Carboxylic Acids, Amides and Nitriles

Based on McMurry’s *Organic Chemistry, 7th edition*
The Importance of Carboxylic Acids (RCO$_2$H)

- Starting materials for *acyl derivatives* (esters, thioester, amides, acid anhydrides, and acid halides)
- Abundant in nature from oxidation of aldehydes and alcohols in metabolism
  - Acetic acid, CH$_3$CO$_2$H, - vinegar
  - Butanoic acid, CH$_3$CH$_2$CH$_2$CO$_2$H (rancid odor of butter)
  - A major component of human bile
  - Long-chain aliphatic acids from the breakdown of fats (palmitic acid) CH$_3$(CH$_2$)$_{14}$CO$_2$H
Naming Carboxylic Acids and Nitriles

- Carboxylic Acids, $RCO_2H$
- If derived from open-chain alkanes, replace the terminal -e of the alkane name with -oic acid
- The carboxyl carbon atom is C1

![Chemical structures and names](image_url)
Alternative Names

- Compounds with $\text{CO}_2\text{H}$ bonded to a ring are named using the suffix -carboxylic acid.
- The $\text{CO}_2\text{H}$ carbon is not itself numbered in this system.
- Use common names for formic acid (HCOOH) and acetic acid (CH$_3$COOH) – see Table 20.1.

trans-4-Hydroxycyclohexane carboxylic acid
1-Cyclopentene carboxylic acid
(a) \[\text{CH}_3\text{CHCH}_2\text{COH}\] 3-methylbutanoic acid

(b) \[\text{Br} \quad \text{CH}_3\text{CHCH}_2\text{CH}_2\text{COH}\] 4-bromopentanoic acid

(c) \[\text{CO}_2\text{H} \quad \text{CH}_3\text{CH}_2\text{CHCH}_2\text{CH}_2\text{CH}_3\] 2-ethylpentanoic acid

(d) \[\text{cis-hex-4-enoic acid}\]

(e) \[\text{CH}_3\text{CN} \quad \text{CH}_3\text{CHCH}_2\text{CHCH}_3\] 2,4-dimethylpentanenitrile

(f) \[\text{cis-cyclopentane-1,3-dicarboxylic acid}\]
Draw structures corresponding to the following IUPAC names

a) 2,3-dimethylhexanoic acid
b) Trans- cyclobutane-1,2-dicarboxylic acid
c) Pent-2-enenitrile
d) O-Hydroxybenzoic acid
<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
<th>Acyl group</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCO$_2$H</td>
<td>Formic</td>
<td>Formyl</td>
</tr>
<tr>
<td>CH$_3$CO$_2$H</td>
<td>Acetic</td>
<td>Acetyl</td>
</tr>
<tr>
<td>CH$_3$CH$_2$CO$_2$H</td>
<td>Propionic</td>
<td>Propionyl</td>
</tr>
<tr>
<td>CH$_3$CH$_2$CH$_2$CO$_2$H</td>
<td>Butyric</td>
<td>Butyryl</td>
</tr>
<tr>
<td>HO$_2$CCO$_2$H</td>
<td>Oxalic</td>
<td>Oxalyl</td>
</tr>
<tr>
<td>HO$_2$CCH$_2$CO$_2$H</td>
<td>Malonic</td>
<td>Malonyl</td>
</tr>
<tr>
<td>HO$_2$CCH$_2$CH$_2$CO$_2$H</td>
<td>Succinic</td>
<td>Succinyl</td>
</tr>
<tr>
<td>HO$_2$CCH$_2$CH$_2$CO$_2$H</td>
<td>Glutaric</td>
<td>Glutaryl</td>
</tr>
<tr>
<td>HO$_2$CCH$_2$CH$_2$CH$_2$CO$_2$H</td>
<td>Adipic</td>
<td>Adipoyl</td>
</tr>
<tr>
<td>H$_2$C═CHCO$_2$H</td>
<td>Acrylic</td>
<td>Acryloyl</td>
</tr>
<tr>
<td>HO$_2$CCH═CHCO$_2$H</td>
<td>Maleic (cis)</td>
<td>Maleoyl</td>
</tr>
<tr>
<td>HO$_2$CCH$_2$CH$_2$CH$_2$CO$_2$H</td>
<td>Fumaric (trans)</td>
<td>Fumaroyl</td>
</tr>
<tr>
<td>HOCH$_2$CO$_2$H</td>
<td>Glycolic</td>
<td>Glycoloyl</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td>Name</td>
<td>Acyl Group</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>( \text{CH}_3\text{CHCO}_2\text{H} )</td>
<td>Lactic</td>
<td>Lactoyl</td>
</tr>
<tr>
<td>( \text{CH}_3\text{CCO}_2\text{H} )</td>
<td>Pyruvic</td>
<td>Pyruvoyl</td>
</tr>
<tr>
<td>( \text{HOCH}_2\text{CHCO}_2\text{H} )</td>
<td>Glyceral</td>
<td>Glyceroyl</td>
</tr>
<tr>
<td>( \text{HO}_2\text{CCHCH}_2\text{CO}_2\text{H} )</td>
<td>Malic</td>
<td>Maloyl</td>
</tr>
<tr>
<td>( \text{HO}_2\text{CCCH}_2\text{CO}_2\text{H} )</td>
<td>Oxaloacetic</td>
<td>Oxaloacetyl</td>
</tr>
<tr>
<td>( \text{CO}_2\text{H} )</td>
<td>Benzoic</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>( \text{CO}_2\text{H} )</td>
<td>Phthalic</td>
<td>Phthaloyl</td>
</tr>
</tbody>
</table>
Nitriles, RCN

- Closely related to carboxylic acids named by adding -nitrile as a suffix to the alkane name, with the nitrile carbon numbered C1

- Complex nitriles are named as derivatives of carboxylic acids.
  - Replace -ic acid or -oic acid ending with -onitrile

Acetonitrile (from acetic acid)  
Benzonitrile (from benzoic acid)  
2,2-Dimethylcyclohexanecarbonitrile (from 2,2-dimethylcyclohexane-carboxylic acid)
structure and properties of carboxylic acids

- carboxyl carbon $sp^2$ hybridized: carboxylic acid groups are planar with C–C=O and O=C–O bond angles of approximately 120°
- carboxylic acids form hydrogen bonds, existing as cyclic dimers held together by two hydrogen bonds
- strong hydrogen bonding causes much higher boiling points than the corresponding alcohols
Dissociation of Carboxylic Acids

- Carboxylic acids are proton donors to weak and strong bases, producing metal carboxylate salts, $\text{RCO}_2^- + \text{M}$
- Carboxylic acids with more than six carbons are only slightly soluble in water, but their conjugate base salts are water-soluble

\[
\begin{align*}
\text{O} & \quad \text{R} \quad \text{C} \quad \text{OH} \quad + \quad \text{NaOH} \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{O} \\
\text{C} & \quad \text{R} \quad \text{O}^- \quad \text{Na}^+ \quad + \quad \text{H}_2\text{O}
\end{align*}
\]

A carboxylic acid (water-insoluble)  A carboxylic acid salt (water-soluble)
Acidity Constant and $pK_a$

- Carboxylic acids transfer a proton to water to give $H_3O^+$ and carboxylate anions, $RCO_2^-$, but $H_3O^+$ is a much stronger acid.
- The acidity constant, $K_a$, is about $10^{-5}$ for a typical carboxylic acid ($pK_a \sim 5$)

$$
\begin{align*}
\text{R-COOH} + \text{H}_2\text{O} & \rightleftharpoons \text{RCO}_2^- \text{H}^+ + \text{H}_3\text{O}^+ \\
K_a &= \frac{[\text{RCO}_2^-][\text{H}_3\text{O}^+]}{[\text{RCO}_2\text{H}]} \\
\text{and} \quad pK_a &= -\log K_a
\end{align*}
$$
Substituent Effects on Acidity

- Electronegative substituents promote formation of the carboxylate ion

<table>
<thead>
<tr>
<th>Structure</th>
<th>$K_a$</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF$_3$CO$_2$H</td>
<td>0.59</td>
<td>0.23</td>
</tr>
<tr>
<td>HCO$_2$H</td>
<td>$1.77 \times 10^{-4}$</td>
<td>3.75</td>
</tr>
<tr>
<td>HOCH$_2$CO$_2$H</td>
<td>$1.5 \times 10^{-4}$</td>
<td>3.84</td>
</tr>
<tr>
<td>C$_6$H$_5$CO$_2$H</td>
<td>$6.46 \times 10^{-5}$</td>
<td>4.19</td>
</tr>
<tr>
<td>H$_2$C═CHCO$_2$H</td>
<td>$5.6 \times 10^{-5}$</td>
<td>4.25</td>
</tr>
<tr>
<td>CH$_3$CO$_2$H</td>
<td>$1.75 \times 10^{-5}$</td>
<td>4.76</td>
</tr>
<tr>
<td>CH$_3$CH$_2$CO$_2$H</td>
<td>$1.34 \times 10^{-5}$</td>
<td>4.87</td>
</tr>
<tr>
<td>CH$_3$CH$_2$OH (ethanol)</td>
<td>$(1.00 \times 10^{-16})$</td>
<td>(16.00)</td>
</tr>
</tbody>
</table>
Inductive Effects on Acidity

- Fluoroacetic, chloroacetic, bromoacetic, and iodoacetic acids are stronger acids than acetic acid.
- Multiple electronegative substituents have synergistic effects on acidity.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{OH} & \quad \text{p}K_a = 16 \\
\text{HO} & \quad \text{p}K_a = 9.89 \\
\text{CH}_3\text{COH} & \quad \text{p}K_a = 4.76 \\
\text{HCl} & \quad \text{p}K_a = -7
\end{align*}
\]
Biological Acids and the Henderson-Hasselbalch Equation

If pK$_a$ of given acid and the pH of the medium are known, % of dissociated and undissociated forms can be calculated using the Henderson-Hasselbalch eqn

$$\text{pH} = \text{pK}_a + \log \frac{[\text{A}^-]}{[\text{HA}]}$$  \hspace{1cm} \text{Henderson–Hasselbalch equation}

$$\text{pH}-\text{pK}_a = \log [\text{A}^-]/[\text{HA}]$$
Example:

Calculate the percentages of dissociated and undissociated forms are present in 0,0010M solution of acetic acid at pH=3,4.

\[ \text{pH-pKa}= \log[A^-]/[HA] \]
7.3-4.76=2.54

\[ \text{Log}[A^-]/[HA]=2.54 \]

\[ [A^-]/[HA]=\text{antilog} 2.54= 3.5.10^2 \text{ so } [A^-]=(3.5.10^2)[AH] \]

In addition, we know that \([A^-]+[HA]=0,0010M\)

\[ [A^-]=0,0010M \quad , \quad [HA]=3.10^{-6} \]

In other words, at physiological pH of 7,3 essentially 100% of acetic acid molecules in a 0,0010M solution are dissociated to the acetate ion.
Substituent Effects on Acidity

An electron-withdrawing chlorine atom, makes chloroacetic acid approximately 80 times as strong as acetic acid, introduction of two chlorines makes dichloroacetic acid 3000 times as strong as acetic acid, introduction of three chlorines makes trichloroacetic acid 12000 times as strong as acetic acid,

\[
\begin{align*}
\text{HCCOOH} & \quad pK_a = 4.76 \\
\text{ClCOCOOH} & \quad pK_a = 2.85 \\
\text{ClClCOCOOH} & \quad pK_a = 1.48 \\
\text{ClClClCOCOOH} & \quad pK_a = 0.64
\end{align*}
\]
Substituent Effects on Acidity

- The effect of halogen substitution decreases as the substituent moves farther from the carboxyl.

\[
\begin{align*}
\text{ClCH}_2\text{CH}_2\text{CH}_2\text{COH} & \quad \text{Cl} \quad \text{CH}_3\text{CHCH}_2\text{COH} & \quad \text{Cl} \quad \text{CH}_3\text{CH}_2\text{CHCOH} \\
pK_a = 4.52 & \quad pK_a = 4.05 & \quad pK_a = 2.86
\end{align*}
\]
Substituent Effects on Acidity

- Aromatic rings with electron-donating groups are activated toward further electrophilic substitution,
- and Aromatic rings with electron-withdrawing groups are deactivated.
Aromatic Substituent Effects

- An electron-withdrawing group (-NO₂) increases acidity by stabilizing the carboxylate anion, and an electron-donating (activating) group (OCH₃) decreases acidity by destabilizing the carboxylate anion.

\[
\begin{align*}
\text{p-Methoxybenzoic acid} & \quad (pK_a = 4.46) \\
\text{Benzoic acid} & \quad (pK_a = 4.19) \\
\text{p-Nitrobenzoic acid} & \quad (pK_a = 3.41)
\end{align*}
\]
Preparation of Carboxylic Acids

- Oxidation of a substituted alkylbenzene with \( \text{KMnO}_4 \) or \( \text{Na}_2\text{Cr}_2\text{O}_7 \) gives a substituted benzoic acid (see Section 16.9)
- 1° and 2° alkyl groups can be oxidized, but tertiary groups are not

\[ \text{O}_2\text{N} \quad \text{CH}_3 \quad \text{KMnO}_4 \quad \text{H}_2\text{O}, \text{95 °C} \quad \text{O}_2\text{N} \quad \text{COH} \]

\( p \)-Nitrotoluene \[ \rightarrow \] \( p \)-Nitrobenzoic acid (88%)
Oxidative cleavage of an alkene with KMnO₄ gives a carboxylic acid if the alkene has at least one vinylic hydrogen (see Section 7.9)
From Alcohols

- Oxidation of a primary alcohol or an aldehyde with CrO$_3$ in aqueous acid

4-Methyl-1-pentanol $\xrightarrow{\text{CrO}_3, H_3O^+} 4$-Methylpentanoic acid

Hexanal $\xrightarrow{\text{CrO}_3, H_3O^+} \text{Hexanoic acid}$
Hydrolysis of Nitriles

- Hot acid or base yields carboxylic acids
- Conversion of an alkyl halide to a nitrile (with cyanide ion) followed by hydrolysis produces a carboxylic acid with one more carbon \( (\text{RBr} \rightarrow \text{RC}≡\text{N} \rightarrow \text{RCO}_2\text{H}) \)
- Best with primary and secondary halides because elimination reactions occur with tertiary alkyl halides
Carboxylation of Grignard Reagents

- Grignard reagents react with dry CO$_2$ to yield a metal carboxylate followed by protonation to give the carboxylic acid.

- The biosynthesis of fatty acid involves formation of a carbanion from acetyl CoA, followed by carboxylation to yield malonyl CoA.
Preparing phenylacetic acid from benzyl bromide

- The first method involves an Sn2 reaction then cyanid ion displacement followed by hydrolysis.
- The second method involves formation of a Grignard reagent. (limited to use with organic halides that have no acidic hydrogens or functional groups.)
How would you prepare the following carboxylic acids?

(a) \((\text{CH}_3)_3\text{CCCO}_2\) from \((\text{CH}_3)_3\text{CCl}\)

(b) \(\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}\) from \(\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}\)
Reactions of Carboxylic Acids: An Overview

- Carboxylic acids transfer a proton to a base to give anions, which are good nucleophiles in $S_N2$ reactions.
- Like ketones, carboxylic acids undergo addition of nucleophiles to the carbonyl group.
- In addition, carboxylic acids undergo other reactions characteristic of neither alcohols nor ketones.
- Reaction of carboxylic acids can be grouped into the four categories.
Nucleophilic Acyl Substitution
Reactions of carboxylic Acids

- Carboxylic acids are converted into acid chlorides by treatment with thionyl chlorides, SOCl₂. Similar reaction of carboxylic acids with (PBr₃).

- Conversion of carboxylic acids into acid anhydrides: acid anhydrides can be derived from two molecules of carboxylic acid by strong heating.
Conversion of Carboxylic Acids into Esters by Sn2 reaction of a carboxylate anion with a primary alkyl halide

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{COO}^- + \text{CH}_3\text{I} \xrightarrow{\text{Sn}^2\text{ reaction}} \text{CH}_3\text{CH}_2\text{CH}_2\text{COOCH}_3^- + \text{NaI}
\]

Sodium butanoate

Methyl butanoate (97%)

Ester can also be synthesized by an acid-catalyzed nucleophilic acyl substitution reaction of a carboxylic acid with an alcohol, the process called the Ficher esterification reaction.

\[
\text{H}_2\text{C} = \text{C} = \text{O} + \text{CH}_3\text{CH}_2\text{OH} \xrightarrow{\text{HCl}} \text{H}_2\text{C} = \text{C} = \text{O} - \text{OCCH}_3\text{CH}_3 + \text{H}_2\text{O}
\]

Mandelic acid

Ethyl mandelate (86%)
Reactions of Acid Halides

- Acid halides can be converted into many other kinds of compounds by nucleophilic acyl substitution mechanisms.
Chemistry of Nitriles

- Nitriles and carboxylic acids both have a carbon atom with three bonds to an electronegative atom, and contain a $\pi$ bond.
- Both are electrophiles.

A nitrile—three bonds to nitrogen

An acid—three bonds to two oxygens
Preparation of Nitriles by Dehydration

- Reaction of primary amides $\text{RCONH}_2$ with $\text{SOCl}_2$ or $\text{POCl}_3$ (or other dehydrating agents)

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CHC}\text{NH}_2 \xrightarrow{\text{SOCl}_2, \text{benzene, } 80 \degree\text{C}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CHC}\equiv\text{N} + \text{SO}_2 + 2\text{HCl}
\]

2-Ethylhexanamide

2-Ethylhexanenitrile (94%)
Reactions of Nitriles

- $\text{RC}≡\text{N}$ is strongly polarized and with an electrophilic carbon atom
- Attacked by nucleophiles to yield $sp^2$-hybridized imine anions

![Diagram of reactions involving nitriles and imine anions]
Hydrolysis: Conversion of Nitriles into Carboxylic Acids

- Hydrolyzed in with acid or base catalysis to a carboxylic acid and ammonia or an amine

\[
\begin{align*}
R\text{−}C≡N & \overset{H_3O^+ \text{ or } NaOH, H_2O}{\longrightarrow} CO & \overset{H_3O^+ \text{ or } NaOH, H_2O}{\longrightarrow} \text{CO}_2H \\
\text{A nitrile} & \text{An amide} & \text{A carboxylic acid}
\end{align*}
\]

- Reduced to yield an amine, and Grignard reaction to yield a ketone.
Reduction: Conversion of Nitriles into Amines

Reduction of a nitrile with LiAlH₄ gives a primary amine

- Nucleophilic addition of hydride ion to the polar C≡N bond, yields an imine anion

- The C≡N bond undergoes a second nucleophilic addition of hydride to give a dianion, which is protonated by water
Reaction of Nitriles with Organometallic Reagents

- Grignard reagents add to give an intermediate imine anion that is hydrolyzed by addition of water to yield a ketone.

```
R-C≡N + :R' - + MgX → \[ \text{Imine anion} \] + H₂O → R-C-R' + NH₃
```

Benzonitrile

1. CH₃CH₂MgBr, ether
2. H₃O⁺ → Propiophenone (89%)
With unsubstituted —NH₂ group. replace -oic acid or -ic acid with -amide, or by replacing the -carboxylic acid ending with –carboxamide.

If the N is further substituted, identify the substituent groups (preceded by “N”) and then the parent amide.
Chemistry of Amides

- Amides are abundant in all living organisms...proteins, nucleic acids, and other pharmaceuticals have amid functional groups.
Preparation of Amides

- Prepared by reaction of an acid chloride with ammonia, monosubstituted amines, or disubstituted amines.
Aminolysis: Conversion of Acid Halides into Amides

- Amides result from the reaction of acid chlorides with NH$_3$, primary (RNH$_2$) and secondary amines (R$_2$NH).
- The reaction with tertiary amines (R$_3$N) gives an unstable species that cannot be isolated.
- HCl is neutralized by the amine or an added base.
Reactions of Amides

- Heating in either aqueous acid or aqueous base produces a carboxylic acid and amine
- Acidic hydrolysis by nucleophilic addition of water to the protonated amide, followed by loss of ammonia
Basic Hydrolysis of Amides

- Addition of hydroxide and loss of amide ion
Reduction: Conversion of Amides into Amines

- Reduced by LiAlH$_4$ to an amine rather than an alcohol
- Converts C=O → CH$_2$

\[
\text{CH}_3(\text{CH}_2)_9\text{CH}_2\text{C} = \text{O} \quad \text{N-} \text{CH}_3 \\
\overset{1. \text{LiAlH}_4 \text{ in ether}}{\Rightarrow} \overset{2. \text{H}_2\text{O}}{\Rightarrow} \text{CH}_3(\text{CH}_2)_9\text{CH}_2\text{C} - \text{N} - \text{CH}_3
\]

*N-Methyldodecanamide*

*Dodecylmethylamine (95%)*
Uses of Reduction of Amides

- Works with cyclic and acyclic
- Good route to cyclic amines

\[ \text{A lactam} \xrightarrow{1. \text{LiAlH}_4, \text{ether}} \xrightarrow{2. \text{H}_2\text{O}} \text{A cyclic amine (80%)} \]