BP202T. PHARMACEUTICAL ORGANIC CHEMISTRY –I (Theory)

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UNIT-II

UNIT-II 10 hours

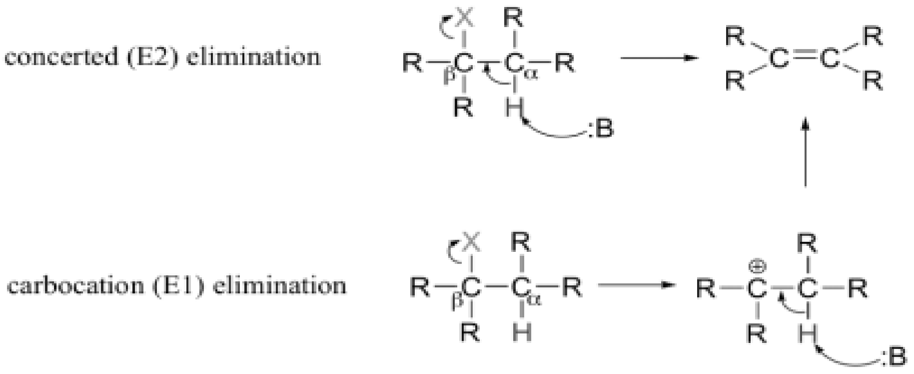
Alkanes*, Alkenes* and Conjugated dienes*

- E1 and E2 reactions – kinetics, order of reactivity of alkyl halides, rearrangement of carbocations, Saytzeffs orientation and evidences. E1 verses E2 reactions, Factors affecting E1 and E2 reactions. Ozonolysis, electrophilic addition reactions of alkenes, Markownikoff's orientation, free radical addition reactions of alkenes, Anti Markownikoff's orientation.
- Stability of conjugated dienes, Diel-Alder, electrophilic addition, free radical addition reactions of conjugated dienes, allylic rearrangement

PART 4

Elimination reaction

- Elimination reaction is a type of organic reaction in which two substituents are removed from a molecule in either a one or two-step mechanism.
- The one-step mechanism is known as the E2 reaction, and the two-step mechanism is known as the E1 reaction.
- In most organic elimination reactions, at least one hydrogen is lost to form the double bond: the unsaturation of the molecule increases.
- It is also possible that a molecule undergoes reductive elimination, by which the valence of an atom in the molecule decreases by two, though this is more common in inorganic chemistry.
- There are three fundamental events in these elimination reactions:
  - ✓ removal of a proton
  - ✓ formation of the CC π bond
  - ✓ breaking of the bond to the leaving group



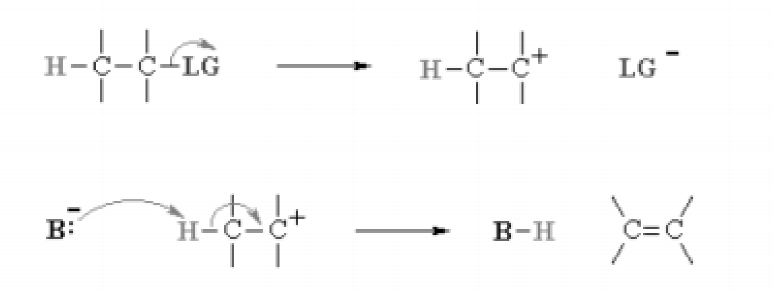
Characteristics of E1 reaction	Characteristics of E2 reaction
Unimolecular reaction	Biomolecular reaction
Two step reaction	Single step reaction
Carbocation intermediate formed	Hydrogen removes from beta carbon.
Reactivity order of RX is 3°>2°>1°	Trans elimination because low energy consumption.

No stereospecific.	Anti periplanar attack
Follow ziatsev rule	Polar aprotic solvent best
Polar protic solvent good because stabilized ionic intermediate.	Phenyl group influence elimination because product alkene further stabilised by resonance.
Rate of reaction increases when concentration of substrate increases.	Reactivity order 3°>2°>1°. No steric effect
Rearrangement may take place.	Strong nucleophile influence elimination
	No intermediate formed.

E1 mechanism

E1 indicates a elimination, unimolecular reaction,

where rate = k [R-LG]. (R-LG = Substrate).

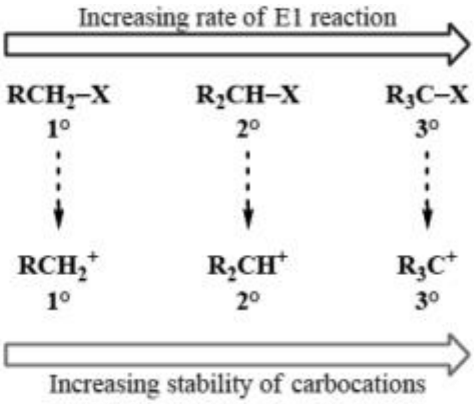


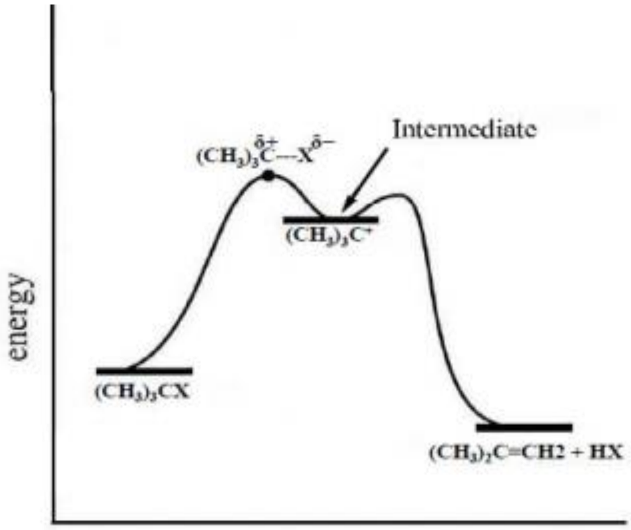
loss of the leaving group, LG, to generate a carbocation intermediate, then

loss of a proton, H^+, from the carbocation to form the π-bond

Reaction influence the reaction pathway:

- E1 mechanistic pathway is most common with:
  - ✓ Good leaving groups
  - ✓ Stable carbocations
  - ✓ Weak bases.
- -E1 Reactions is Non-stereospecific- follows Zaitsev (Saytseff) Rule - Does NOT occur with primary alkyl halides (leaving groups)
  Effect of R-
- Reactivity order: $(CH_3)_3C$- > $(CH_3)_2CH$- > CH_3CH_2- > CH_3-
- In an E1 reaction, the rate determining step is the loss of the leaving group to form the intermediate carbocation.
- The more stable the carbocation is, the easier it is to form, and the faster the E1 reaction.
- -The rate of an E1 reaction increases as the number of R groups on the carbon with the leaving group increases.





Energy Profile for an E_1 Reaction

(ii) Leaving Group (LG)

- The only event in the rate determining step of the E1 is breaking the C-LG bond. Therefore, there is a very strong dependence on the nature of the leaving group, the better the leaving group, the faster the E1 reaction will be.

- In the acid catalysed reactions of alcohols, the -OH is protonated first to give an oxonium ion, providing the much better leaving group, a water molecule.

(iii) Base (B)

- Since the base is not involved in the rate determining step, the nature of the base is unimportant in an E1 reaction.
- Favored by weaker bases such as H2O and ROH.

(iv) Type of Solvent

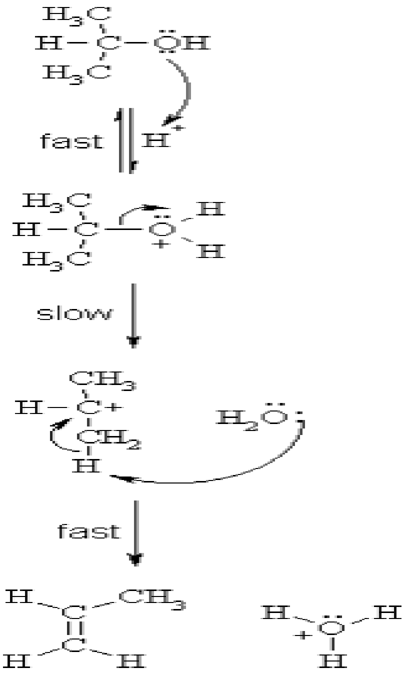
- Favored by polar protic solvents, which can stabilize the ionic intermediates.

E1 Mechanism for Alcohols

Step 1: An acid/base reaction. Protonation of the alcoholic oxygen to make a better leaving group. This step is very fast and reversible. The lone pairs on the oxygen make it a Lewis base.

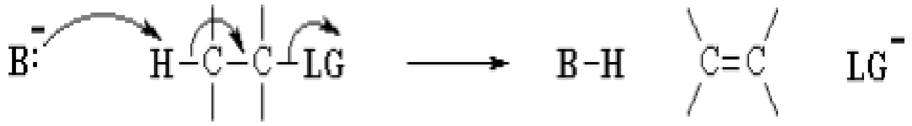
Step 2: Cleavage of the C-O bond allows the loss of the good leaving group, a neutral water molecule, to give a carbocation intermediate. This is the rate determining step (bond breaking is endothermic)

Step 3: An acid/base reaction. Deprotonation by a base (a water molecule) from a C atom adjacent to the carbocation center leads to the creation of the C=C



E1 Mechanism for Alkyl Halides

- E2 indicates an elimination, bimolecular reaction, where rate = k [B][R-LG].
- This implies that the rate determining step involves an interaction between these two species, the base B, and the organic substrate, R-LG



Removal of the proton, H+, by the base, loss of the leaving group, LG, and formation of the π-bond

Reaction influence the reaction pathway:

Kinetics – Second order

Mechanism – Single step

Stereospecific (Anti-periplanar geometry preferred, Syn-periplanar geometry possible)0

Concerted - all bonds form and break at same time.

Bimolecular - rate depends on concentration of both base and substrate - Favoured by strong bases.

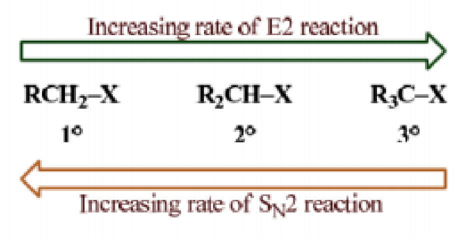
Favored by polar aprotic solvents.

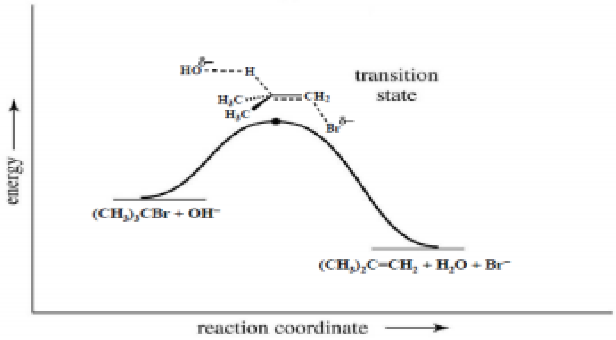
Better leaving group leads to faster reaction rates.

Identity of R group - More substituted halides react faster Rate: R3CX > R2CHX > RCH2X

(i) Effects of R-

- ✓ Reactivity order: (CH3)3C-> (CH3)2CH- > CH3CH2- > CH3- -
- ✓ In an E2 reaction, the reaction transforms 2 sp3 C atoms into sp2 C atoms. This moves the substituents further apart decreasing any steric interactions.
- ✓ So more highly substituted systems undergo E2 eliminations more rapidly. This is the same reactivity trend as seen in E1 reactions.
- ✓ As the number of R groups on the carbon with the leaving group increases, the rate of the E2 reaction increases.





Energy Profile for an E_2 Reaction

(ii) Leaving Group (LG)

The C-LG bond is broken during the rate determining step, so the rate does depend on the nature of the leaving group.

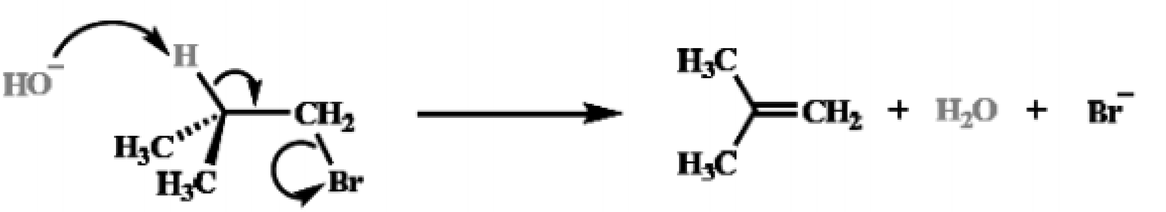
However, if a leaving group is too good, then an E1 reaction may result. - Rate of reaction follows the order Rate of reaction follows the order, **R−I > R−Br > R−Cl > R−F**

(iii) Base (B)

Stronger bases favor the reaction. Since the base is involved in the rate determining step, the nature of the base is very important in an E2 reaction.

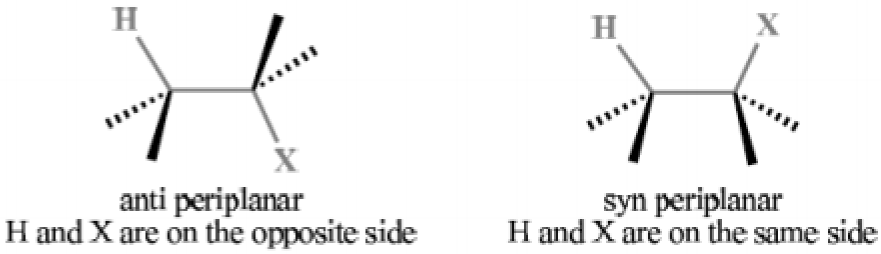
More reactive bases will favor an E2 reaction.

E_2 Mechanism



Stereochemistry of the E2 Reaction

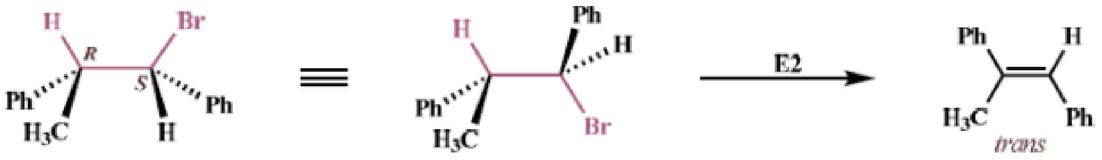
- ✓ The transition state of an E2 reaction consists of four atoms from the substrate (one hydrogen atom, two carbon atoms, and the leaving group, X) aligned in a plane.
- ✓ There are two ways for the C—H and C—X bonds to be coplanar.

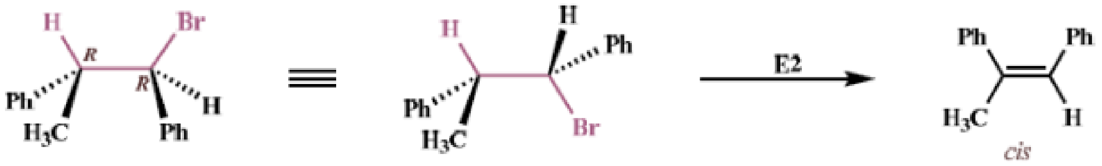


anti periplanar
H and X are on the opposite side

syn periplanar
H and X are on the same side

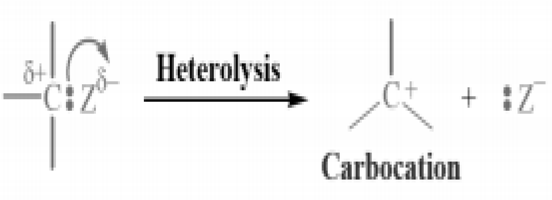
- ✓ **E2 elimination** occurs most often in the anti periplanar geometry. This arrangement allows the molecule to react in the lower energy staggered conformation, and allows the incoming base and leaving group to be further away from each other.





Rearrangement of Carbocations

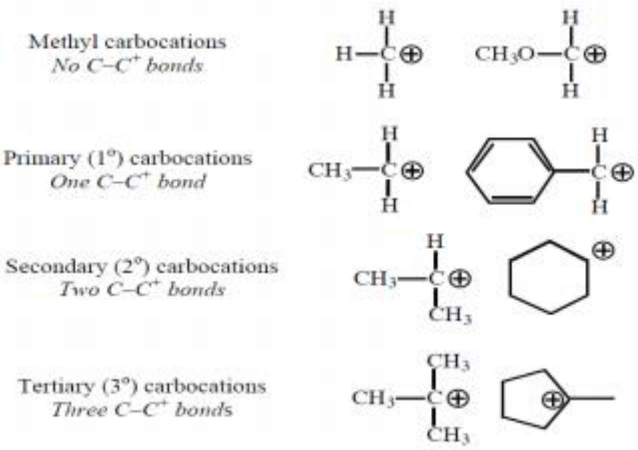
A carbocation is molecule in which a carbon atom bears three bonds and a positive charge. Carbocations are generally unstable because they do not have eight electrons to satisfy the octet rule. It generate through heterolysis fusion.



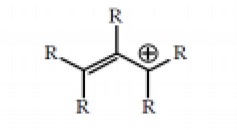
All carbocations were called carbonium ions. Some carbocations may have two or more positive charges, on the same carbon atom or on different atoms; such as the ethylene dication $C_2H_4^{2+}$.

Carbocation Classification:

A primary carbocation is one in which there is one carbon group attached to the carbon bearing the positive charge. A secondary carbocation is one in which there are two carbons attached to the carbon bearing the positive charge. Likewise, a tertiary carbocation is one in which there are three carbons attached to the carbon bearing the positive charge.

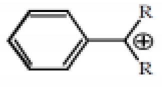


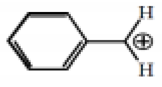
If the carbon bearing the positive charge is immediately adjacent to a carbon-carbon double bond, the carbocation is termed an allylic carbocation. The simplest case (all R =H) is called the allyl carbocation.


Generic allylic carbocation

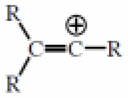

The allyl carbocation

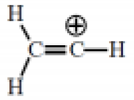
If the carbon bearing the positive charge is immediately adjacent to a benzene ring, the carbocation is termed a benzylic carbocation. The simplest case is called the benzyl carbocation.


Generic benzylic carbocation

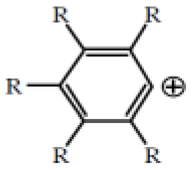

The benzyl carbocation

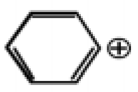
If the carbon bearing the positive charge is part of an alkene, the carbocation is termed a vinylic carbocation. The simplest case is called the vinyl carbocation. Note that the carbon bearing the positive charge has two attachments and thus adopts sp hybridization and linear geometry.


Generic vinylic carbocation


The vinyl carbocation

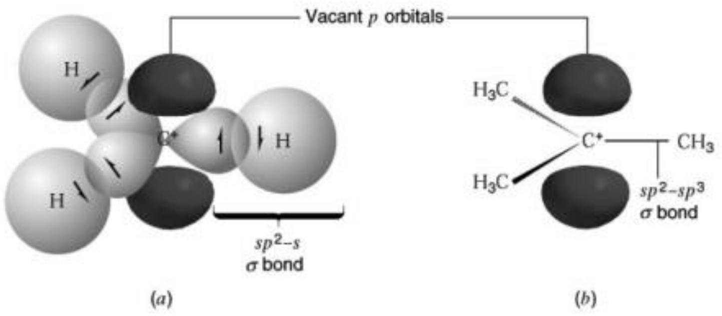
If the carbon bearing the positive charge is part of a benzene ring, the carbocation is termed an aryl carbocation. The simplest case is called the phenyl carbocation.


Generic aryl carbocation


The phenyl carbocation

The structure of carbocations

- The structure of carbocations is trigonal planar



a) A stylized orbital structure of the methyl cation. The bonds are sigma (σ) bonds formed by overlap of the carbon atom’s three sp2 orbitals with 1s orbitals of the hydrogen atoms. The p orbital is vacant.

(b) A dashed line-wedge representation of the tertbutyl cation. The bonds between carbon atoms are formed by overlap of sp3 orbitals of the methyl group with sp2 orbitals of the central carbon atom.

Factors That Stabilize Carbocations

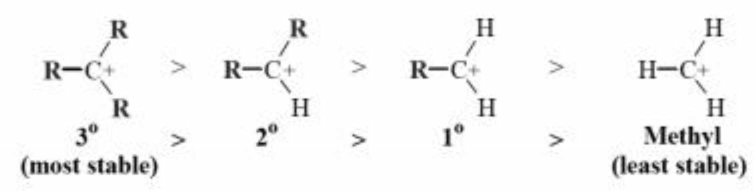
Three main structural factors that help to stabilize carbocations.

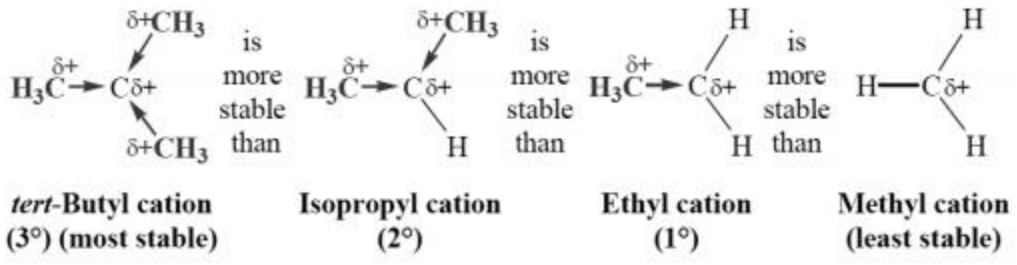
- ✓ Neighboring carbon atoms.

- Neighboring carbon-carbon multiple bonds
- Neighboring atoms with lone pairs.
- The order of stability of alkyl-substituted carbocations to be 30⎞> 20 >10 . One carbon atom of the carbocation is sp2 hybridized and contains one un-hybridized p-orbital. This p-orbital contains no electrons.
- The sp2 hybridized carbon atom has a formal positive charge.

The stability of carbocation through inductive effect:

- Ionic species are more stable if the charge can be delocalized (spread out) throughout the molecule. Alkyl groups (such as -CH3) are electron donating. They donate electrons through a single, σ bond. The donation or withdrawal of electrons through a σ bond is called an inductive effect.
- By donating electrons to the electron-deficient sp^2 hybridized carbon atom, the positive charge is delocalized. The full positive charge on the sp^2 hybridized carbon atom is decreased somewhat and a small amount of positive charge is transferred to the alkyl groups, increasing the stability of the carbocation species. The 3^0 carbocation has three methyl groups that donate electrons.
- The 2^0 carbocation has two methyl groups that donate electrons. The 1^0 carbocation has only one methyl group that donates electrons. The greater the number of electron-donating groups, the greater the stability of the carbocation.





Electron Donating Group:
stabilizes a carbocation

Electron Withdrawing Group:
*de*stabilizes a carbocation

The stability of carbocation through hyperconjugation:

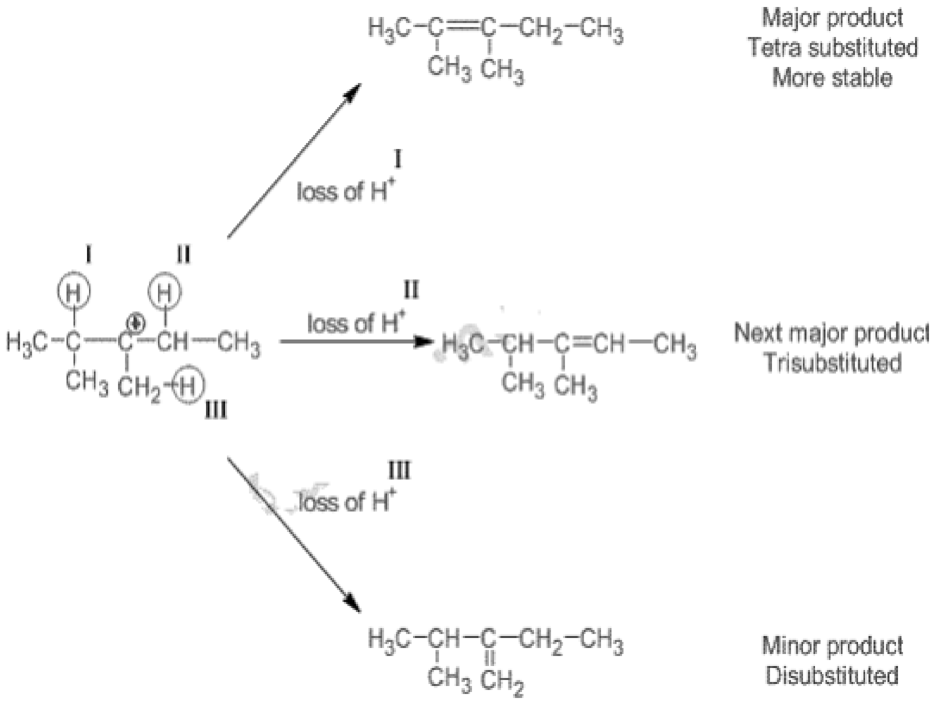
- ✓ Hyper conjugation is a special type of resonance in which delocalization of electrons takes place through overlap between sigma bond orbital and pi-bond orbital or p- orbitals.
- ✓ The sp3 -s orbitals containing the bonding electrons in the C-H bond adjacent to the sp2 hybridized carbon atom can overlap with the unhybridized, empty p-orbital on the sp2 hybridized carbon atom and share the bonding electrons. Sharing electrons in this manner is called hyperconjugation.

  By donating electrons to the electron-deficient sp^2 hybridized carbon atom, the positive charge is delocalized. The full positive charge on the sp^2 hybridized carbon atom is decreased somewhat and a small amount of positive charge is transferred to the alkyl groups, increasing the stability of the carbocation species.

  The 3^0 carbocation has nine opportunities (there are nine adjacent C-H bonds) for hyperconjugation; while 1^0 carbocation has only three opportunities (there are three adjacent C-H bonds) for hyperconjugation.

Saytzeffs Rule

- ✓ Saytzeffs rule (or Zaitsev's rule, Saytzev rule) is an empirical rule for predicting the favored alkene product(s) in elimination reactions.
- ✓ This reaction predicted by Russian chemist Sir Alexander Zaitsev. - Saytzeffs rule states that when alternative exist hydrogen is preferentially eliminated from the carbon atom with fewer number of hydrogen atoms.
- ✓ Saytzeff Rule implies that base-induced eliminations (E2) will lead predominantly to the olefin in which the double bond is more highly substituted, i.e. that the product distribution will be controlled by thermodynamics.



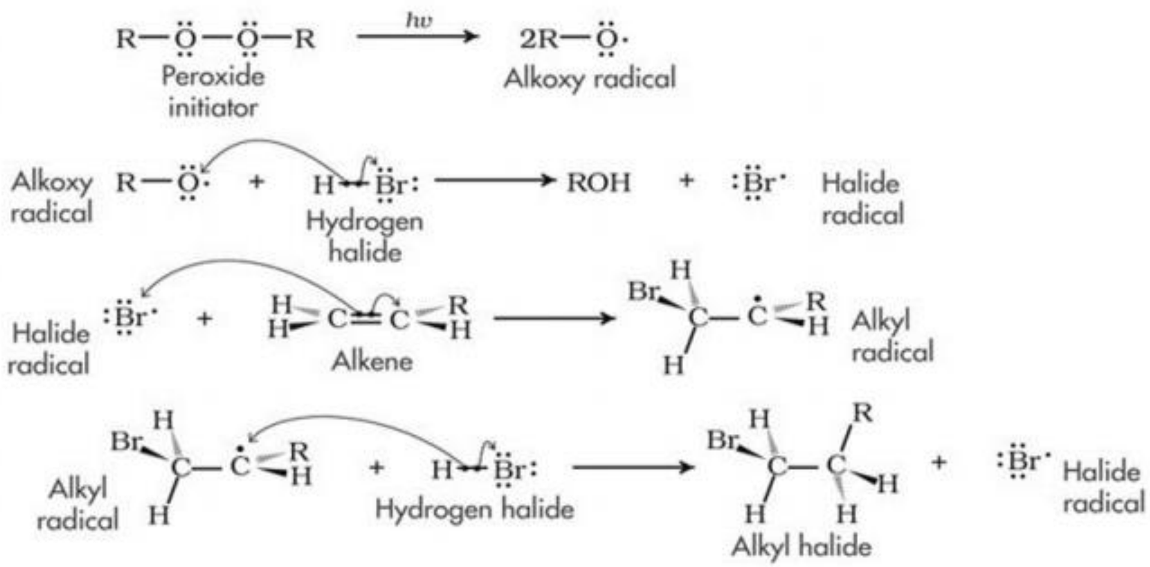
Markownikoff's rule:

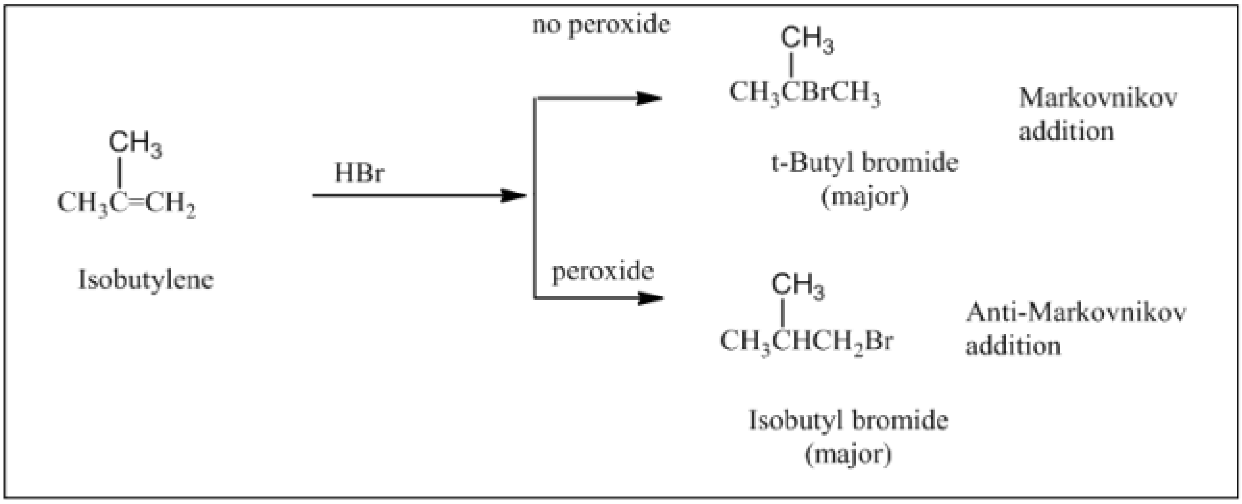
- ✓ The rule states that with the addition of a protic acid HX to an asymmetric alkene, the acid hydrogen (H) becomes attached to the carbon with more hydrogen substituents, and the halide (X) group becomes attached to the carbon with more alkyl substituents.
- ✓ Alternatively, the rule can be stated that the hydrogen atom is added to the carbon with the greatest number of hydrogen atoms while the X component is added to the carbon with the least number of hydrogen atoms .

- ✓ .

Anti- Markownikoff's rule (free radical addition reactions of alkenes)

- ✓ In an addition reaction of a generic electrophile HX to an alkene or alkyne, the hydrogen atom of HX becomes bonded to the carbon atom that had the least number of hydrogen atoms in the starting alkene or alkyne.
- ✓ In the presence of Peroxide for H-Br, the reaction will always yield the Anti-Markovnikov product.
- ✓ Anti Markovnikov addition reaction is found to follow a free radical mechanism. The peroxide compound involved helps in the generation of free radicals. Generation of free radical through homolytic cleavage of peroxide compound. Attack of generated free radical on hydrogen halide to form halide radical through homolysis
- ✓ Attack of generated halide radical on alkene molecule to form alkyl radical through homolysis.
- ✓ Attack of generated alkyl radical on hydrogen halide to form alkyl halide through homoltyic cleavage of hydrogen halide bond.





Diene

An unsaturated hydrocarbon containing two double bonds between carbon atoms.

Dienes can be divided into three classes, depending on the relative location of the double bonds:

(i) Cumulated dienes have the double bonds sharing a common atom as in a group of compounds called allenes.

(ii) Conjugated dienes have conjugated double bonds separated by one single bond.

(iii) Unconjugated dienes have the double bonds separated by two or more single bonds. They are usually less stable than isomeric conjugated dienes. This can also be known as an isolated dienes.

Isolated Dienes

- The bonding in isolated dienes is the same as that in alkenes.

Conjugated Dienes

- ✓ The C-C single bond between conjugated double bonds is shorter than a typical alkane This is due to the difference is the hybridisation of the C atoms involved (check the % s character) andthe conjugation of the two π bonds.
- ✓ Two conformations of conjugated dienes are important, s-cis and s-trans, as for 1,3-butadiene. The "s" refers rotation about a σ bond. Stability of conjugated dienes: The s-trans conformation of 1,3-butadiene is about 12 kJ/mol (2.8 kcal/mol) more stable than the s-cis due to the unfavourable steric interaction of substituents at C1 and C4

Cumulated Dienes

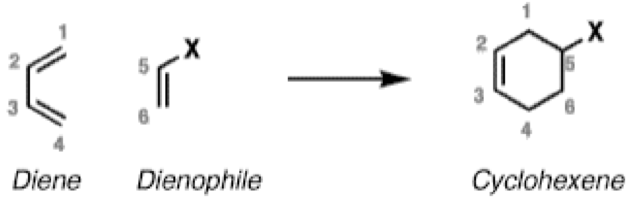
- ✓ Like the triple bond unit of an alkyne, the C=C=C unit of allenes are linear.

- ✓ The central sphybridised C atom
- ✓ The C=C bonds in allenes are slightly shorter (131 pm) than those in a typical alkene C=C (134 pm)
- ✓ Allenes are non-planar. Note the perpendicular nature of the C-H bonds.

Diels-Alder Reaction

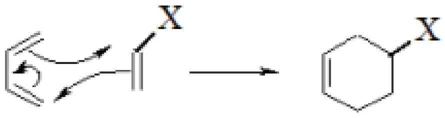
The Diels Alder reaction converts a diene (an unsaturated hydrocarbon containing two double bonds between carbon atoms.) and an alkene (usually electron-poor, called a ―dienophile”) into a six-membered ring containing an alkene (cyclohexene).

The Diels Alder Reaction

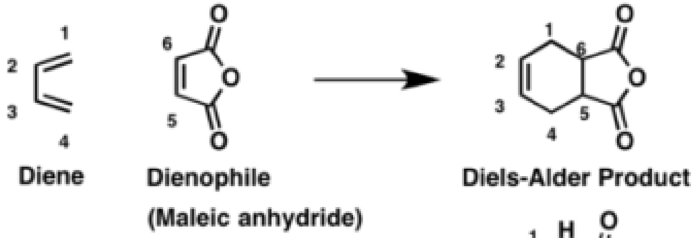


Bonds Formed	Bonds Broken
C_1–C_5	C_1–C_2 (π)
C_2–C_3 (π)	C_3–C_4 (π)
C_4–C_6	C_5–C_6 (π)

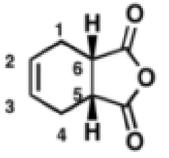
Mechanism



Diels-Alder reaction of a cyclic dienophile

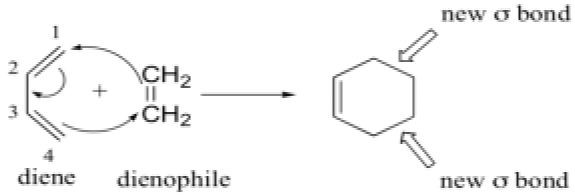


Bonds Formed	Bonds Broken
C_1–C_6	C_1–C_2 (π)
C_2–C_3 (π)	C_3–C_4 (π)
C_4–C_5	C_5–C_6 (π)

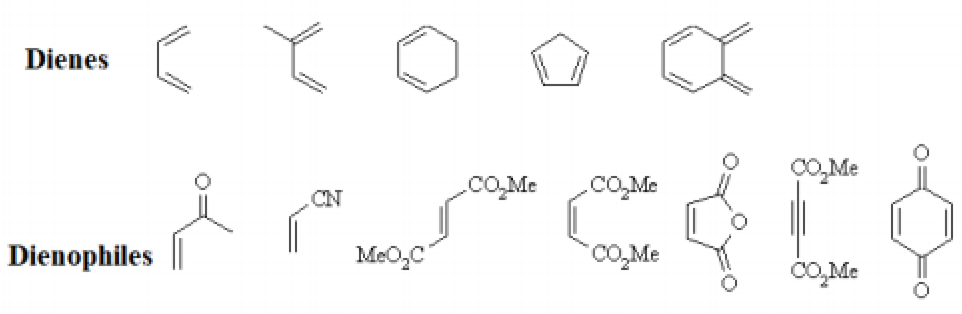


with stereochemistry

Diels Alder reaction usually thermodynamically favourable due to the conversion of 2 π-bonds into 2 new stronger σ-bonds.

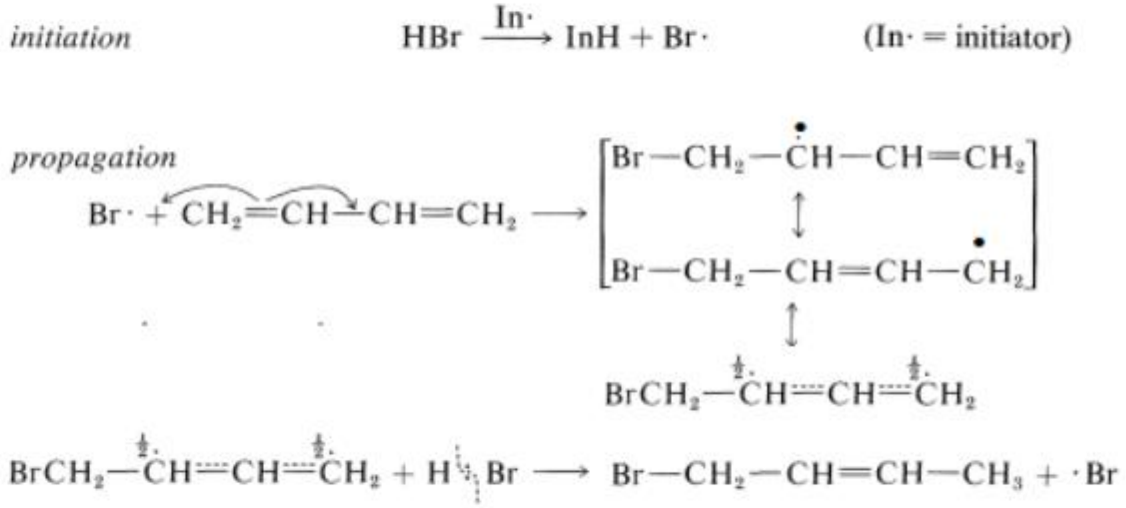


The normal Diels-Alder reaction is favoured by electron withdrawing groups on the electrophilic dienophile and by electron donating groups on the nucleophilic diene.



Free radical addition reactions of conjugated dienes

Conjugated dienes also undergo addition reactions by radical-chain mechanisms. Here, the addition product almost always is the 1,4 adduct. Thus radical addition of hydrogen bromide to 1,3-butadiene gives l-bromo-2-butene.



initiation $$\mathrm{HBr} \xrightarrow{\mathrm{In}\cdot} \mathrm{InH} + \mathrm{Br}\cdot \qquad (\mathrm{In}\cdot = \text{initiator})$$

propagation $$\mathrm{Br}\cdot + \mathrm{CH_2{=}CH{-}CH{=}CH_2} \longrightarrow \left[\mathrm{Br{-}CH_2{-}\dot{C}H{-}CH{=}CH_2} \updownarrow \mathrm{Br{-}CH_2{-}CH{=}CH{-}\dot{C}H_2}\right]$$

$$\updownarrow$$

$$\mathrm{BrCH_2{-}\overset{\frac{1}{2}\cdot}{C}H{\cdots}CH{\cdots}\overset{\frac{1}{2}\cdot}{C}H_2}$$

$$\mathrm{BrCH_2{-}\overset{\frac{1}{2}\cdot}{C}H{\cdots}CH{\cdots}\overset{\frac{1}{2}\cdot}{C}H_2} + \mathrm{H{-}Br} \longrightarrow \mathrm{Br{-}CH_2{-}CH{=}CH{-}CH_3} + \cdot\mathrm{Br}$$

Allylic Rearrangement

- Allylic compounds are those which have a functional group on a carbon atom α to an olefinic bond, e.g., Alkenes are also called Olefins because they form oily liquids on reaction with chlorine gas.
- An alkene consists of atleast one double bond. This double bond is known as the olefinic bond.

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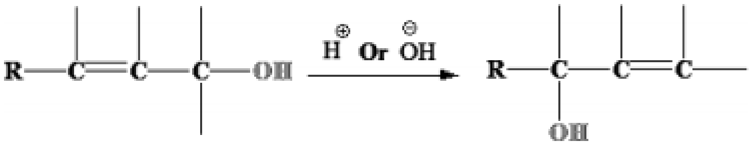


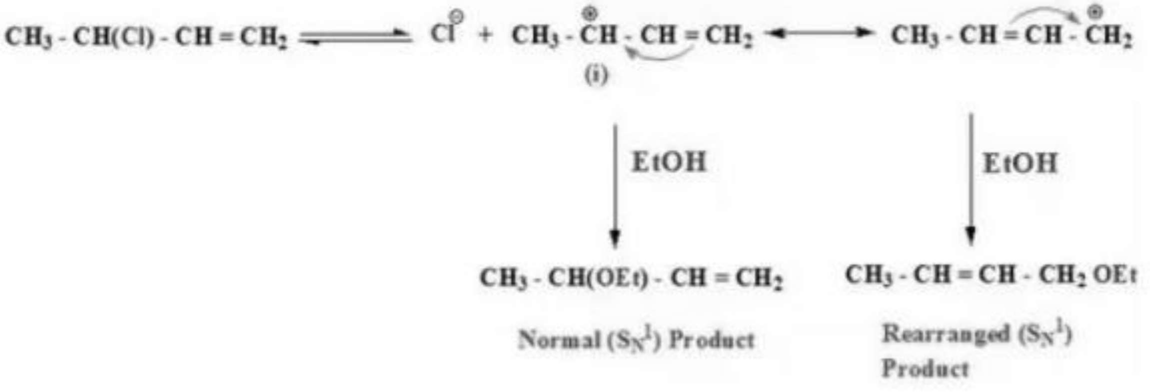
$$CH_3-CH=CH-CH_2OH \xrightarrow{\overset{\oplus}{H}} CH_3-CH(OH)-CH=CH_2$$

α – Methylallyl Alcohol

$$CH_3-CH(Cl)-CH=CH_2 \xrightarrow{EtOH} CH_3-CH(OEt)-CH=CH_2 + CH_3-CH=CH-CH_2OEt$$

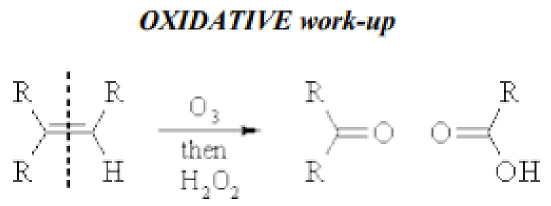
α – Methylallyl Chloride; 3-Ethoxybutene -1; 1-Ethoxybutene -2

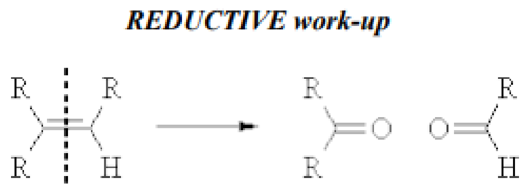
Mechanism: Allylic rearrangement is observed generally in nucleophilic substitution reactions which may be SN1 or SN2 type.



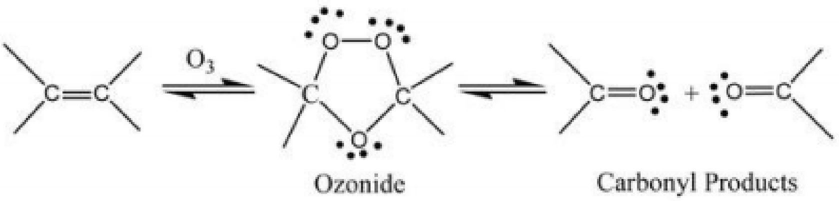
Ozonolysis

- Ozonolysis is an organic reaction where the unsaturated bonds of alkenes, alkynes, or azo compounds are cleaved with ozone.
- Alkenes and alkynes form organic compounds in which the multiple carbon–carbon bond has been replaced by a carbonyl group while azo compounds form **nitrosamines.**
- **Reaction type**: Electrophilic Addition.



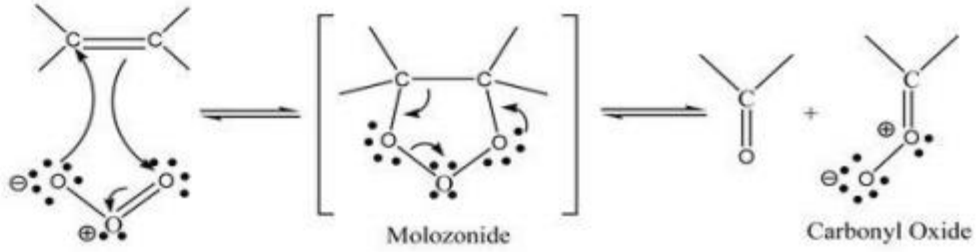


- **Reaction:**

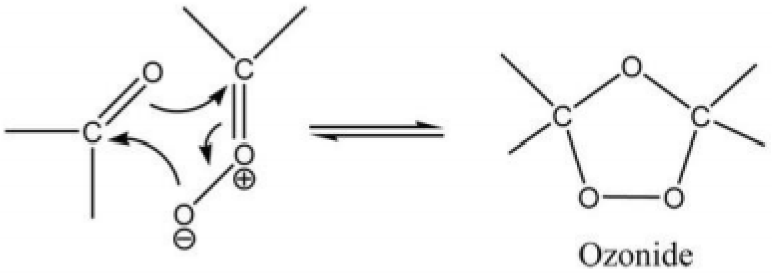


Reaction Mechanism:

Step 1: The first step in the mechanism of ozonolysis is the initial electrophilic addition of ozone to the CarbonCarbon double bond, which then forms the molozonide intermediate. Due to the unstable molozonide molecule, it continues further with the reaction and breaks apart to form a carbonyl and a carbonyl oxide molecule.



Step 2: The carbonyl and the carbonyl oxide (zwitterions) rearranges itself and reforms to create the stable ozonide intermediate. A reductive workup could then be performed to convert the ozonide molecule into the desired carbonyl products.



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