Carbonyl χ-substitution and Condensation Reactions
We have so far studied two types of reactions of carbonyl compounds.

I. Nucleophilic addition reaction

\[
\begin{align*}
\text{H and Nu are added.}
\end{align*}
\]

II. Nucleophilic acyl substitution (Z = electronegative)

Both reactions involved nucleophilic attack at the electrophilic carbonyl carbon.
The reactions we are going to see now are those that involve the carbon that is next to the carbonyl, the \( \alpha \)-carbon. Hydrogen atoms on the \( \alpha \) carbon are called \( \alpha \) hydrogens.

\[ \begin{align*}
\text{R} & \quad \alpha \\
\text{H} & \quad \beta \\
\text{H} & \quad \chi \\
O & \quad \delta
\end{align*} \]

\( \alpha - \text{Hydrogen} \)

In these reactions the \( \alpha \)-carbon as nucleophile attacks electrophiles.
Acidity of the $\alpha$-hydrogens of Carbonyl Compounds

A hydrogen bonded to an $sp^3$ hybridized carbon adjacent to a carbonyl carbon is much more acidic than hydrogens bonded to other hybridized carbons.

<table>
<thead>
<tr>
<th>Compound</th>
<th>pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldehyde</td>
<td>16 - 20</td>
</tr>
<tr>
<td>Ketone</td>
<td>25</td>
</tr>
<tr>
<td>Ester</td>
<td>50</td>
</tr>
<tr>
<td>Alkane</td>
<td></td>
</tr>
</tbody>
</table>
Why is a hydrogen bonded to a carbon that is adjacent to a carbonyl carbon is acidic?

\[ \text{Resonance stabilized enolate} \]
If the $\alpha$-carbon is between two carbonyl groups, the acidity of the $\alpha$-hydrogen is even greater.

$\beta$-Diketone

\[
\begin{align*}
H_3C & \quad \text{CH}_3 \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

$pK_a$ 8.9

$\beta$-Ketoester

\[
\begin{align*}
H_3C & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{CH}_3 \\
\end{align*}
\]

$pK_a$ 10.7

An enolate stabilized by two oxygens.
A carbonyl compound with \( \alpha \) hydrogen atom on its carbon rapidly equilibrates with its corresponding enol isomer.

This spontaneous interconversion between two isomers, usually with the change in position of a hydrogen, is called tautomerism.
The same compounds that are the most electrophilic are also the most easily enolizable. This makes acyl chlorides very enolizable. As a result acid chlorides are the most enolizable while amides are the least.

Assignment 29

Draw mechanisms for these reactions

a) 

\[ \text{Acid or Base} \]

\[ \text{Acetyl chloride} \rightarrow \text{Acetaldehyde} \]

b) 

\[ \text{H}_3\text{O}^+ \]

\[ \text{Cyclopentanone} \rightarrow \text{Acetone} \]
What kind of chemistry do enols have?

Enols have an electron rich double bonds and as a result just like alkenes react with electrophiles. However, the neighboring oxygen donates its lone-pair of electrons through resonance making enols more electron-rich and thus more reactive than alkenes.
Therefore, enols react with electrophiles leading to alpha-substituted carbonyl compounds.

Enolates which are formed when a base abstracts the alpha hydrogens also react similarly.
Electrophilic substitution occurs at the alpha position of carbonyl compounds through either an enol or enolate ion:

The electrophile could be a halogen, an alkyl halide, a carbonyl compound or any other electron deficient species.
Alpha (α)-Substitution Reaction

Halogenation at the α Carbon

Carbonyl compounds bearing an α hydrogen can undergo halogen substitution at the α carbon in the presence of acid. The most commonly used acid is acetic acid, AcOH.

\[
\text{R}_1\text{H} + \text{X} - \text{X} \xrightarrow{\text{AcOH}} \text{R}_1\text{X} + \text{H} - \text{X}
\]

Example

\[
\text{Cyclic ketone} + \text{Br}_2 \xrightarrow{\text{AcOH}} \text{Cyclic brominated ketone}
\]
Alpha-halogenated carbonyls are useful in synthesis because they can be dehydrohalogenated by base to yield, $\alpha,\beta$-unsaturated carbonyl compounds.

Unlike its acid-catalyzed counterpart, halogenation in base cannot normally be limited to monohalogenation. It is often difficult to stop the reaction after addition of just one halogen atom to the $\alpha$ carbon.

Both $\alpha$ H's are replaced by Br
Halogenation of a methyl ketone with excess halogen in a base, called the haloform reaction, results in cleavage of a carbon–carbon σ bond and formation of two products, a carboxylate anion and CHX₃ (commonly called haloform).

Halogenation of carbonyl compounds should be carried out in acid solution. Attempts in basic solution lead to multiple substitutions and C–C bond cleavage.
Assignment 30

I. Show the mechanism of both acid and base catalyzed halogenation of carbonyl compounds.

II. Show how you might prepare pent-1-en-3-one from pentan-3-one.

III. Propose the mechanism of the haloform reaction given below:
Alkylation at the $\alpha$ Carbon

Treatment of an aldehyde or ketone with base and an alkyl halide (RX) results in alkylation—the substitution of R for H on the $\alpha$ carbon atom.

\[
\begin{align*}
\text{R}_3\text{R}_1\text{H} & \xrightleftharpoons{\text{LDA, THF, -78°C}} \text{R}_3\text{R}_1\Theta \quad \xrightarrow{\text{S}_{\text{N}2}} \text{R}_3\text{R}_2\text{R}_1\text{R} \\
\end{align*}
\]

The reaction works best with a strong non-nucleophilic base like LDA in THF solution at low temperature ($-78 \, ^{\circ}\text{C}$).

In LDA, the enolate is rapidly generated and no ketone remains.
Examples

Ester enolates and carbanions derived from nitriles are also alkylated under these conditions.
Assignment 31

I. What product is formed when each compound is treated first with LDA in THF solution at low temperature, followed by CH₃CH₂I?

a) \( \text{CH}_3\text{CH}_2\text{O} \)

b) \( \text{CH}_3\text{CH}_2\text{C}_6\text{H}_4\text{CH} = \text{CH}_2 \)

c) \( \text{C}_6\text{H}_5\text{O} \)

d) \( \text{CHC}_6\text{H}_4\text{CH}_2\text{CN} \)

II. Show step by step how the analgesic naproxen can be prepared from ester A.
Alpha – Halogenation of Carboxylic Acids

\[ \text{R-CH}_2\text{COOH} \xrightarrow{1. \text{PX}_3} \xrightarrow{2. \text{X}_2} \xrightarrow{3. \text{H}_2\text{O}} \text{R-CH}_2\text{COX} \]

\( X = \text{Cl, Br} \) \( \alpha \)-Halocarboxylic acid

This reaction is called Hell - Vollhard – Zeliski (HVZ) reaction.

Carboxylic acids do not tautomerize readily and thus do not undergo \( \alpha \)-halogeneration. However, the halogenation of acid halides provides a technique by which we can obtain \( \alpha \)-halocarboxylic acids.
Mechanism

$\text{R-CHOH} \xrightarrow{\text{PX}_3} \text{Keto} \xrightarrow{\text{Tautomerization}} \text{Enol} \xrightarrow{\text{H}_2\text{O}} \text{α-Halocarboxylic acid}$
Example

α-Halocarboxylic acids are important synthetic intermediates because they are capable of reaction with a variety of nucleophiles.

Conversion to α-hydroxy acids
Conversion to $\alpha$-amino acids

$\alpha$-Halocarboxylic acid $\rightarrow$ Amino acid

$2 \text{NH}_3 \rightarrow \text{NH}_4\text{Cl}$
I. Identify the reagents that you would use to accomplish each of the following transformations

a) \[
\text{Br} \quad \text{Br} \quad \text{OH}
\]

b) \[
\text{Br} \quad \text{Br}
\]

c) \[
\text{CN} \quad \text{CO}_2\text{H}
\]

II. If methanol rather than water is added at the end of a Hell–Volhard–Zelinskii reaction, an ester rather than an acid is produced. Show how you could carry out the following transformation, and propose a mechanism for the ester forming step.

\[
\text{HO} \quad \text{Br} \quad \text{OCH}_3
\]
Carbonyl Condensation Reactions

Carbonyl compounds can behave as either electrophiles or nucleophiles.

In a nucleophilic addition reaction or a nucleophilic acyl substitution reaction, the carbonyl group behaves as an electrophile by accepting electrons from an attacking nucleophile.

In an α-substitution reaction, the carbonyl compound behaves as a nucleophile after being converted into an enol or enolate ion.

Carbonyl condensation reactions involve both kinds of reactivity of carbonyl compounds.
Carbonyl condensation reactions take place between two carbonyl partners and involve a combination of nucleophilic addition and $\alpha$-substitution steps. One partner (the nucleophilic donor) is converted into an enolate ion and undergoes an $\alpha$-substitution reaction, while the other partner (the electrophilic acceptor) undergoes a nucleophilic addition reaction.

There are numerous variations of carbonyl condensation reactions, depending on the two carbonyl partners, but the general mechanism remains the same.
General Mechanism of Carbonyl Condensation Reaction
Condensations of Aldehydes and Ketones: The Aldol Reaction

Aldehydes and ketones with an $\alpha$-hydrogen atom undergo a base-catalyzed carbonyl condensation reaction called the aldol reaction. The product is a $\beta$-hydroxy-substituted carbonyl compound.

For example, treatment of acetaldehyde with a base such as sodium ethoxide or sodium hydroxide in a protic solvent leads to rapid and reversible formation of 3-hydroxybutanal, known commonly as *aldol* (*aldehyde alcohol*).
Dehydration of Aldol Products: Synthesis of Enones

The β-hydroxy aldehydes and β-hydroxy ketones formed in aldol reactions are easily dehydrated to yield α,β-unsaturated products, or conjugated enones (ene + one). In fact, it’s this loss of water that gives the aldol condensation its name, because water condenses out of the reaction.

A β-hydroxy ketone or aldehyde

\[
\begin{align*}
&\text{H}_3\text{O}^+ \\
\Theta &\text{:OH}
\end{align*}
\]

\[\text{A conjugated enone} + \text{H}_2\text{O}\]
Assignment 33

I. Which of the following compounds would you expect to undergo aldol condensation? Draw the product in each case.

   a) \[
   \begin{align*}
   \text{CH}_3\text{-C(}\text{O})\text{CH}_2\text{-C(OH)} - \\
   \end{align*}
   \]

   b) \[
   \begin{align*}
   \text{C}_2\text{H}_4\text{O} - \\
   \end{align*}
   \]

   c) \[
   \begin{align*}
   \text{C}_6\text{H}_5\text{-C(}\text{O})\text{-C}_6\text{H}_5 - \\
   \end{align*}
   \]

II. Write the complete stepwise mechanism for the reactions below. Show all intermediate structures and all electron flow with arrows.

   \[
   \begin{align*}
   \text{H}_2\text{C(}\text{O})\text{-C}_7\text{H}_13\text{-C(}\text{O})\text{-H} \rightarrow \text{NaOEt} \rightarrow \text{C}_6\text{H}_5\text{-C(}\text{C}_6\text{H}_5\text{)CH}_2\text{-C(}\text{O})\text{-H} - \\
   \end{align*}
   \]
III. Propose mechanism for the following transformation

(a) \( \text{Base catalyst} \)

(b) \( \text{NaOH, MeOH} \)

(c) \( \text{NaOH} \)
Phenols

Compounds that have a hydroxyl group directly attached to a benzene ring.

\[
\begin{align*}
\text{OH} & & \text{OH} \\
\text{PHENOL} & & \text{METHYLPHENOL} \\
\end{align*}
\]

Thus, phenol is the specific name for hydroxybenzene, and it is the general name for the family of compounds derived from hydroxybenzene.
Physical Properties of Phenols

The presence of \(-\text{OH}\) in the molecule means that phenols are like alcohols in being able to form intermolecular hydrogen bonding, and therefore have higher boiling points than hydrocarbons of the same molecular weight.

Phenols are also modestly soluble in water because of their ability to form strong hydrogen bonds with water molecules.
Acidity of Phenols

This is because, benzene is electron rich and therefore acts like an EWG. This will cause the –OH bond to be weak and as a result the hydrogen is easier to be picked by a base as compared to cyclohexanol.

\[
pKa = 9.89
\]

\[
pKa = 18
\]
Resonance forms of the phenol will put a positive charge on the oxygen which will force the oxygen to withdraw electrons from the phenolic hydrogen making the O-H bond weak.
The phenoxide ion once formed is stabilized by resonance compared to phenol.

Resonance stabilization of the phenoxide ion explains why phenol is eight orders of magnitude (100,000,000 times) more acidic than cyclohexanol.
Electron withdrawing groups make the substituted phenol more acidic than phenol itself.

2,4,6-Trinitrophenol (Picric acid)

\[ pK_a = 0.38 \]
I. Why is benzoic acid more acid than phenol?

II. Consider the structures of 2-nitrophenol and 3-nitrophenol. These compounds have very different $pK_a$ values. Predict which one has the lower $pK_a$, and explain why.

I. Rank the following compounds in order of increasing acidity.
Reaction of Phenols

React with acid anhydrides and acid chlorides to form esters.

\[
\text{Phenol} + \text{Acid Anhydride} \rightarrow \text{Esters}
\]

\[
\text{Phenol} + \text{Acid Chloride} \rightarrow \text{Esters}
\]
Reaction of phenols with alkylhalides

\[
\begin{align*}
\text{PhOH} & \xrightarrow{\text{NaOH}} \text{PhO}^- \\
\text{PhO}^- & \xrightarrow{\text{R}–\text{X}} \text{PhOR}
\end{align*}
\]

**Williamson Ether Synthesis**

\[
\begin{align*}
\text{PhOH} & \xrightarrow{\text{NaOH}} \text{PhO}^- \\
\text{PhO}^- & \xrightarrow{\text{H}_3\text{C}–\text{I}} \text{PhOMe}
\end{align*}
\]
Preparation of Aspirin

Chemical reaction steps:

1. **Initial Compound**: A benzene ring with a hydroxyl group.
2. **Activation**: Formation of a negative charge on the benzene ring.
3. **Acetylation**: Attachment of an acetyl group to the benzene ring, resulting in acetyl salicylic acid.
4. **Final Product**: Acetyl salicylic acid, which is Aspirin.

The reaction involves the formation of a negative charge, followed by an acetylation reaction to yield the final product.
Aliphatic and Aryl Amines

Amines are organic compounds derived from ammonia with one or more alkyl groups bonded to nitrogen.

The chemistry of amines is dominated by the lone pair of electrons on the nitrogen.

The lone pair of electrons on the nitrogen of amines is a powerful electron source, so the most important chemical properties of amines are their basicity and nucleophilicity.

Amines are stronger bases and better nucleophiles than other neutral organic compounds.
Unlike alcohols and alkyl halides, which are classified as primary, secondary, or tertiary according to the degree of substitution at the carbon that bears the functional group, amines are classified according to their degree of substitution at nitrogen.

**Primary amines**

**Secondary amines**

**Tertiary amines**

**Quaternary ammonium salts**
Nomenclature

The IUPAC nomenclature is analogous to that for alcohols, except the -e ending is replaced with -amine.

Other substituents on the carbon chain are given numbers, and the prefix N- is used for each substituent on nitrogen.

2-Butanamine

N-Methyl-2-butanamine

3-Methyl-1-butanamine

N,N,2-Trimethylpentan-3-amine
Aniline

3-Bromoaniline

N,N-Dimethylaniline

1-Amino-2,4-dimethylcyclohexane
Physical Properties of Amines

Amines exhibit dipole–dipole interactions because of the polar C – N and N – H bonds.

Primary and secondary amines are capable of intermolecular hydrogen bonding, because they contain N – H bonds.
Because nitrogen is less electronegative than oxygen, however, intermolecular hydrogen bonds between N and H are weaker than those between O and H. Primary (1°) and 2° amines have higher bp’s than similar compounds (like ethers) incapable of hydrogen bonding, but lower bp’s than alcohols that have stronger intermolecular hydrogen bonds.

\[
\begin{align*}
\text{O} & \quad \text{MW} = 74 \quad \text{bp} \ 38^\circ \text{C} \\
\text{NH}_2 & \quad \text{MW} = 73 \quad \text{bp} \ 78^\circ \text{C} \\
\text{OH} & \quad \text{MW} = 74 \quad \text{bp} \ 118^\circ \text{C}
\end{align*}
\]
Tertiary (3°) amines have lower boiling points than 1° and 2° amines of comparable molecular weight, because they have no N – H bonds and are incapable of hydrogen bonding.

\[
\text{MW} = 73 \\
\text{no N – H bond} \\
\text{bp 38°C}
\]

\[
\text{MW} = 74 \\
\text{N – H bond} \\
\text{bp 56°C}
\]
Basicity of Amines

The chemistry of amines is dominated by the lone pair of electrons on nitrogen, which makes amines both basic and nucleophilic.

They react with acids to form acid–base salts, and they also react with electrophiles.
Ammonia is $10^{10}$ times more basic than water. This is because oxygen is more electronegative than nitrogen. Oxygen tends to hold on to its electrons than nitrogen and is therefore less likely to donate them to a proton. Nitrogen bases (amines) are the strongest neutral bases commonly encountered by the organic chemist.
Amines are much stronger bases than alcohols and ethers, their oxygen containing analogs. When an amine is dissolved in water, an equilibrium is established in which water acts as an acid and transfers a proton to the amine. Just as the acid strength of a carboxylic acid can be measured by defining an acidity constant $K_a$, the base strength of an amine can be measured by defining an analogous basicity constant $K_b$.

\[
K_b = \frac{[RNH_3^+][OH^-]}{[RNH_2]} \quad \text{and} \quad pK_b = -\log K_a
\]
The larger the value of $K_b$, and the smaller the value of $pK_b$, the more favorable the proton-transfer equilibrium and the stronger the base.

In practice, $K_b$ values are not often used. Instead, the most convenient way to measure the basicity of an amine ($RNH_2$) is to look at the acidity of the corresponding ammonium ion ($RNH_3^+$).

$$RNH_3^+ + H_2O \rightleftharpoons RNH_2 + H_3O^+$$

$$K_a = \frac{[RNH_2][H_3O^+]}{[RNH_3^+]} \quad pK_a = -\log K_a$$

The lower the $pK_a$, the weaker the base.
The strength of basicity is determined by:

1. Accessibility of the lone pair of electrons on nitrogen.
2. The extent to which the resultant positive charge is stabilized.
Electron-releasing alkyl groups stabilize the ammonium ion.

\[(\text{CH}_3)_3\text{N} > (\text{CH}_3)_2\text{NH} > \text{CH}_3\text{NH}_2 > \text{NH}_3\]

$3^0$ Amine       $2^0$ Amine       $1^0$ Amine       Ammonia

Aromatic amines are less basic than aliphatic amines.
Why? Two factors account for this:

1) Resonance delocalization of the electron pair

The lone pair of electrons on the nitrogen through resonance are given to the aromatic carbons making it less available to pick a proton from an acid.

2) Electron-withdrawing effect of the phenyl group
Substituted arylamines can be either more basic or less basic than aniline, depending on the substituent.

Electron-donating substituents, such as −CH₃ and −OCH₃, which increase the reactivity of an aromatic ring toward electrophilic substitution, also increase the basicity of the corresponding arylamine.

Electron-withdrawing substituents, such as −Cl, −NO₂, and −CN, which decrease ring reactivity toward electrophilic substitution, also decrease arylamine basicity.
### Base Strength of Some $p$-Substituted Anilines

\[
Y-\text{NH}_2 + \text{H}_2\text{O} \rightleftharpoons Y-\text{NH}_3^+ + \text{OH}^- 
\]

<table>
<thead>
<tr>
<th>Substituent, Y</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$-\text{NH}_2$</td>
<td>6.15</td>
</tr>
<tr>
<td>$-\text{OCH}_3$</td>
<td>5.34</td>
</tr>
<tr>
<td>$-\text{CH}_3$</td>
<td>5.08</td>
</tr>
<tr>
<td>$-\text{H}$</td>
<td>4.63</td>
</tr>
<tr>
<td>$-\text{Cl}$</td>
<td>3.98</td>
</tr>
<tr>
<td>$-\text{Br}$</td>
<td>3.86</td>
</tr>
<tr>
<td>$-\text{CN}$</td>
<td>1.74</td>
</tr>
<tr>
<td>$-\text{NO}_2$</td>
<td>1.00</td>
</tr>
</tbody>
</table>

- **Stronger base**
- **Weaker base**

 Activating groups

 Deactivating groups
Effect of hybridization

\[
\text{pK}_b \quad 2.55 \quad 8.75 \quad 24
\]

\[
\text{SP}^3 \quad \text{SP}^2 \quad \text{SP}
\]
Rank the following compounds in order of increasing basicity:

A. \( p \)-Nitroaniline, \( p \)-aminobenzaldehyde, \( p \)-bromoaniline

B. \( p \)-Chloroaniline, \( p \)-aminoacetophenone, \( p \)-methylaniline

C. \( p \)-(Trifluoromethyl)aniline, \( p \)-methylaniline, \( p \)-(fluoromethyl)aniline
Synthesis of Amines

I. Reduction of nitriles

\[ \text{RCH}_2\text{X} + \text{NaCN} \xrightarrow{S_2\text{N}} \text{RCH}_2\text{C}≡\text{N} \xrightarrow{1. \text{LiAlH}_4, \text{Ether}} \text{RCH}_2\text{C}≡\text{N} \xrightarrow{2. \text{H}_2\text{O}} \text{RH}_2\text{C} \text{NH}_2 \]

Alkyl halide \rightarrow Alkyl nitrile \rightarrow Primary amine

II. Reduction of amides

\[ \text{RCOOH} \xrightarrow{1. \text{SOCl}_2, 2. \text{NHR}_1\text{R}_2} \text{RCONR}_1\text{R}_2 \xrightarrow{1. \text{LiAlH}_4, \text{Ether}} \text{RCONR}_1\text{R}_2 \xrightarrow{2. \text{H}_2\text{O}} \text{RNR}_1\text{R}_2 \]

Carboxylic acid \rightarrow Amide \rightarrow 1^\circ, 2^\circ \text{ or } 3^\circ \text{ amine}
III. Reductive Amination of Aldehydes/Ketones

Amines can be synthesized in a single step by treatment of an aldehyde or ketone with ammonia or an amine in the presence of a reducing agent, a process called reductive amination.
IV. Reduction of nitrobenzenes

Arylamines are usually prepared by nitration of an aromatic starting material, followed by reduction of the nitro group.

\[
\text{Ar}-\text{H} \xrightarrow{\text{HNO}_3, \text{H}_2\text{SO}_4} \text{Ar}-\text{NO}_2 \xrightarrow{\text{reduce}} \text{Ar}-\text{NH}_2
\]

The reduction step can be carried out in different ways, depending on the circumstances. Catalytic hydrogenation over platinum works well but is sometimes incompatible with the presence elsewhere in the molecule of other reducible groups, such as C-C double bonds. Iron, tin, and stannous chloride (SnCl\(_2\)) in aqueous acid are also effective.
1-(tert-butyl)-4-nitrobenzene

\[ \text{Pt catalyst, ethanol} \]

\[ \text{H}_2 \]

4-(tert-butyl)aniline

\[ \]

\[ m\text{-Nitrobenzaldehyde} \]

\[ 1. \text{SnCl}_2, \text{H}_3\text{O}^+ \]

\[ 2. \text{NaOH} \]

\[ m\text{-Aminobenzaldehyde} \]