Anhydrides are somewhat less reactive than acid chlorides, but still readily react with most nucleophiles. Nucleophilic attack occurs at one carbonyl group, while the second carbonyl becomes part of the leaving group.

**General Reaction of Anhydrides**

- Anhydrides are somewhat less reactive than acid chlorides, but still readily react with most nucleophiles.
- Nucleophilic attack occurs at one carbonyl group, while the second carbonyl becomes part of the leaving group.

**General reaction**

\[
\text{R-O-C-O-R} + \text{H-Nu} \rightarrow \text{Nu} - \text{RCOO} + \text{R-COOH}
\]

**Mechanism of Anhydride Substitution**

- Besides the usual steps for nucleophilic addition and elimination of the leaving group, the mechanism involves an additional proton transfer.

**Mechanism 22.4 Conversion of an Anhydride to an Amide**

\[
\begin{align*}
\text{R-O-C-O-R} & \rightarrow \text{R-O-C-Nu} + \text{RCOO}^- \\
\text{R-O-C-Nu} & \rightarrow \text{R-O-C-NH}_2 + \text{Nu}^- \\
\text{Nu}^- & \rightarrow \text{Nu} + \text{H}_2\text{O}
\end{align*}
\]

- In Step [1], nucleophilic attack by NH\(_3\) forms a tetrahedral intermediate.
- Removal of a proton followed by elimination of the leaving group, RCOO\(^-\) (Steps [2]–[3]), forms the substitution product, a 1° amide.

**Reactions of Anhydrides**

- Reactions that result in the transfer of an acetyl group are known as acetylations.

**Anhydrides Use in Acetylation Reactions**

- Reactions that result in the transfer of an acetyl group are known as acetylations.

\[
\begin{align*}
\text{Acetyl group} & \rightarrow \text{Acetylated product (aspirin)} \\
\text{Acetaminophen} & \rightarrow \text{Acetaminophen (active ingredient in Tylenol)} \\
\text{Morphine} & \rightarrow \text{Heroin}
\end{align*}
\]
General Reactions of Carboxylic Acids

- Nucleophiles that are also strong bases react with carboxylic acids by removing a proton first, before any nucleophilic substitution reaction can take place.
- The first reaction – a simple Bronsted-Lowry acid-base reaction – is both kinetically and thermodynamically favored with most common nucleophiles.

Acyl Substitution Reactions of Carboxylic Acids

- Although carboxylic acids cannot readily be converted into anhydrides, dicarboxylic acids can be converted to cyclic anhydrides by heating to high temperatures.
- This is a dehydration reaction because a water molecule is lost from the diacid.

Dehydration of Carboxylic Acids

- Treatment of a carboxylic acid with an alcohol in the presence of an acid catalyst forms an ester.
- This reaction is called a Fischer esterification.
- The reaction is an equilibrium, so it is driven to the right by exploiting LeChatelier’s Principle.

Fischer Esterification of Carboxylic Acids

- The mechanism of acid-catalyzed esterification was provided at the start of this unit.
**Intramolecular Fischer Esterification**

- Intramolecular esterification of γ- and δ-hydroxy carboxylic acids forms five- and six-membered lactones.

![reaction diagram](image)

**Reactions of Esters**

- Esters react with NH₃ and amines to form 1°, 2°, or 3° amides.

![reaction diagram](image)

- Esters can undergo trans-esterification reactions by reacting with excess alcohol under acidic conditions.
  - The mechanism is similar to acid-catalyzed esterification/hydrolysis.

- Esters can also undergo trans-esterification reactions by reacting with excess alkoxide ion under basic conditions, but this is less commonly used.

**Reactions of Esters**

- Esters are hydrolyzed with water in the presence of either acid or base to form carboxylic acids or carboxylate anions, respectively.

![reaction diagram](image)

- Basic hydrolysis of an ester is also called saponification.
  - This mechanism was provided as part of the introduction to this unit.

**Structure of Triacylglycerols**

- Each triacylglycerol is a triester, containing three long hydrocarbon side chains.
- Unsaturated triacylglycerols have one or more double bonds in their long hydrocarbon chains, whereas saturated triacylglycerols have none.

![structure diagram](image)
Lipid Hydrolysis

- The first step in the metabolism of a triacylglycerol is hydrolysis of the ester bonds to form glycerol and three fatty acids.
- The three bonds of the triacylglycerol drawn in red are cleaved in hydrolysis.
- In cells, this reaction is catalyzed by lipases.
- The fatty acids produced on hydrolysis are then oxidized, ultimately yielding CO$_2$ and H$_2$O, as well as nearly twice as much energy as an equal amount of carbohydrate.

\[
\text{triacylglycerol} \xrightarrow{\text{H}_2\text{O}} \text{glycerol} + \text{three fatty acids}
\]

Fat Substitutes

- One recent attempt to reduce calories in common snack foods has been to substitute “fake fats” such as olestra for triacylglycerols.

\[
\text{Olestra} \quad \text{a polyester of sucrose} \\
\text{a synthetic fat} \\
[R \text{ groups contain } 11-19 \text{ C's.}]
\]

Soap Formation

- Soap is prepared by the basic hydrolysis or saponification of a triacylglycerol.
- Heating an animal fat or vegetable oil with aqueous base hydrolyzes the three esters to form glycerol and sodium salts of three fatty acids.

\[
\text{triacylglycerol} \xrightarrow{\text{NaOH, } \text{H}_2\text{O}} \text{glycerol} + 3\text{Na}^+ - \text{O} - \text{C} - \text{R}^* + \text{Na}^+ - \text{O} - \text{C} - \text{R}^* + \text{Na}^+ - \text{O} - \text{C} - \text{R}^*
\]

Amide Formation from Carboxylic Acids

- Carboxylic acids cannot be converted into amides by reaction with NH$_3$ or an amine because amines are bases, and undergo an acid–base reaction to form an ammonium salt before nucleophilic substitution occurs.
- However, heating the ammonium salt at high temperature (>100°C) dehydrates the resulting ammonium salt of the carboxylate anion to form an amide, although the yield can be low.

\[
\text{O} - \text{C} - \text{H} \quad + \quad \text{NH}_3 \quad \xrightarrow{[1]} \quad \text{O} - \text{C} - \text{NH}_4^+ \quad \xrightarrow{[2]} \quad \text{O} - \text{C} - \text{NH}_2 + \text{H}_2\text{O}
\]

For example:

\[
\text{O} - \text{C} - \text{H} \quad + \quad \text{NH}_3 \quad \xrightarrow{\text{acid-base reaction}} \quad \text{O} - \text{C} - \text{NH}_4^+ \quad \xrightarrow{\text{dehydration}} \quad \text{O} - \text{C} - \text{NH}_2 + \text{H}_2\text{O}
\]

3-D structure of olestra

The ester groups are so crowded that hydrolysis does not readily take place.
DCC in Amide Formation

- A carboxylic acid and an amine readily react to form an amide in the presence of dicyclohexylcarbodimide (DCC).
- DCC promotes amide formation by converting the carboxy group OH group into a better leaving group.

Reactions of Amides

- Amides are the least reactive of the carboxylic acid derivatives.
- Amides are hydrolyzed in acid or base to form carboxylic acids or carboxylate anions.

Amide Hydrolysis

- The mechanism of amide hydrolysis in acid is the same as the mechanism of ester hydrolysis in acid.
- The mechanism of amide hydrolysis in base is similar to the saponification of an ester and is presented as such in the text.
- Likely, however, the mechanism is a bit more complex, as the -NR₂ leaving group would be too basic to depart without the corresponding addition of a proton.
- Mechanism of base-promoted amide hydrolysis
**β-Lactam Antibiotics**

- Penicillin and related β-lactams kill bacteria by a nucleophilic acyl substitution reaction.
- All penicillins have an unreacted side chain and a very reactive amide that is part of a β-lactam.
- The β-lactam is more reactive than other amides because it is part of a strained, four membered ring that is readily opened with nucleophiles.

![β-Lactam Antibiotics Diagram](image)

**The Mechanism of Action of β-Lactam Antibiotics**

- Bacterial cell walls are composed of carbohydrates linked together by peptide chains containing amide linkages formed by the enzyme glycopeptide transpeptidase.
- A nucleophilic OH group of the glycopeptide transpeptidase enzyme cleaves the β-lactam ring of penicillin by a nucleophilic acyl substitution reaction.
- The reaction causes covalent modification of the enzyme, thus inactivating it and halting cell wall construction killing the bacterium.

![The Mechanism of Action of β-Lactam Antibiotics Diagram](image)

**Structure and Formation of Nitriles**

- Nitriles have the general structural formula RC≡N.
- Nitriles are prepared by S_N2 reactions of methyl, 1°, and unhindered 2° alkyl halides with "CN.

![Structure and Formation of Nitriles Diagram](image)

**Reactions of Nitriles**

- Nitriles will react with water, hydride and organometallics.

![Reactions of Nitriles Diagram](image)
Hydrolysis of Nitriles

- Nitriles are hydrolyzed with water in the presence of acid or base to yield carboxylic acids or carboxylate anions.
- In this reaction, the three C–N bonds are replaced by three C–O bonds.

**Examples**

\[ \text{CH}_3\text{C}≡\text{N} \xrightarrow{\text{H}_2\text{O}, \text{H}^+} \text{CH}_3\text{C}\text{O}^- \]  

**Mechanisms for nitrile hydrolysis under acidic & basic conditions**

Reduction of Nitriles

- Treatment of a nitrile with LiAlH₄ followed by H₂O adds two equivalents of H₂ across the triple bond, forming a 1° amine.

**Example**

\[ (\text{CH}_3)_2\text{C}≡\text{N} \xrightarrow{\text{LiAlH}_4, \text{H}_2\text{O}} (\text{CH}_3)_2\text{C}\text{CH}_2\text{NH}_2 \]  

**Mechanisms for LAH reduction of a nitrile with aqueous workup**

- Treatment of a nitrile with a milder reducing agent such as DIBAL-H followed by water forms an aldehyde.

**Example**

\[ \text{C}_6\text{H}_5\text{C}≡\text{N} \xrightarrow{\text{DIBAL-H, H}_2\text{O}} \text{C}_6\text{H}_5\text{C}=\text{CH}_2 \]  

**Reduction of Nitriles with Organometallics**

- Both Grignard and organolithium reagents react with nitriles to form ketones with a new C–C bond.

**Example**

\[ \text{C}_6\text{H}_5\text{C}≡\text{N} \xrightarrow{\text{CH}_3\text{CH}_2\text{MgBr, H}_2\text{O}} \text{C}_6\text{H}_5\text{C}=\text{CH}_2\text{CH}_3 \]  

**Mechanism for the ethylmagnesium bromide reduction of benzonitrile with aqueous workup**