Organic Chemistry II Lecture Note

CHAPTER-1
1. THE CHEMISTRY OF AROMATIC COMPOUNDS

At the end of this chapter, the students will be able to:

- Understand the concept of the aromaticity.
- Distinguish aromatic compounds from the non-aromatic ones.
- Describe the mechanism of electrophilic and nucleophilic aromatic substitution reactions.
- Develop the way of synthesis of derivatives of aromatic compounds.

Brainstorming

What is an aromatic compound? Do you think benzene is the only aromatic compound? What makes aromatic compounds different from others? What type reaction aromatic compounds mainly undergo? How can you synthesis aromatic derivatives?

Session-1: At the end of this session you should be able to:

- Define aromatic compounds, aromaticity and antiaromaticity,
- Discuss aromaticity criteria,
- Distinguish aromatic compounds from the nonaromatic,
- Discuss the properties of benzene and its derivatives,
- Define heterocyclic aromatic compounds and give examples

Portion coverage: 1.1-1.3

1.1. Introduction

Aromatic compounds are special class of cyclic unsaturated compounds that are far more stable than they should be and resist addition reactions typical of ***unsaturated aliphatic compounds*.** Early chemists called such compounds **aromatic** compounds because of their pleasing fragrances or aromas. Examples are benzene and related compounds. Monocyclic hydrocarbons with alternating single and double bonds are called **annulenes**.

1.2. Aromaticity

What is aromaticity? Aromaticity is an extra stability possessed by a molecule that meets the following specific criteria:

1) It must have an uninterrupted cyclic cloud of π electrons (often called a π cloud) above and below the plane of the molecule. This means:
   - ✓ For the π cloud to be cyclic, *the molecule must be cyclic*.
   - ✓ For the π cloud to be uninterrupted, *every atom in the ring must have a* p *orbital*.
   - ✓ For the π cloud to form, each *p* orbital must overlap with the *p* orbitals on either side of it. Therefore, *the molecule must be planar*.

2) The π cloud must contain an odd number of pairs of π electrons.

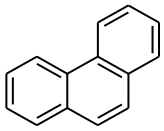
Hückel's rule or (4n+2) rule: states that for a planar, cyclic compound to be aromatic, its uninterrupted cloud must contain (4n+2)π electrons, where *n* is any whole number. According to this rule, then, an aromatic compound must have 2 (n=0), 6 (n=1), 10 (n=2) etc., electrons.

Example1: Benzene

- ☞ it is cyclic and planar,
- ☞ every carbon in the ring has a *p* orbital, and
- ☞ the cloud contains *three* pairs of electrons. The value of n can be calculated as: 4n+2=6, 4n=4, n=1and 1 is a whole number. Therefore, benzene is an aromatic compound

Example2: phenanthrene

- ☞ it is cyclic and planar,
- ☞ every carbon in the ring has a *p* orbital, and



phenanthrene

- ☞ the cloud contains *three* pairs of electrons. 4n+2=14, 4n=10, n=5 and 5 is a whole number. Therefore, benzene is an aromatic compound

Example3: furan

- ☞ it is cyclic and planar,
- ☞ every carbon in the ring has a *p* orbital (B/c one of the orbital of oxygen containing lone pair of electron is can be considered as **p**) and
- ☞ It has 2π bonds i.e. 4π electrons and one lone pair (2π electrons) which can possibly delocalize. Hence, the total π electrons will be 6. Calculating the value of n using Hückel's Rule, you will get 1. Therefore, furan is aromatic.

Antiaromaticity: *Aromaticity is characterized by stability, whereas antiaromaticity is characterized by instability*. A compound that fulfills the first criterion of aromaticity but does not fulfill the second criterion is antiaromatic. Examples, Cyclobutadiene & cyclopentadienyl cation.

Relative stabilities aromatic compounds and related compounds:

aromatic compound > cyclic compound with localized electrons > antiaromatic compound

Exercise #1.1

Classify the following structures as aromatic or non-aromatic compounds.

a.  cyclopropene

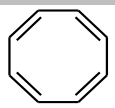
b.  cyclobutadiene

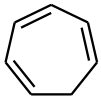
c.  cyclopropenyl cation

d.  cyclopropenyl anion

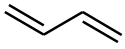
e.  cyclopentadienyl cation

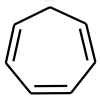
f.  cyclopentadienyl anion

g.  cyclooctatetraene

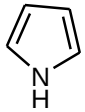
h.  cycloheptatriene

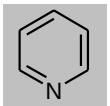
i.  cycloheptatrienyl anion

j.  1,3-butadiene

k.  cycloheptatrienyl cation

l.  Thiophene

m.  pyrrole

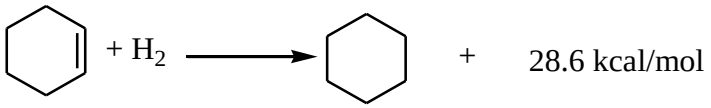
n.  pyridine

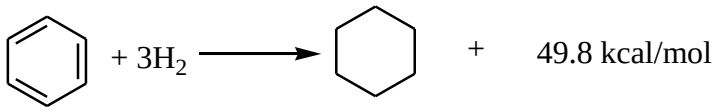
Aromatic compounds possessing aromaticity do have **conjugation** which is the source of special stability provided by three or more adjacent parallel overlapping p orbitals. Aromaticity is like conjugation, but with extra stability.

1.3. Properties of Benzene and its Derivatives

Benzene and related compounds shown a special stability recognized to its aromaticity. Some of these properties are the following. N.B: benzene derivatives are also aromatic compounds.

1) Benzene displays unusual thermodynamic stability. Example, heat of hydrogenation of benzene is 36 kcal/mol less than expected. Hydrogention of cyclohexene produces 28.6 kcal/mol of heat. Hence, from this we will expect the heat produced from hydrogention benzene should be 3x28.6 kcal/mol which can be calculated to be 85.8 kcal/mol. But the actual heat for the hydrogenation of benzene is 49.8 kcal/mol. The difference between the expected and the actual heat of hydrogenation is called **resonance energy of benzene** (36 kcal/mol).





2) The NMR signal of the benzene proton appears at 7.3 ppm. This is to say the protons are deshielded by resonance. Hence, small energy is required to induce resonance of the protons.

3) Benzene is generally less reactive than simple alkenes. Example, unlike alkenes benzene does not undergo bromination (addition of bromine); rather it undergoes ***substitution*** in the presence of **iron catalyst.**

Benzene is also a planar molecule with bond angles of 120^0**.** All six C to C bonds have identical length of 0.139 nm being between single (0.154 nm) and double (0.133 nm) bonds.

☝ **These all special property of benzene also appears in its derivatives.**

1.4. Heterocyclic Aromatic Compounds

Session-2: At the end of this session you should be able to:

- Define heterocyclic aromatic compounds and give examples
- Show a general electrophilic aromatic substitution reactions with mechanism
- Write a step-by-step process of halogenation and alkylation

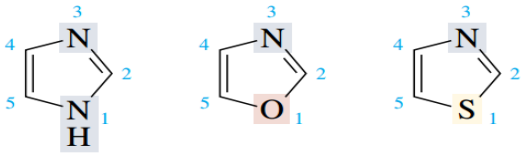
Cyclic compounds that contain at least one atom other than carbon within their ring are called **heterocyclic compounds**, and those that possess aromatic stability are called **heterocyclic aromatic compounds**. Some representative heterocyclic aromatic compounds are pyridine, pyrrole, furan, and thiophene.

Hückel's rule can be extended to heterocyclic aromatic compounds. A single heteroatom can contribute either 0 or 2 of its lone-pair electrons as needed to the π system so as to satisfy the (4n + 2) π electron requirement. The lone pair in **pyridine**, for example, is associated entirely with nitrogen and is not delocalized into the aromatic, π system. The nitrogen is sp2-hybridized, and the three double bonds of the ring contribute the necessary six, π electrons to make pyridine a heterocyclic aromatic compound. The unshared electron pair of nitrogen occupies an sp2 orbital in the plane of the ring, not a p orbital aligned with the, π system.

In **pyrrole**, on the other hand, the unshared pair belonging to nitrogen must be added to the four, π electrons of the two double bonds in order to meet the six π electron requirement. The nitrogen of pyrrole is sp2-hybridized and the pair of electrons occupies a p orbital where both electrons can participate in the aromatic, π system. Pyridine and pyrrole are both weak bases, but pyridine is much more basic than pyrrole. When pyridine is protonated, its unshared pair is used to bond to a proton and, because the unshared pair is not involved in the resonance

system, the aromatic character of the ring is little affected. When pyrrole acts as a base, the two electrons used to form a bond to hydrogen must come from the π system, and the aromaticity of the molecule is sacrificed on protonation.

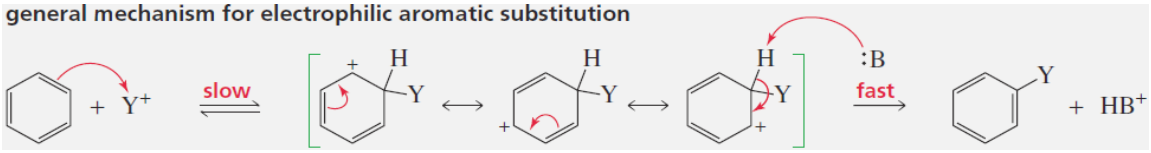
A large group of heterocyclic aromatic compounds are related to pyrrole by replacement of one of the ring carbons β to nitrogen by a second heteroatom. Compounds of this type are called *azoles.*



Exercise #1.2
Draw the resonance structures of pyridine, pyrrole, furan, thiophene, Imidazole and Thiazole.

1.5. Aromatic Electrophilic Substitution Reactions and their Mechanism.

Because electrophilic substitution of benzene involves the reaction of an electrophile with an aromatic compound, it is more precisely called an **electrophilic aromatic substitution reaction**. It is the most common aromatic reaction.

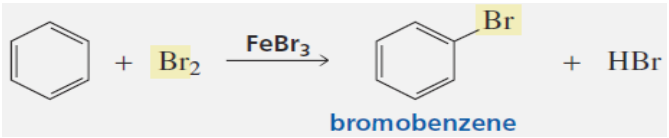


Notice that *the proton is always removed from the carbon that has formed the new bond with the electrophile*.

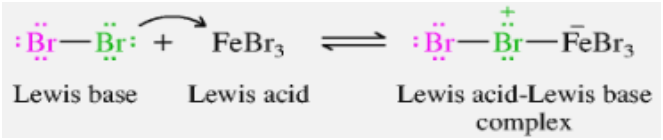
The following are the five most common electrophilic aromatic substitution reactions:

1.4.1. Halogenation: bromine (Br), chlorine (Cl), or an **iodine (I)** substitutes for a hydrogen. The bromination or chlorination of benzene requires a **Lewis acid** such as ferric bromide or ferric chloride. Recall that a *Lewis acid* is a compound that shares a pair of electrons.

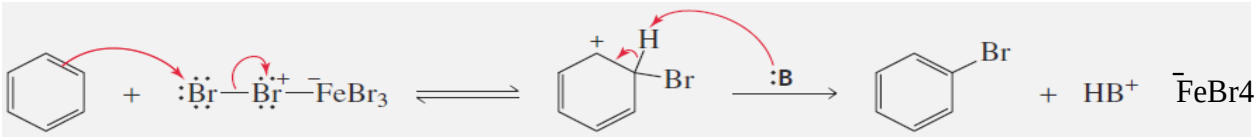
Bromination



Mechanism



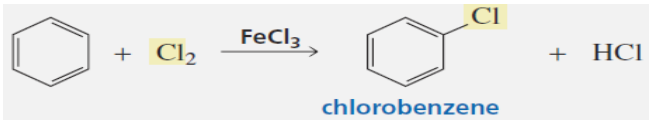
Hence, on the product the left bromine can act as electrophile; because, the positively charged bromine in the structure above attracts the bonding electrons towards itself strongly.



Where, :B is a base in the reaction mixture. Since the use of ferric bromide catalysis it will be reformed as follow.

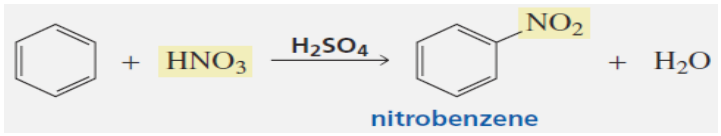
Exercise #1.3

Draw similar mechanisms of the following reaction.

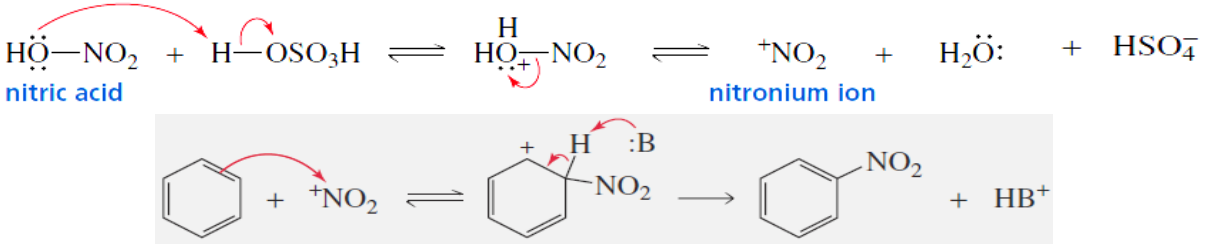


- **Electrophilic iodine** (I^+) is obtained by treating I_2 with an oxidizing agent such as nitric acid.

1.4.2. Nitration: A nitro (NO_2) group substitutes for a hydrogen. Nitration of benzene with nitric acid requires sulfuric acid as a catalyst.



To generate the necessary electrophile sulfuric acid protonates nitric acid. Loss of water from protonated nitric acid forms a **nitronium ion**, the electrophile required for nitration. Remember that any base (:B) present in the reaction mixture (H_2O, HSO_4-, solvent) can remove the proton in the second step of the aromatic substitution reaction.



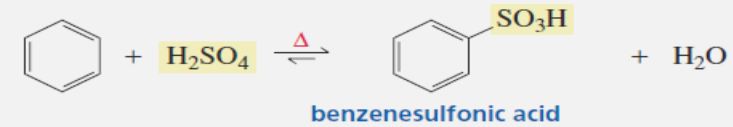
1.4.3. Sulfonation: A sulfonic acid (-SO_3H) group substitutes for a hydrogen.

Session-3: At the end of this session you should be able to:

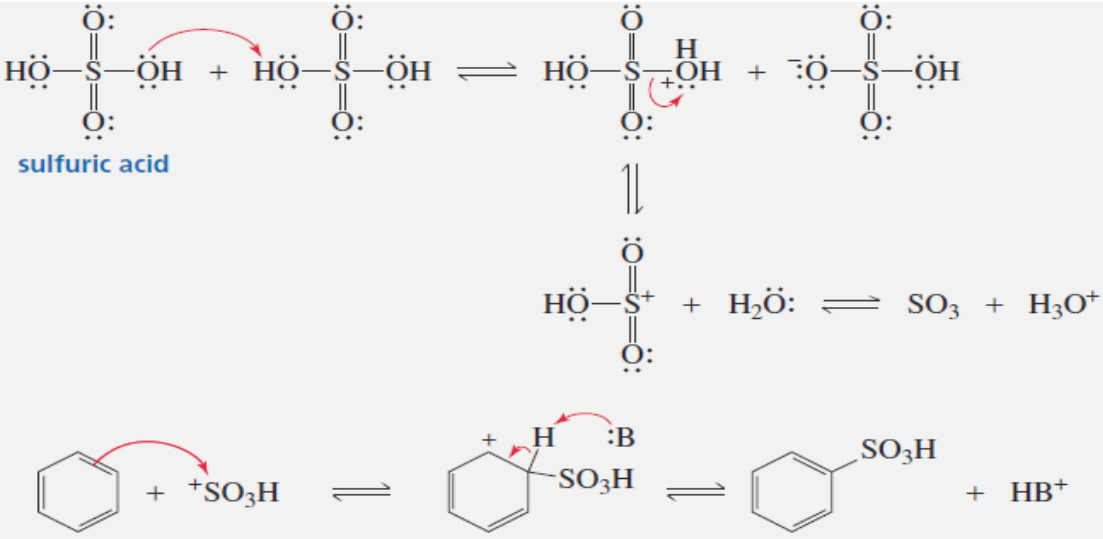
- Discuss sulfonation, **Friedel–Crafts** acylation and **Friedel–Crafts** alkylation of benzene
- Categorize substituents of benzene based on their directing effect(s)

Fuming sulfuric acid (a solution of SO_3 in sulfuric acid) or concentrated sulfuric acid is used to sulfonate aromatic rings.

Sulfonation

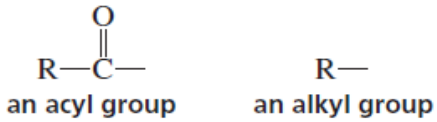


Mechanism for sulfonation (the electrophile will be formed by heating)

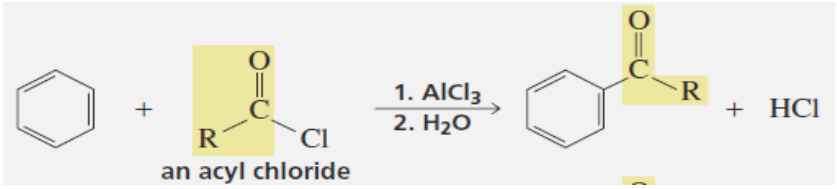


1.4.4. Friedel–Crafts Reactions

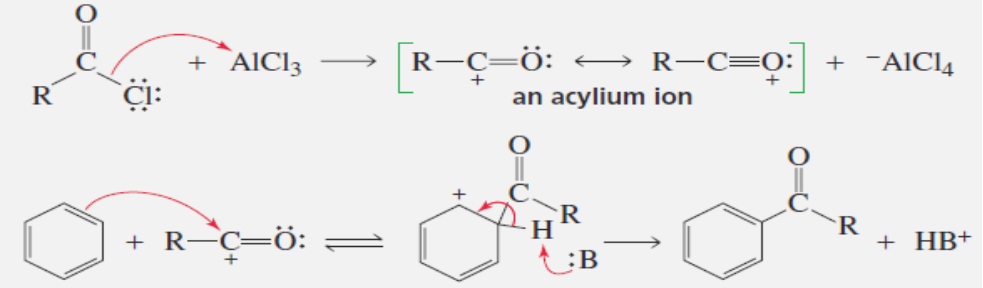
Two electrophilic substitution reactions bear the names of chemists **Charles Friedel** and **James Crafts**. ***Friedel–Crafts acylation*** places an acyl group on a benzene ring, and ***Friedel–Crafts alkylation*** places an alkyl group on a benzene ring.



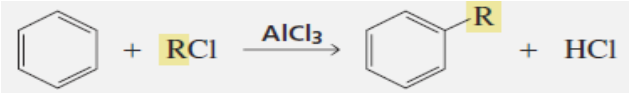
Friedel–Crafts acylation: An acyl group (RC=O) substitutes for a hydrogen. General representation of the reaction is:



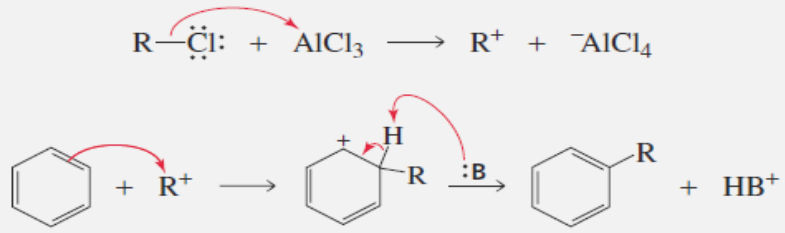
An **acylium ion** is the electrophile required for a Friedel–Crafts acylation reaction. This ion is formed by the reaction of an *acyl chloride* or an *acid anhydride* with a Lewis acid. Because the product of a Friedel–Crafts acylation reaction contains a carbonyl group that can complex with $AlCl_3$, Friedel–Crafts acylation reactions must be carried out with more than one equivalent of $AlCl_3$. When the reaction is over, **water** is added to the reaction mixture to liberate the product from the complex.



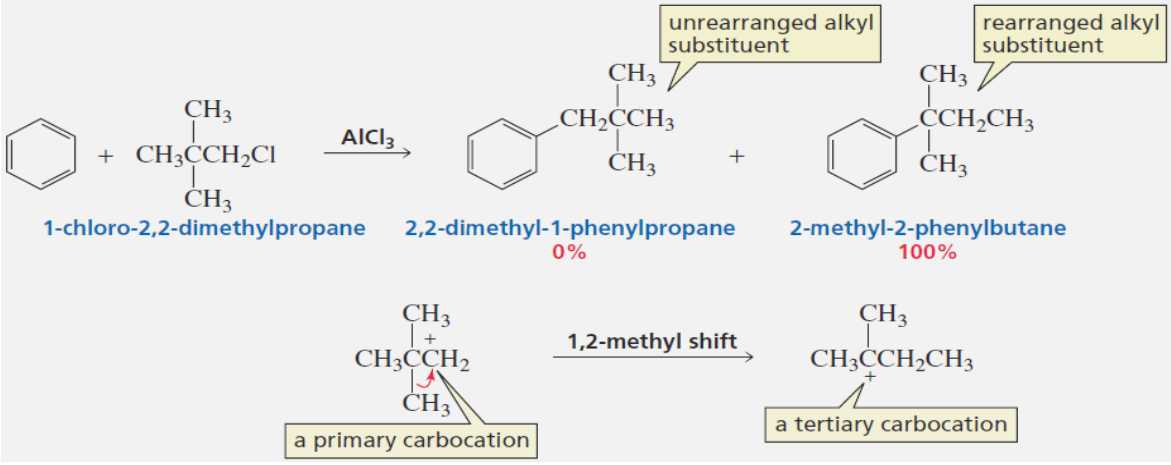
1.4.5. Friedel–Crafts alkylation: an alkyl (R) group substitutes for a hydrogen. General representation of the reaction



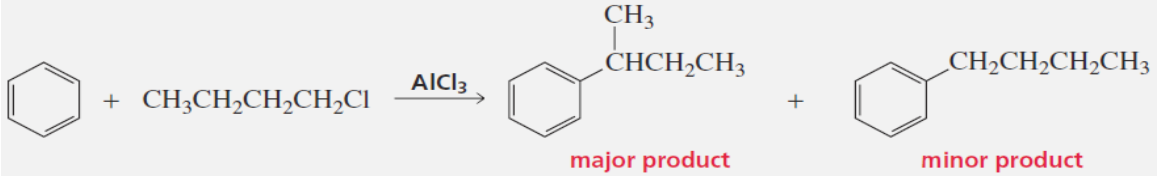
Mechanism



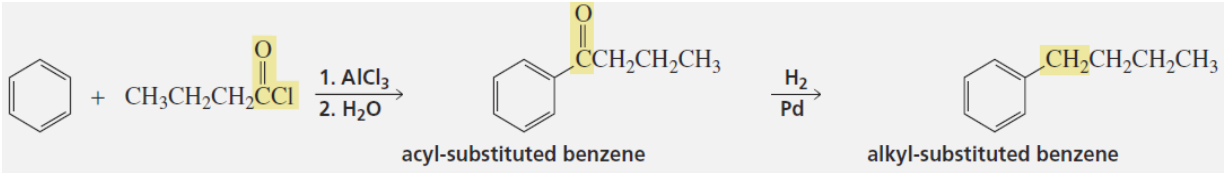
When benzene reacts with 1-chloro-2,2-dimethylpropane, a primary carbocation rearranges to a tertiary carbocation. Thus, there is a greater increase in carbocation stability and, therefore, a greater amount of rearranged product—100% of the product (under all reaction conditions) has the rearranged alkyl substituent.



It is **not** possible to obtain a good yield of an alkylbenzene containing a straight-chain alkyl group via a Friedel–Crafts alkylation reaction, because the incipient primary carbocation will rearrange to a more stable carbocation.



We can overcome this problem by using acylation followed by alkylation. This is because the acylium ions do not rearrange.



1.4.6. Directing effects of substituents

Session-4: At the end of this session you should be able to:

- Estimate the reactivity of monosubstituted benzene towards elctrophile,
- Give examples of reaction of monsubstituted benzene ring.

A problem arises when substitution occurs on a benzene ring that already bears a substituent. In such a compound there are three nonequivalent positions on the ring (ortho, meta and para). It is therefore important to be able to predict the predominant substitution site(s) so that one can design a rational synthesis of polysubstituted aromatic compounds. Fortunately, this is usually not a difficult task.

There are three classes of substituents: these are

1. **Meta directing and deactivating. Examples:**

Nitro	$-NO_2$	nitrile	$-CN$
Ammonium	$-\overset{+}{N}R_3$	aldehyde	$-CHO$

2. **Ortho-para directing and activating. Examples:**

Hydroxyl	$-OH$	phenyl	$-C_6H_5$
Alkoxyl	$-OR$	amino	$-NH_2$
Alkyl	$-R$		

3. **Ortho-para directing and deactivating. Examples:**

Halogens $-Cl$, $-Br$, $-I$

Relative rates of electrophilic substitution

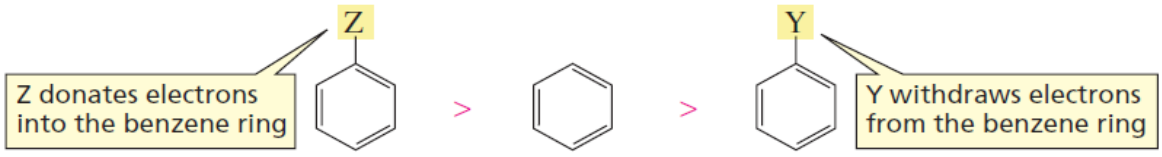
Substituents that are capable of donating electrons into the benzene ring will stabilize both the carbocation intermediate and the transition state leading to its formation, thereby increasing the rate of electrophilic aromatic substitution. In contrast, substituents that withdraw electrons

from the benzene ring will destabilize the carbocation intermediate and the transition state leading to its formation, thereby decreasing the rate of electrophilic aromatic substitution.

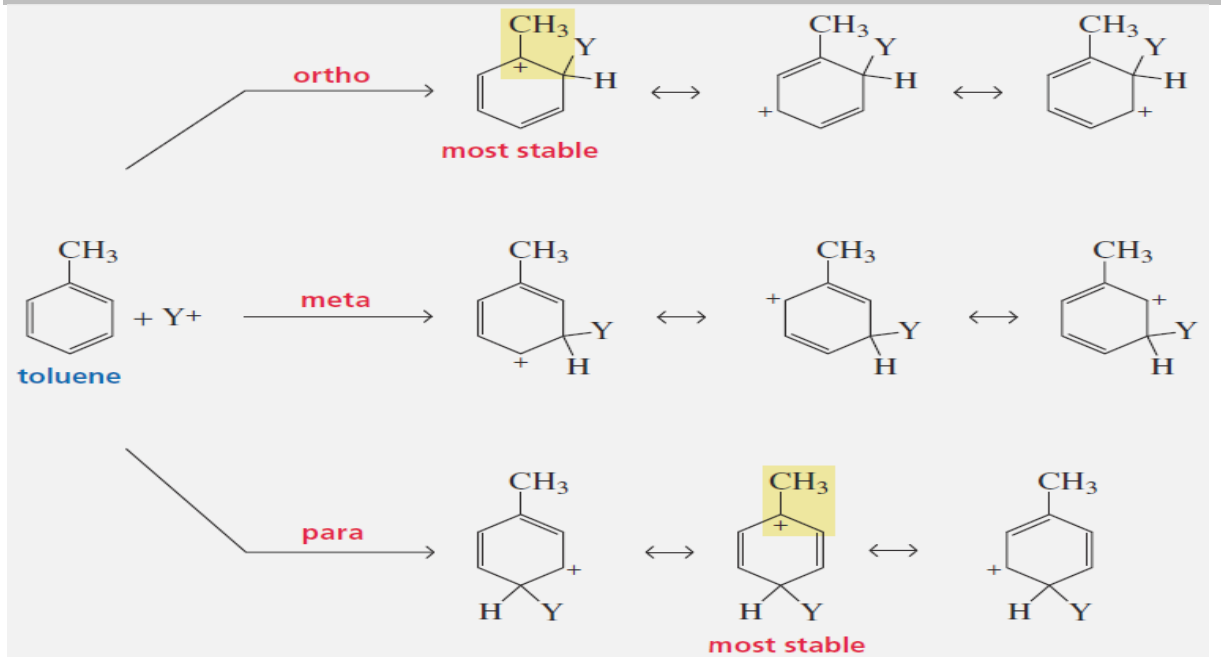
There are two ways in which substituents can donate electrons into a benzene ring: *inductive* electron donation and electron donation by *resonance*. There are also two ways substituents can withdraw electrons from a benzene ring: *inductive* electron withdrawal and electron withdrawal by *resonance*.

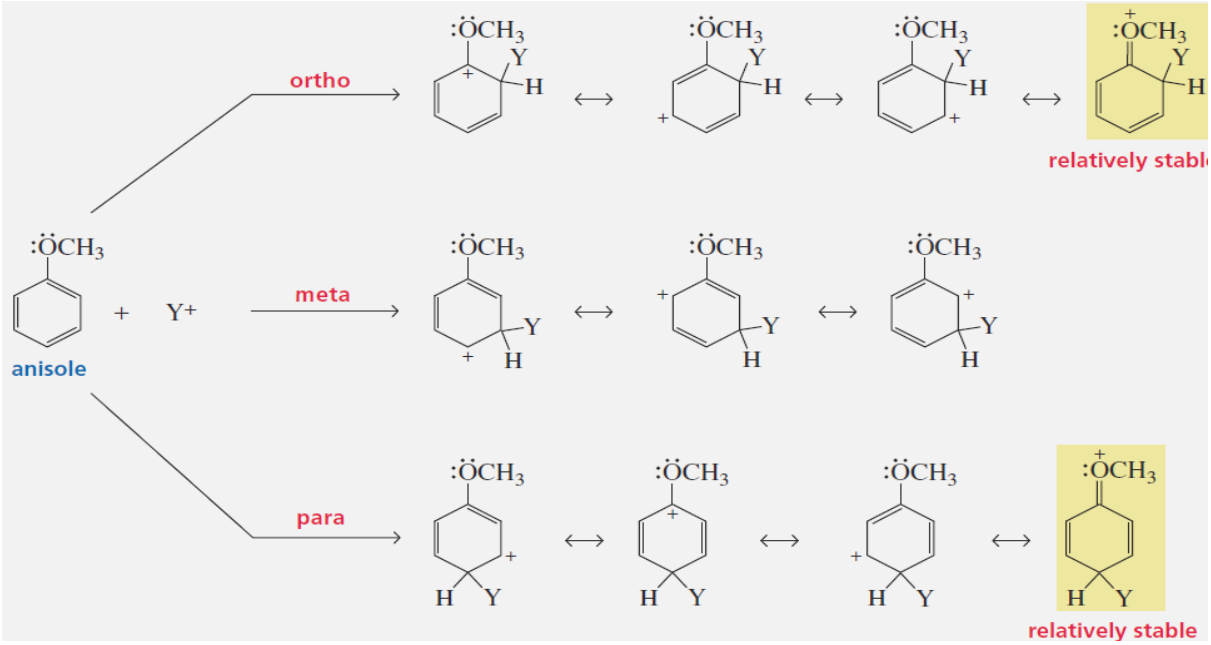
- Electron-donating substituents increase the reactivity of the benzene ring toward electrophilic aromatic substitution.
- Electron-withdrawing substituents decrease the reactivity of the benzene ring toward electrophilic aromatic substitution.

For the substituents Y and Z given below, the reactivity can be written as:

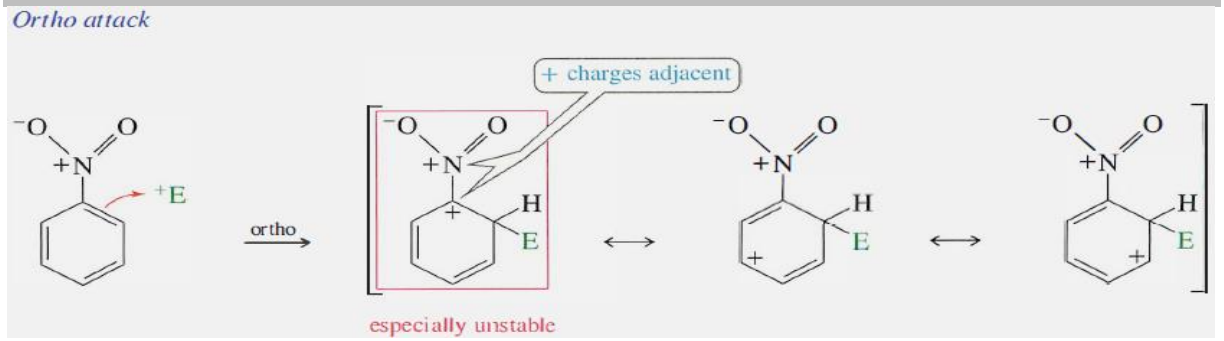


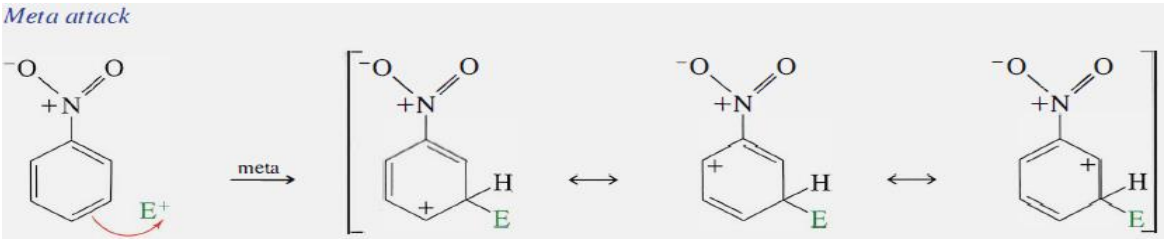
Why methyl and methoxy groups are ortho-para directing activating?

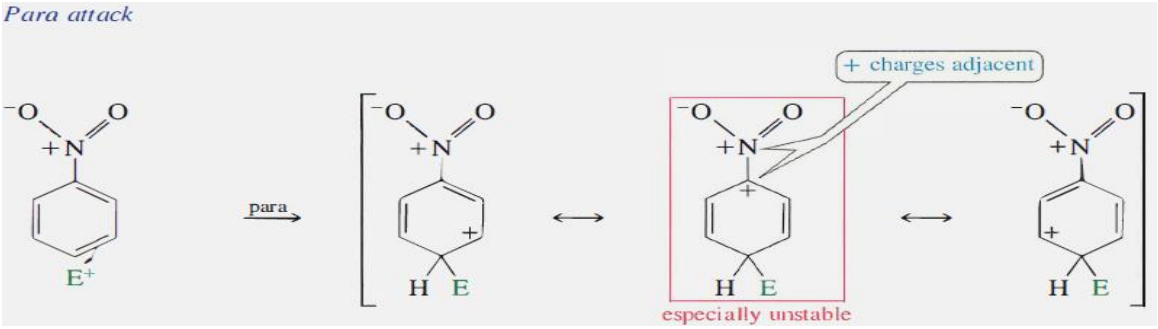




Why nitro group is Meta directing deactivating?

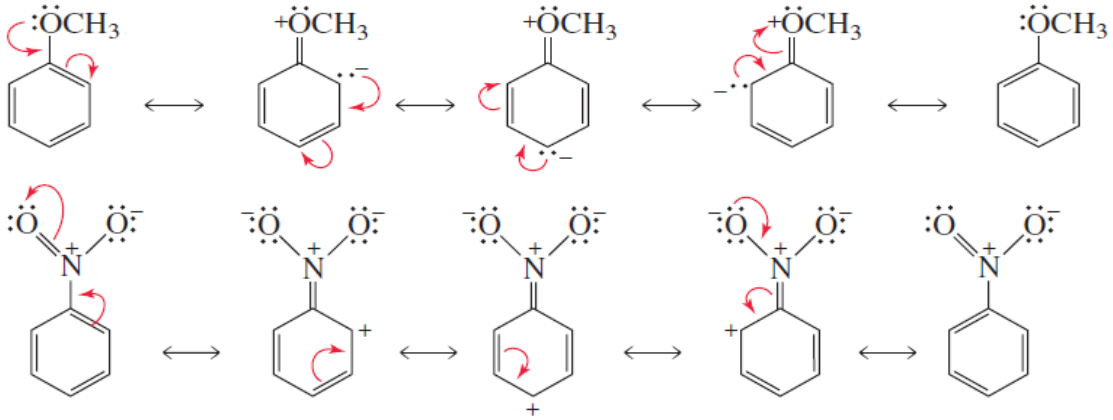






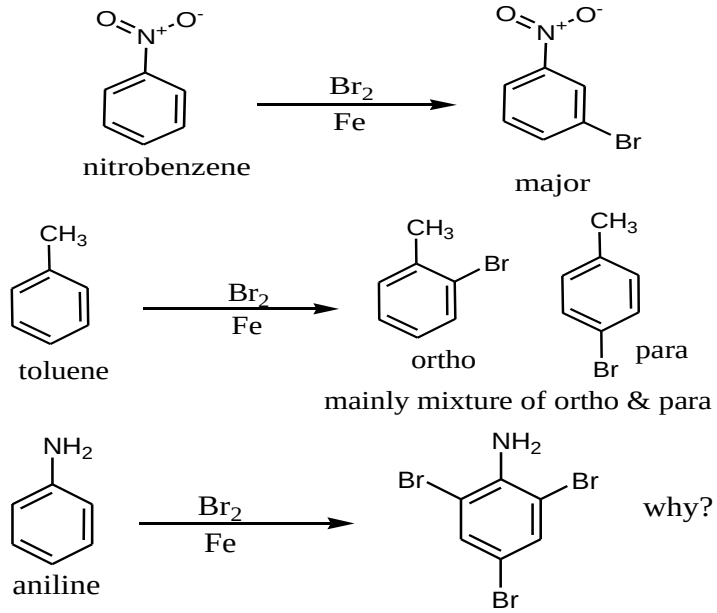
Exercise #1.4

1. Can you guess directing effect of substituents on the electrophile from the resonance structures given below?



2. Show how aldehyde group is meta directing deactivating while hydroxyl group is ortho-para directing activating.

1.4.7. Examples of electrophilic substitution of mono substituted aromatic compounds.



1.4.8. Representative reactions of pyrrole, furan, thiophene and pyridine

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Session-5: At the end of this session you should be able to:

- Identify preferential electrophilic substitution of representative reactions of pyrrole, furan, thiophene and pyridine

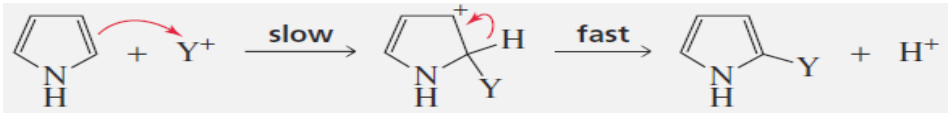
Pyrrole, **furan**, and **thiophene** are five-membered-ring heterocycles. Each has three pairs of delocalized π electrons: Two of the pairs are shown as π bonds, and one pair is shown as a

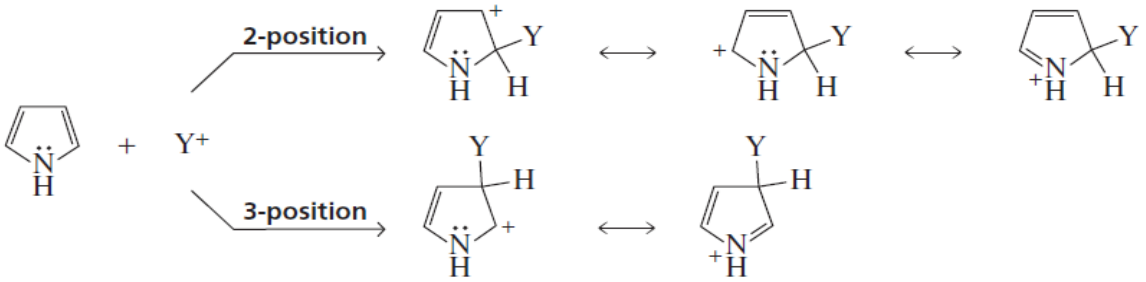
lone pair on the heteroatom. Because pyrrole, furan, and thiophene are aromatic, they undergo electrophilic aromatic substitution reactions.

They undergo electrophilic substitution preferentially at C-2. Substitution occurs preferentially at C-2 because the intermediate obtained by attaching a substituent at this position is more stable than the intermediate obtained by attaching a substituent at C-3.

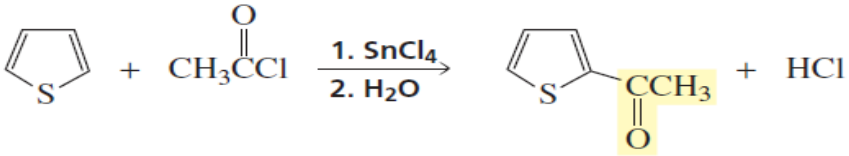
Mechanisms for electrophilic aromatic substitution

Pyrrole: General mechanism



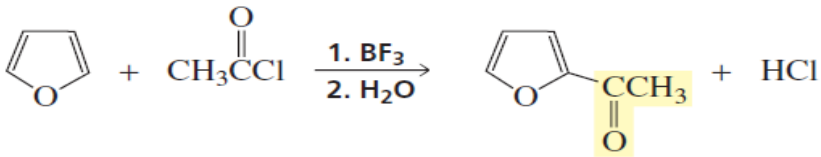


Examples:



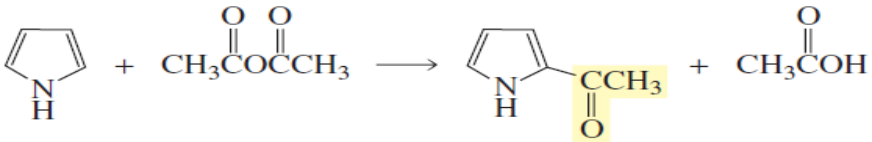
2-acetylthiophene

weak SnCl4 catalyst



2-acetylfuran

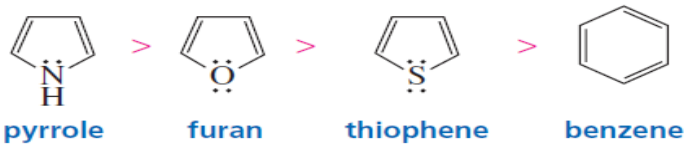
weak BF_3 catalyst



2-acetylpyrrole

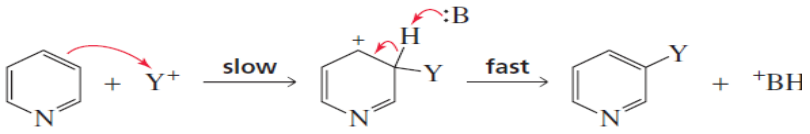
catalyst is not required

Relative reactivity toward electrophilic aromatic substitution

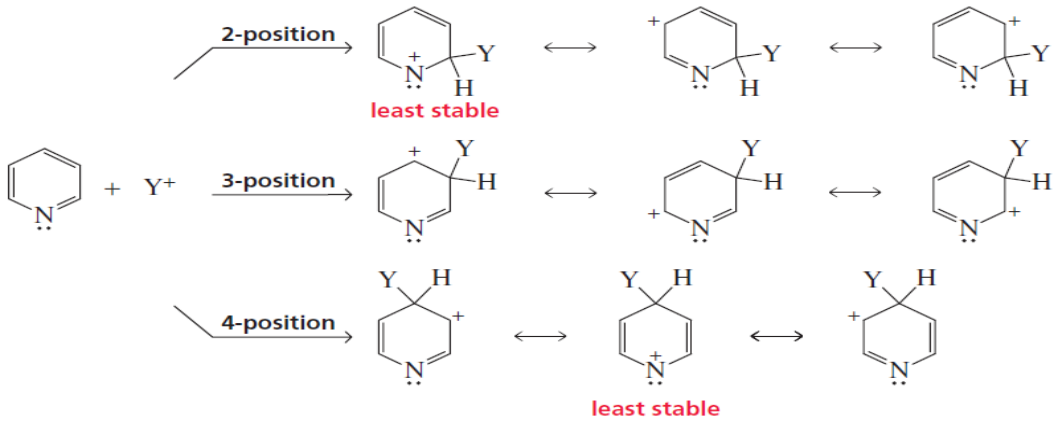


Furan is not as reactive as pyrrole in electrophilic aromatic substitution reactions. The oxygen of furan is more electronegative than the nitrogen of pyrrole, so the oxygen is not as effective as nitrogen in stabilizing the carbocation. Thiophene is less reactive than furan toward electrophilic substitution because sulfur's π electrons are in a 3*p* orbital, which overlaps less effectively than the 2*p* orbital of nitrogen or oxygen with the 2*p* orbital of carbon.

Pyridine: General mechanism



Where is the preferred substitution site?



Pyridine does not undergo Friedel–Crafts alkylation because its reactivity is highly affected by electronegative nitrogen. Therefore, undergoes electrophilic aromatic substitution reactions only under vigorous conditions (very high T), and the yields of these reactions are often quite low.

1.6. Nucleophilic Aromatic Substitution Reactions

Session-6: At the end of this session you will be able to:

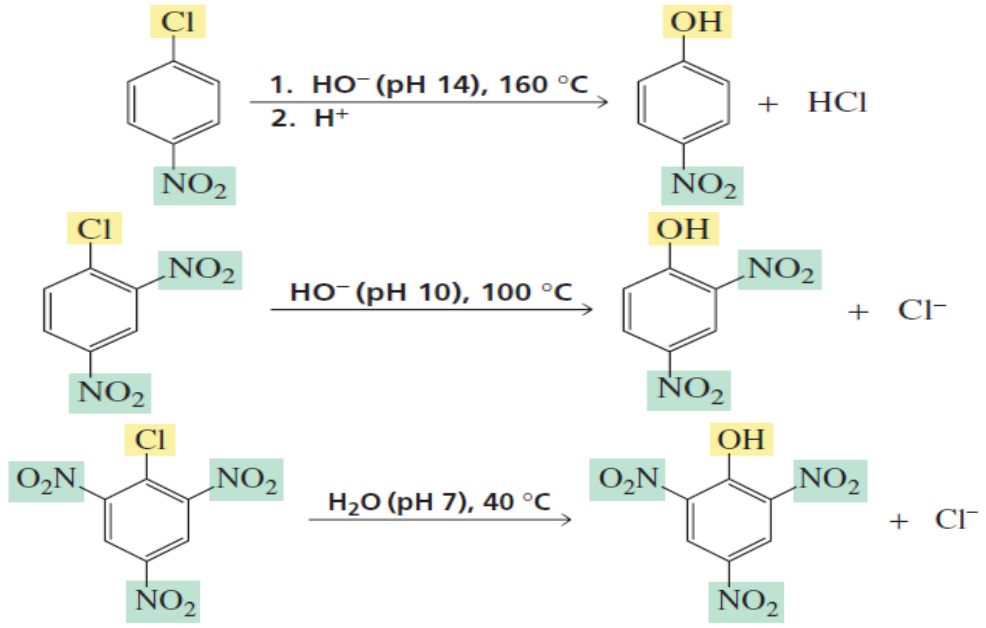
- Differentiate nucleophilic aromatic substitution from electrophilic rxn.
- Estimate the reactivity of monosubstituted benzene relative to benzene.

❥ Give examples of reaction of nucleophilic aromatic substitution of monsubstituted benzene ring.

We have seen that aryl halides do not react with nucleophiles under standard reaction conditions because the π electron clouds repel the approach of a nucleophile.

1.5.1. Reactions of Aryl halides

If, however, the aryl halide has one or more substituents that strongly withdraw electrons from the ring by resonance, **nucleophilic aromatic substitution** reactions can occur without using extreme conditions. The electron-withdrawing groups must be positioned ortho or para to the halogen. The greater the number of electron-withdrawing substituents, the easier it is to carry out the nucleophilic aromatic substitution reaction. Notice the different conditions under which the following reactions occur: **Examples:**

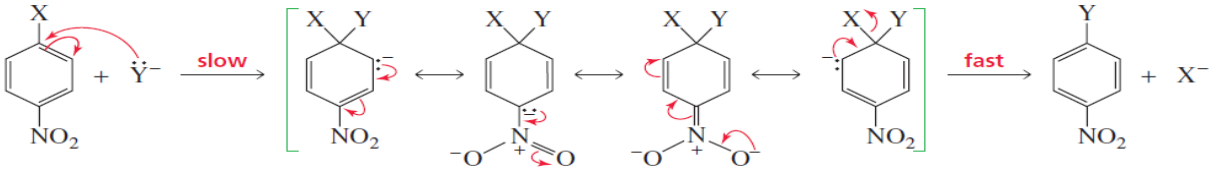


Electron-withdrawing substituents increase the reactivity of the benzene ring toward nucleophilic substitution and decrease the reactivity of the benzene ring toward electrophilic substitution.

1.5.2. Mechanisms of nucleophilic aromatic substitution reactions

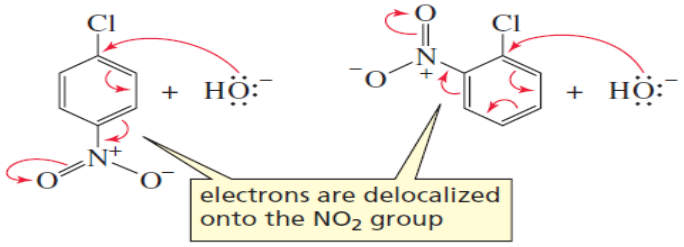
Nucleophilic aromatic substitution takes place by a two-step reaction known as an **S_NAr reaction** (Substitution nucleophilic aromatic). In the first step, the nucleophile attacks the carbon bearing the leaving group from a trajectory that is nearly perpendicular to the aromatic ring. Nucleophilic attack forms a resonance-stabilized carbanion intermediate called a *Meisenheimer complex*, after Jakob Meisenheimer (1876–1934). In the second step of the reaction, the leaving group departs, reestablishing the aromaticity of the ring.

Mechanism for nucleophilic aromatic substitution



In a nucleophilic aromatic substitution reaction, the incoming nucleophile must be a stronger base than the substituent that is being replaced, because the weaker of the two bases will be the one eliminated from the intermediate.

The electron-withdrawing substituent must be ortho or para to the site of nucleophilic attack because the electrons of the attacking nucleophile can be delocalized onto the substituent only if the substituent is in one of those positions.



1.6. Reactions of Aromatic Side Chains

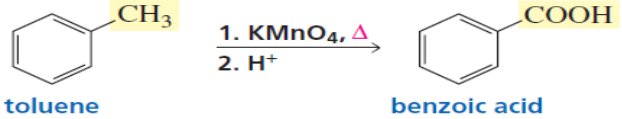
Session-7: At the end of this session you should be able to:

- Discuss the reactivity of Aromatic side chains.
- Give examples of reaction of Aromatic Side Chains.
- Discuss ways of reductions of niro substituent and aryl ketone.
- Show the conversion of halides to organometallic reagents

1.6.1. Oxidation and substitution of alkyl side-chains

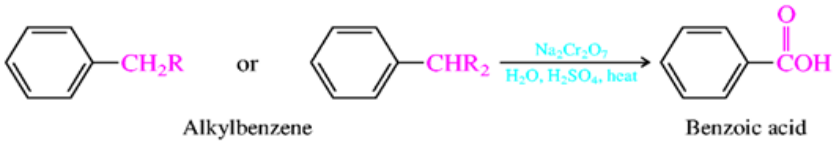
Oxidation reactions of alkyl side chain

An alkyl group bonded to a benzene ring can be oxidized to a carboxyl group. When an organic compound is *oxidized*, either the number of C-O, C-N, or C-X (where X denotes a halogen atom) bonds increases or the number of C-H bonds decreases. Commonly used oxidizing agents are potassium permanganate ($KMnO_4$) or acidic solutions of sodium dichromate (H^+, $Na_2Cr_2O_7$) because the benzene ring is so stable, it will not be oxidized—only the alkyl group is oxidized.

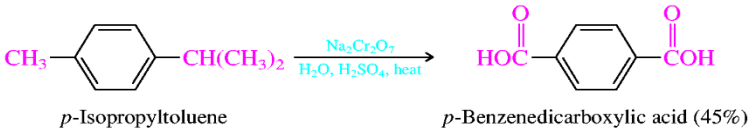


Regardless of the length of the alkyl substituent, it will be oxidized to a -COOH group, provided that a hydrogen is bonded to the benzylic carbon. If the alkyl group lacks a benzylic

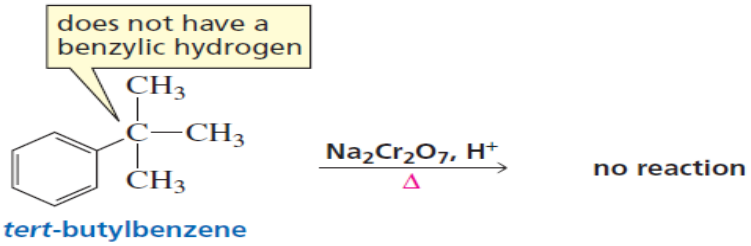
hydrogen, the oxidation reaction will not occur because the first step in the oxidation reaction is removal of a hydrogen from the benzylic carbon.



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

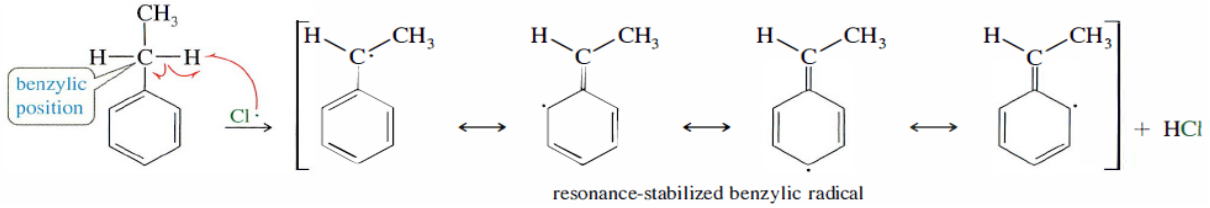


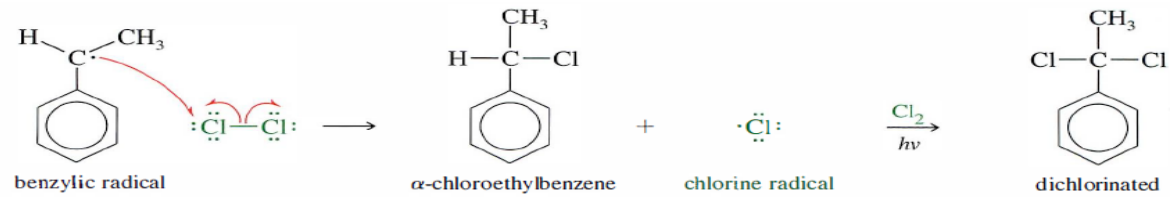
Note that alkyl groups, regardless of their chain length, are converted to carboxyl groups (-CO_2H) attached directly to the ring. An exception is a substituent of the type -CR_3 because it lacks benzylic hydrogens, such a group is not susceptible to oxidation under these conditions.



Radical halogenation of alkyl side chain

Alkylbenze undergo free radical halogenation much more easily than alkanes. Why? Because abstraction of hydrogen atom at a benzylic position gives a resonance stabilized benzylic radical. Example, ethylbenzene reacts with chlorine in the presence of light to give α-chlorobenzene. The reaction can possibly give mixture of α-cholorobenzene (major), β-chlorobenze because chrlorine radical is very reactive. Further oxidation may also result dichlorbenzene. But bromine (using Br_2 or NBS with *hv*) reacts exclusively at the benzylic position. Why? B/c bromine is less reactive than chlorine.

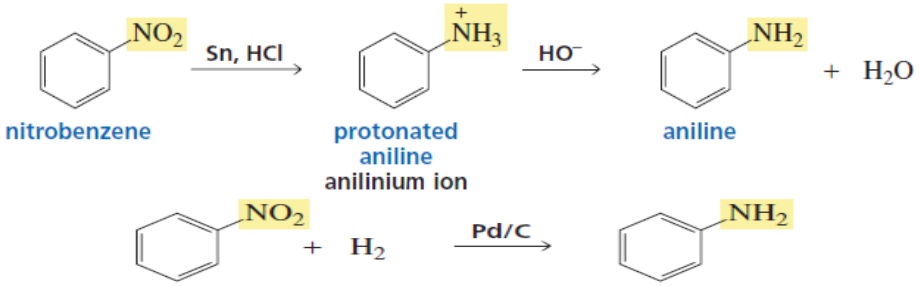




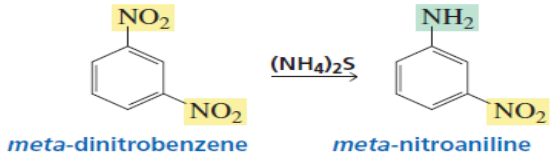
1.6.2. Reduction of nitro groups and aryl ketones

Reducing a nitro substituent

A nitro substituent can be reduced to an amino substituent. Either a metal (tin, iron, or zinc) plus an acid (HCl) or catalytic hydrogenation can be used to carry out the reduction. If acidic conditions are employed, the product will be in its acidic form (anilinium ion). When the reaction is over, base can be added to convert the product into its basic form (aniline).

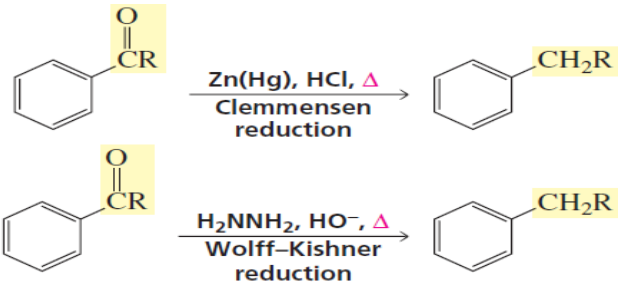


It is possible to selectively reduce just one of two nitro groups.

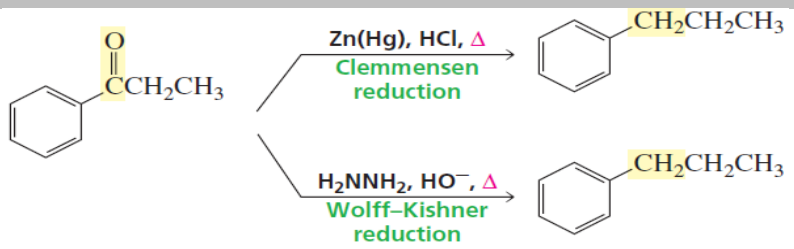


Reducing aryl ketones

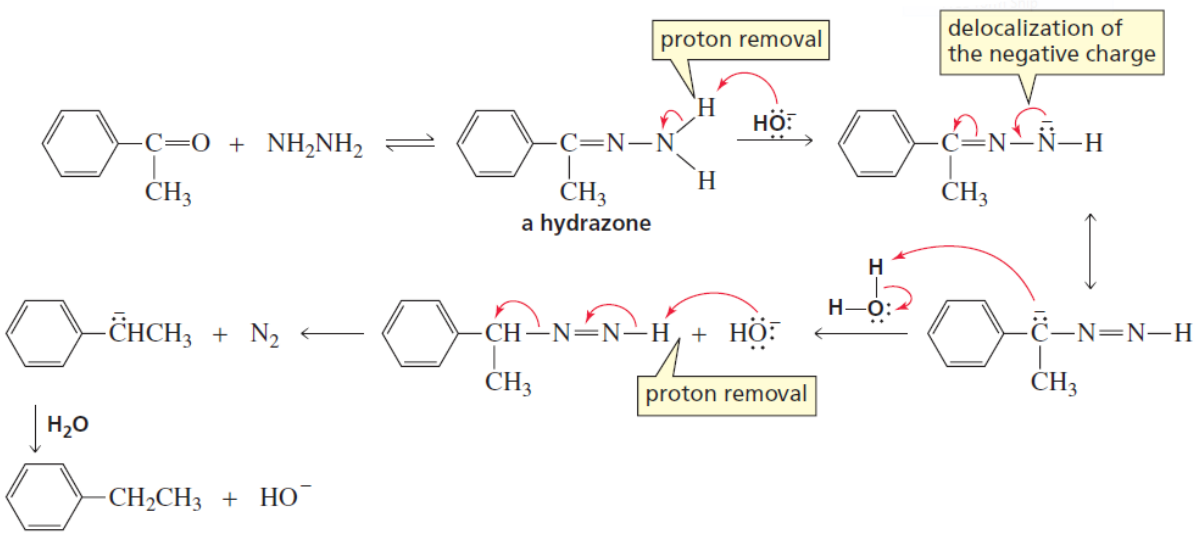
There are more general methods available to reduce a ketone carbonyl group to a methylene group—methods that reduce all ketone carbonyl groups, not just those that are adjacent to benzene rings. Two of the most effective are the Clemmensen reduction and the Wolff–Kishner reduction. The **Clemmensen reduction** uses an acidic solution of zinc dissolved in mercury as the reducing reagent. The **Wolff–Kishner reduction** employs hydrazine under basic conditions. Generally, Clemmensen and Wolff–Kishner reductions can be represented as:



Example

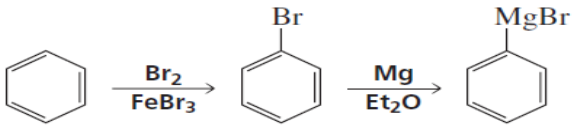


Mechanism of Wolff-Kishner reduction reaction



1.6.3. Conversion of halides to organometallic reagents

Organometalic reagents can be can be prepared from benzene by:



Hence, this organometallic reagent is important to prepare other aromatic derivatives.

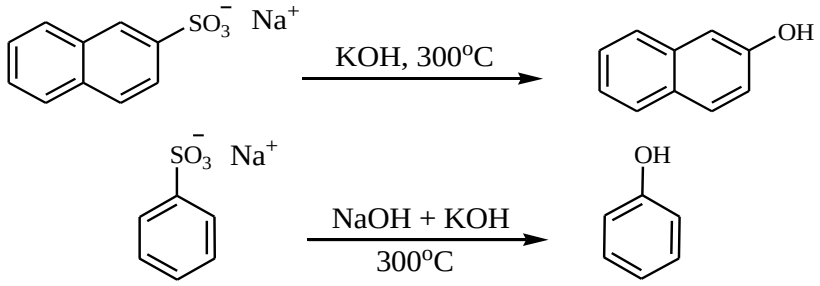
Examples:

1.6.4. Hydrolysis and fusion of sulfonic acids

Session-8: At the end of this session the students should be able to:

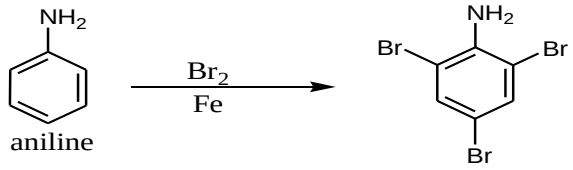
- Discuss hydrolysis and fusion of sulfonic acids.
- Modify the influence of strong activating groups.
- Use diazonium ion for synthesis of different aromatic derivatives.

Sulfonic acids are not in themselves very important. However, it is usually easy to convert sodium salts of sulfonic acids into phenolic compounds which do have great synthetic, commercial, and biological importance. This reaction is carriedout by melting or "fusing" the sulfonic acid in the presence of NaOH and/or KOH. Although the conditions seem drastic, the yields are often quite good: Examples:



1.6.5. Modifying the influence of strong activating groups

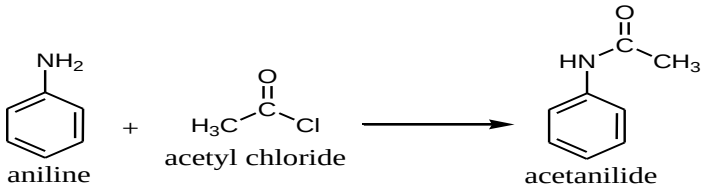
Aryl amines and phenols are so reactive towards electrophilic aromatic substitution that multiple halogenation occurs. Example:



aniline

2,4,6-tribromobenzenamine

In order to prepare p-bromoaniline, aniline must be acylated with acetyl chloride. The acylated group is important to direct the coming group preferentially to the para position b/c of its steric effect on the ortho.

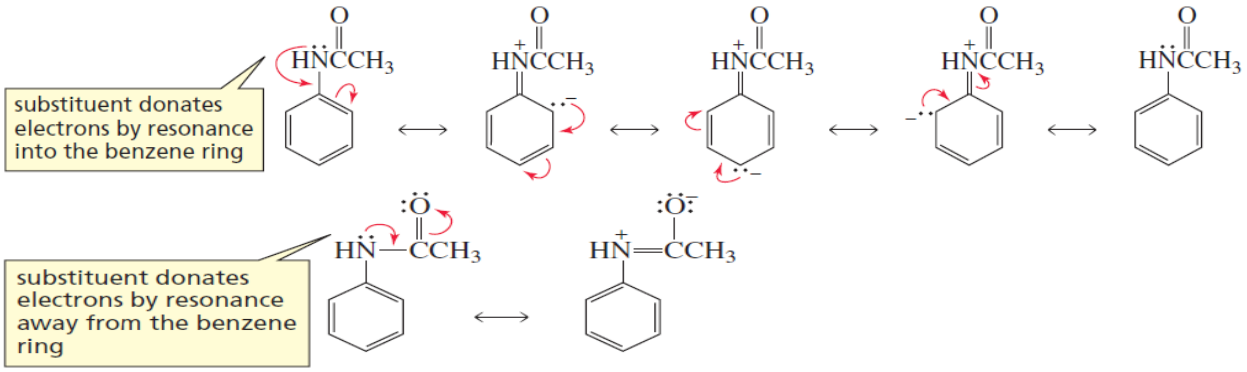


aniline

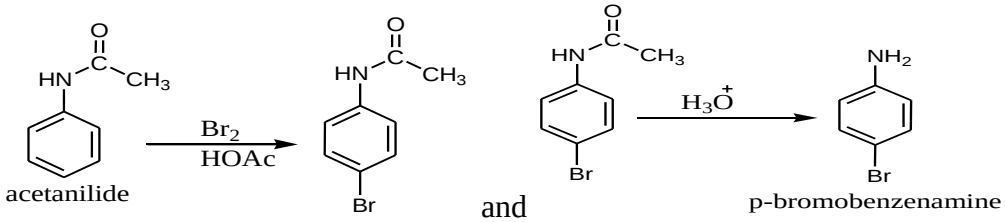
acetyl chloride

acetanilide

substituents are less effective at donating electrons into the ring by resonance because, unlike the strongly activating substituents that donate electrons by resonance only *into* the ring, the moderately activating substituents can donate electrons by resonance in two competing directions: *into* the ring and *away from* the ring.

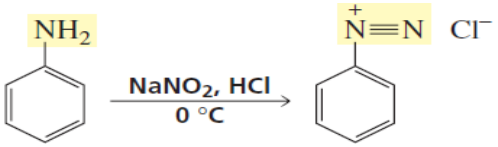


Nevertheless, the amide group is still ortho-para directing and activating and the amino group is reformed by the hydrolysis of the amide.

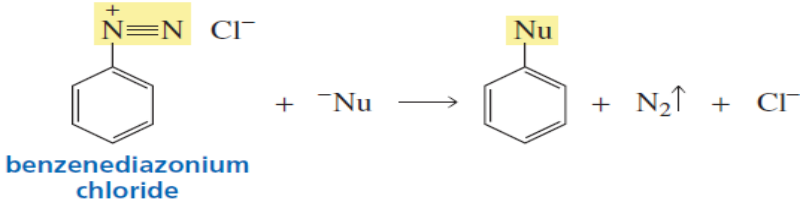


1.6.6. Diazotization of primary aromatic amines and their usefulness in synthesis of aromatic derivatives

A primary amine can be converted into a diazonium salt by treatment with nitrous acid because nitrous acid (HNO_2). is unstable, it is formed in situ, using an aqueous solution of sodium nitrite and HCl or HBr; indeed, N2 is such a good leaving group [NH_2] that the diazonium salt is synthesized at 0 °C and used immediately without isolation. (The mechanism for conversion of a primary amino group [+N≡N] to a diazonium group is shown below.

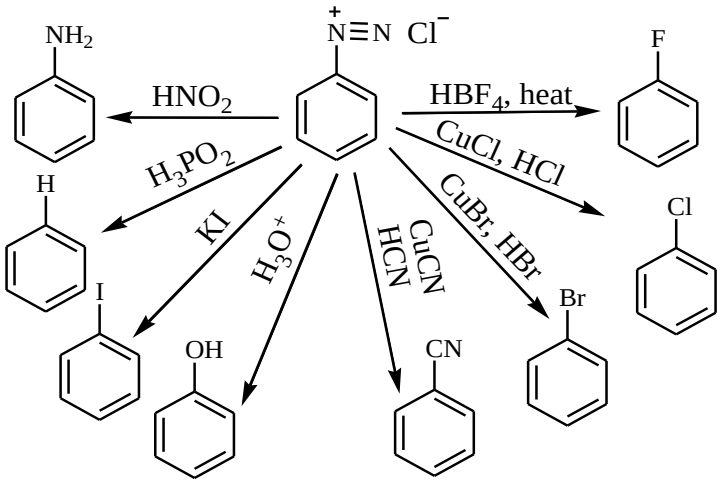


The drive to form a molecule of stable nitrogen gas (N2) causes the leaving group of a diazonium ion to be easily displaced by a wide variety of nucleophiles. The mechanism by which a nucleophile displaces the diazonium group depends on the nucleophile: Some displacements involve phenyl cations, while others involve radicals.



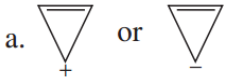
Nucleophiles such as $^-C{\equiv}N$, Cl^- and Br^- will replace the diazonium group if the appropriate cuprous salt is added to the solution containing the arenediazonium salt. The reaction of an arenediazonium salt with a cuprous salt is known as a **Sandmeyer reaction**.

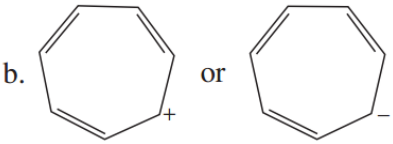
Aromatic diazonium salt can be converted to a variety of compounds as follow:

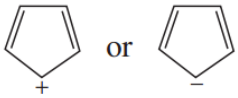


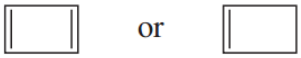
Exercise #1.4 (review)

1. Which ion in each of the following pairs is more stable?

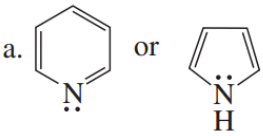
a.  or

b. 

c. 

d. 

2. Which can lose a proton more readily, a methyl group bonded to cyclohexane or a methyl group bonded to benzene? Why?
3. Which compound in each of the following pairs is a stronger base? Why?

a. 

b. $CH_3\overset{\overset{NH_2}{|}}{C}HCH_3$ or $CH_3\overset{\overset{NH}{\|}}{C}NH_2$

4. Show the step by step procedure for the preparation of
   a. P-nitroaniline
   b. Benzoic acid (write at least 2 possibilities)
   c. Terephthalic acid by oxidation of alkyl arenes (do not include the mechanism): read Kevlar and Dacron

CHAPTER-2

2. AMINES

At the end of this chapter the students will be able to:

- ☞ Describe the various physical and chemical properties of amines.
- ☞ Devise the way of synthesis of amines.

2.1. Introduction

Session-9: At the end of this session the students should be able to:

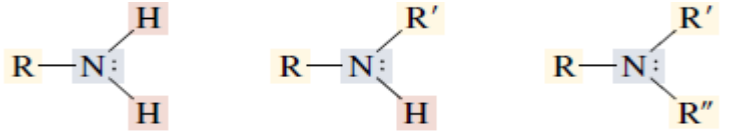
- ❥ Classify amines as primary, secondary and tertiary.
- ❥ Apply IUPAC rules in naming of amines.
- ❥ Discuss the structures of amines.
- ❥ Estimate the physical and chemical properties of amines.

Amines are aliphatic and aromatic derivatives of ammonia. Amines, like ammonia, are weak bases (Kb = 10^{-4} to 10^{-6}). This **basicity** is due to the unshared electron pair on the nitrogen atom. Their ultimate source is atmospheric nitrogen which, by a process known as nitrogen fixation, is reduced to ammonia, then converted to organic nitrogen compounds. They are also essential to life. General representation,

R = alkyl group: alkylamine Ar = aryl group: arylamine

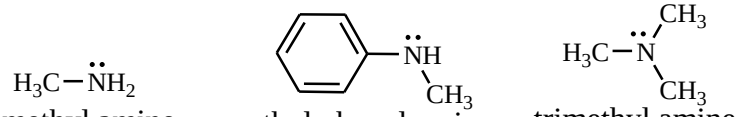
2.1. Classification, nomenclature and structures of amines

Classification: Amines are classified as **primary, secondary,** or **tertiary** based upon the number of carbon-containing groups that are attached to the nitrogen atom. Those amine compounds that have only **one carbon group** attached to the nitrogen atom are primary, while those with **two or three carbon groups** attached to the nitrogen atom are secondary and tertiary, respectively. Generally,



Primary amine Secondary amine Tertiary amine

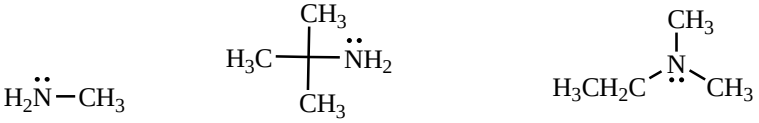
Nomenclature: In the common system, you name amines by naming the group or groups attached to the nitrogen atom and adding the word amine.



methyl amine | methyl phenyl amine | trimethyl amine

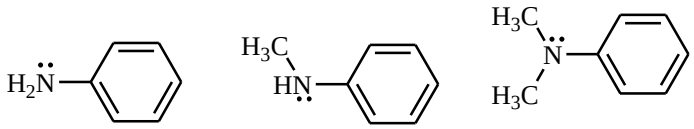
In the IUPAC System, apply the following rules to name amines:

1. Pick out the longest continuous chain of carbon atoms. The parent name comes from the alkane of the same number of carbons.
2. Change the -e of the alkane to "amine."
3. Locate and name any substituents, keeping in mind that the chain is numbered away from the amine group. Substituents, which are attached to the nitrogen atom instead of the carbon of the chain, are designated by a capital N.



methanamine | 1,1-dimethylethanamine | N,N-dimethylethanamine

4. Aromatic amines belong to specific families, which act as parent molecules. For example, an amino group (—NH_2) attached to benzene produces the parent compound aniline.

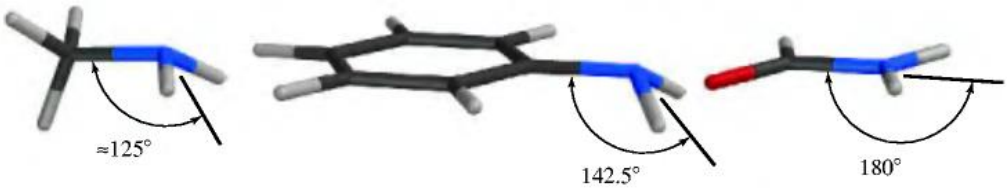


aniline (parent) | N-methylaniline (N-substituted) | N,N-dimethylaniline (N,N-disubstituted)

Structures of alkylarmines: methylamine is like ammonia having a pyramidal arrangement of bonds to nitrogen. Its H-N-H angles (**106^o**) are slightly smaller than the tetrahedral value of **109.5^o**, whereas the C-N-H angle (**112^o**) is slightly larger. The C-N bond distance 147 pm lies between the typical C-C bond distances in alkanes (153 pm) and C-O bond distances in alcohols (143 pm). Nitrogen and carbon are both sp3-hybridized and are joined by a σ bond. The unshared electron pair on nitrogen occupies an sp3-hybridized orbital.

Arylarmines: Aniline, like alkylamines, has a pyramidal arrangement of bonds around nitrogen, but its pyramid is somewhat shallower. One measure of the extent of this flattening is given by the angle between the carbon-nitrogen bond and the **bisector** of the **H-N-H** angle. For sp3-hybridized nitrogen, this angle (not the same as the **C-N-H** bond angle) is 125^o, and the measured angles in simple alkylamines are close to that. The corresponding angle for sp2

hybridization at nitrogen with a planar arrangement of bonds, as in amides, for example, is 180**o**. The measured value for this angle in aniline is 142.5**o**, suggesting a hybridization somewhat closer to sp3 than to sp2. The structure of aniline reflects a compromise between two modes of binding the nitrogen lone pair. The electrons are more strongly attracted to nitrogen when they are in an orbital with some s character an sp3-hybridized orbital, for example--than when they are in a p orbital. On the other hand, delocalization of these electrons into the aromatic π system is better achieved if they occupy a p orbital. A p orbital of nitrogen is better aligned for overlap with the p orbitals of the benzene ring to form an extended π system than is an sp3-hybridized orbital. As a result of these two opposing forces, nitrogen adopts an orbital hybridization that is between sp3 and sp2. See the following.



Methylamine	Aniline	Formamide
(CH_3NH_2)	($C_6H_5NH_2$)	($O{=}CHNH_2$)

2.2. Properties of Amines:

Physical properties: We have often seen that the **polar nature** of a substance can affect physical properties such as boiling point. This is true for amines, which are more polar than alkanes but less polar than alcohols. For similarly constituted compounds, alkylamines have boiling points higher than those of alkanes but lower than those of alcohols.

$CH_3CH_2CH_3$	$CH_3CH_2\ddot{N}H_2$	$CH_3CH_2\ddot{O}H$
propane	ethylamine	ethanol
μ = 0 D	μ = 1.2 D	μ = 1.7 D
bp -42°C	bp 17°C	bp 78°C

Dipole-dipole interactions, especially **hydrogen bonding**, are present in amines but absent in alkanes. But because nitrogen is less electronegative than oxygen, an N-H bond is less polar than an O-H bond and hydrogen bonding is weaker in amines than in alcohols.

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

Example: $CH_3CH_2CH_2\ddot{N}H_2$	$CH_3CH_2\ddot{N}HCH_3$	$(CH_3)_3\ddot{N}$
bp 50°C	bp 34°C	bp 3°C

Primary and secondary amines can participate in intermolecular hydrogen bonding, but tertiary amines **lack N-H** bonds and so cannot. Amines that have fewer than six or seven carbon atoms are soluble in water. All amines, even tertiary amines, can act as proton acceptors in hydrogen bonding to water molecules.

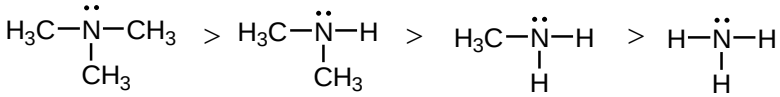
The simplest arylamine, aniline, is a liquid at room temperature and has a boiling point of 184^{o}C. Almost all other arylamines have higher boiling points. Aniline is only slightly soluble in water (3 g/100mL).

Chemical properties: Amines act as a base due to lone pairs of electrons on nitrogen. They also can act as nucleophile in different reactions i.e. they are reactive relative to other organic compounds like alkanes.

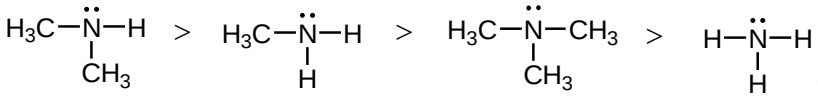
2.3. Basicity of Nitrogen Compounds

Amines are basic because they possess a pair of unshared electrons, which they can share with other atoms. These unshared electrons create an electron density around the nitrogen atom. ***The greater the electron density present, the more basic the molecule.*** Groups that donate or supply electrons will increase the basicity of amines while groups that decrease the electron density around the nitrogen decrease the basicity of the molecule.

For alkyl amines in the gas phase, the order of base strength is given below:



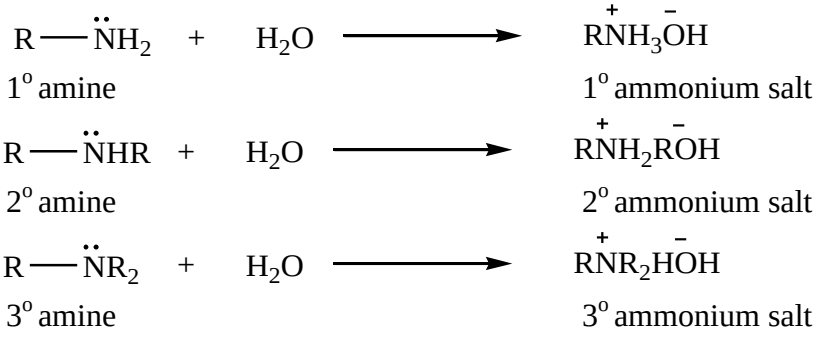
However, in aqueous solutions, the order of basicity changes,



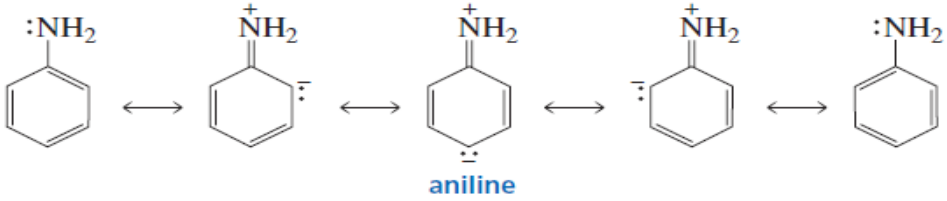
The difference in basicity between ammonia, and primary, secondary, and tertiary alkylamines result from the interplay between **steric** and **electronic effects** on the molecules themselves and on the solivation of their conjugate acids. In total, the effects are small, and most alkylamines are very similar in basicity. In water, the ammonium salts of primary and secondary amines undergo solvation effects (due to hydrogen bonding) to a much greater degree than ammonium salts of tertiary amines. These solvation effects increase the electron density on the amine nitrogen to a greater degree than the inductive effect of alkyl groups.

Alkyl groups donate electrons to nitrogen cations formed during the acid base reaction and thus they can stabilize the positive charge.

But steric crowding *of tertiary amines is where a reactive site is difficult to reach because of the alkyl groups surrounding it.* This crowding decreases the number of water molecules that can be involved in stabilizing the ion. As a result, trimethylamine is *less* basic than either dimethylamine or methylamine.



Arylamines are weaker bases than cyclohexylamines because of resonance. Aniline, a typical arylamine, exhibits the resonance structures shown.



aniline

As there is delocalization of the unshared electron pair throughout the ring, the electrons will be less available for reaction. As a result, the molecule becomes less basic.

Their basicity provides a means by which amines may be separated from neutral organic compounds. A mixture containing an amine is dissolved in diethyl ether/water mixture and shaken with **dilute** hydrochloric acid to convert the amine to an ammonium salt. The ammonium salt, being ionic, dissolves in the aqueous phase, which is separated from the ether layer and enters to the water layer. Addition of sodium hydroxide to the aqueous layer converts the ammonium salt back to the free amine which is then removed from the aqueous phase by extraction with a fresh ether.

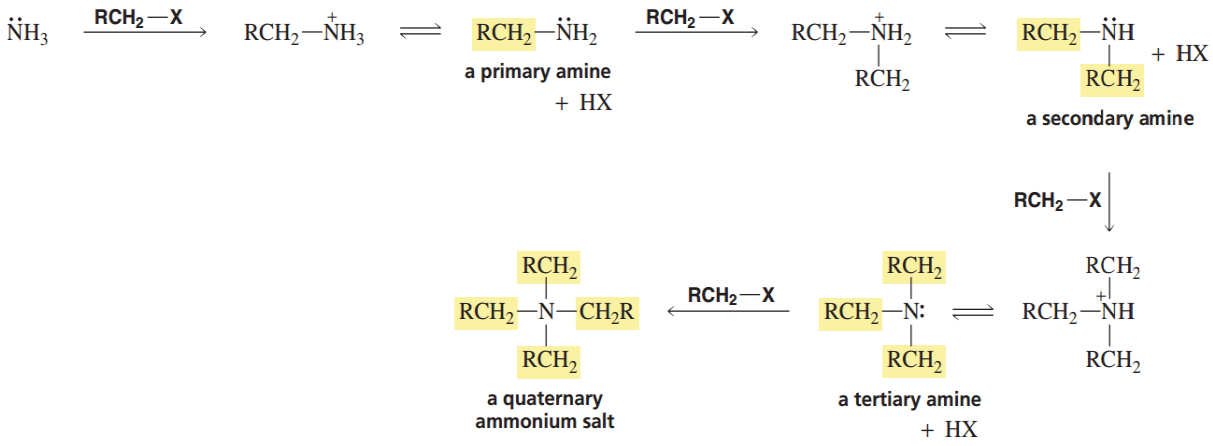
Exercise #2.1
Pyridine (pKb = 8.8), for example, resembles arylamines in being almost 1 million times less basic than piperidine (pKb = 2.8).

2.4. Preparation of 1°-, 2° & 3°-Amines

Session-10: At the end of this session the students should be able to:

- Prepare primary, secondary and tertiary amines.
- Explain reactions of amines.
- Explain the means of identification of type of amine.

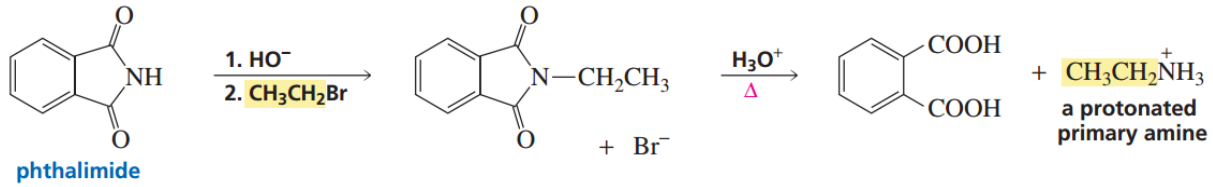
Because ammonia and amines are good nucleophiles, they readily undergo S_N2 reactions **with** alkyl halides. (X denotes a halogen.



Although these S_N2 reactions can be used to synthesize amines, the yields are poor because it is difficult to stop the reaction after a single alkylation since ammonia and primary, secondary, and tertiary amines have similar reactivities. Therefore, the alkylation of ammonia leads to a **mixture of products.**

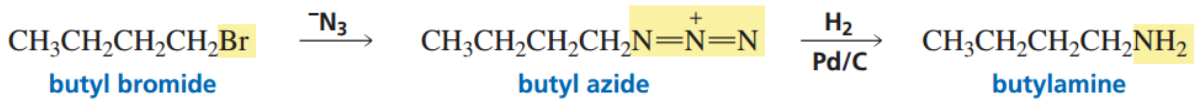
A much better way to prepare a primary amine is by means of a Gabriel synthesis. This reaction involves alkylating phthalimide and then hydrolyzing the *N*-substituted phthalimide.

Gabriel synthesis

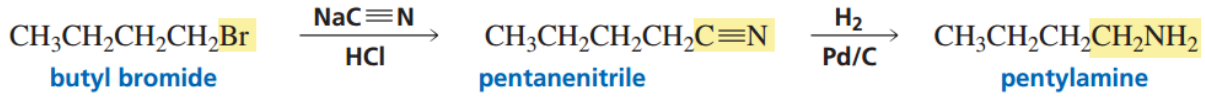


phthalimide

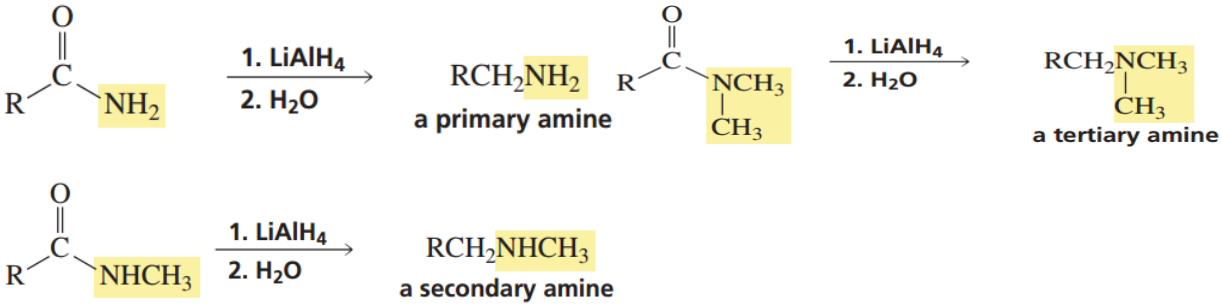
Primary amines also can be prepared in good yields if **azide ion** ($^-N_3$) is used as the nucleophile in an S_N2 reaction. The product of the reaction is an alkyl azide, which can be reduced to a primary amine.



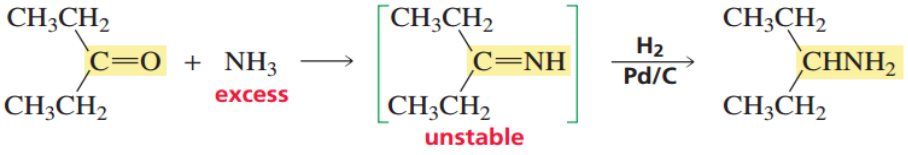
Other reduction reactions also result in the formation of primary amines. For example, the **catalytic reduction of a nitrile** forms a primary amine. (Recall that a nitrile can be obtained from the reaction of cyanide ion with an alkyl halide.)



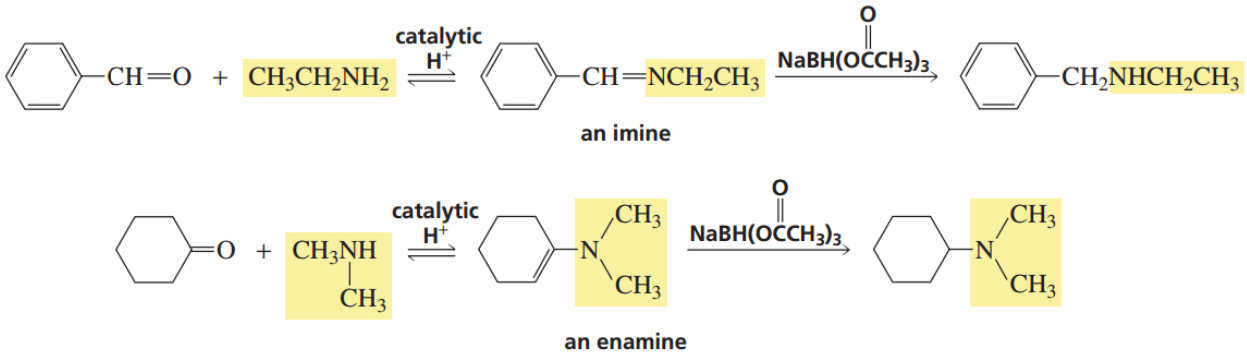
Amines are obtained from the **reduction of amides with $LiAlH_4$**. This method can be used to synthesize primary, secondary, and tertiary amines. The class of amine obtained depends on the number of substituents on the nitrogen atom of the amide.



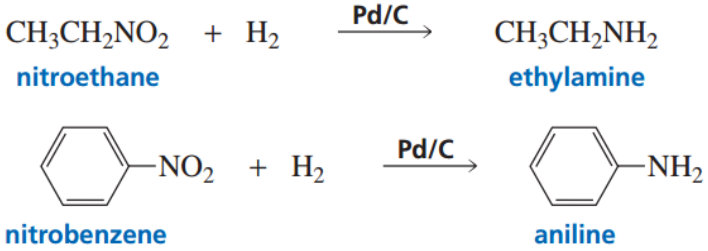
A primary amine can be obtained from **the reaction of an aldehyde or a ketone with excess ammonia in the presence of H_2 and Raney nickel**. Because the imine does not have a substituent other than a hydrogen bonded to the nitrogen, it is relatively unstable, so the amine is obtained by H_2 adding to the C=N bond as it is formed. This is called **reductive amination**.



Secondary and tertiary amines can be prepared from **imines** and **enamines** by reducing the imine or enamine. Sodium triacetoxyborohydride is a commonly used reducing agent for this reaction.



Reduction of nitrocompounds: A primary amine is obtained from the reduction of a nitroalkane, and an arylamine is obtained from the reduction of nitrobenzene. Aromatic amines are normally prepared by reduction of the corresponding aromatic nitrocompound.



2.5. Reactions of Amines

Lone-pair electrons of the nitrogen atom cause amines to react as bases, sharing their lone pair with a proton, and as nucleophiles, sharing their lone pair with an atom other than a proton.

an amine is a base:

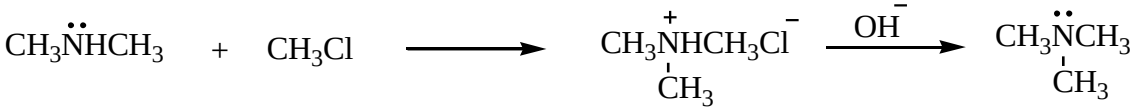
an amine is a nucleophile:

Alkylation and Acylation// Electrophilic Substitution at Nitrogen

Primary, secondary, and tertiary amines can be alkylated by reaction with a primary alkyl halide. Alkylations of primary and secondary amines are difficult to control and often give mixtures of products, but tertiary amines are cleanly alkylated to give quaternary ammonium salts. The reaction of ammonia with an alkyl halide leads to the formation of a primary amine. The primary amine that is formed can also react with the alkyl halide, which leads to a disubstituted amine that can further react to form a trisubstituted amine. Therefore, the alkylation of ammonia leads to a **mixture of products.**

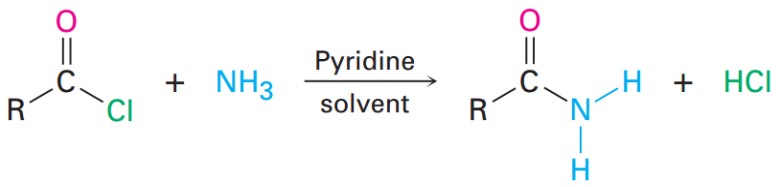
Alkylation of ammonia

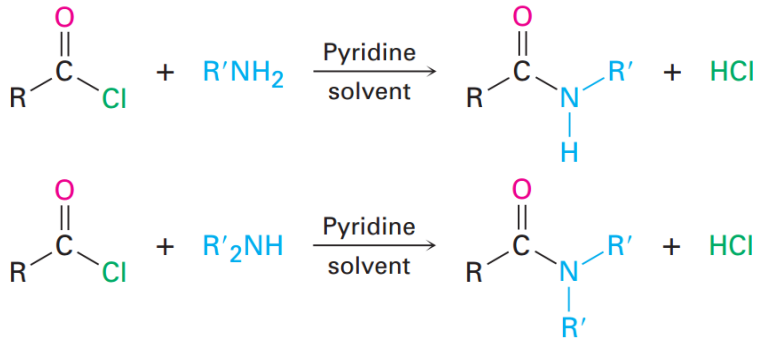
Alkylation of a 1° amine



Alkylation of a 2° amine

Primary and secondary (but not tertiary) amines can also be acylated by nucleophilic acyl substitution reaction with an acid chloride or an acid anhydride to yield amides. Note that overacylation of the nitrogen does not occur because the amide product is much less nucleophilic and less reactive than the starting amine.



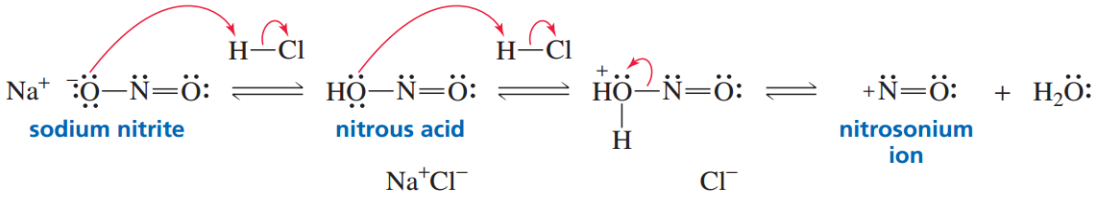


Reaction of Amines with Nitrous Acid: We have seen (in chapter 1) that the reaction of a primary amine with nitrous acid produces a diazonium salt. Both aryl amines and alkyl amines undergo this reaction, and both follow the same mechanism.

$$\text{aryl—NH}_2 \xrightarrow[0\ ^\circ\text{C}]{\text{NaNO}_2,\ \text{HCl}} \text{aryl—}\overset{+}{\text{N}}\equiv\text{N}\ \ \text{Cl}^-$$

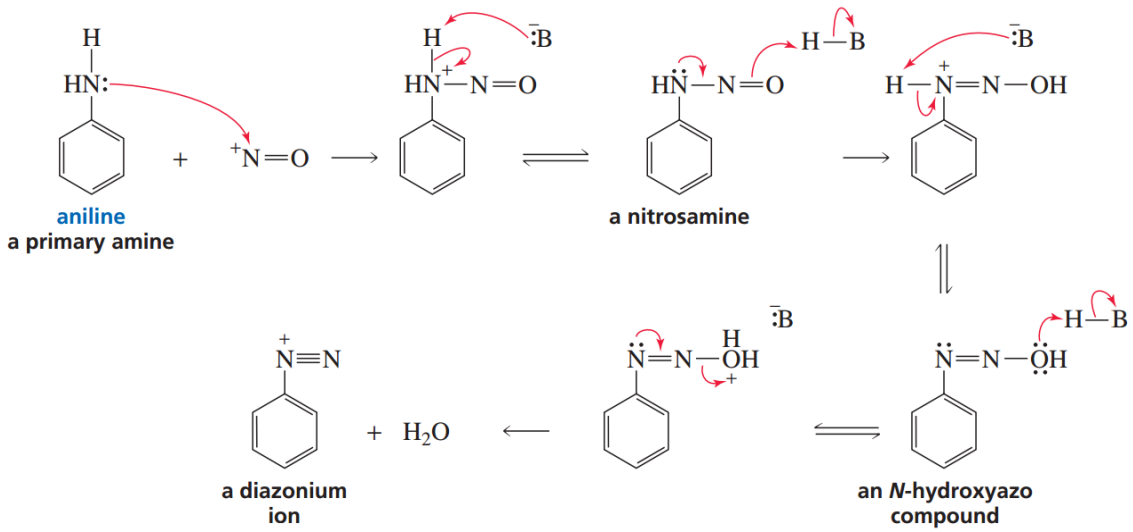
$$\text{alkyl—NH}_2 \xrightarrow[0\ ^\circ\text{C}]{\text{NaNO}_2,\ \text{HCl}} \text{alkyl—}\overset{+}{\text{N}}\equiv\text{N}\ \ \text{Cl}^-$$

Conversion of a *primary* amino group to a diazonium group requires a **nitrosonium ion** that is formed when water is eliminated from protonated nitrous acid.

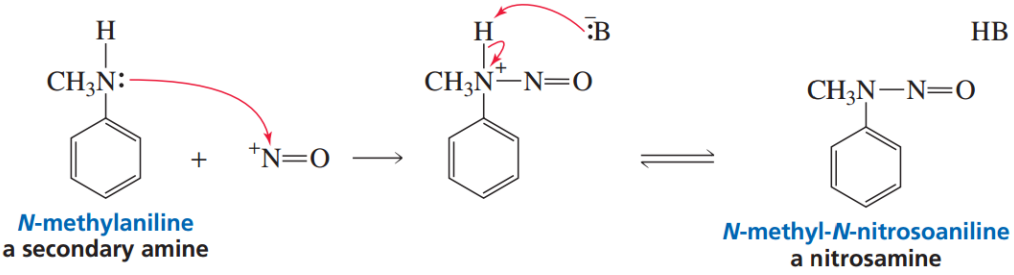


The nitrosonium ion accepts a share of the amino nitrogen's lone pair. Loss of a proton from nitrogen forms a **nitrosamine** (also called an ***N*-nitroso compound** because a nitroso substituent is bonded to a nitrogen). Delocalization of nitrogen's lone pair and protonation of oxygen form a protonated *N*-hydroxyazo compound. This compound is in equilibrium with its nonprotonated form, which can be reprotonated on nitrogen (reverse reaction) or protonated on oxygen (forward reaction). Elimination of water forms the diazonium ion.

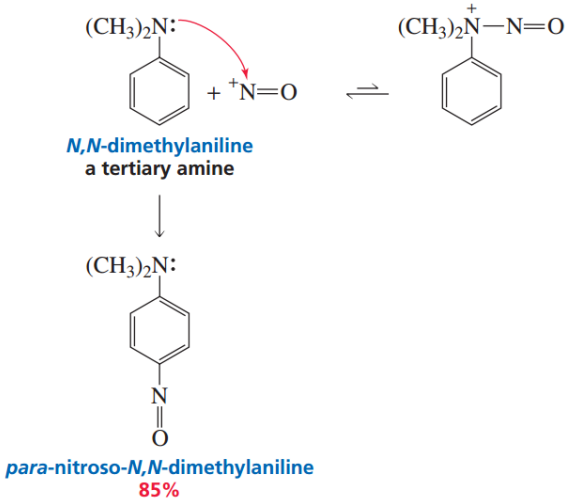
Remember that reactions in which arenediazonium ions are involved must be carried out at 0 °C because they are unstable at higher temperatures. Alkanediazonium ions are even less stable. They lose molecular N_2 even at 0 °C as they are formed, reacting with whatever nucleophiles are present in the reaction mixture by both E1/S_N1 and E2/S_N2 mechanisms. Because of the mixture of products obtained, alkanediazonium ions are of limited synthetic use.



Secondary aryl and alkyl amines react with a nitrosonium ion to form nitrosamines rather than diazonium ions. The mechanism of the reaction is similar to that for the reaction of a primary amine with a nitrosonium ion, except that the reaction stops at the nitrosamine stage. The reaction stops because a secondary amine, unlike a primary amine, does not have the second proton that must be lost in order to generate the diazonium ion.



The product formed when the nitrogen of a *tertiary* amine shares its lone pair with a nitrosonium ion cannot be stabilized by loss of a proton. A tertiary aryl amine, therefore, can undergo an electrophilic aromatic substitution reaction with a nitrosonium ion. The product of the reaction is primarily the para isomer because the bulky dialkylamino group blocks approach of the nitrosonium ion to the ortho position.

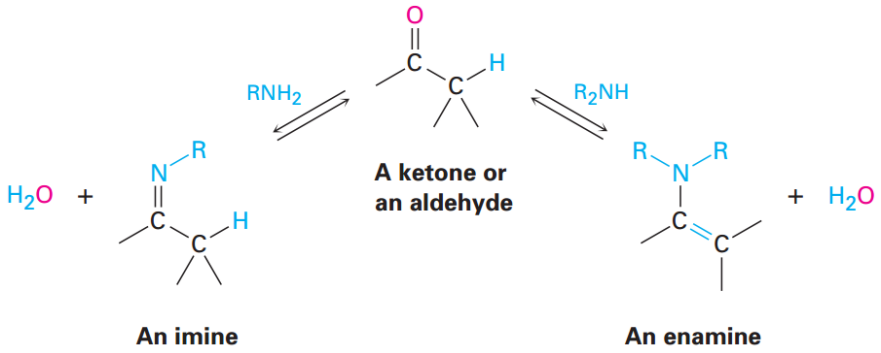


Reaction with aldehydes and ketones:

Session-11: At the end of this session the students should be able to describe:

- reaction of amine with **aldehydes and ketones**
- reaction of aryl diazonium **Intermediates**
- Hofmann elimination

Primary amines, RNH_2, add to aldehydes and ketones to yield **imines, $R_2C{=}NR$**. Secondary amines, R_2NH, add similarly to yield **enamines, $R_2N\text{-}CR{=}CR_2$** (*ene* + amine unsaturated amine).

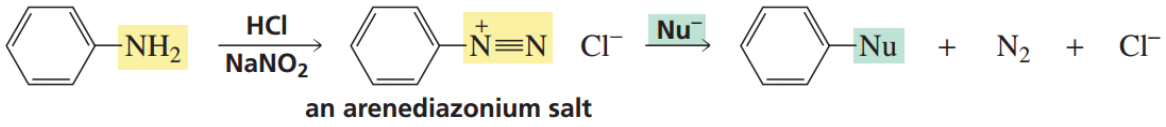


Imine formation and enamine formation appear different because one leads to a product with a C=N bond and the other leads to a product with a C=C bond. Actually, though, the reactions are quite similar. Both are typical examples of nucleophilic addition reactions in which water is eliminated from the initially formed tetrahedral intermediate and a new C=Nu bond is formed. An imine is formed in a reversible, acid-catalyzed process that begins with nucleophilic addition of the primary amine to the carbonyl group, followed by transfer of a proton from nitrogen to oxygen to yield a neutral amino alcohol, or *carbinolamine.* Protonation of the carbinolamine oxygen by an acid catalyst then converts the –OH into a better leaving group ($–OH_2^+$), and E1-like loss of water produces an iminium ion. Loss of a proton from nitrogen gives the final product and regenerates the acid catalyst.

Reaction of an aldehyde or ketone with a secondary amine, R_2NH, rather than a primary amine yields an enamine. The process is identical to imine formation up to the iminium ion stage, but at this point there is no proton on nitrogen that can be lost to form a neutral imine product. Instead, a proton is lost from the *neighboring* carbon (the α-carbon), yielding an enamine.

2.6. Reactions of Aryl Diazonium Intermediates (See Diazotization Reactions)

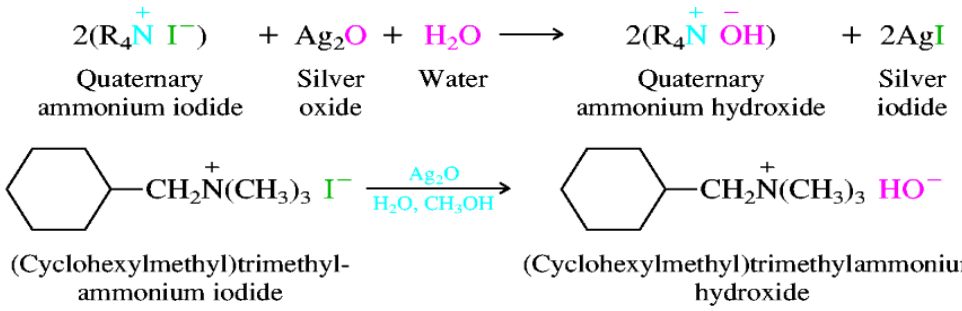
Diazonium salts of aromatic amines are very useful as intermediates to other compounds. Because aromatic diazonium salts are only stable at very low temperatures (zero degrees and below), warming these salts initiates decomposition into **highly reactive** cations. These cations can react with any anion (nucleophile) present in solution to form a variety of compounds. Generally,



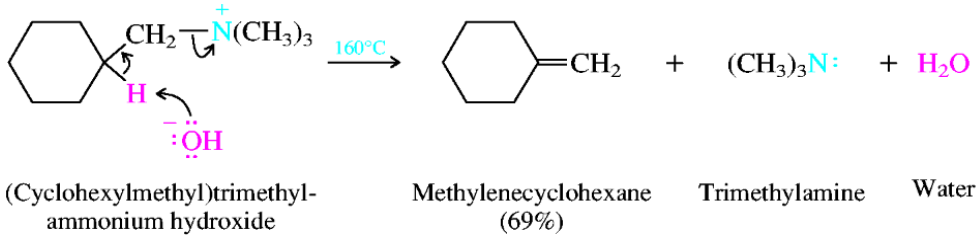
an arenediazonium salt

2.7. Elimination Reactions of Amines (Hofmann Eliminations)

The halide union of quaternary ammonium iodides may be replaced by hydroxide by treatment with aqueous slurry of silver oxide. Silver iodide precipitates, and a solution of the quaternary ammonium hydroxide is formed.

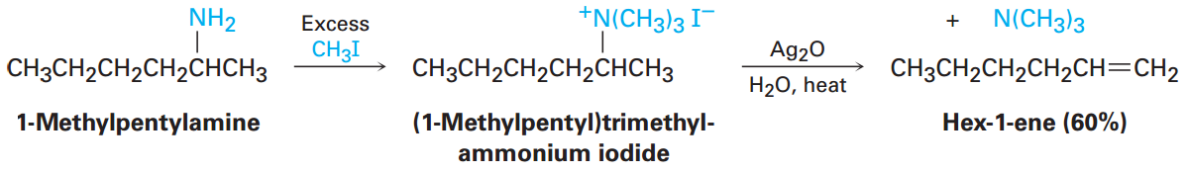


When quaternary ammonium hydroxides are heated, they undergo β elimination to form an alkene and an amine.



This reaction is known as the **Hofmann elimination;** the least sterically hindered **β hydrogen** is removed by the base in Hofmann elimination reactions. Methyl groups are deprotonated in preference to methylene groups, and methylene groups are deprotonated in preference to methines.

Because an amide ion, NH_2, is such a poor leaving group, however, it must first be converted into a better leaving group by methylation reaction with excess iodomethane to produce a quaternary ammonium salt.

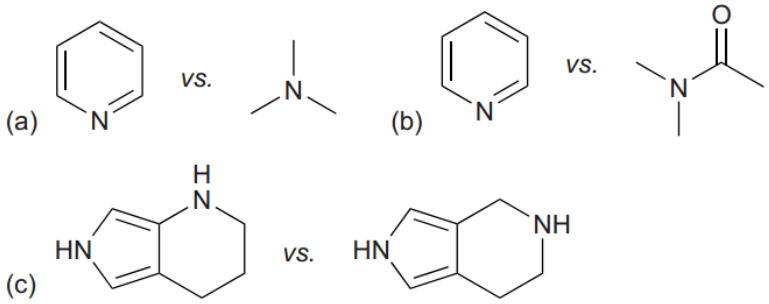


1-Methylpentylamine | **(1-Methylpentyl)trimethyl-ammonium iodide** | **Hex-1-ene (60%)**

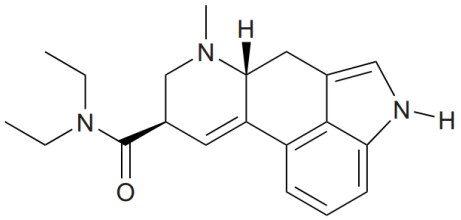
The **regioselectivity** of Hofmann elimination is opposite to that predicted by the Zaitsev rule. Elimination reactions of **alkyltrimethylammonium hydroxides** are said to obey the Hofmann rule; they yield the less substituted alkene.

Skill builder and assignment

1. For each pairs of compounds, identify the stronger base.



2. Draw the structure of each of the following compounds:
   a. N-Ethyl- N-isopropylaniline
   b. N,N -Dimethylcyclopropylamine
   c. (2R,3S)-3-(N,N -Dimethylamino)-2-pentanamine
   d. Benzylamine
3. Consider the structure of lysergic acid diethylamide (LSD), a potent hallucinogen containing three nitrogen atoms. One of these three nitrogen atoms is significantly more basic than the other two. Identify the most basic nitrogen atom in LSD, and explainyour choice.



LSD

4. meta-Bromoaniline was treated with $NaNO_2$ and HCl to yield a diazonium salt. Draw the product obtained when that diazonium salt is treated with each of the following reagents: (a) H_2O (b) HBF_4 (c) CuCN (d) H_3PO_2 (e) CuBr

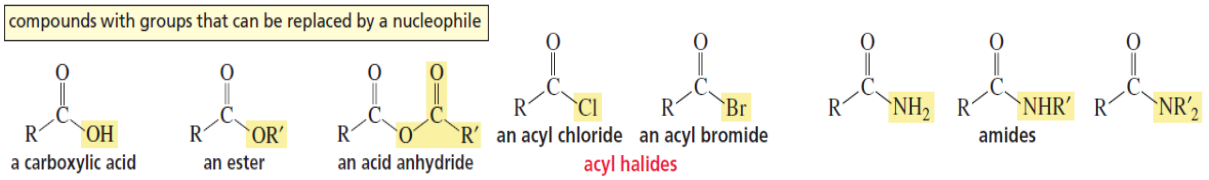
CHAPTER-3
3. REACTIONS OF CARBONYL COMPOUNDS

Session 12: At the end of this session the students should be able to:

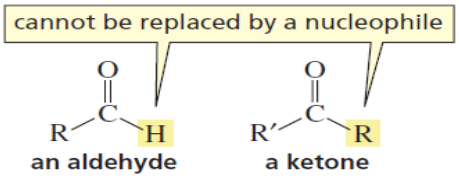
- Explain the basis of classification of carbonyl compounds as class I or class II.
- Classify common carbonyl compounds as class I or class II.
- List the basic reactions of carbonyl compounds.
- Explain the reactions of aldehydes and ketones

The **carbonyl group** is a carbon double bonded to oxygen and is probably the most important functional group found in organic compounds. Compounds containing carbonyl groups are called **carbonyl compounds** and are abundant in nature. Many play important roles in biological processes. Hormones, vitamins, amino acids, drugs, and flavorings are just a few of the carbonyl compounds that affect us daily. An **acyl group** *consists of a carbonyl group attached to an alkyl group or to an aryl group.* Carbonyl compounds can be placed in one of two classes: those that contain a group that can be replaced by another group (**Class I**) and those that do *not* contain a group that can be replaced by another group (**Class II**).

Class I carbonyl compounds are those in which the acyl group is attached to an atom or a group that *can* be replaced by another group. Carboxylic acids, acyl halides, acid anhydrides, esters, and amides belong to this class. All of these compounds contain a group (–OH, –Cl, –Br, –O(CO)R, –OR, $–NH_2$, –NHR, or $–NR_2$, that can be replaced by a **nucleophile.** Acyl halides, acid anhydrides, esters, and amides are all called **carboxylic acid derivatives** because they differ from a carboxylic acid only in the nature of the group that has replaced the OH group of the carboxylic acid.



Class II carbonyl compounds are those in which the acyl group is attached to a group that *cannot* be readily replaced by another group. Aldehydes and ketones belong to this class. The –H and alkyl or aryl (–R or –Ar) groups of aldehydes and ketones cannot be replaced by a nucleophile.



The weaker the basicity of a group, the better will be its leaving ability.

Nucleophile can be either negatively charged (-:Nu) or neutral (:Nu). If it's neutral, however, it usually carries a hydrogen atom that can subsequently be eliminated, :Nu–H. For example:

Some negatively charged nucleophiles

- $HO:^-$ (hydroxide ion)
- $H:^-$ (hydride ion)
- $R_3C:^-$ (a carbanion)
- $RO:^-$ (an alkoxide ion)
- $N{\equiv}C:^-$ (cyanide ion)

Some neutral nucleophiles

- HOH (water)
- ROH (an alcohol)
- $H_3N:$ (ammonia)
- RNH_2 (an amine)

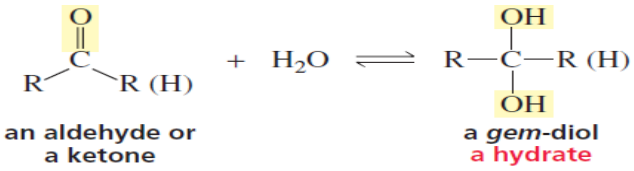
Carbonyl Compounds can undergo three basic reactions types:

1. Addition Reactions
2. Addition-elimination and
3. Enolization-ketonization.

3.1. Addition Reactions

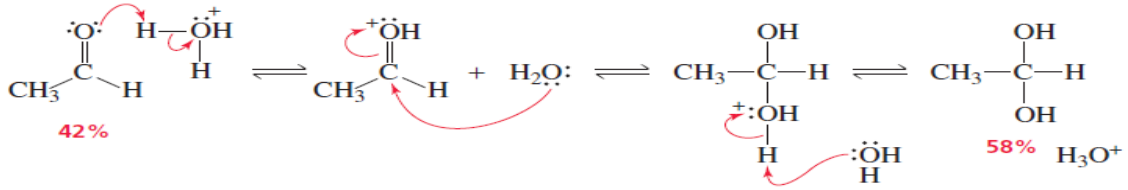
3.1.1. Hydrates

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



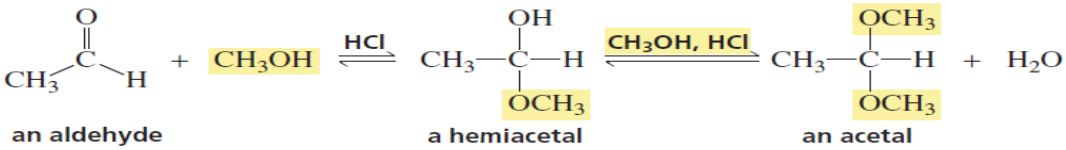
Water is a poor nucleophile and therefore adds relatively slowly to a carbonyl group. The rate of the reaction can be increased by an acid catalyst keep in mind that a catalyst has no effect on the **position** of the equilibrium.

Mechanism for acid-catalyzed hydrate formation

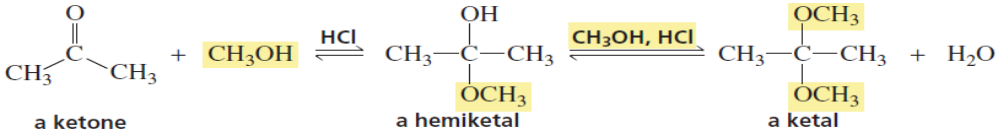


3.1.2. Hemiacetals and hemiketals

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



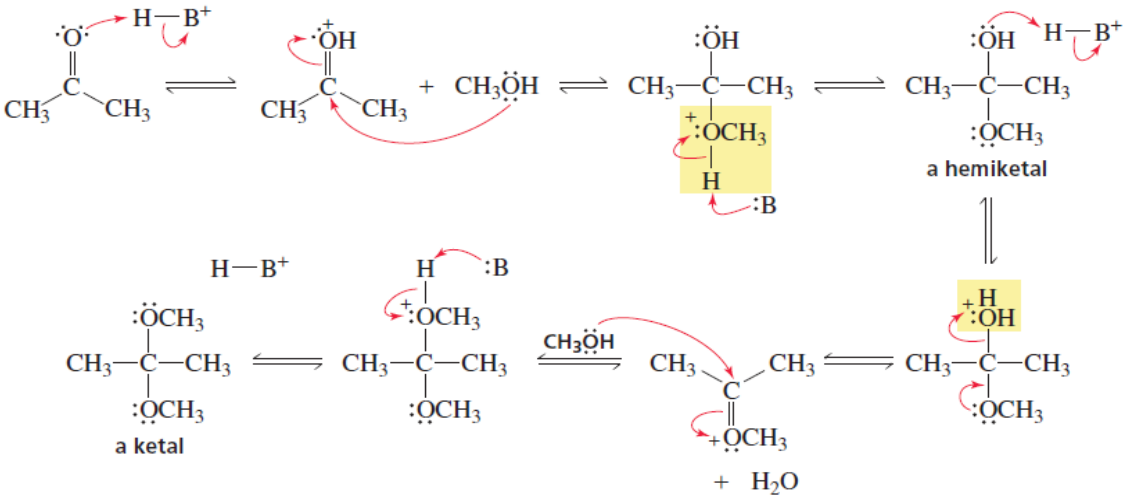
When the carbonyl compound is a ketone instead of an aldehyde, the addition products are called a **hemiketal** and a **ketal**, respectively.



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

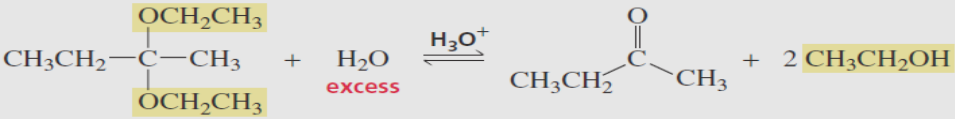
In the first step of acetal (or ketal) formation, the acid protonates the carbonyl oxygen, making the carbonyl carbon more susceptible to nucleophilic attack. Loss of a proton from the protonated tetrahedral intermediate gives the hemiacetal (or hemiketal). Because the reaction is carried out in an acidic solution, the hemiacetal (or hemiketal) is in equilibrium with its protonated form. The two oxygen atoms of the hemiacetal (or hemiketal) are equally basic, so either one can be protonated. Loss of water from the tetrahedral intermediate with a protonated OH group forms a compound that is very reactive because of its electron-deficient carbon. Nucleophilic attack on this compound by a second molecule of alcohol, followed by loss of a proton, forms the acetal (or ketal).

Mechanism for acid-catalyzed acetal or ketal formation



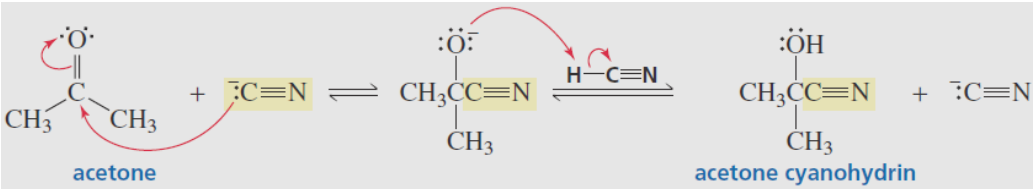
Although the tetrahedral carbon of an acetal or ketal is bonded to two oxygen atoms, causing us to predict that the acetal or ketal is not stable, the acetal or ketal can be isolated if the water eliminated from the hemiacetal (or hemiketal) is removed from the reaction mixture. This is because, if water is not available, the only compound the acetal or ketal can form is an O-methylated carbonyl compound, which is less stable than the acetal or ketal.

The acetal or ketal can be transformed back to the aldehyde or ketone in an acidic aqueous solution.



3.1.3. Cyanohydrins

Hydrogen cyanide adds to aldehydes and ketones to form **cyanohydrins**. This reaction forms a product with one more carbon atom than the reactant. In the first step of the reaction, the cyanide ion attacks the carbonyl carbon. The alkoxide ion then accepts a proton from an undissociated molecule of hydrogen cyanide.



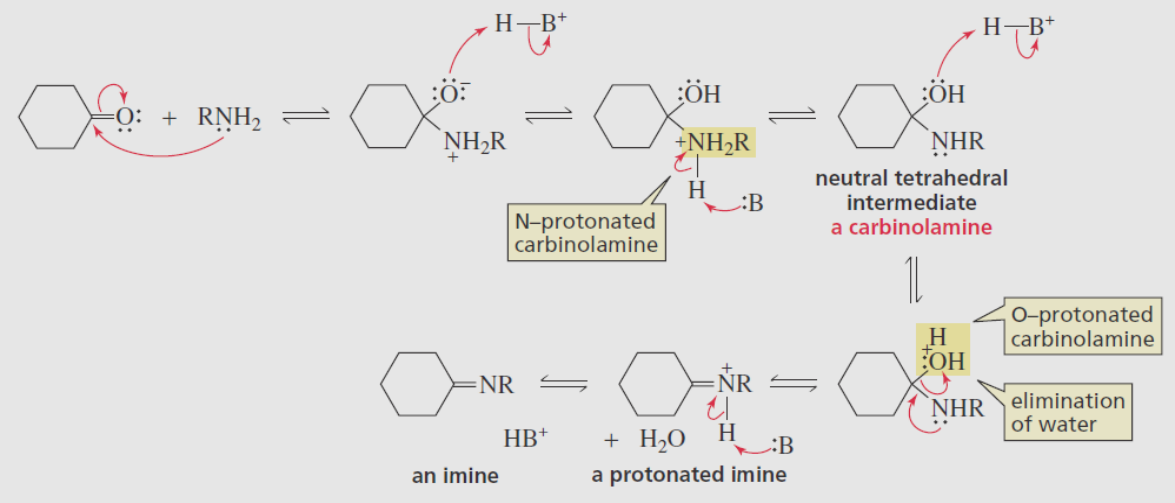
Because hydrogen cyanide is a toxic gas, the best way to carry out this reaction is to generate hydrogen cyanide during the reaction by adding HCl to a mixture of the aldehyde or ketone and excess sodium cyanide. Excess sodium cyanide is used in order to make sure that some cyanide ion is available to act as a nucleophile.

In basic solutions, since oxygen is coming to be negatively charged having lost its proton and cyanohydrin is converted back to the carbonyl compound. The addition of hydrogen cyanide to aldehydes and ketones is a synthetically useful reaction because of the subsequent reactions that can be carried out on the cyanohydrin.

3.1.4. Carbinolamines

carbinolamine are neutral tetrahedral intermediate (unstable) formed when primary amines, reacts with aldehydes or ketones in the presence of catalytic amount of acid and can exist in equilibrium with two protonated forms. Protonation can take place on either the nitrogen or the oxygen atom. Elimination of water from the oxygen-protonated intermediate forms a protonated imine that loses a proton to yield the imine.

Mechanism for imine formation



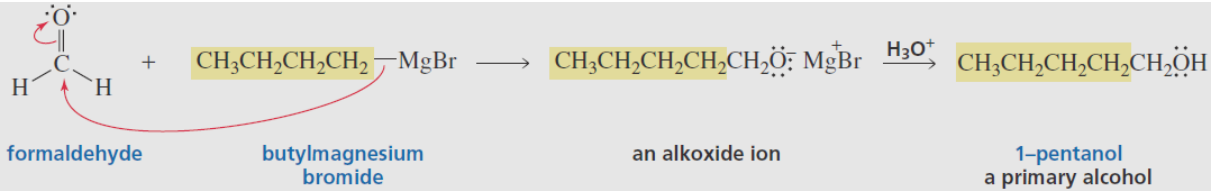
The equilibrium favors the nitrogen-protonated tetrahedral intermediate because nitrogen is more basic than oxygen. The equilibrium can be forced toward the imine by removing water as it is formed or by precipitation of the imine product. Overall, the addition of a nitrogen nucleophile to an aldehyde or a ketone is a ***nucleophilic addition–elimination reaction***: nucleophilic addition of an amine to form an unstable tetrahedral intermediate, followed by elimination of water. The tetrahedral intermediates are unstable because the newly formed *sp*3 carbon is bonded to an oxygen and to a nitrogen which is another electronegative atom. Water is eliminated, and loss of a proton from the resulting protonated imine forms a stable imine.

3.1.5. Addition of Grignard Reagents

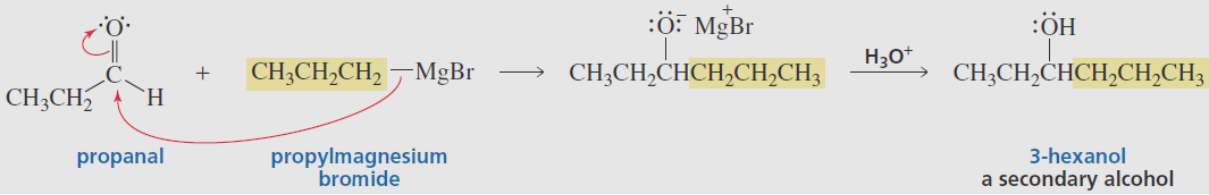
Session-13: At the end of this session the students should be able to:

- Explain the difference between addition of Grignard reagent to class I and class II carbonyl compounds.
- Explain how addition of hydrogen and hydride reductions works.

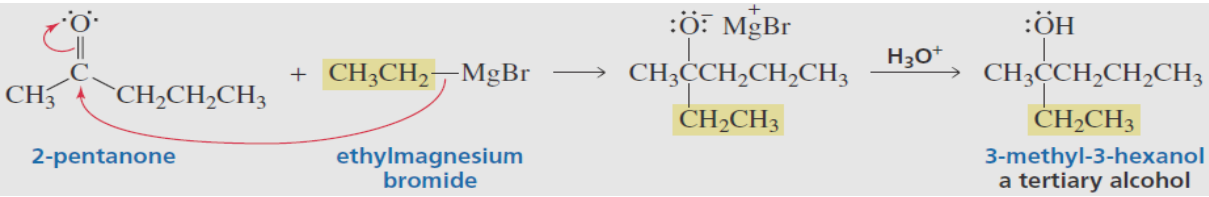
Attack of a Grignard reagent on a carbonyl carbon forms an **alkoxide ion** that is complexed with magnesium ion. Addition of water or dilute acid breaks up the complex. When a Grignard reagent reacts with formaldehyde, the addition product is a **primary alcohol**.



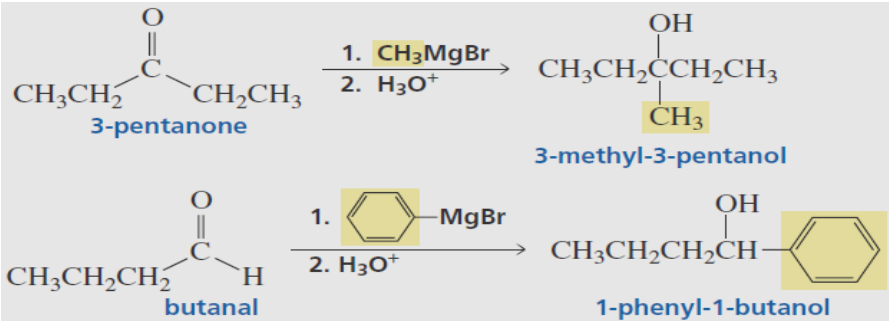
When a Grignard reagent reacts with an aldehyde other than formaldehyde, the addition product is a **secondary alcohol**.



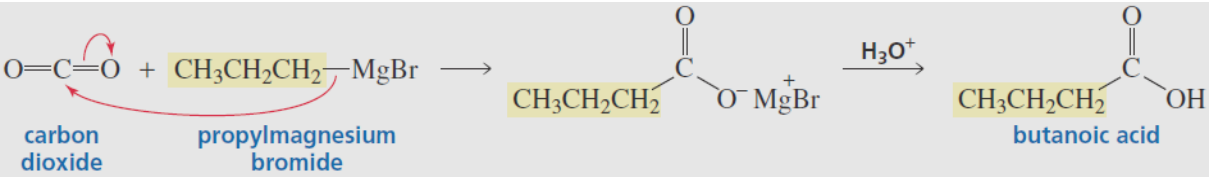
When a Grignard reagent reacts with a ketone, the addition product is a **tertiary alcohol**.



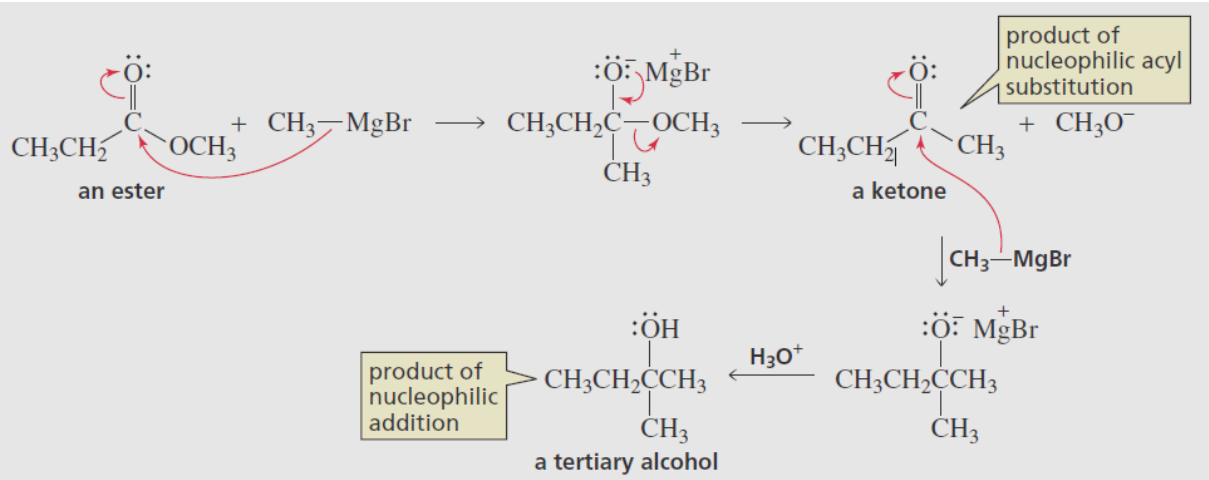
In the following reactions, numbers are used with the reagents to indicate that the acid is not added until the reaction with the Grignard reagent is complete:



A Grignard reagent can also react with carbon dioxide. The product of the reaction is a carboxylic acid with one more carbon atom than the Grignard reagent has.

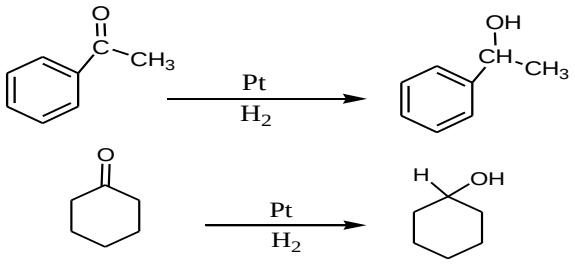


In addition to reacting with aldehydes and ketones which are Class II carbonyl compounds, Grignard reagents react with Class I carbonyl compounds which have groups that can be replaced by another group.



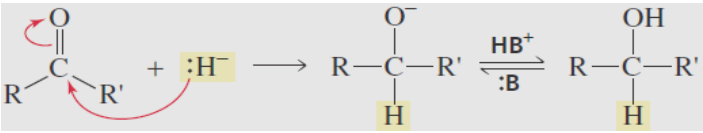
3.1.6. Addition of Hydrogen

Aldehydes and ketones can be reduced to alcohols by molecular hydrogen in the presence of **metal catalysts** such as **platinum**, **palladium** or **nickel**. The reaction is similar to catalytic reduction of alkenes to alkanes. Examples:

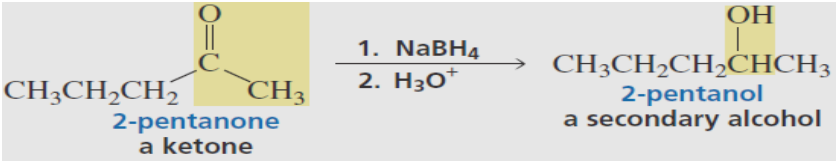


3.1.7. Hydride Additions (lithium-aluminum hydride and sodium-boro hydride)

Addition of hydride ion to an aldehyde or ketone forms an alkoxide ion. Subsequent protonation by an acid produces an alcohol. The overall reaction adds H_2 to the carbonyl group. Recall that the addition of hydrogen to an organic compound is a **reduction reaction.**



Aldehydes and ketones are generally reduced using sodium borohydride ($NaBH_4$) as the source of hydride ion. **Aldehydes** other than formaldehyde are reduced to *primary* alcohols, and **ketones** are reduced to *secondary* alcohols. Notice that the acid is not added to the reaction mixture until the reaction with the hydride donor is complete.

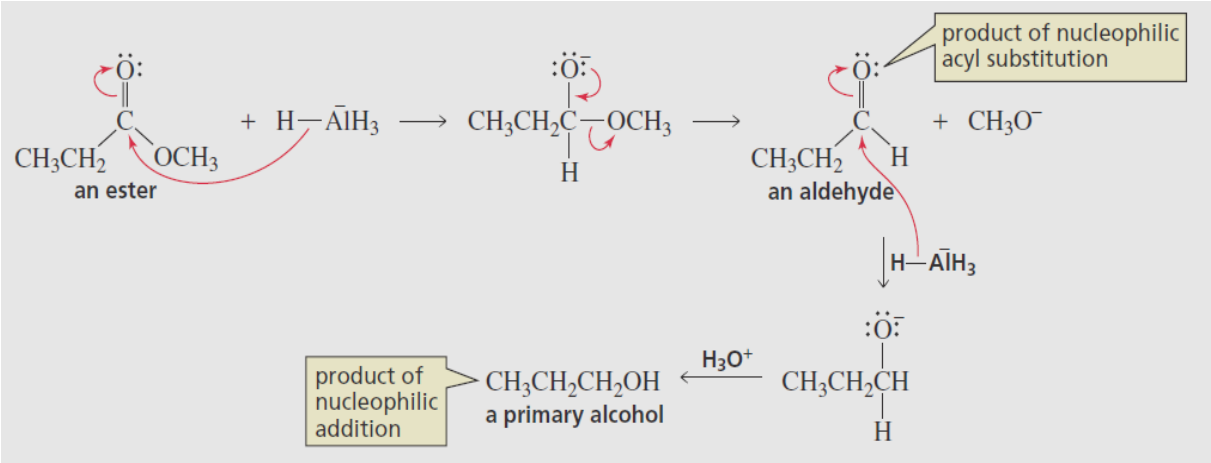


The reaction of a Class I carbonyl compound (i.e., a carbonyl compound with a group that can be replaced by another group) with hydride ion involves **two successive reactions** with the nucleophile. (Recall that Class I carbonyl compounds also undergo two successive reactions with a Grignard reagent). Sodium borohydride ($NaBH_4$) is not a sufficiently strong hydride donor to react with the less reactive (compared with aldehydes and ketones) esters, carboxylic acids, and amides, so esters, carboxylic acids, and amides must be reduced with lithium aluminum hydride ($LiAlH_4$), a more reactive hydride donor. Because lithium aluminum hydride is more reactive than sodium borohydride, it is not as safe or as easy to use. Since it reacts violently with protic solvents, lithium aluminum hydride must be used in a dry, aprotic solvent. The reaction of an ester with $LiAlH_4$ produces two alcohols, one corresponding to the acyl portion of the ester and one corresponding to the alkyl portion.

Q: Explain why lithium aluminum hydride is more reactive than sodium borohydride.

When an ester reacts with hydride ion, the first reaction is a nucleophilic acyl substitution reaction because an ester has a group that can be substituted by hydride ion. The product of this reaction is an aldehyde. The aldehyde then undergoes a nucleophilic addition reaction with a second equivalent of hydride ion, forming an alkoxide ion, which when protonated gives a primary alcohol. The reaction cannot be stopped at the aldehyde stage because an aldehyde is more reactive than an ester toward nucleophilic attack.

Mechanism for the reaction of an ester with hydride ion



3.2. Addition-Elimination Reactions

Session-14: At the end of this session the students should be able to:

- List at least four addition elimination reactions of carbonyl compounds.
- Explain why formation of imine, acetals and ketals are addition elimination reaction.
- Discuss witting reaction.

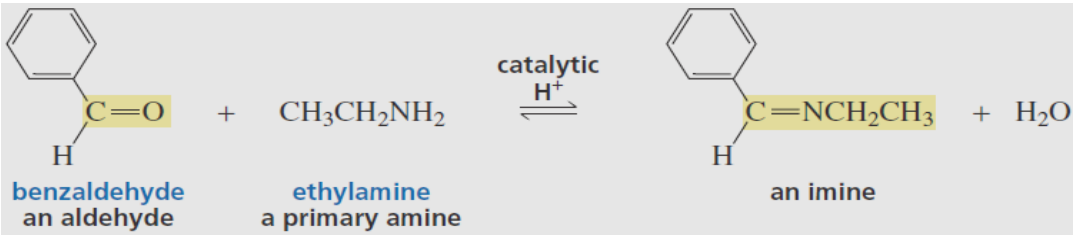
3.2.1. Imines and related compounds (see part 3.1.4)

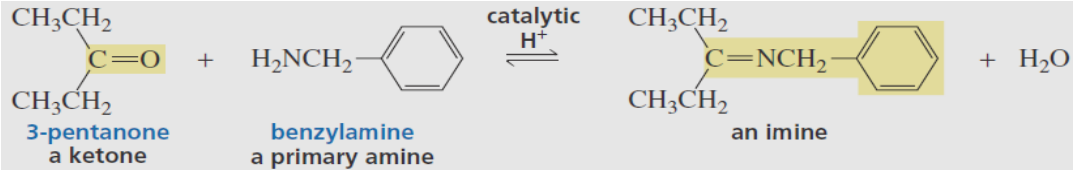
Explain the source of the difference for the following reactions.

aldehyde or ketone + 1^o amine ⟶ imine

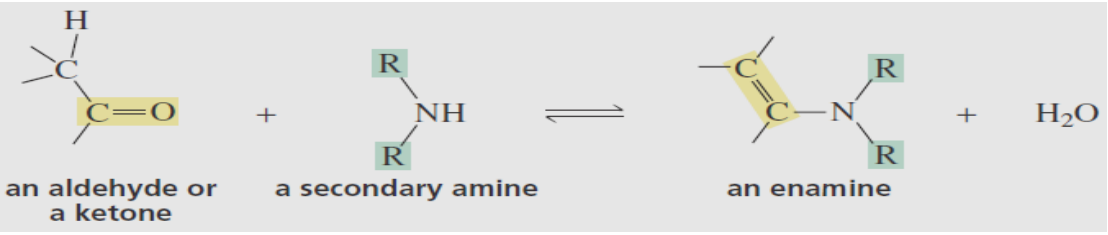
aldehyde or ketone + 2^o amine ⟶ enamine

Examples of imine formation reactions;





Aldehydes and ketones react with a *secondary amine* to form an enamine (pronounced "ENE-amine"). An **enamine** is *an α,β-unsaturated tertiary amine with a double bond in the α,β - position relative to the nitrogen atom.* Notice that the double bond is in the part of the molecule that comes from the aldehyde or ketone. The name "enamine" comes from "**ene**" + "**amine**" with the "e" omitted in order to avoid two successive vowels.

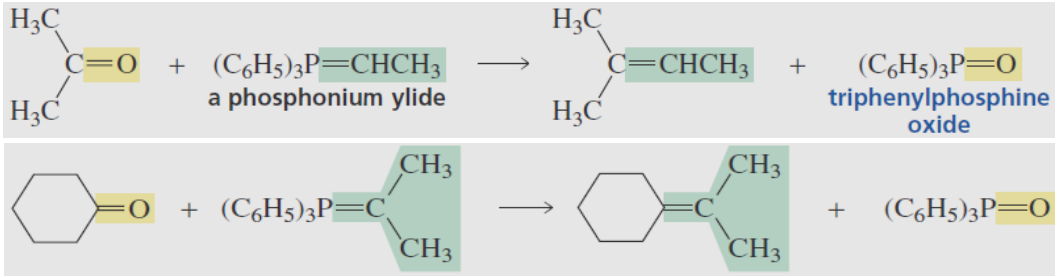


The mechanism of the reaction is the same as imine but not the last deprotonation step.

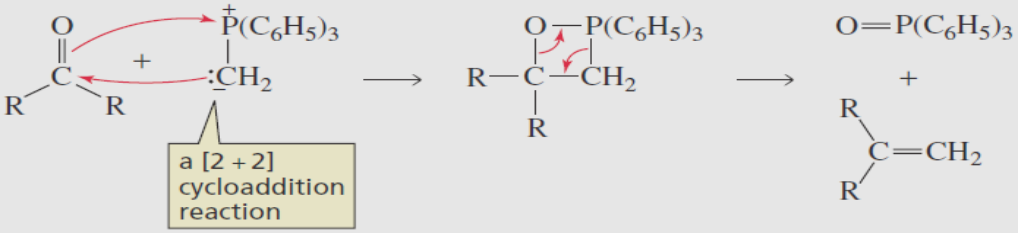
3.2.2. Wittig reaction

An aldehyde or a ketone reacts with a phosphonium ylide (pronounced "ILL-id") *to form an alkene.* An **ylide** is a compound that has opposite charges on adjacent covalently bonded atoms with complete octets. The ylide can also be written in the double bonded form because phosphorus can have more than eight valence electrons.

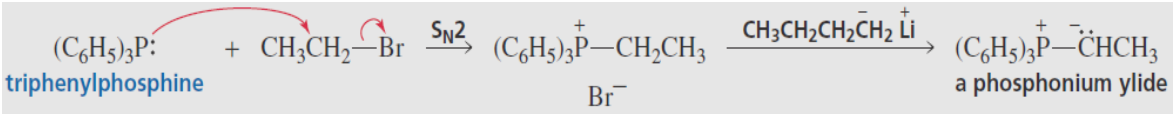
The reaction of an aldehyde or a ketone with a phosphonium ylide to form an alkene is called a **Wittig reaction**. The overall reaction amounts to interchanging the double-bonded oxygen of the carbonyl compound and the double-bonded carbon group of the phosphonium ylide.



Evidence has accumulated that the Wittig reaction is a concerted **[2 + 2] cycloaddition** reaction, with the nucleophilic carbon of the ylide attacking the electrophilic carbon of the carbonyl compound. It is called a [2 + 2] cycloaddition reaction because, of the four π electrons involved in the cyclic transition state, two come from the carbonyl group and two come from the ylide. Elimination of triphenylphosphine oxide forms the alkene product.

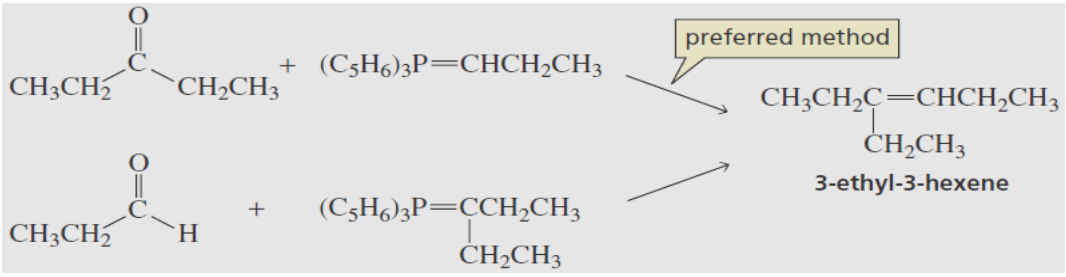


The phosphonium ylide needed for a particular synthesis is obtained by an **S_N2** reaction between **triphenylphosphine** and an **alkyl halide** with the appropriate number of carbon atoms. A proton on the carbon adjacent to the positively charged phosphorus atom is sufficiently acidic (pKa = 35) to be removed by a strong base such as **butyllithium.**

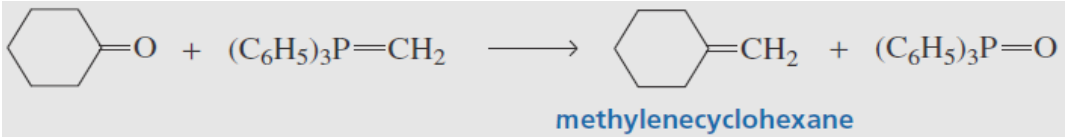


If two sets of reagents are available for the synthesis of an alkene, it is better to use the one that requires the *less sterically hindered alkyl halide* for synthesis of the ylide. Recall that the more sterically hindered the alkyl halide, the less reactive it is in an S_N2 reaction.

Example:



The Wittig reaction is a very powerful way to make an alkene because the reaction is completely regioselective—the double bond will be in only one place.

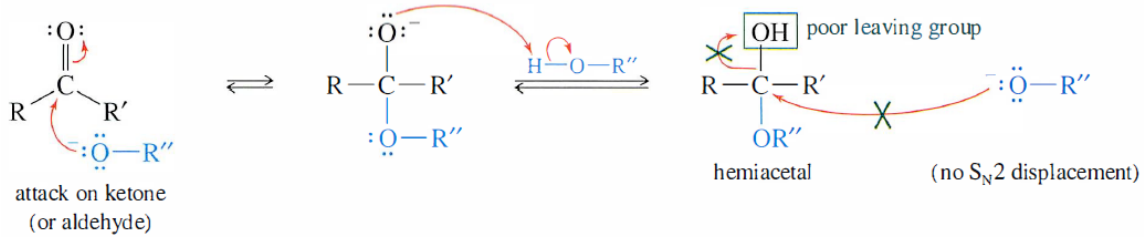


The Wittig reaction also is the best way to make a **terminal alkene** such as methylenecyclohexane because other methods would form a terminal alkene only as a minor product.

3.2.3. Acetals

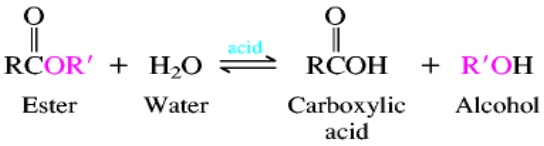
Acetal formation begins by ***acid catalytic addition*** of alcohol, then ***acid catalyzed dehydration*** followed by addition of another alcohol.

1. Explain why hemiacetal formation can be catalyzed by an acid or a base whereas acetal formation is catalyzed by an acid only. See the acid catalysis on part 3.1.2.
2. Draw the general structure of hemiacetals, hemiketals, acetals and ketals.



3.2.4. Ester hydrolysis and formation

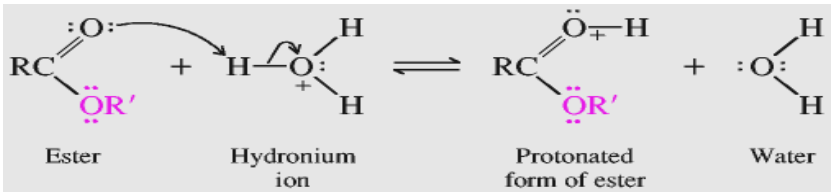
Ester hydrolysis is the most studied and best understood of all nucleophilic acyl substitutions. Esters are fairly stable in neutral aqueous media but are cleaved when heated with water in the presence of strong acids or bases. The hydrolysis of esters in dilute aqueous acid is the reverse of the Fischer esterification.



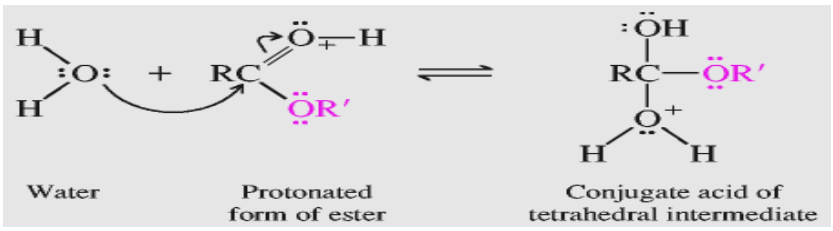
The mechanism of acid-catalyzed ester hydrolysis

Steps 1 through 3 show the formation of the tetrahedral intermediate. Dissociation of the tetrahedral intermediate is shown in steps 4 through 6.

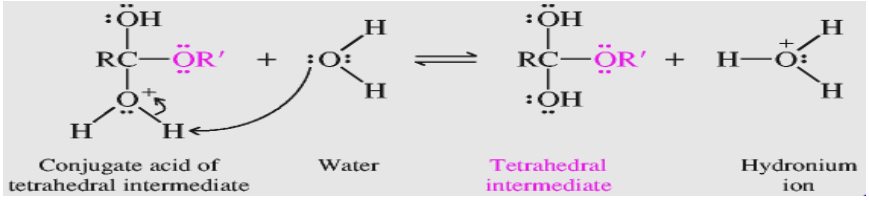
Step 1: Protonation of the carbonyl oxygen of the ester



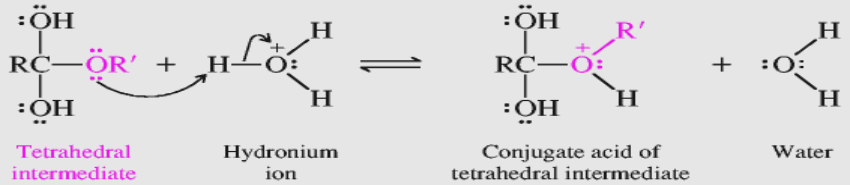
Step 2: Nucleophilic addition of water to protonated form of ester



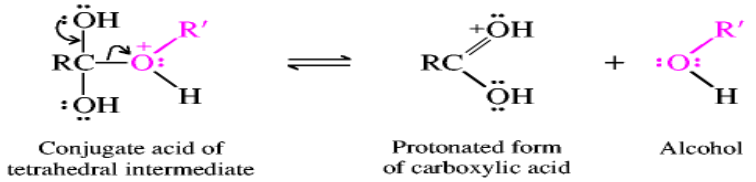
Step 3: Deprotonation of the oxonium ion to give the neutral form of the tetrahedral intermediate



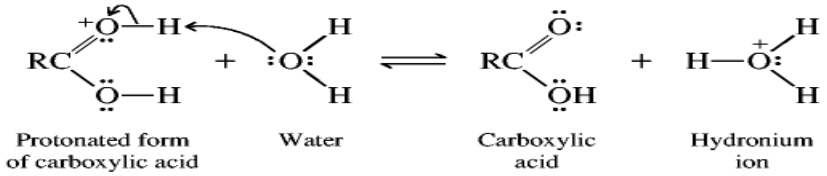
Step 4: Protonation of the tetrahedral intermediate at its alkoxy oxygen.



Step 5: Dissociation of the protonated form of the tetrahedral intermediate to an alcohol and the protonated form of the carboxylic acid.



Step 6: Deprotonation of the protonated carboxylic acid



Protonation of the carbonyl oxygen, as emphasized earlier, makes the carbonyl group more *susceptible* to nucleophilic attack.

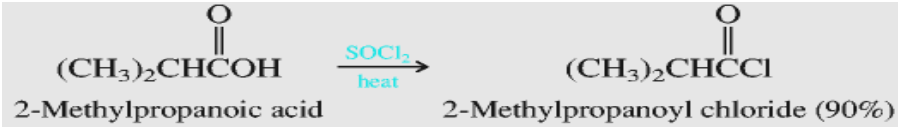
On the basis of the general mechanism for acid-catalyzed ester hydrolysis, write an analogous sequence of steps for the specific ethyl benzoate hydrolysis.

3.2.5. Reactions of acid chlorides (Carey, 5th edn, 838-840)

Session-15: At the end of this session the students should be able to discuss:

- Reactions of acid derivatives.
- Reactions of acid anhydrides
- Reactions of amides and reductions of acid derivatives.

Acyl chlorides are readily prepared from carboxylic acids by reaction with **thionyl chloride.**

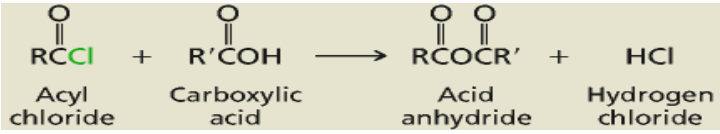


On treatment with the appropriate nucleophile, an acyl chloride may be converted to an acid anhydride, an ester, an amide, or a carboxylic acid.

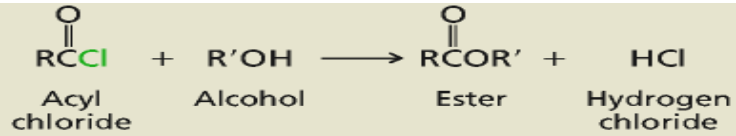
Predict the major organic product obtained by reaction of benzoyl chloride with each of the following:
(a) Acetic acid (d) Methylamine, CH_3NH_2
(b) Benzoic acid (e) Dimethylamine, $(CH_3)_2NH$
(c) Ethanol (f) Water

Conversion of acyl chlorides to other carboxylic acid derivatives reaction with carboxylic acids

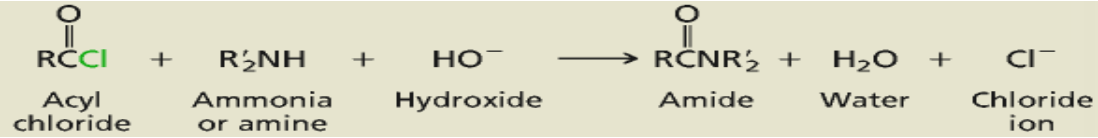
Acyl chlorides react with *carboxylic acids* to yield acid **anhydrides**. When this reaction is used for preparative purposes, a weak organic base such as pyridine is normally added. Pyridine is a catalyst for the reaction and also acts as a base to neutralize the hydrogen chloride that is formed.



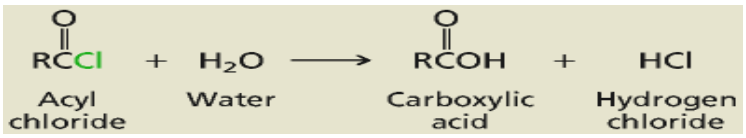
Reaction with alcohols: Acyl chlorides react with *alcohols* to form **esters**. The reaction is typically carried out in the presence of pyridine.



Reaction with ammonia and amines: Acyl chlorides react with ammonia and *amines* to form **amides**. A base such as sodium hydroxide is normally added to react with the hydrogen chloride produced.

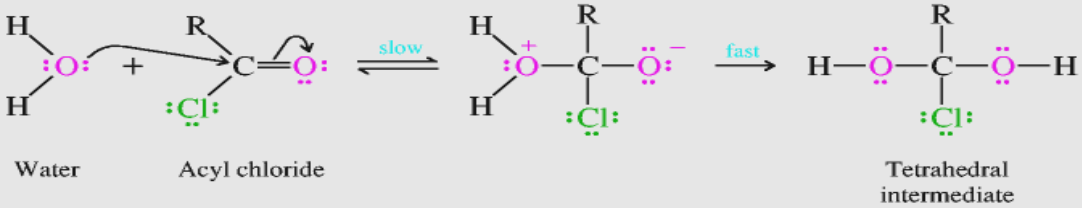


Hydrolysis: Acyl chlorides react with water to yield **carboxylic acids**. In base, the acid is converted to its carboxylate salt. The reaction has little preparative value because the acyl chloride is chloride nearly always prepared from the carboxylic acid rather than vice versa.

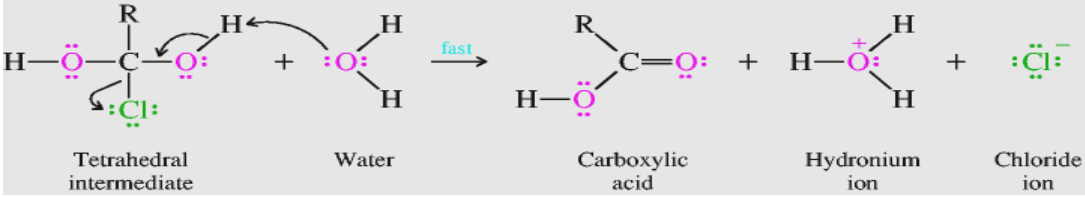


If you see the mechanism of hydrolysis, the tetrahedral intermediate has three potential leaving groups on carbon: **two hydroxyl** groups and a **chlorine**. In the second stage of the reaction, the tetrahedral intermediate dissociates, restoring the resonance-stabilized carbonyl group. Loss of chloride from the tetrahedral intermediate is faster than loss of hydroxide; chloride is less basic than hydroxide and is a better leaving group.

First stage: Formation of the tetrahedral intermediate by nucleophilic addition of water to the carbonyl group.



Second stage: Dissociation of the tetrahedral intermediate by dehydrohalogenation.



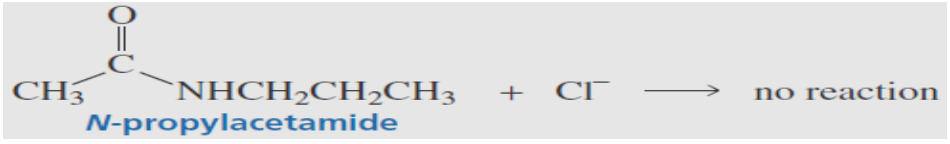
3.2.6. Reactions of acid anhydrides

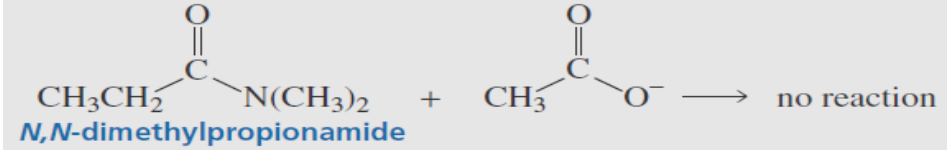
Nucleophilic acyl substitution in acid anhydrides involves cleavage of a bond between oxygen and one of the carbonyl groups. One acyl group is transferred to an attacking nucleophile; the other retains its single bond to oxygen and becomes the acyl group of a carboxylic acid.

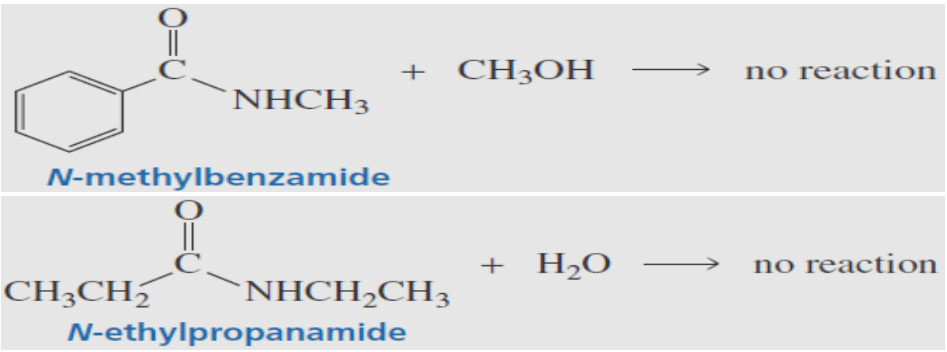
One reaction of this type, Friedel-Crafts acylation is already familiar to us.

3.2.7. Reactions of amides

Amides are very unreactive compounds, which is comforting, since proteins are composed of amino acids linked together by amide bonds. Amides do not react with **halide ions**, **carboxylate ions**, **alcohols**, or **water** because, in each case, the incoming nucleophile is a weaker base than the leaving group of the amide.



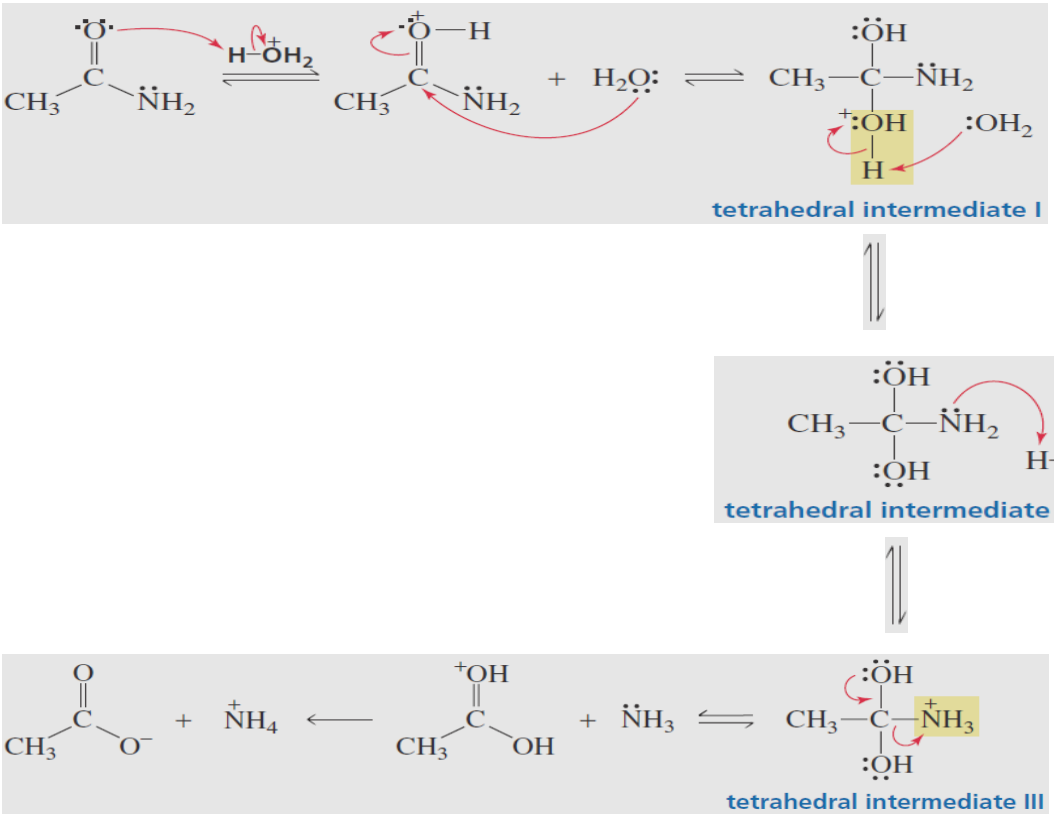




Amides do, however, react with water and alcohols if the reaction mixture is heated in the presence of an acid.

When an amide is hydrolyzed under acidic conditions, the acid protonates the carbonyl oxygen and increases the susceptibility of the carbonyl carbon to nucleophilic attack. Nucleophilic attack by water on the carbonyl carbon leads to tetrahedral intermediate I, which is in equilibrium with its nonprotonated form, tetrahedral intermediate II. Reprotonation can occur either on oxygen to reform tetrahedral intermediate I or on nitrogen to form tetrahedral intermediate III. Protonation on nitrogen is favored because the NH_2 group is a stronger base than the OH group.

Mechanism for acid-catalyzed hydrolysis of an amide



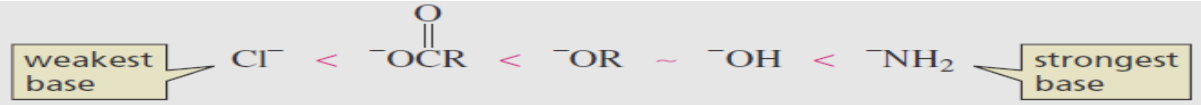
Why an amide cannot be hydrolyzed without a catalyst? In the uncatalyzed reaction, the amide is not protonated. Therefore, water, a very poor nucleophile, must attack a neutral amide that is much less susceptible to nucleophilic attack than a protonated amide would be.

3.2.8. Reductions of acid derivatives (on next chapter)

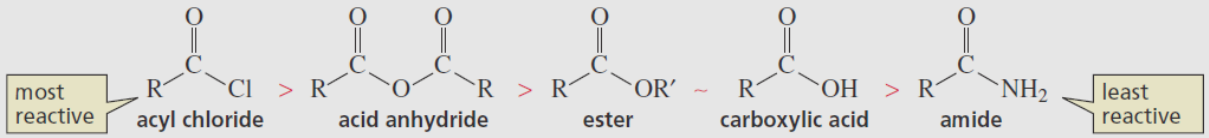
NB: Relative Reactivities of Carboxylic Acids and Carboxylic Acid Derivatives

We have just seen that there are two steps in a nucleophilic acyl substitution reaction: formation of a tetrahedral intermediate and collapse of the tetrahedral intermediate. The weaker the base attached to the acyl group, the easier it is for *both steps* of the reaction to take place. In other words, the reactivity of a carboxylic acid derivative depends on the basicity of the substituent attached to the acyl group: The less basic the substituent, the more reactive the carboxylic acid derivative.

Relative basicities of the leaving groups

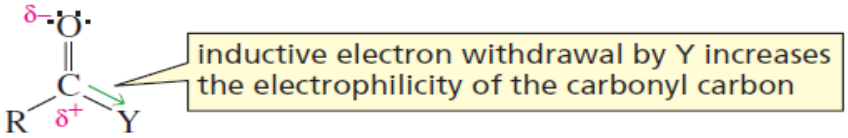


Relative reactivities of carboxylic acid derivatives



Where shall aldehydes and ketones be?

How does having a weak base attached to the acyl group make the *first* step of the nucleophilic substitution reaction easier? First of all, a weaker base is a more electronegative base; that is, it is better able to accommodate its negative charge. Thus, weaker bases are better at *withdrawing* electrons inductively from the carbonyl carbon; electron withdrawal increases the carbonyl carbon's susceptibility to nucleophilic attack.



3.3. Enolization-Ketonization reactions

Session-16: At the end of this session, the students should be able to:

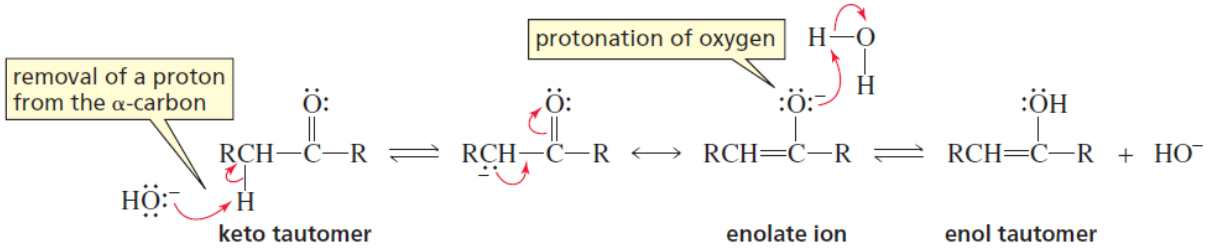
- Explain the mechanisms acid and base catalyzed ketonization-enolization reactions.
- Explain haloform and alkylation reactions.
- Write the mechanism of aldol condensations,

We know that hydrogen on a carbon adjacent to a carbonyl carbon is somewhat acidic, we can understand why keto and enol tautomers interconvert. **Keto–enol interconversion** is also

called **keto–enol tautomerization** or **enolization**. The inter-conversion of the tautomers can be catalyzed by either *acids or bases*.

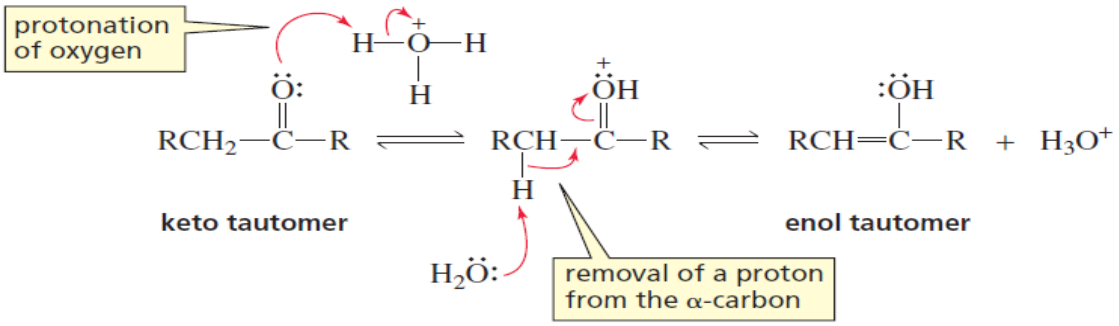
In a ***basic solution***, hydroxide ion removes a proton from the **α-carbon** of the keto tautomer. The anion that is formed has two resonance contributors: a **carbanion** and an **enolate ion**. The enolate ion contributes more to the resonance hybrid because the negative charge is better accommodated by oxygen than by carbon. Protonation on oxygen forms the **enol tautomer**, whereas protonation on the α-carbon reforms the **keto tautomer**.

Base-catalyzed keto–enol interconversion

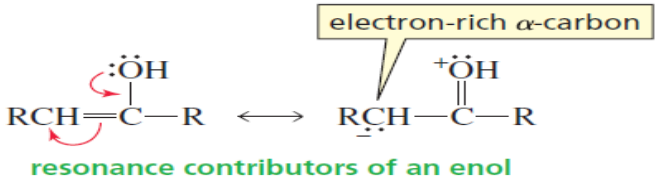


In an ***acidic solution***, the carbonyl oxygen of the keto tautomer is protonated and water removes a proton from the α-carbon forming the enol.

Acid-catalyzed keto–enol inter-conversion



Notice that the steps are reversed in the base and acid-catalyzed reactions. In the base-catalyzed reaction, the base removes the α-proton in the first step and the oxygen is protonated in the second step. In the acid-catalyzed reaction, the acid protonates the oxygen in the first step and the α-proton is removed in the second step. Notice also how the catalyst is regenerated in both the acid- and base-catalyzed mechanisms. The carbon–carbon double bond of an enol suggests that it is a nucleophile like an alkene. An enol is more electron rich than an alkene because the oxygen atom donates electrons by resonance. An enol, therefore, is a better nucleophile than an alkene.

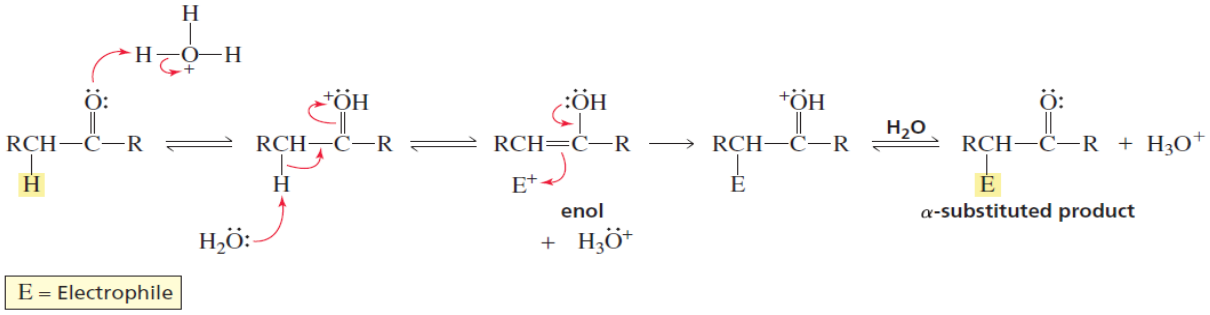


Carbonyl compounds that form enols undergo substitution reactions at the α-carbon. When an α-substitution reaction takes place under acidic conditions, water removes a proton from the

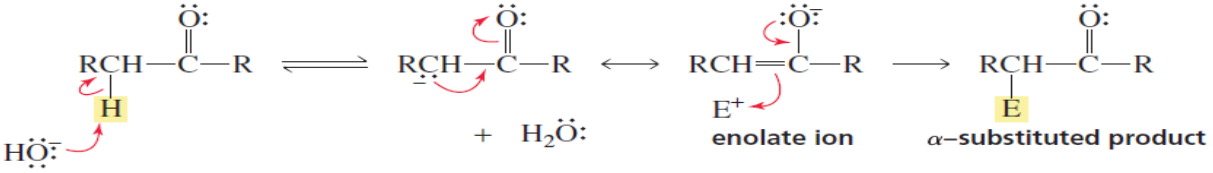
α-carbon of the protonated carbonyl compound. The nucleophilic enol then reacts with an electrophile. The overall reaction is an α-substitution reaction in which one **electrophile** (E+) is substituted for another (H+).

Mechanisms

Acid-catalyzed α-substitution reaction

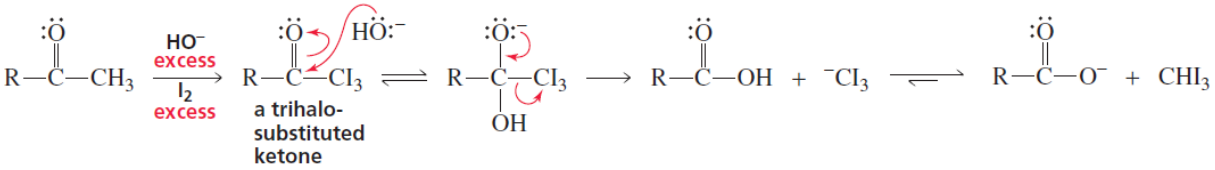


Base-catalyzed α-substitution reaction



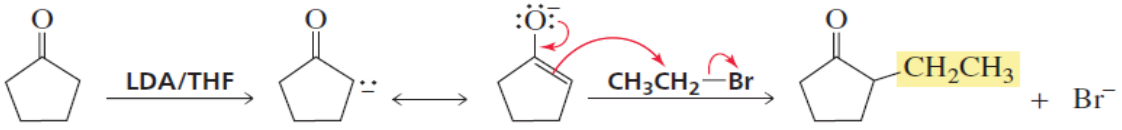
3.3.1. Haloform Reaction of Methyl Ketones

In the presence of excess base and excess halogen, a methyl ketone is first converted into a trihalo-substituted ketone. Then hydroxide ion attacks the carbonyl carbon of the trihalo-substituted ketone. Because the trihalomethyl ion is a weaker base than hydroxide ion, the trihalomethyl ion is the group more easily expelled from the tetrahedral intermediate, so the final product is a carboxylic acid. The conversion of a methyl ketone to a carboxylic acid is called a **haloform reaction** because one of the products is haloform— $CHCl_3$ (chloroform), $CHBr_3$ (bromoform), or CHI_3 (iodoform).



3.3.2. Alkylations at the α-Carbon

Alkylation of the α-carbon of a carbonyl compound is an important reaction because it gives us another way to form a carbon–carbon bond. Alkylation is carried out by first removing a proton from the α-carbon with a strong base such as lithium diisopropylamide (LDA) and then adding the appropriate alkyl halide. Because the alkylation is an S_N2 reaction, it works best with methyl halides and primary alkyl halides.



Ketones, esters, and nitriles can be alkylated at α-carbon the in this way. Aldehydes, however, give poor yields of α-alkylated products.

3.3.3. Aldol and Related Condensation reactions

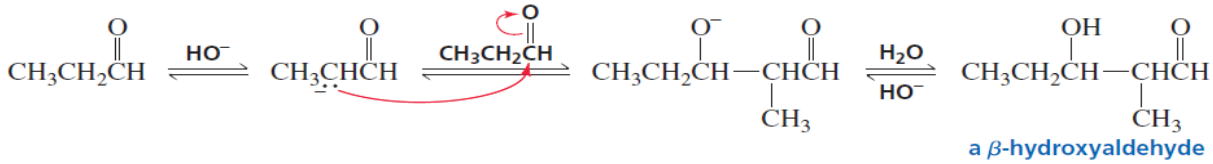
Aldol condensation

Aldehydes and ketones are electrophiles and therefore react with nucleophiles. When a proton is removed from the α-carbon of an aldehyde or a ketone, the resulting anion is a nucleophile and therefore reacts with electrophiles. An **aldol addition** is a reaction in which both of these activities are observed: One molecule of a carbonyl compound after a proton is removed from an α-carbon reacts as a *nucleophile* and attacks the *electrophilic* carbonyl carbon of a second molecule of the carbonyl compound.

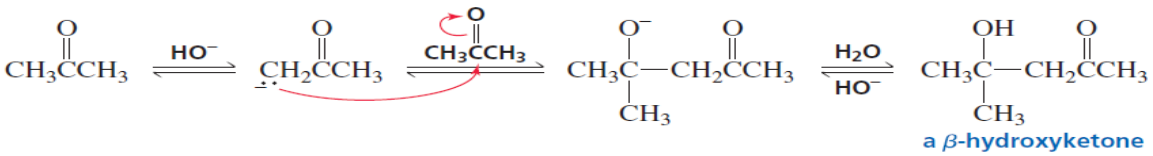
An aldol addition is a reaction between two molecules of an *aldehyde* or two molecules of a *ketone*. When the reactant is an aldehyde, the addition product is a **β-hydroxyaldehyde** that is why the reaction is called an aldol addition ("ald for aldehyde, "ol" for alcohol. When the reactant is a ketone, the addition product is a β-hydroxyketone, Because the addition reaction is reversible, good yields of the addition product are obtained only if it is removed from the solution as it is formed.

In the first step of an aldol addition, a base removes an α-proton from the carbonyl compound, creating an enolate. The enolate adds to the carbonyl carbon of a second molecule of the carbonyl compound, and the resulting negatively charged oxygen is protonated by the solvent.

Mechanism for the aldol addition



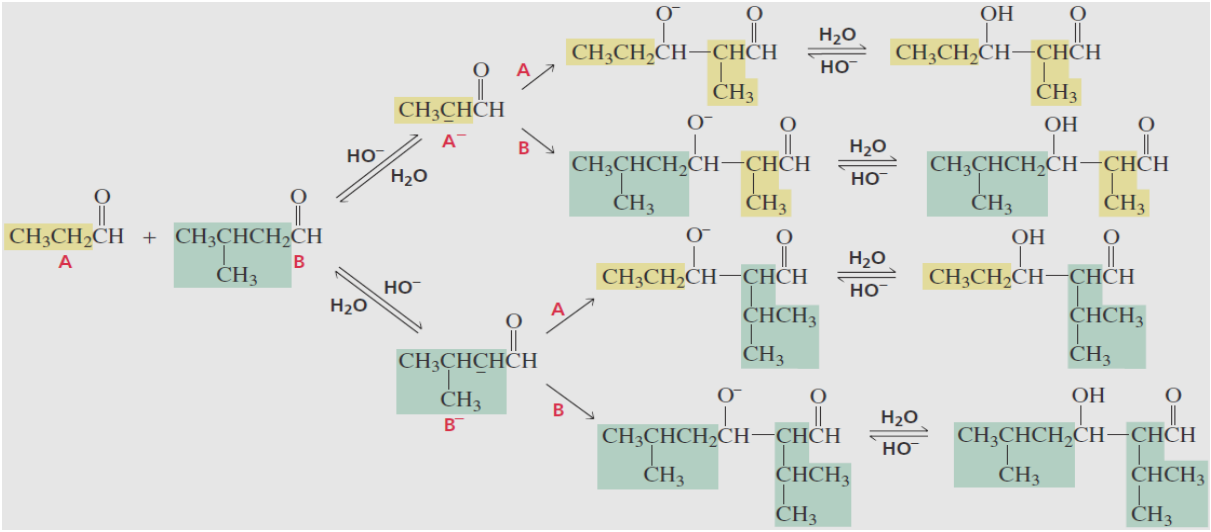
Ketones are less susceptible than aldehydes to attack by nucleophiles, so aldol additions occur more slowly with ketones. The relatively high reactivity of aldehydes in competing aldol addition reactions is what causes them to give low yields of α-alkylation products,



Because an aldol addition reaction occurs between two molecules of the same carbonyl compound, the product has twice as many carbons as the reacting aldehyde or ketone.

Mixed Aldol Addition

If two different carbonyl compounds are used in an aldol addition, four products can be formed because each enolate can react both with another molecule of the carbonyl compound from which the enolate was formed and with the other carbonyl compound. In the following example, both carbonyl compound A and carbonyl compound B can lose a proton from an α-carbon to form enolates A^- and B^-; A^- can react with either A or B, and can react with either A or B:



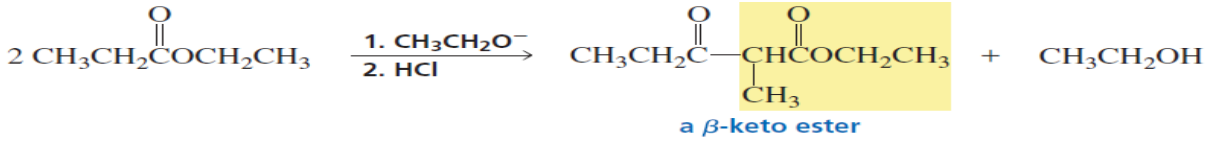
The four products have similar physical properties, making them difficult to separate. Consequently, a mixed aldol addition that forms four products is not a synthetically useful reaction.

How many possible products can be formed if one of the carbonyl compound has no an α-hydrogen? Which one will be major?

The Claisen Condensation

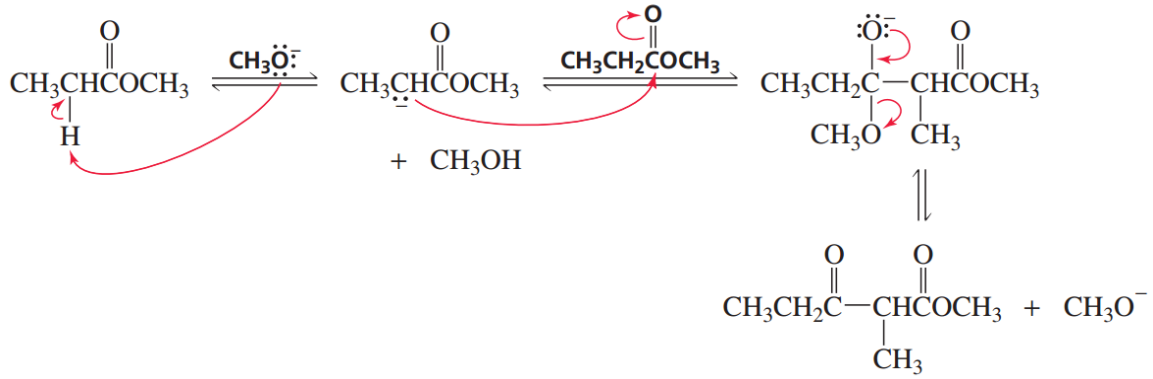
When two molecules of an *ester* undergo a condensation reaction, the reaction is called a **Claisen condensation**. The product of a Claisen condensation β-keto is ester.

Example:

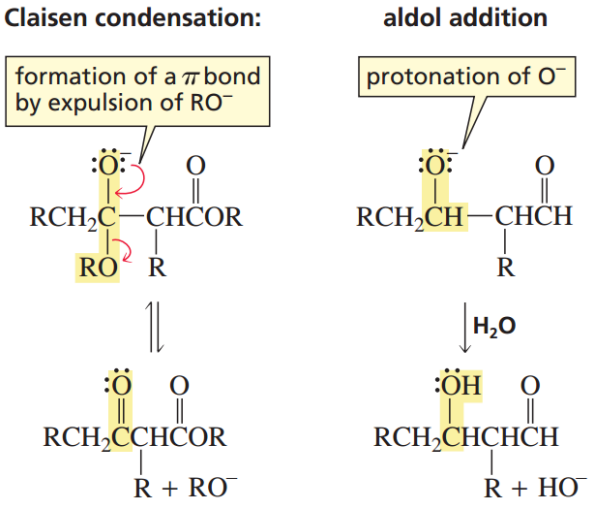


As in an aldol addition, in a Claisen condensation one molecule of carbonyl compound is converted into an enolate when an α-hydrogen is removed by a strong base. The enolate attacks the carbonyl carbon of a second molecule of ester. The base employed corresponds to the leaving group of the ester so that the reactant is not changed if the base acts as a nucleophile and attacks the carbonyl group

mechanism for the Claisen condensation

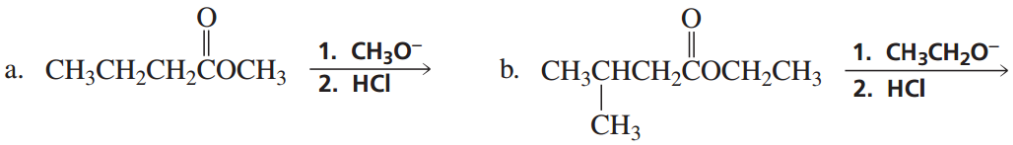


After nucleophilic attack, the Claisen condensation and the aldol addition differ. In the Claisen condensation, the negatively charged oxygen reforms the carbon–oxygen π bond and expels the ⁻OR group. In the aldol addition, the negatively charged oxygen obtains a proton from the solvent.



Thus, the Claisen condensation is a substitution reaction, whereas the aldol addition is an addition reaction.

Q: Give the products of the following reactions:



Mixed Claisen Condensation: A **mixed Claisen condensation** is a condensation reaction between two different esters. Like a mixed aldol addition, a mixed Claisen condensation is a useful reaction only if it is carried out under conditions that foster the formation of primarily one product. Otherwise, a mixture of products that are difficult to separate will be formed.

Mannich condensation: The condensations of imines with aldehydes or ketones in a manner similar aldol condensation.

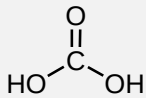
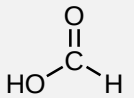
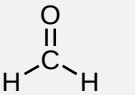
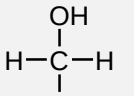
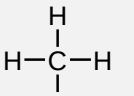
CHAPTER-4
3. OXIDATION–REDUCTION REACTIONS

Session 17: At the end of this session the students should be able to:

- Identify a given reaction whether it is oxidation or reduction.
- Write the mechanisms of the oxidations of alcohols, aldehyde and multiple bonds by using respective reagents.

Many of the organic reactions can be classified as either oxidation or reductions. Simple way to identify a given reaction whether it is oxidation or reduction is **oxidation count**. It is the number of π-bond, cyclic system and bonds with the hetero atoms like oxygen, nitrogen, halogens etc. Comparing the result of oxidation count of reactants and products, if the oxidation count of the product is greater than that of the product then we can conclude as the reaction to be **oxidation**. The reverse will be **reduction** reaction.

Examples: Oxidation count of some organic compounds

Structures	 carbonic acid	 formic acid	 formaldhyde	 methanol	 methane
Oxidation count	4	3	2	1	0

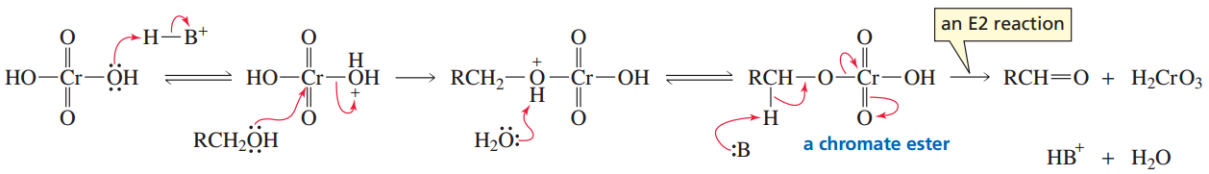
4.1. Oxidation Reactions

Oxidations of almost all organic compounds involves either introductions of a heteroatom (mostly O atom) or losing hydrogen atoms.

4.1.1. Alcohols

A reagent that is often used to oxidize alcohols is chromic acid (H_2CrO_4), which is formed when chromium trioxide (CrO_3) or sodium dichromate ($Na_2Cr_2O_7$) is dissolved in aqueous acid. These reactions are easily recognized as oxidations because the number of C-H bonds in the reactant decreases and the number of C-O bonds increases.

mechanism for alcohol oxidation by chromic acid



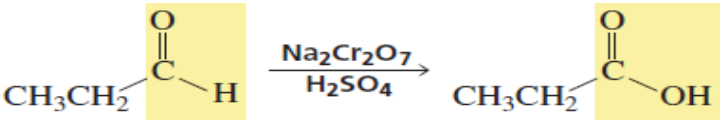
Primary alcohols are initially oxidized to aldehydes by chromic acid. The reaction, however, does not stop at the aldehyde. Instead, the aldehyde is further oxidized to a carboxylic acid.

Secondary alcohols are oxidized to ketones by chromic acid. The reaction does not continue to give carboxylic acid. Because the carbonyl carbon of the ketone does not contain H to be lost in the further oxidation reaction. Hence, **ketones are inert towards oxidation by chromic acid reaction.**

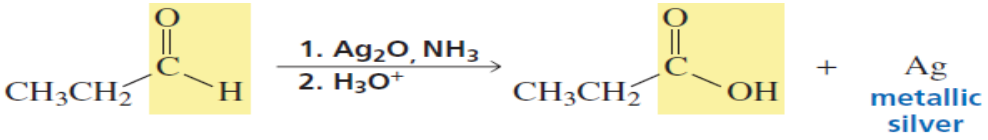
The carbon bearing the OH group in a tertiary alcohol is not bonded to a hydrogen, so the OH group cannot be oxidized to a carbonyl group. Hence. tertiary alcohols are inert towards oxidation.

4.1.2. Aldehydes

Aldehydes are oxidized to carboxylic acids. Because aldehydes are generally easier to oxidize than primary alcohols, any of the reagents described in the preceding section for oxidizing primary alcohols to carboxylic acids can be used to oxidize aldehydes to carboxylic acids.
Example:



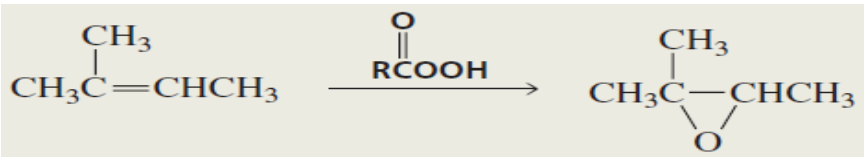
Silver oxide is a mild oxidizing agent. A dilute solution of silver oxide in aqueous ammonia (*Tollens reagent*) will oxidize an aldehyde, but it is too weak to oxidize an alcohol or any other functional group. An advantage to using Tollens reagent to oxidize an aldehyde is that the reaction occurs under basic conditions. Therefore, you do not have to worry about harming other functional groups in the molecule that may undergo a reaction in an acidic solution.
Example:

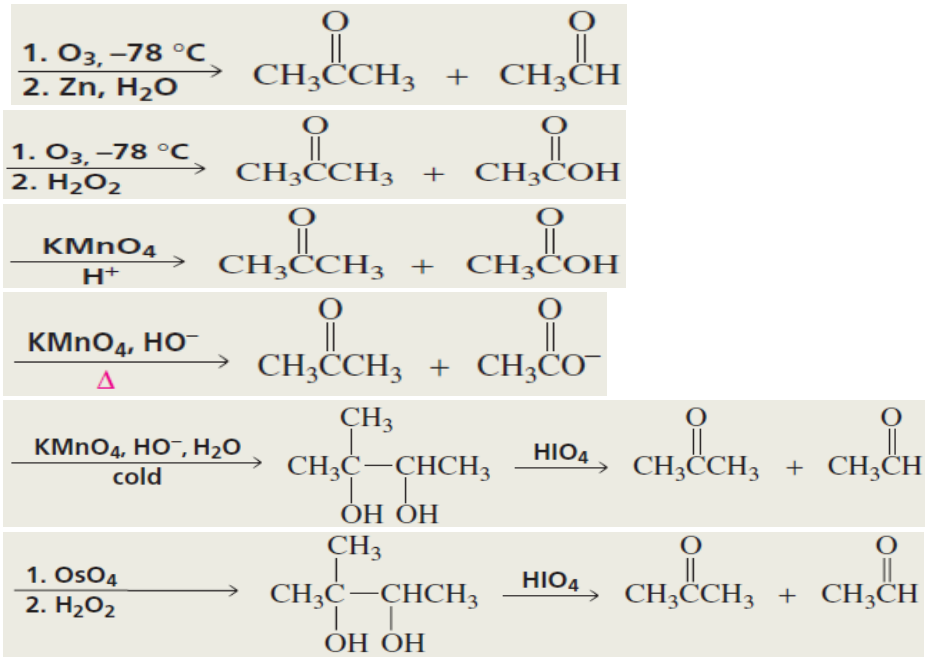


The oxidizing agent in Tollens reagent is Ag^+, which is reduced to metallic silver. The **Tollens test** is based on this reaction: If Tollens reagent is added to a small amount of an aldehyde in a test tube, the inside of the test tube becomes coated with a shiny mirror of metallic silver.

4.1.3. Multiple Bonds

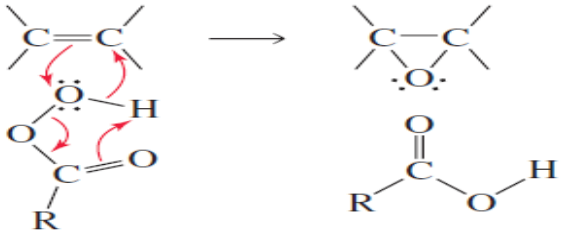
Multiple Bonds can be possibly oxidized to different products by different reagents.
Examples:





- **Oxidation of Alkenes with Peroxyacids**

Mechanism for epoxidation of an alkene



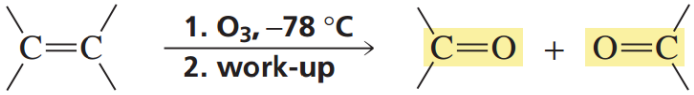
The addition of oxygen to an alkene is a stereospecific reaction. Because the reaction is concerted, the C-C bond cannot rotate, so there is no opportunity for the relative positions of the groups bonded to the *sp*2 carbons of the alkene to change. Therefore, a cis alkene forms a cis epoxide. Similarly, a trans alkene forms a trans epoxide.

Example: *trans*-2-butene forms a pair of enantiomers; *cis*-2-butene forms a meso compound. **Draw the structures of the products.**

Increasing the electron density of the double bond increases the rate of epoxidation because it makes the double bond more nucleophilic. Alkyl substituents increase the electron density of the double bond.

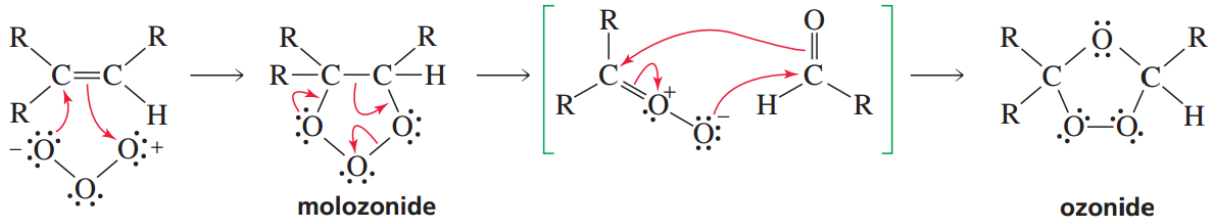
- **Ozonolysis**

When an alkene is treated with ozone at low temperatures, the double bond breaks and the carbons that were doubly bonded to each other find themselves doubly bonded to oxygens instead. This oxidation reaction is known as **ozonolysis**.



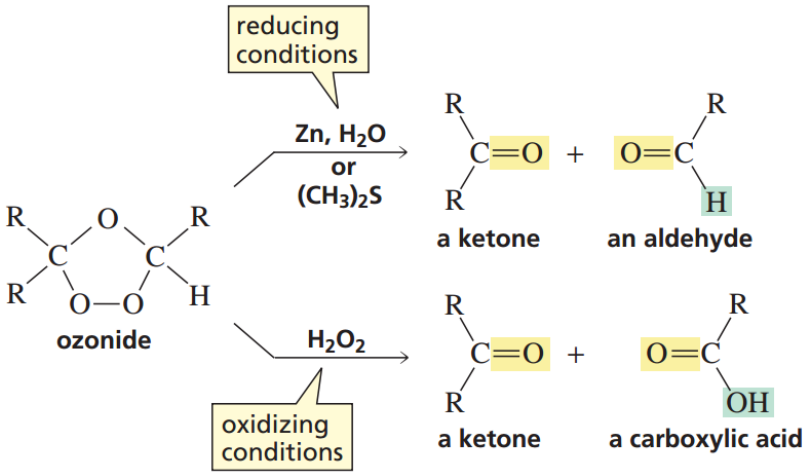
The product of ozone addition to an alkene is a **molozonide**. (The name "molozonide" indicates that one mole of ozone has added to the alkene.) The molozonide is unstable because it has two O-O bonds; it immediately rearranges to a more stable **ozonide**.

mechanism for ozonide formation



Ozonides are explosive, so they are seldom isolated. In solution, they are easily cleaved to carbonyl compounds. If the ozonide is cleaved in the presence of a reducing agent such as zinc or dimethyl sulfide, the products will be ketones and/or aldehydes.

The reducing agent prevents aldehydes from being oxidized to carboxylic acids. Cleaving the ozonide in the presence of zinc or dimethyl sulfide is referred to as "working up the ozonide under reducing conditions."



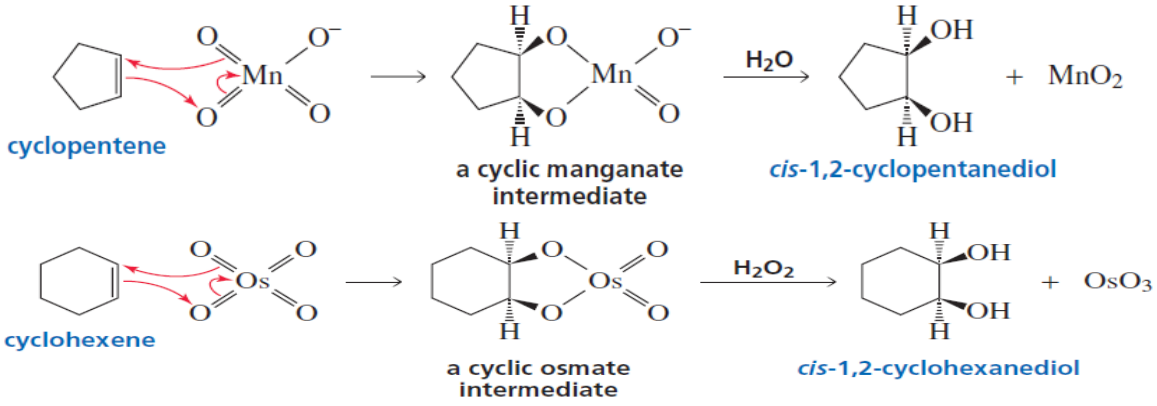
Cleavage in the presence of H_2O_2 is referred to as "working up the ozonide under oxidizing conditions."

☝ Hydroxylation of Alkenes

An alkene can be oxidized to a 1,2-diol either by potassium permanganate ($KMnO_4$) in a cold basic solution or by osmium tetroxide (OsO_4). The solution of potassium permanganate must be basic, and the oxidation must be carried out at room temperature or below. If the solution is heated or if it is acidic, the diol will be oxidized further. A diol is also called a **glycol**. The OH groups are on adjacent carbons in 1,2-diols, so 1,2-diols are also known as **vicinal diols** or **vicinal glycols**.

Both $KMnO_4$ and OsO_4 form a cyclic intermediate when they react with an alkene. The reactions occur because manganese and osmium are in a highly positive oxidation state and, therefore, attract electrons. Formation of the cyclic intermediate is a syn addition because both oxygens are delivered to the same side of the double bond. Therefore, the oxidation reaction is stereospecific—a cis cycloalkene forms only a cis diol.

mechanism for cis glycol formation



Unlike permanganate, cyclic osmate intermediate is hydrolyzed with hydrogen peroxide that reoxidizes osmium to osmium tetroxide. Higher yields of the diol are obtained with osmium tetroxide because the cyclic osmate intermediate is less likely to undergo side reactions.

4.2. Reduction Reaction

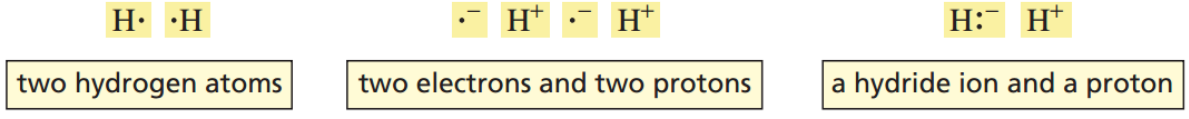
Session 18: At the end of this session the students should be able to:

- Explain the catalytic reductions, hydride reductions and dissolving metal reduction.
- Write the mechanisms of catalytic reductions, hydride reductions and dissolving metal reduction.

Reduction reactions usually involves gaining hydrogen and, in many cases, losing a heteroatom (such as O, N & halogen).

An organic compound is reduced when hydrogen (H_2) is added to it. A molecule of H_2 can be thought of as being composed of (1) two hydrogen atoms, (2) two electrons and two protons, or (3) a hydride ion and a proton. In the sections that follow, you will see that these three ways to describe H_2 correspond to the three mechanisms by which H_2 is added to an organic compound.

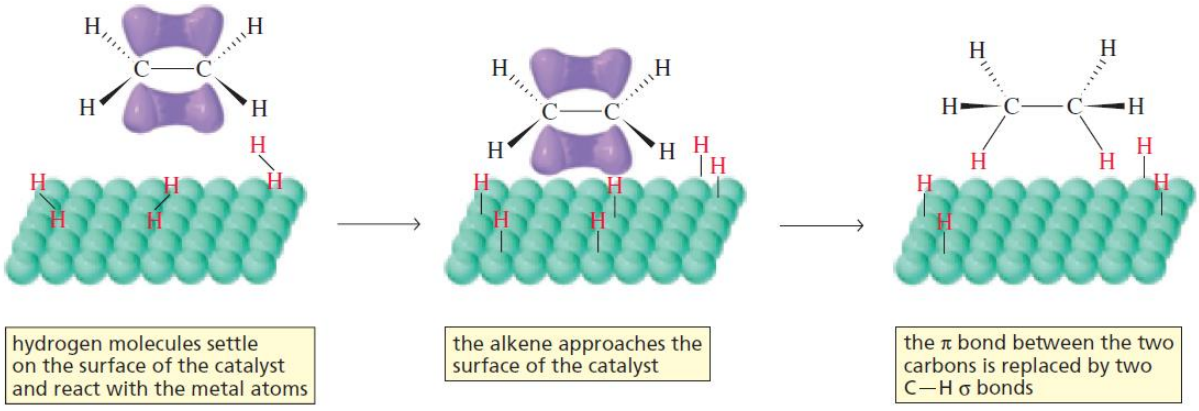
components of H:H



4.2.1. Catalytic Hydrogenation/Reduction by Addition of Two Hydrogen Atoms

In the presence of a metal catalyst such as **platinum**, **palladium**, or **nickel**, hydrogen (H_2) adds to the double bond of an alkene to form an alkane. Without the catalyst, the energy barrier to the reaction would be enormous because the H-H bond is so strong. The catalyst decreases the energy of activation by breaking the H-H bond. Platinum and palladium are used in a finely divided state adsorbed on charcoal (Pt/C, Pd/C). The platinum catalyst is frequently used in the form of PtO_2, which is known as Adams catalyst.

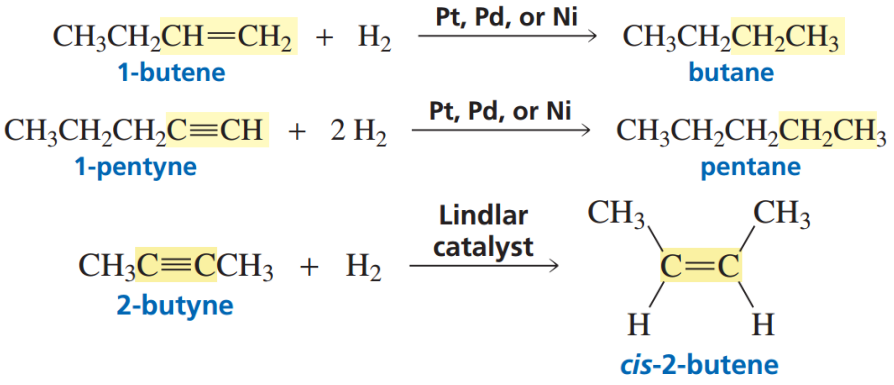
Catalytic hydrogenation of an alkene.



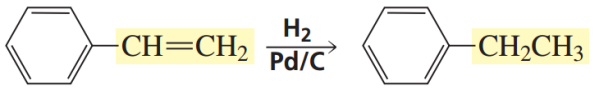
The details of the mechanism of catalytic hydrogenation are not completely understood. We know that hydrogen is adsorbed on the surface of the metal and that the alkene complexes with the metal by overlapping its own *p* orbitals with vacant orbitals of the metal. Breaking π the bond of the alkene and the σ bond of H_2 and forming the C H σ bonds all occur on the surface of the metal. The alkane product diffuses away from the metal surface as it is formed

In a catalytic hydrogenation, the H-H bond breaks homolytically. This means that the reduction reaction involves the addition of two hydrogen atoms to the organic molecule. The catalytic hydrogenation of an alkyne can be stopped at a cis alkene if a partially deactivated catalyst is used

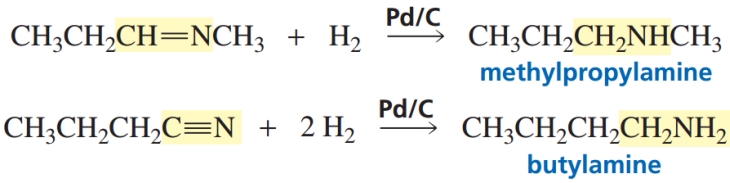
Examples:



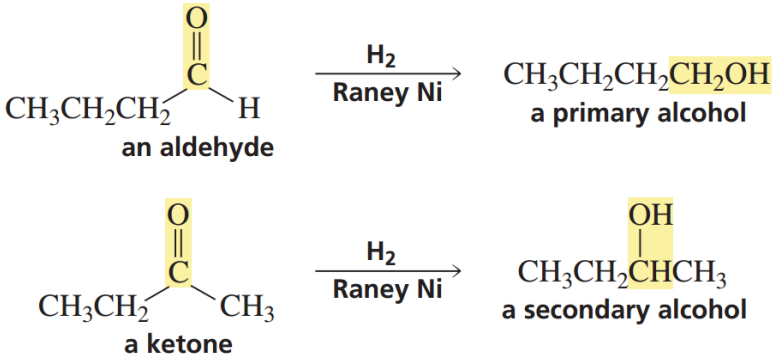
Only the alkene substituent is reduced in the following reaction. The very stable benzene ring can be reduced only under special conditions.



Catalytic hydrogenation can also be used to reduce carbon–nitrogen double and triple bonds. The reaction products are amines.

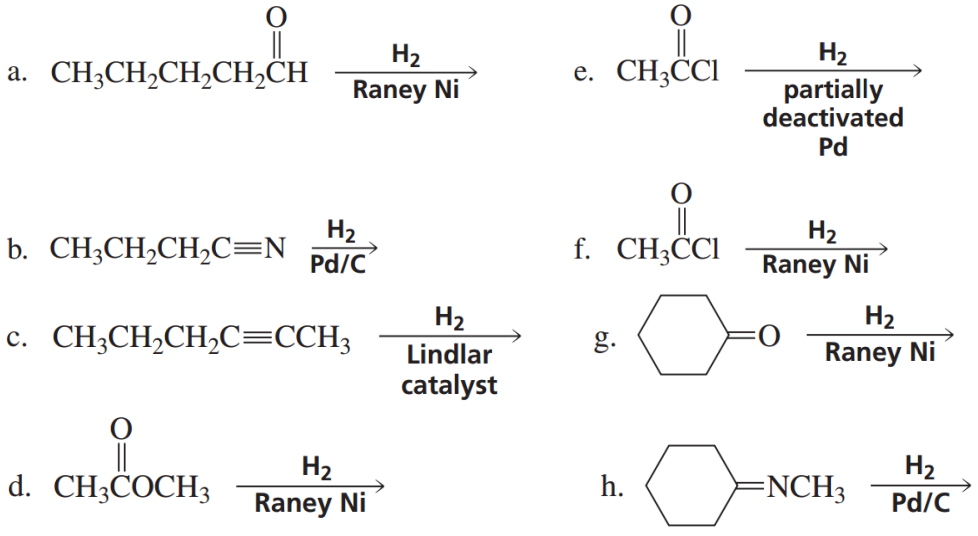


The carbonyl group of ketones and aldehydes can be reduced by catalytic hydrogenation, with Raney nickel as the metal catalyst. (Raney nickel is finely dispersed nickel with adsorbed hydrogen, so an external source of H_2 is not needed.) Aldehydes are reduced to primary alcohols, and ketones are reduced to secondary alcohols.



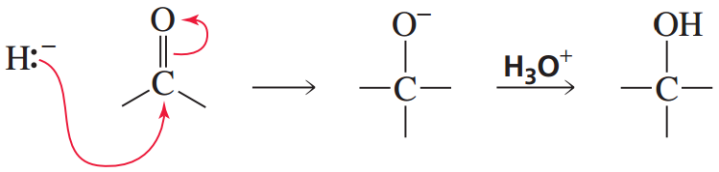
The carbonyl groups of carboxylic acids, esters, and amides are less reactive, so they are harder to reduce, by catalytic hydrogenation (except under extreme conditions).

Q: Give the products of the following reactions:

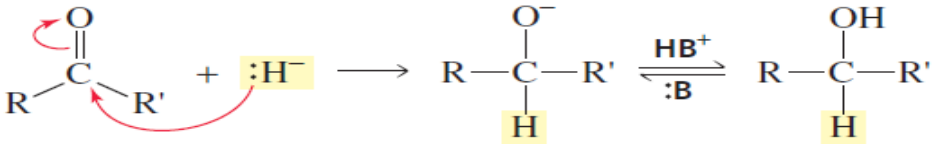


4.2.2. Hydride Reduction/Reduction by Addition of a Hydride Ion and a Proton

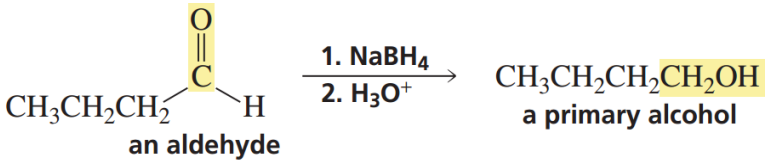
Carbonyl groups are easily reduced by metal hydrides such as sodium borohydride ($NaBH_4$) or lithium aluminum hydride ($LiAlH_4$). The actual reducing agent in **metal-hydride reductions** is hydride ion Hydride ion (H^-) adds to the carbonyl carbon, and the alkoxide ion that is formed is subsequently protonated. In other words, the carbonyl group is reduced by adding an (H^-) followed by an (H^+). The mechanisms for reduction by these reagents. The mechanism can be represented by:

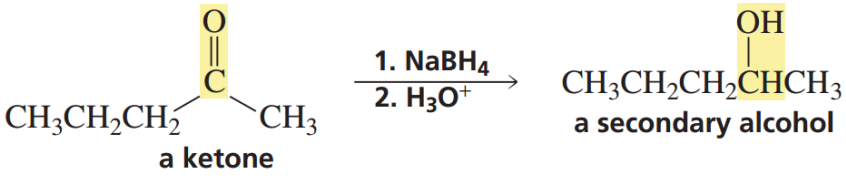


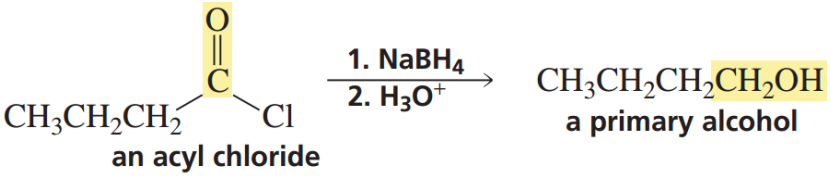
Or



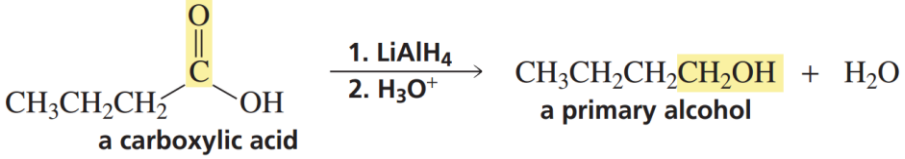
Aldehydes, ketones, and acyl halides can be reduced by sodium borohydride.

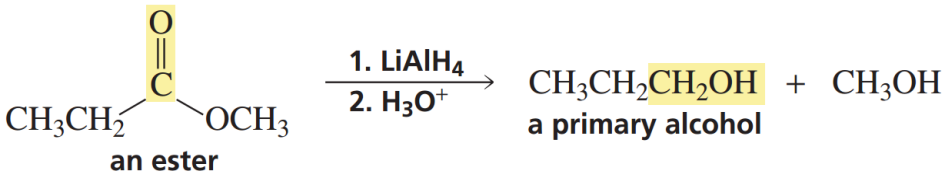




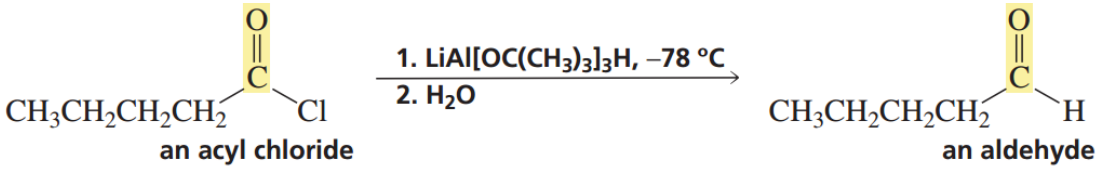


The metal–hydrogen bonds in lithium aluminum hydride are more polar than the metal–hydrogen bonds in sodium borohydride. As a result, $LiAlH_4$ is a stronger reducing agent than $NaBH_4$. Consequently, both $LiAlH_4$ and $NaBH_4$ reduce aldehydes, ketones, and acyl halides, but $LiAlH_4$ is not generally used for this purpose since $NaBH_4$ is safer and easier to use. $LiAlH_4$ is generally used to reduce only compounds—such as carboxylic acids, esters, and amides—that cannot be reduced by the milder reagent.

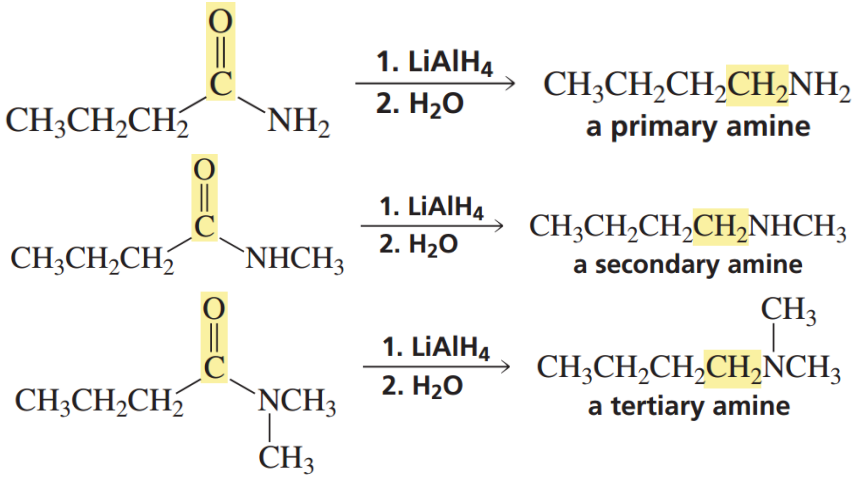




Replacing some of the hydrogens of $LiAlH_4$ with OR groups decreases the reactivity of the metal hydride. For example, lithium tri-*tert*-butoxyaluminum hydride reduces an acyl chloride to an aldehyde, whereas reduces the acyl chloride all the way to an alcohol.

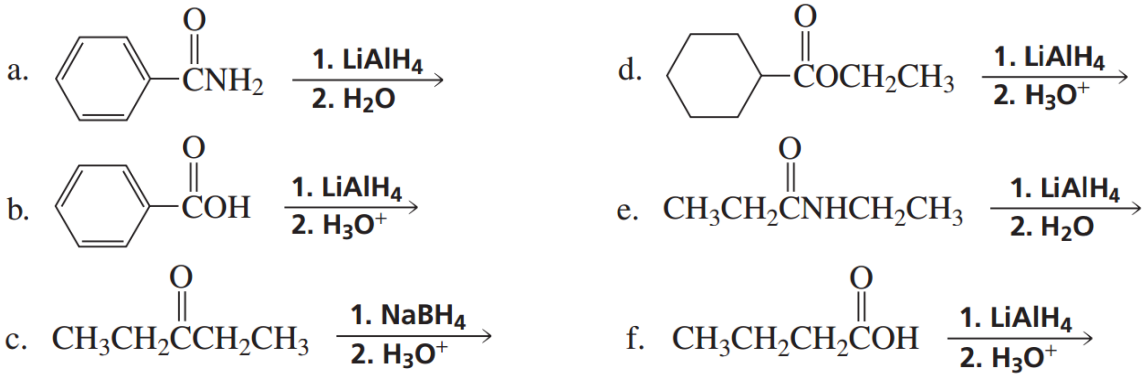


The carbonyl group of an amide is reduced to a methylene group (CH_2) by lithium aluminum hydride. Primary, secondary, and tertiary amines are formed, depending on the number of substituents bonded to the nitrogen of the amide. To obtain the amine in its neutral basic form, acid is not used in the second step of the reaction.

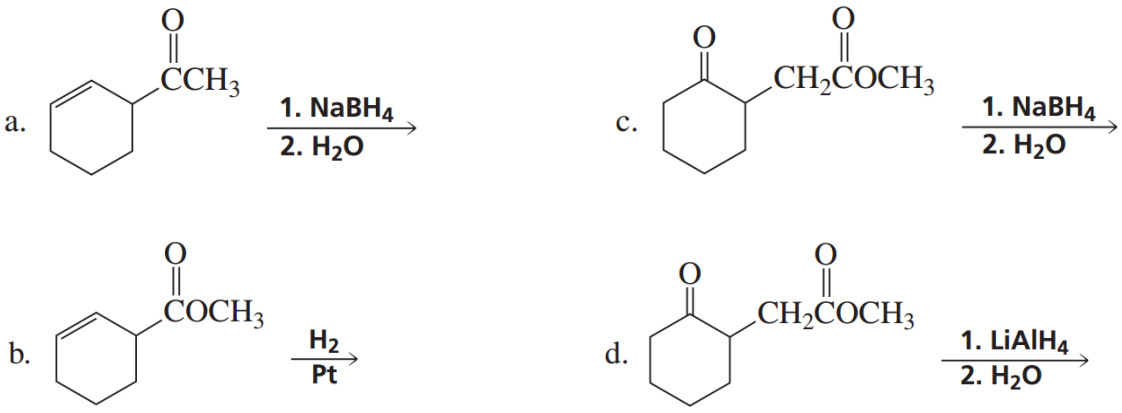


Because sodium borohydride cannot reduce an ester, an amide, or a carboxylic acid, it can be used to selectively reduce an aldehyde or a ketone group in a compound that also contains a less reactive group. Carbon-carbon unsaturation cannot be reduced by $NaBH_4$ due to lack of polarity.

Q: Give the products of the following reactions:



Q: Give the products of the following reactions (assume that excess reducing agent is used in d):

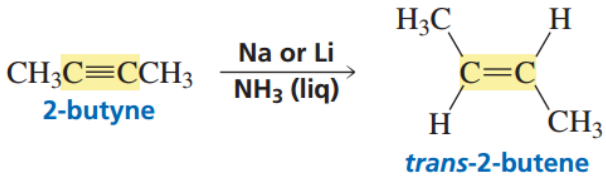


4.2.3. Dissolving metal reduction/Reduction by Addition of an Electron, a Proton, an Electron, and a Proton

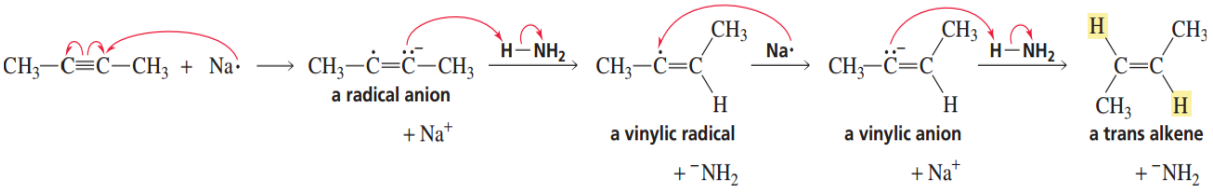
When a compound is reduced using sodium or lithium in liquid ammonia, sodium donates an electron to the compound and ammonia donates a proton. This sequence is then repeated, so the overall reaction adds two electrons and two protons to the compound. Such a reaction is known as a **dissolving-metal reduction**.

Sodium (or lithium) in liquid ammonia cannot reduce a carbon–carbon double bond. This makes it a useful reagent for reducing a triple bond in a compound that also contains a double bond.

Examples:



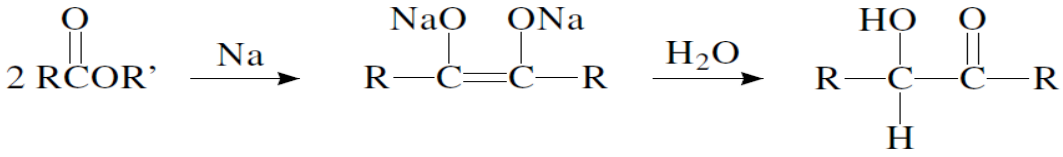
Mechanism



The vinylic anion can have either the cis or the trans configuration. The cis and trans configurations are in equilibrium, but the equilibrium favors the more stable trans configuration because in this configuration the bulky alkyl groups are as far from each other as possible.

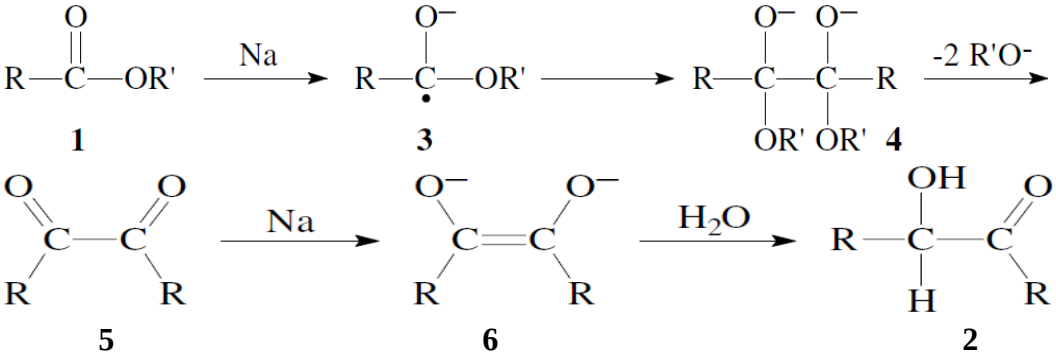
4.2.4. Acyloin Ester Condensation

Synthesis of α-Hydroxyketones from carboxylic esters



1 **2**

Upon heating of a carboxylic ester **1** with sodium in an inert solvent, a condensation reaction can take place to yield α-hydroxy ketone **2** after hydrolytic workup. This reaction is called *Acyloin condensation*, named after the products thus obtained. It works well with alkanoic acid esters. For the synthesis of the corresponding products with aryl substituents (R= aryl), the *Benzoin condensation* of aromatic aldehydes is usually applied. For the mechanistic course of the reaction the diketone **5** is assumed to be an intermediate, since small amounts of **5** can sometimes be isolated as a minor product. It is likely that the sodium initially reacts with the ester **1** to give the radical anion species **3**, which can dimerize to the dianion **4**. By release of two alkoxides $R'O^-$ the diketone **5** is formed. Further reaction with sodium leads to the dianion **6**, which yields the α-hydroxy ketone **2** upon aqueous workup:



1 **3** **4**

5 **6** **2**

An intramolecular reaction is possible with appropriate substrates containing two ester groups, leading to the formation of a carbocyclic ring. This reaction is especially useful for the formation of rings with ten to twenty carbon atoms, the yield depending on ring size. The presence of carbon–carbon double or triple bonds does not affect the reaction. The strong tendency for ring formation with appropriate diesters is assumed to arise from attachment of the chain ends to the sodium surface and thereby favoring ring closure.

Summary of reduction reactions

It is important to know not only which functionalities will react with a reagent but also which once will not react. Such information regarding certain useful reducing agents is summarized below.

1. **Pd/H_2**
    - alkene to alkane
    - alkyne to alkene then to alkane

    Comment: it is possible to stop this reduction at the olefin stage by using poisoned Pd (Lindlar catalyst). Dissolved metal catalyst can be also possible used.
    - acid chloride to aldehyde
    - nitro group to 1^o amine

    Comment: Except for acid chlorides, Pd/H2 will not readily reduced carbonyl compounds.
2. **Pt/ H_2**
    - alkene to alkane
    - alkyne to alkene then to alkane
    - acid chloride, aldehyde or ketone to alcohol
    - nitro group to 1^o amine

    Comment: Pd/H_2 will not reduce the carbonyl compounds of esters, acids and amides.
3. **$LiAlH_4$**
    - generally, carbonyl compounds

    Comment: $LiAlH_4$ will not generally reduce C-C unsaturation.
4. **NaBH4**
    - aldehydes and ketones to alcohol
    - acid chloride to primary alcohol

    Comment: $NaBH_4$ will not reduce C-C unsaturation, esters, acids or amides.