Organic Reactions & Reaction Mechanisms/2

Organic reactions are chemical reactions involving organic compounds. The basic organic chemistry reaction types are addition reactions, elimination reactions, substitution reactions, pericyclic reactions, rearrangement reactions, photochemical reactions, and redox reactions. In organic synthesis, organic reactions are used in the construction of new organic molecules.

Substitution Reactions

In organic chemistry, substitution reactions are reactions where substituents get replaced by other species. Depending on the conditions and reagents involved, these reactions are categorized into three classes.

1. Free-radical substitution reactions.
2. Nucleophilic substitution reactions.
3. Electrophilic substitution reactions.

Free-radical Substitution Reactions

Free radical substitution is a chemical reaction that involves free radical species in which one or more hydrogen atoms of an organic compound are replaced by another species. This reaction occurs under the influence of UV light, a significant amount of heat energy, or radical initiators. Halogenation of hydrocarbons is one of the most important reactions in organic chemistry. It is performed via free radical substitution, and it is characterized by three steps: initiation, propagation, and termination.

Alkanes Halogenation

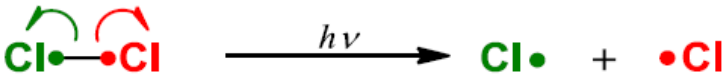
Alkanes are saturated hydrocarbons that contain only carbon and hydrogen atoms connected with single covalent bonds. In general, these compounds are considered unreactive since they lack reactive functional groups or unsaturation. Nevertheless, alkanes can undergo some reactions such as combustion "destruction of alkanes", pyrolysis "cracking", reactions with magic acids such as $HF\text{-}SbF_5$ and $FSO_3H\text{-}SbF_5$, and free radical halogenation. This latter is the most used reaction, and it consists in transforming the unreactive alkane into a more reactive substance "alkyl halides, alkyl dihalides, alkyl trihalides, and alkyl tetrahalides.

Mechanism

Free radical halogenation of alkanes is a chain reaction that passes through three stages.

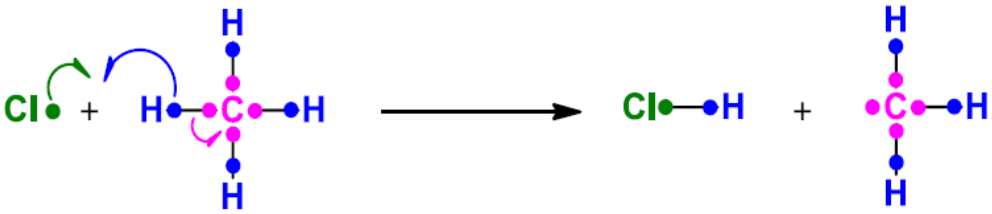
Initiation

The first step of halogenation requires UV light or sufficient heat energy to generate free radical halogens from dihalogen molecules. However, once free radicals are formed, the reaction is self-sustaining and UV light or heat is no longer necessary. For example, when UV light radiation penetrates a dichlorine molecule, the covalent bond connecting the two chlorine atoms breaks in such a way that each chlorine atom would carry away one unshared electron. This process creates, as a result, two free radicals of chlorine.



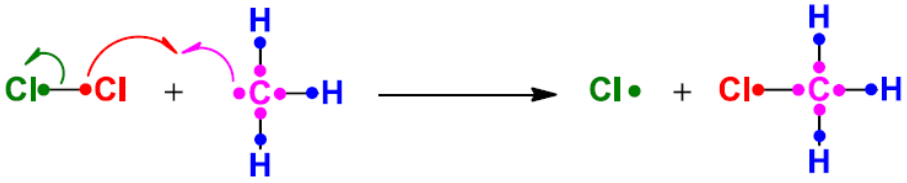
Propagation

The next step is called propagation where free radical halogens formed in the first step react with the substrate "methane". At this point, two types of reactions might occur; the first one is the reaction of chlorine-free radical with methane in which chlorine grabs one hydrogen atom from methane resulting in the formation of two new species; hydrogen chloride and methyl free radical.

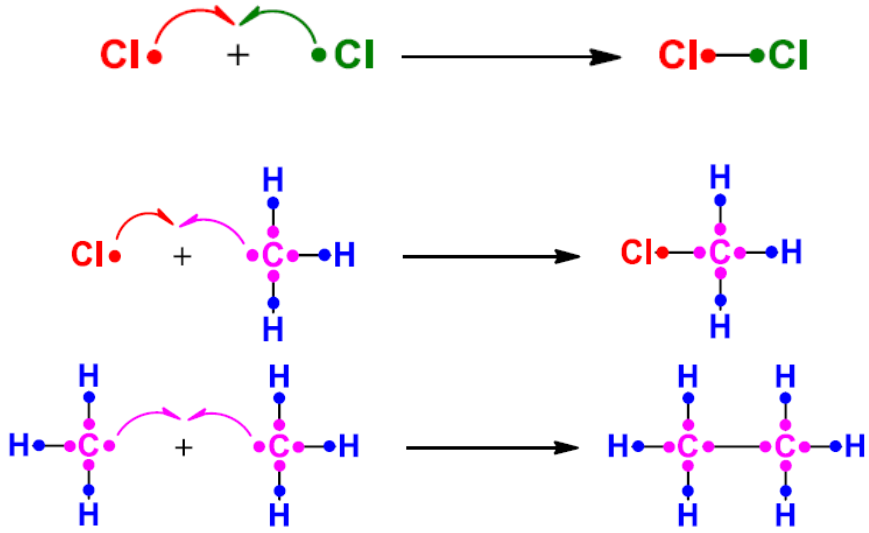


The second reaction proceeds in a similar way but in this case with the methyl free radical and another molecule of dichlorine, which produces a chloromethane molecule and a new chlorine free radical.

Termination

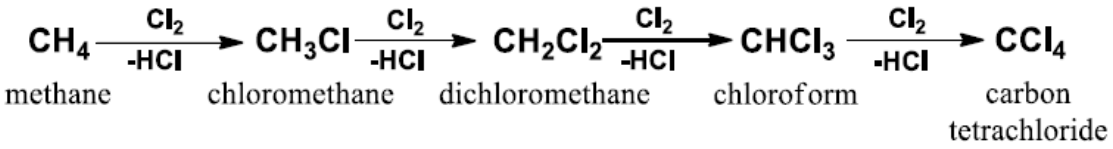


In the final step, free radicals combine and form new molecules. In this case, either two chlorine-free radicals combine to give dichlorine, a chlorine-free radical combines with an alkyl radical, or two alkyl radicals combine to form a higher alkane.



Control of Free Radical Halogenation

Free radical halogenation of alkanes does not usually stop at one substitution. If it is not controlled, a mixture of all potential products would be obtained. For example, chloromethane can undergo further substitution reaction and produces dichloromethane. Similarly, dichloromethane can also react with other dichlorine molecules and form chloroform then carbon tetrachloride.

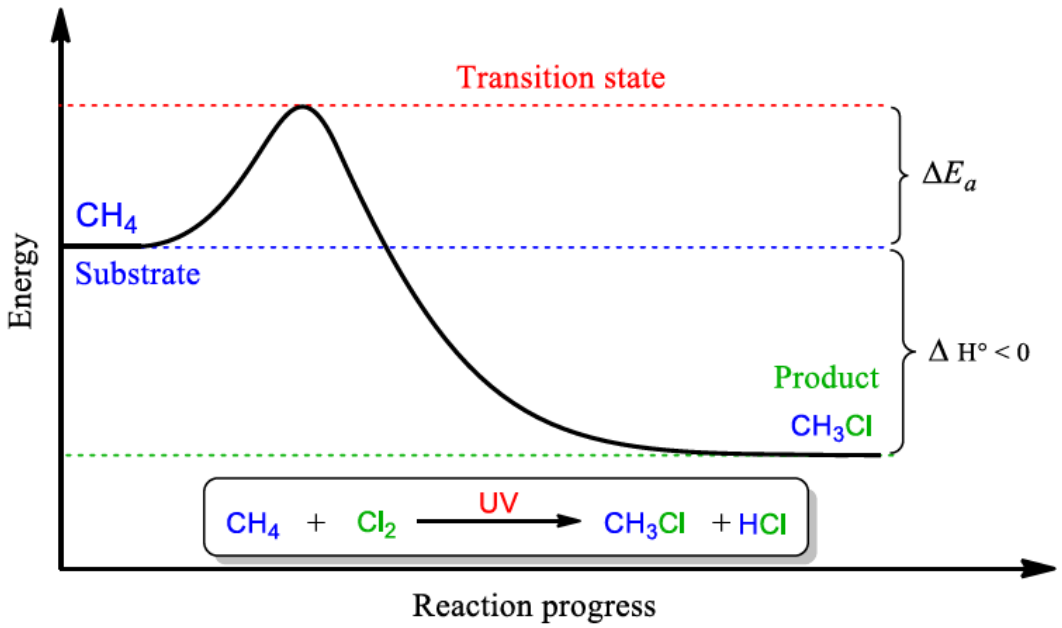


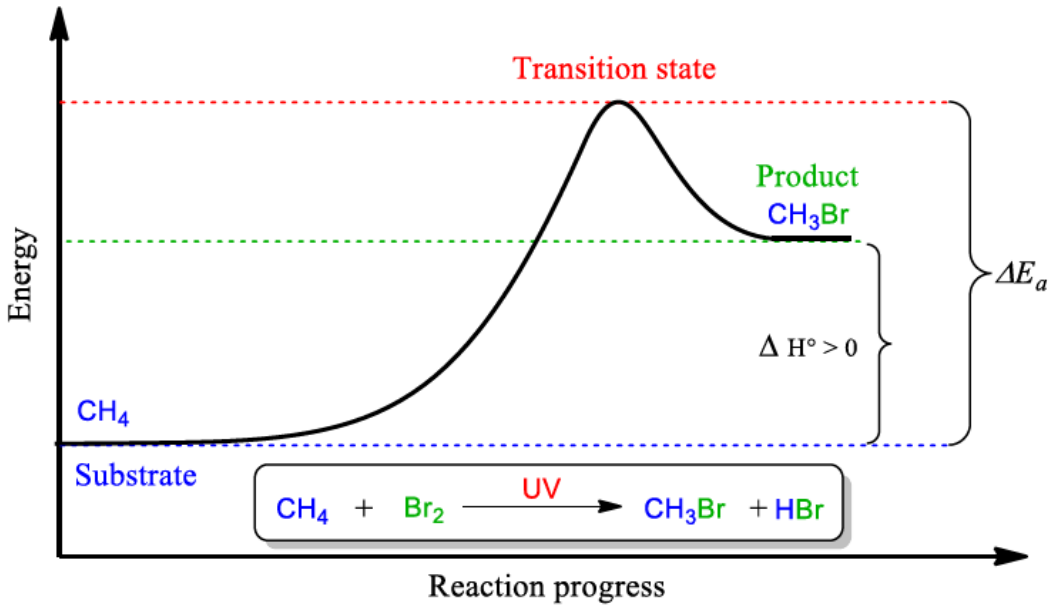
Moreover, free radical carbon species can also react with one another to form new C-C covalent bonds.

Relative Reactivity and Selectivity of Halogens

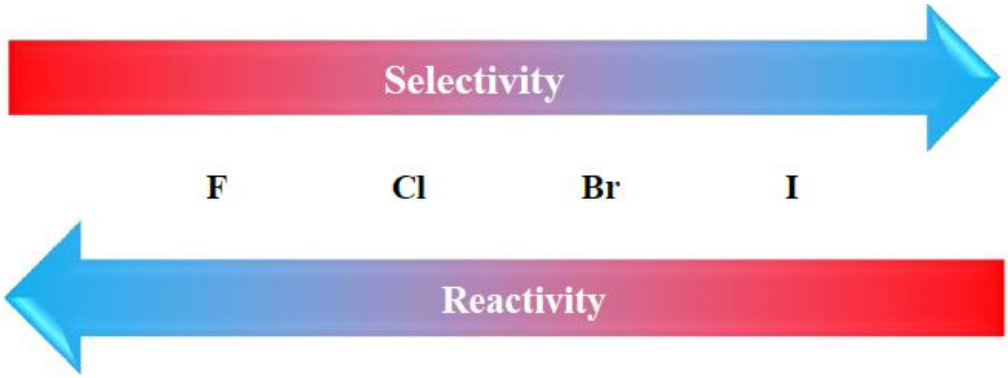
Although both bromine and chlorine undergo free radical halogenation, they do not behave in the same way and give different yields for the same products. This differentiation is related to the relative selectivity of each halogen. For instance, methane reacts with bromine in a similar way to chlorine and produces bromomethane, methylene bromide, bromoform, and carbon tetrabromide.

However, in contrast to chlorination, bromination is a slower reaction due to the stability of free radical bromine, which is maintained by the bromine polarizability. As a result, more energy must be provided to bromine to surpass the activation energy barrier and generate bromine free radicals. The diagrams below illustrate the difference between chlorination and bromination of methane. The activation energy of chlorination is smaller than the activation energy of bromination. In addition, chlorination of alkanes is an exothermic reaction where the products are more stable than the starting material. In contrast, bromination is an endothermic reaction that requires more energy to proceed.



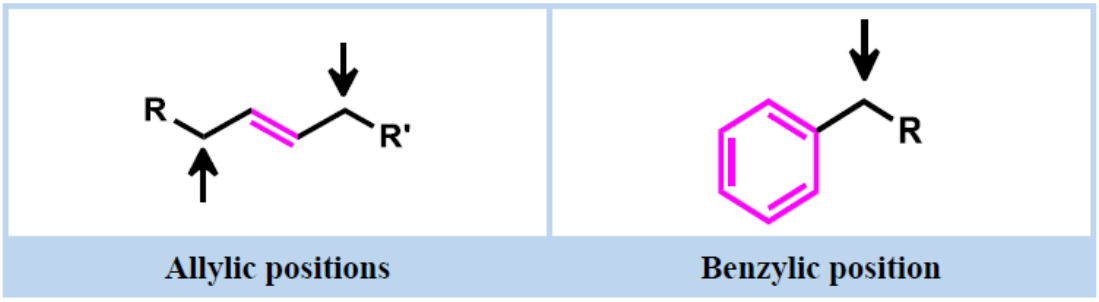


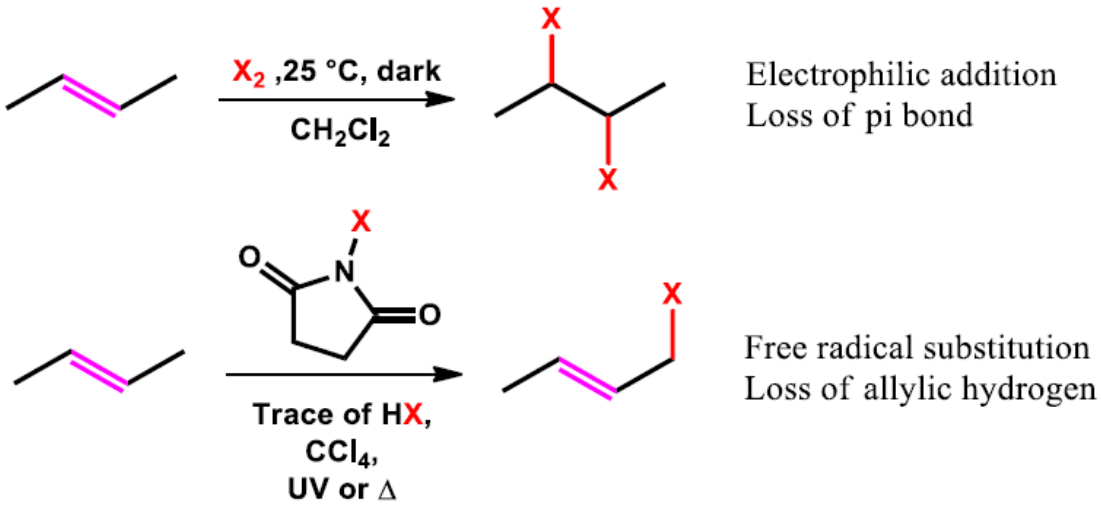
Unlike bromine and chlorine, fluorine reacts vigorously with methane so even in the dark and at room temperature, fluorination must be carefully controlled. The reason behind this is that fluorine has a higher reactivity than all the other halogens due to its higher electronegativity and small size. Iodine, on the other hand, does not react with methane because of its higher stability.



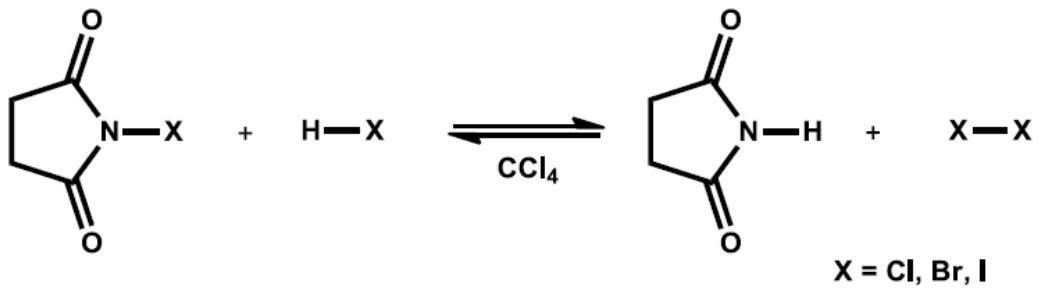
Allylic and Benzylic Halogenation

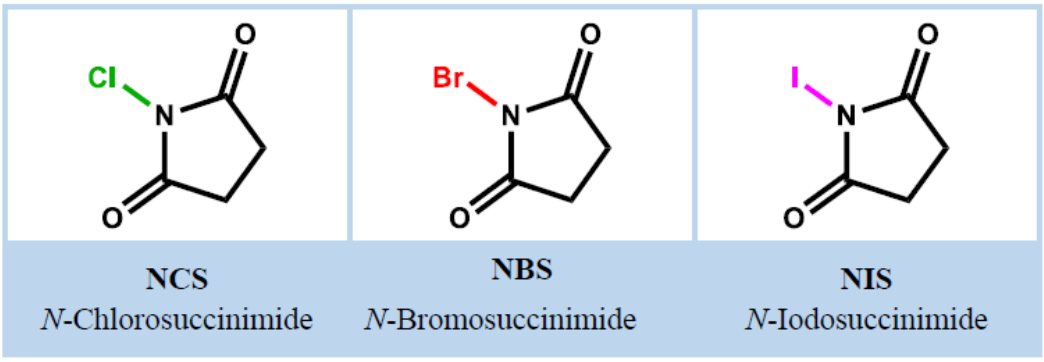
Unlike saturated hydrocarbons, allylic compounds may follow different pathways depending on reaction conditions. At high concentrations of halogens, allylic compounds undergo electrophilic addition rather than a free radical substitution reaction. However, when the concentration of halogens is controlled and kept low, a free radical substitution reaction takes place whereby the allylic hydrogen atom gets replaced by the halogen.





N-halo succinimides are halogen source reagents typically used in allylic and benzylic halogenation reactions to avoid electrophilic addition to the double bond. In this reaction, a stoichiometric amount of *N*-halo succinimide is required along with a small amount of the corresponding hydrogen halide to produce a low concentration of the corresponding dihalide making free radical substitution reaction possible.

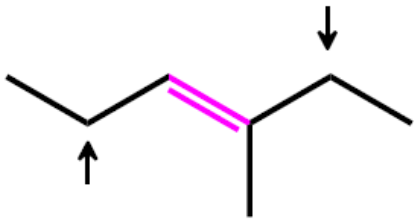




NCS	NBS	NIS
N-Chlorosuccinimide	*N*-Bromosuccinimide	*N*-Iodosuccinimide

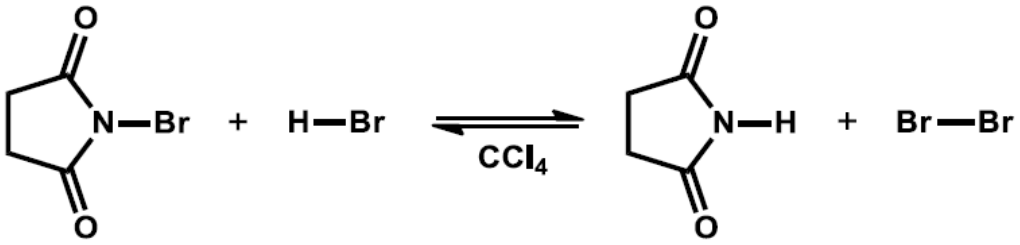
Mechanism

The Allylic bromination reaction is also known as the *Wohl-Ziegler* reaction, which consists in converting olefins into olefin bromides. The reaction mechanism is like regular alkanes halogenation except that the *Wohl-Ziegler* reaction requires NBS to keep bromine concentration adequate for allylic substitution.



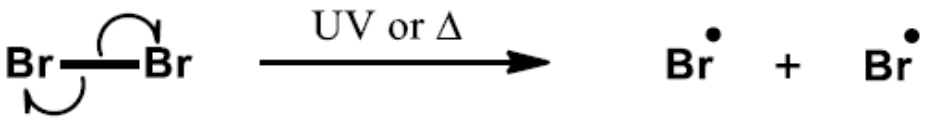
Production of dibromine

This is a reversible reaction where NBS reacts with HBr to produce dibromine and succinimide. This process is repeated whenever a new HBr is available.



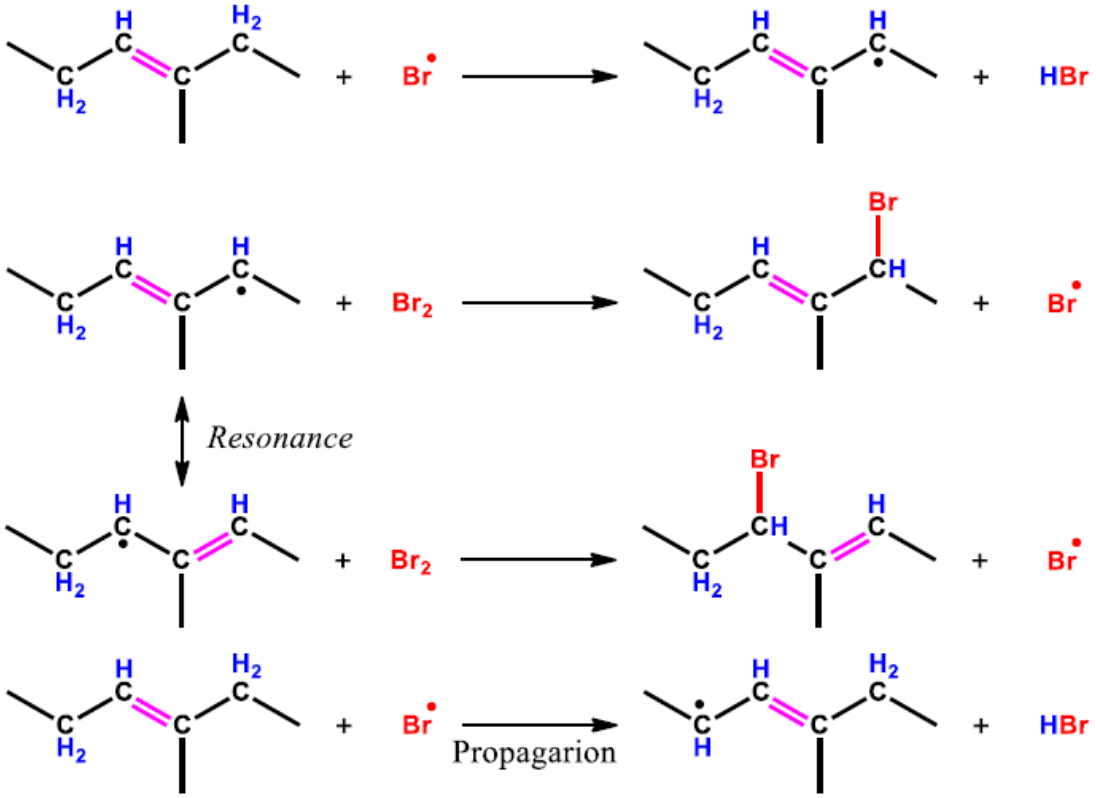
Initiation

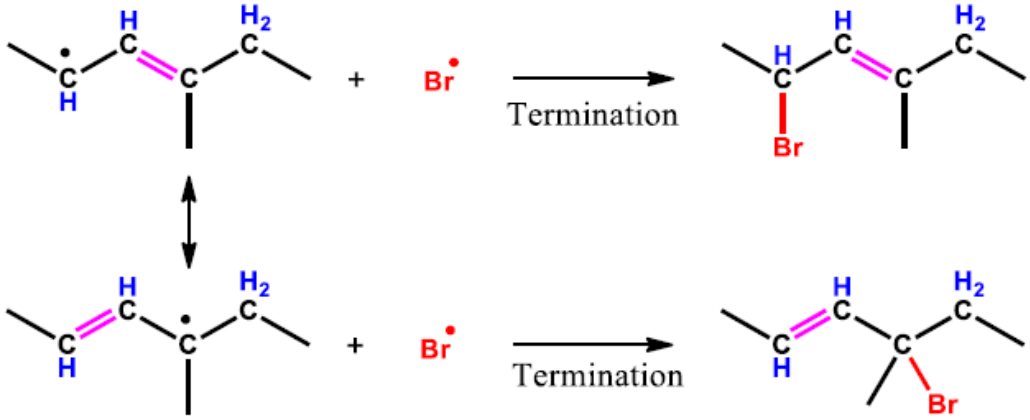
Under UV light or at high temperature, the dibromine formed would give two bromine free radicals upon homolytic fission of the covalent bond.



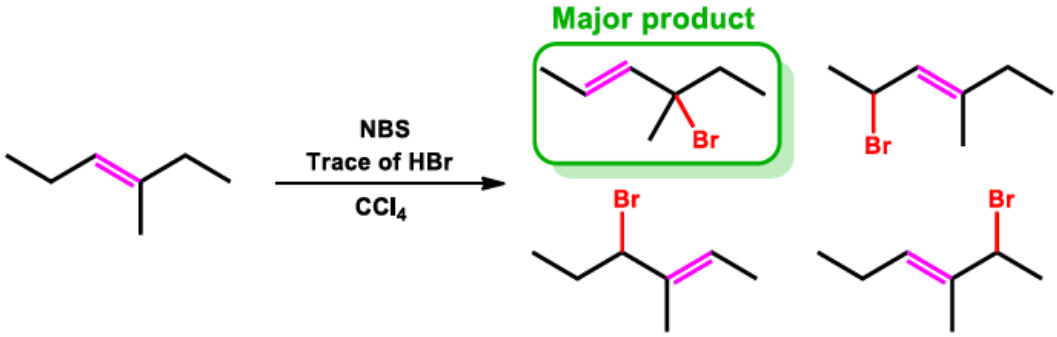
Propagation and Termination

When free radical carbon forms on the allylic position, resonance becomes possible and as a result, bromine can add on either radical allylic carbon atoms.

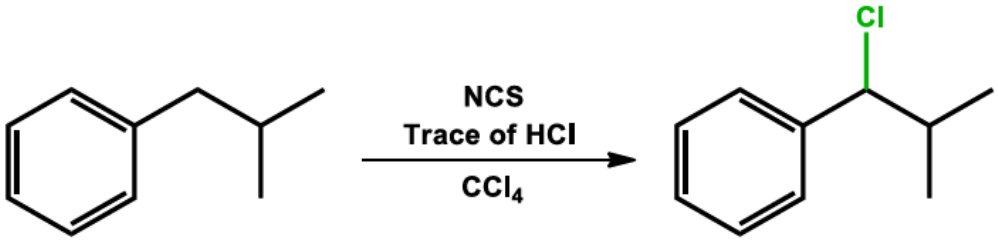




Moreover, although this reaction may produce four compounds, only one product would be predominant over the others because bromine preferentially adds to the most substituted allylic radical.

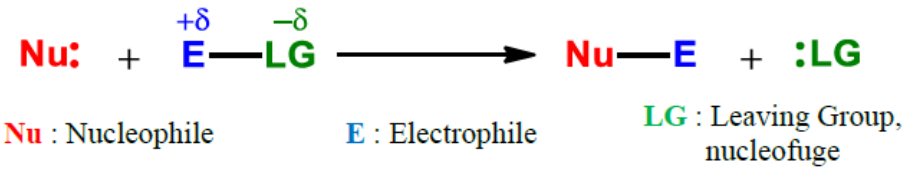


Under UV radiation, at high temperature, or with radical initiators, benzylic compounds undergo free radical substitution reactions on the benzylic position when they are treated with NCS and HCl in CCl_4. Nevertheless, this reaction is also possible with Cl_2 and UV light.



Nucleophilic Substitution Reactions

Nucleophilic substitution reactions are one of the fundamental chemical reactions in organic chemistry. They are characterized by the replacement of a nucleofuge with a nucleophile.



Furthermore, depending upon the substrate type, nucleophilic substitution reactions are classified into two main categories: nucleophilic aliphatic substitutions, and aromatic nucleophilic substitutions.

Nucleophilic Aliphatic Substitution Reactions

Nucleophilic aliphatic reactions are subdivided into two types of reactions: unimolecular nucleophilic substitution reaction, and bimolecular nucleophilic substitution reaction. Although both reactions involve the same process "the displacement of leaving group", each type requires specific conditions to proceed.

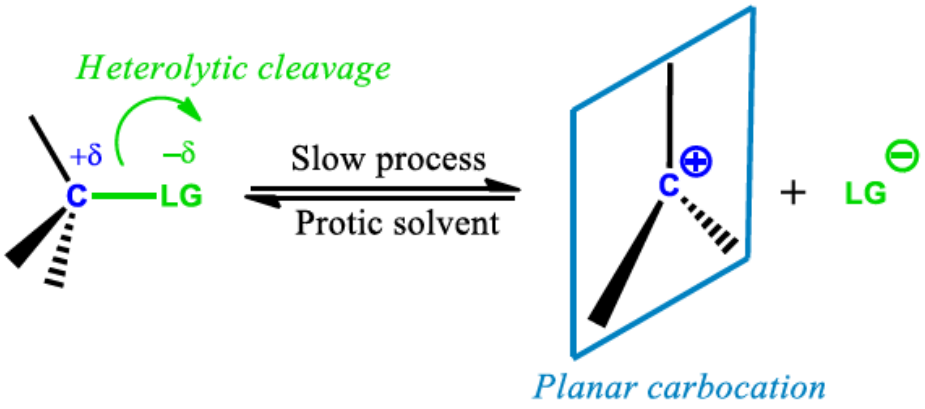
Unimolecular Nucleophilic Substitution Reactions S_N1

S_N1 Mechanism

S_N1 reaction proceeds in two steps and involves a carbocation intermediate.

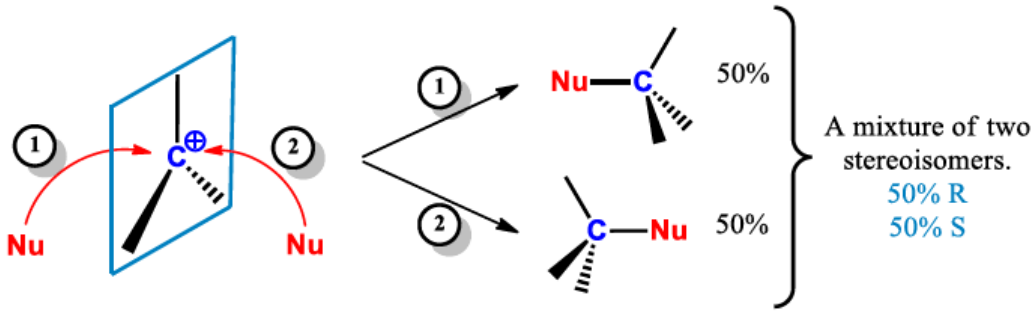
Step One

The first step is a slow process characterized by the heterolytic fission of the C-LG bond, which leads to the formation of a planar carbocation. This step may or may not be reversible.



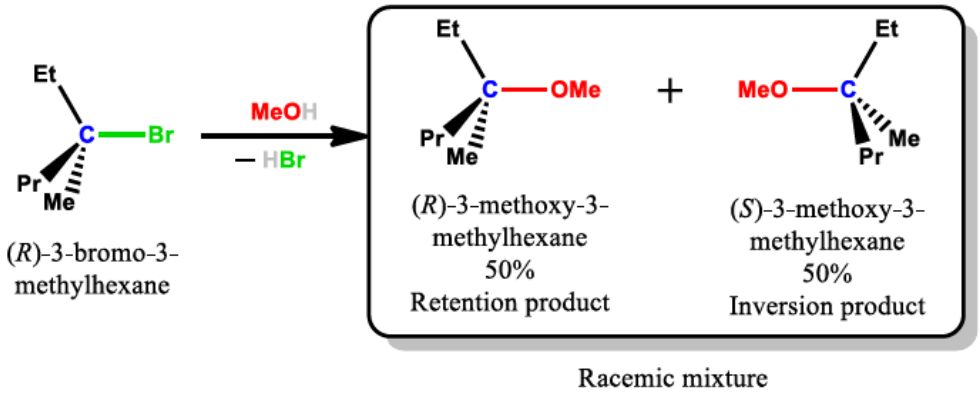
Step Two

The second step, on the other hand, is a fast process whereby the nucleophile attacks the planar carbocation from either side creating a new covalent bond with it. If this carbocation is formed from a chiral carbon, the reaction will give a mixture of two stereoisomers. This propriety makes S_N1 reaction a **non-stereoselective** reaction.



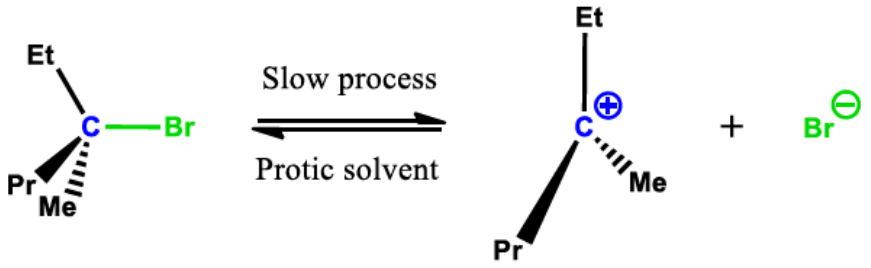
Example 1:

If the substrate contains only one chiral center, S_N1 reaction would lead to an enantiomeric mixture "racemic mixture", which is **optically inactive**.



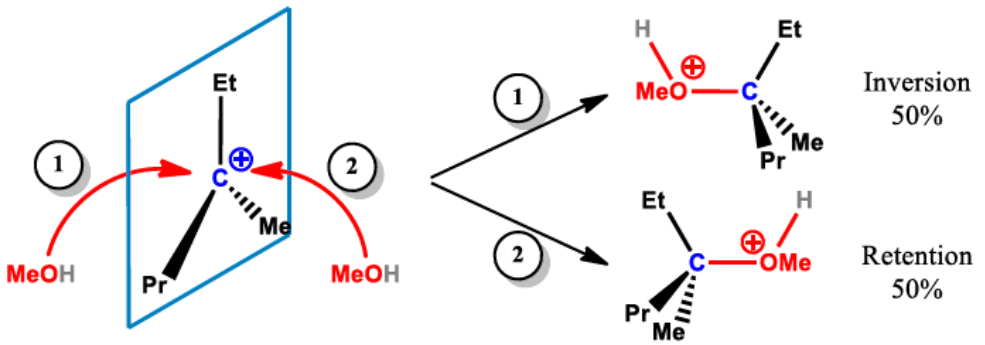
Step one

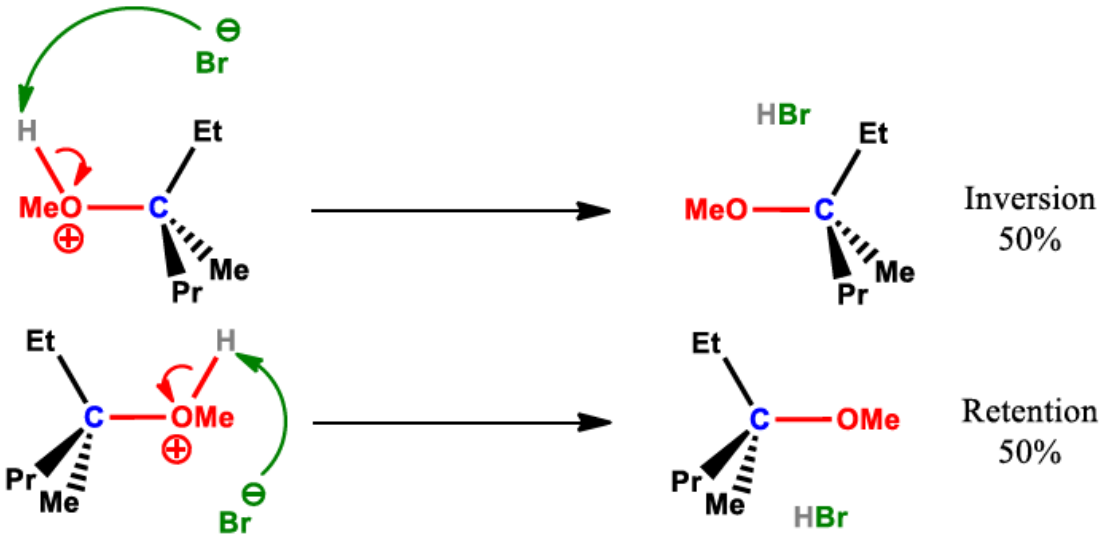
Formation of carbocation intermediate.



Step two

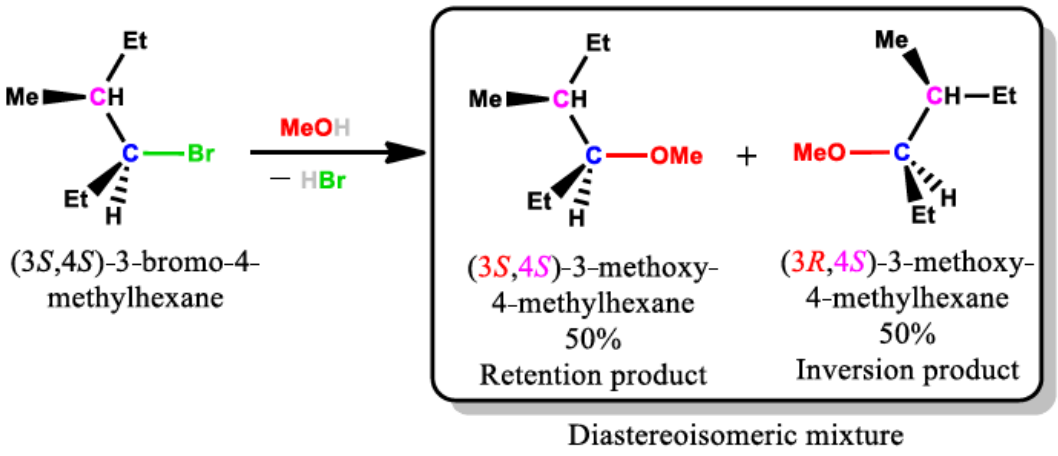
Attack of the nucleophile.





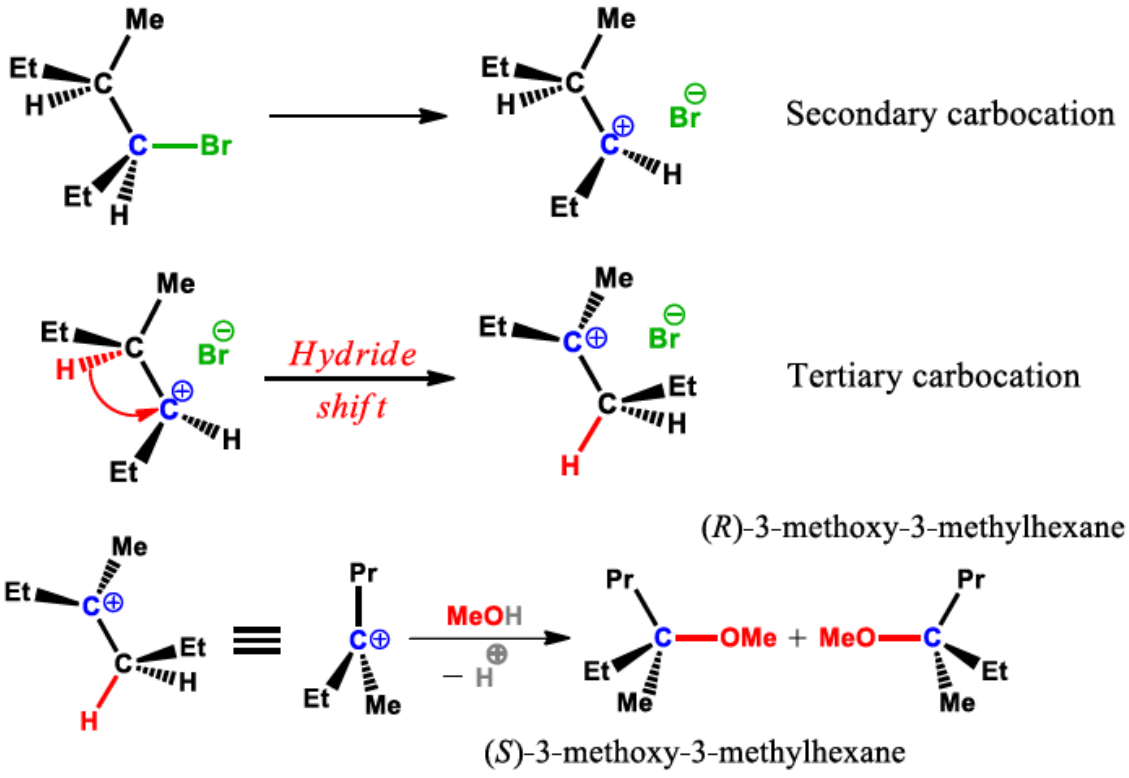
Example 2:

If the substrate contains more than one chiral center, the reaction outcome would be a diastereoisomeric mixture. In this case, the mixture obtained is **optically active**.



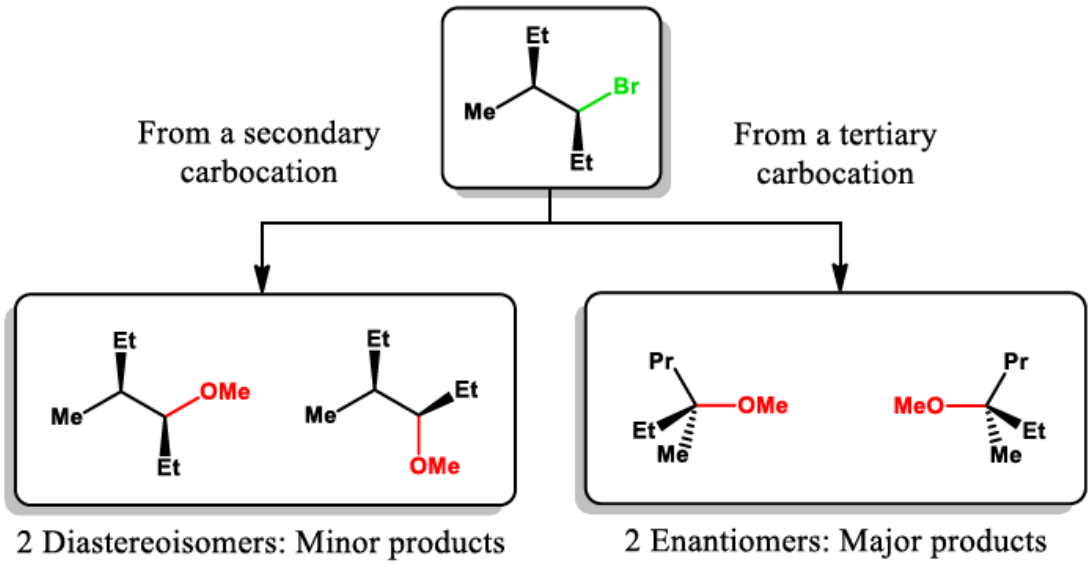
Carbocation Rearrangement (hydride, methyl, and aryl shifts)

As mentioned before, carbocations tend to acquire a more stable state by delocalizing the positive charge to a more substituted carbon atom via a 1.2-shift. In this example, the secondary carbocation intermediate can rearrange into a



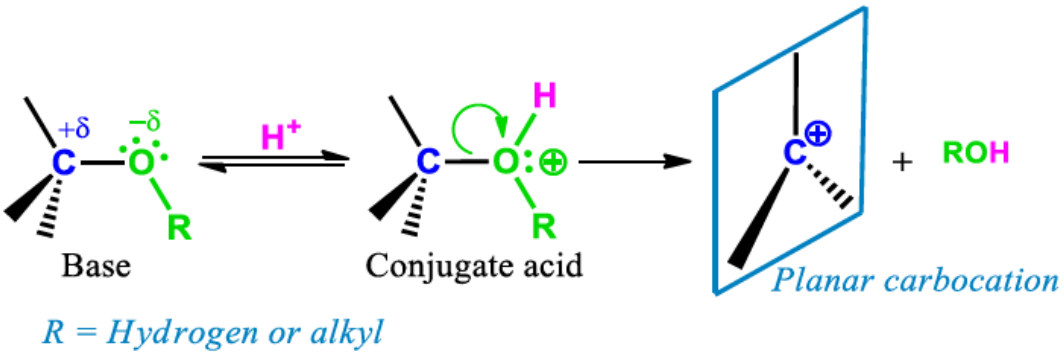
tertiary carbocation via hydride shit, which will then get captured by the nucleophile “MeOH”.

Because of carbocation rearrangement, the reaction outcome would be four isomers. However, one stereoisomeric mixture would predominate over the other making this reaction a **regioselective reaction**.



SN1cA (Conjugate Acid) Mechanism

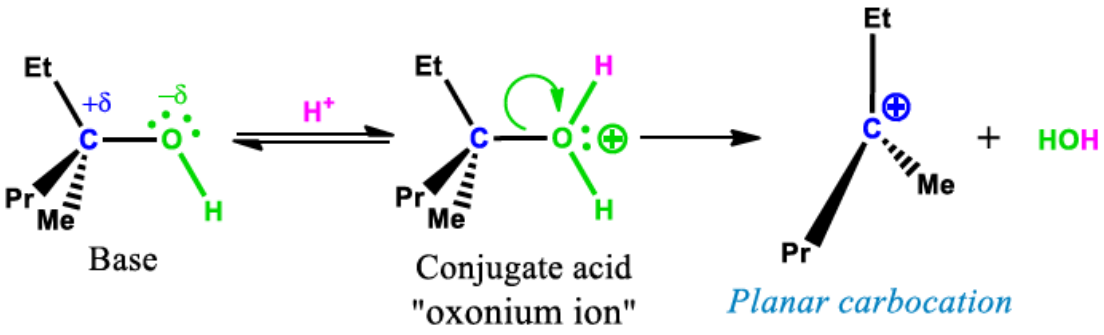
Unimolecular substitution can also proceed through an S_N1cA, mechanism also known as the A1 mechanism, which differs from S_N1 only in the first step where an acid-base interaction occurs. This reaction occurs with alcohols and ethers “bases” where the oxygen gets protonated to form a better-leaving group “conjugate acid”.



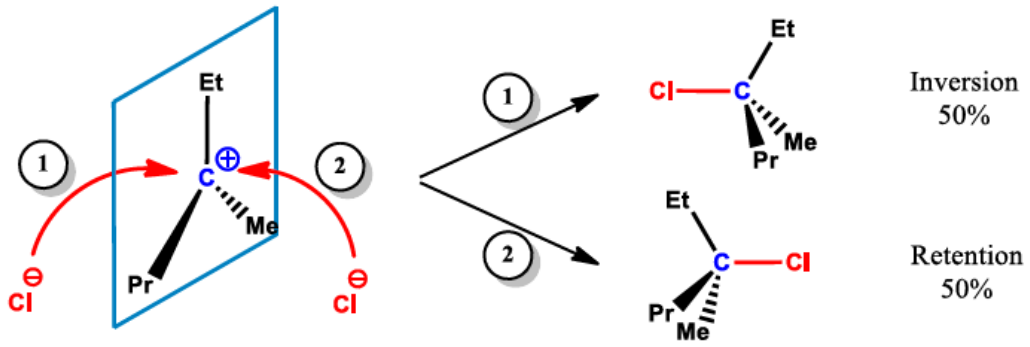
R = Hydrogen or alkyl

Example

A good example of S_N1cA reactions is the reaction of tertiary alcohol with hydrogen halide. In this case, the hydroxy group of the alcohol abstracts a hydrogen proton from the hydrogen halide molecule to form an oxonium ion "conjugate base". Once protonation is done, the leaving group "water" departs from the substrate creating, this way, a carbocation intermediate.

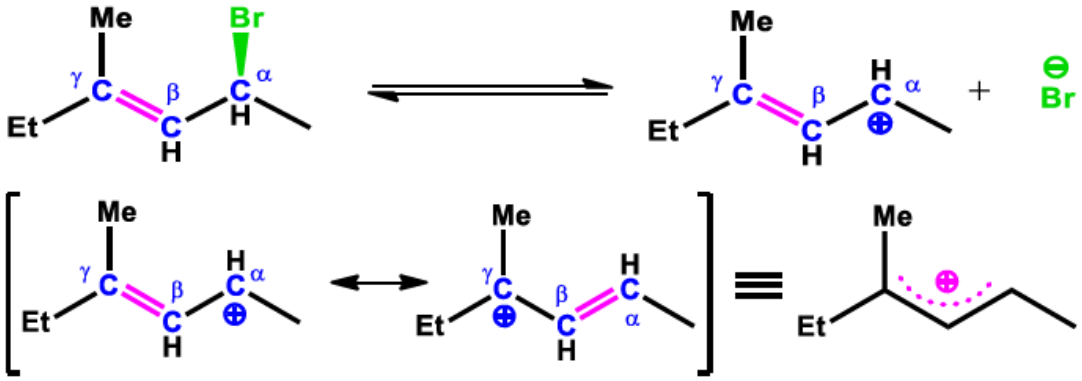


Next, the reaction proceeds according to the S_N1 mechanism where the nucleophilic halide attacks the carbocation from either side.

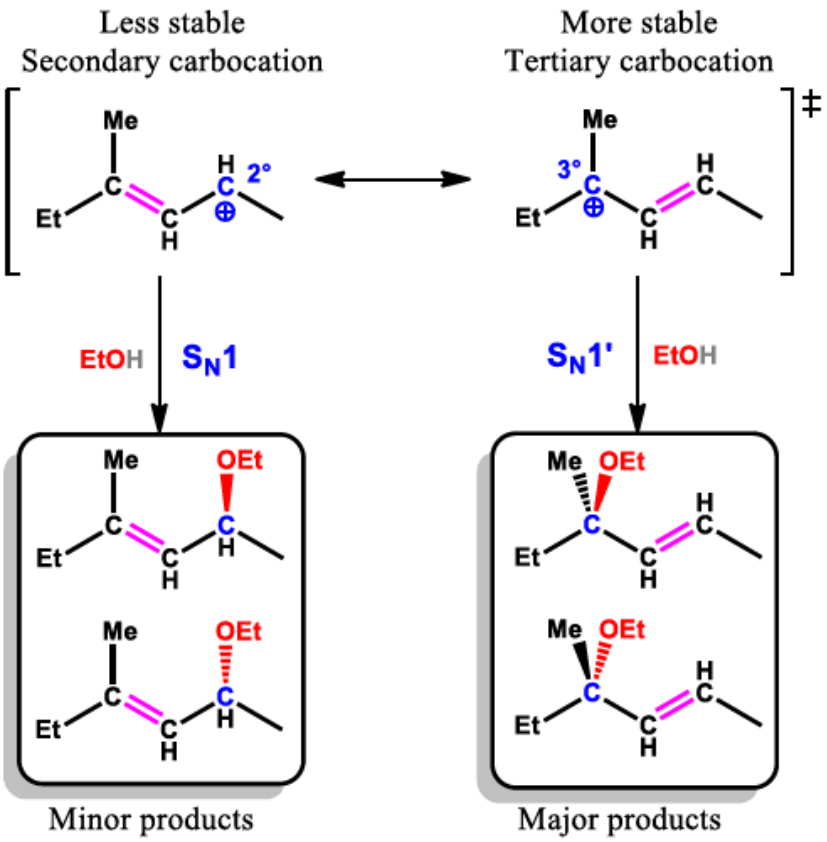


S_N1' (Allylic Substitution) Mechanism

When the nucleofuge is attached to an allylic carbon atom, the substrate undergoes nucleophilic substitution reaction via an S_N1 mechanism. In such a case, the carbocation intermediate formed is stabilized by resonance where the positive charge is distributed between the two carbons α and γ.



At this point, the nucleophile can attack α carbon via the S_N1 mechanism or γ carbon via the S_N1 mechanism. Reactions that involve the S_N1 mechanism are **non-stereoselective** because both stereoisomers form. Nevertheless, they are **regioselective** since the nucleophile preferentially attacks the most substituted allylic carbocation.



Kinetics

Unimolecular substitution reactions follow the first-order kinetics where the reaction rate depends solely on the substrate concentration. As mentioned earlier, in unimolecular substitution reactions, nucleophiles do not intervene in the first step, which determines the overall rate of reaction. As a result, increasing or decreasing the concentration of the nucleophile will not change the velocity of the reaction.

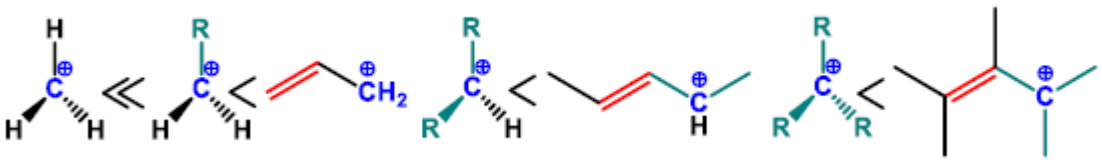
Rate = K[Substrate]

Reaction Conditions

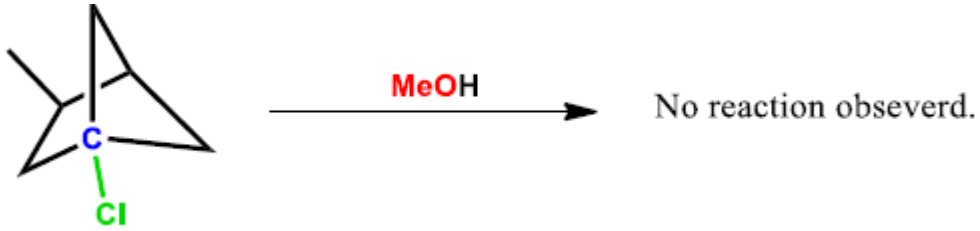
Unimolecular substitution reactions are not possible unless certain conditions are met. These conditions include substrate type, nucleophile strength, stability of the nucleofuge, and the solvent used.

Substrate

Since the S_N1 reaction involves an ionic intermediate, it is important that the carbocation intermediate be stable. As a result, S_N1 is more likely to occur when the stability of carbocation is optimized by ERGs, 1,2-shifts, and allylic rearrangement. Consequently, S_N1 reaction is more favorable with tertiary carbocation, and can occur with secondary carbocation, but never with a primary carbocation or methylium compounds. *Primary allylic and benzylic carbocations are exceptions*.



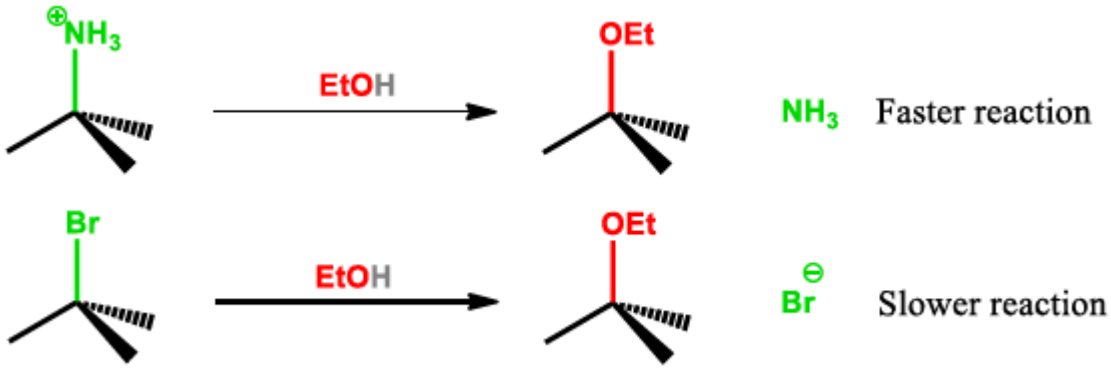
Furthermore, S_N1 reaction is rarely observed with fused system substrates in which the leaving group is attached to the bridgehead carbon atom. The reason behind this is that the overall shape of the substrate prevents the targeted bridgehead atom from attaining the planar geometry as the leaving group gets expelled. Nonetheless, if one ring is sufficiently large to allow the bridgehead atom to attain a planar geometry, an S_N1 reaction becomes possible.



Leaving Group

In general, nucleophilic substitution reactions require a good leaving group that can be stable when it gets expelled from the substrate. However, the speed of the S_N1 reaction is subjected to the stability of the leaving group. *The better a nucleofuge, the faster the reaction*. This is because the leaving group is involved in the rate-determining step. The illustration below shows some common nucleofuges arranged according to their stability in ascending order.

In the example below, both reactions involve the same nucleophile, and both give the same product. However, the first reaction is faster than the second one because ammonia is a better-leaving group than bromine.

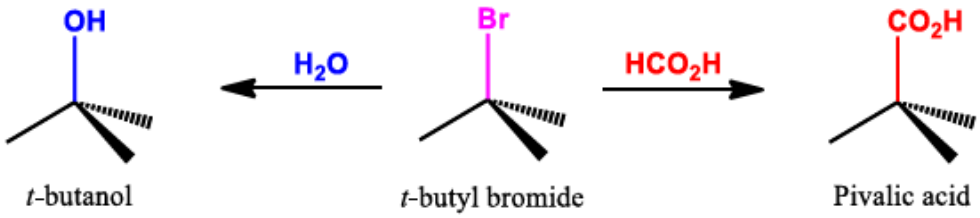


Nucleophiles

In most cases, nucleophiles involved in the S_N1 reaction are weak and neutral molecules such as MeOH, EtOH, and NH_3. Moreover, since nucleophiles are not involved in the rate-determining step, the strength of these nucleophiles is not important. Nevertheless, when more than one nucleophile is present in the reaction medium, they compete. In such a case, the strength and the concentration of each nucleophile become significant and affects the distribution of products.

Example

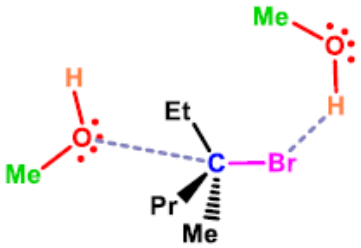
If *t*-butyl bromide is treated with distilled water and formic acid, a mixture of two products would be obtained; *t*-butanol and pivalic acid where the yield of each product depends upon the concentrations and the nucleophilicity of HO^- and HCO_2^-.



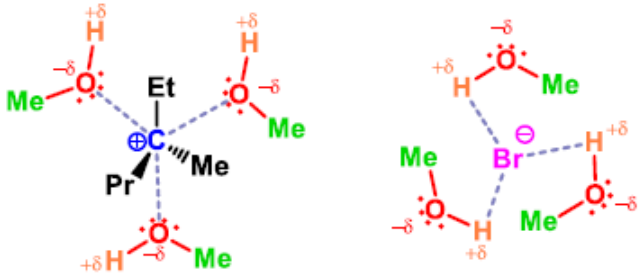
Solvent Effect

Polar protic solvents are efficient for S_N1 reaction; they facilitate the heterolysis of the nucleofuge and help stabilize the carbocation intermediate. In contrast, polar aprotic solvents are not suitable for S_N1 reactions because they may react with the intermediate and thus lead to the formation of unwanted products.

In the first step, polar protic solvents form hydrogen bonds with the leaving group and therefore polarize the covalent bond that connects it to the substrate. This process facilitates bond heterolysis.



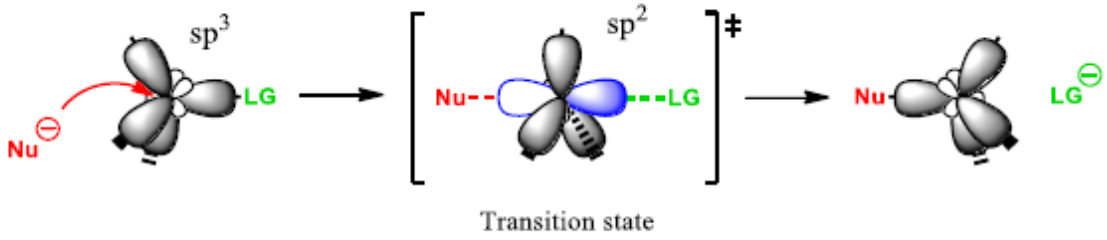
After the leaving group gets expelled, solvent molecules would surround it and form hydrogen bonds with it. Similarly, the carbocation formed would also get surrounded by the negative side of the solvent, which makes it more stable.

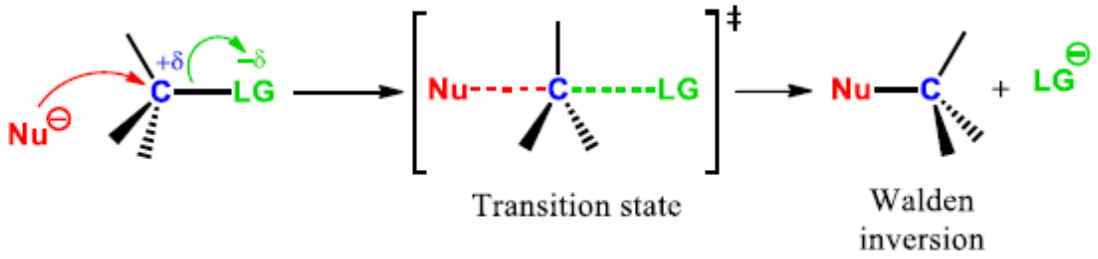


Bimolecular Nucleophilic Substitution Reactions S_N2

S_N2 Mechanism

S_N2 reactions are second-order reactions that occur in one step only passing through a transition state to give a single product. At the transition state, the targeted carbon atom goes from sp^3 hybridization to sp^2 hybridization where the unhybridized p orbital is perpendicular on the trigonal plane. The nucleophile approaches the substrate and overlaps with one lobe of the unhybridized p orbital, which is on the opposite side of the leaving group. At this point, a new bond starts forming between the nucleophile and the substrate while the bond connecting the nucleofuge to the substrate breaks.

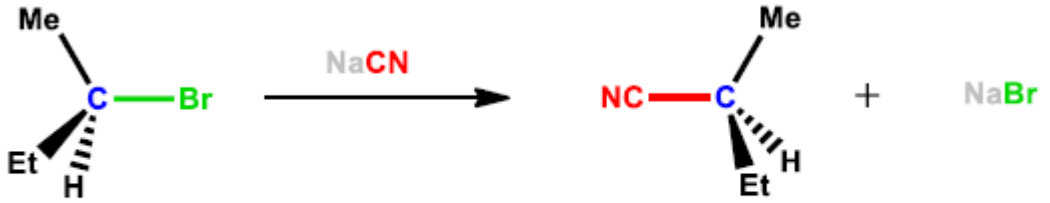




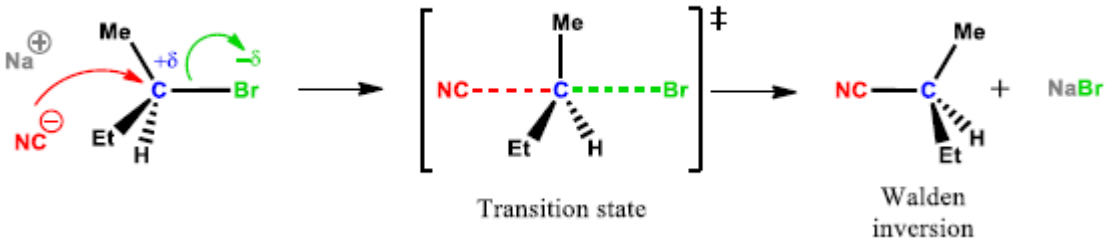
The S_N2 reaction is a **regiospecific** reaction whereby the nucleophile attacks the targeted carbon atom exclusively from the opposite side of the leaving group "*anti*-attack". As a result, the stereochemistry of the final product depends upon the stereochemistry of the substrate, which makes the S_N2 reaction **stereospecific** that gives the inversion product.

Example:

The reaction of (*R*)-2-bromobutane with aqueous sodium cyanide gives (*S*)-2-methylbutanenitrile.

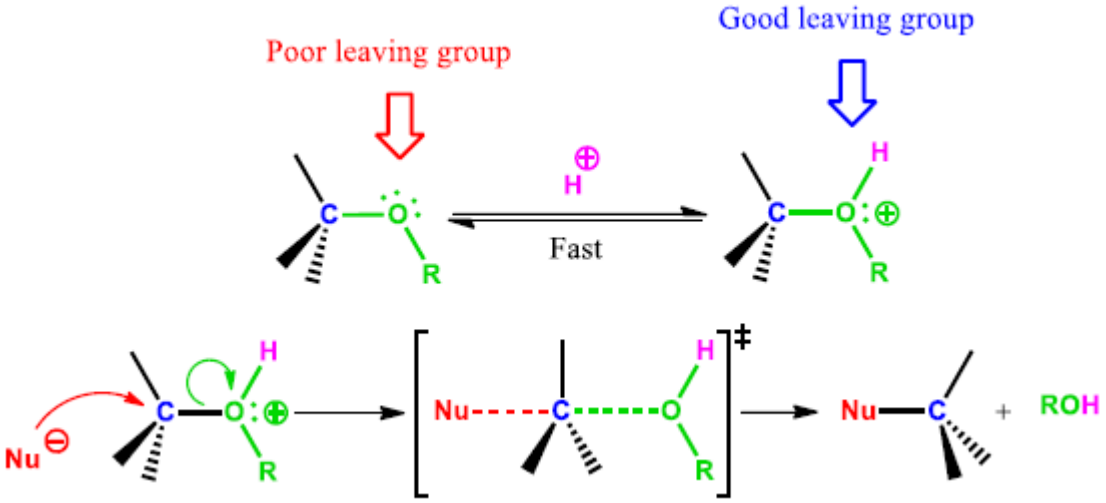


(*R*)-2-bromobutane (*S*)-2-methylbutanenitrile



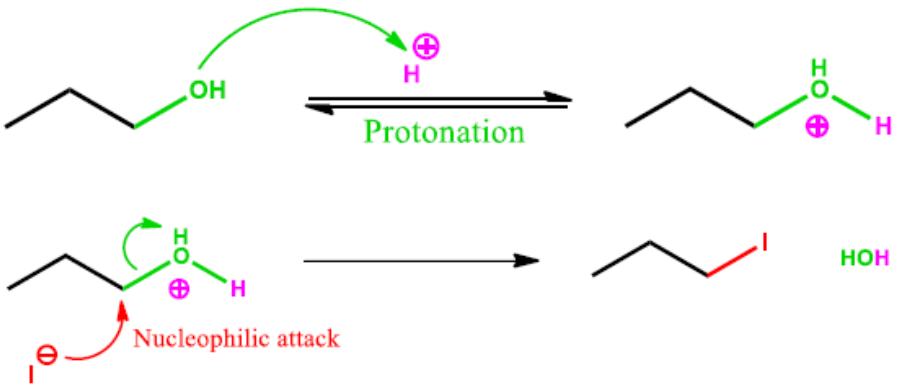
S_N2cA (Conjugate acid) Mechanism

Before undergoing a bimolecular substitution reaction, certain substrates require an additional step that consists in converting the leaving group into a better nucleofuge. In this case, the overall reaction is known as the S_N2cA reaction, which involves acid-base interaction whereby the leaving group gets protonated (conjugate acid). This reaction is common with alcohol and ethers.



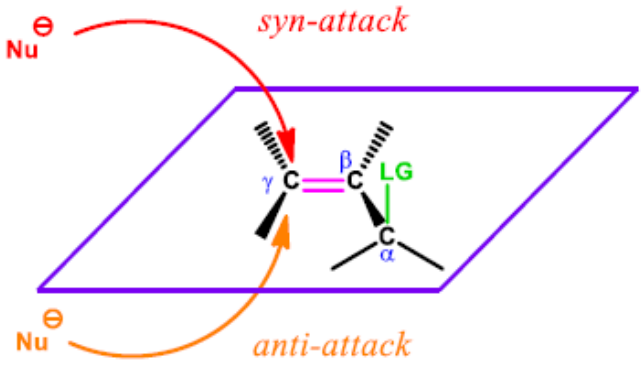
Example:

Primary alcohols react with strong hydrogen halides such as HBr and HI to give the corresponding alkyl halide and a water molecule. In such a reaction, the hydroxy group cannot be displaced by the nucleophilic halide unless it is protonated. For that, before nucleophilic attacks take place, the hydroxy group must get protonated to generate a better-leaving group. At this point, the nucleophile attacks the targeted carbon atom from the backside, which leads to the formation of alkyl iodide and a water molecule.



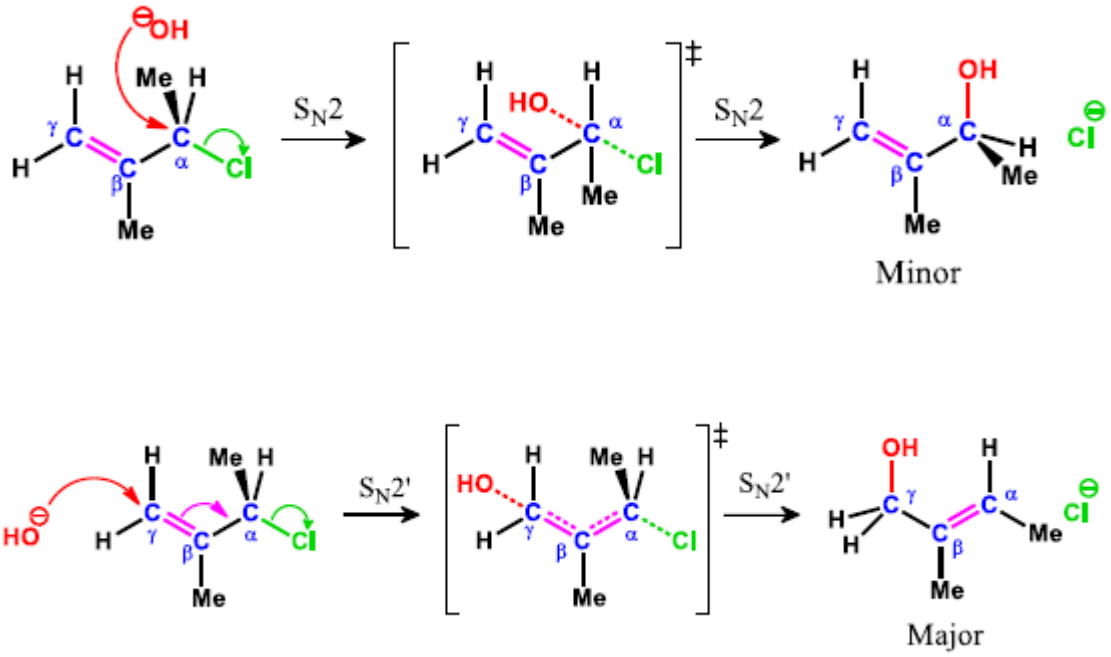
S_N2' (Allylic Substitution) Mechanism

Allylic and benzylic compounds can also undergo S_N2 reactions when reaction conditions are met. In such a case, the nucleophile may attack α carbon via the S_N2 mechanism or γ carbon via the S_N2 mechanism depending upon the steric hindrance of each carbon atom. Allylic compounds with a primary or secondary α carbon favor S_N2 reaction. However, tertiary α carbons or secondary α carbon with bulky alkyl group disfavor S_N2 reaction. In this case, the reaction proceeds exclusively via the S_N2 mechanism. Furthermore, the size of the nucleophile also plays an important role in determining which mechanism is more favorable. In addition, in the case of the S_N2 mechanism, the nucleophile can attack from either side of the π bond. If the nucleophile attacks the γ carbon from the same side of the leaving group, the attack is referred to as a *syn-attack*. On the other hand, when a nucleophilic attack occurs on the opposite side of the leaving group, then it is called *anti-attack*.



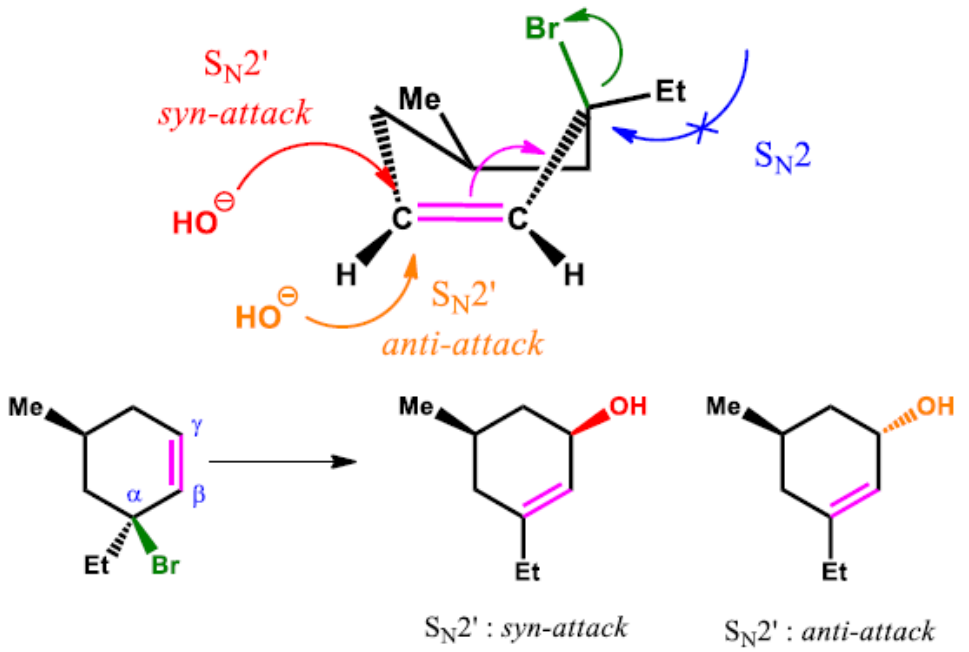
Example 1

In this example, α carbon is secondary whereas γ is primary. In this case, the nucleophile can attack both because although α carbon is secondary, it is not sterically hindered enough to impede the nucleophilic attack. Besides, the nucleophile used is not bulky. However, there would be more S_N2 products than S_N2 products, which makes reactions that involve the S_N2 mechanism **regioselective** since the nucleophile preferentially attacks the least hindered carbon atom.



Example 2

In this example, α carbon is tertiary whereas γ carbon is secondary. As a result, the reaction would exclusively proceed via the S_N2 mechanism.



Because the nucleophilic attack can occur via *syn* or *anti* attacks, S_N2'reaction is **non-stereoselective**.

Kinetics

Bimolecular nucleophilic substitutions follow the second-order kinetics. Their rates depend upon the concentration of both reagents, the nucleophile, and the substrate. This is because both are involved in the rate-determining step.

Rate = K[Substrate][Nucleophile]

Although this equation was found to be accurate for many reactions in organic chemistry, experiments showed that when undergoing reactions that involve an excess of nucleophiles, the rate will be first order instead of second order. In this case, the rate of the reaction would depend solely on the concentration of the substrate. These reactions are referred to as pseudo-first order.

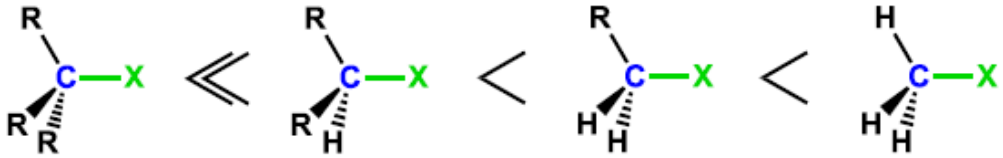
Rate = K[Substrate]

Reaction Conditions

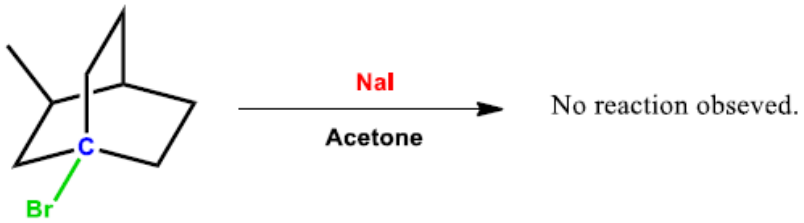
The following conditions determine whether an S_N2 reaction is possible or not.

Substrate

S_N2 reaction depends upon the steric hindrance of the targeted carbon atom. the more sterically hindered the substrate, the less reactive. As a result, the S_N2 reaction is more favorable with methylium compounds "methyl halides, primary alcohols" and primary substrates. For secondary substrates, on the other hand, S_N1 and elimination reactions compete with S_N2 reactions where a mixture of products may be produced. In the case of tertiary alkyl compounds, S_N2 reaction is not observed.

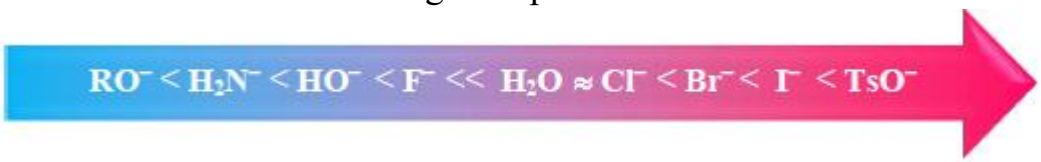


Moreover, when the leaving group is attached to a bridgehead carbon of a polycyclic, an S_N2 reaction cannot take place due to the steric hindrance that prevents the nucleophile from approaching the targeted bridgehead carbon atom.



Leaving Group

Just like the S_N1 reaction, the S_N2 reaction also requires a good leaving group that forms a stable ion when it gets expelled from the substrate.



Nucleophile

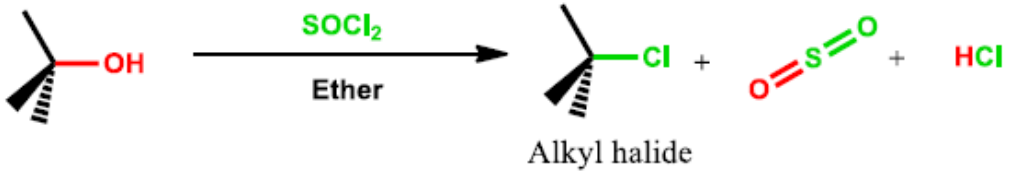
In the S_N2 reaction, the concentration, strength, and size of the nucleophile are important. As the concentration of the nucleophile increases, the reaction proceeds faster. Furthermore, the S_N2 reaction requires strong nucleophiles "generally anionic" to avoid the formation of a carbocation intermediate and therefore turn into an S_N1 reaction. In addition, the nucleophile must be small enough to be able to attack the targeted carbon atom.

Solvent

Polar protic solvents slow down S_N2 reactions as they capture the strong nucleophile forming hydrogen bonds with it. However, using a polar aprotic solvent improves nucleophile nucleophilicity and helps polarize the bond attaching the nucleofuge to the substrate.

Internal Nucleophilic Substitution S_Ni

Internal nucleophilic substitution reaction is a relatively rare reaction that follows first-order kinetic. In contrast to the S_N2 reaction that leads to the inversion of configuration, the S_Ni reaction gives the retention product. This reaction consists in converting a substrate "alcohol" to an alkyl halide.



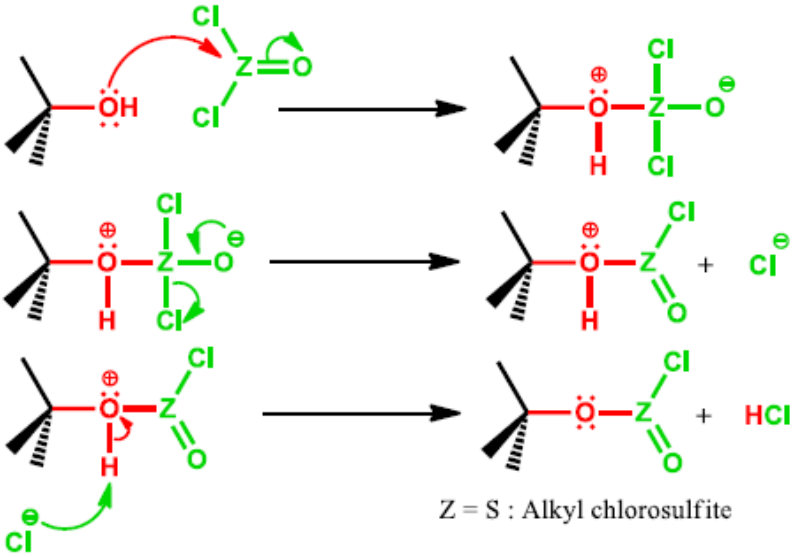
Alkyl halide

Mechanism

S_Ni reaction is carried out with thionyl chloride $SOCl_2$ or phosgene $COCl_2$ in the presence of an ether and it proceeds in two steps after the preparation step.

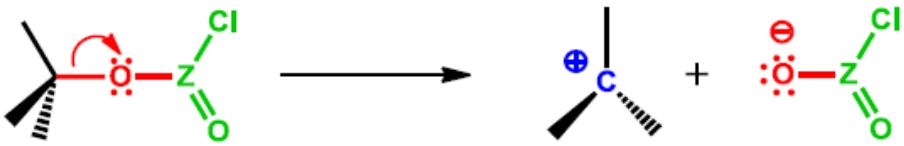
Preparation step

This step consists in converting the substrate into an alkyl chlorosulfite or an alkyl chloroformate. At this point, an S_N2 reaction takes place whereby the hydroxy group of the substrate attacks either thionyl chloride or phosgene to create a better-leaving group.



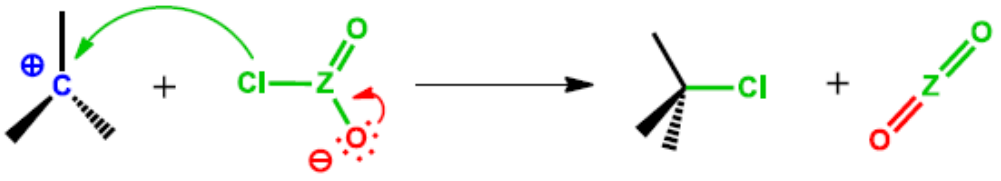
Step one

The first step is like the S_N1 reaction. At this point, the bond between the substrate and the leaving group gets polarized, and then the nucleofuge gets expelled resulting in a carbocation intermediate.

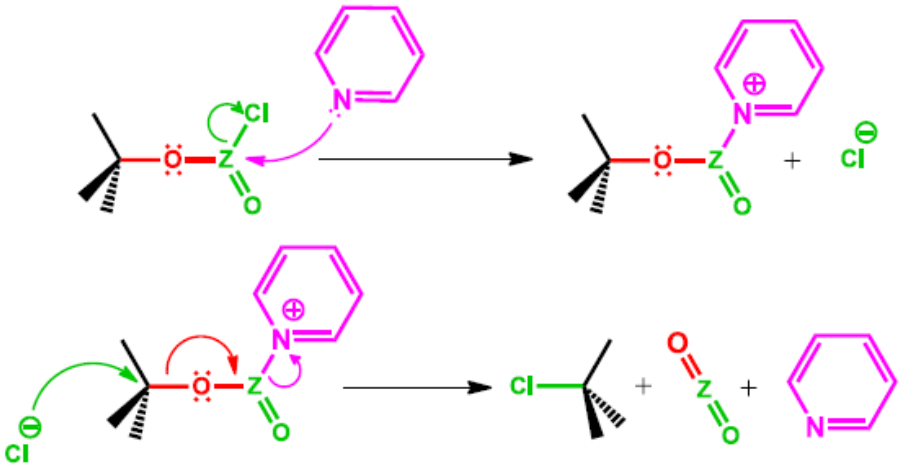


Step two

In the second step, the nucleofuge expelled would act as a nucleophile and attack the carbocation from the same side the nucleofuge got expelled forming, as a result, the product with retention of configuration.

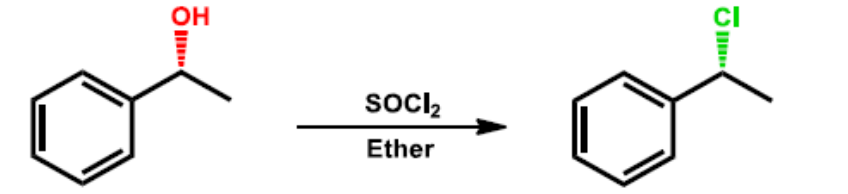


In the case of performing the reaction under a basic condition, the S_N2 reaction would take place instead of the S_Ni reaction. In this case, the base would react with the substrate "alkyl chlorosulfite or alkyl chloroformate" at first to form an organic salt. Then, the chloride ion would attack the targeted carbon from the opposite side to the leaving group resulting in an inversion of configuration.



Example

The reaction of (*R*)-1-phenyl ethanol with thionyl chloride in ether.



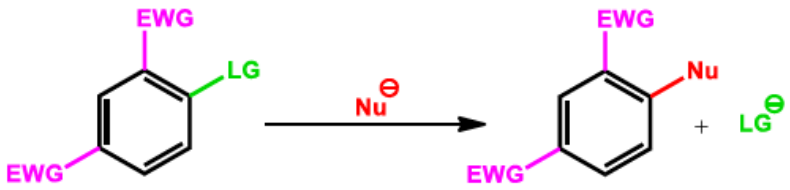
(*R*)-1-phenylethanol (*R*)-(1-chloroethyl)benzene

Nucleophilic Aromatic Substitution Reactions

Aromatic compounds are so stable that nucleophilic substitution reactions are impossible when the targeted carbon atoms belong to the aromatic system. Nevertheless, some aromatic compounds that have specific structural properties do undergo nucleophilic substitution reactions such as S_NAR, S_N1, and $S_{RN}1$.

S_NAr Reaction

S_NAr reaction is specific for aromatic compounds that contain electron-withdrawing groups EWGs, mainly on *ortho* and *para* positions with respect to the leaving group, which help in minimizing electron density of the targeted sp^2 carbon of the aromatic ring.

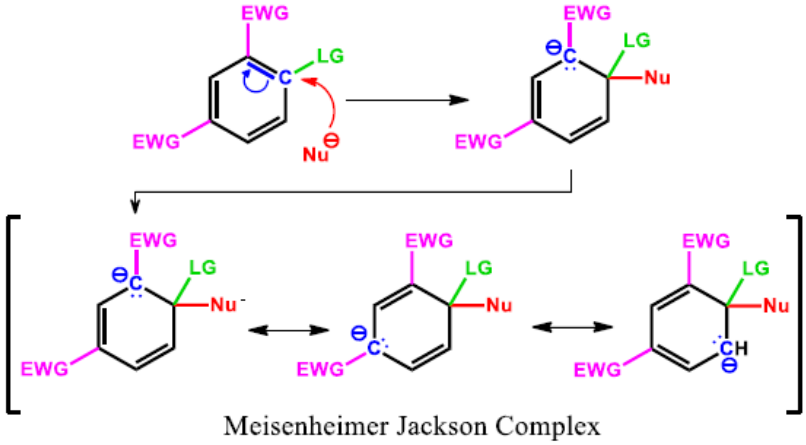


Mechanism

S_NAr reaction is the most common aromatic nucleophilic substitution reaction, and it proceeds in two steps.

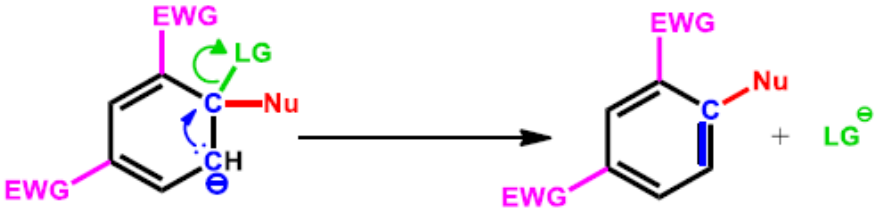
Step one

The first step is a slow process in which the nucleophile adds to the carbon atom attached to the leaving group. At this point, an anionic intermediate form is known as ***Meisenheimer Jackson complex***. This intermediate can be isolated from the reaction medium due to its stability, which is maintained by the electron-withdrawing effect of the EWG on *ortho* and/or *para* positions.



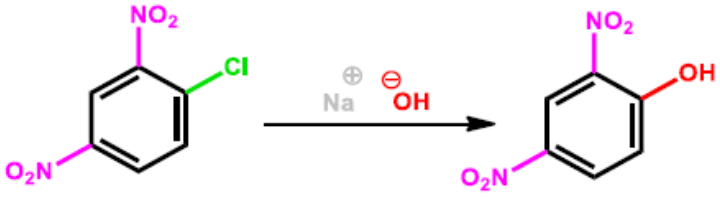
Step two

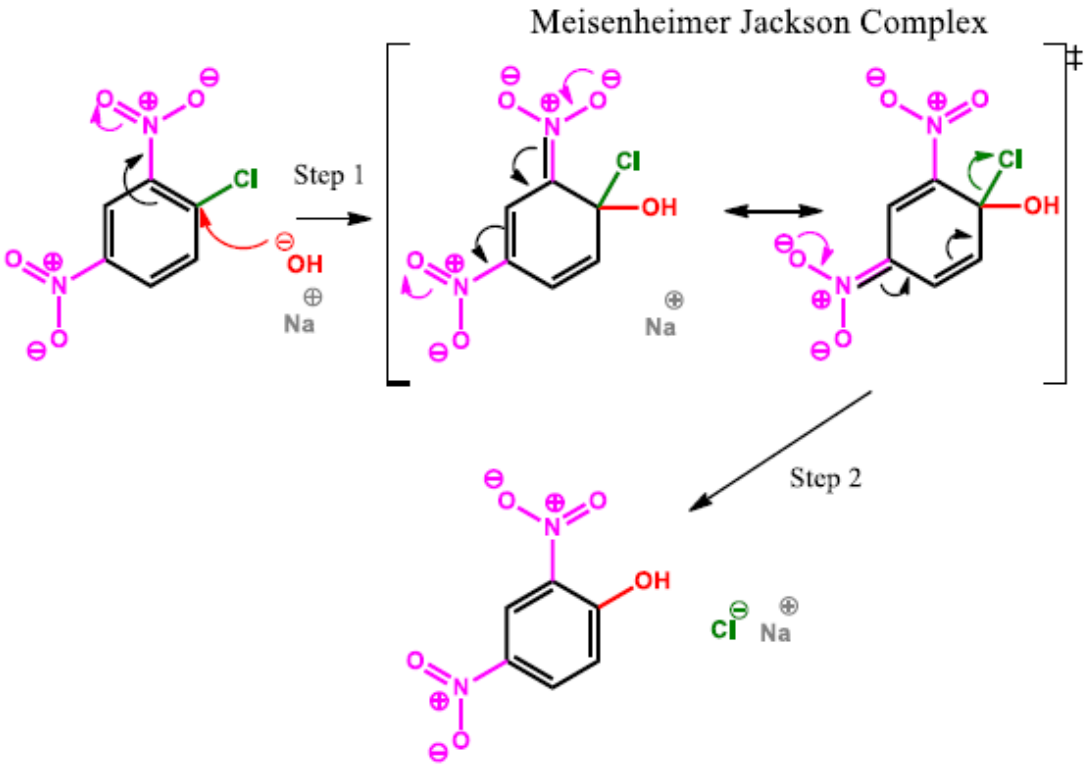
The second step is a fast process where the leaving group gets removed from the substrate, which leads to the restoration of the compound aromaticity.



Furthermore, it is important to know that EWGs are activating groups that favor S_NAr reaction especially when they are in positions *ortho* and/or *para*. In contrast, electron-releasing groups ERGs disfavor S_NAr reaction.

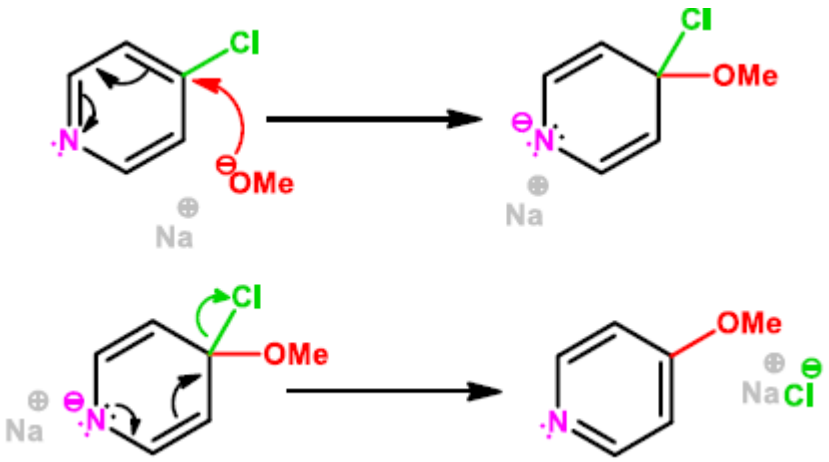
Example 1





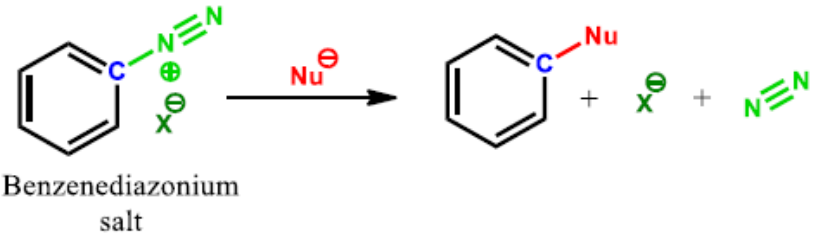
Example 2

S_NAr reaction is also possible and largely used with pyridine compounds.



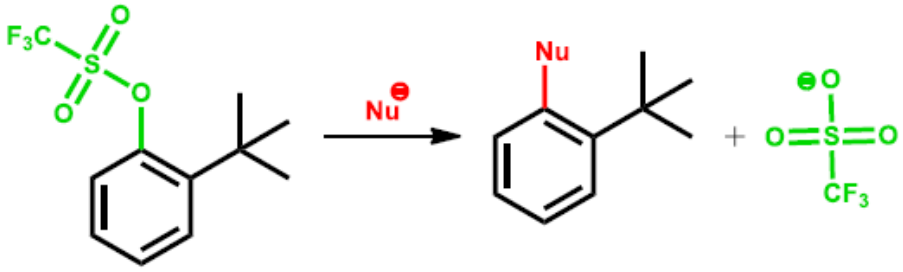
S_N1 Aromatic Reaction

The S_N1 reaction is exclusive for benzene diazonium salts and their derivatives and exceptional for aryl triflate compounds that contain a bulky substituent on ortho position.



Benzenediazonium salt

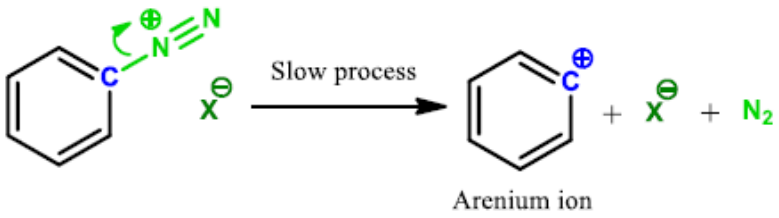
Aryl Triflate



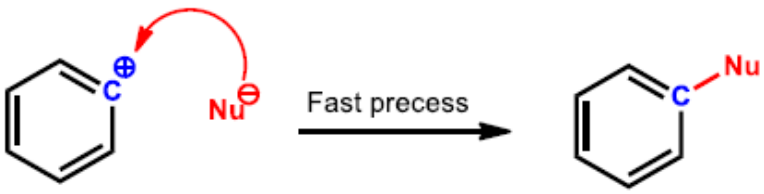
2-(*tert*-butyl)phenyl trifluoromethanesulfonate

Mechanism

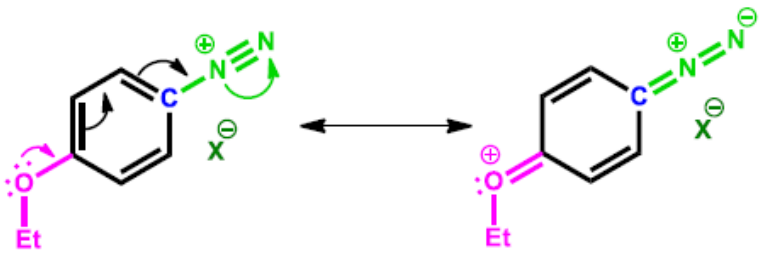
Just like the aliphatic S_N1 reaction, the aromatic S_N1 reaction is a first-order reaction that proceeds in two steps.



Arenium ion



Furthermore, it is important to know that electron-releasing groups ERG on para position disfavor S_N1 aromatic reaction for they stabilize the benzenediazonium ion through donor mesomeric effect $+M$.



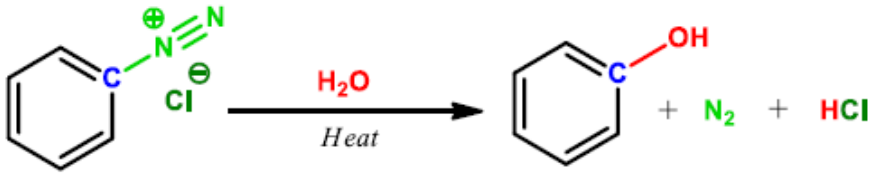
Deactivated compound

Similarly, electron-withdrawing groups EWG on para position also disfavor S_N1 aromatic reaction due to the $-M$ effect that stabilizes the benzo diazonium ion.

Deactivated compound

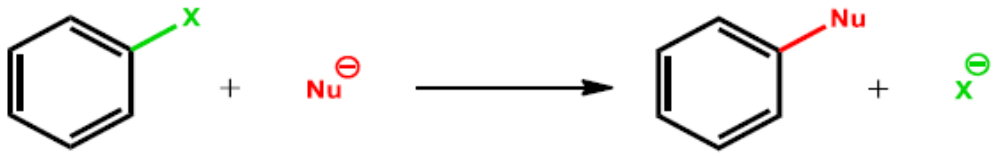
Example

Preparation of phenol from benzenediazonium chloride is accomplished by treating the benzenediazonium chloride with water in a warm condition.

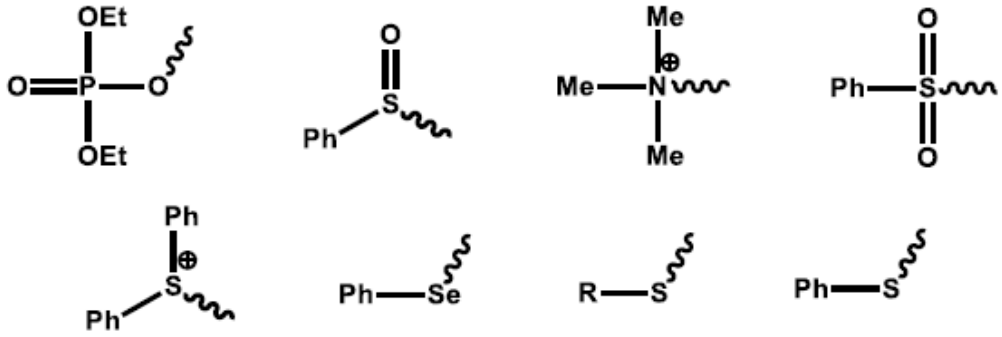


$S_{RN}1$ Reaction

$S_{RN}1$ reaction stands for unimolecular radical-nucleophilic substitution reaction. It is a chain reaction that consists in replacing a leaving group with a nucleophile through intermediary free radical species.



$S_{RN}1$ reaction is suitable for benzene, benzene derivatives, polycyclic aromatic compounds, and heteroaromatic compounds that contain a leaving group. In most cases, this leaving group is a halogen atom, however, many other leaving groups -*listed below*- have been found to be compatible with the $S_{RN}1$ reaction.



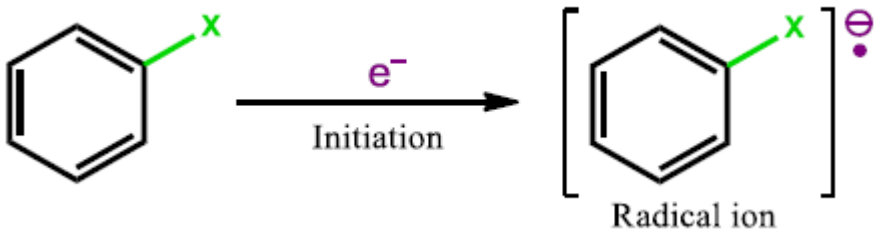
Furthermore, $S_{RN}1$ reactions involve carbanion nucleophiles that have a general formula R-$\bar{C}$H-Z where R is an alkyl or phenyl group while Z is CN, C(O)R', C(O)OR', or C(O)N(R')(R").

Mechanism

$S_{RN}1$ reaction mechanism proceeds in three steps, initiation, propagation, and finally termination.

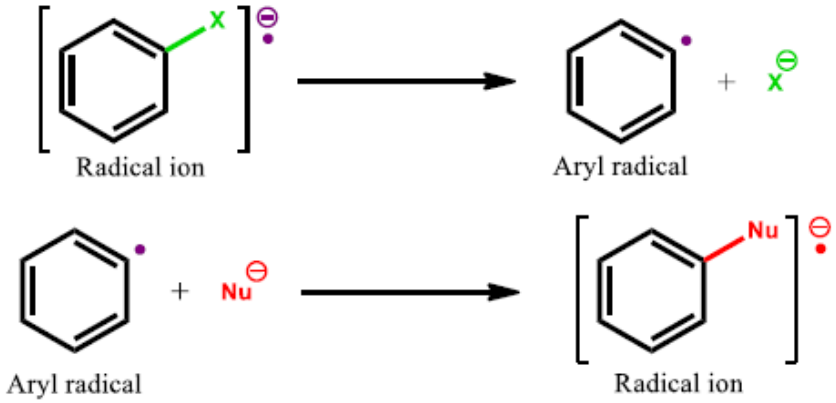
Initiation

The first step is characterized by a single electron transfer **SET** in which the substrate accepts one electron from an electron donor species resulting in a radical ion intermediate. This process can be accomplished by several methods such as photostimulation, solvated e1ectrons, or by electrochemical methods.

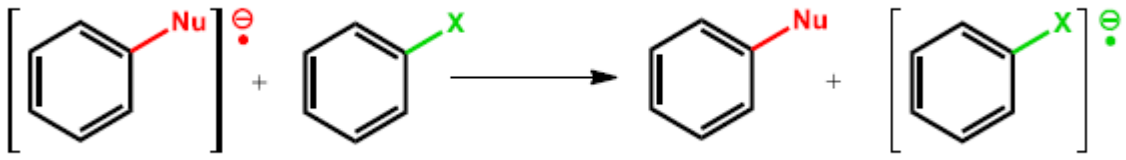


Propagation

In this step, the radical anion collapses into an aryl radical and a halide anion. Later, the nucleophile would react with the aryl radical resulting in a new radical anion.



Later, this radical anion, which bears the nucleophile would react with another aryl halide to form a new radical anion along with the final aromatic product.

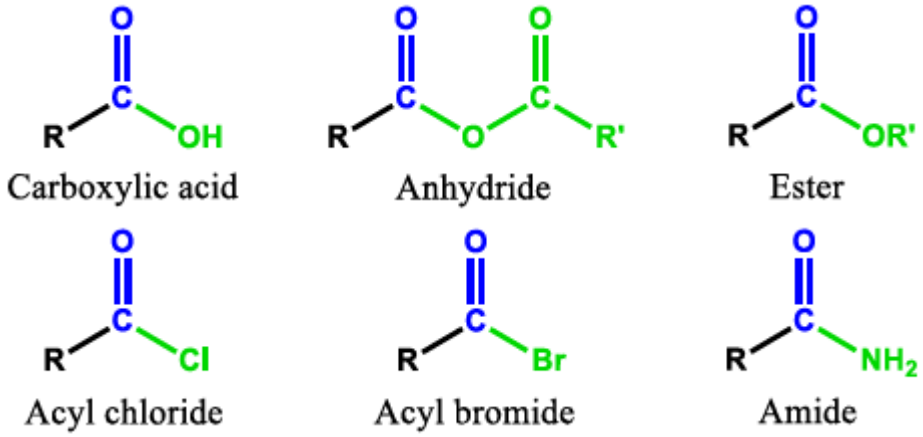


Termination

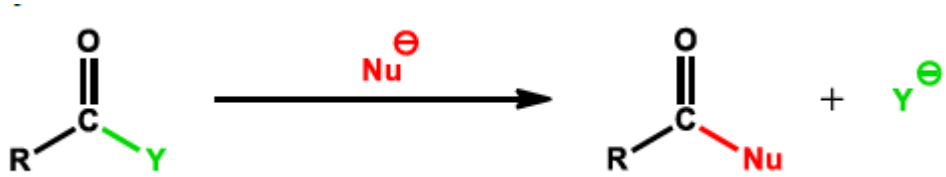
Finally, the reaction stops when there are no more reagents left to react. This step may depend upon several factors including the type of initiation, the intermediates involved, and the solvent used, and it is not thoroughly understood yet.

Nucleophilic Substitution of Carboxylic Acids and their Derivatives

Carboxylic acids are organic compounds that possess a carboxy group -C(O)OH. This functional group consists of a carbonyl attached to a hydroxy group. Carboxylic acid derivatives are modified carboxylic acids where the hydroxy group is replaced by another substituent. These compounds are represented by the general formula "RC(O)Y" where Y is a halogen for acyl halides, -OC(O)R' for anhydrides, -OR for esters, or $-NR_2$ for amides. Moreover, all carboxylic acid derivatives can be converted into their corresponding carboxylic acid by hydrolysis.



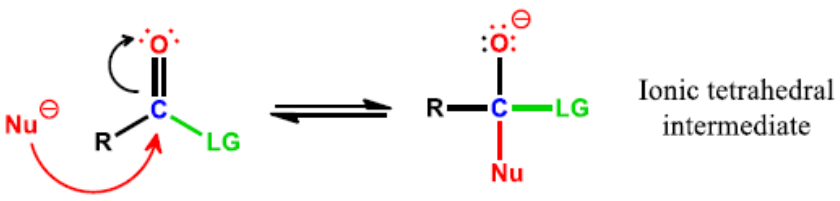
Carboxylic acids and their derivatives undergo nucleophilic substitution reaction whereby the leaving group -Y gets displaced upon nucleophilic attack on the carbonyl carbon.



Mechanism

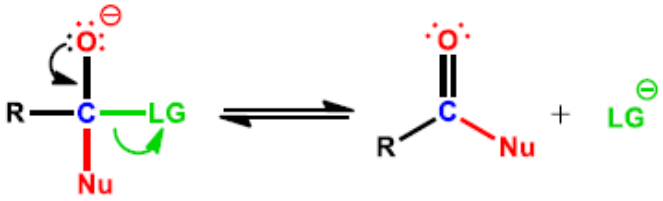
Step one

The first step is characterized by nucleophilic addition to the carbonyl carbon and the formation of an ionic tetrahedral intermediate.



Step two

The next step consists in reforming the carbonyl functional gro up and the elimination of the leaving group.

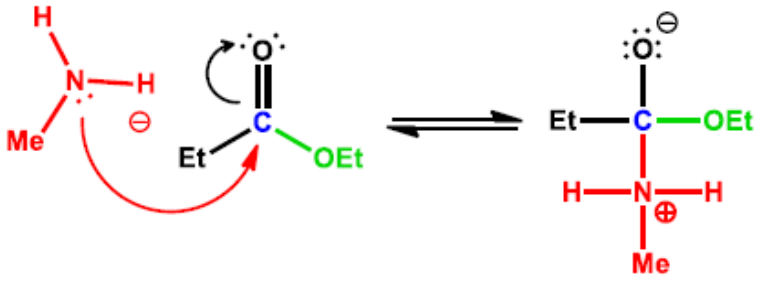


Example

The reaction of esters with amines leads to the formation of the corresponding amides. In this case, although the amine is a weak nucleophile, it is sufficiently strong to react with ester because the leaving group alkoxide RO^{-} can easily be removed from the carbonyl (good leaving group).

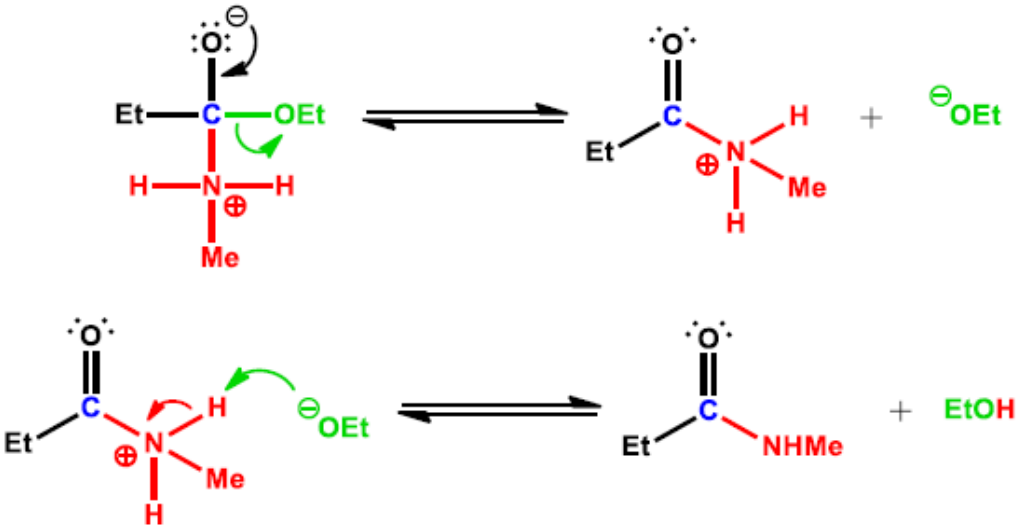
Step one

Addition of amine to the carbonyl and the formation of a tetrahedral ionic intermediate.



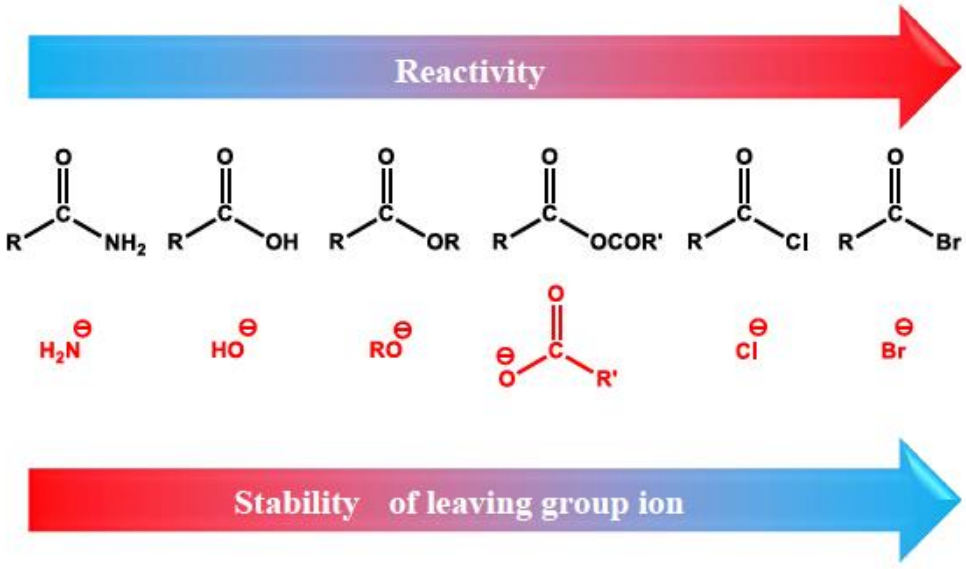
Step two

Elimination of ethoxide followed by deprotonation of amines.



Reactivity of Carboxylic Acids and their Derivatives

The reactivity of carboxylic acids and their derivatives towards nucleophiles varies from one compound to another according to the stability of the leaving group they contain. The most reactive compound is the one that releases the most stable nucleofuge. As a result, acyl halides rank the most reactive compounds in nucleophilic substitution reactions because halide ions are weak bases. The next reactive compounds are anhydrides for they release a resonance-stabilized conjugate base. Esters are more reactive than carboxylic acids because alkoxides are more stable than the hydroxide ion due to the donating inductive effect of the alkyl group.



Electrophilic Substitution Reactions

Electrophilic Aromatic Substitution Reactions S_EAr

Most chemical reactions that aromatic compounds undergo are electrophilic substitution reactions whereby a hydrogen atom attached to the aromatic system gets replaced by an electrophile. During an electrophilic aromatic substitution reaction, the aromatic ring acts as a Lewis base "electron donor" by providing the electrophile "electron-acceptor" with a pair of electrons to create a new σ bond. Moreover, because π bonds of the aromatic ring are involved in the aromatic system, they are not readily available to be shared with the electrophile. As a result, in most cases, electrophilic aromatic substitution reactions require the use of an appropriate catalyst to proceed.

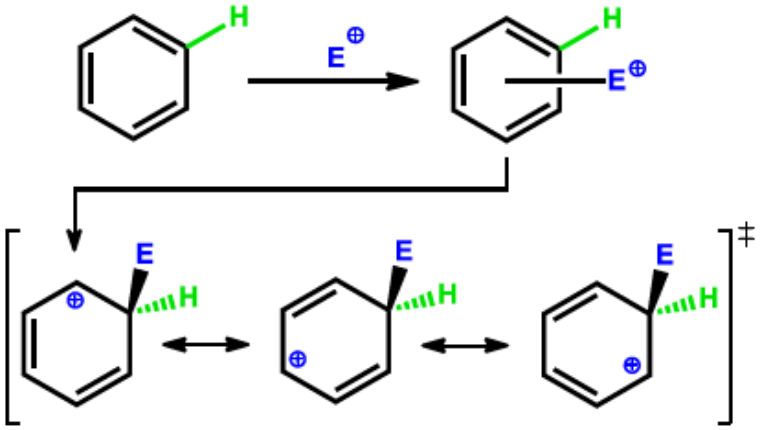
Furthermore, electrophilic aromatic substitution reactions share one common mechanism known as S_EAr, which involves a carbocation intermediate "arenium ion". Nevertheless, depending on the electrophile used, this mechanism may differ from one reaction to another.

Mechanism

The general mechanism for an electrophilic aromatic substitution reaction proceeds in two steps.

Step one

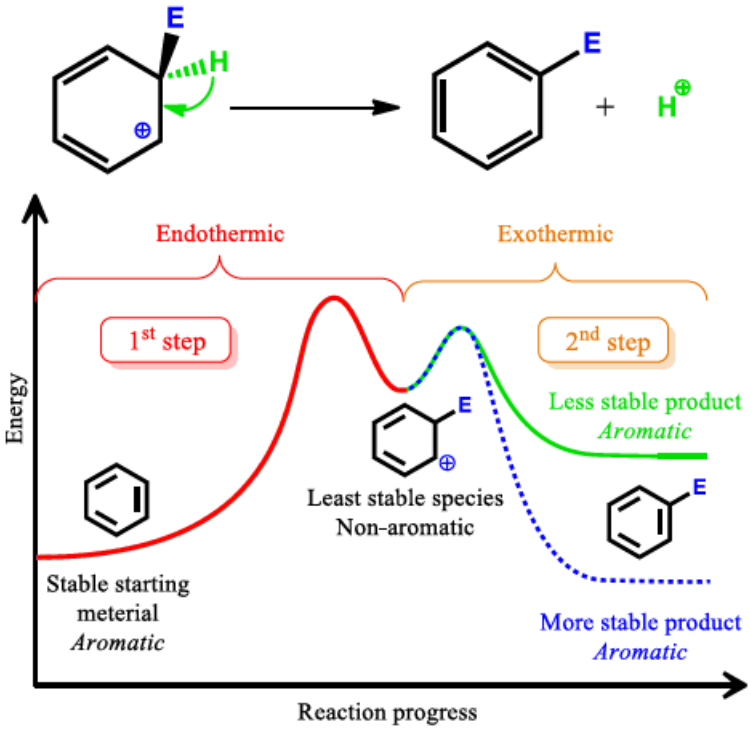
In the first step, the aromatic compound donates one pair of electrons to the electrophile creating, this way, a new σ bond with it. This process results in the loss of the aromaticity of the starting material and the formation of a carbocation intermediate known as σ complex or *Wheland* intermediate, which is resonance stabilized. Since the carbocation intermediate formed is less stable than the aromatic starting material, this step is a slow endothermic process.



Wheland intermediate

Step two

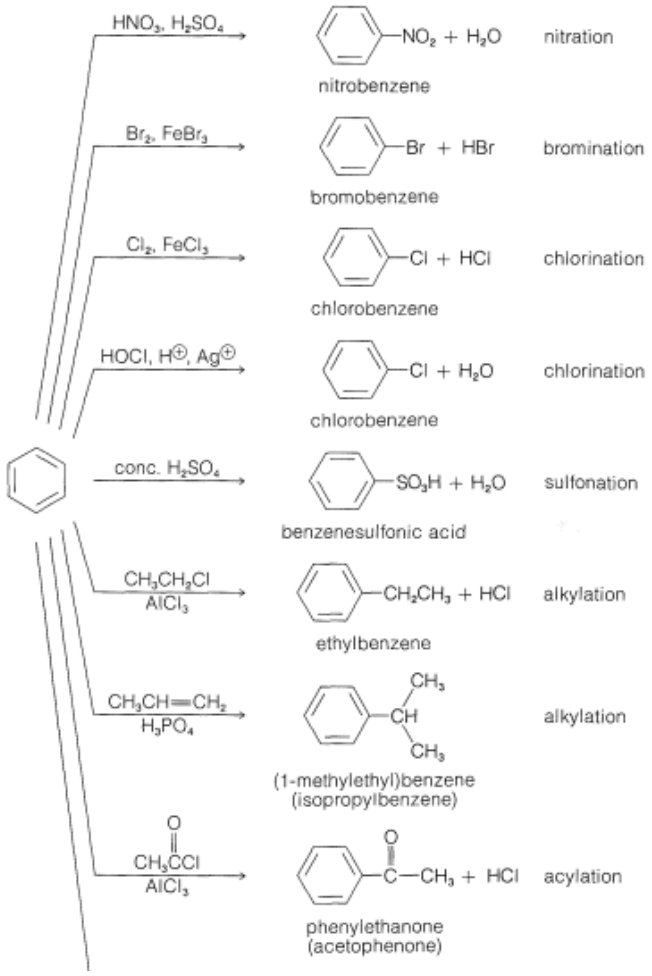
The second step is a fast exothermic process characterized by the elimination of the electrofuge H^+ and the restoration of compound aromaticity. At this point, a base would abstract a hydrogen proton from the carbon atom attached to the electrophile, which leads to the formation of a new π bond. Moreover, the final product can either be more stable than the starting material or less stable based on the nature of the electrophile used.



Common Reactions

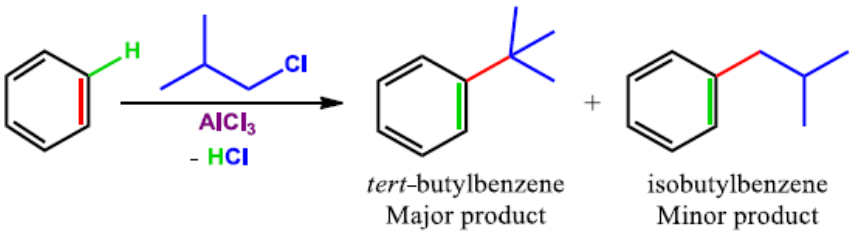
Electrophilic aromatic substitution reactions can be classified into five main categories "shown in the table below" depending upon the electrophile used. These reactions allow chemists to introduce new functional groups on aromatic compounds, which can be used for further organic syntheses.

Reaction	Reagents	Electrophile	Product
Nitration	$HNO_3 : H_2SO_4$	NO_2	Ar-NO2
Sulfonation	$SO_3 : H_2SO_4$	SO_3	Ar-SO3H
Halogenation	$X_2 : AlX_3$ or FeX_3	X	Ar-X
Alkylation	$RCl : AlX_3$ or FeX_3	R	Ar-R
Acylation	$RCOCl : AlX_3$ or FeX_3	RCO	Ar-COR

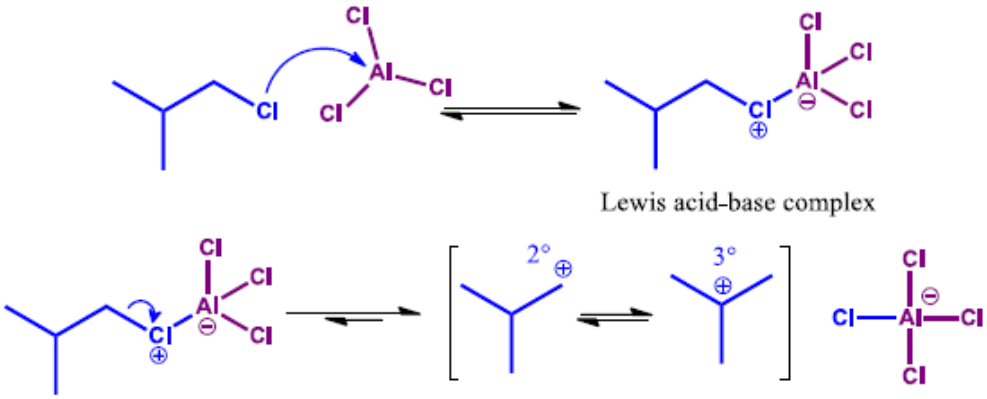


Example

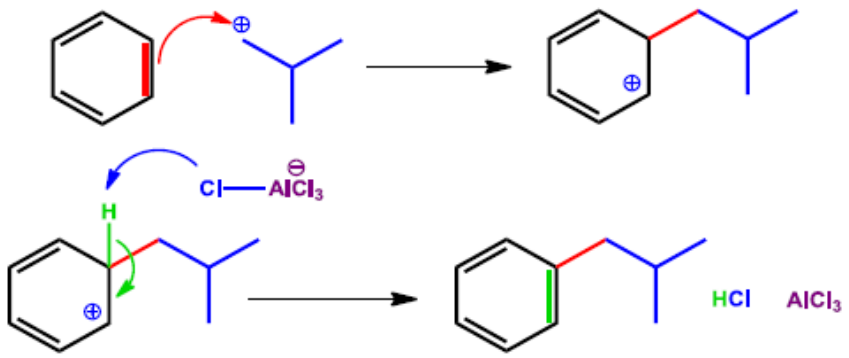
Alkylation of benzene with 1-chloro-2-methylpropane in the presence of aluminum trichloride $AlCl_3$ gives two products with one predominant isomer.

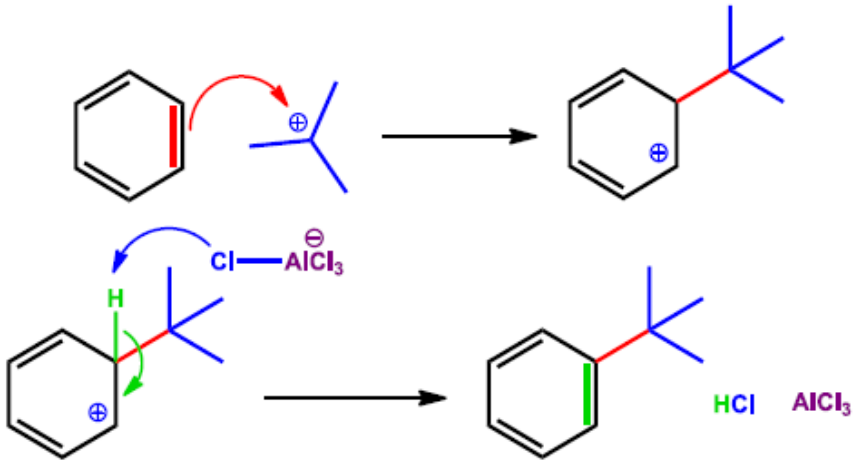


Because $AlCl_3$ is a strong Lewis acid, the dissociation of Lewis acid-base complex shifts towards the carbocation and tetrachloroaluminate $AlCl_4^-$. In this case, the secondary carbocation intermediate formed can attain a more stable state via 1,2 - hydride shift.



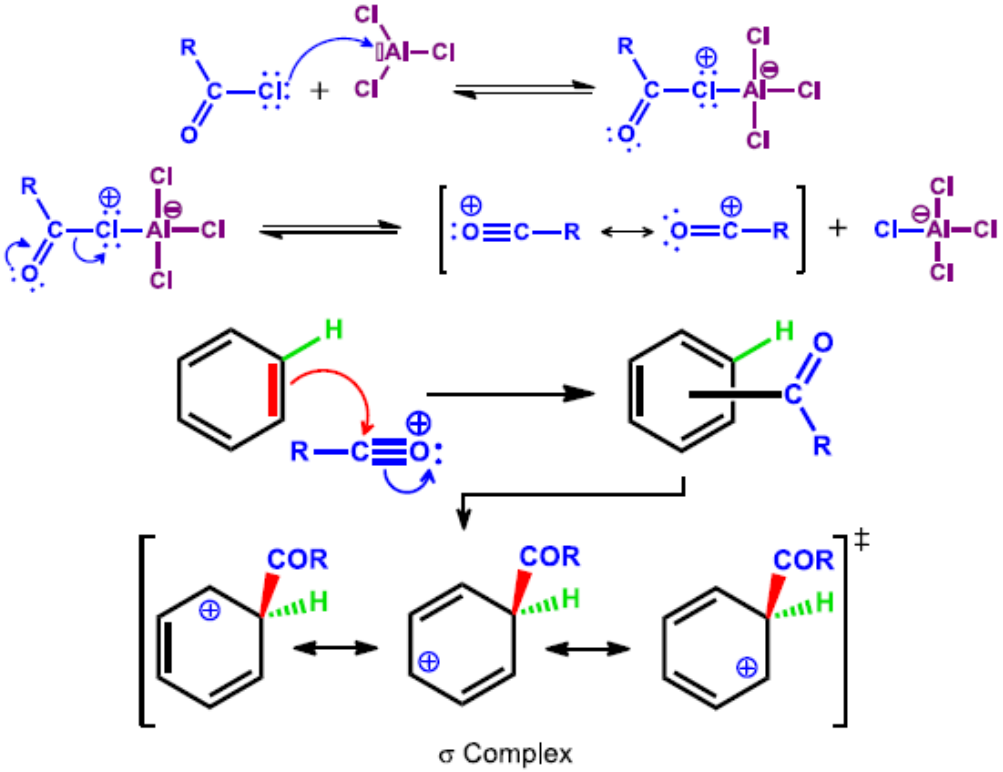
As a result, there would be two possible electrophiles, with which the aromatic ring can react. Nevertheless, because tertiary carbocation is more stable than secondary, the reaction would yield more *tert*-butylbenzene than isobutylbenzene.

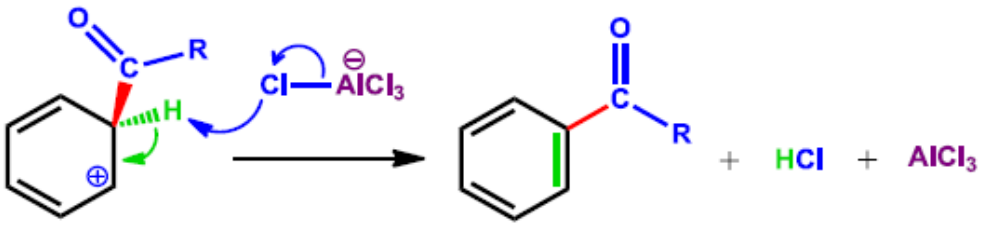




Acylation

Friedel–Crafts acylation is the reaction whereby an acyl group displaces a hydrogen atom of an aromatic ring. This reaction involves an acyl halide, which generates the electrophile upon reaction with a Lewis acid catalyst and it proceeds in a similar way to Friedel–Crafts alkylation.

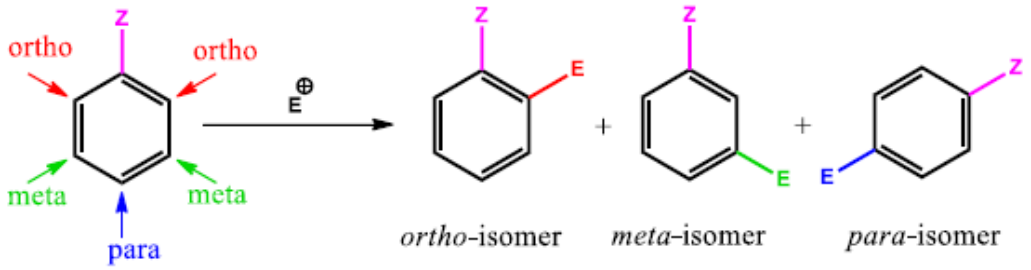




Regioselectivity

Mono-substituted Benzenes

When a mono-substituted benzene C_6H_5Z undergoes a SEAR reaction, the electrophile can be added to different positions of the aromatic ring. In this case, the reaction outcome would either be exclusive, to nearly so, *meta* isomer or a mixture of *ortho* and *para* isomers. The regioselectivity of such reactions depends upon the nature of the substitute Z and it can be explained by *Holleman's rule*.

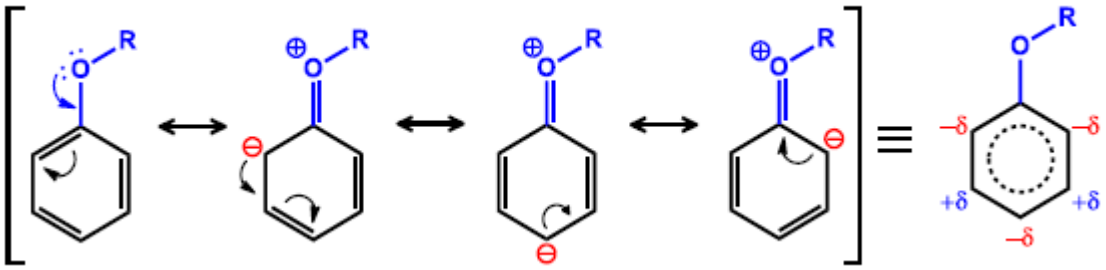


Holleman's Rule

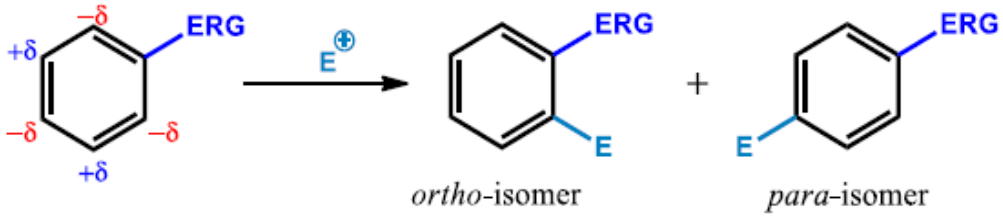
According to Holleman's rule, an electron-releasing group is an activating group that directs electrophilic substitution towards *ortho*- and *para* positions with the para orientation being generally more favorable. On the other hand, an electron-withdrawing group is a deactivating *meta*-directing group except for halogens, which are deactivating, *ortho*- and *para*-directing groups.

Activating Groups

Activating groups are electron-releasing groups ERG that helps in optimizing the aromatic compound nucleophilicity. Electron-releasing groups increase the electron density of the aromatic ring via donating mesomeric $+M$ or donating inductive effect $+I$ and therefore, making it more reactive towards electrophile s. In the example below, the alkoxy group is an activating group where it provides the aromatic ring with additional electron density via $+M$. In this case, the negative charge is delocalized by the resonance effect, and it can be in two main positions with respect to the methoxy group, ortho, and para.

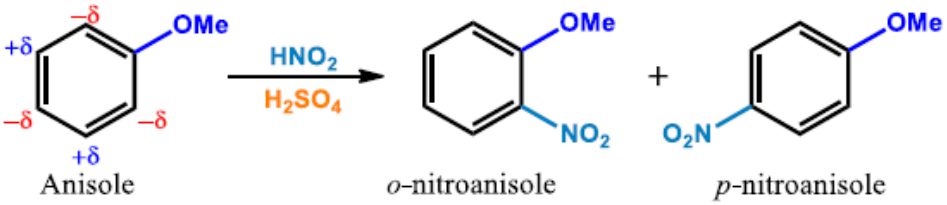


As a result, *ortho* and *para* positions are more nucleophilic than *meta* positions, and thus, electrophilic substitution is more likely to take place there. However, *para* isomers will generally predominate over ortho-isomer.



Example

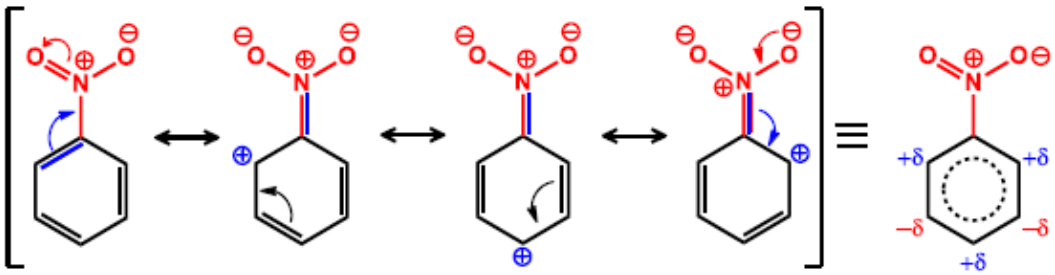
Nitration of anisole gives a mixture of nitroanisole isomers.

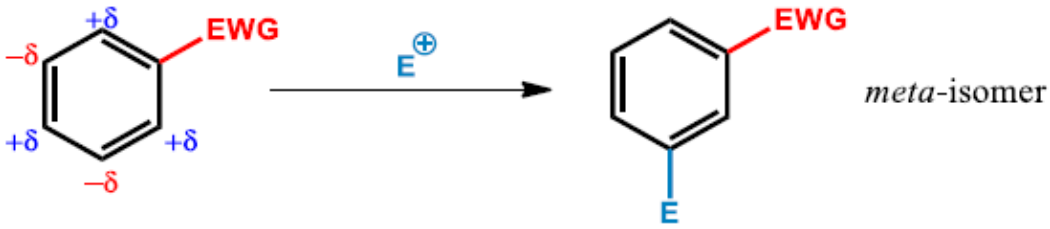


Deactivating Groups

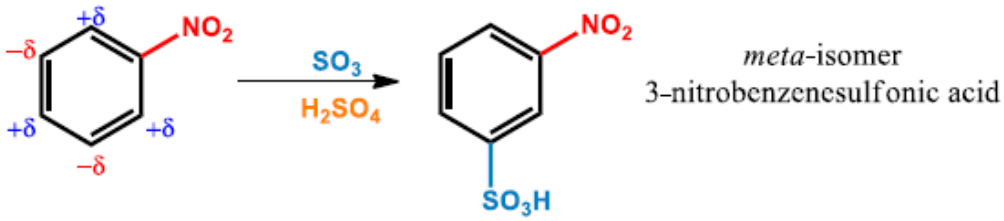
Deactivating groups are electron-withdrawing groups EWGs that decrease the electron density of the aromatic ring via withdrawing mesomeric effect -*M* and withdrawing inductive effect -*I*, which makes the aromatic substrate less reactive towards electrophiles. In the example below, the nitro group is a deactivating group where it pulls away a π bond from the aromatic ring via withdrawing mesomeric effect -*M*. This process will result in the formation of a positive charge on the ring, which can be delocalized into two main positions with respect to the nitro group, *ortho,* and *para*. In this case, *ortho* and *para* positions have less

electron density than the *meta* position and therefore the electrophile is more likely to add to the *meta* potion, which is the most nucleophilic position.

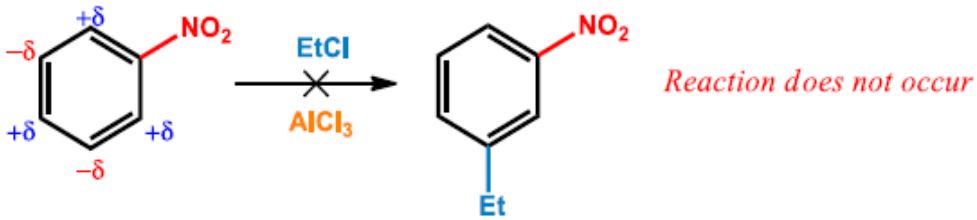




Example



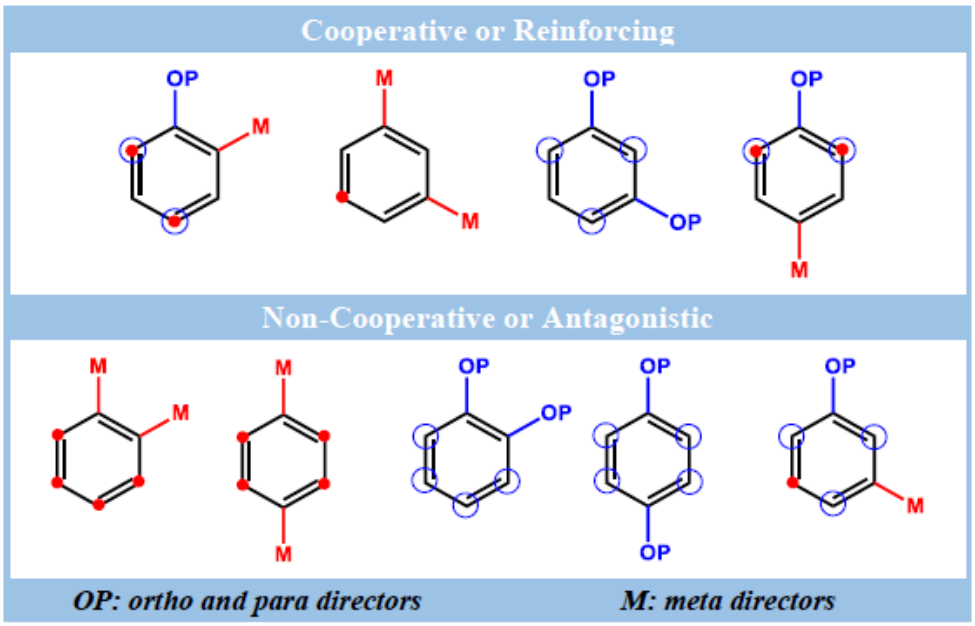
Note: In the case of strongly deactivated arenes like nitrobenzene, it is important to know that Friedel-Craft alkylation is not possible.



Disubstituted Benzenes

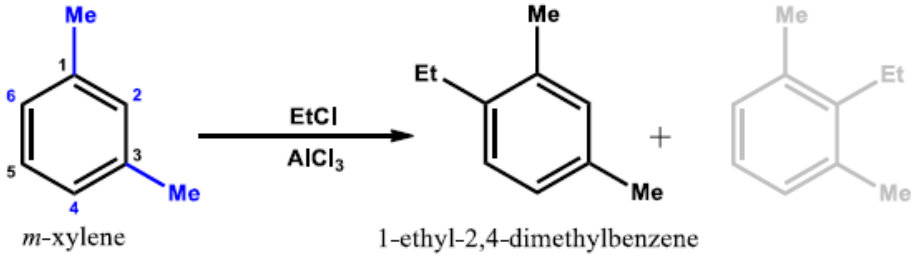
When disubstituted benzene undergoes an electrophilic aromatic substitution reaction, each substituent exerts an influence over reaction rate and regioselectivity. In other words, the position to which the electrophile adds depends upon the sum of the directing effects of both substituents and which one is stronger. For that, substituents can be classified into classes, cooperative systems, and non-cooperative systems.

In the case of cooperative systems, determining the position at which the electrophilic substitution will take place is more predictable because the directing effects of both substituents intersect at the same positions. On the other hand, in non -cooperative systems the directing effects of each substituent do not intersect. In this case, each substituent should be examined based on its strength and steric hindrance.

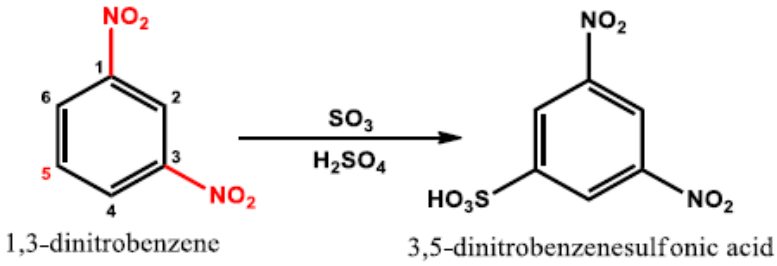


Cooperative systems

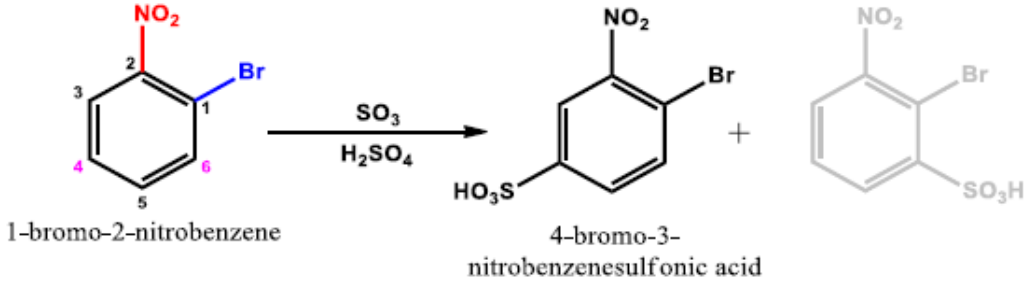
Alkylation of *m*-xylene with ethyl chloride and aluminum trichloride catalyst gives 1-ethyl-2,4-dimethylbenzene. In this case, the electrophile “ethyl” adds to carbon 4 or 6 because carbon 2 is more sterically hindered.



Sulfonation of 1,3-dinitrobenzene produces 3,5-dinitrobenzene sulfonic acid where sulfonic acid adds to carbon 5 because it is the only available position.



Sulfonation of 1-bromo-2-nitrobenzene would produce two isomers with 4-bromo-3-nitrobenzene sulfonic acid at a higher rate because position 6 is somewhat disfavored due to the steric hindrance.

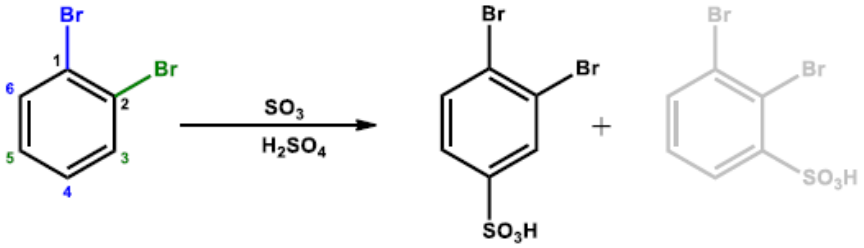


Non-cooperative systems

For non-cooperative systems, three factors can help in predicting the position where electrophilic substitution is more likely to occur.

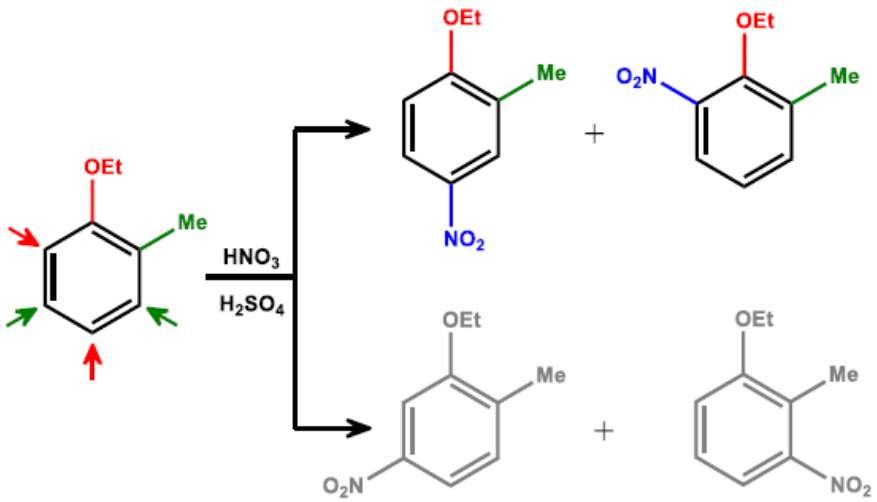
* The stronger substituent predominates over the weaker one in determining the regioselectivity of the reaction.
* Mesomeric effect is always stronger than the inductive effect.
* Electrophiles tend to add to the least hindered position.

Sulfonation of 1,2 -dibromobenzene gives 3,4-dibromo benzene sulfonic acid as a major product because positions 3 and 6 are more sterically hindered than positions 4 and 5. In this case, because both substituents are identical, the reaction will give the same product whether the electrophile adds to carbon 4 or 5.

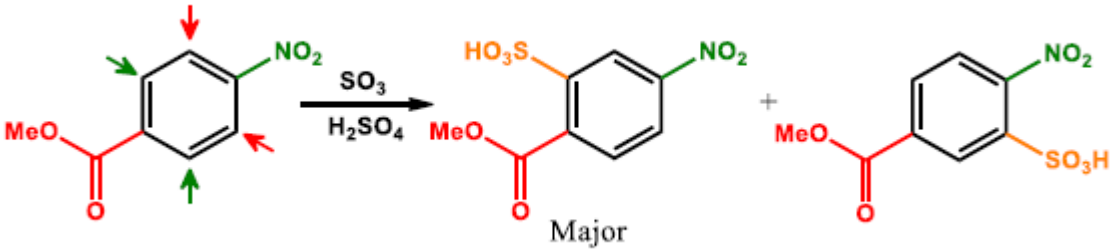


1,2-dibromobenzene 3,4-dibromobenzenesulfonic acid

In the case of non-identical substituents on positions 1 and 2, all potential isomers may form where priority goes to the stronger substituent and the electrophile adds to the least hindered position. For example, nitration of 1-ethoxy-2-methylbenzene may give four isomers where two of them are predominant. In this case, because the ethoxy group is stronger than methyl, nitration is more likely to take place at the positions determined by the ethoxy group.

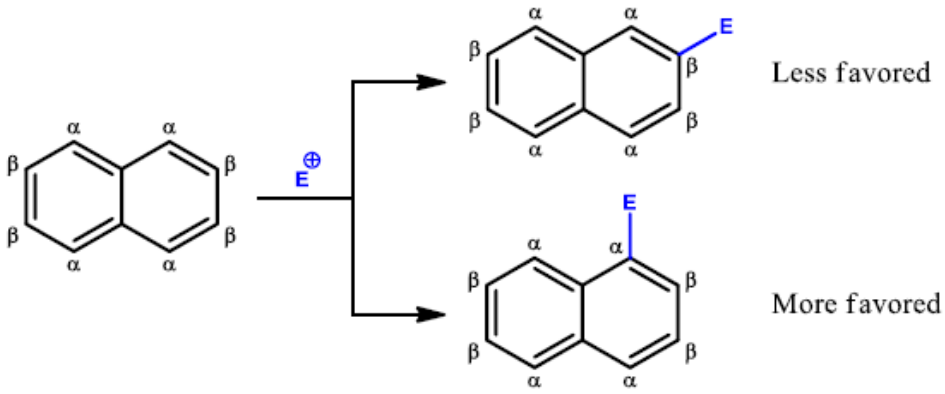


In the next example, both substituents are deactivating, meta-directing groups. In this case, priority goes to the nitro group because its electron-withdrawing effect *–M* is stronger than the electron-withdrawing effect *–M* of the carbonyl. As a result, sulfonation will take place at position *meta* with respect to the nitro group.

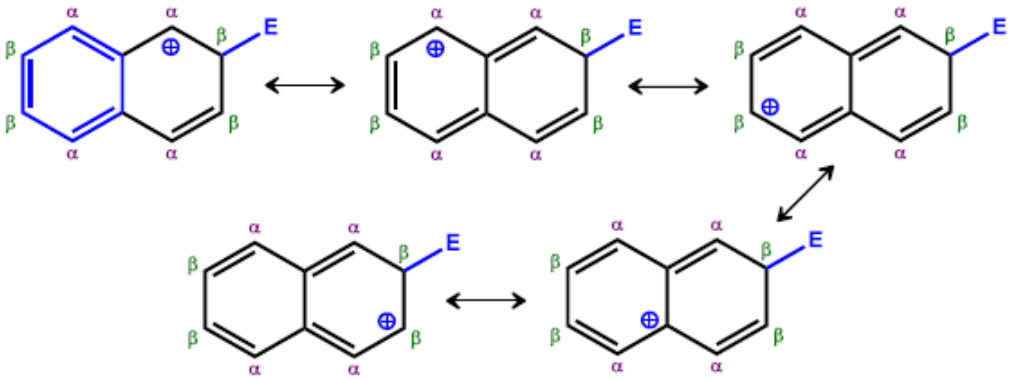


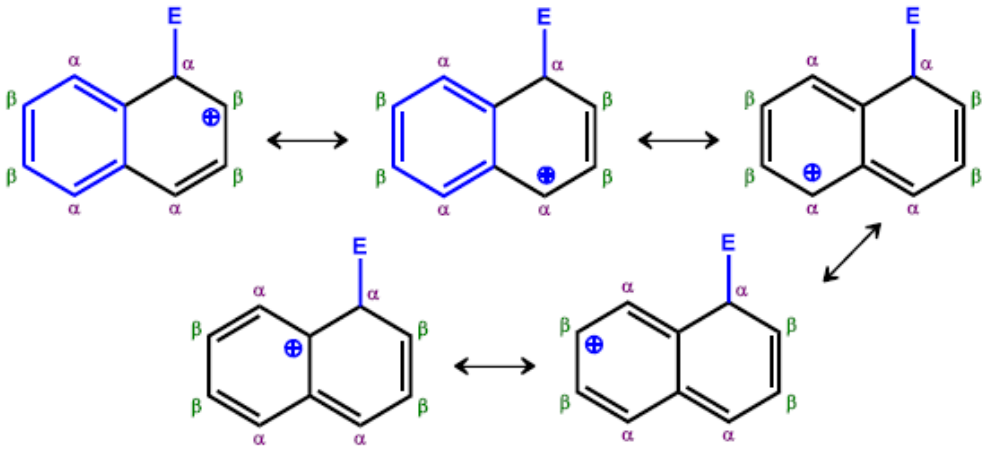
Polycyclic Arenes "Naphthalene"

Electrophilic aromatic substitution of naphthalene is more likely to occur at the α-position than at the β-position. The reason behind this is the stability of the arenium ion intermediate for each case.



When the electrophile adds to the position α, the arenium ion intermediate will have five resonance contributors with two forms having a full aromatic ring. In contrast, when the electrophile adds to the β position, only one resonance contributor will have a full aromatic ring. As a result, the α position is more reactive towards electrophiles than the β position.

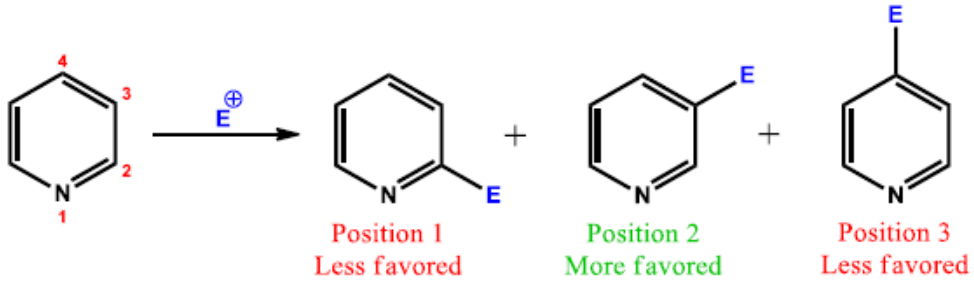




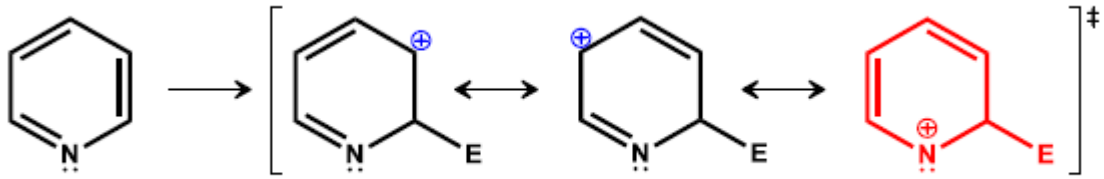
Heteroaromatic Compounds

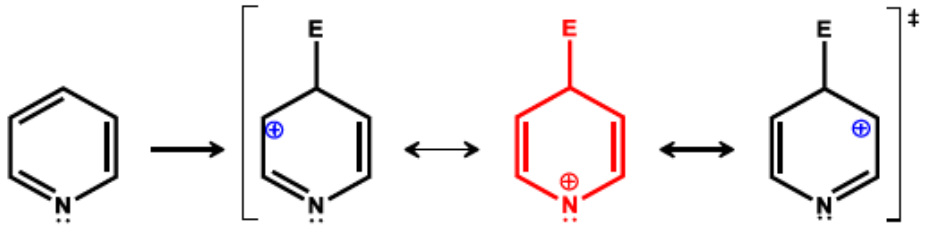
Pyridine

Pyridine is a six-membered heteroaromatic compound that possesses a sp2 nitrogen atom. When this compound undergoes an electrophilic substitution reaction, the electrophile is more likely to add to position 2.

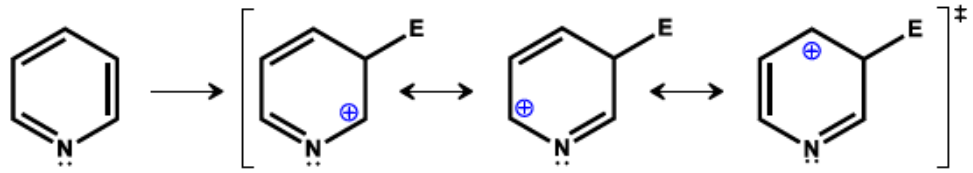


This regioselectivity is determined by which position will generate the most stabilized pyridinium ion intermediate. In all cases, the pyridinium ion has three resonance contributors. However, when the electrophile adds to position 1 or 3, one resonance contributor will be unstable because the positive charge will be located on a nitrogen atom that does not have a fully saturated valence.



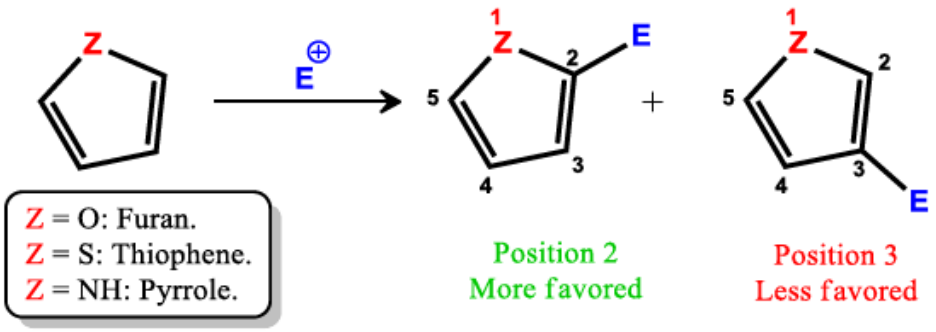


On the other hand, when the electrophile adds to position 2, the positive charge will be distributed between three carbon atoms, which makes this pyridinium ion the most stable one.

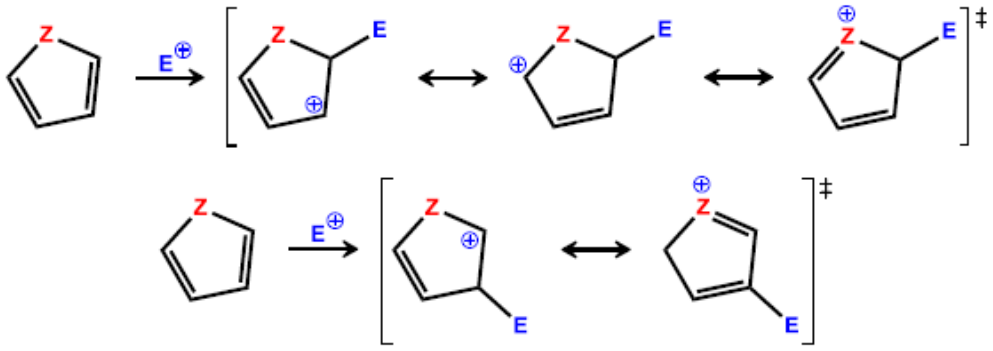


Furan, Pyrrole, Thiophene

Electrophilic aromatic substitution reaction is more favorable at position 2 than 3 in five-membered heteroaromatic compounds such as furan, pyrrole, and thiophene. This regioselectivity is determined by the stability of the intermediate formed in each case.

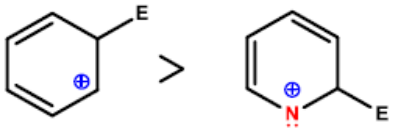
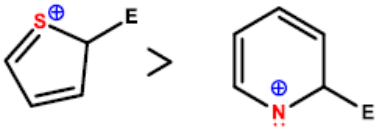
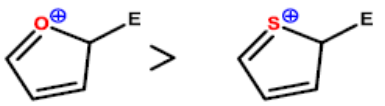


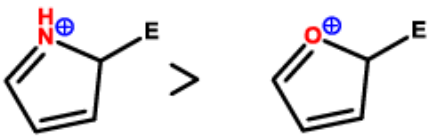
If the electrophile adds to position 2, three resonance contributors will stabilize the intermediate formed. On the other hand, when the electrophile adds to position 3, only two resonance contributors are possible, which makes position 2 more favorable than position 3.



Reactivity

In the case of the heteroaromatic compound, the nature of the heteroatom does affect the overall rate of reaction by making the aromatic ring reactive. The reactivity of a heteroaromatic compound is related to the stability of its arenium ion.

	Benzenium ion is more stable than pyridinium ion because sp ^{2} hybridized carbocation is more stable than nitrogen cation, which does not obey the octet rule. Here, the nitrogen atom in pyridine acts as a deactivating group. As a result, benzene is more reactive towards electrophiles than pyridine.
	Thiophenium ion is more stable than pyridinium ion because in contrast to nitrogen cation, sulfur cation does obey the octet rule. As a result, thiophene is more reactive than pyridine.
	Furanium ion is more stable than thiophenium ion because electron lone pairs of sulfur belong to 3p orbitals, which makes them less effective to overlap with 2p electrons of the sp ^{2} aromatic carbon atom. Oxygen lone pairs, on the other hand, are more prone to overlap with the aromatic p orbitals.

	Pyrrolium ion is more stable than furanium ion due to the diffe rence in electronegativity. Because nitrogen is less electronegative than oxygen, it forms a more stable cation than the oxygen.