

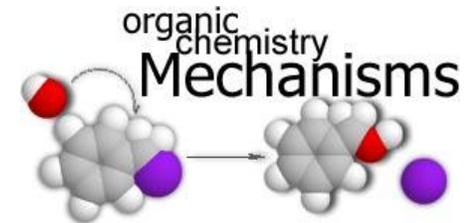
CHEM 344

ORGANIC REACTION MECHANISM

FOR CHEMISTRY' STUDENTS, COLLEGE OF SCIENCE

PRE-REQUISITES COURSE; CHEM 241

CREDIT HOURS; 2 (2+0+0)



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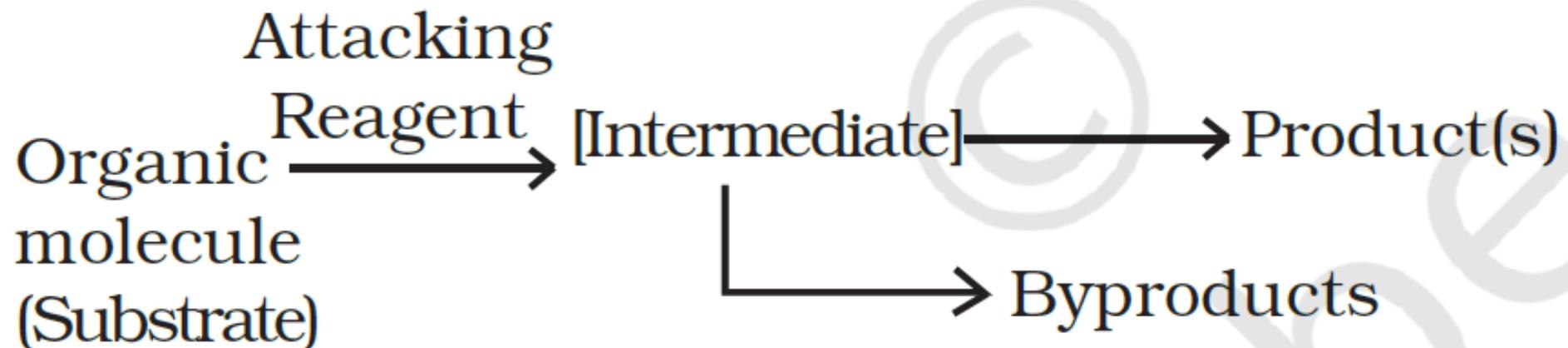
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INTRODUCTION

Fundamental Principles

FUNDAMENTAL CONCEPTS IN ORGANIC REACTION MECHANISM

- The general reaction is depicted as follows :



- Substrate; A molecule whose carbon is involved in new bond formation
- and the other one is called reagent.

DEFINITION

- A *mechanism* is the actual process by which a reaction takes place:
 - Which bonds are broken, in what order;
 - How many steps are involved;
 - The relative rate of each step, etc.
- A detailed study of the sequence of steps which are involved in the conversion of reactants into product(s) is known as *reaction mechanism*.
- In order to state a mechanism completely, we should have to specify the *position of all atoms*, including those in *solvent molecules*, and the *energy of the system*, at every point in the process

ELECTRON DISPLACEMENT EFFECTS IN COVALENT BONDS

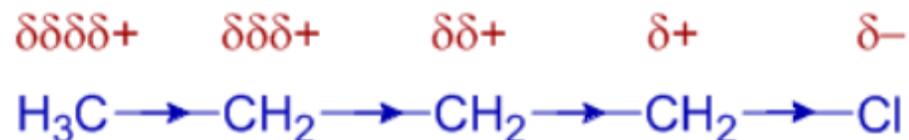
- The electron displacement in an organic molecule may take place either in
 - The ground state under the influence of an atom or a substituent group cause permanent polarization of the bond (*Inductive effect and resonance effects*).

Or

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

INDUCTIVE EFFECT

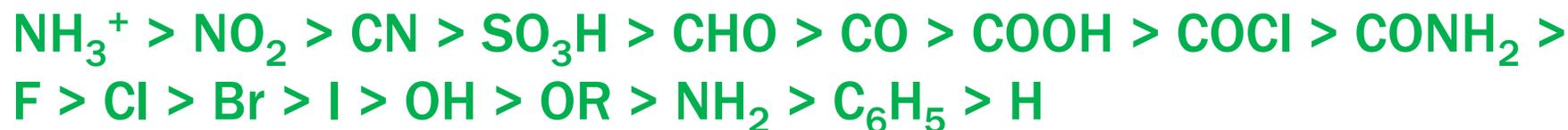
- Inductive effects are electronic effects that occur through sigma σ bonds caused by electronegativity differences of atoms.



- **Types of inductive effect:**

1) Negative inductive effect (-I):

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



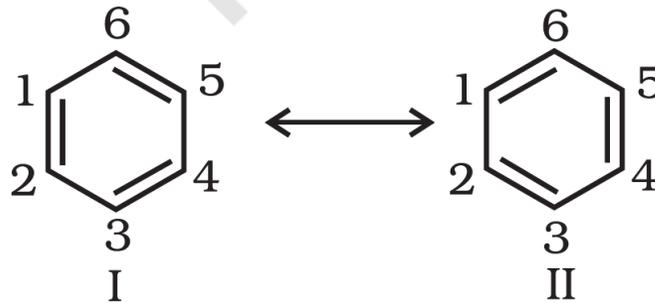
2) Positive inductive effect (+I):

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

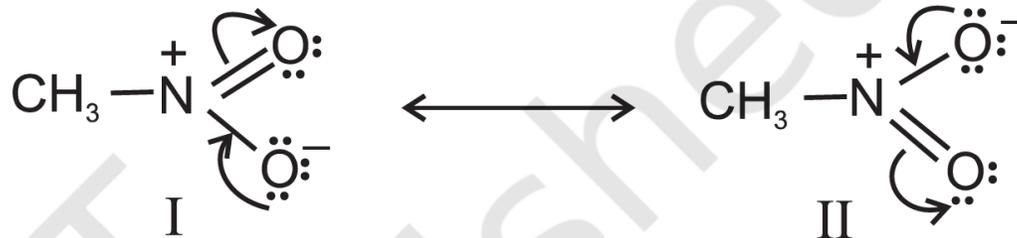


RESONANCE STRUCTURE

- 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 (CH_3NO_2); It is therefore a resonance hybrid of the two canonical forms I and II.



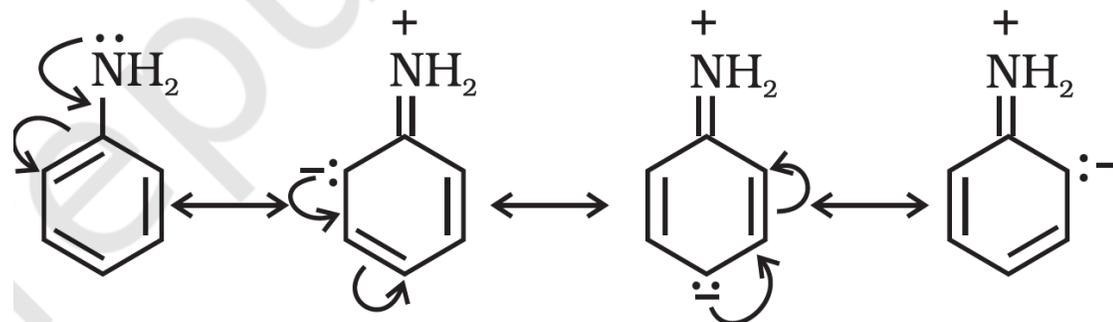
RESONANCE OR MESOMERIC EFFECT

- The resonance effect is defined as 'the polarity produced in the molecule by the interaction of two π -bonds or between a π -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.

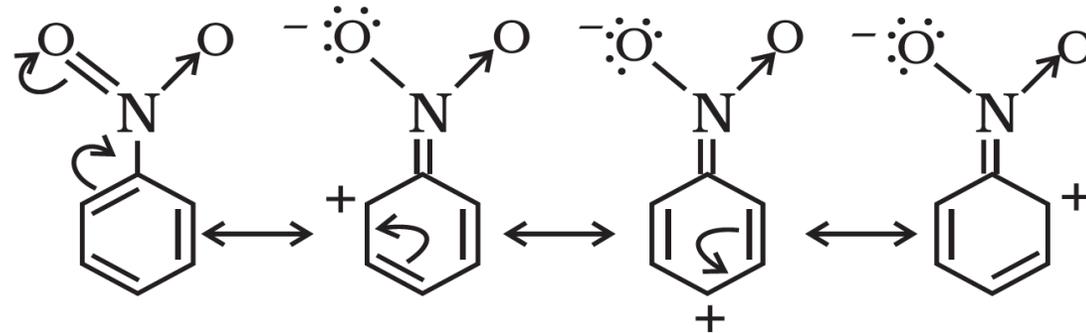
Examples; - halogen, -OH, -OR, -OCOR, -NH₂,
-NHR, -NR₂, -NHCOR,



(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, -NO₂

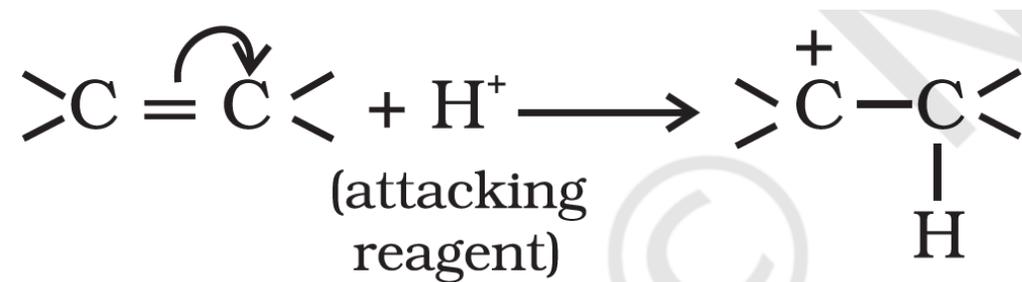


ELECTROMERIC EFFECT (E EFFECT)

- 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 π -electrons to one of the atoms joined by a multiple bond on the demand of an attacking reagent.

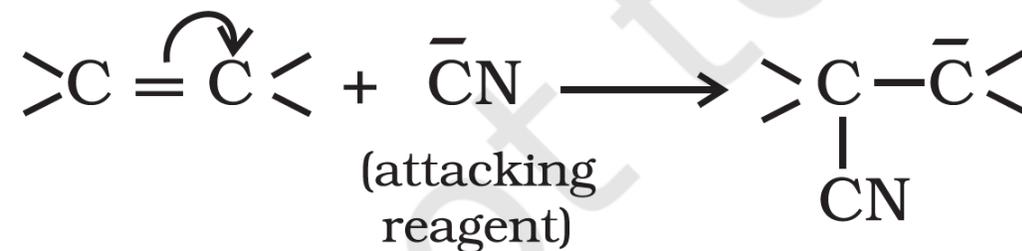
(i) Positive Electromeric Effect (+E effect):

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



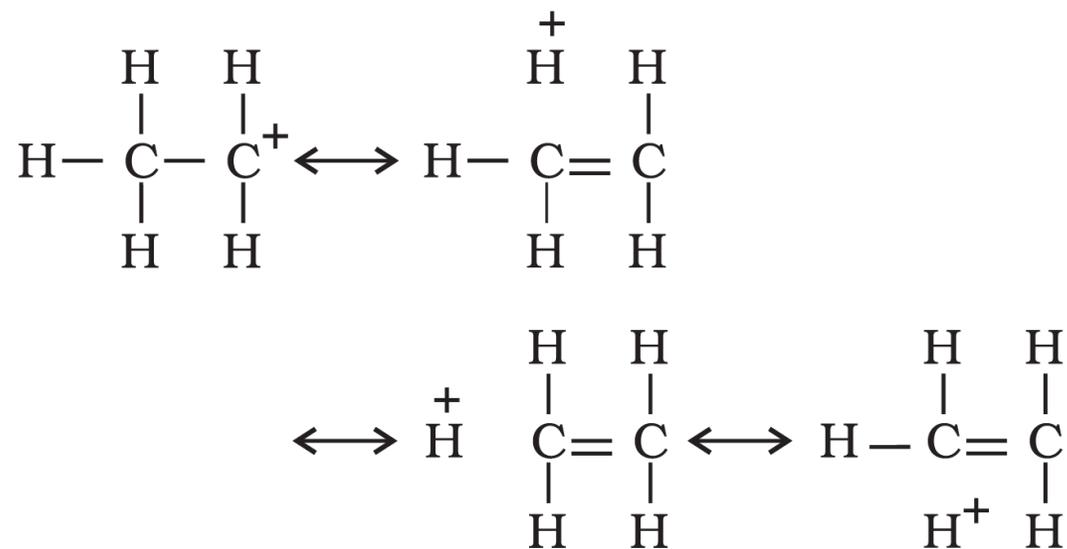
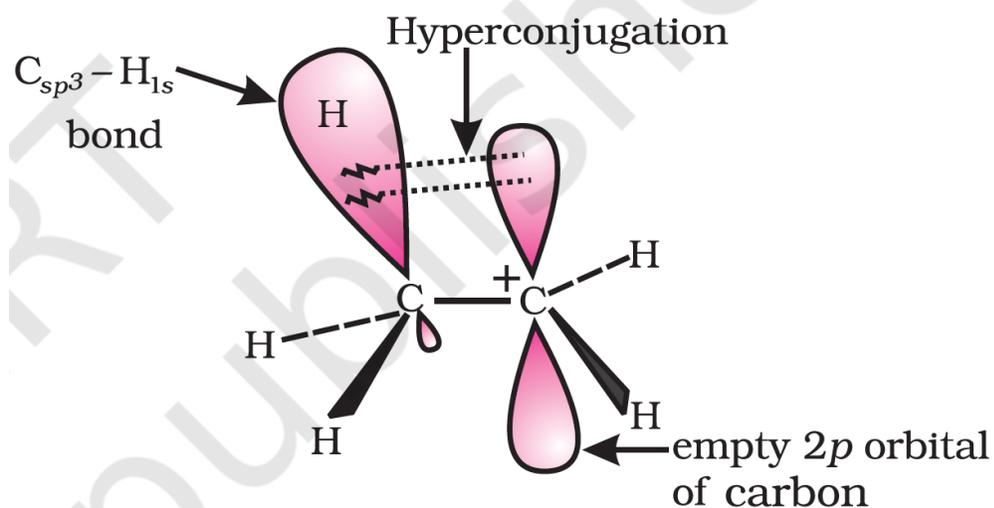
(ii) Negative Electromeric Effect (-E effect):

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



HYPERCONJUGATION

- It involves delocalization of σ 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.



TYPES OF ORGANIC REACTIONS

1) Substitution Reactions

- a. Nucleophilic substitution*
- b. Electrophilic substitution*
- c. Free-radical substitution*

2) Addition Reactions

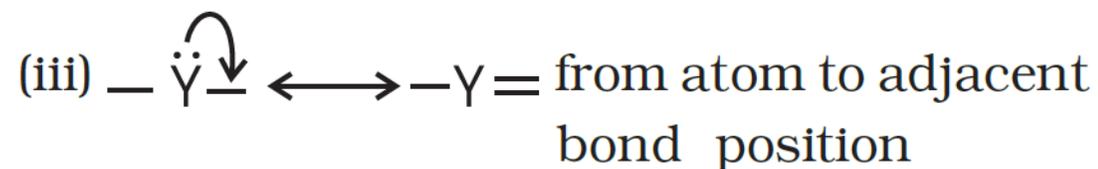
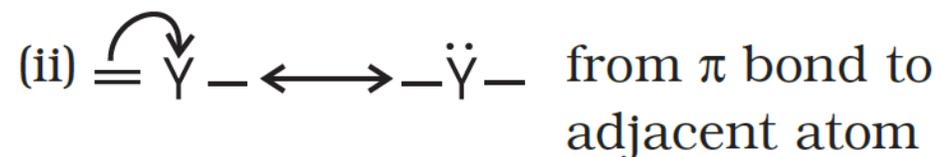
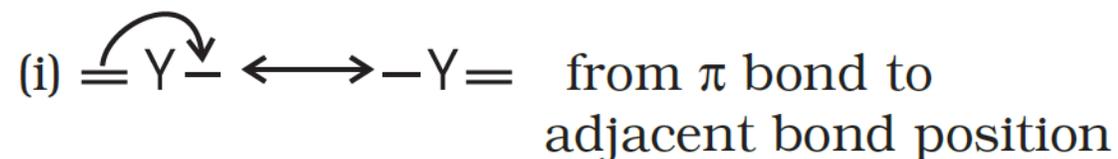
- a. Nucleophilic addition*
- b. Electrophilic addition*
- c. Free-radical addition*

3) Elimination Reactions

4) Rearrangement reactions

ELECTRON MOVEMENT IN ORGANIC REACTIONS: THE ARROW NOTATION

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



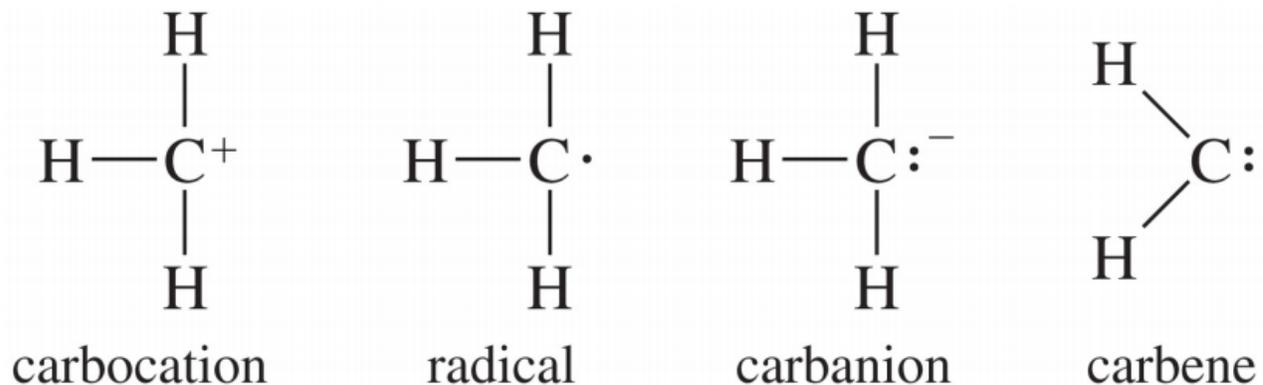
- Movement of single electron is indicated by a single barbed 'fish hooks' (i.e. *half headed curved arrow*).



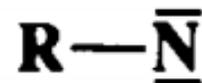
REACTIVE INTERMEDIATE

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

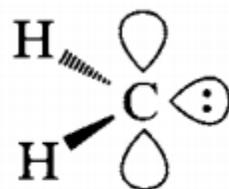
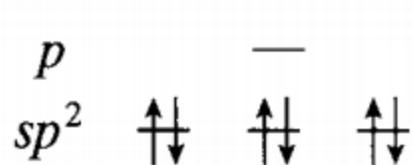
Carbon Reactive Intermediates



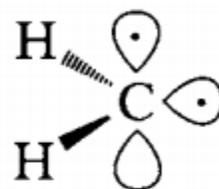
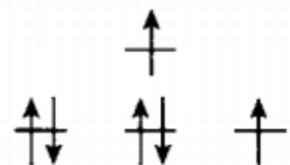
- Nitrenes (*nitrogen analogs of carbenes*)



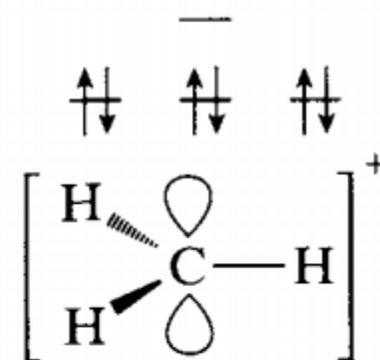
REACTIVE INTERMEDIATE



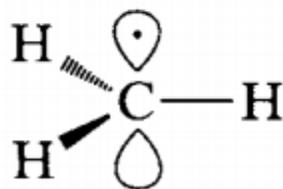
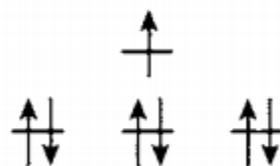
Singlet
Carbene



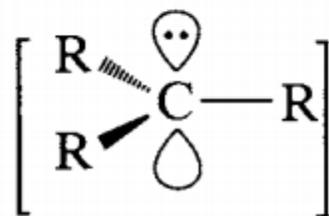
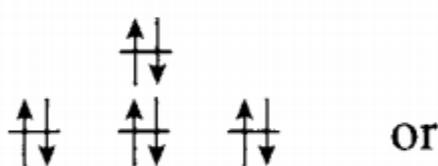
Triplet
Carbene



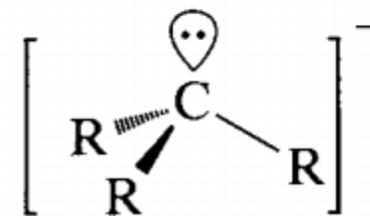
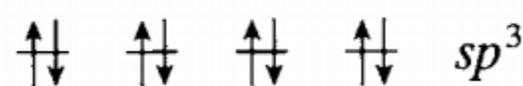
Carbocation



Radical



Carbanion

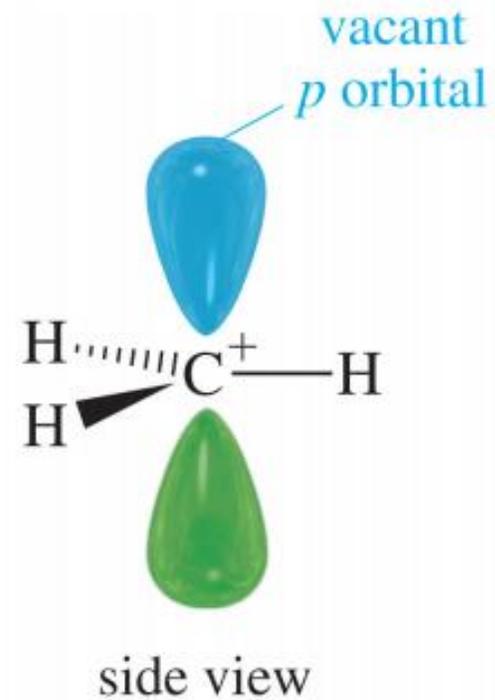
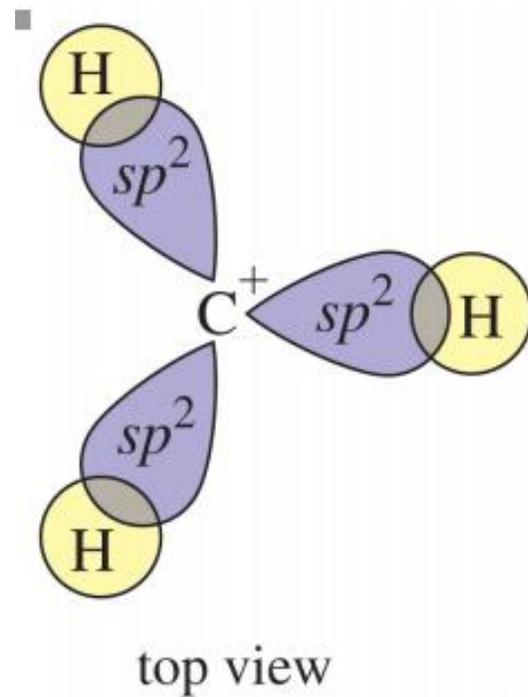


Carbanion

CARBOCATION

Carbocation Structure

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

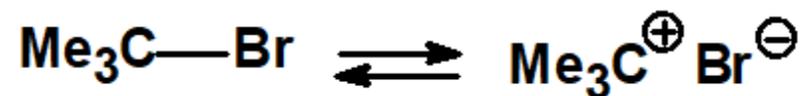


CARBOCATION

Methods of Forming Carbocation

(A) Heterolytic fission of neutral species

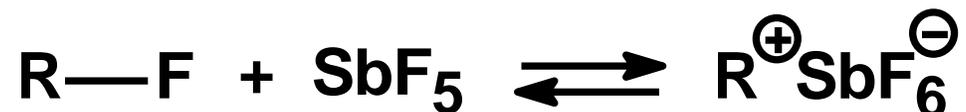
- Simple ionization; *the electron pair remains with departing group, which is called leaving group and tertiary butyl group carries positive charge.*



- Ionization may also be induced by Lewis acids, e.g. BF_3 , AlCl_3 to yield in this case an acyl cation.



- With antimony pentafluoride (SbF_5) as a Lewis acid, with either liquid SO_2 or excess SbF_5 as solvent,

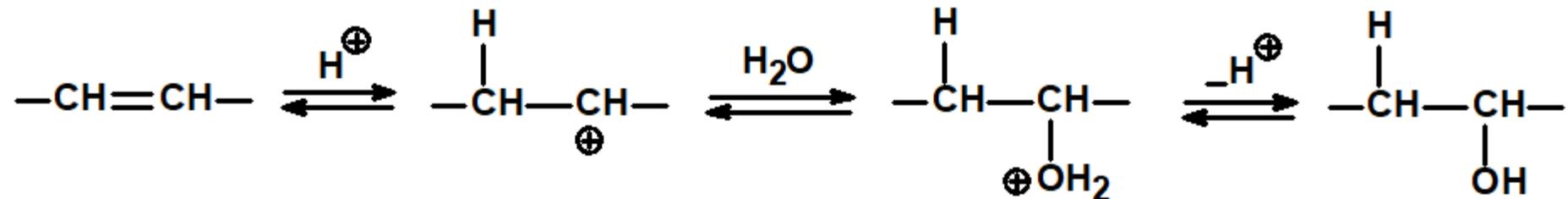


CARBOCATION

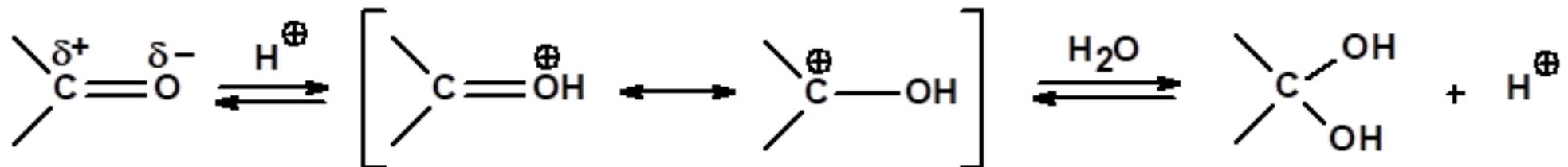
Methods of Forming Carbocation

(B) Addition of cations to neutral species

- The most common cation is 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,



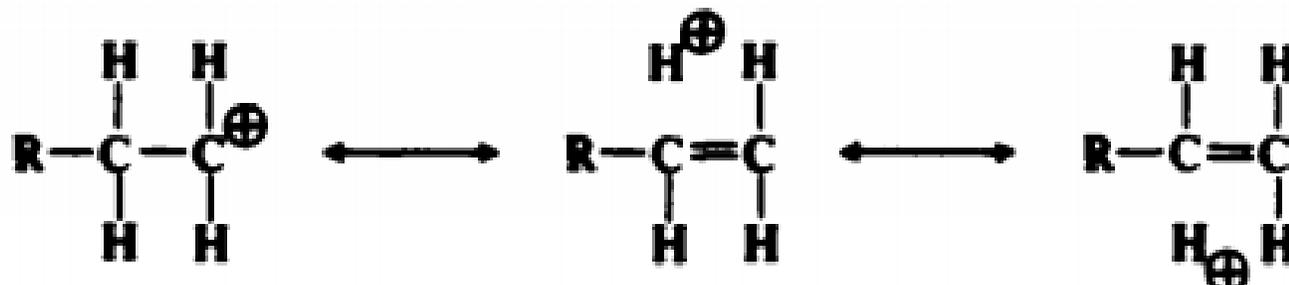
CARBOCATION

Stability and Structure of Carbocation

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



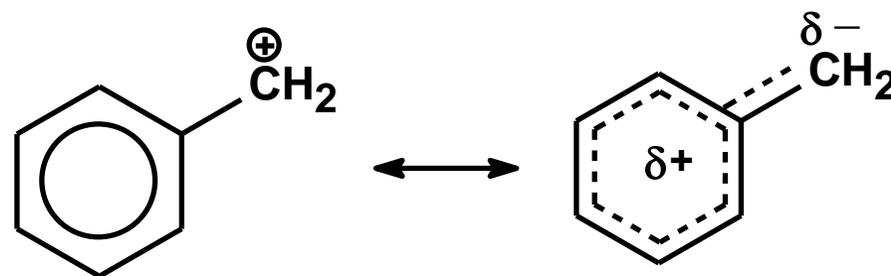
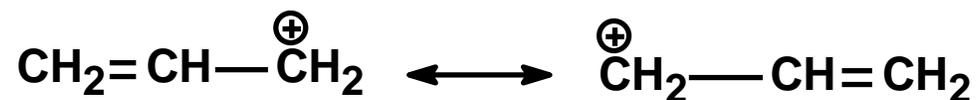
- The stability order can be explained by hyperconjugation and inductive effect
- Quantum mechanical calculations for simple alkyl cations do indeed suggest that the planar (sp^2) configuration is more stable than the pyramidal (sp^3) by ≈ 84 kJ (20 kcal) mol^{-1} .



CARBOCATION

Stability and Structure of Carbocation

- The possibility of delocalizing the charge, particularly where this can involve π orbitals:

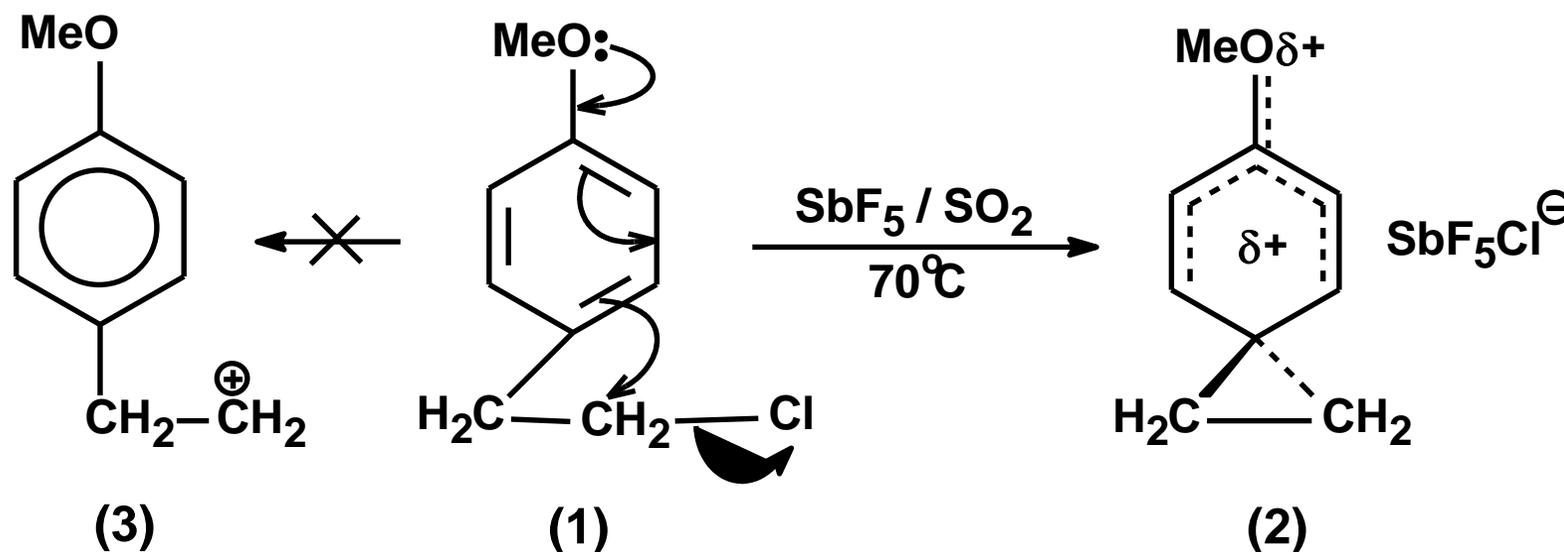


CARBOCATION

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.

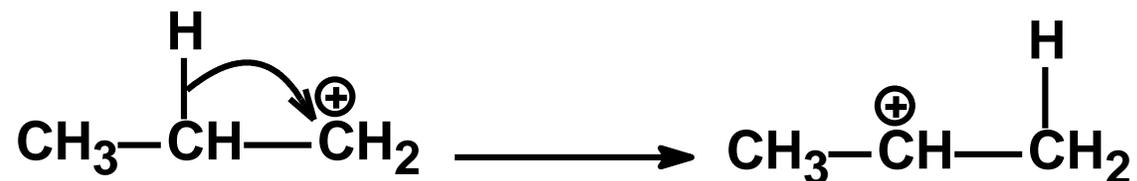
Thus the action of SbF_5 in liquid SO_2 on $p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{Cl}$ (1) results in the formation of (2) rather than the expected cation (3), phenyl acting as a neighboring group:



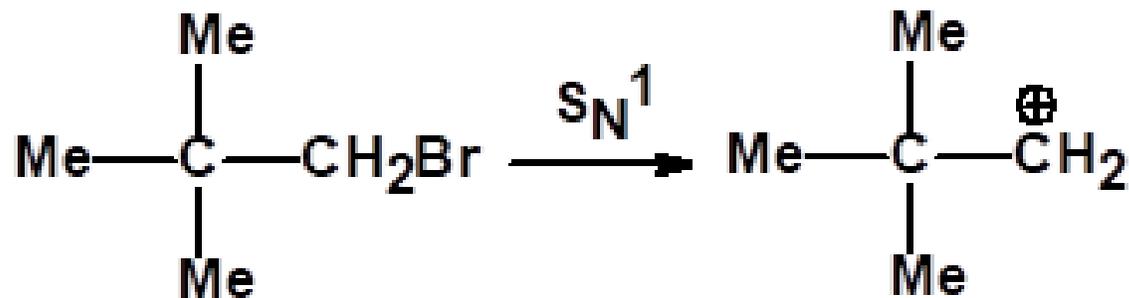
CARBOCATION

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 H⁻), from C₂ to the carbocationic C₁, a 1,2-hydride shift:



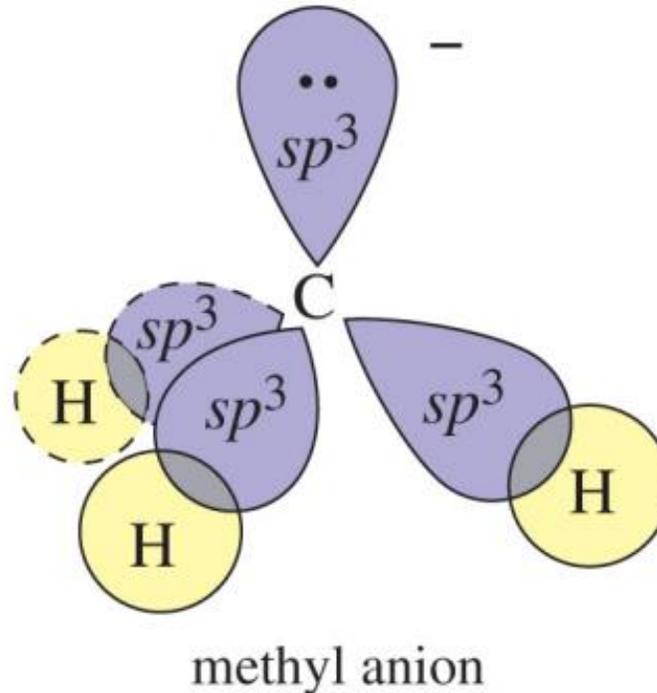
- With change in carbon skeleton; Neopentyl rearrangements



CARBANION

Carbanion Structure

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



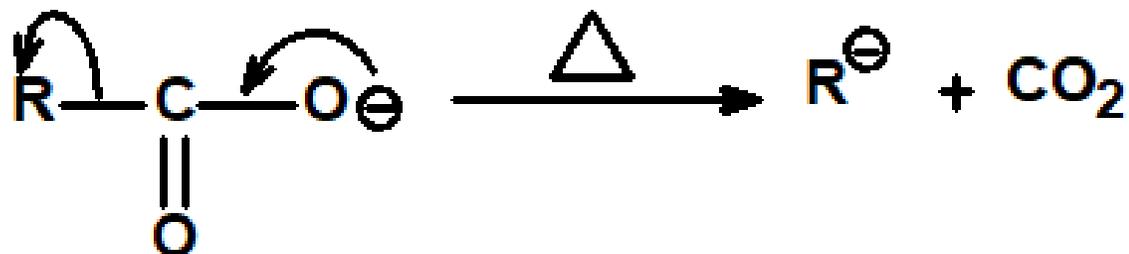
CARBANION

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

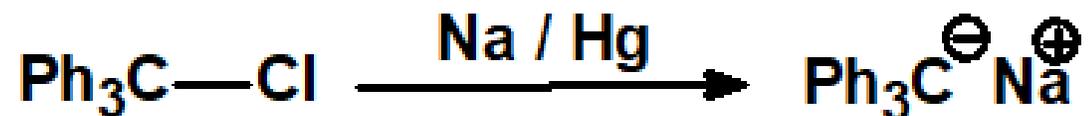
- *Removal of a proton*



- *Removal of CO₂ from decarboxylation of RCO₂⁻*



- *Removal of Cl from Ph₃C-Cl*

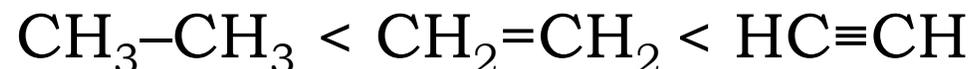


CARBANION

Stability of Carbanion

○ The main features that serve to stabilize carbanions are

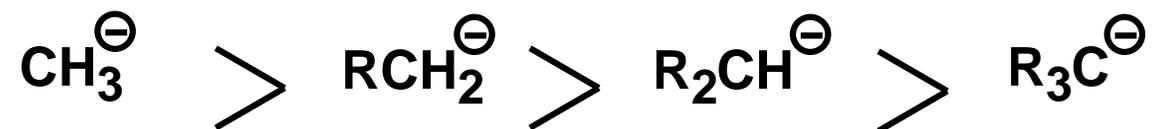
- *increase in s character at the carbanion carbon*



- *electron-withdrawing inductive effects*

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

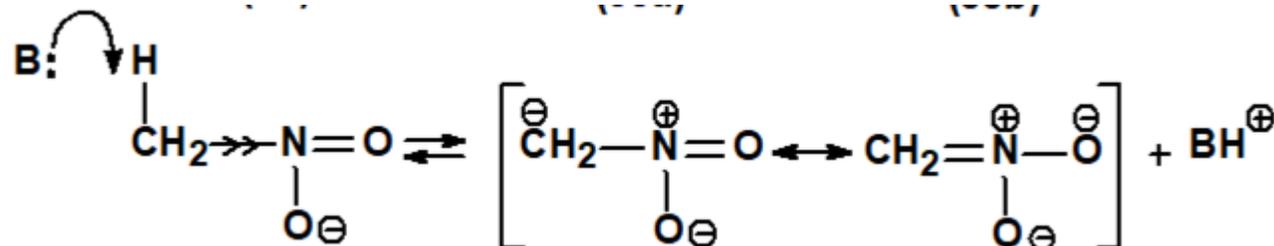
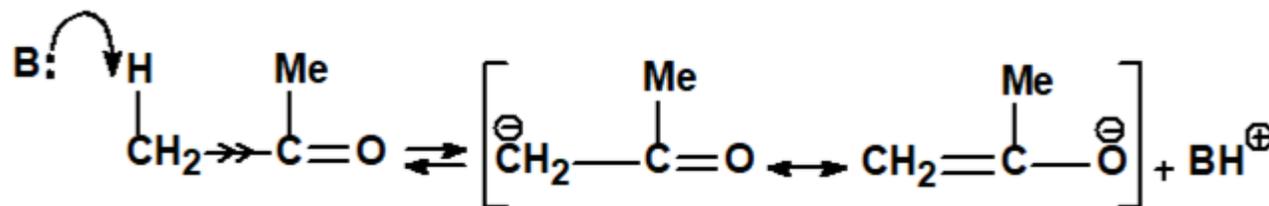
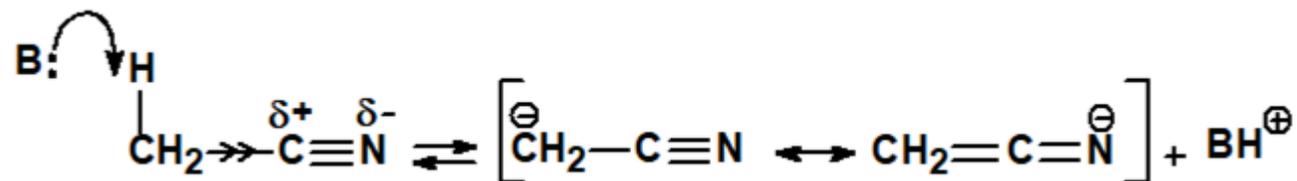
The destabilizing influence of the electron-donating inductive effect of alkyl groups is seen in the observed carbanion stability sequence:



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, NO₂



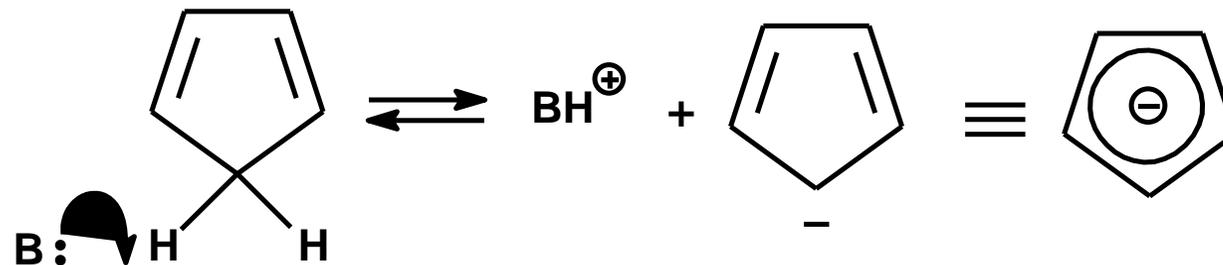
CARBANION

Stability of Carbanion

- The main features that serve to stabilize carbanions are

- *aromatization*

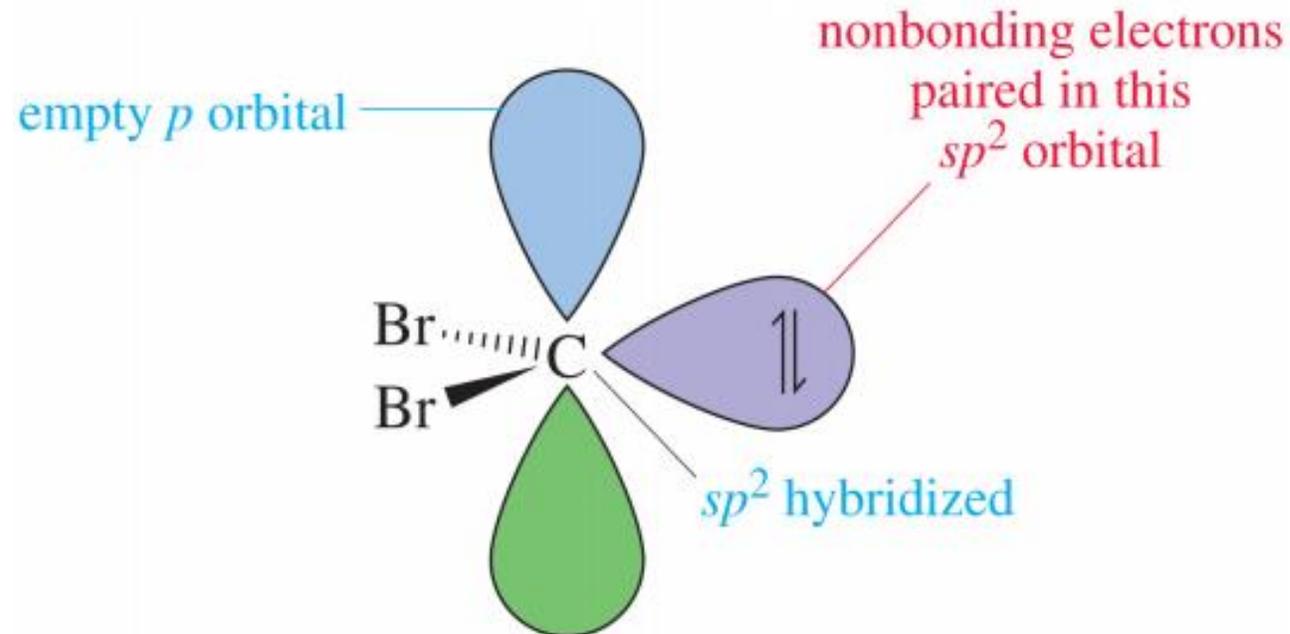
the cyclopentadienyl anion, being a 6π electron delocalized system, The 6 electrons can be accommodated in three stabilized π molecular orbitals, like benzene, and the anion thus shows quasi-aromatic stabilization; it is stabilized by *aromatization*:



CARBENES AND NITRENES

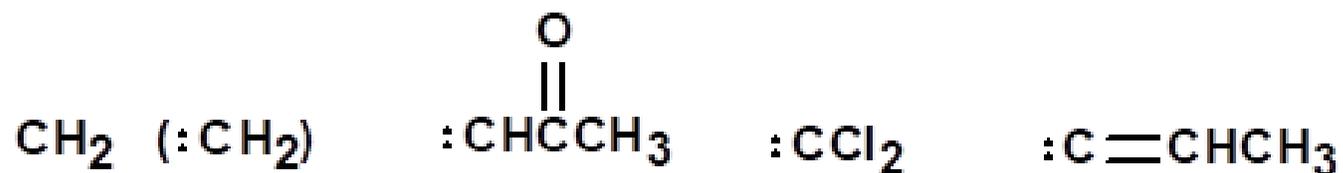
Carbenes Structure

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



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.

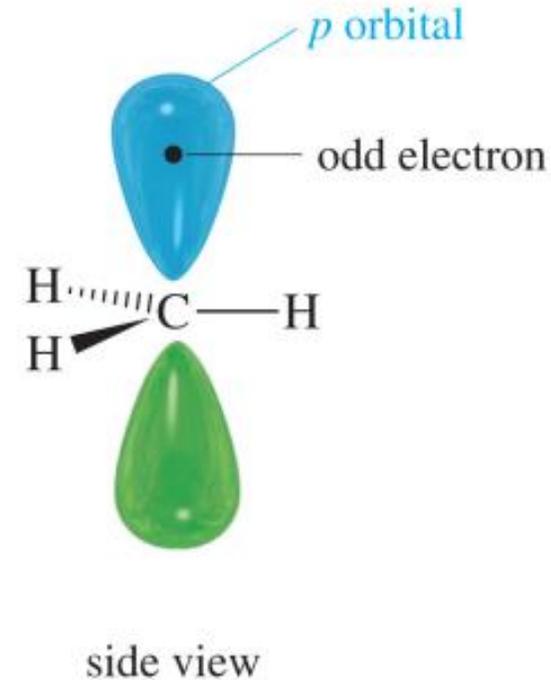
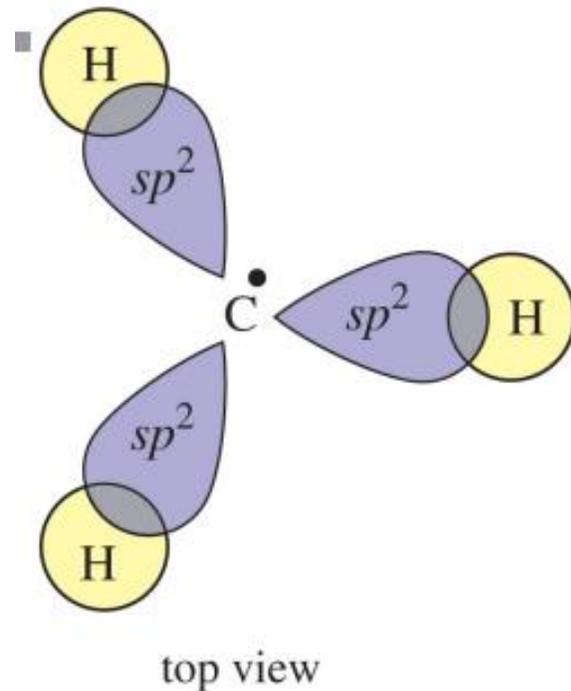


- **Nitrenes** are compounds, such as $:\text{NC}_6\text{H}_5$, that contain monovalent nitrogen atoms.

FREE RADICALS

Free radical Structure

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



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

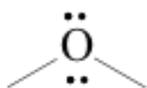
- **Electrophile (E^+);** (electron-loving) are electron-deficient species and tend to attack the substrate at a site of high electron density and the reaction is called **electrophilic**.
- **Examples of electrophiles** include
 - **Positively charged species** as exemplified by proton (H^+), cations (such as Cl^+ , NR_4^+) and carbocations ($^+CH_3$) and
 - **Neutral species** as exemplified by Lewis acids (such as BF_3 , $AlCl_3$, $ZnCl_2$) and carbenes ($Cl_2C:$) or neutral molecules having functional groups like carbonyl group ($>C=O$) or alkyl halides (R_3C-X , where X is a halogen atom).
- They have six valence electrons (except H^+) 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.



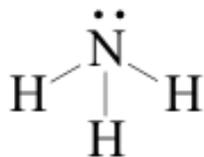
NUCLEOPHILES AND ELECTROPHILES

NUCLEOPHILES

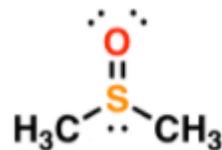
- **Nucleophile (Nu:);** a reagent that brings an electron pair to the reactive site and the reaction is then called *nucleophilic*.
- **Some examples of nucleophiles** are
 - the negatively charged ions with lone pair of electrons such as hydroxide (HO^-), cyanide (NC^-) ions and carbanions (R_3C^-).
 - Neutral molecules having nonbonding lone pair(s) of electrons such as water, ammonia, alcohols, dimethylsulfide and triphenylphosphine



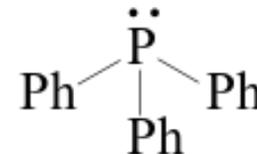
water



ammonia



dimethylsulfide



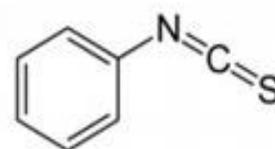
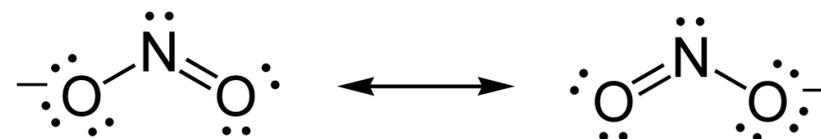
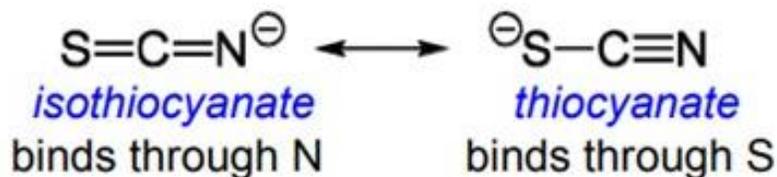
triphenylphosphine

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

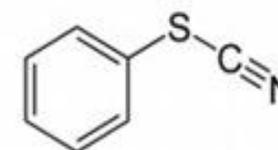
NUCLEOPHILES AND ELECTROPHILES

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.



phenyl isothiocyanate



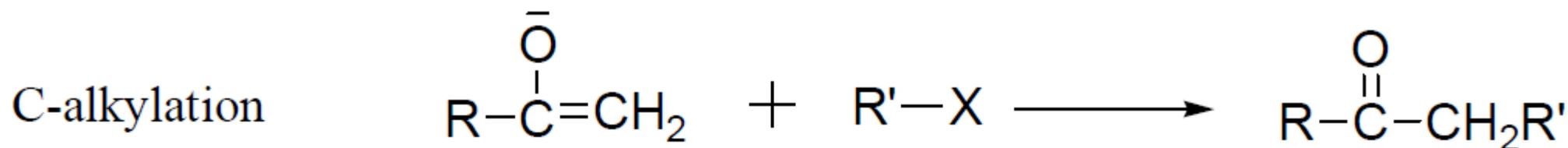
phenyl thiocyanate

NUCLEOPHILES AND ELECTROPHILES

NUCLEOPHILES

○ 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.



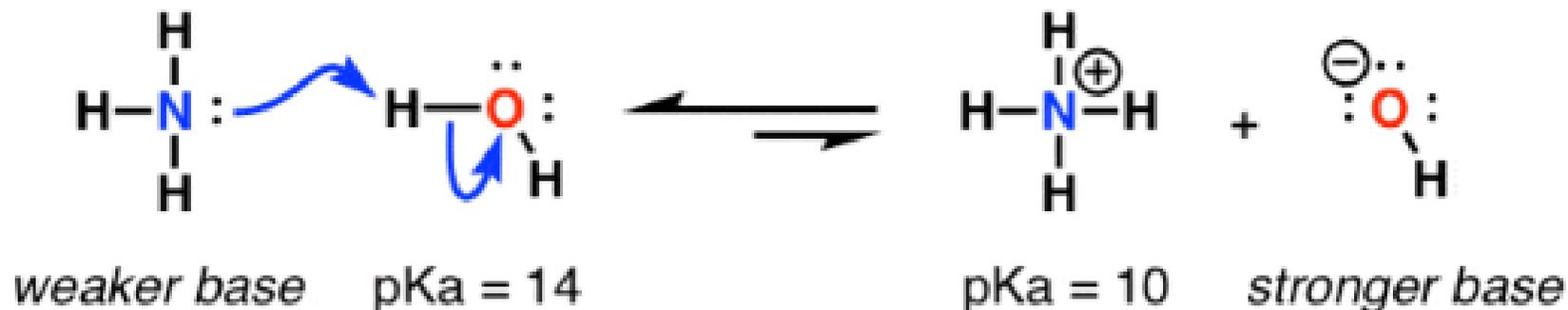
NUCLEOPHILES AND ELECTROPHILES

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).



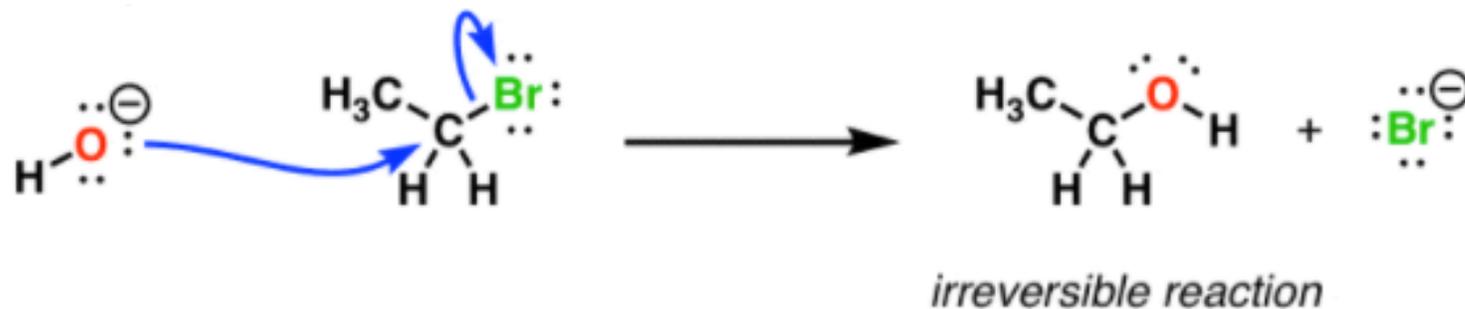
NUCLEOPHILES AND ELECTROPHILES

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).

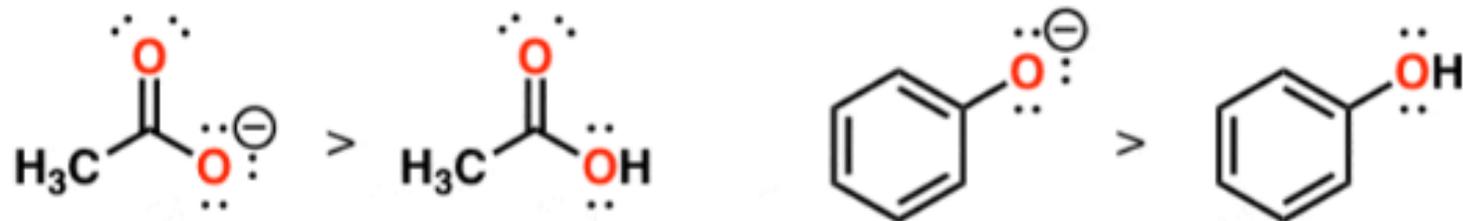
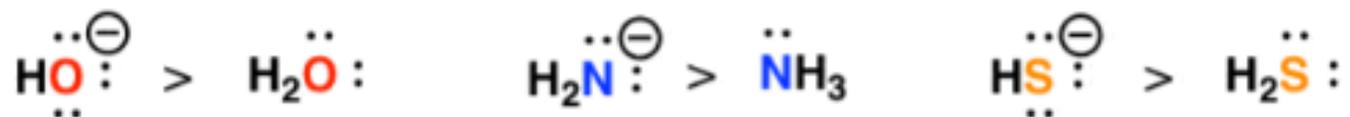
e.g. the *nucleophilicity is measured by the rate of the reaction.*



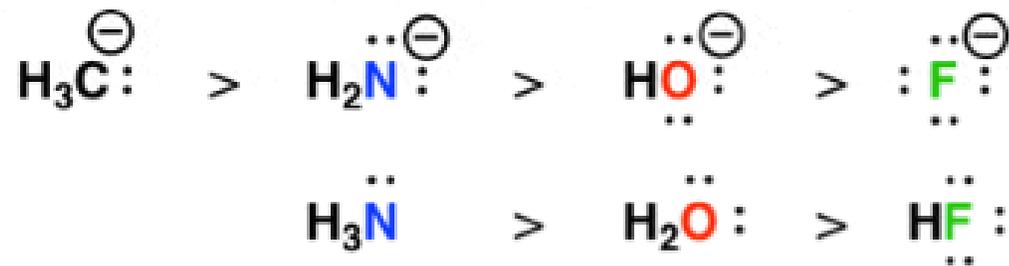
NUCLEOPHILES AND ELECTROPHILES

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.

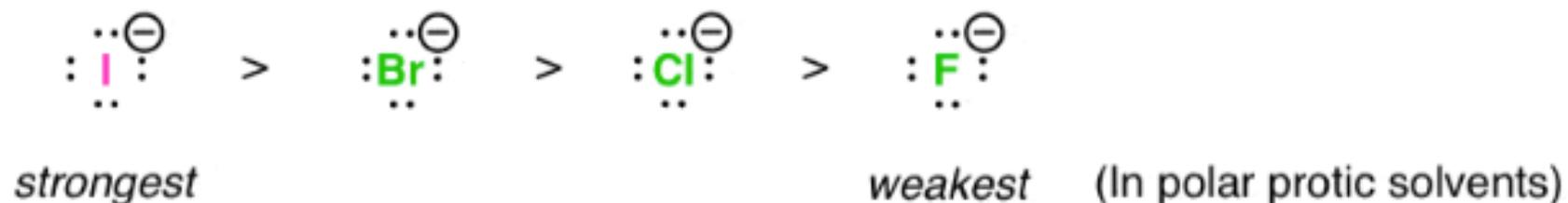


These two factors correlate strongly with basicity.

NUCLEOPHILES AND ELECTROPHILES

FACTORS AFFECTING NUCLEOPHILICITY

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



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

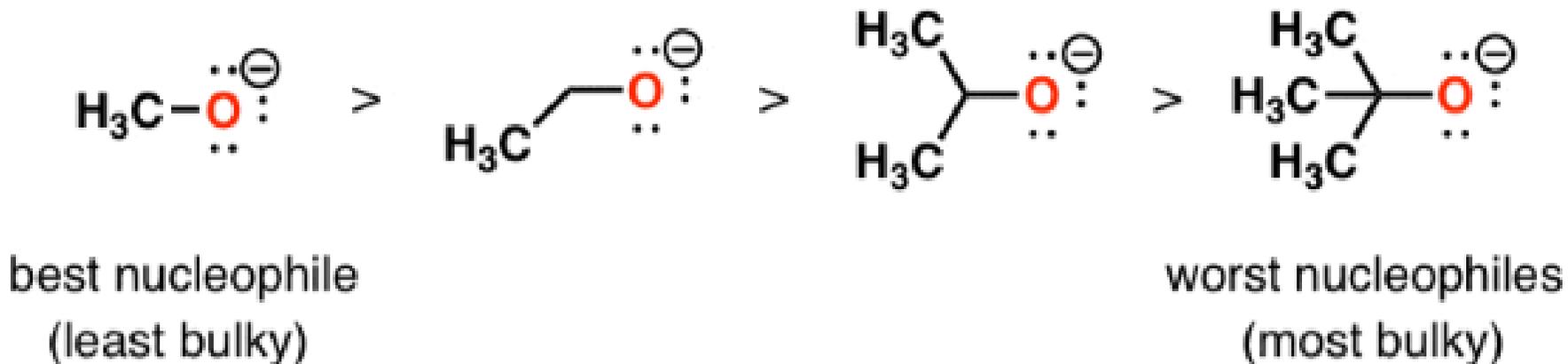


Nucleophilicity is essentially correlated with basicity.

NUCLEOPHILES AND ELECTROPHILES

FACTORS AFFECTING NUCLEOPHILICITY

- **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: RO^- , OH^- , RLi , $\text{RC}\equiv\text{C:}^-$, and 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

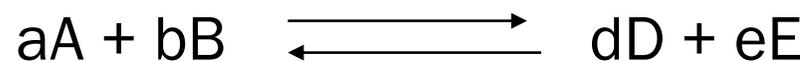
I^- is a weak base, but it is a good nucleophile because the large electron cloud is highly polarizable.

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 ΔG (*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:



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

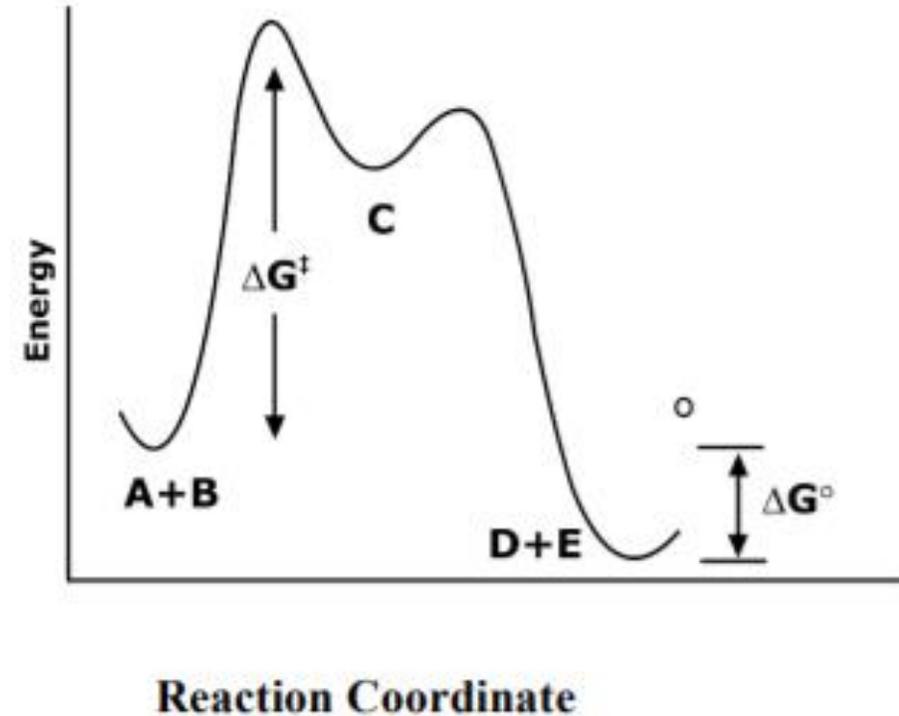
WHY DO THESE REACTIONS OCCUR?

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 ΔG° :

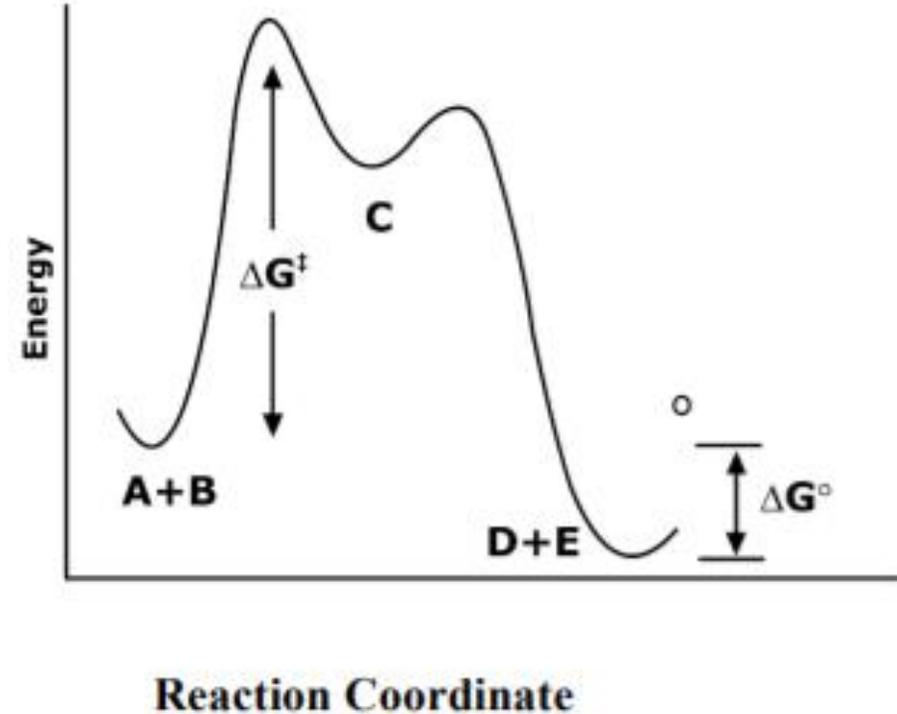
If ΔG° is **negative** the product is thermodynamically stable compared to reactant and the reaction is said to be *exergonic reaction*.

If ΔG° 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 ΔG^\ddagger :

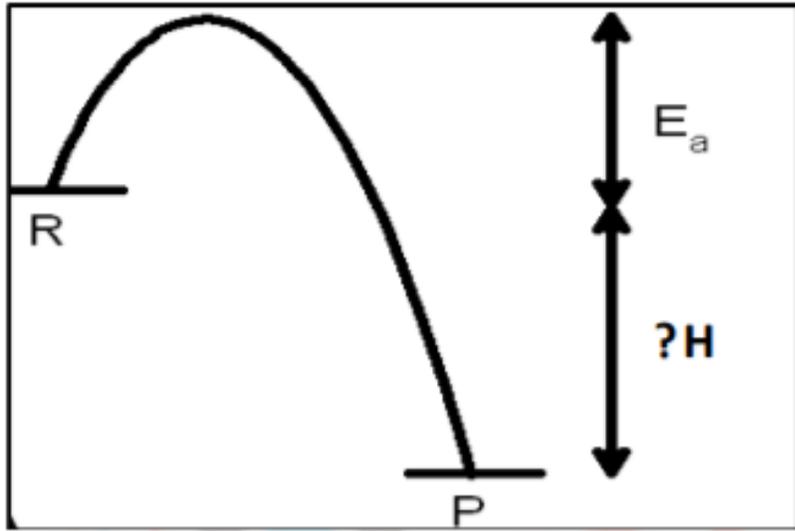
If ΔG^\ddagger is **large**, the compound (the reactant) is kinetically stable i.e., it does not undergo that reaction rapidly.

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



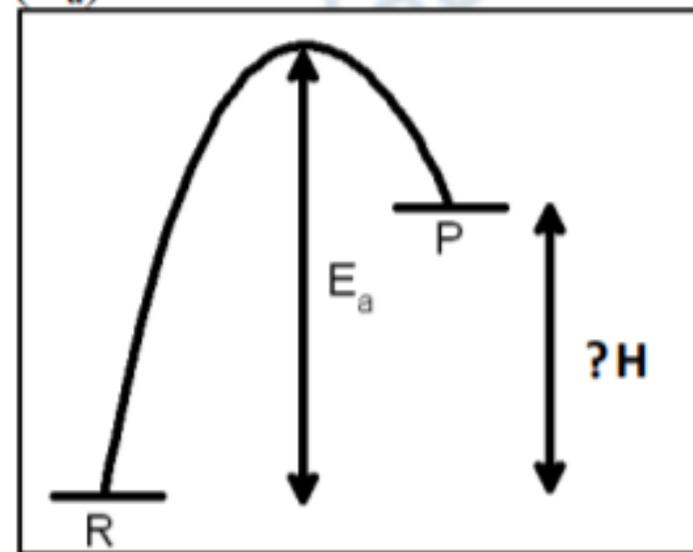
WHY DO THESE REACTIONS OCCUR?

THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION



Exothermic/spontaneous Reactions

- More energy will be released to the surrounding.
- ΔH 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.
- ΔH 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

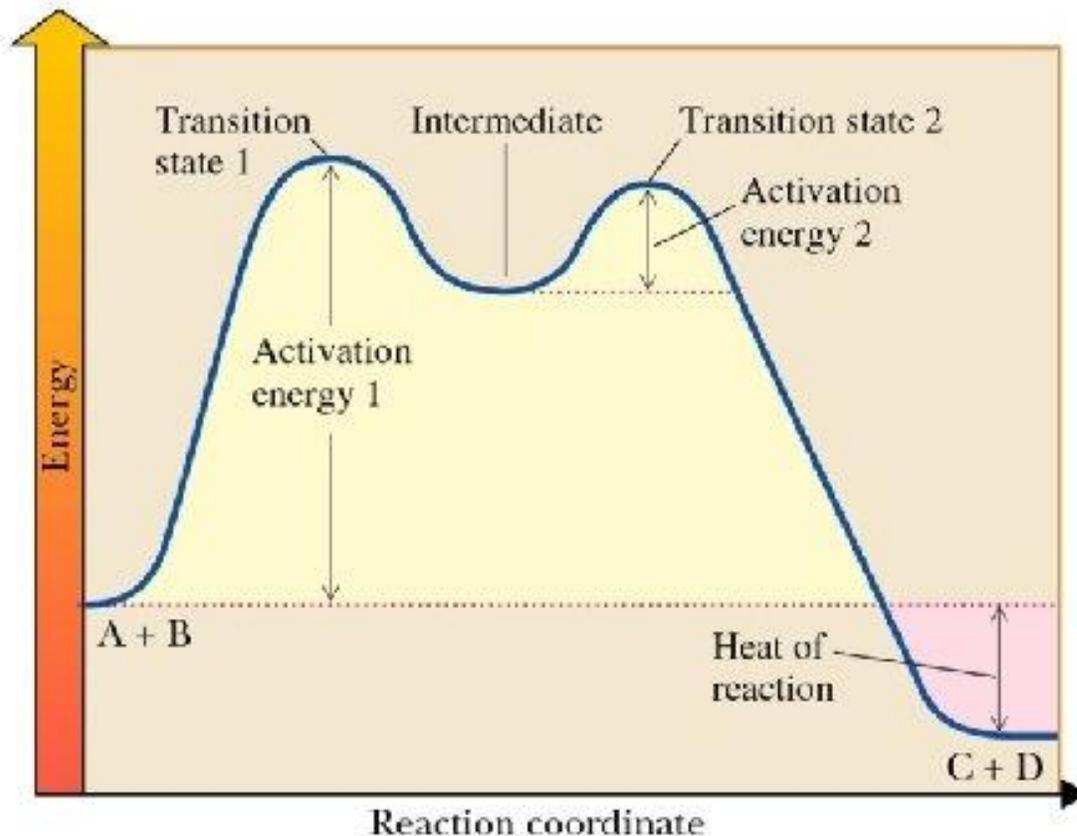
Multi-Step Reactions

Step 1: $A + B \rightarrow \text{Intermediate}$

Step 2: $\text{Intermediate} \rightarrow C + D$

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

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

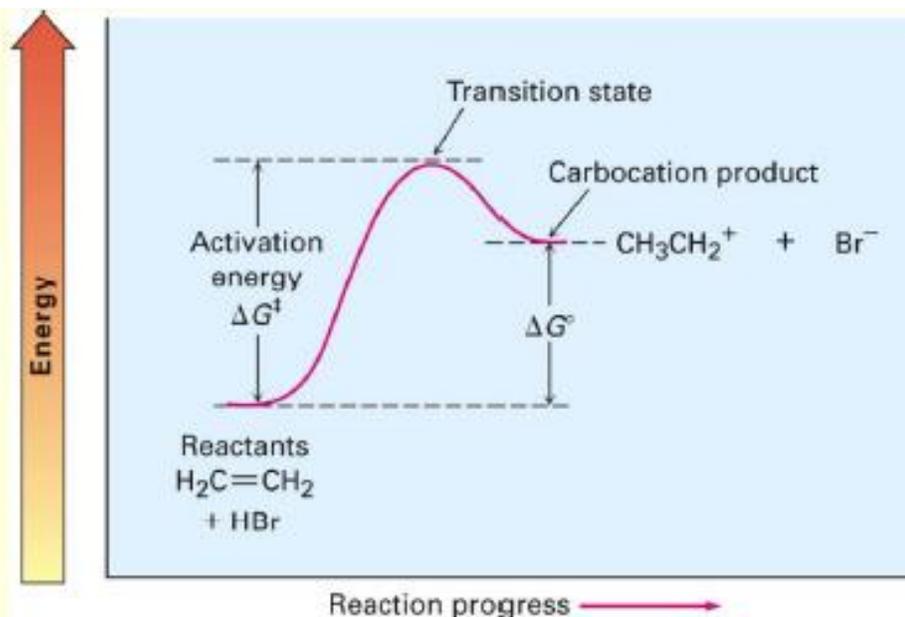
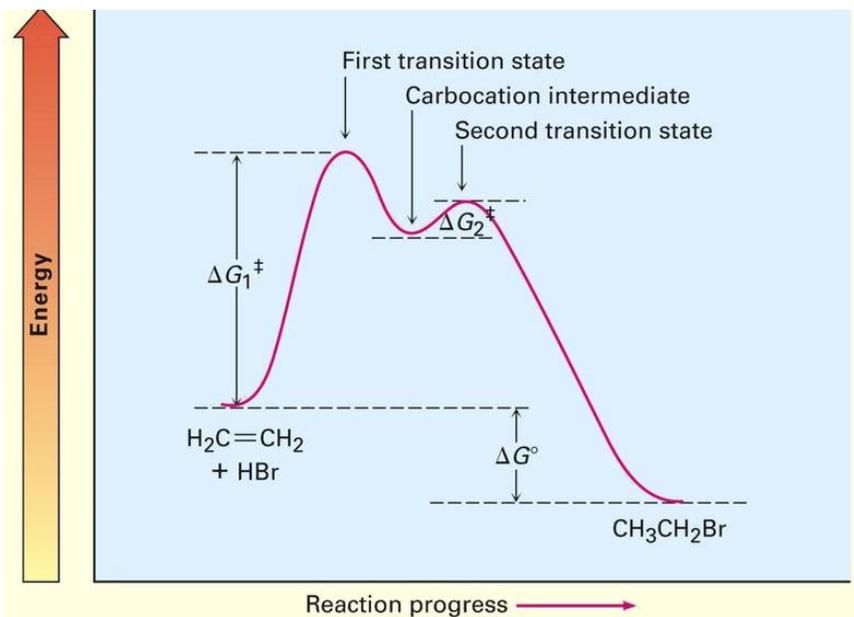


Step 2:
exergonic, small
energy of
activation. Fast
Process.

WHY DO THESE REACTIONS OCCUR?

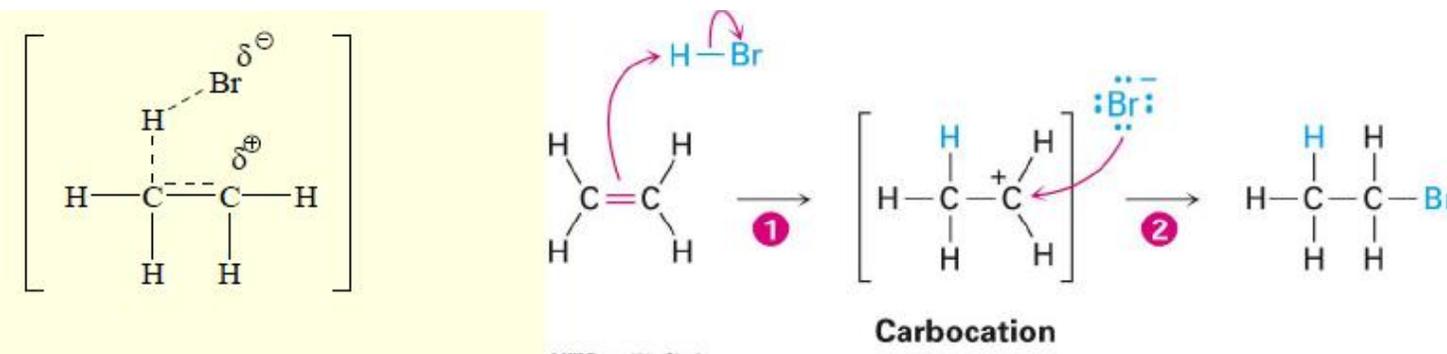
THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION

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* (ΔG^\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