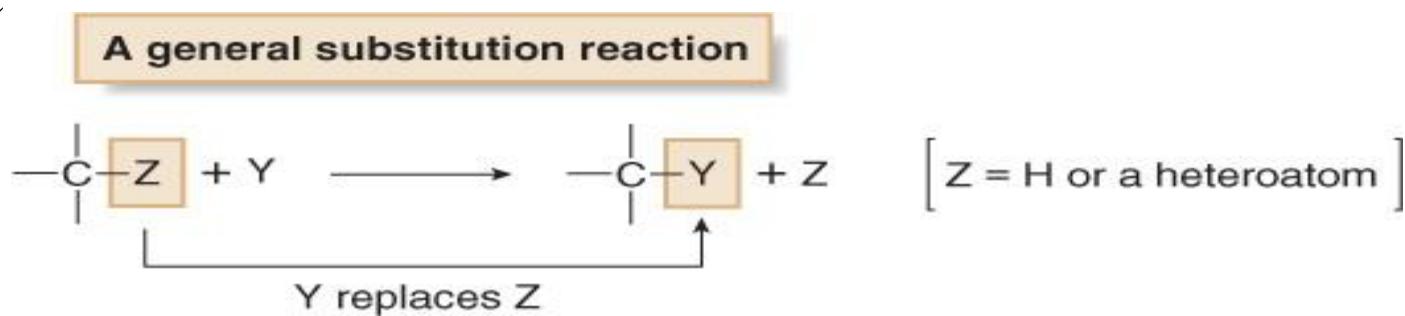


Chapter 4

Major organic reactions

Major organic reactions

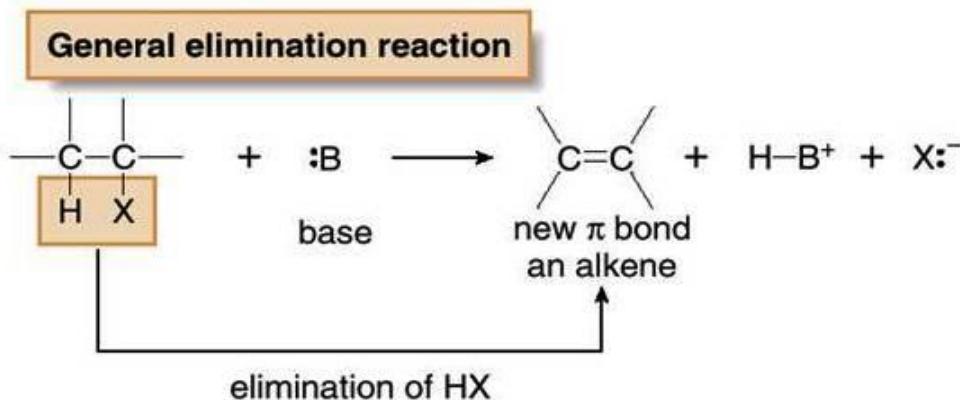
- In organic chemistry there are four major organic reactions
- Those are
 - ☞ Substitution reaction
 - ☞ Elimination reaction
 - ☞ Addition reaction
 - ☞ Rearrangement reaction
- Substitution reaction
 - ✓ An atom or groups of atoms are replaced by another atom/groups of atoms.
 - ✓ example



■ Elimination reaction

✓ Is a reaction that involves the loss of elements from the starting material to form a new π bond in the product.

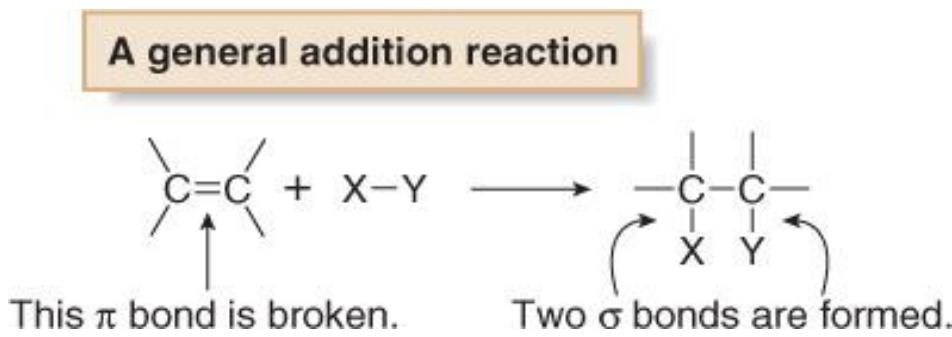
✓ Example



■ Addition reaction

✓ is a reaction in which elements are added to the starting material.

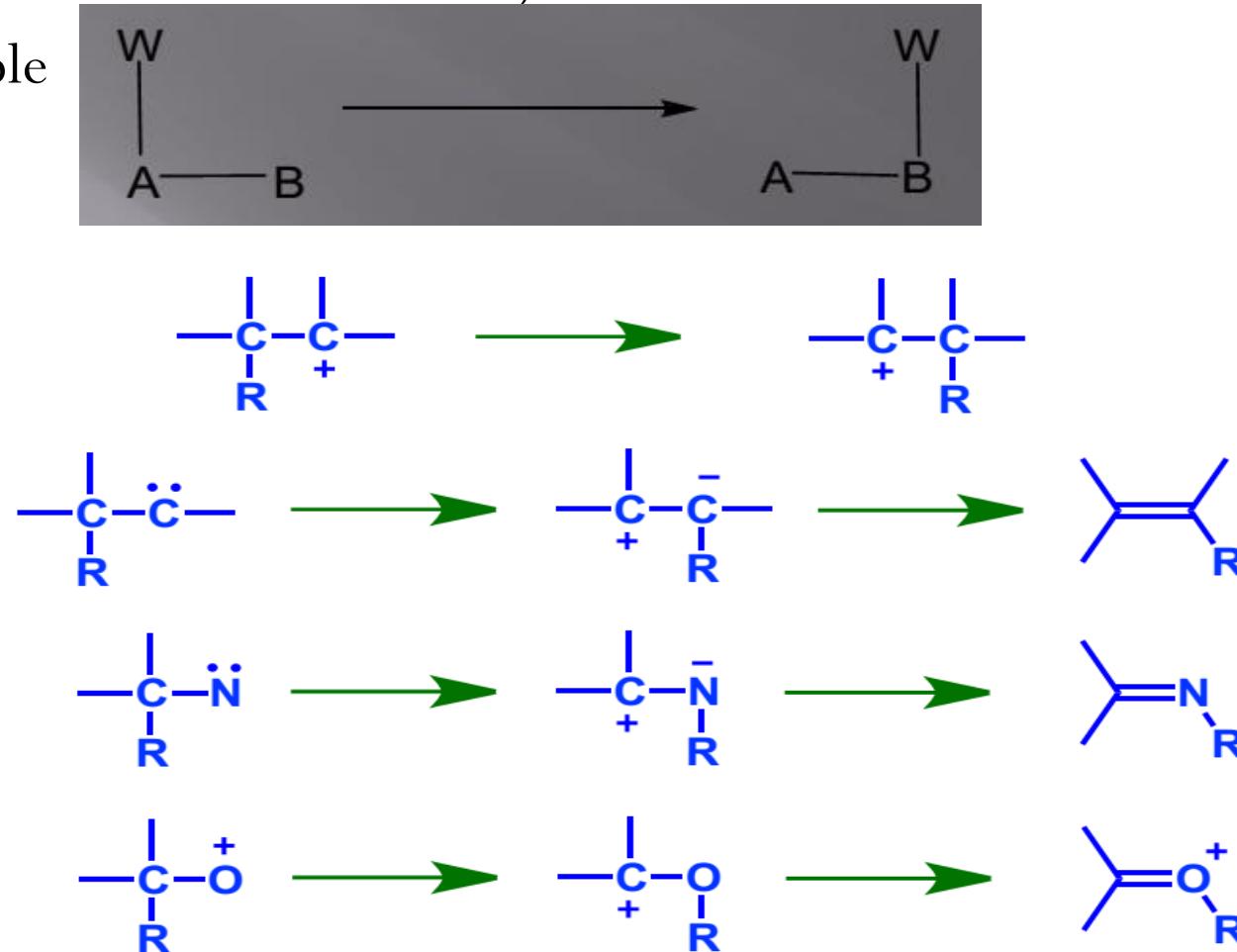
✓ Example



Rearrangement reaction

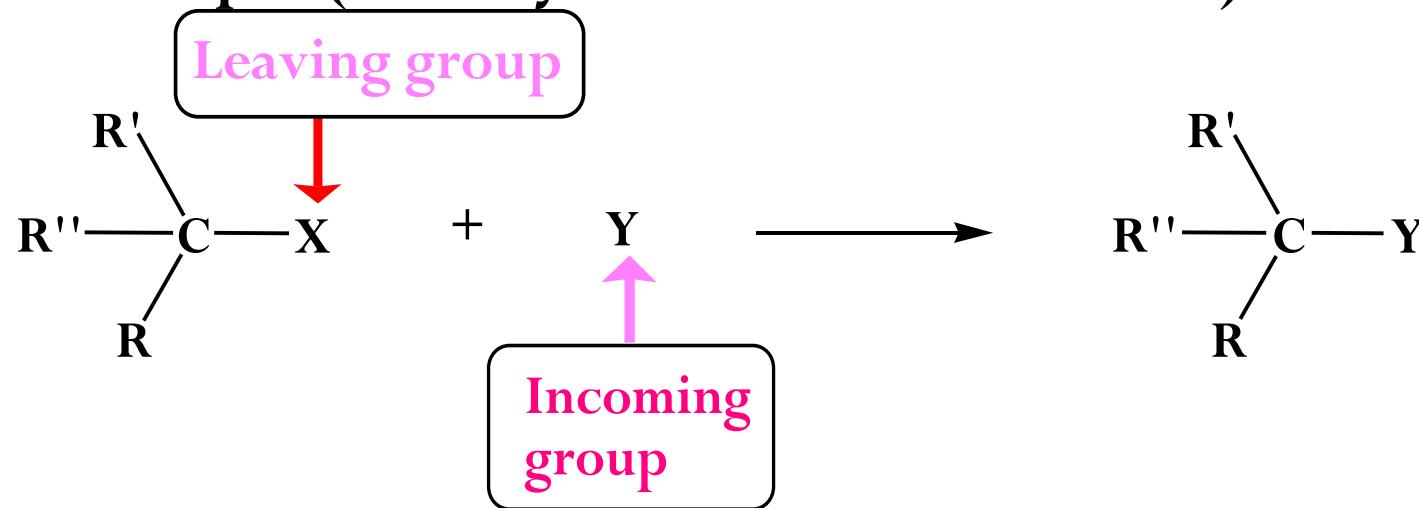
✓ reactions involve the migration of a group or an atom from one center (migration origin) an adjacent atom (migration terminus, having six electrons in the valence shell) within the same molecule.

✓ Example



4.1 SUSTITUTION REACTION

- A **substitution** is a reaction in which an **atom or a group** of atoms is/are **replaced** by another atom or group of atoms.
- See the reaction that takes place Below, **Y** replaces **X** on a carbon atom.
- Example (for any substitution reaction)



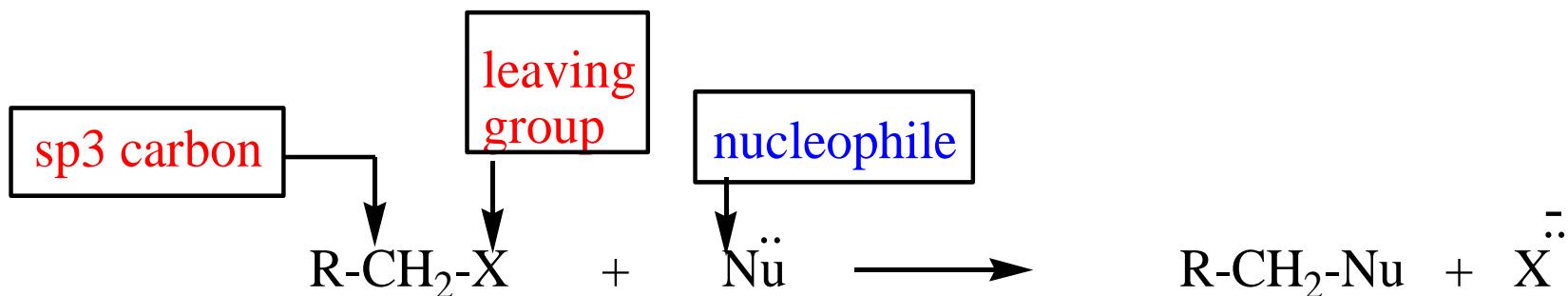
- Note
 - $Y = \text{electrophile, nucleophile or radical}$
 - $X = \text{H, C or heteroatoms}$

Nucleo-philic Substitution Reaction(NSR)

- **Nucleo-philic Substitution Reaction** is a reaction in which the leaving group is replaced by the nucleophile.
- A nucleophile donate a pair of electrons to the electrophilic carbon atom of forming a new bond and displacing the leaving group.
- What is/are nucleophile/s?
- **Nucleophiles** :- are any **negative ions** or any **neutral molecules** that contains at least one unshared electron pair. **Or**
 - Are lewis bases(electron pair donors).
- Examples-4.1



❖ General reaction of nucleo-philic substitution reaction.



when X = leaving group
like halogens, O,N etc

❖ To draw any nucleophilic substitution product:

- Find the *sp³* hybridized carbon with the leaving group.
- Identify the nucleophile, the species with a lone pair or π bond.
- Substitute the nucleophile for the leaving group and assign charges (if necessary) to any atom that is involved in bond breaking or bond formation.

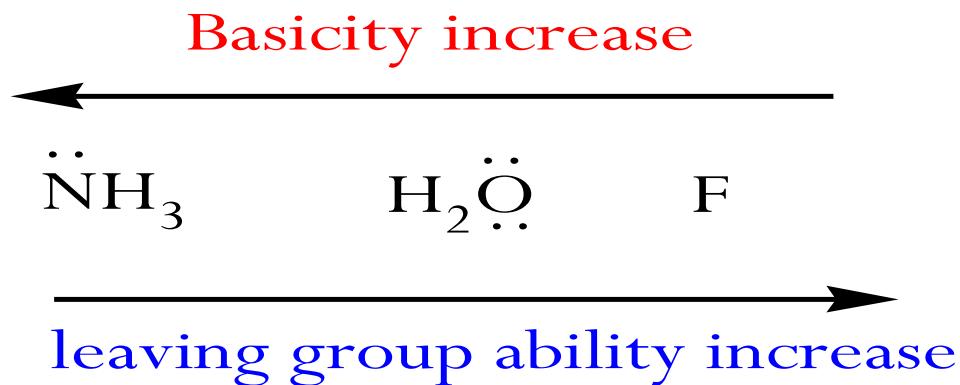
Leaving groups

- Are groups that departs from sp³-C with the electron pairs present between sp³ carbon and X
- Depending on their ability to depart from sp³-carbon they are divide as
 - Good leaving groups
 - Bad leaving groups

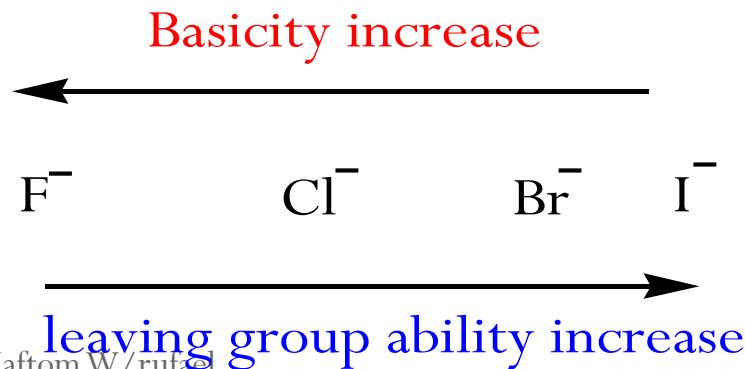
- Good leaving groups:-** groups that departs easily during reaction
- To be a good leaving group the substituent must be able to leave as a relatively stable, weakly basic molecule or ion
- Example-4.2:- H₂O, NH₃, I, Br etc

- Bad leaving groups :-** groups that are difficult to depart
- Example -4.3:- OH , NH₂ etc

- Across a period in the periodic table leaving ability increase from left to right.



- Down a group in the periodic table leaving ability increases. This is because when size an atom increase bond strength decrease.



Example 4.4 good leaving groups

Good leaving group for nucleophilic substitution

starting material	leaving group
R-Cl	Cl ⁻
R-Br	Br ⁻
R-I	I ⁻
R-OH ₂ ⁺	H ₂ O

undergo nucleophilic
substitution

good leaving
group

Example-4.5 Poor leaving groups

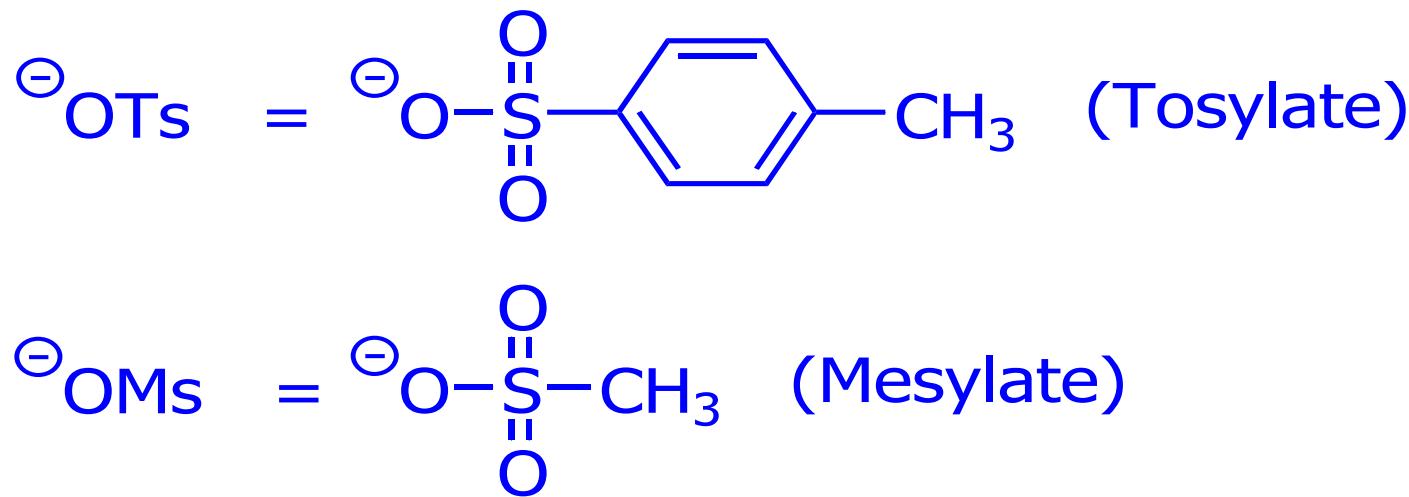
poor leaving group for nucleophilic substitution

starting material	leaving group
R-F	F ⁻
R-OH	OH ⁻
R-NH ₂	NH ₂ ⁻
R-H	H ⁻
R-R	R ⁻

do not undergo
nucleophilic substitution

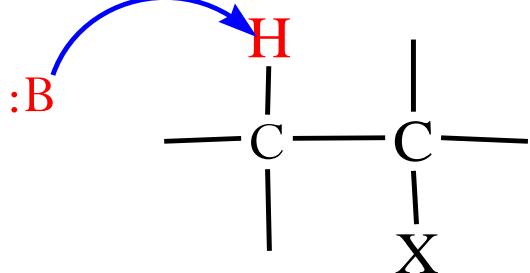
poor leaving
group

- ❖ To be a good leaving group, the substituent must be able to leave as a relatively stable, weakly basic molecule or ion
- ❖ e.g.: I^\ominus , Br^\ominus , Cl^\ominus , TsO^\ominus , MsO^\ominus , H_2O , NH_3



Difference between Nucleophile and Base

- **Base(:B)** :-attacks proton

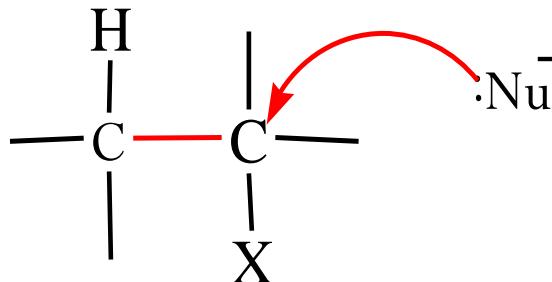


- **Basicity** is a measure of how readily an atom donates its electron pair to a proton.

- It is characterized by an **equilibrium constant**, K_a in an acid-base reaction, making it a **thermodynamic property**.

- **Nucleophile (:Nu or :Nu⁻)**

- attacks other Electron Deficient (ED) groups (usually carbon).



- **Nucleophilicity** is a measure of how readily an atom donates its electron pair to ED groups.

- It is characterized by a **rate constant**, k , making it a **kinetic property**.

■ Similarity of Bases and nucleophiles is both have a *lone pair* or a π bond but they differs in what they attack.

■ Nucleophilicity parallels basicity in three instances:

1. For two nucleophiles with the same nucleophilic atom, the stronger base is the stronger nucleophile.

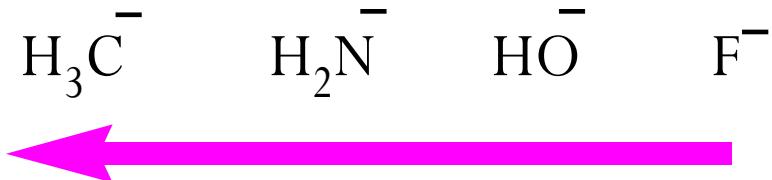
➤ The relative nucleophilicity of HO^- and CH_3COO^- , two oxygen nucleophiles, is determined by comparing the pK_a values of their conjugate acids ($\text{H}_2\text{O}^- = 15.7$, and $\text{CH}_3\text{COOH} = 4.8$).

➤ HO^- is a stronger base and stronger nucleophile than CH_3COO^- .

2. A **negatively charged nucleophile** is always a *stronger nucleophile* than its *conjugate acid*.

➤ HO^- is a stronger base and stronger nucleophile than H_2O .

3. Right-to-left-across a row of the periodic table, nucleophilicity increases as basicity increases:



Increase Basicity

Increase Nucleophilicity

- + Nucleophilicity does not parallel basicity when steric hindrance becomes important.
- + Steric hindrance is a decrease in reactivity resulting from the presence of bulky groups at the site of a reaction.
- + Steric hindrance *decreases nucleophilicity* but not basicity.
- + Sterically hindered bases that are poor nucleophiles are called nonnucleophilic bases.

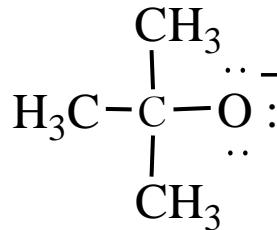
Example-4.6



Ethoxide

+ Stronger nucleophile

+ Sterically Unhindered Oxygen



tert-butoxide

+ Stronger base

+ The three CH_3 sterically hinder O atom makes it *weak nucleophile*

Effects of solvents on basicity and nucleo-phility

■ In **polar protic solvents**, nucleophilicity and basicity increases and decreases down a column of the periodic table as the size of the anion increases respectively.

■ $\text{F}^- < \text{Cl}^- < \text{Br}^- < \text{I}^-$ in nucleophilicity

■ Because the cations are solvated by ion-dipole interactions with polar protic solvents, and also the anions are solvated by strong hydrogen bonding interactions.

■ **Examples of polar protic solvents**

➤ H_2O , CH_3NH_2 , $(\text{CH}_3)_3\text{OH}$,
 $\text{CH}_3\text{CH}_2\text{OH}$, CH_3COOH etc....

■ **Polar aprotic solvents** also exhibit dipole—dipole interactions, but they have no O—H or N—H bonds. Thus, they are incapable of hydrogen bonding.

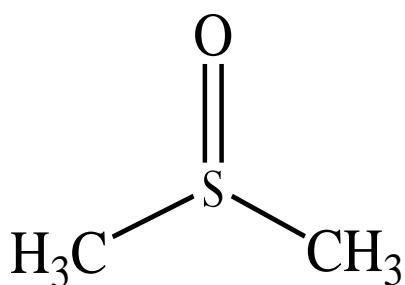
■ Basicity and nucleophilicity decreases down a group.

$\text{F}^- > \text{Cl}^- > \text{Br}^- > \text{I}^-$

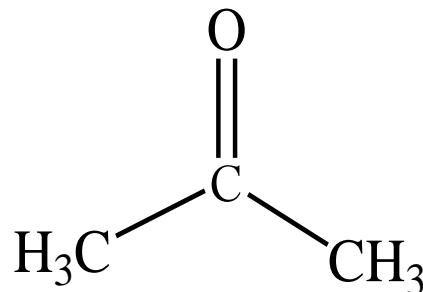
■ Polar aprotic solvents solvate cations by ion—dipole interactions.

■ Anions are not well solvated by polar aprotic solvents. These anions are said to be “naked”.

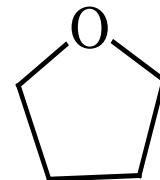
Examples of polar aprotic solvents



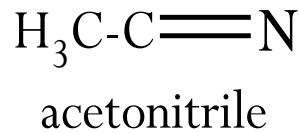
dimethyl sulfoxide
(DMSO)



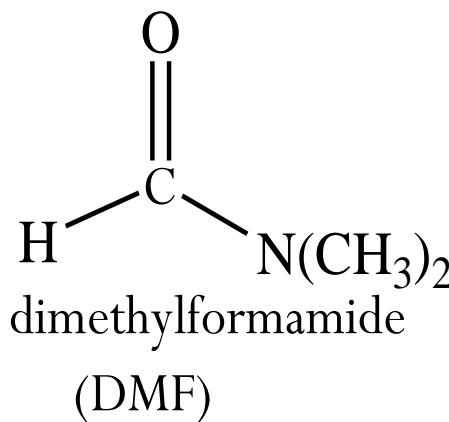
acetone



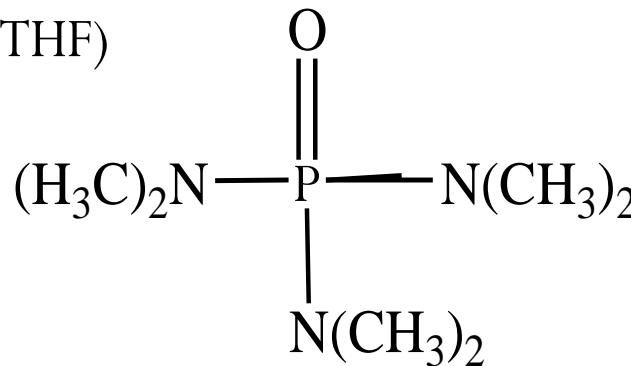
tetrahedrafurane (THF)



acetonitrile



dimethylformamide (DMF)



Hexamethylphosphoramide (HMPA)

- All the listed polar aprotic solvents does not form hydrogen bond with the nucleophile due to this nucleophilicity and basicity do not affect by these solvents.

Some examples of nucleophiles used in organic reactions

elements found in Nu	Negatively charged nucleophiles			neutral nucleophiles	
Oxygen	HO	RO	CH ₃ COO	H ₂ O	ROH
Nitrogen	N ₃			NH ₃	RNH ₂
Carbon	CN	HC≡C			
Halogen	Cl	Br	I		
Sulfur	HS	RS		H ₂ S	RSH

Mechanism of Nucleophilic Substitution

⊕ Mechanisms of nucleo-philic substitution reaction divided in to two.

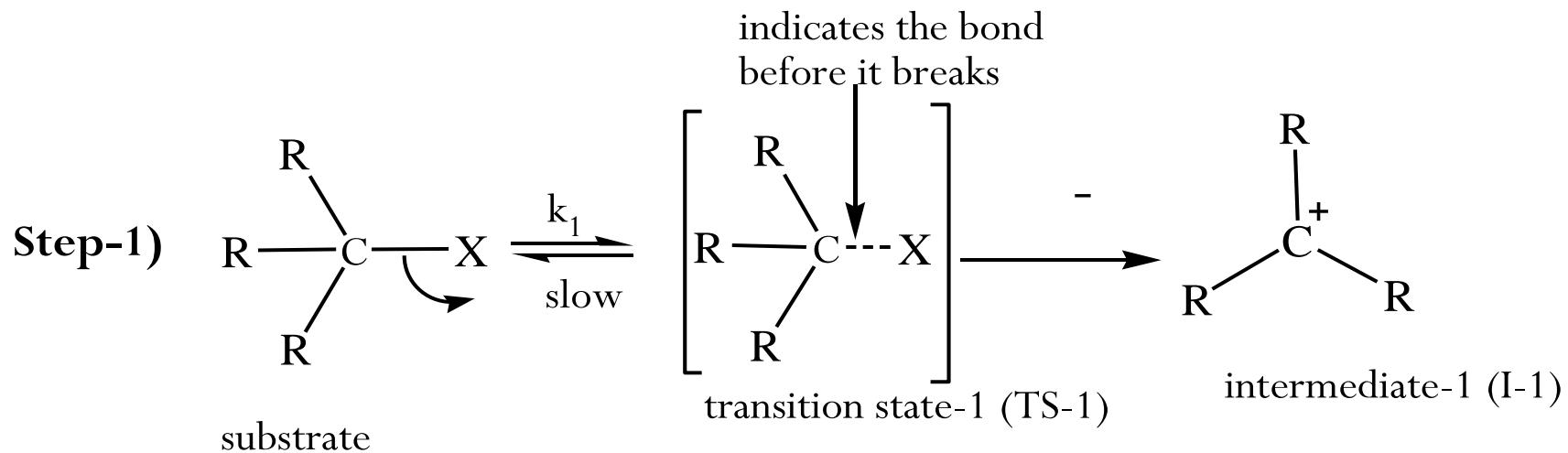
I. SN1(Uni-molecular nucleo-philic substitution)

II. SN2(Bi-molecular nucleo-philic substitution)

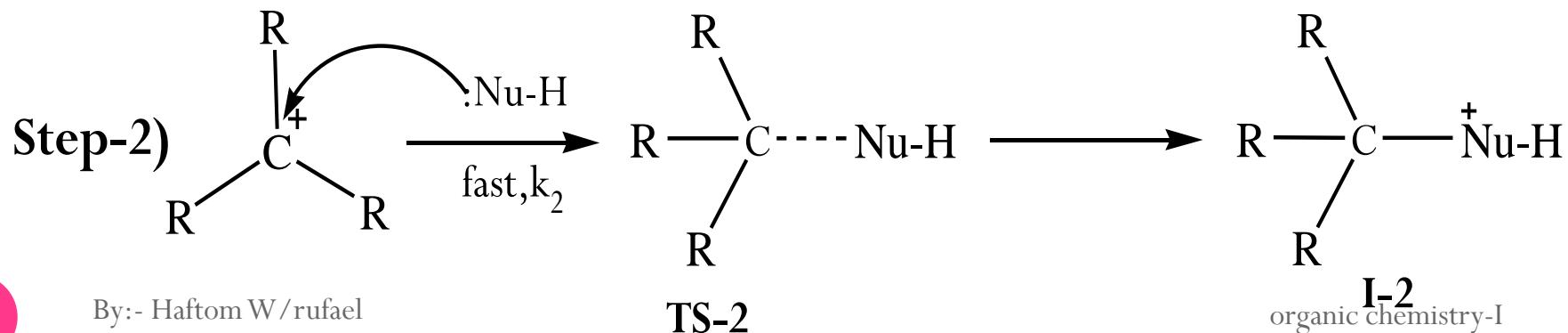
SN1(Uni-molecular nucleo-philic substitution)

- ⊕ Bond breaking occurs before bond making
- ⊕ An intermediate (carbocation) is formed.
- ⊕ The product is obtained by reacting the intermediate with the nucleophile.
- ⊕ This kind of mechanism is called two step or multistep mechanism depending on the substrate and the nucleophile.
- ⊕ Because the first step is rate-determining, the rate depends on the concentration of RX only; that is, the rate equation is first order.

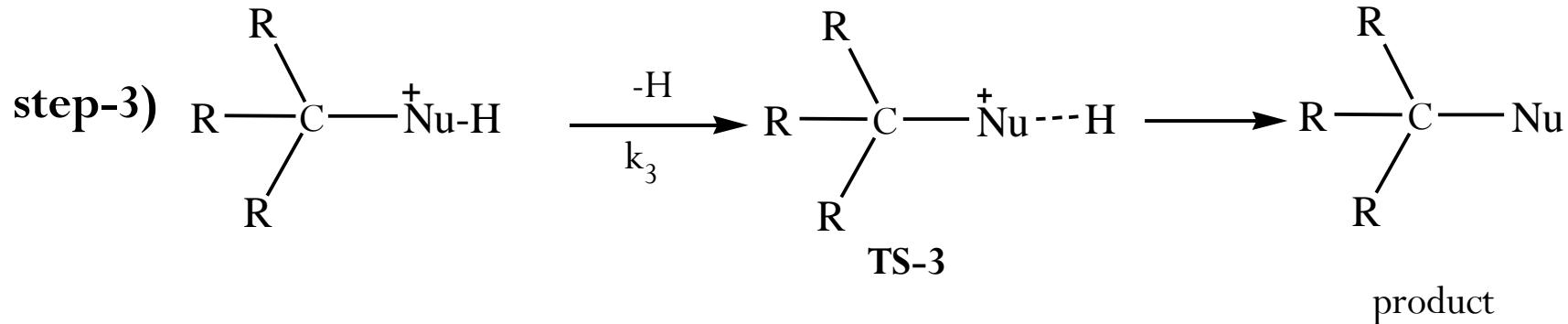
The SN1 (substitution, nucleophilic, unimolecular) mechanism involves an initial slow ionization of $\text{sp}^3 \text{ C-X}$,



- Followed by a rapid reaction of the carbocation with the nucleophilic reagent



- Since SN1 requires weak(usually neutral) nucleophiles, the third step need deprotonation



- In this type of mechanism the first , slow , process is rate-determining , and the rate is therefore proportional to the concentration of $\text{R}_3\text{C-X}$ and not to that of Nu-H ; the kinetics is **first order**(rate = $k[\text{R}_3\text{C-X}]$)
- In multistep reactions ,the rate of the slowest step will be the rate of the entire reaction. This is called the rate determining step. In the case to the right, $k_1 \ll k_2$ or k_3 and the first step is rate determining.

TRANSITION STATE THEORY: FREE-ENERGY DIAGRAMS

- The **reaction coordinate** indicates the progress of the reaction, in terms of the conversion of reactants to products
- The top of the energy curve corresponds to the **transition state** for the reaction
- The **free energy of activation (ΔG^\ddagger)** for the reaction is the difference in energy between the reactants and the transition state
- The **free energy change for the reaction (ΔG°)** is the difference in energy between the reactants and the products
- A reaction that proceeds with a **negative** free-energy change (releases energy to its surroundings) is said to be **exergonic**.
- A reaction that proceeds with a **positive** free-energy change (absorbs energy from its surroundings) is said to be **endergonic**

FREE ENERGY

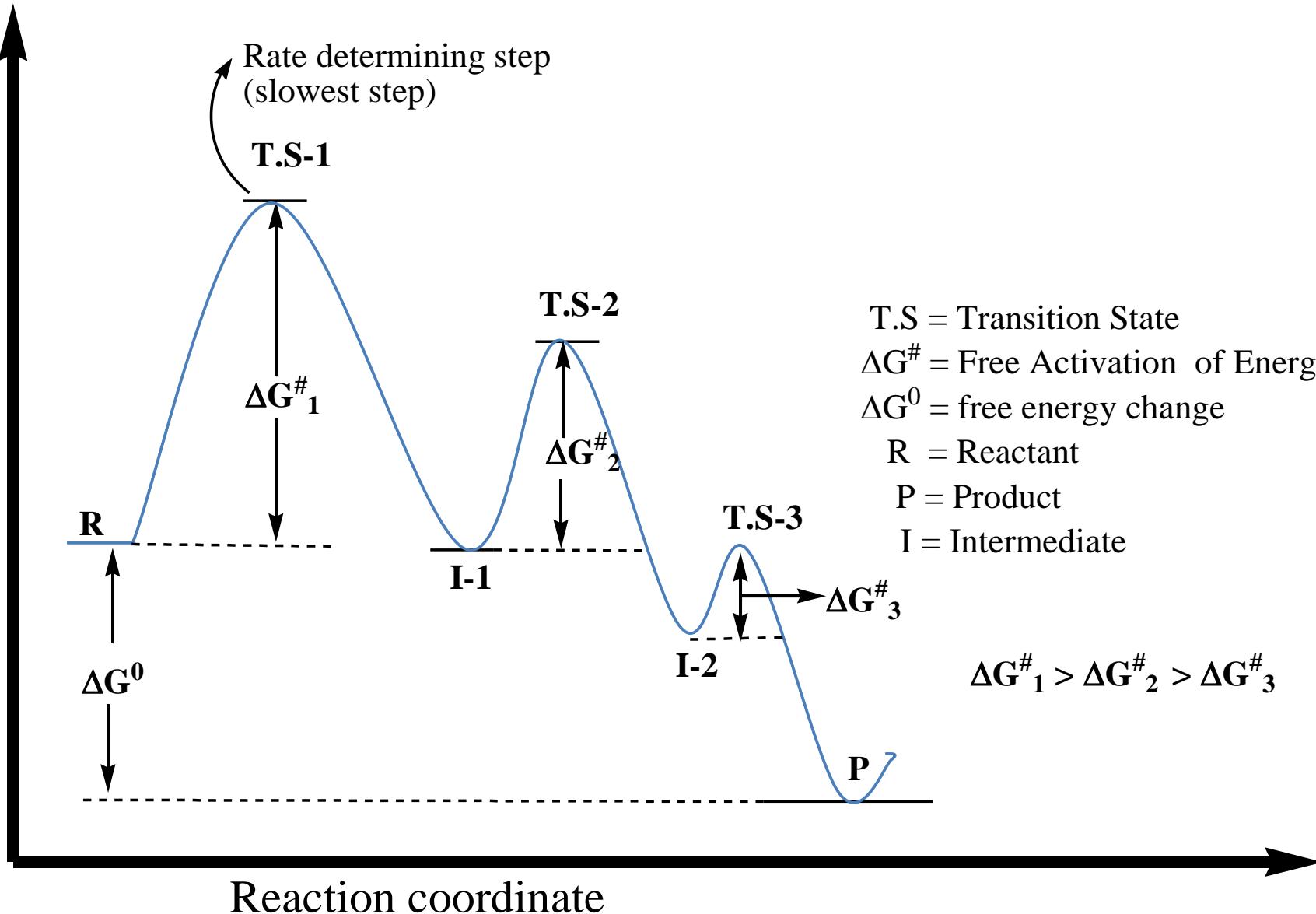
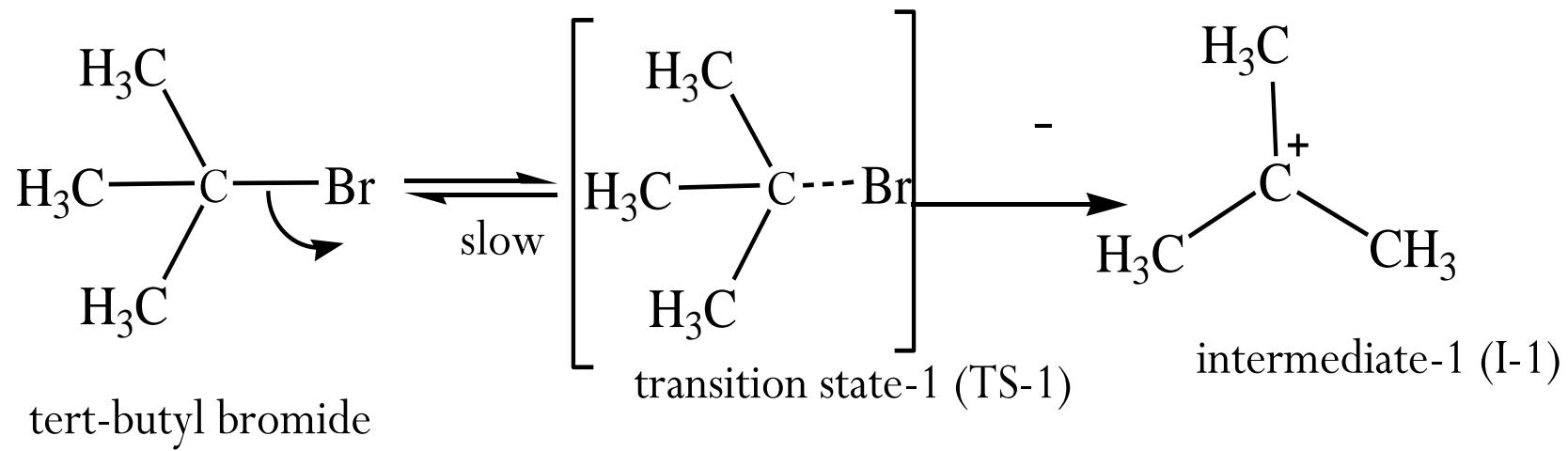


Figure :- Energy diagram for multistep reaction mechanism

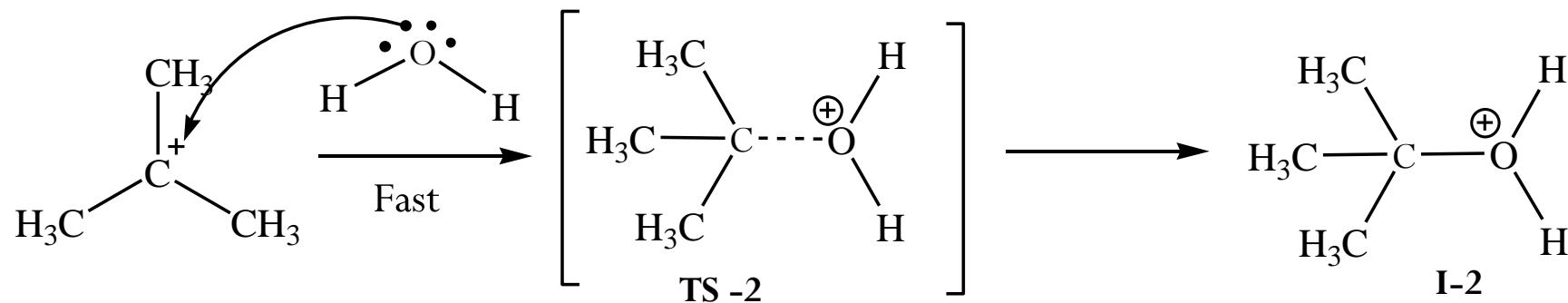
By:- Haftom W/rufael

Example-4.7:- Hydrolysis of tert-butyl bromide with water forming tert-butyl alcohol.

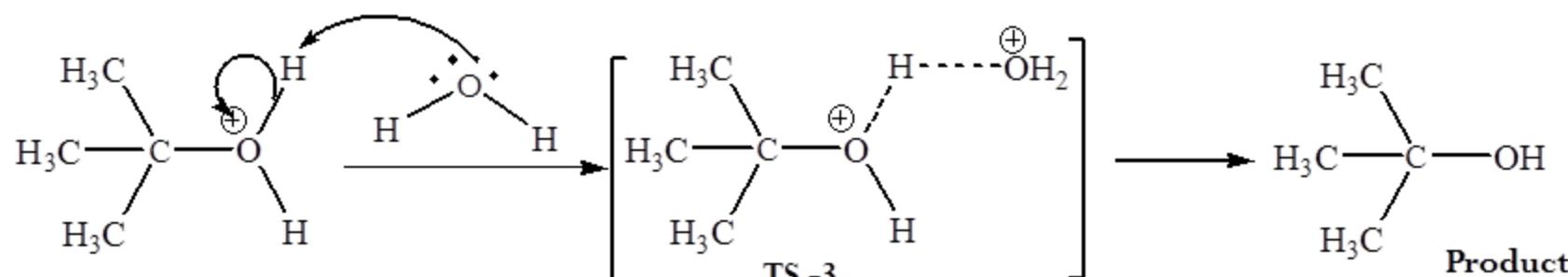
1. *tert*-butyl carbocation is formed by separating a leaving group (a bromide anion) from the carbon atom. This step is slow and reversible.

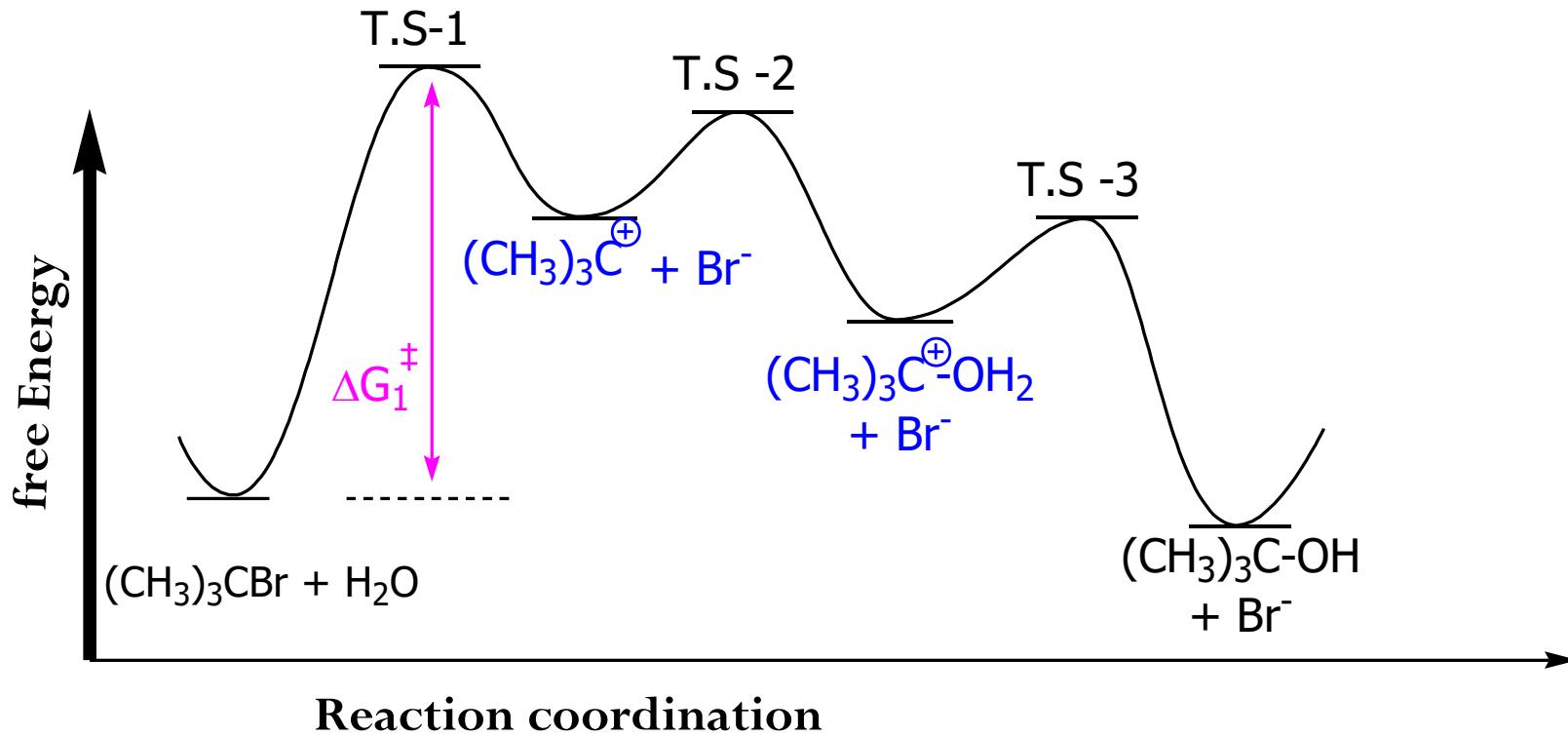


2. Nucleophilic attack: the carbocation reacts with the nucleophile. Since the nucleophile is a neutral molecule (a solvent, water) a third step is required to complete the reaction and the intermediate is an oxonium ion. This is a fast step in the reaction.



3. Deprotonation: Water which acts as a base removes a proton on the protonated nucleophile to form alcohol and a hydronium ion. This is a fast step as well.

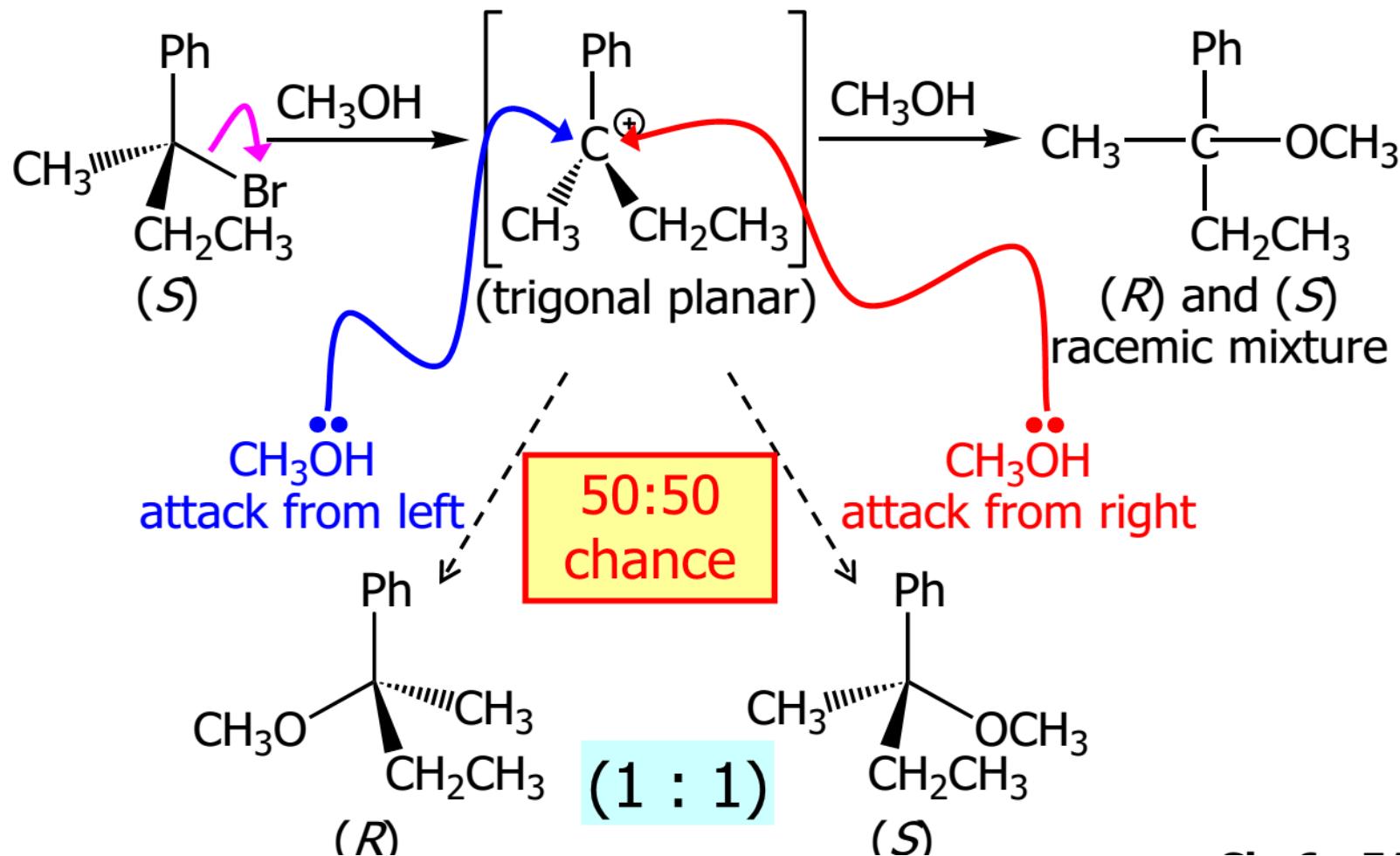




- In $\text{S}_{\text{N}}1$ reaction mechanism the first step (T.S - 1) is the rate determining step(slow step) , which indicates the reaction only depends on the substrate only.
- Rate = $k[(\text{CH}_3)_3\text{C-Br}]$
- This step has high activation energy than the remaining.
- This kinds of reaction is called multistep reaction mechanism.

Stereochemistry of S_N1 Reactions

- Since the nucleophile approaches the intermediate from back side and front side the product will have mixture of R and S configuration which is racemic mixture (50%R and 50%S).

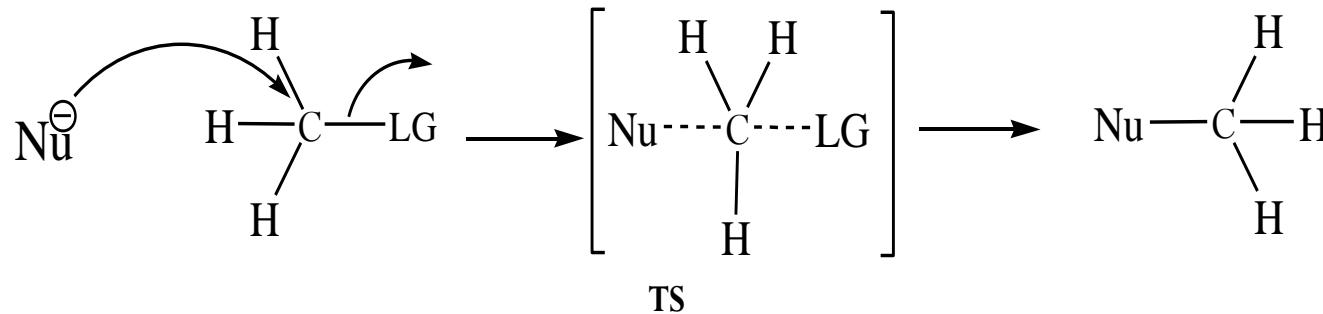


S_N2 (Bimolecular nucleophilic substitution)

- S= substitution N= nucleophilic 2= Bimolecular (second order)
- The SN2 reaction is also known as bimolecular nucleophilic substitution.
- It is a type of nucleophilic substitution, where a lone pair from a nucleophile attacks an electron deficient electrophilic center and bonds with it, leaving behind what may be called as a leaving group. So, the leaving group is replaced by the incoming group in the very first step.
- In the SN2 mechanism , the reaction goes in one stage , and involves the attack by **nucleophile** on the R_3C-X which is rate determining step . The kinetics are now **second order** , the rate being proportional to both concentrations .

- SN₂ is Concerted reaction(new bond forming and old bond breaking at same time).

- Both reactants are involved in Rate Determining Step
- is one-step reaction with no intermediate
- Only Back side attack (opposite to leaving group) is possible



- The Nu[⊖] donates an e[⊖] pair to the substrate
- The bond between C and LG breaks, giving both e[⊖] from the bond to LG
- The Nu[⊖] uses its e[⊖] pair to form a new covalent bond with the substrate C
- The LG gains the pair of e[⊖] originally bonded in the substrate

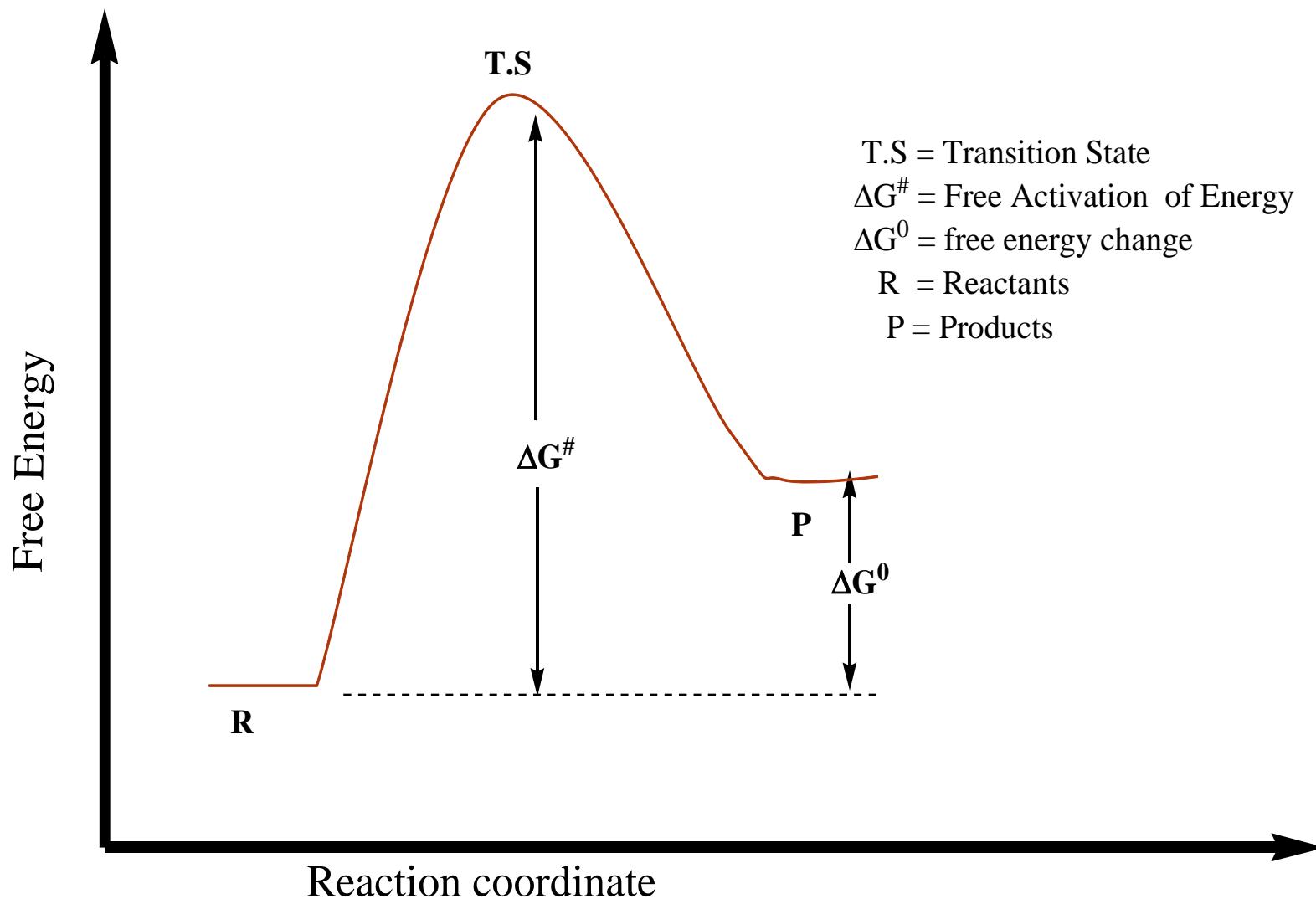
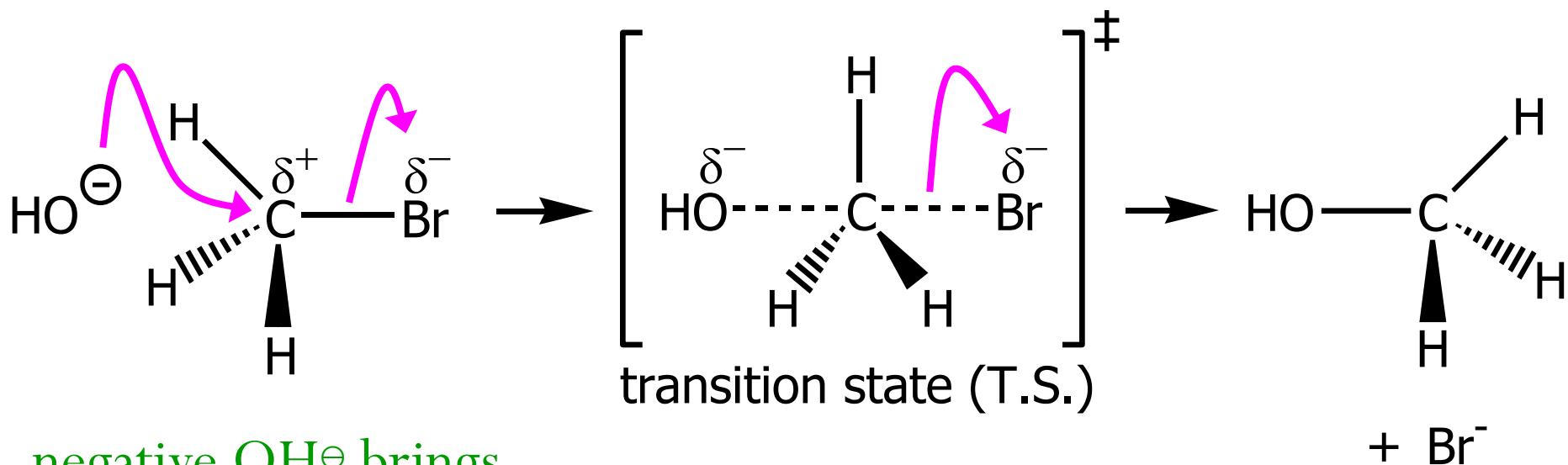


Figure :- Energy diagram for concerted or one step reaction

Mechanism for the S_N2 Reaction



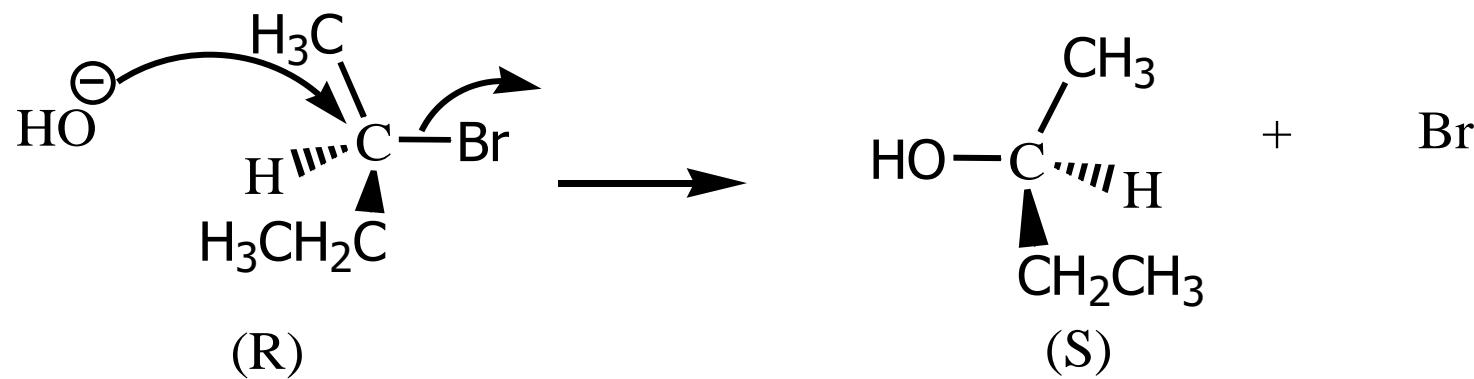
negative OH[⊖] brings
an e[⊖] pair to δ⁺ C;
δ⁻ Br begins to move
away with an e[⊖] pair

O–C bond partially
formed; C–Br bond
partially broken.
Configuration of C
begins to invert

O–C bond
formed; Br[⊖]
departed.
Configuration of
C inverted

Stereochemistry of S_N2 Reactions

- ❖ Since the nucleophile attacks the carbon from back side position(180° to the leaving group) the product will be with 100 % Inversion configuration



Factors that affects S_N1 and S_N2 reactions

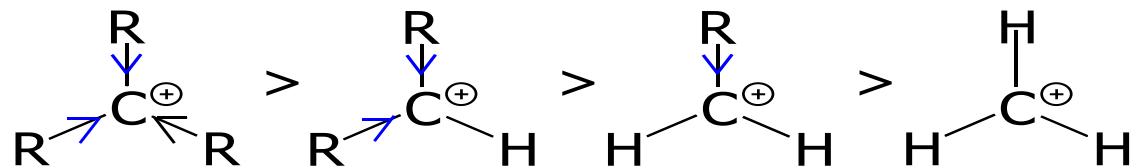
- ❖ There are four basic factor that affects S_N1 and S_N2 reactions
 - 1. The structure of the substrate
 - 2. The concentration and reactivity of the nucleophile
 - 3. The effect of the solvent
 - 4. The nature of the leaving group
- The structure of the substrate:- In S_N1 since an intermediates are formed groups that stabilize the intermediate reacts faster. But in S_N2 the nucleophile needs free environment to approach to the carbon. Due to this compounds with unhindered carbon center reacts faster.
- Methyl > 1° > 2° >> 3° > vinyl or aryl (relative reactivity of S_N2)

DO NOT undergo
S_N2 reactions

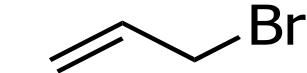
3° > 2° >> 1° > methyl (reactivity order in S_N1)

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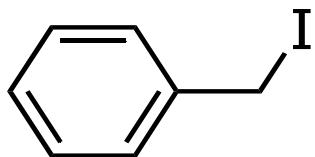
- The more stable the carbocation formed, the faster the S_N1 reaction
- Stability of cations



- Allylic halides and benzylic halides also undergo S_N1 reactions at reasonable rates.

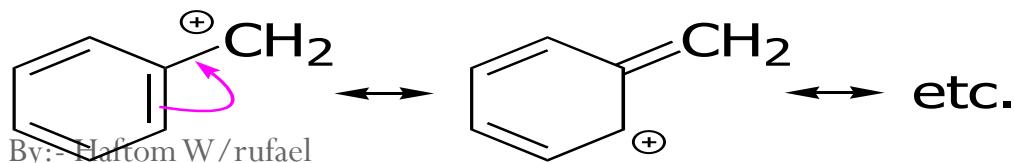
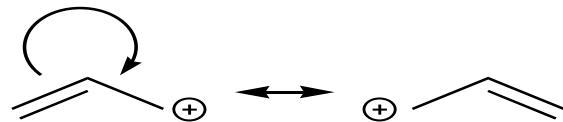


an allylic bromide



a benzylic iodide

- allylic and benzylic cations are stabilized through Resonance.



The Effect of the Concentration & Strength of the Nucleophile

❖ For S_N1 reaction

Recall: **Rate = k[RX]**

- The Nu[⊖] does NOT participate in the r.d.s.
- Rate of S_N1 reactions are NOT affected by either the **concentration** or the **identity** of the Nu[⊖]

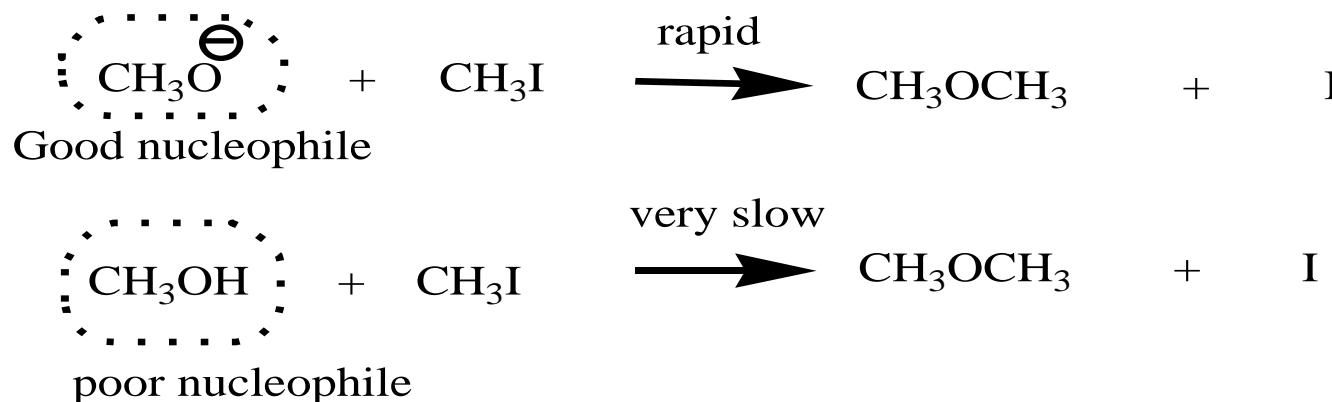
❖ For S_N2 reaction

Recall: **Rate = k[RX][Nu]**

- The rate of S_N2 reactions depends on both the **concentration** and the **identity** of the attacking Nu[⊖]

❖ **Identity** of the Nu[⊖]

- The relative strength of a Nu[⊖] (its **nucleophilicity**) is measured in terms of the relative rate of its S_N2 reaction with a given substrate

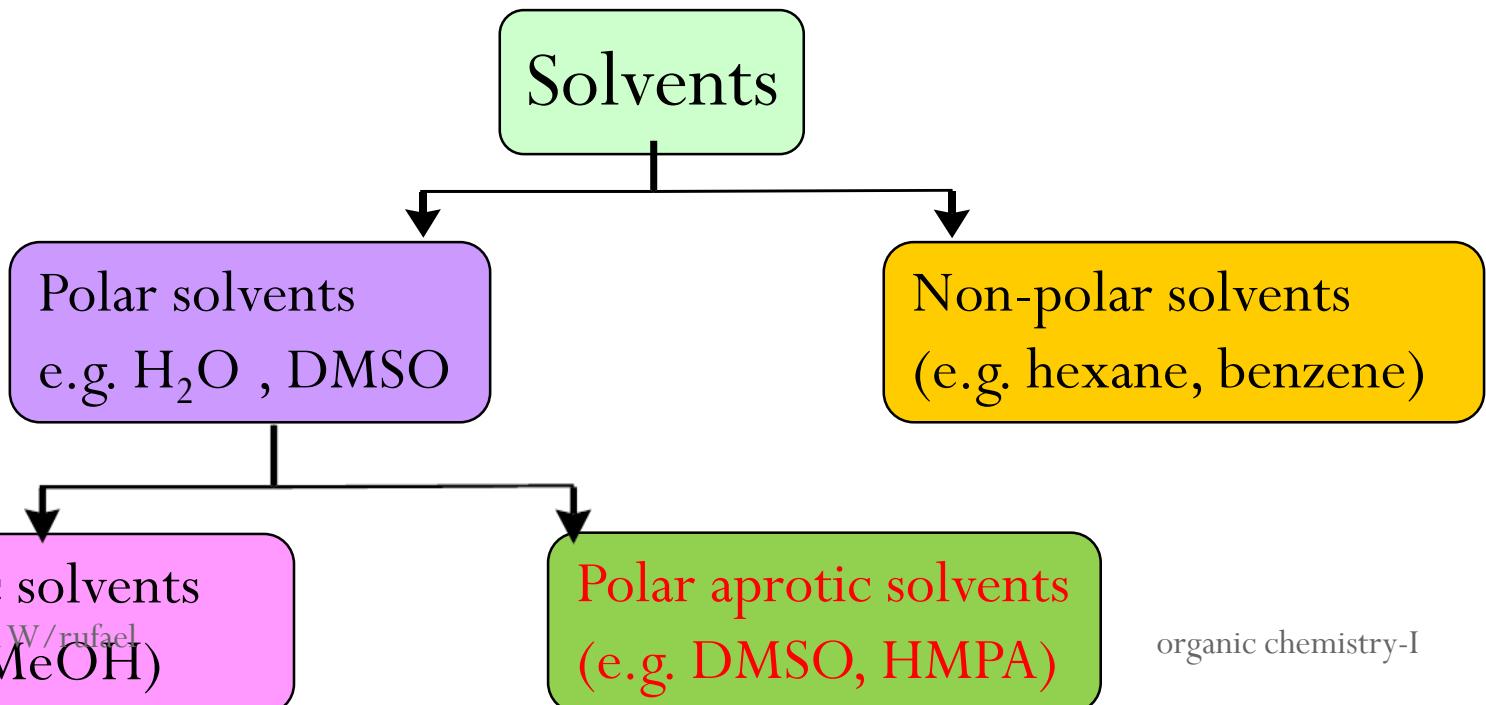


- ❖ The relative strength of a Nu^\ominus can be correlated with 3 structural features
 - A negatively charged Nu^\ominus is always a more reactive Nu^\ominus than its conjugated acid
 - ✓ e.g. HO^\ominus is a better Nu^\ominus than H_2O and RO^\ominus is better than ROH
 - In a group of Nu^\ominus 's in which the nucleophilic atom is the same, nucleophilicities parallel basicities
 - ✓ e.g. for O compounds,
$$\text{RO}^\ominus > \text{HO}^\ominus >> \text{RCO}_2^\ominus > \text{ROH} > \text{H}_2\text{O}$$

- When the nucleophilic atoms are different, then nucleophilicities may not parallel basicities
 - ✓ e.g. in protic solvents HS^\ominus , CN^\ominus , and I^\ominus are all weaker bases than HO^\ominus , yet they are **stronger Nu[⊖]s** than HO^\ominus
- $\text{HS}^\ominus > \text{CN}^\ominus > \text{I}^\ominus > \text{HO}^\ominus$

Solvent Effects on $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}1$ Reaction

- ❖ Solvents are classified as the following



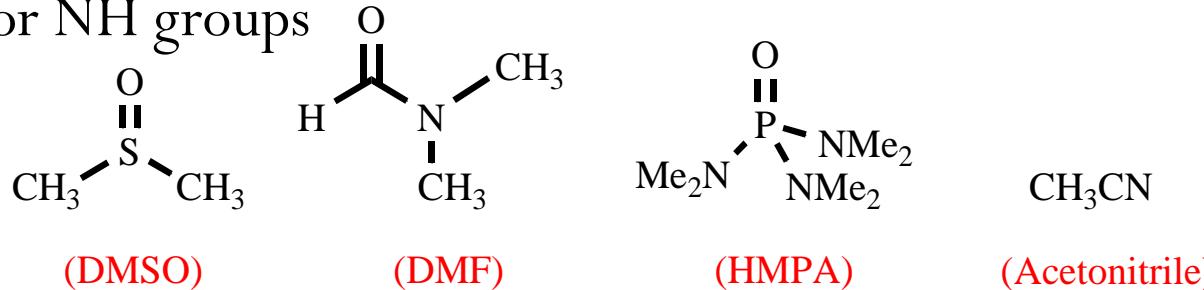
Solvent Effects on S_N2 reaction

❖ S_N2 Reactions in Polar Aprotic Solvents

➤ The best solvents for S_N2 reactions are

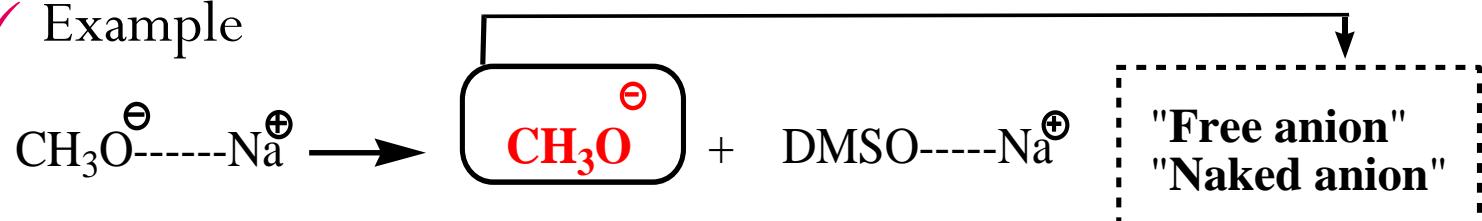
- ✓ **Polar aprotic solvents**, which have strong dipoles but do not have OH or NH groups

- ✓ Examples



➤ Polar aprotic solvents tend to solvate metal cations rather than nucleophilic anions, and this results in “naked” anions of the Nu[⊖] and makes the e[⊖] pair of the Nu[⊖] more available

- ✓ Polar aprotic solvents tend to solvate metal cations rather than nucleophilic anions, and this results in “naked” anions of the Nu^\ominus and makes the e^\ominus pair of the Nu^\ominus more available.
- ✓ Example



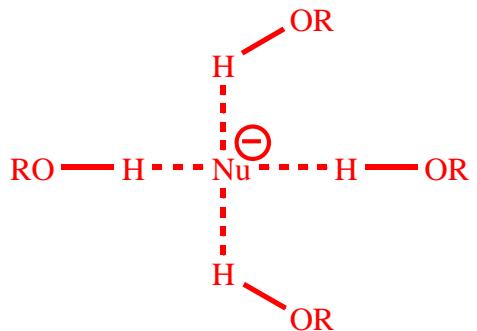
- ✓ Tremendous acceleration in S_N2 reactions with polar aprotic solvent.



Solvent	Relative Rate
MeOH	1
DMF	10^6

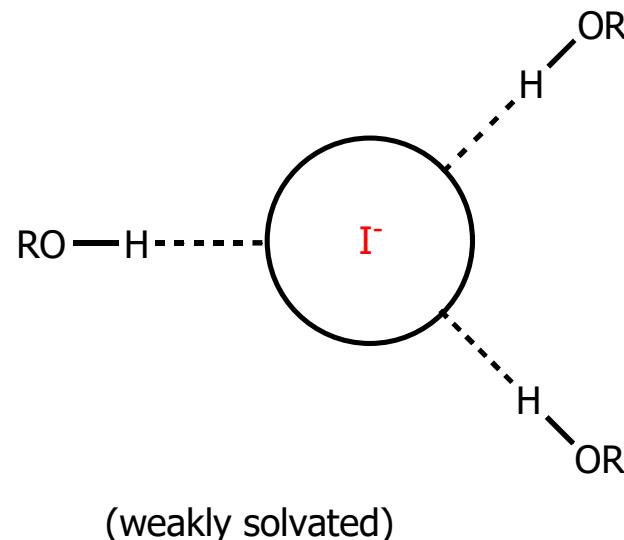
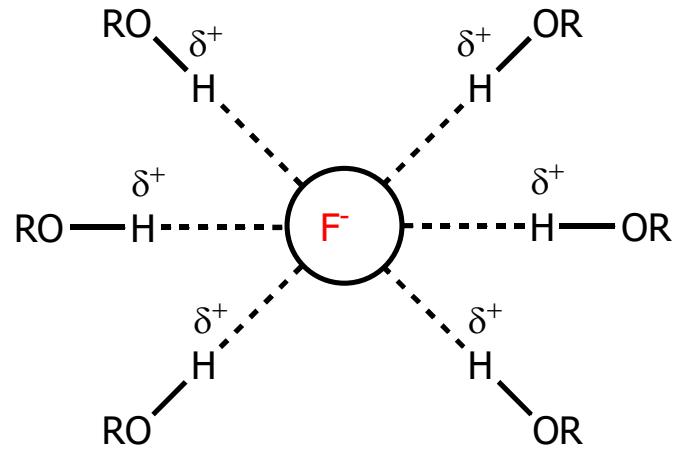
❖ S_N2 Reactions in Polar Protic Solvents

- In **polar protic solvents**, the **Nu^\ominus anion** is **solvated** by the surrounding *protic solvent* which makes the e^\ominus pair of the Nu^\ominus less available and thus less reactive in S_N2 reactions



□ Here **the Nu^\ominus anion** is **solvated** by the surrounding *protic solvent* of alcohol

- Halide Nucleophilicity in Protic Solvents
- $I^\ominus > Br^\ominus > Cl^\ominus > F^\ominus$

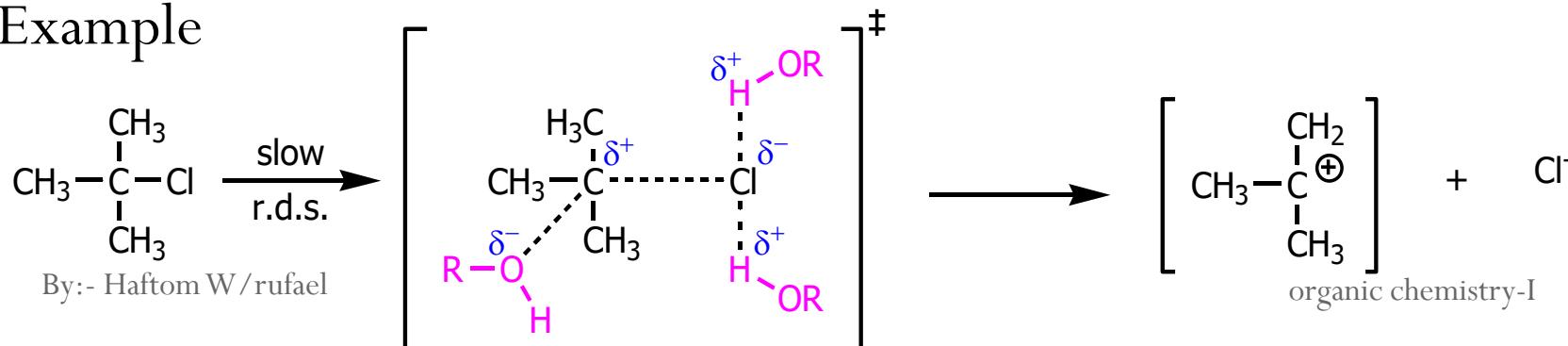


(weakly solvated)

- ❖ Thus, I^\ominus is a stronger Nu^\ominus in protic solvents, as its e^\ominus pair is more available to attack the substrate in the S_N2 reaction.
- ❖ Halide Nucleophilicity in Polar Aprotic Solvents (e.g. in DMSO)
 - 👉 $F^\ominus > Cl^\ominus > Br^\ominus > I^\ominus$
 - 👉 Polar aprotic solvents **do not solvate anions** but **solvate the cations**
 - 👉 The “naked” anions act as the Nu^\ominus
 - 👉 Since F^\ominus is smaller in size and the **charge per surface area is larger** than I^\ominus , the nucleophilicity of F^\ominus in this environment is greater than I^\ominus

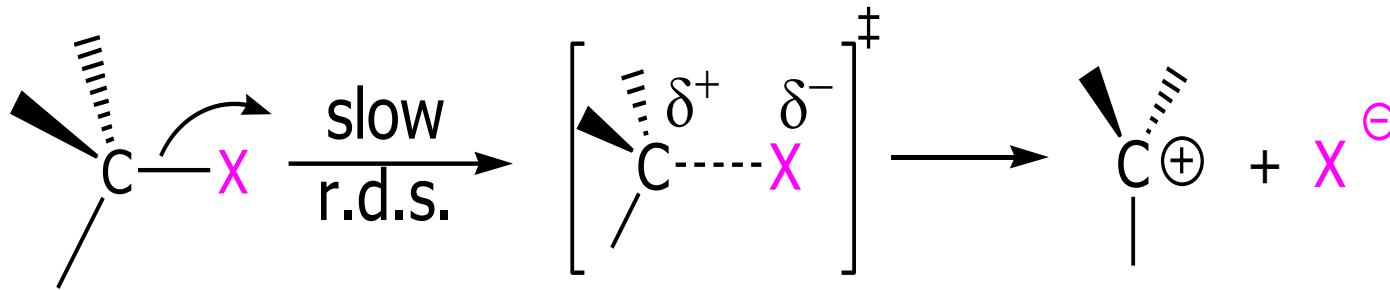
Solvent Effects on S_N1 Reactions: The Ionizing Ability of the Solvent

- ❖ Solvent plays an important role in S_N1 reactions but the reasons are different from those in S_N2 reactions
- ❖ Solvent effects in S_N1 reactions are due largely to stabilization or destabilization of the transition state.
- ❖ Polar protic solvents stabilize the development of the polar transition state and thus accelerate this rate-determining step (r.d.s) but polar aprotic solvent do not contribute anything on the development of transition state
- ❖ Example

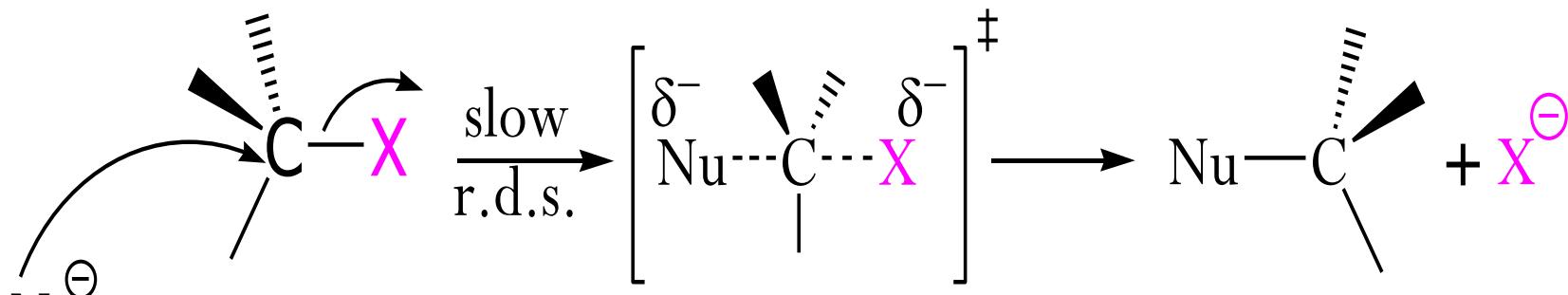


The Nature of the Leaving Group

- A better leaving group increases the rate of both S_N1 and S_N2 reactions.
- **S_N1 Reaction:**



- **S_N2 Reaction:**



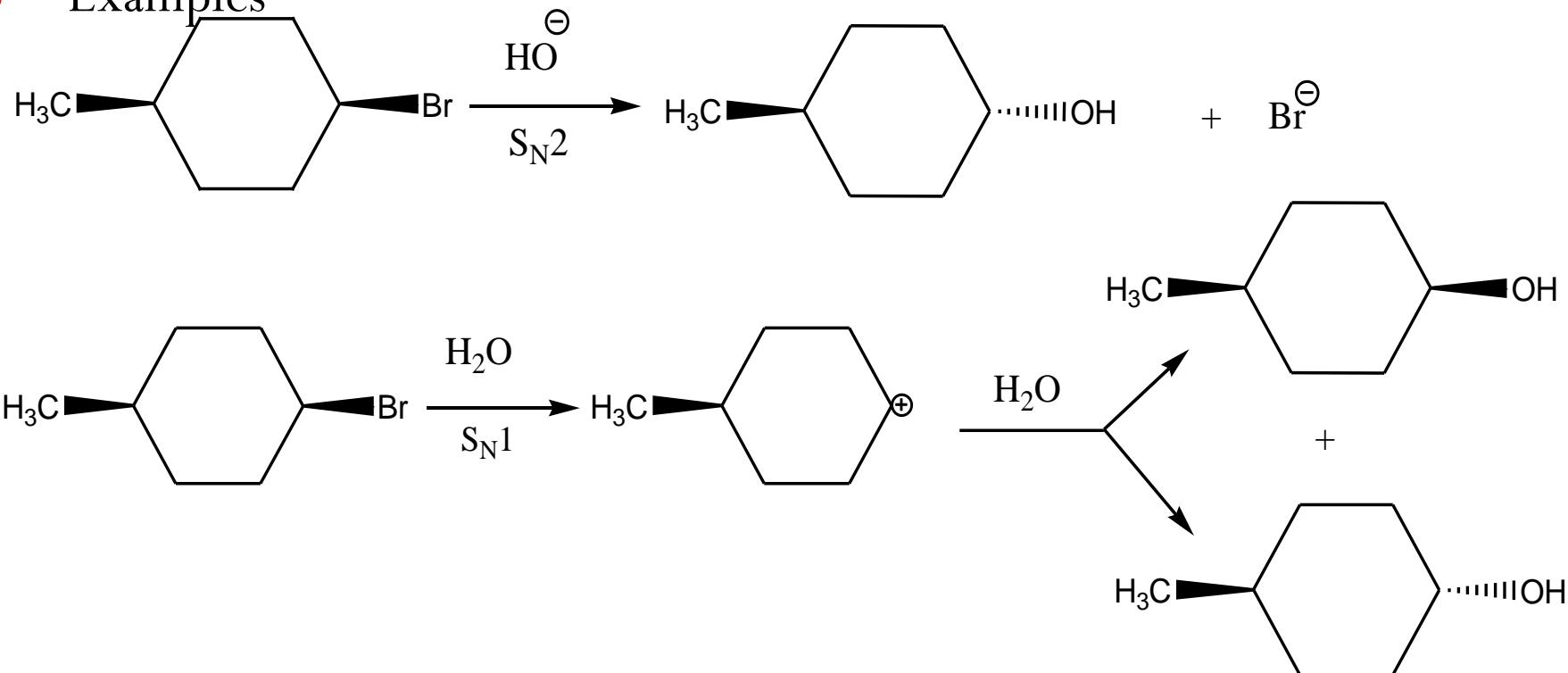
	SN1	SN2
Mechanism	2 or more steps involving carbocation intermediate	1 step bimolecular process
Kinetics	First order in substrate	Second order, first in substrate and nucleophile
Substrate Dependence	Those substrates that form stable carbocations. 3° , allylic, benzylic	Those substrates that are uncluttered at the reaction site: 1° , 2° . Good nucleophiles.
Stereochem	Racemization.	Stereospecific inversion.
Importance of Base/nucleophile	Not involved in RDS, but less basic form of nucleophile .	Reactivity of nucleophile is important since it is involved in RDS.
Importance of Leaving group	Involved in RDS so is important.	Involved in RDS so is important.
Solvent	Polar protic best	Polar aprotic best By: Haftom W/rufael

Application of substitution reaction

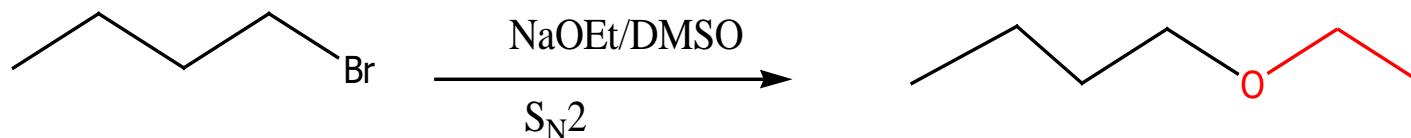
I. Alcohols

- Depending on the substrate and nucleophile alcohols are prepared by S_N1 and S_N2

- Examples

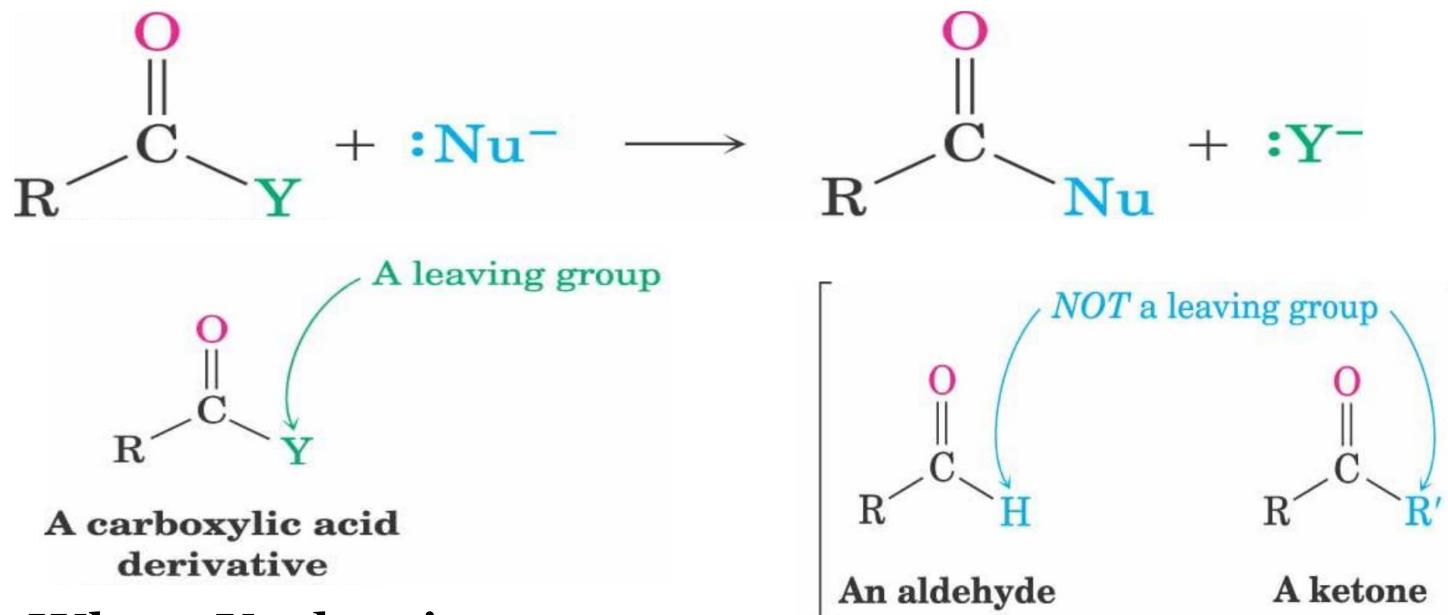


II. Ethers



III. Carboxylic acids

- ☞ Carboxylic acids are prepared by nucleophilic substitution reaction from its derivatives.
- ☞ Carboxylic acid derivatives have an acyl carbon bonded to a group Y that can leave
- ☞ A tetrahedral intermediate is formed and the leaving group is expelled to generate a new carbonyl compound, leading to substitution

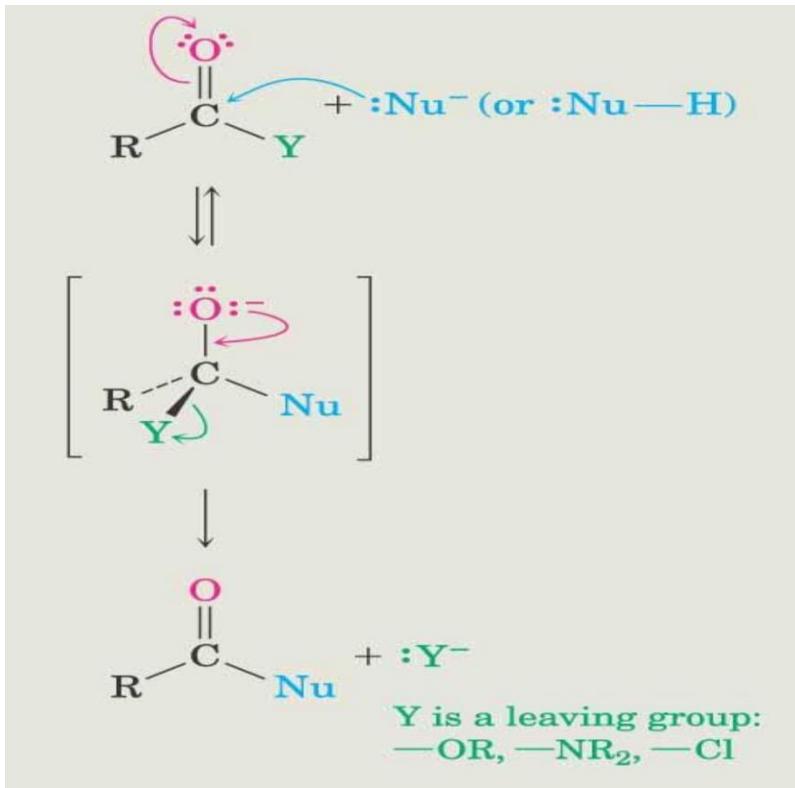


○ Where Y = leaving group

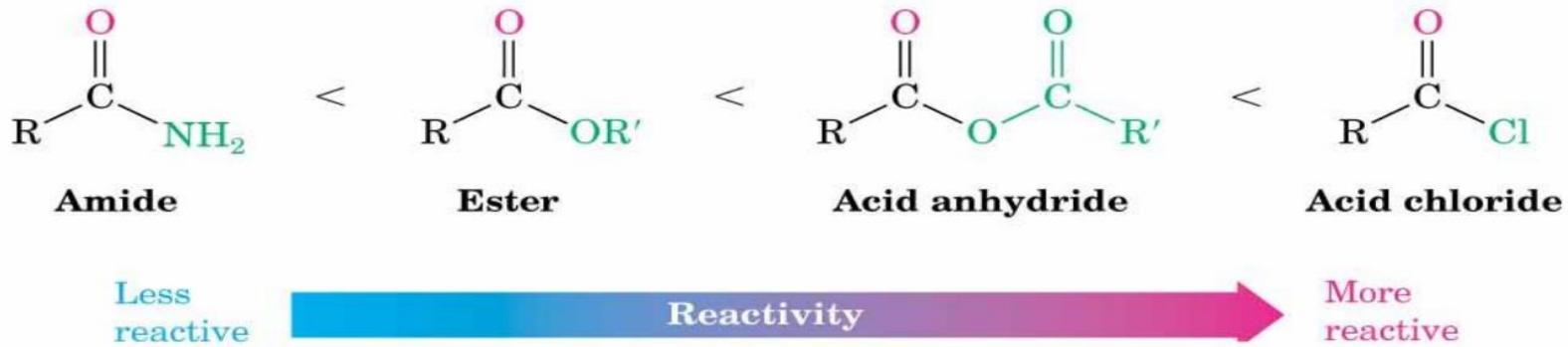
$$Y = OR, NR_2, Cl \dots$$

- This reaction is called **nucleophilic acyl substitution reaction**
- Step-1: addition of a nucleophile to the carbonyl group occurs, yielding a tetrahedral intermediate.
- Step -2 :- an electron pair from oxygen displaces the leaving group (Y) , generating a new carbonyl compound as a product.

- Mechanism

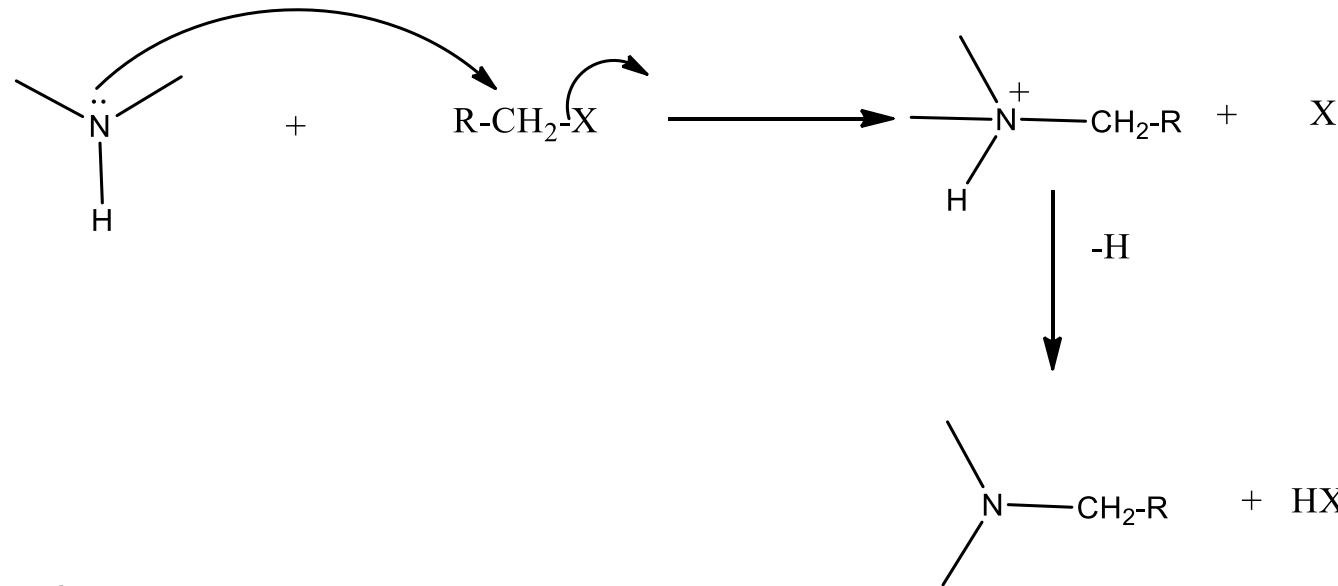


- Nucleophiles react more readily with unhindered carbonyl groups
- More electrophilic carbonyl groups are more reactive to addition (acyl halides are most reactive, amides are least)
- The intermediate with the best leaving group decomposes fastest

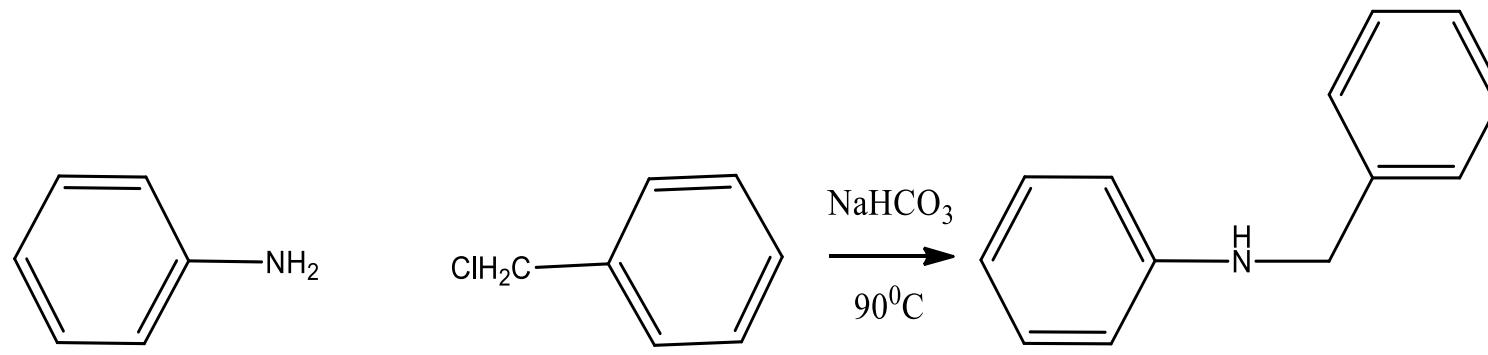


IV. Amines

- Amines are prepared by SN1 and SN2 reaction mechanisms.

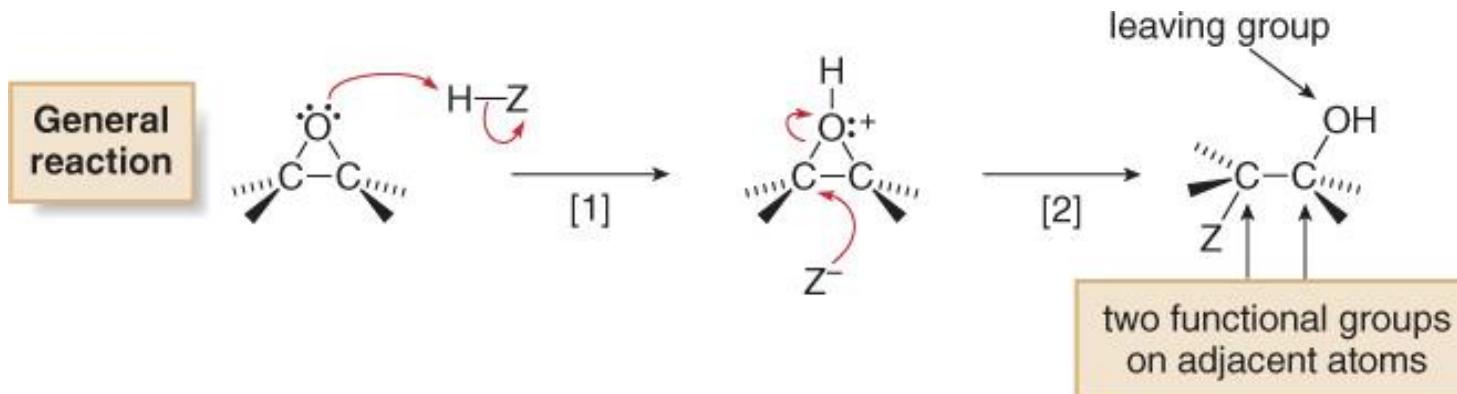


- Example

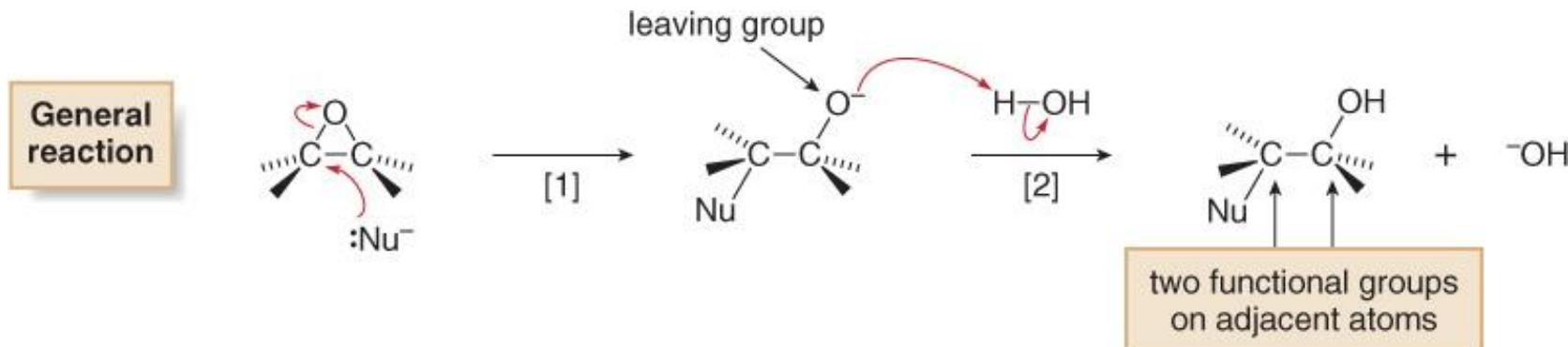


V. Epoxide Ring opening

- The reaction occurs readily with strong nucleophiles and with acids like HZ, where Z is a nucleophilic atom.

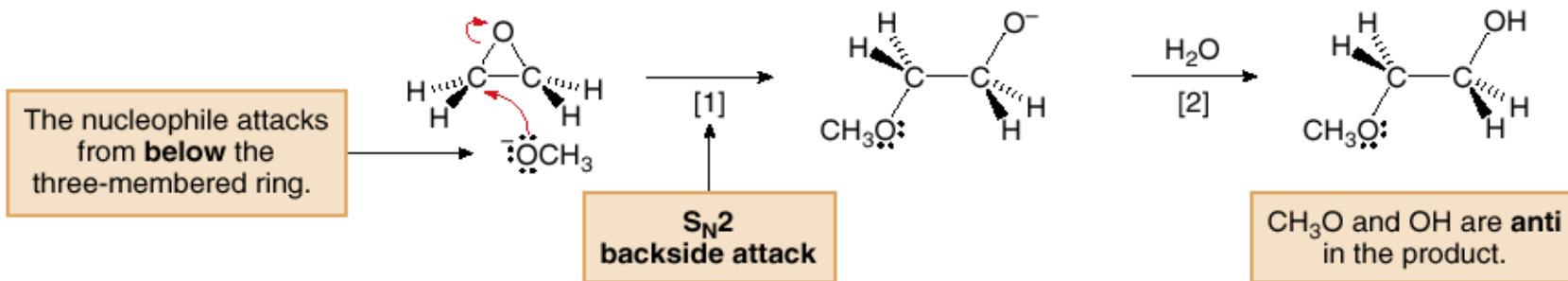


- all strong nucleophiles open an epoxide ring by a two-step reaction sequence:

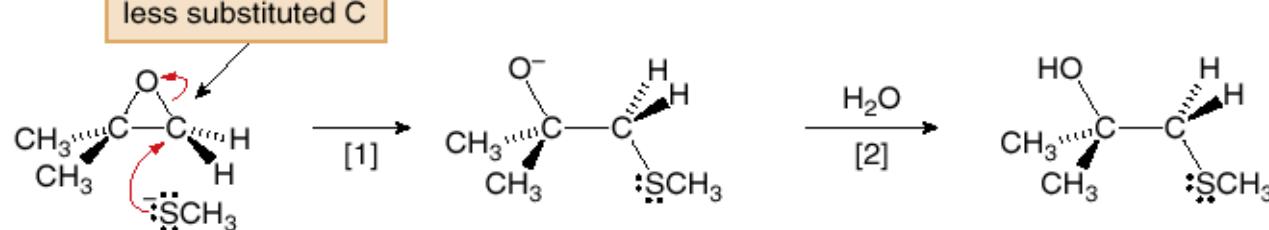


- In step 1, the nucleophile attacks an electron-deficient carbon, thus cleaving the C—O bond and relieving the strain of the three-membered ring.
- In step 2 the alkoxide is protonated with water to generate a neutral product with two functional groups on adjacent atoms.
- Common nucleophiles that open the epoxide ring include ^-OH , ^-OR , ^-CN , ^-SR and NH_3 . With these strong nucleophiles, the reaction occurs by an S_N2 mechanism.

- The nucleophile opens the epoxide ring from the back side.

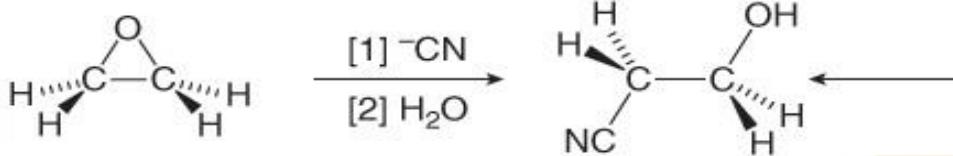


- In an unsymmetrical epoxide, the nucleophile attacks at the less substituted carbon atom.



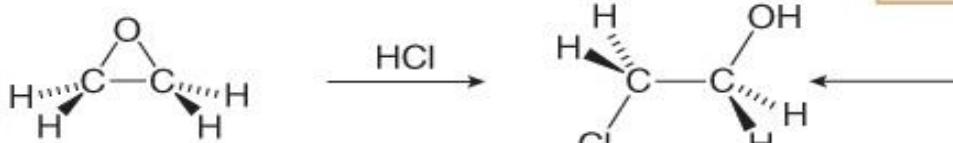
- General reaction mechanism of ring opening

Reaction with a strong nucleophile



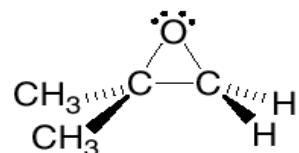
The nucleophile opens the three-membered ring.

Reaction with HZ

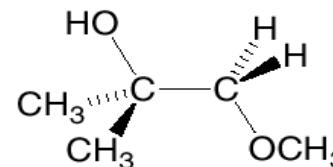


- Ring opening of an epoxide with either a strong nucleophile or an acid HZ is regioselective because one constitutional isomer is the major or exclusive product.
- Note that the site selectivity of these two reactions is exactly opposite.

With a strong nucleophile:



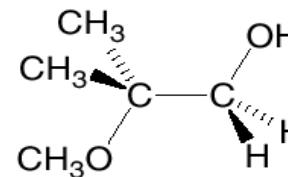
[1] -OCH_3
[2] H_2O



CH_3O ends up on the **less substituted C.**

With acid:

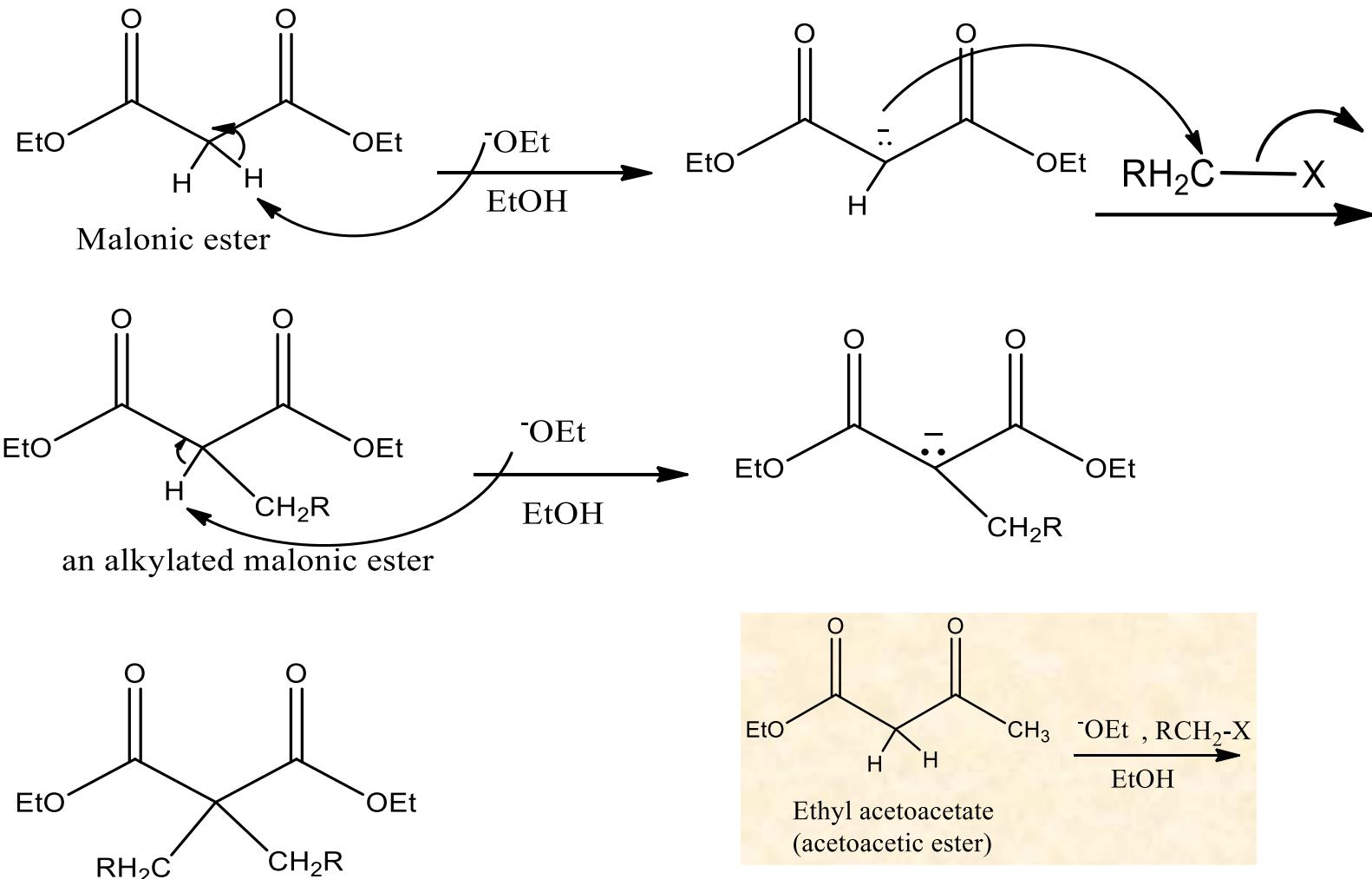
CH_3OH
 H_2SO_4



CH_3O ends up on the **more substituted C.**

- With a strong nucleophile, $:\text{Nu}^-$ attacks at the less substituted carbon.
- With an acid HZ, the nucleophile attacks at the more substituted carbon.

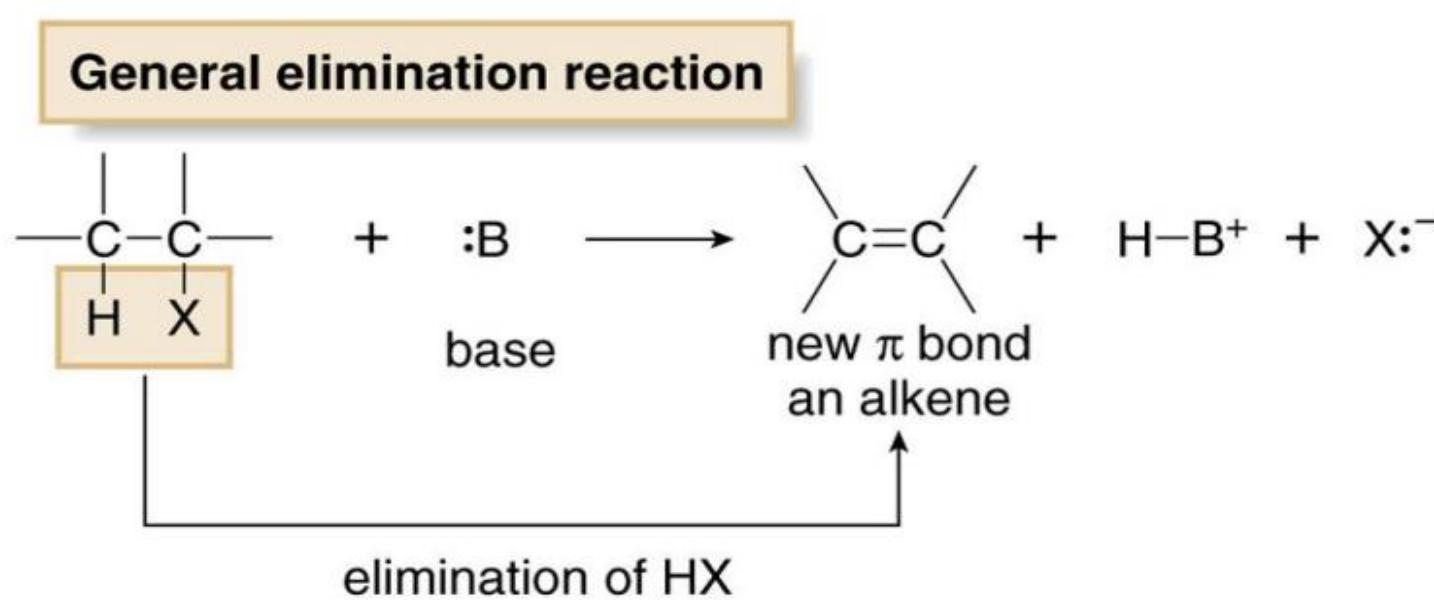
VI. Reactions of malonic ester and acetoacetic ester



Question :- complete the reaction between acetoacetic ester ethoxide anion alkyl halide in the presence of ethanol

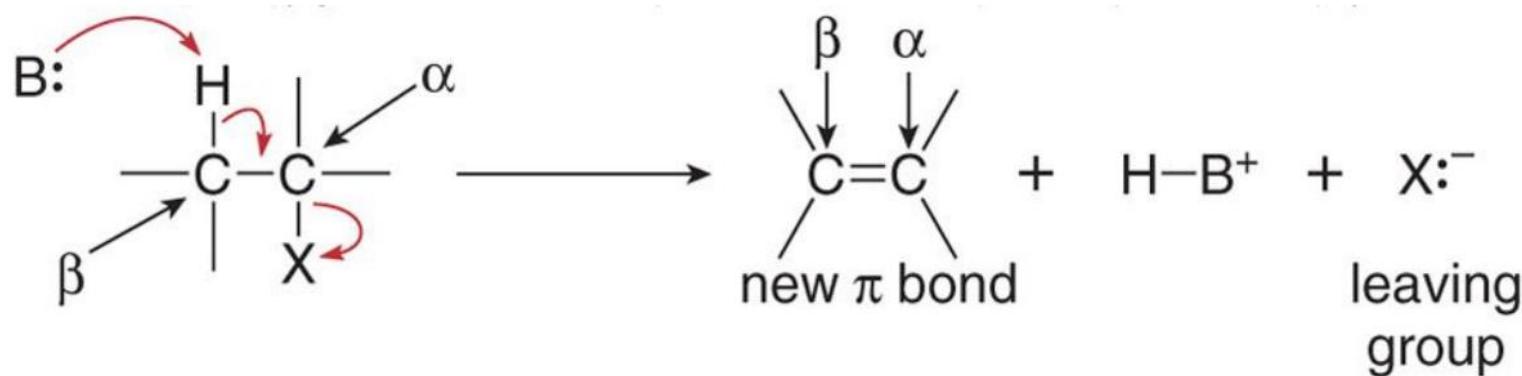
4.2 Elimination reactions

- ☞ **Elimination reactions** involve the loss of elements from the starting material to form a new π bond in the product.



- ☞ When X is leaving group

☞ General Mechanism for elimination reaction



- ☞ Base removes a proton from the β -carbon atom, while the halogen atom leaves from the α -carbon resulting in the formation of a π -bond. Such eliminations are also called β -elimination reactions
- ☞ But this mechanism depends on the type of base

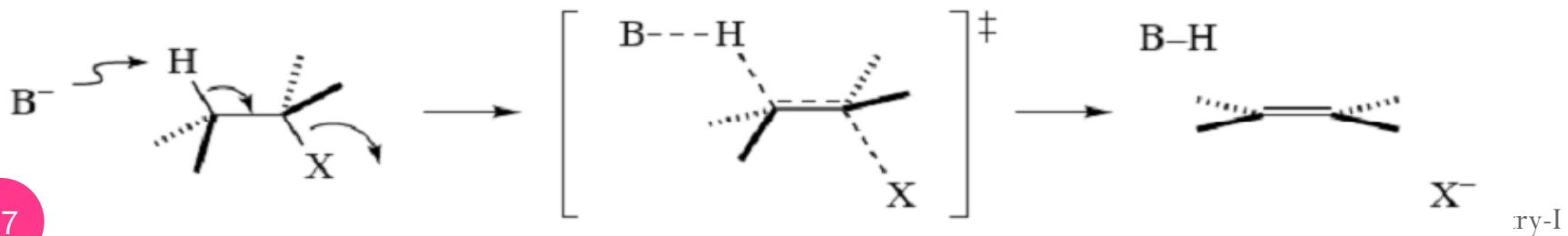
Mechanisms of Elimination

- 👉 There are two mechanisms of elimination reaction.
- 👉 Those are E2 and E1,E stands for the elimination pathway, and the number describes the kinetics of the reaction either uni-molecular or bimolecular.
 - ✓ E2 mechanism—bimolecular elimination
 - ✓ E1 mechanism—unimolecular elimination
- 👉 The E2 and E1 mechanisms differ in the timing of bond cleavage and bond formation

E2 mechanism

- In the E2 mechanism, a base attacks a H atom bound to C next to the electrophilic Carbon .(B^- here is the base, not boron. The base might or might not be charged).
- As the base forms its bond to H, the electrons in the C–H bond must leave H and find somewhere else to go. They move to form a π bond to the electrophilic Carbon next door.
- The electrophilic Carbon next door, though, has an octet, so at the same time as the π bond forms, the C–X bond must break. In the end, the base has been protonated, X^- has left, and an alkene has been formed.

Transition state



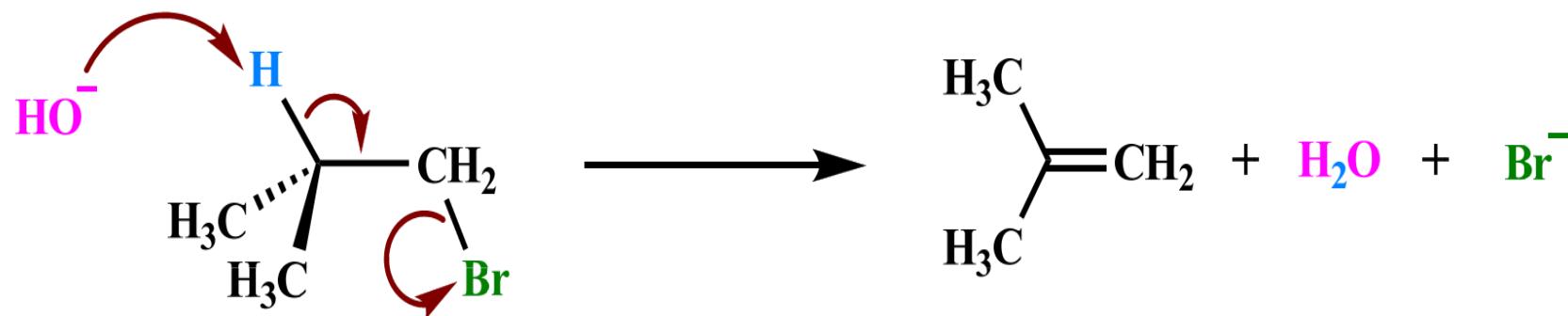
- ☞ This mechanism, like the SN2 mechanism, has no intermediates. The rate-determining step is bimolecular; that is, the rate of the reaction is described by the following equation.

$$\text{rate} = k[B^-][\text{organic substrate}]$$

- ☞ (The bimolecularity of the rate-determining step provides the "2" in "E2").
- ☞ The rate of the reaction is proportional to both the concentration of the base and the concentration of the organic substrate.
- ☞ The E2 mechanism requires that a strong base be available to pull the H off the Carbon adjacent to the electrophilic Carbon. Strong bases cannot exist under acidic conditions.
- ☞ Therefore, the E2 mechanism occurs only under basic conditions.

Cont'd

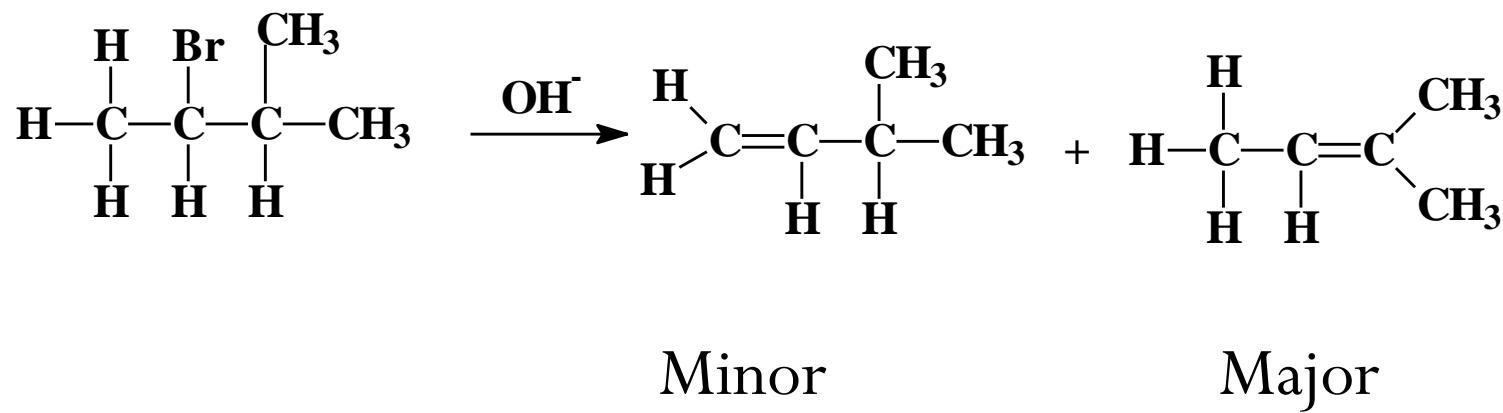
- The most common mechanism for dehydrohalogenation is the E2 mechanism.
- It exhibits second-order kinetics, and both the alkyl halide and the base appear in the rate equation



- $\text{rate} = k[(\text{CH}_3)_3\text{CBr}][\text{HO}^-]$
- The reaction is concerted—all bonds are broken and formed in a single step.

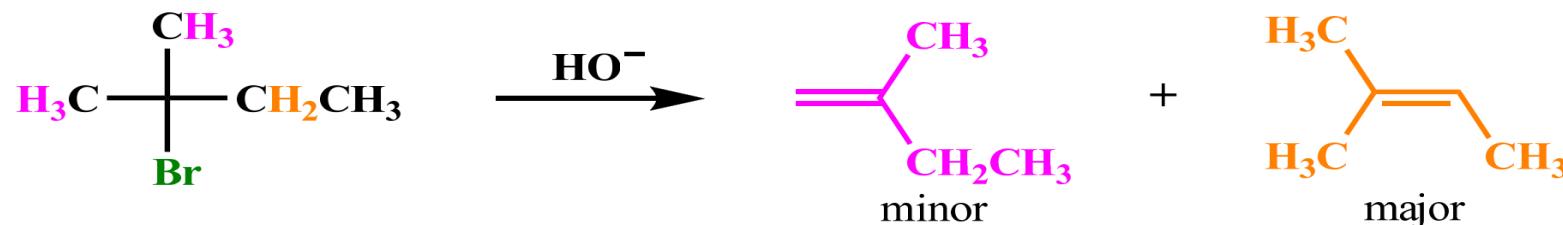
Saytzeff's Rule

- If more than one elimination product is possible, the most-substituted alkene is the major product (most stable).
- $R_2C=CR_2 > R_2C=CHR > RHC=CHR > H_2C=CHR$
tetra > tri > di > mono



Cont'd

- E2 reactions are **regioselective** and favor the formation of Zaitsev products

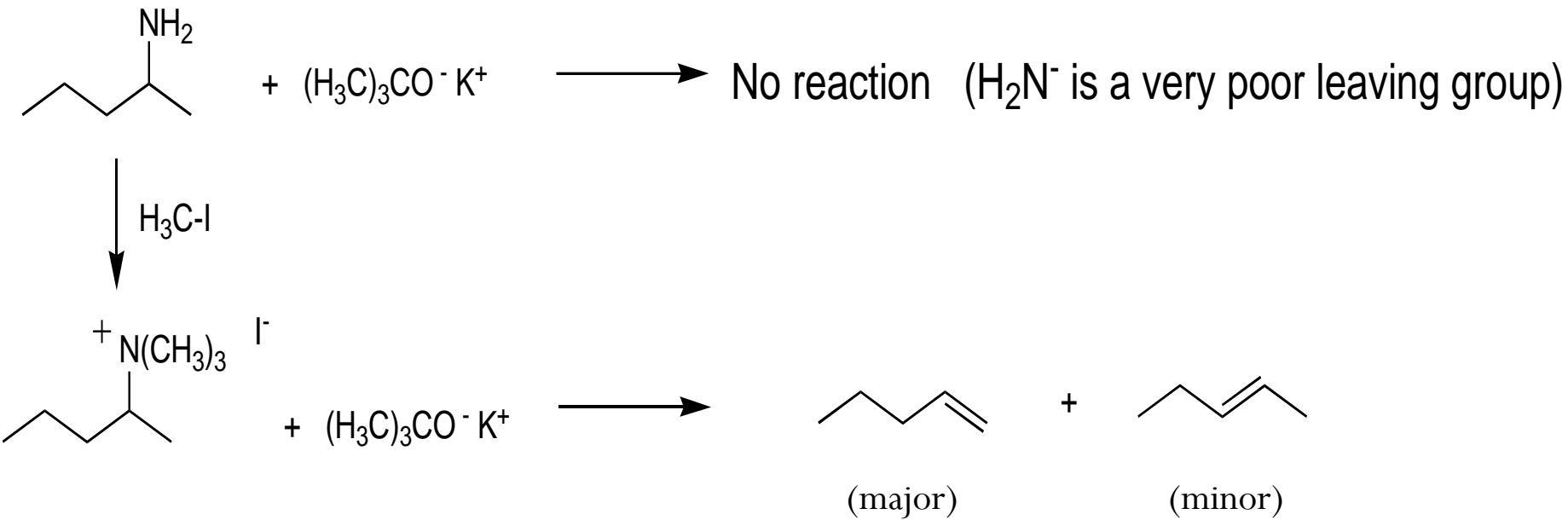


Hoffman rule

- states that the less substituted alkene is the more stable
- Example hoffman elimination
- a quaternary ammonium hydroxide is the reactant and an alkene is the product
- is an anti elimination
- the leaving group is a trialkylamine
- the regioselectivity is opposite to the Zaitsev rule

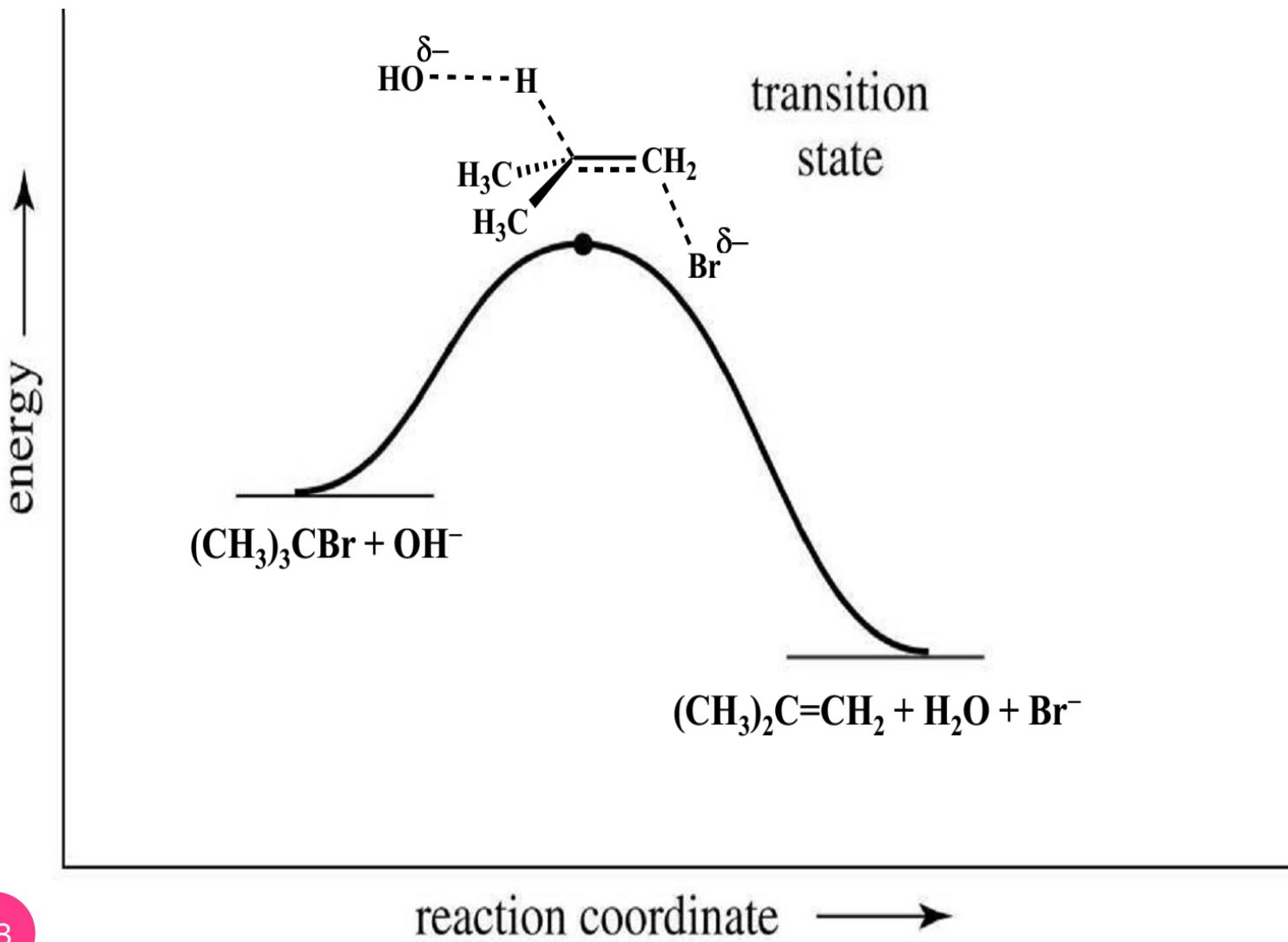
Hoffmann Elimination

- The Hoffmann Elimination. 1° amine react with excess methyl iodide yield quaternary (4°) ammonium salts.
- E2 elimination of the resulting trimethyl ammonium group gives an alkene.

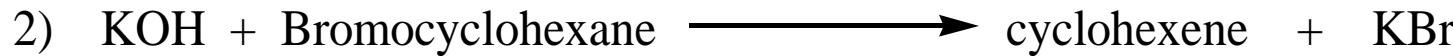
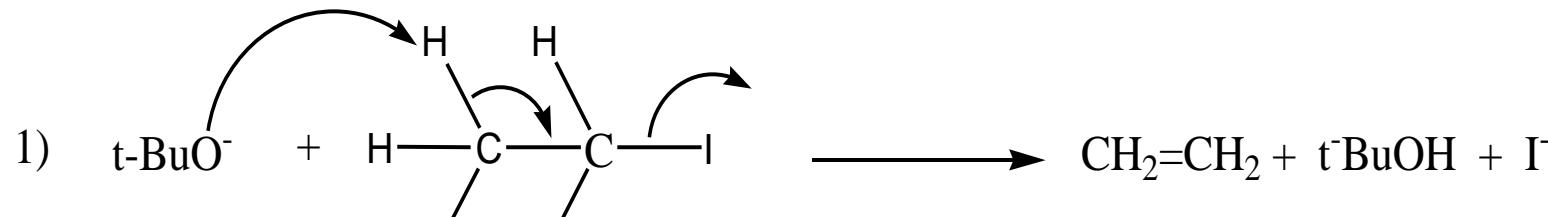


Energy Profile for an E2 Reaction

- E₂ mechanism is a concerted reaction

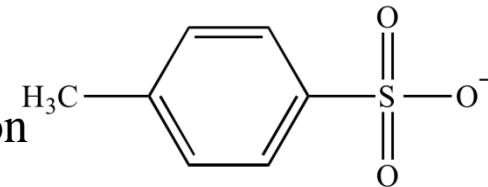


- Any kind of alkyl halide (1° , 2° , 3°) can undergo E2 elimination, as long as there is a C–H bond adjacent to the leaving group.
- CH_3X and PhCH_2X electrophiles cannot undergo E2 elimination.
- Examples of E2 eliminations:



where
 $\text{Et} = \text{Ethyl}$
 $\text{Ph} = \text{phenyl}$

$\text{TsO}^- = \text{p-toluenesulfonate anion}$



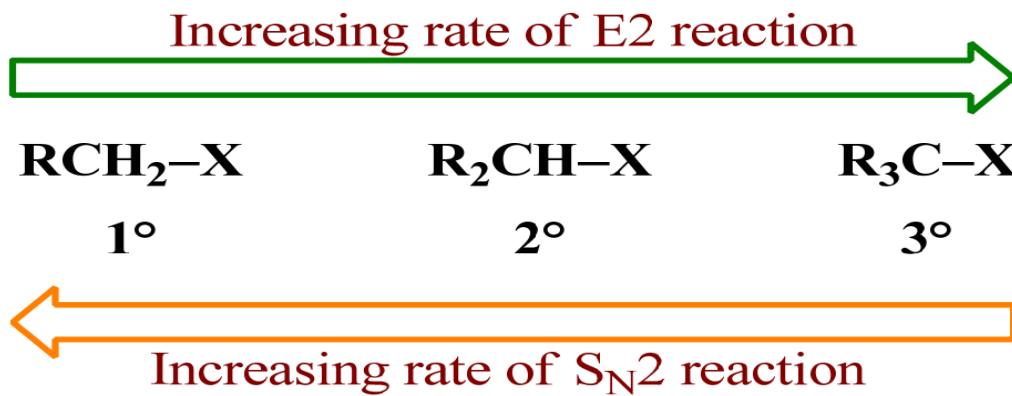
➤ please write a mechanism for example 2 & 3

Factors Affecting the Rate of an E2 Reaction

- There are close parallels between E2 and SN2 mechanisms in how the identity of the base, the leaving group and the solvent affect the rate.
 - ☞ The base appears in the rate equation, so the rate of the E2 reaction increases as the strength of the base increases.
 - ☞ E2 reactions are generally run with strong negatively charged bases like OH⁻, negatively charged bases like OH⁻ and OR⁻.
 - ☞ Polar aprotic solvents increase the rate of E2 reactions. There is a partial breaking of the bond to the leaving group in the transition state. So, the better the leaving group the faster the E2 reaction.
- ☞ Rate of reaction follows the order, R-I > R-Br > R-Cl > R-F

Factors Affecting the Rate of an E2 Reaction

- The S N2 and E2 mechanisms differ in how the R group affects the reaction rate.



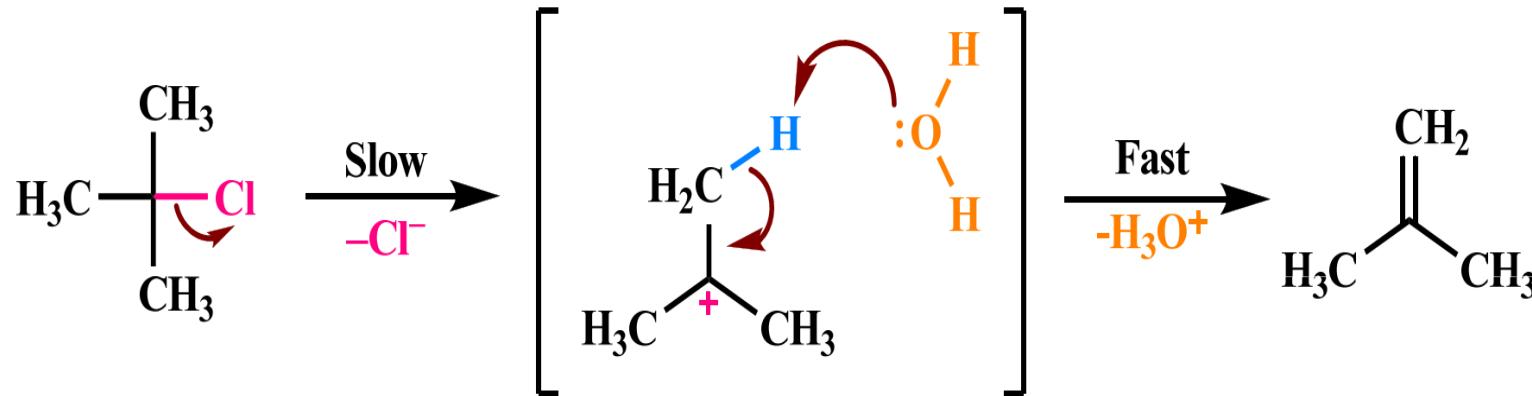
- As the number of R groups on the carbon with the leaving group increases, the rate of the E2 reaction increases.
- The increase in E2 reaction rate with increasing alkyl substitution can be rationalized in terms of transition state stability.
- In the transition state, the double bond is partially formed. Thus, the transition state for a more substituted alkene is lower in energy, reducing the activation energy for the reaction and making the reaction faster.

Characteristics of an E2 Reaction

- Kinetics – Second order
- Mechanism – Single step
- Identity of R group – More substituted halides react faster
 - Rate: $\text{R}_3\text{CX} > \text{R}_2\text{CHX} > \text{RCH}_2\text{X}$
- Strength of the base – Stronger bases favor the reaction
- Leaving group – Better leaving group leads to faster reaction rates
- Type of solvent – Favored by polar aprotic solvents

E1 Mechanism

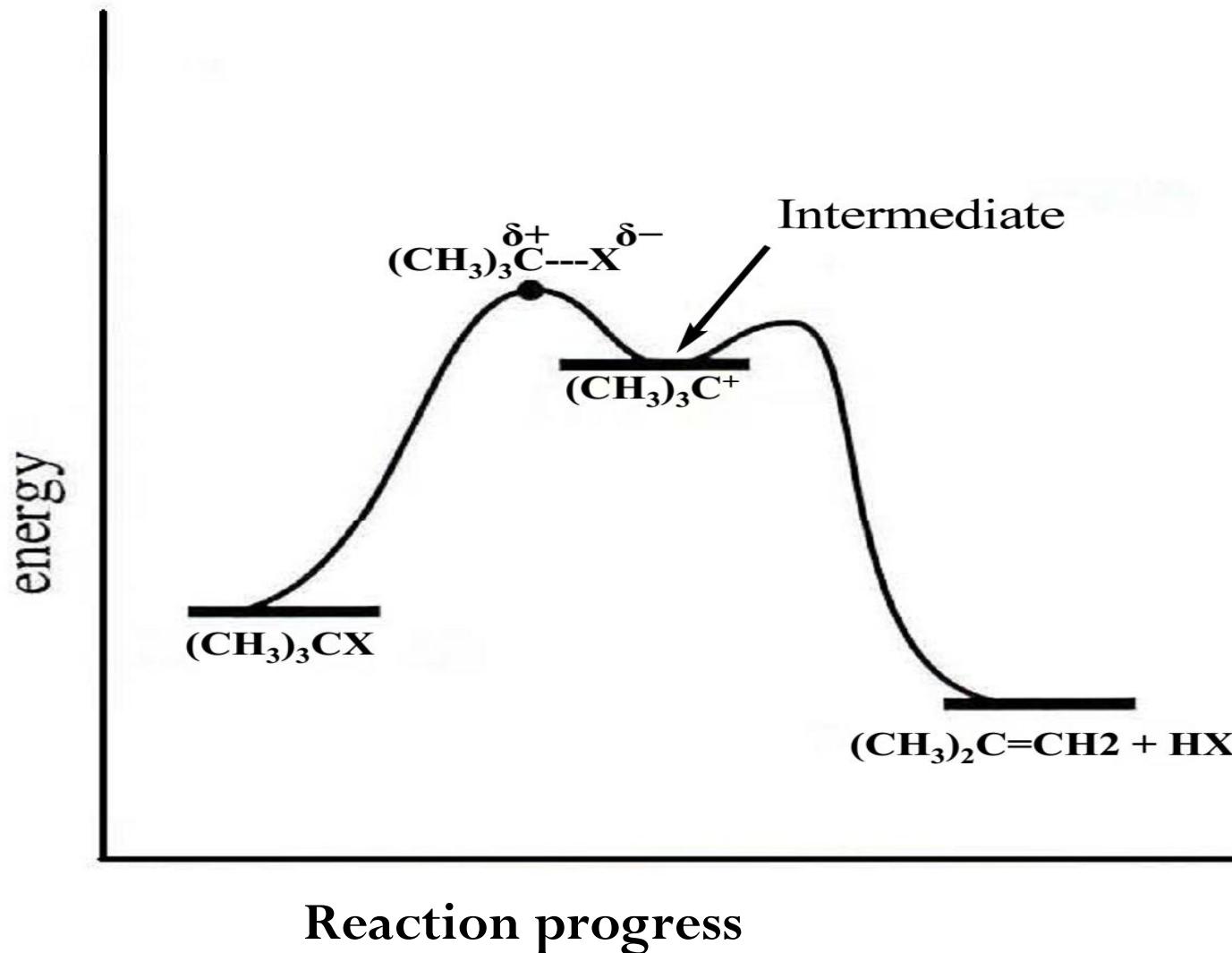
- The E1 reaction proceeds via a two-step mechanism: the bond to the leaving group breaks first before the π bond is formed.
- The slow step is unimolecular, involving only the alkyl halide.
- It exhibits first-order kinetics,
- rate = $k[\text{organic substrate}]$
- Let see the mechanism for the reaction between *tert*-butylchloride and water



rat k[(e = k[(CH₃)₃CCl]

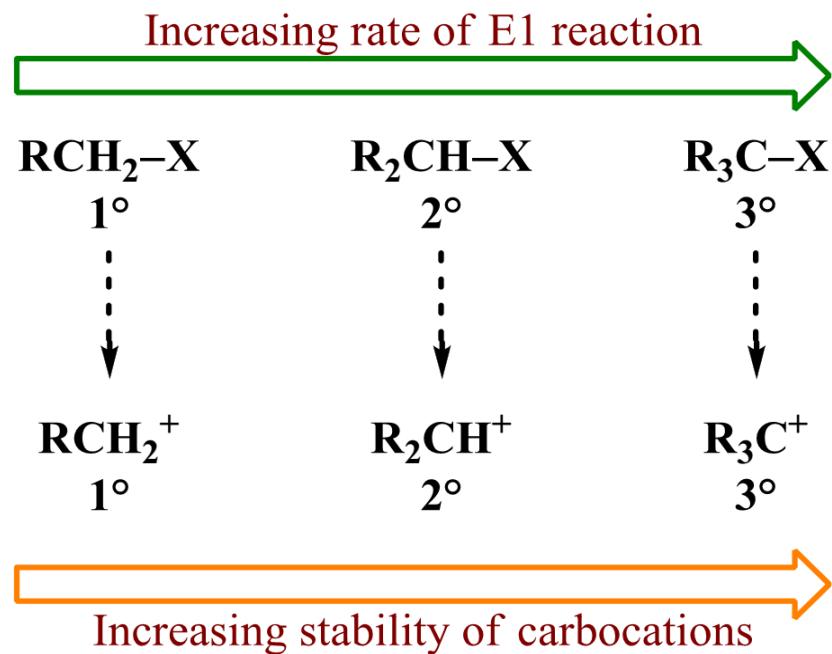
Energy Profile for an E1 Reaction

- It is a multistep reaction mechanism



Factors Affecting the Rate of an E1 Reaction

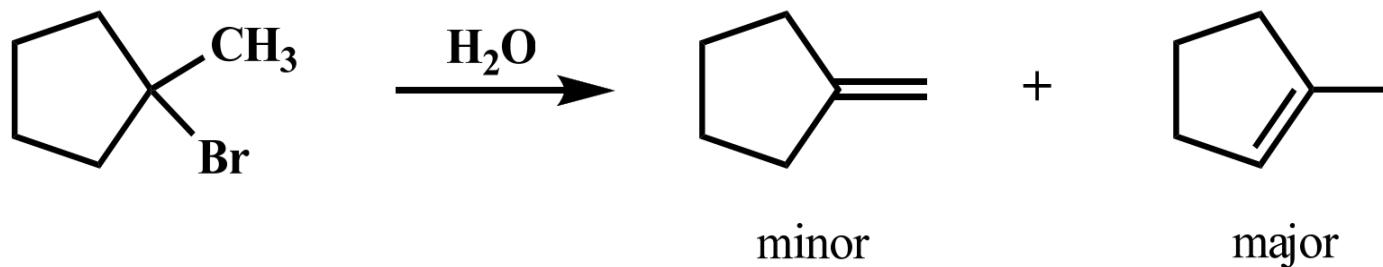
- The rate of an E1 reaction increases as the number of R groups on the carbon with the leaving group increases.



- The strength of the base usually determines whether a reaction follows the E1 or E2 mechanism. Strong bases like OH^- and OR^- favor E2 reactions, whereas weaker bases like H_2O and ROH favor E1 reactions.

cont'd

- E1 reactions also are regioselective and follow Zaitsev rule



Characteristics of an E1 Reaction

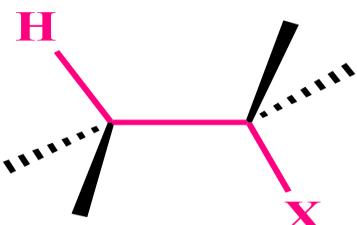
- Kinetics – First order
- Mechanism – Two steps
- Identity of R group :- More substituted halides react faster
:-Rate: $\text{R}_3\text{CX} > \text{R}_2\text{CHX} > \text{RCH}_2\text{X}$
- Strength of the base – Favored by weaker bases such as H_2O and ROH
- Leaving group :-Better leaving group leads to faster reaction rates.
 - Just as in SN1 reactions, the rate determining step
 - involves the C—X bond cleavage
- Type of solvent :- Favored by polar protic solvents, which can stabilize the ionic intermediates

SN1, SN2, E1 or E2

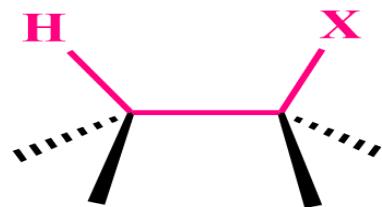
- **3° Alkyl Halides**
 - ☞ With strong bases: E2 elimination occurs
 - ☞ With weak nucleophiles or bases: A mixture of products from SN1 and E1 reactions
- **1° Alkyl Halides**
 - ☞ With strong nucleophiles: Substitution occurs by an SN2 mechanism
 - ☞ With strong sterically hindered bases: Elimination occurs by an E2 mechanism
- **2° Alkyl Halides**
 - ☞ With strong bases and nucleophiles: A mixture of SN2 and E2 reaction products are formed
 - ☞ With strong sterically hindered bases: Elimination occurs by an E2 mechanism
 - ☞ With weak nucleophiles or bases: A mixture of SN1 and E1 products results

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

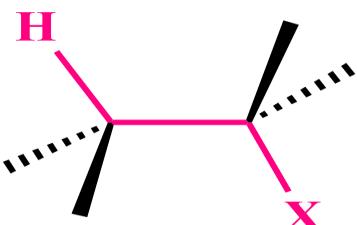


syn periplanar
H and X are on the same side

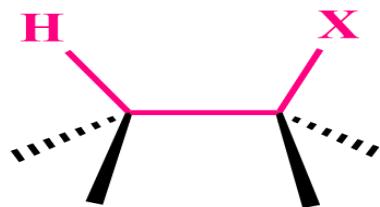
- E2 elimination occurs most often in the anti periplanar geometry. This arrangement allows the molecule to react in the lower energy staggered conformation, and allows the incoming base and leaving group to be further away from each other.
- The anti periplanar geometry also allows direct interaction between the bonding electrons of C—H bond and the anti-bonding orbital of the C—X bond.

Stereochemistry of the E2 Reaction

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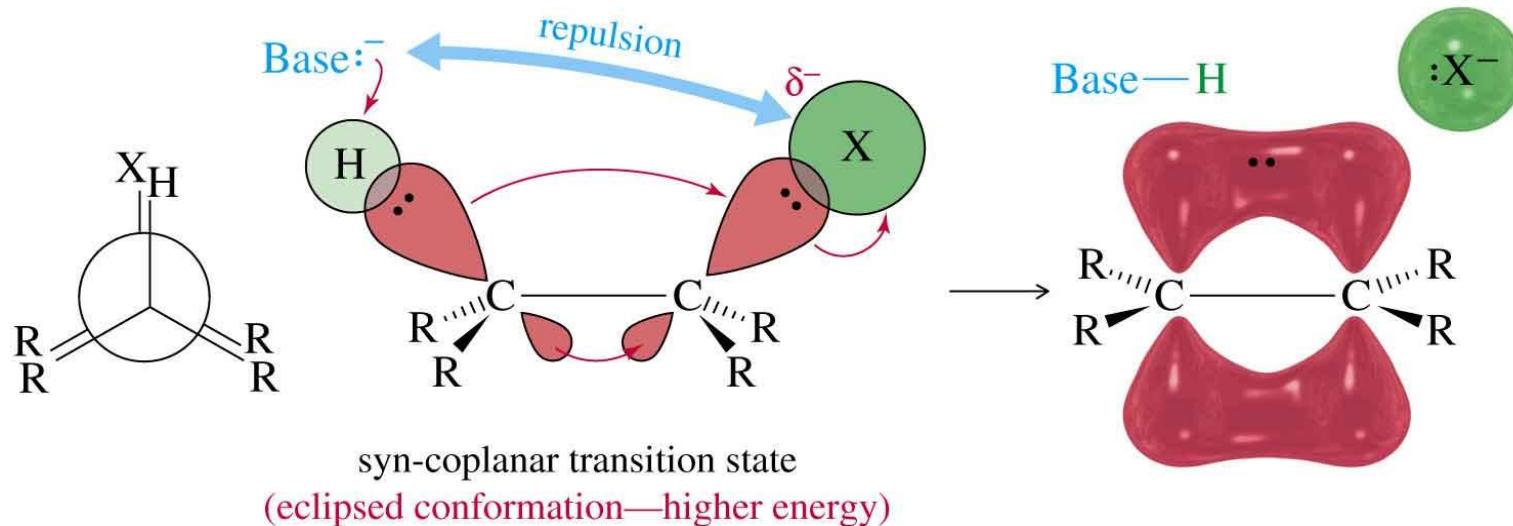
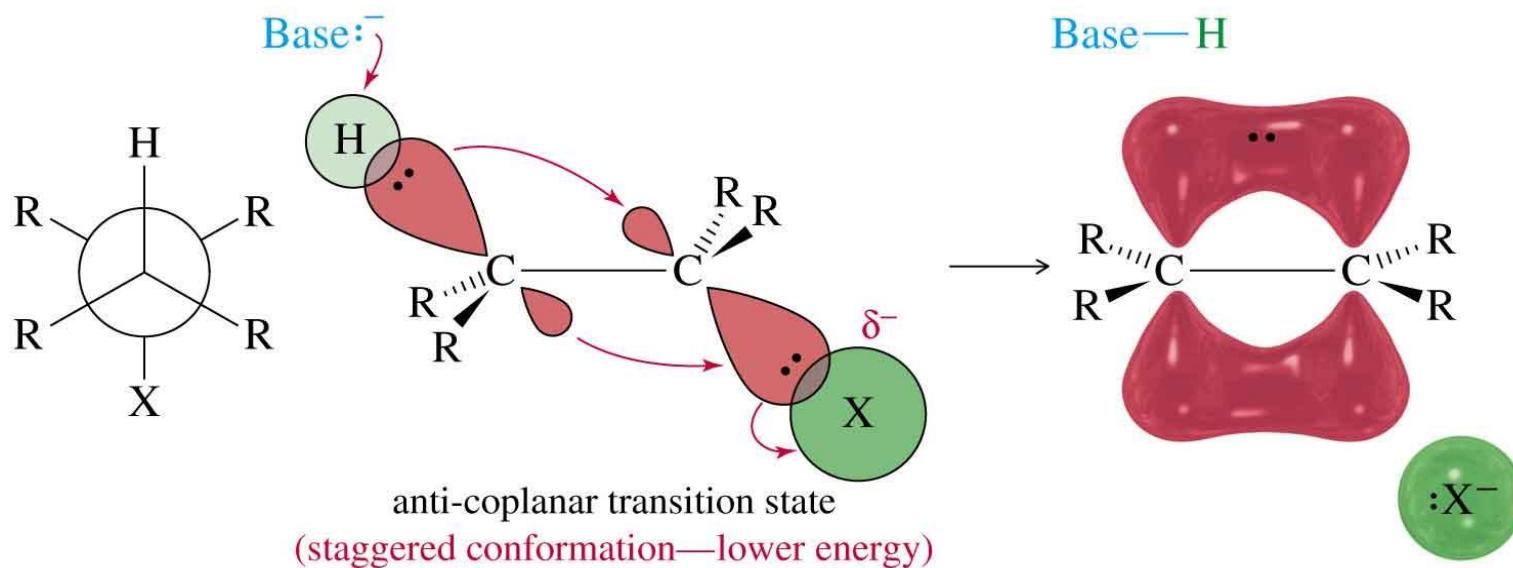
anti periplanar
H and X are on the opposite side



syn periplanar
H and X are on the same side

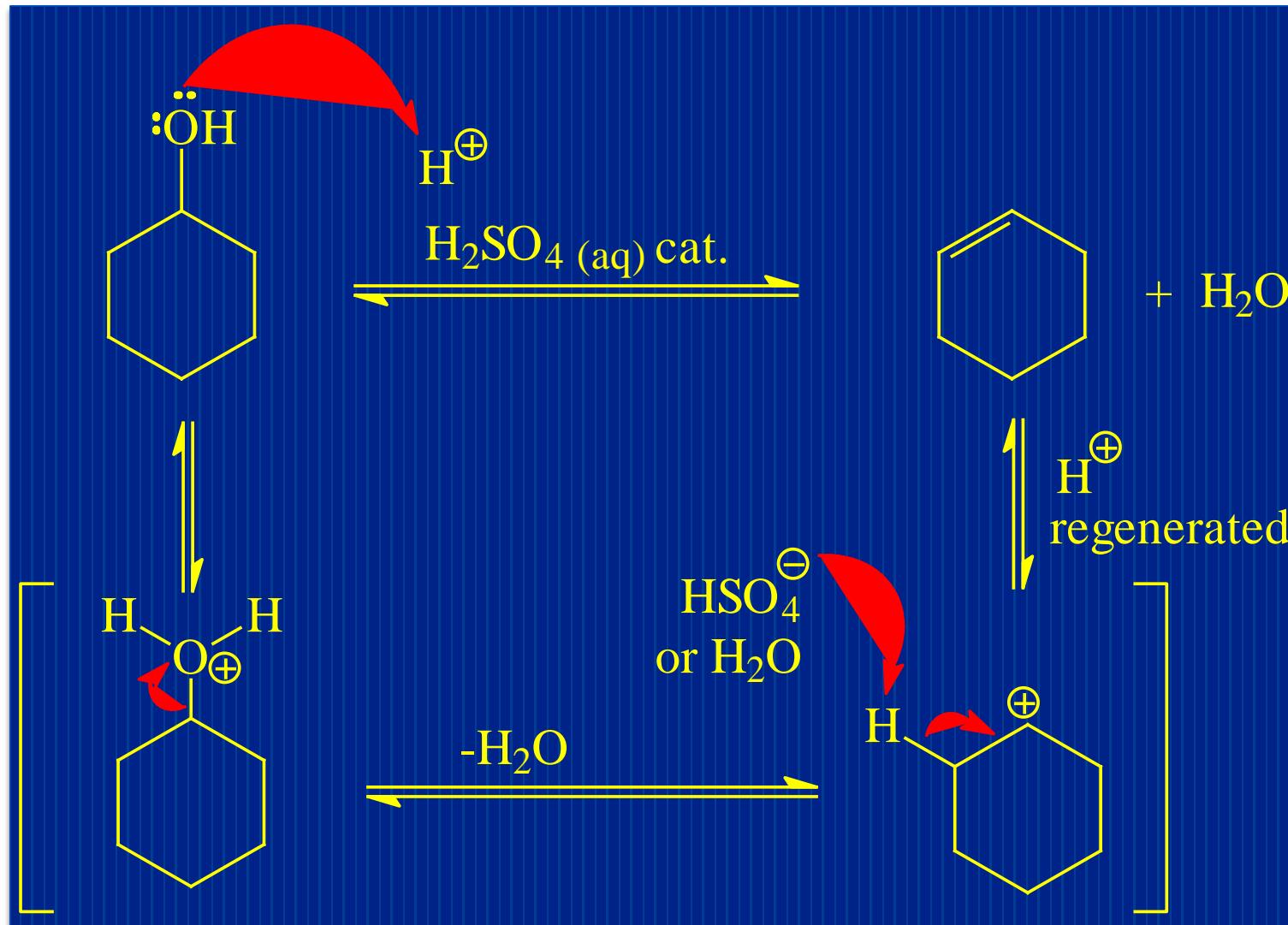
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E2 Stereochemistry



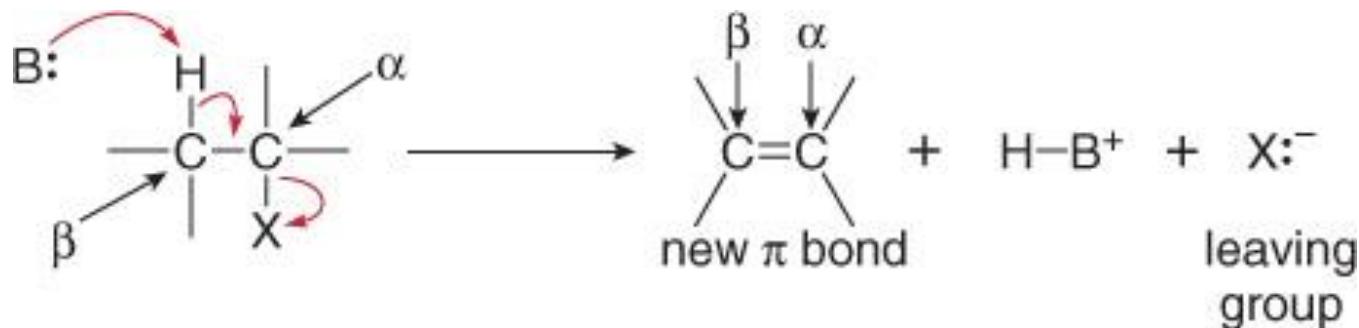
Applications of Elimination Reactions

- Dehydration of Alcohols

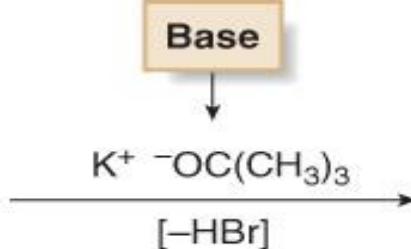
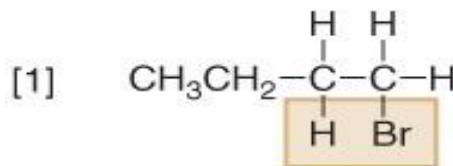


Dehydrohalogenation reaction

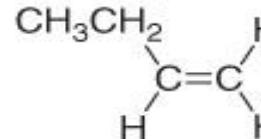
- Removal of the elements HX is called dehydrohalogenation.
- Dehydrohalogenation is an example of β elimination.
- The curved arrow formalism shown below illustrates how four bonds are broken or formed in the process.



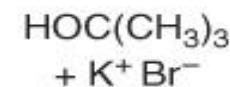
Examples



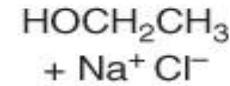
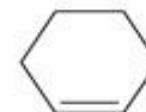
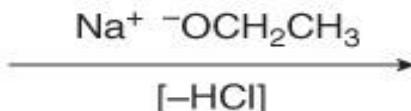
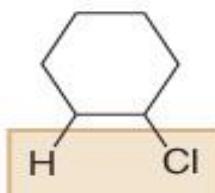
Alkene



By-products

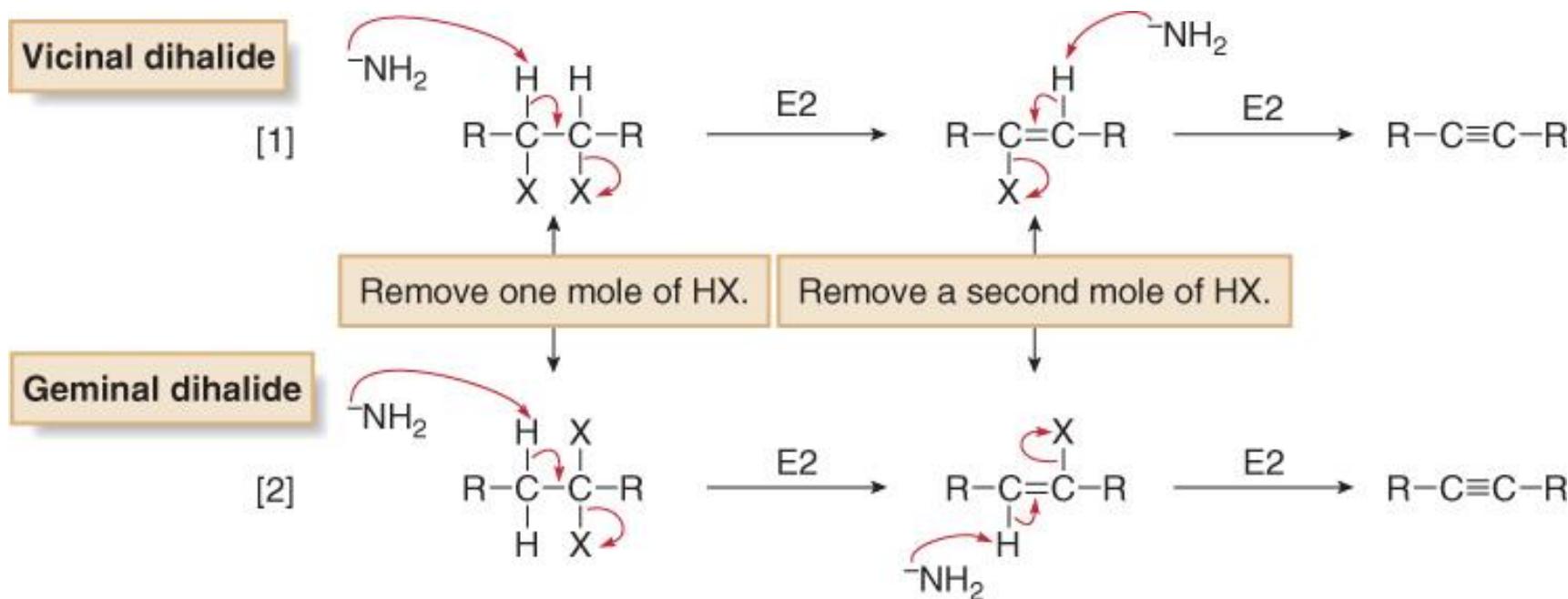


[2]



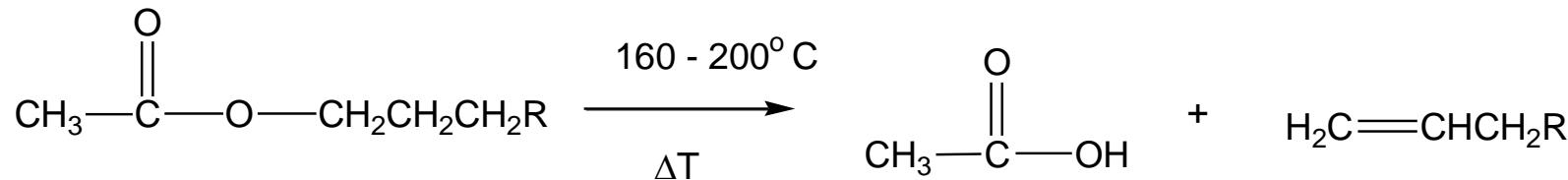
Dehydrohalogenation reaction

- Stronger bases are needed to synthesize alkynes by dehydrohalogenation than are needed to synthesize alkenes.
- The typical base used is -NH_2 (amide), used as the sodium salt of NaNH_2 . $\text{KOC(CH}_3)_3$ can also be used with DMSO as solvent.

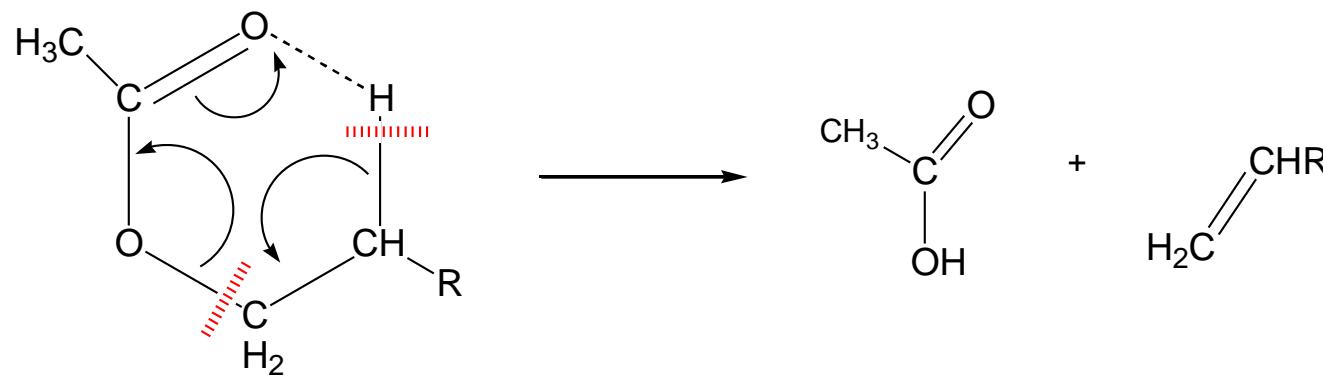


Acetates pyrolysis

- Reactions are characteristic for acetates— Cope elimination



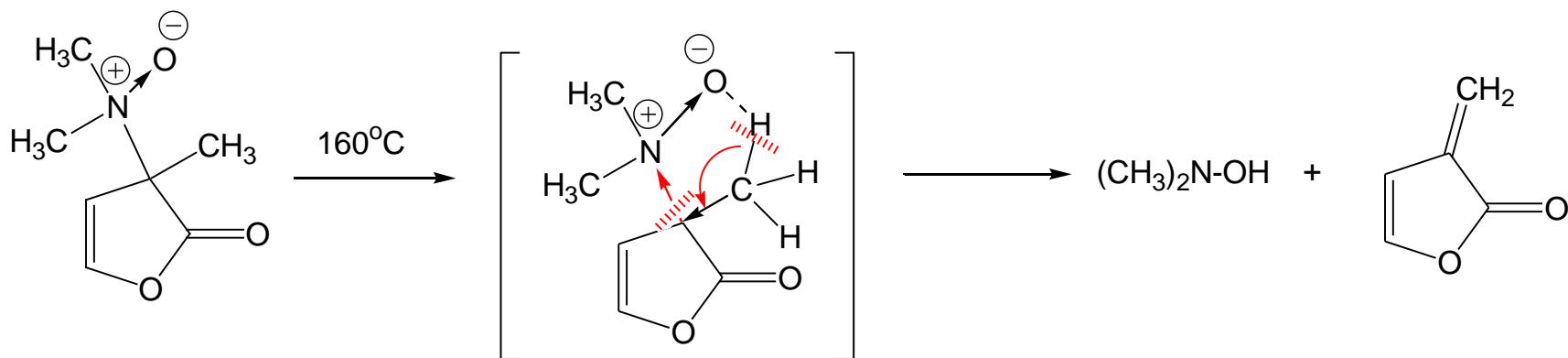
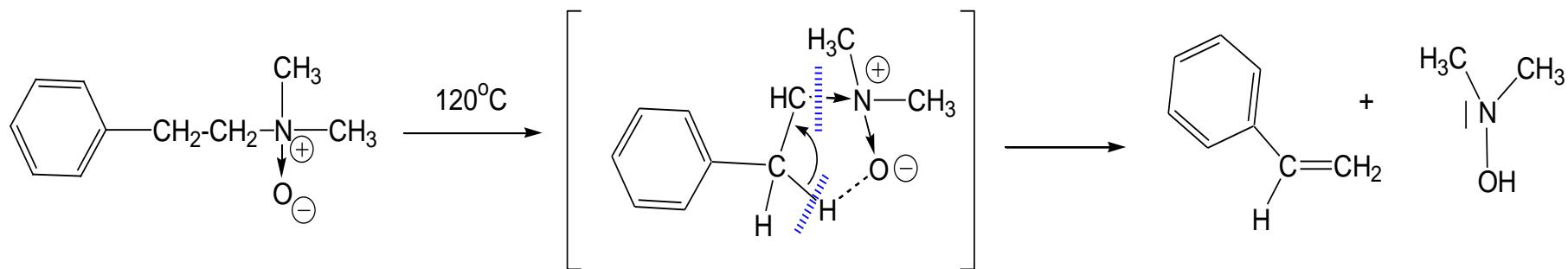
- Reaction proceeds via cyclic intermediate



Cope reaction

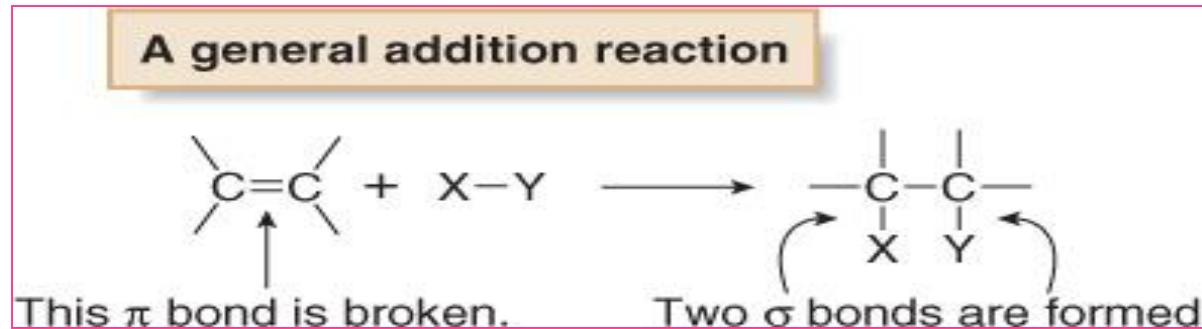
Cope elimination of N-oxides.

- Reactions proceed via cyclic intermediate



4.3 ADDITION REACTIONS

- **Addition** is a reaction in which elements are added to the starting material.

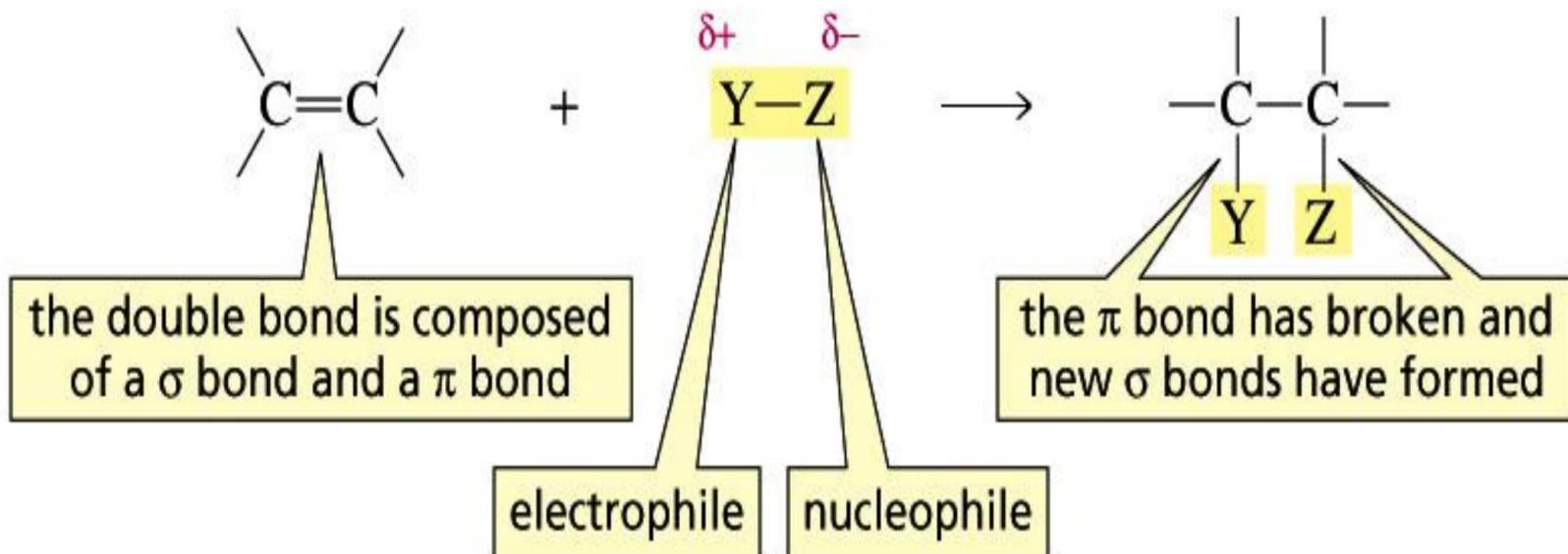


- The π bond of an alkene is weaker than typical σ bonds. Replacing a π bond with a σ bond usually results in a lower energy state.
- The π orbitals of a double bond are exposed to attack. Steric hindrance is minimal.
- The π orbitals contain relatively loosely associated electrons, and are subject to **electrophilic** attack.

Electrophile = “electron-loving

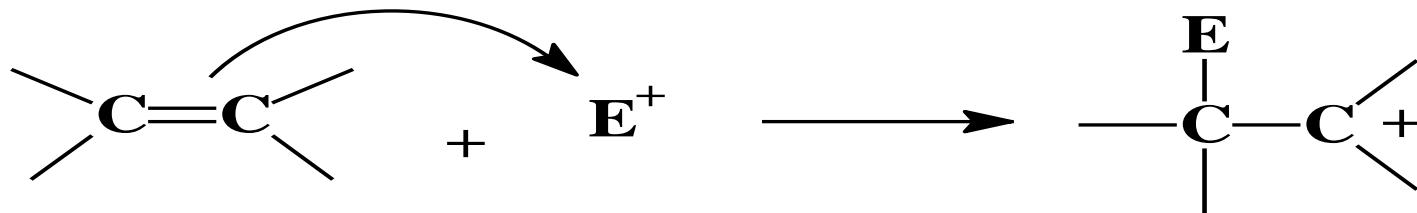
Reactivity of C=C

- Electrons in pi bond are loosely held.
- Electrophiles are attracted to the pi electrons.
- Carbocation intermediate forms.
- Nucleophile adds to the carbocation.
- Net result is addition to the double bond.

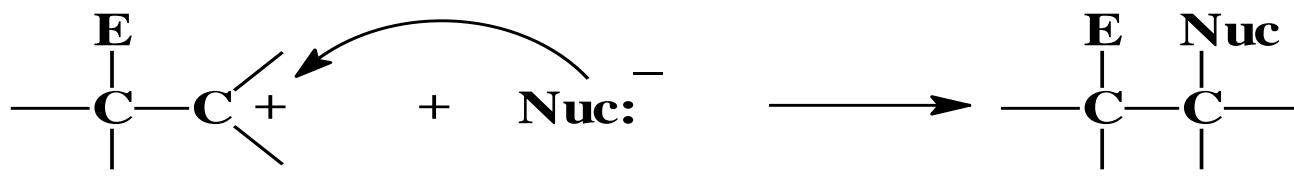


Electrophilic Addition

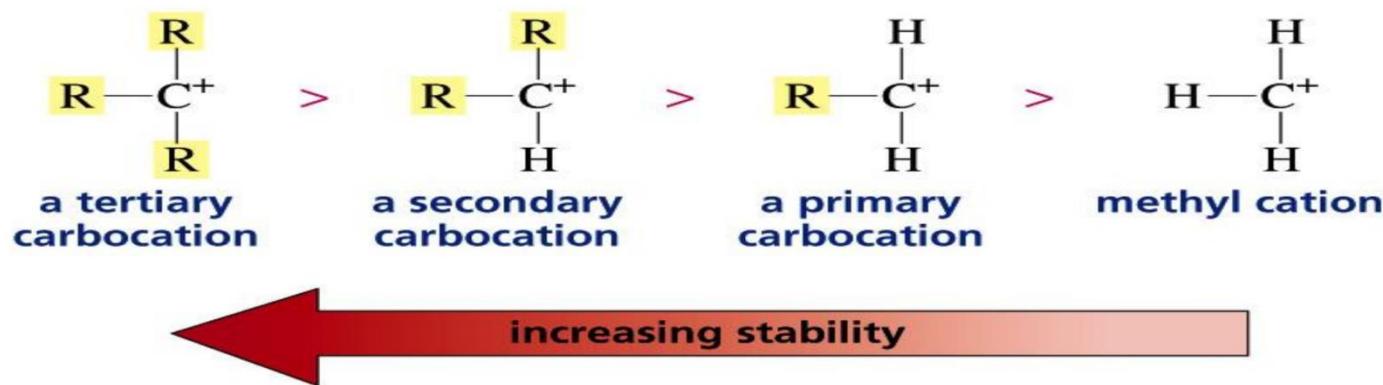
- Step 1: Pi electrons attack the electrophile.



- Step 2: Nucleophile attacks the carbocation.



Carbocation stability

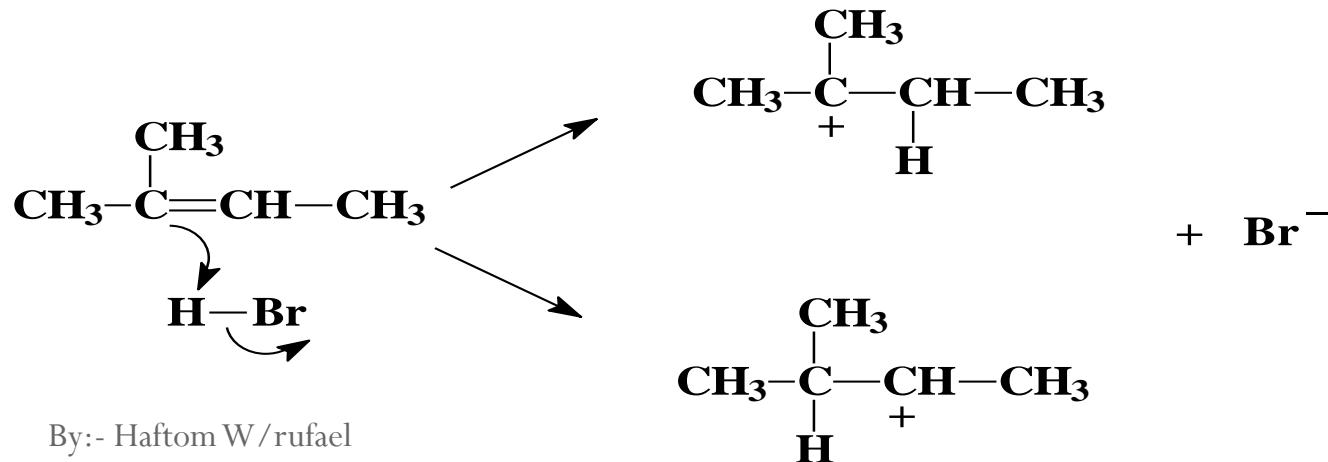


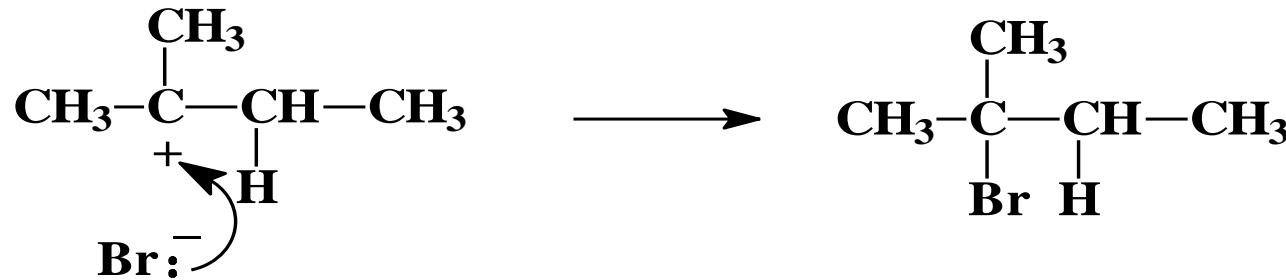
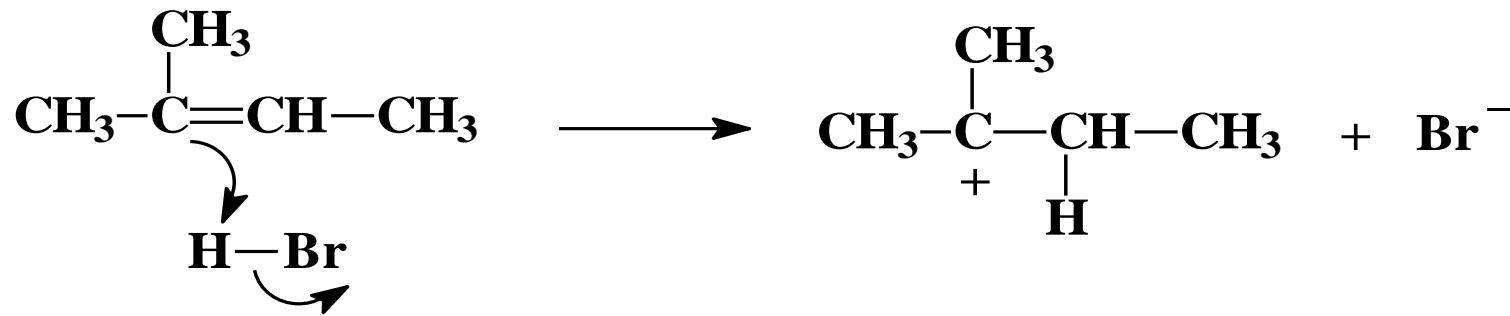
Markovnikov's Rule

- When an unsymmetrically substituted alkene reacts with HX , The electrophile(Hydrogen) adds to the sp^2 carbon that is bonded to the greater number of hydrogen's and the X adds to the carbon that has fewer hydrogen substituent's.

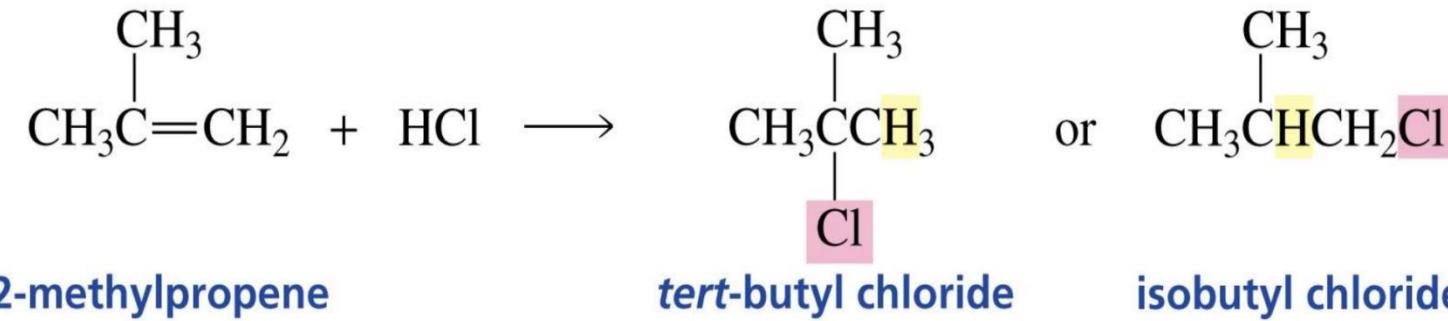
Addition of Hydrogen halides

- Protonation of double bond yields the most stable carbocation. Positive charge goes to the carbon that was not protonated.

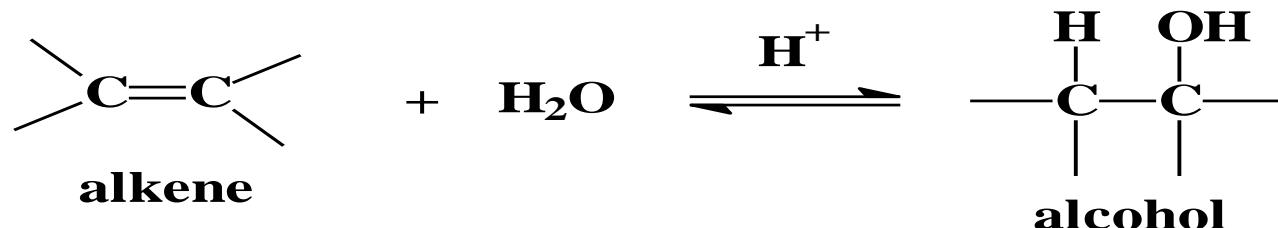




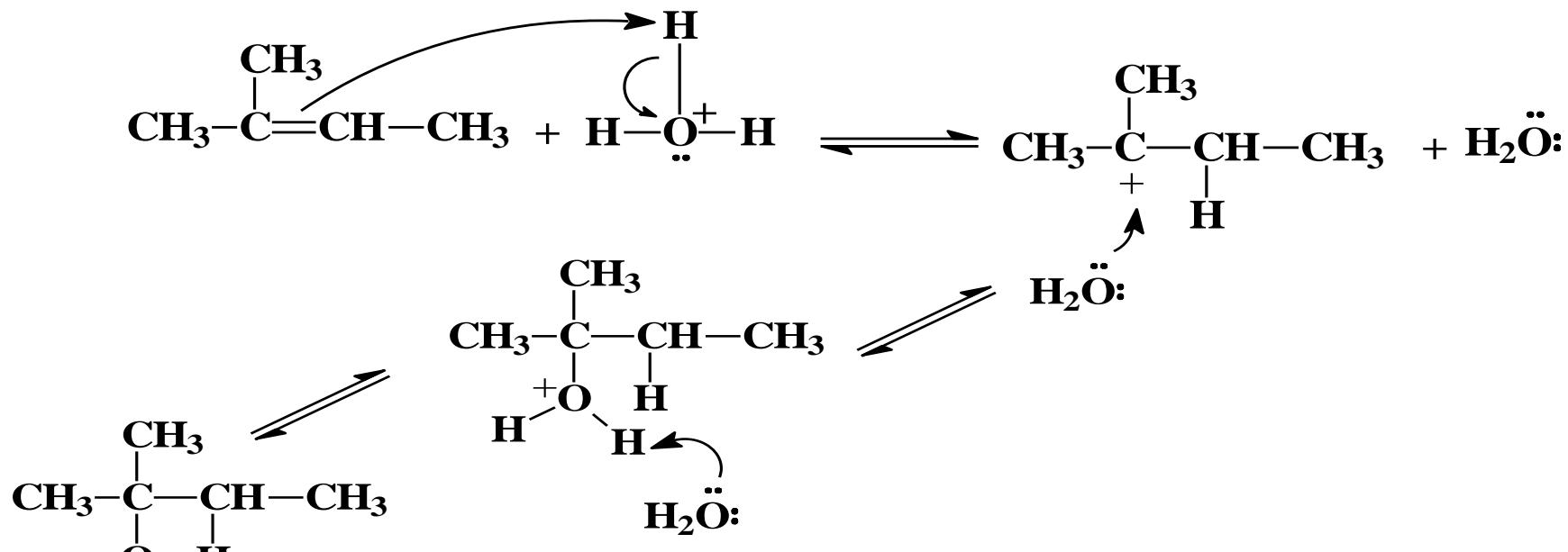
What is the product?



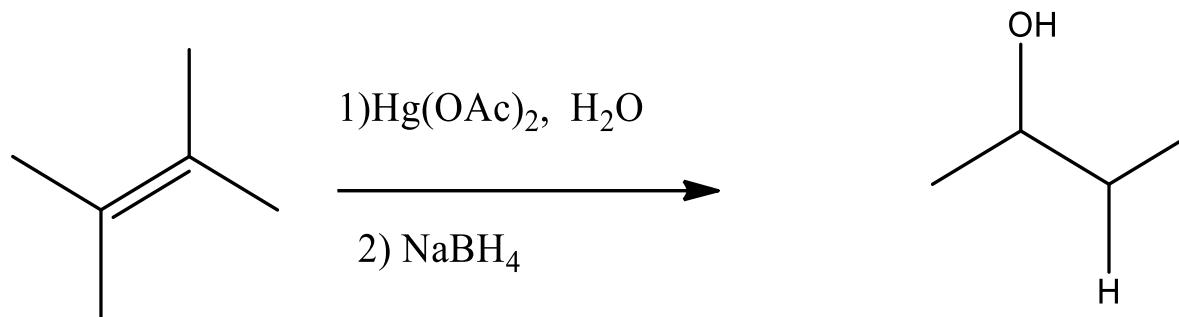
Hydration of Alkenes



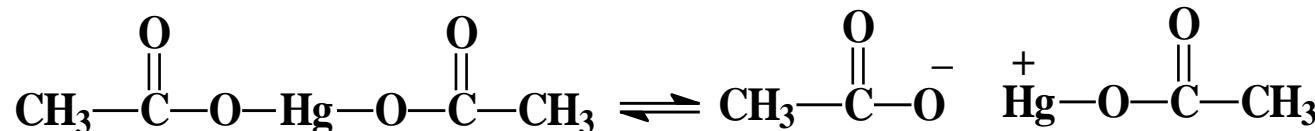
- Use very dilute solutions of H_2SO_4 or H_3PO_4 to drive equilibrium toward hydration.
- Markovnikov product is formed during acid catalysed hydration of alkene.
- See the following mechanism



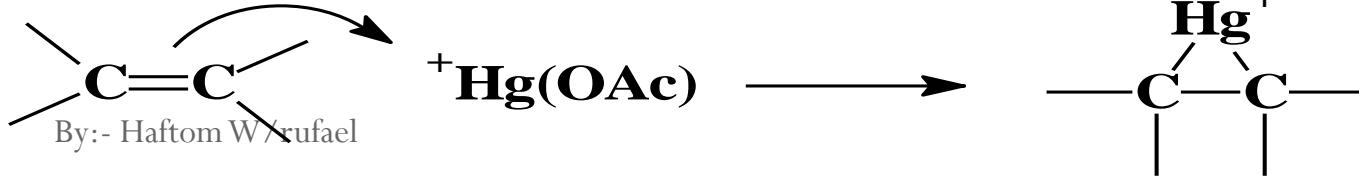
Oxymercuration-demercuration



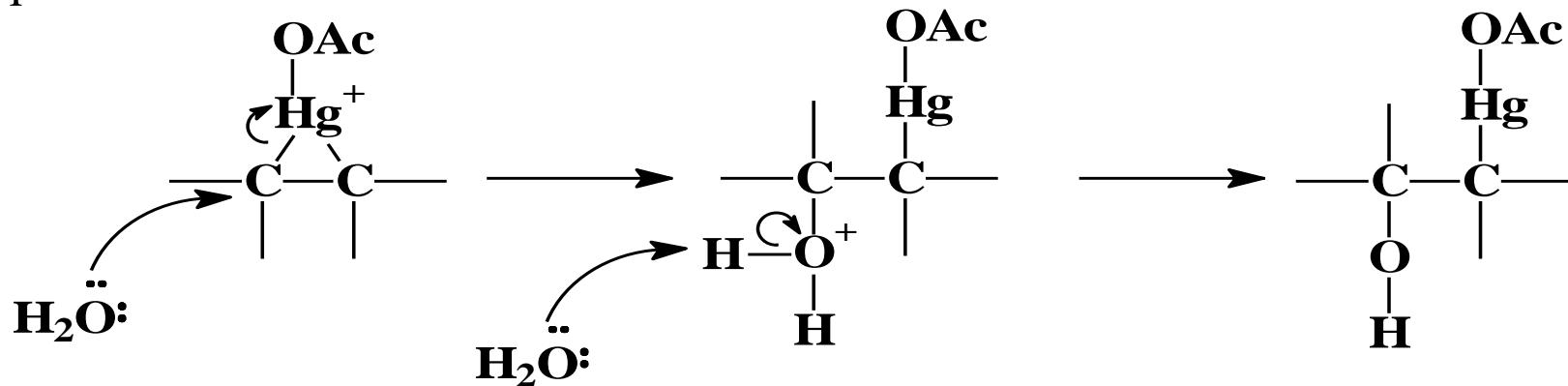
- Reagent is mercury(II) acetate which dissociates slightly to form $^+\text{Hg(OAc)}$.
- $^+\text{Hg(OAc)}$ is the electrophile that attacks the pi bond.



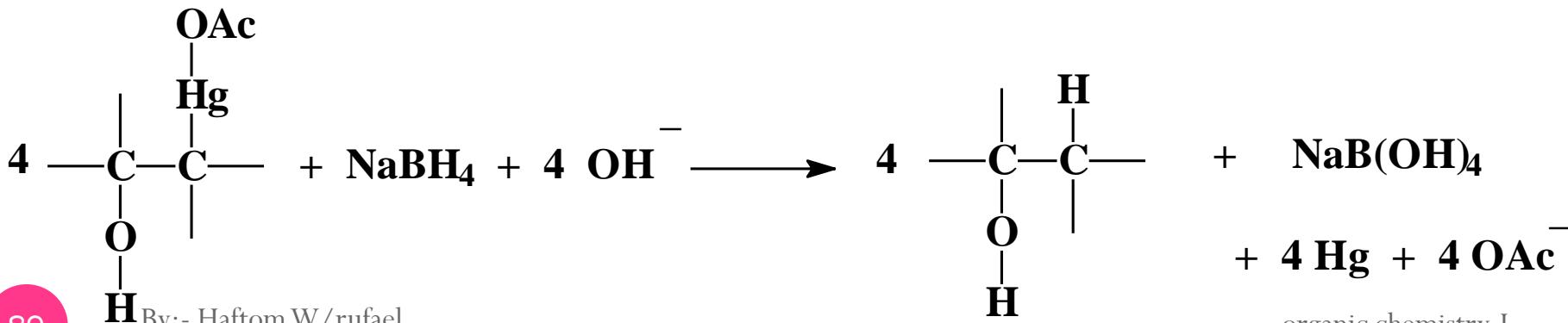
- The intermediate is a cyclic mercurinium ion, a three-membered ring with a positive charge.



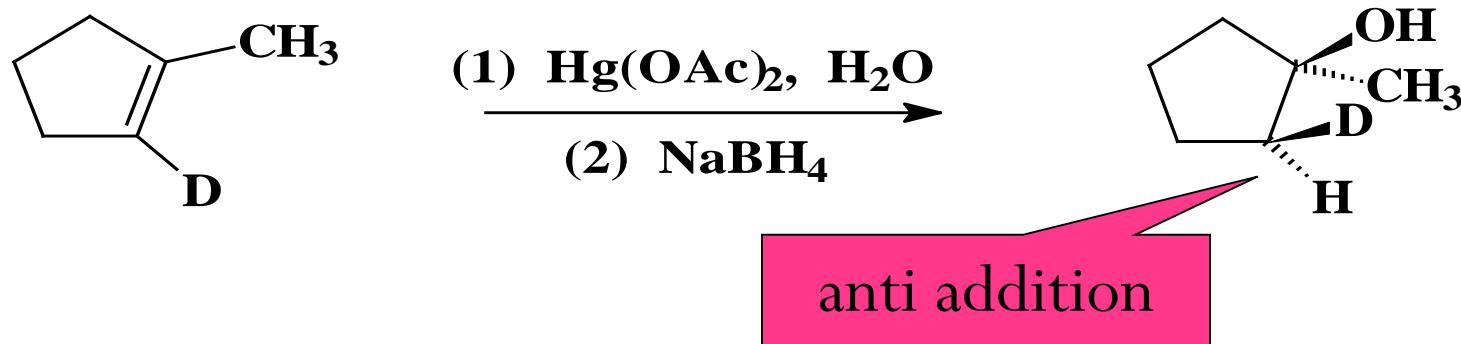
- Water approaches the mercurinium ion from the side opposite the ring (anti addition).
- Water adds to the more substituted carbon to form the Markovnikov product.



- Sodium borohydride, a reducing agent, replaces the mercury with hydrogen.



- o What is the product when the given alkene reacts with aqueous mercuric acetate, followed by reduction with sodium borohydride.



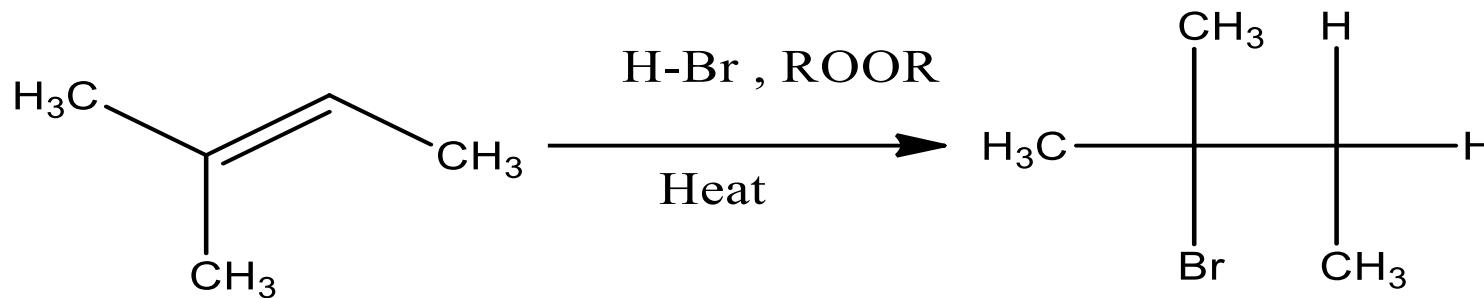
Anti-Markovnikov rule

- When an unsymmetrically substituted alkene reacts with HX , The electrophile(Hydrogen) adds to the sp^2 carbon that is bonded to the fewer number of hydrogen's and the X adds to the carbon that has greater hydrogen substituent's.
- Example

A. Free-Radical Addition of HBr

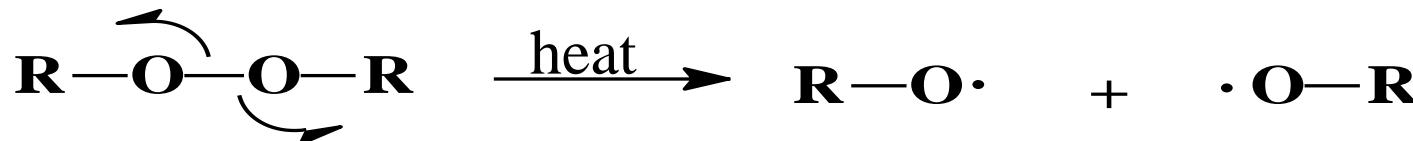
- In the presence of peroxides, HBr adds to an alkene to form the “anti-Markovnikov” product.
- Only HBr has the right bond energy.
- HCl bond is too strong.
- HI bond tends to break heterolytically to form ions.

Example

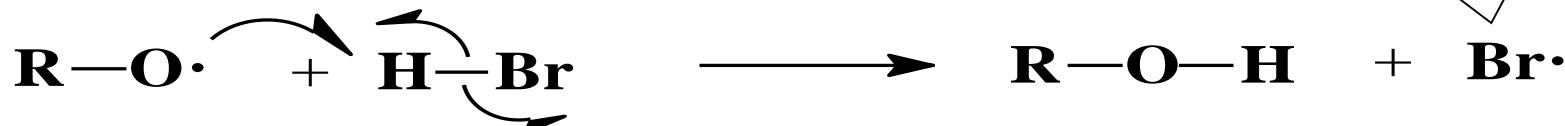


Free Radical Initiation

- Peroxide O-O bond breaks easily to form free radicals.

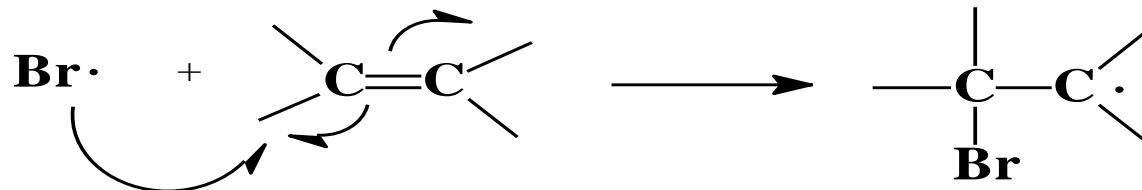


- Hydrogen is abstracted from HBr.

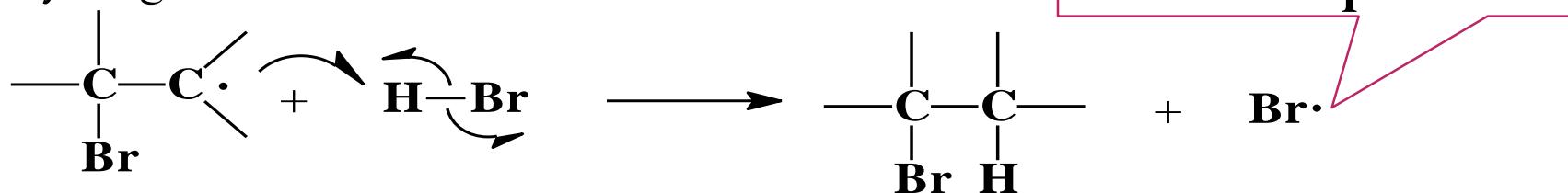


Propagation Steps

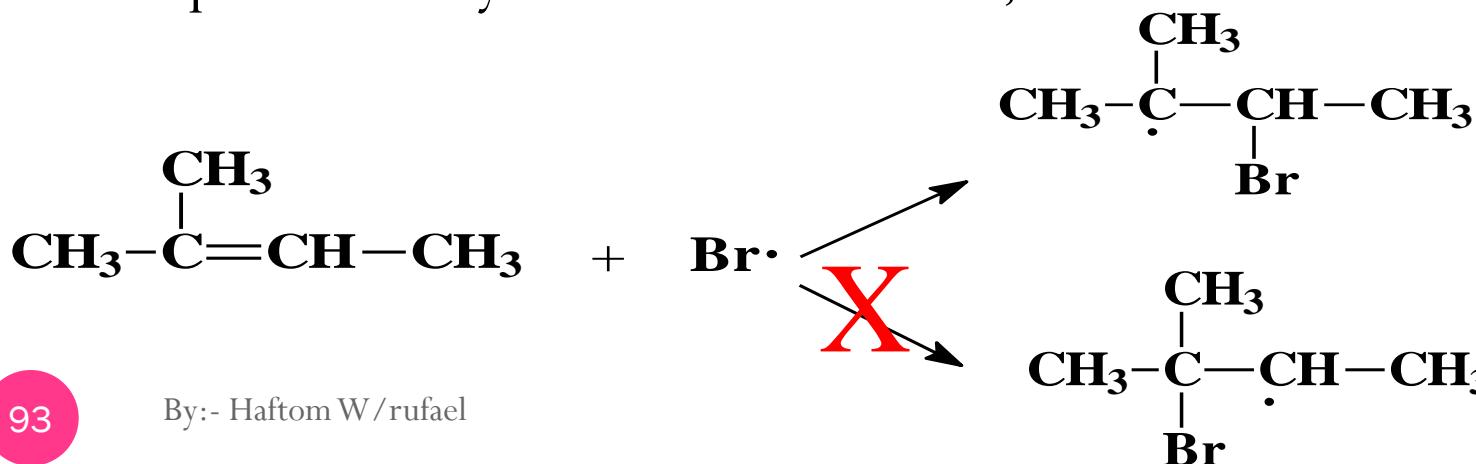
- Bromine adds to the double bond.



- Hydrogen is abstracted from HBr.

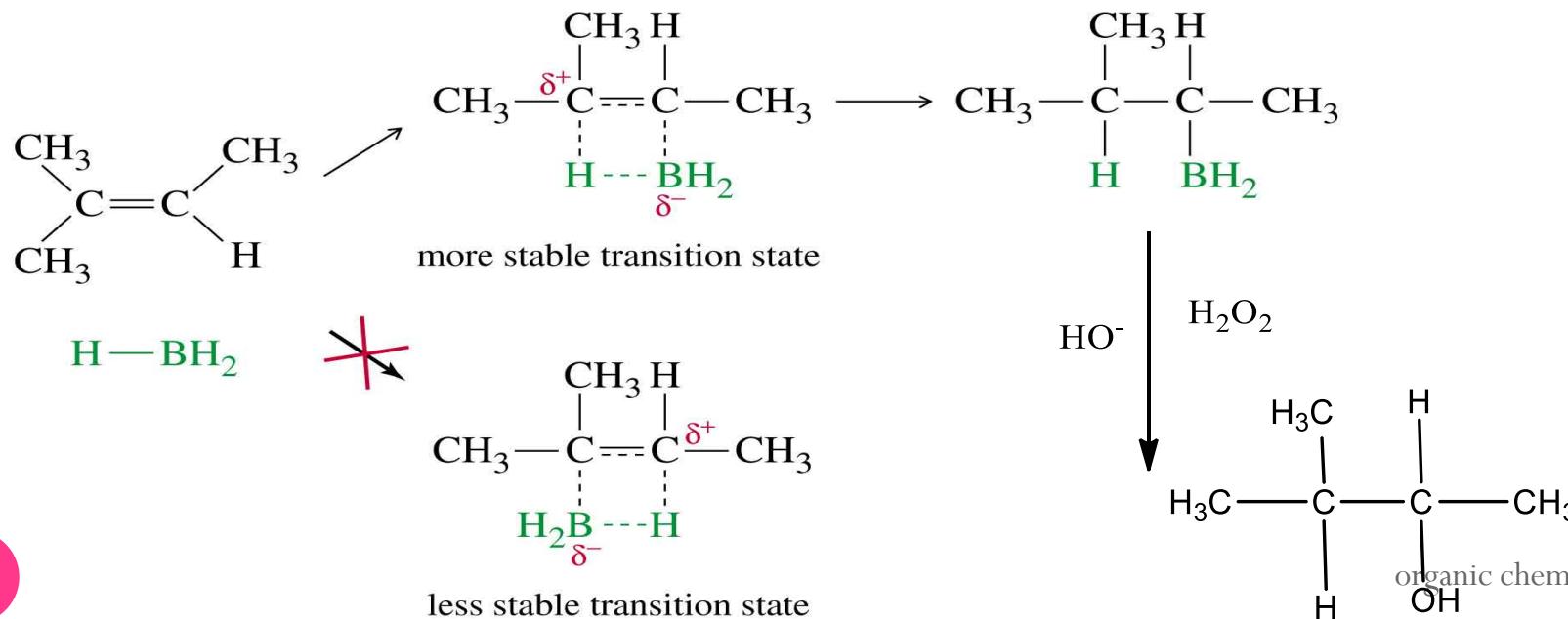
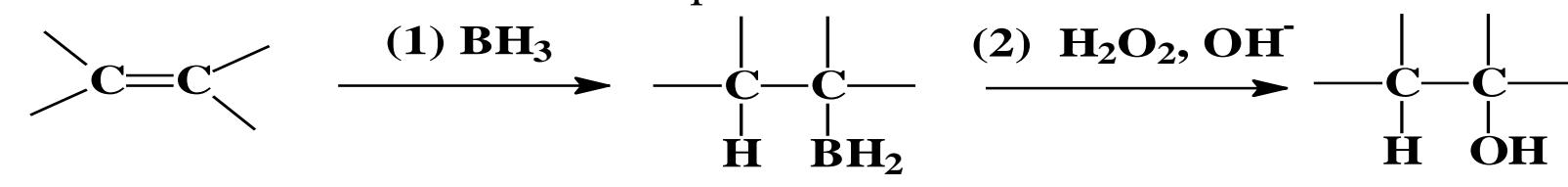


- Example :- Tertiary radical is more stable, so that intermediate forms faster.

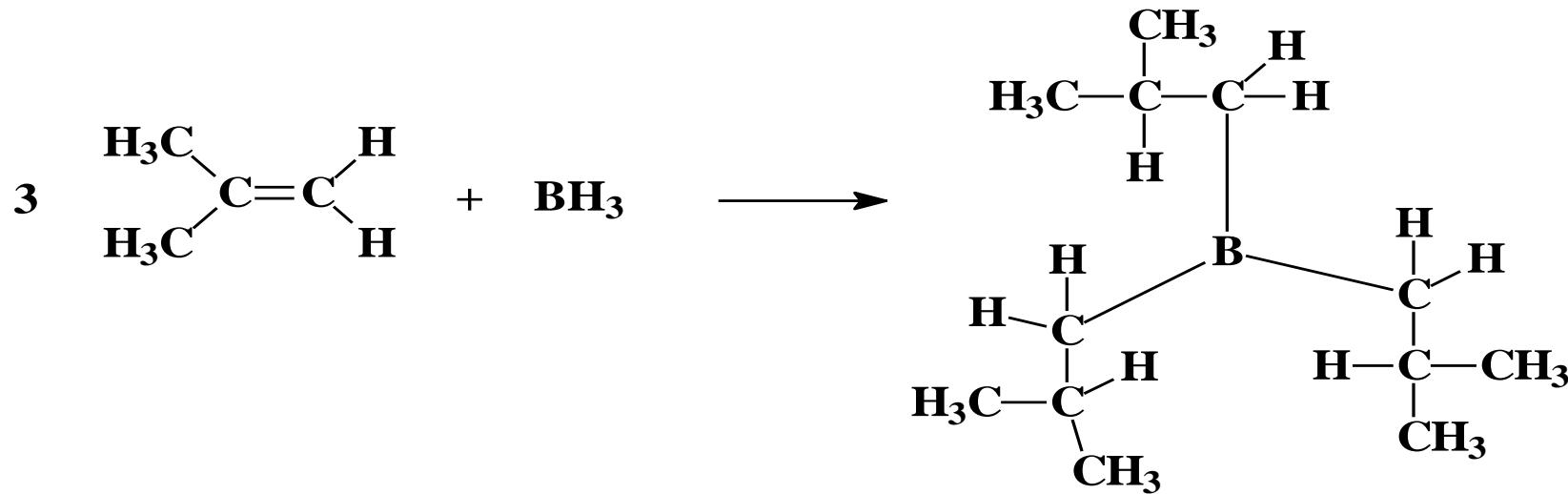


B. Hydroboration

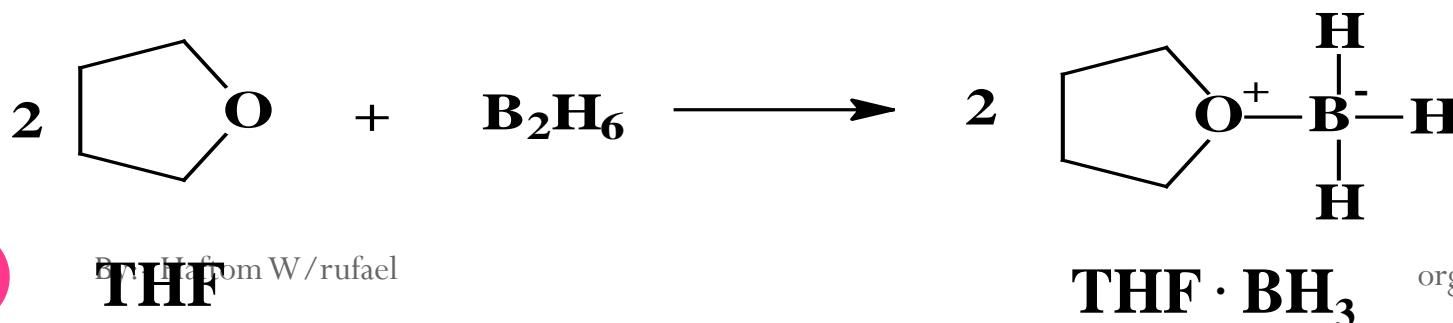
- The electron-deficient borane adds to the least-substituted carbon.
- The other carbon acquires a positive charge.
- H adds to adjacent C on same side (syn) which is then oxidized to the alcohol which is the anti-Mark product.



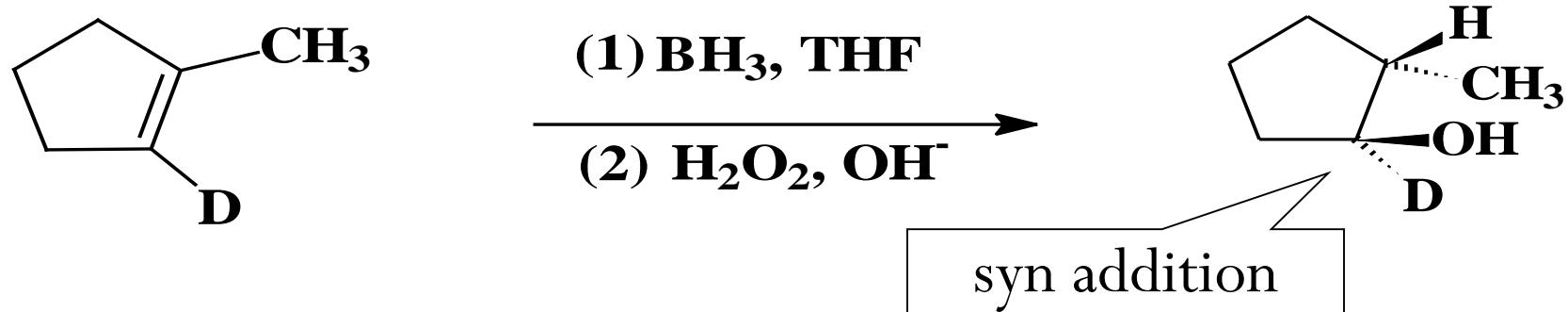
- Borane prefers least-substituted carbon due to steric hindrance as well as charge distribution.



- Borane exists as a dimer, B_2H_6 , in equilibrium with its monomer.
- Borane is a toxic, flammable, explosive gas.
- Safe when complexed with tetrahydrofuran.

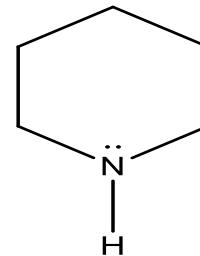
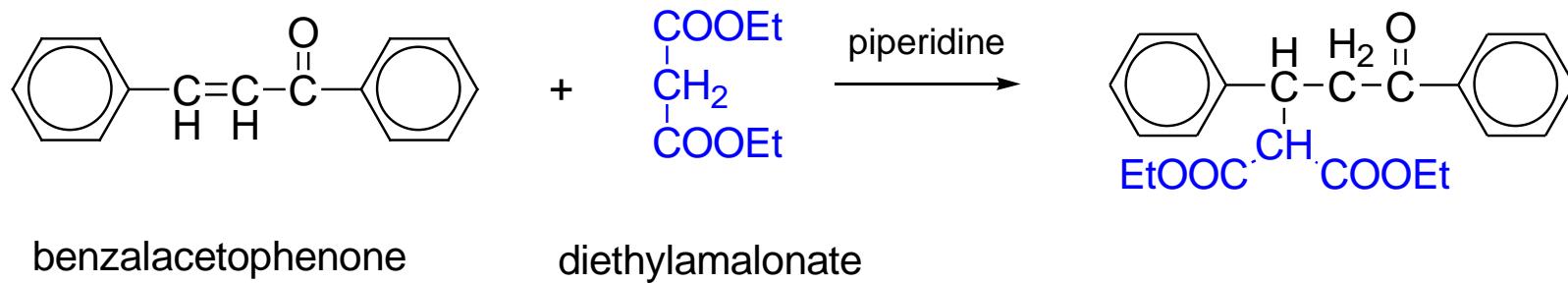


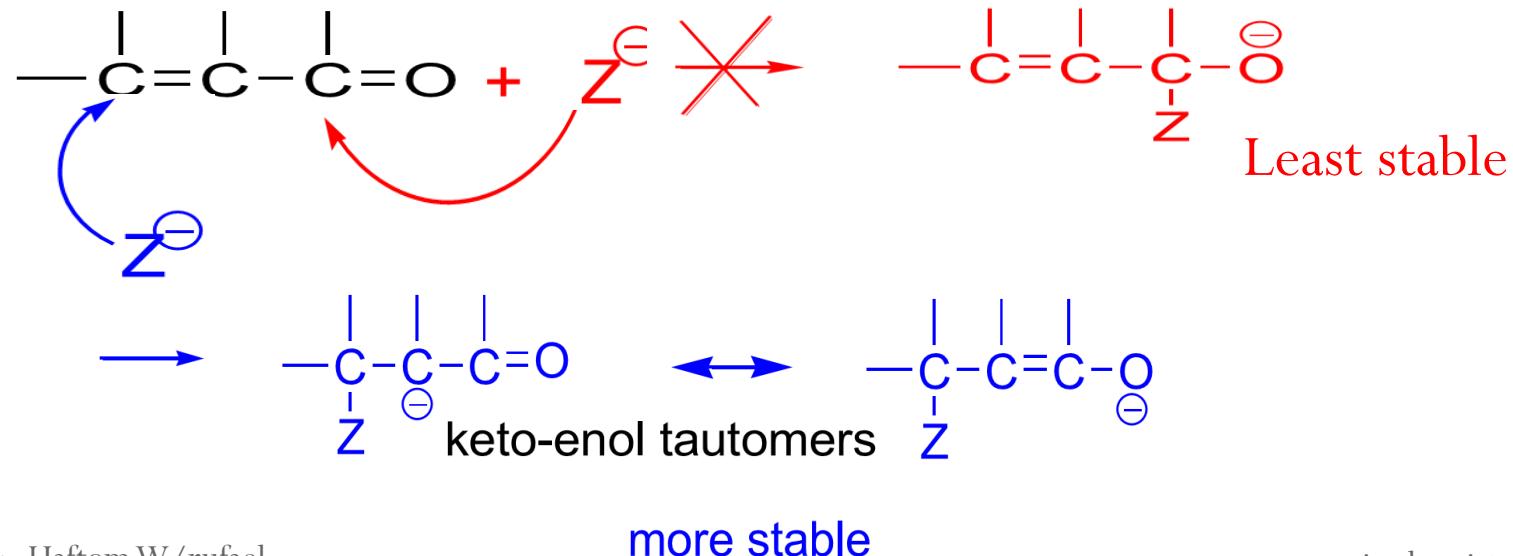
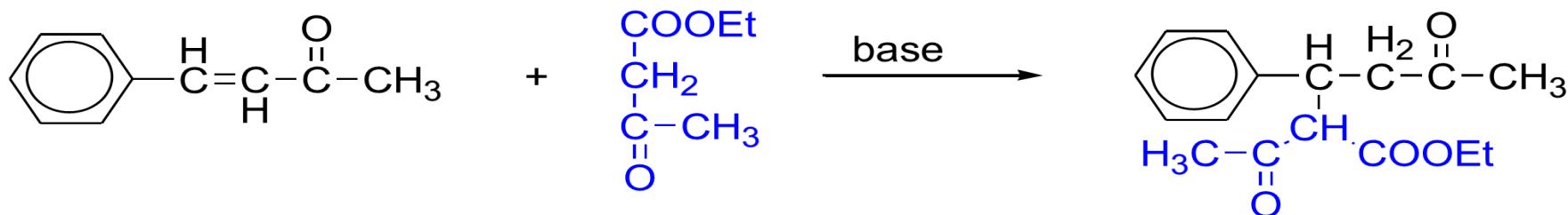
- What is the product when the given alkene reacts with borane in THF, followed by oxidation with basic hydrogen peroxide. Is that the product is the result of syn addition or anti addition?



Michael Addition.

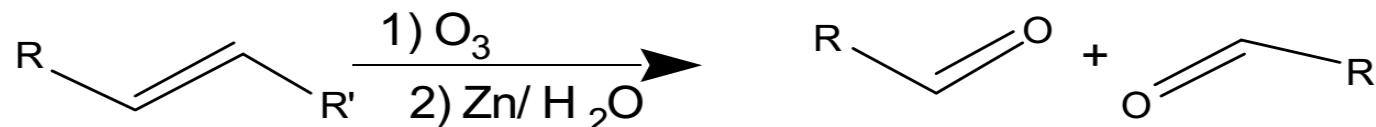
- Is an addition reaction where the nucleophile is added to α,β -unsaturated carbonyls.
- Carbanions as the nucleophiles in nucleophilic addition to α,β -unsaturated carbonyls. (The enolate anion must be in reasonably high concentration for the Michael Addition to take place. Such enolates can be obtained from removal of alpha-hydrogens that are next to two electron withdrawing groups.)





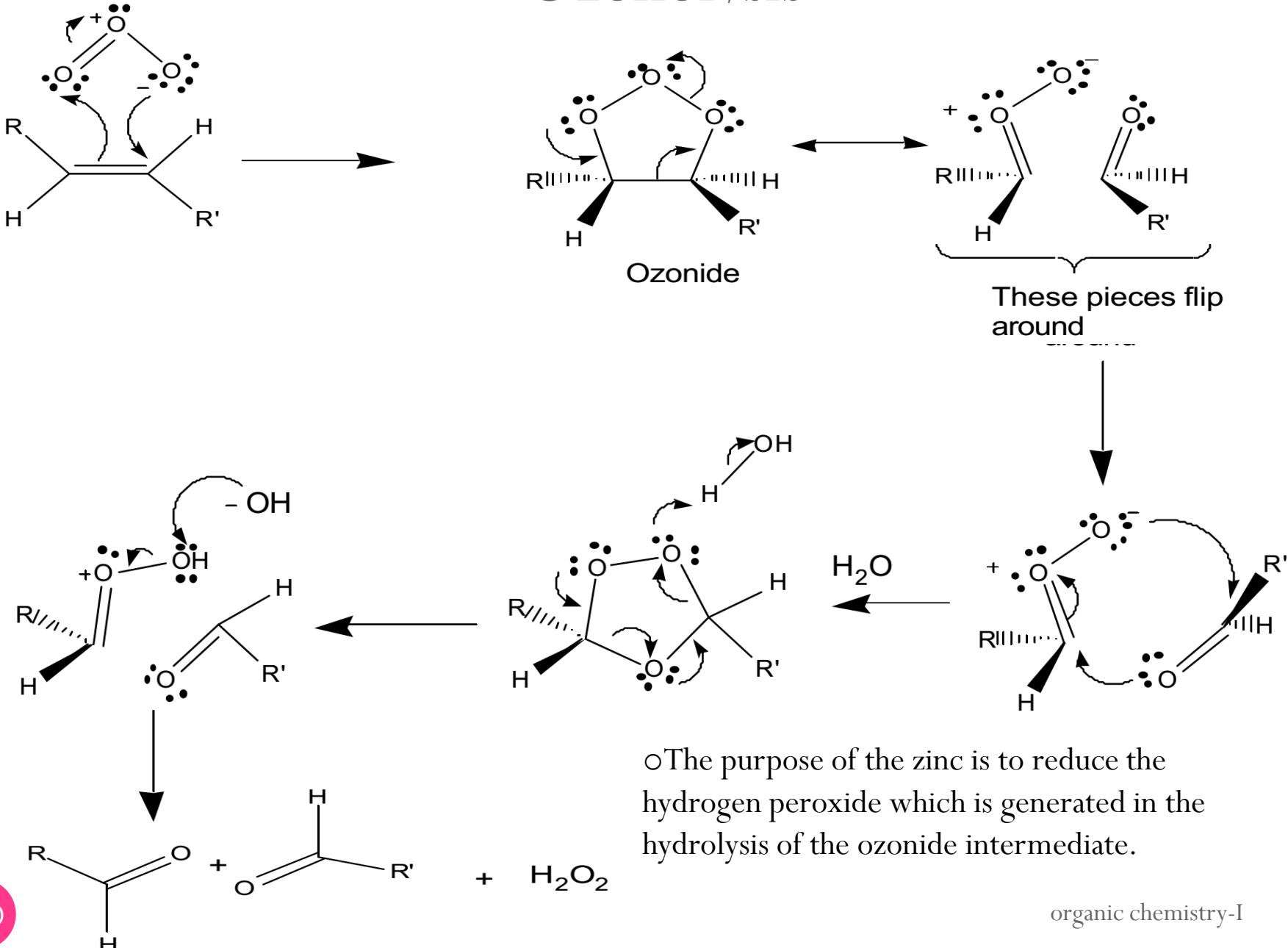
Ozonolysis

- The general reaction is as follows:

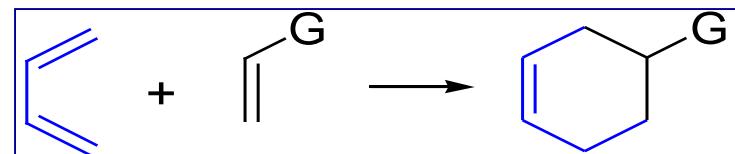


- Notice both of s and p bonds of the alkene are broken, to produce two new carbon oxygen double bonds.
- A mechanism is presented below. Try to follow the motion of the electrons through each step of this mechanism. Remember each arrow indicates the motion of two electrons, either
 - a) from a lone pair to a bond,
 - b) from a bond to a lone pair,
 - c) from a bond to another bond.
- Try to find examples of each of these types of electron motion in the following mechanism.

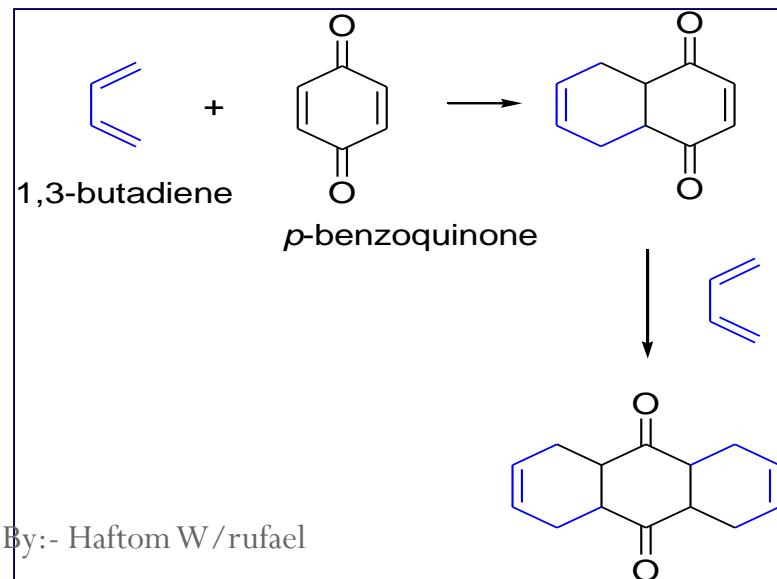
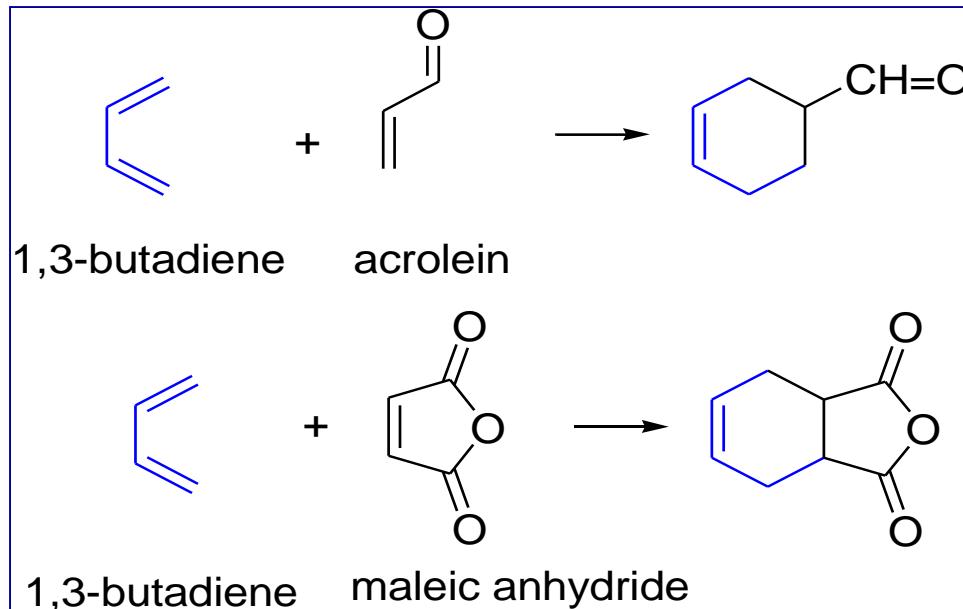
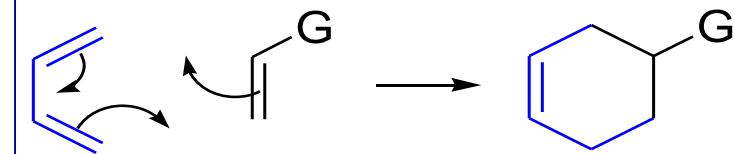
Ozonolysis



Diels-Alder reaction: diene + dienophile → cyclohexene



mechanism: (concerted)

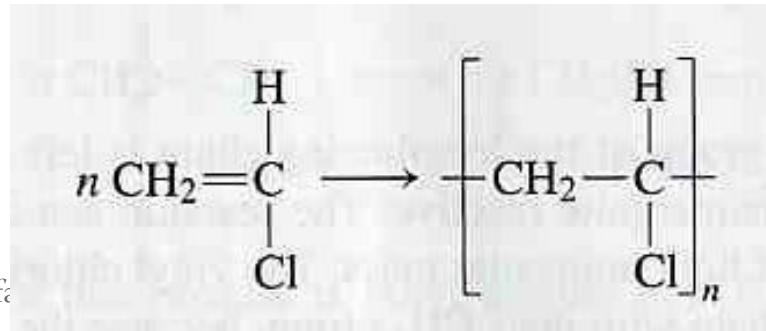


Addition Polymerization

- Polymers are large molecules made up of repeating units called Monomers. The synthetic process is Polymerization.
- **Polymers:** Macromolecules formed by the covalent attachment of a set of small molecules termed monomers.



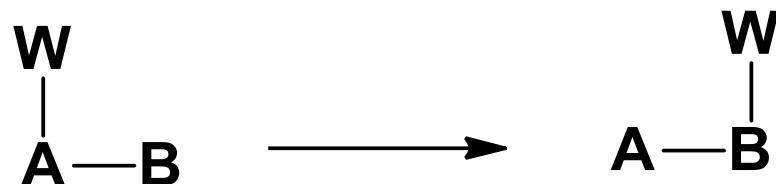
- **Addition polymerization:** monomers react to form a polymer without net loss of atoms.



Rearrangement reaction

- Reactions involve the **migration of a group** or an atom from one center (migration origin) an adjacent atom (migration terminus, having six electrons in the valence shell) within the same molecule.

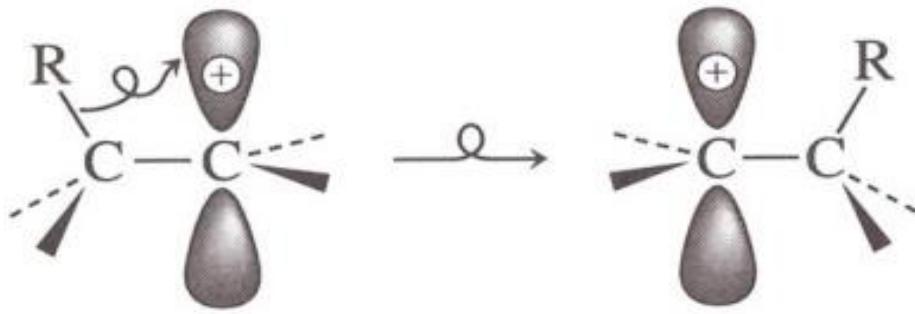
✓ Example



- There are three common rearrangement reactions
 - Wagner-Meerwein Rearrangement
 - The Baeyer-Villiger Oxidation
 - Beckmann Rearrangement

Migrations to Electron-Deficient Carbons: Wagner-Meerwein Rearrangements

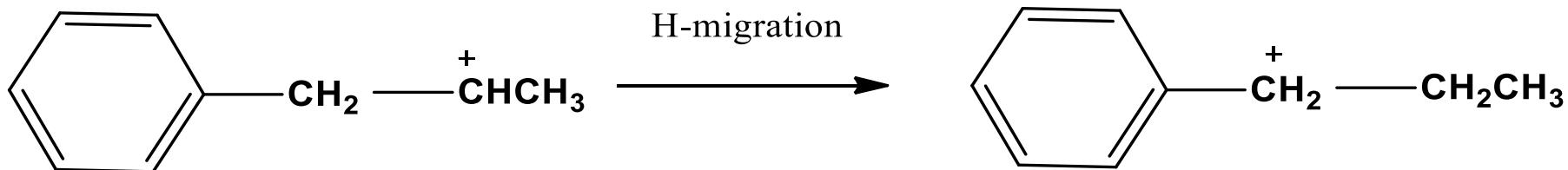
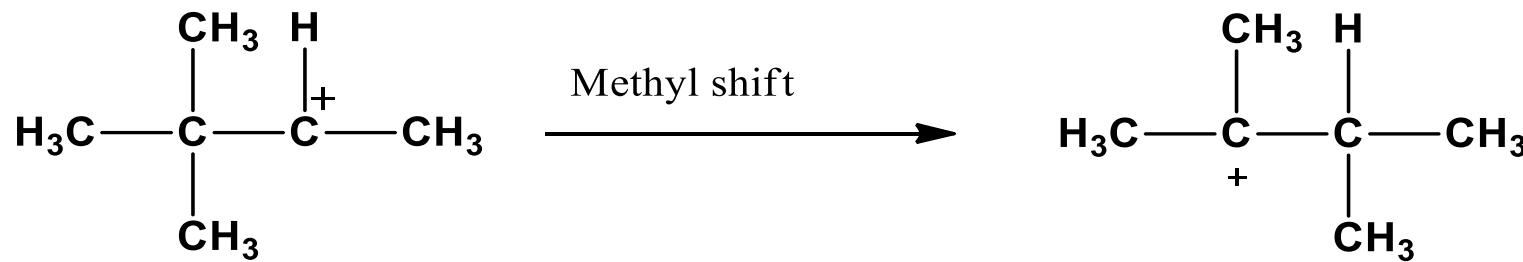
- 1,2-Shifts of migrating groups to empty orbitals in carbocations or toward partially empty orbitals in developing carbocations are the most common rearrangements of organic molecules.
- Especially, migration of hydrogen atom or alkyl or aryl groups in carbocations are called “Wagner-Meerwein Rearrangements”



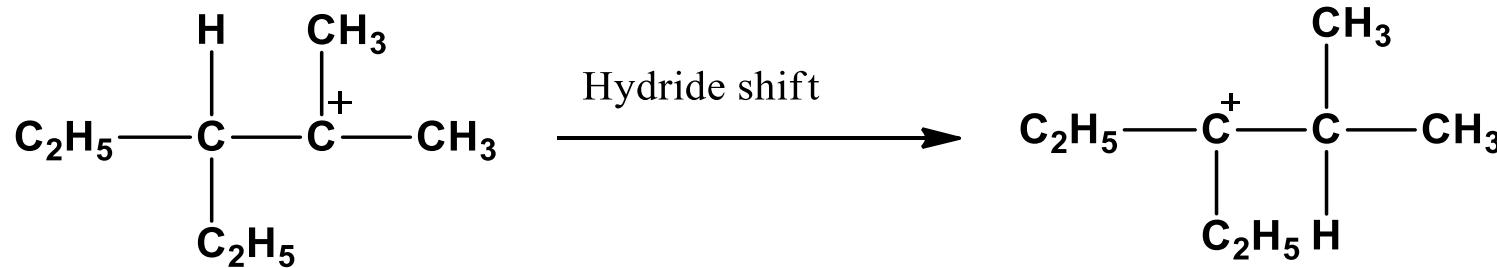
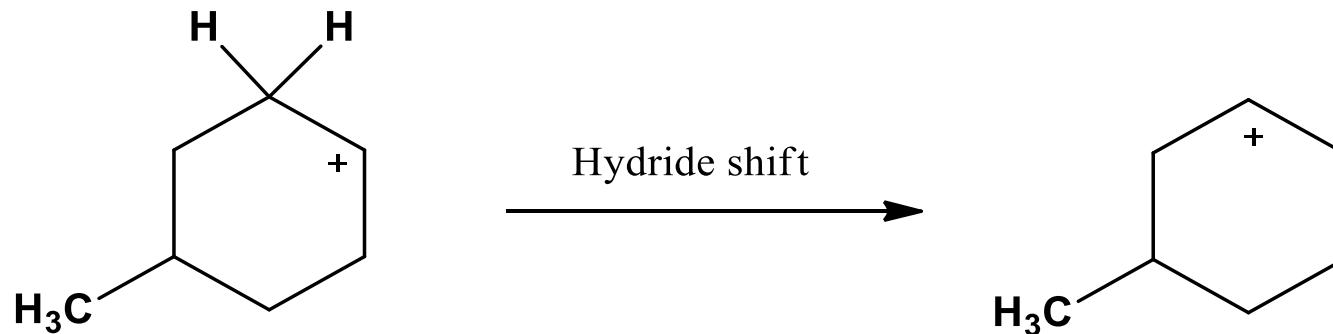
Rearrangement of a carbocation

- “Wagner-Meerwein Rearrangements” proceed most easily when the carbocations are converted to more stable forms.

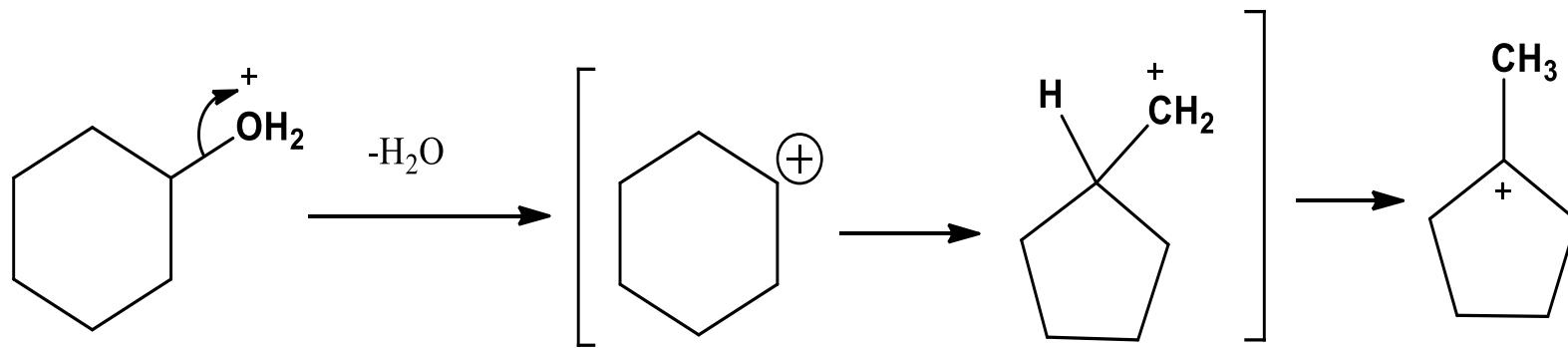
- Secondary cation to tertiary cation
- Simple cation to resonance-stabilized cation



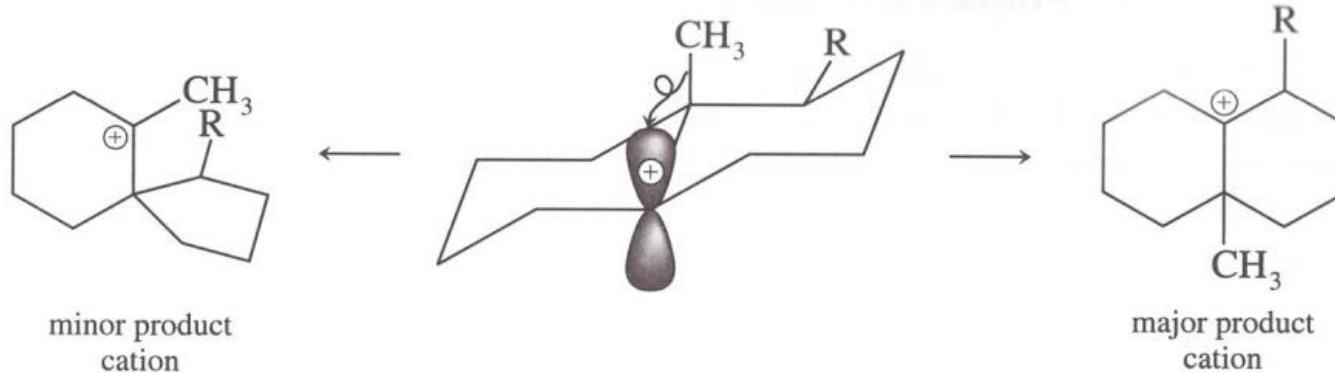
- “Wagner-Meerwein Rearrangements” also proceed in the cases of same stability of carbocations.
- Secondary cation to secondary cation
- Tertiary cation to tertiary cation



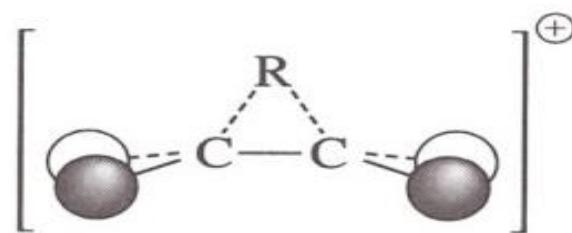
- “Wagner-Meerwein Rearrangements” must form the final products that are thermodynamically more stable than the starting materials. Some processes proceeding do appear to require uphill steps (formation of less stable carbocation).



- Migratory Aptitudes
 - (1) The relative yields of products from migrations of different groups are not related to the abilities of the groups to migrate
 - (2) Geometric factors can be important in migration.
 - A methyl group at the ring juncture of the two fused carbocyclic rings will migrate in preference to the migration of a primary or secondary alkyl group forming part of one of the rings.

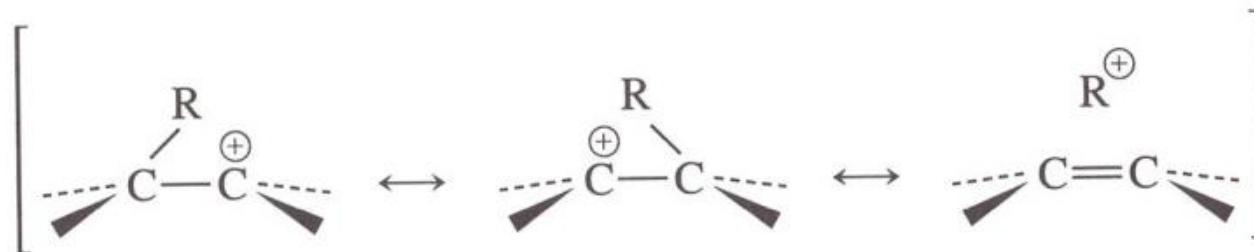
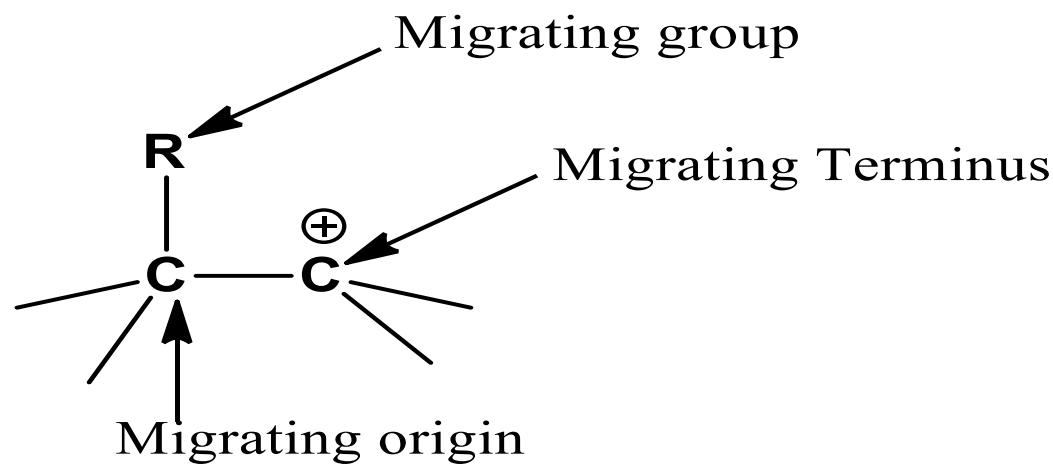


- 3) Methyl groups at axial positions of six-membered rings are almost ideally positioned to migrate because the bonds between the methyl groups and the rings are nearly coplanar with the empty orbitals of the cations. Equatorial substituents are unlikely to migrate.
- 4) Steric factors may also significantly affect the open-chain cations. Non-migrating substituents are forced into “eclipsed position in the TS for rearrangement.



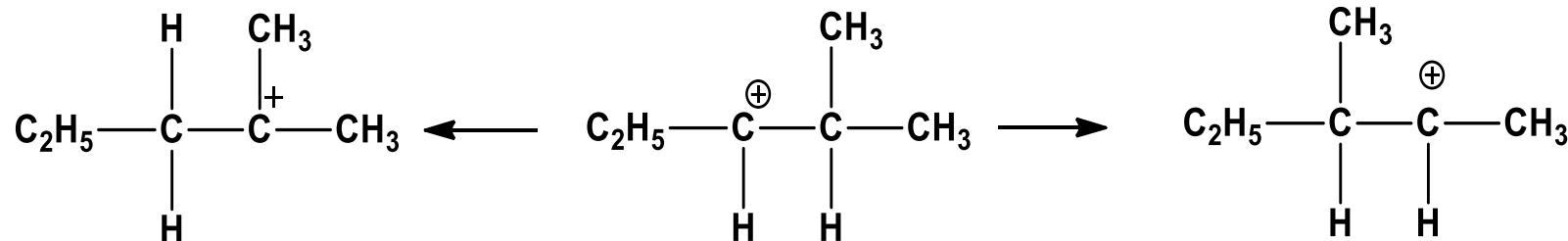
“Eclipsing” of stationary groups in Wagner-Meerwein migrations

- The general trend is that migration tendencies of alkyl groups in carbocation rearrangements increase with increasing substitution at the migrating carbon atoms.



Resonance description of the transition state for a Wagner-Meerwein rearrangement

- Hydrogens usually migrate more rapidly than alkyl group in Wagner-Meerwein rearrangements.



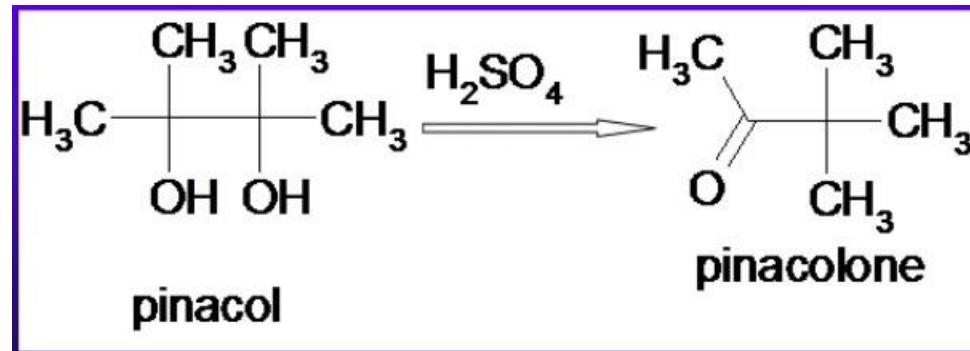
**Hydrogen migration yields
tertiary carbocation**

**Methyl migration yields
Secondary carbocation**

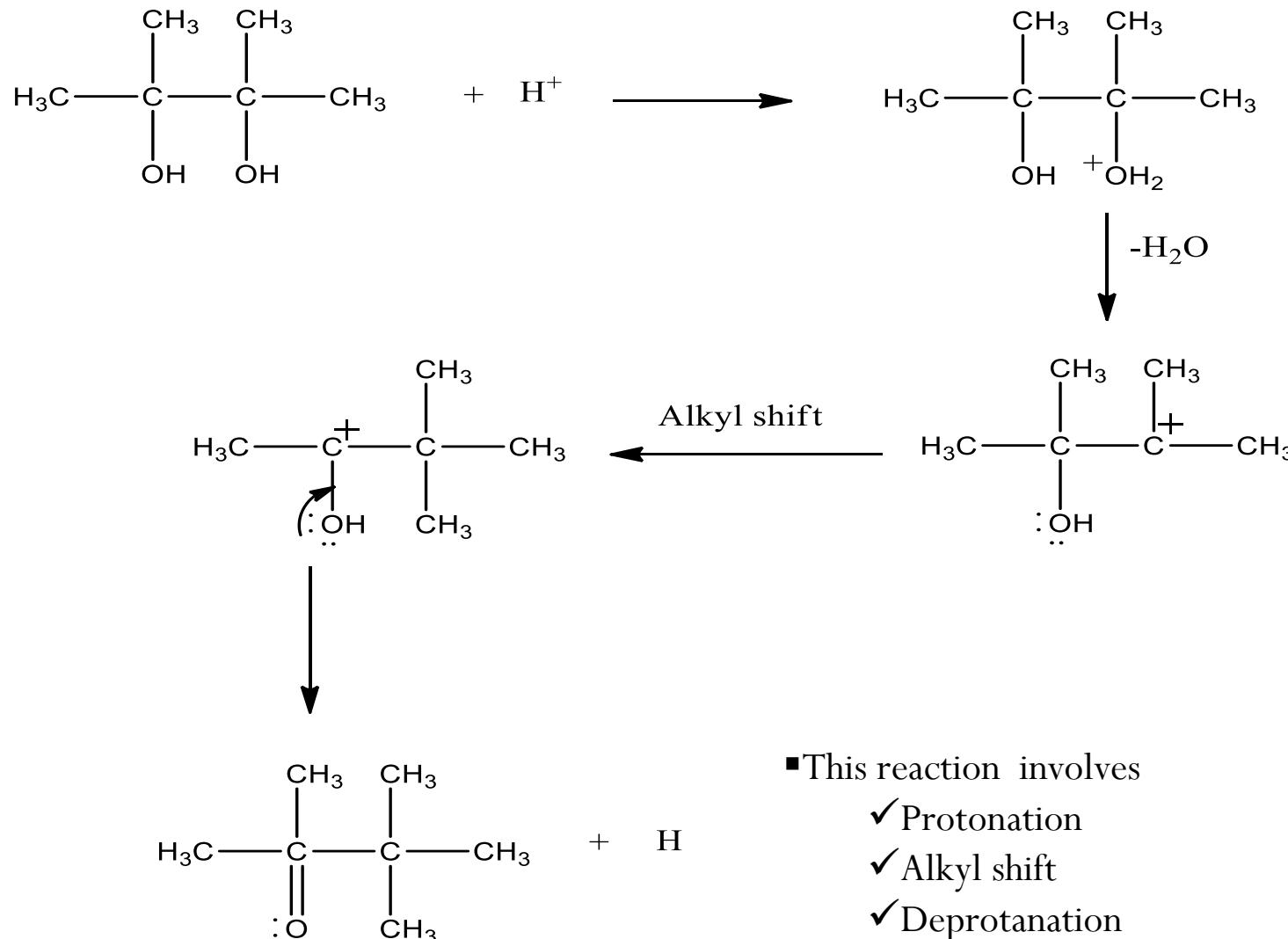
- The hydrogen atom is only a slightly better migrator than the methyl group and is probably a less effective migrator than most larger alkyl groups.

Pinacol pinacol rearrangements

- conversion of an alcohol having two adjacent OH groups (pinacol) to a ketone (pinacolone) by the action of acid



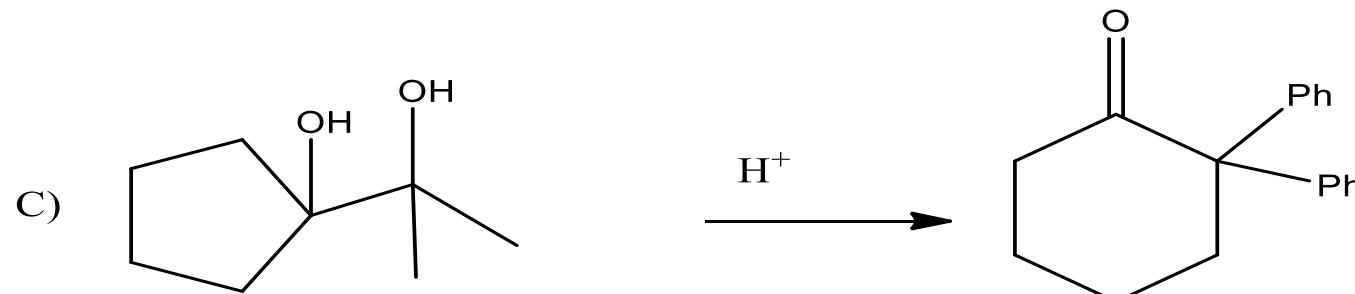
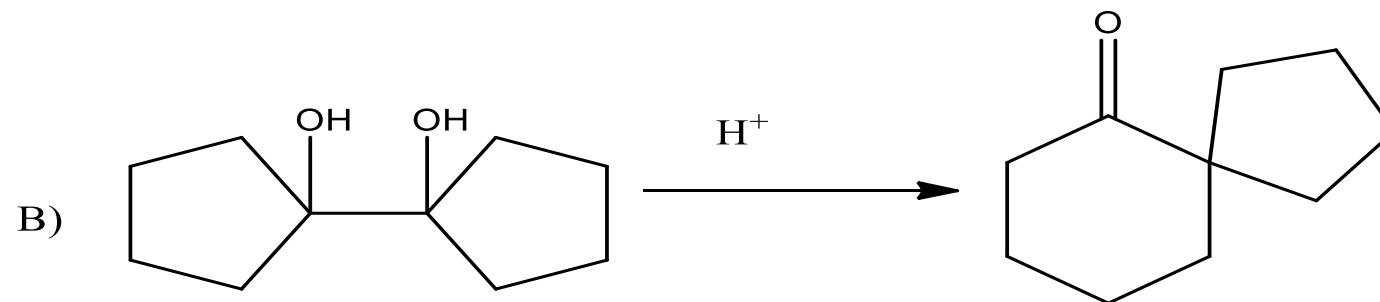
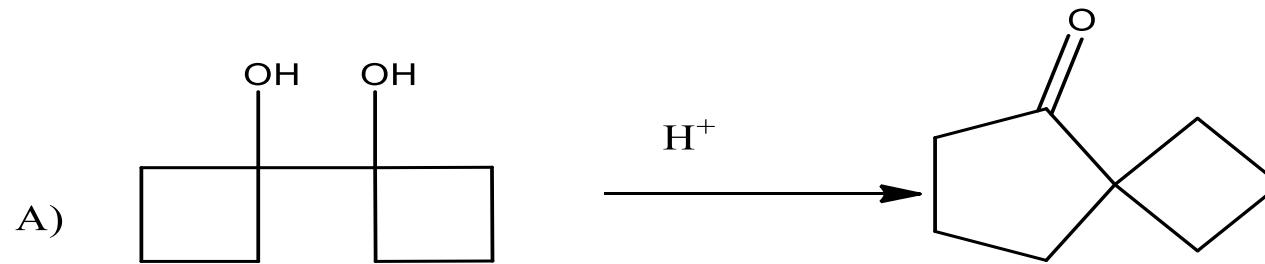
Mechanism



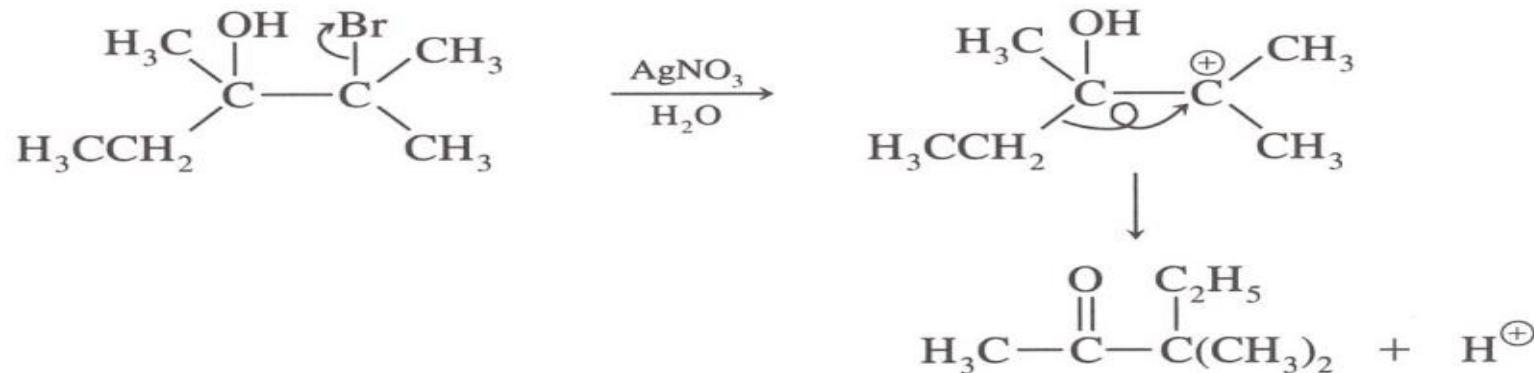
- This reaction involves
 - ✓ Protonation
 - ✓ Alkyl shift
 - ✓ Deprotonation
 - ✓ Removal of H_2O

■ Formation of a new bond (p bond) provides the driving force

Question :- Write a mechanism for the following reactions

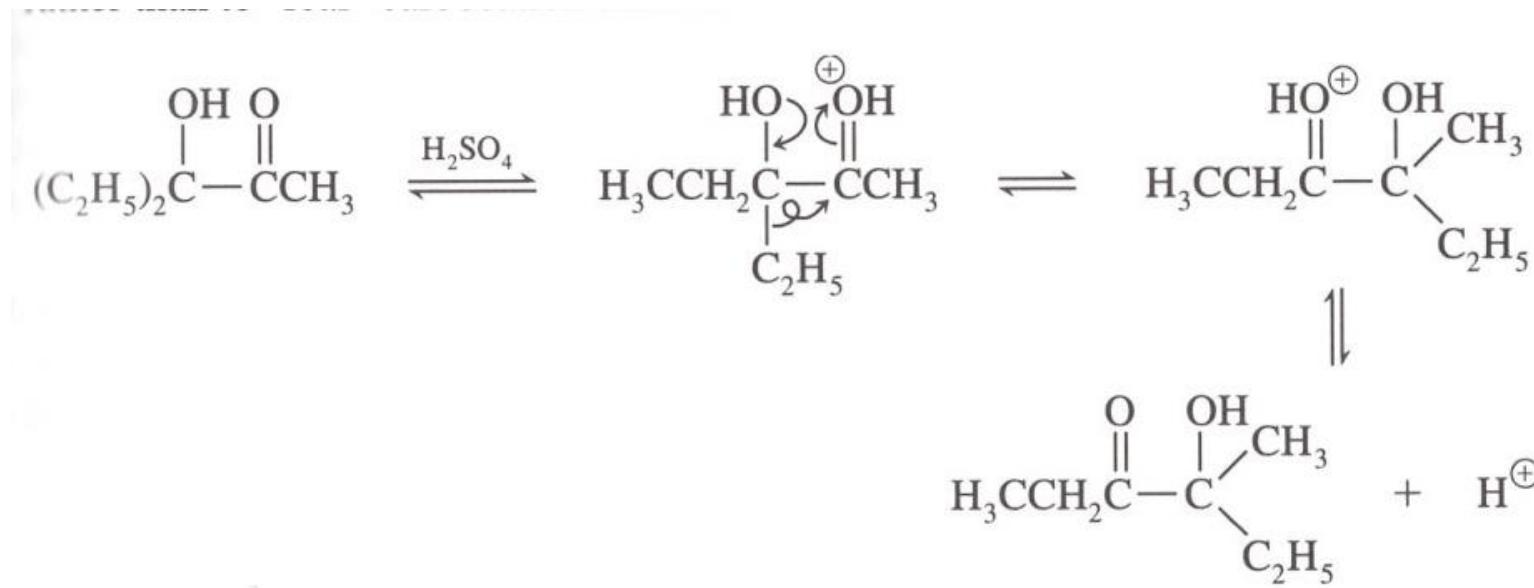


■ β -Halo alcohols and 1,2-epoxides are common starting materials for semipinacolic rearrangements.



Rearrangements of α -hydroxyaldehydes and α -hydroxy- ketones (acyloin rearrangement)

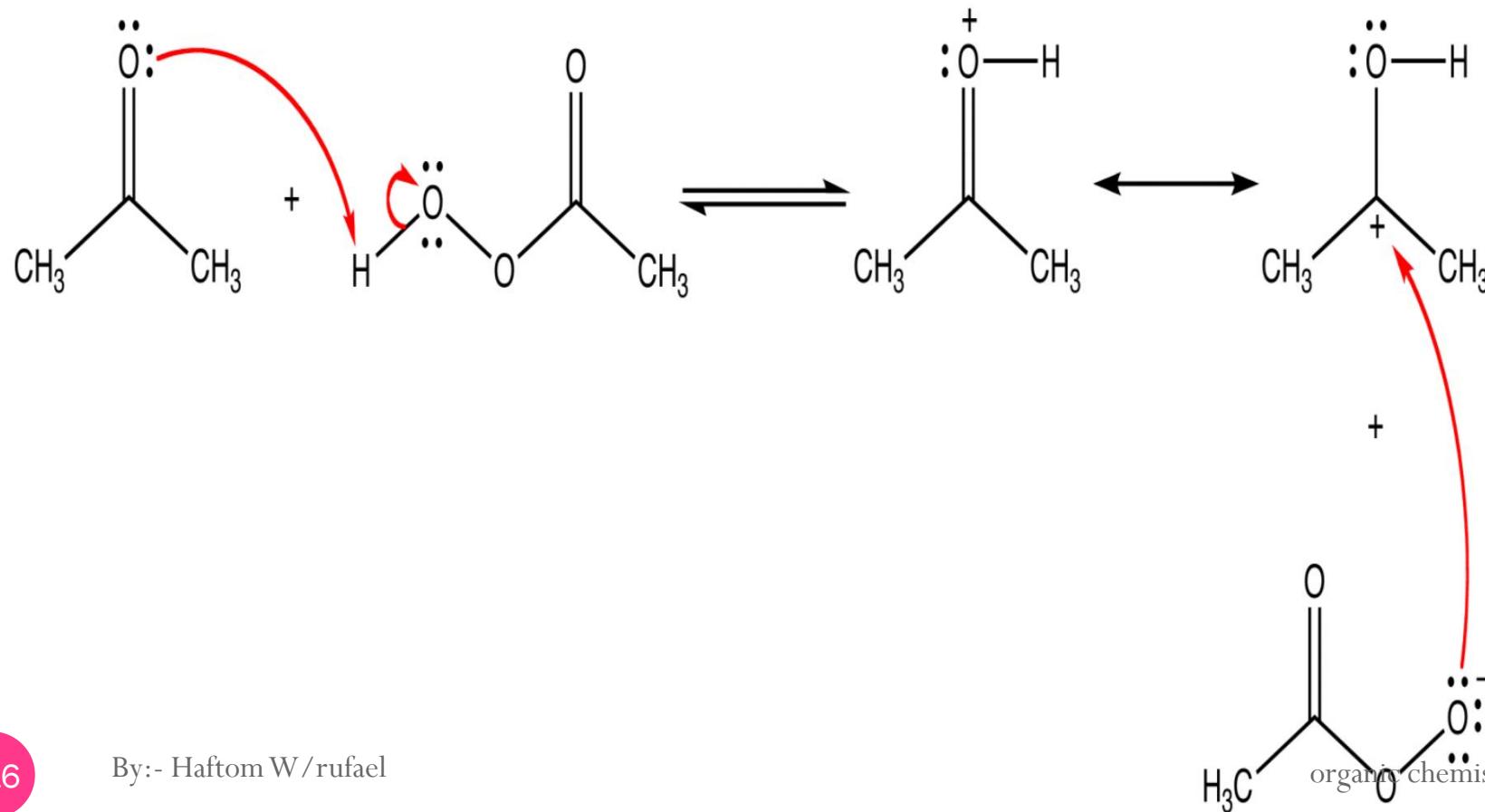
- In acid-catalyzed rearrangements of α -hydroxyaldehydes or α -ketones, the migrating groups migrate to carbon atoms of protonated carbonyl groups rather than to carbocation centers.

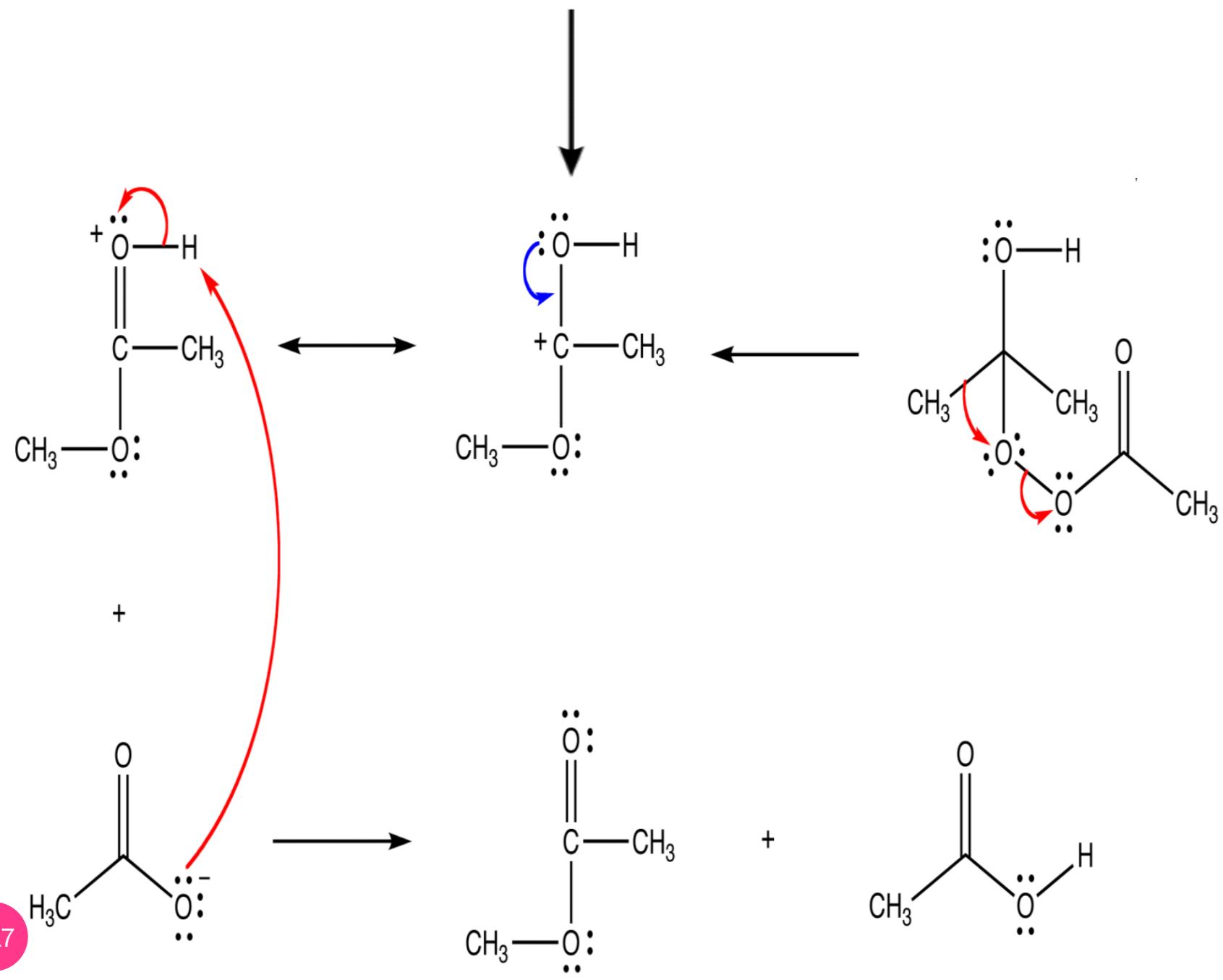


- Difference between acyloin and pinacolic rearrangements
- Competing elimination and substitution reactions of the alcohol functions are unlikely to occur in acyloin one
- Pinacol rearrangements are usually highly exothermic, but acyloin rearrangements are often similar in energy, so that acyloin one are readily reversible
- Acyloin rearrangements can take place under basic as well as acidic conditions

Migration to Electron Deficient Oxygen (Baeyer-Villiger Oxidation)

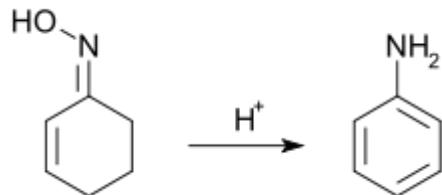
- The Baeyer–Villiger (BV) rearrangement¹ which involves the oxidation of a ketone to an ester or lactone Using peroxyacid



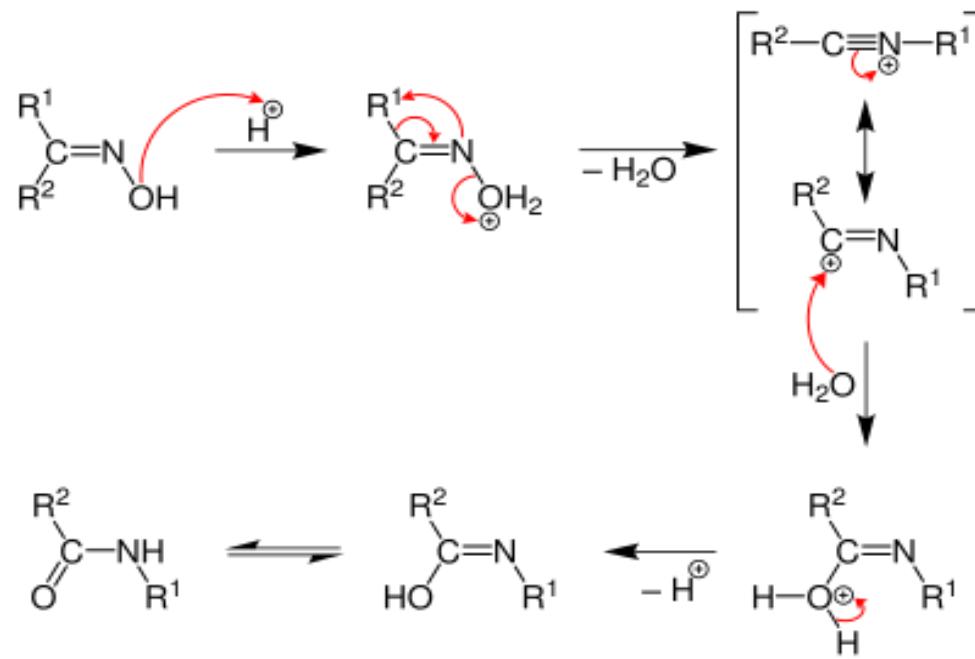


Migration to Electron Deficient Nitrogen (Beckmann Rearrangement)

- **Beckmann Rearrangement** is an acid-catalyzed rearrangement of an oxime to an amide. Cyclic oximes yield lactams
- Example

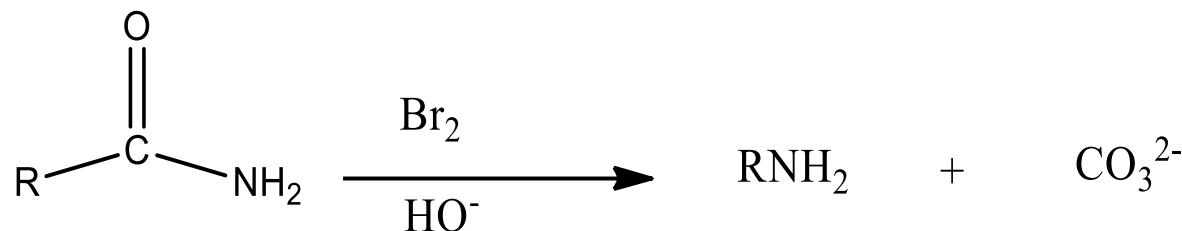


- Reaction mechanism

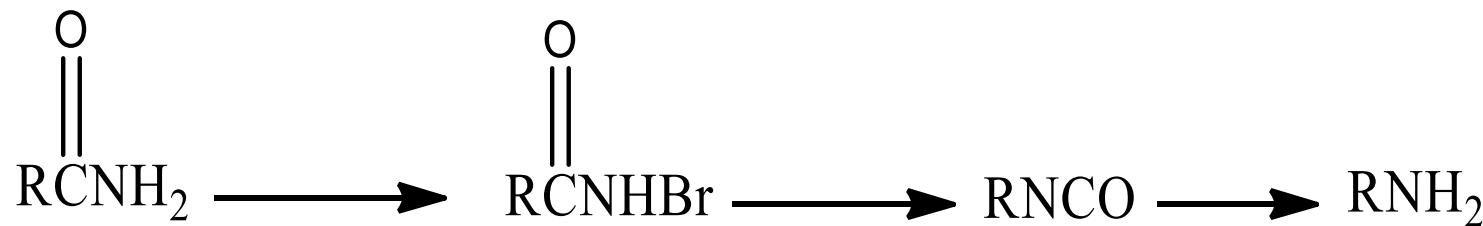


Migration to Electron Deficient Nitrogen (hoffman Rearrangement)

- Treatment of amides with bromine in basic solution gives an amine with loss of the carbonyl carbon.



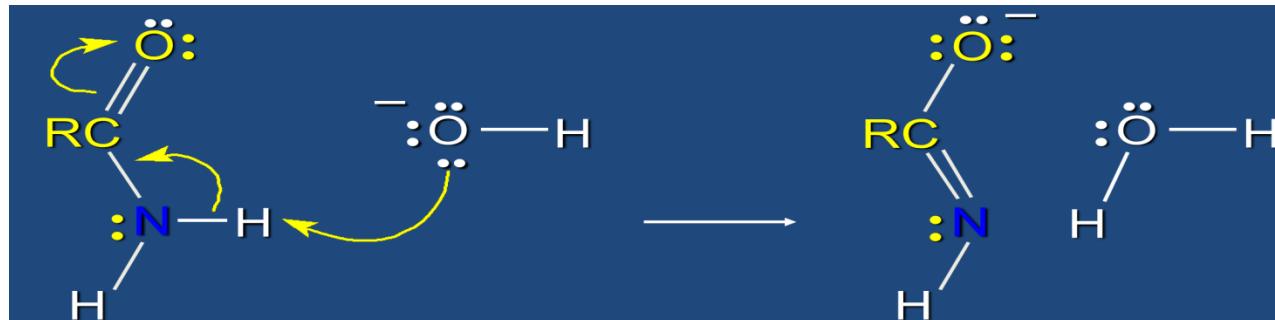
- General mechanism of hoffman Rearrangement follows the following



Migration to Electron Deficient Nitrogen (Hoffmann Rearrangement)

- The Hoffmann rearrangement involves 6 steps in 3 stages.
 - formation of an N-bromo amide (2 steps)
 - conversion of the N-bromo amide to An isocyanate (2 steps)
 - hydrolysis of the isocyanate (2 steps)

- Step-1



- Step-2

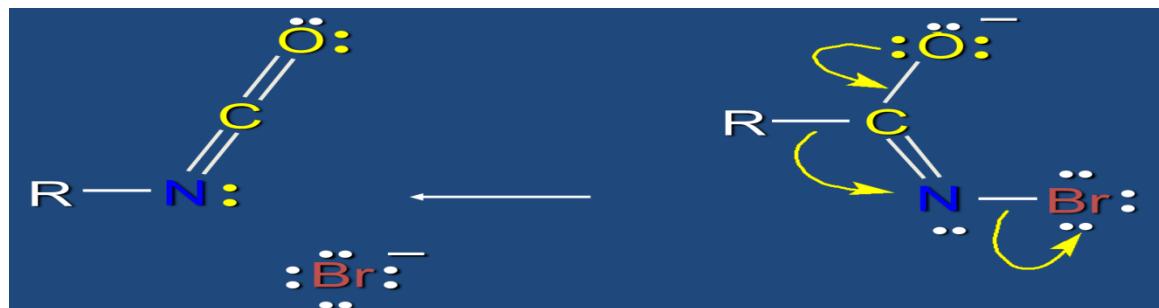


Migration to Electron Deficient Nitrogen (Hoffmann Rearrangement)

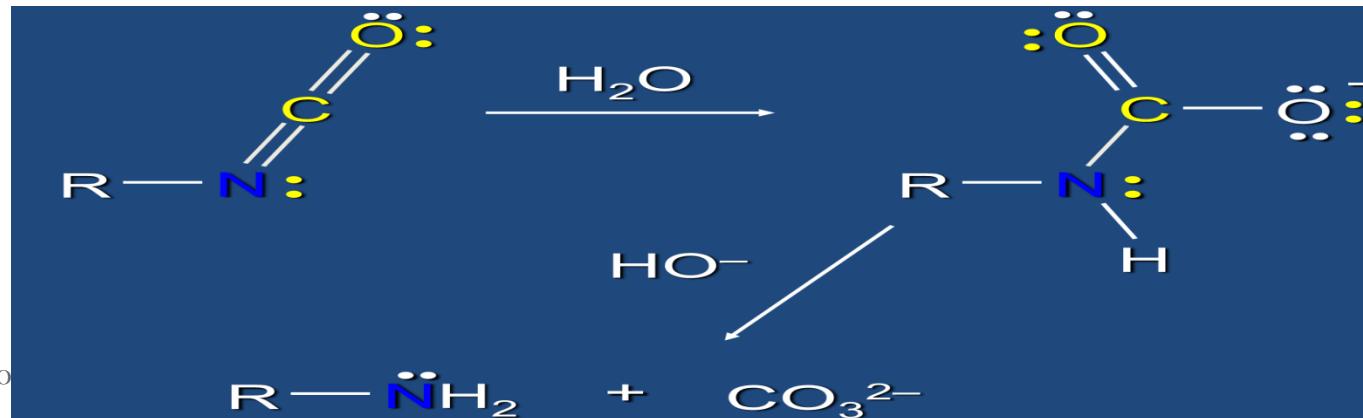
- Step-3



- Step-4



- Step-5 & 6



Thank
You

