

//
Organic Reactions and
Synthesis of a Drug
molecule.

By Monika S

Chapter - 4

M.S

A chemical reaction involves the breaking of old bonds and formation of new bonds in the form of product. but in between the reactant and product there are some intermediate species, which exists only for some time and soon get converted into products. These species are known as Intermediates.
For Example

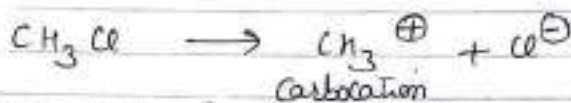
- 1) Carbocation
- 2) Carbanion
- 3) Free Radical
- 4) Carbenes
- 5) Nitrenes.

First three are most important and common intermediates.

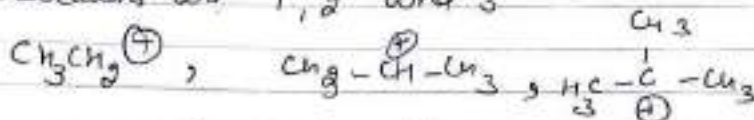
1.) Carbocations: - The chemical species which are bearing a positive charge on carbon and carrying six electrons in their valence shell. Also known as Carbenium ion.
A carbocation is formed by the heterolytic fission of a covalent

Reason of stability \rightarrow Effect of 3 methyl grps increases in electron density and hence stability increases $\text{3}^\circ > \text{2}^\circ > \text{1}^\circ$

bon where one of the atoms have more electron density than the other.



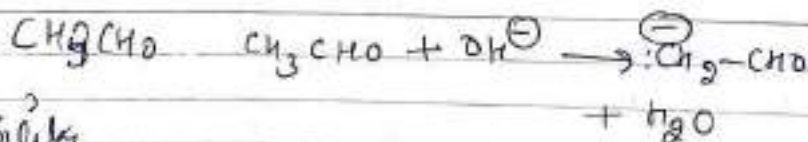
Carbocations are $1^\circ, 2^\circ$ and 3°



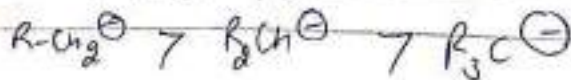
Stability $3^\circ > 2^\circ > 1^\circ$ due to +I effect.

2) Carbanion: - Chemical species bearing a negative charge and having eight electrons in their shell.

They are also produced by heterolytic fission of a covalent bond

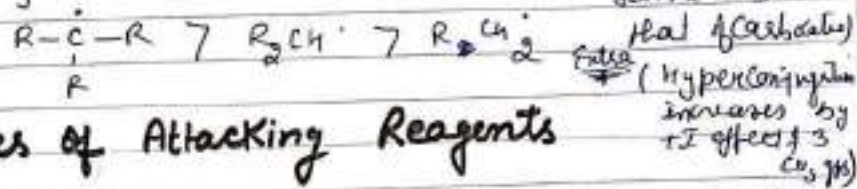
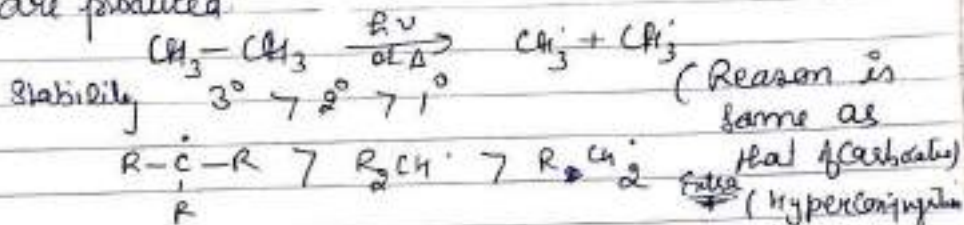


Stability $1^\circ > 2^\circ > 3^\circ$



Reason \rightarrow greater is the s-character (sp hybridisation)
 greater is the stability
 \rightarrow Less the effect of (-) electrons greater is the stability
 because energy is less. $1^\circ > 2^\circ > 3^\circ$ Carbanions

3) **Free Radicals**:- An atom or group of atoms having an odd or unpaired electron. These are produced by homolytic fission which means same type of Radicals are produced.



Types of Attacking Reagents

1) Electrophilic Reagents (Electrophiles)

It is an electron loving species which always attacks at the centre of high electron density. Classification of Electrophiles

(i) **Positive Electrophiles**:- $\text{H}^\oplus, \text{Cl}^\oplus, \text{R}^\oplus$

(ii) **Neutral Electrophiles**:- $\text{H}_3\text{O}^\oplus, \text{R}^\oplus, \text{BF}_3, \text{AlCl}_3, \text{ROCl}$

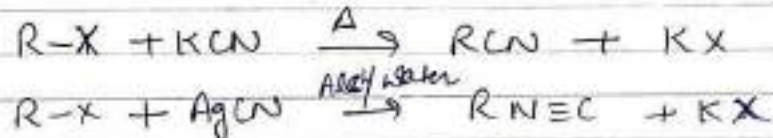
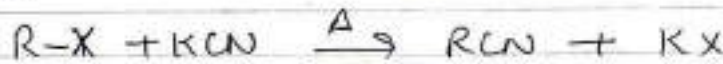
2) Nucleophilic Reagent (Nucleophiles)

It is an electron rich species. It always attack on the lower density. Types:-

(i) Negative nucleophiles: $F^{\ominus}, Cl^{\ominus}, I^{\ominus}, OH^{\ominus}$
 $CN^{\ominus}, OR^{\ominus}, NH_2^{\ominus}$

(ii) Neutral nucleophiles: H_2O, ROH, ROR, KOH
 NH_3, RNH_2

(iii) Ambident Nucleophiles: - when electron rich species attack from both sides.
 eg CN^{\ominus} and NO_2^{\ominus}



Types of Organic Reactions

- 1) Substitution
- 2) Addition
- 3) Elimination
- 4) Cyclisation Reactions
- 5) Condensation

Substitution Reactions: - A Reaction in which there is direct replacement of an atom or group of atoms in an

Organic molecule by another atom or group of atoms without any change in the remaining part of a molecule.

New atom or group which enters in the molecule is called substituent.

There are two types of Substituent Reactions

1) Nucleophilic Substitution Reactions

→ which are carried out by nucleophiles
 → here a stronger nucleophile displaces a weaker nucleophile.

→ Usually Alkyl halides have Nucleophilic substitution reactions.

Types of Nucleophilic Substitution Reactions

(i) S_N^1 → (Nucleophilic Substitution, Unimolecular) Reactions

(ii) S_N^2 → (Nucleophilic Substitution Bimolecular) Reactions

1) S_N^1 Reaction :- Reaction in which the rate of kinetics depends upon the conc. of only one reactant is called

SN¹ Reaction

$$\text{Rate} = k[\text{RX}]$$

Mechanism



Rate of Reaction depends on the
 Conc. of tert-butyl bromide only
 $\text{Rate} = k(\text{CH}_3)_3\text{CBr}$

Factors which influence SN¹ Reactions

(i) Effect of Solvent :- As the transition state of SN¹ Reaction is polar, therefore polar solvents will stabilize it and lowers its activation energy. Hence Polar Solvents favour SN¹ Reaction.

- (ii) Nature of nucleophiles:- Nucleophiles do not take part in the rate-determining step of S_N1 Reaction. Hence nucleophile has no effect on the rate of reaction.
- (iii) Effect on structure of alkyl halide:- Carbocations are the intermediates in S_N1 Reaction. More stable the carbocation more rapid should be the S_N1 Reaction.
Benzyl > Allyl > Tertiary > Secondary > Primary
- (iv) Effect of nature of the leaving group:- better the leaving group, lesser is the activation for the transition state hence more should be the reactivity of the alkyl halide in S_N1 Reaction. Order of reactivity of the different leaving group follows the sequence

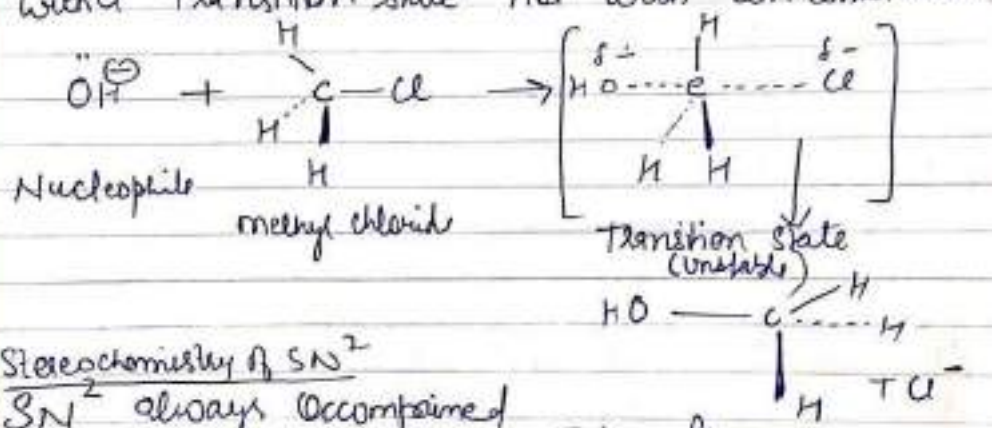
$$I^- > Br^- > Cl^- > F^-$$
- Stereochemistry of S_N1 → S_N1 reactions are accompanied by racemisation if alkyl halide is optically active. Attack of nucleophile can occur in both directions. But due to hindrance of bulky groups attack occurs from opposite side of halide ion.

2) S_N^2 (Bimolecular)

Rate of Reaction depends on both nucleophile and reactant. Here reaction take place in one step only, and r^n is of 2nd order.

$$\text{Rate} = k[\text{Nucleophile}][\text{Reactant}]$$
$$\text{Rate} = k[\text{OH}^-][\text{RX}]$$

Bond Breaking and Bond formation take place simultaneously. Reaction journeyed with a transition state not with an intermediate.



Stereochimistry of S_N^2
(S_N^2 always Occompsied with inversion of Configuration Product also called as Walden Inversion)

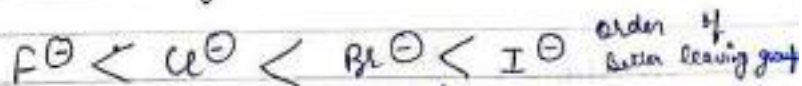
Reactivity of S_N^2 mechanism

As the bulky group increases around the carbon atom, reactivity will get on decrease.
 $SO_2CH_3X > \text{Primary carbocation} > \text{Secondary} > \text{Tertiary}$
 allyl & Benzyl

Factors affecting S_N^2

① Nature of halogen atom: - Better the leaving group, more stable is the transition state due to greater stability of the negative charge by the leaving group, and hence more rapid is the reaction. Best leaving groups are weak bases. So order of ease of elimination of leaving group $\propto \frac{1}{\text{basicity}}$

hence



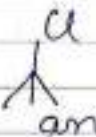

Reactivity of haloalkanes should also decrease in the order $R-F > R-Cl > R-Br > R-I$ as suggested.

R-I > R-Br > R-Cl > R-F 10

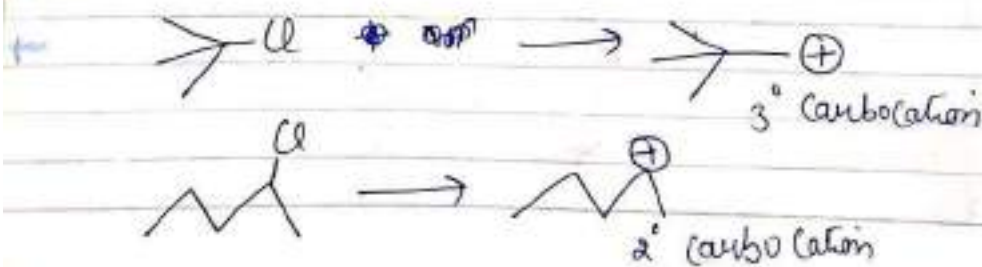
But the actual order is like this
C-I has the minimum bond dissociation energy while C-F has maximum. Hence it is easy to break R-I bond than C-F and hence C-I is more reactive than C-F

2) Effect of Solvent in S_N^2 Reaction

The transition state in S_N^2 Reaction is non-polar, hence non polar solvent will only stabilise it and hence lower the activation energy of the S_N^2 Reaction. Hence non-polar solvent favours S_N^2 Mechanism.

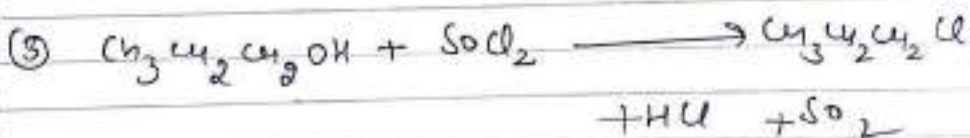
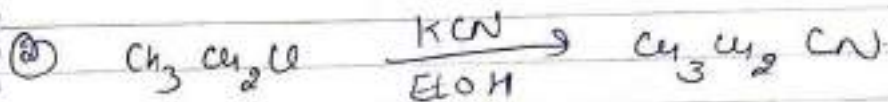
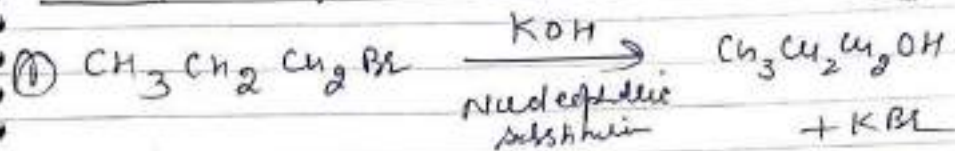
Q1 Out of  and  which is more reactive and why

Ans



3° is more stable than \cdot and hence S_N1 mechanism occur most readily in 3° .

Examples of Nucleophilic Substitution

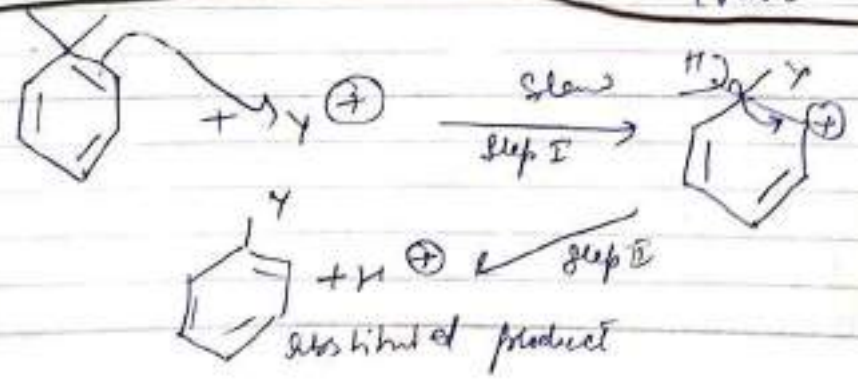
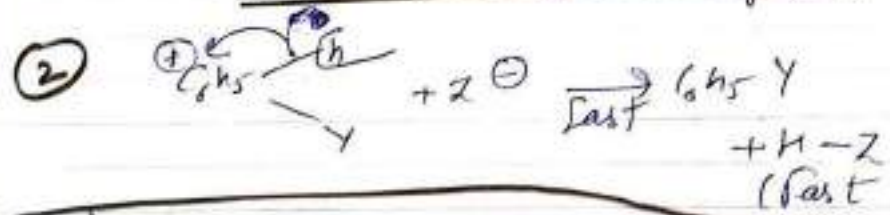
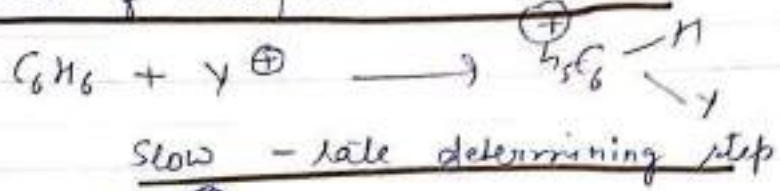


Electrophilic Substitution Reactions

The type of reactions which are carried out by electrophiles are called Electrophilic substitution reactions.

These reactions are typical of
aromatic and other aromatic
Compounds. For: Nitration, Sulphonation
and Friedel Craft.

① Attack of electrophile on molecule



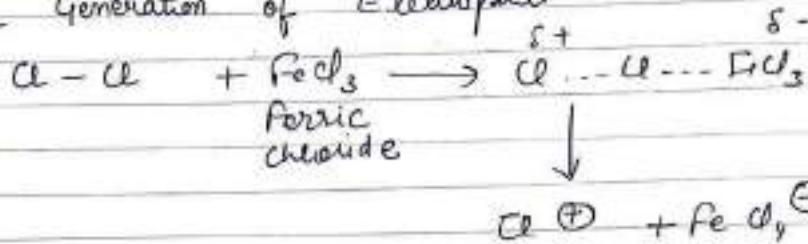
① Rate depends on $= k [C_6H_6] [Y^+]$

Examples
Halogenation

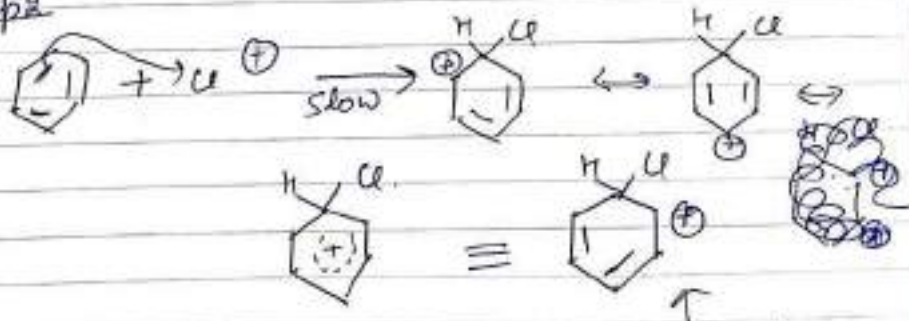


Mechanism

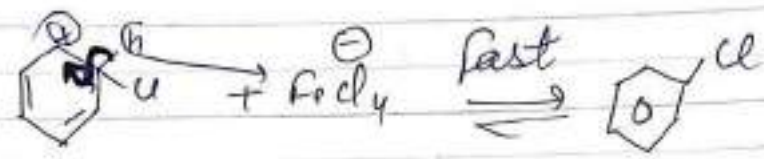
Step 1 Generation of Electrophile



Step 2

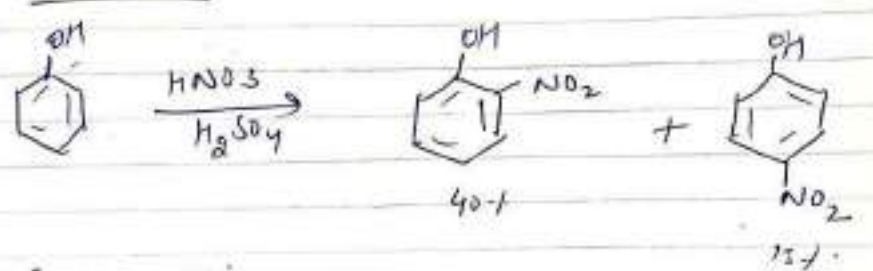


Abstraction of Proton from Carbocation



Examples
② Nitration

+ FeCl_3 + HCl.



③ Sulphonation

