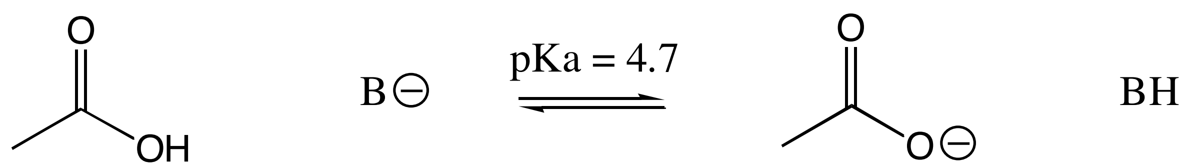
Carboxylic Acids

A carbonyl with one OH attached is called a carboxylic acid

One important property of carboxylic acids is the acidity



carboxylic acid

carboxylate ion

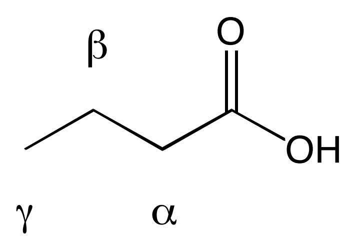
Upon deprotonation a carboxylate is formed

Nomenclature

There are two important guidelines to know about carboxylic acids:

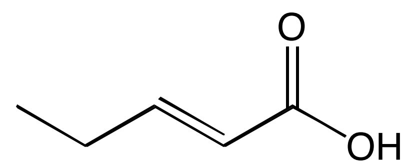
1) the carboxylic acid has the highest priority in naming

2) in common names the point of substitution is labeled by the Greek letter counting from the carbonyl

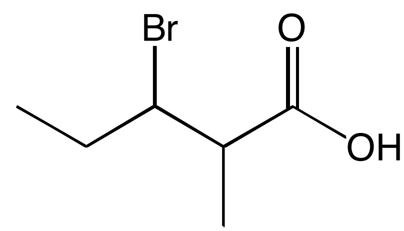


this naming is common practice amongst organic chemists, e.g. substitution at α-carbon

Examples



(E)-2-pentenoic acid



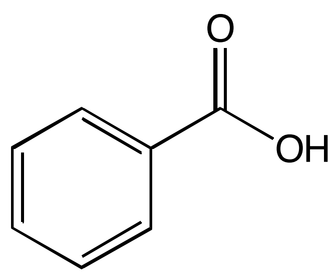
3-bromo-2-methylpentanoic acid

or β-bromo-α-methylpentanoic acid (common)

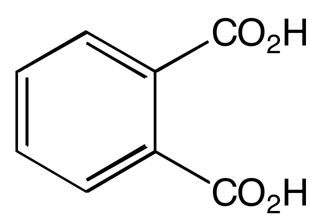
Common Names

Many acid compounds have a common name

Most prevalent amongst these are aromatic compounds



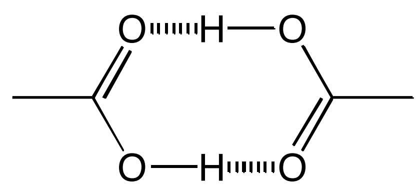
benzoic acid



phthalic acid

Physical Properties

Most physical properties of carboxylic acids are a result of hydrogen bonding



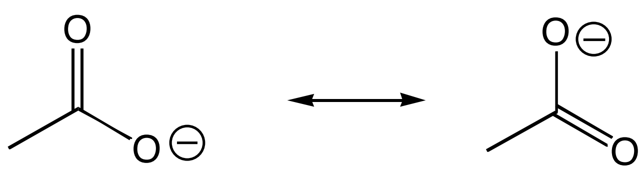
the carboxylic acids form dimers through hydrogen bonding

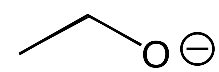
this hydrogen bonding causes a higher melting point and boiling point compared to compounds of similar molecular weight

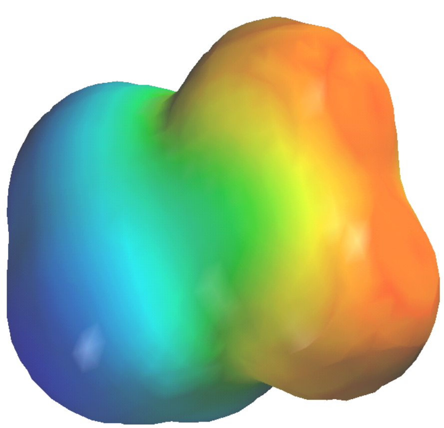
Acidity

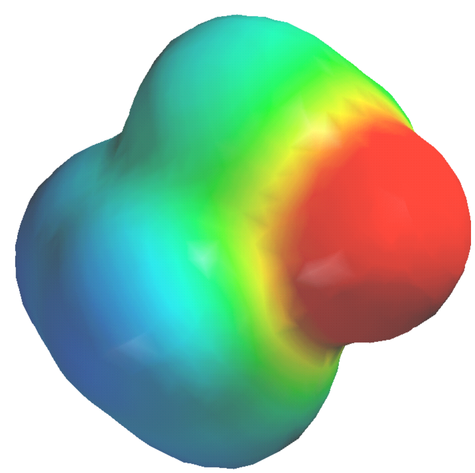
As observed previously, carboxylic acids are far more acidic than alcohols

This is due to the stability of the anion formed after deprotonation





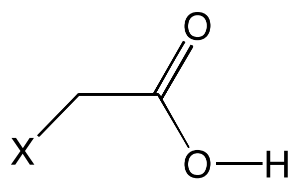




Can also stabilize anion through inductive effects

Polar bonds near anion source can stabilize negative charge (inductive effect)

Consider the acetate group again:



	pK_a
X = H	4.7
I	3.18
Br	2.90
Cl	2.86
F	2.59

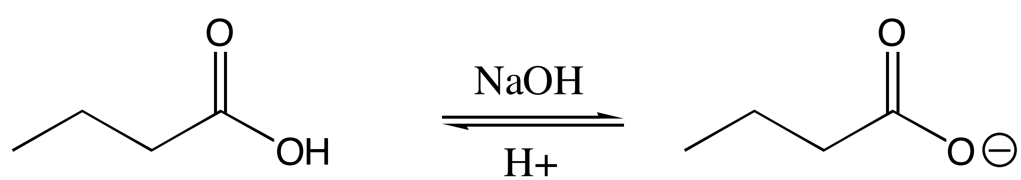
Carboxylate Salts

Upon deprotonation of a carboxylic acid obtain a carboxylate salt

This salt has different physical properties than the acid form

(similar to the difference in amine salts discussed in chapter 19)

for carboxylates these physical differences are used often for separation

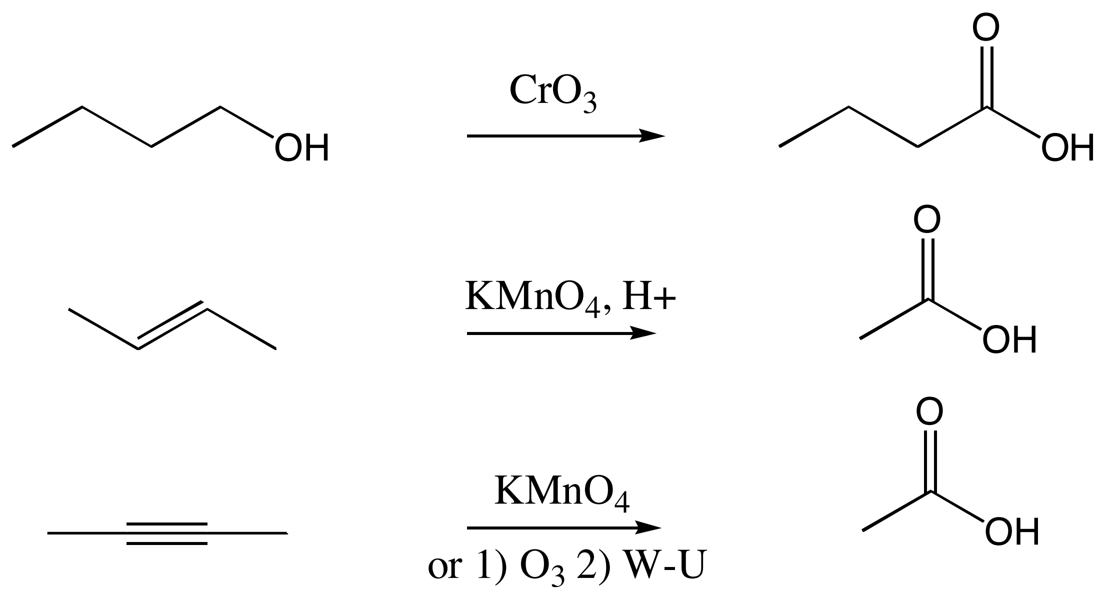


high organic solubility

high aqueous solubility

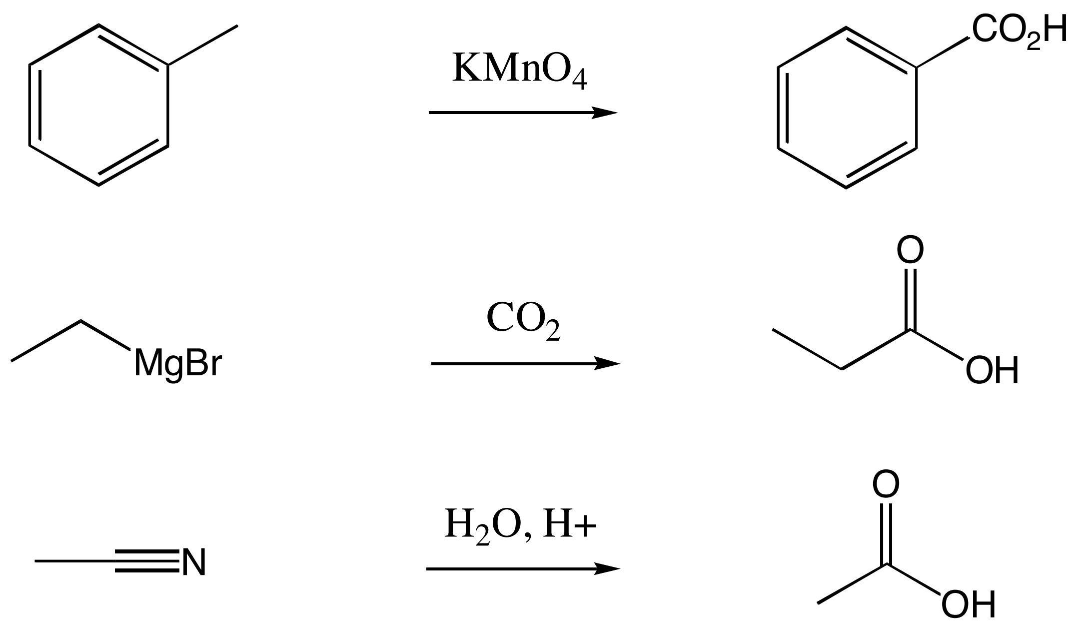
Synthesis of Carboxylic Acids

We have already learned many ways to synthesize a carboxylic acid



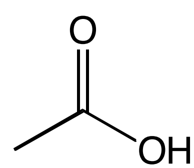
Synthesis (Review)

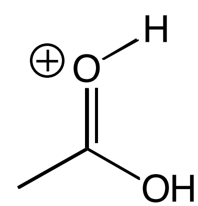
Part 2

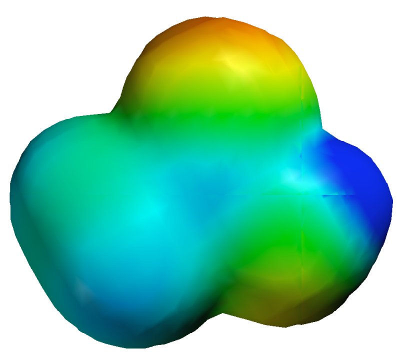


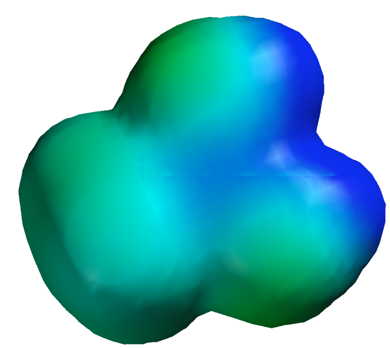
Reactions of Acid Compounds

Almost all Acyl compounds react through a nucleophilic reaction through either the carbonyl or protonated carbonyl



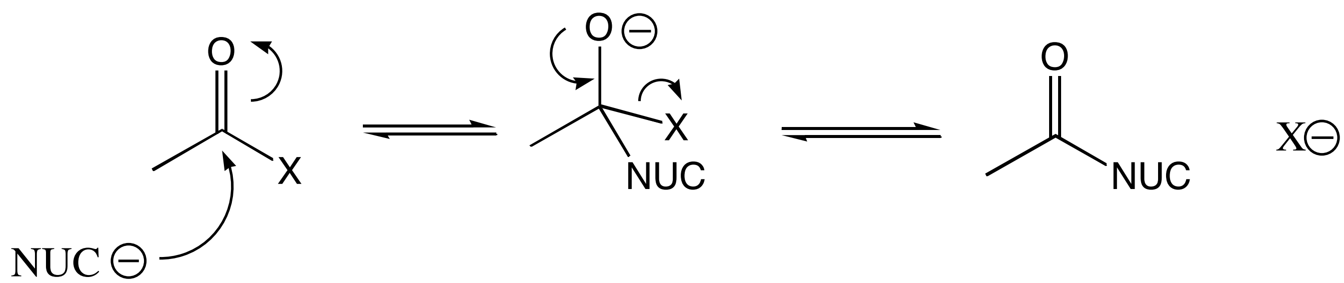






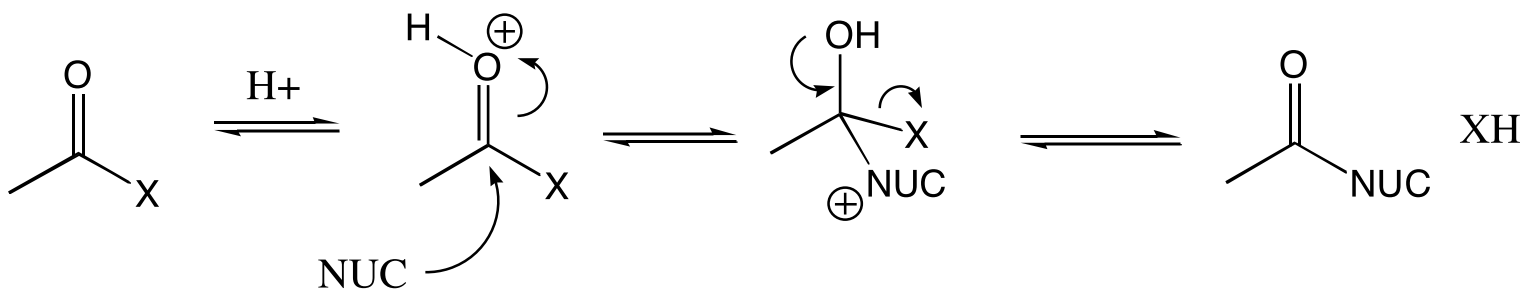
General Mechanism for Acyl Reactions

There is a commonality amongst all carbonyl reactions observed



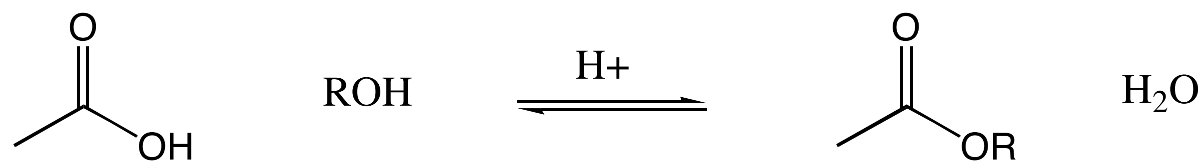
generate a tetrahedral intermediate that can expel a leaving group

in acidic conditions have same mechanism but protonate carbonyl first



Can apply this general mechanism to reactions in chapters 20 and 21

Fischer esterification: one example



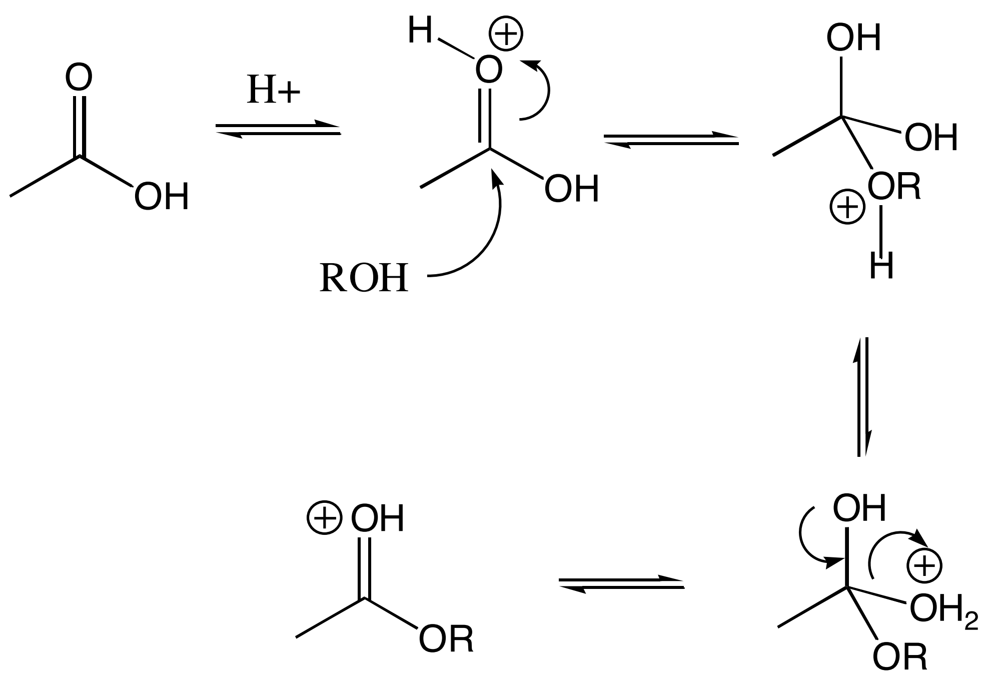
carboxylic acid

ester

key points: this is an equilibrium reaction

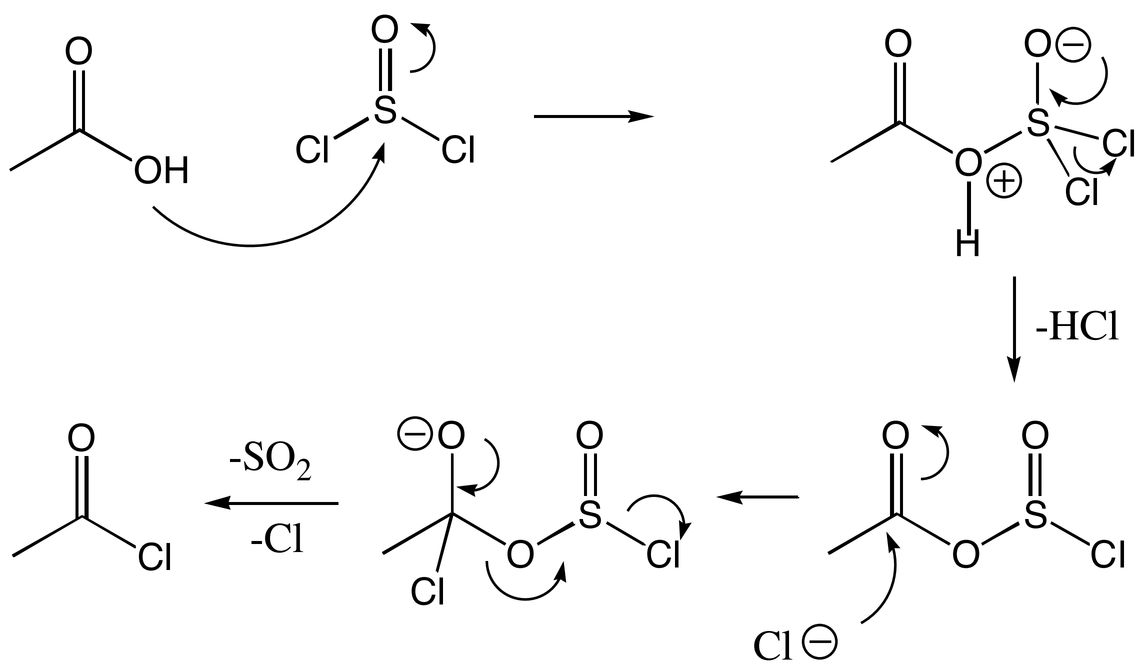
reaction can be driven either direction by Le Chatelier's principle

Mechanism for Fischer Esterification

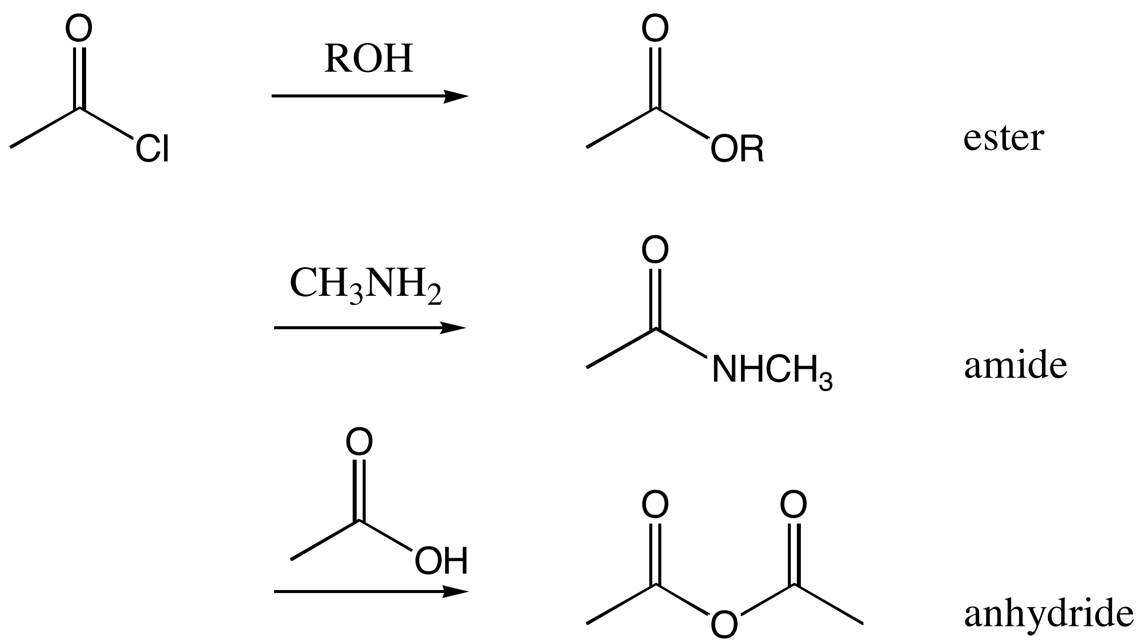


Acid Chlorides

We have already seen how carboxylic acids can be converted into acid chlorides with thionyl chloride

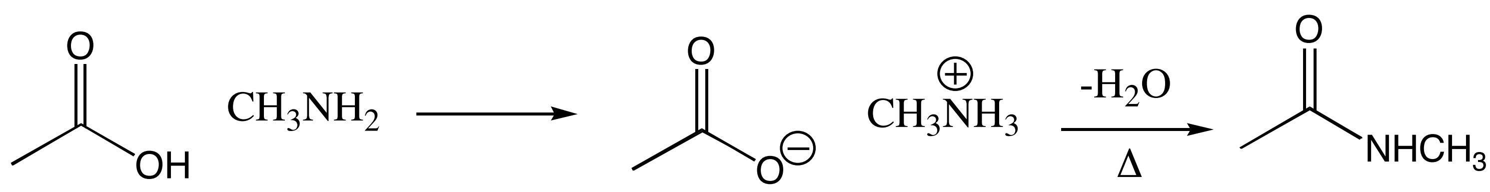


The Acid Chloride Can Be Converted to Other Carbonyl Compounds



Direct Acid to Amide Interconversion

An amide can be formed directly from the carboxylic acid by combining the two reagents



this procedure is not as mild as first converting acid to acid chloride,

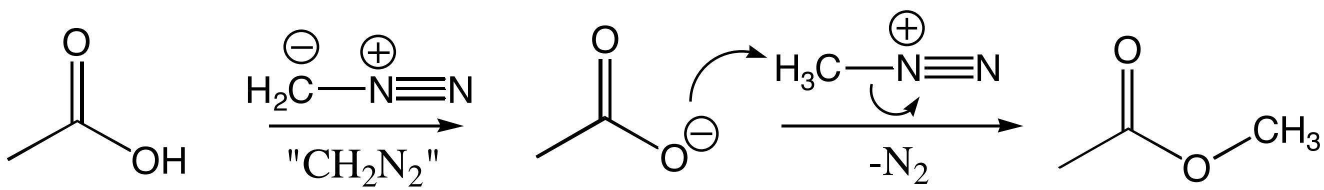
need to heat the reaction (usually ~100˚C) to drive off water

loss of water as steam shifts the reaction to products

Diazomethane

Another route to form esters from carboxylic acids is to use diazomethane

**only use for small quantities - in large reactions diazomethane is dangerous

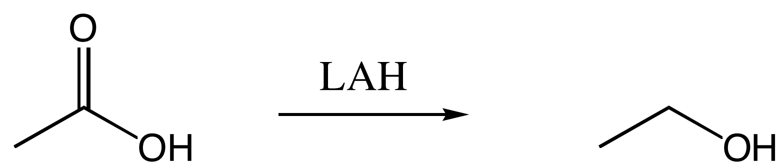


yields are quite high, but reaction is potentially dangerous

for most lab-scale reactions a different route to esters is preferred

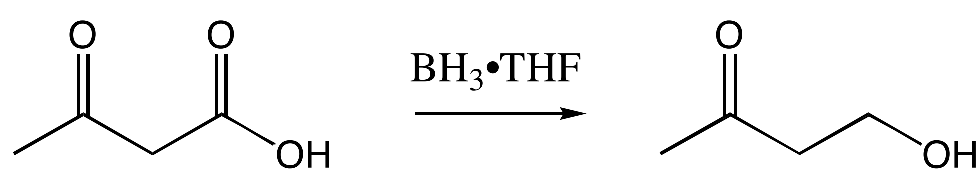
Reduction of Carboxylic Acids

We have already seen how LAH can reduce carboxylic acids to alcohols

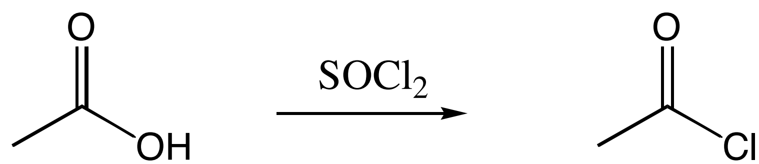


the problem with LAH is it is relatively unselective - it will reduce every carbonyl

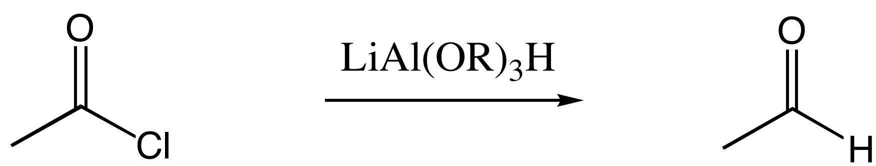
another option is borane - it reduces carboxylic acids faster than other carbonyls



Another Option is Convert the Carboxylic Acid to Acid Chloride



as observed previously the acid chloride can be reduced to the aldehyde

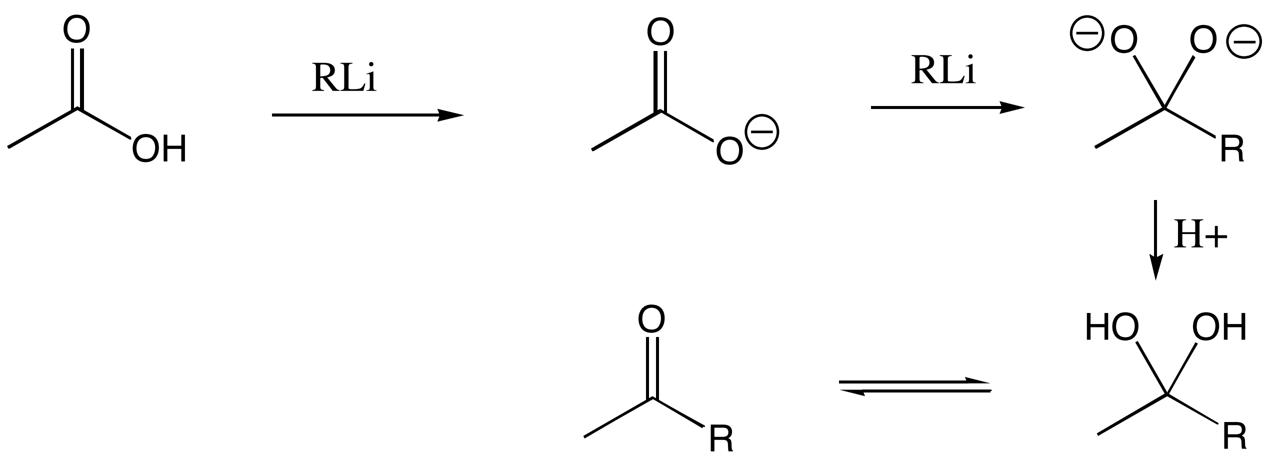


need to use a reducing agent weaker than LAH

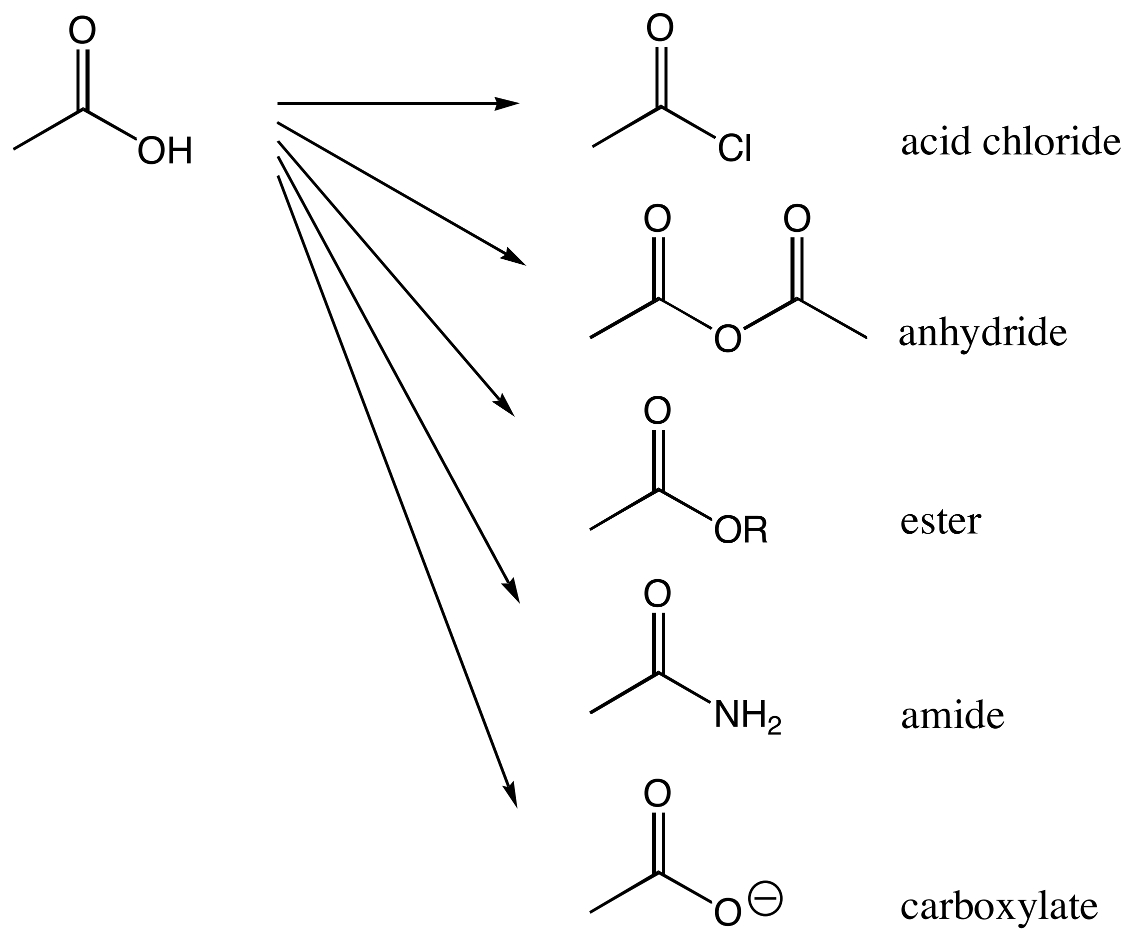
Conversion of Carboxylic Acids to Ketones

Another reaction observed previously is to convert a carboxylic acid to ketone

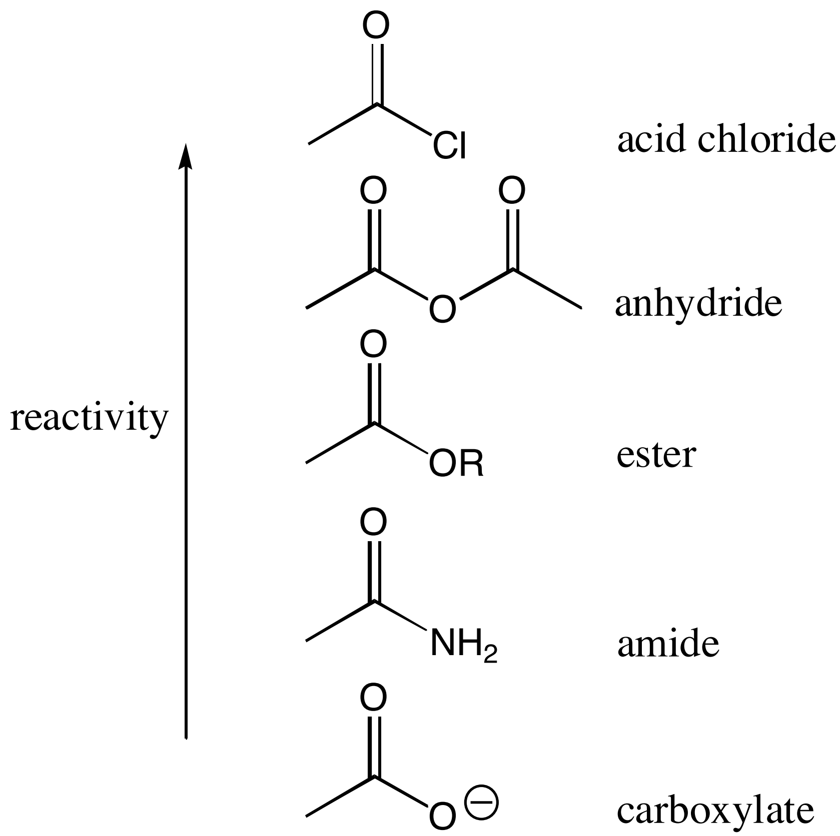
Need to use two equivalents of organolithium



Interconversion of Carboxylic Acid Derivatives



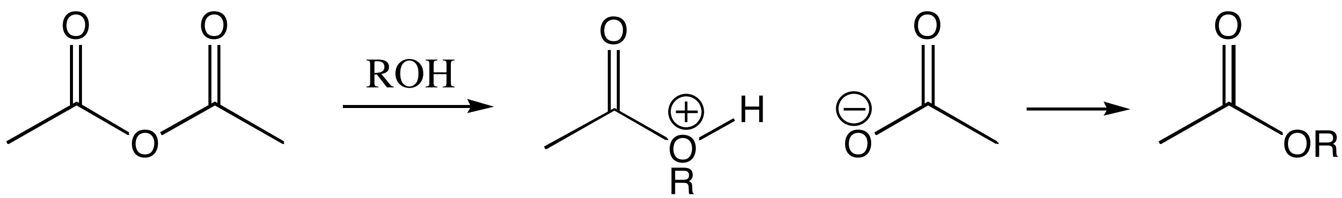
Reactivity Trend



these acid derivatives can also be interconverted to a less reactive form

Anhydrides

An anhydride can be converted to any other less reactive carboxylic acid derivative



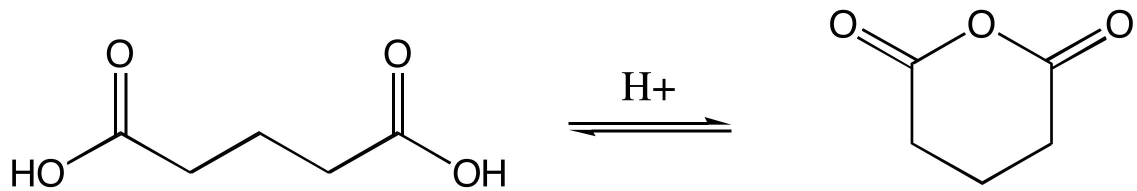
the anhydride is less reactive than an acid chloride

lose one carbonyl as a leaving group

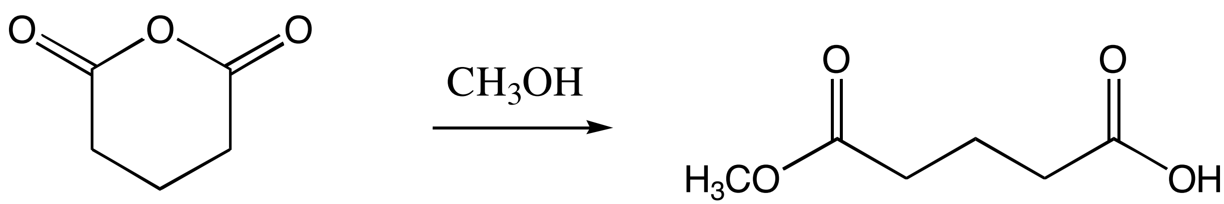
(therefore with acetic anhydride shown lose one equivalent of acetic acid)

Cyclic Anhydride

Can form a cyclic version of an anhydride



the cyclic anhydride reacts to form unsymmetrical dicarbonyl compounds

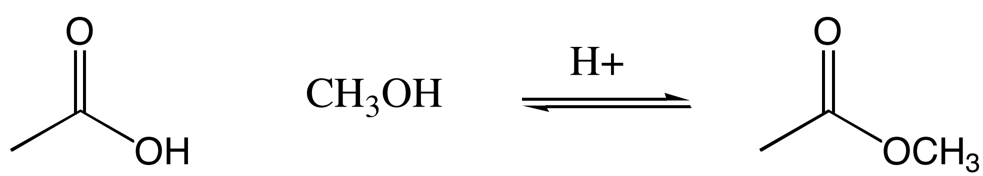


also both carbonyls are now part of product

Esters

Seen many ways to synthesize an ester

Can react in a Fischer esterification directly from acid

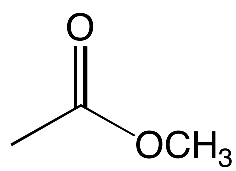


Can also react either an acid chloride or anhydride with an alcohol to form ester

Nomenclature of Esters

Esters are named with an -ate suffix (from carboxylate)

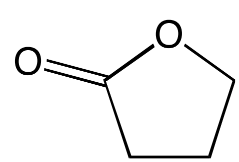
with the alkyl ester part named in front of the root



methyl ethanoate

common - methyl acetate

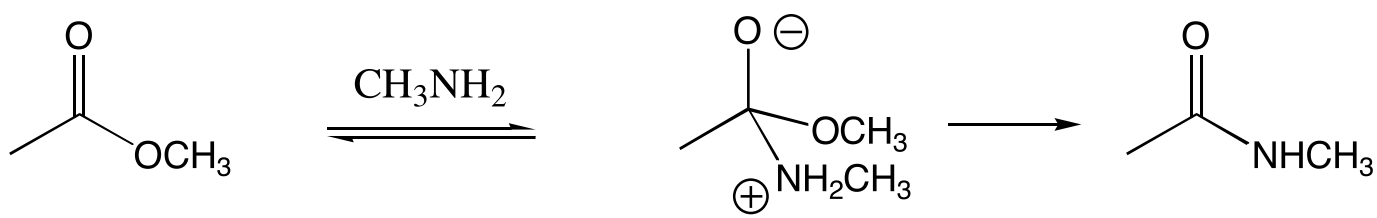
cyclic esters are called lactones (for IUPAC place lactone after name for acid)



4-hydroxybutanoic acid lactone

Esters can react to form either amides or carboxylates

Follows same nucleophilic reaction pathway as seen with other carbonyl compounds

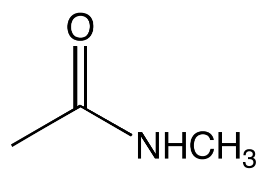


an ester is less reactive than either an acid chloride or anhydride

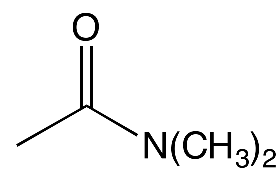
(primarily due to a worse leaving group in comparison)

Amides

Amides are named according to root name with amide suffix

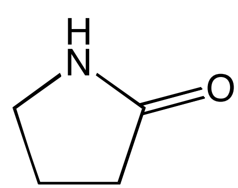


N-methylethanamide



N,N-dimethylethanamide

Substituents on nitrogen are named as N-alkyl substituents

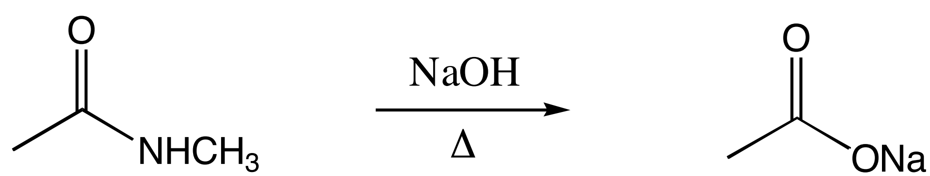


4-aminobutanoic acid lactam

A cyclic amide is called a lactam

Amides

An amide can be hydrolyzed to a carboxylic acid under either acidic or basic mechanism

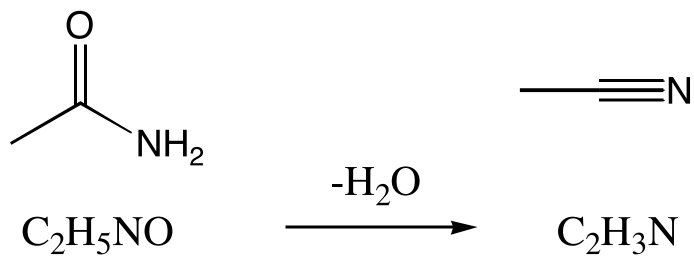


An amide is the most stable of any of the carboxylic acid derivatives observed

Therefore it will require stronger conditions to hydrolyze compared to other derivatives

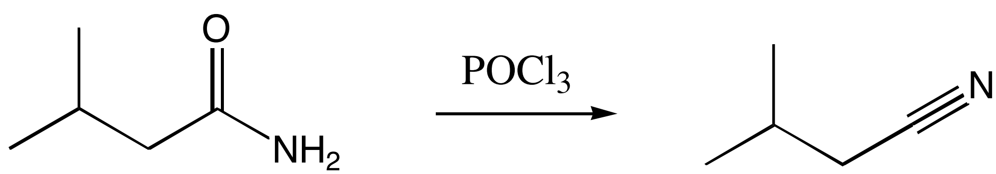
Formation of Nitriles

Amides can also be dehydrated to form nitriles



can cause this interconversion with strong dehydrating agents

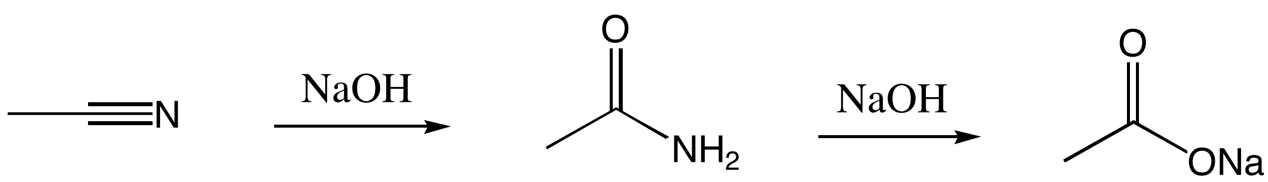
(e.g. $POCl_3$ or P_2O_5 are common)



one of two common routes to nitriles (other is S_N2 reaction with sodium cyanide)

Nitriles

As observed previously, nitriles can also be hydrolyzed to carboxylic acids



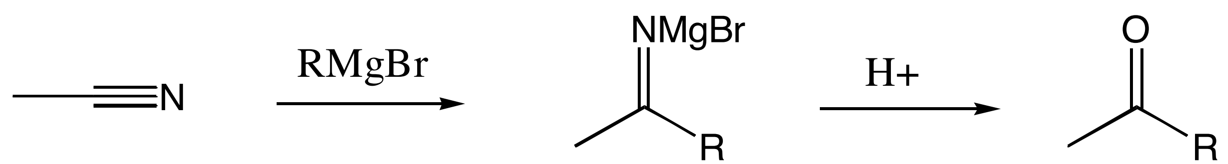
upon work-up will protonate carboxylate to form acid

can also run this reaction under acidic conditions

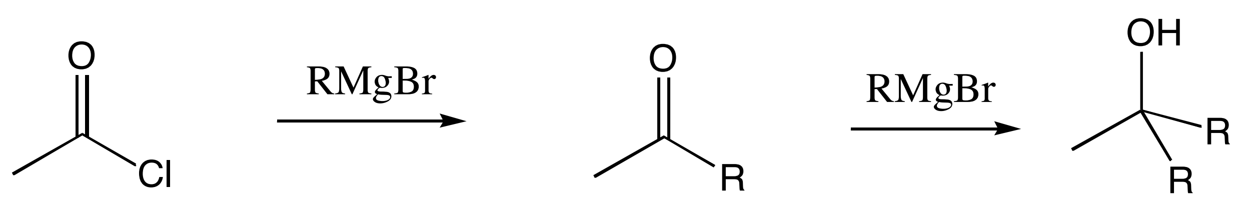
both require strong conditions - with weaker conditions can stop at amide stage

Grignard Reactions with Nitriles

As seen in synthesis of ketones, can also react nitriles with Grignard reagents

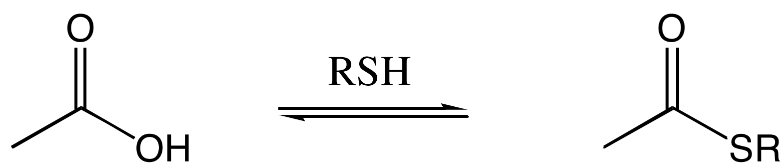


with other carbonyl compounds synthesize alcohols with Grignard reaction



Thioesters

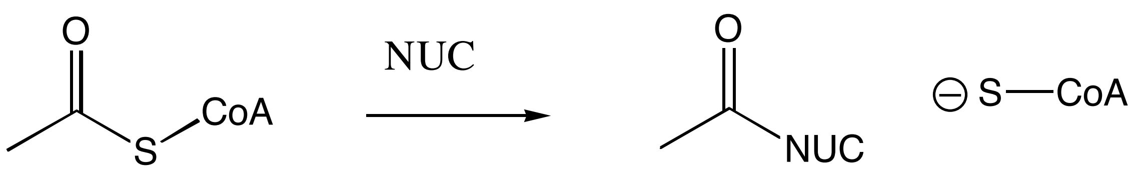
Thioesters are formed in the same manner as esters, but use a thiol



thioesters are more reactive toward nucleophiles than esters

(but less than acid chlorides or anhydrides)

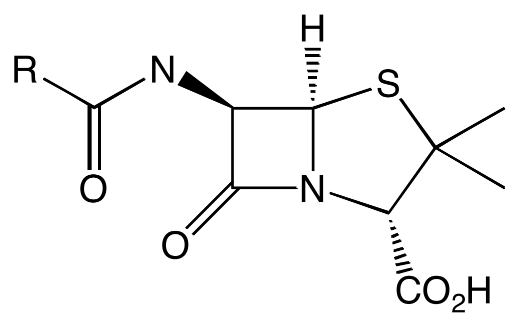
biologically we take advantage of this fact to selectively acylate nucleophiles



β-Lactams

another carboxylic acid derivative that is used biologically are β-lactams

β- refers to nitrogen of amide attached to second carbon from carbonyl (hence β-position)

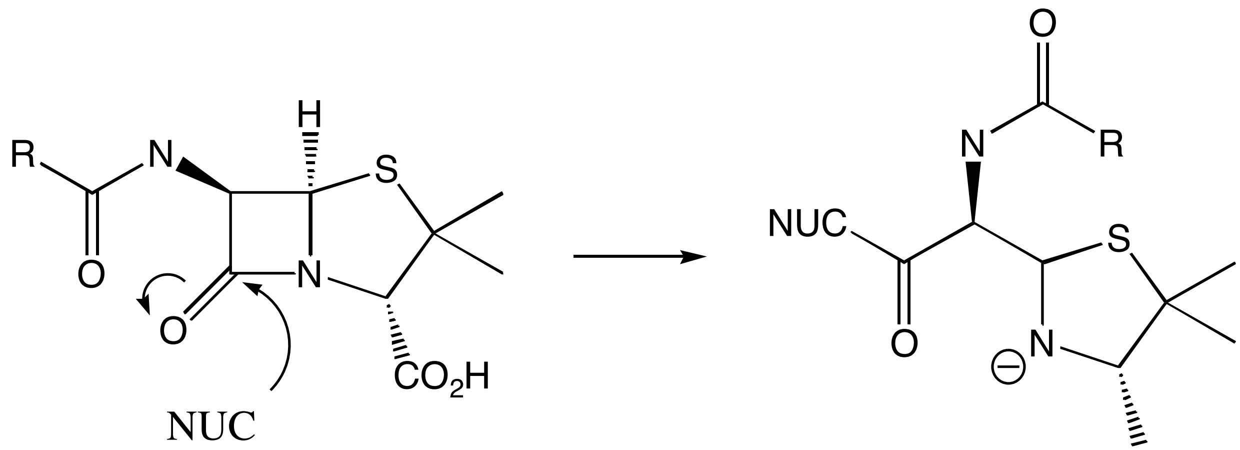


penicillin

unlike normal amides or lactams, β-lactams are more reactive

due to the strain of the 4-membered ring therefore nucleophiles will react with the amide carbonyl of the ring

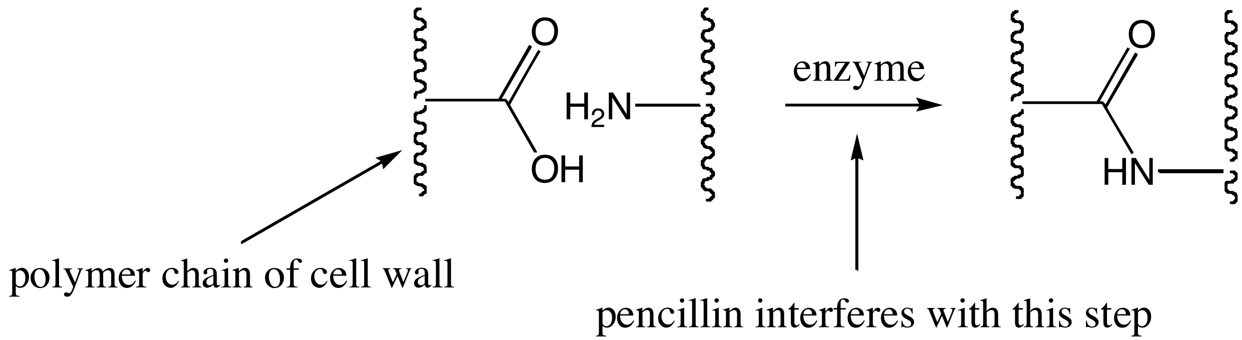
to open the ring and release the strain



the other amide is unreactive because it does not have ring strain

reacts like other amides we have discussed earlier

Bacterial cells survive many conditions that mammalian cells do not due to a rigid cell wall composed of carbohydrates linked together by peptide bonds

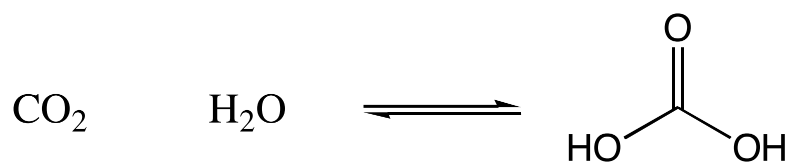


with the β-lactam penicillin present, the cell walls of the bacterial cell are disrupted because the enzyme that forms the cell walls is turned off by undergoing a nucleophilic reaction with penicillin and thus the bacterial cells eventually die

penicillin does not disrupt mammalian cells since they are surrounded by a lipid bilayer and not a cell wall

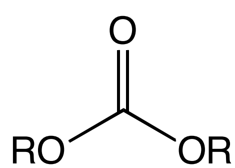
Carbonic Acid

Carbonic acid is formed by dissolving carbon dioxide in water

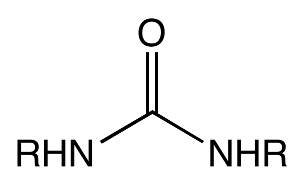


carbonic acid

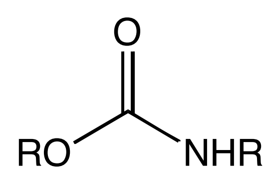
While carbonic acid is unstable many derivatives are prevalent



carbonate ester



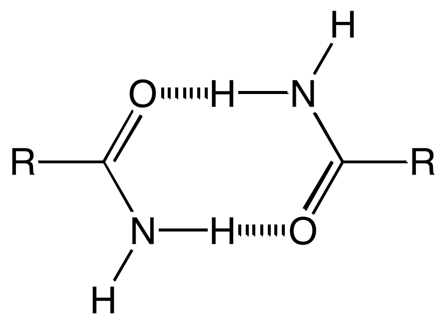
urea

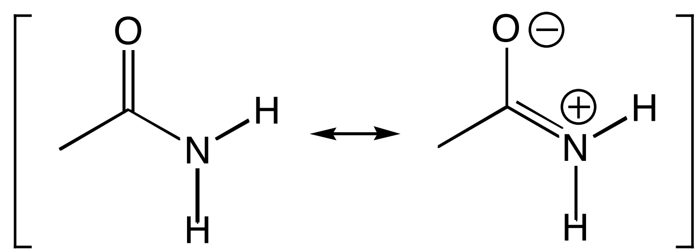


urethane

Physical Properties of Carboxylic Acid Derivatives

A main factor to consider for the physical properties is the hydrogen bond ability





Both carboxylic acids and amides have high boiling points and melting points relative to their molecular weight due to hydrogen bonding,

amides are higher due to greater charged resonance contributor

Esters and anhydrides, on the other hand, have lower boiling points due to lack of hydrogen bonding

Nomenclature

The compounds with one carbonyl are named according to the rules presented earlier

With compounds with multiple functional groups need priority for naming

Remember that carboxylic acid derivatives outrank all other substituents

Amongst carbonyls however the following priorities apply:

Acid > ester > amide > nitrile > aldehyde > ketone

IR Spectroscopy

Most of the carbonyl containing compounds can be distinguished
by their carbonyl IR stretching

two derivatives not discussed earlier are acid chlorides and anhydrides

acid chlorides have a high energy stretch (relative to other carbonyls) at ~1800 cm-1

anhydrides have two stretches in the IR region at ~1750 and 1810 cm-1
(the two carbonyls resonant with each other to afford two peaks)

Example of IR for Anhydride