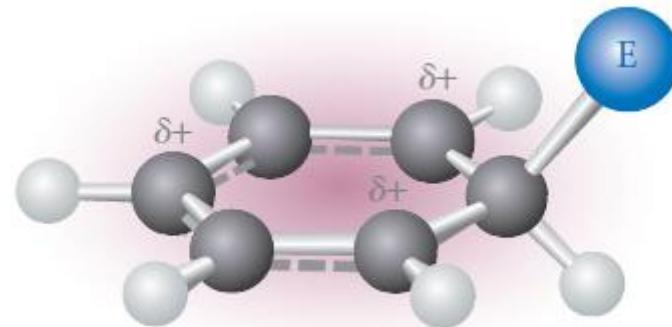


Organic Chemistry II

(Chem3451)

Israel A.

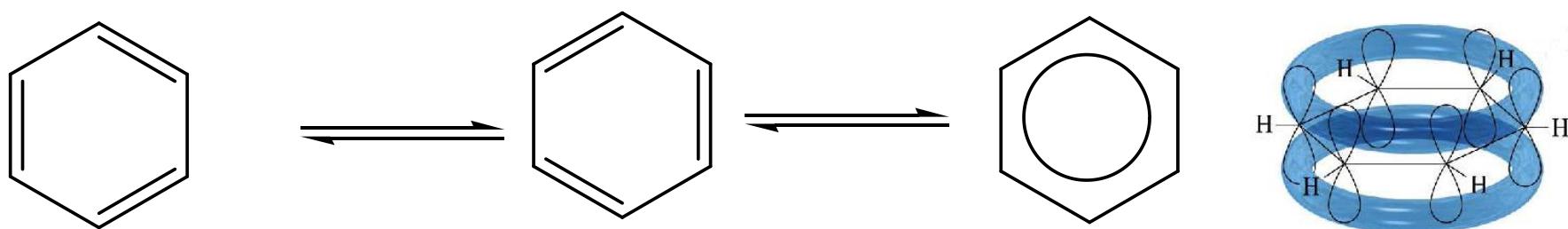
Chapter 1



The Chemistry Of Aromatic Compounds

Aromaticity

- Kekulé suggested that two forms of benzene were in rapid equilibrium, and it was also found that benzene was a flat (planar) molecule:



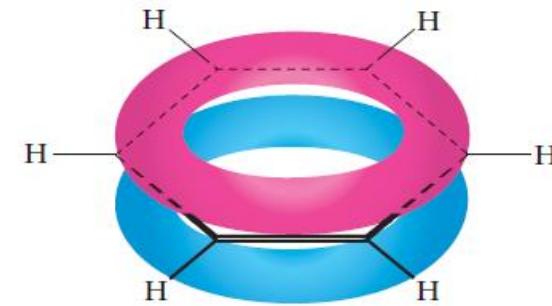
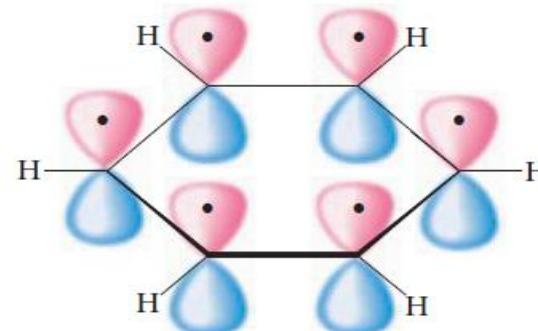
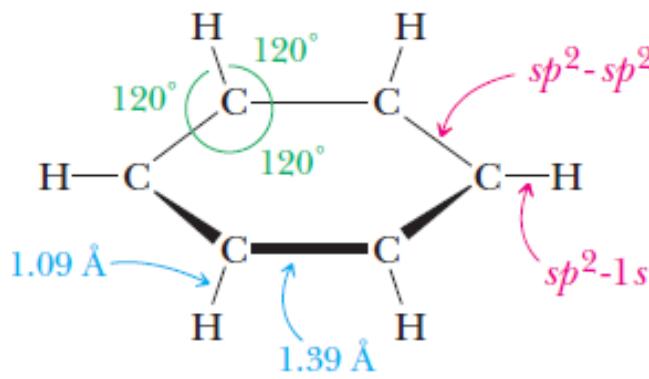
- with resonance structures, neither of the extremes exists, the structure is somewhere in between, all bond angles in benzene are 120° and π electrons are **delocalized**

Cont'd...

- the concepts of the **hybridization of atomic orbitals** and the **theory of resonance**, developed by Linus Pauling in the 1930s, provided the first adequate description of the structure of benzene
- the carbon skeleton of benzene forms a regular hexagon with C-C-C and H-C-C bond angles of 120°
- bonding in benzene carbon uses sp^2 hybrid orbitals, each carbon forms sigma bonds to two adjacent carbons by the overlap of sp^2-sp^2 hybrid orbitals and one sigma bond to hydrogen by the overlap of sp^2-1s orbitals
- as it was determined experimentally, all carbon–carbon bonds in benzene are the same length, 1.39 \AA , a value almost midway between the length of a single bond between sp^3 hybridized carbons (1.54 \AA) and that of a double bond between sp^2 hybridized carbons (1.33 \AA)

Cont'd...

- each carbon also has a single unhybridized $2p$ orbital that contains one electron, these six $2p$ orbitals lie perpendicular to the plane of the ring and overlap to form a continuous pi cloud encompassing all six carbons
- the electron density of the pi system of a benzene ring lies in one torus (a doughnut-shaped region) above the plane of the ring and a second torus below the plane

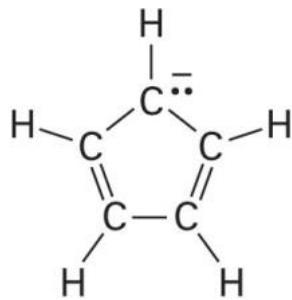


Aromatic, Antiaromatic and Nonaromatic Compounds

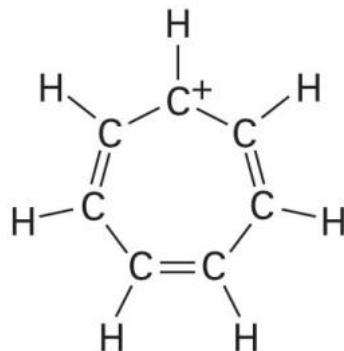
- regarding aromaticity, a compound can be classified in one of three ways:
 1. **Aromatic:** A cyclic, planar, completely conjugated compound with $4n + 2 \pi$ electrons.
 2. **Antiaromatic:** A cyclic, planar, completely conjugated compound with $4n \pi$ electrons.
 3. **Nonaromatic:** A compound that lacks one (or more) of the following requirements for aromaticity: being cyclic, planar, and completely conjugated.
- A completely conjugated, monocyclic hydrocarbon is called an **Annulene** (may not necessarily be aromatic)

Cont'd...

- the $(4n + 2)\pi$ rule applies to ions as well as neutral species
- both the cyclopentadienyl anion and the cycloheptatrienyl cation are aromatic
- the key feature of both is that they contain 6π electrons in a ring of continuous p orbitals



Cyclopentadienyl anion



Cycloheptatrienyl cation

Six π electrons; aromatic ions

Properties of Benzene and its Derivatives

- considering benzene's high degree of unsaturation, benzene is expected to show many of the reactions characteristic of alkenes
- yet, benzene is remarkably **unreactive**! It does not undergo the characteristic of reactions alkenes addition, oxidation, and reduction,
- benzene does not react with bromine, hydrogen chloride, or other reagents that usually add to carbon–carbon double bonds
- Nor is benzene oxidized by peracids under conditions that readily oxidize alkenes
- When benzene reacts, it does so by substitution in which a hydrogen atom is replaced by another atom or a group of atoms

Cont'd...

- the term **aromatic** was originally used to classify benzene and its derivatives because many of them have distinctive odour
- however, that a sounder classification for these compounds would be one based on structure and chemical reactivity, not aroma
- as it is now used, the term **aromatic** refers instead to the fact that benzene and its derivatives are highly unsaturated compounds that are unexpectedly stable toward reagents that react with alkenes
- the term **arene** is used to describe aromatic hydrocarbons, by analogy with alkane and alkene where benzene is the parent arene
- as we call a group derived by the removal of an H from an alkane an alkyl group and give it the symbol **R-**, we call a group derived by the removal of an H from an arene an **aryl group** and give it the symbol **Ar -**

7.2 Heterocyclic Aromatic Compounds

- aromatic compounds can have **elements other than carbon** in the ring and called **heterocyclic aromatic compounds**
- heterocyclic compounds contain elements other than carbon in a ring, such as N,S,O,P

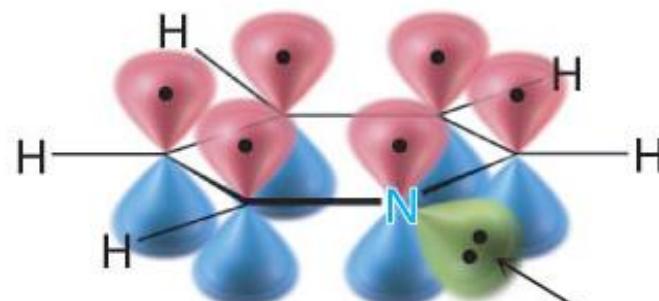
➤ Pyridine

- A six-membered heterocycle with a nitrogen atom in its ring where the π electron structure resembles benzene (6 electrons)
- lone pair electrons of nitrogen are not part of the aromatic system (perpendicular orbital)

- lone pair electrons on nitrogen are not part of the aromatic system (perpendicular orbital)

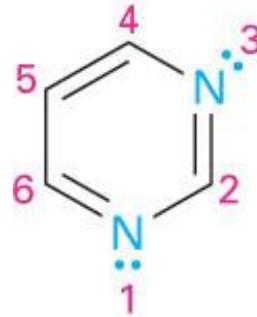


Pyridine

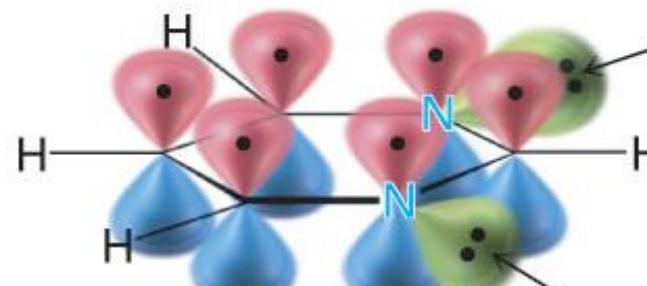


(Six π electrons)

Lone pair in
 sp^2 orbital



Pyrimidine



(Six π electrons)

Lone pair in
 sp^2 orbital

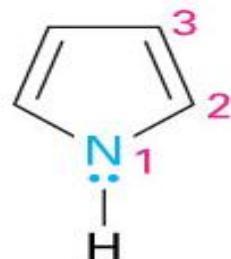
Lone pair in
 sp^2 orbital

➤ Pyrrole and Imidazole

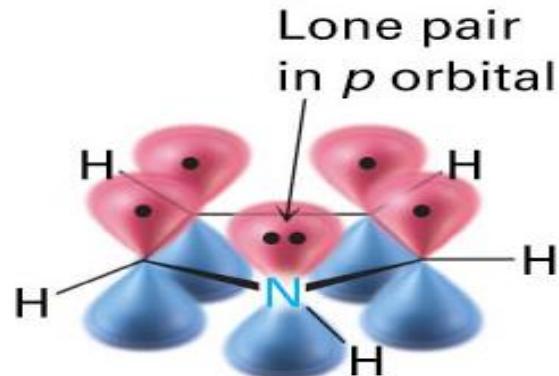
- A five-membered hetero cycle with one and two nitrogens respectively
- π electron system similar to that of cyclo pentadienyl anion where four sp^2 -hybridized carbons with 4 p orbitals perpendicular to the ring and 4 p electrons
- nitrogen atom is sp^2 -hybridized, and lone pair of electrons occupies a p orbital (6π electrons)
- Since lone pair electrons are in the aromatic ring, protonation destroys aromaticity, making pyrrole a very weak base

Heterocyclic Aromatic Compounds

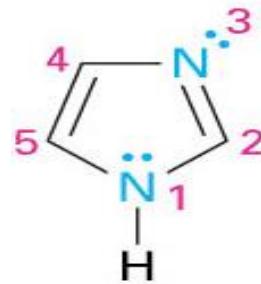
➤ Pyrrole and Imidazole



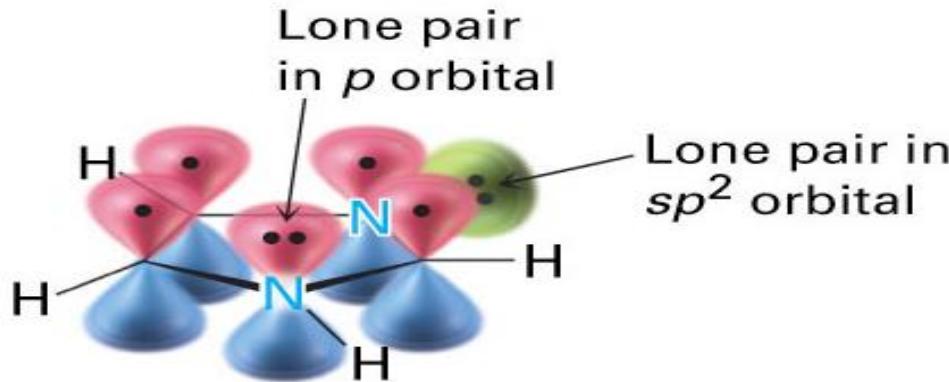
Pyrrole



(Six π electrons)



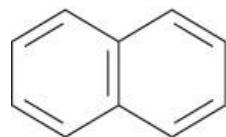
Imidazole



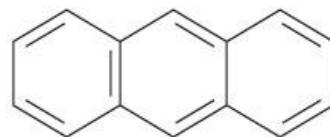
(Six π electrons)

Polycyclic Aromatic Compounds

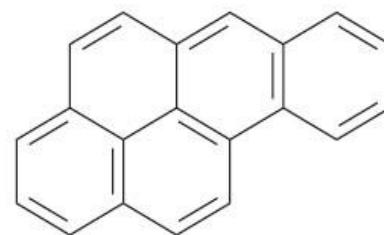
- Aromatic compounds can have rings that share a set of carbon atoms (fused rings)
- Compounds from fused benzene or aromatic heterocycle rings are themselves aromatic



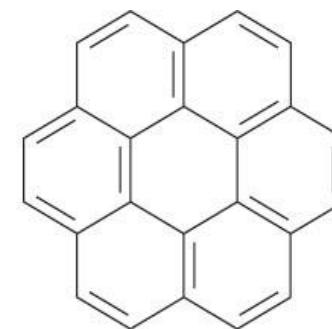
Naphthalene



Anthracene



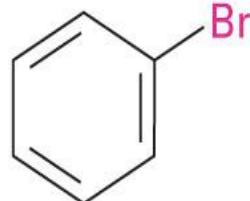
Benzo[a]pyrene



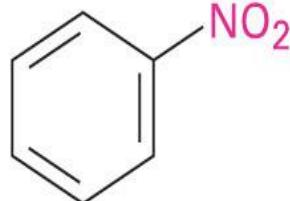
Coronene

➤ Naming Aromatic Compounds

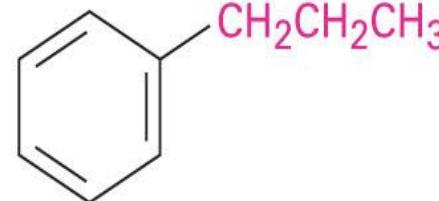
- mono substituted compounds; toluene=methylbenzene; aniline=aminobenzene)
- mono substituted benzenes systematic names as hydrocarbons with –benzene
 - ✓ C_6H_5Br - bromo benzene
 - ✓ $C_6H_5NO_2$ - nitro benzene,
 - ✓ $C_6H_5CH_2CH_2CH_3$ - propyl benzene etc.



Bromo**benzene**



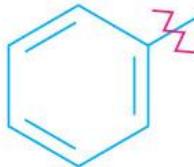
Nitro**benzene**



Propyl**benzene**

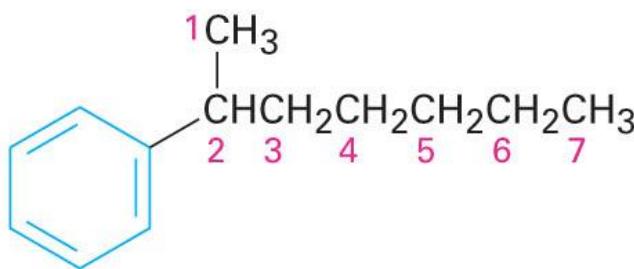
- When a benzene ring has a substituent;

- ✓ “Phenyl” is used for (C_6H_5-)
- ✓ “Benzyl” refers to “ $C_6H_5CH_2-$ ”

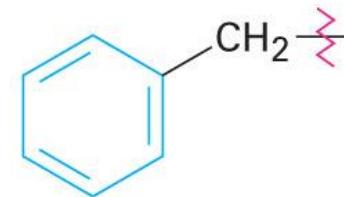


A phenyl group

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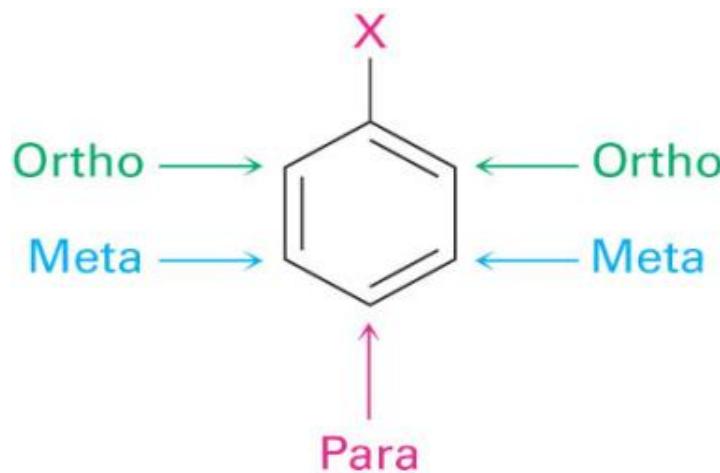
2-Phenylheptane



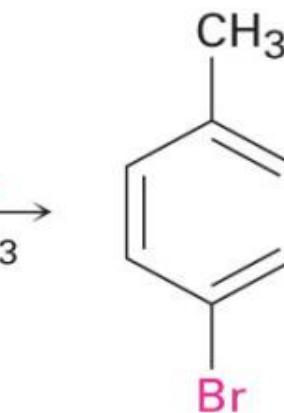
A benzyl group

► Di-substituted Benzenes

- 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)

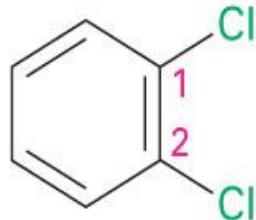


Toluene

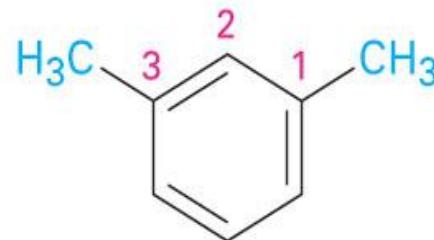


***p*-Bromotoluene**

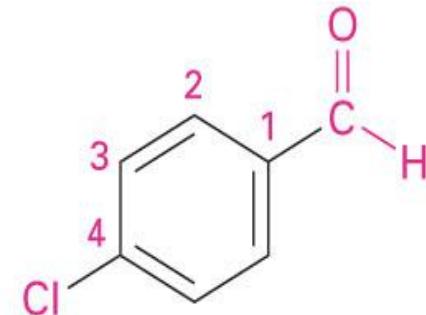
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ortho-Dichlorobenzene
1,2 disubstituted



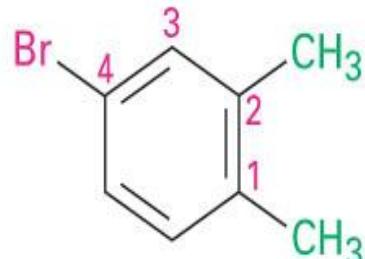
meta-Dimethylbenzene
(*meta*-xylene)
1,3 disubstituted



para-Chlorobenzaldehyde
1,4 disubstituted

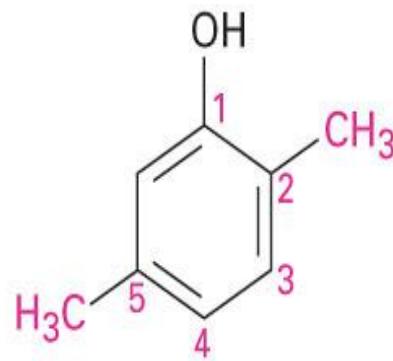
➤ Naming benzene with more than two substituents

- choose numbers to get lowest possible values
- list substituents alphabetically with hyphenated numbers
- common names, such as “toluene” can serve as root name (as in _____)

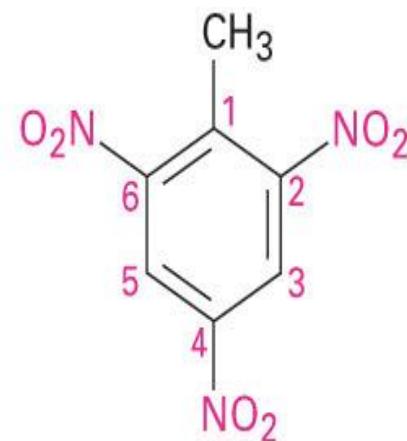


4-Bromo-1,2-dimethylbenzene

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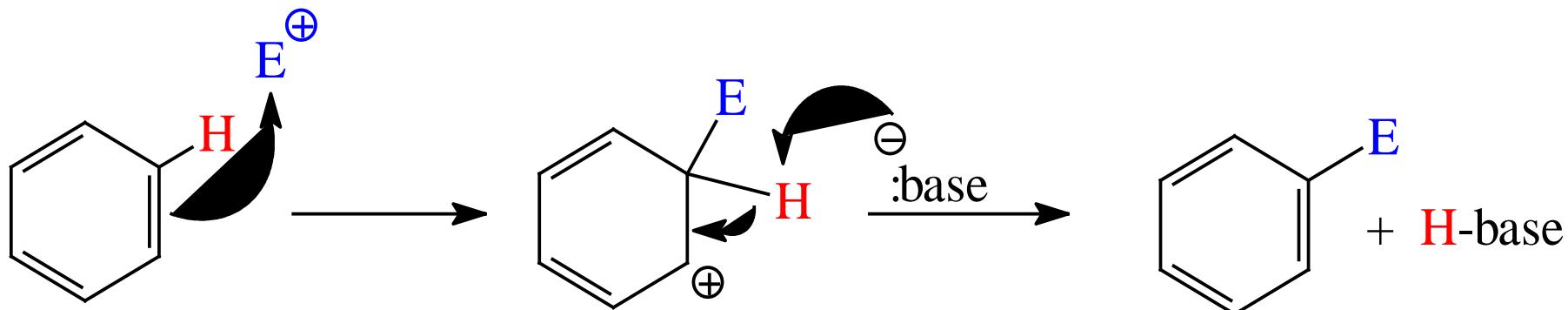
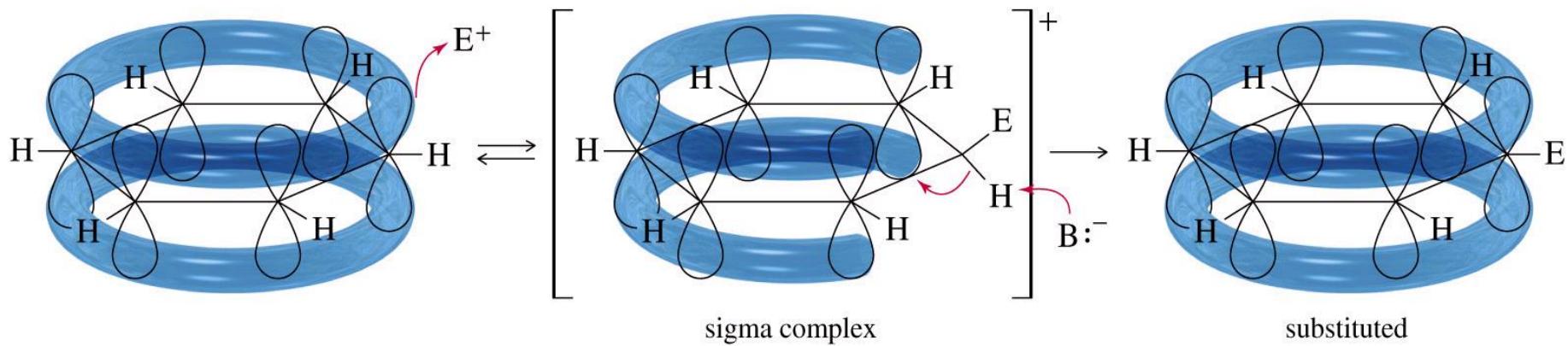
2,5-Dimethylphenol



2,4,6-Trinitrotoluene (TNT)

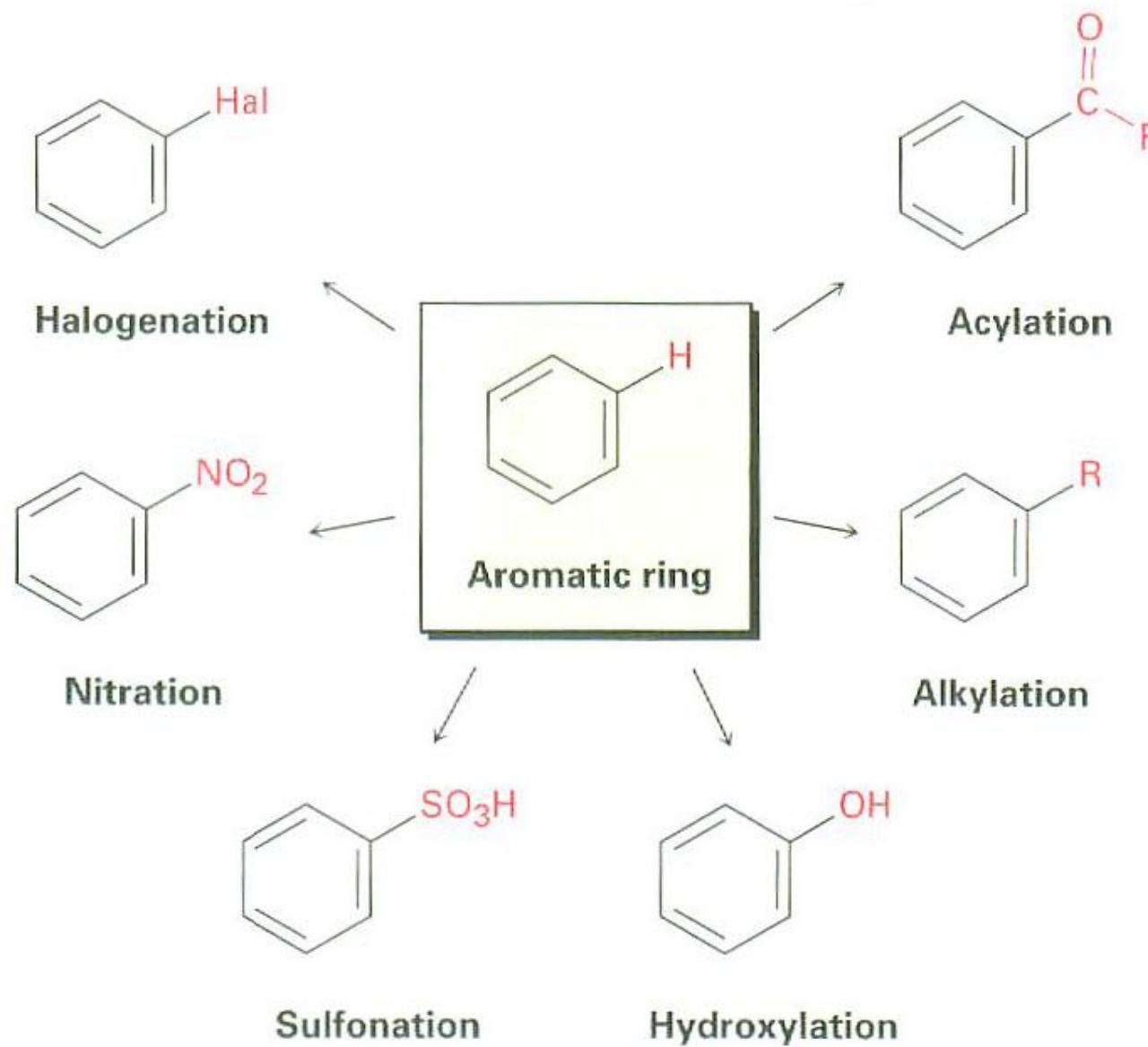
REACTIONS OF AROMATIC COMPOUNDS

7.3 Electrophilic Aromatic substitution reaction



Electrophilic Aromatic substitution reactions

... Cont'd



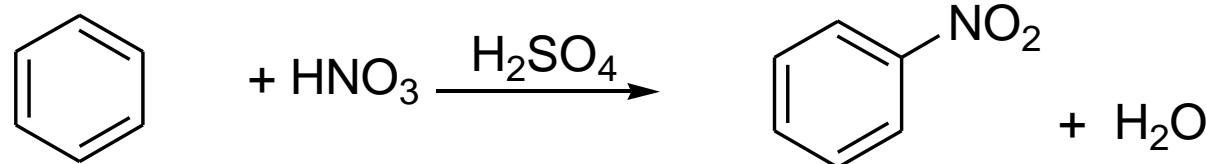
Halogenation of Benzene

Bromination of Benzene

- follows the same general mechanism for the electrophilic aromatic substitution
- bromine itself is **not** electrophilic enough to react with benzene but the addition of a strong **Lewis acid** (electron pair acceptor), such as FeBr_3 , catalyses the reaction, and leads to the **substitution** product

Nitration of Benzene

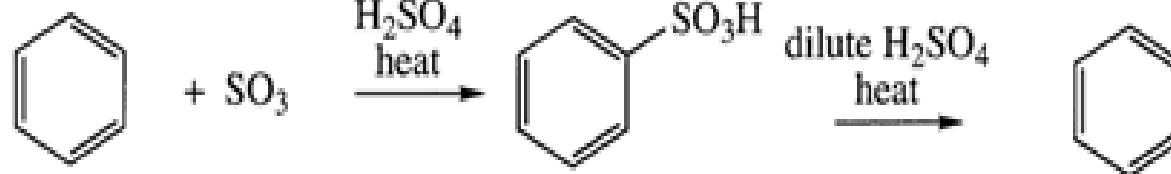
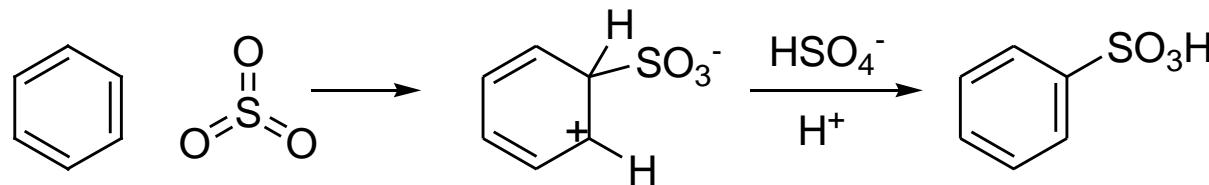
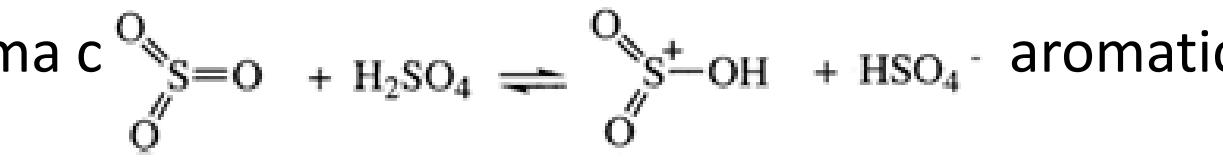
- Benzene will react with hot concentrated nitric acid to produce nitrobenzene proceeds slowly



- involves a mixture of **nitric** and **sulfuric acid** where sulfuric acid behaves as a catalyst
- sulfuric acid reacts with nitric acid to generate a **nitronium ion** (NO_2^+), which is a very powerful electrophile

Sulfonation of Benzene

- benzene will react with sulfur trioxide, and in the presence of an acid forming aryl sulfonic acids are produced
- sulfonic acid is very reactive electrophile which will sulfonate benzene
- the sigma c $\text{O}=\text{S}=\text{O}$ + $\text{H}_2\text{SO}_4 \rightleftharpoons \text{O}=\text{S}^+-\text{OH} + \text{HSO}_4^-$ aromaticity

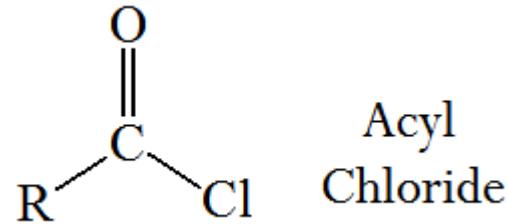


Friedel-Crafts Reaction

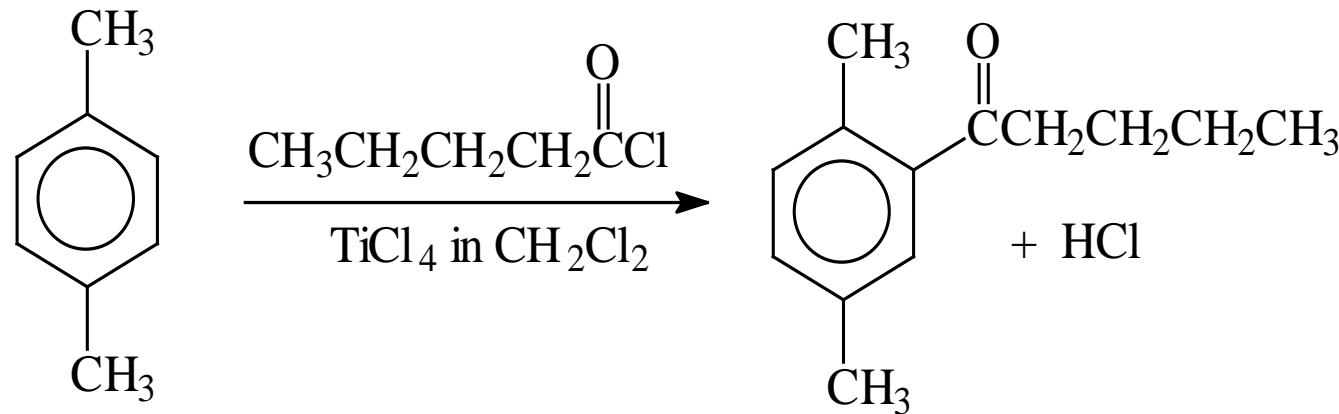
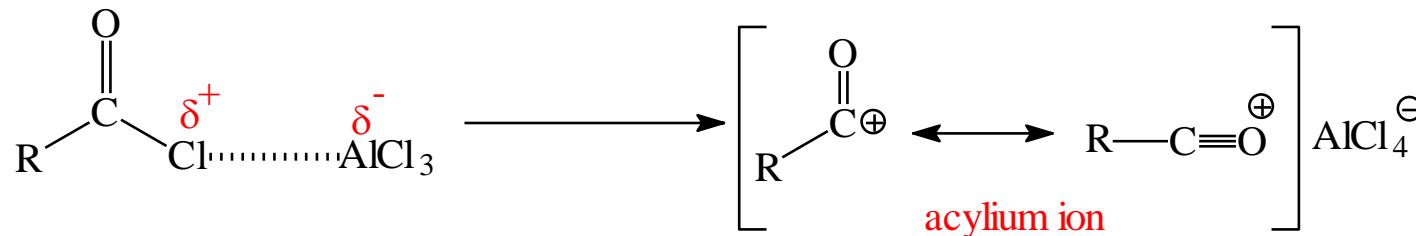
Alkylation

- Reaction of benzene with alkyl halides in the presence of a Lewis acid (such as AlCl_3) to produce alkyl benzenes and this reaction became known as Friedel-Crafts alkylation
- The **t-butyl chloride** reacts with the **Lewis acid** to generate the t-butyl carbocation
- The **t –butyl chloride** carbocation acts as the electrophile, and forms a sigma complex followed by loss of a proton, giving **t-butyl benzene** as the product regenerating Lewis acid catalyst

Acylation



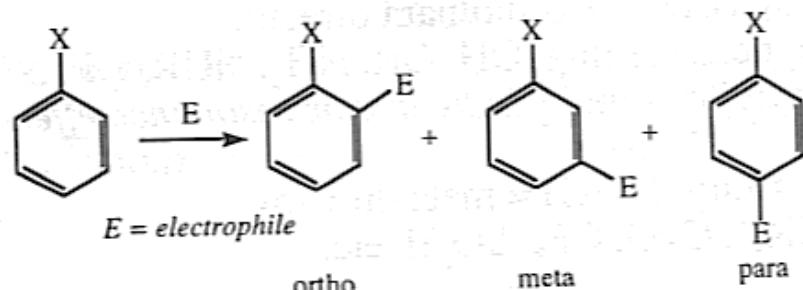
➤ 1st Formation of Electrophile



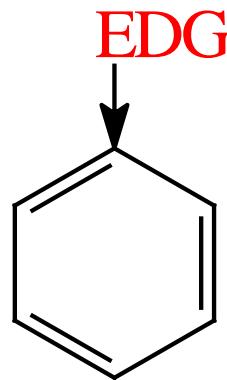
Directing effect of substituents on benzene

- the **electrophile attacks** the nucleophilic pi-bond on the benzene ring, but the **substituent** on the benzene influences where the **electrophile attaches** in order to have the **fastest rate**

✓ Ortho/Para and Meta

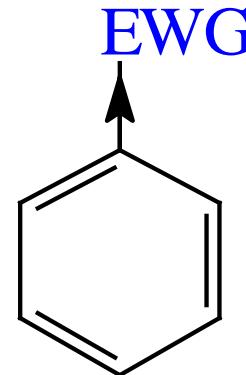


- **Directing Effects of groups attached to benzene ring**



electron donating groups
activate ring

atom attached is
usually sp^3



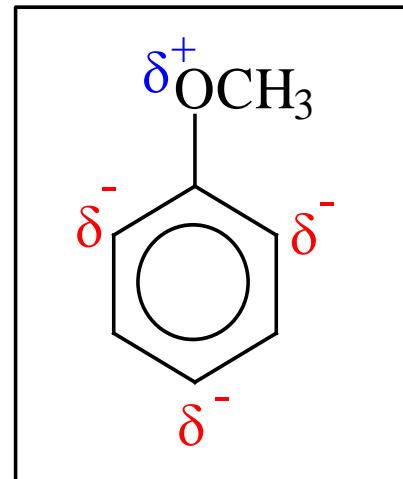
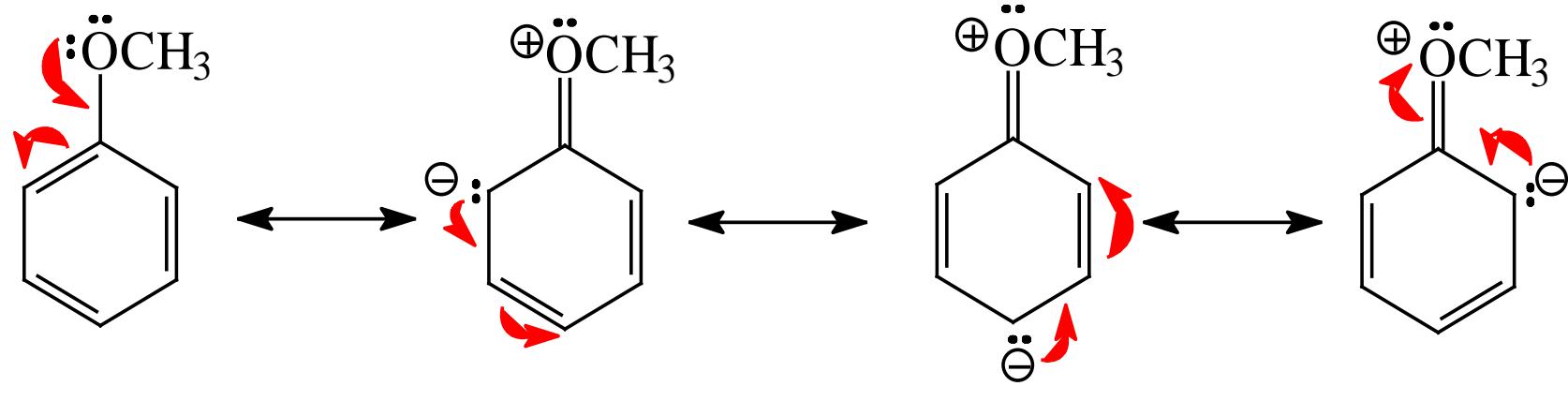
electron withdrawing groups
deactivate ring

atom attached is
usually sp^2 or sp

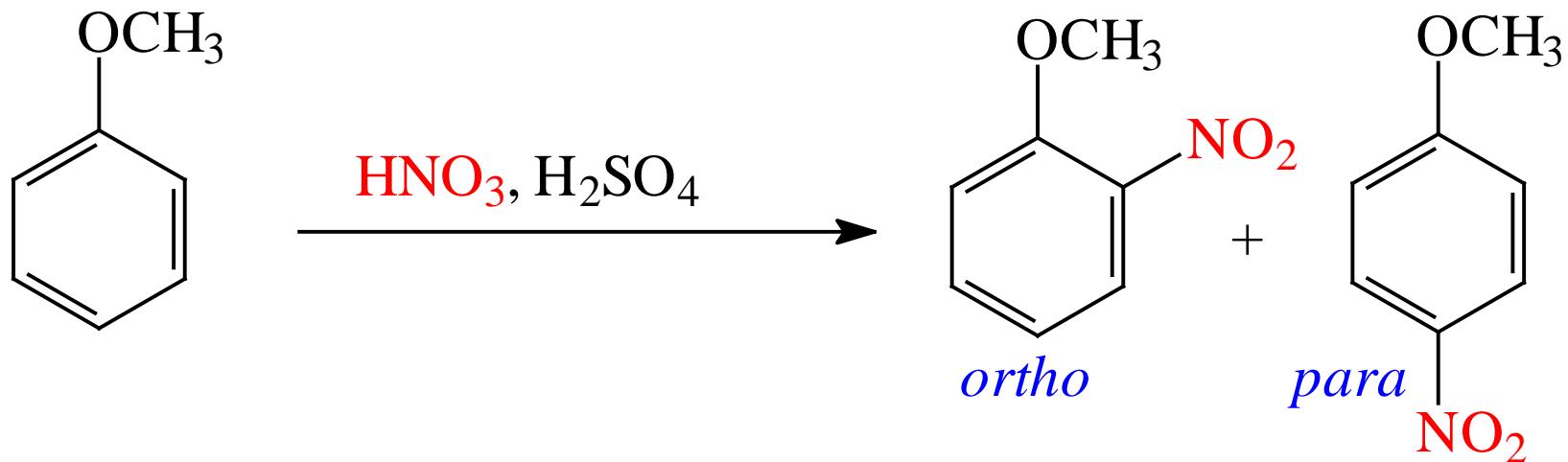
► Activators, *ortho*-/*para*- directing substituents

- substituents that make benzene **more reactive** donate electrons into the benzene ring
- increase benzene nucleophilicity (more reactive towards electrophiles)
- stabilizes carbocation intermediate and transition state leading to carbocation formation
- faster reaction rate for electrophilic attack

ortho-/para-Directing ... Activating Groups

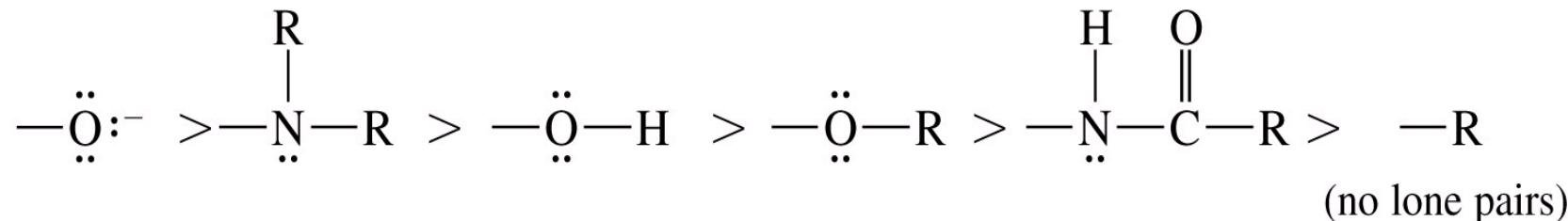


Nitration Affords *ortho*- and *para*- Products

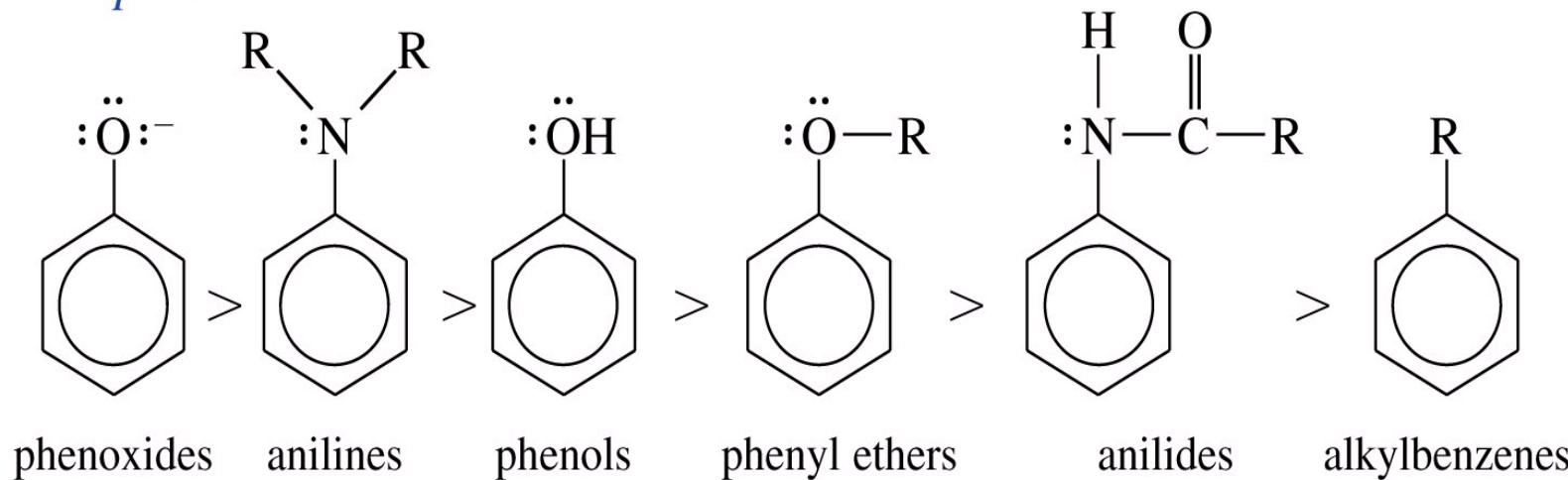


Activating and *ortho/para* directors

Groups:

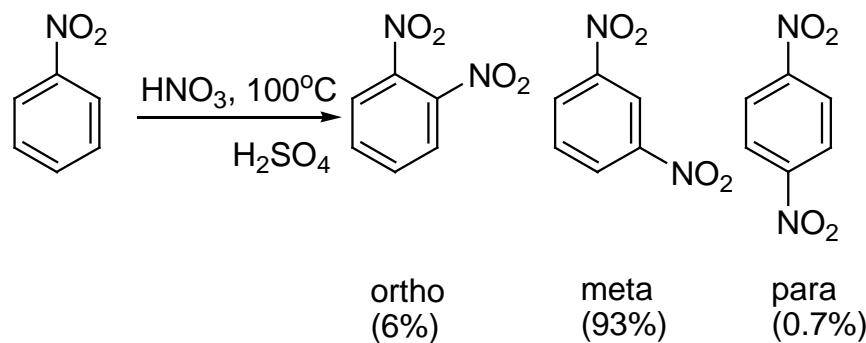


Compounds:

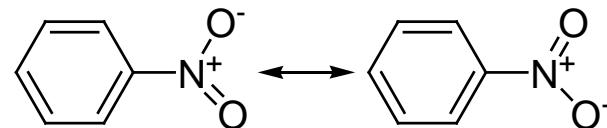


B. Deactivating, meta directing substituents

- nitrobenzene is about 100,000 times **less** reactive than benzene towards EAS
- dinitrobenzene product produces three isomers, with the meta isomer being the major product



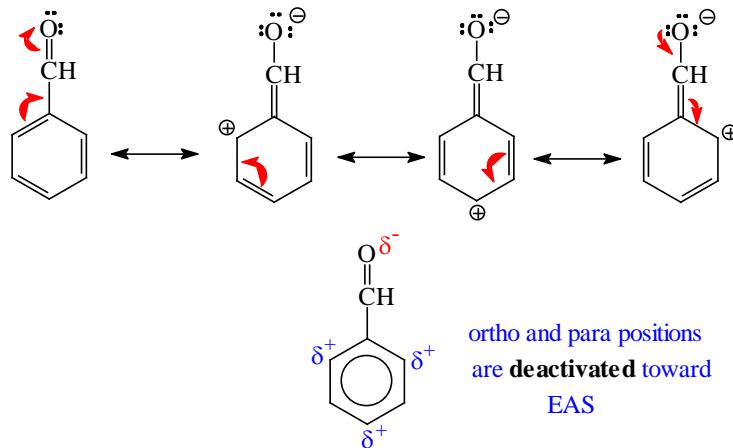
- an electron withdrawing group deactivates the **ortho** and **para** positions and this selective deactivation leaves the **meta position** as the most reactive site for attack



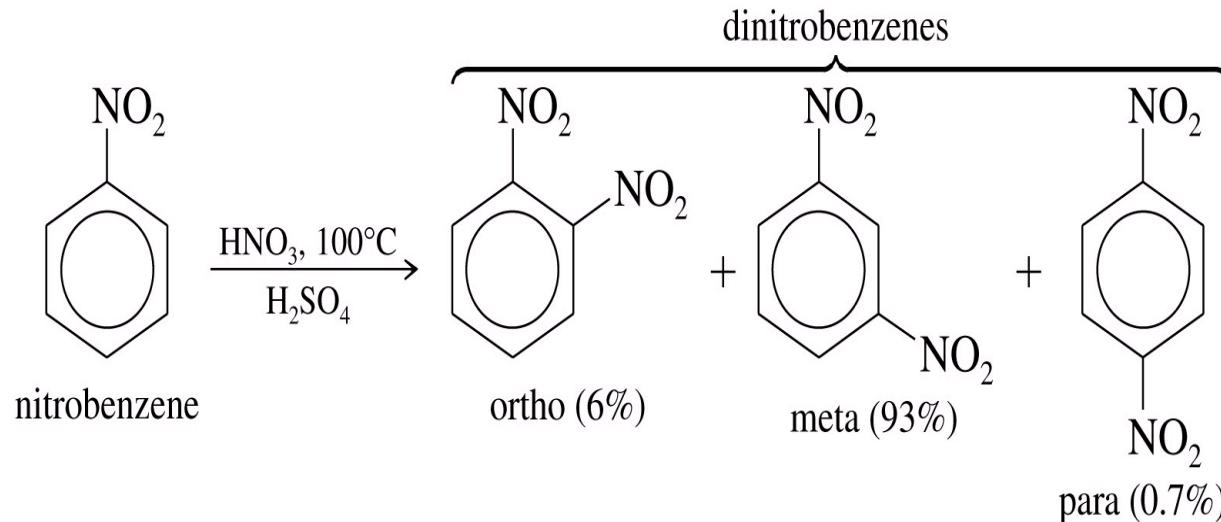
➤ Deactivators

- Substituents that make benzene **less reactive** withdraw electrons from the benzene ring
- **decrease** benzene **nucleophilicity** (less reactive towards electrophiles)
- **destabilize** carbocation intermediate (increases the net positive charge on the carbocation)
- **destabilize transition state** leading to carbocation formation slower rate of electrophilic attack

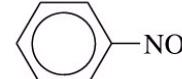
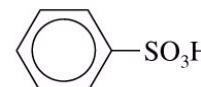
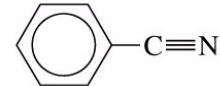
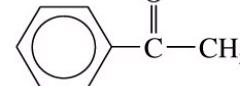
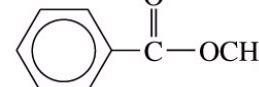
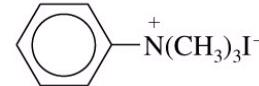
meta-Directing Deactivating Groups



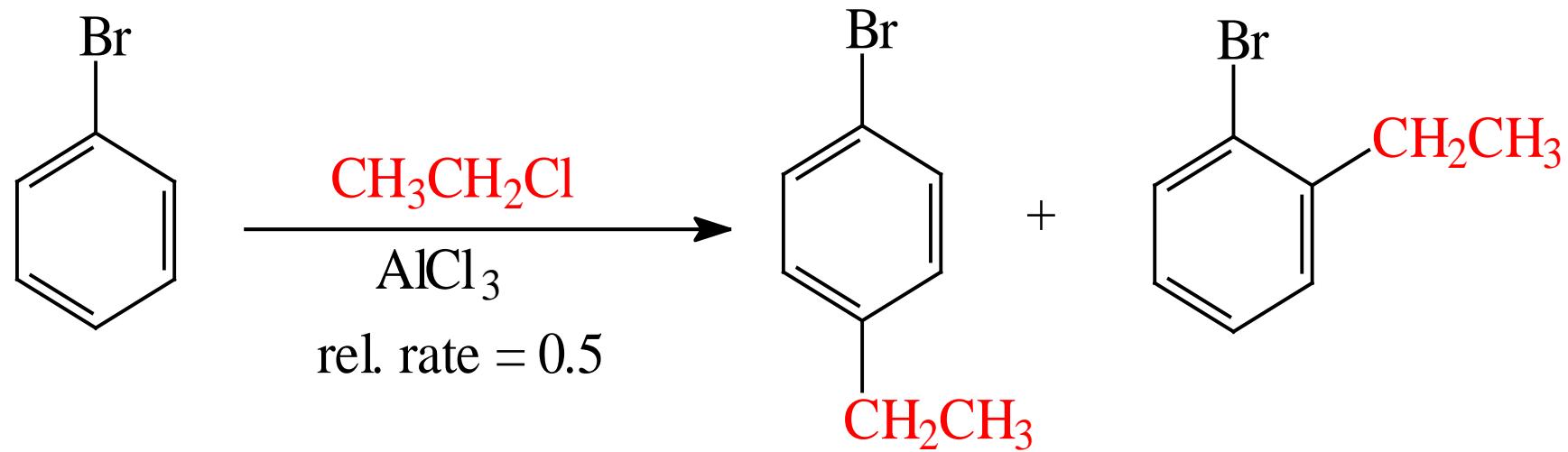
➤ Electron-withdrawing nitro group directs *meta*



Meta- Directors

Group	Resonance Forms	Example
$-\text{NO}_2$ nitro	$\left[\begin{array}{c} \ddot{\text{O}}: \\ \\ -\text{N}^+ \\ \\ \ddot{\text{O}}^- \end{array} \longleftrightarrow \begin{array}{c} \ddot{\text{O}}^- \\ \\ -\text{N}^+ \\ = \text{O}: \end{array} \right]$	 nitrobenzene
$-\text{SO}_3\text{H}$ sulfonic acid	$\left[\begin{array}{c} \ddot{\text{O}}: \\ \parallel \\ -\text{S}-\ddot{\text{O}}-\text{H} \\ \\ \ddot{\text{O}}: \end{array} \longleftrightarrow \begin{array}{c} \ddot{\text{O}}^-: \\ \parallel \\ -\text{S}^+-\ddot{\text{O}}-\text{H} \\ \\ \ddot{\text{O}}: \end{array} \longleftrightarrow \begin{array}{c} \ddot{\text{O}}: \\ \parallel \\ -\text{S}^+-\ddot{\text{O}}-\text{H} \\ \\ \ddot{\text{O}}^-: \end{array} \right]$	 benzenesulfonic acid
$-\text{C}\equiv\text{N}:$ cyano	$\left[\begin{array}{c} \text{C}\equiv\text{N}: \\ \longleftrightarrow \\ -\text{C}^+=\ddot{\text{N}}: \end{array} \right]$	 benzonitrile
$-\text{C}(=\text{O})-\text{R}$ ketone or aldehyde	$\left[\begin{array}{c} \ddot{\text{O}}: \\ \parallel \\ -\text{C}-\text{R} \\ \\ \text{C}^+ \end{array} \longleftrightarrow \begin{array}{c} \ddot{\text{O}}^-: \\ \parallel \\ -\text{C}^+-\text{R} \\ \\ \text{C}^+ \end{array} \right]$	 acetophenone
$-\text{C}(=\text{O})-\text{O}-\text{R}$ ester	$\left[\begin{array}{c} \ddot{\text{O}}: \\ \parallel \\ -\text{C}-\ddot{\text{O}}-\text{R} \\ \\ \text{C}^+ \end{array} \longleftrightarrow \begin{array}{c} \ddot{\text{O}}^-: \\ \parallel \\ -\text{C}^+-\ddot{\text{O}}-\text{R} \\ \\ \text{C}^+ \end{array} \longleftrightarrow \begin{array}{c} \ddot{\text{O}}^-: \\ \parallel \\ -\text{C}^+=\ddot{\text{O}}-\text{R} \\ \\ \text{C}^+ \end{array} \right]$	 methyl benzoate
$-\text{NR}_3^+$ quaternary ammonium	$\begin{array}{c} + \\ \text{N} \\ \\ \text{R} \\ \\ \text{R} \end{array}$	 trimethylanilinium iodide

Halogens are the Anomaly - Deactivators & *o*, *p*-Directors



- Inductively withdrawing, hence deactivating and donation causes *o*, *p* directing

Substituent Summary

π Donors	σ Donors	Halogens	Carbonyls	Other
$-\ddot{\text{N}}\text{H}_2$	$-\text{R}$	$-\text{F}$	$\begin{matrix} \text{O} \\ \parallel \\ -\text{C}-\text{R} \end{matrix}$	$-\text{SO}_3\text{H}$
$-\ddot{\text{O}}\text{H}$	(alkyl)	$-\text{Cl}$	$\begin{matrix} \text{O} \\ \parallel \\ -\text{C}-\text{OH} \end{matrix}$	$-\text{C}\equiv\text{N}$
$-\ddot{\text{O}}\text{R}$		$-\text{Br}$		$-\text{NO}_2$
$-\ddot{\text{N}}\text{HCOCH}_3$		$-\text{I}$	$\begin{matrix} \text{O} \\ \parallel \\ -\text{C}-\text{OR} \end{matrix}$	$-\text{NR}_3^+$
	(aryl)			

ortho, para-directing

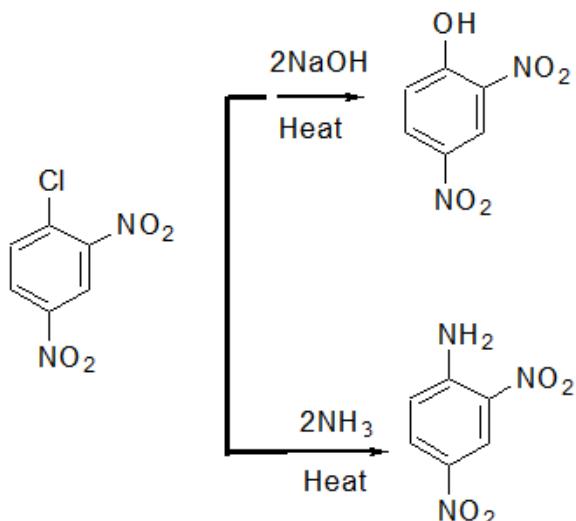
meta-directing

ACTIVATING

DEACTIVATING

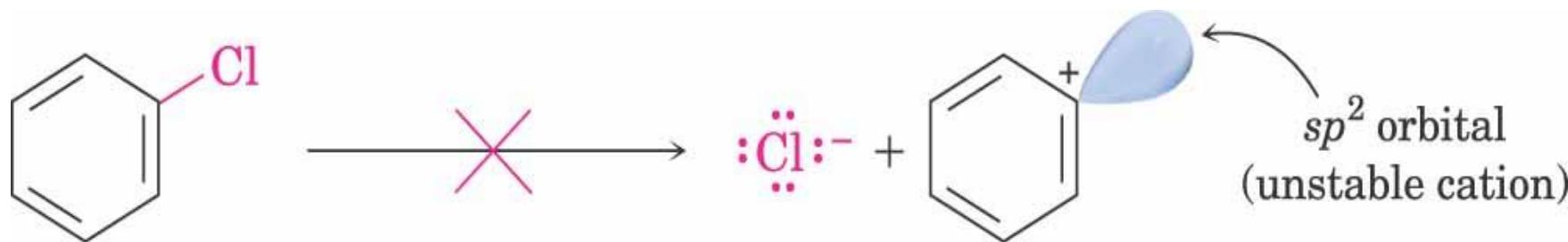
Nucleophilic aromatic substitution reaction, NAS

- nucleophile could displace halide ions from aryl halides if there are strong EWGs bound to the ring (and especially if they are located ortho and para to the halide)
- when a nucleophile substitute the leaving group on the benzene ring, this is called nucleophilic aromatic substitution
- For example; 2, 4-dinitrochlorobenzene



Reaction of Aryl Halides

- as S_N1 reaction of aliphatic compounds, there will not be usual ionization of alkyl halide substrates to form carbocation

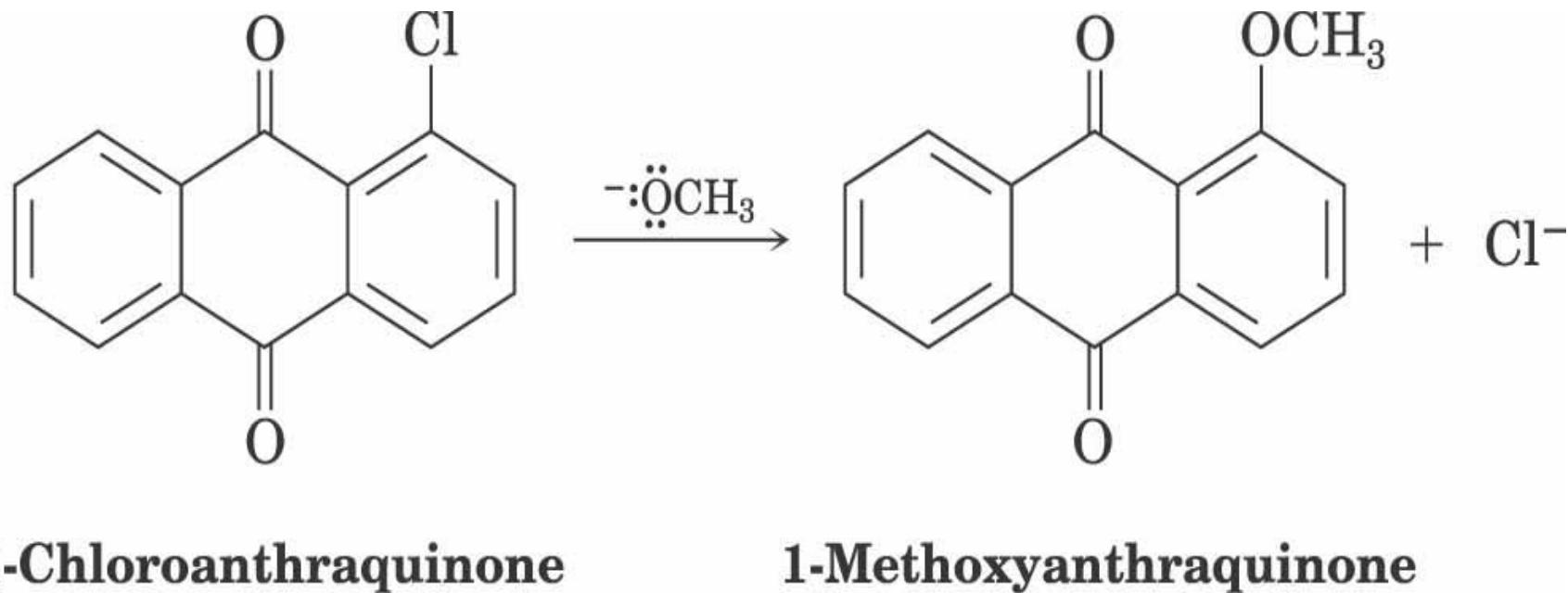


Dissociation does *NOT* occur;
therefore, no S_N1 reaction

Nucleophilic Aromatic Substitution reaction, “NAS” criteria:

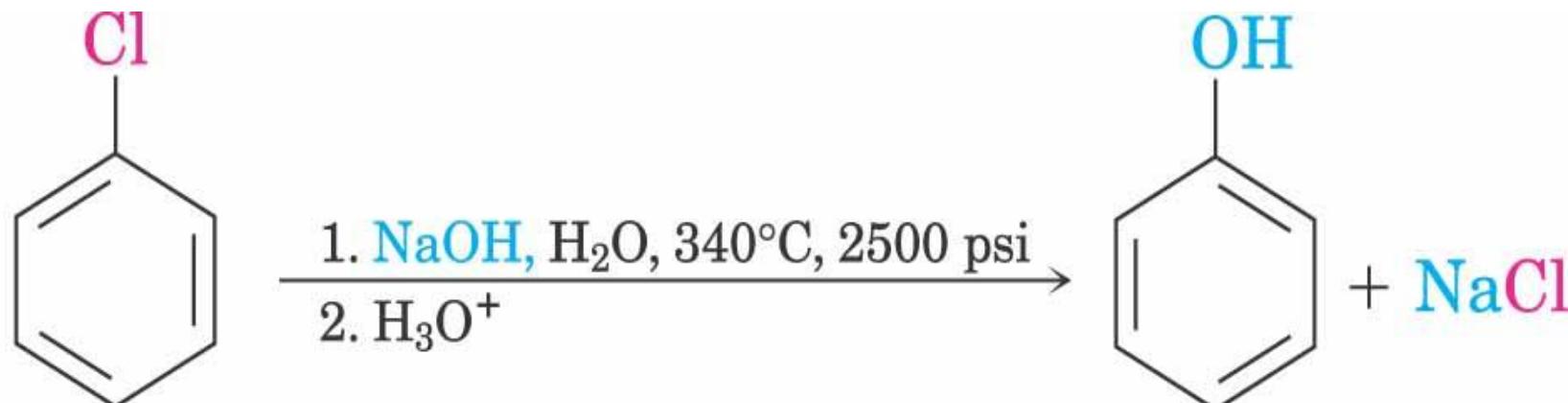
- Strongly deactivated ring
- Leaving group
- Deactivating group(s) *ortho* &/or *para* to leaving group (preferably)
- Strong base (nucleophile) such as RO^- , NH_2^-

Methoxide as a nucleophile



➤ Aryl Halide (Ar-X) With no EWG

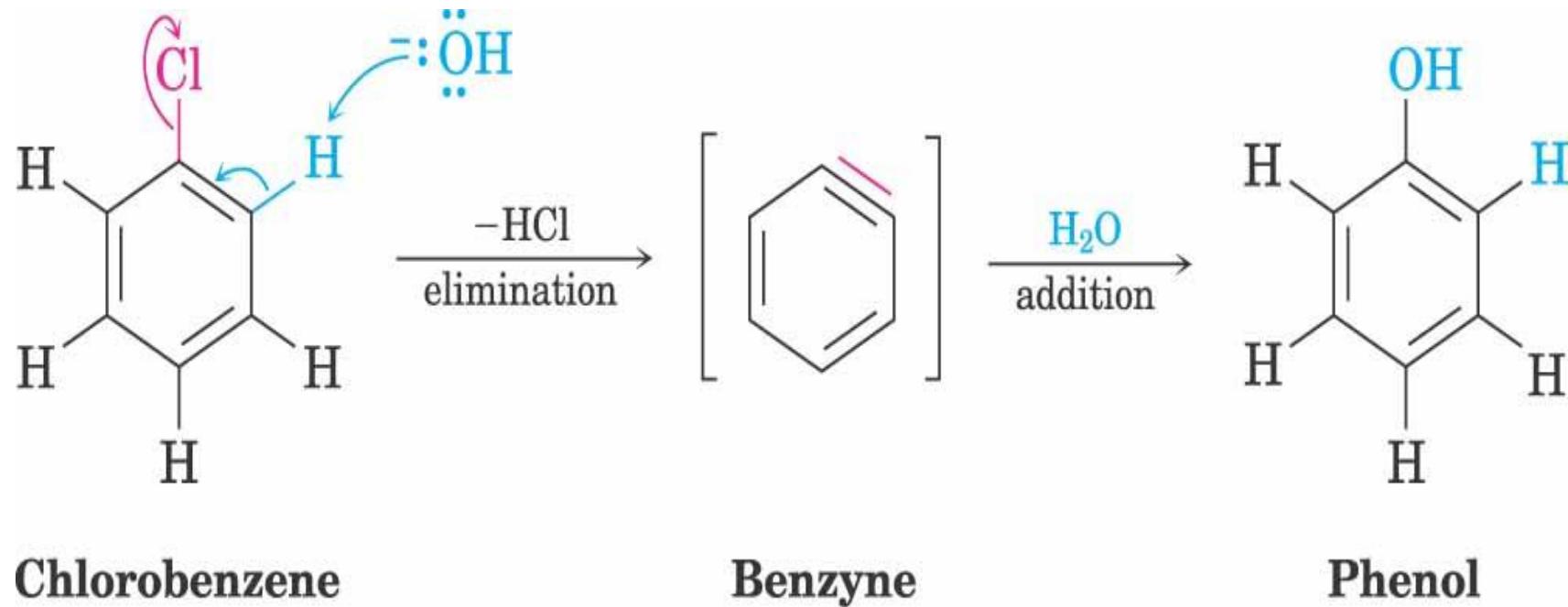
- reaction conditions are more extreme, following **elimination** and **addition** mechanism to form **benzyne** intermediate



Chlorobenzene

Phenol

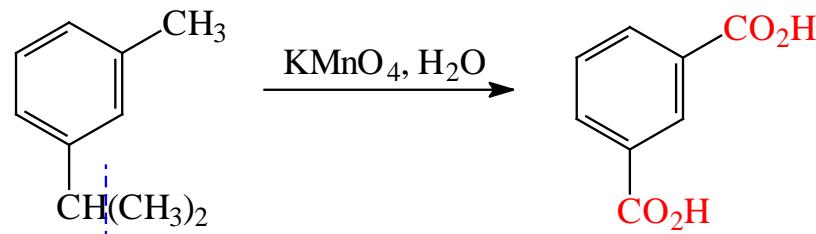
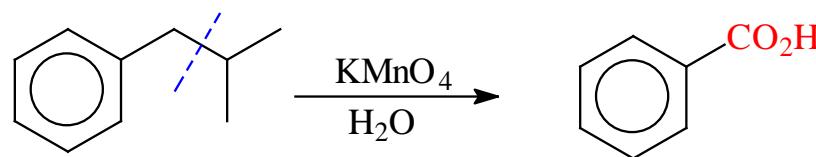
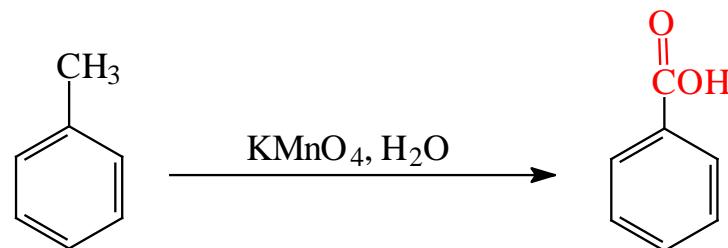
- formation of “**Benzyne**” intermediate during chemical reaction



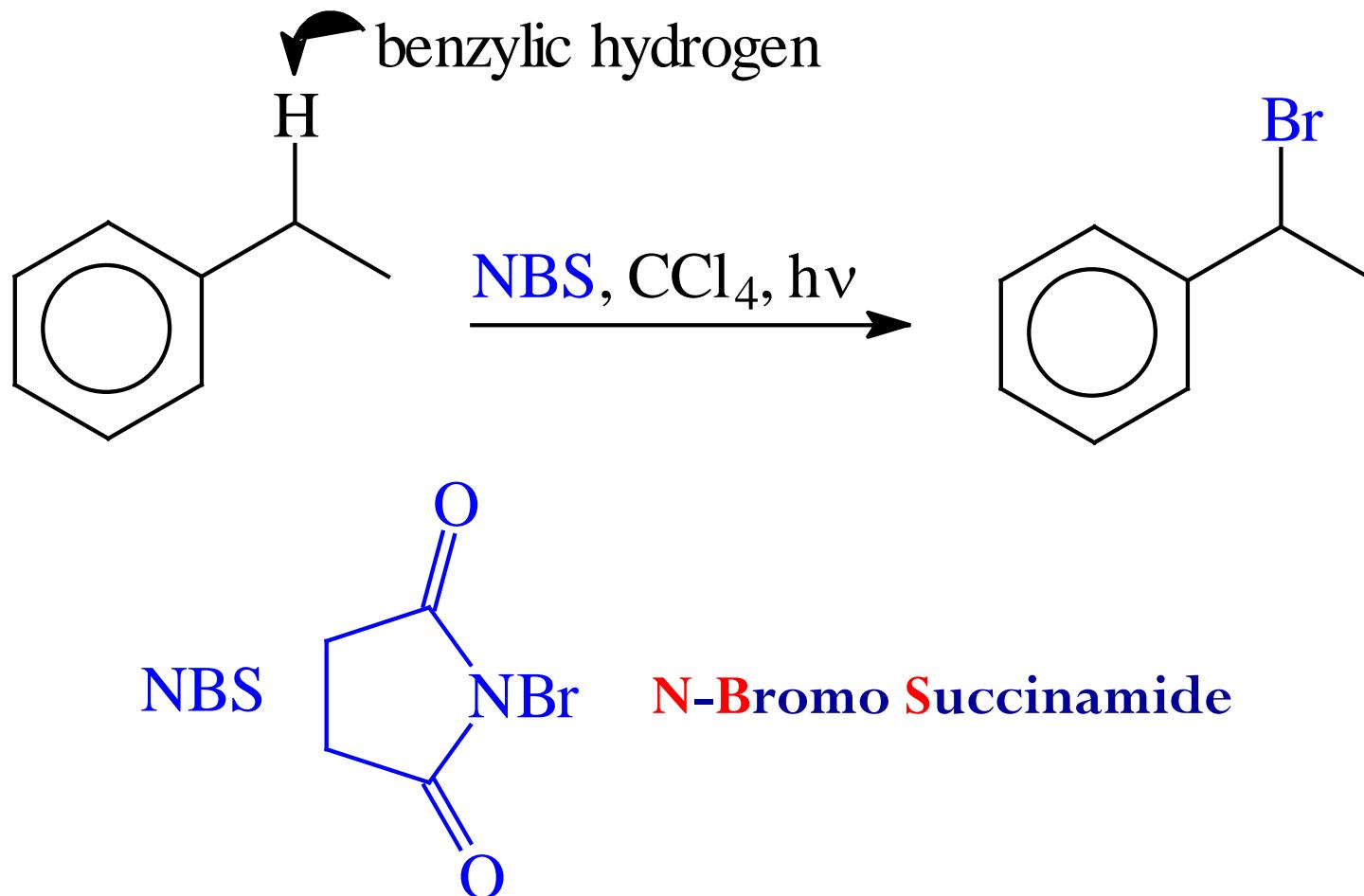
Reactions of Aromatic Side Chain

Oxidation and substitution of alkyl side chains

i. Oxidation of Alkyl Substituents



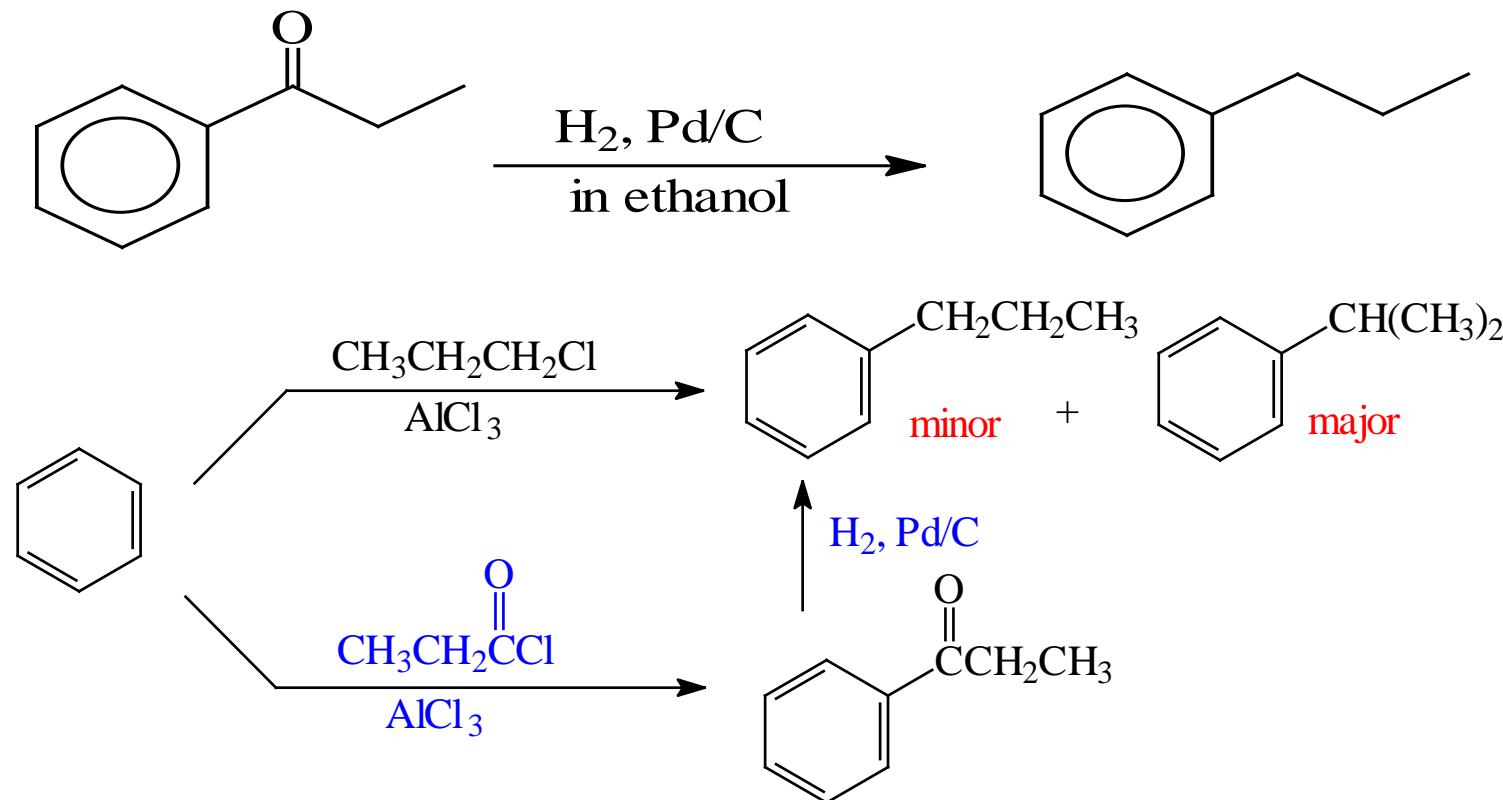
ii. Substitution of Benzylic hydrogen with NBS... Bromination



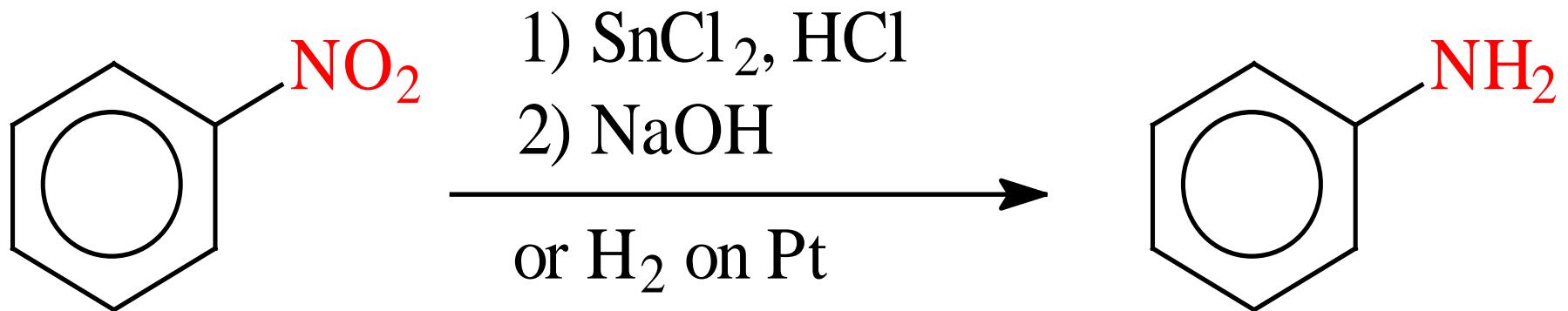
Reduction of Aryl Ketones and Nitro Groups

i. Reduction of aromatic ketones

- Straight-chain alkylation can be accomplished in two steps; **Acylation** and then **Reduction**



ii. Reduction of Nitro Groups



Conversion of Halogens into Organometallic Compounds

Aryl halide reactions:

I. Grignard Reagent Formation

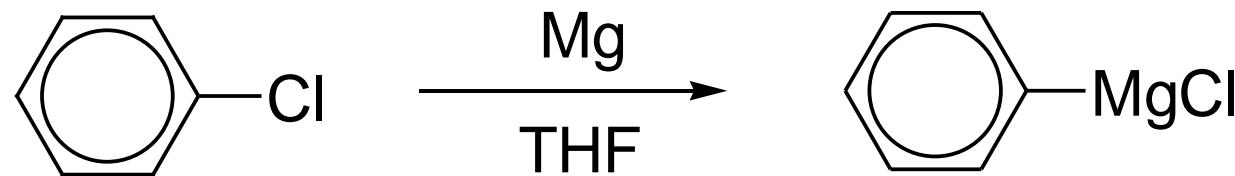
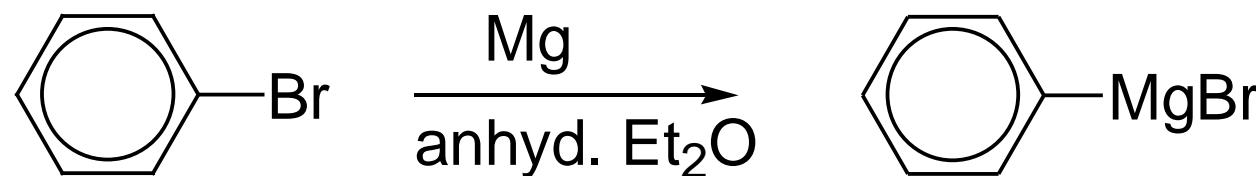
II. EAS

III. Nucleophilic aromatic substitution (bimolecular displacement)

(Ring must contain strong **EWGs** ortho and/or para to X)

IV. Nucleophilic aromatic substitution (elimination-addition)

Grignard reagent formation



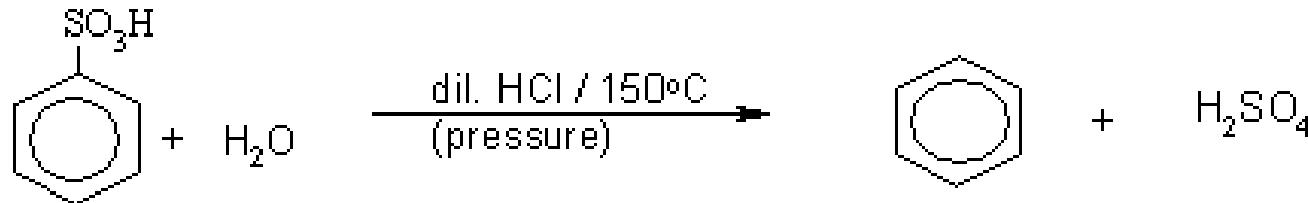
THF - Tetrahydrofuran

Hydrolysis and fusion of sulphonic acids

i. Replacement of the SO_3H with H

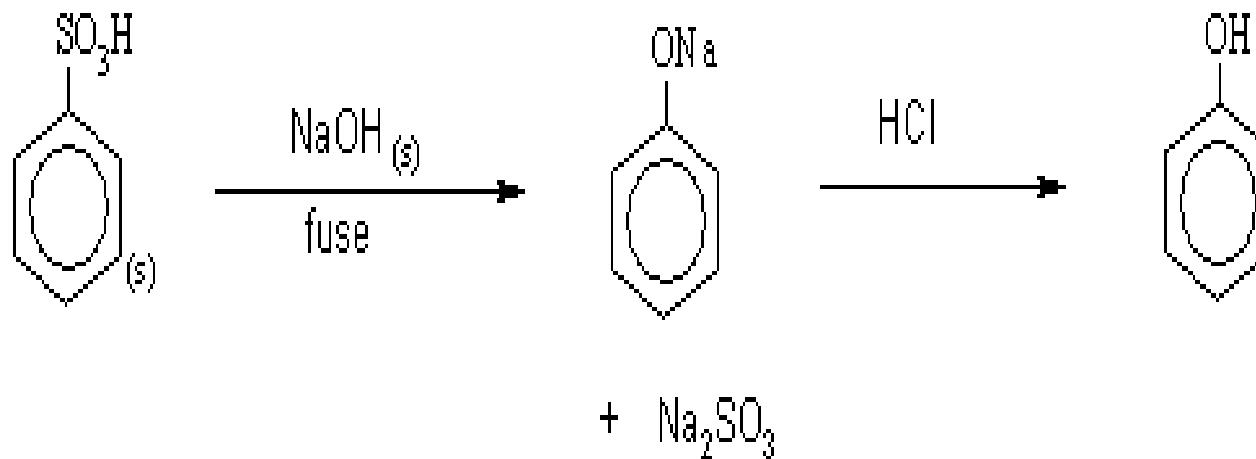
Formation of parent arene ($\text{PhSO}_3\text{H} \dots \text{PhH}$)

- Hydrolysis of the benzene sulfonic acids with dilute HCl at 150°C, under pressure, yields the parent arene (**Benzene**), which is the exact reverse reaction of the sulfonation process

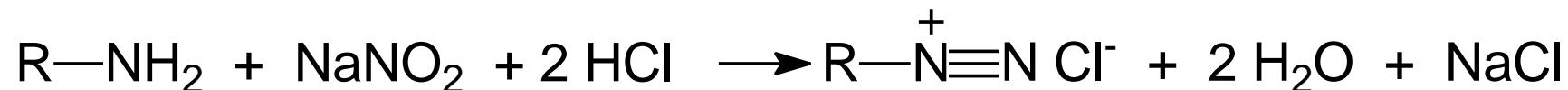


ii. Replacement of SO_3H with formation of phenols

- Fusion of the sulfonic acids with sodium hydroxide initially gives the phenate salt with the phenol being released by the subsequent addition of mineral acid.



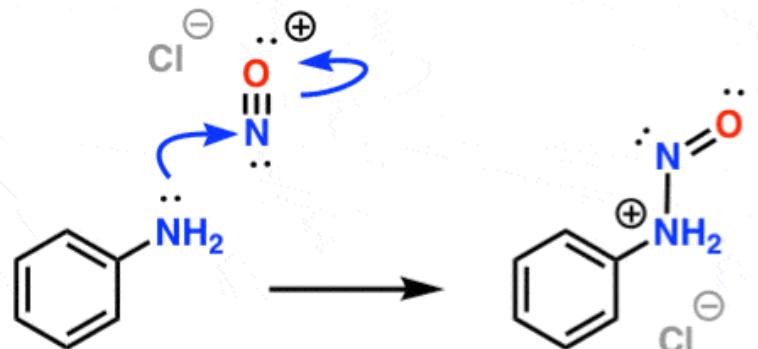
Diazotization of primary amines



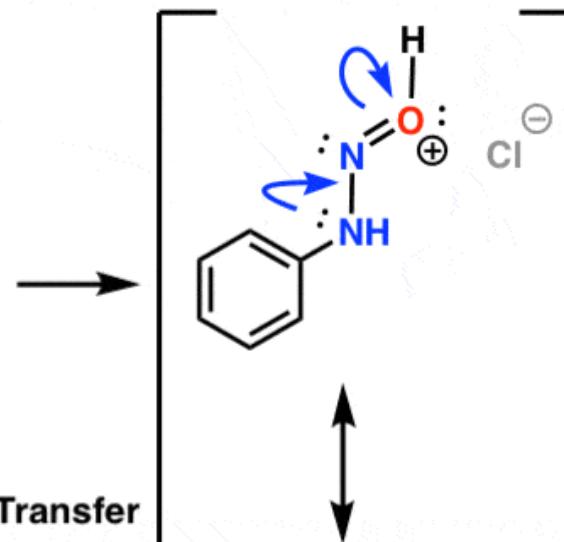
- Primary amines react with nitrous acid (HNO_2) to form di-alkyl diazonium salts
- The diazonium salts are unstable and decompose into carbocations and nitrogen molecule

Mechanism: Formation of Diazonium Ions From Aromatic Amines

Step 1: Addition to nitrosonium ion



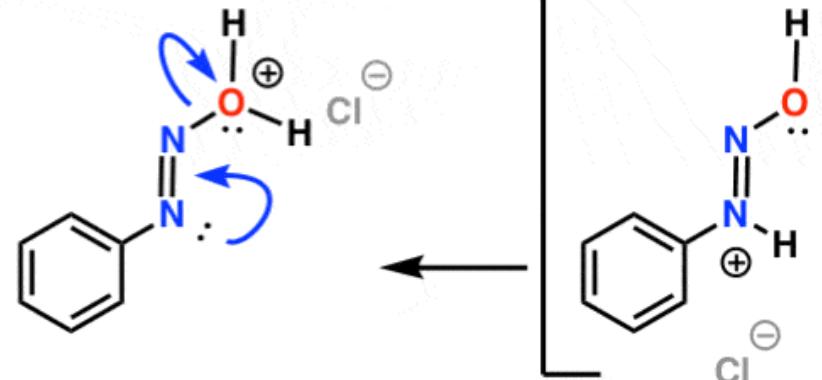
Step 2: Proton Transfer



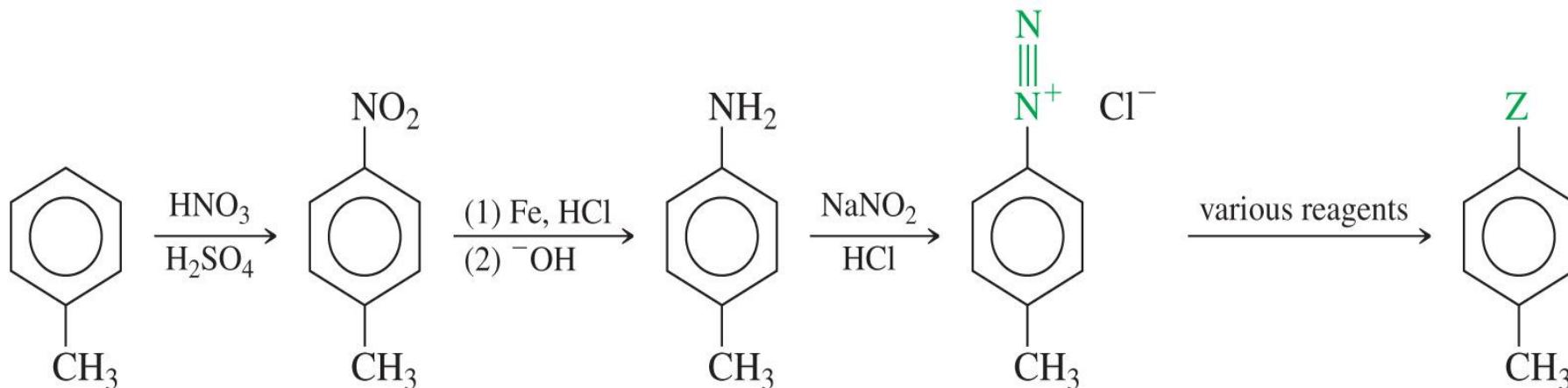
Step 4: Elimination of H_2O



Step 3: Proton Transfer



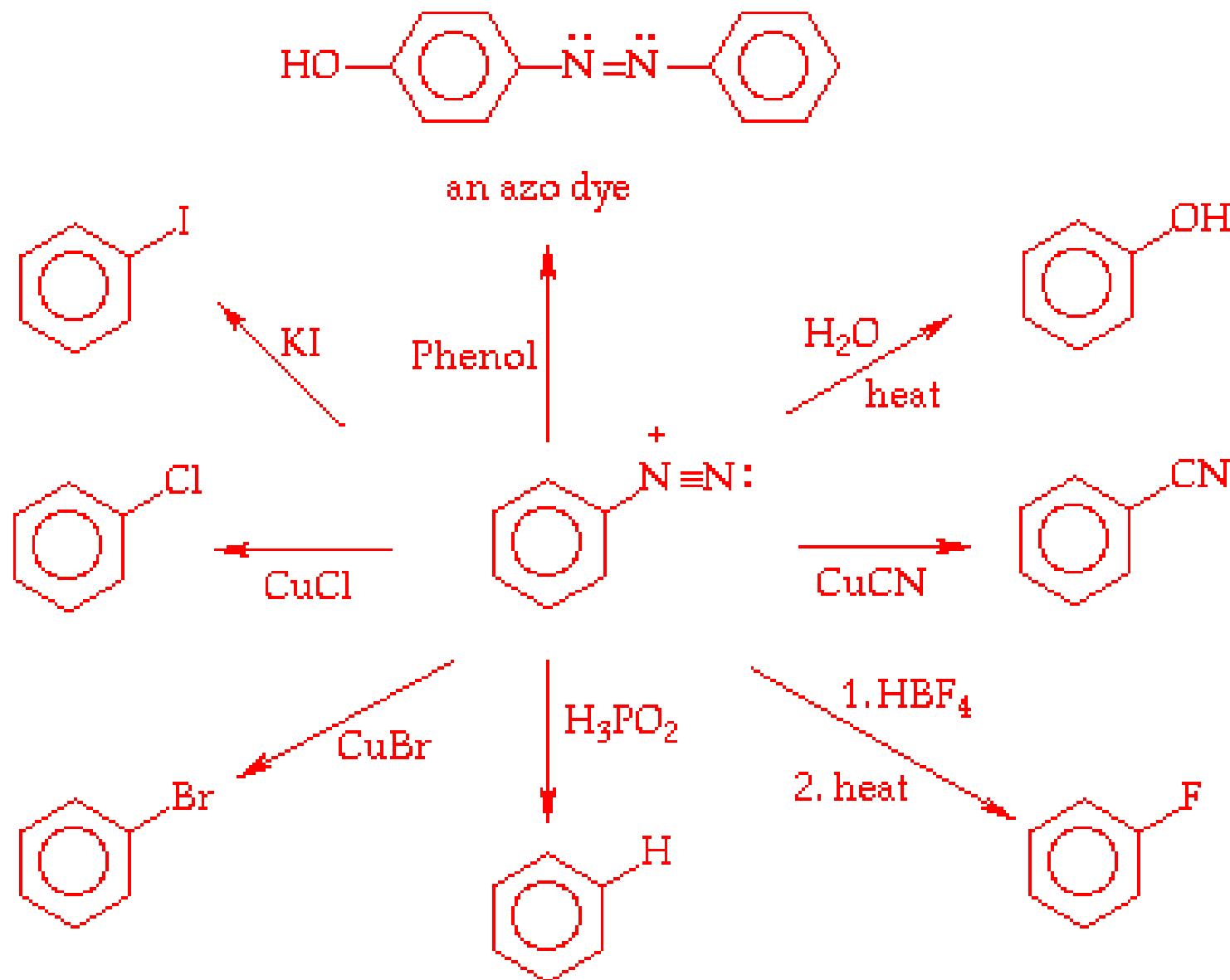
Arene diazonium Salts



- by forming and diazotizing an amine, an activated aromatic position can be converted into a wide variety of functional groups

Reactions of Arene diazonium Salts

... Cont'd



CHAPTER TWO

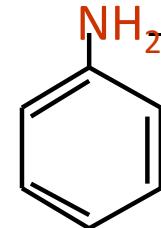
AMINES

Introduction

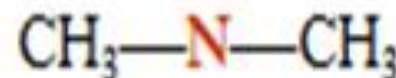
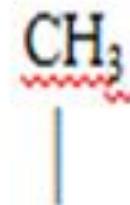
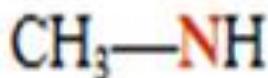
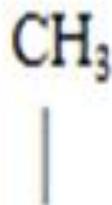
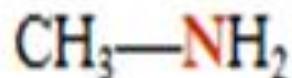
Amines

- derivatives of ammonia NH_3 , containing N attached to one or more alkyl (aliphatic amine) or aromatic groups (aromatic amine)

Examples;



- classified into **three** depending on the **number of carbon groups** bonded to nitrogen



Primary 1°

Secondary 2°

Tertiary 3°

Nomenclature and Structure of Amines

Nomenclature of Amines

Rules to be follow in naming amines

Rule 1: as parent carbon chain select the longest chain to which the nitrogen atom is attached

Rule 2: name the parent chain by changing the -e ending of the corresponding alkane name to -amine

Rule 3: number the parent chain from the end nearest the nitrogen atom

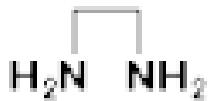
Rule 4: the position of attachment of the nitrogen atom is indicated by a number in front of the parent chain name

Rule 5: the identity and location of any substituents are appended to the front of the parent chain name

Nomenclature of Amines

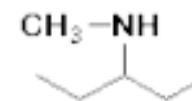
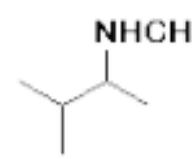
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Examples: Primary Amines

IUPAC Name	Structure
methanamine	CH_3-NH_2
ethanamine	
propan-1-amine	
propan-2-amine	
ethane-1,2-diamine	
cyclopentanamine	

Examples : Secondary Amines

- the **longest chain** of carbons takes the **root name** (alkanamine), and the **other chain** becomes a **substituent** with the locant *N*
- N** is a **lower locant** than **numerical locants**, and so is placed **ahead of** the name

IUPAC Name	Structure
N-methylmethanamine	$\text{CH}_3\text{-NH-CH}_3$
N-methylethanamine	$\text{CH}_3\text{-NH-CH}_2\text{CH}_3$
N-ethylethanamine	$\text{CH}_3\text{CH}_2\text{-NH-CH}_2\text{CH}_3$
N-methylpentan-3-amine	$\text{CH}_3\text{-NH}$ 
N,3-dimethylbutan-2-amine	NHCH_3 

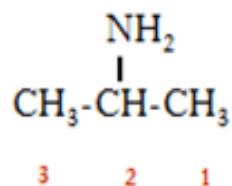
Examples : Tertiary Amines

- the longest chain of carbons takes the root name (alkanamine) and the other chains become a substituents with the locant *N*
- the *N* is a lower locant than numerical locants, and so is placed ahead of them

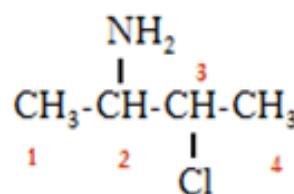
IUPAC Name	Structure
N,N -dimethylmethanamine	$(\text{CH}_3)_2\text{-NH-CH}_3$
N,N -dimethylethanamine	$(\text{CH}_3)_2\text{-NH-CH}_2\text{CH}_3$
N -ethyl- N -methylethanamine	$\text{CH}_3-\text{N}(\text{CH}_3)\text{-CH}_3$
N -ethyl- N -methylheptan-4-amine	

Nomenclature of Amines

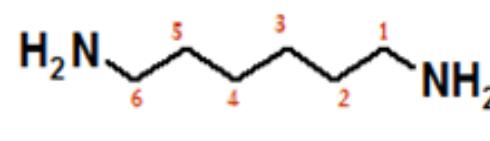
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2-propanamine



3-chloro-2-butanamine



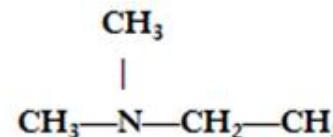
1,6-hexanediamine



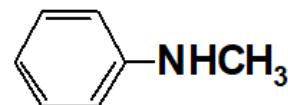
ethylamine



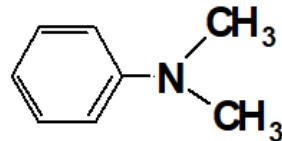
dimethylamine



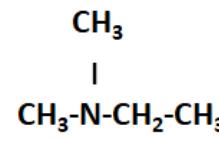
ethyldimethylamine



N-Methylaniline

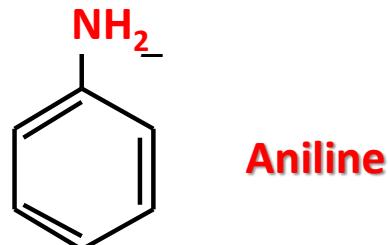


N,N-Dimethylaniline

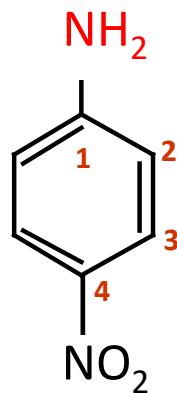


N,N-Dimethylethanamine

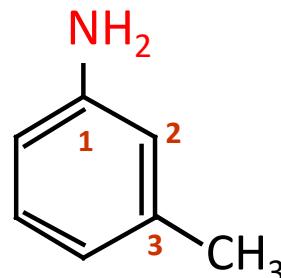
Common name-Aniline and its derivatives



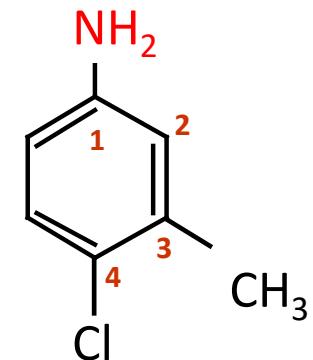
Aniline



4-Nitroaniline



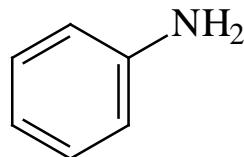
3-Methylaniline



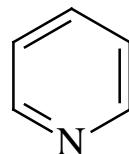
4-Chloro-3-methylaniline

Heterocyclic amines

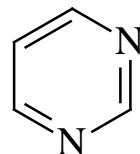
- the important heterocyclic amines have nitrogen as part of a ring
- these group of compounds have common names as follows



aniline



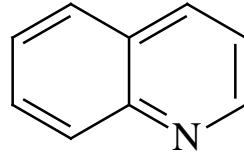
pyridine



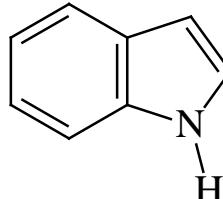
pyrimidine



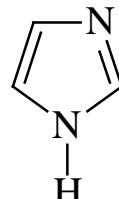
pyrrole



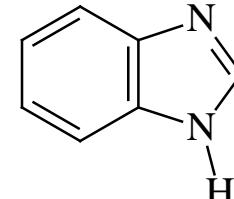
quinoline



indole



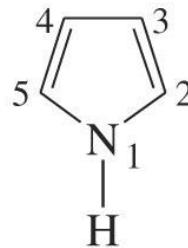
imidazole



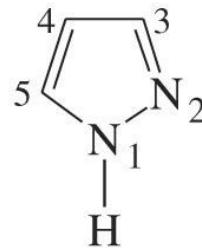
benzimidazole

- in IUPAC nomenclature the prefixes *aza*-, *diaza*- and *triaza* are used to indicate that nitrogen has replaced carbon in the corresponding hydrocarbon
- nitrogen atom is assigned position 1 and the ring is numbered to give the lowest overall set of locants

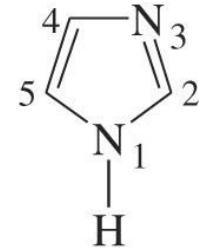
Examples



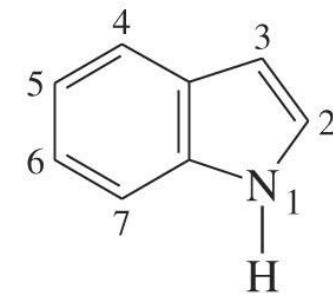
Pyrrole
(1-azacyclopenta-2,4-diene)



Pyrazole
(1,2-diazacyclopenta-2,4-diene)

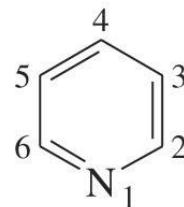


Imidazole
(1,3-diazacyclopenta-2,4-diene)

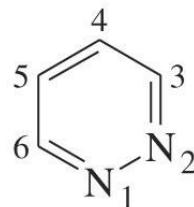


Indole
(1-azaindene)

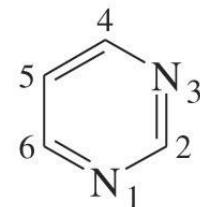
Examples



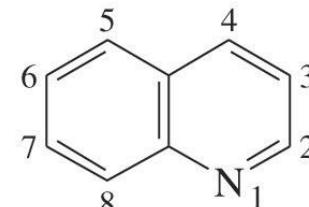
Pyridine
(azabenzene)



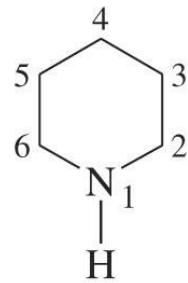
Pyridazine
(1,2-diazabenzene)



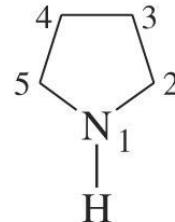
Pyrimidine
(1,3-diazabenzene)



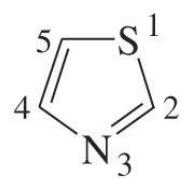
Quinoline
(1-azanaphthalene)



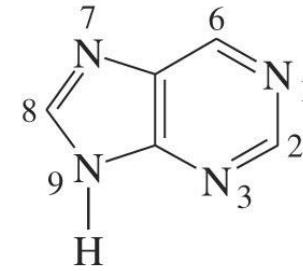
Piperidine
(azacyclohexane)



Pyrrolidine
(azacyclopentane)



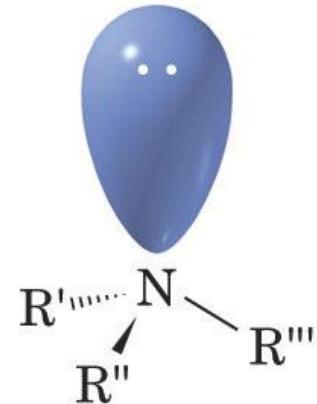
Thiazole
(1-thia-3-
azacyclopenta-
2,4-diene)



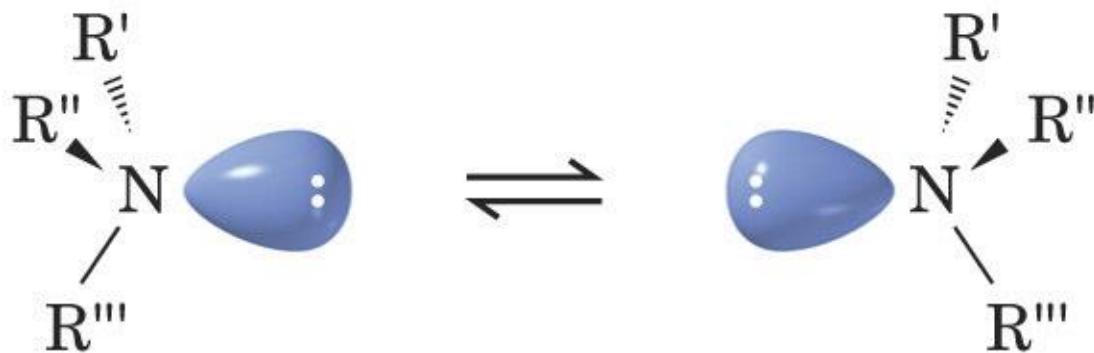
Purine

Structure of amines

- amines have sp^3 hybridized nitrogen
- in principle, tertiary amines with three different -R groups should be **chiral** (i.e., have a stereocenter)
- however, rapid pyramidal inversion of the amine nitrogen prevents isolation of the enantiomers except where the nitrogen is part of a ring or has other geometrical constraint



Structure of an amine



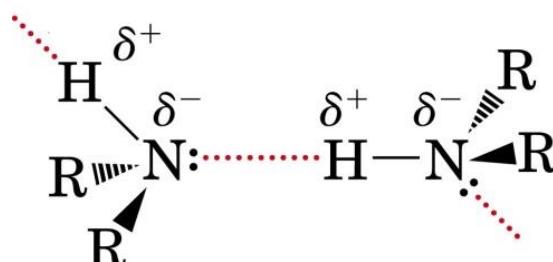
Properties of Amines

Physical properties of Amines

- i. they have unpleasant odors (rotting fish like ammonia)
- ii. they are polar compounds

Difference in electro negativity between N - H ($3.0 - 2.1 = 0.9$)

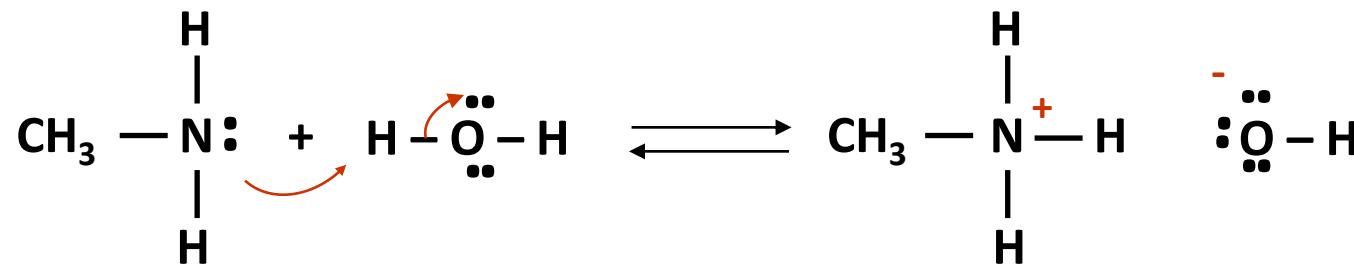
- iii. 1° and 2° amines have hydrogen bonds (N-H) which is weaker than alcohols (O-H), however, 3° amines do not form hydrogen bonds (no H atom)



- iv. boiling points: Hydrocarbons < Amines < Alcohols
- v. almost soluble in water (hydrogen bonding)

Chemical properties of Amines

- amines are weak bases (like ammonia)
- react with acids and form water soluble salts)



- some amines present in our blood and make it approximately basic ($\text{pH} = 7.4$)

Cont'd...

- aliphatic amines are weak bases in comparison with inorganic bases such as NaOH, however, they are strong bases among organic compounds
- aliphatic amines are stronger bases than aromatic amines (slightly stronger than NH₃)

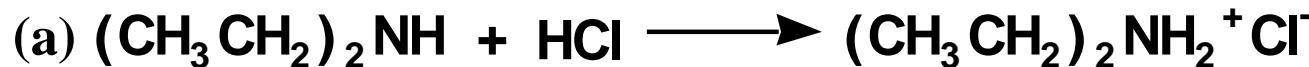
Class	pK _b	Example	Name	
Aliphatic	3.0 - 4.0	CH ₃ CH ₂ NH ₂	Ethanamine	Stronger base
Ammonia	4.74			
Aromatic	8.5 - 9.5	C ₆ H ₅ NH ₂	Aniline	Weak base

Cont'd...

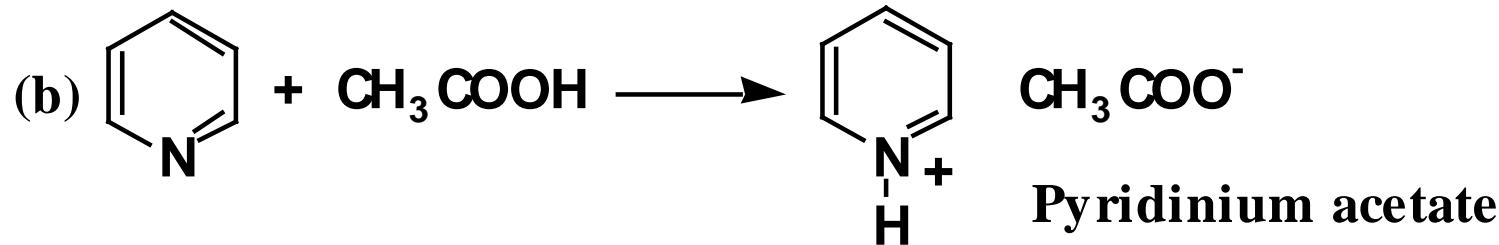
Examples:

Complete each acid-base reaction and name the salt formed.

Solutions:

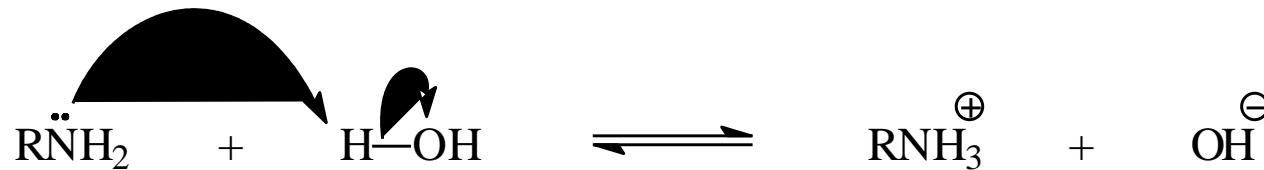


Diethylammonium
chloride



Basicity of amines

- amines are **slightly basic** because they have a **lone pair** of electrons to donate to a proton
- this same feature makes them **nucleophiles**



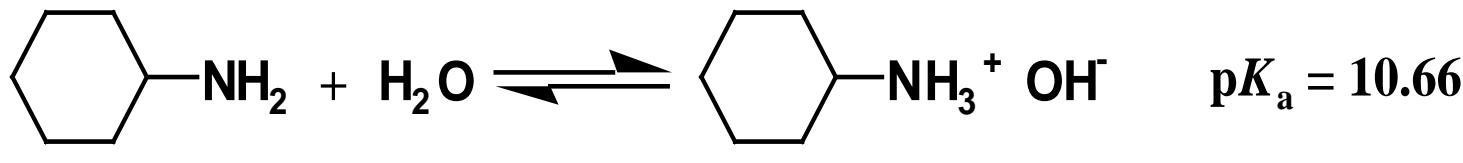
$$K_b = \frac{[\text{RNH}_3^+] [\text{OH}^-]}{[\text{RNH}_2]}$$

- typical amines have K_b values = 10^{-3} to 10^{-4}

Basicity of amines

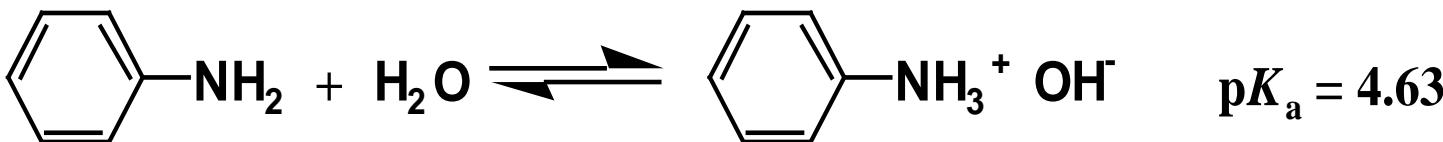
... Cont'd

- aromatic amines are considerably weaker bases than aliphatic amines



Cyclohexylamine

Cyclohexylammonium hydroxide



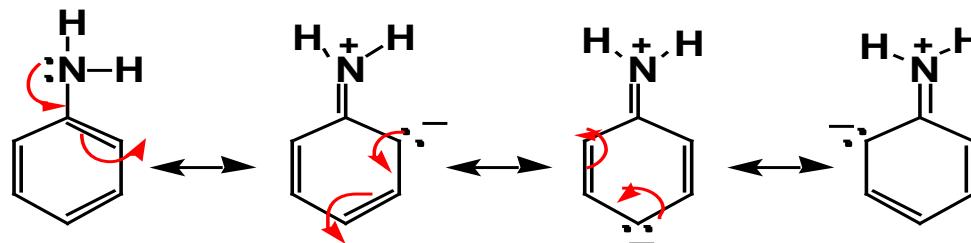
Aniline

Anilinium hydroxide

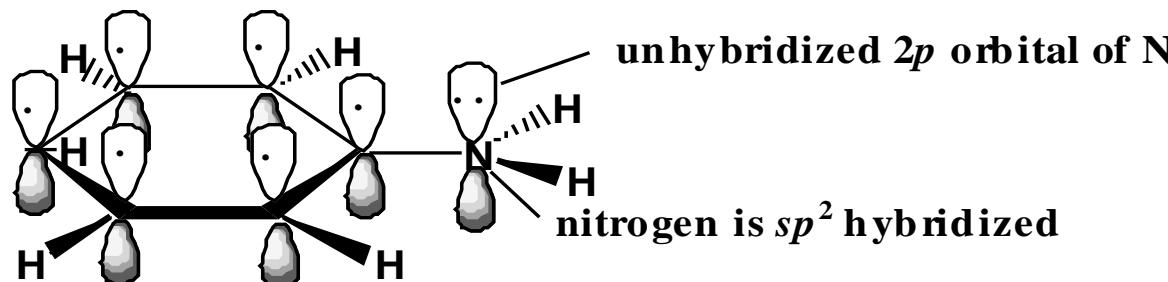
Basicity of amines

... Cont'd

- aromatic amines are weaker bases than aliphatic amines because of two factors:
 - ✓ resonance stabilization of the free base, which is lost on protonation



- ✓ the greater electron-withdrawing inductive effect of the ***sp*²-hybridized** carbon of an **aromatic amine** compared with that of the ***sp*³-hybridized** carbon of an **aliphatic amine**



Basicity of amines

... Cont'd

And the effect of substituents

- ❖ **Electron-Donating groups (EDG), such as alkyl groups, increase the basicity of aromatic amines**

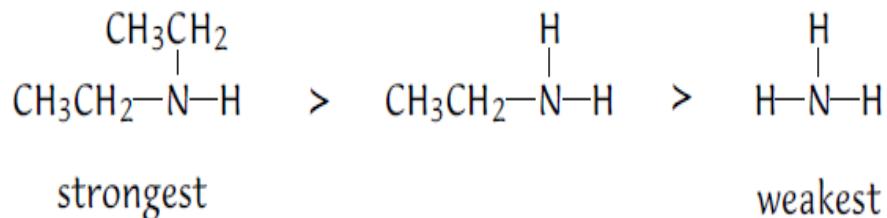
- ❖ **Electron-withdrawing groups (EWG), such as halogens, the nitro group, and a carbonyl group decrease the basicity of aromatic amines by a combination of resonance and inductive effects**

Basicity of amines

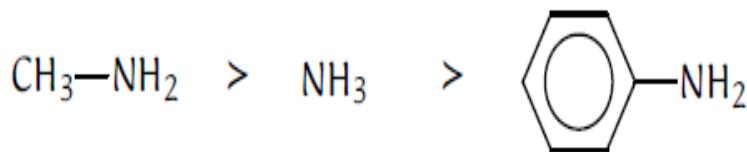
... Cont'd

Example:

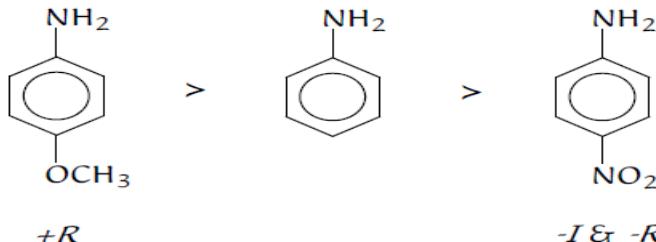
- The **+I** (Inductive) effect competes with **steric effects** in alkyl-amines



- The **+I** effect makes a **stronger base**; **-R** (resonance) effect makes a **weaker base**



- +R** & **-R** effects of aromatic ring substituent cause basicity to vary in aryl amines



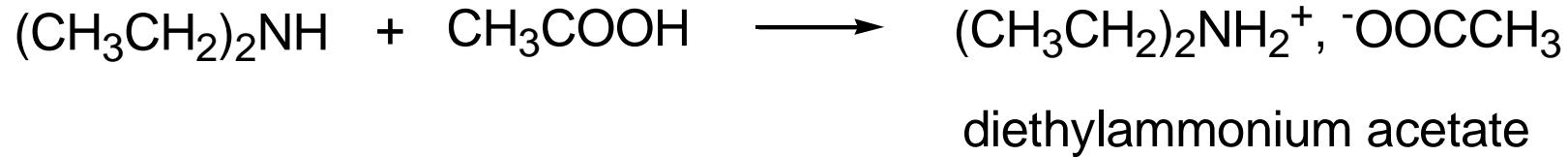
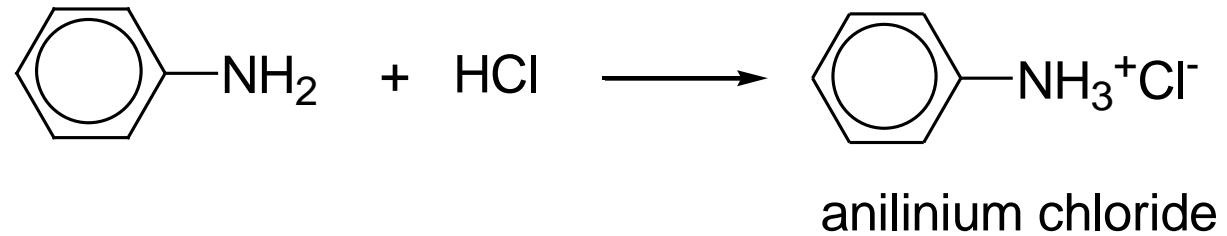
Reactions of Amine

- amines are **similar with ammonia** in their reactions
- like ammonia, amines are **nucleophilic** and **react with alkyl halides, acid chlorides, and carbonyl compounds**
- the **aromatic amines** are **highly reactive** in **electrophilic aromatic substitution(EAS)**

Amine reactions:

- i. As bases (with acids)
- ii. Alkylation
- iii. Reductive amination
- iv. Conversion into amides
- v. EAS
- vi. Hofmann elimination from quaternary ammonium salts
- vii. Reactions with nitrous acid

i. As Bases



Common substituent groups:

-NH₂, -NHR, -NR₂

-OH

-OR

-NHCOCH₃

-C₆H₅

-R

-H

-X

-CHO, -COR

-SO₃H

-COOH, -COOR

-CN

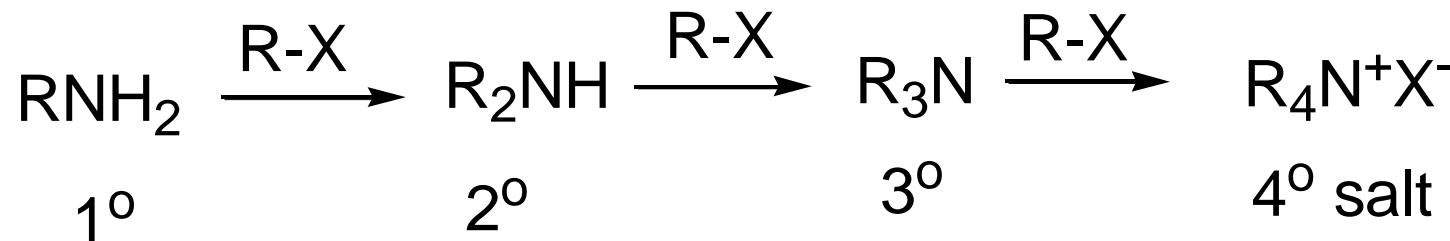
-NR₃⁺

-NO₂

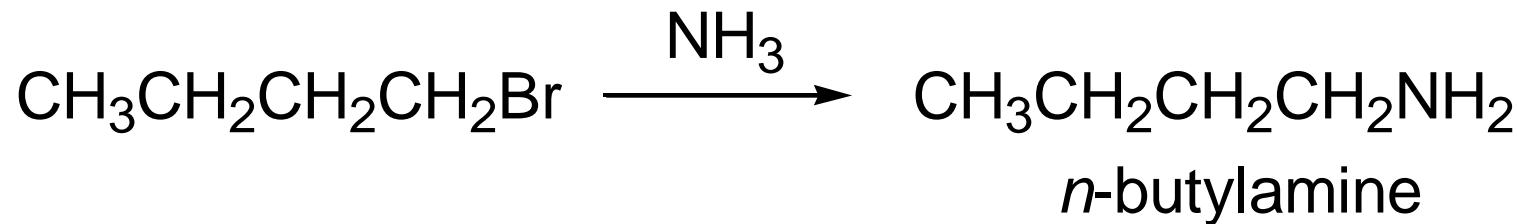
} **electron donating
groups (EDG)**

} **electron withdrawing
groups (EWG)**

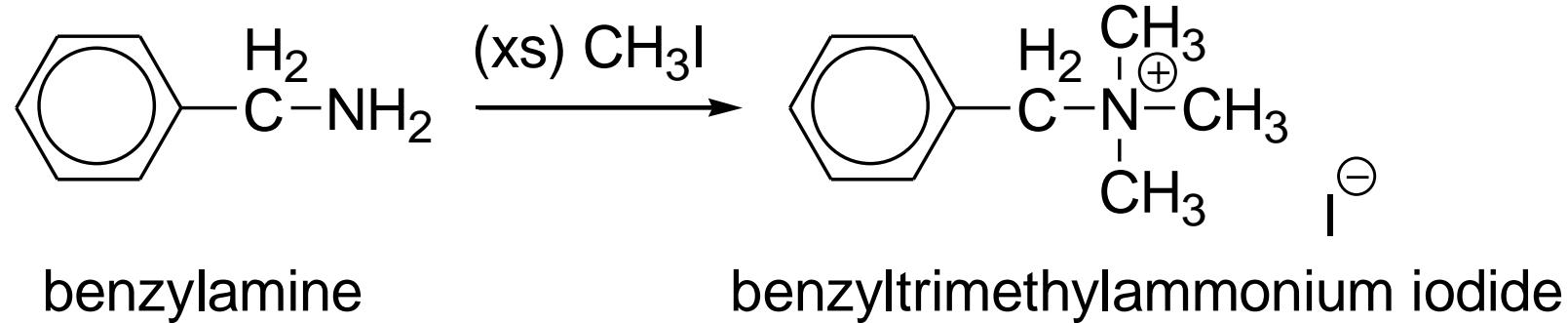
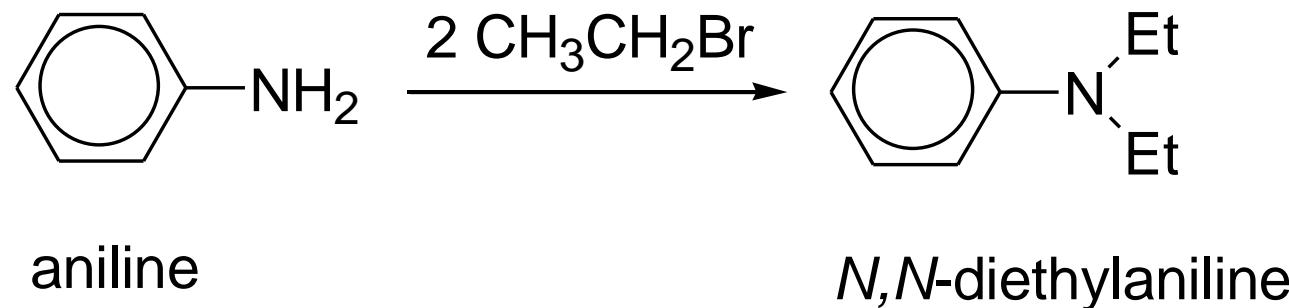
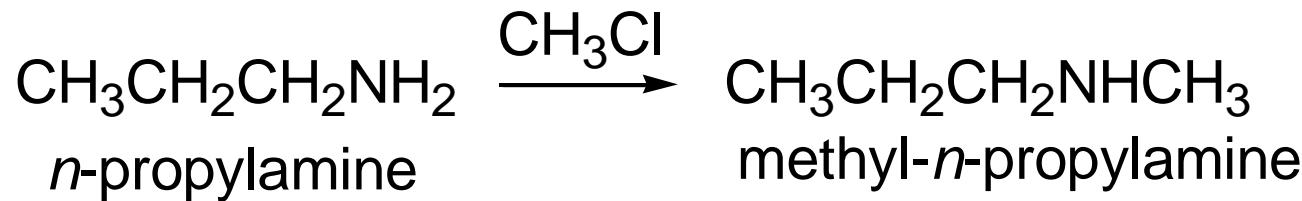
ii. Alkylation (ammonolysis of alkyl halides)



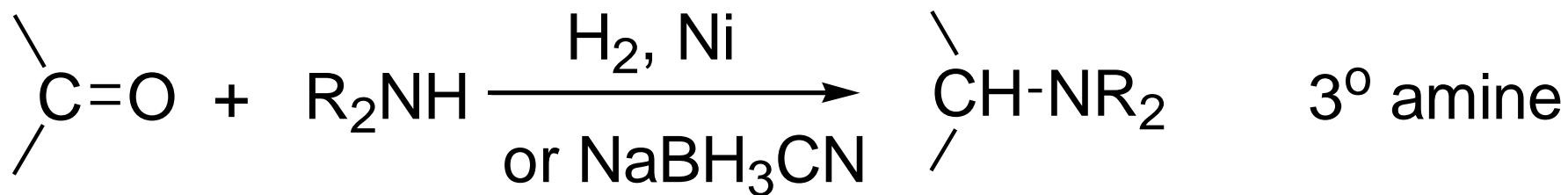
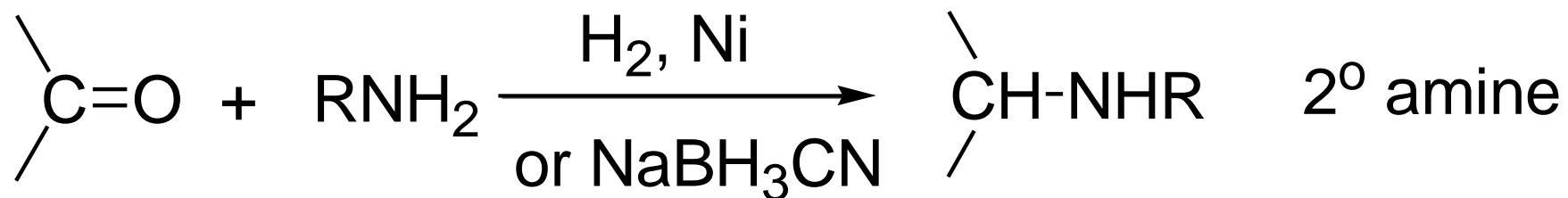
S_N2: R-X must be 1° or CH₃



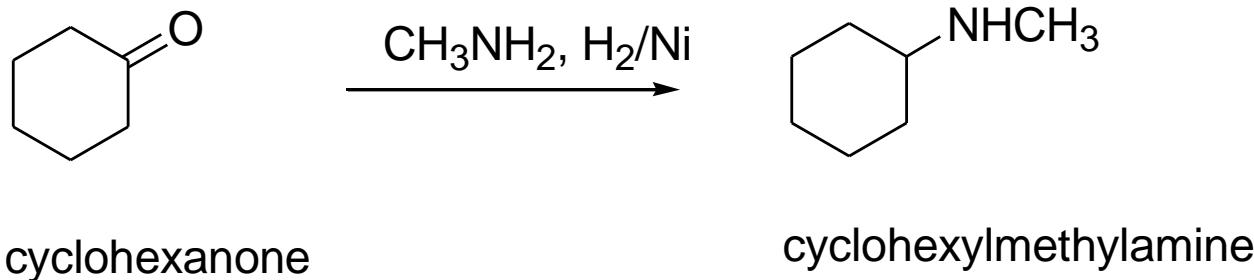
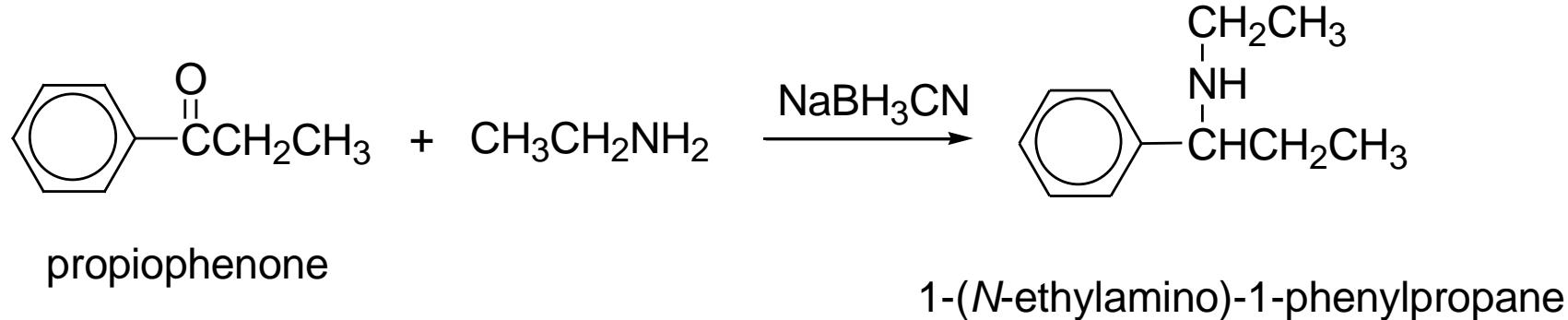
Examples



iii. Reductive amination



Examples



iv. Conversion into amides



1° N -subst. amide

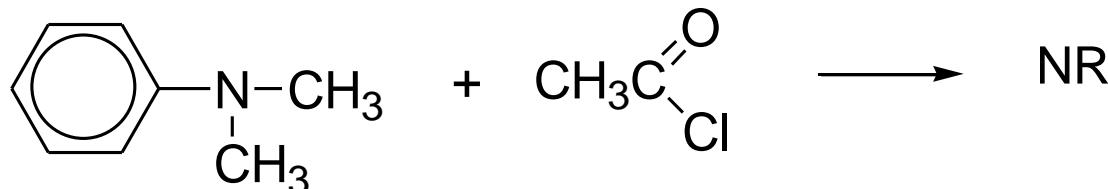
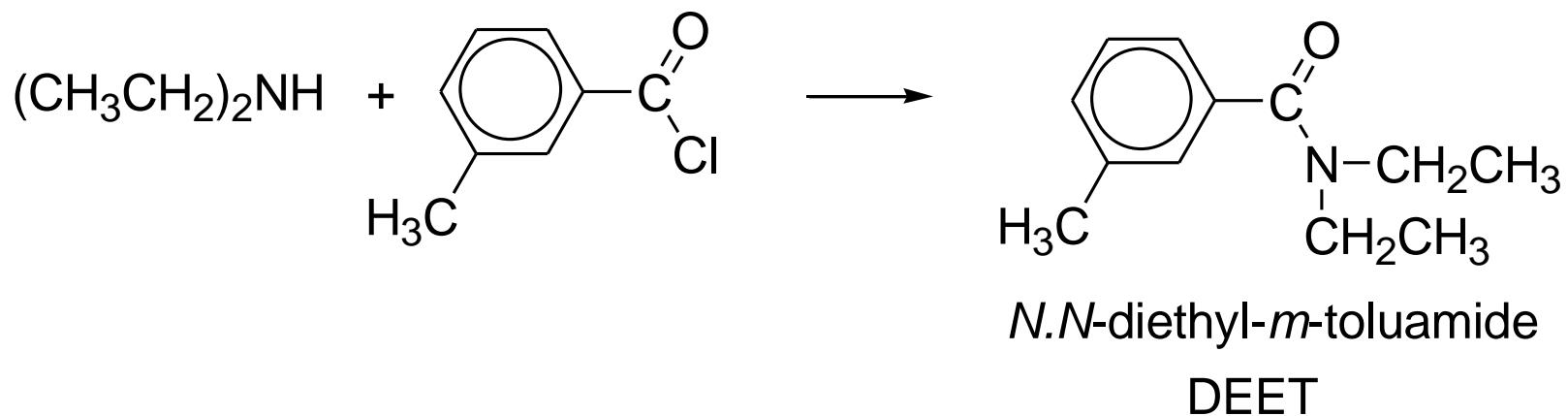
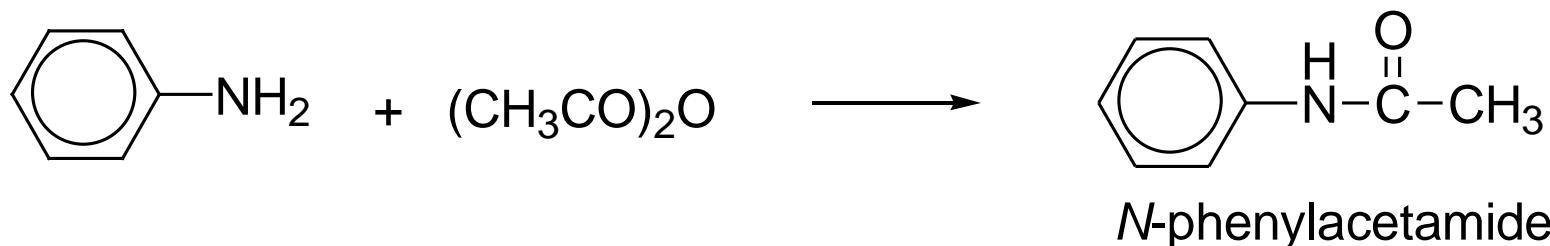


2° N,N -disubstituted amide



3°

Examples



❖ Conversion into sulfonamides



1°

N-substituted sulfonamide



2°

N,N-substituted

sulfonamide

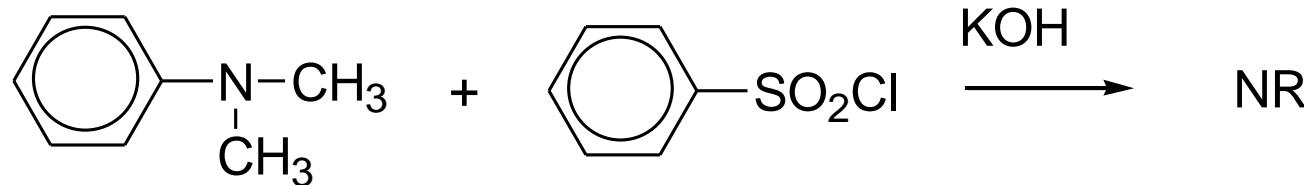
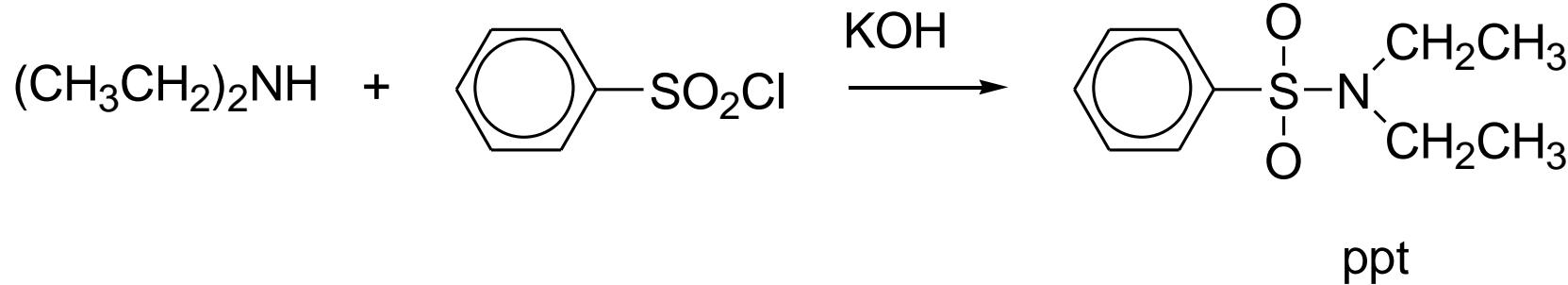
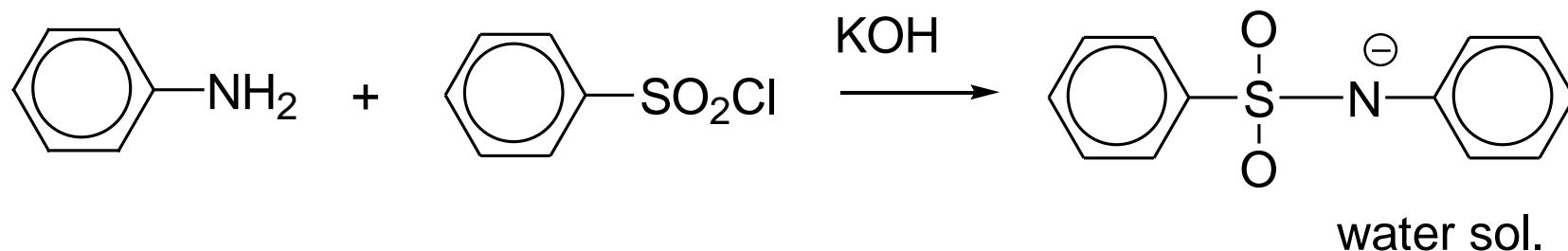


Hinsberg Test

unknown amine + benzene sulfonyl chloride, KOH (aq)

- ✓ reacts to produce a clear solution and then gives a ppt upon acidification → **primary amine**
- ✓ reacts to produce a ppt → **secondary amine**
- ✓ doesn't react → **tertiary amine**

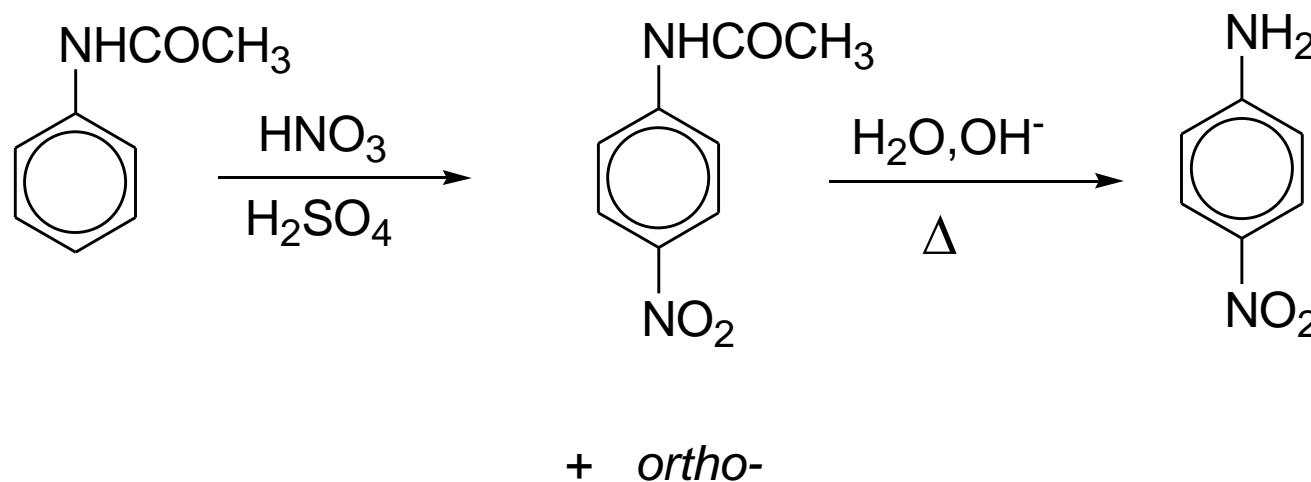
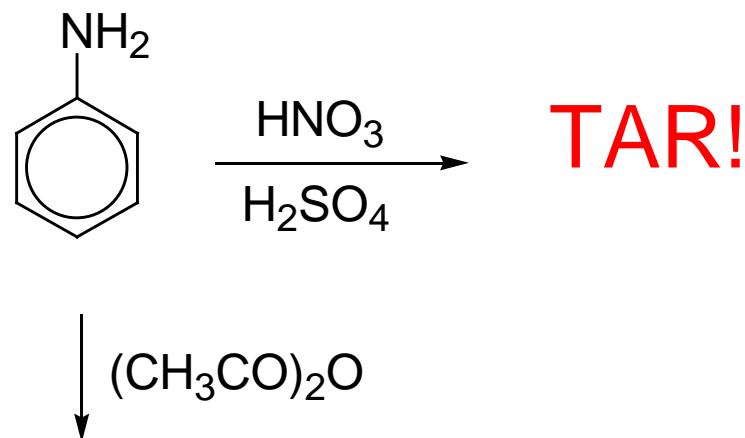
Examples



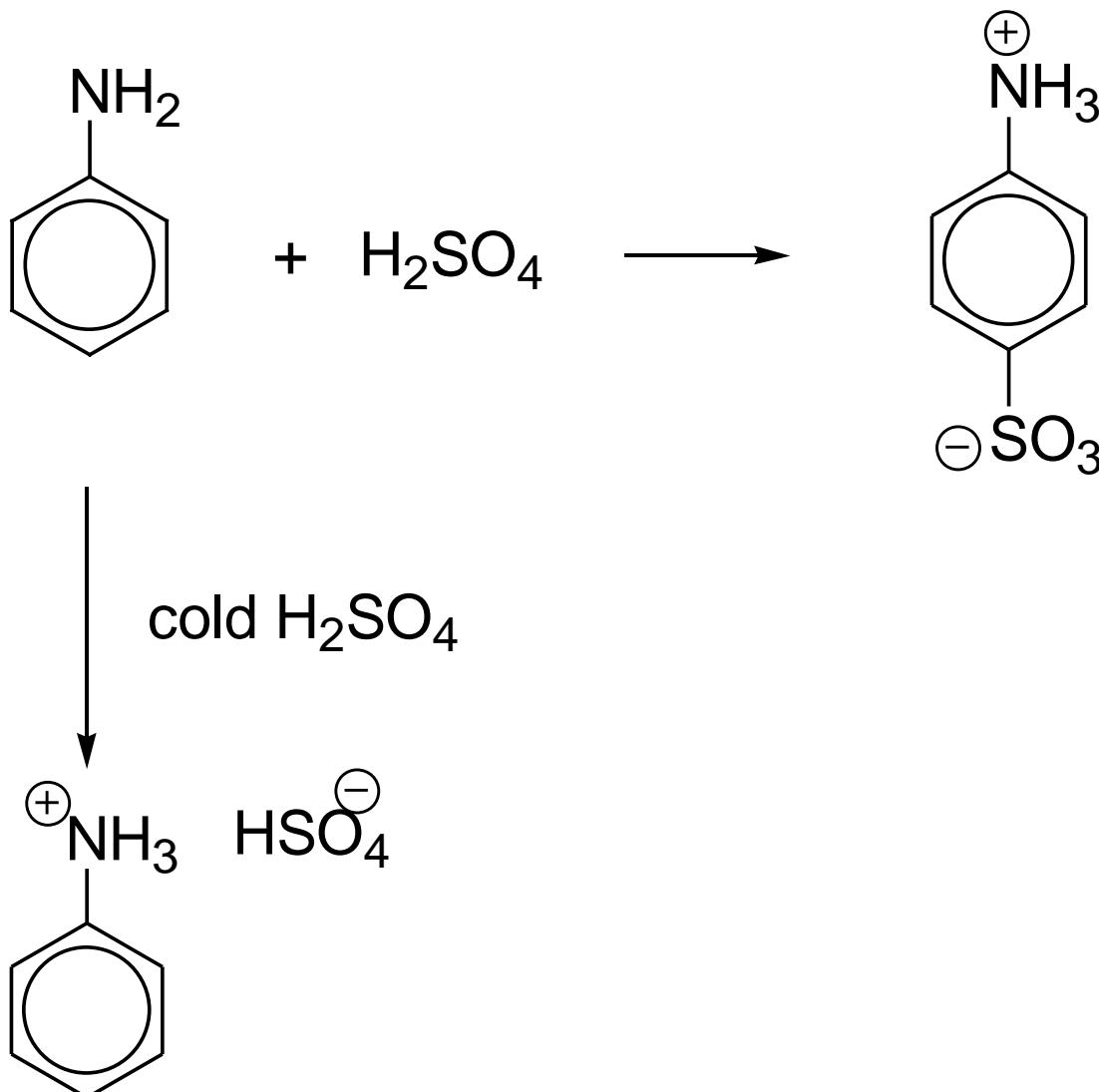
v. Electrophilic Aromatic Substitution

- ❖ -NH₂, -NHR, -NR₂ are powerful activating groups and *ortho/para* directors
 - a) nitration
 - b) sulfonation
 - c) halogenation
 - d) Friedel-Crafts alkylation
 - e) Friedel-Crafts acylation
 - f) coupling with diazonium salts
 - g) nitrosation

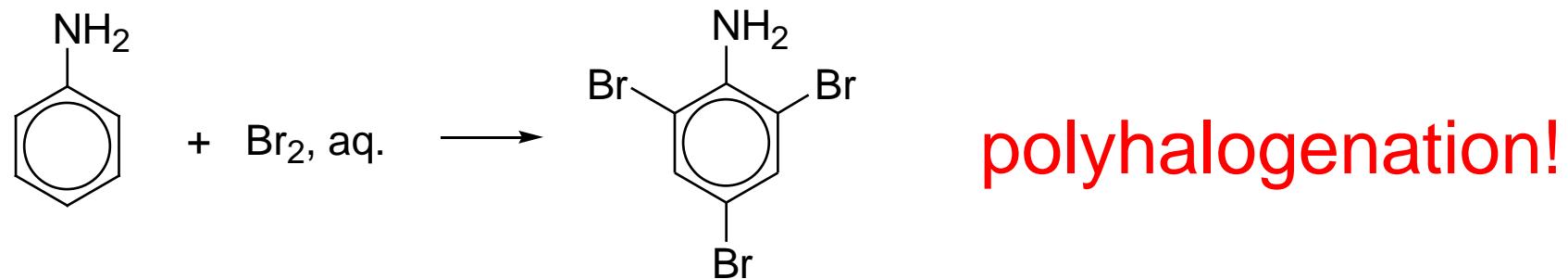
a) Nitration



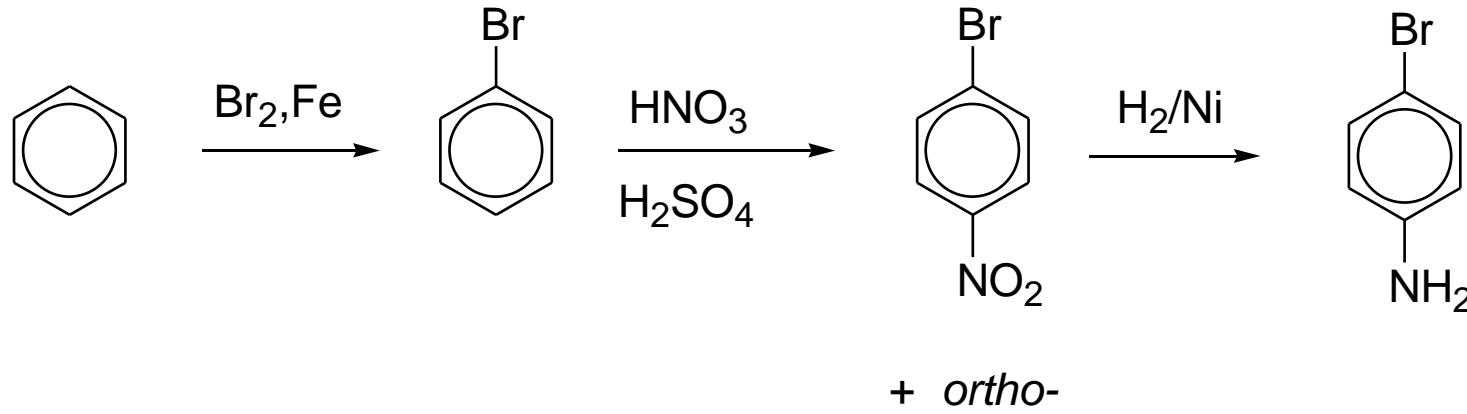
b) Sulfonation



c) Halogenation

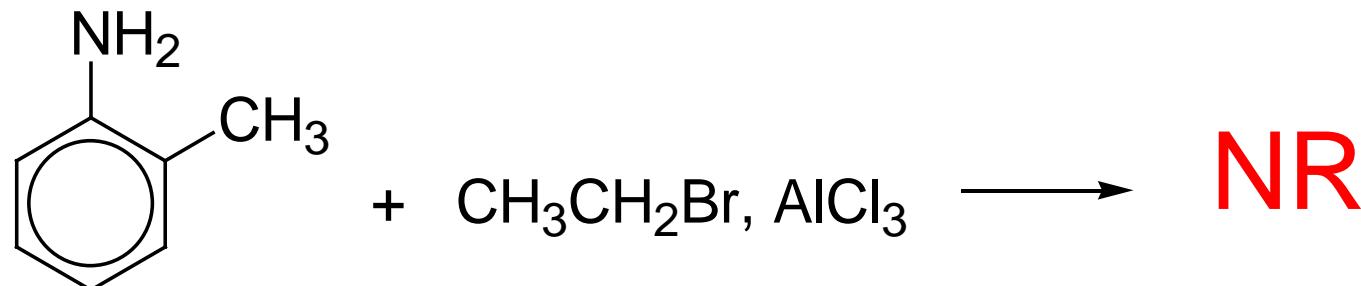


no catalyst needed
use polar solvent

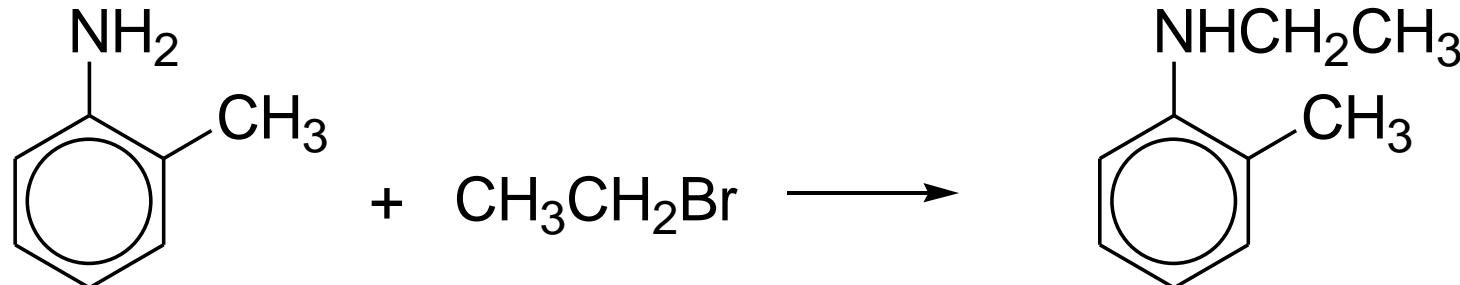


e) Friedel-Crafts Alkylation

NR with $-\text{NH}_2$, $-\text{NHR}$, $-\text{NR}_2$

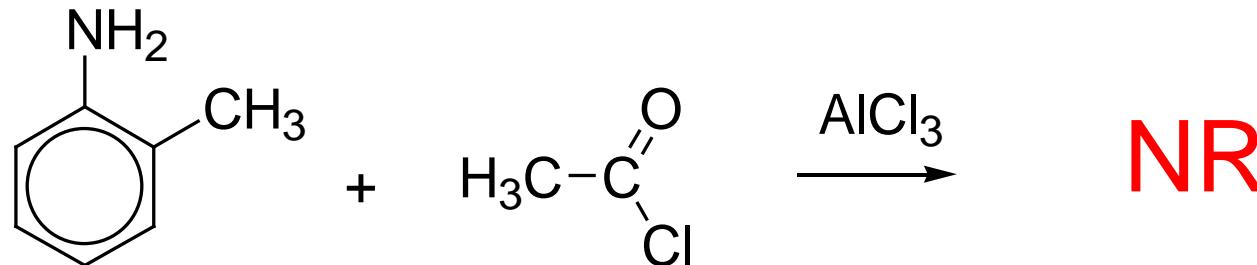


Do not confuse the above with the alkylation reaction:

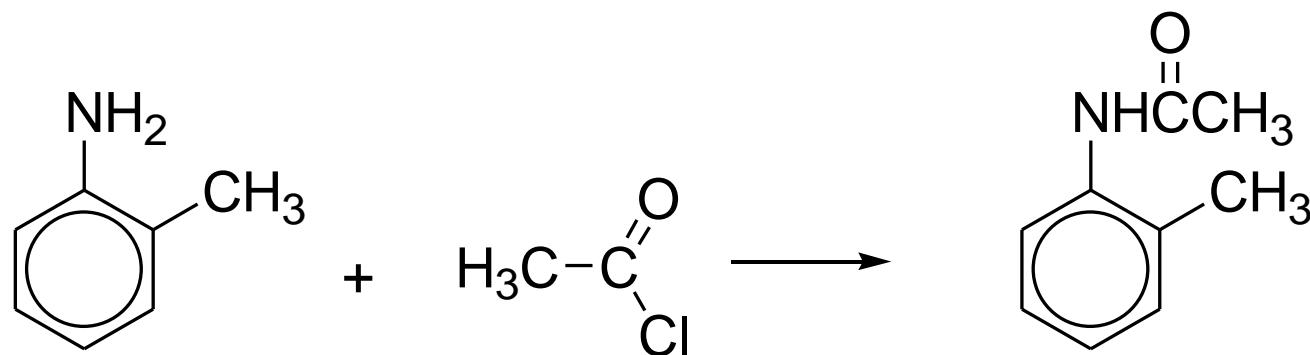


f) Friedel-Crafts Acylation

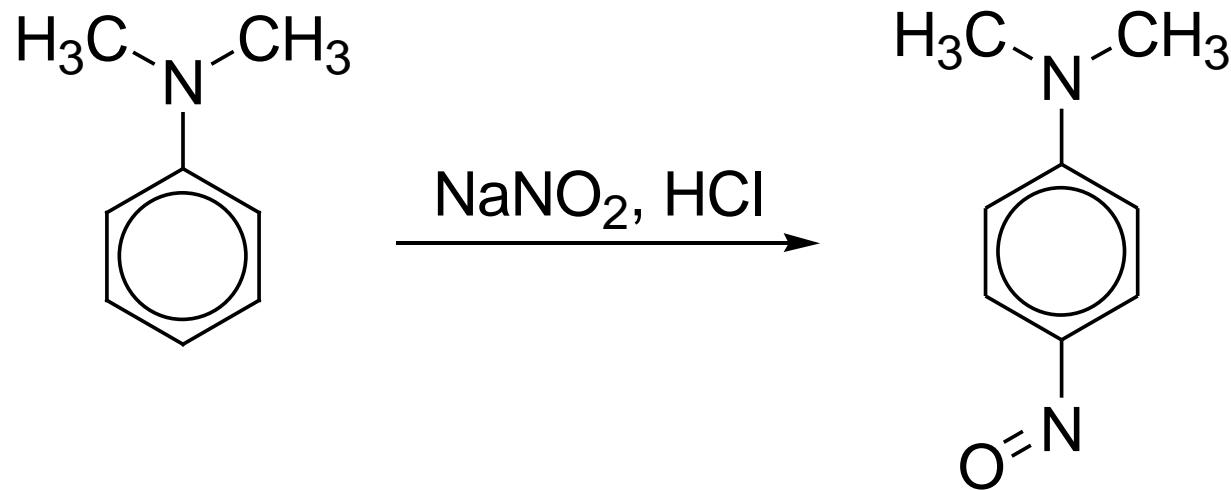
NR with $-\text{NH}_2$, $-\text{NHR}$, $-\text{NR}_2$



Do not confuse the above with the formation of amides:



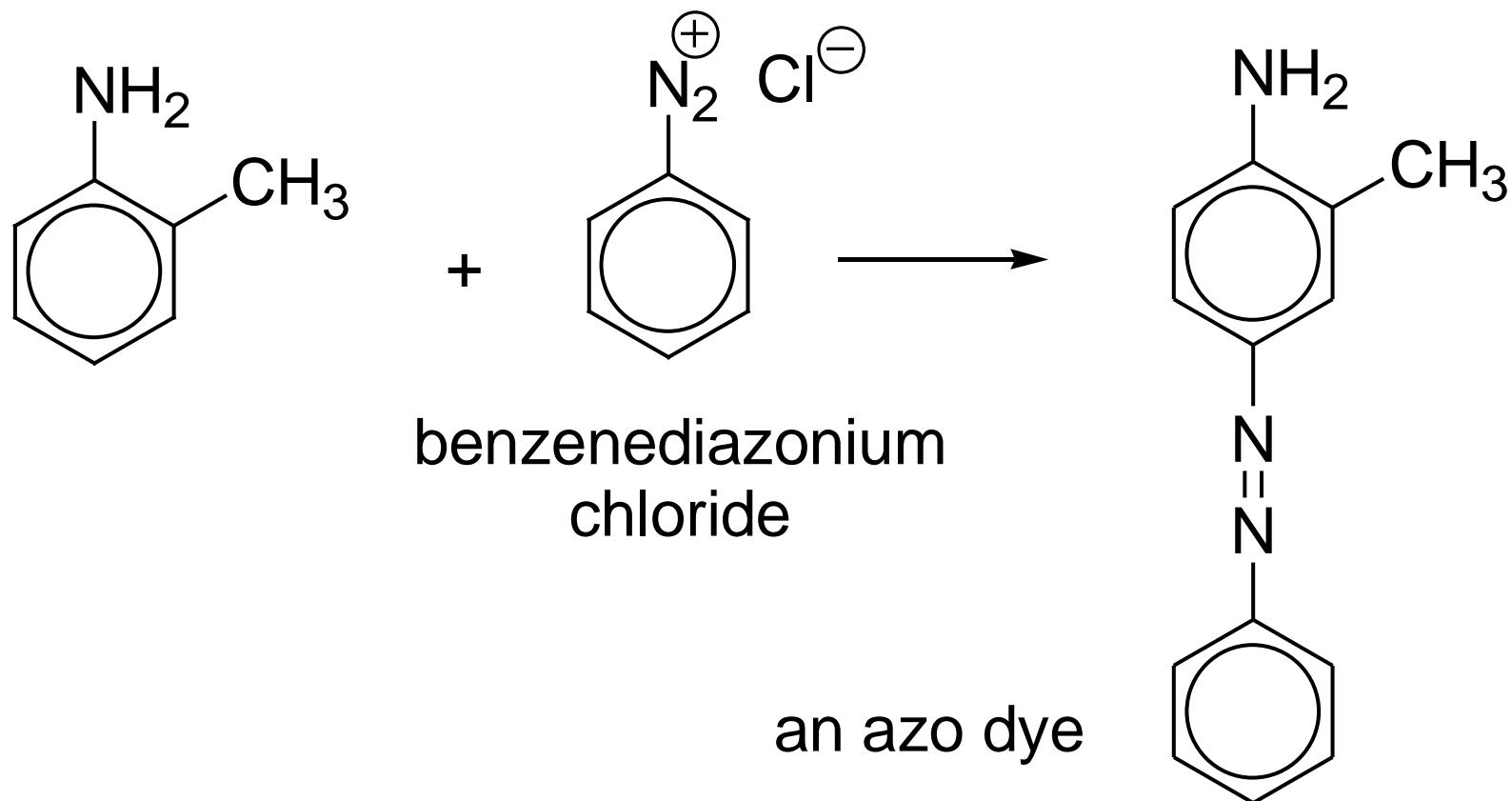
g) Nitrosation



The ring is sufficiently activated towards EAS to react with the weak electrophile NO^+

h) coupling with diazonium salts → azo dyes

- ❖ reaction with aryl diazonium intermediate

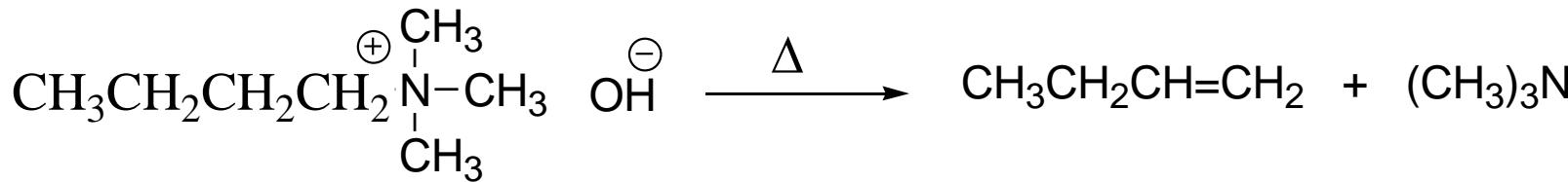
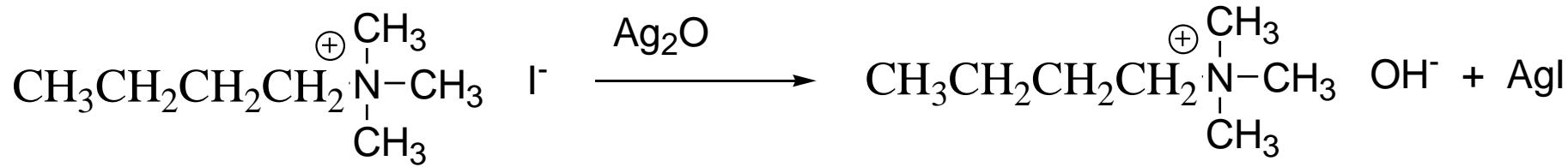
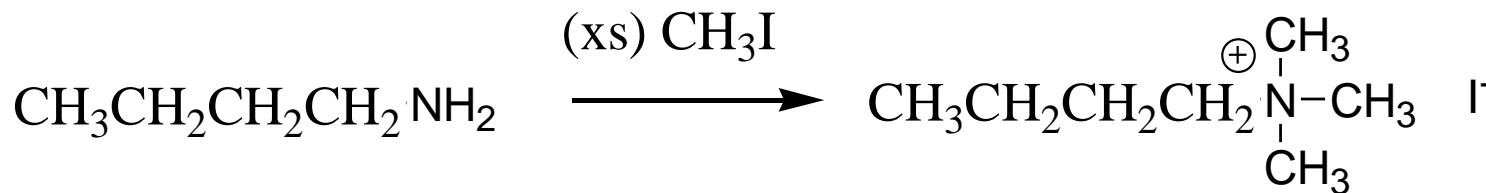


vi. Hofmann elimination from quaternary hydroxides

Step 1. Exhaustive methylation \rightarrow 4° salt

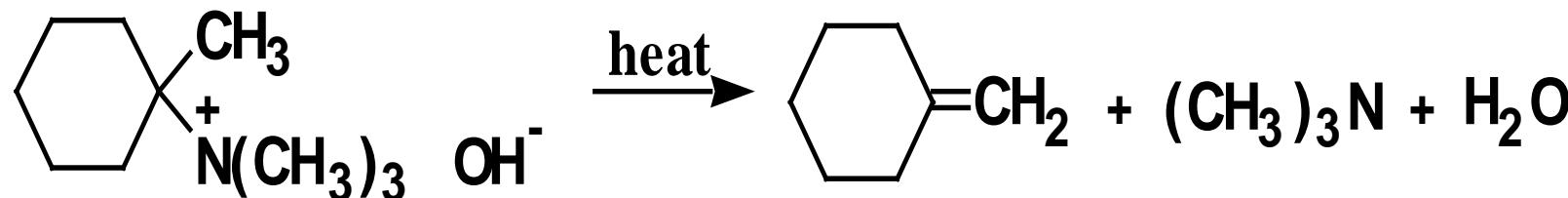
Step 2. Reaction with Ag_2O \rightarrow 4° hydroxide + AgX

Step 3. Heat to eliminate \rightarrow alkene(s) + R_3N



Cont'd...

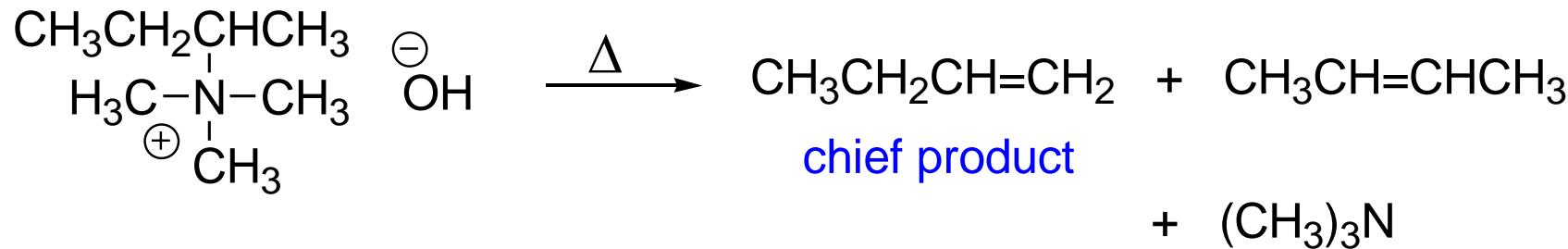
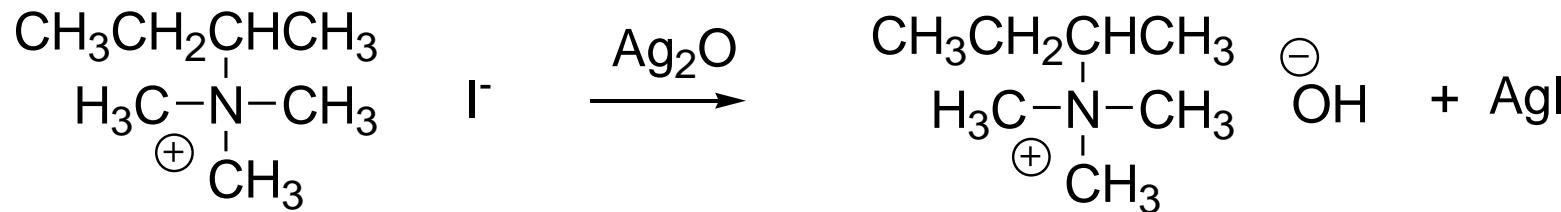
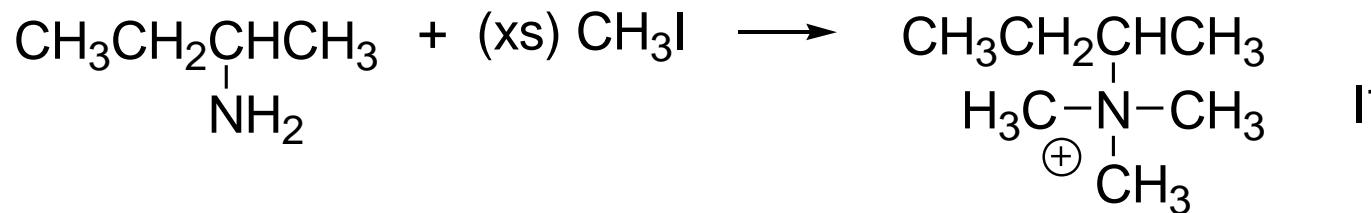
- **Hofmann elimination** is regioselective - the major product is the least substituted alkene



Hofmann's rule

- ❖ any β -elimination that occurs preferentially to give the **least substituted alkene** as the **major product** is said to follow **Hofmann's rule**

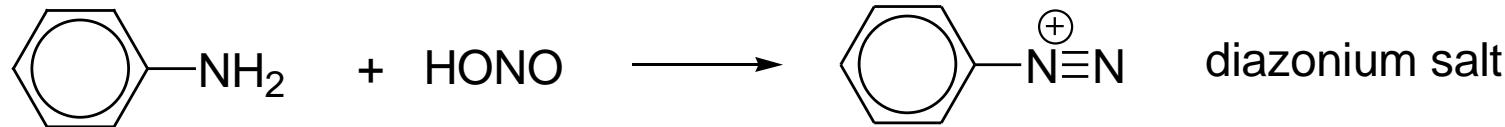
Examples



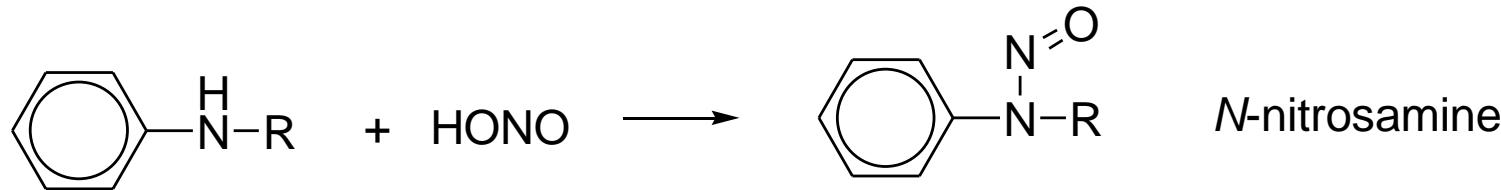
Hofmann orientation

Reactions with nitrous acid

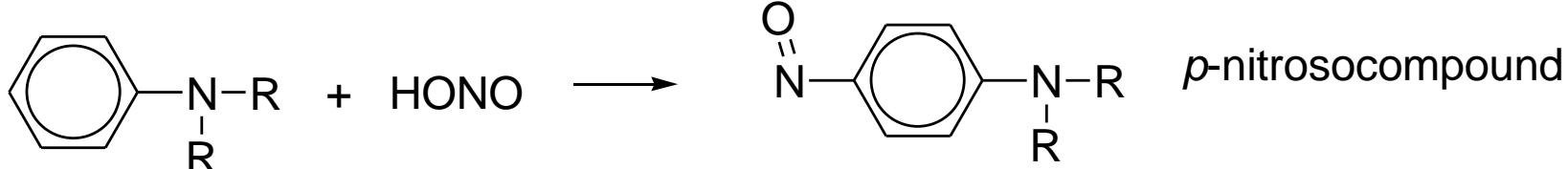
primary amines



secondary amines

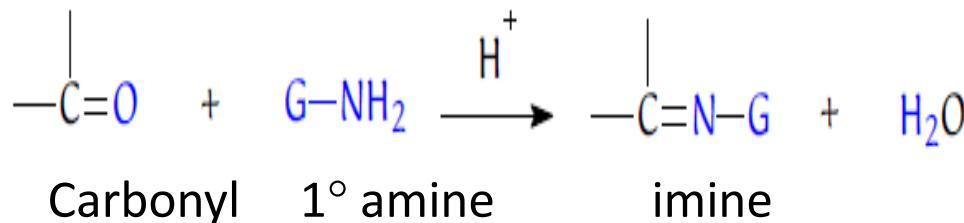


tertiary amines

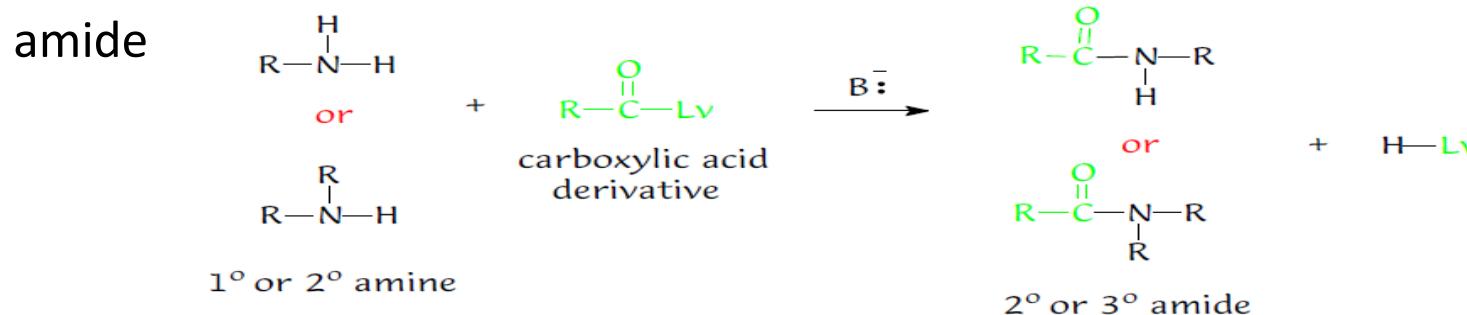


Reaction with Carbonyls

- nucleophilic addition of a primary amine to a carbonyl compound to produce an imine



- A primary or secondary amine is acylated by a carboxylic acid derivative (ammonolysis reaction) to produce the corresponding secondary or tertiary amide

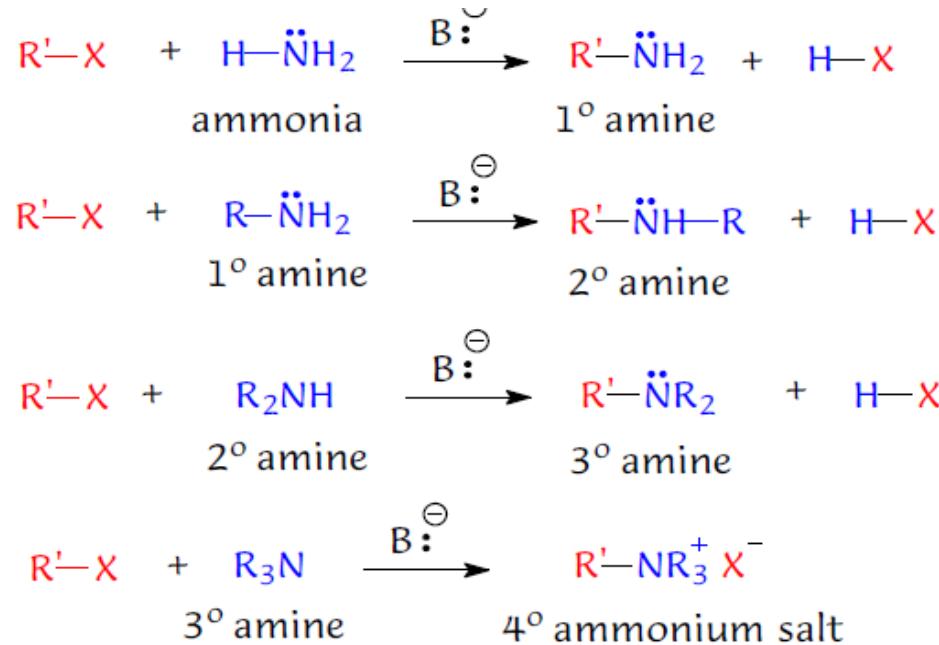


- $\text{B} = \text{OH}^-$, OAc^- , CO_3^{2-} (Neutralizes HLv)
- $\text{Lv} = -\text{Cl}$, $-\text{OCOR}$, $-\text{OR}$

Preparation of 1°-, 2° & 3°-Amines

A. Alkylation of ammonia and amine

- Ammonia or an amine is treated with an alkyl halide; substituting an R group on the nitrogen

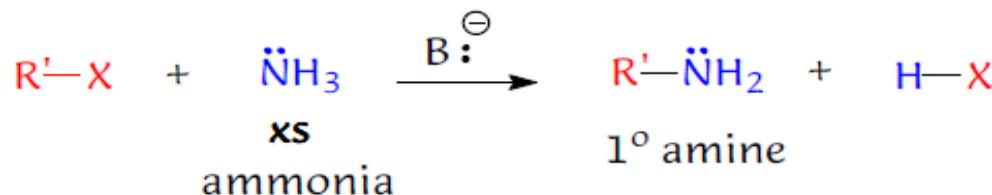


- R, R' can be alkyl or aryl

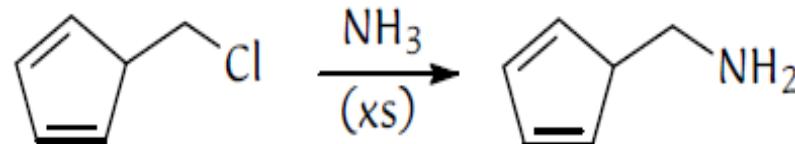
Preparation of amines

...Cont'd

❖ Excess ammonia produces a primary amine in good yield:

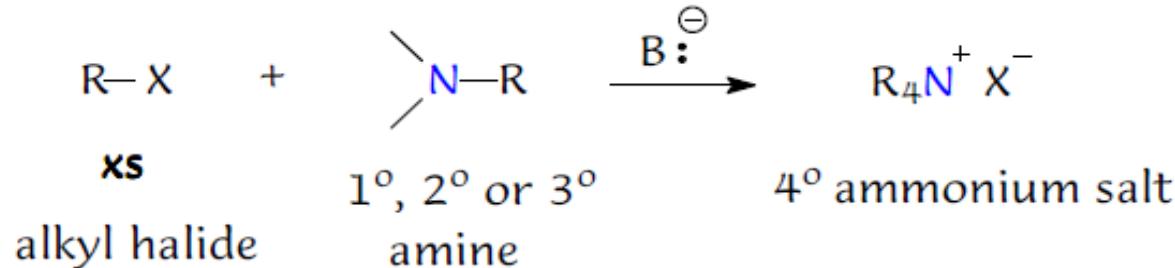


Example:



❖ excess alkyl halide produces a 4° ammonium salt in good yield

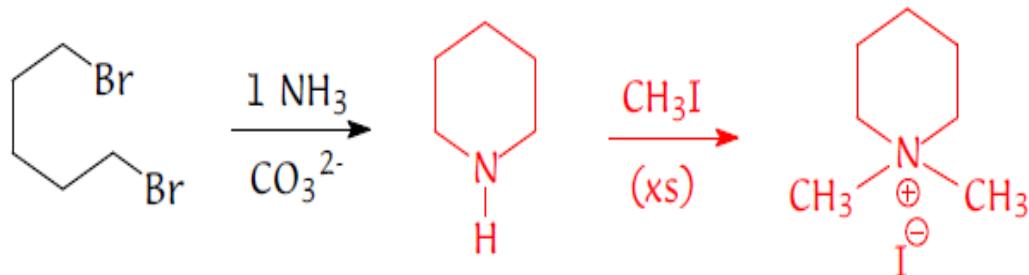
- known as **exhaustive alkylation**, the method often employs excess **methyl halide** (exhaustive methylation)



Preparation of amines

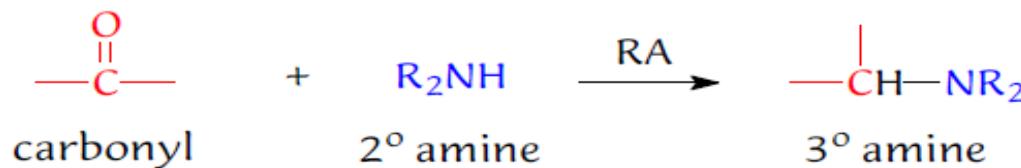
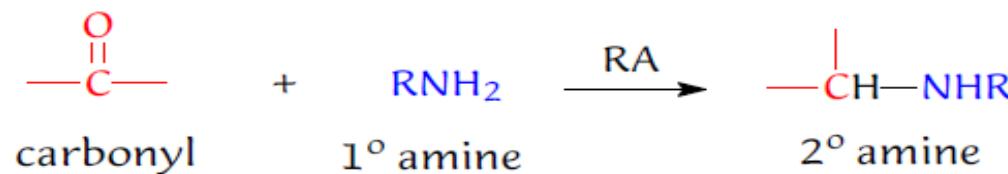
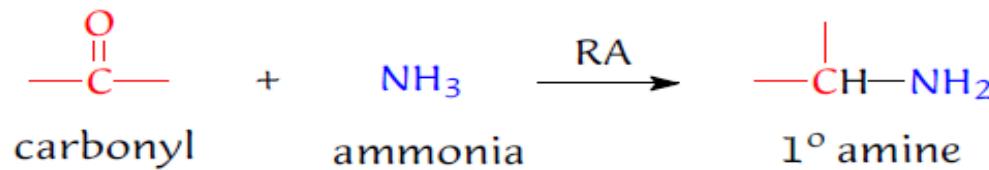
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Example:



B. Reductive Amination

- reduction of the carbon-nitrogen double bond produces an amine with the same substitution level as provided by alkylation



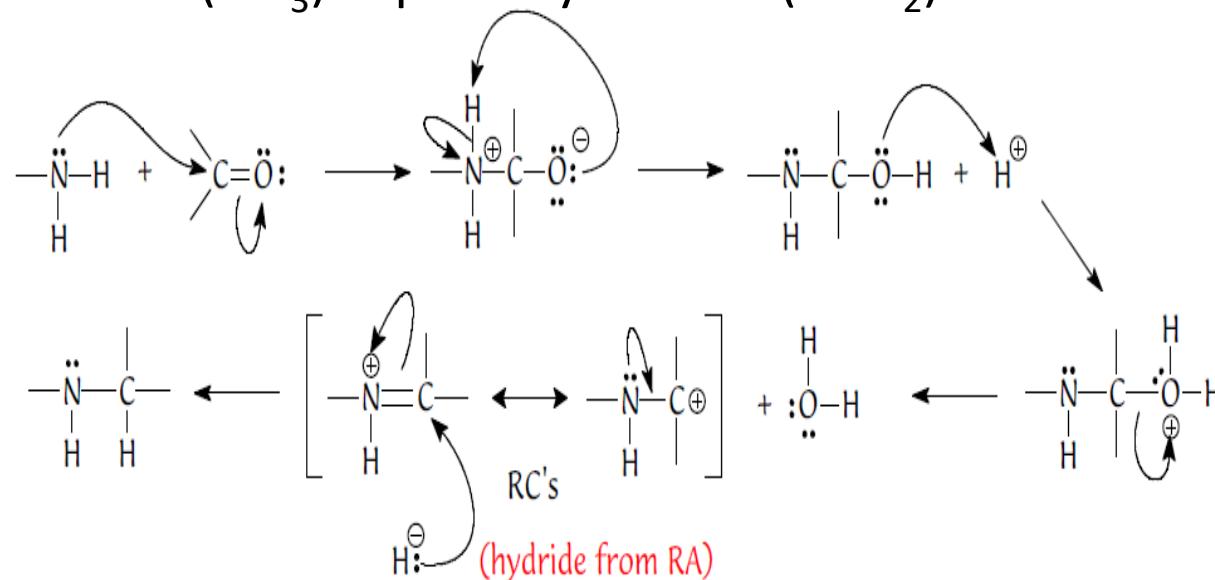
Preparation of amines

...Cont'd

- R = Ar, also $\text{NH}_3 = \text{NH}_2\text{OH}$, also
- RA = H_2/Ni ; H_2/Pd ; (Catalytic)
- = NaBH_3CN , $\text{NaB(OAc)}_3\text{H}$, (Hydride)

Mechanism

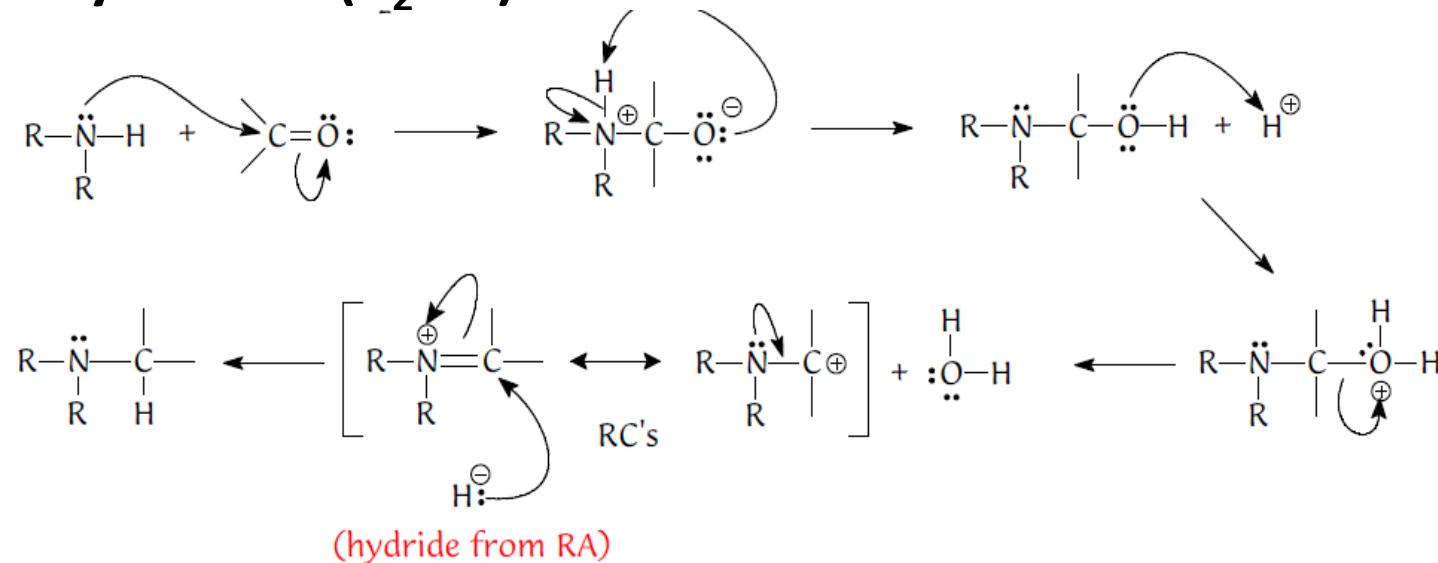
- The process varies slightly with the level of substitution on the nitrogen:
 - ❖ Ammonia (NH_3) & primary amines (RNH_2)



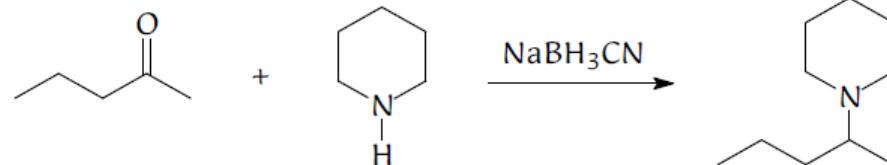
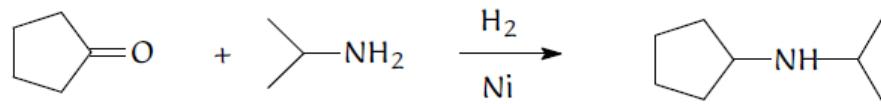
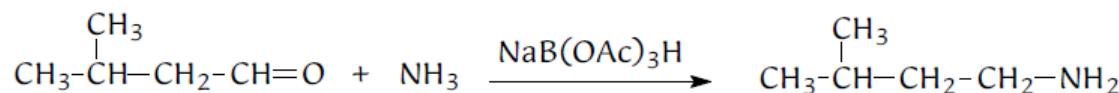
Preparation of amines

...Cont'd

❖ Secondary amines (R_2NH)

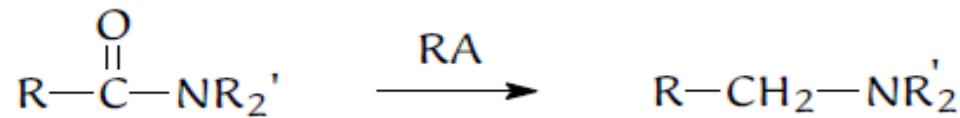


Example:



c. Reduction of Amides

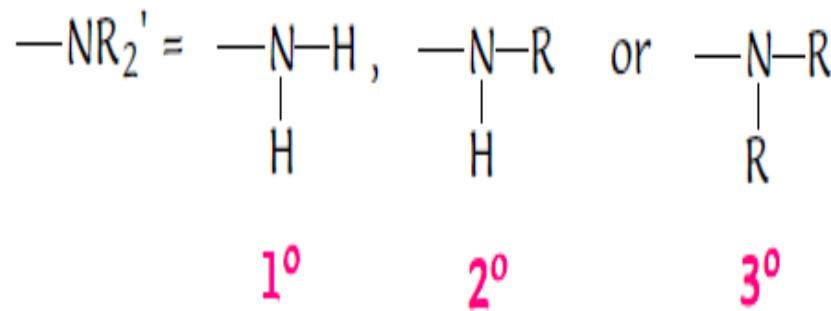
- amide can be converted to its corresponding amine by reduction:



1°, 2° or 3° amide

1°, 2° or 3° amine

RA = LiAlH₄, BH₃/LB ,...

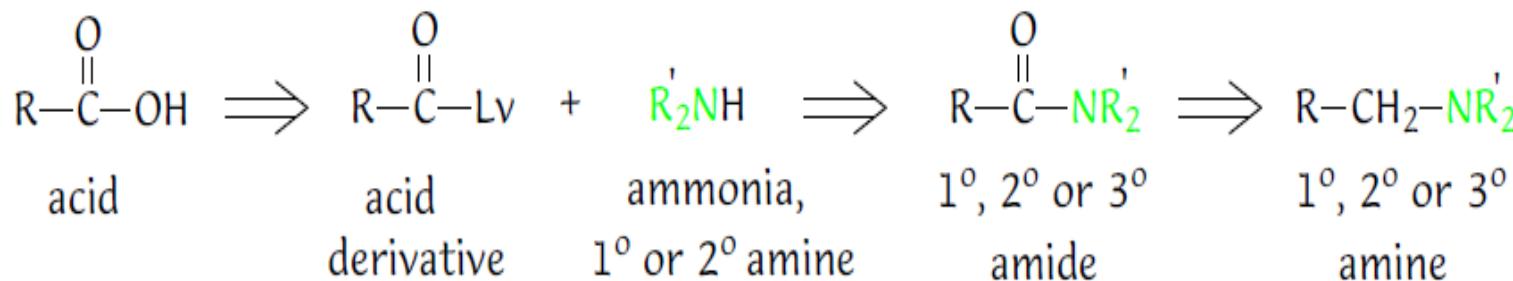


- amides, reduction provides an excellent methodology for the preparation of all classes of amines

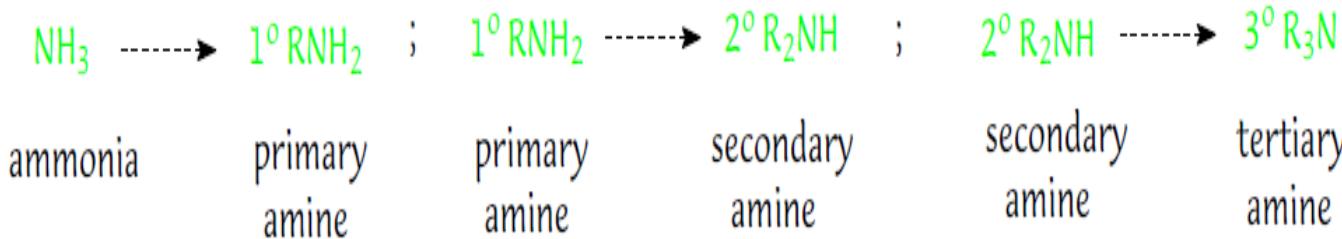
Preparation of amines

...Cont'd

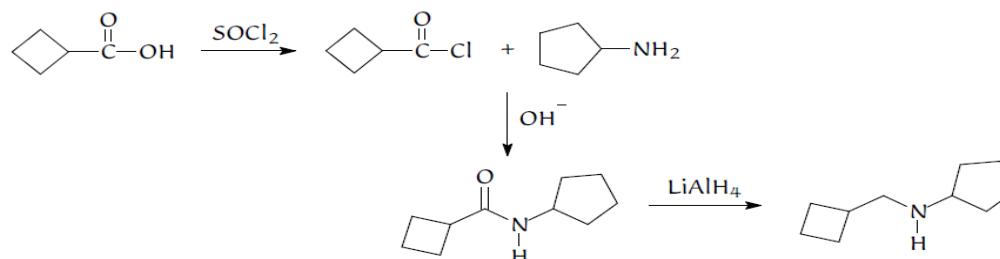
- this synthetic sequence produces an amine (as final product) which is one level of substitution above the initial reacting ammonia or amine



- Lv = Cl, OCOR or OR R' = H or Ar

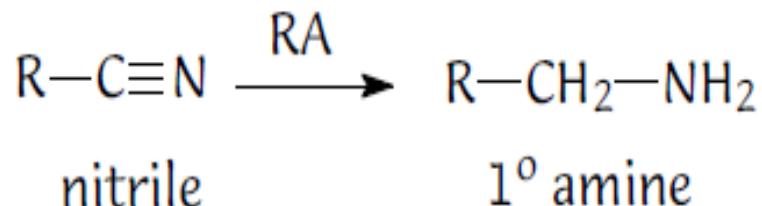


- Example



d. Reduction of Nitriles

- primary amines can be obtained from nitriles by way of reduction:



R = Ar, A = H₂/Ni ; H₂/Pd ; (Catalytic), RA= LiAlH₄,(Hydride)

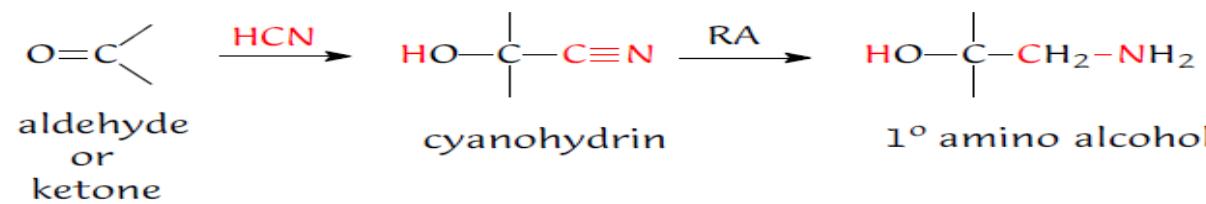
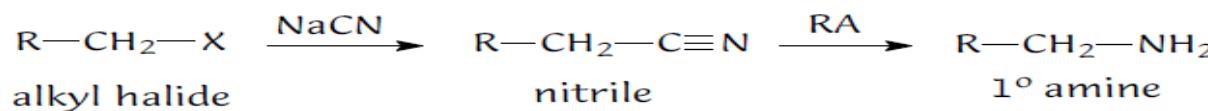
Mechanism

- analogous to carbon-carbon triple bond reduction, the transformation requires four hydrogen
- recall that nitriles can be prepared from alkyl halides or carbonyl compounds, making nitrile reduction part of a versatile synthetic sequence

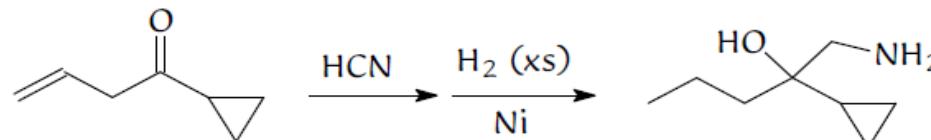
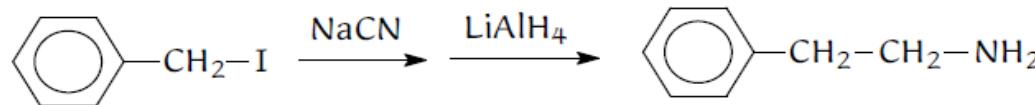
Preparation of amines

...Cont'd

- recall that nitriles can be prepared from alkyl halides or carbonyl compounds, making nitrile reduction part of a versatile synthetic sequence

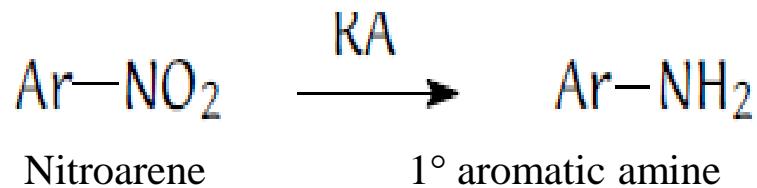


- Example



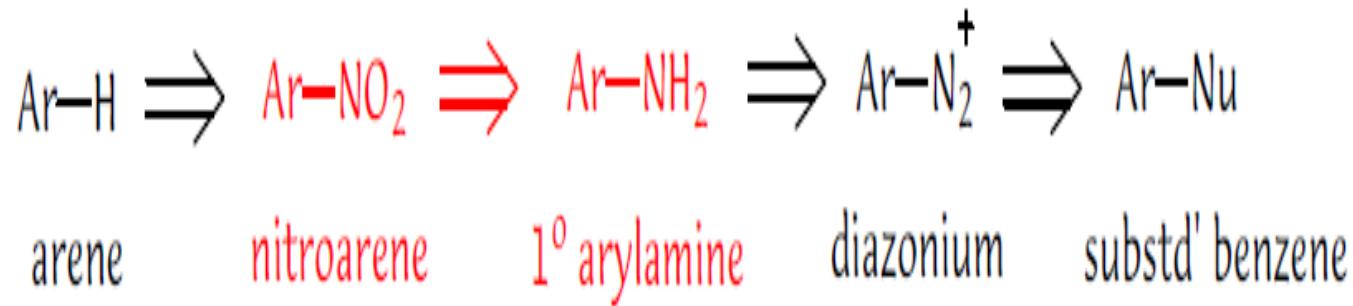
E. Reduction of aromatic nitro compounds

- this reductive method provides facile access to primary arylamines



RA = Sn/H⁺; Fe/H⁺; Zn/H⁺; ... (Reagents) RA= H₂/Ni; H₂/Pd; ... (Catalysts)

Mechanism

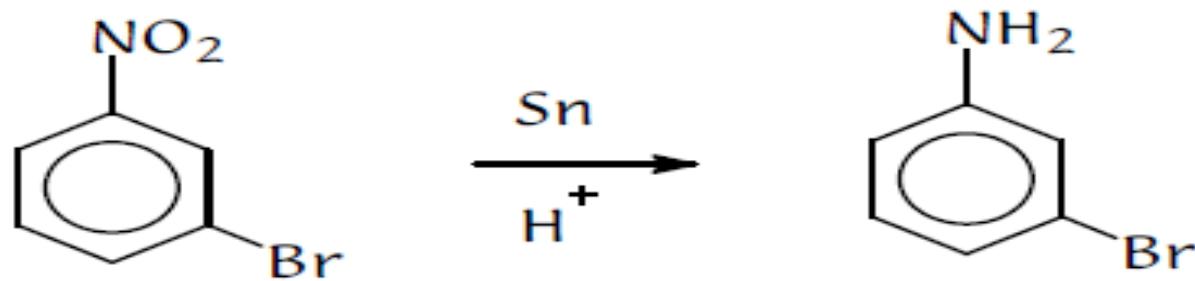


Preparation of amines

...Cont'd

- the “dissolving metal” provides the electrons & the acid provides the hydrogen for a free radical process which replaces the nitro group O's with H's

Example:

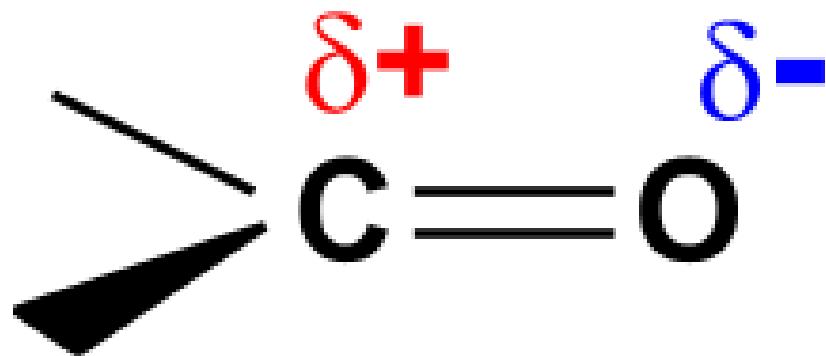


Chapter III

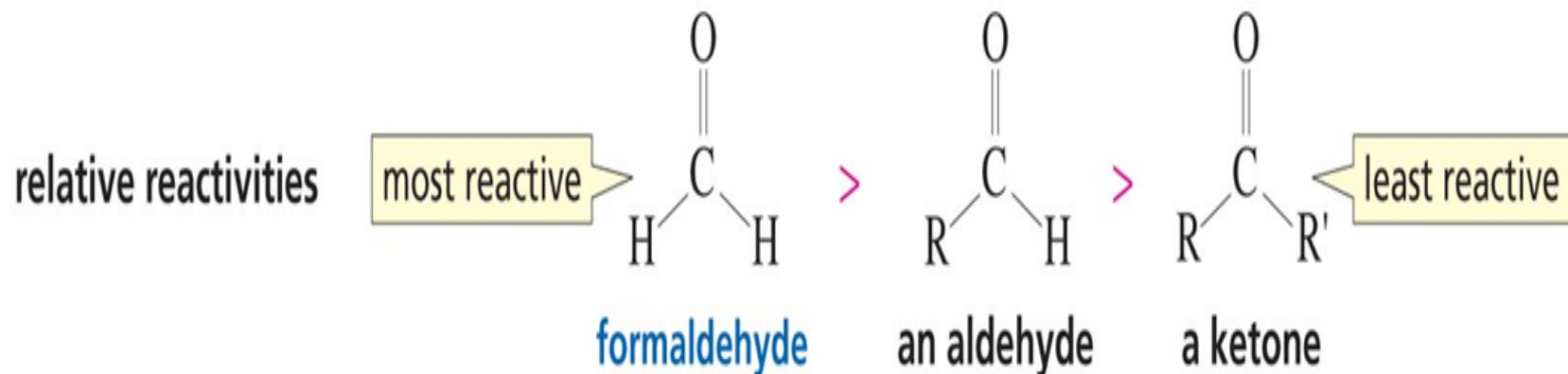
REACTION OF CARBONYL COMPOUNDS

Introduction

- organic compounds which consists of a carbon-oxygen double bond Includes
 - ✓ aldehydes
 - ✓ ketones
 - ✓ carboxylic acids
 - ✓ esters
 - ✓ amides
 - ✓ acid chlorides and etc
- the C-O bond is polar due to the difference in electro negativity

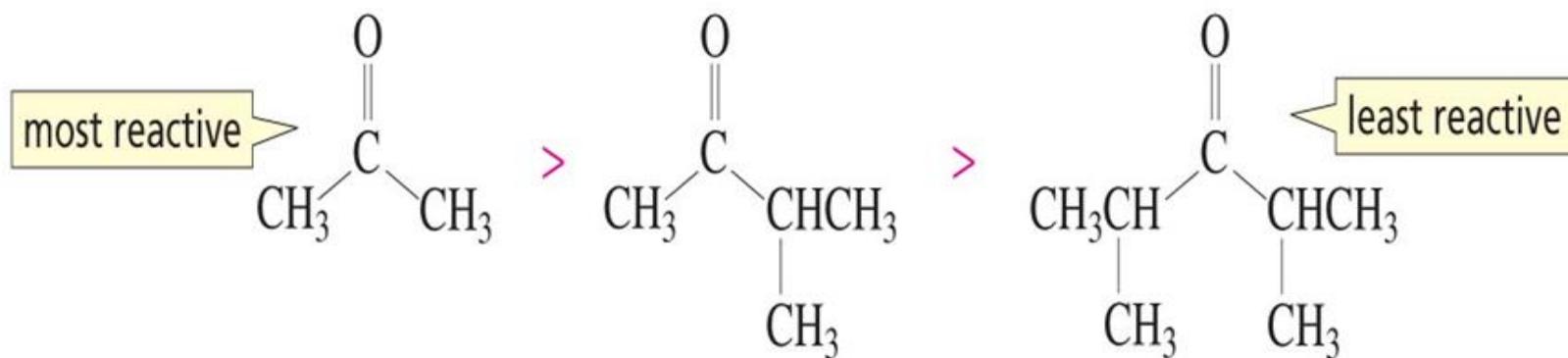


Relative reactivities of aldehydes and ketones



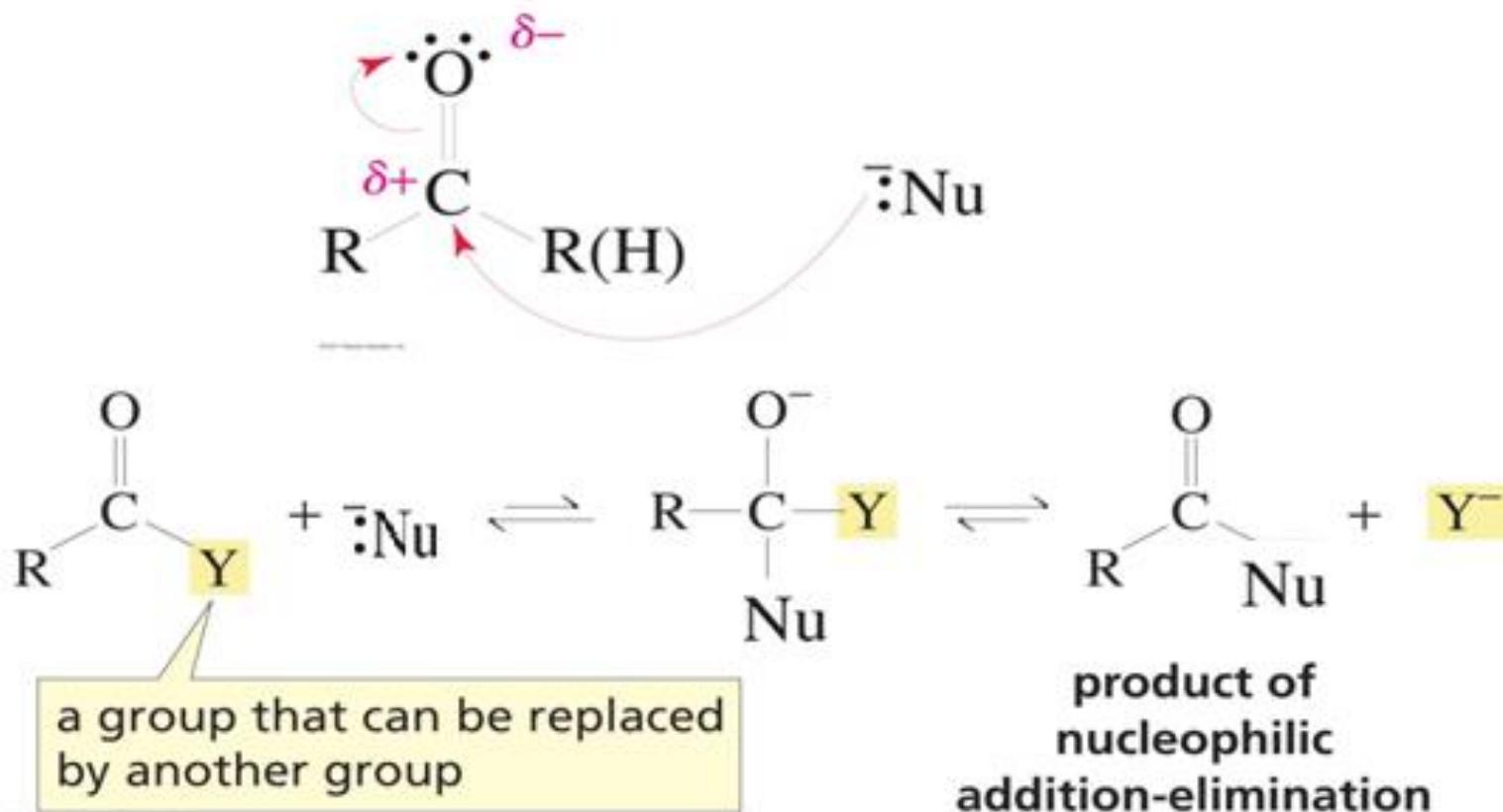
❖ aldehydes are more reactive than ketones

relative reactivities of ketones



Undergo nucleophilic acyl substitution reactions

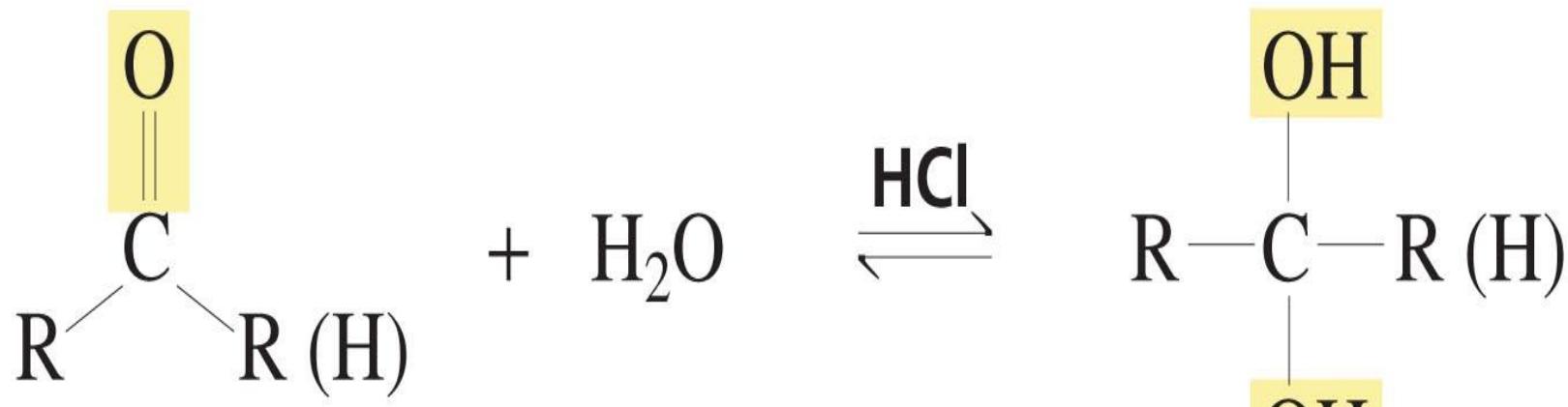
- the partial positive charge on the carbonyl carbon causes that carbon to be attacked by nucleophiles



Addition Reactions

Hydrates

- formed up on addition of water to an aldehyde or ketone

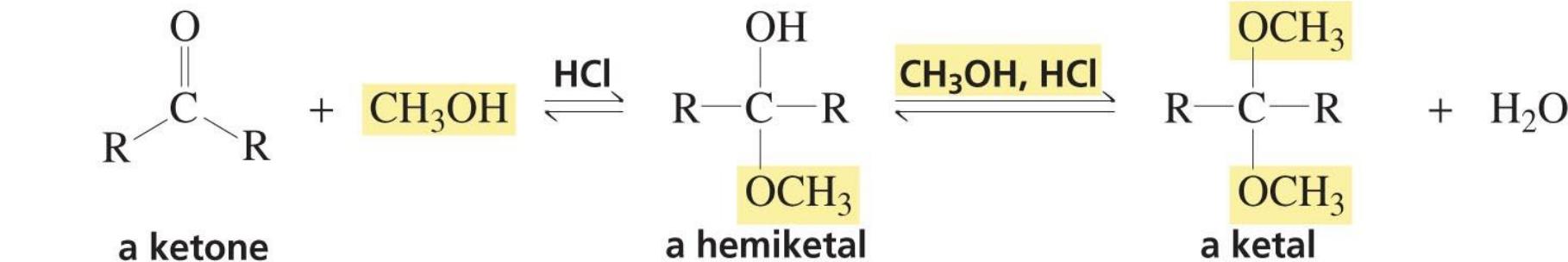
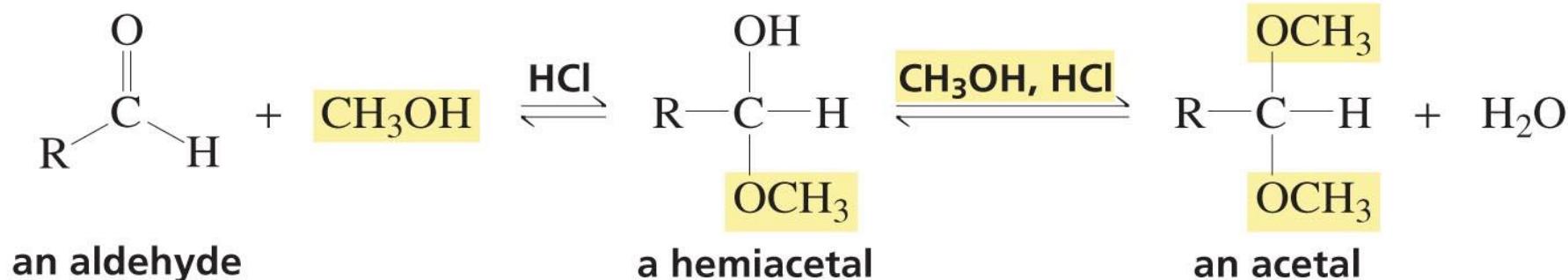


an aldehyde or
a ketone

a *gem-diol*
a hydrate

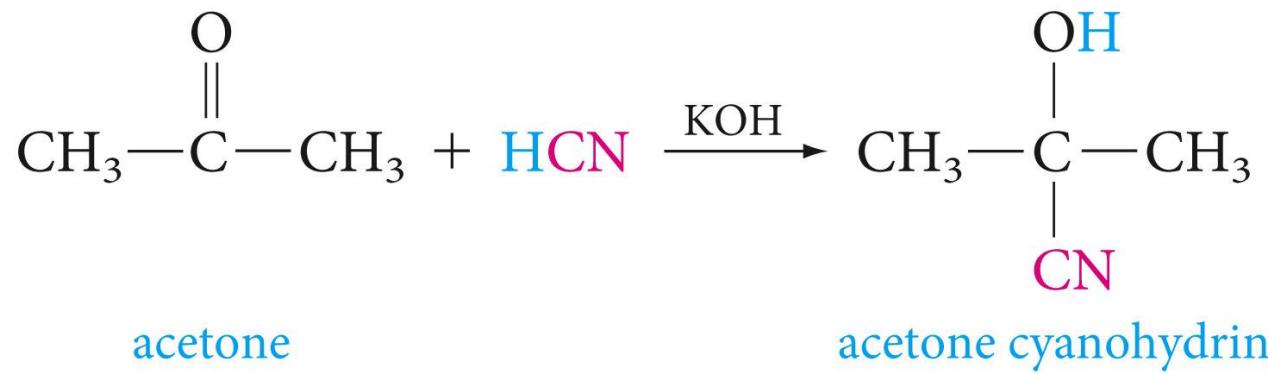
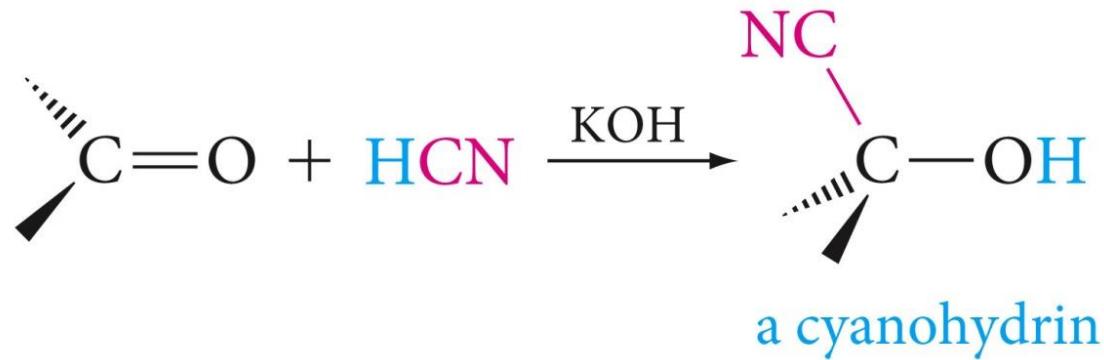
Hemiacetal and an Acetal

- Formed up on addition of an alcohol to an aldehyde or ketone in the presence of mineral acid



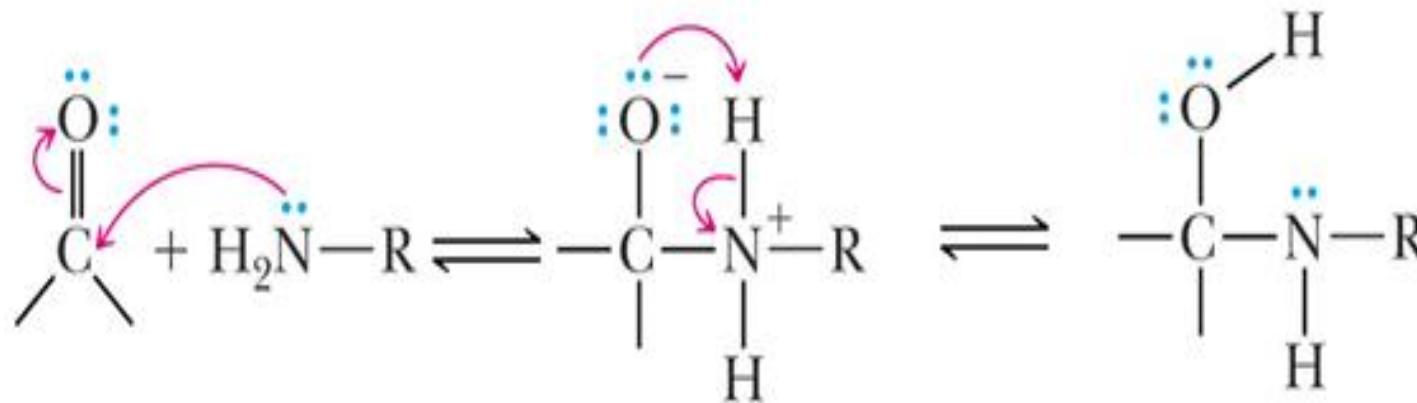
Cyanohydrins

- formed up on addition of hydrogen cyanide (HCN) to aldehydes or ketones



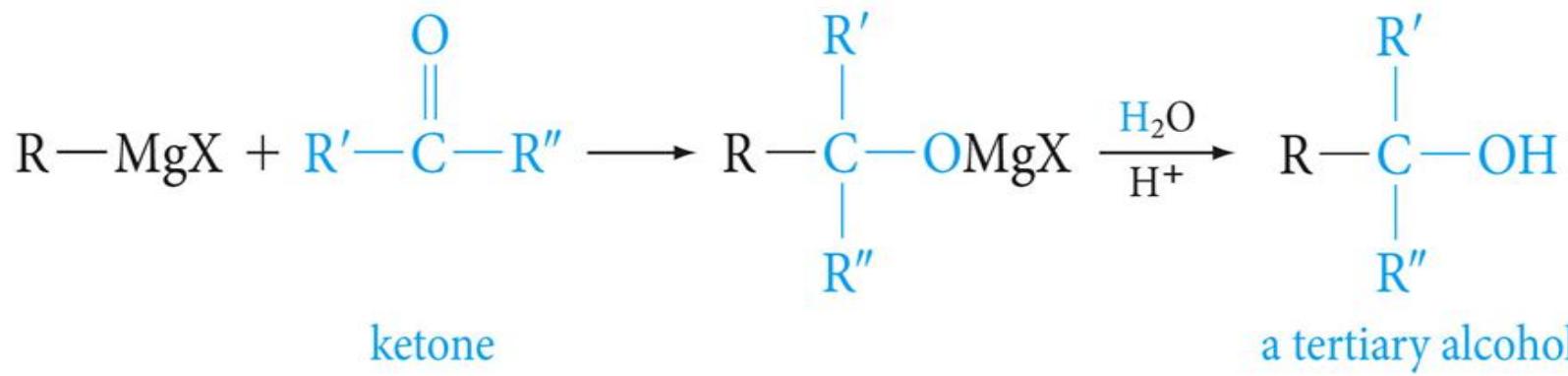
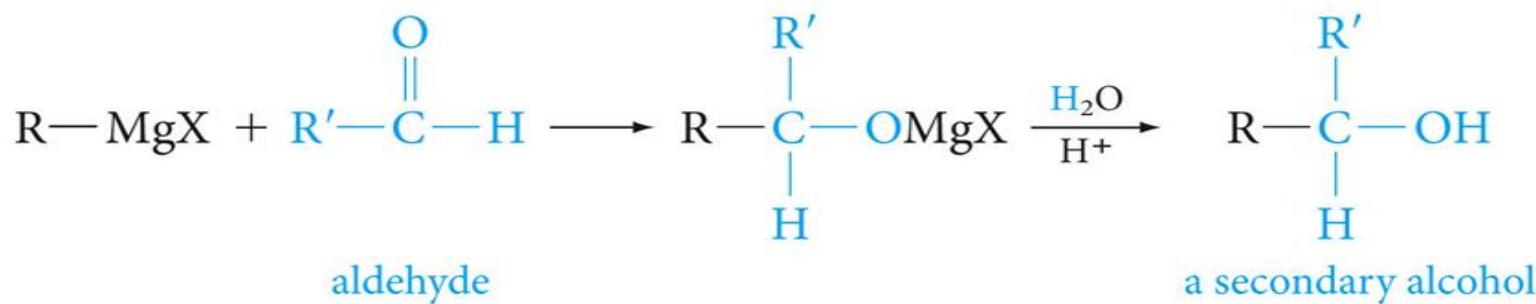
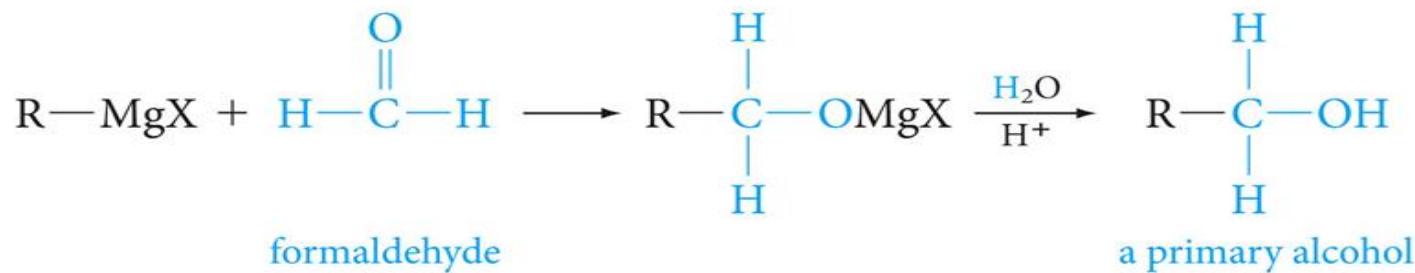
Carbinolamines

- formed up on addition amine group to aldehydes or ketones

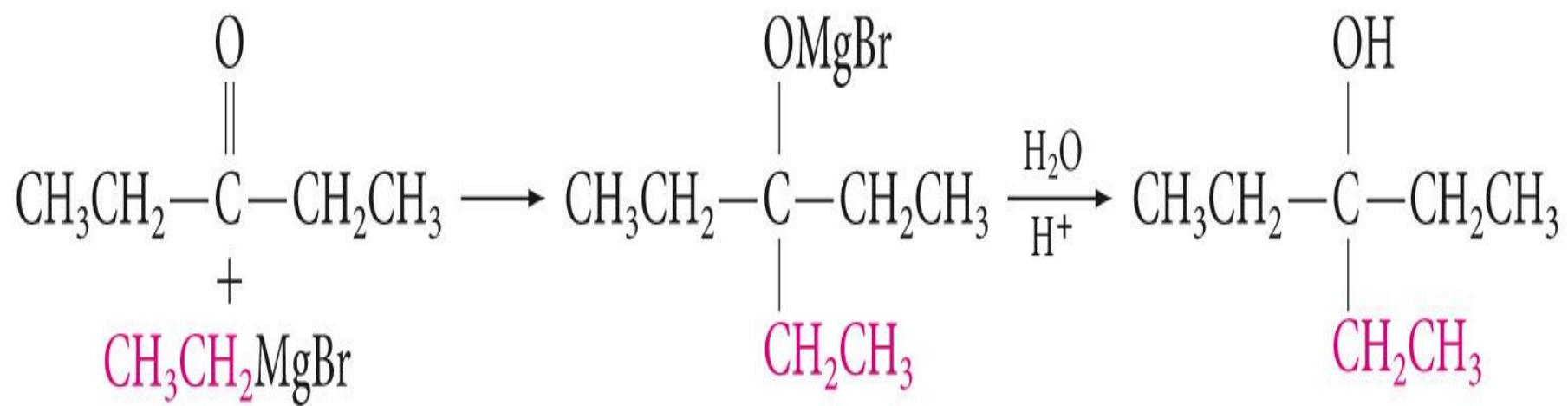


A tetrahedral carbonyl
addition compound

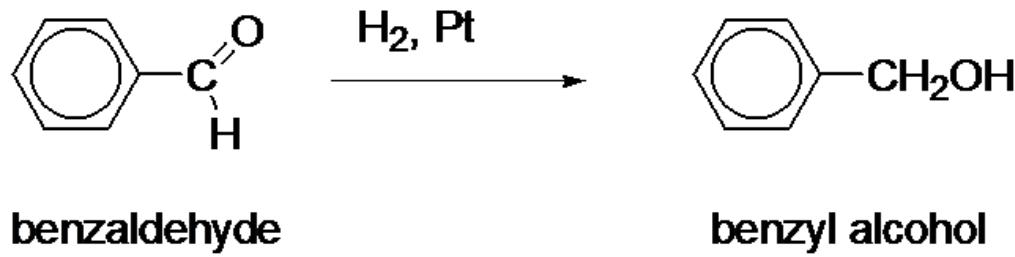
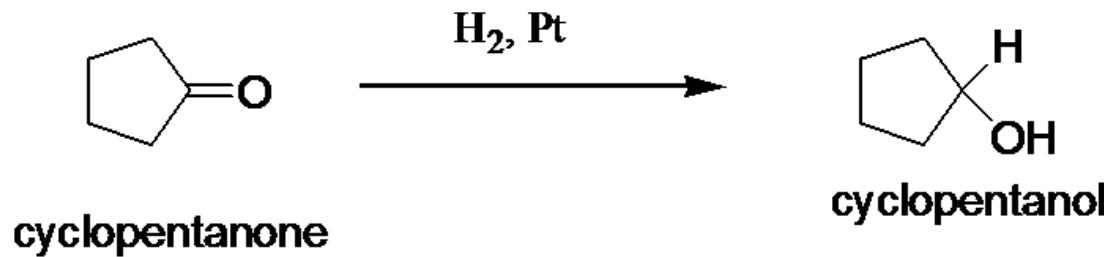
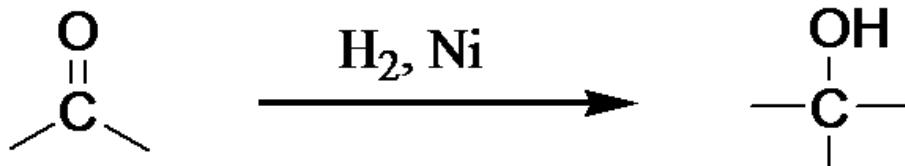
Addition of Grignard Reagents



Example:

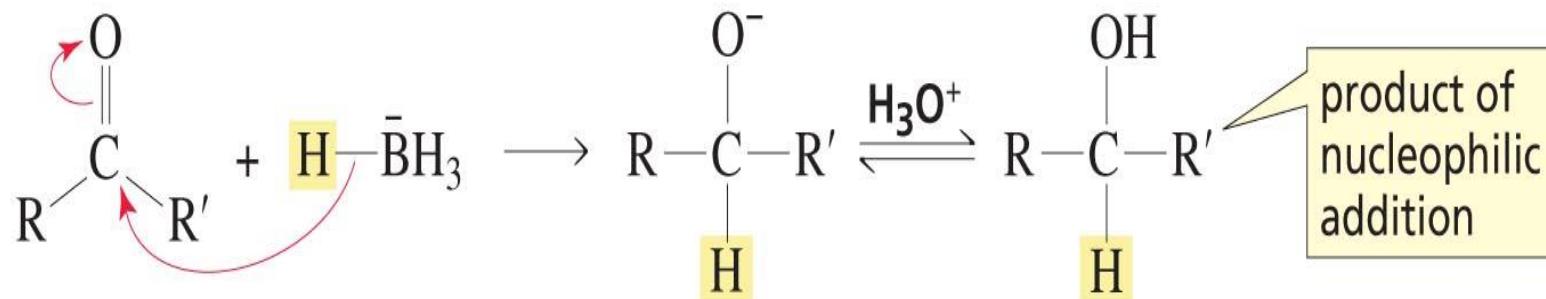


Addition of Hydrogen

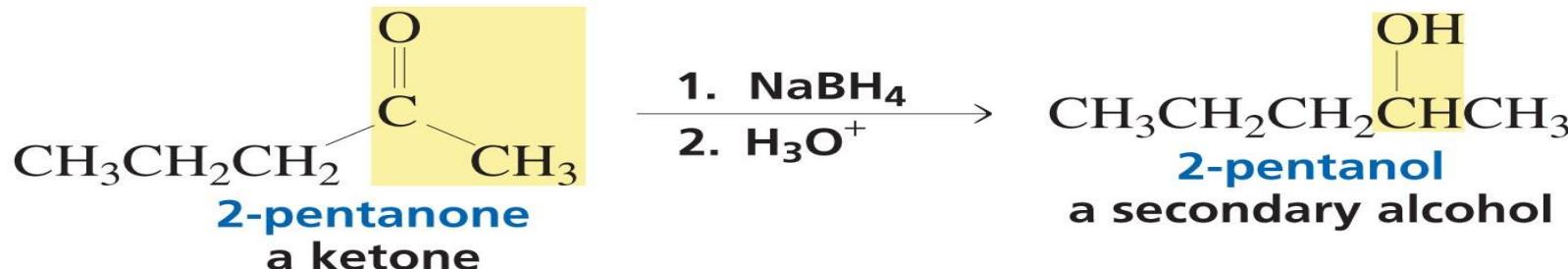
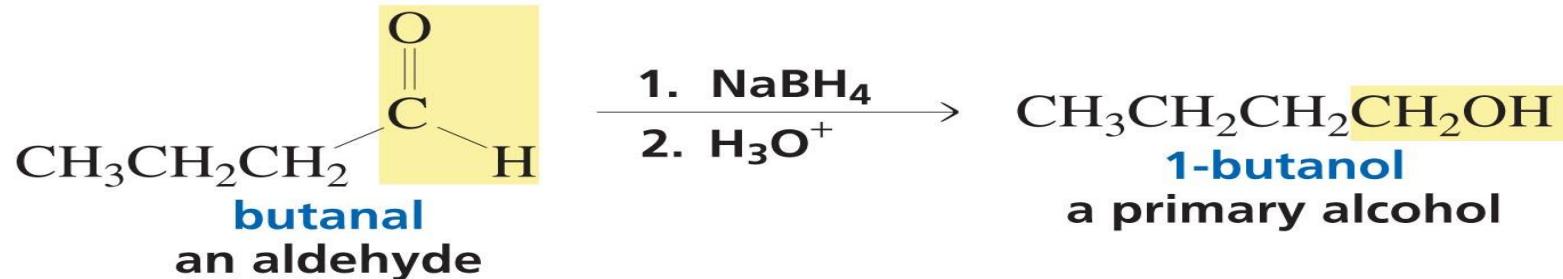


Hydride addition (LiAlH_4 and NaBH_4)

mechanism for the reaction of an aldehyde or a ketone with hydride ion



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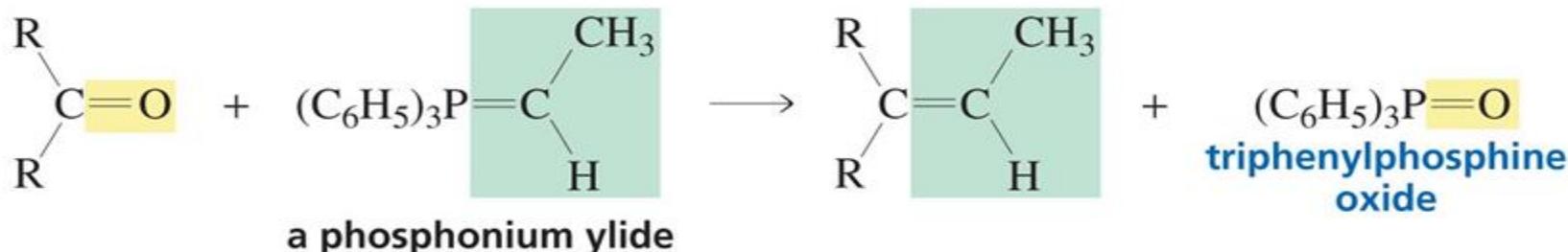
Addition Elimination Reactions

Wittig Reaction

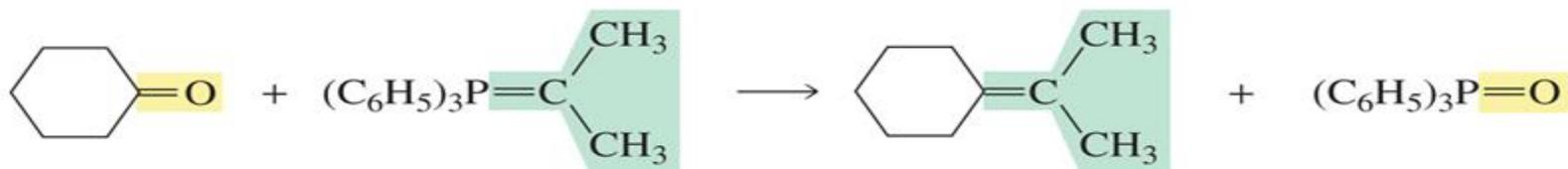
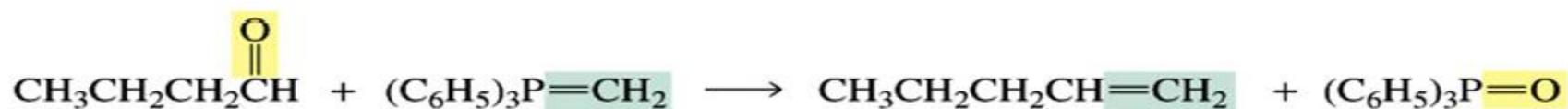
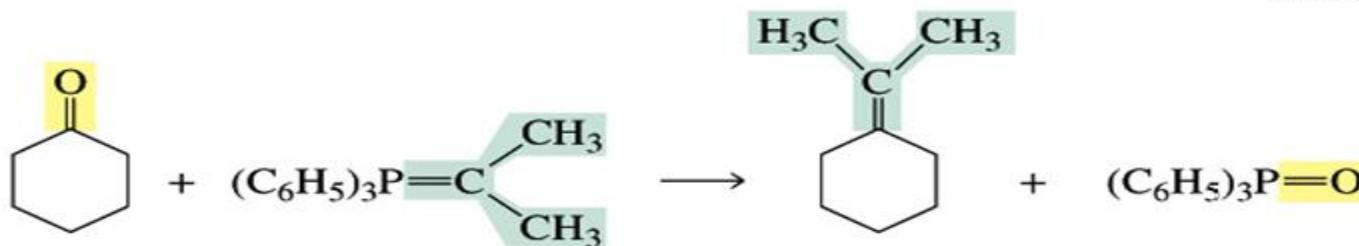
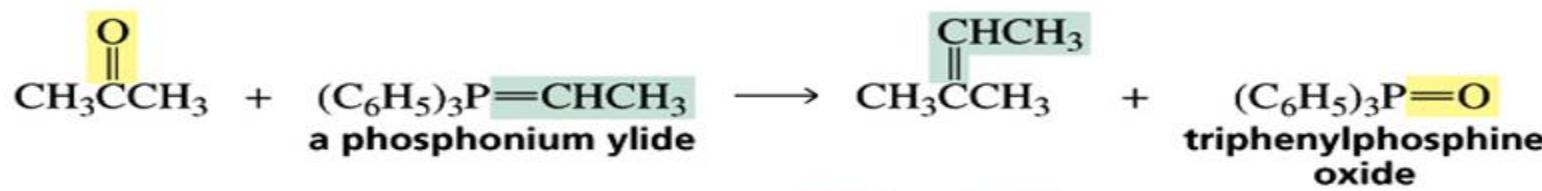
➤ Formation of Alkenes

- the sequence converts **C=O** to **C=C**
- **phosphorus ylide** adds to an aldehyde or ketone to yield a dipolar intermediate called a **betaine**
- an intermediate spontaneously decomposes to yield **alkene** and **triphenylphosphine oxide**, $(\text{Ph})_3\text{P}=\text{O}$

► Nucleophilic addition of phosphorus ylides to carbonyl carbon

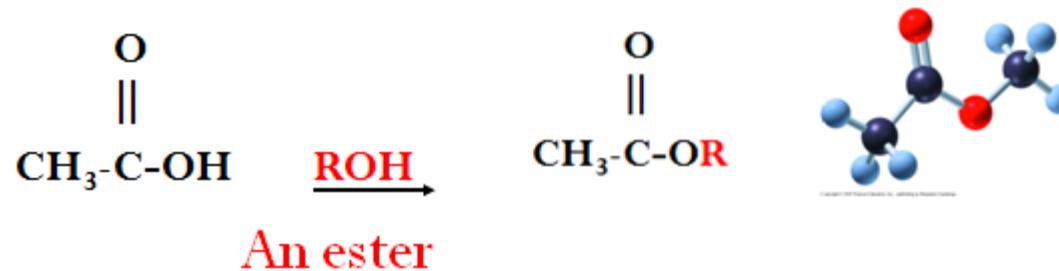


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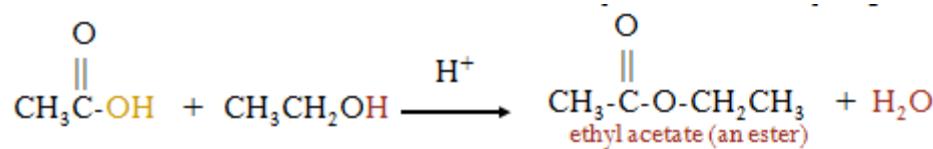


Esters and Esterification

- an ester is formed when H in the carboxyl group is replaced with an alkyl group(-R) from alcohol

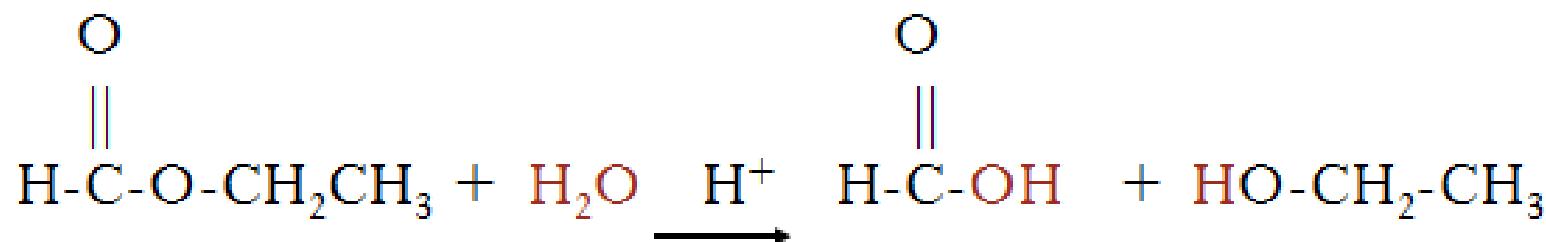


- Esterification-the reaction of a carboxylic acid with alcohol in the presence of acid catalyst to produce an ester

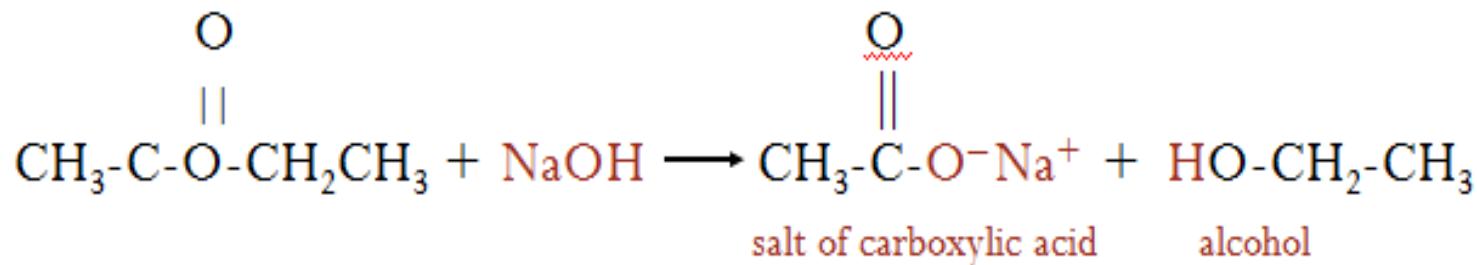


Hydrolysis of Esters (Acid catalyzed and Basic hydrolysis)

- reaction of ester with water to produce a carboxylic acid and an alcohol in the presence of acid catalyst

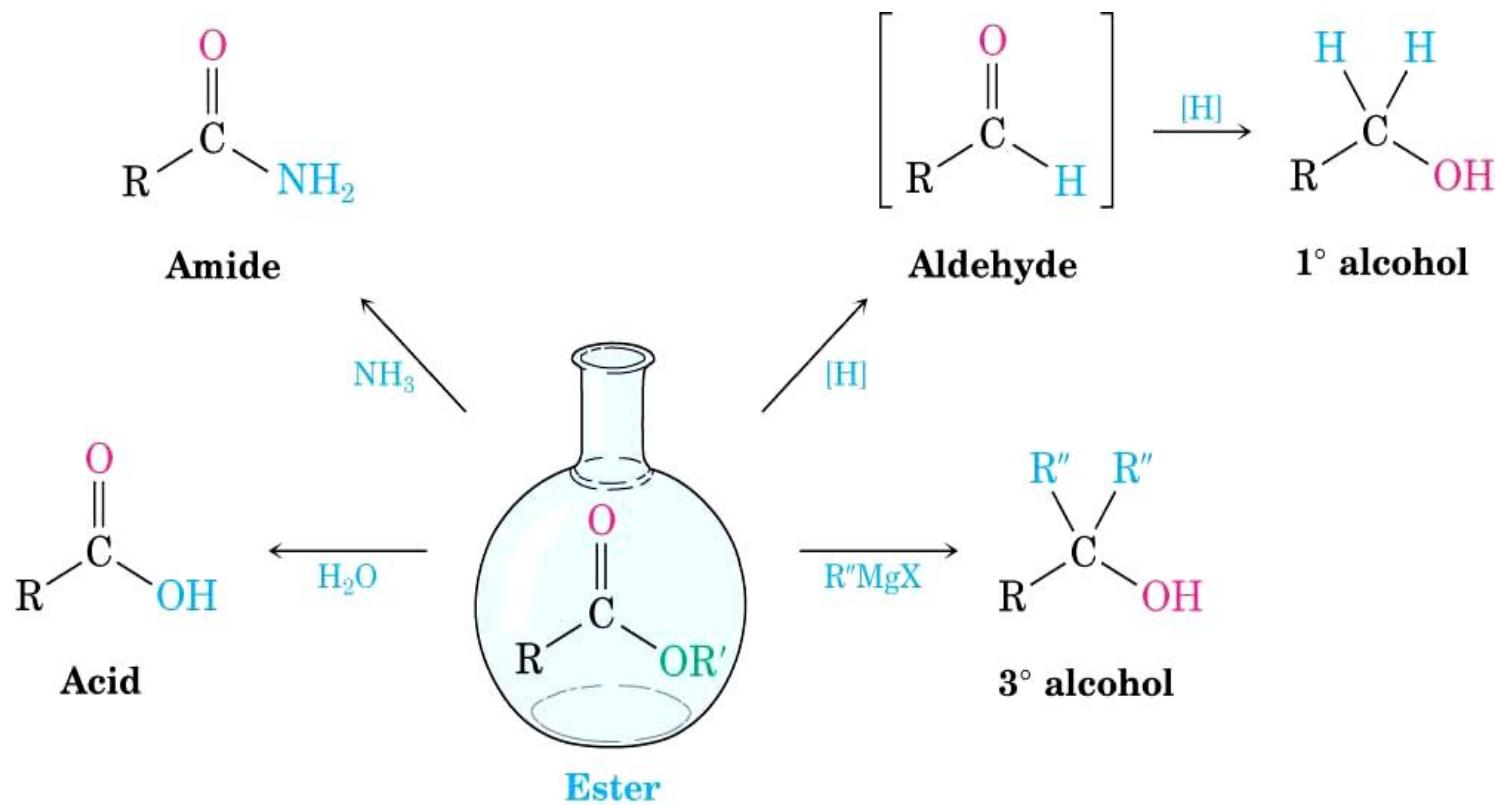


- reaction of ester with strong base to produce salt of carboxylic acid and an alcohol (also called saponification)

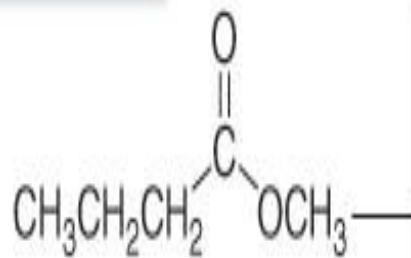


Esters

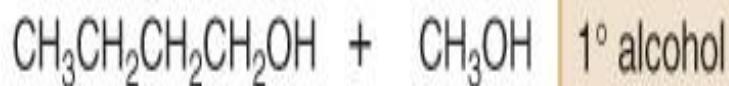
- less reactive toward nucleophiles than are acid chlorides or anhydrides



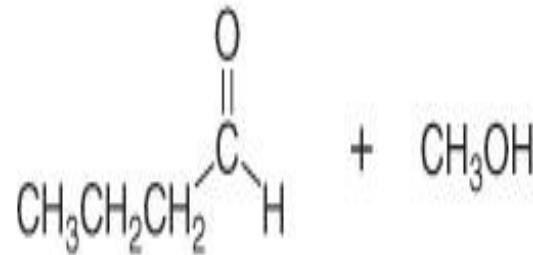
Reduction of esters



strong reducing agent

[1] LiAlH_4 [2] H_2O  1° alcohol

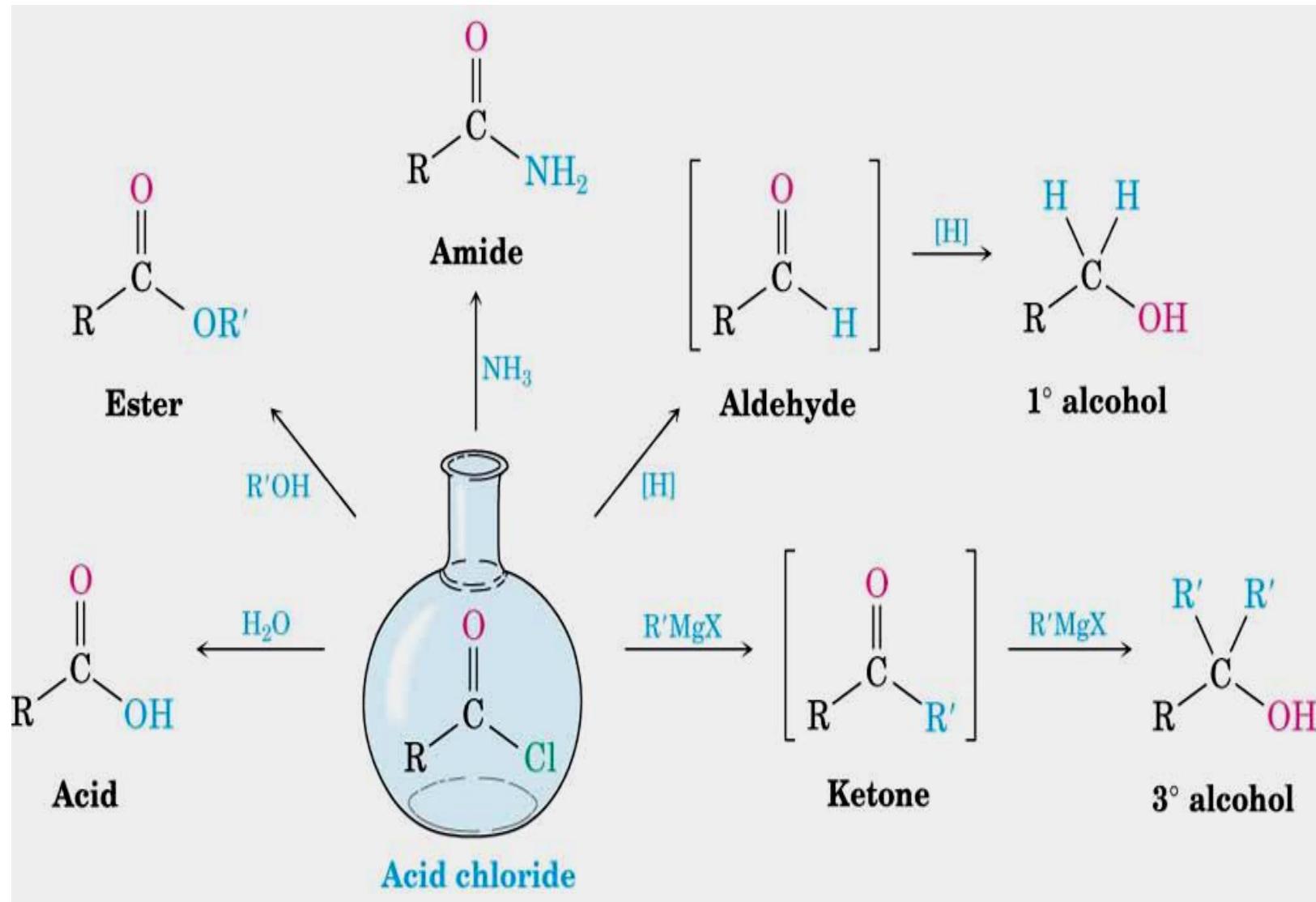
[1] DIBAL-H

[2] H_2O 

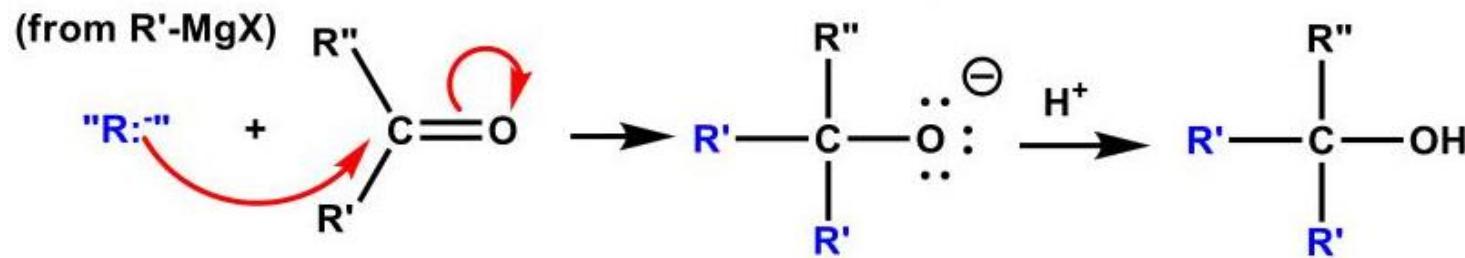
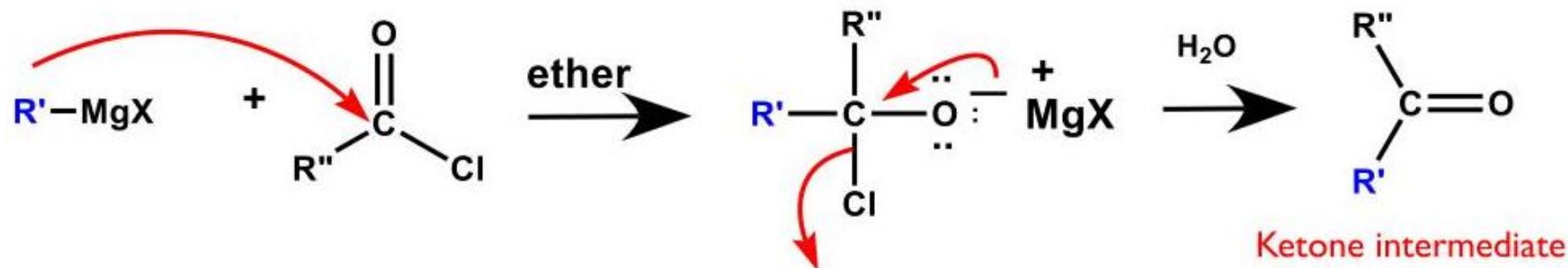
aldehyde

mild reducing agent

Reactions of Acid Chlorides

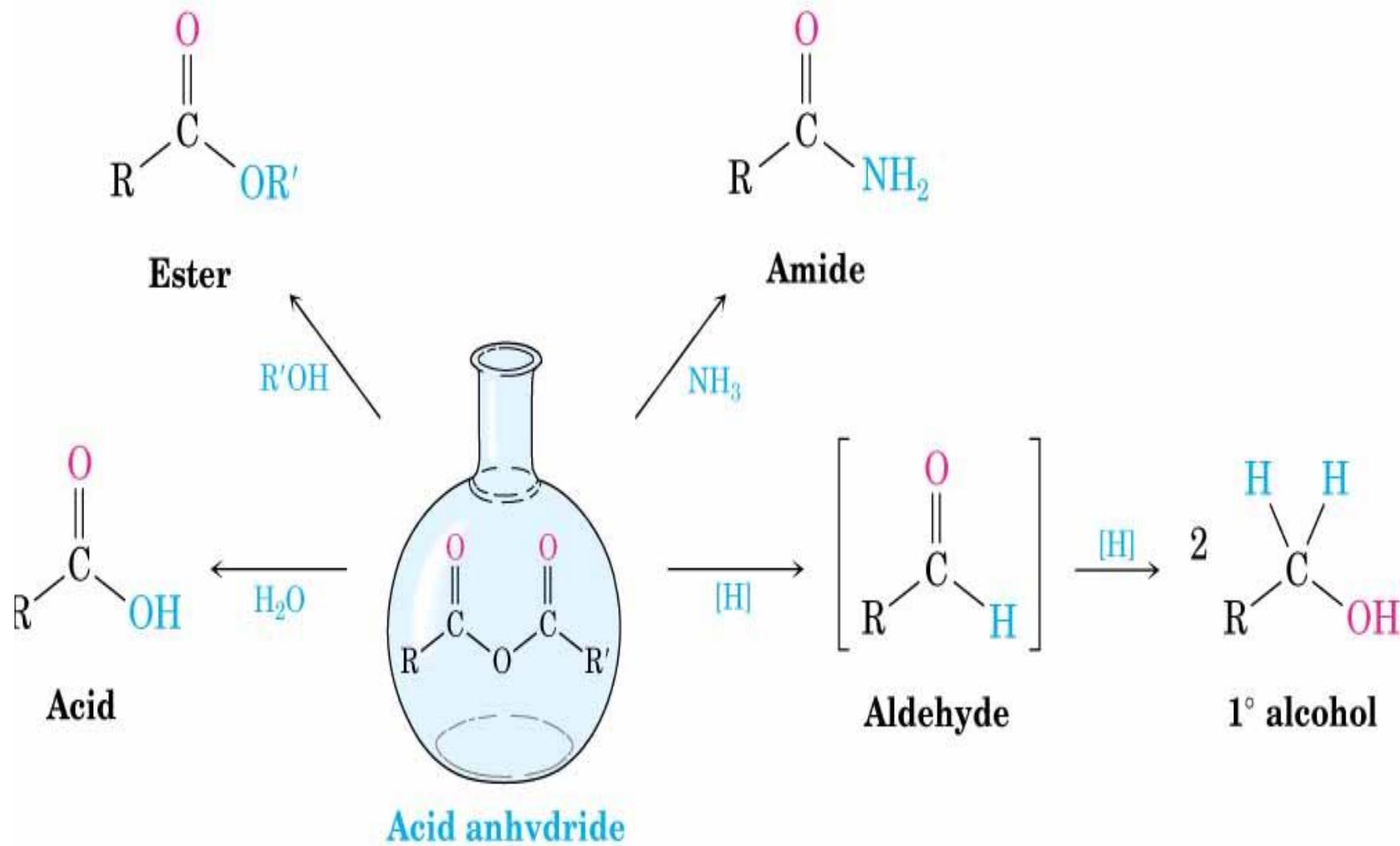


Grignard attacks the carbonyl and Chloride ion leaves.



$\text{R}'', \text{R}' = \text{H, alkyl, or aryl}$

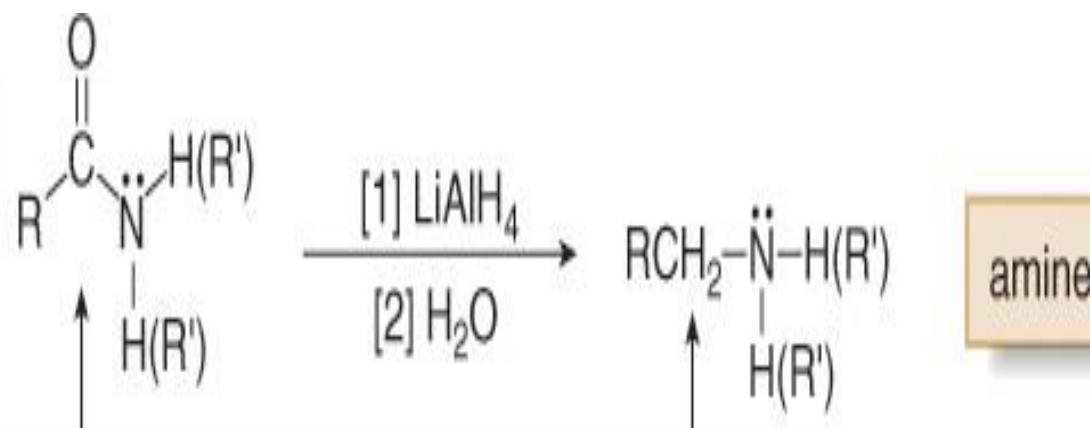
Reactions of Acid Anhydrides



Reduction of amides

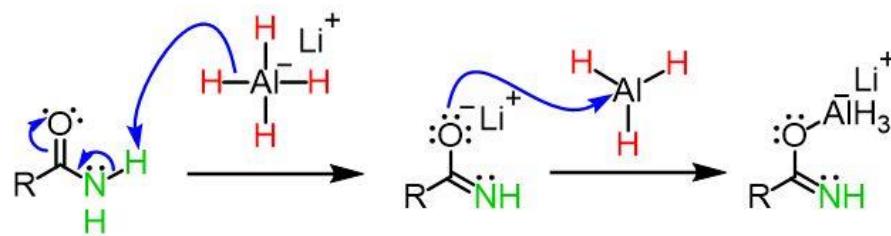
- unlike the LiAlH_4 reduction of all other carboxylic acid derivatives, which affords 1° alcohols, the LiAlH_4 reduction of **amides** forms **amines**

Reduction of an amide—
General reaction



Both C–O bonds are replaced by C–H bonds.

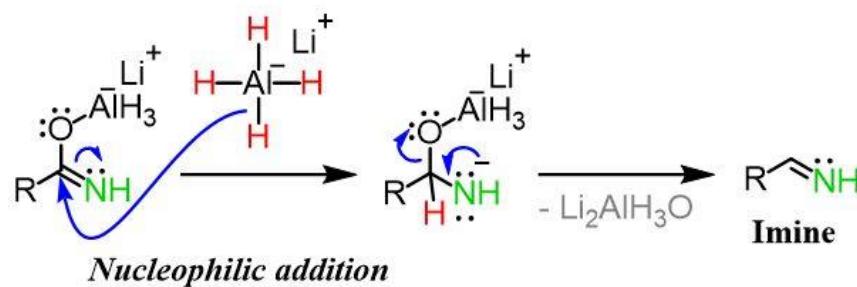
The Mechanism of Amide Reduction to Amine by LiAlH_4



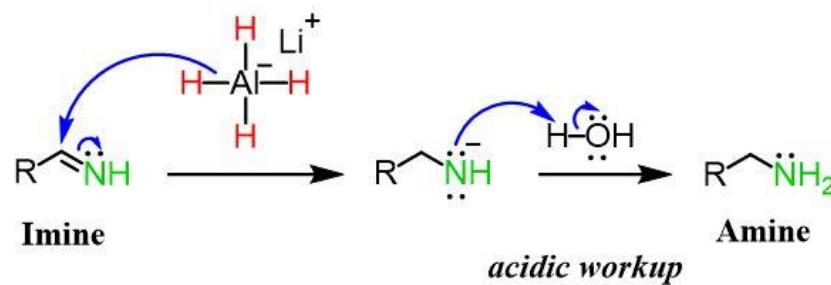
Deprotonation

Lewis Acid-Base reaction

converts O into good LG



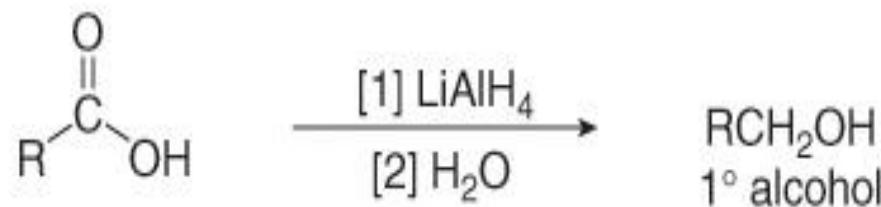
Nucleophilic addition



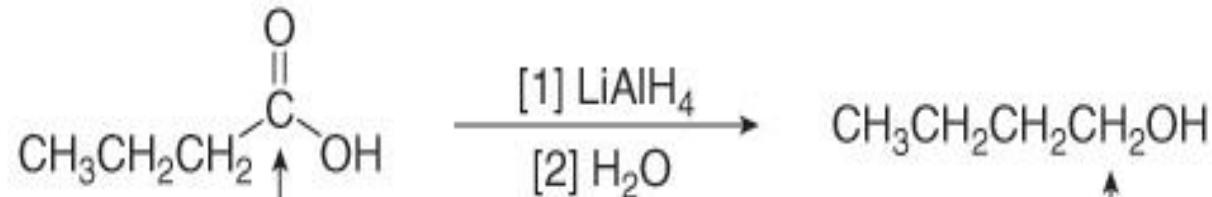
Cont'd...

- carboxylic acids are reduced to 1° alcohols with LiAlH_4
- LiAlH_4 is too strong a reducing agent to stop the reaction at the aldehyde stage
- milder reagents are not strong enough to initiate the reaction

Reduction of a RCOOH —
General reaction



Example

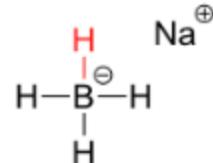


Two C–O bonds are replaced by C–H bonds.

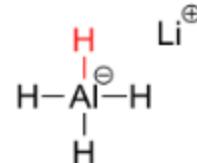
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TABLE A Summary of Metal Hydride Reducing Agents

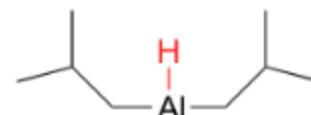
Reagent	Starting material	→	Product
strong reagent	LiAlH ₄	→	RCH ₂ OH
	R ₂ CO	→	R ₂ CHOH
	RCOOH	→	RCH ₂ OH
	RCOOR'	→	RCH ₂ OH
	RCOCl	→	RCH ₂ OH
	RCONH ₂	→	RCH ₂ NH ₂
milder reagents	NaBH ₄	→	RCH ₂ OH
	R ₂ CO	→	R ₂ CHOH
	LiAlH[OC(CH ₃) ₃] ₃	→	RCHO
	DIBAL-H	→	RCHO



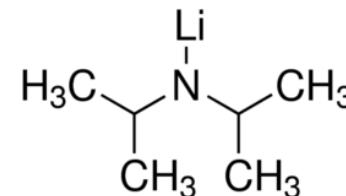
NaBH₄



LiAlH₄



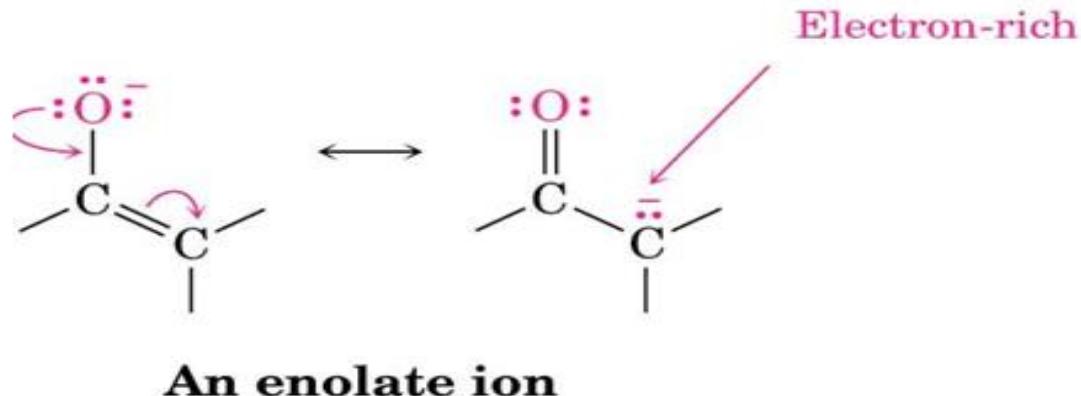
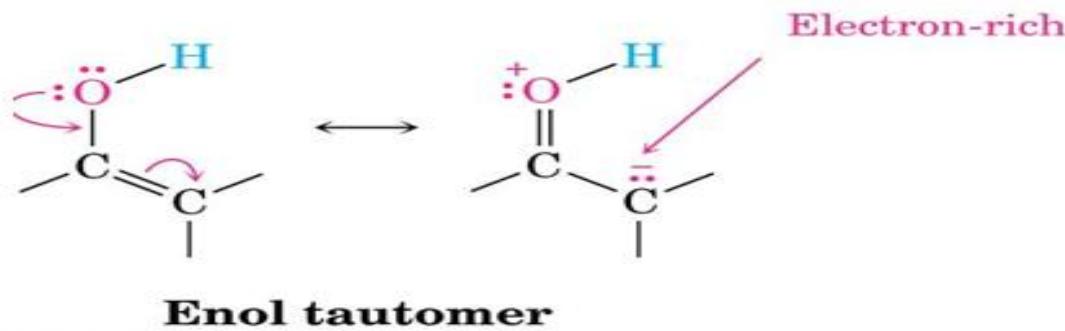
DIBAH



Lithium diisopropyl amide

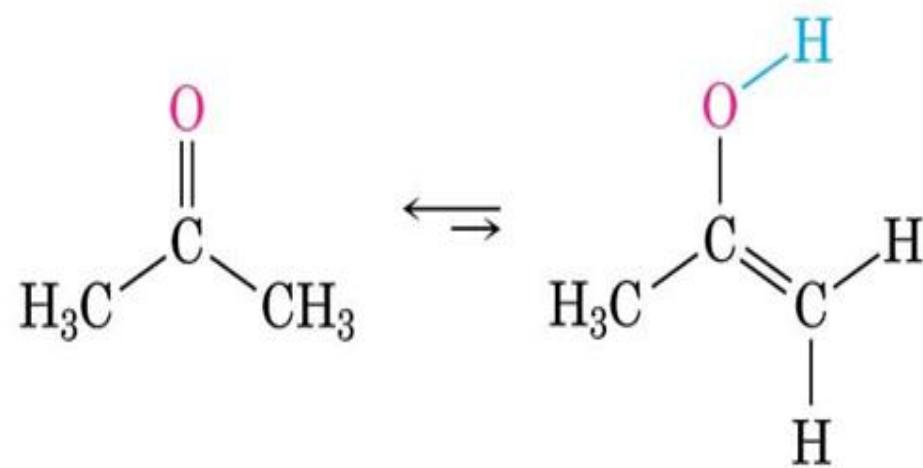
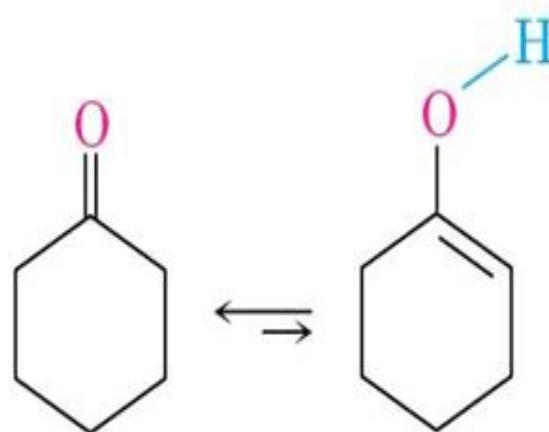
Enols and enolate

- Enols and enolate anions behave as **nucleophiles** and react with **electrophiles** because the **double bonds** are **electron-rich**



Keto–Enol Tautomerism

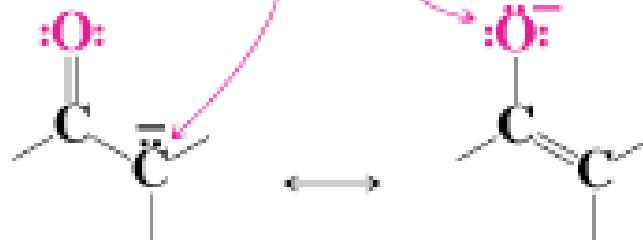
- compounds that differ only by the position of a moveable proton are called **tautomers**



Two Reactions Sites on Enolates

- reaction on oxygen yields an enol derivative
- reaction on carbon yields an α -substituted carbonyl compound

Reaction here OR Reaction here

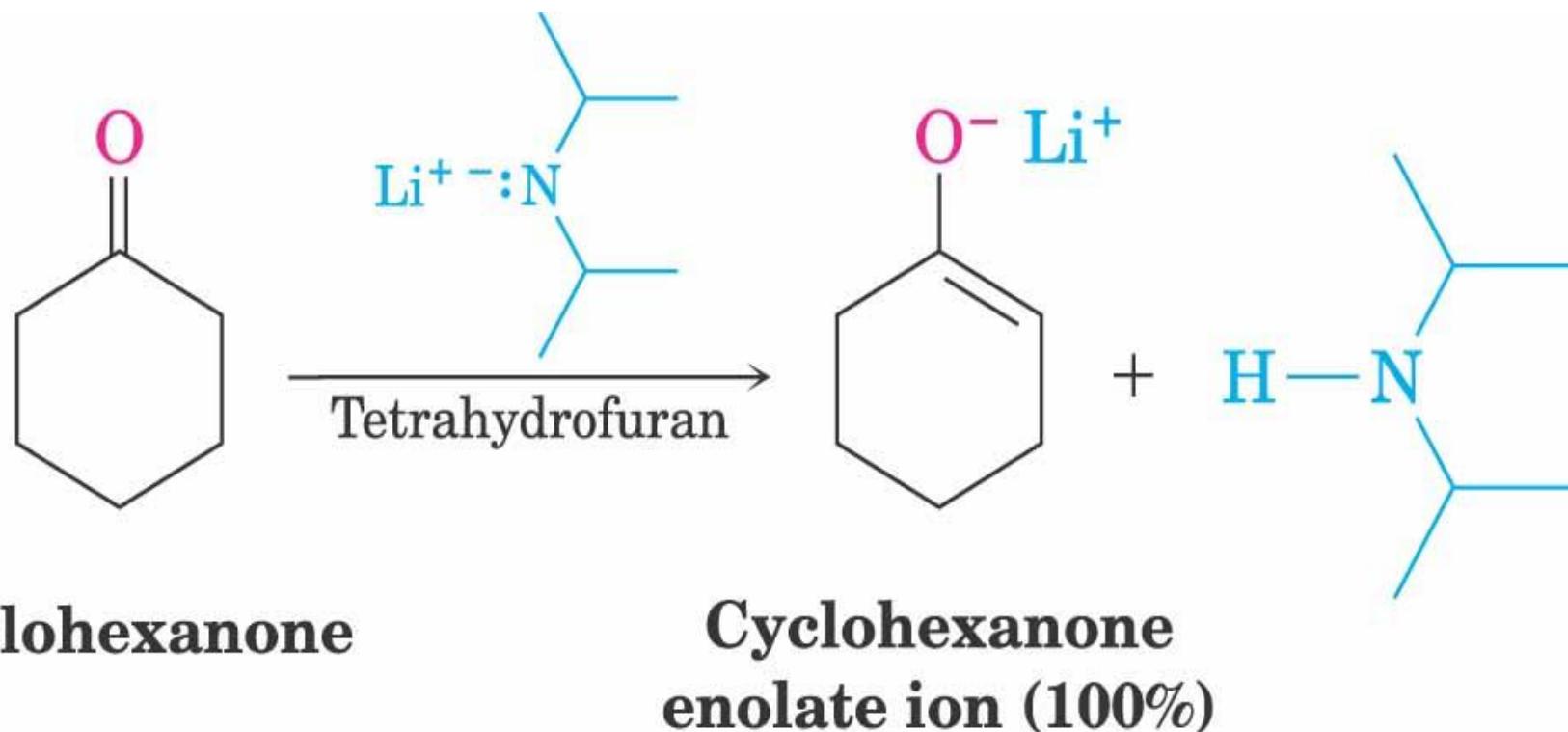


α -Keto carbanion Vinylic alkoxide



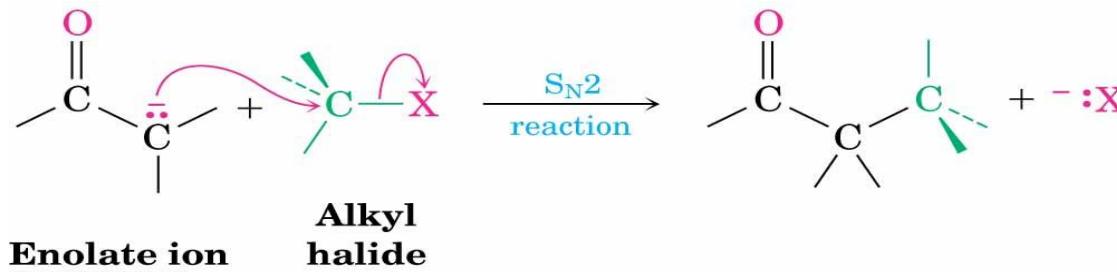
Alkylation of Enolate Ions at α -Carbon

- even unreactive ketones will be easily deprotonated with LDA to give stable, isolable lithium enolate salts

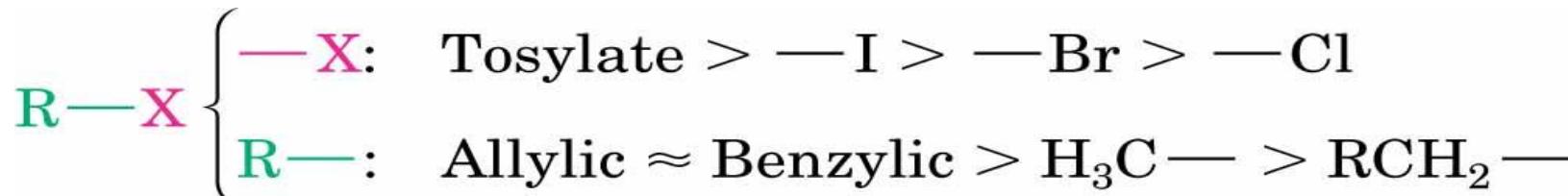


α -Alkylation of Enolate Ions

- alkylation occurs when the nucleophilic enolate ion reacts with the electrophilic alkyl halide or tosylate and displaces the leaving group



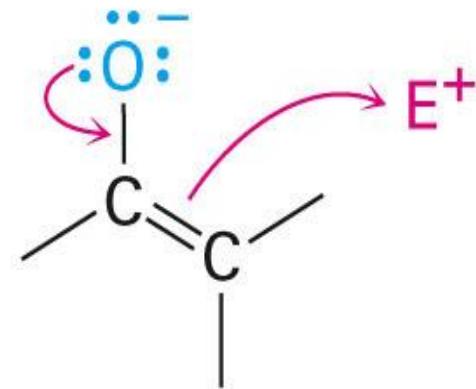
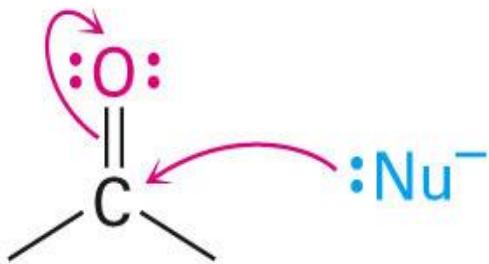
- S_N2 reaction: the leaving group X can be Cl^- , Br^- , I^- , or tosylate
- R should be **primary or methyl** and preferably should be allylic or benzylic
- secondary halides react poorly, and tertiary halides don't react at all** because of **competing elimination**



Aldol and Related Condensation

Condensation Reactions

- carbonyl compounds are both the electrophile and nucleophile in carbonyl condensation reactions

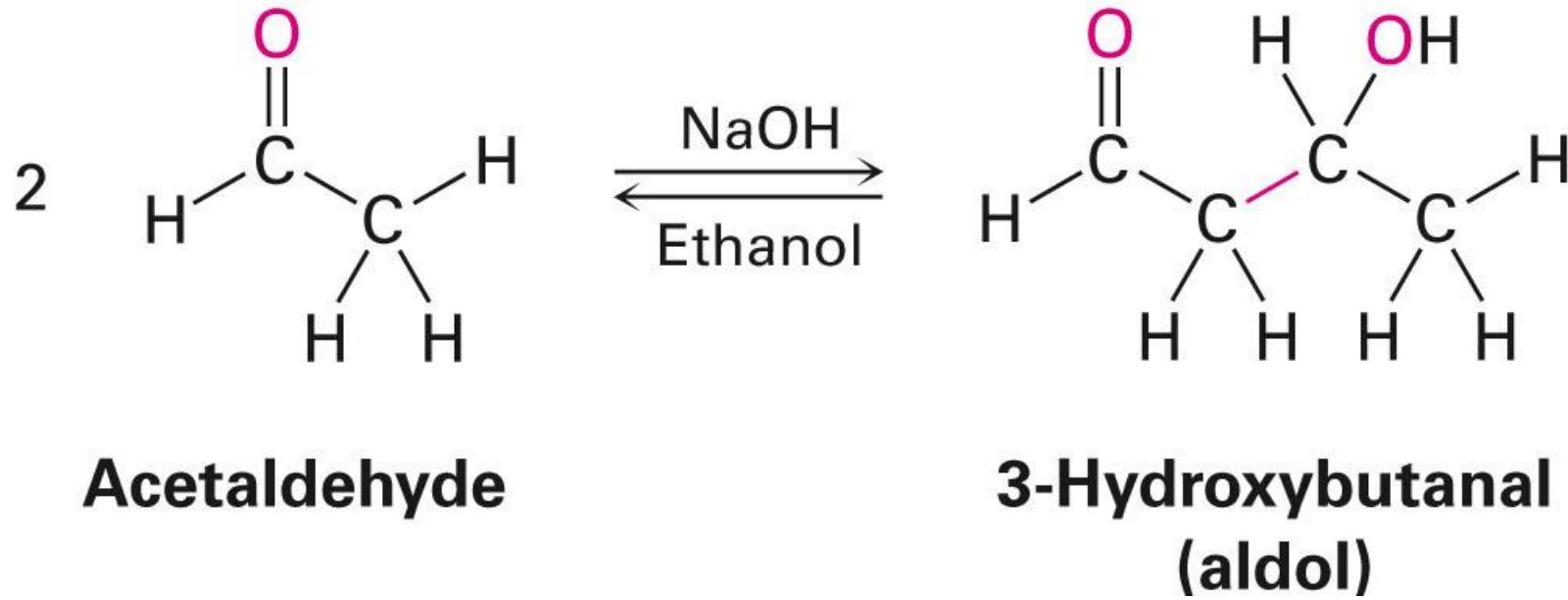


Electrophilic carbonyl group reacts with nucleophiles.

Nucleophilic enolate ion reacts with electrophiles.

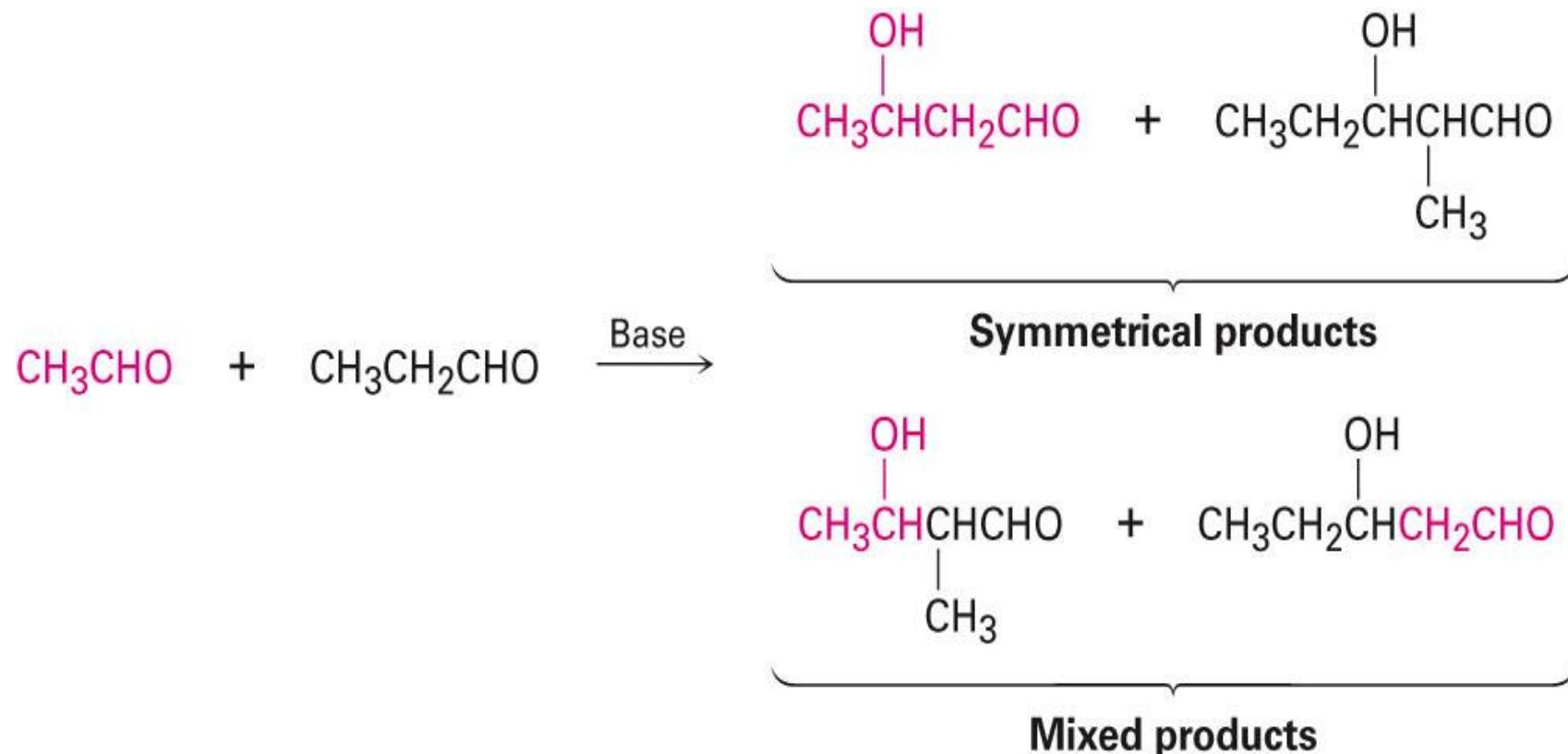
Cont'd...

- acetaldehyde reacts in basic solution (NaOEt , NaOH) with another molecule of acetaldehyde
- the β -hydroxy aldehyde product is **aldol** (aldehyde + alcohol)
- this is a **general reaction of aldehydes and ketones**

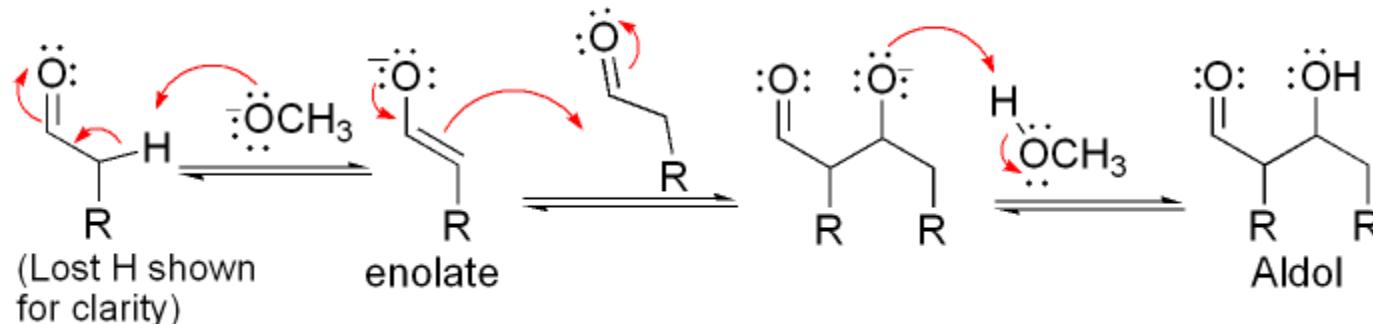


Mixed Aldol Reactions

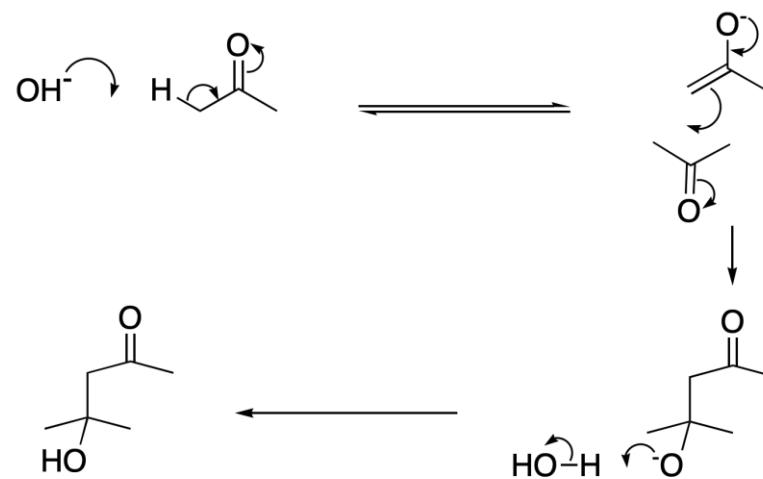
- mixed aldol reaction between two different aldehyde molecules lead to a mixture of four possible products

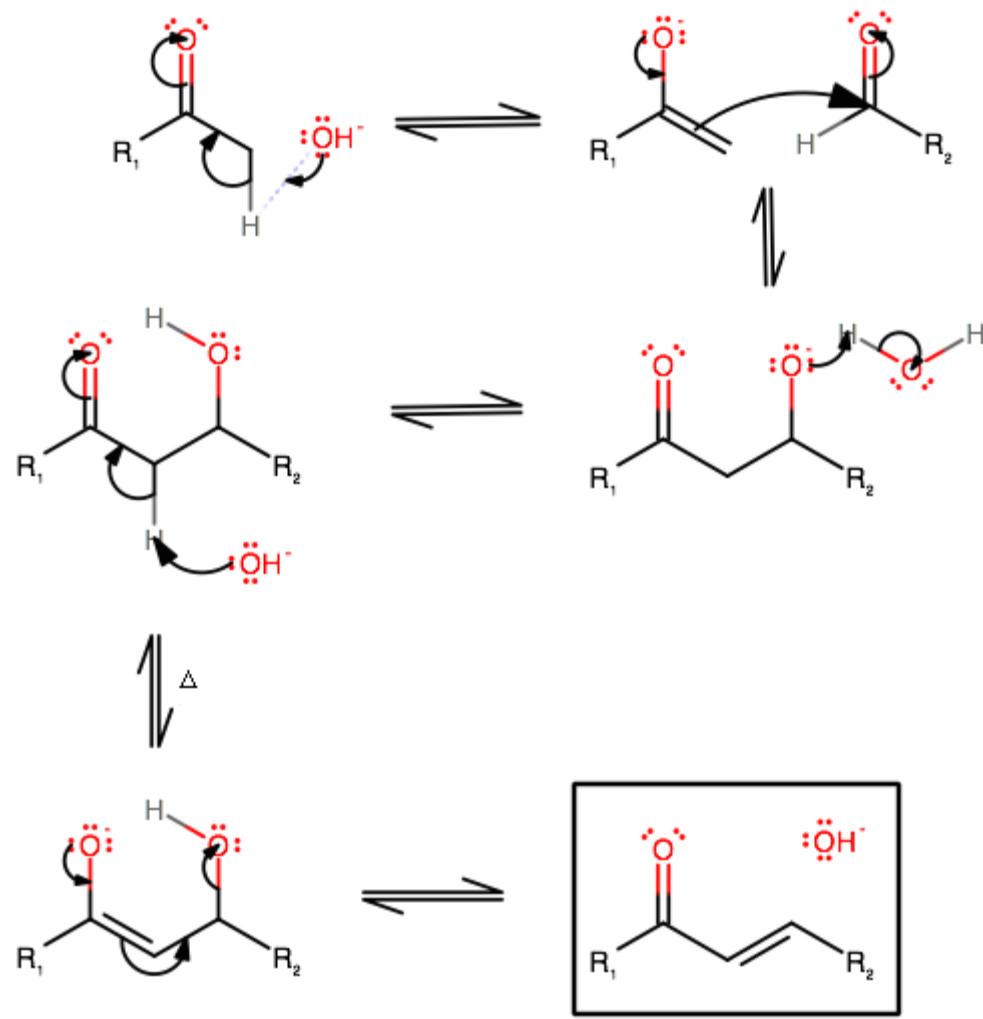


Base catalyzed aldol reaction (shown using -OCH_3 as base)



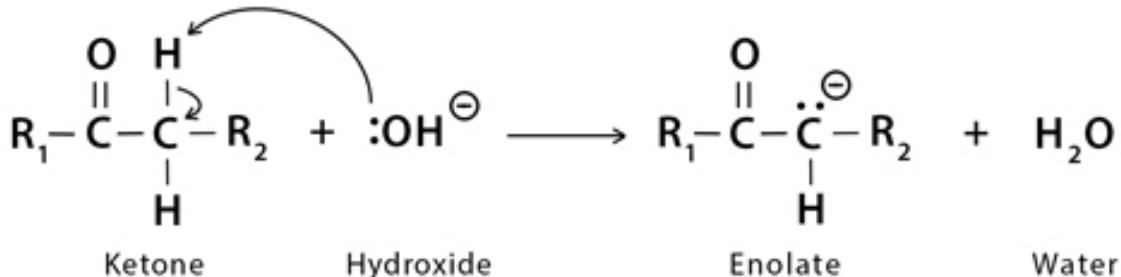
A base-catalysed aldol reaction



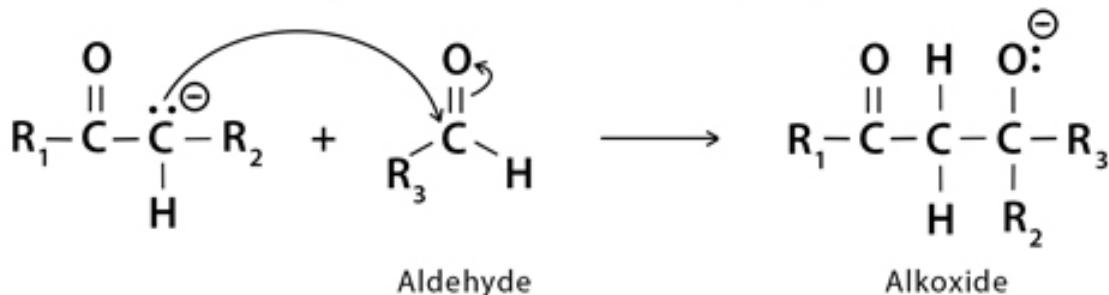


Mechanism of Aldol Reaction

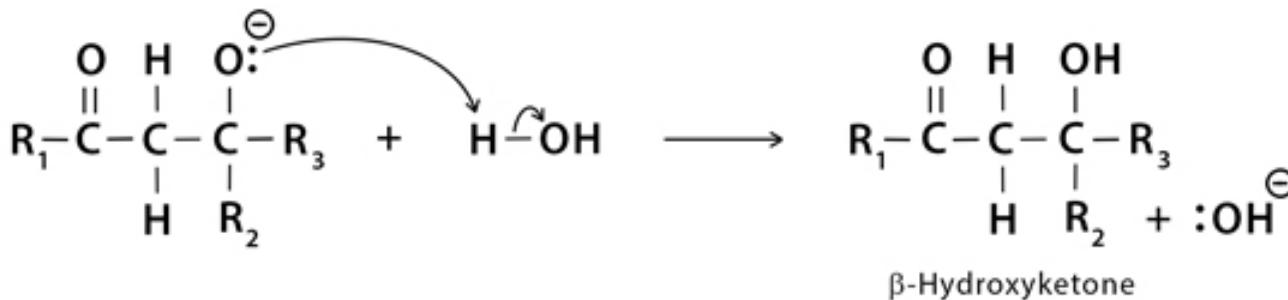
Step 1: Removal of the acidic α -hydrogen by a base hydroxide giving a reactive enolate



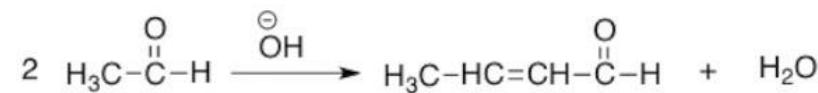
Step 2: Nucleophilic attack on the aldehyde at the electrophilic carbonyl C by the enolate in a nucleophilic addition reaction giving an intermediate alkoxide



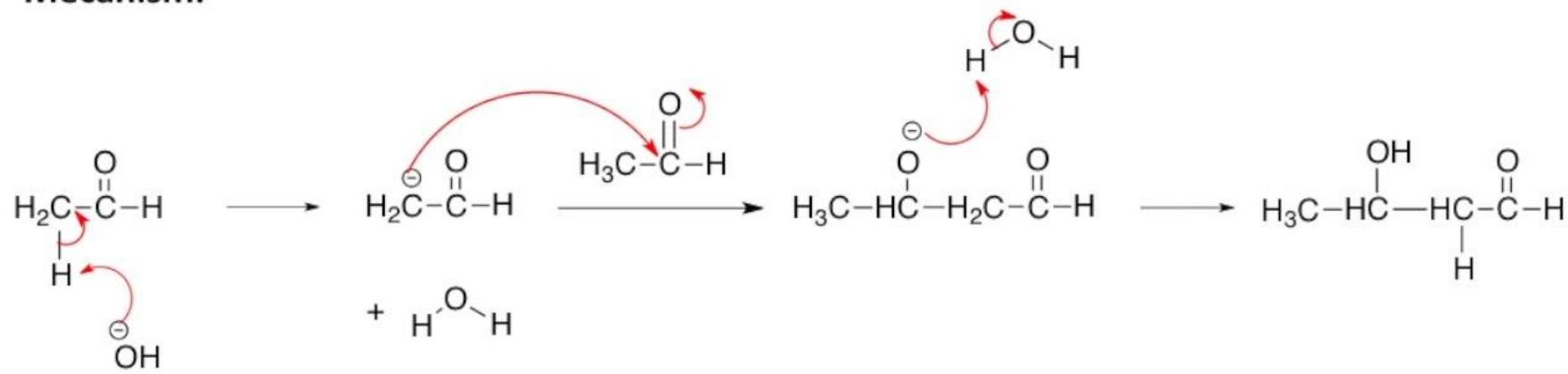
Step 3: Deprotonation of the water molecule creating a hydroxide and a β -hydroxyketone (aldol product)

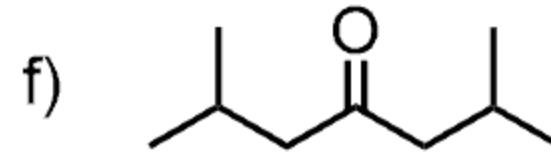
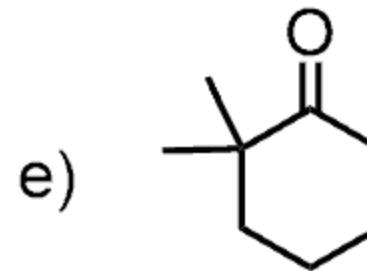
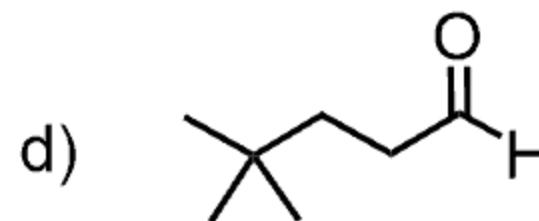
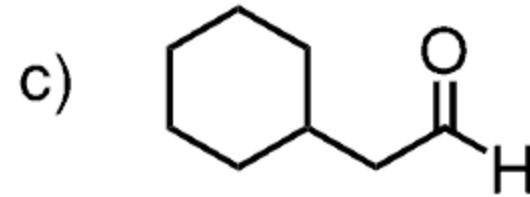
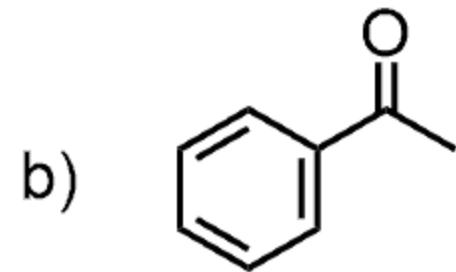
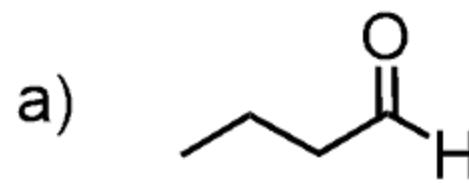


Aldol condensation



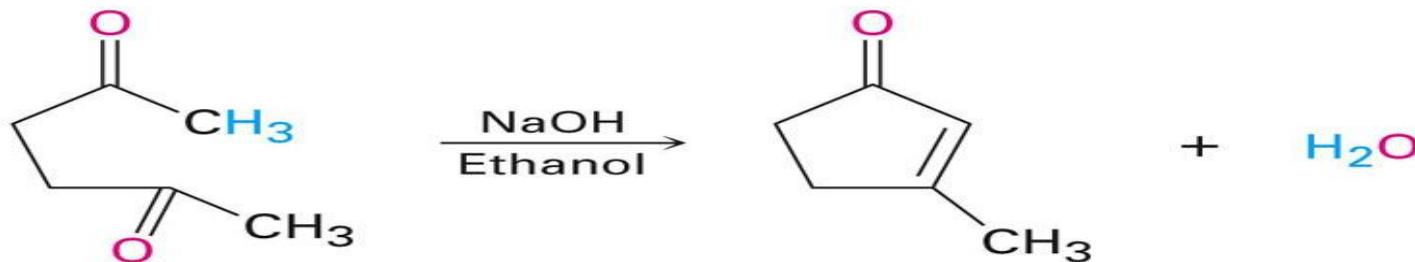
Mecanism:





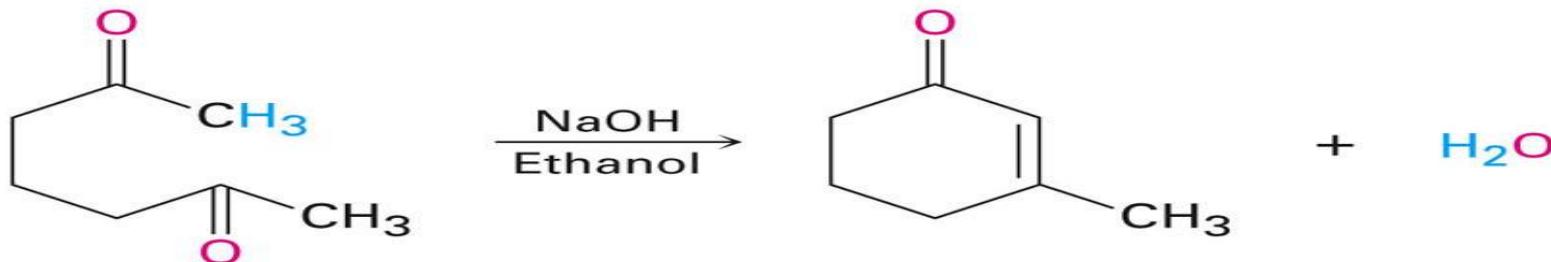
Intramolecular Aldol Reactions

- treatment of certain di-carbonyl compounds with base produces cyclic products by intramolecular reaction



2,5-Hexanedione
(a 1,4-diketone)

3-Methyl-2-cyclopentenone



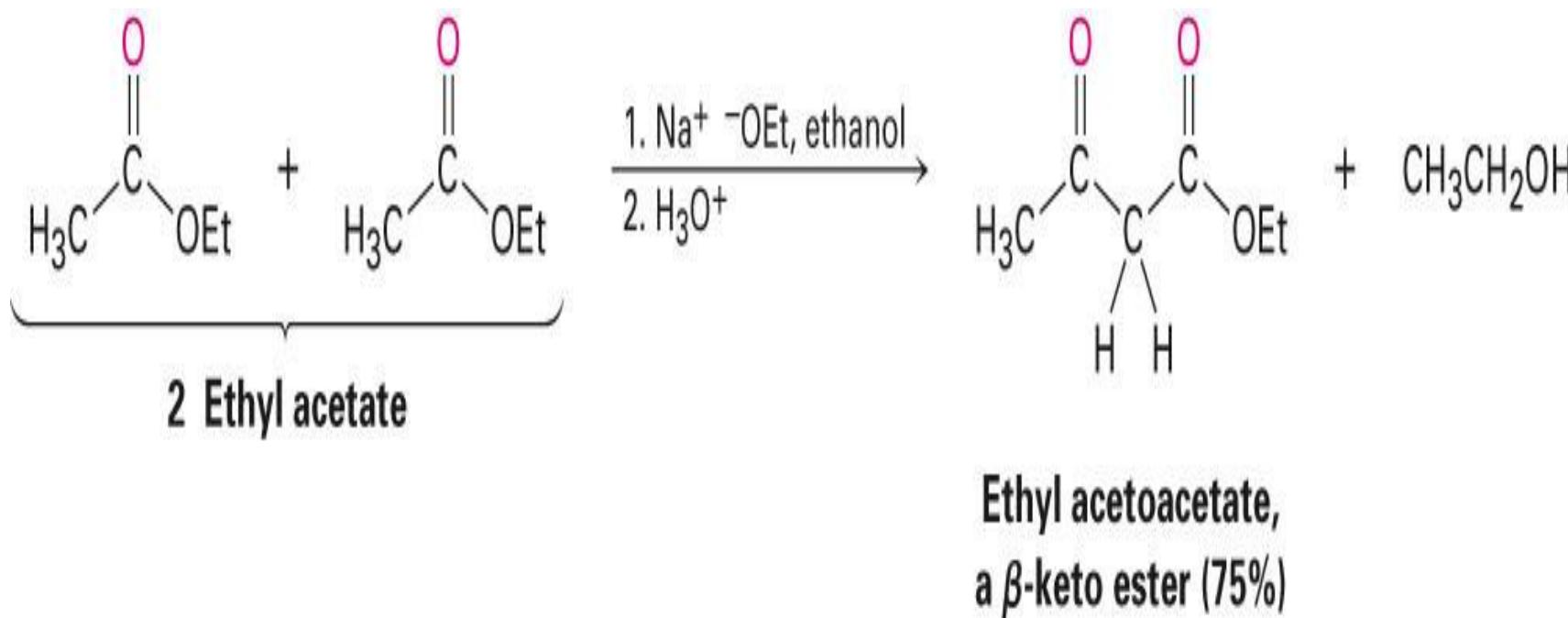
2,6-Heptanedione
(a 1,5-diketone)

3-Methyl-2-cyclohexenone

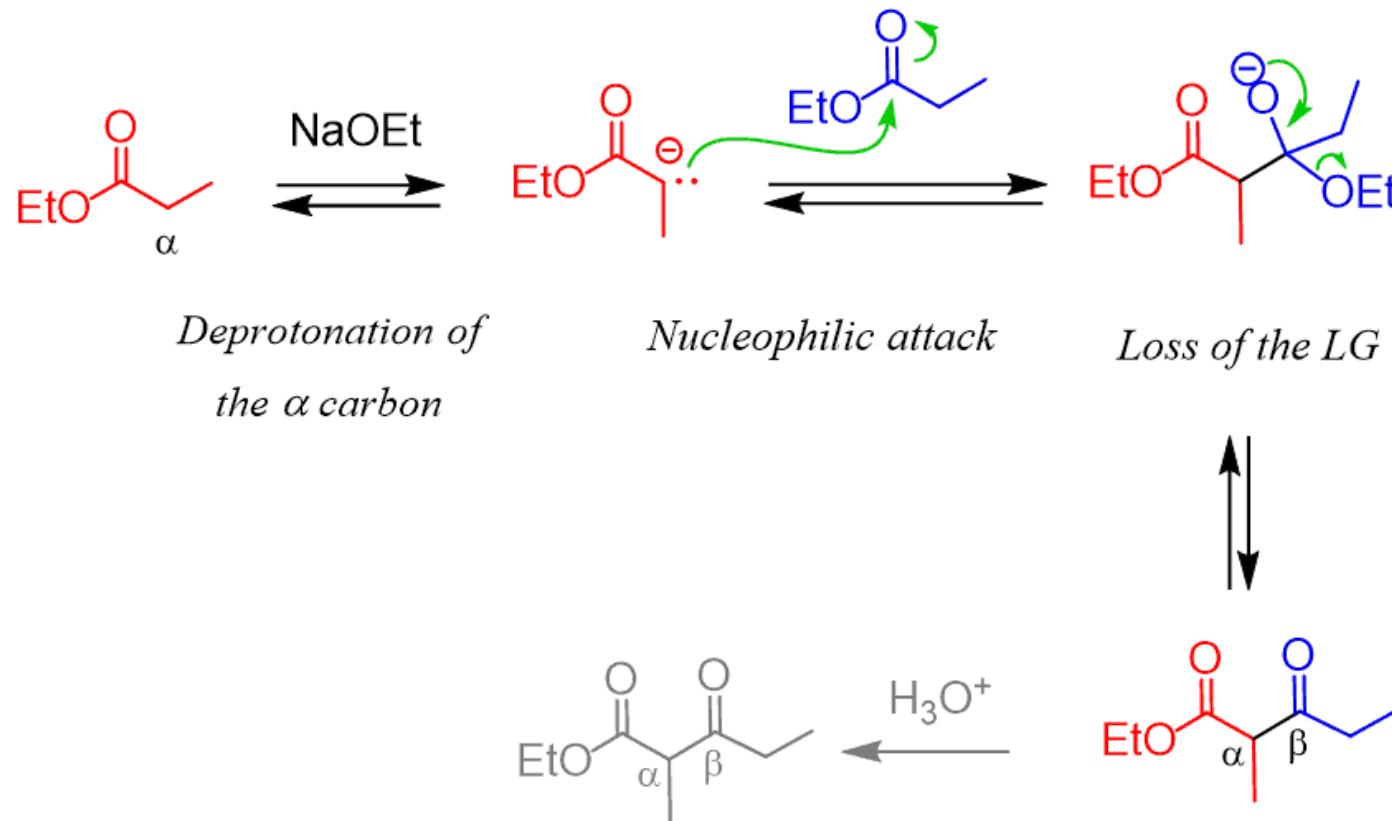
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Claisen Condensation Reaction

- reaction of an ester having an α -hydrogen with 1 equivalent of base to yield a β -keto ester



The Mechanism of Claisen Condensation

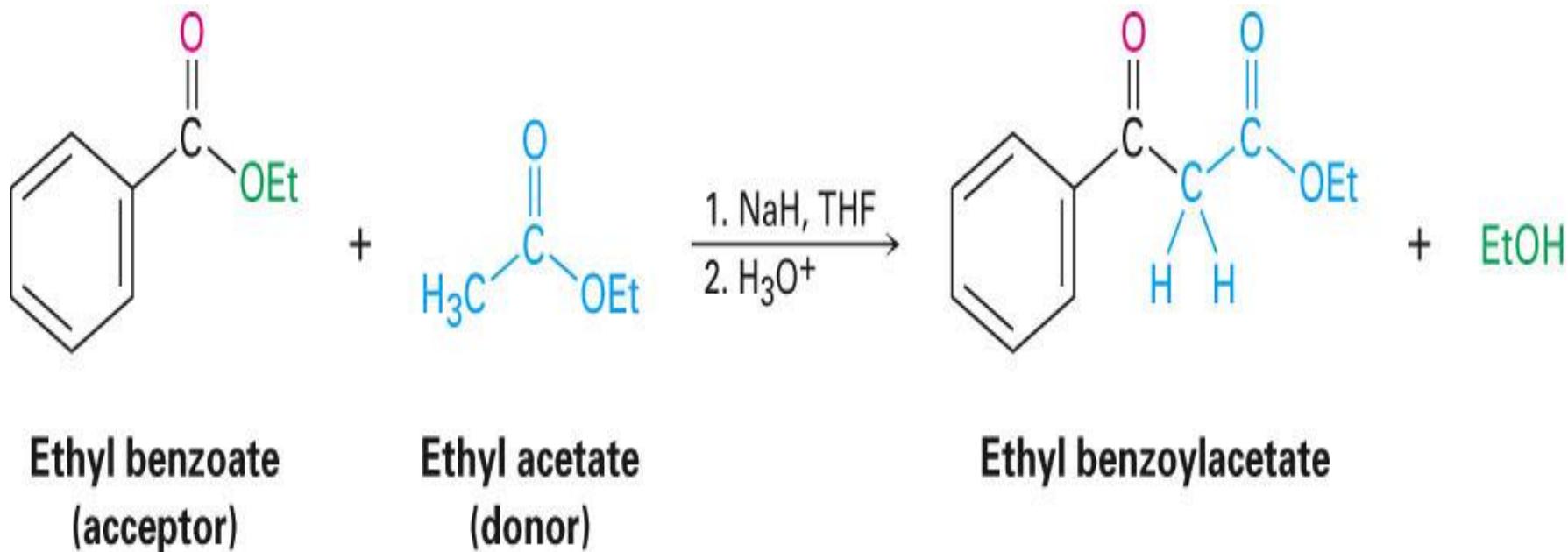


The β -keto ester has a very acidic proton which is removed by the base. Therefore, an acidic workup is needed.

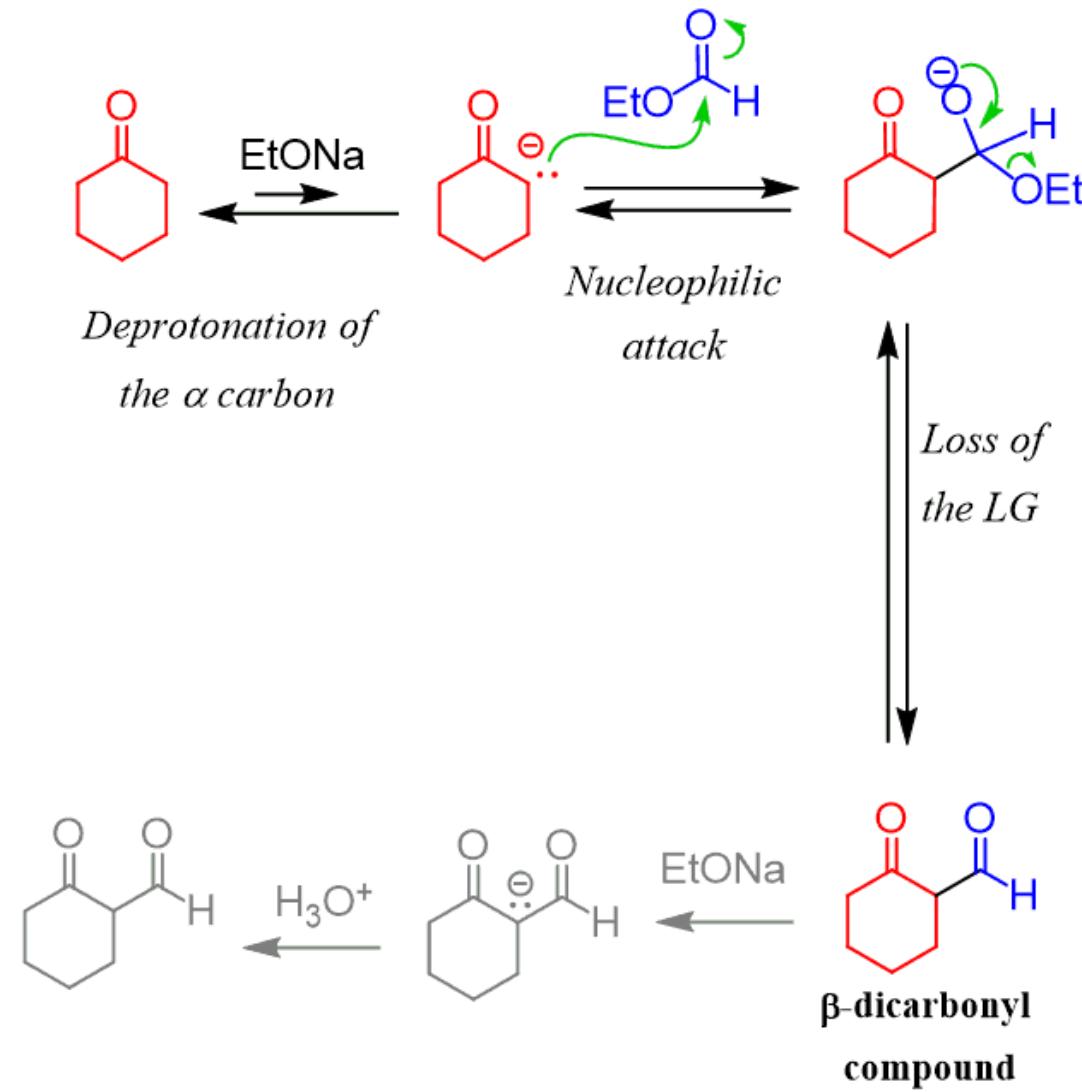
a β -keto ester

Mixed Claisen Condensations

- successful when one of the two esters acts as the electrophilic acceptor in reactions with other ester anions to give mixed β -keto esters

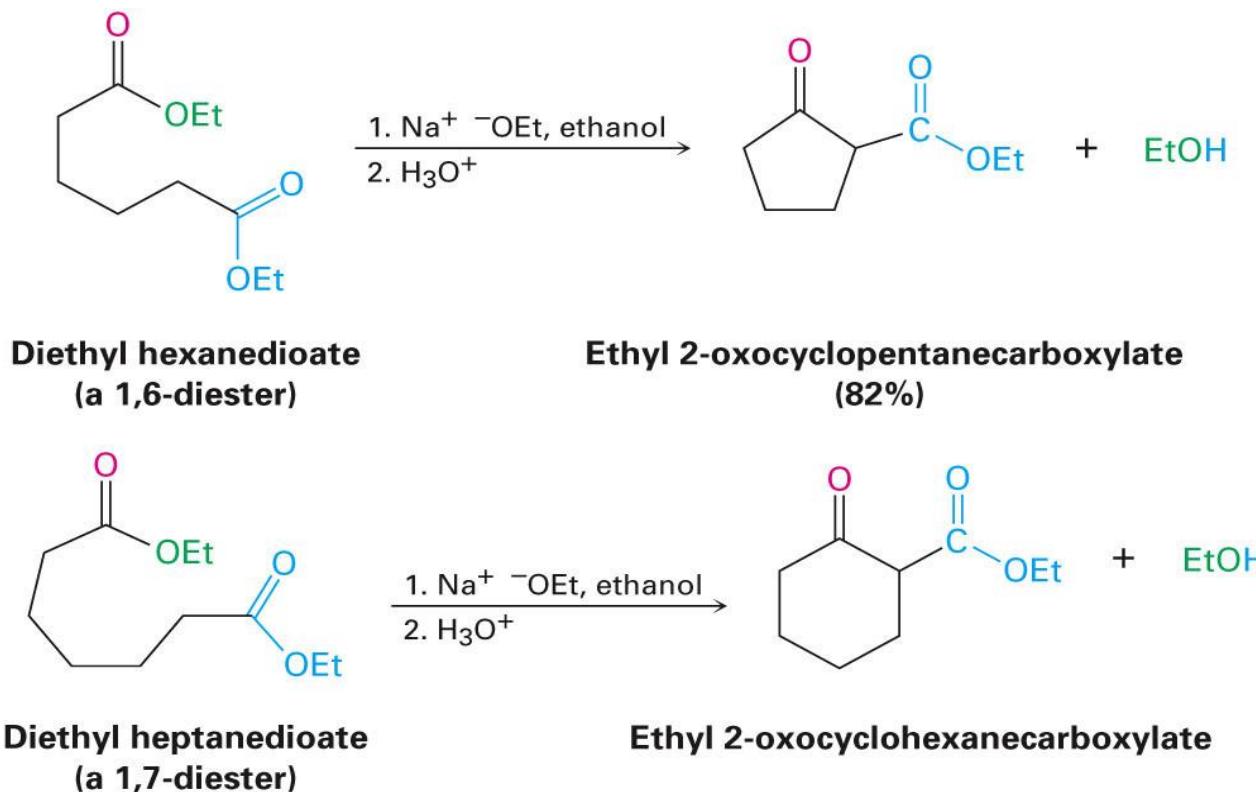


Crossed Claisen Reaction with Ketones using Ethyl Formate

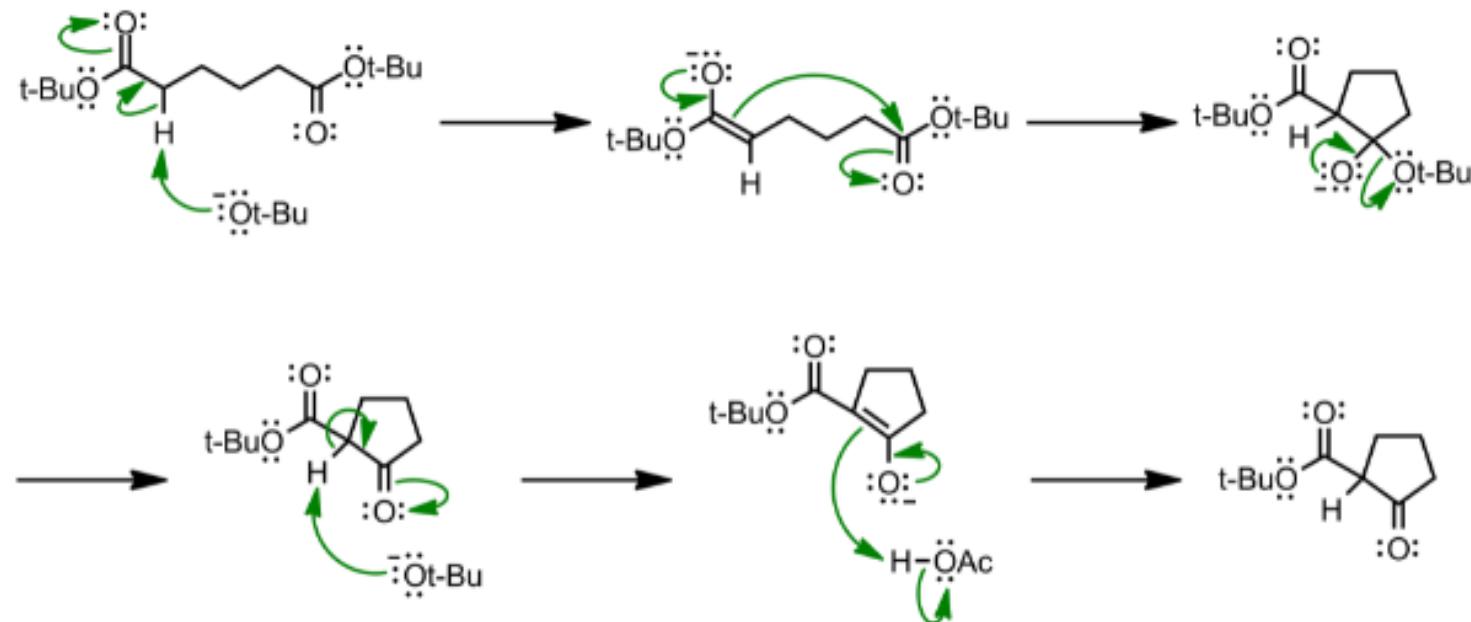


Intramolecular Claisen Condensations: Dieckmann Cyclization

- intramolecular Claisen condensation
- best with **1,6-diesters** (product: 5-membered β -ketoester) and **1,7-diesters** (product: 6-membered β -ketoester)

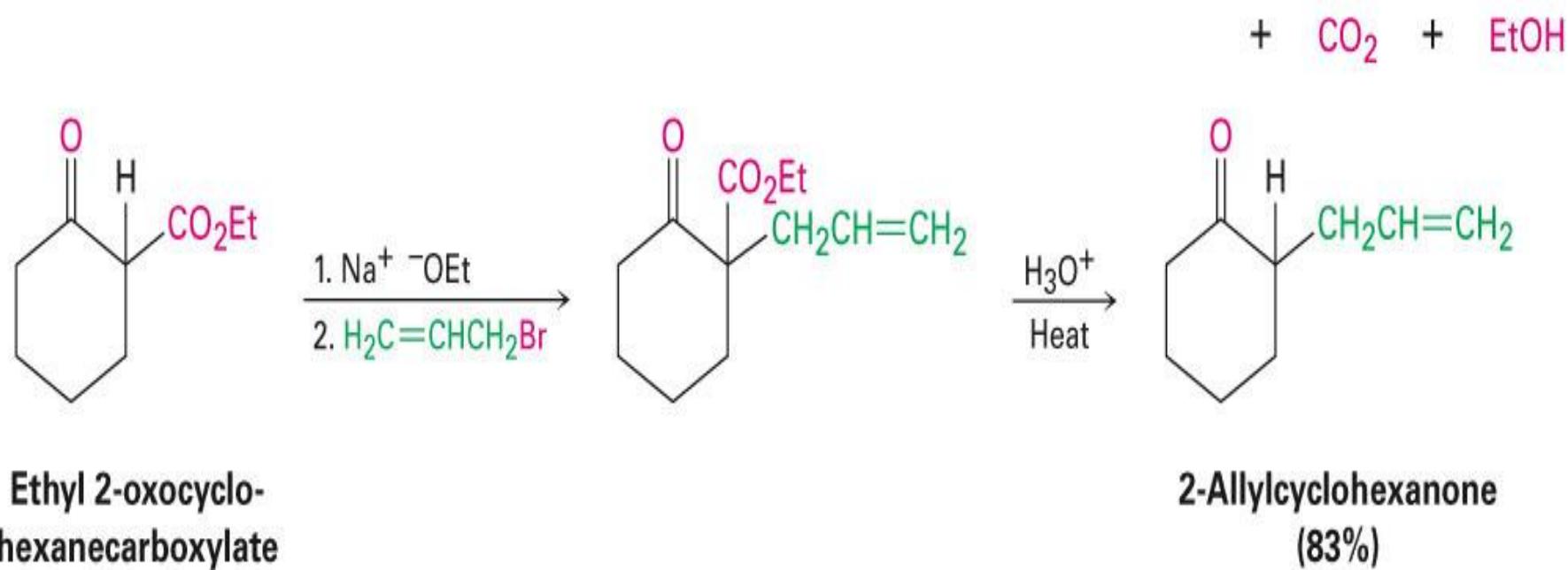


Mechanism of the Dieckmann Condensation



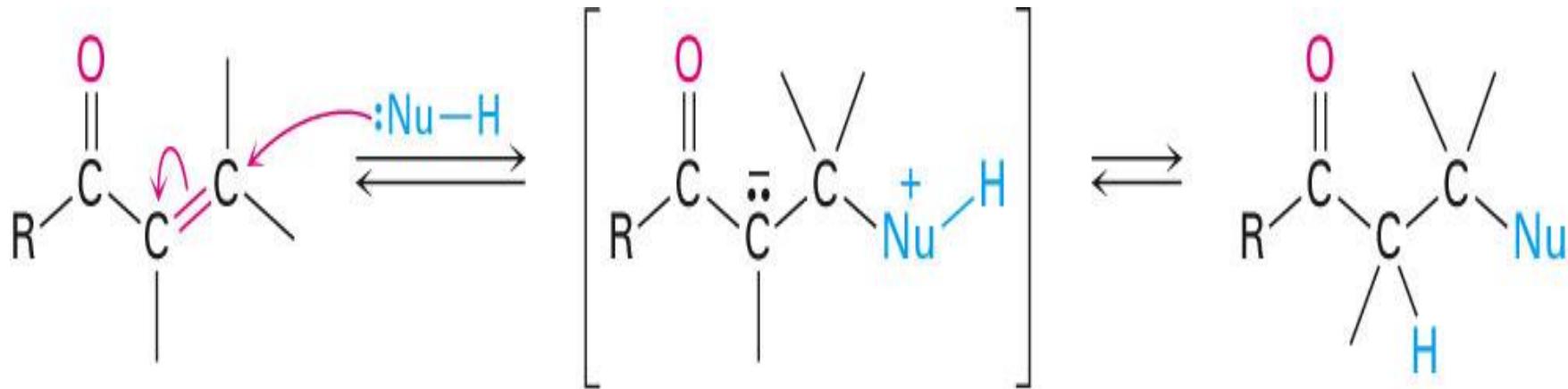
Alkylation of Dieckmann Product

- the cyclic β -keto ester can be further alkylated and decarboxylated as in the acetoacetic ester synthesis

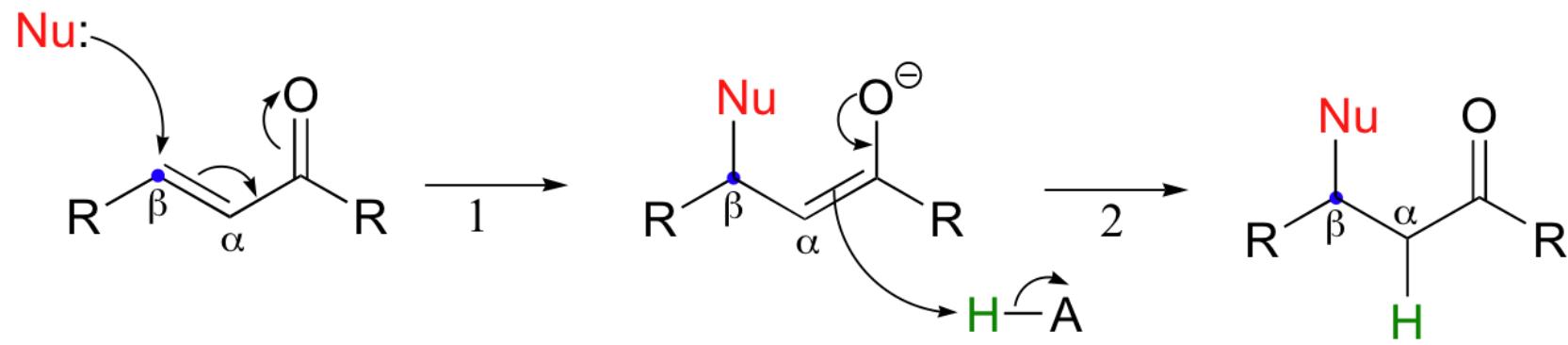


Conjugate Carbonyl Additions: Michael Reaction

- enolates can add as nucleophiles to α,β -unsaturated aldehydes and ketones to give the conjugate addition product

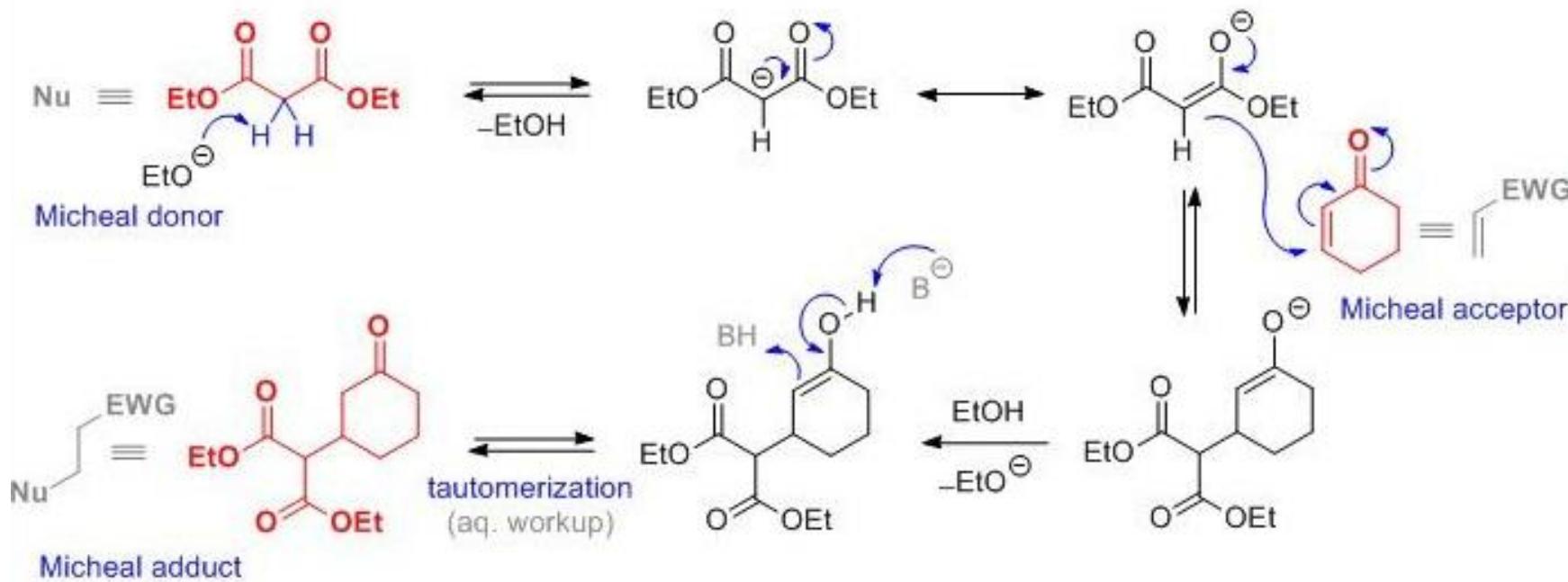


Conjugate addition
product



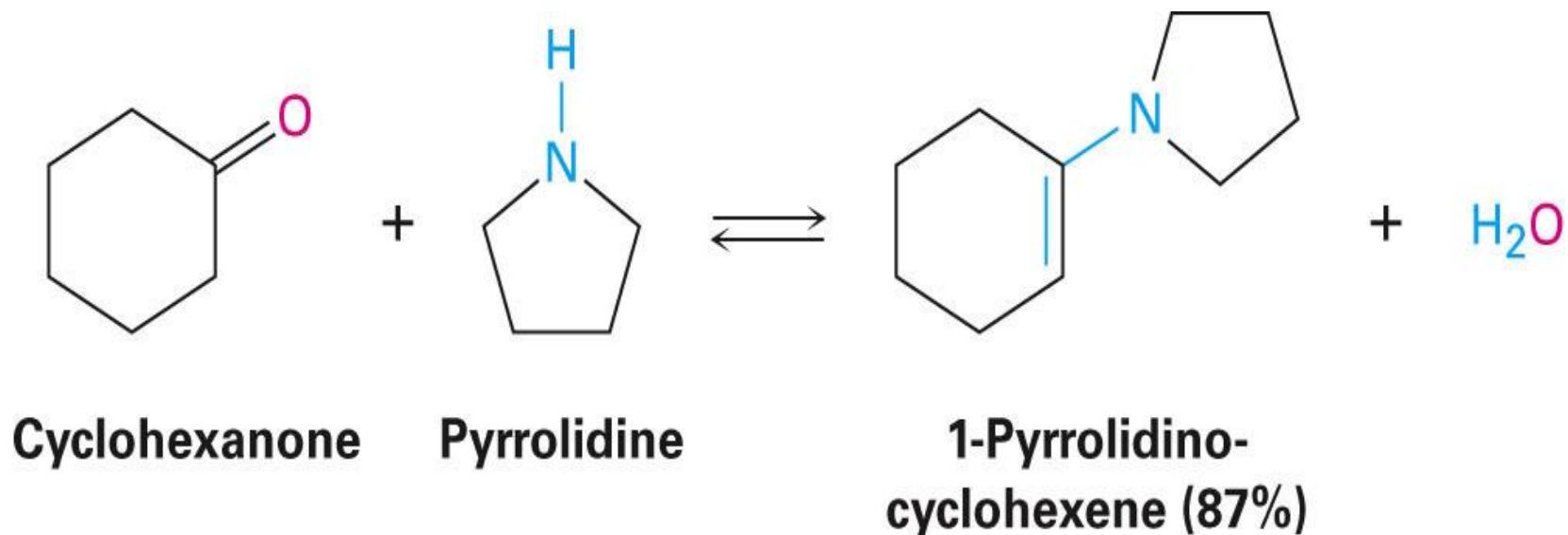
Michael Addition

[1887]

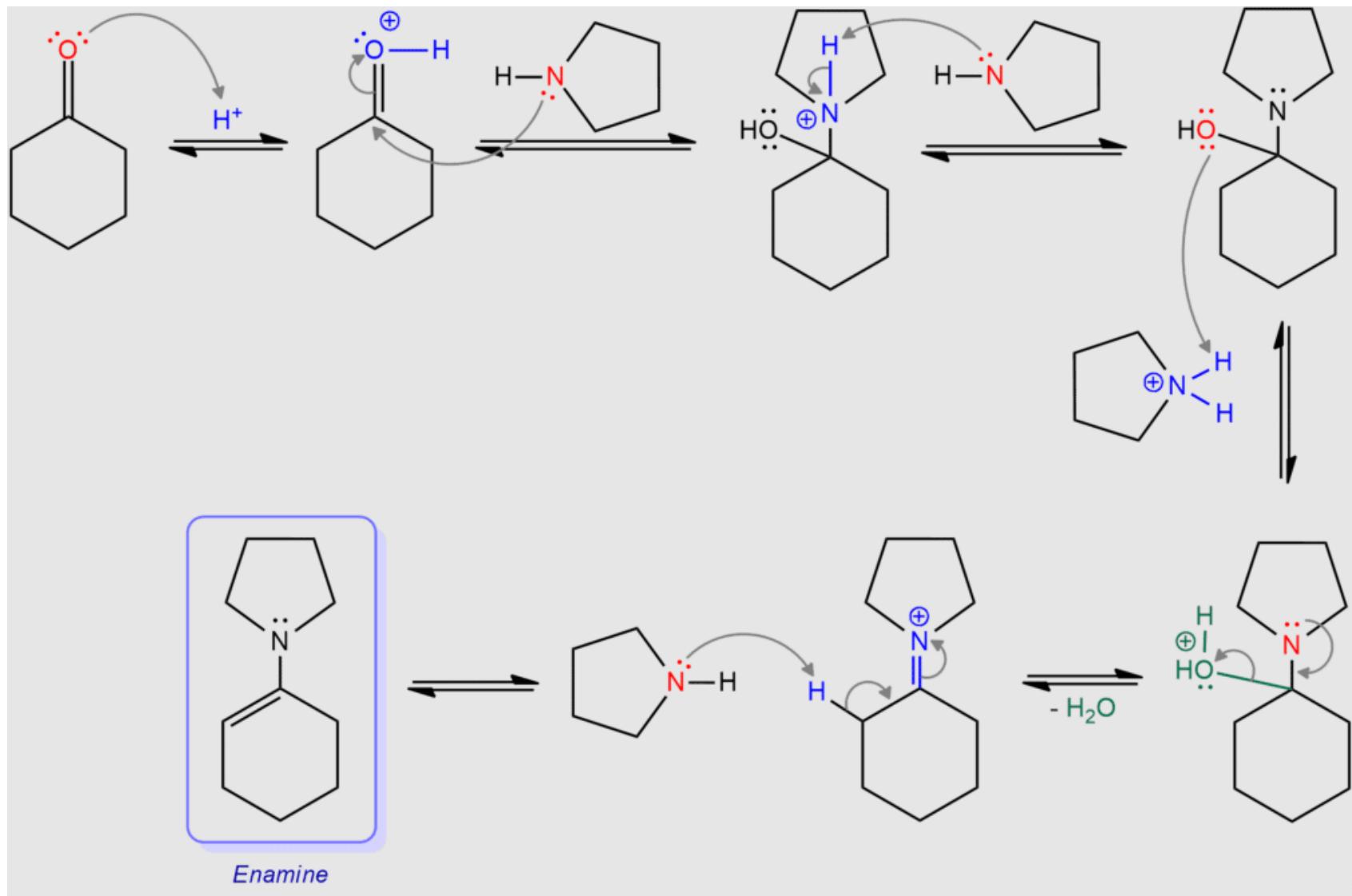


Carbonyl Condensations with Enamines: Stork Reaction

- enamines are equivalent to enolates in their reactions and can be used to accomplish the **transformations** under **milder conditions**
- enamines are prepared from **ketone** and **secondary amine**



Stork Reaction Mechanism

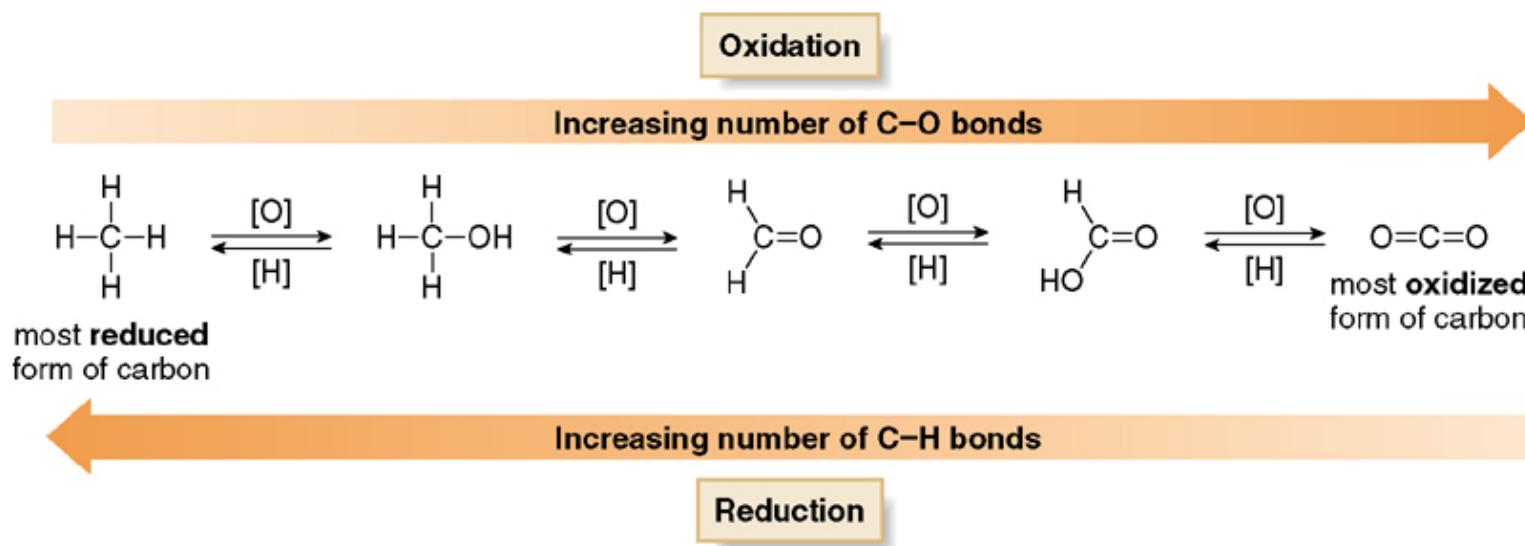


CHAPTER FOUR

REDOX REACTIONS

Oxidation and Reduction Reactions

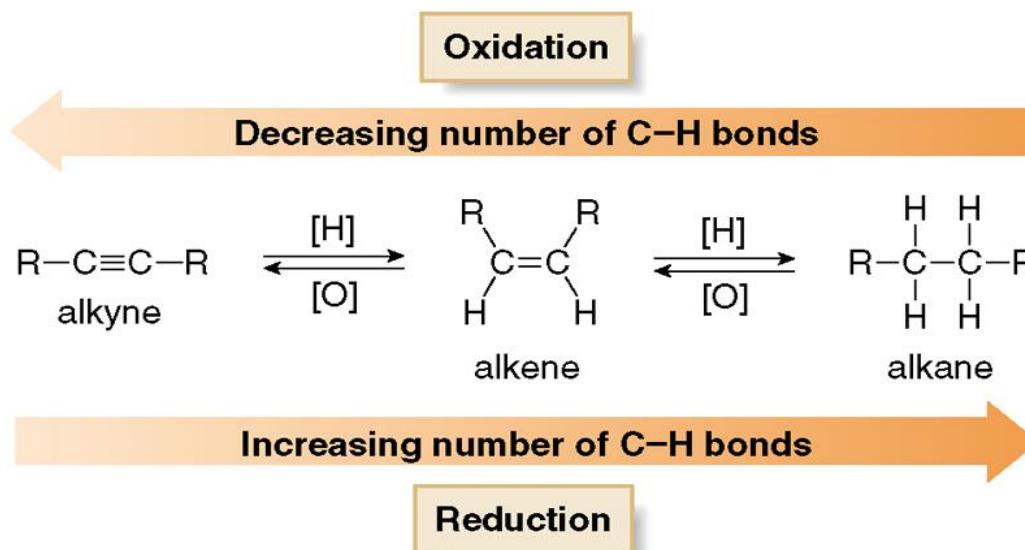
- **oxidation** results in an **increase** in the number of C—O bonds or a **decrease** in the number of C—H bonds, however,
- **reduction** results in a **decrease** in the number of C—O bonds or an **increase** in the number of C—H bonds



RedOx Reactions

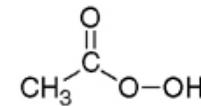
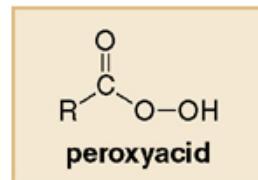
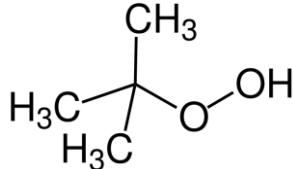
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- sometimes **two carbon** atoms are involved in a **single oxidation or reduction reaction**, and the **net change** in the number of C—H or C—Z bonds at both atoms **must be considered**
 - conversion of an **alkyne** to an **alkene**, or an **alkene** to an **alkane** are examples of **reduction** because each process **adds** two new C—H bonds to the starting material

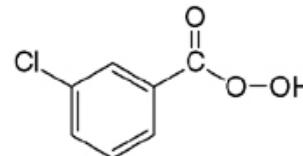


Oxidizing Agents

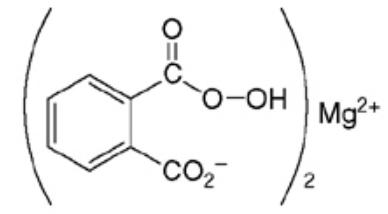
- two main categories of **oxidizing agents**:
 - ✓ reagents that contain an **oxygen-oxygen** bond
 - ✓ reagents that contain **metal-oxygen** bonds
- oxidizing agents containing an **O-O** bond include O_2 , O_3 (ozone), H_2O_2 (hydrogen peroxide), $(\text{CH}_3)_3\text{COOH}$ (*tert*-butyl hydroperoxide), and peroxyacids
- peroxyacids (or peracids) have the general formula RCO_3H .



peroxyacetic acid



meta-chloroperoxybenzoic acid
mCPBA

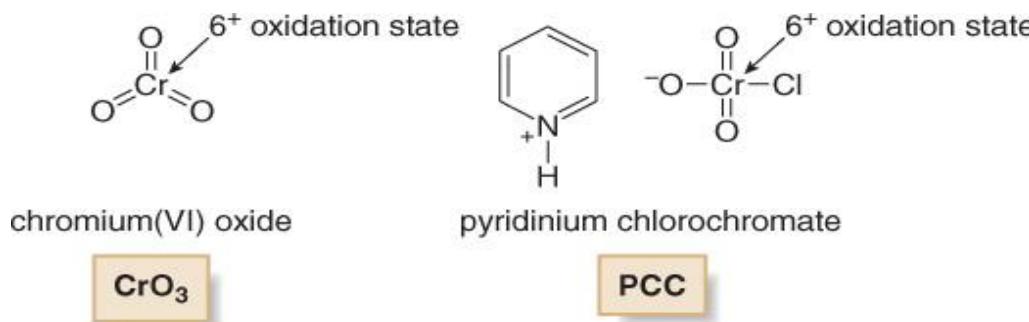


magnesium monoperoxyphthalate
MMPP

Oxidizing Agents

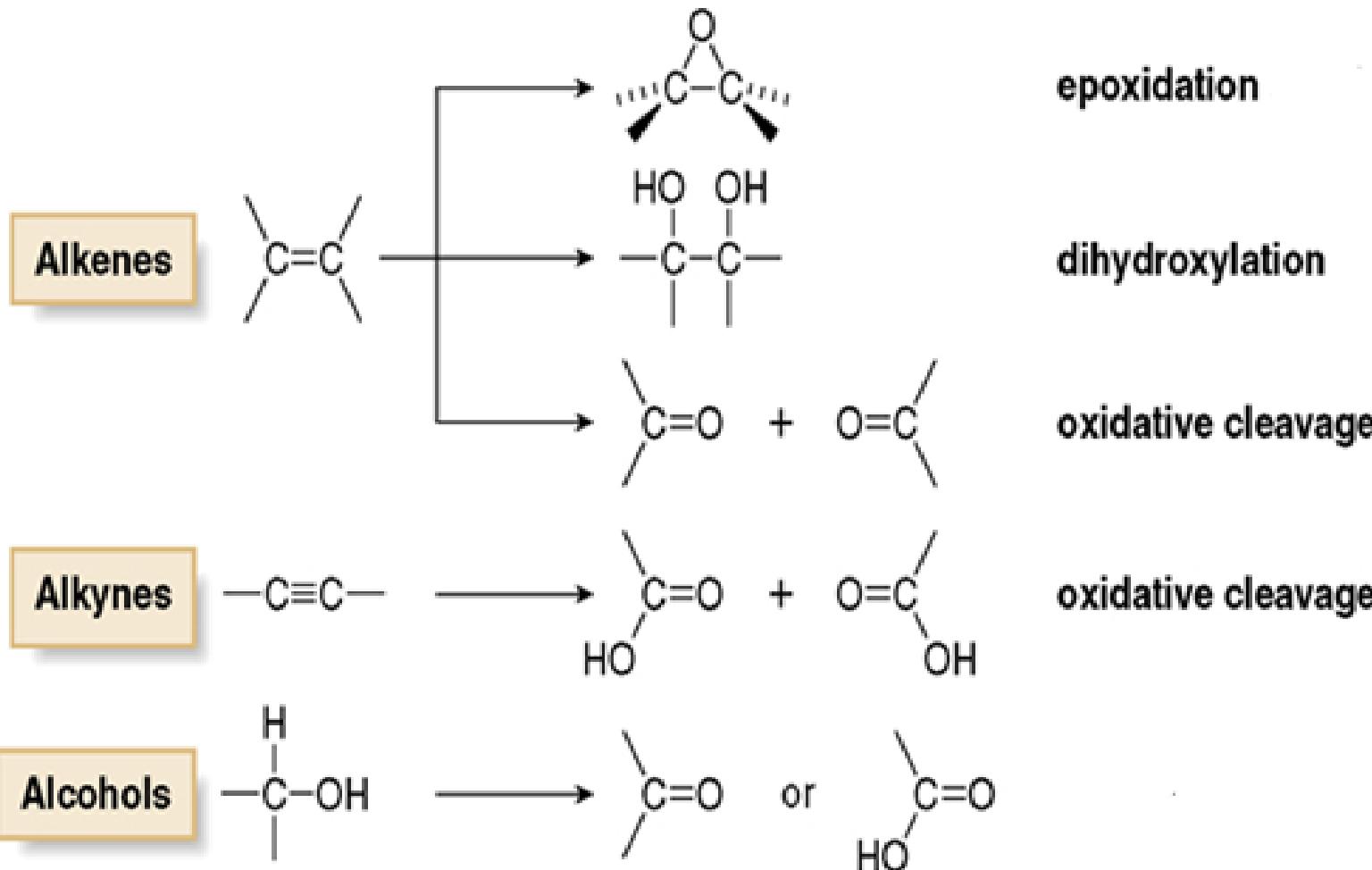
... Cont'd

- the most common oxidizing agents with **metal-oxygen** bonds contain either **Cr⁶⁺** (six Cr—O bonds) or **Mn⁷⁺** (seven Mn—O bonds)
- common Cr⁶⁺ reagents include **CrO₃** and **sodium or potassium dichromate** (**Na₂Cr₂O₇** and **K₂Cr₂O₇**)
- Pyridinium chlorochromate (PCC) is a more selective Cr⁶⁺ oxidant.



- the most common Mn⁷⁺ reagent is **KMnO₄**
- other metal containing oxidizing agents include **OsO₄** (osmium tetroxide) and **Ag₂O** [silver(I) oxide]

■ some of oxidation reactions



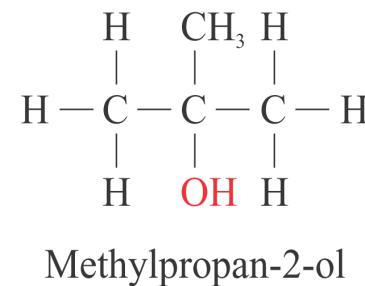
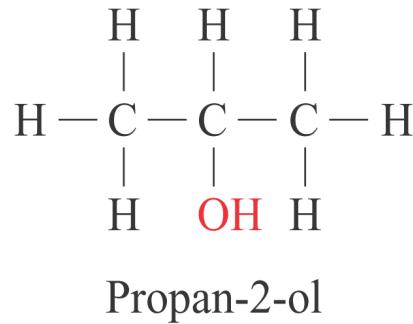
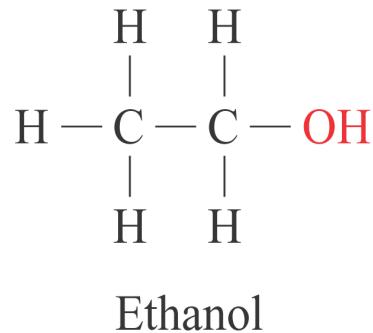
Oxidation of Alcohols

- group of compounds with **one or more hydroxyl groups (-OH)** attached to an alkyl group
- **monohydric alcohols**, having only **one hydroxyl group** their general formula is $C_nH_{2n+1}OH$

Oxidation of Alcohols

...Cont'd

Examples of alcohols

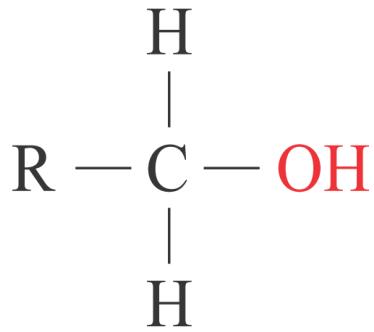


- depending on the **number of alkyl groups** attached to the **carbon** to which the hydroxyl group is linked, alcohols can be classified as **primary**, **secondary** and **tertiary alcohols**

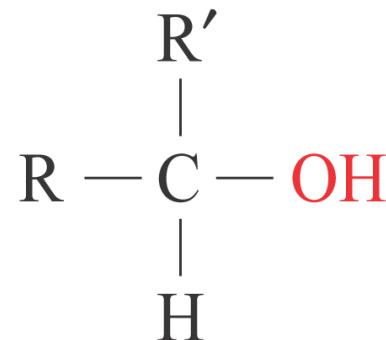
Oxidation of alcohols

...Cont'd

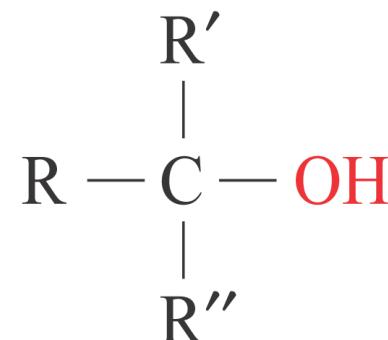
- **Differentiating** an alcohol as a **1° alcohol**, a **2° alcohol** or a **3° alcohol** is extremely important because **oxidation** of these alcohols will give **different products**



Primary alcohol



Secondary alcohol



Tertiary alcohol

Oxidation of Alcohols

...Cont'd

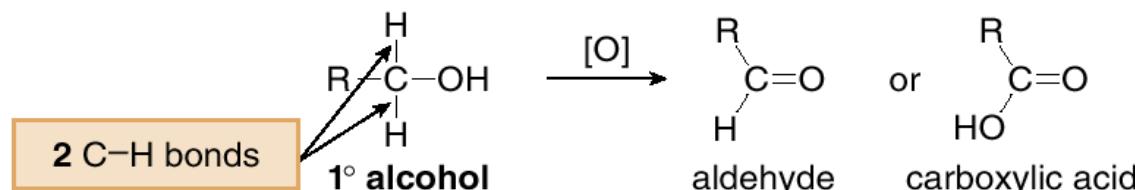
Primary alcohols	Secondary alcohols	Tertiary alcohols
<ul style="list-style-type: none">■ Can be oxidized to aldehydes■ Further oxidized to carboxylic acids	<ul style="list-style-type: none">■ Can be oxidized to ketones■ Cannot be further oxidized to carboxylic acids	<ul style="list-style-type: none">■ generally resistant to oxidation

Oxidation of alcohols

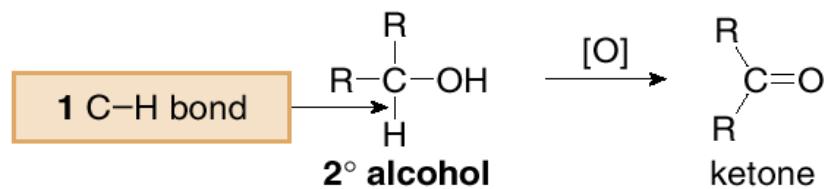
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- alcohols are oxidized to a variety of carbonyl compounds.

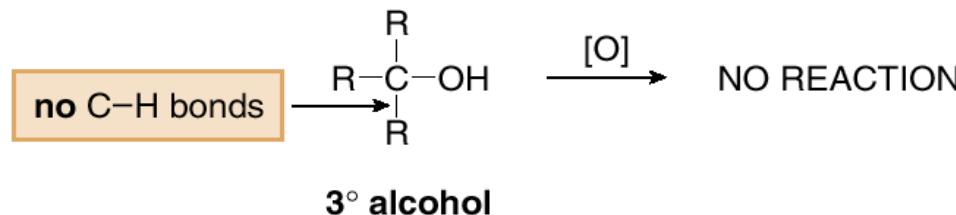
- 1° Alcohols are oxidized to either **aldehydes** or **carboxylic acids** by replacing either one or two C–H bonds by C–O bonds.



- 2° Alcohols are oxidized to **ketones** by replacing the one C–H bond by a C–O bond.



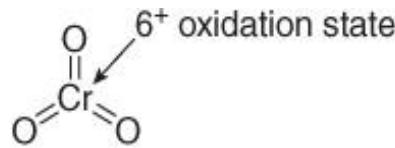
- 3° Alcohols have no H atoms on the carbon with the OH group, so they are not easily oxidized.



Oxidation of alcohols

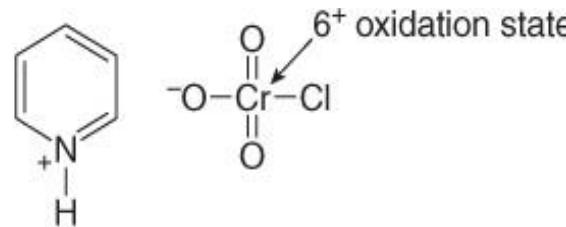
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- oxidation of **alcohols to carbonyl** compounds is typically carried out with **Cr⁶⁺ oxidants**, which are reduced to **Cr³⁺ products**
- **CrO₃**, **Na₂Cr₂O₇**, and **K₂Cr₂O₇** are **strong** and **non-selective** oxidants used in **aqueous acid** ($H_2SO_4 + H_2O$)
- PCC is **soluble** in **CH₂Cl₂** (dichloromethane) and can be used **without strong acid** present, making it a **more selective** and **milder oxidant**



chromium(VI) oxide

CrO₃

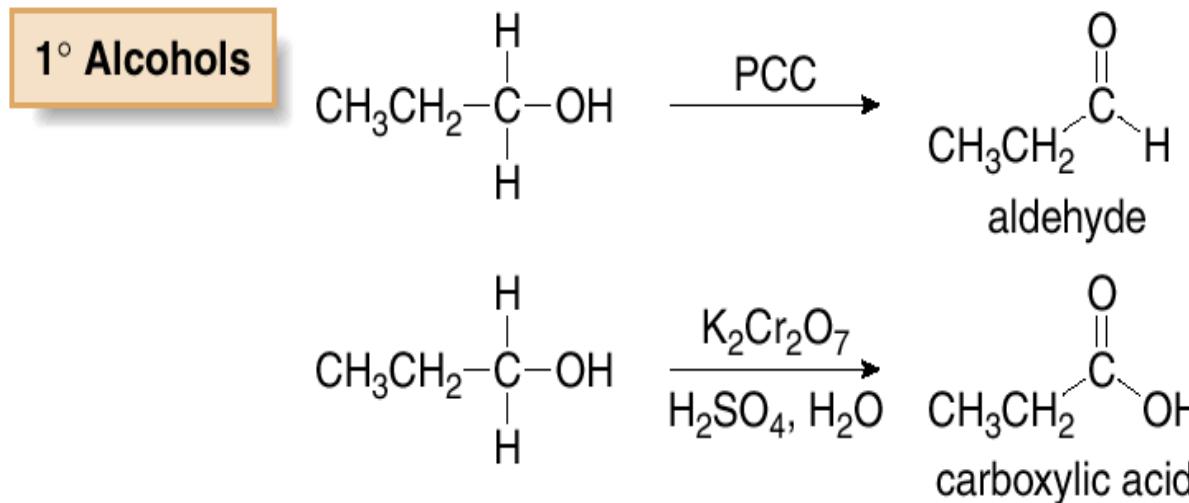


pyridinium chlorochromate

PCC

Oxidation of Primary Alcohols

- primary alcohols are **oxidized** to either **aldehydes** or **carboxylic acids**, depending on the reagent used
 - 1° Alcohols are oxidized to aldehydes (RCHO) under mild reaction conditions—using PCC in CH_2Cl_2 .
 - 1° Alcohols are oxidized to carboxylic acids (RCOOH) under harsher reaction conditions: $\text{Na}_2\text{Cr}_2\text{O}_7$, $\text{K}_2\text{Cr}_2\text{O}_7$, or CrO_3 in the presence of H_2O and H_2SO_4 .

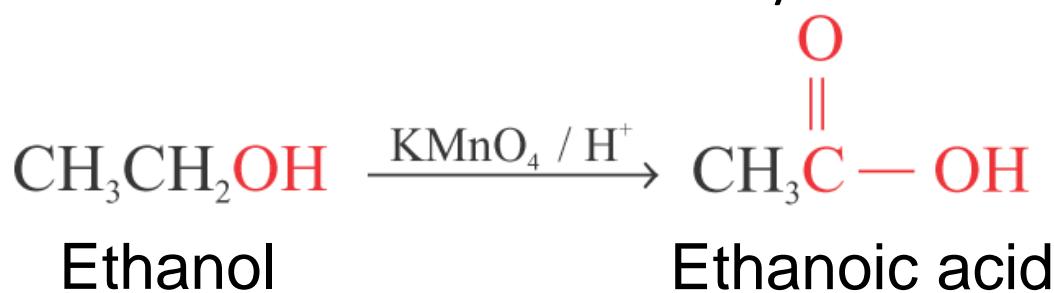


Oxidation of primary alcohols

...Cont'd

- if acidified KMnO_4 is used the **oxidation** of the alcohols will **not stop** at the **aldehydes** but go directly to the **carboxylic acids**, as the oxidation of alcohols is **difficult to stop** at the **aldehyde** stage as **aldehydes** formed act as **reducing agent**
 - one way of solving this problem is **removing the aldehyde** as soon as it is formed by **distilling off** the aldehydes formed from the reaction mixture

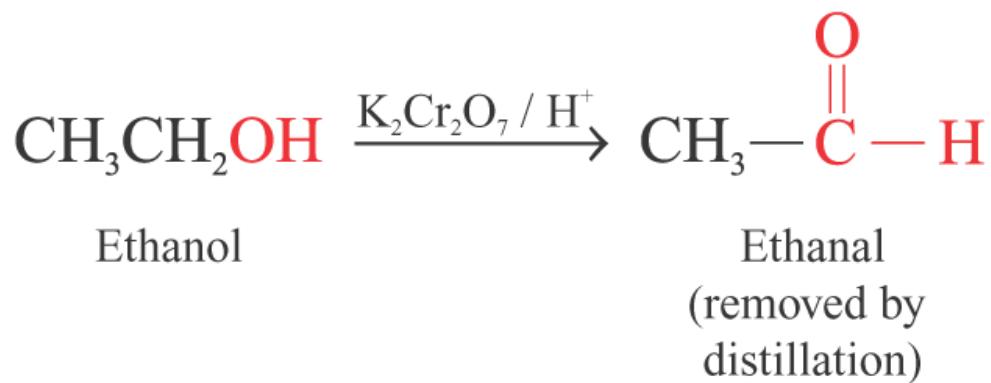
Example: ethanol can be oxidized to ethanoic acid by acidified KMnO_4



Oxidation of primary alcohols

...Cont'd

- **ethanal** can be synthesized from **ethanol** using acidified $\text{K}_2\text{Cr}_2\text{O}_7$ where ethanal is **removed** by **distillation**



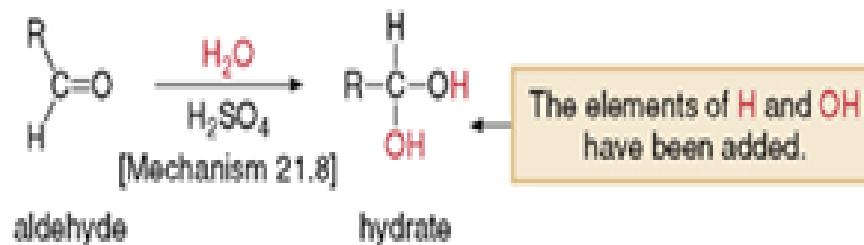
Oxidation of primary alcohols to carboxylic acid

Part [1] Oxidation of a 1° alcohol to an aldehyde



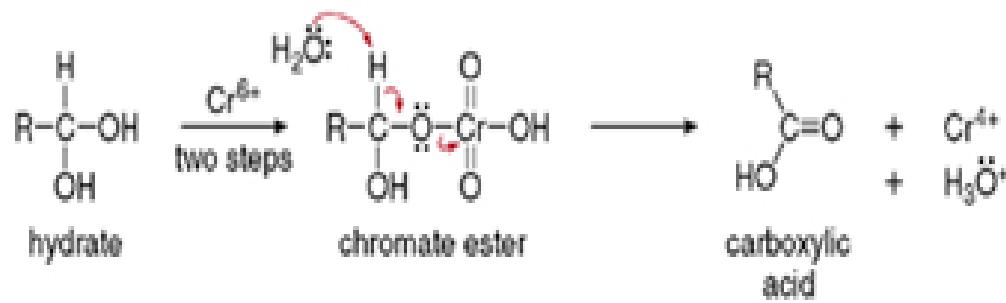
- Oxidation of a 1° alcohol to an aldehyde occurs by the three-step mechanism detailed in Mechanism 12.5.

Part [2] Addition of H_2O to form a hydrate



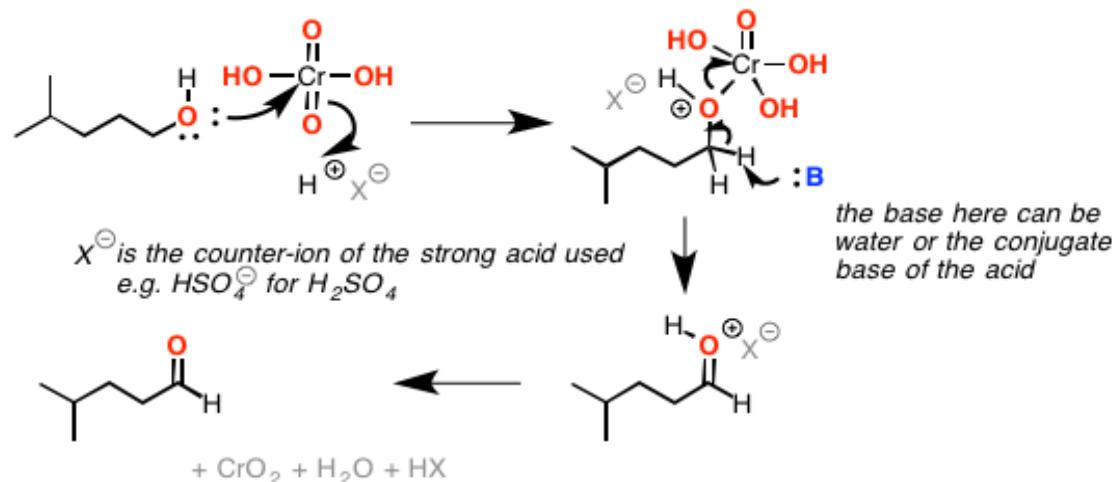
- The aldehyde reacts with H_2O to form a hydrate, a compound with two OH groups on the same carbon atom. Hydrates are discussed in greater detail in Section 21.13.

Part [3] Oxidation of the hydrate to a carboxylic acid



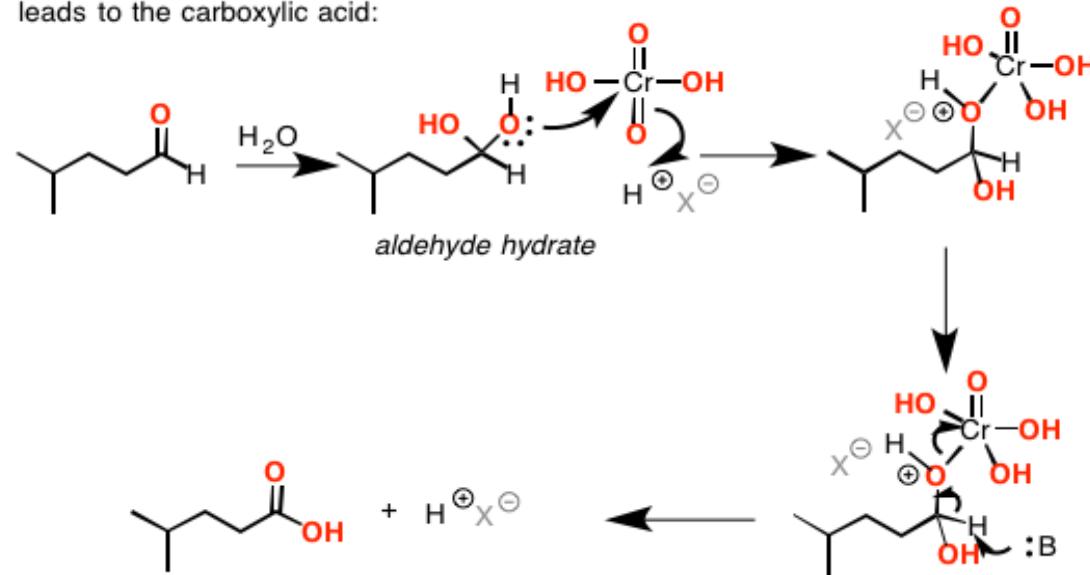
- The C–H bond of the hydrate is then oxidized with the Cr^{6+} reagent, following Mechanism 12.5. Because the hydrate contains two OH groups, the product of oxidation is a carboxylic acid.

➤ Oxidation of primary Alcohols with acidified potassium chromate

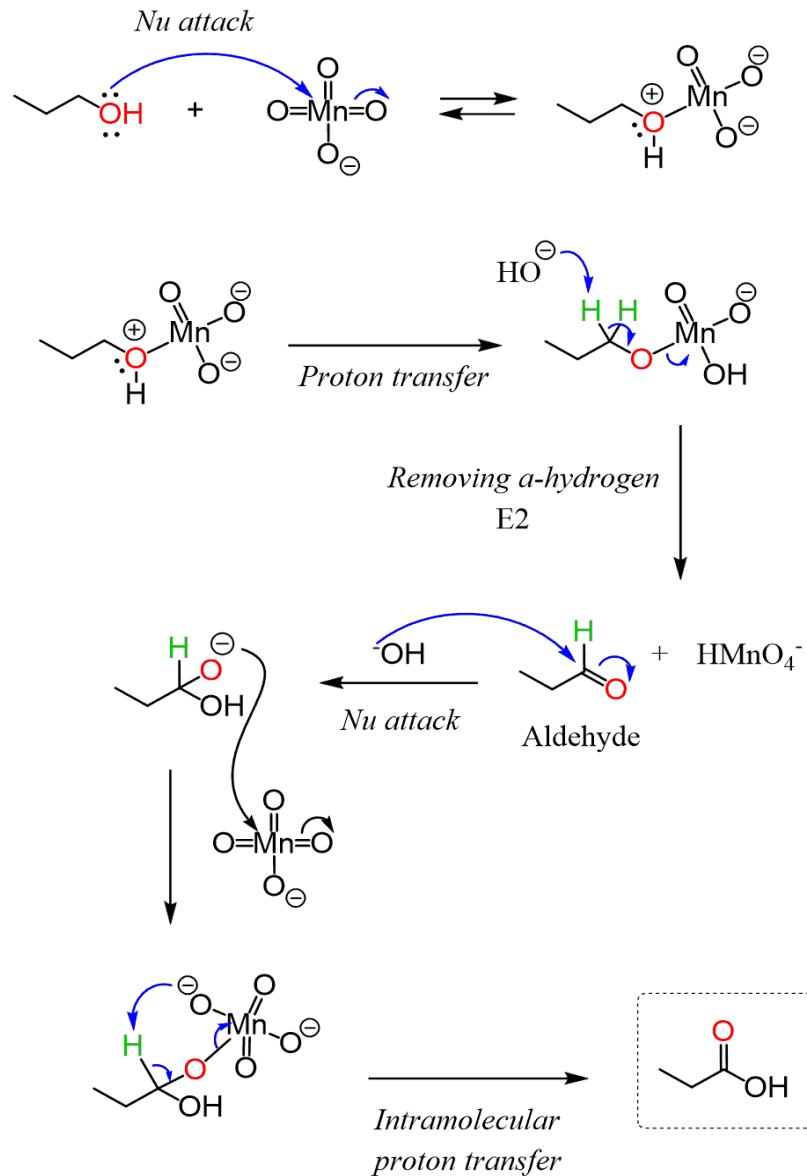


Oxidation to carboxylic acids

Addition of a molecule of water to the aldehyde followed by a second oxidation leads to the carboxylic acid:



➤ Oxidation of primary Alcohols with acidified potassium permanganate



Oxidation of Primary Alcohols to Carboxylic Acids

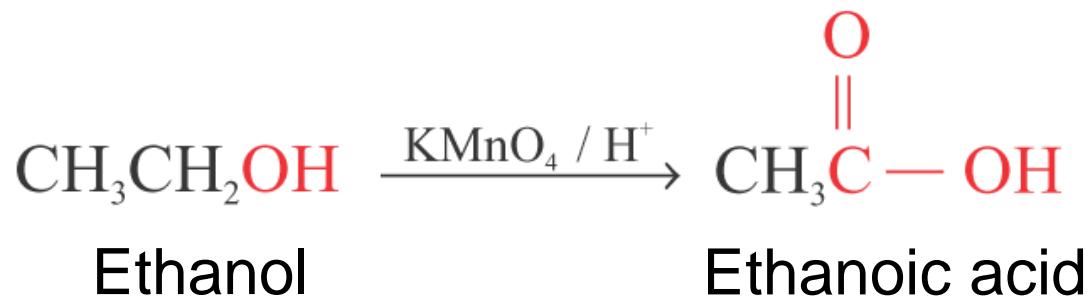
- the oxidation of ethanol by acidified K_2Cr_2O the basis of the **breathalyzer** used by the **police** to rapidly estimate the **ethanol content** of the breath of suspected **drunken** drivers



Demonstration of the use of the breathalyzer

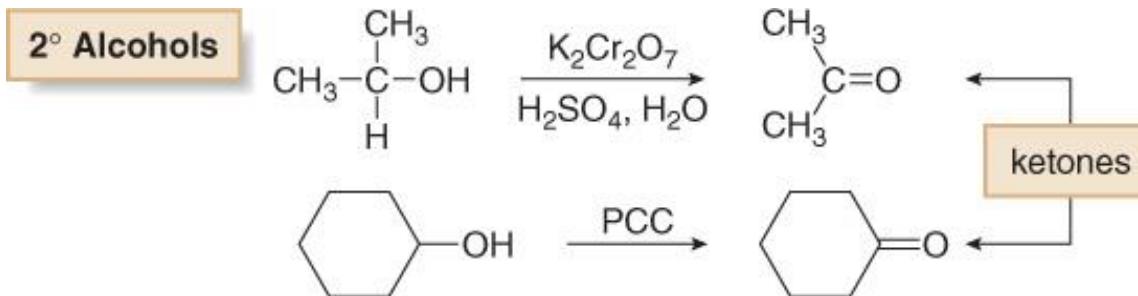
Oxidation of Primary Alcohols to Carboxylic Acids

- when the drunken driver blows into the bag the ethanol molecules reduce the **orange** $\text{Cr}_2\text{O}_7^{2-}$ ions to **green** Cr^{3+} ions
 - if **more than a certain amount** of the **orange** crystal changes **color**, the driver is likely to be “**over the limit**”



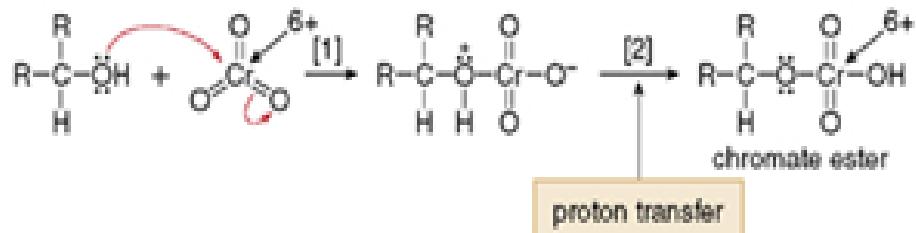
Oxidation of 2° Alcohols

- any of the Cr⁶⁺ oxidants can effectively oxidize 2° alcohols to ketones



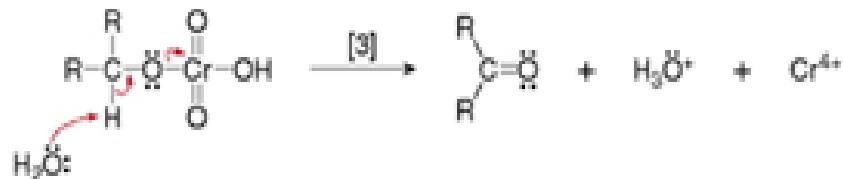
Oxidation of an alcohol with CrO₃

Steps [1] and [2] Formation of the chromate ester



- Nucleophilic attack of the alcohol on the electrophilic metal followed by proton transfer forms a **chromate ester**. The C–H bond in the starting material (the 2° alcohol) is still present in the chromate ester, so there is no net oxidation in Steps [1] and [2].

Step [3] Removal of a proton to form the carbonyl group



- In Step [3], a base (H₂O or a molecule of the starting alcohol) removes a proton, with the electron pair in the C–H bond forming the new π bond of the C=O. **Oxidation at carbon occurs in this step** because the number of C–H bonds decreases and the number of C–O bonds increases.

Oxidation of Tertiary Alcohols

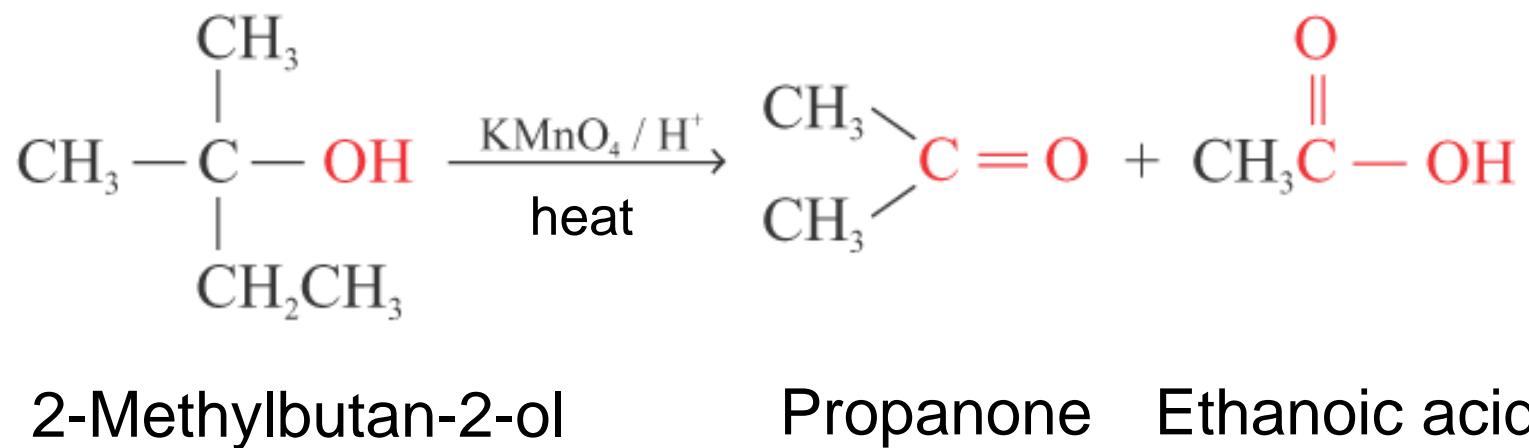
- tertiary alcohols are **generally resistant to oxidation** unless they are subjected to **severe oxidation conditions**
- any oxidation involving **severe oxidation conditions** would immediately bring up the **cleavage of the strong C - C bonds** in the alcohol molecule

Oxidation of Tertiary Alcohols

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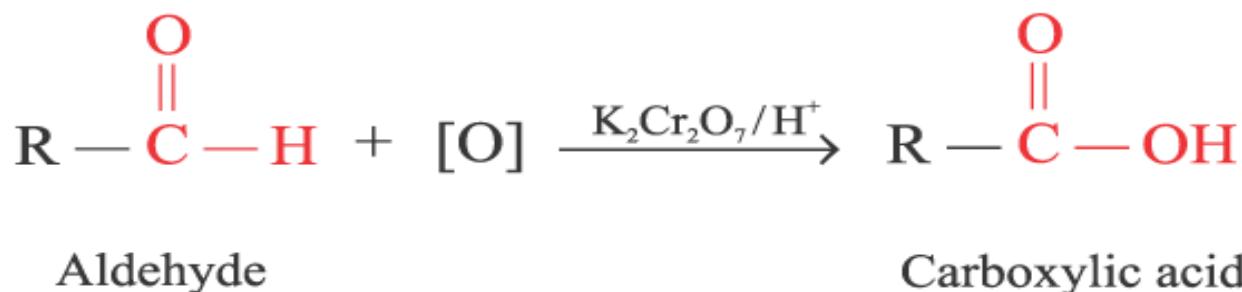
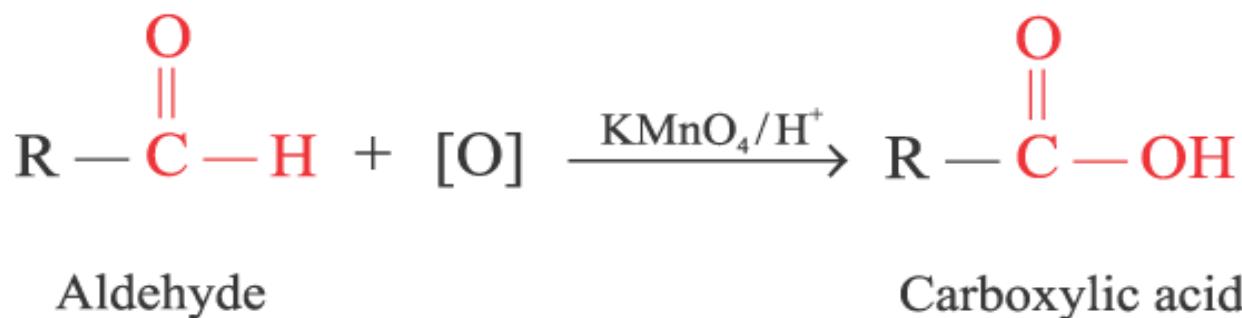
- tertiary alcohols can be oxidized by acidified KMnO_4 give a mixture of ketones and carboxylic acids both with fewer carbon atoms than the original alcohol

Example

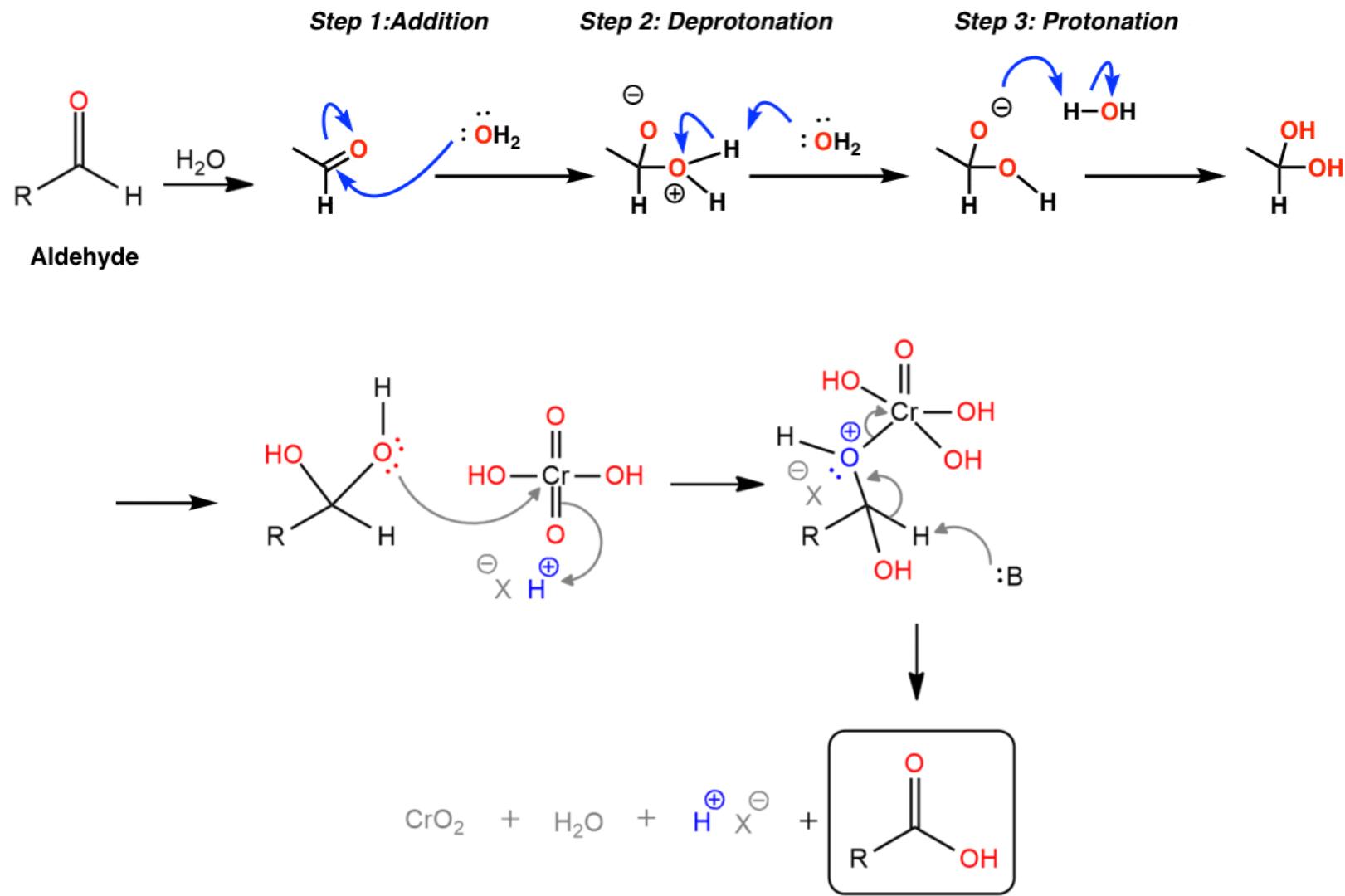


Oxidation of Aldehydes

- aldehydes are readily oxidized by acidified KMnO_4 or $\text{K}_2\text{Cr}_2\text{O}_7$ to form carboxylic acids



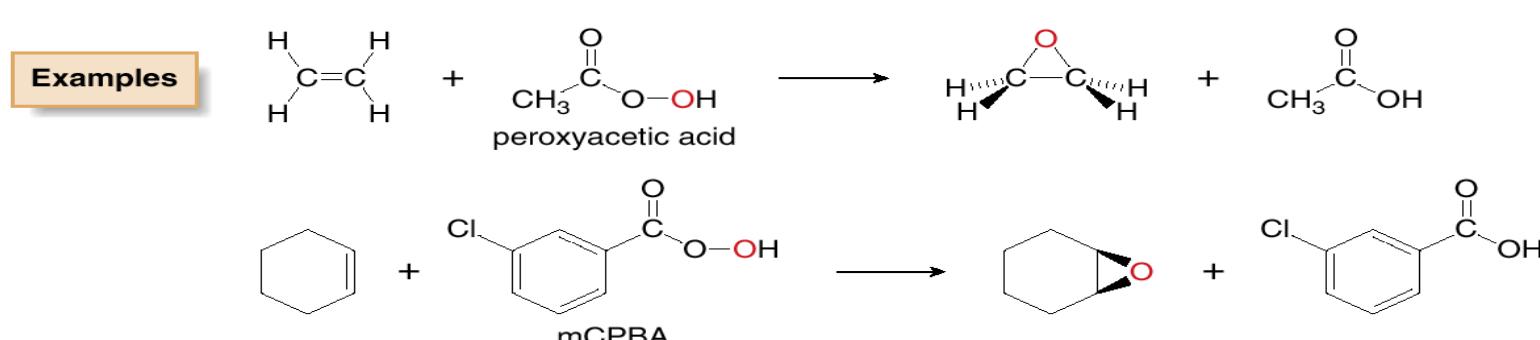
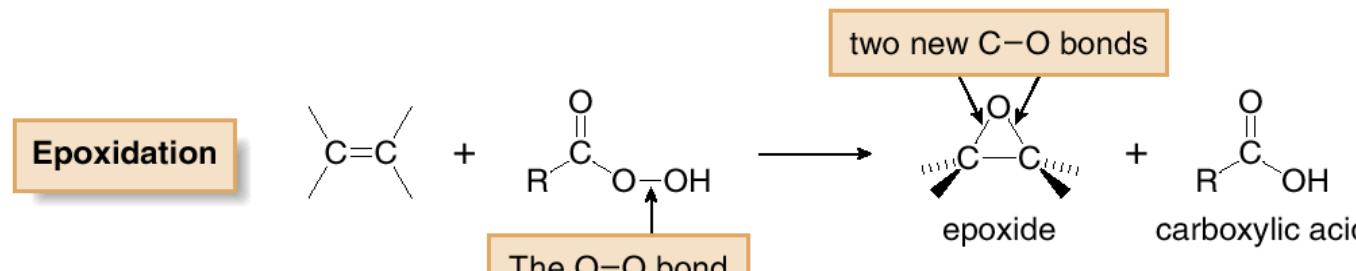
Mechanism of oxidation of aldehydes



Oxidation of Multiple Bonds

Epoxidation

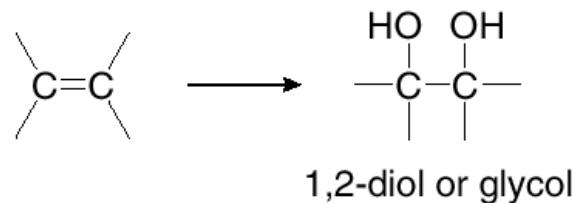
- epoxidation is the addition of a **single oxygen atom** to an **alkene** to **form** an **epoxide** which is typically **carried out** with a **peroxyacid**



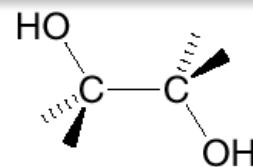
Dihydroxylation

- dihydroxylation is the addition of two hydroxy groups to a double bond, forming a 1,2-diol or glycol
- depending on the reagent, the two new OH groups can be added to the opposite sides (anti addition) or the same side (syn addition) of the double bond

Dihydroxylation—General reaction

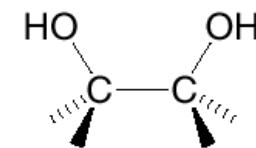


Stereochemistry



anti addition product

2 OH's added on **opposite**
sides of the $\text{C}=\text{C}$

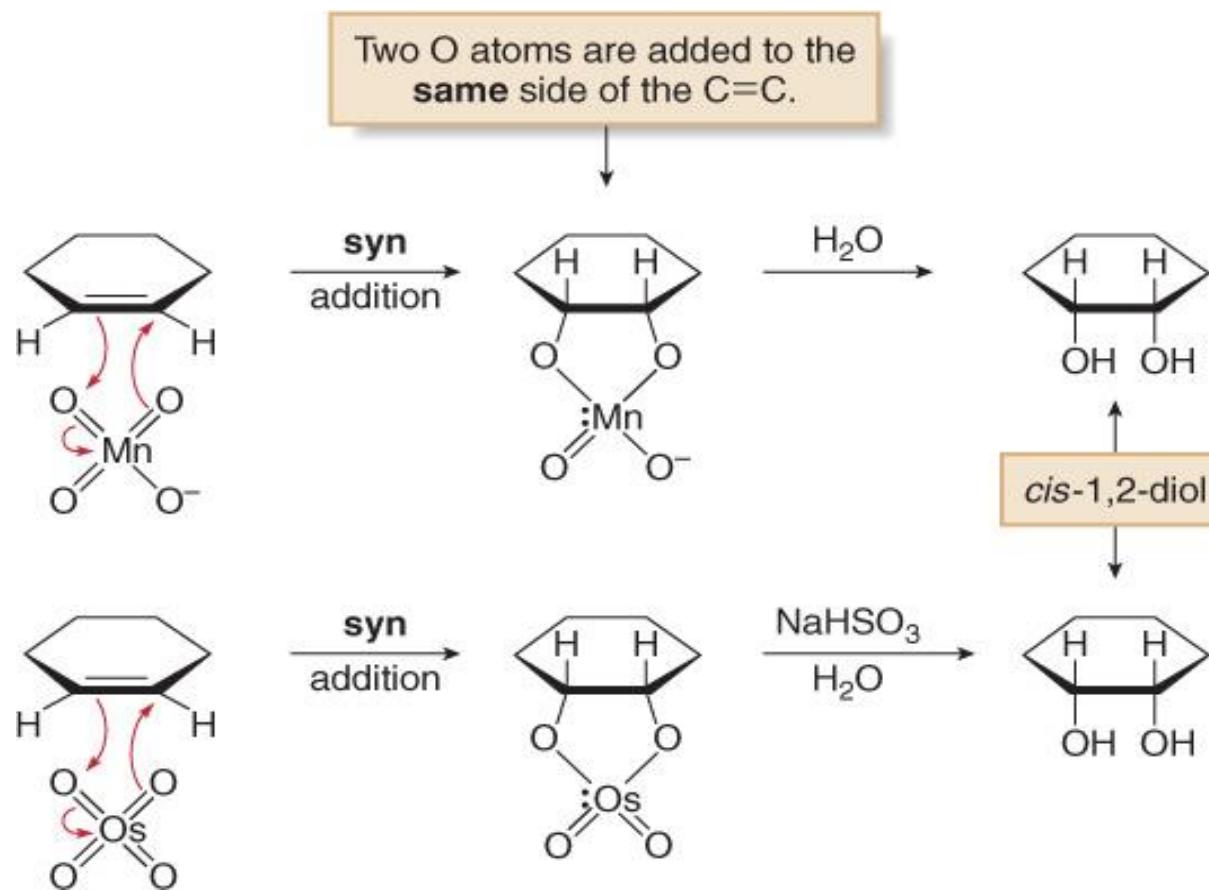


syn addition product

2 OH's added on the
same side of the $\text{C}=\text{C}$

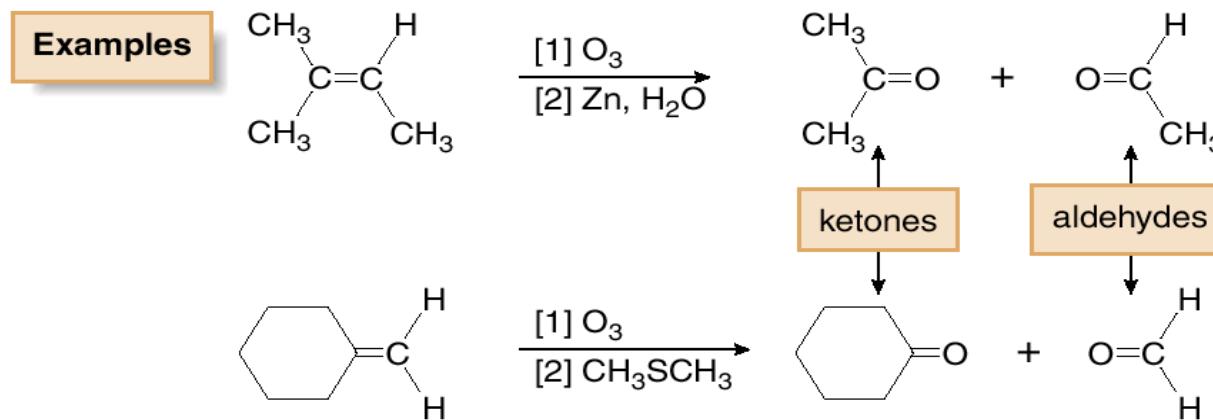
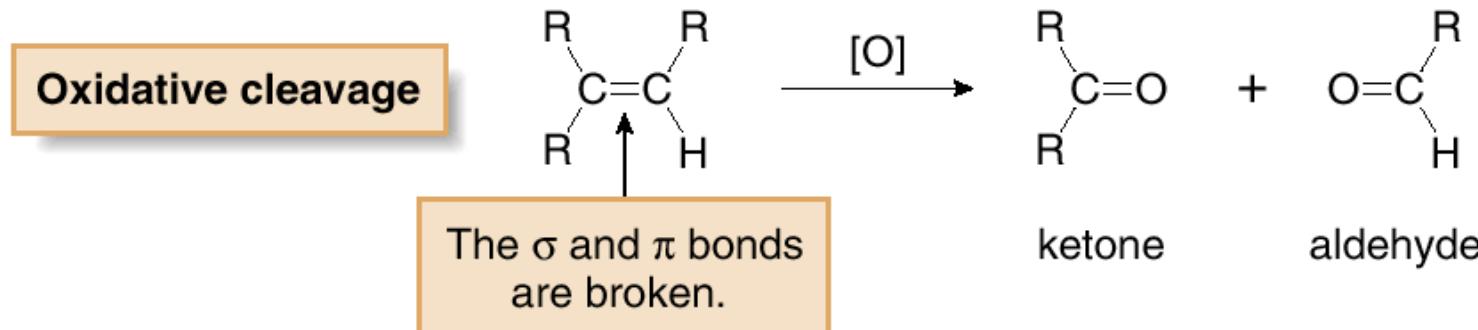
Cont'd...

- each reagent adds two oxygen atoms in a syn fashion
- hydrolysis of the cyclic intermediate cleaves the metal oxygen bonds, forming a **cis-1,2-diol**



Oxidative Cleavage of Alkenes

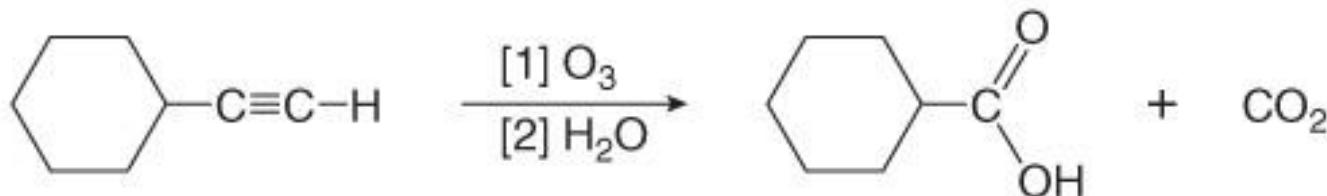
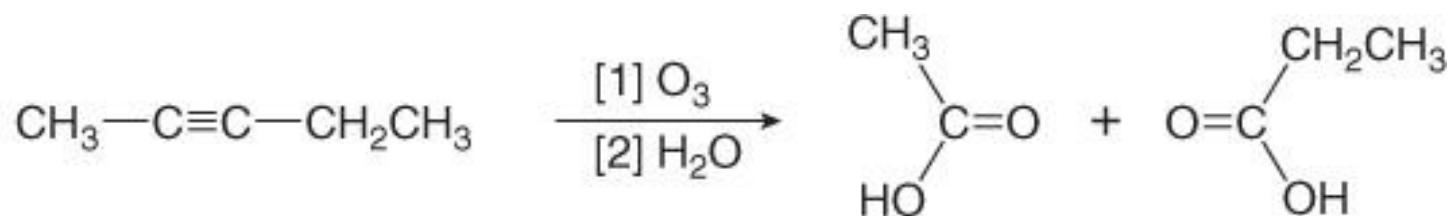
- oxidative cleavage of an alkene breaks both the σ and π bonds of the double bond to form two carbonyl compounds
- cleavage undergone with ozone (O_3) is called ozonolysis



Oxidative Cleavage of Alkynes

- alkynes undergo **oxidative cleavage** of the σ and **both π bonds**
- internal alkynes are oxidized to **carboxylic acids** (RCOOH)
- terminal alkynes afford a **carboxylic acid** and CO_2 from the *sp* hybridized C—H bond

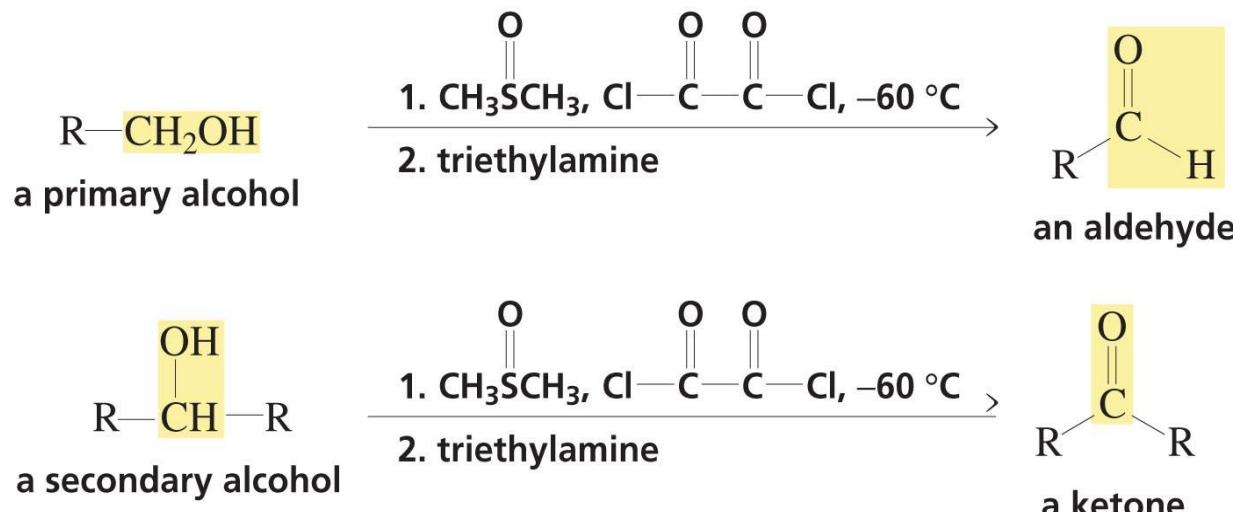
Examples



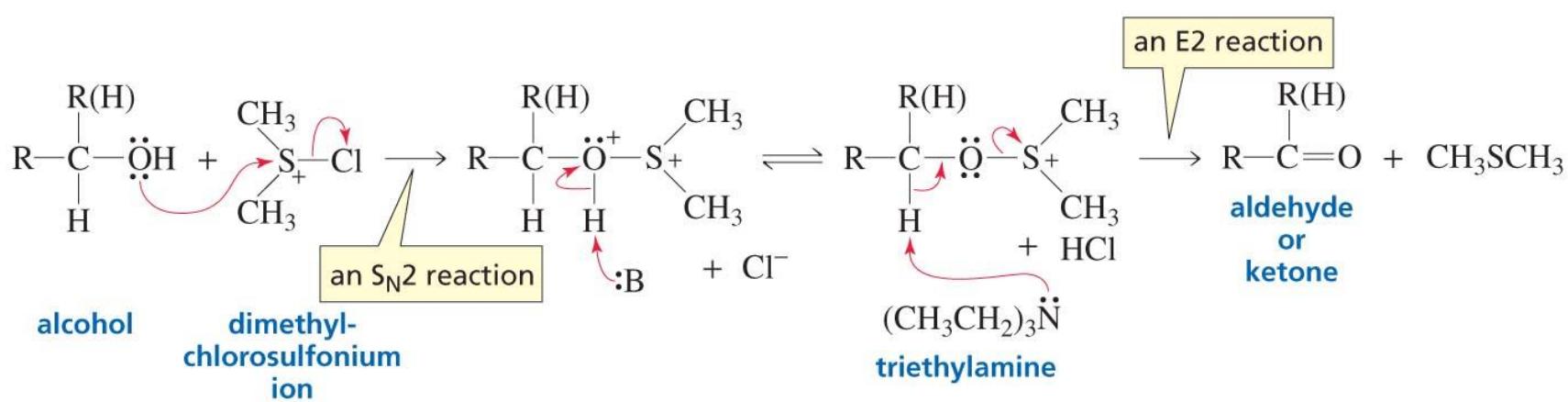
Swern Oxidation of primary or secondary alcohol

- the Swern oxidation, named after Daniel Swern
- a chemical reaction where a primary or secondary alcohol is oxidized to an aldehyde or ketone
- This reaction use oxalyl chloride, dimethyl sulfoxide (DMSO) and an organic base, such as triethylamine

Mechanism of Swern Oxidation

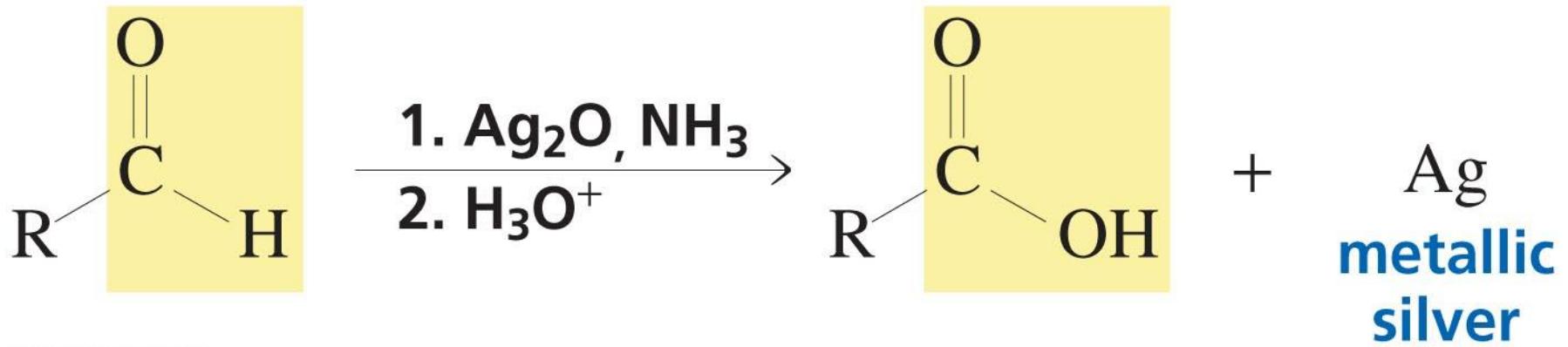


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- the tollens reagent oxidizes only aldehydes:

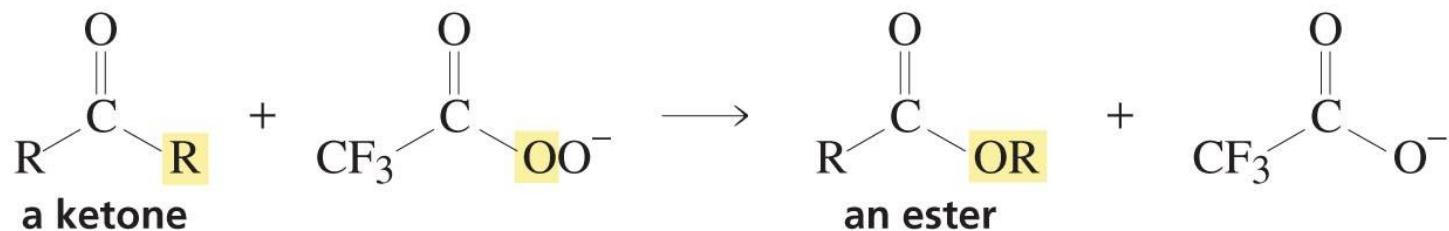
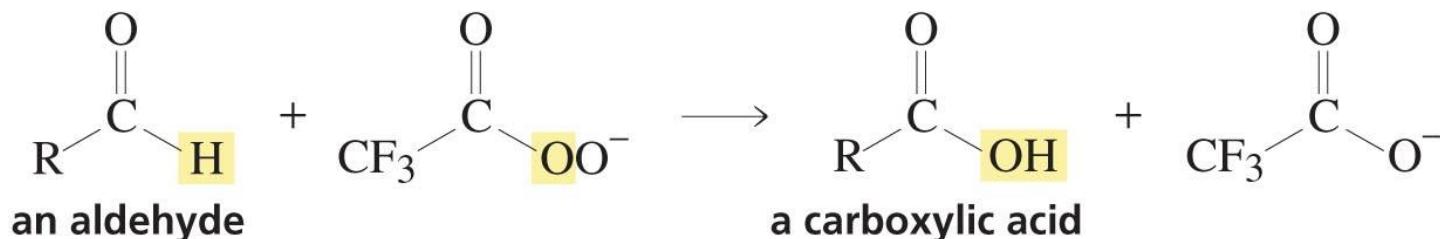


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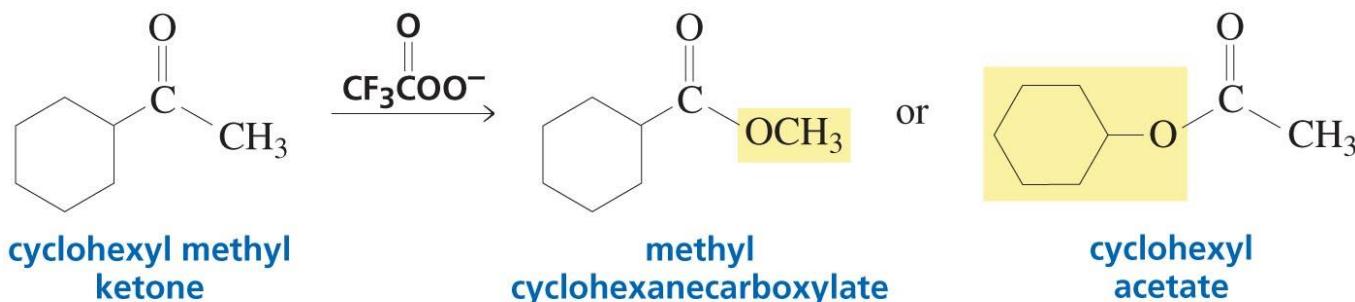
Baeyer–Villiger oxidation

- Oxidation of by both aldehydes and ketones by peroxyacid

Baeyer-Villiger oxidations

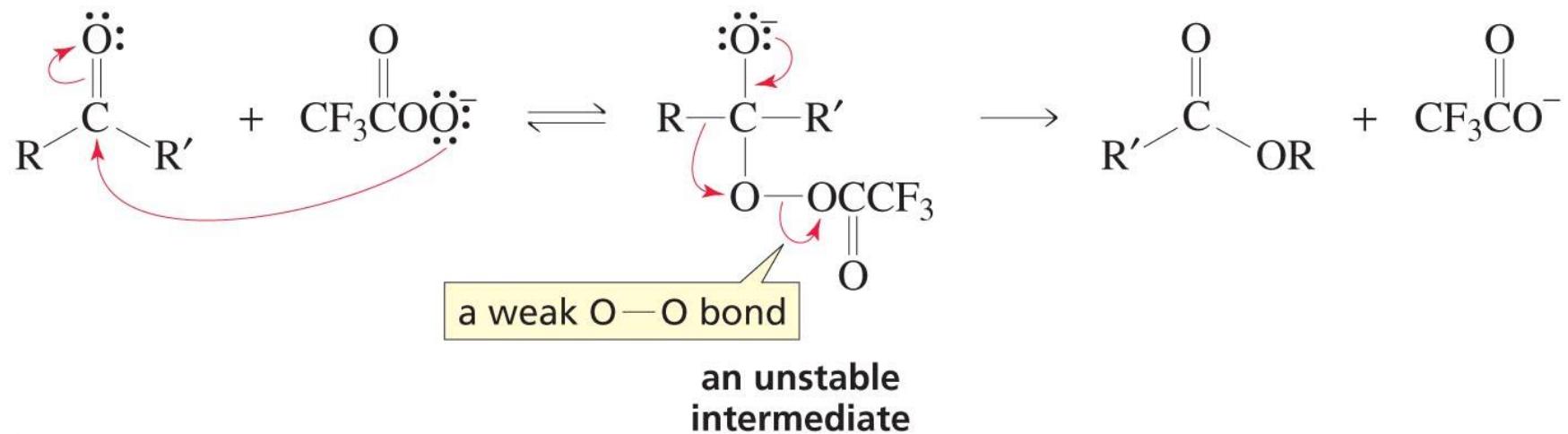


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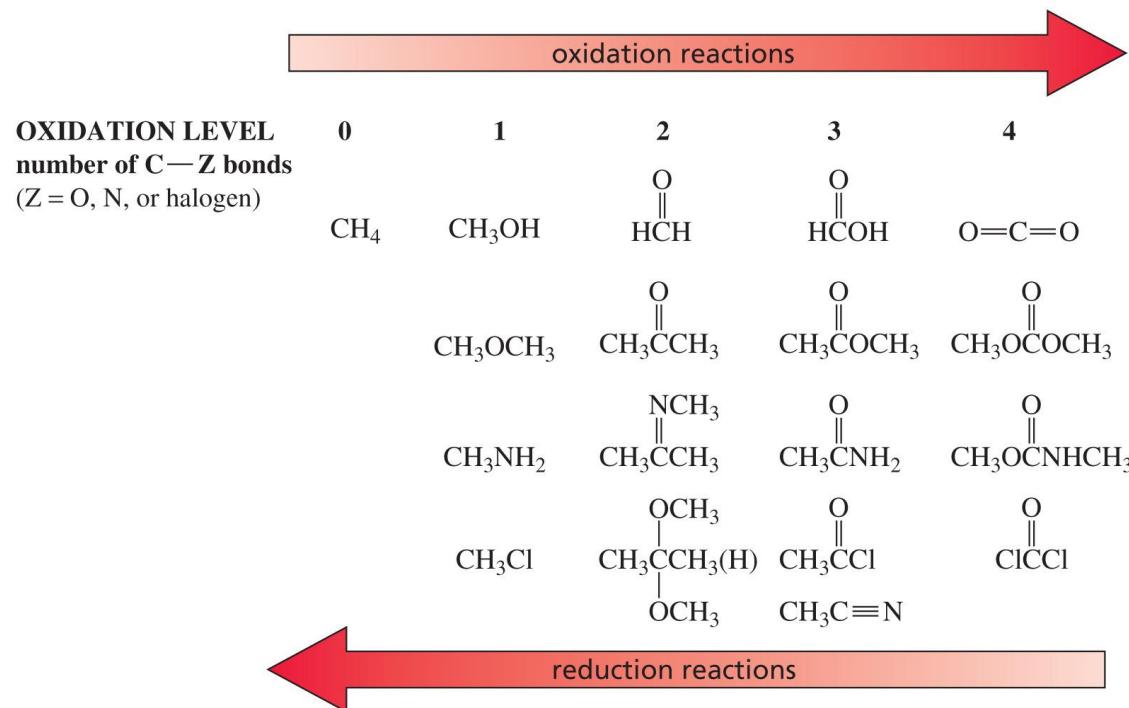
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Mechanism of the Baeyer–Villiger Oxidation



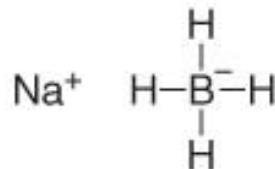
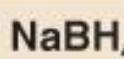
Reduction reactions

- reduction at carbon increases the number of C—H bonds or decreases the number of C—O, C—N, or C—X bonds
- oxidation at carbon decreases the number of C—H bonds or increases the number of C—O, C—N, or C—X bonds

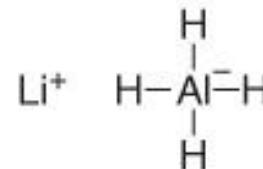


Reducing Agents

- the most common **hydride reducing agents** contain a **H-atom bonded to boron or aluminum**
- simple examples include **sodium borohydride (NaBH_4)** and **lithium aluminum hydride (LiAlH_4)**
- NaBH_4 and LiAlH_4 deliver H^- to the substrate, and then a proton is added from H_2O or an alcohol

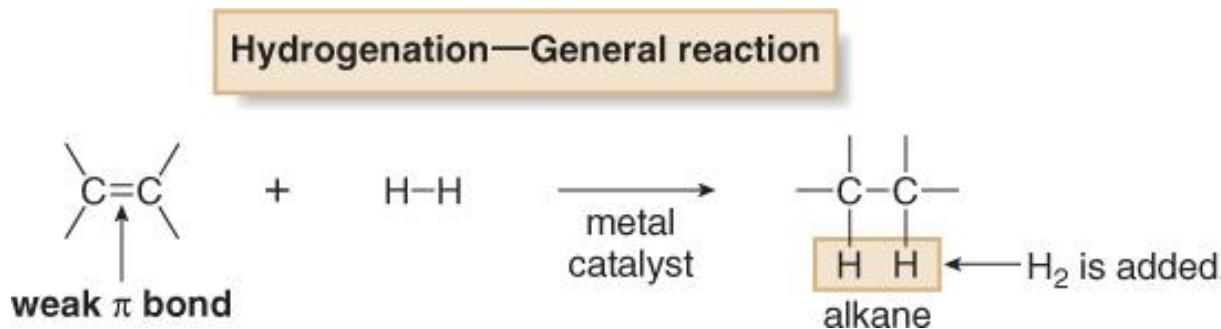


sodium borohydride



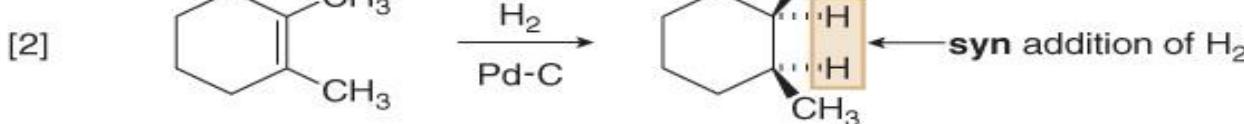
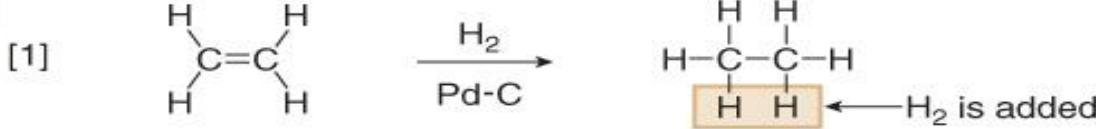
lithium aluminum hydride

Reduction of Alkenes - Catalytic Hydrogenation



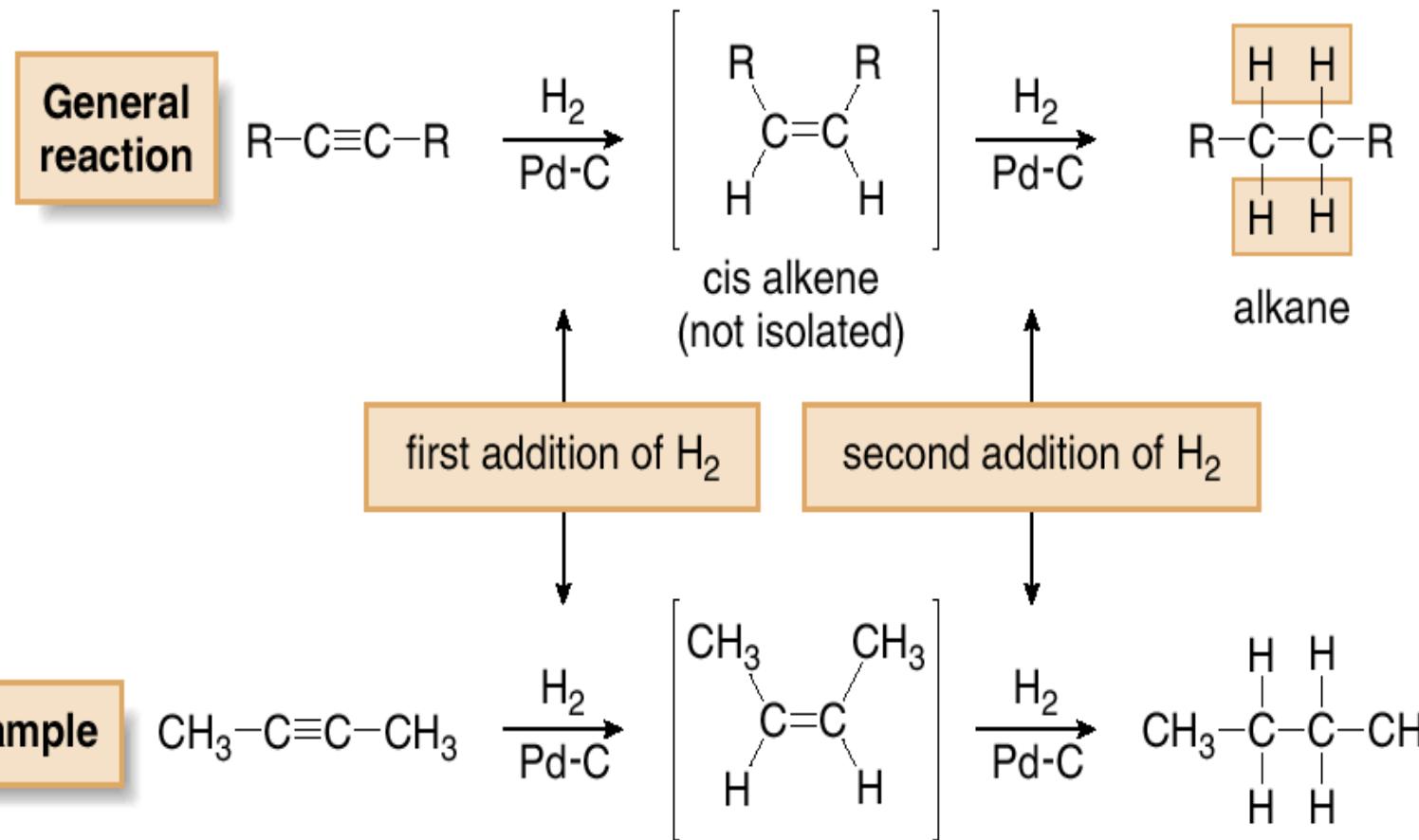
- addition of H_2 occurs only in the presence of a metal catalyst, and thus it is called catalytic hydrogenation
- the catalyst consists of a metal—usually Pd, Pt, or Ni, adsorbed onto a finely divided inert solid, such as charcoal.
- H_2 adds in a syn fashion.

Examples



Reduction of an Alkyne

Alkane formation:

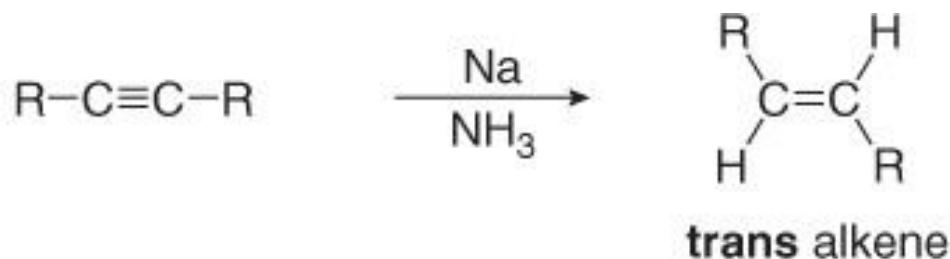


Dissolving metal reduction

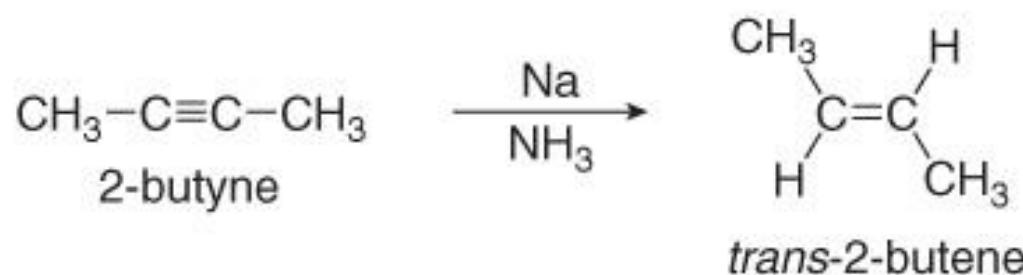
Reduction of an Alkyne to a Trans Alkene

- in a dissolving metal reduction (such as Na in NH₃), the elements of H₂ are added in an anti fashion to form a trans alkene

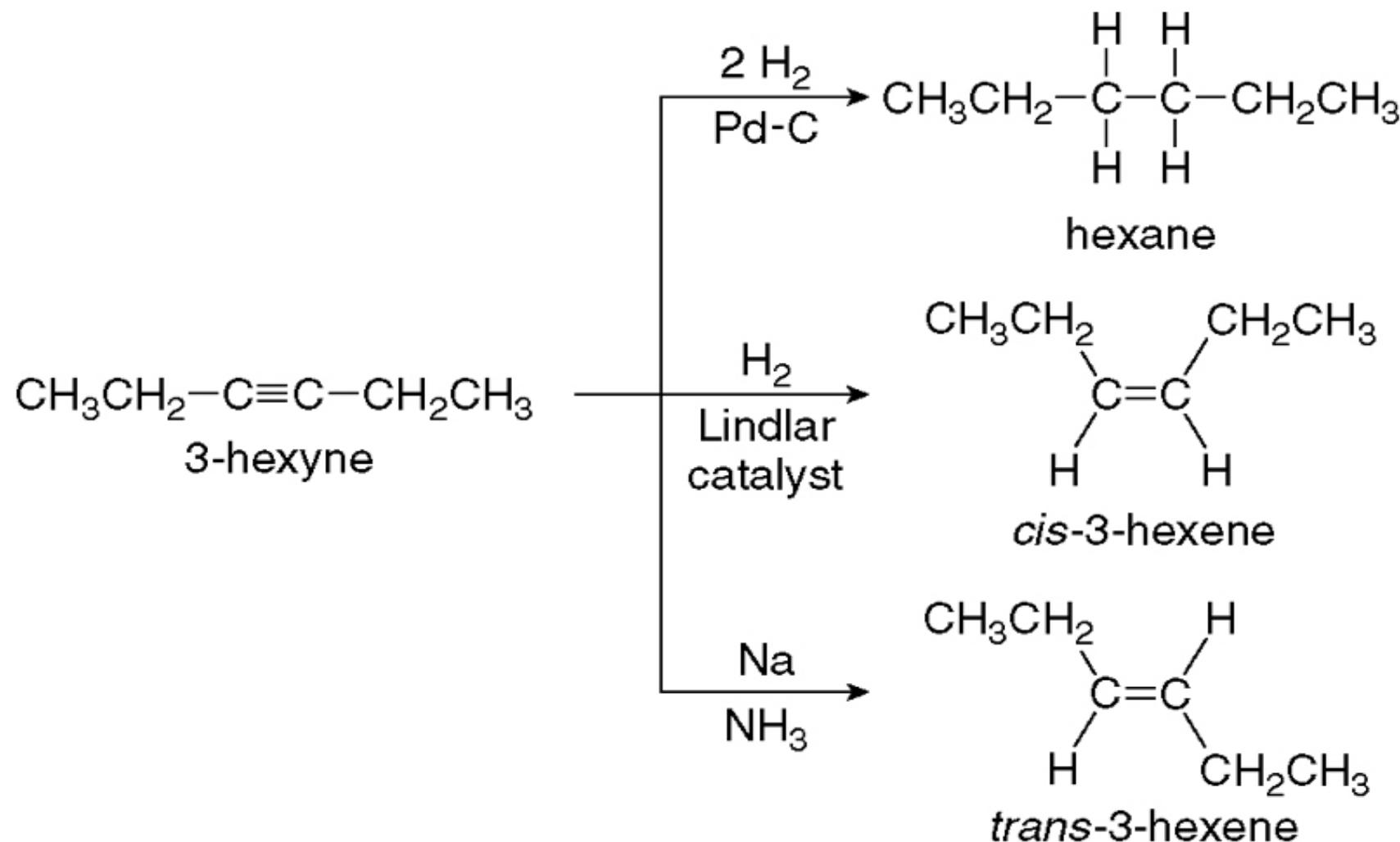
General reaction



Example

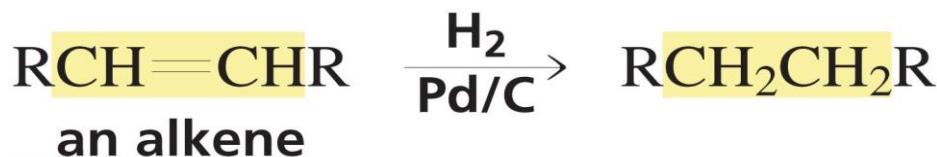


■ Summary of Alkyne Reductions

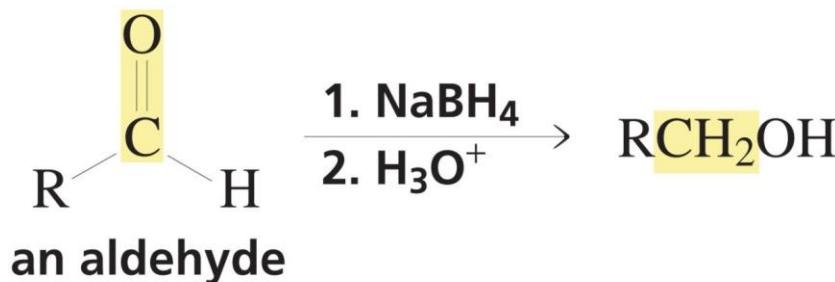
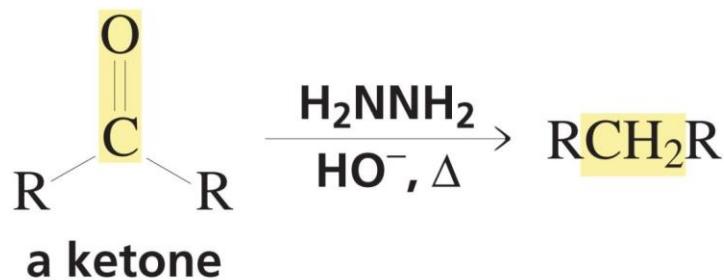


Miscellaneous reduction reactions

- hydrogen, sodium borohydride, and hydrazine are the reducing agents



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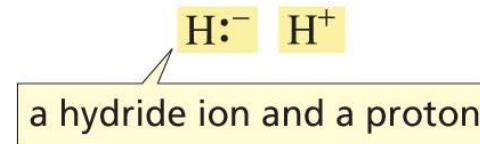
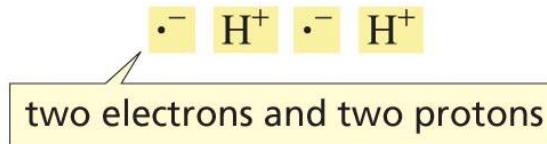
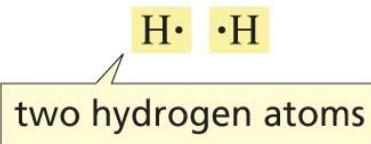


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Miscellaneous reduction reactions

■ H₂ as a reducing agent

components of H:H



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H₂, Pd on charcoal



Na or Li metal in
liq NH₃

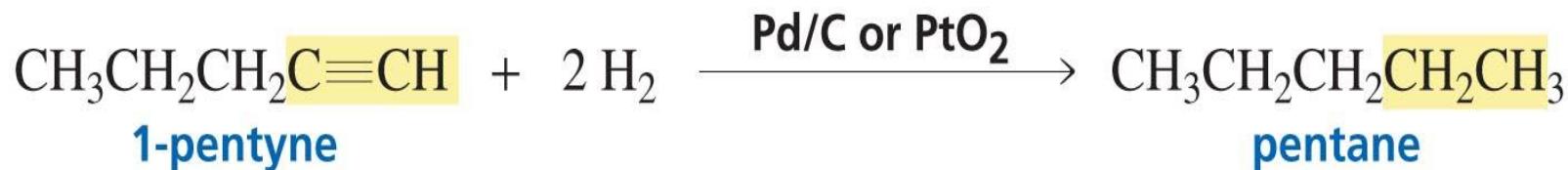


NaBH₄ or LiAlH₄

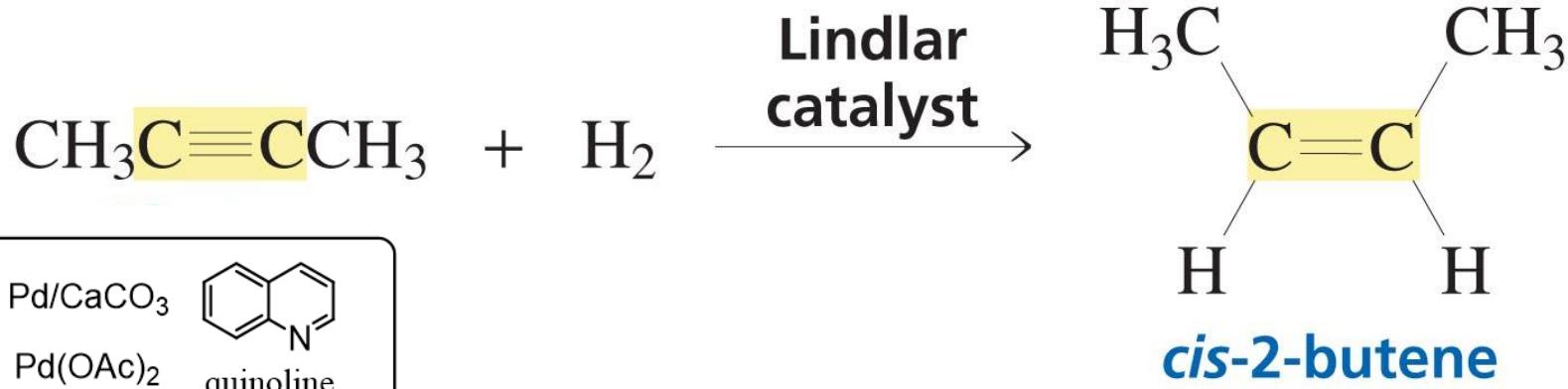


Miscellaneous reduction reactions

- reduction by catalytic hydrogenation - addition of two hydrogen atoms:



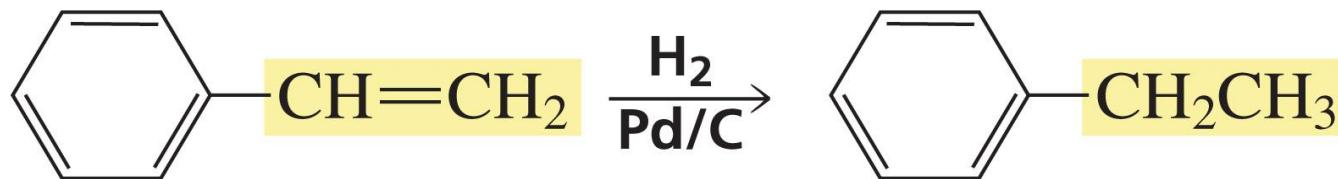
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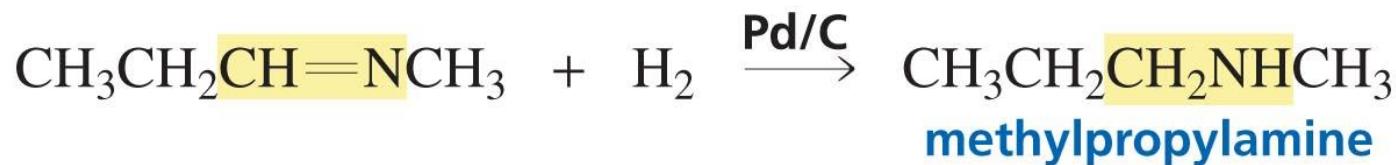
Lindlar catalyst

Miscellaneous reduction reactions

- only the alkene substituted to benzene is reduced:

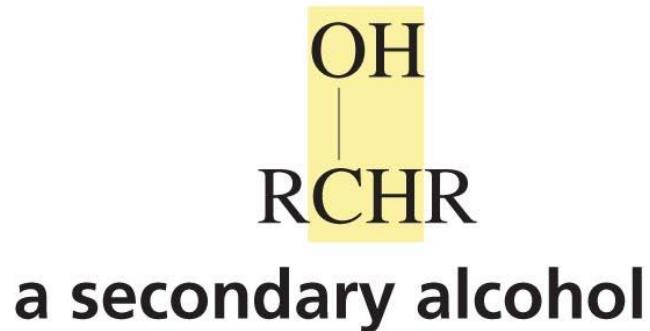
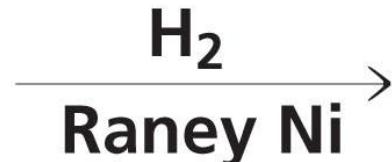
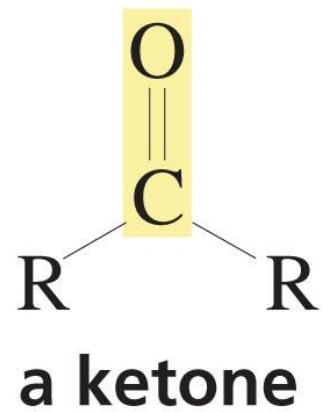
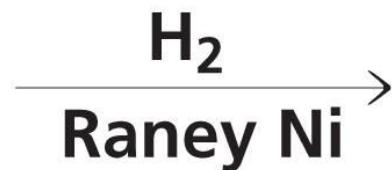
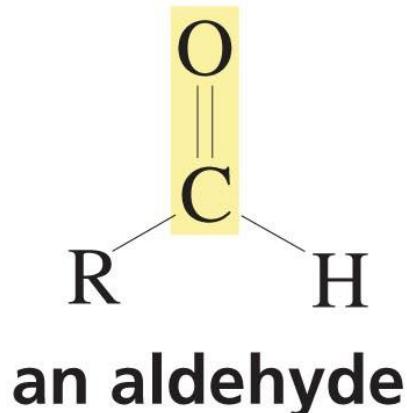


- reduction of carbon–nitrogen double and triple bonds:



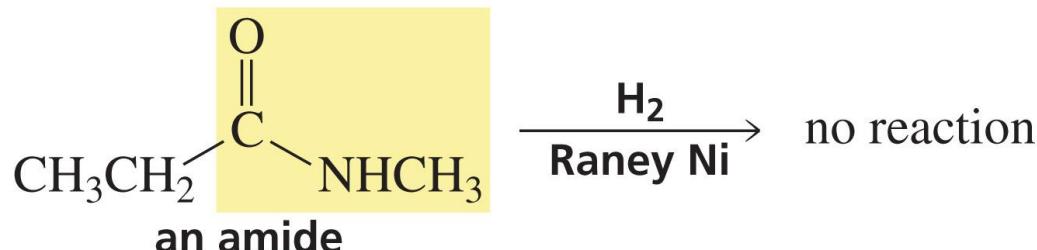
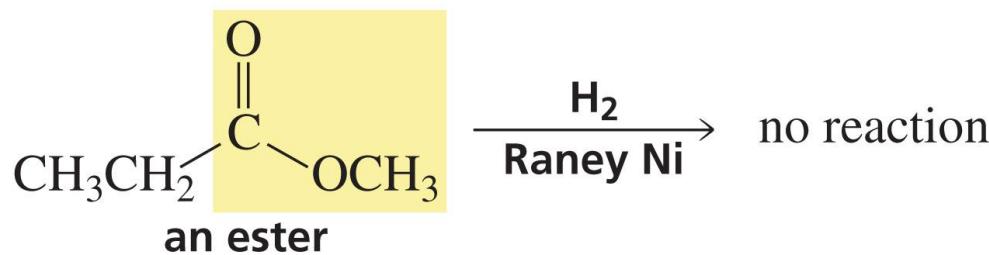
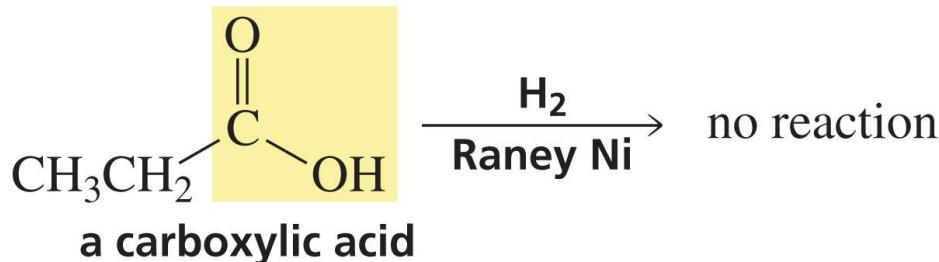
Miscellaneous reduction reactions

- reduction of ketones and aldehydes



Miscellaneous reduction reactions

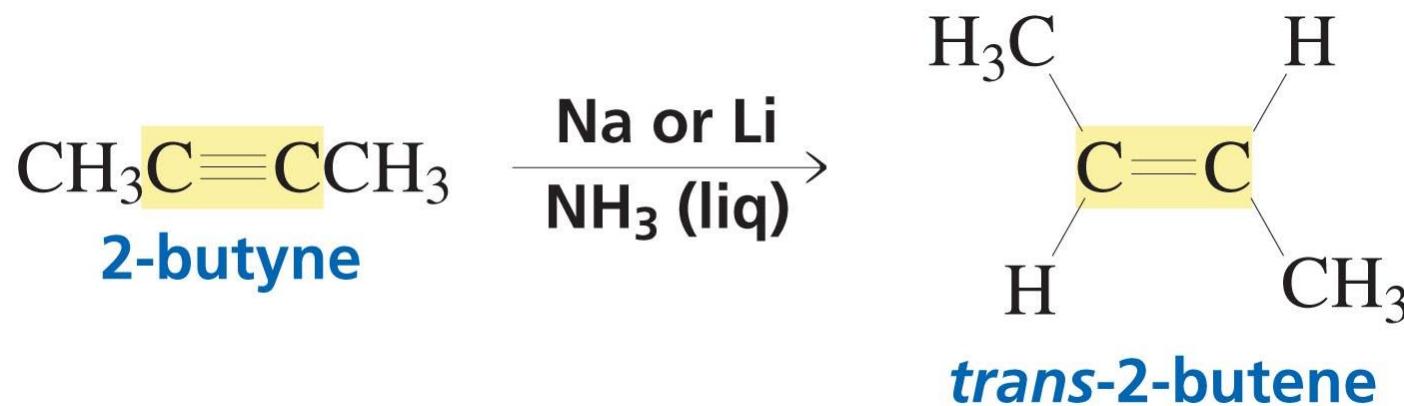
- esters do not undergo reduction under normal condition



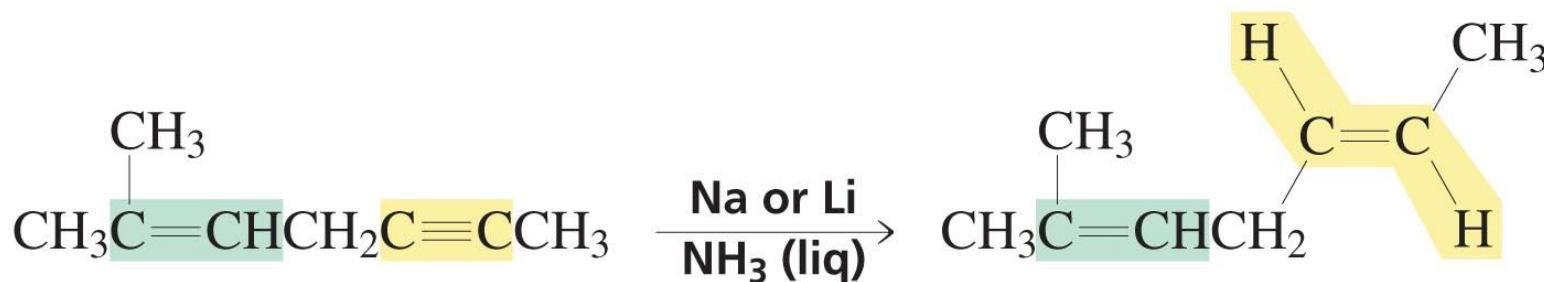
- Raney nickel (spongy nickel) - fine-grained solid composed mostly of nickel derived from a nickel–aluminium alloy

Miscellaneous reduction reactions

- dissolving-metal reduction - addition of an electron, and a proton:



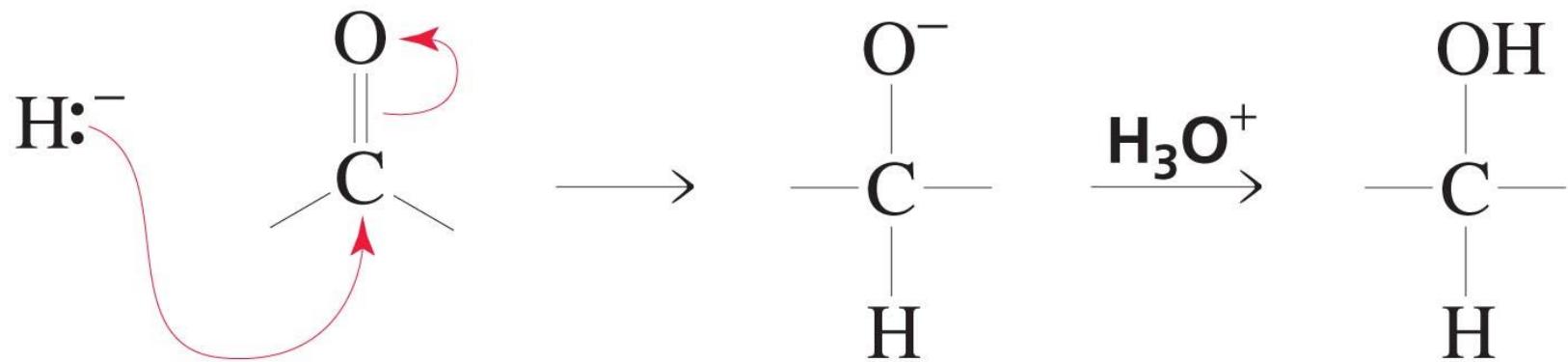
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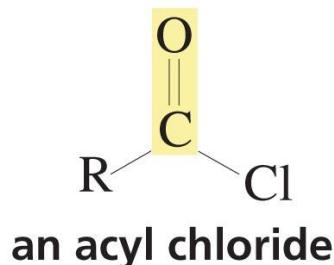
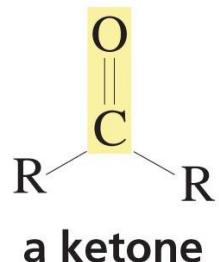
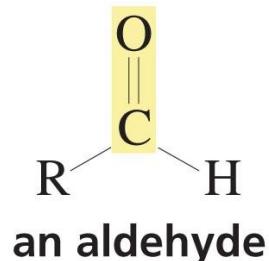
Miscellaneous reduction reactions

- reduction by addition of a hydride ion and a proton



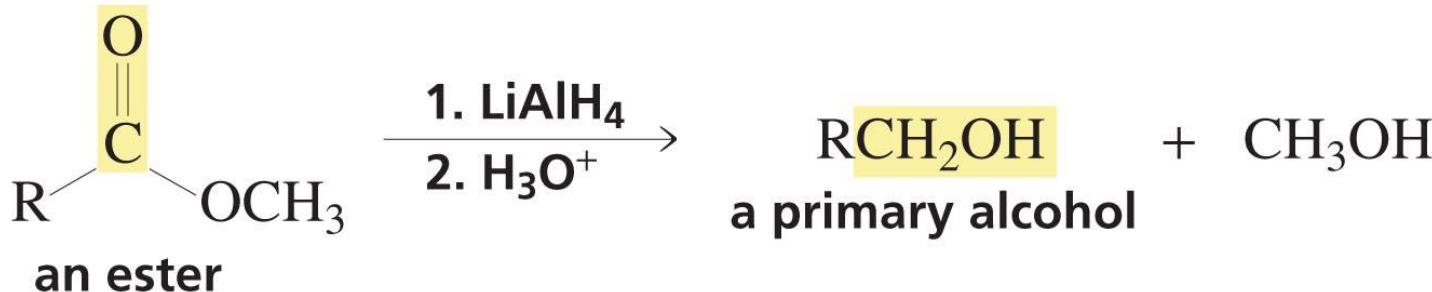
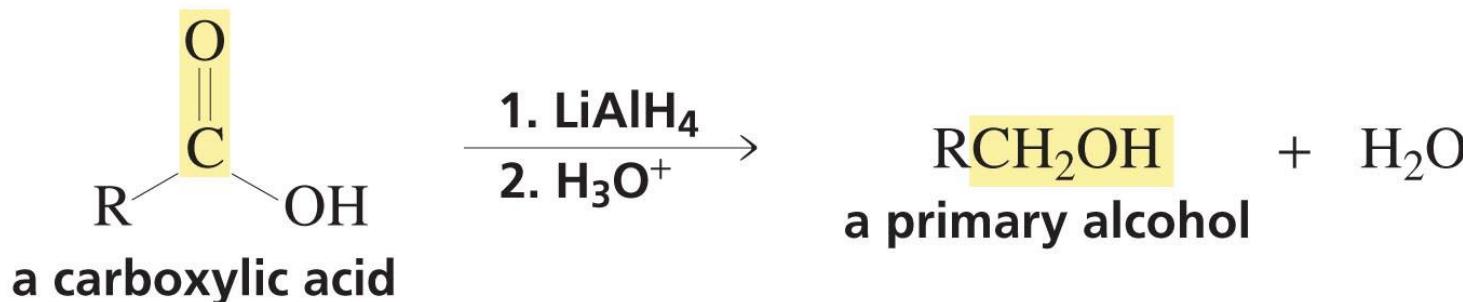
Miscellaneous reduction reactions

- aldehydes, ketones, and acyl halides can be reduced to alcohols by sodium borohydrides:



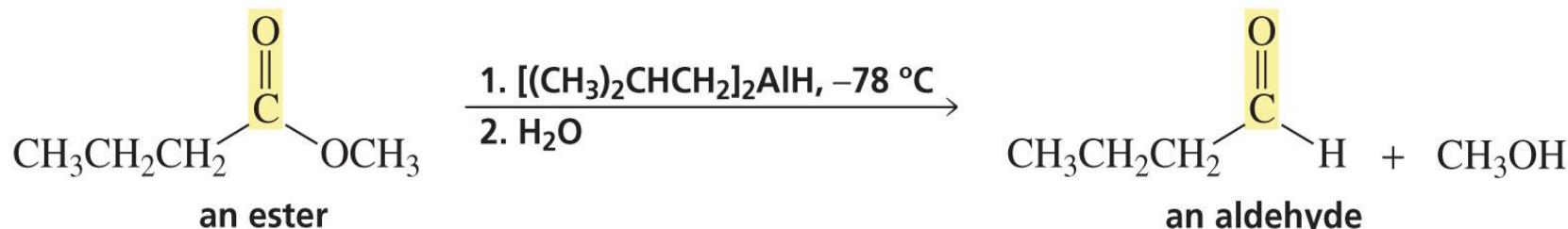
Miscellaneous reduction reactions

- LiAlH₄ is a stronger reducing agent than NaBH₄ which is used to reduce compounds that are unreactive toward NaBH₄



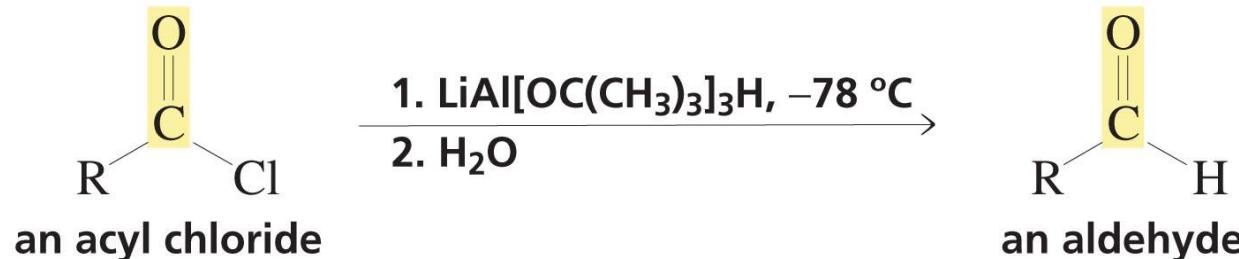
Miscellaneous reduction reactions

- DIBALH allows the addition of one equivalent of hydride to an ester:



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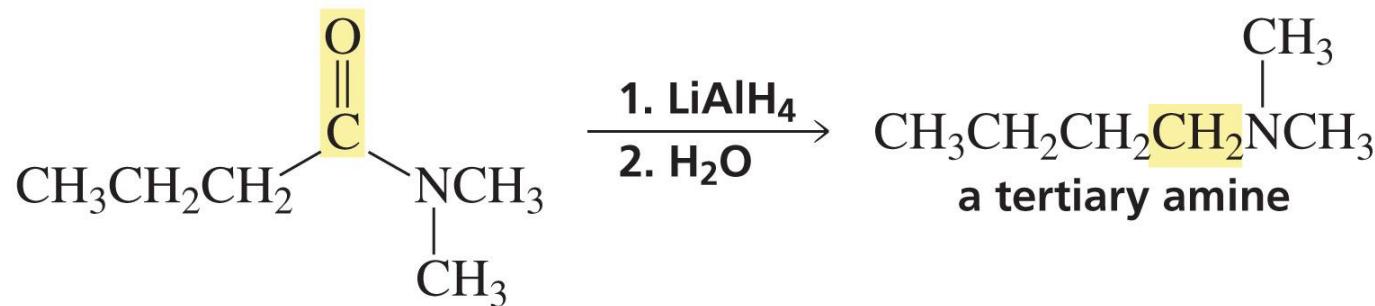
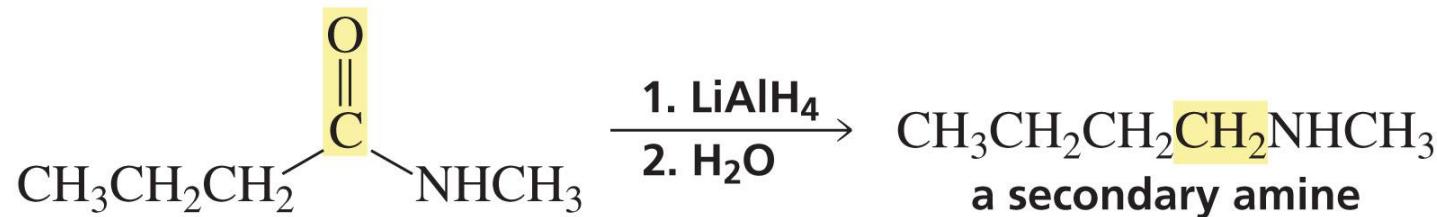
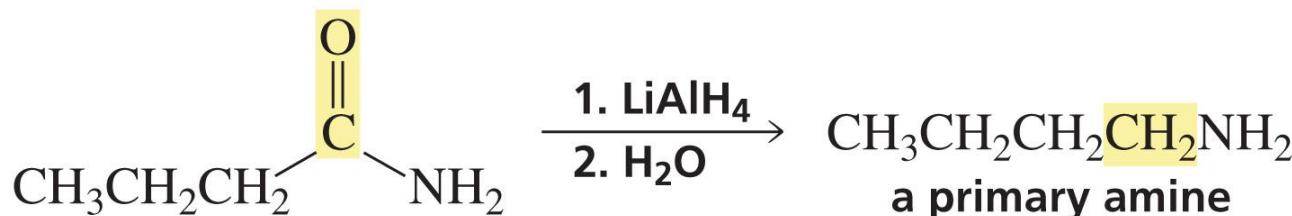
- replacing some of the hydrogens of LiAlH_4 with $-\text{OR}$ groups decreases the reactivity of the metal hydride:



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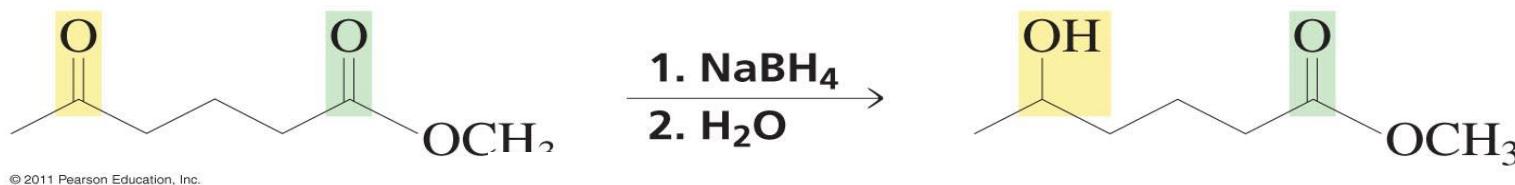
Miscellaneous reduction reactions

- formation of amines by reduction



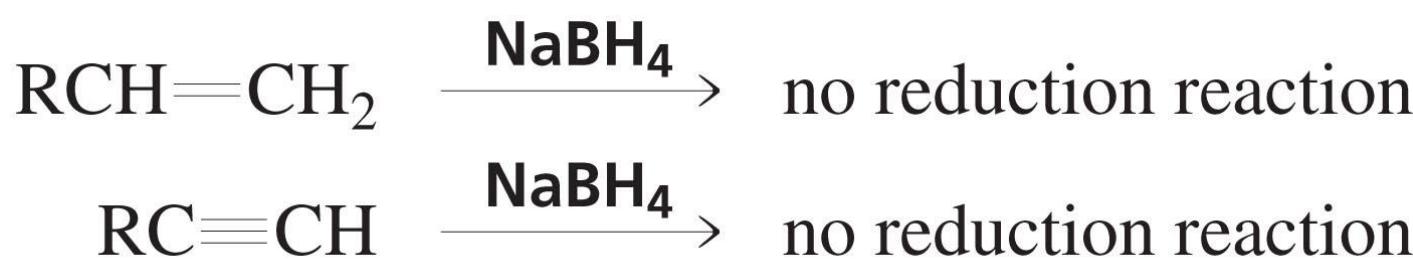
Miscellaneous reduction reactions

- NaBH_4 can be used to selectively reduce an aldehyde or a keto group in a compound:



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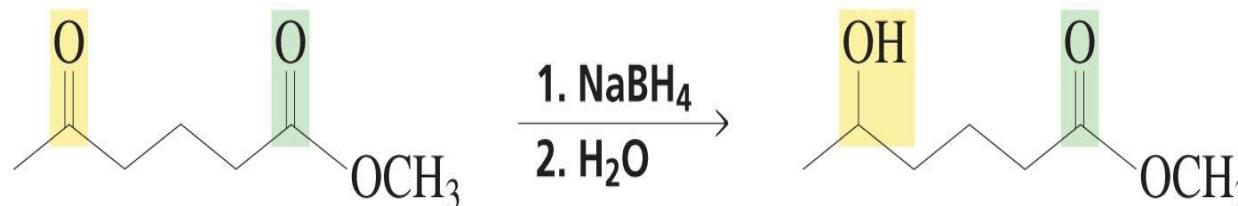
- alkenes and alkynes do not possess a partial positive charge:



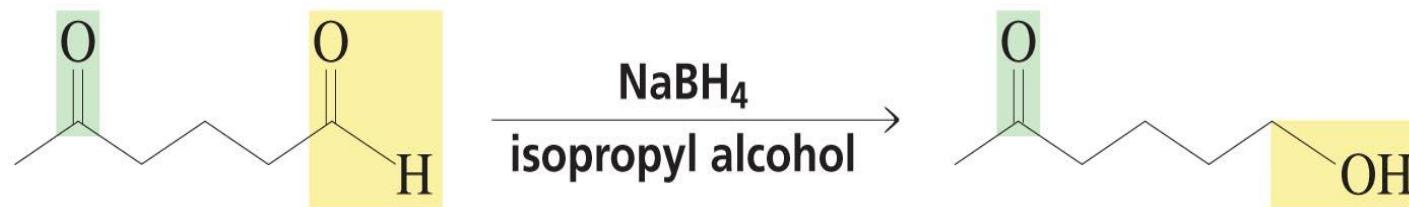
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Miscellaneous reduction reactions

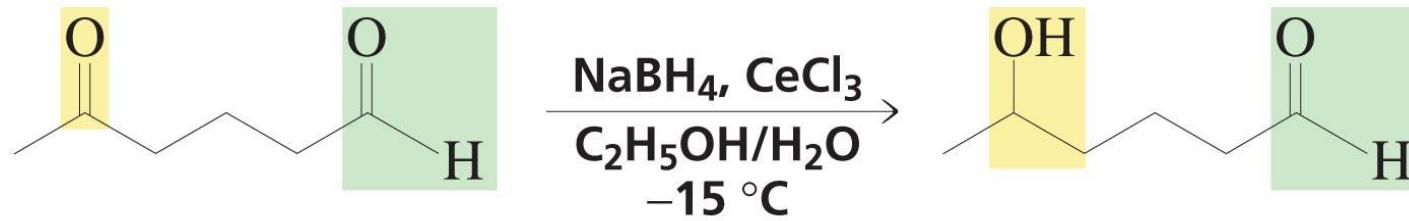
- Sodium borohydride can be used as a chemoselective reducing agent:



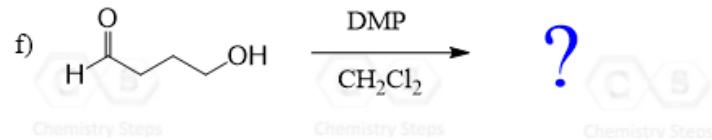
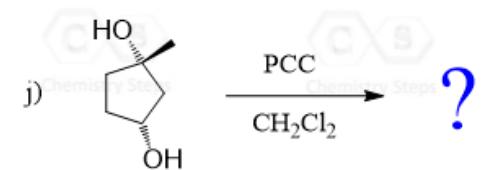
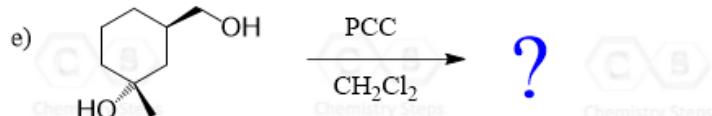
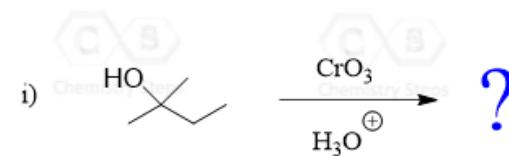
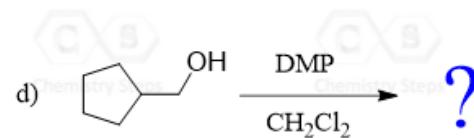
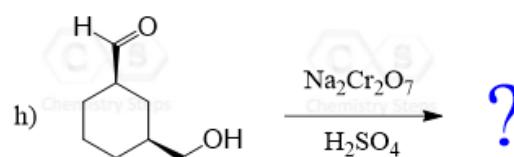
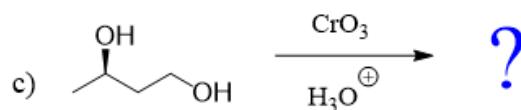
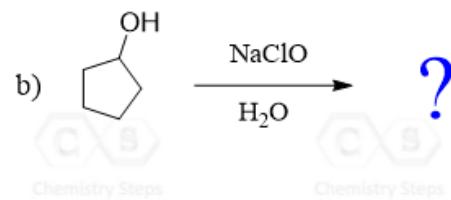
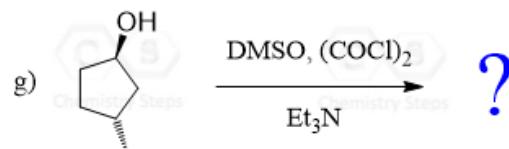
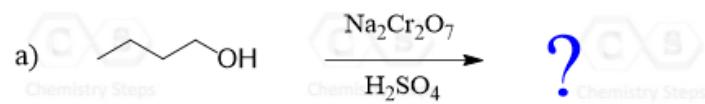
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CHAPTER FIVE

INTRODUCTION TO CHEMISTRY OF BIOMOLECULES



Carbohydrates



Proteins

Categories

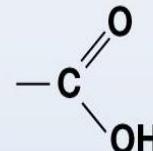
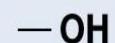
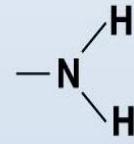
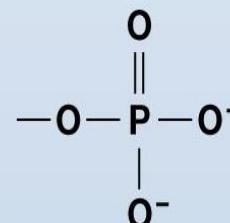


Nucleic Acids

INTRODUCTION

- our body, plants and other animals are made up of many chemical substances
- there are certain complex organic molecules which form the basis of life and build up living organisms and required for growth and maintenance
- Such molecules are called biomolecules including the main classes such as
 - Carbohydrates
 - Proteins
 - Lipids
 - Nucleic acids
 - Enzymes
 - Hormones

Functional Groups in Biomolecules

Group:	Structural formula:	Found in:
Carboxyl (-COOH)		fatty acids, amino acids
Hydroxyl (-OH)		alcohols, carbohydrates
Amino (-NH ₂)		amino acids
Phosphate (-PO ₄)		DNA, ATP

INTRODUCTION

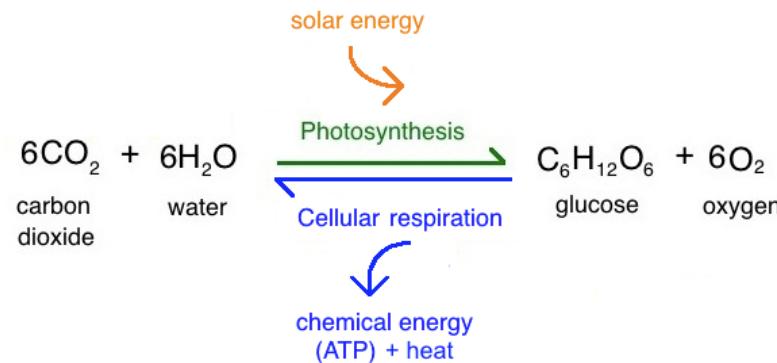
Concepts in this Chapter

- Macromolecules are polymers, built from monomers
- Carbohydrates serve as fuel and building material
- Lipids are a diverse group of hydrophobic molecules
- Proteins have many structures, resulting in a wide range of functions
- Nucleic acids store and transmit hereditary information

INTRODUCTION

Carbohydrates

- polyhydroxy aldehydes(aldose) or ketones(ketose) which are primarily produced by plants and form a very large group of naturally occurring organic substances
- include common examples such as cane sugar, glucose, starch, etc. having general molecular formulas that make them appear to be hydrates of carbon, $C_n(H_2O)_n$
- formed in the plants by photosynthesis from carbon dioxide and water in the presence of sunlight
- the most abundant carbohydrate in nature, **D-glucose**, converted into polymers called **glycogen** and **starch** by **animals** and **plants** respectively



INTRODUCTION

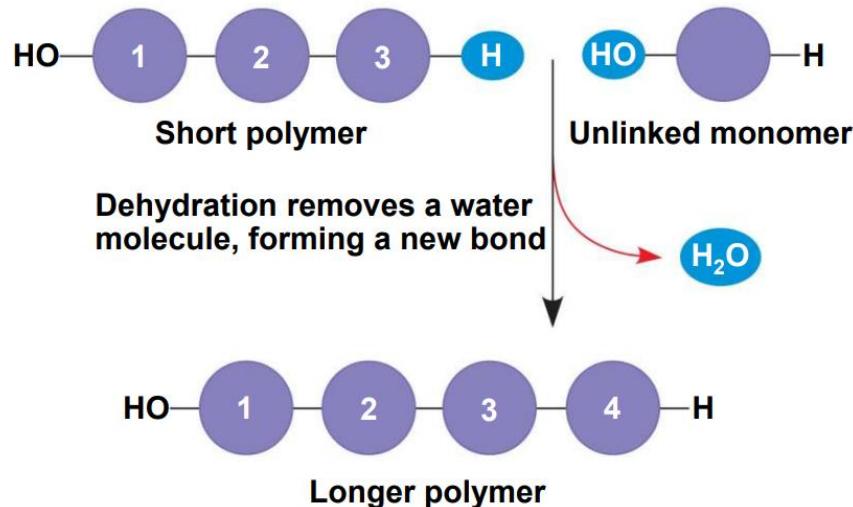
The Diversity of Polymers

- each cell has thousands of different kinds of macromolecules
- macromolecules vary among cells of an organism, vary more within a species, and between species
- an immense variety of polymers can be built from a small set of monomers
 - ✓ **Polymer** – A long molecule consisting of many similar building blocks
 - ✓ **Monomer** – Small building blocks that make polymers
 - ✓ **Dehydration reaction** – The process by which two/more monomers are bonded together to form polymer
 - ✓ **Hydrolysis** – The reaction that disassembles polymers

INTRODUCTION

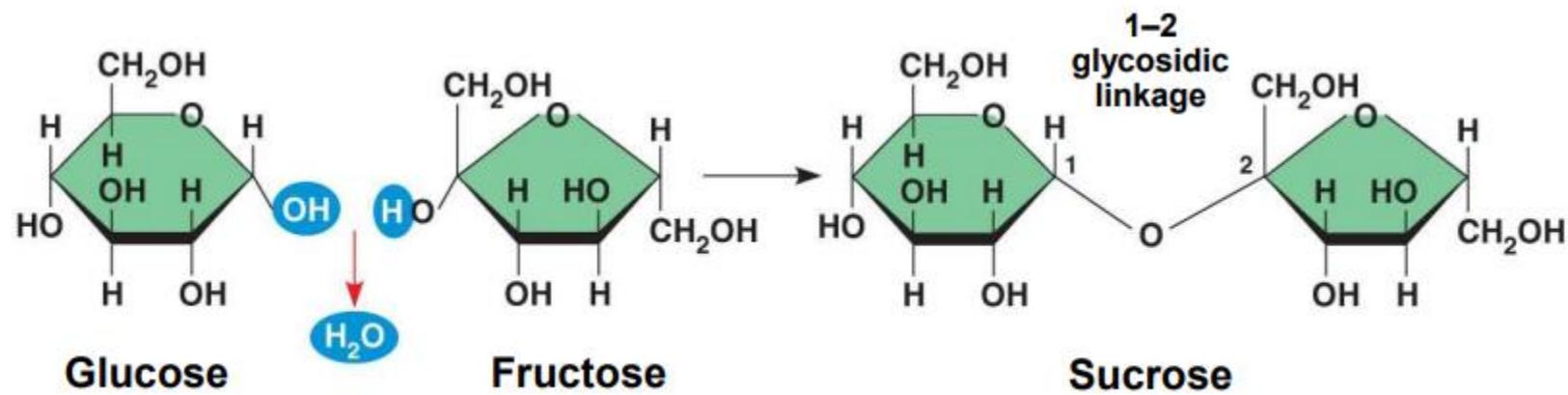
Dehydration reaction - Synthesis of Polymers

- monomers are connected by a condensation reaction or more specifically a dehydration reaction
- occurs when two monomers bond together through the loss of a water molecule
- enzymes are macromolecules that speed up the dehydration process



INTRODUCTION

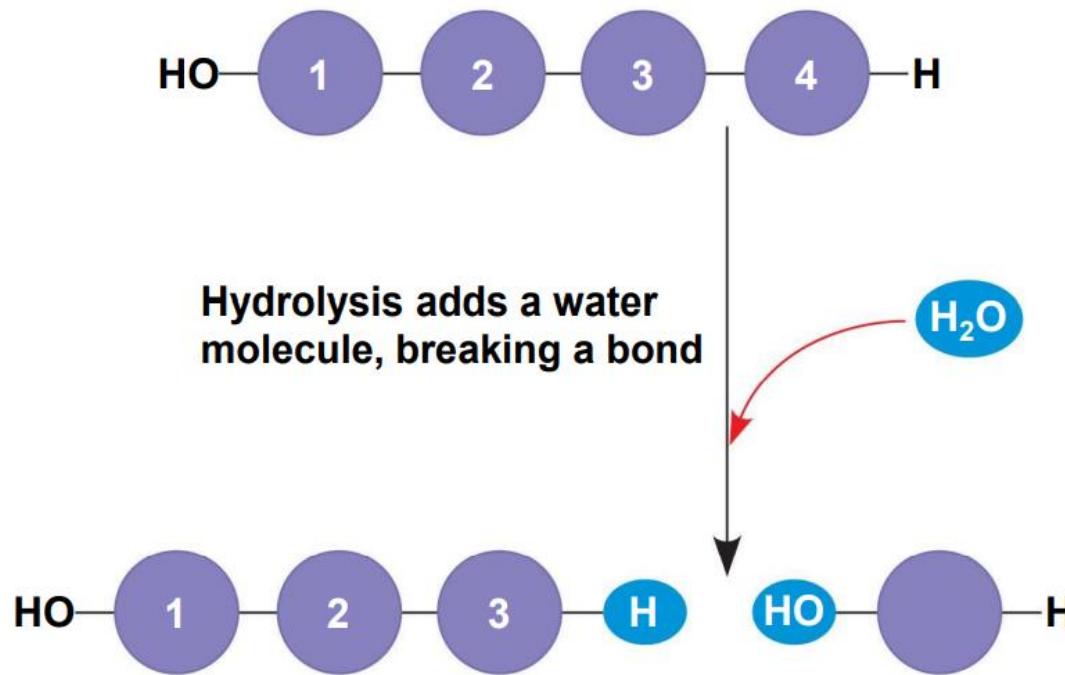
Dehydration reaction in the synthesis of sucrose



INTRODUCTION

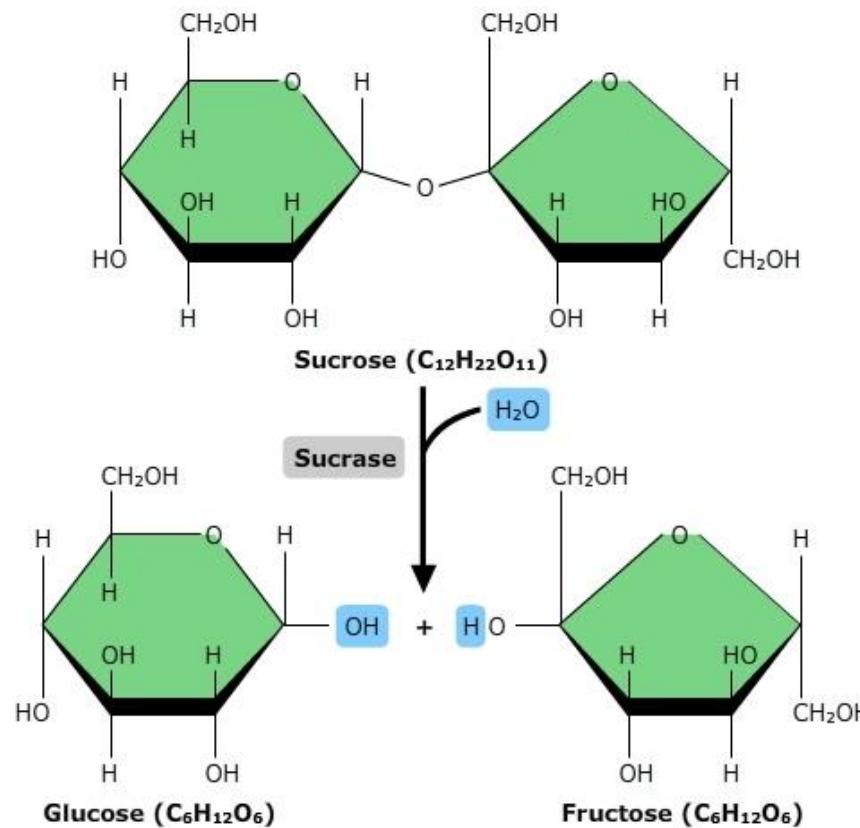
Hydrolysis reaction – breaking down of Polymers

- Polymers are disassembled to monomers by hydrolysis
- a reaction that is essentially the reverse of the dehydration reaction



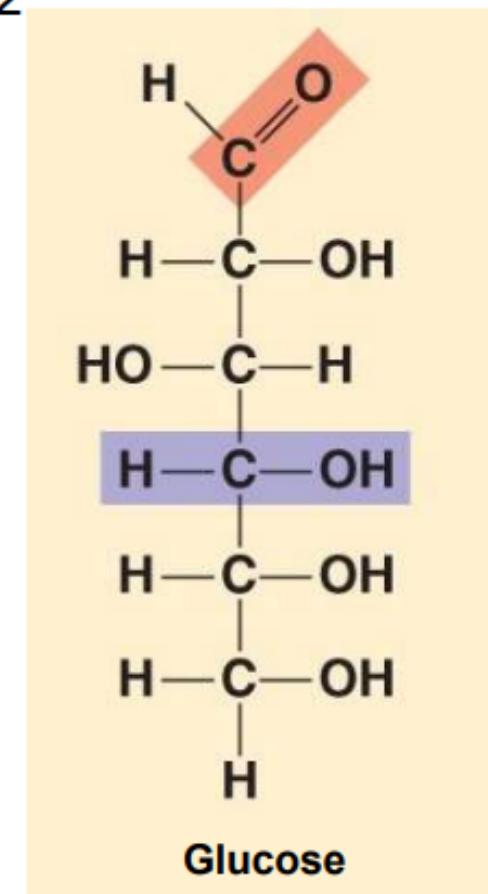
INTRODUCTION

- hydrolysis reaction of sucrose into glucose and fructose



INTRODUCTION

- **Monosaccharides** have molecular formulas that are usually multiples of CH_2O
- Glucose ($\text{C}_6\text{H}_{12}\text{O}_6$) is the most common monosaccharide
 - Trademarks of sugars
 - Carbonyl group
 - Multiple –OH groups



INTRODUCTION

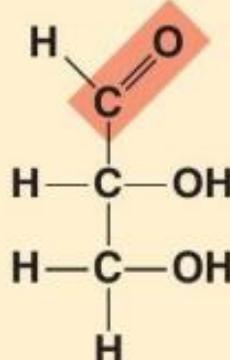
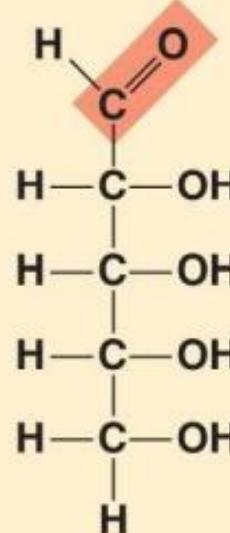
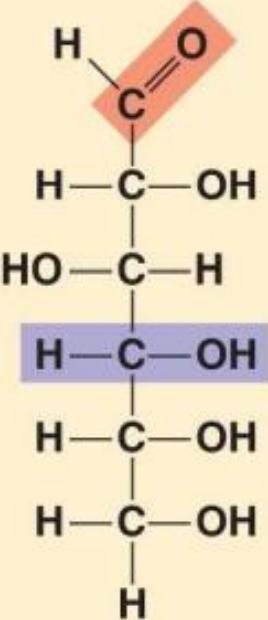
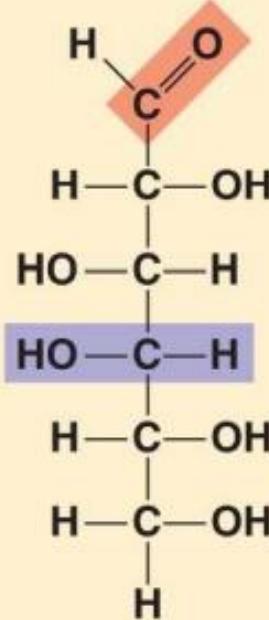
Monosaccharides are classified by:

1. The location of the carbonyl group
 - aldose or ketose
2. The number of carbons in the carbon skeleton
 - 3-7 carbons long

Aldoses		Trioses ($C_3H_6O_3$)	Hexoses ($C_6H_{12}O_6$)
Aldoses	Ketoses	<p>Glyceraldehyde</p>	<p>Fructose</p>

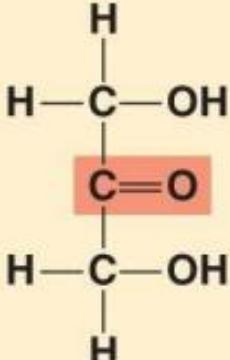
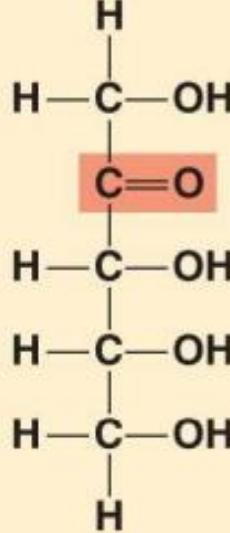
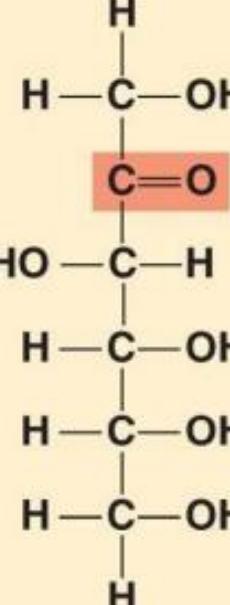
Introduction

■ aldoses

	Trioses ($C_3H_6O_3$)	Pentoses ($C_5H_{10}O_5$)	Hexoses ($C_6H_{12}O_6$)
Aldoses	 Glyceraldehyde	 Ribose	 Glucose
			 Galactose

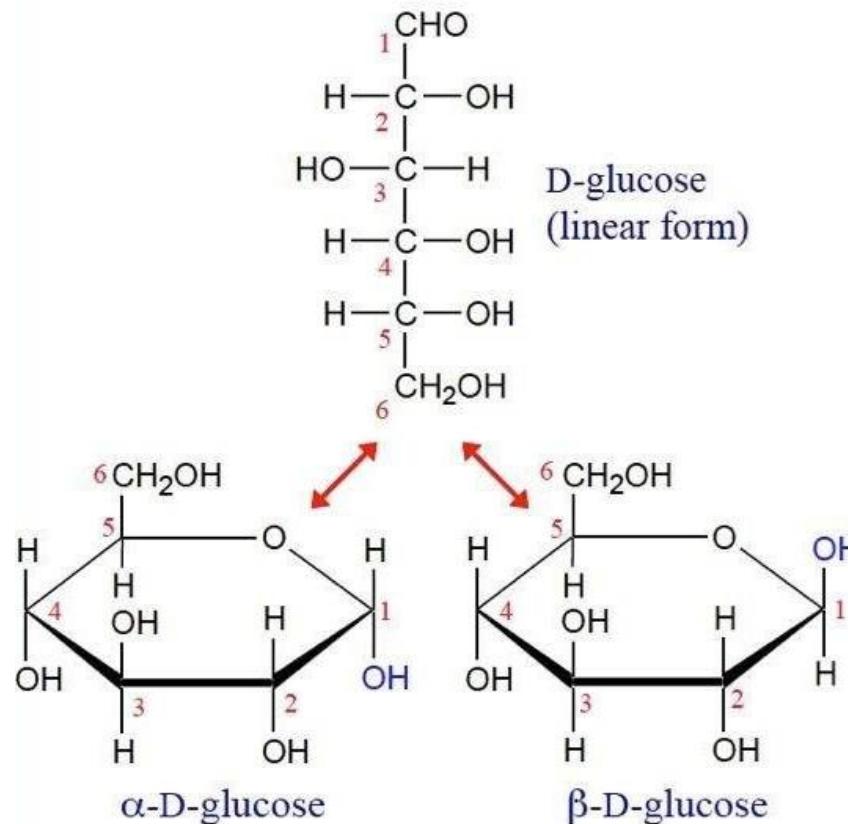
Introduction

■ Ketoses

	Trioses ($C_3H_6O_3$)	Pentoses ($C_5H_{10}O_5$)	Hexoses ($C_6H_{12}O_6$)
Ketoses	 Dihydroxyacetone	 Ribulose	 Fructose

Glucose

- the most abundant monosaccharide occurring free in fruits, plants, honey, in the blood of animals, and combined in many glycosides, disaccharides, and polysaccharides
- it is an aldohexose, which is a six-carbon sugar with a terminal aldehyde group

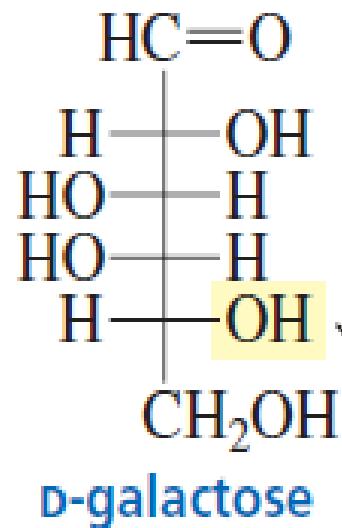


Glucose

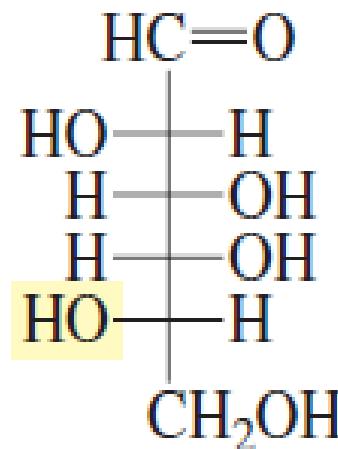
The D- and L- notation

- describe the configurations of carbohydrates
- are divided into two families: **D** form and **L** form sugars
 - ✓ if the **OH** group attached to the bottom-most asymmetric carbon (the carbon that is second from the bottom) is **on the right**, then the compound is a **D-sugar**
 - ✓ if the OH group is **on the left**, then the compound is an **L-sugar**
- almost all sugars found in nature are **D-sugars**

- illustrations



the OH group
is on the right



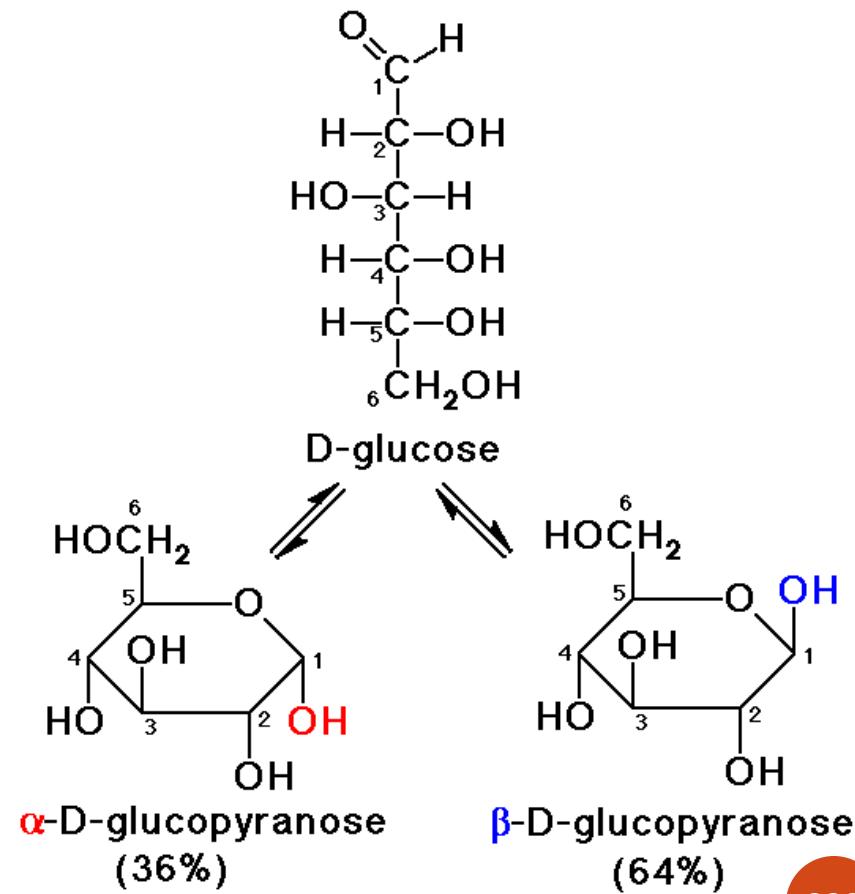
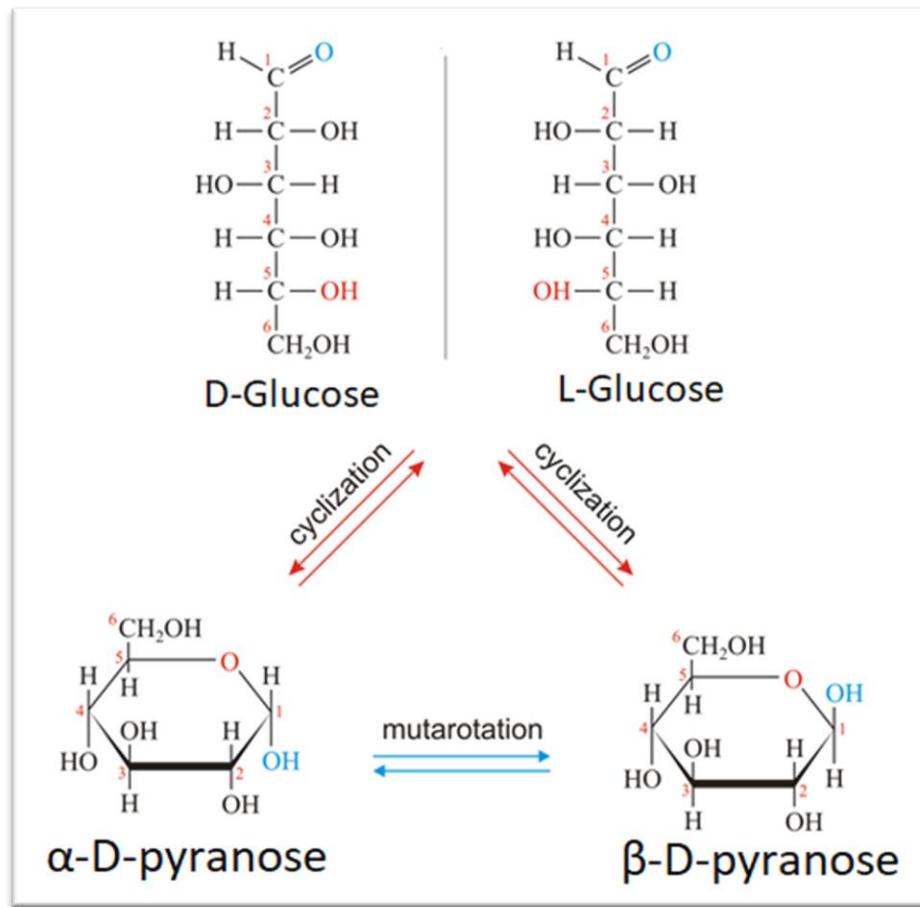
mirror image of D-galactose

- notice that the **mirror image of a D-sugar is an L-sugar**

Glucose

... Cont'd

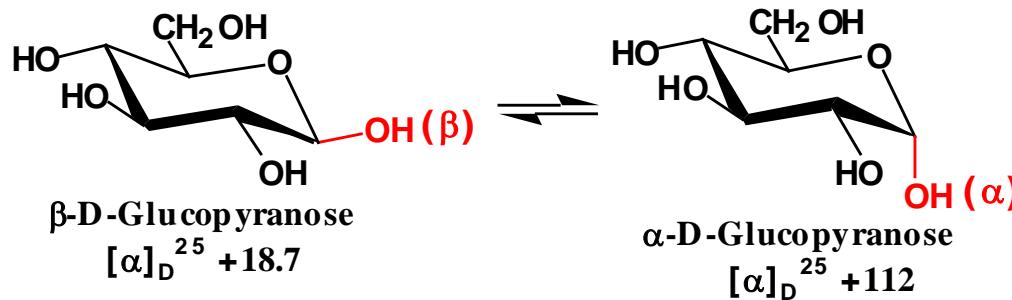
- the common name of the monosaccharide, together with the D- or L- designation, completely defines its structure



Mutarotation

- the change in specific rotation that occurs when an α or β form of a carbohydrate is converted to an equilibrium mixture of the two

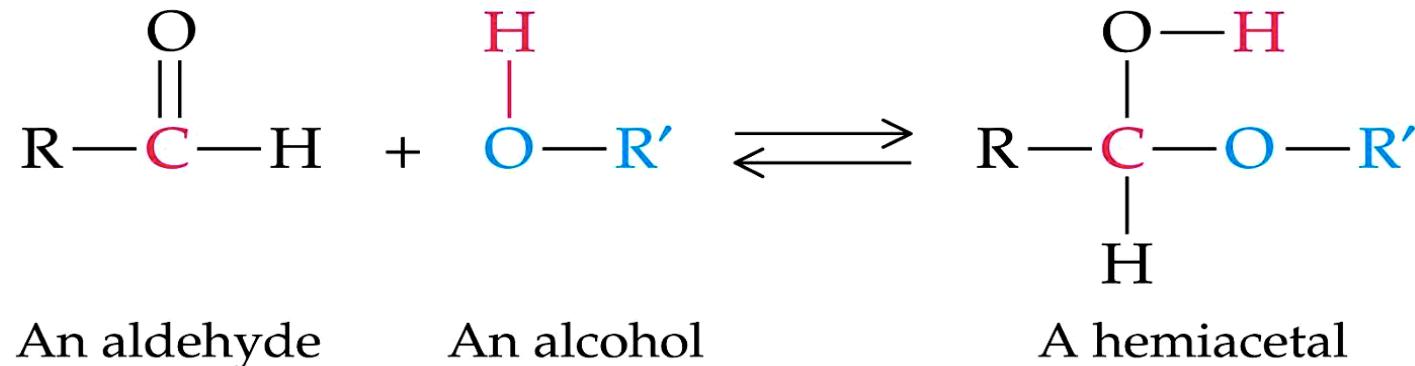
Monosaccharide	$[\alpha]$	$[\alpha]$ after Mutarotation	% Present at Equilibrium
α -D-glucose	+112.0	+52.7	36
β -D-glucose	+18.7	+52.7	64
α -D-galactose	+150.7	+80.2	28
β -D-galactose	+52.8	+80.2	72

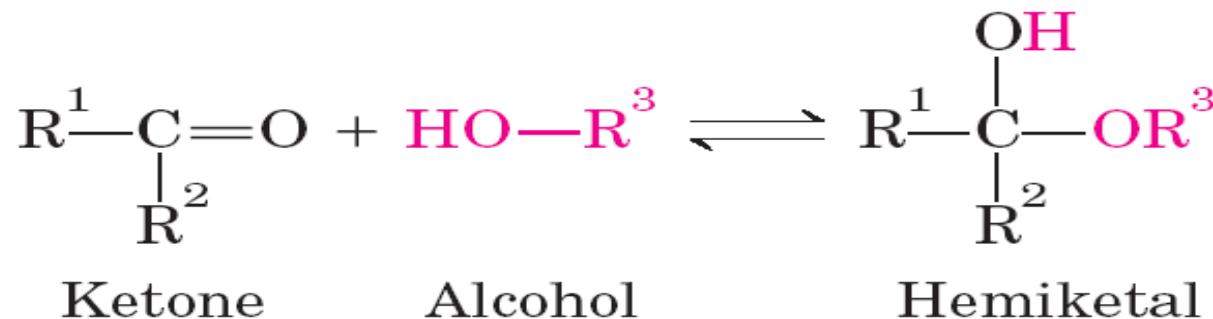


Cyclic Structure of Monosaccharides

How can D-glucose exist in a cyclic form?

- Hemiacetals are made by the reaction of an **aldehyde** with an **alcohol**
- Hemiketals are made by the reaction of **ketone** with an **alcohol**



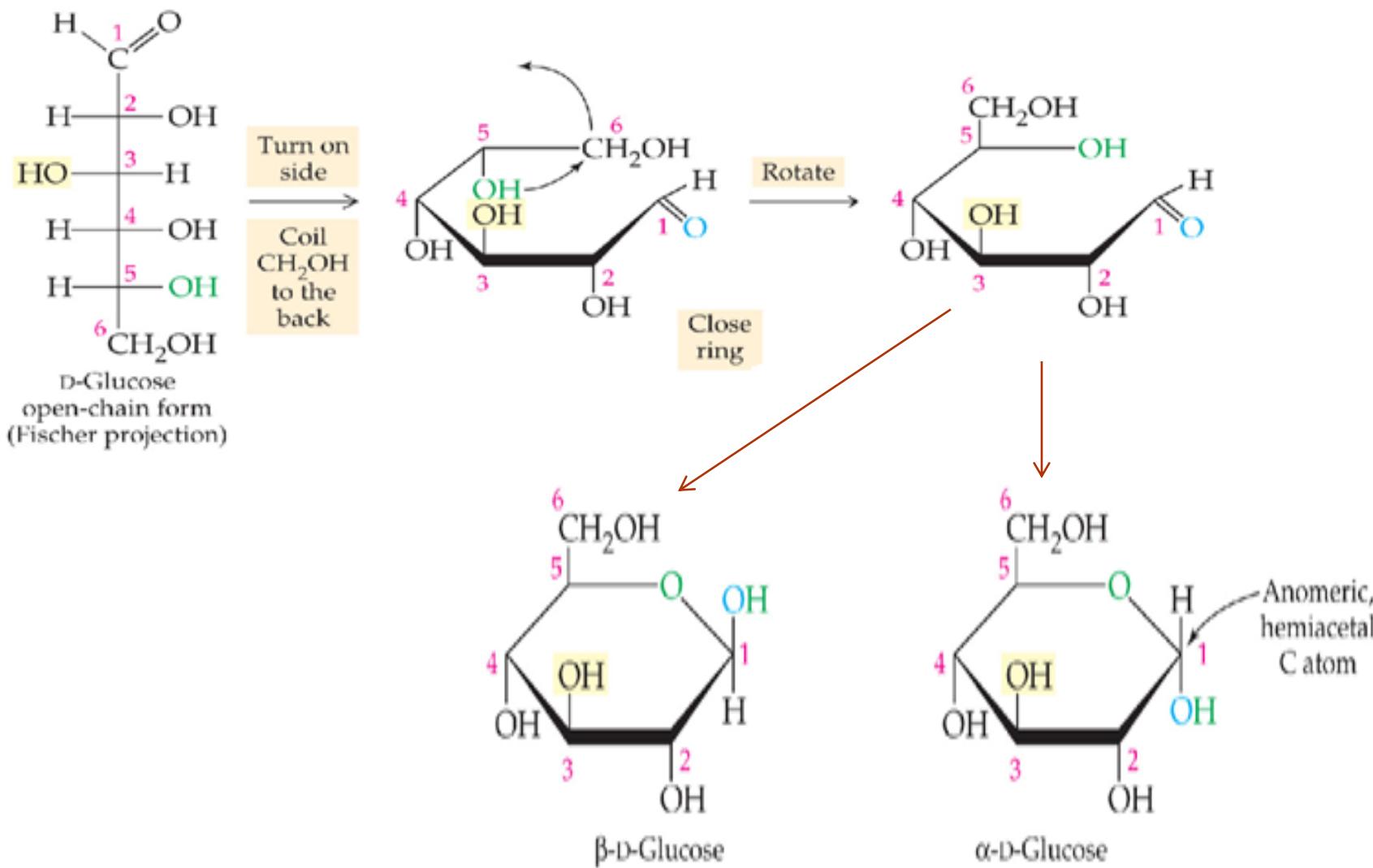


Note: A hemiacetal contains a C atom bonded to an **-OH** and an **-OR** group

- the alcohol group bonded to **C-5** of D-glucose reacts intramolecularly with the **aldehyde group**, forming a six-membered-ring hemiacetal

Glucose

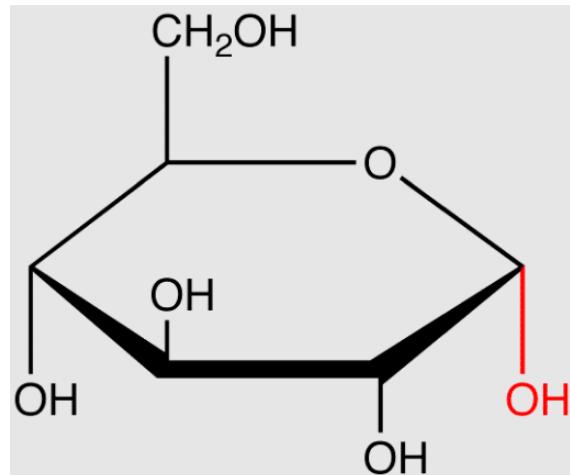
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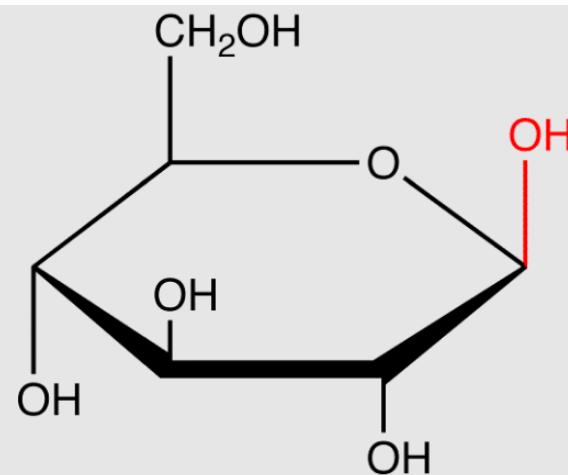
Glucose

... Cont'd

- the **α -anomer** has the -OH pointing **down**, however the **β -anomer** has the -OH pointing **up**



α -anomer of
D-glucopyranose
(α -D-glucopyranose)



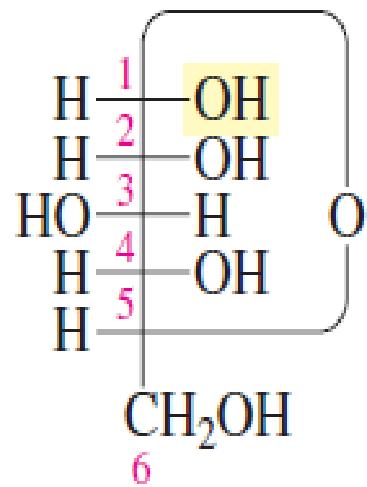
β -anomer of
D-glucopyranose
(β -D-glucopyranose)

Go to Settings to activate Windows.

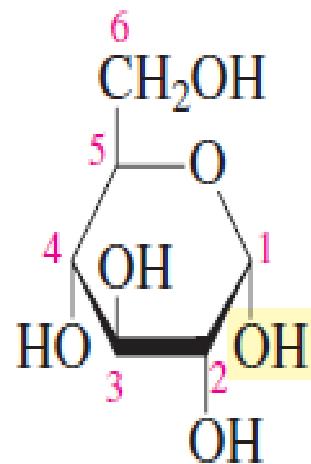
Glucose

... Cont'd

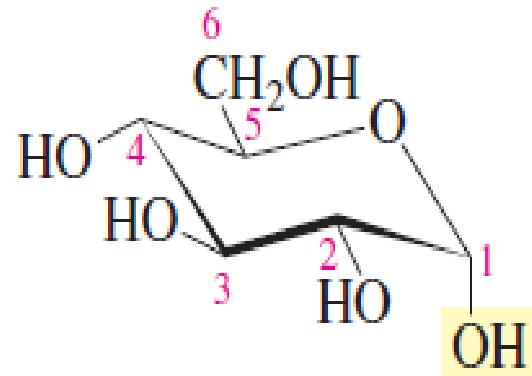
- in general, the α -position is to the **right** in a Fischer projection, **down** in a Haworth projection, and **axial** in a chair conformation



Fischer projection



Haworth projection
 α -D-glucose

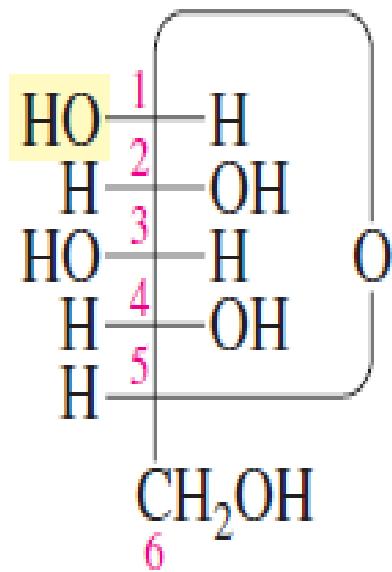


chair conformation

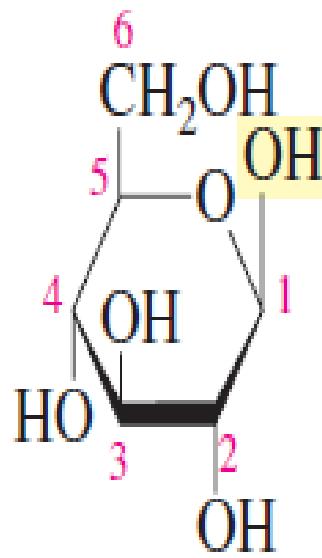
Glucose

... Cont'd

- the β -position is to the **left** in a Fischer projection, **up** in a Haworth projection, and **equatorial** in a chair conformation

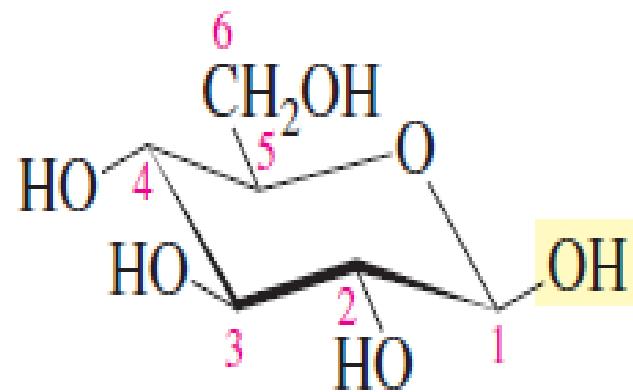


Fischer projection



Haworth projection

β -D-glucose



chair conformation

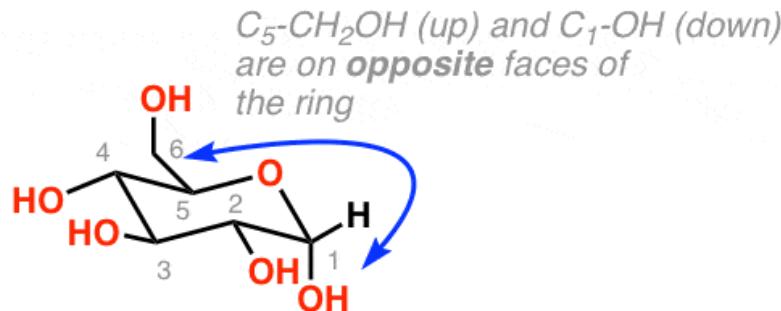
Glucose

... Cont'd

Alpha (α) and beta (β) isomers ("anomers") differ in the orientation of the OH at the C-1 hemiacetal carbon

Example: D-glucose

"alpha" (α) isomer:

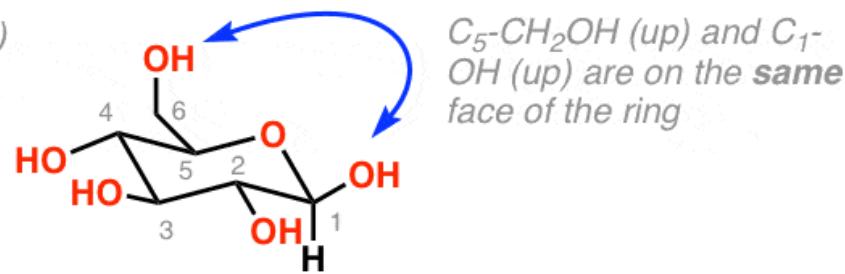


α -D-Glucose

drawn as "chair"

Specific rotation: $[\alpha]_D^{20} + 112^\circ$

"beta" (β) isomer:

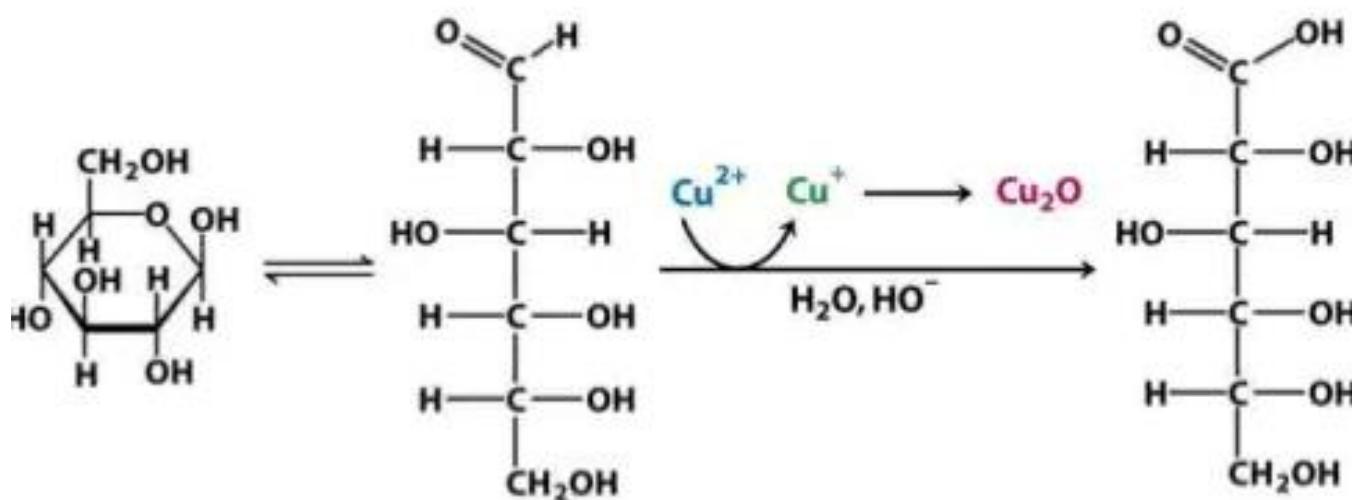


β -D-Glucose
drawn as "chair"

Specific rotation: $[\alpha]_D^{20} + 18.7^\circ$

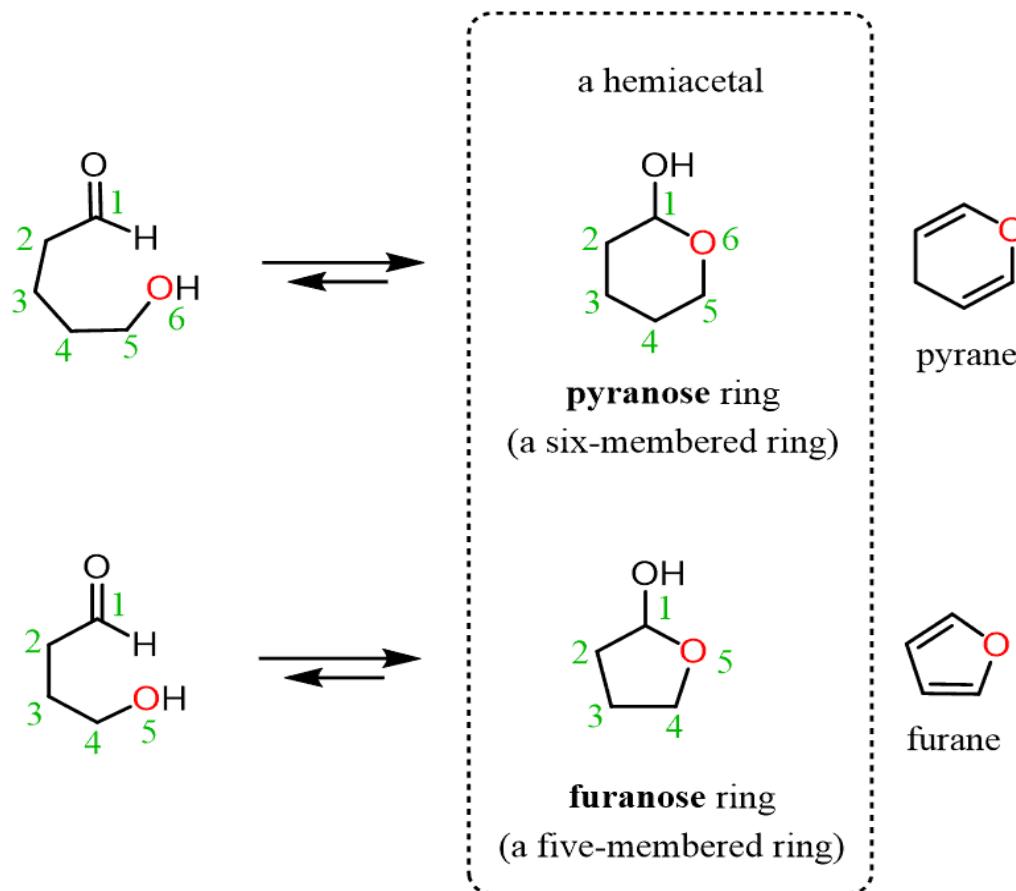
Note different specific rotations!

- the oxidation of the aldehyde C=O group produces carboxylic acid sugars
- a sugar that reacts with **Benedict's solution** is called a ***reducing sugar*** since it reduces the ion $\text{Cu}^{2+} \rightarrow \text{Cu}^+$



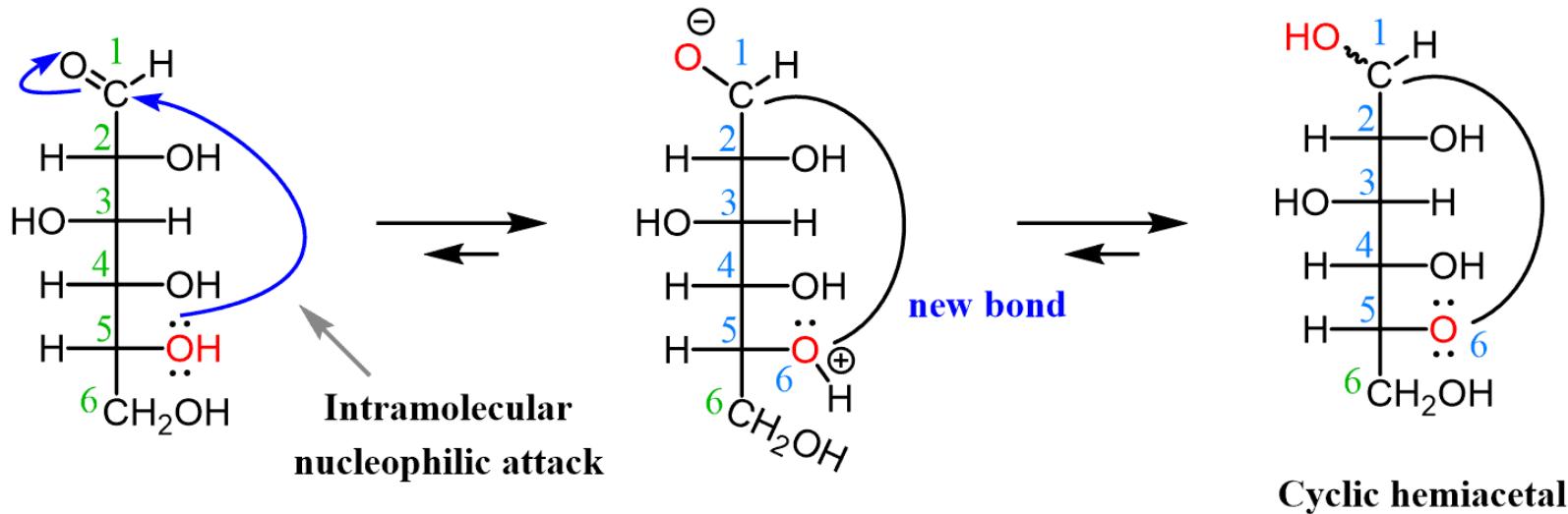
Anomeric forms of monosaccharides

- cyclic forms of carbohydrates are favored when 5- 6-membered rings can be formed which are classified as a **furanose** and a **pyranose ring** respectively which is a **general nomenclature** for **oxygen-containing 5– 6-membered rings**



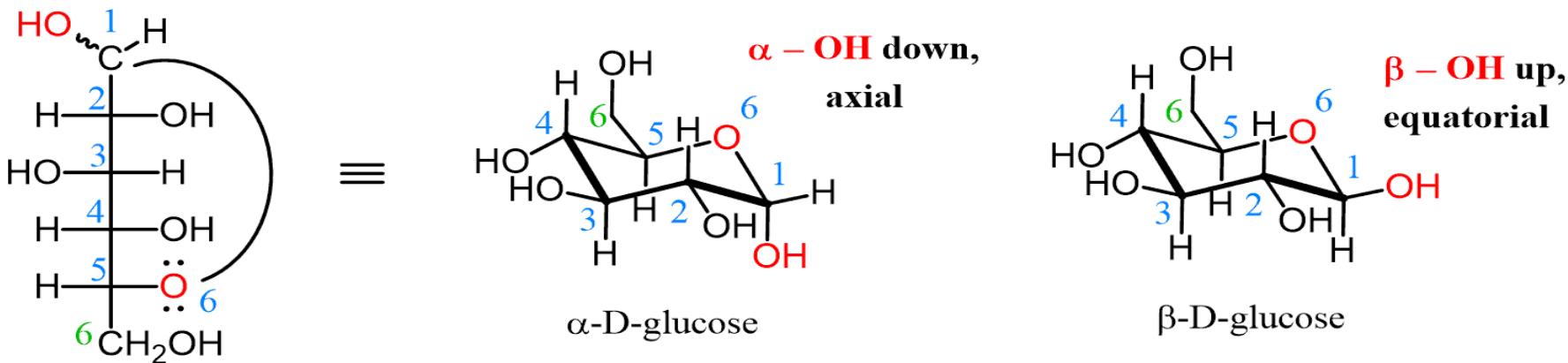
Anomeric forms of monosaccharides

- they are formed through an **intramolecular hemiacetal formation**, for instance, **linear D-Glucose converts** into a **pyranose ring** through the **attack of C5-OH group** on the **carbonyl** forming a **new asymmetric center** which is formed in **both configurations**



Anomeric forms of monosaccharides

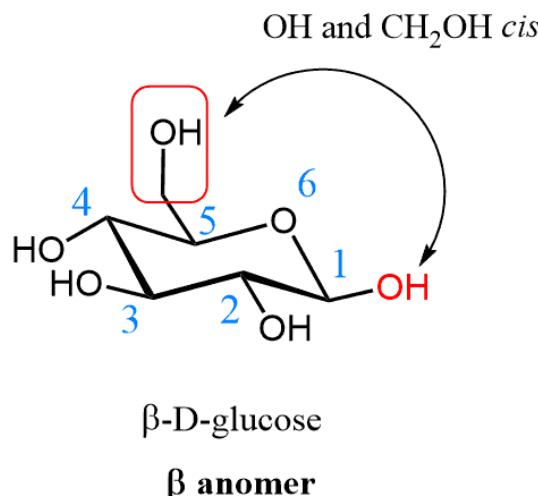
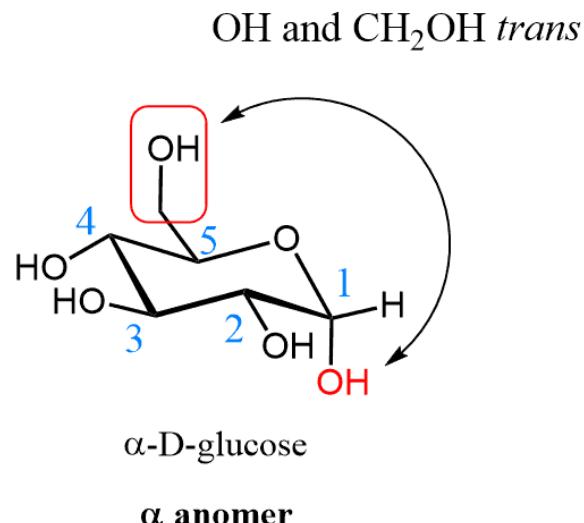
- carbon 1 is the new stereogenic center shown with a wiggly line, the structure on the right is the cyclic form of D-Glucose which, as a six-membered ring adopts a **chair conformation**



- all the initial chiral centers remain intact, and the two cyclic forms differ in the configuration of **only one chiral center** and are termed as epimers, and in the case of sugars, they are said to be **anomers**

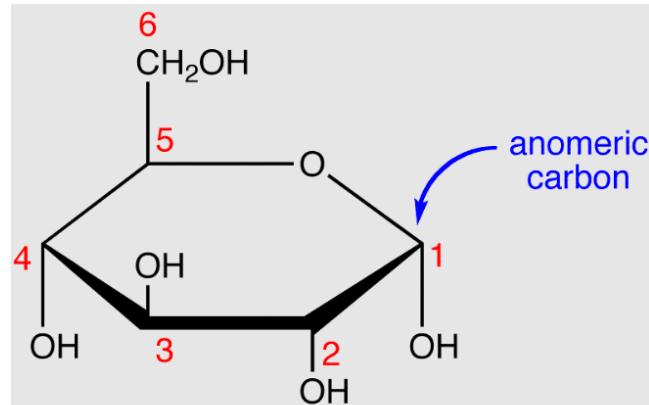
Anomeric forms of monosaccharides

- an **anomer** is **type of epimer** characterized by the carbon in two possible configurations of a cyclic saccharide, such a carbon is called the **anomeric carbon** (carbon 1 in the picture above) and the configuration about it is denoted by prefixes **α – and β**
- if the newly formed **OH group** on the asymmetric center is pointing **down** (trans to CH_2OH group at C-5), then it is **α -D-glucose**, however if the **OH group** is pointing **up** (cis to the CH_2OH group at C-5), then the hemiacetal is **β -D-glucose**

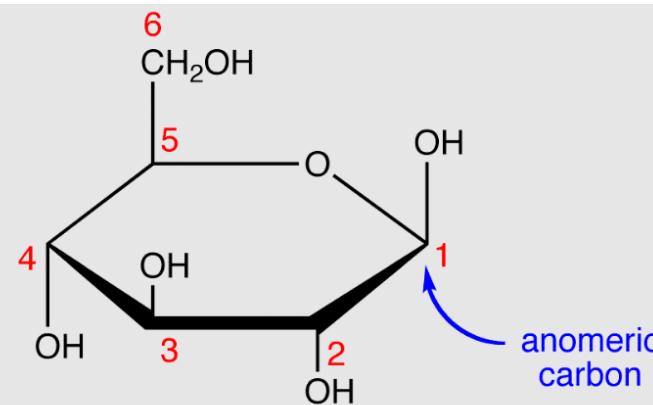


Anomeric forms of monosaccharides

- anomers are cyclic monosaccharides differing from each other in the configuration of **C-1** if they are **aldoses** or in the configuration at **C-2** if they are **ketoses**, and these carbon in anomers are known as anomeric carbon or anomeric center
- Example
 - ✓ α -D-Glucopyranose and β -D-glucopyranose are anomers



α -D-glucopyranose

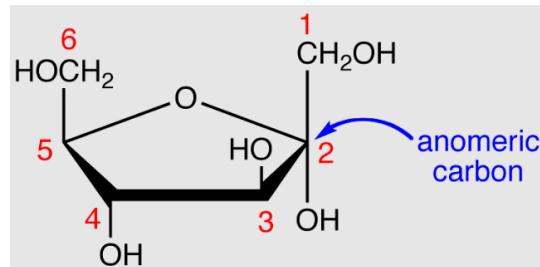


β -D-glucopyranose

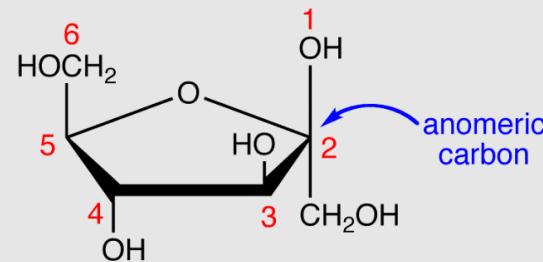
Anomeric forms of monosaccharides

... Cont'd

- ✓ α -D-Fructofuranose and β -D-fructofuranose are anomers

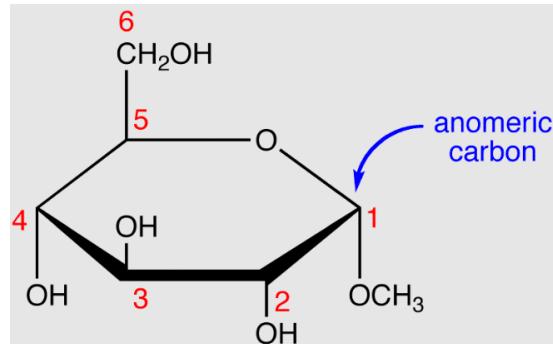


α -D-fructofuranose

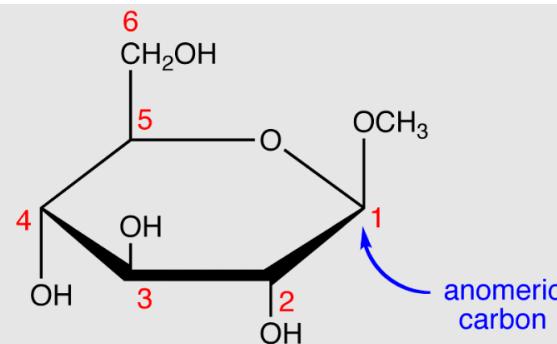


β -D-fructofuranose

- ✓ ethyl α -D-glucopyranoside and methyl β -D-glucopyranoside are anomers



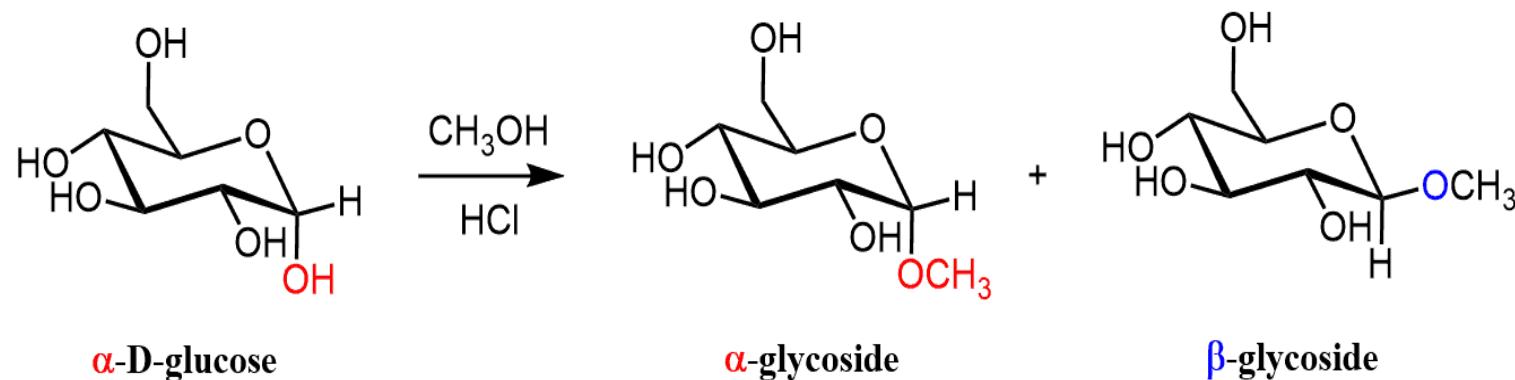
methyl α -D-glucopyranoside



methyl β -D-glucopyranoside

Glycosides

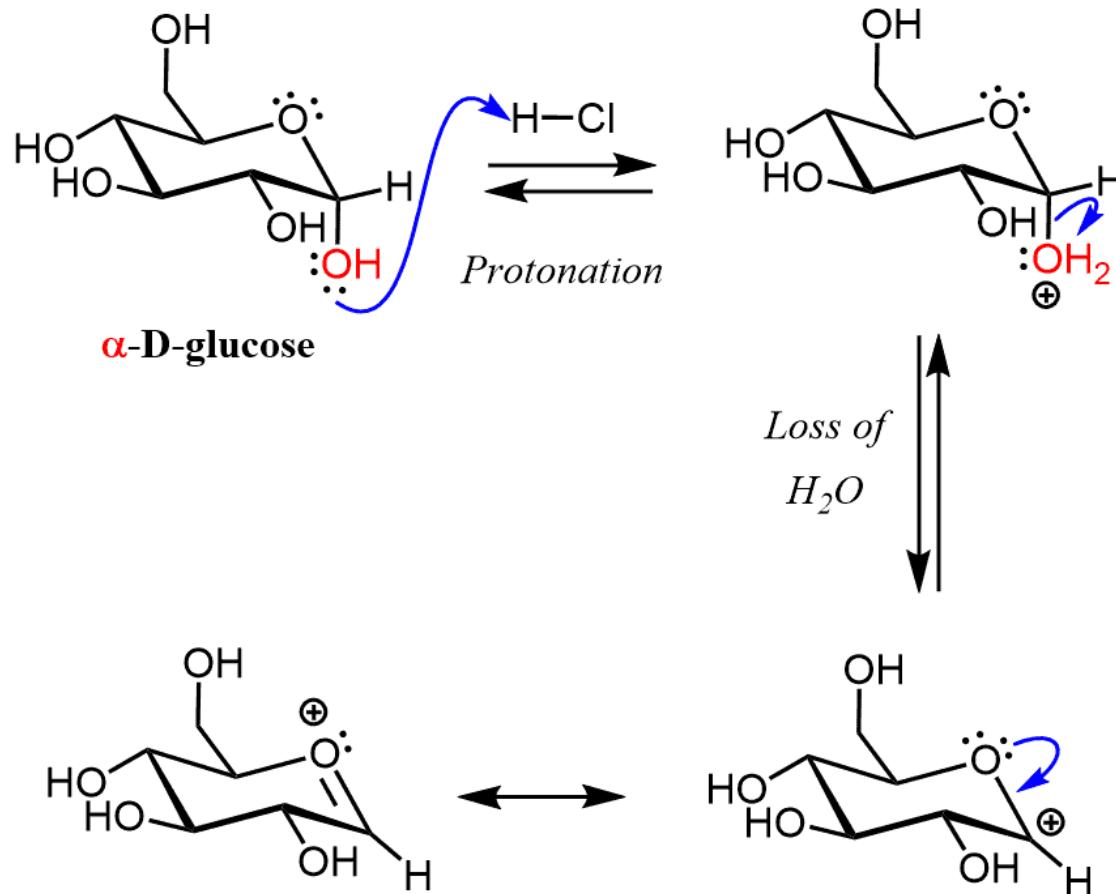
- carbohydrates exist mainly in their cyclic forms **when 5- or 6-membered rings** are possible
- cyclic carbohydrates are **hemiacetals** which can be transformed into **acetals**
- the **acetals** of **monosaccharides** are called **glycosides** where **acetals** with an **alkoxy group (OR)** bonded to the **anomeric carbon**
- the bond between the **anomeric carbon** and the **alkoxy oxygen** is called a **glycosidic bond**
- treatment of **α - or β -D-glucose** with **CH_3OH** and **HCl** forms **two anomeric glycosides** where the **OR group** is now **pointing up and down**



Glycosides

...Cont'd

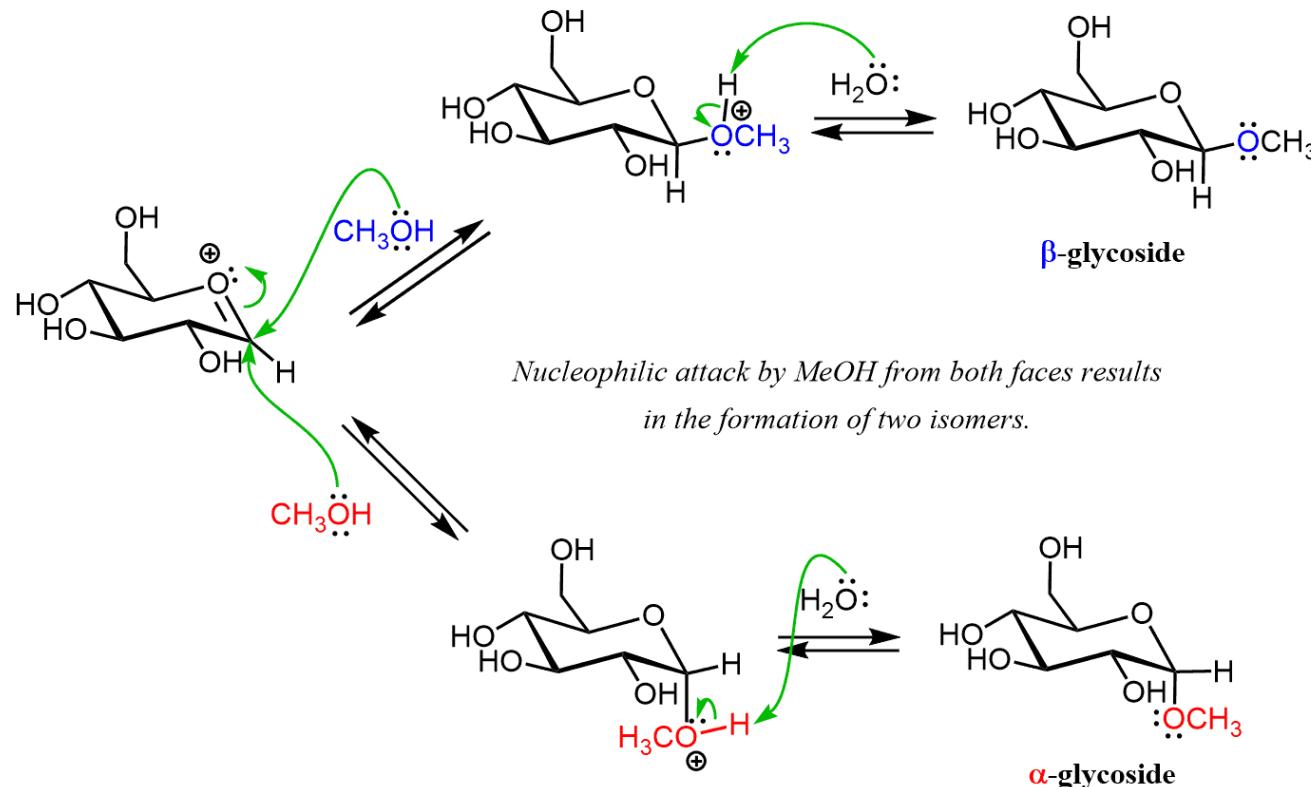
- in the first step, the anomeric hydroxyl group is protonated and expelled by the lone pairs of the neighboring oxygen in the ring



Glycosides

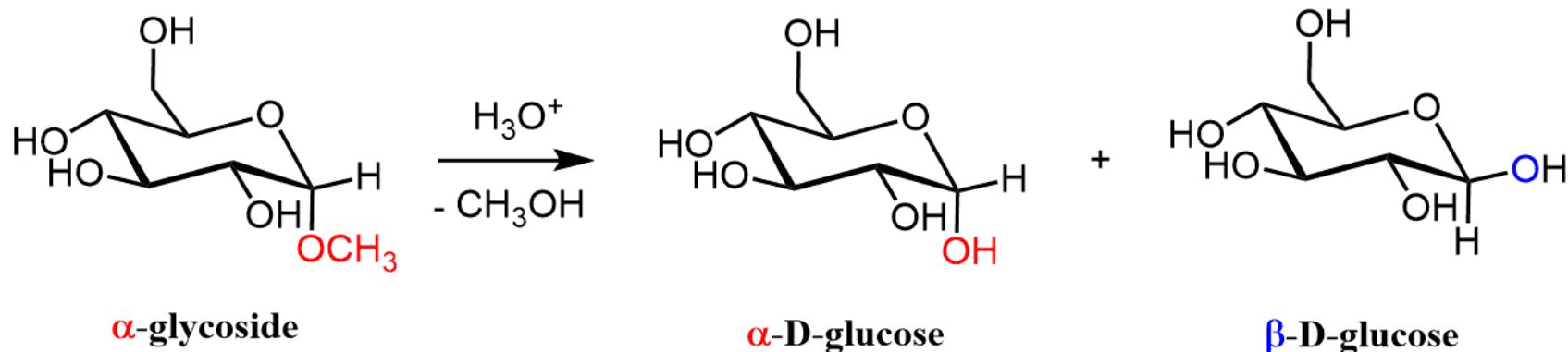
...Cont'd

- the resulting carbocation is **resonance stabilized** and this explains why out of all the OH groups of the sugar, only the one on the anomeric carbon reacts
- in **both resonance structures** there is a **planar carbocation**, the geometry which allows for a **nucleophilic attack** by CH_3OH from **both faces** and therefore, two isomers are formed



Glycoside Hydrolysis

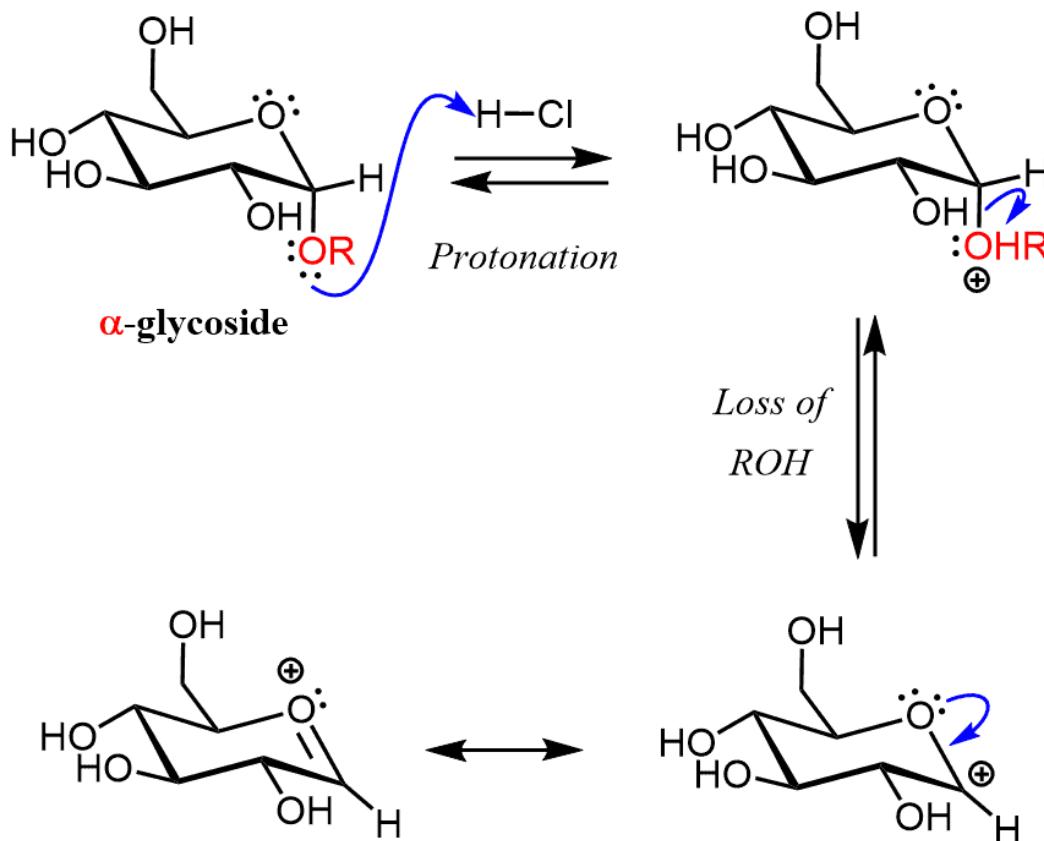
- stable in neutral/basic conditions and can be isolated and crystallized
- such stability allows for their use as protecting groups for aldehydes and ketones in reactions involving strong bases and nucleophiles, however, the acetal protecting group is removed by hydrolysis with acid and water back to cyclic hemiacetals



Glycoside Hydrolysis

...Cont'd

- hydrolysis starts with the protonation of the alkoxy group on the anomeric carbon followed by the formation of a planar carbocation

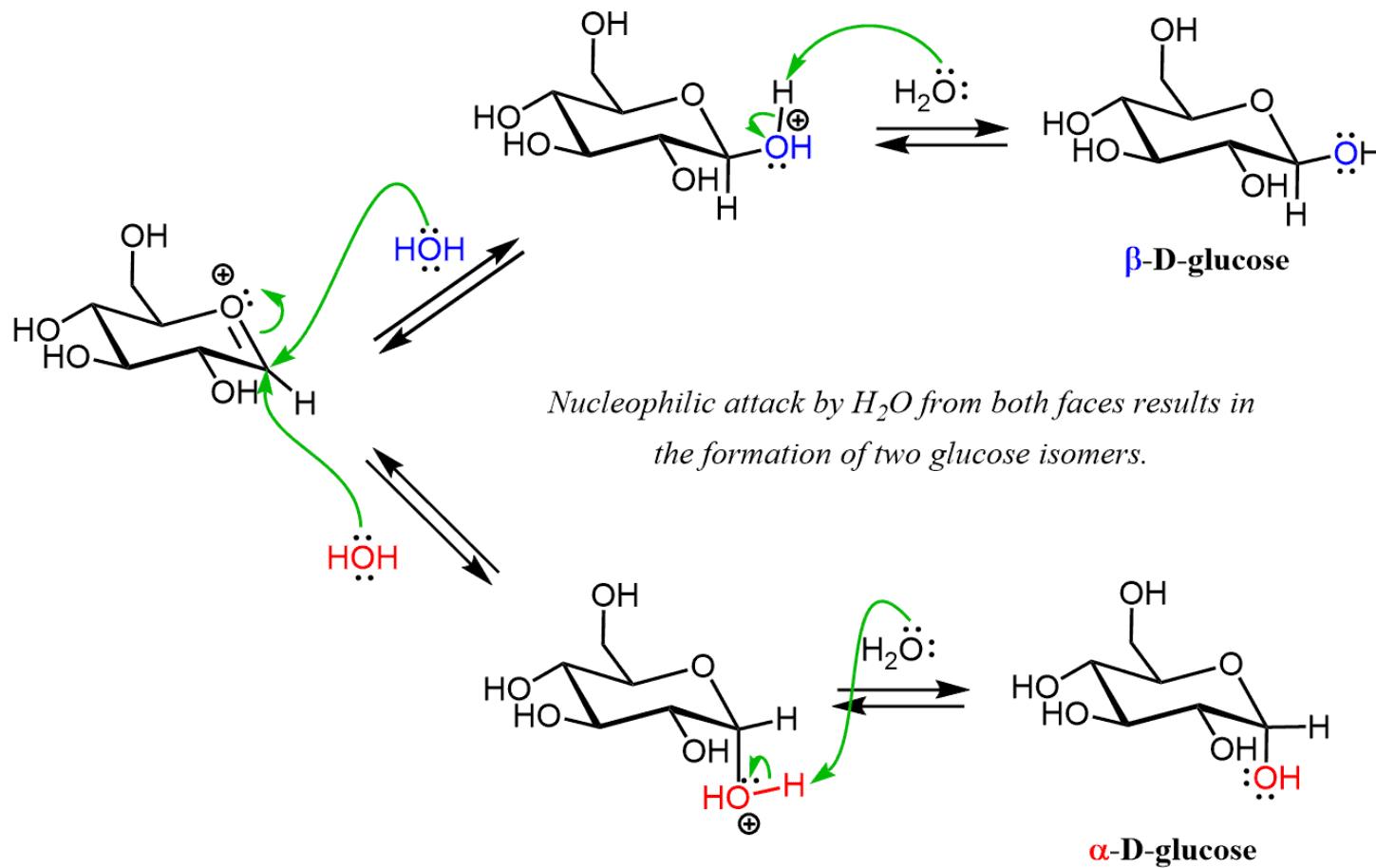


Resonance stabilized planar carbocation

Glycoside Hydrolysis

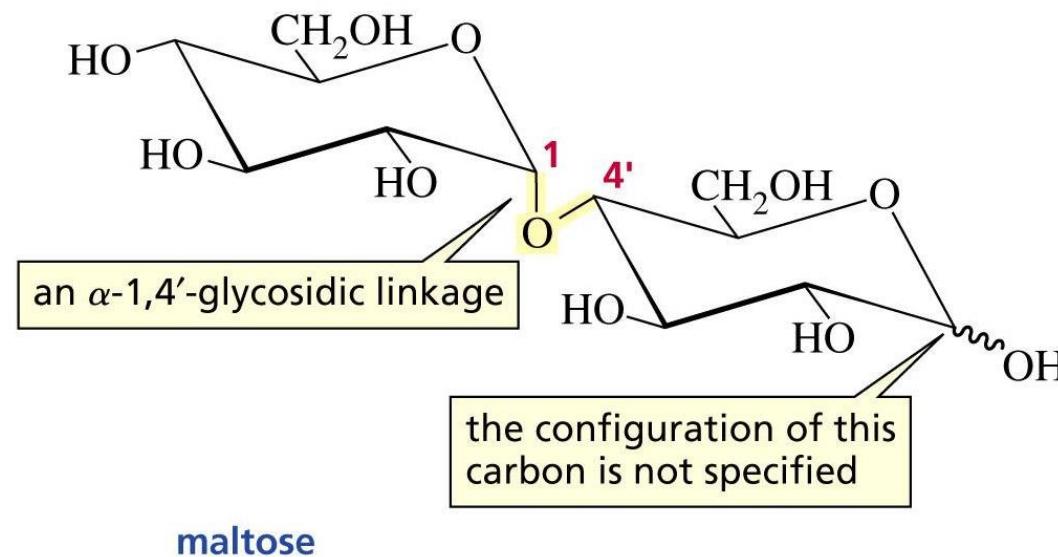
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- after the nucleophilic attack by water and a deprotonation step, the two isomers of glucose are formed

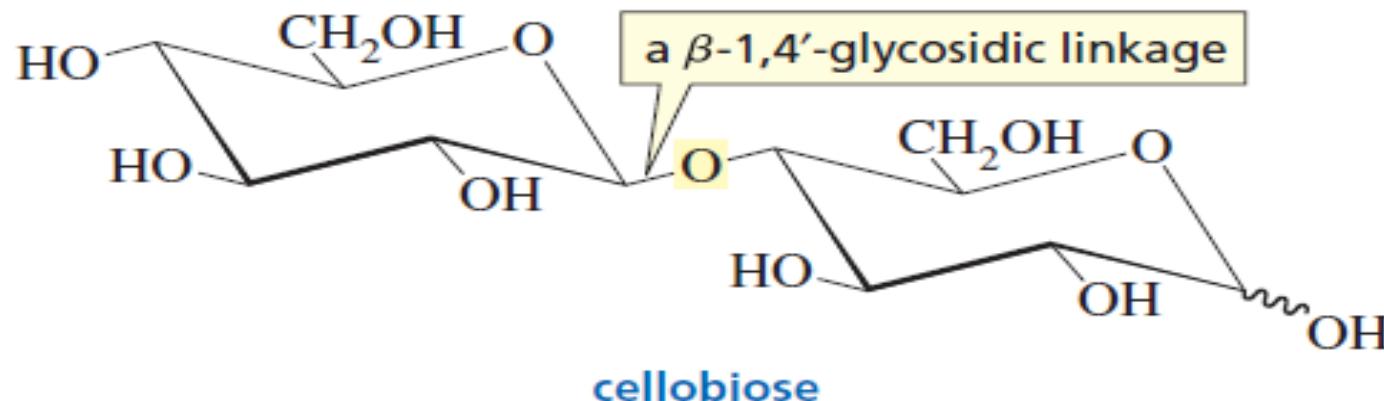


Disaccharides

- two monosaccharide (D-glucose) subunits hooked together by an acetal linkage
 - an α -1,4'-glycosidic linkage e.g., maltose



- **cellobiose**, a disaccharide obtained from the hydrolysis of cellulose
- the two glucose subunits are hooked together by a β -1, 4'-glycosidic linkage

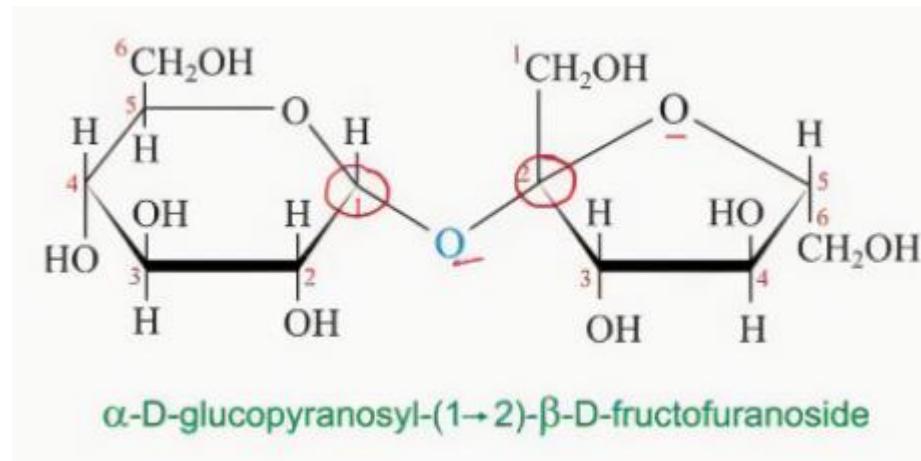


Disaccharide

... Cont'd

sucrose

- the most common **disaccharide** is **sucrose (table sugar)** obtained from **sugar beets** and **sugarcane**
- consists of a **D-glucose** subunit and a **D-fructose** by a **glycosidic bond** between **C-1 of glucose** (in the α -position) and **C-2 of fructose** (in the β -position)
- sucrose is **not a reducing sugar** because the **glycosidic bond** is between the **anomeric carbon of glucose** and the **anomeric carbon of fructose**



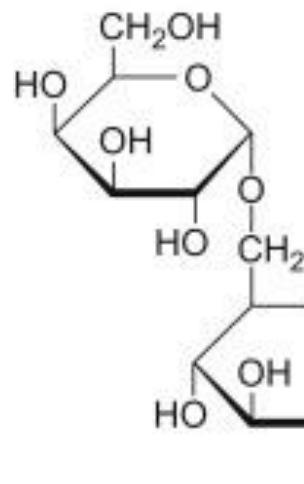
Oligosaccharides

- polymers containing **3-10 monosaccharide units**
- residues are bonded to each other by **glycosidic bonds** (can be either α or β)
- involved in $\alpha-(1\rightarrow6)$ glycosidic bonds that humans lack the enzyme to hydrolyze, i.e. **indigestible**

- **raffinose, stachyose and verbascose** are **not-digestible short-chain carbohydrates** or oligosaccharides
- humans **do not have enzymes to** digest them, so they pass unchanged to the colon where the normal **intestinal bacteria ferment** them to gases (methane, carbon dioxide, hydrogen), which can cause **abdominal bloating**
- an **enzyme alpha-galactosidase** that can break them down and thus prevent gas after eating beans is available as an **over-the-counter supplement**

Oligosaccharides

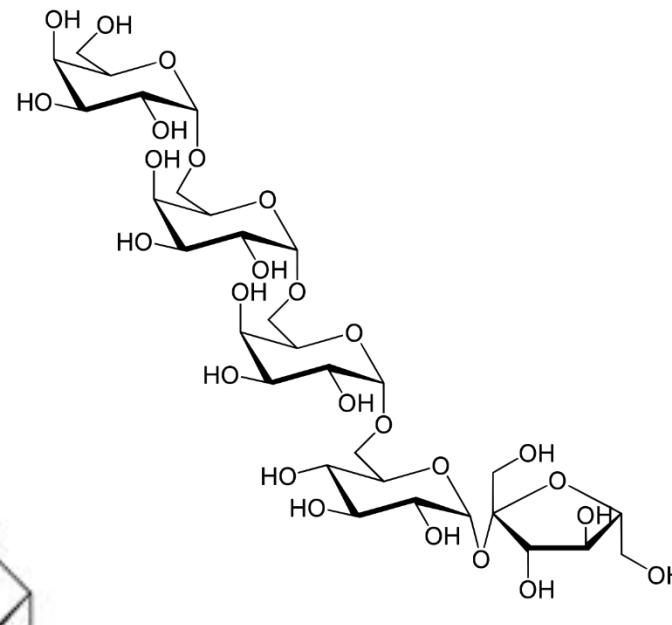
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Raffinose



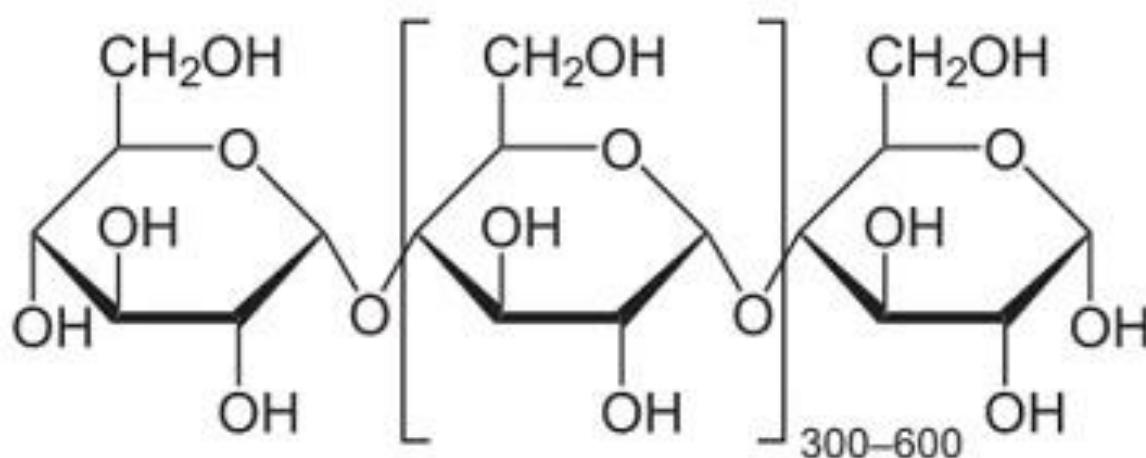
Stachyose



verbascose

Polysaccharides

- contain as few as 10 or as many as several thousand monosaccharide units joined together by glycosidic linkages



Structure of amylose

Polysaccharides

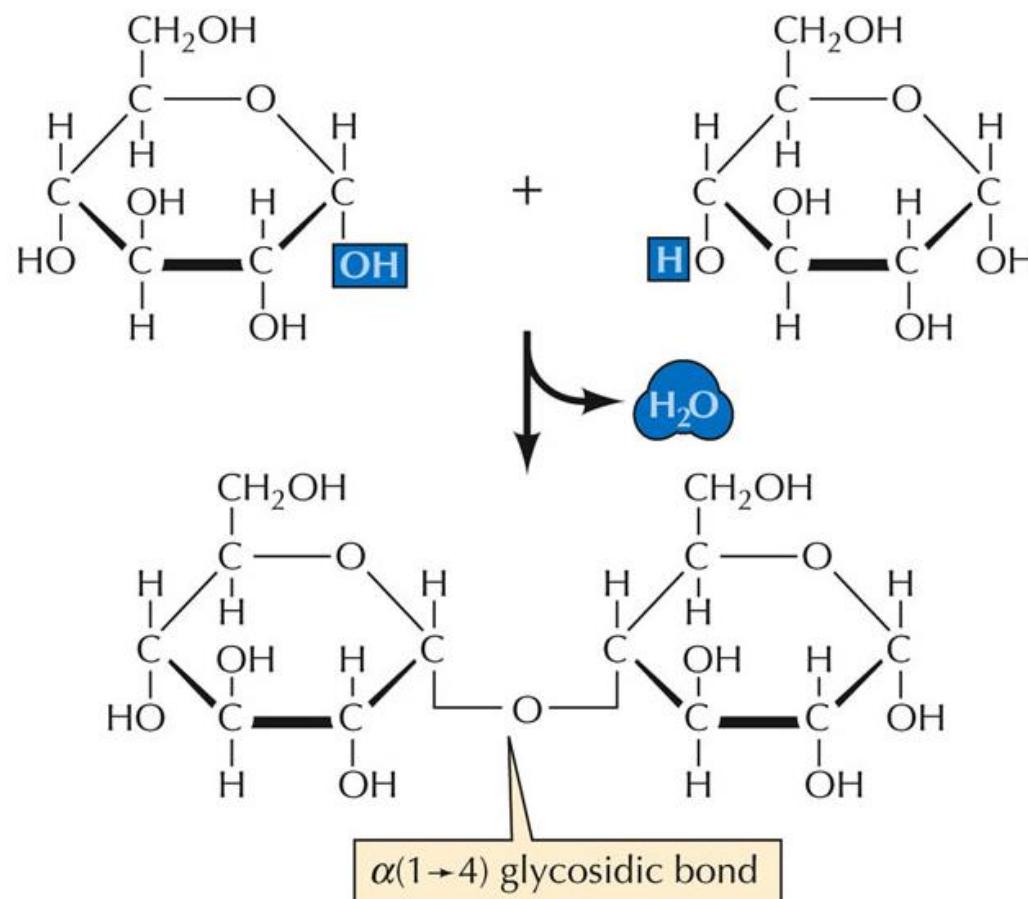
Starch

- **carbohydrate reserve** of plants which is the **most important dietary source** for **higher animals, including man**
- **high content** of starch is found in **cereals, roots, tubers, vegetables** etc.
- **homopolymer** composed of **D-glucose units** held together by **α -glycosidic bonds**, consist **two polysaccharide component-** **water soluble amylose** (15-20%) and a **water insoluble amylopectin** (80-85%)
- **hydrolyzed** by **amylase** (pancreatic or salivary) to liberate **dextrin** and finally maltose and **glucose units**
- **amylase** acts specifically on **α (1→4) glycosidic bonds**, however, **α (1→6) glycosidic bond** at branch point are attacked by de-branching enzyme **α (1→6) glucosidase**

Polysaccharides

...Cont'd

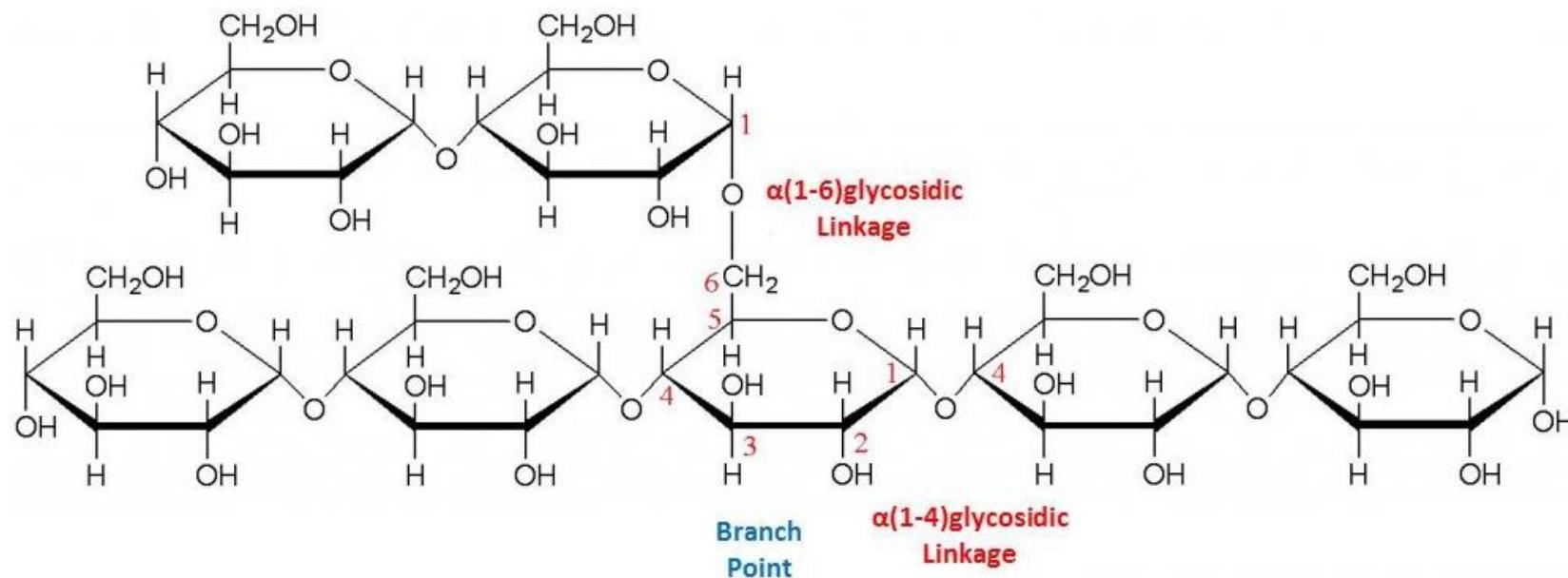
- amylose is composed of a long unbranched chain with 200 -1000 D-glucose units held by $\alpha(1 \rightarrow 4)$ glycosidic linkages



Polysaccharides

...Cont'd

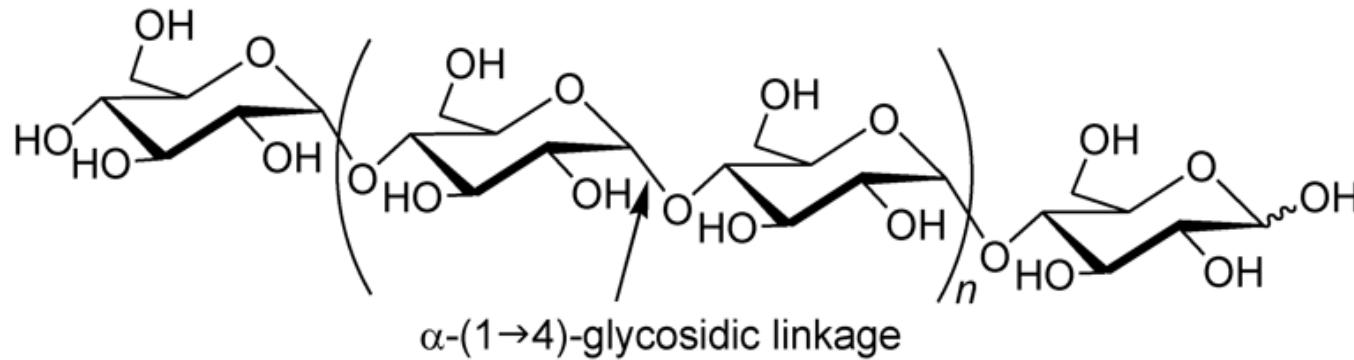
- amylopectin, on the other hand, is a **branched chain** with $\alpha(1 \rightarrow 6)$ glycosidic bond at the **branching points** and $\alpha(1 \rightarrow 4)$ glycosidic bond everywhere, contain a **few thousand glucose units** looks like a **branched tree (20-30 glucose units per branch)**



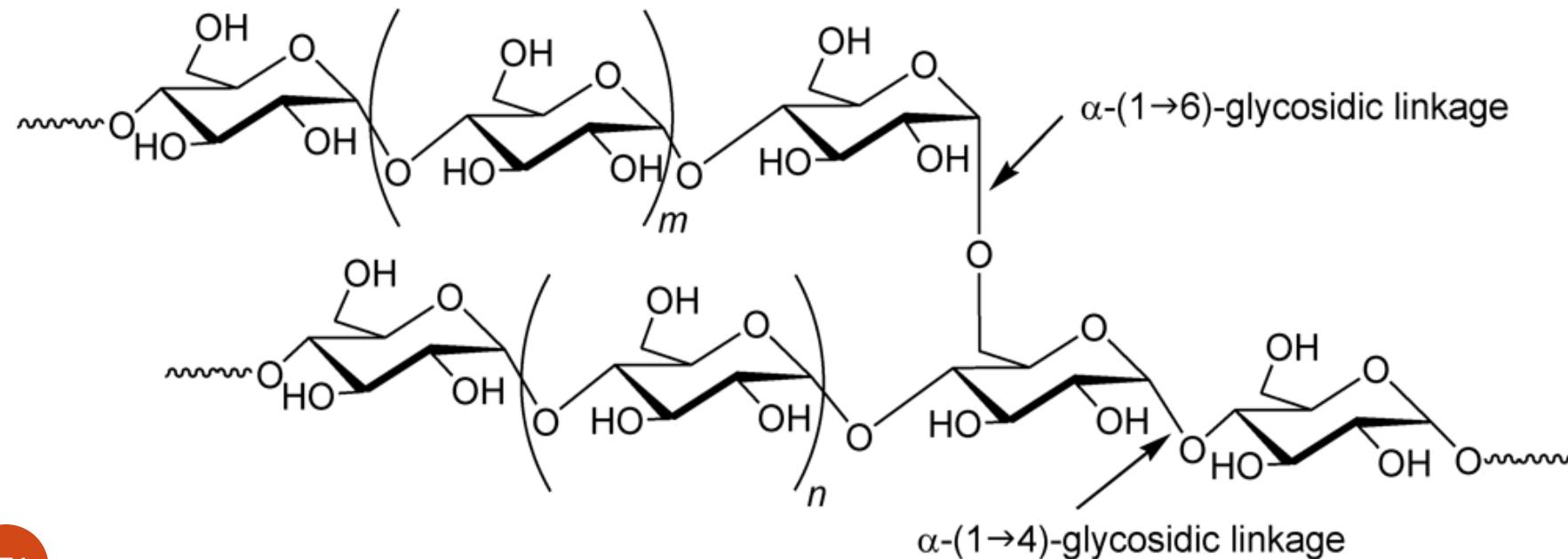
Polysaccharides

...Cont'd

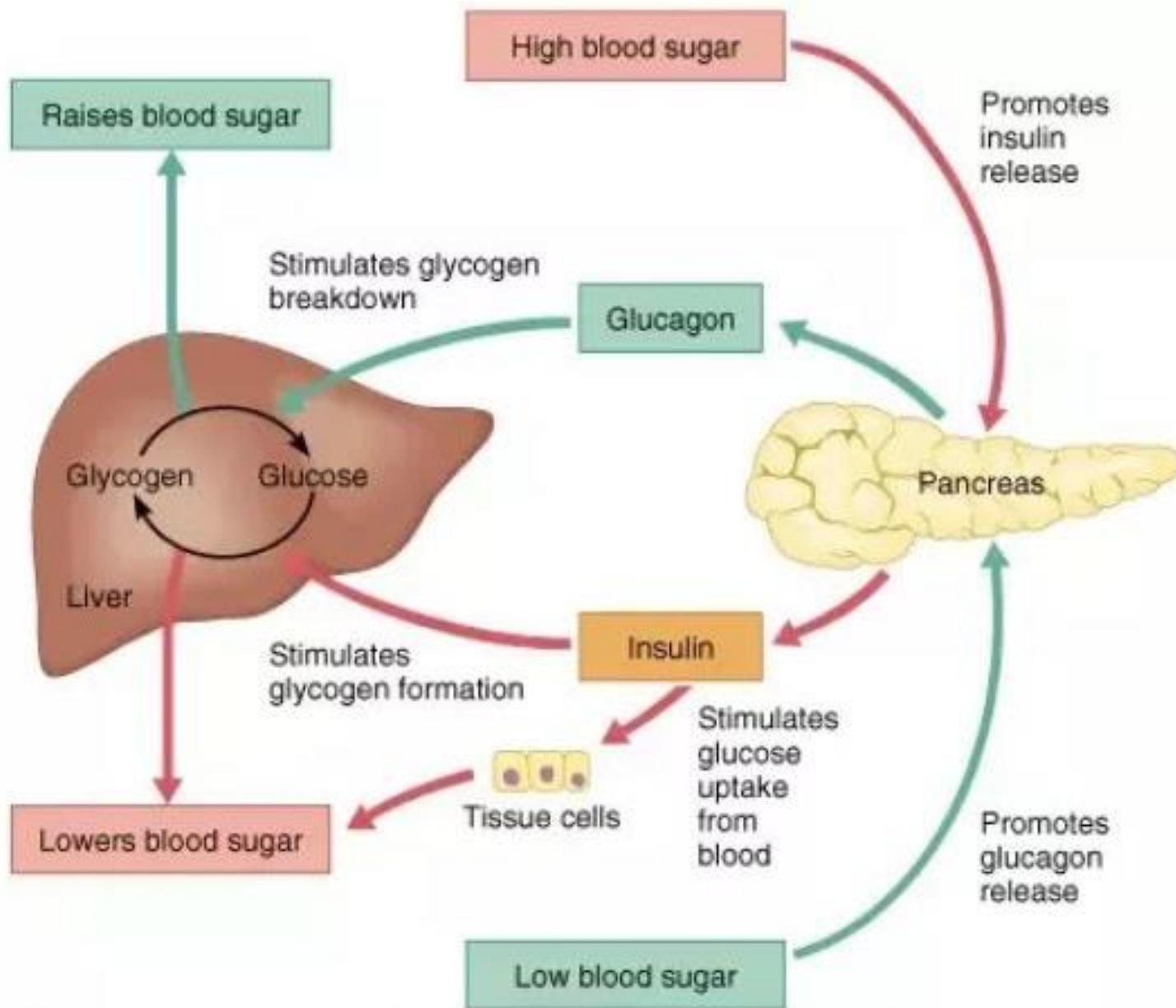
Amylose



Amylopectin



- animals stored **excess glucose** as a polysaccharide known as **glycogen**
- **glycogen** has a structure like that of **amylopectin**, but **glycogen** has more branches
- when the body **needs energy**, many individual **glucose units** can be **simultaneously removed** from the **ends of branches**



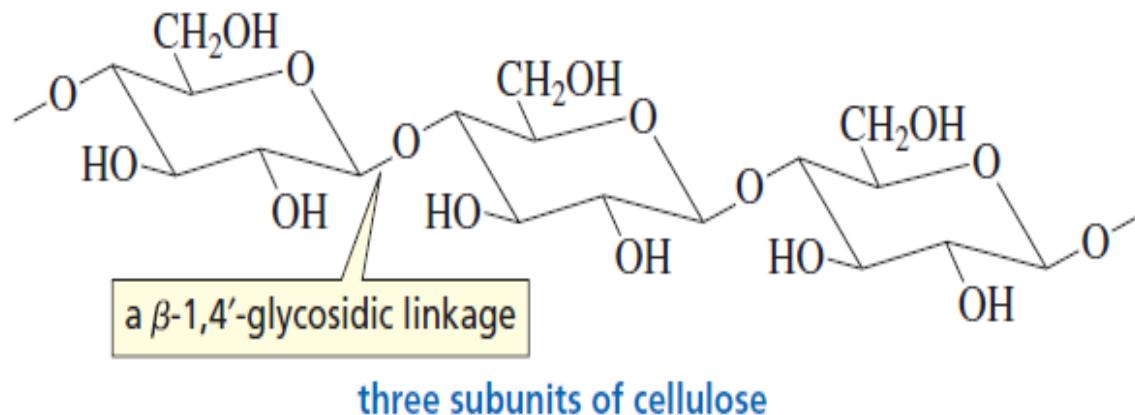
Cellulose

- **structural material** of higher plants, **cotton**, for example, is composed of about **90% cellulose**, and **wood** is about **50% cellulose**
- like **amylose**, **cellulose** is composed of **unbranched** chains of D-glucose units
- unlike **amylose**, however, the **glucose units in cellulose** are joined by **β -1, 4'-glycosidic** linkages rather than by **α -1, 4'- glycosidic** linkages

Polysaccharides

...Cont'd

- all mammals have the enzyme called α -glucosidase that hydrolyzes the α -1, 4'-glycosidic linkages that join glucose units
- however, they do not have the enzyme called β -glucosidase that hydrolyzes β -1,4'-glycosidic linkages
- α -1,4'-glycosidic linkages are easier to hydrolyze than β -1,4'-glycosidic linkages because of the anomeric effect that weakens the bond to the anomeric carbon

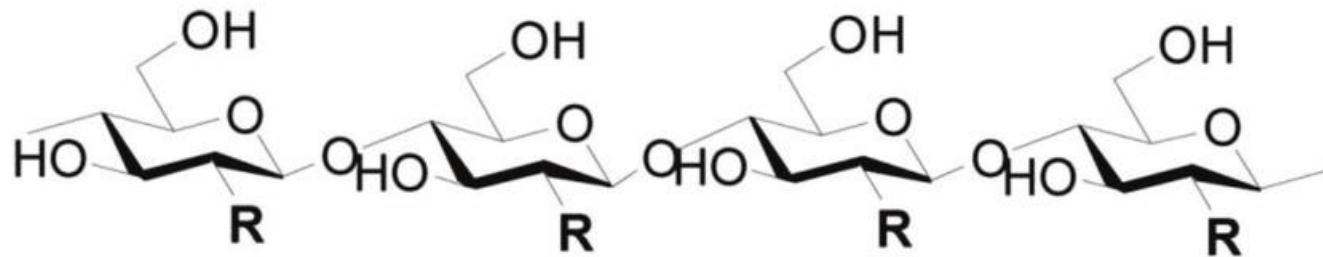


Polysaccharides

...Cont'd

Chitin

- β -1 \rightarrow 4 linked N-acetyl glucosamine monomer units
- instead of glucose, use N-acetyl glucosamine (C-2s are N-acetyl instead of -OH)
- cellulose strands are parallel, chitins can be parallel or antiparallel
- exoskeleton of arthropods and cell walls of fungi



Chemical structures of cellulose (R = OH), chitin (R = NHCOCH₃), and chitosan (R = NH₂).

Lipids

- bio-molecules that are **hydrophobic in nature** because of the **high number** of hydrocarbons in their structure
- **relatively insoluble in water** but readily **soluble in non-polar solvents** such as chloroform
- examples of lipids

- | | |
|------------|--|
| ✓ Fats | ✓ Waxes |
| ✓ Oils | ✓ Fat-soluble Vitamins (Vitamins A, D, E and K), |
| ✓ Steroids | |

Lipids

- contains the element **C, H and O**
- lipid can be either **fats, oils or waxes**
- the main **biological functions** of lipids include **energy storage** and as **structural components** of **cell membranes** (Phospholipid)
- the ratio of H to O in lipids is 2:1

Lipids

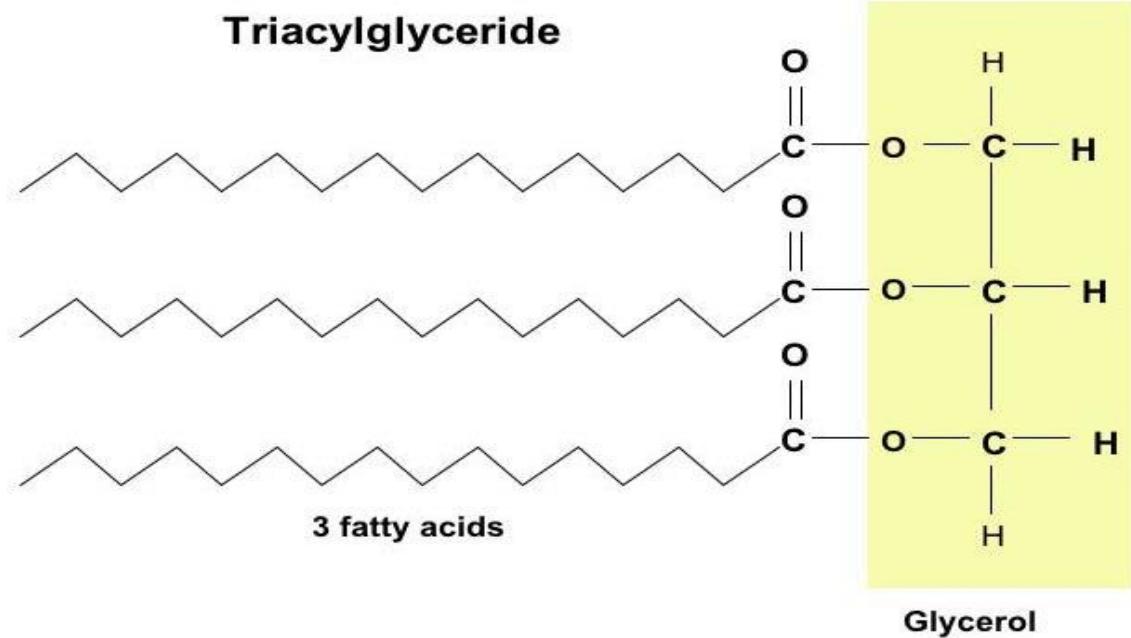
Functions

- ✓ store energy
- ✓ biological membrane
- ✓ waterproof coverings
- ✓ hormone: steroid

Lipids

Structure

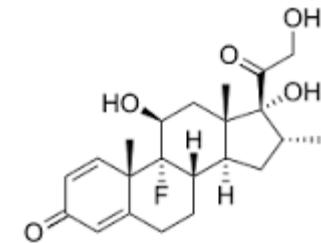
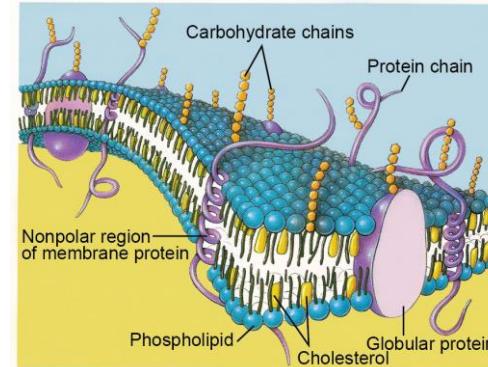
- each lipid is made up of small chemical sub-unit called fatty acids and glycerol



Lipids

Functions

- **fats and oils** - store energy
- **Phospholipids** - structural role in cell membranes
- **steroids** - hormones and vitamins
- **animal fat** - thermal insulation
- **lipid coating around nerves** - provides electrical insulation
- **oil and wax on skin, fur, and feathers** - repels water



Fatty Acids

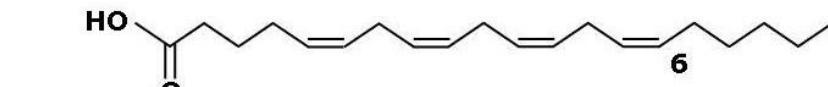
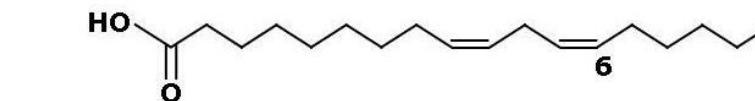
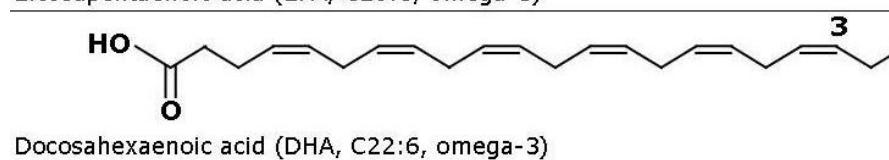
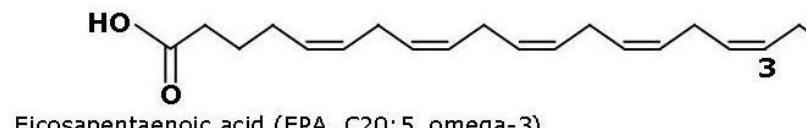
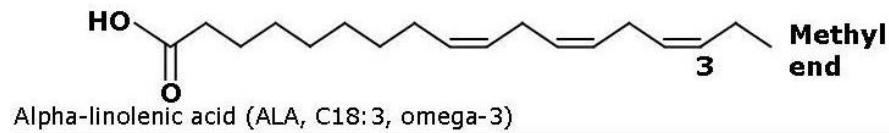
- unbranched carboxylic acids having long hydrocarbon chains
- most of the **naturally available fatty acids** bears an **even number** of carbon atoms due to **their synthesis from acetate**
- both **saturated** and **unsaturated fatty acids** are available
- in **unsaturated fatty acids**, the **double bonds** have **cis-configuration** and are **separated by CH₂ group**
- **unsaturated FAs** have **less intermolecular interactions** compared to saturated FAs, thus **have lower melting points** in comparison to saturated fatty acids
- the **melting point decreases** as the **number of double bonds increases**

Fatty Acids

- consist of a long chain of carbons with a carboxyl group at one end
 - Saturated fatty acid

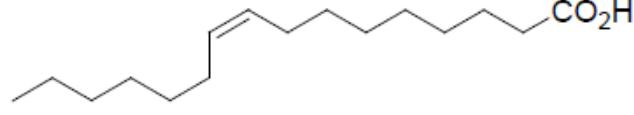
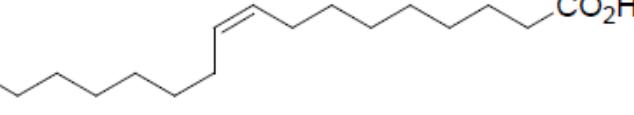
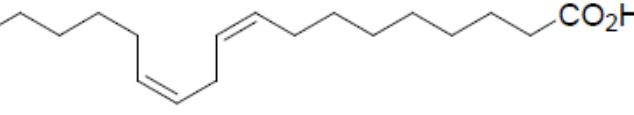
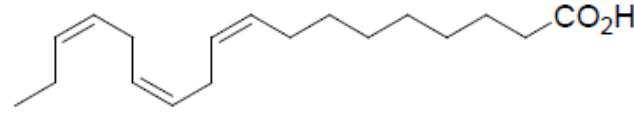


- Unsaturated fatty acid, Omega-3 and Omega-6



Fatty Acids

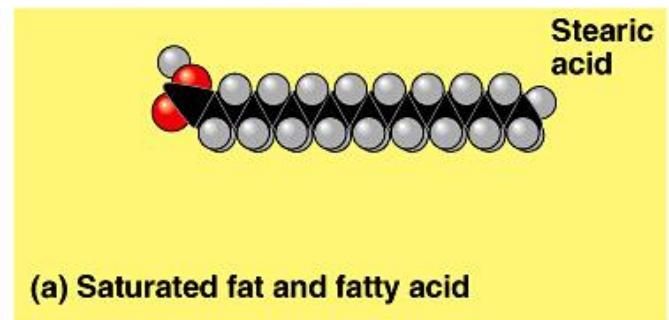
Variation of melting point with C# and unsaturation

Number of Carbons	Common Name	Structure	Melting Point (°C)
Saturated			
12	Lauric acid		44
14	Lauric acid		58
16	Palmitic acid		63
18	Stearic acid		69
20	Arachidic acid		77
Unsaturated			
16	Palmitoleic acid		0
18	Oleic acid		13
18	Linoleic acid		-5
18	Linolenic acid		-11

Fatty Acids

Saturated fats

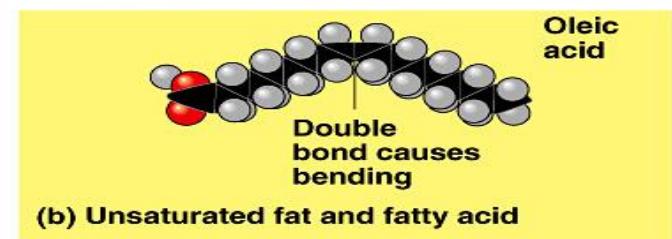
- ✓ no double bonds between carbons
- ✓ it is saturated with H atoms
- most animal fats
- ✓ solid at room temperature
- limit the amount in your diet
- ✓ contributes to heart disease
- ✓ deposits in arteries



Fatty Acids

Unsaturated fatty acid

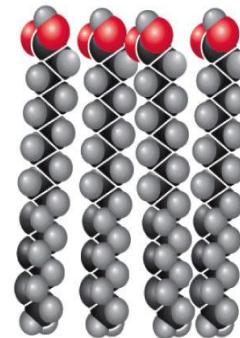
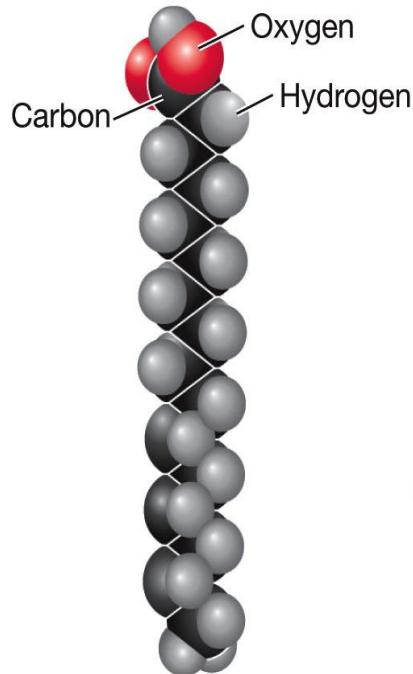
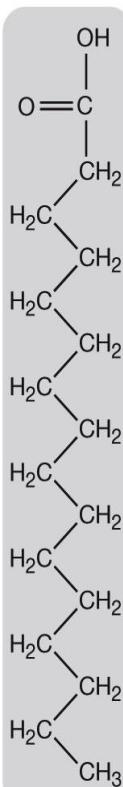
- **Unsaturated fatty acids:** some double bonds in carbon chain
 - ✓ *monounsaturated*: one double bond
 - ✓ *polyunsaturated*: more than one
- plant, vegetable & fish fats
 - ✓ liquid at room temperature
 - ✓ the fat molecules don't stack tightly together
- better choice in your diet



Fatty Acids

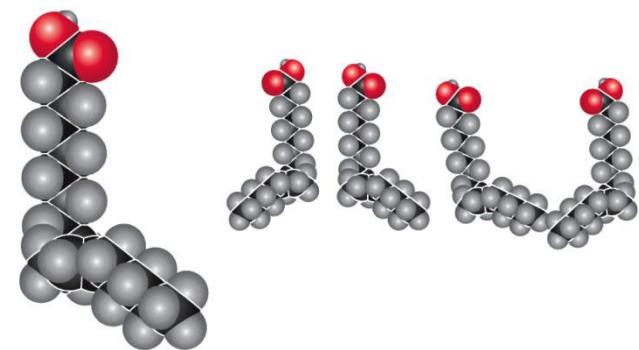
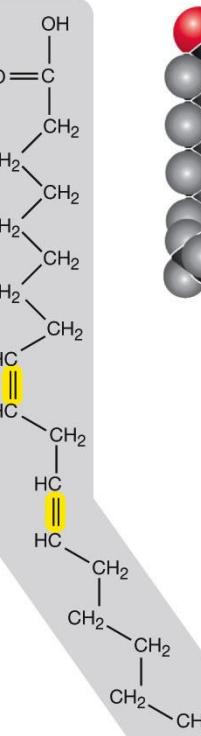
Saturated Fatty Acids

(A) Palmitic acid



Saturated Fatty Acids

(B) Linoleic acid



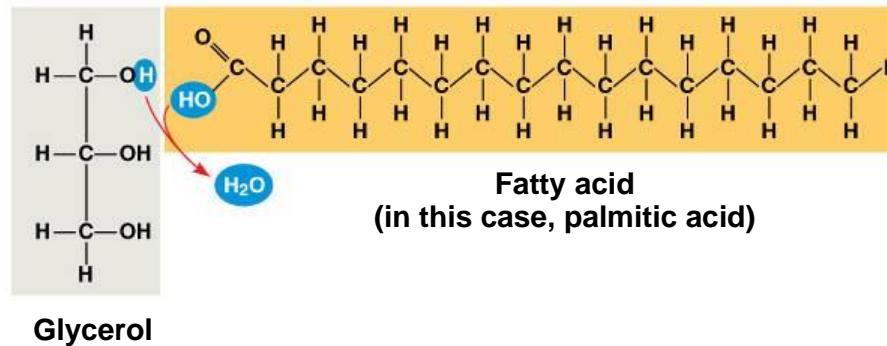
Fats and Oils

- fats are solids/semi-solid triglycerides, and the oils are liquids at room temperature
- fats are generally obtained from animals, while oils come from plant products
- in fats, saturated fatty acid is involved in the formation of ester with glycerol, whereas in oils, unsaturated fatty acid is involved
- in case of fats, the saturated fatty acid chain can pack closely together causing them to be solids at room temperature
- in case of oil, the unsaturated fatty acid chain can not pack tightly together, and therefore, that leads to usually have low melting points

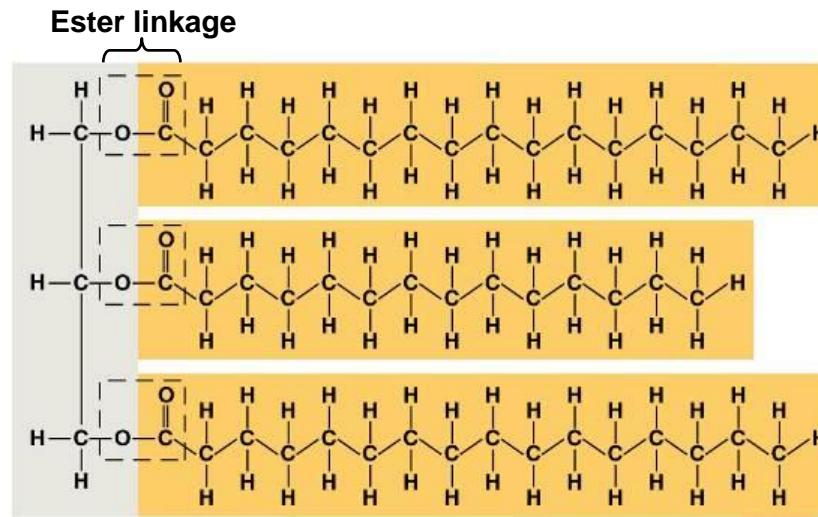
Fats

- **fats are constructed from two types of smaller molecules: glycerol and fatty acids**
- **glycerol is a three-carbon alcohol with a hydroxyl group attached to each carbon**
- **a fatty acid consists of a carboxyl group attached to a long carbon skeleton**

Fats



(a) One of three dehydration reactions in the synthesis of a fat

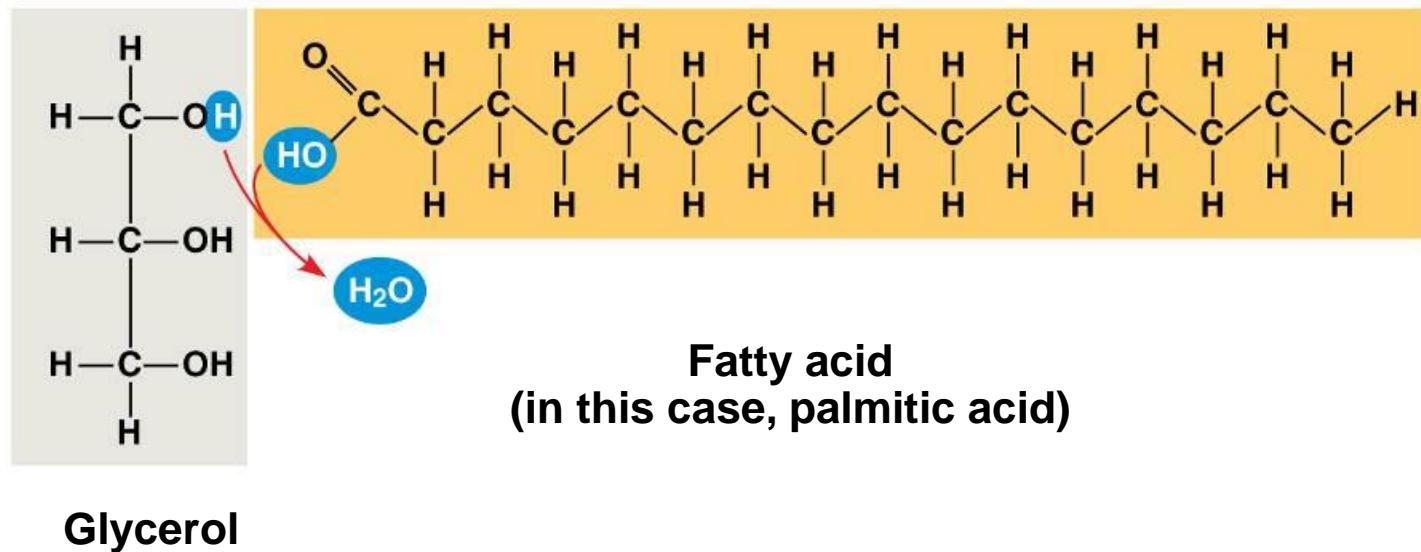


(b) Fat molecule (triacylglycerol)

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Fats

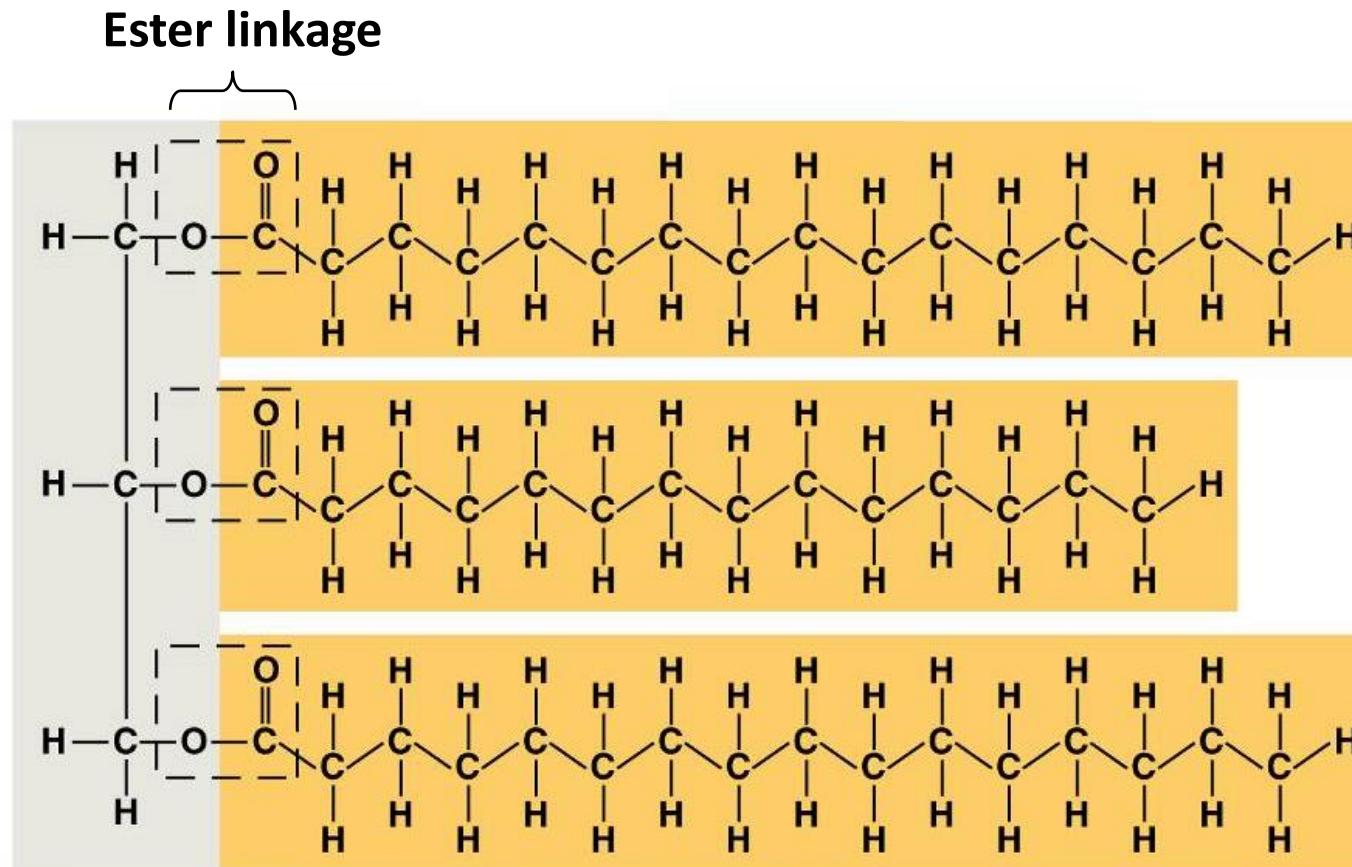
- three fatty acids are joined to glycerol by an ester linkage, creating a **triacylglycerol**, or triglyceride



(a) One of three dehydration reactions in the synthesis of a fat

Fats

- three fatty acids are joined to glycerol by an ester linkage, creating a **triacylglycerol**, or **triglyceride**

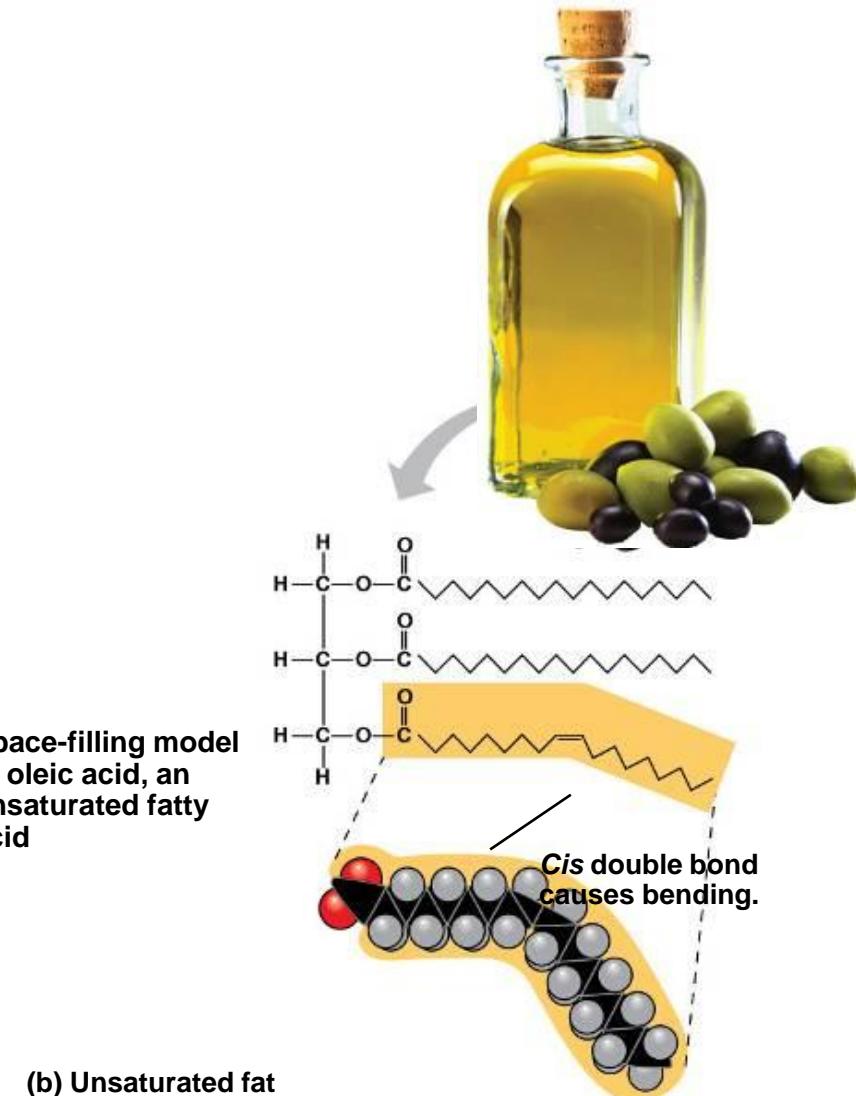
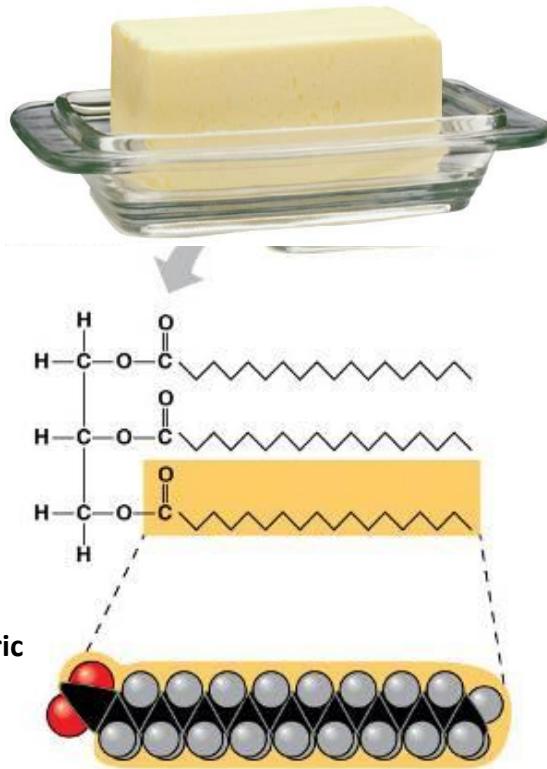


(b) Fat molecule (triacylglycerol)

Fats

- **fatty acids vary in length** (number of carbons) and **in the number and locations of double bonds**
- **saturated fatty acids have the maximum number of hydrogen atoms possible and no double bonds**
- **unsaturated fatty acids have one or more double bonds**

Fats



Fats

structural formula	space-filling model	generic simplified depiction
<p>phospholipid (phosphatidylcholine)</p> <p>fatty acid (stearic acid)</p>	<p>phospholipid molecule</p> <p>fatty acid molecule</p>	<p>phospholipid molecule</p> <p>lipid bilayer</p> <p>fatty acid molecule</p> <p>micelle</p>

Fats

- fats made from **saturated fatty acids** are called **saturated fats**, and are **solid at room temperature**, and most **animal fats** are **saturated**
- fats made from **unsaturated fatty acids** are called **unsaturated fats** or **oils**, and are **liquid at room temperature**
- **plant fats** and **fish fats** are usually **unsaturated**

Fats

- a diet rich in saturated fats may contribute to cardiovascular disease through plaque deposits
- hydrogenation - the process of converting unsaturated fats to saturated fats by adding hydrogen
- hydrogenating vegetable oils also creates unsaturated fats with *trans* double bonds
- these *trans* fats may contribute more than saturated fats to cardiovascular disease

Fats

- certain **unsaturated fatty acids** cannot be synthesized in the **human body** and must be supplied in the **diet**, and called **essential fatty acids**
- among these essential fatty acids, **omega-3 fatty acids** are required for **normal growth**, and thought to **provide protection** against **cardiovascular disease**
- **humans** and **other mammals** store their fat in **adipose cells**, which **cushions vital organs** and **insulates** the body

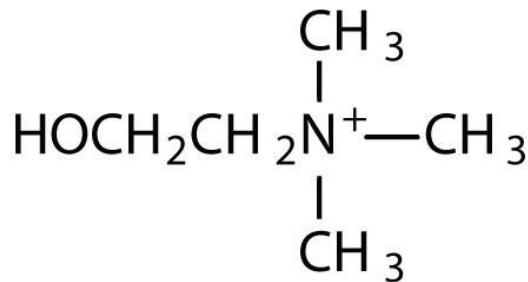
Phospholipids

- **amphiphilic lipids** consisting of a **glycerol** or an **amino-alcohol sphingosine backbone**, which is **esterified** to **one or two fatty acids**, a **phosphate group** and a **hydrophilic residue**
- the **two fatty acid tails** are **hydrophobic**, but the **phosphate group** and its **attachments** form a **hydrophilic head**
- dietary **phospholipids** mainly derived from **soybeans**, **egg yolk**, **milk**, or **marine organisms** (such as **fish**)
- supposed to be **highly effective** in **delivering** their **fatty acid residues** for **cell membrane incorporation**

Phospholipids

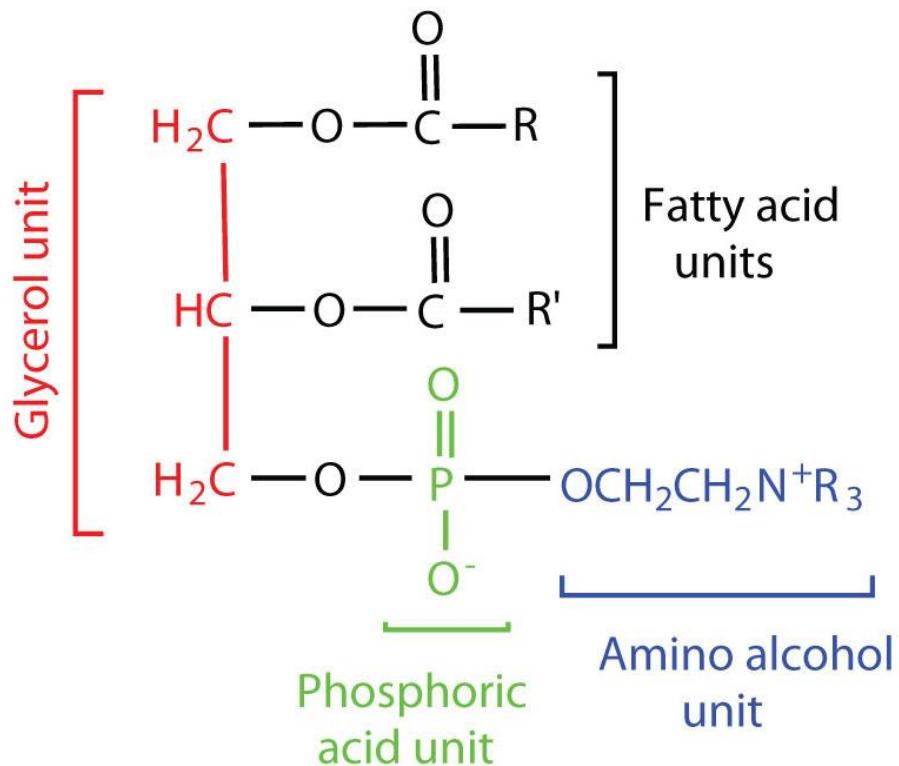


Ethanolamine

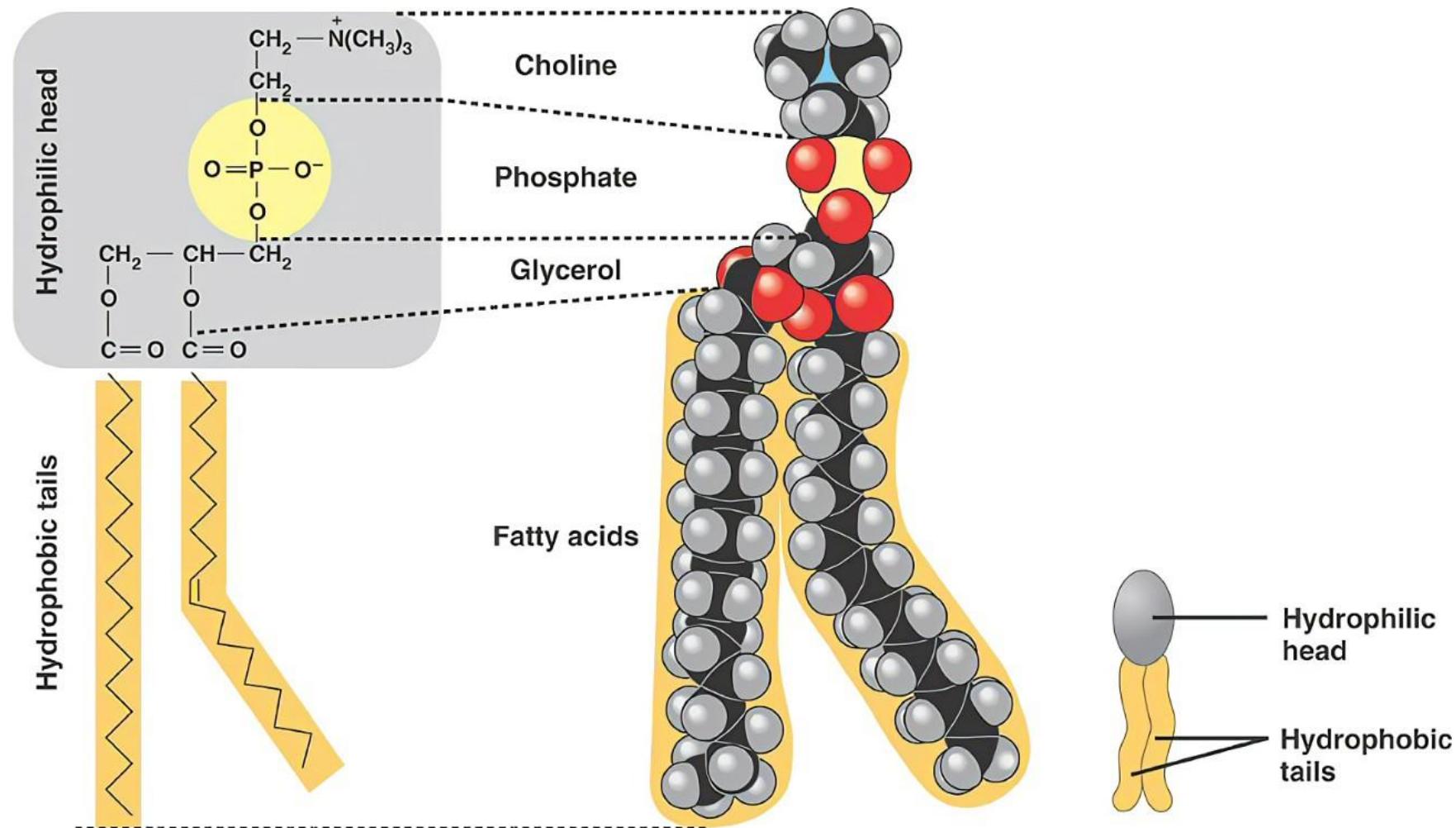


Choline

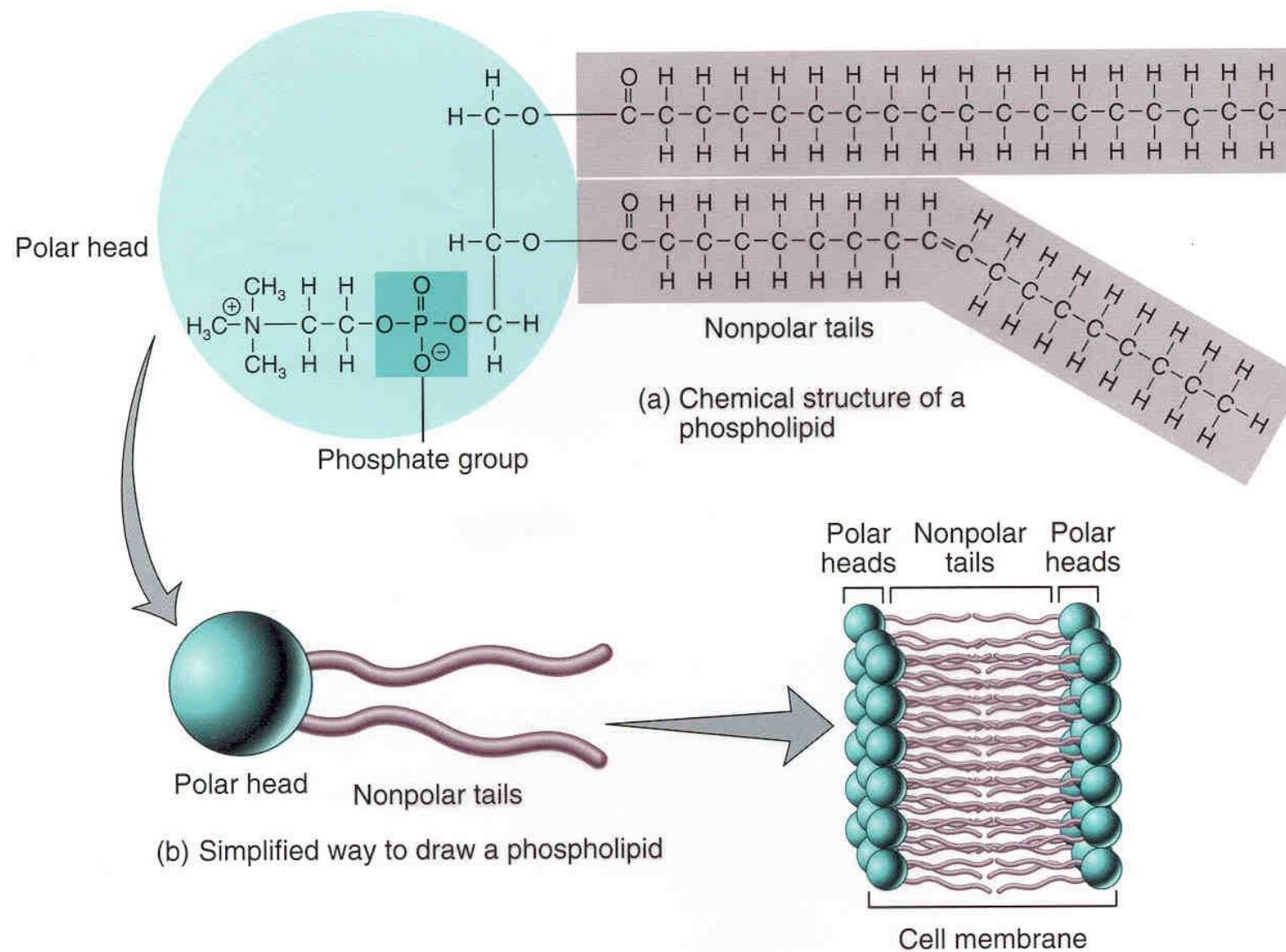
The components
of
phospholipids



Phospholipids

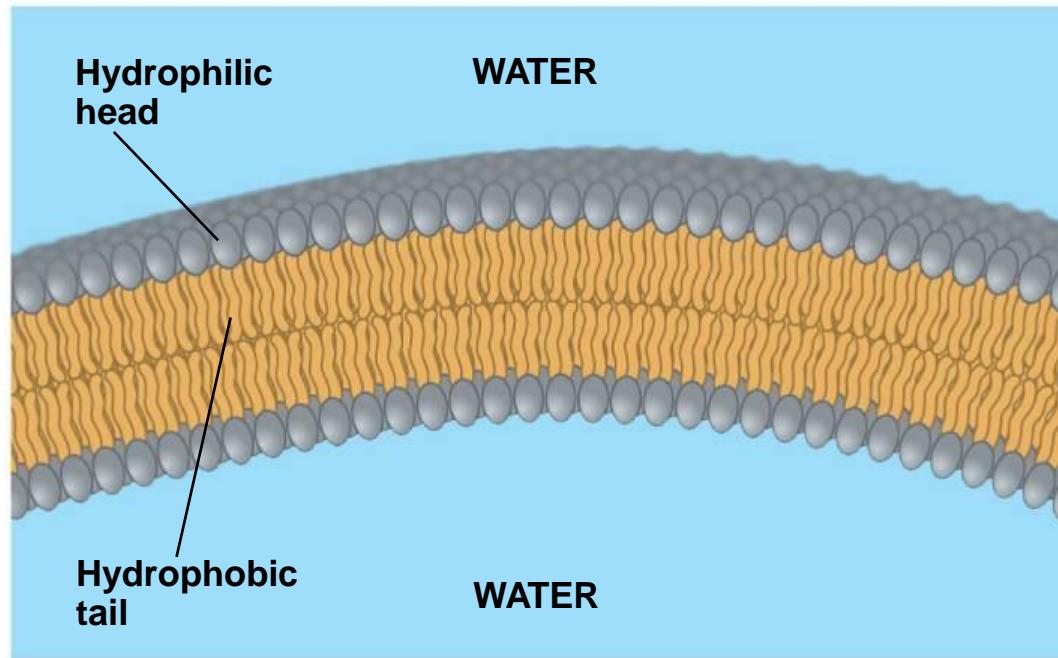


Phospholipids



Phospholipids

- when phospholipids are added to water, they self-assemble into a bilayer, with the hydrophobic tails pointing toward the interior
- the structure of phospholipids results in a bilayer arrangement found in cell membranes
- phospholipids are the major component of all cell membranes



Phospholipids

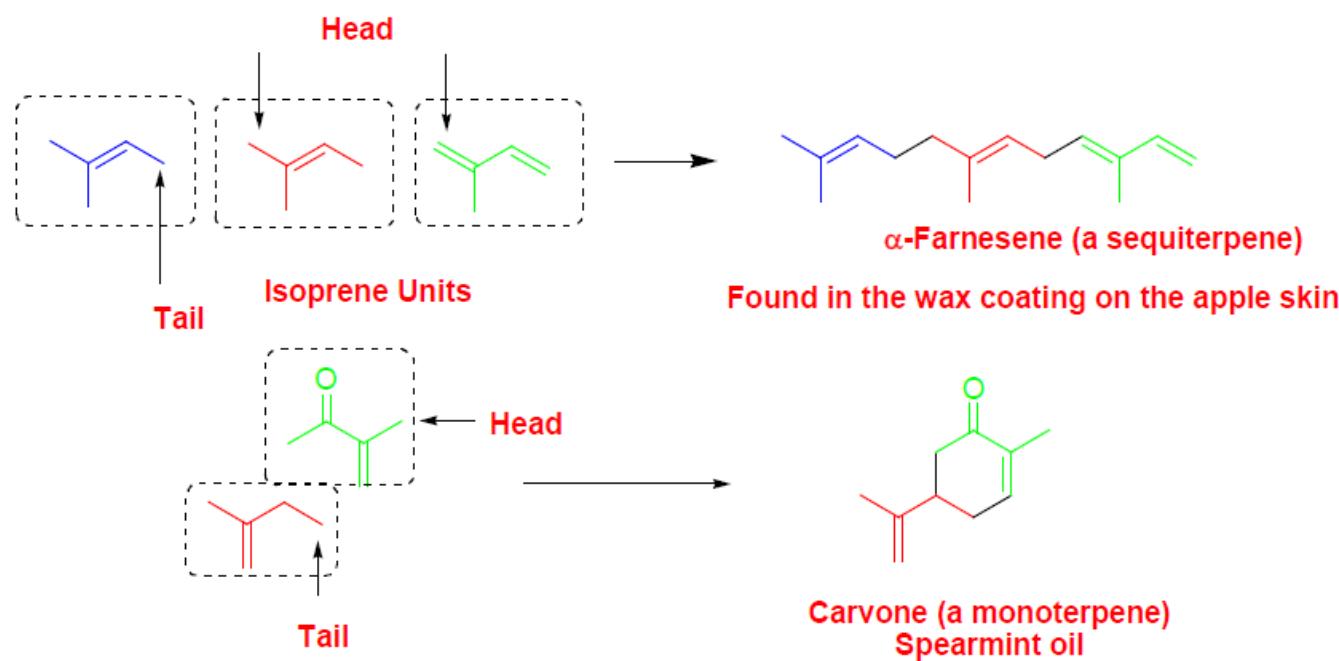
- **bioactive lipids which are essential in living organisms as a major component of cell membranes** and their **metabolism** is important in regulating cellular functions
- **synthesized in the cells**, however, it has been demonstrated that **dietary phospholipids have positive impacts in different illnesses and diseases**, raising the possibility of using **synthetic or natural phospholipid isolates as nutraceuticals or functional foods**
- widely used as **emulsifiers** to control **lipid oxidation** as natural antioxidants

Terpenes

- terpenes are organic compounds consisting of **isoprene**, a **five-carbon building block** however, **terpenoids** are a class of **secondary metabolites** derived from **terpenes** with **multiple cyclic groups and oxygen**
- a **monoterpene** is a **cyclic molecule** composed of **two isoprene units**
- **terpenes** are typically **volatile** and believed to play **critical roles** in plant **defense**, while **terpenoids** may be **non-volatile** or **semi-volatile** as they normally contain other **polar moieties**
- **terpenes** and **terpenoids** can be used as **flavors, drugs, and fragrances**

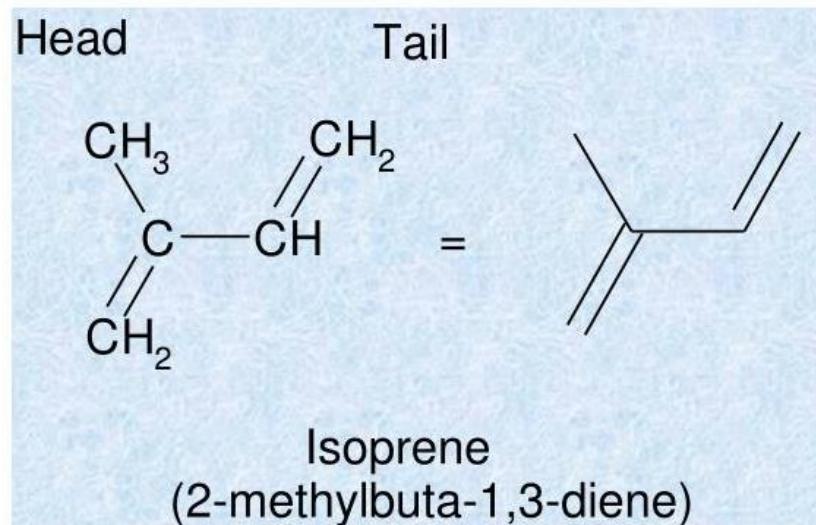
Terpenes

- naturally available terpenes are usually made by joining together the isoprene units, usually in head-to-tail fashion
- for example, the following scheme shows the head-to-tail joining of the isoprene units

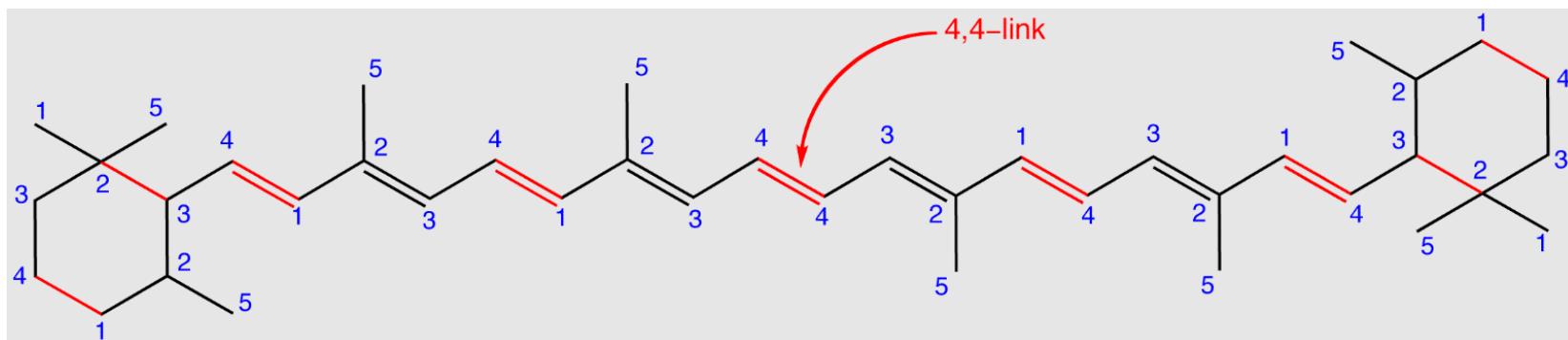


Terpenes

Isoprene



One isoprene unit contains five carbon atoms



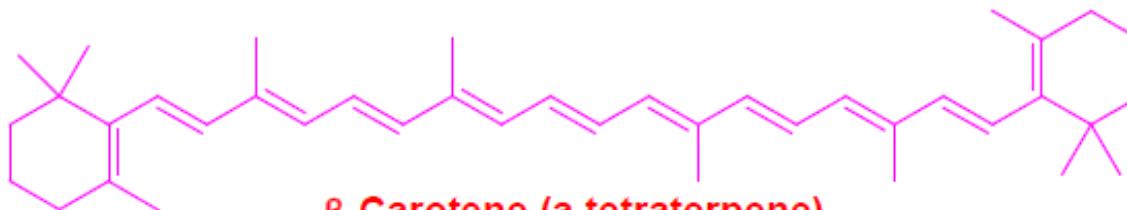
Terpenes

- the following scheme shows examples for **tetraterpenes** having **eight isoprene units** which are responsible for **colors of tomatoes and carrots**



Lycopene (a tetraterpene)

Responsible for the red colour of tomatoes and watermelon

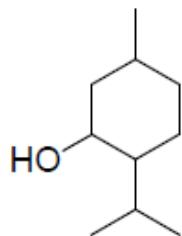


β -Carotene (a tetraterpene)

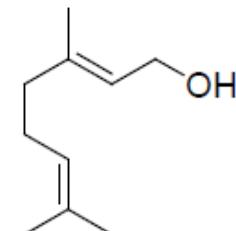
Responsible for the orange colour of carrots

Terpenes

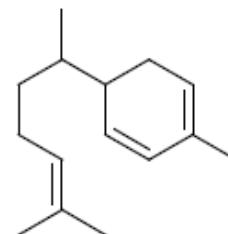
- depending on the combination of units, can be subdivided into **biogenetic classes** such as **monoterpenes**, **sesquiterpenes**, **diterpenes**, **sesterpenes**, **triterpenes (steroids)**, and **tertraterpenes (carotenoids)**
- terpenes are available in nature as a diverse class of lipids
- some of them are used as spices, perfumes and medicines for thousands of years
- the terpenes having functional groups such as OH and carbonyl group are called **terpenoids**



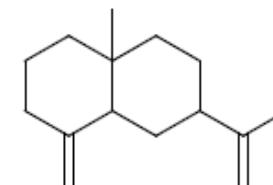
Menthol
Peppermint oil



Geraniol
Geranium oil



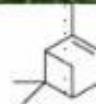
Zingiberene
Ginger oil



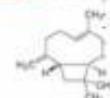
β -Selinene
Celery oil

Terpenes

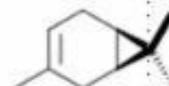
Common Terpenes & Terpenoids



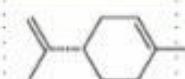
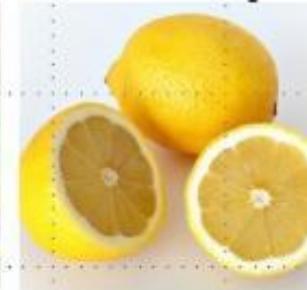
Pinene
(Pines)



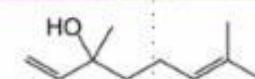
Caryophyllene
(Peppercorns)



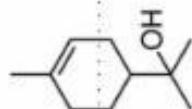
Carene
(Cedar, Rosemary)



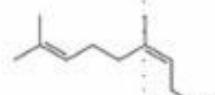
Limonene
(Citrus Lemon)



Linalool
(Mints, Lavender)



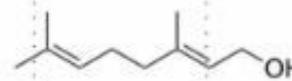
Terpineols
(Junipers, Orange Peel)



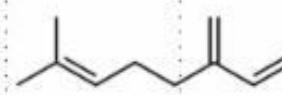
Nerol
(Lemon Grass)



Humulene
(Hops)



Geraniol
(Roses & Wine Grapes)

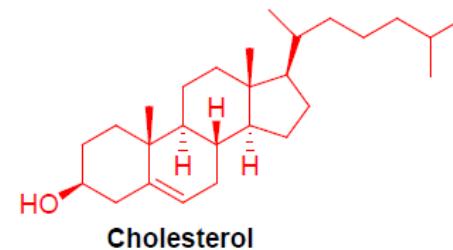
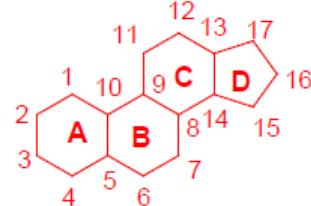


Myrcene
(Myrtles & Cannabis)

Steroids

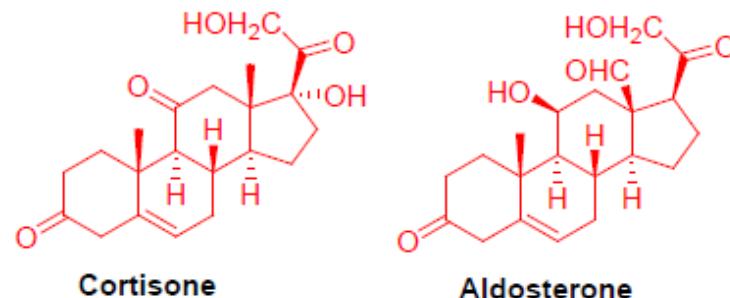
- lipids having a **tetracyclic system** composed of **three six membered rings** and **one five membered ring**
- their **non-polar character allows** them to **cross the cell membranes**, so they can **leave the cells** in that they are produced and **enter their target cells**
- in **animals**, the most abundant member of steroid is **cholesterol**, which is the **precursor of all other steroids**
- **cholesterol** is an important component of **cell membranes** and **related to heart disease**

The Steroid Ring System



Steroids

- broadly classified into **five groups: glucocorticoids, mineralocorticoids, androgens, estrogens, and progesterone**
- **Glucocorticoids**
 - ✓ involved in metabolism of glucose, proteins and fatty acids
 - ✓ cortisone is an example for this type of steroid which is used as anti- inflammatory agent to treat arthritis
- **Mineralocorticoids**
 - ✓ responsible for the increased reabsorption of Na^+ , Cl^- and HCO_3^- ions by the kidneys that can lead to an increase in the blood pressure
 - ✓ aldosterone is an example of a mineralocorticoid



Steroids

▪ Androgens

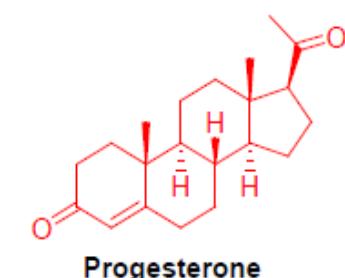
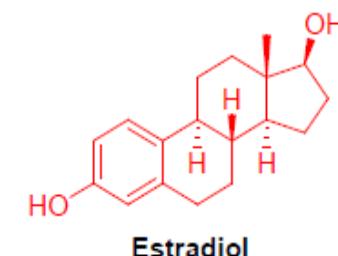
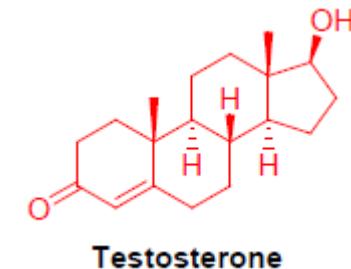
- ✓ male sex hormones
- ✓ they are responsible for the development of male secondary sex characteristics during puberty
- ✓ testosterone is an example of androgens

▪ Estrone and estradiol

- ✓ female sex hormones known as estrogens
- ✓ responsible for the development of female secondary characteristics and secreted by the ovaries
- ✓ estrogens also regulate the menstrual cycle

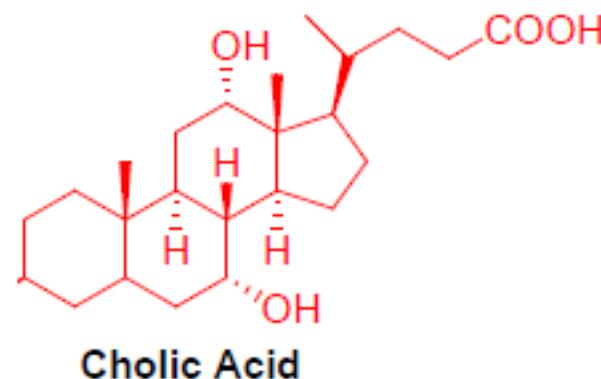
▪ Progesterone

- ✓ the hormone that is essential for the maintenance of pregnancy
- ✓ it also prevents ovulation during pregnancy



Steroids

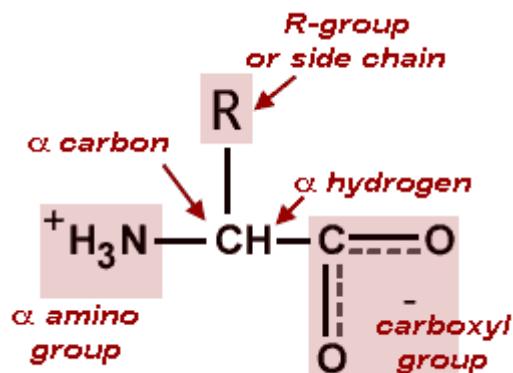
- cholesterol is also precursor of the synthesis of the bile acids in addition to that of all steroid hormones in animals
- for example, the bile acid, cholic acid synthesized in liver, stored in gallbladder and secreted into the small intestine, where it acts as an emulsifying agent so that fats and oils can be digested by water-soluble enzymes



Amino acids and Proteins

Amino acids

- molecule containing both an **amino group** and **acid group**
- the term is always used to refer to an **α -amino** carboxylic acid
- the simplest α -amino acid is amino-acetic acid, called **glycine**



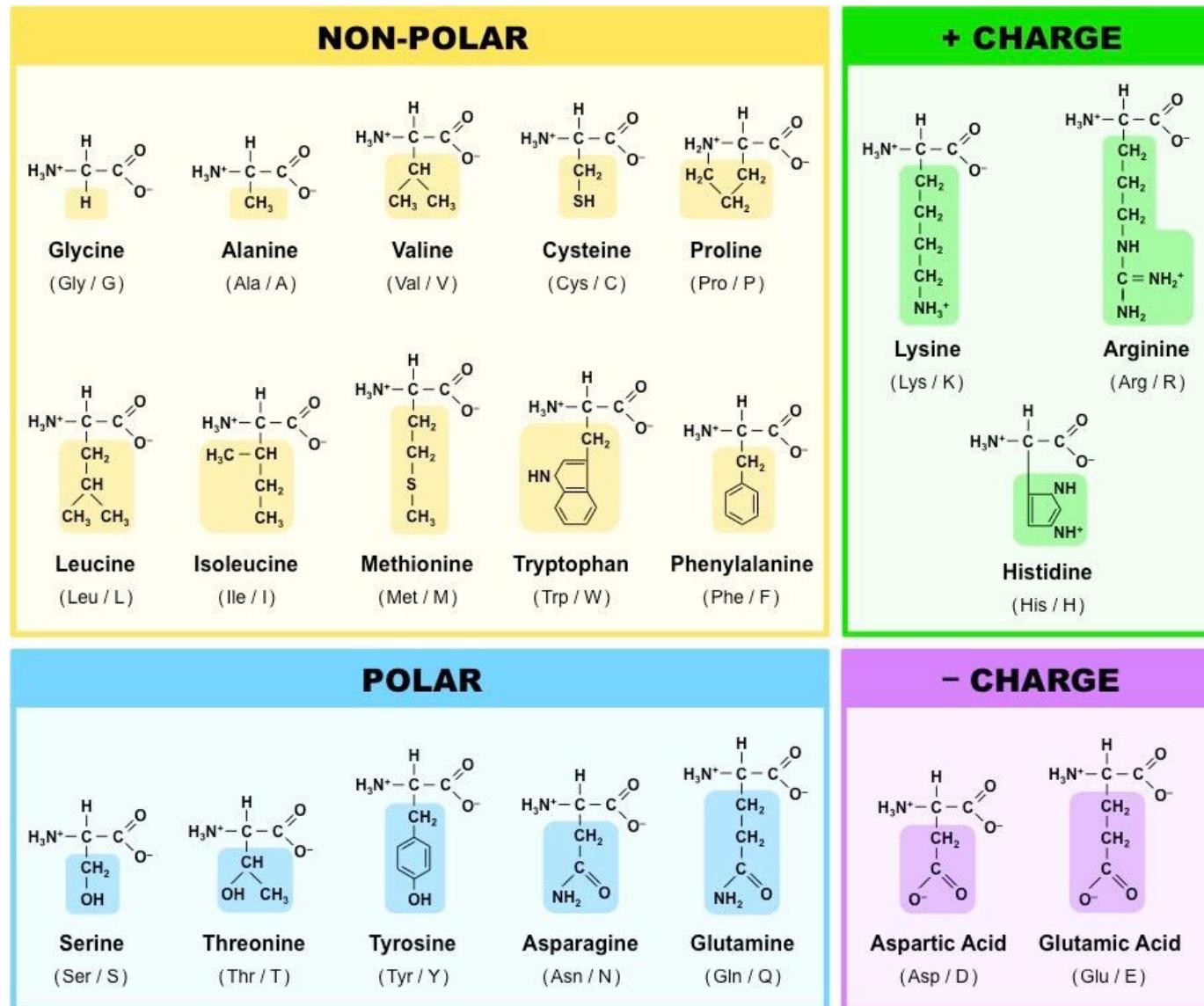
the general structure of an **α -amino acid**

- common amino acids have side chains (symbolized by R) substituted on the α - carbon atom

Amino acids and Proteins

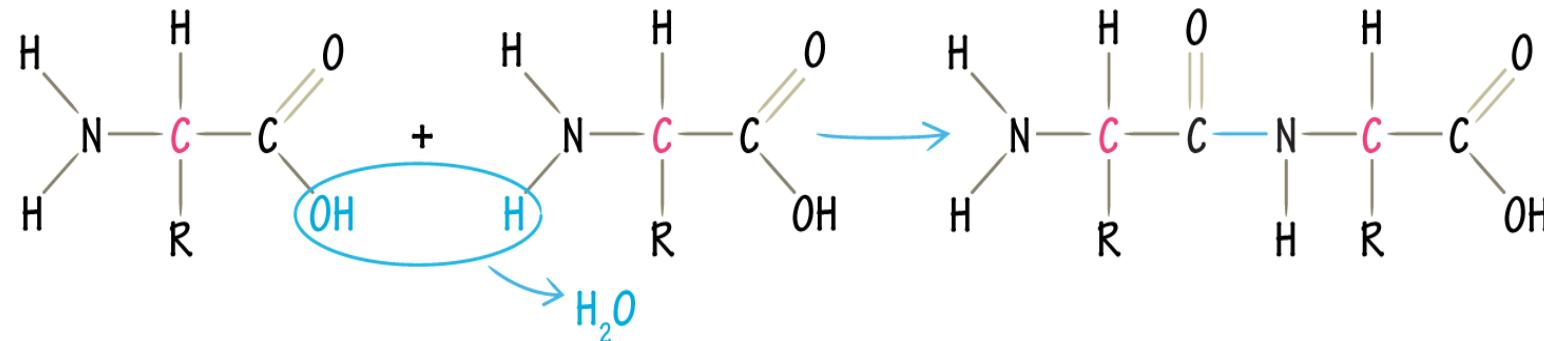
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➤ amino acids are varied in the difference in their - R groups



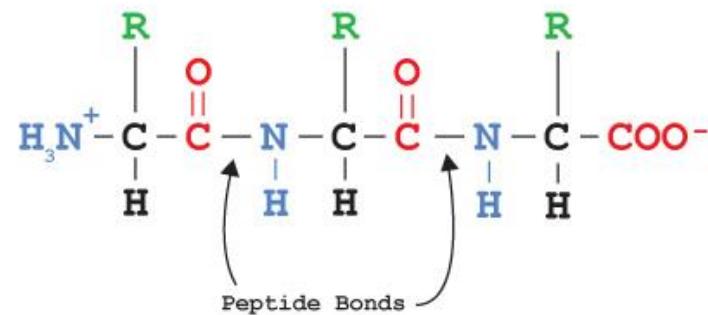
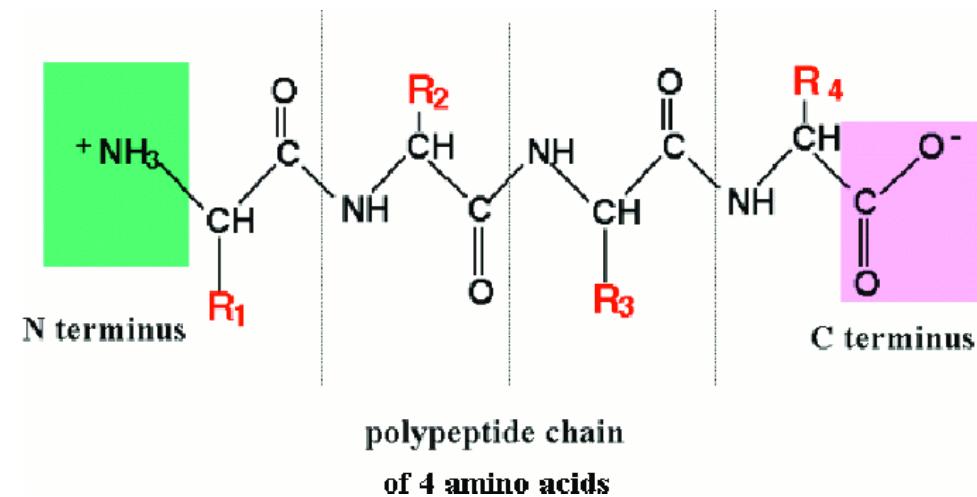
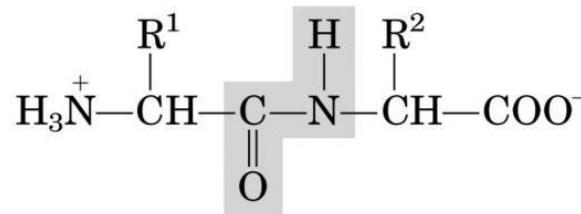
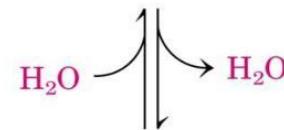
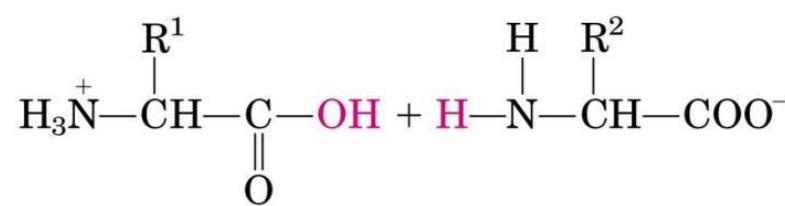
- except for **glycine**, all α -amino acids are **chiral**, in all chiral amino acids, the chirality center is the asymmetric α - carbon atom
- naturally occurring (*S*)-amino acids are classified as **L-amino acids**, **D-amino acids** are **never** found in proteins
- proteins are **biopolymers** of α -amino acids, which are the most **abundant organic molecules** in animals playing **important roles** in all aspects of **cell structure** and **function**
- **physical** and **chemical properties** of a protein are determined by its **constituent amino acids**
- individual **amino acid subunits** are joined by amide **linkages** called **peptide bonds**

- peptide bond formation is a condensation reaction leading to the polymerization of amino acids into peptides and proteins
- the simplest peptide, a **dipeptide**, contains a **single peptide bond** formed by the condensation of the **carboxyl group** of one AA with the **amino group** of the second with the concomitant elimination of water



Amino acids

... Cont'd



- peptide bond is **rigid** because the **π -electrons** of C=O bond extend over **C-N** also giving it a partial **double bond** character

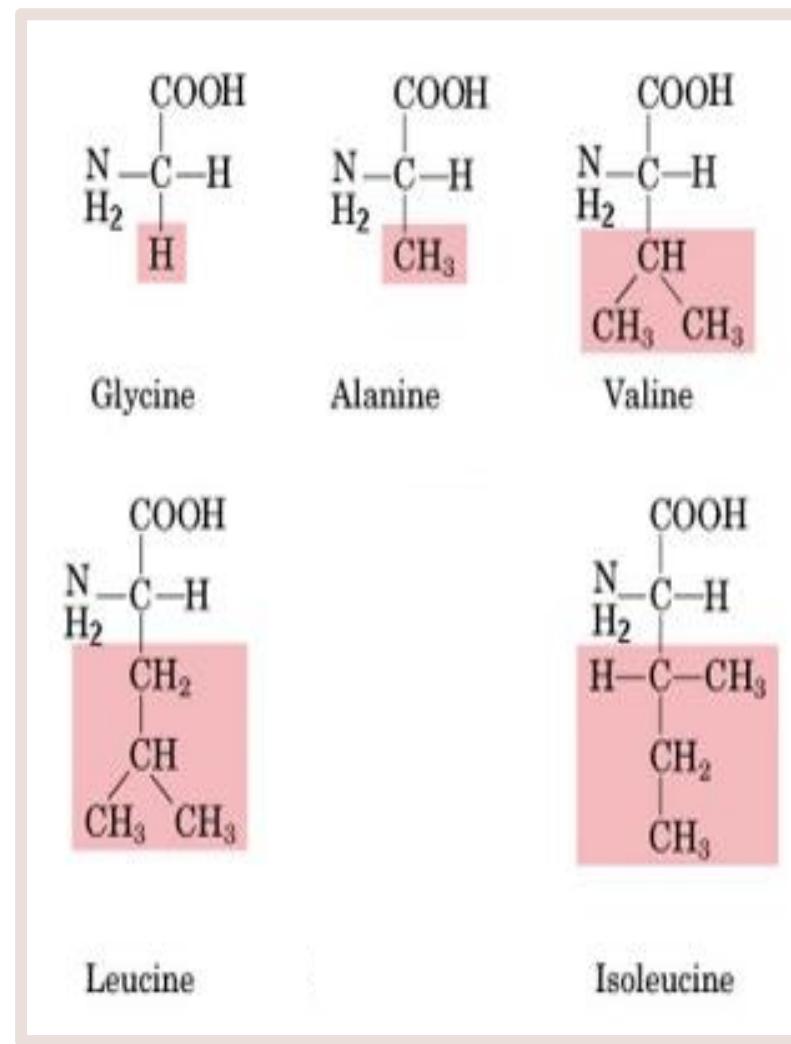
Classification of amino acids

- classified into various classes based on different criteria

I. Based on side chain, -R

A. aliphatic side chain

- alanine (R = methyl)
- valine (R = isopropyl)
- leucine (R = isobutyl)
- isoleucine (R = *sec*-butyl)
- glycine (R = H)

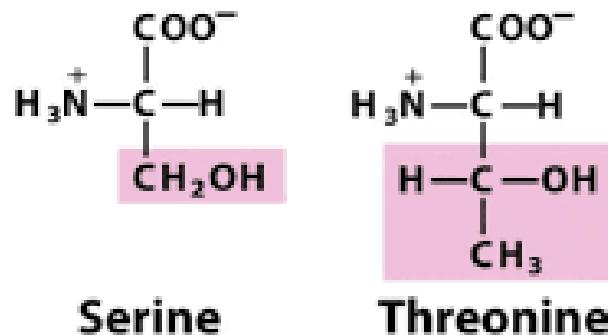


Classification of amino acids

... Cont'd

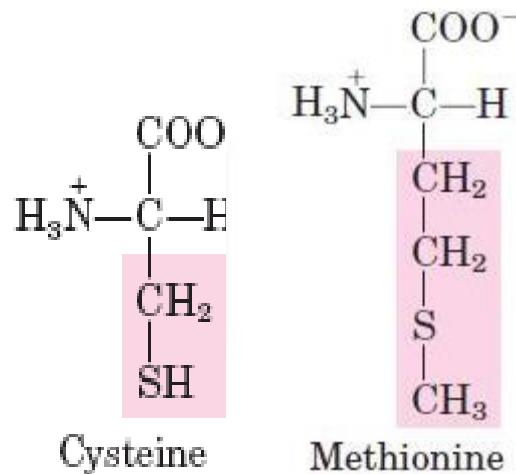
B. Alcohol side chain

- serine and threonine



C. sulfur-containing amino acids

- cysteine and methionine

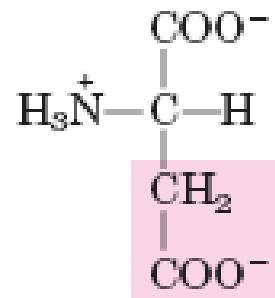


Classification of amino acids

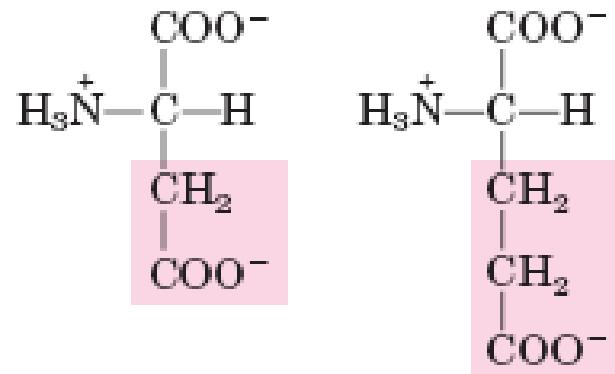
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D. acidic amino acids (amino acids with two carboxylic acid groups):

- **aspartate and glutamate**



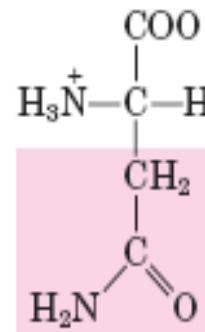
Aspartate



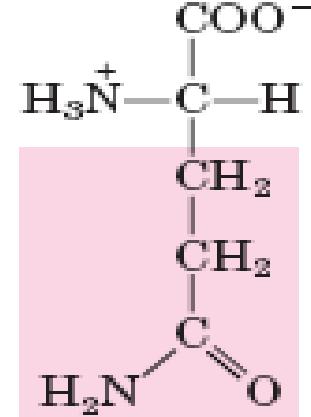
Glutamate

E. amides of the acidic amino acids

- **asparagine** is the amide of aspartate and
- **glutamine** is the amide of glutamate



Asparagine



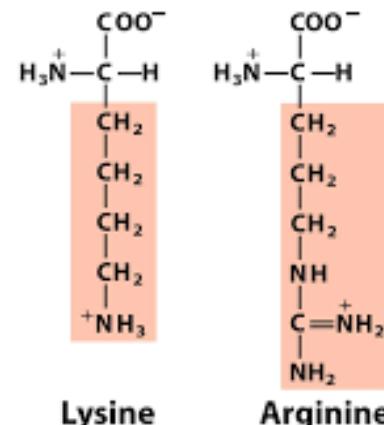
Glutamine

Classification of amino acids

... Cont'd

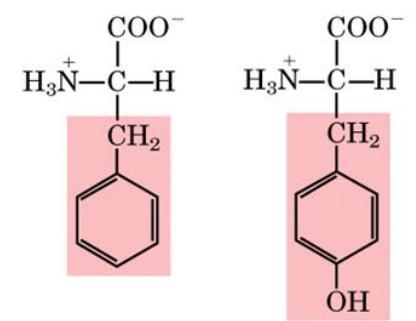
F. basic amino acids (amino acids with two basic N - containing groups)

- **Lysine** has an ϵ -amino group
- **arginine** (δ -guanidino group)



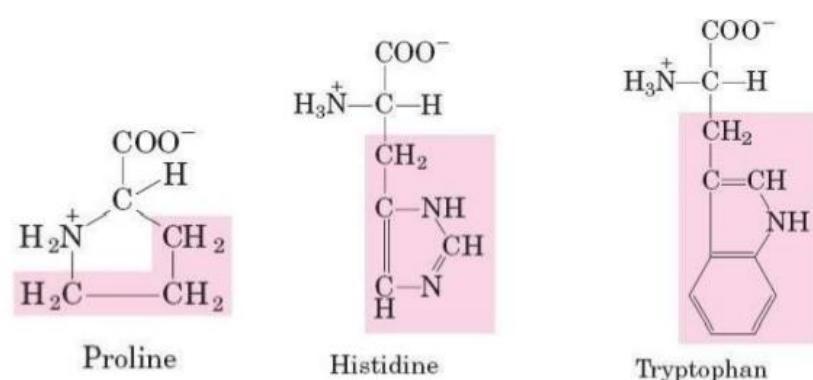
G. amino acids contain benzene rings

- **phenylalanine** and
- **tyrosine**



H. Heterocyclic no acids

- **Proline, histidine and tryptophan**



II. Based on its synthesis

- AA can be synthesized in human body or not
 - ✓ essential or indispensable and
 - ✓ non-essential or dispensable AA

A. Essential AA

- cannot be synthesized by the body
 - ✓ supplied in the diet
 - ✓ plants and bacteria can synthesize all 20 of the AAs

- humans cannot synthesize 10 of them
- these ten AA must come from our diets and are called **essential AA**
- these essential AA are:-
 - ✓ Histidine ✓ Methionine,
 - ✓ Isoleucine ✓ Phenylalanine
 - ✓ Leucine ✓ Lysine
 - ✓ Threonine ✓ Valine
 - ✓ Arginine ✓ Tryptophan

B. Non-essential AA

These AA are synthesized by simple pathways which include:

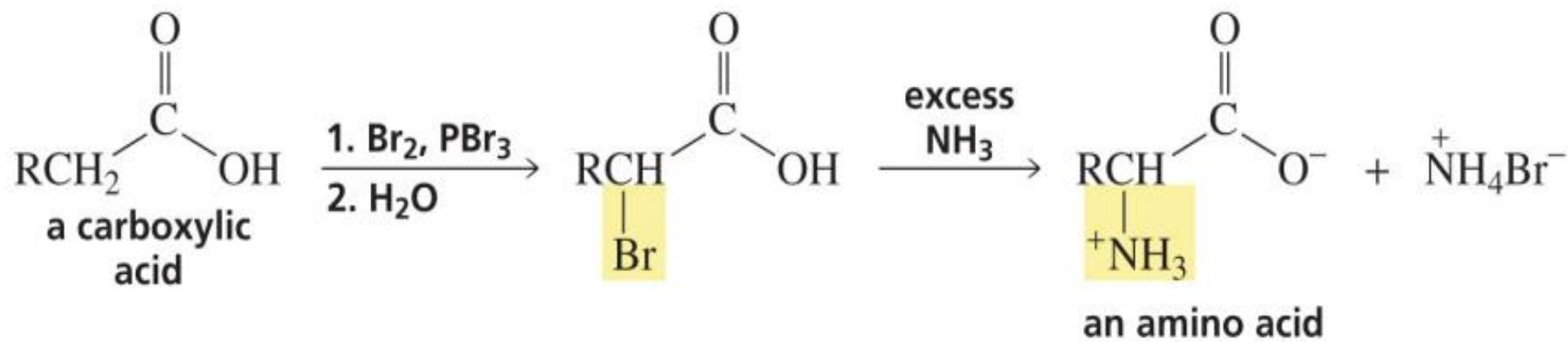
- ✓ Alanine
- ✓ Glutamine,
- ✓ Asparagine
- ✓ Glycine
- ✓ Aspartate
- ✓ Proline
- ✓ Cysteine
- ✓ Serine
- ✓ Glutamate
- ✓ Tyrosine

Reactions of Amino Acids

- carboxyl groups form amides & esters
- amino groups form Schiff bases and amides
- Edman reagent (phenyl isothiocyanate) reacts with the α -amino group of an amino acid or peptide to produce a phenyl thiohydantoin (PTH) derivative
- side chains show unique reactivities
 - ✓ Cys-residues can form disulfides and can be easily alkylated
 - ✓ few reactions are specific to a single kind of side chain

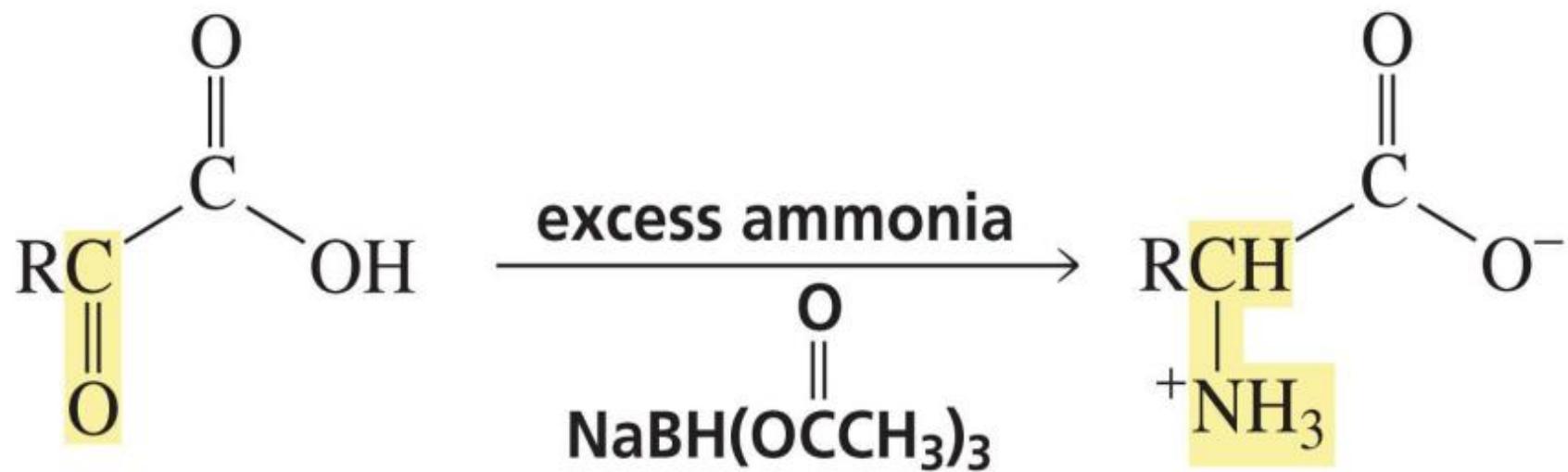
Synthesis of Amino acid

- Hell-Volhard-Zelinski reaction



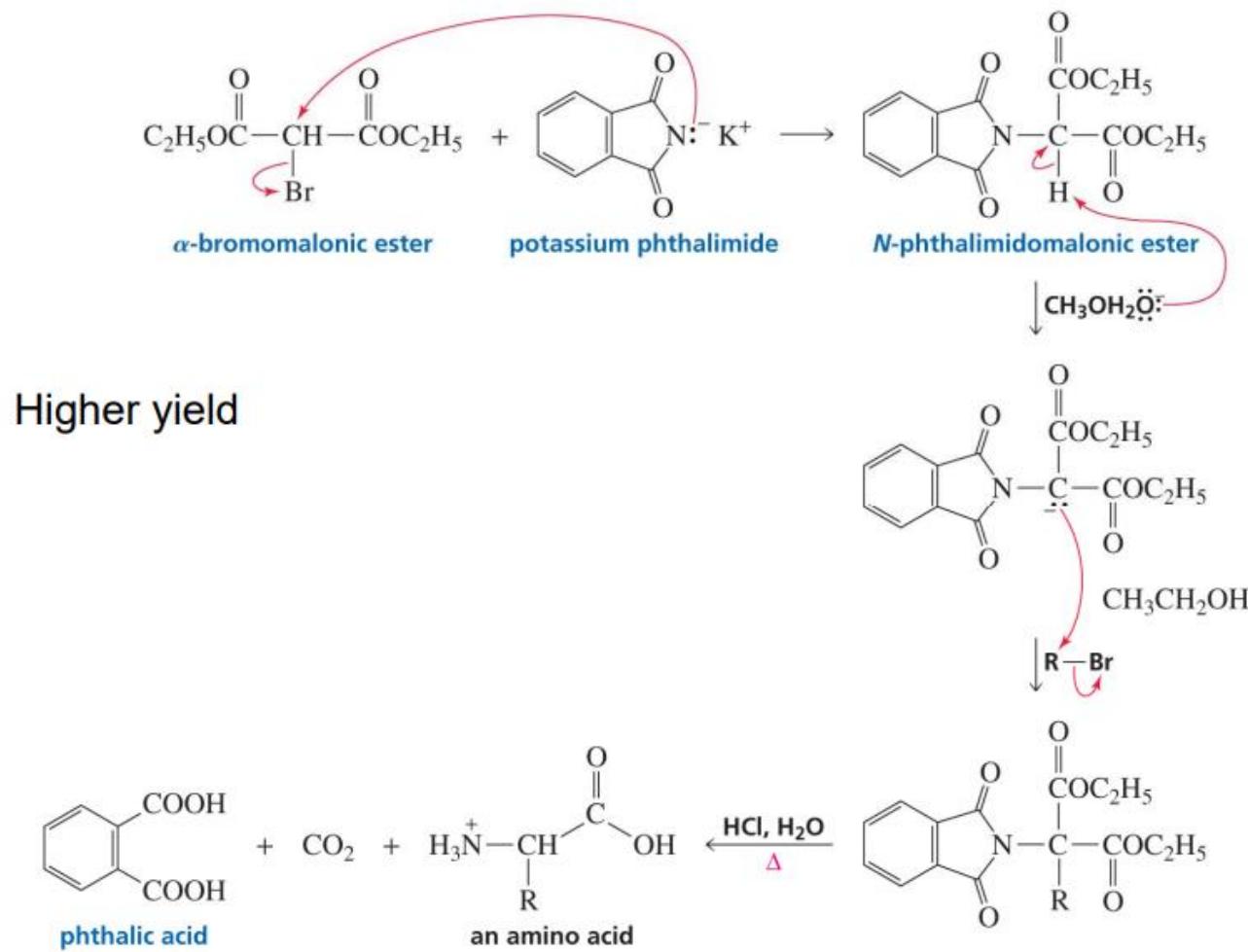
Synthesis of Amino acid

- Hell-Volhard-Zelinski reaction



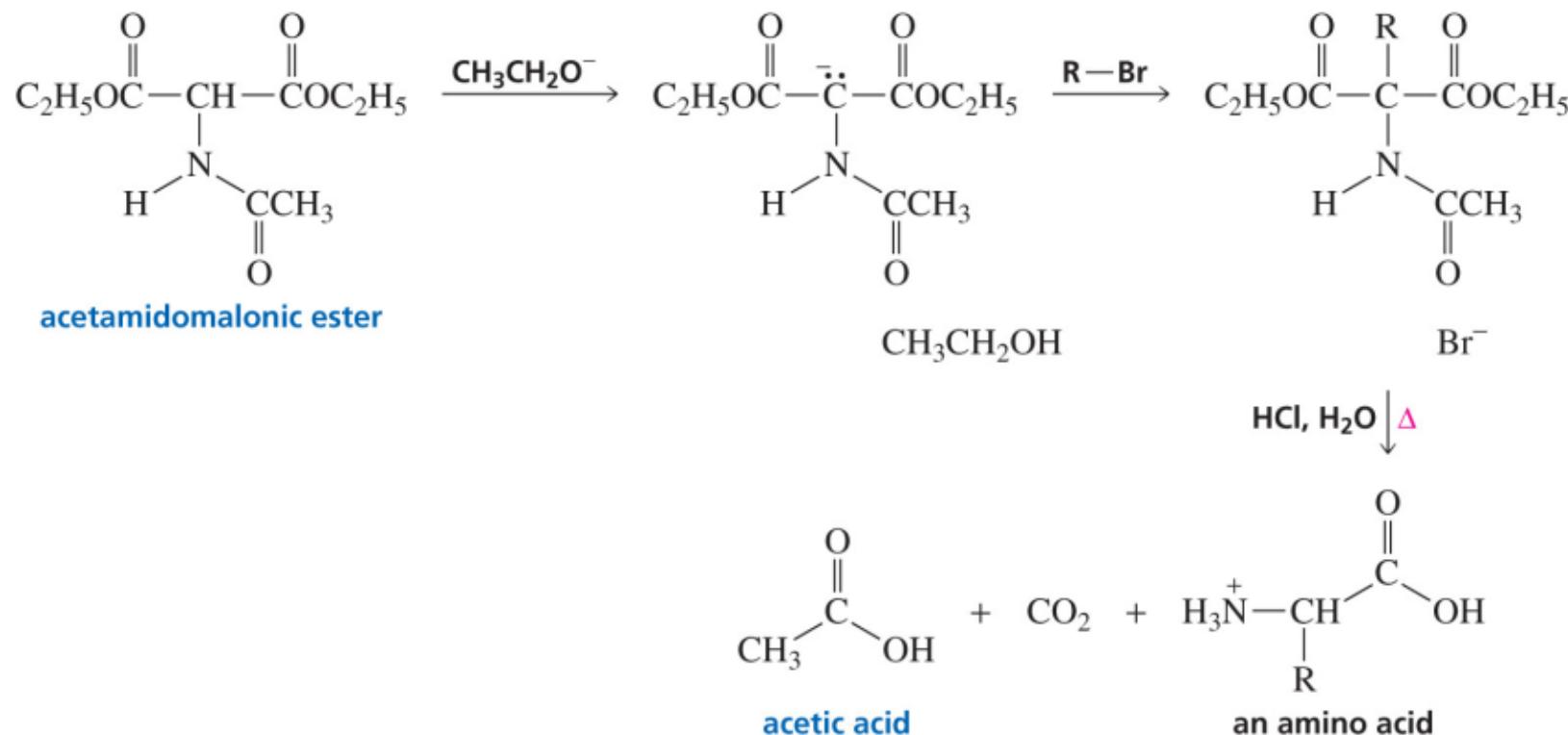
Synthesis of Amino acid

- Hell-Volhard-Zelinski reaction



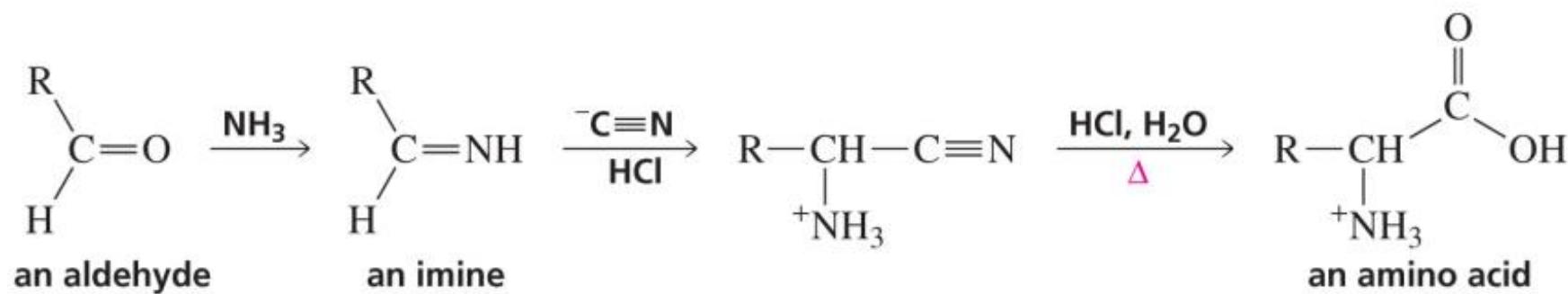
Synthesis of Amino acid

■ Hell-Volhard-Zelinski reaction



Synthesis of Amino acid

- Strecker synthesis



Peptides

- Short polymers of amino acids
- Each unit is called a residue
- 2 residues – dipeptide
- 3 residues – tripeptide
- 12-20 residues – oligopeptide
- many - polypeptide

Protein

- one or more polypeptide chains
- one polypeptide chain - a monomeric protein
- more than one - multimeric protein
- homo multimer - one kind of chain
- hetero multimer - two or more different chains
- hemoglobin, for example, is a hetero tetramer
- it has two alpha chains and two beta chain

Structure of Proteins

They are **Primary Structure**,

Secondary structure,

Tertiary structure and

Quaternary structure

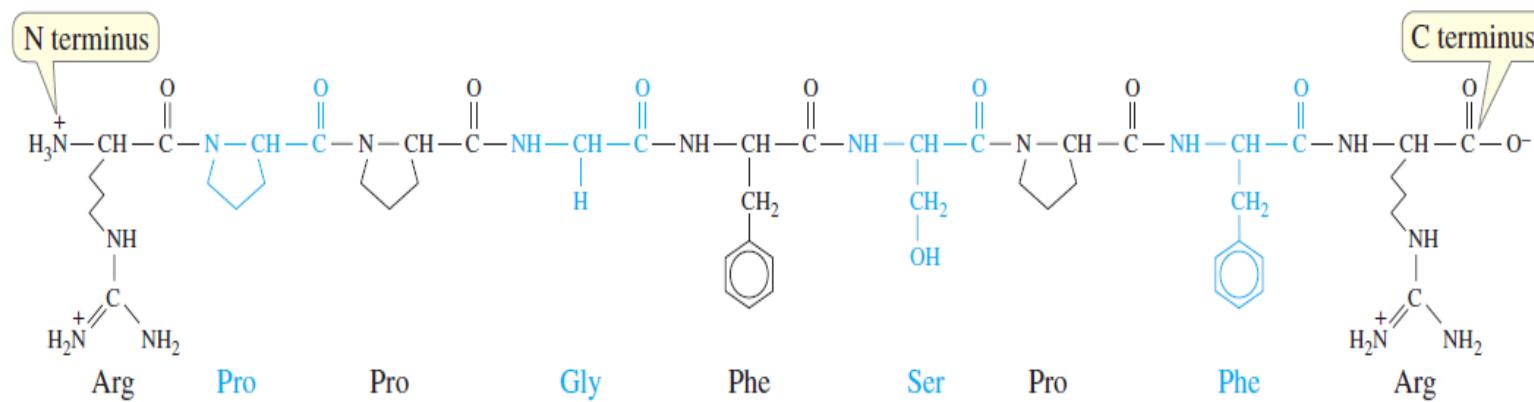
➤ Primary Structure of Protein

- A. Linear sequence of amino acids that make up the polypeptide chain
- B. Specifies total number of amino acids
 - the properties of the protein are determined, directly or indirectly,
 - by the primary structure

Structure of Proteins

... Cont'd

- conventionally, peptide sequence is written **left to right**. The left side terminal AA is the peptide's **N-terminal** and the final AA towards the right end is the peptide's **C-terminal**;



- when the identities of the AAs in a peptide are known but their sequence is not known, the AAs are written **separated by commas**

- when the sequence of AAs is known, the AAs are written separated by hyphens

Glu, Cys, His, Val, Ala

the pentapeptide contains the indicated amino acids, but their sequence is not known

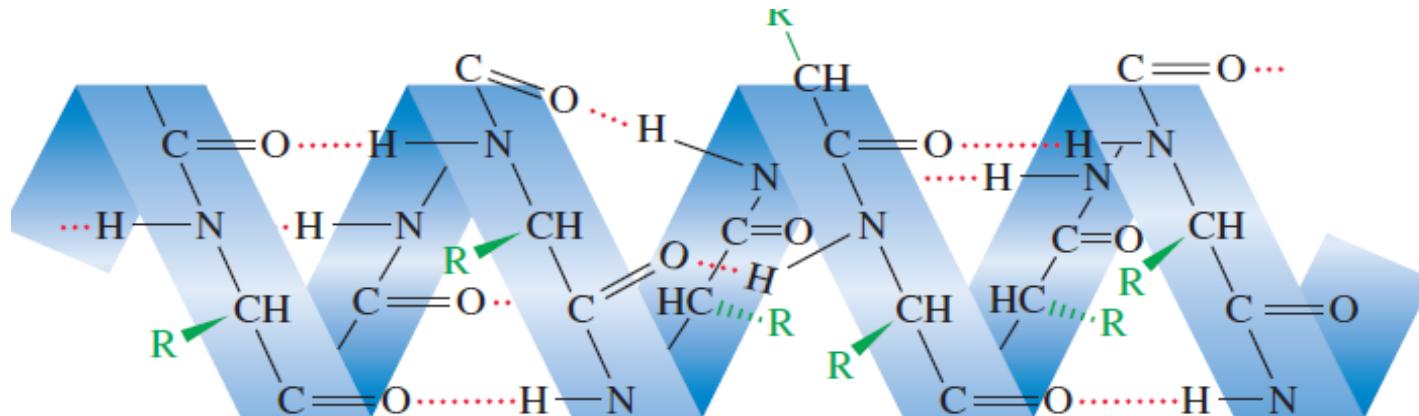
Val-Cys-Ala-Glu-His

the amino acids in the pentapeptide have the indicated sequence

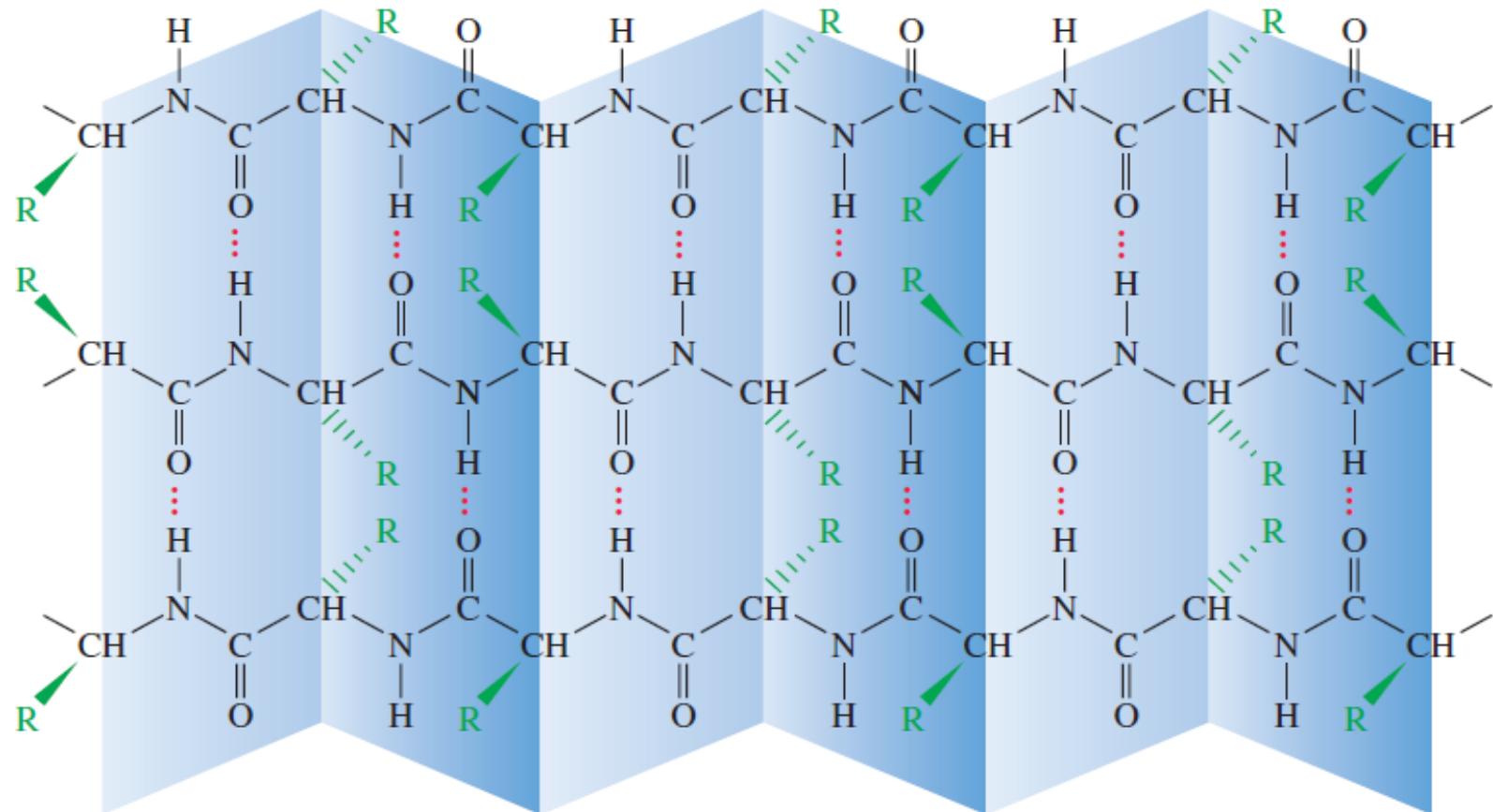
- in naming the peptide, adjective names (ending in "yl") are used for all the AAs except the C-terminal AA
- thus, this **pentapeptide** is named **valyl cysteylalanylglutamylhistidine**

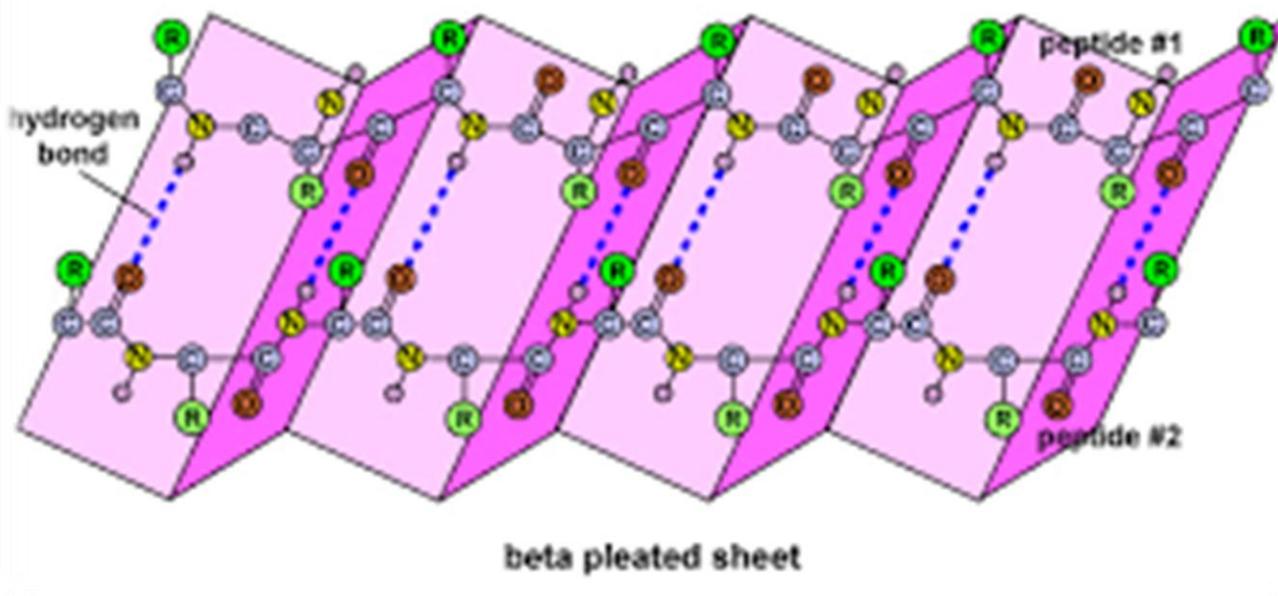
B. Secondary Structure of Proteins

- the carbonyl oxygen atoms form hydrogen bonds with the amide (N-H) hydrogens
- these hydrogen-bonded arrangements, if present, are called the **secondary structure** of the protein
- when a peptide chain **winds into a helical coil**, each carbonyl oxygen can hydrogen- bond with an N-H hydrogen on the next turn of the coil



- involve many peptide molecules lined-up side-by-side, resulting in a **two-dimensional sheet (β -plate sheet)**.

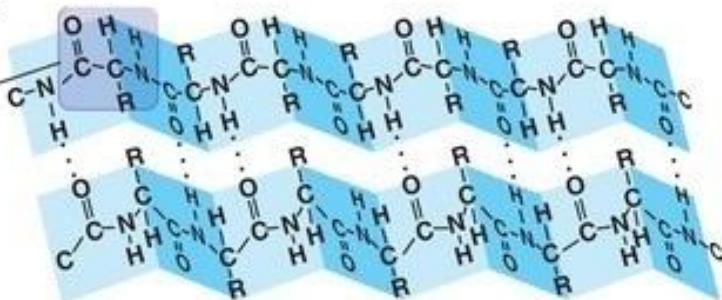




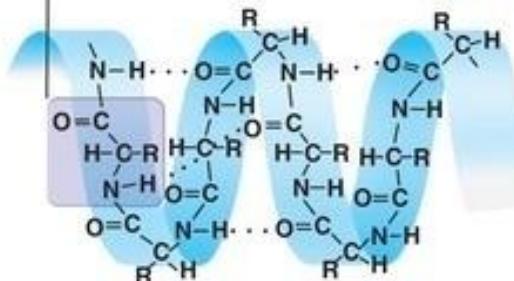
Secondary Structure

β pleated sheet

Examples of
amino acid
subunits



α helix



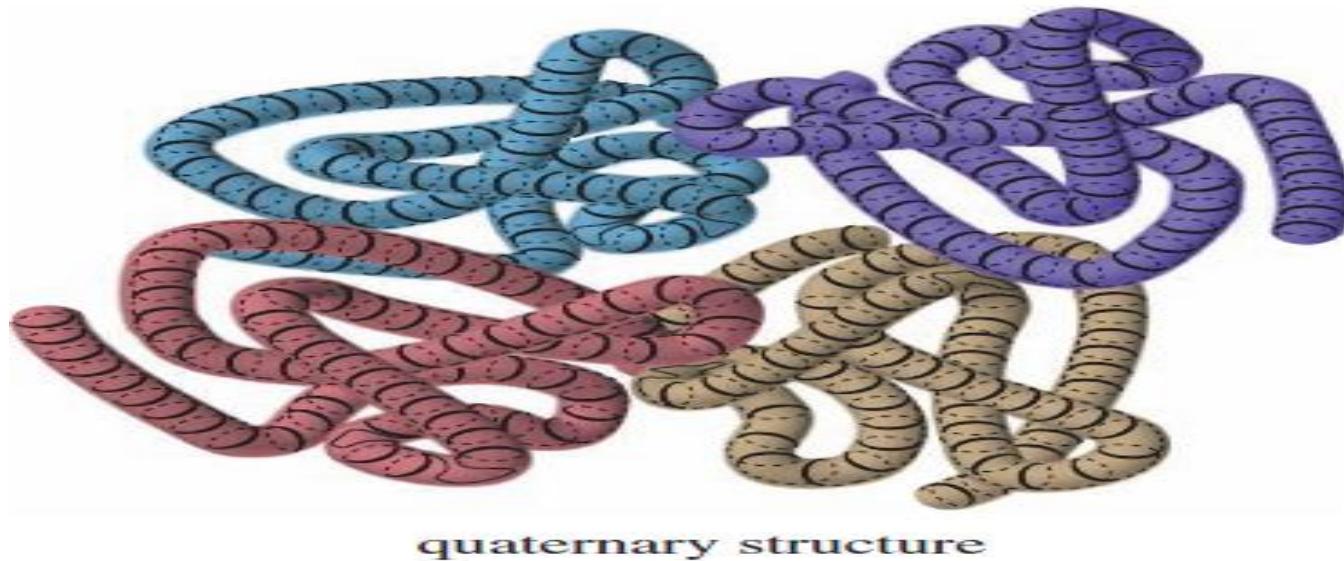
C. Tertiary Structure of Protein

- the **tertiary structure** of a protein is its complete three-dimensional conformation
- parts of the protein may have the **α helical structure**, other parts may have the **pleated-sheet structure**, and still other parts may be **random coils**



D. Quaternary Structure

- **quaternary structure** refers to the association of two or more peptide chains in the complete protein
- **not** all proteins have quaternary structure

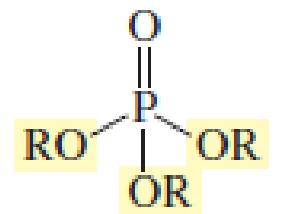
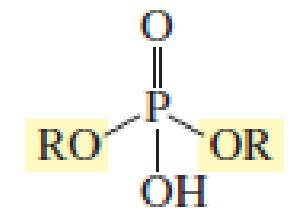
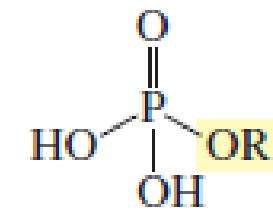
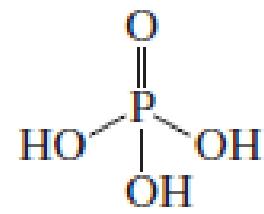


Structure and Chemistry of Nucleic acids

- the **anomeric carbon** of each sugar is bonded to nitrogen of a **heterocyclic compound** (amines) in a **β -glycosidic linkage**
- they are commonly referred to as **bases**
- in **RNA** the five-membered-ring sugar is **D-ribose**
- in **DNA** it is 2-deoxy-D-ribose (D-ribose without an OH group in the 2-position)
- **phosphoric acid links** the sugars in both **RNA** and **DNA**

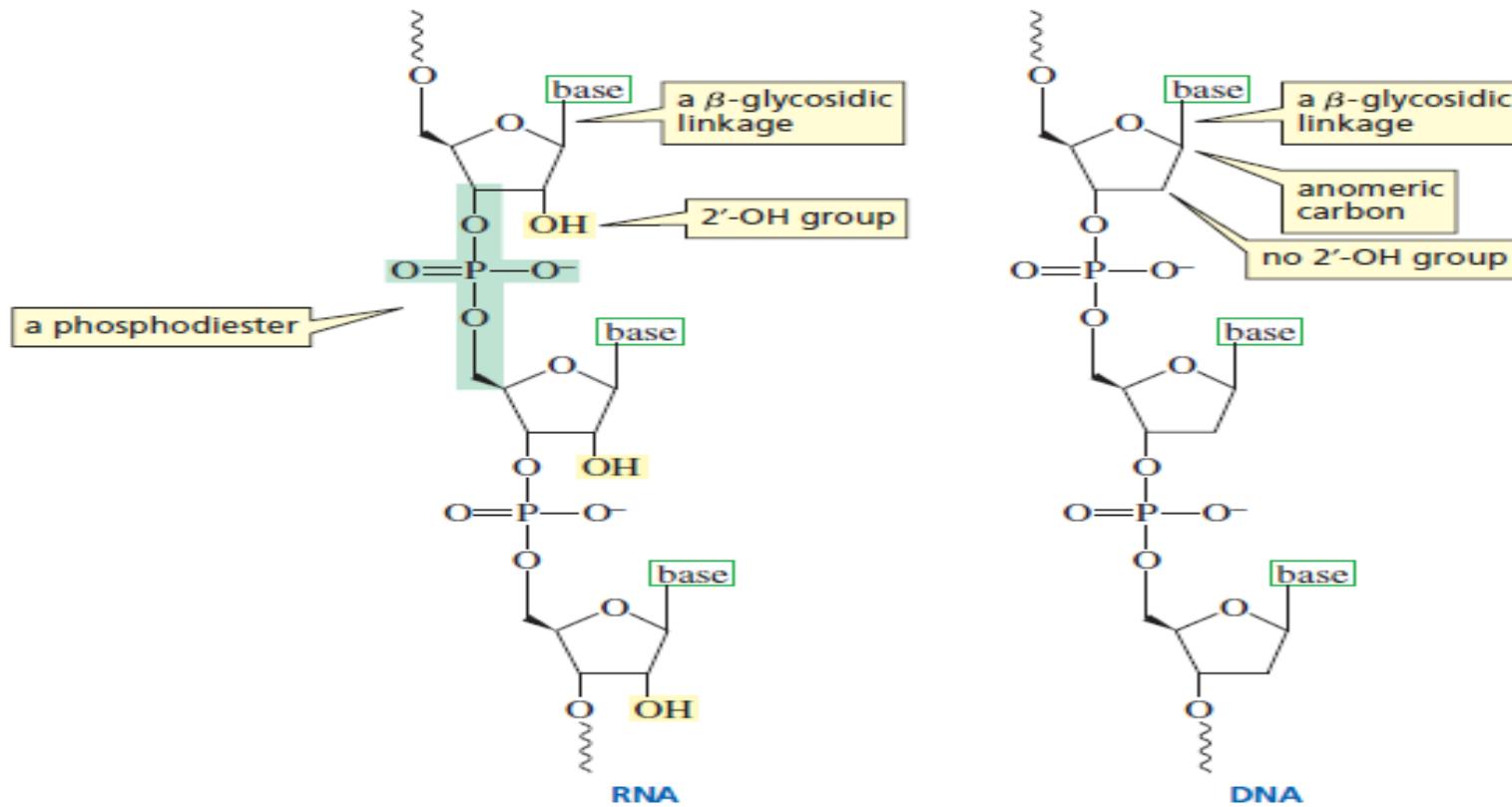
Structure and Chemistry RNA and DNA

- the acid has three dissociable OH groups, with an alcohol forms
 - ✓ a phosphomonoester,
 - ✓ a phosphodiester, or
 - ✓ a phosphotriester



- in nucleic acids the phosphate group is a **phosphodiester**

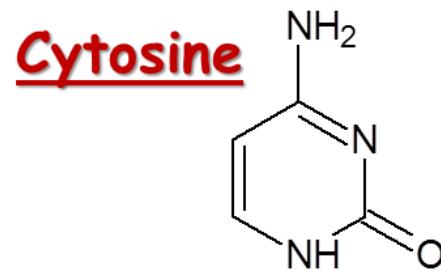
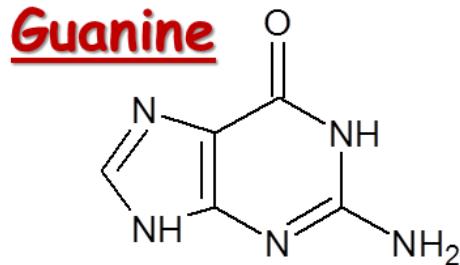
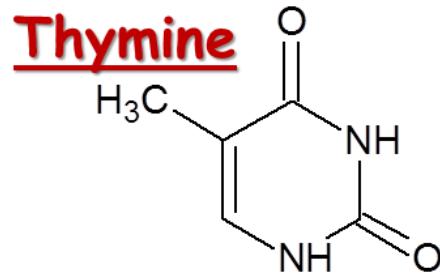
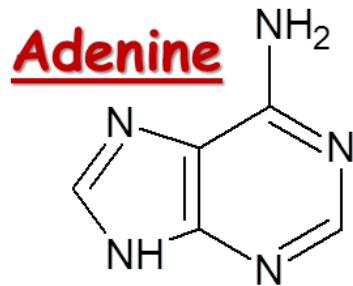
Structure and Chemistry RNA and DNA



- Nucleic acids consist of a chain of **five-membered-ring** sugars, **phosphate groups** & **amine** in a β -glycosidic linkage

Structure and Chemistry RNA and DNA

- there are **four** bases in DNA
 - ✓ two are substituted purines (**adenine** and **guanine**), and
 - ✓ two are substituted pyrimidines (**cytosine** and **thymine**)



Structure and Chemistry RNA and DNA

RNA also contains four bases;

- three (**adenine**, **guanine**, and **cytosine**) are the same as those in DNA, but the fourth base in RNA is **uracil** instead of **thymine**
- the purines and pyrimidines are bonded to the anomeric carbon of the furanose ring purines at N-9 and pyrimidines at N-1—in a β -glycosidic linkage

