{=}CH\text{—}CH_2\text{—}X \xrightarrow{{}^{\ominus}OH} \underset{\text{100\% at equilibrium}}{\underset{\text{I}}{Ph\text{—}CH{=}CH\text{—}CH_2\text{—}OH}} + \underset{\text{major product if equilibrium not reached}}{\underset{\text{II}}{Ph\text{—}\underset{\displaystyle OH}{\underset{|}{CH}}\text{—}CH{=}CH_2}}$$

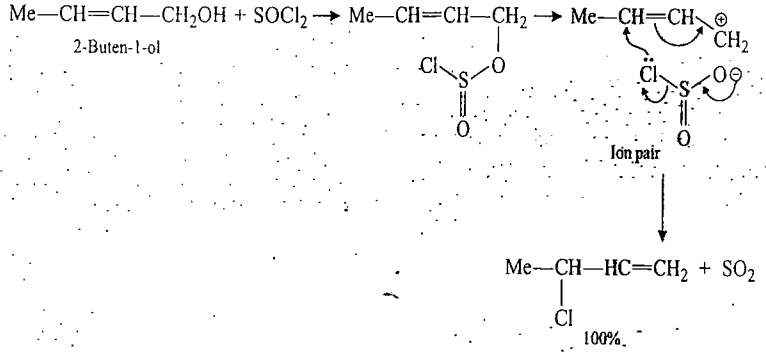
100% of the I is formed at equilibrium because it is more stable due to conjugation of its double bond with the phenyl ring. If equilibrium is not reached, then II is the major product.

Nucleophilic substitution at an allylic carbon may also take place by SN2 mechanism without allylic rearrangement. However, allylic rearrangement can also take place under SN2 conditions through the following mechanism in which the nucleophile attacks at the γ-carbon instead of at the usual position. This mechanism is called SN2′ *mechanism* and is an allylic rearrangement :

SN2′ mechanism takes place under SN2 conditions where α substitution sterically retards the normal SN2 mechanism.



If a compound has in allylic position a leaving group capable of giving SNi reaction, then it is possible for nucleophile to attack at the γ-position instead of the α-position. This is called SNi′ mechanism, for example,



Similarly, 3-buten-2-ol ($MeCHOHCH{=}CH_2$) gives 100% $MeCH{=}CHCH_2Cl$.

An allylic rearrangement in which the nucleophile is the same as the leaving group is an isomerisation, *e.g.*,

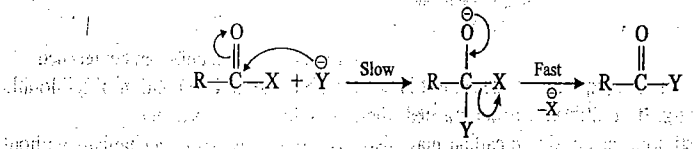
$$R{-}CH{=}CH{-}CH_2{-}X \rightleftharpoons R{-}CH{-}CH{=}CH_2$$

III IV (X)

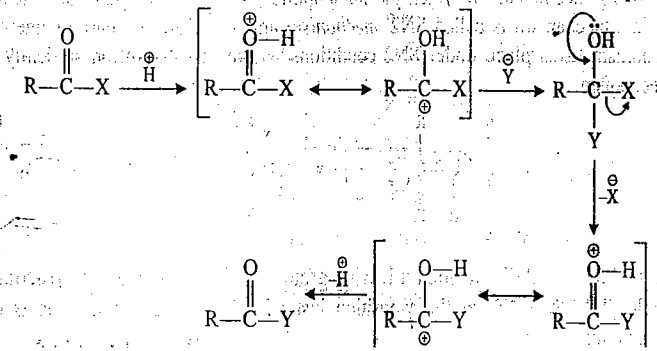
This type of isomerisation may proceed by SN1′, SN2′, or SNi′. At the equilibrium thermodynamically controlled isomer (stabler isomer) will predominate. More substituted alkenes are more stable, hence, in the above example the isomer III will predominate at equilibrium.

4.9 NUCLEOPHILIC SUBSTITUTION AT AN ALIPHATIC TRIGONAL CARBON

Compounds containing a trigonal (sp^2) carbon attached to an oxygen, a sulphur, or a nitrogen undergo nucleophilic substitution through *tetrahedral mechanism*, often called as addition-elimination (Ad_N—E). The reaction follows second-order kinetics but the mechanism is not the same as simple SN2 mechanism. In the tetrahedral mechanism first the nucleophile attacks to give a tetrahedral intermediate, and then the leaving group (X) departs :



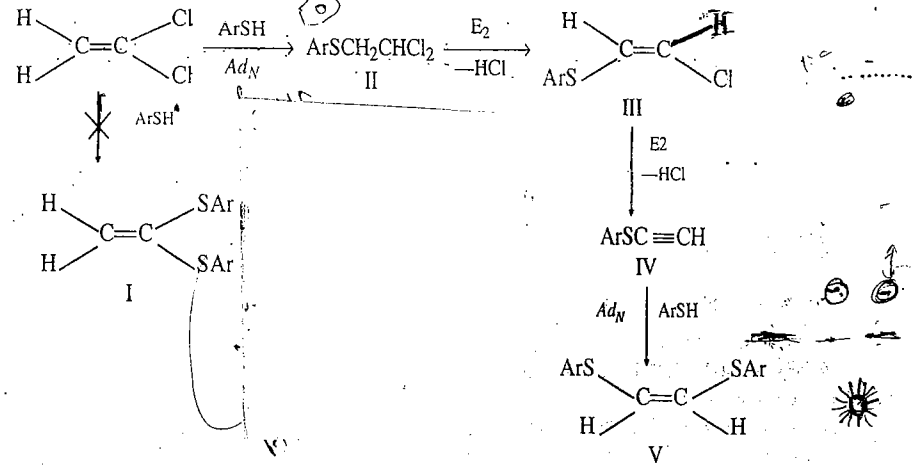
As expected, this reaction is catalysed by acids because protonation decreases the electron density at the carbon undergoing substitution, which facilitates the attack of nucleophile :



The tetrahedral mechanism is supported by the second-order kinetics, and isotopic labelling (*e.g.*, see $A_{AC}2$ and $B_{AC}2$ mechanisms of ester hydrolysis, Section 4.14). In a few cases, the tetrahedral intermediates have been isolated or detected spectrally.

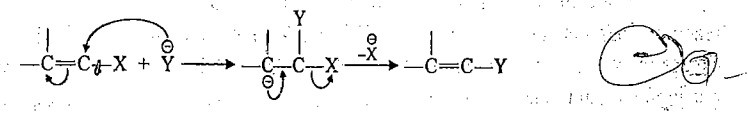
4.10 NUCLEOPHILIC SUBSTITUTION AT A VINYLIC CARBON

Nucleophilic substitution at a vinylic carbon is difficult, but many examples are known. It may take place through: addition-elimination (Ad_N—E) mechanism, the closely related tetrahedral mechanism, elimination-addition mechanism, or SN1 mechanism. For example, the addition-elimination mechanism has been demonstrated for ethoxide ion catalysed reaction between 1,1-dichloroethylene and thiophenol.

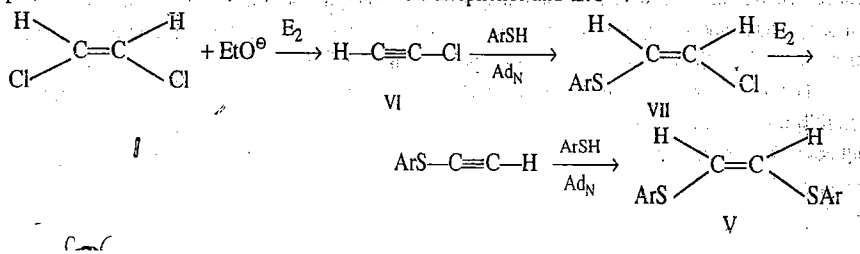


The product is not I but the "rearranged" V. The isolation of II and III is a strong evidence for the above Ad_N—E mechanism.

The tetrahedral mechanism, often called addition-elimination (Ad_N—E) takes place with much less facility at vinylic carbon than with compounds containing $C{=}X$ (X = O, S, or N) group because the negative charge of the tetrahedral intermediate is borne by carbon in the case of vinyl substrate, which is less electronegative than O, S, or N. Remember, the greater the electronegativity of the atom bearing a negative charge, the more is the stabilisation of the anion.



Elimination-addition (E—Ad_N) mechanism has also been observed in **vinyl systems.** For example, the reaction of *cis*-1,2-dichloroethene with thiophenol and $EtO^{\ominus}$:



Evidence for the above mechanism :

(i) The reaction does not proceed without $EtO^{\ominus}$, and the rate depends on the concentration of $EtO^{\ominus}$ and not on that of $ArS^{\ominus}$.

(ii) *trans*-1,2-dichloroethene does not react under these conditions because there is no hydrogen *trans* to either chlorine, so the E2 reaction is greatly retarded.

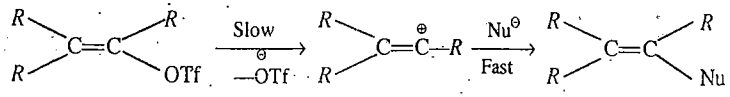
(iii) Under the same reaction conditions, chloroacetylene (VI) gave VII and V.

(iv) VII did not react with $ArS^{\ominus}$, but when $EtO^{\ominus}$ was added, V was obtained.

In general, vinyl substrates are resistant towards SN1 reactions, but they can be made to do so in two ways:

(i) By use of an α-group which stabilises the vinyl cation, *e.g.*, aryl vinyl halides $ArCBr{=}CR_2$ often undergo SN1 reactions. The vinyl substrates with cyclopropyl, vinyl and adjacent double bond ($R_2C{=}C{-}C{=}CR'X$) stabilising group also exhibit SN1 reactions.

(ii) By use of a very good leaving group, *e.g.*,
$CF_3SO_2O^{\ominus}$ ($^{\ominus}OTf$, triflate anion).



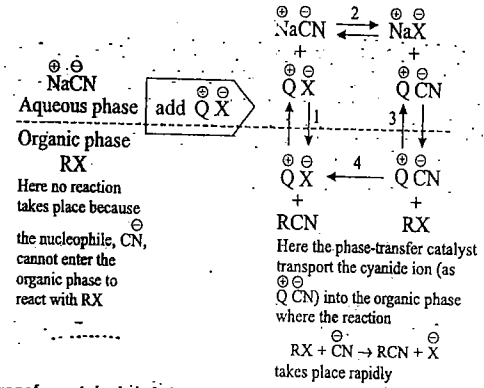
4.11 PHASE TRANSFER CATALYSIS AND ULTRASOUND

In nucleophilic substitutions the substrate is usually insoluble in water and other polar solvents, whereas the nucleophile which is often negatively charged is soluble in water but not in the substrate or other organic solvents. Thus, when the reaction is carried out, the concentration of the two reactants in the same phase is too low for appreciable reaction rates. A dipolar aprotic solvent like DMF, DMSO, etc. may overcome this difficulty. Another way often used to solve this problem is *phase transfer catalysis*.

In phase transfer catalysis a catalyst is used to carry the nucleophile from the aqueous into the organic phase. For example, simply heating and stirring a two-phase mixture of 1-chlorooctane and aqueous NaCN for several days gives no yield of the substitution product 1-cyanooctane. When a small amount of appropriate quaternary salt is added to the above reaction mixture, the product is formed in almost 100% yield in about 2 hour. Phase transfer catalysts are mainly of two types both of which take the nucleophile into the organic phase and allow it to be free to react with the substrate.

1. Quaternary ammonium or phosphonium salts : In the above example, the uncatalysed reaction does not take place because $CN^{\ominus}$ ions cannot cross the interface between the two phases, except in very low concentration. The reason is that $Na^{\oplus}$ ions are strongly solvated in water and do not prefer organic phase where such a strong solvation is not possible, thus they do not cross. The $CN^{\ominus}$ ions cannot cross without $Na^{\oplus}$ ions because that would destroy the electrical neutrality of each phase. Unlike $Na^{\oplus}$ ions, quaternary ammonium ($R_4N^{\oplus}$) and phosphonium ($R_4P^{\oplus}$) ions with sufficiently large *R* groups are poorly solvated in water and prefer organic solvents. On addition of a small amount of such a salt to the reaction mixture, the following three equilibria are set up :

The $Q^{\oplus}$ ions cross the interface and carry $CN^{\ominus}$ anions with them into the organic phase (equilibrium 3) where they react with *R*CN to give *R*CN and $X^{\ominus}$. The $X^{\ominus}$ is then carried into the aqueous phase (equilibrium 1). $Q^{\oplus}CN^{\ominus}$ is generated in the aqueous phase (equilibrium 2) by exchange of ions.



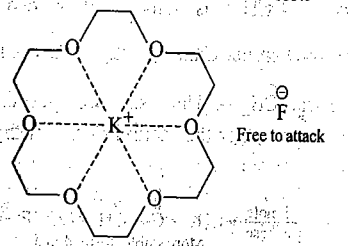
Scheme : Phase transfer catalysis of the SN reaction between sodium cyanide and alkyl halide

2. Crown ethers and other cryptands : *Crown ethers* are large ring polyethers. Macrocyclic systems containing one or more than one kind of heteroatom, and resembling crown ethers, have also been prepared. Bicyclics or cycles of higher order are called *cryptands* and the complexes formed by them are called *cryptates* (sometimes monocyclics are also called *cryptands*).

The rates of nucleophilic substitutions are highly increased in the presence of suitable crown ether or other cryptand. The crown ether 18-crown-6 coordinates very effectively with $K^{\oplus}$. Salts like KF, KCN and AcOK which are insoluble in non-polar solvents like benzene are dissolved in it in the presence of 18-crown-6. Thus, in the organic phase relatively unsolvated (free) anions are present to bring about nucleophilic substitutions. For example, KF is insoluble in benzene and is unreactive to organic halides, brings about an efficient nucleophilic substitution in the presence of 18-crown-6 :

$$PhCH_2Cl + K^{\oplus}F^{\ominus} \xrightarrow[\text{Acetonitrile}]{\text{18-crown-6}} PhCH_2F + K^{\oplus}Cl^{\ominus}$$

100%



Crown ether (18-crown-6) complex soluble in organic solvents

A crown ether or other cryptand acts as a phase transfer catalyst which brings the anion into the organic phase.

Both of the above catalyst types bring the anions into the organic phase. In addition, due to much less ion pairing with quaternary ions ($R_4N^{\oplus}$ or $R_4P^{\oplus}$) and with the positive cryptate ions, the anions are naked, *i.e.*, quite free to attack in these cases. Not only nucleophilic substitutions but also any reaction that needs an insoluble anion dissolved in an organic solvent can be accelerated by an appropriate phase transfer catalyst.

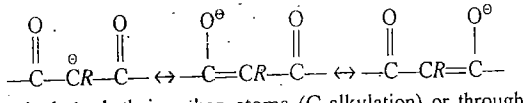
Ultrasound is another technique to increase reaction rates. A frequency of 20 kHz is about the upper limit of human hearing. In the ultrasound technique the reaction mixture is subjected to high

energy sound waves (most often 20 kHz, but sometimes higher). This results in the formation of small bubbles (*cavitation*). Collapse of these bubbles produces powerful shock waves that greatly increase the temperatures and pressures within these tiny regions, resulting in an increased reaction rate. Ultrasound technique is advantageous because it may increase yields, reduce side reactions, and permit the use of lower temperatures and/or pressures.

4.12 AMBIDENT NUCLEOPHILES, REGIOSELECTIVITY

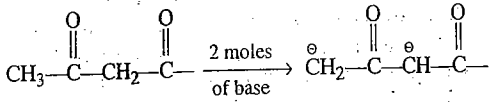
Nucleophiles which can attack the substrate through two or more atoms to give different products are called *ambident nucleophiles*. When a reaction is capable of giving two or more structural isomers (*e.g.*, *R*OCN or *R*NCO) but actually gives only one, the reaction is called regioselective reaction and this phenomenon is known as regioselectivity. The following are some important ambident nucleophiles :

1. Ions derived from malonic esters, β-keto esters, β-diketones, etc. are resonance hybrids,

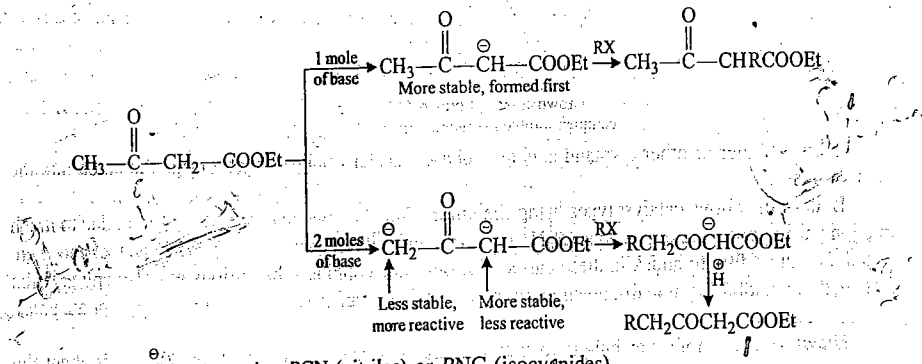


and can attack through their carbon atoms (C-alkylation) or through their oxygen atoms (O-alkylation) to give three products in case of unsymmetrical ions.

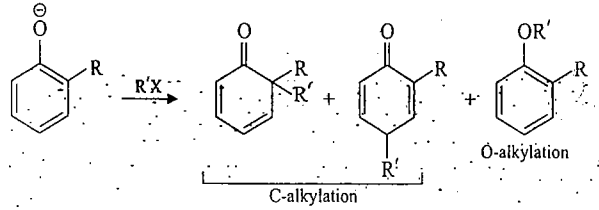
2. Compounds of the type $CH_3CO—CH_2—CO—$ can form a dianion on treatment with a strong base :



Such ambident nucleophiles can attack through two carbon atoms besides the attack through oxygen. In such cases the attack is always through the more basic (nucleophilic) carbon. The negative charge of $\overset{\ominus}{C}H—$ is delocalised on two C=O groups, whereas that of $\overset{\ominus}{C}H_2—$ on only one C=O group. Consequently, $\overset{\ominus}{C}H—$ is less basic than $\overset{\ominus}{C}H_2—$, and the attack takes place through $\overset{\ominus}{C}H_2—$. Thus, such compounds, *e.g.*, ethyl acetoacetate, can be regioselectively alkylated at either the methyl or the methylene group :



3. The $\overset{\ominus}{C}N$ ion can give *R*CN (nitriles) or *R*NC (isocyanides).



4. The nitrite ion $NO_2^{\ominus}$ can give *R*—O—N=O (nitrite esters) or *R*—NO_2 (nitro compounds)
5. Phenoxide ions (which are analogous to enolate ions) can undergo C-alkylation or O-alkylation :

Factors governing the regioselectivity in ambident nucleophiles

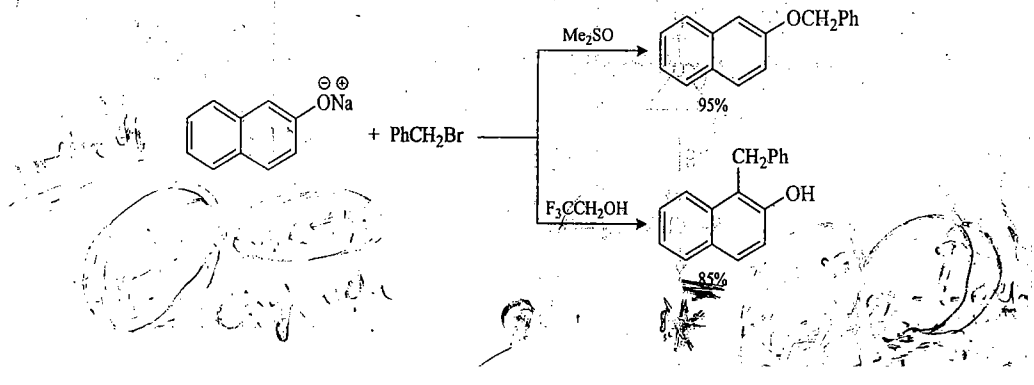
Although exceptions are there, the following general rules are useful in predicting which atom of an ambident nucleophile would attack the substrate under the given conditions :

1. As the character of a given reaction changes from SN1 like to SN2 like, an ambident nucleophile is more likely to attack through its less electronegative atom. This is because in SN1 nucleophile attacks a harder carbon and in SN2 a softer, the more electronegative atom is harder and the less one is softer, and hard-hard and soft-soft interaction is preferred according to the HSAB principle. Thus, changing from SN1 to SN2 conditions should favour C attack by CN, N attack by NO_2, C attack by enolate or phenoxide ions, etc.
2. If the positive counterion of a negatively charged nucleophile helps in removing the leaving group, *e.g.*, Ag^+, Hg^{2+} or Hg_2^{2+} rather than Na^+ or K^+, then the TS is more SN1, like and the attack through a more electronegative atom is favoured. For example, alkyl halides on treatment with NaCN generally give mostly *R*CN, but the use of AgCN increases the yield of *R*NC.

$$R—Br + Ag^{\oplus}(CN)^{\ominus} \longrightarrow AgBr\downarrow + R—NC$$

3. An increase in the electron-withdrawing character of *X* in *R*—*X* gives the carbon atom a higher positive charge, making it a harder acid. Thus, such a change increases the extent of attack through the more electronegative atom. For example, O/C ratio increases in the order :

   *R*I < *R*Br < *R*Cl < *R*OTs for a series of alkylations of the sodium salt of $CH_3COCH_2COCH_3$ (acetylacetone).
4. In many cases solvent affects the position of attack. The freer the nucleophile, the more likely it is to attack through its more electronegative atom, but more this atom is either solvated or is close to positive counterion, the more likely is attack through the less electronegative atom. In protic solvents the more electronegative atom is better solvated by hydrogen bonding than the less electronegative atom. In polar aprotic solvents neither atom



of the nucleophile is greatly solvated, but the positive counterion is very effectively solvated. Thus, in a polar aprotic solvent the more electronegative end of the nucleophile is freer from entanglement from both the solvent and the cation, so that a change from a protic to a polar aprotic solvent often increases the extent of attack through a more electronegative atom, *e.g.*,

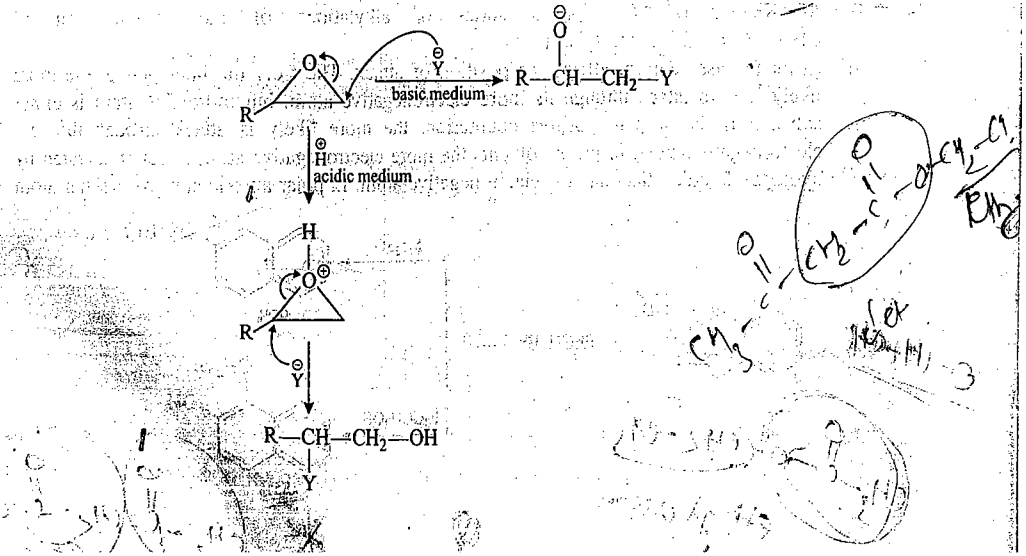
Changing the cation from $Li^{\oplus}$ to $Na^{\oplus}$ to $K^{\oplus}$ (in nonpolar solvents) favours O-alkylation over C-alkylation because $K^{\oplus}$ leaves the nucleophile much freer than $Li^{\oplus}$, as does the use of crown ethers. It is interesting to note that alkylation of the enolate ion of cyclohexanone in the gas phase, where the nucleophile is completely free, undergoes only O-alkylation and no C-alkylation.

5. Steric effects can also govern the regioselectivity.

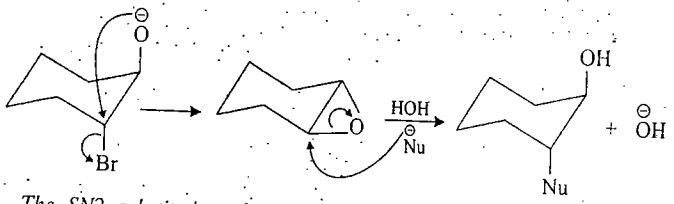
4.13 AMBIDENT SUBSTRATES

The substrates (*e.g.*, 1,3-dichlorobutane) which can be attacked at two or more positions are called ambident substrates. Ambident substrates like 1,3-dichlorobutane have two leaving groups, but there are some ambident substrates which have only one leaving group, *e.g.*, allylic substrates (Section 4.8), and epoxy (or aziridine or episulphide) substrates.

Epoxide oxygen is a poor leaving group, and leaves only if pushed by a strong nucleophile (SN2 reaction) or protonated (SN1 and SN2 reactions). Since primary substrates undergo SN2 reaction more readily than secondary, unsymmetrical epoxides undergo SN2 reaction (with inversion of configuration) in neutral or basic medium, and the attack take place at the less substituted carbon. In acidic medium, it is the protonated epoxide that undergoes SN1 or SN2 reaction, because it has a better leaving group, the positively charged oxygen. In SN1 reaction, the attack takes place at the more substituted carbon. However, even when protonated epoxides react by the SN2 mechanism, attack is usually at the more substituted carbon because it has greater $\delta\oplus$, or the oxygen will leave this carbon more easily. Thus, it is often possible to change the direction of ring opening by changing the conditions from basic to acidic or vice-versa.

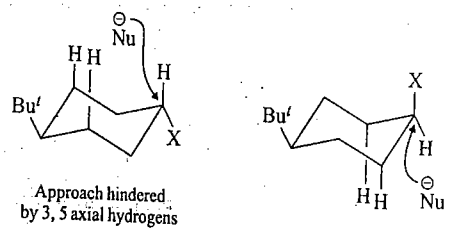


When an epoxide ring is fused with a cyclohexane ring, SN2 ring opening always gives diaxial rather than diequatorial ring opening. The diaxially substituted product may then subsequently flip to the diequatorial one. Since ring closure is only possible when the starting material is diaxially substituted (otherwise backside attack is not possible), this means that the ring opening is similarly only possible if the product is diaxial. The nucleophile and hydroxyl group end up *trans* in the product due to the backside attack.



Problem 10. *The SN2 substitution of an axial substituent is faster than that of an equatorial substituent. Explain.*

Solution : In an SN2 reaction, the nucleophile must attack from the just opposite side to the leaving group. In the case of an equatorial leaving group, the backside attack is hindered by the axial hydrogens at positions 3 and 5. For an axial leaving group, the direction of attack is parallel to the 2,6 axial hydrogens which are antiperiplanar to the leaving group and approach is much less hindered. The 3,5 axial hydrogens are far away from the side of attack in this case, hence, do not cause any hindrance.



4.14 ESTERIFICATION AND ESTER HYDROLYSIS

The usual method of formation of an ester by the reaction of an acid and an alcohol is known as *esterification*. The conversion of an ester into its acid and alcohol moieties is called *ester hydrolysis*. In the following example,

$$RCOOH + R'OH \rightleftharpoons RCOOR' + H_2O$$

the forward reaction is *esterification* and the reverse is *ester hydrolysis*. Esterification is catalysed by acids, whereas ester hydrolysis may be catalysed by an acid or a base When bases catalyse ester hydrolysis, the reaction is called *saponifcation* and it gives the salt of the acid.

There are eight possible mechanisms through which esterification and ester hydrolysis may take place. This is because they may be (1) acid or base-catalysed, (2) Unimolecular or bimolecular, (3) may involve acyl-oxygen or alkyl-oxygen bond fission.

Acyl-oxygen bond fission :