

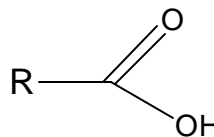
## Chapter 18

### Carboxylic Acids and Their Derivatives.

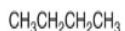
#### Nucleophilic Addition-Elimination at the Acyl Carbon

#### Carboxylic Acids

- ◆ Organic compounds characterized by their acidity
- ◆ Contains COOH group (must be at the end of a chain)
- ◆ Widely distributed in nature
- ◆ Easily separated because of acidity



## Physical Properties of Carboxylic Acids



MW = 58

bp 0 °C

MW = 58

bp 48 °C

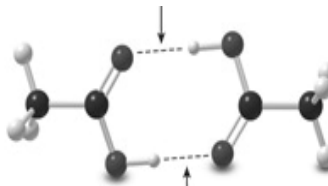
MW = 60

bp 97 °C

MW = 60

bp 118 °C

### High Boiling Points



Acetic acid, melting point = 16°C

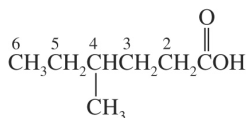
Carboxylic acids soluble in organic solvents

Carboxylic acids with 5 or fewer carbons are water soluble

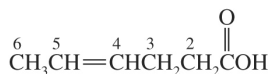
Carboxylic acids with longer chains insoluble (called “fatty acids”)

## Nomenclature

- ◆ In IUPAC nomenclature, a carboxylic acid is named changing the -e of the corresponding parent alkane to -oic acid
  - The carboxyl carbon is position 1 and is not numbered



4-Methylhexanoic acid



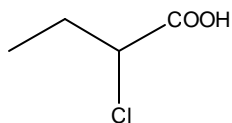
4-Hexenoic acid  
(or hex-4-enoic acid)

- ◆ The common names for many carboxylic acids remain in use

## Some straight chain acids

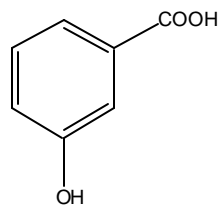
Structure	Systematic Name	Common Name	mp (°C)	bp (°C)	Water Solubility (g 100 mL <sup>-1</sup> H <sub>2</sub> O),		pK
					25°C		
HCO <sub>2</sub> H	Methanoic acid	Formic acid	8	100.5	∞		3.7
CH <sub>3</sub> CO <sub>2</sub> H	Ethanoic acid	Acetic acid	16.6	118	∞		4.7
CH <sub>3</sub> CH <sub>2</sub> CO <sub>2</sub> H	Propanoic acid	Propionic acid	-21	141	∞		4.8
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	Butanoic acid	Butyric acid	-6	164	∞		4.8
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> H	Pentanoic acid	Valeric acid	-34	187	4.97		4.8
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> H	Hexanoic acid	Caproic acid	-3	205	1.08		4.8
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> CO <sub>2</sub> H	Octanoic acid	Caprylic acid	16	239	0.07		4.8
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub> CO <sub>2</sub> H	Decanoic acid	Capric acid	31	269	0.015		4.8
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> CO <sub>2</sub> H	Dodecanoic acid	Lauric acid	44	179 <sup>18</sup>	0.006		5.3
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>12</sub> CO <sub>2</sub> H	Tetradecanoic acid	Myristic acid	59	200 <sup>20</sup>	0.002		
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>14</sub> CO <sub>2</sub> H	Hexadecanoic acid	Palmitic acid	63	219 <sup>17</sup>	0.0007		6.4
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>16</sub> CO <sub>2</sub> H	Octadecanoic acid	Stearic acid	70	383	0.0003		

## Naming Carboxylic Acids



◆ **a-chlorobutyric acid**

◆ **2-chlorobutanoic acid**

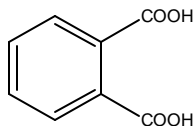


**m-hydroxybenzoic acid**

## Some other acids with common names

### ◆ Diacids

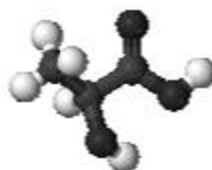
- Oxalic                     $\text{HOOC-COOH}$
- Malonic                  $\text{HOOC-CH}_2\text{-COOH}$
- Succinic                 $\text{HOOC-CH}_2\text{CH}_2\text{-COOH}$
- Phthalic



### • Hydroxyacid

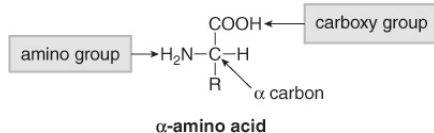
#### • Lactic acid

(S)-2-hydroxypropanoic acid

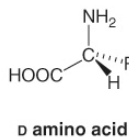
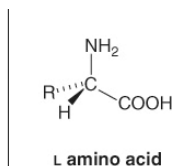
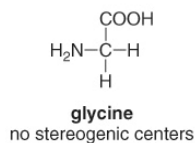


## Amino Acids

- Amino acids contain two functional groups—an amine group ( $\text{NH}_2$ ) and a carboxy group ( $\text{COOH}$ ).
- Amino acids are the building blocks of proteins.

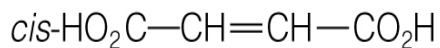


- The simplest amino acid, glycine, has  $\text{R} = \text{H}$ . When R is any other group, the carbon is a stereogenic center.



\*

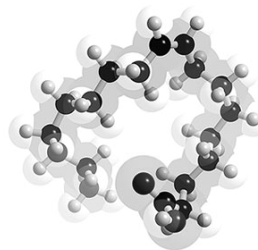
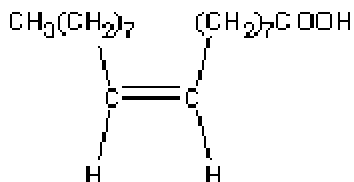
## Unsaturated acids



Maleic acid



Fumaric acid



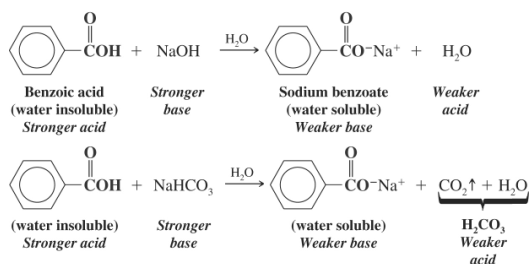
**Oleic acid = cis-9-octadecenoic acid**

**75% of olive oil is oleic acid**

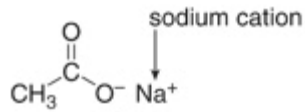
## Carboxylic Acid Salt

◆ **Most carboxylic acids have a  $pK_a = 4 - 5$**

- Carboxylic acids are readily deprotonated by sodium hydroxide or sodium bicarbonate to form carboxylate salts
- Carboxylate salts are more water soluble than the corresponding carboxylic acid

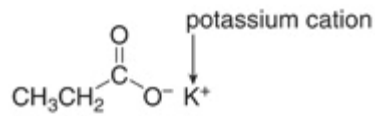


## Naming Carboxylic Acid Salts



parent + suffix  
acet-     -ate

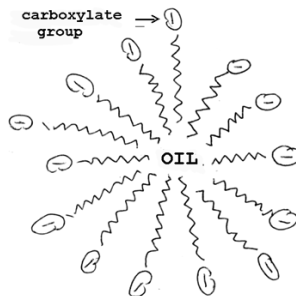
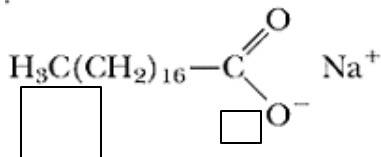
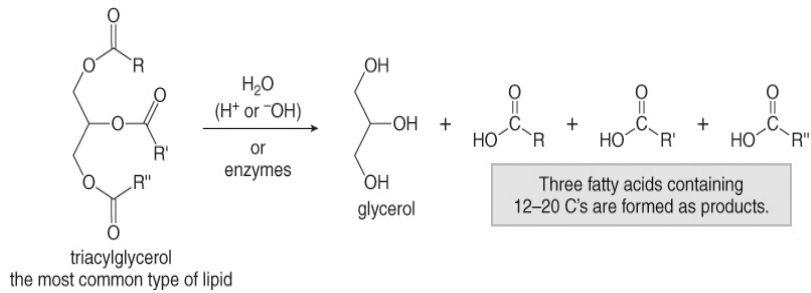
sodium acetate



parent + suffix  
propan-     -oate

potassium propanoate

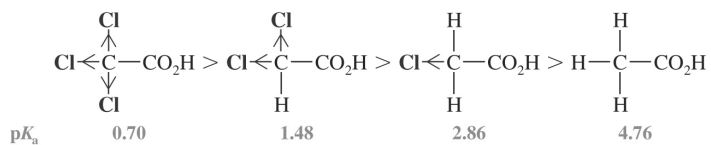
## Sodium salts of fatty acids are soaps



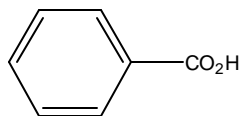
## Acidity of Carboxylic Acids

Electron-withdrawing groups increase the carboxylic acid's acidity

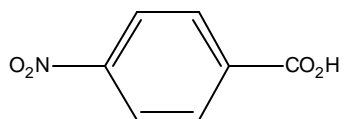
1. By inductive delocalization of charge



Predict the  $\text{p}K_a$  of p-nitrobenzoic acid



$$\text{p}K_a = 4.2$$



$$\text{p}K_a = ?$$

A.  $> 4.2$

B.  $4.2$

C.  $< 4.2$

$$\text{p}K_a = 3.48$$

## Acidity of Substituted Benzoic Acids

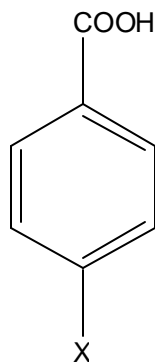
[2] Electron-withdrawing groups stabilize the conjugate base, making an acid more acidic  
electron density removed from the carboxylate anion.



Stabilization effect much greater in anion

## Acidity of Benzoic Acids

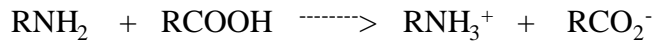
X =	
H	4.19
CH <sub>3</sub>	4.31
NH <sub>2</sub>	4.92
Cl	3.98
NO <sub>2</sub>	3.48





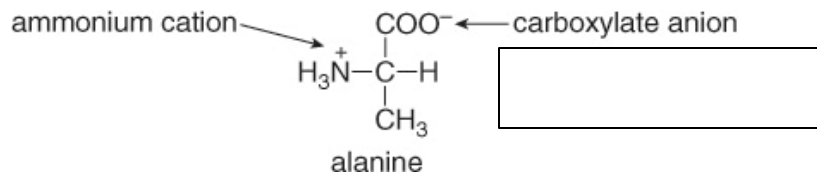
## Acidity of Amino Acids

**Since amines are basic and carboxylic acid groups are acidic, the two groups undergo a proton transfer**

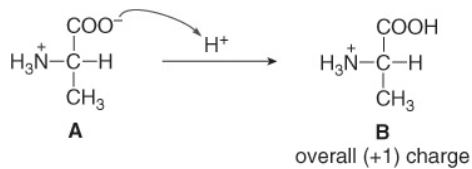


**Amino acids exist in three different forms depending on pH.**

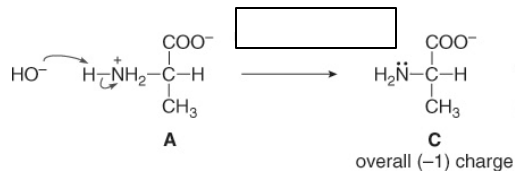
The “zwitterion” exists at neutral pH (7)



**At low pH (<2),  
alanine exists as a  
positive ion**



**At high pH (>11),  
alanine exists as an  
anion**

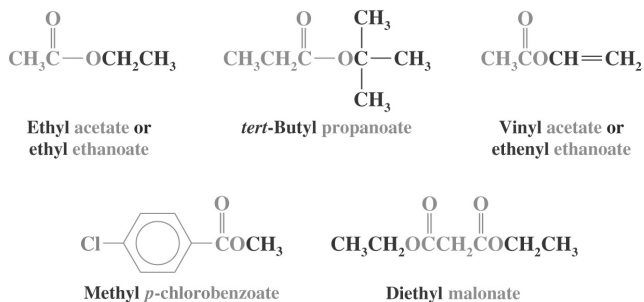


- ◆ The carboxyl group is the parent group of a family of compounds called *acyl compounds* or *carboxylic acid derivatives*

Structure	Name	Structure	Name
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{Cl} \end{array}$	Acyl (or acid) chloride	$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{NH}_2 \end{array}$	Amide
$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{R}-\text{C}-\text{O}-\text{C}-\text{R}' \end{array}$	Acid anhydride	$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{NHR}' \end{array}$	
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{O}-\text{R}' \end{array}$	Ester	$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{NR}'\text{R}'' \end{array}$	
$\text{R}-\text{C}\equiv\text{N}$	Nitrile		

## Esters

- ◆ Esters are named from the corresponding carboxylic acid and alcohol from which the ester would be made
  - The alcohol portion is named first and has the ending -yl
  - The carboxylic acid is named ending with -ate or -oate.

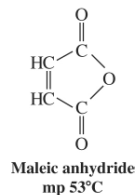
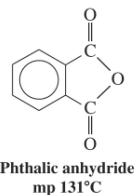
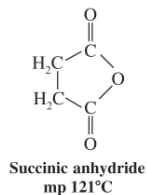
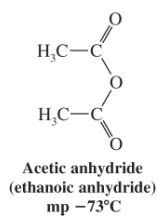


- ◆ Esters cannot hydrogen bond to each other and therefore have lower boiling points than carboxylic acids
  - Esters can hydrogen bond to water and have appreciable water solubility

Name	Structure	mp (°C)	bp (°C)	Solubility in Water (g 100 mL <sup>-1</sup> at 20°C)
Methyl formate	HCO <sub>2</sub> CH <sub>3</sub>	-99	31.5	Very soluble
Ethyl formate	HCO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	-79	54	Soluble
Methyl acetate	CH <sub>3</sub> CO <sub>2</sub> CH <sub>3</sub>	-99	57	24.4
Ethyl acetate	CH <sub>3</sub> CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	-82	77	7.39 (25°C)
Propyl acetate	CH <sub>3</sub> CO <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	-93	102	1.89
Butyl acetate	CH <sub>3</sub> CO <sub>2</sub> CH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	-74	125	1.0 (22°C)
Ethyl propanoate	CH <sub>3</sub> CH <sub>2</sub> CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	-73	99	1.75
Ethyl butanoate	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	-93	120	0.51
Ethyl pentanoate	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	-91	145	0.22
Ethyl hexanoate	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	-68	168	0.063
Methyl benzoate	C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> CH <sub>3</sub>	-12	199	0.15
Ethyl benzoate	C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	-35	213	0.08
Phenyl acetate	CH <sub>3</sub> CO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>		196	Slightly soluble
Methyl salicylate	o-HOC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> CH <sub>3</sub>	-9	223	0.74 (30°C)

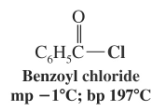
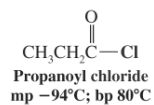
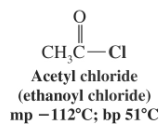
### ◆ Acid Anhydrides

- Most anhydrides are named by dropping the word *acid* from the carboxylic acid name and adding the word *anhydride*



### ◆ Acid Chlorides

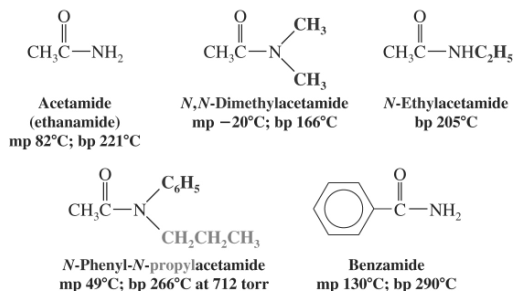
- Acid chlorides are named by dropping the *-ic acid* from the name of the carboxylic acid and adding *-yl chloride*



## ◆ Amides

- Amides are named by replacing *-ic acid* in the name with *amide*

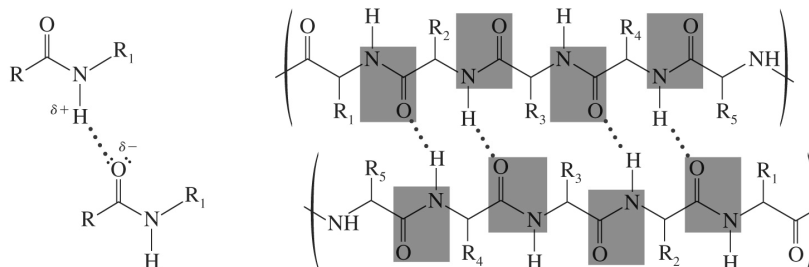
➔ Groups on the nitrogen are named as substituents and are given the locants *N-* or *N,N-*



- Amides with one or two hydrogens on nitrogen form very strong hydrogen bonds and have high melting and boiling points

➔ *N,N*-disubstituted amides cannot form hydrogen bonds to each other and have lower melting and boiling points

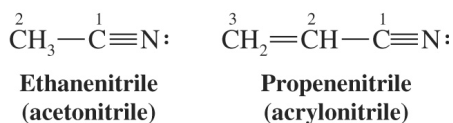
- ## ◆ Hydrogen bonding between amides in proteins and peptides is an important factor in determining their 3-dimensional shape



## Nitriles

◆ Acyclic nitriles are named by adding the suffix -*nitrile* to the alkane name

- The nitrile carbon is assigned position 1
- Ethanenitrile is usually called acetonitrile



## Infrared Spectra of Acyl Compounds

◆ The 1700 carbonyl stretching frequency varies slightly according to the type of carboxylic acid derivative present

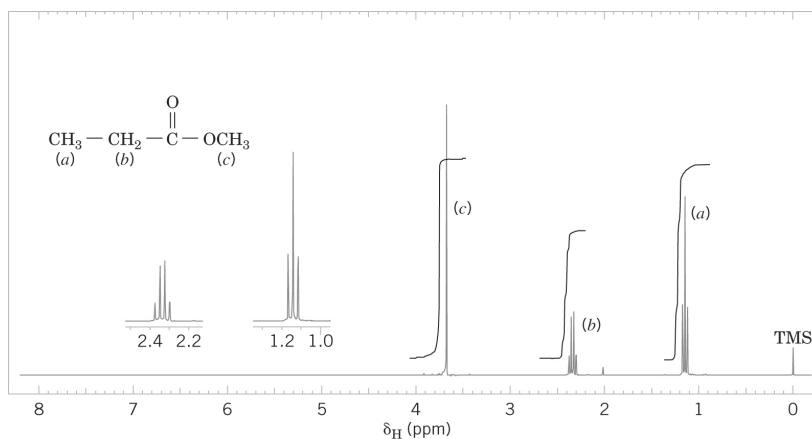
- O-H stretching vibrations of the carboxylic acid give a broad band at 2500-3100 cm<sup>-1</sup>
- N-H stretching vibrations of amides appear at 3140-3500 cm<sup>-1</sup>

Functional Group	Approximate Frequency Range (cm <sup>-1</sup> )	1840 1820 1800 1780 1760 1740 1720 1700 1680 1660 1640 1620 1600
Acid chloride	1815-1785 1800-1770 (conj.)	
Acid anhydride	1820-1750 1775-1720 (conj.)	
Ester/Lactone	1750-1735 1730-1715 (conj.)	
Carboxylic acid	-1760 or 1720-1705 1710-1680 (conj.)	
Aldehyde	1740-1720 1710-1685 (conj.)	
Ketone	1720-1710 1685-1665 (conj.)	
Amide/lactam	1650-1640	
Carboxylate salt	1650-1550	

\*Orange bars represent absorption ranges for conjugated species.

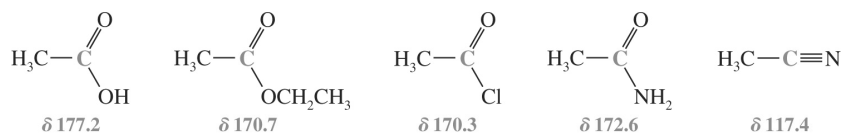
### ◆ $^1\text{H}$ NMR Spectra

- The  $\alpha$  hydrogens of carboxylic derivatives appear at  $\delta$  2.0-2.5
- The carboxyl group proton appears downfield at  $\delta$  10-12



### ◆ $^{13}\text{C}$ NMR Spectra

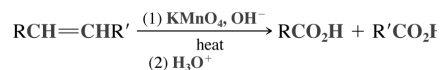
- The carbonyl carbon signal for carboxylic acids and their derivatives appears at  $\delta$  160 to 180



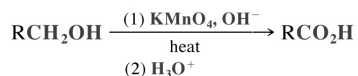
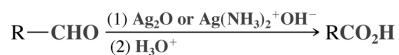
$^{13}\text{C}$  NMR chemical shifts for the carbonyl or nitrile carbon atom

## Preparation of Carboxylic Acids

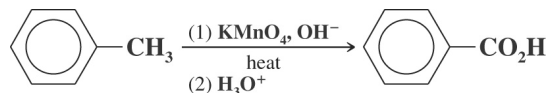
### ◆ By Oxidation of Alkenes



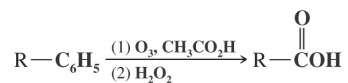
### ◆ By Oxidation of Aldehydes and Primary Alcohols



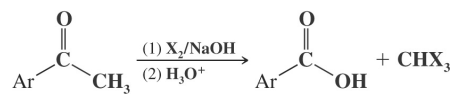
### ◆ By Oxidation of Alkylbenzenes



### ● By Oxidation of the Benzene Ring

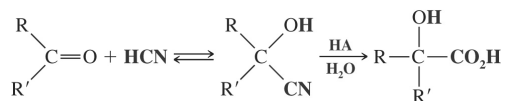


### ● By Oxidation of Methyl Ketones (The Haloform Reaction)

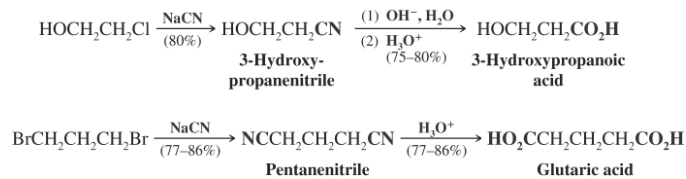


### ● By Hydrolysis of Cyanohydrins and Other Nitriles

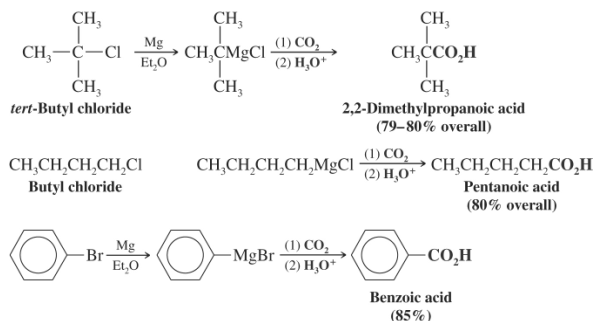
★ Hydrolysis of a cyanohydrin yields an α-hydroxy acid



- ◆ Primary alkyl halides can react with cyanide to form nitriles and these can be hydrolyzed to carboxylic acids

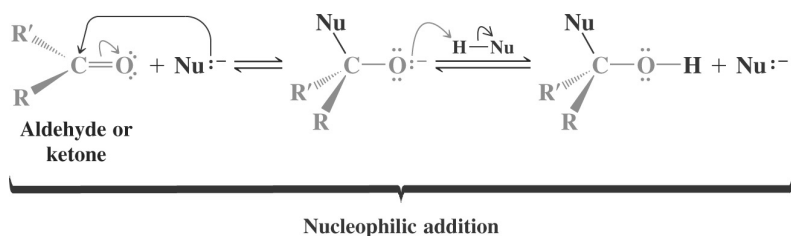


- ◆ By Carbonation of Grignard Reagents



## Nucleophilic Addition-Elimination at an Acyl Carbon

- ◆ Recall that aldehydes and ketones undergo nucleophilic addition to the carbon-oxygen double bond

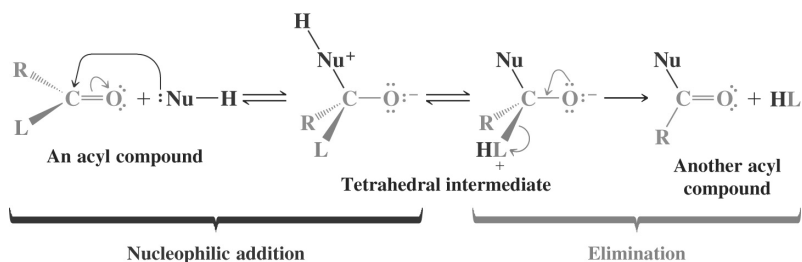


Tetrahedral intermediate is created and maintained, unless it can easily dehydrate

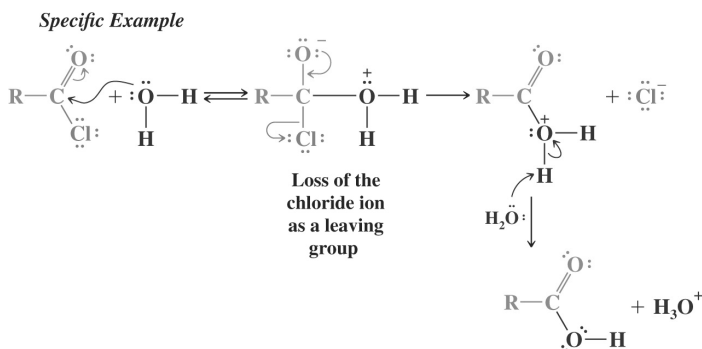


## Nucleophilic Addition-Elimination at the Acyl Carbon

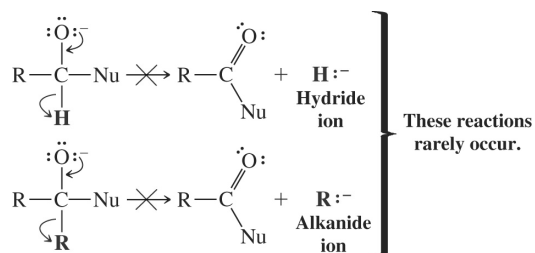
- ◆ The carbonyl group of carboxylic acids and their derivatives undergo nucleophilic addition-elimination
  - The nucleophile reacts at the carbonyl group to form a tetrahedral intermediate
  - The tetrahedral intermediate eliminates a leaving group (L)
  - The carbonyl group is regenerated; the net effect is an acyl substitution



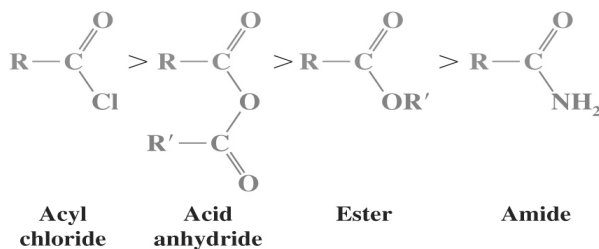
- ◆ To undergo nucleophilic addition-elimination the acyl compound must have a good leaving group or a group that can be converted into a good leaving group
  - Acid chlorides react with loss of chloride ion
  - Anhydrides react with loss of a carboxylate ion



- ◆ Esters, carboxylic acids and amides generally react with loss of the leaving groups alcohol, water and amine, respectively
  - These leaving groups are generated by protonation of the acyl compound
- ◆ Aldehydes and ketones cannot react by this mechanism because they lack a good leaving group



### Relative Reactivity of Acyl Compounds



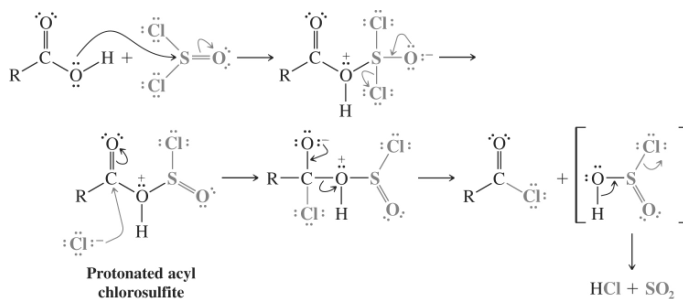
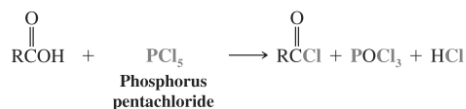
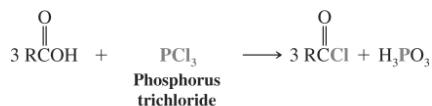
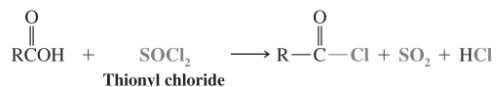
- ◆ Based on the ability of the leaving group (L) to depart
  - Leaving group ability is inversely related to basicity
  - Chloride is the weakest base and the best leaving group
  - Amines are the strongest bases and the worst leaving groups
- ◆ As a general rule, less reactive acyl compounds can be synthesized from more reactive ones
  - ➔ Synthesis of more reactive acyl derivatives from less reactive ones is difficult and requires special reagents (if at all possible)

## ◆ Acid Chlorides

### ● Synthesis of Acid Chlorides

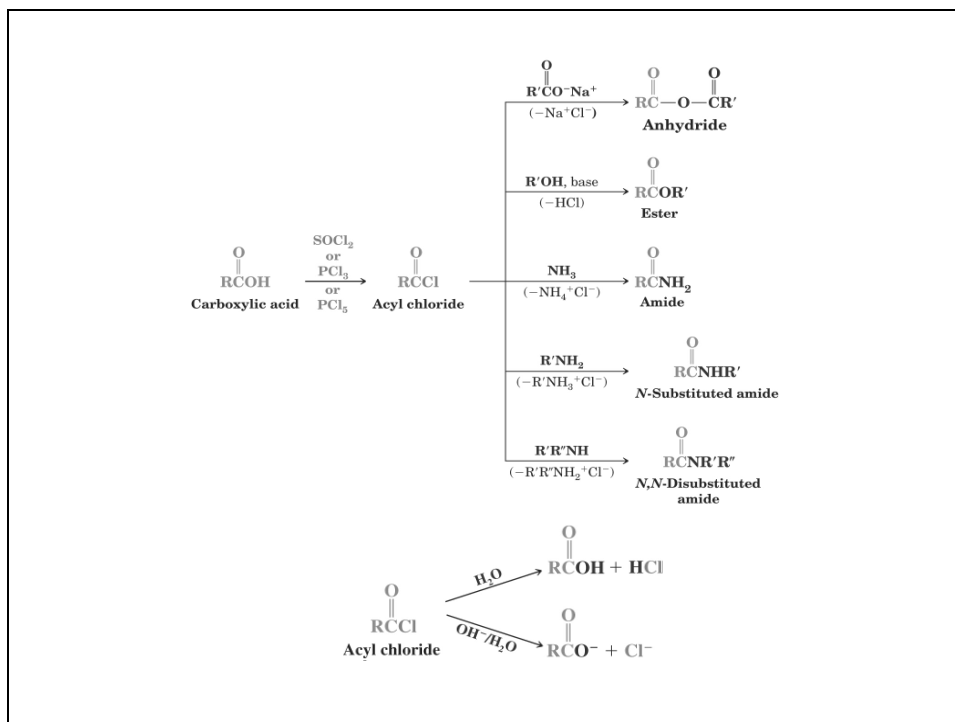
➔ Acid chlorides are made from carboxylic acids by reaction with thionyl chloride, phosphorus trichloride or phosphorus pentachloride

★ These reagents work because they turn the hydroxyl group of the carboxylic acid into an excellent leaving group



### ● Reactions of Acyl Chlorides

- ➔ Acyl chlorides are the most reactive acyl compounds and can be used to make any of the other derivatives
- ➔ Since acyl chlorides are easily made from carboxylic acids they provide a way to synthesize any acyl compound from a carboxylic acid
- ➔ Acyl chlorides react readily with water, but this is not a synthetically useful reaction

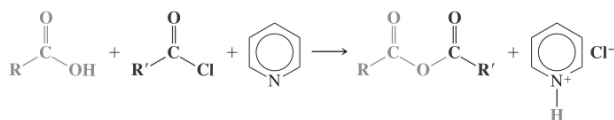


## ◆ Carboxylic Acid Anhydrides

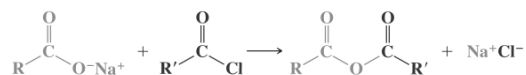
### ● Synthesis of Carboxylic Acid Anhydrides

➔ Acid chlorides react with carboxylic acids to form mixed or symmetrical anhydrides

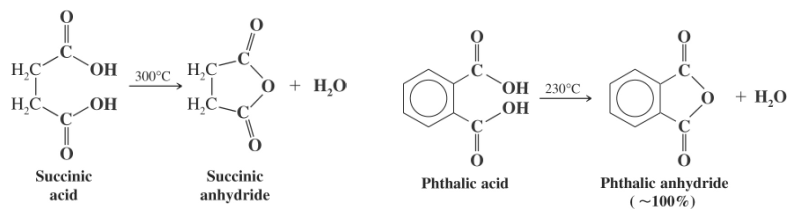
★ It is necessary to use a base such as pyridine



➔ Sodium carboxylates react readily with acid chlorides to form anhydrides

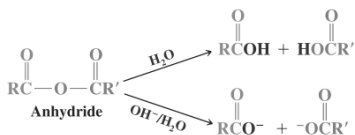
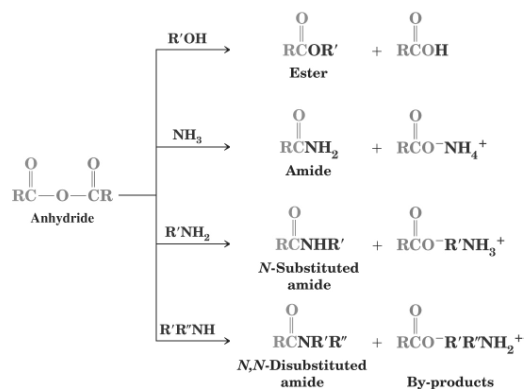


- ◆ **Cyclic anhydrides with 5- and 6-membered rings can be synthesized by heating the appropriate diacid**



- ◆ **Reactions of Carboxylic Acid Anhydrides**

- **Carboxylic acid anhydrides are very reactive and can be used to synthesize esters and amides**
  - ➔ **Hydrolysis of an anhydride yields the corresponding carboxylic acids**



## ◆ Esters

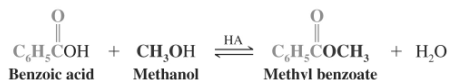
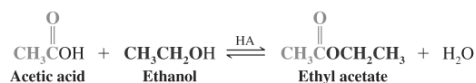
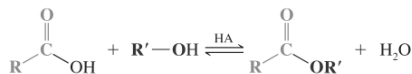
### ● Synthesis of Esters: Esterification

➔ Acid catalyzed reaction of alcohols and carboxylic acids to form esters is called Fischer esterification

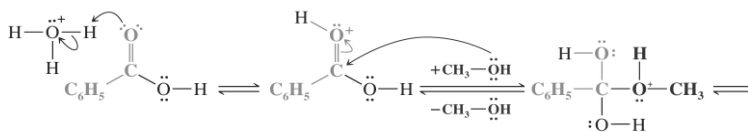
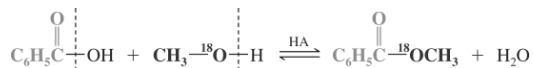
➔ Fischer esterification is an equilibrium process

★ Ester formation is favored by use of a large excess of either the alcohol or carboxylic acid

★ Ester formation is also favored by removal of water



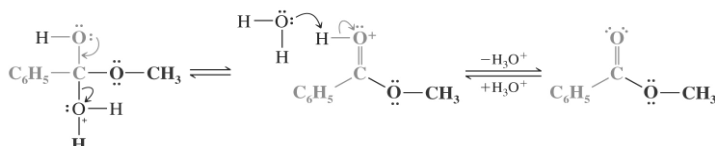
### ◆ Esterification with labeled methanol gives a product labeled only at the oxygen atom bonded to the methyl group



The carboxylic acid accepts a proton from the strong acid catalyst.

The alcohol attacks the protonated carbonyl group to give a tetrahedral intermediate.

A proton is lost at one oxygen atom and gained at another.

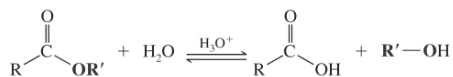


Loss of a molecule of water gives a protonated ester.

Transfer of a proton to a base leads to the ester.

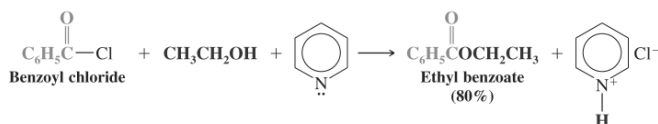
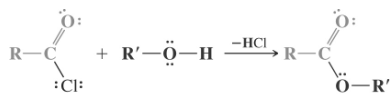
◆ The reverse reaction is acid-catalyzed ester hydrolysis

- Ester hydrolysis is favored by using lots of water



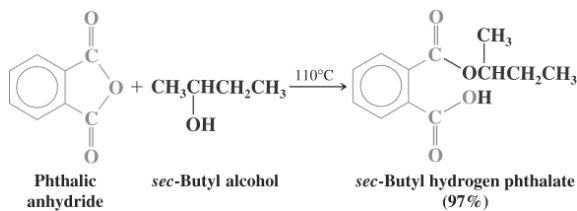
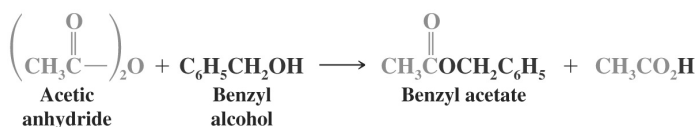
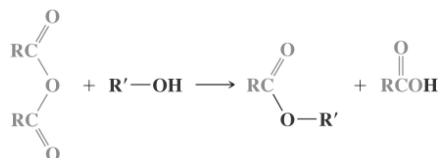
◆ Esters from Acid Chlorides

- Acid chlorides react readily with alcohols in the presence of a base (e.g. pyridine) to form esters



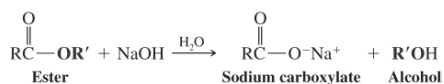
◆ Esters from Carboxylic Acid Anhydrides

- Alcohols react readily with anhydrides to form esters

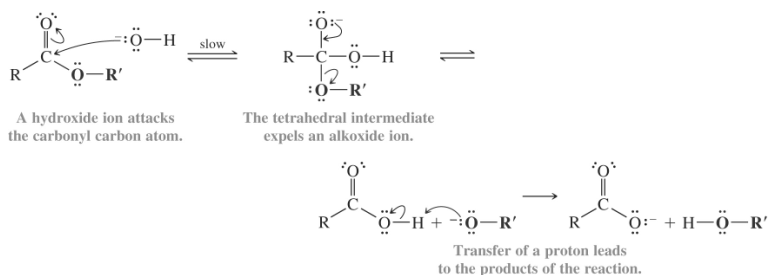


## Base-Promoted Hydrolysis of Esters: Saponification

- ◆ Reaction of an ester with sodium hydroxide results in the formation of a sodium carboxylate and an alcohol

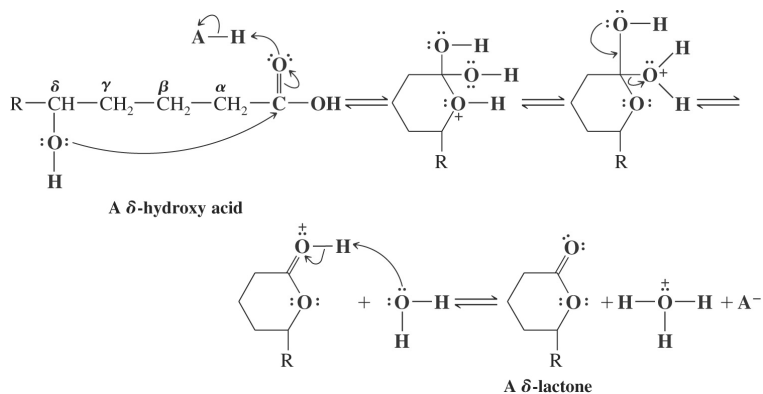


- ◆ The mechanism is reversible until the alcohol product is formed
- ◆ Protonation of the alkoxide by the initially formed carboxylic acid is irreversible, driving the overall reaction to completion



## Lactones

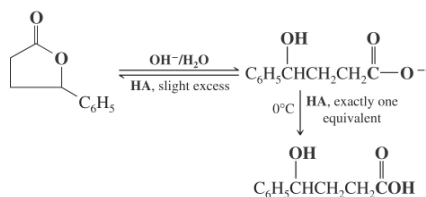
- ◆ g- or d-Hydroxyacids undergo acid catalyzed reaction to give cyclic esters known as g- or d-lactones, respectively





◆ **Lactones can be hydrolyzed with aqueous base**

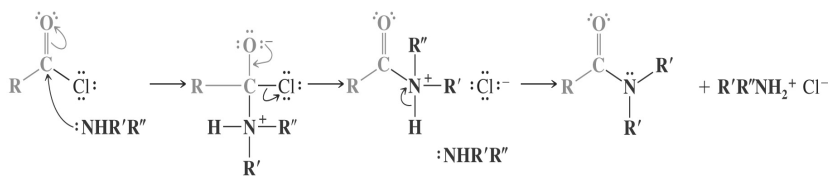
- **Acidification of the carboxylate product can lead back to the original lactone if too much acid is added**



## Synthesis of Amides

◆ **From Acyl Chlorides**

- **Ammonia, primary or secondary amines react with acid chlorides to form amides**
- **Excess amine is needed to neutralize the HCl formed**
- **Carboxylic acids can be converted to amides via the corresponding acid chloride**

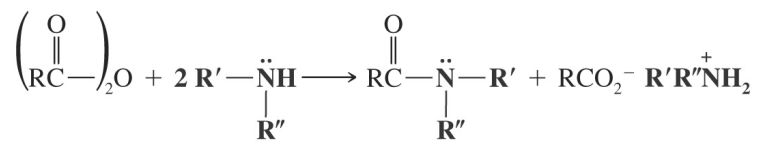


*Reactant*  
 Ammonia; R', R'' = H  
 1° Amine; R' = H, R'' = alkyl, aryl  
 2° Amine; R', R'' = alkyl, aryl

*Product*  
 Unsubstituted amide; R', R'' = H  
 N-Substituted amide; R' = H, R'' = alkyl, aryl  
 N,N-Disubstituted amide; R', R'' = alkyl, aryl

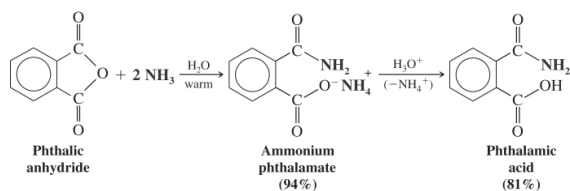
◆ **Amides from Carboxylic Anhydrides**

- Anhydrides react with 2 equivalents of amine to produce an amide and an ammonium carboxylate

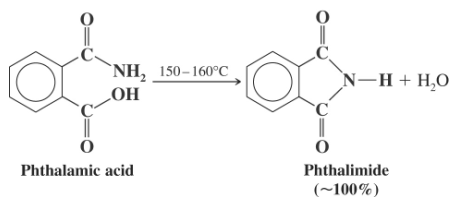


R', R'' can be H, alkyl or aryl

- ◆ **Reaction of a cyclic anhydride with an amine, followed by acidification yields a product containing both amide and carboxylic acid functional groups**

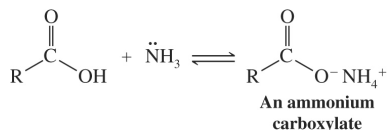


- ◆ **Heating this product results in the formation of a cyclic imide**

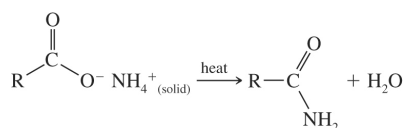


◆ **Amides from Carboxylic Acids and Ammonium Carboxylates**

- Direct reaction of carboxylic acids and ammonia yields ammonium salts



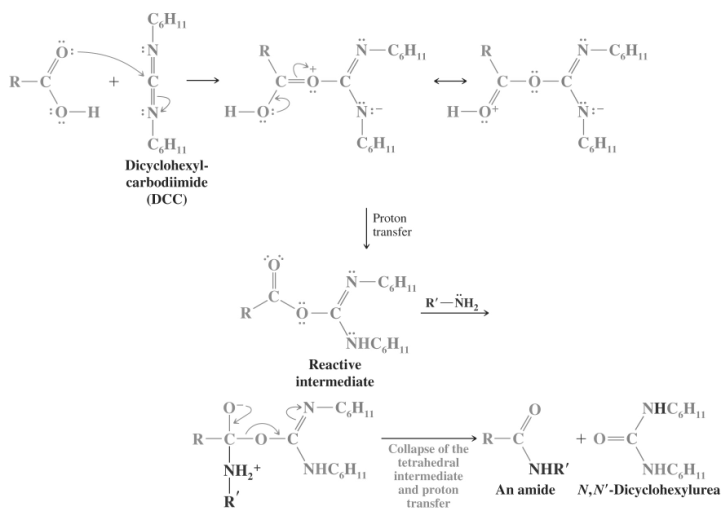
- Some ammonium salts of carboxylic acids can be dehydrated to the amide at high temperatures
- This is generally a poor method of amide synthesis



- ◆ A better way to prepare an amide is to convert a carboxylic acid to an acid chloride and react the acid chloride with ammonia or an amine

- ◆ Dicyclohexylcarbodiimide (DCC) is a reagent used to form amides from carboxylic acids and amines in one step

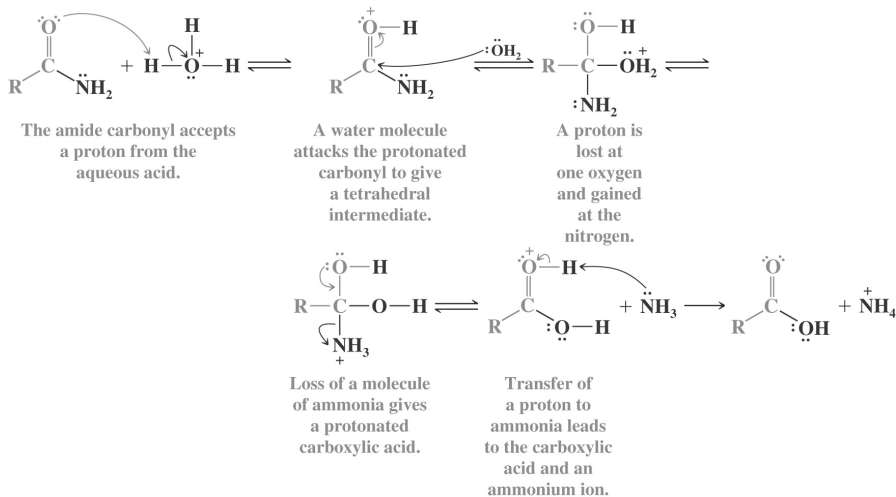
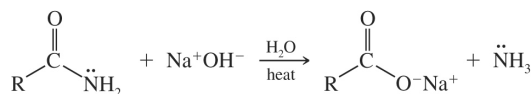
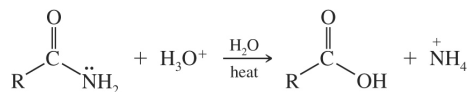
- ◆ DCC activates the carbonyl group of a carboxylic acid toward nucleophilic addition-elimination

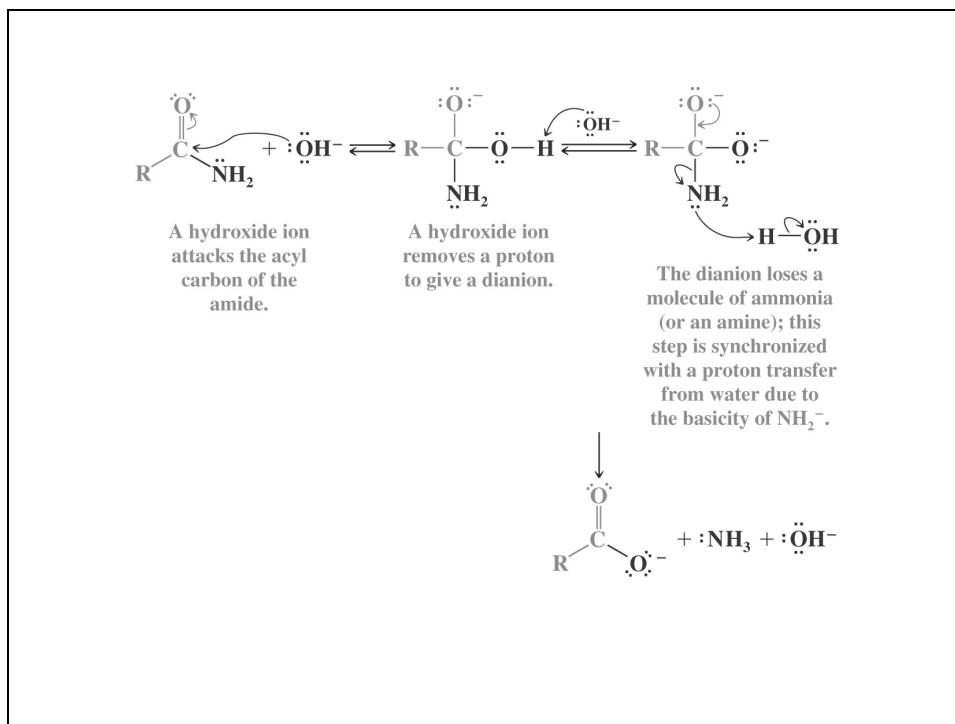


## ◆ Hydrolysis of Amides

- Heating an amide in concentrated aqueous acid or base causes hydrolysis

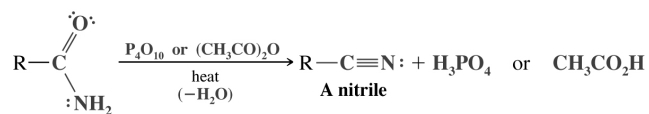
➔ Hydrolysis of an amide is slower than hydrolysis of an ester





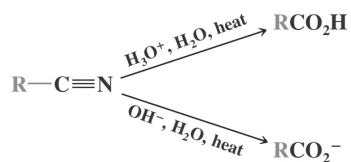
### ◆ Nitriles from the Dehydration of Amides

- A nitrile can be formed by reaction of an amide with phosphorous pentoxide or boiling acetic anhydride

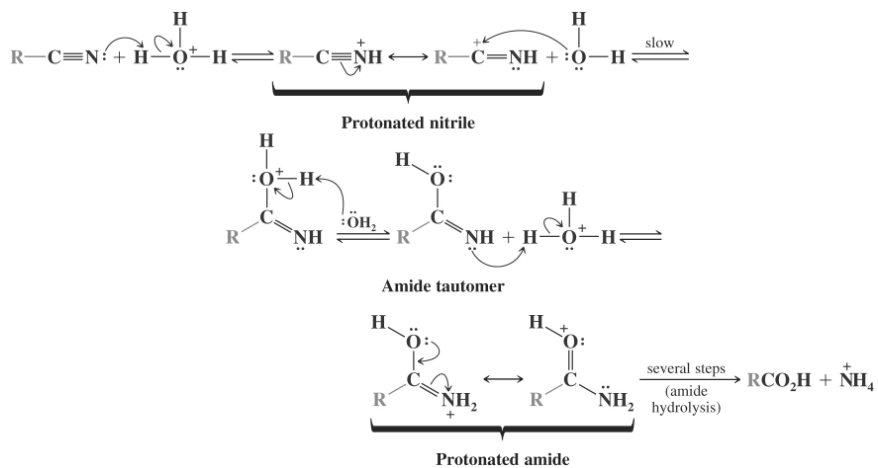


### ◆ Hydrolysis of Nitriles

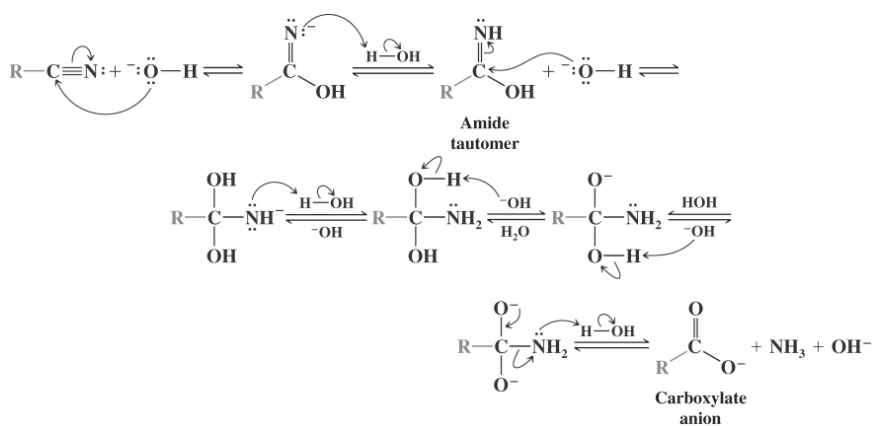
- A nitrile is the synthetic equivalent of a carboxylic acid because it can be converted to a carboxylic acid by hydrolysis



## Hydrolysis in acid



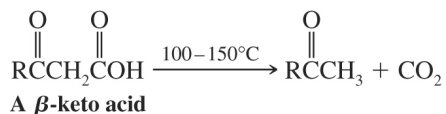
## Hydrolysis in base



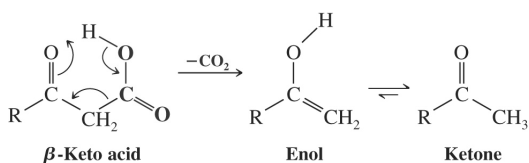
## Decarboxylation of Carboxylic Acids

- ◆  **$\beta$ -Keto carboxylic acids and their salts decarboxylate readily when heated**

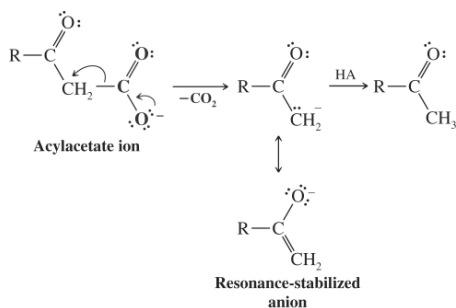
- Some even decarboxylate slowly at room temperature



- The mechanism of  $\beta$ -keto acid decarboxylation proceeds through a 6-membered ring transition state



- ◆ **Carboxylate anions decarboxylate rapidly because they form a resonance-stabilized enolate**



- ◆ **Malonic acids also decarboxylate readily**

