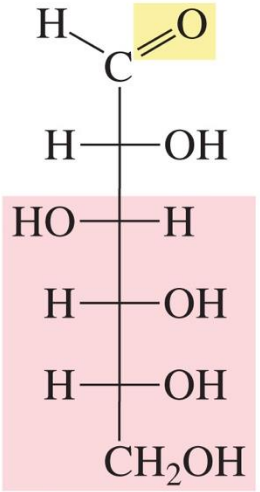
EPFL

Bio-organic chemistry

Lecture 9

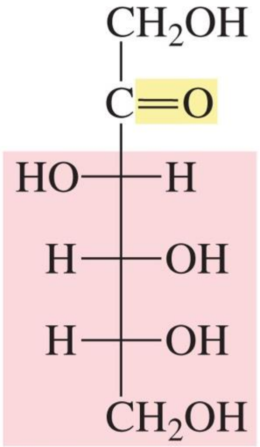
Carbohydrates are Polyhydroxy Aldehydes or Polyhydroxy Ketones



Fischer projection

D-glucose

a polyhydroxy aldehyde



Fischer projection

D-fructose

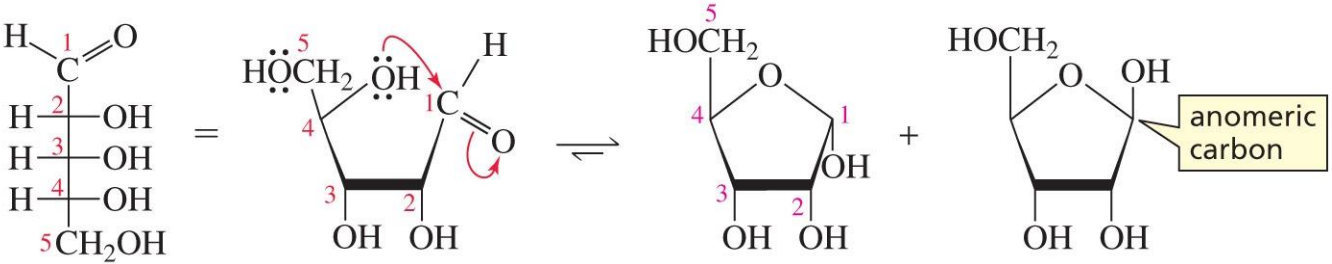
a polyhydroxy ketone

molecular formula = $C_n(H_2O)_n$

The structures of glucose and fructose differ only at the top two carbons.

Monosaccharides Form Cyclic Hemiacetals

Haworth projection



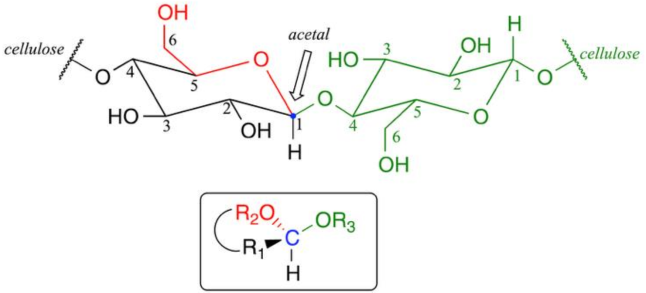
D-ribose D-ribose α-D-ribose β-D-ribose

Haworth projections

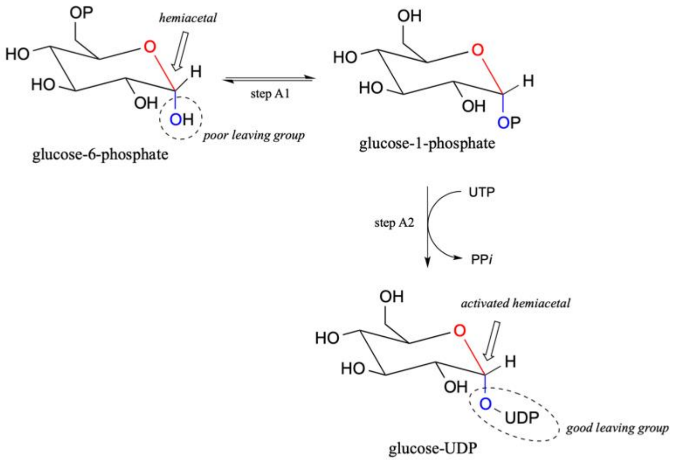
Formation and breaking of Glycosidic bonds in sugars

Glycosyltransferases: These enzymes catalyze the **formation** of **glycosidic bonds** by transferring sugar moieties, enabling the creation of acetal linkages crucial in the synthesis of complex carbohydrates.

Glycosidases: These enzymes facilitate the **breakdown** of **glycosidic bonds** through hydrolysis, cleaving acetal linkages and releasing simple sugar units, essential for digestion and nutrient absorption in biological systems.



First we get a good leaving group

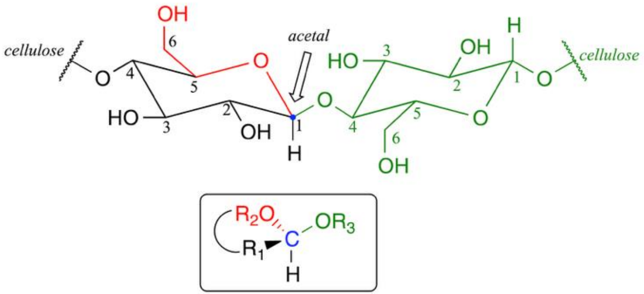


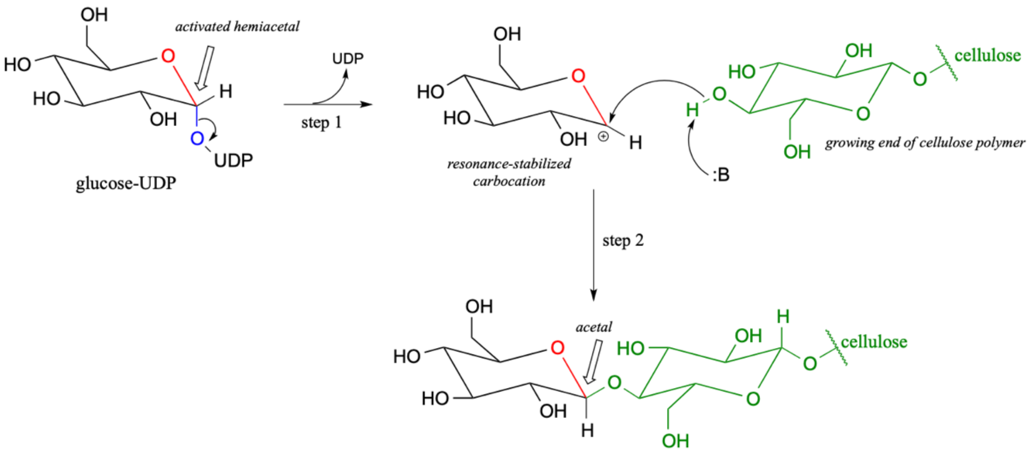
Formation and breaking of Glycosidic bonds in sugars

Glycosyltransferases: These enzymes catalyze the **formation** of **glycosidic bonds** by transferring sugar moieties, enabling the creation of acetal linkages crucial in the synthesis of complex carbohydrates.

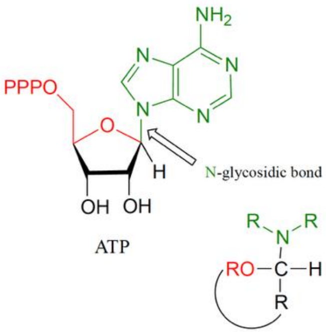
Glycosidases: These enzymes facilitate the **breakdown** of **glycosidic bonds** through hydrolysis, cleaving acetal linkages and releasing simple sugar units, essential for digestion and nutrient absorption in biological systems.

Second an acetal bond is formed

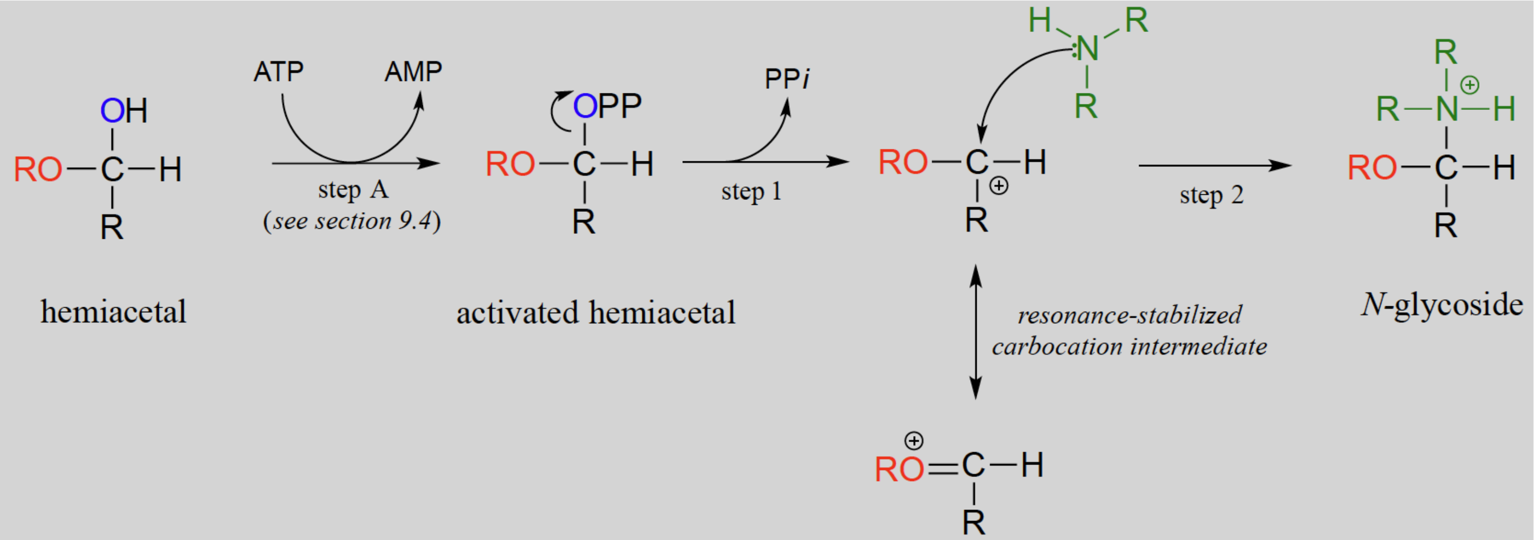




N- glycosidic bonds



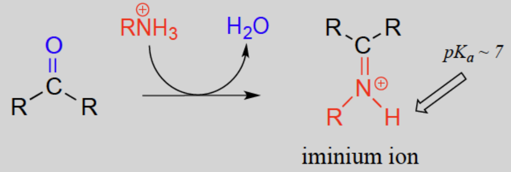
- Hemiacetals can form acetal or ketal bonds when reacted with alcohols, while reacting with amines results in N-glycosidic bonds.
- N-glycosidic bonds involve the anomeric carbon of a sugar linked to both an oxygen and a nitrogen atom from an amine.
- These bonds are vital in nucleosides and nucleotides, connecting the nitrogenous bases (A, G, C, T, U) to the sugar backbone in DNA and RNA.



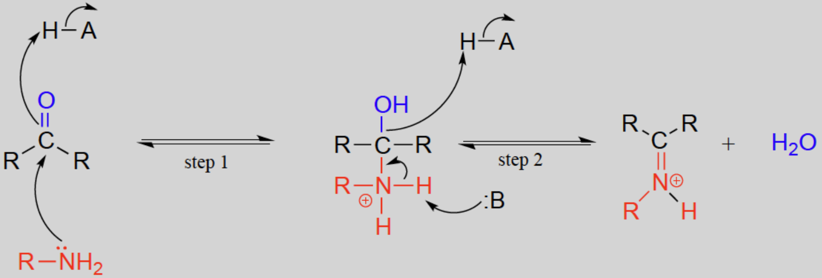
Imines and iminium ions

Functional group in which the C=O double bond is replaced by a **C=N double bond** -> Also known as **Schiff-Base**

Iminium ion formation



Mechanism (enzymatic):



The conversion of an iminium **back to an aldehyde or ketone** is a **hydrolytic process** (bonds are broken by a water molecule), and mechanistically is simply the reverse of iminium formation

Nucleophilic Addition Step

- Amine's nitrogen attacks the carbonyl carbon, leading to hemiacetal/hemiketal formation.
- Forms an intermediate with the nitrogen bonded to the carbon, resembling early acetal/ketal formation.

Elimination of Oxygen

- Instead of a second amine attacking, nitrogen's lone pair displaces the oxygen from the carbon.
- Results in the displacement of a water molecule and the formation of a carbon-nitrogen double bond (C=N), creating an iminium ion.

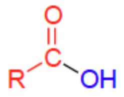
Let's take a look at a reaction

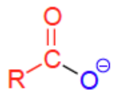
This lecture

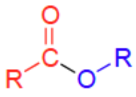
Nucleophilic Acyl substitution reactions
(Chapter 11)

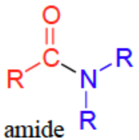
Carboxylic acid derivatives – Important nomenclature

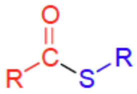
Simple carbonyls, in which the carbon of the C=O bond is attached to **other carbons**, or possibly to **hydrogens**
Carboxylic acid derivatives, or **carboxyloids**, in which the carbonyl carbon is attached to a "**heteroatom**"

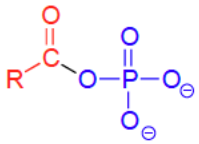

carboxylic acid

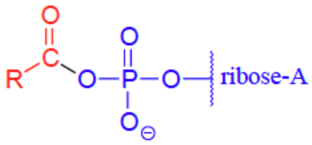

carboxylate

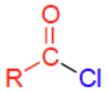

ester

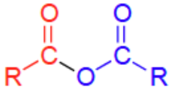

amide

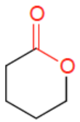

thioester

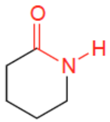

acyl phosphate


acyl-AMP

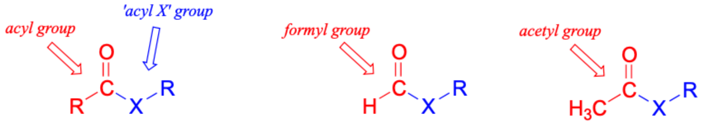

acid chloride


acid anhydride

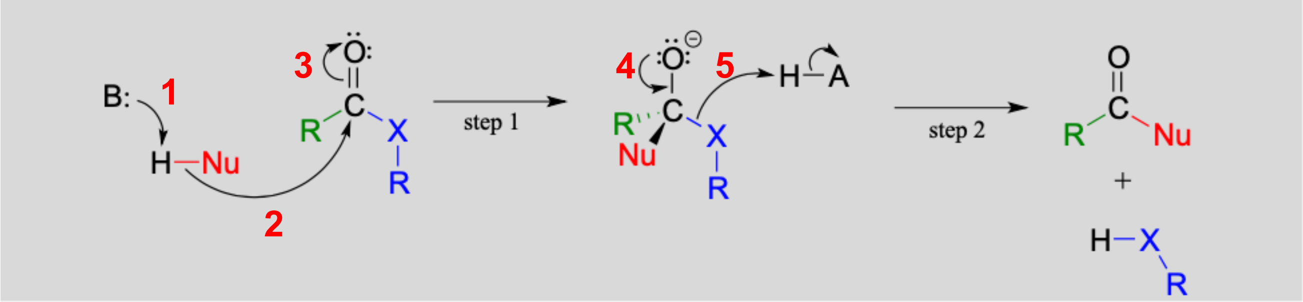

a lactone


a lactam

Carboxylic acids are distinct from aldehydes and acetones by the presence of a group containing an electronegative heteroatom (O,N,S)



Nucleophilic acyl substitution mechanism



1- Base extracts proton from nucleophile – activating the nucleophile - you can think about it now as (Nu^-)

2- Attack to the electrophilic carbon

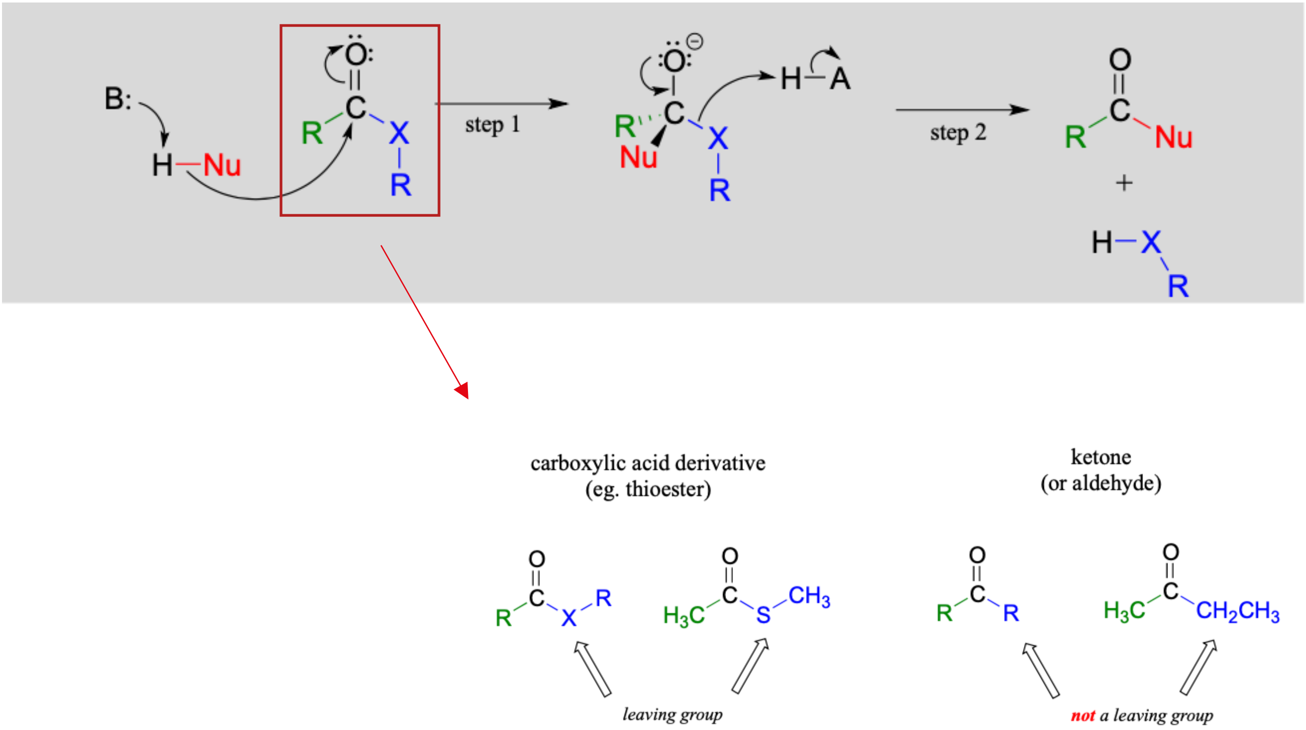
3- Delocalization of electrons to the carbonyl oxygen to fulfill the valency of the carbon

4- Formation of the tetrahedral intermediate

Delocalization of the electrons carbonyl oxygen to the acyl-X group

5 - Attack to the electron donor (acid)

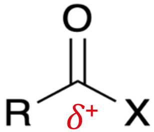
Nucleophilic acyl substitution mechanism



- Carboxylic acid derivatives have potential leaving groups while ketones and aldehydes do not and typically undergo additions rather than substitutions.

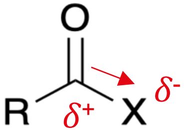
Carboxylic acid derivatives – Reactivity

In all cases, the carbonyl carbon is electrophilic. However, the reactivity of carboxlic acid derivatives depends on the properties of the substituent (X). Think about how “electrophile” (partial positive charge) the carbonyl carbon is.



X = – I	δ^+ increase
X = + I	δ^+ decrease
X = + M	δ^+ strong decrease

Let's start with the easy one: **Induction Effects (+/- I)**



More electronegative X pulls electron density from carbon, thus making the carbonyl carbon more electrophilic (-I Effect) and therefore more reactive. If X is a hydrocarbon chain, it stabilizes the carbonyl carbon with a +I Effect (Remember reactivity Ketone/Aldehyde).

Carboxylic acid derivatives – Reactivity

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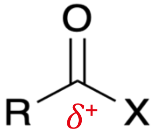
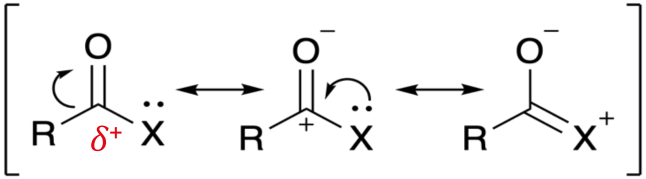
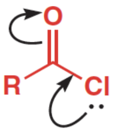


X = – I δ^+ increase
X = + I δ^+ decrease
X = + M δ^+ strong decrease

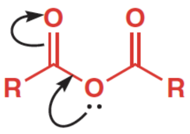
More complex: **Mesomeric Effect (+ M) or Resonance Effect**



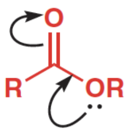
Lone pair of electrons on X atom can resonate to create a C=X double bond and a C-O single bond, stabilizing the carbonyl. The degree of delocalization depends on the electron-donating power of the substituent.



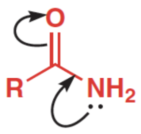
very weak delocalization



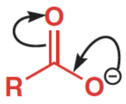
weak delocalization



some delocalization



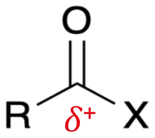
strong delocalization



complete delocalization

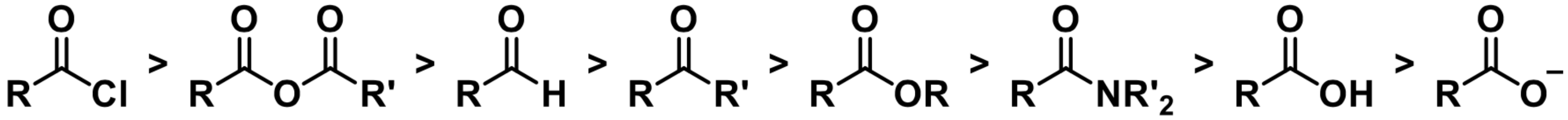
Carboxylic acid derivatives – Reactivity

By combining both Inductive and Resonance Effects, we get an idea about the reactivity of different types of derivatives. Be aware: Effects like steric hindrance can always interfere with these general rules.



Generally, the greater the difference in electronegativity between C and X, the more dominant the inductive effect becomes.

General reactivity:

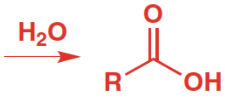


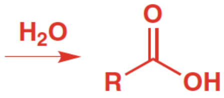
fast at 20 °C

slow at 20 °C

only on heating with acid or base catalyst

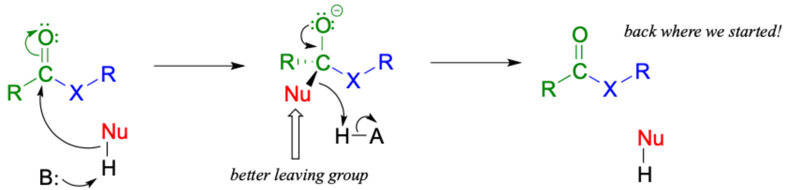
prolonged heating needed with strong acid or base catalyst





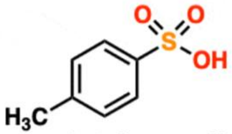
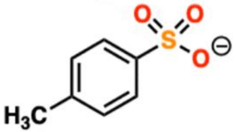
Carboxylic acid derivatives
Understanding Reactivity through the leaving group

-Weaker bases are better leaving groups -> this takes us to pKa values of the conjugated acids



better leaving group

back where we started!

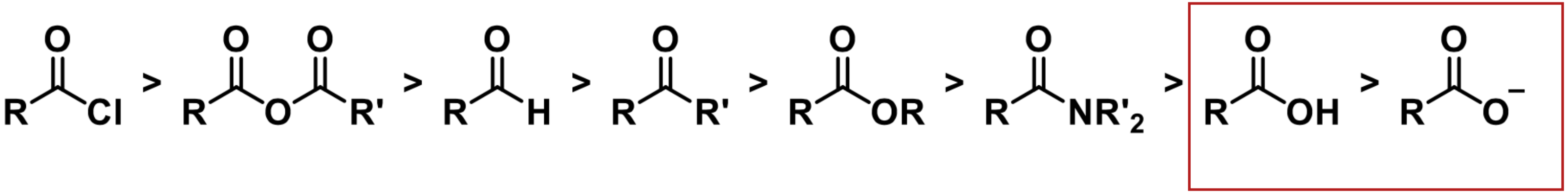
Functional group / Example		pK_a	Conjugate base (Leaving group)
Hydroiodic acid	$H–I$	–9	$I^{\ominus}$
Hydrobromic acid	$H–Br$	–9	$Br^{\ominus}$
Hydrochloric acid	$H–Cl$	–6	$Cl^{\ominus}$
Sulfuric acid	H_2SO_4	–3	$HSO_4^{\ominus}$
Sulfonic acids	 (p-toluenesulfonic acid)	–3	
Hydronium ion	$H_3O^{\oplus}$	0	H_2O

Excellent leaving groups (extremely weak bases)

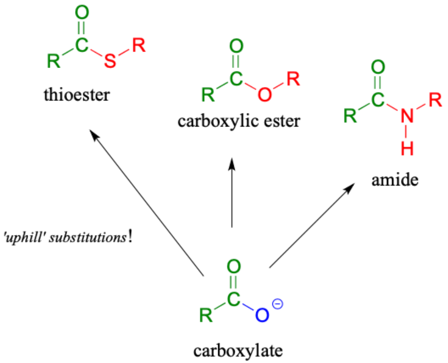
Lets look at a reaction together

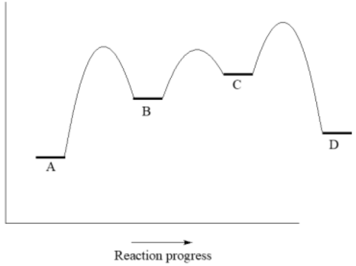
How to deal with non reactive acyl derivatives ?

High reactivity **Low reactivity**

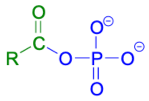


-In biological reactions carboxylates are often converted to thioesters carboxyester and amides

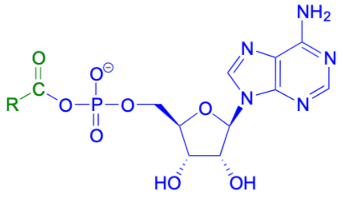




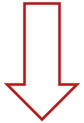
Generate acyl phosphate groups



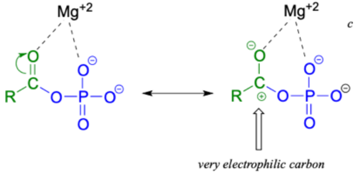
acyl monophosphate



acyl adenosine monophosphate
(acyl AMP)

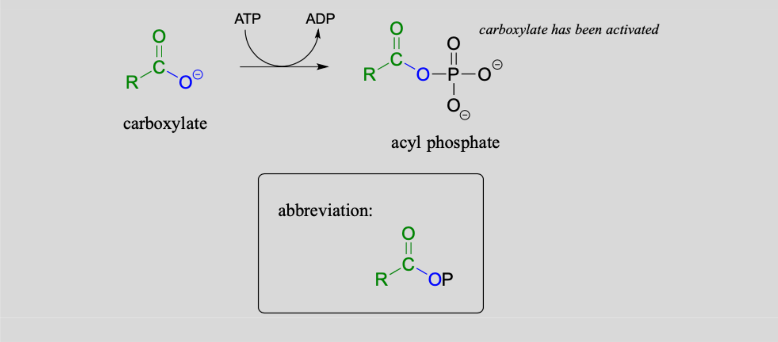


Magnesium and enzymes turn the reactivity up

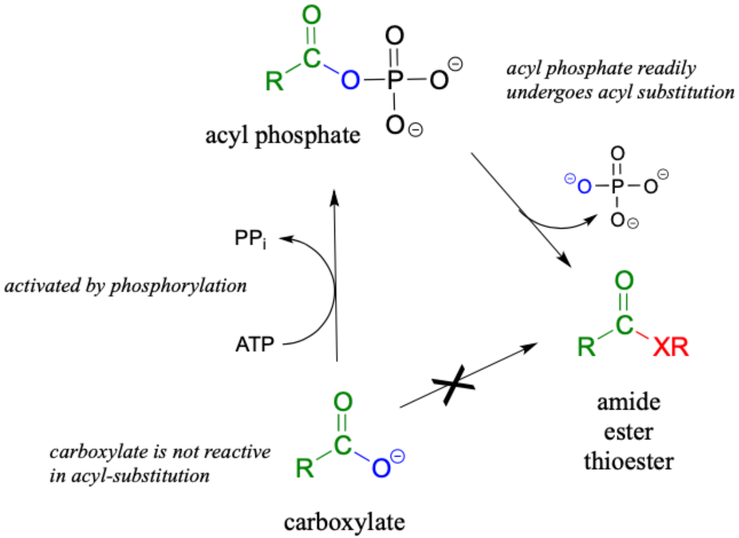


Reactions with phosphate activated acyl groups

Formation of acyl phosphate



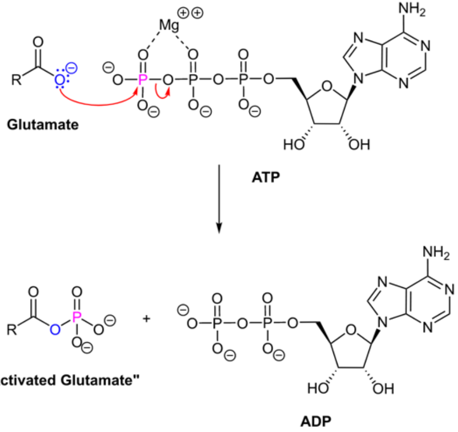
carboxylate has been activated



acyl phosphate readily undergoes acyl substitution

activated by phosphorylation

carboxylate is not reactive in acyl-substitution

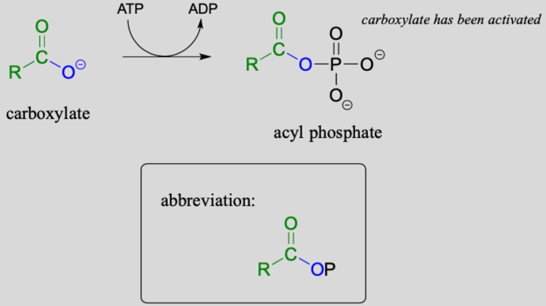


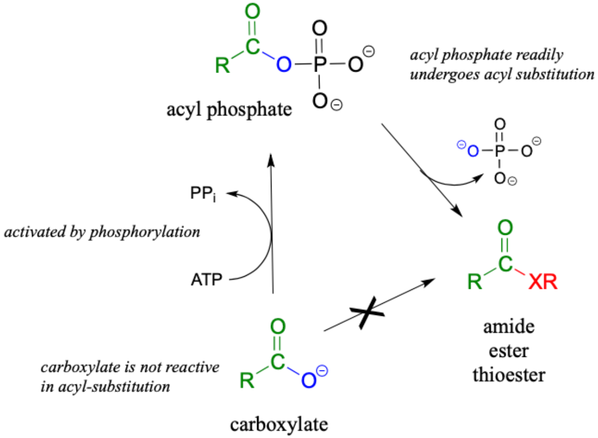
-Phosphorus becomes a good electrophilic center induced by Mg

- O^- is not a good leaving group but can act as a nucleophile

Reactions with phosphate activated acyl groups

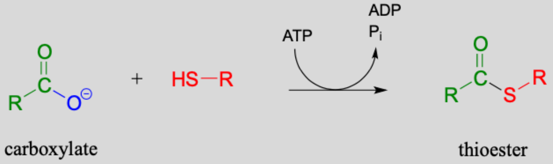
Formation of acyl phosphate





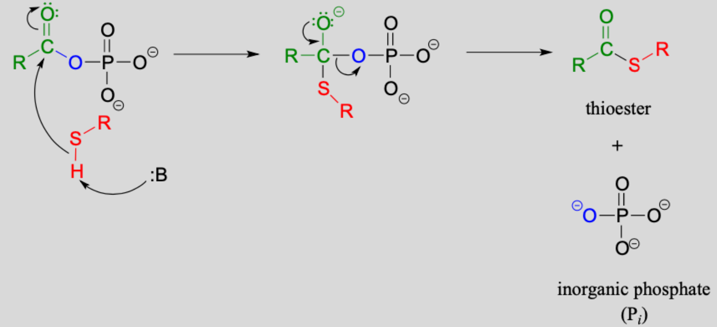
1^{st} step

Thioesterification reaction:



2^{nd} step

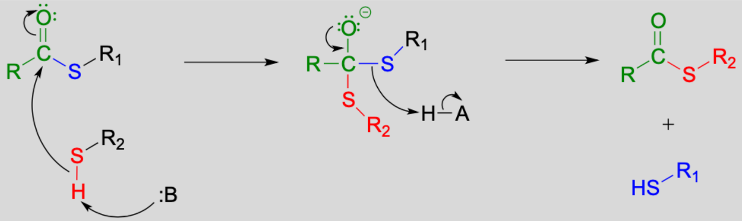
acyl substitution phase:



Many other reactions on carboxyls follow the same patterns

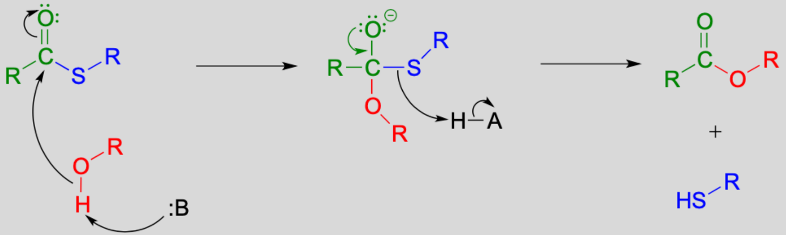
Transthioesterification:

Mechanism:

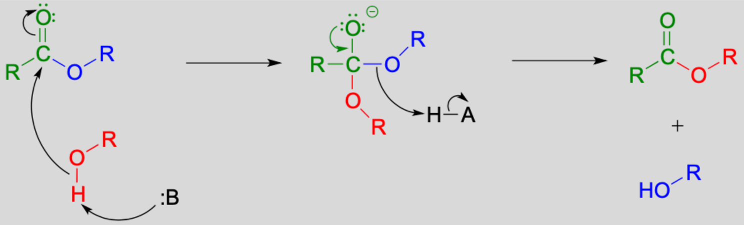


Esterification reaction (from thioester):

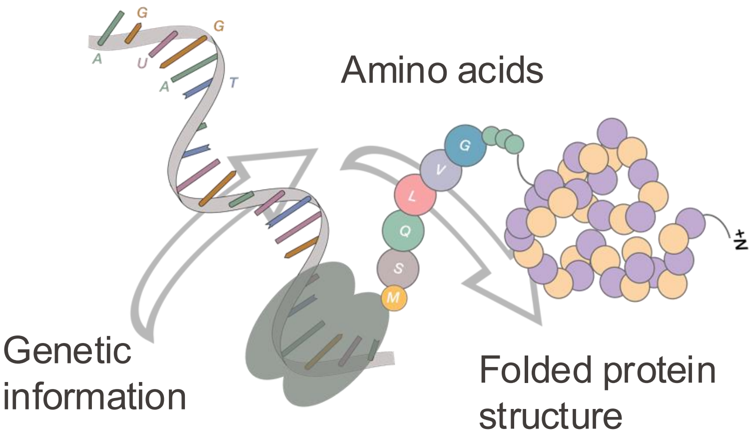
Mechanism:

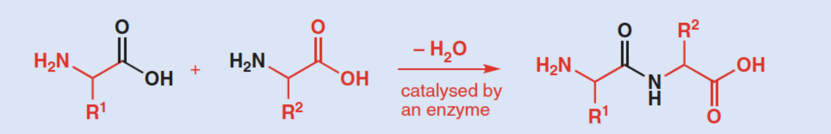


Mechanism for a transesterification reaction:

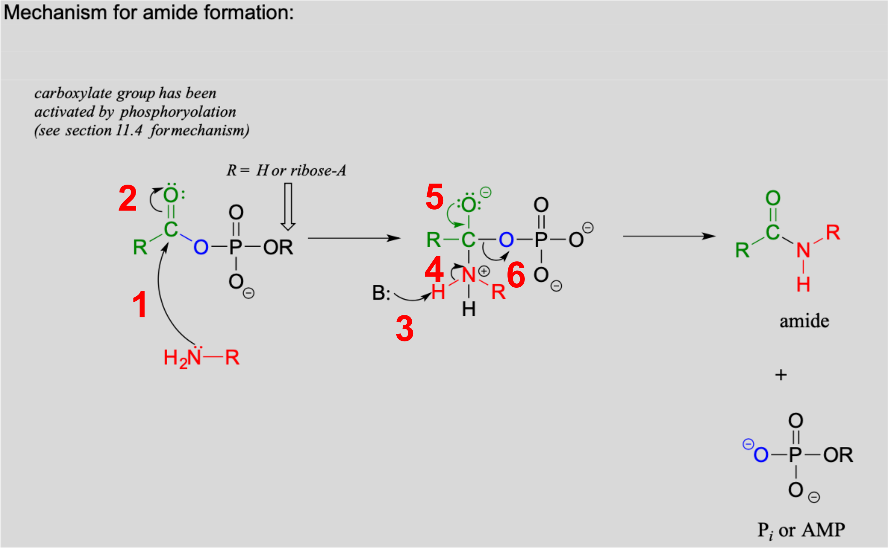


Amide formation from carboxylic acids





two amino acids, joined together by a peptide bond, form a dipeptide



Mechanism for amide formation:

carboxylate group has been activated by phosphoryolation (see section 11.4 formechanism)

1 - Amine attacks the electrophilic carbonyl carbon

2 – Delocalization of electrons

3 – Base attack to the nitrogen proton

4 – Electrons become a nonbonded pair in N

5 – Delocalization of electrons to make a double bond

6 – Bond breakage to release leaving group

Looking at the previous reaction one might ask

What is the difference between a nucleophile and a base ?

Base – any electron rich species that can share/donate lone pairs of electrons

Nucleophile – any electron rich species that can donate lone pairs of electrons

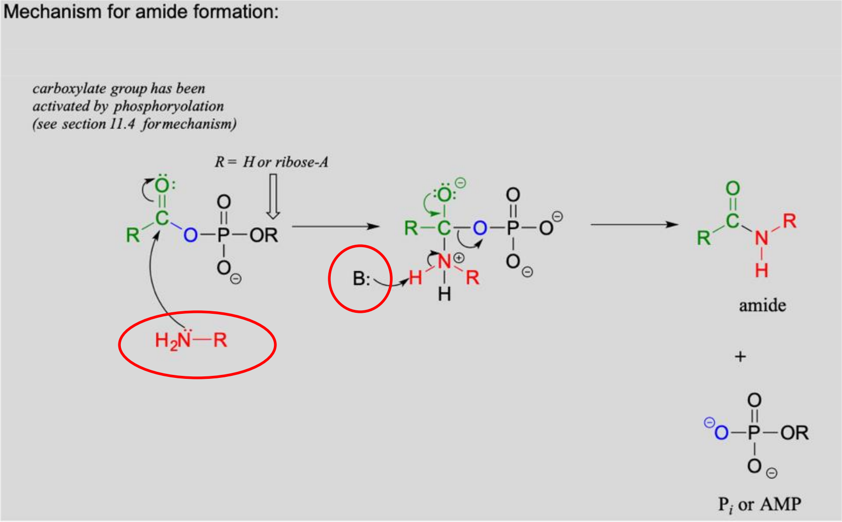
Base

Donates lone pair of electrons to H (abstract hydrogens)

Nucleophile

Donates lone pair of electrons to carbon to make a bond

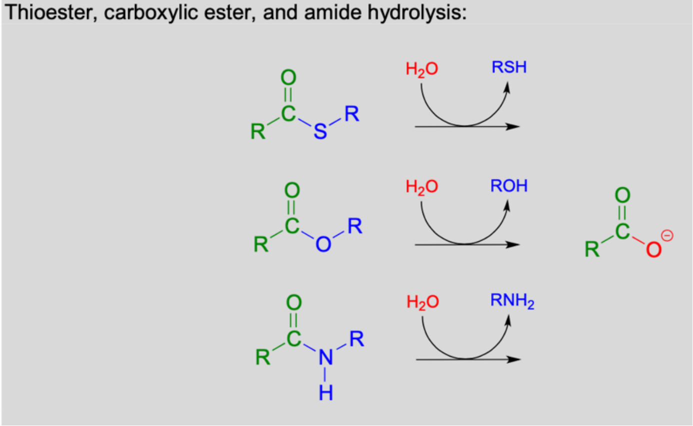
- So it depends on the action they are taken in the reaction


Mechanism for amide formation:

carboxylate group has been activated by phosphoryolation (see section 11.4 formechanism)

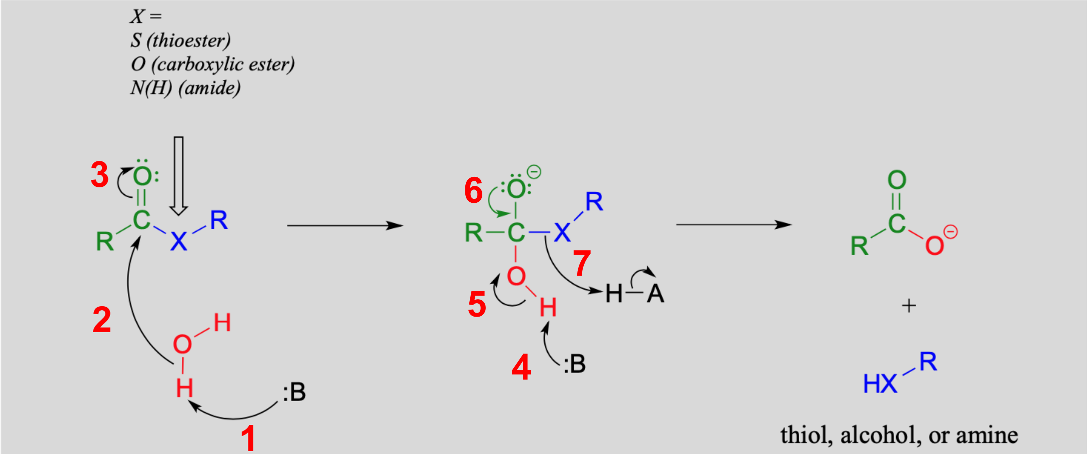
Lets take a look at the reverse reaction – hydrolysis

Overall reaction:



Thioester, carboxylic ester, and amide hydrolysis:

Mechanism:



1 – Base activates water extracting proton generating (OH^-)

2 – Nucleophilic attack of (OH^-) to electrophilic carbon

3 – Delocalization of electrons generating negative oxygen

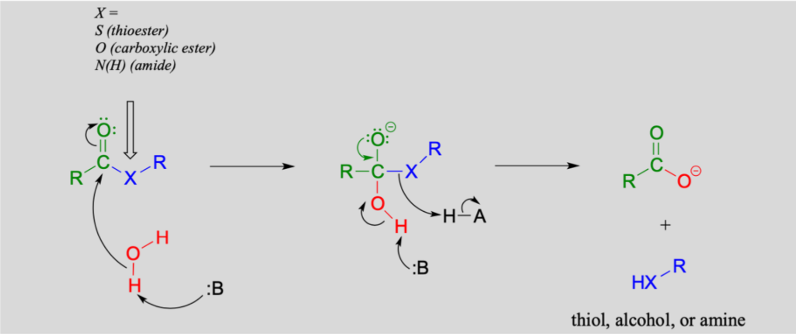
4 – Base extracts proton from the alcohol of the tetrahedral intermediate

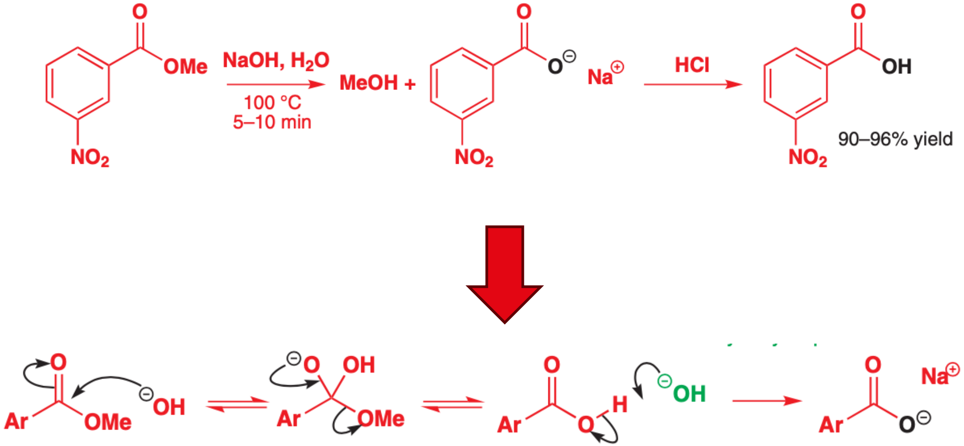
5 – Oxygen takes the electrons staying with a negative charge

6 – Delocalization of electrons for double bond

7 – Electron rich X element attacks an acid or proton donor to form the final species

Different ways of showing the reaction mechanisms for hydrolisys





What to know

-Recognize and draw carboxylic acid derivative functional groups

-Understand and draw the mechanism of nucleophilic acyl substitutions

-Understand and draw other mechanisms such as amide formation

-Reactivity of carboxylic acid derivatives

-Understand the hydrolysis of esters, thioesters, amides

-Activation of acyl groups by phosphate

-The principles to understand the leaving groups

Questions ?