**Carboxylic Acids**

When a carbonyl carbon also bears a hydroxyl group, then these compounds are appreciably acidic, and are called *carboxylic acids*.

\[
\begin{align*}
\text{O} & \quad \text{RCO}_2\text{H} \\
\text{R} & \quad \text{RCOOH}
\end{align*}
\]

Carboxylic acids are classified according to the substituent that is bonded to the carboxyl carbon:

*Aliphatic* acids have an *alkyl* group bound to the carboxyl group.

An *aromatic* acid has an *aryl* group bound to the carboxyl group.

The simplest acid is *formic acid*.

A carboxylic acid donates protons by the heterolytic cleavage of the O-H bond, generating a *carboxylate* ion.

\[
\begin{align*}
\text{O} & \quad \text{H} \quad \text{C} \quad \text{O} \quad \text{H} \\
\text{H} & \quad \text{C} \quad \text{O} \quad \text{H}
\end{align*}
\]

\[\text{H}^+ \quad \text{RCO}_2\text{H} \quad \text{RCOO}^-
\]
**Nomenclature**

IUPAC formulation
The root name is based on the longest continuous chain of carbon atoms bearing the carboxyl group.

The -e is replaced by -oic acid.

The chain is numbered **starting with the carboxyl carbon atom**.

The carboxyl group takes priority over any other functional groups previously discussed.

E.g.
Unsaturated acids are named using the name of the alkene with -e replaced with -oic acid.

The chain is numbered starting with the carboxyl group, and a number designates the location of the multiple bond (and may include Z or E).

E.g.

![Structural formulas showing examples of unsaturated acids.](image)

Old IUPAC name: (E)-4-methyl-3-hexenoic acid
New IUPAC name: (E)-4-methylhex-3-enoic acid

Trans-3-phenyl-2-propenoic acid
(E)-3-phenylprop-2-enoic acid (cinnamic acid)

Cycloalkanes with carboxyl substituents are named as cycloalkanecarboxylic acids.

E.g.

![Structural formula showing an example of a cycloalkanecarboxylic acid.](image)

3,3-dimethylocyclohexanecarboxylic acid

(Notice that -CO₂H as a substituent makes the carbon it is bound to C-1, not itself).
Typically *aromatic* acids of the form $\text{Ar-CO}_2\text{H}$ are named as derivatives of benzoic acids, with *ortho*, *meta* and *para* indicating the location relative to the carboxyl group. (*Recall that this is non-IUPAC*).
Dicarboxylic Acids
Aliphatic dicarboxylic acids are named by simply adding the suffix -dioic acid to the root name.

The root name comes from the longest carbon chain containing both carboxyl groups.

Numbering starts at the end closest to a substituent.

E.g.

Structure of the Carboxyl Group
The most stable conformation of formic acid is an almost planar arrangement of the molecule.

The carbon is sp² hybridized, and the O-H bond lies in the plane described by the sp² carbon, eclipsing the C=O double bond.

This unexpected geometric arrangement can be explained by resonance (or conjugation).
Three resonance forms can be written for formic acid.

\[
\begin{align*}
\text{O} & \quad \text{H} - \text{C} \equiv \text{O} - \text{H} \\
\text{H} - \text{C} - \text{O} - \text{H} & \quad \text{H} - \text{C} \equiv \text{O} - \text{H} \\
\text{H} - \text{C} = \text{O} - \text{H} &
\end{align*}
\]

*major*  
*minor*  
*very minor*

The second structure requires the C-O-H bonds to be *co-planar*.

One of the unshared lone pairs of oxygen is delocalized into the electrophilic \( \pi \) system of the carbonyl group.

(One of the lone pairs on the hydroxyl oxygen is *conjugated* with the C=O double bond).

**Acidity**

Carboxylic acids can dissociate in aqueous solution into carboxylate ions and protons.

The equilibrium constant for this process is \( K_a \), and more frequently we talk in terms of \( pK_a \).

\[
\begin{align*}
\text{R} - \text{C} - \text{O} - \text{H} + \text{H}_2\text{O} & \rightleftharpoons \text{R} - \text{C} - \text{O}^- + \text{H}_3\text{O}^+ \\
K_a & = \frac{[\text{R} - \text{CO}_2^-][\text{H}_3\text{O}^+]}{[\text{R} - \text{CO}_2\text{H}]} \\
pK_a & = -\log_{10} K_a
\end{align*}
\]
Values of $pK_a$ for common alkyl carboxylic acids are around 5 ($K_a \sim 10^{-5}$).

<table>
<thead>
<tr>
<th>Formula</th>
<th>Name</th>
<th>$K_a$ (at 25 °C)</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Simple carboxylic acids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCOOH</td>
<td>formic acid</td>
<td>$1.77 \times 10^{-4}$</td>
<td>3.75</td>
</tr>
<tr>
<td>CH₃COOH</td>
<td>acetic acid</td>
<td>$1.76 \times 10^{-5}$</td>
<td>4.74</td>
</tr>
<tr>
<td>CH₃CH₂COOH</td>
<td>propionic acid</td>
<td>$1.34 \times 10^{-5}$</td>
<td>4.87</td>
</tr>
<tr>
<td>CH₃(CH₂)₂COOH</td>
<td>butyric acid</td>
<td>$1.54 \times 10^{-5}$</td>
<td>4.82</td>
</tr>
<tr>
<td>CH₃(CH₂)₃COOH</td>
<td>pentanoic acid</td>
<td>$1.52 \times 10^{-5}$</td>
<td>4.81</td>
</tr>
<tr>
<td>CH₃(CH₂)₄COOH</td>
<td>hexanoic acid</td>
<td>$1.31 \times 10^{-5}$</td>
<td>4.88</td>
</tr>
<tr>
<td>CH₃(CH₂)₅COOH</td>
<td>octanoic acid</td>
<td>$1.28 \times 10^{-5}$</td>
<td>4.89</td>
</tr>
<tr>
<td>CH₃(CH₂)₆COOH</td>
<td>decanoic acid</td>
<td>$1.43 \times 10^{-5}$</td>
<td>4.84</td>
</tr>
<tr>
<td>C₆H₅COOH</td>
<td>benzoic acid</td>
<td>$6.46 \times 10^{-5}$</td>
<td>4.19</td>
</tr>
<tr>
<td>$p$-CH₃C₆H₄COOH</td>
<td>$p$-toluic acid</td>
<td>$4.33 \times 10^{-5}$</td>
<td>4.36</td>
</tr>
<tr>
<td>$p$-ClC₆H₄COOH</td>
<td>$p$-chlorobenzoic acid</td>
<td>$1.04 \times 10^{-4}$</td>
<td>3.98</td>
</tr>
<tr>
<td>$p$-NO₂C₆H₄COOH</td>
<td>$p$-nitrobenzoic acid</td>
<td>$3.93 \times 10^{-4}$</td>
<td>3.41</td>
</tr>
<tr>
<td><strong>Dicarboxylic acids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOOC—COOH</td>
<td>oxalic</td>
<td>$5.4 \times 10^{-2}$</td>
<td>1.27</td>
</tr>
<tr>
<td>HOOCCH₂COOH</td>
<td>malonic</td>
<td>$1.4 \times 10^{-3}$</td>
<td>2.85</td>
</tr>
<tr>
<td>HOOC(CH₂)₂COOH</td>
<td>succinic</td>
<td>$6.4 \times 10^{-5}$</td>
<td>4.19</td>
</tr>
<tr>
<td>HOOC(CH₂)₃COOH</td>
<td>glutaric</td>
<td>$4.5 \times 10^{-5}$</td>
<td>4.35</td>
</tr>
<tr>
<td>HOOC(CH₂)₄COOH</td>
<td>adipic</td>
<td>$3.7 \times 10^{-5}$</td>
<td>4.43</td>
</tr>
<tr>
<td>cis-HOOCCH═CHCOOH</td>
<td>maleic</td>
<td>$1.0 \times 10^{-2}$</td>
<td>2.00</td>
</tr>
<tr>
<td>trans-HOOCCH═CHCOOH</td>
<td>fumaric</td>
<td>$9.6 \times 10^{-4}$</td>
<td>3.02</td>
</tr>
<tr>
<td>1,2-C₆H₄(COOH)₂</td>
<td>phthalic</td>
<td>$1.1 \times 10^{-3}$</td>
<td>2.96</td>
</tr>
<tr>
<td>1,3-C₆H₄(COOH)₂</td>
<td>isophthalic</td>
<td>$2.4 \times 10^{-4}$</td>
<td>3.62</td>
</tr>
<tr>
<td>1,4-C₆H₄(COOH)₂</td>
<td>terephthalic</td>
<td>$2.9 \times 10^{-4}$</td>
<td>3.54</td>
</tr>
</tbody>
</table>
E.g. ethanoic acid has $pK_a = 4.74$, (alcohols have $pK_a \sim 16$, so carboxylic acids are about $10^{11}$ times more acidic than alcohols).

The reason why carboxylic acids are much more acidic than alcohols is because the carboxylate anion is much more stable than the alkoxide anion.

Both alcohols and carboxylic acids are acidic since their respective O-H bonds can be broken heterolytically, giving a proton and an oxygen anion.

![Diagram showing the difference in stability between alcohol and carboxylic acid anions]

The difference lies in the fact that the carboxylate anion has the negative charge spread out over two oxygen atoms, whereas the alkoxide has the negative charge localized on a single oxygen atom.
The carboxylate anion can be viewed as a *resonance hybrid* of the two anionic structures, or as a *conjugated* system of three interacting p orbitals containing four electrons (like the allylic anion system).

The C and two oxygens are all sp\(^2\) hybridized, and the remaining p orbitals create the \(\pi\) MO system giving rise to the half \(\pi\) bond between each C and O, and the half negative charge on the end oxygens.

**Dicarboxylic Acids**

These have **two** dissociation constants, since they can lose **two** protons.

\[
\text{HO-C-CH}_2\text{CH-COOH} \quad K_{a1} = 1.4 \times 10^{-3} \quad \text{anion} \quad K_{a2} = 2.0 \times 10^{-6} \quad \text{dianion} \\
+ 2 \text{ H}_2\text{O} \quad + \text{ H}_3\text{O}^+ + \text{ H}_2\text{O} \quad + 2 \text{ H}_3\text{O}^+
\]

\(K_{a1}\) for the first dissociation, and \(K_{a2}\) for the second dissociation (which generates a dianion). \(K_{a2}\) is always *less* than \(K_{a1}\) (the second carboxyl group is less acidic) since it takes extra energy to overcome the second negative charge being so close to the first negative charge.
Substituent Effects on Acidity

Any substituent that stabilizes a negative charge is going to enhance the dissociation process, and therefore result in a stronger acid.

Thus electronegative elements can enhance the acid strength, through inductive effects.

E.g.

\[
\begin{align*}
\text{H-C-C-OH} & \quad \text{Cl-C-C-OH} & \quad \text{Cl-C-C-OH} & \quad \text{Cl-C-C-OH} \\
\text{H} & \quad \text{H} & \quad \text{Cl} & \quad \text{Cl} \\
pK_a = 4.74 & \quad 2.86 & \quad 1.26 & \quad 0.64
\end{align*}
\]

The closer the substituent to the anion, the more profound the effect.

\[
\begin{align*}
\text{Cl-C-C-C-C-O-H} & \quad \text{Cl-C-C-C-O-H} & \quad \text{Cl-C-C-C-O-H} \\
pK_a = 4.52 & \quad 4.05 & \quad 2.86
\end{align*}
\]
Salts of carboxylic Acids
Strong bases can *completely* deprotonate carboxylic acids, thus *salts* of carboxylic acids are formed.

E.g.

\[
\begin{align*}
\text{R–C–O–H} & \quad + \quad \text{M}^+ \cdot \text{OH} \quad \Leftrightarrow \quad \text{R–C–O}^- \quad \text{M}^+ \quad + \quad \text{H}_2\text{O} \\
\text{carboxylic acid} & \quad \text{strong base} & \quad \text{acid salt} & \quad \text{water}
\end{align*}
\]

The acid can be *regenerated* by protonation (acidification) of the salt.

E.g.

\[
\begin{align*}
\text{R–C–O}^- \quad \text{M}^+ & \quad + \quad \text{H}^+ \quad \Leftrightarrow \quad \text{R–C–O}^- \quad \text{H}^+ \quad + \quad \text{M}^+ \\
\text{acid salt} & \quad \text{H}^+ & \quad \text{regenerated acid}
\end{align*}
\]

**Example**

\[
\begin{align*}
\text{CH}_3\text{–C–O}^- \quad \text{Na}^+ & \quad + \quad \text{H}^+ \quad \text{Cl}^- \quad \Leftrightarrow \quad \text{CH}_3\text{–C–O–H} \quad + \quad \text{Na}^+ \quad \text{Cl}^- \\
\text{sodium acetate} & \quad \text{acidification} & \quad \text{acetic acid}
\end{align*}
\]
Syntheses of Carboxylic Acids

The previously seen syntheses (three) all involved oxidation:
(a) oxidation of primary alcohols and aldehydes.
(b) oxidative cleavage of alkenes and alkynes.
(c) side chain oxidation of alkyl benzenes.

Oxidation of Primary Alcohols and Aldehydes

These oxidations are best performed using chromic acid (made from Na$_2$Cr$_2$O$_7$ and H$_2$SO$_4$). Potassium permanganate can be used but gives lower yields.

E.g.

\[
\text{Ph} - \text{C} - \text{CH}_2 - \text{O} - \text{H} \xrightarrow{\text{Na}_2\text{Cr}_2\text{O}_7, \text{H}_2\text{SO}_4} \text{Ph} - \text{C} - \text{CH}_2 - \text{C} - \text{O} - \text{H}
\]
Cleavage of Alkynes and Alkenes

Alkenes react with *concentrated* KmnO₄ to produce intermediate glycols which react further to produce either carboxylic acids or ketones (depending on the original alkene substituents).

E.g.

\[
\begin{array}{c}
R - \text{C} = \text{C} - R' \\
\text{conc. K MnO}_4 \\
\end{array} \xrightarrow{1) \text{O}_3} \xrightarrow{2) \text{H}_2\text{O}} \text{not isolated}
\]

\[
\begin{array}{c}
R - \text{CO}_2\text{H} \\
R' - \text{CO}_2\text{H}
\end{array}
\]

Alkynes also react with conc. KMnO₄ to give carboxylic acids, and the same transformation can be achieved by the use of ozonolysis.

E.g.

\[
\begin{array}{c}
\text{Ph} - \text{C} = \text{C} - \text{C}_2\text{H}_5 \\
\text{conc. K MnO}_4
\end{array} \xrightarrow{\text{not isolated}} \text{Ph} - \text{CO}_2\text{H} \quad \text{C}_2\text{H}_5\text{CH}_2 - \text{CO}_2\text{H}
\]
Alkylbenzenes
Benzoic acid derivatives can be made by the oxidation of alkylbenzenes with either hot KMnO₄ or hot chromic acid.

The vigorous conditions means this can only be used when there are no oxidizable groups present in the molecule.

E.g.
New methods

Carboxylation of Grignard Reagents
Grignard reagents can react as nucleophiles and attack carbon dioxide.

\[
\begin{align*}
\text{R} - \text{X} & \xrightarrow{\text{Mg, ether}} \text{R} - \text{MgX} & \xrightarrow{\text{CO}_2} & \text{R} - \text{C} - \text{O}^- + \text{MgX} & \xrightarrow{\text{H}^+} & \text{R} - \text{C} - \text{OH} \\
\text{(alkyl or aryl halide)} & & & & & \\
\end{align*}
\]

This results in magnesium salts of carboxylic acids, and treatment with dilute acid produces a carboxylic acid.
The overall transformation is from alkyl halide to a carboxylic acid with an extra carbon atom.

E.g.
Formation and Hydrolysis of Nitriles

Nitriles can be hydrolyzed by dilute acid to generate carboxylic acids.

E.g.

\[
R-C≡N \xrightarrow{\text{H}_3\text{O}^+ \text{ or } \text{OH}^-} R-CO_2H
\]

Nitriles are easily made by the action of cyanide ion as a nucleophile on alkyl halides (or tosylates).

Again the overall transformation is from alkyl halide to a carboxylic acid with an *extra carbon atom*.
Reactions of Carboxylic Acids (and Derivatives)

Ketones and aldehydes have a carbonyl group and undergo nucleophilic addition, whereas carboxylic acids (and their derivatives) undergo nucleophilic acyl substitution - this is where one nucleophile replaces a leaving group on the acyl carbon.

E.g.

\[
\text{Nucleophilic acyl substitution} \\
\begin{array}{c}
\text{R} - \text{C} - \text{X} + \text{Nuc}^- \\
\implies \\
\text{R} - \text{C} - \text{Nuc} + :\text{X}^-
\end{array}
\]

**Acid derivatives**

- **R—C—OH** carboxylic acid
- **R—C—X** acyl halide
- **R—C—O—C—R** anhydride
- **R—C—O—R’** ester
- **R—C—NH₂** amide

Carboxylic acid derivatives differ in the nature of the group bound to the acyl group.

- -OH is an *acid*
- -Cl is the *acid chloride*
- -OCOR’ is the *anhydride*
- -OR’ is the *ester*
- -NR₂ is the *amide*

*Nucleophilic acyl substitution* can interconvert all of these different acid derivatives.
The mechanism for *nucleophilic acyl substitution* varies depending if it occurs under *acidic* or *basic* conditions (similar to acid and base varieties of nucleophilic addition to aldehydes/ketones).

Under *basic* conditions, a strong nucleophile can attack the carbonyl carbon, thus generating a *tetrahedral intermediate*.

This intermediate can then expel its leaving group.

E.g. the above ester hydrolysis to a carboxylic acid.

Under *acidic* conditions, the carbonyl group becomes protonated, and thus activated toward nucleophilic acyl substitution.

Then attack by a weak nucleophile generates the tetrahedral intermediate.

The leaving group (often in its protonated form) is then expelled (often as a neutral molecule). (See next slide).
The Fischer Esterification

Recall that $\text{acid and alcohol} \rightarrow \text{ester and water}$

The overall transformation is that the -OH of an acid is replaced by the -OR' of an alcohol.

E.g.

The overall reaction:

$$\text{R-C-O-H} + \text{R'-O-H} \xrightarrow{\text{H}^+} \text{R-C-O-R'} + \text{H}_2\text{O}$$

The Fischer esterification is an example of acid catalyzed nucleophilic acyl substitution.

The carbonyl group of a carboxylic acid is not sufficiently electrophilic to be attacked by the alcohol.

$$\text{R-C-OH} \xrightarrow{\text{H}^+} \left[ \text{R-C-OH} \right] \xrightarrow{\text{H}^+} \text{R-C-OH} + \text{R'OH}_2$$

(Species in brackets are resonance-stabilized.)

The acid catalyst protonates the carbonyl oxygen, and activates it toward nucleophilic attack.

The alcohol attacks, and after deprotonation of the alcohol oxygen, the hydrate of an ester is formed.

The ester is produced via acid catalyzed dehydration of the ester hydrate.
As usual, the hydroxyl oxygen is protonated, thus creating a good leaving group.

\[
\begin{align*}
\text{As usual, the hydroxyl oxygen is protonated, thus creating a good leaving group.} \\
\text{This leaves with assistance from the neighboring hydroxyl oxygen.} \\
\text{The cation remaining is resonance stabilized, and deprotonation yields the desired ester.} \\
\text{The overall mechanism is quite long, but both steps have been seen before (acid catalyzed addition to a carbonyl; acid catalyzed dehydration), and so should not be viewed as difficult, or as new work to learn.}
\end{align*}
\]
Esterification reactions such as this one are *equilibrium* reactions, and the equilibrium normally will lie to the left.

\[
\text{CH}_3\text{C} \equiv \text{OH} + \text{CH}_3\text{CH}_2\text{OH} \rightleftharpoons \text{CH}_3\text{C} \equiv \text{OCH}_2\text{CH}_3 + \text{H}_2\text{O} \quad K_{eq} = 3.38
\]

$K_{eq} = 3.4$, so this would be a good case.

To drive the reaction to completion we can either use an *excess* of one of the reagents, or *remove* one of the products.

Often it is the water produced which is removed by a dehydrating agent such as MgSO$_4$, or molecular sieves.

A simpler (yet more expensive) way to make esters in the laboratory (not industrially) is to react an alcohol with an acid chloride.
Synthesis of Acid Chlorides

Both the carbonyl oxygen and the chlorine are electron withdrawing, and thus make the carbonyl carbon very electrophilic.

Therefore acid chlorides are very reactive with nucleophiles, usually through the nucleophilic acyl substitution mechanism.

The best way to make acid chlorides is the reaction of a carboxylic acid with either thionyl chloride (SOCl₂) or (COCl)₂, which is called oxalyl chloride.

E.g.

Both these methods are good since they generate gaseous by-products, and thus do not contaminate the acid chloride product.
The mechanism of formation of acid chloride is similar to the reaction of alcohols with thionyl chloride.

The lone pair of the acid carbonyl oxygen attacks the electrophilic sulfur (sulfur analogue of an acid chloride), and chloride is expelled from the tetrahedral intermediate.

Deprotonation yields a chlorosulfite anhydride.
The liberated chloride ion now attacks the electrophilic carbon of the mixed anhydride.

This tetrahedral intermediate then expels the leaving group which fragments into SO$_2$ and chloride ion.

\[
\begin{align*}
\text{R} & \quad \text{O} \quad \text{S} \quad \text{Cl} \\
\text{Cl}^{-} & \quad \text{Cl}^- \\
\rightarrow & \quad \text{R} & \quad \text{O} \quad \text{S} \quad \text{Cl} \\
\rightarrow & \quad \text{R} & \quad \text{O} \quad \text{Cl} \\
\rightarrow & \quad \text{R} & \quad \text{C} \quad \text{Cl} & \quad \text{SO}_2 & \quad \text{Cl}^{-}
\end{align*}
\]

Acid chlorides react with alcohols to give esters through a nucleophilic acyl substitution by the addition elimination mechanism.

\[
\begin{align*}
\text{R} & \quad \text{C} \quad \text{Cl} & \quad \text{R} & \quad \text{C} \quad \text{O} \quad \text{R}' \\
\text{R} & \quad \text{OH} & \quad \text{HCl}
\end{align*}
\]

The overall transformation of this two step scheme is a carboxylic acid is converted into an acid chloride, then into an ester.

\[
\begin{align*}
\text{R} & \quad \text{C} \quad \text{OH} & \quad \text{SOCl}_2 & \quad \text{R} & \quad \text{C} \quad \text{Cl} & \quad \text{R} & \quad \text{C} \quad \text{OR}'
\end{align*}
\]
The *acid chloride* to *ester* transformation is standard *nucleophilic acyl substitution*.

\[
\begin{align*}
R-C-Cl + R'-OH & \rightleftharpoons \left[ \begin{array}{c}
\text{R-C-Cl} \\
\text{R'-OH} \\
\end{array} \right] \\
& \longrightarrow \text{R-C-OH} + \text{Cl}^- \\
& \downarrow \\
& \text{R-C-O-R' + HCl}
\end{align*}
\]

Ammonia and amines react with acid chlorides to give *amides*, also through this addition-elimination version of nucleophilic acyl substitution.

E.g.

\[
\begin{align*}
R-C-Cl + 2R'-NH_2 & \rightarrow R-C-NHR' + R'NH_3^+ + Cl^- 
\end{align*}
\]
Esterification using Diazomethane
The addition of an ethereal solution of diazomethane smoothly converts carboxylic acids to their methyl esters.

\[
\begin{array}{c}
\text{CO}_2\text{H} \\
\text{CH}_2\text{N}_2 \\
\text{CO}_2\text{CH}_3 \\
\text{+ N}_2
\end{array}
\]

The only by-product is nitrogen gas.

E.g.

Diazomethane is a toxic, explosive yellow gas that dissolves in ether, and requires special glassware.

The mechanism involves the deprotonation of the hydroxyl oxygen, which generates a methyl diazonium salt, which is a potent methylating agent.

**Step 1:** Proton transfer, forming a carboxylate ion and a methyl diazonium ion.
The carboxylate anion becomes methylated, thus generating the methyl ester, and nitrogen gas is evolved.

**Step 2:** Nucleophilic attack on the methyl group displaces nitrogen.

![Chemical reaction]

Condensations of Acids with Amines (→ Amides)
Although the acid chloride/amine reaction generates amides, it is also possible (and cheaper) to synthesize amides directly from carboxylic acids.

The direct reaction of an amine and a carboxylic acid initially forms a carboxylate anion and an ammonium cation.

Normally the reaction would stop at this point since the carboxylate anion is a poor electrophile, but by heating the reaction to over 100°C, the water can be driven off as steam, and amide products are formed.

E.g.

![Chemical reaction]

This is an important commercial process.
Reduction of Carboxylic Acids
Lithium aluminum hydride reduces carboxylic acids back to primary alcohols.

\[
\begin{align*}
R\text{--}C\text{--}OH & \xrightarrow{(1) \text{ LiAlH}_4} R\text{--}CH_2\text{--}OH \\
\text{acid} & \xrightarrow{(2) \text{ H}_3\text{O}^+} \text{primary alcohol}
\end{align*}
\]

**Example**

\[
\begin{align*}
\begin{array}{c}
\text{O} \\
\text{ phenylacetic acid} \\
\text{O} \\
\end{array} & \xrightarrow{(1) \text{ LiAlH}_4} \begin{array}{c}
\text{O} \\
\text{2-phenylethanol} \\
\text{(75%)} \\
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{phenylacetic acid} \\
\text{O} \\
\end{array} & \xrightarrow{(2) \text{ H}_3\text{O}^+} \begin{array}{c}
\text{O} \\
\text{2-phenylethanol} \\
\text{(75%)} \\
\end{array}
\end{align*}
\]

The reaction proceeds through an *aldehyde* but it cannot be stopped at that stage since aldehydes are more easily reduced than carboxylic acids.
Carboxylic acids are also reduced by borane (BH$_3$) to generate primary alcohols.

This reaction has good selectivity since the carboxyl group reacts faster than any other carbonyl derivative.

\[
\begin{array}{c}
\text{H}_3\text{C}-\text{C}-\text{O} \quad \text{BH}_3\cdot\text{THF} \quad \text{H}_3\text{C}-\text{C}-\text{O} \quad \text{H}_3\text{C}-\text{C}-\text{CH}_2\text{OH}
\end{array}
\]

Therefore carboxylic acids can be reduced in the presence of ketone functionalities using borane.

**Reduction to Aldehydes**
(We have seen this before, Ch18). The carboxylic acid must first be converted into a group more easily reduced than an aldehyde.

The reactive acid derivative is the *acid chloride*, and the mild reducing agent is *lithium aluminum tri('butoxy)hydride*.

E.g.

\[
\begin{array}{c}
\text{R-} \text{C-} \text{OH} \quad \text{SOCl}_2 \quad \text{R-} \text{C-} \text{Cl} \quad \text{LiAlH(O-tBu)$_3$} \quad \text{R-} \text{C-} \text{H}
\end{array}
\]

\[
\begin{array}{c}
\text{R-} \text{C-} \text{Cl} \quad + \quad \text{LiAlH(O-t-Bu)$_3$} \quad \Leftrightarrow \quad \text{R-} \text{C-} \text{Cl} \quad + \quad \text{Al(O-t-Bu)$_3$} \quad \text{R-} \text{C-} \text{H} \quad + \quad \text{LiCl}
\end{array}
\]

*Ch20 Carboxylic Acids (landscape).doc*
Alkylation of Carboxylic Acids (→ Ketones)  
(Also seen this before, Ch18). A general method to form ketones is the reaction of a carboxylic acid with two equivalents of organolithium reagent.

E.g.

\[
\begin{align*}
\text{PhCO}_2\text{H} & \quad 1) \quad 2\text{CH}_3\text{-Li} \\
& \quad 2) \quad \text{H}_2\text{O}
\end{align*}
\]

The first equivalent just deprotonates the carboxylic acid, and then the second performs a nucleophilic attack to generate a dianion.

\[
\begin{align*}
\text{PhCO}_2\text{H} & \quad \text{PhCO}_2\text{H} - \text{CH}_3 \quad \text{PhCO}_2\text{H} - \text{CH}_3 \\
& \quad \text{PhCO}_2\text{H} - \text{CH}_3 \quad \text{PhCO}_2\text{H} - \text{CH}_3 \\
& \quad \text{PhCO}_2\text{H} - \text{CH}_3 \quad \text{PhCO}_2\text{H} - \text{CH}_3
\end{align*}
\]

On acid hydrolysis a ketone hydrate is formed, which loses water (H\textsubscript{2}O) to yield the ketone.