Chapter 4
Reaction mechanism

Introduction :

The reaction mechanism can be defined as the set of steps that a reaction can have from the reactants to the formation and obtaining of the products. The reactions can occur all at once, in a single step, or through several steps. Each of these steps is known as an elementary reaction or also called an elementary process.

4.1. Substitution reactions: where one atom or group of atoms is replaced by another atom or group of atoms.

Example:

$$CH_3\text{-}H + Cl{-}Cl \longrightarrow CH_3\text{-}Cl + H{-}Cl$$

These reactions can be radical, nucleophilic or electrophilic.

4.1.1. Radical substitution:

In a saturated compound one or more hydrogen atoms can be replaced by one or more atoms or groups of atoms according to a homolytic process. Simple thermal agitation or the absorption of a light photon of sufficient energy (by irradiation) can trigger a reaction which propagates in a chain.

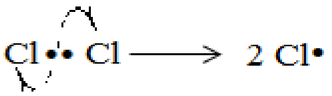
Light (hν)

$$R\text{-}H + X_2 \longrightarrow R\text{-}X + HX$$

Example: Chlorination of methane:

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$$

- **Initiation:**



- **Propagation:**

$$CH_3^{\bullet} + Cl_2 \longrightarrow CH_3\text{-}Cl + Cl^{\bullet}$$

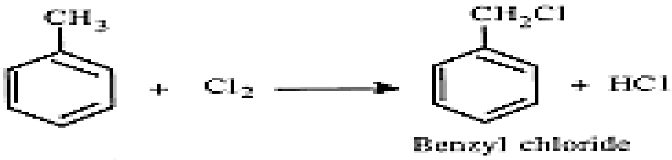
$$CH_4 + Cl^{\bullet} \longrightarrow CH_3^{\bullet} + H\text{-}Cl$$

- **Termination:**

$$Cl^{\bullet} + Cl^{\bullet} \longrightarrow Cl_2$$

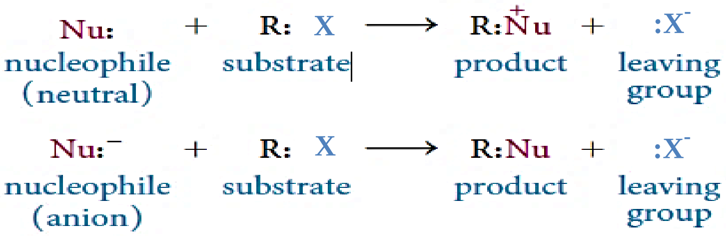
$$CH_3^{\bullet} + CH_3^{\bullet} \longrightarrow CH_3\text{-}CH_3$$

This type of reaction is also found with benzene derivatives.



4.1.2. Nucleophilic substitution :

Nucleophilic substitution results from the nucleophilic attack on a substrate by an electron-rich species (neutral molecule or anion) and the departure of a leaving group carrying a pair of electrons.



As the main nucleophilic reagents, we mainly encounter:

Anions: OH^-; RO^-; CN^-; NO_2^-
Neutral molecules containing a non-bonding pair of electrons: H_2O; NH_3; RNH_2; CH_3CH_2OH…

- In the latter case, the solvent can play the role of nucleophile. We then speak of solvolysis (and hydrolysis if the solvent is H_2O).
- Note that anions are much more reactive because they are more nucleophilic than the corresponding neutral molecules: RO- more nucleophilic than ROH.

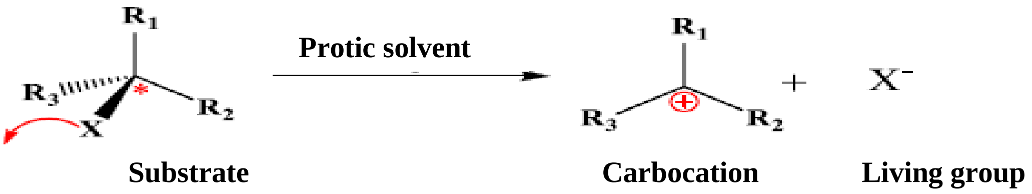
Nucleophilic substitution is represented by two different mechanisms.
- SN_1: Nucleophilic substitution of order 1
- SN_2: Nucleophilic substitution of order 2.

4.1.2.1. SN_1 Mechanism:

A. Reaction mechanism:

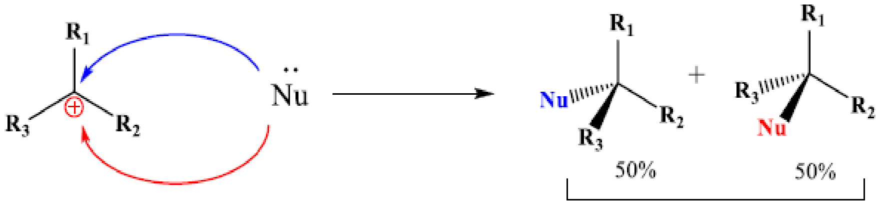
The **SN_1 mechanism** is a two-step process.

- The first step is slow: it consists of the ionization of the C-X bond (of the RX molecule) under the effect of a polar protic solvent.



- The electrons of the C – X bond go with the leaving group, and a carbocation is formed.

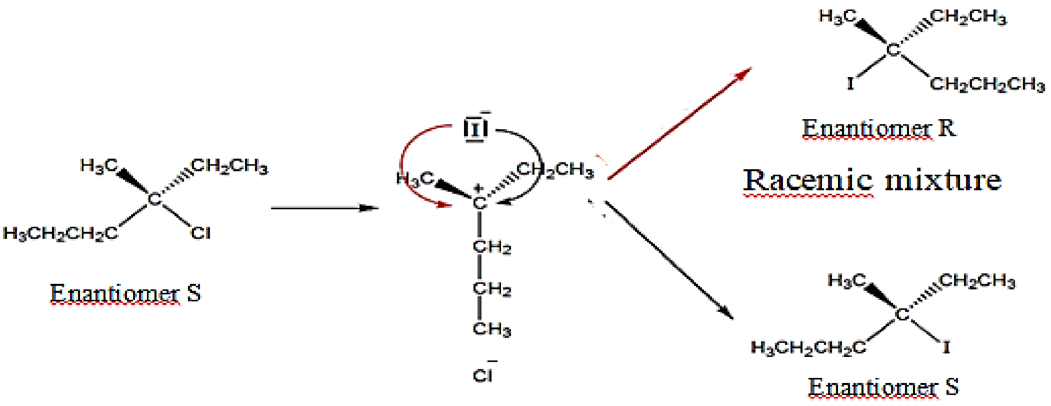
In the second step, which is fast, the second step: is the attack by the nucleophile of the planar carbocation formed, the attack can be done from one side or the other of the plant.



Racemic mixture

When the nucleophile is a neutral molecule, such as water or an alcohol, loss of a proton from the nucleophilic oxygen, in a third step, gives the final product.

<u>Example:</u>



<u>B. Stereochemistry:</u> The carbocation formed is planar, it can be attacked from both sides of this plane. If the compound is optically active, we will have formation of a mixture of enantiomers in equal quantities: Non-stereospecific reaction.

<u>C. Reaction rate:</u> The SN_1 nucleophilic substitution is said to be of order 1 because it obeys a first-order rate law:

$$\mathbf{v = k\ [RX]}$$

In the case of a first-order reaction, the reaction rate is proportional to the concentration of the substrate and independent of the concentration of the nucleophilic reagent.

D. Energy diagram of a SN1:

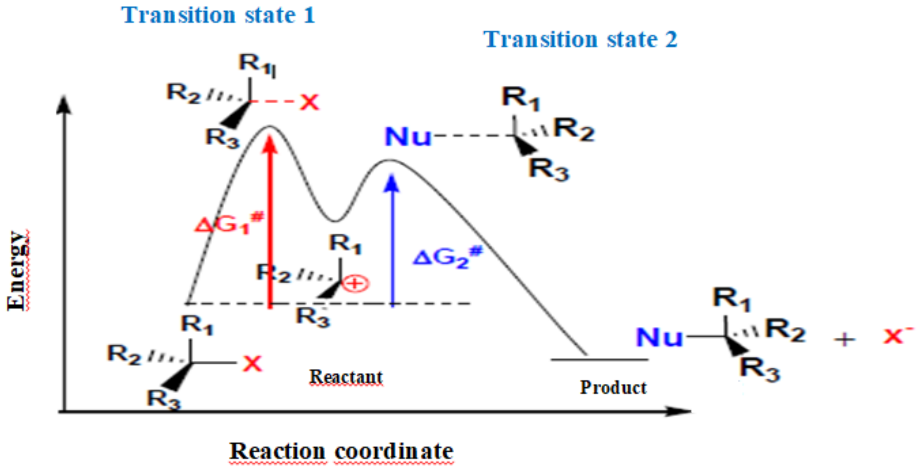
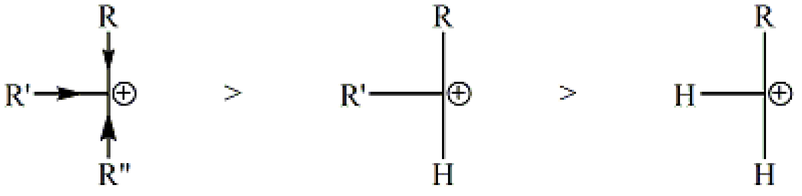


Figure 4.1: Reaction energy diagram for an SN_1 reaction.

E. Influence of different parameters:

E.1. Influence of the C carrying the leaving group:

The SN_1 reaction is all the faster as the carbocation formed is stable. The alkyl groups with an inductive donor effect further stabilize the carbocation. The reactivity increases in the series:



Tertiary Secondary Primary

SN_1 occur favorably on tertiary and secondary haloalkanes.

b- Nature of the leaving group:

The C– X bond breaks more easily when it is more polarizable, especially when it is longer. The length of the bond increases as the volume of X increases. The ease of breaking the CX bond thus increases from C–F to C–I, and the reactivity increases from R–F to R–I.

c- Influence of the nucleophile:

The nucleophile does not intervene in the kinetically determining step of the SN_1 mechanism. Its influence is therefore weak in this mechanism and is not of great importance given the ease of attack on the carbocation.

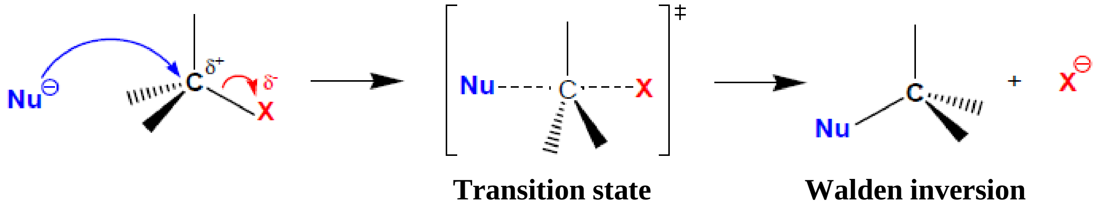
d- Influence of the solvent:

A polar protic solvent increases the speed of the SN_1 mechanism by forming hydrogen bonds with the leaving group. These bonds further polarize the C—X bond and facilitate its breakage, thus promoting the formation of the carbocation.

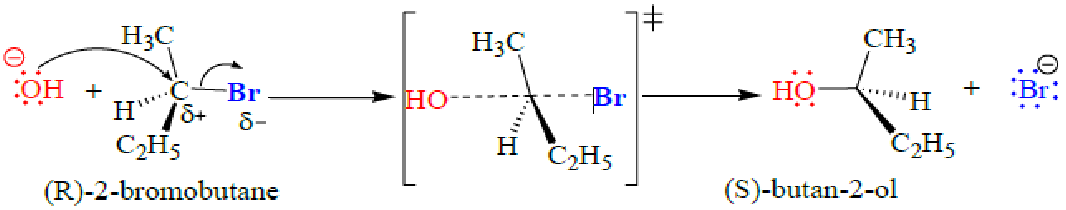
4.1.2.2. SN_2 Mechanism:

A. Reaction mechanism:

The mechanism is concerted, the attack of the nucleophile which is dorsal on the substrate and the departure of the nucleofuge (leaving group) occurs at the same time.



Example:



B. Stereochemistry: if the carbon is asymmetric, the reaction leads to an inversion of configuration (Walden inversion). We have a single enantiomer: stereospecific reaction.

C. Reaction rate: SN_2 is said to be second order because the rate law is of second order:

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

D. Energy diagram of a SN_2:

The mechanism of the SN_2 reaction can be represented by the following diagram:

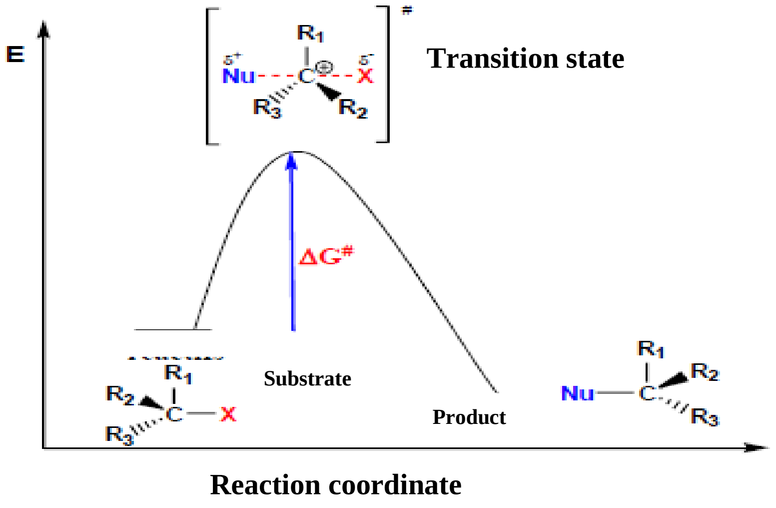


Figure 4.2: Reaction energy diagram for an SN_2 reaction.

E. Influence of different parameters:

E.1. Substrate class: The reactivity order for SN_2 is opposite to that observed for SN_1. Methyl or primary carbons are very reactive. $C_{III} < C_{II} < C_I <$ Methyl

E.2. Leaving group nature: similar to SN_1.

E.3. The nucleophile: charged nucleophiles (anions: RO^-, HO^-, CN^-, X^- ...) are stronger than nucleophiles (Nu) (NH_3, H_2O, ROH ...).

E.4. The solvent: a polar aprotic solvent favors the SN_2 reaction.

We summarize the distinctive characteristics of SN1 and SN2 substitution reactions in the summary table (Table 4.1).

Reaction mechanism	**Stereochemistry**	**Kinetic**	**Substrate**	**Solvent**	**Reactant**
SN1	two enantiomeric configurations	v = k [substrate] monomolecular	tertiary or secondary	protic polar	weak nucleophile
SN2	- walden inversion - a single configuration, inverse to that of the substrate	v = k [substrate][reactant]	methyl or primary	aprotic polar	good nucleophile

4.1.3. Electrophilic substitution:

Electrophilic substitution is an organic reaction in which an electrophilic entity replaces another group, most often a hydrogen atom, carried on an electron-rich compound, particularly aromatic compounds. Thus, the main reaction of this type is the electrophilic aromatic substitution noted SEa.

- In these aromatic compounds, the presence of π electrons gives the aromatic cycle a nucleophilic character which favors a substitution of an atom under the action of an electrophile.

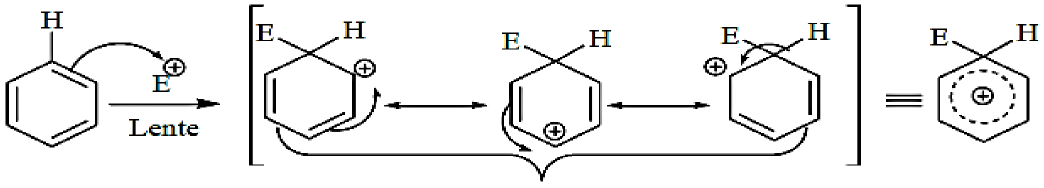
- Electrophilic substitution reactions are catalyzed by strong acids such as: H_2SO_4, H_3PO_4, or by Lewis acids such as $AlCl_3$, $FeCl_3$……

We can distinguish 4 successive steps in an electrophilic substitution reaction.

a. Formation of the electrophilic reagent E^+:

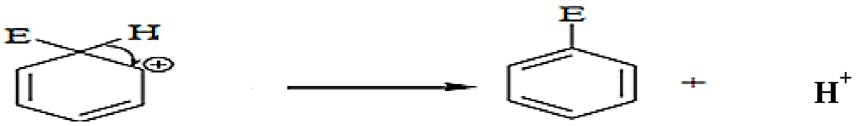
$E{:}Z + AlCl_3 \longrightarrow [Z{:}AlCl_3]^- + E^+$

b. Formation of carbocation :



Wheland Intermediate

c. Expulsion of H^+ :



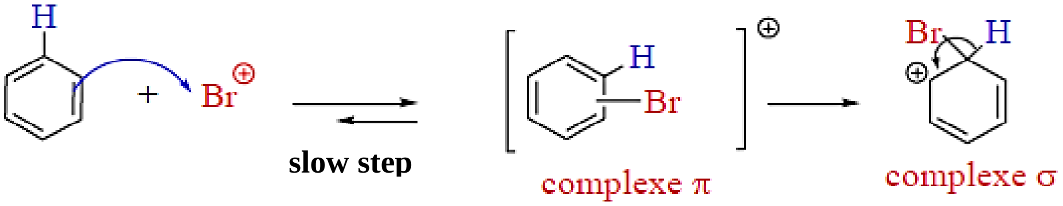
d. Catalyst regeneration:

$H^+ + [Z:AlCl_3]^- \longrightarrow H:Z + AlCl_3$

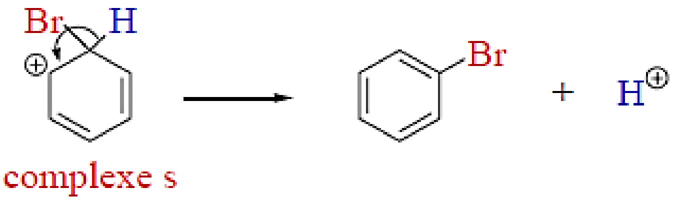
Example: Bromination of Benzene

1st step: formation of the electrophilic reagent Br + :

2nd step (slow): formation of the Wheland intermediate:



Step 3 (quick): obtaining substitute products:



Step 4: Catalyst regeneration

$$\mathbf{FeBr_4^- + H^+ \longrightarrow FeBr_3 + HBr}$$

Several electrophilic substitutions can take place on the same benzene nucleus. The study of polysubstitution will be done in the chapter relating to benzene hydrocarbons.

4.2. Addition reaction:

As the name suggests, an addition reaction implies that one or more reactants (electrophile, nucleophile, or radical) add to the substrate to yield a final product. The substrates are unsaturated (C=C, C≡C, C=O, C≡N...).

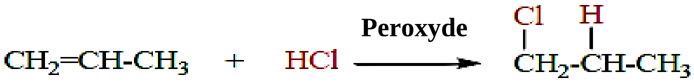
$$A{=}B + C\text{-}D \longrightarrow C\text{-}A\text{-}B\text{-}D$$

Substrat Réactif

There are three types of addition mechanisms: electrophilic, nucleophilic and radical.

4.2.1. Radical addition:

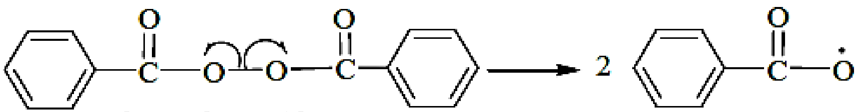
It occurs mainly with alkenes and alkynes. It is a chain reaction, goes through several stages: **initiation**, **propagation** and **termination**. These reactions are catalyzed by peroxides "radical initiators". Radical addition is an anti-Markovnikov addition (Karash effect).



$$CH_2{=}CH\text{-}CH_3 + HCl \xrightarrow{\textbf{Peroxyde}} \underset{|}{\overset{Cl}{}}CH_2\text{-}\overset{H}{\underset{|}{}}CH\text{-}CH_3$$

This reaction takes place in three stages:

Production of initiator radicals

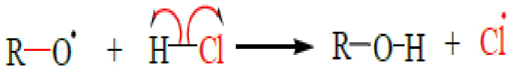


benzoyl peroxide

Or

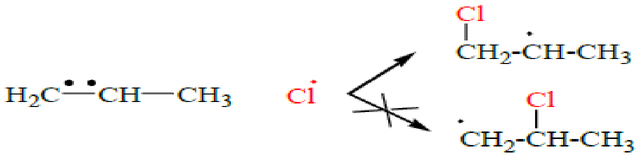
$$R{-}O{-}O{-}R \longrightarrow 2\ R{-}O^{\bullet}$$

Initiation phase:



$$R{-}O^{\bullet} + H{-}Cl \longrightarrow R{-}O{-}H + Cl^{\bullet}$$

Propagation:



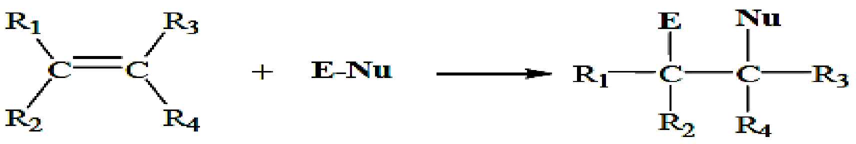
Then the reaction propagates, the new radical formed reacts on another molecule of reactant.

- **Termination:**

The reaction ends with exhaustion of the substrate or radicals in the reaction medium.

4.2.2. Electrophilic addition:

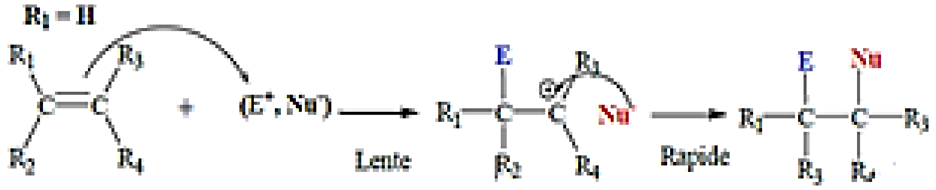
In this case, the reactant is electrophilic (electron-poor). This generally involves addition to electron-rich unsaturated systems such as alkenes (or alkynes), where a π bond is broken under the action of an E-Nu reagent in which the σ bond is heterolytically cleaved.



$$\text{E-Nu} \longrightarrow \text{E}^{+} + \text{Nu}^{-}$$

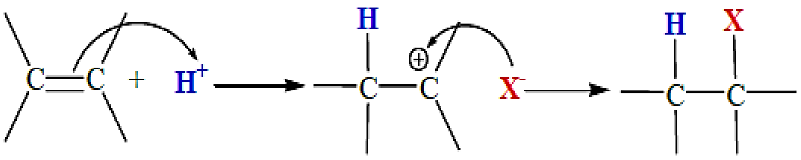
We have two steps:

- ✓ The first step is slow, the electrophile attaches to the least substituted carbon (or the most hydrogenated) to form the most stable carbocation. The electrophilic addition reaction follows the Markovnikov rule.
- ✓ In the second step, the formed carbocation will be attacked by the nucleophile Nu- originating from the E-Nu bond cleavage.

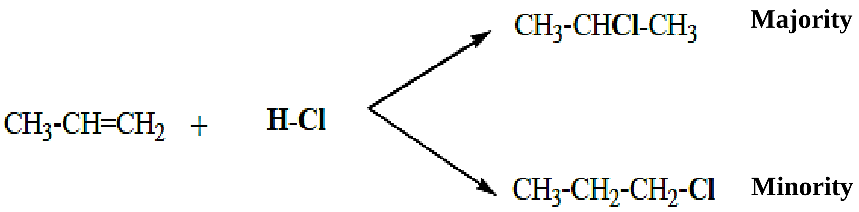


4.2.2.1. Addition of a hydrogen halide H – X (hydrohalogenated acids)

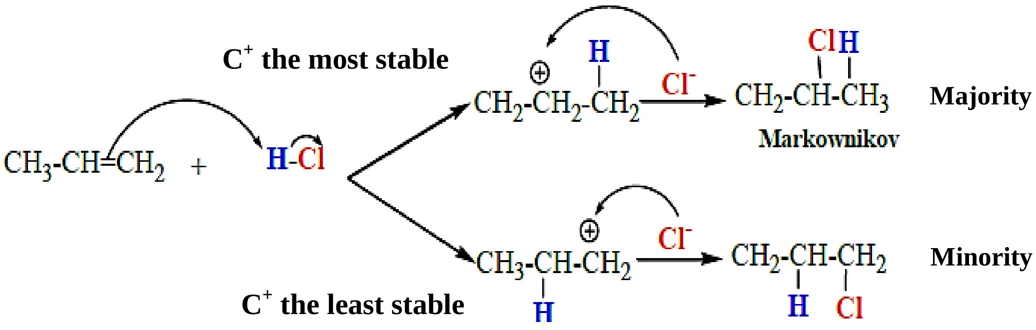
The hydrohalogenated acids HCl, HBr, HI are added directly on the double bonds, to give a saturated monohalogenated derivative. The electrophile is the H+ ion, resulting from the dissociation of HX into H^+ and X^-.



Example :

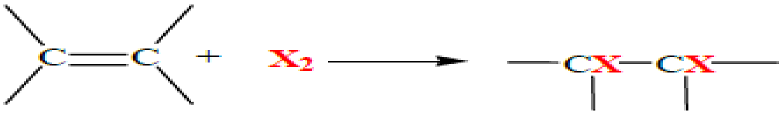


Mechanism :



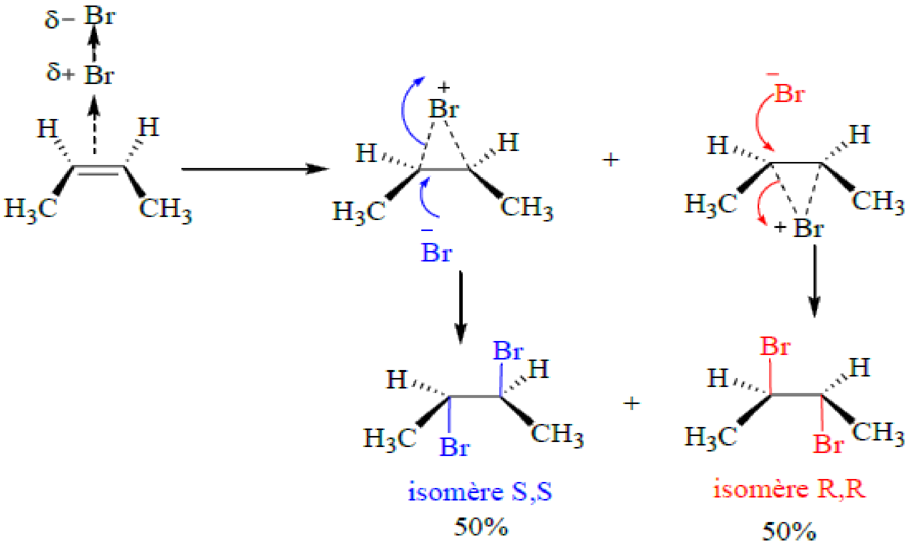
4.2.2.2. Addition of dihalogens X_2:

The dihalogens Cl_2, Br_2, I_2 add to the double bonds, giving a dihalogen derivative in which the two halogen atoms are carried by two neighboring carbons.



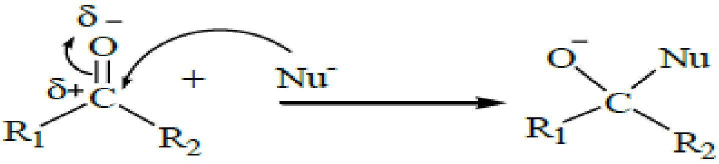
- ✓ The X-X bond (non-polar) polarizes in the presence of an alkene "bond π" as follows: $X^{\delta+}$-$X^{\delta-}$
- ✓ The X^+ forms a bridged ion (halonium ion) with the double bond. The attachment can be done on both sides.

Examples: The addition of Br_2 on (Z)-But-2-ene



4.2.3. Nucleophilic addition:

Nucleophilic additions result from the attack of an electron-rich entity Nu^- on an unsaturated molecule “carbonyls ($C=O$), nitriles ($C\equiv N$) or imines ($C=N$)”.
First, the nucleophile Nu- attacks the electron-poor site of the substrate followed by the addition of the electrophilic entity E+.



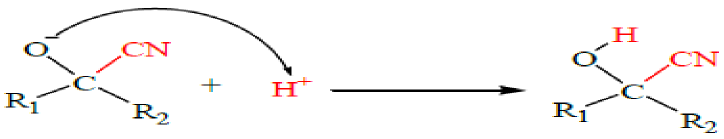
Example: The addition of hydrocyanic acid to ketones

1st step: this is a slow step, the cyanide ion plays the role of nucleophilic reagent, attacks the carbon which carries a positive charge.

1

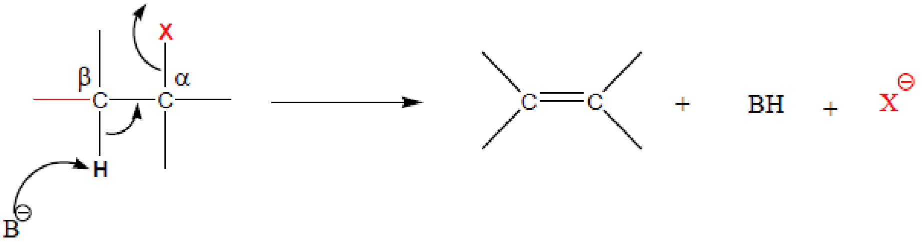
2nd stage: the slow stage followed by the fast reaction 2

2



4.3. Elimination reaction:

Elimination reactions (or β-elimination) are the reverse of addition reactions. It is a reaction that transforms a substituted alkane (haloalkane, alcohol, etc.) into an alkene.



Elimination reactions are favored by an increase in temperature and the presence of strong basic groups: sodium hydroxide (Na+, HO-); potassium hydroxide (K+, HO-); alcoholate ions (Na+, RO-).

Concerning this type of reaction, two different mechanisms are considered:

- Departure of X$^-$ and formation of a carbocation "mechanism E1"
- Departure of H and X$^-$ at the same time "mechanism E1".

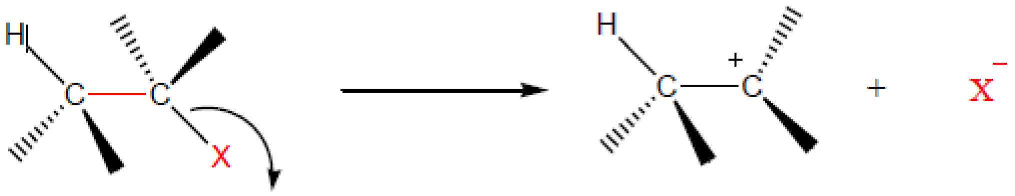
4.3.1. Mechanism E1 (unimolecular elimination)

A. Reaction mechanism:

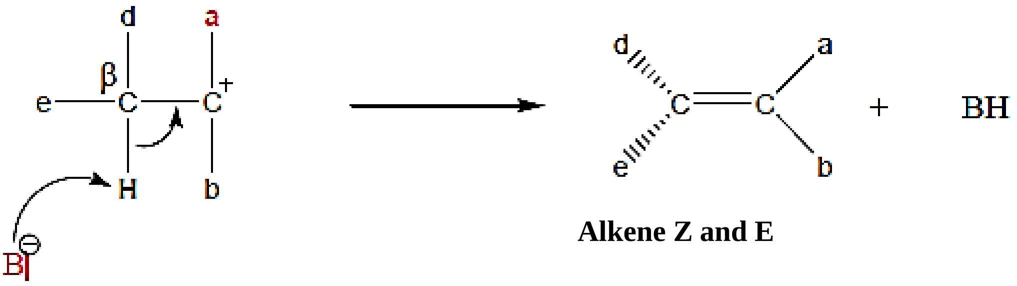
The reaction occurs in two steps

Step 1: Formation of a carbocation "slow step, rate-determining step"

The C-X bond breaks under the influence of a polar protic solvent.



The carbocation once formed is quickly attacked by base B:$^-$ which removes an H$^+$ proton with formation of a double bond.

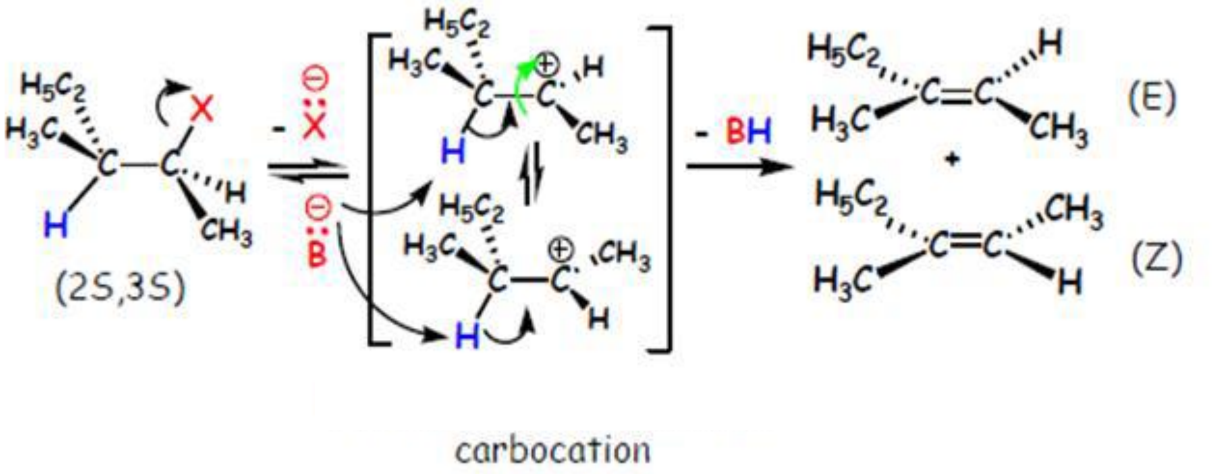


Alkene Z and E

B. Stereochemistry:

The reaction results in a mixture of Z and E stereoisomers, due to free rotation around the C-C bond: Non-stereospecific reaction.

Example:



Zaitsev's Rule:

In an elimination reaction, the proton preferentially leaves the least hydrogenated or most substituted carbon to give the most substituted alkene (thermodynamically the most stable): regioselective reaction.

C. Reaction rate:

The reaction is said to be first-order or unimolecular because it obeys a first-order rate law:

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

The reaction rate is proportional to the substrate concentration and independent of the base concentration.

D. Factors influencing the reaction:

Substrate class: the presence of bulky groups on the carbon linked to the halogen accelerates the elimination of the latter: bulky and electron-donating alkyl groups favor the E1 mechanism (tertiary substrate: more stable carbocation).

base: The reaction rate is independent of the concentration of the base. However, the base must be weak and less nucleophilic to prevent proton abstraction during the first step of the mechanism (NH_3, $R\text{-}NH_2$, R-OH...).

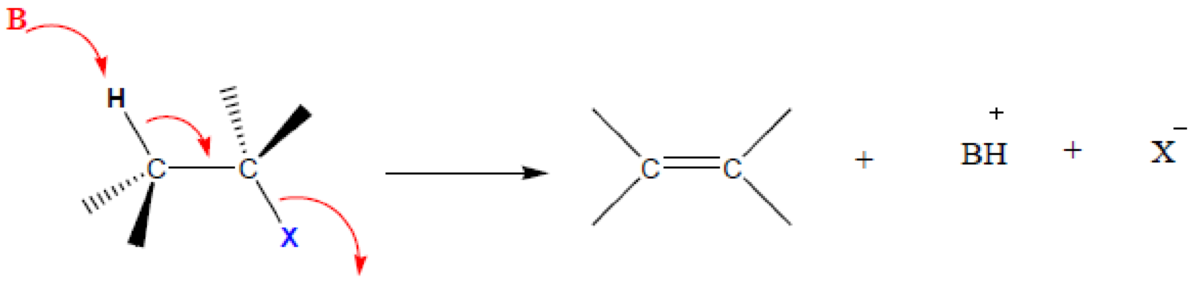
The nucleofuge (leaving group): The more polarizable (and longer) the C-X bond is, the easier it is to break. The bond length increases as the volume of X increases.

$$I^- > Br^- > Cl^- > F^-$$

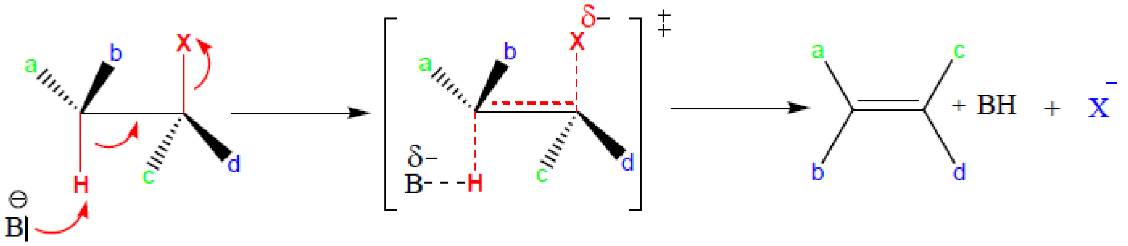
Solvent: A polar protic solvent increases the rate of the E1 mechanism, by forming hydrogen bonds with the nucleofuge: H_2O, ROH.

4.3.1. Mechanism E2 (bimolecular elimination)

A. Reaction mechanism: the mechanism is concerted: passage through a transition state.

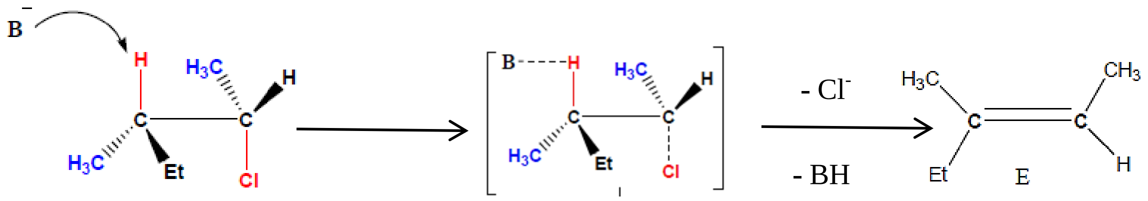


The attack of the base and the breaking of the C-X and C-H bonds occur simultaneously: the base attacks the C-H bond which weakens, while the C-X bond polarizes.



The C-X and C-H bonds must be antiperiplanar (same plane), X and H must be on two opposite sides (in anti position).

B. Stereochemistry: The reaction occurs in a single step. Elimination occurs exclusively when H and X are in the same plane. Obtaining a single alkene of Z or E configuration: Stereospecific reaction.

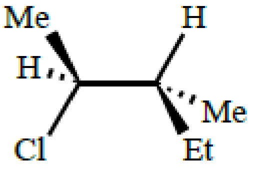


C. Reaction rate: The E2 mechanism is bimolecular (order 2) because it obeys a second-order rate law: **v = k [R-X] [Nu]** The reaction rate depends on the concentrations of the substrate and the base.

The E2 elimination reaction is favored in polar aprotic solvents.

Exercise:

The treatment of compound A with hot soda leads to the formation of two products, one of which is the majority.



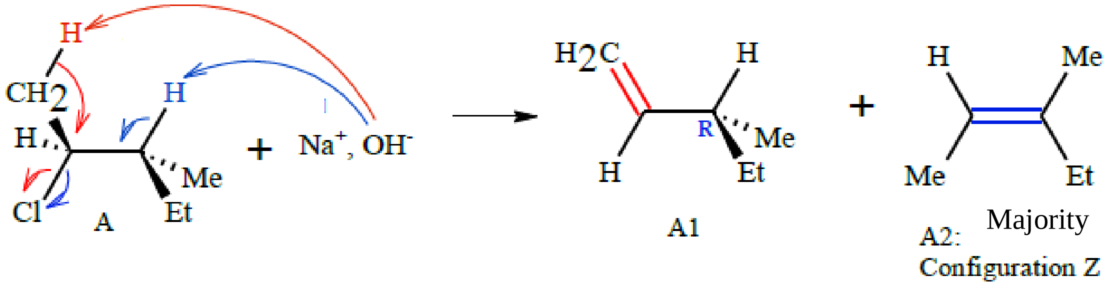
A

1) Knowing that the rate is V = [A] [OH$^-$], what type of reaction is it?

2) Detail the reaction mechanism and give the configuration of each product.

Correction:

1) As compound A is treated with hot soda, it is an elimination reaction, type E2 because the speed of the reaction V = K [A] [OH-].
2) 2) As this is an E2 elimination reaction, it occurs in a single step where the removal of the proton in the β position by the base, the departure of the Cl- nucleofuge and the formation of the double bond occur simultaneously. It is also noted that the E2 reaction occurs when the proton in the β position and the nucleofuge are in an antiperiplanar position. A single alkene of Z or E configuration is obtained.



The formation of the major product (A2) is justified by Zaitsev's rule (the formation of the most substituted alkene)