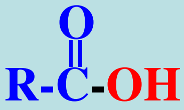
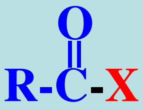
Carboxylic Acid Derivatives

The carboxyl group consists of two parts, the acyl group and the attached hydroxyl group:

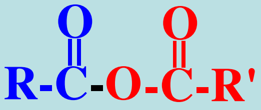


$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}OH}$

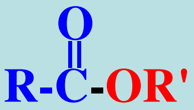
The acid derivatives are compounds in which the hydroxyl group is replaced with another group or a halogen atom. The principal examples are:



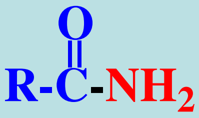
$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}X}$ **Acyl (acid) halides**



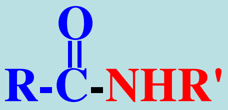
$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}{-}R'}$ **Acid anhydrides**



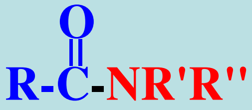
$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}OR'}$ **Esters**



$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}NH_2}$ **Amides**



$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}NHR'}$ ***N*-Monosubstituted Amides**



$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}NR'R''}$ ***N,N*-Disubstituted Amides**

Another class of carboxylic acid derivatives are the nitriles, which qualify because on hydrolysis, like all of the other derivatives above, they yield carboxylic acids.

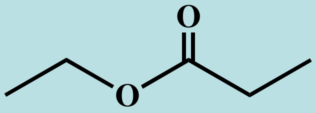
$\mathrm{R{-}C{\equiv}N}$ **Nitriles**

10.9

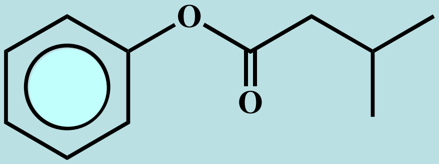
Esters

Their two-part names follow the pattern:
[Name of alkyl or aryl group derived from parent alcohol] [Name of carboxylate ion derived from parent acid]

Examples:



Made from ethanol and propanoic acid, so name is ethyl propanoate.

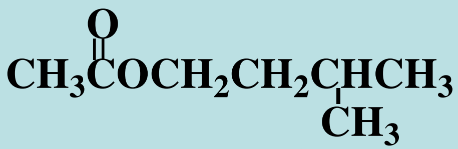


Made from phenol and 3-methylbutanoic acid, so name is phenyl 3-methylbutanoate.

Esters are hydrogen-bond acceptors, enhancing their water solubility, but they are not hydrogen-bond donors, lacking a hydrogen on oxygen. Consequently they cannot associate and so have low boiling points and high volatility. Fortunately, they have pleasant, fruit-like odors.

Esters as Perfumes and Flavoring Agents

Many esters have pleasant odors and tastes and are used in perfumes and as flavoring agents. A number of these compounds occur in nature where they are responsible for the characteristic odor of fruits.



$CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_2\underset{\underset{CH_3}{|}}{C}HCH_3$

Isoamyl acetate (banana)

$CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_2CH_2CH_3$

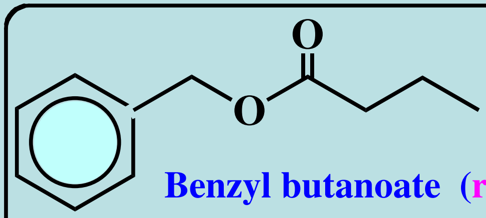
Butyl butanoate (pineapple)

$CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_2CH_2CH_2CH_3$

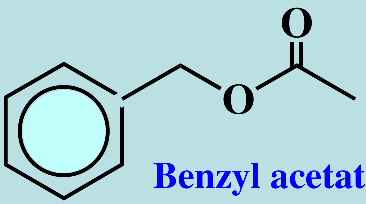
Pentyl butanoate (apricot)

$CH_3\overset{\overset{O}{\|}}{C}O(CH_2)_7CH_3$

Octyl acetate (orange)



Benzyl butanoate (rose)



Benzyl acetate (Chanel No. 5)

$H\overset{\overset{O}{\|}}{C}OCH_2CH_3$

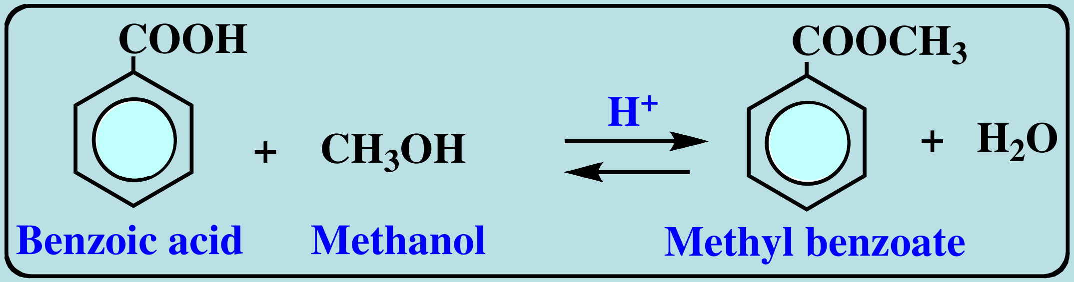
Ethyl formate (rum)

10.10

Esters
Synthesis of Esters

Direct Esterification of Carboxylic Acids

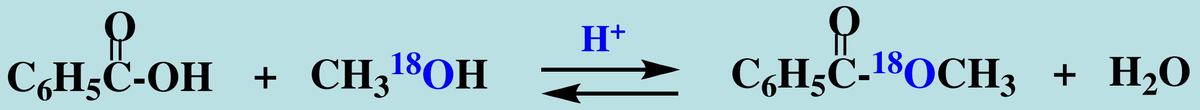
Carboxylic acids and alcohols react in the presence of a small amount of strong acid to give esters.



Esterifications are acid-catalyzed equilibrium reactions. Catalytic amounts of concentrated sulfuric acid or hydrochloric acid are used. Usually a large excess of the alcohol (10- or 15-fold) is used to drive the equilibrium to the product side. Product formation can also be promoted by removing the water as it is formed.

Mechanistic Studies by Isotopic Labeling

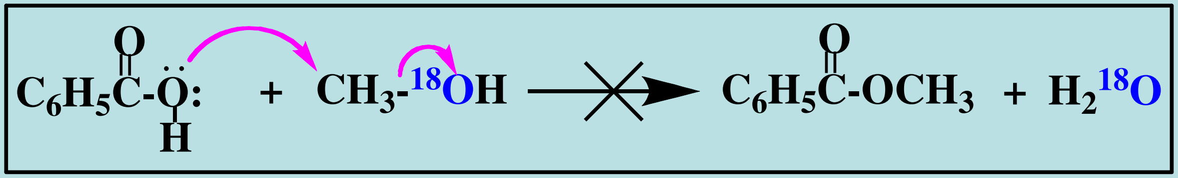
Insight into the key bonding changes during esterification was obtained by studies using isotopically enriched methanol.



$$C_6H_5\overset{\overset{O}{\|}}{C}\text{-}OH + CH_3{}^{18}OH \overset{H^+}{\rightleftarrows} C_6H_5\overset{\overset{O}{\|}}{C}\text{-}{}^{18}OCH_3 + H_2O$$

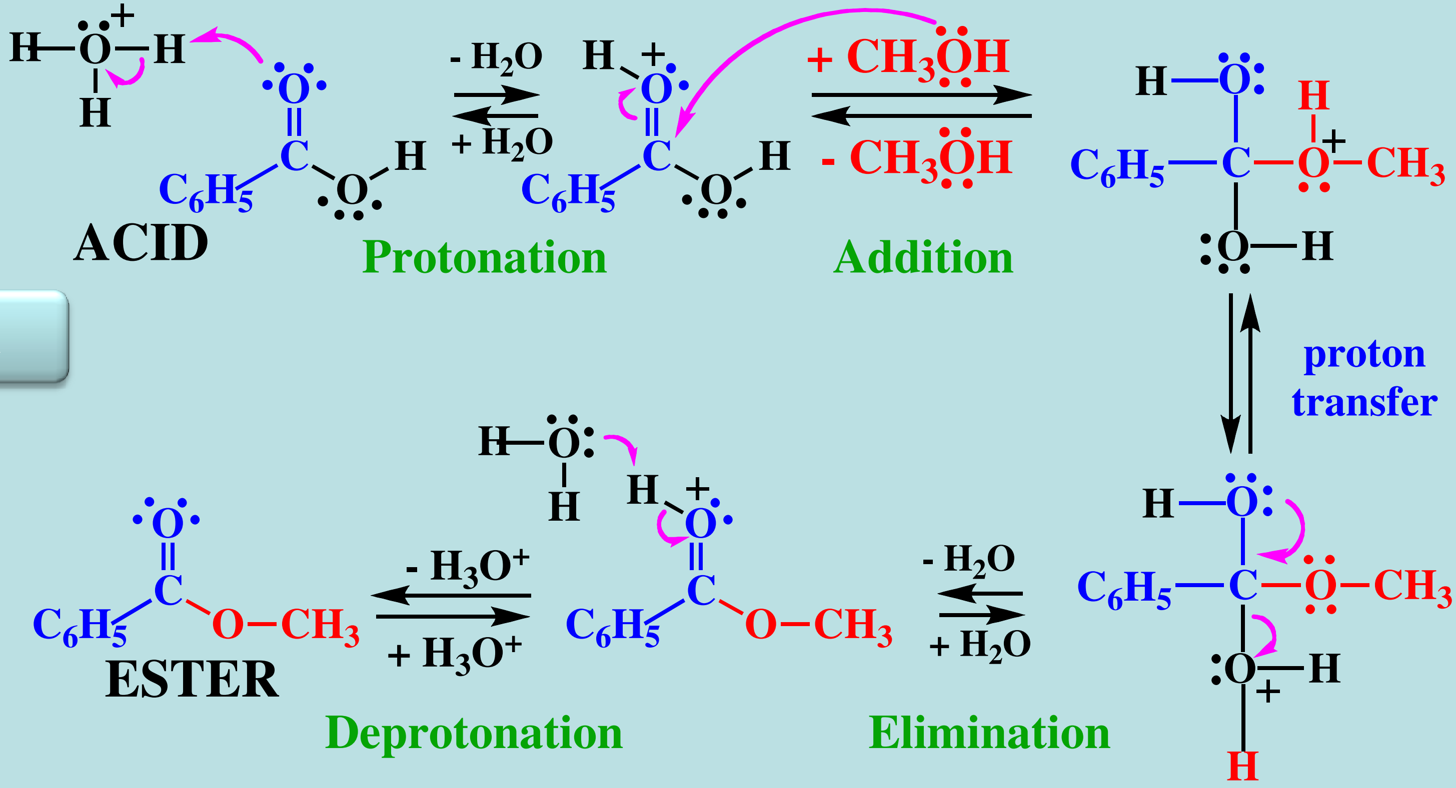
All the isotopic label appears in the methoxy oxygen.

This result rules out an S_N2 mechanism:



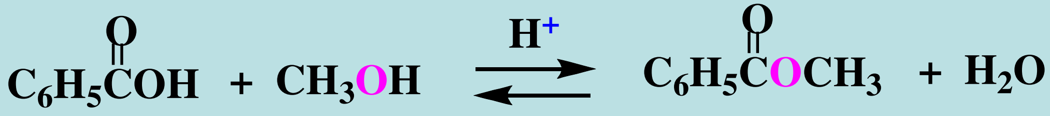
$$C_6H_5\overset{\overset{O}{\|}}{C}\text{-}\underset{H}{\ddot{O}}: + CH_3\text{-}{}^{18}OH \not\longrightarrow C_6H_5\overset{\overset{O}{\|}}{C}\text{-}OCH_3 + H_2{}^{18}O$$

The Mechanism of Acid-Catalyzed Esterification



10.11

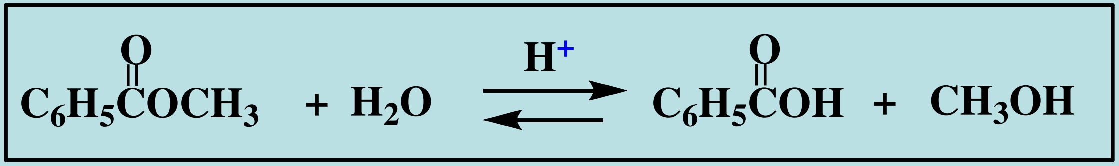
This mechanism for esterification is consistent with the incorporation of the isotopic label:



$$C_6H_5\overset{O}{\overset{\|}{C}}OH + CH_3OH \overset{H^+}{\rightleftharpoons} C_6H_5\overset{O}{\overset{\|}{C}}OCH_3 + H_2O$$

A Mechanism for Acid-Catalyzed Hydrolysis of Esters

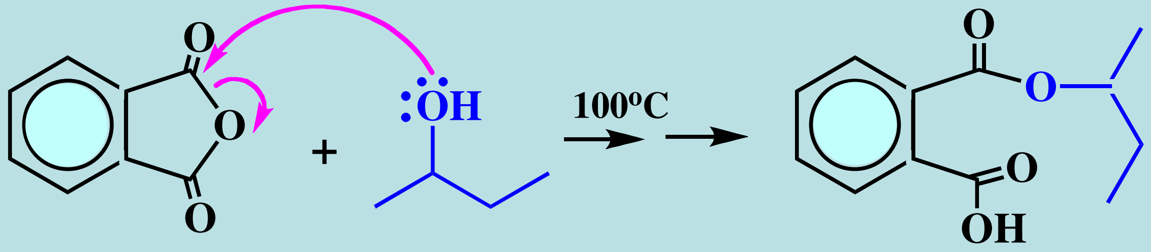
Since every step is reversible, the reverse of the esterification scheme is the mechanism for the acid-catalyzed hydrolysis of esters.



$$C_6H_5\overset{O}{\overset{\|}{C}}OCH_3 + H_2O \overset{H^+}{\rightleftharpoons} C_6H_5\overset{O}{\overset{\|}{C}}OH + CH_3OH$$

The direction of the reaction is controlled by the relative concentrations of water versus alcohol.

Cyclic Anhydrides Undergo Similar Reactions

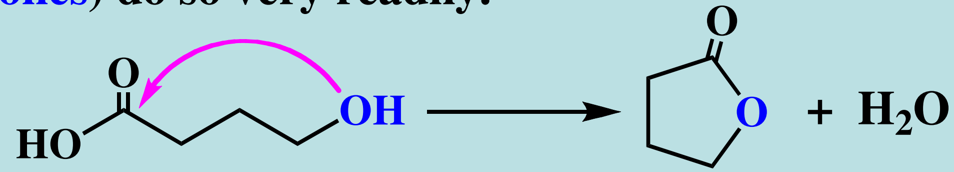


Phthalic anhydride **_sec_-Butyl alcohol** **_sec_-Butyl hydrogen phthalate**

Intramolecular Esterification: Lactone Formation

Carboxylic acids that contain alcohol functions that can react intramolecularly to form 5- or 6-membered cyclic esters (lactones) do so very readily.

10.12

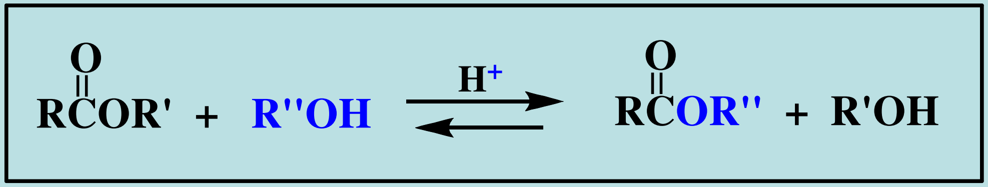


4-Hydroxybutanoic acid (γ-Hydroxybutyric acid) **γ-Butyrolactone**

A trace of strong acid catalyst hastens the conversion.

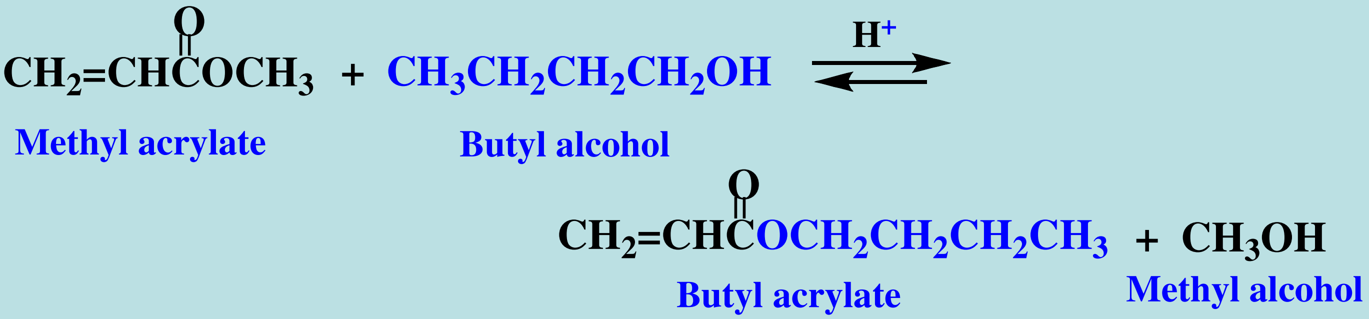
Transesterification

This is a process whereby the ester of one alcohol may be converted into the ester of a second alcohol by the equilibrium:



$$R\overset{O}{\overset{\|}{C}}OR' + R''OH \underset{}{\overset{H^+}{\rightleftharpoons}} R\overset{O}{\overset{\|}{C}}OR'' + R'OH$$

An example



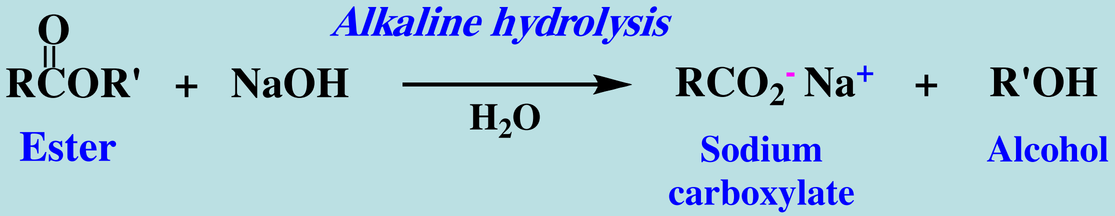
$$CH_2{=}CH\overset{O}{\overset{\|}{C}}OCH_3 + CH_3CH_2CH_2CH_2OH \overset{H^+}{\rightleftharpoons} CH_2{=}CH\overset{O}{\overset{\|}{C}}OCH_2CH_2CH_2CH_3 + CH_3OH$$

The equilibrium is shifted to the product side by using an excess of butyl alcohol and/or distilling out the lower boiling methanol from the reaction mixture.

10.13

Base-Promoted Hydrolysis of Esters: Saponification

Base-promoted hydrolysis of esters is called saponification (from the Latin *sapo*, soap) because traditional soap-making involves the alkaline hydrolysis of fats (esters of glycerol).



$$\overset{\overset{\displaystyle O}{\|}}{RCOR'} + NaOH \xrightarrow[H_2O]{\textit{Alkaline hydrolysis}} RCO_2^- Na^+ + R'OH$$

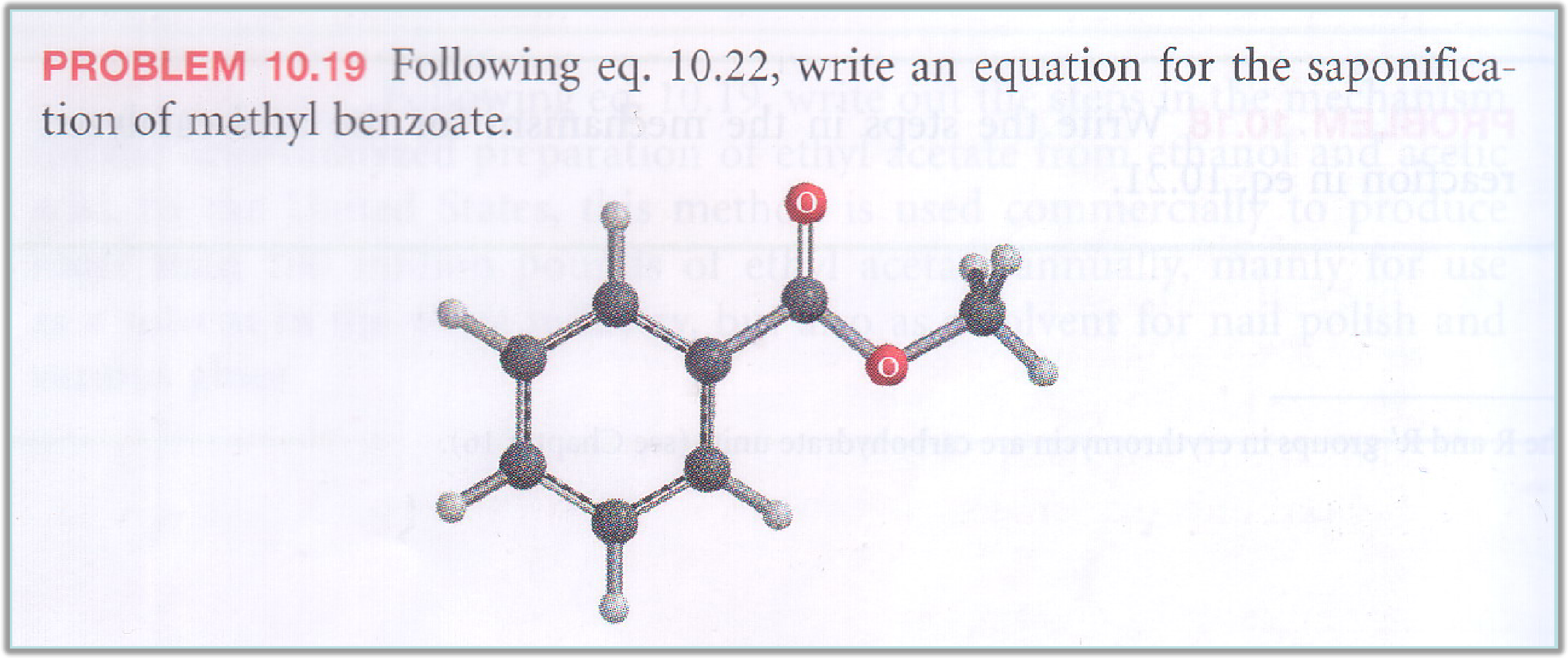
Alkaline hydrolysis

Ester

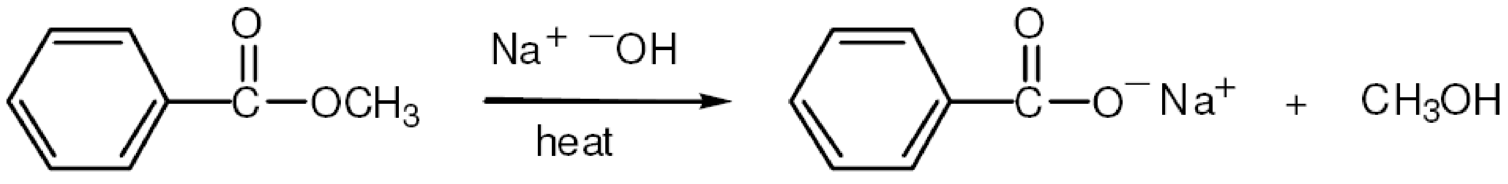
Sodium carboxylate

Alcohol

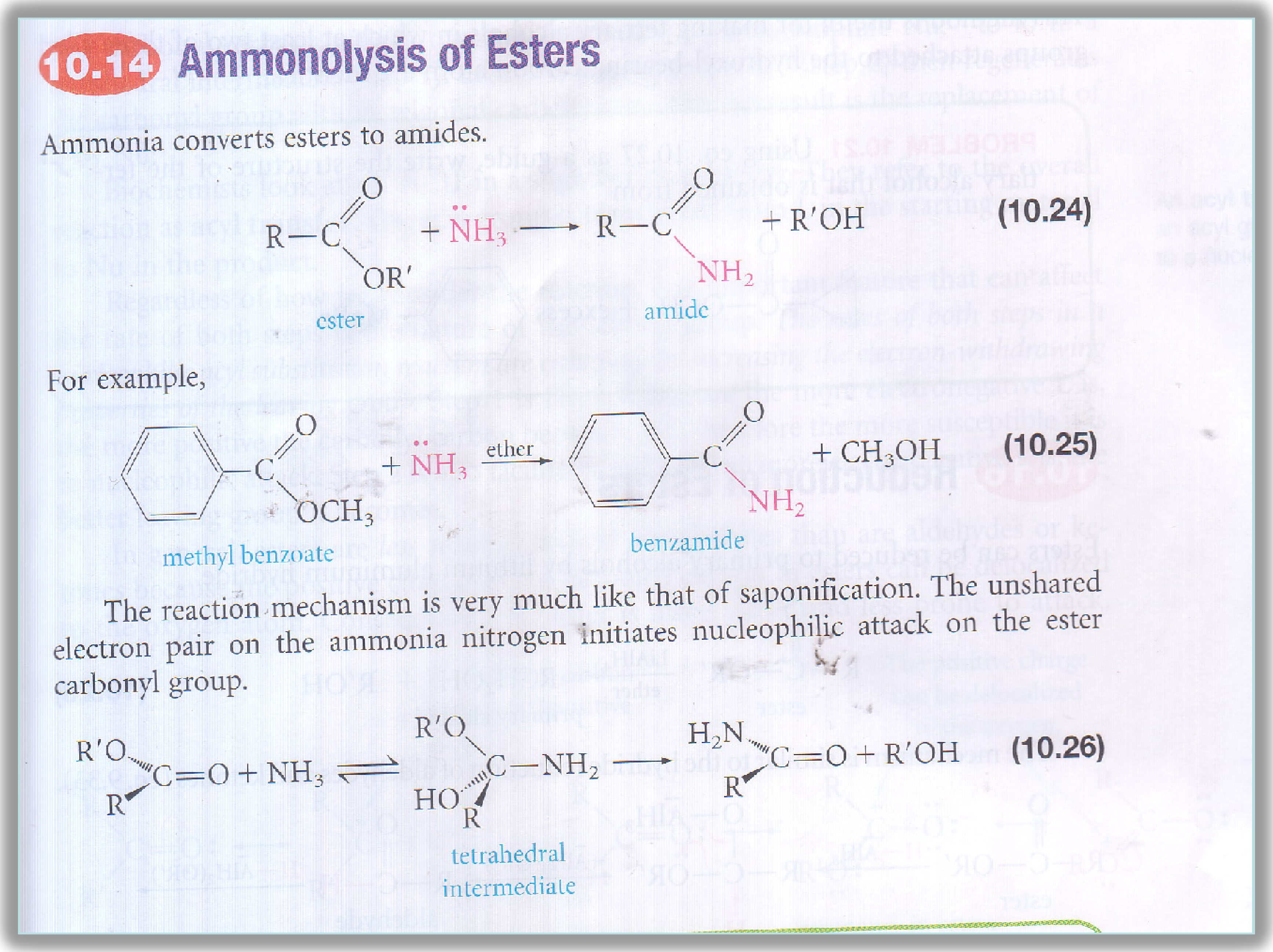
In the case of soaps, the R in the carboxylate ion typically is a straight-chain alkyl containing eleven to seventeen carbon atoms.



PROBLEM 10.19 Following eq. 10.22, write an equation for the saponification of methyl benzoate.



methyl benzoate · sodium benzoate · methanol



10.14 Ammonolysis of Esters

Ammonia converts esters to amides.

(10.24)

ester

amide

For example,

(10.25)

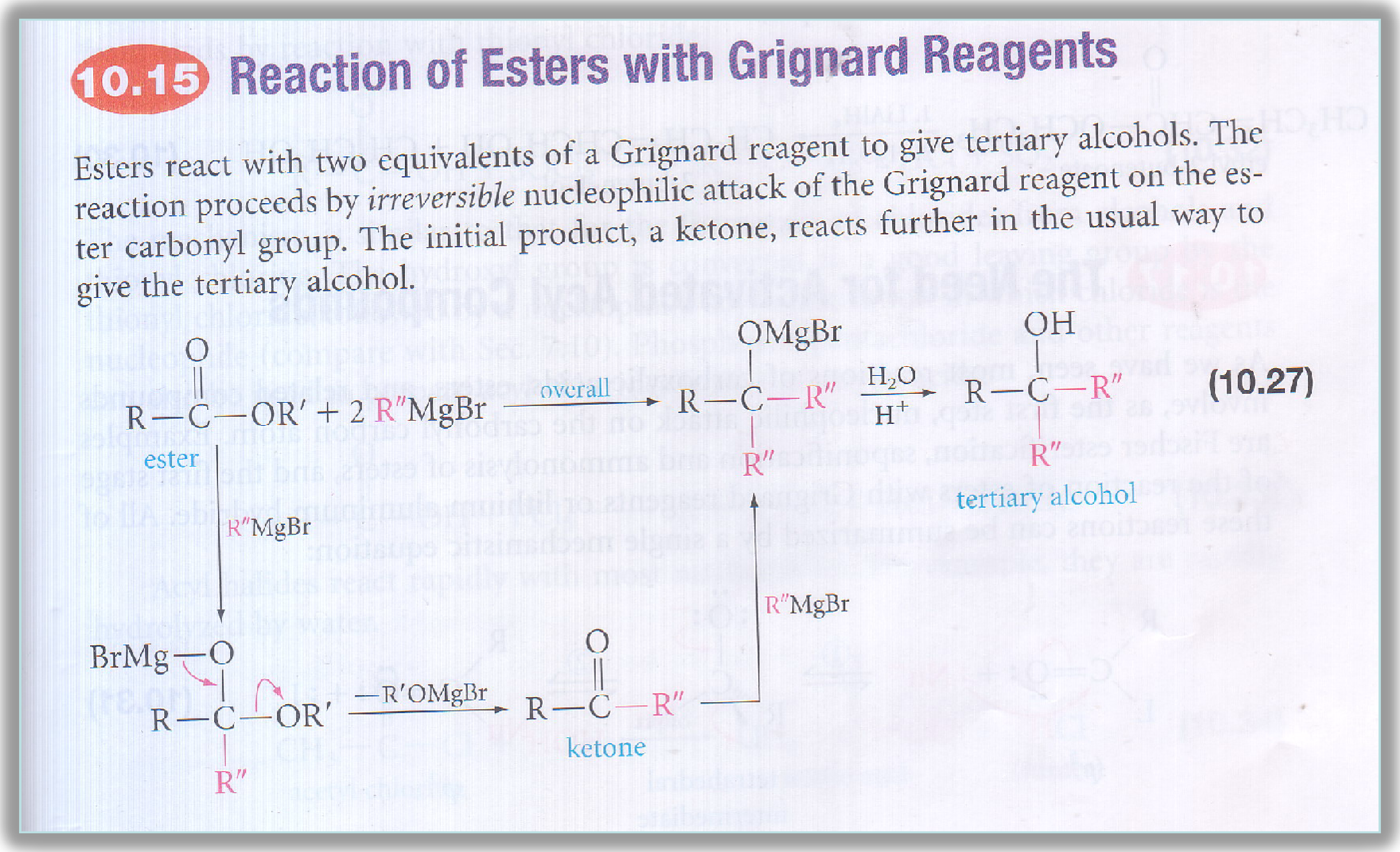
methyl benzoate

benzamide

The reaction mechanism is very much like that of saponification. The unshared electron pair on the ammonia nitrogen initiates nucleophilic attack on the ester carbonyl group.

(10.26)

tetrahedral intermediate



10.15 Reaction of Esters with Grignard Reagents

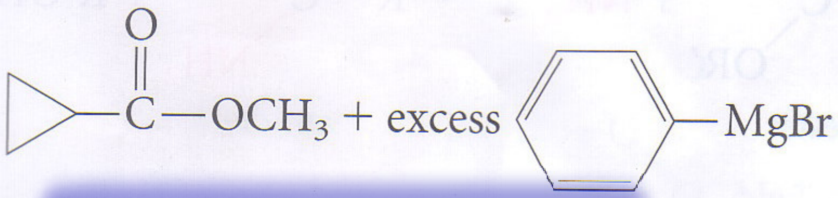
Esters react with two equivalents of a Grignard reagent to give tertiary alcohols. The reaction proceeds by *irreversible* nucleophilic attack of the Grignard reagent on the ester carbonyl group. The initial product, a ketone, reacts further in the usual way to give the tertiary alcohol.

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-OR' + 2\,R''MgBr \xrightarrow{\text{overall}} R-\underset{\underset{\displaystyle R''}{|}}{\overset{\overset{\displaystyle OMgBr}{|}}{C}}-R'' \xrightarrow[H^+]{H_2O} R-\underset{\underset{\displaystyle R''}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}-R'' \qquad \textbf{(10.27)}$$

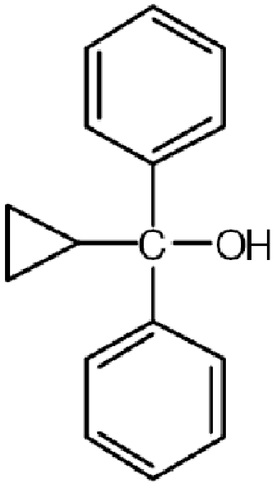
$$R-\overset{\overset{\displaystyle O}{\|}}{C}-OR' \xrightarrow{R''MgBr} \overset{BrMg-O}{} R-\underset{\underset{\displaystyle R''}{|}}{\overset{|}{C}}-OR' \xrightarrow{-R'OMgBr} R-\overset{\overset{\displaystyle O}{\|}}{C}-R'' \xrightarrow{R''MgBr} R-\underset{\underset{\displaystyle R''}{|}}{\overset{\overset{\displaystyle OMgBr}{|}}{C}}-R''$$

This method is useful for making tertiary alcohols in which at least two of three alkyl groups attached to the hydroxyl-bearing carbon atom are identical.

PROBLEM 10.21 Using eq. 10.27 as a guide, write the structure of the tertiary alcohol that is obtained from

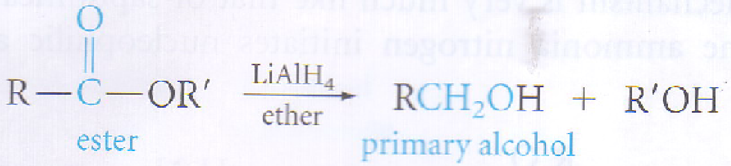


we get the tertiary alcohol



10.16 Reduction of Esters

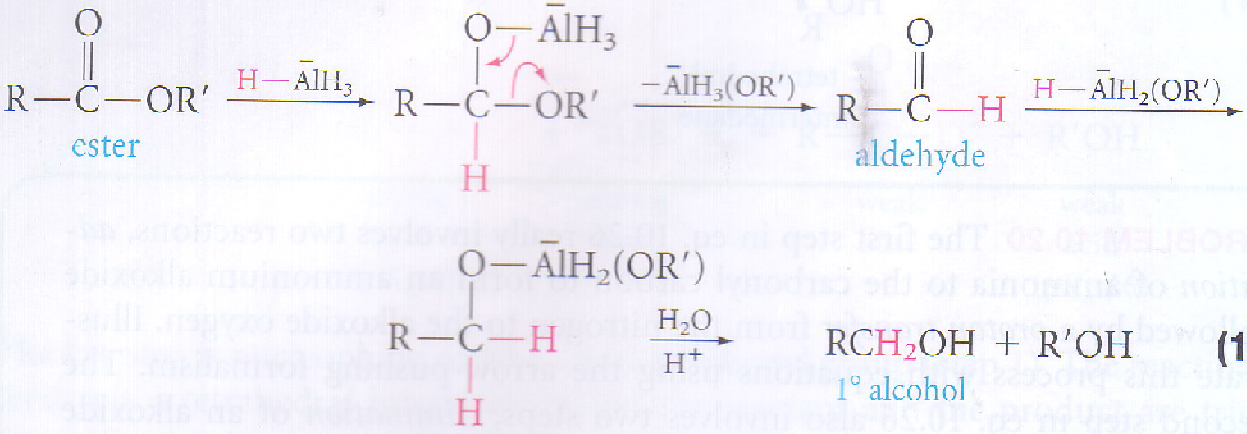
Esters can be reduced to primary alcohols by lithium aluminum hydride.



$$R-\overset{O}{\overset{\|}{C}}-OR' \xrightarrow[\text{ether}]{LiAlH_4} RCH_2OH + R'OH$$

(10.28)

The mechanism is similar to the hydride reduction of aldehydes and ketones (eq. 9.33).

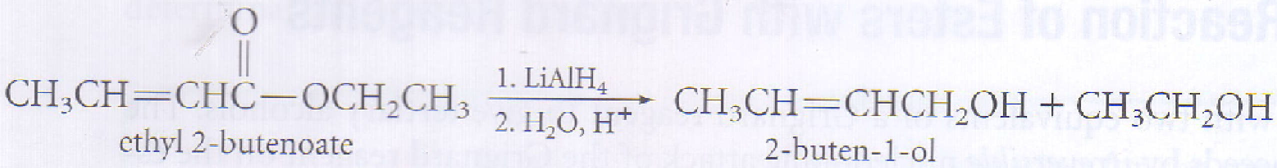


$$RCH_2OH + R'OH$$

(10.29)

The intermediate aldehyde is not usually isolable and reacts rapidly with additional hydride to produce the alcohol.

It is possible to reduce an ester carbonyl group without reducing a C=C bond in the same molecule. For example,



$$CH_3CH=CH\overset{O}{\overset{\|}{C}}-OCH_2CH_3 \xrightarrow[2.\ H_2O,\ H^+]{1.\ LiAlH_4} CH_3CH=CHCH_2OH + CH_3CH_2OH$$

(10.30)