Chapter 10. Carboxylic Acids and Derivatives

The common structural feature of all these compounds is that they contain an acyl group bonded to an electronegative atom or substituent that can act as a leaving group in substitution reaction.

10.1 Naming Carboxylic Acids and Derivatives

**Carboxylic Acids: RCO₂H**

1) Simple open-chain carboxylic acids
Replace the terminal –e of the alkane name with –oic acid.
The carboxyl group carbon is always numbered C1.

- 4-Methylpentanoic acid
- 3-Ethyl-6-methyloctanedioc acid

2) Cyclic carboxylic acids
Use the suffix –carboxylic acid.
The carboxylic acid carbon is attached to C1 on the ring but is not itself numbered.

- 3-Bromocyclohexanecarboxylic acid
- 5-Methylcyclopent-1-ene-carboxylic acid

There are a large number of acids with common names.
Acid Halides: RCOX
Acid halides are named by identifying first the acyl group and then the halide. The acyl group name is derived from the acid name by replacing the –ic acid ending with –yl, or the –carboxylic acid ending with –carbonyl.

Acetyl chloride (from acetic acid)  
Benzoyl bromide (from benzoic acid)  
Cyclohexanecarbonyl chloride (from cyclohexanecarboxylic acid)

Acid Anhydrides: RCO₂COR’
Replace the word acid with anhydride.

Acetic anhydride  
Benzoic anhydride  
Succinic anhydride

Amides: RCONH₂
1) Amides with an unsubstituted –NH₂ group are named by replacing the –oic acid or –ic acid ending with –amide, or by replacing the –carboxylic acid ending with –carboxamide.

Acetamide (from acetic acid)  
Hexanamide (from hexanoic acid)  
Cyclopentanecarboxamide (from cyclopentanecarboxylic acid)

2) If the nitrogen atom is substituted, the amide is named by first identifying the substituent group and then the parent. The substituents are preceded by the letter N to identify them as being directly attached to nitrogen.

N-methylpropanamide  
N,N-Diethylcyclohexanecarboxamide
Esters: $RCO_2R'$
First give the name of the alkyl group attached to oxygen and then identify the carboxylic acid. The –ic acid ending is replaced by –ate.

![Chemical structures of esters](image)

Ethyl acetate  Dimethyl malonate  tert-Butyl cyclohexanecarboxylate

Nitriles: $R\text{--C}≡\text{N}$
1) Simple acyclic nitriles are named by adding –nitrile as a suffix to the alkane name, with the nitrile carbon numbered C1.

![Chemical structure of 4-Methylpentanenitrile](image)

4-Methylpentanenitrile

2) Nitriles are named as derivatives of carboxylic acids by replacing the –ic acid or –oic acid ending with –onitrile, or by replacing the –carboxylic acid ending with –carbonitrile.

![Chemical structures of nitriles](image)

Acetonitrile (from acetic acid)  Benzonitrile (from benzoic acid)  2,2-Dimethylcyclohexanecarbonitrile (from 2,2-dimethylcyclohexanecarboxylic acid)

10.2 Occurrence and Properties of Carboxylic Acids and Derivatives

Carboxylic acids are foul in order, and form strong intermolecular hydrogen bonds. Most carboxylic acids exist as dimers held together by two hydrogen bonds, thereby giving high boiling points.

![Chemical structure of carboxylic acid dimer](image)

Carboxylic acid dimer
Esters are pleasant-smelling liquids, which are responsible for the fragrant aromas of fruits and flowers.

\[
\begin{array}{cccc}
\text{Methyl butanoate} & \text{Isopentyl acetate} & \text{Fat (R = C}_{11-17}\text{ chain)}
\end{array}
\]

![Methyl butanoate](from pineapples) ![Isopentyl acetate](from bananas) ![Fat](R = C_{11-17} chain)

Amides are less reactive than esters; this stability makes amide ideal linkages in peptide and proteins. Hydrogen bonding between amides increases their boiling points. A diverse range of biological events – from protein folding to the action of drugs – depend on hydrogen bonding between amides.

\[
\begin{array}{c}
\text{Acyl chlorides and anhydrides}
\end{array}
\]

Acyl chlorides and anhydrides are commonly used in the chemical and pharmaceutical industries. These groups are not found in nature due to their reactivity.

10.3 Acidity of Carboxylic Acids

- Acetic acid \( pK_a = 4.75 \)
- Ethanol \( pK_a = 16 \)
Why are carboxylic acids so much more acidic than alcohols even though both contain O-H groups?

Compare the relative stabilities of carboxylate anions versus alkoxide anions.

\[
\begin{align*}
\text{Ethoxide ion} & \quad \text{(localized charge)} \\
\text{Acetate ion} & \quad \text{(delocalized charge)}
\end{align*}
\]

The presence of an electron-withdrawing chlorine atom spreads out the negative charge on the anion and makes chloroacetic acid stronger than acetic acid.

\[
\begin{align*}
pK_a &= 4.75 \\
& 2.85 \\
& 1.48 \\
& 0.64
\end{align*}
\]

### 10.4 Synthesis of Carboxylic Acids

**Oxidation reactions**

- \(\text{O}_{2}\text{N-}\text{CH}_3\) + \(\text{KMnO}_4\) → \(\text{O}_{2}\text{N-}\text{CO}_2\text{H}\) (88%)
- \(\text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{-OH}\) + \(\text{CrO}_3\) → \(\text{CH}_3(\text{CH}_2)_8\text{C}^{-}\text{OH}\) (93%)
- \(\text{CH}_3(\text{CH}_2)_4\text{C}^{-}\text{H}\) + \(\text{AgNO}_3\) → \(\text{CH}_3(\text{CH}_2)_4\text{C}^{-}\text{OH}\) (85%)

Tollen’s reagent
From alkyl halide to carboxylic acid

\[
\begin{align*}
&\text{1. NaCN} \\
&\text{2. OH/H}_2\text{O} \\
&\text{3. H}_3\text{O}^+ \\
\end{align*}
\]

Fenoprofen (antiarthritic agent)

10.5 Nucleophilic Acyl Substitution Reactions
Nucleophilic addition vs. acyl substitution – substrate dependent

ketones and aldehydes: nucleophilic addition

\[
\begin{align*}
\text{R} & + \text{Nu}^- & \xrightarrow{\text{H}_3\text{O}^+} & \text{R}\text{Nu} \\
\end{align*}
\]

Carboxylic acid derivatives: nucleophilic acyl substitution

\[
\begin{align*}
\text{R} \text{Y} & + \text{Nu}^- & \xrightarrow{\text{H}_3\text{O}^+} & \text{R}\text{Nu} + \text{Y}^- \\
\end{align*}
\]

The different behavior toward nucleophiles of aldehydes/ketones and carboxylic acid derivatives is a consequence of structure – carboxylic acid derivatives have an acyl carbon bonded to a group that can leave as a stable anion (Y).

Comparison of the reactivity of different acyl derivatives
The more electron poor the C=O carbon, the more readily the compound reacts with nucleophile.

Reactivity toward nucleophile

<table>
<thead>
<tr>
<th>Acid chloride</th>
<th>Anhydride</th>
<th>Ester</th>
<th>Amide</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{R} \text{Cl} )</td>
<td>( \text{R}^+ \text{O}_2\text{CR} )</td>
<td>( \text{R}^+ \text{OR}' )</td>
<td>( \text{R} \text{CONH}_2 )</td>
</tr>
</tbody>
</table>

It is possible to convert a more reactive acid derivative into a less reactive one.
A nucleophile attacks the carbonyl carbon, forming a tetrahedral intermediate. A group is expelled, resulting in a new carbon-carbon bond.

Relative basicities of the leaving groups:

- Weakest base: $\text{Cl}^-$
- $\text{OR} < \text{OH} < \text{NH}_2^-$ (Strongest base)

Relative reactivities of carboxylic acid derivatives:

- Most reactive: Acyl chloride
- Ester
- Carboxylic acid
- Amide

Least reactive
10.6 The Tetrahedral Intermediate

**Fischer esterification reaction**

\[
\begin{align*}
\text{RCO}_2\text{H} & \quad + \quad \text{ROH} & \quad \overset{\text{H}^+}{\Longleftrightarrow} & \quad \text{RCO}_2\text{OR} \quad + \quad \text{H}_2\text{O} \\
\end{align*}
\]

**Mechanism**

Tetrahedral Intermediate

All steps are reversible, and the position of the equilibrium depends on the reaction conditions. Ester formation is favored when alcohol is used as a solvent, but a carboxylic acid is favored when the solvent is water.

10.7 Overview of Reactions

- **hydrolysis**
- **nucleophilic acyl substitution**
10.8 Reactions of Carboxylic Acids

Conversion of Acids into Alcohols by Reduction

\[
\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{C}-\text{OH} \xrightarrow{1. \text{LiAlH}_4} \text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CH}_2\text{OH} \quad 87\%
\]

Conversion of Acids into Acid Chlorides

\[
\text{O} \quad \text{SOCl}_2 \quad \text{CHCl}_3 \xrightarrow{\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{C}-\text{OH}} \quad \text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CHCl} \quad + \quad \text{HCl} \quad + \quad \text{SO}_2 \quad 90\%
\]

Conversion of Acids into Esters

\[
\text{O} \quad \text{O} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H}
\]

Conversion of Acids into Amides

Amides are difficult to prepare directly from acids by substitution with an amine because amines are bases, which convert acidic carboxyl groups into their carboxylate anions.

\[
\text{R}-\text{OH} \quad + \quad \text{NH}_3 \quad \leftrightarrow \quad \text{R}-\text{O} \quad + \quad \text{NH}_4^+
\]

10.9 Chemistry of Acid Halides

Preparations

\[
\text{O} \quad \text{SOCl}_2 \quad \text{R}-\text{OH} \quad \xrightarrow{\text{R}-\text{Cl}} \quad \text{R}-\text{Cl}
\]

Conversion of Acid Chlorides into Acids
Conversion of Acid Chlorides into Esters

\[
\begin{align*}
\text{CH}_3\text{C}-\text{Cl} & \quad + \quad \text{H}_3\text{C}-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} & \quad \xrightarrow{\text{Pyridine}} & \quad \text{CH}_3\text{C}-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\
90\% & 
\end{align*}
\]

Since HCl is generated as a byproduct, the reaction is carried out in the presence of amine base such as pyridine.

Conversion of Acid Chlorides into Amides

\[
\begin{align*}
\text{CH}_3\text{C}-\text{Cl} & \quad + \quad 2\text{NH}_3 & \quad \rightarrow & \quad \text{CH}_3\text{C}-\text{NH}_2 \quad + \quad \text{NH}_4\text{Cl} \\
\end{align*}
\]

One extra equivalent of ammonia is added to react with the HCl generated.

10.10 Chemistry of Acid Anhydrides

Preparations

\[
\begin{align*}
\text{HO}-\text{O}^- & \quad + \quad \text{Cl-CH}_3 \quad \xrightarrow{\text{Ether, 25 oC}} & \quad \text{HO}-\text{O}^- + \quad \text{HO}-\text{O}^- \quad 64\% \\
\end{align*}
\]

Reactions

The chemistry of acid anhydrides is similar to that of acid chlorides. Acid anhydrides react with water to form acids.

Ester formation

\[
\begin{align*}
\text{Salicylic acid} & \quad + \quad \text{Aspirin} \\
\text{Salicylic acid} & \quad + \quad \text{Aspirin} \\
\end{align*}
\]

Amide formation

\[
\begin{align*}
\text{p-Hydroxyaniline} & \quad + \quad \text{Acetaminophen (Tylenol)} \\
\text{p-Hydroxyaniline} & \quad + \quad \text{Acetaminophen (Tylenol)} \\
\end{align*}
\]
10.11 Chemistry of Esters

**Preparations**

\[
\begin{align*}
\text{ROH} & \xrightarrow{\text{H}^+ \text{ catalyst}} \text{ROR'} \quad & \text{Pyridine} & \xrightarrow{\text{R'O}} & \text{RCl}
\end{align*}
\]

**Conversion of Esters into Acids**

Esters are hydrolyzed either by aqueous base or aqueous acid to yield a carboxylic acid and an alcohol.

**Mechanism of the base hydrolysis (saponification – soap making)**

\[
\begin{align*}
\text{RO} & \xrightarrow{\text{OH}^-} \text{R''OH} \\
\text{R''OR'} & \xrightarrow{\text{R'O}} \text{R''O} \\
\text{R'O} & \xrightarrow{\text{OH}^-} \text{R''O} \\
\text{R''O} & \xrightarrow{\text{H}_2\text{O}} \text{R'O} + \text{R'OH}
\end{align*}
\]

**Conversion of Esters into Alcohols by Reduction**

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH} & = \text{CH} - \text{C} - \text{OCH}_2\text{CH}_3 \\
& \xrightarrow{1. \text{LiAlH}_4, \text{ether}} \text{CH}_3\text{CH}_2\text{CH} & = \text{CHCH}_2\text{OH} + \text{CH}_3\text{CH}_2\text{OH}
\end{align*}
\]

91%

**Conversion of Esters into Alcohols by Reaction with Grignard Reagents**

\[
\begin{align*}
\text{CH}_3\text{MgBr} & \xrightarrow{1. \text{CH}_3\text{MgBr}} \text{CH}_3\text{CH}_2\text{CH} & = \text{CHCH}_3 \\
& \xrightarrow{2. \text{H}_3\text{O}^+} \text{HO} \text{CH}_3
\end{align*}
\]

95%

10.12 Chemistry of Amides

**Preparations**

Nucleophilic acyl substitution reaction of acid chloride, acid anhydride, or ester with ammonia, monosubstituted amine, and disubstituted amine.

**Conversion of Amides into Acids**

\[
\begin{align*}
\text{R} & \xrightarrow{\text{H}_3\text{O}^+ \text{ or OH}^- \text{, H}_2\text{O}} \text{Heating} & \text{R} & \xrightarrow{\text{NH}_3} & \text{R'} & \text{OH} + \text{NH}_3
\end{align*}
\]

Amides undergo hydrolysis to yield carboxylic acids and amine on heating in either aqueous acid or base. The reaction is slow and requires prolonged heating.
Conversion of Amides into Amines by Reduction

\[
\begin{align*}
\text{O} & \quad \text{NH}_2 \\
\text{1. LiAlH}_4, \text{ ether} & \rightarrow \quad \text{H}_2\text{N} - \text{NH}_2 \\
\text{2. H}_2\text{O} & \\
\end{align*}
\]

Notice that the product is an amine instead of an alcohol.

10.13 Chemistry of Nitriles

Preparation

\[
\text{RCH}_2\text{Br} + \text{Na}^+\text{CN}^- \rightarrow \text{RCH}_2\text{CN} + \text{NaBr}
\]

Conversion of Nitriles into Carboxylic Acids

\[
\begin{align*}
\text{RCN} & \quad \xrightarrow{\text{H}_3\text{O}^+ \text{ or NaOH, H}_2\text{O}} \quad \text{RO} - \text{OH} + \text{NH}_3 \\
\end{align*}
\]

Mechanism

Conversion of Nitriles into Amines by Reduction

\[
\begin{align*}
\text{\text{C\text{\equiv N}}} & \quad \xrightarrow{\text{1. LiAlH}_4, \text{ ether}} \quad \text{CH}_2\text{NH}_2 \\
\text{CH}_3 & \quad \xrightarrow{\text{2. H}_2\text{O}} \quad \text{CH}_3\text{NH}_2 \\
\end{align*}
\]

88%

Conversion of Nitriles into Ketones by Reaction with Grignard Reagents

Grignard reagents, RMgX, add to nitrile to give intermediate imine anions that can be hydrolyzed to yield ketones.
R-C=N + R’ MgX → [\( \text{RC} \) \( \text{N}^+ \text{MgX} \) \( \text{R-C-R'} \)] \( \text{H}_3\text{O}^+ \) → \( \text{R-C-R'} \) + \( \text{NH}_3 \)

1. EtMgBr, ether
2. \( \text{H}_3\text{O}^+ \)
mechanism for acid-catalyzed ester hydrolysis

the acid protonates the carbonyl oxygen

\[
\begin{align*}
\text{CH}_3\text{C} & \text{OCH}_3 \\
& \xrightarrow{\text{H}^+} \\
& \text{CH}_3\text{C}^+\text{OCH}_3 + \text{H}_2\text{O} \\
& \xrightarrow{\text{proton dissociation}} \\
& \text{CH}_3\text{C} \text{OCH}_3
\end{align*}
\]

the nucleophile attacks the carbonyl group

\[
\begin{align*}
\text{CH}_3\text{C} & \text{OCH}_3 \\
& \xrightarrow{\text{proton dissociation}} \\
& \text{CH}_3\text{C}^+\text{OCH}_3 \\
& \xrightarrow{\text{proton dissociation}} \\
& \text{CH}_3\text{C} \text{OCH}_3
\end{align*}
\]

tetrahedral intermediate I

\[
\begin{align*}
\text{CH}_3\text{C} & \text{OCH}_3 \\
& \xrightarrow{\text{proton dissociation}} \\
& \text{CH}_3\text{C}^+\text{OCH}_3 \\
& \xrightarrow{\text{proton dissociation}} \\
& \text{CH}_3\text{C} \text{OCH}_3 \\
& \xrightarrow{\text{either OH or OCH}_3 \text{ can be protonated}} \\
& \text{CH}_3\text{C} \text{OCH}_3
\end{align*}
\]

tetrahedral intermediate II

\[
\begin{align*}
\text{CH}_3\text{C} & \text{OCH}_3 \\
& \xrightarrow{\text{proton dissociation}} \\
& \text{CH}_3\text{C}^+\text{OCH}_3 \\
& \xrightarrow{\text{proton dissociation}} \\
& \text{CH}_3\text{C} \text{OCH}_3 \\
& \xrightarrow{\text{the weaker base is expelled}} \\
& \text{CH}_3\text{C} \text{OCH}_3
\end{align*}
\]

tetrahedral intermediate III
mechanism for acid-catalyzed hydrolysis of an amide

the acid protonates the carbonyl oxygen

\[ \text{CH}_3\text{C}^\cdot\text{ONH}_2 + \text{H}^+ \rightarrow \text{CH}_3\text{C}^\cdot\text{NH}_2 + \text{H}_2\text{O}^\cdot \]

the nucleophile attacks the carbonyl carbon

\[ \text{CH}_3\text{C}^\cdot\text{NH}_2 + \text{H}_2\text{O}^\cdot \rightarrow \text{CH}_3\text{C}^\cdot\text{NH}_2 + \text{CH}_3\text{OH} \]

tetrahedral intermediate I

proton dissociation

\[ \text{CH}_3\text{C}^\cdot\text{NH}_2 \rightarrow \text{CH}_3\text{C}^- + \text{NH}_2 \]

either \( \text{NH}_2 \) or \( \text{OH} \) can be protonated

tetrahedral intermediate II

proton dissociation

\[ \text{CH}_3\text{C}^- + \text{H}_2\text{O}^\cdot \rightarrow \text{CH}_3\text{C}^- + \text{H}_3\text{O}^+ \]

the weaker base is expelled

tetrahedral intermediate III

\[ \text{CH}_3\text{C}^- + \text{NH}_3 \rightarrow \text{CH}_3\text{C}^- + \text{NH}_4^+ \]