

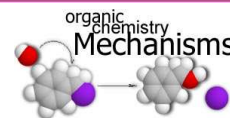
**CHEM 344**

# **ORGANIC REACTION MECHANISM**

FOR CHEMISTRY' STUDENTS, COLLEGE OF SCIENCE

PRE-REQUISITES COURSE; CHEM 241

CREDIT HOURS; 2 (2+0+0)



**Prof. Mohamed El-Newehy**

<http://fac.ksu.edu.sa/melnewehy>

**Dr. Zainab Almarhoon**

<https://fac.ksu.edu.sa/zalmarhoon>

**Dr. Monirah A. Al-Shaikh**

<https://faculty.ksu.edu.sa/ar/mshaikh>

Chemistry Department, College of Science, King Saud University

1

# **INTRODUCTION**

Fundamental Principles

2



## ELECTRON DISPLACEMENT EFFECTS IN COVALENT BONDS

- The electron displacement in an organic molecule may take place either in
  - The ground state under the influence of an atom or a substituent group cause permanent polarization of the bond (*Inductive effect and resonance effects*).

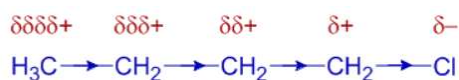
Or

- in the presence of an appropriate attacking reagent.
- Temporary electron displacement effects (*electromeric effect or polarizability effect*).

5

## INDUCTIVE EFFECT

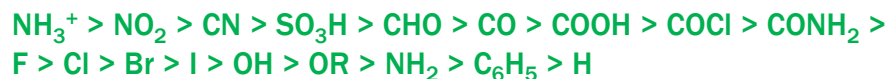
- Inductive effects are electronic effects that occur through sigma  $\sigma$  bonds caused by electronegativity differences of atoms.



- *Types of inductive effect:*

### 1) Negative inductive effect (-I):

- This is the electron-withdrawing inductive effect, also known as the *-I effect*



### 2) Positive inductive effect (+I):

- This is electron releasing character and is indicated by the *+I effect*



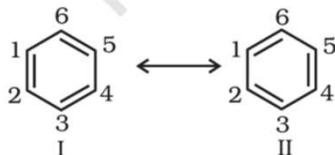
6

## RESONANCE STRUCTURE

- The resonance structures are hypothetical and individually do not represent any real molecule.

- An example:

Benzene; Its cyclic structure containing alternating C–C single and C=C double bonds



- An example:

Nitromethane ( $\text{CH}_3\text{NO}_2$ ); It is therefore a resonance hybrid of the two canonical forms I and II.



7

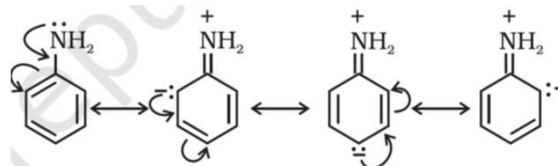
## RESONANCE OR MESOMERIC EFFECT

- The resonance effect is defined as 'the polarity produced in the molecule by the interaction of two  $\pi$ -bonds or between a  $\pi$ -bond and lone pair of electrons present on an adjacent atom'.

### (i) Positive Resonance Effect (+R effect):

The transfer of electrons is away from an atom or substituent group attached to the conjugated system.

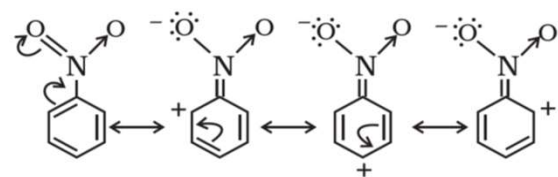
Examples; - halogen, -OH, -OR, -OCOR, -NH<sub>2</sub>, -NHR, -NR<sub>2</sub>, -NHCOR,



### (ii) Negative Resonance Effect (- R effect):

The transfer of electrons is towards the atom or substituent group attached to the conjugated system.

Examples; - COOH, -CHO, >C=O, - CN, -NO<sub>2</sub>



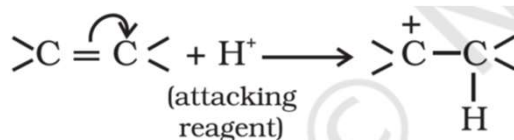
8

## ELECTROMERIC EFFECT (E EFFECT)

- The organic compounds having a multiple bond (a double or triple bond) show this effect in the presence of an attacking reagent only.
- The complete transfer of a shared pair of  $\pi$ -electrons to one of the atoms joined by a multiple bond on the demand of an attacking reagent.

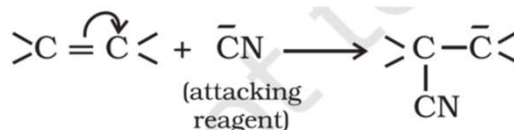
### (i) Positive Electromeric Effect (+E effect):

the  $\pi$ -electrons of the multiple bond are transferred to that atom to which the reagent gets attached.



### (ii) Negative Electromeric Effect (-E effect):

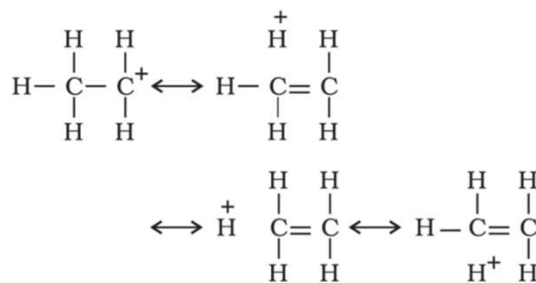
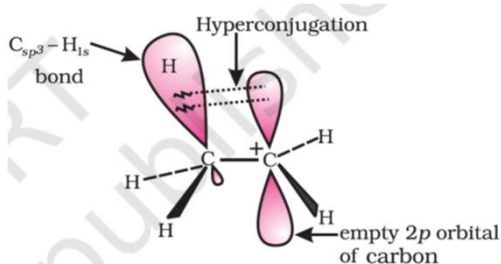
the  $\pi$ -electrons of the multiple bond are transferred to that atom to which the attacking reagent does not get attached.



9

## HYPERCONJUGATION

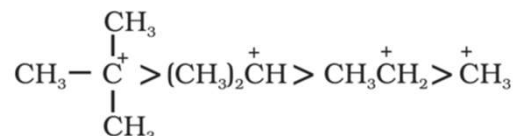
- It involves delocalization of  $\sigma$  electrons of C-H bond of an alkyl group directly attached to an atom of unsaturated system or to an atom with an unshared  $p$  orbital.
- $CH_3CH_2^+$  (ethyl cation); the positively charged carbon atom has an empty  $p$  orbital. One of the C-H bonds of the methyl group can align in the plane of this empty  $p$  orbital and the electrons constituting the C-H bond in plane with this  $p$  orbital can then be delocalized into the empty  $p$  orbital.



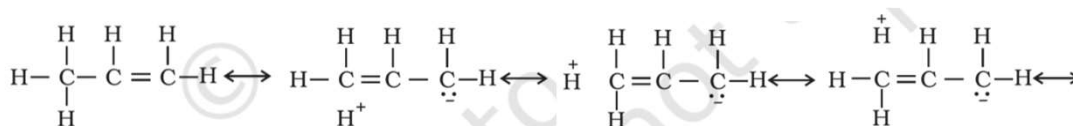
10

## HYPERCONJUGATION

- This type of overlap stabilizes the carbocation because electron density from the adjacent  $\sigma$  bond helps in dispersing the positive charge.
- In general, greater the number of alkyl groups attached to a positively charged carbon atom, the greater is the hyperconjugation interaction and stabilization of the cation.



- Hyperconjugation is also possible in alkenes and alkylarenes.



11

## TYPES OF ORGANIC REACTIONS

### 1) Substitution Reactions

- Nucleophilic substitution
- Electrophilic substitution
- Free-radical substitution

### 2) Addition Reactions

- Nucleophilic addition
- Electrophilic addition
- Free-radical addition

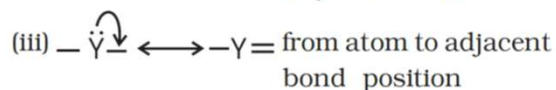
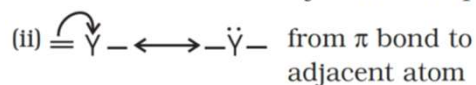
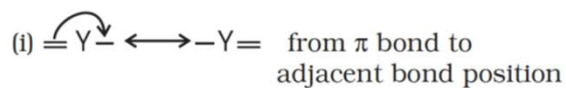
### 3) Elimination Reactions

### 4) Rearrangement reactions

12

## ELECTRON MOVEMENT IN ORGANIC REACTIONS: THE ARROW NOTATION

- The movement of electrons in organic reactions can be shown by **curved-arrow notation**.



- Movement of single electron is indicated by a single barbed 'fish hooks' (i.e. **half headed curved arrow**).

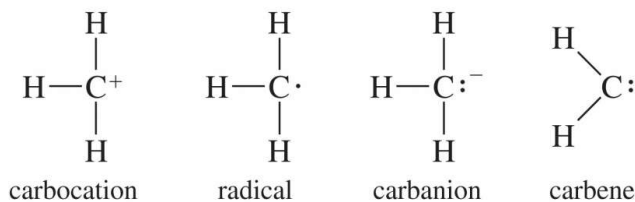


13

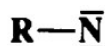
## REACTIVE INTERMEDIATE

- There are four types of organic species; *very short-lived and exist only as intermediates that are quickly converted to more stable molecules*

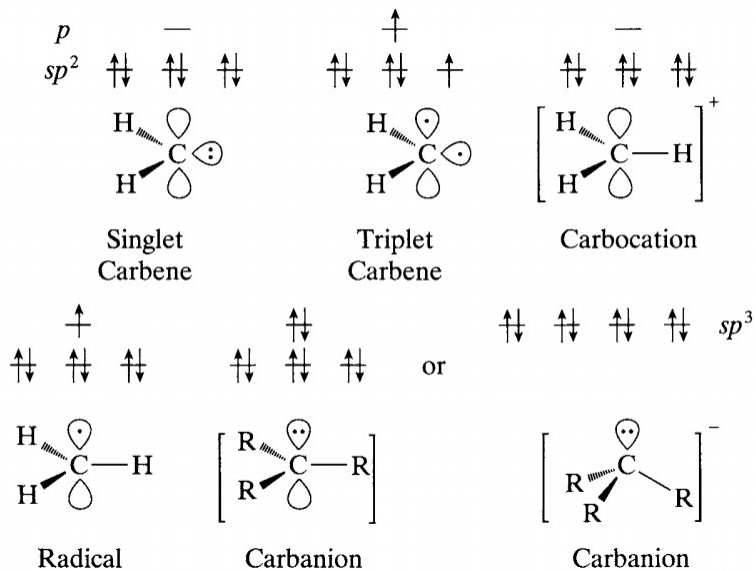
### Carbon Reactive Intermediates



- Nitrenes (*nitrogen analogs of carbenes*)



## REACTIVE INTERMEDIATE



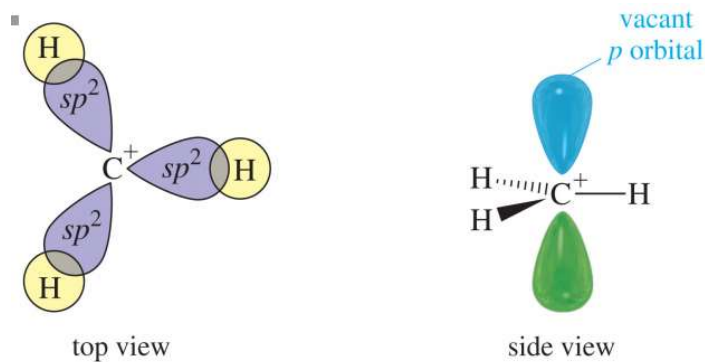
15

## REACTIVE INTERMEDIATE

### CARBOCATION

#### Carbocation Structure

- Carbon has 6 electrons, positively charged.
- Carbon is  $sp^2$  hybridized with vacant  $p$  orbital





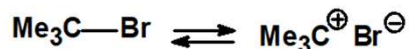
## REACTIVE INTERMEDIATE

### CARBOCATION

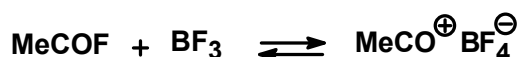
#### Methods of Forming Carbocation

##### (A) Heterolytic fission of neutral species

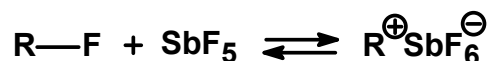
- Simple ionization; *the electron pair remains with departing group, which is called leaving group and tertiary butyl group carries positive charge.*



- Ionization may also be induced by Lewis acids, e.g.  $\text{BF}_3$ ,  $\text{AlCl}_3$  to yield in this case an acyl cation.



- With antimony pentafluoride ( $\text{SbF}_5$ ) as a Lewis acid, with either liquid  $\text{SO}_2$  or excess  $\text{SbF}_5$  as solvent,



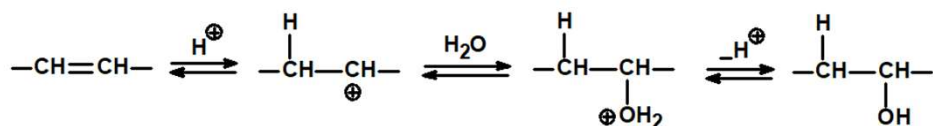
## REACTIVE INTERMEDIATE

### CARBOCATION

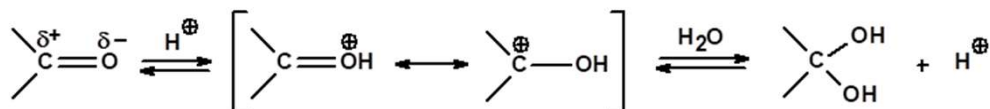
#### Methods of Forming Carbocation

##### (B) Addition of cations to neutral species

- The most common cation is  $\text{H}^+$ , adding to unsaturated linkages, i.e. protonation, in for example the acid-catalyzed hydration of alkenes:



- Protonation can also occur on oxygen in a carbon-oxygen double bond,

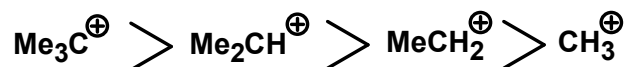


## REACTIVE INTERMEDIATE

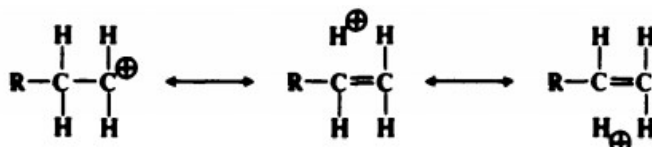
### CARBOCATION

#### Stability and Structure of Carbocation

- The simple alkyl carbocation have already been seen to follow the stability sequence,



- The stability order can be explained by hyperconjugation and inductive effect
- Quantum mechanical calculations for simple alkyl cations do indeed suggest that the planar ( $sp^2$ ) configuration is more stable than the pyramidal ( $sp^3$ ) by  $\approx 84$  kJ (20 kcal)  $\text{mol}^{-1}$ .

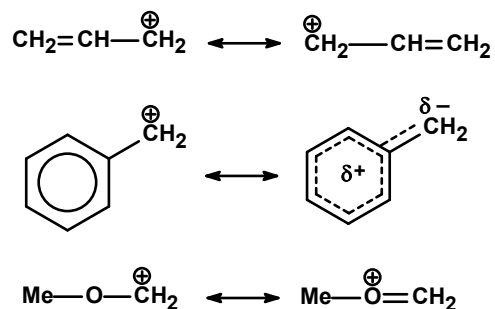


## REACTIVE INTERMEDIATE

### CARBOCATION

#### Stability and Structure of Carbocation

- The possibility of delocalizing the charge, particularly where this can involve  $\pi$  orbitals:



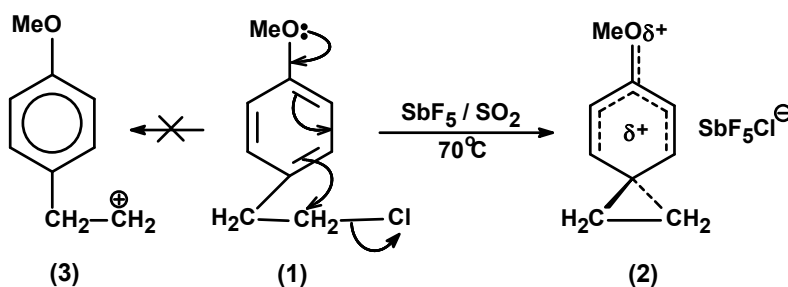
## REACTIVE INTERMEDIATE

### CARBOCATION

#### Stability and Structure of Carbocation

- Stabilization can also occur, again by delocalization, through the operation of a neighboring group effect resulting in the formation of a 'bridged' carbocation.

*Thus the action of  $\text{SbF}_5$  in liquid  $\text{SO}_2$  on  $p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{Cl}$  (1) results in the formation of (2) rather than the expected cation (3), phenyl acting as a neighboring group:*

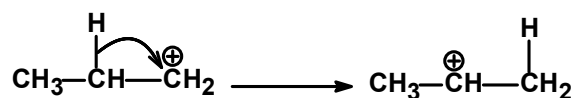


## REACTIVE INTERMEDIATE

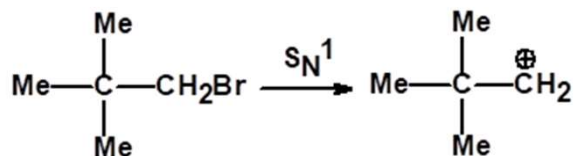
### CARBOCATION

#### Carbocation Rearrangements

- Without change in carbon skeleton;  
*1-propyl cation rearranged to the 2-propyl cation by the migration of a hydrogen atom, with its electron pair (i.e. as  $\text{H}^-$ ), from  $\text{C}_2$  to the carbocationic  $\text{C}_1$ , a 1,2-hydride shift:*



- With change in carbon skeleton; Neopentyl rearrangements

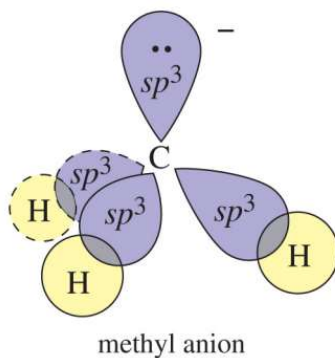


## REACTIVE INTERMEDIATE

### CARBANION

#### Carbanion Structure

- Eight electrons on carbon: 6 bonding plus one lone pair.
- Carbon has a negative charge.
- Destabilized by alkyl substituents.



## REACTIVE INTERMEDIATE

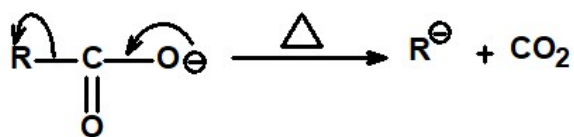
### CARBANION

- **Carbanion** possess an unshared pair of electrons and is therefore a base.
- Carbanion can be formed by

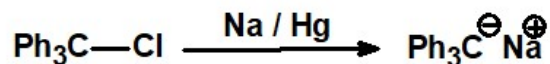
- *Removal of a proton*



- *Removal of CO<sub>2</sub> from decarboxylation of RCO<sub>2</sub><sup>-</sup>*



- *Removal of Cl from Ph<sub>3</sub>C-Cl*



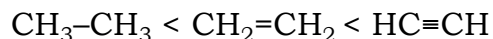
## REACTIVE INTERMEDIATE

### CARBANION

#### Stability of Carbanion

- The main features that serve to stabilize carbanions are

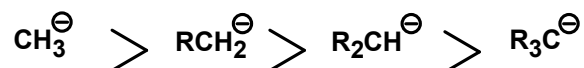
- increase in s character at the carbanion carbon



- electron-withdrawing inductive effects

$-\text{CF}_3$  and  $-\text{C}(\text{CF}_3)_3$  by electron-withdrawal.

The destabilizing influence of the electron-donating inductive effect of alkyl groups is seen in the observed carbanion stability sequence:



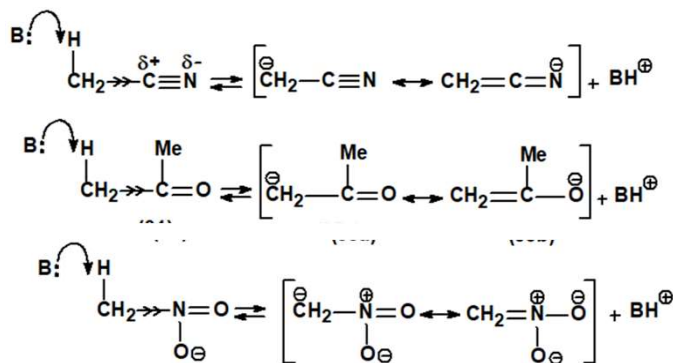
## REACTIVE INTERMEDIATE

### CARBANION

#### Stability of Carbanion

- The main features that serve to stabilize carbanions are

- conjugation of the carbanion lone pair with a polarized multiple bond  
the most common stabilizing feature, e.g. with CN, C=O, NO<sub>2</sub>



## REACTIVE INTERMEDIATE

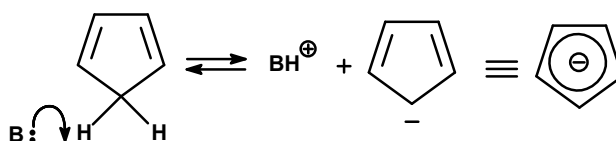
### CARBANION

#### Stability of Carbanion

- The main features that serve to stabilize carbanions are

- *aromatization*

the cyclopentadienyl anion, being a  $6\pi$  electron delocalized system, The 6 electrons can be accommodated in three stabilized  $\pi$  molecular orbitals, like benzene, and the anion thus shows quasi-aromatic stabilization; it is stabilized by *aromatization*:

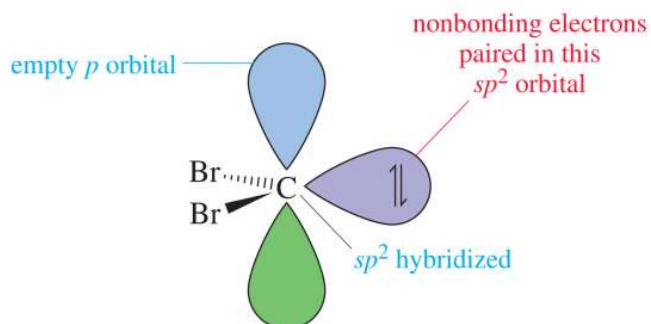


## REACTIVE INTERMEDIATE

### CARBENES AND NITRENES

#### Carbenes Structure

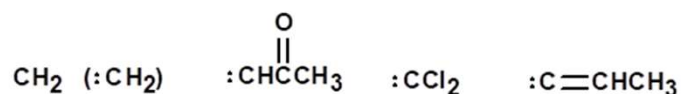
- Carbon is neutral
- Vacant p orbital, so can be electrophilic
- Lone pair of electrons, so can be nucleophilic



## REACTIVE INTERMEDIATE

### CARBENES AND NITRENES

- **Carbenes** (also called methylenes) are highly reactive species.
- **Carbenes** are molecules containing divalent carbon atoms.
- Each divalent carbon has two unshared electrons, which are often shown when writing the structures of carbenes.
- However, carbenes are neutral molecules, not carbanions.



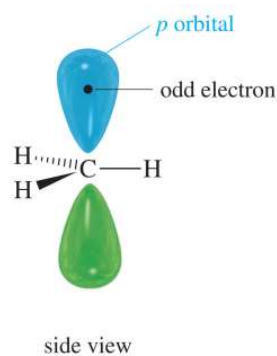
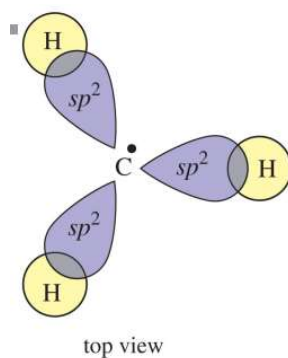
- **Nitrenes** are compounds, such as  $\text{:NC}_6\text{H}_5$ , that contain monovalent nitrogen atoms.

## REACTIVE INTERMEDIATE

### FREE RADICALS

#### Free radical Structure

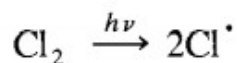
- Electron-deficient
- Stabilized by alkyl substituents.
- Order of stability:  $3^\circ > 2^\circ > 1^\circ$ .



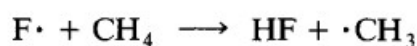
## REACTIVE INTERMEDIATE

### FREE RADICALS

- Radicals are species that contain one or more unpaired electrons.
- Many radicals are produced by homolytic cleavage of bonds.



- Hydrogen abstraction; many radicals can remove hydrogen atoms from organic molecules to form carbon radicals.



## NUCLEOPHILES AND ELECTROPHILES

### ELECTROPHILES

- **Electrophile (E<sup>+</sup>)**; (electron-loving) are electron-deficient species and tend to attack the substrate at a site of high electron density and the reaction is called **electrophilic**.
- **Examples of electrophiles** include
  - **Positively charged species** as exemplified by proton (H<sup>+</sup>), cations (such as Cl<sup>+</sup>, NR<sub>4</sub><sup>+</sup>) and carbocations (<sup>+</sup>CH<sub>3</sub>) and
  - **Neutral species** as exemplified by Lewis acids (such as BF<sub>3</sub>, AlCl<sub>3</sub>, ZnCl<sub>2</sub>) and carbenes (Cl<sub>2</sub>C:) or neutral molecules having functional groups like carbonyl group (>C=O) or alkyl halides (R<sub>3</sub>C-X, where X is a halogen atom).
- They have six valence electrons (except H<sup>+</sup>) and can accept an electron pair from a nucleophile to acquire the stable octet.
- For example, hydroxide ion combines with a proton to give water.





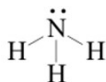
## NUCLEOPHILES AND ELECTROPHILES

### NUCLEOPHILES

- **Nucleophile (Nu:)**; a reagent that brings an electron pair to the reactive site and the reaction is then called **nucleophilic**.
- Some examples of nucleophiles are
  - the negatively charged ions with lone pair of electrons such as hydroxide ( $\text{HO}^-$ ), cyanide ( $\text{NC}^-$ ) ions and carbanions ( $\text{R}_3\text{C}^-$ ).
  - Neutral molecules having nonbonding lone pair(s) of electrons such as water, ammonia, alcohols, dimethylsulfide and triphenylphosphine



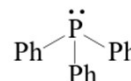
water



ammonia



dimethylsulfide



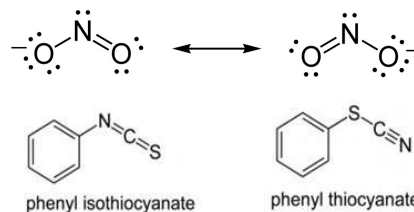
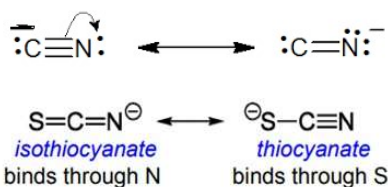
triphenylphosphine

- Nucleophilic reagents tend to attack the electron deficient species (electrophiles).

## NUCLEOPHILES AND ELECTROPHILES

### NUCLEOPHILES

- The nucleophiles which have more than one (generally two) suitable atoms through which they can attack the substrate are known as **ambident nucleophiles**.
- An **ambident nucleophile** is an anionic nucleophile whose negative charge is delocalized by resonance over two unlike atoms or over two like but non-equivalent atoms.
- Some examples are
  - Cyanide, isothiocyanate and nitrite ions are some examples of ambident nucleophiles, since they have more than one reactive site.

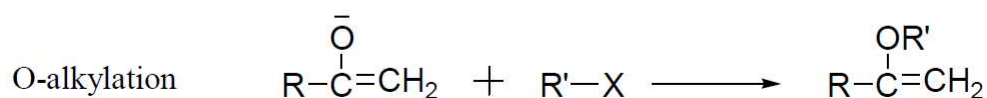
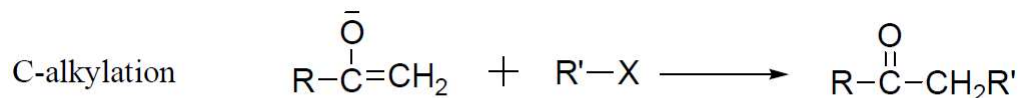


## NUCLEOPHILES AND ELECTROPHILES

### NUCLEOPHILES

#### o Example

- Alkylation of enolate can either occur at C or O. since most negative charge of an enolate is on the Oxygen atom, the O-alkylated product is dominated.



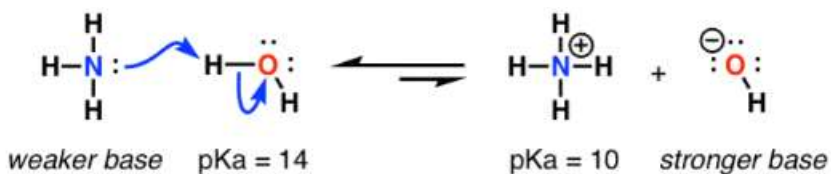
## NUCLEOPHILES AND ELECTROPHILES

### NUCLEOPHILICITY AND BASICITY?

- Basicity:** nucleophile attacks hydrogen (proton).
- Nucleophilicity:** nucleophile attacks any atom other than hydrogen (e.g. carbon).

Most species can participate in reversible acid-base reactions.

*Basicity can be measured by the position of an equilibrium (e.g. stability is a thermodynamic property).*



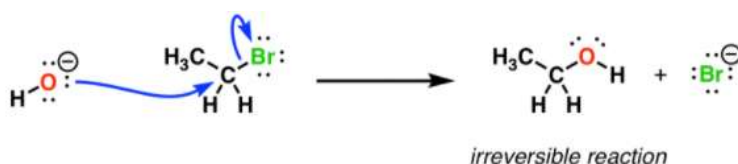
## NUCLEOPHILES AND ELECTROPHILES

### NUCLEOPHILICITY AND BASICITY?

- **Basicity:** nucleophile attacks hydrogen (proton).
- **Nucleophilicity:** nucleophile attacks any atom other than hydrogen (e.g. carbon).

Reactions of nucleophiles with carbon are irreversible and are not in equilibrium (e.g. A bond forms, a bond breaks, and that's the end of the reaction).

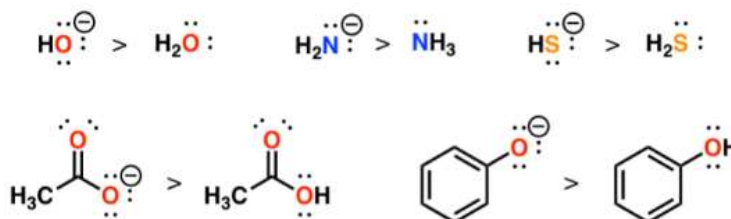
e.g. the *nucleophilicity is measured by the rate of the reaction.*



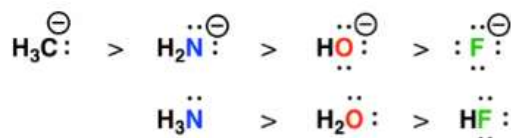
## NUCLEOPHILES AND ELECTROPHILES

### FACTORS AFFECTING NUCLEOPHILICITY

- **Charge:** the conjugate base is always a stronger nucleophile as the nucleophilicity increases with increasing electron density on an atom.



- **Electronegativity:** nucleophilicity increases with decreasing electronegativity as the less electronegative the atom, the less “tightly held” those electrons will be.

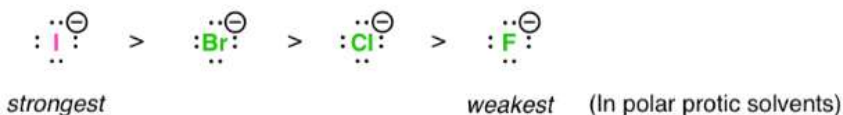


These two factors correlate strongly with basicity.

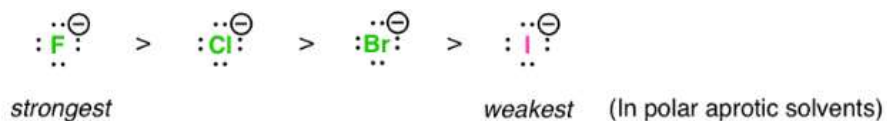
## NUCLEOPHILES AND ELECTROPHILES

### FACTORS AFFECTING NUCLEOPHILICITY

- o **solvent:** in *polar protic solvents*, nucleophilicity increases going **down** the periodic table (solvation).



- o **solvent:** in *polar aprotic solvents*, nucleophilicity increases going **up** the periodic table (solvation).

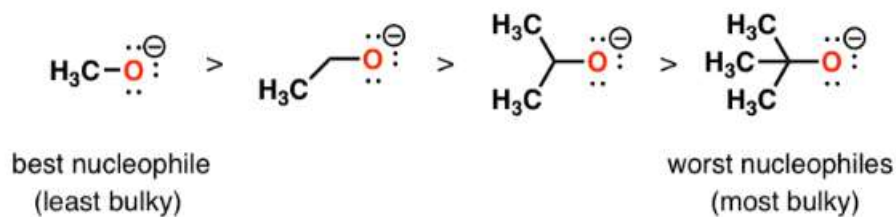


Nucleophilicity is essentially correlated with basicity.

## NUCLEOPHILES AND ELECTROPHILES

### FACTORS AFFECTING NUCLEOPHILICITY

- o **Steric Hindrance "Bulkiness":** in *polar protic solvents*, nucleophilicity increases going **down** the periodic table (solvation).



## NUCLEOPHILES AND ELECTROPHILES

### NUCLEOPHILICITY AND BASICITY?

#### Strong Bases/Strong Nucleophiles

A good base is usually a good nucleophile. So, strong bases – substances with negatively charged O, N, and C atoms – are strong nucleophiles.

Examples are:  $\text{RO}^-$ ,  $\text{OH}^-$ ,  $\text{RLi}$ ,  $\text{RC}\equiv\text{C}^-$ , and  $\text{NH}_2^-$ .

#### Strong Bases/Poor Nucleophiles

Some strong bases are poor nucleophiles because of steric hindrance.

Examples are  $t\text{-BuO}^-$ ,  $t\text{-BuLi}$ , and  $\text{LiN}[\text{CH}(\text{CH}_3)_2]$

#### Weak Bases/Good Nucleophiles

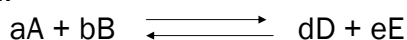
$\text{I}^-$  is a weak base, but it is a good nucleophile because the large electron cloud is highly polarizable.

## WHY DO THESE REACTIONS OCCUR?

### THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION

- When we look at an organic reaction we have to take into account two main concepts:
  - (1) The equilibrium
  - (2) The rate of the reaction.
- The conversion between reactants and products is governed by the reaction free energy  $\Delta G$  (*free energy of the products*) – (*free energy of the reactants*).
- The reactants must be supplied with enough *activation energy* to enable the reaction to proceed in the forward direction.
- All organic reactions will reach equilibrium that favors the more stable side.

For a reaction:



$$K_{eq} = [\text{products}] / [\text{reactants}] = [\text{D}]^d [\text{E}]^e / [\text{A}]^a [\text{B}]^b$$

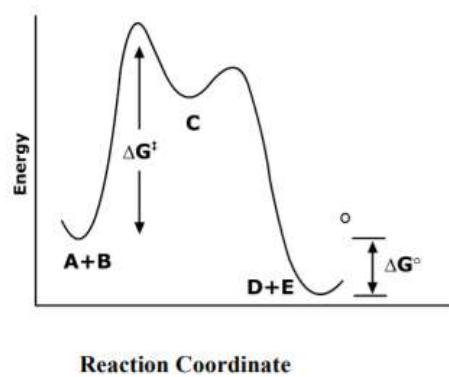
## WHY DO THESE REACTIONS OCCUR?

### THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION

Energy profile for reaction  $A + B \longrightarrow C \longrightarrow D + E$

$\Delta G^\circ = (\text{free energy of products}) - (\text{free energy of reactants})$

$\Delta G^\ddagger = (\text{free energy of transition state}) - (\text{free energy of reactants})$



Any quantity that refers to the transition state is represented by the doubledagger superscript ( $\ddagger$ )

## WHY DO THESE REACTIONS OCCUR?

### THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION

The thermodynamic stability is indicated by  $\Delta G^\circ$ :

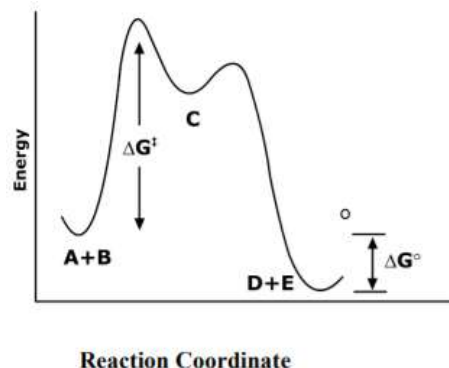
If  $\Delta G^\circ$  is **negative** the product is **thermodynamically stable** compared to reactant and the reaction is said to be **exergonic reaction**.

If  $\Delta G^\circ$  is **positive** the product is **thermodynamically unstable** compared to reactant and the reaction is said to be **endergonic reaction**.

The kinetic stability of a component is indicated by  $\Delta G^\ddagger$ :

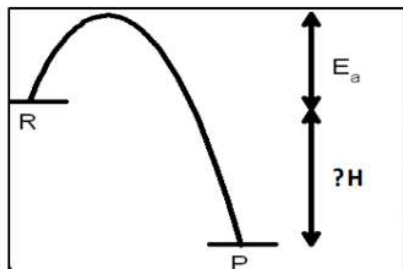
If  $\Delta G^\ddagger$  is **large**, the compound (the reactant) is **kinetically stable** i.e., it does not undergo that reaction rapidly.

If  $\Delta G^\ddagger$  is **small**, the compound (the reactant) is **kinetically unstable** i.e., it undergoes the reaction rapidly.



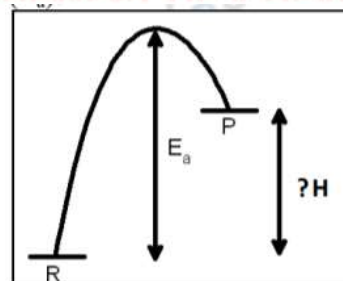
## WHY DO THESE REACTIONS OCCUR?

### THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION



#### Exothermic/spontaneous Reactions

- More energy will be released to the surrounding.
- $\Delta H$  will be negative.
- The products are thermodynamically stable than the reactants ( $-\Delta G$ ).
- The equilibrium constant for the reaction will be large ( $K_{eq} > 1$ ).



#### Endothermic/nonspontaneous Reactions

- More energy will be absorbed from the surrounding.
- $\Delta H$  will be positive.
- The reactants are thermodynamically stable than the products ( $+\Delta G$ ).
- The equilibrium constant for the reaction will be small ( $K_{eq} < 1$ ).

## WHY DO THESE REACTIONS OCCUR?

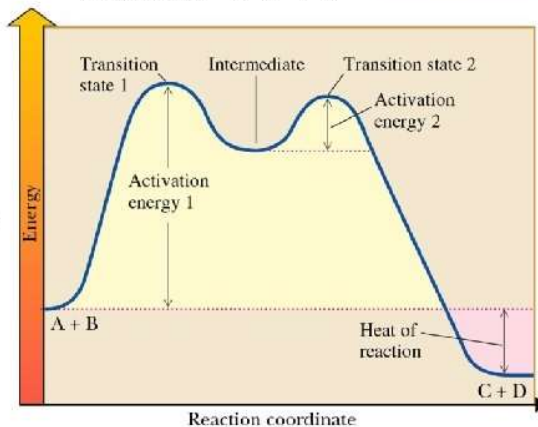
### THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION

#### Multi-Step Reactions



Step 1 is the "slow step", the rate determining step.

Step 1: endergonic, high energy of activation. Slow process

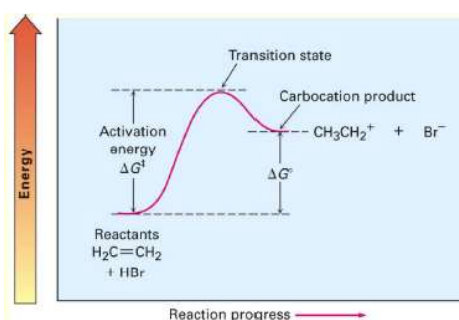
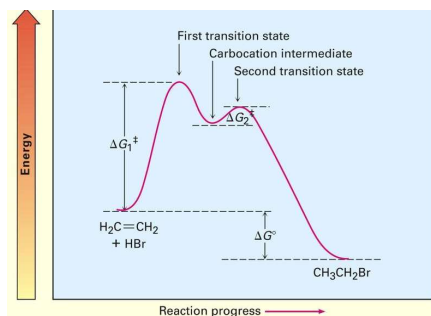


Step 2: exergonic, small energy of activation. Fast Process.

## WHY DO THESE REACTIONS OCCUR?

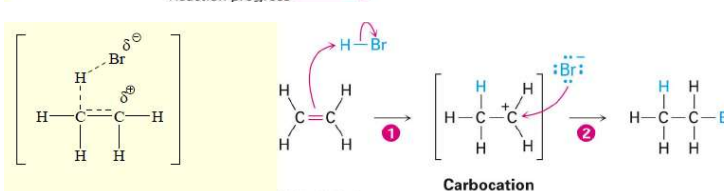
### THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION

#### Energy diagram for the reaction of Ethylene with HBr



- If a reaction occurs in more than one step, it must involve species that are neither the reactant nor the final product.
- These are called reaction **intermediates**.
- Each step has its own free energy of activation

- The energy needed to go from reactant to transition state is the **activation energy ( $\Delta G^\ddagger$ )**.
- The highest energy point in a reaction step is called the **transition state**



## WHY DO THESE REACTIONS OCCUR?

### THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION

#### Kinetics Overview; The smaller the $E_a$ the faster is the reaction:

- If the activation energy is low then the reaction will be fast even at low temperatures. Such reactions do increase their rates with increasing temperature as well
- If the activation energy is high then at low temperatures the reaction will be slow. It can be made faster by increasing the temperature

#### First order reaction

For the reaction:



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

If the rate of a reaction depends on the concentration of only one reactant,

#### Second-order reaction:



$$\text{Rate} = k [A] [B]$$

A reaction whose rate depends on the concentrations of two reactants