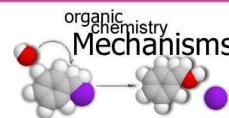CHEM 344

ORGANIC REACTION MECHANISM

FOR CHEMISTRY' STUDENTS, COLLEGE OF SCIENCE

PRE-REQUISITES COURSE; CHEM 241
CREDIT HOURS; 2 (2+0+0)

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INTRODUCTION

Fundamental Principles

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FUNDAMENTAL CONCEPTS IN ORGANIC REACTION MECHANISM

▪ The general reaction is depicted as follows :

Organic molecule (Substrate) —Attacking Reagent→ [Intermediate] —→ Product(s)
[Intermediate] —→ Byproducts
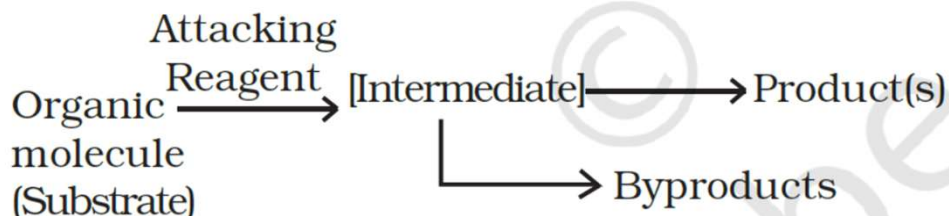
▪ Substrate; A molecule whose carbon is involved in new bond formation
▪ and the other one is called reagent.

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DEFINITION

o 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.

o A detailed study of the sequence of steps which are involved in the conversion of reactants into product(s) is known as *reaction mechanism*.

o 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
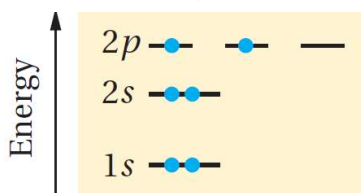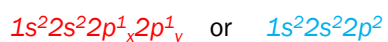
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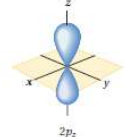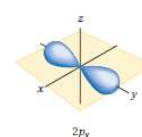## ATOMIC ORBITALS

o **The element carbon (atomic number 6)**
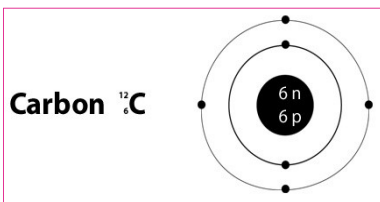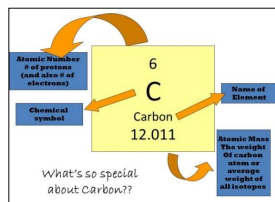
o **The electronic configuration of carbon (atomic number 6) can be represented as**

$1s^2 2s^2 2p^1_x 2p^1_y$ or $1s^2 2s^2 2p^2$

▪ **s orbital** is spherically shaped electron cloud with the atom's nucleus and its center.

▪ **p orbital** is a dumbbell-shaped electron cloud with the nucleus between the two lobes.

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SIGMA (σ) AND pi (π) BONDS
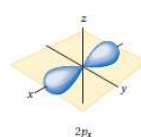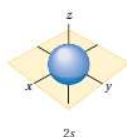
o **Sigma bonds (σ bonds) can be formed from**

▪ The overlap of **two s** atomic orbitals.

▪ The overlap of two an **s** atomic orbital with a **p** atomic orbital.

▪ The end-on overlap of two *p* atomic orbitals.

o **pi bonds (π bonds) can be formed from**

▪ The side-side overlap between two *p* atomic orbitals.

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HYBRIDIZATION

CARBON sp^3 HYBRID ORBITALS

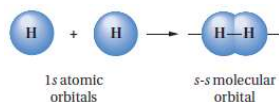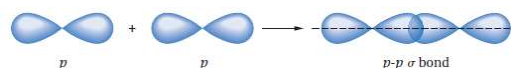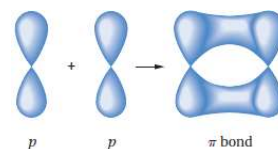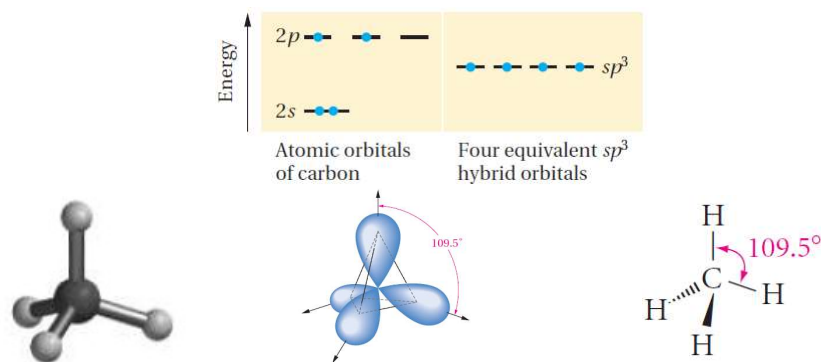○ The angle between any two of the four bonds formed from sp^3 orbitals is approximately 109.5° with Regular tetrahedral geometry.

$$1s^2 2s^2 2p_x^1 2p_y^1 \quad \textit{Equivalent to} \quad :\dot{C}\cdot$$

Atomic orbitals of carbon

Four equivalent sp^3 hybrid orbitals

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HYBRIDIZATION

CARBON sp^2 HYBRID ORBITALS

○ Combine only three of the orbitals, to make three equivalent sp^2-hybridized orbitals (called sp^2 because they are formed by combining one s and two p orbitals)

○ The angle between them is 120° with A trigonal carbon

Atomic orbitals of carbon

The 2s and two 2p orbitals are combined to form three hybrid sp^2 orbitals, leaving one electron still in a p orbital.

side view

side view with the sp^2 orbitals represented by lines

top view

two sp^2-hybridized carbons with p orbitals parallel

the σ bond is formed by two electrons in overlapping sp^2 orbitals

the π bond is formed by two electrons in overlapping parallel p orbitals

Schematic formation of a carbon–carbon double bond. Two sp^2 carbons form a sigma (s) bond (end-on overlap of two $sp2$ orbitals) and a pi (p) bond (lateral overlap of two properly aligned p orbitals).

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HYBRIDIZATION

CARBON *sp* HYBRID ORBITALS

o The carbon atom of an acetylene is connected to only *two* other atoms. Therefore, we combine the 2s orbital with only one 2*p* orbital to make two *sp*-hybrid orbitals
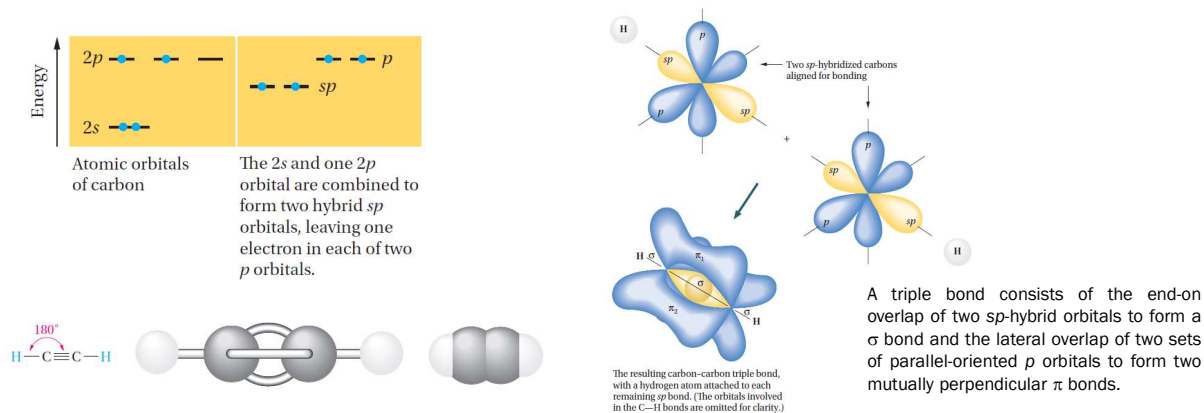
o The angle between the two hybrid orbitals is 180° and Linear

Energy

2*p* — — —   — — *p*
                    — — *sp*

2*s* —

Atomic orbitals of carbon

The 2*s* and one 2*p* orbital are combined to form two hybrid *sp* orbitals, leaving one electron in each of two *p* orbitals.

180°
H—C≡C—H

Two *sp*-hybridized carbons aligned for bonding

The resulting carbon–carbon triple bond, with a hydrogen atom attached to each remaining *sp* bond. (The orbitals involved in the C—H bonds are omitted for clarity.)

A triple bond consists of the end-on overlap of two *sp*-hybrid orbitals to form a σ bond and the lateral overlap of two sets of parallel-oriented *p* orbitals to form two mutually perpendicular π bonds.

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BONDING IN CARBON COMPOUNDS

CARBON-CARBON BONDS

o The combination of two carbons results from the axial overlap of two sp^3 atomic orbitals

o With increasing the s component, the bond length decreases as the electron in s orbital in held closer and tightly by the nucleus.
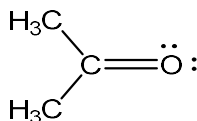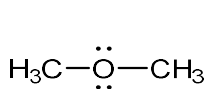
	sp^3—sp^3	sp^2—sp^2	sp—sp		
	—C—C—	=C—CH= H	≡C—C≡	—C=C—	—C≡C—
Bond length (A)	1.54	1.47	1.38	1.33	1.20
Bond energy (kJ)	347			598	812

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BONDING IN CARBON COMPOUNDS

CARBON-OXYGEN BONDS

- The electronic configuration of oxygen atom is $1s^2 2s^2 2p_x^2 2p_y^1 2p_z^1$

- C – O –C ; the oxygen atom could use four sp^3 hybrid orbitals: two to form sigma bonds by overlap with an sp^3 orbital of each of the two carbon atoms and the other two to accommodate its two lone pairs of electrons.

- C = O ; the oxygen atom could use three sp^2 hybrid orbitals: one to form sigma bonds by overlap with an sp^2 orbital of the carbon atom and the other two to accommodate its two lone pairs of electrons.

- *Leaves an unhybridized p orbital on both oxygen and carbon to form pi bond.*

$$H_3C-\overset{..}{\underset{..}{O}}-CH_3 \qquad \overset{H_3C}{\underset{H_3C}{>}}C=\overset{..}{\underset{..}{O}}:$$

- *Bond energy is greater than twice due to the stability in C=O as the lone pairs on oxygen are further apart.*

Bond length (A)	1.42	1.22
Bond energy (kJ)	360	750

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BONDING IN CARBON COMPOUNDS

CARBON-NITROGEN BONDS

- The electronic configuration of nitrogen atom is $1s^2 2s^2 2p_x^1 2p_y^1 2p_z^1$

	$C-\overset{..}{N}$	$C=\overset{..}{N}$	$C\equiv\overset{..}{N}$
Bond length (A)	1.47	1.29	1.16
Bond energy (kJ)	305	616	893

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ELECTRON DISPLACEMENT EFFECTS IN COVALENT BONDS

o 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
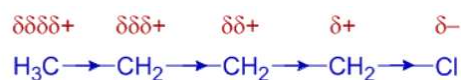 cause permanent polarization of the bond (*Inductive effect and resonance effects*).

Or

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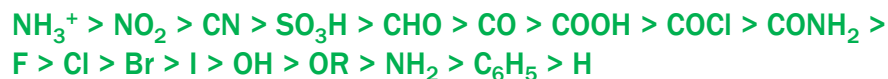
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INDUCTIVE EFFECT

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

$$\overset{\delta\delta\delta\delta+}{H_3C} \longrightarrow \overset{\delta\delta\delta+}{CH_2} \longrightarrow \overset{\delta\delta+}{CH_2} \longrightarrow \overset{\delta+}{CH_2} \longrightarrow \overset{\delta-}{Cl}$$

o *Types of inductive effect:*

1) Negative inductive effect (-I):

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

$NH_3^+ > NO_2 > CN > SO_3H > CHO > CO > COOH > COCl > CONH_2 > F > Cl > Br > I > OH > OR > NH_2 > C_6H_5 > H$

2) Positive inductive effect (+I):

- This is electron releasing character and is indicated by the +*I* effect
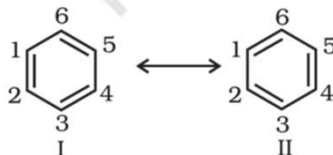
$C(CH_3)_3 > CH(CH_3)_2 > CH_2CH_3 > CH_3 > H$

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RESONANCE STRUCTURE

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

o An example:

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

o An example:

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


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RESONANCE OR MESOMERIC EFFECT

o 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.
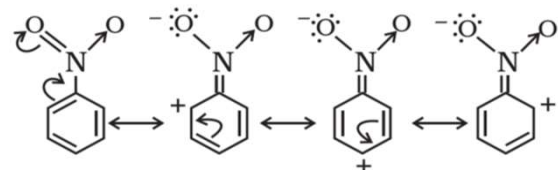
Examples; – halogen, –OH, –OR, –OCOR, –NH₂, –NHR, –NR₂, –NHCOR,
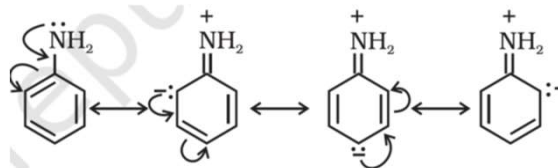
(ii) Negative Resonance Effect (- R effect):

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

Examples; – COOH, –CHO, >C=O, – CN, –NO₂

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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.
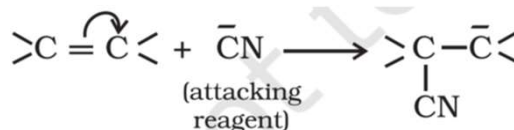
(i) **Positive Eelctromeric Effect (+E effect):**

the π–electrons of the multiple bond are transferred to that atom to which the reagent gets attached.
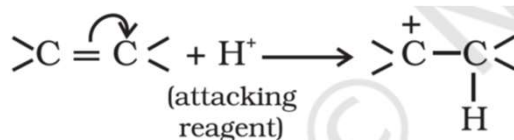
(ii) **Negative Electromeric Effect (−E effect):**

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

$$>C = C< \; + \; H^+ \longrightarrow \; >\overset{+}{C}-\underset{H}{C}<$$
(attacking reagent)

$$>C = C< \; + \; \overset{-}{C}N \longrightarrow \; >\overset{-}{C}-\underset{CN}{C}<$$
(attacking reagent)

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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.
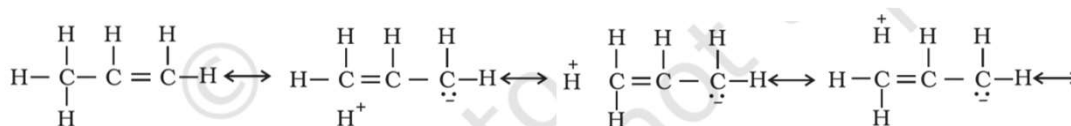

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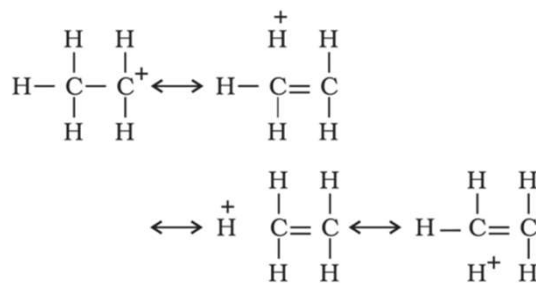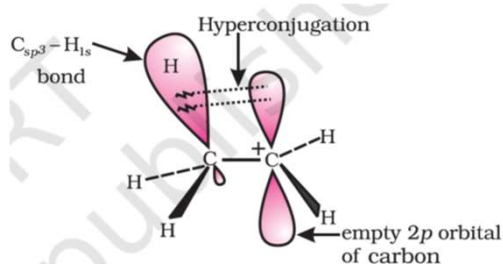
HYPERCONJUGATION

○ This type of overlap stabilizes the carbocation because electron density from the adjacent σ 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.

$$CH_3- \overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{C}}}}{}^+ > (CH_3)_2\overset{+}{C}H > CH_3\overset{+}{C}H_2 > \overset{+}{C}H_3$$
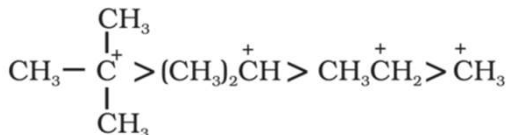
○ Hyperconjugation is also possible in alkenes and alkylarenes.

$$H-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-\overset{H}{\underset{|}{C}}=\overset{H}{\underset{|}{C}}-H \longleftrightarrow H-\underset{\underset{H^+}{|}}{\overset{\overset{H}{|}}{C}}=\overset{H}{\underset{|}{C}}-\overset{H}{\underset{\cdot\cdot}{C}}-H \longleftrightarrow \overset{+}{H}\quad \overset{H}{\underset{\underset{H}{|}}{C}}=\overset{H}{\underset{|}{C}}-\overset{H}{\underset{\cdot\cdot}{C}}-H \longleftrightarrow H-\overset{\overset{+}{H}}{\underset{\underset{H}{|}}{C}}=\overset{H}{\underset{|}{C}}-\overset{H}{\underset{\cdot\cdot}{C}}-H \longleftrightarrow$$
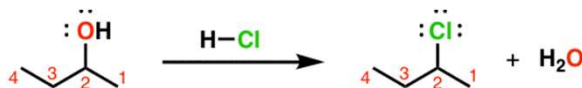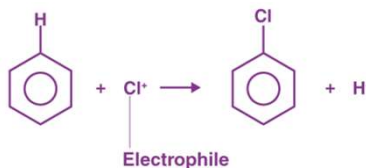
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TYPES OF ORGANIC REACTIONS

1) Substitution Reactions

a. Nucleophilic substitution

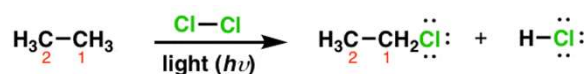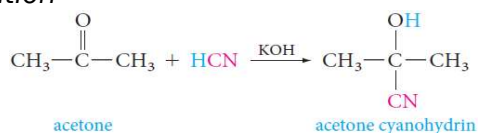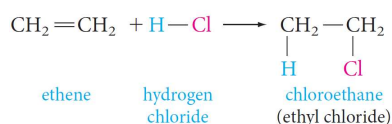*b. Electrophilic substitution*

Electrophile

c. Free-radical substitution

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TYPES OF ORGANIC REACTIONS

3) Addition Reactions

a. Nucleophilic addition

$$CH_3-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3 \ + \ HCN \ \xrightarrow{\text{KOH}} \ CH_3-\overset{\displaystyle OH}{\underset{\underset{\displaystyle CN}{|}}{\overset{|}{C}}}-CH_3$$

acetone   acetone cyanohydrin

b. Electrophilic addition

$$CH_2{=}CH_2 \ + \ H-Cl \ \longrightarrow \ \underset{\underset{\displaystyle H \quad \ Cl}{|\quad \ |}}{CH_2-CH_2}$$

ethene   hydrogen   chloroethane
         chloride   (ethyl chloride)

c. Free-radical addition

Polymerization

$$\left[\overset{H}{\underset{H}{}}C{=}C\overset{Cl}{\underset{H}{}}\right]_n \longrightarrow -C-C-C-C-C-C-$$

Vinyl chloride   Polyvinyl chloride
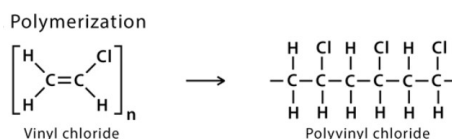
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TYPES OF ORGANIC REACTIONS

3) Elimination Reactions

$$\xrightarrow{-\ HBr}$$

4) Rearrangement reactions

A rearrangement reaction is a board class of organic reactions in which an atom, ion, group of atoms, or chemical unit migrates from one atom to another atom in the same or different species, resulting in a structural isomer of the original molecule

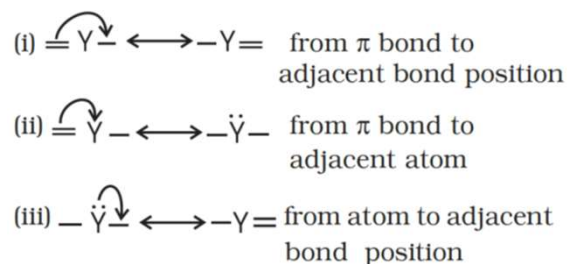Example: Bamberger Rearrangement (Preparation of 4-aminophenol)
The Bamberger rearrangement is an organic reaction used to convert N-phenylhydroxylamine to 4-aminophenol in the presence of strong aqueous acid.

$$\xrightarrow[\text{H}_2\text{O}]{\text{H}_2\text{SO}_4}$$

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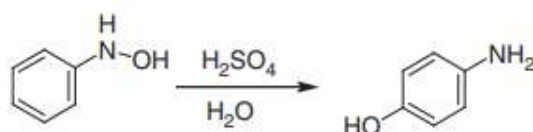
ELECTRON MOVEMENT IN ORGANIC REACTIONS: THE ARROW NOTATION

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

(i) $\overset{\frown}{=Y\downarrow} \longleftrightarrow -Y=$ from π bond to adjacent bond position

(ii) $\overset{\frown}{=\ddot{Y}}- \longleftrightarrow -\ddot{Y}-$ from π bond to adjacent atom

(iii) $-\ddot{Y}\downarrow \longleftrightarrow -Y=$ from atom to adjacent bond position

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

$$\overset{\frown}{CH_3} \overset{\frown}{-} \overset{\cdot}{Cl} \longrightarrow \dot{C}H_3 + \dot{C}l$$

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HOW DO THESE REACTIONS OCCUR?

NOTATIONS FOR BOND BREAKING

o There are two types of mechanisms depending on the way bonds are broken and made:

1) Heterolytic bond fission

$$A\overset{\frown}{-}B \longrightarrow A^{\oplus} + B^{\ominus}$$
$$A\overset{\frown}{-}B \longrightarrow A^{\ominus} + B^{\oplus}$$
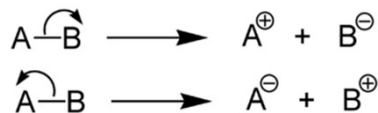
- The bonds are broken in such a way that the bond electron pair is assigned completely to one fragment.
- These reactions are also called *ionic reactions*, since ionic reactants, products, or intermediates are usually involved.

2) Homolytic bond fission

$$A\overset{\frown}{-}\overset{\frown}{B} \xrightarrow{\text{(heat or light)}} A\cdot + \cdot B$$
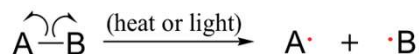
- The bonds are broken in such a way that one bond electron remains with one fragment and the other one bond electron with the other atom.
- Free radical intermediates are therefore involved and these transformations are consequently called *radical reactions*.

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HOW DO THESE REACTIONS OCCUR?

NOTATIONS FOR BOND MAKING

o **Symmetrical bond-making (radical):**
   one bonding electron is donated by each reactant

$$A\cdot \quad + \quad \cdot B \quad \longrightarrow \quad A:B$$

o **Unsymmetrical bond-making (polar):**
   two bonding electrons are donated by one reactant

$$A^+ \quad + \quad :B^- \quad \longrightarrow \quad A:B$$

REACTIVE INTERMEDIATE

o 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

$$H-\overset{\displaystyle H}{\underset{\displaystyle H}{C^+}} \qquad H-\overset{\displaystyle H}{\underset{\displaystyle H}{C}}\cdot \qquad H-\overset{\displaystyle H}{\underset{\displaystyle H}{C}}:^- \qquad \overset{\displaystyle H}{\underset{\displaystyle H}{>}}C:$$

carbocation   radical   carbanion   carbene
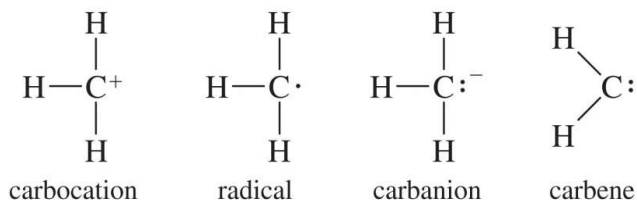
o **Nitrenes** (*nitrogen analogs of carbenes*) $\mathbf{R-\overline{\underline{N}}}$

p
sp^2

Singlet
Carbene

Triplet
Carbene

Carbocation

or sp^3

Radical

Carbanion

Carbanion

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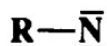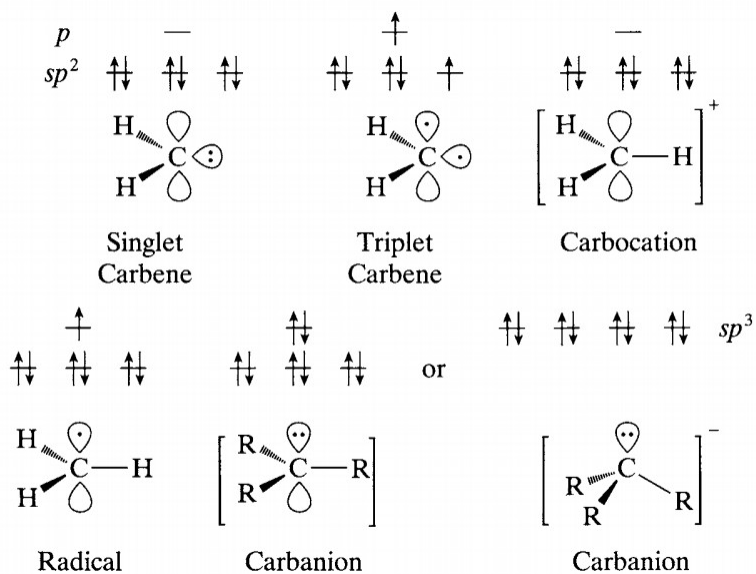
CARBOCATION

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

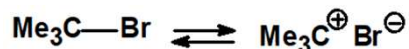sp^2

sp^2

sp^2

top view

vacant
p orbital

side view

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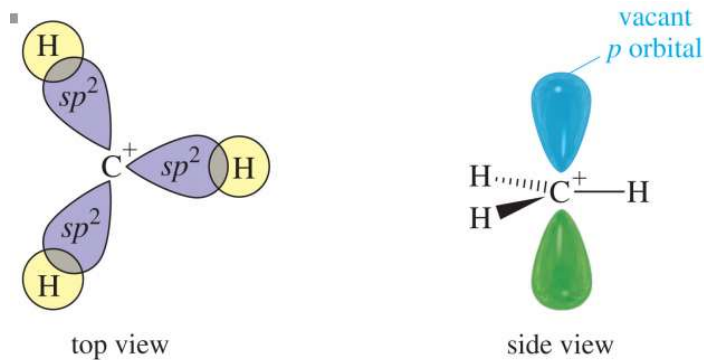
CARBOCATION

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.*

$$Me_3C-Br \rightleftharpoons Me_3C^{\oplus} Br^{\ominus}$$

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

$$MeCOF + BF_3 \rightleftharpoons MeCO^{\oplus} BF_4^{\ominus}$$
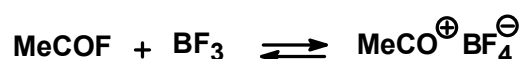
- With antimony pentaflouride (SbF_5) as a Lewis acid, with either liquid SO_2 or excess SbF_5 as solvent,

$$R-F + SbF_5 \rightleftharpoons R^{\oplus} SbF_6^{\ominus}$$
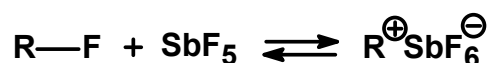
CARBOCATION

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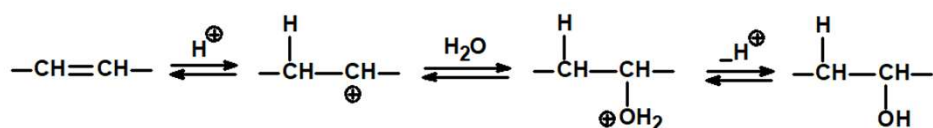
- Protonation can also occur on oxygen in a carbon-oxygen double bond,
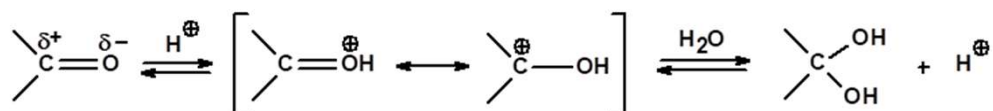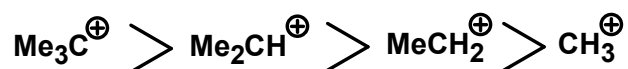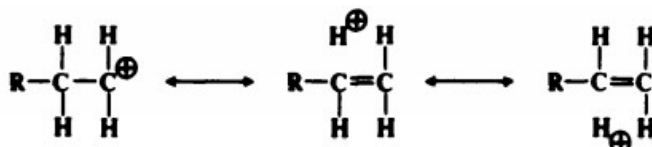
CARBOCATION

Stability and Structure of Carbocation

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

$$Me_3C^{\oplus} > Me_2CH^{\oplus} > MeCH_2^{\oplus} > CH_3^{\oplus}$$

- o The stability order can be explained by hyperconjugation and inductive effect

- o 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) mol^{-1}.
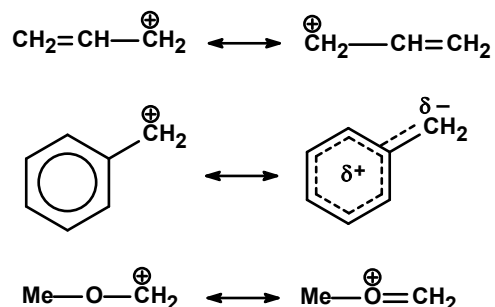
CARBOCATION

Stability and Structure of Carbocation

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

CARBOCATION

Stability and Structure of Carbocation

- o 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 $p\text{-}MeOC_6H_4CH_2CH_2Cl$ (1) results in the formation of (2) rather than the expected cation (3), phenyl acting as a neighboring group:
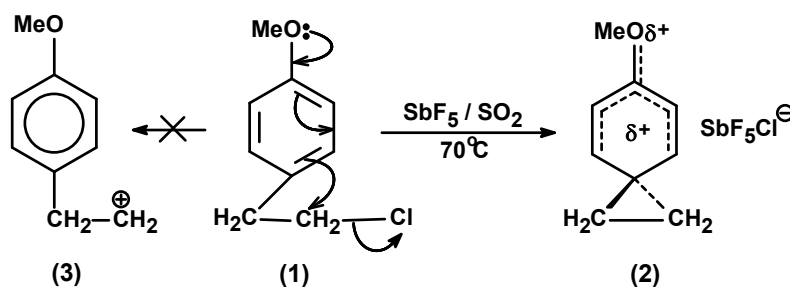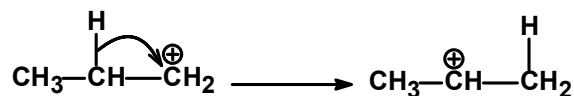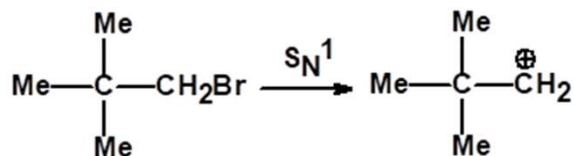
CARBOCATION

Carbocation Rearrangements

- o 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 C_2 to the carbocationic C_1, a 1,2-hydride shift:

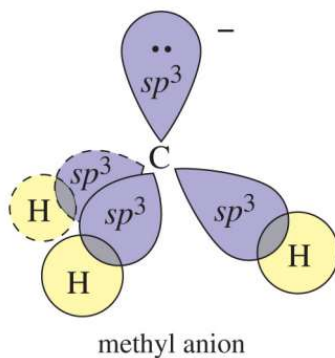- o With change in carbon skeleton; Neopentyl rearrangements

CARBANION

Carbanion Structure

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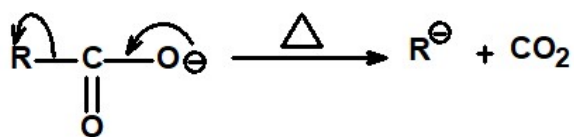o *Destabilized by alkyl substituents.*

methyl anion

CARBANION

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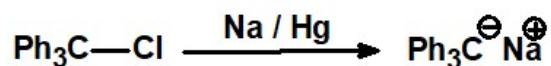
o Carbanion can be formed by

- *Removal of a proton*

$$R_3C—H + B\colon \rightleftharpoons R_3C^{\ominus} + BH^{\oplus}$$

- *Removal of CO_2 from decarboxylation of RCO_2^-*

$$\xrightarrow{\triangle} R^{\ominus} + CO_2$$

- *Removal of Cl from Ph_3C-Cl*

$$Ph_3C—Cl \xrightarrow{Na\,/\,Hg} Ph_3C^{\ominus}Na^{\oplus}$$
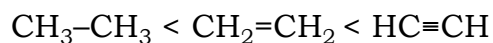
CARBANION

Stability of Carbanion

o The main features that serve to stabilize carbanions are

- *increase in s character at the carbanion carbon*

$$CH_3–CH_3 < CH_2=CH_2 < HC\equiv CH$$

- *electron-withdrawing inductive effects*

$$^-CF_3 \text{ and } ^-C(CF_3)_3 \text{ by electron-withdrawal.}$$

The destabilizing influence of the electron-donating inductive effect of alkyl groups is seen in the observed carbanion stability sequence:
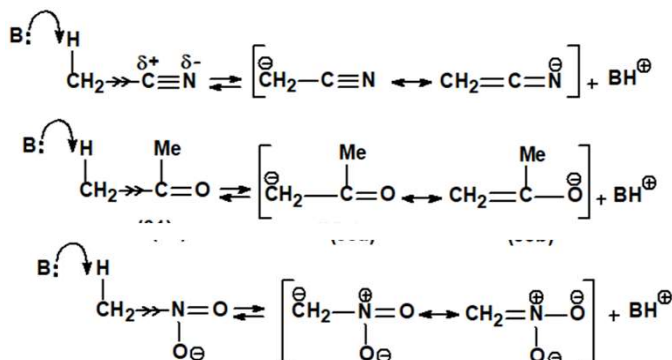
$$CH_3^{\ominus} > RCH_2^{\ominus} > R_2CH^{\ominus} > R_3C^{\ominus}$$

CARBANION

Stability of Carbanion

o 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$_2$
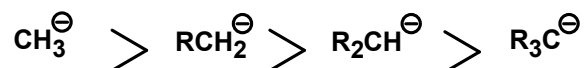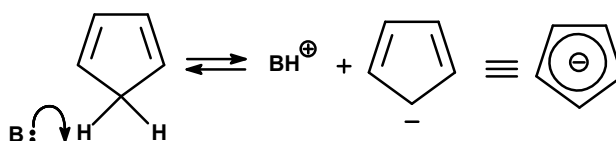
CARBANION

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*:
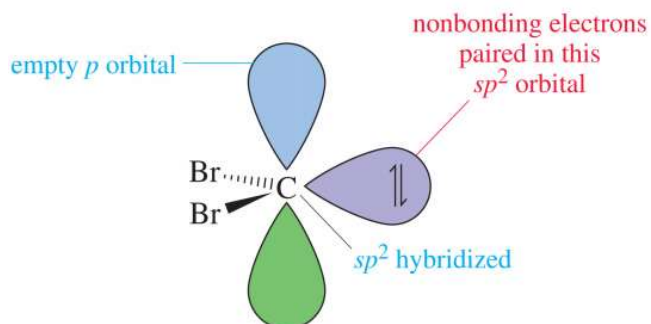
CARBENES AND NITRENES

Carbenes Structure

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

CARBENES AND NITRENES

o *Carbenes* (also called methylenes) are highly reactive species.

o *Carbenes* are molecules containing divalent carbon atoms.
o Each divalent carbon has two unshared electrons, which are often shown when writing the structures of carbenes.
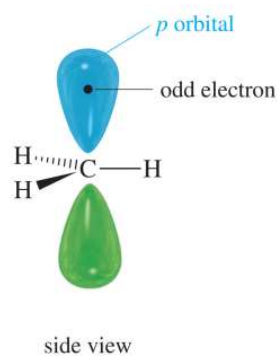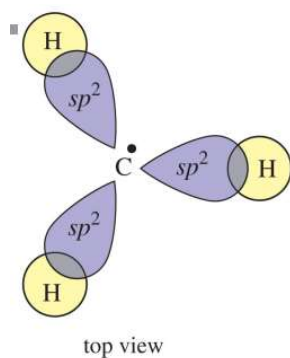o However, carbenes are neutral molecules, not carbanions.

$$CH_2 \ (:CH_2) \qquad :CH\overset{\overset{\displaystyle O}{\|}}{C}CH_3 \qquad :CCl_2 \qquad :C=CHCH_3$$
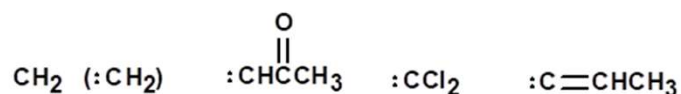
o *Nitrenes* are compounds, such as $:NC_6H_5$, that contain monovalent nitrogen atoms.

FREE RADICALS

Free radical Structure

o Electron-deficient
o Stabilized by alkyl substituents.
o Order of stability: $3° > 2° > 1°$.

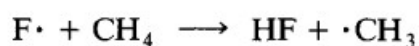top view   side view

REACTIVE INTERMEDIATE

FREE RADICALS

- o Radicals are species that contain one or more unpaired electrons.

- o Many radicals are produced by homolytic cleavage of bonds.

$$Cl_2 \xrightarrow{h\nu} 2Cl^{\bullet}$$
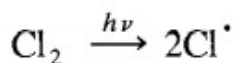
- o Hydrogen abstraction; many radicals can remove hydrogen atoms from organic molecules to form carbon radicals.

$$F^{\bullet} + CH_4 \longrightarrow HF + {\bullet}CH_3$$

NUCLEOPHILES AND ELECTROPHILES

ELECTROPHILES

- o 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*.

- o 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$_2$C:) or neutral molecules having functional groups like carbonyl group (>C=O) or alkyl halides (R$_3$C-X, where X is a halogen atom).

- o They have six valence electrons (except H$^+$) and can accept an electron pair from a nucleophile to acquire the stable octet.

- o For example, hydroxide ion combines with a proton to give water.

$$H^{\oplus} + {}^{\ominus}OH \longrightarrow H-O-H$$
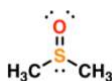
NUCLEOPHILES AND ELECTROPHILES

NUCLEOPHILES

o **Nucleophile (Nu:);** a reagent that brings an electron pair to the reactive site and the reaction is then called *nucleophilic*.

o **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
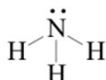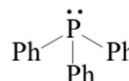

| water | ammonia | dimethylsulfide | triphenylphosphine |

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

NUCLEOPHILES AND ELECTROPHILES

NUCLEOPHILES

o The nucleophiles which have more than one (generally two) suitable atoms through which they can attack the substrate are known as **ambident nucleophiles.**

o *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.*

o **Some examples** are

- Cyanide, isothiocyanate and nitrite ions are some examples of ambident nucleophiles, since they have more than one reactive site.
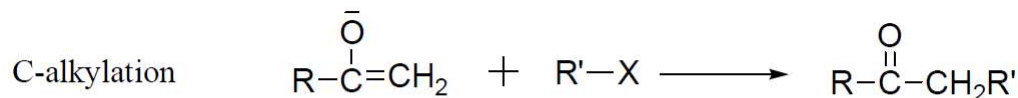

isothiocyanate
binds through N

thiocyanate
binds through S

phenyl isothiocyanate

phenyl thiocyanate
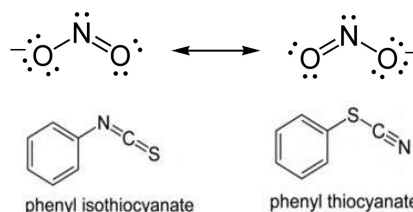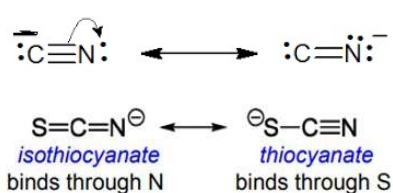
NUCLEOPHILES AND ELECTROPHILES

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.

C-alkylation $\quad R-\overset{\overset{\bar{O}}{\|}}{C}=CH_2 \ + \ R'-X \longrightarrow R-\overset{\overset{O}{\|}}{C}-CH_2R'$

O-alkylation $\quad R-\overset{\overset{\bar{O}}{|}}{C}=CH_2 \ + \ R'-X \longrightarrow R-\overset{\overset{OR'}{|}}{C}=CH_2$

NUCLEOPHILES AND ELECTROPHILES

NUCLEOPHILICITY AND BASICITY?

o *Basicity:* nucleophile attacks hydrogen (proton).

o *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.*
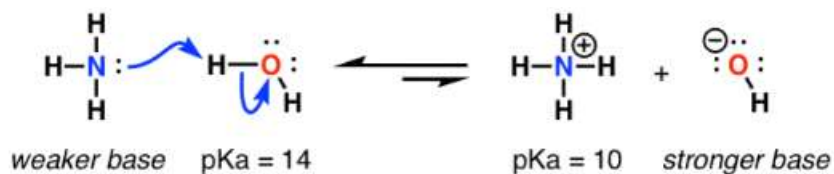
weaker base pKa = 14 $\qquad$ pKa = 10 *stronger base*

NUCLEOPHILICITY AND BASICITY?

o *Basicity:* nucleophile attacks hydrogen (proton).

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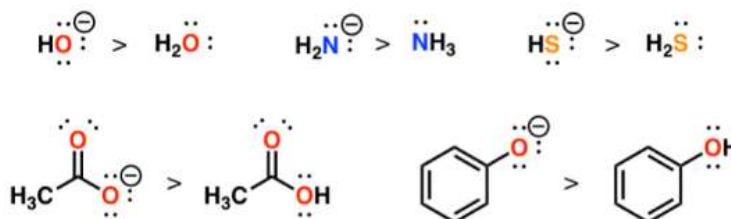*e.g. the nucleophilicity is measured by the rate of the reaction.*

irreversible reaction
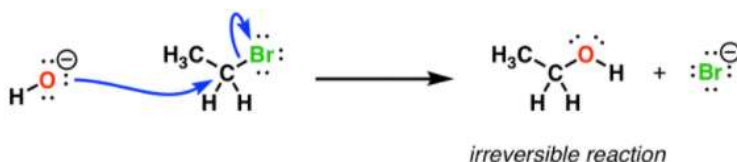
FACTORS AFFECTING NUCLEOPHILICITY

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

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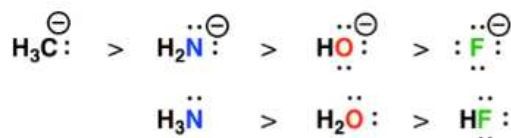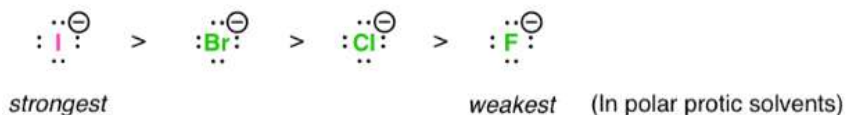

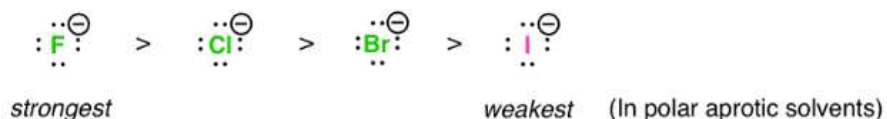These two factors correlate strongly with basicity.

NUCLEOPHILES AND ELECTROPHILES

FACTORS AFFECTING NUCLEOPHILICITY

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

$$:\overset{..}{\underset{..}{I}}:^{\ominus} \quad > \quad :\overset{..}{\underset{..}{Br}}:^{\ominus} \quad > \quad :\overset{..}{\underset{..}{Cl}}:^{\ominus} \quad > \quad :\overset{..}{\underset{..}{F}}:^{\ominus}$$

strongest　　　　　　　weakest　(In polar protic solvents)

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

$$:\overset{..}{\underset{..}{F}}:^{\ominus} \quad > \quad :\overset{..}{\underset{..}{Cl}}:^{\ominus} \quad > \quad :\overset{..}{\underset{..}{Br}}:^{\ominus} \quad > \quad :\overset{..}{\underset{..}{I}}:^{\ominus}$$

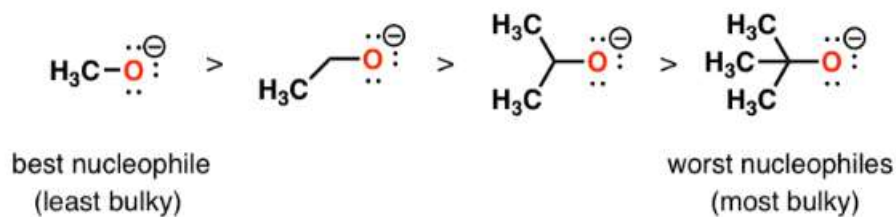strongest　　　　　　　weakest　(In polar aprotic solvents)

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).

$$H_3C-\overset{..}{\underset{..}{O}}:^{\ominus} \; > \; H_3C\!\!\diagup\!\!\overset{..}{\underset{..}{O}}:^{\ominus} \; > \; \overset{H_3C}{\underset{H_3C}{\diagup}}\!\!\overset{..}{\underset{..}{O}}:^{\ominus} \; > \; \overset{H_3C}{\underset{H_3C}{H_3C\!-\!}}\!\!\overset{..}{\underset{..}{O}}:^{\ominus}$$

best nucleophile　　　　　　　worst nucleophiles
(least bulky)　　　　　　　　(most bulky)

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, $RC{\equiv}C{:}^-$, and NH_2^-.

Strong Bases/Poor Nucleophiles

Some strong bases are poor nucleophiles because of steric hindrance.

Examples are t-BuO^-, t-BuLi, and $LiN[CH(CH_3)_2]$

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

o When we look at an organic reaction we have to take into account two main concepts:
- The equilibrium
- The rate of the reaction.

o The conversion between reactants and products is governed by the reaction free energy ΔG (*free energy of the products) – (free energy of the reactants*).

- A reaction is thermodynamically allowed when the free energy of the products is lower than that of the reactants (i.e. ΔG is negative).

- When ΔG = zero, the equilibrium is reached and an equilibrium constant K_{eq} of the reaction can be defined as a function of $\Delta G°$, the variation in the standard free energies.

    The equilibrium constant K_{eq} is the ratio between the equilibrium concentration of the products and that of the reactants.

WHY DO THESE REACTIONS OCCUR?

THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION

o 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.

o The conversion between reactants and products is governed by the reaction free energy ΔG (*free energy of the products) – (free energy of the reactants*).

o The reactants must be supplied with enough *activation energy* to enable the reaction to proceed in the forward direction.

o All organic reactions will reach equilibrium that favors the more stable side.

For a reaction:

$$aA + bB \rightleftharpoons dD + eE$$
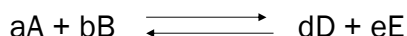
$$K_{eq} = [products] / [reactants] = [D]^d [E]^e / [A]^a [B]^b$$
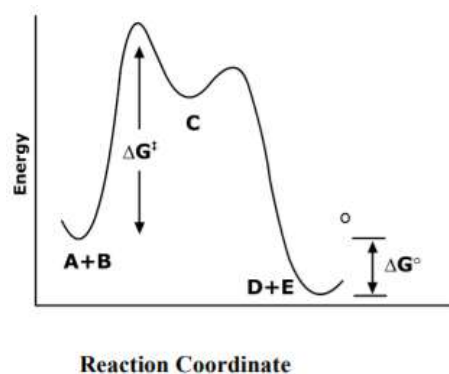

WHY DO THESE REACTIONS OCCUR?

THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION

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

$\Delta G^o =$ *(free energy of products) – (free energy of reactants)*

$\Delta G^{\ddagger} =$ *(free energy of transition state) – (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‡ :

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

If **ΔG‡ is small,** the compound (the reactant) is **kinetically unstable** i.e., it undergoes the reaction rapidly.
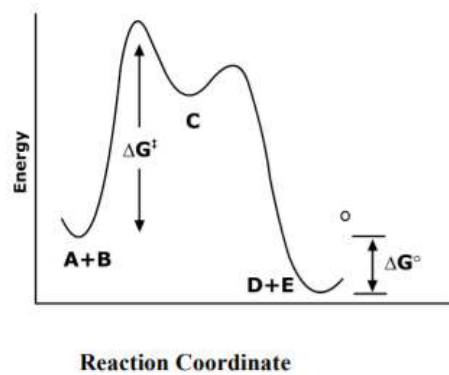
Reaction Coordinate

WHY DO THESE REACTIONS OCCUR?

THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION

o **For a reaction to take place spontaneously;**
the free energy of the products must be lower than the free energy of the reactants; i.e., ΔG must be negative.

o The Gibbs standard free-energy (ΔG) change has an enthalpy component and an entropy component, which are related by the following equation:

$$\Delta G° = - RT \ln K_{eq} = \Delta H - T \Delta S$$

The enthalpy term (ΔH);
When new bonds are formed, heat is given off and when bonds are broken, heat is consumed.
Thus, ΔH is a measure of the bond-making and bond-breaking processes that occur as reactants are converted into products.
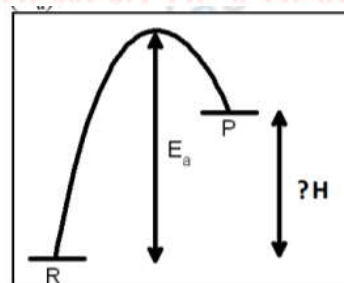
Entropy (ΔS) is defined as the degree of disorder of a system.

WHY DO THESE REACTIONS OCCUR?

THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION
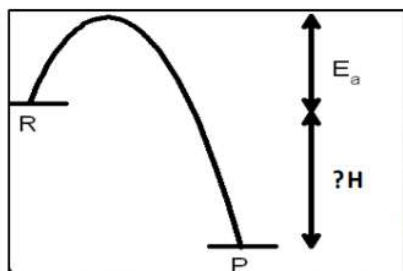
Exothermic/spontaneous Reactions

- 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 ($K_{eq} < 1$).
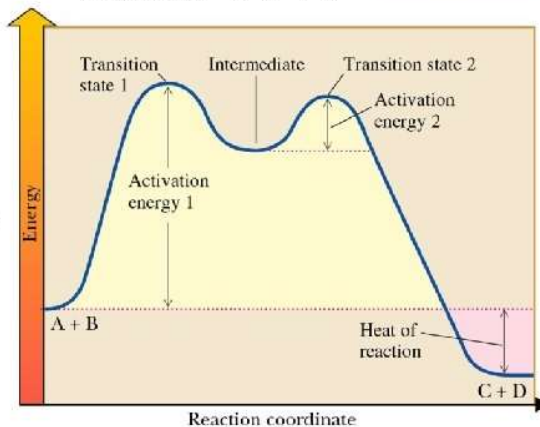

WHY DO THESE REACTIONS OCCUR?

THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION

Multi-Step Reactions

Step 1: A + B → Intermediate

Step 2: Intermediate → C + D

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

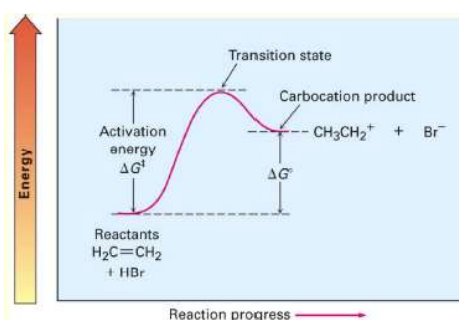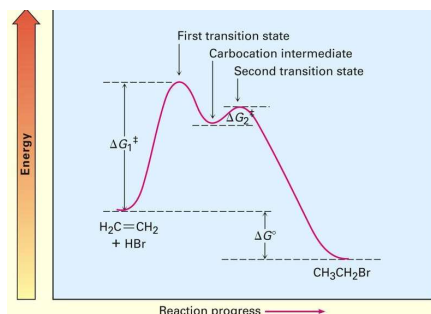Step 1: endergonic, high energy of activation. Slow process

Step 2: exergonic, small energy of activation. Fast Process.
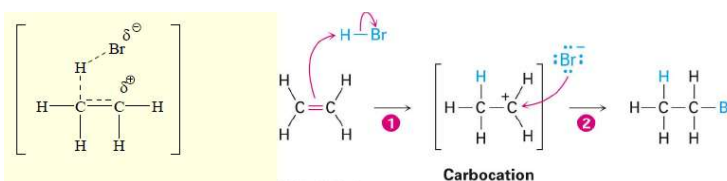
WHY DO THESE REACTIONS OCCUR?

THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION

Energy diagram for the reaction of Ethylene with HBr

o If a reaction occurs in more than one step, it must involve species that are neither the reactant nor the final product.

o These are called reaction *intermediates*.

o Each step has its own free energy of activation

o The energy needed to go from reactant to transition state is the *activation energy ($\Delta G^\ddagger$)*.

o 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

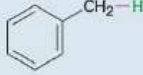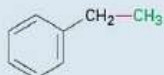| Table 5.2	Explanation of Thermodynamic Quantities: $\Delta G° = \Delta H° - T\Delta S°$	
Term	**Name**	**Explanation**
$\Delta G°$	Gibbs free-energy change	The energy difference between reactants and products. When $\Delta G°$ is negative, the reaction is **exergonic**, has a favorable equilibrium constant, and can occur spontaneously. When $\Delta G°$ is positive, the reaction is **endergonic**, has an unfavorable equilibrium constant, and cannot occur spontaneously.
$\Delta H°$	Enthalpy change	The heat of reaction, or difference in strength between the bonds broken in a reaction and the bonds formed. When $\Delta H°$ is negative, the reaction releases heat and is **exothermic**. When $\Delta H°$ is positive, the reaction absorbs heat and is **endothermic**.
$\Delta S°$	Entropy change	The change in molecular randomness during a reaction. When $\Delta S°$ is negative, randomness decreases; when $\Delta S°$ is positive, randomness increases.

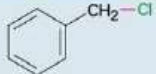© 2007 Thomson Higher Education
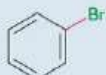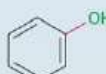
WHY DO THESE REACTIONS OCCUR?

THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION

Table 5.3 | Some Bond Dissociation Energies, D

Bond	D (kJ/mol)	Bond	D (kJ/mol)	Bond	D (kJ/mol)
H—H	436	$(CH_3)_3C$—I	209	C_2H_5—CH_3	355
H—F	570	H_2C=CH—H	444	$(CH_3)_2CH$—CH_3	351
H—Cl	432	H_2C=CH—Cl	368	$(CH_3)_3C$—CH_3	339
H—Br	366	H_2C=$CHCH_2$—H	361	H_2C=CH—CH_3	406
H—I	298	H_2C=$CHCH_2$—Cl	289	H_2C=$CHCH_2$—CH_3	310
Cl—Cl	243	(benzene ring)—H	464	H_2C=CH_2	611
Br—Br	193			(benzene ring)—CH_3	427
I—I	151				
CH_3—H	438	(benzene ring)—Cl	405	(benzene ring)—CH_2—CH_3	332
CH_3—Cl	351				
CH_3—Br	293				
CH_3—I	234	(benzene ring)—CH_2—H	368		
CH_3—OH	380			$CH_3\overset{O}{C}$—H	368
CH_3—NH_2	335				

Bond	D (kJ/mol)	Bond	D (kJ/mol)	Bond	D (kJ/mol)
C_2H_5—H	420	(benzene ring)—CH_2—Cl	293	HO—H	498
C_2H_5—Cl	338			HO—OH	213
C_2H_5—Br	285			CH_3O—H	437
C_2H_5—I	222	(benzene ring)—Br	337	CH_3S—H	371
C_2H_5—OH	380			C_2H_5O—H	436
$(CH_3)_2CH$—H	401				
$(CH_3)_2CH$—Cl	339	(benzene ring)—OH	469	$CH_3\overset{O}{C}$—CH_3	322
$(CH_3)_2CH$—Br	274				
$(CH_3)_3C$—H	390			CH_3CH_2O—CH_3	339
$(CH_3)_3C$—Cl	330	HC≡C—H	552	NH_2—H	449
$(CH_3)_3C$—Br	263	CH_3—CH_3	376	H—CN	518

WHY DO THESE REACTIONS OCCUR?

THERMODYNAMIC AND KINETIC REQUIREMENT OF A REACTION

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

o 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

o 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	**Second-order reaction:**
For the reaction: $A \longrightarrow B$	$A + B \longrightarrow C + D$
Rate = k [A]	Rate = k [A] [B]
If the rate of a reaction depends on the concentration of only one reactant,	*A reaction whose rate depends on the concentrations of two reactants*