Pharmaceutical Organic Chemistry-1

Chapter-7: Carboxylic Acids and their derivatives

Structure of Carboxylic Acids

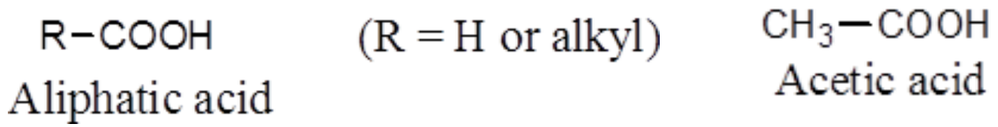
- **The functional group common to all carboxylic acids is the carboxyl group.**
  - *The name is a contraction of the parts: the carbonyl and hydroxyl groups.*
- **The general formula for a carboxylic acid can be written in expanded or abbreviated forms.**

carboxyl group | three ways to represent a carboxylic acid | acid derivatives

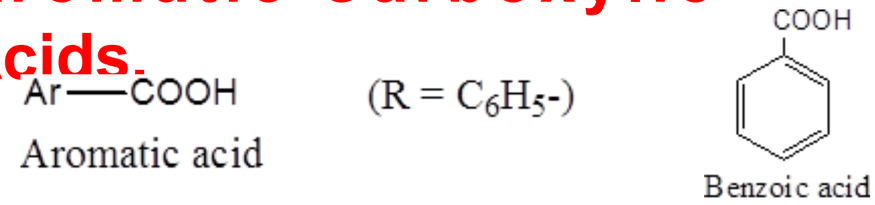
Structure of Carboxylic Acids

- **Depending on whether an R or an Ar.** residue is attached to the carboxyl group; Carboxylic acids are classified as aliphatic or aromatic.

  - **Aliphatic Carboxylic Acids.**



  - **Aromatic Carboxylic Acids.**



- **Fatty acids.**

  Long straight-chain carboxylic acids with even numbers of carbons, which were first isolated from fats and waxes.

Nomenclature of Acids

Common Names

- The **common names** of carboxylic acids all end in *-ic acid*.
  - These names usually come from some Latin or Greek word that indicates the original source of the acid.
  - **Common name**, substituents are located with Greek letters, beginning with the α–carbon atom.

IUPAC System

- We replace the final *e* in the name of the corresponding alkane with the suffix *-oic* and add the word *acid*.

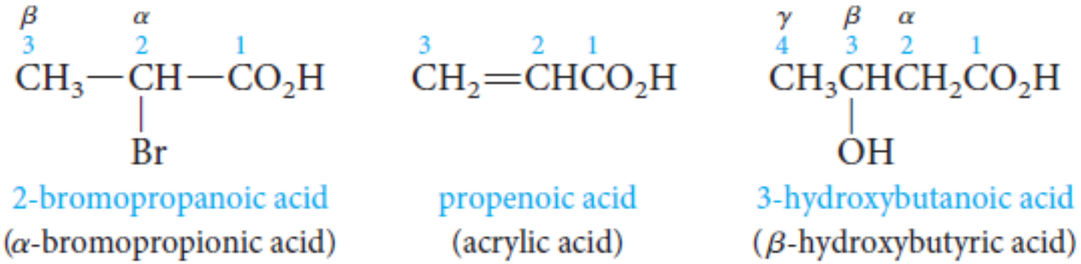
Alkane- e + *oic acid* = *Alkanoic acid*

  - **IUPAC system**, the chain is numbered beginning with the carboxyl carbon atom, and substituents are located in the usual way.

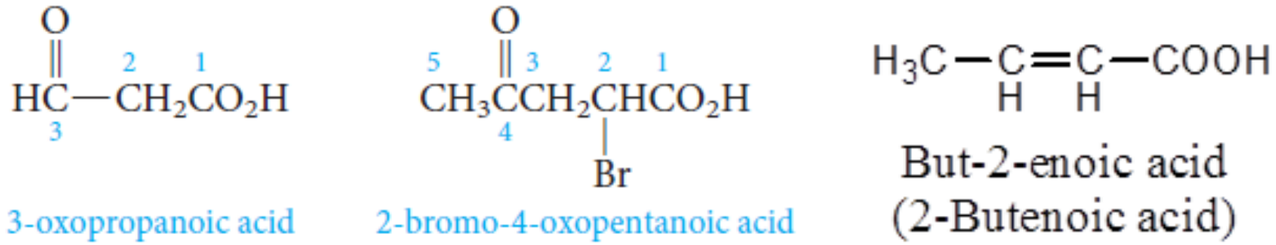
Nomenclature of Acids

Carbon atoms	Formula	Source	Common name	IUPAC name
1	$HCOOH$	ants (Latin, *formica*)	formic acid	methanoic acid
2	CH_3COOH	vinegar (Latin, *acetum*)	acetic acid	ethanoic acid
3	CH_3CH_2COOH	milk (Greek, *protos pion*, first fat)	propionic acid	propanoic acid
4	$CH_3(CH_2)_2COOH$	butter (Latin, *butyrum*)	butyric acid	butanoic acid
5	$CH_3(CH_2)_3COOH$	valerian root (Latin, *valere*, to be strong)	valeric acid	pentanoic acid
6	$CH_3(CH_2)_4COOH$	goats (Latin, *caper*)	caproic acid	hexanoic acid
7	$CH_3(CH_2)_5COOH$	vine blossom (Greek, *oenanthe*)	enanthic acid	heptanoic acid
8	$CH_3(CH_2)_6COOH$	goats (Latin, *caper*)	caprylic acid	octanoic acid
9	$CH_3(CH_2)_7COOH$	pelargonium (an herb with stork-shaped seed capsules; Greek, *pelargos*, stork)	pelargonic acid	nonanoic acid
10	$CH_3(CH_2)_8COOH$	goats (Latin, *caper*)	capric acid	decanoic acid

Nomenclature of Acids



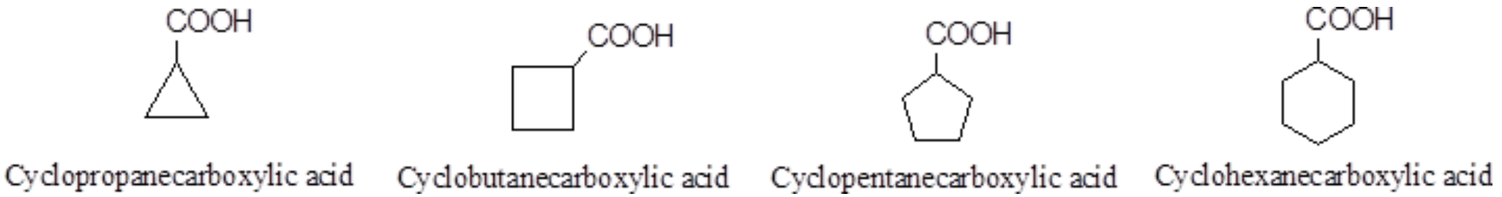
- **The carboxyl group has priority over alcohol, aldehyde, or ketone** functionality in naming.
- The prefix ***oxo-*** is used to locate the carbonyl group of the aldehyde or ketone.



Nomenclature of Acids

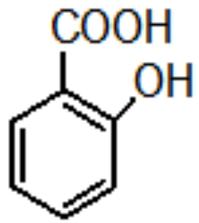
- **Cycloalkane carboxylic acid**

  When the carboxyl group is attached to a ring, the ending ***-carboxylic acid*** *is added to the name of the parent* ***cycloalkane*****. (i.e.** ***Cycloalkanecarboxylic acid*****)**



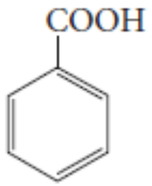
Cyclopropanecarboxylic acid | Cyclobutanecarboxylic acid | Cyclopentanecarboxylic acid | Cyclohexanecarboxylic acid

- **Aromatic acids** are named by attaching the suffix *-oic acid* or *-ic acid* to an appropriate prefix derived from the aromatic hydrocarbon.

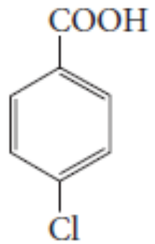


Common name: Salicylic acid

IUPAC name : 2-Hydroxybenzenecarboxylic acid



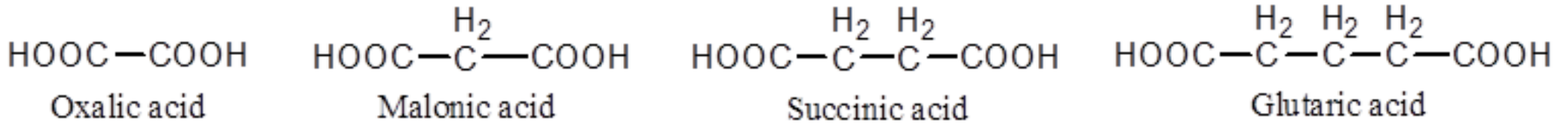
benzoic acid (benzenecarboxylic acid)



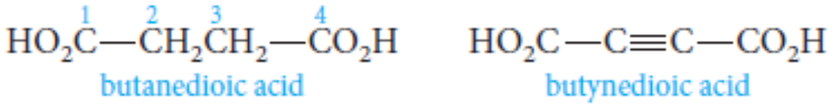
p-chlorobenzoic acid (4-chlorobenzenecarboxylic acid)

Nomenclature of Acids

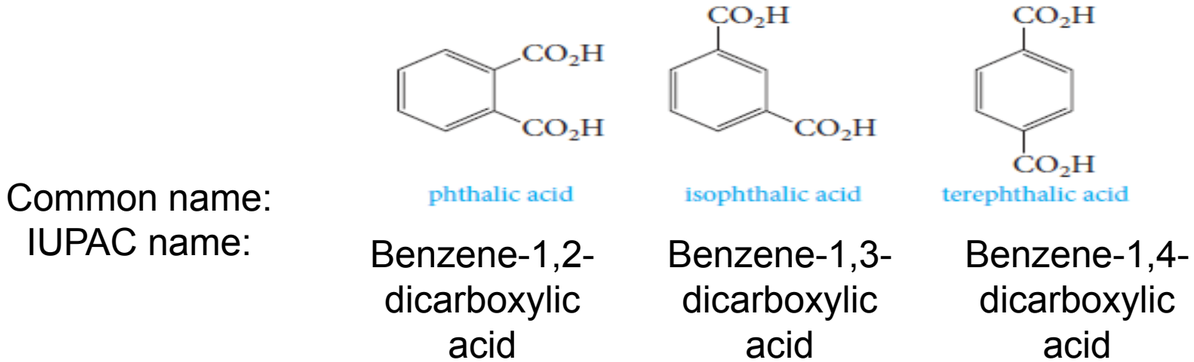
- **Dicarboxylic acids** (*acids that contain two carboxyl groups*) are known almost exclusively by their common names.



- **Aliphatic dicarboxylic acids** are given the suffix *-dioic acid* in the IUPAC system.

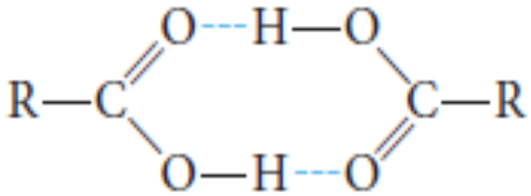


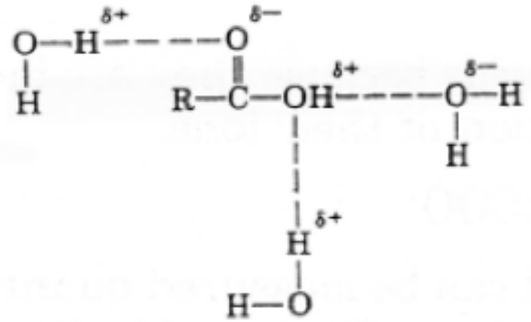
- The three **benzenedicarboxylic acids** are generally known by their common names.



Physical Properties of Acids

- **Carboxylic acids** are polar and they form hydrogen bonds with themselves or with other molecules.
- **Carboxylic acids form dimer,** with the individual units held together by two hydrogen bonds between the electron-rich oxygens and the electron-poor hydrogens.





Boiling Points

Therefore, they have high boiling points for their molecular weights-higher even those of comparable alcohols.

Physical Properties of Acids

Solubility in water

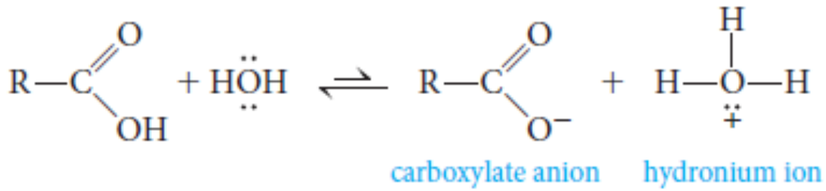
Hydrogen bonding also explains the water solubility of the lower molecular weight carboxylic acids.

- The first four aliphatic acids (formic through butyric) are completely miscible in water.
- Aromatic acids are insoluble in water.

Solubility in H_2O at 25°C	b.p. °C	Mol. Wt.	Name	Structure
Very soluble	100	46	Formic acid	HCOOH
Very soluble	78	46	Ethyl alcohol	CH_3CH_2OH
Very soluble	118	60	Acetic acid	CH_3COOH
Very soluble	97	60	*n*-Propyl alcohol	$CH_3CH_2CH_2OH$
4.0 g/100 g H_2O	187	102	Valeric acid	$CH_3(CH_2)_3COOH$
0.6 g/100 g H_2O	156	102	*n*-Hexyl alcohol	$CH_3(CH_2)_4CH2OH$
Insoluble	250	122	Benzoic acid	Ph-COOH
Insoluble	250	122	3-Phenylethanol	$Ph-CH_2CH_2OH$

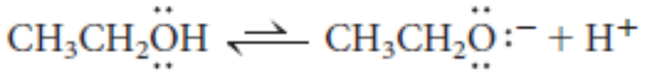
Acid Strength and Structure

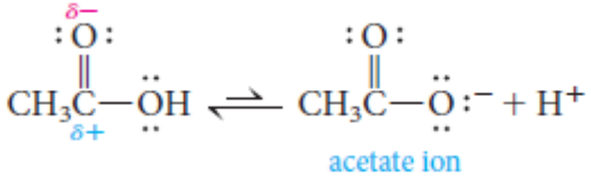
- **Carboxylic acids** (RCOOH) dissociate in water, yielding a carboxylate anion ($RCOO^-$) and hydronium ion.

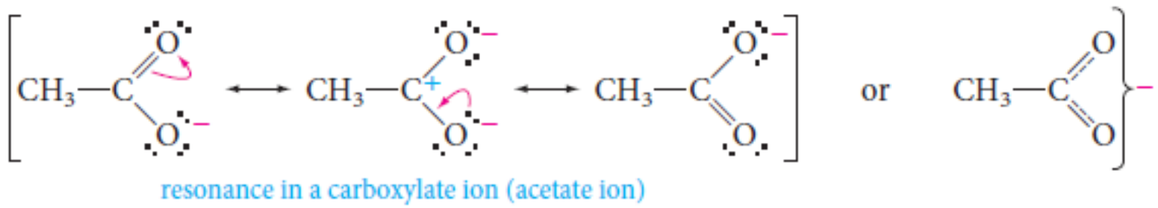


Why carboxylic acids are more acidic than alcohols?

- In ethoxide ion, the negative charge is localized on a single oxygen atom.
- In acetate ion, on the other hand, the negative charge can be delocalized through resonance.



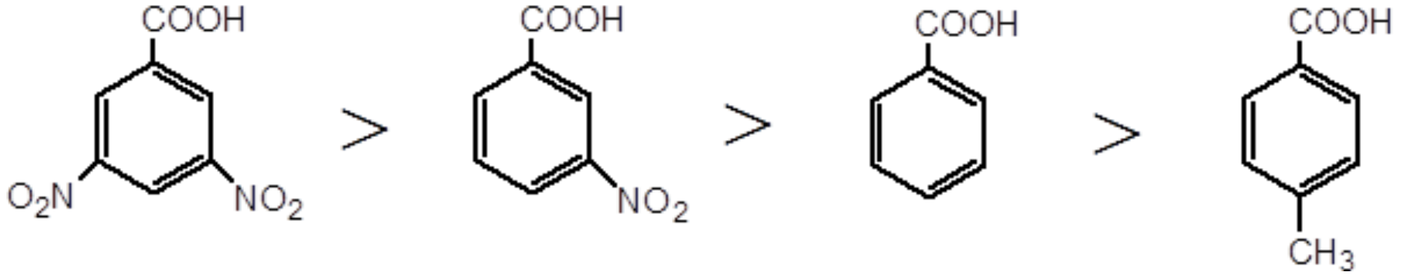




Acid Strength and Structure

Effect of Structure on Acidity; the Inductive Effect

- Acidities can vary depending on what other groups are attached to the molecule.
- Recall that *electron-withdrawing groups (-I) enhance acidity*, *and electron-releasing groups (+I) reduce acidity*.
  This effect relays charge through bonds, by displacing bonding electrons toward electronegative atoms, or away from electropositive atoms.



Effect of Structure on Acidity; the Inductive Effect

- **Formic acid is a substantially stronger acid than acetic acid.**

  This suggests that the methyl group is more electron-releasing (hence anion-destabilizing and acidity-reducing) than hydrogen.

$$HCOOH > CH_3COOH > CH_3CH_2COOH > CH_3CH_2CH_2COOH$$

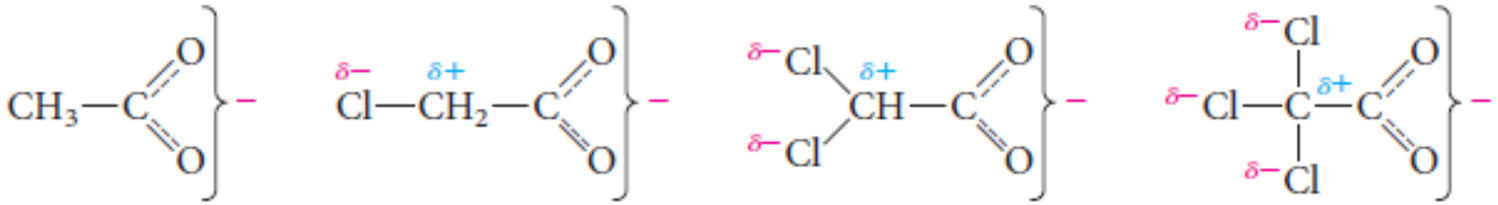
- **Example:** acetic acid with those of mono-, di-, and trichloroacetic acids.

  Comparison of acid strengths of acetic Acid and chlorinated acetic acids

$$Cl_3CCOOH > Cl_2CHCOOH > ClCH_2COOH > CH_3COOH$$

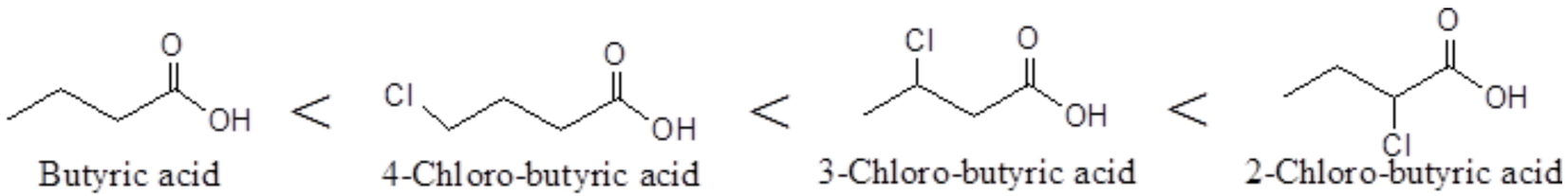
Acid Strength and Structure

Effect of Structure on Acidity; the Inductive Effect



The more chlorines, the greater the effect and the greater the strength of the acid.

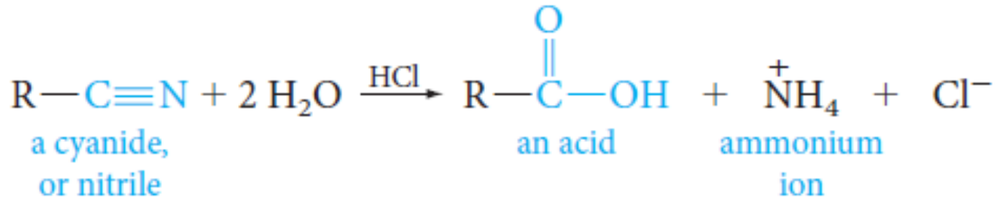
- **Comparison of acid strengths** of butyric acid and the monochlorinated acids.



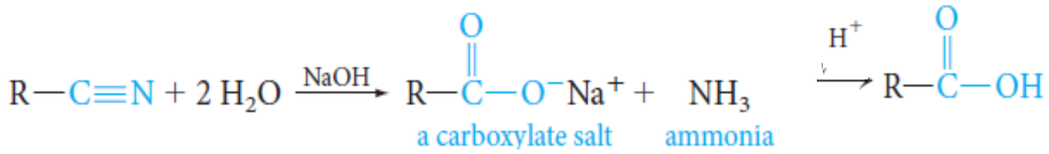
Preparation of Acids

1) Hydrolysis of Cyanides (Nitriles)

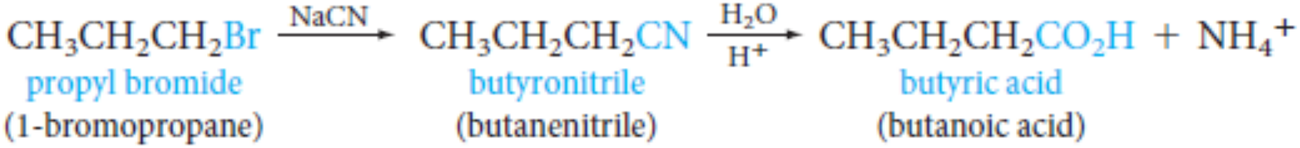
- **The reaction requires either acid or base.**
  - **In acid**, the nitrogen atom of the cyanide is converted to an ammonium ion.



  - **In base**, the nitrogen atom is converted to ammonia and the organic product is the carboxylate salt, which must be neutralized in a separate step to give the acid.



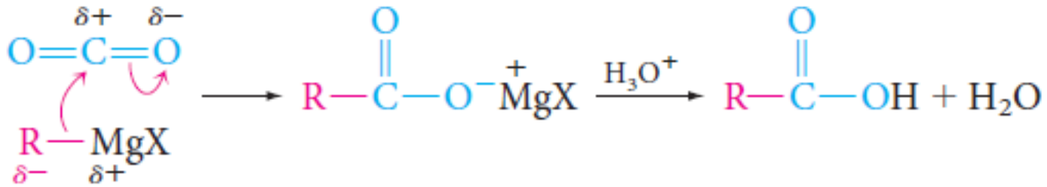
- **Alkyl cyanides** are generally made from the corresponding alkyl halide.



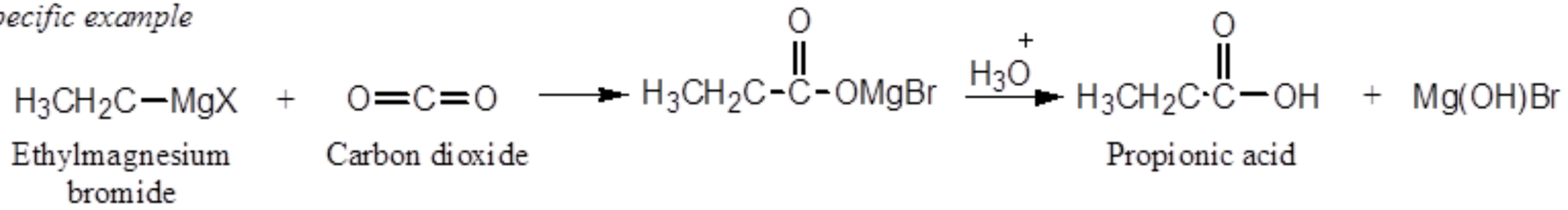
Preparation of Acids

2) Reaction of Grignard Reagents with Carbon Dioxide (Carbonation of Grignard Reagent)

- **Grignard reagents** add to the carbonyl group of carbon dioxide to give acids, after protonation of the intermediate carboxylate salt with a mineral acid like aqueous HCl.
- **The acid obtained has one more carbon atom** (*the reaction provides a way to increase the length of a carbon chain*).



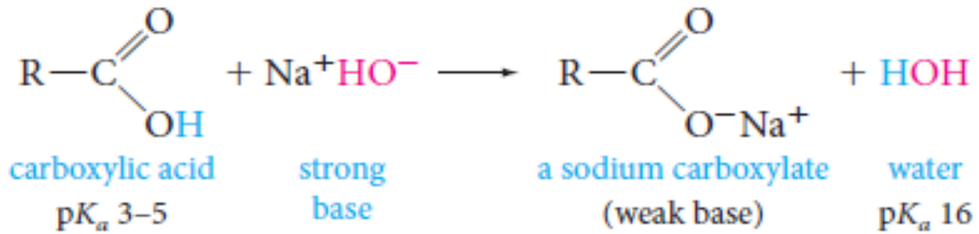
Specific example

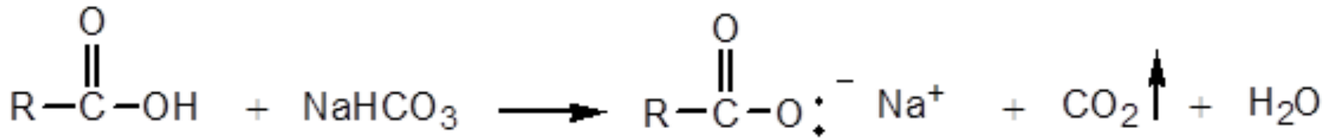


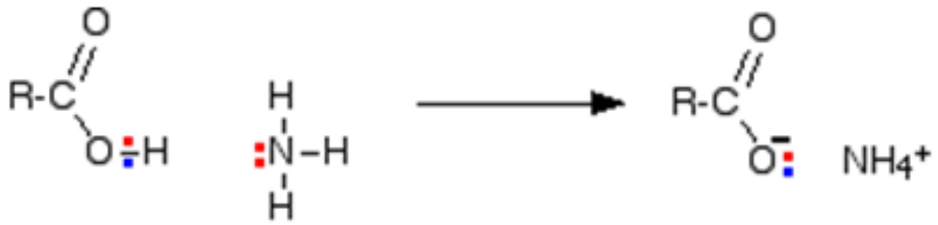
Reactions of Acids

1) Reactions with Bases: Salt Formation

- Carboxylic acids, when treated with a strong base, form **carboxylate salts**.







Reactions of Acids

1) Reactions with Bases: Salt Formation

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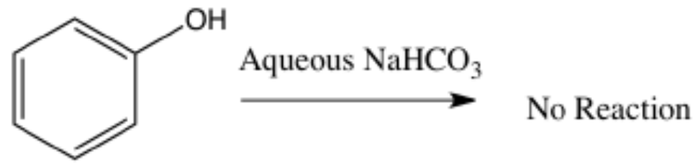
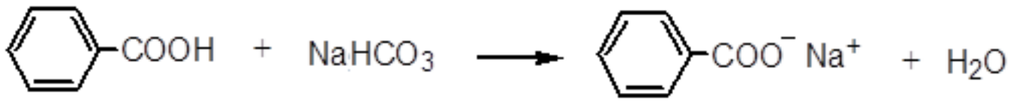
Examples.

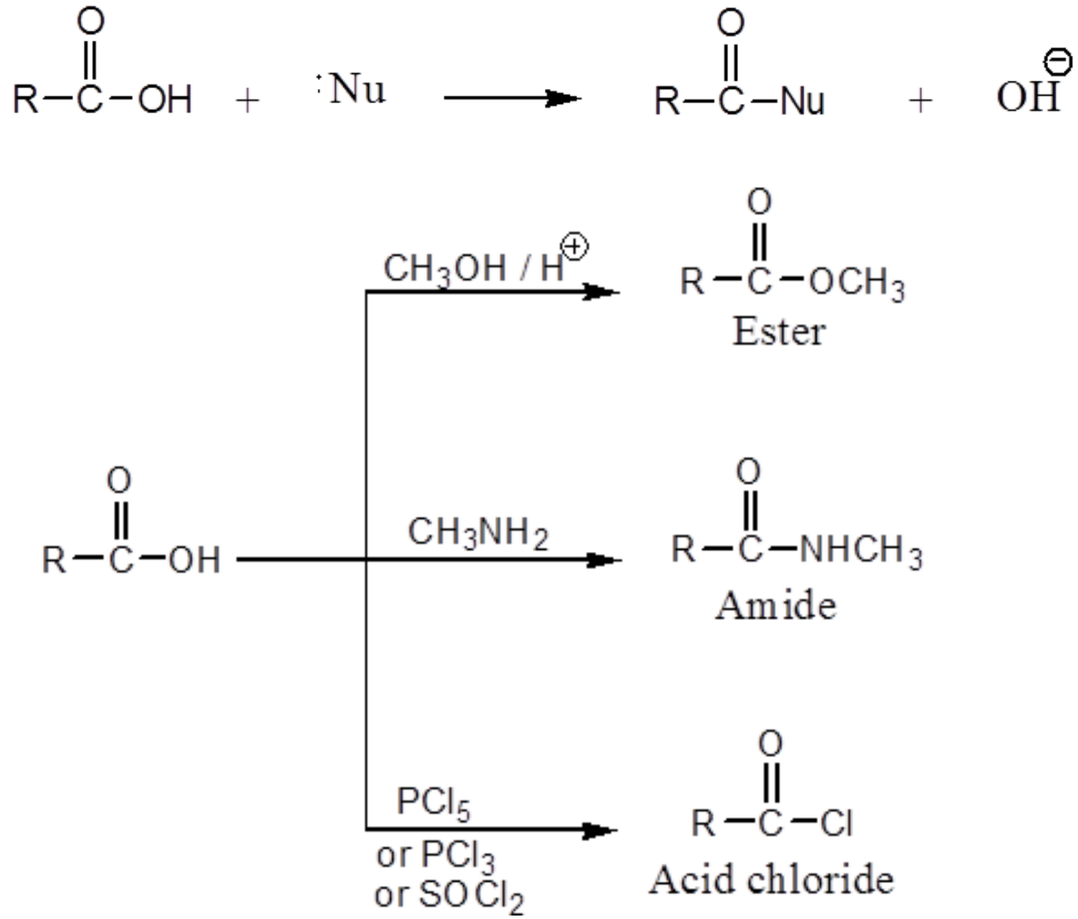


Phenol



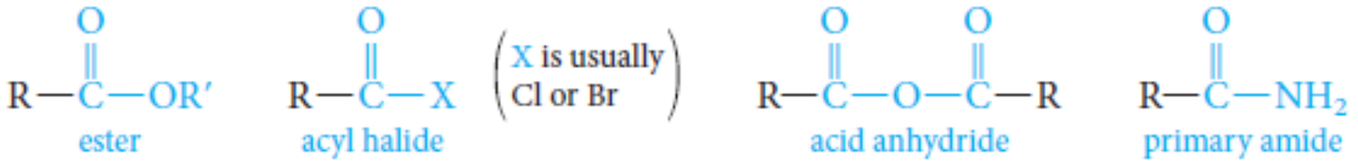
Benzoic acid Sodium benzoate

2) Nucleophilic Substitution Reactions

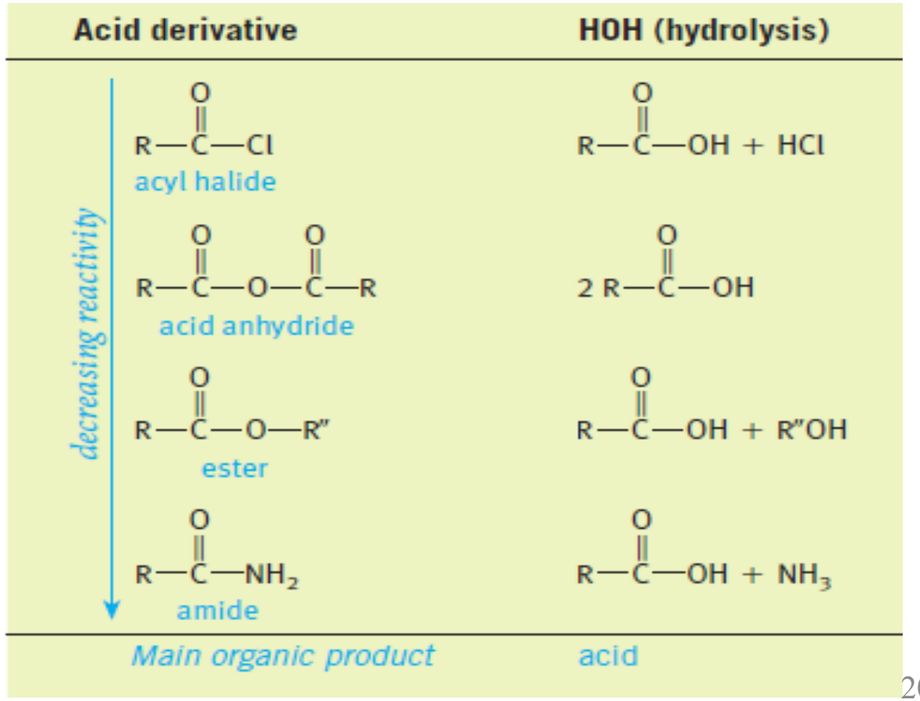


Carboxylic Acid Derivatives

- **Carboxylic acid derivatives** are compounds in which the hydroxyl part of the carboxyl group is replaced by various other groups.



- All acid derivatives can be hydrolyzed to the corresponding carboxylic acid.

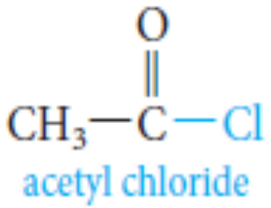


Carboxylic Acid Derivatives

Acid Chloride

- **Acyl chlorides** have the general formula RCOCl.
- **Acyl chlorides** are more common and less expensive than bromides or iodides.
- **Nomenclature:**

Acyl chlorides, or acid chlorides, are named by replacing the *-ic acid* ending of the parent acid by *-yl chloride*.



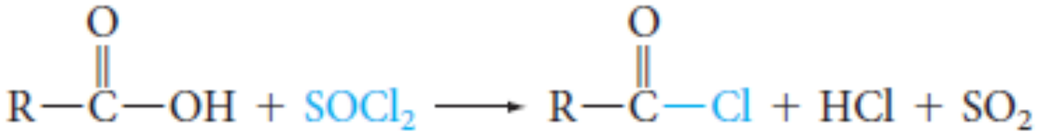
acetyl chloride

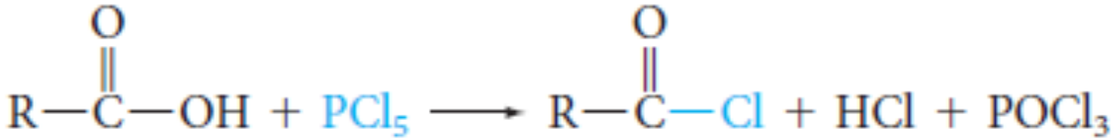
IUPAC Ethanoyl Chloride

Acid Chloride

➤ **Preparation:**

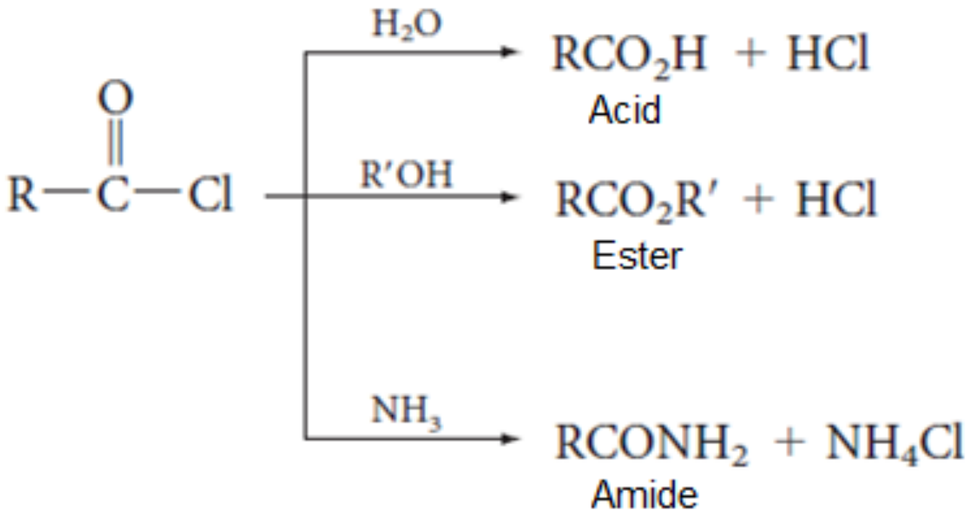
They can be prepared from acids by reaction with thionyl chloride or phosphorous pentachloride.





Acid Chloride

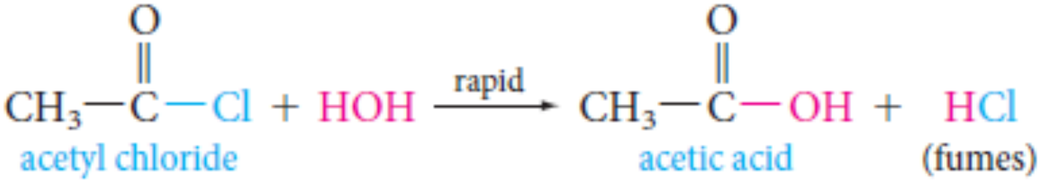
- **Reactions:** *They can react rapidly with most nucleophile*.

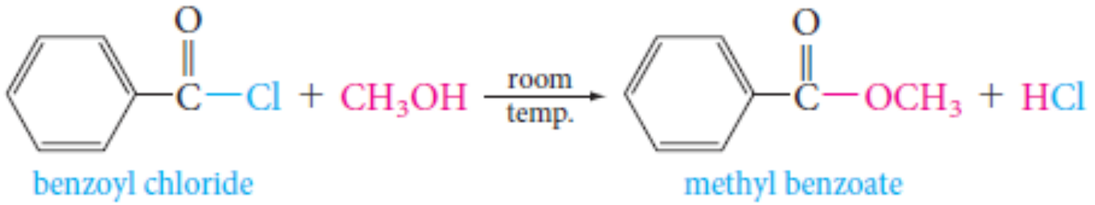


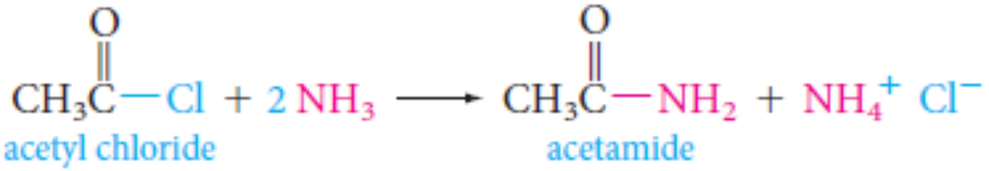
Carboxylic Acid Derivatives

Acid Chloride

? Examples:





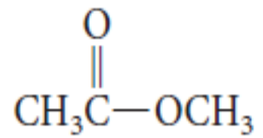


Carboxylic Acid Derivatives

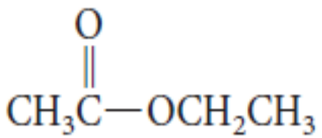
Esters

- **Esters** are derived from acids by replacing the –OH group by an –OR group and have the general formula R/COOR.

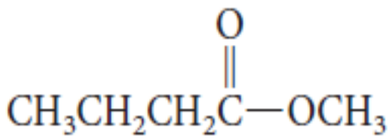
- **Nomenclature:**
  - They are named in a manner analogous to carboxylic acid salts.
  - The R part of the –OR group is name first, followed by the name of the acid, with the *–ic acid* ending changed to *–ate*.



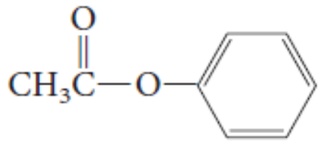
methyl acetate
(methyl ethanoate)



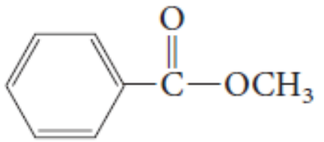
ethyl acetate
(ethyl ethanoate)



methyl butanoate
bp 102.3°C



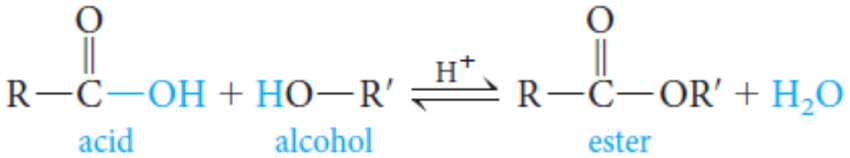
phenyl acetate



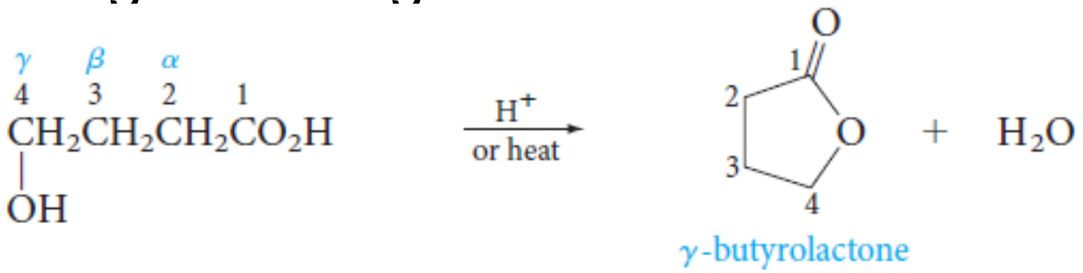
methyl benzoate

Esters

- **Preparation:**
  When a carboxylic acid and an alcohol are heated in the presence of an acid catalyst (HCl or H_2SO_4), an equilibrium is established with the ester and water.



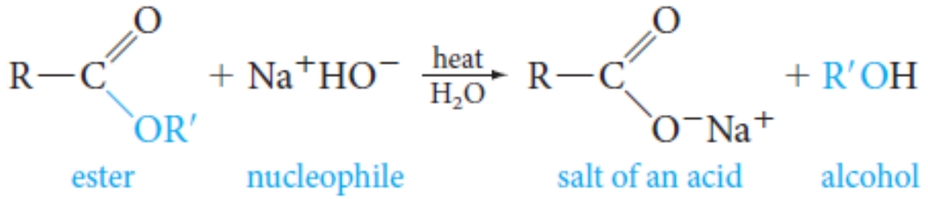
- **Cyclic esters (lactones)** can be prepared from hydroxy acids if these groups can come in contact through bending of the chain.



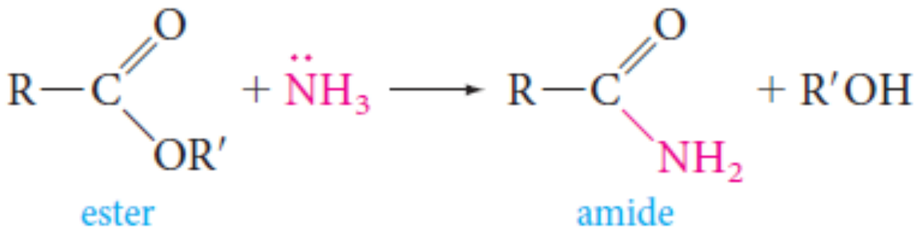
Esters

➤ Reactions

- **Saponification;** esters are commonly hydrolyzed with base.



- Ammonia converts esters to **amides.**

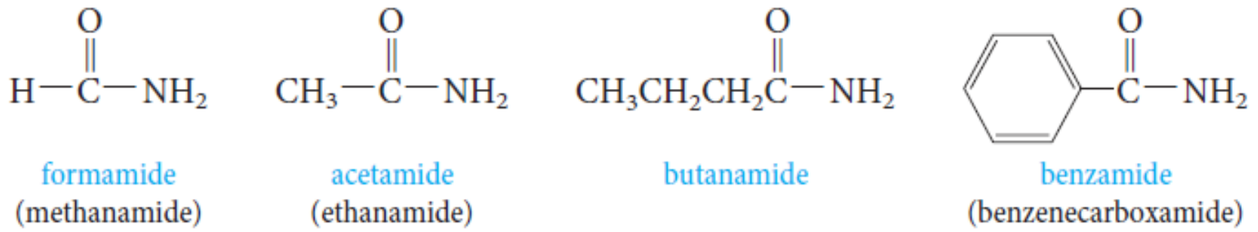


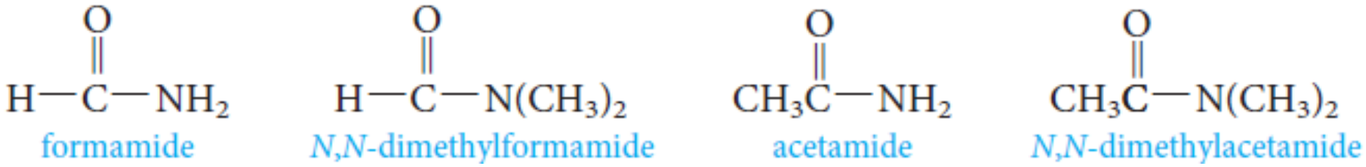
Carboxylic Acid Derivatives

Amides

- **Amides** are the least reactive of the common carboxylic acid derivatives.
- Primary amides have general formula **$RCONH_2$.**
- **Nomenclature:**

  Amides are named by replacing the *–ic* or *–oic acid* ending of the acid name, either the common or the IUPAC name, with the *–amide* ending.

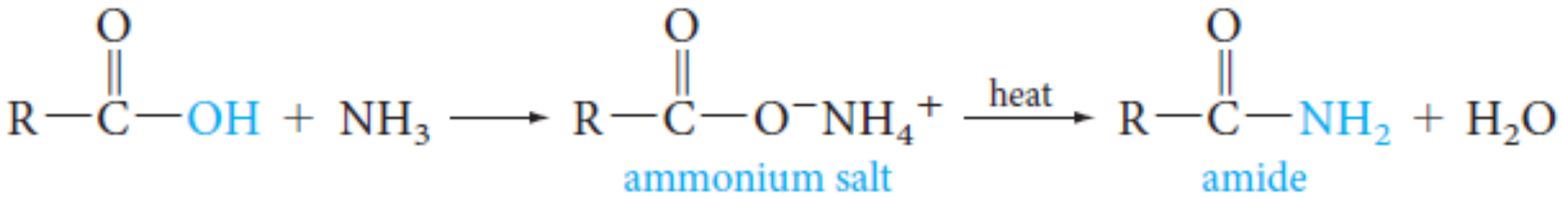




Amides

➤ **Preparation:**

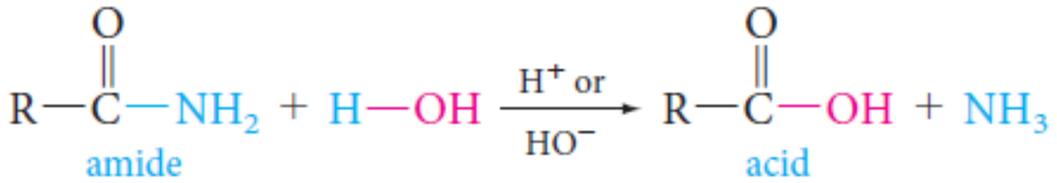
- They can be prepared by the reaction of ammonia with esters, with acyl halides, or with acid anhydrides.
- Amides can also prepared by heating the ammonium salts of acids.



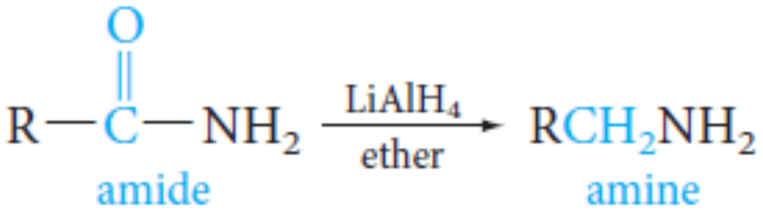
Amides

➤ Reactions

- **Amides** react with nucleophiles and they can be hydrolyzed by water.



- **Amides** can be reduced by lithium aluminums hydride to give amines.

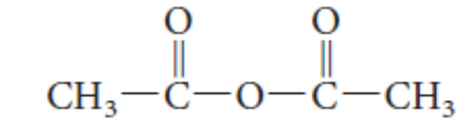


Carboxylic Acid Derivatives

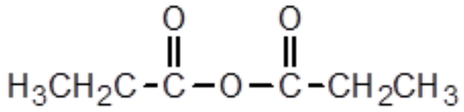
Acid Anhydrides

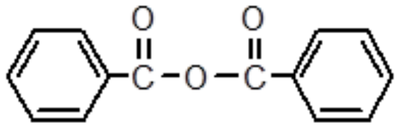
- **Acid anhydrides** have general formula RCOOCOR.
- **Nomenclature:**

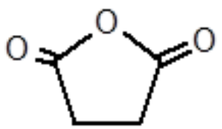
  The name of an anhydrides is obtained by naming the acid from which is derived and replacing the word acid with anhydride.



ethanoic anhydride or acetic anhydride





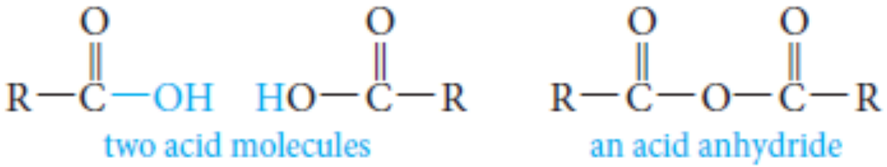


IUPAC name:	Propanoic anhydride	Benzoic anhydride	Succinic anhydride
Common name:	Propionic anhydride		

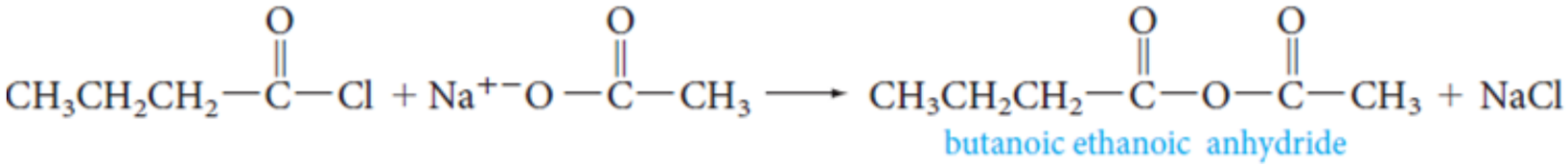
Acid Anhydrides

➤ Preparation

- **Acid anhydrides** are derived from acids by removing water from two carboxyl groups and connecting the fragments.



- **Anhydrides** can also be prepared from acid chlorides and carboxylate salts.
  This method is used for preparing anhydrides derived from two different carboxylic acids (mixed anhydrides).



Acid Anhydrides

Reactions

- **Anhydrides** undergo nucleophilic acyl substitution reactions (*They are more reactive than esters, but less reactive than acyl halides*).