

CHAPTER 3

Reaction Mechanism: Structure and Reactivity

❖ Types of Mechanisms

Although the number of mechanisms by which different organic reactions proceed is very large, certain patterns can still be used to profile them for more systematic and simplistic analysis. Now before we classify different types of organic reaction mechanisms in brief, it is better to recall the basic terminology involved first.

1. Substrate and reagent: A typical organic reaction is thought to proceed via the breaking or making of one or more covalent bonds, and it is very suitable to call one reactant “substrate” and the other as “reagent”. Generally, more reactive species is labeled as the reagent whereas the less reactive species is considered as the substrate.

2. Molecularity: The molecularity of a chemical reaction may simply be defined as the number of colliding molecular species involved in a single step. The most common types are unimolecular and bimolecular reactions that involve one and two molecular entities, respectively.

3. Electrophiles and nucleophiles: An electrophile is an electron-loving species or electron pair acceptor. Generally, the electrophiles are positively charged or neutral entities with vacant orbitals that are attracted to an electron-rich center. The electrophiles participate in the chemical reactions by accepting an electron pair to form a bond with the nucleophilic reactant. Now since the electrophiles accept electrons, they are seen as Lewis acids. A nucleophile is a nucleus (i.e. positive center) loving species or electron-pair donor. Normally, the nucleophiles are negatively charged or neutral electron-rich entities with lone pairs of electrons that are attracted to an electron-deficient center. The nucleophiles participate in the chemical reactions by donating an electron pair to form a bond with the electrophilic reactant. Now since the nucleophiles donate electrons, they are seen as Lewis bases.

4. Leaving Group: The part of the substrate molecule that gets detached is typically called as the leaving group. The leaving groups with electron-pair and without electron pairs are labeled as nucleofuges and electrofuges, respectively.

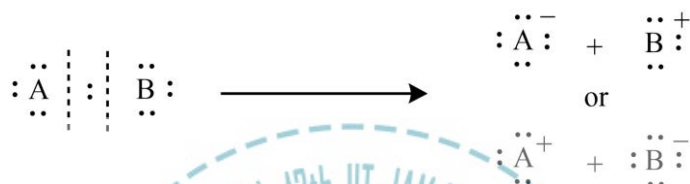
5. Reaction intermediates: The chemical species that are formed somewhere during the course of a chemical reaction are called as reaction intermediates. These are actual molecules that are short-lived and unstable. Sometimes they are called temporary reactants or products because they are neither present in actual reactants nor the actual products.

6. Transition states: The transition state of an organic reaction is a specific configuration along the reaction coordinate and corresponds to the highest potential energy along with this reaction coordinate. Unlike “reaction intermediate”, the transition state is not an actual molecule that can be isolated, and therefore it is often marked with the double dagger ‡ symbol to differentiate.

Now depending upon the bonds-breaking, the reaction mechanism of organic compounds can be divided basically into three basic types as given below.

➤ **1. Polar Mechanism (Bond Heterolysis)**

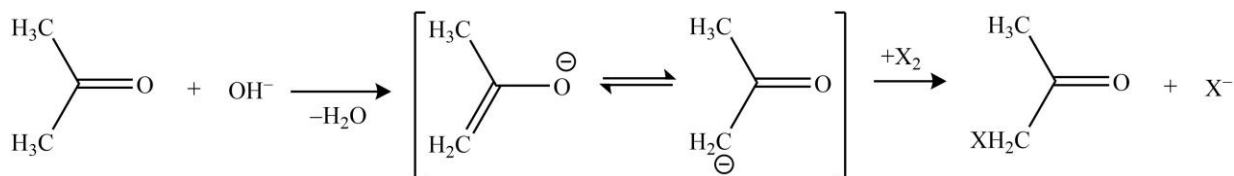
Polar or ionic or bond-heterolysis mechanisms have the characteristic feature of the electron-pair migrating from a well-defined source (such as lone pair or a nucleophilic bond) to a well-defined sink (some electrophilic center having low-lying antibonding molecular orbitals). This mechanism results from the heterolytic or unsymmetrical breaking of the covalent bond in which the bonding pair goes with one of the fragments.



The participating atoms in this type of mechanism undergo a change in their charges (formally as well as in reality). Most of the organic reactions fall into this category. For instance, the hydrolytic cleavage of tert-butyl bromide generates a carbocation and bromide ion.



Similarly, the acetone's reaction with halogen in the presence of base occurs through the formation of carbonian.



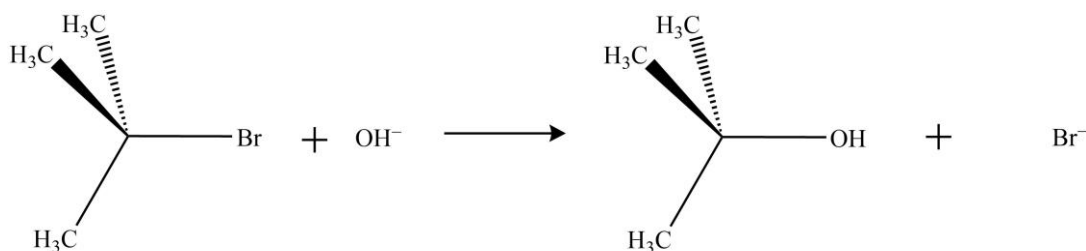
In an ionic mechanism, it's the electronegativity of the binding atom that primarily determines the fragment with bonding pair of electrons. The bond pair goes with the more electronegative atom and generates the anion. Now owing to the very small value of carbon's electronegativity, the heterolytic cleavage gives rise to carbocation most of the time; and therefore, carbocations are much more common than the carbanions.

❖ Types of Reactions

Although the number of possible organic reactions and corresponding mechanisms is very large, certain patterns can still be observed which are used to describe numerous useful organic reactions. Each type of reaction has a stepwise route which explains how it occurs, though the actual picture of these steps cannot always be visualized only by looking at the reactants' list. Furthermore, despite their basic classification, many organic reactions may fall into more than one category. For instance, some of the substitution reactions follow an addition-elimination route. Hence, this classification doesn't mean to include all the organic reactions but most of them for general studies.

➤ Substitution Reactions

A substitution or single displacement reaction may simply be defined as a chemical change where one functional group in an organic compound is displaced by another functional group.



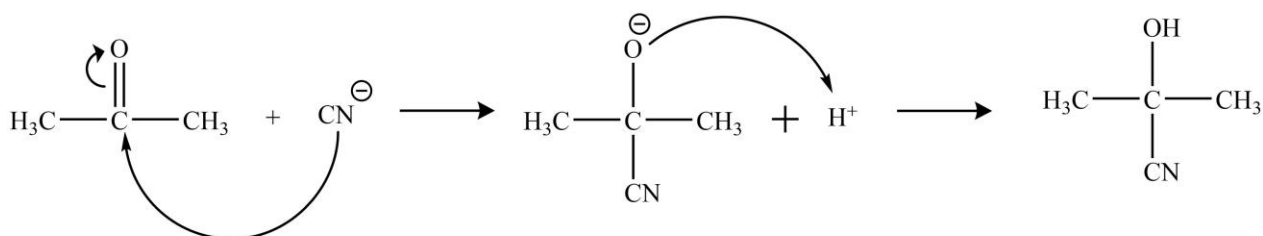
Unimolecular Aliphatic Nucleophilic Substitution Reactions

These types of organic reactions can be classified primarily into three categories; electrophilic substitution, nucleophilic substitution, and radical substitution depending upon the type and nature of the attacking reagent involved. Further classification is also possible by considering whether the reactive intermediate is a carbanion, a carbocation, or a free radical; or if the substrate is aliphatic or aromatic.

➤ Addition Reaction

The addition reaction in organic chemistry may simply be defined as a chemical change where two or more molecular entities combine to give rise to a bigger molecule (i.e., the adduct). Also, since the incoming group needs to bind to substrate, addition reactions are pretty much limited to organic compounds with multiple bonds, like molecules with carbon-carbon double or triple bonds (alkenes), and compounds that possess rings in them (i.e. also a kind of unsaturation). Furthermore, besides alkenes, alkynes, or ring structures, the organic compound can also have carbon-hetero multiple double bonds like imine (C=N) groups or carbonyl (C=O) groups; and therefore, are also capable of undergoing addition reactions.

The addition reaction can also be treated as the opposite of an elimination reaction. For example, the alkene's hydration to alcohol is the opposite of the dehydration reaction. The addition reactions can primarily be classified into two types: polar addition and non-polar addition. Polar additions are further divided into electrophilic addition and nucleophilic additions; whereas the non-polar addition reactions can be subdivided into free-radical addition and cycloaddition types.



Nucleophilic Addition Reaction

Finally, it is also worthy to note that addition reactions are also found in polymerization processes and are typically labeled as addition polymerization.

➤ Elimination Reactions

An elimination reaction in organic chemistry may simply be defined as a chemical change where two substituents are detached from a molecule in either a one- or two-step pathway. The one-step pathway is abbreviated as the E_2 mechanism, whereas the two-step pathway is abbreviated as the E_1 mechanism. Hence, the subscript in E_1 or E_2 reactions does not represent the number of steps involved, but the kinetics followed; E_1 is unimolecular (first-order) while E_2 is bimolecular (second-order).



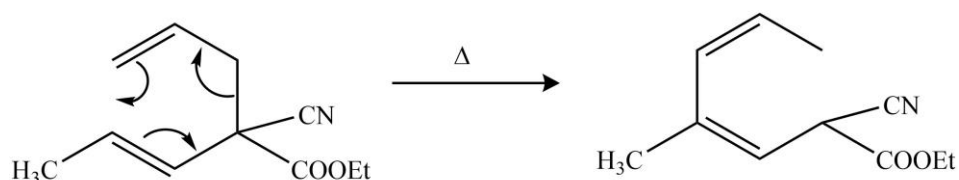
E1 Elimination Reaction

Furthermore, if the molecule can stabilize an anion but does not have a poor leaving group, the third kind of mechanism, called E_1CB , also exists. Lastly, a fourth kind, called the internal elimination (E_i), also exists which is generally followed by pyrolysis of xanthate and acetate esters.

➤ Rearrangement Reactions

A rearrangement reaction in organic chemistry may simply be defined as a chemical change where the carbon skeleton of an organic compound rearranges itself to give rise to a structural isomer. Generally, a group moves from one atom to another atom within the same molecule.

Now although the domain of rearrangement reactions is extremely wide, these changes can still primarily be classified into four categories; 1, 2 rearrangements, metathesis reactions, sigmatropic rearrangements, and electrocyclic reactions. A fifth kind called group transfer reactions also exist but are far less important than what we have mentioned. One of the most common examples of rearrangement reactions is the 'Cope rearrangement' which is a 1, 3-sigmatropic rearrangement involving the movement of an R group from 1st carbon to 3rd carbon in the same molecule.

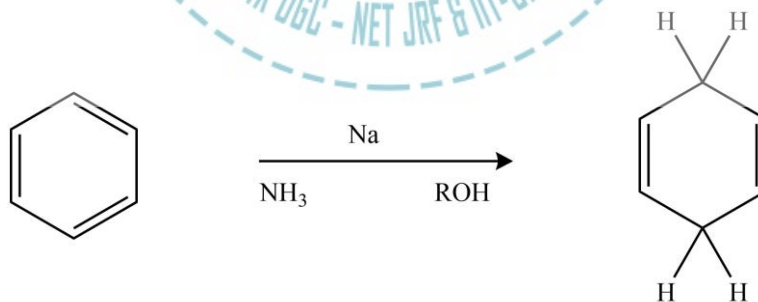


Cope Rearrangement

Besides intramolecular rearrangements, intermolecular rearrangements are also possible in many organic compounds; the group transfer reaction we mentioned is an example. It is also worthy to note that a rearrangement cannot be represented by the simple and discrete electron in a very good manner. For instance, in Wagner-Meerwein rearrangement, the actual mechanism of alkyl group migration involves the transfer of the alkyl group fluidly along with a bond, and not the typical bond breaking-making. Similarly, the pericyclic rearrangements are explained in terms of orbital interactions rather than discrete electron transfers. Nevertheless, it is quite possible to draw the curved arrows mechanism for rearrangement reaction for simple and fast understanding, even if these are not realistic necessarily, excepting in allylic rearrangement.

➤ Redox Reactions

Redox reactions in organic chemistry may simply be defined as the chemical changes where the reduction or oxidation of organic compounds occurs to give rise to new products. It is also worthy to note that the meaning of oxidations and reductions in organic chemistry is different from simple redox reactions because numerous reactions bear the label but do not include the actual electron transfer in the electrochemical context. In its place, organic oxidation is the gain of oxygen or loss of hydrogen; whereas organic reduction means the gain of hydrogen or the loss of oxygen. Nevertheless, simple functional groups can still be organized in the ascending order of oxidation states for approximation.



Birch Reduction

Finally, we need to remember that the reactant can undergo both oxidation and reduction in the same chemical reaction to give rise to two separate compounds (disproportionation reactions).

❖ Thermodynamic and Kinetic Requirements

In this section, we will discuss a brief idea of the thermodynamic and kinetic requirements of an organic reaction.

➤ Thermodynamic Requirements for a Reaction

A reaction takes place spontaneously if the magnitude of ΔG is negative i.e. the free energy of the reactants must be higher than the free energy of the products and vice-versa. From thermodynamics, we know that

$$\Delta G = \Delta H - T\Delta S \quad (1)$$

$$\Delta G = -RT \ln K \quad (2)$$

Where $\Delta H = \Sigma H_{products} - \Sigma H_{reactants}$, $\Delta S = \Sigma S_{products} - \Sigma S_{reactants}$ and T is the temperature. The symbols R and K represent the gas constant and equilibrium constant, respectively. Now, as the entropy changes for most of the organic reactions is quite small, the free energy change is primarily governed by the value of ΔH . Furthermore, it follows from equation (1) that ΔG will become more negative with a more negative value of ΔH , which in turn would increase the value of equilibrium constant K . Hence, more and more product will be formed as the enthalpy of the system decreases.

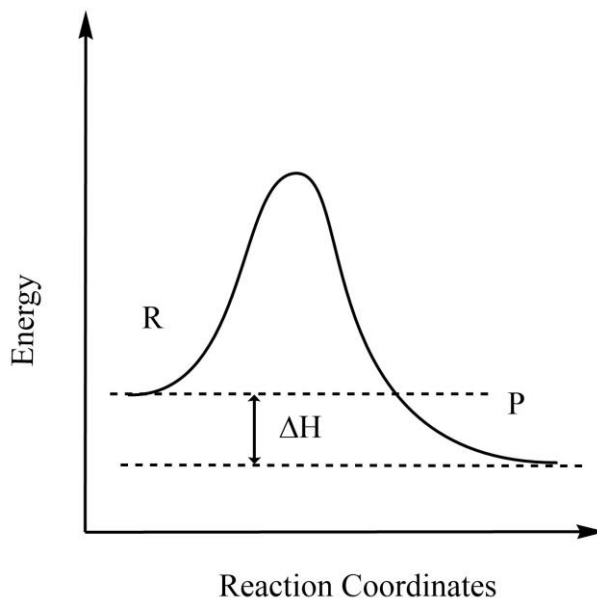


Figure 1. Energy profile diagram for thermodynamics of a typical organic reaction.

Furthermore, it is also very obvious from equation (1) that entropy becomes more important as the temperature of the reaction vessel is raised.

➤ **Kinetic Requirements for a Reaction**

The kinetic requirements of an organic reaction depend upon the activation energy of the same. If the activation energy barrier is low, the reaction will take place at a higher speed. If the activation energy barrier is high, the substance will react slowly and will take a very long time to complete.

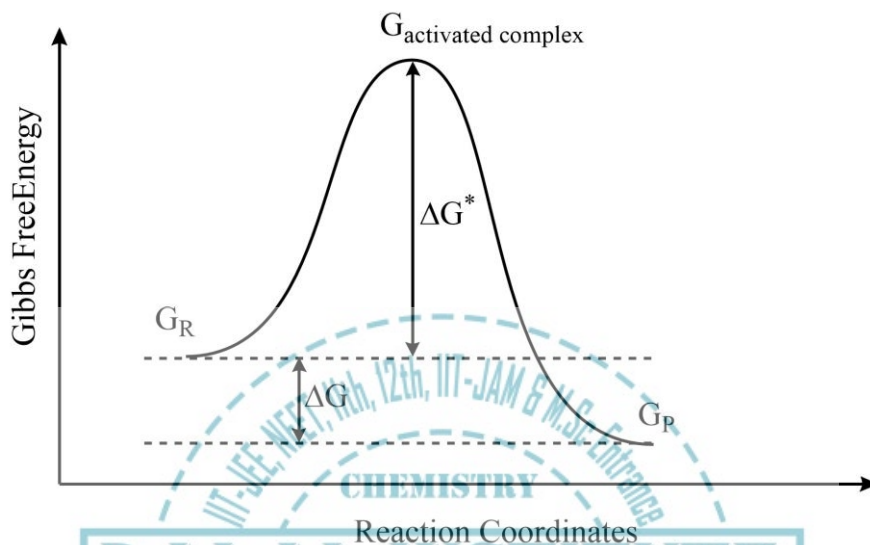


Figure 2. Energy profile diagram for kinetics of a typical organic reaction.

Since the kinetics of organic reactions is generally studied in the framework of “Activated complex Theory”, which states that the rate constant for a typical reaction is

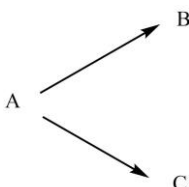
$$k = \frac{RT}{Nh} e^{-\frac{\Delta G^*}{RT}} = \frac{RT}{Nh} \times e^{\frac{\Delta S^*}{R}} \times e^{-\frac{\Delta H^*}{RT}} \quad (3)$$

Where ΔG^* , ΔH^* and ΔS^* are free energy change, enthalpy change, and the entropy change of the activation step, respectively. As far as equation (3) is concerned, it can easily be seen that as the free energy change of the activation step increases, the rate constant would decrease.

However, if we look at the simplified form i.e. equation (3), we find three factors; one is RT/Nh which is constant if the temperature is kept constant. The second factor involves ΔS^* , and therefore, we can conclude that the reaction rate would show an exponential increase if the entropy of activation increases. The third factor includes ΔH^* , and therefore, we can conclude that the reaction rate would show an exponential decrease if the enthalpy of activation increases. It is also worthy to note that the first two terms collectively make the frequency factor.

❖ Kinetic and Thermodynamic Control

The thermodynamic or the kinetic control in a chemical reaction can dictate the composition in the final product mixture when two or more competing pathways giving rise to different products and the selectivity or stereoselectivity is influenced by the reaction conditions. Consider a typical reaction in which reactant A can transform into product B and C i.e.



Now, will discuss the two cases of thermodynamic and kinetic control of the overall reaction depending upon the nature of the product.

➤ *Different Products from Thermodynamic and Kinetic Control*

The difference will be obvious when product C forms at a faster rate than product B because the activation energy for product C is lower than that for product B (even if B is more stable than A). In such a scenario, C is favored kinetically and called as the kinetic product; whereas B is favored thermodynamically controlled and is called as the thermodynamic product. The exact nature of the final product (thermodynamic or kinetic) will be dictated by many reaction conditions like temperature, pressure, solvent, or any other factor which might affect the reaction pathway. Also, it must be kept in mind that the above-mentioned statement is true only if the activation energy of the two routes are different; with dominating yield for the pathway having lower activation energy (E_a) than the other.

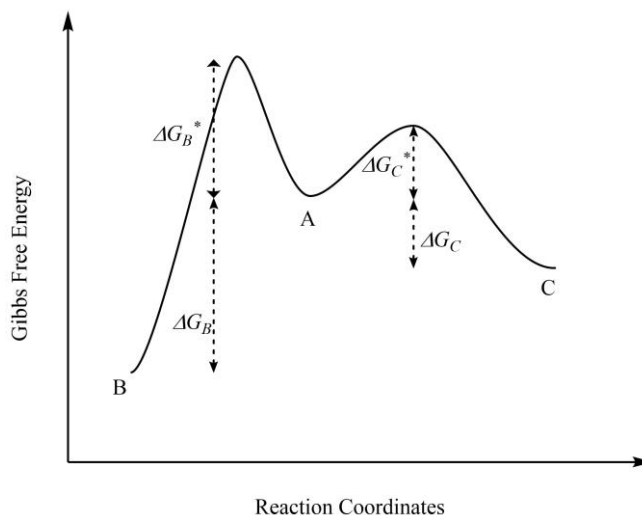


Figure 3. Energy profile diagram for kinetic versus thermodynamic product reaction.

➤ **Same Products from Thermodynamic and Kinetic Control**

In this case, product B forms at a faster rate than product C because the activation energy for product B is lower than that for product C. Also, since $\Delta G_B > \Delta G_C$, B is more stable thermodynamically than C. Therefore, the thermodynamic as well kinetic control of the reaction will favor the formation of product B. The activation of thermodynamic or kinetic control dictates the composition of the end product when these competing pathways give rise to different products influencing the selectivity of the reaction.

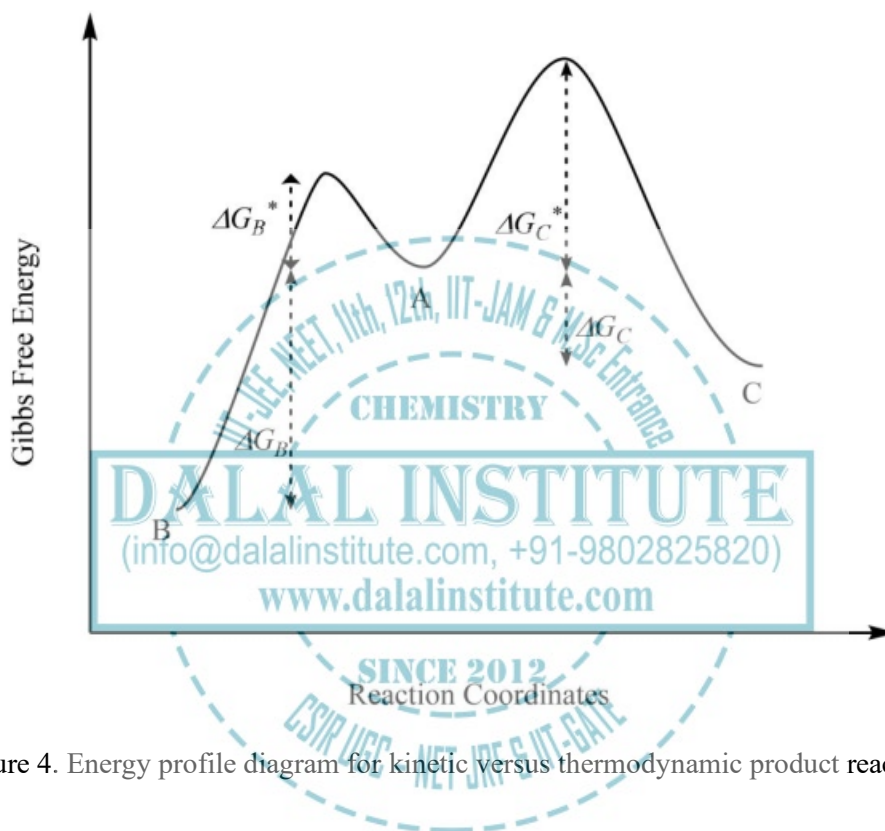


Figure 4. Energy profile diagram for kinetic versus thermodynamic product reaction.

The selectivity arising from kinetic vs thermodynamic control is extremely important in the case of asymmetric synthesis. This can be attributed to the fact that the pairs of enantiomers have the same Gibbs free energy; and therefore, the thermodynamic control will yield a racemic mixture by obligation. So, any catalytic reaction that gives the product with enantiomeric excess different than zero must be under some kind of kinetic control. Several stoichiometric asymmetric syntheses occur giving enantiomeric products due to a chiral substrate i.e., the reaction is actually a diastereoselective type; and therefore, even if such transformations are kinetically controlled, thermodynamic control is at least theoretically possible.

❖ Hammond's Postulate

Hammond's postulate states when a transition state gives rise to an unstable reaction intermediate (or product) it will have comparable energy to that intermediate, and both will be interconvertible by a very minute reorganization of molecular structure.

This hypothesis was first proposed by George Hammond in 1955 to correlate the transition states with intermediates and products. Nevertheless, besides Hammond's postulate, another chemist J. E. Leffler also gave an assumption that the transition state will have a greater resemblance to the less stable species (i.e., reactant, or intermediate, or product). Since many teachers or textbooks state 'Leffler assumption' but refer to the statement as 'Hammond's postulate' due to their similar arguments, it is better to use 'Hammond- Leffler postulate' to give the credit where it is due.

Therefore, the geometric structure of a state can be predicted by comparing its energy to the species neighboring it along with the reaction coordinate. For instance, the geometry of the transition state resembles reactants in an exothermic reaction; whereas the endothermic reactions will have transition states closer to products. This kind of assessment is very useful especially when most transition states cannot be analyzed experimentally.

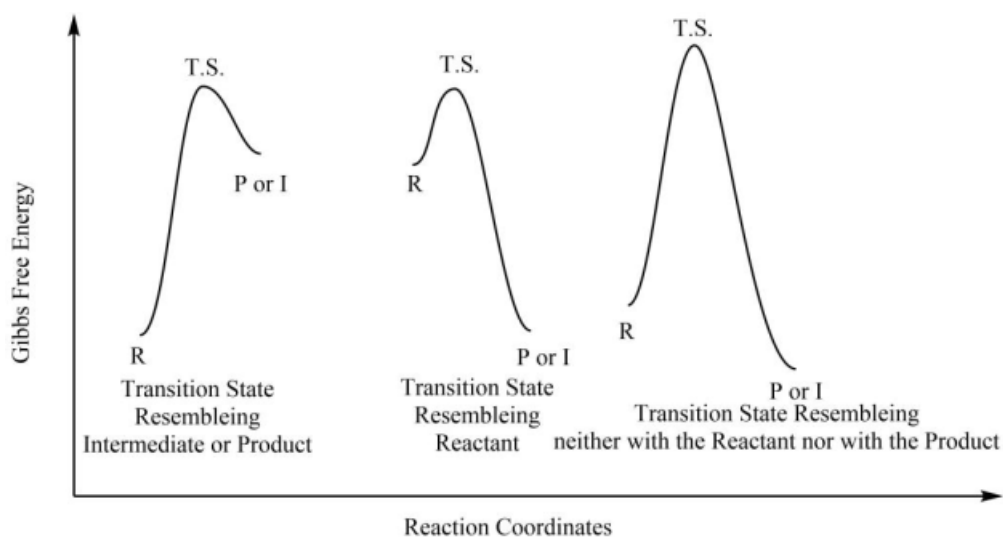


Figure 5. Three cases of according to Hammond's postulate.

Hammond's postulate can also be used to rationalize the Bell-Evans-Polanyi principle describes the experimental observation that the rate of a reaction (and so the activation energy) is influenced by the enthalpy of that reaction. Hammond's postulate describes this observation by explaining how does enthalpy variation results in the structure change of the transition state; which in turn, would change the energy of the transition state, and so the reaction rate as well (via changing activation energy).

❖ Curtin-Hammett Principle

The Curtin–Hammett principle in chemical kinetics was proposed by David Yarrow Curtin and Louis Plack Hammett to predict the relative ratio of the products obtained from a conformational equilibrium.

It states that the relative ratio of the products obtained from a conformational equilibrium is independent of the relative concentration of participating conformers and is a function of the free-energy-gap of the corresponding transition states provided that the rate of conformational-interconversion is much larger than the rate of formation of products.

To understand the Curtin-Hammett principle in perspective, consider a typical reaction in which products C and D are formed from two conformers A and B as



Since the enthalpy of activation for most of the organic reactions is greater than the equilibrium between participating conformers ($\Delta G_A^* > \Delta G^o$ and $\Delta G_B^* > \Delta G^o$), the reactants A and B are will remain abundant.

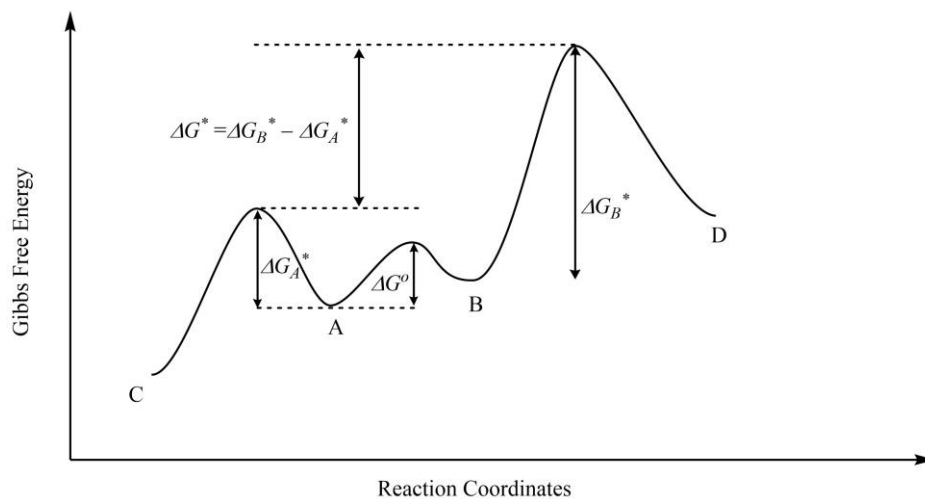


Figure 6. Potential energy diagram for Curtin-Hammett principle.

For the conformational equilibrium, the equilibrium constant (K) will be

$$K = \frac{B}{A} \quad (5)$$

The formation rate for C can be given as

$$\frac{dC}{dt} = k_C[A] \quad (6)$$

$$\frac{dD}{dt} = k_D[B] \quad (7)$$

Now considering the reaction is first-order or pseudo-first-order in nature, the ratio of the products can simply be obtained by dividing equation (7) by equation (6) i.e.

$$\frac{dD}{dt} \times \frac{dt}{dC} = \frac{k_D[B]}{k_C[A]} \quad (8)$$

$$\frac{dD}{dC} = \frac{k_D[B]}{k_C[A]} \quad (9)$$

Using the value of $[B]/[A]$ from equation (5), we get

$$\frac{dD}{dC} = \frac{k_D}{k_C} K \quad (10)$$

But we know from chemical kinetics that

$$K = e^{-\Delta G^0/RT} \quad (11)$$

$$k_C = \frac{RT}{Nh} e^{-\Delta G_A^*/RT} \quad (12)$$

$$k_D = \frac{RT}{Nh} e^{-\Delta G_B^*/RT} \quad (13)$$

Using equations (11–13) in equation (10), we get

$$\frac{dD}{dC} = \frac{\frac{RT}{Nh} e^{-\Delta G_B^*/RT}}{\frac{RT}{Nh} e^{-\Delta G_A^*/RT}} e^{-\Delta G^0/RT} \quad (14)$$

$$\frac{dD}{dC} = \text{Products Ratio} = e^{-\Delta G_B^*/RT} e^{+\Delta G_A^*/RT} e^{-\Delta G^0/RT} \quad (15)$$

$$\text{Products Ratio} = e^{-\frac{\Delta G_B^* + \Delta G_A^* - \Delta G^0}{RT}} \quad (16)$$

However, it is obvious from Figure 5 that $-\Delta G_B^* + \Delta G_A^* - \Delta G^0 = -\Delta G^*$; therefore, we have

$$\text{Products Ratio} = e^{-\frac{\Delta G^*}{RT}} \quad (17)$$

Hence, the product ratio is governed by the energy gap between the transition states rather than ΔG^0 , which is the famous Curtin-Hammett principle.

❖ Potential Energy Diagrams: Transition States and Intermediates

The potential energy diagrams or the reaction progress curves are nothing but a visual representation of the energy changes that occur during a chemical reaction. The energy of various species participating in the reaction is plotted on the y -axis (ordinate) whereas the progress of the reaction on the x -axis (abscissa). Now since a reaction can have transition states and intermediates (in addition to the reactants and final product), we must discuss the corresponding potential energy diagrams.

➤ Potential energy Diagram of Reactions with Reactant, Product and Transition State

The transition state of an organic reaction is a specific configuration along the reaction coordinate and corresponds to the highest potential energy along with this reaction coordinate. Furthermore, the transition state is not an actual molecule that can be isolated, and therefore it is often marked with the double dagger or star symbol to differentiate. The typical potential energy diagrams of endothermic and exothermic reactions with reactants, products, and transition states are shown below.

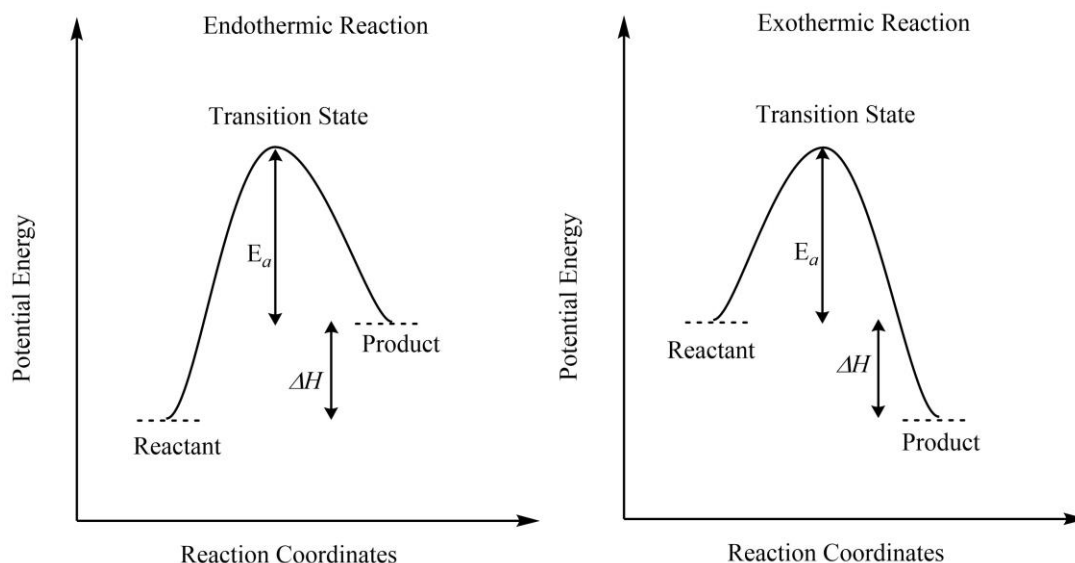


Figure 7. Typical potential energy curves for exothermic and endothermic reactions.

It is obvious from the potential energy diagrams that the enthalpy change is positive for an endothermic reaction ($\Delta H > 0$) and negative for an exothermic reaction ($\Delta H < 0$). For exothermic reactions, the potential energy of the reacting species first increases, attains a maximum at the transition state, and then decreases even more than the reactants. For endothermic reactions, the potential energy of the reacting species first increases, attains a maximum at the transition state, and then decreases less than the reactants.

Furthermore, it should also be noted that the energy gap between the transition state and reactant is the activation energy (E_a) which is responsible for the speed of the reaction. The higher activation energy leads to slow transformation and vice-versa.

➤ **Potential energy Diagram of Reactions with Reactant, Product, Transition State, and Intermediates**

The chemical species that are formed somewhere during the course of a chemical reaction are called as reaction intermediates. Unlike transition states, these are actual molecules that are short-lived and unstable. Sometimes they are called temporary reactants or products because they are neither present in actual reactants nor the actual products. The typical potential energy diagram of a typical exothermic reaction with a reactant, product, intermediate, and transition state is shown below.

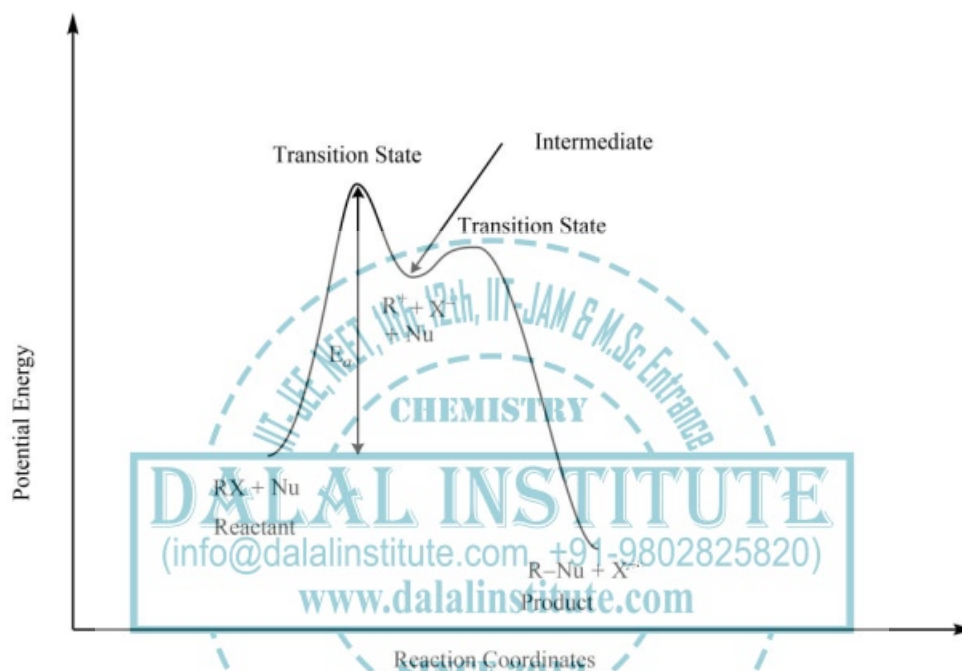


Figure 8. Potential energy diagram for the S_N1 reaction.

It is obvious from the potential energy diagrams that the intermediates are situated at the minima whereas the transition states are shown at the maxima. Also, just like the previous case, the energy gap between the transition state and reactant is the activation energy (E_a) which is responsible for the speed of the reaction i.e. the higher activation energy leads to slow transformation and vice-versa.

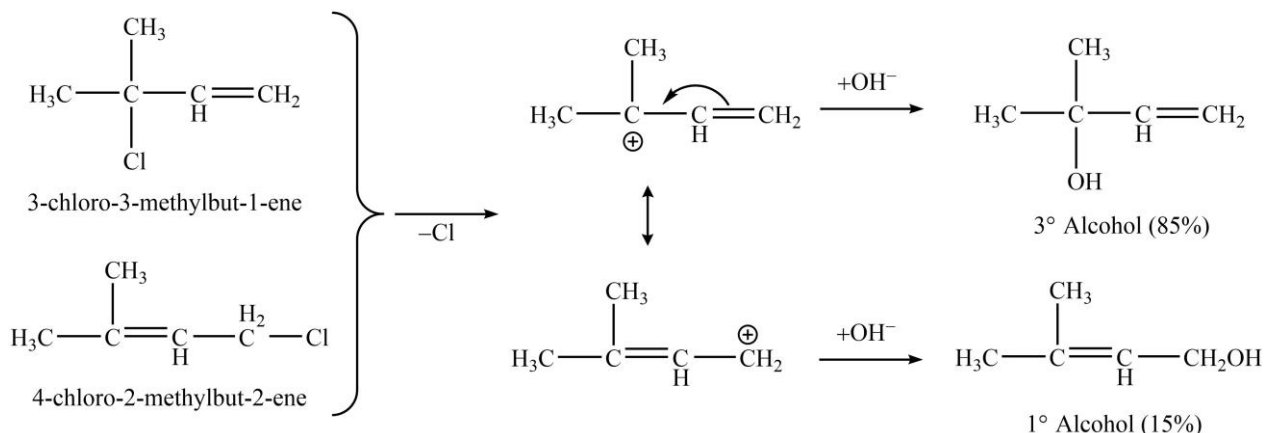
Reaction coordinate diagrams also give information about the equilibrium between a reactant or a product and an intermediate. If the barrier energy for going from intermediate to product is much higher than the one for the reactant to intermediate transition, it can be safely concluded that a complete equilibrium is established between the reactant and intermediate. Nevertheless, if the reactant-to-intermediate barrier is almost equal in energy to intermediate-to-product change, then no full equilibrium is set and steady-state approximation becomes activated to dictate the kinetic rate expressions.

❖ Methods of Determining Mechanisms

The reaction mechanism of organic compounds can be determined via several individual routes; however, it is quite common to use multiple methods for confirmatory results. Some of the major methods to determine the organic reaction mechanism are given below.

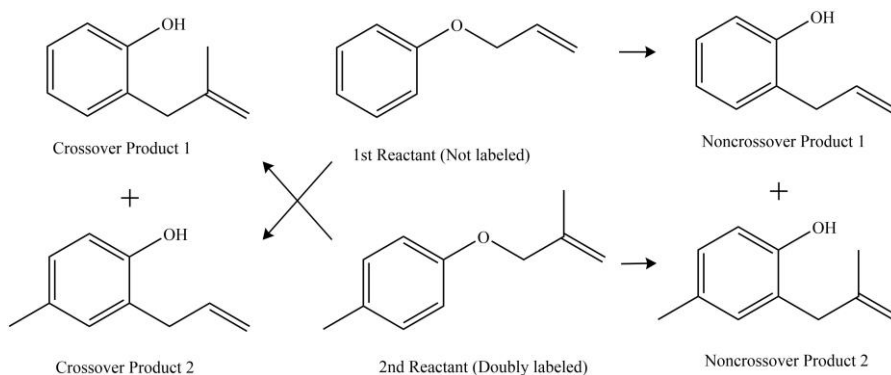
➤ 1. Product Identification

The proposed mechanism must account for all the products in the experimental reaction including by-products. Therefore, the theoretically proposed mechanisms are shortlisted depending upon the nature and number of the products. This can be illustrated by the hydrolysis of isomeric allyl chlorides. Since the hydrolysis of 3-chloro-3-methylbut-1-ene or 4-chloro-2-methylbut-2-ene give rise to 15% of primary alcohol and 85% tertiary alcohol in each case, a common intermediate must be proposed to rationalize the results.



➤ 2. Crossover Experiments

The crossover experiments are carried out to determine whether the reaction mechanism involves one step or two steps. To do so, a mixture of two similar but non-identical reactants is subjected to the reaction, and then the resulting products are investigated. Now because the migrating group needs to be free in a two-step process (intermolecular rearrangement), a mixture of the products corresponding to both reactants is expected (crossover products).



On the other hand, if the process is single-step (intramolecular rearrangement) we will not get any crossover products. This can be illustrated by the Claisen-rearrangement in which allyl aryl ethers are transformed into allyl phenols.

The concept underlying the crossover experiment is a basic one: provided that the labeling method chosen does not affect the way a reaction proceeds, a shift in the labeling as observed in the products can be attributed to the reaction mechanism. The most important limitation in crossover experiment design is therefore that the labeling does not affect the reaction mechanism itself.

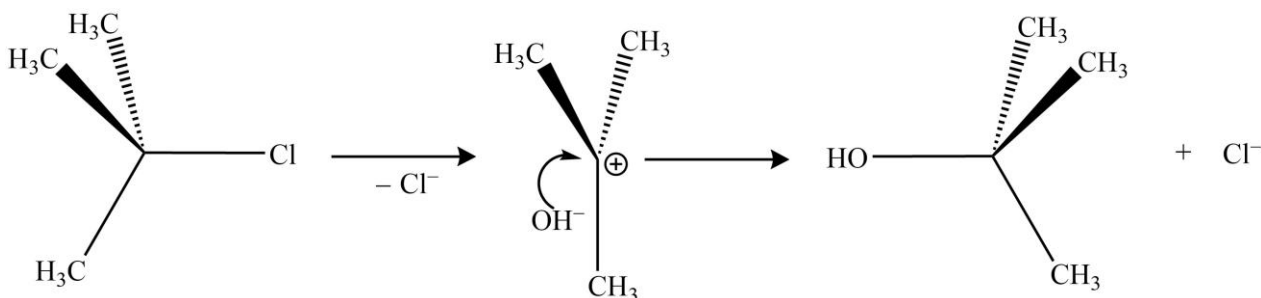
➤ 3. Isolation, Detection, and Trapping of Intermediates

Several organic reactions proceed via the generation of intermediates. If these intermediates are identified experimentally, the writing of a reasonable mechanism becomes very easy. These intermediates are usually detected by spectrophotometric methods directly; however, some unstable intermediates are first isolated by trapping them with reactive substrates.

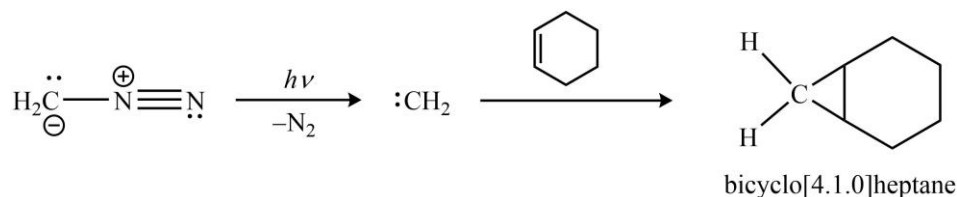
i) Isolation: In some cases, the isolation of an intermediate from the reaction mixture is possible either under mild conditions or by ending the reaction after some time. For instance, three intermediates can be isolated in the transformation of primary amides to primary amines (Hofmann rearrangement).



ii) Detection: If the intermediate formed in the course of the chemical reaction is very unstable, it is better to use spectrophotometric methods to detect them. For instance, the carbocation formed in the E_1 and SN_1 pathways can be detected via NMR spectroscopy confirming the route.



iii) Trapping: In some reactions, the intermediate formed is so unstable and short-lived that the conventional techniques cannot be used to identify them. In such cases, it is better to mix the reactant with a special reactive agent which can react with the intermediate to form detectable species. For instance, the formation of carbene during the decomposition of diazomethane can be detected by trapping them via cyclohexene.



➤ 4. Isotopic Labelling

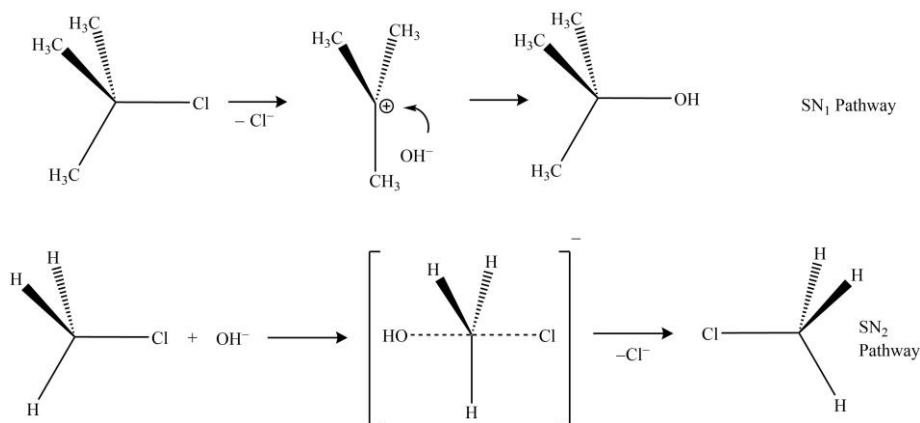
Isotopic labeling is a technique that is used to track the passage of reactants through a chemical reaction. The reactant is 'labeled' by displacing specific atoms by the corresponding isotope. The reactants are then permitted to undergo the chemical change, and the sites of the isotopes in the products are analyzed to find the sequence of the isotopes followed in the reaction mechanism. For instance, the mechanism of ester hydrolysis can be understood by replacing the normal water with H_2O^{18} .



It is obvious from the above reaction that it is the acyl-oxygen bond that gets broken rather than the alkyl-oxygen bond.

➤ 5. Kinetic Studies

The kinetic of an organic reaction is very useful in identifying the correct reaction mechanism. The rate-determining step (slowest step) infers about the reaction route from the overall rate law. One of the most popular examples where the reaction kinetics has been found to be exceptionally useful to determine reaction mechanism aliphatic nucleophilic substitution.



For instance, the hydrolysis of methyl bromide follows second order kinetics i.e.

$$-\frac{d[\text{CH}_3\text{Br}]}{dt} = k[\text{CH}_3\text{Br}][\text{OH}^-] \quad (18)$$

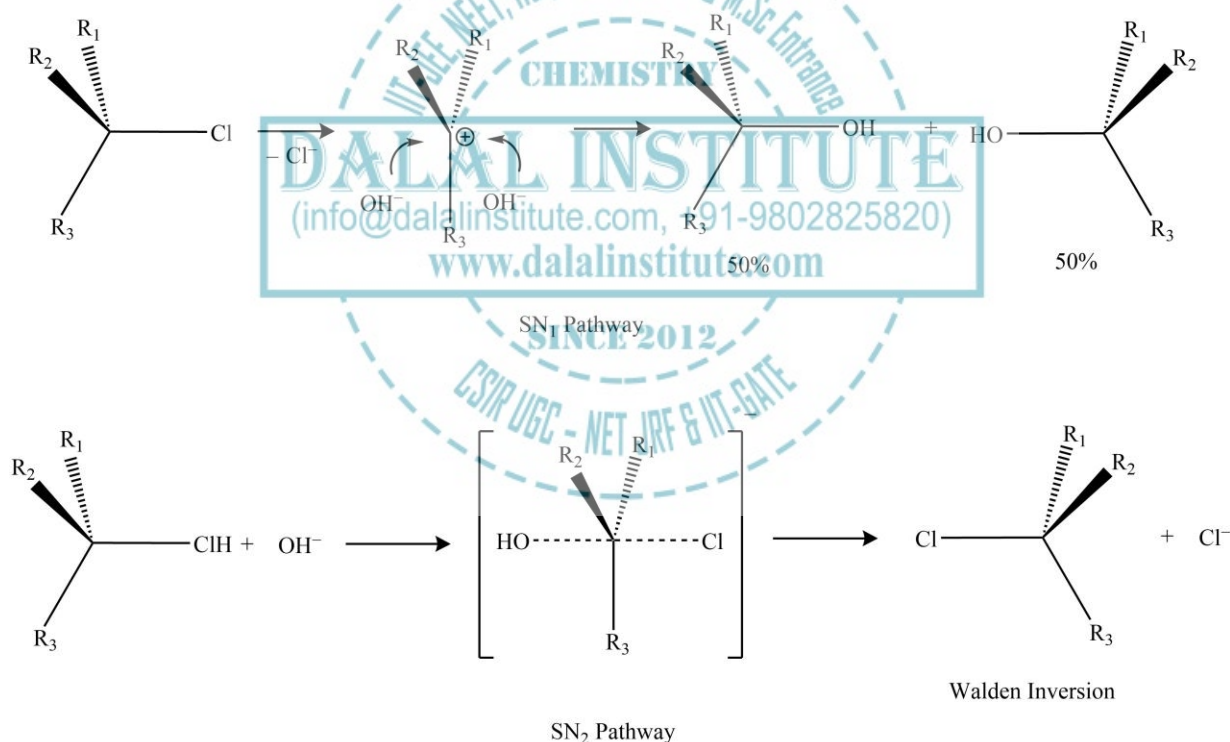
This is possible only if both reactants undergo a transition state instated of an intermediate. On the other hand, the hydrolysis of tert-butyl bromide follows first-order kinetics i.e.

$$-\frac{d[\text{CH}_3\text{Br}]}{dt} = k[(\text{CH}_3)_3\text{CBr}] \quad (19)$$

This is possible only if the substrate forms an intermediate instated transition state.

➤ 6. Stereochemical Analysis

In some cases, the stereochemistry of the reactants and products can also be used to identify the pathway of an organic reaction. For instance, the optical purity of the resulting product in aliphatic nucleophilic substitution in chiral compounds can infer whether it occurs via $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$.



The racemization of the product showed that the reaction has proceeded via a dissociative pathway where the attack on the two faces of the carbocation has happened. On the other hand, we get a mostly optically pure compound, which suggests that the reaction has proceeded via a dissociative pathway where the inversion has happened through a transition state.

❖ Isotope Effects

In the previous section of this chapter, we studied isotopic labeling as a tool to detect the reaction mechanism. There we assumed that the isotopic substitution has no effect on the chemical profile of the reaction whatsoever which is far from the truth because the isotopic substitution can change the rate of chemical reactions in a significant manner.

The changes in the reaction rate when a particular atom in the reactant molecule is replaced by one of its isotopes are termed as isotopic effects.

Formally, it is called as “kinetic isotope effect”, and it is calculated rate constants for the reactions with the lighter isotope (k_L) by the rate constant for reaction with the heavier isotope (k_H) i.e.

$$KIE = \frac{k_L}{k_H} \quad (20)$$

This variation in the rate of reaction because the heavier isotopologues have lower vibrational frequencies relative to their lighter isotopes, and can easily be rationalized quantum mechanically. In general, this means that greater energy is needed for heavier isotopologues to cross the transition state (or the dissociation limit in rare cases), and therefore, a lower reaction rate is observed. The kinetic isotopic effect can primarily be classified into two categories; primary and secondary isotope effects.

➤ Primary Isotope Effects

The primary kinetic isotope effect is observed if a bond to the isotopically-labeled atom is being broken or formed. Now depending on the nature of the route followed to study kinetic isotope effect (parallel measurement of rates vs intramolecular competition vs intermolecular competition), we can find if the bond-formation or bond-breaking has happened at the rate-determining step, or in the subsequent product-determining step. Furthermore, it is also worthy to note that many textbooks are propagating the misconception that a primary kinetic isotope effect must echo bond breaking or formation to the isotope at the rate-determining step always.

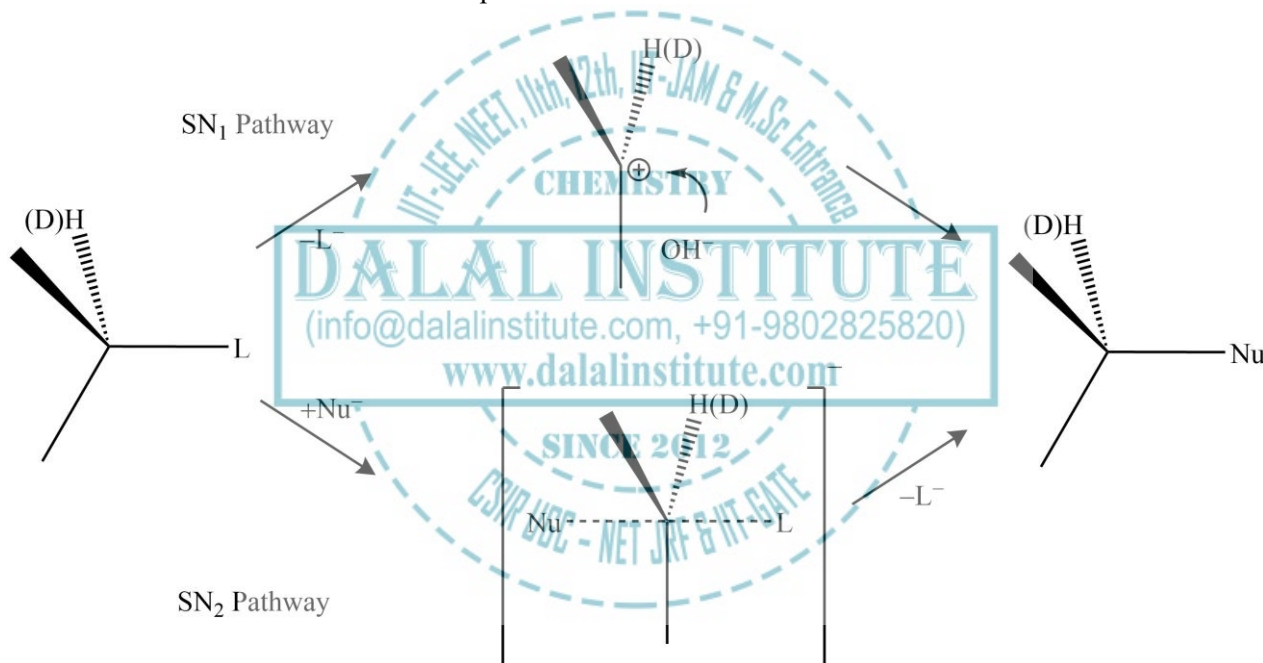
For nucleophilic substitutions mentioned earlier, the primary kinetic isotope effects have been studied for the attacking nucleophiles, leaving groups, and the α -carbon at which the displacement occurs. The interpretation of the kinetic isotope effects as a function of the leaving group had been very complicated at first because of the significant contributions from temperature-independent factors. Though the primary kinetic isotope effect is less sensitive than the ideal, and the contribution from non-vibrational factors; the kinetic isotope effects at the α -carbon are employed to advance the understanding of the transition state's symmetry of the S_N2 pathway.

➤ Secondary Isotope Effects

We will get a secondary kinetic isotope effect if no bond formation or breaking happens to the isotopically-labeled atom in the reactant. Also, the secondary kinetic isotope effects are much smaller in magnitude than primary kinetic isotope effects; though the secondary isotope effects of deuterium can reach

up to 1.4 per atom. Furthermore, many experimental techniques have been invented and refined to measure heavy-element isotope effects with extremely good precision; and therefore, these kinds of effects are still very valuable for mechanisms-elucidating of many organic reactions.

In the case of many nucleophilic substitution reactions, secondary isotope effects of H at α -carbon offer a direct route to differentiate between S_N2 and S_N1 type reactions. It is observed that S_N1 reactions generally give rise to great secondary isotope effects (up to a theoretical maximum of 1.22); whereas S_N2 reactions usually have primary isotope effects which are close to or less than one in most cases. Kinetic isotope effects having a value greater than unity are typically labeled as 'normal kinetic isotope effects', whereas isotope effects having a value less than unity are called as 'inverse kinetic isotope effects'. On the whole, transition states with smaller force constants are expected to have a normal kinetic isotope effect; and transition states with larger force constants are expected to have an inverse kinetic isotope effect when stretching vibrational contributions control the isotope effect.



The $C\alpha$ -H(D) vibration at the α -carbon dictates the magnitudes of these secondary isotope effects. Now because the carbon is converted into an sp^2 hybridized carbocation during an S_N1 reaction, the transition state for the rate-limiting step will have an increase in $C\alpha$ -H(D) bond order; and therefore, an inverse kinetic isotope effect would be expected if only the stretching vibrations were the chief factors. On the other hand, large normal kinetic isotope effects are observed which are induced by significant out-of-plane bending vibrational contributions if we go from the reactants to the transition state of carbocation formation. In the case of S_N2 reactions, bending vibrations will still play a vital role in the kinetic isotope effect, but stretching vibrational contributions are also of significant importance; and therefore, the resulting isotope effect may be inverse or normal depending upon the dominating factor.

❖ Hard and Soft Acids and Bases

Most of the Lewis acids can be distributed into two categories; class *a* and class *b* acids. Generally speaking, class *a* acids prefer to bind with Lewis bases with donor atom from second row non-metal (i.e. F, O or N); whereas class *b* acids prefer to bind with Lewis bases with donor atom coming from third or below row (i.e. Br, I, S or P). An American chemist Ralph Pearson then developed a model where Lewis acids and bases can be characterized by strength and softness. To understand the concept, consider a typical acid-base reaction i.e.



Where *A* is the acid, \ddot{B} is the base and *A:B* represents the complex. The equilibrium constant for the reaction (21) can be written as

$$\log K = S_A S_B + \sigma_A \sigma_B \quad (22)$$

Where S_A and S_B represent the strength of acid *A* and base *B*, respectively. The symbol σ_A and σ_B represent the softness of acid *A* and base *B*, respectively. The experimental data showed that class *a* metals form stable complexes with ligands having N, O, or F as the donor site; whereas class *b* metals form stable complexes with ligands having P, S, or Cl like donor atoms. Therefore, Ralph Pearson articulated his observation as given below.

This trend is explainable by the hard-soft acid-base principle which states that hard acid prefers a hard base while soft acid prefers a soft base for binding to yield stable systems.

The typical classification of different species based on hardness or softness is quite useful in the understanding of the chemical reactivity of organic reactions.

➤ Hard and Soft Acids

Metals such as Li^{1+} , Ba^{2+} , Mg^{2+} , and Al^{3+} , which have large negative reduction potential have a lesser tendency to attract electrons, and hence, form stable complexes with highly electronegative groups like N, F, or O so that they become unable to draw the unwanted electron density due to polarization. However, Metals like Pd^{2+} or Pt^{2+} which have large positive reduction potential have a greater tendency to accept electrons and hence form stable complexes with less electronegative groups like P so that they can easily grab the electron density by polarizing the surrounding.

A typical hard acid has a small size, high polarizing power, less distortable outer cloud, and high positive oxidation sometimes. On the other hand, a typical soft acid has a large size, low polarizing power, a highly distortable outer cloud, and zero or low positive oxidation sometimes.

Borderline cases are also identified: borderline acids are trimethylborane, sulfur dioxide and ferrous Fe^{2+} , cobalt Co^{2+} cesium Cs^+ and lead Pb^{2+} cations. It is also very important to mention that the borderline list may vary from book to book it is also medium-dependent.

Table 1. The class *a*, class *b*, and borderline metals.

Hard acid	Soft acid	Borderline acids
H^+ , Li^+ , Na^+ , K^+	Cu^+ , Ag^+ , Au^+ , Tl^+	
Be^{2+} , Mg^{2+} , Ca^{2+} , Sr^{2+}	Hg^{2+} , Pd^{2+} , Pt^{2+}	Mn^{2+} , Fe^{2+} , Co^{2+} , Sr^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+}
Al^{3+} , Ga^{3+} , In^{3+} , Cr^{3+} , Mn^{3+} , Fe^{3+} , Co^{3+} , La^{3+} , Ce^{3+} , Gd^{3+}	Tl^{3+}	
In^{4+} , Zr^{4+} , Hf^{4+} , Th^{4+} , U^{4+} , Pu^{4+}	Pt^{4+}	

➤ **Hard and Soft Bases**

The base becomes more and more soft as the donor atom is selected from the lower part of a particular group in the periodic table. For instance, F^- is the hardest, and I^- is the softest base in its group.

A typical soft base has the donor atom of low polarizability, high electronegativity, high negative charge density, and tightly held electron cloud. On the other hand, a typical soft base the donor atom of high polarizability, low electronegativity, less negative charge density, and loosely held electron cloud.

Borderline cases are also identified: borderline bases are aniline, pyridine, nitrogen N_2 , and the azide, chloride, bromide, nitrate, and sulfate anions. It is also very important to mention that the borderline list may vary from book to book it is also medium-dependent.

Table 2. The hard, soft, and borderline bases.

Hard bases	Soft bases	Borderline bases
F^- , OH^- , F^- , CH_3COO^- , H_2O , SO_4^{2-}	RSH , R_2S , R_3P	$C_6H_5NH_2$
NO_3^- , Cl^- , ROH , R_2O , RO^-	RS^- , I^- , SCN^- , H^- , $(RO)_3P$, CN^- , Alkenes, R^-	N_3^- , Br^- , NO_2^- , N_2
N_2H_4 , NH_3 , RLi , $RMgX$ $RCOOR$, RNH_2		SO_2^{2-}

It is also worthy to mention that hard nucleophiles or hard bases have the highest occupied molecular orbitals (HOMO) of higher energy whereas soft nucleophiles or soft bases have HOMOs of lower energy.

❖ Generation, Structure, Stability and Reactivity of Carbocations, Carbanions, Free Radicals, Carbenes and Nitrenes

A number of chemical reactions proceed via the formation of certain chemical species which are formed somewhere during the overall pathway. These species are called as reaction intermediates and are actual molecules that are short-lived and unstable. Sometimes they are called temporary reactants or products because they are neither present in actual reactants nor the actual products. Here, we will study the generation, structure, stability, reactivity of carbocations, carbanions, free radicals, carbenes, and nitrenes.

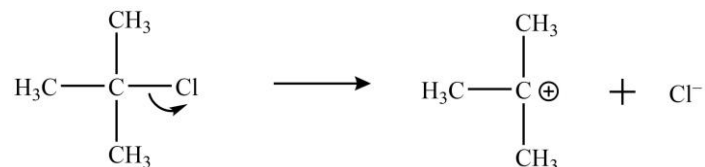
➤ Carbocations

The term carbocations in organic chemistry may simply be defined as the chemical species that carries a positive charge on the carbon with only six valence electrons.

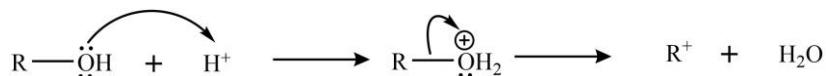
Since the carbon in carbocations has only six electrons, it is electron deficient; and therefore, acts as an electrophile in chemical reactions.

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

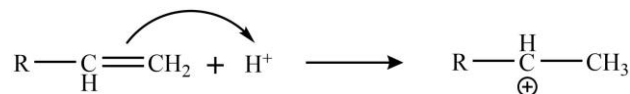
i) Ionization of alkyl halides in polar solvents:



ii) Protonation of alcohols followed by dehydration:



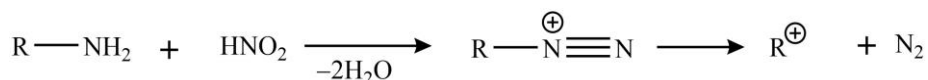
iii) Protonation of unsaturated systems:



iv) Action of super acids on alkyl fluorides:



v) Deamination of primary aliphatic amines by nitrous acid:



2. Structure of carbocations: It has been experimentally found that the 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 a positive charge is in sp^2 hybridization with three hybrid orbitals oriented at 120° in a plane with an empty p_z orbital at the perpendicular.

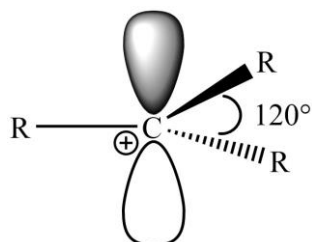
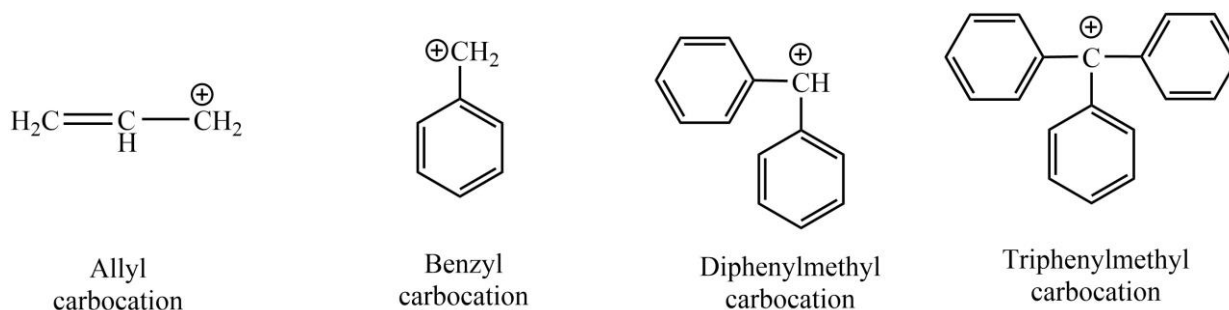


Figure 9. Orbital structure of carbocation.

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



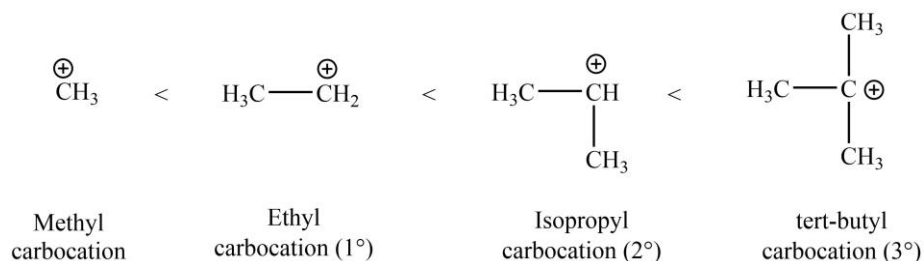
The second case is of unsaturated carbocations where the carbon bearing positive charge is directly connected to a carbon participating in multiple bond i.e.



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.

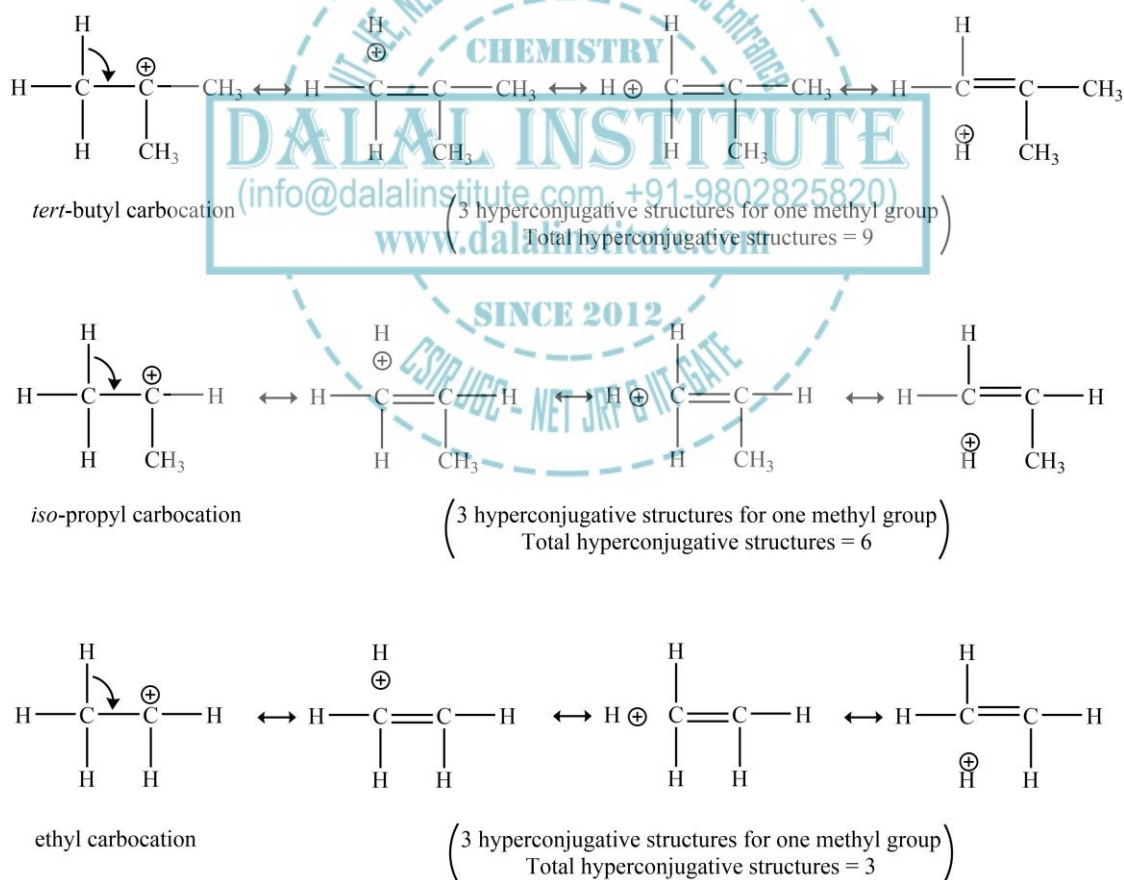
i) Stability of alky carbocations on the basis of inductive effect:

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



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

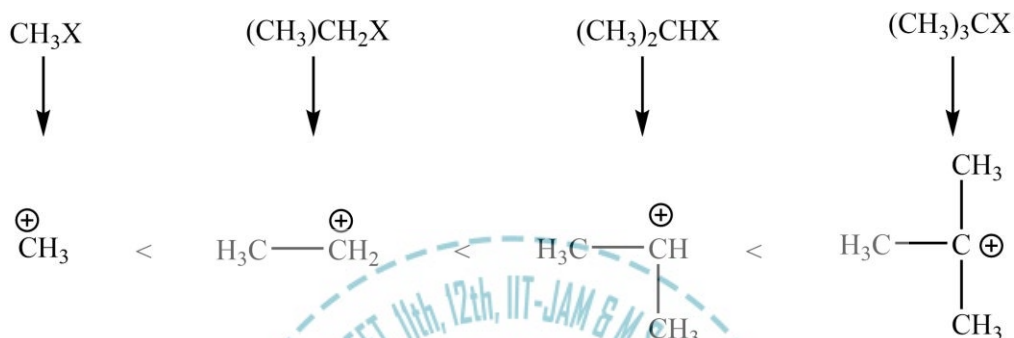
The existence of the hyperconjugation effect can be used to rationalize the relative stability of different carbocations as shown below.



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.

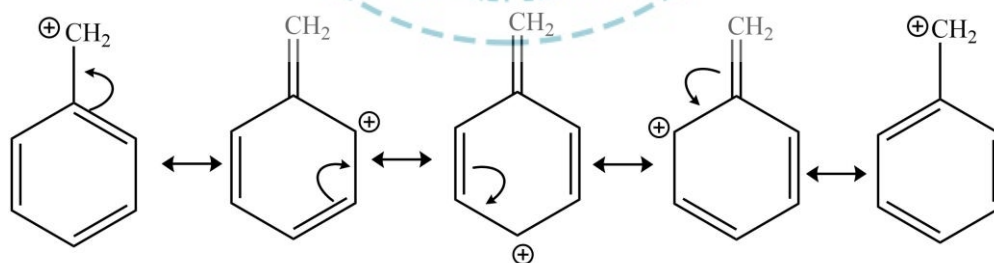
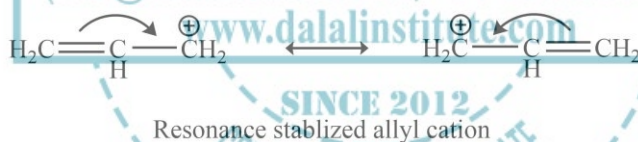
iii) Stability of alkyl carbocations on the basis of steric effect:

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 $109^{\circ}28'$ to 120° . Therefore, the carbon with bulky groups around is expected to get more relief from this carbocationic conversion. The stability order of alkyl carbocations on the basis of steric effect is given below.

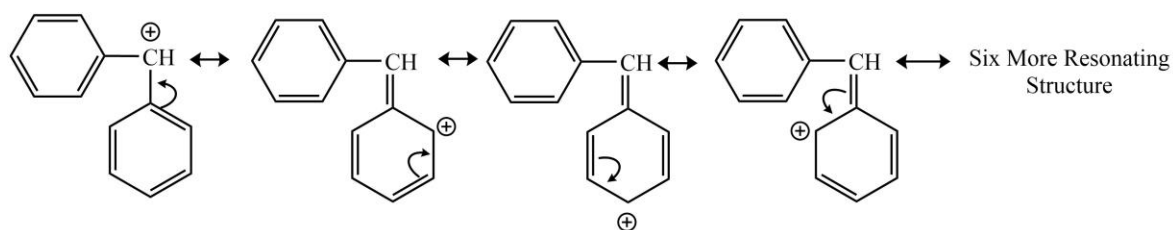


iv) Stability of allyl and benzyl carbocations:

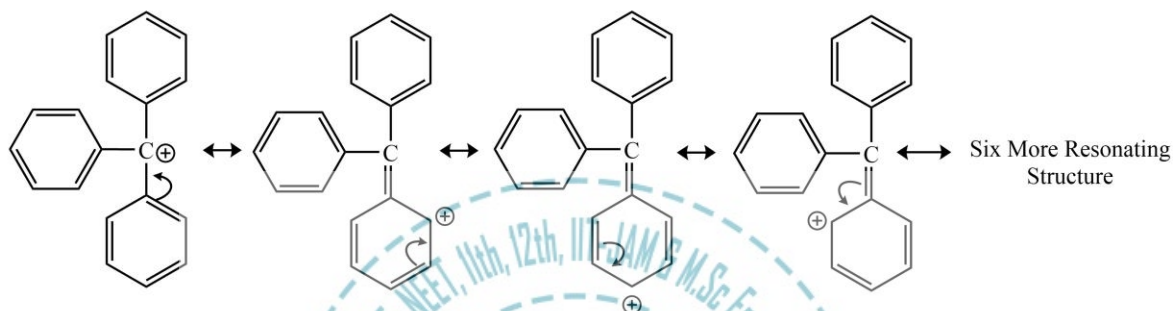
The stability of the carbocations in which the carbon bearing positive charge is adjacent to the double or triple bond can be rationalized in terms of resonance effect. First of all, let us draw the resonance structures allyl and benzyl carbocations.



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 stabilized diphenylmethyl carbocation



Resonance stabilized triphenylmethyl carbocation

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



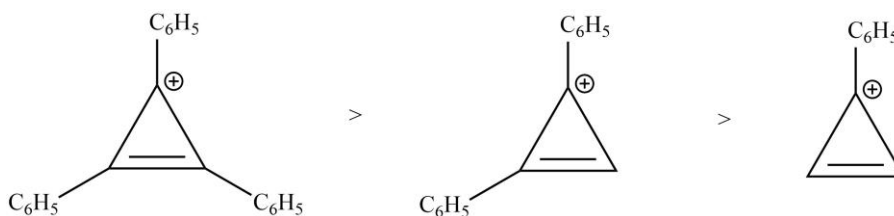
Triphenylmethyl carbocation

Diphenylmethyl carbocation

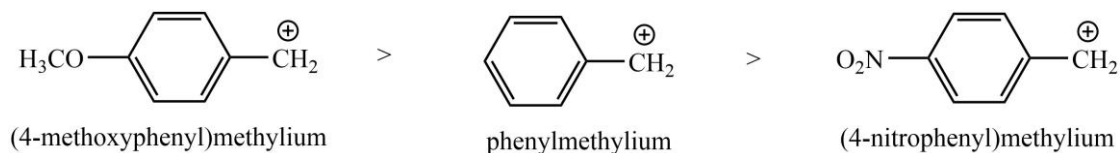
Benzyl carbocation

Allyl carbocation

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



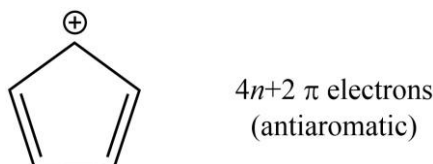
v) *Stability of substituted benzyl carbocations:* Since the carbon with positive charge is electron deficient in nature, any group with +R effect will stabilize the system and vice-versa. The order of stability of some typically substituted carbocations is given below.



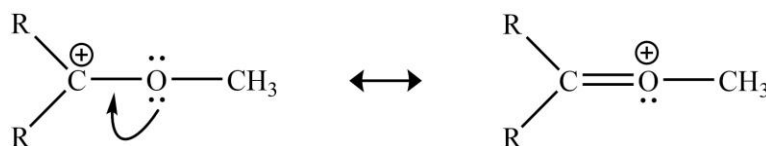
vi) *Stability of tropylium ion:* The cycloheptatrienyl cation or tropylium ion is exceptionally stable due to its aromatic character (planar and $4n+2$ π electrons). According to molecular orbital theory, its delocalization energy is significantly greater than the delocalization energy of its acyclic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



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.

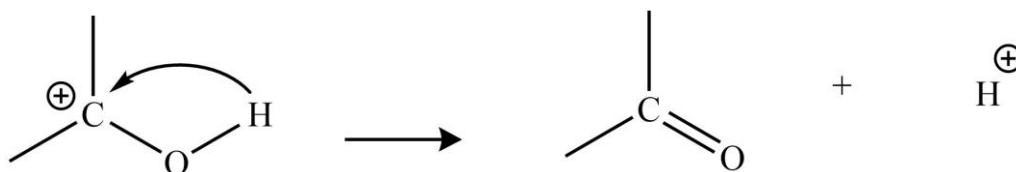


4. Reactivity of carbocations: The principal routes by which the carbocations can react to give rise to stable products are given below.

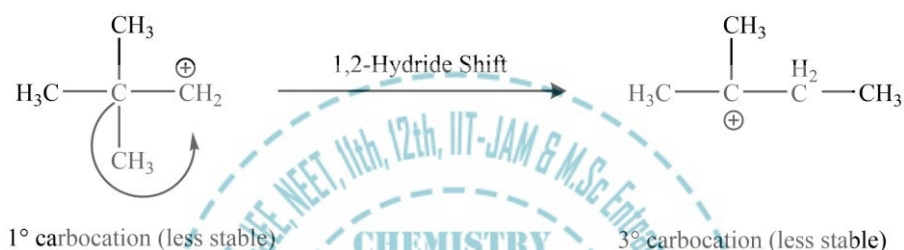
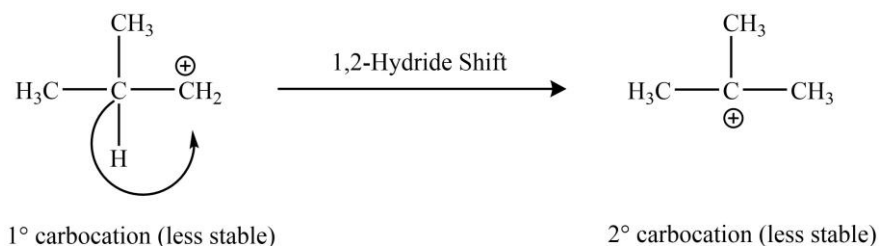
i) *Nucleophilic attack*: In these types of reactions, a carbocation may combine with a species by accepting an electron pair. Furthermore, it should also be noted that if all the three groups on the carbocation are different, a racemic mixture will be obtained.



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 shift 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.



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.



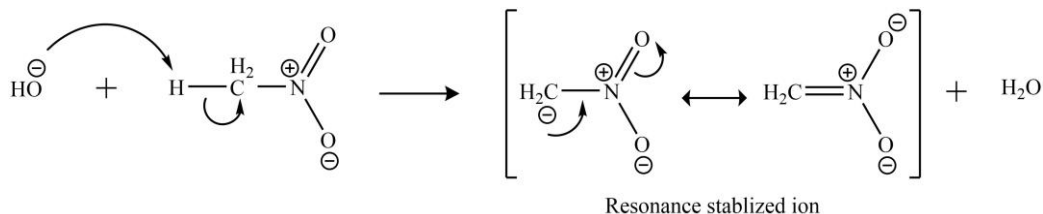
➤ Carbanions

The term carbanions in organic chemistry may simply be defined as the chemical species that carries a negative charge on the carbon with only eight valence electrons.

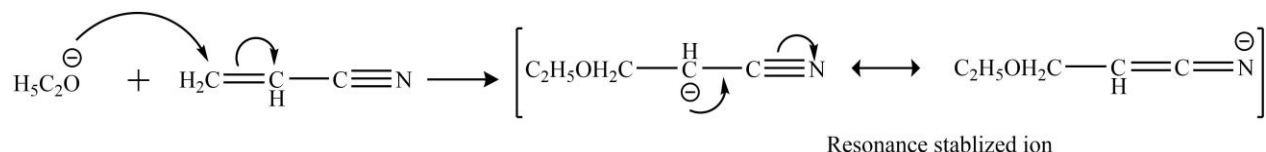
Since the carbon in carbanions has its octet complete, it is electron-rich; and therefore, acts as a nucleophile in chemical reactions.

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

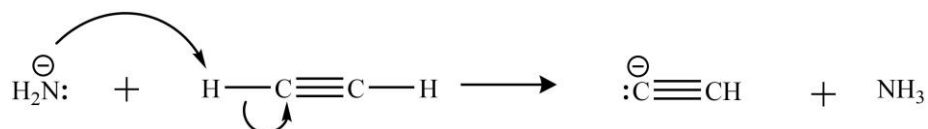
i) *Hydrogen abstraction by a strong base from the carbon alpha to cyano, nitro, or carbonyl groups:*



ii) Nucleophilic addition to α, β -unsaturated species:



iii) Abstraction of terminal hydrogen from acetylene:



2. Structure of carbanions: It has been experimentally found that the carbanions are trigonal pyramidal around the carbon bearing negative 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 a negative charge is in sp^3 hybridization with three hybrid orbitals forming bonds and the fourth hybrid orbital containing lone pair of electrons.



Figure 10. Orbital structure of carbonation.

Furthermore, it should also be kept in mind that if the carbon bearing negative charge is adjacent to multiple bonds, the carbanions will adopt a planar structure to get stable by dispersing the negative charge.

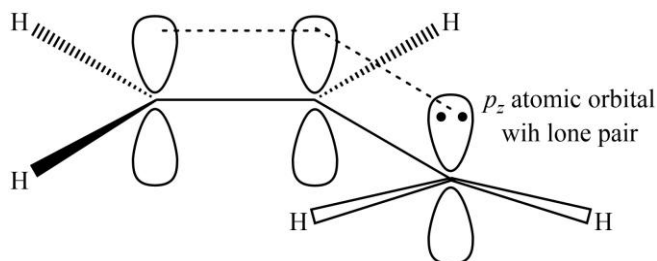
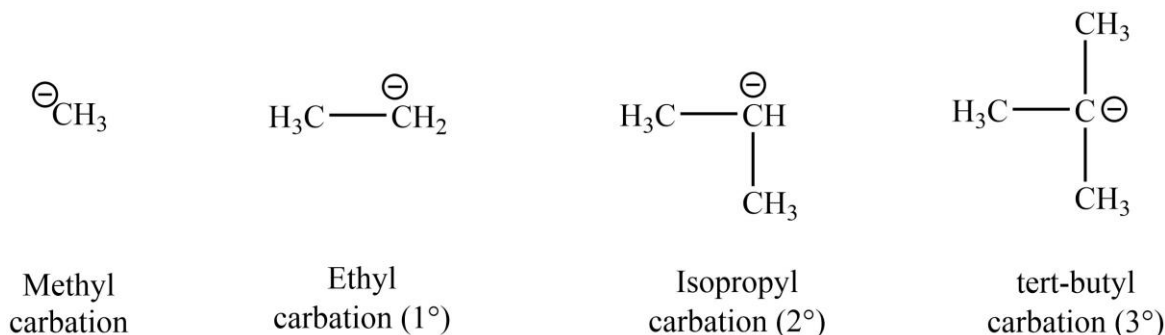
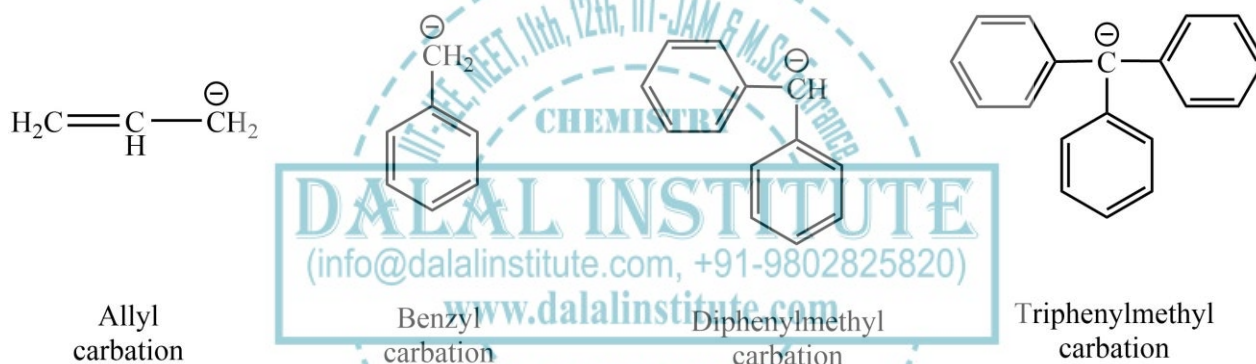


Figure 11. The planar structure of allyl carbanion.

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



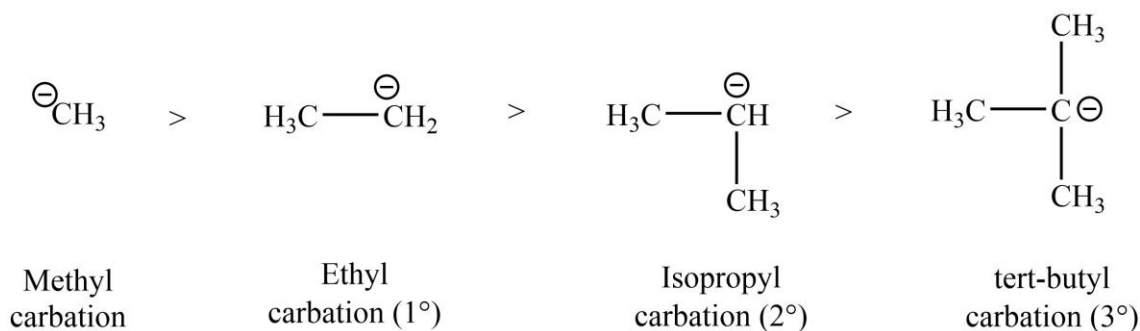
The second case is of unsaturated carbanions where the carbon bearing negative charge is directly connected to a carbon participating in multiple bonds i.e.



Since the carbon in carbanions has eight valence electrons, it is electron-rich; and therefore, any effect that can compensate the electron density accumulation will stabilize the carbanions.

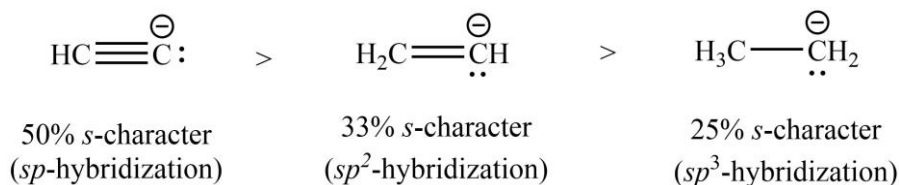
i) Stability of alkyl carbanions on the basis of inductive effect:

Since the alkyl group has an electron donating effect (+I), the stability of the carbanion will increase as the number of donating ability of the attached group increases. The stability order of alkyl carbanions on the basis of inductive effect is given below.



ii) Stability of carbanions on the basis of hybridization:

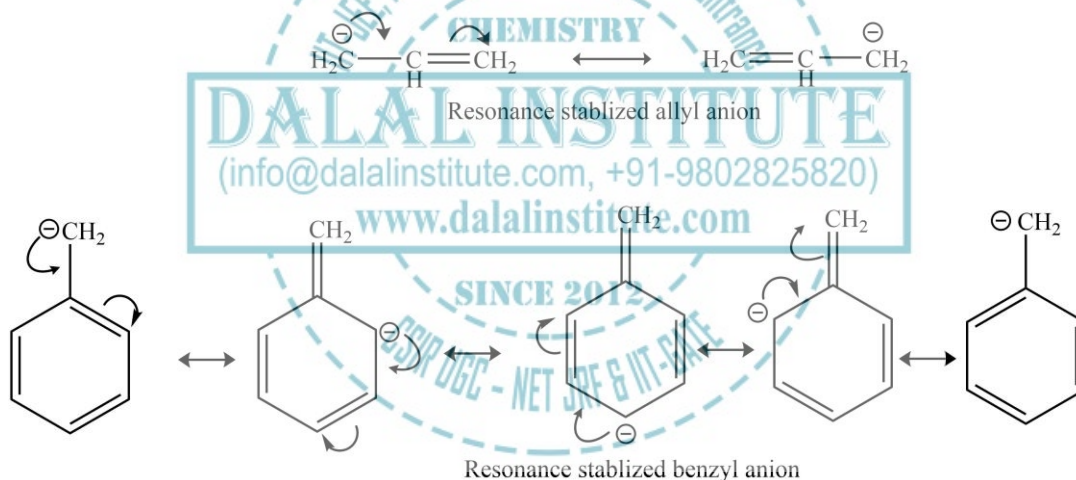
The nature and type of hybridization effect can be used to rationalize the relative stability of different carbanions as shown below.



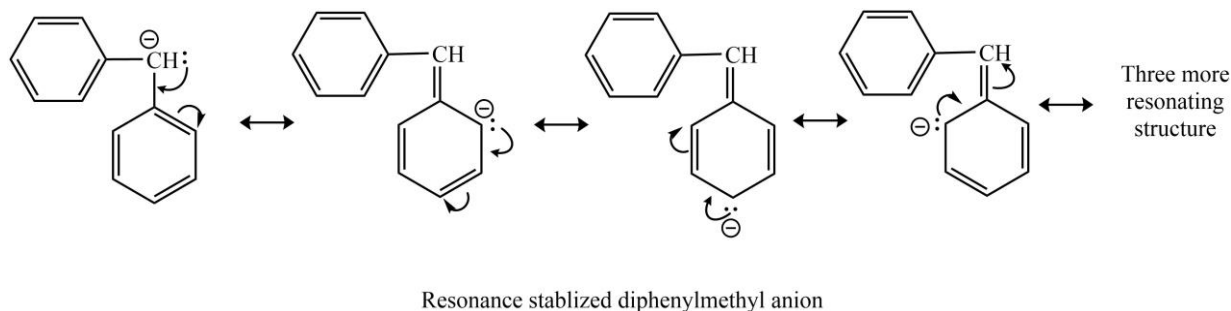
Hence, we can say that as the s-character of carbon bearing negative charge increases, the lone pair gets better stabilization; and therefore, overall carbanionic stability also increases.

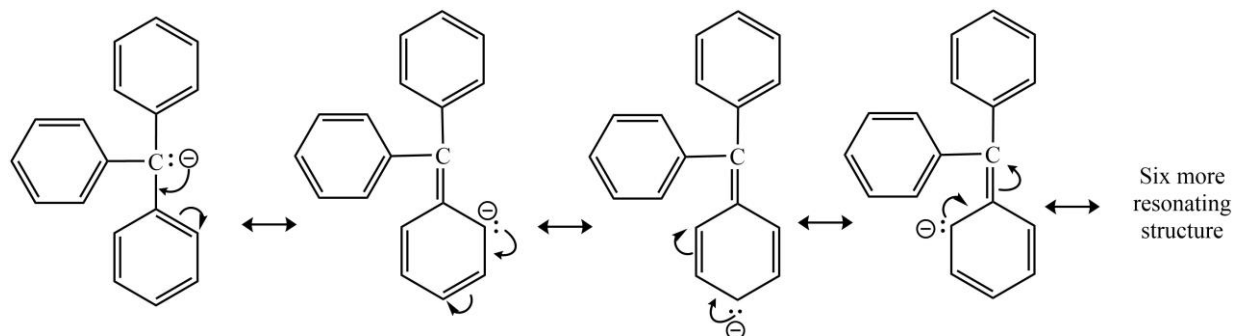
iii) Stability of allyl and benzyl carbanions:

The stability of the carbanions in which the carbon bearing negative 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 of allyl and benzyl carbanions.



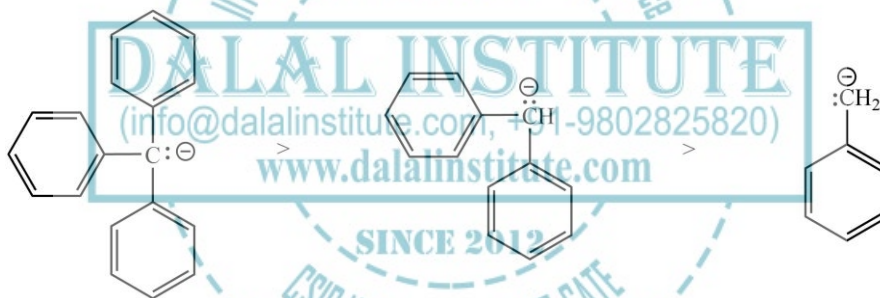
Now, as the number of phenyl groups attached to carbon bearing negative charge increases, the number of resonating structures will also increase, and hence the stability.



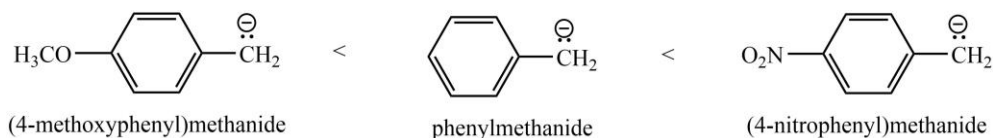


Resonance stabilized triphenylmethyl anion

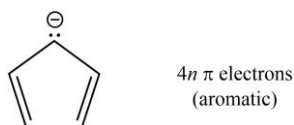
Therefore, the expected order of the stability of unsaturated systems with carbon bearing negative charge should be as given below.



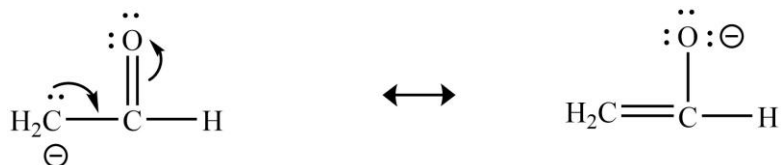
iv) *Stability of substituted benzyl carbanions*: Since the carbon bearing negative charge is electron-rich in nature, any group with $-R$ effect will stabilize the system and vice-versa. The order of stability of some typically substituted carbanions is given below.



v) *Instability of cyclopentadienyl anion*: The cyclopentadienyl anion is very unstable 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.



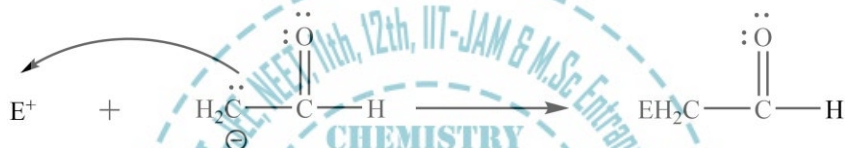
vi) *Stability of carbanions with electron-withdrawing groups:* The presence of electron-withdrawing group will distribute the charge over a wider range; and therefore, will result in a greater stabilization.



Resonance stabilization in acetaldehyde anion

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

i) *Lone pair donation:* One of the most common pathways of carbanions reaction is the donation of electrons to a positive species like proton, or some species with an empty orbital.



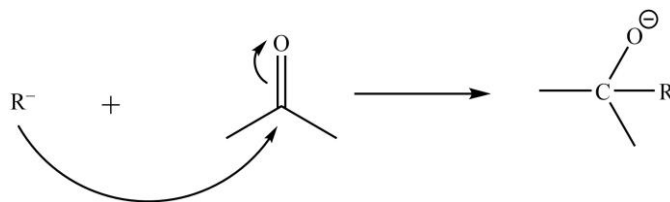
ii) *Associative reaction:* The carbanions can bond with a tetra-coordinated carbon followed by displacement of one of the previously attached groups.



iii) *Rearrangement reaction:* Like carbocations, the carbanions can also undergo rearrangement reaction although it is not very common.



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



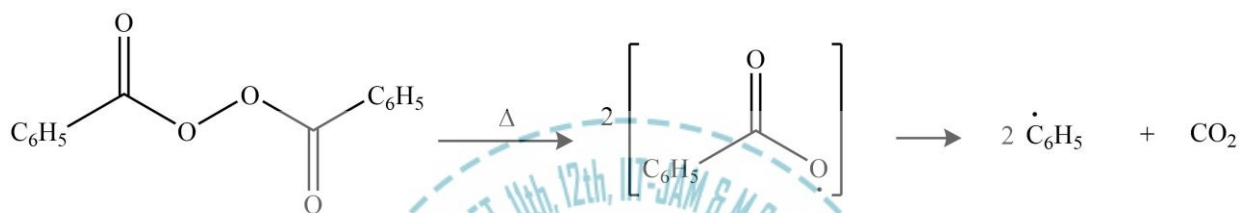
➤ Free Radicals

The term free radicals in organic chemistry may simply be defined as the chemical species that carries odd or unpaired electrons on the carbon with only seven valence electrons.

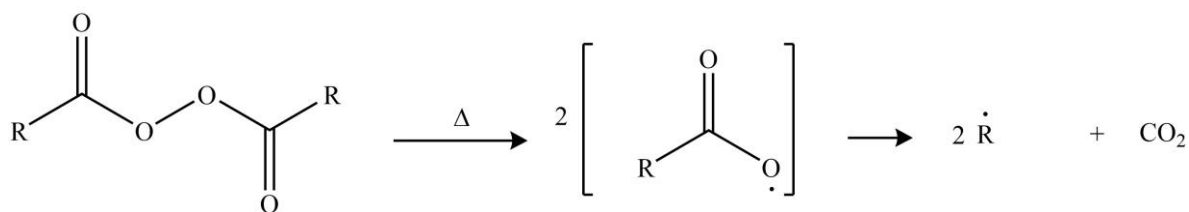
Since the carbon in free radicals has only seven electrons, it is electron deficient; and therefore, acts as an electrophile in chemical reactions.

1. Generation of free radicals: The homolytic cleavage of the covalent bond is responsible for the generation of most of the free radicals species. Some reactions involving the production of free radicals are given below.

i) Thermal cleavage:



ii) Photochemical Cleavage:



2. Structure of free radicals: It has been experimentally found that the free radicals are trigonal planar around the carbon bearing odd electron. 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 odd electron is in sp^2 hybridization with three hybrid orbitals oriented at 120° in a plane perpendicular to p_z orbital occupied by the odd electron.

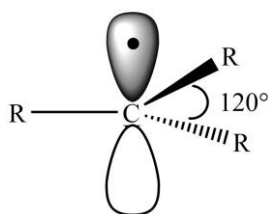
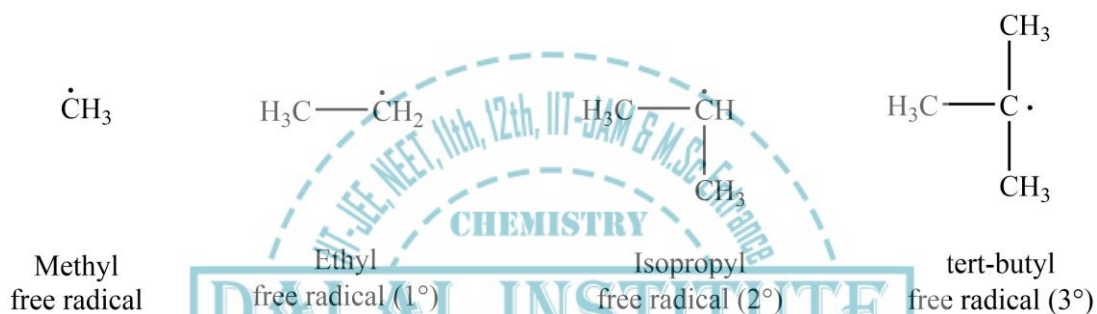
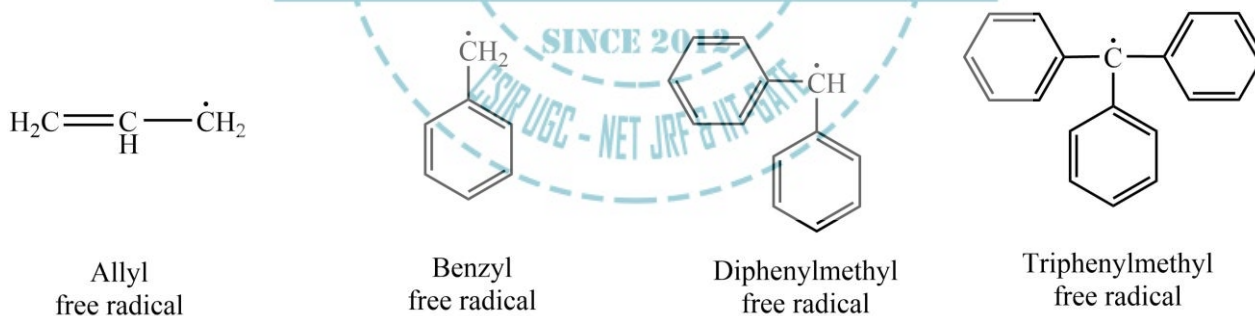


Figure 12. Orbital structure of free radical.

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



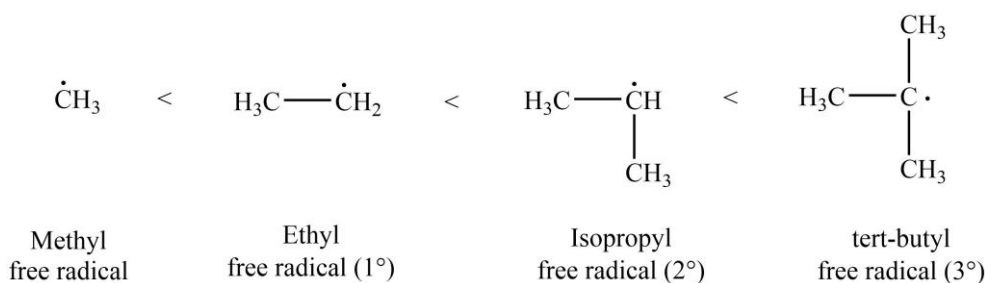
The second case is of unsaturated free radicals where the carbon bearing odd electron is directly connected to a carbon participating in multiple bonds i.e.



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

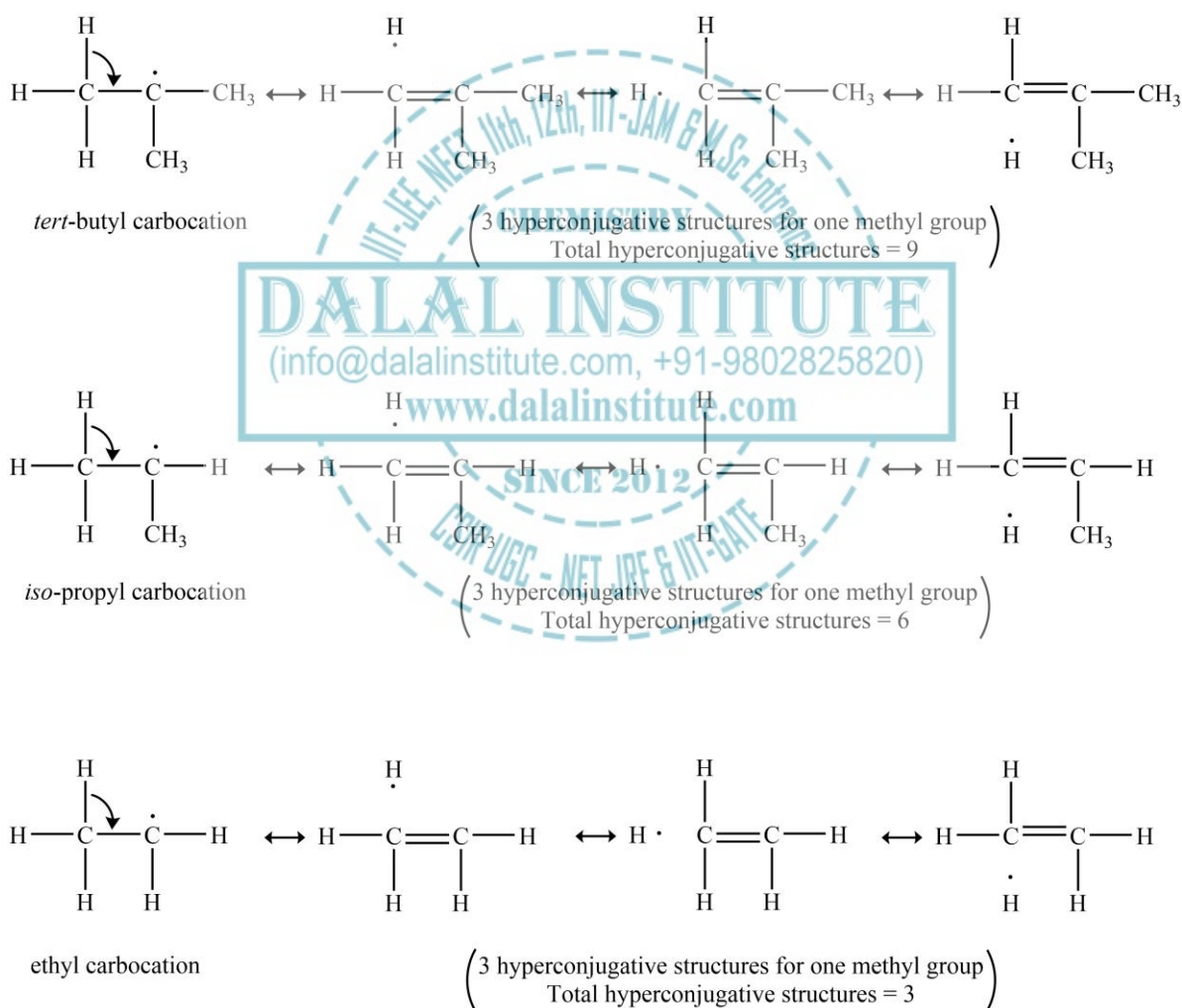
i) Stability of alkyl free radicals on the basis of inductive effect:

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



ii) Stability of alky free radicals on the basis of hyperconjugation:

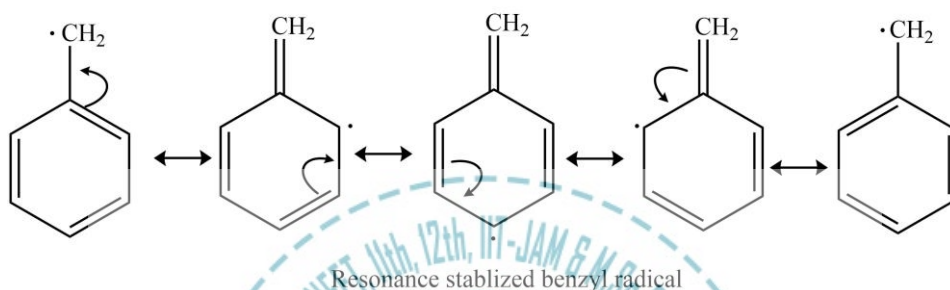
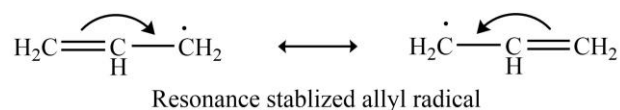
The existence of the hyperconjugation effect can be used to rationalize the relative stability of different free radicals as shown below.



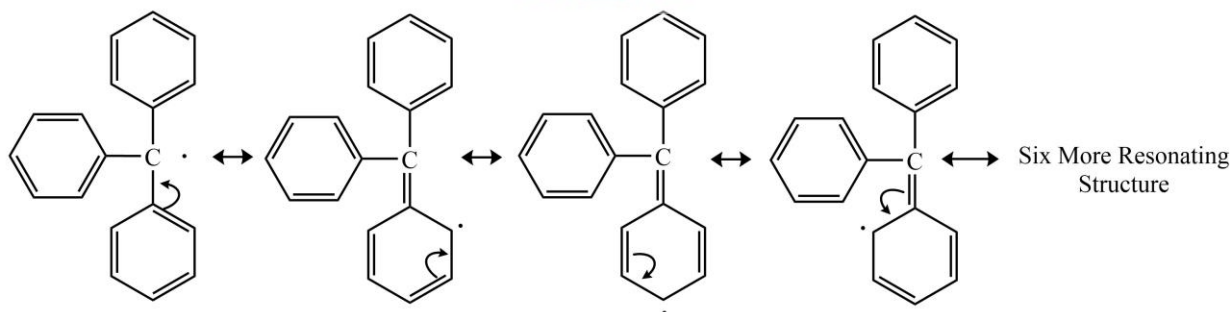
Hence, as far as the number of possible hyper-conjugative structures possible is concerned, tertiary free radicals should be more stable than secondary, which in turn should be more stable than primary.

iii) Stability of allyl and benzyl free radicals:

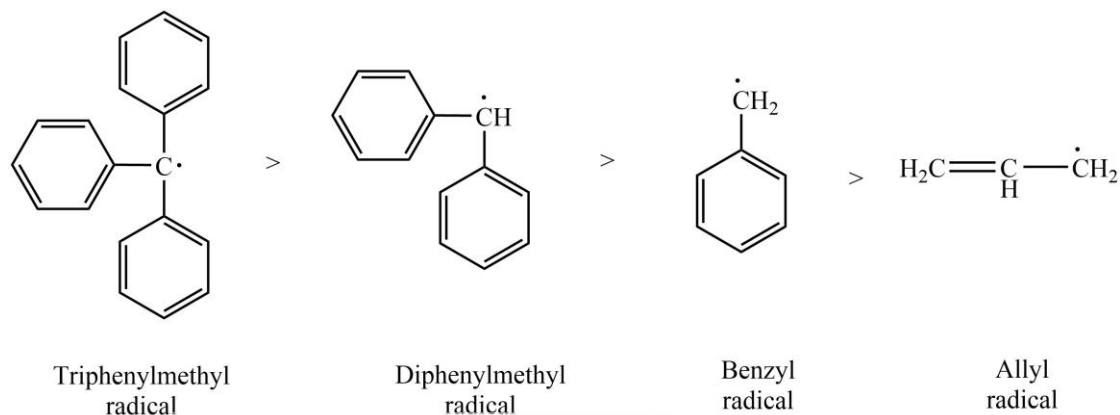
The stability of the free radicals in which the carbon bearing odd electron is adjacent to the double or triple bond can be rationalized in terms of resonance effect. First of all, let us draw the resonance structures of allyl and benzyl free radicals.



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



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



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

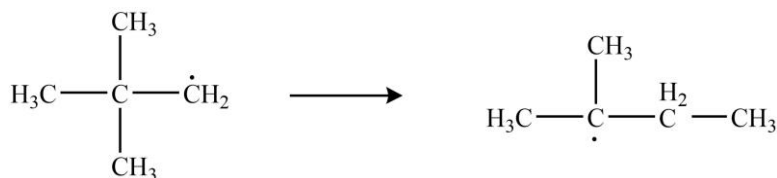
i) *Decomposition reactions:* One of the most common examples of this type of process is the decomposition of the benzyloxy radical.



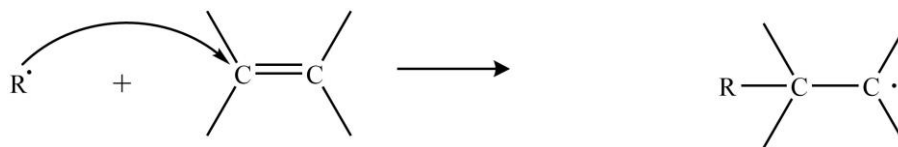
ii) *Hydrogen abstraction:* In these types of reactions, a free radical may result in the removal of a proton from the same (intermolecular process) or another molecule (intramolecular process).



iii) *Rearrangement reaction:* Free radicals may undergo rearrangement reactions to yield different but stable free radical counterparts.



iv) *Addition reactions:* The free radical obtained from an alkene may attack the triangular face of the double bond of another alkene molecule, and the process continues to yield polymers.



➤ Carbenes

The term carbenes in organic chemistry may simply be defined as the chemical species that carries two non-bonding electrons (paired or unpaired) on the carbon with a total of six valence electrons.

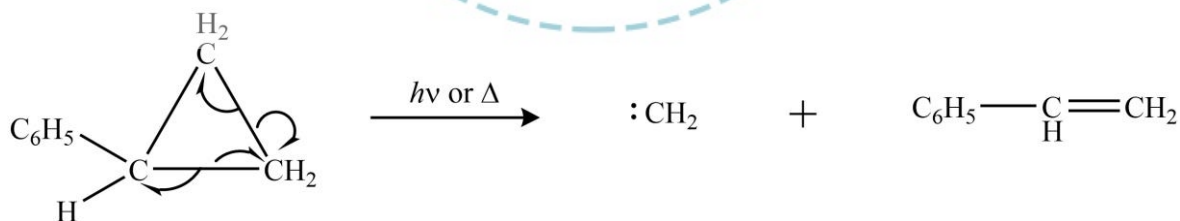
Since the carbon in carbenes has only six electrons, it is electron deficient; and therefore, acts as an electrophile in chemical reactions.

1. Generation of carbenes: Some of the most common pathways involving the production of carbenes are given below.

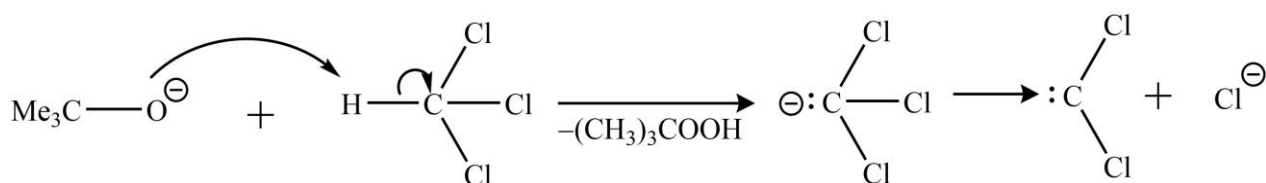
i) *Decomposition of ketones or diazoalkanes:*



ii) *Thermal or photolytic cleavage of cyclopropanes and oxiranes:*



iii) *Attack of strong base on chloroform:*



2. Structure of carbenes: Before we discuss the structure of carbenes, it is better to understand how carbenes can be classified on the basis of the distribution of non-bonding electrons. There are primarily two types carbenes; singlet carbenes and triplet carbenes.

It has been experimentally found that the singlet carbenes are V-shaped and are derivatives of trigonal planar geometry. 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 central carbon is in sp^2 hybridization with three hybrid orbitals oriented at 120° in a plane; two half-filled orbitals participating in bonding whilst the third hybrid orbital contains the lone pair. The p_z orbital remains empty and is perpendicular to the molecular plane.

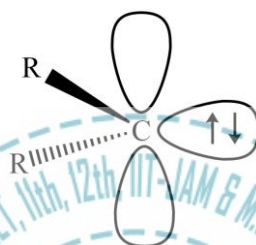


Figure 13. Orbital structure of singlet carbenes.

The triplet carbenes are either linear or V-shaped (depending upon the reaction requirement). 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 central carbon in linear triplet carbene is in sp hybridization with two hybrid orbitals oriented at 180° along the z -axis participating in bonding; whilst the atomic p_x and p_y atomic orbitals containing the unpaired electrons.

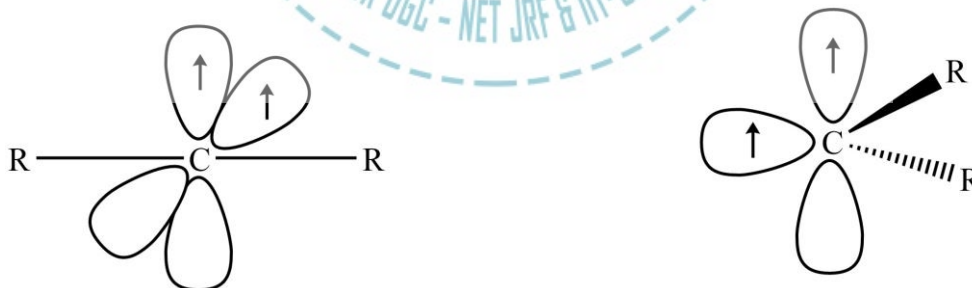
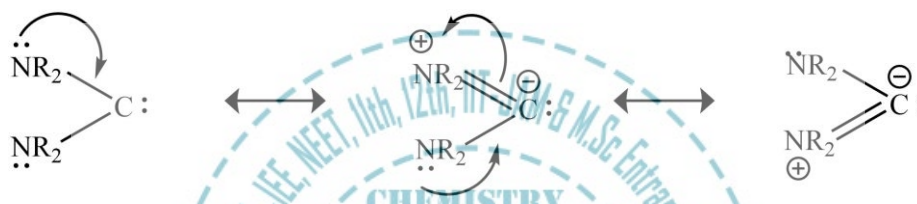


Figure 14. Orbital structure of triplet carbenes.

The central carbon in bent triplet carbene is in sp^2 hybridization with three hybrid orbitals oriented at 120° in a plane; two half-filled orbitals participating in bonding whilst the third hybrid orbital contains an unpaired electron. The other unpaired electron is in the atomic p_z orbital perpendicular molecular plane.

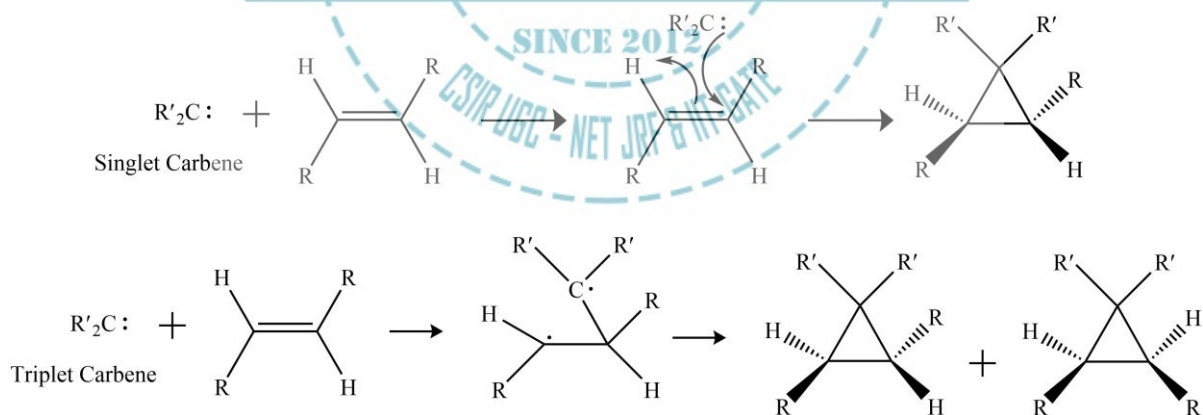
3. Stability of carbenes:

In the case of simple hydrocarbons, triplet carbenes typically have energies 8 kcal/mol less than singlet carbenes due to Hund's rule of maximum multiplicity; and therefore, as a whole, we can conclude that the triplet is the ground state and singlet one is the excited state entities. Also, groups that can donate electron pairs can stabilize the singlet carbene by delocalizing the pair into an empty p_z orbital. Furthermore, the singlet state can become the ground state if its energy is significantly reduced. However, triplet carbenes cannot be stabilized by this strategy. A carbene 9-fluorenylidene is found to exist in a rapid equilibrating mixture of triplet and singlet states with an energy difference of roughly 1.1 kcal/mol. Nevertheless, it is disputed if diaryl carbenes like fluorene carbene are true carbenes since the electrons can be delocalized to such a level that they become biradicals in nature. The experimental studies have suggested that triplet carbenes can be stabilized thermodynamically with heteroatoms of electropositive nature (like in silyl and silyloxy carbenes).

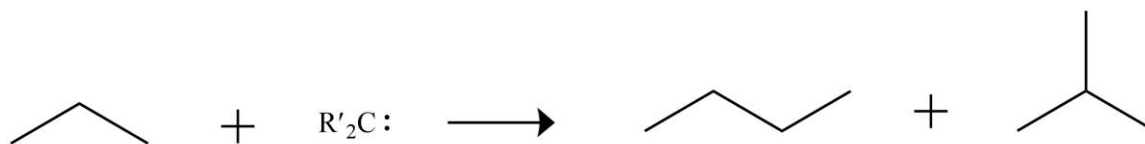


4. Reactivity of carbenes: The principal routes by which the carbenes can react to give rise to stable products are given below.

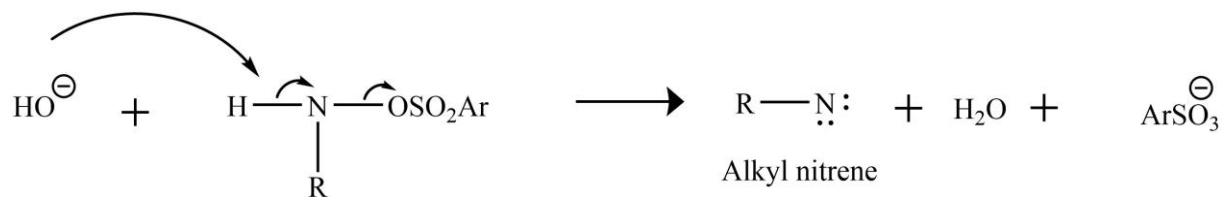
i) *Addition reactions:* besides the carbon-carbon double bonds (including aromatic systems), carbenes may also add to carbon-heteroatom multiple bonds.



ii) *Insertion reaction:* In these reactions, carbenes get inserted into CH bonds to give stable products.



ii) Elimination of sulphonate ion from certain compounds:



2. Structure of nitrenes: Before we discuss the structure of nitrenes, it is better to understand how nitrenes can be classified on the basis of the distribution of non-bonding electrons. There are primarily two types of nitrenes; singlet nitrenes and triplet nitrenes.

It has been experimentally found that the singlet nitrenes are linear and are derivatives of trigonal planar geometry. 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 nitrogen is in sp^2 hybridization with three hybrid orbitals oriented triangularly in a plane; one half-filled hybrid orbital participating in bonding with carbon whilst the second and third hybrid orbitals contain the lone pairs. The p_z orbital remains empty and is perpendicular to the above-mentioned triangular plane.

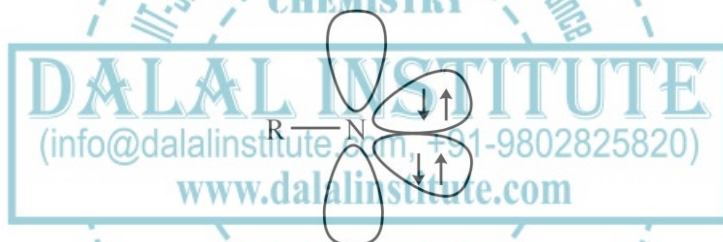


Figure 15. Orbital structure of singlet nitrenes.

The triplet nitrenes are also linear. The nitrogen in triplet nitrenes is in sp hybridization with two hybrid orbitals oriented at 180° along the z -axis; one hybrid orbital (half-filled) participating in bonding whilst the other hybrid orbital contains a lone pair. The atomic p_x and p_y atomic orbitals containing the unpaired electrons.

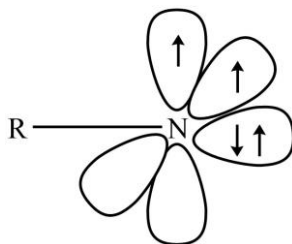
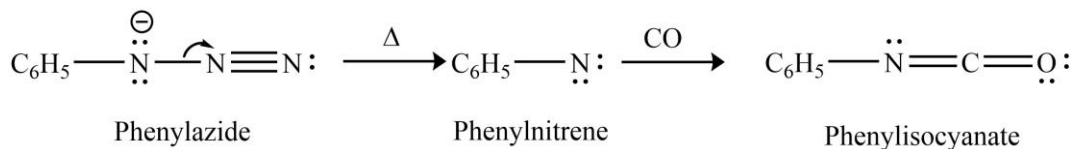


Figure 16. Orbital structure of triplet nitrenes.

3. Stability of nitrenes:

Although nitrenes are too reactive to isolate under normal conditions, in 2019, an authentic triplet nitrene was isolated by Betley and Lancaster, stabilized by coordination to a copper center in a bulky ligand. Furthermore, triplet nitrenes are thermodynamically more stable but react stepwise allowing free rotation and thus producing a mixture of stereochemistry. They are usually detected by adding carbon monoxide as it can form isocyanates with nitrenes which can be isolated easily.



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

i) *Addition reactions:* Nitrenes may add to carbon-carbon multiple bonds to give rise to some stable product.



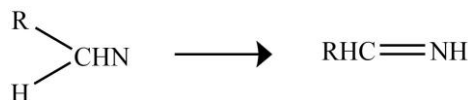
ii) *Insertion reaction:* In these types of reactions, nitrenes get inserted into CH bonds to give stable products.



iii) *Dimerization reaction:* Nitrenes may undergo dimerization to form diamide.



iv) *Rearrangement reactions:* The nitrenes can also undergo rearrangement reactions to yield very stable products as given below.



v) *Hydrogen abstraction:* Nitrenes are also able to abstract hydrogen or any other groups or atoms to yield free radicals' as given below.

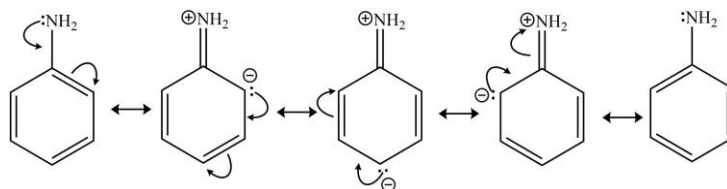


❖ Effect of Structure on Reactivity

When chemical equations are used to represent chemical reactions, functional groups are usually represented as a condensed formula because all the compounds with a particular functional group give more or less the same products. It enables us to categorize a large number of reactions in the same class for a better understanding and memorization. However, it must be kept in mind that two compounds with the same functional group may react in an entirely different manner because the structure of the rest of the molecule affects the overall reactivity at the corresponding functional group. Moreover, even if the two compounds with the same functional group undergo the same reaction, their rate rates may be slightly or largely different. The effects of molecular structure on the overall reactivity can be fragmented into three main classes; resonance or mesomeric effect, inductive effect, and steric effect. Now although we see a combined result of two or all three phenomena in most of the cases; it is still possible to extract information about their individual effects. A brief idea of all the three effects of molecular structure on reactivity is discussed below.

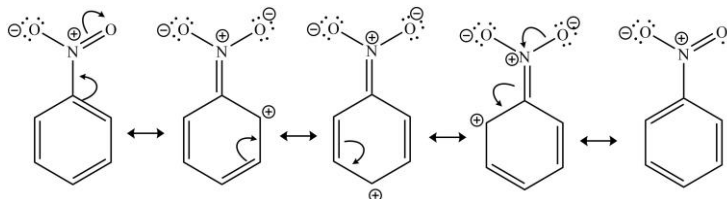
➤ Impact of Resonance Effect on Reactivity

The resonance or mesomeric effect in organic compounds may affect the reactivity up to a great as it can produce polarity by creating centers of high and low electron density. For instance, +R groups increase the electron density at *o*- and *p*- positions making them more susceptible to attacking electrophile.



It is also worthy to mention that groups showing the +R effect are having lone pair of electrons that can be put into conjugation with the double of the chain or ring to which it gets attached with. Some of the typical groups showing +R effect are $\text{O}^- > \text{NH}_2 > \text{NHR} > \text{OR} > \text{NHCOR} > \text{OCOR} > \text{Ph} > \text{F} > \text{Cl} > \text{Br} > \text{I}$

Similarly, groups with the –R effect tends to decrease the electron density at *o*- and *p*- positions in the benzene ring making the *m*-position more susceptible towards attacking electrophile.

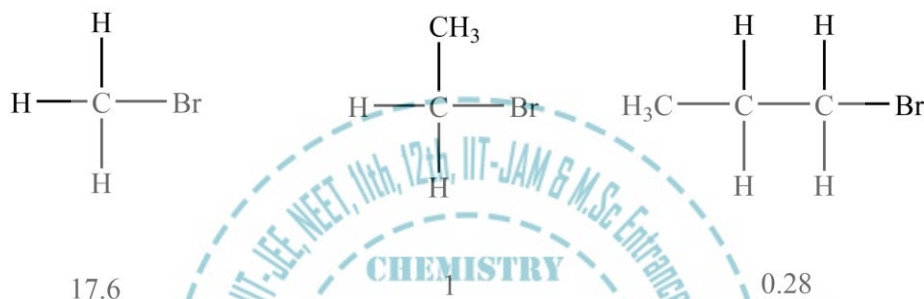


It is also worthy to mention that groups showing the –R effect are having a double bond that can be put into conjugation with the double of the chain or ring to which it gets attached with. Some of the typical groups showing –R effect is $\text{NO}_2 > \text{CN} > \text{S(=O)}_2\text{OH} > \text{CHO} > \text{C=O} > \text{COCOR} > \text{COOR} > \text{COOH} > \text{CONH}_2 > \text{COO}^-$. It is also worthy to recall that the alkyl groups, which do not have multiple bonds or unshared pairs, can also show the +M effect due to hyperconjugation.

➤ **Impact of Inductive Effect on Reactivity**

The inductive effect in organic compounds may affect the reactivity up to a greater as it can produce polarity by its electron-donating or electron-withdrawing ability. For instance, groups with the +I effect tend to increase the electron density and making them less or more stable or susceptible to attacking electrophile. Relative inductive effects have been experimentally measured with reference to hydrogen, in increasing order of +I effect or decreasing order of -I effect, as follows:

$-\text{NH}_3^+ > -\text{NO}_2 > -\text{SO}_2\text{R} > -\text{CN} > -\text{SO}_3\text{H} > -\text{CHO} > -\text{CO} > -\text{COOH} > -\text{COCl} > -\text{CONH}_2 > -\text{F} > -\text{Cl} > -\text{Br}$
 $> -\text{I} > -\text{OR} > -\text{OH} > -\text{NR}_2 > -\text{NH}_2 > -\text{C}_6\text{H}_5 > -\text{CH}=\text{CH}_2 > -\text{H}$ and $\text{C}-\text{H} < \text{C}-\text{D} < \text{C}-\text{T}$ in increasing order of +I effect, where H is Hydrogen and D or T are hydrogen's isotopes.



Relative rates of reaction of RBr with ethanol

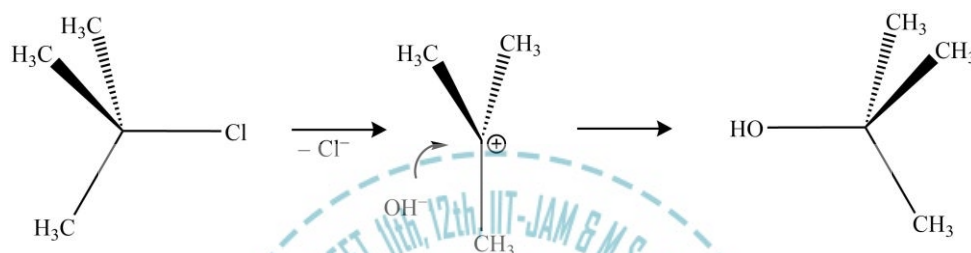
The inductive effect is extremely useful to describe the molecular stability depending on the sign and magnitude of the charge present on the atom and the substituent that is attached to this atom. For instance, if an atom carries a positive charge and binds to a group with -I effect, its charge becomes 'boosted' and the molecule tends to be less stable. Likewise, if an atom carries a negative charge and binds to a group with +I effect, its charge will also get 'amplified' making it less stable. Conversely, if an atom has a positive charge and binds to a +I effect, its charge will get 'de-boosted' and therefore, the molecule will become more stable. Similarly, if an atom has a negative charge and is attached to a -I group its charge becomes 'de-amplified' and the molecule will get more stable. The attribution can be found for such behavior in the fact more charge on an atom cuts stability and less charge on an atom raises the stability.

The basicity and acidity of a molecular species are also affected by the inductive effect. If substituents with +I inductive effect are attached to a molecule, the electron density at the donor site increases, which in turn, makes it more basic. Likewise, if substituents with -I inductive effect are attached to a molecule, the electron density at the acceptor site decreases, which in turn, makes it more acidic. Furthermore, the acidity also increases as the number of -I groups attached to a molecule increases; and the same is true for bases since the increased number of +I groups on a molecule increases its basicity.

It is also worthy to recall that some groups can also affect the reactivity in the same way as an effect but through space i.e. field effect.

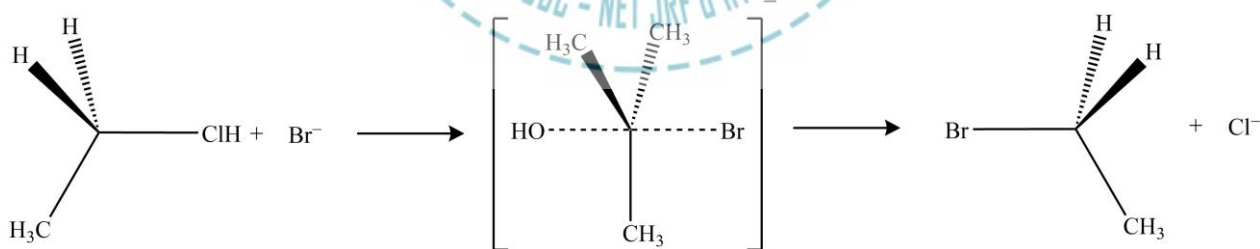
➤ **Impact of Steric Effect on Reactivity**

The steric effect in organic compounds may affect the reactivity up to a greater extent by affecting the stability of reactants, intermediates, or transition states. These effects are primarily of nonbonding interactions that affect the reactivity and conformation of various ions and molecules. Also, these effects also couple with electronic effects which usually govern reactivity and shape. Steric effects primarily arise from repulsive interactions between overlapping electronic clouds. These effects are largely employed in academic and applied chemistry for many purposes. For instance, the reaction-rate increases with the increase in bulky groups in the S_N1 pathway.



Steric effects also give rise to steric hindrance which slows down the chemical reactions due to bulk presence. Nevertheless, it should be kept in mind that steric hindrance is primarily an intermolecular phenomenon, whilst the dialogue of steric effects usually emphasizes intramolecular interactions. The steric hindrance is mainly employed to dictate the reaction selectivity like slowing down unwanted concurrent reactions.

Also, the steric hindrance between *cis* substituents can disturb the torsional bond angles; and is responsible for the observed profile of rotaxanes and the small rates of racemization of compounds like 2,2'-disubstituted biphenyls and their derivatives. The rate of reaction also increases with the decrease in the number size of bulky groups in the S_N2 pathway.



Comparative reaction rates give a very useful vision into the effects of the steric bulk of different groups. When standard experimental conditions were used, the solvolysis of methyl bromide is 10^7 times faster than what in neopentyl bromide. The variance shows the oppose of attack on the substrate with the sterically bulky $(CH_3)_3C$ substituent. These values (resulting from equilibrium measurements of monosubstituted cyclohexanes) provide another measure of the bulk of various substituents. Also, the bulk of a substituent can be measured by the extent that it favors the equatorial position.

❖ The Hammett Equation and Linear Free Energy Relationship

In this section, we will discuss the quantitative treatments of the effect of structure on reactivity i.e. how the resonance effect, field-effect, and steric effect impact the reaction rate in measurable numbers.

➤ The Hammett Equation

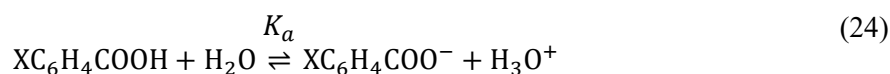
Consider an organic reaction is carried out on a substrate which can be denoted as XRY, X a variable substituent and Y is the reaction spot, and R represents the basic substrate structure. In this type of case, replacing X = H with X = CH₃ results in an increment in the rate of reaction up ten times. However, it is still a mystery what part of the rate enhancement comes from resonance effect, field-effect, or steric effect. To do so, it is reasonable to use compounds where one or two effects are so small that they simply can be neglected. Although it is the oversimplification of the problem, quantitative results can still be obtained. The Hammett equation is the first attempt to give numerical values for the quantitative treatment of structure on reactivity. Hammett proposed the equation for the cases of *m*- and *p*-XC₆H₄Y as given below.

$$\log \frac{k}{k_0} = \sigma \rho \quad (23)$$

where *k* and *k*₀ are the constant for the group X ≠ H and X = H; ρ and σ are the constants for reaction conditions and substituent X, respectively.

➤ Derivation of Hammett Equation

To derive the Hammett equation, we need to recall the quantitative relationship between the structure and reactivity first. To do so, we need to find some mathematical parameter that can be used to represent the combined magnitude of inductive and resonance effects of different substituents. This can be achieved by considering the hydrolysis of a series of different benzoic acids as given below.



Where X is a substituent at the *m*- or *p*-position and *K*_a is the dissociation constant. As expected, the dissociation constant was found to be different for differently substituted substrates.

Since an electron-withdrawing group will better stabilize the conjugate base (i.e., XC₆H₄COO⁻), resulting in a larger magnitude of *K*_a (lower *pK*_a). On the other hand, an electron-donating group will destabilize the conjugate base (i.e., XC₆H₄COO⁻), resulting in a smaller magnitude of *K*_a (higher *pK*_a). Therefore, we can say that the electronic effect (inductive plus mesomeric effect) of a substituent can be represented as the difference between the *pK*_a value of its benzoic acid derivative and the *pK*_a value of benzoic acid itself; mathematically, we can say

$$\sigma_X = \log(K_a) - \log(K_a)_0 = -p(K_a) + p(K_a)_0 \quad (25)$$

Where the parameter σ_X (or simply σ) is called as substituent constant; and was found for several different groups just subtracting its benzoic acid derivative's *pK*_a value from *pK*_a value of benzoic acid.

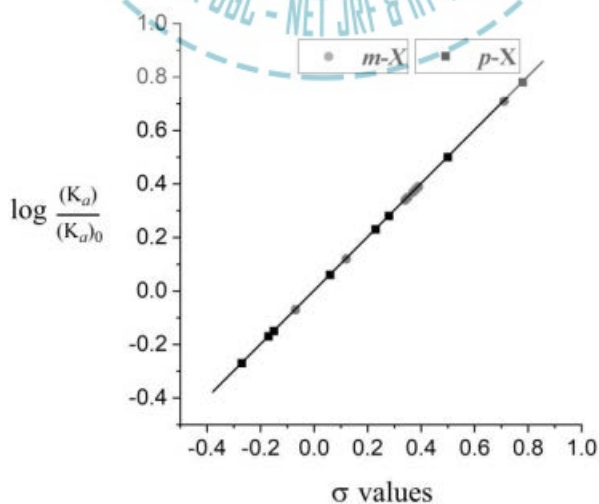
Table 1. pK_a values and substituent constants for $\text{XC}_6\text{H}_4\text{COOH}$ using benzoic acids $p(K_a)_0 = 4.21$.

Substituent	$p_m(K_a)$	$p_p(K_a)$	$\sigma_m = p(K_a)_0 - p_m(K_a)$	$\sigma_p = p(K_a)_0 - p_p(K_a)$
NO_2	3.50	3.43	0.71	0.78
CH_3	4.28	4.38	-0.07	-0.17
OCH_3	4.09	4.48	0.12	-0.27
$\text{CH}(\text{CH}_3)_2$	4.28	4.36	-0.07	-0.15
F	3.87	4.15	0.34	0.06
Br	3.82	3.98	0.39	0.23
Cl	3.84	3.98	0.37	0.23
I	3.86	3.93	0.35	0.28
COCH_3	3.83	3.71	0.38	0.50

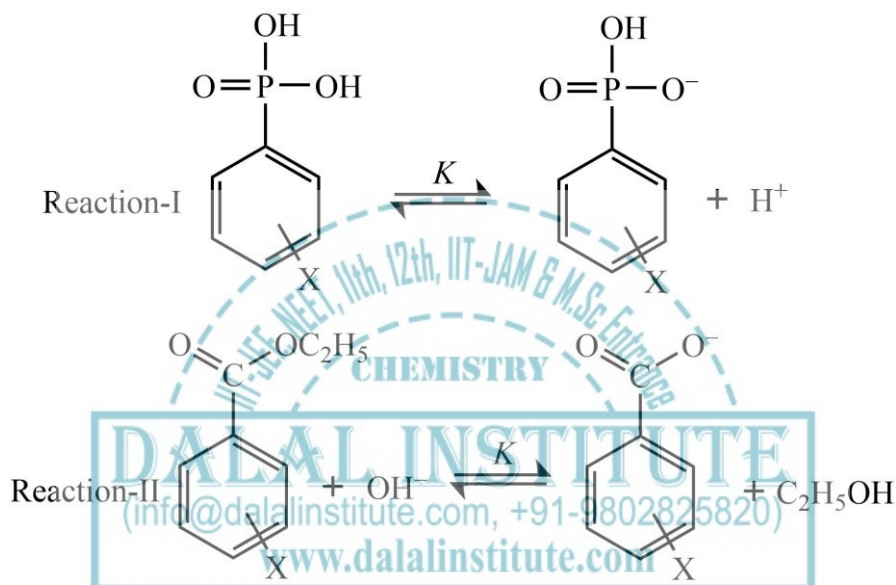
Using $\log m - \log n = \log m/n$, equation (36) can also be written as

$$\log \frac{(K_a)}{(K_a)_0} = \sigma \quad (26)$$

Now if we plot a curve between $\log(K_a)/(K_a)_0$ vs σ , we will definitely get a straight line with a slope = 1.

Figure 17. Variation of $\log(K_a)/(K_a)_0$ vs σ for substituted benzoic acids.

Now we need to check if these σ values (i.e., of substituted benzoic acids) can also be used for other meta- or para-substituted benzene derivatives. To do so, consider two series of reactions; the first one is the acid dissociation of phenyl phosphonic acid, and the second one is the base hydrolysis of substituted ethyl benzoate. Here we will find if different substituents affect their dissociation constants or rates in the same manner as affected in the case of substituted benzoic acid. Also, we did not use ortho-substituents or substituents in the aliphatic system because they also contain steric factors and don't not linear variation.



The experimental $\log(K_a)/(K_a)_0$ for the reaction-I and experimental $\log k/k_0$ for reaction-II are given below.

Table 2. Experimental values of $\log(K_a)/(K_a)_0$ and $\log k/k_0$ for the acid dissociation of phenyl phosphonic acid and base hydrolysis of substituted ethyl benzoates, respectively.

Substituent	<i>meta</i> - $\log(K_a)/(K_a)_0$	<i>para</i> - $\log(K_a)/(K_a)_0$	<i>meta</i> - $\log k/k_0$	<i>para</i> - $\log k/k_0$
NO ₂	0.53	0.59	1.83935	2.06423
Br	0.29	0.23	–	–
Cl	0.28	0.17	0.88536	0.63347
CH ₃	–	–0.15	–0.16115	–0.34679
OCH ₃	–	–	–	–0.67923

When plotted the experimental $\log(K_a)/(K_a)_0$ for the reaction-I and experimental $\log k/k_0$ for reaction-II vs the substituent constants obtained for the substituted benzoic acids, we get the following curves.

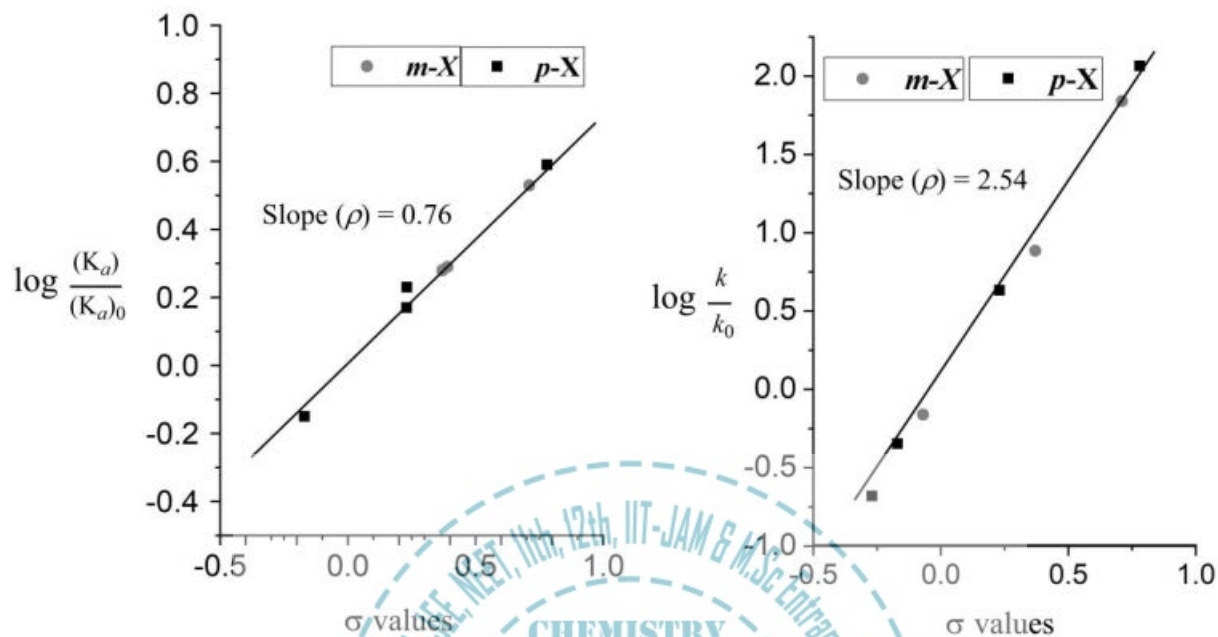


Figure 18. $\log(K_a)/(K_a)_0$ and $\log k/k_0$ vs σ for reaction-I and reaction-II.

It is obvious that the plots are still linear like in Figure 3 but the slope has changed. This implies that the order and relative effects for different substituents on both reactions remain the same though the magnitude has been changed which can be attributed to the different nature reaction considers from 'base reaction'.

Therefore, our aim, in this case, should be the determination of the slope (let us say ρ). Since on the vertical side we have ' $[\log(K_a)/(K_a)_0]_{sppa}$ ' for reaction-I (acid dissociation of phenyl phosphonic acid) and on the horizontal side we have ' σ or $[\log(K_a)/(K_a)_0]_{sba}$ ' for base reaction (hydrolysis of substituted benzoic acid), the slope should be

$$\rho = \frac{[\log(K_a)/(K_a)_0]_{seb}}{[\log(K_a)/(K_a)_0]_{sba}} \quad (27)$$

or

$$\rho[\log(K_a)/(K_a)_0]_{sba} = [\log(K_a)/(K_a)_0]_{seb} \quad (28)$$

But from equation (26), we know that $[\log(K_a)/\log(K_a)_0]_{sba} = \sigma$; and therefore, equation (40) takes the form

$$\left[\log \frac{(K_a)}{(K_a)_0} \right]_{seb} = \rho \sigma \quad (29)$$

For any reactions,

$$\log K_a = \rho\sigma - \log (K_a)_0 \quad (30)$$

Similarly, on the vertical side we have ‘ $\log k/k_0$ ’ for reaction-II (base hydrolysis of substituted ethyl benzoate) and on the horizontal side we have ‘ σ or $[\log(K_a)/(K_a)_0]_{sba}$ ’ for base reaction (hydrolysis of substituted benzoic acid), the slope should be

$$\rho = \frac{[\log k/k_0]_{seb}}{[\log(K_a)/(K_a)_0]_{sba}} \quad (31)$$

or

$$\rho[\log(K_a)/(K_a)_0]_{sba} = [\log k/k_0]_{seb} \quad (32)$$

But from equation (26), we know that $[\log(K_a)/\log(K_a)_0]_{sba} = \sigma$; and therefore, equation (32) takes the form

$$\left[\log \frac{k}{k_0} \right]_{sppa} = \rho\sigma \quad (33)$$

For any reactions,

$$\log k = \rho\sigma - \log k_0 \quad (34)$$

The results given by equation (29, 30, 33, 34) are called as Hammett's equations; which shows that the rates of ortho and para-substituted benzene derivatives can be obtained if the substituent contents for substituted benzoic acid are known. Now we will discuss the substituent and reaction constants in more detail

➤ Linear Free Energy Relationship (LFER)

The Hammett equation is a linear free energy relationship that can be proved for any group X by recalling the kinetics of organic reactions is in the framework of “Activated complex Theory”, which states that the rate constant (k) for a typical reaction is

$$k = \frac{RT}{Nh} e^{-\frac{\Delta G^*}{RT}} \quad (35)$$

Where ΔG^* is the free energy change of the activation step at temperature T. The symbols R , N , and h are the gas constant, Avogadro number, and Planck's constant, respectively. Similarly, for k_0 we have

$$k_0 = \frac{RT}{Nh} e^{-\frac{\Delta G_0^*}{RT}} \quad (36)$$

After putting the value of equation (35) and equation (36) in Hammett equation (23), we get

$$\log \frac{\frac{RT}{Nh} e^{-\frac{\Delta G^*}{RT}}}{\frac{RT}{Nh} e^{-\frac{\Delta G_0^*}{RT}}} = \sigma\rho \quad (37)$$

$$\log \frac{e^{-\frac{\Delta G^*}{RT}}}{e^{-\frac{\Delta G_0^*}{RT}}} = \sigma\rho \quad (38)$$

Multiplying both sides by 2.303, we have

$$2.303 \log \frac{e^{-\frac{\Delta G^*}{RT}}}{e^{-\frac{\Delta G_0^*}{RT}}} = 2.303 \sigma\rho \quad (39)$$

$$\ln \frac{e^{-\frac{\Delta G^*}{RT}}}{e^{-\frac{\Delta G_0^*}{RT}}} = 2.303 \sigma\rho \quad (40)$$

$$\ln e^{-\frac{\Delta G^*}{RT}} - \ln e^{-\frac{\Delta G_0^*}{RT}} = 2.303 \sigma\rho \quad (41)$$

or

$$\left(-\frac{\Delta G^*}{RT} \ln e\right) - \left(-\frac{\Delta G_0^*}{RT} \ln e\right) = 2.303 \sigma\rho \quad (42)$$

or

$$-\frac{\Delta G^*}{RT} + \frac{\Delta G_0^*}{RT} = 2.303 \sigma\rho \quad (43)$$

Which implies

$$\frac{\Delta G_0^*}{RT} - \frac{\Delta G^*}{RT} = 2.303 \sigma\rho \quad (44)$$

or

$$\frac{\Delta G_0^* - \Delta G^*}{RT} = 2.303 \sigma\rho \quad (45)$$

or

$$\Delta G_0^* - \Delta G^* = 2.303RT \sigma\rho \quad (46)$$

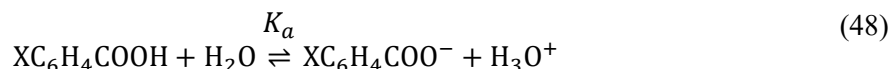
or

$$-\Delta G^* = 2.303RT \sigma\rho - \Delta G_0^* \quad (47)$$

Hence, the variation of negative of the free energy of activation varies linearly with slope $2.303RT\rho$ and $-\Delta G_0^*$ as intercept.

❖ Substituent and Reaction Constants

To discuss the substituent and reaction constants, we need to recall the quantitative relationship between the structure and reactivity first. To do so, we need to find some mathematical parameter that can be used to represent the combined magnitude of inductive and resonance effects of different substituents. This can be achieved by considering the hydrolysis of a series of different benzoic acids as given below.



Where X is a substituent at the *m*- or *p*-position and K_a is the dissociation constant. As expected, the dissociation constant was found to be different for differently substituted substrates.

Since an electron-withdrawing group will better stabilize the conjugate base (i.e., $\text{XC}_6\text{H}_4\text{COO}^-$), resulting in a larger magnitude of K_a (lower pK_a). On the other hand, an electron-donating group will destabilize the conjugate base (i.e., $\text{XC}_6\text{H}_4\text{COO}^-$), resulting in a smaller magnitude of K_a (higher pK_a). Therefore, we can say that the electronic effect (inductive plus mesomeric effect) of a substituent can be represented as the difference between the pK_a value of its benzoic acid derivative and the pK_a value of benzoic acid itself; mathematically, we can say

$$\sigma_X = \log(K_a) - \log(K_a)_0 = -p(K_a) + p(K_a)_0 \quad (49)$$

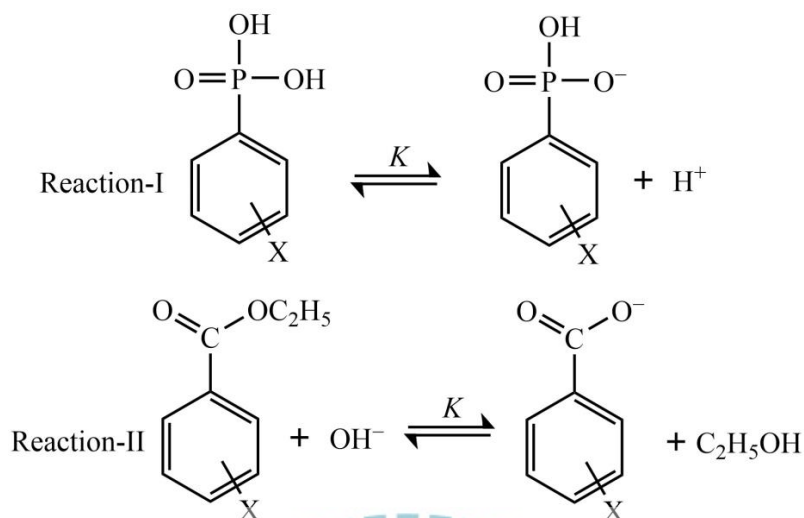
Where the parameter σ_X (or simply σ) is called as substituent constant; and was found for several different groups just subtracting its benzoic acid derivative's pK_a value from pK_a value of benzoic acid. Using $\log m - \log n = \log m/n$, equation (49) can also be written as

$$\log \frac{(K_a)}{(K_a)_0} = \sigma \quad (50)$$

Now if we plot a curve between $\log(K_a)/(K_a)_0$ vs σ , we will definitely get a straight line with a slope which is equal to unity.

Now we need to check if these σ values (i.e., of substituted benzoic acids) can also be used for other meta- or para-substituted benzene derivatives. To do so, consider two series of reactions; the first one is the acid dissociation of phenyl phosphonic acid, and the second one is the base hydrolysis of substituted ethyl benzoate.

Here we will find if different substituents affect their dissociation constants or rates in the same manner as affected in the case of substituted benzoic acid. Also, we did not use ortho-substituents or substituents in the aliphatic system because they also contain steric factors and don't not linear variation.



When plotted the experimental $\log(K_a)/(K_a)_0$ for the reaction-I and experimental $\log k/k_0$ for reaction-II vs the substituent constants obtained for the substituted benzoic acids, we get the following curves. It is obvious that the plots will still be linear like but the slope will be changed. This implies that the order and relative effects for different substituents on both reactions remain the same though the magnitude has been changed which can be attributed to the different nature reaction considers from 'base reaction'.

Therefore, our aim, in this case, should be the determination of the slope (let us say ρ). Since on the vertical side we have ' $[\log(K_a)/(K_a)_0]_{sppa}$ ' for reaction-I (acid dissociation of phenyl phosphonic acid) and on the horizontal side we have ' σ or $[\log(K_a)/(K_a)_0]_{sba}$ ' for base reaction (hydrolysis of substituted benzoic acid), the slope should be

But from equation (50), we know that $[\log(K_a)/\log(K_a)_0]_{sba} = \sigma$; and therefore, we get

$$\left[\log \frac{(K_a)}{(K_a)_0} \right]_{sppa} = \rho \sigma \quad (51)$$

For any reactions,

$$\log K_a = \rho \sigma - \log (K_a)_0 \quad (52)$$

Similarly, on the vertical side we have ' $\log k/k_0$ ' for reaction-II (base hydrolysis of substituted ethyl benzoate) and on the horizontal side we have ' σ or $[\log(K_a)/(K_a)_0]_{sba}$ ' for base reaction (hydrolysis of substituted benzoic acid), the slope should be

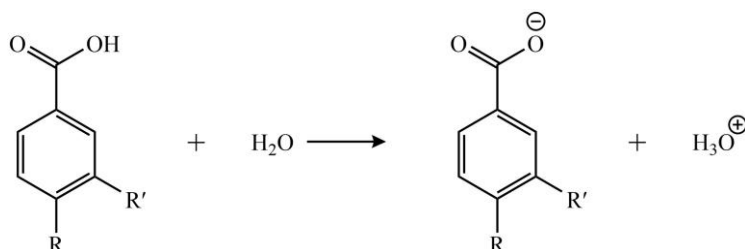
But from equation (50), we know that $[\log(K_a)/\log(K_a)_0]_{sba} = \sigma$; and therefore, we get

$$\left[\log \frac{k}{k_0} \right]_{sppa} = \rho \sigma \quad (53)$$

Equation (51, 53) are Hammett equations where ρ and σ are the substituent and reaction constants.

➤ **Substituent Constants (σ)**

From the derivation of Hammett's equation, we know that the substituent constants can be collected by finding the change in the pK_a value of substituted benzoic acid in water at 25 °C. The reaction constant for this 'base reaction' will simply be equal unity.

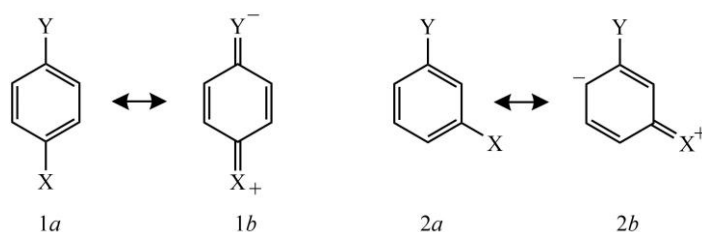


Since an electron-withdrawing group will better stabilize the conjugate base (i.e., $XC_6H_4COO^-$), resulting in a larger magnitude of K_a (lower pK_a). On the other hand, an electron-donating group will destabilize the conjugate base (i.e., $XC_6H_4COO^-$), resulting in a smaller magnitude of K_a (higher pK_a). Therefore, we can say that the electronic effect (inductive plus mesomeric effect) of a substituent can be represented as the difference between the pK_a value of its benzoic acid derivative and the pK_a value of benzoic acid itself.

Various substituent effects can be concluded by looking at σ values displayed in Table 1. With $\rho = 1$, the group of substituents with increasing positive values (such as nitro) makes the equilibrium constant increase relative to the hydrogen as the substituent, which in turn, means that the acidity of the benzoic acid has been increased. This is because the substituents like NO_2 stabilize the negative charge on the carboxylate ion by an inductive effect ($-I$) and also by a negative resonance effect ($-R$).

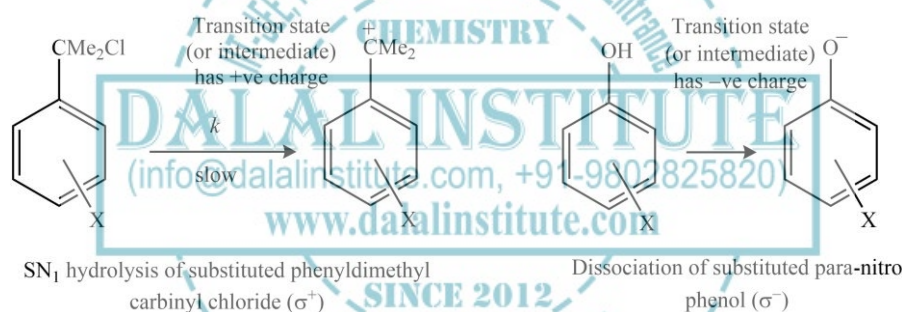
The second kind of substituents is the halo- groups, for which the substituent effect is modestly positive. This can be attributed to the fact that even though the inductive effect is still negative, the resonance effect is positive ($+R$), canceling the former partially. Experimental data also demonstrated that for these substituents, the m -effect is much bigger than the p -effect, because the resonance effect is largely reduced in the m -substituent. In the case of m -substituted substrates, a C atom with the negative charge is further away from the COOH group.

The behavior of resonance effect in the perspective of substituent constants can be understood by the given below, where, in a p -substituted arene (1a), one resonance structure (1b) is a quinoid with the positive charge on the substituent X, freeing electrons and so destabilizing the Y group. This kind of destabilizing outcome is not likely to happen when X is at the m -site.



Furthermore, groups such as ethoxy and methoxy can even show opposite signs for the substituent constant due to the opposing nature of the inductive and resonance effects. It's just the aryl and alkyl substituents like methyl are electron-donating in w.r.t. inductive as well as resonance effects. Finally, If the reaction constant's sign is negative, substituents with a negative substituent constant will raise K_a values.

Now although the substituent constants derived from substituted benzoic acid were quite accurate in predicting $\log(K_a)/(K_a)_0$ or $\log k/k_0$ for several reactions, cases where the rates or dissociations constants predicted were not in line if the substituent is either strongly electron-withdrawing or strongly electron-donating in nature. For instance, $\log(K_a)/(K_a)_0$ of substituted phenols for *p*-CN and *p*-NO₂ are above the line indicating that systems with these substituents act as stronger acids than expectations. This is because if electron-withdrawal arising from mesomeric effects is extended to the reaction site via 'through conjugation', the conjugated acid will be exceptionally stable. Since the substituent is developing a negative charge during this process, the modified substituent constant will be labeled as σ_p^- . Similarly, if the electron-donating arising from mesomeric effects is extended to the reaction site via 'through conjugation', the conjugated acid will be less stable. Since the substituent is developing a positive charge during this process, the modified substituent constant will be labeled as σ_p^+ .



The magnitude by which $\log(K_a)/(K_a)_0$ or $\log k/k_0$ deviate from σ value is added to produce a new scale of substituent constants. The same is true for the *m*-site excepting the fact that values of σ_m^+ will be the same as the σ_m values.

Table 3. Substituent constants: para and meta substituted benzene rings.

Group	σ_p	σ_m	σ_p^+	σ_m^+	σ_p^-
COOH	0.44	0.35	0.42	0.32	0.73
COOR	0.44	0.35	0.48	0.37	0.48
CN	0.70	0.62	0.66	0.56	1.00
NO ₂	0.81	0.71	0.79	0.73	1.27
Cl	0.24	0.37	0.11	0.40	–

➤ **Reaction Constants (ρ)**

After knowing the values of substituent constants, the reaction constant (ρ) can be obtained for an extensive range of reactions. The 'prototype or base' reaction is the alkaline hydrolysis of ethyl benzoate in a water mixture at 25 °C. For instance, plotting experimental values of $\log(K_a)/(K_a)_0$ and $\log k/k_0$ for the acid dissociation of phenyl phosphonic acid and base hydrolysis of substituted ethyl benzoates vs substituent constants yielded the ρ values equal to 0.76 and 2.4, respectively.

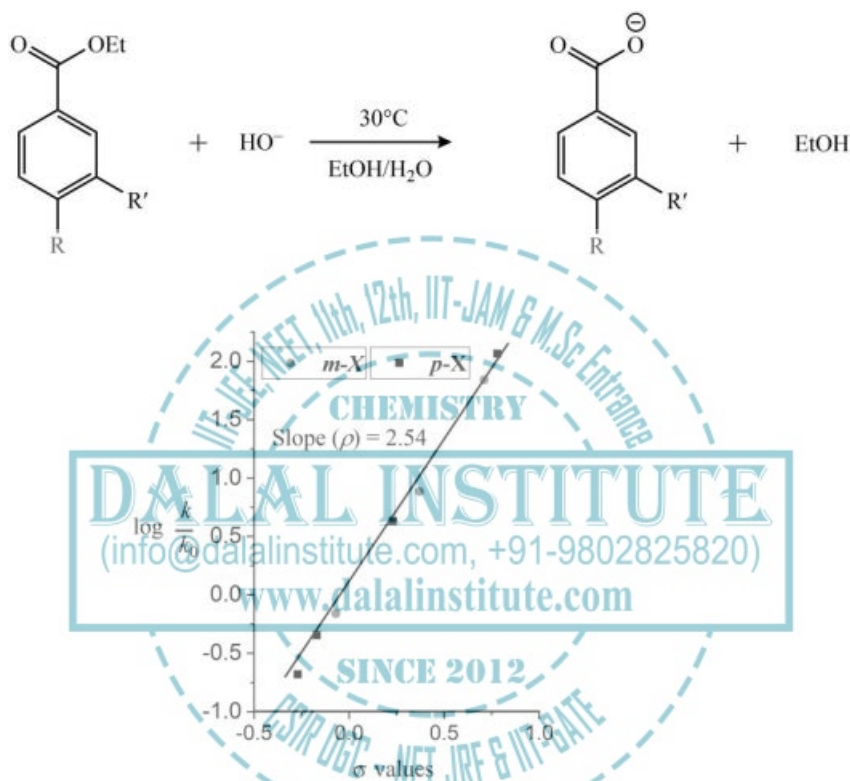


Figure 19. $\log k/k_0$ vs σ for alkaline hydrolysis of substituted ethyl benzoate.

Reaction constants or ρ values for many other reactions and equilibria have been obtained over years. P-values for some of the important reactions provided by Hammett himself are given below.

- i) Hydrolysis of substituted cinnamic acid ester in water /ethanol (+1.267).
- ii) Acid-catalyzed esterification of substituted benzoic esters in C₂H₅OH (-0.085).
- iii) Ionization of substituted phenols in H₂O (+2.008).
- iv) Substituted benzyl chlorides' hydrolysis in H₂O-acetone at 69.8 °C (-1.875).
- v) The acid-catalyzed bromination of substituted acetophenones in CH₃COOH (acetic acid) or water or hydrochloric acid (+0.417).

Now, as far as the significance is concerned, the sensitivity constant (i.e. reaction constant ρ), defines the reaction's susceptibility to different substituents, relative to the ionization of benzoic acid; and is equal to the slope of the Hammett's equation or plot. The reaction's information and the mechanism involved can be found using the value of ρ as given below.

Case 1: if $\rho > 1$, the reaction has a greater sensitivity to substituents than the benzoic acid and a negative charge will accumulate (or a loss of positive charge) in the course of the reaction.

Case 2: if $0 < \rho < 1$, the reaction will be less sensitive to substituents than the benzoic acid and a negative will accumulate (or a loss of positive charge).

Case 3: if $\rho = 0$, the reaction will show no sensitivity to substituents, and no charge will be lost or built.

Case 4: if $\rho < 0$, a positive will accumulate (or a loss of negative charge) during the reaction.

The correlations given above can be used to explain the mechanism of an organic reaction. Since the ρ -value is connected to the charge in the course of the rate-limiting step, the mechanism involved can be developed using the data obtained. For instance, if an aromatic compound's reaction is believed to happen via one of two routes, the organic compound can simply be modified with substituents with dissimilar σ values and then the shortlisting can be done by taking kinetic measurements. After the measurements we mentioned, the Hammett plot can be raised to find the ρ value. Now, if the mechanisms we believe to be true encompass the charge formation, the ρ value will easily confirm our predictions. On the other hand, if the Hammett plot demonstrates that no charge is created during the reaction (i.e., slope or $\rho = 0$), the mechanism with the charge development can simply be neglected.

It is also worthy to note that the Hammett plots may not always be flawlessly linear. For example, a plot may have an unexpected or rapid change in the ρ value or slope. A case like this means that the mechanism responsible for the reaction has simply been changed due to the addition of different substituents. Some other kinds of deviations from linear variation may be attributed to a change in the site of the transition state. A situation like this means that certain substituents may cause the transition state to form later (or earlier) during the mechanism involved.

Table 4. The reaction constants (ρ -values) for a relative analysis for some typical organic chemical reaction types.

Reaction type	ρ -value
Ionization of acids	1.464
Alkaline hydrolysis of ethyl esters	2.494
Acids with diphenyldiazomethane	0.937
Acid dissociation of phenyl phosphonic acid	0.76

❖ Taft Equation

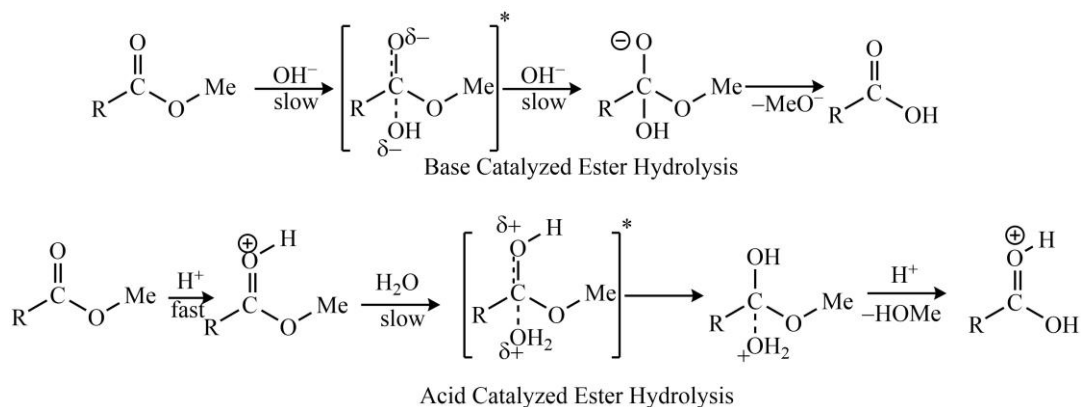
The Taft equation, just like the Hammett equation, is also a linear free energy relationship (LFER) that is employed in physical organic chemistry in the analysis of reaction mechanisms and to develop the quantitative relationships between structure and activity for organic species. Robert W. Taft developed this equation in 1952 as an amendment to the Hammett equation. Nevertheless, unlike the Hammett equation (accounts only for inductive, field, and resonance effects on rate of reaction), the Taft equation also explains the steric effects of a substituent. The mathematical form of the Taft equation is given below.

$$\log \frac{k}{k_0} = \sigma^* \rho^* + \delta E_s \quad (56)$$

where k and k_0 are the constant for the group $X \neq H$ and $X = H$, respectively; ρ^* and σ^* are the modified reaction constants (sensitivity factor for the reaction to polar effects) and substituent X (describes the field and inductive effects), respectively. The symbol δ is the sensitivity factor for the reaction to steric effects, and E_s is the steric substituent constant.

➤ Polar Substituent Constants (σ^*)

The polar substituent constants explain the way a substituent affects a reaction pathway via polar (field, inductive, and mesomeric effect) influences. Taft examined the hydrolysis of methyl esters to get σ^* values. The idea of using rates of ester hydrolysis to study polar effects was initially proposed by Ingold in early 1930. Esters hydrolysis can proceed via either acid- or base-catalyzed pathway, and both routes involve a tetrahedral intermediate species. During the base-catalyzed pathway, the reactant transforms from a neutral entity to a negatively charged intermediate in the rate-limiting step; whereas in the acid-catalyzed pathway, a positively charged reactant transforms to an intermediate species with a positive charge.



Owing to the same nature of intermediates (tetrahedral), Taft suggested that any steric factors under identical conditions should be approximately the same for the two pathways; and so would not affect the rates' ratio. Nevertheless, since a charge difference is built up in the rate-limiting steps it was suggested that polar effects would only affect the rate of reaction for base-catalyzed transformation because a new charge was created. The mathematical formulation of polar substituent constant (σ^*) can be written as given below.:

$$\sigma^* = \frac{1}{2.48\rho^*} \left[\left(\log \frac{k}{k_0} \right)_B - \left(\log \frac{k}{k_0} \right)_A \right] + \delta E_s \quad (57)$$

Where $(\log k/k_0)_B$ represents the ratio of the base-catalyzed reaction rate compared to the reference transformation; whilst $(\log k/k_0)_A$ represents the ratio of the acid-catalyzed reaction rate relative to the reference transformation. The symbol ρ^* shows the reaction constant which explains the sensitivity of the series of reactions. For the base reaction series, we use $\rho^* = 1$ and $R = \text{CH}_3$ is set as the reference transformation with $\sigma^* = 0$. The incorporation of $1/2.48$ is to make the magnitude σ^* equal σ values given by Hammett.

➤ Steric Substituent Constants (E_s)

Though the base- and acid-catalyzed esters' hydrolysis yield transition states for the rate-limiting steps which have different densities of charge, their molecular structures differ by 2 H atoms only. Therefore, Taft thought that the steric effects should affect both pathways by equal extent. Owing to this fact, the magnitude of E_s (steric substituent constant) can be obtained from purely the acid-catalyzed pathway since polar effects would be excluded this way. E_s was defined as:

$$E_s = \frac{1}{\delta} \log \frac{k}{k_0} \quad (58)$$

Where symbol δ represents the reaction constant which explains the reaction's susceptibility to steric factor. The values $\delta = 1$ and $E_s = 0$ were used for the definition reaction series. The equation (49) can be combined with equation (48) to write the complete form of the Taft equation. Comparing E_s values for CH_3 , C_2H_5 , isopropyl, and tert-butyl; it is obvious that it increases with growing steric bulk. Nevertheless, E_s values can deviate from expectation due to steric interactions. For instance, the phenyl's E_s is larger than tert-butyl; however, if we compare these groups using another measure, the tert-butyl will come out to be dominant.

Table 5. Constants used in the Taft equation.

Group	E_s	σ^*
-H	1.24	0.49
-CH ₃	0	0
-CH ₂ CH ₃	-0.07	-0.1
-CH(CH ₃) ₂	-0.47	-0.19
-C(CH ₃) ₃	-1.54	-0.3
-CH ₂ Ph	-0.38	0.22
-Ph	-2.55	0.6

➤ **Sensitivity Factors**

A brief discussion on the nature and significance of all the sensitivity factors used in the Taft equation is given below.

1. Polar sensitivity factor (ρ^*): Just like Hammett's ρ -values, Taft's ρ^* -values describe the reaction's susceptibility to polar effects. If the steric effects of substituents do not influence the rate of reaction significantly, the Taft equation will reduce to Hammett equation as given below.

$$\log \frac{k}{k_0} = \sigma^* \rho^* \quad (59)$$

The ρ^* value can be found by plotting the log of the ratio of the experimental rates (k) to the reference reaction (k_0) vs the σ^* values of different substituents. The slope of such plot will be equal to ρ^* . Just like Hammett's ρ -value:

- i) If $\rho^* > 1$, a negative charge will accumulate in the transition state during the reaction, and the reaction will be accelerated by electron-withdrawing substituents.
- ii) If $1 > \rho^* > 0$, a negative charge will accumulate in the transition state during the reaction, and the reaction will show mild sensitivity to polar effects.
- iii) If $\rho^* = 0$, the reaction will simply not get influenced by polar effects.
- iv) If $0 > \rho^* > -1$, a positive charge will accumulate in the transition state during the reaction, and the reaction will show mild sensitivity to polar effects.
- v) If $-1 > \rho^*$, a positive charge will accumulate in the transition state during the reaction, and the reaction will be accelerated by electron-donating substituents.

2. Steric sensitivity factor (δ): Just like the polar sensitivity factor, δ or the steric sensitivity factor of reaction explains to what extent the rate of reaction is affected by steric effects. If the polar effects of substituents do not influence the rate of reaction significantly, the Taft equation will reduce to the equation as given below.

$$\log \frac{k}{k_0} = \delta E_s \quad (60)$$

By plotting the log of the ratio rates vs the E_s value of different substituents, we get a straight line with a slope equal to δ . Similarly to Hammett's ρ -value, the magnitude of δ gives the extent of steric effects:

- i) If the δ -value is very high, the reaction will be extremely sensitive to steric effects, whereas a smaller δ -value implies that the reaction has little to no sensitivity to steric influence.

Also, owing to larger and negative E_s -values for bulkier substituents, we may conclude that the flowing point about the reaction profile.

- i) If $\delta > 1$, the raise in steric bulk cuts the rate of reaction and steric effects will be higher in the transition state.
- ii) If $\delta < 1$, the raise in steric bulk will raise the rate and steric effects will be reduced in the transition state.

3. Reactions influenced by polar and steric effects: If the steric, as well as polar effects, influence the rate of chemical reaction, the Taft equation can be employed to evaluate ρ^* - and δ -values via the use of standard least-squares fitting for getting a bivariant regression plane. The application of this technique was outlined by Taft in 1957 as a demonstration of accuracy.



❖ Problems

- Q 1. What is the reaction mechanism? How it can be used as a basis to classify different types of organic reactions?
- Q 2. What are the thermodynamic and kinetic requirements of an organic reaction to occur? Explain with a suitable example.
- Q 3. What do you mean by kinetically controlled product? How is it different from a thermodynamically controlled reaction?
- Q 4. State and explain Hammond's postulate.
- Q 5. Derive the mathematical formulation of the Curtin-Hammett principle.
- Q 6. Draw and explain the potential energy diagrams of different kinds of organic reactions.
- Q 7. Discuss the methods of determining the reaction mechanism with special reference to the detection of reaction intermediates.
- Q 8. Define isotope effect.
- Q 9. State and explain Pearson's hard-soft-acid-base principle.
- Q 10. What are the differences and similarities in carbocations and carbanions?
- Q 11. How does the structure of the substrate affect the reaction rate?
- Q 12. Give Hammett equation. How it can be used to prove the linear free energy relationship?
- Q 13. Write down the Taft equation. Discuss its scope and physical significance.

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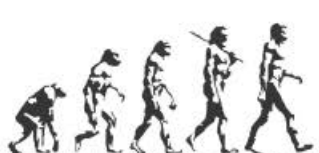
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Volume I

MANDEEP DALAL



First Edition

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