Chapter 17
Carboxylic Acids and Their Derivatives. Nucleophilic Addition-Elimination at the Acyl Carbon

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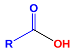
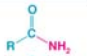
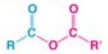
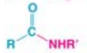
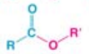
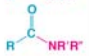
♦ Introduction

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



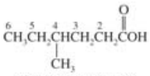
Carboxylic acids - Substitution of hydroxyl group will produce

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

♦ Nomenclature and Physical Properties

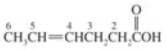
➔In IUPAC nomenclature, the name of a carboxylic acid is obtained by **changing the -e of the corresponding parent alkane to -oic acid**

- The carboxyl carbon is assigned position 1 and need not be explicitly numbered



$$\overset{6}{C}H_3\overset{5}{C}H_2\overset{4}{C}H(CH_3)\overset{3}{C}H_2\overset{2}{C}H_2\overset{O}{\overset{\|}{C}}OH$$

4-Methylhexanoic acid



$$\overset{6}{C}H_3\overset{5}{C}H{=}\overset{4}{C}H\overset{3}{C}H_2\overset{2}{C}H_2\overset{O}{\overset{\|}{C}}OH$$

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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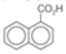
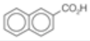
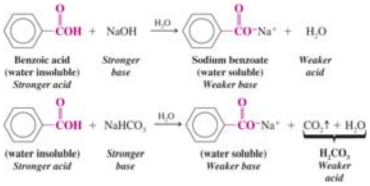
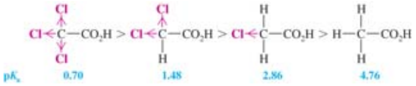
Carboxylic acids – Physical Properties

Structure	Systematic Name	Common Name	mp (°C)	bp (°C)	Water Solubility (g 100 mL^{-1} H_2O), 25°C	pK_a
HCO_2H	Methanoic acid	Formic acid	8	100.5	∞	3.75
CH_3CO_2H	Ethanoic acid	Acetic acid	16.6	118	∞	4.76
$CH_3CH_2CO_2H$	Propanoic acid	Propionic acid	−21	141	∞	4.87
$CH_3(CH_2)_2CO_2H$	Butanoic acid	Butyric acid	−6	164	∞	4.81
$CH_3(CH_2)_3CO_2H$	Pentanoic acid	Valeric acid	−34	187	4.97	4.82
$CH_3(CH_2)_4CO_2H$	Hexanoic acid	Caproic acid	−3	205	1.08	4.84
$CH_3(CH_2)_6CO_2H$	Octanoic acid	Caprylic acid	16	239	0.07	4.89
$CH_3(CH_2)_8CO_2H$	Decanoic acid	Capric acid	31	269	0.015	4.84
$CH_3(CH_2)_{10}CO_2H$	Dodecanoic acid	Lauric acid	44	179^{18}	0.006	5.30
$CH_3(CH_2)_{12}CO_2H$	Tetradecanoic acid	Myristic acid	59	200^{20}	0.002	
$CH_3(CH_2)_{14}CO_2H$	Hexadecanoic acid	Palmitic acid	63	219^{17}	0.0007	6.46
$CH_3(CH_2)_{16}CO_2H$	Octadecanoic acid	Stearic acid	70	383	0.0003	
CH_2ClCO_2H	Chloroethanoic acid	Chloroacetic acid	63	189	Very soluble	2.86
$CHCl_2CO_2H$	Dichloroethanoic acid	Dichloroacetic acid	10.8	192	Very soluble	1.48
CCl_3CO_2H	Trichloroethanoic acid	Trichloroacetic acid	56.3	198	Very soluble	0.70
$CH_3CHClCO_2H$	2-Chloropropanoic acid	α-Chloropropionic acid		186	Soluble	2.83
$CH_2ClCH_2CO_2H$	3-Chloropropanoic acid	β-Chloropropionic acid	61	204	Soluble	3.98
$C_6H_5CO_2H$	Benzoic acid	Benzoic acid	122	250	0.34	4.19
p-$CH_3C_6H_4CO_2H$	4-Methylbenzoic acid	p-Toluic acid	180	275	0.03	4.36
p-$ClC_6H_4CO_2H$	4-Chlorobenzoic acid	p-Chlorobenzoic acid	242		0.009	3.98
p-$NO_2C_6H_4CO_2H$	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 of Carboxylic Acids**
  - ➔ The carboxyl proton of most carboxylic acids has 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



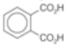
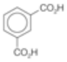
- ➔ Electron-withdrawing groups near the carboxyl group increase the carboxylic acid's acidity
  - They stabilize the carboxylate anion by inductive delocalization of charge



- **Dicarboxylic Acids**

Dicarboxylic acids are named as alkanedioic acids in the IUPAC system

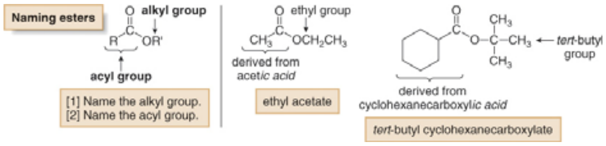
- Common names are often used for simple dicarboxylic acids

			pK_a (at 25°C)	
Structure	Common Name	mp (°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
	Phthalic acid	206–208 dec	2.9	5.4
	Isophthalic acid	345–348	3.5	4.6
	Terephthalic acid	Sublimes	3.5	4.8

Carboxylic Acids and Their Derivatives

Nomenclature—Esters

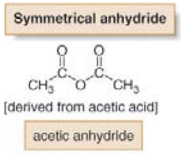
- **Name the R' as an alkyl group. This becomes the first part of the name.**
- **Name the acyl group by changing the *ic acid* ending of the parent carboxylic acid to the suffix *–ate*.**

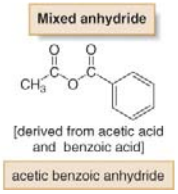


Carboxylic Acids and Their Derivatives

Nomenclature—Anhydrides

- **Symmetrical anhydrides are named by changing the acid ending of the carboxylic acid to the word *anhydride*.**
- **Mixed anhydrides, which are derived from two different carboxylic acids, are named by alphabetizing the names for both acids and replacing the word *acid* with the word *anhydride*.**

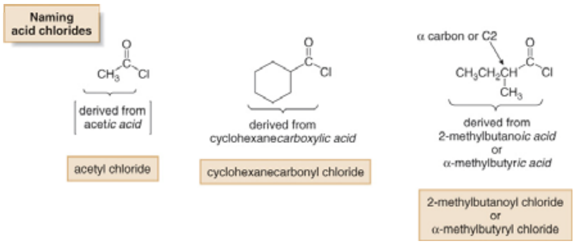




Carboxylic Acids and Their Derivatives

Nomenclature—Acid Chlorides

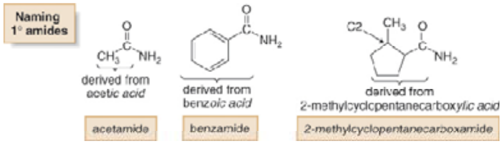
- **For acyclic acid chlorides: change the suffix –*ic acid* of the parent carboxylic acid to the suffix –*yl chloride*; or**
- **When the –COCl group is bonded to a ring: change the suffix –*carboxylic acid* to –*carbonyl chloride*.**



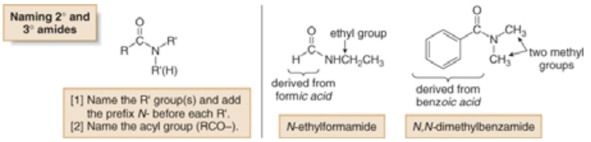
Carboxylic Acids and Their Derivatives

Nomenclature—Amides

- **All 1^0 amides are named by replacing the *-ic acid*, *-oic acid*, or *-ylic acid* ending with the suffix amide.**



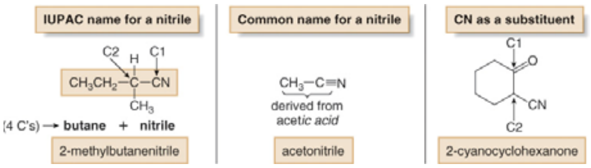
- **For 2^o and 3^0 amides, use the prefix "*N-*" preceding the name of each alkyl group to show that it is bonded to a nitrogen atom. If the two alkyl groups are different, alphabetize their names. Use additional prefix "di-". One "*N-*" is needed for each alkyl group, even if both R groups are identical.**



Carboxylic Acids and Their Derivatives

Nomenclature—Nitriles

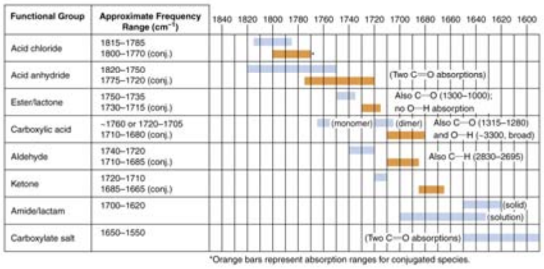
- **In naming a nitrile, the CN carbon is carbon atom ONE of the longest chain. Number the chain to put CN at C1, and omit this number from the name. So, CH_3CH_2CN is propanenitrile, not ethanenitrile.**
- **Common names of nitriles are derived from the names of the carboxylic acid having the same number of carbon atoms by replacing the –*ic acid* ending of the carboxylic acid by the suffix –*onitrile*.**
- **When the CN is named as a substituent it is called a cyano group.**



Carboxylic Acids and Their Derivatives

Spectral Properties of Acyl Compounds:

IR spectra is important in identifying carboxylic acids, because C=O stretching bond occurs at different frequencies for acid, ester & amides (1620-1780 cm^{-1})



Functional Group	Approximate Frequency Range (cm^{-1})	
Acid chloride	1815–1785 1800–1770 (conj.)	
Acid anhydride	1820–1750 1775–1720 (conj.)	(Two C=O absorptions)
Ester/lactone	1750–1735 1730–1715 (conj.)	Also C–O (1300–1000); no O–H absorption
Carboxylic acid	~1760 or 1720–1705 1710–1680 (conj.)	(monomer) (dimer) Also C–O (1315–1280) and O–H (~3300, broad)
Aldehyde	1740–1720 1710–1685 (conj.)	Also C–H (2830–2695)
Ketone	1720–1710 1685–1665 (conj.)	
Amide/lactam	1700–1620	(solid) (solution)
Carboxylate salt	1650–1550	(Two C=O absorptions)

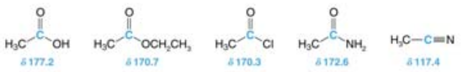
*Orange bars represent absorption ranges for conjugated species.

Carboxylic Acids and Their Derivatives

^{13}C NMR Spectral Properties of Acyl Componds:

•^{13}C NMR spectra is also important in identifying carboxylic acids derivatives. The carbonyl carbon of acyl derivatives occurs downfield in the δ 160-180 region. Please note that they resonates not as far as ketones and aldehydes which have their peaks at δ 180-200.

• The nitrile carbon absorbs in the δ 115-120 region.



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

♦ Preparation of Carboxylic Acids

- By Oxidation of Alkanes

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

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

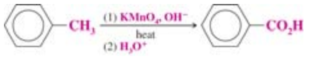
- By Oxidation of Aldehydes and Primary Alcohols

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

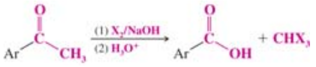
$$RCH_2OH \xrightarrow[\text{heat} \quad (2)\ H_3O^+]{(1)\ KMnO_4,\ OH^-} RCO_2H$$

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

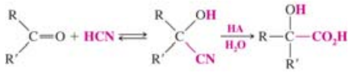
- By Oxidation of Alkylbenzenes



- 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

$$HOCH_2CH_2Cl \xrightarrow[(80\%)]{NaCN} HOCH_2CH_2CN \xrightarrow[(2)\ H_3O^+ \ (75\text{–}80\%)]{(1)\ OH^-,\ H_2O} HOCH_2CH_2CO_2H$$

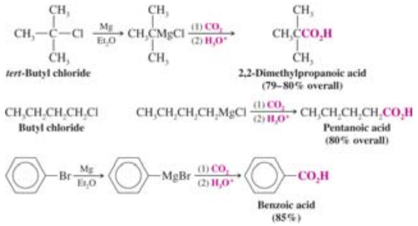
3-Hydroxy-propanenitrile; 3-Hydroxypropanoic acid

$$BrCH_2CH_2CH_2Br \xrightarrow[(77\text{–}86\%)]{NaCN} NCCH_2CH_2CH_2CN \xrightarrow[(77\text{–}86\%)]{H_3O^+} HO_2CCH_2CH_2CH_2CO_2H$$

Pentanenitrile; Glutaric acid

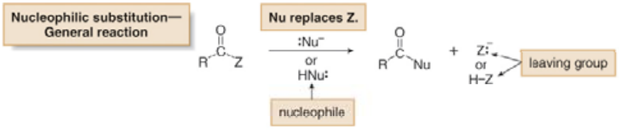
- By Carbonation of Grignard Reagents

Experiment which you did in Org. Chem lab.



Carboxylic Acids and Their Derivatives—Nucleophilic Acyl Substitution – Critical Concept.

- **This is the characteristic reaction of carboxylic acid derivatives.**
- **This reaction occurs with both negatively charged nucleophiles and neutral nucleophiles.**

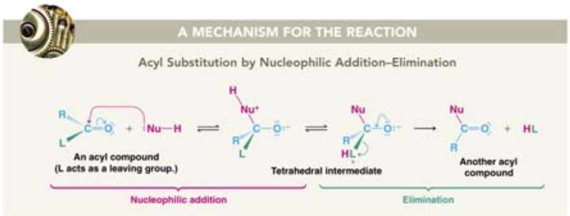


◆ Carboxylic acid derivatives (RCOZ) react with nucleophiles because they contain an electrophilic, unhindered carbonyl carbon.

◆ Substitution occurs, *not* addition, because carboxylic acid derivatives (RCOZ) have a leaving group Z on the carbonyl carbon.

Carboxylic Acids and Their Derivatives—Nucleophilic Acyl Substitution - MECHANISM

Acyl Substitution occurs by a Nucleophilic Addition – Elimination mechanism (Important new concept !)



[1] Find the *sp*² hybridized carbon with the leaving group.

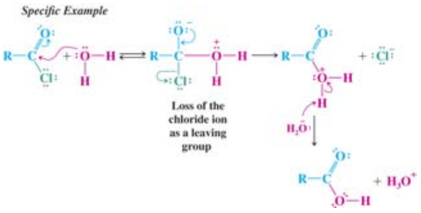
[2] Identify the nucleophile.

[3] Substitute the nucleophile for the leaving group. With a neutral nucleophile, the proton must be lost to obtain a neutral substitution product.

Acyl substitution requires a leaving group (LG) at the carbonyl carbon Review the relative strength of acids (pK) (See table 3.1 on p

REMEMBER: The stronger the acid (lower pK_a) OR the weaker the conjugated base - the better the leaving group)

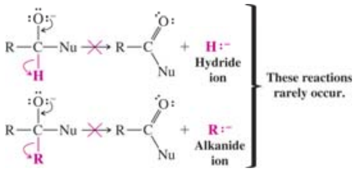
- **➔To undergo nucleophilic addition-elimination the acyl compound must have a good leaving group or a group that can be converted into a good leaving group**
  - **Acid chlorides react with loss of chloride ion**
  - **Anhydrides react with loss of a carboxylate ion**



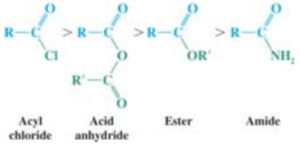
- **➔Esters, carboxylic acids and amides generally react with loss of the leaving groups alcohol, water and amine, respectively**
  - **These leaving groups are generated by protonation of the acyl compound**

BUT

- **➔Aldehydes and ketones cannot react by this mechanism because they lack a good leaving group**



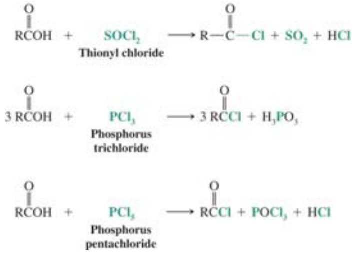
- **Relative Reactivity of Acyl Compounds**
  - ➔ **The relative reactivity of carboxylic acids and their derivatives is as follows:**



- ➔ **In general, 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**
- ➔ **As a general rule, less reactive acyl compounds can be synthesized from more reactive ones (CRITICAL: help in avoiding memorization)**
  - **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**

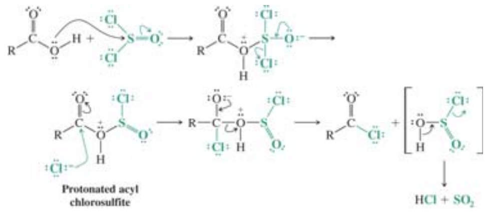


$$\overset{O}{\overset{\|}{RCOH}} + \underset{\text{Thionyl chloride}}{SOCl_2} \longrightarrow R-\overset{O}{\overset{\|}{C}}-Cl + SO_2 + HCl$$

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

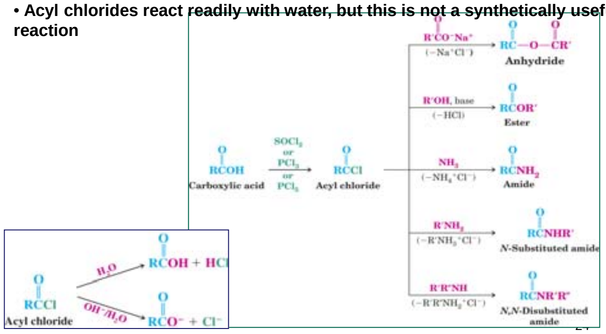
$$\overset{O}{\overset{\|}{RCOH}} + \underset{\text{Phosphorus pentachloride}}{PCl_5} \longrightarrow \overset{O}{\overset{\|}{RCCl}} + POCl_3 + HCl$$

A mechanism for the reaction of thionyl chloride with carboxylic acids.



Reactions of Acyl Chlorides

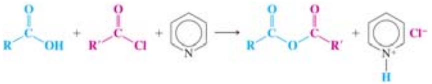
- Acyl chlorides are the most reactive acyl compounds and can be used to make any of the other derivatives (Why? Because chloride ion is the best LG. Why is the best LG?)
- Since acyl chlorides are easily made from carboxylic acids they provide a way to synthesize any acyl compound from a carboxylic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



♦ Carboxylic Acid Anhydrides

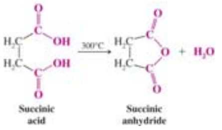
● Synthesis of Carboxylic Acid Anhydrides

- ➔ **Acid chlorides react with carboxylic acids to form mixed or symmetrical anhydrides**
  - **It is necessary to use a base such as pyridine**



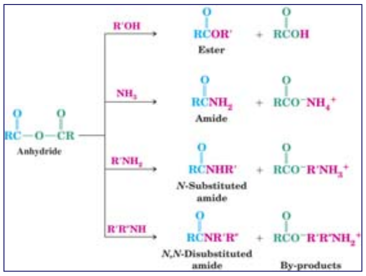
- ➔ **Sodium carboxylates react readily with acid chlorides to form anhydrides**

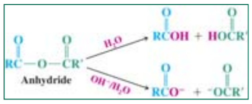
Cyclic anhydrides with 5- and 6-membered rings can be synthesized by heating diacid



● 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**

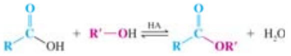




♦ Esters

● 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**

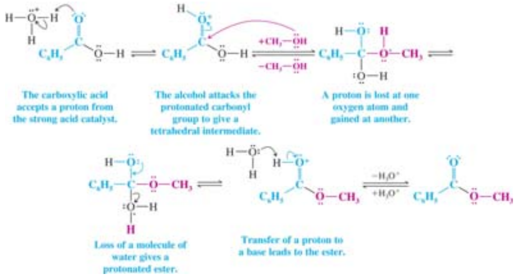


$$RCOOH + R'{-}OH \xrightleftharpoons{HA} RCOOR' + H_2O$$

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

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

Mechanism of the Fischer Esterification



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

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

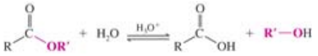
A proton is lost at one oxygen atom and gained at another.

Loss of a molecule of water gives a protonated ester.

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

To remember: reaction is catalyzed by acid and is reversible

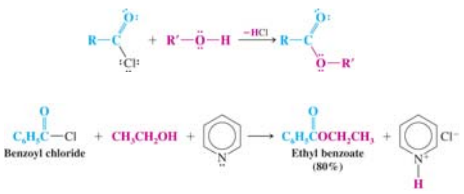
The reverse reaction is called: **ACID CATALYZED ESTER HYDROLYSIS**



$$RCOOR' + H_2O \xrightleftharpoons{H_3O^+} RCOOH + R'{-}OH$$

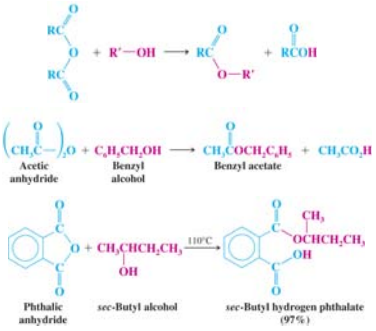
➔Esters from Acid Chlorides

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



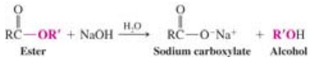
➔Esters from Carboxylic Acid Anhydrides

- Alcohols react readily with anhydrides to form esters

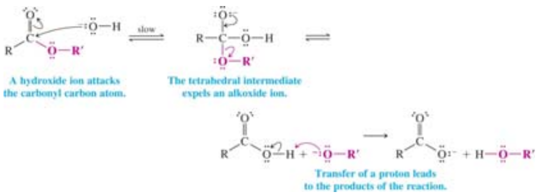


What is the mechanism? Nucleophilic Addition –Elimination:
Hint: Find carbonyl carbon and nucleophile

- **Base-Promoted Hydrolysis of Esters: Saponification**
  - ➔**Reaction of an ester with sodium hydroxide results in the formation of a sodium carboxylate and an alcohol**

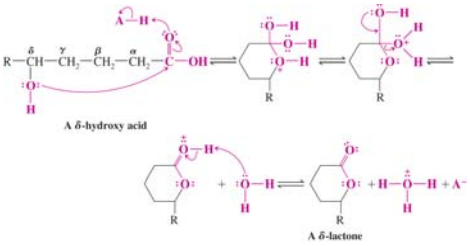


- ➔**This mechanism is IRREVERSIBLE because the salt of the carboxylic acid is formed**
  - The last step draws the overall equilibrium toward completion of the hydrolysis



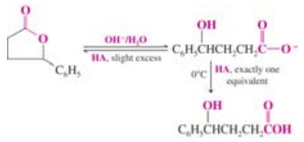
Please workout problem 17.5 (p. 802) at home

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

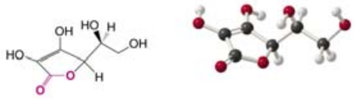


➔Lactones can be hydrolyzed with aqueous base

- Since reaction is reversible acidification of the carboxylate product can lead back to the original lactone if too much acid is added. Exactly one equivalent of acid produced hydroxycaid



Lactones in nature



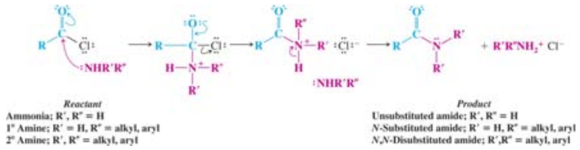
Vitamin C
(ascorbic acid)

♦ Amides

● Synthesis of Amides

➔Amides From Acyl Chlorides (widely used)

- 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



➔Amides can be also prepared from Esters

Please note chemoselectivity of the Nucleophilic Addition –Elimination vs. Nucleophilic Substitution

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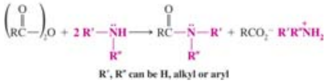
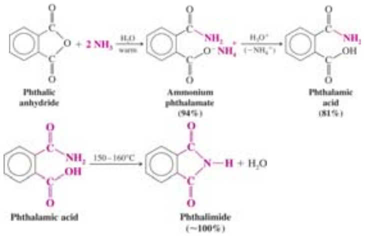
➔Amides from Carboxylic Anhydrides

- Anhydrides (carbonyl substrate) react with 2 equivalents of amine (nucleophile) to produce an amide and an ammonium carboxylate



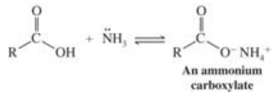
$$\left(RC(=O)—\right)_2O + 2\,R'—\ddot{N}H(R'') \longrightarrow RC(=O)—\ddot{N}(R'')—R' + RCO_2^- \; R'R''\overset{+}{N}H_2$$

- 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

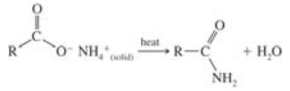


➔Amides from Carboxylic Acids and Ammonium Carboxylates

- 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

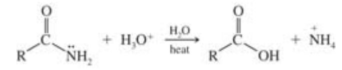


- THE BEST way to synthesize an amide is to convert a carboxylic acid to an acid chloride and to then to react the acid chloride with ammonia or an amine

Note: Amides are the linkages that join individual amino acids together to form proteins.
Formation of amide bonds is therefore of great importance in biochemistry.
Please see useful dicyclohexylcarbodiimide(DCC)-promoted amide synthesis on

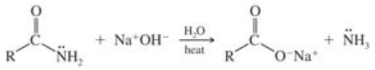
- **Hydrolysis of Amides**
  - ➔ **Heating an amide in concentrated aqueous acid or base causes hydrolysis**
    - **Hydrolysis of an amide is slower than hydrolysis of an ester**

Acid hydrolysis



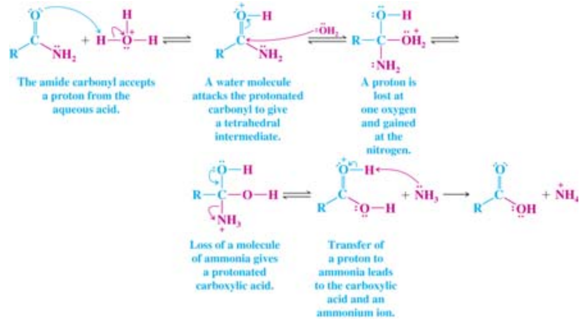
$$RC(=O)\ddot{N}H_2 + H_3O^+ \xrightarrow[\text{heat}]{H_2O} RC(=O)OH + \overset{+}{N}H_4$$

Basic hydrolysis

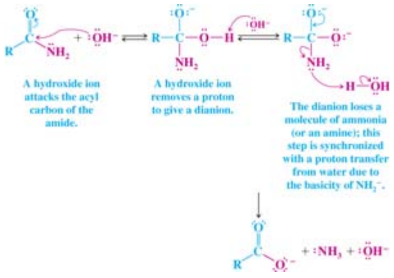


$$RC(=O)\ddot{N}H_2 + Na^+OH^- \xrightarrow[\text{heat}]{H_2O} RC(=O)O^-Na^+ + \ddot{N}H_3$$

Acid hydrolysis of an Amide



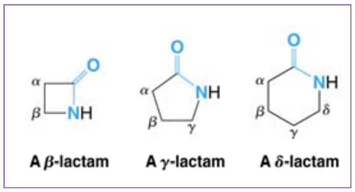
Basic hydrolysis of an Amide



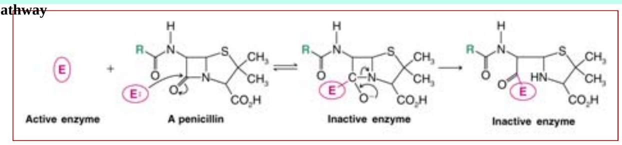
♦ Lactams: Cyclic Amides

The size of the rings designed by greek letters

Recall: lactones (cyclic esters)

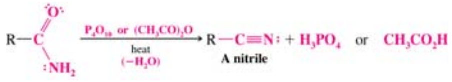


The penicillin antibiotic is β-lactam: It acts by interfering with the synthesis of bacterial cell walls by reaction with an amino group of the essential enzymes of the cell wall biosynthetic pathway

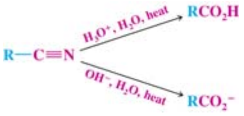


Nitriles: Preparation and Chemical Properties

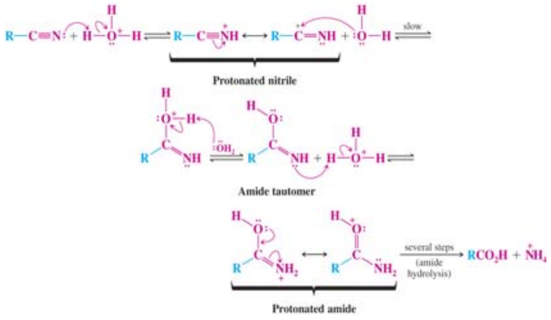
- **Nitriles by the Dehydration of Amides**
  - ➔A nitrile can be formed by reaction of an amide with phosphorous pentoxide or boiling acetic anhydride



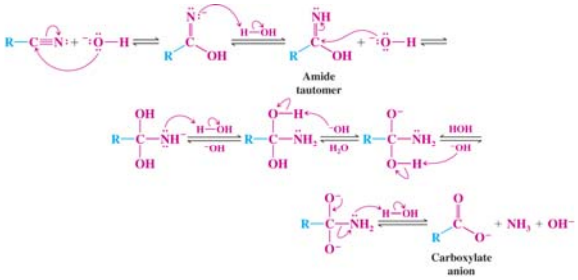
- **Hydrolysis of Nitriles**
  - ➔A nitrile is the synthetic equivalent of a carboxylic acid because it can be converted to a carboxylic acid by hydrolysis



Acidic Hydrolysis of Nitriles

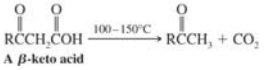


Basic Hydrolysis of Nitriles



♦ Decarboxylation of Carboxylic Acids

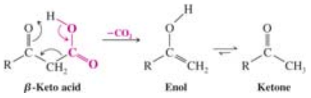
- ➔β-Keto carboxylic acids decarboxylate (release of CO_2) readily when heated.
  - Some even decarboxylate slowly at room temperature



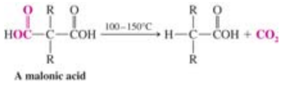
$$\overset{O}{\overset{\|}{RC}}CH_2\overset{O}{\overset{\|}{C}}OH \xrightarrow{100-150°C} \overset{O}{\overset{\|}{RC}}CH_3 + CO_2$$

A β-keto acid

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



- ➔Malonic acids (which are too β-keto acids) also decarboxylate readily (malonic ester synthesis: more in Chapter 19)



Here dicarboxylic acid is converted to mono carboxylic acid