Carboxylic Acids and Their Derivatives

- Nomenclature
- Preparation
- Nucleophilic Addition – Elimination at the Acyl Carbon
- Acyl Chlorides
- Carboxylic Acid anhydrides
- Esters
- Amides

Carboxylic Acids

Carboxylic acids are a family of organic compounds with the functional group \(-\text{C}=\text{O}\text{H}\) which is also written as \(-\text{CO}_2\text{H}\) or \(\text{COOH}\).

The carbon-oxygen double bond is made up of a \(\sigma\)-bond and a \(\pi\)-bond. The carbon atom is sp\(^2\) hybridized, which explains the trigonal planar geometry at this center.

\[
\begin{align*}
\text{R} & \equiv \text{alkyl, aryl or simply H} \\
\end{align*}
\]

Carboxylic Acid Derivatives

The carboxyl group consists of two parts, the acyl group and the attached hydroxyl group: \(\text{R}-\text{C}=\text{O}\text{H}\).

The acid derivatives are compounds in which the hydroxyl group is replaced with another group or a halogen atom. The principal examples are:

- Acyl (acid) halides \(\text{R}-\text{C}=\text{X}\)
- Acid anhydrides \(\text{R}-\text{C}=\text{O}\text{-C}=\text{R'}\)
- Esters \(\text{R}-\text{C}=\text{OR'}\)
- Amides \(\text{R}-\text{C}=\text{NH}_2\)
- N-Monosubstituted Amides \(\text{R}-\text{C}=\text{NR'}\)
- N,N-Disubstituted Amides \(\text{R}-\text{C}=\text{NR'R''}\)

Another class of carboxylic acid derivatives are the nitriles, which qualify because on hydrolysis, like all of the other derivatives above, they yield carboxylic acids. \(\text{R}-\text{C}=\text{N}\).
Nomenclature of Carboxylic Acids

Common names are frequently used for the simpler carboxylic acids that have been known for hundreds of years.

<table>
<thead>
<tr>
<th>Common Name</th>
<th>IUPAC Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formic acid</td>
<td>HCOOH</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>CH₃COOH</td>
</tr>
<tr>
<td>Butyric acid</td>
<td>CH₃CH₂CH₂COOH</td>
</tr>
</tbody>
</table>

In common names, the positions of substituents are often given by α, β, γ, ....

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Chlorobutyric acid</td>
<td>COOH-CH₂CH₂CH₂CH₂Cl</td>
</tr>
<tr>
<td>β-Phenylpropionic acid</td>
<td>CH₃CH₂CH₂CH(C₆H₅)COOH</td>
</tr>
</tbody>
</table>

The simple dicarboxylic acids have common names, they are the ones usually used, and it is advisable to learn them at least through the six-carbon one. These are oxalic, malonic, succinic, glutaric, and adipic acid.

<table>
<thead>
<tr>
<th>Common Name</th>
<th>IUPAC Name</th>
<th>Common Name</th>
<th>IUPAC Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxalic acid</td>
<td>HOOC-CH₂-CHO</td>
<td>Adipic acid</td>
<td>HOOC-CH₂-CH₂-CH₂-CHO</td>
</tr>
</tbody>
</table>

Systematic Names of Carboxylic Acids

IUPAC systematic names are derived from the name of the longest-chain alkane present (the parent compound), dropping the final -e, and adding -oic acid.

Examples:

- 3-Methylpentanoic acid
- (E)-2-Hexenoic acid

Dicarboxylic acids can be named similarly although most have common names that are the ones usually used.

- 3-Methylhexanedioic acid
- (Z)-4-Octenedioic acid

Aromatic Acids: Benzoic Acids

The carboxylic acids derived from benzene are named as derivatives of benzoic acid, using the standard notations to indicate positions of substituent groups.

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>m-Nitrobenzoic acid</td>
<td>COOH-C₆H₄-NO₂</td>
</tr>
<tr>
<td>2-Chloro-4-nitrobenzoic acid</td>
<td>COOH-C₆H₄-ClNO₂</td>
</tr>
</tbody>
</table>

Salts of Carboxylic Acids

To name a salt, use the name of the cation (sodium, ammonium, etc.) followed by the name of the acid with "ic acid" changed to "ate."

<table>
<thead>
<tr>
<th>Cation</th>
<th>Anion</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>CO₂⁻</td>
<td>Sodium benzoate</td>
</tr>
<tr>
<td>(CH₃CH₂CO₂)⁺</td>
<td>Mg²⁺</td>
<td>Magnesium propanoate</td>
</tr>
</tbody>
</table>

Physical Properties of Carboxylic Acids

Carboxylic acids are polar protic molecules. They form strong hydrogen bonds. One example of this is that they exist as dimers in the liquid state.

The boiling points are about 20 °C higher than alcohols of comparable size.

Carboxylic acids, in neutral solvents, have solubility properties similar to those of alcohols. The first members of the aliphatic series (formic acid through butanoic acid) are miscible with water. Water solubility decreases with increasing chain length, with hexanoic acid being marginally soluble. On neutralization, because of ionic salt formation, most carboxylic acids become water soluble.
The Acid Strength of Carboxylic Acids

Carboxylic acids are weaker acids than mineral acids like HCl, HNO₃, or H₂SO₄, but they are more acidic than organic weak acids such as aliphatic alcohols. Carboxylic acids are converted into their carboxylate salts by aqueous solutions of hydroxide.

\[
\text{RCOOH} + \text{HO}^- / \text{H}_2\text{O} \rightarrow \text{RCO}_2^- + \text{H}_3\text{O}^+ \\
\text{Carboxylate anion of resulting salt}
\]

Aqueous solutions of mineral acids convert the salts back into the carboxylic acids.

Large carboxylic acids with limited or no solubility in water (those with 6 or more C’s per carboxyl group) may be solubilized through their carboxylate salts:

\[
\text{R-COOH} + \text{Na}^+ / \text{OH}^- \rightarrow \text{R-CO}_2^-\text{Na}^+ + \text{H}_2\text{O} \\
\text{Water insoluble} \rightarrow \text{Water soluble}
\]

These solubility properties are the basis for separating carboxylic acids from neutral organic compounds.

A Comparison of the Acid Strength of Carboxylic Acids and Alcohols

Carboxylic acids are considerably more acidic than alcohols in the absence of special electronic influences.

\[
\text{RCOOH} + \text{H}_2\text{O} \rightleftharpoons \text{RCO}_2^- + \text{H}_3\text{O}^+ \quad \text{pK}_a \sim 5 \\
\text{ROH} + \text{H}_2\text{O} \rightleftharpoons \text{RO}^- + \text{H}_3\text{O}^+ \quad \text{pK}_a \sim 16
\]

The enhanced acidity of carboxylic acids is attributed to the greater stability of the carboxylate anion compared with the alkoxide anion, which shifts the equilibrium more to the product side.

Resonance theory explains this stability through two equivalent resonance structures that contribute to the hybrid.

\[
\text{[Resonance structures]} \rightleftharpoons \text{Hybrid}
\]

X-ray analysis of sodium formate shows equivalent C-O bond lengths of 1.27 Å, consistent with this picture of a resonance hybrid.

Effect of Substituents on Acidity

Any factor that stabilizes the anion more than it stabilizes the acid should increase acidity (decrease the magnitude of pKₐ). Any factor that destabilizes the anion relative to the acid should decrease acidity.

\[
\text{RCOOH} + \text{H}_2\text{O} \rightleftharpoons \text{RCO}_2^- + \text{H}_3\text{O}^+
\]

Electronic Influences

The electronic effect of a substituent G operates more strongly on the anion (charged species) than on the carboxylic acid (neutral species).

\[
\begin{align*}
G & \text{[Electron withdrawal]} \\
\text{Stabilizes the anion and increases acidity} & \\
\text{G} & \text{[Electron release]} \\
\text{Destabilizes the anion and decreases acidity}
\end{align*}
\]
Some Examples of Substituent Effects

Electron-withdrawing α-substituents increase acidity:

\[
\begin{align*}
\text{pK}_a & \quad \text{OH} \quad \text{Cl} \quad \text{OH} \\
2.86 & \quad 1.48 & \quad 0.70
\end{align*}
\]

The more remote an electron-withdrawing substituent is from the carbonyl group, the less its effect:

\[
\begin{align*}
\text{pK}_a & \quad 2.85 \quad 4.05 \quad 4.50 \\
2\text{-Chlorobutanoic acid} & \quad 3\text{-Chlorobutanoic acid} & \quad 4\text{-Chlorobutanoic acid}
\end{align*}
\]

Substituent Effects in Benzoic Acids

Substituents introduced into the \textit{para} position of a benzoic acid affect the acidity as expected for the electronic influence on the stability of the benzoate anion:

\[
\begin{align*}
\text{pK}_a & \quad \text{NO}_2 \quad \text{Cl} \\
3.41 & \quad 3.98 \quad 4.19 \quad 4.36
\end{align*}
\]

Esters

Their two-part names follow the pattern:

[Name of alkyl or aryl group derived from parent alcohol] [Name of carboxylate ion derived from parent acid]

Examples:

- Made from ethanol and propanoic acid, so name is ethyl propanoate.
- Made from phenol and 3-methylbutanoic acid, so name is phenyl 3-methylbutanoate.

Esters are hydrogen-bond acceptors, enhancing their water solubility, but they are not hydrogen-bond donors, lacking a hydrogen on oxygen. Consequently, they cannot associate and so have low boiling points and high volatility. Fortunately, they have pleasant, fruit-like odors.

Carboxylic Anhydrides

As the term implies, they are prepared by removing a molecule of water from between two carboxyl groups. They are usually named from the parent acid, simply by replacing the word “acid” with “anhydride.”

Examples:

- Parent acid is propionic acid, so this is propionic anhydride.
- Parent acid is succinic acid, so this is succinic anhydride.

Acyl Chlorides (Acid Chlorides)

These are named from the parent acid by dropping “-ic acid” from its name and replacing it with “-yl chloride.”

Example:

- Propionyl chloride

NOTE: Both of the above types of derivatives have intermolecular attractions similar to those of esters, and so they have boiling points in the same range as esters of comparable size.

Both of these types of derivatives are important, powerful donors of their acyl groups and find much use in synthesis.
Amides
The amides considered here need to be distinguished from the metal amide bases like NaNH$_2$ and LiN(i-Pr)$_2$ studied earlier. The present ones are of general structure R$_2$CNRR$''$ where the different R's may be H's, alkyl groups, or aryl groups. They are named by dropping "-ic acid" from the name of the parent acid and adding "amide."

Examples:

<table>
<thead>
<tr>
<th>Name</th>
<th>MP (°C)</th>
<th>BP (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetamide</td>
<td>82</td>
<td>221</td>
</tr>
<tr>
<td>N-Methylacetamide</td>
<td>28</td>
<td>205</td>
</tr>
<tr>
<td>N,N-Dimethylacetamide</td>
<td>-20</td>
<td>166</td>
</tr>
</tbody>
</table>

Note how both MP and BP decrease with decreasing opportunity for intramolecular hydrogen bonding.

Nitriles
These derivatives are named by adding the suffix "-nitrile" to the name of the parent hydrocarbon, with the C of the CN group counting as part of the parent. Note: chain numbering begins with the nitrile C.

When the CN is attached to a cyclic parent, add "carbonitrile" to the parent name.

Examples:

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Chloropropanenitrile</td>
<td><img src="structure_3-chloropropanenitrile" alt="Structure" /></td>
</tr>
<tr>
<td>Cyclopentanecarbonitrile</td>
<td><img src="structure_cyclopentanecarbonitrile" alt="Structure" /></td>
</tr>
</tbody>
</table>

Infrared Spectroscopy
Acyl compounds show characteristic IR absorption due to C=O stretch. This band is typically very prominent. The exact location (frequency) depends on the type of group (acid, ester, amide, etc.) and its electronic environment.

1) Carboxylic acids are readily identified by a C=O stretch near 1715 cm$^{-1}$ and a broad O-H stretch between 2400-3500 cm$^{-1}$.
2) Esters show the C=O stretch somewhere between 1735-1750 cm$^{-1}$ and C-O stretch at 1000-1300 cm$^{-1}$.
3) Acyl chlorides have their C=O band at 1785-1815 cm$^{-1}$.
4) Anhydrides have two C=O bands in the region 1750-1820 cm$^{-1}$.
5) Amides have their C=O band at 1640-1650 cm$^{-1}$ and N-H (if present) stretch in the range 3140-3500 cm$^{-1}$ (two bands if has NH$_2$, one if NH).
6) The related derivative type nitriles have their characteristic absorption in the triple bond stretching region, at about 2250 cm$^{-1}$.

Inductive and Resonance Effects
The electronic environment of a carbonyl affects its vibrational frequency, often in a predictable way. The frequency is a measure of a C=O group's bond multiplicity. As usual in IR spectrometry, as bond order decreases, C=O vibrational frequency decreases.

Examples of how to predict approximately where a C=O absorption will be:

A simple ketone (or carboxyl) C=O absorbs at about 1715 cm$^{-1}$ and may be represented by these resonance forms, which indicate the carbonyl bond order is between single and double.

Conjugation effect: This introduces a contribution by one additional resonance form, one that decreases the bond multiplicity. So the vibrational frequency of the C=O group is decreased (to about 1695 cm$^{-1}$).

Inductive effect: Bonding a chlorine to the carbonyl, as in an acyl chloride, decreases the contribution of the C-O resonance form, and thus increases the multiplicity of the carbonyl. This increases its vibrational frequency (to about 1800 cm$^{-1}$).

IR Spectrum of Propanoic Acid
"neat", i.e., without dilution)
The C=O stretch frequency is at 1715 cm$^{-1}$; in the absence of hydrogen bonding (which enhances carbonyl single-bond character) it would be at about 1760 cm$^{-1}$.
**1H NMR Spectroscopy**

The acidic proton of a carboxylic acid is highly deshielded and appears far downfield in the range $\delta$ 10-12. Protons on a carbon $\alpha$ to a carbonyl appear in the $\delta$ 2.0-2.5 region. The chemical shifts, splitting patterns, and relative intensities of the H resonances of a typical ester are depicted in this methyl propionate spectrum.

![Methyl Propionate Spectrum](image1.png)

---

**13C NMR Spectroscopy**

The carbonyl carbons of aldehydes and ketones appear at $\delta$ 180-220. When an O, N, or Cl is attached in place of the aldehyde H, the carbonyl carbon absorbs at a higher field position, $\delta$ 160-180.

![13C NMR Resonances](image2.png)

A nitrile carbon absorbs even further upfield, at $\delta$ 115-120.

---

**Preparation of Carboxylic Acids**

**Oxidation of Alkenes**

Alkenes can be oxidatively cleaved to carboxylic acids by use of either KMnO$_4$ or ozone.

\[
\begin{align*}
R-CH=CH-R' & \rightarrow (1) KMnO_4, OH^- (hot) \\
& \rightarrow (2) H_2O \\
R-CH-CH-R' & \rightarrow (1) O_3 \\
& \rightarrow (2) H_2O_2 \\
& \rightarrow R' - COOH + R - COOH
\end{align*}
\]

**Oxidation of Aldehydes and 1° Alcohols**

Aldehydes are easily oxidized to carboxylic acids, even by mild oxidants such as Ag(NH$_3$)$_2^+$OH-, which is used in the Tollens’ test for distinguishing aldehydes from ketones. Stronger reagents such as chromic acid (H$_2$CrO$_4$) or KMnO$_4$ can oxidize either aldehydes or 1° alcohols to carboxylic acids.

\[
\begin{align*}
R-CHO & \rightarrow Ag(NH_3)_2^+OH^-
\end{align*}
\]

\[
\begin{align*}
R-OH & \rightarrow H_2CrO_4 \text{ or KMnO}_4 \\
& \rightarrow R-COOH
\end{align*}
\]

---

**Oxidation of Alkylbenzenes**

Vigorous oxidation by KMnO$_4$ of primary and secondary (but not tertiary) alkyl groups directly attached to a benzene ring produces aromatic acids.

\[
\begin{align*}
C_6H_5R' & \rightarrow (1) KMnO_4, HO^-, H_2O \\
& \rightarrow (2) H_2O \\
& \rightarrow C_6H_4R' - COOH
\end{align*}
\]

The benzene ring of an alkylbenzene can be converted to a carboxyl group by ozonolysis.

\[
\begin{align*}
C_6H_5R & \rightarrow (1) O_3, CH_3COOH \\
& \rightarrow (2) H_2O_2 \\
& \rightarrow R-COOH
\end{align*}
\]
Oxidative Cleavage of Methyl Ketones

The haloform reaction converts methylketones to carboxylic acids (on acidification of the product).

\[
\text{CCH}_3\text{O} \rightarrow \text{Acetophenone} \xrightarrow{\text{Br}_2, \text{NaOH}, \text{H}_2\text{O}} \text{CO}_2^- \text{Na}^+ \xrightarrow{\text{H}_2\text{O}} \text{Benzoic acid}
\]

Hydrolysis of Cyanohydrins and Other Nitriles

Cyanohydrins, prepared by addition of HCN to aldehydes or ketones, can be hydrolyzed to \(\alpha\)-hydroxy acids.

Nitriles can also be prepared by nucleophilic substitution reactions of 1° alkyl halides with sodium cyanide. Hydrolysis then provides a carboxylic acid of increased chain length.

\[
\text{Br} \xrightarrow{\text{NaCN}} \text{NC} \xrightarrow{\text{H}_2\text{O}, \sim 80\%} \text{C}_3\text{H}_6\text{N}_2\text{O} \xrightarrow{\sim 80\%} \text{C}_3\text{H}_6\text{O}_4
\]

Because of the elimination-promoting basicity of cyanide ion, the S_N2 reaction proceeds in good yield only with CH_3X and 1° halides. Aryl halides (except for those with \(\alpha\)- or \(p\)-nitro groups) do not readily undergo nucleophilic substitution reactions.

Hydrolysis of nitriles may be carried out under either basic or acidic conditions.

Carbonation of Grignard Reagents

A more general way to prepare carboxylic acids from alkyl or aryl halides is by carbonation (reaction with CO_2) of the corresponding Grignard reagents.

The strongly nucleophilic organomagnesium reagents add to CO_2 to produce magnesium carboxylates. Acidification of these salts yields the carboxylic acids.

\[
\text{R}-\text{MgX} + \text{O} = \text{C} = \text{O} \rightarrow \text{Nu}^- \xrightarrow{\text{Nu-H}} \text{R}-\text{C}-\text{OH}
\]

All alkyl (1°, 2°, 3°) and aryl Grignard reagents undergo the carboxylation reaction. This reaction is accomplished by either bubbling dry gaseous CO_2 through an ether solution of the Grignard reagent or by pouring the Grignard reagent onto crushed dry ice (solid CO_2).

Nucleophilic Addition-Elimination at Acyl Carbon

Aldehydes and ketones undergo nucleophilic additions to the carbonyl group:

\[
\text{R}^\text{m}\text{C}=\text{O} + \text{Nu}^- \rightarrow \text{Nu-H} + \text{R}^\text{m}\text{C}^-\text{Nu} + \text{X}^-
\]

A typical reaction of carboxylic acids and their derivatives is nucleophilic addition-elimination. The first step is nucleophilic addition to the carbonyl to give a tetrahedral intermediate, but the presence of a good leaving group (X) at this site results in an elimination that regenerates the trigonal carbonyl.

This reaction mechanism is employed in many biological systems, and biochemists call them acyl transfer reactions.
Example: Hydrolysis of an Acyl Chloride

**Nucleophilic addition**

\[
\begin{align*}
\text{Nucleophile} & \quad \text{R-C-Cl} + \text{Nu}^{-} \rightarrow \text{R-C-Nu} + \text{H}^{+} + \text{H}_{2}\text{O} \\
\text{Tetrahedral intermediate} & \quad \text{R-C-Nu} + \text{Nu}^{-} \rightarrow \text{R-C-Nu}^{-} + \text{H}^{+} + \text{H}_{2}\text{O}
\end{align*}
\]

This reaction proceeds well because of the great reactivity of the acyl chloride towards nucleophilic addition and the good leaving group ability of Cl\(^{-}\) in the cleavage step.

**Elimination**

\[
\begin{align*}
\text{R-C-Cl} + \text{Nu}^{-} \rightarrow \text{R-C-Nu} + \text{H}^{+} + \text{H}_{2}\text{O}
\end{align*}
\]

Important Factors in the Addition-Elimination Reaction

**Reactivity of the Acyl Carbon**

Electronic influences that increase the electropositive character of the acyl carbon enhance the rate of nucleophilic addition.

As the electronegativity of X increases, the rate of nucleophilic addition increases.

**Stability of the Leaving Group**

As the stability of X\(^{-}\) increases, it becomes a better leaving group.

Acid Catalysis

Acid catalysis is important in both the addition and elimination steps.

**Protonation of the carbonyl**

\[
\begin{align*}
\text{R-C-X} + \text{H-Nu}^{-} \rightarrow \text{R-C-Nu} + \text{H}^{+} + \text{H}_{2}\text{O}
\end{align*}
\]

Provides electrophilic catalysis of addition.

**Electrophilic catalysis of elimination**

\[
\begin{align*}
\text{R-C-Nu} + \text{Nu}^{-} \rightarrow \text{R-C-Nu}^{-} + \text{H}^{+} + \text{H}_{2}\text{O}
\end{align*}
\]

**Protonation of leaving group**

\[
\begin{align*}
\text{R-C-X} + \text{H-Nu}^{-} \rightarrow \text{R-C-Nu} + \text{H}^{+} + \text{H}_{2}\text{O}
\end{align*}
\]

**Deprotonation**

\[
\begin{align*}
\text{R-C-Nu}^{-} + \text{Nu}^{-} \rightarrow \text{R-C-Nu} + \text{H}^{+} + \text{H}_{2}\text{O}
\end{align*}
\]

Relative Reactivity of Acyl Compounds

The basicity of the leaving group can explain the relative reactivity of acid derivatives below. The weaker the basicity of the leaving group, the more reactive the acid derivative.

\[
\begin{align*}
\text{RC-Cl} > \text{RC-OCR} > \text{RC-OR'} > \text{RC-NR'R''}
\end{align*}
\]

Acyl chloride Acid anhydride Ester Amide

In general, a less reactive acyl compound can be prepared from more reactive acyl compounds. The reverse is usually difficult and, when possible, requires special reagents.
**Synthesis of Acyl Chlorides**

Because of their reactivity, acyl chlorides must be prepared under conditions that exclude exposure to good nucleophiles like water. Common reagents that convert carboxylic acids into acyl chlorides are phosphorus trichloride (PCl₃), phosphorus pentachloride (PCl₅), and thionyl chloride (SOCl₂).

**Typical Synthetic Procedures**

The carboxylic acid is heated with the reagent, with or without the presence of an inert solvent.

\[
\text{Benzoic acid} + \text{SOCl}_2 \xrightarrow{\text{heat}} \text{Benzoyl chloride}
\]

Thionyl chloride is an especially convenient reagent because the byproducts are gases and easily removed. Excess thionyl chloride is easy to remove by distillation.

---

**Use of Phosphorus Pentachloride**

\[
\text{3,5-Dinitrobenzoic acid} + \text{POCl}_3 \xrightarrow{\text{heat}} \text{3,5-Dinitrobenzoyl chloride}
\]

The acyl chlorides are usually isolated and purified, often by distillation. They are reasonably stable in the absence of water and other nucleophiles.

Both SOCl₂ and PCl₅ are strong electrophiles that transform the hydroxyl into a much better leaving group, thereby promoting substitution at the acyl carbon.

---

**Mechanism for Acyl Chloride Synthesis Using Thionyl Chloride**

\[
\begin{align*}
\text{RC} \equiv \text{O} & \xrightarrow{\text{Cl}^-} \text{RC} \equiv \text{O}^- \\
\text{RC} \equiv \text{O}^- & \xrightarrow{\text{Cl}^-} \text{RC} \equiv \text{O}^- \text{Cl}^- \\
\text{RC} \equiv \text{O}^- \text{Cl}^- & \xrightarrow{\text{H}^+} \text{RC} \equiv \text{O}^- \text{H}^+ \\
\text{RC} \equiv \text{O}^- \text{H}^+ & \xrightarrow{\text{Cl}^-} \text{RC} \equiv \text{O}^- \text{Cl}^- \\
\text{RC} \equiv \text{O}^- \text{Cl}^- & \xrightarrow{\text{SO}_2 + \text{HCl}} \text{acyl chloride}
\end{align*}
\]

---

**Reactions of Acyl Chlorides**

Acyl chlorides are easily converted into other acyl compounds (acid anhydrides, esters, amides, etc.) by reaction with the appropriate nucleophile.

**General Scheme**

\[
\begin{align*}
\text{R}^+\text{CO}^- & \xrightarrow{\text{Na}^+} \text{R}^+\text{OCR}' \text{ Anhydride} \\
\text{R}^+\text{OH} & \xrightarrow{\text{base}} \text{R}^+\text{OCR}' \text{ Ester} \\
\text{NH}_3 & \xrightarrow{\text{RC-NH}_2} \text{R}^+\text{OCR}' \text{ Amide} \\
\text{R}^+\text{NHR}^' & \xrightarrow{\text{RC-NH}_2} \text{N-Substituted amide} \\
\text{R}^+\text{NR}'^\text{N} & \xrightarrow{\text{RC-NHR}^'} \text{N,N-Disubstituted amide}
\end{align*}
\]
Hydrolysis of Acyl Chlorides

Hydrolysis converts acyl chlorides into carboxylic acids. Note that reaction with water yields HCl as a byproduct. Alkaline hydrolysis proceeds faster than acid hydrolysis.

These reactions are rarely useful; usually they are accidental and need to be guarded against.

\[
\begin{align*}
&\text{slower} \\
\text{O} &\quad \text{RCCl} + \text{H}_2\text{O} \rightarrow \text{RCO}_2\text{H} + \text{HCl}
\end{align*}
\]

\[
\begin{align*}
&\text{faster} \\
\text{HO}^- &\quad \text{RCCl} + \text{H}_2\text{O} \rightarrow \text{RCO}_2^- + \text{Cl}^-
\end{align*}
\]

Carboxylic Acid Anhydrides

The reaction of a carboxylic acid and an acyl chloride in the presence of pyridine (a base) gives carboxylic acid anhydrides that may contain different R groups.

\[
\begin{align*}
\text{RCOOH} + \text{R'CCL} &\quad \rightarrow \quad \text{RC-O-CCR'} + \text{Pyridinium chloride} \\
\text{RCO}_2^- + \text{Cl}^- &\quad \rightarrow \quad \text{RCO}_2\text{H} + \text{HCl}
\end{align*}
\]

On heating, dicarboxylic acids yield cyclic anhydrides, if they have 5- or 6-membered rings.

\[
\begin{align*}
\text{Phthalic acid} &\quad \rightarrow \quad \text{Phthalic anhydride}
\end{align*}
\]

Reactions of Carboxylic Acid Anhydrides

Carboxylic acid anhydrides and acyl chlorides show parallel patterns of reactions. The latter react faster because of the better leaving group ability of Cl.

\[
\begin{align*}
\text{faster} \\
\text{O} &\quad \text{RC-Cl} + :\text{Nu} \rightarrow \text{RC-Nu} + \text{Cl}^-
\end{align*}
\]

\[
\begin{align*}
\text{slower} \\
\text{O} &\quad \text{RC-O-OCR'} + :\text{Nu} \rightarrow \text{RC-Nu} + \text{R'CO}_2^-
\end{align*}
\]

Examples:

\[
\begin{align*}
\text{O} &\quad \text{O} \\
\text{R'C-OCR'} &\quad \text{R'C-OR''} + \text{R'COOH}
\end{align*}
\]

Esters

Synthesis of Esters

Direct Esterification of Carboxylic Acids

Carboxylic acids and alcohols react in the presence of a small amount of strong acid to give esters.

Carboxylic acids and alcohols react in the presence of a small amount of strong acid to give esters.

\[
\begin{align*}
\text{COOH} &\quad + \text{CH}_3\text{OH} \rightarrow \text{COOCH}_3 \\
\text{H}^+ &\quad \rightarrow \quad \text{Methyl benzoate}
\end{align*}
\]

Esterifications are acid-catalyzed equilibrium reactions. Catalytic amounts of concentrated sulfuric acid or hydrochloric acid are used. Usually a large excess of the alcohol (10- or 15-fold) is used to drive the equilibrium to the product side. Product formation can also be promoted by removing the water as it is formed.
Mechanistic Studies by Isotopic Labeling

Insight into the key bonding changes during esterification was obtained by studies using isotopically enriched methanol.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{C}-\text{OH} + \text{CH}_3\text{D} & \xrightleftharpoons{H^+} \text{C}_6\text{H}_5\text{C}-\text{OCH}_3 + \text{H}_2\text{O}
\end{align*}
\]

All the isotopic label appears in the methoxy oxygen.

This result rules out an Sn2 mechanism:

\[
\begin{align*}
\text{C}_6\text{H}_5\text{C}-\text{OH} + \text{CH}_3\text{D} & \xrightarrow{H^+} \text{C}_6\text{H}_5\text{C}-\text{OCH}_3 + \text{H}^+ \text{D} \\
\text{C}_6\text{H}_5\text{C}-\text{OCH}_3 + \text{H}_2\text{D} & \xrightarrow{H^+} \text{C}_6\text{H}_5\text{C}-\text{OH} + \text{H}_2\text{O}
\end{align*}
\]

This mechanism for esterification is consistent with the incorporation of the isotopic label:

\[
\begin{align*}
\text{C}_6\text{H}_5\text{COH} + \text{CH}_3\text{D} & \xrightleftharpoons{H^+} \text{C}_6\text{H}_5\text{COCH}_3 + \text{H}_2\text{D}
\end{align*}
\]

A Mechanism for Acid-Catalyzed Hydrolysis of Esters

Since every step is reversible, the reverse of the esterification scheme is the mechanism for the acid-catalyzed hydrolysis of esters.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{COCH}_3 + \text{H}_2\text{D} & \xrightarrow{H^+} \text{C}_6\text{H}_5\text{COH} + \text{CH}_3\text{D}
\end{align*}
\]

The direction of the reaction is controlled by the relative concentrations of water versus alcohol.

Steric Factors in Direct Esterification

The rate of esterification slows down as bulky groups are introduced into the structure near the carbonyl group of the acid or in the alcohol.

\[
\begin{align*}
\text{HCOOH} & > \text{CH}_3\text{COOH} > \text{R'}\text{CH}_2\text{COOH} > \text{R''}2\text{CHCOOH} > \text{R''}3\text{COOH (no reaction)}
\end{align*}
\]

Relative reactivity of RCOOH

Relative reactivity of R'OH

In the presence of strong acids, tertiary alcohols tend to dehydrate rather than undergo esterification reactions.

\[
\begin{align*}
\text{RCOOH} + \text{(CH}_3)_3\text{COH} & \xrightarrow{H^+} \text{RCOO(C(CH}_3)_3}
\end{align*}
\]

Sterically hindered esters have to be prepared by other methods.
Esters from Acyl Chlorides

The reaction of alcohols with acyl chlorides gives esters. No acid catalysis is needed, but a tertiary amine, usually pyridine, is usually added to capture the HCl formed and drive the reaction to completion. These bases also appear to enhance the reactivity of acyl halides.

\[
\text{Benzoyl chloride} + \text{EtOH} \rightarrow \text{Ethyl benzoate} + \text{Pyridinium chloride}
\]

Esters from Carboxylic Acid Anhydrides

Alcohols react with acid anhydrides to give esters. As seen earlier, acyl chlorides and carboxylic acid anhydrides often undergo similar nucleophilic substitution reactions at the acyl carbon.

\[
\text{Acetic anhydride} + \text{Propyl alcohol} \rightarrow \text{Propyl acetate} + \text{CH}_3\text{COOH}
\]

Cyclic Anhydrides Undergo Similar Reactions

Phthalic anhydride + sec-Butyl alcohol \rightarrow sec-Butyl hydrogen phthalate

Intramolecular Esterification: Lactone Formation

Carboxylic acids that contain alcohol functions that can react intramolecularly to form 5- or 6-membered cyclic esters (lactones) do so very readily.

\[
\text{4-Hydroxybutanoic acid (\(\gamma\)-Hydroxybutyric acid)} \rightarrow \text{\(\gamma\)-Butyrolactone} + \text{H}_2\text{O}
\]

A trace of strong acid catalyst hastens the conversion.

Transesterification

This is a process whereby the ester of one alcohol may be converted into the ester of a second alcohol by the equilibrium:

\[
\text{RCOR}' + \text{R''OH} \rightleftharpoons \text{RCOR''} + \text{R'OHH}
\]

An example

\[
\text{Methyl acrylate} + \text{Butyl alcohol} \rightarrow \text{Butyl acrylate} + \text{Methyl alcohol}
\]

The equilibrium is shifted to the product side by using an excess of butyl alcohol and/or distilling out the lower boiling methanol from the reaction mixture.

Base-Promoted Hydrolysis of Esters: Saponification

Base-promoted hydrolysis of esters is called saponification (from the Latin sapo, soap) because traditional soap-making involves the alkaline hydrolysis of fats (esters of glycerol).

\[
\text{RCOR}' + \text{NaOH} \rightarrow \text{RCO}_2\text{Na}^+ + \text{R'OHH}
\]

In the case of soaps, the R in the carboxylate ion typically is a straight-chain alkyl containing eleven to seventeen carbon atoms.
Two Possible Mechanisms for the Alkaline Hydrolysis of Esters

(1) Addition-Elimination:

\[
\begin{align*}
R\text{CO}_2^- + NaOH & \rightarrow \text{Tetrahedral Intermediate} \\
& \rightarrow RCO + R'\text{Na}^+ \\
R\text{COH} + R'\text{Na}^+ & \rightarrow \text{fast} \\
& \rightarrow RCO_2^- + R'\text{OH}
\end{align*}
\]

(2) SN2 Nucleophilic Substitution:

\[
\begin{align*}
R\text{CO}_2^- + NaOH & \rightarrow \text{Transition state} \\
& \rightarrow \text{RCH} - \text{Na}^+ \\
R\text{COH} + \text{R'OH} & \rightarrow \text{fast} \\
& \rightarrow RCO + R'\text{Na}^+
\end{align*}
\]

To distinguish between these possibilities, information on the mechanism was obtained by carefully designed experiments using stereochemical and isotopic probes.

Some Observations

Kinetic Studies

The rate of alkaline hydrolysis follows the second-order rate expression:

\[
\text{rate} = k \cdot [\text{RCO}_2\text{R'}] \cdot [\text{HO}^-]
\]

Since this result is consistent with either mechanism, it cannot elucidate the operating pathway for alkaline hydrolysis.

Stereochemical Probe

An ester with a stereocenter at the alkyl carbon can serve as a stereochemical probe of the mechanism. Such a probe molecule may be synthesized by the following stereospecific reaction.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CCl} + \text{C}_2\text{H}_5\text{OH} & \rightarrow \text{C}_6\text{H}_5\text{CO}\text{CH}_2\text{CH}_3 \quad \text{(S)-(+)2-Butanol} \\
(100\% \text{ ee})
\end{align*}
\]

Predictions of Stereochemical Outcomes

Retention of configuration

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CO}_2^- + \text{C}_2\text{H}_5\text{OH} & \rightarrow \text{C}_6\text{H}_5\text{COH} + \text{C}_2\text{H}_5\text{OH} \\
(\text{S})-(+)2-\text{Butanol}
\end{align*}
\]

Inversion of configuration

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CO}_2^- + \text{C}_2\text{H}_5\text{OH} & \rightarrow \text{C}_6\text{H}_5\text{COH} + \text{C}_2\text{H}_5\text{OH} \\
(\text{R})-(+)2-\text{Butanol}
\end{align*}
\]

Isotopic Probe

It is possible to prepare esters enriched with oxygen-18 in either the carbonyl or alkoxy oxygen position. The location of the isotopic label after alkaline hydrolysis provides mechanistic information.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{C}^{18}\text{OCH}_2\text{CH}_3 + \text{NaOH} & \rightarrow \text{CH}_3\text{CH}_2\text{CO}_2\text{Na} + \text{CH}_3\text{CH}_2^{18}\text{OH} \\
\text{Ethyl propanoate} & \rightarrow \text{Sodium propanoate} \quad \text{Ethanol}
\end{align*}
\]

The recovery of all the isotopic label in the ethanol product is consistent with nucleophilic attack by the hydroxide ion at the acyl carbon followed by cleavage of the acyl carbon-alkoxy oxygen bond.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{C}^{18}\text{OCH}_2\text{CH}_3 & \rightarrow \text{CH}_3\text{CH}_2\text{CO}_2\text{Na} + \text{CH}_3\text{CH}_2^{18}\text{OH}
\end{align*}
\]

That is, the addition-elimination mechanism is employed.

Stereochemical Outcome

Alkaline hydrolysis of (S)-2-butyl benzoate produced only (S)-(+)2-butanol which is consistent with mechanism (1), cleavage at the acyl carbon.
Amides

Amides like amines are classified according to the number of substituents on the ammonia-type nitrogen:

\[ RCNH \]

1°

\[ R CNHR' \]

2°

\[ R CNR'R'' \]

3°

Synthesis of Amides from Acyl Chlorides

The nucleophiles ammonia and primary and secondary amines all react rapidly with acyl chlorides to produce amides. For complete reaction, the byproduct HCl must be neutralized.

\[ \text{RCCl} + 2 \text{R''NH}_2 \rightarrow \text{RCNH}_2 + \text{R''NH}_3 + \text{Cl}^- \]

Secondary amide

(N-substituted amide)

Note: Two equivalents of the amine are required for complete reaction.

Tertiary amines react with acyl chlorides to produce salts, not stable amide products.

\[ \text{RCCl} + \text{R''N}: \rightarrow \text{RCNR''}_2 \text{Cl}^- \]

An acylammonium chloride

Amides from Carboxylic Acid Anhydrides

Analogous reactions occur between acid anhydrides and ammonia or amines.

Acetic anhydride

\[ \text{O} + \text{O} \]

\[ \text{CH}_3\text{COCCH}_3 + :\text{NH}_3 \rightarrow \text{H}_2\text{O} \]

Nucleophilic attack at acyl carbon

Amides from Esters

Esters undergo nucleophilic addition-elimination at the acyl carbon with nitrogen nucleophiles such as ammonia (ammonolysis) or amines (amination).

\[ \text{O} \]

\[ \text{CH}_3\text{COCH}_3 + :\text{NH}_3 \rightarrow \text{CH}_3\text{CNH}_2 + \text{C}_2\text{H}_5\text{OH} \]

Amides from Carboxylic Acids

Carboxylic acids react with aqueous ammonia to produce ammonium carboxylates in an acid-base reaction:

\[ \text{RCOH} + 2 \text{NH}_3 \rightarrow \text{RCO}^- + \text{NH}_4^+ \]

Recovery of the ammonium carboxylate and heating of the dry salt leads to dehydration and formation of the amide.

\[ \text{RCNH}_2 + \text{H}_2\text{O} \rightarrow \text{RCNH}_2 + \text{H}_2\text{O} \]

As the dry salt

Heat

This method is generally not used in organic synthesis because the vigorous heating required will often decompose the sample.
Amides by a Condensation Synthesis Using Dicyclohexylcarbodiimide (DCC)

Amides may be prepared from carboxylic acids and amines in an indirect dehydration synthesis using DCC. This method was developed for synthesizing the amide bond in biological systems under very mild conditions.

\[
\begin{align*}
\text{DCC} + \text{RCOH} + \text{R'}\text{N} & \rightarrow \text{RCNH}^+ + \text{C}_6\text{H}_{11}\text{NHCNHC}_6\text{H}_{11}\\
\text{Amide} & \quad \text{N,N'-Dicyclohexylurea}
\end{align*}
\]

Note that the H\(_2\)O byproduct ends up hydrating the diimide function to an urea compound.

A Proposed Mechanism for the DCC Synthesis of Amides

The central carbon of the diimide function is electropositive and subject to nucleophilic attack.

\[
\begin{align*}
\text{Nucleophilic addition} & \quad \text{Fast deprotonation and protonation}\\
\text{RC-OH} & \rightarrow \text{C}_6\text{H}_{11}\text{N}=\text{C}=\text{N}\text{C}_6\text{H}_{11}\\
\text{R-C-O-H} & \rightarrow \text{H}^+ + \text{C}_6\text{H}_{11}\text{N}=\text{C}=\text{N}\text{C}_6\text{H}_{11}\\
\text{R'-NH}_2 & \rightarrow \text{RCNH}^+ + \text{C}_6\text{H}_{11}\text{NHCNHC}_6\text{H}_{11}\\
\text{Amide} & \quad \text{N,N'-Dicyclohexylurea}
\end{align*}
\]

Hydrolysis of Amides

Amides hydrolyze much more slowly than other acyl derivatives of carboxylic acids such as acyl chlorides, esters, or anhydrides. This decreased reactivity is associated with the greater stability of the amide functional group compared with the other acyl derivatives.

This enhanced stability is explained by resonance theory through these contributors to a hybrid structure:

\[
\begin{align*}
\text{Amides are neutral compounds despite the presence of the amino-type nitrogen. Their decreased base strength compared with amines is also explained by the resonance stabilization of the amide function illustrated above, which much diminishes the electron density on the nitrogen. Much of this resonance stabilization is lost when the amide group is protonated.}
\end{align*}
\]

Hydrolysis of Amides: Mechanisms

The rate of hydrolysis of amides is faster at lower or higher pH than at pH 7.

At low pH (electrophilic catalysis)

\[
\begin{align*}
\text{RC-NH}_2 + \text{H}_2\text{O} & \rightarrow \text{RC-NH}_2 + \text{H}_2\text{O} + \text{H}^+ + \text{NH}_3 & \text{enhanced reactivity}\\
\text{RCO}_2\text{H} + \text{NH}_3 & \rightarrow \text{RCO}_2\text{H} + \text{NH}_3 + \text{H}^+ & \text{nucleophile}
\end{align*}
\]

At high pH (a better nucleophile)

\[
\begin{align*}
\text{RC-NH}_2 + \text{H}_2\text{O} & \rightarrow \text{RC-NH}_2 + \text{H}_2\text{O} + \text{OH}^- + \text{H}^+ & \text{nucleophile}\\
\text{RCO}_2\text{H} + \text{OH}^- & \rightarrow \text{RCO}_2\text{H} + \text{OH}^- + \text{H}^+ & \text{nucleophile}
\end{align*}
\]

N-Substituted and N,N-disubstituted amides react similarly. Typical hydrolysis conditions involve extensive heating of the amide in 6 M HCl or 40% aqueous NaOH.