Generally, amides can be hydrolyzed in either acidic or basic solution. The mechanisms are much like those of ester hydrolysis (Section 18-7A), but the reactions are very much slower, a property of great biological importance (which we will discuss later):

\[
\begin{align*}
\text{R–C–O} & + \text{H}_2\text{O} \xrightarrow{\text{H}^+ \text{ or } \text{OH}^-} \text{R–C–O} + \text{R}_2\text{NH} \\
\text{NR}_2 & \quad \text{OH}^{-} \\
\text{O} & \quad \text{C} \quad \text{O} \quad \text{OH} \quad \text{R} \quad \text{C} \quad \text{OH} \quad \text{R} \quad \text{C} \quad \text{OH} \\
\text{NR}_2 & \quad \text{OH}^{-} \\
\text{H}_2\text{NR}_2 & \xrightarrow{\text{OH}^-} \text{R–C–OH} + \text{HNR}_2 \\
\text{OH}^{-} & \quad \text{C} \quad \text{O} \quad \text{OH} \quad \text{R} \quad \text{C} \quad \text{OH} \\
\text{HNR}_2 & \quad \text{OH}^{-} \\
\end{align*}
\]

As we have indicated in Section 23-12, amide hydrolysis can be an important route to amines. Hydrolysis under acidic conditions requires strong acids such as sulfuric or hydrochloric, and temperatures of about \(100{}^\circ\text{C}\) for several hours. The mechanism involves protonation of the amide on oxygen followed by attack of water on the carbonyl carbon. The tetrahedral intermediate formed dissociates ultimately to the carboxylic acid and the ammonium salt:

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

In alkaline hydrolysis the amide is heated with boiling aqueous sodium or potassium hydroxide. The nucleophilic hydroxide ion adds to the carbonyl carbon to form a tetrahedral intermediate, which, with the help of the aqueous solvent, expels the nitrogen as the free amine:

\[
\begin{align*}
\text{R–C–O} & \xrightarrow{\text{OH}^-} \text{R–C–OH} \\
\text{OH}^{-} & \quad \text{C} \quad \text{O} \quad \text{OH} \quad \text{R} \quad \text{C} \quad \text{OH} \\
\text{HNR}_2 & \quad \text{OH}^{-} \\
\end{align*}
\]

Biological amide hydrolysis, as in the hydrolysis of peptides and proteins, is catalyzed by the proteolytic enzymes. These reactions will be discussed in Chapter 25.

An indirect method of hydrolyzing some amides utilizes nitrous acid. Primary amides are converted easily to carboxylic acids by treatment with nitrous acid. These reactions are very similar to that which occurs between a primary amine and nitrous acid (Section 23-10):

\[
\begin{align*}
\text{R–C–O} & + \text{HONO} \rightarrow \text{R–C–O} + \text{N}_2 + \text{H}_2\text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{NH}_3 & \quad \text{OH}^{-} \\
\end{align*}
\]
Secondary amides give \(N\)-nitroso compounds with nitrous acid, whereas tertiary amides do not react:

\[
\begin{align*}
\text{R} & \text{-C} \text{-O} + \text{HONO}^{(1)} \text{NO} \rightarrow \text{R} \text{-C} \text{-O} + \text{H}_2\text{O} \\
\text{N} & \text{-H} \quad \text{N} \quad \text{-N=O} \\
\text{CH}_3 & \text{CH}_3
\end{align*}
\]

A brief summary of important amide reactions follows:

- **Reduction** \(\rightarrow \text{R'}\text{CH}_2\text{NR}_2\)  (Section 18-7C)
- **Hydrolysis** \(\rightarrow \text{R'}\text{CO}_2\text{H} + \text{HN} \text{R}_2\)  (Section 24-4)
- **Rearrangement** (R = H) \(\rightarrow \text{R'}\text{NH}_3 + \text{CO}_3\)  (Section 23-12E)
- **Dehydration** (R = H) \(\rightarrow \text{R'}\text{CN} + \text{H}_2\text{O}\)  (Section 24-5)
- **Nitrosation** \(\rightarrow \text{R'}\text{CO}_2\text{H} \text{ or } \text{R'}\text{CON} \text{-N=O}_\text{R}\)  (Section 24-4)

Of the many other types of organonitrogen compounds known, the more important include

- nitriles, \(\text{R} \text{-C}=\text{N}\)  (Section 24-5)
- isonitriles, \(\text{R} \text{-N}=\text{C}:\)  (Section 24-6)
- nitro compounds, \(\text{R} \text{-NO}_2\)  (Section 24-6C)
- nitroso compounds, \(\text{R} \text{-NO}\)  (Section 23-11B)
- nitrile oxides, \(\text{R} \text{-C}=\text{N} \text{-O} \text{-O}\)  (Section 23-12E)
- amine oxides, \(\text{R}_2\text{N}=\text{O}\)  (Section 24-7A)
- isocyanates, \(\text{R} \text{-N}=\text{C}=\text{O}\)  (Sections 23-10C and 24-7B)
- hydrazines, \(\text{R}_2\text{N} \text{-NR}_2\)  (Section 24-7C)
- azo compounds, \(\text{R} \text{-N}=\text{N}=\text{R}\)  (Section 24-7D)
- diazo compounds, \(\text{R}_2\text{C}=\text{N} \text{-N}=\text{O}\)  (Section 23-12E, Table 23-6, and Section 24-7D)
- azides, \(\text{R} \text{-N}=\text{N}=\text{N}\)  (Section 24-6C)
- diazonium ions, \(\text{R} \text{-N}=\text{N} \text{-O}\)  (Section 23-10)
- aroxy compounds, \(\text{R} \text{-N}=\text{N}-\text{R}\)  (Section 24-6C)

Although it is impractical to discuss all of these compounds in detail, we now will discuss briefly several that have not been given much attention heretofore.

### Contributors and Attributions