20.6
Sources of Esters
Esters are very common natural products

\[
\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH(CH}_3)_2
\]

3-methylbutyl acetate

also called "isopentyl acetate" and "isoamyl acetate"

contributes to characteristic odor of bananas
Esters of Glycerol

R, R’, and R” can be the same or different called "triacylglycerols," "glyceryl triesters," or "triglycerides"

fats and oils are mixtures of glyceryl triesters
Esters of Glycerol

\[
\begin{align*}
\text{CH}_3(\text{CH}_2)_{16}\text{COCH} & \quad \text{CH}_2\text{OC}(\text{CH}_2)_{16}\text{CH}_3 \\
\text{O} & \quad \text{CH}_2\text{OC}(\text{CH}_2)_{16}\text{CH}_3 \\
\end{align*}
\]

Tristearin: found in many animal and vegetable fats
Cyclic Esters (Lactones)

\[(Z)(Z)-5\text{-Tetradecen-4-olide}\]

(sex pheromone of female Japanese beetle)
Preparation of Esters

Fischer esterification (Sections 15.8 and 19.14)
from acyl chlorides (Sections 15.8 and 20.3)
from carboxylic acid anhydrides (Sections 15.8 and 20.5)
Baeyer-Villiger oxidation of ketones (Section 17.16)
20.7
Physical Properties of Esters
Esters have higher boiling points than alkanes because they are more polar. Esters cannot form hydrogen bonds to other ester molecules, so have lower boiling points than alcohols.
Esters can form hydrogen bonds to water, so low molecular weight esters have significant solubility in water. Solubility decreases with increasing number of carbons.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solubility (g/100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$COCH$_3$</td>
<td>~0</td>
</tr>
<tr>
<td>CH$_3$CHCH$_2$CH$_3$</td>
<td>33</td>
</tr>
<tr>
<td>OH</td>
<td></td>
</tr>
<tr>
<td>CH$_3$CHCH$_2$CH$_3$</td>
<td>12.5</td>
</tr>
</tbody>
</table>
20.8
Reactions of Esters:
A Review and a Preview
Reactions of Esters

with Grignard reagents (Section 14.10)
reduction with LiAlH$_4$ (Section 15.3)
with ammonia and amines (Sections 20.13)
hydrolysis (Sections 20.9 and 20.10)
20.9
Acid-Catalyzed Ester Hydrolysis
Acid-Catalyzed Ester Hydrolysis

is the reverse of Fischer esterification

\[
\text{RCOR'} + \text{H}_2\text{O} \xrightleftharpoons{\text{H}^+} \text{RCOH} + \text{R'OH}
\]

maximize conversion to ester by removing water

maximize ester hydrolysis by having large excess of water

equilibrium is closely balanced because carbonyl group of ester and of carboxylic acid are comparably stabilized
Example

\[
\text{Ph} - \text{CHCOOCH}_2\text{CH}_3 + \text{H}_2\text{O}
\]

\[
\text{Cl}\quad \text{HCl, heat}
\]

\[
\text{Ph} - \text{CHCOH} + \text{CH}_3\text{CH}_2\text{OH}
\]

(80-82%)
Mechanism of Acid-Catalyzed Ester Hydrolysis

Is the reverse of the mechanism for acid-catalyzed esterification.

Like the mechanism of esterification, it involves two stages:

1) formation of tetrahedral intermediate (3 steps)
2) dissociation of tetrahedral intermediate (3 steps)
First stage: formation of tetrahedral intermediate

\[ RCO\text{OR'} + H_2O \rightarrow RCO\text{OH} + \text{OR'}\text{OH} \]

Water adds to the carbonyl group of the ester. This stage is analogous to the acid-catalyzed addition of water to a ketone.

\[ H^+ \]

\[ \text{OR'}\text{OH} \]

\[ \text{OR'}\text{OH} \]
Second stage: cleavage of tetrahedral intermediate

\[
\text{RCOH} + \text{R'OH} \rightarrow \text{H}^+ \rightarrow \text{RC} \text{OR'} + \text{OH}
\]
Mechanism of formation of tetrahedral intermediate
Step 1
Step 1

\[
\begin{align*}
\text{RC} & \quad \text{OO} \quad \text{R}^' \\
\text{O} & \quad \text{O} \\
\text{RC} & \quad \text{OO} \\
\text{O} & \quad \text{O} \\
\text{RC} & \quad \text{OO} \\
\end{align*}
\]
Step 1

carbonyl oxygen is protonated because cation produced is stabilized by electron delocalization (resonance)
Step 2

Chemical reaction diagram showing the interaction between molecules labeled RC and R'. The reaction involves the transfer of a proton (H+) from one molecule to another, indicated by the arrows and chemical structures.
Step 2

\[
\begin{align*}
\text{RC} \quad & \text{O} \\
\text{O} \quad & \text{H} \\
\text{OR'} \\
\text{O} \quad & \text{H} \\
\end{align*}
\]
Cleavage of tetrahedral intermediate
Step 5

\[
\begin{align*}
\text{RC} & \quad \text{OH} \\
\text{O}^+ & \quad \text{H} \\
\text{R} & \quad \text{O} \\
\end{align*}
\]
Step 5

\[
\begin{align*}
\text{RC} \quad \text{OH} \\
\text{RC} \quad \text{OH} \\
\text{RC} \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{RC} \quad \text{OH} \\
\text{RC} \quad \text{OH} \\
\text{RC} \quad \text{OH} \\
\end{align*}
\]
Step 5

\[ \text{RC} + \text{OH} \rightarrow \text{RC} = \text{OH} \]

\[ \text{RC} = \text{OH} \rightarrow \text{RC} + \text{OH} \]
Key Features of Mechanism

Activation of carbonyl group by protonation of carbonyl oxygen

Nucleophilic addition of water to carbonyl group forms tetrahedral intermediate

Elimination of alcohol from tetrahedral intermediate restores carbonyl group
Ethyl benzoate, labeled with $^{18}O$ at the carbonyl oxygen, was subjected to acid-catalyzed hydrolysis.

Ethyl benzoate, recovered before the reaction had gone to completion, had lost its $^{18}O$ label.

This observation is consistent with a tetrahedral intermediate.
$^{18}$O Labeling Studies

\[
\text{phenyl} - \text{COCH}_2\text{CH}_3 + \text{H}_2\text{O} \quad \xrightarrow{H^+} \quad \text{phenyl} - \text{C} - \text{OCH}_2\text{CH}_3 \quad \text{OH} \quad \text{OH}
\]

\[
\text{phenyl} - \text{COCH}_2\text{CH}_3 \quad \xrightarrow{H^+} \quad \text{phenyl} - \text{COCH}_2\text{CH}_3 + \text{H}_2\text{O}
\]
20.10
Ester Hydrolysis in Base:
Saponification
Ester Hydrolysis in Aqueous Base

\[
\text{RCOR'} \quad + \quad \text{HO}^- \quad \rightarrow \quad \text{RCO}^- \quad + \quad \text{R'O}H
\]

is called \textit{saponification}

is irreversible, because of strong stabilization of carboxylate ion

if carboxylic acid is desired product, saponification is followed by a separate acidification step (simply a pH adjustment)
Ester Hydrolysis in Aqueous Base

\[
\text{RCOR} + \text{HO}^- \xrightarrow{\text{H}^+} \text{RCO}^- + \text{R'}\text{OH}
\]
Example

\[
\text{CH}_2\text{OCCH}_3 \quad + \quad \text{NaOH} \\
\text{CH}_2\text{OH} \quad + \quad \text{CH}_3\text{COONa}
\]

(95-97%)

Water-methanol, heat
Example

\[ \text{H}_2\text{C} = \text{C} \text{COCH}_3 \]

1. NaOH, H\(_2\)O, heat
2. H\(_2\)SO\(_4\)

\[ \rightarrow \]

\[ \text{H}_2\text{C} = \text{C} \text{COOH} + \text{CH}_3\text{OH} \]

(87%)
Basic hydrolysis of the glyceryl triesters (from fats and oils) gives salts of long-chain carboxylic acids. These salts are soaps.
Which bond is broken when esters are hydrolyzed in base?

One possibility is an $S_{N}2$ attack by hydroxide on the alkyl group of the ester (alkyl-oxygen cleavage). Carboxylate is the leaving group.
Which bond is broken when esters are hydrolyzed in base?

A second possibility is nucleophilic acyl substitution (acyl-oxygen cleavage).
$^{18}O$ Labeling gives the answer

$^{18}O$ retained in alcohol, not carboxylate; therefore nucleophilic acyl substitution (acyl-oxygen cleavage).
Stereochemistry gives the same answer

alcohol has same configuration at stereogenic center as ester; therefore, nucleophilic acyl substitution (acyl-oxygen cleavage) not $S_{N2}$
Does it proceed via a tetrahedral intermediate?

Does nucleophilic acyl substitution proceed in a single step, or is a tetrahedral intermediate involved?
Ethyl benzoate, labeled with $^{18}$O at the carbonyl oxygen, was subjected to hydrolysis in base. Ethyl benzoate, recovered before the reaction had gone to completion, had lost its $^{18}$O label. This observation is consistent with a tetrahedral intermediate.
18O Labeling Studies

\[
\text{COCH}_2\text{CH}_3 + \text{H}_2\text{O} \rightleftharpoons \text{HO}^- \quad \text{COCH}_2\text{CH}_3 + \text{H}_2\text{O} \\
\text{OH}^- \quad \text{C-OCH}_2\text{CH}_3 \quad \text{OH}^- \\
\text{COCH}_2\text{CH}_3 + \text{H}_2\text{O} \rightleftharpoons \text{HO}^- \quad \text{COCH}_2\text{CH}_3 + \text{H}_2\text{O}
\]
Involves two stages:

1) formation of tetrahedral intermediate
2) dissociation of tetrahedral intermediate
First stage: formation of tetrahedral intermediate

$$\text{RCOR} + \text{H}_2\text{O} \rightarrow \text{HO}^- \text{RCOR} + \text{HO}^- \text{OR}$$

Water adds to the carbonyl group of the ester.

This stage is analogous to the base-catalyzed addition of water to a ketone.
Second stage: cleavage of tetrahedral intermediate

\[ RCOH + R'OH \]

\[ \text{HO} \]

\[ \text{OH} \]

\[ \text{RC} \text{--OR'} \]

\[ \text{OH} \]
Mechanism of formation of tetrahedral intermediate
Step 2
Step 2

\[
\begin{align*}
\text{RC} & \quad \text{O} \\
\text{OR'} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{H} & \quad \text{O}
\end{align*}
\]
Dissociation of tetrahedral intermediate
Step 4
Nucleophilic addition of hydroxide ion to carbonyl group in first step

Tetrahedral intermediate formed in first stage

Hydroxide-induced dissociation of tetrahedral intermediate in second stage
20.11
Reactions of Esters
with Ammonia and Amines
Reactions of Esters

RCOR' → O

RCOR' → RCNR'R₂ → O

RCO⁻
Esters react with ammonia and amines to give amides:

\[
\text{RCOR'} + \text{R}_2\text{NH} \rightarrow \text{RCNR}_2' + \text{R'}\text{OH}
\]
Reactions of Esters

Esters react with ammonia and amines to give amides:

\[
\text{RCOR'} + \text{R'}_2\text{NH} \rightarrow \text{RCNRR'}_2 + \text{R'OH}
\]

via:

\[
\text{RCNRR'}_2 + \text{R'OH}
\]
Example

\[
\text{H}_2\text{C} = \text{C}=\text{C}=\text{C} = \text{COCH}_3 + \text{NH}_3 \\
\text{CH}_3 \quad \downarrow \quad \text{H}_2\text{O} \\
\text{O} \\
\text{H}_2\text{C} = \text{C}=\text{C}=\text{C} = \text{CONH}_2 + \text{CH}_3\text{OH} \\
\text{CH}_3 \\
(75\%)
Example

$$FCH_2COCH_2CH_3 + \text{NH}_2\text{NH} \xrightarrow{\text{heat}} FCH_2CNH + \text{CH}_3\text{CH}_2\text{OH}\quad (61\%)$$
20.12
Thioesters
Thioesters

Thioesters are compounds of the type:

\[ \text{RC} - \text{O} - \text{CS} - \text{R'} \]

Thioesters are intermediate in reactivity between anhydrides and esters.

Thioester carbonyl group is less stabilized than oxygen analog because C—S bond is longer than C—O bond which reduces overlap of lone pair orbital and C=O \( \pi \) orbital.
Many biological nucleophilic acyl substitutions involve thioesters.

\[
\text{RC\textit{SR'}} + \text{Nu}\rightarrow \text{H} \rightarrow \text{RC\textit{Nu}} + \text{R'S}\rightarrow \text{H}
\]

via:

\[
\begin{align*}
\text{R} & \text{C} \rightarrow \text{Nu} \\
\text{SR'} & \rightarrow \text{H}
\end{align*}
\]