CH 310 N T TH 2-3:30 LECTURE 13

Textbook Assignment: Chapter 17

Homework (for credit): POW 6 posted

Today's Topics: Derivatives of Carboxylic Acids

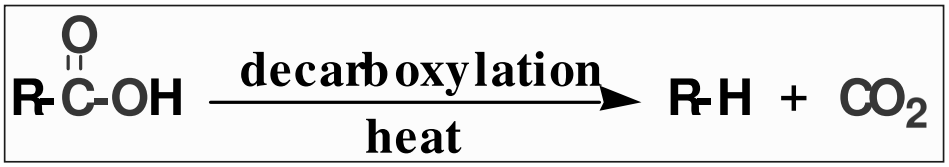
Notice & Announcements:

ORGANIC LECTURE SERIES

Carboxylic Acids

Decarboxylation

- Decarboxylation: loss of CO_2 from a carboxyl group
  - carboxylic acids, ***if heated to a very high temperature***, undergo thermal decarboxylation

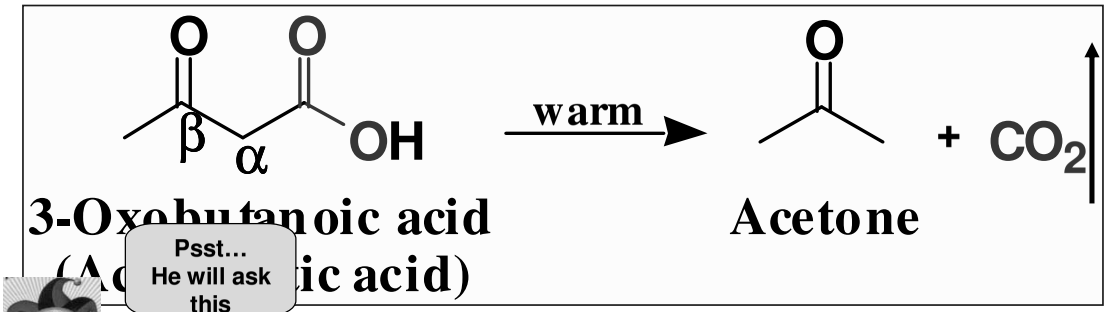


  - most carboxylic acids, however, are quite resistant to moderate heat and melt or even boil without decarboxylation

Decarboxylation

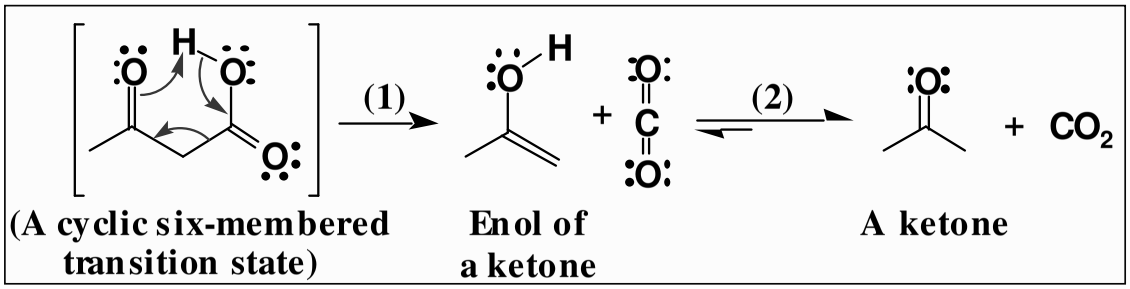
The most importan exceptions are carboxylic acids that have a carbonyl group beta to the carboxyl group **i.e.- β keto-acids**

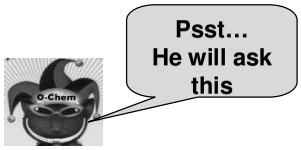
–this type of carboxylic acid undergoes decarboxylation on mild heating



Decarboxylation

– thermal decarboxylation of a β-ketoacid involves rearrangement of six electrons in a cyclic six-membered transition state

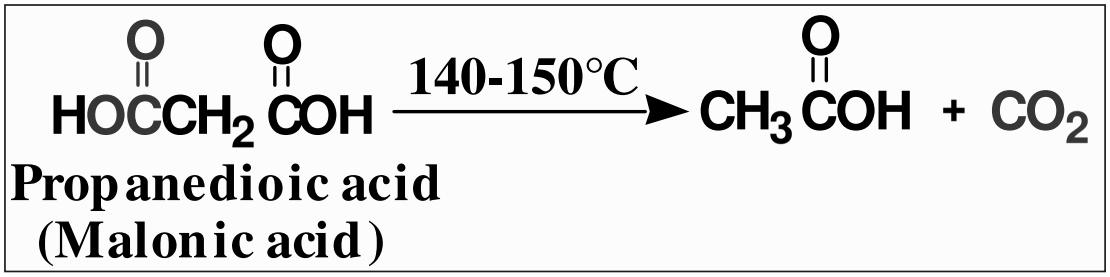




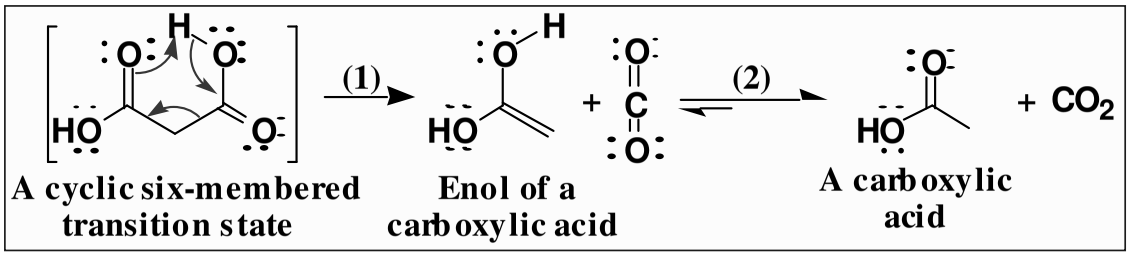
Decarboxylation

– decarboxylation occurs if there is any carbonyl group beta to the carboxyl

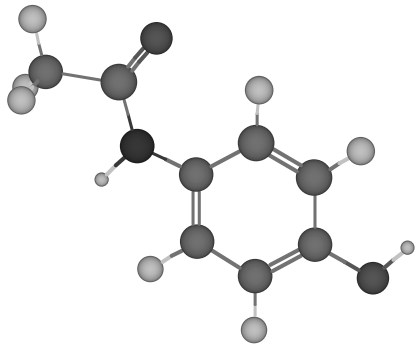
– malonic acid and substituted malonic acids, for example, also undergo thermal decarboxylation



– thermal decarboxylation of malonic acids also involves rearrangement of six electrons in a cyclic six-membered transition state

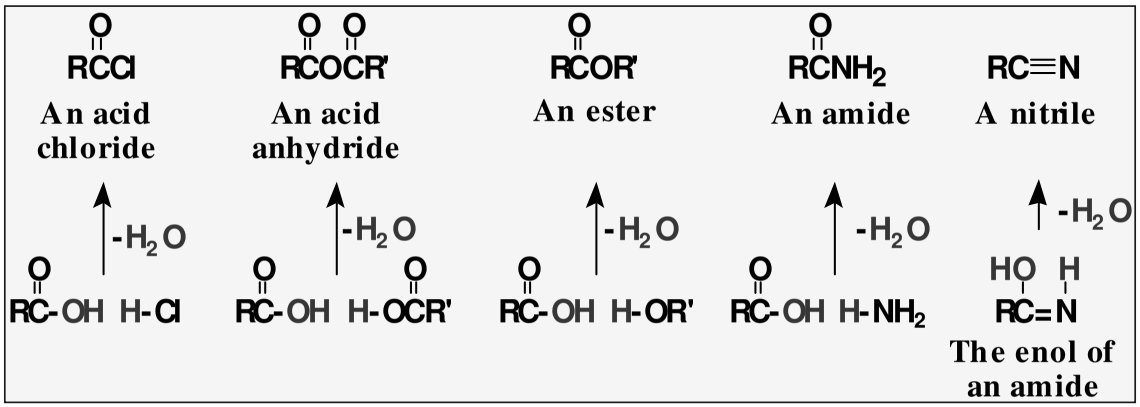


Functional Derivatives of Carboxylic Acids



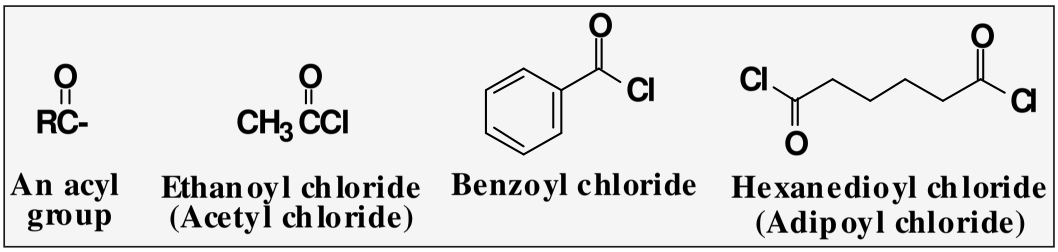
Organic acid derivatives

- There are five classes of organic acid derivatives
- Each arises from a dehydration reaction, usually a **condensation**
- Therefore, each derivative can also be hydrolyzed



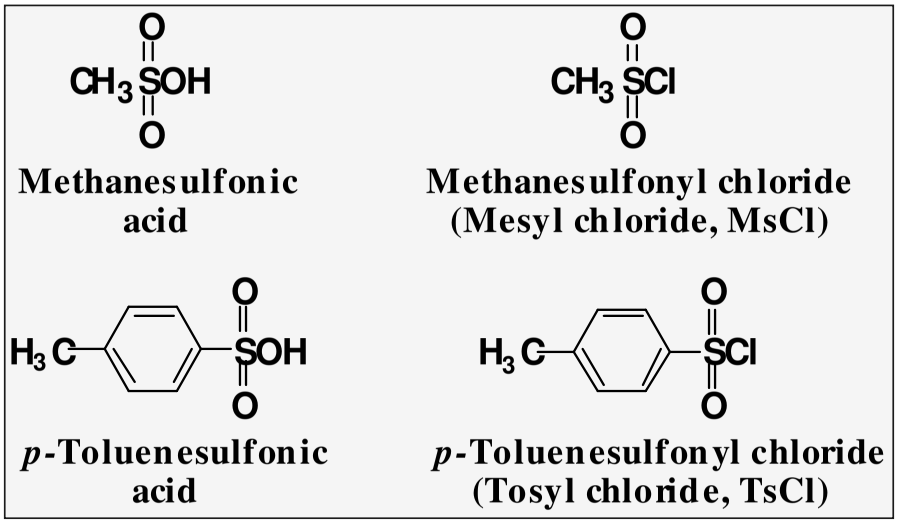
Acid halides

- The functional group of an acid halide is an acyl group bonded to a halogen
  - the most common are the acid chlorides
  - to name, change the suffix -ic acid to -yl halide



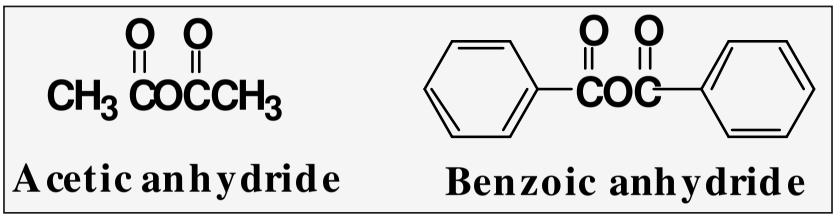
Sulfonyl Chlorides

– replacement of -OH in a sulfonic acid by -Cl gives a **sulfonyl chloride**



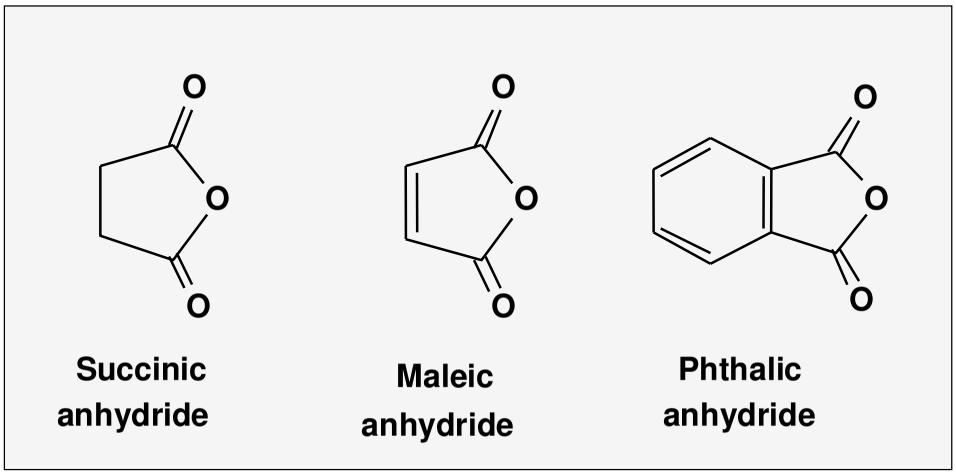
Acid Anhydrides

- The functional group of an acid anhydride is two acyl groups bonded to an oxygen atom
  – the anhydride may be symmetrical (two identical acyl groups) or mixed (two different acyl groups)
  – to name, replace acid of the parent acid by anhydride



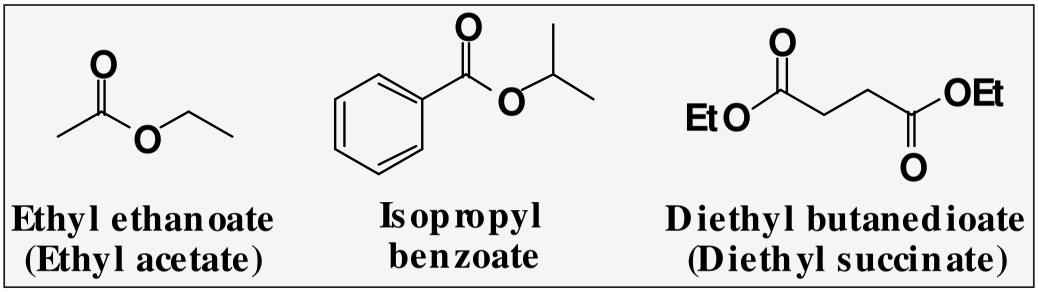
Acid Anhydrides

- Cyclic anhydrides are named from the dicarboxylic acids from which they are derived



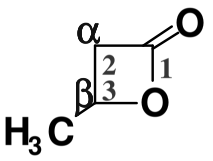
Esters

- The functional group of an ester is an acyl group bonded to -OR or -OAr
  - name the alkyl or aryl group bonded to oxygen followed by the name of the **acid**
  - change the suffix -ic acid to -ate

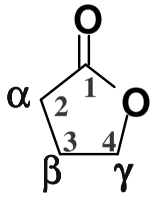


Esters

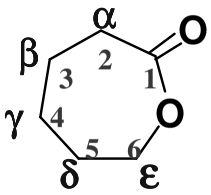
- Cyclic esters are called **lactones**
  - name the parent carboxylic acid, drop the suffix -ic acid and add -olactone



3-Butanolactone (β-Butyrolactone)



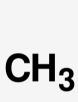
4-Butanolactone (γ-Butyrolactone)



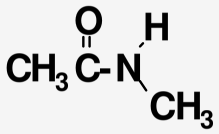
6-Hexanolactone (ε-Caprolactone)

Amides

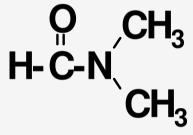
- The functional group of an amide is an acyl group bonded to a nitrogen atom
  - IUPAC: drop -oic acid from the name of the parent acid and add -amide
  - if the amide nitrogen is bonded to an alkyl or aryl group, name the group and show its location on nitrogen by *N*-



Acetamide (a 1° amide)



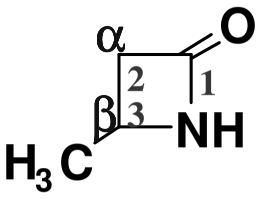
***N*-Methylacetamide (a 2° amide)**



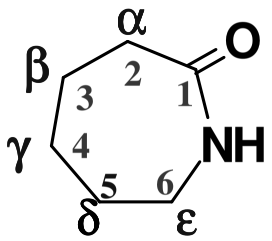
***N*,*N*-Dimethylformamide (DMF) (a 3° amide)**

Amides

- Cyclic amides are called **lactams**
  - name the parent carboxylic acid, drop the suffix -ic acid and add -lactam



3-Butanolactam
(β-Butyrolactam)



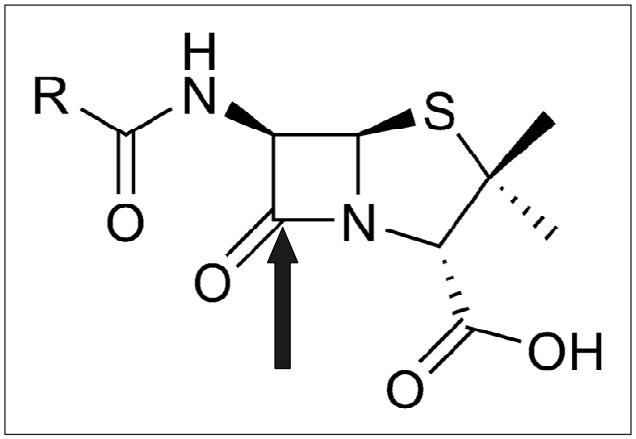
6-Hexanolactam
(ε-Caprolactam)

penam –old term for β-lactam

Penicillins

the penicillins are a family of **β-lactam antibiotics**

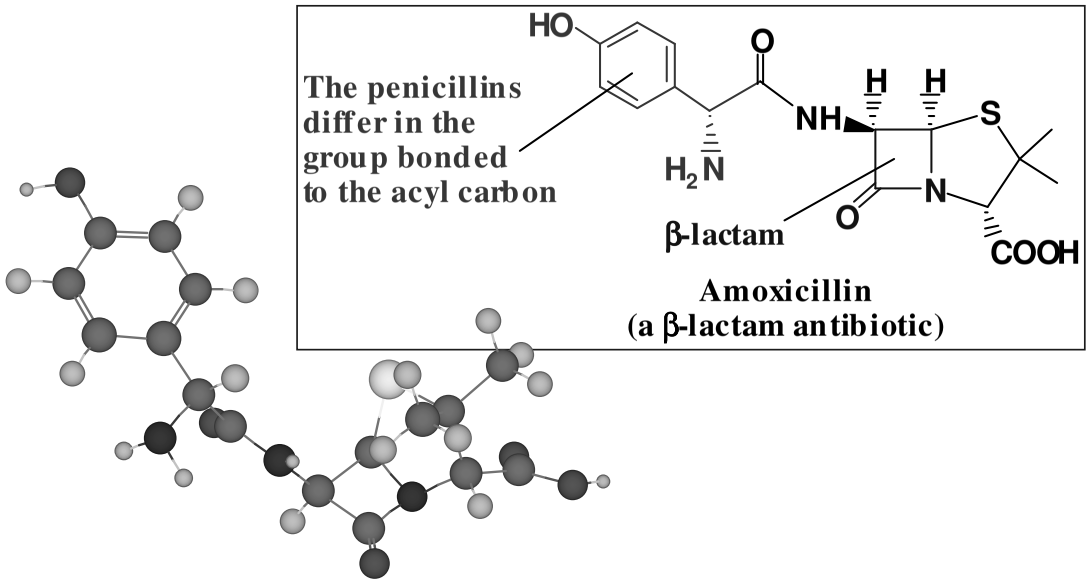
The compound is an exceptional "acylating" agent because of the ring strain of the lactam.



Inhibit cell wall synthesis by acylating and de-activating the required enzymes.

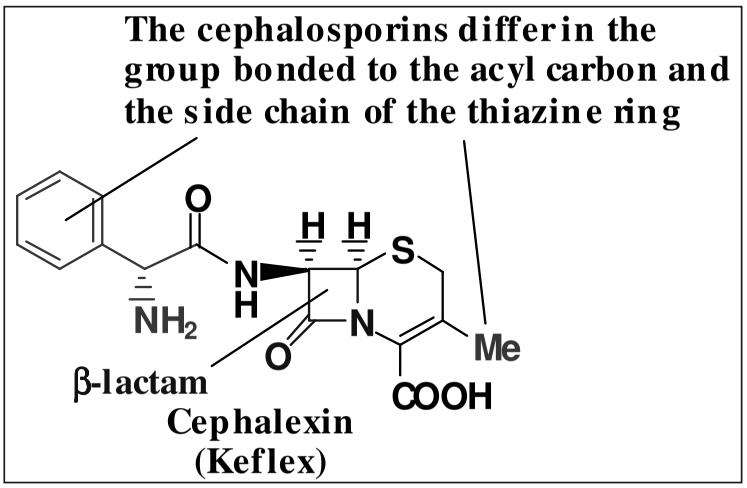
Penicillins

the penicillins are a family of **β-lactam antibiotics**



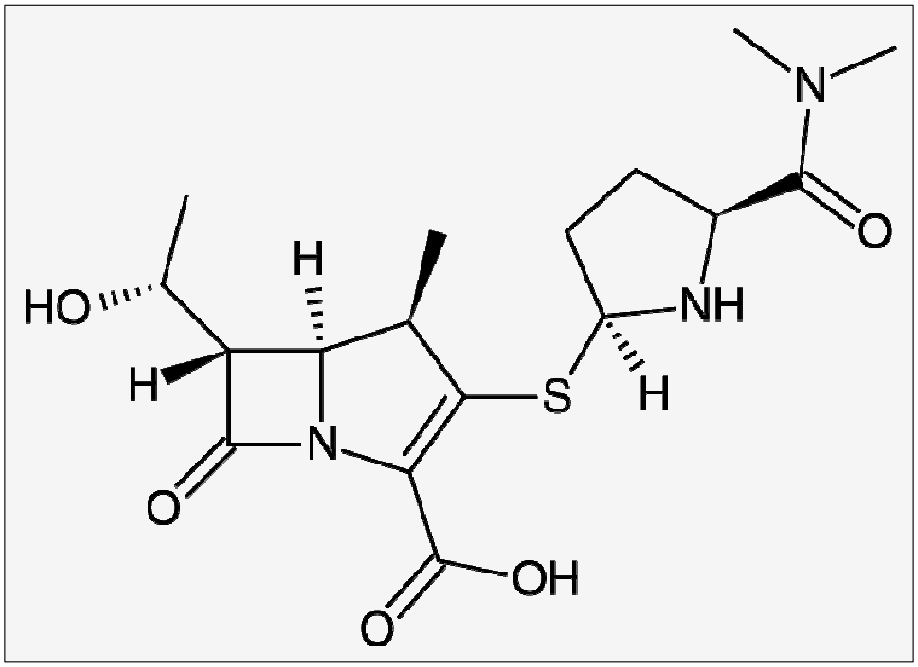
Cephalosporins

the cephalosporins are also **β-lactam antibiotics**



Bacteria develop resistance by producing **β-lactamases-**enzymes, which can hydrolyze the lactam before it can inhibit cell wall synthesis.

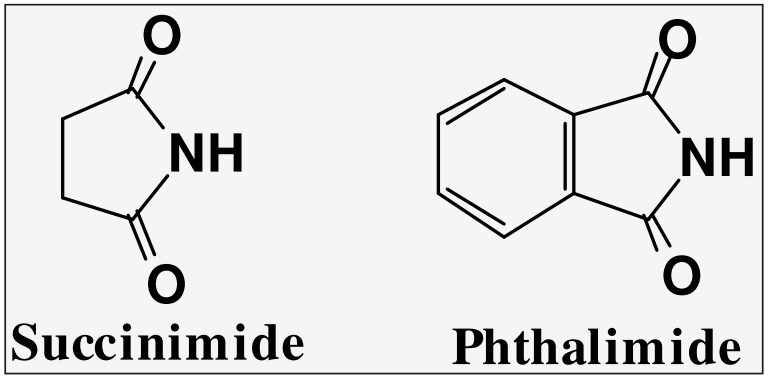
Meropenem



Highly resistant to degradation by β-lactamases or cephalosporinases.

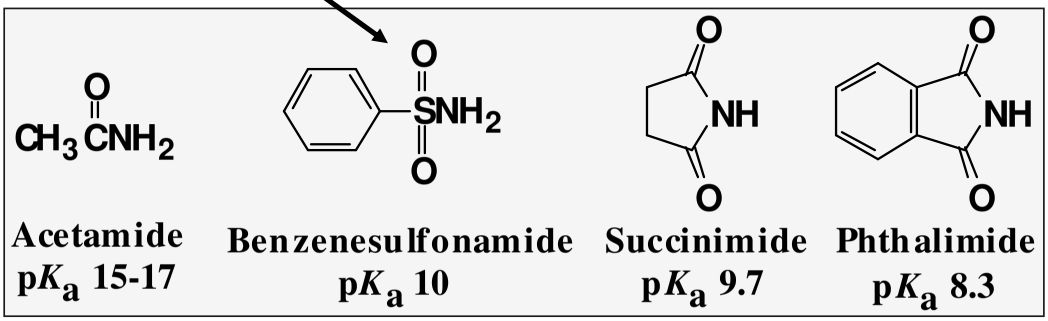
Imides

- The functional group of an **imide** is two acyl groups bonded to nitrogen
  - both succinimide and phthalimide are cyclic imides



Acidity of N-H bonds

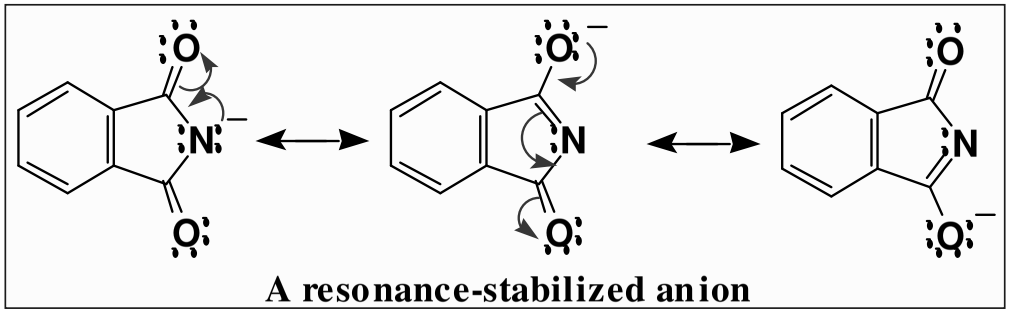
- **Amides** are comparable in acidity to alcohols
  - water-insoluble amides do not react with NaOH or other alkali metal hydroxides to form water-soluble salts
- Sulfonamides and imides are more acidic than amides



Acidity of N-H bonds

Imides are more acidic than amides because:

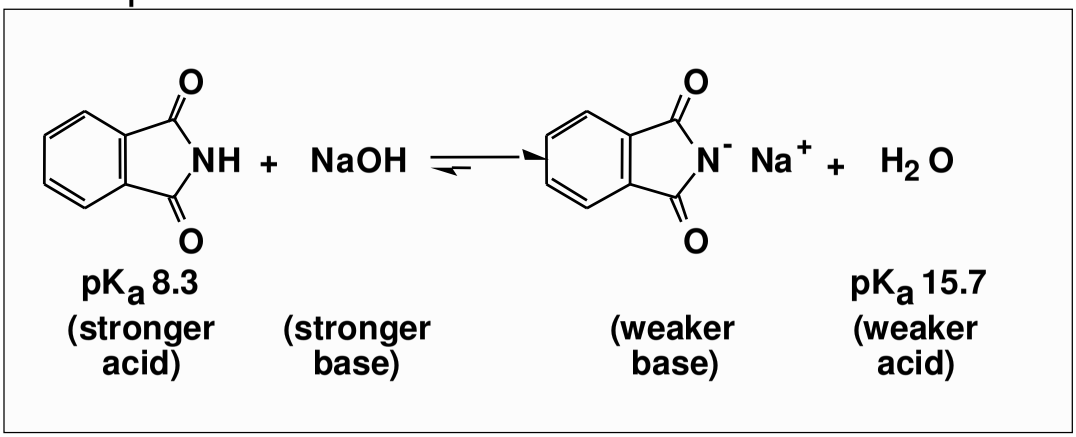
1. the electron-withdrawing inductive of the two adjacent C=O groups weakens the N-H bond, and
2. the imide anion is stabilized by resonance delocalization of the negative charge



A resonance-stabilized anion

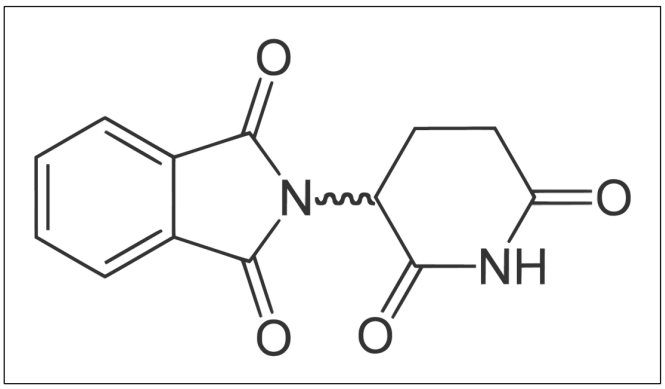
Acidity of N-H bonds

– imides such as phthalimide readily dissolve in aqueous NaOH as water-soluble salts



This property is used to render pharmaceutical agents water soluble:

Thalidomide-sedative, hypnotic

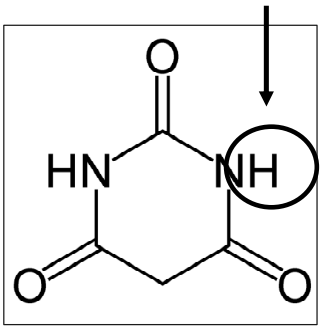


1. Sedative was used in pregnant women from 1956~1962 in Europe/Africa

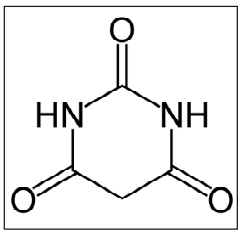
1. **Never approved in US**
2. **Caused birth defects (teratogen)**
3. **Later found use in leprosy treatment**

Barbituric Acid

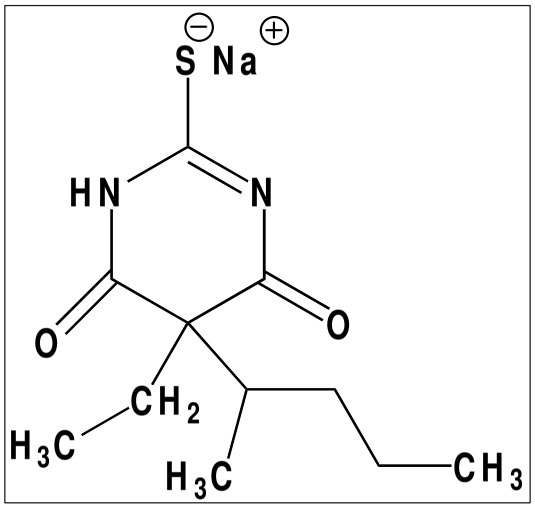
Acidity of this H is used to Make the derivatives soluble



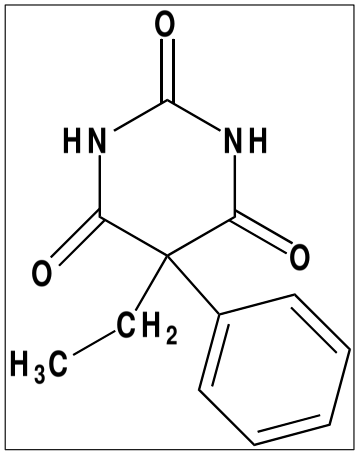
Barbituric Acid



Sodium Pentothal® -Sodium thiopental



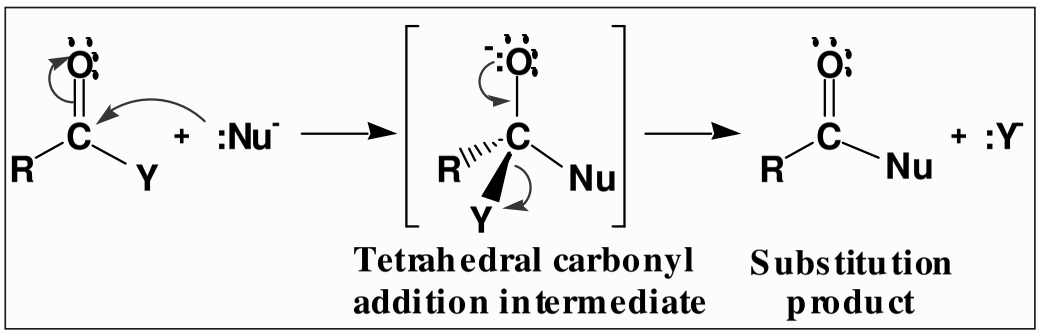
Phenobarbital



Anticonvulsant, hypnotic, anxiolytic

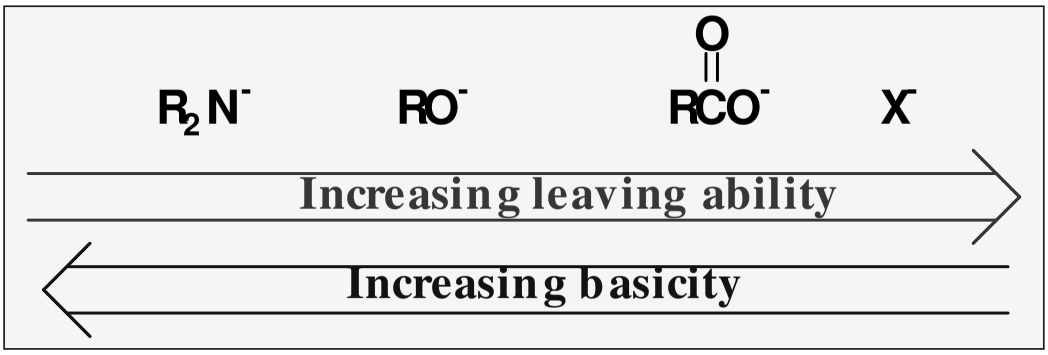
Characteristic Reactions

- **Nucleophilic acyl substitution:** an addition-elimination sequence resulting in substitution of one nucleophile for another



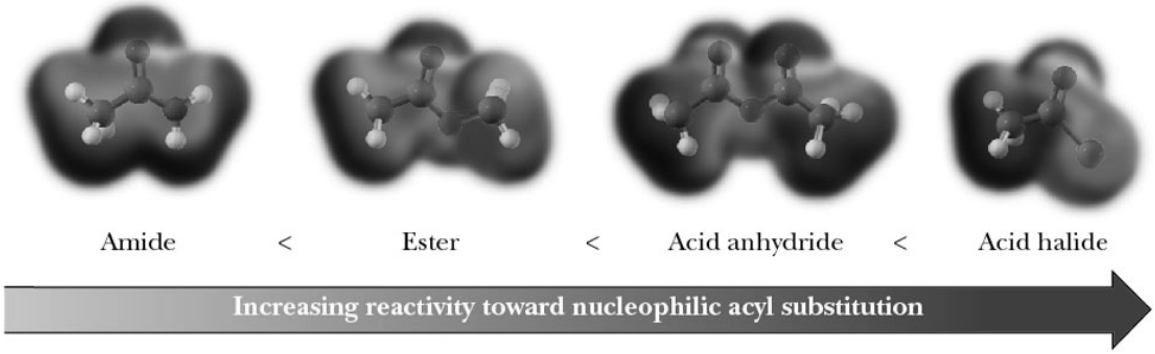
Characteristic Reactions

- in the general reaction, the leaving group, as an anion, illustrates an important point:
- the weaker the base, the better the leaving group



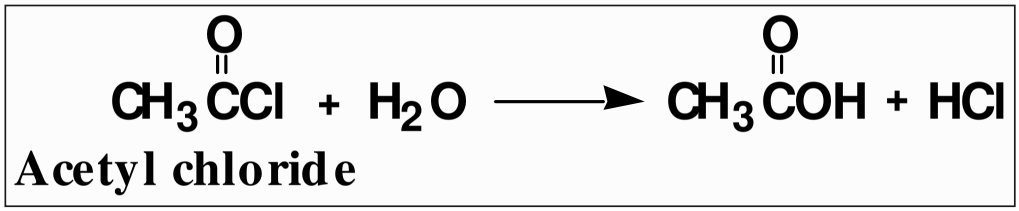
Characteristic Reactions

- halide ion is the weakest base and the best leaving group; acid halides are the most reactive toward nucleophilic acyl substitution
- amide ion is the strongest base and the poorest leaving group; amides are the least reactive toward nucleophilic acyl substitution



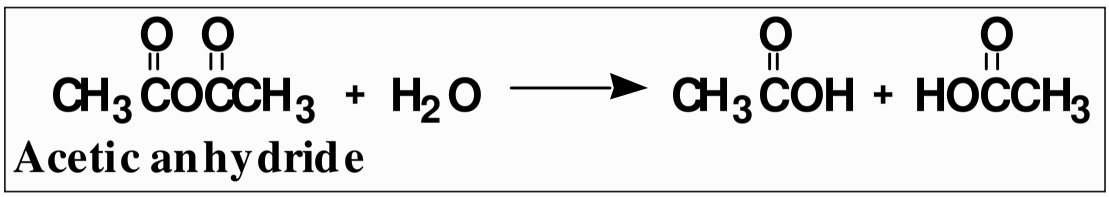
Reaction with H_2O - Acid Chlorides

- low-molecular-weight acid chlorides react rapidly with water
- higher molecular-weight acid chlorides are less soluble in water and react less readily

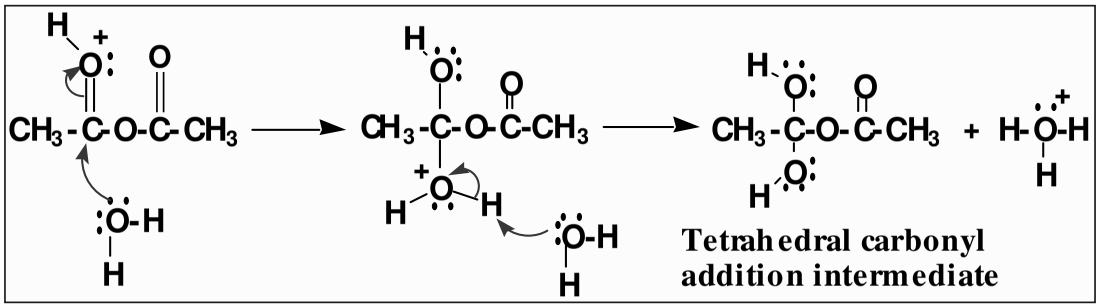


Reaction with H_2O - Anhydrides

- low-molecular-weight acid anhydrides react readily with water to give two molecules of carboxylic acid
- higher-molecular-weight acid anhydrides also react with water, but less readily



– Step 1: addition of H_2O to give a TCAI



– Step 2: protonation followed collapse of the TCAI