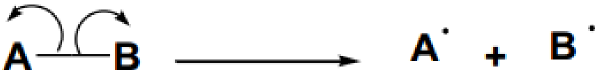
Chapter V
Study of Reaction Mechanisms

1. Electronic aspect

There are two main types of bond breaks, distinguished by the number of electrons involved in the electron transfer.

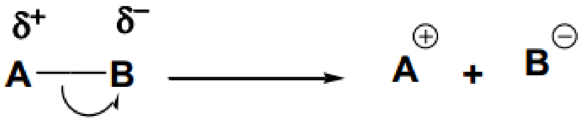
a. Homolytic Cleavage

Homolytic cleavage leads to a radical reaction process through the formation of two highly reactive radicals. This type of cleavage occurs easily upon heating in the presence of peroxides (**R-O-O-R**) or through irradiation (photochemical radiation, **hν**).



b. Heterolytic Cleavage

Heterolytic cleavage involves the transfer of the electron pair from the A-B bond to the more electronegative atom, creating an electron deficiency on the other atom. This process results in the formation of two oppositely charged ions.

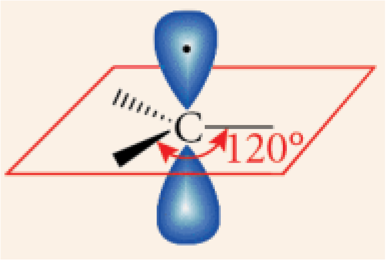


2. Reaction Intermediates

Reaction intermediates are unstable chemical species with a very short lifespan that form between the initial and final stages of a chemical reaction. They are completely consumed by the end of the reaction, and therefore do not appear in the stoichiometric equation.

2.1. Radicals

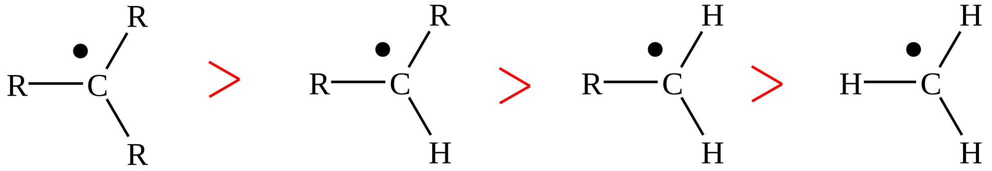
Radicals are neutral atoms that possess a single unpaired electron in an atomic orbital (•CH_3).



Planar Triangular Geometry (SP^2 hybridization)

Stability of Radicals

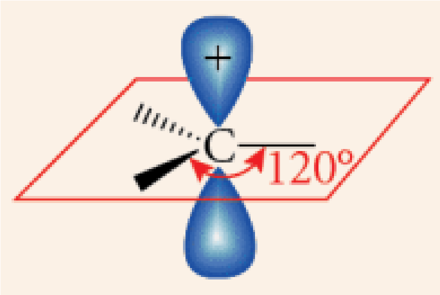
The stability of carbon radicals is influenced by inductive or resonance effects from Donor groups (**+I**, **+M**), which can stabilize them by reducing their electron deficiency. This stability is analogous to that of carbocations.



Teriary Radical **Secondary Radical** **Primary Radical**

2.2. Carbocations

Carbocations are cations in which the positive electronic charge is carried by a carbon atom.

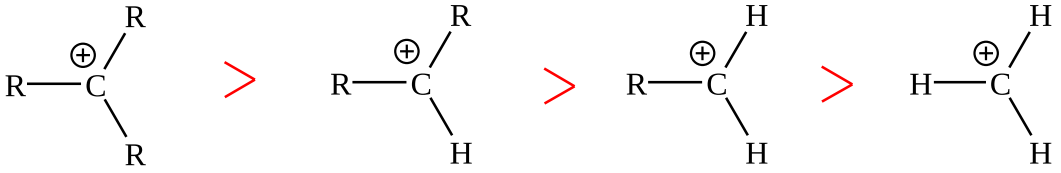


Planar Triangular Geometry (SP^2 hybridization)

Stability of Carbocations

Carbocations have an electron deficiency, making these species highly reactive and resulting in high energy levels.

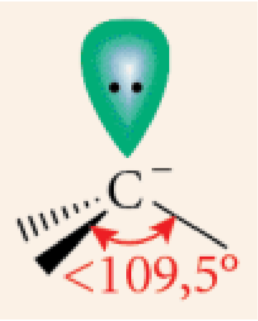
- Donor inductive or resonance effects (**+I**, **+M**) can stabilize them by reducing their electron deficiency.
- Attractor inductive effect (**-I**) destabilizes the carbocation by increasing its positive charge.
- Resonance effects stabilize the carbocation; for instance, an allylic carbocation is more stable than an aliphatic carbocation.



Teriary Carbocation **Secondary Carbocation** **Primary Carbocation**

2.3. Carbanions

Carbanions are anions in which the negative charge is carried by a carbon atom.

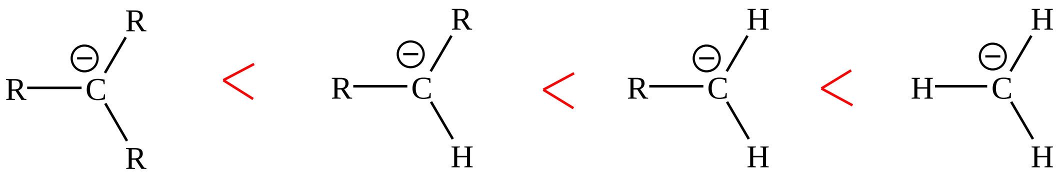


Tetrahedral Geometry (SP^3 Hybridization)

Stability of Carbanions

Carbanions are highly unstable, high-energy species that are not isolable.

- Alkyl groups, through their Donor inductive effect (**+I**), increase the electron excess and destabilize the species.
- Attractor inductive effect (**-I**) has the opposite effect, stabilizing the carbanion.
- The delocalization of the negative charge through resonance is a stabilizing factor, similar to that observed in carbocations.



Teriary Carbanion **Secondary Carbanion** **Primary Carbanion**

3. Electrophilic and Nucleophilic Reagents

3.1. Electrophilic Reagents

Electrophiles are species that carry a complete or partial positive charge, or compounds with an incomplete octet. The three categories of electrophiles are presented as below:

Species with an **incomplete octet:** **$AlCl_3$; BF_3 ; $FeBr_3$; $ZnCl_2$**

Species with **a positive charge:** **H_3O^+ ; NH_4^+ ; $CH_3NH_3^+$; NO_2^+ ; HSO_3^+ ; R^+ ; $R\text{-}C^+{=}O$**

Species with **a partial positive charge** and **a complete octet:** **H-X (X = F, Cl, Br, I) ; CH_3-Cl ; R-CO-R ; R-O-H ; R-C≡N**

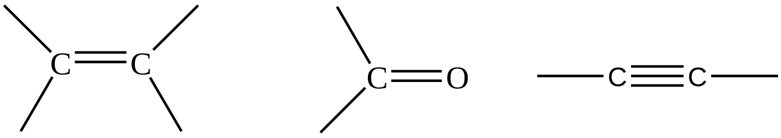
3.2. Nucleophilic Reagents

Nucleophiles can carry a negative charge or be neutral while possessing lone pairs of electrons or π electrons. Three categories of nucleophiles can be distinguished:

Anions (negative charge): OH^- ; RO^- ; NH_2^- ; H^- ; R^- ; X^- ; CN^-

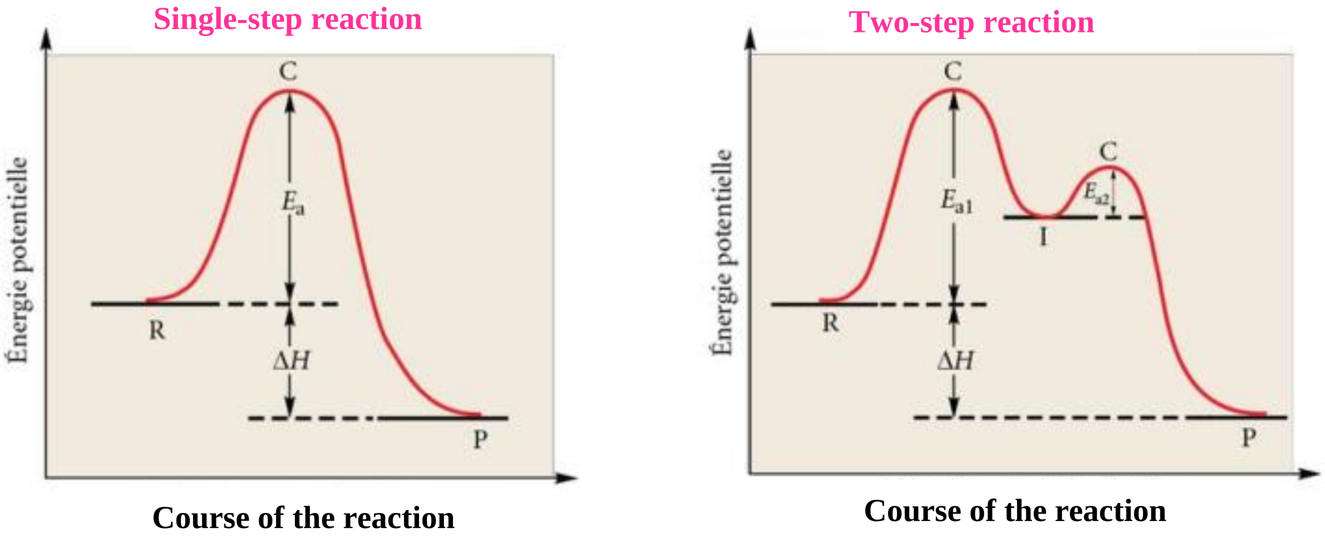
Lone pairs of electrons: H-O-H ; CH_3-O-H ; NH_3 ; R-NH_2

π Electrons:



4. Energy Diagrams

Energy diagrams are schematic representations of the fluctuation of potential energy (expressed in kJ/mol) of various constituents during a chemical reaction. In this section, the progress of simple reactions occurring in one step, as well as that of more complex reactions taking place in two or more steps (**Figure 1**).


Single-step reaction

Two-step reaction

Figure 1. Energy diagram of an exothermic reaction occurring in one step and in two steps.

R = Reagents
C = Activated Complex in the transition state
ΔH = Enthalpy change ($H_{Products} – H_{Reagents}$)

Ea = Activation energy
P = Products
I = Reaction Intermediate

Activation energy E_a (in J mol^{-1}) can be determined experimentally by measuring the rate constant of the reaction in question at various temperatures and using the Arrhenius equation below:

$$\boldsymbol{k = A.e^{-\frac{E_a}{R.T}}}$$

with k *as* the rate constant of the reaction, A as the Arrhenius constant specific to the reaction, R = 8,314 $J{\cdot}mol^{-1}{\cdot}K^{-1}$ as the ideal gas constant and T as the temperature (K).

5. Study of the Main Reaction Mechanisms

The reaction mechanism is the set of elementary steps that actually occur during the transformation of reactants into products. The reaction mechanism involves the reactants and products, as well as the reaction intermediates. Reactions in organic chemistry have been subdivided into four main categories:

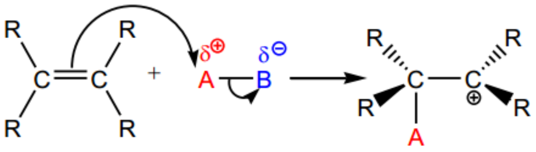
- Addition reaction.
- Substitution reaction.
- Elimination reaction.
- Rearrangement reaction.

5.1. Addition Reaction

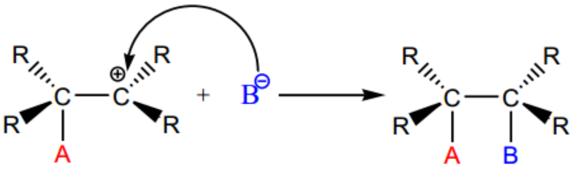
5.1.1. Electrophilic Addition

- ***Mechanism of the addition reaction on alkenes*** **(C=C)**

First step: Nucleophilic attack of the alkene on the electrophilic site of the reagent, leading to the formation of a carbocation.



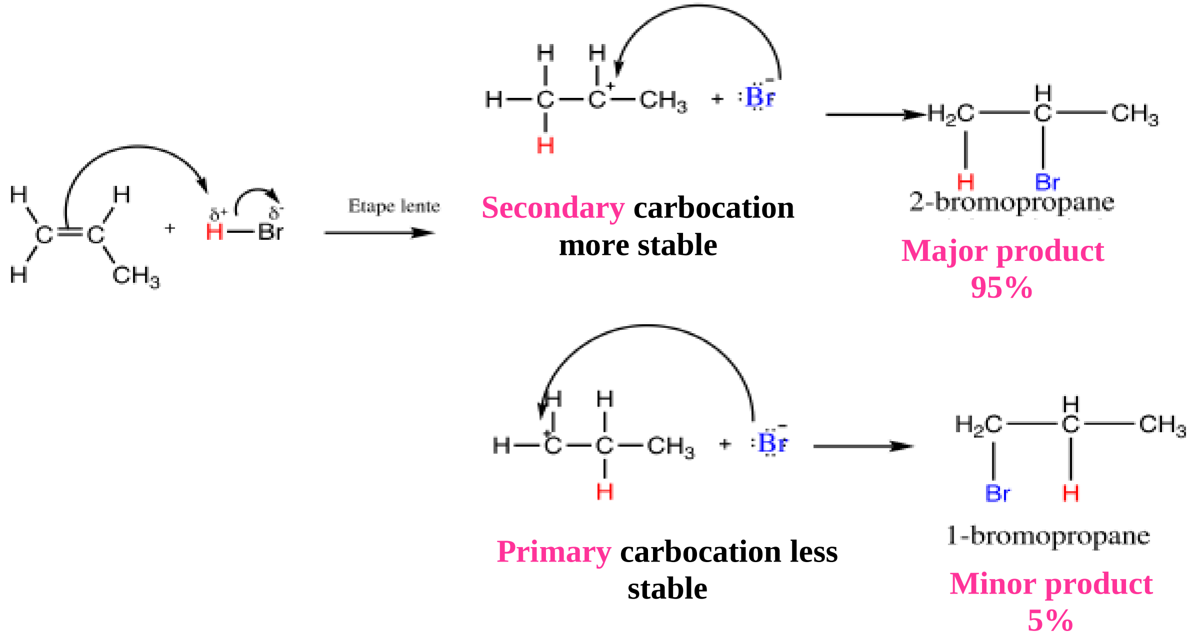
Second step: Attack of the nucleophilic reagent on the carbocation derived from the alkene.



Addition HX : Hydrohalogenation Reaction

This reaction involves the addition of an acid HX (X = Cl, Br, I) across the double bond of an alkene to yield the corresponding haloalkane.

Example 1: Electrophilic Addition of HBr to propene**.**



Secondary carbocation more stable

Major product 95%

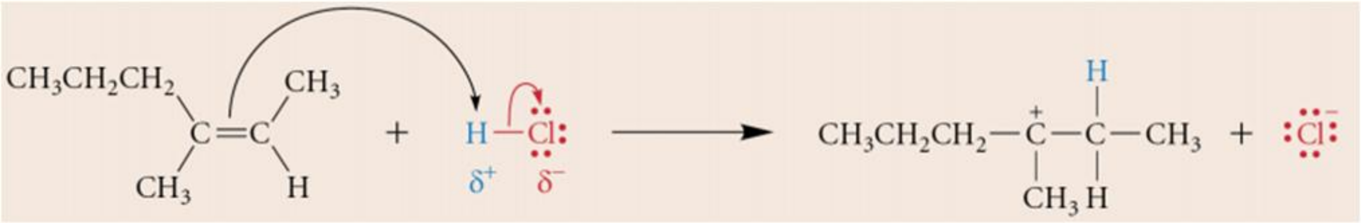
Primary carbocation less stable

Minor product 5%

Markovnikov Rule: ***When a dissymmetric alkene reacts with a reagent HX, the hydrogen atom adds to the carbon of the alkene that is more hydrogenated to form the most stable carbocation, which consequently leads to the formation of the major product.***

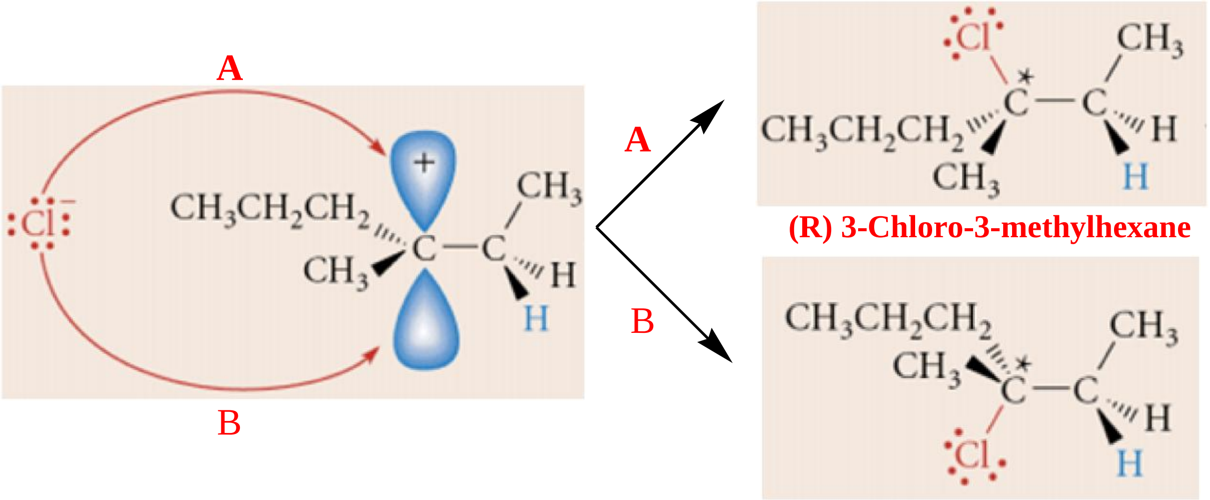
Example 2: Mechanism of the Addition Reaction of HCl on 3-methylhex-2-ene.

First step of the mechanism



(Z)-3-methylhex-2-ene **Major tertiary carbocation**

Second step: Two possible attacks on the tertiary carbocation leading to the major products.

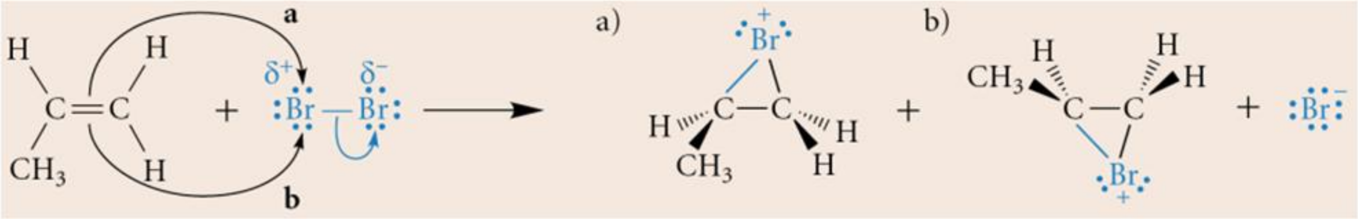


(R) 3-Chloro-3-methylhexane

(S) 3-Chloro-3-methylhexane

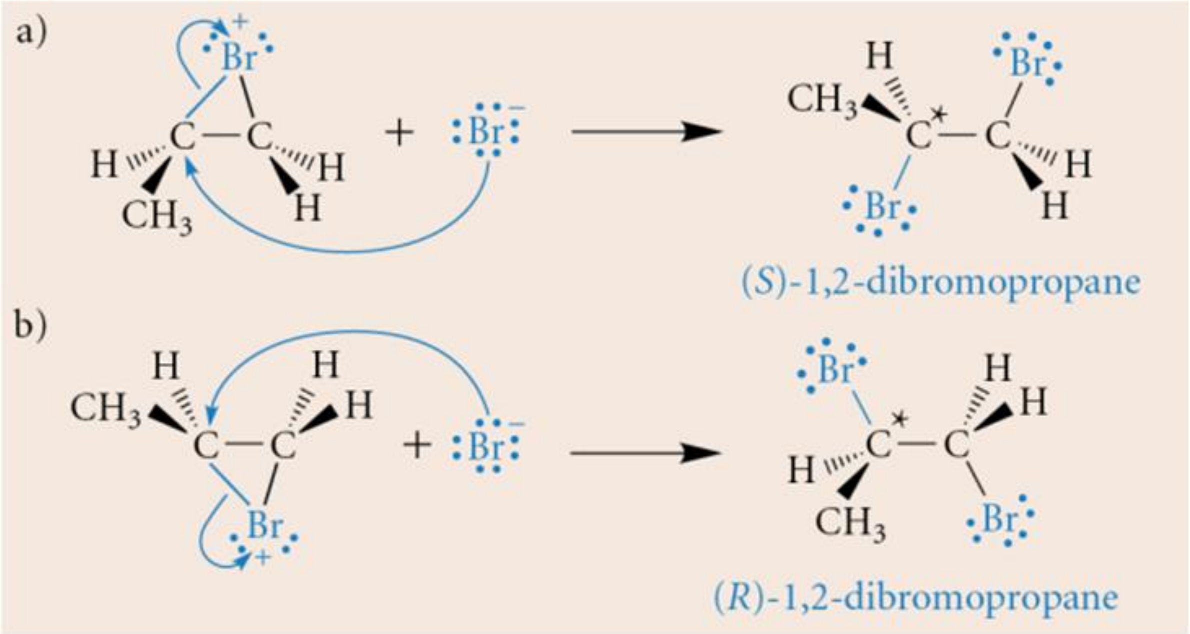
Example 3: Mechanism of the Addition Reaction of Dihalogen (Br_2) on an Alkene.

First step: Attack of the alkene on Br_2 and formation of the bromonium ion.



Propene **Induced dipole** **Two possible bromonium ions, of similar stability and abundance**

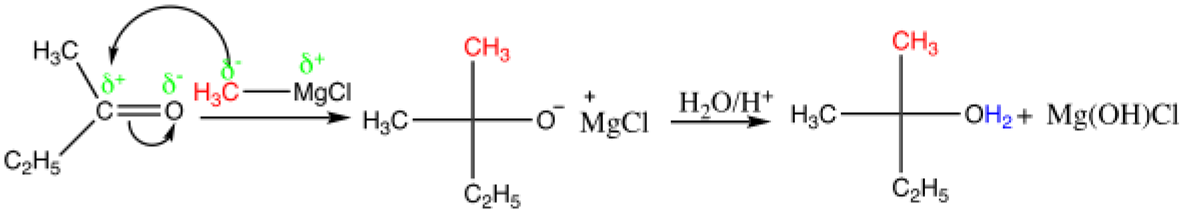
Second step: Attack of the bromide ion on the most substituted carbon and ring opening.



Two possible enantiomers obtained in a 50:50 ratio (racemic mixture), with no stereoselectivity observed.

5.1.2. Nucleophilic Addition

Example: Addition of Organomagnesiens.

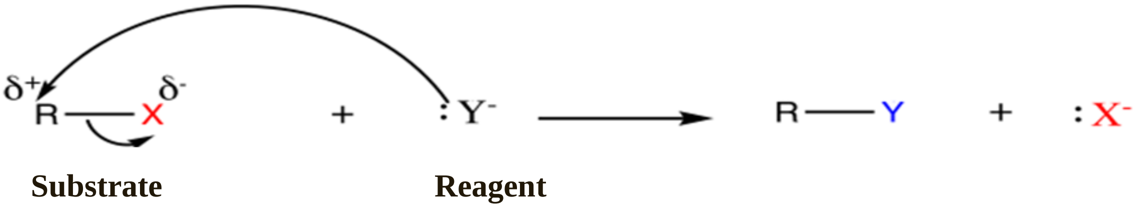


- The addition of organomagnesium reagents to aldehydes leads to the formation of a secondary alcohol.
- The addition of organomagnesium reagents to ketones leads to the formation of a tertiary alcohol.

5.2. Substitution Reaction

5.2.1. Nucleophilic Substitution Reaction

Halogenated derivatives undergo ***nucleophilic substitution*** reactions with charged or neutral reagents according to the following scheme:



Y$^-$: Attaquing nucleophilic reagent

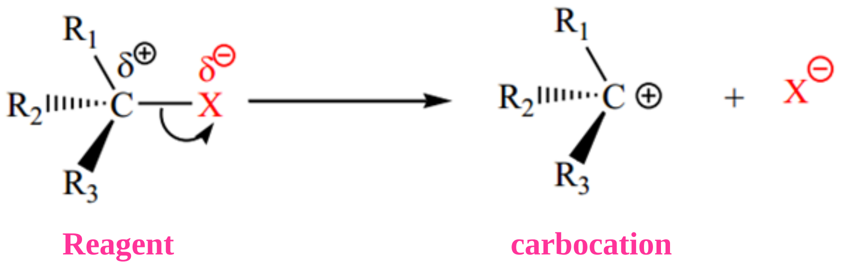
X$^-$: Nucleofuge Group (leaving Group)

There are mainly two types of nucleophilic substitution that differ only in their reaction mechanism: SN1 and SN2.

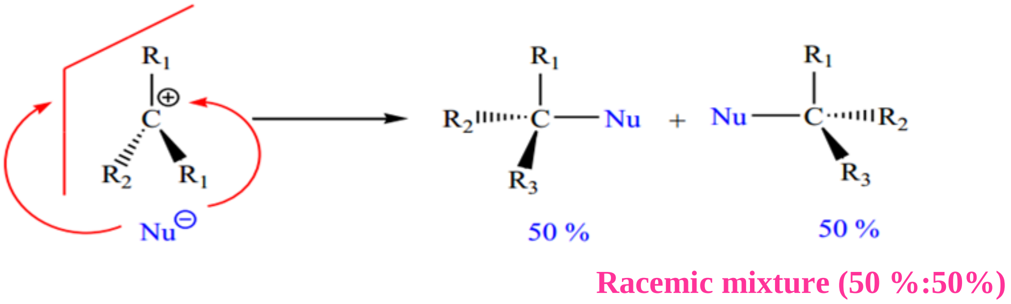
a. First-Order Nucleophilic Substitution Reaction (SN1)

Mechanism: SN1 Nucleophilic substitution reaction is unimolecular and occurs in two steps.

First step (slow): The first step is a heterolytic cleavage of the C-X bond, with the departure of a nucleofug (**X**$^-$) and formation of a carbocation.



Second step (fast): Attack of the nucleophilic reagent (***Nu⁻***) on the carbocation from both sides of the plane.



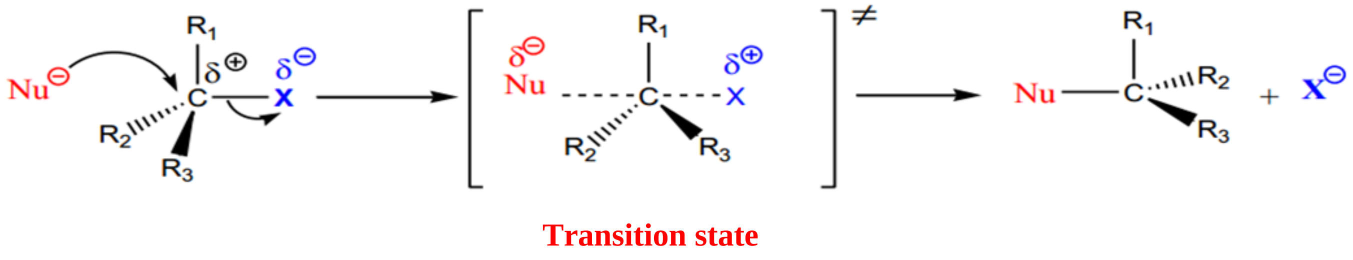
The experimental rate law is the first-order rate law: **$V = k [R\text{-}X]$**.

The attack of the nucleophile from both sides of the plane of the carbocation in the case of an asymmetric carbon leads to a pair of enantiomers in equal amounts (***racemic mixture***). Therefore, SN1 substitution is ***non-stereospecific***.

b. Second-Ordre Nucleophile Substitution Reaction (SN2)

The attack by the nucleophile ***Nu⁻*** occurs from the side opposite to the halogen to minimize electronic repulsions. The transition state is a "***charge-dispersed***" state that involves both the nucleophile and the substrate.

Mechanism

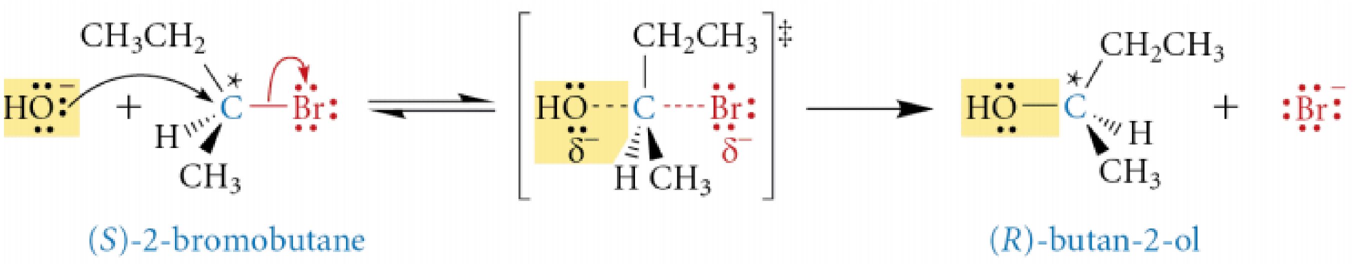


The experimental rate law is a second-order rate law and is expressed by the following relationship:

$$v = k[R\text{-}X][Nu^-]$$

The product obtained undergoes a configuration inversion if it is chiral (***Walden inversion***). Therefore, SN2 substitution is ***stereospecific***.

Example:



Transition state **Configuration Inversion**

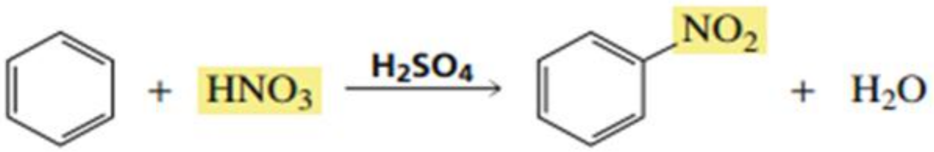
(Walden Inversion)

The carbon bearing the halogen atom is a stereogenic carbon (C*), so a ***configuration inversion*** will be observed (***Walden inversion***)

5.2.2. Electrophilic Substitution Reaction

Example: Nitration of Benzene.

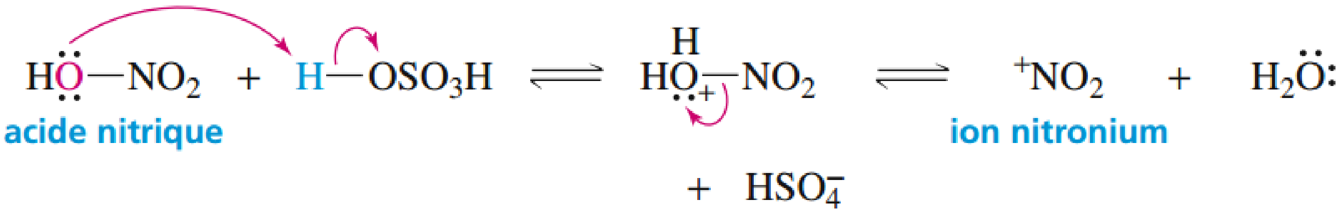
Sulfuric acid must be used as a catalyst for the nitration of benzene by nitric acid (HNO_3).



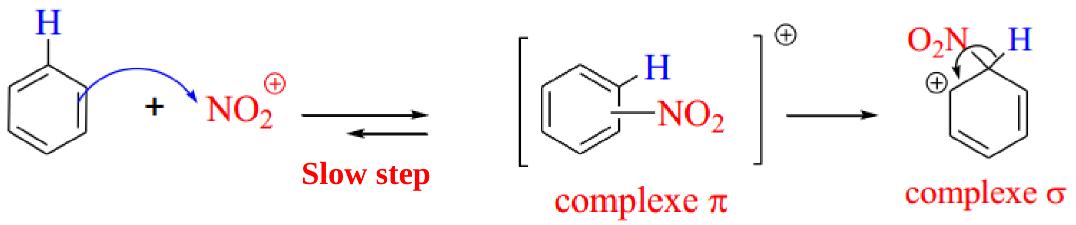
Nitrobenzene

Mechanism

First step: Formation of the electrophilic reagent: the nitronium ion (NO_2^+) from nitric acid (HNO_3) or by the action of concentrated H_2SO_4 on concentrated HNO_3

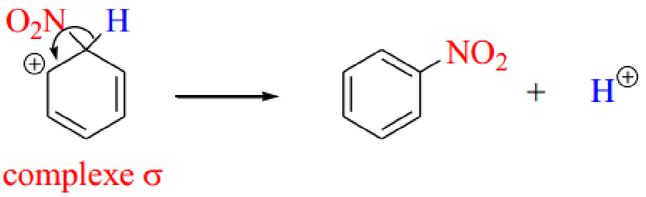


Second step (slow): Formation of the Wheland intermediate.



Third step: Formation of substitution products.

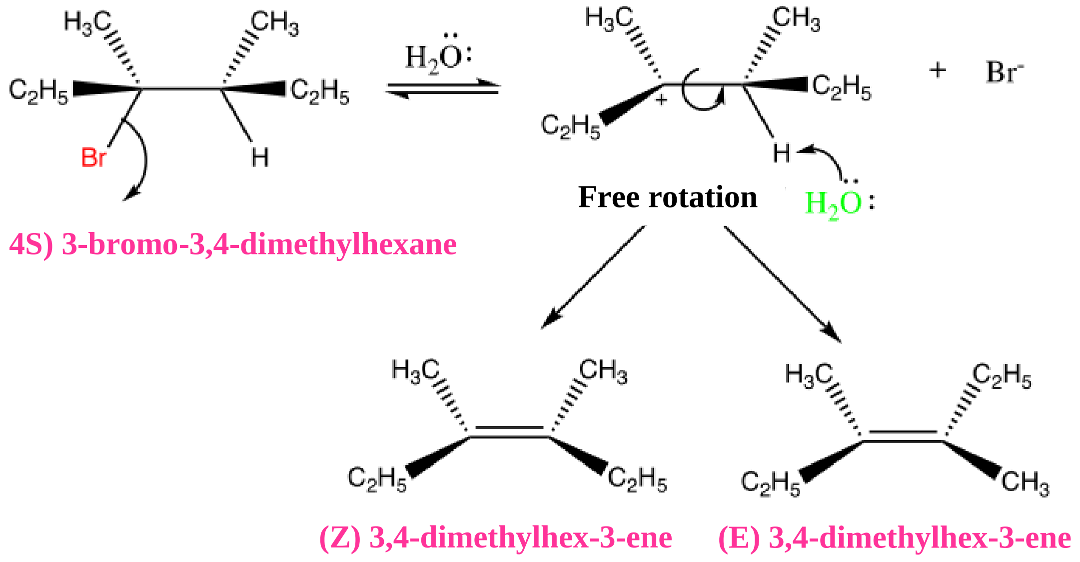
Once the electrophile NO_2^+ is formed, it attacks the aromatic nucleus to produce a "σ-complex", which is unstable, and the elimination of a proton allows the conjugated system of the three π electron double bonds to reformed.



5.3. Elimination Reaction

5.3.1. First-Order Elimination Mechanism (E1)

Example: The action of H_2O on 3-bromo-3,4-dimethylhexane.

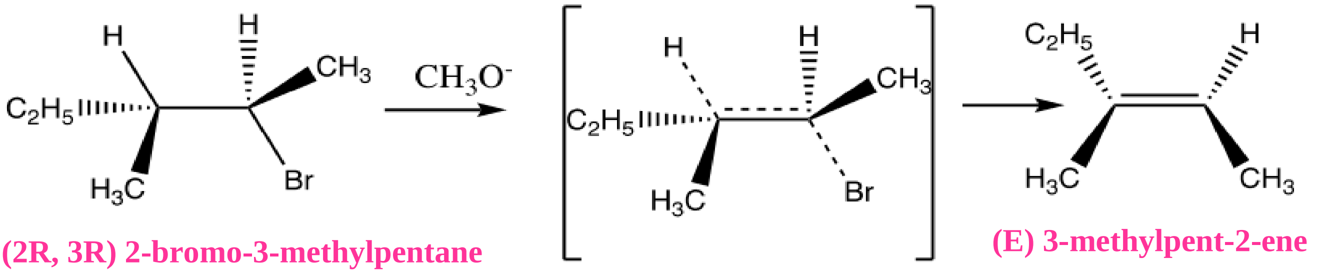


The stability of an alkene depends on the number of alkyl substituents attached to its Sp² carbons; the more substituted an alkene is, the more stable it becomes.

Zaïtsev Rule : *If there are two protons that can be eliminated, the one that is removed is the one that leads to the most substituted alkene, which is the most thermodynamically stable.*

5.3.1. Second-Order Elimination Mechanism (E2)

Example: E2 reaction of (2R, 3R) 2-bromo-3-methylpentane.



(2R, 3R) 2-bromo-3-methylpentane

(E) 3-methylpent-2-ene

5.4. Rearrangement Reaction

A rearrangement is the restructuring of a molecule, where the substrate reorganizes its atoms. This reorganization can be spontaneous or induced by an energy input such as heat. During a rearrangement, atoms may migrate to optimize the stability of a molecule. Thus, the substrate and the final product are constitutional isomers.

Example: Rearrangement by hydrogen atom migration.

Enol
C_3H_6O

Ketone
C_3H_6O