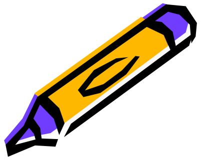
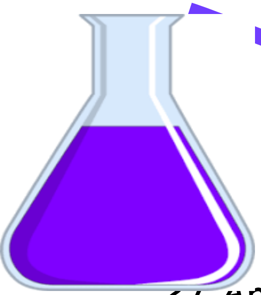
Chapter 1

Organic Chemistry II

BY

Dale Abdissa (M.Sc)





Course Objectives

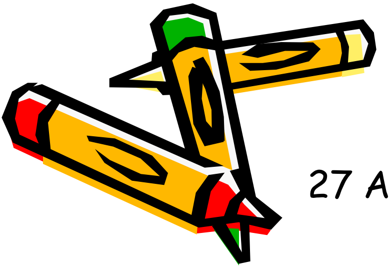
objectives: At the end of the course the students will be able to:

- ✓ Elaborate the concept of the aromaticity
- ✓ Distinguish aromatic compounds from the non-aromatic ones.
- ✓ Describe the mechanism of electrophilic and nucleophilic aromatic substitution reactions
- ✓ Describe the various chemical properties & reactions of carbonyl compound
- ✓ Describe the various chemical properties and reactions of amines.
- ✓ Classify various biological molecule such as carbohydrates, lipids, amino acids and proteins, & their important chemical properties

Course content outline

Chapter 1. The Chemistry of Aromatic Compounds

- 1.1 Aromaticity
- 1.2 Properties of Benzene and its Derivatives
- 1.3 Heterocyclic Aromatic Compounds
- 1.4 Aromatic Substitution Rxns and their Mechanism
- 1.4.1 Halogenations
- 1.4.2 Nitration
- 1.4.3 Friedel Crafts Alkylation
- 1.4.4 Acylation
- 1.4.5 Sulphonation



Course content outline

1.4.6 Directing Effects of Substituents

1.4.7 Examples of Electrophilic Aromatic Substitution Reactions (was Covered in 1.4 Sub-title)

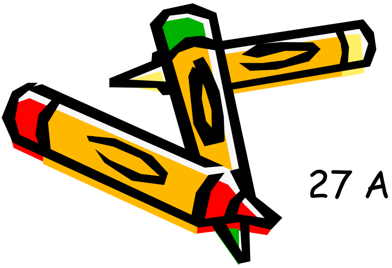
1.5 Nucleophilic Aromatic Substitution Reactions

1.5.1 Reactions of Aryl halides

1.5.2 Mechanisms of Nucleophilic Aromatic Substitution Rxns

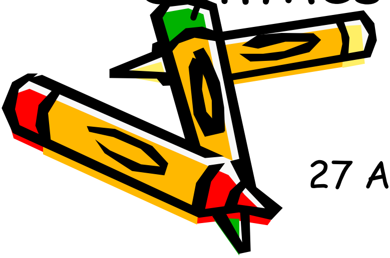
1.6 Reactions of Aromatic Side Chains

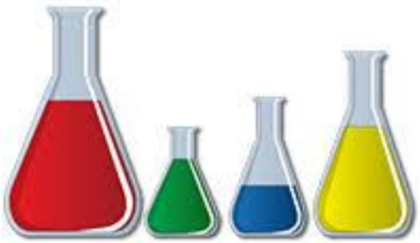
1.6.1 Oxidation and Substitution of Alkyl Side Chains

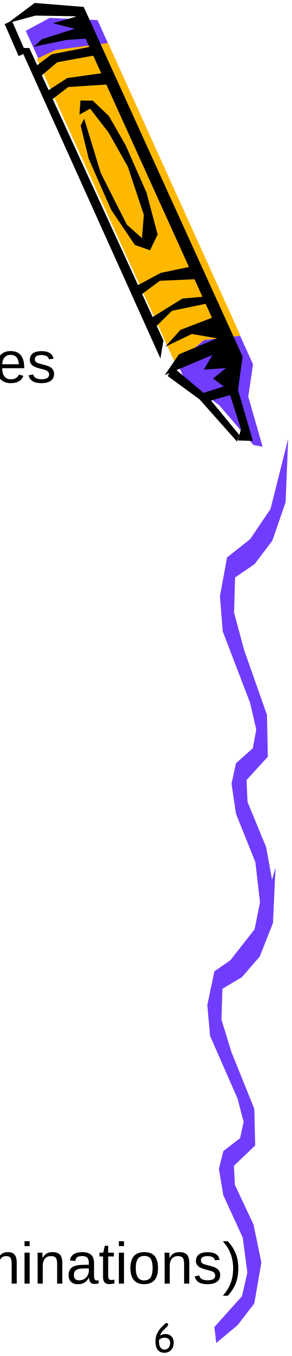


Course content outline

- 1.6.2 Reduction of Nitro Groups and Aryl Ketones
- 1.6.3 Conversion of Halogens to Organ metallic Reagents
- 1.6.4 Hydrolysis and Fusion of Sulphuric Acids
- 1.6.5 Modifying the Influence of Strong Activating Groups
- 1.6.6 Diazotization of Primary Aromatic Amines & their Usefulness (**will be touched in Unit 2 portion**)
- Synthesis of Aromatic Derivatives.

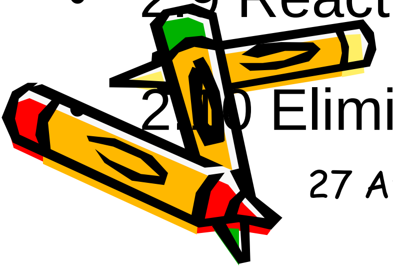






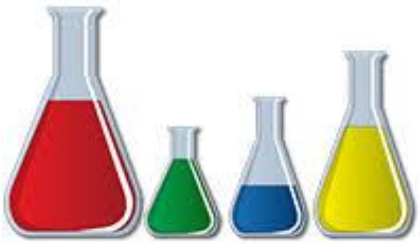
Chapter 2. Amines

- 2.1 Nomenclature and Structure
- 2.2 Properties of Amines: Physical and chemical properties
- 2.3 Basicity of Nitrogen Compounds
- 2.4 Acidity of Nitrogen Compounds
- 2.5 Reactions of Amines
- 2.6 Electrophilic Substitution at Nitrogen
- 2.7 Preparation of 1^{o},2^{o} & 3^{o}Amines
- 2.8 Reactions with Nitrous Acid
- 2.9 Reactions of Aryl Diazonium Intermediates
- 2.10 Elimination Reactions of Amines (See Hofmann Eliminations)



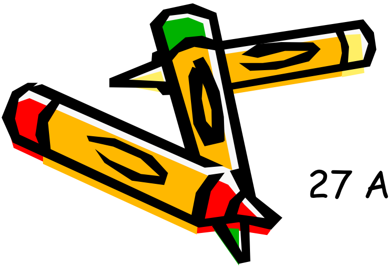
Chapter 3. Reactions of Carbonyl Compounds

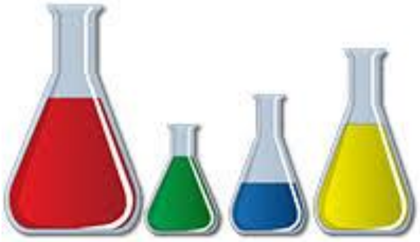
- 3.1 Addition Reactions
- 3.1.1 Hydrates, Hemiacetal; Cyanohydrins and Carbinolamine
- 3.1.2 Addition of Grignard Reagents
- 3.1.3 Addition of Hydrogen
- 3.1.4 Hydride Additions ($LiAlH_4$ and $NaBH_4$)
- 3.2 Addition $\beta-$Elimination Reactions
- 3.2.1 Imines and related compounds
- 3.2.2 Wittig reaction
- 3.2.3 Acetals



Chapter 3. Reactions of Carbonyl Compounds

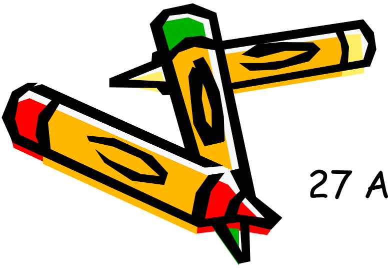
- 3.2.4 Ester hydrolysis and formation
- 3.2.5 Reactions of acid chlorides, acid anhydrides & amides
- 3.2.6 Reductions of acid derivatives
- 3.3 Enolization-Ketonization reactions
- 3.3.1 Halo form Reaction of Methyl Ketones
- 3.3.2 Alkylations at the α-Carbon
- 3.3.3 Aldol and Related Condensation reactions

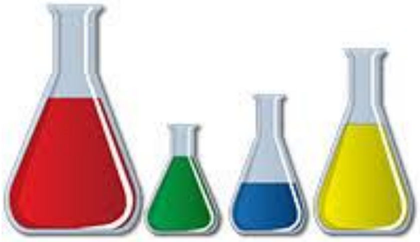




Chapter 4. Oxidation-Reduction reactions

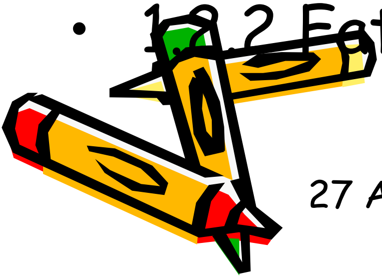
- 4.1. Oxidation Reactions
- 4.1.1 Alcohols and Aldehydes
- 4.1.2 Multiple Bonds
- 4.2. Reduction Reaction
- 4.2. 1 Catalytic Hydrogenation and Hydride Reduction
- 4.2. 3 Dissolving metal reduction





Chapter 5. Introduction to Chemistry of Biomolecules

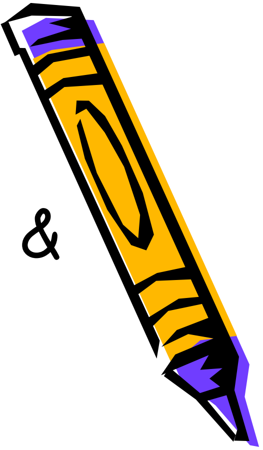
- 1.1 Carbohydrates
- 1.1.1The Structure and Configuration of Glucose
- 1.1.2 Anomeric forms of Monosaccharide's
- 1.1.3 Glycosides
- 1.1.4 Disaccharides and Polysaccharides
- 1.2 Lipids
- 1.2.1 Fatty Acids
- 1.2.2 Fats and Oils and Waxes



Introduction to Chemistry of Biomolecules

- 1.2.3 Phospholipids, Prostaglandins, Steroids and Terpenes
- 1.3 Proteins and Amino Acids
- 1.3.1 α-Amino Acids
- 1.3.2 Reactions and Synthesis of Amino Acids
- 1.3.4 Peptides & Proteins
- 1.3.5 The Primary Structure of Peptides
- 1.3.6 Secondary & Tertiary Structure of Large Peptides and Proteins
- 1.3.7 Peptide Synthesis
- 1 Nucleic Acids

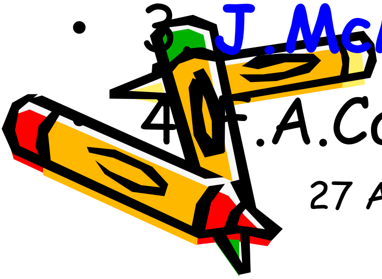
Mode of lesson Delivery



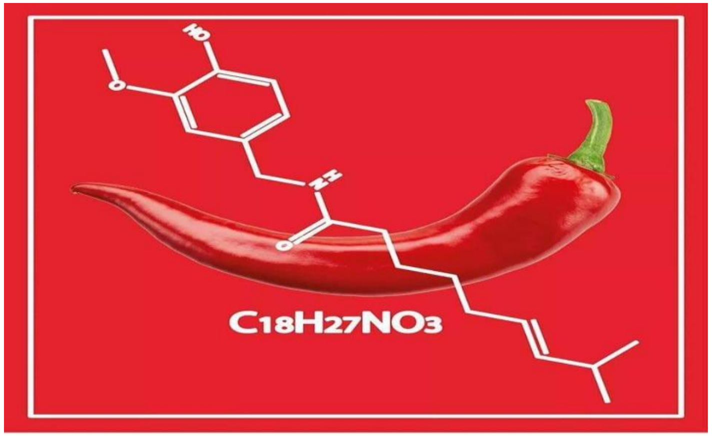
- Gaped lecture, lecture demonstration, group work & presentation & project work.
- **Method of assessment:**
- Short tests at the end of each chapter, assignment or group work (50%), Final exam at the end of the semester (50%)

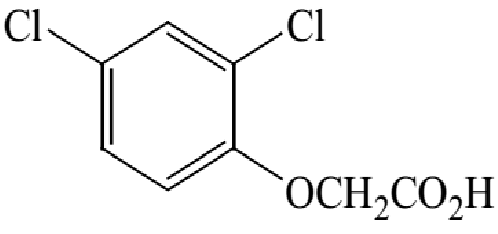
Reference materials:

- 1.F.M.Menger, D.J.Goldsmith;L.Mandle,Organicchemistry:AConciseApproah,2 nd Ed.,1974
- 2. **T.WG.Solomons, OrganicChemistry,7th Ed.,2004.**
- 3. **J.McMurry, OrganicChemistry,4th Ed.,1996.**
- 4. F.A.Carey, OrganicChemistry, 3rd Ed., 1996.



Some of the Aromatic Compounds





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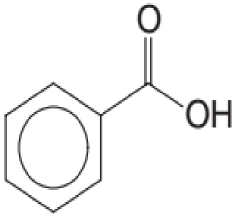
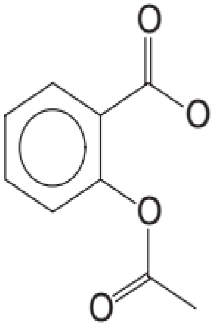
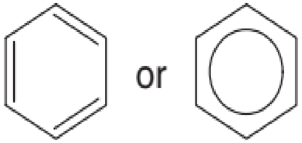


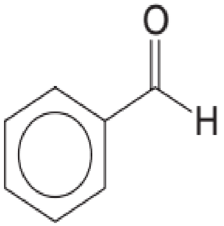
Benzoic acid



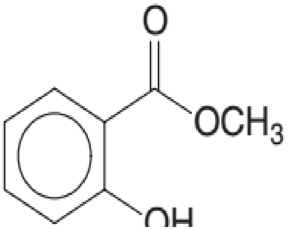
Acetylsalicylic acid (aspirin)

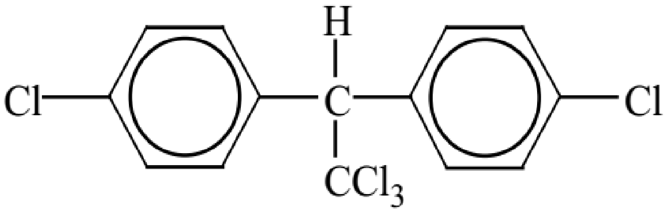


Benzene



Benzaldehyde





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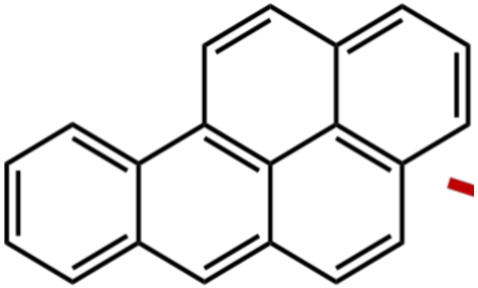
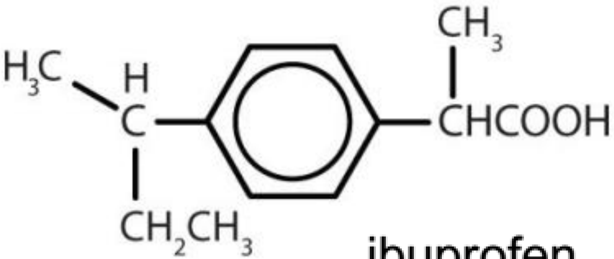


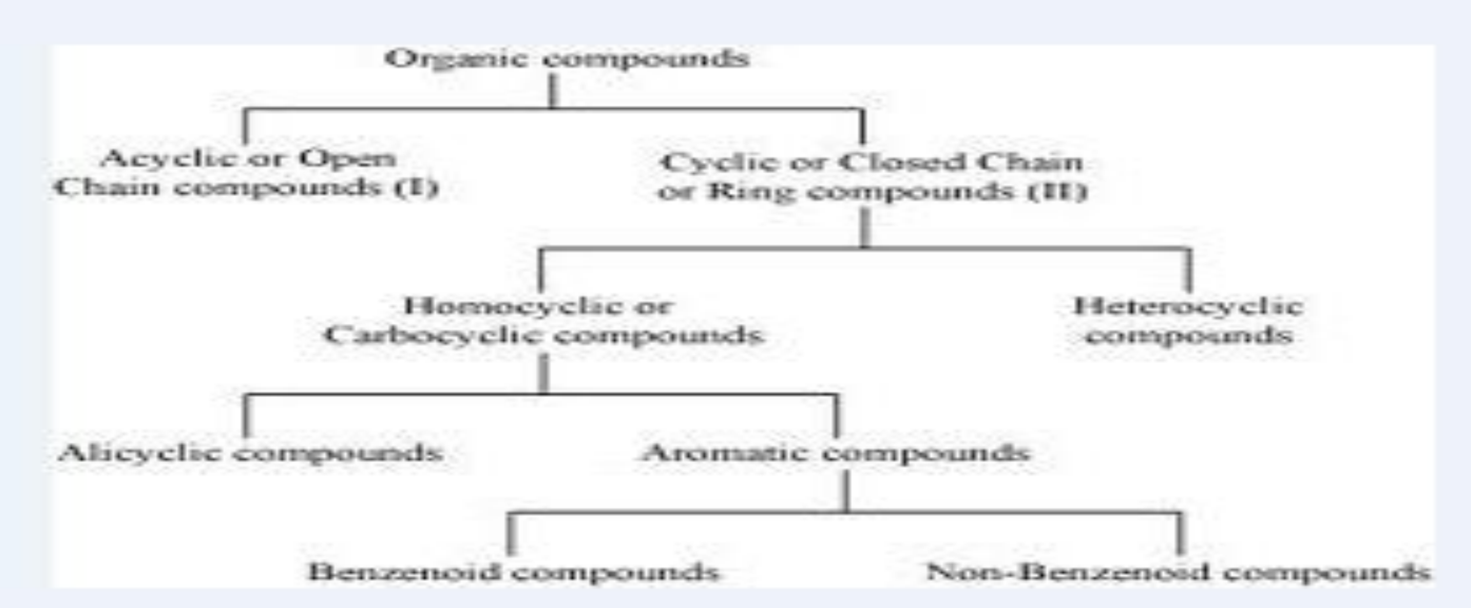
Benzo[a]pyrene



ibuprofen

1.The Chemistry of Aromatic Compounds

- ✓ Organic cpds are a class of complex molecules that are characterized by their use of **C** as a molecular backbone.



What is Aromatic Compound?

Aromatic hydrocarbons are compounds that contain a benzene ring or have similar properties to benzene.

1.1 Aromaticity

- ✓ Aromaticity it is in cyclic conjugated organic cpds such as benzene, that exhibit special stability due to resonance delocalization of π - electrons.

To be aromatic, a cpd must possess all of these characteristics:

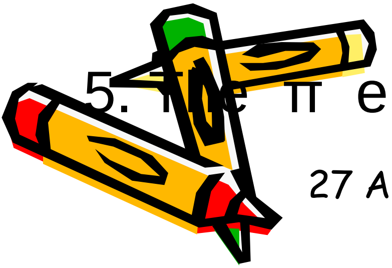
1. An aromatic cpd is cyclic and contains delocalized MOs

2.Fullfil (4 n + 2) π e^- in the ring where n (n = 0, 1, 2, . . .) i.e., Hückel Rule.

3. The atoms in the ring are usually sp^2 hybridized

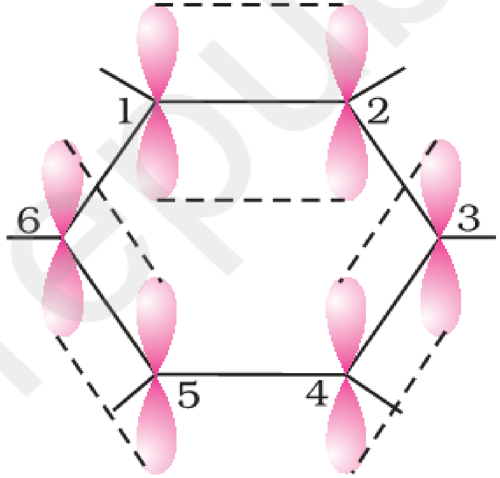
4. The structure of the cpd is planar, or nearly planar.

5. The π electrons are delocalized over the entire ring.



1.1 Aromaticity

- ✓ E.g Benzene meets all five criteria for a continuous ring of overlapping orbitals. Thus, benzene is aromatic.



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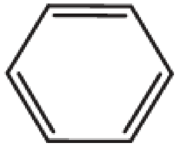

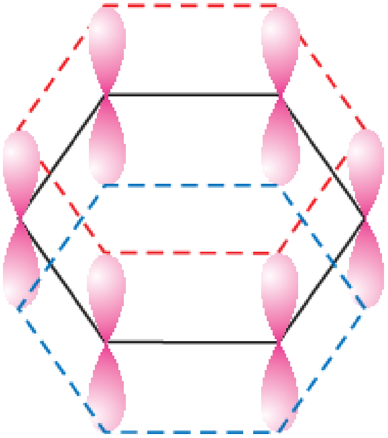

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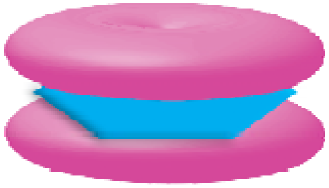
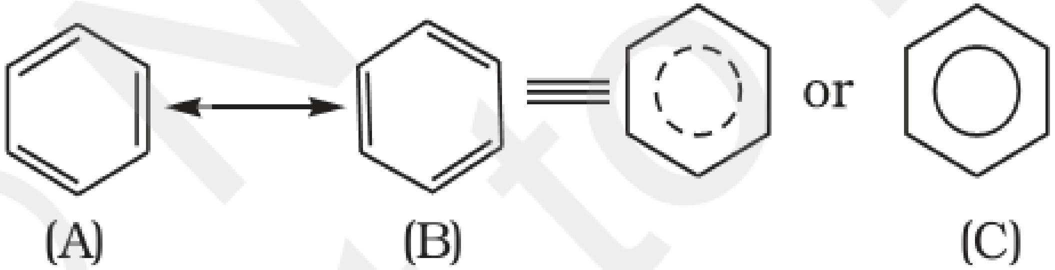
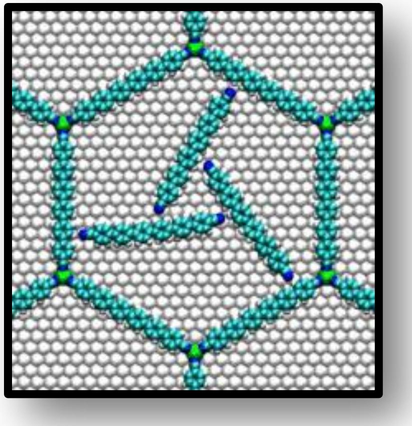
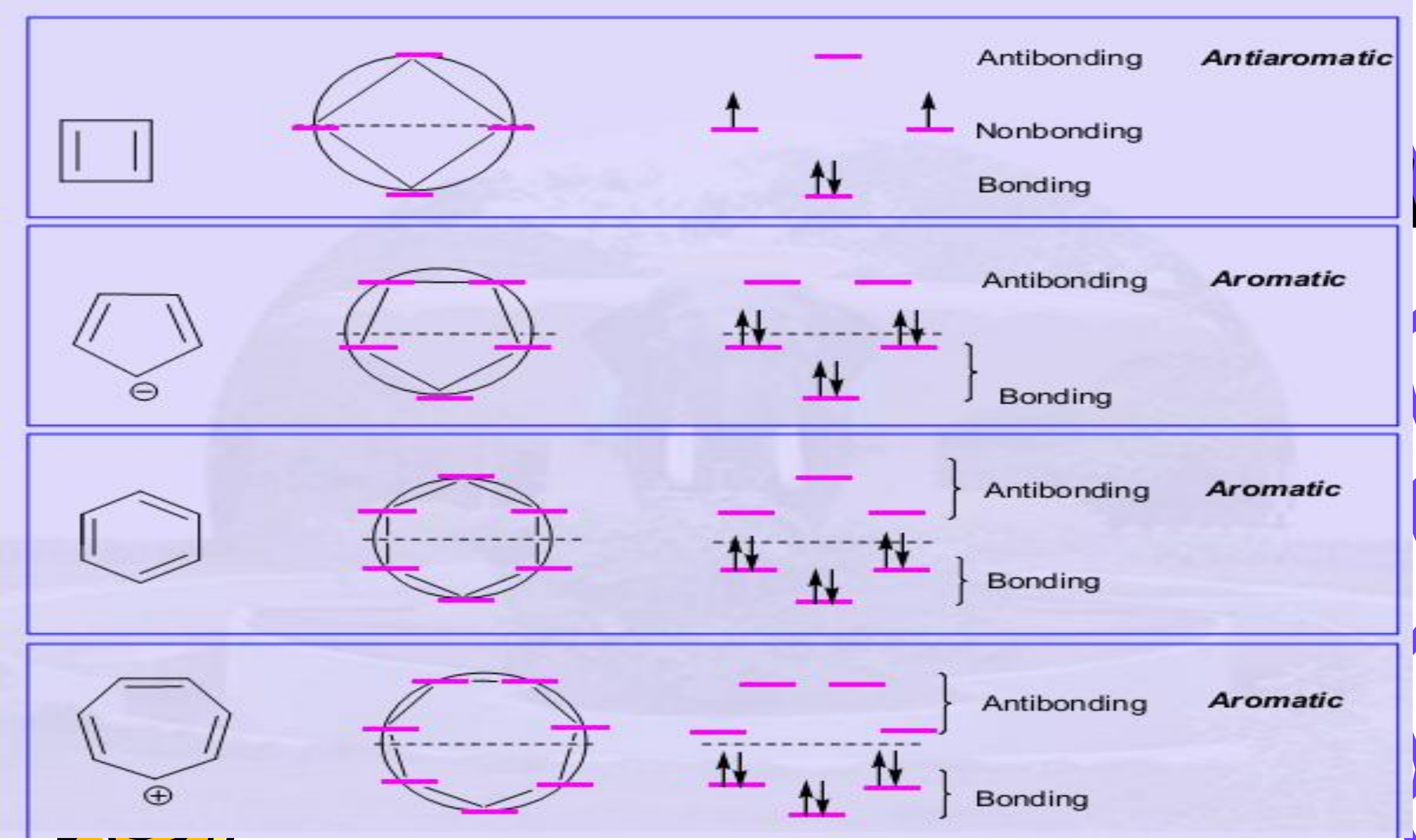


(electron cloud)





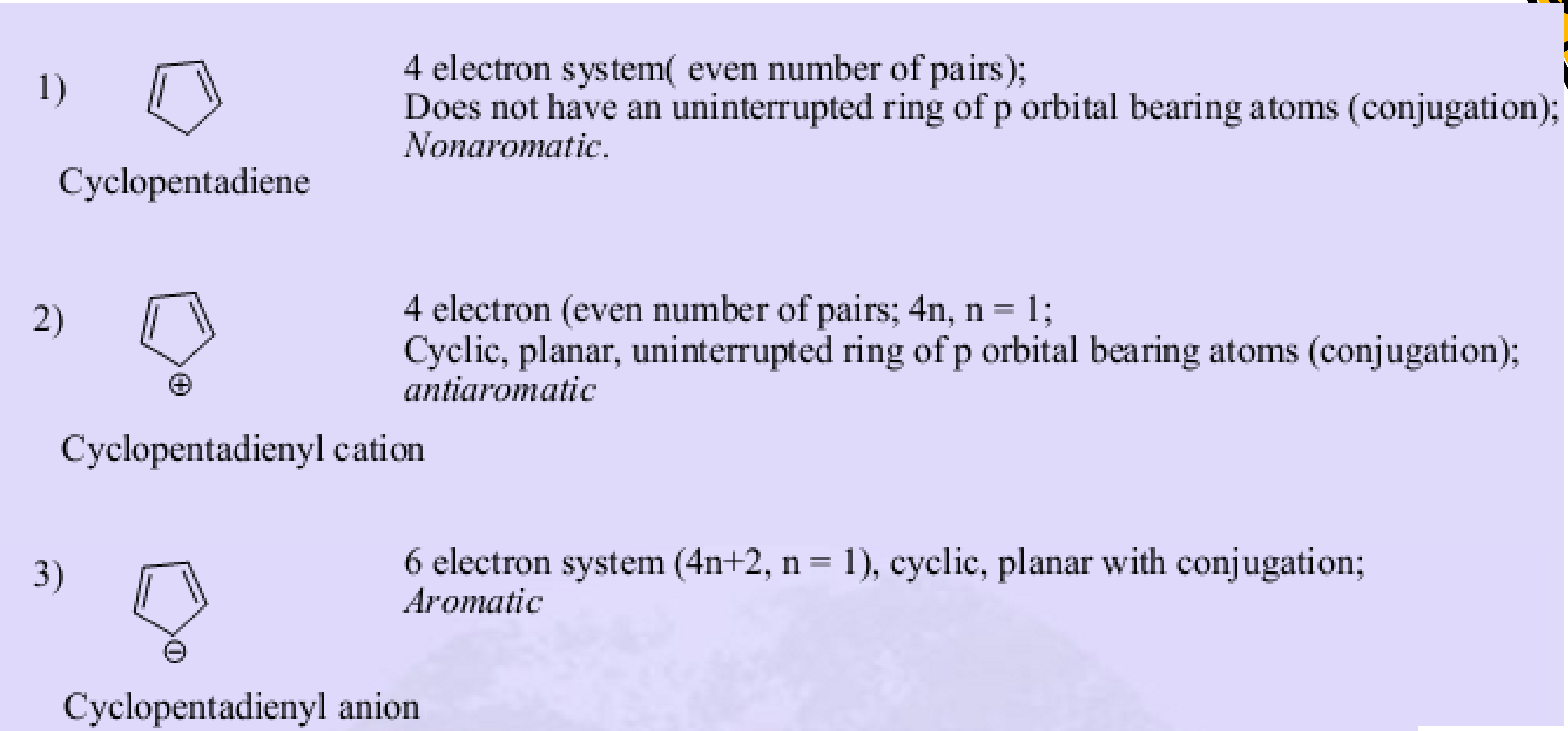
other examples Aromaticity



NB. Antiaromatic state is less stable than aromatic & nonaromatic forms.

cont^{d}

What is the difference b/n Antiaromatic, aromatic & nonaromatic forms



1) Cyclopentadiene

4 electron system(even number of pairs);
Does not have an uninterrupted ring of p orbital bearing atoms (conjugation);
Nonaromatic.

2) Cyclopentadienyl cation

4 electron (even number of pairs; 4n, n = 1;
Cyclic, planar, uninterrupted ring of p orbital bearing atoms (conjugation);
antiaromatic

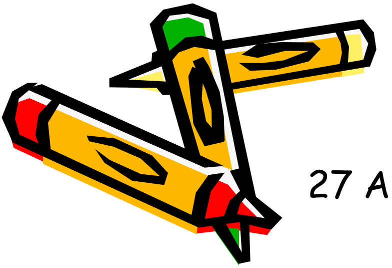
3) Cyclopentadienyl anion

6 electron system (4n+2, n = 1), cyclic, planar with conjugation;
Aromatic

The cyclopentadienyl anion is aromatic because it is cyclic, planar, completely conjugated, and has six π electrons.

Benzene (C_6H_6)

- It is a planar molecule containing a ring of six C atoms, each with a H atom attached.
- It is the simplest aromatic HC (or arene).
- its aromaticity is the major contributor to why it is so unreactive.
- The six C atoms form a perfectly regular hexagon.
- There are delocalized e-s above & below the plane of the ring, which makes benzene particularly stable.
- It resists addition rxns b/c those rxns would involve breaking the delocalization and losing that stability.



Benzene

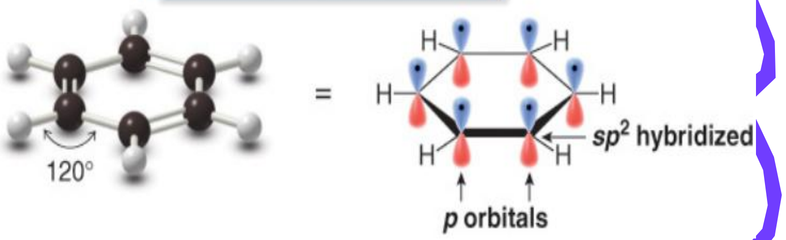
- ✓ If it is forced to react by increasing the temp. and/or by addition of a catalyst. It undergoes substitution reactions.

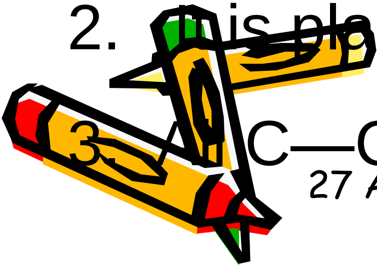
Kekulé description: An equilibrium

- ✓ Current descriptions of benzene are based on resonance and **e-** delocalization due to orbital overlap.
- ✓ Any structure for benzene must account for the <u>ff</u> facts:

1. It contains six-membered ring & 3 additional degrees of unsaturation.
2. It is planar.
3. All C—C bond lengths are equal.

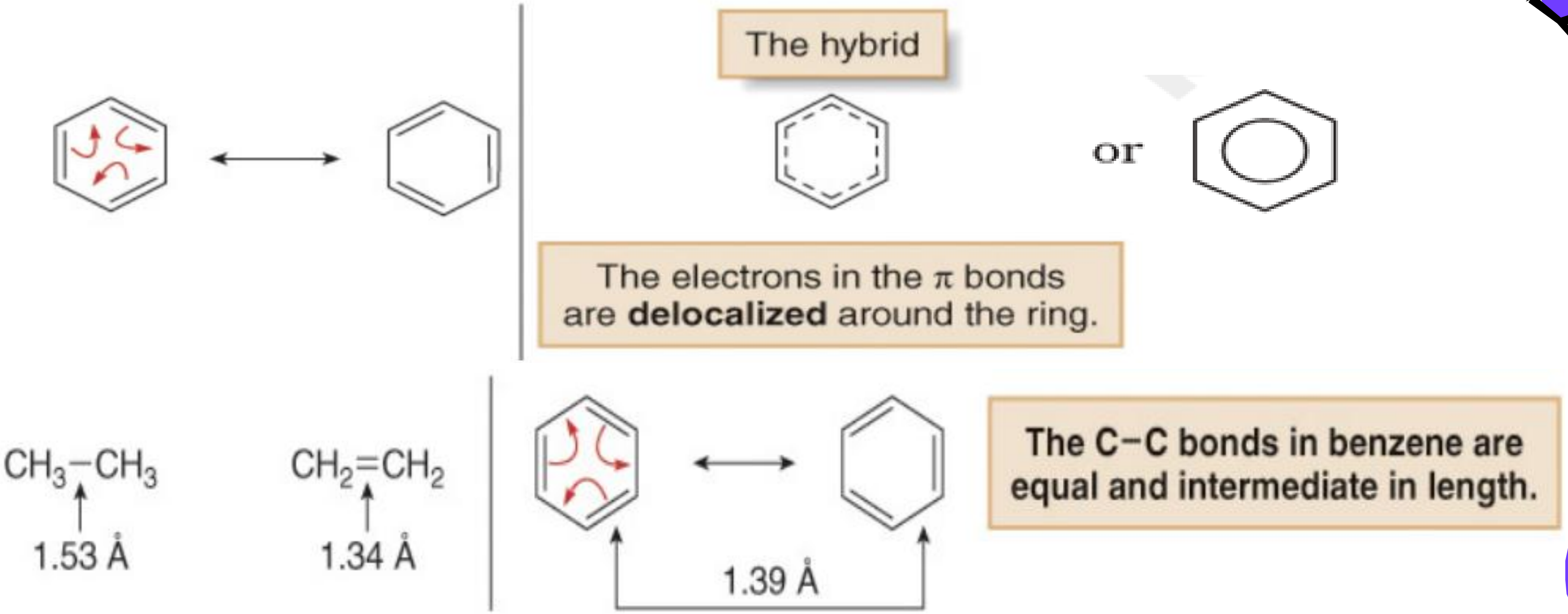
Benzene—A planar molecule





Benzene

- ✓ The true structure of benzene is a resonance hybrid of the two Lewis structures.



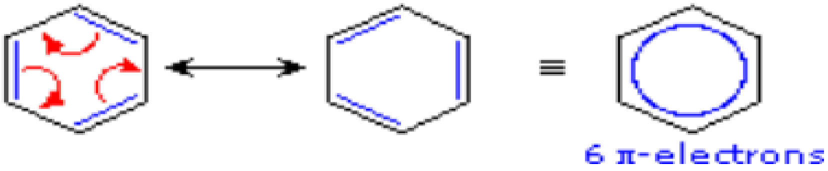
The electrons in the π bonds are **delocalized** around the ring.

The C–C bonds in benzene are equal and intermediate in length.

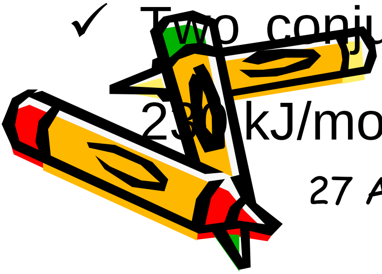
- ✓ Its actual bond length (1.39 Å) is intermediate b/n the C–C (1.53 Å) & the C=C double bond (1.34 Å).

Stability of Benzene

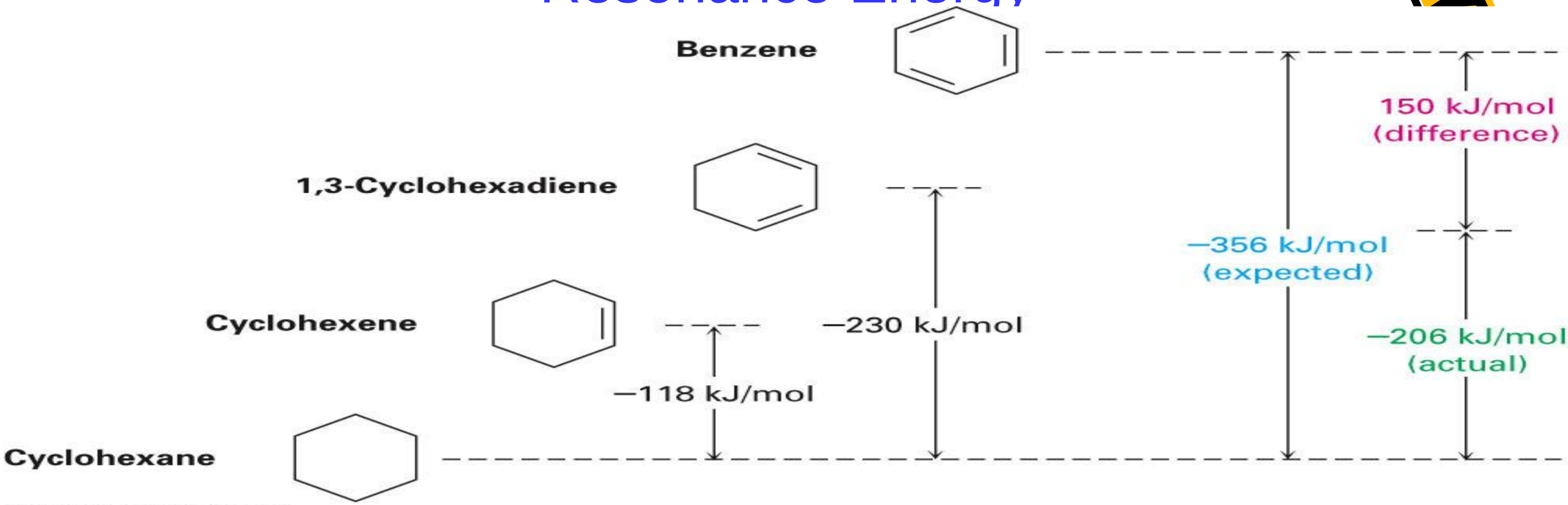
- ✓ the **e-** delocalization described by resonance enhances the stability of the molecules, and compounds composed of such molecules often show exceptional stability.



- ✓ Evidence for its thermodynamic stability was obtained from measurements of the heat released when double bonds in 6-carbon ring are hydrogenated (**H** is added catalytically) to give cyclohexane as a common Product.
- ✓ The addition of H_2 to C=C normally gives off about 118 kJ/mol, 3 double bonds would give off 356kJ/mol
- ✓ Two conjugated double bonds in cyclohexadiene add $2H_2$ to give off 230 kJ/mol



Resonance Energy



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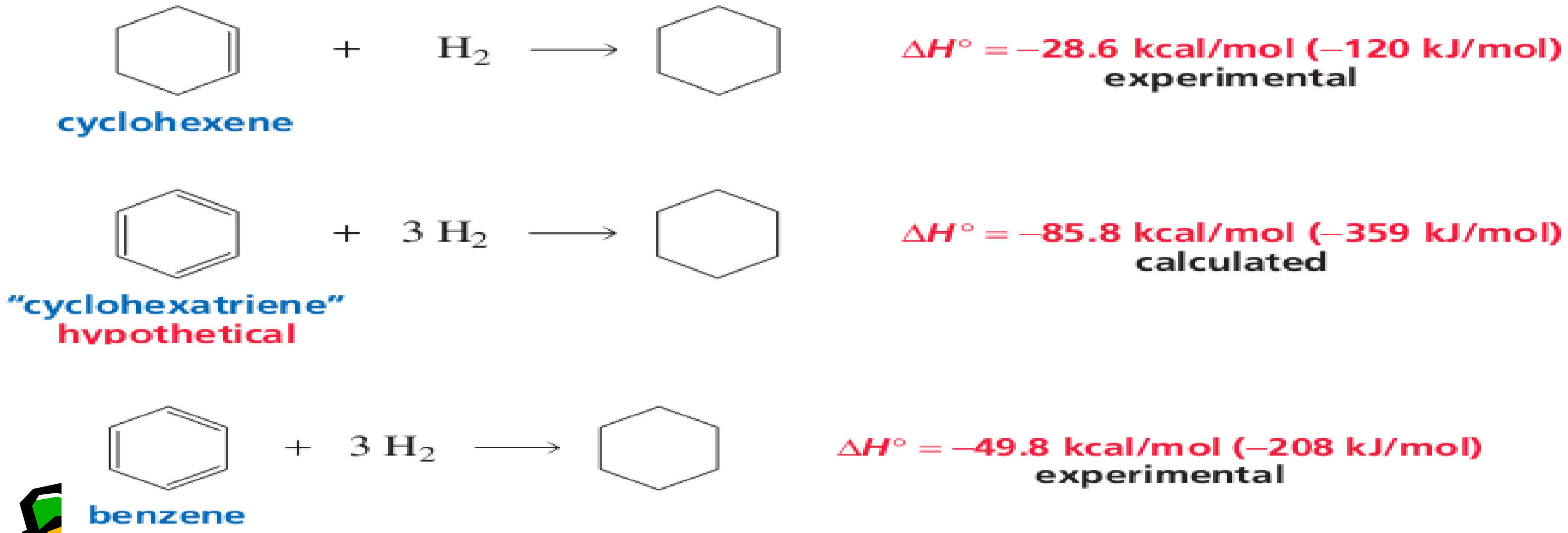
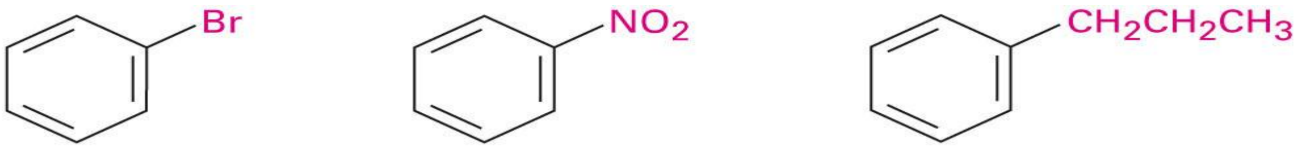


- The resonance energy is a measure of how much more stable a cpd with delocalized e-s is than it would be if its electrons were localized.

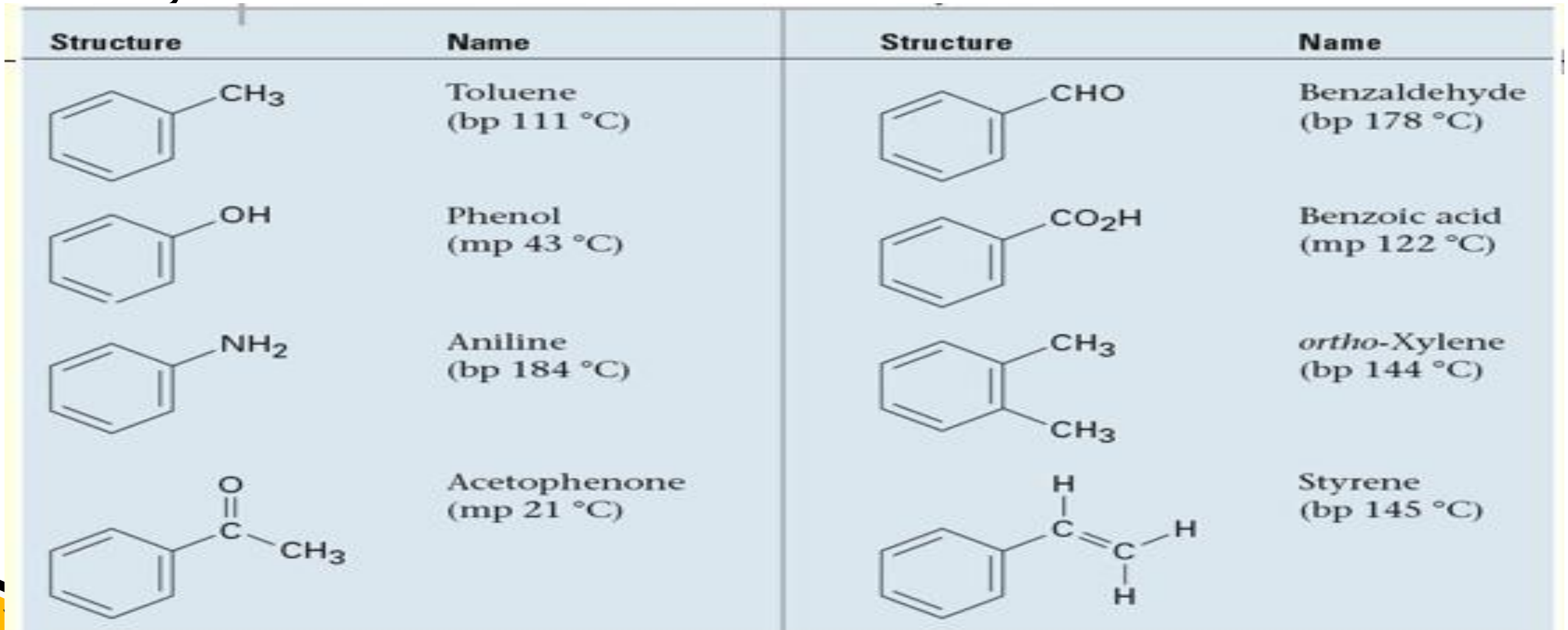
Nomenclature of Benzene Derivatives: Rules

- ✓ To name benzene ring with one substituent, name the substituent & add the word benzene.



Bromobenzene **Nitro**benzene **Propyl**benzene

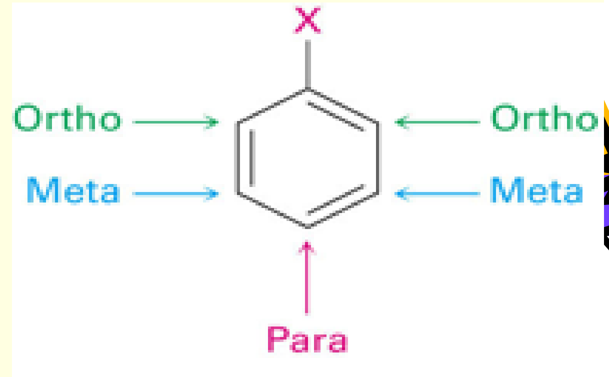
- ✓ Many monosubstituted benzenes have common names

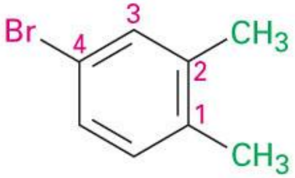


Structure	Name	Structure	Name
CH$_3$	Toluene (bp 111 °C)	CHO	Benzaldehyde (bp 178 °C)
OH	Phenol (mp 43 °C)	CO$_2$H	Benzoic acid (mp 122 °C)
NH$_2$	Aniline (bp 184 °C)	CH$_3$ CH$_3$	*ortho*-Xylene (bp 144 °C)
O C CH$_3$	Acetophenone (mp 21 °C)	H C C H H	Styrene (bp 145 °C)

Nomenclature of Benzene Derivatives: Rules

- ✓ Relative positions on a benzene ring
  - – ***ortho- (o)*** on adjacent carbons (1,2)
  - – ***meta- (m)*** separated by one carbon (1,3)
  - – ***para- (p)*** separated by two carbons (1,4)





4-Bromo-1,2-dimethylbenzene

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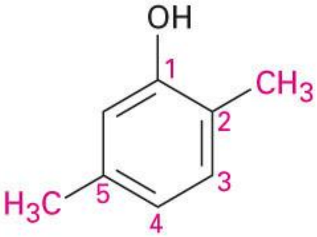
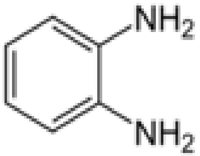
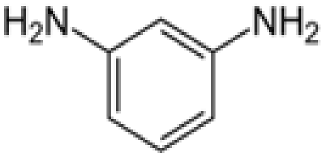


2,5-Dimethylphenol

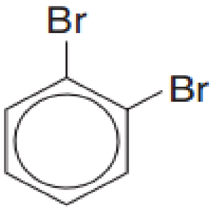
2,4,6-Trinitrotoluene (TNT)



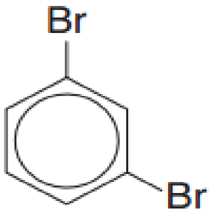
o-Phenylenediamine



m-Phenylenediamine

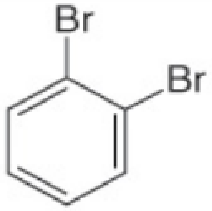


o-dibromobenzene (or)
ortho-dibromobenzene

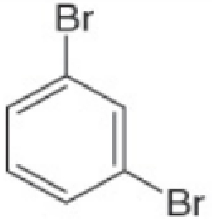


m-dibromobenzene (or)
meta-dibromobenzene

Nomenclature of Benzene Derivatives: Rules



ortho-dibromobenzene
or
o-dibromobenzene
or 1,2-dibromobenzene



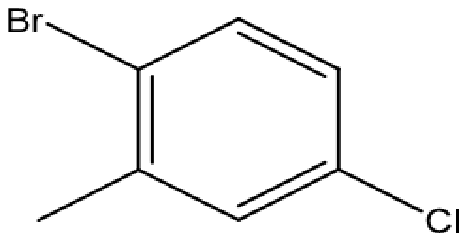
meta-dibromobenzene
or
m-dibromobenzene
or 1,3-dibromobenzene

para-dibromobenzene
or
p-dibromobenzene
or 1,4-dibromobenzene

Use a common root name:

p-bromo**toluene**

o-nitro**phenol**



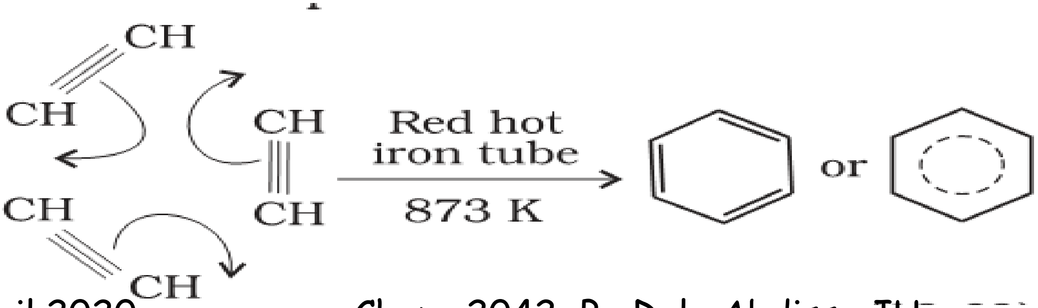
2-bromo-5-chlorotoluene

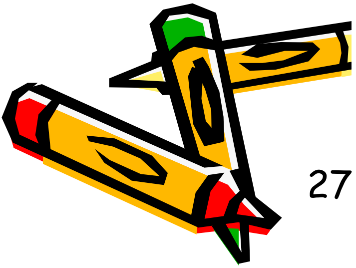
Preparation of Benzene

- Benzene is commercially isolated from coal tar.
- However, it may be prepared in the lab. by the ff methods

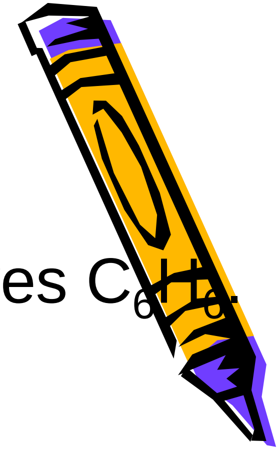
(i) Cyclic polymerisation of ethyne (C_2H_2)

- **C_2H_2** on passing through red hot **Fe** tube at 873K undergoes cyclic polymerization.
- Three molecules polymerise to form benzene, which is the starting molecule for the preparation of derivatives of benzene dyes, drugs & large number of other organic cpds.



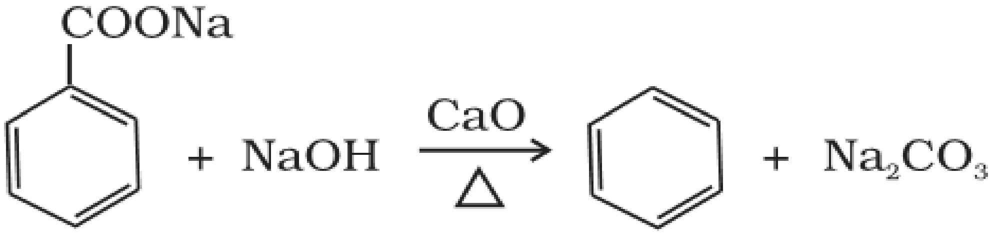


Preparation of Benzene



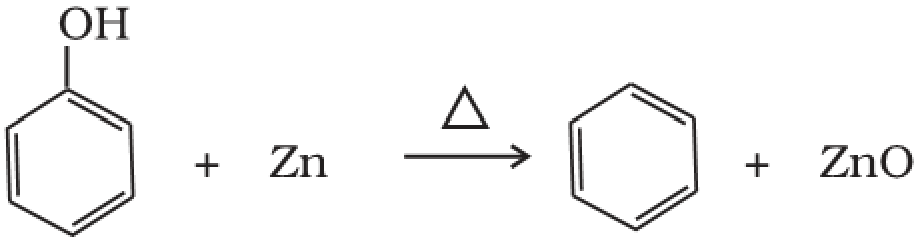
(ii) Decarboxylation of aromatic acids:

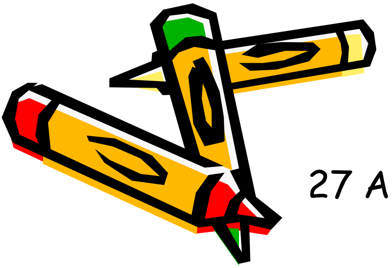
- Sodium salt of benzoic acid on heating with Cao gives C_6H_6.



(iii) Reduction of phenol:

- Phenol is reduced to C_6H_6 by passing its vapors over heated zinc dust.

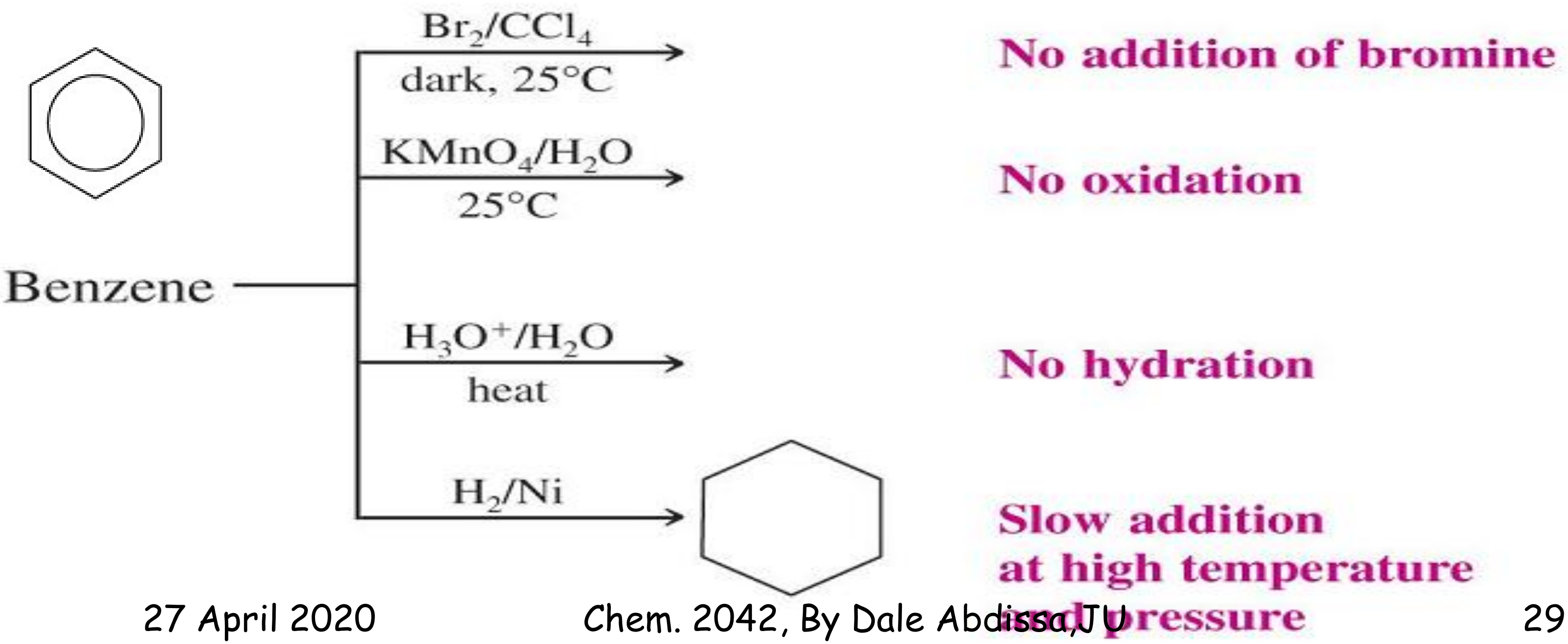




1.2 Properties of Benzene and its Derivatives

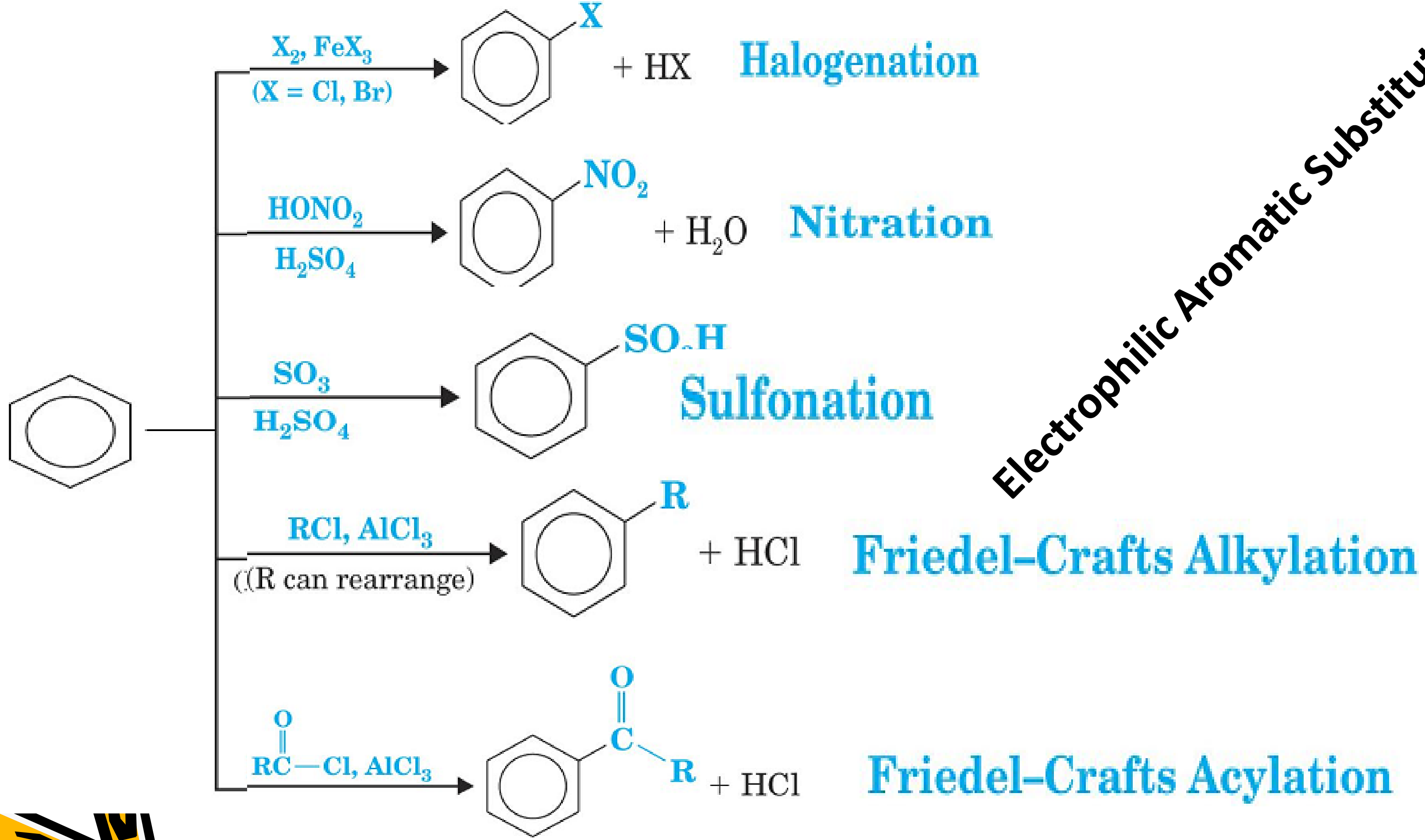
Physical and Chemical **Properties**

- Aromatic HCs are non-polar & usually colorless liquid.
- they are immiscible with H_2O but are readily miscible with organic solvents.
- Resonance hybrid with structure b/n two line-bond structures.



1.2 Properties of Benzene and its Derivatives

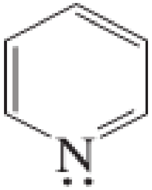
Chemical properties: characterized by electrophilic substitution rxns than electrophilic addition rxn.



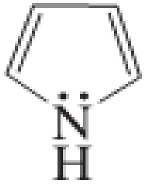
Electrophilic Aromatic Substitution rxns

1.3 Heterocyclic Aromatic Cpds

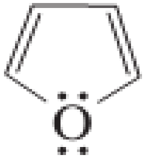
- **A heterocyclic cpd** is a cyclic cpd in which one or more of the ring atoms is an atom other than carbon.
- A ring atom that is not carbon is called a heteroatom.
- The most common heteroatoms found in heterocyclic cpds are **N**, **O**, and **S**. *For example;*



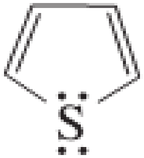
pyridine



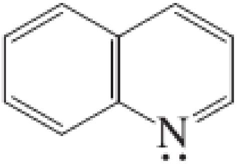
pyrrole



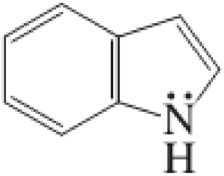
furan



thiophene

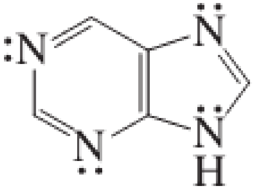


quinoline

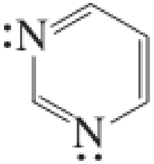


indole

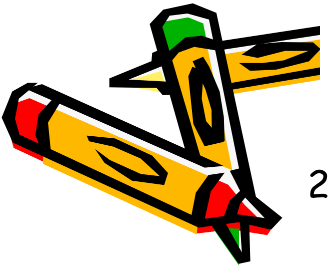
imidazole



purine

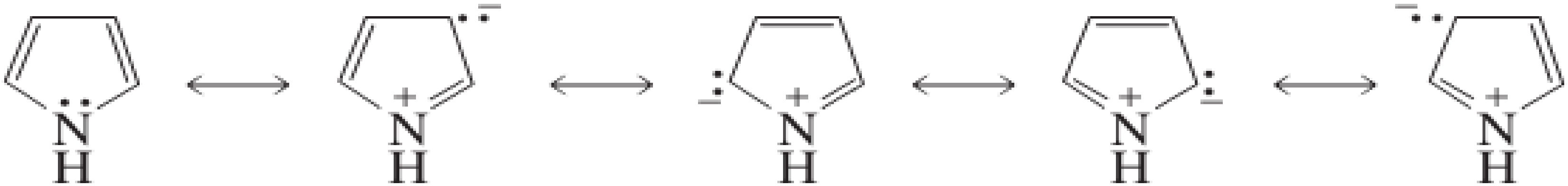


pyrimidine



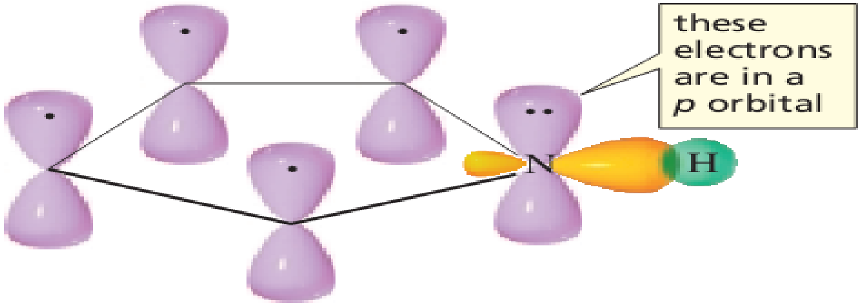
Heterocyclic Aromatic Cpds

- **Pyridine** is an aromatic heterocyclic cpd . Each of the six ring atoms of pyridine is sp^2 hybridized.
- **Pyrrole** has three pairs of e-s & is aromatic. The lone-pair e-s are in a p orbital that overlaps the p orbitals on adjacent C, forming a π –bond, they are π electrons.



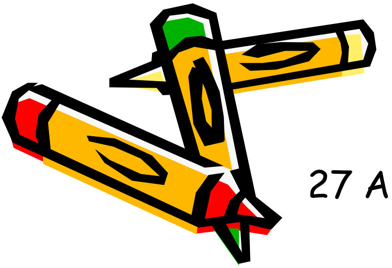
resonance contributors of pyrrole

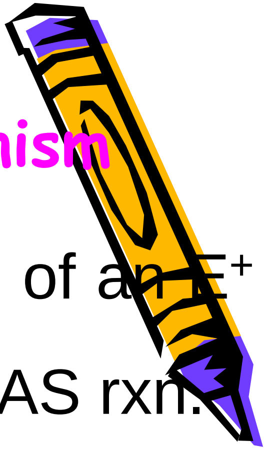
- The resonance contributors, show that the N-atom is *sp*^{2} hybridized & uses its three sp^2 orbitals to bond to two carbons and one hydrogen.



these electrons are in a *p* orbital

orbital structure of pyrrole

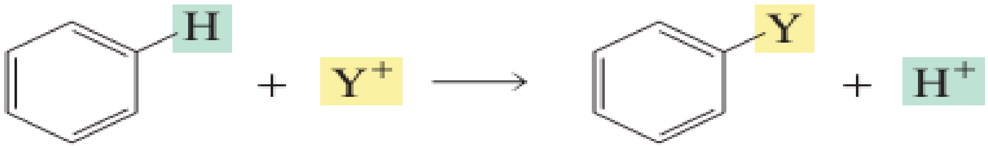




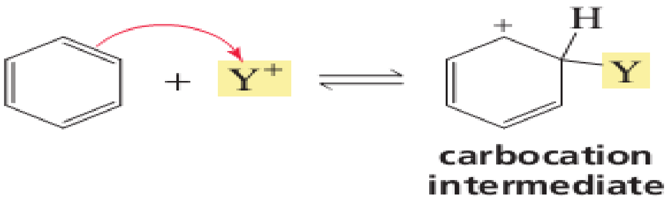
1.4 Aromatic Substitution rxns & their Mechanism

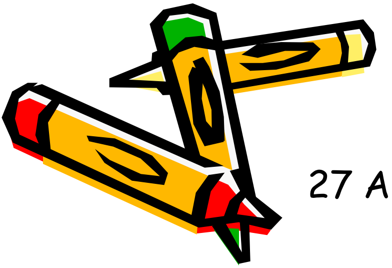
- ✓ B/c electrophilic substitution of C_6H_6 involves the rxn of an E^+ with an aromatic cpd, it is more precisely called an EAS rxn.
- ✓ In an electrophilic aromatic substitution rxn, an E^+ substitutes for a **H** of an aromatic cpd.

an electrophilic aromatic substitution reaction



- ✓ e-s above & below the plane of its ring,C_6H_6 is a nucleophile.
- ✓ It will react with an E^+ When an E^+ attaches itself to a C_6H_6 ring, a C^+ intermediate is formed.





Aromatic Substitution rxns

There are five most common EAS rxns:

1. **Halogenation**: **Br**, **Cl**, or **I** substitutes for a H (proton).

2. **Nitration** : A nitro (NO_2) group substitutes for a H.

3. **Sulfonation**: sulfonic acid (SO_3H) group substitutes for a H.

4.**Friedel–Crafts** acylation: acyl group(RC=O) substitutes for H.

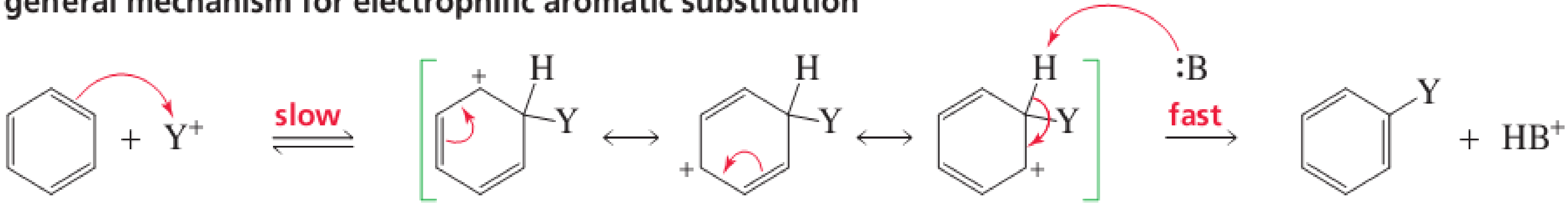
5.**Friedel–Crafts** alkylation: an alkyl (R) group substitutes for H.

- ✓ All of these take place by the same two-step mechanism.
- ✓ 1st benzene reacts with an E^+ forming C^+ intermediate.
- ✓ 2nd step of the rxn, a base in the rxn mixture pulls off a H from the C^+ intermediate, and the e-s that held the H move into the ring to **reestablish its aromaticity**.

Aromatic Substitution rxns

- ✓ Proton (**H**) is always removed from the **C** that has formed the new bond with the E$^+$.

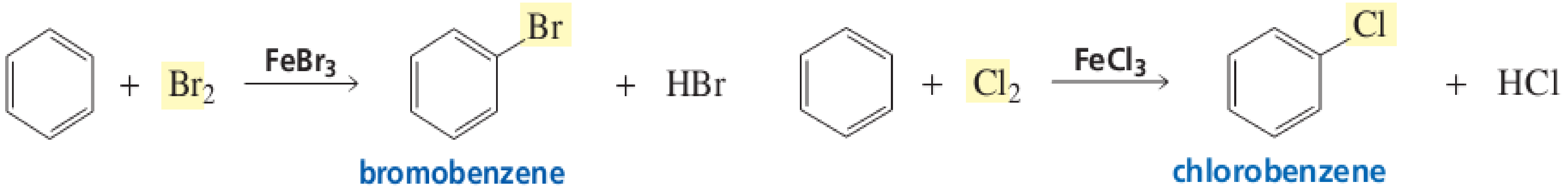
general mechanism for electrophilic aromatic substitution

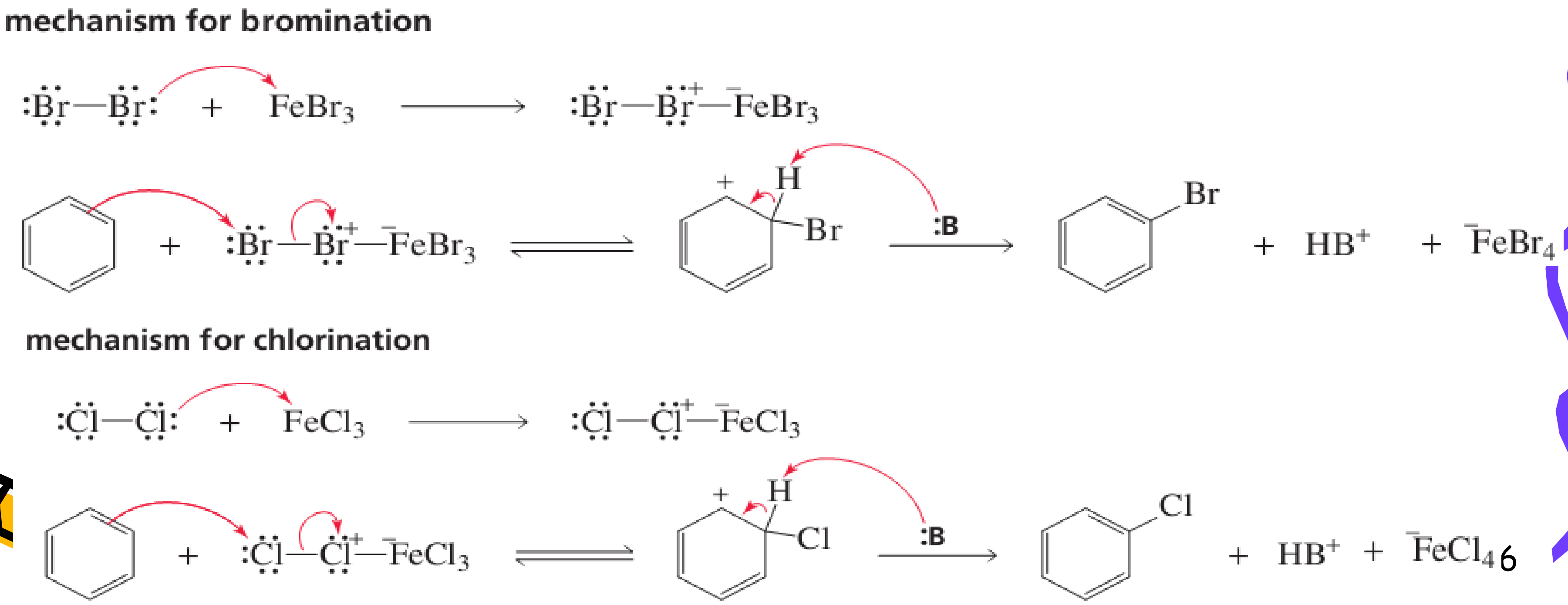


- ✓ 1st step is relatively slow & endergonic b/c an aromatic cpd is being converted into a much less stable non-aromatic intermediate.
- ✓ 2nd step is fast & strongly exergonic b/c this step restores the stability-enhancing aromaticity.
- ✓ Therefore, EAS rxn follows the ff steps, generation of the **E$^+$**, formation of **C$^+$** intermediate, & removal of proton from the C$^+$ intermediate.

1.4.1 Halogenation of Benzene

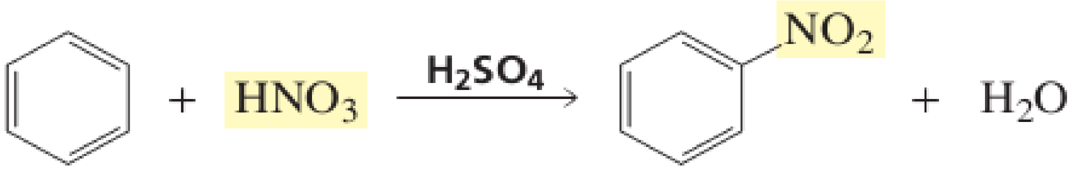
- ✓ The bromination or chlorination of benzene requires a Lewis acid such as ferric bromide or ferric chloride.
- ✓ a Lewis acid is a cpd that accepts a share in a pair of e-s.



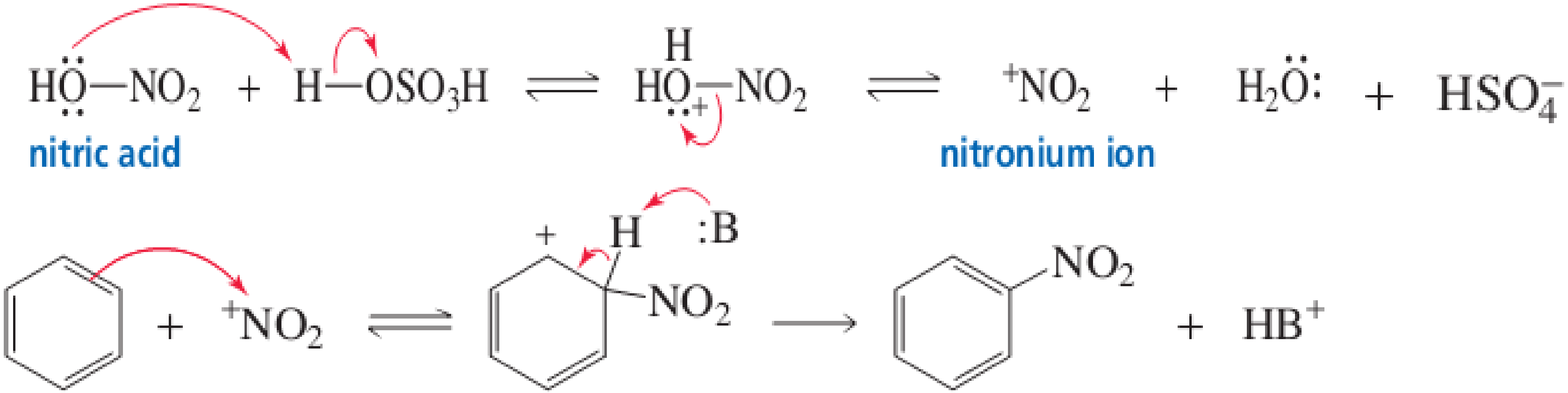


1.4.2 Nitration of Benzene

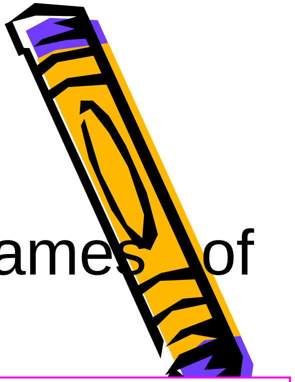
- ✓ Nitration of C_6H_6 with HNO_3 requires H_2SO_4 as a catalyst.



mechanism for nitration

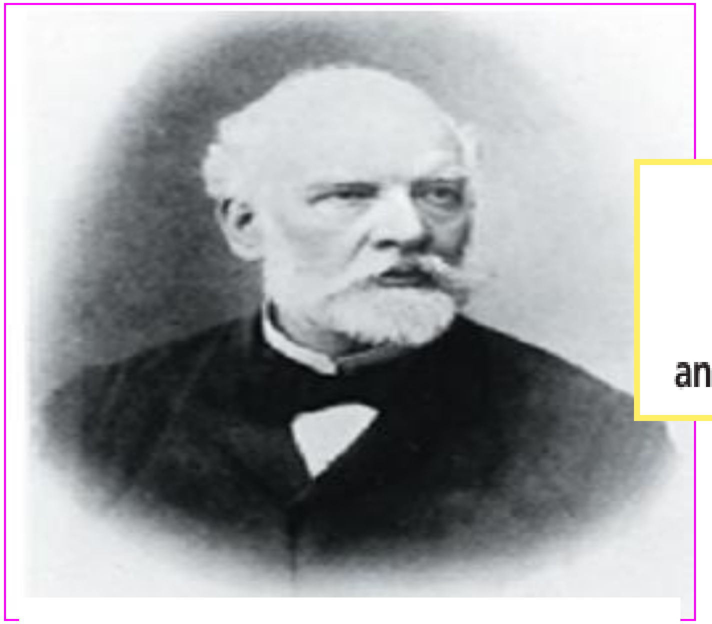


- ✓ To generate the necessary E^+, H_2SO_4 protonates HNO_3 .
- ✓ Loss of water from protonated HNO_3 forms a $^+NO_2$, the E^+, required for nitration.

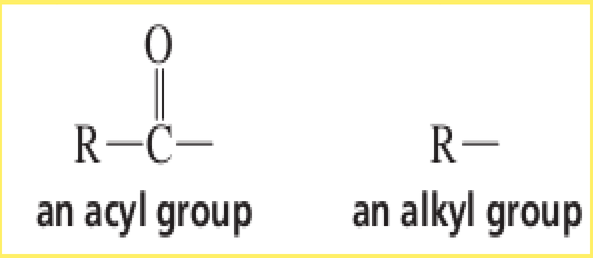


1.4.3 Friedel-Crafts Acylation of Benzene

- ✓ Two electrophilic substitution rxns bear the names of chemists Charles Friedel and James Crafts.



Charles Friedel (1832–1899)

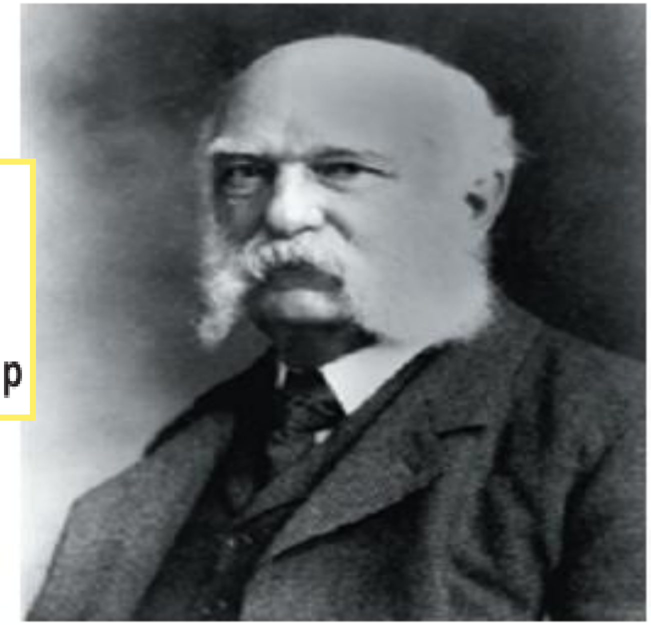


$\mathrm{R}-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-$

an acyl group

$\mathrm{R}-$

an alkyl group

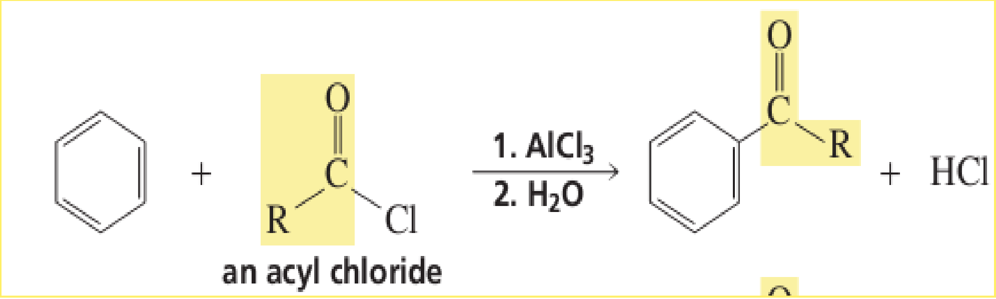


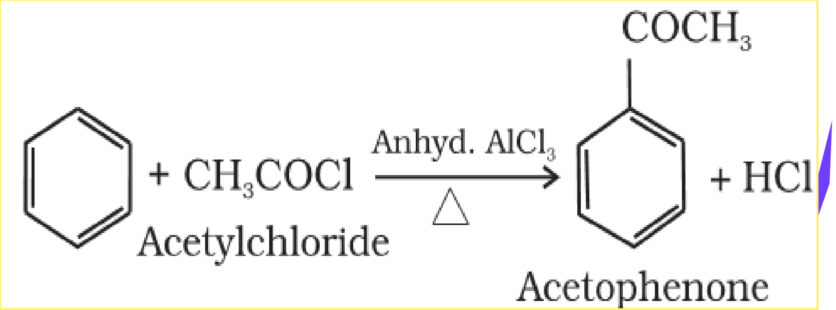
James Mason Crafts (1839–1917)

- ✓ **Friedel–Crafts** acylation places an acyl group on a benzene ring, & Friedel–Crafts alkylation places an alkyl group on a benzene ring.

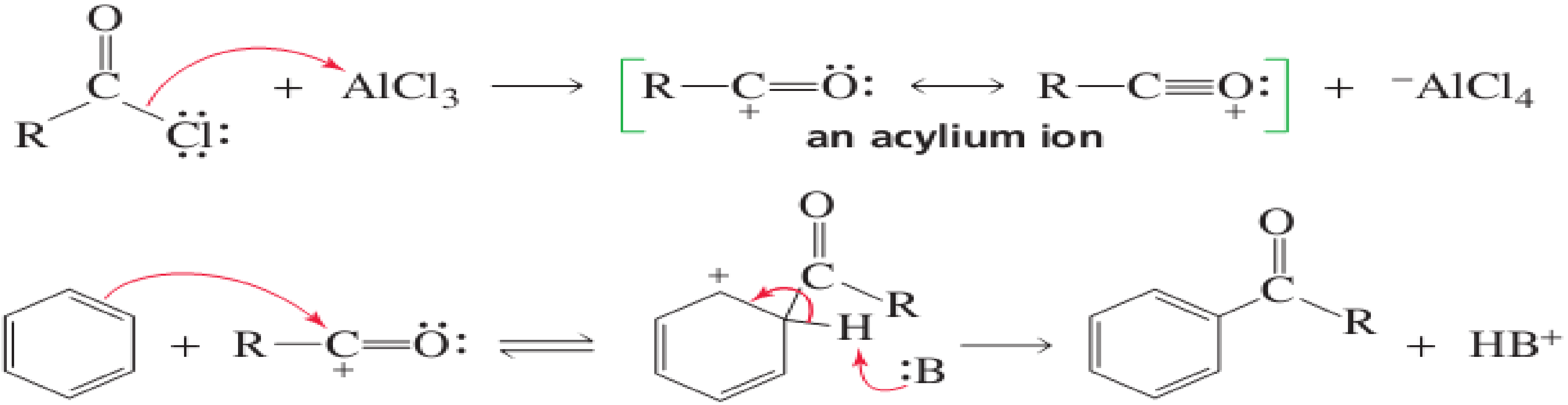
Friedel-Crafts Acylation of Benzene

- ✓ Either an acyl halide or an acid anhydride can be used for Friedel–Crafts acylation. *e.g.*





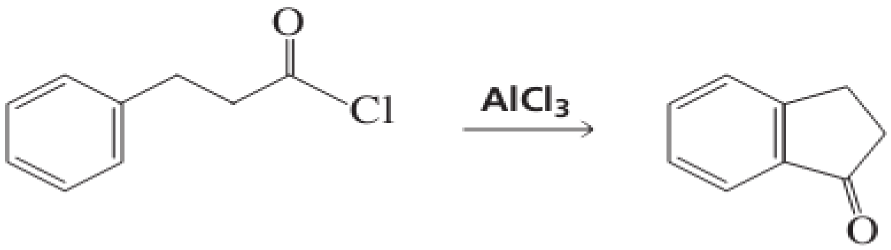
mechanism for Friedel–Crafts acylation



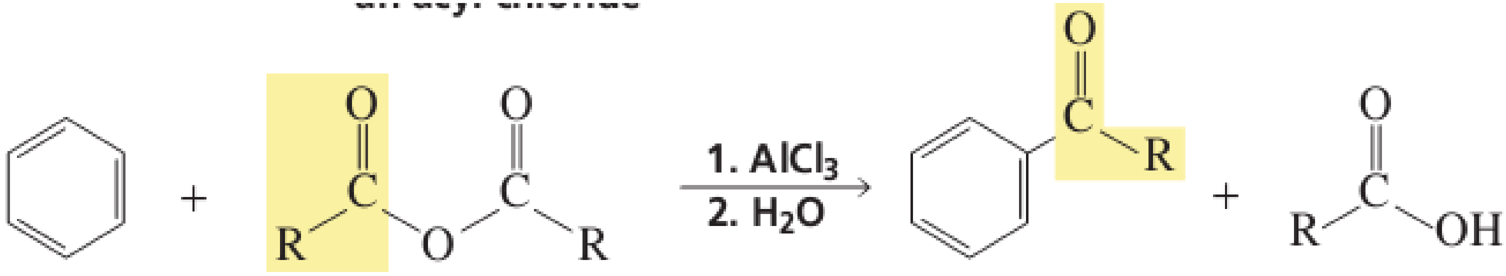
An acylium ion is the E^+ required for a Friedel–Crafts acylation rxn.

Friedel-Crafts **Acylation** of Benzene

- ✓ **Assignment** #1.Propose a mechanism for the ff reaction:

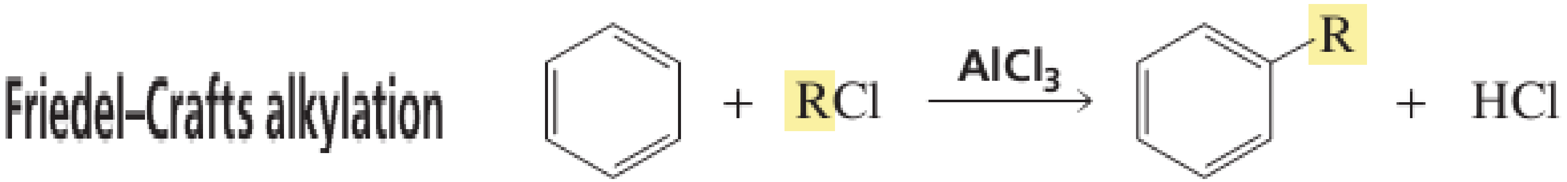


- ✓ **Assignment** #2. Propose a mechanism for the ff reaction:

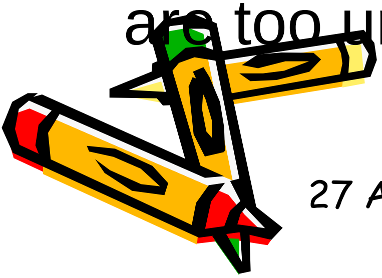


1.4.4 Friedel-Crafts Alkylation of Benzene

- The Friedel–Crafts alkylation rxn substitutes an alkyl group for a **hydrogen**.



- In the first step of the rxn, a C$^+$ is formed from the rxn of an alkyl halide with Alkyl fluorides, alkyl chlorides, alkyl bromides, and alkyl iodides can all be used.
- Vinyl halides and aryl halides **cannot** be used b/c their C$^+$ are too unstable to be formed.



1.4.4 Friedel-Crafts Alkylation of Benzene

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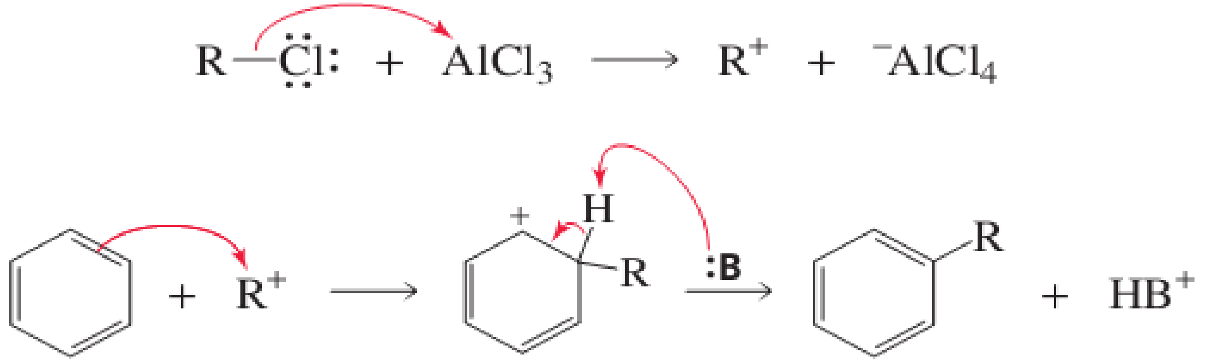
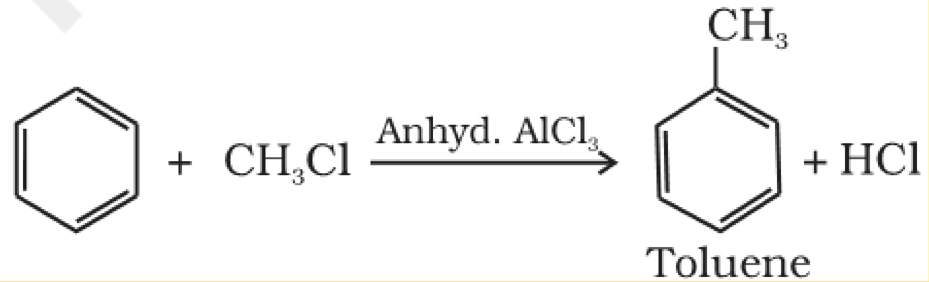
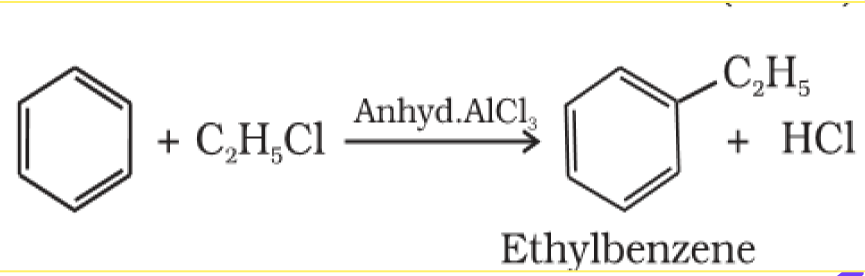
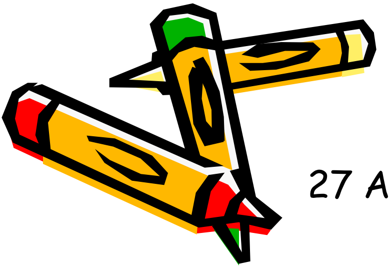
mechanism for Friedel–Crafts alkylation



- ✓ An alkyl-substituted benzene is more reactive than benzene.



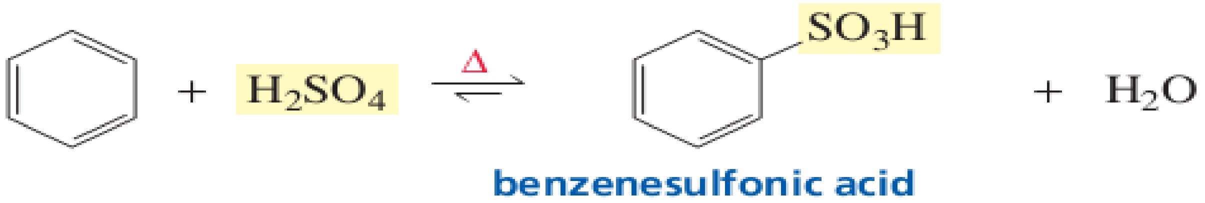




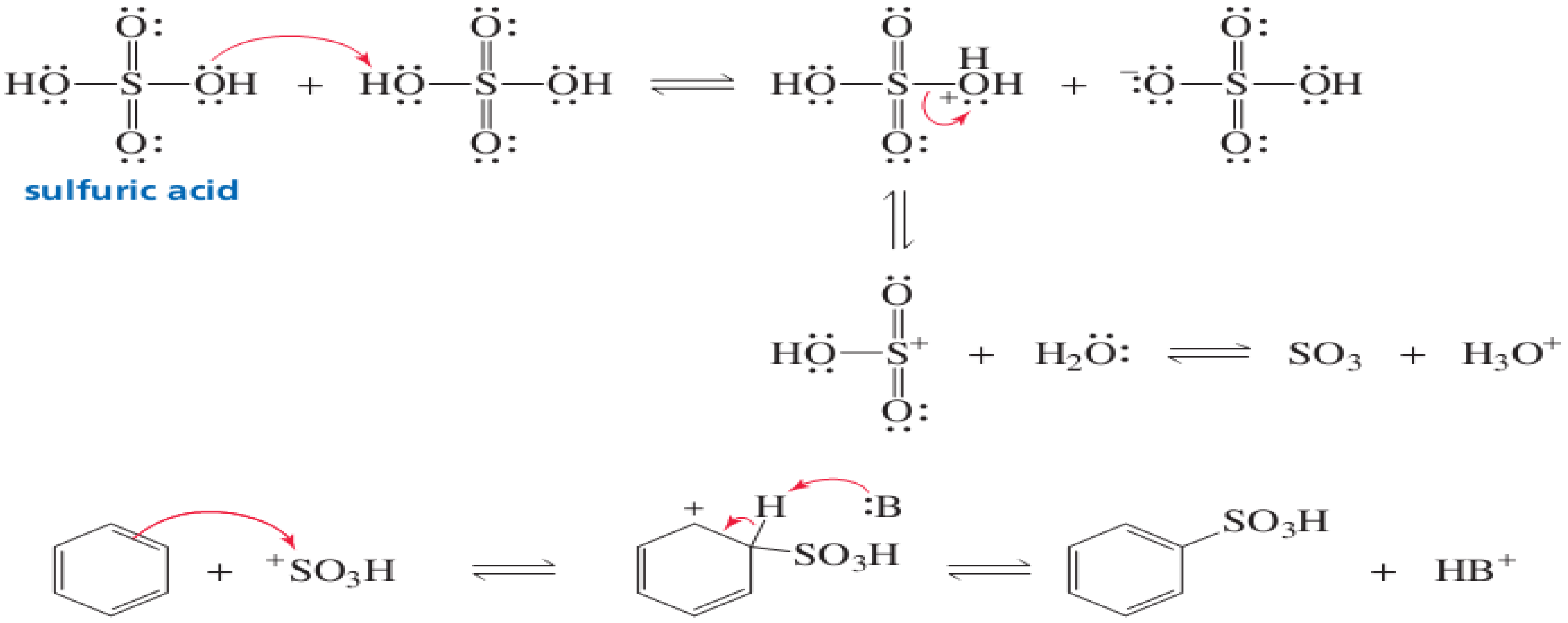
1.4.5 Sulfonation of Benzene

- ✓ Fuming H_2SO_4 (solution of SO_3 in H_2SO_4) or concentrated H_2SO_4 is used to sulfonate aromatic rings.

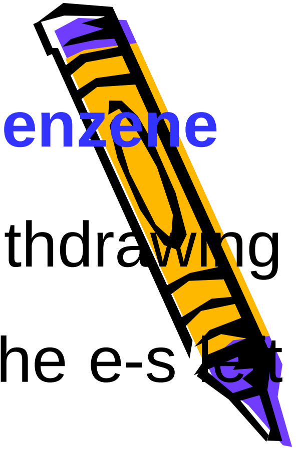
sulfonation



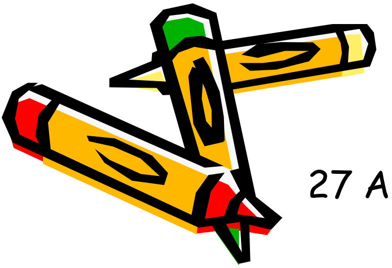
mechanism for sulfonation



Sulfonation of Benzene

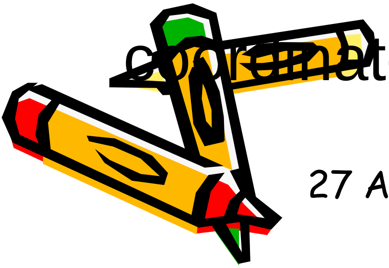


- ✓ H_2SO_4 is a strong acid b/c of the three electron-withdrawing oxygen atoms & the stability of its conjugate base the e-s left behind when a **H** is lost are shared by three oxygen atoms.
- ✓ Sulfonation of C_6H_6 is a reversible rxn.
- ✓ If benzenesulfonic acid is heated in dilute acid, the rxn proceeds in the reverse direction.



Sulfonation of Benzene

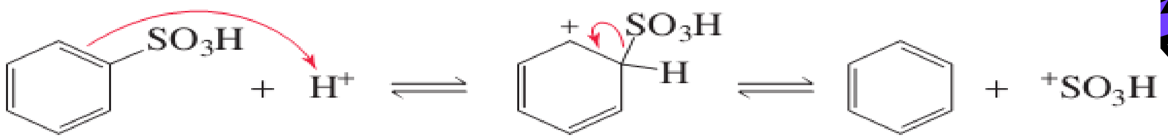
- ✓ The principle of microscopic reversibility applies to all rxns.
- ✓ It states that the mechanism of a rxn in the reverse direction must retrace each step of the mechanism in the forward direction in microscopic detail.
- ✓ This means that the forward & reverse rxns must have the same intermediates & that the rate-determining "energy hill" must be the same in both directions.
- ✓ Therefore, desulfonation is described by the same rxn coordinate diagram going from right to left.

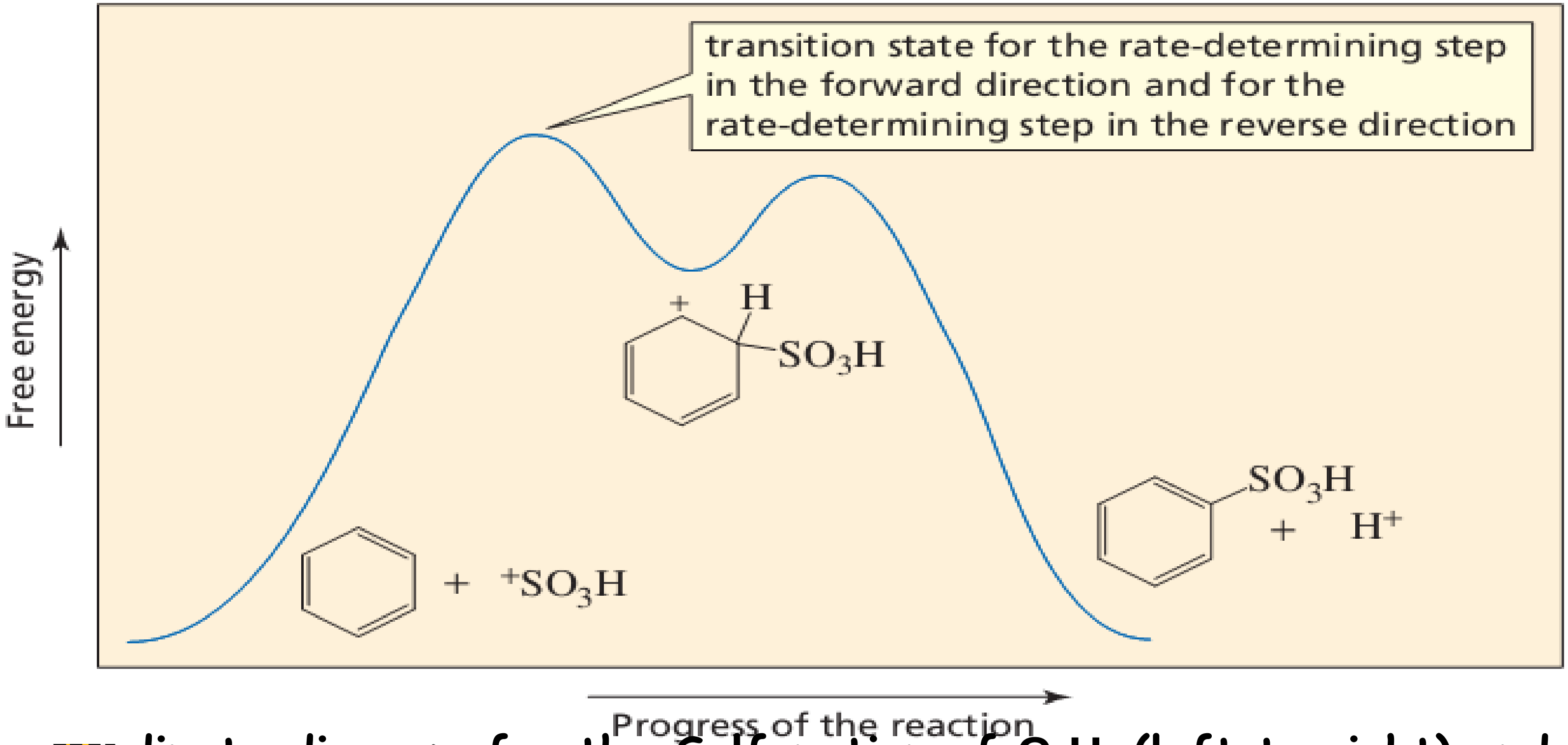


Sulfonation of Benzene

- ✓ In Sulfonation, the RDS is nucleophilic attack of C_6H_6 on the $^+SO_3H$ ion. In desulfonation, the rate-limiting step is loss of the $^+SO_3H$ ion from the C_6H_6 ring.

mechanism for desulfonation



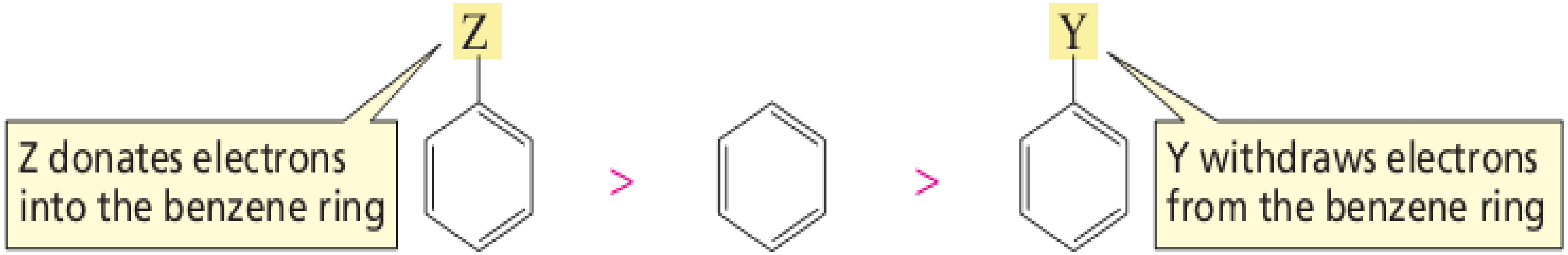


Rxn coordinate diagram for the Sulfonation of C_6H_6 (left to right) and the desulfonation of benzenesulfonic acid (right to left).

1.4.6 Directing Effects of Substituents

- ✓ Is substituted benzene is more reactive or less reactive than benzene itself?
- ✓ Some substituents make the ring more reactive & some make it less reactive than benzene toward EAS.
- ✓ Electron-donating substituents increase the reactivity of the benzene ring toward EAS.
- ✓ Electron-withdrawing substituents decrease the reactivity of the benzene ring toward EAS.

relative rates of electrophilic substitution



Directing Effects of Substituents

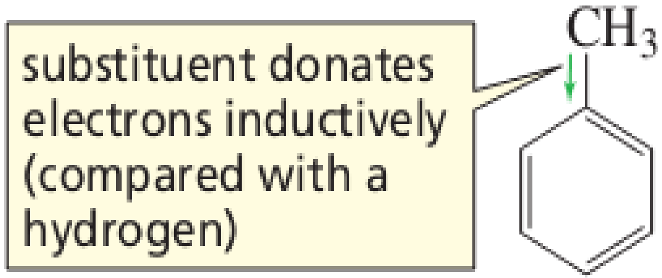
- ✓ two ways substituents can donate e-s into C_6H_6 ring:
  - inductive e-s donation and
  - electron donation by resonance.
- ✓ also two ways substituents can withdraw e-s from C_6H_6 ring:
  - inductive electron withdrawal and
  - electron withdrawal by resonance.

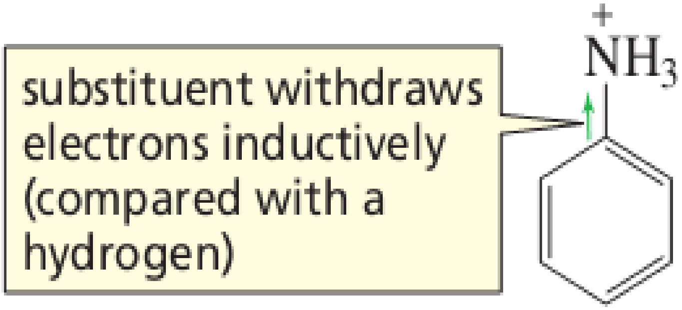
Inductive Electron Donation and Withdrawal

- ✓ If a substituent that is bonded to a C_6H_6 ring is less e-s withdrawing than H, the e-s in the σ –bond that attaches the substituent to the C_6H_6 ring will move toward the ring more readily than will those in the σ bond that attaches the H to the ring.

Directing Effects of Substituents

- Donation of e-s through a **σ** bond is called inductive electron donation.
- Alkyl substituents (such as–CH_3) donate e-s inductively compared with a H.
- **C** is actually slightly less electron donating than **H** (b/c **C** is more electronegative than H; but an alkyl group is more electron donating than H b/c of hyperconjugation.


substituent donates electrons inductively (compared with a hydrogen)


substituent withdraws electrons inductively (compared with a hydrogen)

Directing Effects of Substituents

- ✓ If a substituent is more e- withdrawing than H, it will withdraw the e-s away from the C_6H_6 ring more strongly than will a H.
- ✓ Withdrawal of e-s through a σ bond is called **inductive electron withdrawal.**
- ✓ The $^{+}NH_3$ group is a substituent that withdraws e-s inductively b/c it is more electronegative than H.

Resonance Electron Donation and Withdrawal

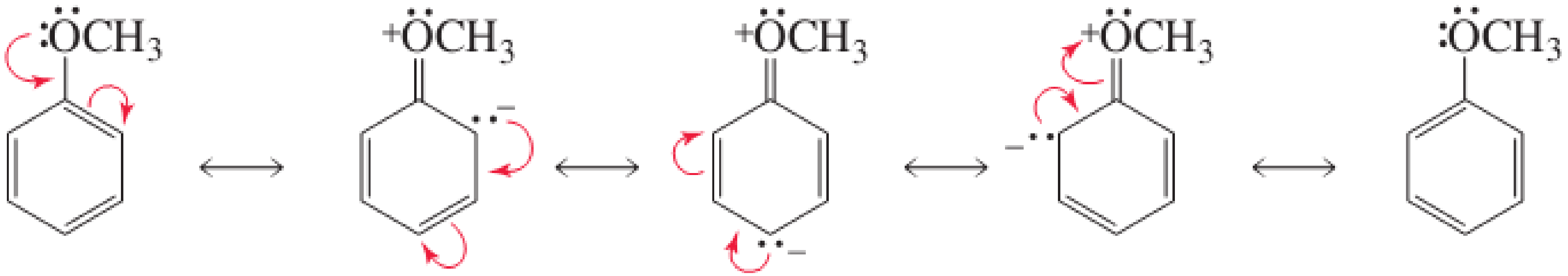
- ✓ If a substituent has a lone pair (LP) on the atom that is directly attached to the benzene ring, the LP can be delocalized into the ring; these substituents are said to donate e-s by resonance.

Directing Effects of Substituents

✓ Substituents like OH, OR, & Cl donate e-s by resonance.

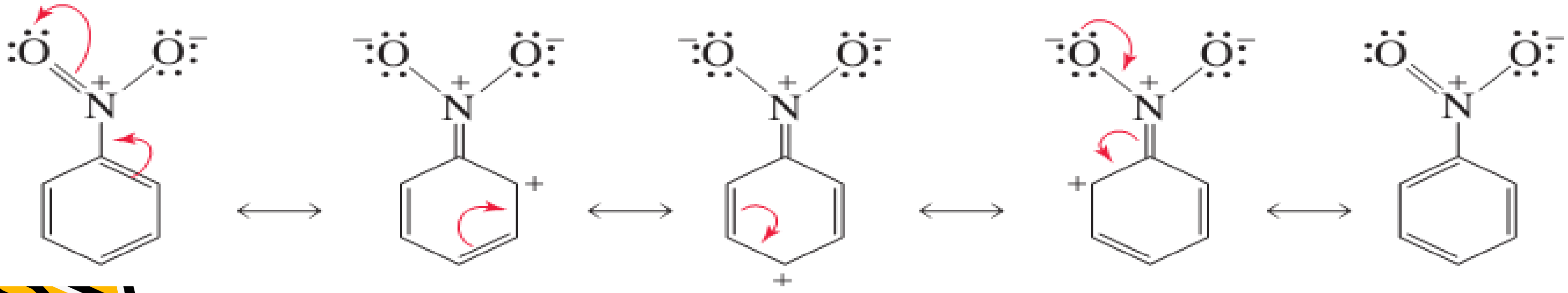
✓ They also withdraw e-s inductively b/c the atom attached to the benzene ring is more electronegative than H.

donation of electrons into a benzene ring by resonance



✓ Substituents like C=O,CN & NO_2 withdraw e-s by resonance.

withdrawal of electrons from a benzene ring by resonance

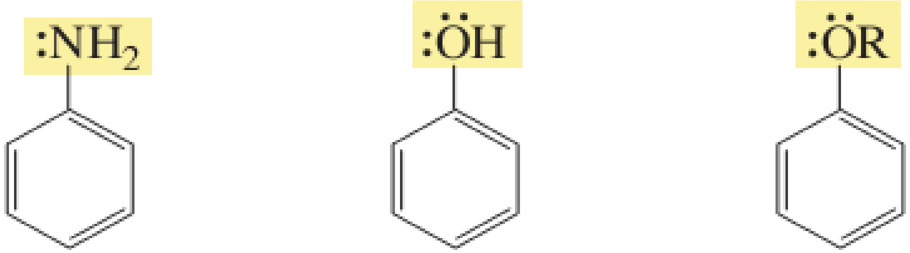


Directing Effects of Substituents

Relative Reactivity of Substituted Benzenes

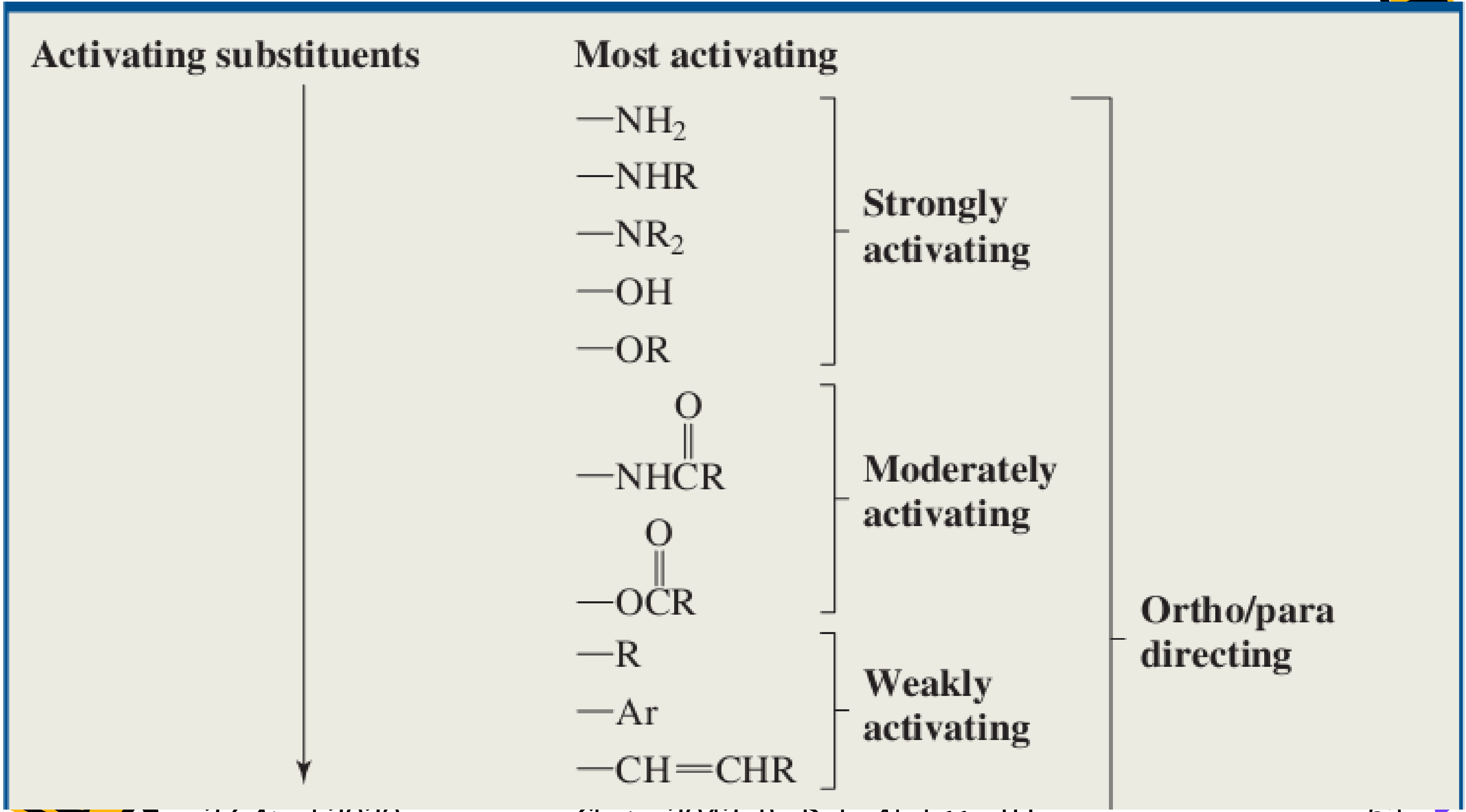
- ✓ The activating substituents make the benzene ring more reactive toward EAS; the deactivating substituents make the benzene ring less reactive toward EAS.
- ✓ All the strongly activating substituents donate e-s into the ring by resonance & withdraw e-s from the ring inductively.

strongly activating substituents



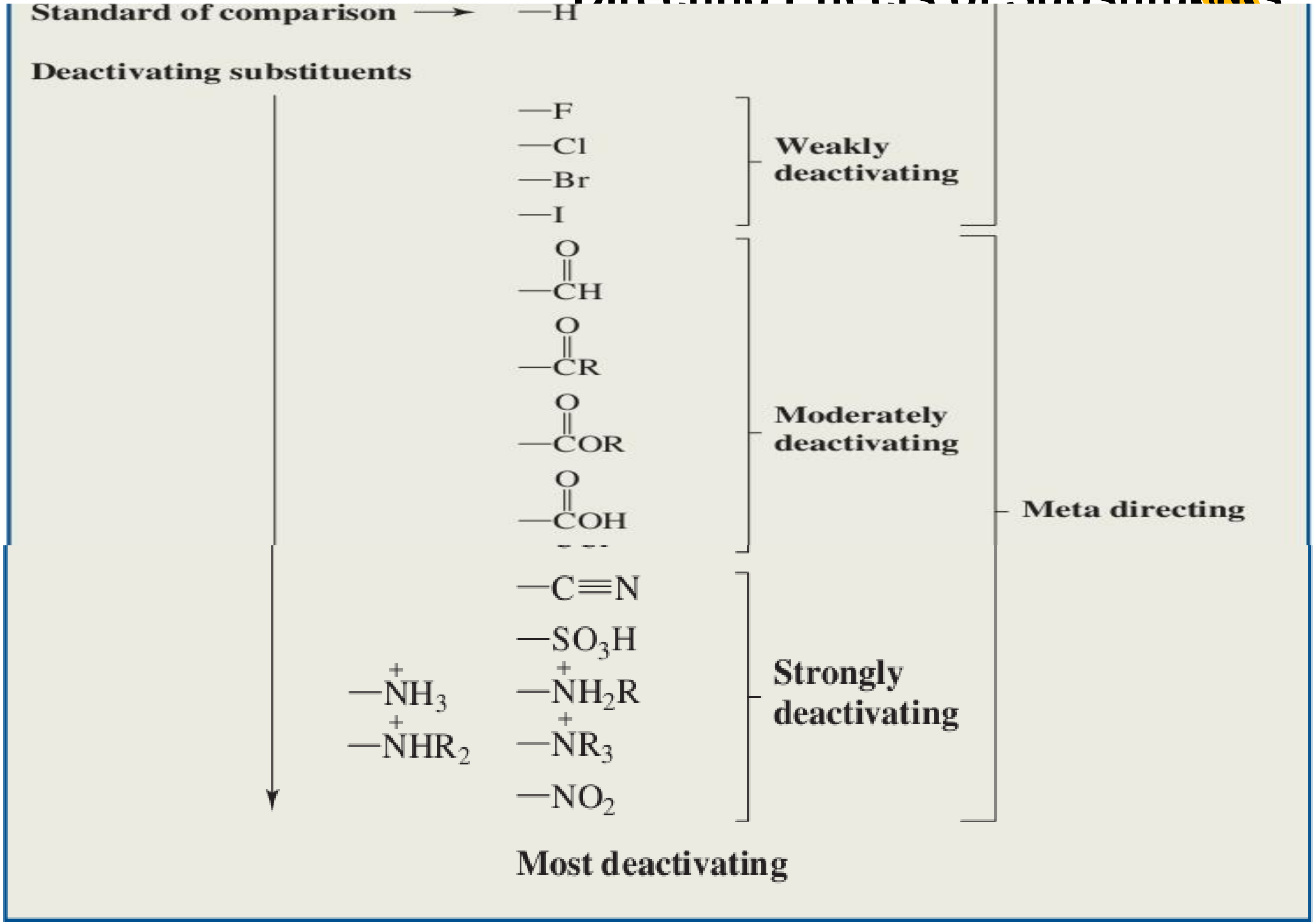
Directing Effects of Substituents

Table 1. The Effects of Substituents on the Reactivity of a Benzene Ring Toward EAS



Activating substituents	Most activating		
	$-\mathrm{NH_2}$	Strongly activating	Ortho/para directing
	$-\mathrm{NHR}$		
	$-\mathrm{NR_2}$		
	$-\mathrm{OH}$		
	$-\mathrm{OR}$		
	$-\mathrm{NH}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{R}$	Moderately activating	
	$-\mathrm{O}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{R}$		
	$-\mathrm{R}$	Weakly activating	
	$-\mathrm{Ar}$		
↓	$-\mathrm{CH{=}CHR}$		

Directing Effects of Substituents



Standard of comparison → —H

Deactivating substituents

$-F$
$-Cl$
$-Br$
$-I$

Weakly deactivating

$-\overset{O}{\overset{\|}{C}}H$
$-\overset{O}{\overset{\|}{C}}R$
$-\overset{O}{\overset{\|}{C}}OR$
$-\overset{O}{\overset{\|}{C}}OH$

Moderately deactivating

$-C\equiv N$
$-SO_3H$
$-\overset{+}{N}H_3$ $-\overset{+}{N}H_2R$
$-\overset{+}{N}HR_2$ $-\overset{+}{N}R_3$
$-NO_2$

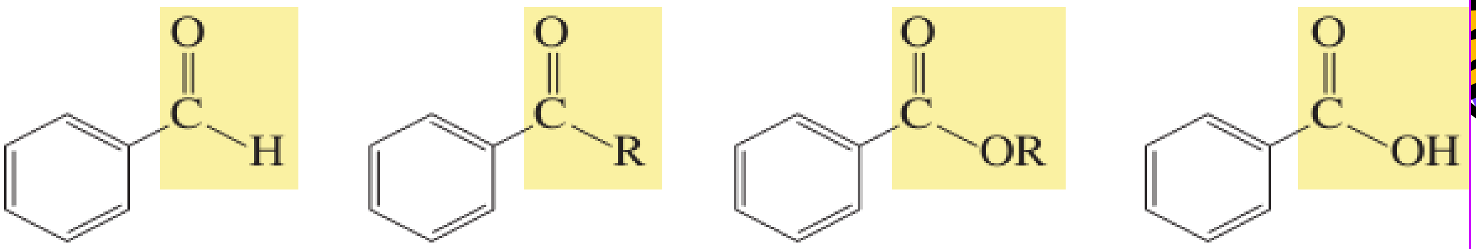
Strongly deactivating

Meta directing

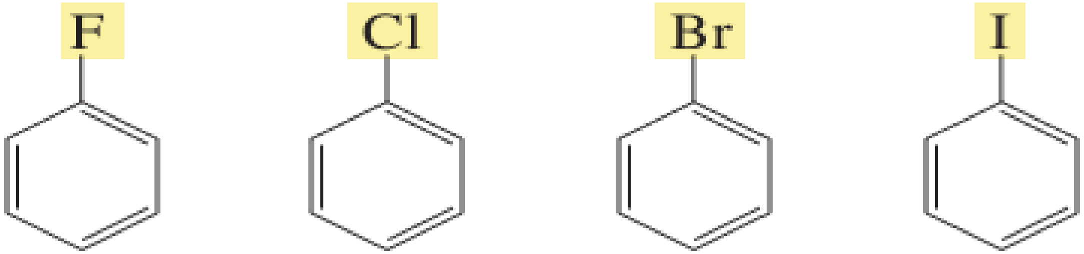
Most deactivating

Directing Effects of Substituents

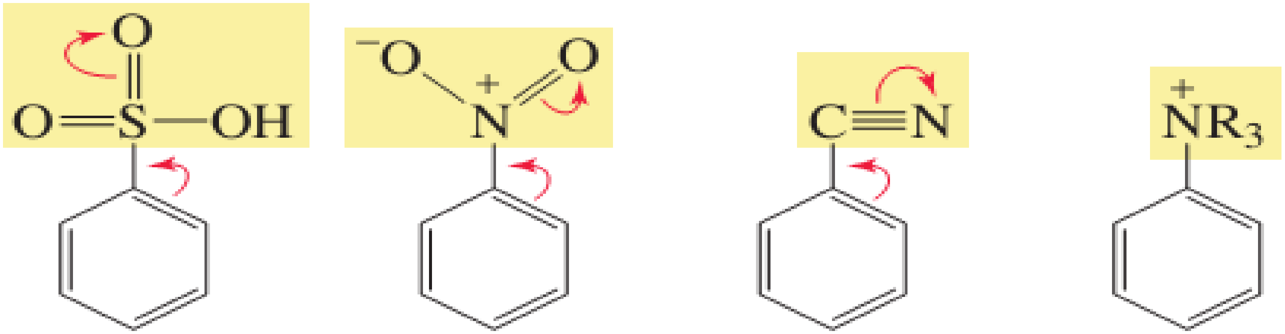
moderately deactivating substituents



weakly deactivating substituents

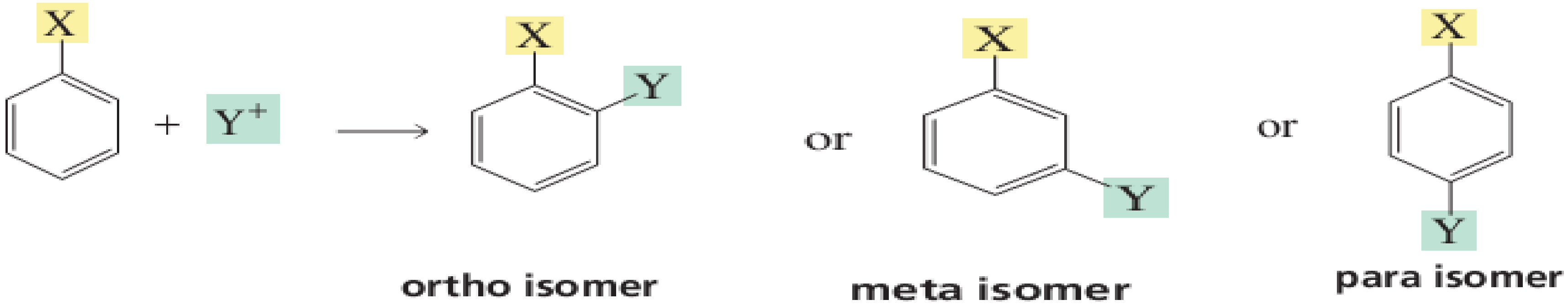


strongly deactivating substituents



The Effect of Substituents on Orientation

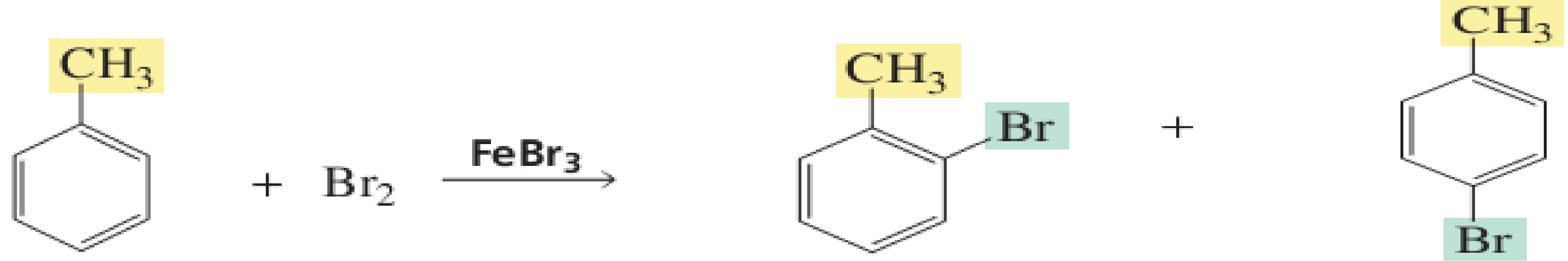
- ✓ When substituted C_6H_6 undergoes EAS rxn, where does the new substituent attach itself?
- ✓ Is the product of the rxn the *o*-, *m*-, or *p*-isomer?



- ✓ ***NB***. A substituent will direct an incoming substituent either to the ortho & para positions, or it will direct an incoming substituent to the meta position.

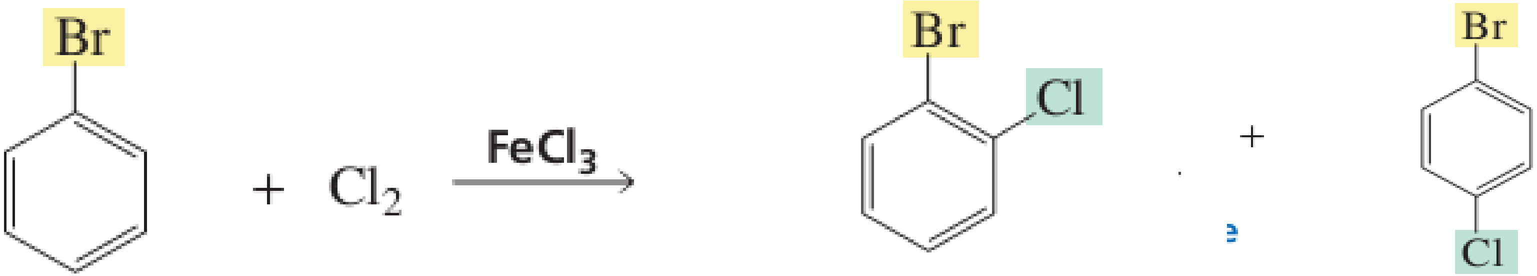
The Effect of Substituents on Orientation

1) All activating substituents direct an incoming electrophile to the ortho and para positions.



toluene o-bromotoluene *p*-bromotoluene

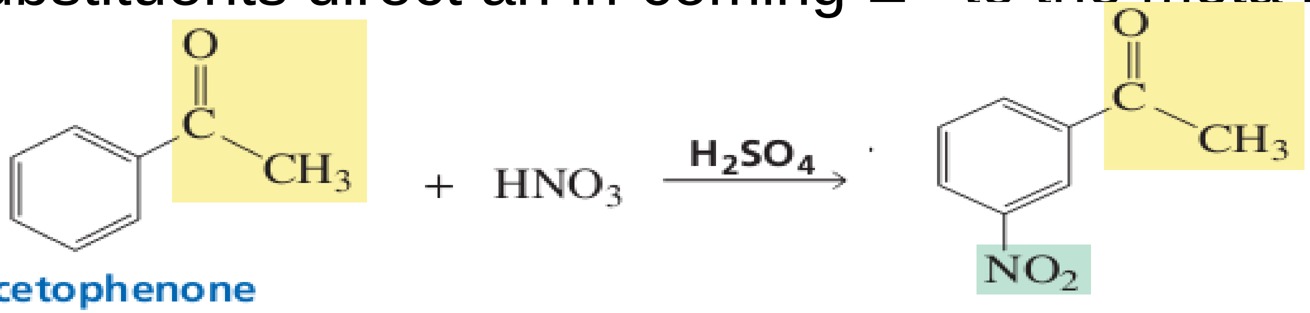
2) The weakly deactivating halogens also direct an incoming electrophile to the ortho and para positions.



bromobenzene o-bromochlorobenzene *p*-bromochlorobenzene

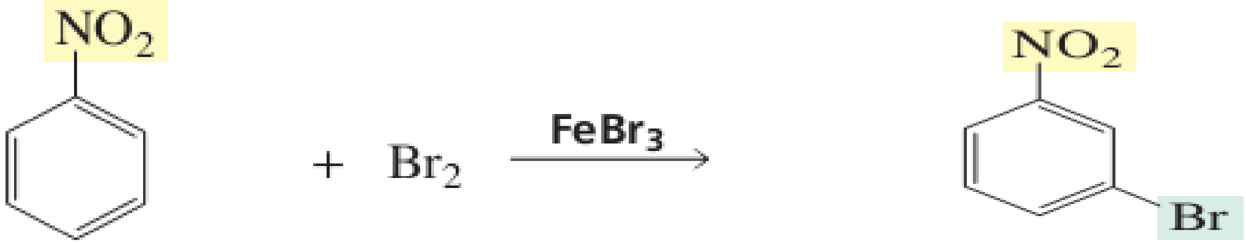
The Effect of Substituents on Orientation

3) All moderately deactivating & strongly deactivating substituents direct an in-coming E+ to the meta position.



acetophenone

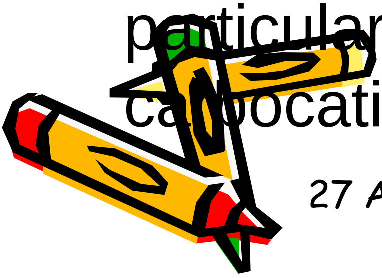
m-nitroacetophenone



nitrobenzene

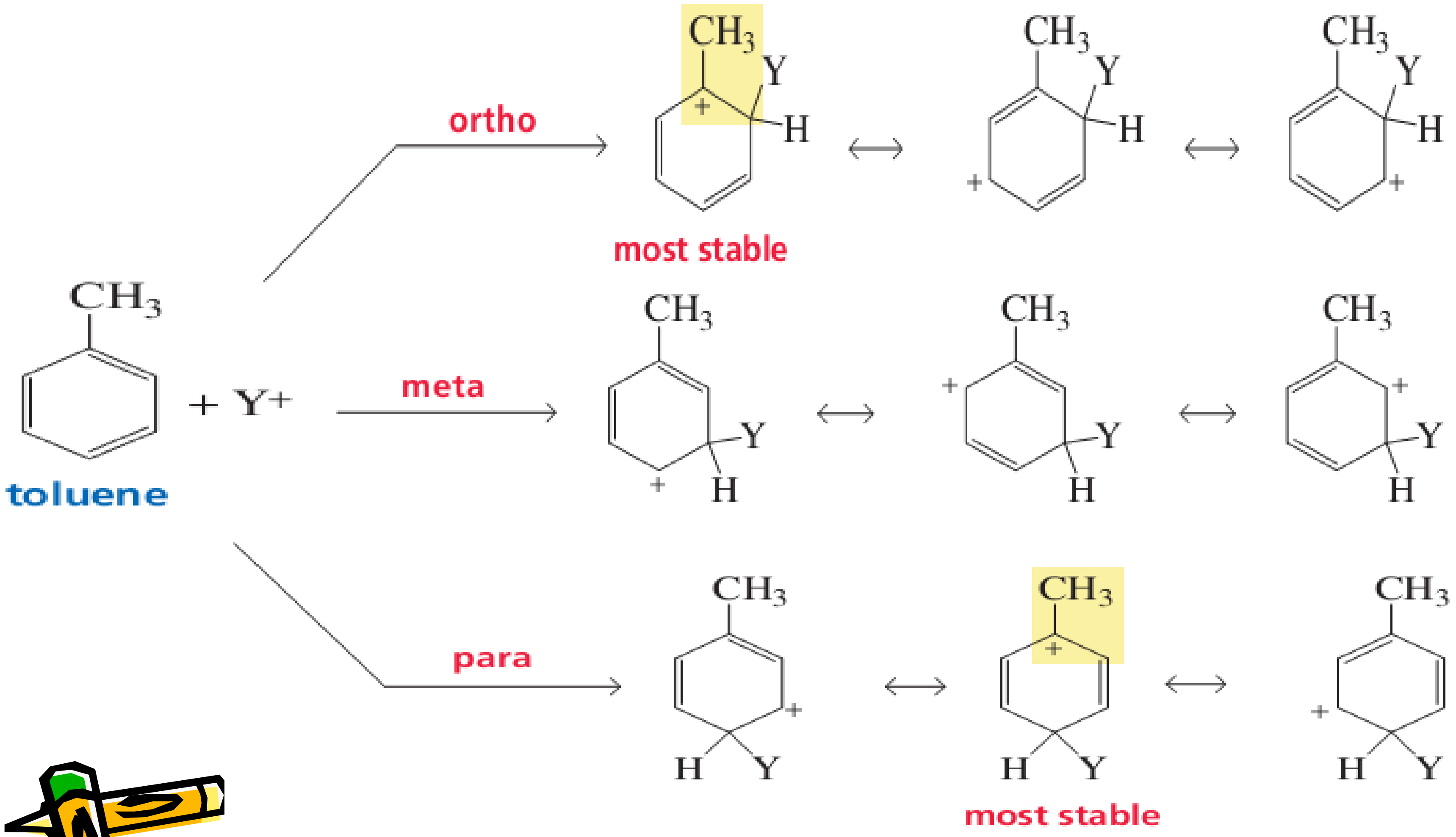
m-bromonitrobenzene

- ✓ To understand why a substituent directs an incoming E+ to a particular position, we must look at the stability of the carbocation intermediate that is formed in the RDS.



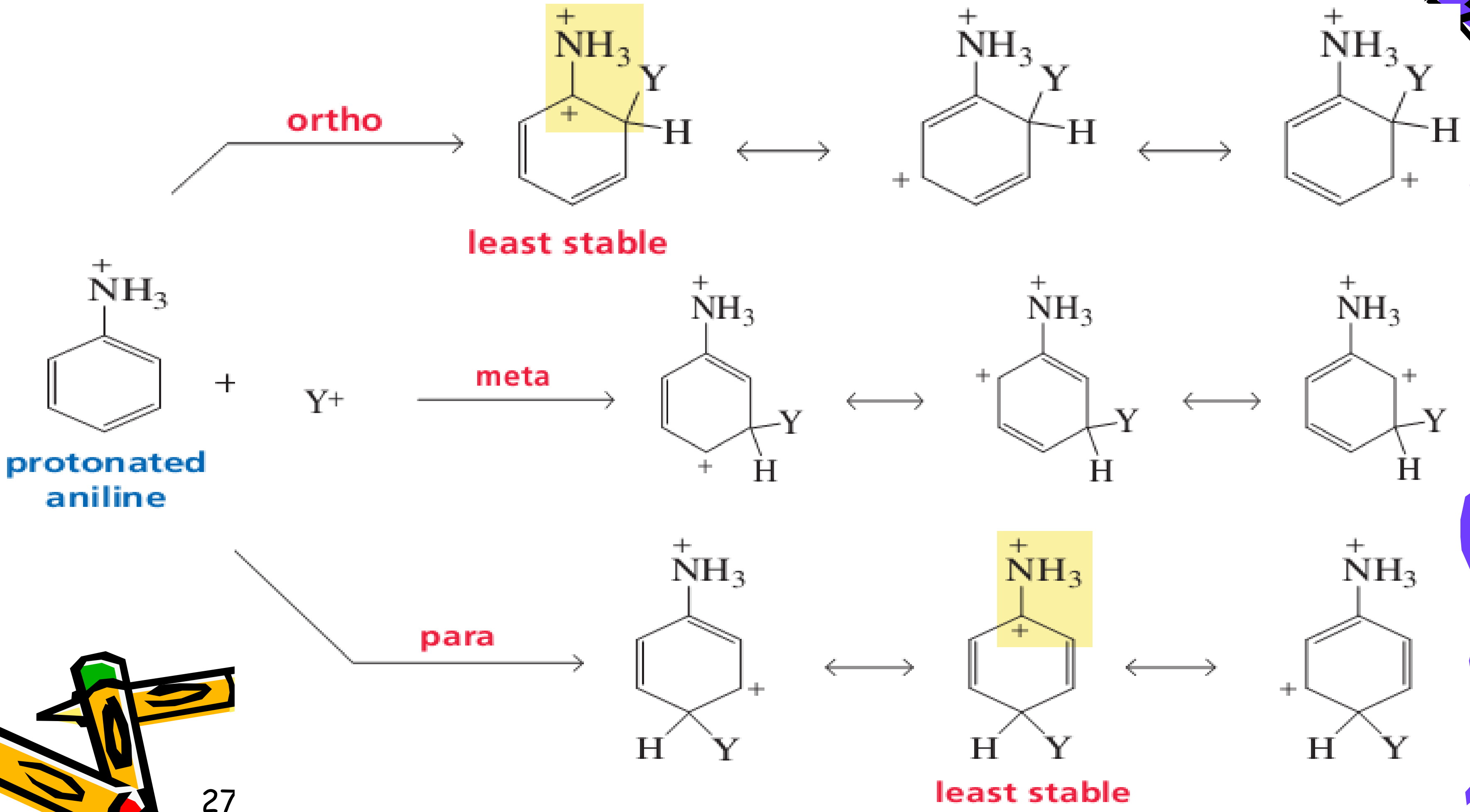
The Effect of Substituents on Orientation

- ✓ Any substituent that donates e-s inductively is an o–p director



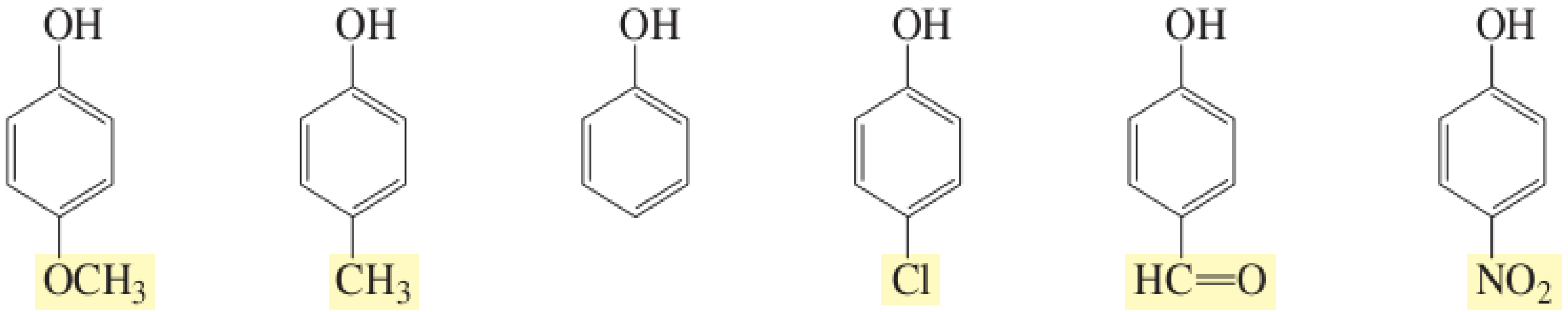
The Effect of Substituents on Orientation

✓ all substituents that withdraw e-s (except for the halogens, which are o-p directors b/c they donate e-s by resonance) are meta directors .



The Effect of Substituents on pKa

- ✓ Electron-withdrawing substituents (EWS) increase the acidity of cpd.
- ✓ The pKa of p-nitro-phenol is lower (7.14) b/c the nitro EWS from the ring, whereas the pKa of *p*-methyl phenol is higher (10.19) b/c the methyl substituent donates e-s into the ring.

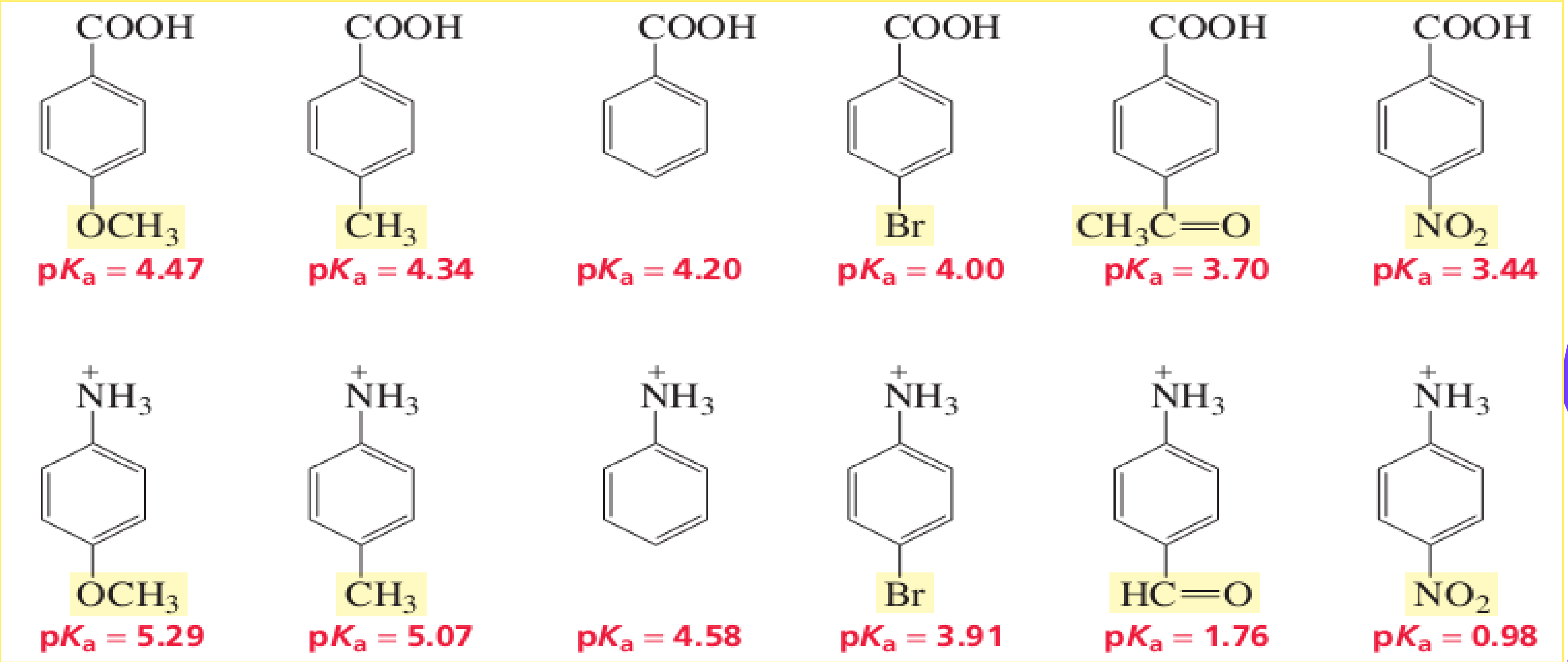


$pK_a = 10.20$ $pK_a = 10.19$ $pK_a = 9.95$ $pK_a = 9.38$ $pK_a = 7.66$ $pK_a = 7.14$

phenol

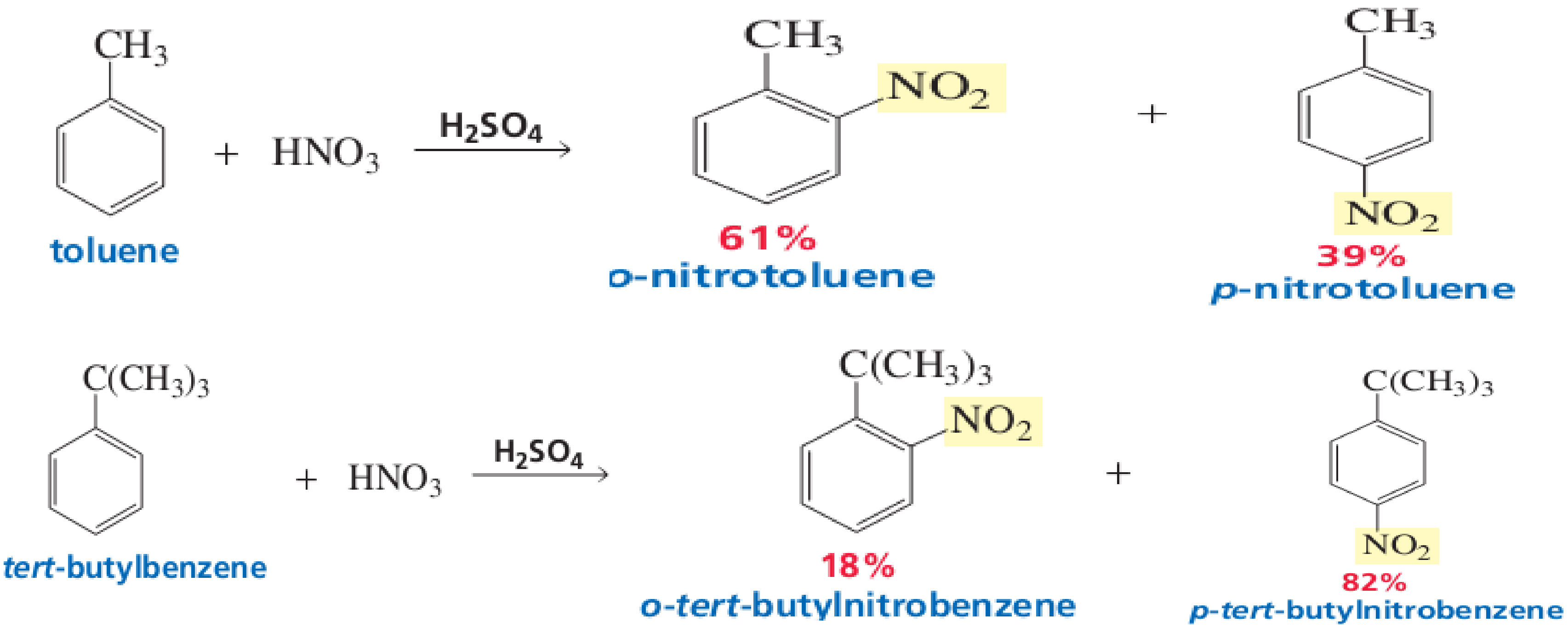
The Effect of Substituents on pKa

- ✓ Electron withdrawal decreases reactivity toward EAS & increases acidity, whereas e- donation increases reactivity toward EAS & decreases acidity.
- ✓ A similar substituent effect on is observed for substituted benzoic acids and substituted protonated anilines.



The Ortho –Para Ratio/EAS rxn

- ✓ The ff nitration rxns illustrate the decrease in the *o*–*p* ratio with an increase in the size of the alkyl substituent:



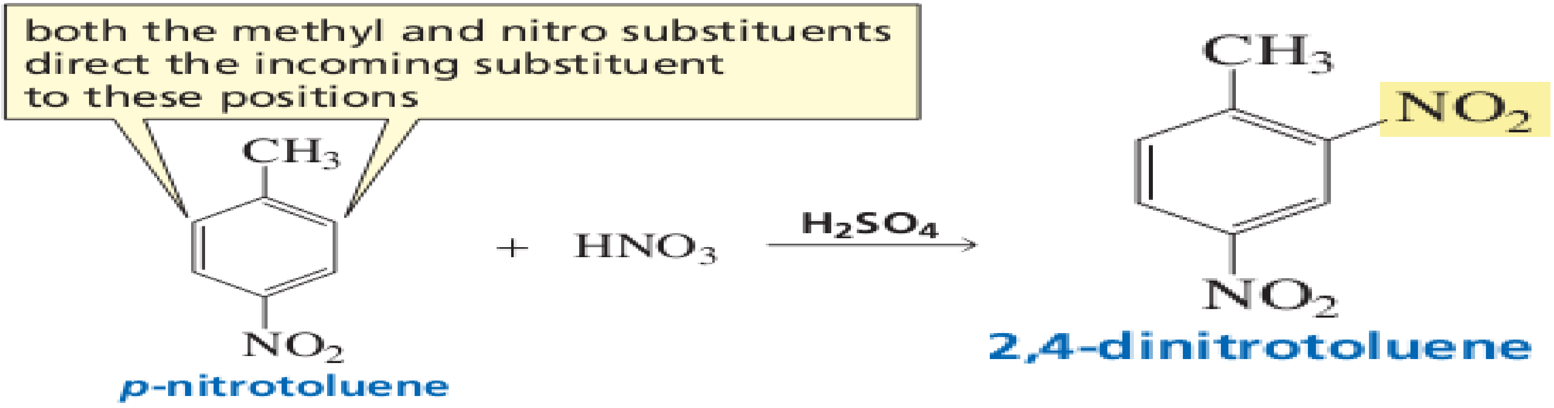
- ✓ EAS rxn that lead to both ortho & para isomers are useful in synthesis b/c the desired product can be easily separated from the rxn mixture.

The Ortho –Para Ratio/EAS rxn

- ✓ When a benzene ring with an o-p directing substituent undergoes EAS rxn what %age of the product is the *O*-omer & what %age is *P*-isomer?
- ✓ The ortho position, is sterically hindered, whereas the para position is not.
- ✓ So, the p-isomer will be formed preferentially if either the substituent on the ring or the incoming electrophile is large.
- ✓ The above nitration rxns illustrate the decrease in the ortho–para ratio with an increase in the size of the alkyl substituent.

Synthesis of Trisubstituted Benzenes

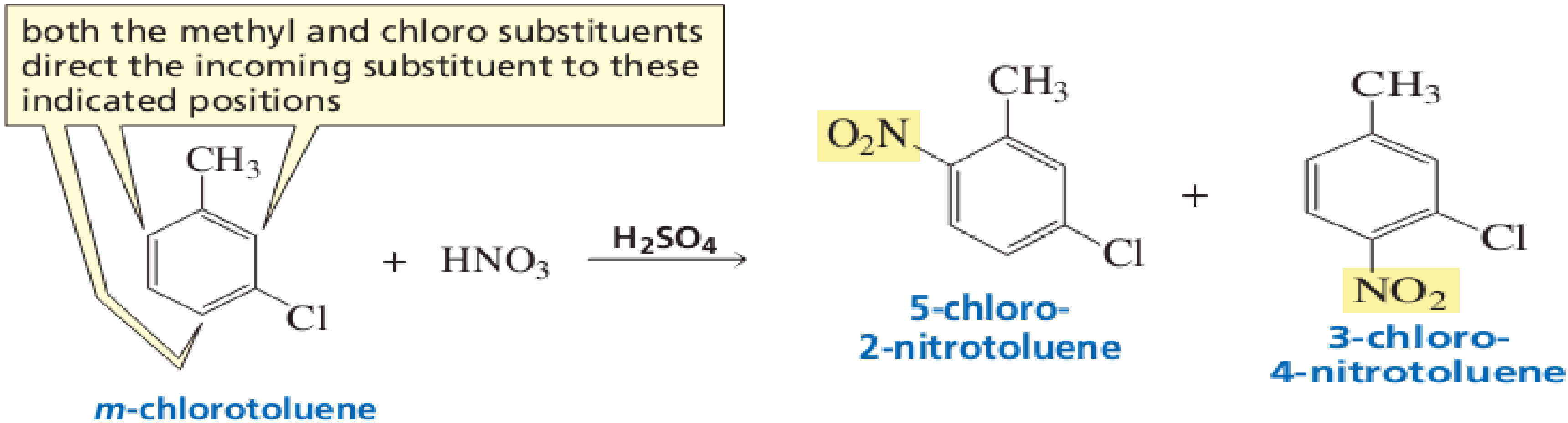
- ✓ If both substituents direct the incoming substituent to the same position, the product of the rxn is easily predicted.



both the methyl and nitro substituents direct the incoming substituent to these positions

p-nitrotoluene

2,4-dinitrotoluene

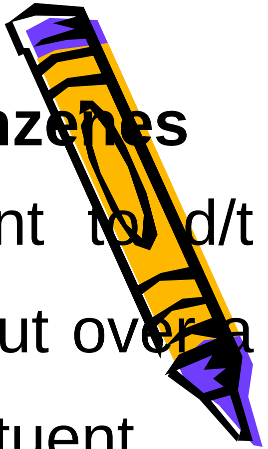


both the methyl and chloro substituents direct the incoming substituent to these indicated positions

m-chlorotoluene

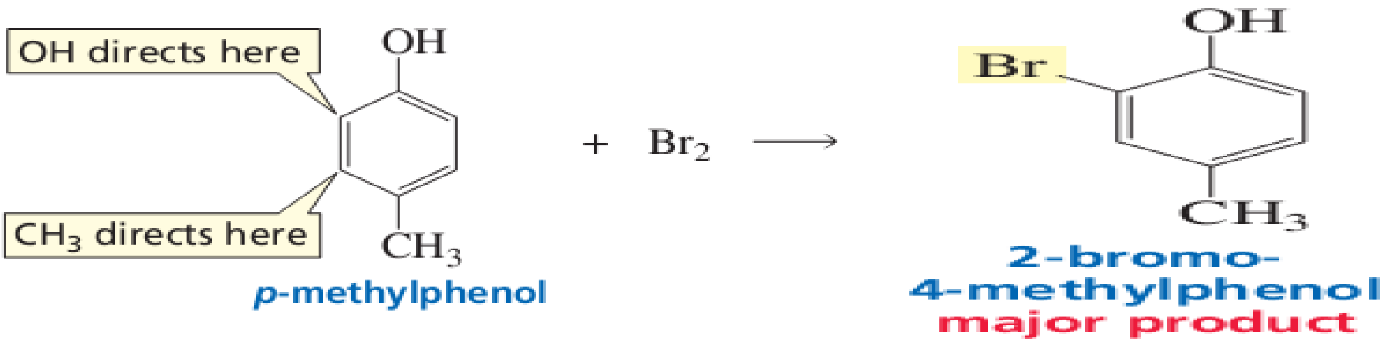
5-chloro-2-nitrotoluene

3-chloro-4-nitrotoluene



Synthesis of Trisubstituted Benzenes

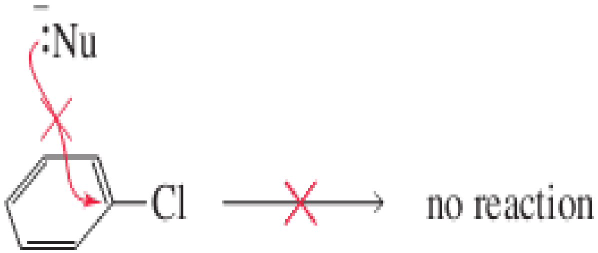
- ✓ If the two substituents direct the new substituent to d/t positions, a strongly activating substituent will win out over a weakly activating substituent or a deactivating substituent.



- ✓ **Assignment #3**) When phenol is treated with Br_2 , a mixture of monobromo-, dibromo-, and tribromophenols is obtained. Design a synthesis that would convert phenol primarily to ortho-bromophenol.

1.5 Nucleophilic Aromatic Substitution (NAS) Reactions

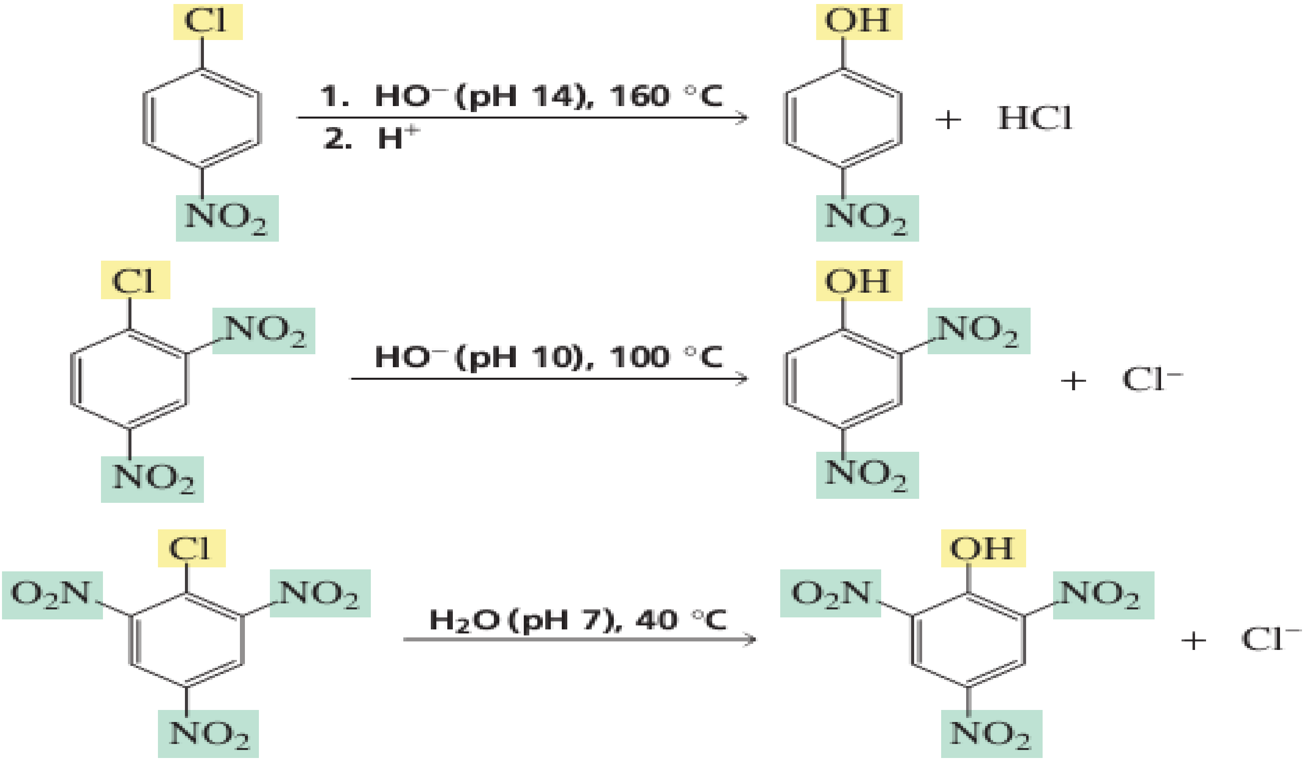
- Aryl halides don't react with NU**:** under standard rxn conditions b/c the e- clouds repel the approach of a NU**:.**



- However, if the aryl halide has one or more substituents that strongly withdraw e-s from the ring by resonance, NAS rxns can occur.

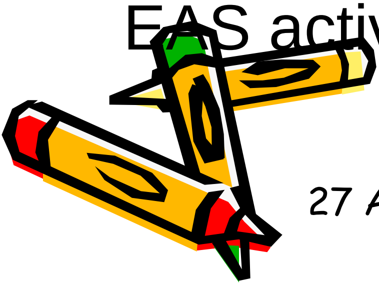
NAS rxns

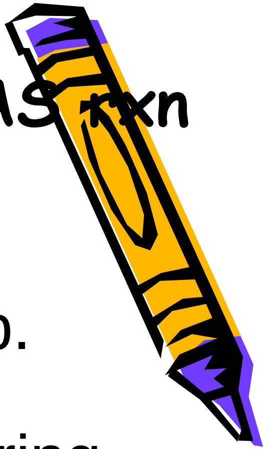
- ✓ The e-withdrawing groups must be positioned *o* or *p* to the halogen.
- ✓ The greater the number of EWG , the easier it is to carry out the NAS rxn.



NAS rxns

- ✓ **EWG** increase the reactivity of the C_6H_6 ring toward NAS & decrease the reactivity of the C_6H_6 ring toward EAS. ***why?***
- ✓ the strongly **EWG** that activate the C_6H_6 ring toward NAS rxns are the same substituents that deactivate the ring toward EAS.
- ✓ making the ring less e- rich makes it easier for a NU**:** but more difficult for an E+ to approach the ring.
- ✓ Thus, any substituent that deactivates the C_6H_6 ring toward EAS activates it toward NAS.





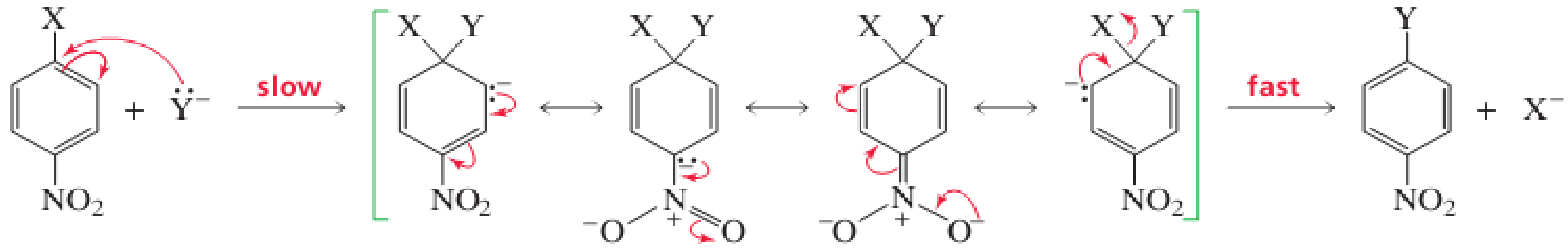
NAS rxn

- ✓ **NAS rxn** takes place by a two-step rxn:

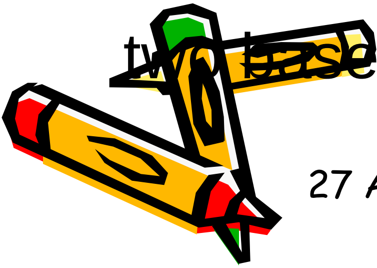
1) the NU**:** attacks the carbon bearing the leaving group.

2) the LG departs, reestablishing the aromaticity of the ring.

general mechanism for nucleophilic aromatic substitution

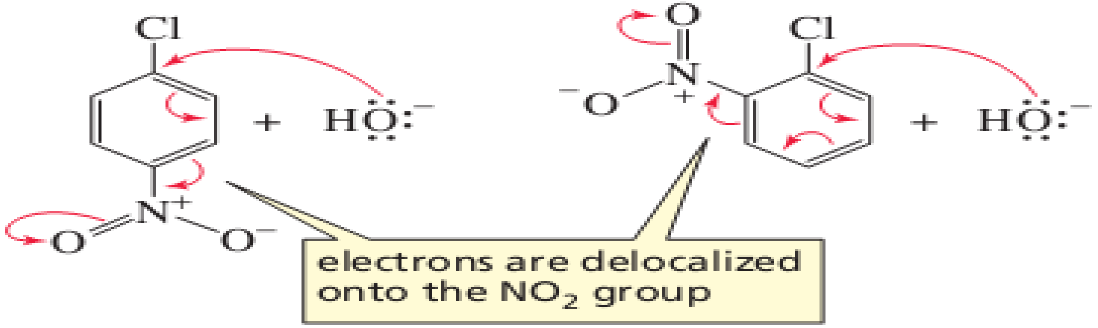


- ✓ Here, the incoming NU**:** must be a stronger base than the substituent that is being replaced, because the weaker of the two bases will be the one eliminated from the intermediate

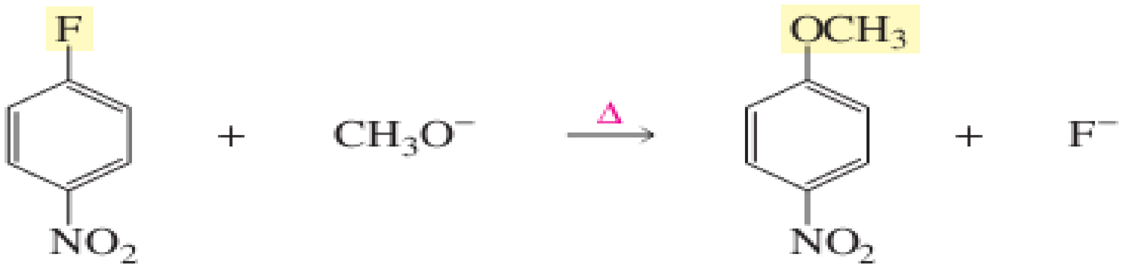


NAS rxn

- ✓ The EWG/S must be *o* or *p* to the site of nucleophilic attack b/c the e-s of the attacking Nu**:** can be delocalized on to the substituent only if the substituent is in one of those positions.

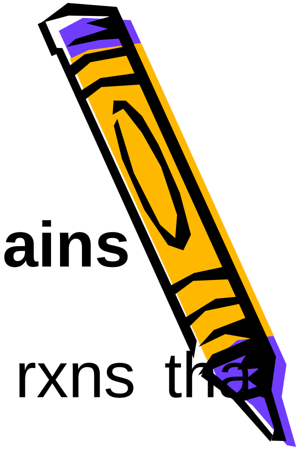


electrons are delocalized onto the NO_2 group



p-fluoronitrobenzene

p-nitroanisole

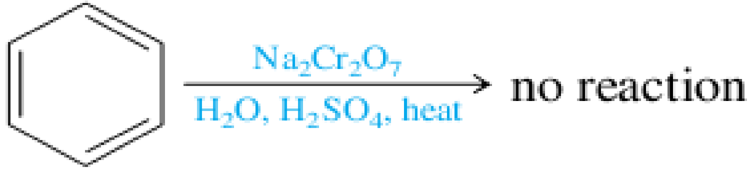


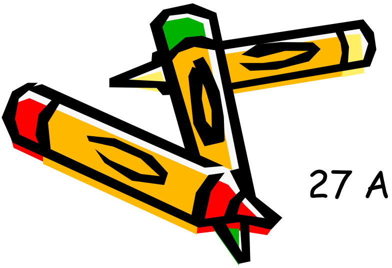
1.6 Rxns of Aromatic Side Chains

1.6.1 Oxidation and Substitution of Alkyl Side Chains

- ✓ the activating effect that a benzene ring has on rxns that take place at benzylic positions may be found in the rxns of alkyl benzenes with oxidizing agents.
- ✓ Chromic acid is prepared by adding H_2SO_4 to aq. $Na_2Cr_2O_7$, is a strong oxidizing agent but does not react either with benzene or with alkanes.

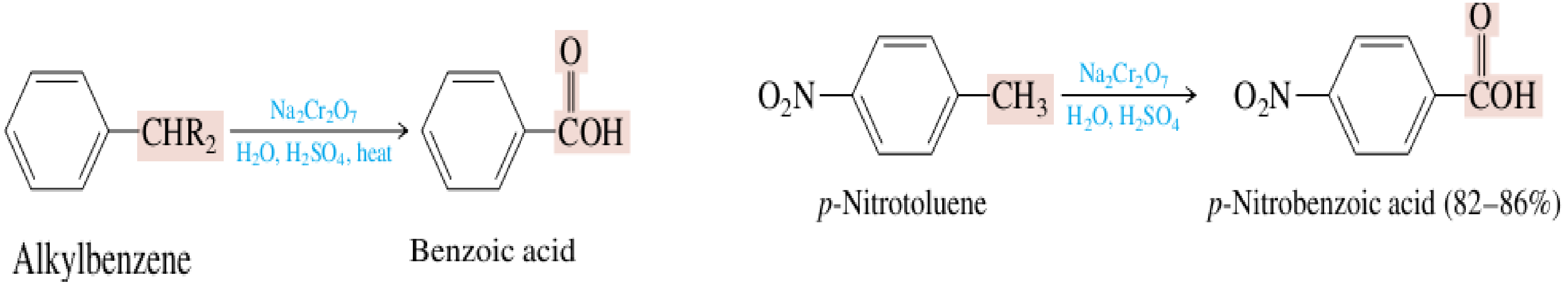
$$RCH_2CH_2R' \xrightarrow[H_2O,\ H_2SO_4,\ heat]{Na_2Cr_2O_7} \text{no reaction}$$



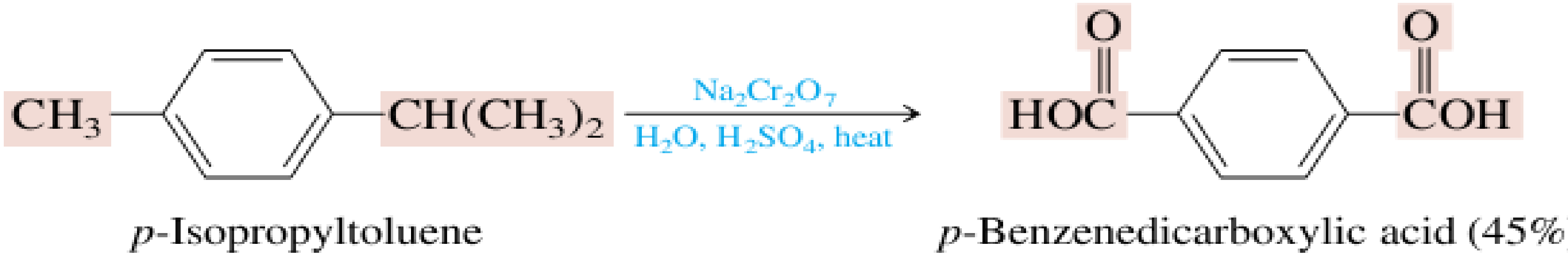


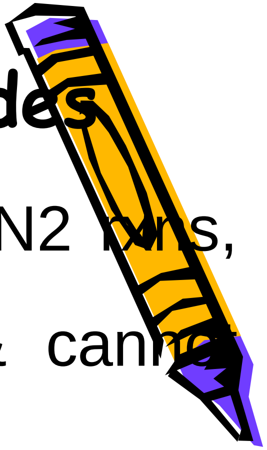
Rxns of Aromatic Side Chains

- An alkyl side chain on a benzene ring is oxidized on being heated with chromic acid.
- The product is benzoic acid or a substituted derivative of benzoic acid.



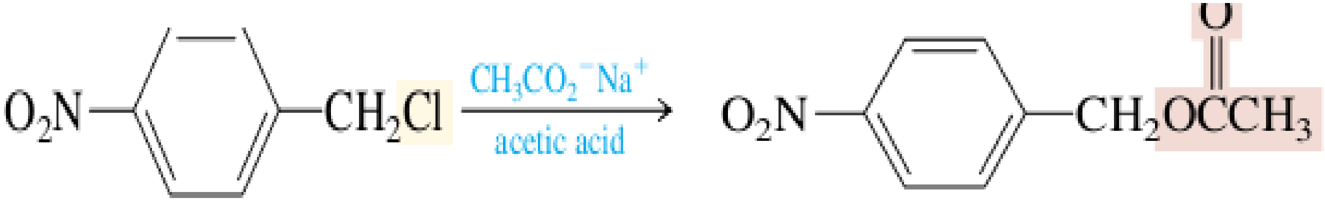
When two alkyl groups are present on the ring, both are oxidized.





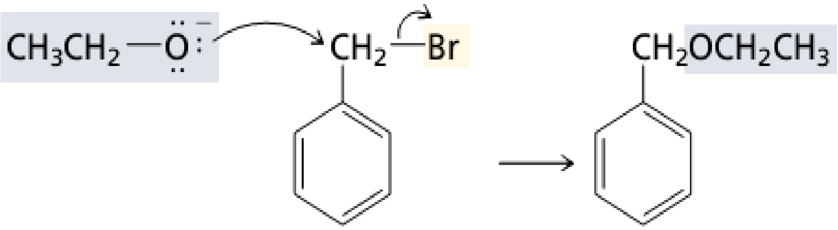
Nucleophilic Substitution in Benzylic Halides

- ✓ Primary benzylic halides are ideal substrates for SN2 rxns, since they are very reactive toward good Nu: & cannot undergo competing elimination.



p-Nitrobenzyl chloride

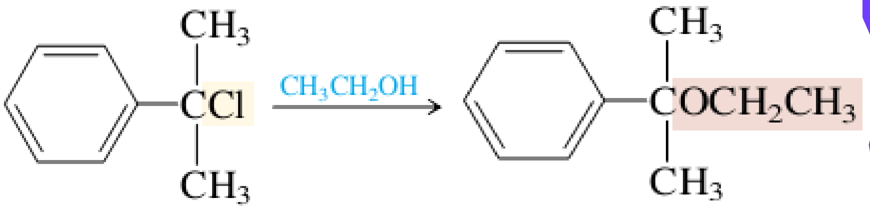
p-Nitrobenzyl acetate (78–82%)



Ethoxide ion

Benzyl bromide

Benzyl ethyl ether

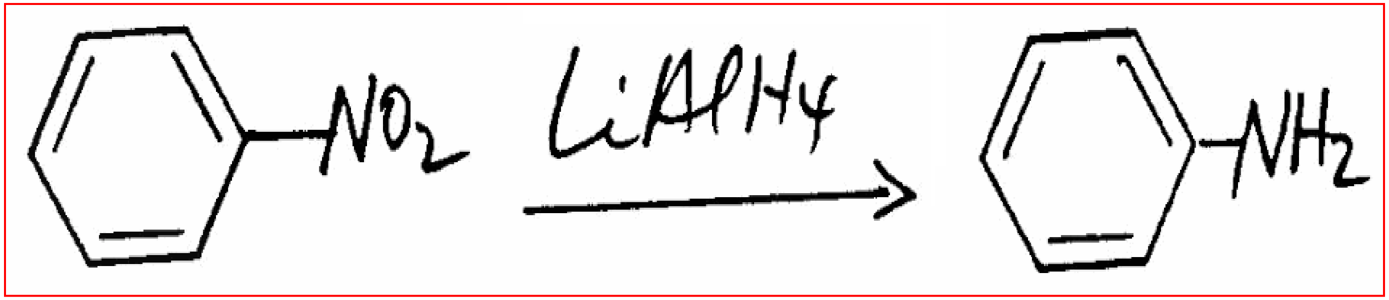


2-Chloro-2-phenylpropane

2-Ethoxy-2-phenylpropane (87%)

1.6.2 Reduction of Nitro Groups & Aryl Ketones

✓ no mechanism for reduction of nitro cpds (R-NO_2), this rxn is useful for synthesis of Anilines from nitrobenzene.



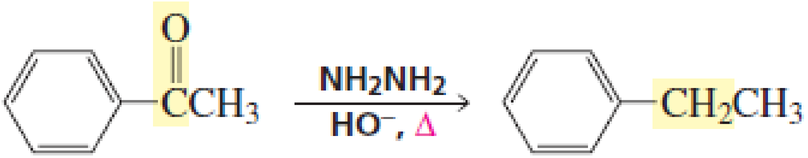
The Wolff–Kishner Reduction

✓ when a ketone or an aldehyde is heated in a basic solution of hydrazine, the carbonyl group is converted into a methylene group.

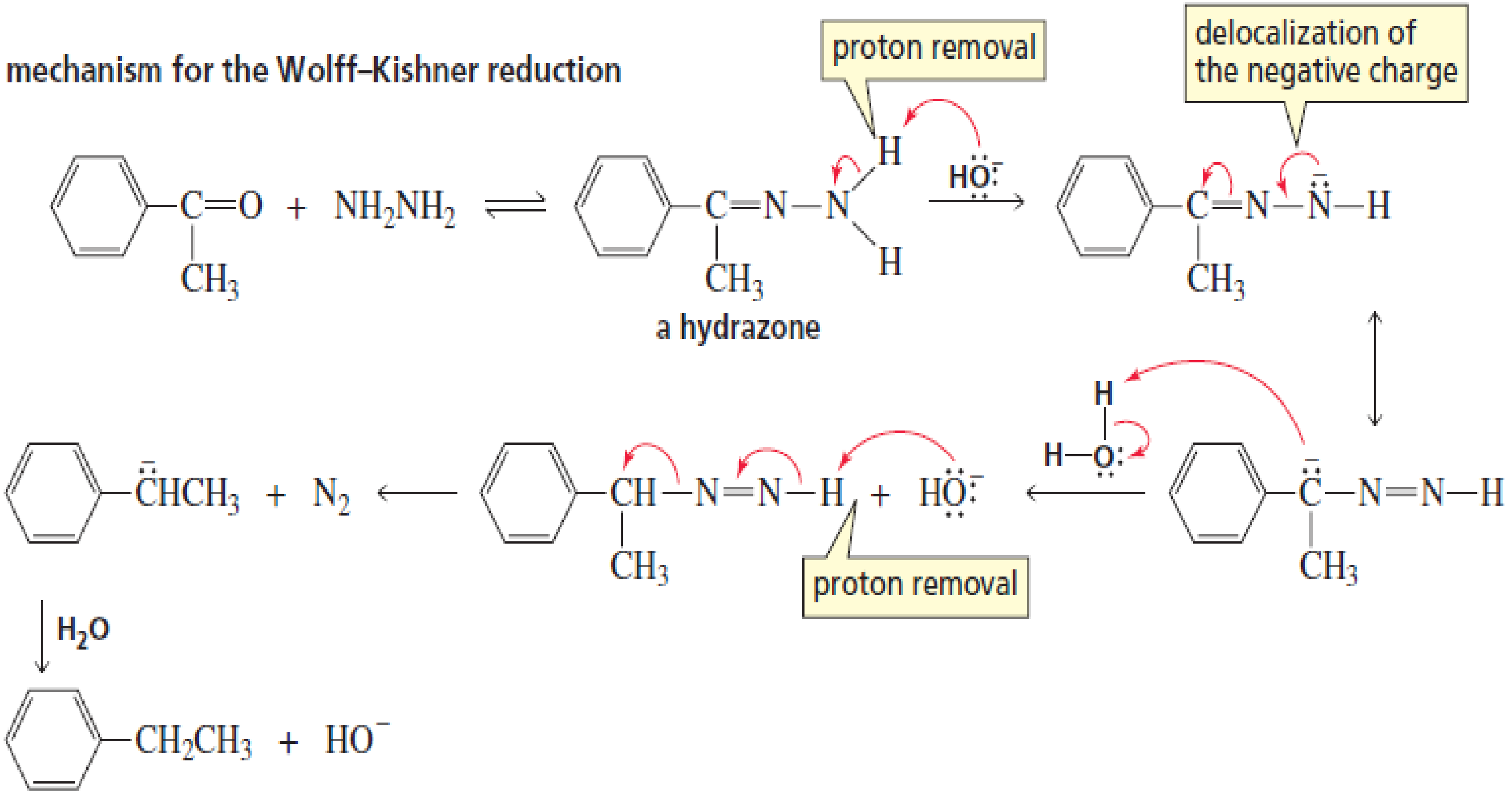
✓ This process is called **deoxygenation b/c an oxygen is removed from the reactant.**

✓ The reaction is known as the *Wolff–Kishner reduction.*

Reduction of Nitro Groups and Aryl Ketones

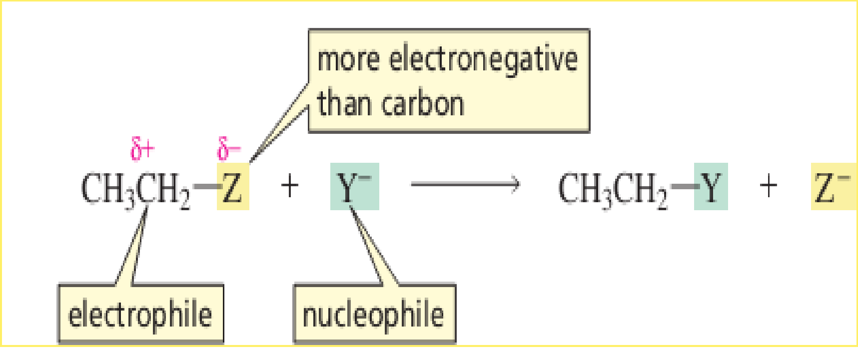


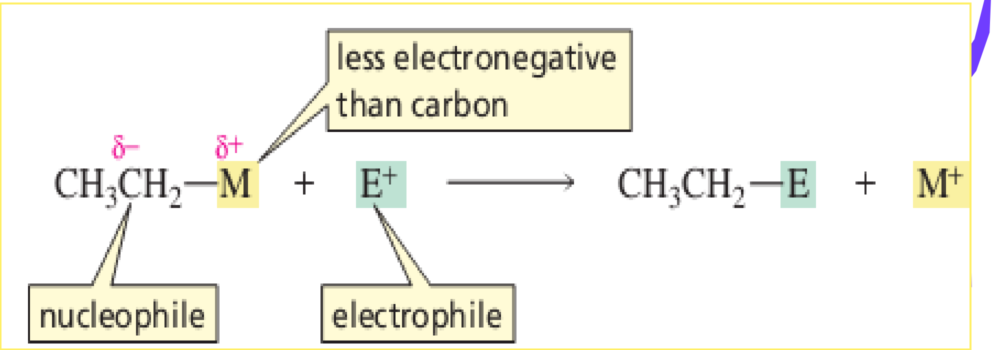
mechanism for the Wolff–Kishner reduction



1.6.3 Conversion of Halogens to Organ metallic Reagents

- ✓ Alcohols, ethers, & alkyl halides all contain a **C** atom that is bonded to a more electronegative atom.
- ✓ The **C** atom is electrophilic & reacts with a nucleophile.





- ✓ To be nucleophilic , **C** would have to be bonded to a less EN atom.
- ✓ A **C** bonded to a metal is Nu**:** b/c most metals are less EN than C.
- ✓ An organometallic cpd is a cpd that contains a **C–metal** bond.

cont^{d}

- ✓ Organolithium cpds & organomagnesium cpds are two of the most common organometallic cpds.
- ✓ Organolithium cpds are prepared by adding lithium to an alkyl halide in a nonpolar solvent such as hexane.

$$CH_3CH_2CH_2CH_2Br + 2\,Li \xrightarrow{\text{hexane}} CH_3CH_2CH_2CH_2Li + LiBr$$

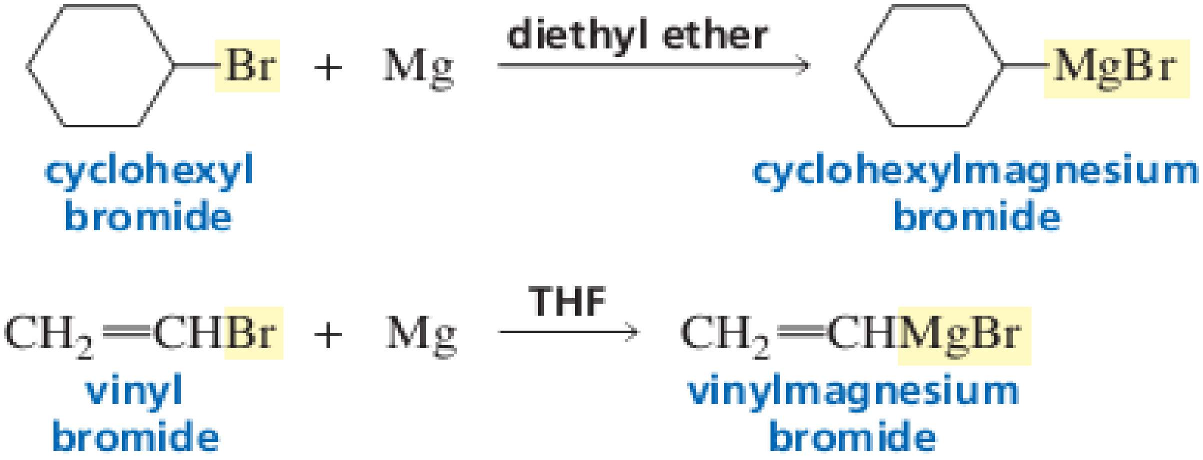
1-bromobutane → butyllithium

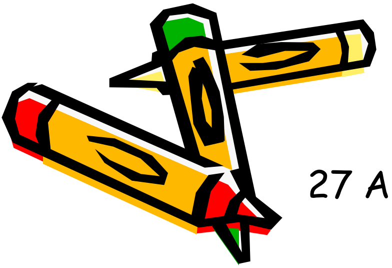
chlorobenzene + 2 Li →(hexane) phenyllithium + LiCl

- ✓ Organomagnesium compounds, frequently called Grignard reagents.
- ✓ The magnesium is inserted b/n the **C** and the halogen.

Cont$^{\underline{d}}$

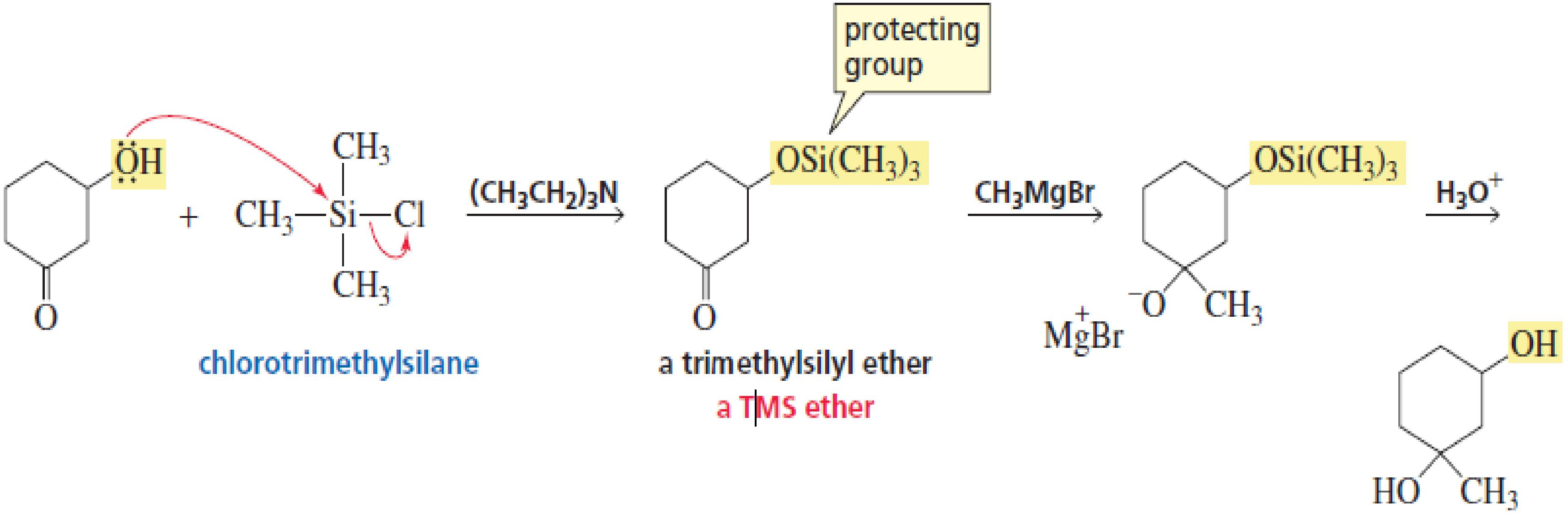
- ✓ The solvent (diethyl ether or tetrahydrofuran) plays a crucial role in the formation of a Grignard reagent.





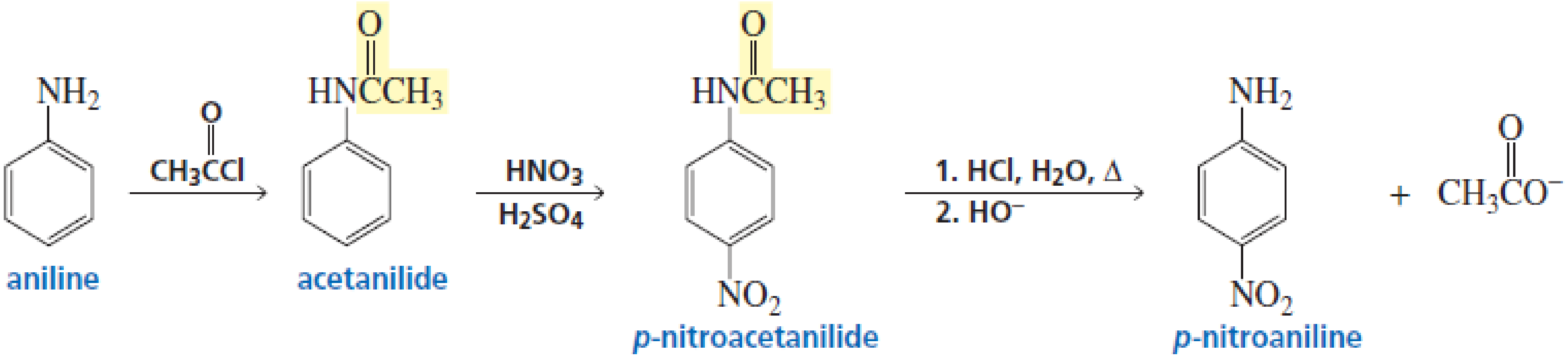
1.6.4 Modifying the Influence of Strong Activating Groups

- ✓ A group that protects a functional group from a synthetic operation that it would not otherwise survive is called a **protecting group.**
- ✓ The strongest activating & ortho/para-directing substituents are the amino (-NH_2) & hydroxyl (-OH) groups.

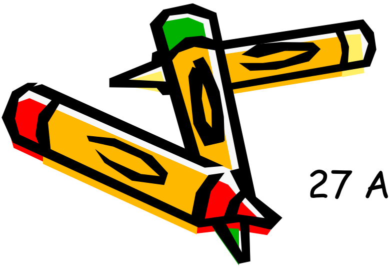


Modifying the Influence of Strong Activating Groups

- ✓ An amino group can be protected by being converted into an amide.
- ✓ The acetyl group can subsequently be removed by acid catalyzed hydrolysis.

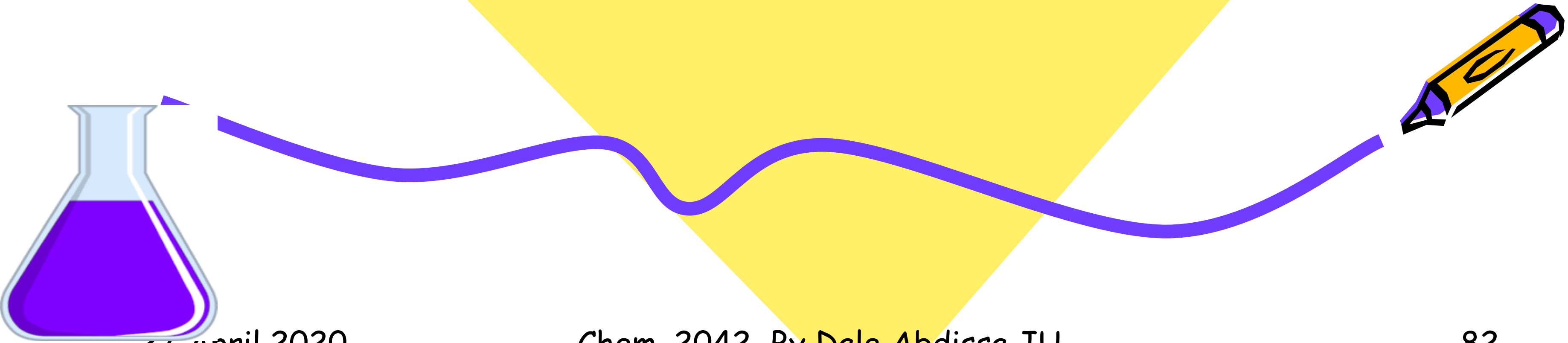


- ✓ **Assignment #4**: **Propose the reaction mechanism for the Synthesis of p-nitroaniline from aniline.**

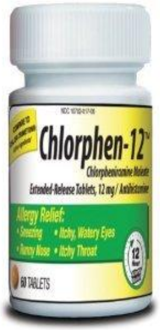


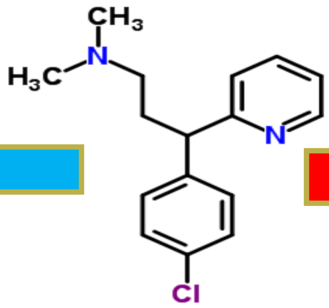
Chapter 2

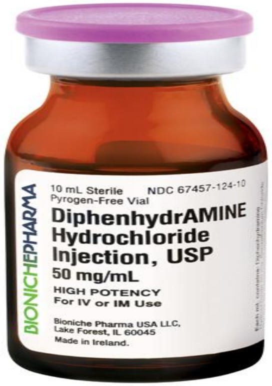
Amines

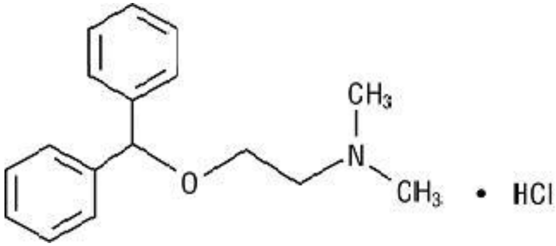


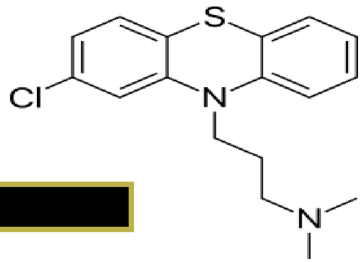
Introduction to Some Amines in Use











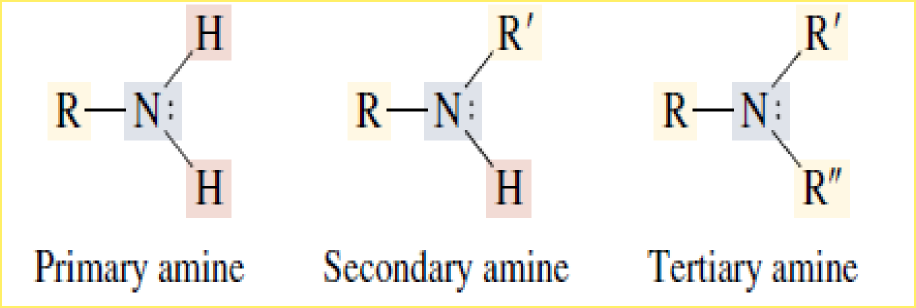
2. Amines

2.1 Nomenclature and Structure of Amines

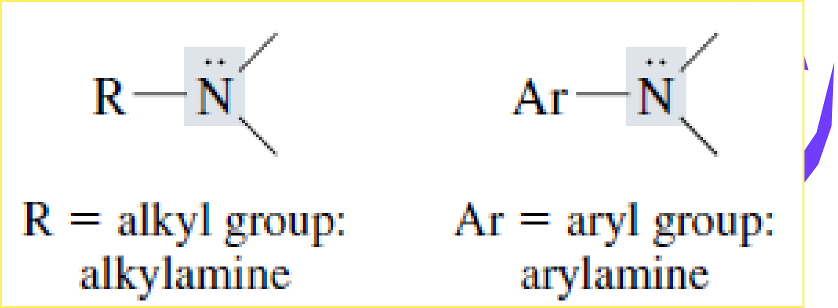
- The word "amine" is derived from ammonia, & the classes of cpds are known as amines.
- They are cpds in which one or more of the hydrogens of ammonia have been replaced by an alkyl group.
- They are classified as primary (1^0), secondary (2^0), or tertiary (3^0), depending on whether one, two, or three Hs of NH_3, respectively, have been replaced by an alkyl group.
- Amines are organic compounds and functional groups that contain a basic nitrogen atom with a lone pair.

Nomenclature and Structure

- ✓ An amine with one **C** attached to **N** is a 1^0 amine, an amine with two is a 2^0 amine, & an amine with three is a 3^0 amine.



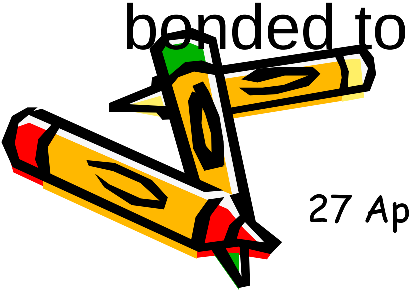
Primary amine Secondary amine Tertiary amine



R = alkyl group: alkylamine

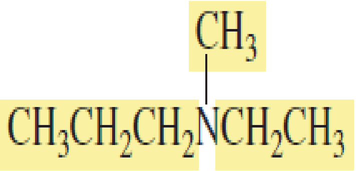
Ar = aryl group: arylamine

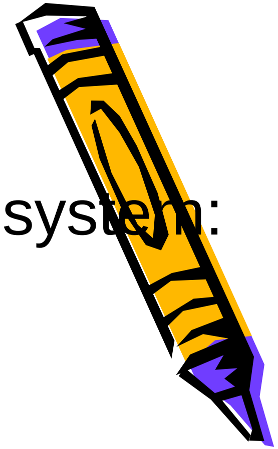
- ✓ **Aliphatic amines:** an amine in which **N** is bonded only to alkyl group or hydrogens.
- ✓ **Aromatic amines (Aryl amine):** an amine in which **N** is bonded to one or more aromatic rings.



2.5.1 Common naming system

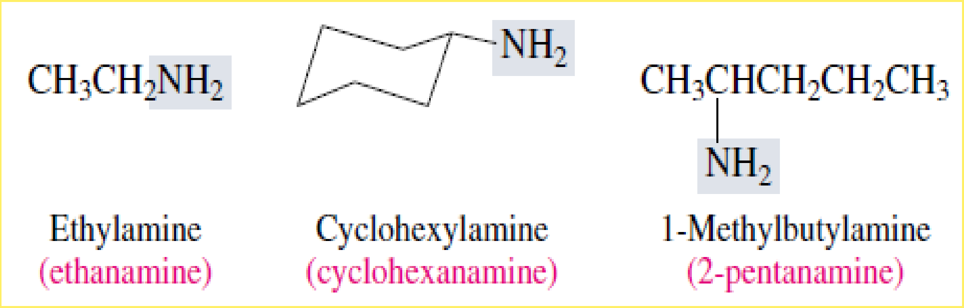
- ✓ Common names are obtained by citing the names of the alkyl substituents (in alphabetical order) that have replaced the hydrogens of ammonia.
- ✓ Systematic names employ “amine” as a functional group suffix.

	$CH_3CH_2CH_2CH_2CH_2NH_2$	$CH_3CH_2CH_2CH_2NHCH_2CH_3$	 $CH_3CH_2CH_2\overset{CH_3}{\overset{\vert}{N}}CH_2CH_3$
	a primary amine	a secondary amine	a tertiary amine
common name:	pentylamine	butylethylamine	ethylmethylpropylamine
systematic name:	1-pentanamine	*N*-ethyl-1-butanamine	*N*-ethyl-*N*-methyl-1-propanamine



2.5.2 IUPAC naming system

- ✓ **Amines** are named in two main ways, in the IUPAC system:
- ✓ Either as alkyl amines or as **alkanamines**
- ✓ When 1^0 amines are named as **alkyl amines**, the ending–amine is added to the name of the alkyl group that bears the N.
- ✓ When named as **alkanamines,** the alkyl group is named as an alkane & the **–e** ending replaced by -*amine*.



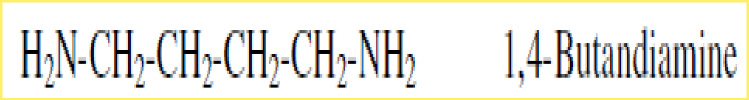
$CH_3CH_2NH_2$

Ethylamine
(ethanamine)

Cyclohexylamine
(cyclohexanamine)

$CH_3CHCH_2CH_2CH_3$ with NH_2 on C-2

1-Methylbutylamine
(2-pentanamine)



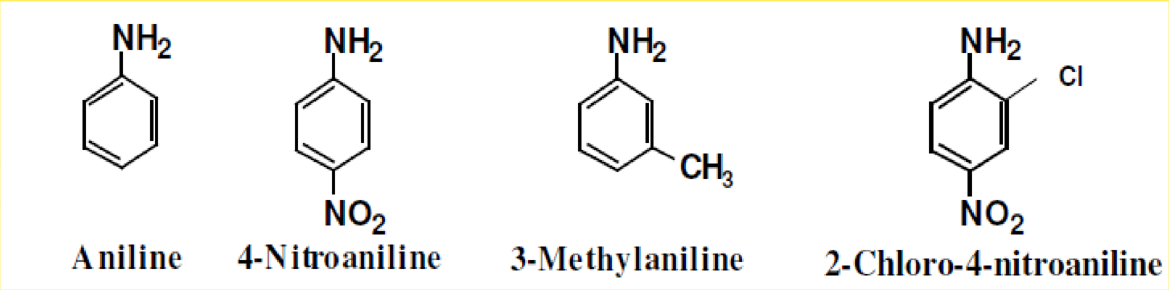
$H_2N\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NH_2$ 1,4-Butandiamine

IUPAC naming system

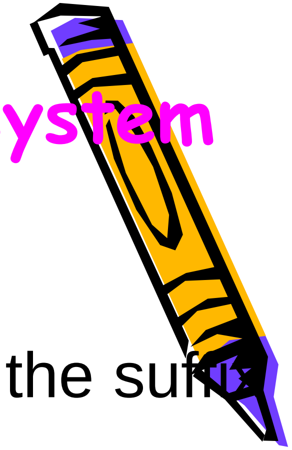
✓ **Aniline** is the parent IUPAC name for amino-substituted derivatives of benzene.

✓Substituted derivatives of aniline are numbered beginning at the **C** that bears the amino group.

✓ Substituents are listed in alphabetical order, and the direction of numbering is governed by the usual “first point of difference” rule.

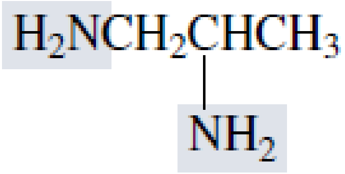


Aniline 4-Nitroaniline 3-Methylaniline 2-Chloro-4-nitroaniline



IUPAC naming system

- ✓ **Aryl amines** may also be named as arenamines.
- ✓ Cpds with two amino groups are named by adding the suffix –diamine to the name of the corresponding alkane or arene.
- ✓ The final **–e** of the parent hydrocarbon is retained.

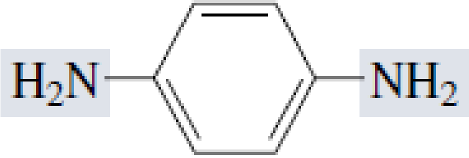


$H_2NCH_2CH(NH_2)CH_3$

1,2-Propanediamine

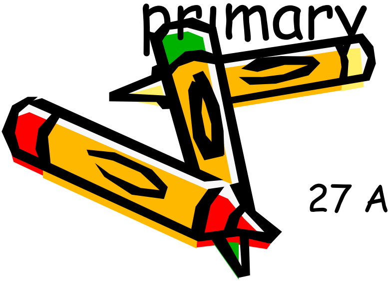
$H_2NCH_2CH_2CH_2CH_2CH_2CH_2NH_2$

1,6-Hexanediamine



1,4-Benzenediamine

- ✓ 2^0 & 3^0 amines are named as **N-substituted** derivatives of primary amines.

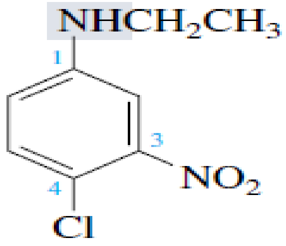


IUPAC naming system

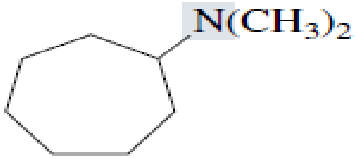
- ✓ The parent 1^0 amine is taken to be the one with the longest *C* chain.
- ✓ The prefix *N-* is added as a locant to identify substituents on the amino nitrogen as needed.

$CH_3NHCH_2CH_3$

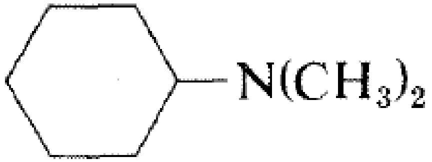
N-Methylethylamine



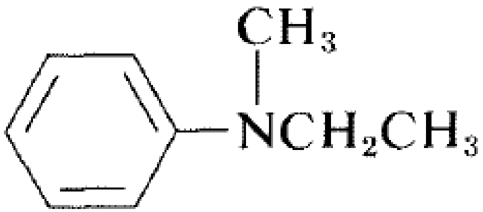
4-Chloro-*N*-ethyl-3-nitroaniline



N,*N*-Dimethylcycloheptylamine

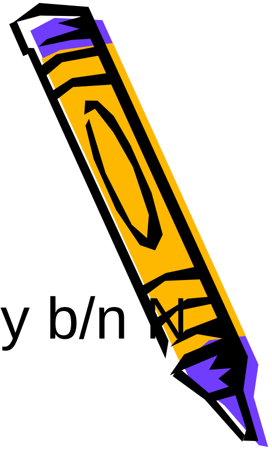


N,*N*-dimethylcyclohexanamine
(*N*,*N*-dimethylcyclohexylamine)

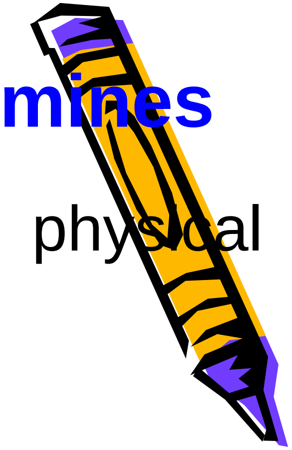


N-ethyl-*N*-methylbenzenamine
(*N*-ethyl-*N*-methylaniline)

2.5.3 Properties of Amines



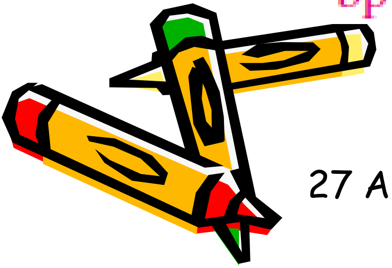
- ✓ They have very sharp, penetrating odors (like rotten fish).
- ✓ They are polar cpds because of the d/c in electronegativity b/n N and H (3.0 – 2.1 = 0.9).
- ✓ Both 1^0& d 2^0amines can form have H-bonds with one another (b/c of N-H).
- ✓ However, the 3^0 amines do not have a H-bonds to N, so, do not form H-bonds with one another (but H-bonds in amines are weaker than H-bonds in alcohols).
- ✓ have higher b.pt than hydrocarbons but lower b.pt compare to alcohols (with the same M. wt).
- ✓ B/c of H-bonding, they are more soluble in water than are hydrocarbons of comparable M. wt).



Properties of Amines

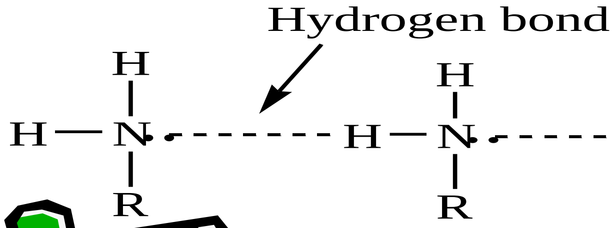
- ✓ The polar nature of a substance can affect physical properties such as b.pt.
- ✓ This is true for amines, which are more polar than alkanes but less polar than alcohols.
- ✓ For similarly constituted cpds, alkyl amines have b.pt higher than those of alkanes but lower than those of alcohols.

$CH_3CH_2CH_3$	$CH_3CH_2NH_2$	CH_3CH_2OH
Propane	Ethylamine	Ethanol
$\mu = 0$ D	$\mu = 1.2$ D	$\mu = 1.7$ D
bp −42°C	bp 17°C	bp 78°C

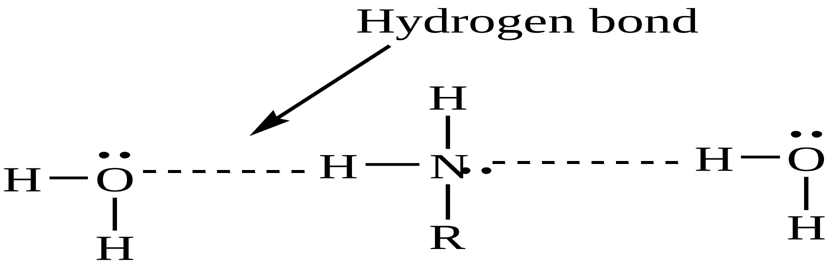


cont$^{\underline{d}}$

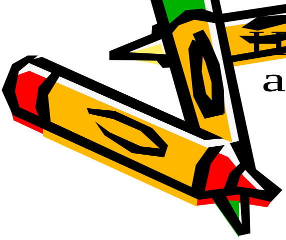
- ✓ Lower amines are gases with characteristic ammonia-like smell.
- ✓ Amines have higher b.pt than non-polar cpds of similar M.wt. This is b/c amines are polar cpds & form intermolecular H-bonds.
- ✓ *E.g.* ethylamine, $C_2H_5NH_2$, boils at 17 ^0C & propane, C_3H_8 at -43 ^0C.



Hydrogen bonding in amine molecules

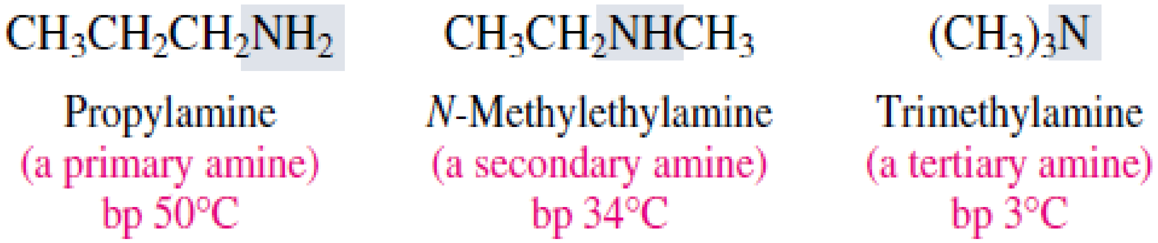


Hydrogen bonding between amine and water



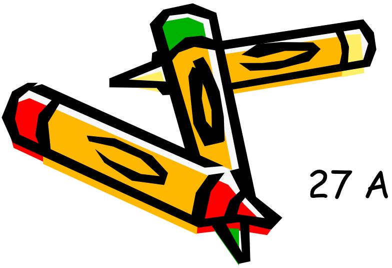
cont^{d}

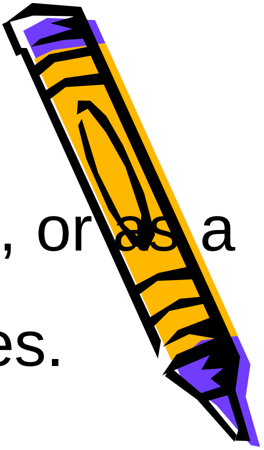
- ✓ Among isomeric amines, primary amines have the highest boiling points, and tertiary amines the lowest.



$CH_3CH_2CH_2NH_2$	$CH_3CH_2NHCH_3$	$(CH_3)_3N$
Propylamine	*N*-Methylethylamine	Trimethylamine
(a primary amine)	(a secondary amine)	(a tertiary amine)
bp 50°C	bp 34°C	bp 3°C

- ✓ Primary & secondary amines can participate in intermolecular H-bonding, but tertiary amines cannot.
- ✓ Almost all other aryl amines have higher boiling points.





2.3 Acidity & Basicity of Nitrogen Compounds

- ✓ An amine can behave as an acid & donate a proton, or as a base & accept a proton. Cpds with groups are amines.

$$CH_3NH_2 + HO^- \rightleftharpoons CH_3\overset{-}{N}H + H_2O$$

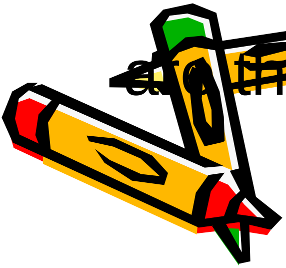
an acid

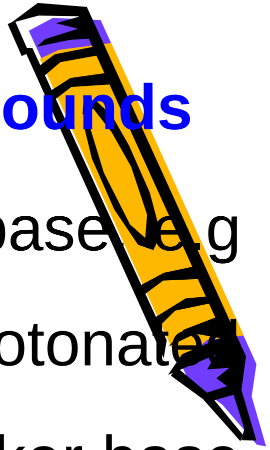
$$CH_3NH_2 + H_3O^+ \rightleftharpoons CH_3\overset{+}{N}H_3 + H_2O$$

a base

CH_3NH_2	NH_3
methylamine	ammonia
$pK_a = 40$	$pK_a = 36$

- ✓ Amines have high p^{ka} values that they rarely behave as acids. Ammonia also has high p^{ka}
- ✓ Amines are much more likely to act as bases. In fact, amines are the most common organic bases.



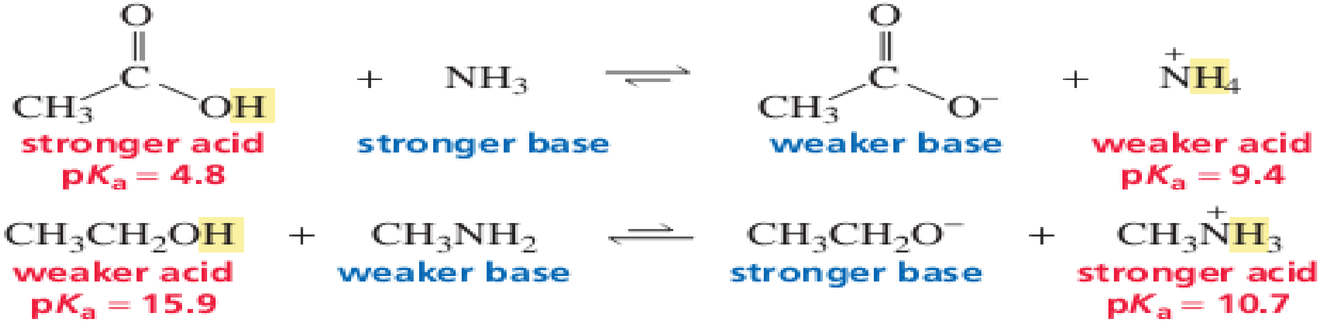


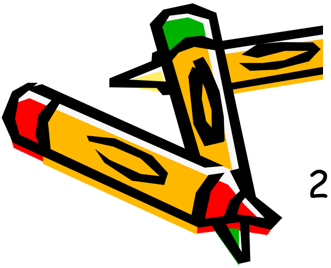
Acidity and basicity of Nitrogen Compounds

- ✓ The stronger the acid, the weaker is its conjugate base e.g protonated methylamine is a stronger acid than protonated ethylamine, which means that methylamine is a weaker base than ethylamine.
- ✓ the p^{ka} values of protonated amines are about 10 to 11.

$CH_3\overset{+}{N}H_3$
protonated methylamine
$pK_a = 10.7$

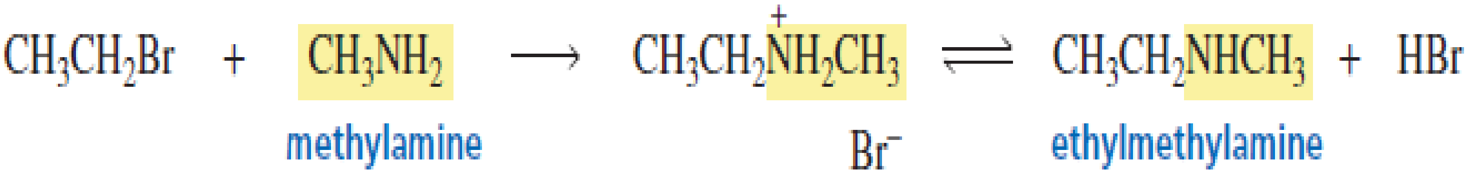
$CH_3CH_2\overset{+}{N}H_3$
protonated ethylamine
$pK_a = 11.0$





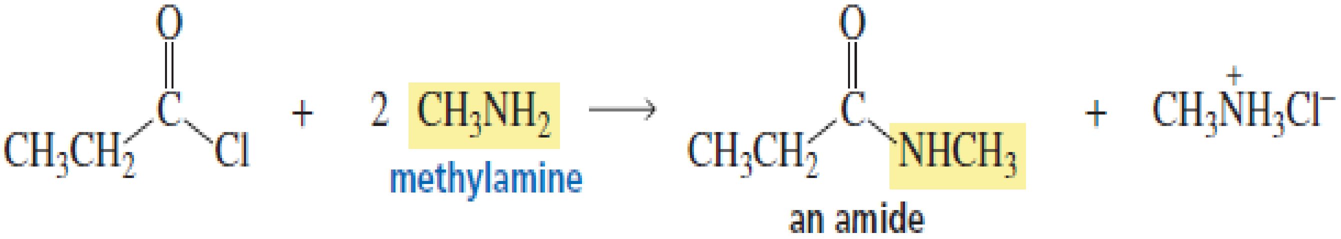
2.4 Reactions of Amine: Alkylation

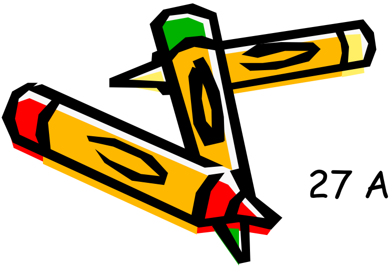
- The lone pair on the **N** of an amine causes it to be nucleophilic as well as basic.
- Amines act as nucleophiles in a number of d/t kinds of rxns: in nucleophilic substitution rxns, rxns that *alkylate the amine.*

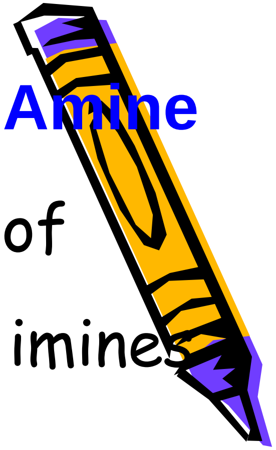


$$CH_3CH_2Br + \underset{\text{methylamine}}{CH_3NH_2} \longrightarrow \underset{Br^-}{CH_3CH_2\overset{+}{N}H_2CH_3} \rightleftharpoons \underset{\text{ethylmethylamine}}{CH_3CH_2NHCH_3} + HBr$$

✓ in nucleophilic acyl substitution rxns, rxns that *acylate the amine*

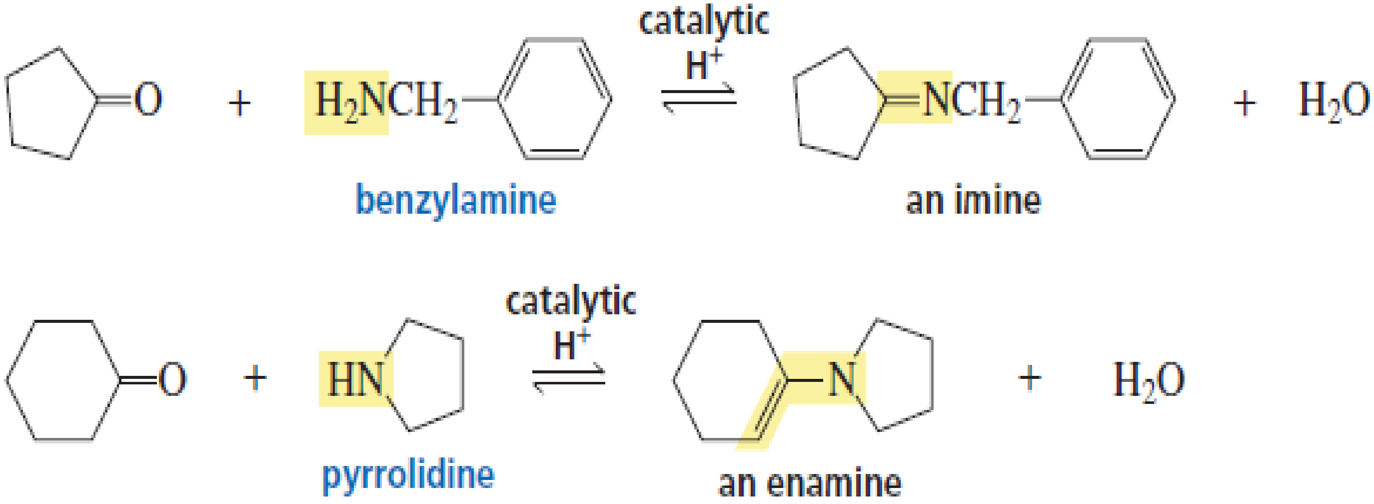




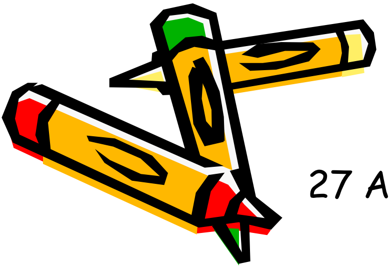


Reactions of Amine

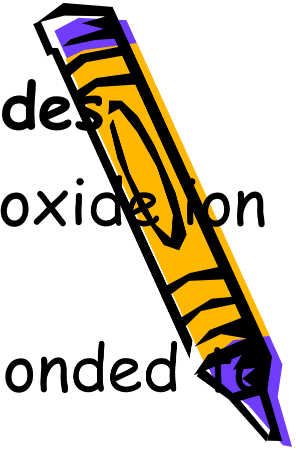
- ✓ in nucleophilic addition-elimination rxns, the rxns of aldehydes & ketones with primary amines to form imines & with secondary amines to form enamines.



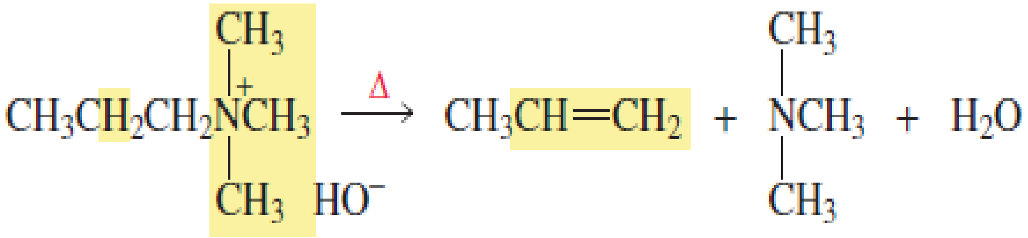
2) Reactions of Quaternary Ammonium Hydroxides



2) Reactions of Quaternary Ammonium Hydroxides



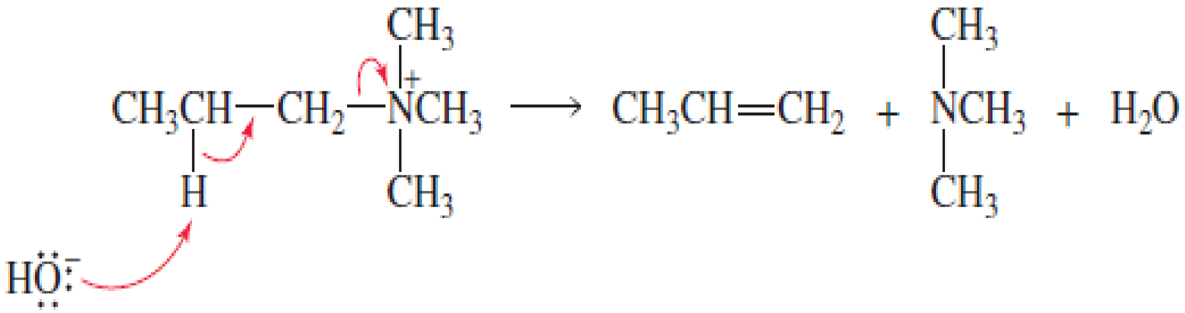
- ✓ The rxn of a quaternary ammonium ion with hydroxide ion is known as a **Hofmann elimination** rxn.
- In this rxn, the **H** is removed from the $\beta-$**C** bonded to the most hydro



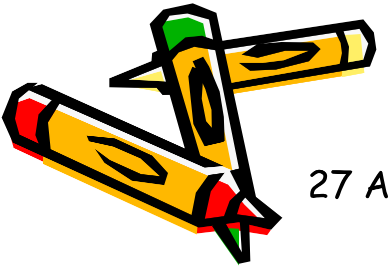
$$CH_3CH_2CH_2\overset{CH_3}{\underset{CH_3}{\overset{+}{N}}}CH_3 \;\; HO^- \xrightarrow{\Delta} CH_3CH{=}CH_2 + \overset{CH_3}{\underset{CH_3}{N}}CH_3 + H_2O$$

- ✓ A Hofmann elimination rxn is an E2 rxn . ***NB***. E2 rxn is a concerted, one-step rxn ,the proton & the tertiary amine are removed in the same step

mechanism of the Hofmann elimination

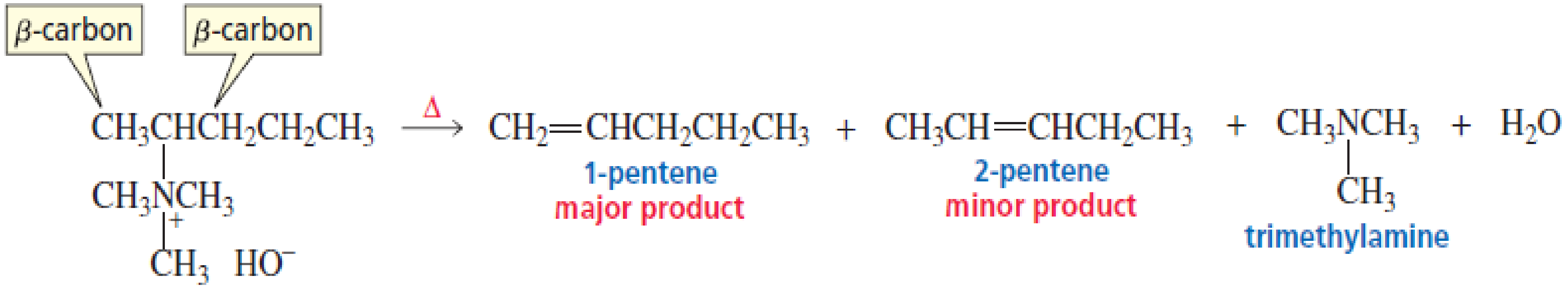


$$H\ddot{O}:^- \quad CH_3\underset{H}{CH}-CH_2-\overset{CH_3}{\underset{CH_3}{\overset{+}{N}}}CH_3 \longrightarrow CH_3CH{=}CH_2 + \overset{CH_3}{\underset{CH_3}{N}}CH_3 + H_2O$$



Reactions of Amine

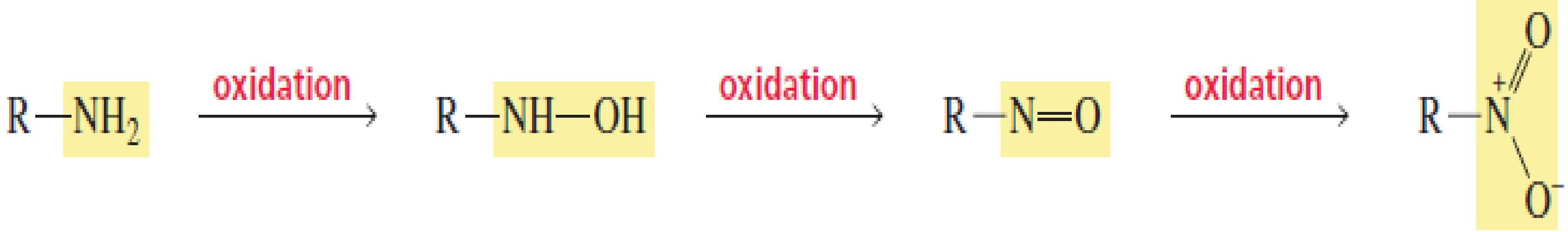
- ✓ If the quaternary ammonium ion has more than one β-C, the major alkene product is the one obtained by removing a proton from the β-C bonded to the greater number of hydrogens.
- ✓ In the ff rxn, the major alkene product is obtained by removing a H from the β-C bonded to three Hs, and the



$$CH_3CHCH_2CH_2CH_3 \ (\text{with } \overset{+}{N}(CH_3)_3 \ HO^-) \xrightarrow{\Delta} CH_2{=}CHCH_2CH_2CH_3 + CH_3CH{=}CHCH_2CH_3 + CH_3N(CH_3)CH_3 + H_2O$$

3) Oxidation of Amines: The Cope Elimination Rxn

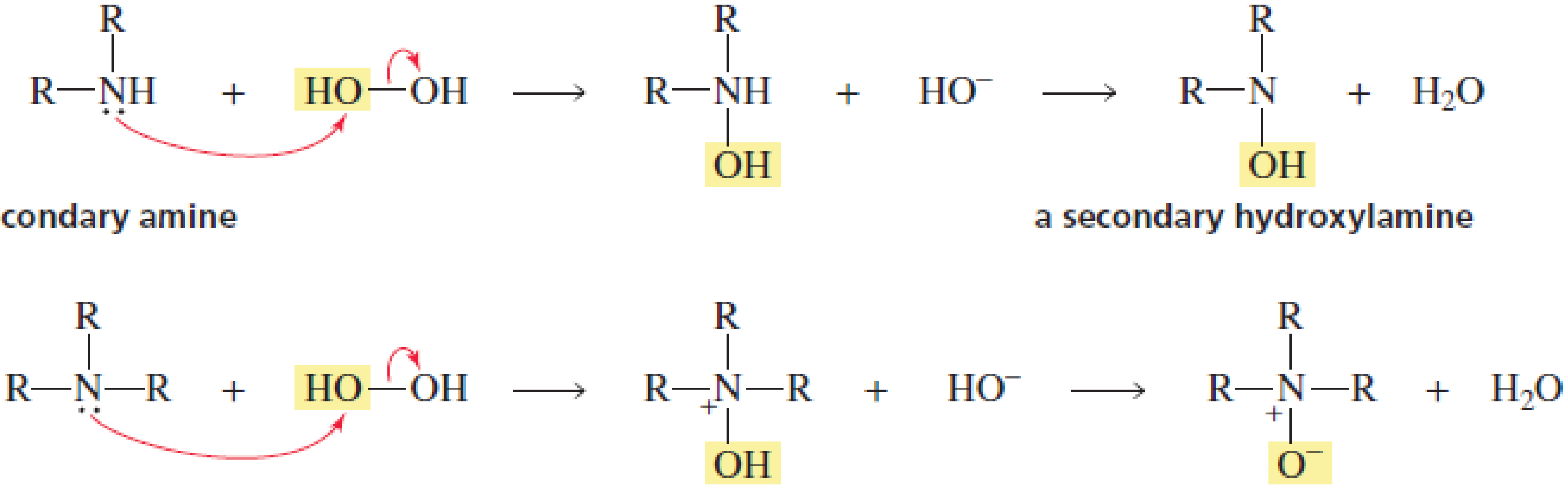
- ✓ Amines are easily oxidized, sometimes by being exposed to air.
- ✓ **Amines**, are stored as salts (e.g., as amine hydrochlorides), & drugs that contain amino groups are often sold as salts.
- ✓ Primary amines are oxidized to hydroxlyamines, which in



a primary amine — a hydroxylamine — a nitroso compound — a nitro compound

3) Oxidation of Amines: The Cope Elimination Rxn

- Secondary amines are oxidized to secondary hydroxylamines, & tertiary amines are oxidized to amine oxides.



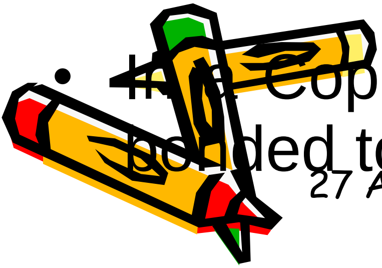
a secondary amine

a secondary hydroxylamine

a tertiary amine

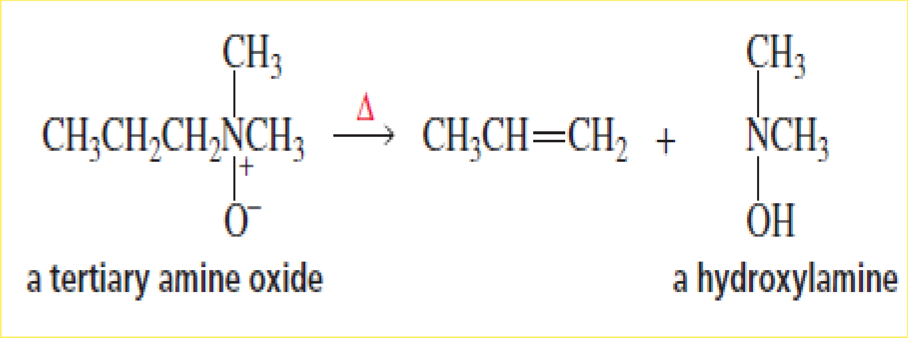
an tertiary amine oxide

- In the Cope elimination, the **H** is removed from the β-carbon bonded to the most hydrogens.



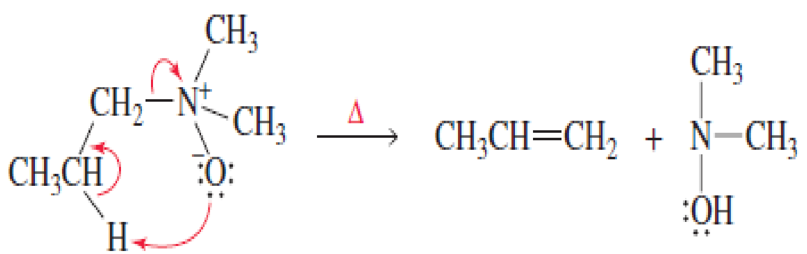
3) Oxidation of Amines: The Cope Elimination Rxn

- ✓ Amine oxides undergo a rxn similar to the Hofmann elimination rxn, called a *Cope elimination* rxn.
- ✓ *In a* ***Cope elimination*** rxn, ***a tertiary amine*** oxide rather than a quaternary ammonium ion undergoes elimination.
- ✓ The Cope elimination rxn occurs under milder conditions than does a Hofmann elimination reaction.



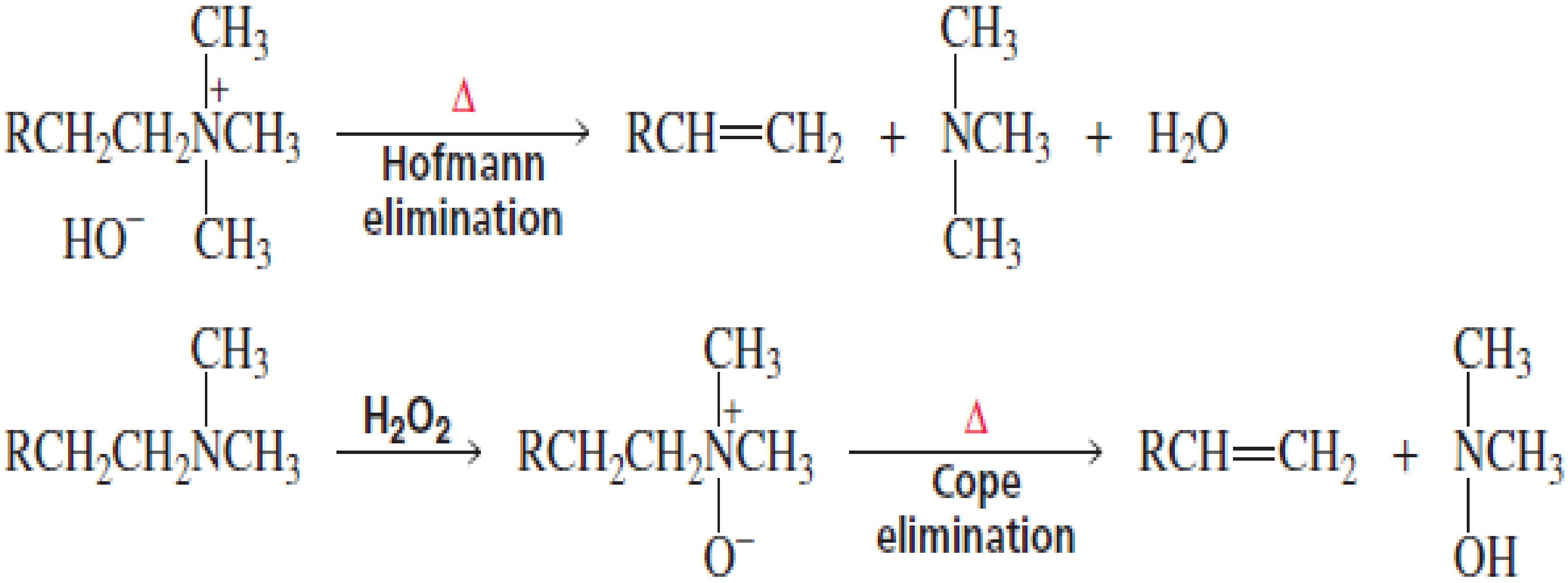
$$CH_3CH_2CH_2\underset{O^-}{\overset{CH_3}{\overset{+}{N}}}CH_3 \xrightarrow{\Delta} CH_3CH{=}CH_2 + \underset{OH}{\overset{CH_3}{N}}CH_3$$

mechanism of the Cope elimination reaction



The Cope Elimination Rxn

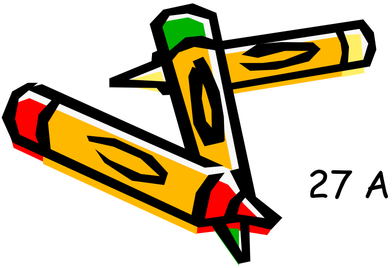
- Elimination rxns of quaternary ammonium hydroxides or tertiary amine oxides.



$$RCH_2CH_2\overset{CH_3}{\underset{CH_3}{\overset{|+}{\underset{|}{N}}}}CH_3\ HO^- \xrightarrow[\text{Hofmann elimination}]{\Delta} RCH{=}CH_2 + \overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{N}}}}CH_3 + H_2O$$

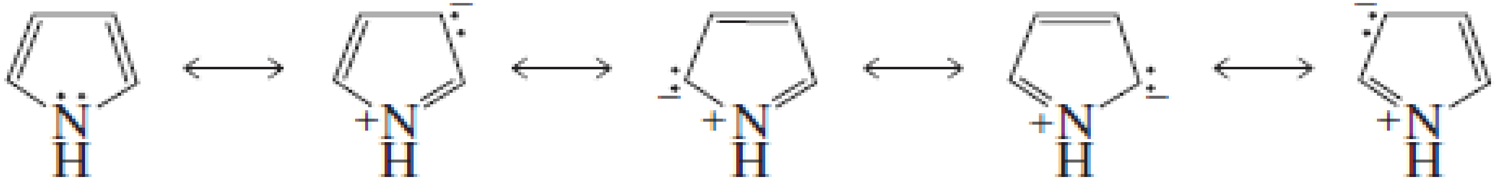
$$RCH_2CH_2\overset{CH_3}{\overset{|}{N}}CH_3 \xrightarrow{H_2O_2} RCH_2CH_2\overset{CH_3}{\underset{O^-}{\overset{|+}{\underset{|}{N}}}}CH_3 \xrightarrow[\text{Cope elimination}]{\Delta} RCH{=}CH_2 + \overset{CH_3}{\underset{OH}{\overset{|}{\underset{|}{N}}}}CH_3$$

in both eliminations, the proton is removed from the β-carbon bonded to the most hydrogens



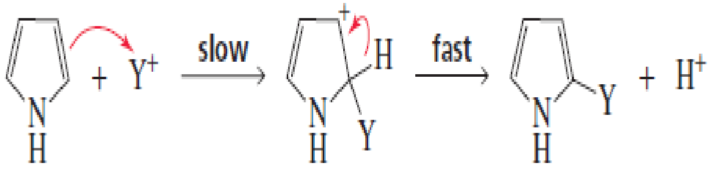
2.6 Electrophilic Substitution at Nitrogen

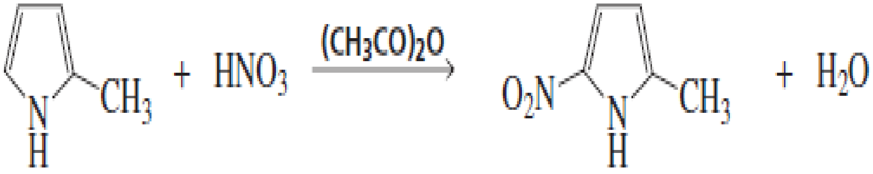
- ✓ Pyrrole is an extremely weak base b/c the pi-electrons shown as a lone pair are part of the cloud.
- ✓ The resonance contributors of pyrrole show that **N** donates the electrons depicted as a lone pair into the fi



resonance contributors of pyrrole

mechanism for electrophilic aromatic substitution





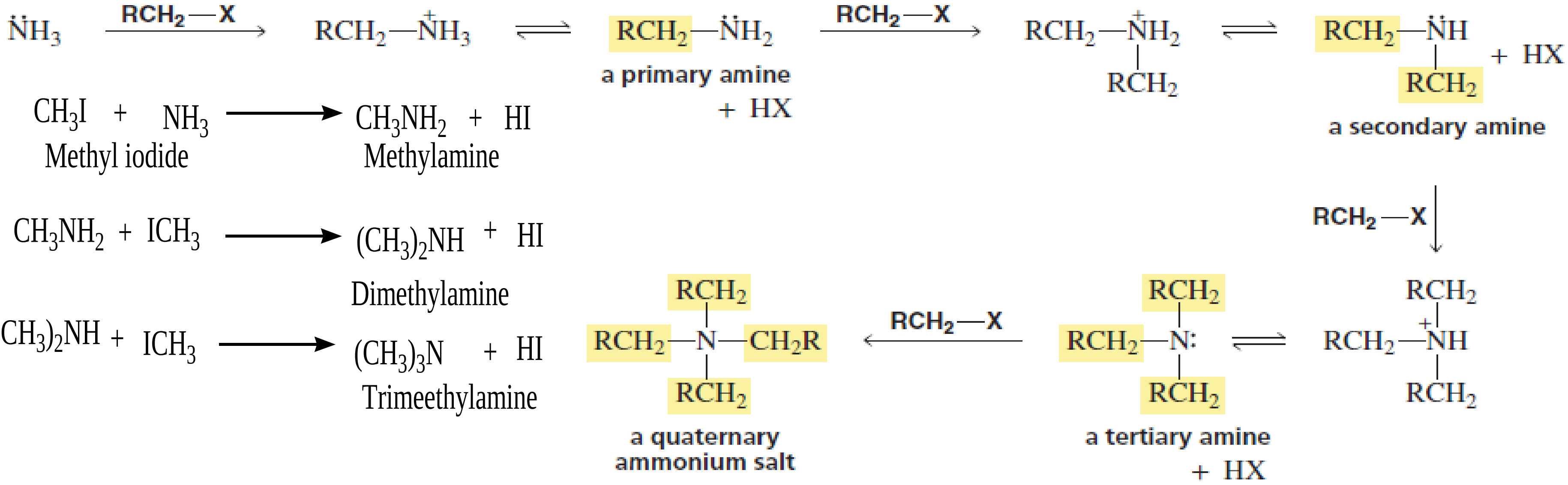
2-methyl-5-nitropyrrole

2.7 Preparation of 1º, 2º & 3ºAmines

1) Method of yielding mixture of amines

a) Reaction of alkyl halides with ammonia (NH_3)

- ✓ Amines can be prepared by heating alkyl halides with alcoholic ammonia in sealed tube.
- ✓ A mixture of **1º, 2º & 3ºAmines** is obtained.
- ✓ B/c NH_3 & amines are good nucleophiles, they readily undergo SN^2 rxns with alkyl halides.



$CH_3I + NH_3 \longrightarrow CH_3NH_2 + HI$

Methyl iodide → Methylamine

$CH_3NH_2 + ICH_3 \longrightarrow (CH_3)_2NH + HI$

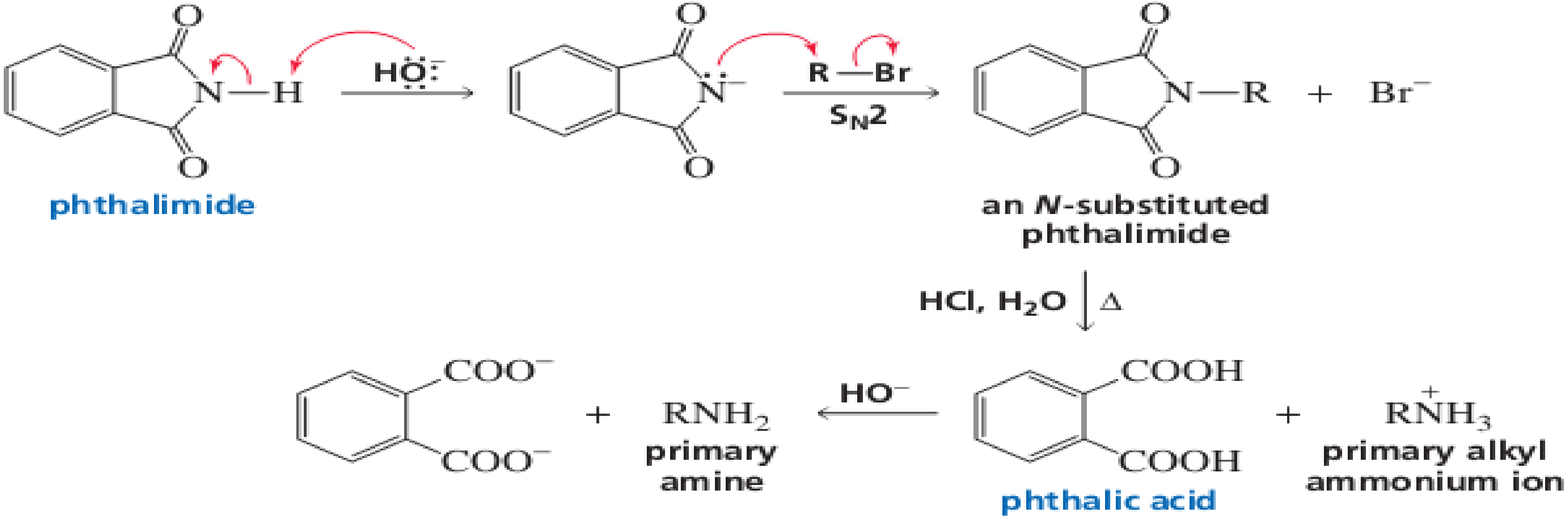
Dimethylamine

$(CH_3)_2NH + ICH_3 \longrightarrow (CH_3)_3N + HI$

Trimeethylamine

Preparation of 1º, 2º & 3ºAmines

- ✓ Although these SN^2 rxns can be used to synthesize amines, the yields are poor b/c it is difficult to stop the rxn after a single alkylation since ammonia and **1º, 2º & 3ºAmines** have similar reactivities..
- ✓ A much better way to prepare a **1º** amine is by means of a **Gabriel synthesis.**
- ✓ This rxn involves alkylating phthalimide & then hydrolyzing the N-substituted phthalimide.



Preparation of 1º, 2º & 3ºAmines

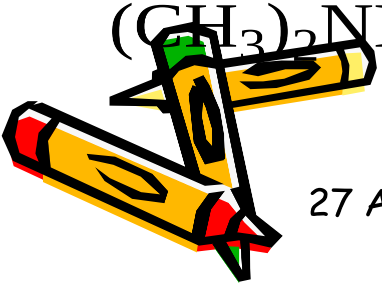
b) Reaction of alcohols with ammonia

- ✓ Amines can be prepared by passing the vapours of alcohol and ammonia over heated alumina at 400^0C.
- ✓ A mixture of 1º, 2º & 3ºamine is produced.

$$\underset{\text{Methanol}}{CH_3OH} + NH_3 \xrightarrow[\Delta]{Al_2O_3} \underset{\text{Methylamine}}{CH_3NH_2} + H_2O$$

$$CH_3NH_2 + HOCH_3 \longrightarrow \underset{\text{Dimethylamine}}{(CH_3)_2NH} + H_2O$$

$$(CH_3)_2NH + HOCH_3 \longrightarrow \underset{\text{Trimeethylamine}}{(CH_3)_3N} + H_2O$$



Preparation of 1º, 2º & 3ºAmines

2) Methods for primary amines : a) Reduction of Nitroalkane

✓ Primary amine can obtained by reduction of nitroalkanes with H_2 & Ni (or Pt) or lithium aluminium hydride.

$$\underset{\text{Nitromethane}}{CH_3NO_2} + 3H_2 \xrightarrow[\Delta]{Pt} \underset{\text{Methylamine}}{CH_3NH_2} + 2H_2O$$

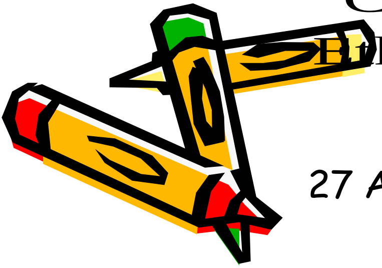
$$\underset{\text{Nitroethane}}{CH_3CH_2NO_2} + 6[H] \xrightarrow[\text{ether}]{LiAlH_4} \underset{\text{Ethylamine}}{CH_3CH_2NH_2} + 2H_2O$$

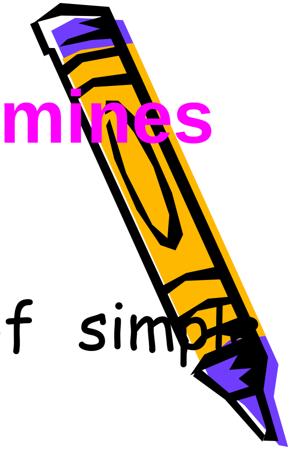
b) Reduction of Nitriles

✓ Primary amine can be prepared by reduction of nitriles (alkyl cyanides) with H_2 + Ni or lithium aluminium hydride.

$$\underset{\text{Methyl cyanide}}{CH_3CN} + 4[H] \xrightarrow[\text{ether}]{LiAlH_4} \underset{\text{Ethylamine}}{CH_3CH_2NH_2}$$

$$\underset{\text{Ethyl cyanide}}{CH_3CH_2CN} + 2H_2 \xrightarrow{Ni} \underset{\text{Propylamine}}{CH_3CH_2CH_2NH_2}$$

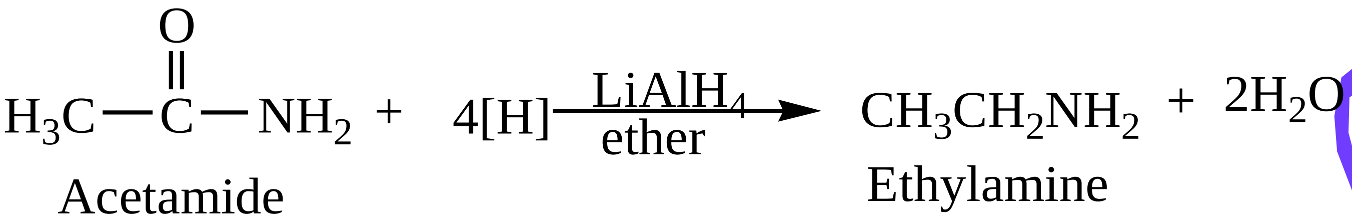




Preparation of 1º, 2º & 3ºAmines

c) Reduction of amides

Primary amine can be obtained by reduction of simple amides with lithium aluminium hydride.



$$H_3C-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2 + 4[H] \xrightarrow[ether]{LiAlH_4} CH_3CH_2NH_2 + 2H_2O$$

Acetamide

Ethylamine

3) Method for secondary amines

a) Reduction of primary amines with alkyl halides

✓ When primary amine is heated with alkyl halides, a dialkyl ammonium salt is formed. This when treated with NaOH solution yields the free secondary amines.

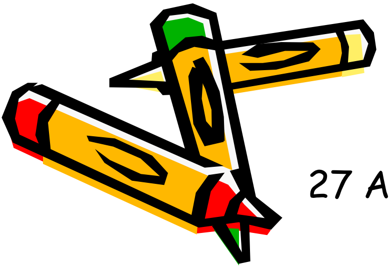
$$R-NH_2 + RX \longrightarrow R_2NH + HX \longrightarrow R_2N^+H_2X^-$$

1^0Amine

2^0Amine

$$R_2N^+H_2X^- + NaOH \longrightarrow R_2NH + NaX + H_2O$$

2^0Amine



Preparation of 1º, 2º & 3ºAmines

b) Reduction of N-substituted amides

✓ Secondary amine can be obtained by reduction of N-substituted amides with lithium aluminium hydride.

$$H_3C-\overset{\overset{O}{\|}}{C}-\overset{H}{N}-CH_3 + 4[H] \xrightarrow[\text{ether}]{LiAlH_4} CH_3CH_2NHCH_3 + H_2O$$

N-methylacetamide

Ethylmethylamine

c) Reduction of Isonitriles

✓ Secondary amine may be obtained by reduction of isonitriles (isocyanides) with H_2 and Pt.

$$R-\overset{+}{N}\equiv\overset{-}{C} + H_2 \xrightarrow{Pt} R-\overset{H}{\overset{|}{N}}-CH_3$$

Alkyl isocyanide

2^0 Amine

Preparation of 1º, 2º & 3ºAmines

4) Methods for tertiary amines.

a) Reaction of alkyl halides with ammonia

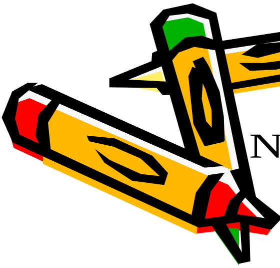
- ✓ When alcoholic ammonia solution is heated with an excess of alkyl halide, a trialkylammonium halide is formed.
- ✓ When the product is treated with NaOH solution, it gives tertiary amine.

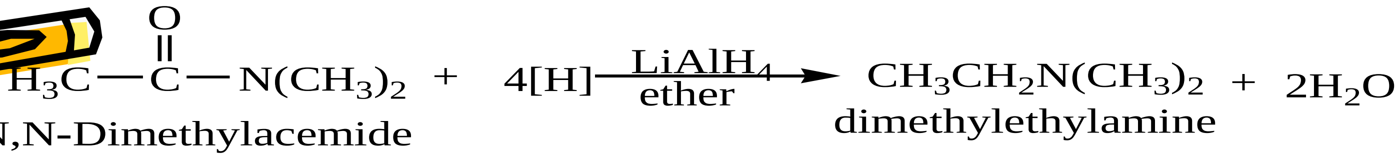
$$3RX + NH_3 \longrightarrow R_3N^+HX^- + 2HX$$

$$R_3N^+HX^- + NaOH \longrightarrow \underset{3^0\text{amine}}{R_3N} + NaX + H_2O$$

b) Reduction of N, N-disubstituted amides

- ✓ Tertiary amines may be obtained by reduction of N, N-disubstituted amides with lithium aluminium hydride.





$$\underset{\text{N,N-Dimethylacemide}}{H_3C-\overset{\overset{O}{\|}}{C}-N(CH_3)_2} + 4[H] \xrightarrow[\text{ether}]{LiAlH_4} \underset{\text{dimethylethylamine}}{CH_3CH_2N(CH_3)_2} + 2H_2O$$

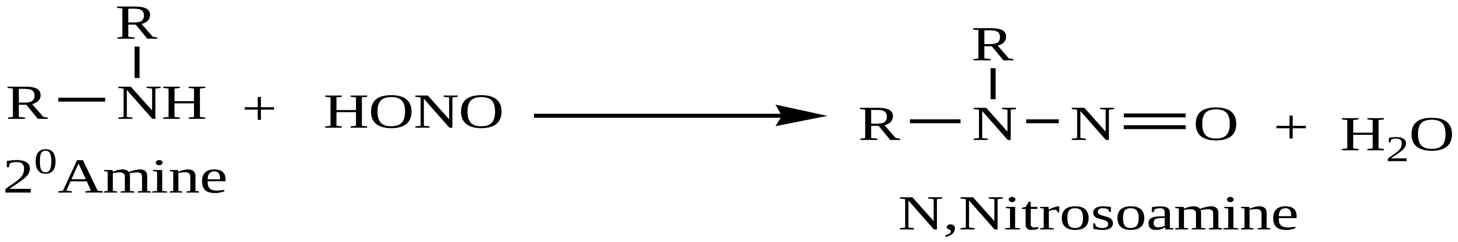
2.8 Reactions with Nitrous Acid

- Nitrious acid (HONO) is unstable substance and therefore they rect with amines.

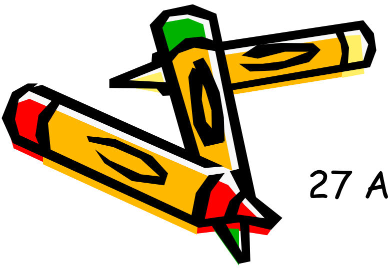
a) Primary amines react with nitrous acids to form alcoho and nitrogen gas.

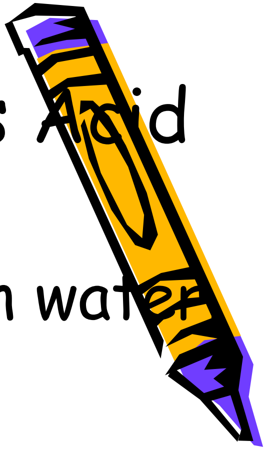
$$\underset{1^0\text{Amine}}{R-NH_2} + HONO \longrightarrow \underset{\text{Alcohol}}{ROH} + N_2\uparrow + H_2O$$

b) Secondary amines react with nitrous acids to form N-nitrosoamines which are water insoluble yellow oils.



$$\underset{2^0\text{Amine}}{R-\overset{\displaystyle R}{\overset{|}{N}}H} + HONO \longrightarrow \underset{\text{N,Nitrosoamine}}{R-\overset{\displaystyle R}{\overset{|}{N}}-N=O} + H_2O$$





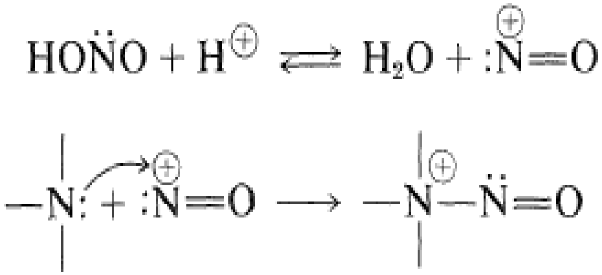
Reactions with Nitrous Acid

c) Tertiary amines react with nitrous acids to form trialkylammonium nitrite salts which are soluble in water

$R_3N + HONO \longrightarrow$ (complex products, but no N_2 evolution)

$$\underset{3^0\text{Amine}}{R_3N} + HONO \longrightarrow R_3\overset{+}{N}HO_2^-$$

Trialkyl ammonium nitrite



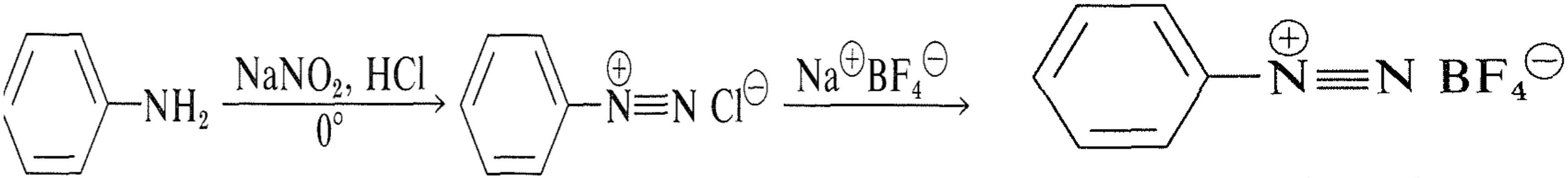
$$HO\ddot{N}O + H^{\oplus} \rightleftharpoons H_2O + :\overset{\oplus}{N}=O$$

$$-\ddot{N}: + :\overset{\oplus}{N}=O \longrightarrow -\overset{\oplus}{N}-\ddot{N}=O$$

- Nitrous acid is unstable and always is prepared as needed, usually by mixing a solution, $NaNO_2$ with a strong acid at 0^0C.
- These conditions provide a source of NO+

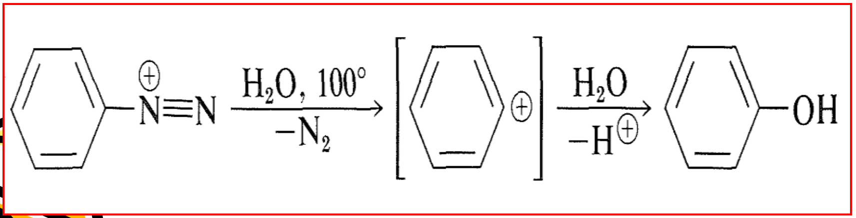
2.9 Reactions of Aryl Diazonium Intermediates

- ✓ Unlike primary alkylamines, primary arenamines react with nitrous acid at 0^0C to give diazonium ions that, in most cases, are stable enough to be isolated as crystalline BF salts.
- ✓ Other salts can be isolated, but some of these, such as benzenediazonium chloride, in the solid state may decompose with explosive violence:

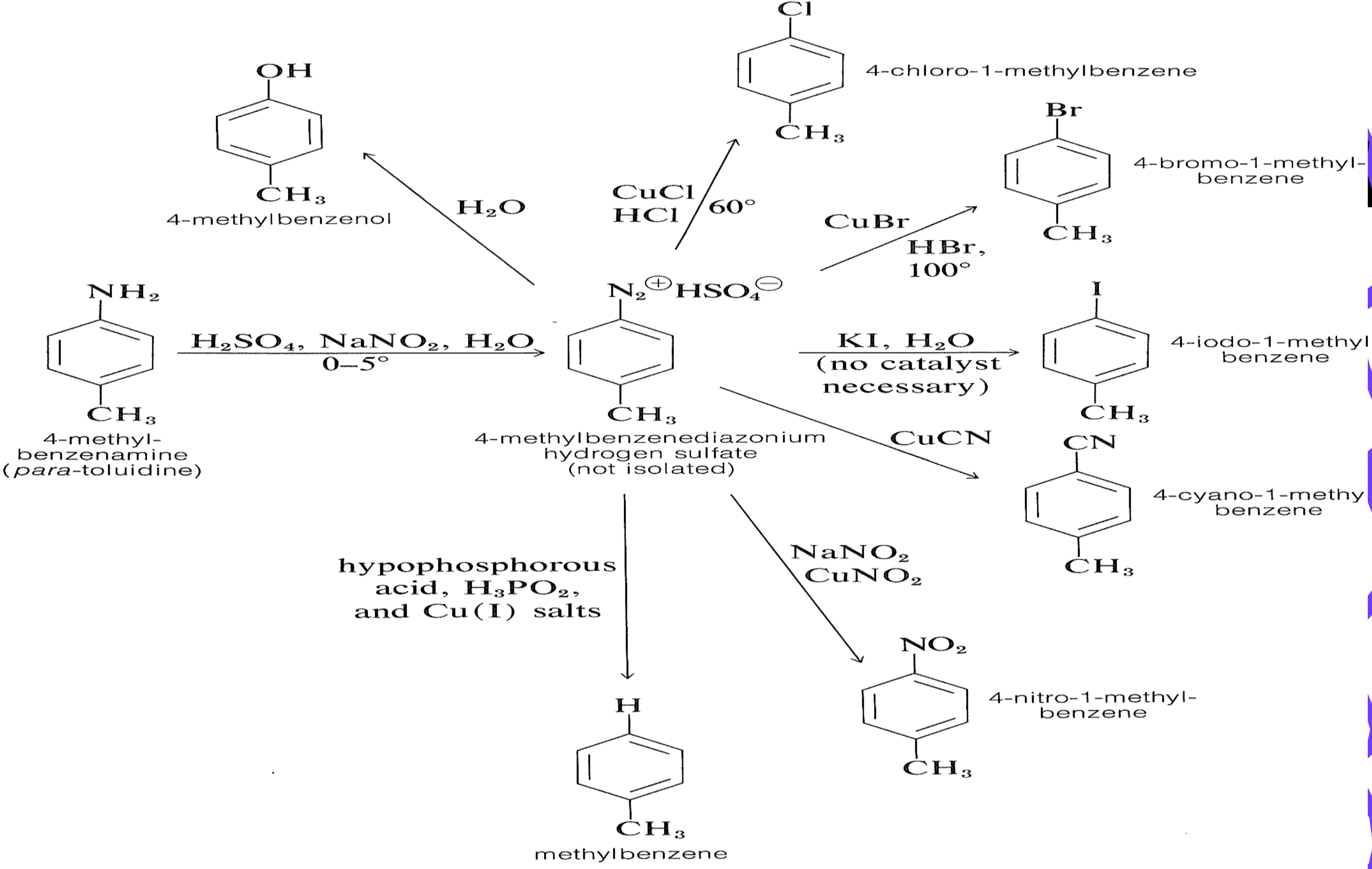


benzenediazonium chloride (water soluble)

benzenediazonium fluoroborate (water insoluble)

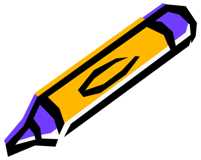


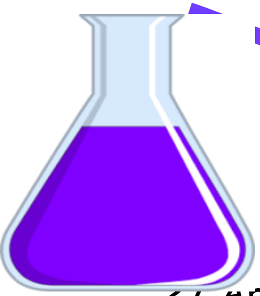
2.9 Rxns of Aryl Diazonium Intermediates: applications



Chapter 3

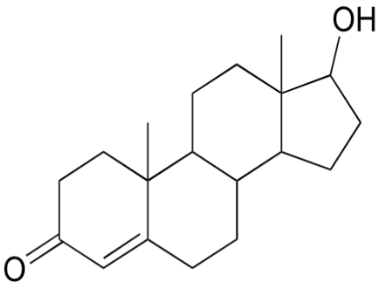
Reactions of Carbonyl Compounds



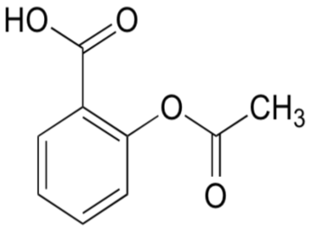


Introduction to Carbonyl Compounds in use

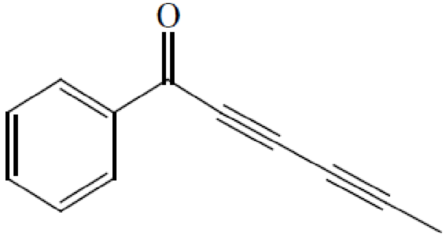
Introduction to Carbonyl Compounds



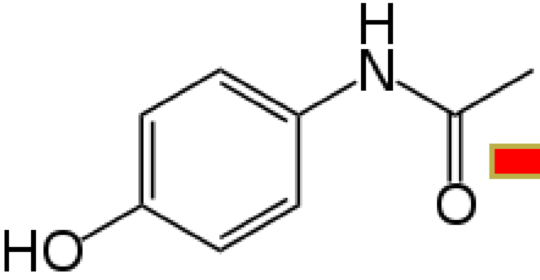
testosterone



acetylsalicylic acid
(aspirin)

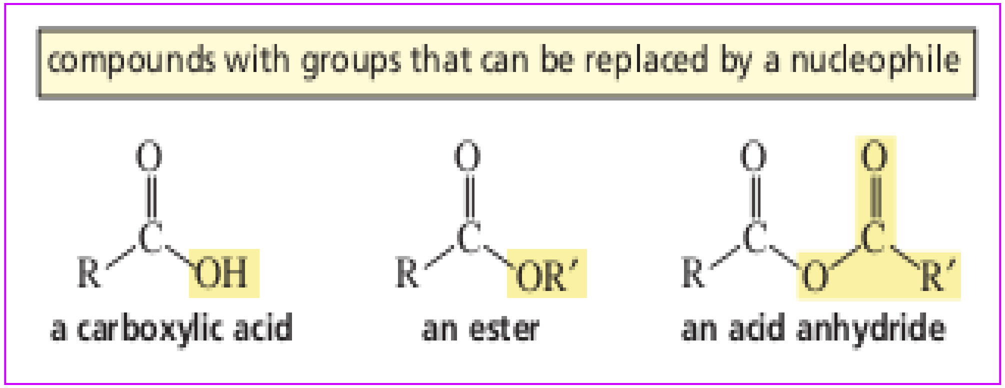


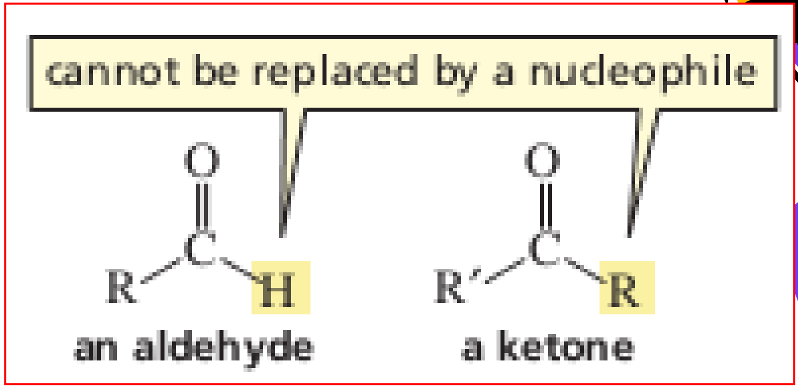
Capilin

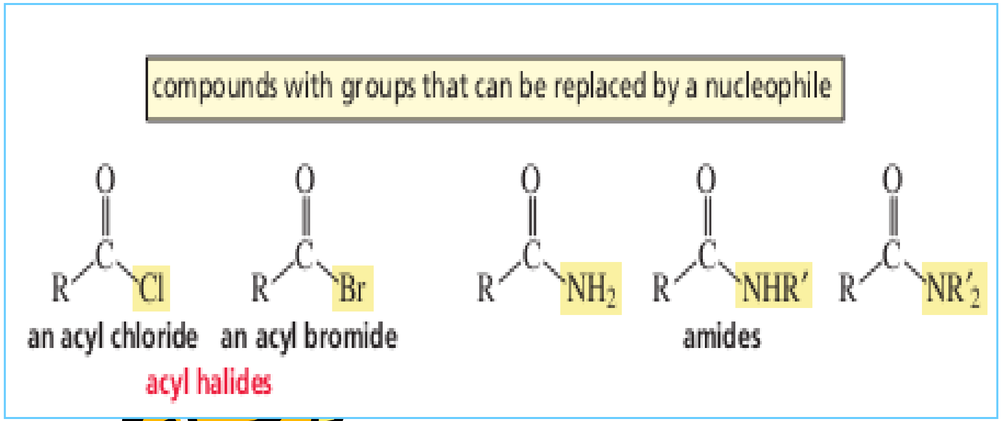


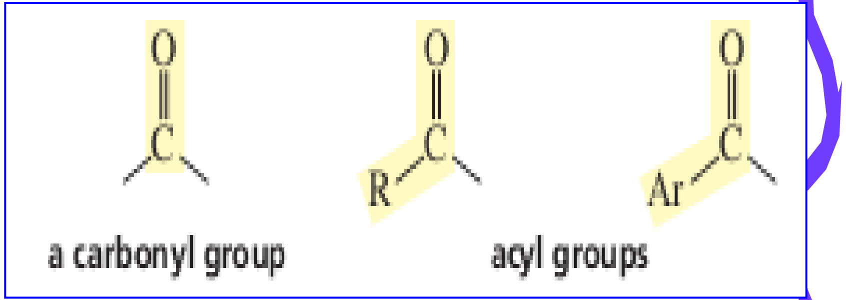
Introduction

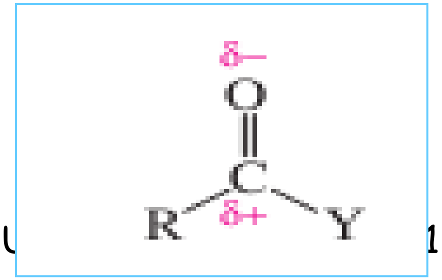
- Carbonyl cpds can be placed in one of two classes:
- Class I   Class II





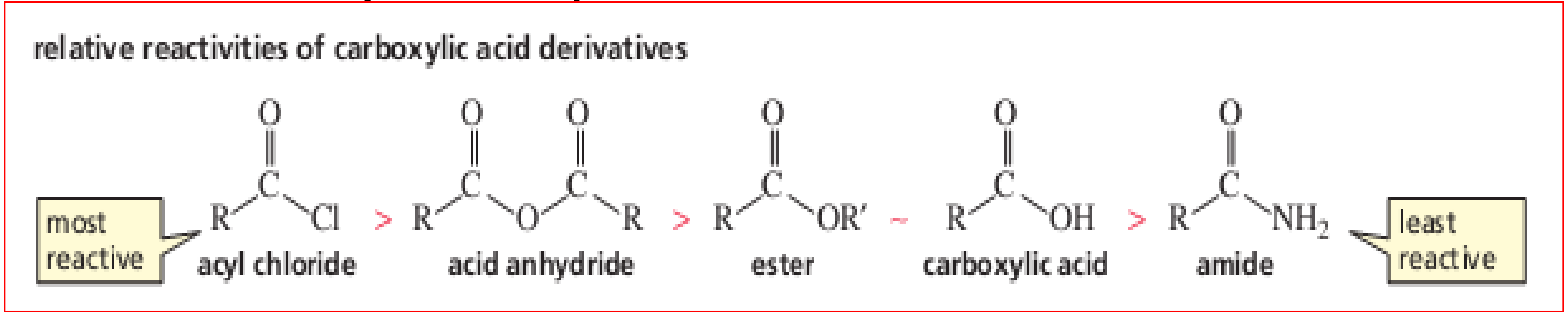


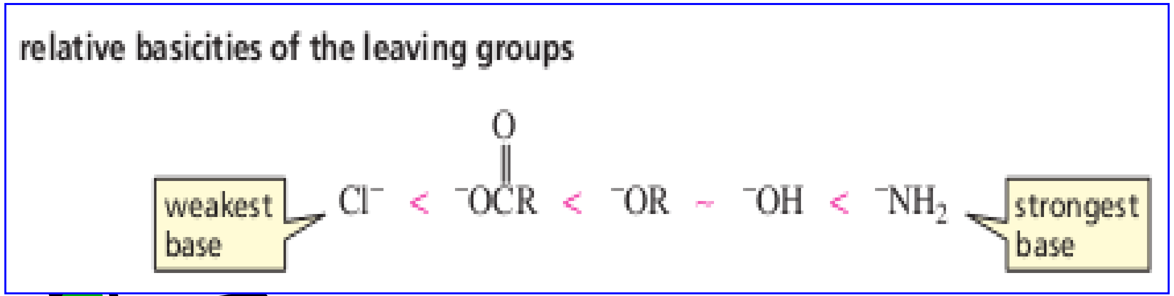


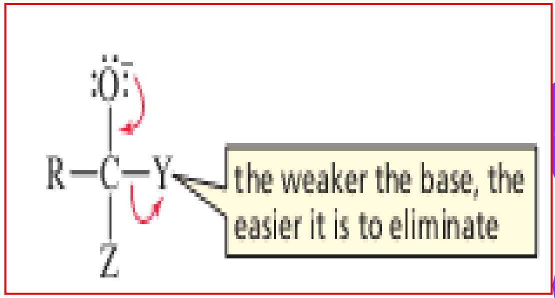


Introduction

- The reactivity of carbonyl cpds resides in the polarity of the carbonyl group; oxygen is more EN than C.
- The carbonyl C, is an electrophile, so that it will be attacked by nucleophiles.

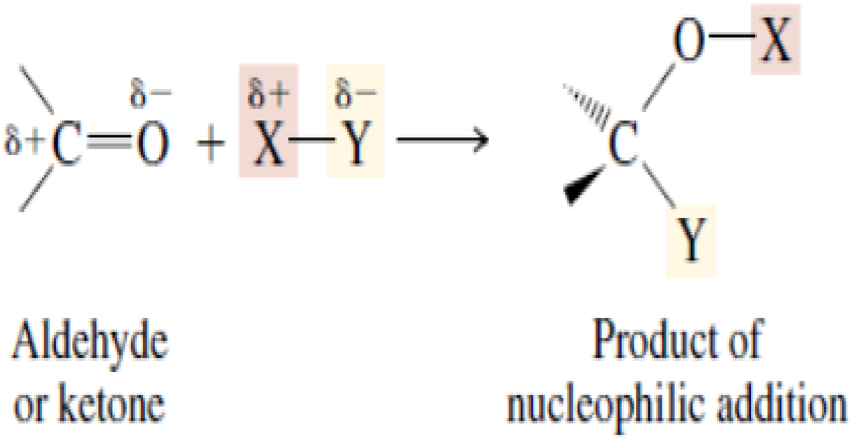

relative reactivities of carboxylic acid derivatives

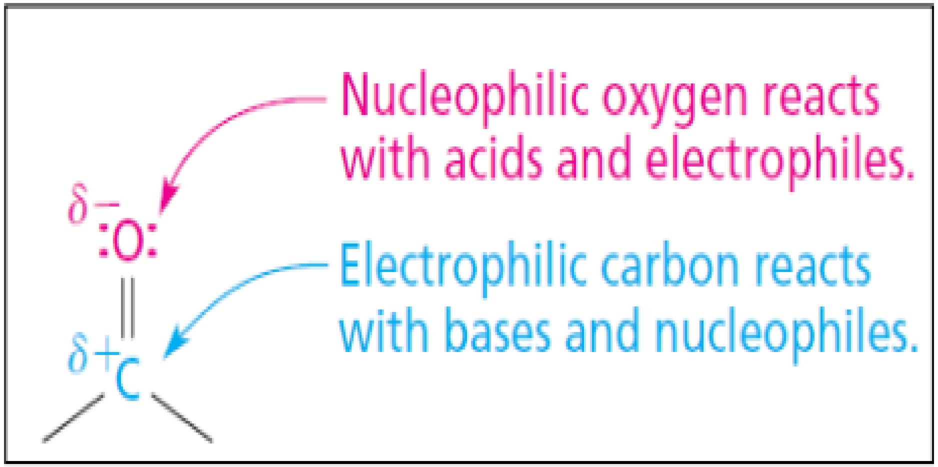

relative basicities of the leaving groups



Introduction

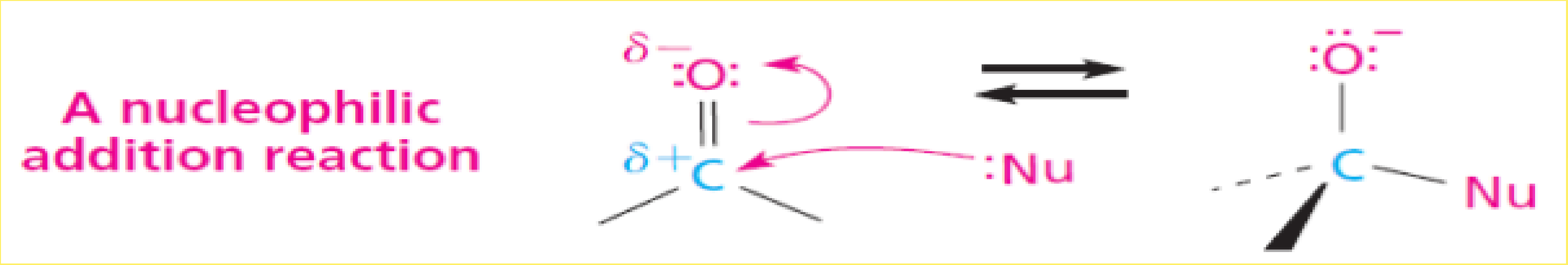
- ✓ A nucleophilic addition rxn is the addition of a nucleophile (:Nu) to the electrophilic carbon (C) of an aldehyde or ketone.
- ✓ As an e- pair from :Nu forms a bond to the C, an e- pair from the C=O bond moves toward O, giving an alkoxide ion, RO.
- ✓ addition rxns represented in the general equation:



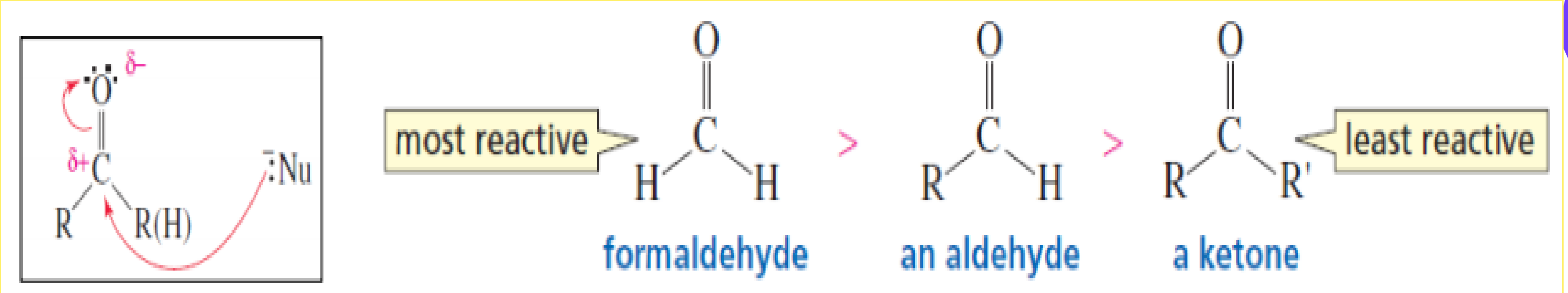


Carbonyl Compounds rxns

- ✓ The reactivity of carbonyl cpds resides in the polarity of the carbonyl group; O is more electronegative (EN) than C.
- ✓ The carbonyl C is an electrophile, so it will be attacked by :Nu



- ✓ The carbonyl group is polar b/c O, being more EN than C, has a greater share of the e-s of the double bond.

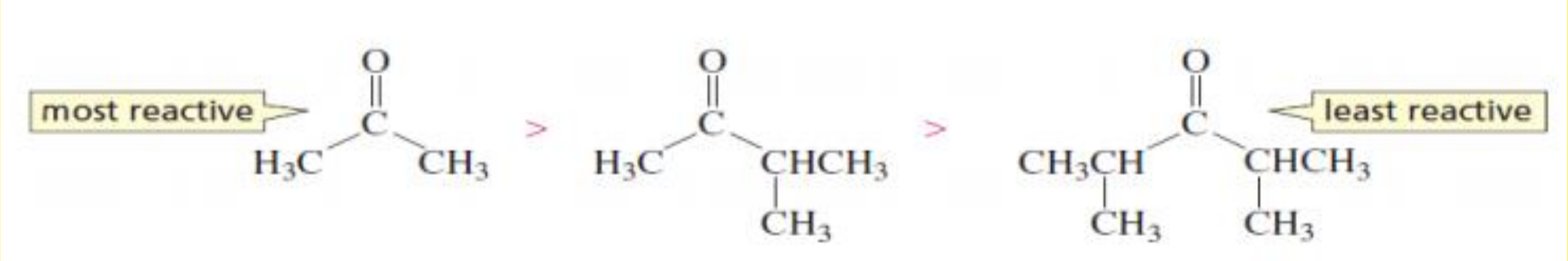


Carbonyl Compounds rxns

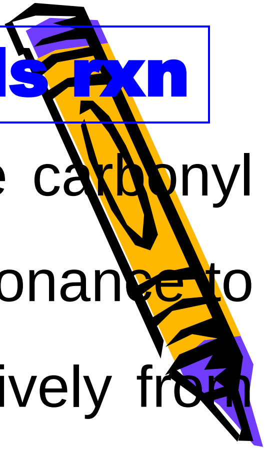
- ✓ An aldehyde has a greater partial positive charge on its carbonyl C than does a ketone b/c H is e- withdrawing compared with an alkyl group.
- ✓ So, an aldehyde is less stable than a ketone, w/c makes it more reactive toward nucleophilic attack.
- ✓ Steric factors also contribute to the greater reactivity of an aldehyde.
- ✓ The carbonyl C of an aldehyde is more accessible to the :Nu than is the carbonyl C of a ketone.

Carbonyl Compounds rxn

- ✓ Ketones have greater steric crowding in their TS, so they have less stable TS than aldehydes.
- ✓ For the same reason, relatives reactivity ketones with small alkyl groups bonded to the carbonyl C are more reactive than ketones with large alkyl groups.

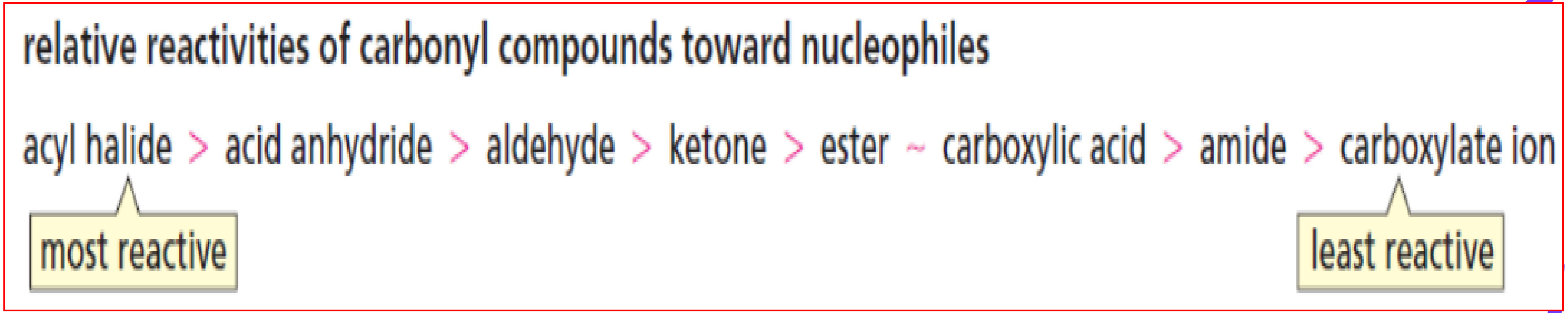


- ✓ Aldehydes & ketones are less reactive than acyl chlorides & acid anhydrides, but are more reactive than esters & amides toward :Nu.



Carbonyl Compounds rxn

- The weaker the basicity (Y:) of the more reactive is the carbonyl group b/c weak bases are less able to donate e-s by resonance to the carbonyl C & are better able to withdraw e-s inductively from the carbonyl C.



relative reactivities of carbonyl compounds toward nucleophiles

acyl halide > acid anhydride > aldehyde > ketone > ester ~ carboxylic acid > amide > carboxylate ion

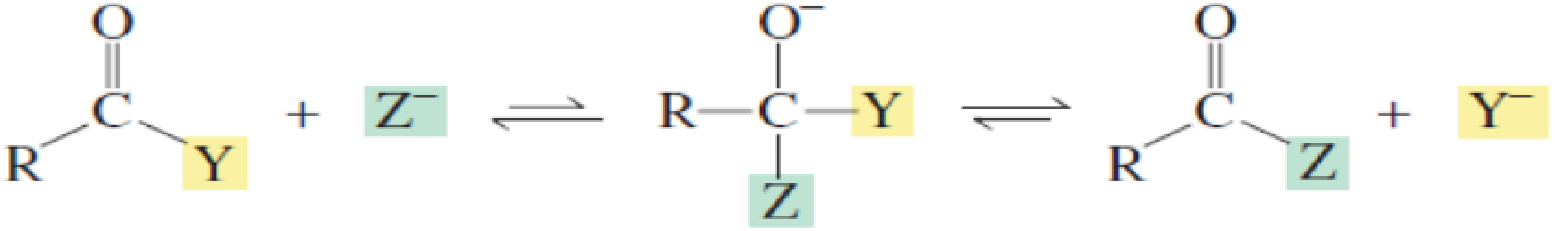
most reactive

least reactive

- aldehydes & ketones are not as reactive as carbonyl cpds in w/c Y: is a very weak base (acyl halides & acid anhydrides), but are more reactive than carbonyl cpds in which Y: is a relatively strong base (carboxylic acids, esters, and amides).

Carbonyl Compounds rxn

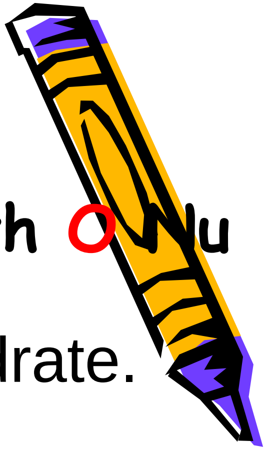
- The reactivity of an aldehyde or a ketone toward nucleophiles to form substitution products:



Product of nucleophilic substitution

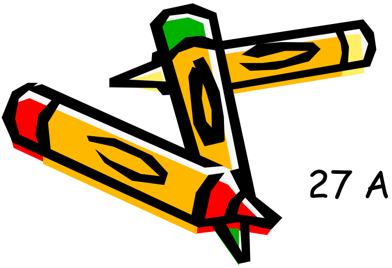
- Aldehydes & ketones react with :nu to form addition products, not substitution products, b/c no LG on the aldehydes & ketones.
- Thus, aldehydes & ketones undergo nucleophilic addition rxns, whereas carboxylic acid derivatives undergo nucleophilic acyl substitution rxns.

3.1 Addition Reactions



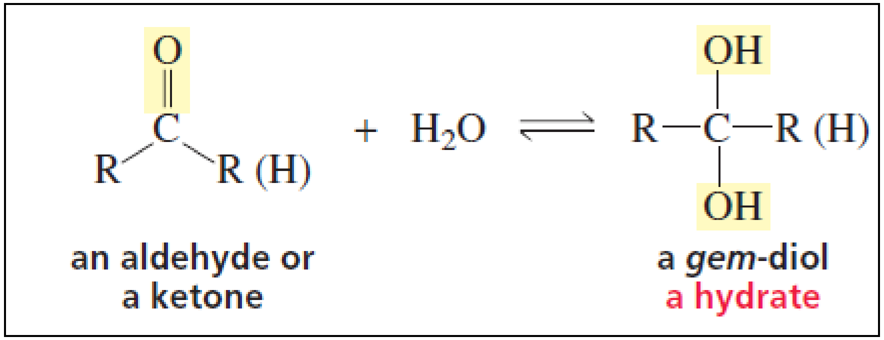
3.1.1 Hydrates: Rxns of Aldehydes & Ketones with O Nu

- Water adds to an aldehyde or a ketone to form a hydrate.
- A **hydrate** is a molecule with two OH groups on the same C.
- Hydrates are also called **gem-diols (gem** comes from geminus, Latin for “twin”).
- Hydrates of aldehydes/ ketones are too unstable to be isolated b/c the tetrahedral **C** is attached to two oxygen atoms.

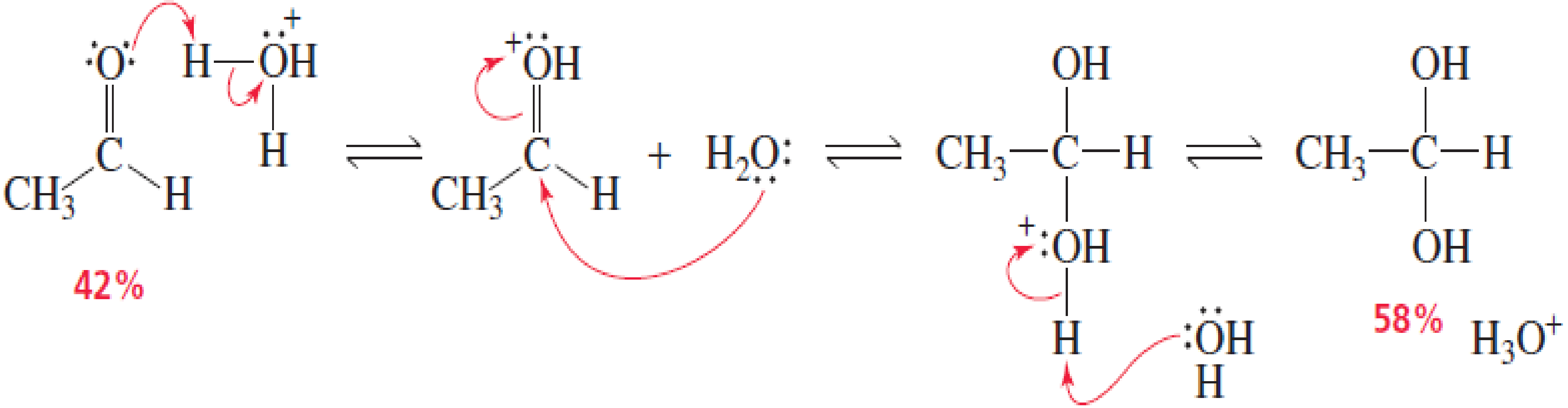


Hydrates

- ✓Water is a poor Nu & adds slowly to a carbonyl group.
- ✓The rate of the rxn can be increased by an acid catalyst.



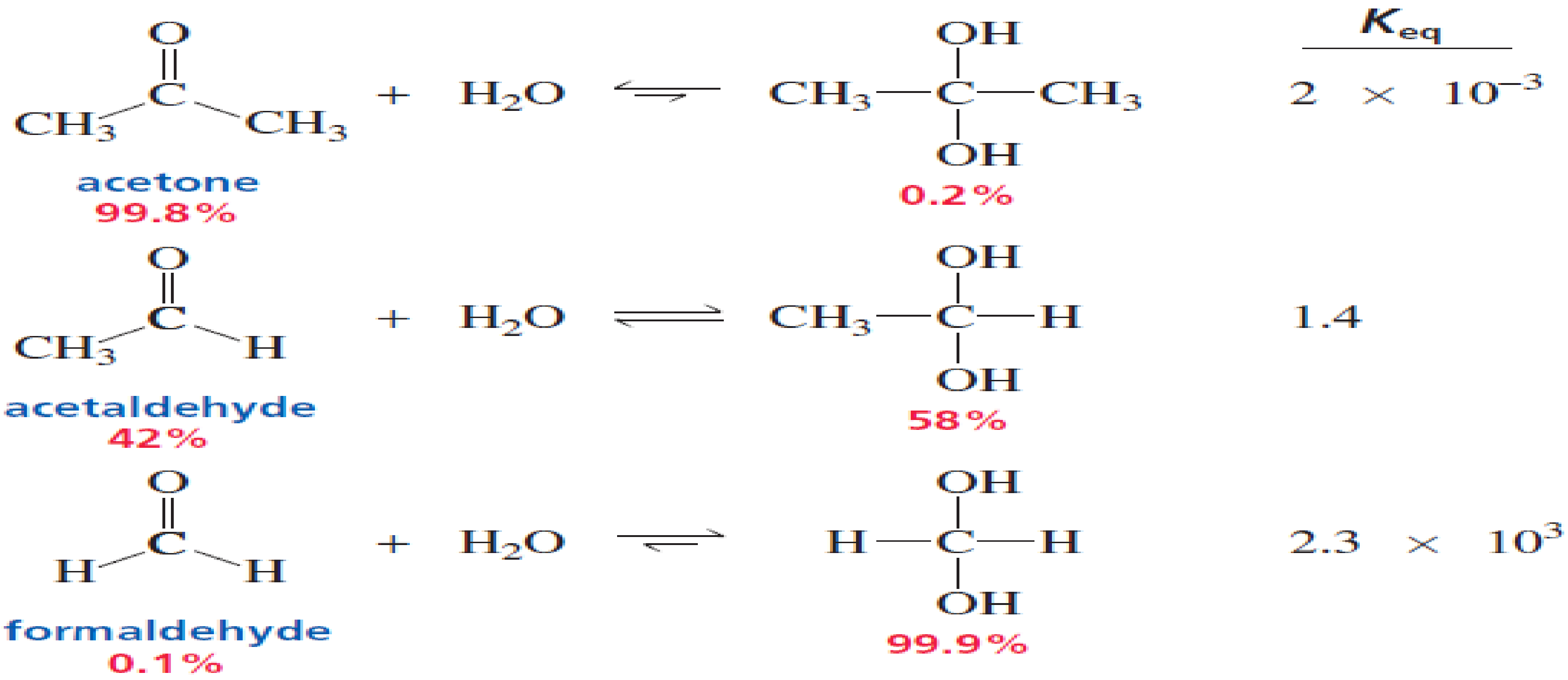
mechanism for acid-catalyzed hydrate formation



Hydrates

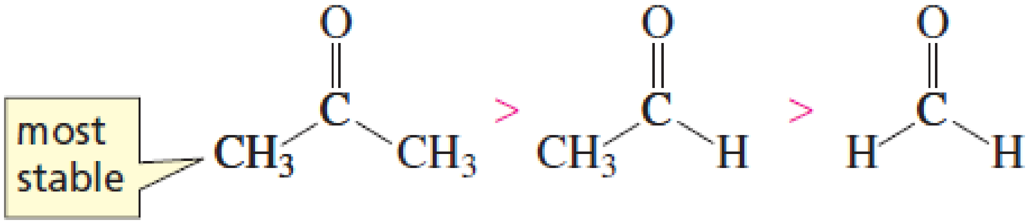
✓The extent to which an aldehyde or a ketone is hydrated in an aqueous solution depends on the aldehyde or ketone.

✓ e.g, only 0.2% of acetone is hydrated at equilibrium, but 99.9% of formaldehyde is hydrated.

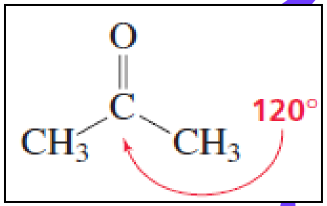


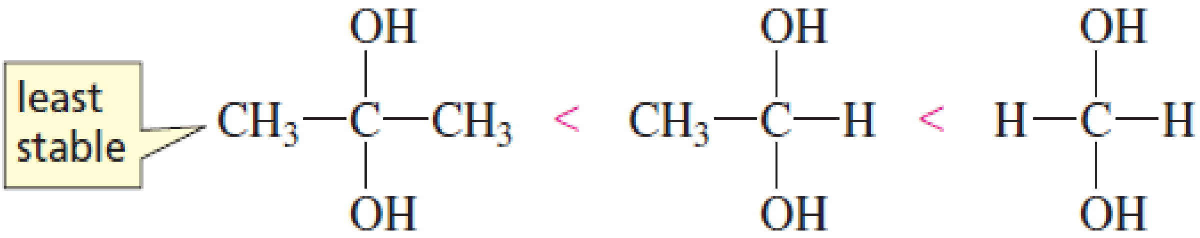
Hydrates

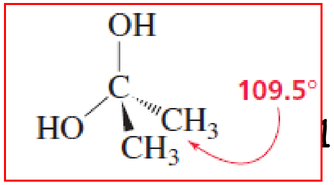
- K_{eq} for a rxn depends on the relative stabilities of the reactants and products.
- K_{eq} for hydrate formation, depends on the relative stabilities of the carbonyl compound and the hydrate.
- EDG alkyl groups make a carbonyl cpd *more stable (less* reactive).

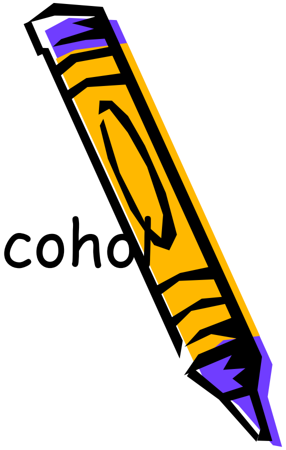


- In contrast, alkyl groups make the hydrate *less stable b/C of steric interactions* b/n the alkyl groups.



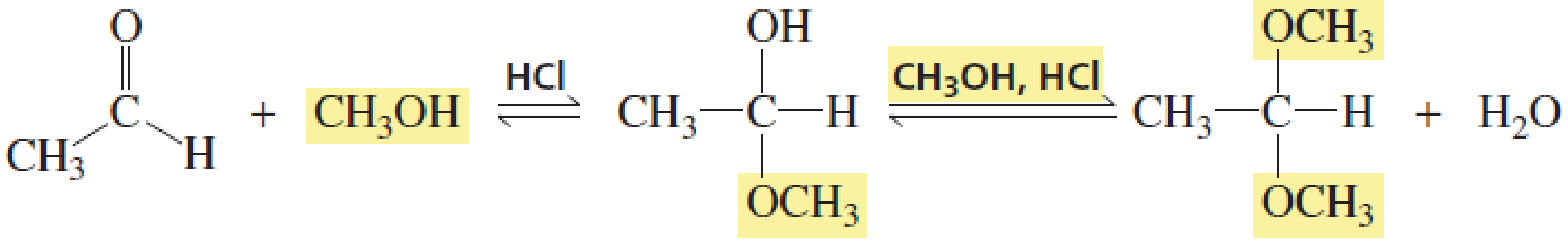




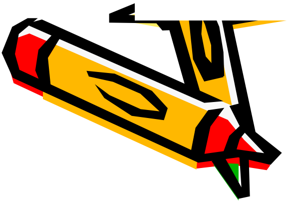


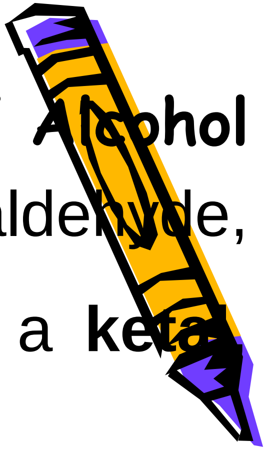
3.1.2 Hemiacetals: Addition of Alcohol

- The product formed when one equivalent of an alcohol adds to an aldehyde is called a **hemiacetal**.
- The product formed when a second equivalent of alcohol is added is called an **acetal**.
- Like water, an alcohol is a poor Nu, so an acid catalyst is required for the rxn to take place at a reasonable rate.



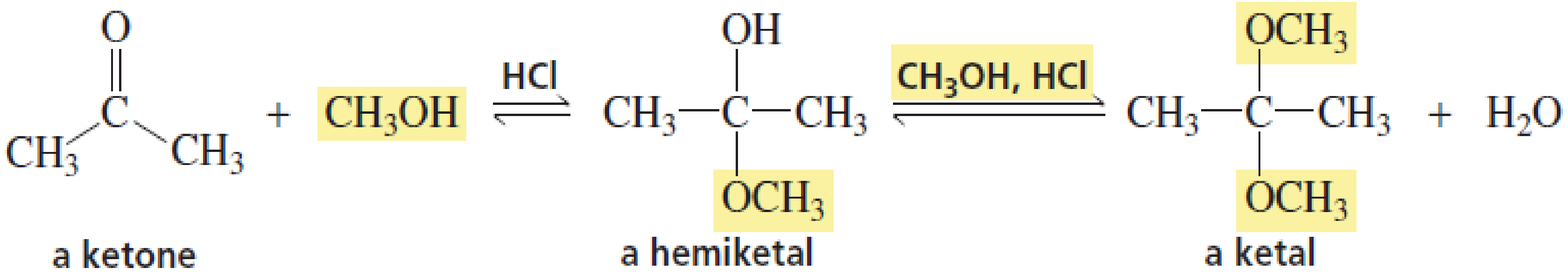
an aldehyde a hemiacetal an acetal





Hemiacetals: Addition of Alcohol

- When the carbonyl cpd is a ketone instead of an aldehyde, the addition products are called a hemiketal and a **ketal**, respectively.

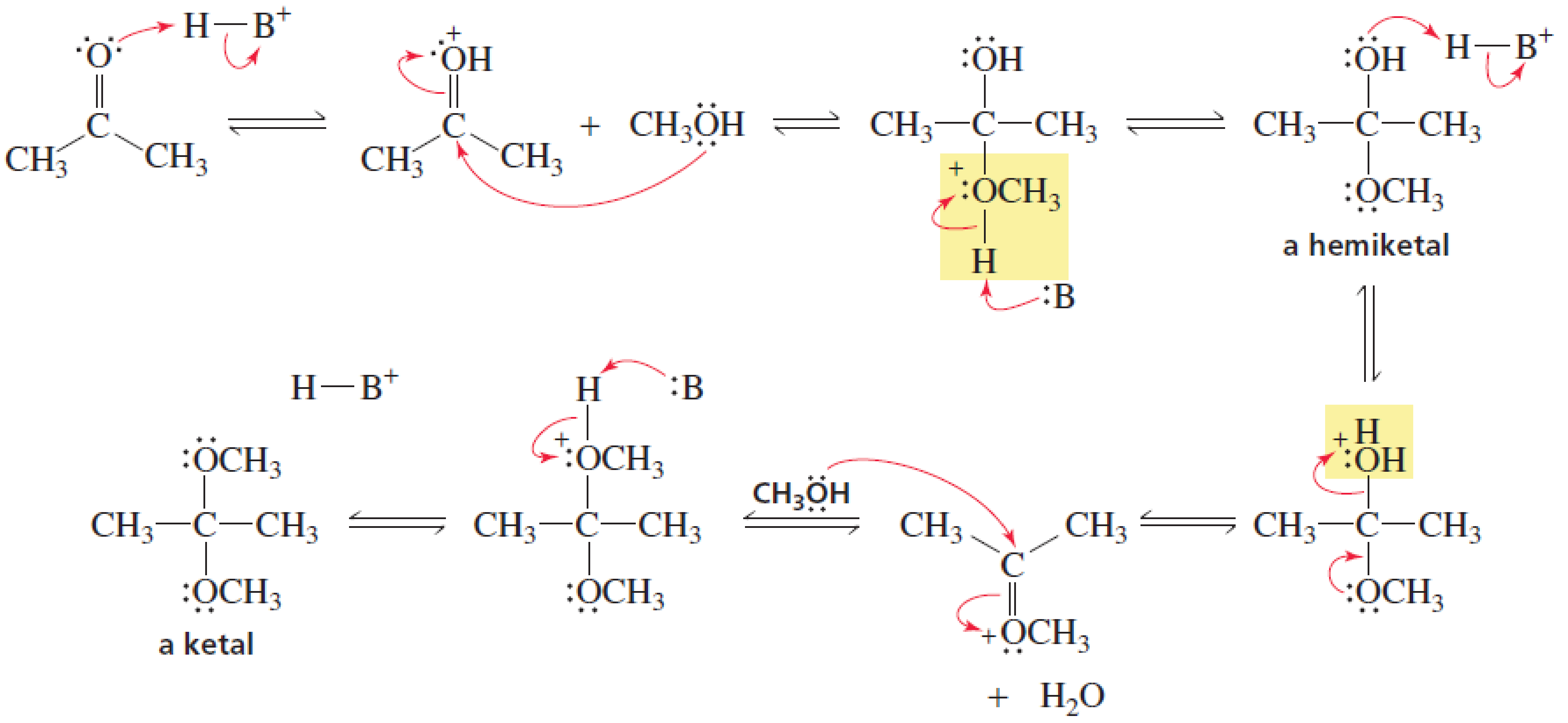


- *Hemi is the Greek word for "half."*
- *When one equivalent of alcohol has added to an* aldehyde or a ketone, the cpd is halfway to the final acetal or ketal, which contains groups from two equivalents of alcohol.

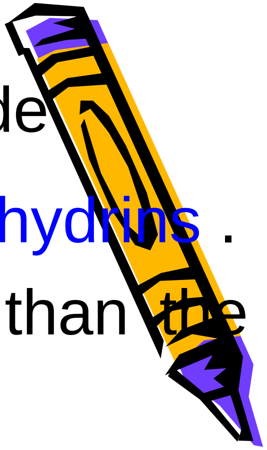
Hemiacetals: Addition of Alcohol

- In the first step of acetal (or ketal) formation, the acid protonates the carbonyl oxygen, making the carbonyl carbon more susceptible to nucleophilic attack.

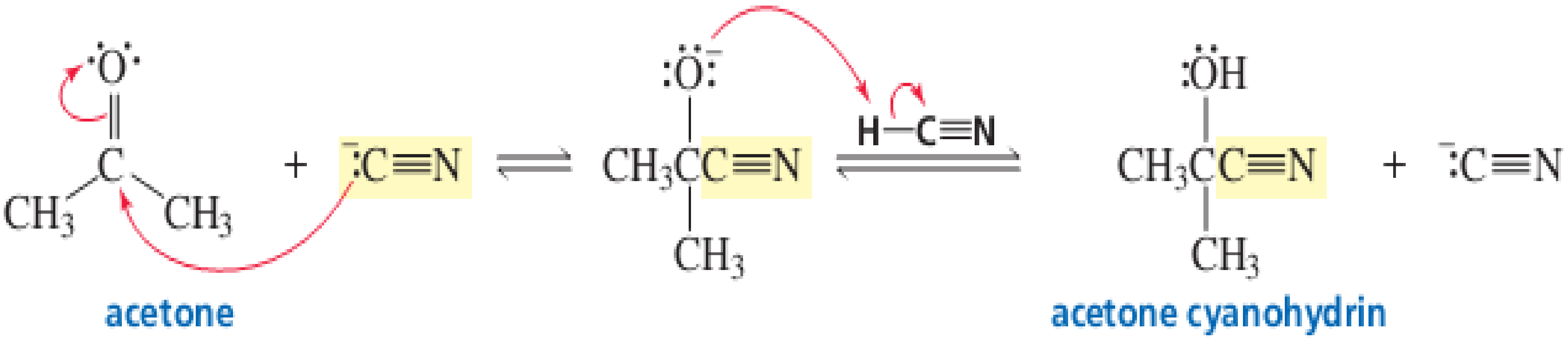
mechanism for acid-catalyzed acetal or ketal formation

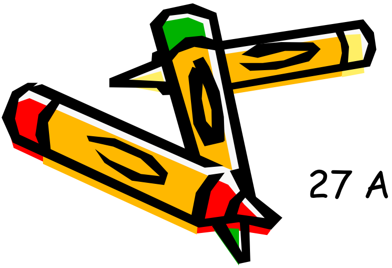


3.1.3 Cyanohydrins: Rxn with Hydrogen Cyanide



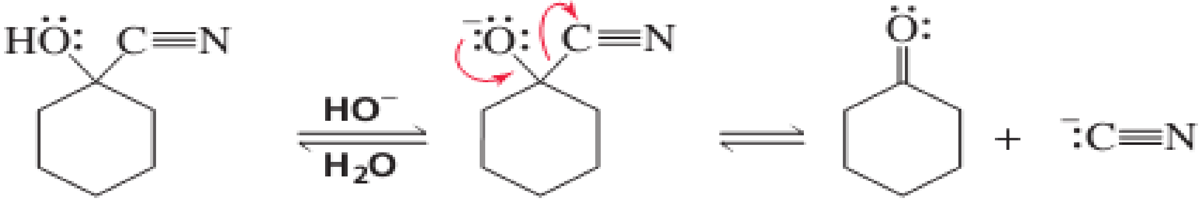
- ✓ **HCN** adds to aldehydes and ketones to form cyanohydrins .
- ✓ This rxn forms a product with one more **C** atom than the reactant.
- ✓ In the 1st step of the rxn, the **CN**- attacks the carbonyl **C**.
- ✓ The alkoxide ion then accepts proton from an undissociated molecule of **HCN**.



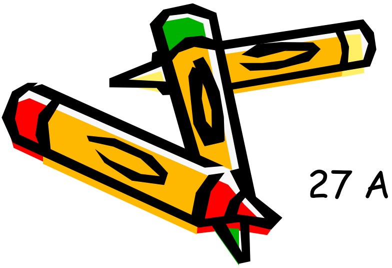


Cyanohydrins: Rxn with Hydrogen Cyanide

- ✓ B/c **HCN** is a toxic gas, the best way to carry out this rxn is to generate **HCN** during the rxn by adding HCl to a mixture of the aldehyde/ketone & excess NaCN.
- ✓ Excess NaCN is used in order to make sure that some cyanide ion is available to act as a nucleophile.
- ✓ Cyanohydrins are stable because the OH group will not eliminate the cyano group.
- ✓ If the OH group loses its H, the **CN** group will be eliminated.

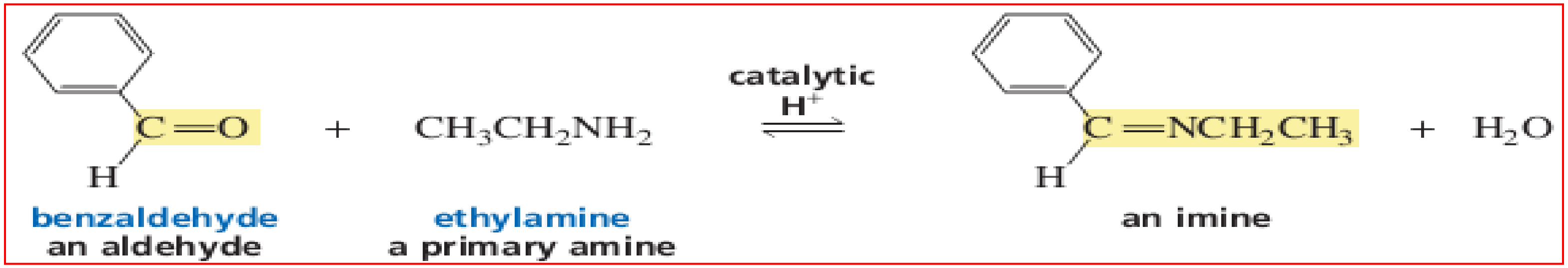


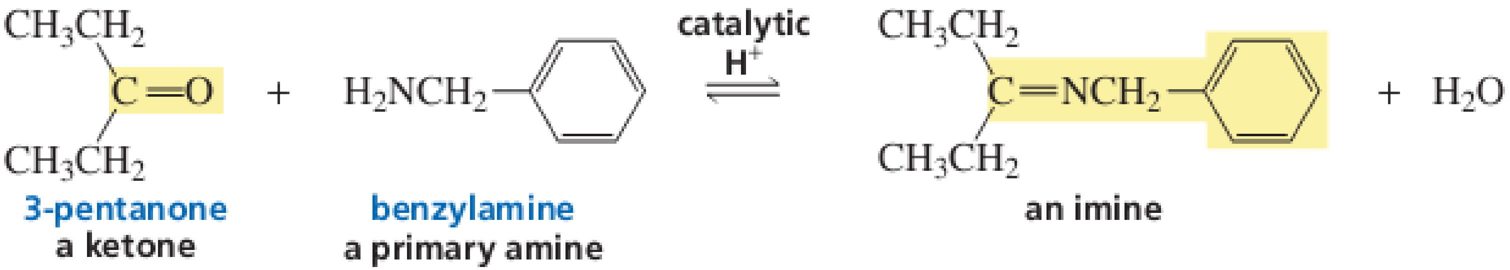
cyclohexanone cyanohydrin



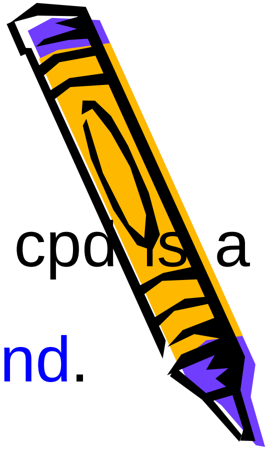
3.1.4 Carbinolamine: Addition of 1^0 Amines

- ✓ Aldehydes & ketones react with **1^0** amines to form imines.
- ✓ The rxn requires a catalytic (small) amount of acid.





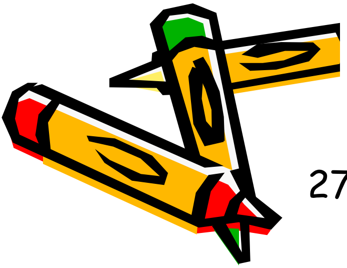
- ✓ In the first step of the mechanism for imine formation, the amine attacks the carbonyl C.
- ✓ The neutral tetrahedral intermediate, called a carbinolamine is in equilibrium with two protonated forms.



3.1.2 Addition of Grignard Reagent

- ✓ Addition of a Grignard reagent (GR) to a carbonyl cpd is a versatile rxn that leads to the formation of a new bond.
- ✓ The rxn can produce cpds with a variety of structures b/c both the structure of the carbonyl cpd & the structure of the GR can be varied.
- ✓ GR can be prepared by adding an alkyl halide to magnesium shavings in diethyl ether.

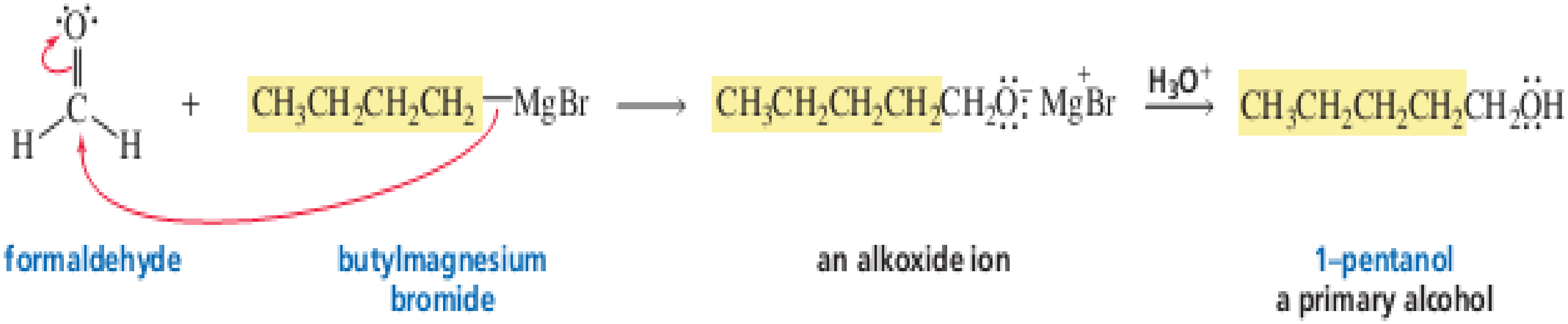
$$CH_3CH_2Br \xrightarrow[Et_2O]{Mg} CH_3CH_2MgBr$$



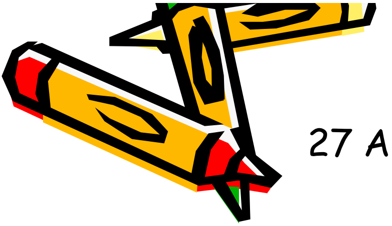
CH_3CH_2MgBr reacts as if it were $CH_3\overset{-}{\ddot{C}}H_2 \quad \overset{+}{Mg}Br$

Addition of Grignard Reagent

- ✓ Attack of a GR on a carbonyl **C** forms an alkoxide ion that is complexed with **Mg** ion.
- ✓ Addition of water or dilute acid breaks up the complex.
- ✓ When a GR reacts with formaldehyde, the addition product is a primary alcohol.

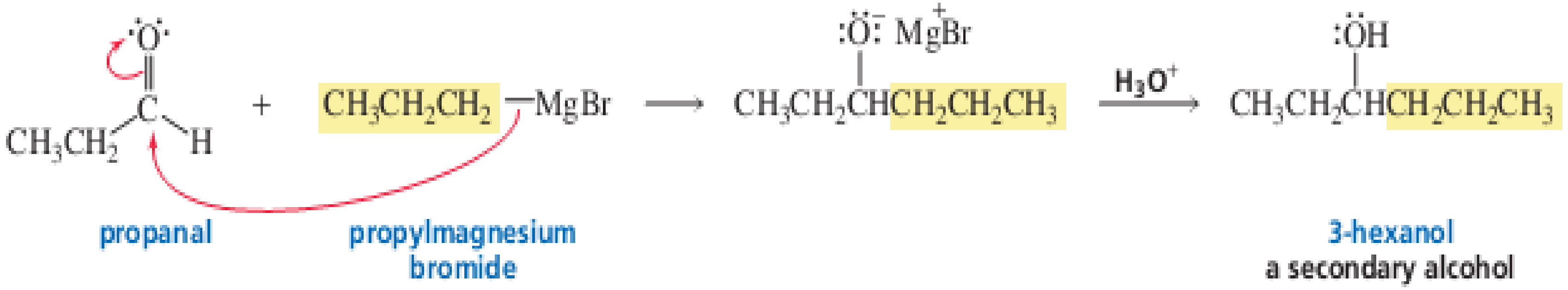


$$H_2C{=}O + CH_3CH_2CH_2CH_2{-}MgBr \longrightarrow CH_3CH_2CH_2CH_2CH_2O^{-}\ \overset{+}{Mg}Br \xrightarrow{H_3O^+} CH_3CH_2CH_2CH_2CH_2OH$$

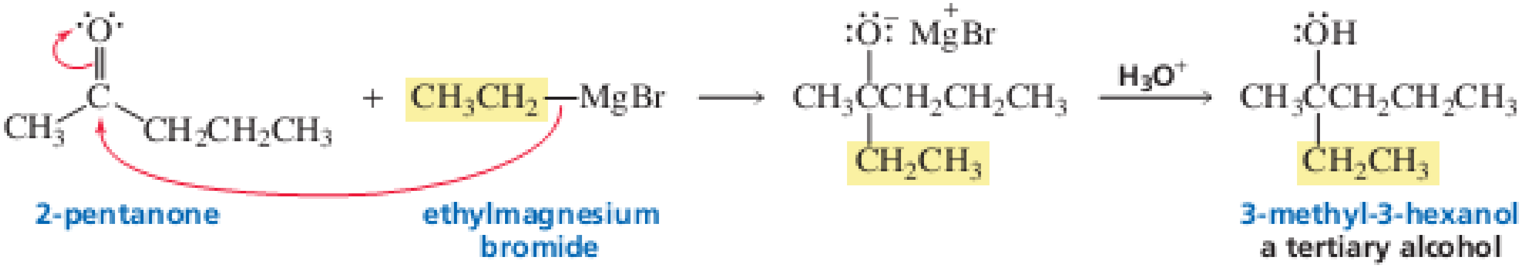


Addition of Grignard Reagent

- ✓ When a GR reacts with an aldehyde other than formaldehyde, the addition product is a secondary alcohol.

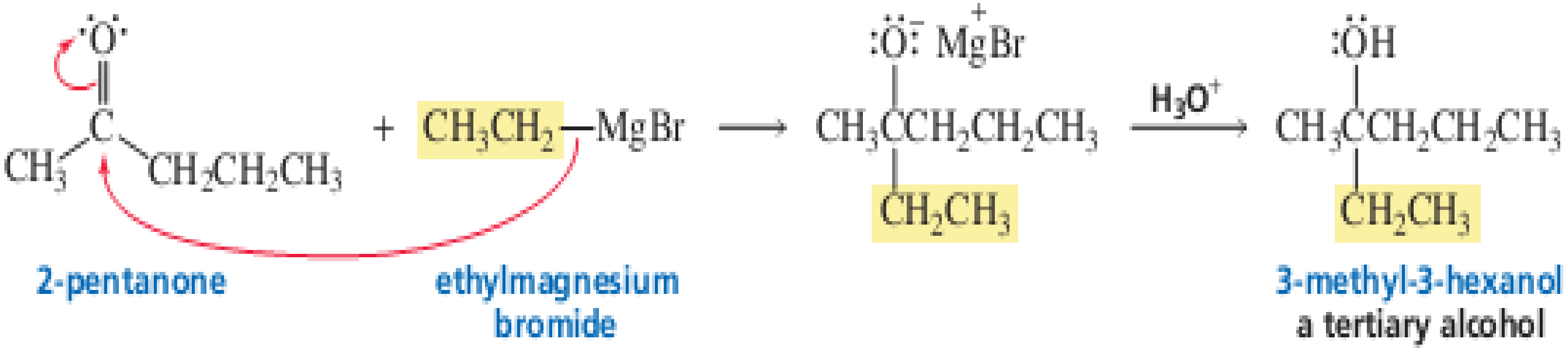


- ✓ When a GR reacts with a ketone, the addition product is a tertiary alcohol.



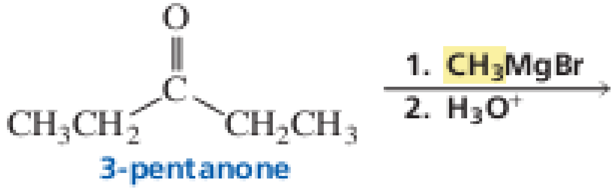
Addition of Grignard Reagent

- ✓ When a Grignard reagent reacts with a ketone, the addition product is a tertiary alcohol.

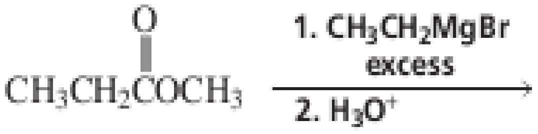


Exercise. Write the product chemical structure for the ff

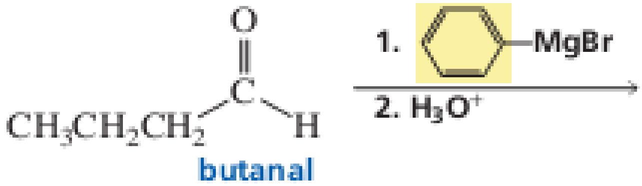
a)



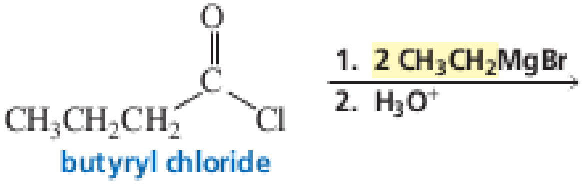
c)

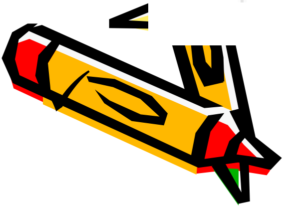


b)



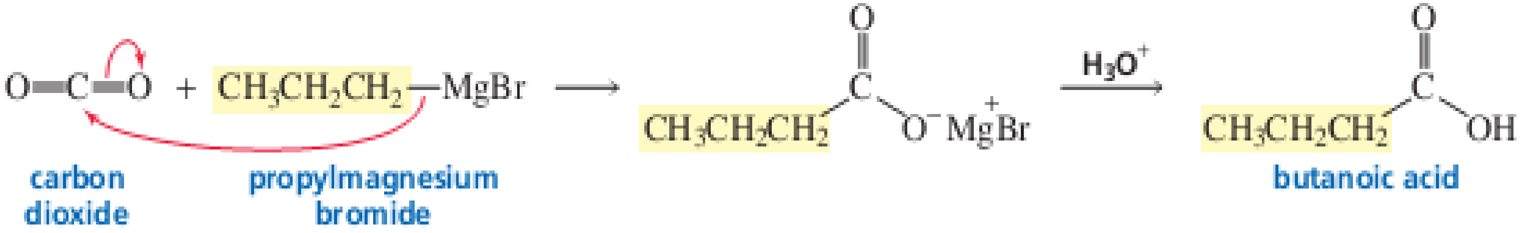
d)





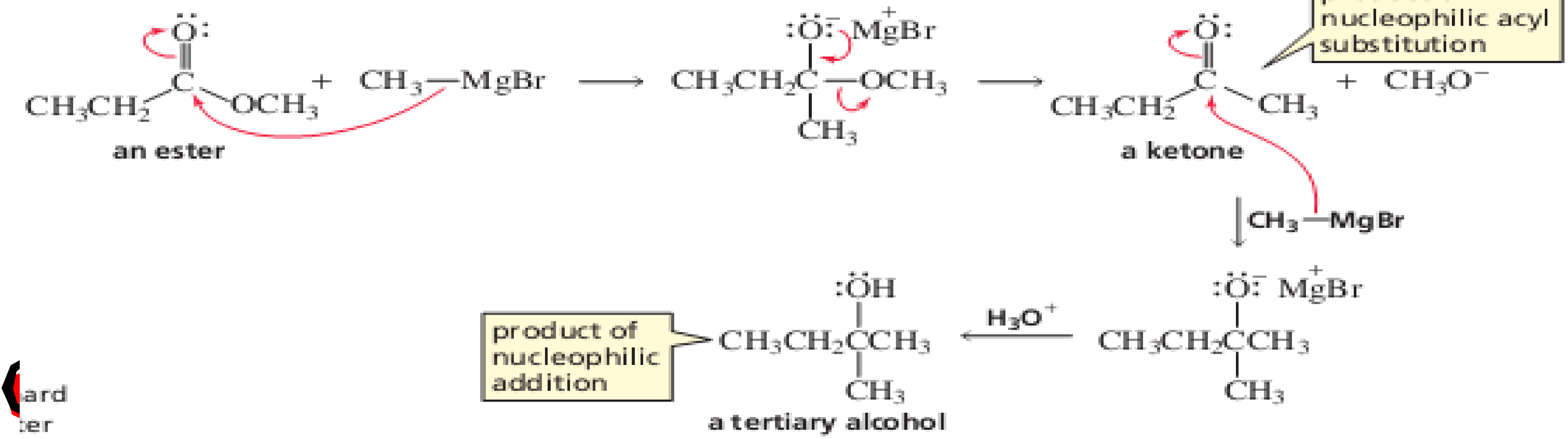
Addition of Grignard Reagent

- ✓ A **GR** can also react with CO_2. The product of the rxn is a carboxylic acid with one more **C** atom than the GR has.



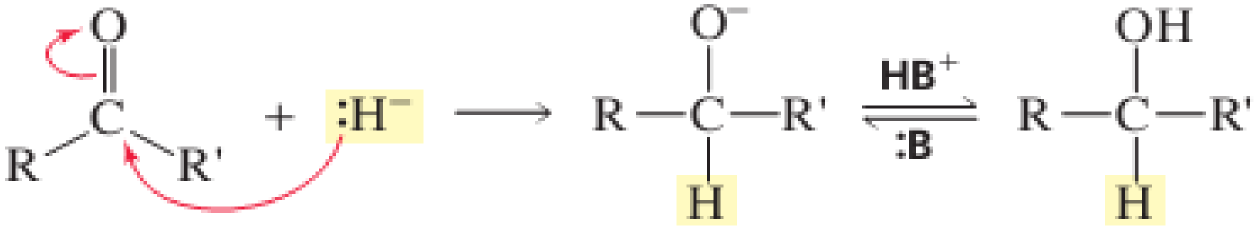
- ✓ when an ester reacts with a GR, the first rxn is a nucleophilic acyl substitution rxn b/c an ester.

mechanism for the reaction of an ester with a Grignard reagent



3.1.4 Hydride Additions ($LiAlH_4$ and $NaBH_4$)

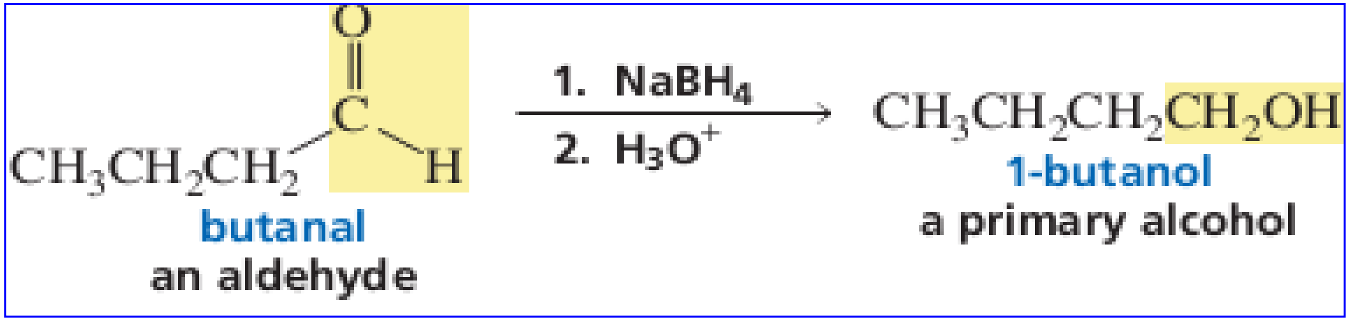
- ✓ Addition of hydride ion ($:H^-$) to an aldehyde or ketone forms an alkoxide ion.
- ✓ Subsequent protonation by an acid produces an alcohol.
- ✓ The overall rxn adds to the carbonyl group.
- ✓ the addition of hydrogen to an organic cpd is a reduction rxn.



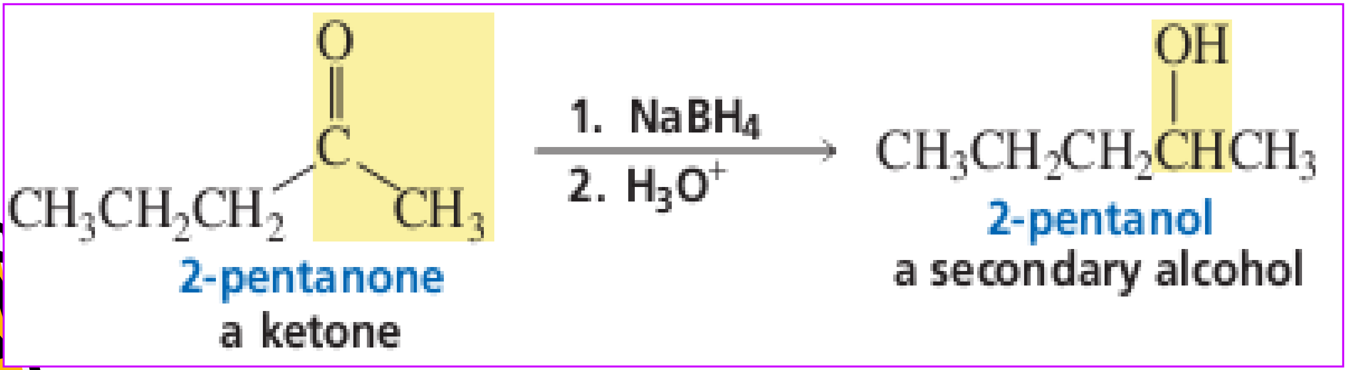
- ✓ Aldehydes & ketones are reduced using sodium borohydride as the source of **hydride ion**.

Hydride Additions ($LiAlH_4$ and $NaBH_4$)

- ✓ Aldehydes are reduced to 1^0 alcohols, & ketones are reduced to 2^0 alcohols.
- ✓ ***Note***. the acid is **not** added to the rxn mixture until the rxn with the hydride donor is complete.



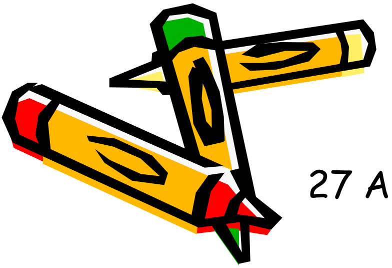
$$CH_3CH_2CH_2CHO \xrightarrow[2.\ H_3O^+]{1.\ NaBH_4} CH_3CH_2CH_2CH_2OH$$



$$CH_3CH_2CH_2COCH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaBH_4} CH_3CH_2CH_2CH(OH)CH_3$$

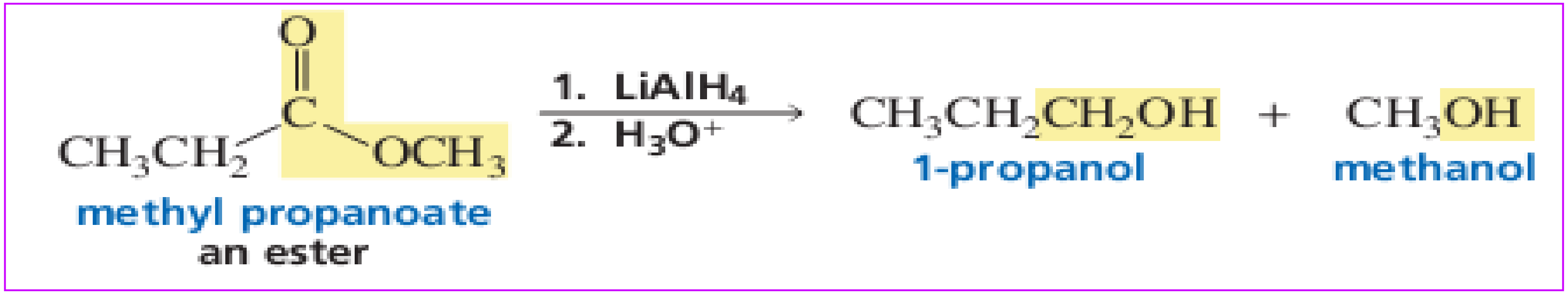
Hydride Additions ($LiAlH_4$ and $NaBH_4$)

- **$NaBH_4$** is not a sufficiently strong hydride donor to react with the less reactive (compared with aldehydes and ketone) esters, carboxylic acids, & amides, so esters, carboxylic acids, & amides must be reduced with **$LiAlH_4$** a more reactive hydride donor.
- The rxn of a Class I carbonyl cpd with hydride ion involves **two** successive rxns with the nucleophile.
- B/c **$LiAlH_4$** is more reactive than **$NaBH_4$.**

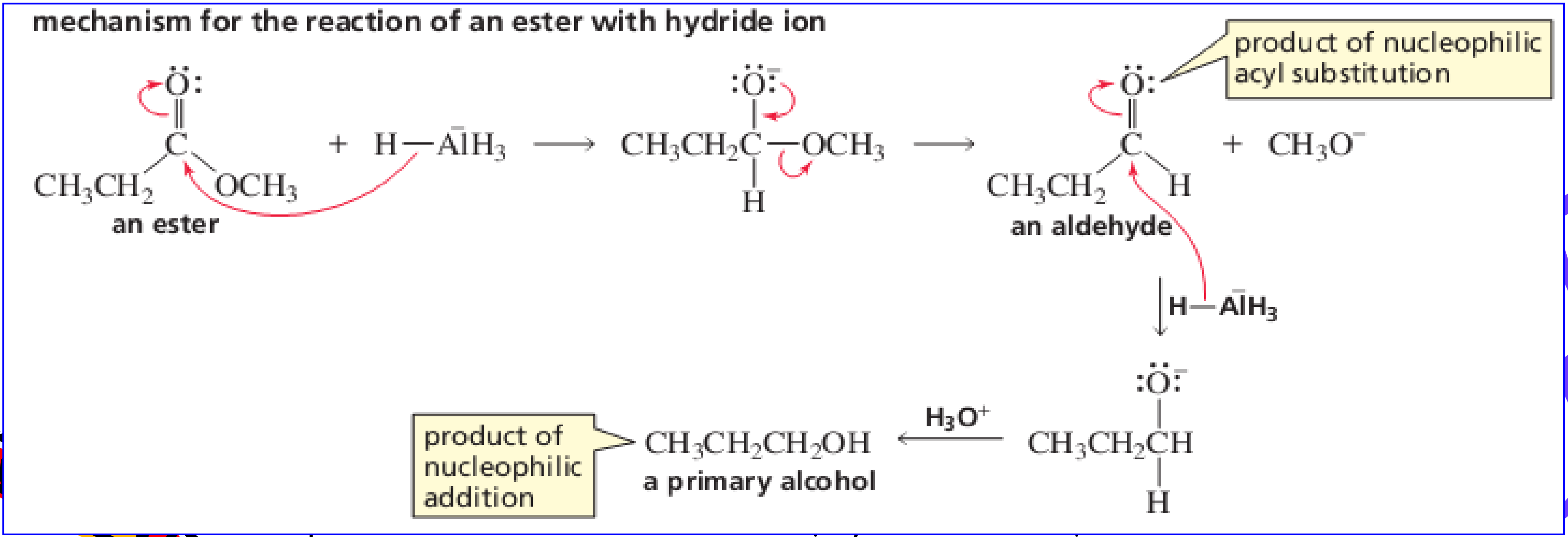


Hydride Additions ($LiAlH_4$ and $NaBH_4$)

- ✓ The rxn of an ester with produces **two** alcohols, one corresponding to the acyl portion of the ester & one corresponding to the alkyl portion.



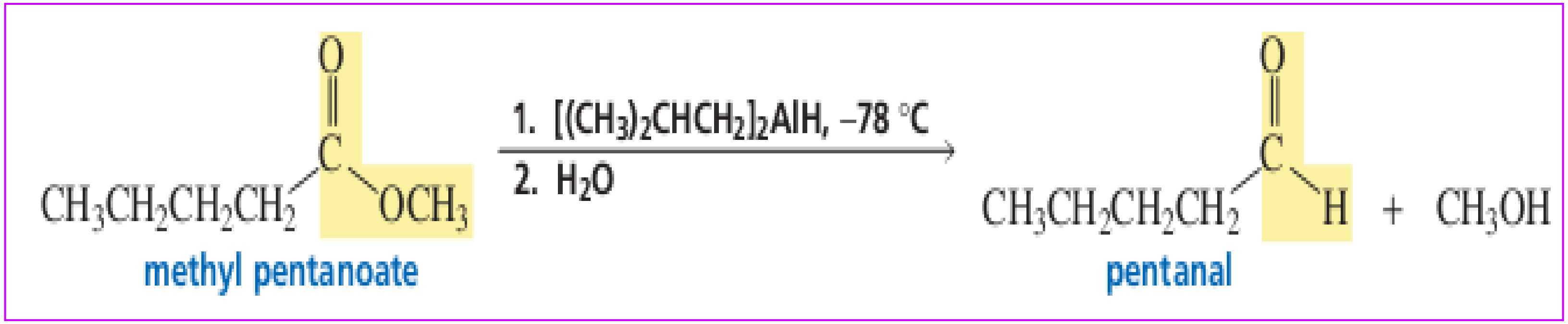
mechanism for the reaction of an ester with hydride ion

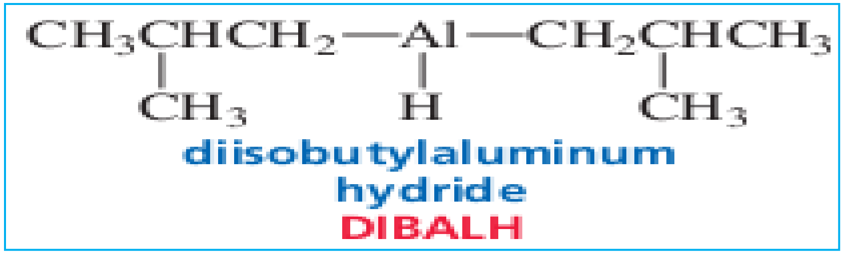

product of nucleophilic acyl substitution

product of nucleophilic addition

Hydride Additions ($LiAlH_4$ and $NaBH_4$)

- ✓ Diisobutylaluminum hydride (DIBALH) is used as the hydride donor at a low temp., the rxn can be stopped after the addition of one equivalent of hydride ion.
- ✓ This reagent, makes it possible to convert esters into aldehydes.

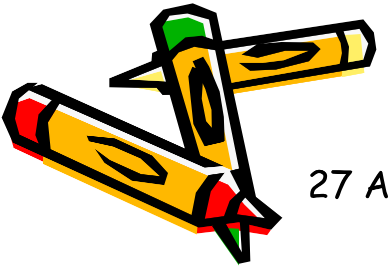




$$CH_3\underset{\displaystyle CH_3}{CH}CH_2-\underset{\displaystyle H}{Al}-CH_2\underset{\displaystyle CH_3}{CH}CH_3$$

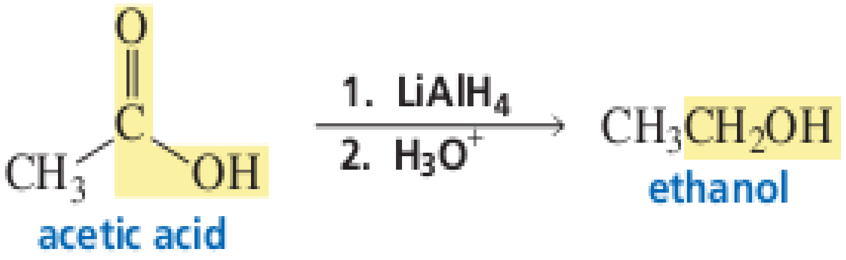
diisobutylaluminum hydride

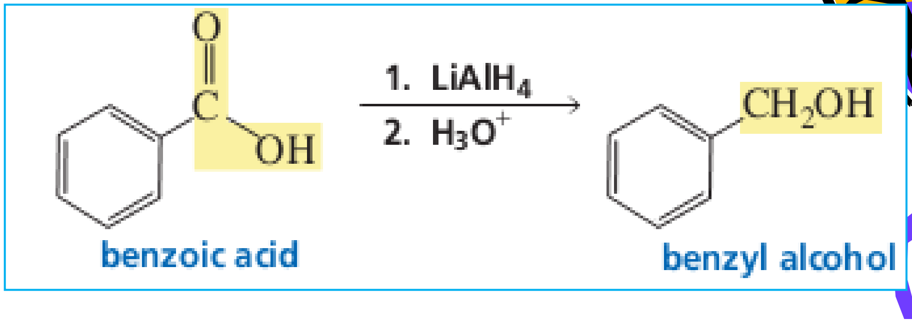
DIBALH



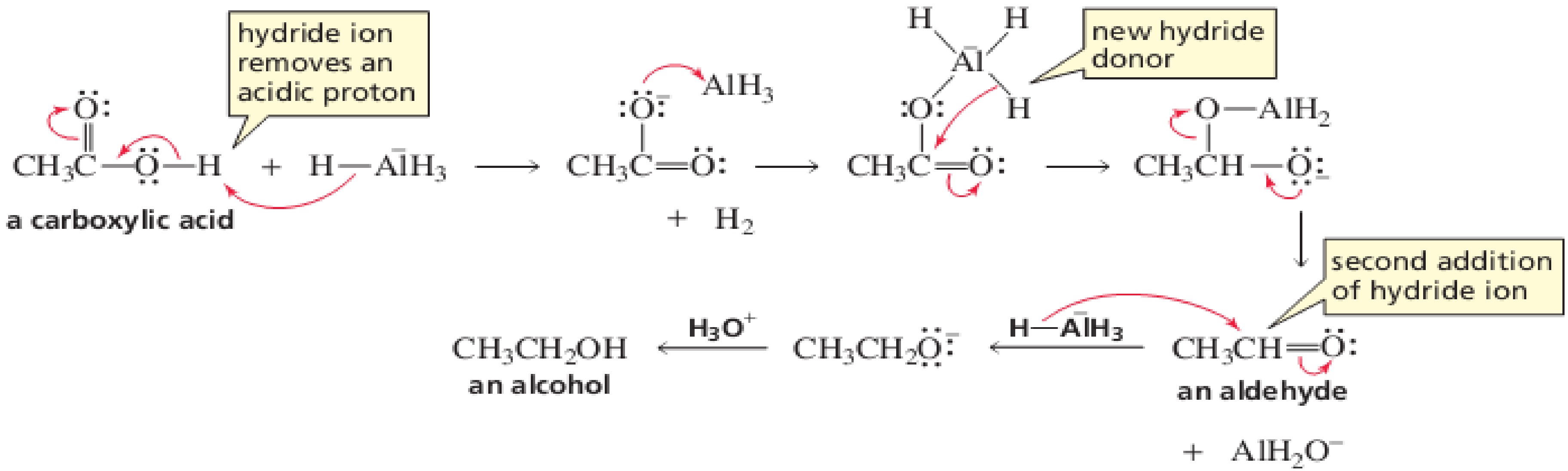
Hydride Additions ($LiAlH_4$ and $NaBH_4$)

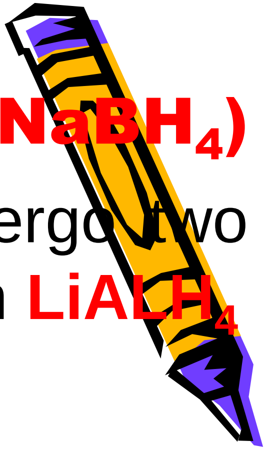
- ✓ The rxn of a carboxylic acid with forms a single primary alcohol.





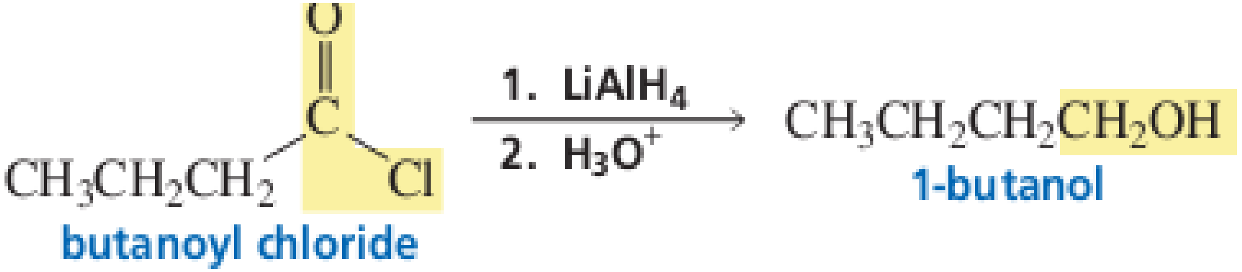
mechanism for the reaction of a carboxylic acid with hydride ion



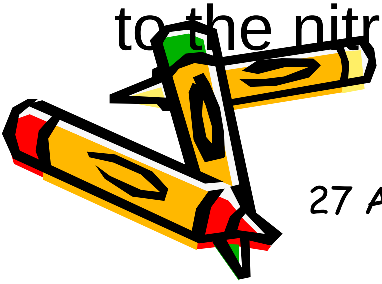


Hydride Additions ($LiAlH_4$ and $NaBH_4$)

- ✓ Acyl chlorides, like esters & carboxylic acids, undergo two successive additions of hydride ion when treated with **$LiALH_4$**

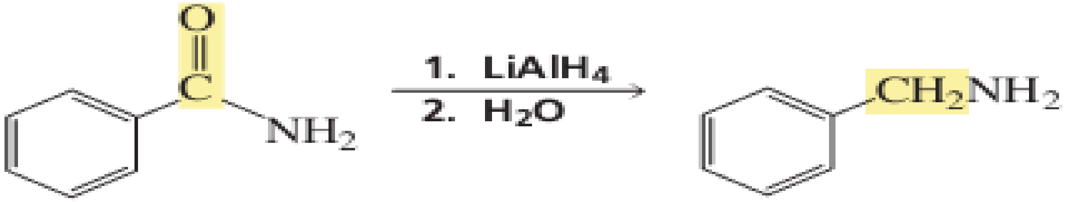


- ✓ Amides also undergo two successive additions of :H- when they react with **$LiALH_4$**
- ✓ The product of the rxn is an amine. 1^0, 2^0, or 3^0 amines can be formed, depending on the number of substituents bonded to the nitrogen of the amide



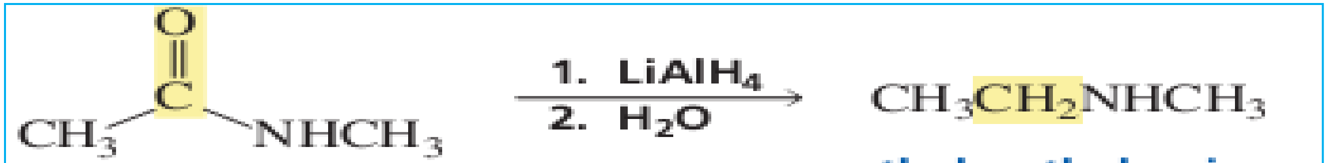
Hydride Additions ($LiAlH_4$ and $NaBH_4$)

- ✓ **Note.** H_2O rather than H_3O^+ is used in the 2nd step of the rxn.



benzamide

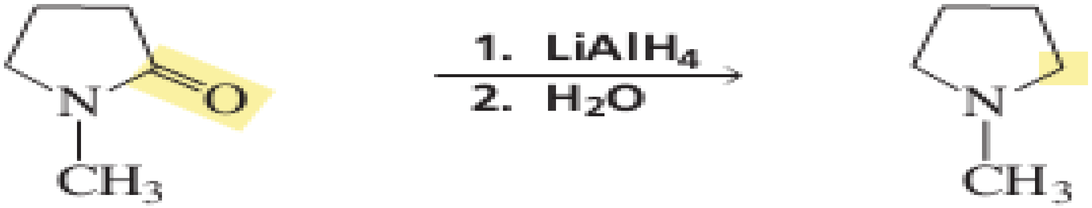
benzylamine
a primary amine



$$CH_3C(=O)NHCH_3 \xrightarrow[2.\ H_2O]{1.\ LiAlH_4} CH_3CH_2NHCH_3$$

N-methylacetamide

ethylmethylamine
a secondary amine

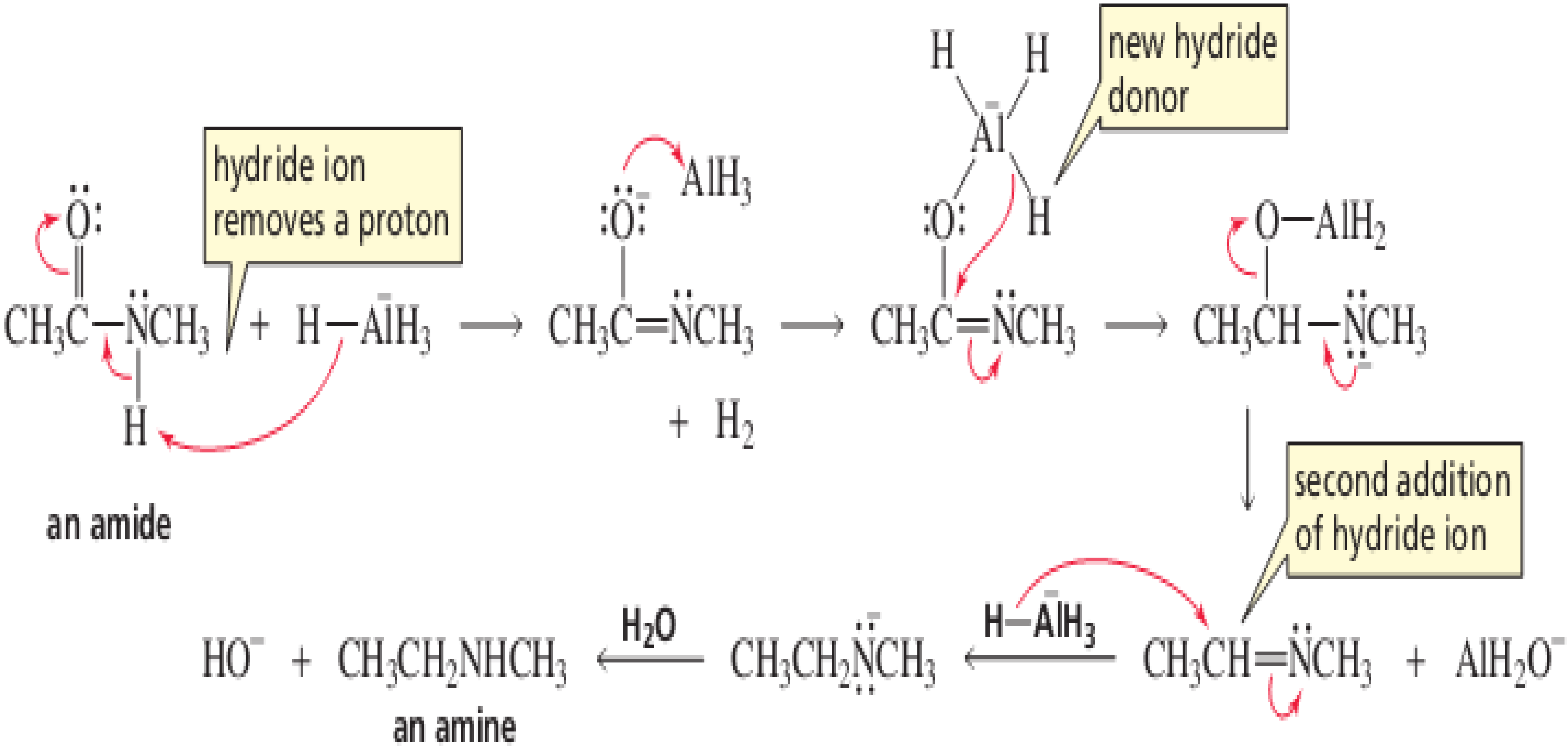


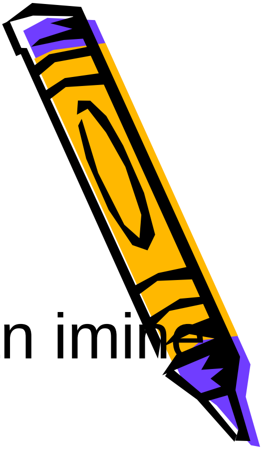
N-methyl-γ-butyrolactam

N-methylpyrrolidine
a tertiary amine

Hydride Additions ($LiAlH_4$ and $NaBH_4$)

mechanism for the reaction of an *N*-substituted amide with hydride ion

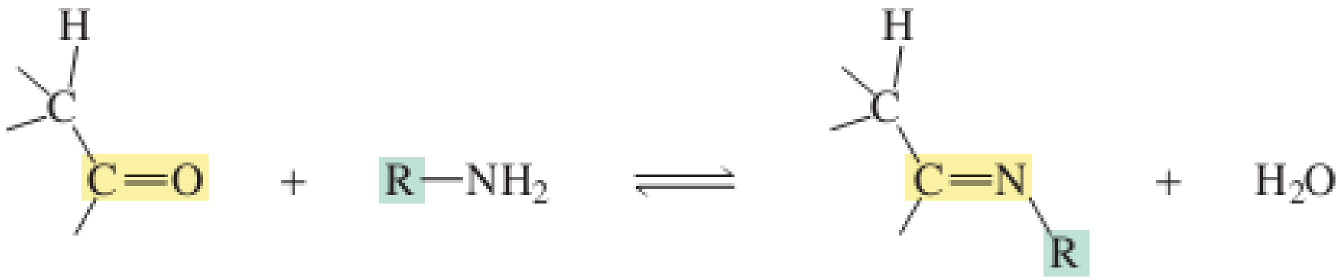




3.2 Addition β−Elimination Reactions

3.2.1 Imines and related compounds

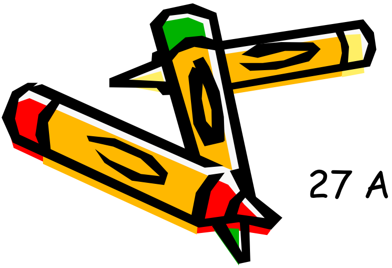
- ✓ Aldehydes & ketones react with a **1**^{0} amine to form an imine
- ✓ An imine is a cpd with a **C–N** double bond.
- ✓ The imine obtained from the rxn of a carbonyl cpd & a primary amine is often called a **Schiff base**.

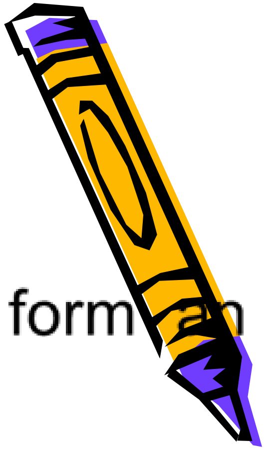


an aldehyde or a ketone

a primary amine

an imine
a Schiff base

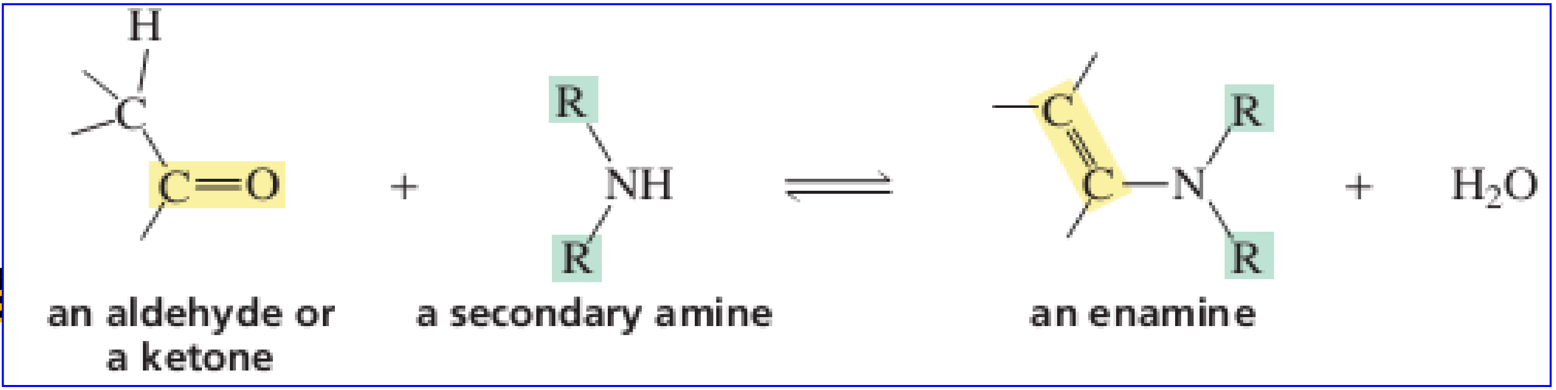


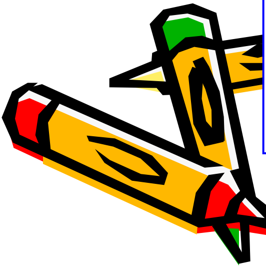


3.2 Addition β−Elimination Reactions

3.2.1 Imines and related compounds

- ✓ Aldehydes & ketones react with a 2^0 amine to form an enamine.
- ✓ An enamine is an α,β-unsaturated 3^0 amine, a 3^0 amine with a double bond in the α,β-position relative to the N atom.
- ✓ the double bond is in the part of the molecule that comes from the aldehyde or ketone.

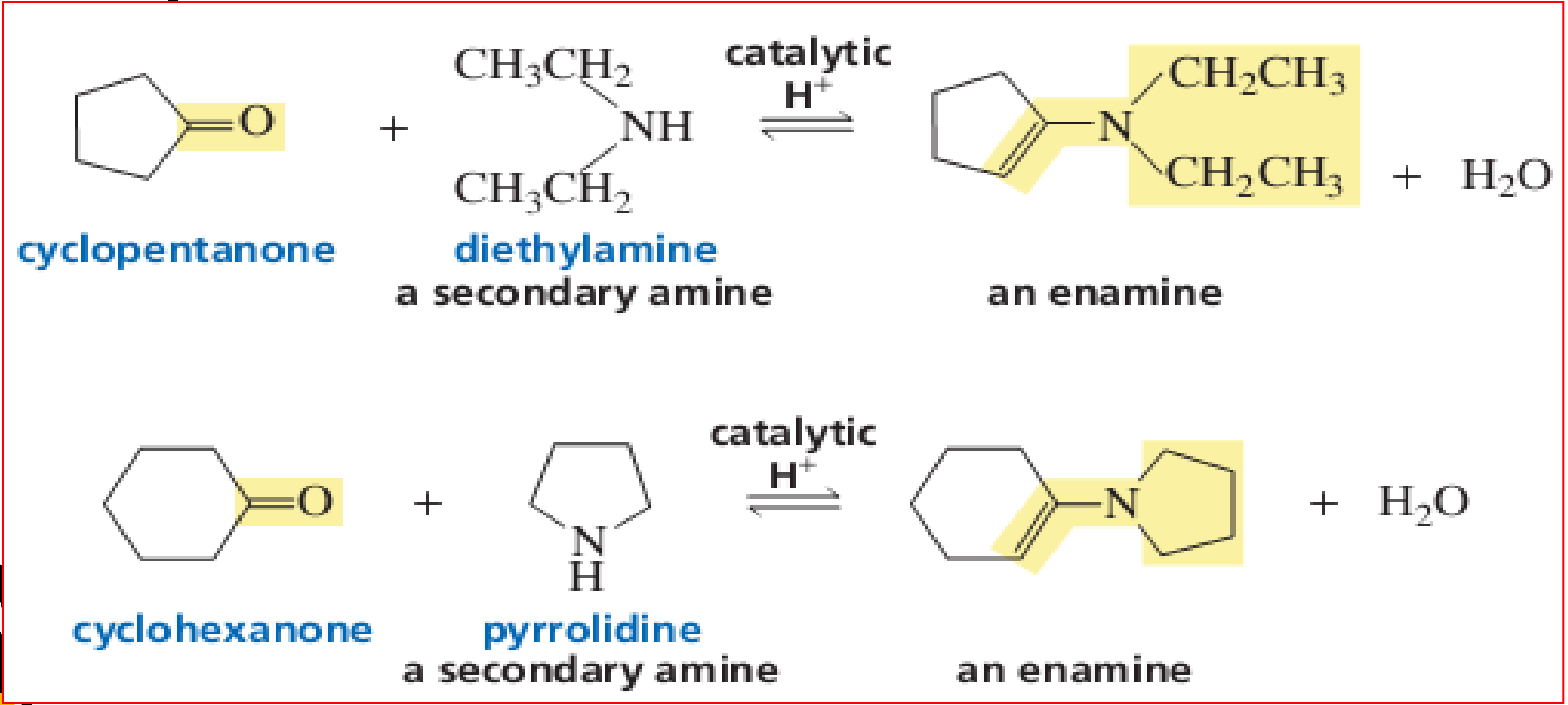




3.2 Addition β−Elimination Reactions

3.2.1 **Imines** and related compounds

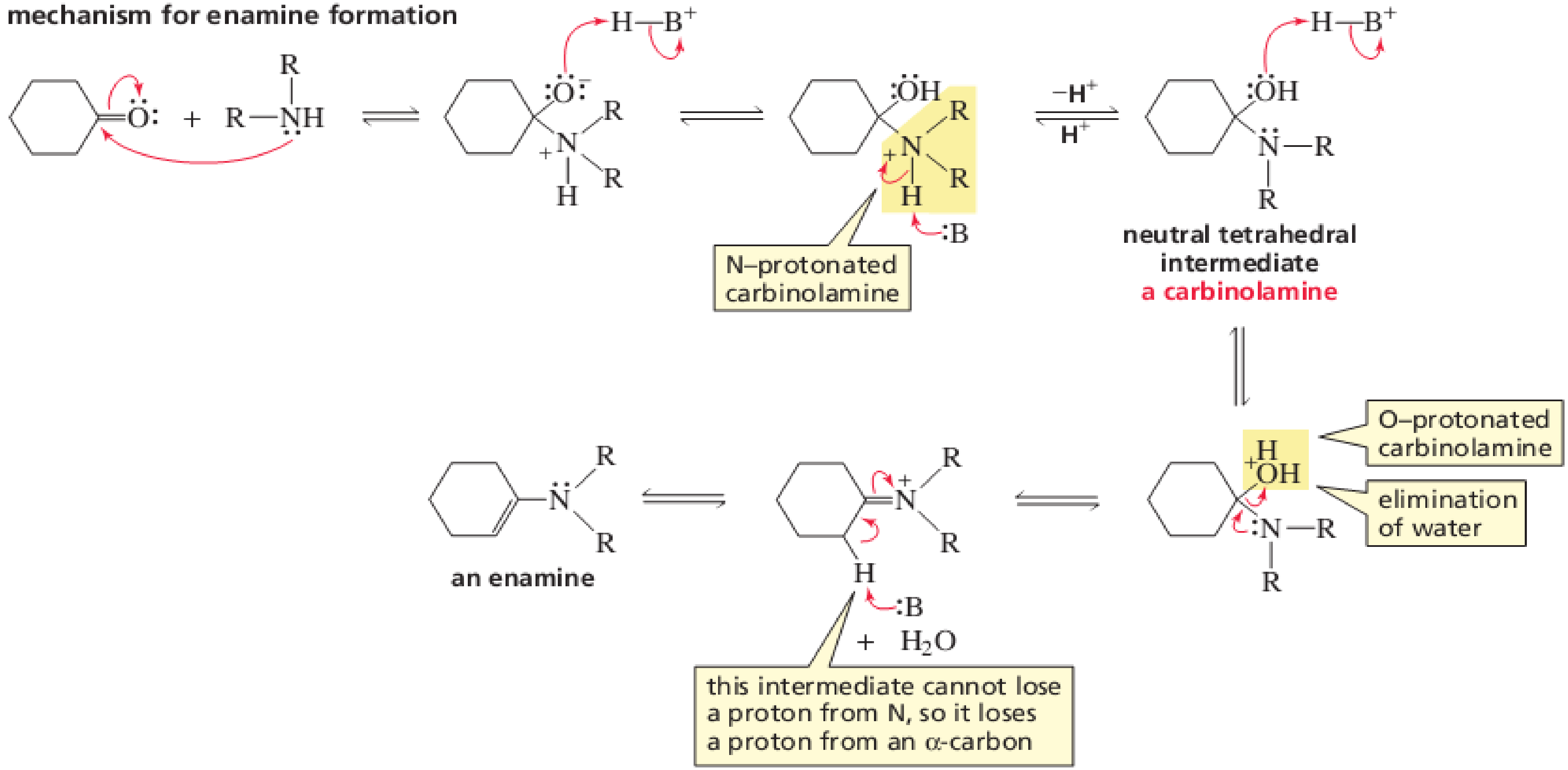
- Aldehydes & ketones react with secondary amines to form enamines.
- Like imine formation, the rxn requires a trace amount of an acid catalyst.



3.2 Addition β−Elimination Reactions

3.2.1 **Imines** and related compounds

- The mechanism for **enamine** formation is exactly the same as that for imine formation, until the last step of the rxn.



mechanism for enamine formation

N–protonated carbinolamine

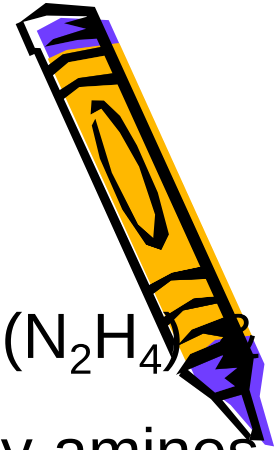
neutral tetrahedral intermediate
a carbinolamine

O–protonated carbinolamine

elimination of water

an enamine

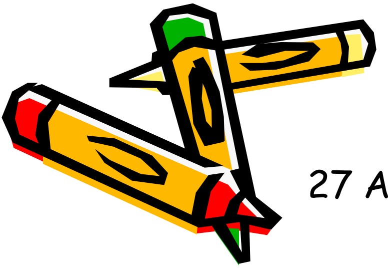
this intermediate cannot lose a proton from N, so it loses a proton from an α-carbon



3.2.1 Imines and related compounds

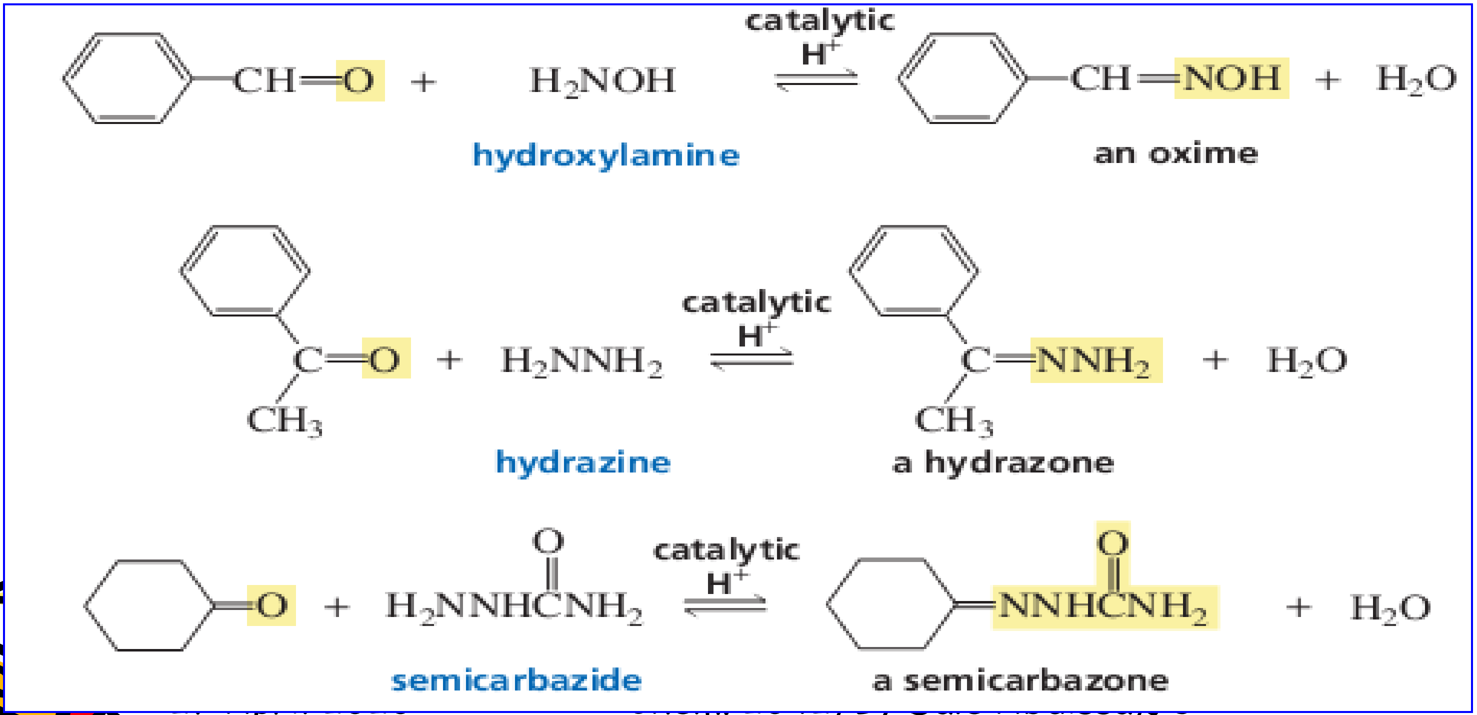
Formation of Imine Derivatives:

- ✓ Cpds such as hydroxylamine (NH_2OH, hydrazine (N_2H_4) & semicarbazide ($NH_2NHCONH_2$) are similar to primary amines in that they all have an group.
- ✓ Thus, like primary amines, they react with aldehydes and ketones to form imines often called imine derivatives b/c the substituent attached to the imine **N** is not an R group.



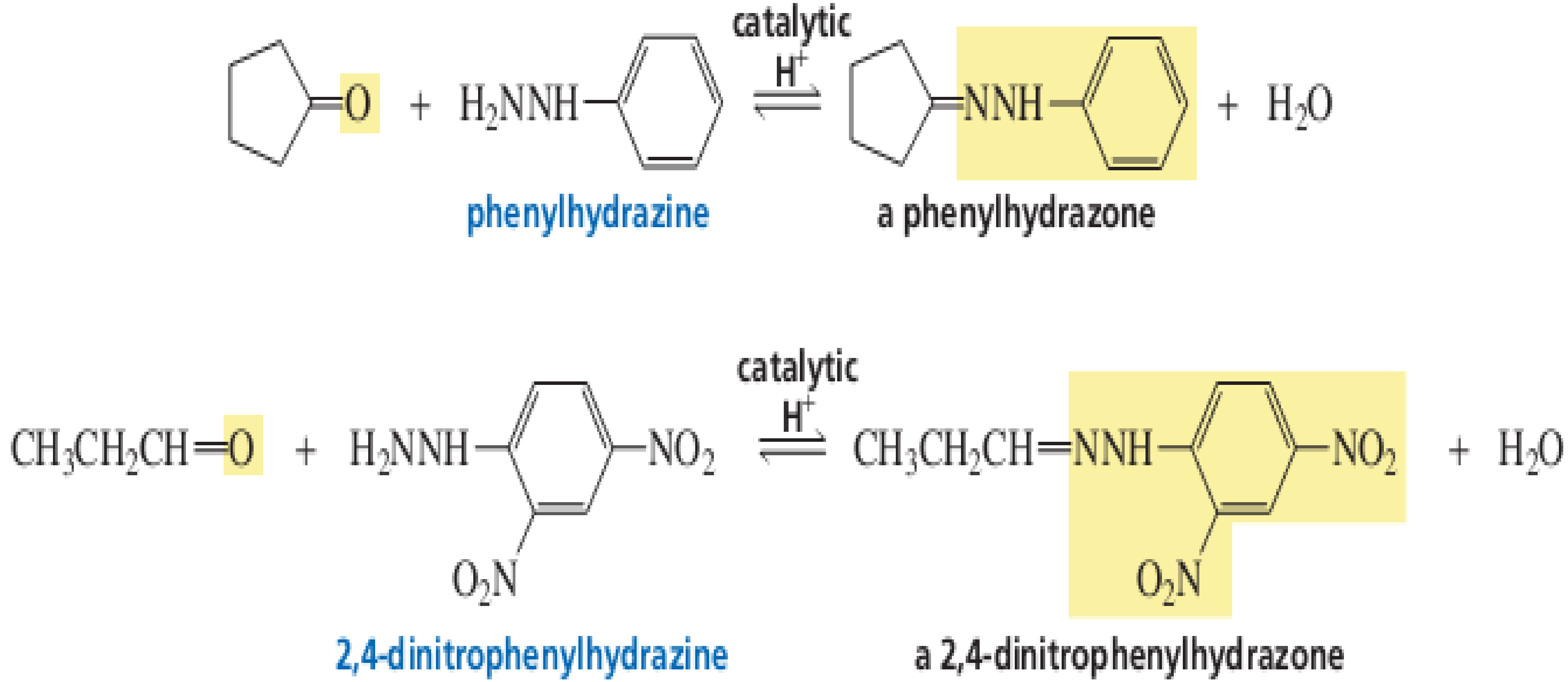
Imines and related compounds

- ✓ The imine obtained from the rxn with hydroxylamine is called an oxime, the imine obtained from the rxn with hydrazine is called a hydrazone, & the imine obtained from the rxn with semicarbazide is called a semicarbazone.

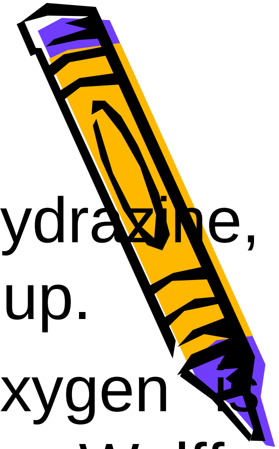


3.2.1 **Imines** and related compounds

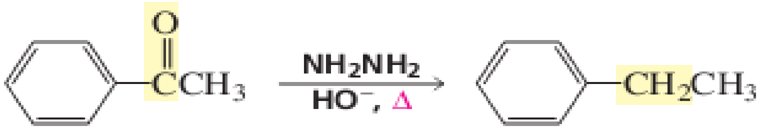
- ✓ Phenyl-substituted hydrazines react with aldehydes & ketones to form phenyl-hydrazones.

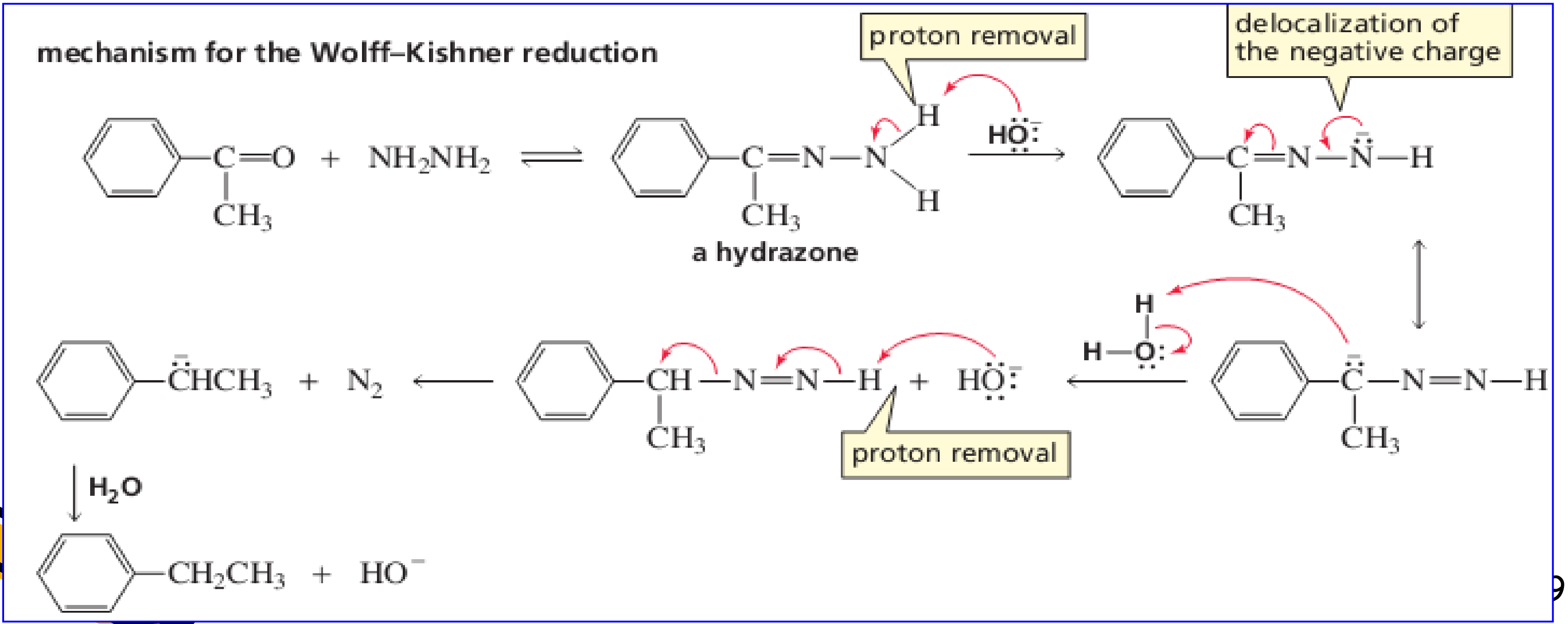


The Wolff-Kishner Reduction



- ✓ When ketone/aldehyde is heated in a basic sol^n of hydrazine, the carbonyl group is converted into a methylene group.
- ✓ This process is called deoxygenation b/c an oxygen is removed from the reactant. The rxn is known as the Wolff–Kishner reduction.

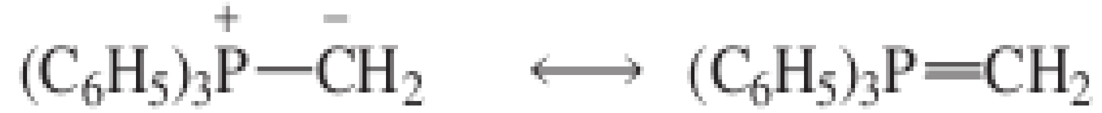




3.2.2 Wittig reaction

- ✓ An aldehyde/ketone reacts with a phosphonium ylide to form an alkene.
- ✓ An ylideis a cpd that has opposite charges on adjacent covalently bonded atoms with complete octets.
- ✓ The ylide can also be written in the double-bonded form b/c phosphorus can have more than eight valence electrons.

Georg Friedrich Karl Wittig

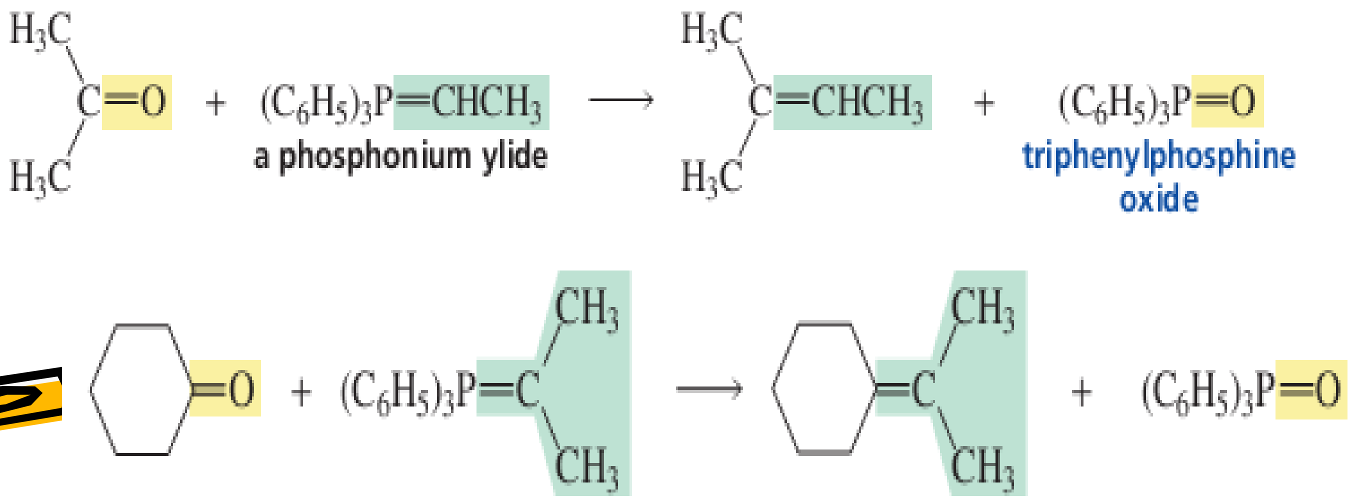


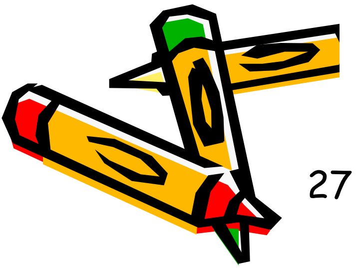
$$(C_6H_5)_3\overset{+}{P}-\overset{-}{C}H_2 \longleftrightarrow (C_6H_5)_3P=CH_2$$

a phosphonium ylide

Wittig reactio

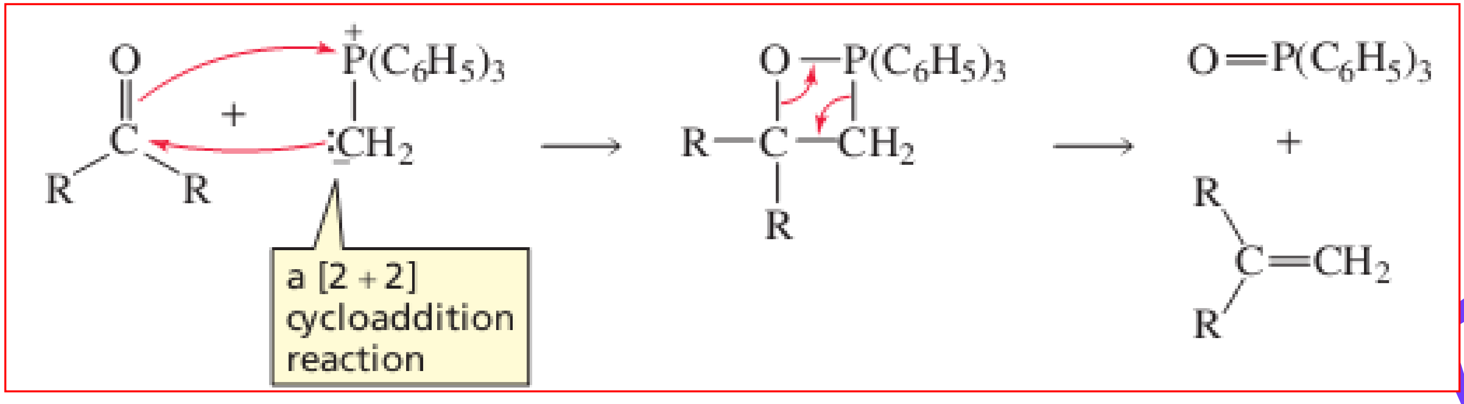
- ✓ The rxn of an aldehyde/a ketone with a phosphonium ylide to form an alkene is called a **Wittig reaction**.
- ✓ The overall rxn amounts to interchanging the double-bonded oxygen of the carbonyl cpd & the double-bonded **C** group of the phosphonium ylide.

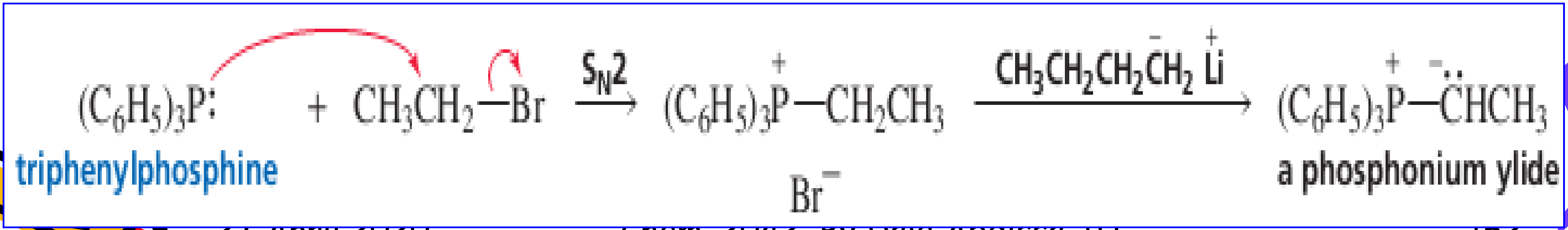




Wittig reactio

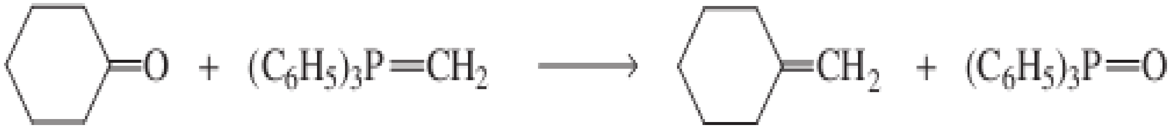
- ✓ the Wittig rxn is a concerted [2+2] cycloaddition rxn, with the nucleophilic carbon of the ylide attacking the electrophilic C of the carbonyl cpd.
- ✓ Elimination of tri-phenylphosphine oxide forms the **alkene** product.





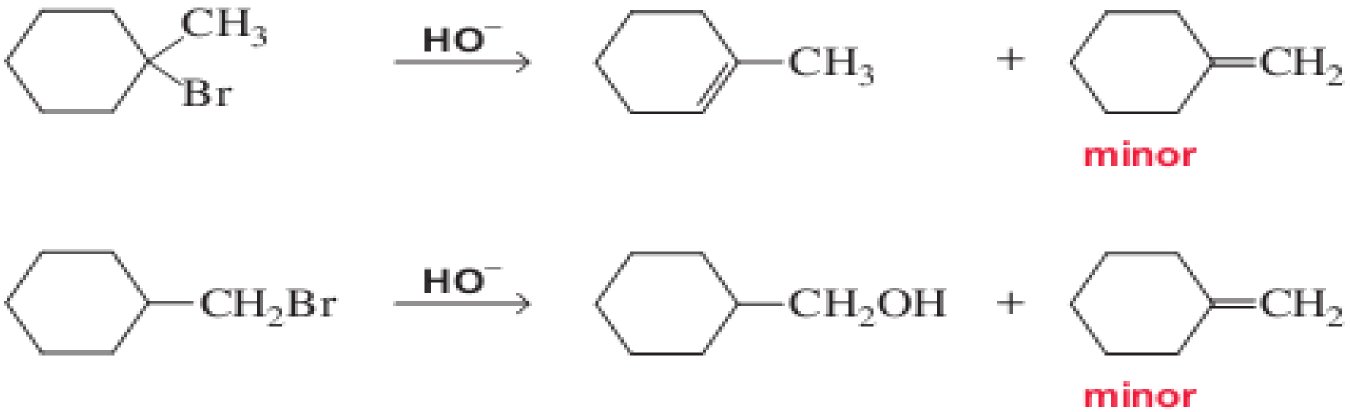
Application of Wittig reaction

- ✓ The Wittig rxn is a very powerful way to make an **alkene** b/c the rxn is completely regioselective the double bond will be in only one place.



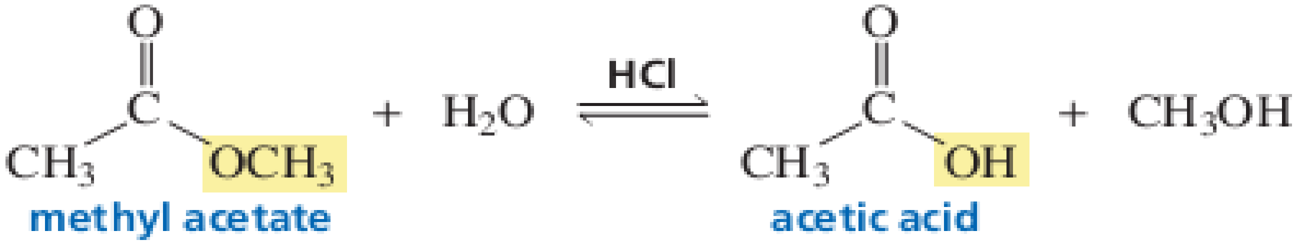
methylenecyclohexane

- ✓ The rxn also is the best way to make a terminal alkene such as methylene-cyclohexane b/c other methods would form a terminal alkene only as a minor product.



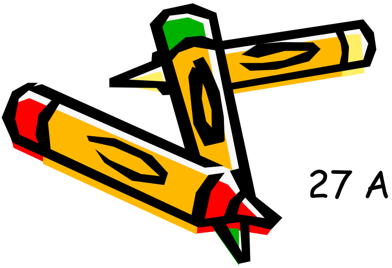
3.2.3 Ester hydrolysis and formation

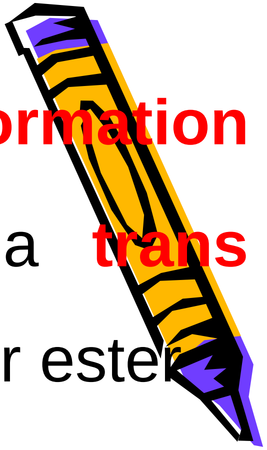
- ✓ Esters do not react with halide ions/with carboxylate ions b/c the **Nu** are much weaker bases than the RO- LG of the ester.
- ✓ An ester reacts with water to form a carboxylic acid & an alcohol. This is an example of a hydrolysis rxn.



$$CH_3C(=O)OCH_3 + H_2O \overset{HCl}{\rightleftharpoons} CH_3C(=O)OH + CH_3OH$$

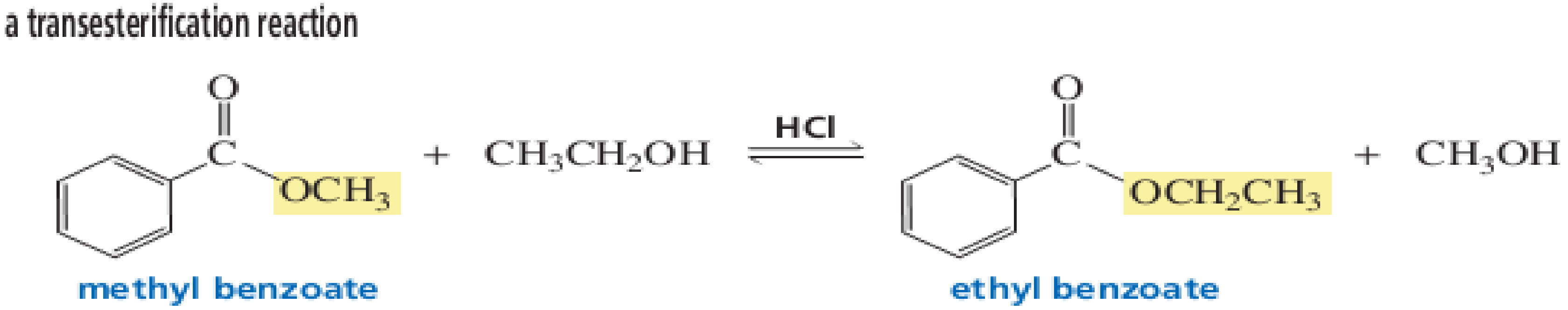
- ✓ An ester reacts with an alcohol to form a new ester & a new alcohol. This is an ex-ample of an **alcoholysis** rxn.





Ester hydrolysis and formation

✓ This particular alcoholysis rxn is also called a **trans** esterification rxn b/c one ester is converted to another ester.



✓ Both the hydrolysis & the alcoholysis of an ester are very slow rxns b/c water & alcohols are poor nucleophiles & esters have very basic leaving groups.

✓ Both hydrolysis & alcoholysis of an ester can be catalyzed by **acids**.

Ester hydrolysis and formation

- ✓ Esters also react with amines to form amides.
- ✓ A rxn with an amine that converts one cpd into two cpd is called **aminolysis**.

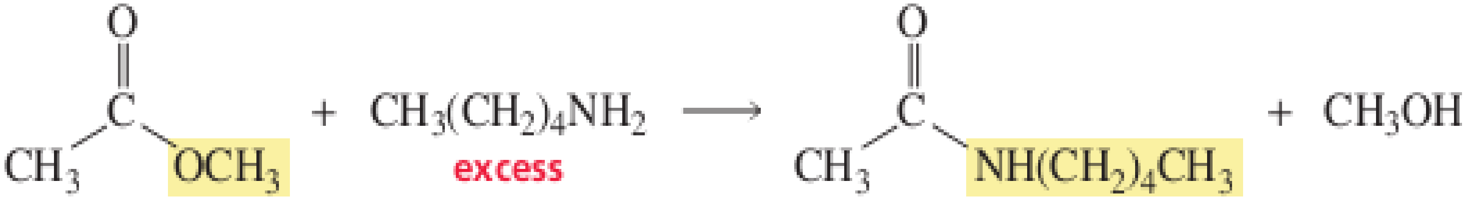
an aminolysis reaction

$$CH_3CH_2C(=O)OCH_2CH_3 + CH_3NH_2 \longrightarrow CH_3CH_2C(=O)NHCH_3 + CH_3CH_2OH$$

ethyl propionate

N-methylpropionamide

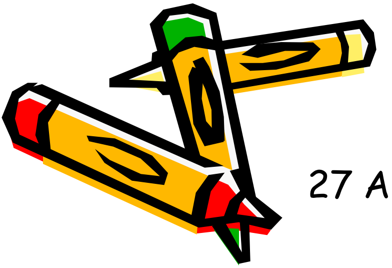
- ✓ The aminolysis of an ester can be driven to completion by using excess amine/by distilling off the alcohol as it is formed.



$$CH_3C(=O)OCH_3 + CH_3(CH_2)_4NH_2 \longrightarrow CH_3C(=O)NH(CH_2)_4CH_3 + CH_3OH$$

Acid-Catalyzed Ester Hydrolysis

- ✓ Esters hydrolyze slowly b/c water is a poor **Nu** & esters have very basic LG.
- ✓ The rate of hydrolysis can be increased by either acid or $^{-}$OH.
- ✓ In an acid-catalyzed rxn, all organic intermediates & products are +vely charged or neutral; -vely charged organic Intermediates & products are not formed in acidic solutions.
- ✓ The first step in the mechanism for acid-catalyzed ester hydrolysis is **protonation** of the carbonyl oxygen by the acid.



Acid-Catalyzed Ester Hydrolysis

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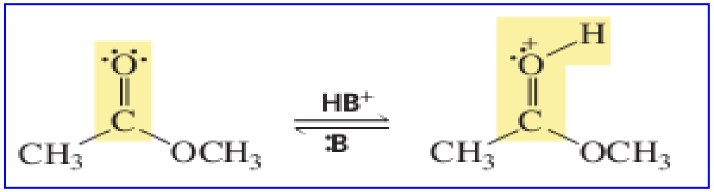
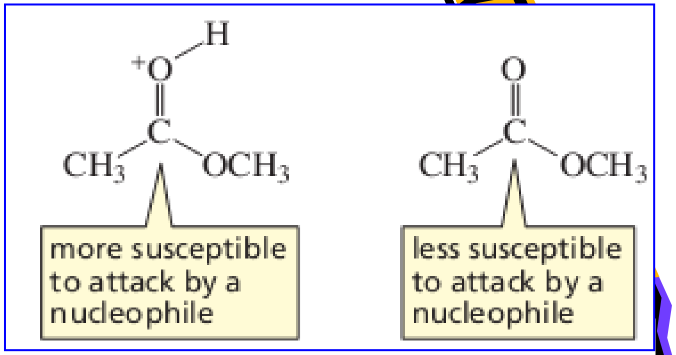
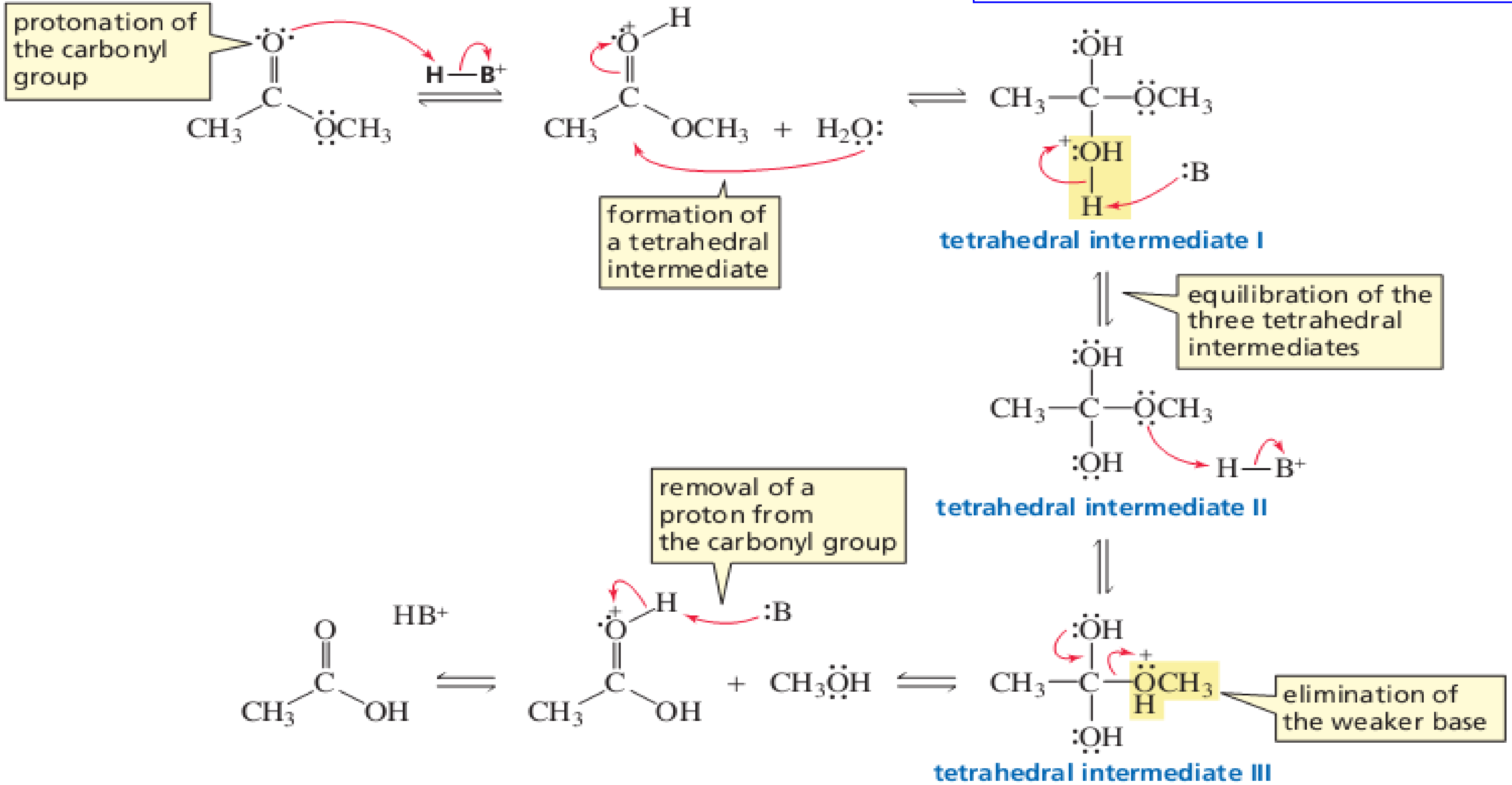




more susceptible to attack by a nucleophile

less susceptible to attack by a nucleophile



protonation of the carbonyl group

formation of a tetrahedral intermediate

tetrahedral intermediate I

equilibration of the three tetrahedral intermediates

tetrahedral intermediate II

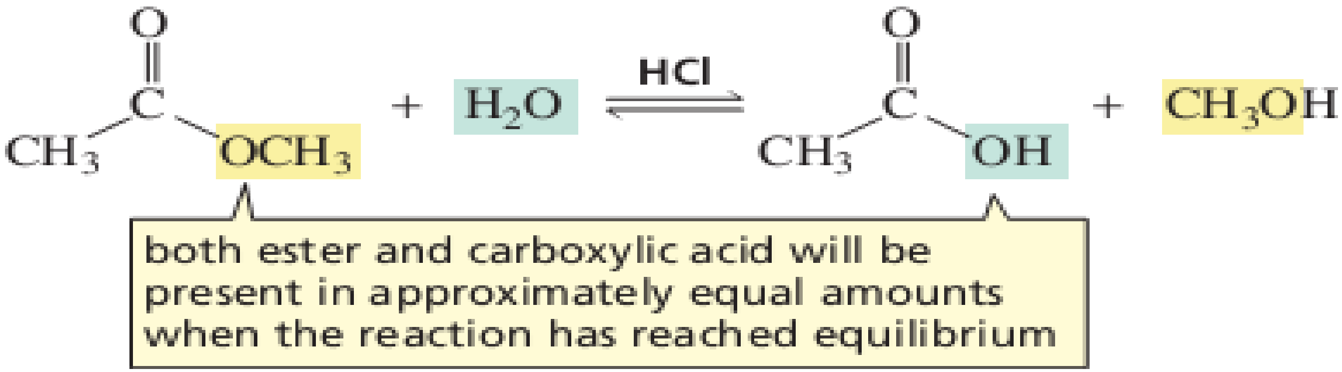
removal of a proton from the carbonyl group

elimination of the weaker base

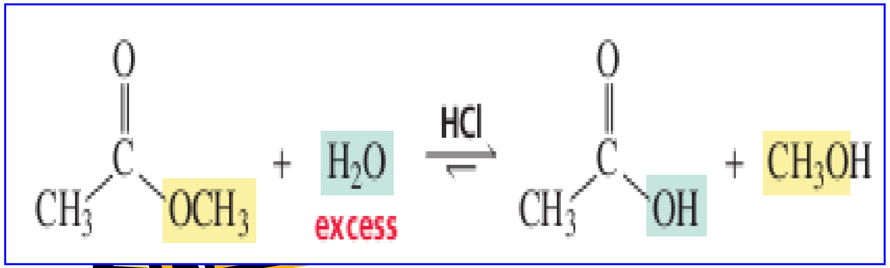
tetrahedral intermediate III

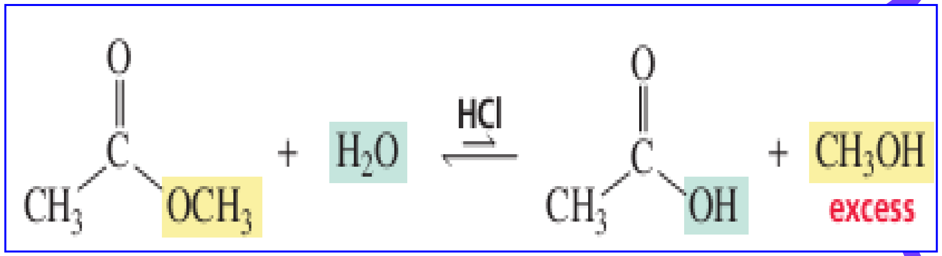
Acid-Catalyzed Ester Hydrolysis

- ✓ B/c H_20 & CH_3OH have approx. the same basicity, it will be as likely for tetrahedral intermediate I to collapse to reform the ester as it will for tetrahedral intermediate III to collapse to form the carboxylic acid.



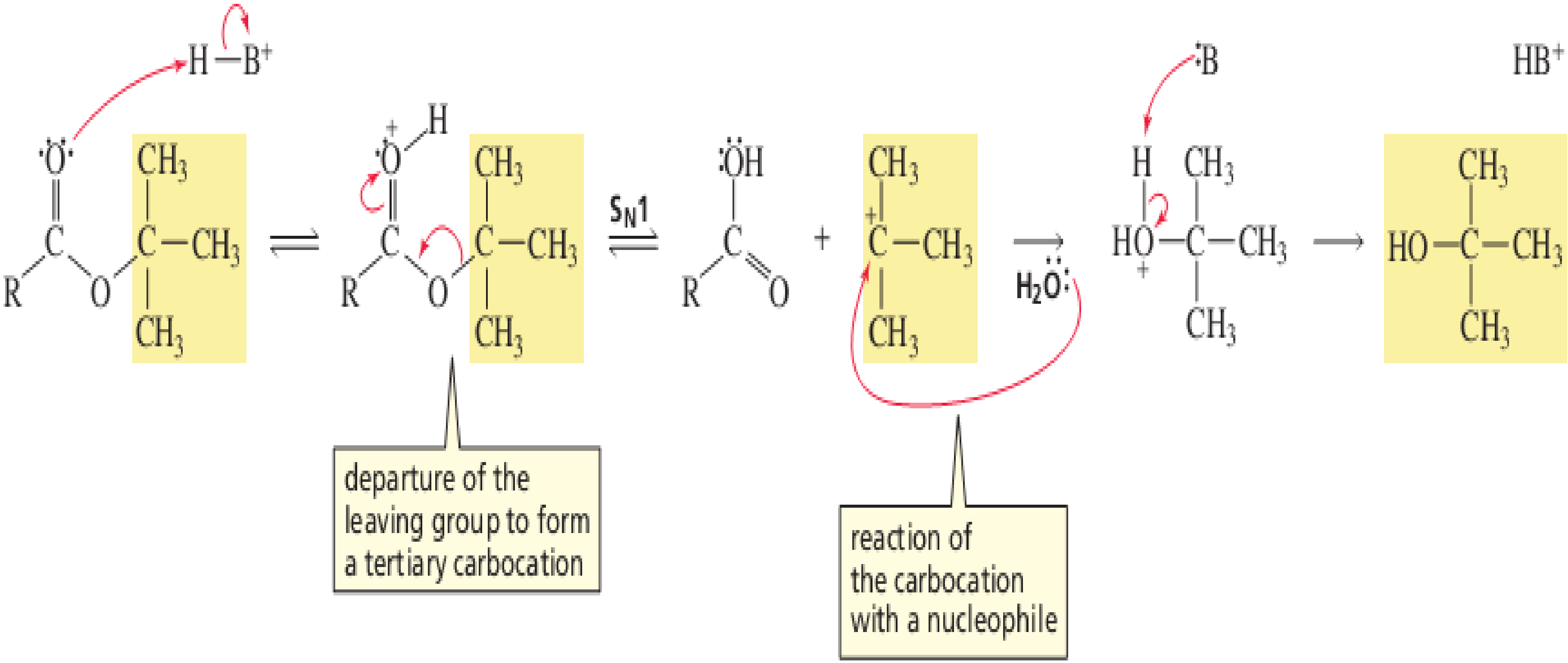
both ester and carboxylic acid will be present in approximately equal amounts when the reaction has reached equilibrium





Acid-Catalyzed Ester Hydrolysis

- ✓ Esters with tertiary alkyl groups undergo hydrolysis much more rapidly than do other esters b/c they hydrolyze by a completely d/t mechanism one that does not involve formation of a tetrahedral intermediate.



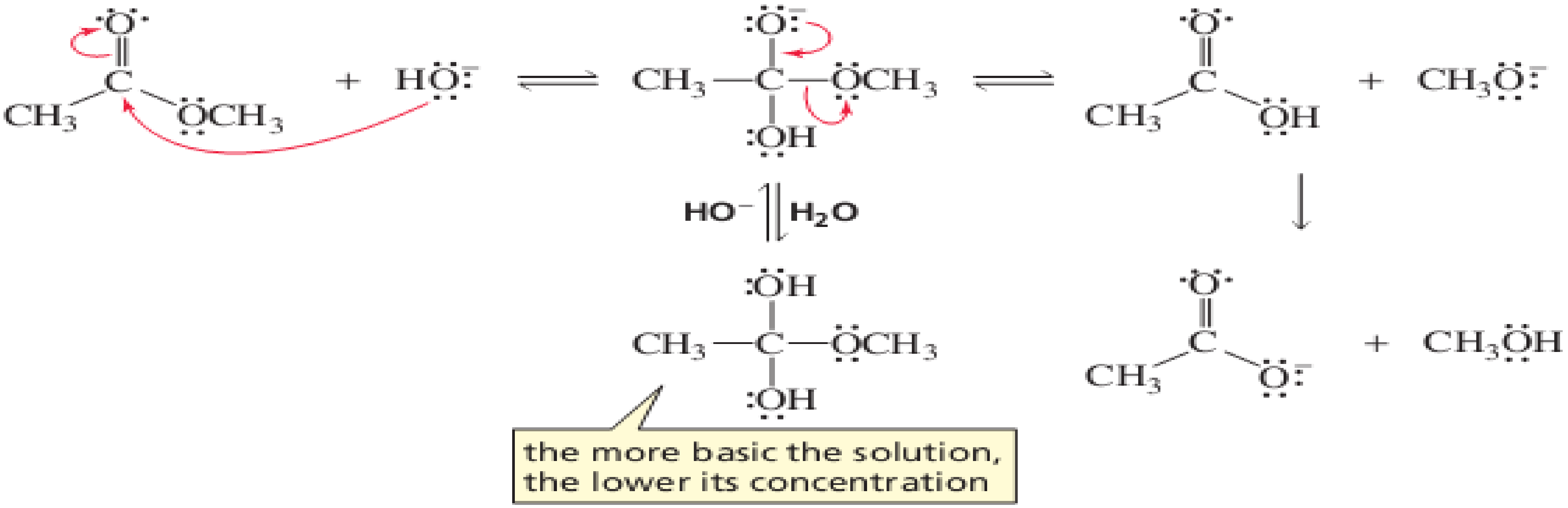
departure of the leaving group to form a tertiary carbocation

reaction of the carbocation with a nucleophile

Base-Catalyzed Ester Hydrolysis

- ✓ The rate of hydrolysis of an ester can be increased by carrying out the rxn in a basic solution.
- ✓ Like an acid, hydroxide ion (-OH) increases the rates of both **slow** steps of the rxn .
- ✓ -OH increases the rate of formation of the tetrahedral intermediate b/c -OH is a better nucleophile than H_2O.

mechanism for hydroxide-ion-promoted hydrolysis of an ester

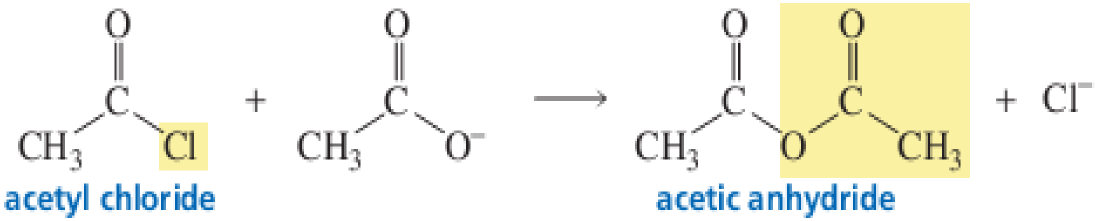


the more basic the solution, the lower its concentration

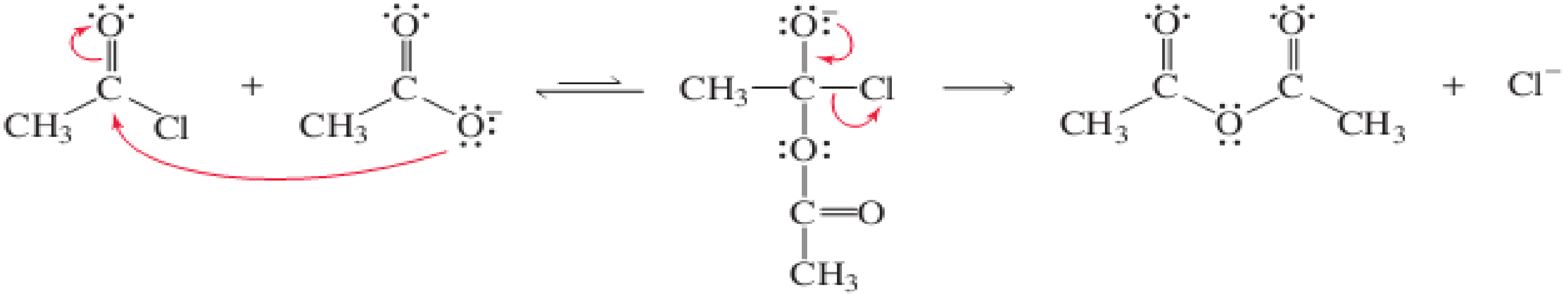
3.2.5 Rxns of acid chlorides, acid anhydrides & amides

i) **Reactions of Acyl Halides**

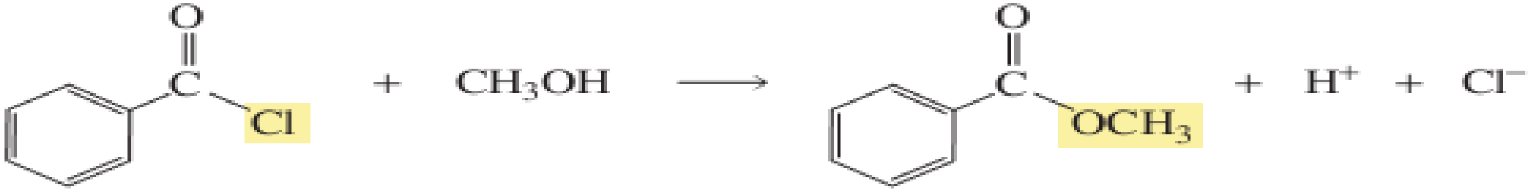
✓ Acyl halides react with carboxylate ions to form anhydrides, with alcohols to form esters, with water to form carboxylic acids, & with amines to form amides b/c in each case the incoming Nu: is a stronger base than the departing halide ion



mechanism for the conversion of an acyl chloride into an acid anhydride

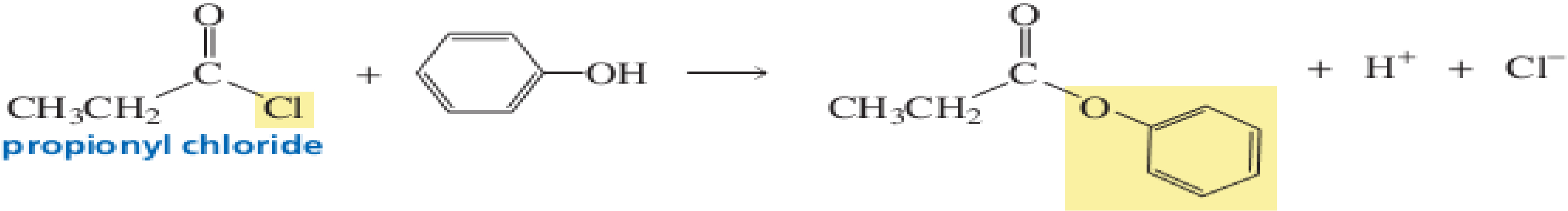


Reactions of Acyl Halides



benzoyl chloride

methyl benzoate

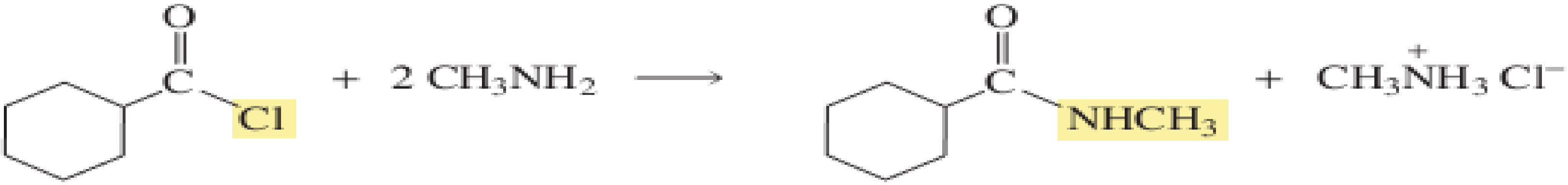


propionyl chloride

phenyl propionate

butyryl chloride

butyric acid



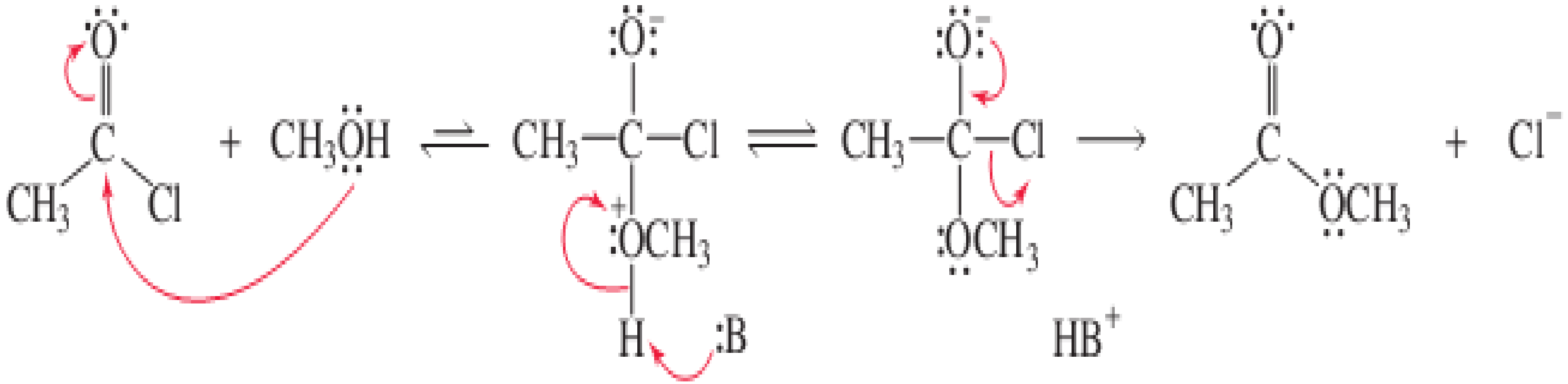
cyclohexanecarbonyl chloride

N-methylcyclohexanecarboxamide

Reactions of Acyl Halides

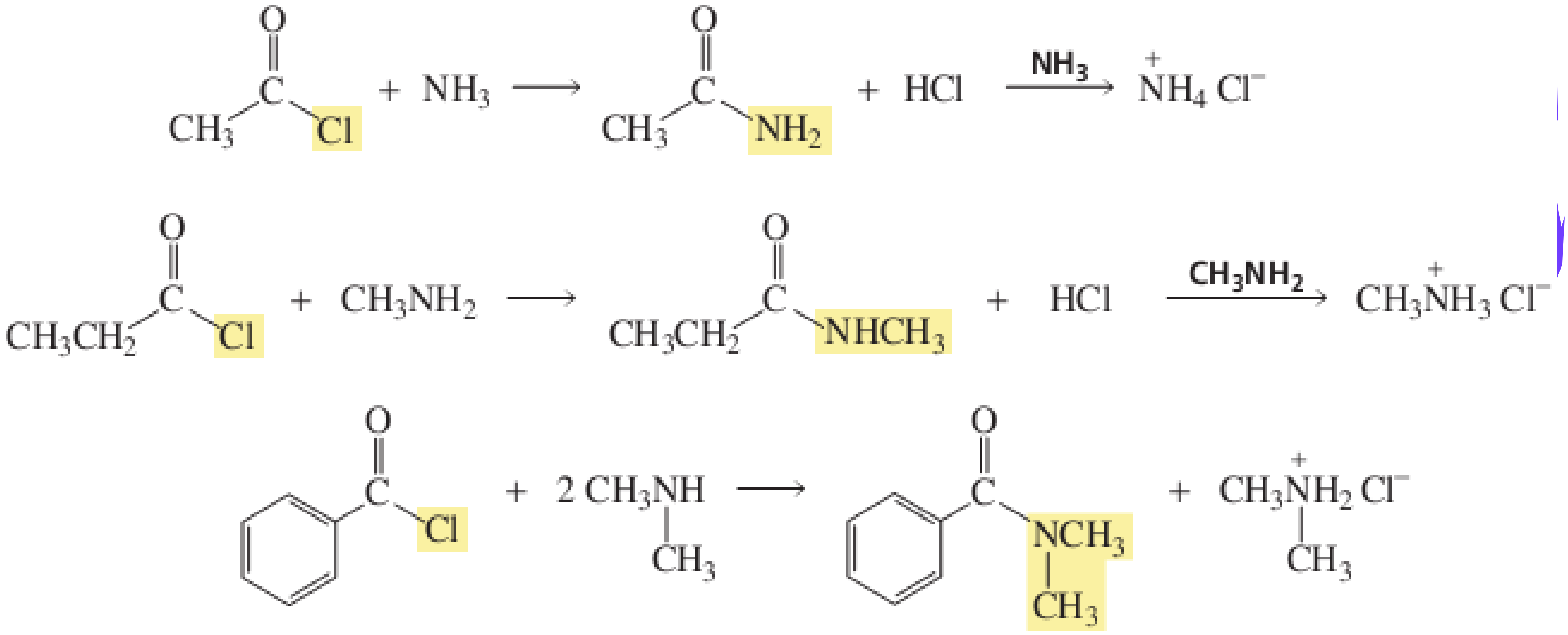
- ✓ In the conversion of an acyl chloride into an ester, the nucleophilic alcohol attacks the carbonyl **C** of the acyl chloride.
- ✓ B/c the protonated ether group is a strong acid, the tetrahedral intermediate loses a proton.
- ✓ Cl- is expelled from the deprotonated tetrahedral intermediate b/c Cl- is a weaker base than the alkoxide ion.

mechanism for the conversion of an acyl chloride into an ester



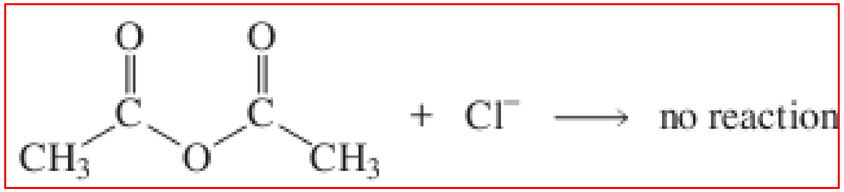
Reactions of Acyl Halides

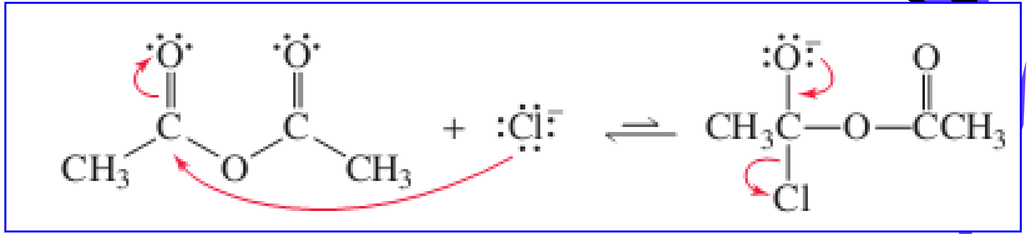
- ✓ The rxn of an acyl chloride with NH_3 or with 1^0 or 2^0 amine forms an **amide** & **HCl**.
- ✓ The acid generated in the rxn will protonate unreacted NH_3 or unreacted amine; b/c they are not Nu, the protonated amines cannot react with the acyl chloride.



Rxns of acid anhydrides

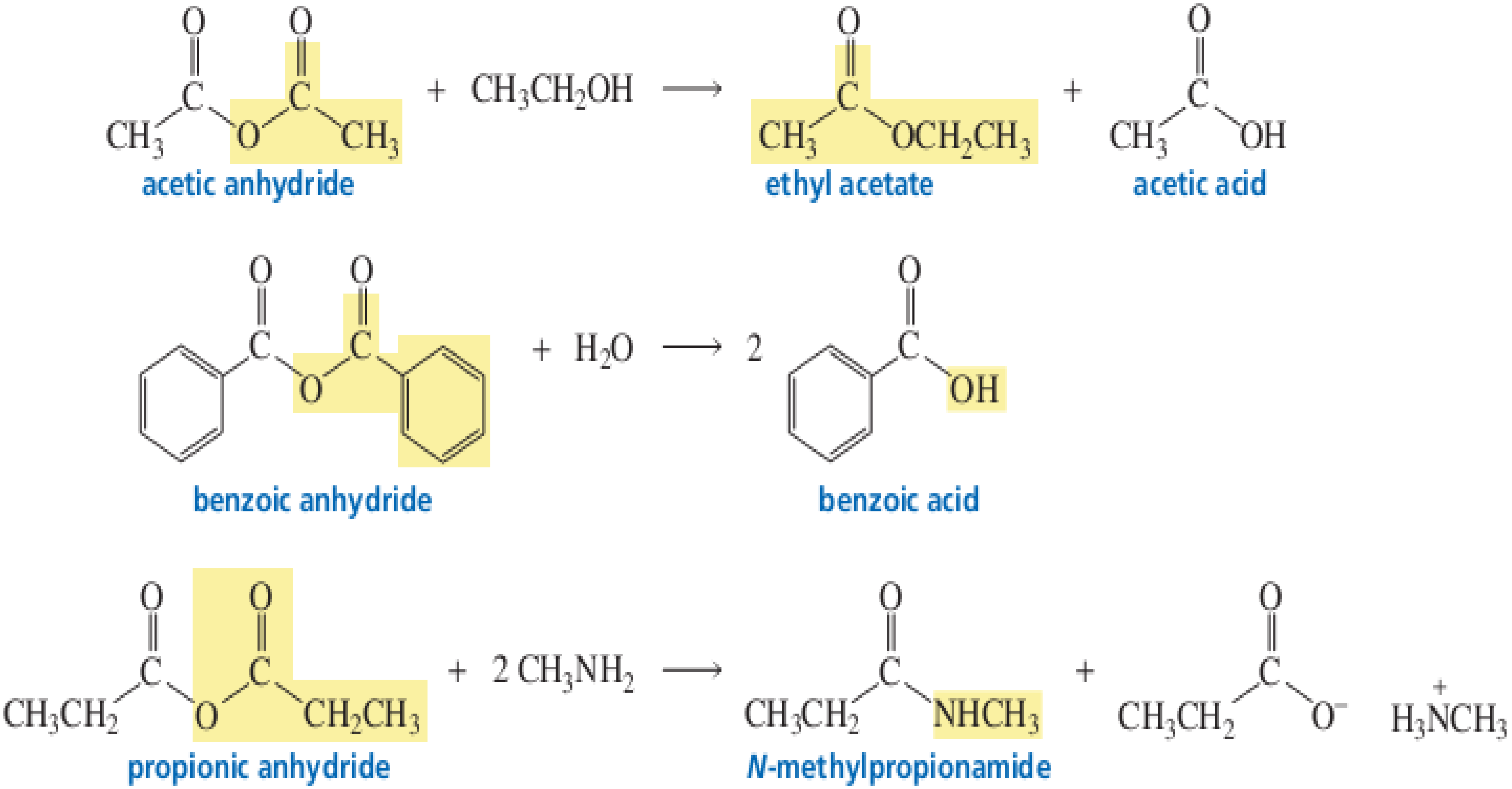
- ✓ Acid anhydrides do not react with NaCl or NaBr b/c the incoming halide ion is a weaker base than the departing carboxylate ion.





- ✓ B/c the incoming halide ion is the weaker base, it will be the substituent expelled from the tetrahedral intermediate.
- ✓ An acid anhydride reacts with an alcohol to form an ester & a carboxylic acid.
- ✓ with water to form two equivalents of a carboxylic acid, & with an amine to form an amide & a carboxylate ion.

Rxns of acid anhydrides



$$(CH_3CO)_2O + CH_3CH_2OH \longrightarrow CH_3COOCH_2CH_3 + CH_3COOH$$

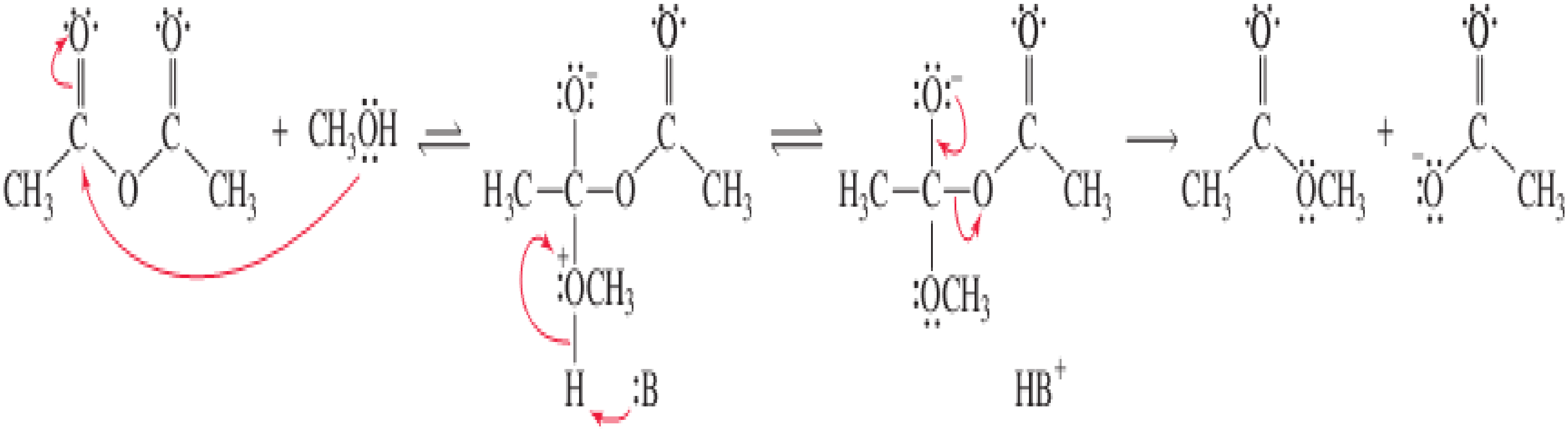
$$(C_6H_5CO)_2O + H_2O \longrightarrow 2\ C_6H_5COOH$$

$$(CH_3CH_2CO)_2O + 2\ CH_3NH_2 \longrightarrow CH_3CH_2CONHCH_3 + CH_3CH_2COO^- \ \overset{+}{H_3N}CH_3$$

Rxns of acid anhydrides

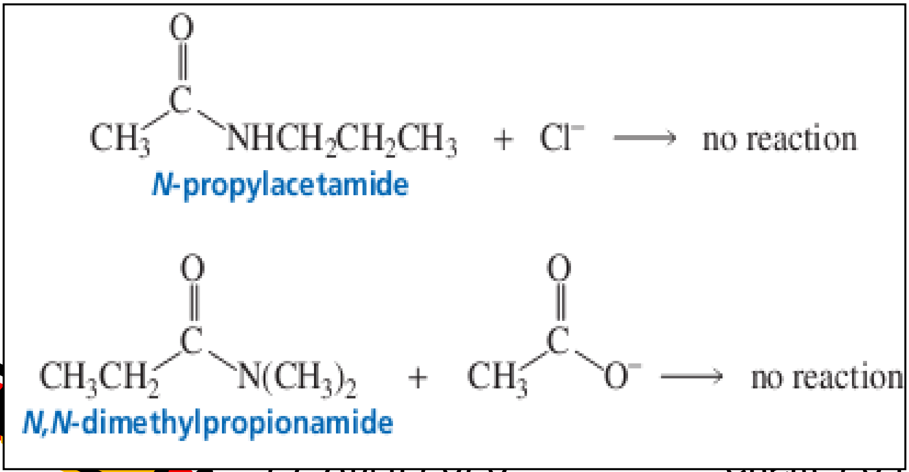
- ✓ All the above rxns follow the general mechanism. For example, the ff mechanism for conversion of an acid anhydride into an ester with the mechanism for conversion of an acyl chloride into an ester.

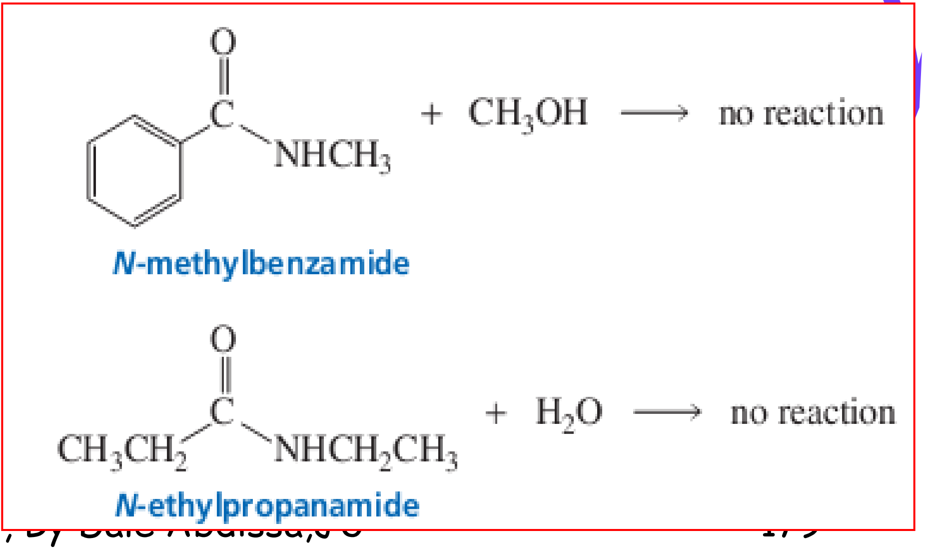
mechanism for the conversion of an acid anhydride into an ester (and a carboxylic acid)



Rxns of amides

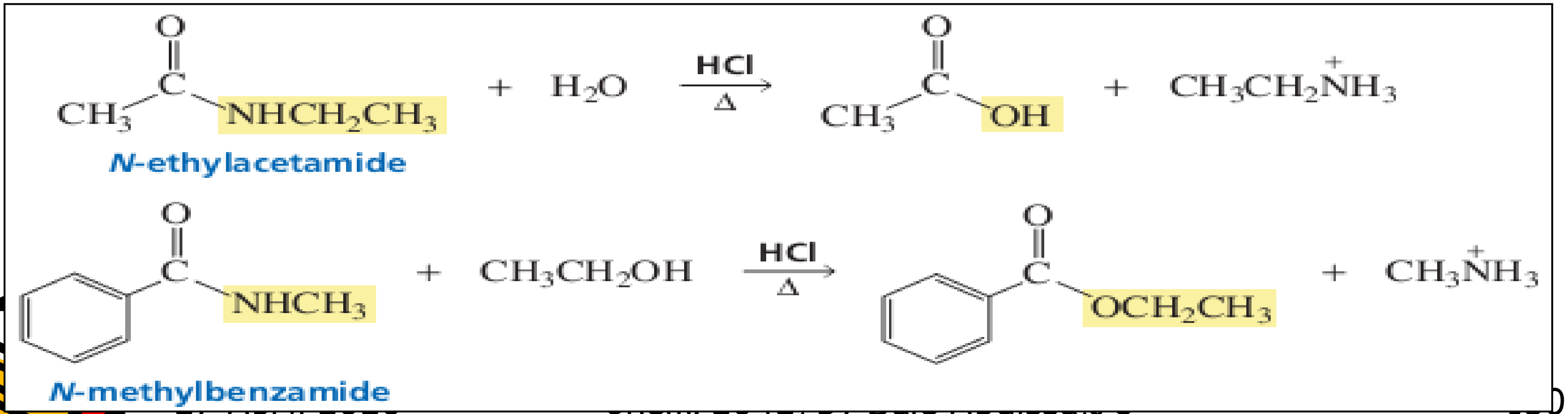
- ✓ Amides are very unreactive cpds, which is comforting, since proteins are composed of amino acids linked together by amide bonds.
- ✓ Amides do **not** react with halide ions, carboxylate ions, alcohols, or water b/c, the incoming Nu**:** is a weaker base than the LG of the amide.





Acid-Catalyzed Hydrolysis of Amides

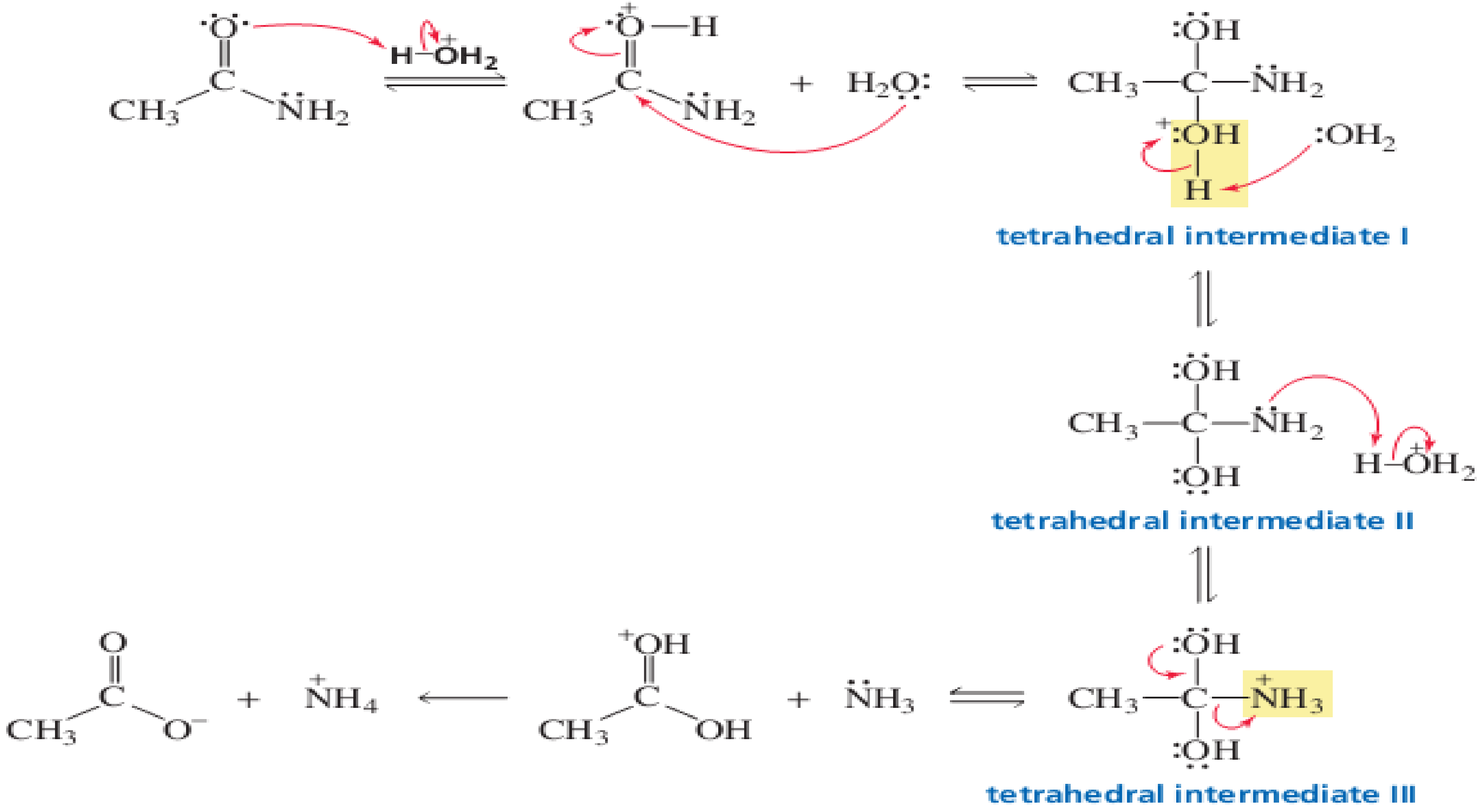
- ✓ When an amide is hydrolyzed under acidic conditions, the acid protonates the carbonyl oxygen, increasing the susceptibility of the carbonyl **C** to nucleophilic attack.
- ✓ Nucleophilic attack by water on the carbonyl **C** leads to tetrahedral intermediate.
- ✓ Amides do react with water & alcohols if the rxn mixture is heated in the presence of an acid.



Acid-Catalyzed Hydrolysis of Amides

- ✓ An acid catalyst increases the reactivity of a carbonyl group

mechanism for acid-catalyzed hydrolysis of an amide



3.3 Enolization-Ketonization reactions

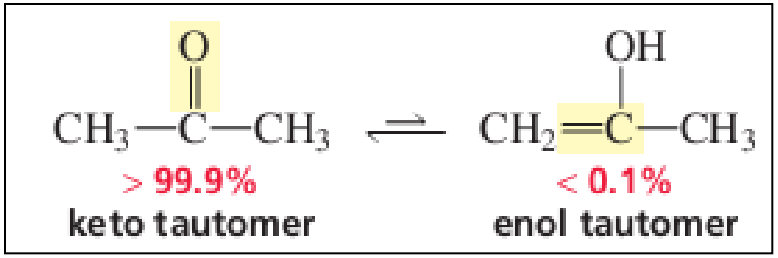
✓ A ketone exists in equilibrium with its enol tautomer.

✓ tautomers are isomers that are in rapid equilibrium.

✓ Keto-enol tautomers differ in the location of a double bond & H.

$$RCH_2-\overset{O}{\overset{\|}{C}}-R \rightleftharpoons RCH=\overset{OH}{\overset{|}{C}}-R$$

keto tautomer enol tautomer



$$CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \rightleftharpoons CH_2=\overset{OH}{\overset{|}{C}}-CH_3$$

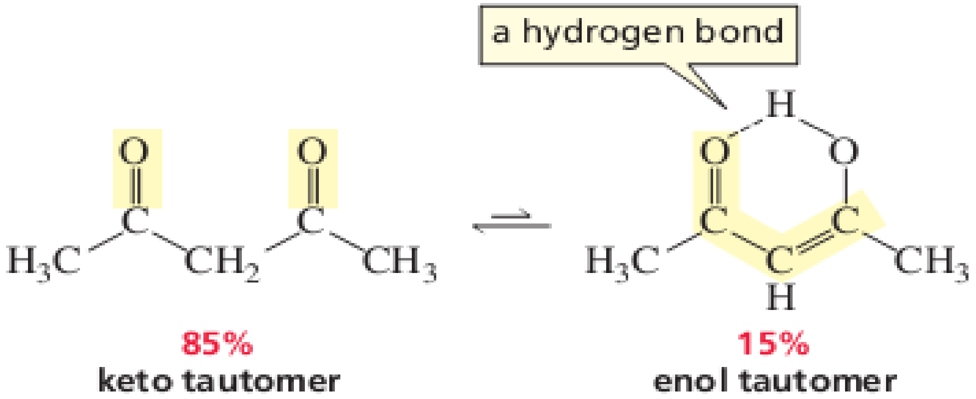
$> 99.9\%$ keto tautomer

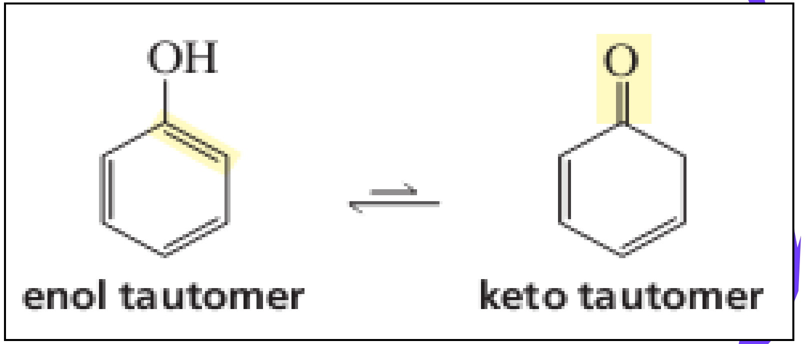
$< 0.1\%$ enol tautomer

✓ For most ketones, the enol tautomer is much less stable than the keto tautomer. e.g. an aqueous soln of acetone exists as an equilibrium mixture of more than 99.9% keto tautomer and less than 0.1% enol tautomer.

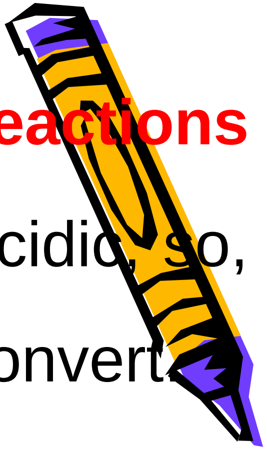
Enolization-Ketonization reactions

- ✓ The fraction of the enol tautomer in an aq. soln is greater for $\beta-$diketone a b/c the enol tautomer is stabilized by intramolecular H-bonding & by conjugation of the C-C double bond with the second carbonyl group.



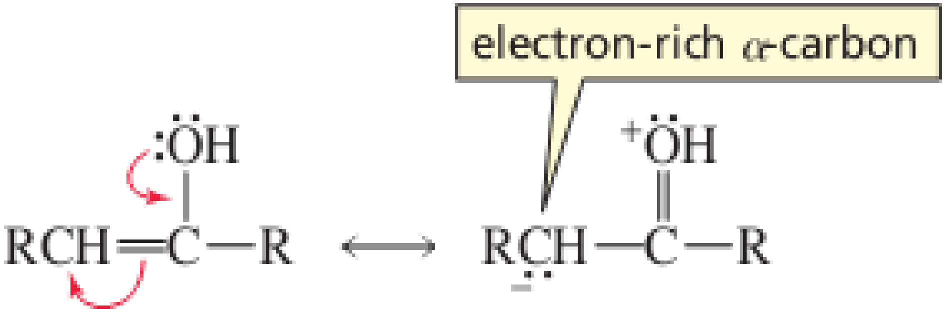


- ✓ Phenol is unusual in that its enol tautomer is more stable than its keto tautomer b/ct he enol tautomer is aromatic, but the keto tautomer is not.

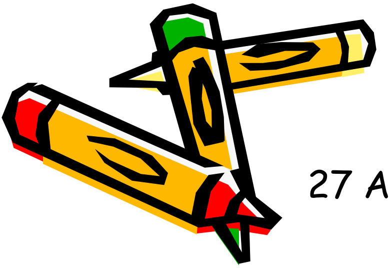


Enolization-Ketonization reactions

- A **H** on a **C** adjacent to a carbonyl **C** is somewhat acidic, so, we can understand why keto & enol tautomers interconvert.
- Keto–enol interconversion is also called keto–enol tautomerization or enolization.
- The interconversion of the tautomers can be catalyzed by either acids or bases.



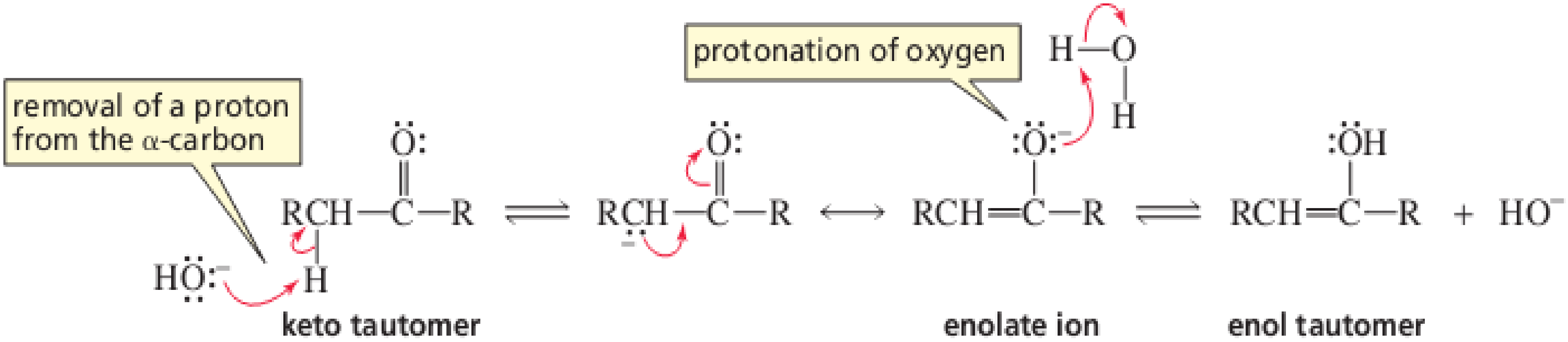
resonance contributors of an enol



Enolization-Ketonization reactions

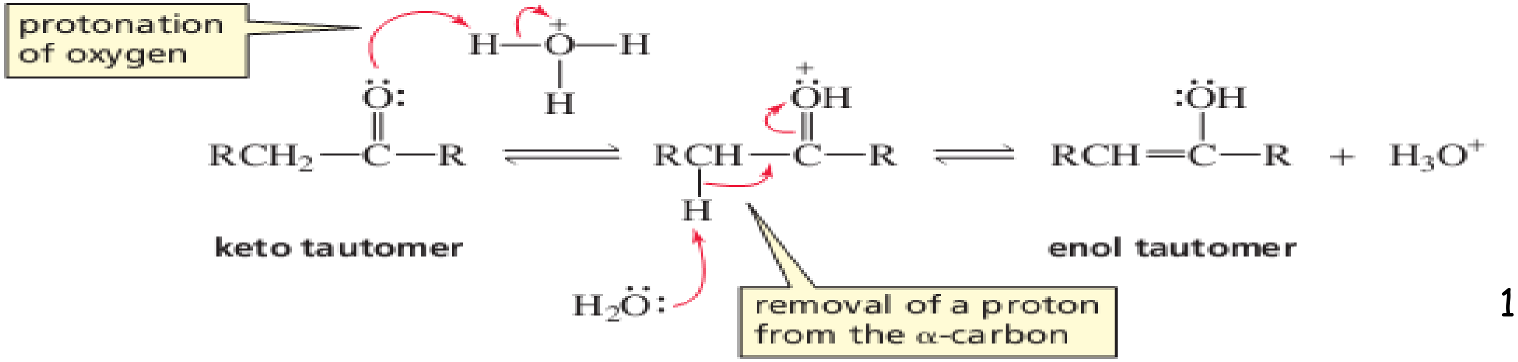
- ✓ In a basic soln,-OH removes H from the of the keto tautomer.

base-catalyzed keto–enol interconversion



- ✓ In an acidic soln, the carbonyl **O** of the keto tautomer is protonated & water removes **H** from the forming the enol.

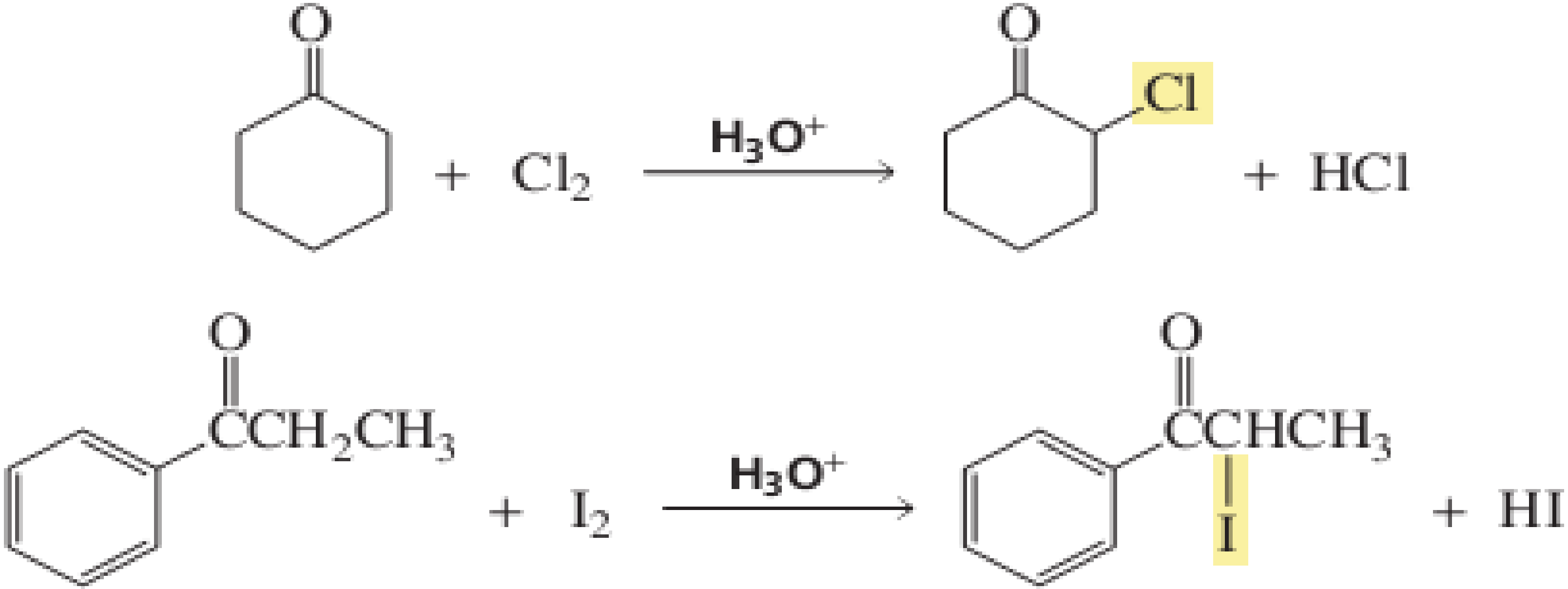
acid-catalyzed keto–enol interconversion



3.3 Halogenation of the α-C of Aldehydes & Ketones

3.3.1 Acid-Catalyzed Halogenation

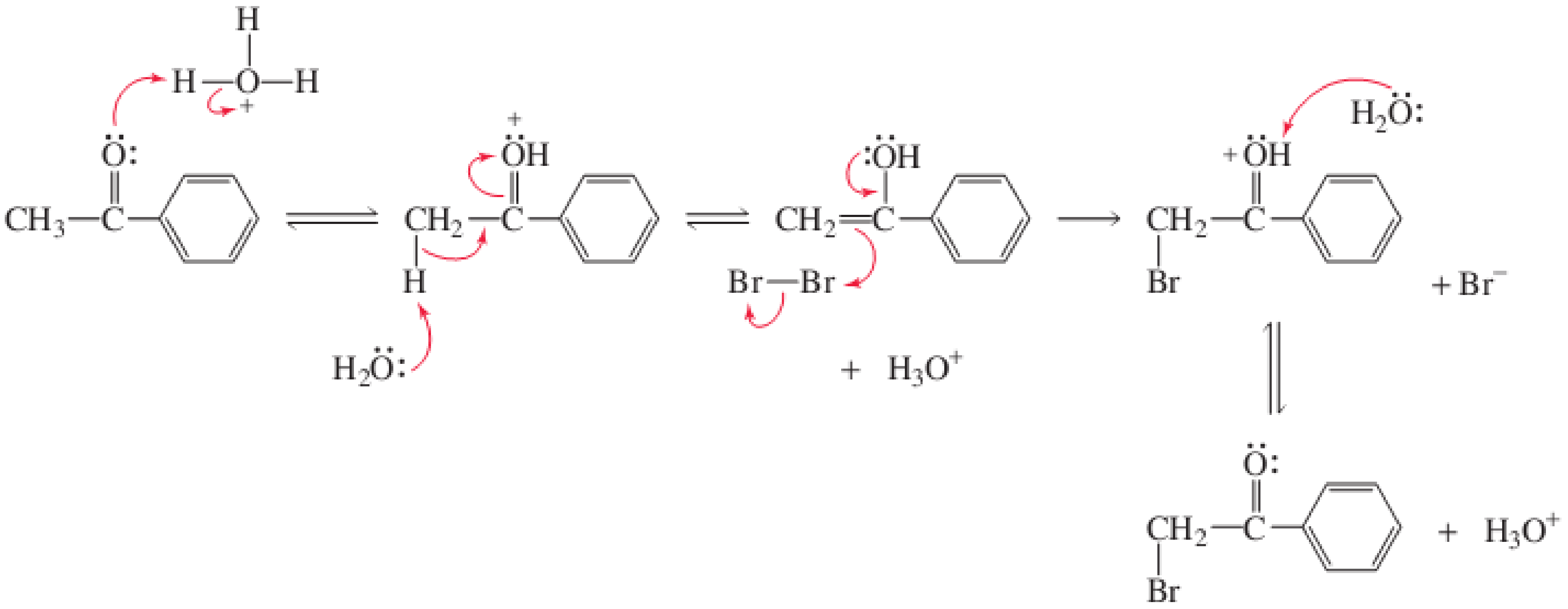
- When Br_2,Cl_2 or I_2 is added to an acidic soln of an aldehyde/ketone, a halogen replaces one of the **α-H** of the carbonyl cpd.



3.3 Halogenation of the α-C of Aldehydes & Ketones

3.3.1 Acid-Catalyzed Halogenation

- ✓ In the first step of rxn, the carbonyl oxygen is protonated.
- ✓ Water is the base that removes a proton from the forming an enol that reacts with an electrophilic halogen.

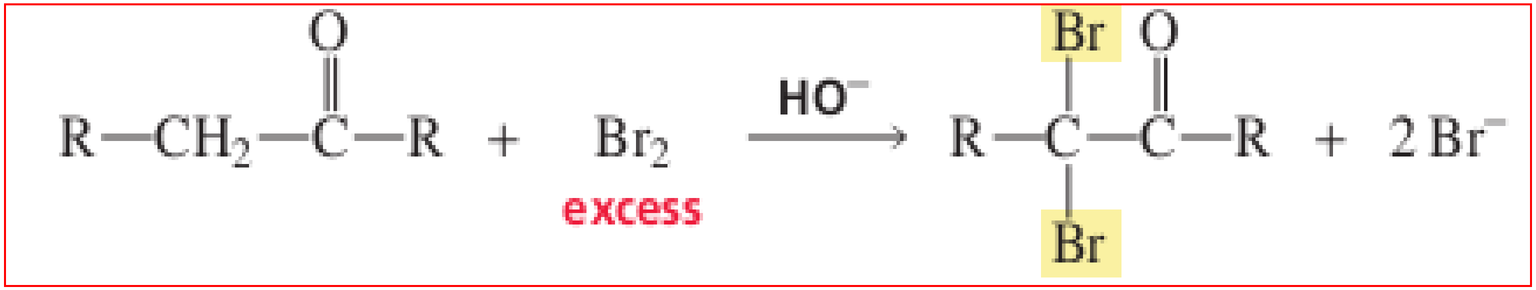


acid-catalyzed halogenation

3.3 Halogenation of the α-C of Aldehydes & Ketones

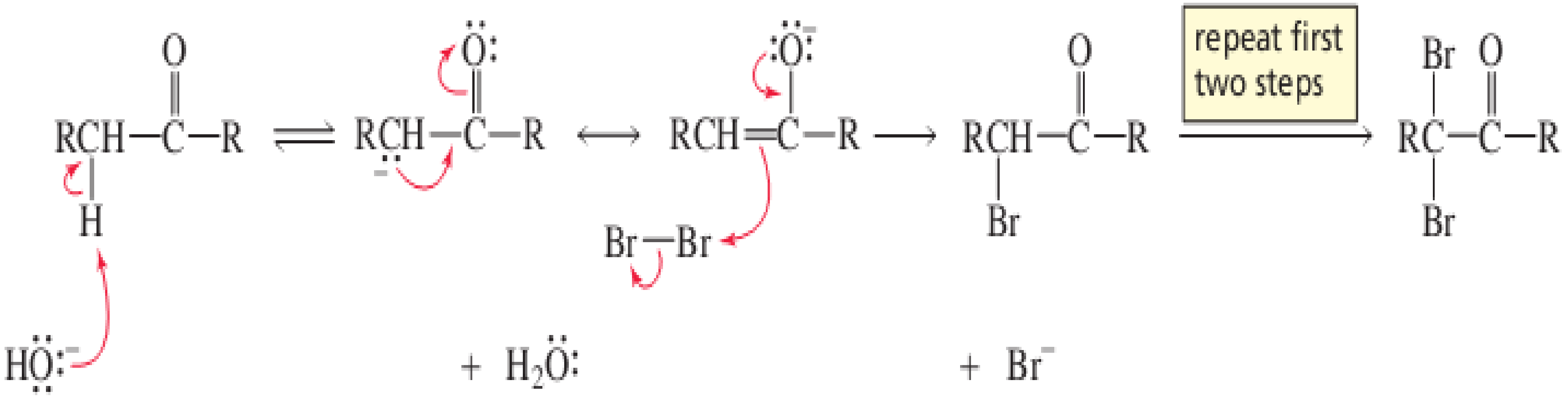
3.3.1 Base-Promoted Halogenation

- ✓ When excess Br_2,Cl_2 or I_2 is added to an basic soln of an aldehyde/ketone, a halogen replaces all of the **α-H.**



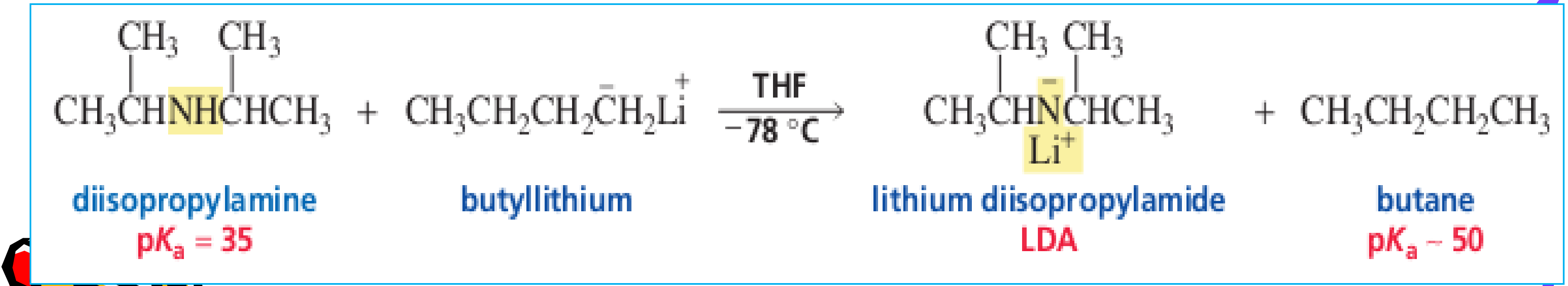
$$R-CH_2-\overset{\overset{O}{\|}}{C}-R + \underset{\text{excess}}{Br_2} \xrightarrow{HO^-} R-\underset{Br}{\overset{Br}{\overset{|}{\underset{|}{C}}}}-\overset{\overset{O}{\|}}{C}-R + 2\,Br^-$$

base-promoted halogenation



Alkylation of the α-C of Carbonyl Cpds

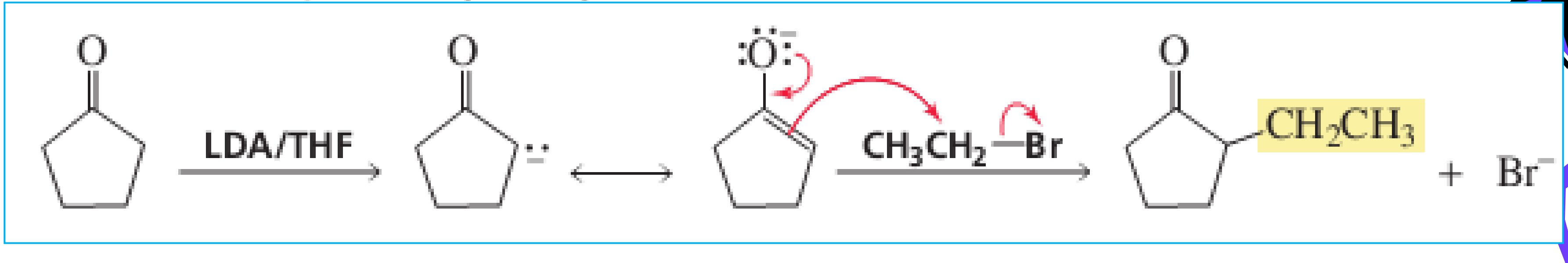
- Alkylation is carried out by first removing **H** from the α-**C** with strong base such as LDA & then adding the alkyl halide.
- LDA is a strong base but a poor Nu, so it removes α-**H** much faster than it attacks a carbonyl C.
- LDA is easily prepared by adding butyllithium to di-isopropylamine (DIA) in THF at -78°C.



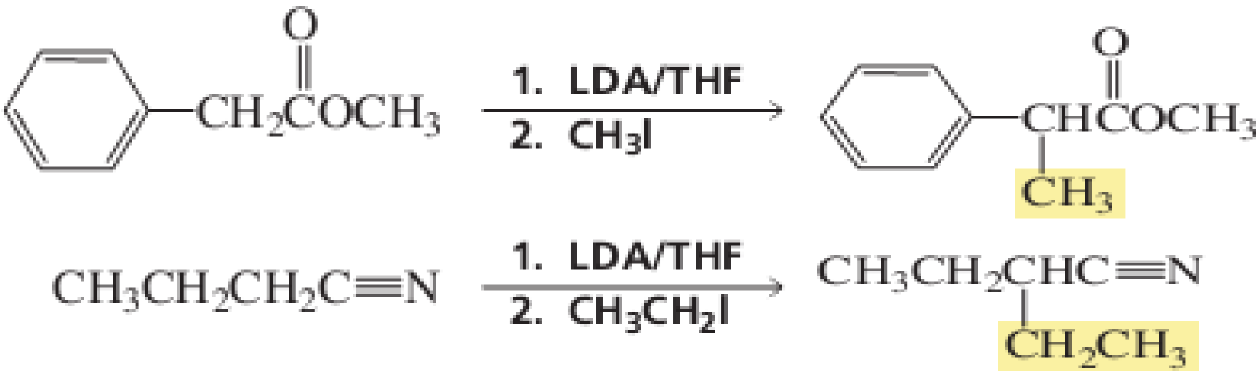
$$CH_3\overset{\overset{CH_3}{|}}{C}HNH\overset{\overset{CH_3}{|}}{C}HCH_3 + CH_3CH_2CH_2\overset{-}{C}H_2\overset{+}{Li} \xrightarrow[-78\,^{\circ}C]{THF} CH_3\overset{\overset{CH_3}{|}}{C}H\underset{Li^+}{\overset{-}{N}}\overset{\overset{CH_3}{|}}{C}HCH_3 + CH_3CH_2CH_2CH_3$$

Alkylation of the α-C of Carbonyl Cpds

- B/c the alkylation is an SN2 rxn, it works best with methyl halides & primary alkyl halide.

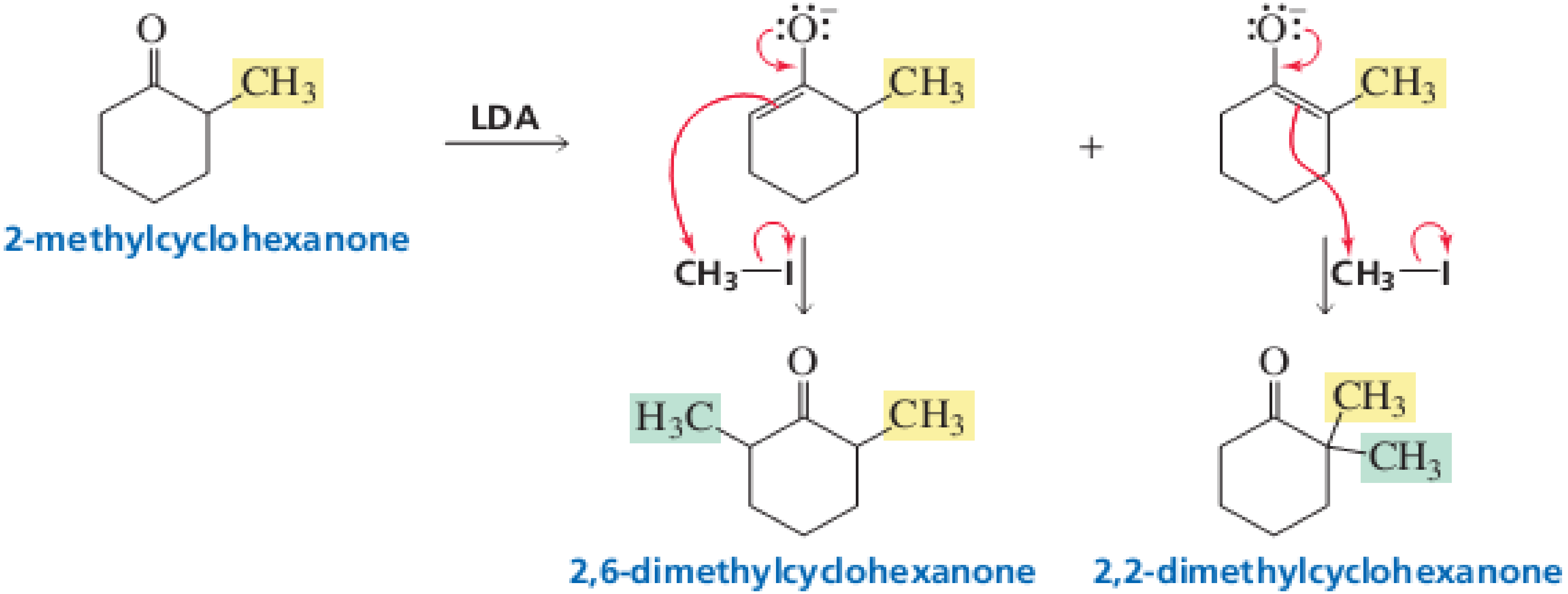


- Ketones, esters, & nitriles can be alkylated at the **α-C** in this way. Aldehydes, give poor yields of **α-alkylated** products



Alkylation of the α-C of Carbonyl Cpds

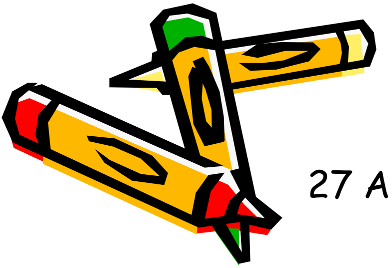
- Two d/t products can be formed when the ketone is **not** symmetrical, b/c either **α-C** can be alkylated.
- e.g. methylation of 2-methylcyclohexanone with one equivalent of CH_3I forms both 2,6-dimethylcyclohexanone & 2,2-dimethylcyclohexanone.



Halogenation of the α-C of Aldehydes & Ketones

3.3.2 Halo form Reaction of Methyl Ketones

- ✓ In the presence of excess base & excess halogen, a methyl ketone is first converted into a trihalo-substituted ketone.
- ✓ Then OH ion attacks the carbonyl **C** of the trihalo-substituted ketone.
- ✓ B/c the trihalomethyl ion is a weaker base than OH ion.
- ✓ The conversion of a methyl ketone to a carboxylic acid is called **haloform** rxn b/c one of the products is haloform like chloroform/$CHCl_3$, bromoform/$CHBr_3$ or CHI_3

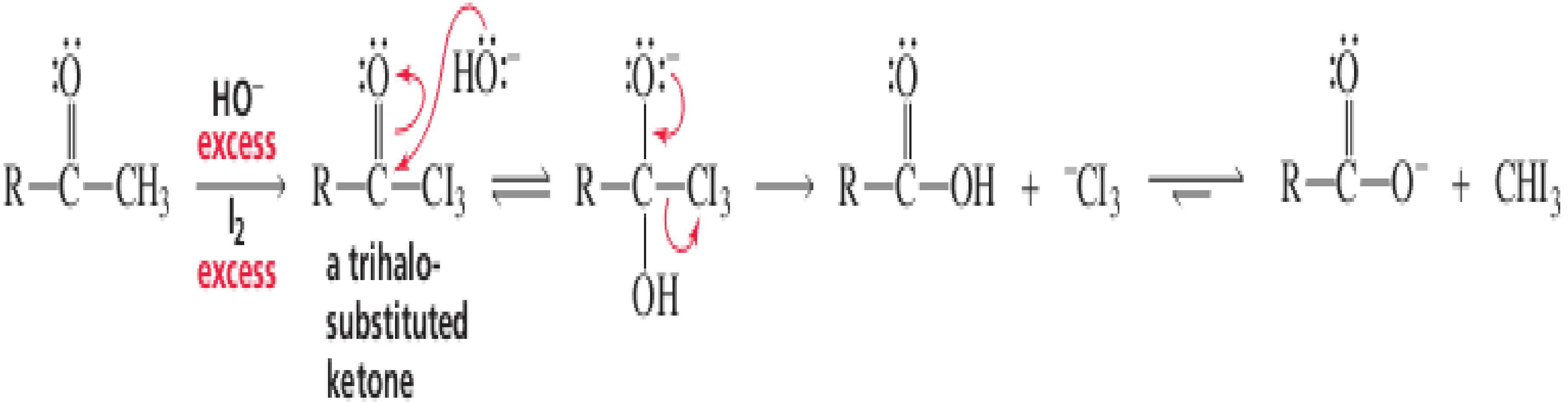


Halogenation of the α-C of Aldehydes & Ketones

3.3.2 Halo form Reaction of Methyl Ketones

- The presence of a methyl ketone was indicated by the formation of iodoform, a bright yellow compound.

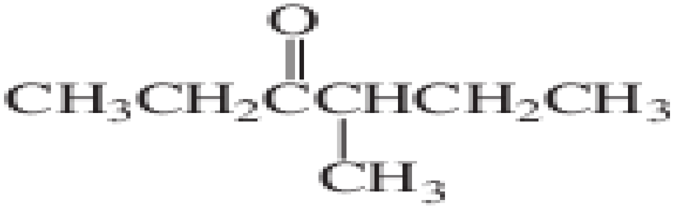
the haloform reaction



Halogenation of the α-C of Aldehydes & Ketones

Assignment #4)

How could you prepare **4-methyl-3-hexanone** from a ketone containing no more than six carbon atoms?



$$CH_3CH_2\overset{O}{\overset{\|}{C}}\underset{\underset{CH_3}{|}}{C}HCH_2CH_3$$

4-methyl-3-hexanone

Hint: Use the ff. starting materials with LDA

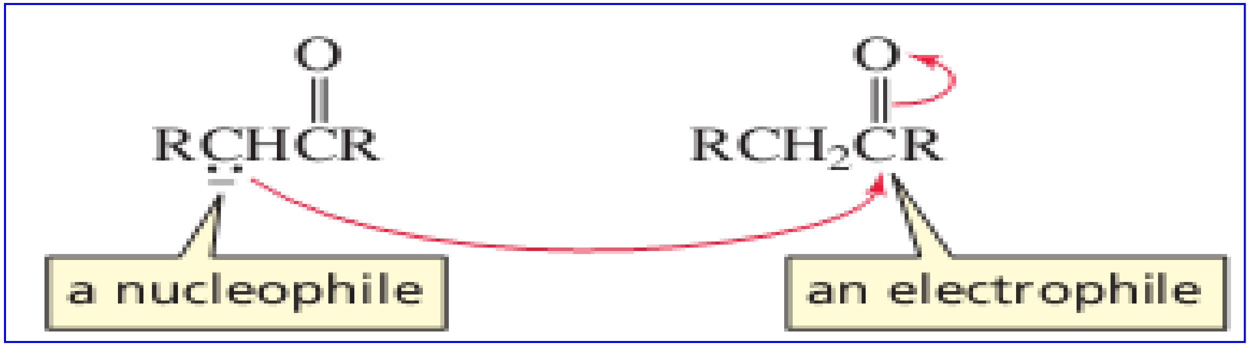
$$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3 + CH_3Br \quad \text{or} \quad CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3 + CH_3CH_2Br$$

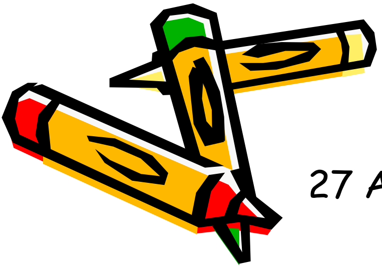
3-hexanone

3-pentanone

3.3.3 Aldol & Related Condensation rxns

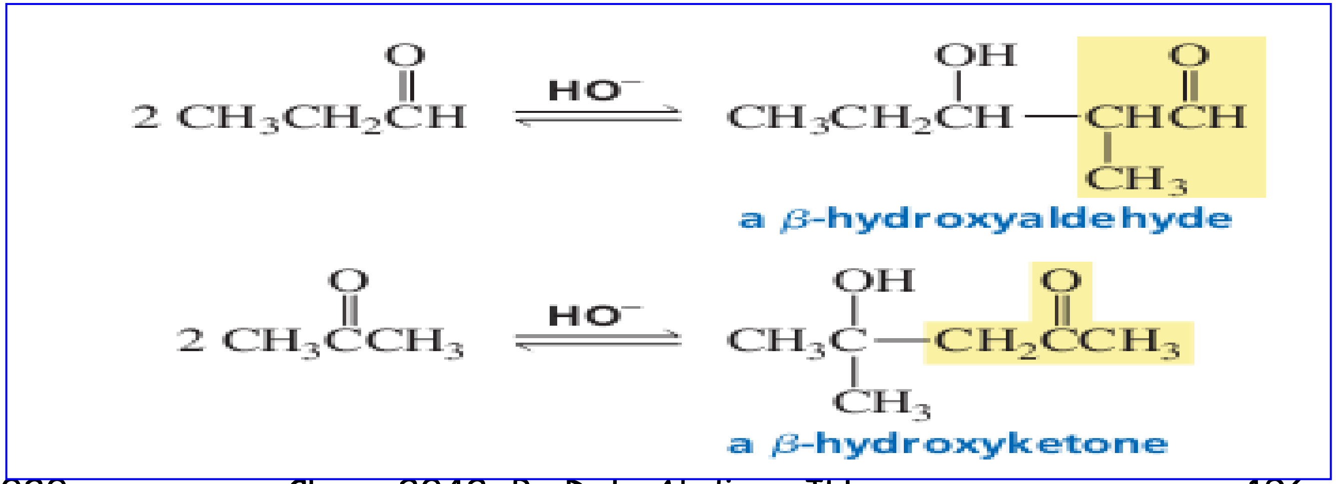
- ✓ When **H** is removed from the $\alpha - C$ of an aldehyde or a ketone, the resulting anion is a Nu & reacts with E+.
- ✓ An **aldol addition** is a rxn in which both of these activities are observed: One molecule of a carbonyl cpd after **H** is removed from an $\alpha - C$ reacts as a Nu and attacks the electrophilic carbonyl **C** of a second molecule of the carbonyl cpd.

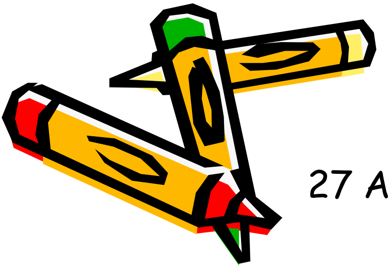




Aldol & Related Condensation rxns

- ✓ An aldol addition is a rxn b/n two molecules of an aldehyde or two molecules of a ketone .
- ✓ When the reactant is an aldehyde, the addition product is ***β* –hydroxyaldehyde** which is why the rxn is called an aldol addition (“ald” for aldehyde, “ol ” for alcohol).
- ✓ When the reactant is a ketone, the addition product is a *β* –hydroxyketone.

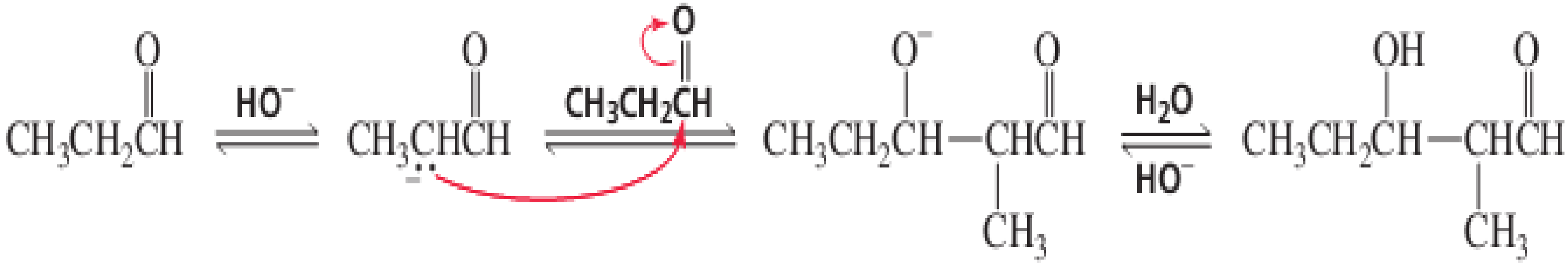




Aldol & Related Condensation rxns

- ✓ In the 1st step of an aldol addition, a base removes an $\alpha - H$ from the carbonyl cpd, creating an **enolate**.
- ✓ The enolate adds to the carbonyl **C** of a second molecule of the carbonyl cpd, & the resulting -vely charged oxygen is protonated by the solvent.

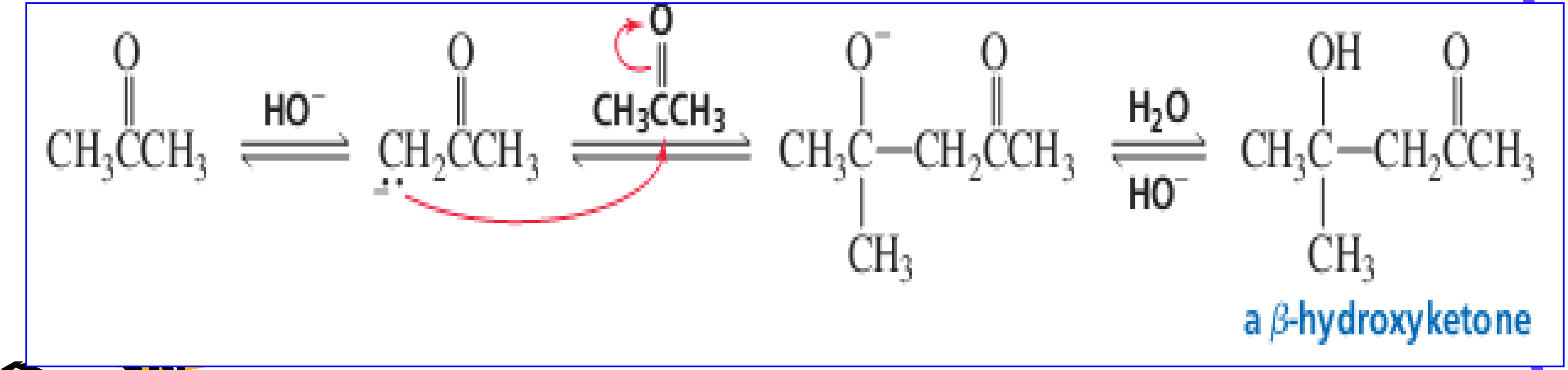
mechanism for the aldol addition



a β-hydroxyaldehyde

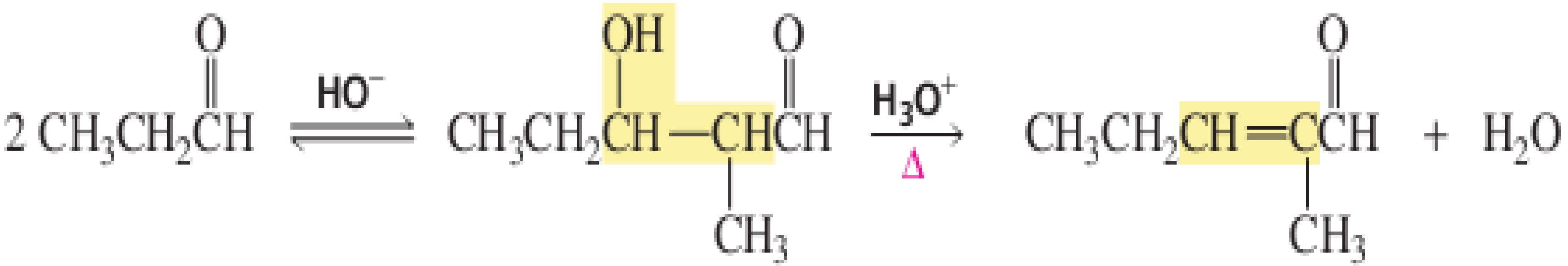
Aldol & Related Condensation rxns

- ✓ Ketones are less susceptible than aldehydes to attack by **Nu**, so aldol additions occur more slowly with ketones.
- ✓ The relatively high reactivity of aldehydes in competing aldol addition rxns is what causes them to give low yields of $\alpha-$ alkylation products.



Aldol & Related Condensation rxns

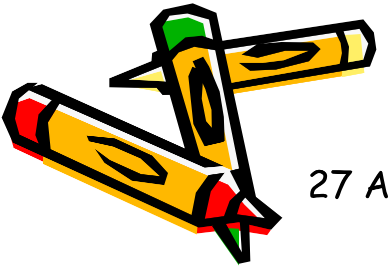
- ✓ If the product of an aldol addition is dehydrated, the overall rxn is called an aldol condensation.
- ✓ A condensation rxn is a rxn that combines two molecules while removing a small molecule (water or an alcohol).
- ✓ Conjugation increases the stability of the product.



$$2\,CH_3CH_2\overset{O}{\overset{\|}{C}}H \overset{HO^-}{\rightleftharpoons} CH_3CH_2\overset{OH}{\overset{|}{C}}H-\underset{\underset{CH_3}{|}}{C}H\overset{O}{\overset{\|}{C}}H \xrightarrow[\Delta]{H_3O^+} CH_3CH_2CH=\underset{\underset{CH_3}{|}}{C}\overset{O}{\overset{\|}{C}}H + H_2O$$

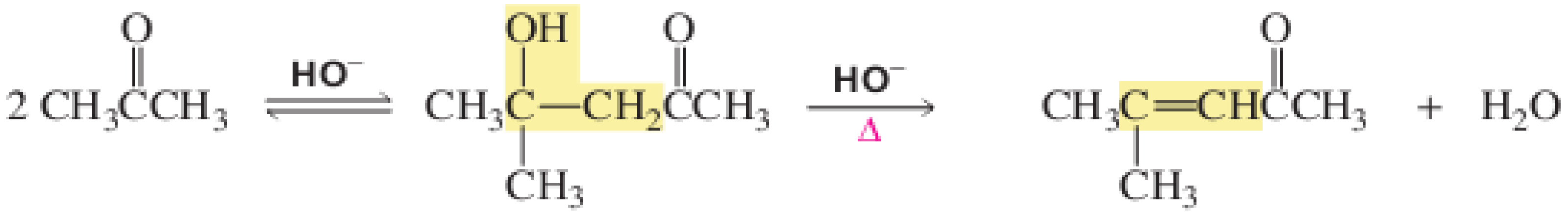
a β-hydroxyaldehyde

an α,β-unsaturated aldehyde



Aldol & Related Condensation rxns

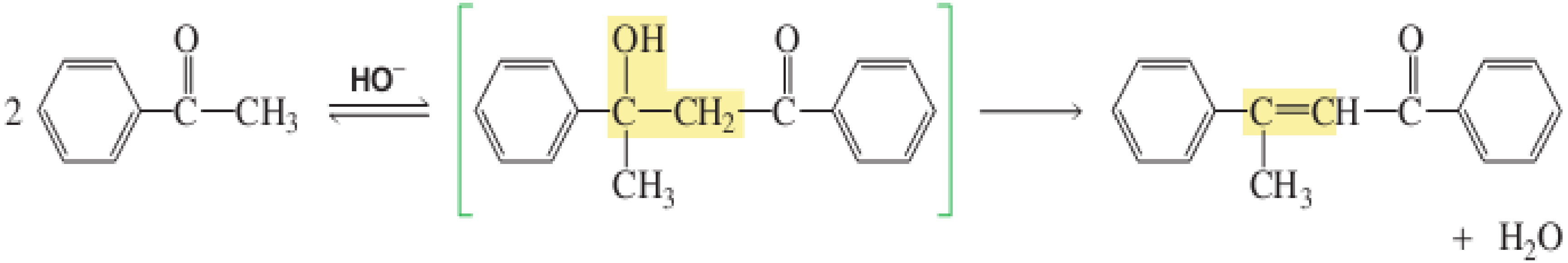
- ✓ β -Hydroxyaldehyde & β -Hydroxyketone can also be dehydrated under basic conditions, so heating the aldol addition product in either acid or base leads to dehydration.
- ✓ The product of dehydration is called an enone.



a β-hydroxyketone

an α,β-unsaturated ketone
an enone

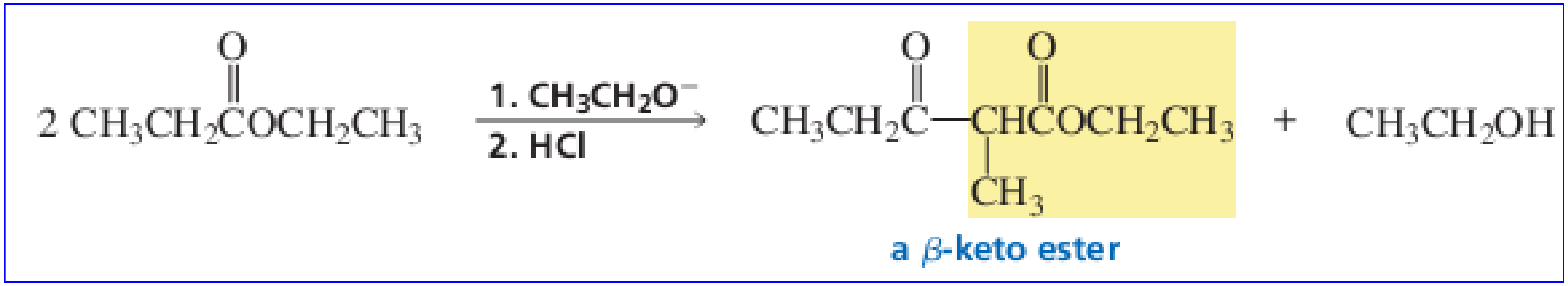
- ✓ Dehydration may occurs without additional heating.



Aldol & Related Condensation rxns

The Claisen Condensation:

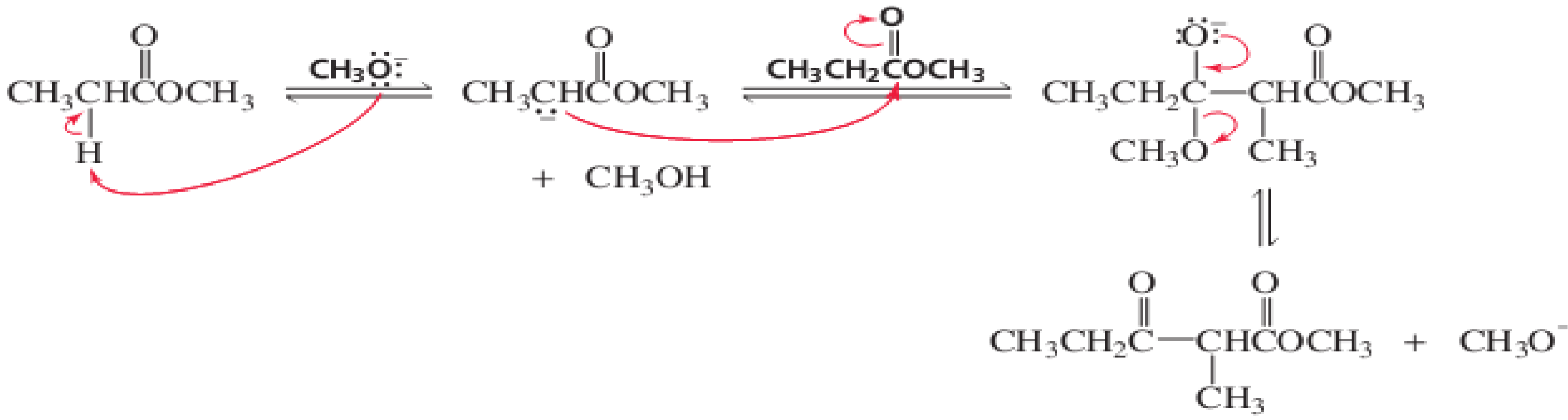
- ✓ When two molecules of an ester undergo a condensation rxn, the rxn is called a Claisen condensation.
- ✓ The product of a Claisen condensation is a $\boldsymbol{\beta}$ **–keto ester.**



$$2\ CH_3CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow[\text{2. HCl}]{\text{1. }CH_3CH_2O^-} CH_3CH_2\overset{O}{\overset{\|}{C}}-\underset{CH_3}{\underset{|}{C}H}\overset{O}{\overset{\|}{C}}OCH_2CH_3 + CH_3CH_2OH$$

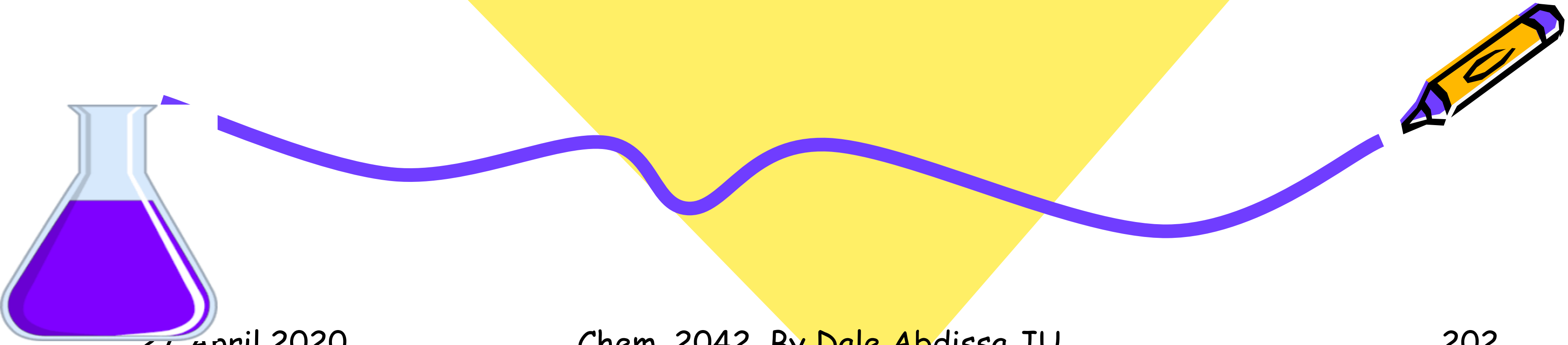
a β-keto ester

mechanism for the Claisen condensation

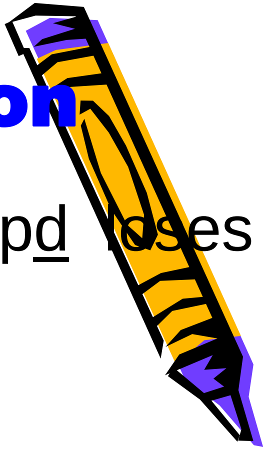


Chapter 4

4.Oxidation-reduction rxn

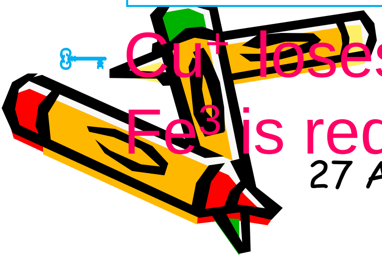


Unit 4. Oxidation-reduction reaction

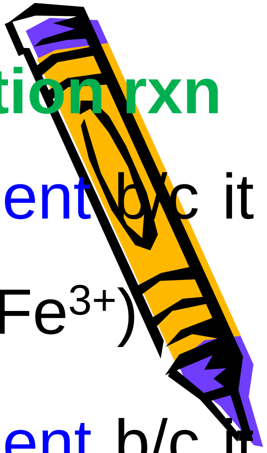


- In an oxidation–reduction rxn (**Redox rxn**) one cpd loses electrons (e-s) & one cpd gains e-s.
- The cpd that loses e-s is oxidized, & the one that gains e-s is reduced.
- Use the ff in order to remember "**LEO** the lion says **GER**": Loss of Electrons is Oxidation; Gain of Electrons is Reduction.
- E.g. oxidation–reduction rxn involving inorganic reagents:

$$Cu^{+} + Fe^{3+} \longrightarrow Cu^{2+} + Fe^{2+}$$

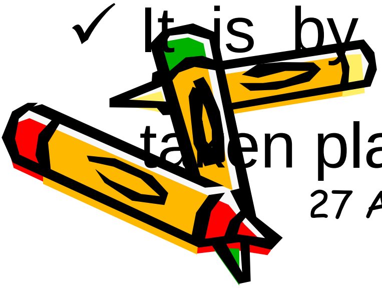


- Cu^{+} loses of an e-, so Cu^{+} is oxidized, Fe^{3+} gains an e-, so Fe^{3+} is reduced.



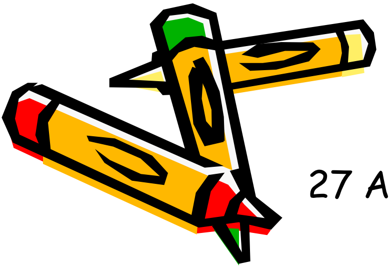
oxidation–reduction rxn

- ✓ cpd that is oxidized (Cu+) is called the reducing agent b/c it loses the e-s that are used to reduce the other cpd (Fe^{3+})
- ✓ cpd that is reduced (Fe^{3+}) is called the oxidizing agent b/c it gains the e-s given up by the other cpd (Cu+) when it is oxidized.
- ✓ It is easy to tell whether an organic cpd has been oxidized or reduced simply by **looking at the change in the structure of the cpd .**
- ✓ It is by looking at rxns where oxidation or reduction has taken place **on carbon.**

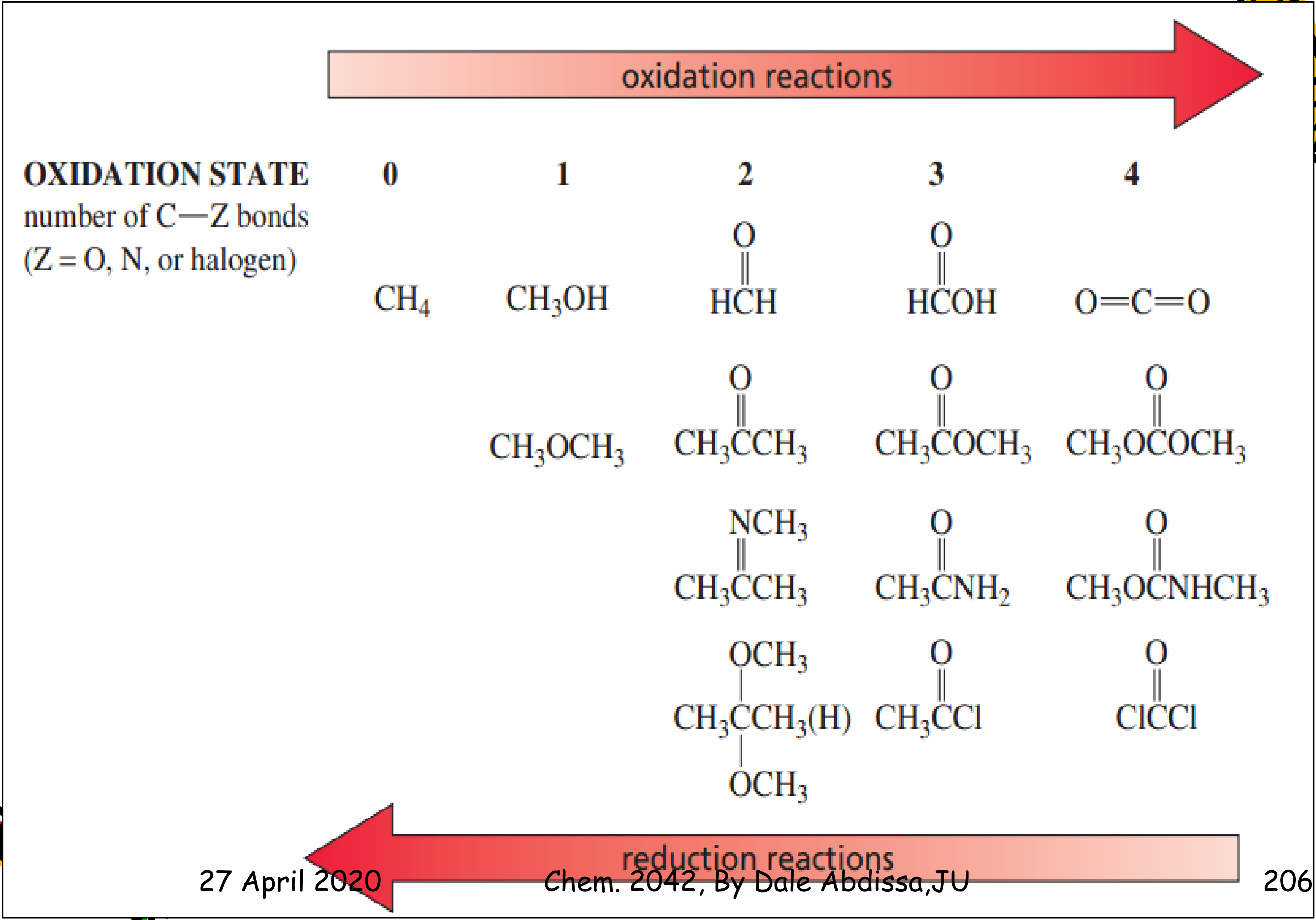


oxidation–reduction rxn

- ✓ If the rxn increases the no of **C-H** bonds or decreases the no of **C-O**, **C-N** or **C-x** bonds (where X denotes a halogen), the cpd has been reduced.
- ✓ If the rxn decreases the no of **C-H** bonds or increases the no of **C-O**, **C-N** or **C-x** bonds (where X denotes a halogen), the cpd has been **oxidized**.
- ✓ the oxidation state of a carbon atom equals the total no of its **C-O**, **C-N** and **C-x** bonds.



oxidation–reduction rxn



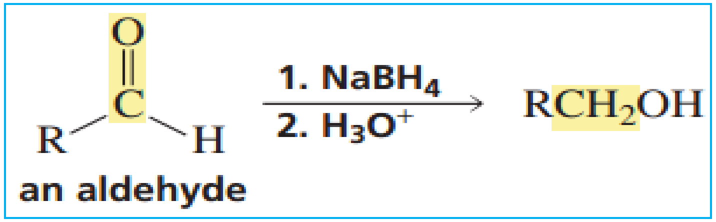
oxidation reactions

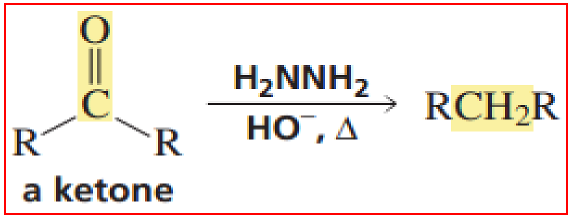
OXIDATION STATE number of C—Z bonds (Z = O, N, or halogen)	**0**	**1**	**2**	**3**	**4**
	CH_4	CH_3OH	$H\overset{O}{\overset{\parallel}{C}}H$	$H\overset{O}{\overset{\parallel}{C}}OH$	$O{=}C{=}O$
		CH_3OCH_3	$CH_3\overset{O}{\overset{\parallel}{C}}CH_3$	$CH_3\overset{O}{\overset{\parallel}{C}}OCH_3$	$CH_3O\overset{O}{\overset{\parallel}{C}}OCH_3$
			$CH_3\overset{NCH_3}{\overset{\parallel}{C}}CH_3$	$CH_3\overset{O}{\overset{\parallel}{C}}NH_2$	$CH_3O\overset{O}{\overset{\parallel}{C}}NHCH_3$
			$CH_3\underset{OCH_3}{\underset{\vert}{\overset{OCH_3}{\overset{\vert}{C}}}}CH_3(H)$	$CH_3\overset{O}{\overset{\parallel}{C}}Cl$	$Cl\overset{O}{\overset{\parallel}{C}}Cl$

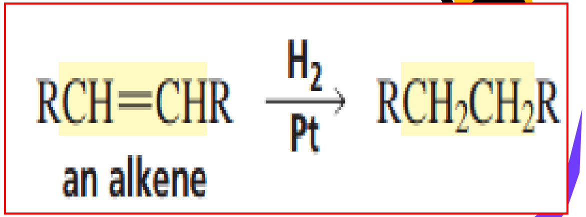
reduction reactions

oxidation–reduction rxn

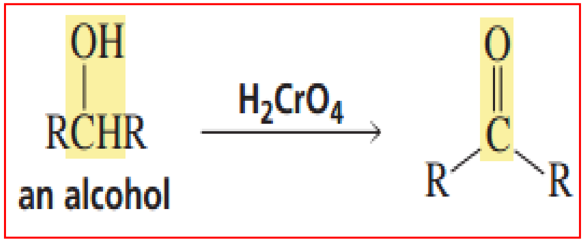
- Example : alkene, aldehyde, ketone are reduced.
- H_2, sodium borohydride & hydrazine are the reducing agents.

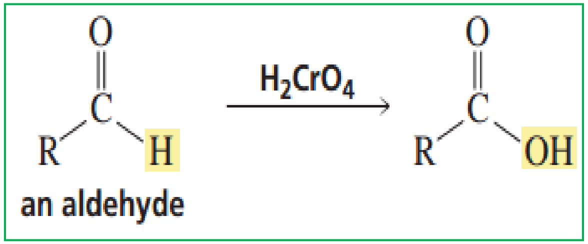


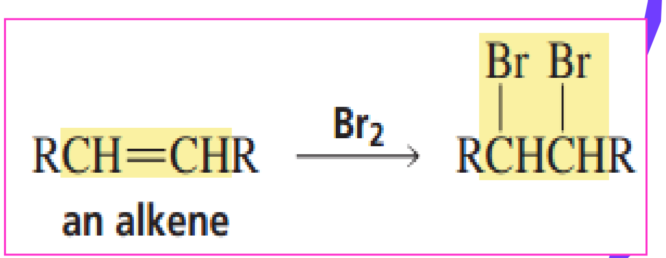


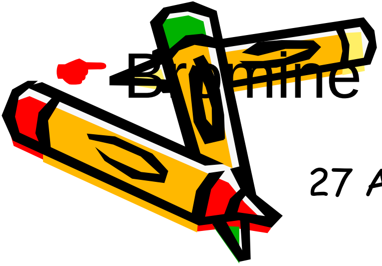


- **Reduction** at **C** increases the no of C-H bonds or decreases the no of C-O,C-N or C-X bonds.
- **Oxidation** at **C** decreases the no of C-H bonds or increases the no of C-O,C-N or C-X bonds.





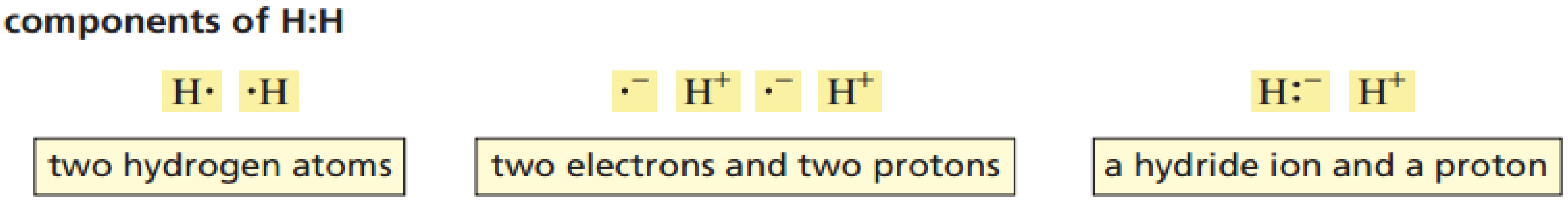




- Bromine & chromic acid (H_2CrO_4) are the **oxidizing agents**.

4.1 Reduction reaction

- An organic cpd is reduced when **H** is added to it.
- A molecule of H_2 is thought as being composed of (1) two H atoms, (2) two e-s & two protons, or (3) hydride ion & proton.



components of H:H

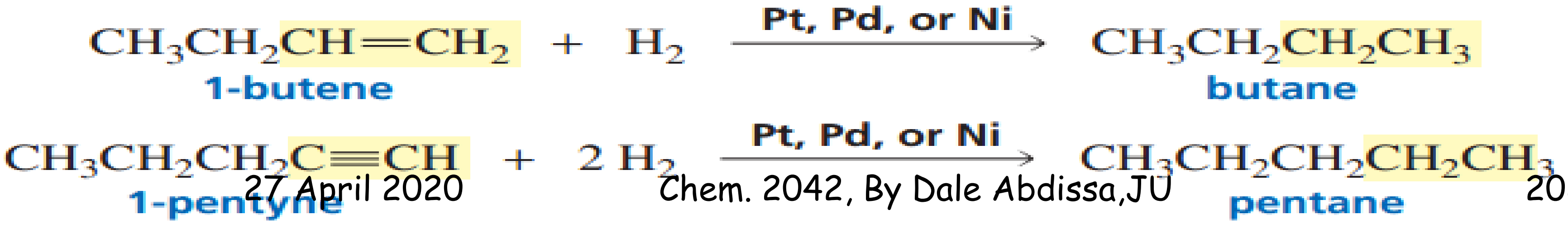
$H\cdot \quad \cdot H$ — two hydrogen atoms

$\cdot^- \quad H^+ \quad \cdot^- \quad H^+$ — two electrons and two protons

$H:^- \quad H^+$ — a hydride ion and a proton

Reduction by Addition of Two Hydrogen Atoms

- **H** can be added to C-C double & triple bonds in the presence of a metal catalyst (catalytic hydrogenations).



$$CH_3CH_2CH{=}CH_2 + H_2 \xrightarrow{\text{Pt, Pd, or Ni}} CH_3CH_2CH_2CH_3$$

1-butene → butane

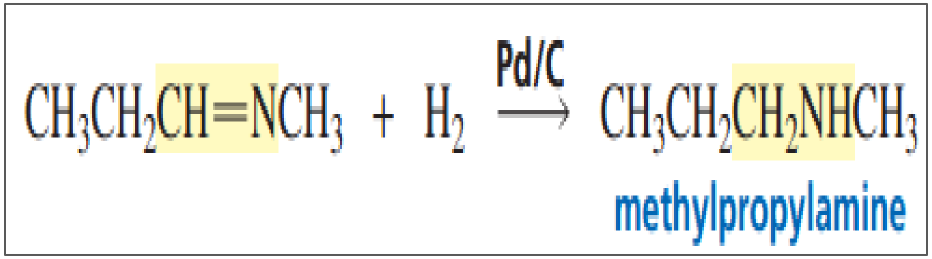
$$CH_3CH_2CH_2C{\equiv}CH + 2\,H_2 \xrightarrow{\text{Pt, Pd, or Ni}} CH_3CH_2CH_2CH_2CH_3$$

1-pentyne → pentane

Reduction reaction

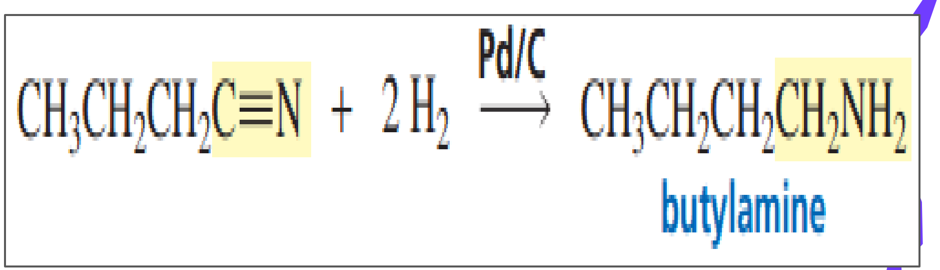
Catalytic Hydrogenation:

- Catalytic hydrogenation can also be used to reduce carbon–nitrogen double & triple bonds. The rxn products are amines.



$CH_3CH_2CH{=}NCH_3 + H_2 \xrightarrow{Pd/C} CH_3CH_2CH_2NHCH_3$

methylpropylamine

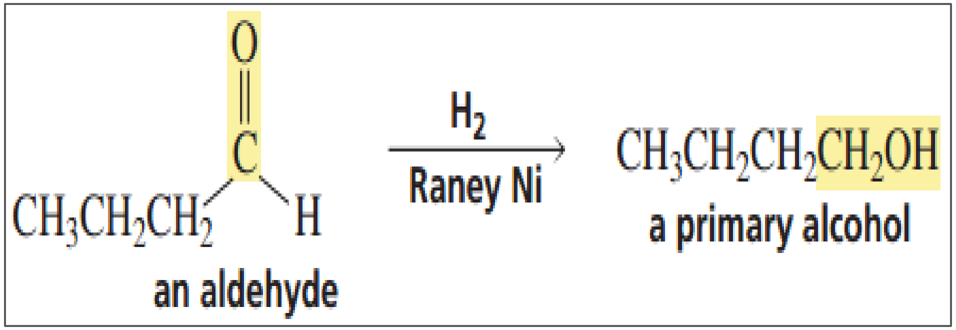


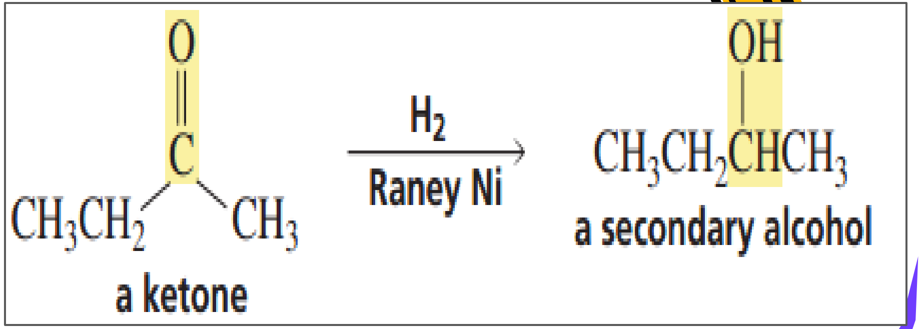
$CH_3CH_2CH_2C{\equiv}N + 2\,H_2 \xrightarrow{Pd/C} CH_3CH_2CH_2CH_2NH_2$

butylamine

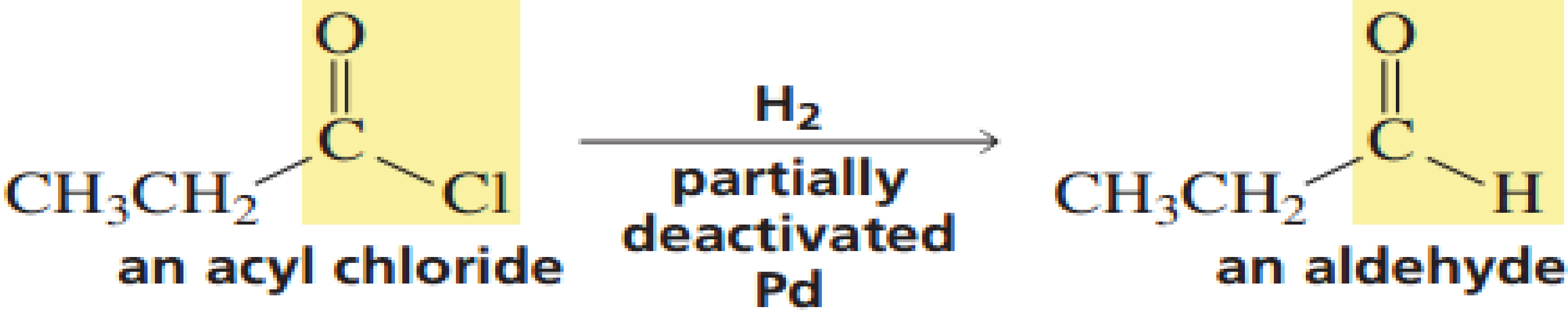
- carbonyl group of ketones & aldehydes can be reduced by catalytic hydrogenation, with Raney nickel as metal catalyst.
- Aldehydes are reduced to primary alcohols, and ketones are reduced to secondary alcohols.

Reduction reaction



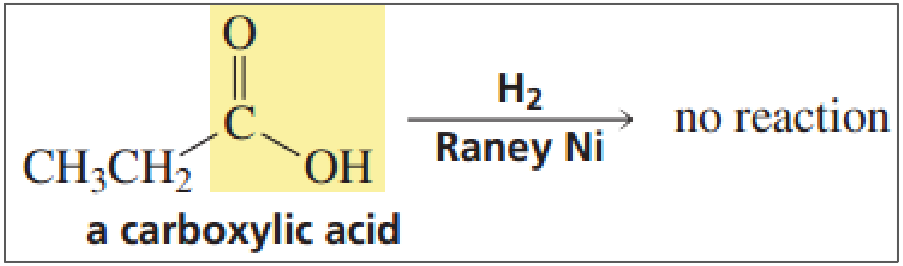


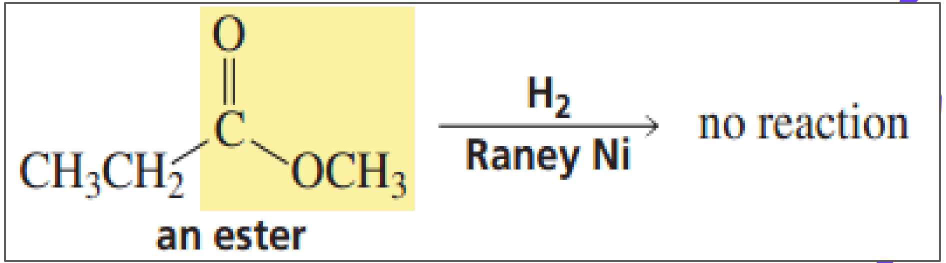
- ✓ The reduction of an acyl chloride can be stopped at an aldehyde if a partially deactivated catalyst is used.
- ✓ This reaction is known as the **Rosenmund reduction**.

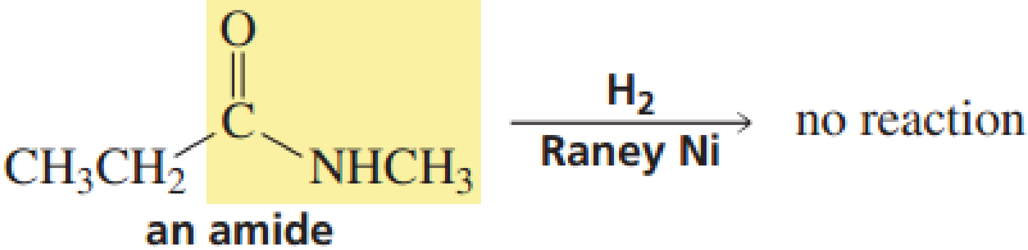


Reduction reaction

- ✓ carbonyl groups of carboxylic acids, esters, & amides are less reactive, so they are harder to reduce than the carbonyl groups of aldehydes & ketones.
- ✓ They cannot be reduced by catalytic hydrogenation (except under extreme conditions.





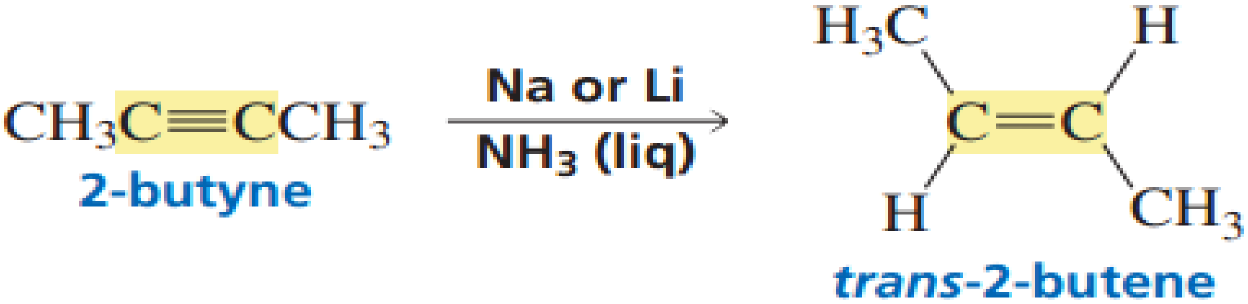


Reduction reaction

Reduction by Addition of an Electron, a Proton, an Electron, and a Proton

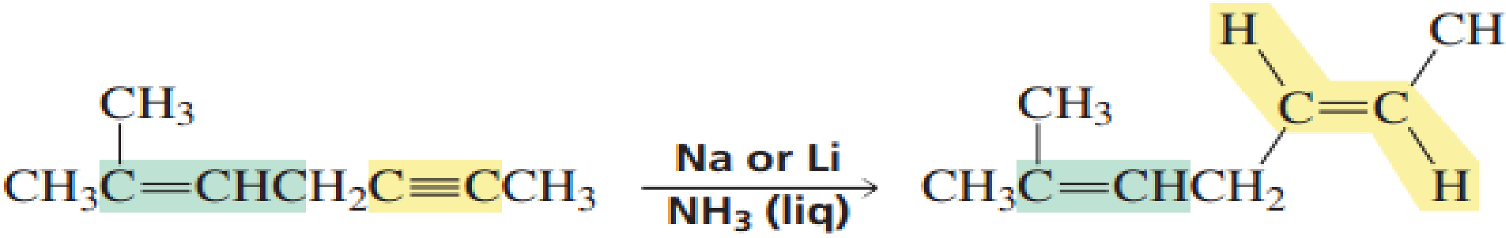
- ✓ When a cpd is reduced using Na in liquid NH_3, Na donates an e- to the cpd & NH_3 donates a proton.
- ✓ so the overall rxn adds two e-s & two protons to the cpd.
- ✓ Such a reaction is known as a **dissolving-metal reduction**.

dissolving-metal reduction that converts alkyne to trans alkene.



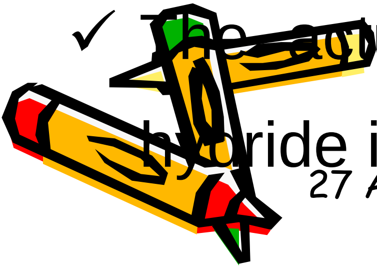
Reduction reaction

- ✓ Na (or Li) in liquid NH_3 cannot reduce a C-C double bond.
- ✓ This makes it a useful reagent for reducing a triple bond in a cpd that also contains a double bond.



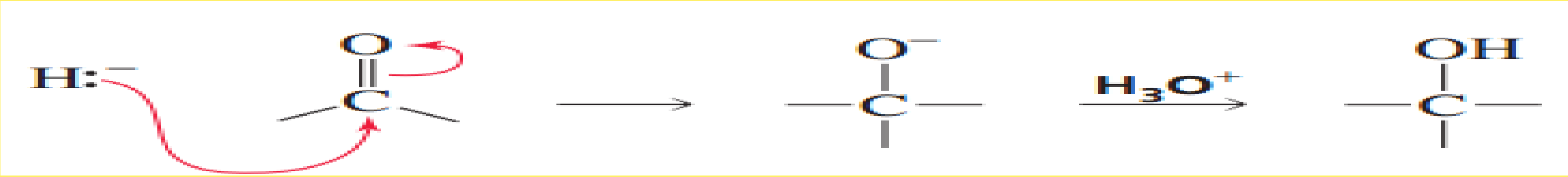
Reduction by Addition of a Hydride Ion and a Proton

- ✓ Carbonyl groups are easily reduced by metal hydrides such as $NaBH_4$ or $LiAlH_4$.
- ✓ The actual reducing agent in metal-hydride reductions is hydride ion (H^-).

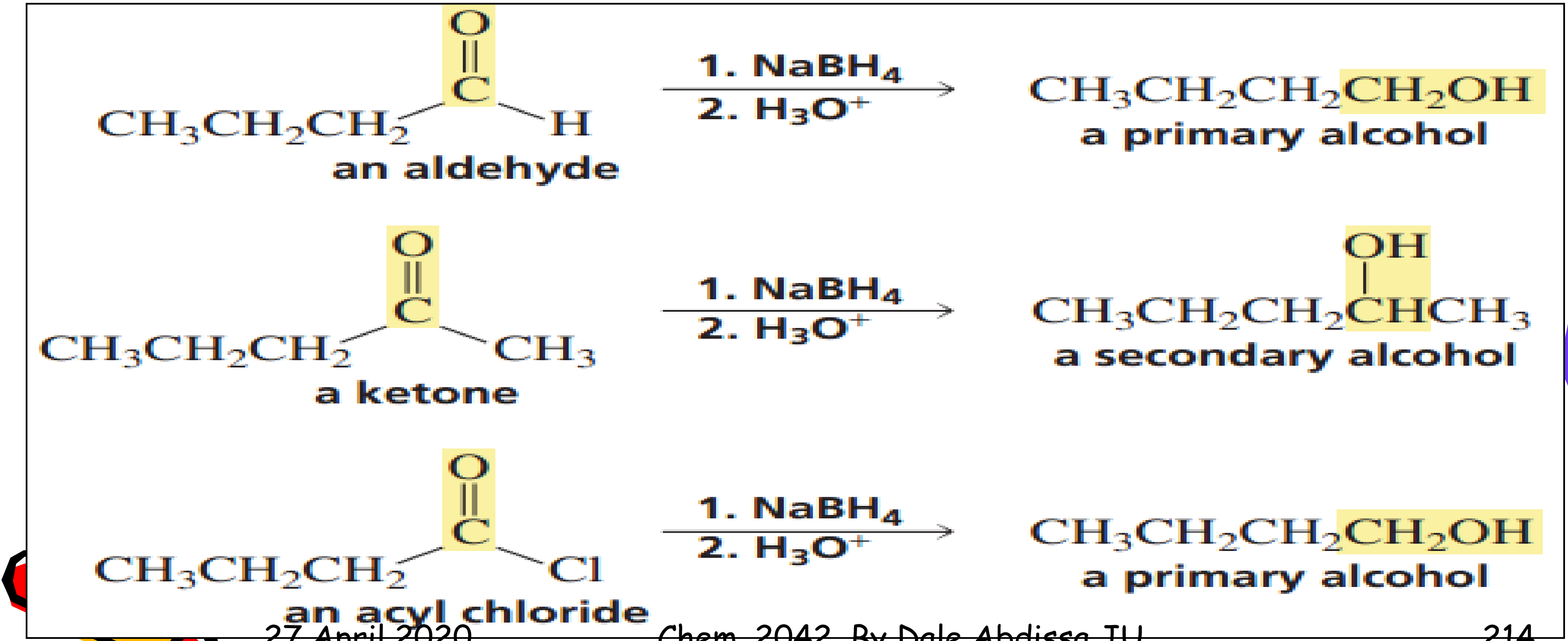


Reduction reaction

- ✓ H^- adds to the carbonyl C, & the alkoxide ion that is formed is subsequently protonated.

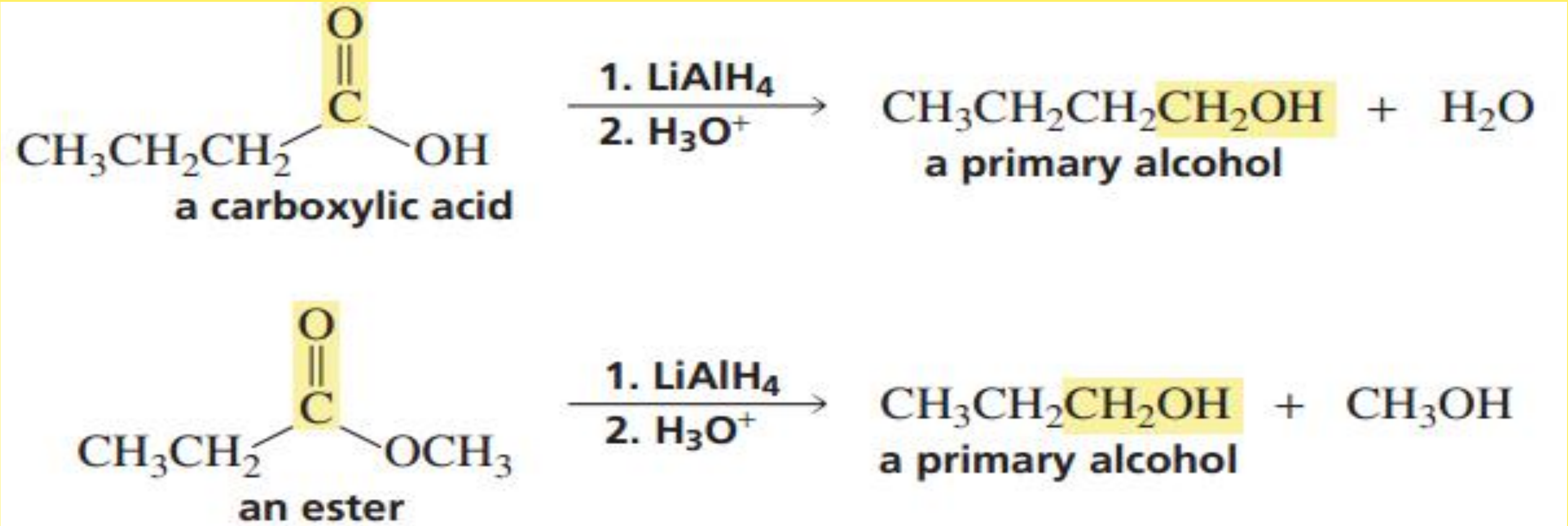


Aldehydes, ketones,& acyl halides can be reduced by $NaBH_4$.



Reduction reaction

- ✓ $NaBH_4$ is reduce aldehydes, ketones & acyl halides.
- ✓ $LiAlH_4$ is generally used to reduce only cpds such as carboxylic acids, esters, & amides that cannot be reduced by the milder reagent.
- ✓ $LiAlH_4$ is a stronger reducing agent than $NaBH_4$.



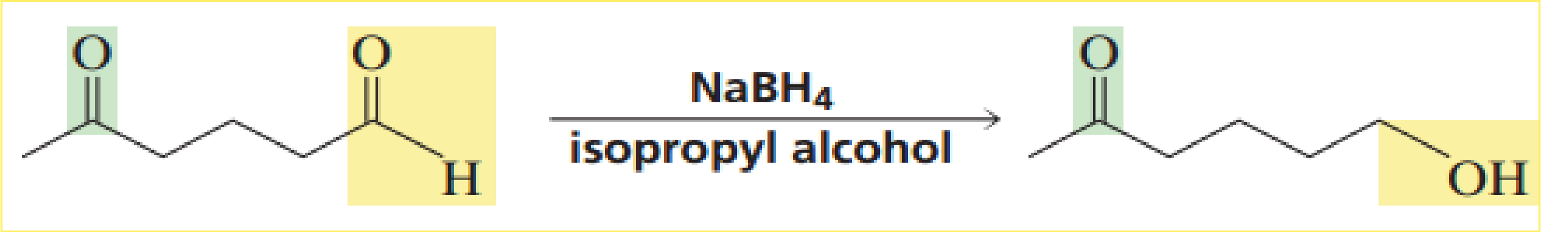
$$CH_3CH_2CH_2C(=O)OH \xrightarrow[2.\ H_3O^+]{1.\ LiAlH_4} CH_3CH_2CH_2CH_2OH + H_2O$$

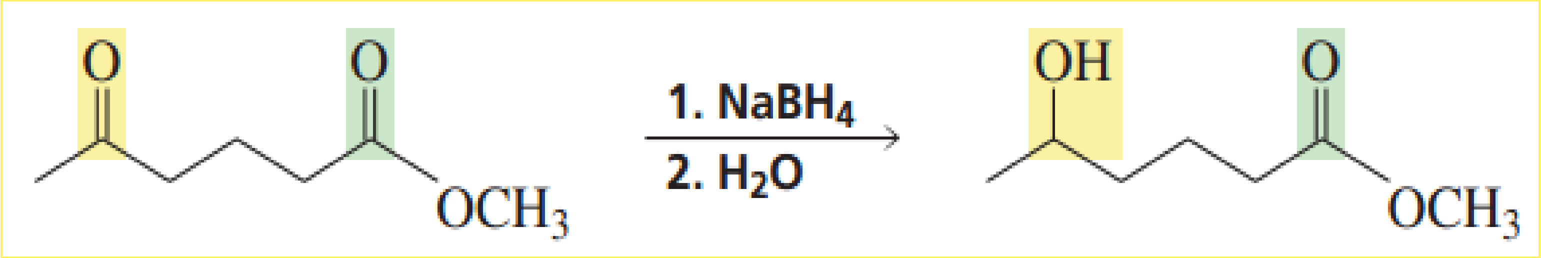
$$CH_3CH_2C(=O)OCH_3 \xrightarrow[2.\ H_3O^+]{1.\ LiAlH_4} CH_3CH_2CH_2OH + CH_3OH$$

Reduction reaction

A chemoselective reactionis is a rxn in which a reagent reacts with one functional group in preference to another.

e.g. $NaBH_4$ in isopropyl alcohol reduces aldehydes faster than it reduces ketones.



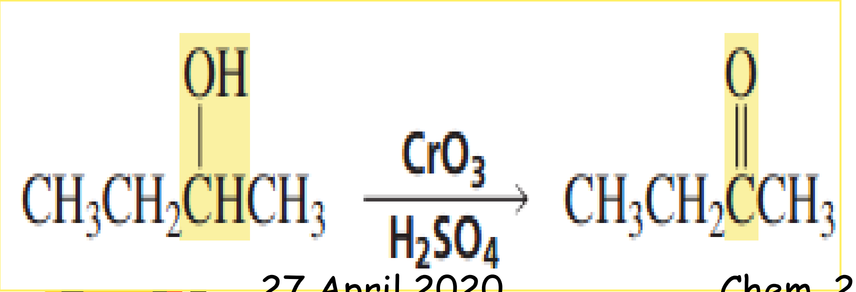


4.2 Oxidation of Alcohols

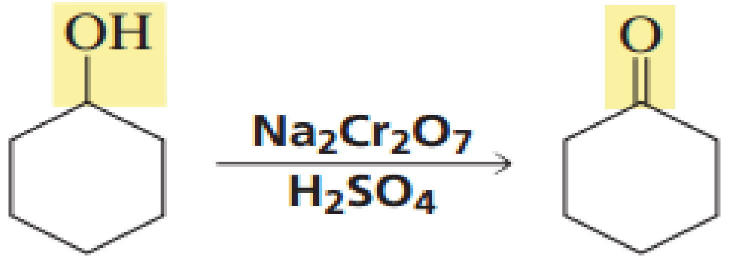
- ✓ Oxidation is the reverse of reduction.
- ✓ ***e.g.*** ketone is reduced to a secondary alcohol & the reverse rxn is the oxidation of a secondary alcohol to a **ketone**.

$$\text{ketone} \underset{\text{oxidation}}{\overset{\text{reduction}}{\rightleftharpoons}} \text{secondary alcohol}$$

- ✓ A reagent that is often used to oxidize alcohols is chromic acid (H_2CO_4) w/c is formed when chromium trioxide (CrO_3) or sodium dichromate ($Na_2Cr_2O_7$) is dissolved in aq. acid.

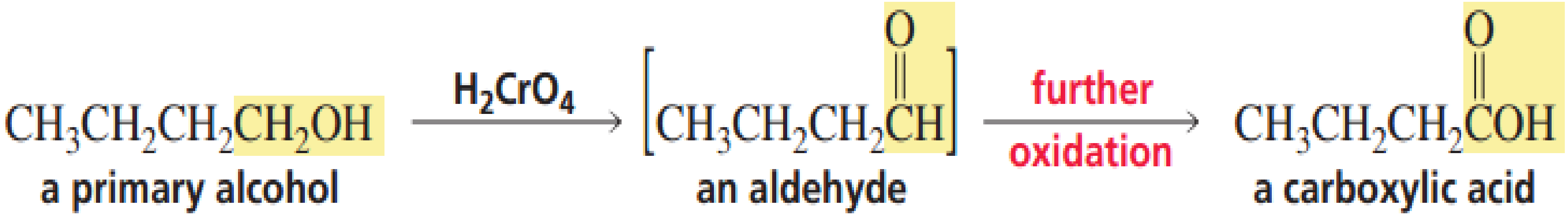


$$CH_3CH_2\overset{\displaystyle OH}{\overset{|}{C}}HCH_3 \xrightarrow[H_2SO_4]{CrO_3} CH_3CH_2\overset{\displaystyle O}{\overset{\|}{C}}CH_3$$



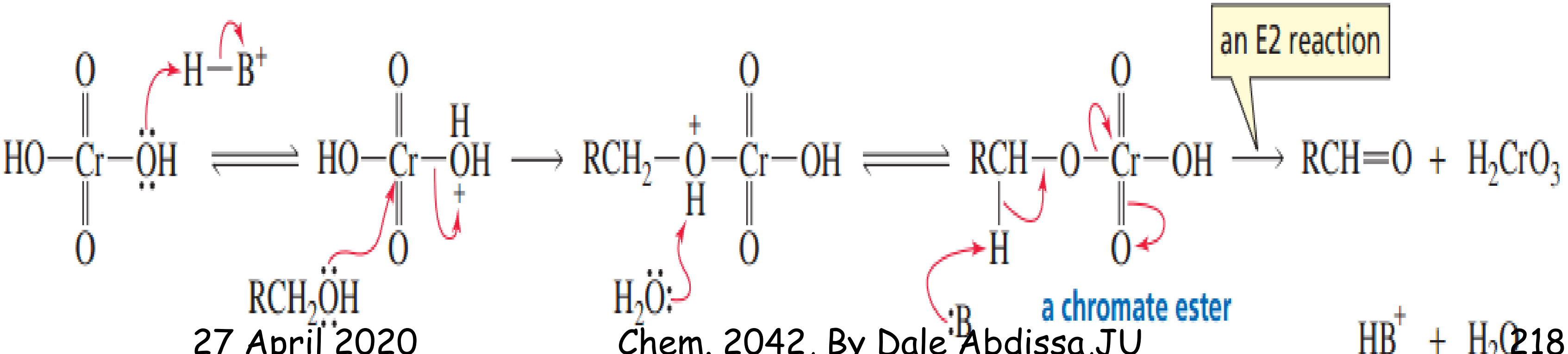
Oxidation of Alcohols

- ✓ 1°alcohols are initially oxidized to aldehydes.
- ✓ The **C** bearing the OH group in a tertiary alcohol is not bonded to **H** , so the OH group cannot be oxidized to a carbonyl group.



$$CH_3CH_2CH_2CH_2OH \xrightarrow{H_2CrO_4} \left[CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}H\right] \xrightarrow[\text{oxidation}]{\text{further}} CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}OH$$

mechanism for alcohol oxidation by chromic acid

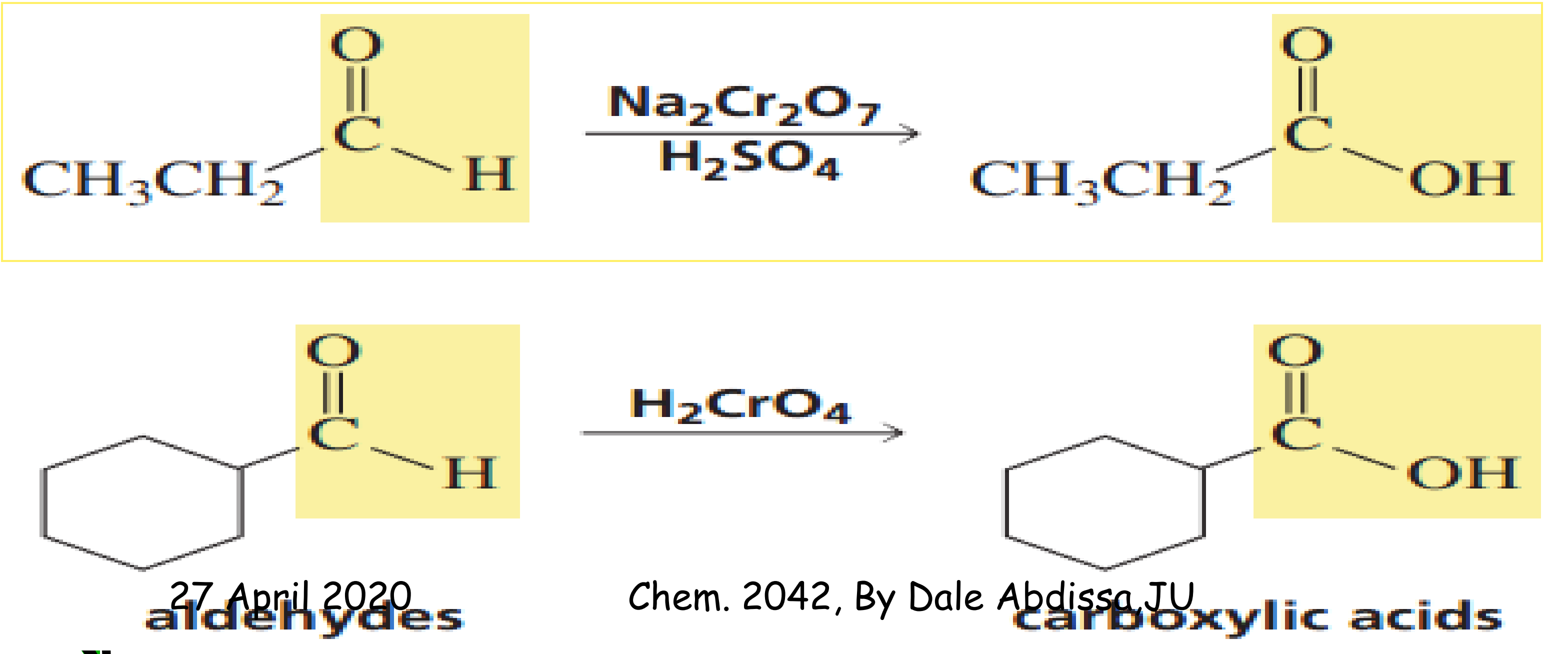


Oxidation rxn

Exercise . propose a mechanism for the chromic acid oxidation of 1-propanol to propanal.

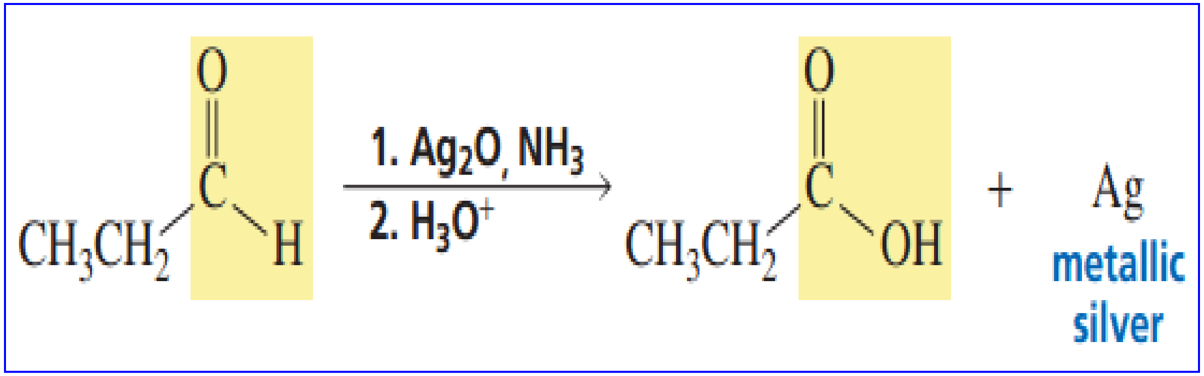
Oxidation of Aldehydes and Ketones

- ✓ Aldehydes are oxidized to carboxylic acids. B/c aldehydes are generally easier to oxidize than primary alcohols.



Oxidation rxn

- ✓ Silver oxide (Ag_2O) is a mild oxidizing agent. A dilute solution of Ag_2O in aq. ammonia (Tollens reagent) will oxidize an aldehyde.

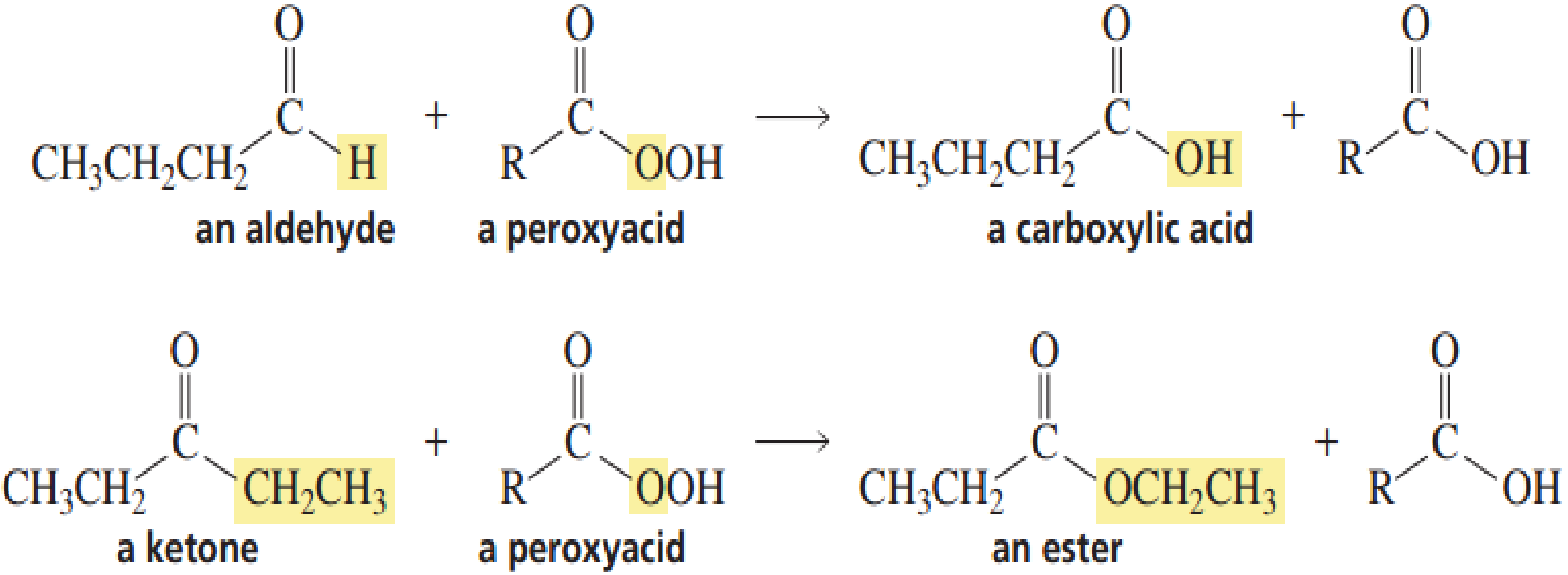


- ✓ The oxidizing agent in Tollens reagent is which is reduced to metallic silver.
- ✓ The Tollens test is based on this rxn: If Tollens reagent is added to a small amount of an aldehyde in a test tube, the inside of the test tube becomes coated with a shiny mirror of metallic silver.

Oxidation rxn

- Ketones do not react with most of the reagents used to oxidize aldehydes.
- However, both aldehydes and ketones can be oxidized by a peroxyacid to carboxylic acids & ketones to esters respectively.

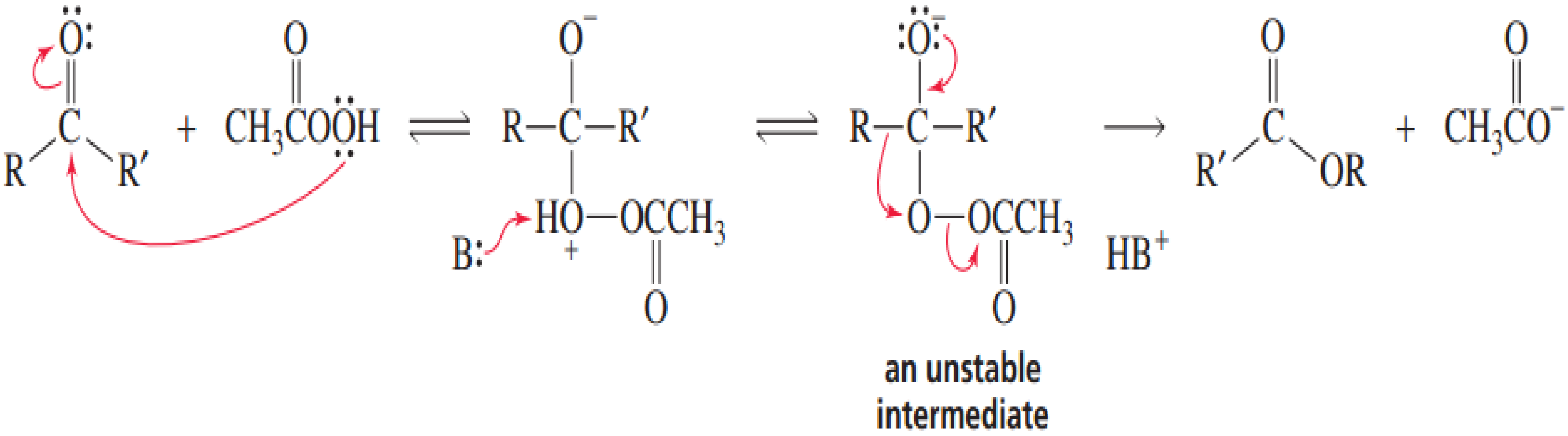
Baeyer-Villiger oxidations



oxidation rxn

- A peroxyacid contains one more oxygen than a carboxylic acid, & it is this **oxygen** that is inserted b/n the carbonyl carbon & the H of an aldehyde or the R of a ketone.
- The reaction is called a **Baeyer-Villiger oxidation**.

mechanism of the Baeyer–Villiger oxidation



Biological Oxidation-Reduction Reactions

✓ oxidation & reduction rxns are important in living systems.

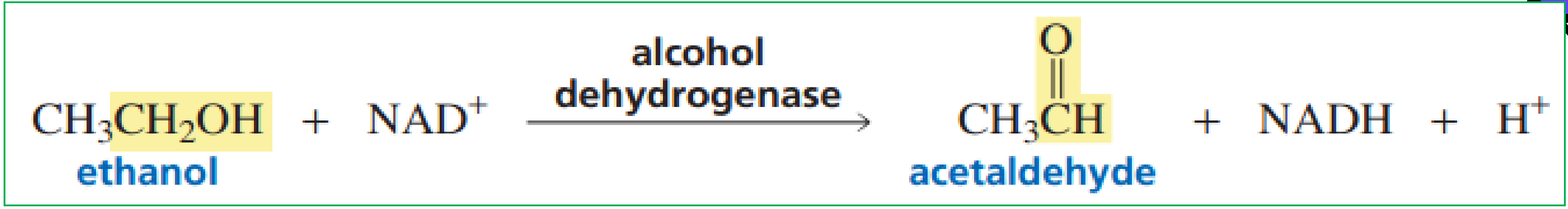
✓ e.g. oxidation rxn that takes place in animal cells is the oxidation of ethanol to acetaldehyde, a rxn catalyzed by the enzyme alcohol dehydrogenase.

✓ Ingestion of a moderate amount of ethanol lowers inhibitions & causes light-headed feeling, but the physiological effects of acetaldehyde are not as pleasant.

✓ Acetaldehyde is responsible for the feeling known as a hangover.

Biological Oxidation-Reduction Reactions

- ✓ The enzyme cannot oxidize ethanol to acetaldehyde unless an oxidizing agent is present.

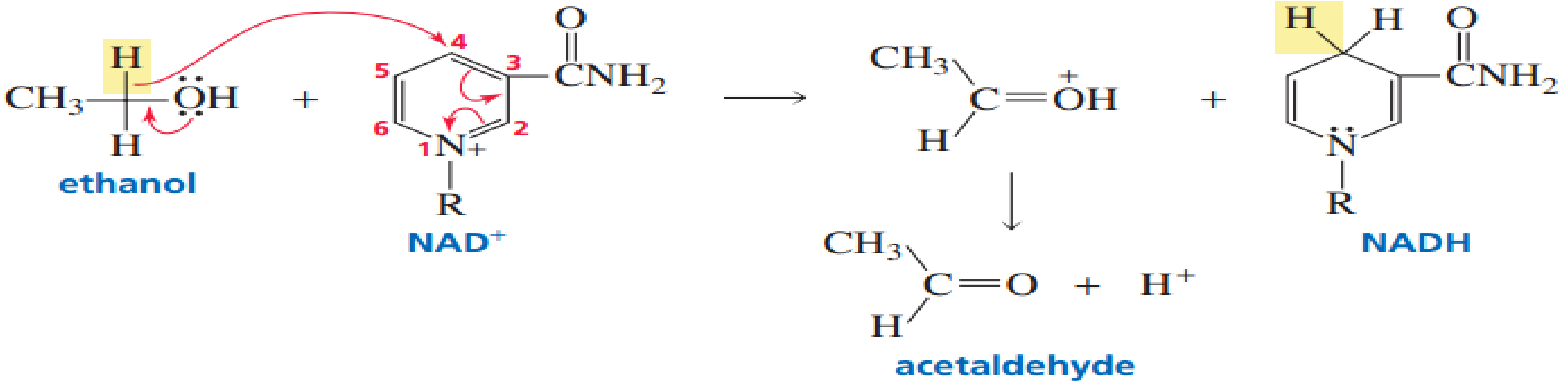


$$CH_3CH_2OH + NAD^+ \xrightarrow{\text{alcohol dehydrogenase}} CH_3\overset{O}{\overset{\|}{C}}H + NADH + H^+$$

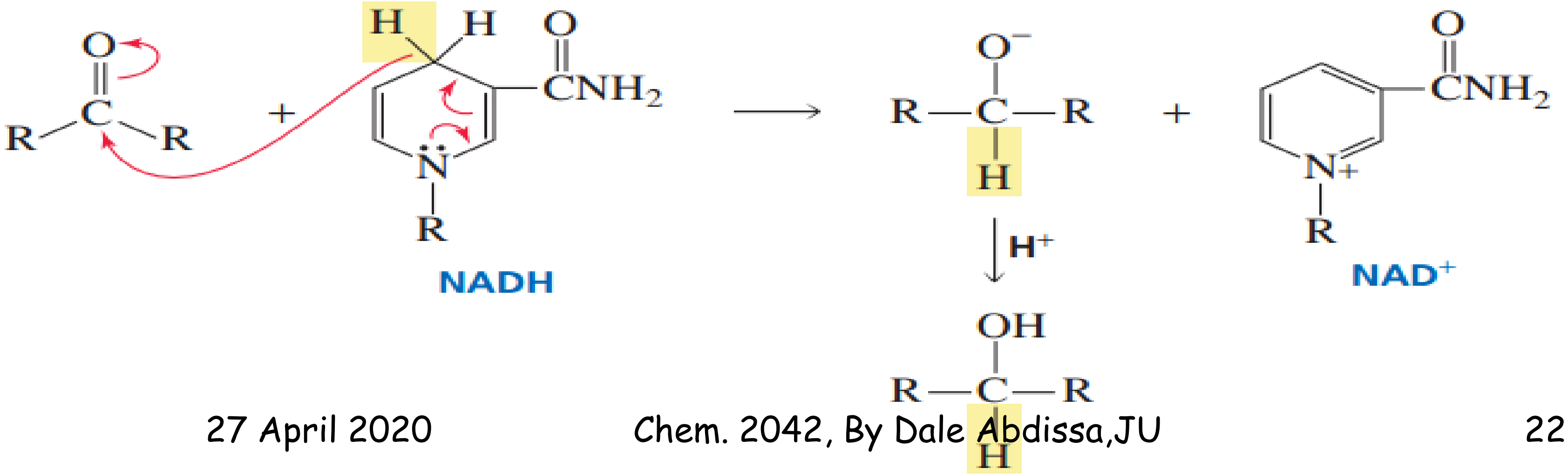
- ✓ **NAD+** (nicotinamide adenine dinucleotide), the most common oxidizing agent available in living systems is used by cells to oxidize alcohols to aldehydes.
- ✓ NAD+ is reduced to **NADH** (reduced nicotinamide adenine dinucleotide) when it oxidizes a compound.
- ✓ NADH is used by the cell as a reducing agent.

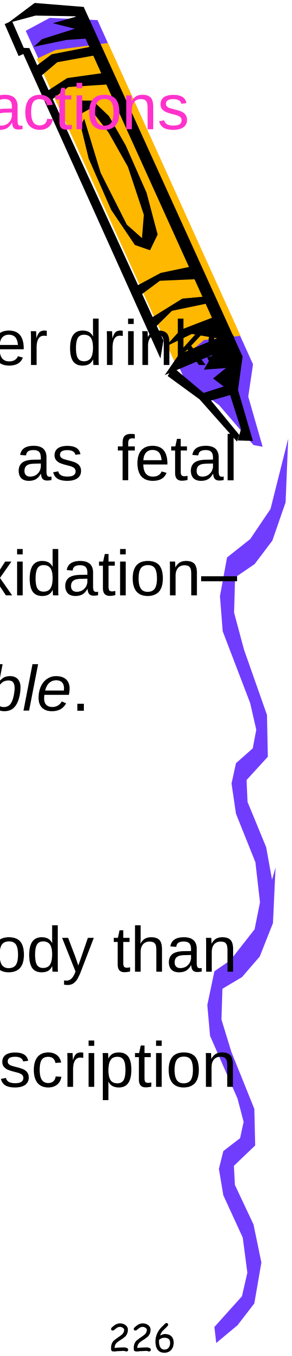
Biological Oxidation–Reduction Reactions

- NAD+ oxidizes a cpd by accepting a hydride ion from it.



- NADH reduces a cpd by donating a hydride ion from the 4-position of the six-membered ring.





Biological Oxidation–Reduction Reactions

Assignment #2)

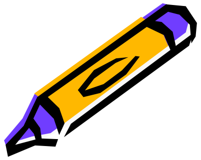
- The damage done to a human fetus when the mother drinks alcohol (ethanol) during her pregnancy is known as fetal alcohol syndrome. Explain this using biological oxidation–reduction reactions, *use chemical equations if possible*.

Assignment #3)

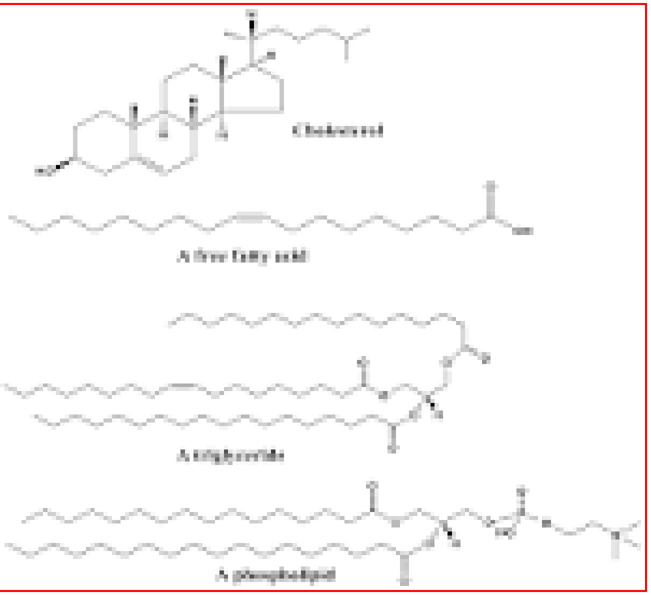
- Why ingestion of methanol is more fatal to human body than ethanol, *use chemical equation* and give brief description with respect to its physiological effects.

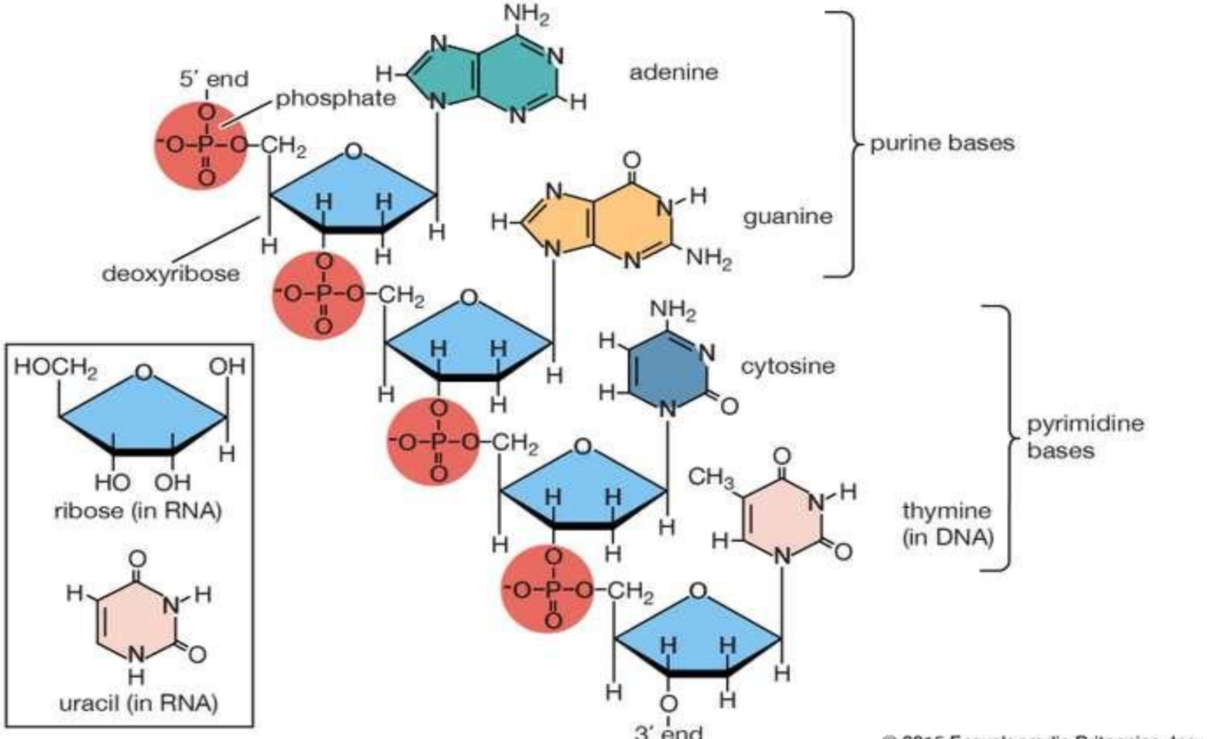
Chapter 5

Introduction to Chemistry of Biomolecules



Unit 5 . Biological molecules





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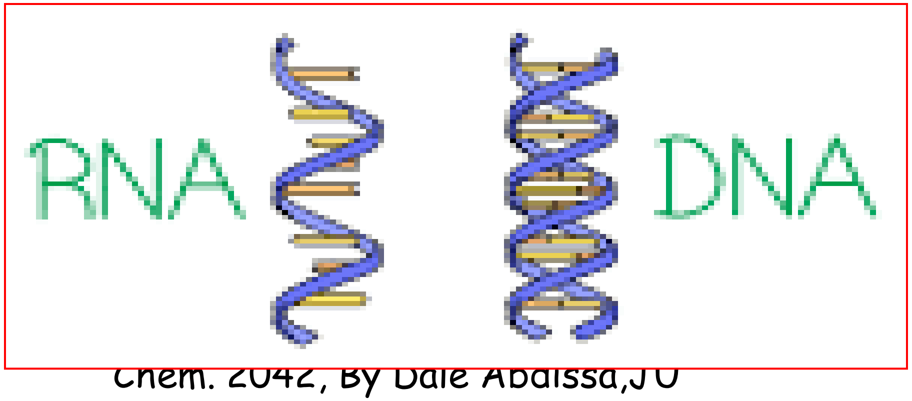
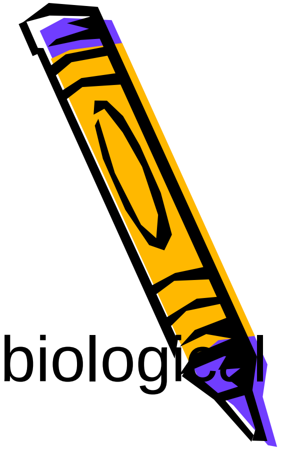
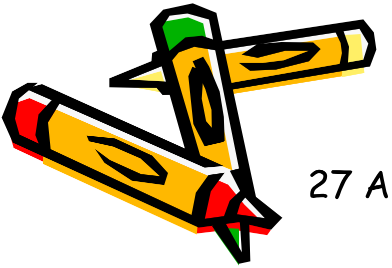




Unit 5 . Biological molecules

5.1. An introduction to carbohydrate chemistry

- Bioorganic compounds are organic cpds found in biological systems.
- There is great similarity b/n the organic rxns chemists carry out in the laboratory & those performed by nature inside the living cell.
- bioorganic rxns can be thought of as organic rxns that take place in tiny flasks called **cells**.

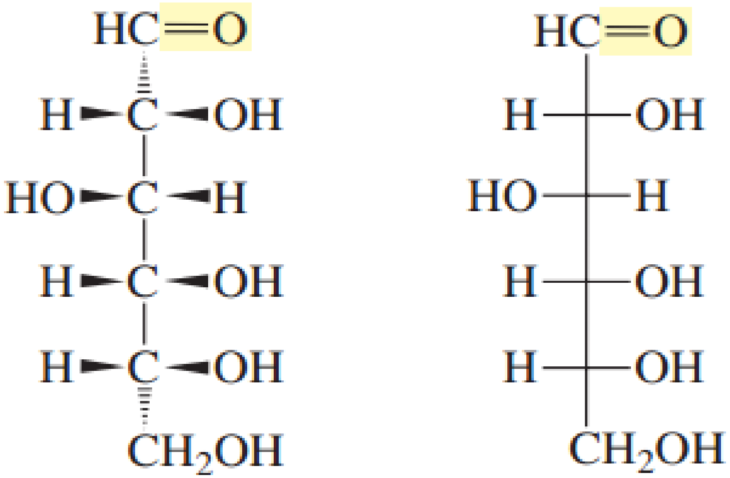


Carbohydrates chemistry

- ✓ **Carbohydrates** are important constituents of all living organisms and have a variety of different functions.
- ✓ Some are important structural components of cells; others act as recognition sites on cell surfaces.
- ✓ *e.g.* the first event in all our lives was a sperm recognizing a carbohydrate on the surface of an egg's wall.
- ✓ Others serve as a major source of metabolic energy.
- ✓ *e.g.*, the leaves, fruits, seeds, stems, & roots of plants contain carbohydrates that plants use for their own metabolic needs.

Carbohydrates chemistry

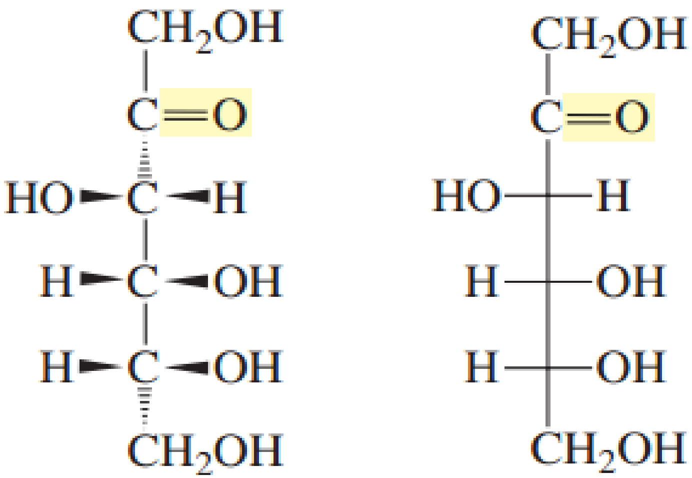
- ✓ Carbohydrates are polyhydroxy aldehydes such as D-glucose, polyhydroxy ketones such as **D-fructose.**



wedge-and-dash structure

Fischer projection

D-glucose
a polyhydroxy aldehyde

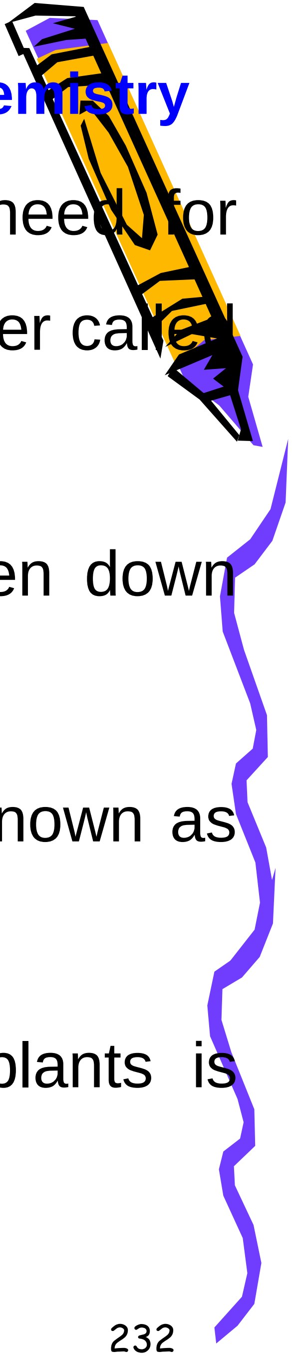


wedge-and-dash structure

Fischer projection

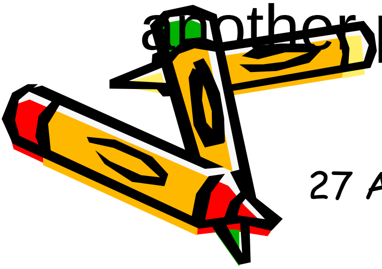
D-fructose
a polyhydroxy ketone

- ✓ The most abundant carbohydrate in nature is **D-glucose**.
- ✓ Living cells oxidize D-glucose in the first of a series of processes that provide them with energy.



Carbohydrates chemistry

- ✓ When animals have more D-glucose than they need for energy, they convert excess D-glucose into a polymer called **glycogen**.
- ✓ When an animal needs energy, glycogen is broken down into individual D-glucose molecules.
- ✓ Plants convert excess D-glucose into a polymer known as starch.
- ✓ Cellulose is the major structural component of plants is another polymer of D-glucose.



Carbohydrates chemistry

- Animals obtain glucose from food such as plants that contains glucose. Plants produce glucose by photosynthesis.
- During photosynthesis, plants take up water through their roots & use CO_2 from the air to synthesize glucose & oxygen.

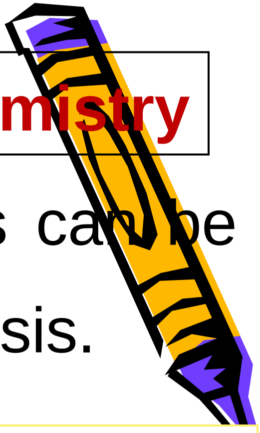
$$\underset{\text{glucose}}{C_6H_{12}O_6} + 6\,O_2 \xrightleftharpoons[\text{photosynthesis}]{\text{oxidation}} 6\,CO_2 + 6\,H_2O + \text{energy}$$

- Plants obtain the energy they need for photosynthesis from sunlight, captured by chlorophyll molecules in green plants.
- Photosynthesis uses the that animals exhale as waste and generates the CO_2 that animals inhale to sustain life.

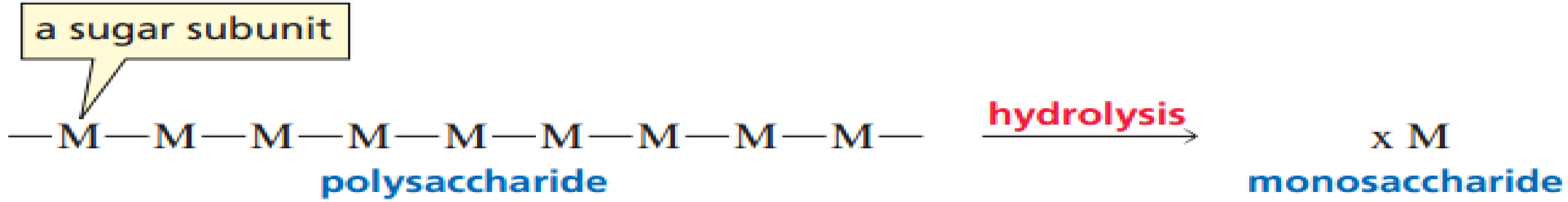
5.1a) Classification of Carbohydrates

- ✓ There are two classes of carbohydrates: simple & **complex carbohydrates**.
- ✓ Simple carbohydrates are monosaccharaides (single sugars), whereas complex carbohydrates contain two or more sugar subunits linked together.
- ✓ Disaccharides have 2 sugar subunits linked together.
- ✓ oligosaccharides have 3 to 10 sugar subunits (oligos is Greek for "*few*") linked together.
- ✓ polysaccharides have more than 10 sugar subunits linked together.

Carbohydrates chemistry



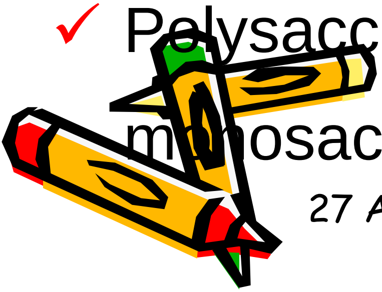
- ✓ Disaccharides, oligosaccharides, & polysaccharides can be broken down to monosaccharide subunits by hydrolysis.



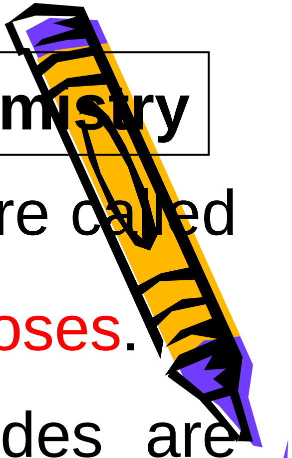
- ✓ E.g. Sucrose common table sugar is a disaccharide that yields one molecule of glucose and one of fructose on hydrolysis.

$$\text{Sucrose } (C_{12}H_{22}O_{11}) + H_2O \longrightarrow \text{glucose } (C_6H_{12}O_6) + \text{fructose } (C_6H_{12}O_6)$$

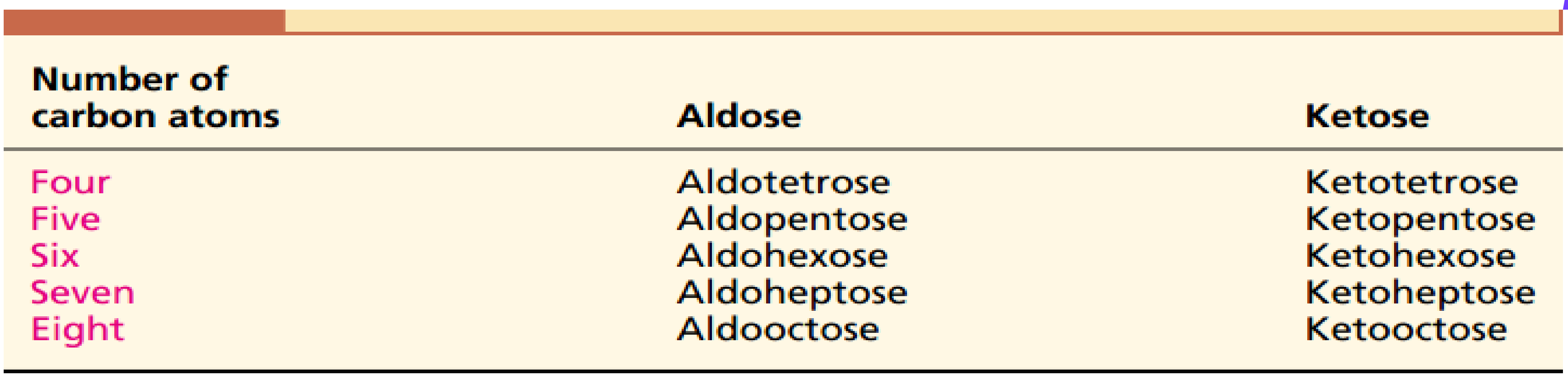
- ✓ Polysaccharides are hydrolyzed to more than 10 monosaccharide units.



Carbohydrates chemistry



- ✓ Monosaccharides that are polyhydroxy aldehydes are called aldoses; those that are polyhydroxy ketones are ketoses.
- ✓ Based on the no C they contain Monosaccharides are classified as:



Number of carbon atoms	Aldose	Ketose
Four	Aldotetrose	Ketotetrose
Five	Aldopentose	Ketopentose
Six	Aldohexose	Ketohexose
Seven	Aldoheptose	Ketoheptose
Eight	Aldooctose	Ketooctose

- ✓ A six-carbon polyhydroxy aldehyde such as D-glucose is an aldohexose, whereas a six-carbon polyhydroxy ketone such as D-fructose is a ketohexose.

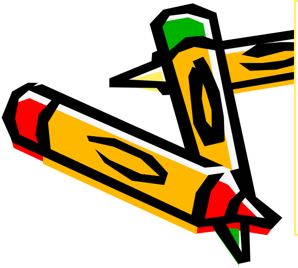
Carbohydrates chemistry

- ✓ A monosaccharide can be a polyhydroxy aldehyde such as D-glucose or a polyhydroxy ketone such as D-fructose.
- ✓ Polyhydroxy aldehydes are called aldoses (“ald” is for alde-hyde; “ose” is the suffix for a sugar), whereas polyhydroxy ketones are called ketoses.

Assignment #1**)** Explain the causes of Diabetes with respect to the blood glucose levels. Use the chemical equation to describe reaction. And predict the solution for this complication in diabetics.

5.2 The D and L Notation

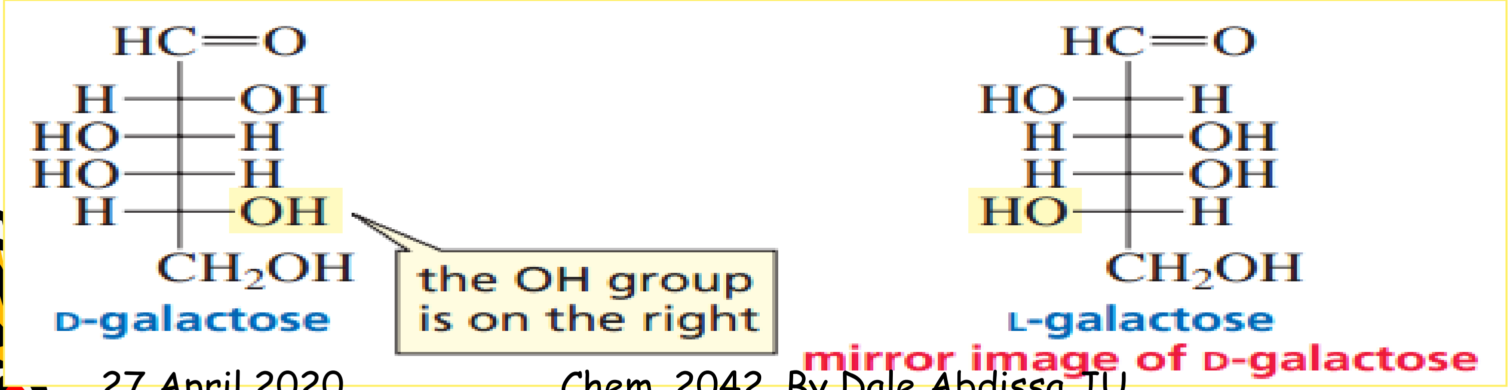
- ✓ The notations D and L are used to describe the configurations of carbohydrates and amino acids
- ✓ A carbon to which four different groups are attached is an asymmetric carbon.
- ✓ The smallest aldose, and the only one whose name does not end in "ose," is glyceraldehyde, an aldotriose.
- ✓ B/c glyceraldehyde has an asymmetric carbon, it can exist as a pair of enantiomers.



D-glyceraldehyde L-glyceraldehyde

D and L Notation

- ✓ Galactose has 4 asymmetric carbons (**C-2**, **C-3**, **C-4,** & **C-5**).
- ✓ If the **OH** group attached to the bottom most asymmetric **C** is on the right, then the cpd is a D-sugar.
- ✓ If the OH group is on the left, then the cpd is an L-sugar.
- ✓ Almost all sugars found in nature are D-sugars.
- ✓ the mirror image of a D -sugar is an L-sugar.



D-galactose

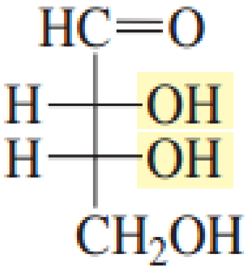
the OH group is on the right

L-galactose

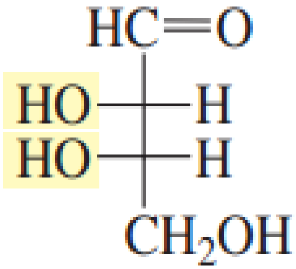
mirror image of D-galactose

5.3 Configurations of Aldoses

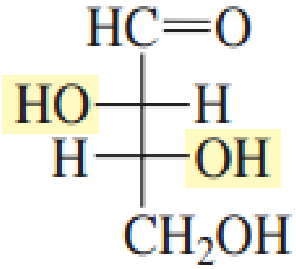
- ✓ Aldotetroses have two asymmetric carbons and therefore four stereoisomers.
- ✓ Two of the stereoisomers are D-sugars & two are L-sugars.



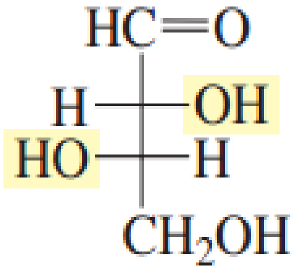
D-erythrose



L-erythrose



D-threose

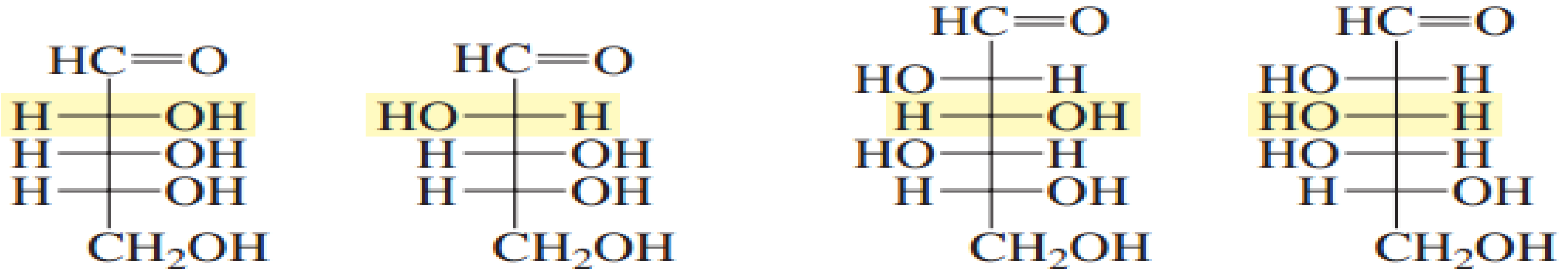


L-threose

Assignment #2) For aldohexoses and ketohexose draw the stereoisomers (D-aldose and D-ketoses, pairs of enantiomers) and show the epimers carbons.

Configurations of Aldoses

- ✓ Diastereomers that differ in configuration at only one asymmetric carbon are called epimers. *e.g.*
- ✓ D-ribose & D-arabinose are C-2 epimers (they differ in configuration only at C-2), & D-idose & D-talose are C-3 epimers.



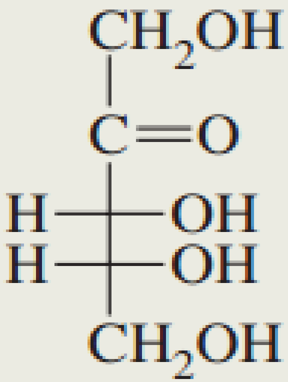
D-ribose D-arabinose D-idose D-talose

C-2 epimers C-3 epimers

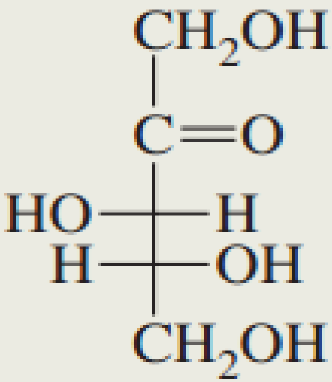
Assignment #3) Are D-glucose and D–galactose enantiomers or diastereomers? If you say diastereomers, show why?

5.4 Configurations of Ketoses

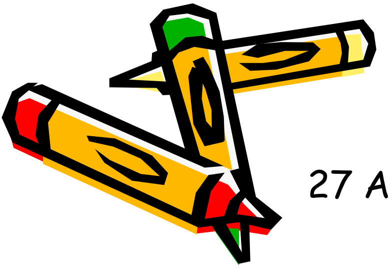
- ✓ Naturally occurring ketoses have the ketone group in the 2-position.
- ✓ A ketose has one fewer asymmetric **C** than does an aldose with the same number of **C** atoms.



D-ribulose



D-xylulose



Reading Assignment

- ✓ Read the Chemistry of;
- ✓ Lipids
- ✓ Proteins
- ✓ Nucleic acid

- **✓Wash Your hands with SOAP & try Your best against COVID-19!!**

Good Bye !!

Thank You !

Stay Safe & Focus on Your Courses!!