Organic Reactions and Synthesis of Drug Molecules

Aromaticity: Aromaticity is defined as "the property possessed by an aromatic compound having a reasonably planar cyclic structure with (4n+2) π electrons and possessing unusual stability due to the delocalization of π electrons".

Aromatic compounds are those that meet the following criteria:

- The structure must be cyclic and planar, containing conjugated π-bonds.
- Delocalization of the π-electrons over the ring lowers the electronic energy of the molecule leading to its extra stability.
- It should follow the Huckel's rule. The rule states that aromatic compounds must contain (4n+2) π-electrons, where n is any whole number.

  Aromatic systems have 2, 6, or 10 π-electrons, for n = 0, 1, or 2

Example is Benzene

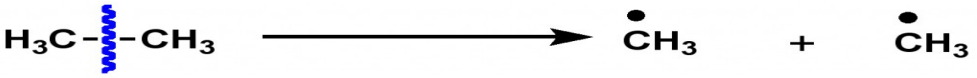
Benzene is cyclic and planar, with a continuous ring of overlapping *p*-orbitals. Huckel's rule predicts that benzene is an aromatic compound as it has (4n+2) π-electron system

Bond fission

Bond fission occurs during a chemical reaction and leads to the formation of reactive intermediates.

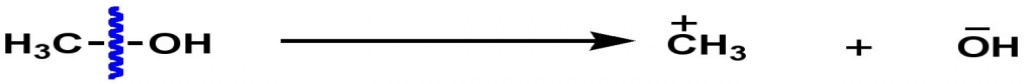
There are two types of fission:

Homolytic fission



Homolytic fission is where each atom of the bond keeps an electron each resulting in an intermediate species called free radicals. Since the bond is breaking to give two similar free radicals (each keeping an electron), this type of fission is called as *Homolytic Fission*.

Heterolytic fission

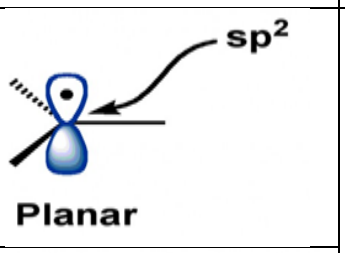
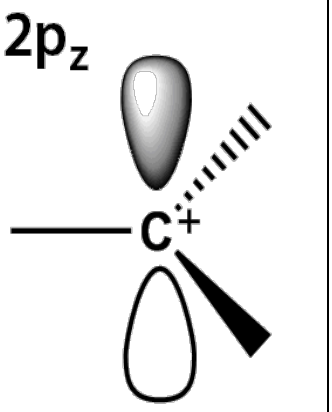
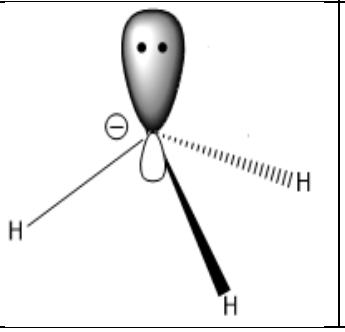


In this case we can see that one of the atoms carry a negative charge after bond cleavage indicating that it has both the electrons of the bond and the other has no electrons at all. Hence it is electron deficient thus positively charged. As the electrons are not divided equally after bond cleavage this is called *Heterolytic Fission*.

Heterolytic fission gives rise to two types of intermediates: Carbocation and Carbanion.

Reactive Intermediates:

Difference between free radical, carbocation and carbanion

S.No	Intermediate	Hybridization	Shape	Structure	Stability
1	Free radical	sp^2	Trigonal planar		3°>2°>1°
		sp^3	pyramidal		
2	Carbocation	sp^2	Trigonal planar		3°>2°>1°
3	Carbanion	sp^3	pyramidal		1°>2°>3°

Electronic displacement in covalent bonds

Electronic displacement in covalent bonds

It is observed that most of the attacking reagents always possess either a positive or a negative charge, therefore for a reaction to take place on the covalent bond the latter must possess oppositely charged centres. This is made possible by displacement (partial or complete) of the bonding electrons. The electronic displacement in turn may be due to certain effects, some of which are **permanent** and others are **temporary**. The former effects are permanently operating in the molecule and are known as **polarization effects**, while the latter are brought into play by the attacking reagent and as soon as the attacking reagent is removed, the electronic displacement disappears; such effects are known as the **polarisability effects.**

I. Inductive Effect
II. Mesomeric Effect
III. Electromeric Effect
IV. Hyperconjugation
V. Steric Effect

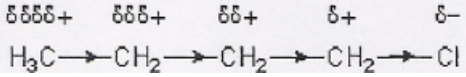
Inductive Effect:

The polarization of a σ bond due to electron withdrawing or electron donating effect of adjacent groups or atoms is called ***inductive effect.***

Salient features of inductive effect

* It arises due to electronegativity difference between two atoms forming a sigma bond.
* It is transmitted through the **sigma bonds.**
* The magnitude of inductive effect decreases while moving away from the groups causing it.
* It is a **permanent** effect.
* It influences the chemical and physical properties of compounds.

The C-Cl bond in the butyl chloride, CH_3-CH_2-CH_2-CH_2-Cl is polarized due to electronegativity difference. The electrons are withdrawn by the chlorine atom. Thus the first carbon atom gets partial positive charge. In turn, this carbon atom drags electron density partially from the next carbon, which also gets partial positive charge. Thus the inductive effect is transmitted through the carbon chain.



TYPES OF INDUCTIVE EFFECT: The inductive effect is divided into two types depending on their strength of electron withdrawing or electron releasing nature with respect to hydrogen.

1) Negative inductive effect (-I): The electron withdrawing nature of groups or atoms is called as negative inductive effect. It is indicated by -I. Following are the examples of groups in the decreasing order of their -I effect:

$NH_3^{\neq} > NO_2 > CN > SO_3H > CHO > CO > COOH > COCl > CONH_2 > F > Cl > Br > I > OH > OR > NH_2 > C_6H_5 > H$

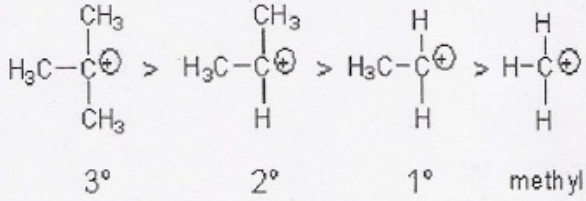
2) Positive inductive effect (+I): It refers to the electron releasing nature of the groups or atoms and is denoted by +I. Following are the examples of groups in the decreasing order of their +I effect.

$C(CH_3)_3 > CH(CH_3)_2 > CH_2CH_3 > CH_3 > H$

Application of Inductive effect

Stability of carbonium ions: The stability of carbonium ions increases with increase in number of alkyl groups due to their +I effect. The alkyl groups release electrons to carbon, bearing positive charge and thus stabilizes the ion.

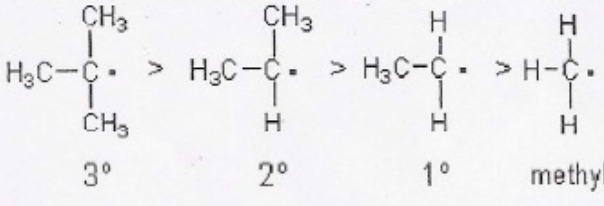
The order of stability of carbonium ions is :



Stability of free radicals:

In the same way the stability of free radicals increases with increase in the number of alkyl groups.

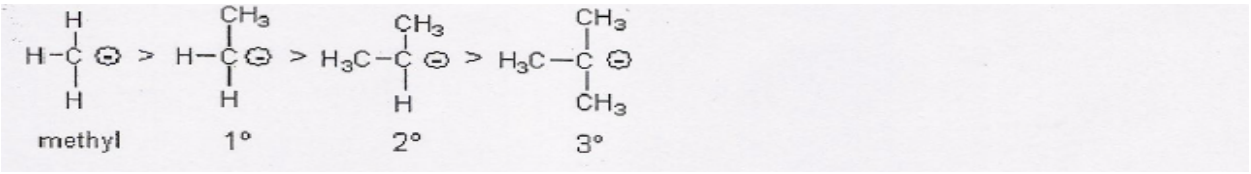
Thus the stability of different free radicals is:



Stability of carbanions:

However the stability of carbanions decreases with increase in the number of alkyl groups since the electron donating alkyl groups destabilize the carbanions by increasing the electron density.

Thus the order of stability of carbanions is:



Acidic strength of carboxylic acids and phenols:

The electron withdrawing groups (-I) decrease the negative charge on the carboxylate ion and thus by stabilizing it. Hence the acidic strength increases when -I groups are present.

However the +I groups decrease the acidic strength.

E.g. i) The acidic strength increases with increase in the number of electron withdrawing Fluorine atoms as shown below.

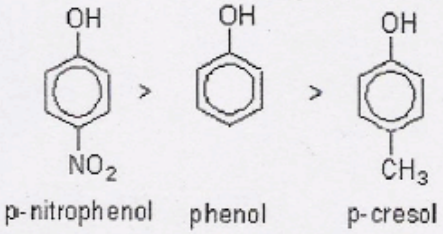
$CH_3COOH < CH_2FCOOH < CHF_2COOH < CF_3COOH$

ii) Formic acid is stronger acid than acetic acid since the $-CH_3$ group destabilizes the carboxylate ion.

On the same lines, the acidic strength of phenols increases when -I groups are present on the ring.

E.g. The p-nitrophenol is stronger acid than phenol since the $-NO_2$ group is a -I group and withdraws electron density. Whereas the para-cresol is weaker acid than phenol since the $-CH_3$ group shows positive (+I) inductive effect.

Therefore the decreasing order of acidic strength is:



Basic strength of amines:

The electron donating groups like alkyl groups increase the basic strength of amines whereas the electron withdrawing groups like aryl groups decrease the basic nature. Therefore alkyl amines are stronger Lewi bases than ammonia, whereas aryl amines are weaker than ammonia.

Thus the order of basic strength of alkyl and aryl amines with respect to ammonia is :$CH_3NH_2 > NH_3 > C_6H_5NH_2$

Mesomesic or Resonance Effect:

The electron withdrawing or releasing effect attributed to a substituent through delocalization of p or π electrons, which can be visualized by drawing various canonical forms, is known as **mesomeric effect or resonance effect**. It is symbolized by M or R.

Negative resonance or mesomeric effect (-M or -R): It is shown by substituents or groups that withdraw electrons by delocalization mechanism from rest of the molecule and are denoted by -M or -R. The electron density on rest of the molecular entity is decreased due to this effect.

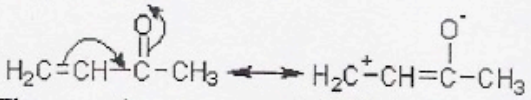
E.g. $-NO_2$, Carbony group (C=O), -C≡N, -COOH, $-SO_3H$ etc.

Positive resonance or mesomeric effect (+M or +R): The groups show positive mesomeric effect when they release electrons to the rest of the molecule by delocalization. These groups are denoted by +M or +R. Due to this effect, the electron density on rest of the molecular entity is increased.

E.g. -OH, -OR, -SH, -SR, $-NH_2$, $-NR_2$ etc.

ILLUSTRATIONS & APPLICATIONS OF RESONANCE EFFECT (OR) MESOMERIC EFFECT

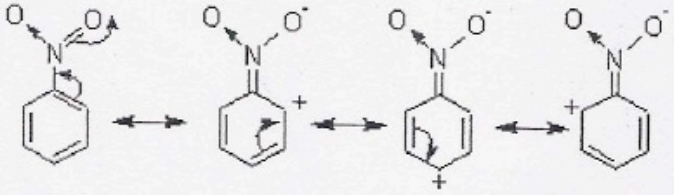
1) The negative resonance effect (-R or -M) of carbonyl group is shown below. It withdraws electrons by delocalization of π electrons and reduces the electron density particularly on 3rd carbon.



2) The negative mesomeric effect (-R or -M) shown by cyanide group in acrylonitrile is illustrated below. The electron density on third carbon decreases due to delocalization of π electrons towards cyanide group.

Because of negative resonance effect, the above compounds act as good micheal acceptors.

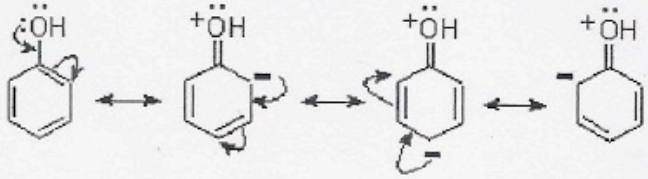
3) The nitro group, $-NO_2$, in nitrobenzene shows -M effect due to delocalization of conjugated π electrons as shown below. Note that the electron density on benzene ring is decreased particularly on ortho and para positions.



I II III IV

This is the reason for why nitro group deactivates the benzene ring towards electrophilic substitution reaction.

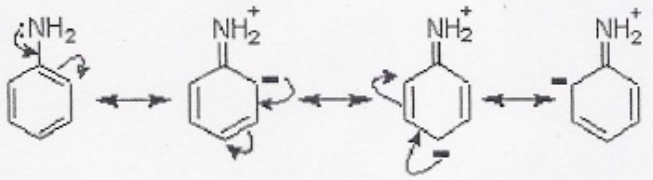
4) In phenol, the -OH group shows +M effect due to delocalization of lone pair on oxygen atom towards the ring. Thus the electron density on benzene ring is increased particularly on ortho and para positions.



I II III IV

Hence phenol is more reactive towards electrophilic substitution reactions. The substitution is favored more at ortho and para positions.

5) The $-NH_2$ group in aniline also exhibits +R effect. It releases electrons towards benzene ring through delocalization. As a result, the electron density on benzene ring increases particularly at ortho and para positions. Thus aniline activates the ring towards electrophilic substitution.

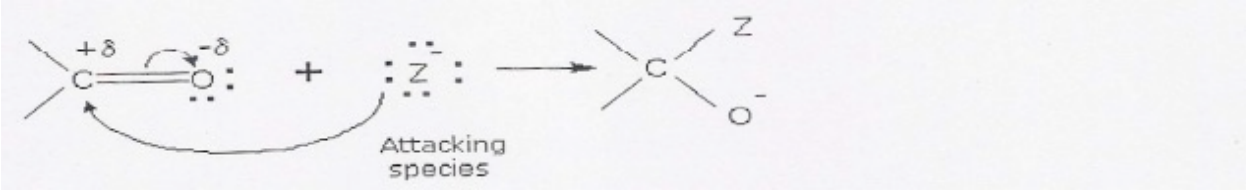


It is also worth mentioning that the electron density on nitrogen in aniline decreases due to delocalization which is the reason for its less basic strength when compared to ammonia and alkyl amines.

Electromeric Effect:

This is a temporary effect and takes place between two atoms joined by a multiple bond, i.e., a double or triple bond. It occurs at the requirements of the attacking reagent, and involves instantaneous transfer of a shared pair of electrons of the multiple bond to one of the linked atoms.

It is temporary in nature because the molecule acquires its original electronic condition upon removal of the attacking reagent.



Types of attacking reagent: Electrophiles and Nucleophiles

S.No	Electrophiles	Nucleophiles
1	Species which are electron deficient	Species which are electron rich
2	Usually positively charged	Usually negatively charged
3	Attacks an electron rich center	Attacks an electron deficient center
4	Examples: (posively charged species): NO_2^+, Br^+, Cl^+, I^+ (Lewis acids): BF_3, $ZnCl_2$, $FeCl_2$ (electron deficient atoms): SO_3, $SOCl_2$	Examples: (negatively charged species): OH^-, OR^-, COO^-) (Lewis base): NH_3, H_2O

Hyperconjugation: *The delocalization of σ-electrons or lone pair of electrons into adjacent π-orbital or p-orbital is called hyperconjugation.*

It occurs due to overlapping of σ-bonding orbital or the orbital containing a lone pair with adjacent π-orbital or p-orbital.

It is also known as "no bond resonance" or "Baker-Nathan effect".

Conditions for hyperconjugation

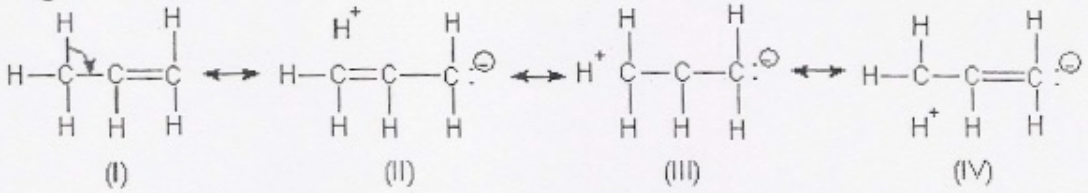
* There must be an α-CH group or a lone pair on atom adjacent to sp^2 hybrid carbon or other atoms like nitrogen, oxygen etc.

E.g., Alkenes, alkyl carbocations, alkyl free radicals, nitro compounds with α- hydrogen

ILLUSTRATION OF HYPERCONJUGATION

E.g. In propene, the σ-electrons of C-H bond of methyl group can be delocalized into the π-orbital of doubly bonded carbon as represented below.

In the same way, the other hydrogens on the methyl group also participate in the hyperconjugation. This is possible due to free rotation of C-C bond so that the other C-H bonds can also participate in the hyperconjugation. Thus the propene molecule can show following resonance structures, which confer stability to it.



(I) (II) (III) (IV)

No bond resonance structures shown by propene due to hyperconjugation.

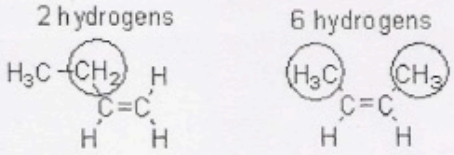
In the contributing structures: (II), (III) & (IV) of propene, there is **NO** bond between an α-carbon and one of the hydrogen atom. Hence the hyperconjugation is also known as "***no bond resonance***".

CONSEQUENCES & APPLICATIONS OF HYPERCONJUGATION

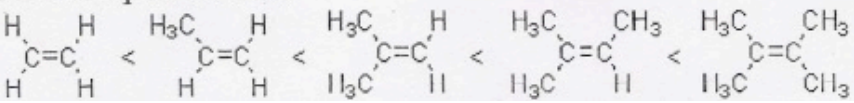
1) Stability of alkenes:

A general rule is that, the stability of alkenes increases with increase in the number of alkyl groups (containing hydrogens) on the double bond. It is due to increase in the number of contributing no bond resonance structures.

For example, 2-butene is more stable than 1-butene. This is because in 2-butene, there are six hydrogens involved in hyperconjugation whereas there are only two hydrogens involved in case of 1-butene. Hence the contributing structures in 2-butene are more and is more stable than 1-butene.

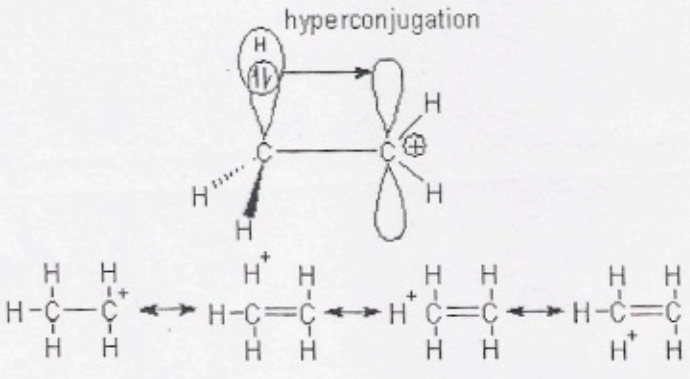


The increasing order of stability of alkenes with increases in the number of methyl groups on the double bond is depicted below.



2) Stability of carbocations (carbonium ions):

The ethyl carbocation, CH_3-CH_2^+ is more stable than the methyl carbocation, CH_3^+. This is because, the σ-electrons of the α-C-H bond in ethyl group are delocalized into the empty p-orbital of the positive carbon center and thus by giving rise to 'no bond resonance structures' as shown below. Whereas hyperconjugation is not possible in methyl carbocation and hence is less stable.

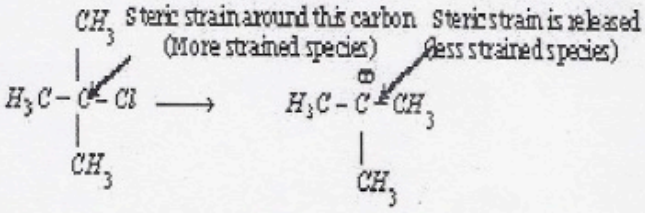


hyperconjugation in ethyl carbonium ion

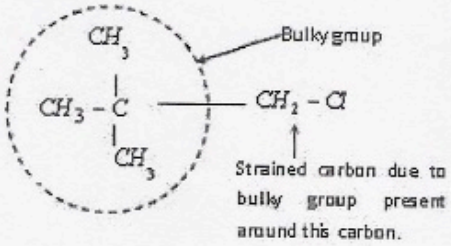
In general, the stability of carbonium ions increases with increase in the number of alkyl groups (containing hydrogen) attached to the positively charged carbon due to increase in the number of contributing structures to hyperconjugation.

Steric Effect: On account of the presence of bulkier groups at the reaction centre, they cause mechanical interference and with the result the attacking reagent finds it difficult to reach the reaction site and thus slows down the reaction. This phenomenon is called **steric hinderance or steric effect.**

(1) Tertiary alkyl halides having bulky groups form tertiary carbocation readily when hydrolysed because of the presence of the three bulky groups on the carbon having halogen.



(2) Primary alkyl halide having quaternary β -carbon does not form transition state because of the steric strain around α- carbon by the - carbon.. To release the strain it converts into carbocation.



Organic Reaction Types:

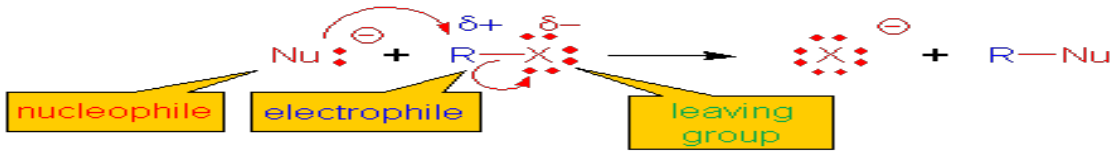
a. Substitution Reaction: These are of two types- Nucleophilic and Electrophilic depending on the nature of the reagent.

b. Addition Reaction: These are of two types- Nucleophilic and Electrophilic depending on the nature of the reagent.

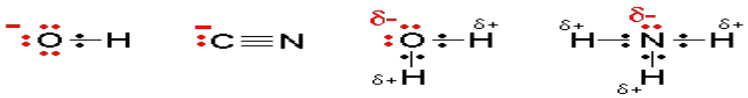
c. Elimination Reaction

Nucleophilic Substitution (S_N) Reaction Mechanism

A general overview



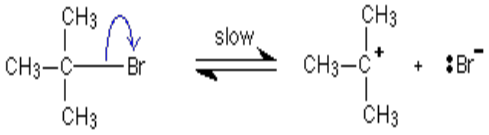
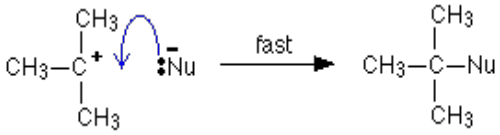
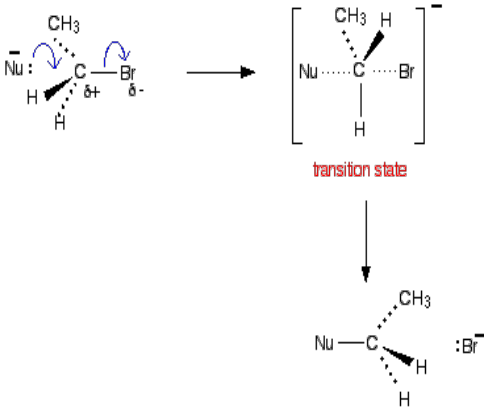
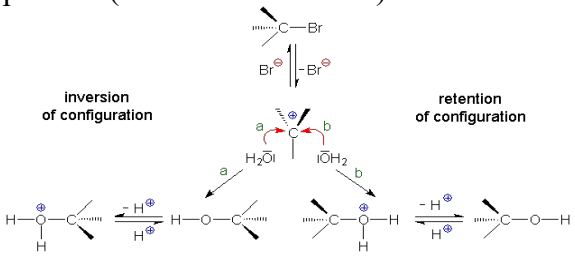
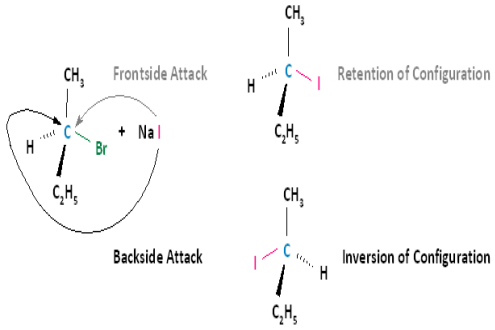
In S_N reactions, the nucleophile always competes with the leaving group. If the potential leaving group is actually a better nucleophile than the attacking nucleophile, the S_N reaction hardly occurs. Common nucleophiles are:



A nucleophile always possesses a lone electron pair. Due to this lone electron pair, a nucleophile may also react as a base. If a nucleophile reacts as a base and not as a nucleophile, an elimination occurs instead of a substitution reaction. The ratio of elimination and substitution products is determined by the competition of elimination and substitution.

S_N reaction occurs by two different mechanisms: S_N1 and S_N2

The major features of the two different mechanisms are:

Factors	S_N1 mechanism	S_N2 mechanism
Number of steps	Mechanism involves two steps	Mechanism involves one step
Mechanism	step ⟶1: (slow)  step ⟶2: (fast) 	
Reaction rate and order	First order: rate =*k*[substrate]	Second order: rate =*k*[substrate][nucleophile]
Molecularity	Unimolecular as the rate determing step involves only one molecule	Bimolecular as the rate determining step involves two molecules
Attack of nucleophile	The nucleophile attacks the carbon of the substrate both on the back and front side although the back side predominates	The nucleophile attacks the carbon of the substrate exclusively from the back side
Stereochemistry	Inversion and retention of configuration of product (racemization occurs) 	Complete inversion of configuration in final product 
Nature of substrate	3°> 2°> 1°> methyl halides Tertiary substrate will favor S_N1	methyl halides >3°> 2°> 1° Primary substrate will favor S_N2
rate determining factor	Electronic factor (stability of R^+)	Steric hindrance
Solvent effect	Polar protic solvents will favor S_N1 as they help to pull the leaving group from the substrate	Aprotic solvents (having low polarity) will favor S_N2 because they stabilize the anionic nucleophile least
Nature of (Nu)	Low concentration of Nu and a weak NU favors S_N1	High concentration of Nu and a strong Nu favors S_N2

Electrophilic Substitution Reaction

Electrophilic substitution is very common in benzene nucleus (aromatic compounds) in which the π electrons are highly delocalized and is hence electron rich. An electrophile can easily attack this region of high electron density.

Example: Nitration of benzene to give nitrobenzene

Reaction mechanism:

Step 1: Formation of an electrophile (E^+)

(Halogenation): $X\text{-}X + FeX_3 \longrightarrow X^+ + FeX^-_4$

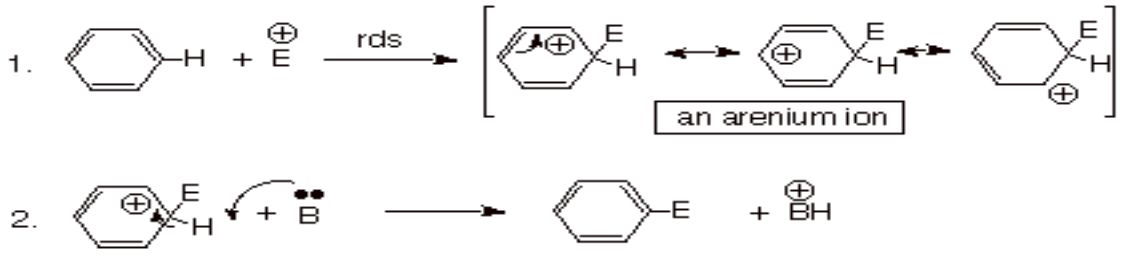
(Nitration): $HNO_3 + 2H_2SO_4 \longrightarrow NO_2^+ + 2HSO_4^- + H_3O^+$

(Friedel Crafts alkylation): $RCl + AlCl_3 \longrightarrow R^{+\cdot} + AlCl_4^-$

(Friedel Crafts acylation): $RCOCl + AlCl_3 \longrightarrow RCO^{+\cdot} + AlCl_4^-$

Step 2-1: Attack of the electrophile:

Step2-2: Loss of H^+



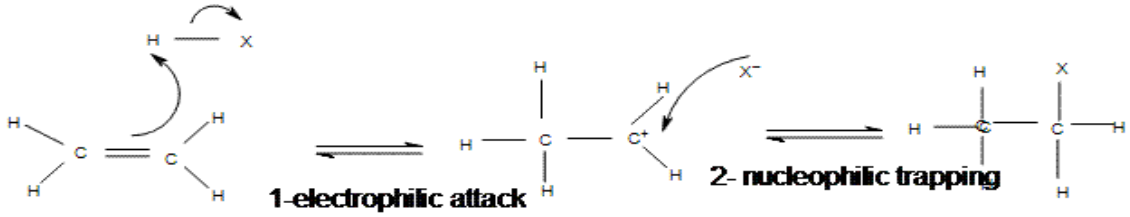
Addition Reaction

***Electrophilic addition reaction*:** In electrophilic addition reaction, an electrophile approaches the double or triple bond of an alkene or alkyne and in the 1st step forms a covalent bond with one of the carbon atoms resulting in the formation of a carbonium ion which then takes up a nucleophile to result in an addition product.

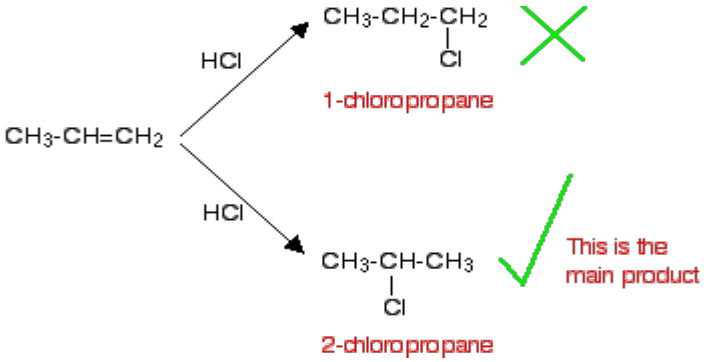
Addition of HX on ethylene is an example of electrophilic addition. Ethylene is a symmetrical olefin.

$CH_2=CH_2 + HX \longrightarrow CH_3\text{-}CH_2X$ (ethyl halide)

Mechanism of Electrophilic Addition of Hydrogen Halide to Ethylene (Symmetrical Alkenes)



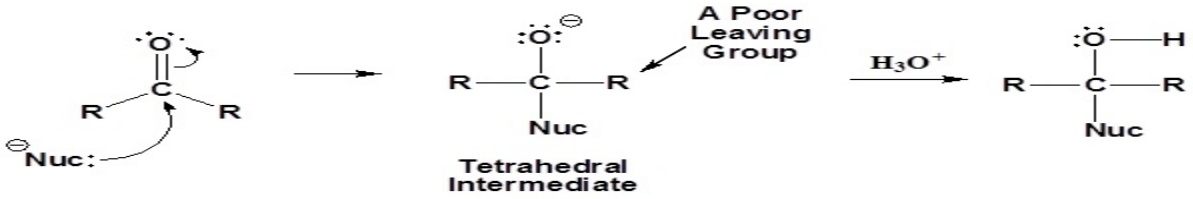
Mechanism of Electrophilic Addition of Hydrogen Halide to Propylene (unsymmetrical alkenes)



This is in line with Markovnikov's Rule which says: "When a compound HX is added to an unsymmetrical alkene, the hydrogen becomes attached to the carbon with the most hydrogens attached to it already"

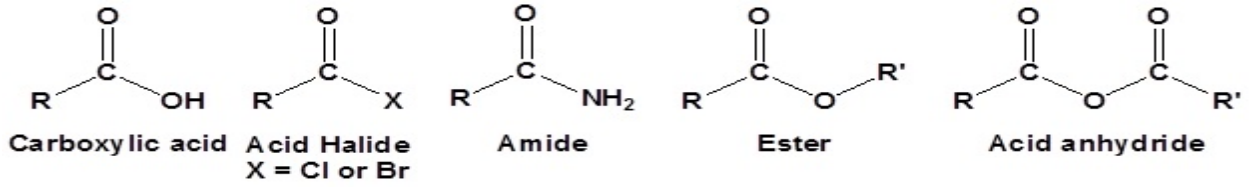
Nucleophilic addition reaction (aldehydes and ketones):

When the addition reaction occurs on account of the initial attack of the nucleophile, the reaction is said to be nucleophilic addition reaction. Due to the presence of strongly electronegative oxygen atom, the π electrons of the carbon-oxygen double bond in C=O group (Aldehydes and ketones) get shifted towards the oxygen atom and thereby such bond is highly polarized. This makes carbon atom of the C=O group electron deficient.



Nucleophilic addition reaction (acids and its derivatives):

Carboxylic acid derivatives too have a carbonyl carbon atom attached to an electronegative oxygen atom. But they have an electronegative substituent that behaves as good leaving groups. Hence they show nucleophile substitution reactions.

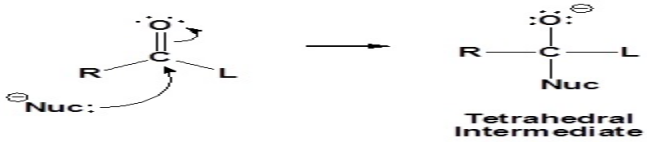


General Reaction of nucleophilic substitution reaction in acid derivatives:

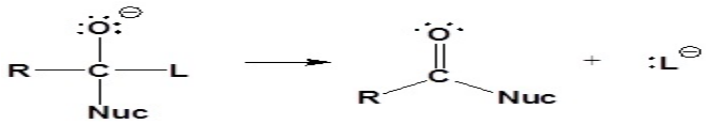
General Mechanism:

Step 1: Formation of Nucleophile Nu^-

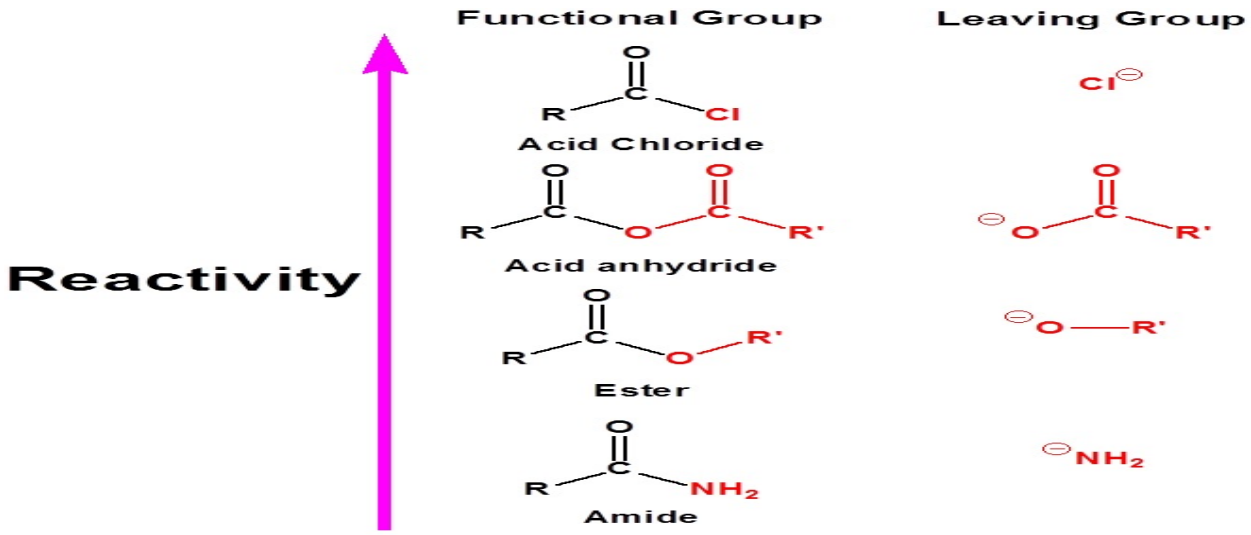
Step 2: Nucleophilic attack on the Carbonyl carbon:



Step 3: Leaving group is removed:



The relative reactivity of carboxylic acid derivatives toward nucleophile substitutions is related to the electronegative leaving group's ability to activate the carbonyl. The more electronegative leaving groups withdraws electron density from the carbonyl, thereby, increasing its electrophilicity.

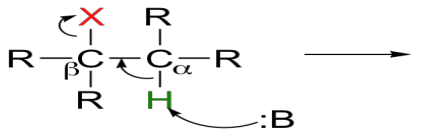


Elimination Reaction

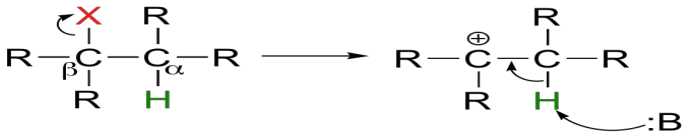
An elimination reaction, generally involves loss of atoms or groups from adjacent carbon atoms resulting in the formation of a π bond between these carbon atoms, so they are reverse of addition reactions. This type of elimination can be described by two model mechanisms: it can occur in a single concerted step (proton abstraction at C_α occurring at the same time as C_β-X bond cleavage), or in two steps (C_β-X bond cleavage occurring first to form a carbocation intermediate, which is then 'quenched' by proton abstraction at the alpha-carbon).

1. E2 reactions: Bimolecular Elimination Reactions
2. E1 reactions: Unimolecular Elimination Reactions

concerted (E2) elimination



carbocation (E1) elimination

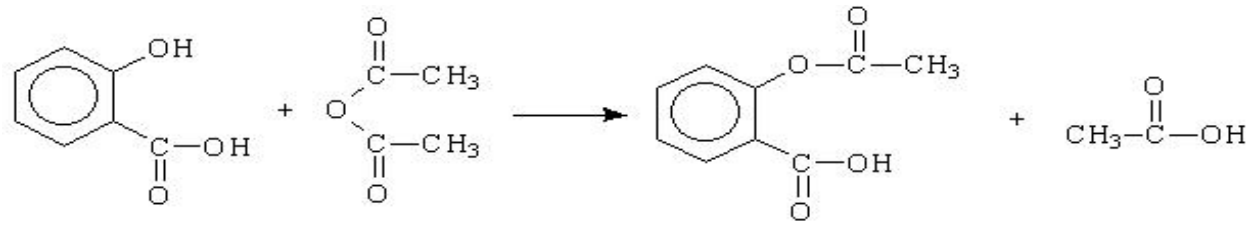


Synthesis of Drugs

1. Aspirin:

It is used as an analgesic (pain killer). Chemical name of Aspirin is 2 acetoxy benzoic acid or acetyl salicylic acid.

Synthesis



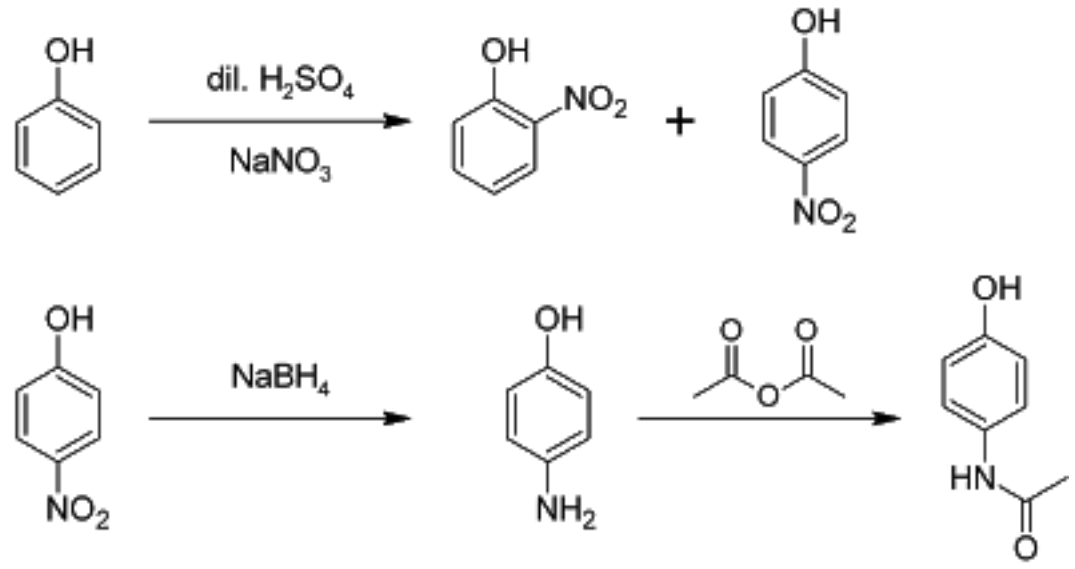
Salicylic acid ($C_7H_6O_3$) + Acetic anhydride ($C_4H_6O_3$) → Acetylsalicylic acid ($C_9H_8O_4$) + Acetic Acid ($C_2H_4O_2$)

In this reaction, an excess of acetic anhydride ($C_4H_6O_3$) is added to a measured mass of salicylic acid ($C_7H_6O_3$) in the presence of a catalyst, sulfuric acid (H_2SO_4). The mixture is heated to form the acetylsalicylic acid ($C_9H_8O_4$) and acetic acid ($C_2H_4O_2$). After the reaction takes place, water is added to destroy the excess acetic anhydride and cause the product to crystallize. The aspirin is then collected, purified by recrystallization, and its melting temperature measured.

2. Paracetamol

It is used as an analgesic and antipyretic for the treatment of both pain and fever. Chemical name is acetaminophen

Synthesis:

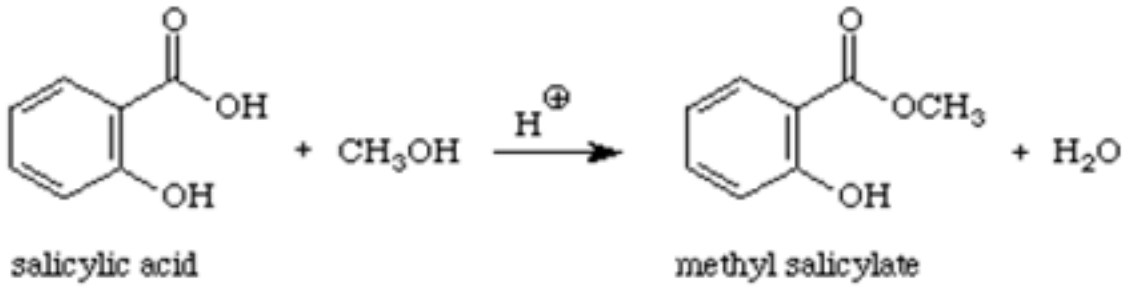


In the laboratory, paracetamol is easily prepared by nitrating phenol with sodium nitrate, separating the desired *p*-nitrophenol from the *ortho*- byproduct, and reducing the nitro group with sodium borohydride. The resultant *p*-aminophenol is then acetylated with acetic anhydride.

3. Oil of Wintergreen

It is used as an analgesic ointment to relive pain. Chemical name is methyl salicylate

Synthesis:



It is synthesized by the esterification of salicylic acid by using methanol and the reaction is catalyzed by concentrated H_2SO_4