

Nucleophilic substitution at saturated carbon atom

Displacement of an atom or a 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. Several mechanisms are possible for aliphatic nucleophilic substitution reactions but the most common are S_N1 and S_N2. In this topic I shall discuss about aliphatic nucleophilic substitution.

The new bond is formed between nucleophile and the carbon using the electrons supplied by the nucleophilic reagent and old bond is broken i.e. leaving group is displaced with bonding electrons.



The compound on which substitution takes place is called the substrate and the group that becomes displaced from carbon, taking the electron pair with it, is called leaving group. The leaving group often leaves as an anion but may also be a neutral molecule. The substrate consists of two parts, alkyl group and leaving group. For example, reaction of methyl bromide with sodium hydroxide affords methanol and sodium bromide. In this reaction methyl bromide is substrate, bromide is leaving group and hydroxide ion is the nucleophile.

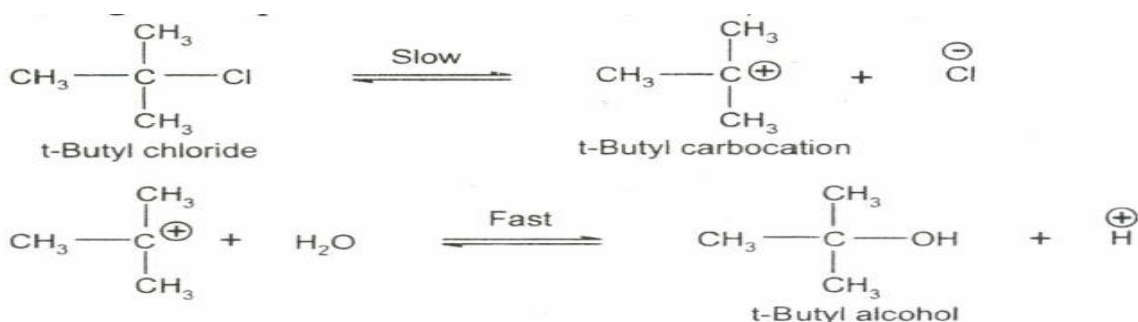


Nucleophilic substitution reactions have been studied extensively from a mechanistic viewpoint. Many factors influence the course of nucleophilic substitution reactions, including the nature of the nucleophile, its strength and concentration, the solvent, the nature of substrate, and the nature of leaving group.

Substitution reactions at saturated carbon can be mechanistically categorized as unimolecular (S_N1) or bimolecular (S_N2).

S_N1 (Nucleophilic Substitution Unimolecular)

Let us take an example of alkaline hydrolysis of tertiary butyl chloride to give tertiary alcohol.



Evidence of reaction mechanism:

1. Kinetics: The S_N¹ reaction is first order following the rate law given below.

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

An S_N¹ reaction proceeds in two steps process where The first step (slow step) is the rate determining step and involves the ionization of the reactant to form a carbocation intermediate and in the second step (fast step), the intermediate carbonation is attacked by the nucleophile to give the final product.

The rate of this reaction depends only on the concentration of the substrate and it is independent of the concentration of nucleophile.

An energy diagram (Following figure) for S_N1 reaction involves two transition states. The transition state for the slow step (the ionization step) is higher in energy than the transition state for the fast step (second step, the capture of the ion by a nucleophile).

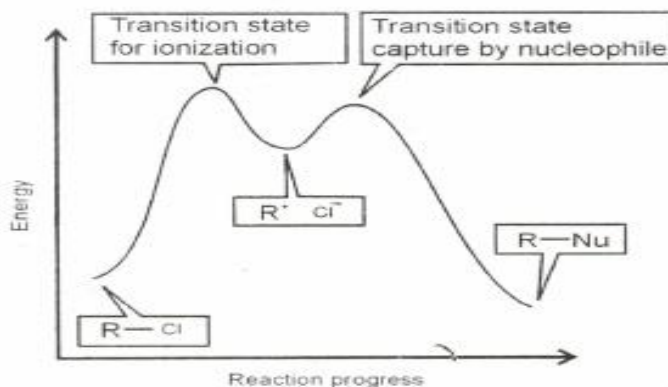
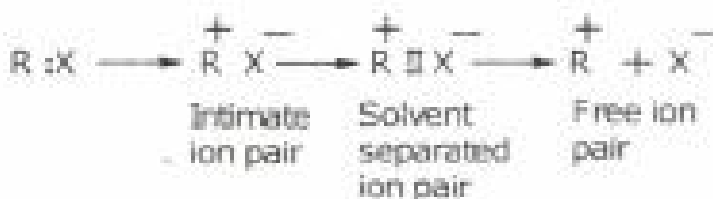


Fig. 1.6 : An energy diagram for the S_N1 reaction. Notice that the transition state for the slow step in the reaction, the ionization is higher in energy than the transition state for the capture of the ion by a nucleophile

Stereochemistry of the S_N1 reaction

This reaction proceeds with partial racemisation and some inversion. An intermediate carbocation is formed which is planar and nucleophile attacks with equal facility from either side of the planar carbocation resulting in complete racemisation. However complete racemisation is rarely observed because inversion product is obtained 5 to 20 %. This can be explained by the ion pair mechanism. In this case it depends on the nature of the substrate and nature of the leaving group.

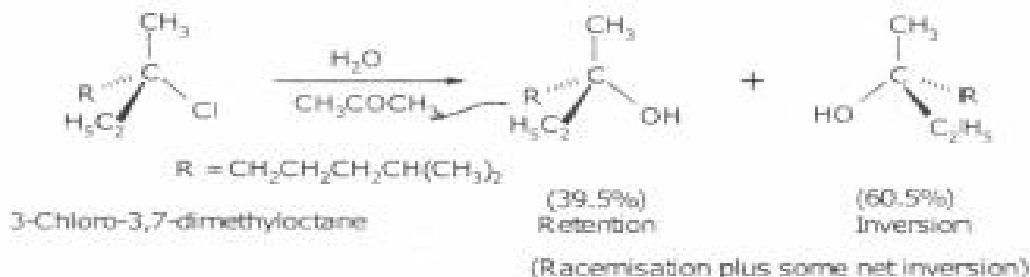
Ion pair mechanism:



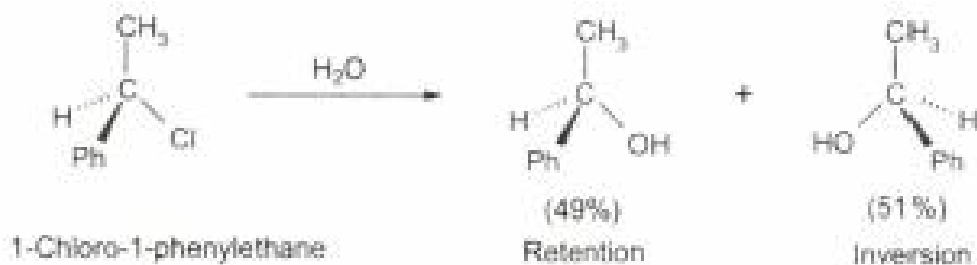
It is believed that carbocation and leaving group exist for a while as an intimate ion pair and the attack of nucleophile during this time takes place only on the back side of carbocation, but not on the front side, giving rise to inversion. Then these ions diffuse apart as solvent intervenes, and become free ions. Now attack of nucleophile on free symmetrical carbocation occurs from the back side or from the front side with equal probability.

If the carbocation is less stable, it is more likely to be attacked by nucleophile before leaving group separates from it, giving rise to inversion. Thus in this case racemisation and some inversion products are obtained.

For example, when 3-chloro-3,7-dimethyloctane is hydrolyzed in presence of acetone, there is a 21% excess of the product resulting from inversion of configuration.



In the second example the reaction proceeds through the stable carbocation so in this case racemization (98%) and only 2% inversion i.e 51% inverted alcohol and 49% alcohol with retention of configuration



Effect of solvent

The solvent plays an important role in S_N1 reactions as the energy required to effect the initial ionization is largely recovered from the energy evolved through solvation of the resulting ion pair. The S_N1 process requires the ionization of a covalent bond which is encouraged by solvents with high dielectric constants. There is a greater charge on the intermediate ions than that on starting substrate as majority of the substrates are neutral. Polar protic solvent (such as water or alcohol) will thus solve 51% inverted alcohol and 49% alcohol with retention of configuration if the intermediate is stabilized more than it does the reactant. Since ions are usually formed in the rate determining step (slow step) of the reaction, therefore the S_N1 reaction will usually be favoured by a polar protic solvent. Good solvents for S_N1 displacements almost always contain hydroxyl groups (as in water, alcohols, or carboxylic acids) because the electronegative oxygen atom interacts with the incipient positive charge, and the electropositive hydrogen atom (through hydrogen bonding) interacts with the incipient negative charge. Thus, in addition to dielectric constant, the ability of protic solvent to form hydrogen bond with leaving group better but aprotic solvent which cannot form hydrogen bond with leaving group. The S_N1 process occurs mainly when water is present as a solvent or as a co-solvent.

Effect of nucleophile on rate

The rate of S_N1 reaction is independent of the nucleophile. A better nucleophile will not accelerate the S_N1 reaction, and yet it may determine which product is formed. For example, t-butyl bromide in water containing small amount of cyanide ions gives t-butyl cyanide. This is

because the cyanide is more reactive towards carbocations than the water. Weak nucleophiles with low concentrations favor the S_N1 mechanism.

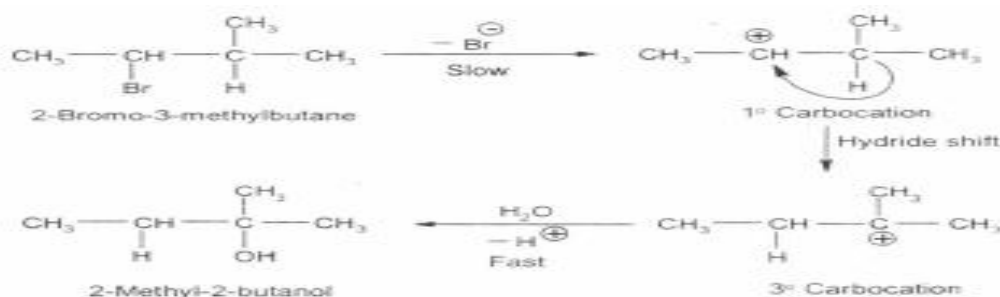
Effect of leaving group on rate

The rate of S_N1 reaction is largely influenced by the nature of the leaving group. The rate of ionization is affected by the stability of the leaving group. The more stable the leaving group, the more easily it will be lost. S_N1 reactions therefore are favoured by the presence of good leaving group such as sulfonates (tosylate or mesylate).

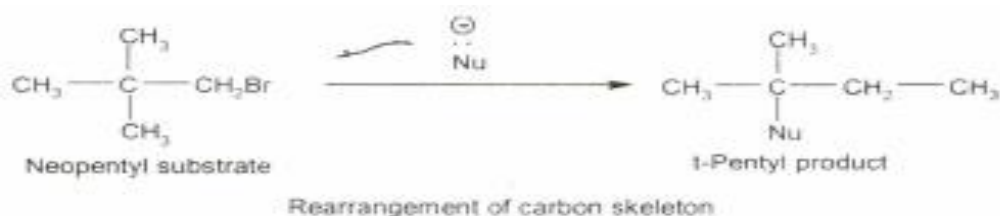
The weaker the Bronsted basicity of X^- , the better leaving group is X. In case of halides the order of basicity is : $I^- < Br^- < Cl^- \ll F^-$, therefore, iodide is a better leaving group than bromide and bromide is a better leaving group than chloride.

Rearrangement in S_N1 reactions

The evidence for the formation of carbocation is that they undergo reactions other than simple addition to nucleophiles. For example, carbocations may rearrange before combining with nucleophiles. Since S_N1 mechanism involves carbocation intermediate, therefore, unexpected products are also formed. For example, hydrolysis of 2-bromo-3-methylbutane yields 2-methyl-2-butanol.



We see that in S_N1 reactions, a carbocation is formed by loss of the leaving group from the substrate. If a 1,2-shift of hydrogen can form a more stable carbocation, then such a rearrangement takes place. The rearranged carbocation can react with nucleophile to afford the substitution product or it may lose proton to yield alkene. If the intermediate carbocation can rearrange to more stable carbocation *via* 1,2-alkyl shift, the reaction often proceeds with rearrangement of the carbon skeleton of the organic substrate.



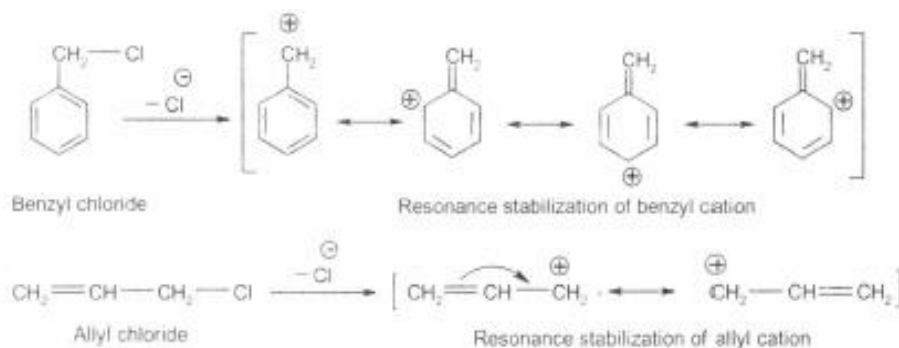
Effect of the nature of substrate on the rate

The rate determining step is the formation of planar carbocation in S_N1 process. Therefore, the order of reactivity among organic substrates will depend upon the stability of carbocation formed after ionization of substrate. Hence tertiary alkyl halides, which give rise to tertiary carbocations, react faster than secondary ones, which react faster than primary halides. The introduction of a methyl group in place of a hydrogen atom attached to the positive carbon of a carbocation appears to stabilize the ion by 15 to 30 kcal / mol (through inductive and hyperconjugation effects). In most of the cases, the substituents which have +I and or +M effects, stabilize the carbocations. Allylic, benzylic, and tert-carbocations are relatively stable carbocations, therefore, allylic, benzylic and tert-halides can react by an S_N1 mechanism.



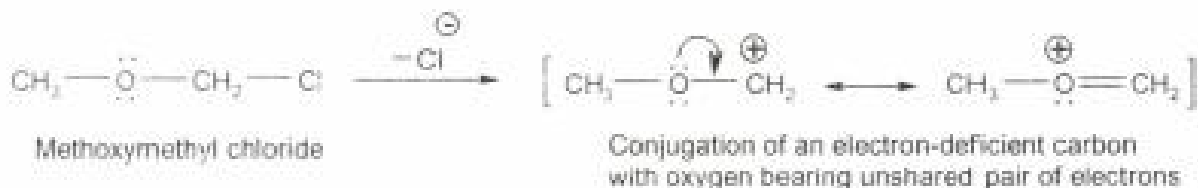
Both benzyl and allyl carbocations disperse the charge by resonance and are more stable than primary alkyl or secondary alkyl carbocations. The primary alkyl and methyl halides, which would form extremely unstable carbocations, do not generally react by the S_N1 process. The order of reactivity among organic halides is as follows:

t-alkyl halides > allyl halides ~ benzyl halides > s-alkyl halides > 1°-alkyl halides



Methoxymethyl chloride undergoes hydrolysis more than 10⁴ times faster than methyl chloride. This is because, the carbocation formed after ionization of methoxymethyl chloride is resonance

stabilized. The CH_3O^- group has unshared pairs of electrons that it tends to share, thus acquiring a positive charge.

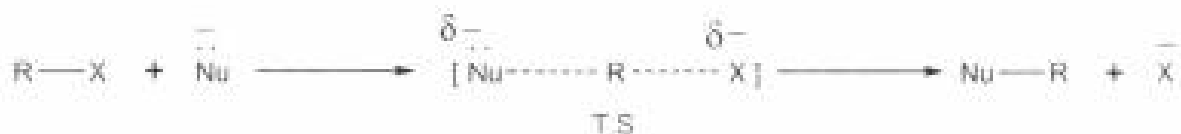


$\text{S}_{\text{N}}1$ displacement in bridged bicyclic compounds at bridgeheads is very slow or does not take place. This is expected as a flat (planar) intermediate carbocation can not be formed at the bridgehead carbon because of the rigid framework of bicyclic systems. Greater is the rigidity about the bridgehead carbon, lower will be its reactivity. For instance, rate of solvolysis of compounds A, B and C in 80% aqueous ethanol at 25°C decreases as the rigidity about the bridgehead carbon increases ($\text{A} < \text{B} < \text{C}$).



S_N2 (Nucleophilic Substitution Bimolecular)

S_N2 process proceeds in one step *via* a transition state. The nucleophile attacks the substrate carbon simultaneously pushing out the leaving group in a concerted fashion.



The reaction between methyl iodide and hydroxide ion is an example of the S_N2 mechanism. Kinetic evidence shows that the rate of this reaction is proportional to both the concentrations of substrate and nucleophile. Thus, S_N2 reaction follows second-order kinetics and is described by the rate expression:

$$\text{rate} = k [\text{RX}] [\text{Nu}]^-$$

Where k is rate constant and quantities in square brackets represent concentrations

In S_N2 process there is synchronous attack by the nucleophile from the opposite side of the carbon atom of substrate bearing the leaving group, such that C-X bond of the substrate breaks only as the new C-Nu bond of the product is forming. Therefore, in transition state, the nucleophile-carbon bond is partially formed and the C-X bond is partially broken. The approach of the nucleophile from the side of the molecule bearing the leaving group is **unfavorable** due to electrostatic repulsion and also due to steric factors. In the transition state for this reaction, the three non reacting substituent's on carbon lie in a plane with the carbon undergoing reaction. This plane is between the incoming and outgoing groups.

An energy diagram (Following figure) for S_N2 process shows the reactants being converted to products by way of **one transition state**, with no energy minimum representing a reactive intermediate. The reactants and products are separated by the high energy point of the reaction, the transition state. The energy difference between the reactants and transition state is called the activation energy and is related to the rate of reaction. Higher is the activation energy, slower is the reaction rate. The reactants and products are not at the same energy level therefore, the forward reaction is exothermic reaction, as read from left to right and backward reaction is endothermic, as read from right to left.

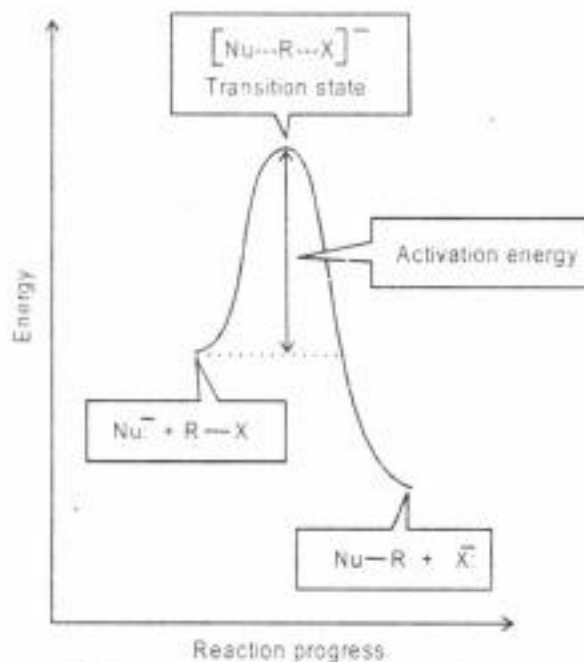
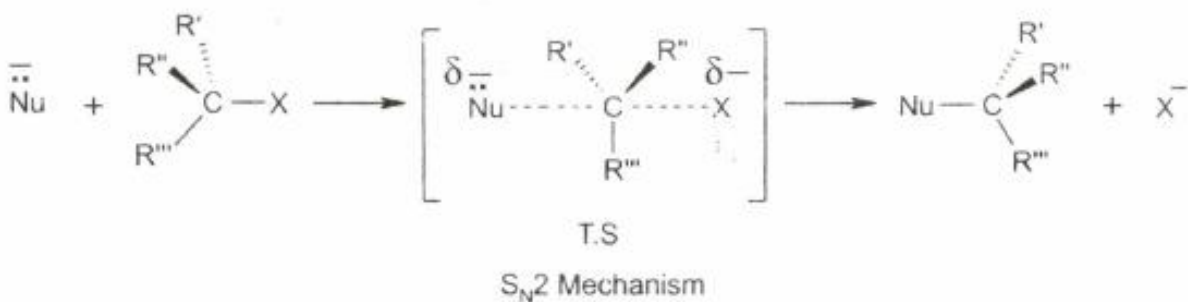


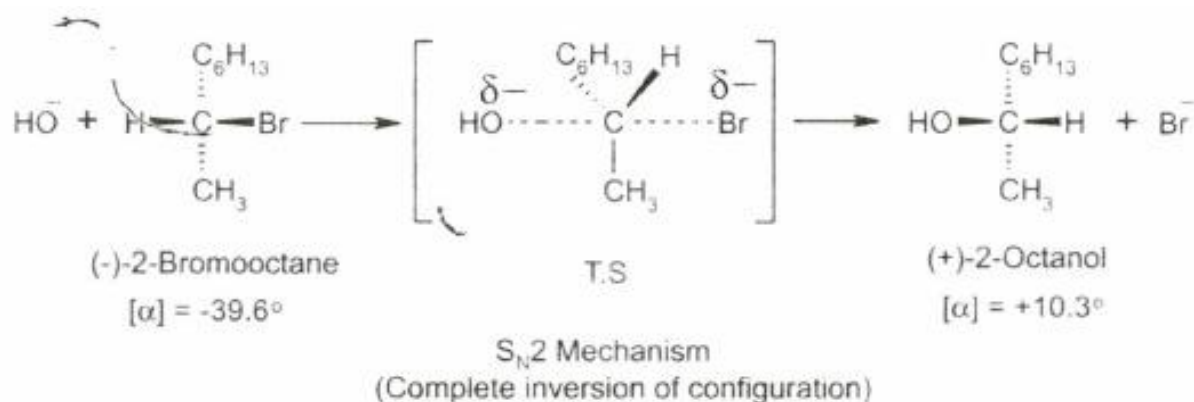
Fig. 1.7 : An energy diagram for the S_N2 reaction.

Stereochemistry of S_N2 reaction

Most of the S_N2 reactions proceed with **complete inversion** of configuration of the substrate. The observation of inversion in S_N2 reaction means that the nucleophile (incoming group) must be approaching the substrate from the side opposite (back-side) to the group being displaced (leaving group). Such an attack will flip the other three groups from one side of the carbon atom to the other. This process is known as **Walden inversion** and produces a product of the opposite configuration.



For example, when optically active substrate, (-)-2-bromooctane reacts with sodium hydroxide under conditions where S_N2 mechanism are followed, inversion of configuration is observed.



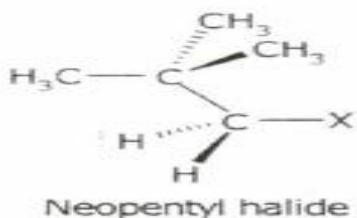
Effect of the nature of substrate on rate

The steric hindrance around the carbon site makes a huge difference in the rate of the S_N2 reaction. The central carbon atom in reactant and product is tetrahedral, whereas carbon in the transition state is bonded to five atoms or groups therefore, there will be an increase in crowding on going from the starting substrate to the transition state. A transition state with five groups crowded around the central carbon atom is a high-energy transition state. The more crowded the transition state relative to substrate, the higher its energy will be, and the slower it will be formed. As hydrogen atoms are replaced by the larger methyl groups, there is increased crowding about the carbon. Therefore, the methyl compounds react faster than primary substrates and primary substrates react faster than the secondary substrates. Tertiary substrates have three bulky alkyl groups attached to reaction center which hinder the approach of the entering nucleophile. Thus, tertiary alkyl halides such as t-butyl bromide normally do not undergo substitution *via* this mechanism. The reactivity of substrates in S_N2 reactions is:



This order is the reverse of that in S_N1 reactions

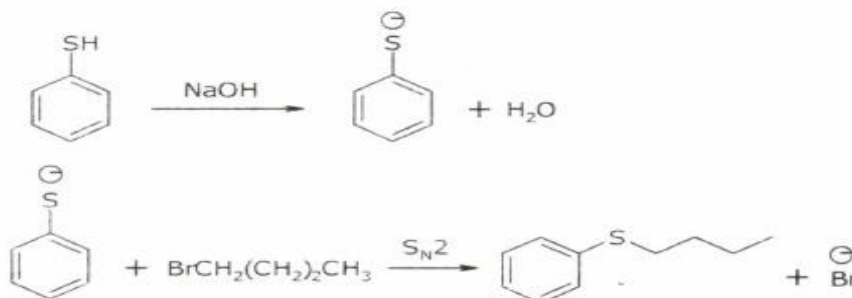
Even though the site of reaction in neopentyl derivatives is primary, the t-butyl group is large enough to slow down the bimolecular (S_N2) displacement.



In allyl and benzyl halides, the π -bond assists in expelling the leaving group, and both halides react faster than the alkyl halides.

Effect of the nucleophile

The rate of S_N2 reaction is strongly dependent on the nature of nucleophilic reagent used, it increases with the nucleophilic strength of the incoming nucleophile. Thus, with the change of nucleophile a shift in mechanistic type may occur, for example, the mechanism which is S_N1 with water may become S_N2 with hydroxide ion. Sulfur nucleophiles are better than oxygen nucleophiles in S_N2 reactions. For example, thiolate anions (excellent nucleophiles in S_N2 reactions) react with alkyl halides to give good yield of the sulfide as illustrated by the following reaction.



Effect of the leaving group

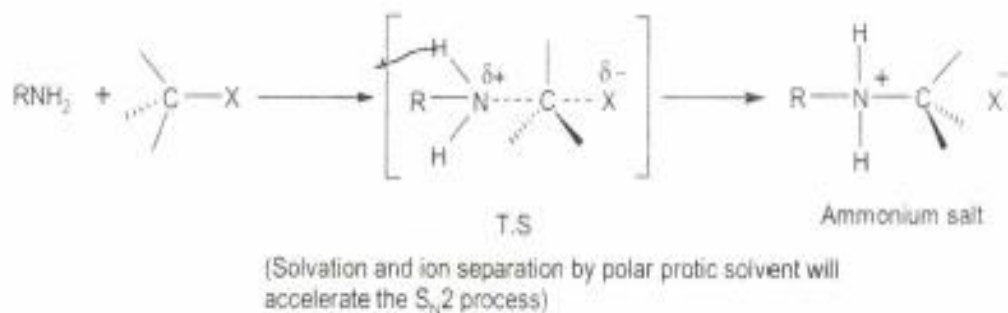
Weak base of strong acid is best leaving group, thus, the rate of S_N2 reaction (same as for S_N1) is higher if the leaving group is a stable ion and a weak base. In case of alkyl halides the order of reactivity is:



Effect of solvent

Normally, S_N2 process involving reaction of anionic nucleophiles with the alkyl halides is suppressed in the presence of polar protic solvent (such as water), since a polar protic solvent will interact (through hydrogen bonding) more favorably with anionic nucleophiles than with the transition state. Therefore, polar protic solvents slow down the reaction, and polar aprotic solvents are preferred for S_N2 reactions. Polar protic solvents can solvate ionic reagents (both the cations and anions), as a result, the anion is "caged" by the solvent molecules. This stabilizes the anion, and makes it less reactive. Thus, S_N2 mechanism becomes less important. However, polar aprotic solvents are not able to form hydrogen bonding with anionic nucleophiles, as a result, nucleophiles are "free" and more reactive. However, if both substrate and nucleophile are neutral but the product is charged, as in the substitution by amines or phosphines on an alkyl halide, the

polar protic solvent will solvate and separate the developing charge in the transition state, ultimately accelerating the S_N2 process.



Competition between S_N1 and S_N2

The structure of substrate, the nature of the nucleophilic reagent, polarity of solvent, and other experimental conditions determine whether nucleophilic substitution will take place by S_N1 or by S_N2 mechanism. In general, primary halides undergo substitution by S_N2 mechanism and tertiary halides undergo substitution by S_N1 mechanism. Secondary halides may undergo substitution by both S_N1 and S_N2 mechanisms, however, one mechanism may be maximized by the selection of appropriate conditions. High concentration of the nucleophile and / or presence of strong nucleophile favors S_N2 , while the factors promoting the S_N1 are, lower concentration of nucleophile or the absence of strong nucleophile, solvents of great ionizing power (such as water) and substrate leading to stable carbocations. The reaction rates of both the S_N1 and S_N2 reactions are increased if the leaving group is a stable ion and a weak base.

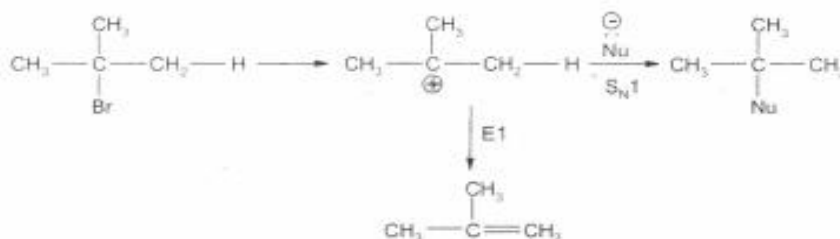
Competition between substitution reaction and elimination reaction

Besides undergoing substitution reaction, another common reaction of substrate is an elimination reaction where nucleophile acts as a base to remove HX instead of adding to the substrate. Elimination can therefore, compete with substitution. Many factors influence the extent of this competition, including the nature of nucleophile, its strength, the solvent and the substrate. The strong bulky Bronsted bases favor E_2 and strong nucleophiles favor S_N2 process. For instance, bulky tert-butoxide anion (Me_3CO^-) can abstract a proton from the periphery of the molecule but is hindered as a nucleophile. However, some anions such as thiol anion (RS^-) are less basic and more strongly nucleophilic.

The $E_2 : S_N2$ ratio increases with increased substitution by alkyl groups. Primary alkyl halides will usually undergo S_N2 substitution reaction in preference to E_2 elimination reaction. As base strength increases, the rate of competitive elimination will increase, but substitution reactions

compete when the base is also a good nucleophile. Polar aprotic solvents are used to maximize the yield of S_N2 products and suppress side reactions such as elimination.

The E_1 and S_N1 involve the formation of the same intermediate, carbocation, by the same rate controlling ionization step. However, the course of the reaction can often be controlled by specific reaction conditions. A high concentration of nonbasic nucleophiles in aqueous media favors the unimolecular substitution (S_N1), whereas unimolecular elimination (E_1) processes are favored with bases of weak to moderate strength that are also poor nucleophiles. In general, unimolecular substitution is faster than unimolecular elimination, since the cationic carbon is more strongly attracted to the electron-rich center.

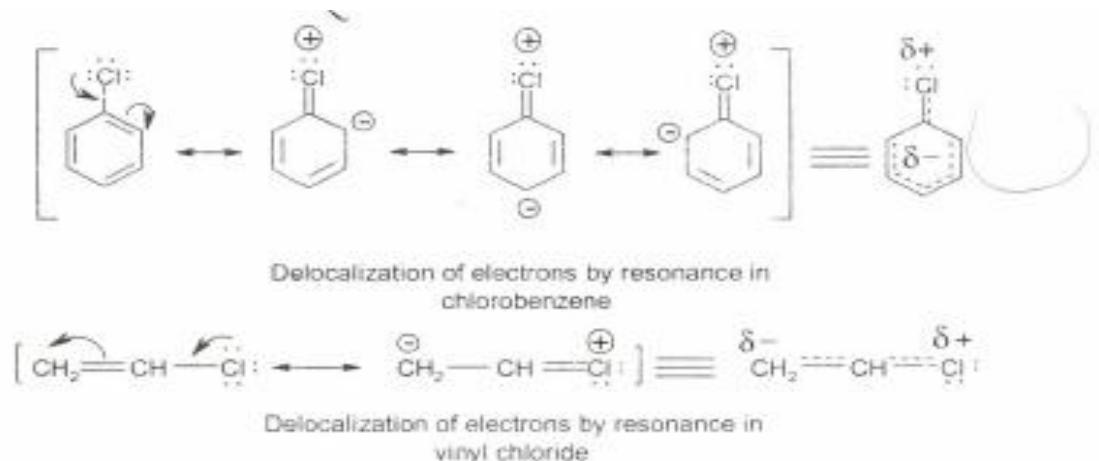


Halogen attached to a doubly bonded carbon or on aromatic nucleus is usually quite unreactive. The aryl halides show extremely low reactivity towards nucleophilic substitution reactions. They usually do not undergo nucleophilic substitution reactions unless electron-withdrawing groups are located ortho or para to the halogen on the aromatic ring. Similarly, vinyl halides are very much unreactive toward nucleophilic substitution reactions than their saturated counterparts.

The low reactivity of alkyl and vinyl halides is because of the fact that they contain shorter and stronger carbon-halogen bond. For example, in chlorobenzene and vinyl chloride the C-Cl bond length is $1.69\text{\AA}$, as compared with a bond length of $1.77\text{--}1.80\text{\AA}$ in a large number of alkyl chlorides. This is attributed to the sp^2 hybridization of the carbon atom holding halogen. Since, carbon atom having sp^2 hybridization is more electronegative than sp^3 hybridized carbon atom, therefore, the carbocation intermediates formed by the ionization of aryl and vinyl halides are thermodynamically less stable than alkyl carbocations. This prevents the S_N1 mechanism from operating in aryl and vinyl halides.

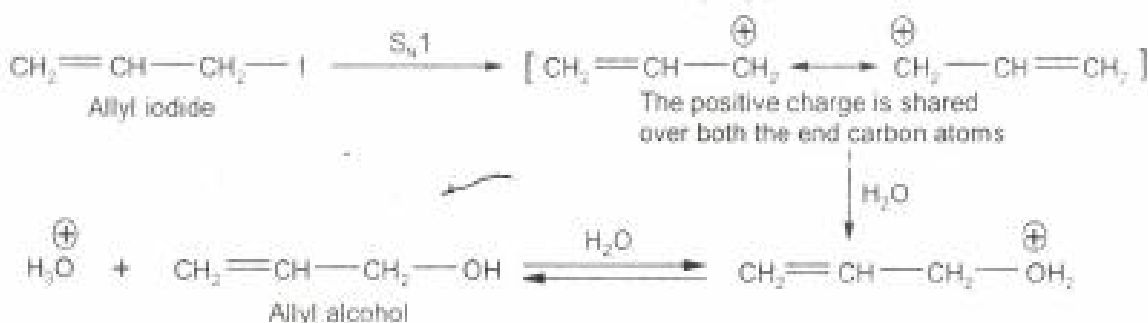
The other reason for this unreactivity is that the π -orbital of the double bond overlaps with the p-orbitals of the halogen atom to form delocalized cloud of the π -electrons with the result that C-X bond attains a partial double bond character. The partial double bond character of the C-X bond results in strengthening of the bond and hence it is difficult to break as compared to single bond.

Both of these effects inhibit nucleophilic substitution reactions of either the S_N1 or S_N2 type, thus net reactivity of the molecule is considerably less than that of saturated alkyl halides.



High reactivity of allyl and benzyl halides

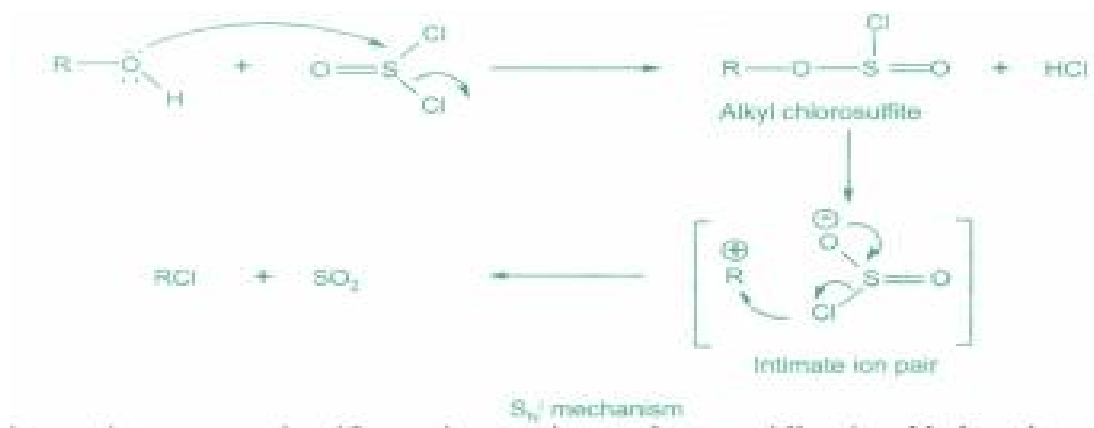
On the other hand, allyl halides and benzyl halides are more reactive than saturated halides. Allyl and benzyl halides are especially reactive under S_N1 conditions because of the resonance stabilization of the intermediate allyl and benzylcarbocations, respectively. The resonance stabilization of intermediate carbocations has an acceleration effect on the ionization of allyl and benzyl halides. For example, solvolysis of allyl iodide in water proceeds much faster than the solvolysis of propyl iodide.



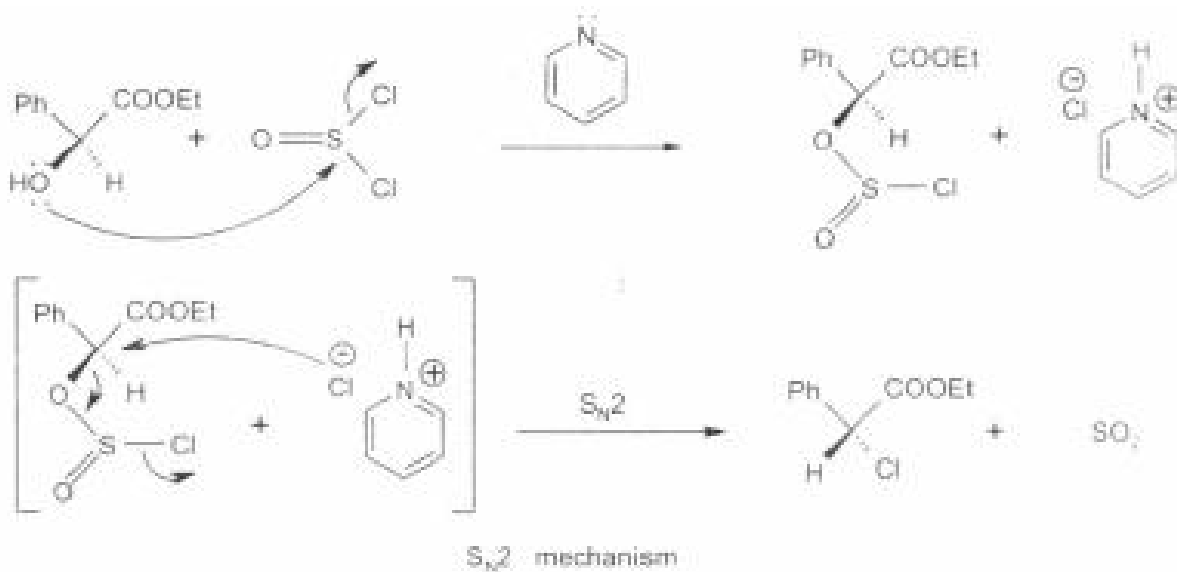
S_Nⁱ (Substitution Nucleophilic internal)

In this process part of leaving group which attacks the substrate detaches itself from the rest of the leaving group. This is exemplified by the conversion of (R)-2-butanol to (R)-2-chlorobutane with SOCl₂ in nonpolar solvent and absence of base. The product formed is with complete retention of configuration, i.e., in which the starting material and product have the same configuration. The mechanism appears to involve the formation of intermediate chlorosulfite

ester, ROSOCl (R = sec-butyl group), which dissociates into an intimate ion pair, $\text{R}^+ \text{ } ^-\text{OSOCl}$ as in $\text{S}_{\text{N}}1$ mechanism. The Cl^- , with pair of electrons, of the anion attacks the R^+ from the same side of the carbocation from which $^-\text{OSOCl}$ departed and the product (RCl) is formed with complete retention of configuration.

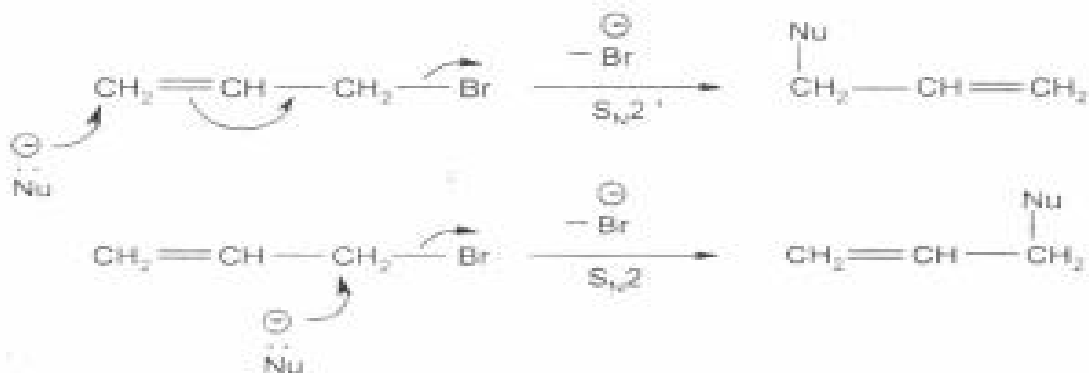


It is interesting to note that if a tertiary amine such as pyridine is added to the reaction mixture, the product RCl is found now to have undergone inversion of configuration. The pyridine coordinates with the HCl , produced during the formation of intermediate chlorosulfite from ROH and SOCl_2 , to form pyridine hydrochloride and the Cl^- is an effective nucleophile. The displacement of the chlorosulfite ester by Cl^- *via* $\text{S}_{\text{N}}2$ mechanism gives product with complete inversion of configuration. The reaction of alcohols with thionyl chloride in presence of pyridine is known as **Darzen's procedure**.



S_N2' reaction:

Some times S_N2 reaction, leads to allylic rearrangement. The attack of nucleophile takes place at the end of the π -system i.e. at C-3 of the allylic-system, with simultaneous expulsion of a leaving group. Such reactions are **referred to as S_N2'** , to distinguish them from the normal S_N2 process the following examples are used.



S_N2' mechanism leads to the same product as S_N2 , however, if the allylic halide is unsymmetrically substituted, we can tell which mechanism operates and the product formed will be from the nucleophilic attack at the less hindered end of the allylic system. Prenyl bromide, for example, reacts entirely *via* S_N2 process. If the secondary butenyl chloride is reacted with an amine then S_N2' product is obtained.

