CHAPTER 7

Aliphatic Electrophilic Substitution

❖ Bimolecular Mechanisms − SE_2 and SE_i

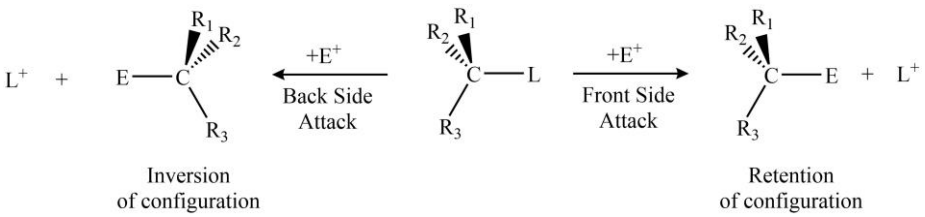
The electrophilic substitution in the aliphatic compounds is just similar to the aliphatic nucleophilic substitution, except for the fact that here an electrophile displaces a functional group rather than an electrophile. In this section, we will discuss the two major types of electrophilic substitutions; SE_2 (substitution electrophilic bimolecular) and SE_i (substitution electrophilic internal) mechanisms.

➢ *SE_2 (Substitution Electrophilic Bimolecular) Mechanism*

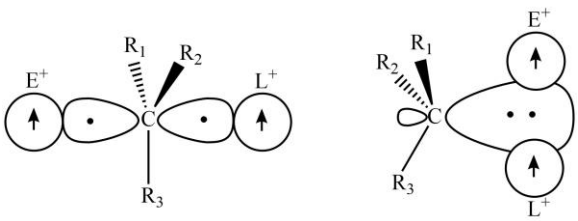
The bimolecular electrophilic substitution (SE_2) reactions may simply be defined as the chemical changes where a stronger electrophile displaces a weaker one in an aliphatic substrate.

This mechanism is quite analogous with the SN_2 route excepting the mode of attack. In the SN_2 mechanism, a stronger nucleophile replaces a weaker one via the backside attack due to its inter-cloud repulsion with the leaving group; however, in the SE_2 route, the attacking electrophile may come from the front, as well as from the backside because it is only using is vacant orbital towards substates causing little to no repulsion. So, the SE_2 mechanism can be divided into SE_2-front and SE_2-back based upon the front and back attacks, respectively.

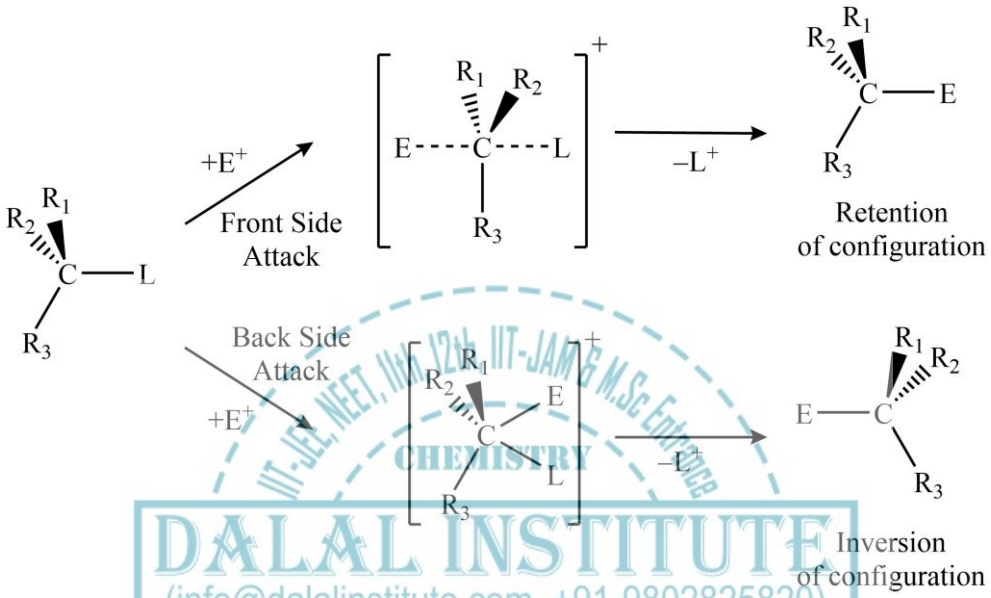
Illustrative reaction: The general reaction showing both types of electrophilic attacks (with their corresponding products), is shown below.



Mechanism involved: The proposed mechanism for the reaction given above says that the two electrons of the carbon-electrophile bond reside in the central orbital. Ingold proposed that the electronic distribution responsible for different stereochemistry of products is a function of bond-extension's magnitude and the extent of bond ionicity of the transition state.



It is obvious that the transition state needs to have high ionicity and good bond extension potential for SE_2-back reactions so that the carbon's orbital is sufficiently spread on both ends, resulting in the inverted configuration in the case of a chiral substrate. On the other hand, if there is a very little bond extension and low ionicity in the transition state, the electron-pair of the original bond pretty much retains its position and gives rise to the retention of the configuration, and we get SE_2-front case.



Where E^+ is the attacking electrophile whereas L+ is the leaving group. Furthermore, it is also worthy to note that organometallic compounds have exceptional susceptibility towards electrophilic substitution.

Salient Features: The main features of the mechanism involved in electrophilic substitution bimolecular or SE_2 type reactions are given below.

i) SE_2 reactions follow second-order kinetics with the rate law

$$Rate = k[RX][E]$$

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

ii) If the substrate is chiral, then the SE_2 mechanism can lead to the inversion, as well as, retention of the configuration; depending upon the mode of attack (front or back).

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

iv) Stereochemical studies can be employed to differentiate between SE_2-front and SE_2-back.

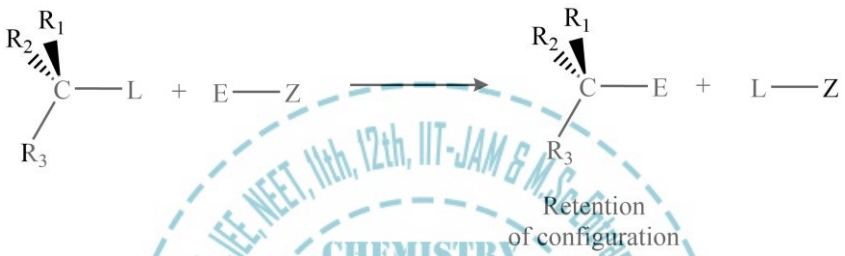
v) The SE_2 reactions are favored by the more polar C–L bond.

➢ ***SE_i (Substitution Electrophilic Internal) Mechanism***

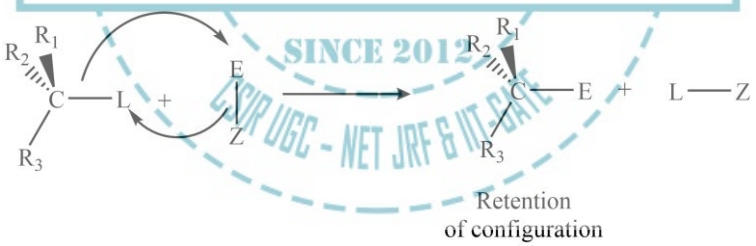
The internal electrophilic substitution (SE_i) reactions may simply be defined as the chemical changes where a stronger electrophile displaces a weaker one in an aliphatic substrate by assisting its departure.

This mechanism is also very analogous with the SN_2 route excepting the mode of attack. In the SN_2 mechanism, a stronger nucleophile replaces a weaker one via the backside attack due to its inter-cloud repulsion with the leaving group; however, in the SE_i route, the attacking electrophile comes from the front and assists the departure of leaving group by forming a bond with it.

Illustrative reaction: The general reaction showing this type of electrophilic attack (with the corresponding product) is shown below.



Mechanism involved: The proposed mechanism for the reaction given above says that the two electrons of the carbon-electrophile bond reside in the central orbital. It is observed that if there is a very little bond extension and low ionicity in the transition state, the electron-pair of the original bond pretty much retains its position and gives rise to the retention of the configuration, and we get SE_i case (like SE_2-front).



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

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

$$Rate = k[RX][EZ]$$

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

ii) Like SE_2-front, SE_i reactions result in the retention of the configuration.

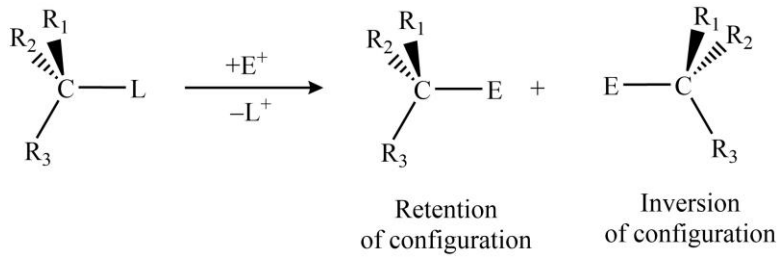
iii) The SE_2 reactions are favored by the more polar C–L bond.

❖ The SE_1 Mechanism

The unimolecular electrophilic substitution (SE_1) reactions may simply be defined as the chemical change in which a stronger electrophile displaces a weaker one in an aliphatic substrate via the formation of a carbanion.

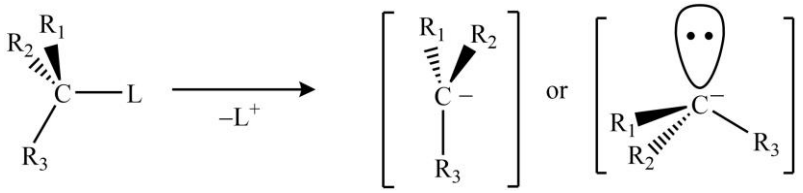
This mechanism is quite analogous with the SN_1 route excepting the nature of intermediate. In the SN_1 mechanism, a stronger nucleophile replaces a weaker one via the formation of a carbocation intermediate; however, in the SE_1 route, before the attacking electrophile attack, the intermediate formed after the dissociation of electrofuge is a carbanion.

Illustrative reaction: The general reaction showing this type of electrophilic attack (with its corresponding product) is shown below.

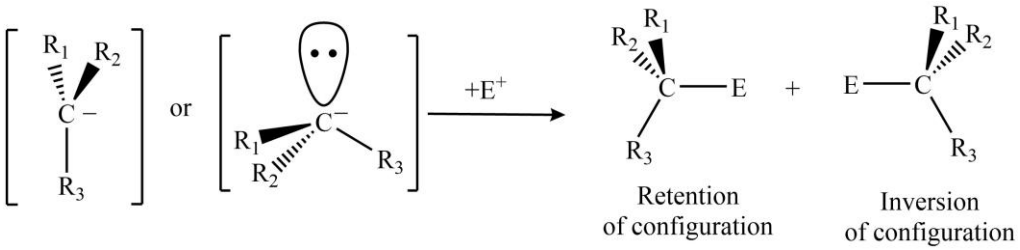


Mechanism involved: The proposed mechanism for the reaction given above involves a three-step route which must be discussed before we give the salient features of the same.

i) Heterolysis in substrate: This is the slowest, and therefore, is the rate-determining step that gives rise to a carbanion.



ii) Electrophilic attack: This is a very fast step and involves the combination of attacking electrophile with the carbanion produced in the previous step.



The stereochemistry of SE_1 reactions is quite complicated to rationalize because of the configuration of intermediatory carbanions obtained via the first step of heterolysis. Generally, we consider carbanions planar (sp^2 hybridization) or pyramidal (sp^3 hybridization), or an in-between configuration. As far as the energy is concerned, pyramidal geometry is more advantageous because lone pair will stay in sp^3 hybridized orbital. Furthermore, a pyramidal carbanion can retain its structure in the course of substitution to result in the retention of the final configuration. However, it does not always go this way because a pyramidal carbanion has been shown to results in racemization due to 'pyramidal inversion'; amines and R_3C^- carbanions are typical examples.

Figure 1. The pyramidal inversion of carbanion.

On the other hand, if the carbanion is of trigonal planar geometry, the electrophile can attack from both sides to give rise to racemized yield. So, we can conclude that racemization is the characteristic feature of the SE_1 route. However, it is quite tedious to determine how the racemization actually occurred; via pyramidal inversion or planar carbanions.

Salient Features: The main features of the mechanism involved in electrophilic substitution unimolecular or SE_1 type reactions are given below.

i) SE_2 reactions follow first-order kinetics with the rate law

$$Rate = k[RX]$$

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

ii) If the substrate is chiral, then this always leads to the racemization of the final product.

iii) Unlike SN_1-type, SE_1 reaction can also occur at bridgehead carbon because the intermediate (carbanion in this case) need not to be planar.

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

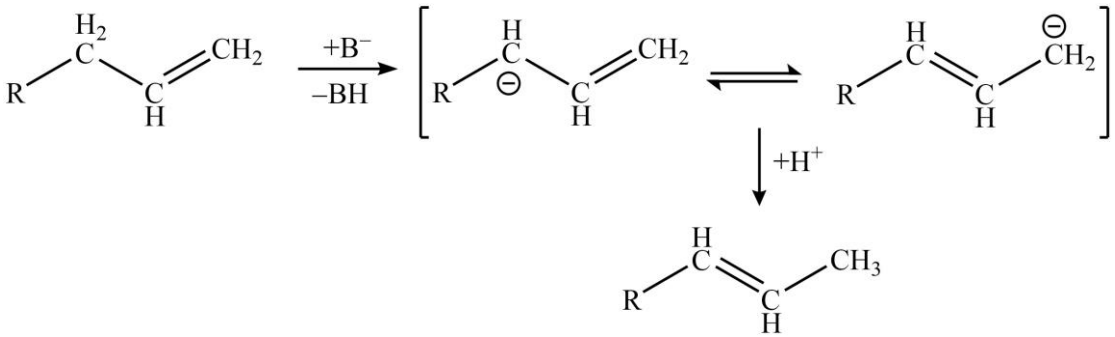
v) The SE_2 reactions are favored by the more polar C–L bond.

❖ Electrophilic Substitution Accompanied by Double Bond Shifts

If the substrate in electrophilic substitution is allylic in nature, the final product may undergo rearrangement, which is quite similar to the allylic rearrangements in nucleophilic substitutions. There are two main routes for this behavior to occur; one is analogous to the SE_1 pathway (leaving group is detached first) giving a resonance-stabilized allylic carbanion which attacks the electrophile E, the second one involves the initial attack on E by the π-bond to yield a carbocation which then which loses X forming new alkene unit.

➢ *Base-catalyzed Double Bond Migration*

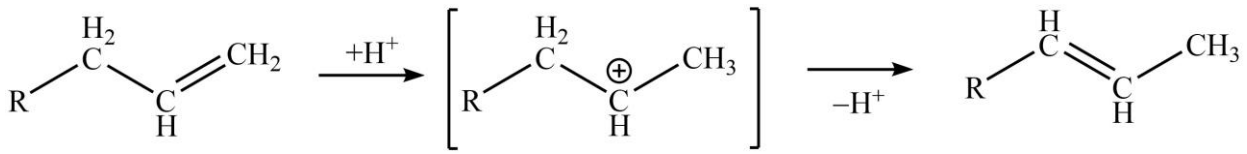
The first pathway is the base-catalyzed double bond migration, where an equilibrium mixture of isomers is obtained with stable configuration as the major product. The reaction occurs in two steps, in which the step is the abstraction of a proton by the base to yield a resonance stabilized carbanion, which in turn, is attacked by electrophile (proton in this case) to give rise to a more stable species. The typical reaction portraying mechanism is given below.



It is also worthy to note that terminal and non-conjugated alkenes can easily be converted into internal and conjugated olefins using this route, proving its significance in synthetic organic chemistry.

➢ *Acid-catalyzed Double Bond Migration*

The second pathway is the acid-catalyzed double bond migration, where an equilibrium mixture of isomers is obtained with a stable configuration as the major product. The reaction initiates with the attack of E on the π-bond to yield a carbocation which then loses L forming a new alkene unit. The typical reaction portraying mechanism is given below.



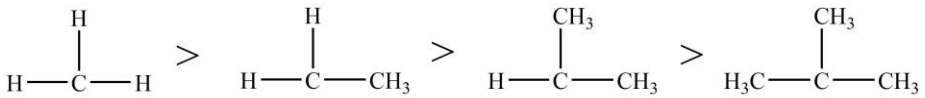
Just like base-catalyzed double bond migration, this route can also be used to convert terminal and non-conjugated alkenes into internal and conjugated olefins.

❖ Effect of Substrates, Leaving Group and the Solvent Polarity on the Reactivity

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

➢ *Effect of Substrate Structure*

The electron-donating groups of the substrate decrease the rate of SE_1 reactions whereas electron-withdrawing groups show an opposite trend. This declining rate in the SE_1 pathway with electron-donating groups is quite normal for a reaction-type where the proton's dissociation is the rate-determining step (like in the case of acidic character). Jensen and Davis proved that the reactivity of alkyl groups is similar in SE_2-back as that for the SN_2 pathway, which can be attributed to the backside attack and steric hindrance, simultaneously.



Reactivity of alkyl groups for SE_2-back pathway

Furthermore, it has also been observed that the rate of front-mode electrophilic substitution in aliphatic compounds increases as the branching in the substrate increases increased, which can be attributed to the electron-releasing effect of the alkyl groups that makes the electron-deficient transition state more stable. However, it is also worthy to note that β-branching will reduce the substitution rate in SE_2-front because of the steric hindrance.

➢ *Effect of Leaving Group*

The ease of electrofuge's detachment in both types (SE_1 and SE_2) increases with the increasing polarity of the C−X bond. Nevertheless, if the leaving group is metallic in nature and metal has a valence greater than one, then any group attached to the metal center will affect its electrofugal ability. For instance, consider the case of $Me_3C-Hg-W$ (organomercurials) where the rate of reaction has decreased. The reason lies in the fact that although Hg and W have less electronegativity than carbon (which is why the C−Hg bond is polar), the C−Hg bond becomes less polar due to the higher electronegativity W than Hg. In other words, carbon will have a lower negative charge in the C−Hg bond when W is attached to Hg because tungsten will support Hg to hold the shared pair more firmly. Therefore, −HgMe will be a better leaving group than −HgCl.

Hg–*t*-Bu > Hg–*i*Pr > HgEt > HgMe

Leaving-group order

Furthermore, it is also worthy to note that carbon-based leaving groups support the SE_1 mechanism, whereas SE_2 or SE_i mechanisms are favored by metal-based leaving groups.

➢ ***Effect of Solvent Polarity***

Just like the case of aliphatic nucleophilic substitution reactions, the raise in solvent polarity boosts the chances of the SE_1 pathway by supporting the ionization because of the better solvation of carbanions. However, if SE_2 and SE_1 reactions are competing with each other in parallel propagation, then less polar solvents favor the SE_2 pathway and polar solvents favor the SE_1 mechanism. Finally, If the nucleophilic character of the solvent is very small, the electrophile with properly placed assisting functionality might support the reaction; and therefore, motivating the reaction towards the SE_i pathway; otherwise, solvent polarity has little to no effect upon SN_i reactions.

❖ Problems

Q 1. Define electrophilic substitution reactions.

Q 2. What is the fundamental difference between SE_2 and SE_i mechanisms?

Q 3. Discuss the step-to-step mechanism of SE_1 reactions.

Q 4. How can electrophilic substitution occur via double bond shift?

Q 5. Discuss the effect of substrate structure and leaving group on the reactivity of electrophilic substitution in aliphatic compounds.

Q 6. How does the nature of nucleophiles affect the rate of aliphatic electrophilic substitution?

Q 7. Write down a short note on the solvent polarity's effect on electrophilic substitution reactions in aliphatic systems.

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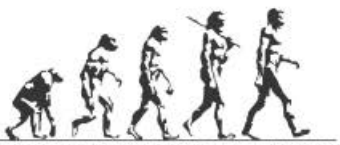

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