Organic Chemistry II / CHEM 252

Chapter 18 – Carboxylic Acids and Their Derivatives.

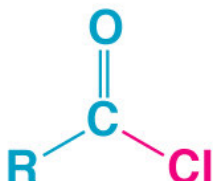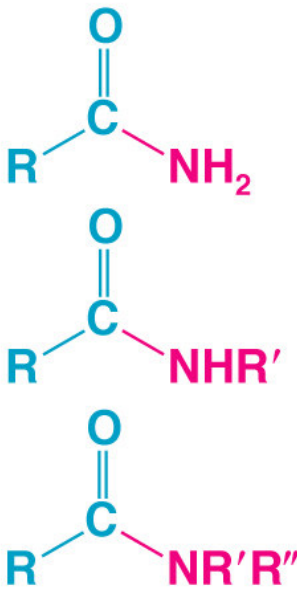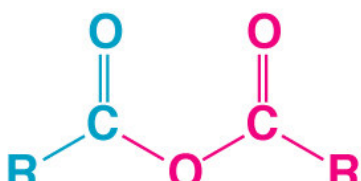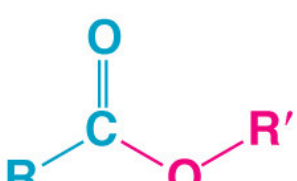Bela Torok

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Introduction

- The carboxyl group (-CO_2H) is the parent group of a family of compounds called *acyl compounds* or *carboxylic acid derivatives*

Structure	Name	Structure	Name
	Acyl (or acid) chloride		Amide
	Acid anhydride		
	Ester		
R—C≡N	Nitrile		

Nomenclature and Physical Properties
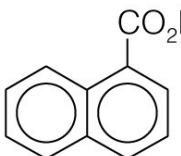
- In IUPAC nomenclature, the name of a carboxylic acid is obtained by changing the -e of the corresponding parent alkane to -oic acid
  - The carboxyl carbon is assigned position 1 and need not be explicitly numbered

4-Methylhexanoic acid

4-Hexenoic acid
(or hex-4-enoic acid)
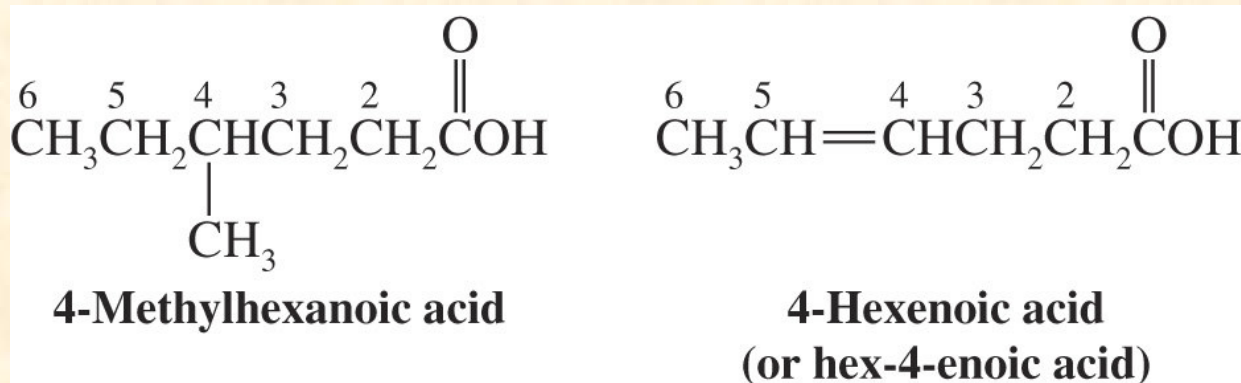
- The common names for many carboxylic acids remain in use
  - Methanoic and ethanoic acid are usually referred to as formic and acetic acid
- Carboxylic acids can form strong hydrogen bonds with each other and with water
  - Carboxylic acids with up to 4 carbons are miscible with water in all proportions

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Nomenclature and Physical Properties

| Structure	Systematic Name	Common Name	mp (°C)	bp (°C)	Water Solubility (g 100 mL^{-1} H$_2$O), 25°C	pK_a
HCO$_2$H	Methanoic acid	Formic acid	8	100.5	∞	3.75
CH$_3$CO$_2$H	Ethanoic acid	Acetic acid	16.6	118	∞	4.76
CH$_3$CH$_2$CO$_2$H	Propanoic acid	Propionic acid	−21	141	∞	4.87
CH$_3$(CH$_2$)$_2$CO$_2$H	Butanoic acid	Butyric acid	−6	164	∞	4.81
CH$_3$(CH$_2$)$_3$CO$_2$H	Pentanoic acid	Valeric acid	−34	187	4.97	4.82
CH$_3$(CH$_2$)$_4$CO$_2$H	Hexanoic acid	Caproic acid	−3	205	1.08	4.84
CH$_3$(CH$_2$)$_6$CO$_2$H	Octanoic acid	Caprylic acid	16	239	0.07	4.89
CH$_3$(CH$_2$)$_8$CO$_2$H	Decanoic acid	Capric acid	31	269	0.015	4.84
CH$_3$(CH$_2$)$_{10}$CO$_2$H	Dodecanoic acid	Lauric acid	44	179[18]	0.006	5.30
CH$_3$(CH$_2$)$_{12}$CO$_2$H	Tetradecanoic acid	Myristic acid	59	200[20]	0.002	
CH$_3$(CH$_2$)$_{14}$CO$_2$H	Hexadecanoic acid	Palmitic acid	63	219[17]	0.0007	6.46
CH$_3$(CH$_2$)$_{16}$CO$_2$H	Octadecanoic acid	Stearic acid	70	383	0.0003	
CH$_2$ClCO$_2$H	Chloroethanoic acid	Chloroacetic acid	63	189	Very soluble	2.86
CHCl$_2$CO$_2$H	Dichloroethanoic acid	Dichloroacetic acid	10.8	192	Very soluble	1.48
CCl$_3$CO$_2$H	Trichloroethanoic acid	Trichloroacetic acid	56.3	198	Very soluble	0.70
CH$_3$CHClCO$_2$H	2-Chloropropanoic acid	α-Chloropropionic acid		186	Soluble	2.83
CH$_2$ClCH$_2$CO$_2$H	3-Chloropropanoic acid	β-Chloropropionic acid	61	204	Soluble	3.98
C$_6$H$_5$CO$_2$H	Benzoic acid	Benzoic acid	122	250	0.34	4.19
p-CH$_3$C$_6$H$_4$CO$_2$H	4-Methylbenzoic acid	p-Toluic acid	180	275	0.03	4.36
p-ClC$_6$H$_4$CO$_2$H	4-Chlorobenzoic acid	p-Chlorobenzoic acid	242		0.009	3.98
p-NO$_2$C$_6$H$_4$CO$_2$H	4-Nitrobenzoic acid	p-Nitrobenzoic acid	242		0.03	3.41
	1-Naphthoic acid	α-Naphthoic acid	160	300	Insoluble	3.70
	2-Naphthoic acid	β-Naphthoic acid	185	−300	Insoluble	4.17

Acidity

- The carboxyl proton of most carboxylic acids has a $pK_a = 4 - 5$
  - Carboxylic acids are deprotonated by NaOH or $NaHCO_3$
  - Carboxylate salts are more water soluble than the acid
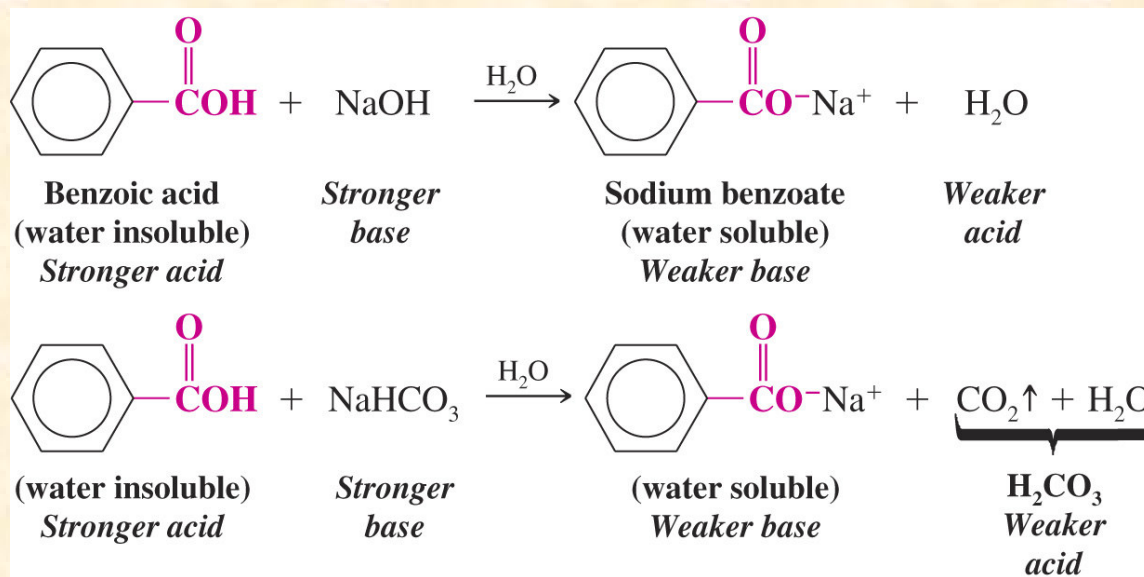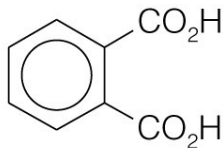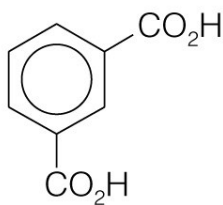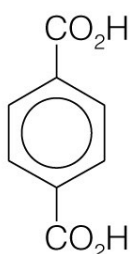

- Electron-withdrawing groups increase the acidity
  - They stabilize the carboxylate anion by inductive delocalization of charge
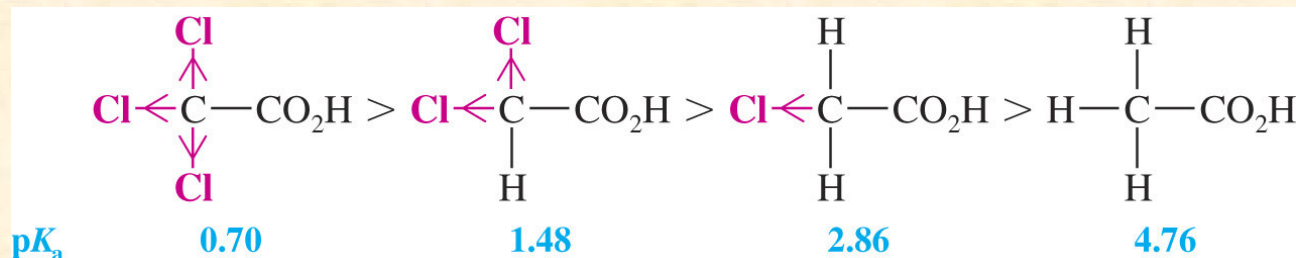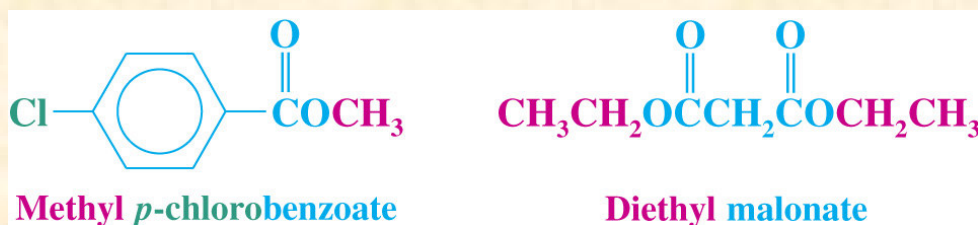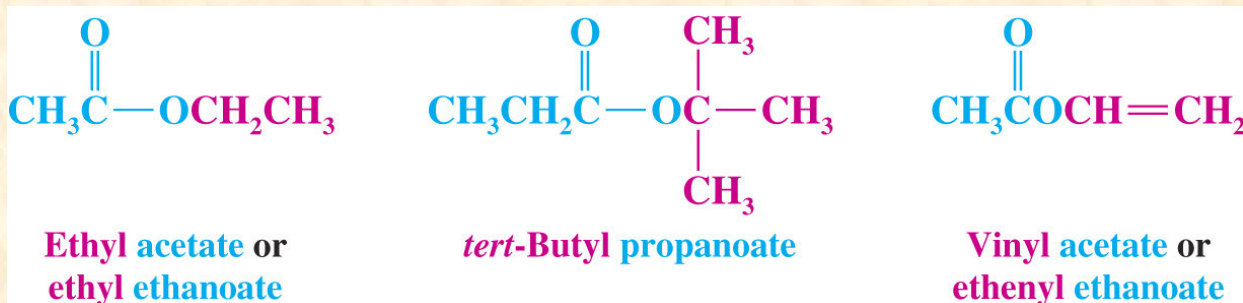
Dicarboxylic Acids

- Dicarboxylic acids are named as alkanedioic acids in the IUPAC system
  - Common names are often used for simple dicarboxylic acids

Structure	Common Name	mp (°C)	pK_a (at 25°C)	
			pK_1	pK_2
$HO_2C—CO_2H$	Oxalic acid	189 dec	1.2	4.2
$HO_2CCH_2CO_2H$	Malonic acid	136	2.9	5.7
$HO_2C(CH_2)_2CO_2H$	Succinic acid	187	4.2	5.6
$HO_2C(CH_2)_3CO_2H$	Glutaric acid	98	4.3	5.4
$HO_2C(CH_2)_4CO_2H$	Adipic acid	153	4.4	5.6
cis-$HO_2C—CH=CH—CO_2H$	Maleic acid	131	1.9	6.1
$trans$-$HO_2C—CH=CH—CO_2H$	Fumaric acid	287	3.0	4.4
(structure: benzene with two ortho CO_2H)	Phthalic acid	206–208 dec	2.9	5.4
(structure: benzene with two meta CO_2H)	Isophthalic acid	345–348	3.5	4.6
(structure: benzene with two para CO_2H)	Terephthalic acid	Sublimes	3.5	4.8

Esters

- The names of esters are derived from the names of 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 portion follows and its name ends with -ate or -oate

Ethyl acetate or ethyl ethanoate

tert-Butyl propanoate

Vinyl acetate or ethenyl ethanoate

Methyl p-chlorobenzoate

Diethyl malonate

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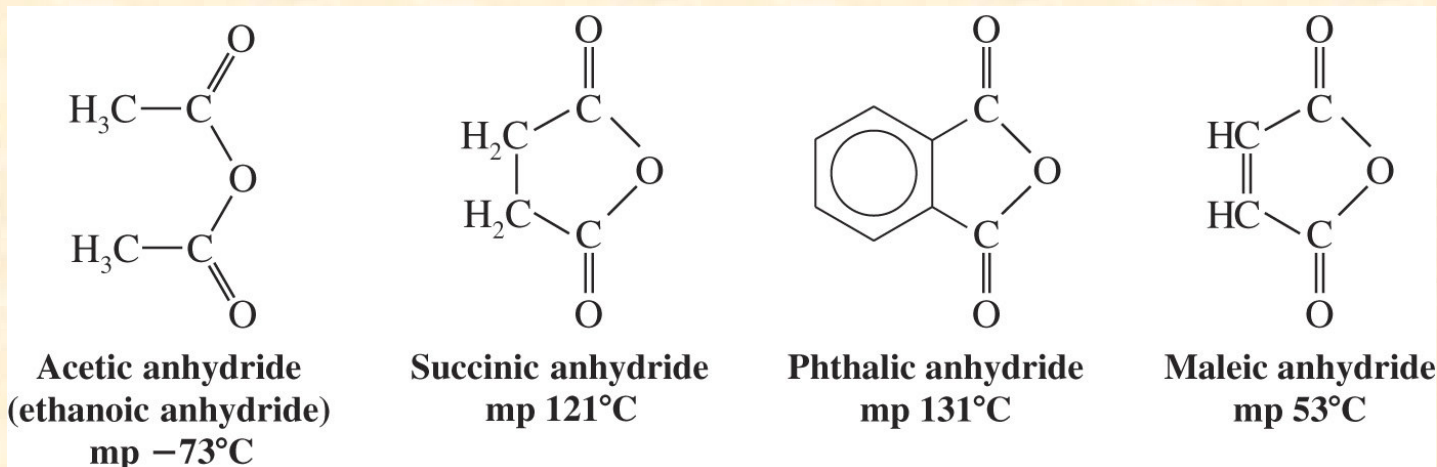 - Esters can hydrogen bond to water and have appreciable water solubility

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Esters

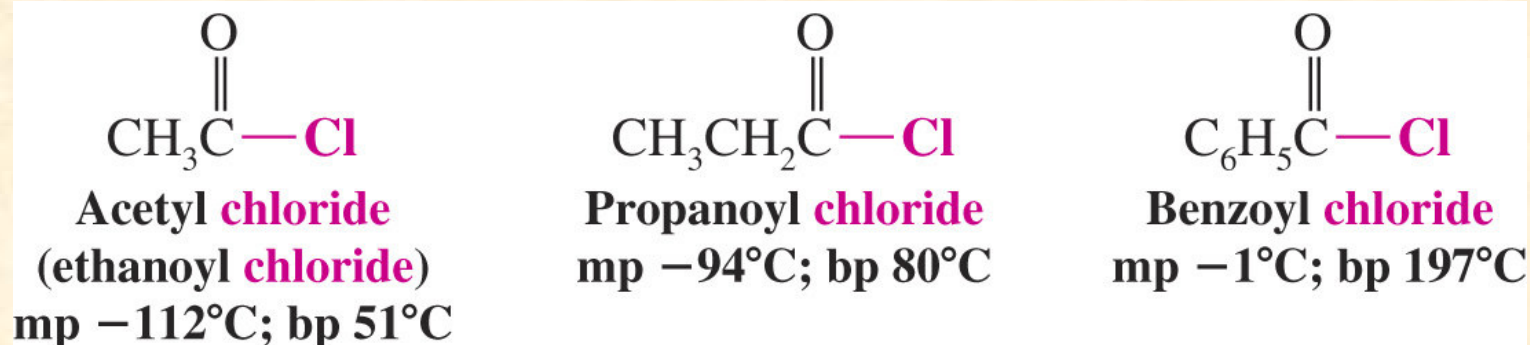| Name	Structure	mp (°C)	bp (°C)	Solubility in Water (g 100 mL^{-1} at 20°C)
Methyl formate	HCO_2CH_3	−99	31.5	Very soluble
Ethyl formate	$HCO_2CH_2CH_3$	−79	54	Soluble
Methyl acetate	$CH_3CO_2CH_3$	−99	57	24.4
Ethyl acetate	$CH_3CO_2CH_2CH_3$	−82	77	7.39 (25°C)
Propyl acetate	$CH_3CO_2CH_2CH_2CH_3$	−93	102	1.89
Butyl acetate	$CH_3CO_2CH_2(CH_2)_2CH_3$	−74	125	1.0 (22°C)
Ethyl propanoate	$CH_3CH_2CO_2CH_2CH_3$	−73	99	1.75
Ethyl butanoate	$CH_3(CH_2)_2CO_2CH_2CH_3$	−93	120	0.51
Ethyl pentanoate	$CH_3(CH_2)_3CO_2CH_2CH_3$	−91	145	0.22
Ethyl hexanoate	$CH_3(CH_2)_4CO_2CH_2CH_3$	−68	168	0.063
Methyl benzoate	$C_6H_5CO_2CH_3$	−12	199	0.15
Ethyl benzoate	$C_6H_5CO_2CH_2CH_3$	−35	213	0.08
Phenyl acetate	$CH_3CO_2C_6H_5$		196	Slightly soluble
Methyl salicylate	$o\text{-}HOC_6H_4CO_2CH_3$	−9	223	0.74 (30°C)

Acid Anhydrides, Chlorides

– Acid Anhydrides

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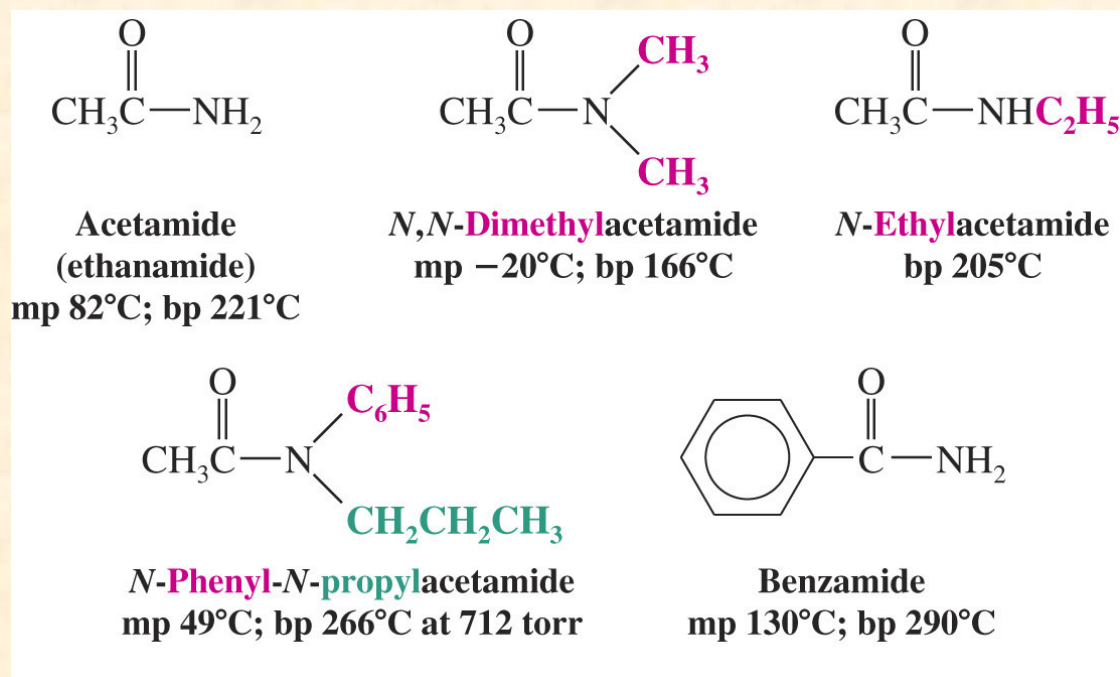

Acetic anhydride
(ethanoic anhydride)
mp −73°C

Succinic anhydride
mp 121°C

Phthalic anhydride
mp 131°C

Maleic anhydride
mp 53°C

– Acid Chlorides

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

Acetyl chloride
(ethanoyl chloride)
mp −112°C; bp 51°C

Propanoyl chloride
mp −94°C; bp 80°C
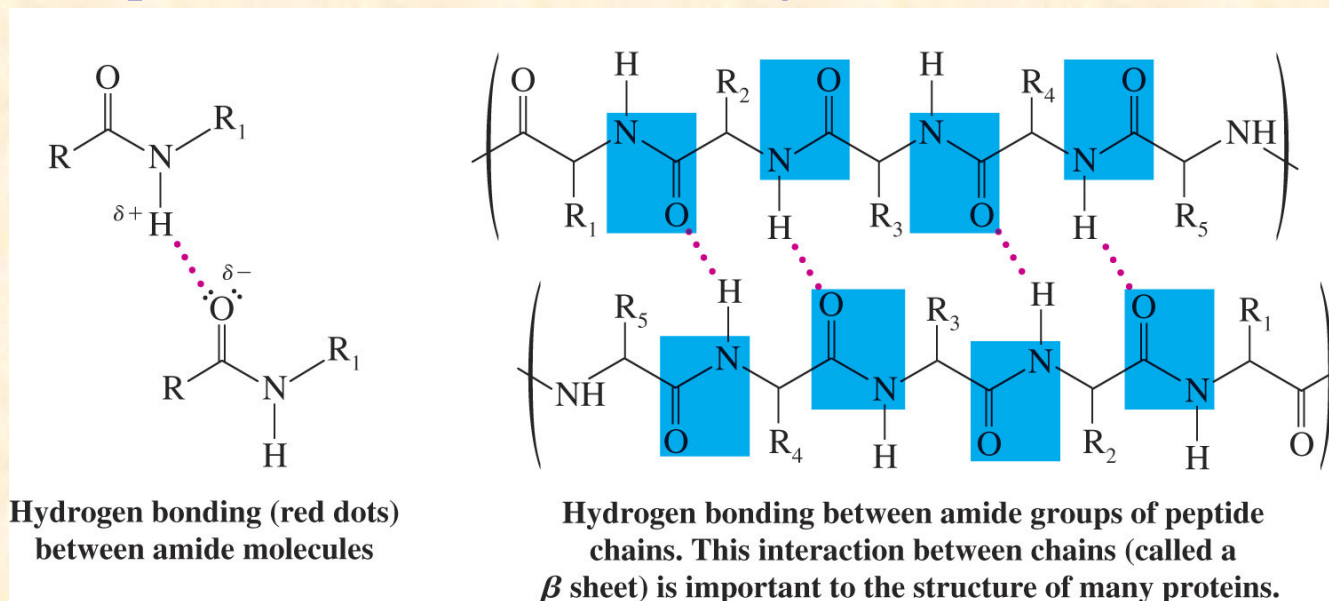
Benzoyl chloride
mp −1°C; bp 197°C

Amides

- Amides with no substituents on nitrogen are named by replacing *-ic acid* in the name with *amide*
  - Groups on the nitrogen are named as substitutents and are given the locants *N-* or *N,N-*

Acetamide
(ethanamide)
mp 82°C; bp 221°C

N,N-**Dimethyl**acetamide
mp −20°C; bp 166°C

N-**Ethyl**acetamide
bp 205°C

N-**Phenyl**-*N*-**propyl**acetamide
mp 49°C; bp 266°C at 712 torr

Benzamide
mp 130°C; bp 290°C

- 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
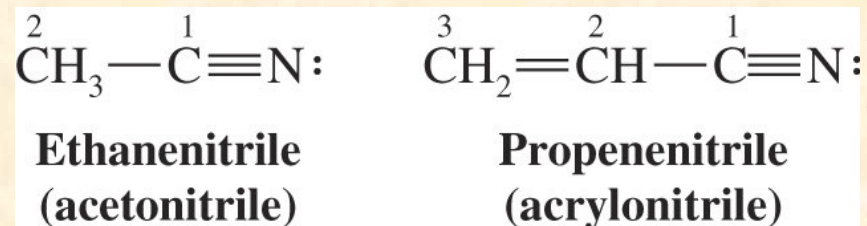
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Amides, Nitriles

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

Hydrogen bonding (red dots) between amide molecules

Hydrogen bonding between amide groups of peptide chains. This interaction between chains (called a β sheet) is important to the structure of many proteins.
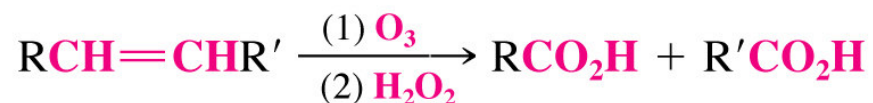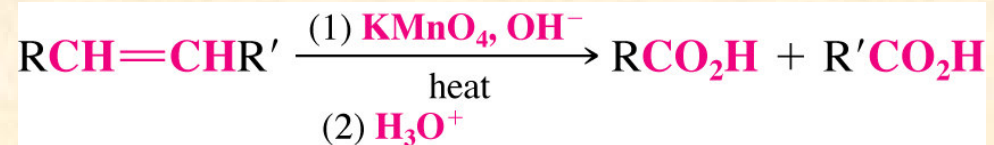
  – Nitriles

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

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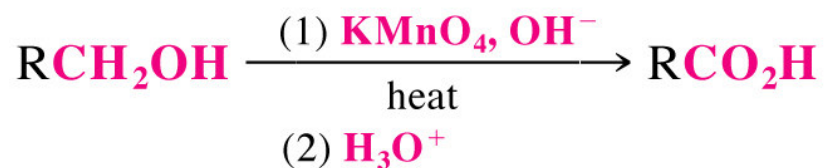   – Ethanenitrile is usually called acetonitrile

Ethanenitrile (acetonitrile)
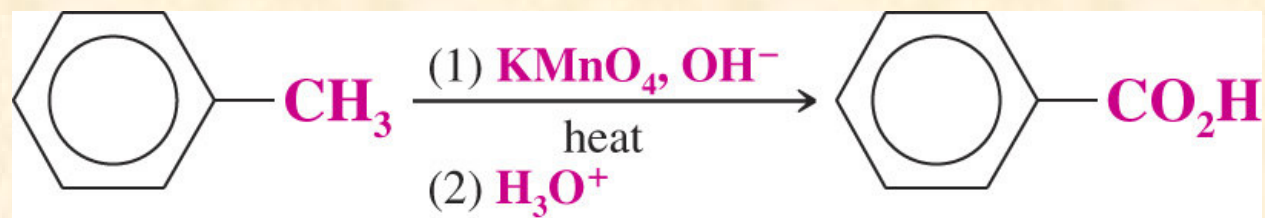
Propenenitrile (acrylonitrile)

Preparation of Carboxylic Acids

– By Oxidation of Alkenes

$$RCH{=}CHR' \xrightarrow[\text{heat} \atop (2)\ H_3O^+]{(1)\ KMnO_4,\ OH^-} RCO_2H + R'CO_2H$$

$$RCH{=}CHR' \xrightarrow[(2)\ H_2O_2]{(1)\ O_3} RCO_2H + R'CO_2H$$

– By Oxidation of Aldehydes and Primary Alcohols

$$R{-}CHO \xrightarrow[(2)\ H_3O^+]{(1)\ Ag_2O\ or\ Ag(NH_3)_2{}^+OH^-} RCO_2H$$

$$RCH_2OH \xrightarrow[\text{heat} \atop (2)\ H_3O^+]{(1)\ KMnO_4,\ OH^-} RCO_2H$$

$$R{-}CHO\ or\ RCH_2OH \xrightarrow{H_2CrO_4} RCO_2H$$

– By Oxidation of Alkylbenzenes

$$C_6H_5{-}CH_3 \xrightarrow[\text{heat} \atop (2)\ H_3O^+]{(1)\ KMnO_4,\ OH^-} C_6H_5{-}CO_2H$$

Preparation of Carboxylic Acids

– By Oxidation of the Benzene Ring

$$R-C_6H_5 \xrightarrow[\text{(2) } H_2O_2]{\text{(1) } O_3,\ CH_3CO_2H} R-\overset{\overset{\displaystyle O}{\|}}{C}OH$$
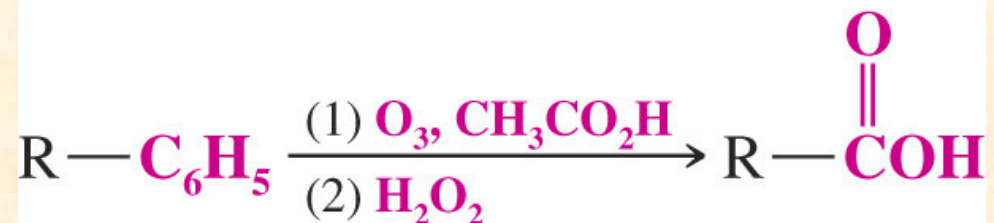
– By Oxidation of Methyl Ketones (The Haloform Reaction)

$$\underset{Ar}{\overset{\overset{\displaystyle O}{\|}}{C}}CH_3 \xrightarrow[\text{(2) } H_3O^+]{\text{(1) } X_2/NaOH} \underset{Ar}{\overset{\overset{\displaystyle O}{\|}}{C}}OH + CHX_3$$
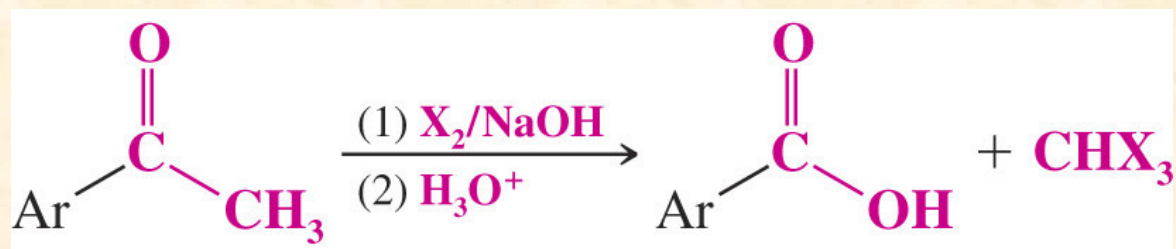
– By Hydrolysis of Cyanohydrins and Other Nitriles
  – Hydrolysis of a cyanohydrin yields an α-hydroxy acid

$$\underset{R'}{\overset{R}{C}}=O + HCN \rightleftharpoons \underset{R'\quad CN}{\overset{R\quad OH}{C}} \xrightarrow[H_2O]{HA} R-\underset{R'}{\overset{OH}{C}}-CO_2H$$
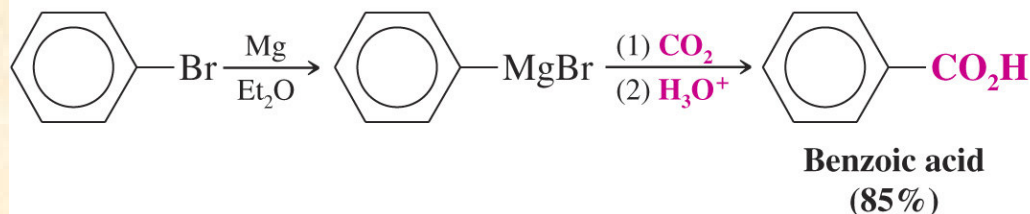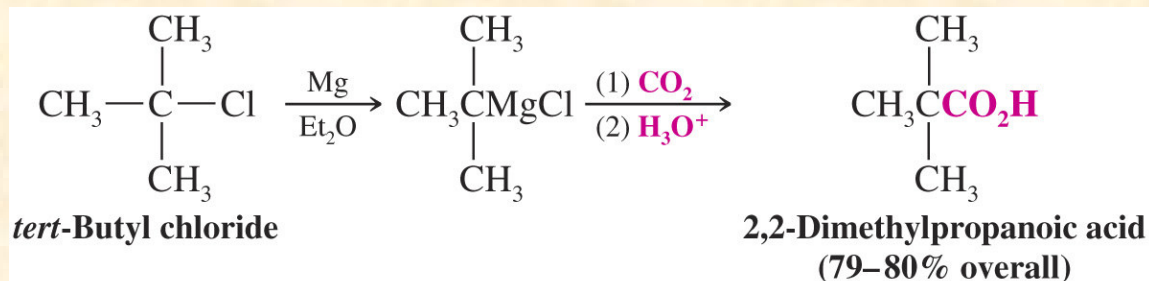
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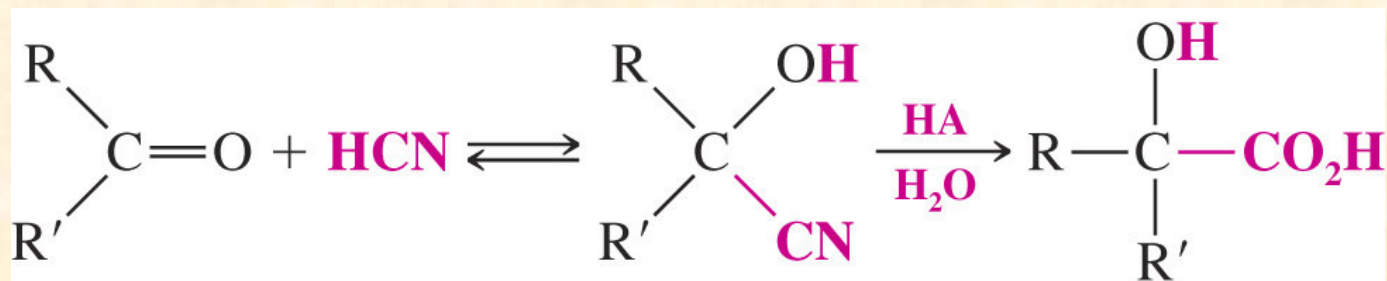
Preparation of Carboxylic Acids

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

$$HOCH_2CH_2Cl \xrightarrow[(80\%)]{\textbf{NaCN}} HOCH_2CH_2\textbf{CN} \xrightarrow[\text{(2) } \textbf{H}_3\textbf{O}^+]{\text{(1) } \textbf{OH}^-, \textbf{H}_2\textbf{O}} HOCH_2CH_2\textbf{CO}_2\textbf{H}$$

3-Hydroxy-propanenitrile (75–80%) **3-Hydroxypropanoic acid**

$$BrCH_2CH_2CH_2Br \xrightarrow[(77-86\%)]{\textbf{NaCN}} \textbf{NC}CH_2CH_2CH_2\textbf{CN} \xrightarrow[(77-86\%)]{\textbf{H}_3\textbf{O}^+} \textbf{HO}_2\textbf{C}CH_2CH_2CH_2\textbf{CO}_2\textbf{H}$$

Pentanenitrile **Glutaric acid**
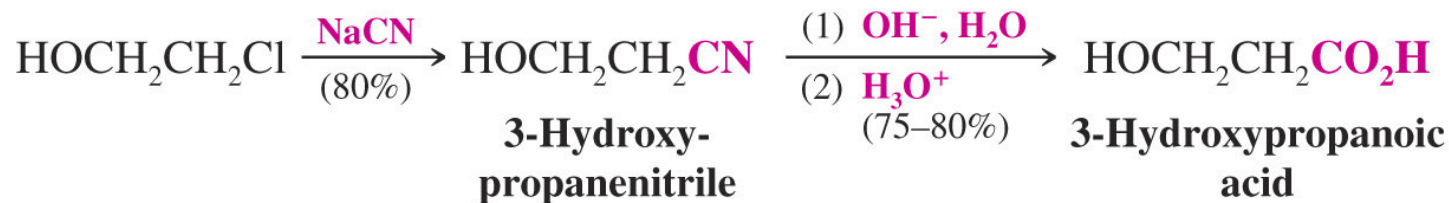
– By Carbonation of Grignard Reagents

$$CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-Cl \xrightarrow[Et_2O]{Mg} CH_3\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}MgCl \xrightarrow[\text{(2) } \textbf{H}_3\textbf{O}^+]{\text{(1) } \textbf{CO}_2} CH_3\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}\textbf{CO}_2\textbf{H}$$

tert-Butyl chloride   2,2-Dimethylpropanoic acid (79–80% overall)

$$CH_3CH_2CH_2CH_2Cl \quad CH_3CH_2CH_2CH_2MgCl \xrightarrow[\text{(2) } \textbf{H}_3\textbf{O}^+]{\text{(1) } \textbf{CO}_2} CH_3CH_2CH_2CH_2\textbf{CO}_2\textbf{H}$$

Butyl chloride   Pentanoic acid (80% overall)

$$\bigcirc-Br \xrightarrow[Et_2O]{Mg} \bigcirc-MgBr \xrightarrow[\text{(2) } \textbf{H}_3\textbf{O}^+]{\text{(1) } \textbf{CO}_2} \bigcirc-\textbf{CO}_2\textbf{H}$$

Benzoic acid (85%)

Nucleophilic Addition-Elimination

- Recall that aldehydes and ketones undergo nucleophilic addition to the carbon-oxygen double bond
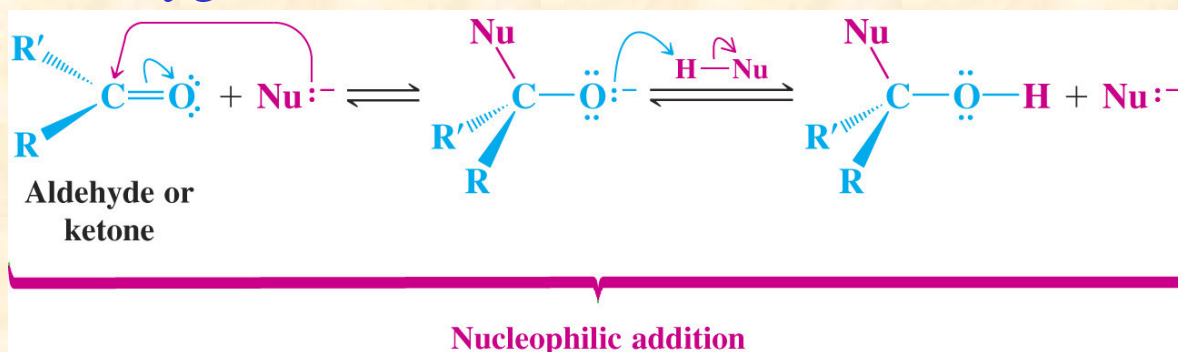
- The carbonyl group of carboxylic acids and their derivatives undergo nucleophilic addition-elimination

  – The nucleophile reacts at the carbonyl group

  – The tetrahedral intermediate eliminates a leaving group (L)

  – The carbonyl group is regenerated; the net effect: acyl substitution


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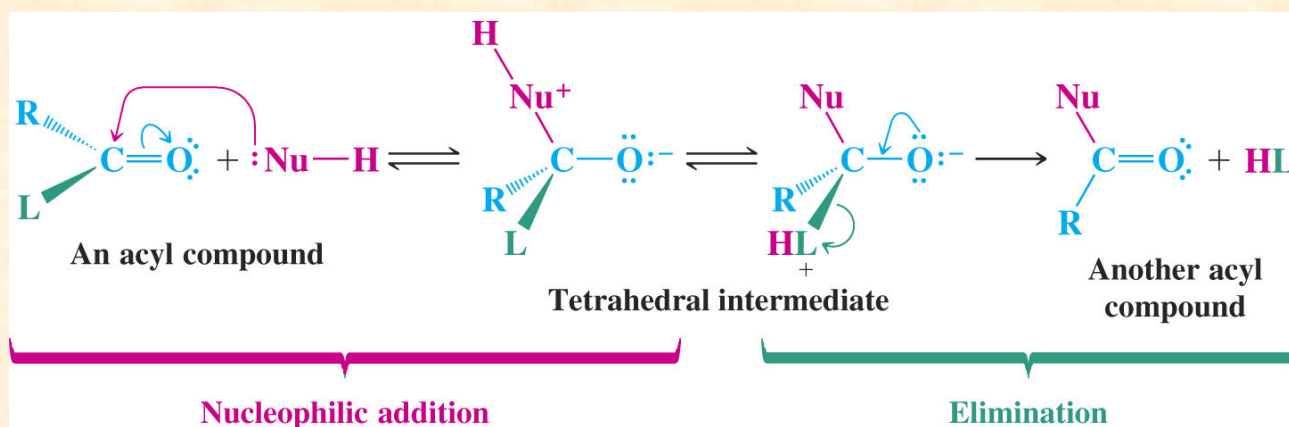
- To undergo nucleophilic addition-elimination the acyl compound must have a good leaving group or a group that can be converted into a good leaving group
  - Acid chlorides react with loss of chloride ion
  - Anhydrides react with loss of a carboxylate ion

Specific Example

Loss of the chloride ion as a leaving group
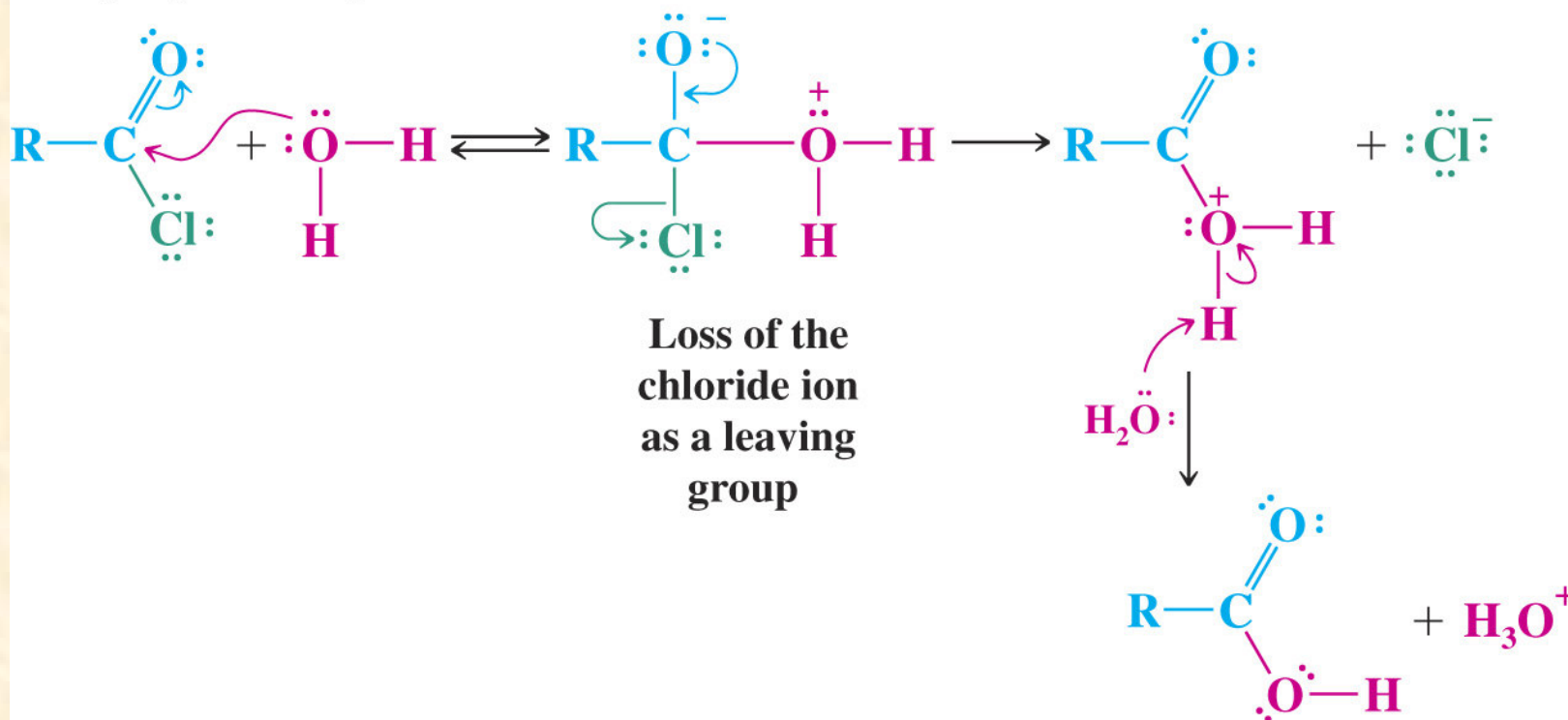
Nucleophilic Addition-Elimination

- 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
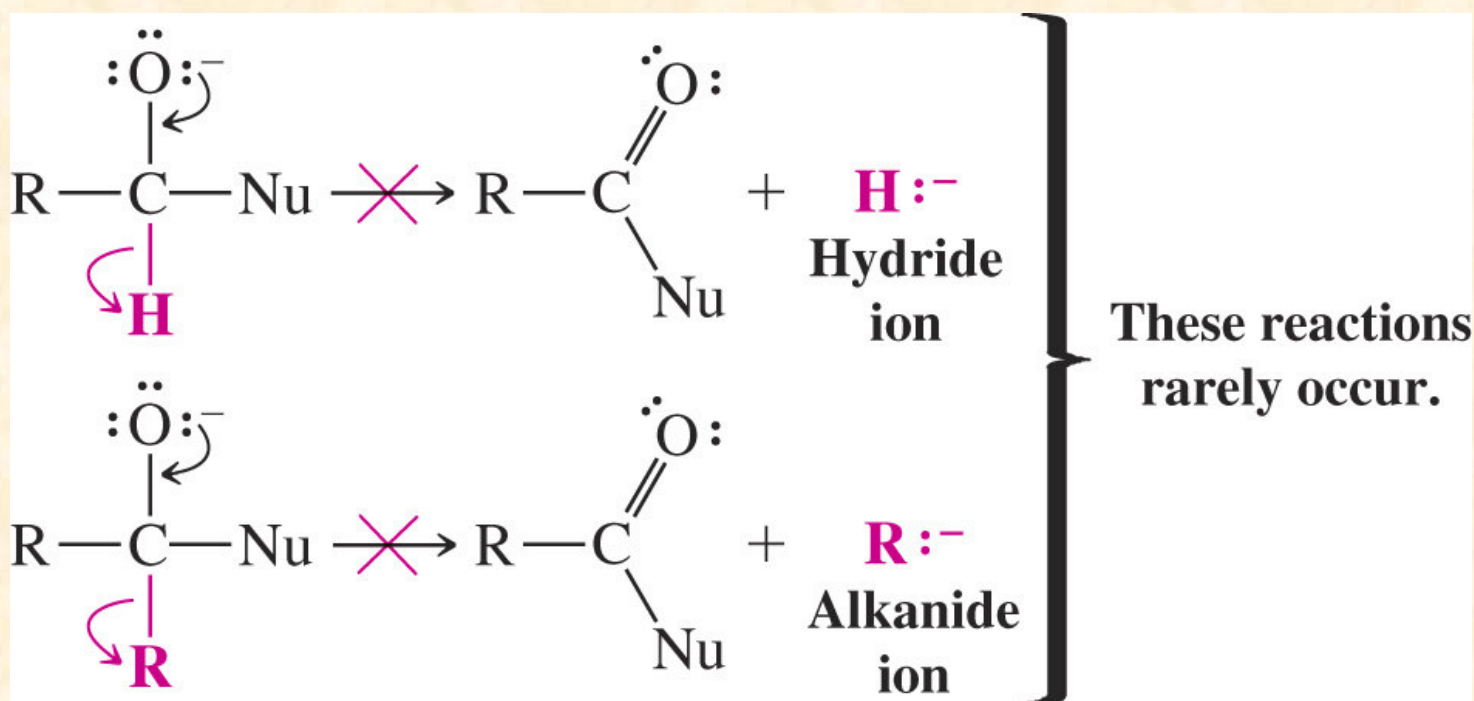
Relative Reactivity

– Relative Reactivity of Acyl Compounds
  - The relative reactivity of carboxylic acids and their derivatives is as follows:

| Acyl chloride | Acid anhydride | Ester | Amide |
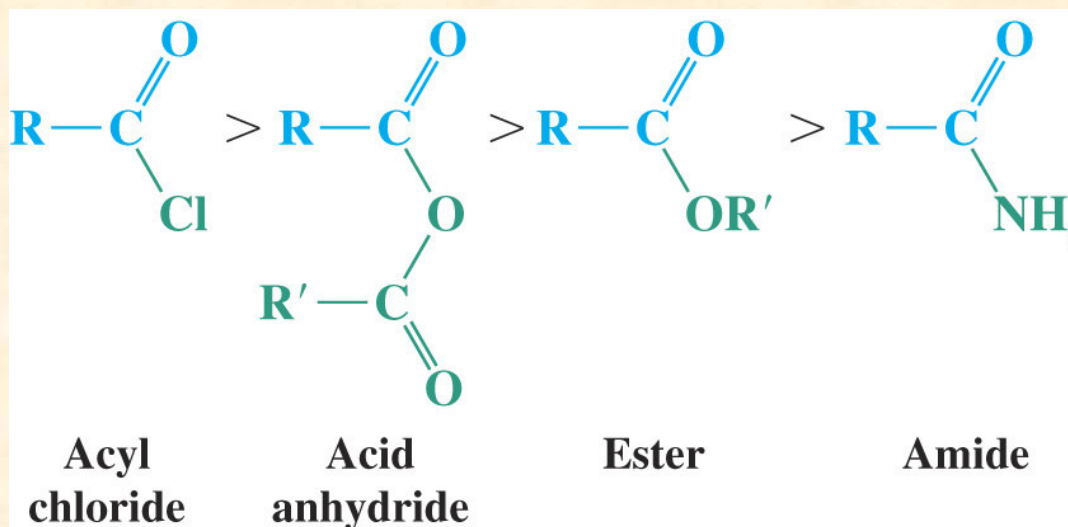
  - Reactivity can be related to the ability of the leaving group (L) to depart
    – Leaving group ability is inversely related to basicity
    – Chloride is the weakest base and the best leaving group
    – Amines are the strongest bases and the worst leaving groups
  - Less reactive acyl compounds can 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)

Acyl 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
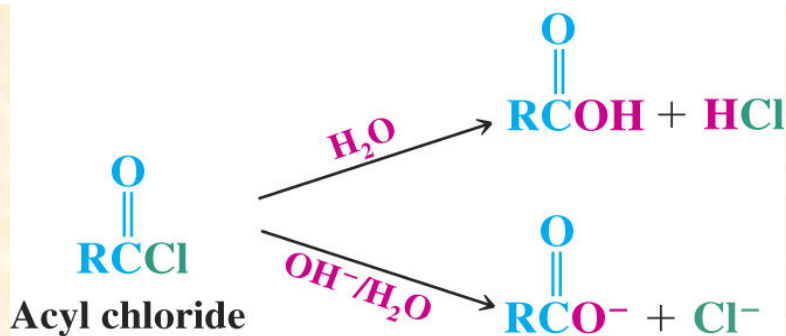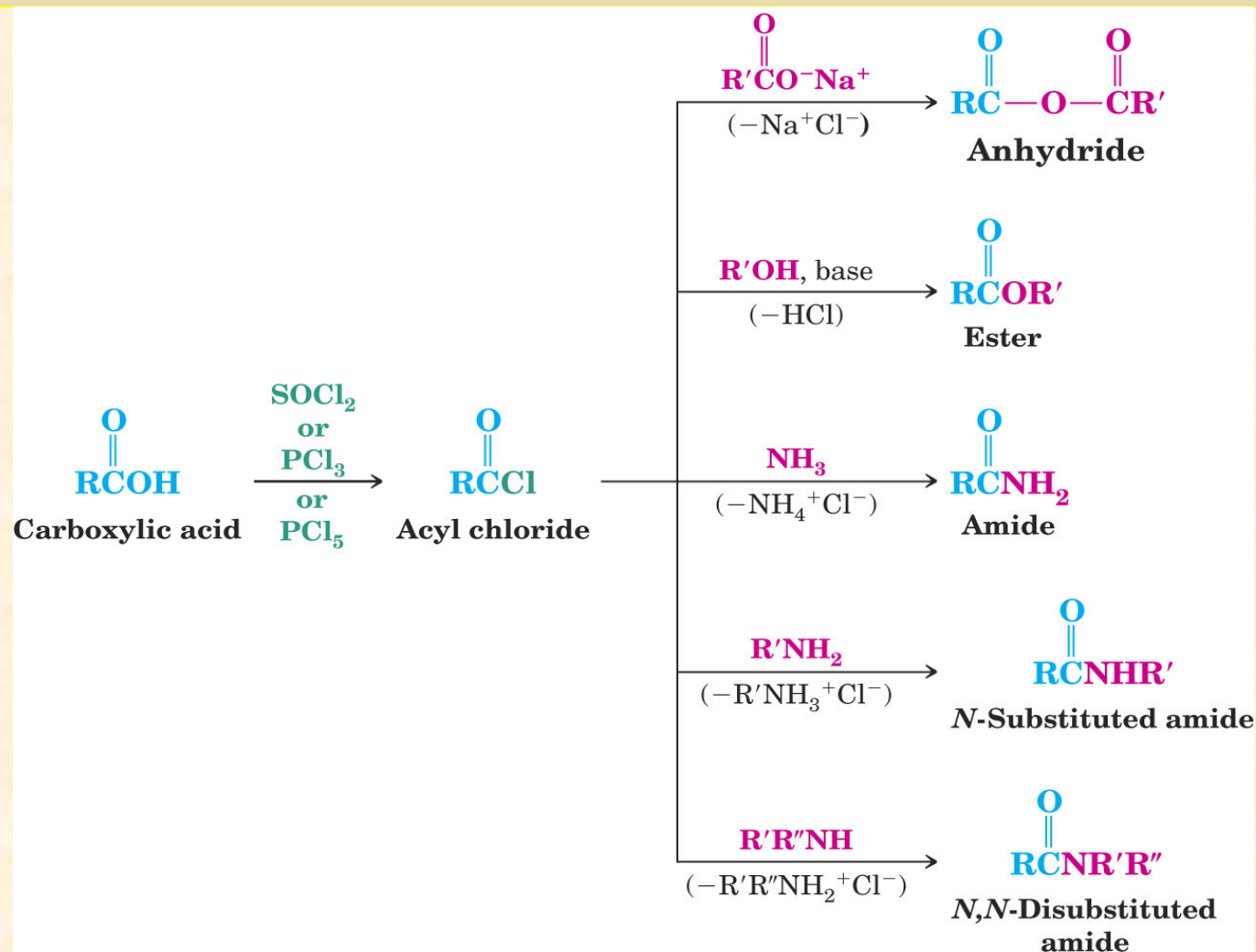
$$\underset{\text{RCOH}}{\overset{O}{\|}} + \underset{\text{Thionyl chloride}}{SOCl_2} \longrightarrow R-\overset{O}{\underset{\|}{C}}-Cl + SO_2 + HCl$$

$$3\ \underset{\text{RCOH}}{\overset{O}{\|}} + \underset{\substack{\text{Phosphorus} \\ \text{trichloride}}}{PCl_3} \longrightarrow 3\ \underset{}{\overset{O}{\|}} RCCl + H_3PO_3$$

$$\underset{\text{RCOH}}{\overset{O}{\|}} + \underset{\substack{\text{Phosphorus} \\ \text{pentachloride}}}{PCl_5} \longrightarrow \overset{O}{\underset{\|}{RCCl}} + POCl_3 + HCl$$

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Acyl Chlorides

Protonated acyl chlorosulfite

HCl + SO₂
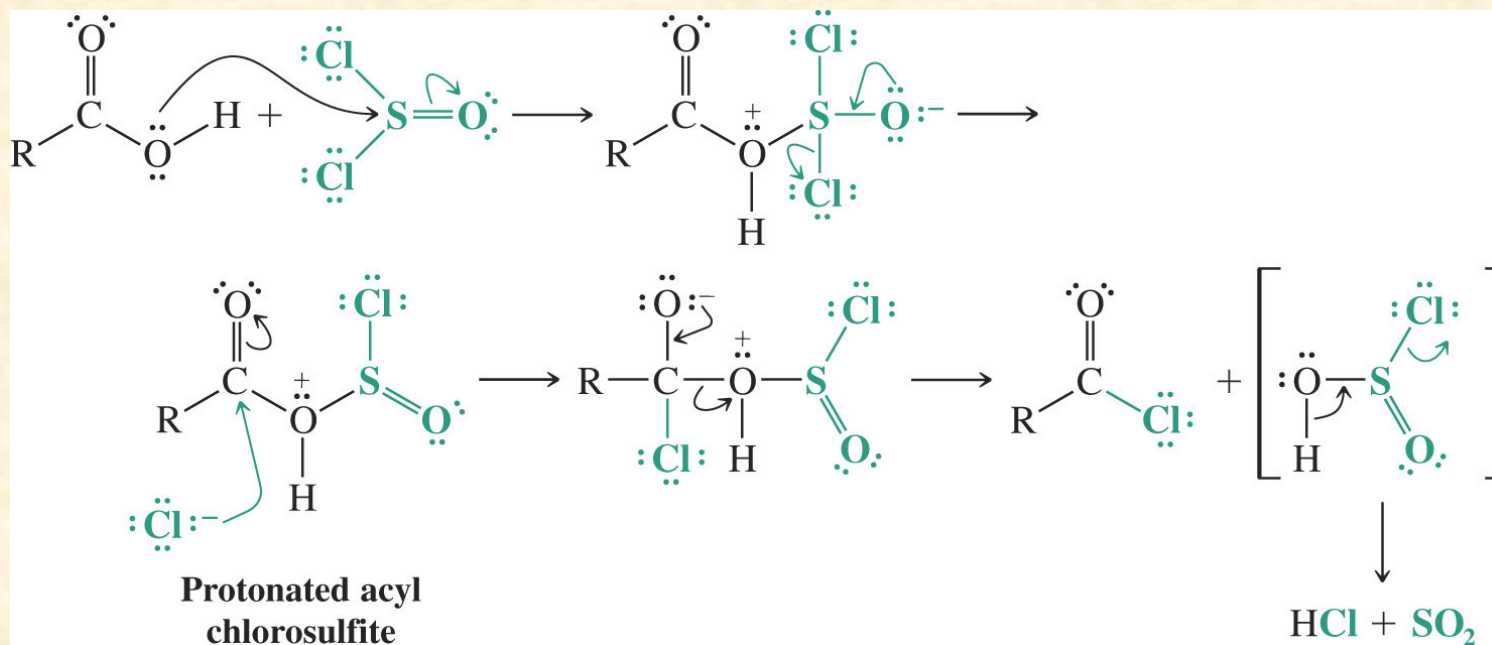
– <u>Reactions of Acyl Chlorides</u>
  - Acyl chlorides are the most reactive acyl compounds and can be used to make any of the other derivatives
  - Since acyl chlorides are easily made from carboxylic acids they provide a way to synthesize any acyl compound from a carboxylic acid
  - Acyl chlorides react readily with water, but this is not a synthetically useful reaction
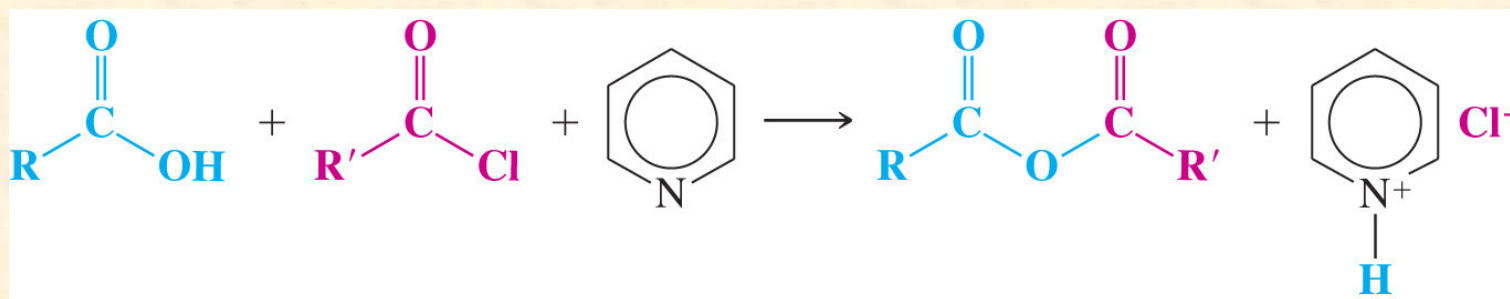
Acyl Chlorides

$$\underset{\textbf{Carboxylic acid}}{\overset{\overset{\textstyle O}{\|}}{\textbf{RCOH}}} \xrightarrow[\textbf{or}]{\overset{\textbf{SOCl}_2}{\underset{\textbf{PCl}_5}{\textbf{or}}}} \underset{\textbf{Acyl chloride}}{\overset{\overset{\textstyle O}{\|}}{\textbf{RCCl}}}$$

$$\xrightarrow[(-\text{Na}^+\text{Cl}^-)]{\textbf{R}'\textbf{CO}^-\textbf{Na}^+} \underset{\textbf{Anhydride}}{\overset{\overset{\textstyle O}{\|}\qquad\overset{\textstyle O}{\|}}{\textbf{RC}-\textbf{O}-\textbf{CR}'}}$$

$$\xrightarrow[(-\text{HCl})]{\textbf{R}'\textbf{OH}, \text{base}} \underset{\textbf{Ester}}{\overset{\overset{\textstyle O}{\|}}{\textbf{RCOR}'}}$$

$$\xrightarrow[(-\text{NH}_4^+\text{Cl}^-)]{\textbf{NH}_3} \underset{\textbf{Amide}}{\overset{\overset{\textstyle O}{\|}}{\textbf{RCNH}_2}}$$

$$\xrightarrow[(-\text{R}'\text{NH}_3^+\text{Cl}^-)]{\textbf{R}'\textbf{NH}_2} \underset{\textbf{\textit{N}-Substituted amide}}{\overset{\overset{\textstyle O}{\|}}{\textbf{RCNHR}'}}$$

$$\xrightarrow[(-\text{R}'\text{R}''\text{NH}_2^+\text{Cl}^-)]{\textbf{R}'\textbf{R}''\textbf{NH}} \underset{\substack{\textbf{\textit{N,N}-Disubstituted}\\ \textbf{amide}}}{\overset{\overset{\textstyle O}{\|}}{\textbf{RCNR}'\textbf{R}''}}$$

$$\underset{\textbf{Acyl chloride}}{\overset{\overset{\textstyle O}{\|}}{\textbf{RCCl}}} \quad \overset{\textbf{H}_2\textbf{O}}{\nearrow} \quad \underset{}{\overset{\overset{\textstyle O}{\|}}{\textbf{RCOH}}} + \textbf{HCl}$$

$$\underset{\textbf{OH}^-/\textbf{H}_2\textbf{O}}{\searrow} \quad \overset{\overset{\textstyle O}{\|}}{\textbf{RCO}^-} + \textbf{Cl}^-$$

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
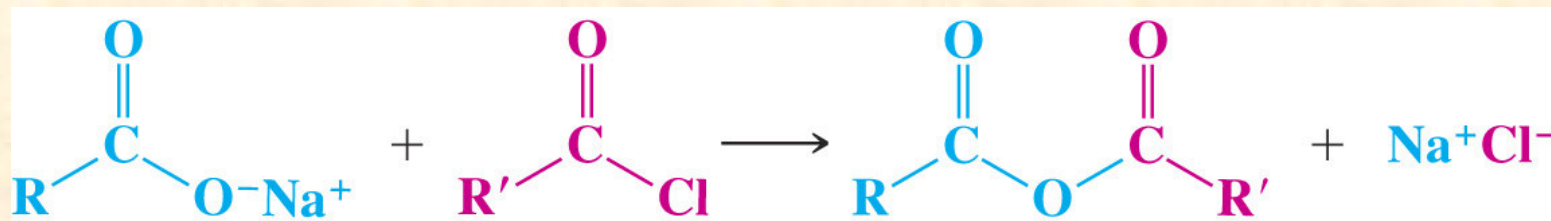
Carboxylic Acid Anhydrides

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

Succinic acid → (300°C) → Succinic anhydride + H_2O
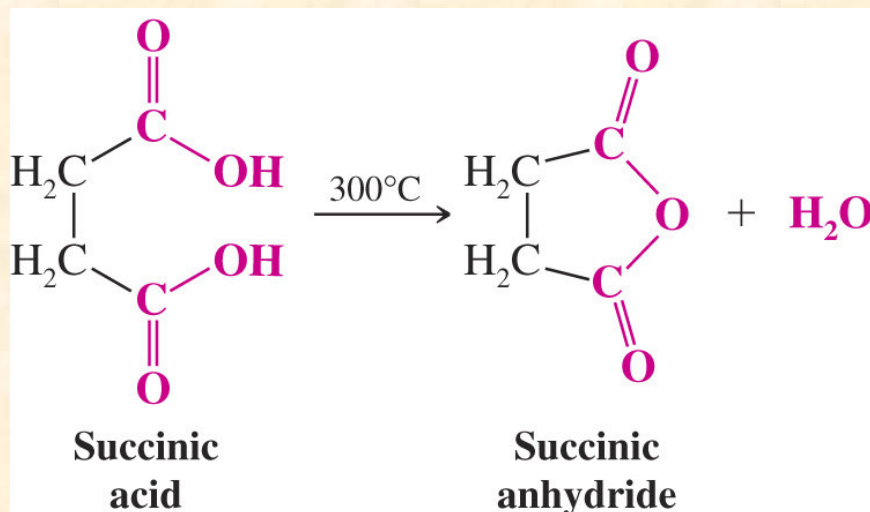
  – <u>Reactions of Carboxylic Acid Anhydrides</u>
    - Carboxylic acid anhydrides are very reactive and can be used to synthesize esters and amides
      – Hydrolysis of an anhydride yields the corresponding carboxylic acids

Carboxylic Acid Anhydrides

$R'OH$ → Ester: $RCOR'$ + $RCOH$

NH_3 → Amide: $RCNH_2$ + $RCO^- NH_4^+$

$R'NH_2$ → N-Substituted amide: $RCNHR'$ + $RCO^- R'NH_3^+$

$R'R''NH$ → N,N-Disubstituted amide: $RCNR'R''$ + By-products: $RCO^- R'R''NH_2^+$

Anhydride: $RC-O-CR$

H_2O → $RCOH$ + $HOCR'$

OH^-/H_2O → RCO^- + $^-OCR'$

Anhydride: $RC-O-CR'$

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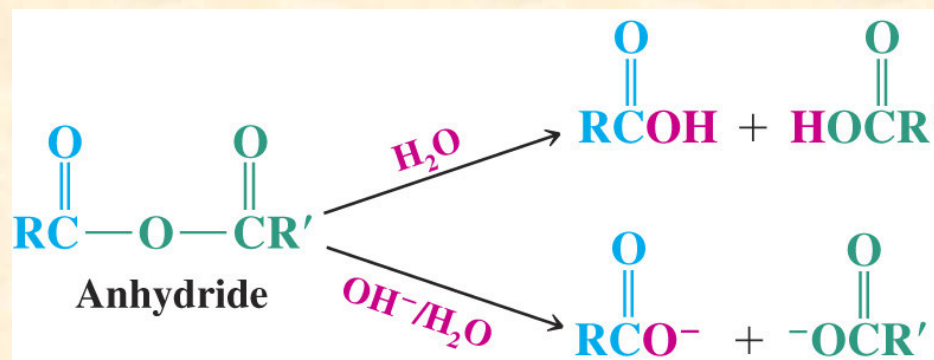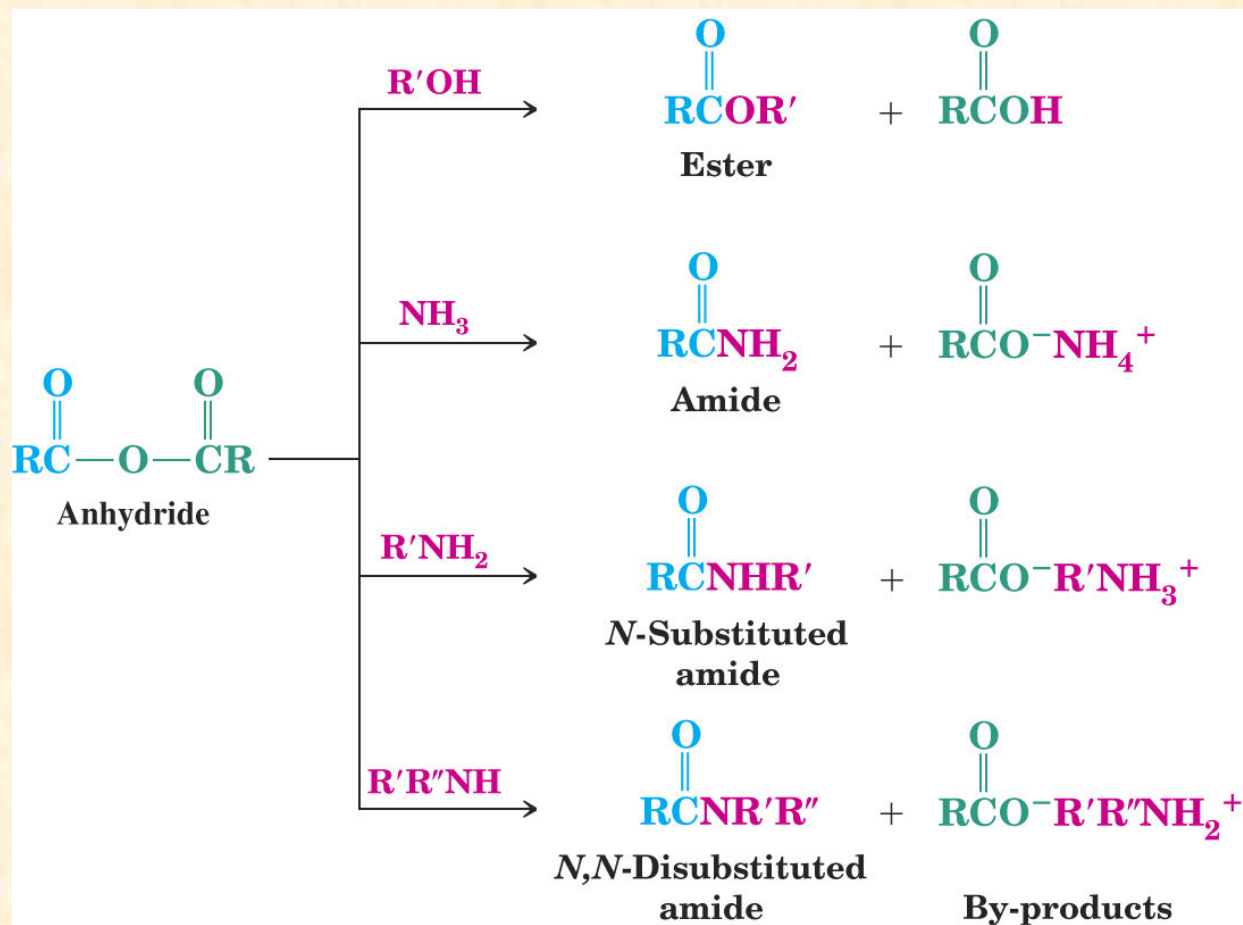
Carboxylic Acid Esters

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

$$\underset{\text{Acetic acid}}{CH_3COH} \;+\; \underset{\text{Ethanol}}{CH_3CH_2OH} \;\underset{}{\overset{HA}{\rightleftharpoons}}\; \underset{\text{Ethyl acetate}}{CH_3COCH_2CH_3} \;+\; H_2O$$

$$\underset{\text{Benzoic acid}}{C_6H_5COH} \;+\; \underset{\text{Methanol}}{CH_3OH} \;\overset{HA}{\rightleftharpoons}\; \underset{\text{Methyl benzoate}}{C_6H_5COCH_3} \;+\; H_2O$$

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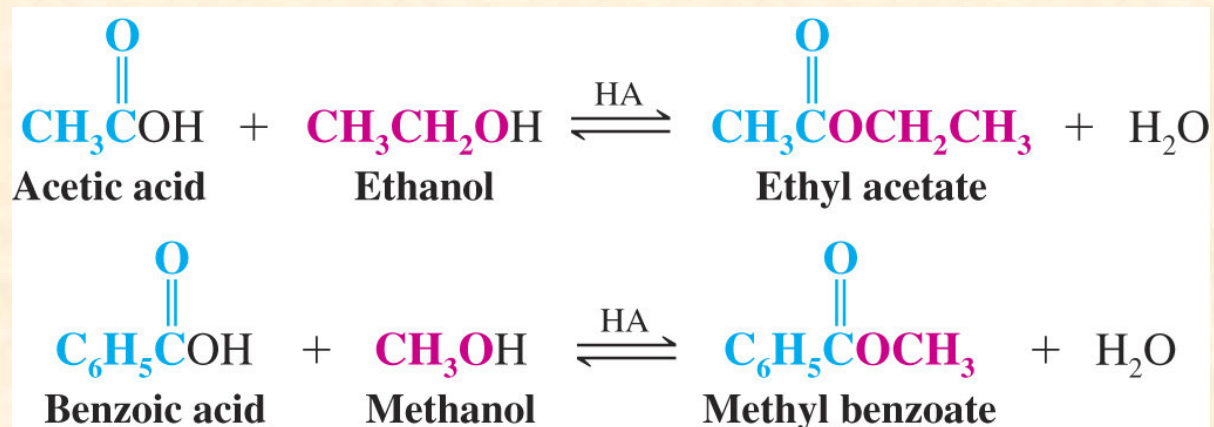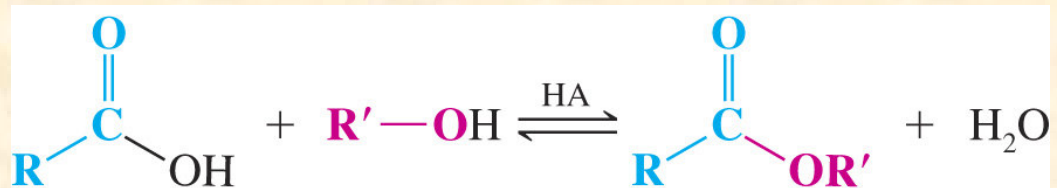
Carboxylic Acid Esters

- Esterification with labeled methanol gives a product labeled only at the oxygen atom bonded to the methyl group
  - A mechanism consistent with this observation is shown below

$$C_6H_5C{-}OH \; + \; CH_3{-}^{18}O{-}H \; \underset{}{\overset{HA}{\rightleftharpoons}} \; C_6H_5C{-}^{18}OCH_3 \; + \; H_2O$$
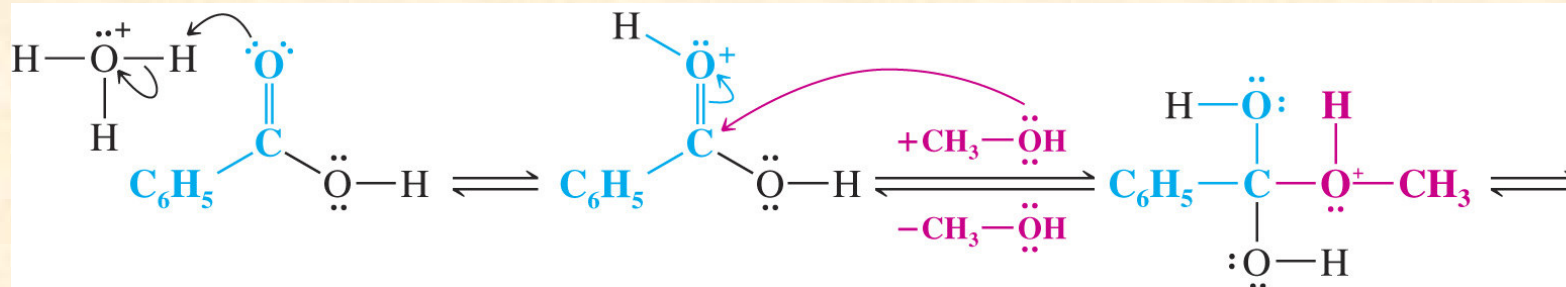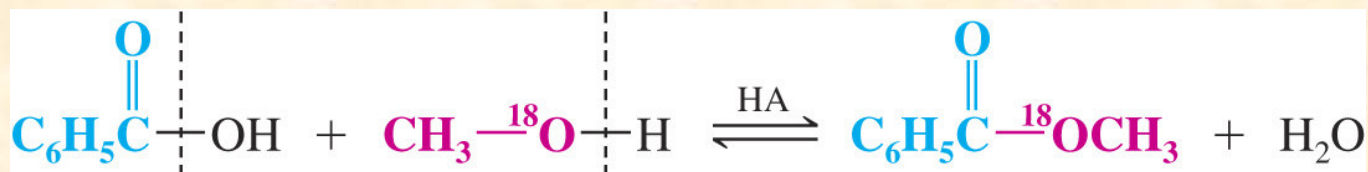
The carboxylic acid accepts a proton from the strong acid catalyst.

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

A proton is lost at one oxygen atom and gained at another.
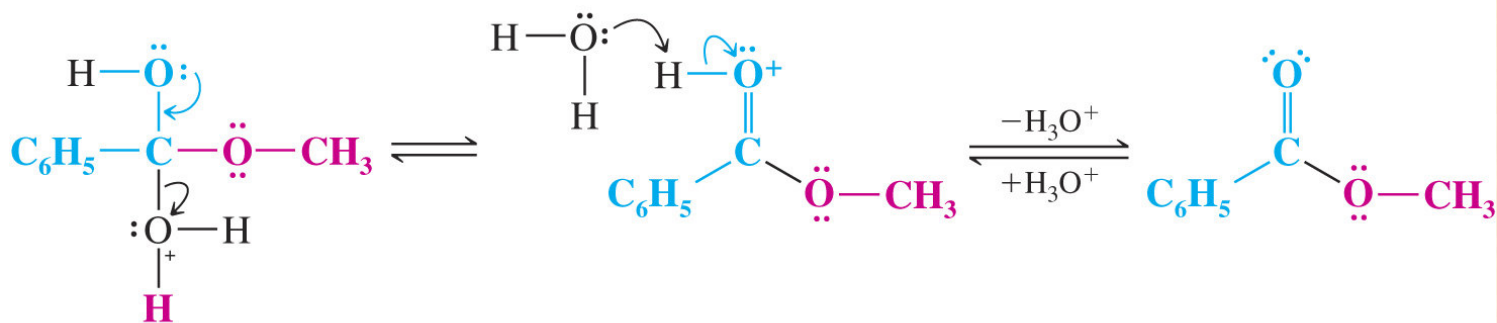
Loss of a molecule of water gives a protonated ester.

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

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- The reverse reaction is acid-catalyzed ester hydrolysis
  - Ester hydrolysis is favored by use of dilute aqueous acid
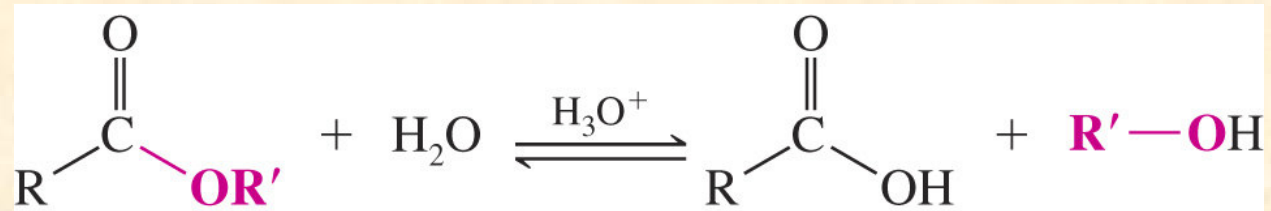
- Esters from Acid Chlorides
  - Acid chlorides react readily with alcohols in the presence of a base (*e.g.* pyridine) to form esters

C_6H_5C-Cl + CH_3CH_2OH + (pyridine) $\longrightarrow$ $C_6H_5COCH_2CH_3$ + (pyridinium) Cl^-

Benzoyl chloride   **Ethyl benzoate** (80%)
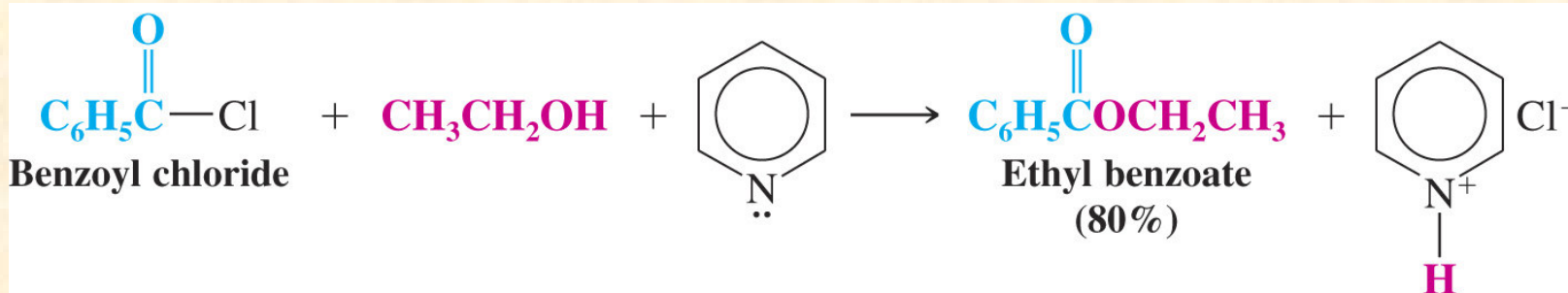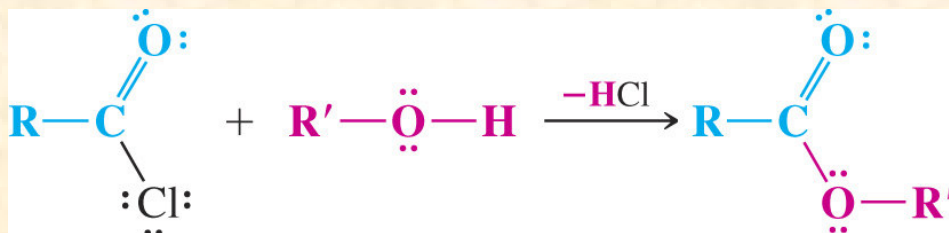
Carboxylic Acid Esters

- Esters from Carboxylic Acid Anhydrides
  - Alcohols react readily with anhydrides to form esters

Acetic anhydride + Benzyl alcohol → Benzyl acetate + CH_3CO_2H

Phthalic anhydride + sec-Butyl alcohol $\xrightarrow{110°C}$ sec-Butyl hydrogen phthalate (97%)
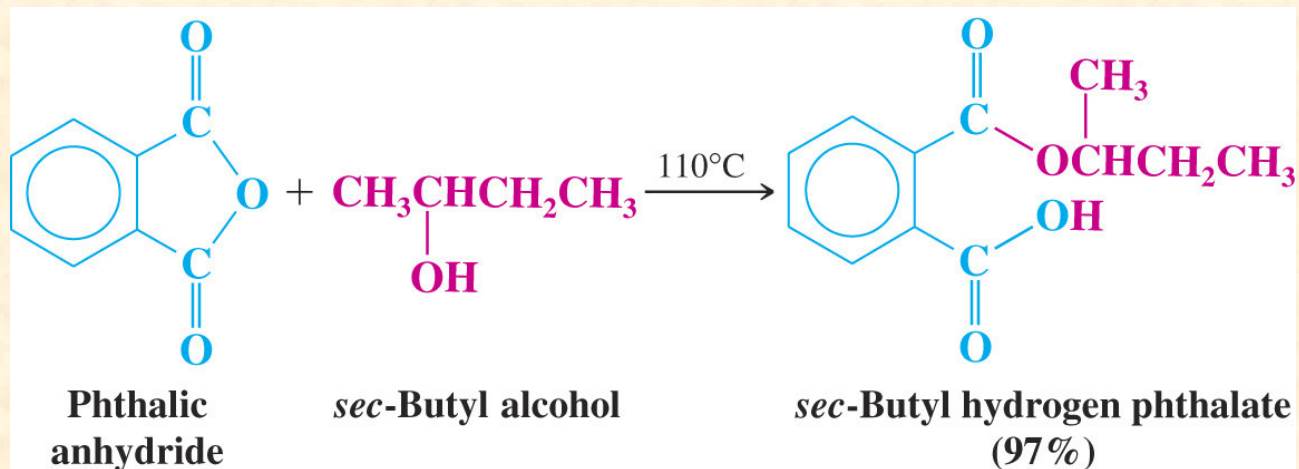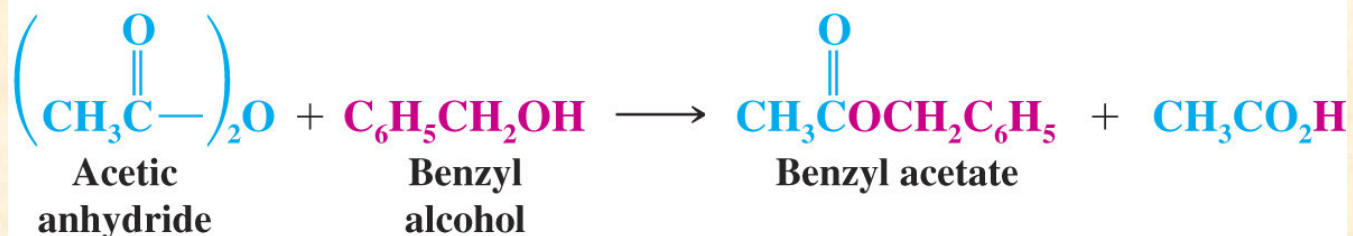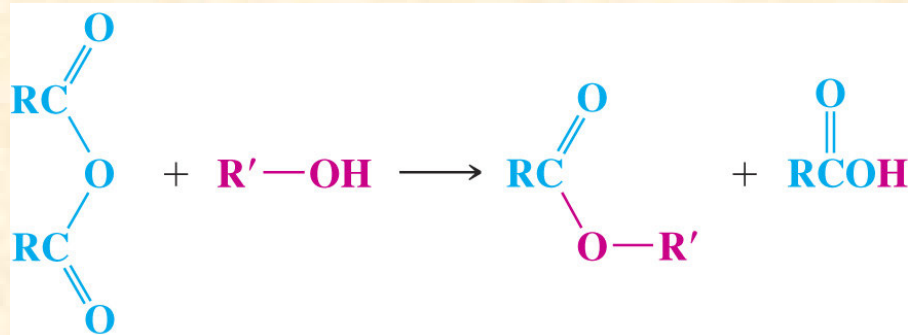
Carboxylic Acid Esters

- Base-Promoted Hydrolysis of Esters: Saponification
  - Reaction of an ester with sodium hydroxide results in the formation of a sodium carboxylate and an alcohol
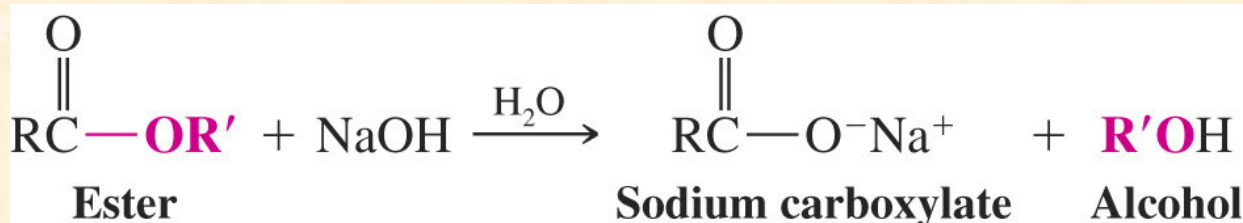
  - The mechanism is reversible until the alcohol product is formed
  - Protonation of the alkoxide by the carboxylic acid is irreversible
    - This step draws the overall equilibrium toward the hydrolysis
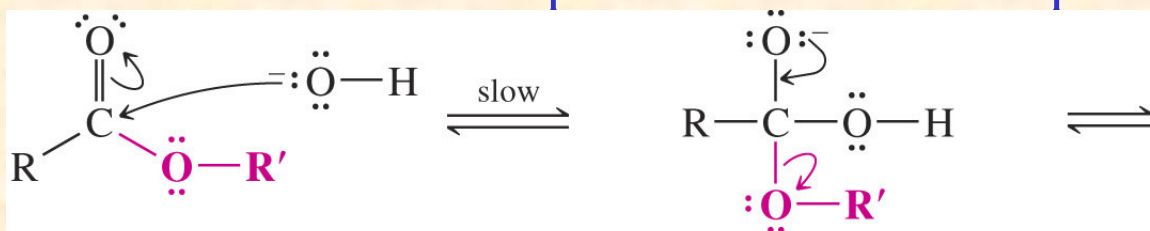
A hydroxide ion attacks the carbonyl carbon atom.

The tetrahedral intermediate expels an alkoxide ion.
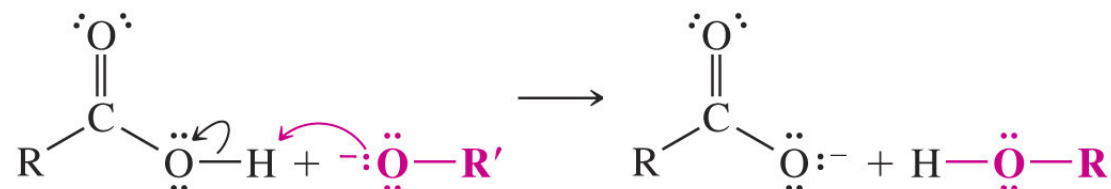
Transfer of a proton leads to the products of the reaction.

– Lactones

γ- or δ-Hydroxyacids undergo acid catalyzed reaction to give
cyclic esters known as γ- or δ-lactones, respectively

A δ-hydroxy acid
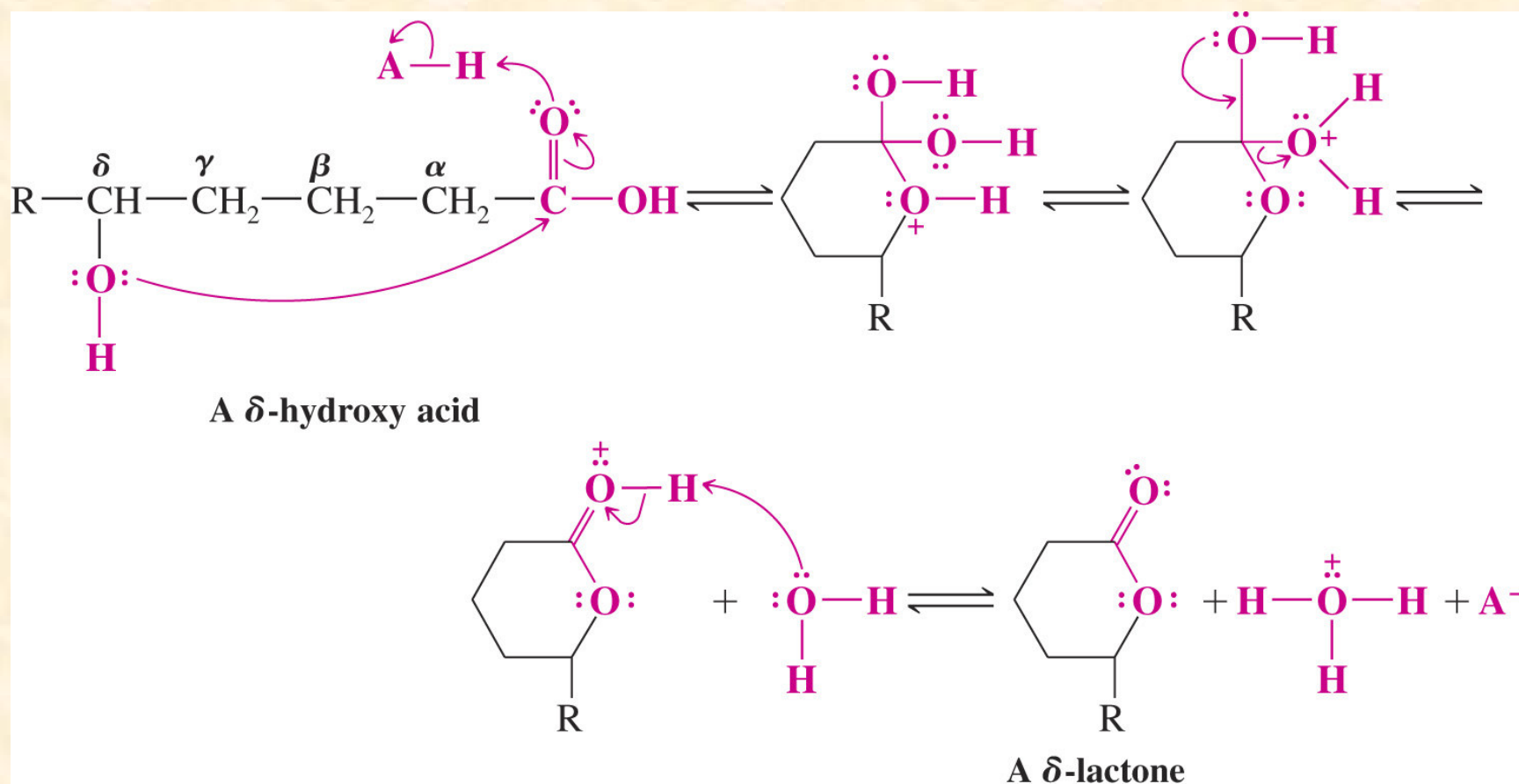
A δ-lactone

- 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
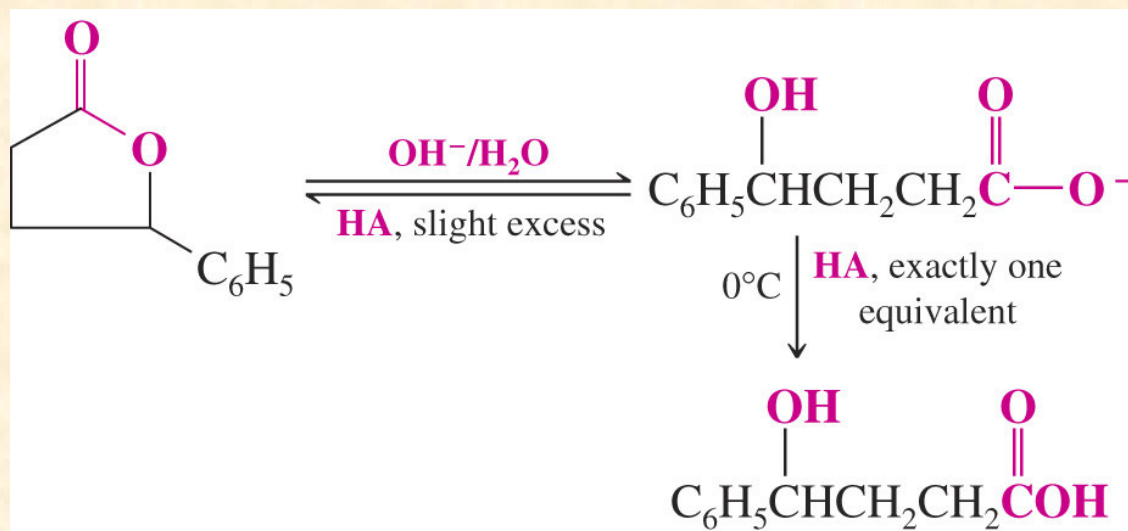
Amides

Synthesis of Amides

- Amides From Acyl Chlorides
    - Ammonia, primary or secondary amines react with acid chlorides to form amides
    - An excess of amine is added to neutralize the HCl formed in the reaction
    - Carboxylic acids can be converted to amides via the corresponding acid chloride
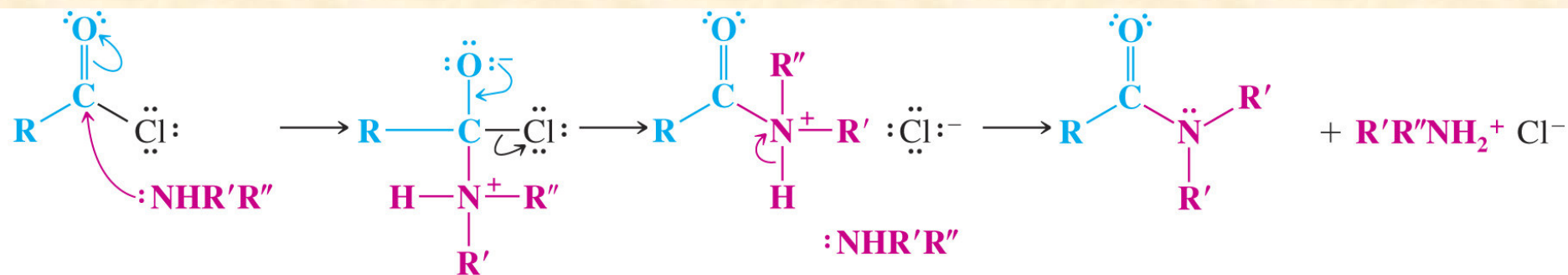
Reactant	*Product*
Ammonia; R', $R'' = H$	Unsubstituted amide; R', $R'' = H$
1° Amine; $R' = H$, $R'' = $ alkyl, aryl	N-Substituted amide; $R' = H$, $R'' = $ alkyl, aryl
2° Amine; R', $R'' = $ alkyl, aryl	N,N-Disubstituted amide; R', $R'' = $ alkyl, aryl

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Amides

- Amides from Carboxylic Anhydrides
  - Anhydrides react with 2 equivalents of amine to produce an amide and an ammonium carboxylate
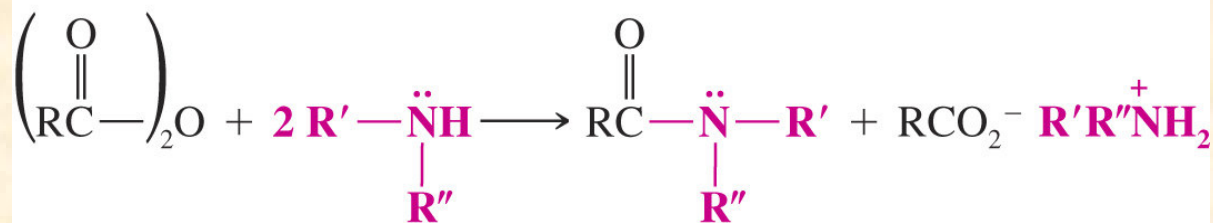
R′, R″ can be H, alkyl or aryl

  - 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

| Phthalic anhydride | Ammonium phthalamate (94%) | Phthalamic acid (81%) |
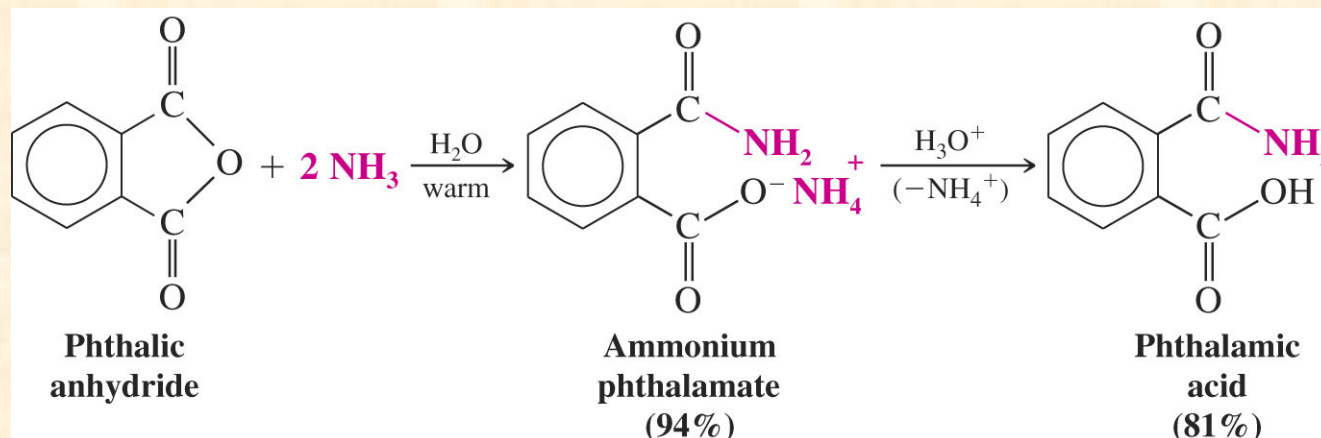
Amides

- Amides from Carboxylic Acids and Ammonium Carboxylates
  - Direct reaction of carboxylic acids and ammonia yields ammonium salts

An ammonium carboxylate
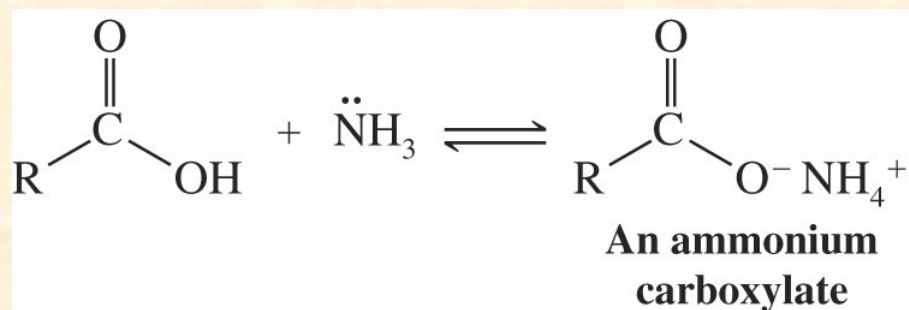
  - Some ammonium salts of carboxylic acids can be dehydrated to the amide at high temperatures
  - This is generally a poor method of amide synthesis
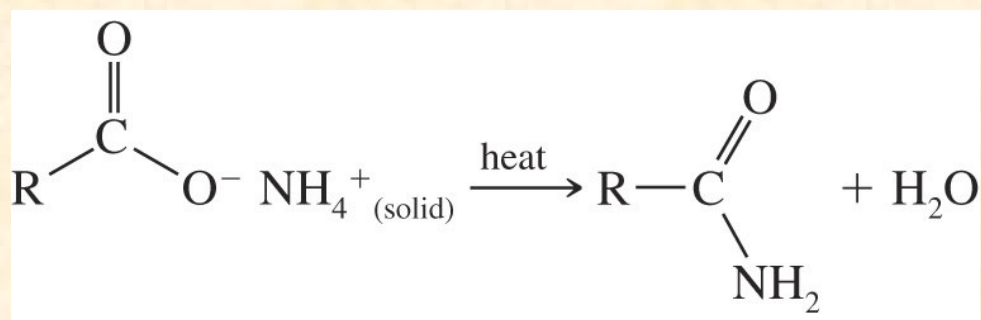
  - A good way to synthesize an amide is to convert a carboxylic acid to an acid chloride and to then to react the acid chloride with ammonia or an amine

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Amides

– Dicylohexylcarbodiimide (DCC) is a reagent used to form amides from carboxylic acids and amines

– DCC activates the carbonyl group of a carboxylic acid

Dicyclohexyl-carbodiimide (DCC)

Proton transfer

Reactive intermediate

Collapse of the tetrahedral intermediate and proton transfer

An amide N,N'-Dicyclohexylurea

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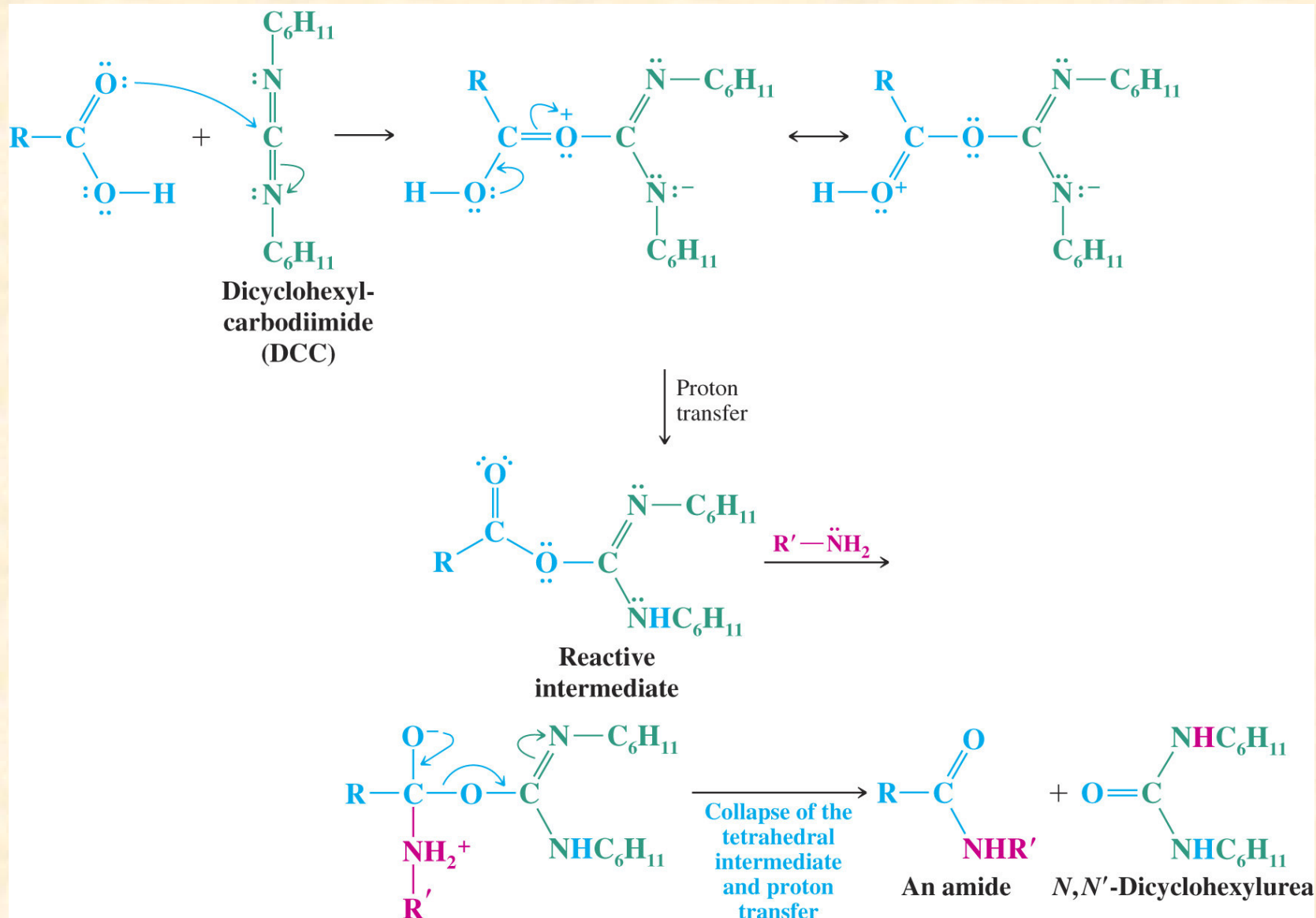
Amides

– 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
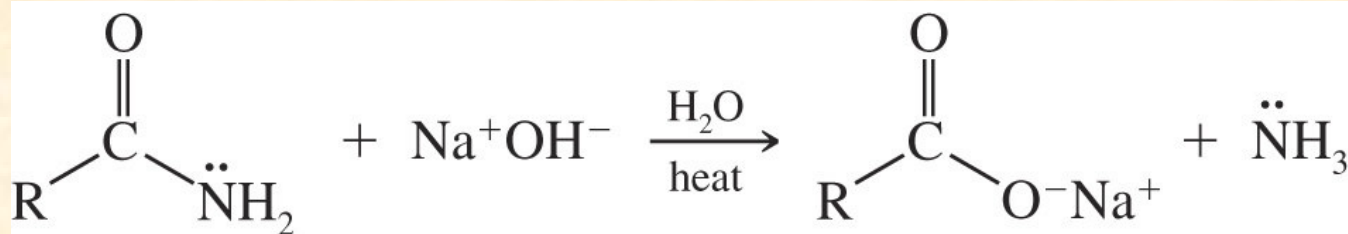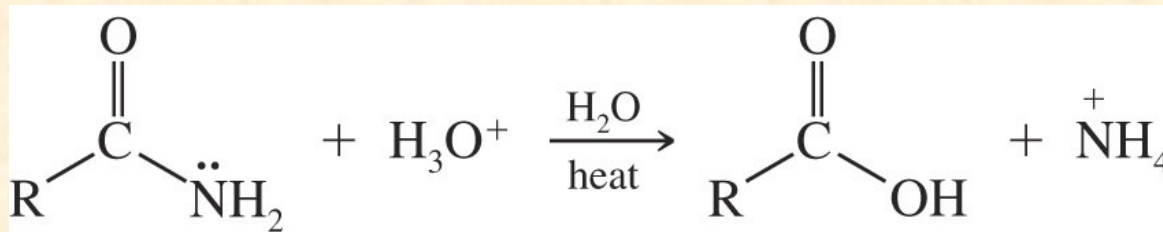
Amides
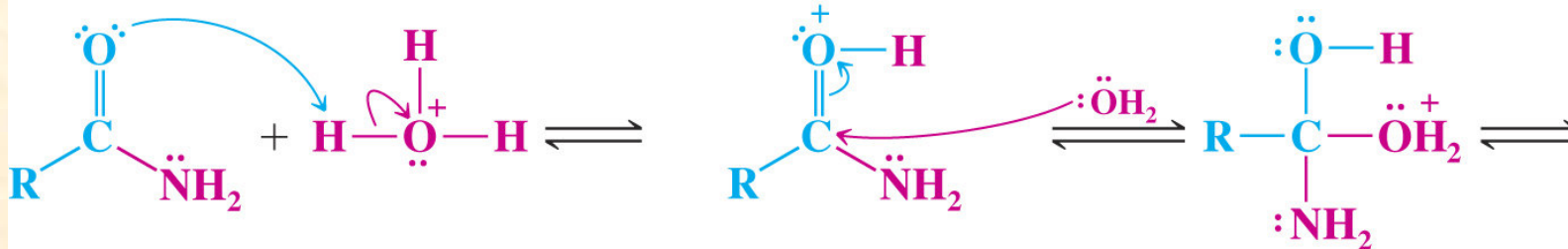
The amide carbonyl accepts a proton from the aqueous acid.

A water molecule attacks the protonated carbonyl to give a tetrahedral intermediate.

A proton is lost at one oxygen and gained at the nitrogen.
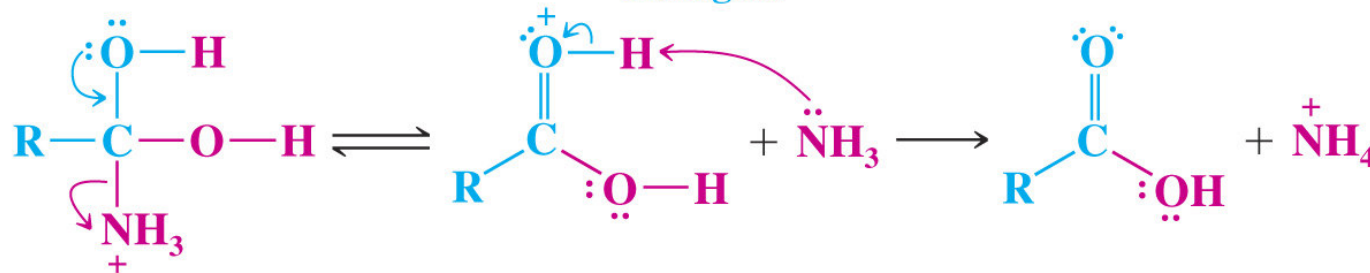
Loss of a molecule of ammonia gives a protonated carboxylic acid.

Transfer of a proton to ammonia leads to the carboxylic acid and an ammonium ion.

Amides

A hydroxide ion attacks the acyl carbon of the amide.

A hydroxide ion removes a proton to give a dianion.

The dianion loses a molecule of ammonia (or an amine); this step is synchronized with a proton transfer from water due to the basicity of NH_2^-.
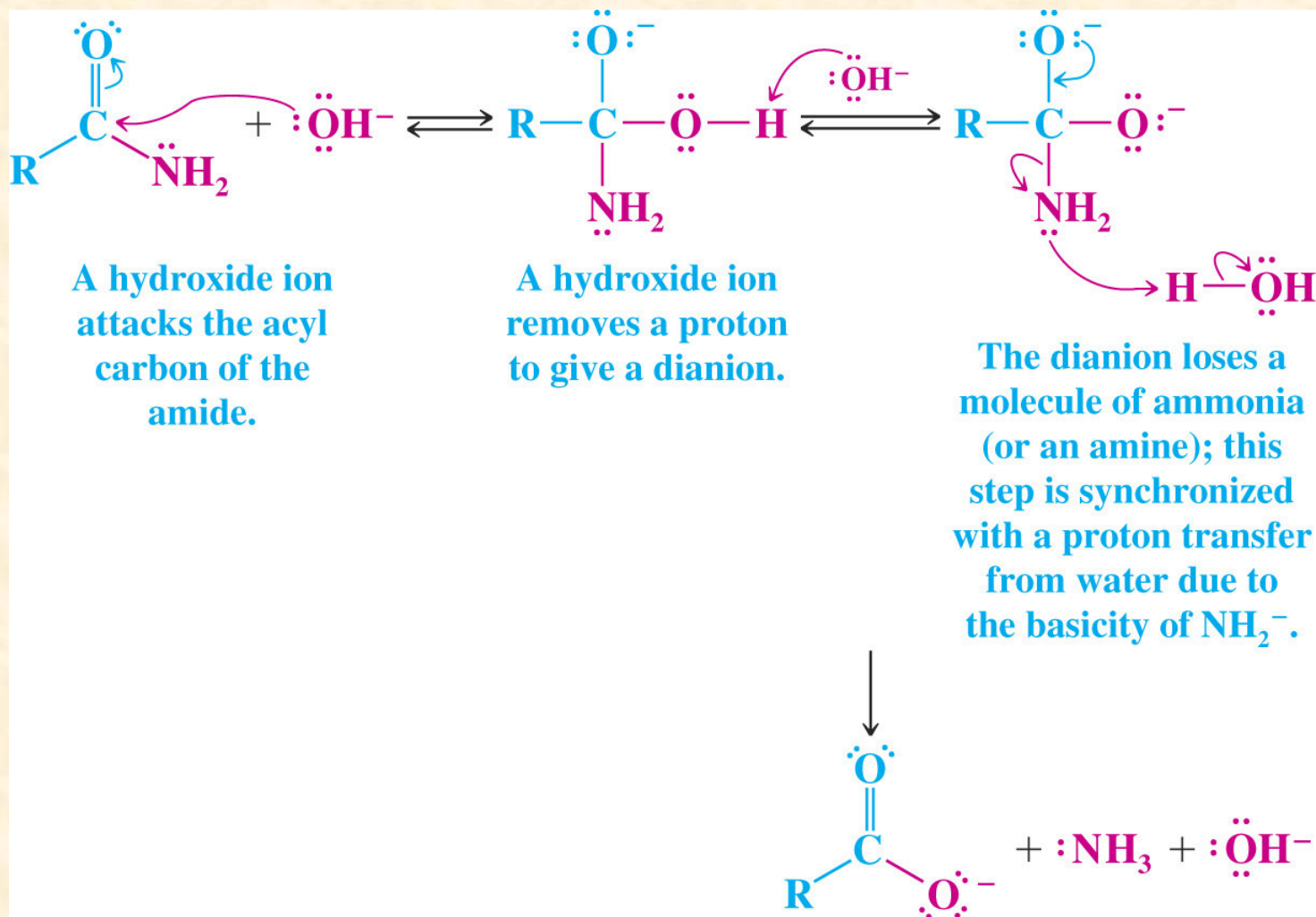
Amides

– Nitriles from the Dehydration of Amides

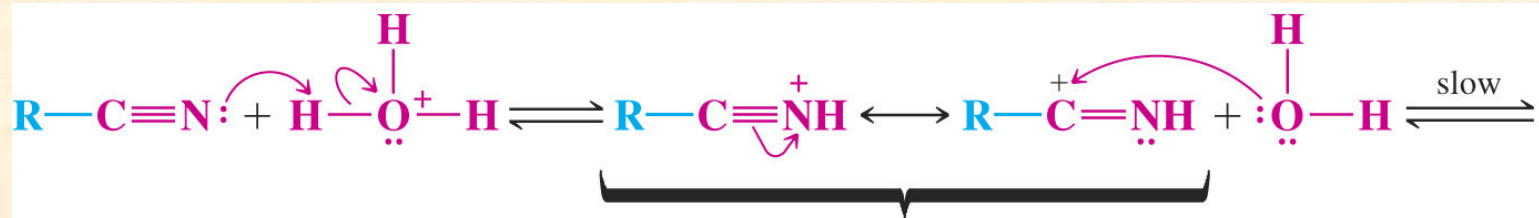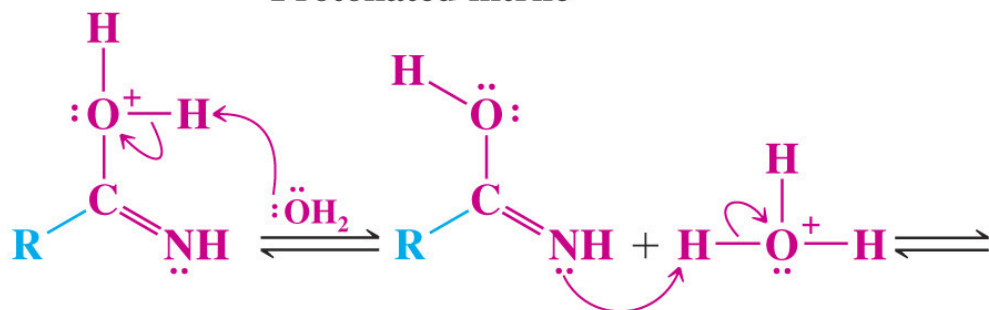 • A nitrile can be formed by reaction of an amide with phosphorous pentoxide or boiling acetic anhydride

$$R-\overset{\displaystyle \overset{..}{\underset{..}{O}}}{\underset{\displaystyle :NH_2}{C}} \xrightarrow[\substack{\text{heat} \\ (-H_2O)}]{P_4O_{10} \text{ or } (CH_3CO)_2O} R-C\equiv N: + H_3PO_4 \quad \text{or} \quad CH_3CO_2H$$
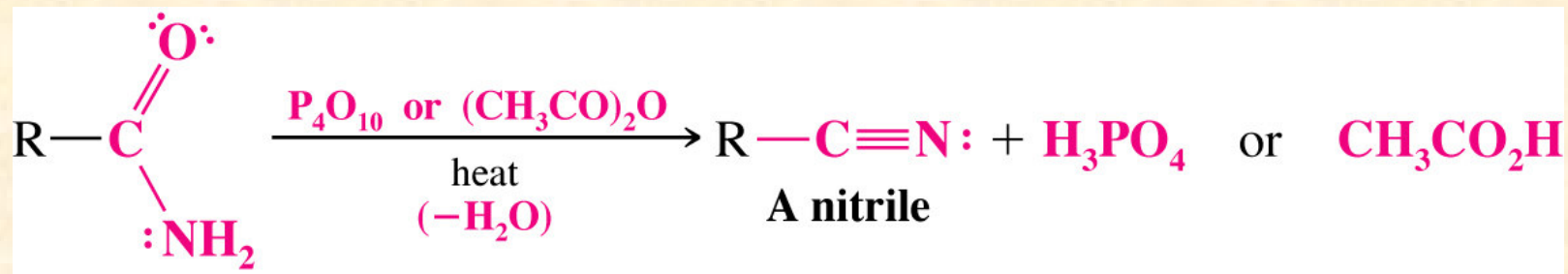
A nitrile

– Hydrolysis of Nitriles

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

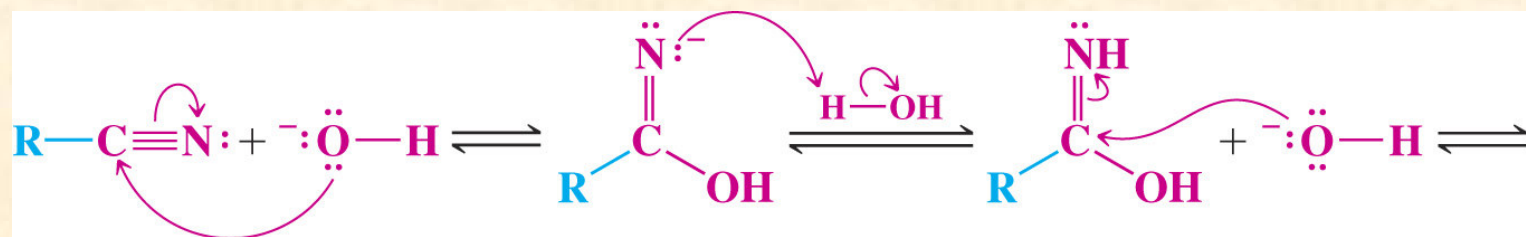$$R-C\equiv N \quad \substack{\xrightarrow{H_3O^+, H_2O, \text{ heat}} RCO_2H \\ \\ \xrightarrow{OH^-, H_2O, \text{ heat}} RCO_2^-}$$
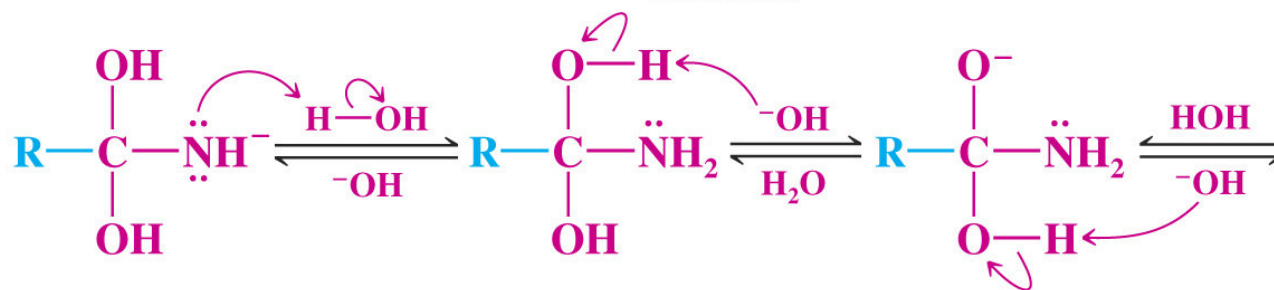
39
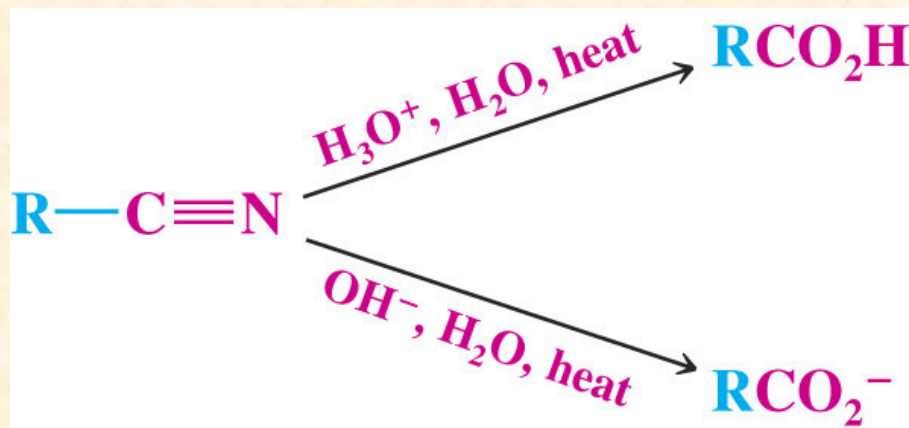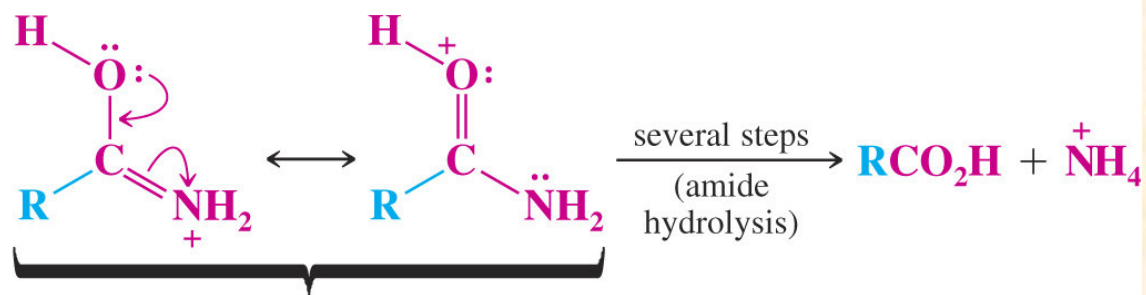
Amides

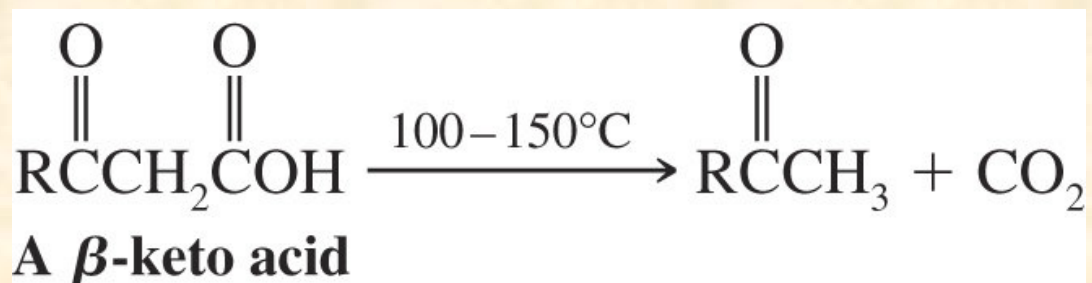# Amides

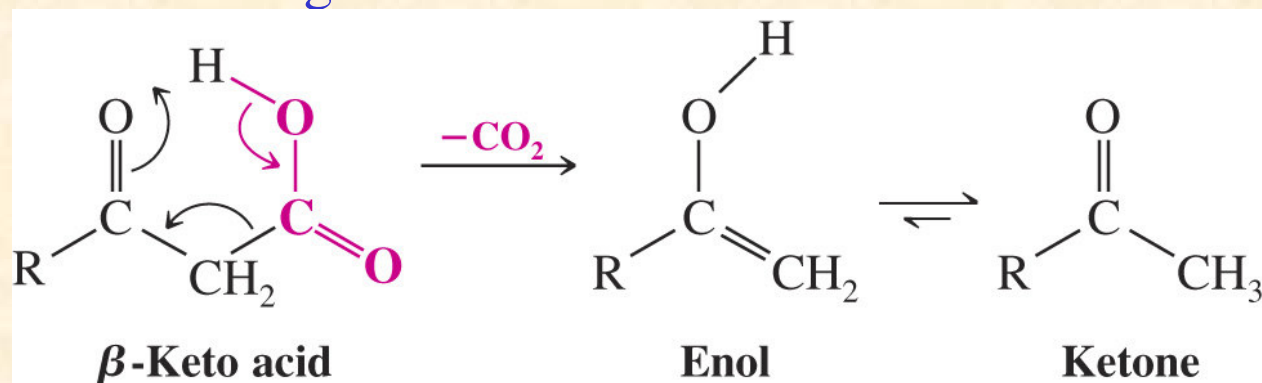Amide tautomer
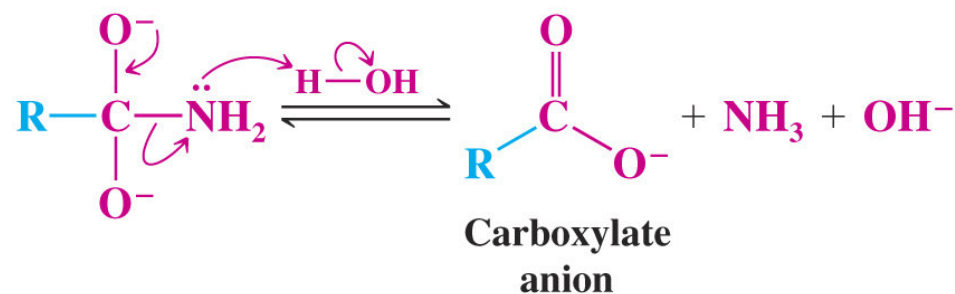
Carboxylate anion

Decarboxylation

- Decarboxylation of Carboxylic Acids

    β-Keto carboxylic acids and their salts decarboxylate readily when heated
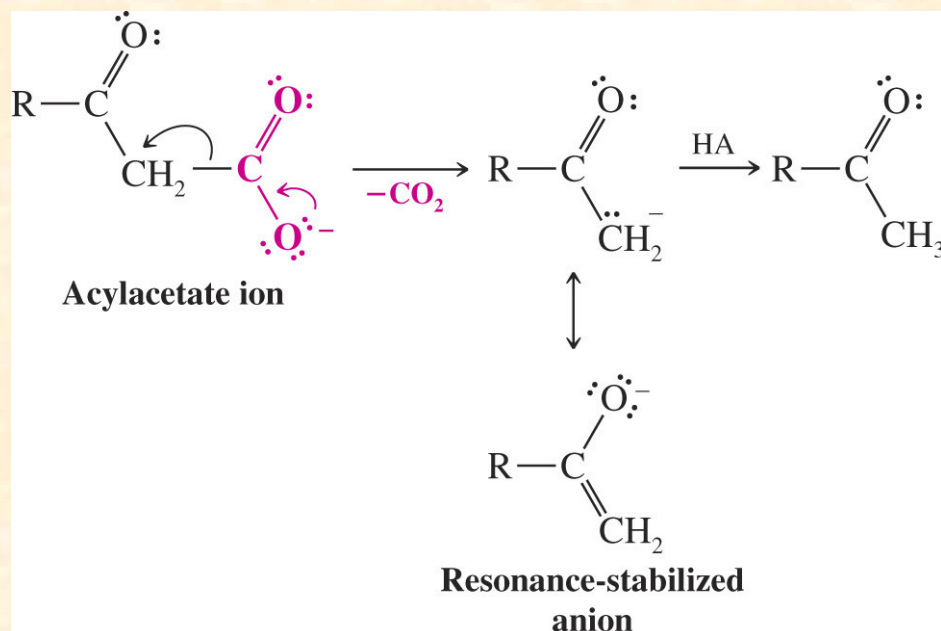
    – Some even decarboxylate slowly at room temperature

- The mechanism of β-keto acid decarboxylation proceeds through a 6-membered ring transition state

Decarboxylation

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

Acylacetate ion

Resonance-stabilized anion

- Malonic acids also decarboxylate readily

A malonic acid