CHAPTER 6

Aliphatic Nucleophilic Substitution

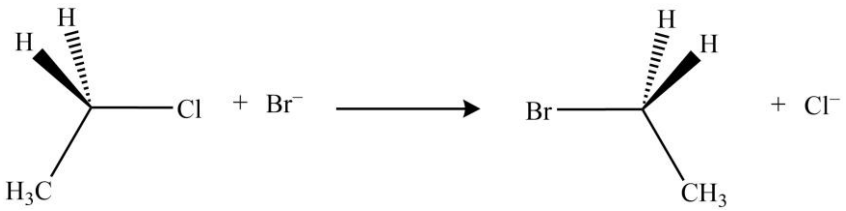
❖ The SN_2, SN_1, Mixed SN_1 and SN_2, SN_i, SN_1', SN_2', SN_i' and SET Mechanisms

Although the number of mechanisms by which the nucleophilic substitutions proceed is very large, certain patterns can still be used to profile them for more systematic and simplistic analysis. Some of the prominent types of aliphatic nucleophilic substitutions are given below.

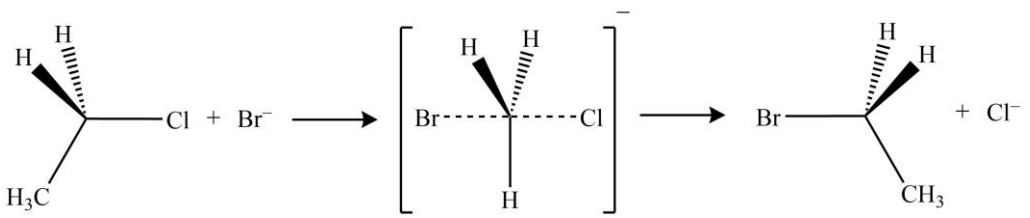
➢ *SN_2 (Substitution Nucleophilic Bimolecular) Mechanism*

In SN_2 reactions, the "SN" stands for "nucleophilic substitution", and "2" means that the rate-determining step is bimolecular. In other words, a stronger nucleophile displaces a weaker one via the formation of a transition state.

Illustrative reaction: One of the most common examples of the SN_2 reaction is the attack of Br^- on ethyl chloride results in ethyl bromide, with chloride ejected as the leaving group.



Mechanism involved: The proposed mechanism for the reaction given above involves a single step which must be discussed before we give the salient features of the same. The process occurs most often at the sp^3 hybridized carbon with a stable electronegative leaving group attached to it (usually halide X^-).



The breaking of the carbon–halogen bond and the formation of the new covalent bond takes place simultaneously via a transition state in which the carbon under nucleophilic attack is in 5-coordination with probable sp^2 hybridization. The nucleophilic attack at the carbon takes place at 180° w.r.t the leaving group to provides a good overlap between the nucleophile's lone pair and the antibonding orbital (σ*) C–X bond. The leaving group is then detached from the opposite side and the product is formed with inversion of the tetrahedral geometry at the central carbon atom if the substrate is chiral.

Salient Features: The main features of the mechanism involved in nucleophilic substitution bimolecular or SN_2 type reactions are given below.

i) SN_2 reactions follow second-order kinetics with the rate law

$$Rate = k[RX][Nu]$$

Where k is the rate constant. The symbol $[RX]$ and $[Nu]$ represent the molar concentration of the substrate and attacking nucleophiles, respectively.

ii) If the alkyl halide is chiral, then this often leads to an inversion of configuration, called the Walden inversion.

iii) The rate of the substitution becomes independent of the concentration of the attacking reagent if its concentration is extremely high in comparison to the substrate.

iv) The rate of the substitution increases as the steric bulk around the carbon center decreases.

v) The SN_2 reactions are favored in polar aprotic solvents.

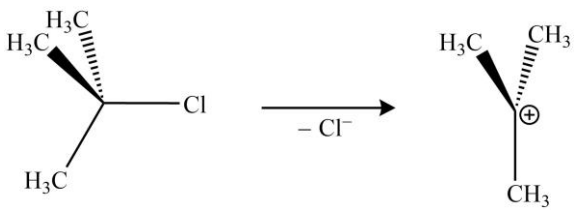
- ***SN_1 (Substitution Nucleophilic Unimolecular) Mechanism***

In SN_1 reactions, the word "SN" stands for "nucleophilic substitution", and "1" means that the rate-determining step is unimolecular in nature. In other words, a stronger nucleophile displaces a weaker one via the formation of an intermediate.

Illustrative reaction: The most common example of an SN_1 reaction is the formation of alcohols from alkyl halides as shown below.

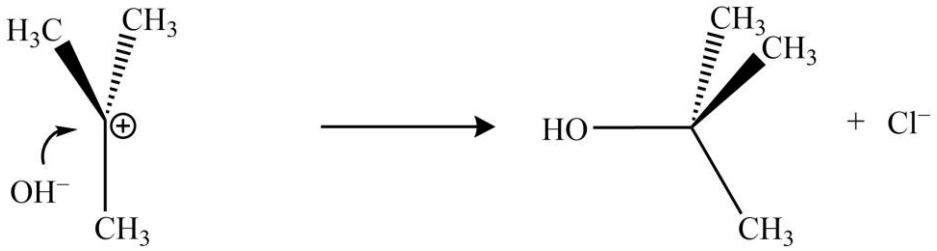
Mechanism involved: The proposed mechanism for the reaction given above involves two steps which must be discussed before we give salient features of the same.

i) Formation of intermediate:



The carbocation formed during this step is trigonal planar in geometry and is open for attack from both sides. Now since the carbocations are electron-deficient species and very reactive, The OH^- will attack from either side to give the same product, which will be the second step of the reaction.

ii) Attack by the Nucleophile:



Now since the faces of the carbocations formed are homotopic, the OH^- can attack from either side to give the same product.

Salient Features: The main features of the mechanism involved in nucleophilic substitution unimolecular or SN_1 type reactions are given below.

i) SN_1 reactions follow first-order kinetics with the rate law

$$Rate = k[RX]$$

Where k is the rate constant and $[RX]$ represents the molar concentration of the substrate (tert-butyl halide in this case).

ii) If the alkyl halide has one or more asymmetric carbons, two stereoisomers (diastereomers or enantiomers) will be formed.

iii) The rate of the nucleophilic substitution unimolecular is almost independent of the concentration of the attacking reagent.

iv) The rate of the substitution increases as the steric bulk around the carbon center increase.

v) Since an unstable intermediate carbocation is formed in course of the SN_1 reactions (rate-determining step), any factor that can support this will boost up the rate. Normal solvents of choice are both protic (to hydrolyze the leaving group in particular) and polar (to simply stabilize ionic intermediates). Archetypal polar protic solvents include alcohol and water, which are also capable of acting as nucleophiles (i.e. support solvolysis). Therefore, we can conclude that the SN_1 reactions are favored in polar and protic solvents.

vi) Since the intermediate formed is carbocation, the possibility of rearrangement to form more stable carbocation and yielding different products is also there.

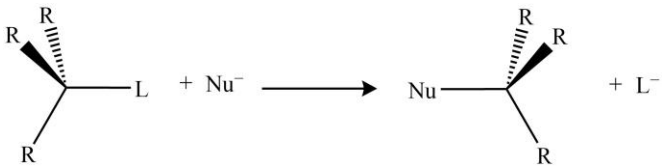
vii) The substitution at bridgehead carbon is either absent or takes place very slowly because the carbocation in such cases cannot attain planar geometry.

viii) In asymmetric alkyl halides, racemization does not take place fully all the time because the nucleophile attacks even before the complete detachment of leaving group. This leads to some inversion also causing unequal racemic mixture.

➢ ***Mixed SN_1 and SN_2 Mechanism***

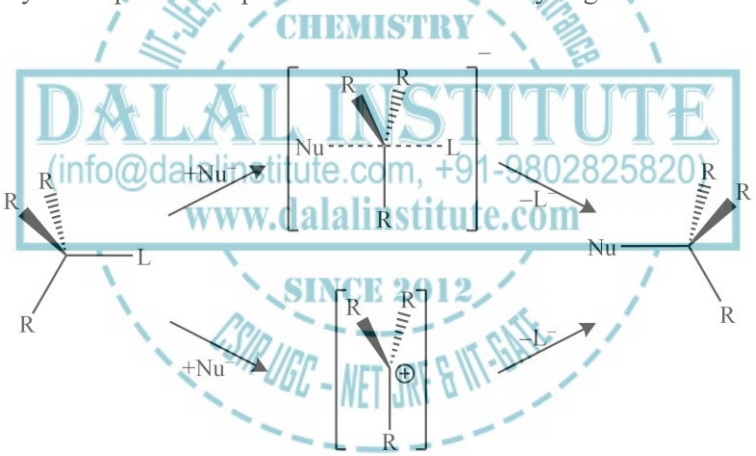
Most of the organic reactions are either SN_1 or SN_2 over a vast range of experimental conditions. However, some reactions show both types of characteristic features under certain conditions indicating that they are neither SN_1 nor SN_2 but a mixture of two. In other words, some nucleophilic substitution reactions proceed via mixed SN_1 and SN_2 mechanisms.

Illustrative reaction: The common depictive example of SN_1-SN_2 mixed-mechanism is shown below.

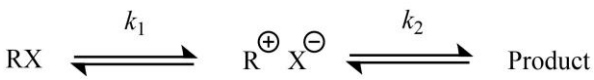


Mechanism involved: There are two theories that are typically used to rationalize the borderline nucleophilic substitution mechanism as given below.

i) Simultaneity of SN_1 and SN_2: As the name suggests, this theory says that the reaction proceeds simultaneously via SN_1 and SN_2 pathways. The pictorial representation of this theory is given below.



ii) Intermediatory mechanism: This theory assumes that the reaction takes place via the formation of an intermediary ion-pair as shown below.



When the formation of ion-pair is the rate-determining step, the reaction becomes SN_1; whereas, if the conversion of ion-pair into the product is the rate-determining step, the reaction becomes SN_2; if $k_1 = k_2$, we get a borderline case.

Salient Features: The main features of the mixed SN_1 and SN_2 mechanism are given below.

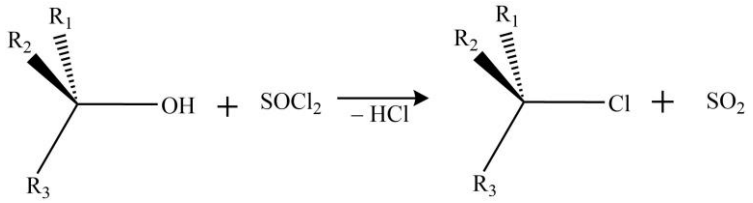
i) SN_1 pathway competes with the SN_2 route to dominate the products' ratio for asymmetric reactants.

ii) The ion-pair theory can be applied to both SN_1 and SN_2 as well.

➢ *SNi (Substitution Nucleophilic Internal) Mechanism*

In SN_i reactions, the "SN" stands for "nucleophilic substitution", and the "*i*" means that the substitution takes place internally in the molecule.

Illustrative reaction: One of the most common examples of the SN_i reaction is the displacement of OH^- of alcohols by Cl^- in the presence of $SOCl_2$.



Mechanism involved: The $SOCl_2$ first reacts with the alcohol to give rise to an alkyl chloro sulfite (i.e. intimate ion pair). The next step is concerted and involves the loss of an SO_2 molecule and its displacement by its own chloride group.

The major point of difference between SN_i and SN_1 is actually that the ion pair is not completely separate, and therefore, no actual carbocation is generated (otherwise we would have got racemized product).

Salient Features: The main features of the mechanism involved in nucleophilic substitution internal or SN_i type reactions are given below.

i) SN_i reactions follow second-order kinetics with the rate law

$$Rate = k[ROH][SOCl_2]$$

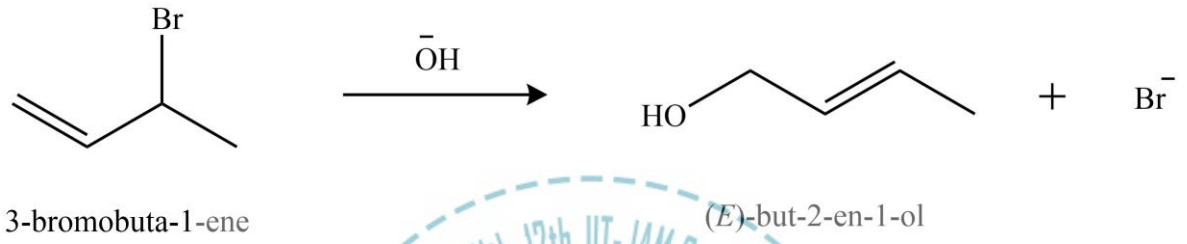
Where *k* is the rate constant. The symbol $[ROH]$ and $[SOCl_2]$ represent the molar concentration of the substrate and species with attacking nucleophiles, respectively.

ii) If the alcohol is chiral, then this leads to the retention of configuration.

➢ ***SN_1' (Substitution Nucleophilic Unimolecular Prime) Mechanism***

In SN_1' reactions, the word "SN" stands for "nucleophilic substitution", "1" means that the rate-determining step is unimolecular in nature, and prime indicates that there is a double bond in the vicinity of leaving group. In other words, a stronger nucleophile displaces a weaker one via the formation of an intermediate that has a delocalization of π-electron density.

Illustrative reaction: The most common example of SN_1' reaction is the formation of but-2-ene-1-ol from 3-bromobuta-1-ene as shown below.



3-bromobuta-1-ene (*E*)-but-2-en-1-ol

Mechanism involved: The proposed mechanism for the reaction given above involves two steps which must be discussed before we give salient features of the same. At first, the detachment of bromide ion gives rise to an allylic carbocation system in which the positive charge is distributed at 1st and 3rd carbon atoms. Now since the terminal carbon is primary but 3rd carbon is secondary, the first carbon is more electron deficient, and therefore, will become the first choice for attacking nucleophile to yield our product.

3-bromobuta-1-ene (*E*)-but-2-en-1-ol

One more reason that why the nucleophile did not attack at the 3rd carbon to give normal SN_1 is that there is more steric hindrance at the 3rd carbon than what it is at 1st.

Salient Features: Almost all of the features of SN_1' prime are similar to the SN_1 mechanism with some exceptions as given below.

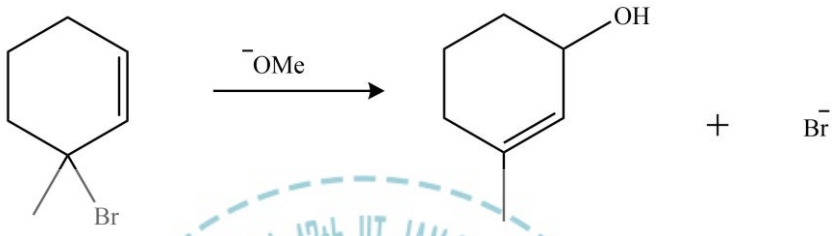
i) The carbonation formed in SN_1 was simple but rearrangeable in the case of allylic systems.

ii) The nucleophile attack on γ-carbon rather than the α- one.

➢ ***SN_2' (Substitution Nucleophilic Bimolecular Prime) Mechanism***

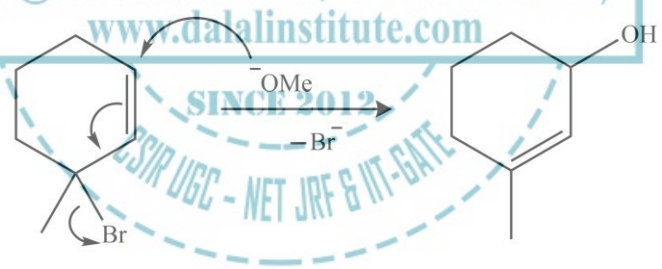
In SN_2' reactions, the "SN" stands for "nucleophilic substitution", "2" means that the rate-determining step is bimolecular, and prime indicates that there is a double bond in the vicinity of leaving group. In other words, a stronger nucleophile displaces a weaker one via the formation of a transition state; though the attachment and detachment are at different carbons.

Illustrative reaction: One of the most common examples of the SN_2' reaction is the conversion of 3-bromo-3-methylcyclohex-1-ene into 3-methylcyclohex-2-en-1-ol, with bromide ejected as the leaving group.



3-bromo-3-methylcyclohex-1-ene 3-methylcyclohex-2-en-1-ol

Mechanism involved: The proposed mechanism for the reaction given above involves the use of a double bond as a relay system of electron density. Instead of attacking at the 3rd carbon in the cycle (would have yield normal SN_2 product), the incoming nucleophile attacks at 1st carbon due to its greater electron deficiency than the 3rd one which is obviously caused by electrons' relay from first carbon to bromine.



3-bromo-3-methylcyclohex-1-ene 3-methylcyclohex-2-en-1-ol

One more reason that why the methoxide ion did not attack at the 3rd carbon to give normal SN_2 is that there is more steric hindrance at the 3rd carbon than what it is at 1st. In other words, the greater electron deficiency and a less steric hindrance at first carbon make it a better site for nucleophilic attack.

Salient Features: Almost all of the features of SN_2' prime are similar to the SN_2 mechanism with some exceptions as given below.

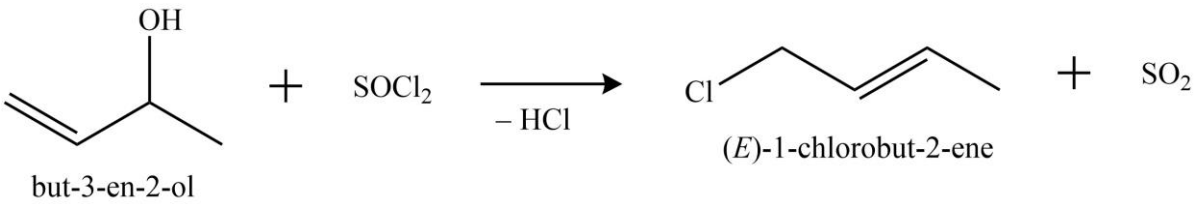
i) The nucleophilic attack and the detachment of leaving group takes place at different carbon atoms.

ii) The double bond is used as an electrons' relay system.

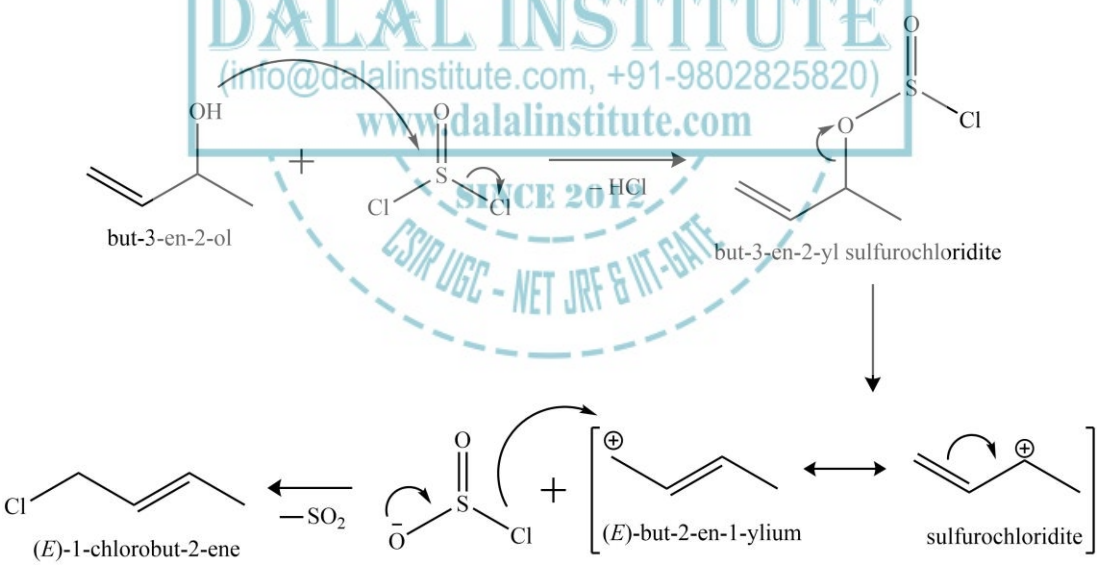
- ***SN_i' (Substitution Nucleophilic Internal Prime) Mechanism***

In SN_i' reactions, the "SN" stands for "nucleophilic substitution", the "*i*" means that the substitution takes place internally in the molecule, and prime indicates that there is a double bond in the vicinity of leaving group.

Illustrative reaction: One of the most common examples of the SN_i' reaction is the displacement of OH of in but-3-en-2-ol by Cl in the presence of $SOCl_2$.



Mechanism involved: The proposed mechanism for the reaction given above initially proceed normally like SN_i; however, the detachment of sulfurochloridite ion gives rise to an allylic carbocation system in which the positive charge is distributed at 1st and 3rd carbon atoms. Now since the terminal carbon is primary but 3rd carbon is secondary, the first carbon is more electron deficient, and therefore, will become the first choice for attacking nucleophile to yield our product.



One more reason that why the nucleophile did not attack at the 2nd carbon to give normal SN_i is that there is more steric hindrance at the 2nd carbon than what it is at 4th.

Salient Features: Almost all of the features of SN_i' prime are similar to the SN_i mechanism with some exceptions as given below.

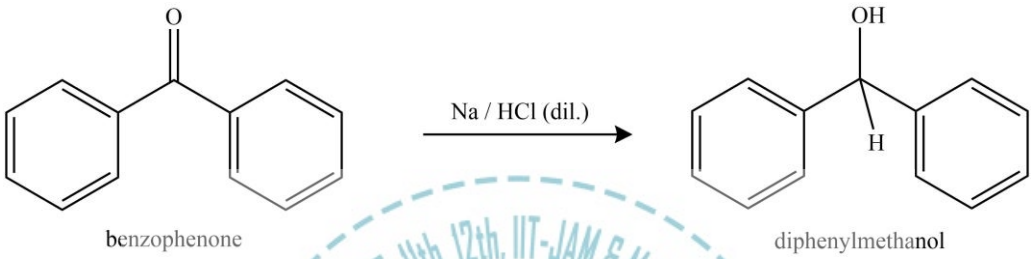
i) The carbonation formed in SN_i was simple but rearrangeable in the case of allylic systems.

ii) The nucleophile attack on the 1st carbon rather than the 3rd one.

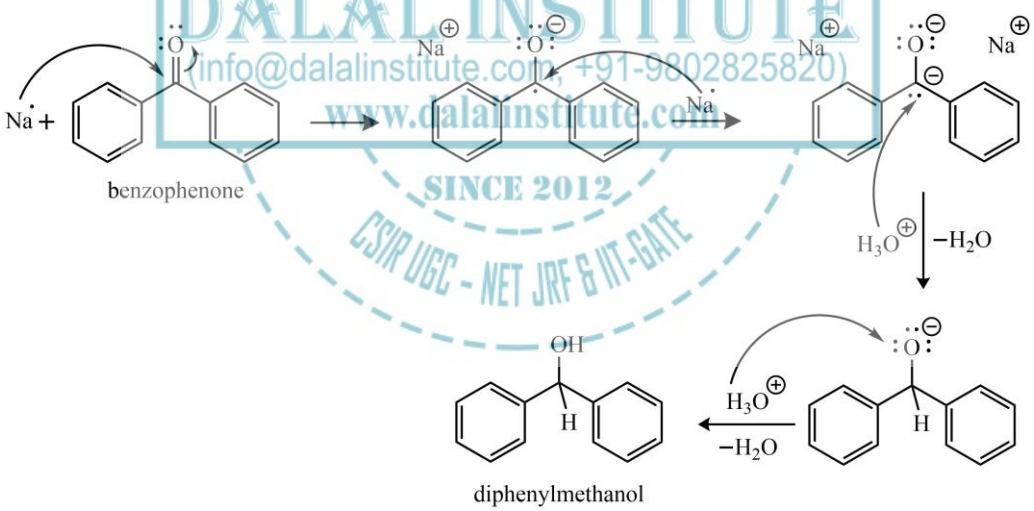
➢ ***SET (Single-Electron Transfer) Mechanism***

SET (single electron transfer) reactions may simply be defined as the organic reaction mechanism in which an electron-rich molecule gives away one of its electrons to an electron-poor molecule to form radical cation and radical anion, respectively. Furthermore, these radical anions and cations can bind to give new bonds or may react in some other way to yield strange products.

Illustrative reaction: One of the most common examples of the SET reactions is the transformation of benzophenone into 1,1-diphenylmethanol in the presence of metallic sodium.



Mechanism involved: The proposed mechanism for the reaction given above involves four steps which must be discussed before we give salient features of the same. The process occurs most often via the formation of benzophenone anion and dianion as given below.



At this stage, some protons are added in the form of very weak (NH_4Cl) or strong acid (HCl). The protonation of benzophenone dianion would yield 1,1-diphenylmethanol.

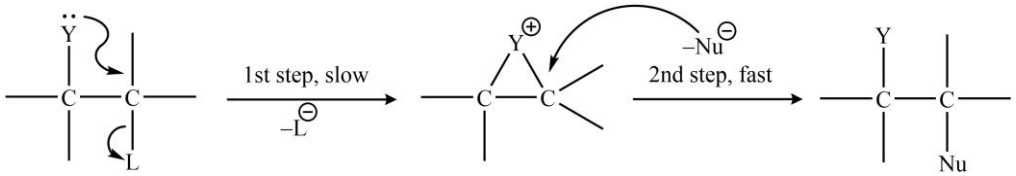
Salient Features: The main features of the mechanism involved in simple electric transfer or SET type reactions are given below.

i) The electron transfer results in radical cation and radical cation.

ii) The SET mechanisms can be distinguished from polar mechanisms by careful analysis of end products.

❖ The Neighbouring Group Mechanisms

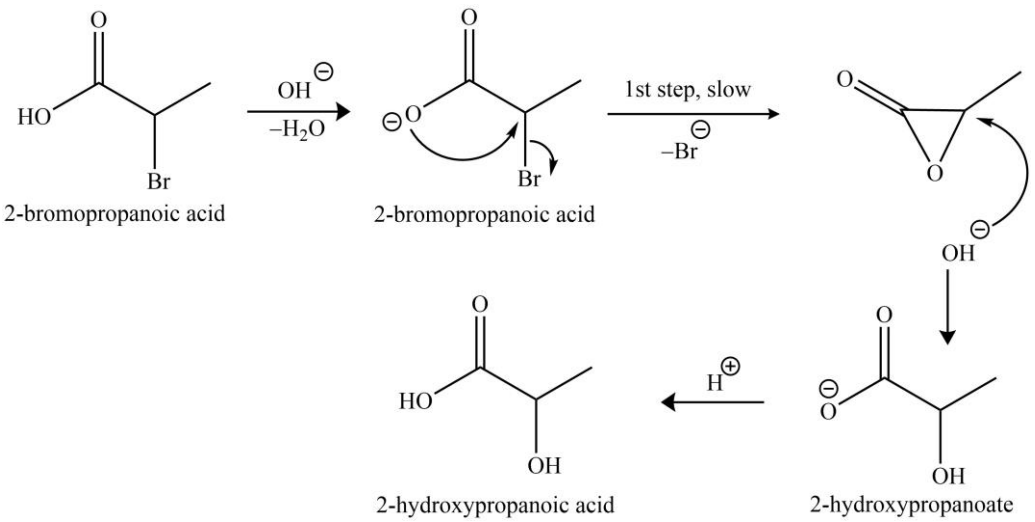
There are many nucleophilic substitution reactions that give rise to the same configuration (i.e., retention) instead of inversion or racemization. Also, the rate of reaction for such reactions is so high that we cannot rationalize them by simple nucleophilic substitutions. However, it has been observed that one feature that is common in these reactions is a group or atom at β-position to the leaving group. The mechanism responsible for such transformations is labeled as neighboring group participation and can be parted into two normal SN_2 consecutive steps. Now since the first SN_2 reaction gives inversion (neighboring group as the nucleophile), the subsequent SN_2 changes will revert the configuration to the original (neighboring group as leaving group).



The faster rate of reaction can be rationalized in terms of the ready availability of nucleophilic attack in the first step (rate-determining step). Furthermore, it should also be noted that the generation of the cyclic intermediate is a characteristic feature of the neighboring group participation. Some typical cases of neighboring group participation are discussed below.

➢ *Reactions Involving Oxygen as Neighbouring Group*

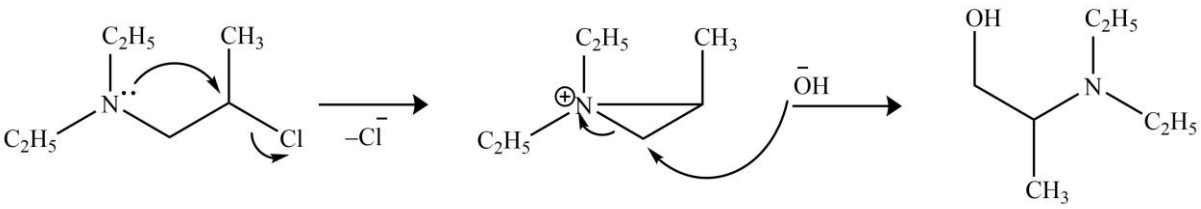
One of the most common examples of this type of neighboring group mechanism is the reaction of 2-bromopropanoic acid with a dilute solution of NaOH.



It is obvious from the above route that the configuration has remained the same (R)-lactate anion), unlike SN_2 where we would have obtained the (S)-lactate anion.

➢ ***Reactions Involving Nitrogen as Neighbouring Group***

One of the most common examples of this type of neighboring group mechanism is the reaction of 2-chloro-N,N-diethylpropan-1-amine with a dilute solution of NaOH.

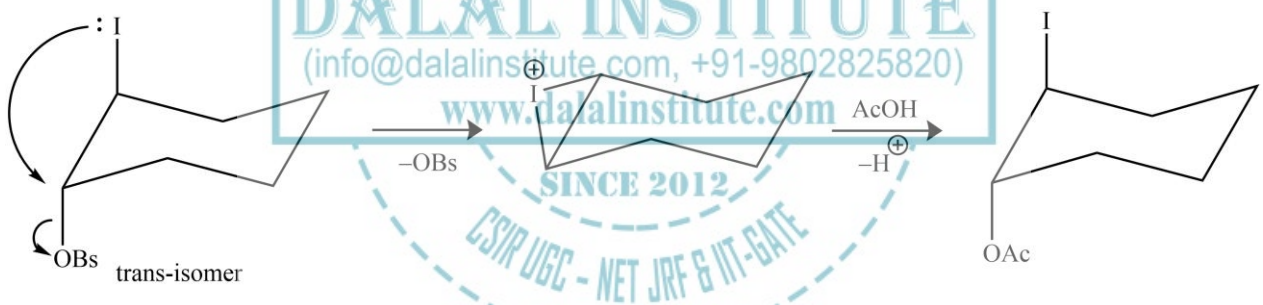


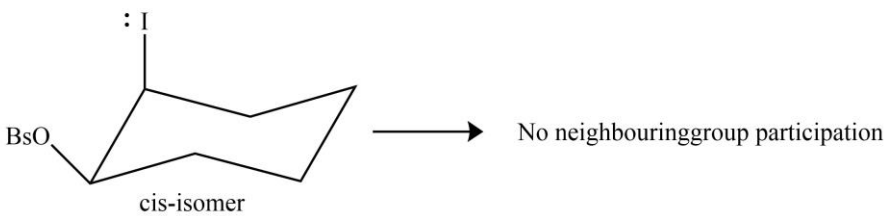
2-chloro-*N*,*N*-diethylpropan-1-amine 1,1-diethyl-2-methylaziridin-1-ium 2-(diethylamino)propan-1-ol

It is obvious from the above route that the configuration has remained the same, unlike SN_2 where we would have obtained the 1-(diethylamino) propan-2-ol.

➢ ***Reactions Involving Halogen as Neighbouring Group***

One of the most common examples of this type of neighboring group mechanism is the reaction involving the acetolysis of trans-2-iodocyclohexyl brosylate in which the configuration remains the same at the asymmetric center.

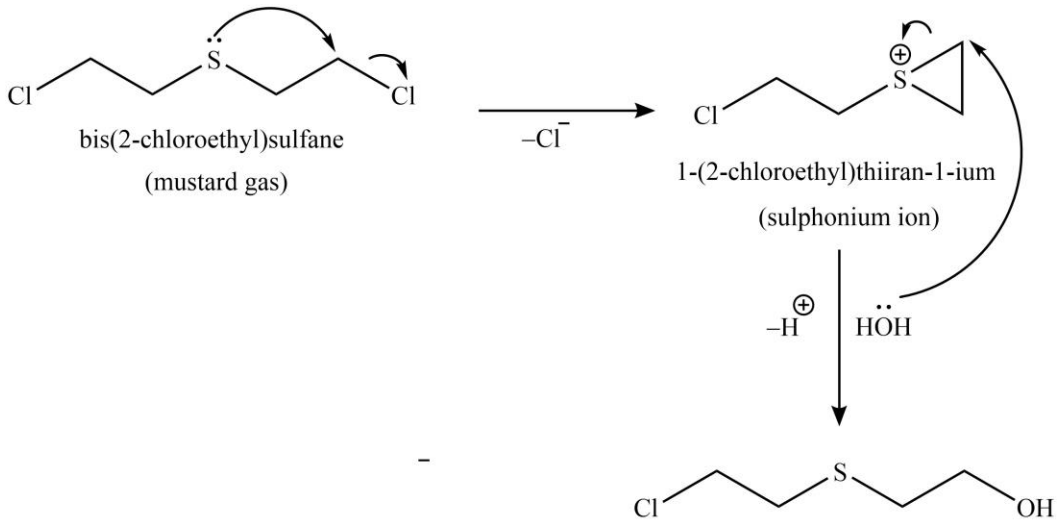




The is obvious from the above route that the configuration would have changed if the reaction had taken place via normal SN_2, which is observed for cis isomer.

➢ ***Reactions Involving Sulphur as Neighbouring Group***

One of the most common examples of this type of neighboring group mechanism is the reaction involving the hydrolysis of bis(2-chloroethyl) sulfane in which the configuration remains the same at the asymmetric center.



It is obvious from the above route that the configuration would have changed if the reaction had taken place via the normal SN_2 route.

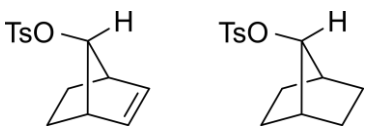
❖ Neighbouring Group Participation by π and σ Bonds

Besides oxygen, nitrogen, sulfur, and halogen; π- and σ-bonds can also act as a nucleophile in 'neighboring group mechanism' causing the retention of the original configuration. In this section, we will study the neighboring group participation by π and σ bonds with illustrative examples.

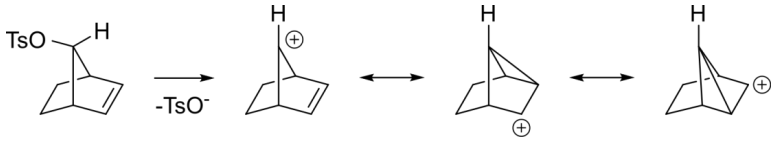
➢ ***π Bond as Neighbouring Group***

This type of neighboring group participation can primarily be classified into two categories as discussed below.

1. Neighbouring group participation by an alkene: The π orbitals of an alkene can stabilize a transition state by helping to delocalize the positive charge of the carbocation. For instance, the saturated tosylate will react very slowly (10^{11} times slower in solvolysis) with a nucleophile than the unsaturated tosylate.

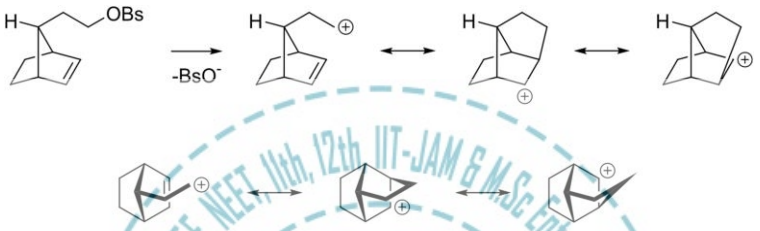


The positively charged intermediate will be stabilized by the phenomenon of resonance where the positive charge is spread over many atoms as shown below.



A different view of the same intermediate is also given below.

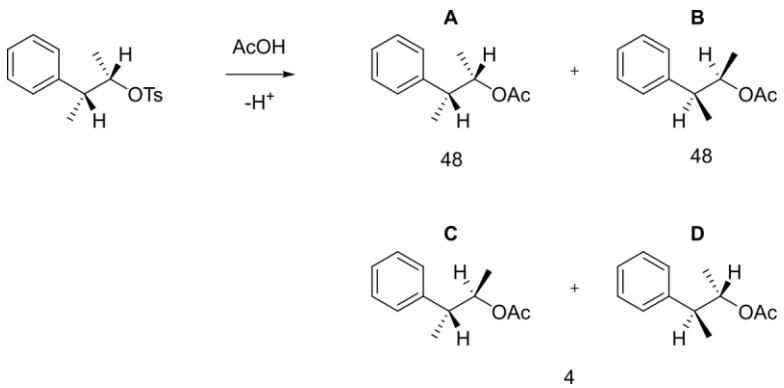
Even if the alkene is more distant from the reacting center, it can still act in this way. For instance, in the following alkyl benzenesulfonate, the alkene can delocalize the carbocation's positive charge.



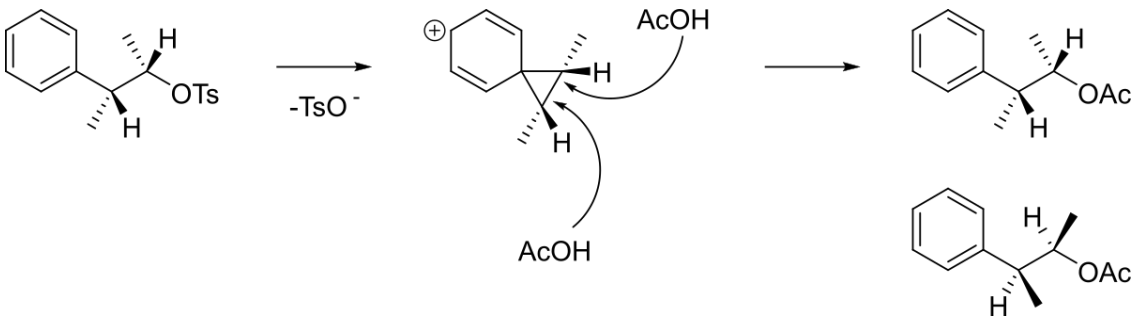
Furthermore, the raise in the SN_2 reaction rate of allyl bromide with a nucleophile relative to the treatment with *n*-propyl bromide is due to the π-bond's orbitals-overlap with transition state's counterparts. Therefore, we can say that the alkene orbitals overlap with the SN_2-transition-state's orbitals in the allyl systems.

2. Neighbouring group participation by an aromatic ring: Just like allyl systems, higher reactivity for benzyl halide is observed because the SN_2 transition state benefits from a similar overlapping effect. Similarly, many aromatic rings support the formation of an carbocation by delocalizing the positive charge density.

If the tosylate given below reacts with acetic acid via solvolysis instead of the normal SN_2 pathway forming B, a 48:48:4 mixture of A, B (i.e., enantiomers), and C+D was formed.



The mechanism which forms A and B is shown below.

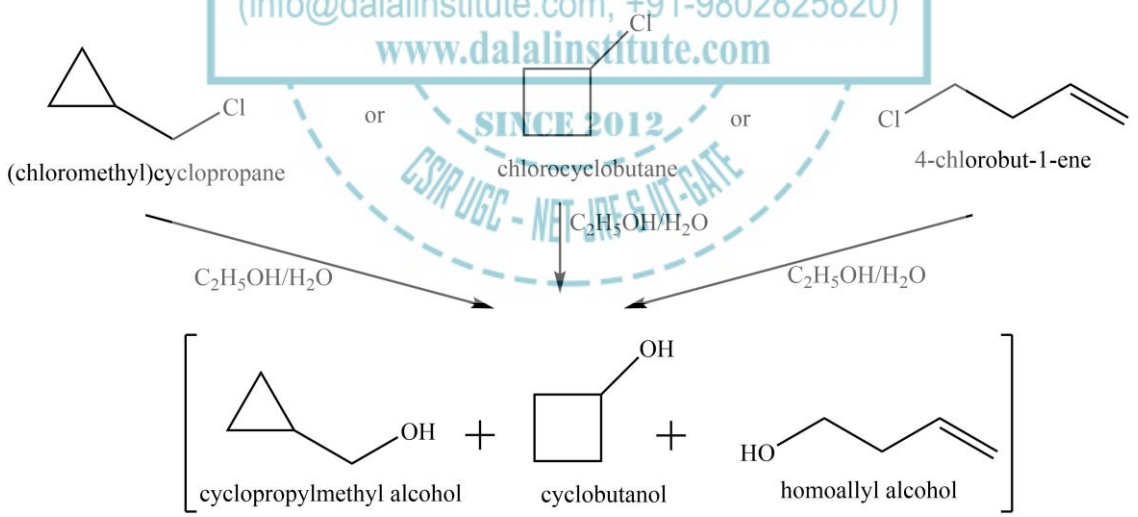


It is obvious from the above routes that the configuration would have changed if the reaction had taken place via the normal SN_2 route.

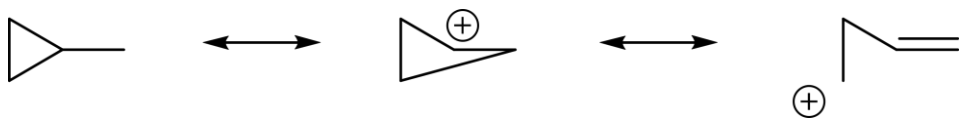
➢ ***σ Bond as Neighbouring Group***

This type of neighboring group participation can primarily be classified into two categories as discussed below.

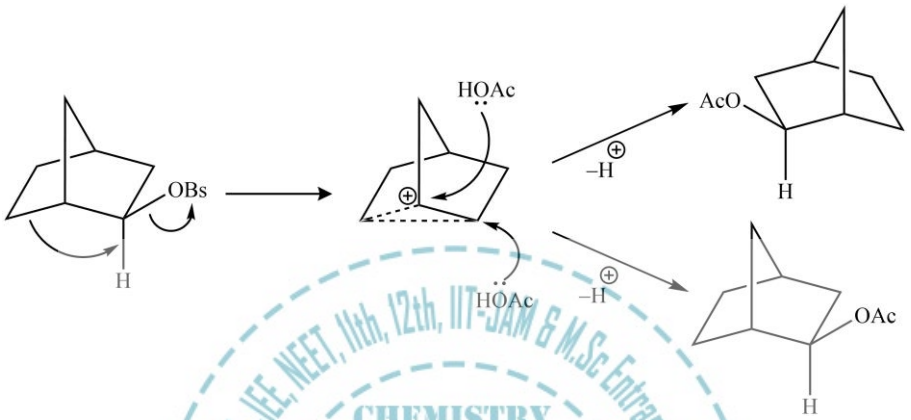
1. Neighbouring group participation by cyclopropylmethyl, cyclobutyl, or a homoallyl group: The treatment of cyclopropylmethyl chloride with dilute ethyl alcohol yields a mixture of 5% homoallyl alcohol, 47% cyclobutanol, and 48% cyclopropylmethyl alcohol. Similar results were obtained if we use cyclobutyl chloride or homoallyl chloride instead of cyclopropylmethyl chloride.



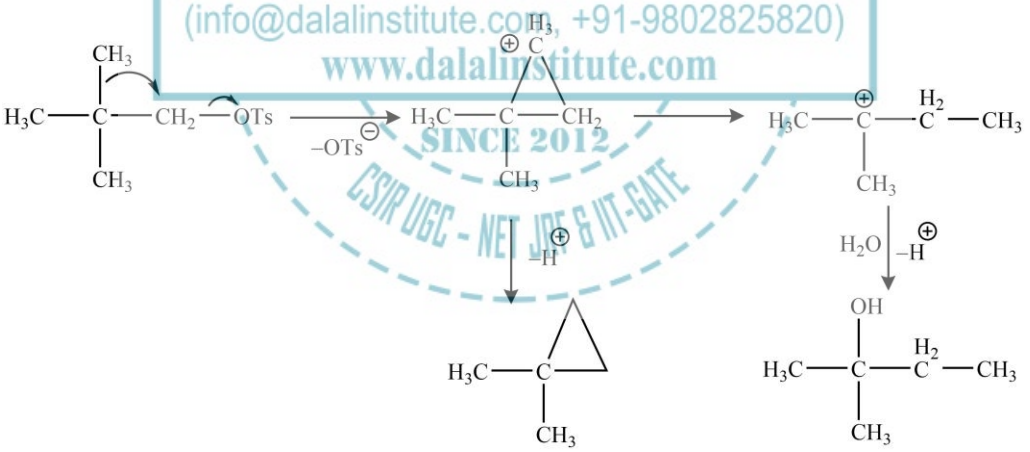
All this suggests that the carbocationic intermediate present in all three reactions must be the same, which in turn, is responsible for the same resulting products.



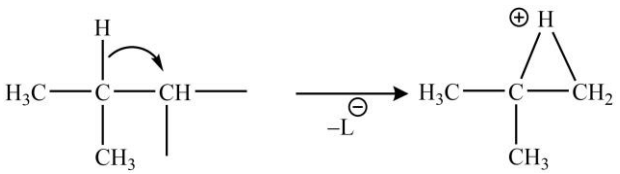
2. Neighbouring group participation by aliphatic C-C or C-H bonds: The aliphatic C–H or C–C bonds can also give rise to delocalization of charge if these bonds are close enough and antiperiplanar to the leaving group. The intermediates corresponding to these mechanisms are nonclassical in nature; and 2-norbornyl system is the most popular of such type. More precisely, the acetolysis of exo-2-norbonyl brosylate yields a racemic mixture of exo-acetates only and no endo product; suggesting neighboring group participation from σ-bond. Furthermore, a very slow rate is observed if we use endo-2-norbonyl brosylate confirming our guess.



Another example of such neighboring petrification by aliphatic bonds is the methyl system where C–H gives rise to the original configuration as depicted below.



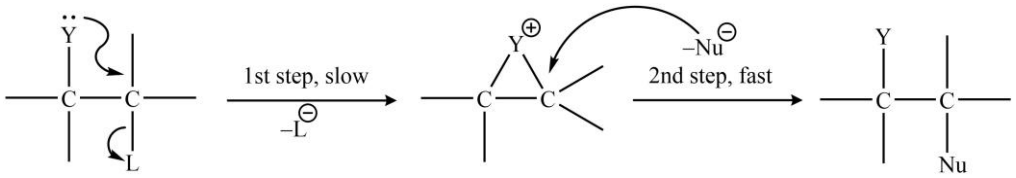
Another example of such neighboring group participation by aliphatic bonds is the methyl system where C–C gives rise to the original configuration as depicted below.



❖ Anchimeric Assistance

The anchimeric assistance may simply be defined as the increase in reaction-rate due to the presence of a neighboring group β- to the leaving group.

It is a well-known fact that many nucleophilic substitution reactions give rise to the same configuration (i.e., retention) instead of inversion or racemization due to neighboring group participation. Also, the rate of reaction for such reactions is very high because the group or atom at β-position to the leaving group is readily available for the nucleophilic attack in the first step (rate-determining step). The schematic representation of the whole process is shown below.



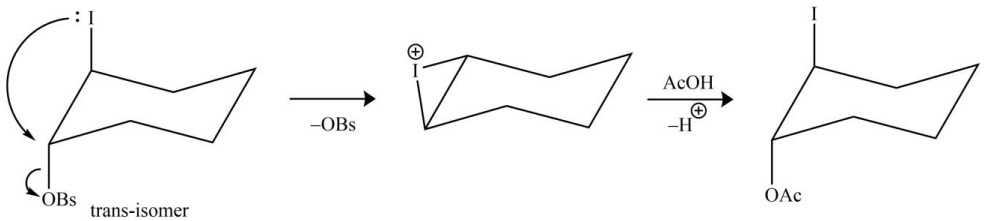
Since the first step is the rate-determining step, the reaction kinetics of the neighboring group mechanism is of the first order, which can be formulated as:

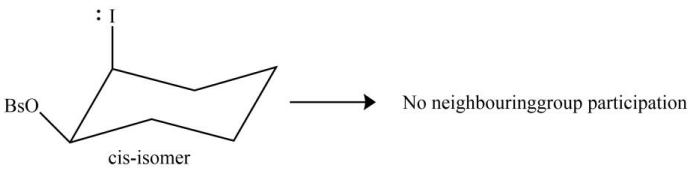
$$Rate = k[RX]$$

Where k is the rate constant and symbol $[RX]$ represents the molar concentration of the substrate.

➢ *Anchimeric Assistance by Heteroatom with Lone Pair*

The typical example of this type of anchimeric assistance that arises via neighboring group mechanisms is the reaction involving the acetolysis of trans-2-iodocyclohexyl brosylate in which the rate is 1.75×10^6 times greater than what is in acetolysis of cis-isomer.

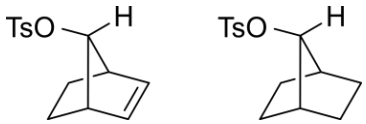




Also, it is obvious from the above route that the configuration would have changed if the reaction had taken place via the normal SN_2 route.

➢ ***Anchimeric Assistance by Alkene***

The typical example of this type of anchimeric assistance that arises via neighboring group mechanism is the reaction involving the solvolysis of unsaturated tosylate in which the rate is 10^{11} times greater than what is in solvolysis of saturated tosylate.

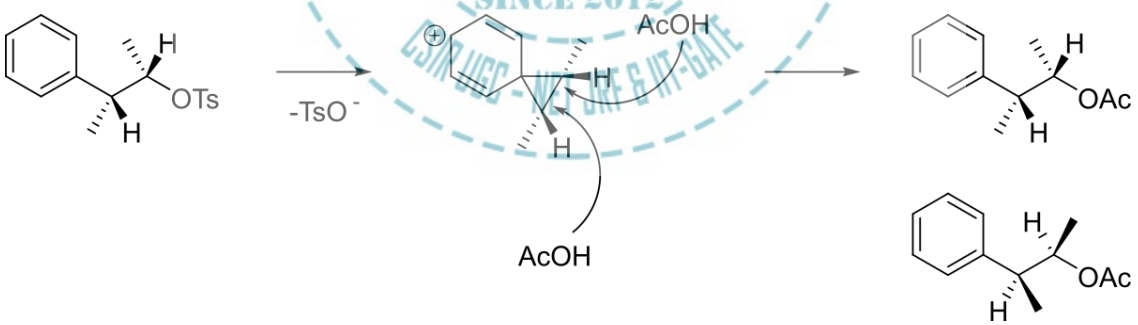


The carbocationic intermediate will be stabilized by resonance where the positive charge is spread over several atoms. In the diagram below this is shown.

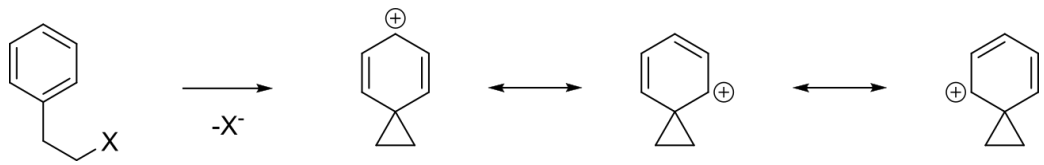
This effect is observed even if the alkene is more remote from the reacting center the alkene can still act in this way.

➢ ***Anchimeric Assistance by Aromatic Ring***

The typical example of this type of anchimeric assistance that arises via neighboring group mechanism is the reaction tosylate with acetic acid in solvolysis in which the rate is much greater than what is in solvolysis via aliphatic counterpart.

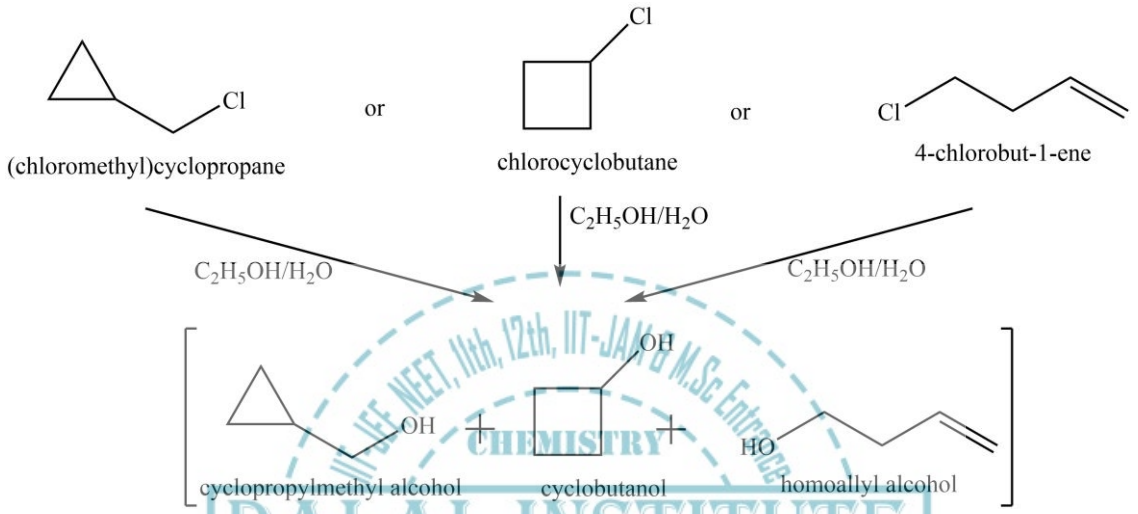


It is obvious from the above routes that the configuration would have changed if the reaction had taken place via the normal SN_2 route. An aromatic ring assists in the formation of a carbocationic intermediate called a phenonium ion by delocalizing the positive charge.



➢ ***Anchimeric Assistance by Cyclopropylmethyl System***

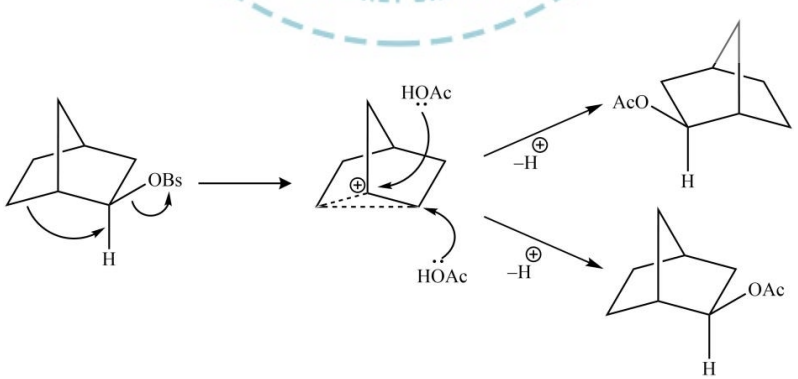
The typical example of this type of anchimeric assistance that arises via neighboring group mechanism is the reaction of cyclopropylmethyl chloride with dilute ethyl alcohol in which the rate is much greater than what is expected in the normal SN_2 route. Similar results were obtained if we use cyclobutyl chloride or homoallyl chloride instead of cyclopropylmethyl chloride.



All this suggests that the carbocationic intermediate present in all three reactions must be the same, which in turn, is responsible for the same resulting products.

➢ ***Anchimeric Assistance by Aliphatic Bonds***

The typical example of this type of anchimeric assistance that arises via neighboring group mechanism is the reaction of the acetolysis of exo-2-norbonyl brosylate yielding an racemic mixture of exo-acetates in which the rate is much greater than what is for endo-2-norbonyl brosylate.



Therefore, we conclude that the enhanced rate can be due to the anchimeric assistance by the aliphatic carbon-carbon single bond.

❖ Classical and Nonclassical Carbocations

It is a well-known fact that a large number of chemical reactions proceed via the formation of certain chemical species called carbocations in which one the carbon carries a positive charge with only six valence electrons. In this section, we will study the generation, structure, stability, and reactivity of two main types of carbocations called classical and non-classical carbocations one by one.

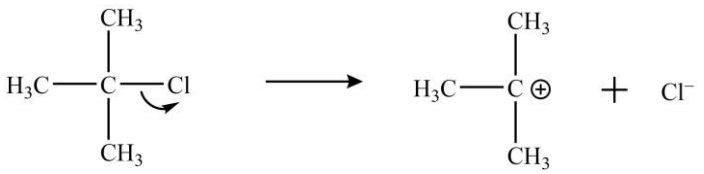
➢ *Classical Carbocations*

Classical carbocations in the organic chemistry may simply be defined as the carbocations that are stabilized by the delocalization of π-bond, or σ-bond, or lone pair of at conjugated site to the carbon bearing positive charge.

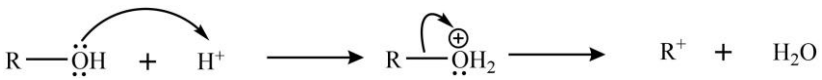
Since the carbon in classical carbocations has only six electrons, it is electron deficient; and therefore, acts as an electrophile in chemical reactions.

1. Generation of classical carbocations: The heterolytic cleavage of the covalent bond is responsible for the generation of most of the classical carbocation species. Some reactions involving the production of carbocations are given.

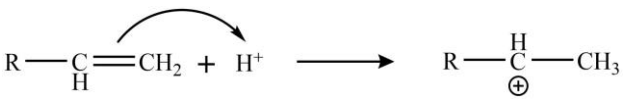
i) Ionization of alkyl halides in polar solvents:



ii) Protonation of alcohols followed by dehydration:

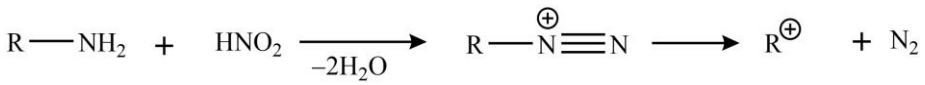


iii) Protonation of unsaturated systems:



iv) Action of superacids on alkyl fluorides:

v) Deamination of primary aliphatic amines by nitrous acid:



2. Orbital structure of classical carbocations: It has been experimentally found that the classical carbocations are trigonal planar around the carbon bearing positive charge. Now valence bond theory, as well as molecular orbital theory, easily accounted for such structure, it is more comfortable to discuss the valence bond approach. The carbon with the positive charge is in sp^2 hybridization with three hybrid orbitals oriented at 120° in a plane with empty p_z-orbital at a perpendicular.

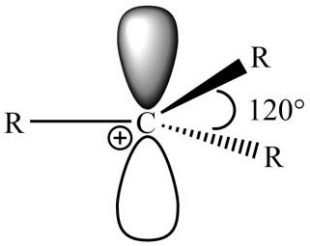
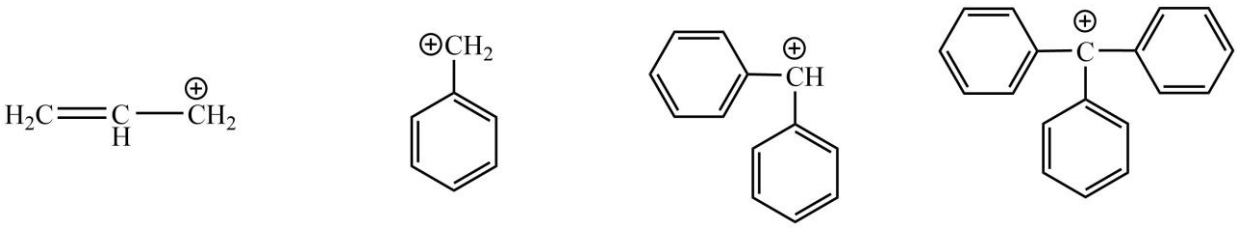


Figure 1. Orbital structure of a classical carbocation.

3. Stability of classical carbocations: Before we discuss the stability of classical carbocations, we need to classify them based on saturation. The first case is alkyl carbocations which are given below.

Methyl carbocation | Ethyl carbocation (1°) | Isopropyl carbocation (2°) | tert-butyl carbocation (3°)

The second case is of unsaturated classical carbocations where the carbon bearing positive charge is directly connected to a carbon participating in multiple bonds i.e.

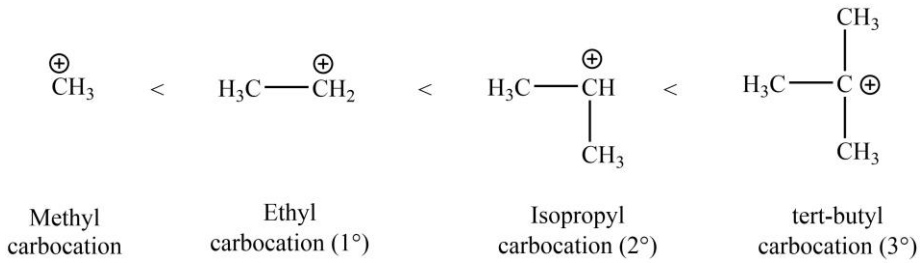


Allyl carbocation | Benzyl carbocation | Diphenylmethyl carbocation | Triphenylmethyl carbocation

Since the carbon in carbocations has only six electrons, it is electron deficient; and therefore, any effect that can compensate for the deficiency will stabilize the carbocation.

i) Stability of alky carbocations on the basis of inductive effect:

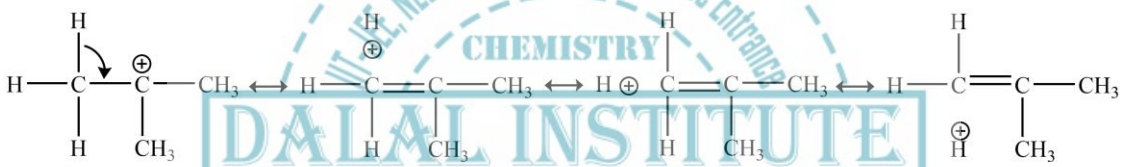
Since the alkyl group has an electron-donating effect (+I), the stability of the classical carbocation will increase as the number of attached donating groups increases. The stability order of alky carbocations based on inductive effect is given below.



Methyl carbocation | Ethyl carbocation (1°) | Isopropyl carbocation (2°) | tert-butyl carbocation (3°)

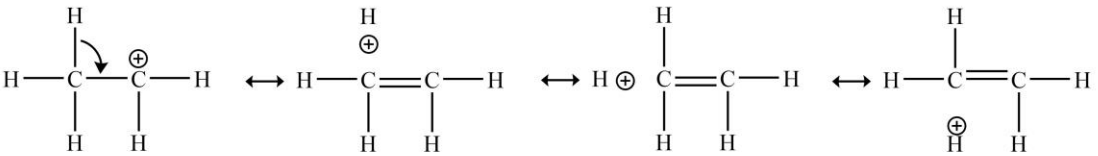
ii) Stability of alky carbocations on the basis of hyperconjugation:

The existence of the hyperconjugation effect can be used to rationalize the relative stability of different carbocations as shown below.



tert-butyl carbocation (3 hyperconjugative structures for one methyl group; Total hyperconjugative structures = 9)

iso-propyl carbocation (3 hyperconjugative structures for one methyl group; Total hyperconjugative structures = 6)

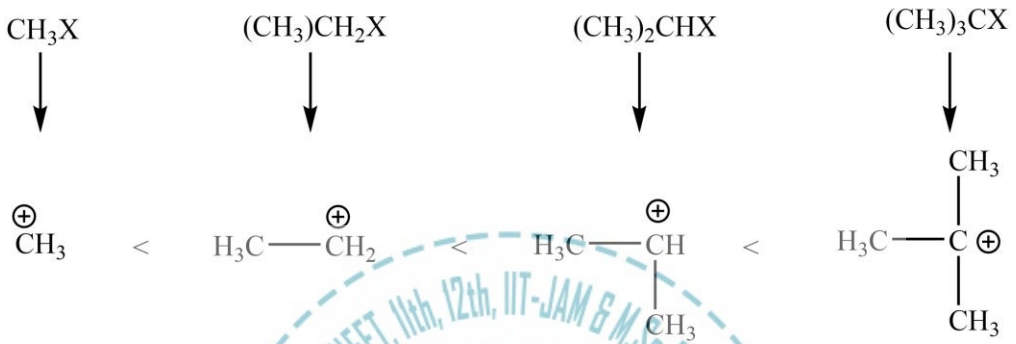


ethyl carbocation (3 hyperconjugative structures for one methyl group; Total hyperconjugative structures = 3)

Hence, as far as the number of possible hyper-conjugative structures possible is concerned, tertiary carbocation should be more stable than secondary, which in turn should be more stable than primary.

iii) Stability of alky carbocations on the basis of steric effect:

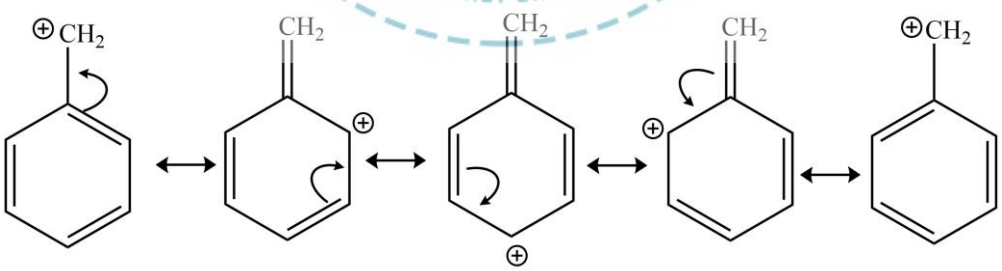
Since the alkyl carbocations are primarily obtained from alkyl halides with tetrahedral geometry, a link between the steric relief and carbocation formed can be established. During the formation of carbocations in such cases, the carbon-carbon bond angles change from 109°28' to 120°. Therefore, the carbon with bulky groups around is expected to get more relief from this carbocationic conversion. The stability order of alky carbocations on the basis of steric effect is given below.



iv) Stability of ally and benzyl carbocations:

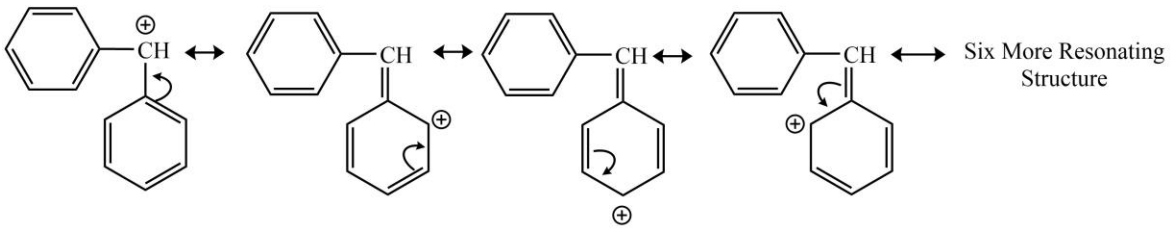
The stability of the carbocations in which the carbon bearing positive charge is adjacent to the double or triple bond can be rationalized in terms of resonance effect. First of all, let us draw the resonance structures allyl and benzyl carbocations.

Resonance stablized allyl cation

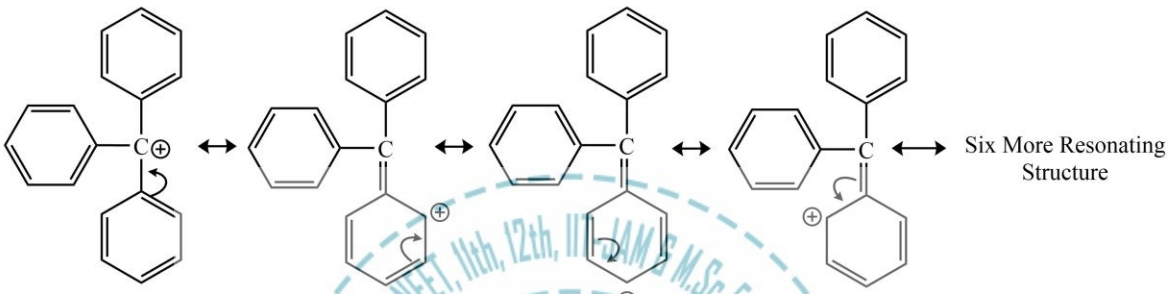


Resonance stablized benzyl cation

Now, as the number of phenyl groups attached to carbon bearing positive charge increases, the number of resonating structures will also increase, and hence the stability.

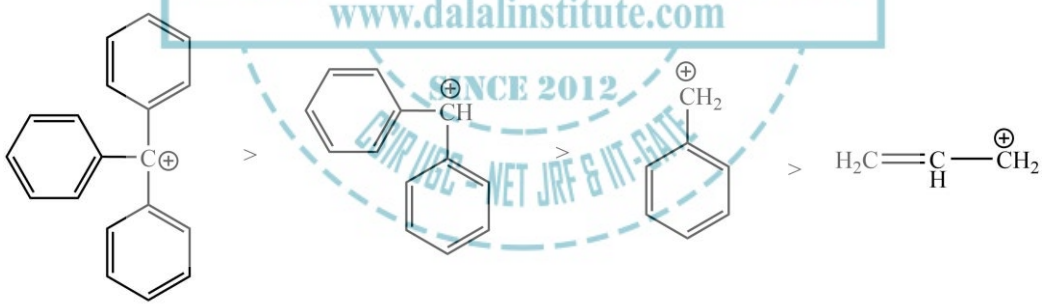


Resonance stablized diphenylmethyl carbocation



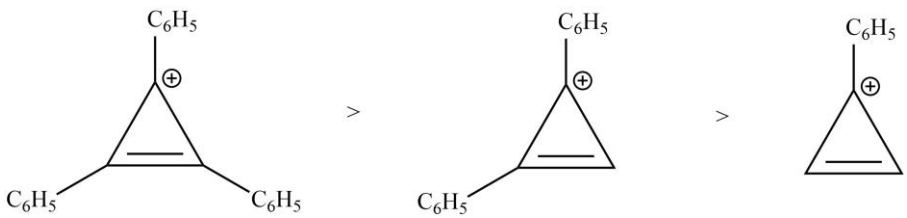
Resonance stablized triphenylmethyl carbocation

Therefore, the expected order of the stability of unsaturated systems with carbon bearing positive charge should be as given below.

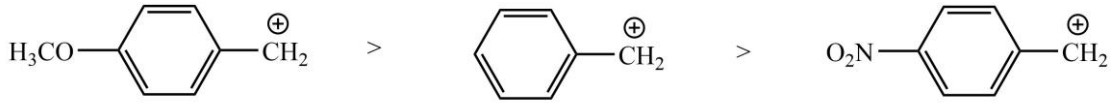


Triphenylmethyl carbocation | Diphenylmethyl carbocation | Benzyl carbocation | Allyl carbocation

Similarly, the order of stability in phenylcyclopropenyl, diphenylcyclopropenyl and triphenylcyclopropenyl should follow the following order.



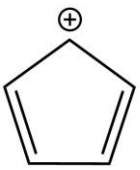
v) Stability of substituted benzyl carbocations: Since the carbon is electron bearing positive charge is electron deficient in nature, any group with +R effect will stabilize the system and vice-versa. The order of stability of some typically substituted carbocations is given below.



(4-methoxyphenyl)methylium phenylmethylium (4-nitrophenyl)methylium

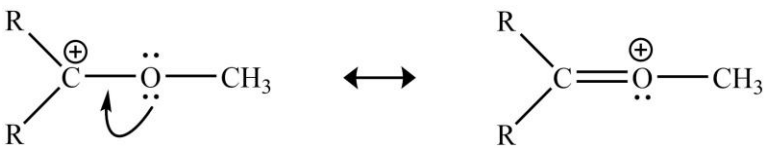
vi) Stability of tropylium ion: The cycloheptatrienyl cation or tropylium ion is exceptionally stable due to its aromatic character (planar and $4n+2$ π electrons). According to molecular orbital theory, its delocalization energy is significantly greater than the delocalization energy of its acyclic counterpart. Similarly, the valence bond theory can also explain its exceptional stability of the basis of resonance as given below.

vii) Instability of cyclopentadienyl cation: The cyclopentadienyl cation is very unstable due to its antiaromatic character (planar and $4n$ π electrons). According to molecular orbital theory, its delocalization energy is significantly less than the delocalization energy of its acyclic counterpart.

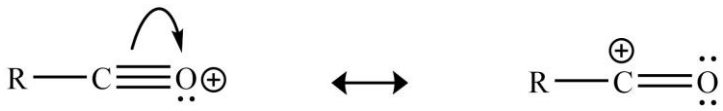


$4n+2$ π electrons
(antiaromatic)

viii) Stability of alkoxyalkyl cation: if the positive charge bearing carbon in the carbocationic species is connected to a hetero atom with lone pair of electrons, the resonance will get it stabilized.



ix) Stability of acyl cation: Just like alkoxyalkyl cation, the resonance will also stabilize the acyl cation as shown below.

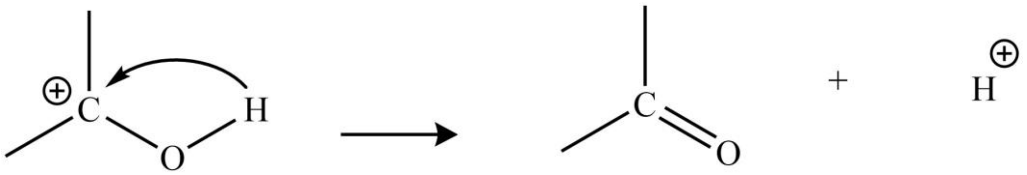


x) Instability of phenyl and vinyl cation: If the positive charge is on the double-bonded carbon atom, the system cannot be stabilized because the sp^2 orbital carrying positive charge will be perpendicular to the orbital of the double bond.

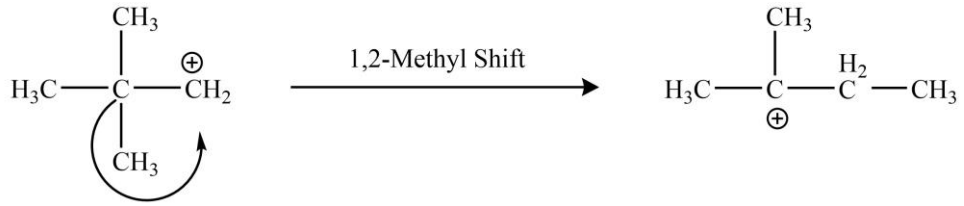
4. Reactivity of classical carbocations: The principal routes by which the carbocations can react to give rise to stable products are given below.

i) Nucleophilic attack: In these types of reactions, a carbocation may combine with a species by accepting an electron pair. Furthermore, it should also be noted that if all the three groups on the carbocation are different, a racemic mixture will be obtained.

ii) Proton removal: In these types of reactions, a carbocation may result in the removal of a proton from the adjacent atom forming a double bond.



iii) Rearrangement reaction: 1-2 methyl shit or 1-2 hydride shifts are very common in carbocation chemistry to attain a more stable counterpart. For instance, a primary and secondary carbocation will prefer to rearrange themselves into a more stable tertiary carbocation via methyl shifts as given below.

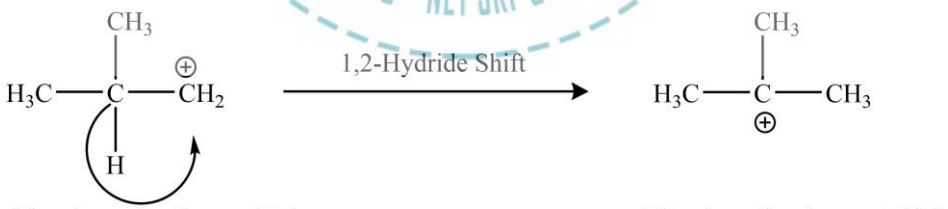


1° carbocation (less stable) 3° carbocation (more stable)

2° carbocation (less stable) 3° carbocation (more stable)

Similarly, primary and secondary carbocation can also rearrange themselves into a more stable tertiary carbocation via hydride shift.

2° carbocation (less stable) 3° carbocation (more stable)



1° carbocation (less stable) 2° carbocation (more stable)

iv) Addition reactions: A carbocation may attack at the triangular face of a double bond to create a new positively charged center as shown below.

➢ ***Non-Classical Carbocations***

Non-classical carbocations in the organic chemistry may simply be defined as the carbocations in which the π-bond is not conjugation with the carbon bearing positive charge, and gets stabilized by neighboring group participation by π- or σ-bond.

Like classical carbocations, the carbon in a non-classical carbocation has only six electrons, it is also electron deficient; and therefore, acts as an electrophile in chemical reactions. Now, whether the neighboring participant is σ-bond or π-bond (not conjugated), non-classical carbocations can be divided into two categories.

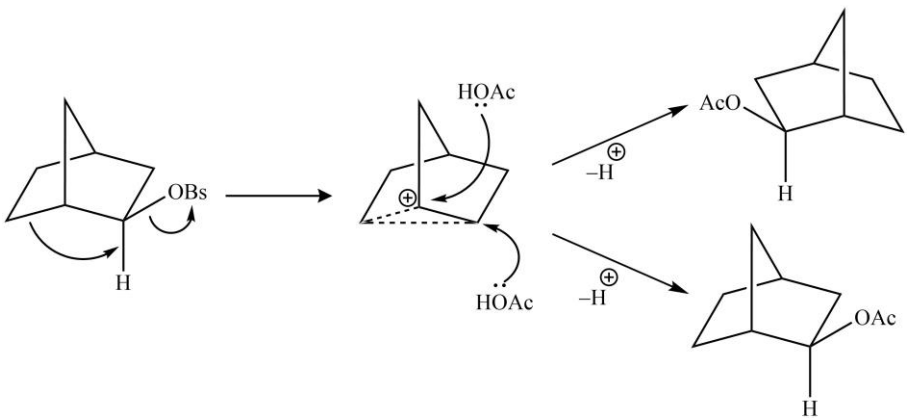
1. Generation of non-classical carbocations: The generation of non-classical carbocations takes place mainly in neighboring group participation via π- or σ-bond. Some reactions involving the production of non-carbocations are given.

i) Neighbouring group participation via π-bond:

In the case of a benzyl halide, the reactivity is higher because the SN_2 transition state enjoys a similar overlap effect to that in the allyl system. An aromatic ring can assist in the formation of a carbocationic intermediate called a phenonium ion by delocalizing the positive charge.

ii) Neighbouring group participation via σ-bond:

The aliphatic C–H or C–C bonds can also give rise to delocalization of charge if these bonds are close enough and antiperiplanar to the leaving group. The intermediates corresponding to these mechanisms are nonclassical in nature; and the 2-norbornyl system is the most popular of such type. More precisely, the acetolysis of exo-2-norbonyl brosylate yields a racemic mixture of exo-acetates only and no endo product; suggesting neighboring group participation from σ-bond. Furthermore, a very slow rate is observed if we use endo-2-norbonyl brosylate confirming our guess.



2. Orbital structure of non-classical carbocations: One of the first (and popular) examples of non-classical ions was the 2-norbornyl cation. Non-classical carbocations are simply the organic cations where the electron density of a filled bonding molecular orbital is distributed over three or more atomic centers and have some sigma-bond property. Satisfying all the requirements, the 2-norbornyl cation is considered an archetypal case.

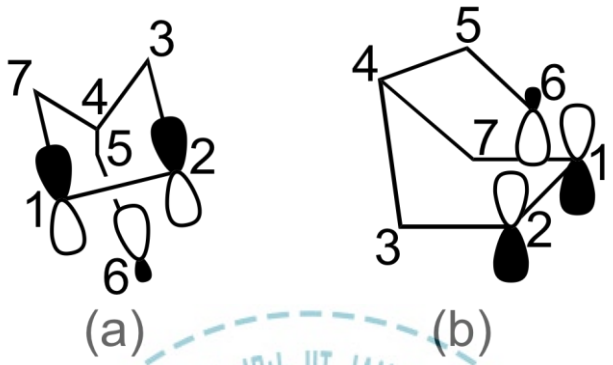
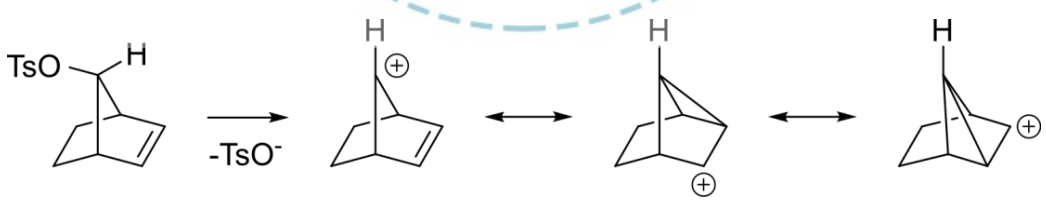


Figure 2. Orbital structure of a non-classical carbocation (2-norbornyl).

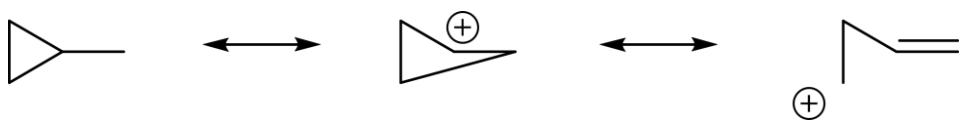
The most widely accepted molecular orbital structure of the 2-norbornyl cation is having two *p*-type orbitals (on carbons 1 and 2) interacting with an sp^3-hybridized orbital on carbon 6 to form the hypervalent bond. Extended Hückel Theory calculations for the 2-norbornyl cation suggest that the orbital on carbon 6 could instead be sp^2-hybridized, though this only affects the geometry of the geminal hydrogens.

3. Stability of non-classical carbocations: The stability profile of nonclassical carbocations can be rationalized by the delocalization of σ- or π-bonds as discussed below.

i) Stability gain via the delocalization of π-bond: The typical example of this type of stabilization is 2-norbornyl cation which is shown below.

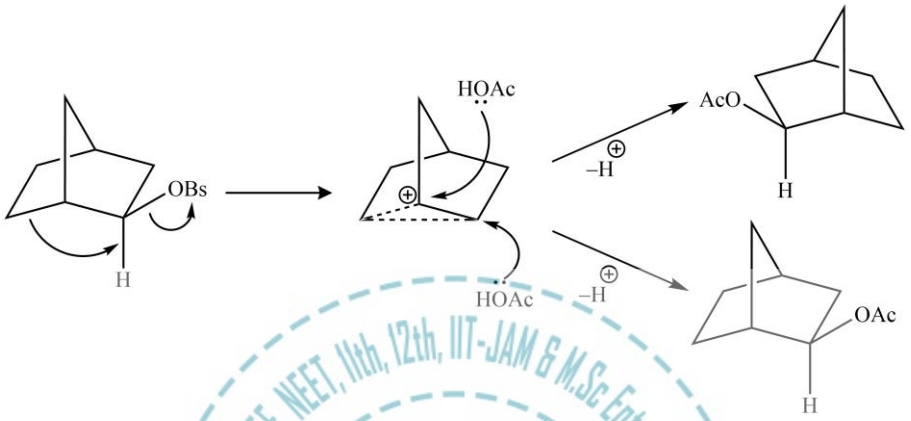


ii) Stability gain via the delocalization of σ-bond: The treatment of cyclopropylmethyl (or cyclobutyl chloride or homoallyl chloride) chloride with dilute ethyl alcohol yields a mixture of 5% homoallyl alcohol, 47% cyclobutanol, and 48% cyclopropylmethyl alcohol. All this suggests that the carbocationic intermediate present in all three reactions must be the same, which in turn, is responsible for the same resulting products.

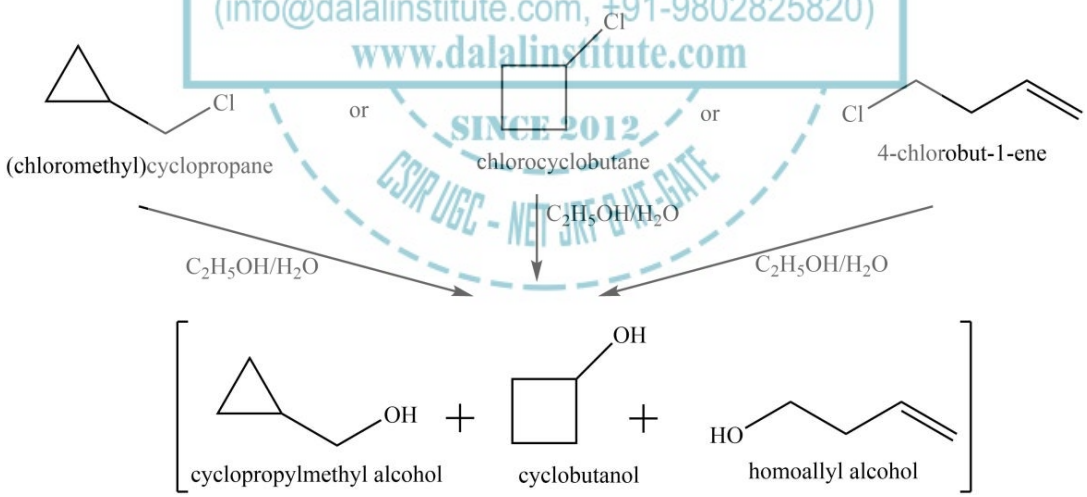


4. Reactivity of non-classical carbocations: The principal routes by which the non-classical carbocations can react to give rise to stable products are given below.

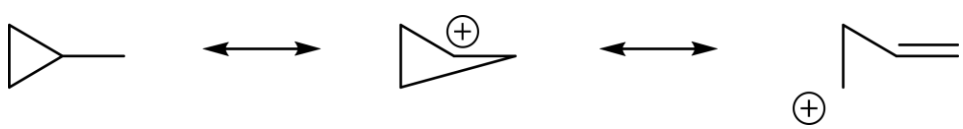
i) Nucleophilic attack: In these types of reactions, a non-classical carbocation may combine with a species by accepting an electron pair. Furthermore, it should also be noted that if all the three groups on the carbocation are different, a racemic mixture will be obtained.



ii) Rearrangement reactions: The treatment of cyclopropylmethyl (or cyclobutyl chloride or homoallyl chloride) chloride with dilute ethyl alcohol yields a mixture of 5% homoallyl alcohol, 47% cyclobutanol and 48% cyclopropylmethyl alcohol.



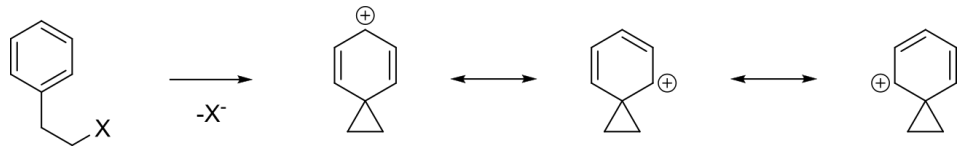
All this suggests that the carbocationic intermediate present in all three reactions must be the same, which in turn, is responsible for the same resulting products.



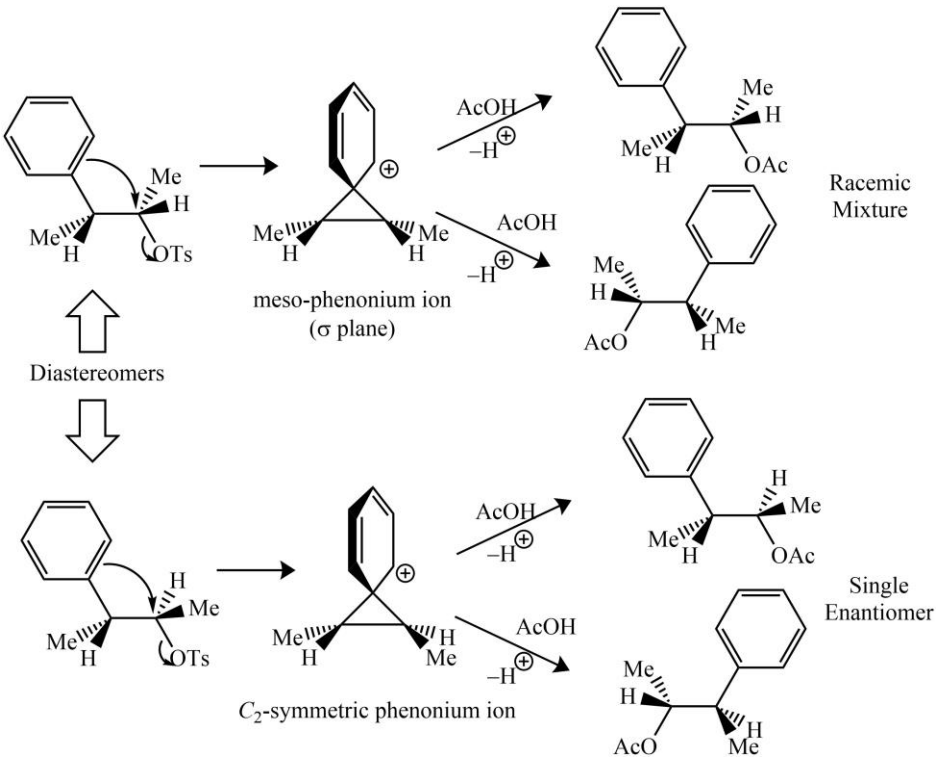
❖ Phenonium Ions

Phenonium ions may simply be defined as cyclohexadienyl cations which are spiro-annulated with a cyclopropane unit.

These ions form an arenium-ions' subclass and greatly affect the reactivity. An aromatic ring can give great support in the formation of a carbocationic intermediate by delocalizing the positive charge. In other words, the aryl group participates in the neighboring mechanism via the formation of phenonium ion yielding retention of the original configuration.



Furthermore, we can have many types of phenonium ions depending upon the degree and nature of substitution affecting its overall reactivity. In addition to the typical phenonium ion given above, two of the most commonly studied disubstituted phenonium ions are meso- and C_2-symmetric phenonium ions. The neighboring group mechanism when we use diastereomeric single enantiomer substrates is shown below.



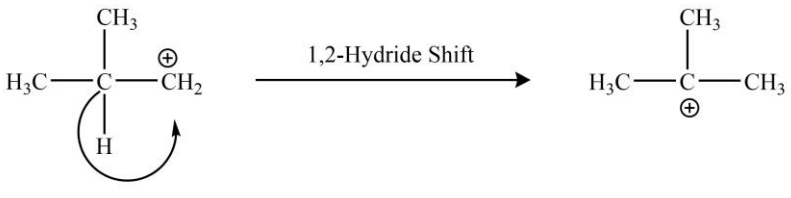
It is obvious from the above routes that the double inversion in meso-phenonium ion created a racemic mixture whereas double inversion in C_2-symmetric phenonium ion has created a single enantiomeric product.

❖ Common Carbocation Rearrangements

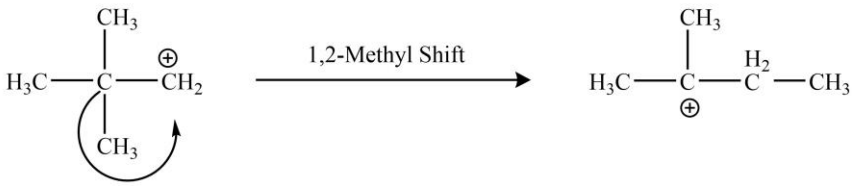
Carbocations may undergo rearrangements to yield their more stable counterparts, and this phenomenon is typically labeled as carbocationic rearrangement. In this section, we will discuss the carbocation rearrangement for classical and non-classical carbocations.

➢ *Rearrangement Reactions in Classical Carbocation:*

The 1-2 methyl shit or 1-2 hydride shifts are very common in carbocation chemistry to attain a more stable counterpart. For instance, a primary carbocation will prefer to rearrange itself into a more stable tertiary carbocation.

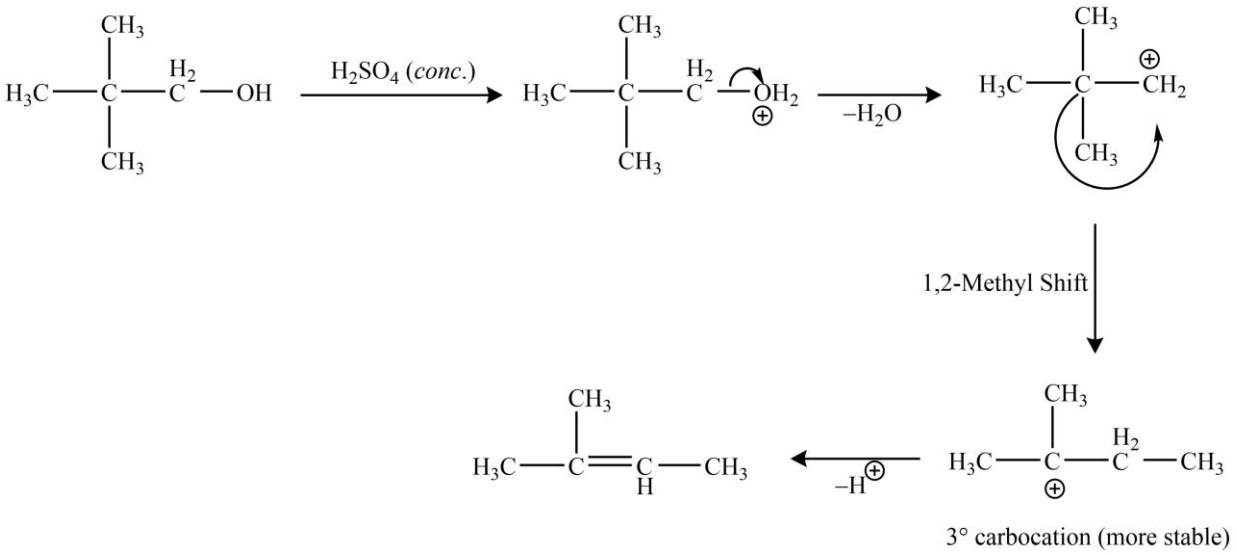


1° carbocation (less stable) 2° carbocation (more stable)



1° carbocation (less stable) 3° carbocation (more stable)

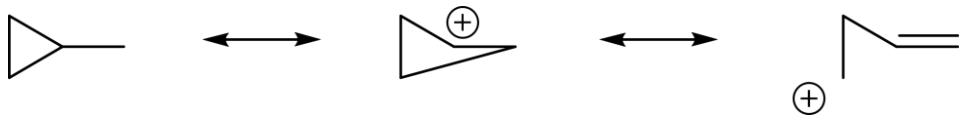
Some typical examples of methyl or hydride shift are given below.



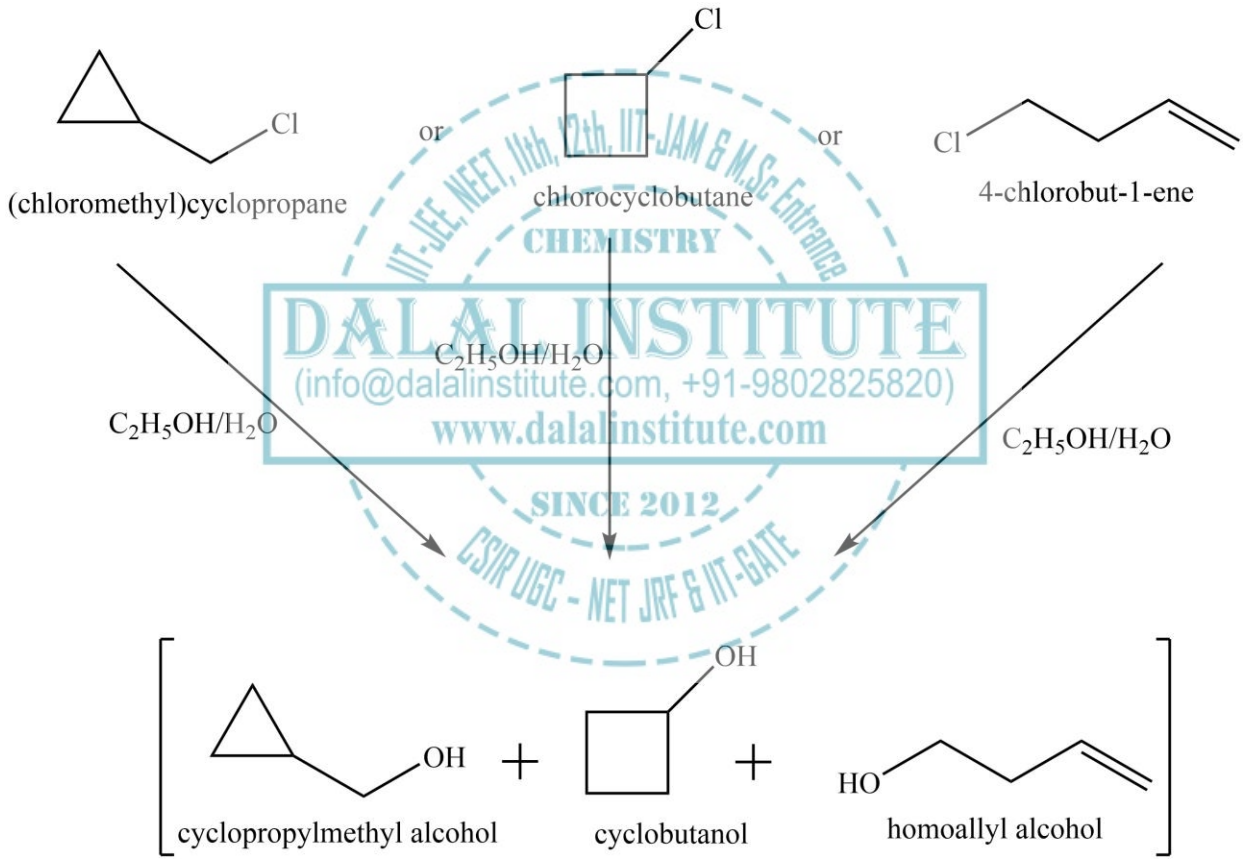
3° carbocation (more stable)

➢ ***Rearrangement Reactions in Non-Classical Carbocation:***

The most common example of this type of rearrangement is the cyclopropylmethyl system in with three rearranged forms of the carbocation exist in equilibrium.



The treatment of cyclopropylmethyl chloride with dilute ethyl alcohol yields a mixture of 5% homoallyl alcohol, 47% cyclobutanol, and 48% cyclopropylmethyl alcohol. Similar results were obtained if we use cyclobutyl chloride or homoallyl chloride instead of cyclopropylmethyl chloride.



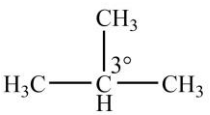
All this suggests that the carbocationic intermediate present in all three reactions must be the same, which in turn, is responsible for the same resulting products.

Furthermore, it is also worthy to note that the participation of σ-bond in the neighboring group mechanism to yield no-classical carbocations results in increased rates of a reaction than what we would have observed in normal SN_2; which is obviously due to anchimeric assistance.

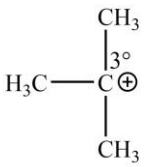
❖ Applications of NMR Spectroscopy in the Detection of Carbocations

Carbocations are the typical example of how the study of reaction intermediates is carried out. Two of the most popular and efficient experimental techniques to analyze the properties and structure of carbocationic species are ^{13}C and PMR (proton magnetic resonance) spectroscopy. The notable work in carbocation chemistry was carried out by George A. Olah, an American chemist who was also awarded the Nobel prize (1994) for the same.

Olah discovered that the NMR spectra of organic precursors in super-acid solutions were indicating relatively stable carbocations. He found that the chemical shifts (^{13}C NMR) of carbocations are much downfield than their parent compounds. For instance, the chemical shift for tertiary carbon in tert-butyl carbocation is at 330 ppm whereas the corresponding carbon in isobutane absorbs at 25.2 only. This can be explained in terms of reduced electron density at the carbon center in the carbonium ion.



δ = 25.2 ppm



δ = 330 ppm

^{13}C NMR in SO_2 ClF-SbF_5 Solution

The argument is also supported by other studies such as the NMR spectrum of substituted benzylic carbocations. More precisely, as the electron-withdrawing group becomes stronger at *p*-position in benzylic carbocation, the NMR peaks of cationic carbon shift towards the more down-field region.

Table 1. Benzylic carbocations' peaks in ^{13}C NMR spectra.

Substituents	δ(ppm)
p-OCH_3	219
p-CH_3	243
p-H	255
p-CF3	269

Now from Table 1, we might conclude that all electron-donating groups (like alky substituents) at carbonium center should behave in the opposite manner and should decrease the chemical shifts. Nevertheless, it is found that though the electron-donating alkyl groups directly attached to carbonium centers raise their stability, but little to no effect was found upon the chemical shift.

For instance, when CS_2 was taken as the reference standard, the chemical shift (^{13}C NMR) of secondary carbon in isopropyl carbonium ion appears at –125 δ whereas the tertiary carbon in tert-butyl carbocation shows the peak at –125 δ. Al this suggests that the replacement of hydrogen by methyl has actually supported the withdraw rather than the donation.

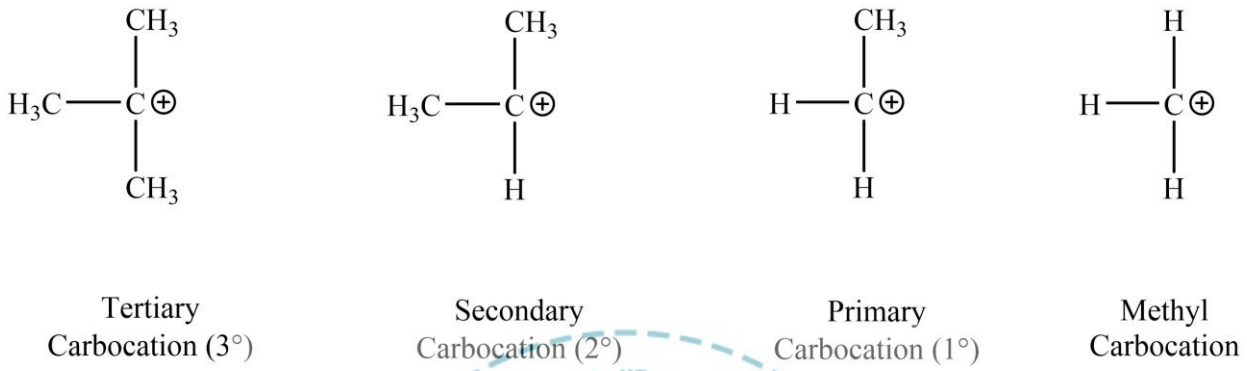
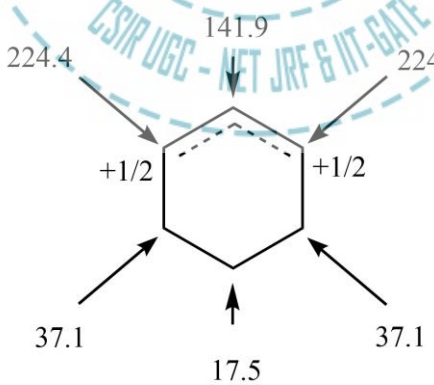


Figure 3. Some typical carbocations.

Furthermore, the molecular orbital theory also proves theoretically that the charges at 2° in isopropyl cation and 3° carbons in tert-butyl carbocations are +0.611 and +0.692, respectively.

Furthermore, the simplest arenium ion produced by the protonation of benzene ring strongly acidic solution can also be detected and studied by employing NMR spectroscopy. The chemical shifts for the o- and *p*- carbons (w.r.t protonation's site) in the ^{13}C NMR of arenium ion show very strong downfield movement which can be rationalized in terms of reduced electron density at the same.



A typical allylic cation with ^{13}CNMR spectrum

It is also worthy to note down from the Figure given above that the similar magnitudes of chemical shifts on the right and left side of carbocation suggest a plane of symmetry in the same.

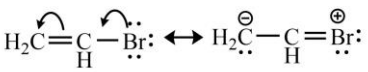
❖ Reactivity – Effects of Substrate Structure, Attacking Nucleophile, Leaving Group and Reaction Medium

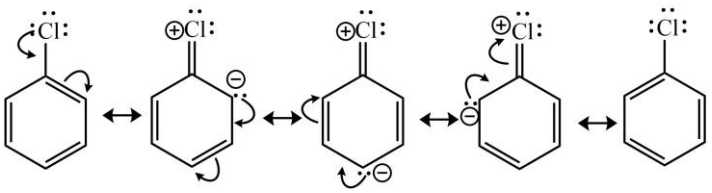
The reactivity of aliphatic nucleophilic substitution reactions is affected by many factors which can be better understood via experimental data and theoretical treatment combined. In this section, we will discuss some major factors that greatly influence the nucleophilic substitution's rate in aliphatic compounds like substrate structure, attacking nucleophile, leaving group, and reaction medium.

➢ *Effect of Substrate Structure on the Reactivity of Aliphatic Nucleophilic Substitution*

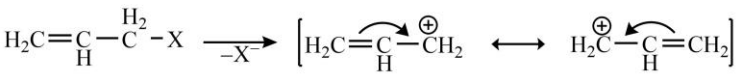
Since the rates in SN_1 and SN_1' reactions are determined by the 1st step (formation of carbocation), the more stable the carbocation is, readily it will be formed, and the faster the rate will be. Also, the neighboring group participation takes place via first-order kinetics; therefore, the enhanced rate (anchimeric assistance) must be analyzed with special reference to the substrate. The effect of substrate structure on the reactivity of aliphatic nucleophilic substitution reactions can be divided into the following categories.

1. Unsaturation at α-carbon: It is quite a well-known fact that aryl halide, vinyl halide, and acetylenic halides show very small reactivity towards nucleophilic substitution reactions because the carbon-halogen bond gains some double bond nature due to resonance. All this makes the breaking of C−X bond more difficult resulting in a lower tendency to undergo nucleophilic substitution.

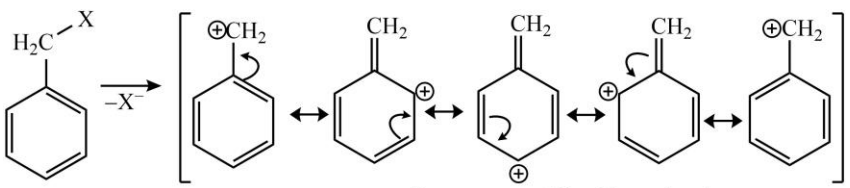




2. Unsaturation at β-carbon: Unlike the unsaturation at α-carbon, the presence of multiple bonds at β-carbon enhances the favourability of nucleophilic substitution because of the generation of resonance stabilized benzyl or allyl carbocation. This is true for SN_1 as well as for SN_2 pathways. For instance, consider the unimolecular nucleophilic substitution in allyl- and benzyl halides.

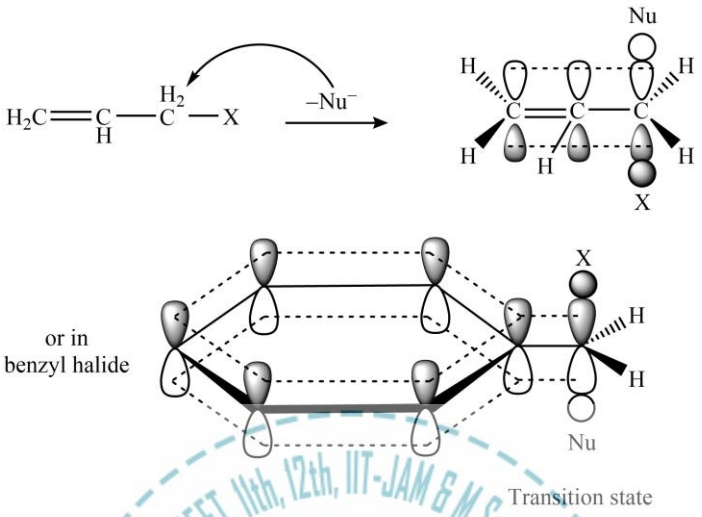


Resonance stablized allyl cation



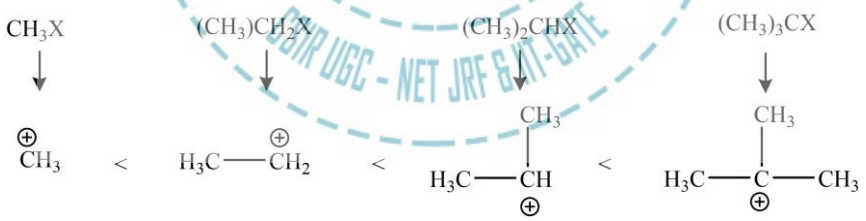
Resonance stablized benzyl cation

Similarly, the transition state formed during the course of the bimolecular nucleophilic substation is also stabilized by the phenomenon of resonance.



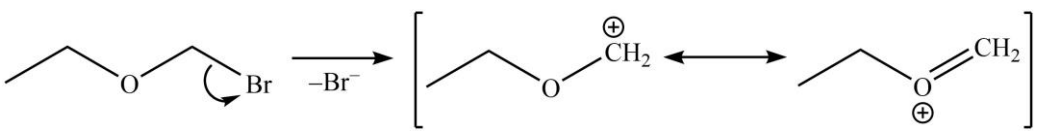
Therefore, we can conclude that allyl and benzyl halides are more reactive than alkyl halides in SN_1 as well in SN_2 pathways.

3. Steric effects: Since the alkyl carbocations are primarily obtained from alkyl halides with tetrahedral geometry, a link between the steric relief and carbocation formed can be established. During the formation of carbocations in such cases, the carbon-carbon bond angles change from 109°28' to 120°. Therefore, the carbon with bulky groups around is expected to get more relief from this carbocationic conversion. The stability order of alky carbocations on the basis of steric effect is given below.

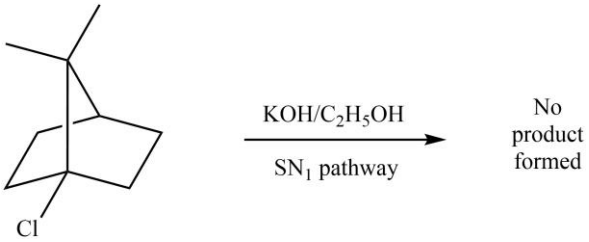


Furthermore, the steric bulk around or near the central carbon also affects the rate of bimolecular nucleophilic substitution (SN_2) but in a negative way. This is because the bulky groups disfavor the formation of transition state resulting in a slower reaction rate.

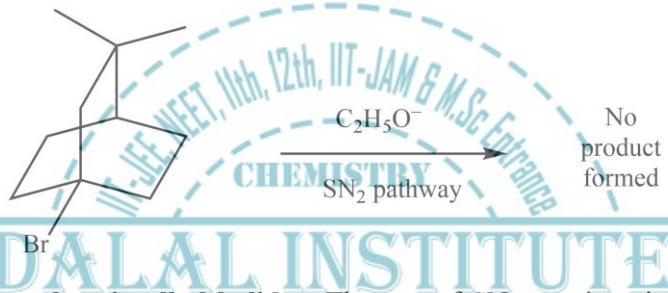
4. Presence of heteroatom at α-carbon: The rate of SN_1 reactions is greatly enhanced by the presence of heteroatom at α-carbon because it stabilizes the carbocation formed during the first step.



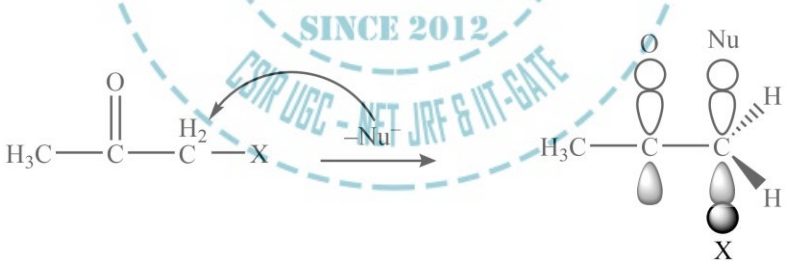
5. Substitution at bridgehead carbon: The nucleophilic substitution at bridgehead carbons is extremely disfavoured both in SN_1 as well as in SN_2 pathways. The reason for low reactivity at bridgehead carbon in the SN_1 pathway is the 'non-planar' structure of carbocation involved.



However, the low reactivity at bridgehead carbon in the SN_2 pathway is due to different reasons i.e. disfavorability of backside attack of nucleophile which an essential request of the same.



6. Carbonyl groups at α-carbon in alkyl halides: The rate of SN_2 reactions is greatly enhanced if some carbonyl group is situated at the α-carbon in alkyl halides. This is because the electron-withdrawing effect raises the stability of the transition state.



Transition state

However, a reverse effect will be observed for SN_1 pathway which is obviously due to the destabilization of carbocation formed.

	H_3C-X	$H_3C-O-CH_2X$	$C_6H_5-C(=O)-CH_2-X$
Reactivity of substrate in SN_2 pathway	202	920	100000

➢ ***Effect of Nucleophile on the Reactivity of Aliphatic Nucleophilic Substitution***

Since the rate in SN_1 reactions is determined by the 1st step (formation of carbocation), and the nucleophile attacks in the second step; the rate of SN_1 reactions is pretty much independent of nucleophilic strength. However, the rate of SN_2 and SN_2' depends upon the strength of the attacking nucleophile due to second-order kinetics. The effect of the nucleophile on the reactivity of aliphatic nucleophilic substitution reactions can be divided into the following categories.

1. Formal charge: The nucleophiles with higher negative charge have more strength than corresponding conjugate acids. In other words, if the conjugate acid of a nucleophile is also a nucleophile, it will be of less strength always. For instance, the amide is a stronger nucleophile than ammonia; and OH^- is stronger than water.

2. Basic character: The strength of different nucleophiles follows the same order as basicity if the attacking atom comes from the same period. For instance, consider the following order.

$$NH_2^- > RO^- > OH^- > R_2NH > ArO^- > NH_3 > \text{pyridine} > F^- > H_2O > ClO_4^-$$

Furthermore, it is also worthy to recall that nucleophilicity is kinetically controlled but basicity is thermodynamically controlled.

3. Solvation level: The strength of different nucleophiles increases as the attacking comes from more down the group. Now, although the basic character of such nucleophiles decreases down the group, the increasing nucleophilicity can be rationalized in terms of higher solvation of smaller anions making them less suitable for attack. For instance, consider the following order.

$$I^- > Br^- > Cl^- > F^-$$

The effect is more prominent in polar protic solvents where smaller nucleophiles are more solvated than usual. Furthermore, it is also worthy to note that this effect becomes inefficient for neutral nucleophile because they don't get much solvated. However, they also show an increase in nucleophilic strength down the group which can be explained in terms of the hard-soft acid-base principle. In other words, the reason for the increasing strength of neutral nucleophiles is that a softer nucleophile prefers an alkyl carbocation (soft acid) over the proton (soft acid).

4. Attacking liberty: As the nucleophile becomes more free to attack, the rate of reaction increases. For instance, consider the case of $(EtOOC)_2CBu^-Na^+$ in C_6H_6, where the addition of Na^+-solvating compound makes the $(EtOOC)_2CBu^-$ ion free to attack, and increasing rate consequently.

Nevertheless, it must be kept in mind that these rules do not hold at all conditions always because there are many factors like steric influences. For instance, the tert-butoxide ion (Me_3CO^-) much weaker nucleophile though it is an even stronger base than OH^- or OEt^-; which can be attributed to the fact that its huge bulk hinders it from approaching a substrate more closely. Finally, we may conclude that only rough estimates can be made about the order of nucleophilic strengths and there is no absolute order of either leaving group and nucleophilicity.

➢ ***Effect of Leaving Group on the Reactivity of Aliphatic Nucleophilic Substitution***

A good leaving group is that becomes stable after the detachment from substrate. The effect of leaving group on the reactivity of aliphatic nucleophilic substitution reactions can be divided into the following categories.

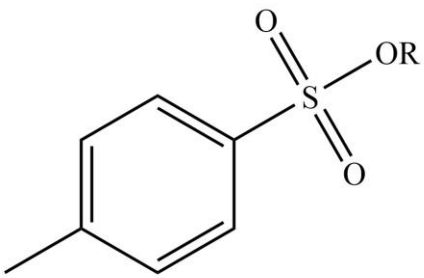
1. Basic character: The betterment of the leaving-group is inversely proportional to the strength of its basic character. In other words, weak bases are good leaving and vice-versa. For instance, consider the order of goodness for halides as leaving group.

$$I^- > Br^- > Cl^- > F^-$$

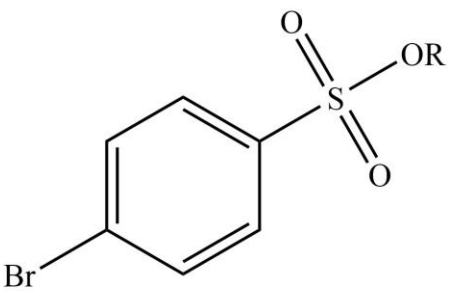
This is just the opposite trend of acidic character order of corresponding their hydro acids i.e., HI > HBr > HCl > HF.

2. Ester conversion: The power of a leaving group can be improved by converting it into its ester, which is why brosylates or tosylates (sulphonic esters) are more popular as leaving group than halides.

3. Ring strain: The leaving-group power can also be increased via ring strain. For instance, simple ethers do not undergo breaking while protonated ethers show cleavage conditions are strenuous; however, epoxides undergo bond cleavage effortlessly whereas protonated epoxides show even more tendency.



Tosylates



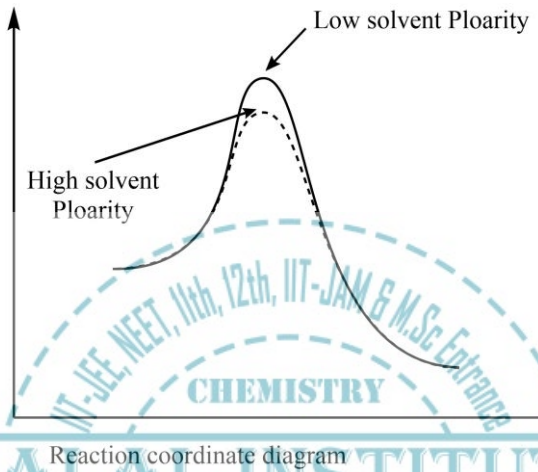
Brosylates

Furthermore, it is also worthy to note that the nature of leaving the group not only affects the reaction speed but can also change the mechanism of the same from associative to dissociative and vice-versa.

➢ ***Effect of Reaction Medium on the Reactivity of Aliphatic Nucleophilic Substitution***

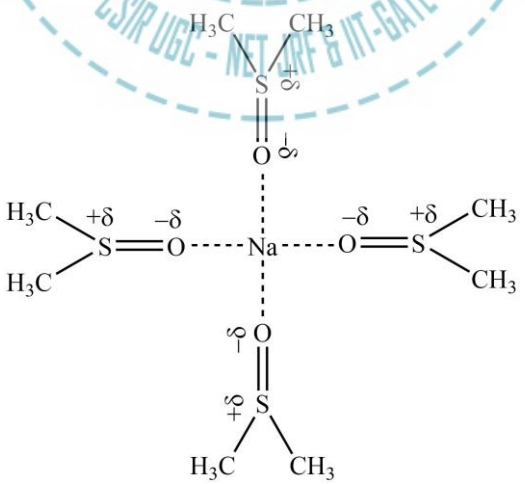
The effect of the reaction medium on the reactivity of aliphatic nucleophilic substitution reactions can be divided into the following categories.

1. Solvent polarity: The rate of reaction in SN_1 transformations increases with the increase in solvent polarity and vice-versa. This is because the polar solvent stabilizes carbocation intermediate greatly, which in turn decreases the activation energy required for the change.



Furthermore, the increasing solvent polarity also raises the rate of the associative pathway (SN_2) which obviously because of the better dissolution of nucleophile involved.

2. Protic-aprotic type: It has been observed that polar protic solvents decrease the nucleophilic strength and enhances the stability of the anionic leaving group; consequently, supporting the dissociative pathway (SN_1).



On the other hand, protic solvents slow down the rate of SN_2 reaction by solvating the nucleophile involved; whereas, aprotic solvents enhance the rate by freeing the nucleophile via the binding cation mechanism.

❖ Ambident Nucleophiles and Regioselectivity

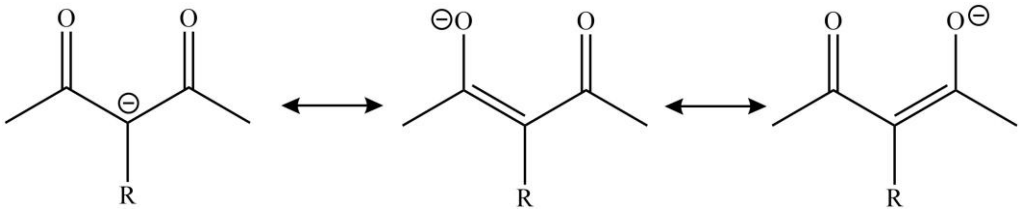
Ambidentate nucleophiles may simply be defined as the nucleophilic species that have more than one atom for the attack to result in different structural isomers; nevertheless, if one isomer is preferred over the other, the phenomenon is called as regioselectivity.

In this section, we will discuss the different types of ambident nucleophiles; and then will try to explain the factors governing the regioselectivity arising from these nucleophiles.

➢ *Different Types of Ambident Nucleophiles*

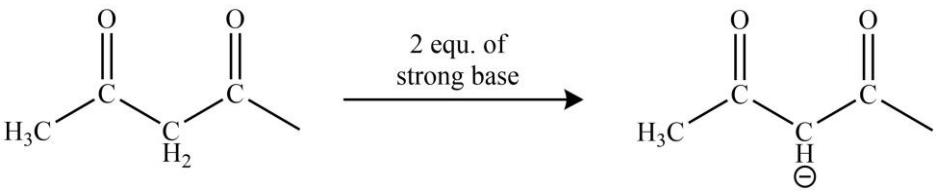
The different types of ambident nucleophiles which are very common in synthetic organic chemistry are discussed below.

1. [−CO−CR−CO−]$^-$-type ions: The ions of this type are obtained by the elimination of a proton from β-keto esters, malonic esters, or b-diketones, and resonance hybrid structures are needed to depict them.



The possibility of nucleophilic attack arises at the saturated carbon through the oxygen or carbon atoms resulting in O-alkylation or C-alkylation, respectively. However, if the ions are unsymmetrical in nature, three different products can be obtained because either oxygen can show an attacking tendency. Furthermore, the O- or C-acylation can be achieved if the substrate has a carbonyl group.

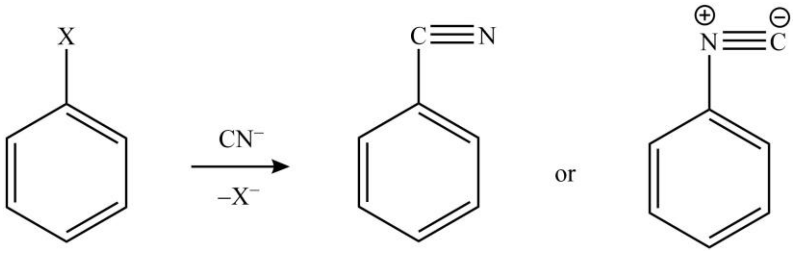
2. [CH_3CH-CH_2-CO-]-type molecules: Upon treating with 2 molar equivalents of a strong a base, these types of molecules can release two protons forming a dicarbanion.



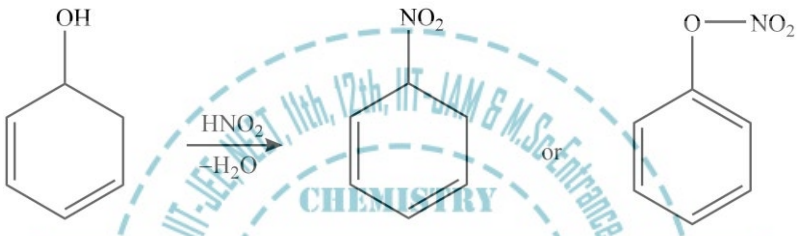
Now although the two atoms bearing negative charge are carbon, these nucleophiles are still called as ambident because they are non-equivalent in nature.; and the possibility of attack by oxygen is also there. Now because the hydrogen at carbon attached to one carbonyl group is less acidic than that of a carbon bonded to two, the CH_2 group should be more basic than the CH group, and therefore, more suitable for the attacks.

All this results in a useful generalization that if there is a stronger acidic group but we need to eliminate a proton from some other carbon to create a nucleophilic site, the removal of both is possible; however, the attack will happen at the weakly acidic position because this conjugate base of the more weak acid. Alternatively, one more acidic proton is needed to be removed if we want to attack a more acidic position.

3. CN^- Ion: This nucleophilic ion can give rise to isocyanides or nitriles depending upon the mode of the chemical bond between carbon and the attacking group.

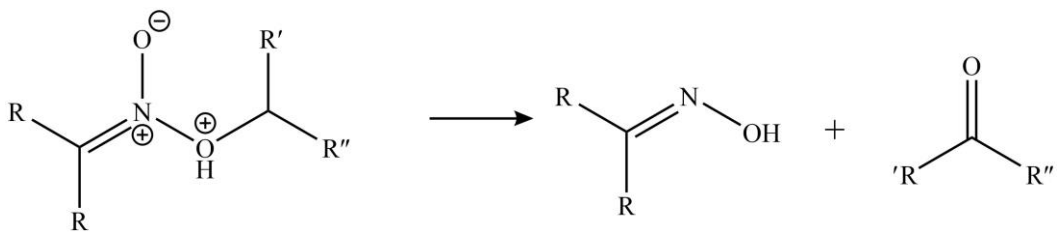


4. NO_2^- Ion: This nucleophilic ion can give rise to nitro compounds or nitrites depending upon the mode of the chemical bond between the carbon and attacking group.



5. Phenoxide Ions: Ions of this type are analogous to enolate anions and can undergo a chemical change to give rise to O-alkylation or C-alkylation.

6. Aliphatic nitro compound's derivatives: In these types of reactions, a carbanion of kind $O_2N{-}R2C^-$ is formed which can be alkylated at carbon or oxygen atom. Furthermore, it is also worthy to remember that the alkylation at oxygen results in the nitronic esters, but these esters would break down to give an aldehyde or ketone or oximes upon simple heat treatment.



➢ ***Factors Dictating the Nature of Regioselectivity***

Following the definition of regioselectivity (one product is favored over the other), various factors dictating this preferential attack are discussed below.

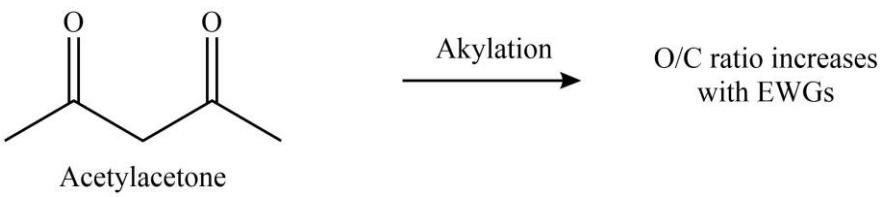
1. Mechanism of the reaction: According to HSAB **(**hard-soft–acid-base) principle, the hard acids prefer to bind with hard bases whereas soft acids prefer to bind with soft bases. Therefore, we can say that ambident nucleophile uses it more electronegative atom to participate in SN_1 mechanism because the carbocation formed is a hard base; whereas it will use it less electronegative atom to participate in SN_2 mechanism because the carbon center of a molecule is soft acid. In other words, we can say that supporting the SN_2 character of a reaction motivates the nucleophile to attack via a less electronegative group and the vice-versa is also true.

2. Nature of the cation: Since a positive counterion exists for each negatively charged nucleophile, the SN_1 mechanism will be supported if this ion helps the elimination of leaving group (such as Ag^+). On the other hand, if this is a more common type like K^+ or Na^+, then SN_2 pathway will be supported.

3. Nature of the solvent: The nature of the solvent also affects the site of the attack by making nucleophile more or less free. A freer nucleophile prefers to attack via its more electronegative atom whereas a more engaged nucleophile prefers to attack via the less electronegative atom. The atom with a higher electronegativity atom is better solvated in protic solvents by the formation of hydrogen bonds. However, neither atom of the nucleophile is significantly solvated in polar aprotic solvents and these solvents are very efficient in solvating different cations making more electronegative atom suitable for attack. Therefore, the higher electronegative end of the nucleophile shows low engagement form both cation as well as from solvent in polar aprotic solvents.

5. Steric effects: It is quite a well-known fact that sterics play a very important role in deciding the final product of a chemical reaction across the domain. If one site surrounded by more bulky groups, is less likely to be attacked in an associative pathway than a less crowded site, and vice-versa is also true. Furthermore, the product with more steric hindrance is less likely to be formed.

4. Electron withdrawing effect: The attachment of more electron-withdrawing groups make the carbon more electron-deficient and suitable for the attack via more electronegative site, whereas the attachment of more electron-donating groups makes the carbon less electron-deficient and suitable for the attack via a less electronegative site.



Acetylacetone

For instance, the shift for the attack from carbon to oxygen takes place for the alkylation of acetylacetone's sodium salts.

❖ Phase Transfer Catalysis

The phase-transfer catalysis may simply be defined as a special form of heterogeneous catalysis that supports the movement of a reactant from one phase into another phase where the reaction occurs.

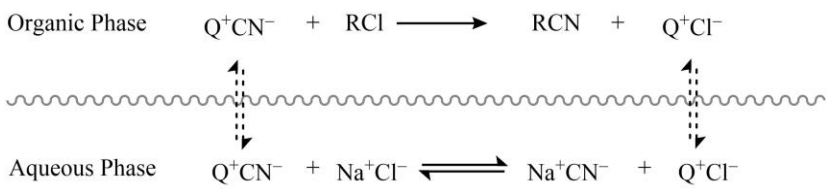
Ionic reactants are often soluble in an aqueous phase but insoluble in an organic phase in the absence of the phase-transfer catalyst (PTC). The function of a phase transfer catalyst resembles detergent to solubilize the salts into the organic-phase. In other words, the phase-transfer catalysis accelerates the reaction rate. By using this type of catalysis, we can get faster rates with better yields, fewer byproducts, eliminate the need for dangerous or expensive solvents that will dissolve all the reactants in one phase, eliminate the need for expensive raw materials and minimize waste-related complications. In this section, we will discuss the prominent mechanisms and applications of phase transfer catalysis.

➢ *Mechanisms of Phase Transfer Catalysis*

The mechanism of phase-transfer catalysis can primarily be divided into two categories where the acting routes are different but the final effects are similar. In other words, the anion is made to enter into the organic phase and permitted to be fairly free to react with the substrate in both types.

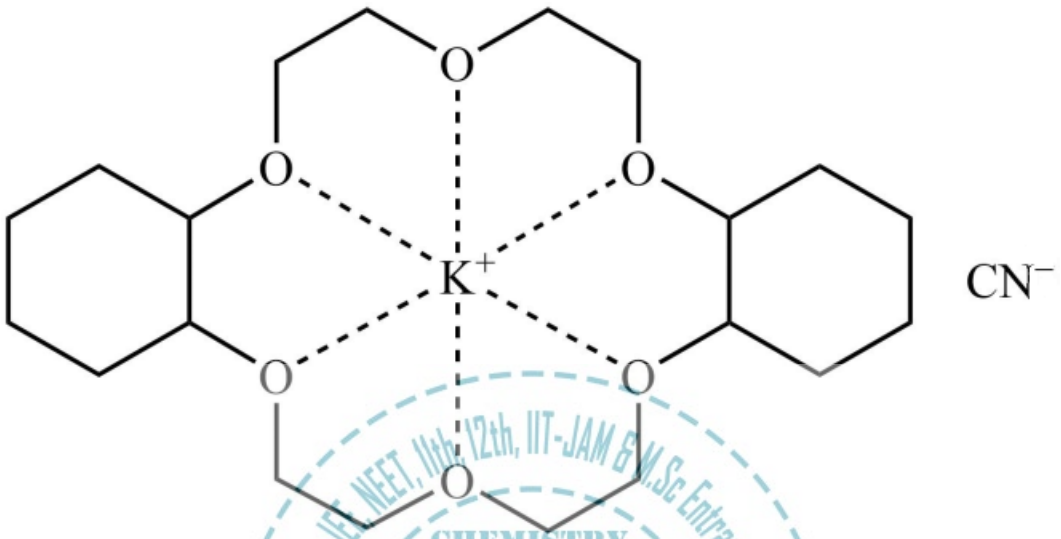
1. Quaternary phosphonium or ammonium salts: This mechanism can be understood by taking the example of the reaction between sodium cyanide and 1-chlorooctane where no substitution product (1-chlorooctane) is formed even after heating (with constant stirring) the mixture for weeks. However, even we add a very small amount of a suitable "quaternary ammonium salt", sufficient amount of 1-chlorooctane is obtained in less than two hours.

The reason for no reaction when "quaternary ammonium salt" is absent is that CN^- ions cannot pass from aqueous phase to organic phase in sufficient concentration all alone, leavening behind Na^+ ions because this would disturb the electrical neutrality of both phases; and Na^+ ions have no motivation go into organic phase since highly hydrated in the aqueous medium. However, "quaternary ammonium or phosphonium salts" are added, the quaternary ammonium (R_4N^+) and quaternary phosphonium ions (R_4P^+) are produced which do have the ability to pass through the interface between two phases. This is because 'R' groups in R_4N^+ and R_4P^+ are quite bulky causes poor solvation in the aqueous phase. Therefore, when they cross the phases' interface, they also carry CN^- ions with them to keep the electrical neutrality of both phases. Once the CN^- ions reach sufficient concentration, they start reacting with RCl to yield RCN and halide anions (Cl^-). The whole process can be depicted as given below.



$Q^+ = R_4N^+$ or R_4P^+

2. Crown Ethers and Other Types of Cryptands: It is quite a well-known fact that some cryptands have the ability to surround certain cations. For instance, when KCN salt is mixed with dicyclohexano-18-crown-6, a new salt is obtained which has the same anion much larger cation as shown below.



dicyclohexano-18-crown-6

This new cation has a much smaller positive charge density than K^+; and therefore, it gets very poorly hydrated. Furthermore, the new cryptate salt is quite soluble in many solvents including organic-types; therefore, we can add this new salt directly to the organic phase without the need for an aqueous phase. Many cryptands have been employed to make salts with OAc^-, F^-, I^-, Br^-, and CN^- to enhance the rates of nucleophilic substitution reactions.

Finally, we can conclude that "quaternary phosphonium or ammonium salts" as well as "cryptands" are quite capable of moving the anion from aqueous to organic phase; however, it has been found that even if sodium and potassium salts were soluble in the organic phase, they don't very fast nucleophilic substitution because they exist as ion pairs with corresponding anions, and are not free to attack the substrate efficiently. On the other hand, R_4N^+ or R_4P^+ and cryptate cations ions don't pair with anions very effectively, letting them, free to attack the substrate.

- ***Applications of Phase Transfer Catalysis***

Although the application domain is quite large, some of the main applications of phase transfer catalysis in synthetic organic chemistry are given below.

i) Phase transfer catalysis is widely used in industries for commercial production.

ii) Phase transfer catalysis is used in the alkylation of phosphothioates to produce pesticides.

iii) Chiral quaternary ammonium salts are used as phase transfer catalysts for the asymmetric alkylations.

iv) Phase transfer catalysis is not bound to systems with hydrophobic and hydrophilic reactants and is employed in liquid-solid and liquid-gas reactions sometimes.

v) Phase-transfer catalysts are especially valuable in green chemistry by allowing the use of water, and therefore, the requirement for organic solvents is lowered.

❖ Problems

Q 1. What are aliphatic nucleophilic substitution reactions? Name various types.

Q 2. What are the major differences between SN_1 and SN_2 reactions?

Q 3. Describe neighboring group participation? How does σ-bond can also place the same role?

Q 4. Define anchimeric assistance. Discuss with suitable examples.

Q 5. Discuss the stability of classical and non-classical carbocations.

Q 6. What are meso-phenonium ions? How are they different from C_2-symmetric phenonium ions?

Q 7. Give major rearrangement reactions of classical carbocations.

Q 8. Write a short note on the SN_i' mechanism with special emphasis on its relative study with normal SN_i.

Q 9. Discuss the effect of substrate structure on the reactivity of nucleophilic substitution reactions.

Q 10. What are nucleophiles? How does their strength affect the rate of nucleophilic substitution reactions?

Q 11. Discuss ambident nucleophiles?

Q 12. State and explain regioselectivity.

Q 13. What is phase transfer catalysis?

Q 14. Discuss the applications of NMR spectroscopy in the structure determination of carbocations.

Q 15. What is the 'single electron transfer (SET)' mechanism? Explain with suitable example.

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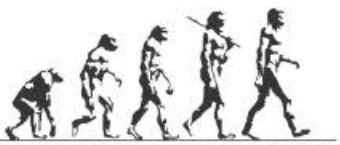

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