Loknete Dr. Balasaheb Vikhe Patil (Padma Bhushan Awardee)
Pravara Rural Education Society
Arts, Science & Commerce College Kolhar

Structure, Stability and Reactions of Reactive Intermediates

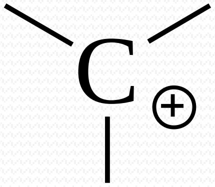
Class- M.Sc.-I

Mr. A. K. Kharde
Asst. Professor Dept. of Chemistry
A. S. C College, Kolhar

Structure, Stability and Reactions of Reactive Intermediates

Carbocation:-

A carbocation is molecule having a carbon atom bearing three bonds and a positive formal charge. Carbocations are generally unstable because they do not have eight electrons to satisfy the octet rule.

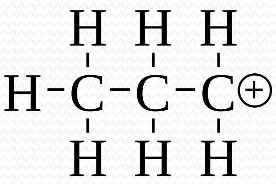


Open valence shell on carbon

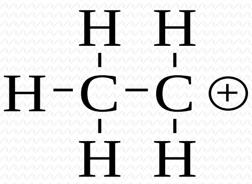
Methyl carbocation

Classification of Carbocations:-

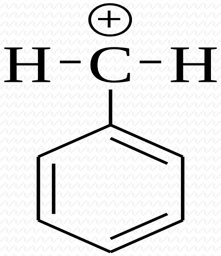
i) Primary carbocation (1^o):- A primary carbocation is one in which there is one carbon (alkyl group) directly attached to the carbon bearing the positive charge.



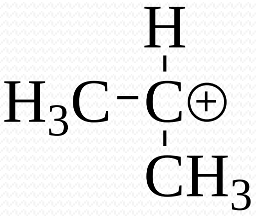
$$\begin{array}{cccccc} & H & H & H & \\ & | & | & | & \\ H- & C- & C- & C^{\oplus} \\ & | & | & | & \\ & H & H & H & \end{array}$$



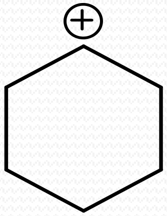
$$\begin{array}{cccc} & H & H & \\ & | & | & \\ H- & C- & C & \oplus \\ & | & | & \\ & H & H & \end{array}$$



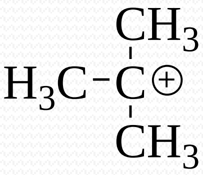
ii) Secondary Carbocation (2^o):- A secondary carbocation is one in which there are two carbons (alkyl groups) directly attached to the carbon bearing the positive charge



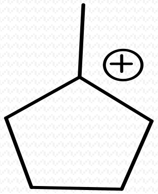
$$\begin{array}{cc} & H \\ & | \\ H_3C- & C^{\oplus} \\ & | \\ & CH_3 \end{array}$$



iii) Tertiary Carbocation (3º):- A tertiary carbocation is one in which there are three carbons (alkyl groups) directly attached to the carbon bearing the positive charge.

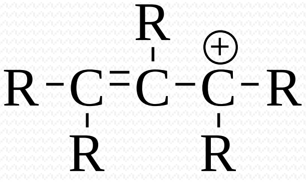


$H_3C-\overset{CH_3}{\underset{CH_3}{C^{\oplus}}}$

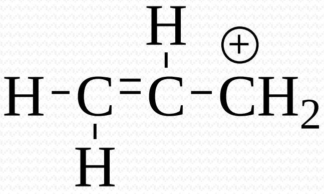


iv) Allylic Carbocation:- When carbon bearing the positive charge is immediately adjacent to a carbon-carbon double bond, the carbocation is termed as allylic carbocation.

General allylic carbocation structure



$R-\underset{R}{C}=\overset{R}{C}-\underset{R}{\overset{\oplus}{C}}-R$

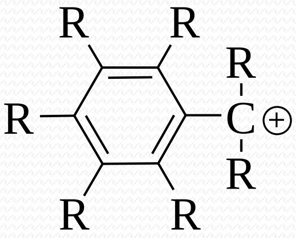


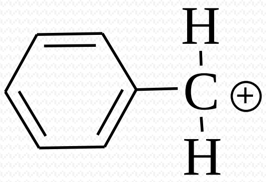
$H-\underset{H}{C}=\overset{H}{C}-\overset{\oplus}{CH_2}$

allyl carbocation

v) Benzylic carbocation:- When the carbon bearing the positive charge is immediately adjacent to benzene ring, the carbocation is termed as benzylic carbocation.

General benzylic carbocation structure

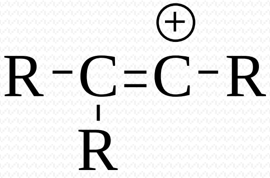




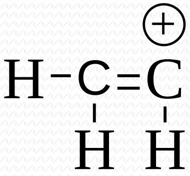
Benzyl carbocation

vi) Vinylic Carbocation:- When the carbon bearing the positive charge is part of an alkene the carbocation is termed as vinylic carbocation.

General Vinylic carbocation structure



$$R-\underset{R}{C}=\overset{+}{C}-R$$

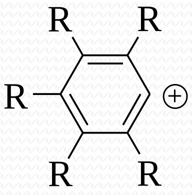


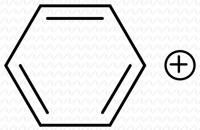
$$H-\underset{H}{C}=\underset{H}{\overset{+}{C}}$$

Vinyl carbocation

vii) Aryl Carbocation:- When the carbon bearing the positive charge is part of a benzene ring the carbocation is termed as aryl carbocation.

General aryl carbocation structure



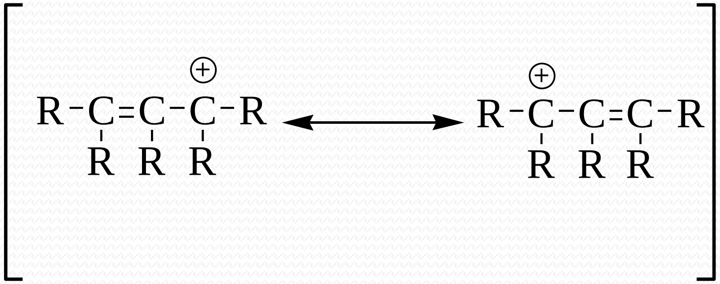


Phenyl carbocation

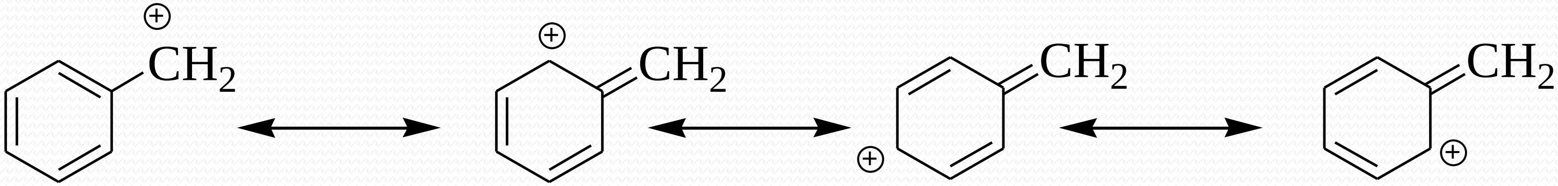
Stability of Carbocation:- Tertiary carbocation is more stable than secondary and secondary carbocation is more stable than primary carbocation because of inductive and resonance effect.

$3^o > 2^o > 1^o > CH_3$ Stability order of carbocation

Allyl cation and benzyl cation are more stable than most other carbocations.

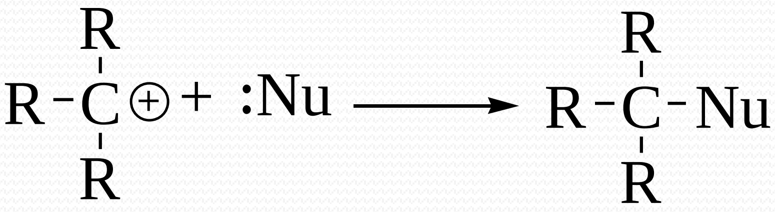


$$\left[R-\underset{R}{C}=\underset{R}{C}-\underset{R}{\overset{+}{C}}-R \longleftrightarrow R-\underset{R}{\overset{+}{C}}-\underset{R}{C}=\underset{R}{C}-R \right]$$



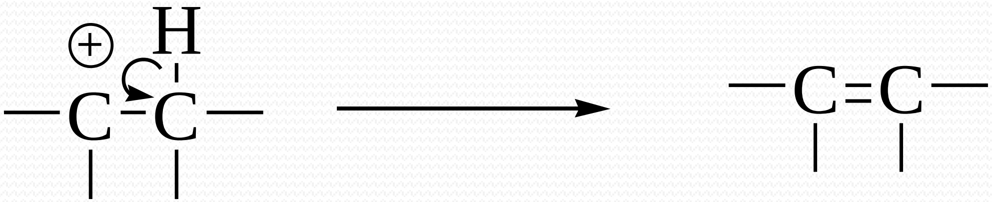
Reactions of Carbocations:-

i) Nucleophilic attack:-

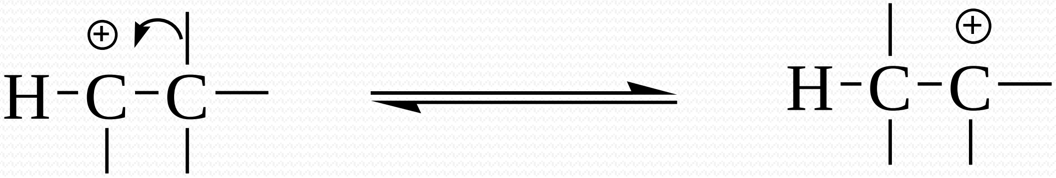


Nu = ROH, RSH, X^- , alkene (Produces new carbocation), Ar

ii) β-elimination:-

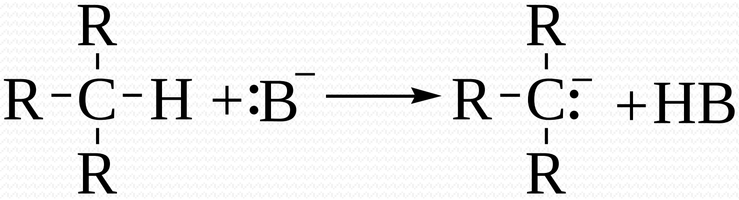


iii) Rearrangements:-

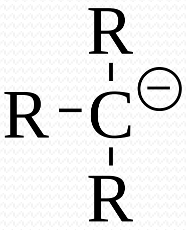


Carbanion:-

A carbanion is an anion in which carbon is trivalent and bears a formal negative charge. Formally carbanion is a conjugate base of carbon acid.



$$R-\underset{R}{\overset{R}{|}}\!\!\!\!\overset{}{\underset{}{C}}-H + :B^{-} \longrightarrow R-\underset{R}{\overset{R}{C}}:^{-} + HB$$



$$R-\underset{R}{\overset{R}{C}}{}^{\ominus}$$

Carbanions are typically nucleophilic and basic. The basicity and nucleophilicity of carbanions are determined by the substituents on carbon. These includes

i) The inductive effect, electronegative atoms adjacent to the charge will stabilize the charge.

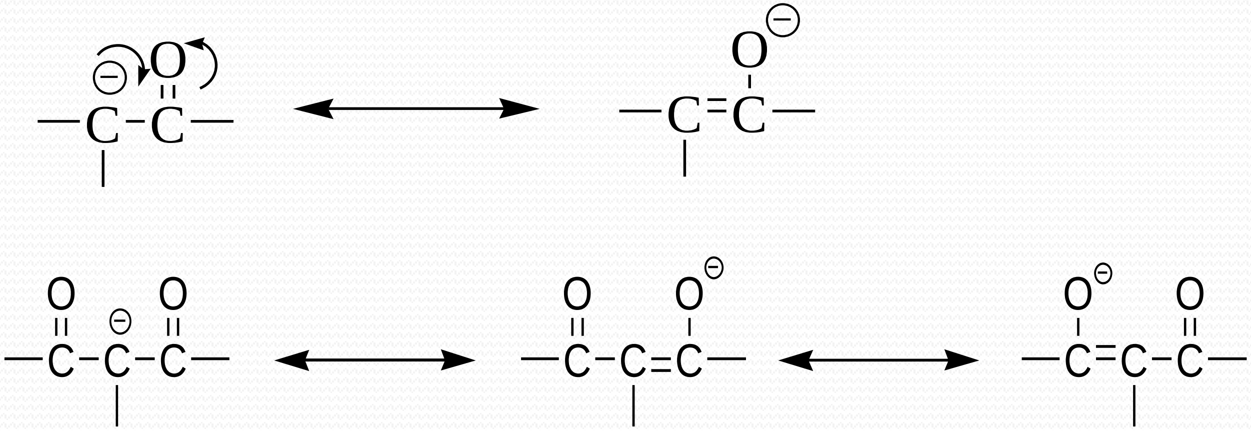
ii) The extent of conjugation of the anion, resonance effect can stabilize the anion.

Halogen stabilize carbanions in the order of Br > Cl > F

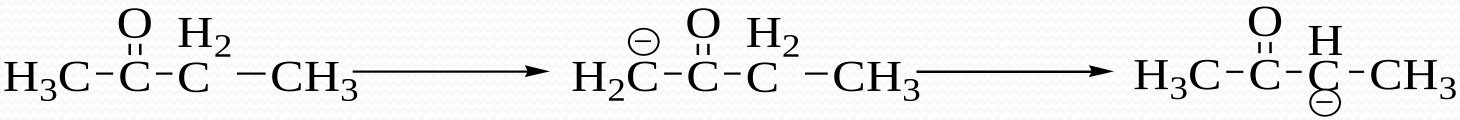
Carbanions are trivalent with SP^3 hybridization. The loan pair of electrons occupies one of the SP^3 orbitals. The geometry is thus trigonal pyramidal.

Stabilization of Carbanions:- The negative charge on carbanion is stabilized by neighbouring electron withdrawing groups (EWG) such as carbonyl, nitron and sulfone.

EWG: $C=O$, NO_2, CN, SO_2



When carbanions are formed in unsymmetrical ketones two carbanions is possible. One the more substituted carbanion is called the thermodynamic anion, while the least substituted and first formed anion is called kinetic anion. LDA is a base of choice for formation of kinetic product, while hydroxide and alkoxides gives the thermodynamic anion.



$$H_3C-\overset{O}{\overset{\|}{C}}-\overset{H_2}{C}-CH_3 \longrightarrow H_2\overset{\ominus}{C}-\overset{O}{\overset{\|}{C}}-\overset{H_2}{C}-CH_3 \longrightarrow H_3C-\overset{O}{\overset{\|}{C}}-\underset{\ominus}{\overset{H}{C}}-CH_3$$

	Kinetic	Thermodynamic
LDA	71	29
t-BuOK	20	80

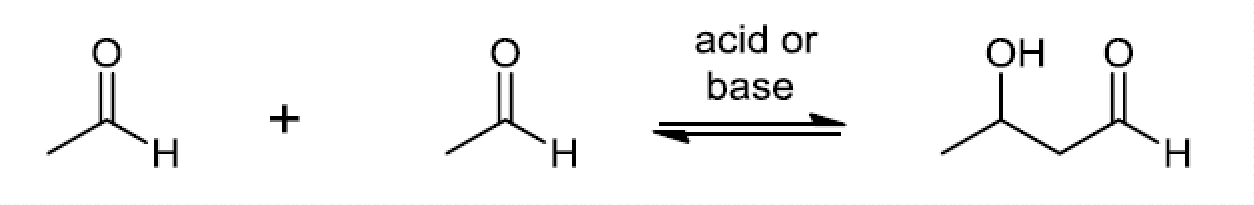
Stability of Carbanion:- A carbanion is a nucleophile, which stability and reactivity determined by several factors: The greater the s-character of the charge-bearing atom, the more stable the anion; The extent of conjugation of the anion. Resonance effects can stabilize the anion.

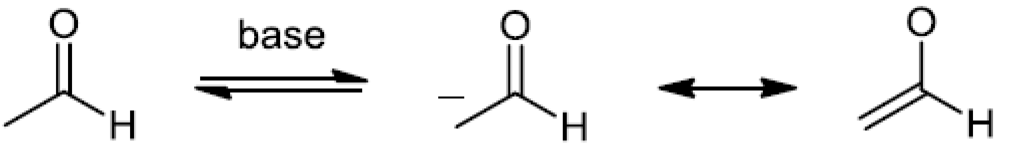
Allylic, benzylic > 1° > 2° > 3°

$sp > sp^2 > sp^3$

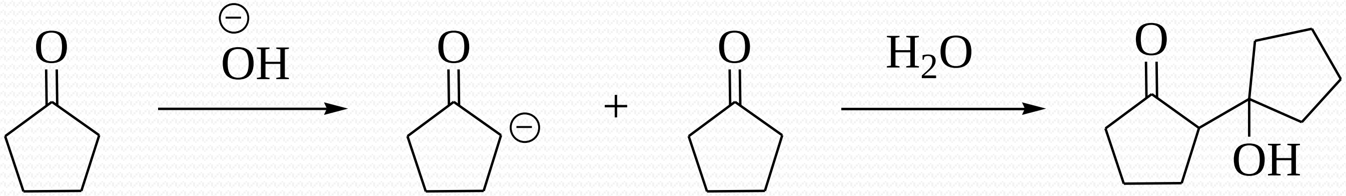
Reactions of Carbanion:-

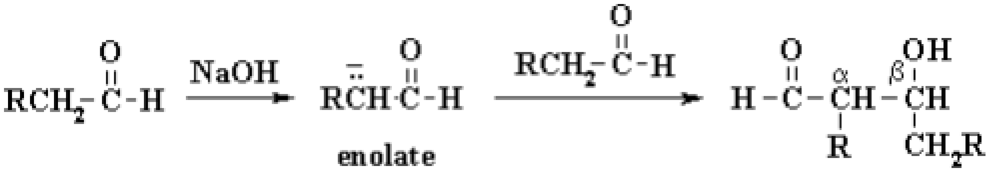
i) Aldol condensation reaction:- Aldehydes and ketones containing α-hydrogen react with base to form enolate which react with another molecule of aldehyde to form product are called aldol condensation reaction.





enolate resonance contributors



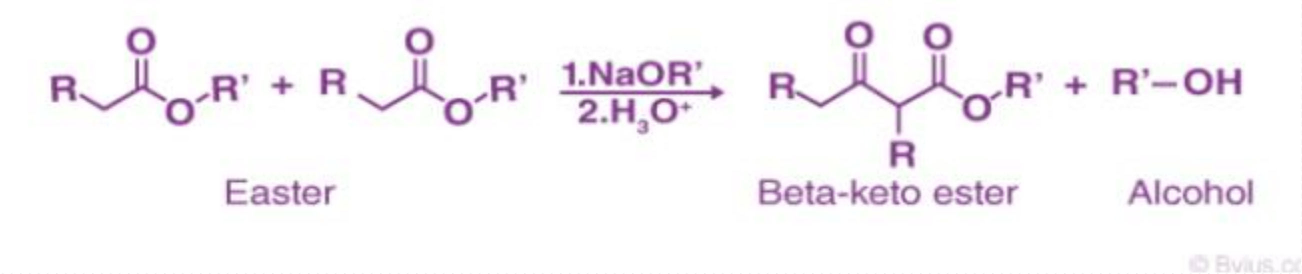


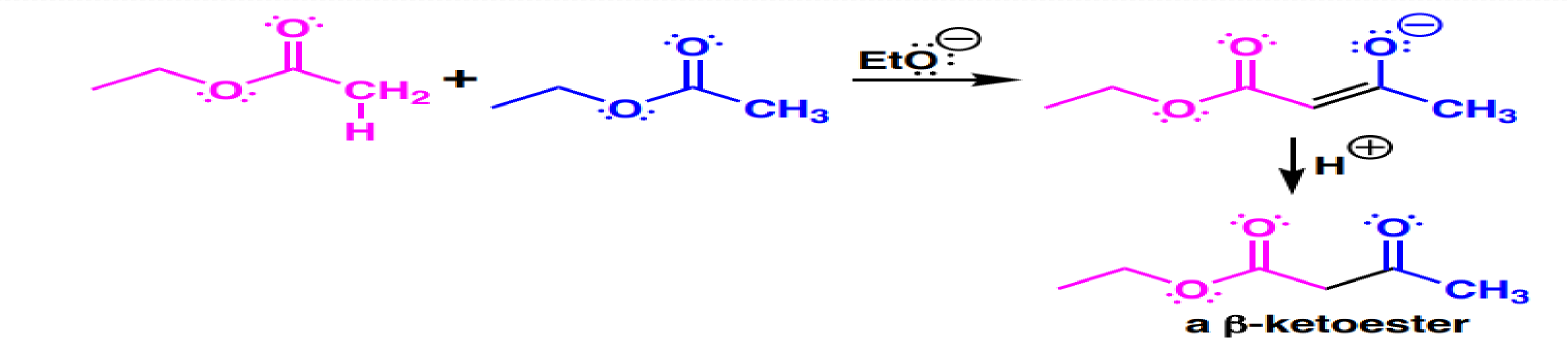
β−hydroxyaldehyde

β-hydroxyketone

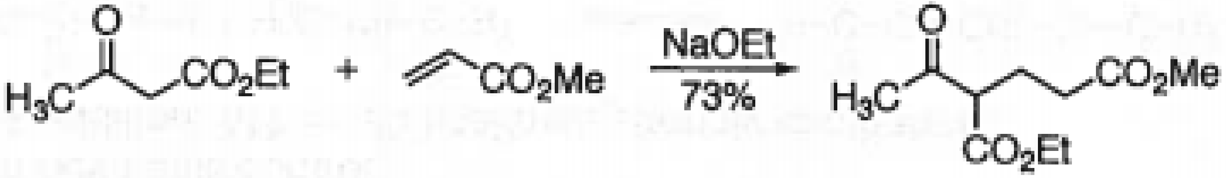
ii) Claisen Condensation:-

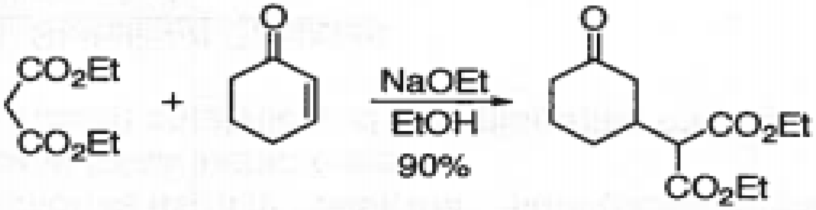
The α-hydrogen of ester is removed by base to give the enolate. The enolate reacts with another molecule of the ester in an addition-elimination reaction resulting product is β-ketoester. The reaction is known as the claise condensation.

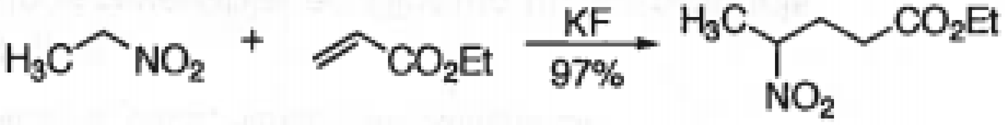




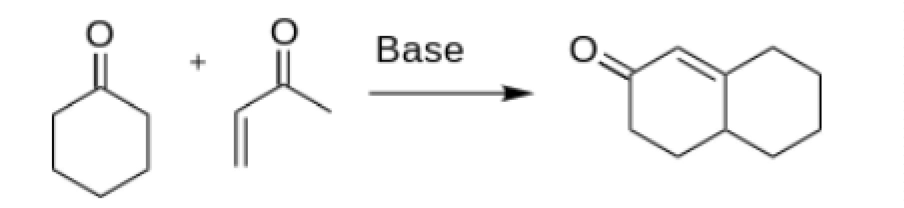
iii) Michael Reaction:- Enolates may also be alkylated with α, β unsaturated carbonyl substrates. The enolates add in the 1,4 fashion to give a product this reaction is known as Michael reaction.

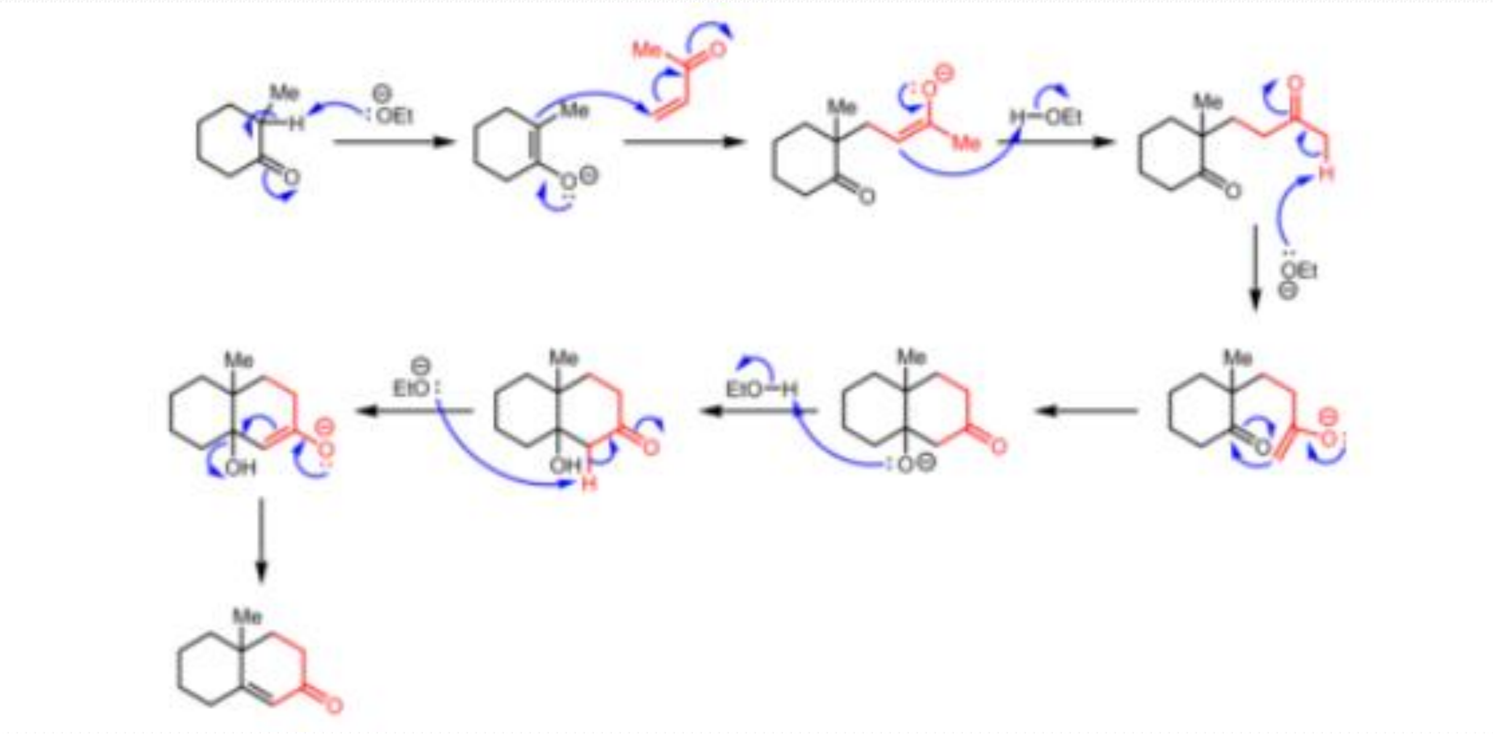


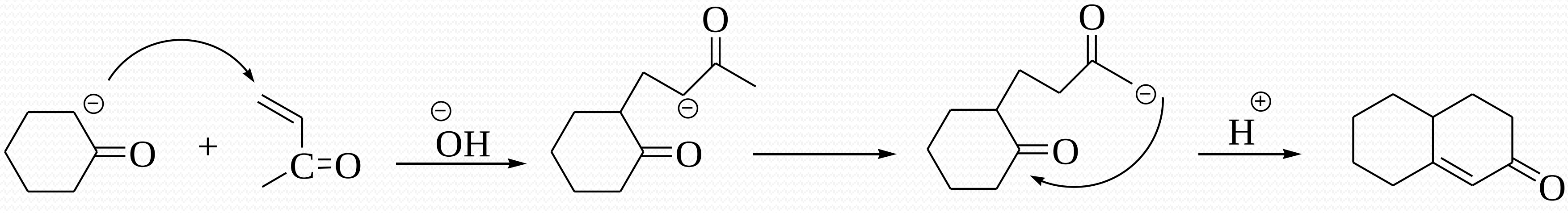




iv) Robinson Ring-forming Reaction:- Robinson annulation is a chemical reaction used in organic chemistry for ring formation. It is unique reaction that produces a new ring containing an α,β-unsaturated ketones. When an enolate derived from a ketone react with methyl vinyl ketone, the enolate add like Michel reaction, then a second enolate in the ketone product is formed that cyclizes in an Aldol condensation to give the final product.

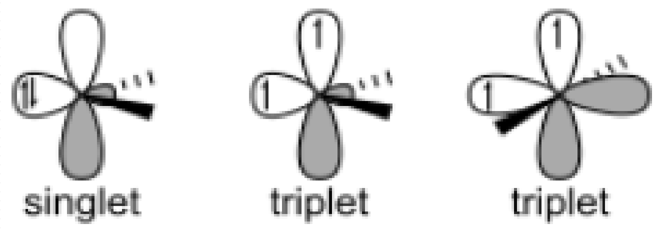



Me
H
⊖ :OEt
Me
O⊖
Me
O
O⊖
Me
H–OEt
O
H
OEt ⊖
Me
O⊖
EtO–H
⊖ EtO:
OH
H


⊖
O
+
C=O
⊖ OH
O
⊖
O
⊖
H ⊕
O

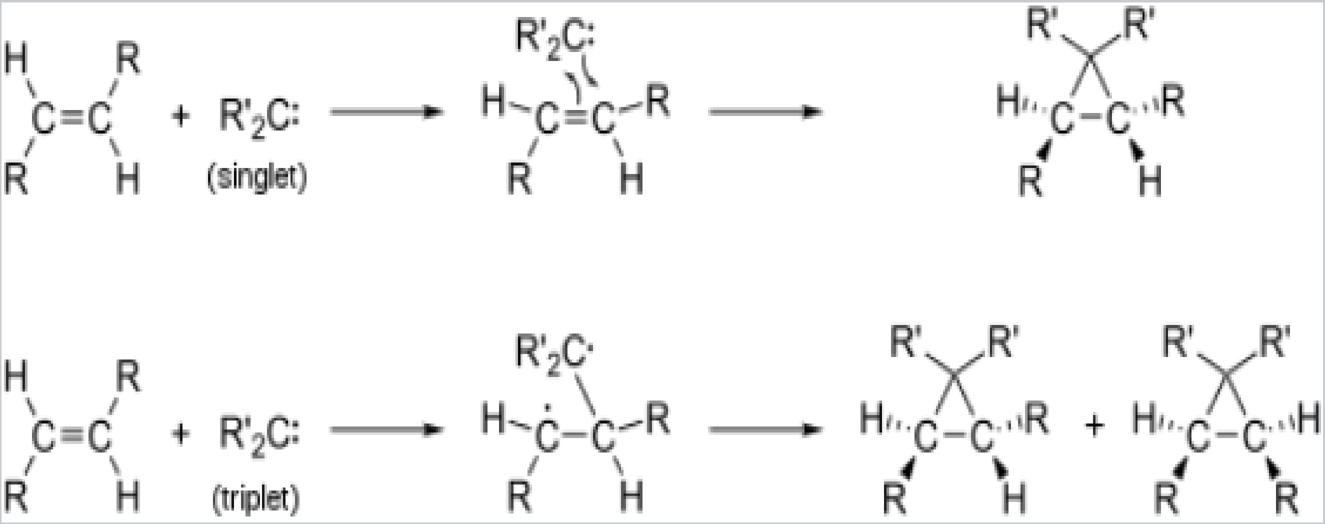
Carbene:- In chemistry a carbene is a molecule containing a neutral carbon atom with a two valence and two unshared valence electrons. The general formula is R-(C:)-R' where R represents substituent or hydrogen atom. The compound H_2C: are called methylene. Well studied carbene is dichlorocarbene Cl_2C:

Structure and Bonding:-



The two class of carbenes are singlet and triplet carbenes. Singlet carbene are spin paired. Triplet carbenes have two unpaired electrons.

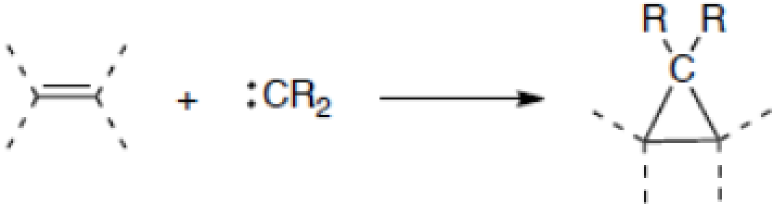
Reactivity:- Singlet and triplet carbenes exhibit divergent reactivity. Singlet carbenes generally participate in cheletropic reactions as either electrophilic or nucleophilic. Singlet carbenes with unfilled p-orbital should be electrophilic. Triplet carbenes can be considered to be diradicals, and participate in stepwise radical additions. Triplet carbenes have to go through an intermediate with two unpaired electrons whereas singlet carbene can react in a single concerted step. Due to these two modes of reactivity, reactions of singlet methylene are stereospecific whereas those of triplet methylene are stereoselective.

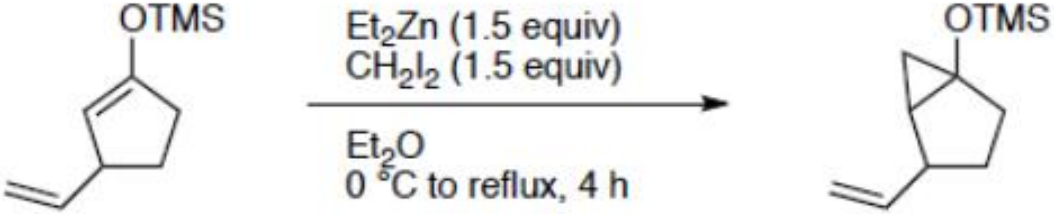


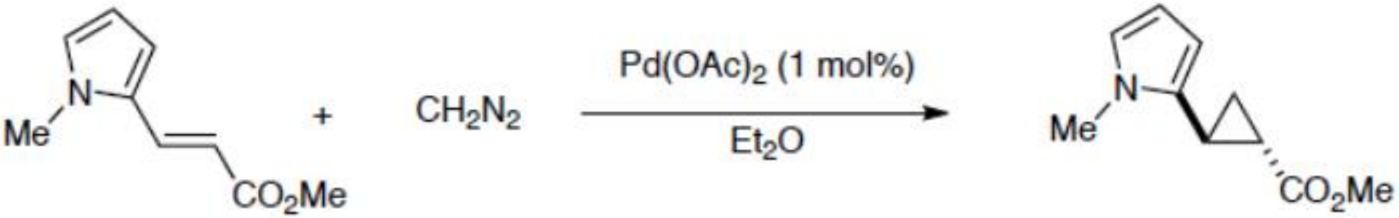
Reactions of Carbene:-

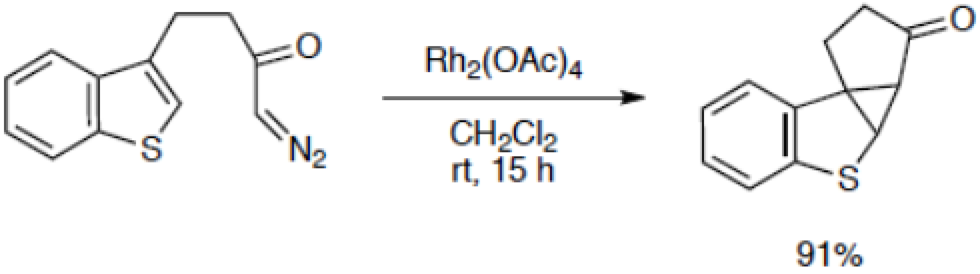
i) Cyclopropanation:- Carbene add to double bonds to form cyclopropanes. A concerted mechanism is available for singlet carbenes.

e.g.

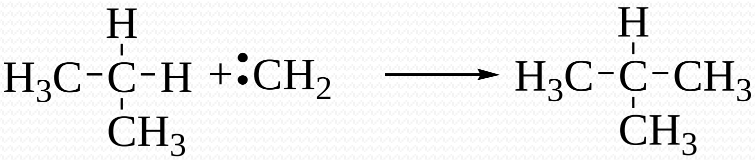

+
:CR$_2$
R R
C


OTMS
Et$_2$Zn (1.5 equiv)
CH$_2$I$_2$ (1.5 equiv)
Et$_2$O
0 °C to reflux, 4 h
OTMS


N
Me
CO$_2$Me
+
CH$_2$N$_2$
Pd(OAc)$_2$ (1 mol%)
Et$_2$O
N
Me
CO$_2$Me

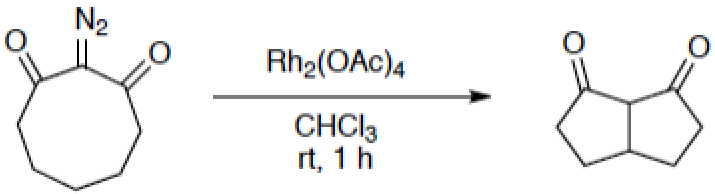

S
O
N$_2$
Rh$_2$(OAc)$_4$
CH$_2$Cl$_2$
rt, 15 h
O
S
91%

ii) C-H insertion:-

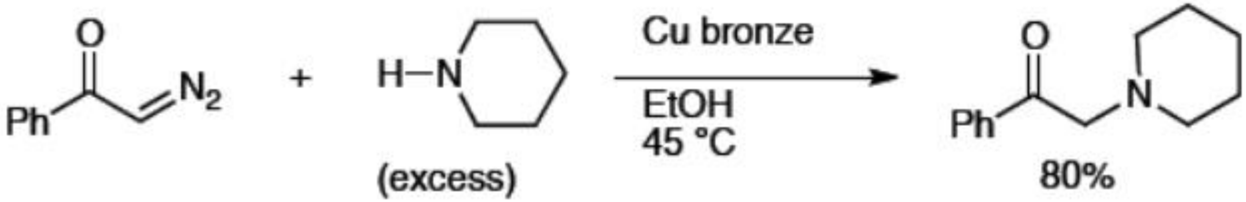


$$H_3C-\underset{CH_3}{\overset{H}{C}}-H + :CH_2 \longrightarrow H_3C-\underset{CH_3}{\overset{H}{C}}-CH_3$$

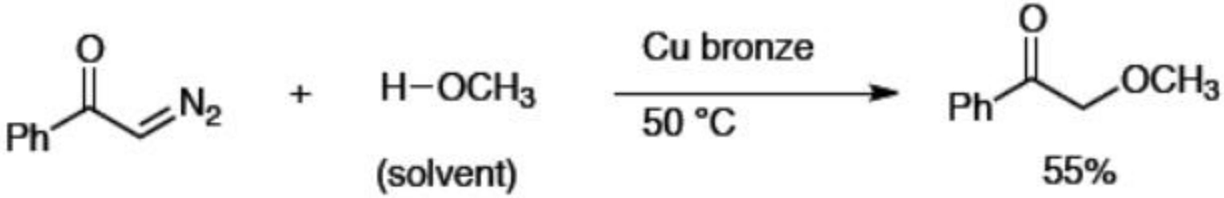
Carbene insertion



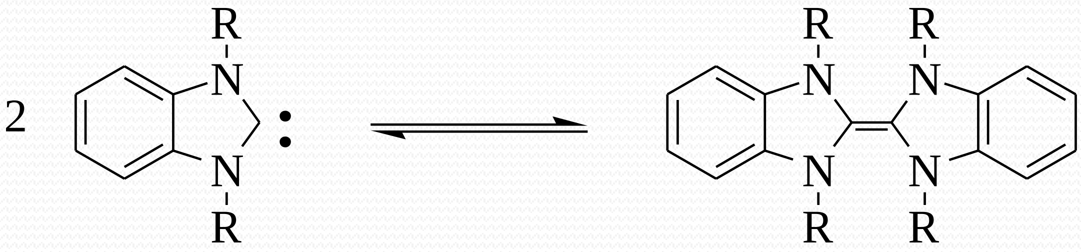
N–H insertion

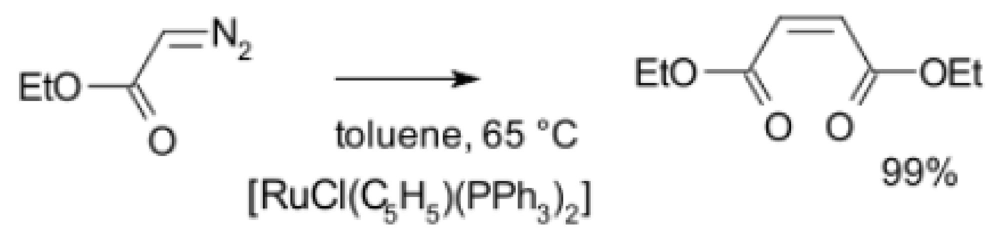


O–H insertion

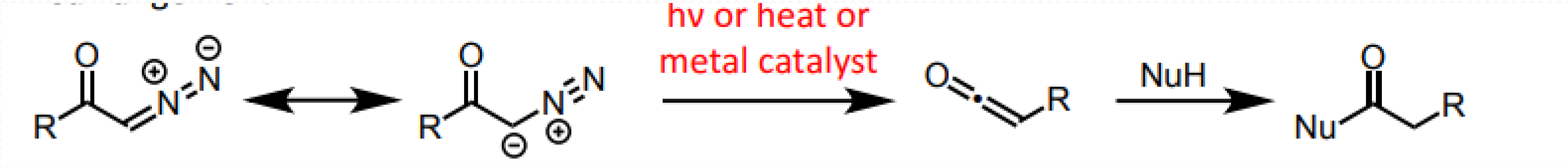


iii) Carbene dimerization:- Carbenes and carbenoid precursors can undergo dimerization reactions to form alkenes.

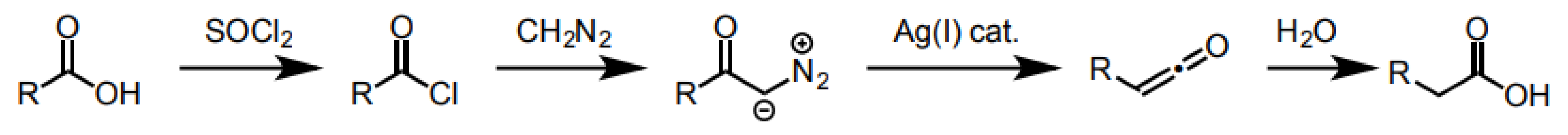




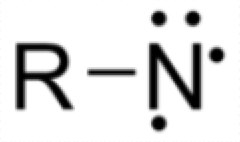
iv) Wolff Rearrangement:- Wolff rearrangement is also proceed via formation of carbene as intermediate.



v) Arndt-Eistert homologation:- In Arndt-Eistert homologation carboxylic acid first converted to acid chloride followed by Wolff rearrangement to give higher carboxylic acid homologue.

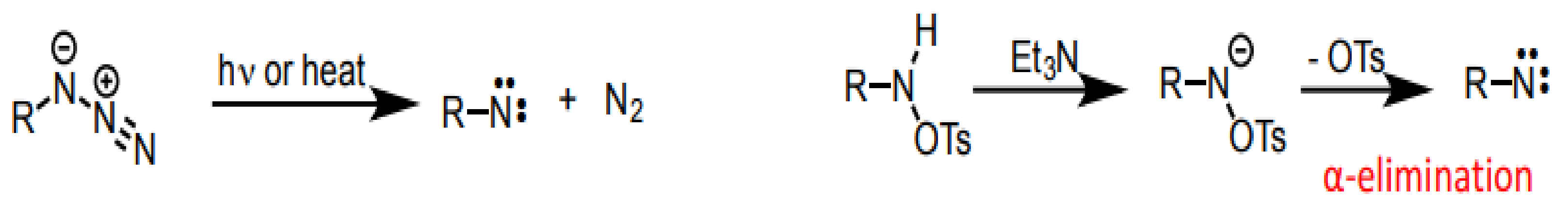


Nitrene:- In chemistry a nitrene or imine (R-N) is the nitrogen analogue of a carbene. The nitrogen atom is uncharged and univalent, so it has only 6 electrons in its valence level two covalent bonded and four non-bonded electrons. It is therefore considered an electrophile due to the unsatisfied octet. A nitrene is reactive intermediate and is involved in many chemical reactions. The simple nitrene, NH is called imidogen.

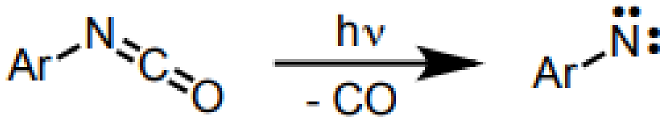


Nitrenes are so reactive, they are not isolated, they are formed as reactive intermediates during a reaction.

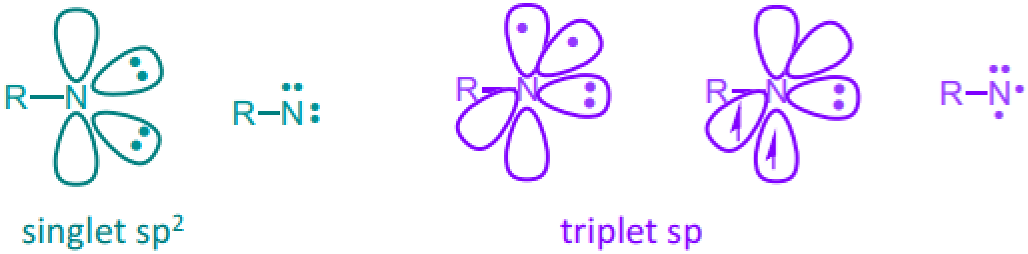
Generation of Nitrene:- Most common method of generation of nitrene is thermolysis or photolysis of azides.



Generation from isocyanate

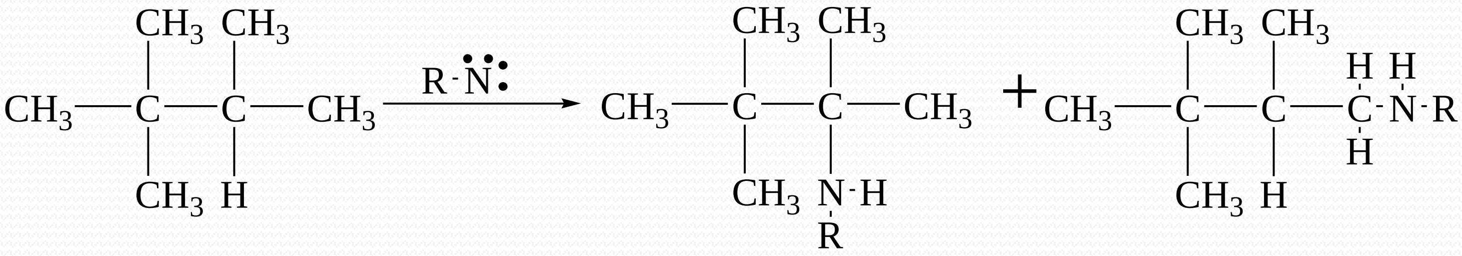


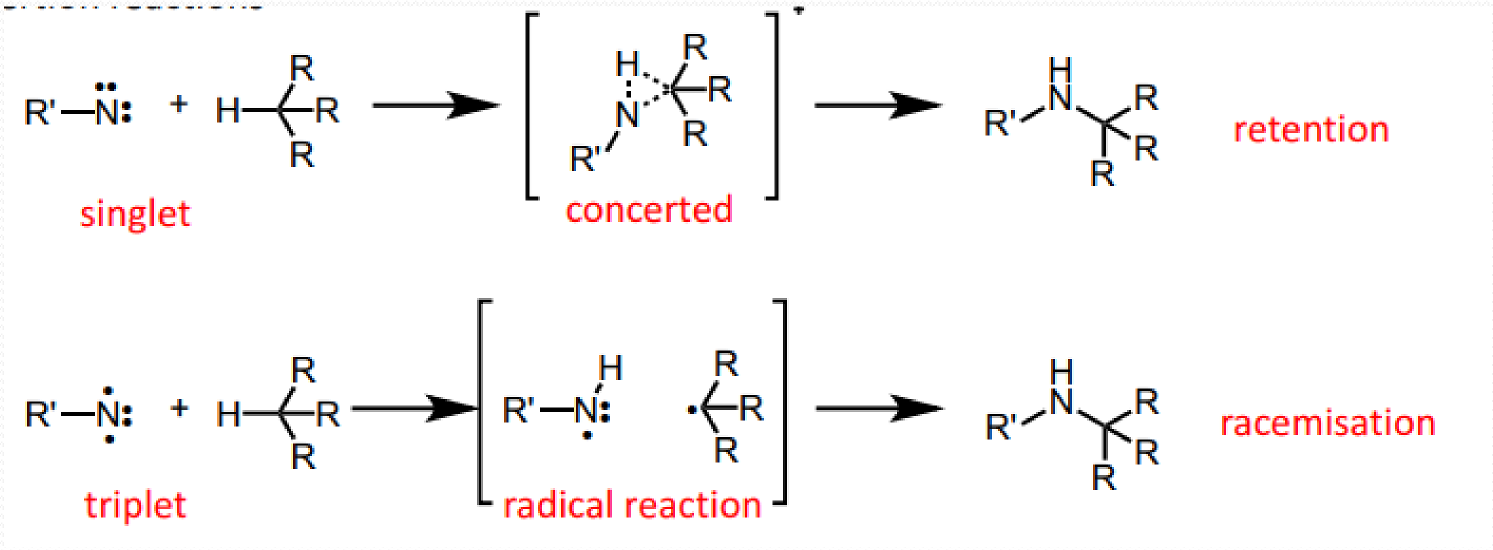
Types of nitrenes:- Nitrenes are of two types singlet nitrene and triplet nitrene.



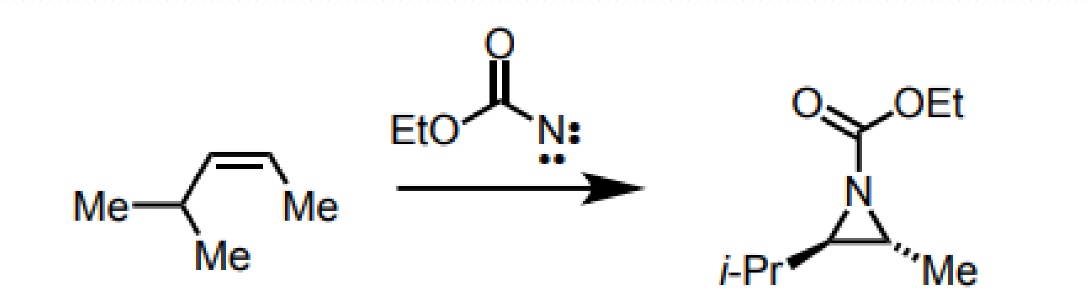
Reactions of Nitrene:-

i) Insertion reaction:-

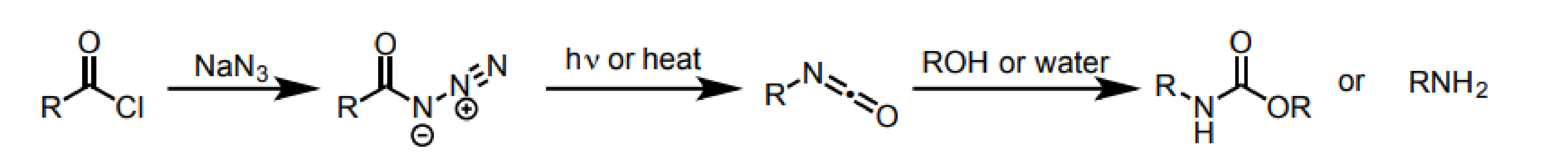




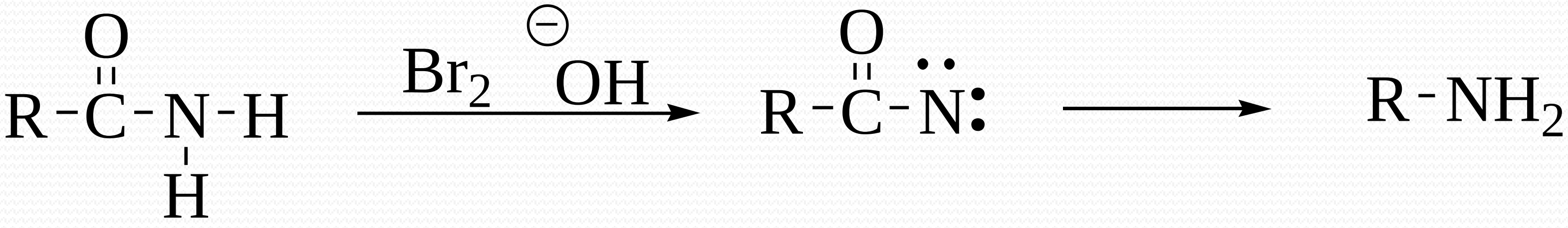
ii) Addition to π-system:- As with carbene, addition of nitrenes to alkenes is stereospecific with singlet nitrenes, and non-stereospecific with triplet nitrenes.



iii) Curtius rearrangement or acyl azides:-

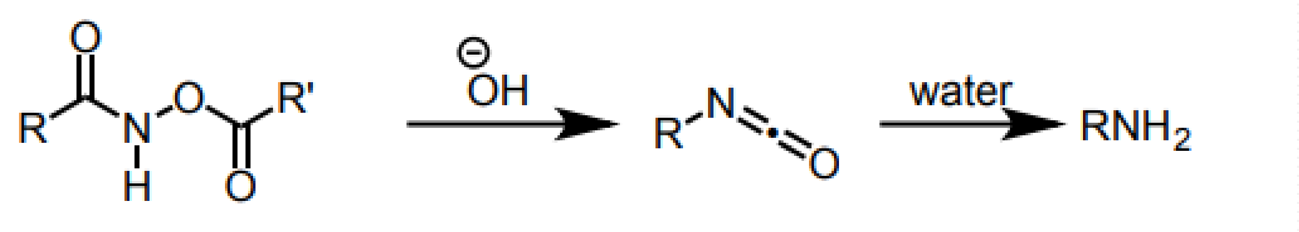


iv) Hoffman Rearrangement:- In Hoffman rearrangement there is formation of nitrene as a intermediate.

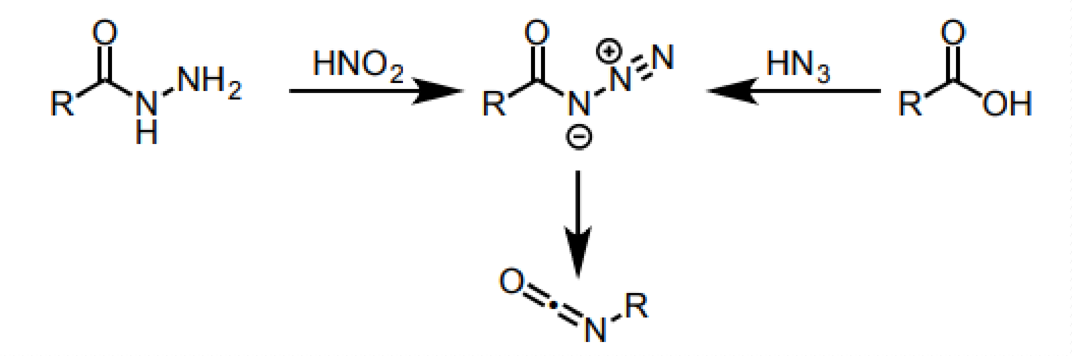


$$R-\overset{O}{\overset{\|}{C}}-\underset{H}{\underset{|}{N}}-H \xrightarrow{Br_2\quad \overset{\ominus}{O}H} R-\overset{O}{\overset{\|}{C}}-\ddot{N}: \longrightarrow R-NH_2$$

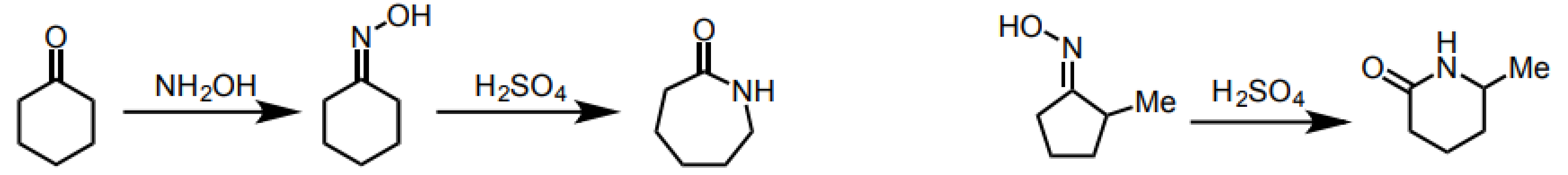
v) Lossen Rearrangement:-



vi) Schmidt Rearrangement:-



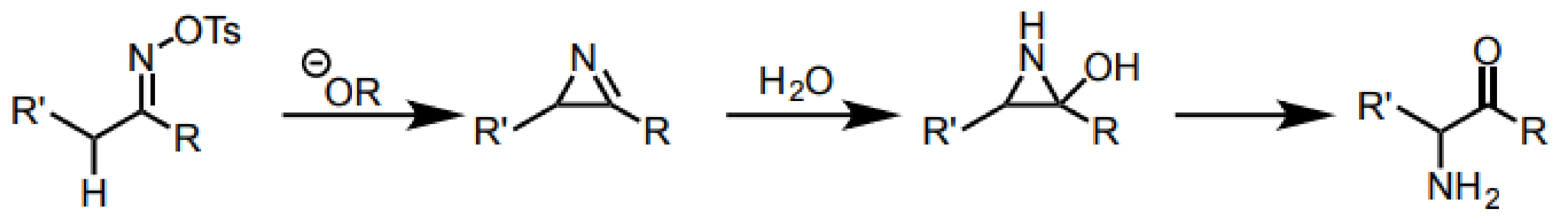
vii) Beckmann Rearrangement:-



carpolactam

most stable oxime with bulky groups trans

viii) Neber Rearrangement:-



Free Radicals:- A free radical is an atom, molecule or ion that has an unpaired valence electron. These unpaired electron make radical highly chemically reactive. Many radicals spontaneously dimerize. Most organic radicals have short life time.

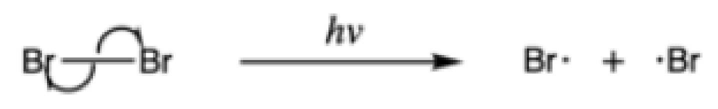
$HO^{\bullet}$ Hydroxyl radical

Radicals may be generated in number of ways, these methods involve redox reactions, ionizing reactions, heat, electrical discharge and electrolysis.

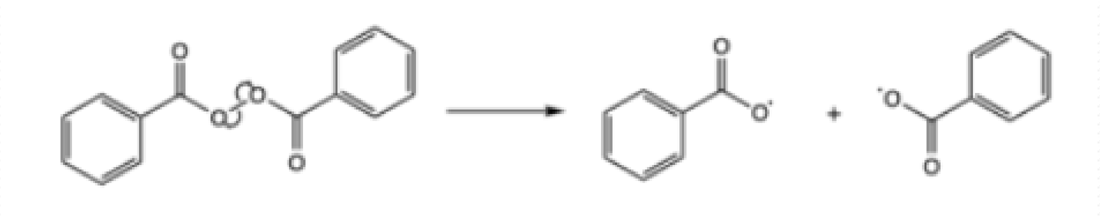
Radicals are important in combustion, atmospheric chemistry, polymerization, plasma chemistry, biochemistry and many other chemical processes.

Radical formation from spin-paired molecules:-

Homolysis:- Homolysis make two new radicals from spin paired molecule by breaking a covalent bond, leaving each of the fragments with one of the electrons in the bond. Breaking of bond requires energy therefore homolysis occur under the addition of heat or energy.

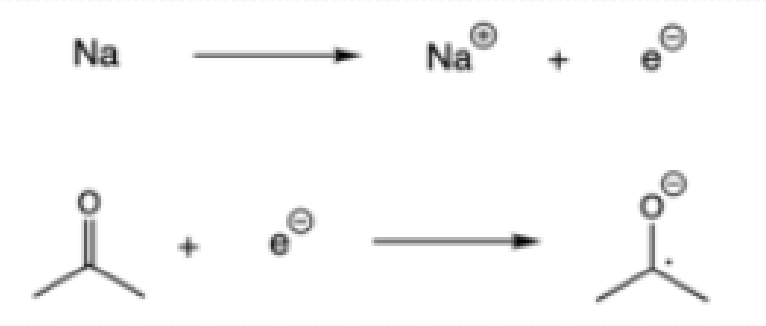


Homolysis of a bromine molecule producing two bromine radicals



Homolysis of dibenzoyl peroxide producing two benzoyloxy radicals

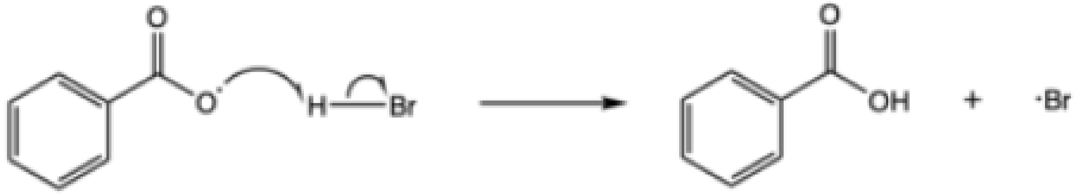
Reduction:- Radicals can also form when a single electron is added to spin-paired molecule, resulting in an electron transfer. This reaction usually takes place with an alkali metal, metal donating an electron to another spin paired molecule.



Reduction of a ketone to form a ketyl radical

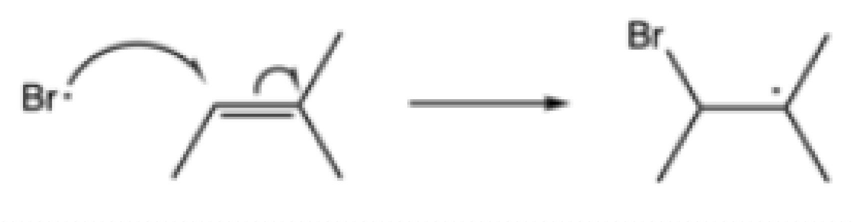
Radical formation from other radicals:-

Abstraction:- Hydrogen abstraction describes when a hydrogen atom is removed from a hydrogen donor molecule with its one electron. Abstraction produces a new radical and a new spin-paired molecule. This is different from homolysis, which results in two radicals from a single spin-paired molecule and doesn’t include a radical as its reactant.



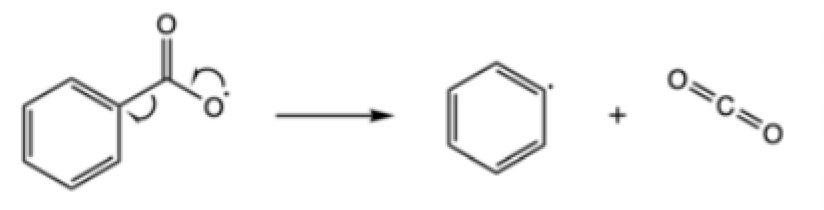
Radical abstraction between a benzoyloxy radical and a hydrogen bromide molecule, resulting in the production of a benzoic acid molecule and a bromine radical.

Addition:- When radical is added to a spin-paired molecule to form a new radical. The addition of bromine radical to an alkene. Radical addition follows the Anti-Markovnikov rule, where the substituent is added to the less substituted carbon atom.



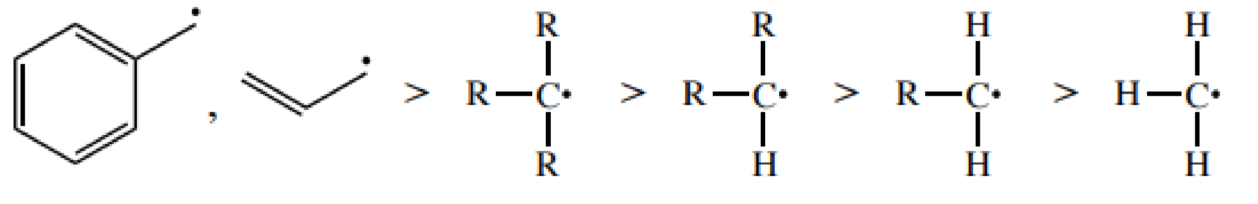
Elimination:-

Radical elimination can be viewed as the reverse of radical addition. In radical elimination, an unstable radical compound breaks down into a spin-paired molecule and a new radical compound. Where a benzoyloxy radical breaks down into phenyl radical and a carbon dioxide molecule.

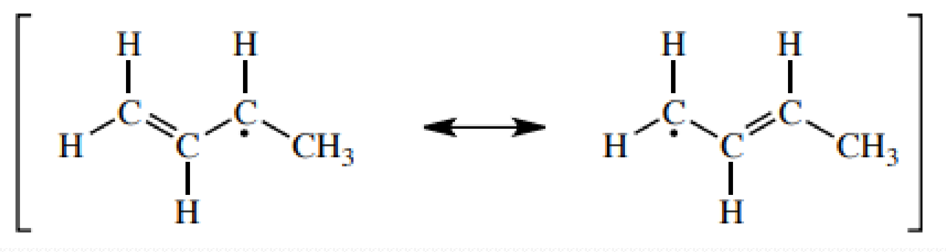


Stability of free radicals:-

Free radicals do not have formal charge but are unstable because of an incomplete octet. Groups that donate electrons towards the free radicals will help to stabilize it. Free radical and carbocations are both electron deficient and they follow a similar order of stability.



Like carbocations, radicals can be stabilized by resonance.



Factor affecting stability of free radicals:-

Four factor which affect the stability of free radical

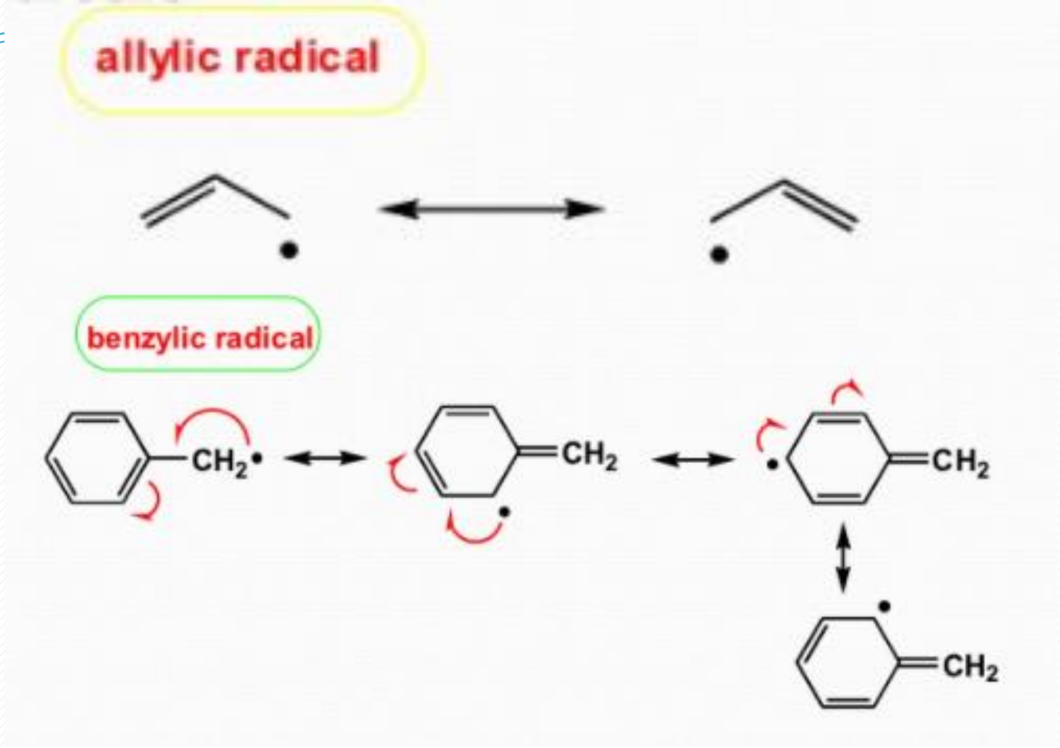
i) Conjugation

ii) Hybridisation

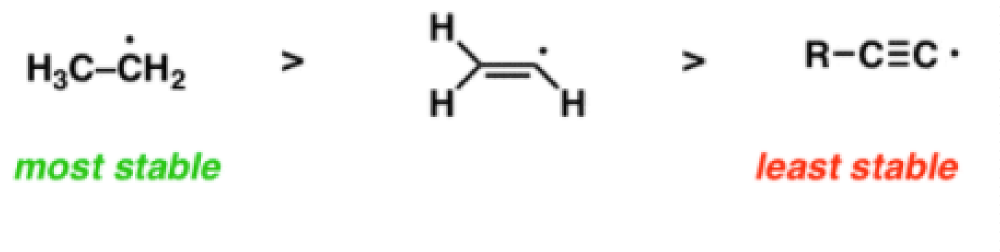
iii) Hyperconjugation

iv) Captodative effect

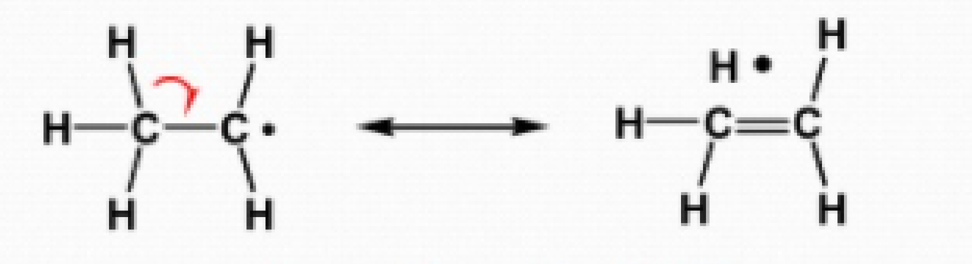
i) Conjugation:- It is a system of connected p-orbitals with delocalized electrons in compounds with alternating single and multiple bonds, which in general may lower the overall energy of the molecule and increase stability.

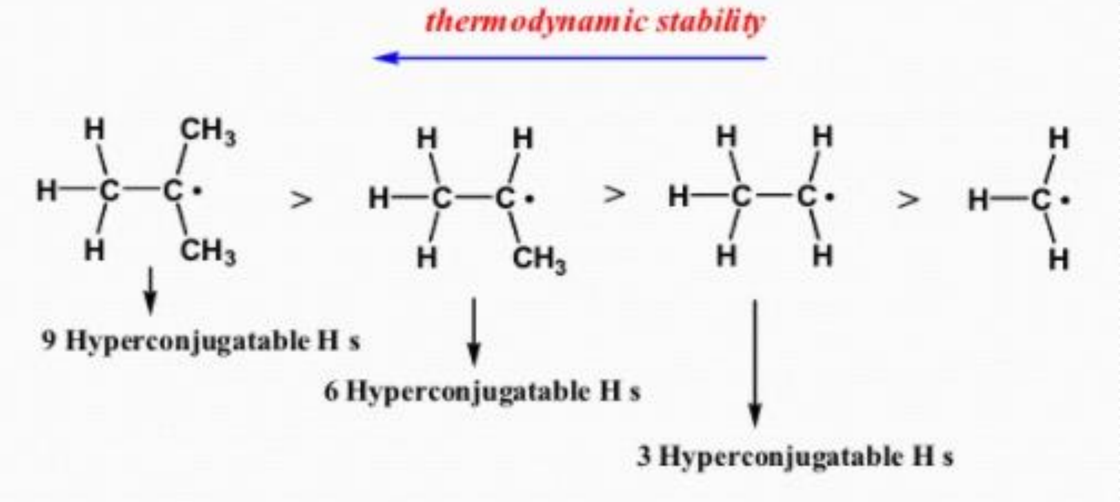


ii) Hybridisation:- The stability of free radicals decreases as the orbital is held closer to the nucleus.



iii) Hyperconjugation:- Hyperconjugation is the interaction of the electrons in a sigma bond (usually C-H or C-C) with an adjacent empty or partially filled non-bonding p-orbital or antibonding π orbital or filled π orbital, to give an extended molecular orbital that increases the stability of the system. Unstable charge on molecule are dispersed over the structure or due to presence of hydrogen attached to stabilize the molecule.

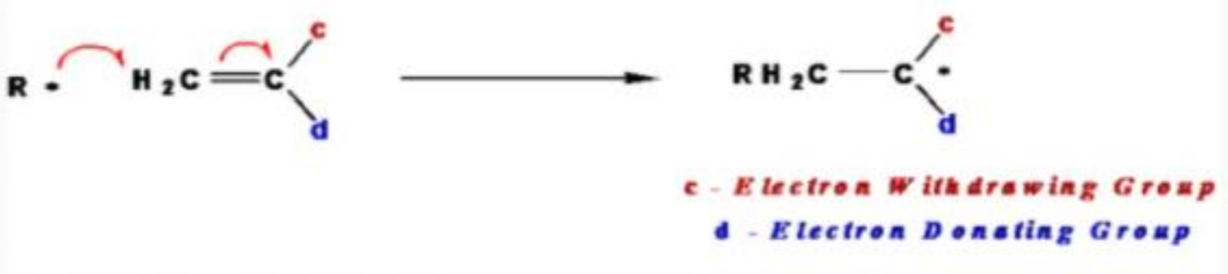




iv) Captodative effect:- The captodative effect is the effect on the stability of a carbon centered radical that is determined by the combined action of a captor (electron-withdrawing) and a dative (electron-donating) substituent, both attached to the radical centre.

When electron donating group and electron with drawing group are near the radical center, the stability of radical center increases.

The substituents can kinetically stabilize radical centers by preventing molecules and other radical centers from reacting with the center.

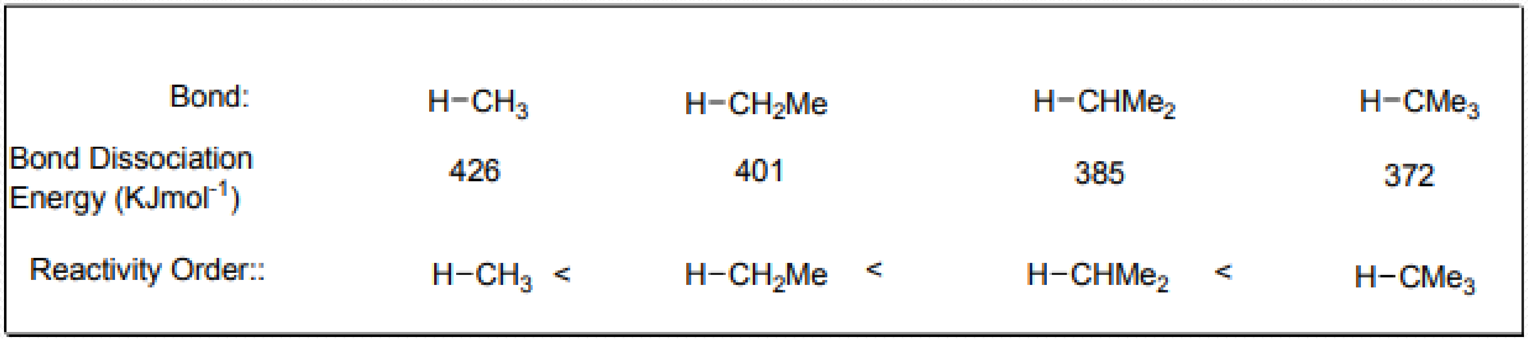


Reactions of free radicals:- There are four principal propagation reactions.

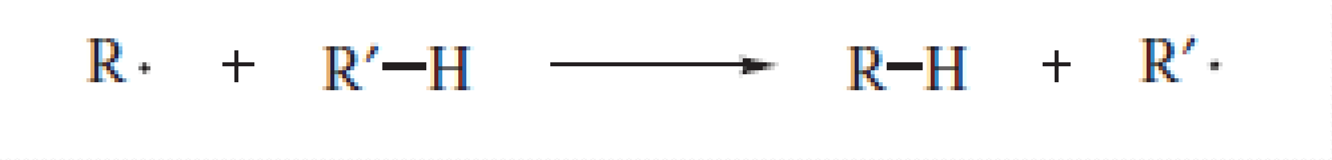
i) Abstraction of another atom or group, usually a hydrogen atom.

Free radicals proceed reactions with saturated organic molecules by abstracting an atom from carbon.

The selectivity of the free radicals towards C-H bonds of different types is determined by bond dissociation energy and polar effects. The rate of the abstraction process increases as bond dissociation energy decreases.

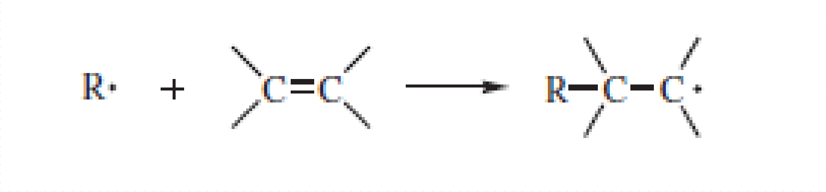


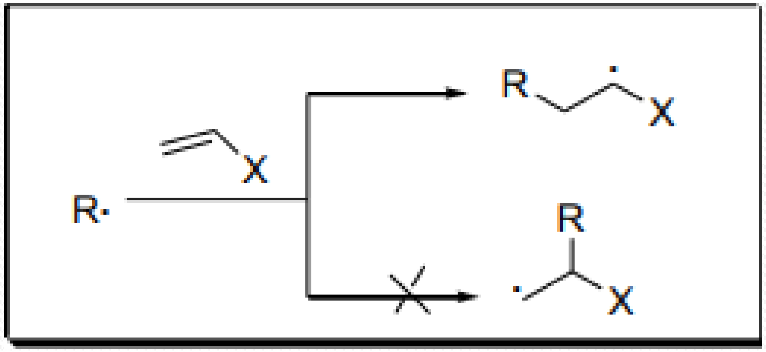
Bond:	$H-CH_3$	$H-CH_2Me$	$H-CHMe_2$	$H-CMe_3$
Bond Dissociation Energy ($KJmol^{-1}$)	426	401	385	372
Reactivity Order::	$H-CH_3$ <	$H-CH_2Me$ <	$H-CHMe_2$ <	$H-CMe_3$



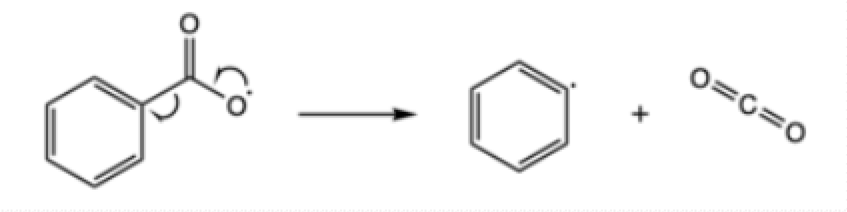
$$R\cdot + R'{-}H \longrightarrow R{-}H + R'\cdot$$

ii) addition to multiple bond:- Free radicals undergo addition to carbon-carbon double bonds. The reaction is generally selective. For example, addition to CH_2=CHX takes place exclusively at the methyl group, irrespective of the nature of X.

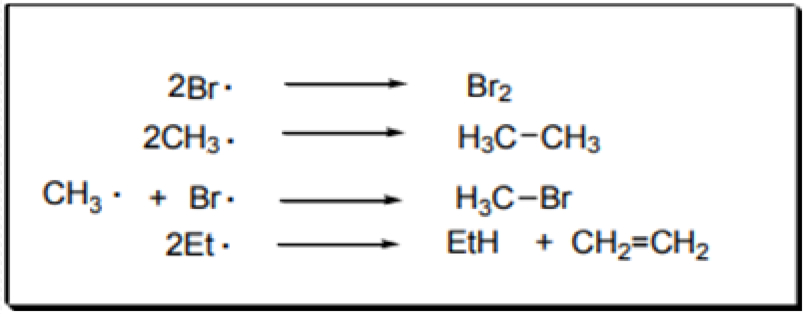




iii) Decomposition:- This can be illustrated by the decomposition of the benzoyloxy radical.



iv) Combination and Disproportionation:- Two free radicals can combine by dimerization or disproportionation.



$2Br\cdot \longrightarrow Br_2$

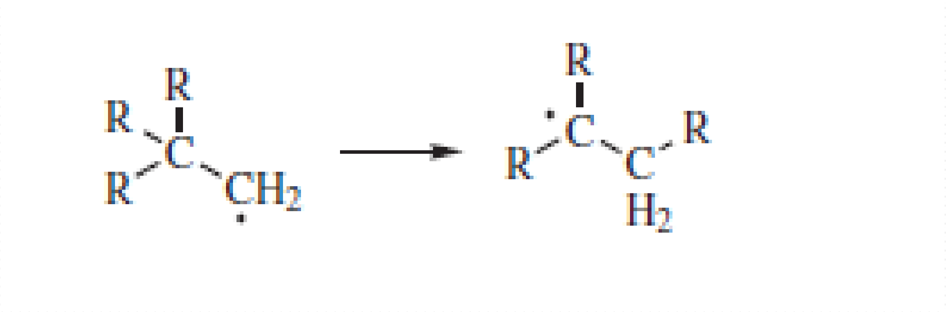
$2CH_3\cdot \longrightarrow H_3C-CH_3$

$CH_3\cdot + Br\cdot \longrightarrow H_3C-Br$

$2Et\cdot \longrightarrow EtH + CH_2{=}CH_2$

These reactions are generally fast, some having negligible activation energy.

v) Rearrangement:-



Neighbouring Group Participation:-

Neighbouring group participation (NGP) also known as anchimeric assistance. In organic chemistry NGP has been defined by IUPAC as the interaction of a reaction centre with lone pair of electrons in an atom or the electrons present in σ bond or π-bond contained within the parent molecule but not conjugated with the reaction centre. NGP increase the rate of reaction.

Characteristics of NGP:-

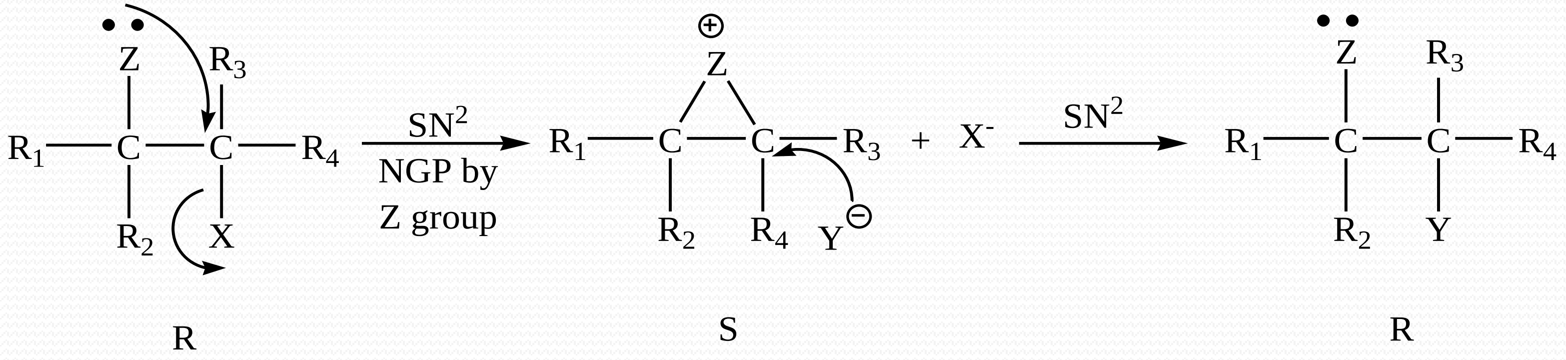
i) In case of certain substrate it is occasionaly found that rate of reaction is greater than expected.

ii) The configuration at chiral carbon is retention not inverted or racemic.

iii) In this cases there is usually a group with an unshared pair of electron on adjacent carbon or β-carbon.

The mechanism operating in such cases is called neighbouring group mechanism which consist essentially two SN^2 substitution which causing an inversion so the net result is retention of configuration.

General Mechanism:-



The important evidence for the existence of this mechanism was the retention of configuration can occur if the substrate is suitable.

Important Neighbouring group:-

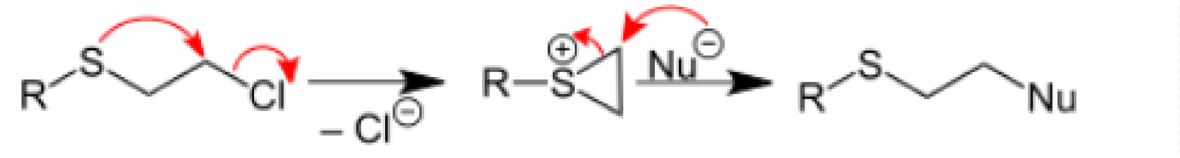
-COO^- (not COOH), -COOR, -COAr, -OCOR, -OR, -OH, O^- ,

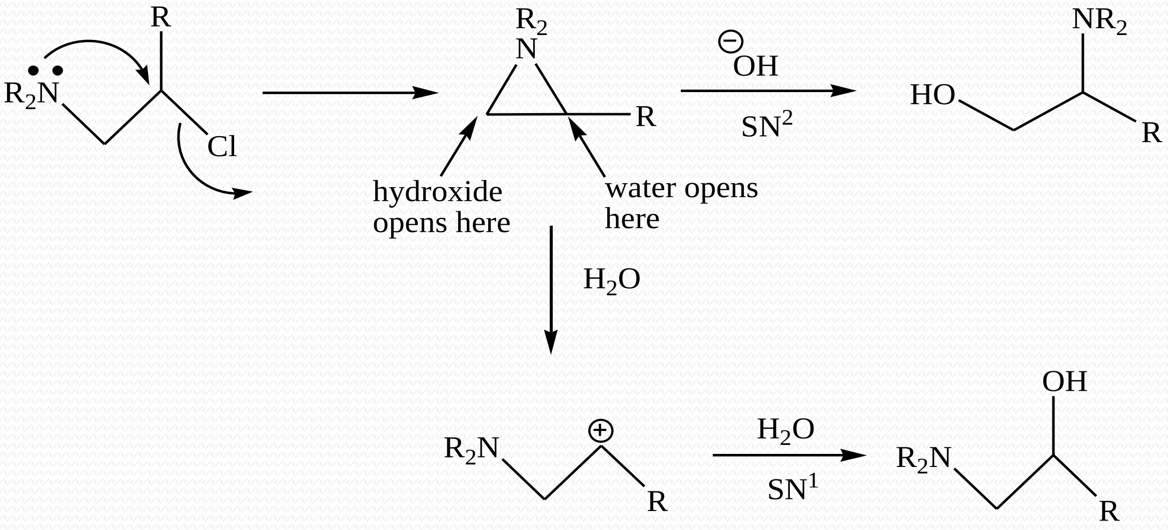
-NH_2, -NHR, -NR_2, -NHCOR, -SH, -SR, S, I, Br, Cl

The decreasing order of the effectiveness of halogens as neighbouring group is I > Br > Cl

i) NGP by heteroatom loan pairs:- A classic example of NGP is the reaction of a sulfur or nitrogen mustard with a nucleophile, the rate of reaction is much higher for the sulfur mustard and a nucleophile than it would be for a primary alkyl chloride without a heteroatom.

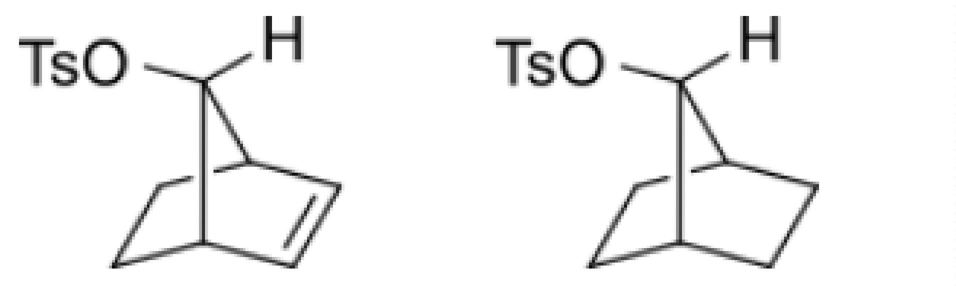
$Ph\text{-}S\text{-}CH_2\text{-}CH_2\text{-}Cl$ reacts with water 600 times faster than $CH_3\text{-}CH_2\text{-}CH_2\text{-}Cl$



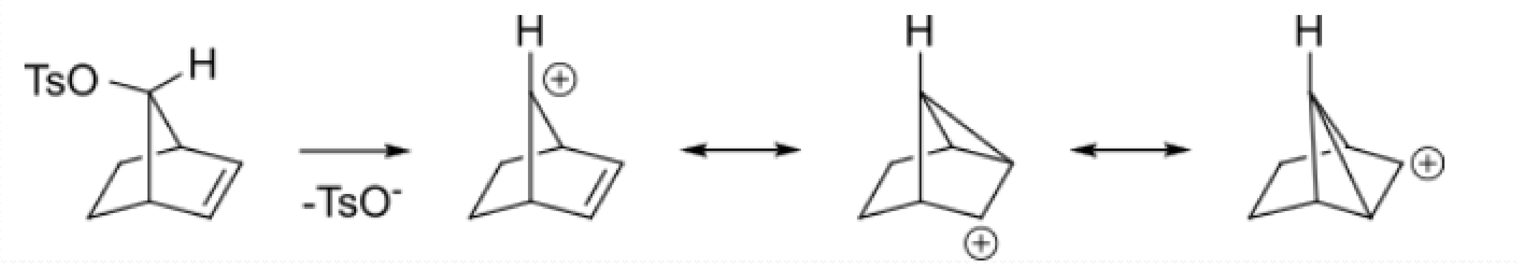


Hydroxide ion is a stronger nucleophile than water. SN^2 reactions are faster at primary carbons and they depend on the nucleophile. Thus a stronger nucleophile (like OH^-) opens the aziridinium ion at the primary carbon i.e at less hindered side. The weak nucleophile water can readily take part in SN^1 reaction, because their rates are independent of nucleophile. Since the primary cation is too unstable to form. Water opens the aziridinium ion at the more hindered site i.e at the secondary carbon which forms stable cation.

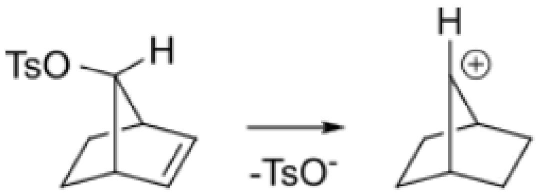
ii) NGP by alkene (C=C):- The π orbitals can stabilize a transition state by helping to delocalize the positive charge of the carbocation. For instance the unsaturated tosylate will react more quickly (10^{11} times faster for aqueous solvolysis) with a nucleophile than the saturates tosylate.



The carbocationic intermediate will be stabilized by resonance where the positive charge is spread over several atoms as shown below.



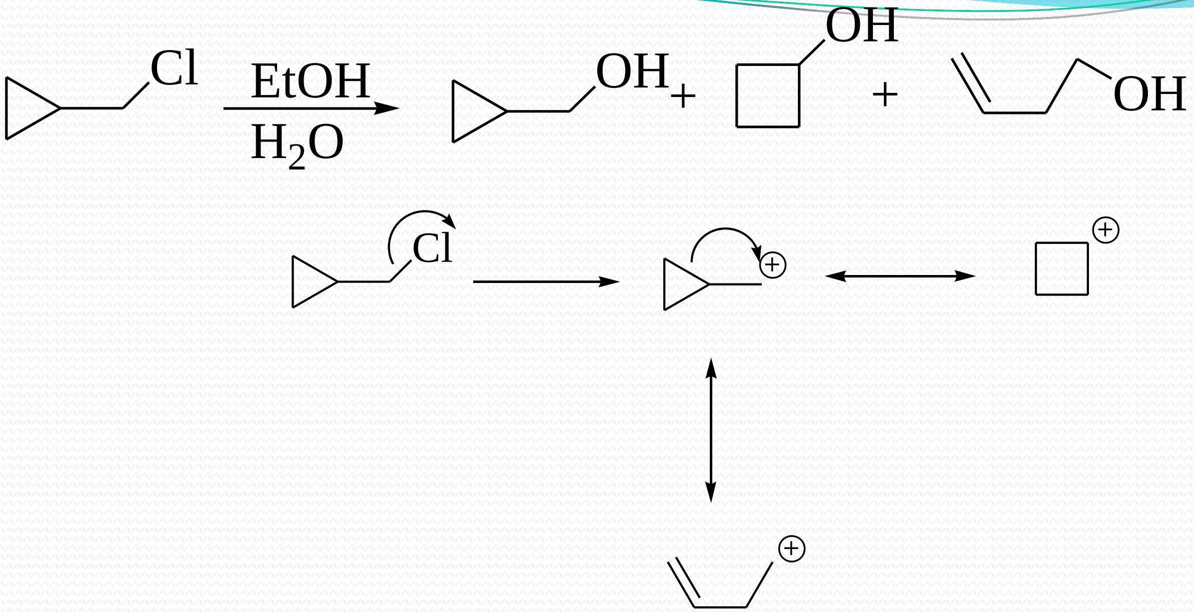
Cation formed is stabilized by delocalization of π-orbitals.



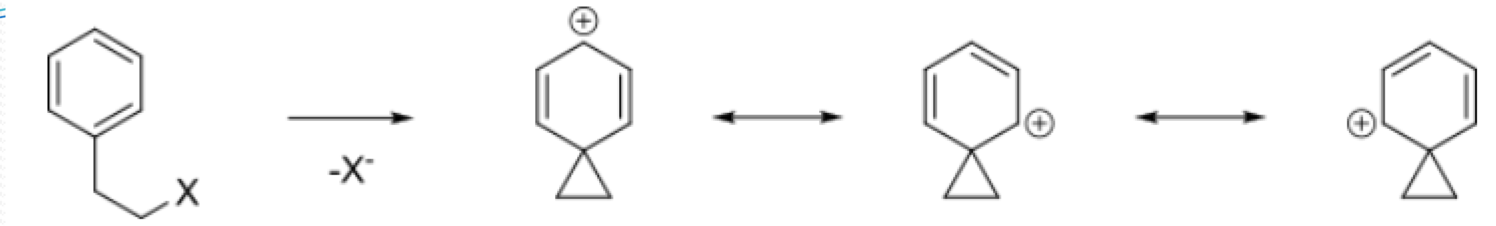
In saturated tosylate carbocation is not stabilized by delocalization of π-orbitals. Due to this reason unsaturated tosylate react 10^{11} times faster than saturated tosylate.

iii) NGP by a cyclopropane, cyclobutane or a homoallyl group:-

Cyclopropylmethyl chloride is reacted wtih ethanol and water then a mixture of 48% cyclopropylmethyl alcohol, 47% cyclobutanol and 5% homoallyl alcohol (but-3-enol) is obtained. This is because the carbocationic intermediate is delocalized onto many different carbons through a reversible ring opening.

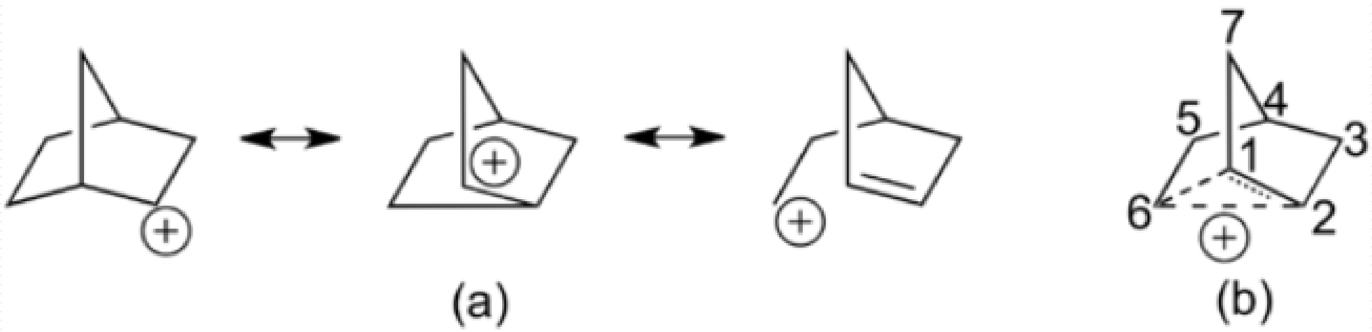


iv) NGP by an aromatic ring:- Aromatic ring in β position can function as neighbouring group. In the case of a benzyl halide the reactivity is higher because the SN^2 transition state enjoys a similar overlap effect to that in the allyl system. An aromatic ring can assist the formation of a carbocationic intermediate called a phenonium ion by delocalizing the positive charge.



v) NGP by aliphatic C-C or C-H Bonds:- Aliphatic C-C or C-H bonds can lead to charge delocalization if these bonds are close and antiperiplanar to the leaving group.

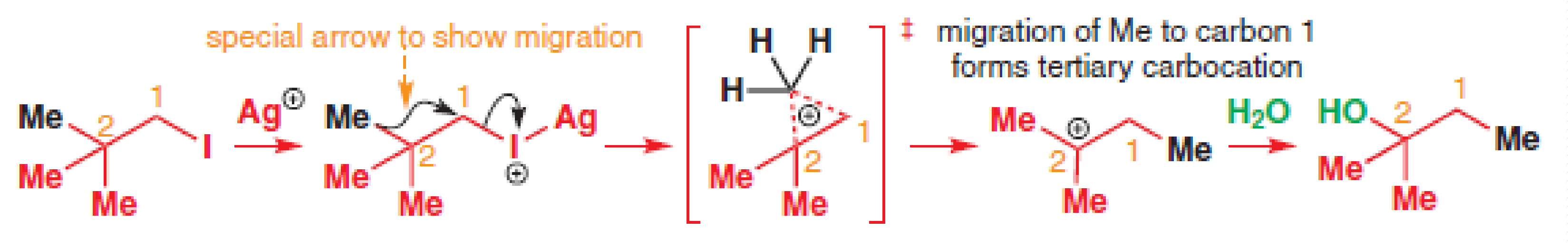
e.g. 2-norbornyl system.



(a)

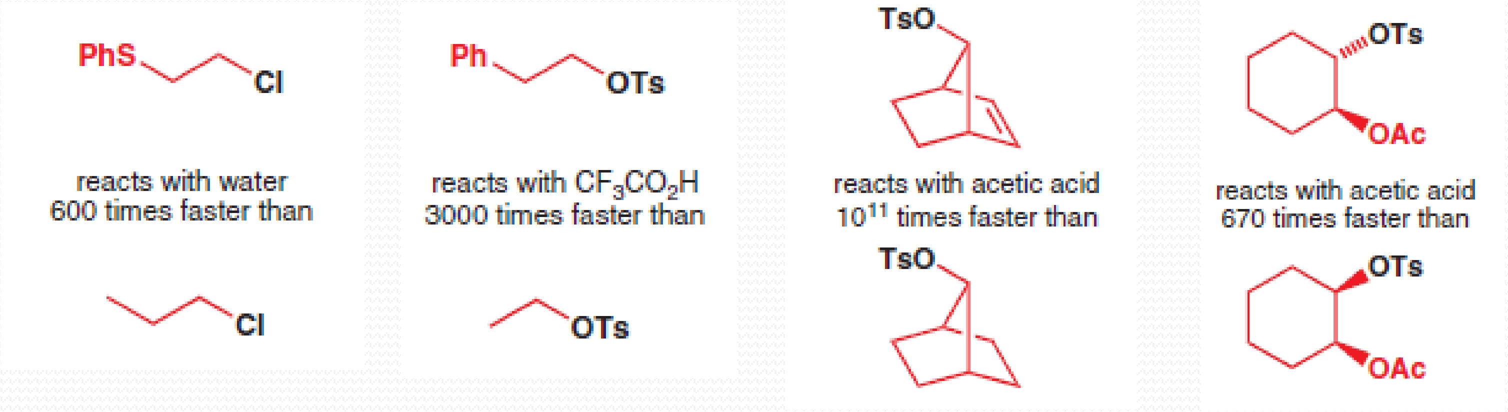
(b)

vi) NGP by methyl group:- Methyl group in the above reaction show NGP because after living I^- primary carbocation is formed which is not stable but after migration of methyl group stable tertiary carbocation is formed.



Neighbouring group can accelerate substitution reactions:-

Compare the rate of following substitution reactions. Substitution of the leaving group (OTs or Cl) by solvent, known as the solvolysis.



Nearby group increases the rate of substitution reaction significantly.

reacts with nucleophiles 10^6 times faster than

reacts with nucleophiles 10^5 times faster than


Thank you!