Chapter 20
Carboxylic Acid Derivatives
Nucleophilic Acyl Substitution
The key to this chapter is the next slide.

It lists the various carboxylic acids in order of decreasing reactivity toward their fundamental reaction type (nucleophilic acyl substitution).

The other way to read the list is in order of increasing stabilization of the carbonyl group.
Decreasing Reactivity
(Nucleophilic Acyl Substitution)
Increasing stabilization of C=O

Acyl chloride

Anhydride

Ester

Amide
20.1
Nomenclature of Carboxylic Acid Derivatives
name the acyl group and add the word *chloride*, *fluoride*, *bromide*, or *iodide* as appropriate.

Acyl chlorides are, by far, the most frequently encountered of the acyl halides.
Acyl Halides

- Acetyl chloride
- 3-butenoyl chloride
- $p$-fluorobenzoyl bromide
Acid Anhydrides

when both acyl groups are the same, name the acid and add the word \textit{anhydride}

when the groups are different, list the names of the corresponding acids in alphabetical order and add the word \textit{anhydride}
Acid Anhydrides

- Acetic anhydride: $\text{CH}_3\text{COCOCCH}_3$
- Benzoic anhydride: $\text{C}_6\text{H}_5\text{COCOC}_6\text{H}_5$
- Benzoic heptanoic anhydride: $\text{C}_6\text{H}_5\text{COCOC(CH}_2)_5\text{CH}_3$
Esters

\[ \text{RCOR}' \]

name as *alkyl alkanoates*

cite the alkyl group attached to oxygen first (R')

name the acyl group second; substitute the suffix -*ate* for the -*ic* ending of the corresponding acid
Esters

\[
\text{CH}_3\text{COOCH}_2\text{CH}_3 \quad \text{ethyl acetate}
\]

\[
\text{CH}_3\text{CH}_2\text{COOCH}_3 \quad \text{methyl propanoate}
\]

\[
\text{O} \quad \text{phenyl-CO-CH}_2\text{CH}_2\text{Cl} \quad 2\text{-chloroethyl benzoate}
\]
Amides having an NH$_2$ group

identify the corresponding carboxylic acid

replace the -ic acid or -oic acid ending by -amide.
Amides having an $\text{NH}_2$ group

- Acetamide: $\text{O} \quad \text{CH}_3\text{C}\text{NH}_2$
- 3-Methylbutanamide: $\text{O} \quad \text{CH}_3\text{CHCH}_2\text{C}\text{NH}_2$
- Benzamide: $\text{C} \quad \text{C} \quad \text{C} \quad \text{NH}_2$
Amides having substituents on N

name the amide as before
precede the name of the amide with the name of the appropriate group or groups
precede the names of the groups by the letter N-(standing for nitrogen and used as a locant)
Amides having substituents on N

- \(\text{CH}_3\text{CNHCH}_3\) \(N\)-methylacetamide
- \(\text{O}\) \(\text{O}\) \(\text{CN(CH}_2\text{CH}_3\text{)}_2\) \(N, N\)-diethylbenzamide
- \(\text{CH}_3\text{CH}_2\text{CH}_2\text{C}^\text{NCH(CH}_3\text{)}_2\) \(N\)-isopropyl-\(N\)-methylbutanamide
Nitriles

RC≡N

add the suffix \textit{-nitrile} to the name of the parent hydrocarbon chain (including the triply bonded carbon of CN)

or: replace the \textit{-ic acid} or \textit{-oic acid} name of the corresponding carboxylic acid by \textit{-onitrile}

or: name as an \textit{alkyl cyanide} (functional class name)
Nitriles

- Ethanenitrile: $\text{CH}_3\text{C}≡\text{N}$
- Acetonitrile: or: methyl cyanide: $\text{CH}_3\text{C}≡\text{N}$
- Benzonitrile: $\text{C}_6\text{H}_5\text{C}≡\text{N}$
- 2-Methylpropanenitrile: or: isopropyl cyanide: $\text{CH}_3\text{CHCH}_3\text{C}≡\text{N}$
20.2
Structure of Carboxylic Acid Derivatives
The main structural feature that distinguishes acyl chlorides, anhydrides, esters, and amides is the interaction of the substituent with the carbonyl group. It can be represented in resonance terms as:
The extent to which the lone pair on X can be delocalized into C=O depends on:

1) the electronegativity of X

2) how well the lone pair orbital of X interacts with the $\pi$ orbital of C=O
Orbital overlaps in carboxylic acid derivatives

π orbital of carbonyl group
Orbital overlaps in carboxylic acid derivatives

lone pair orbital of substituent
Orbital overlaps in carboxylic acid derivatives

electron pair of substituent delocalized into carbonyl $\pi$ orbital
Acyl Chlorides

acyl chlorides have the least stabilized carbonyl group

delocalization of lone pair of Cl into C=O group is not effective because C—Cl bond is too long
least stabilized C=O

most stabilized C=O
lone pair donation from oxygen stabilizes the carbonyl group of an acid anhydride.

the other carbonyl group is stabilized in an manner by the lone pair.
least stabilized C=O

RCCI

most stabilized C=O

RCOCR'}
lone pair donation from oxygen stabilizes the carbonyl group of an ester stabilization greater than comparable stabilization of an anhydride
least stabilized C=O

most stabilized C=O
lone pair donation from nitrogen stabilizes the carbonyl group of an amide

N is less electronegative than O; therefore, amides are stabilized more than esters and anhydrides
amide resonance imparts significant double-bond character to C—N bond

activation energy for rotation about C—N bond is 75-85 kJ/mol

C—N bond distance is 135 pm in amides versus normal single-bond distance of 147 pm in amines
least stabilized C=O

most stabilized C=O
very efficient electron delocalization and dispersal of negative charge

maximum stabilization
least stabilized C=O

most stabilized C=O
Reactivity is related to structure: Table 20.1

<table>
<thead>
<tr>
<th>Stabilization</th>
<th>Relative rate of hydrolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>very small 10^{11}</td>
</tr>
<tr>
<td>RCCl</td>
<td>small 10^7</td>
</tr>
<tr>
<td>RCOCOR'</td>
<td>moderate 1.0</td>
</tr>
<tr>
<td>RCNR'_2</td>
<td>large &lt; 10^{-2}</td>
</tr>
</tbody>
</table>

The more stabilized the carbonyl group, the less reactive it is.
most reactive

least reactive

RCCI

RCOCR'

RCOR'

RCNR'R'

RCO−
In general:

\[
\begin{align*}
\text{RCX} + \text{HY} & \rightarrow \text{RCY} + \text{HX} \\
\end{align*}
\]

Reaction is feasible when a less stabilized carbonyl is converted to a more stabilized one (more reactive to less reactive).
General Mechanism for Nucleophilic Acyl Substitution

involves formation and dissociation of a tetrahedral intermediate
most reactive

\[ \text{RCOCI} \]

\[ \text{RCOCR'} \]

\[ \text{RCOR'} \]

\[ \text{RCNR'_2} \]

\[ \text{RCO}^- \]

least reactive

A carboxylic acid derivative can be converted by nucleophilic acyl substitution to any other type that lies below it in this table.