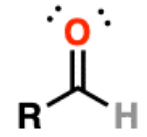
15.05.2025

Carbonyl Reactions

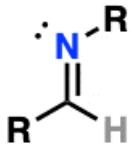
Imine formation

Imines are the nitrogen-containing "cousins" of aldehydes and ketones



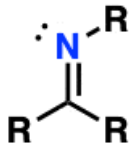
Aldehyde

Ketone



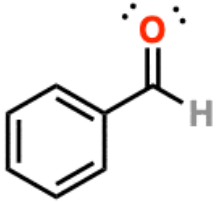
Imine

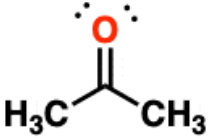
"aldimine"

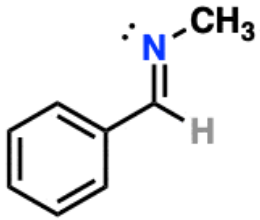


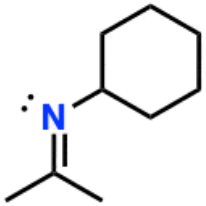
Imine

"ketimine"

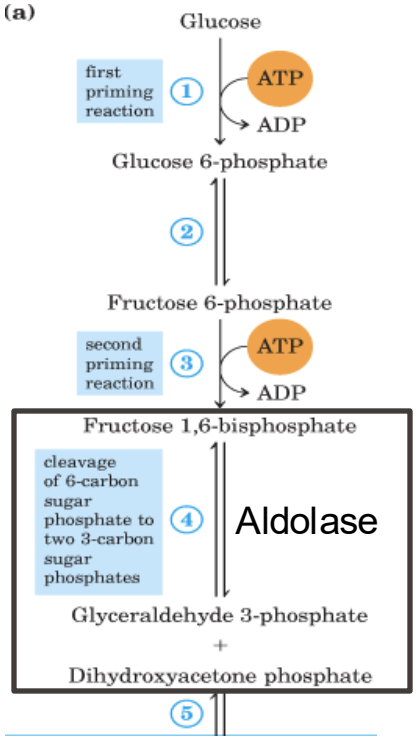








Schiff-Base as common intermediates in enzymatic reactions



Reaction Mechanism

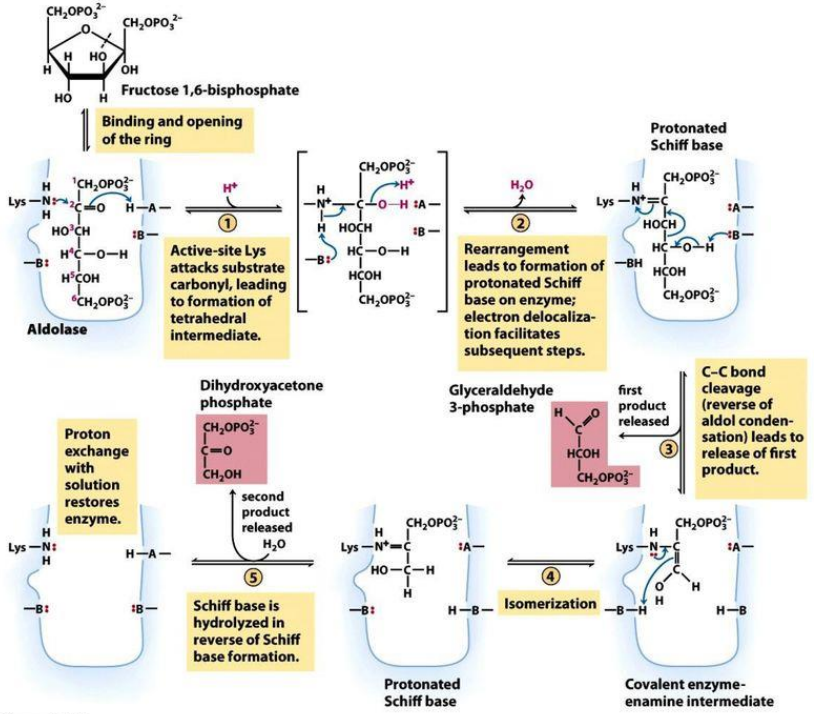
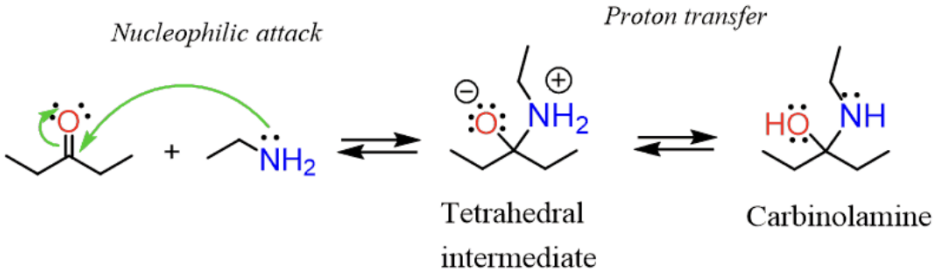


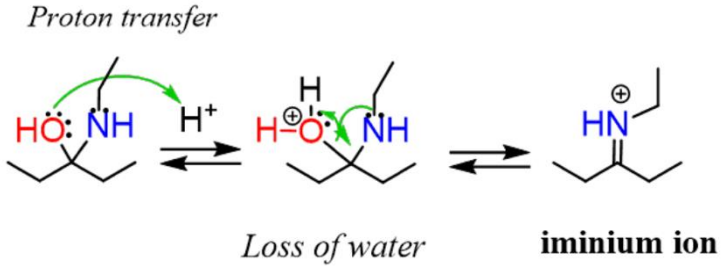
Figure 14-5
Lehninger Principles of Biochemistry, Fifth Edition

Imine formation

A nucleophilic attack of the amine followed by two proton transfer steps produces an unstable intermediate called a **carbinolamine:**

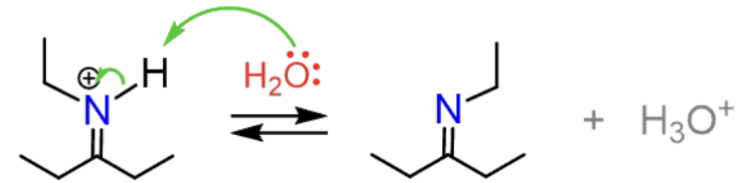


The oxygen of the carbinolamine is then protonated and expelled by the lone pairs of the nitrogen:



Imine formation

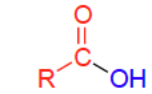
The resulting intermediate (**iminium ion**) is deprotonated to generate an imine as a mixture of (*E*) and (*Z*) isomers when applicable:

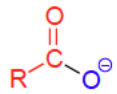


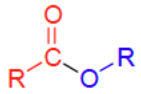
Lab reactions don't need acid catalysis for the **initial nucleophilic attack** because the carbonyl is already electrophilic. But in **enzymes**, acid catalysis is often essential to make the carbonyl more reactive and enable imine (Schiff base) formation efficiently under physiological (aqueous) conditions.

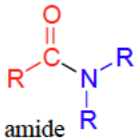
Carboxylic acid derivatives

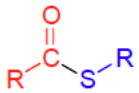
Simple carbonyls, in which the carbon of the C=O bond is attached to **other carbons** or to **hydrogens**
Carboxylic acid derivatives, or **carboxyloids**, in which the carbonyl carbon is attached to a "**heteroatom**"

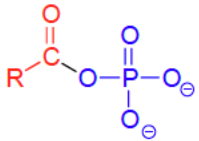

carboxylic acid

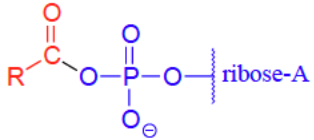

carboxylate


ester

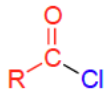

amide

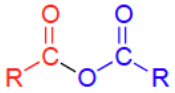

thioester

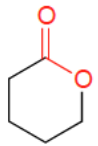

acyl phosphate

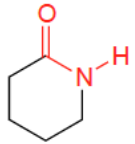


acyl-AMP

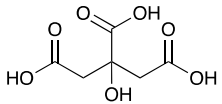

acid chloride

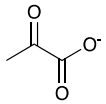

acid anhydride

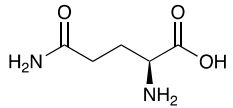

a lactone

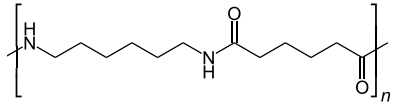

a lactam

Relevant molecules from life sciences


Citric acid


Pyruvate

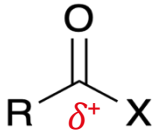

Glutamine


Polyamid 6.6

Original Nylon

Carboxylic acid derivatives – Reactivity

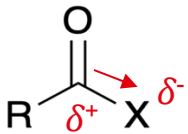
In all cases, the carbonyl carbon is electrophilic. However, the reactivity of carboxlic acid derivatives depends on the properties of the substituent (X). Think about how “electrophile” (partial positive charge) the carbonyl carbon is.



X = – I
X = + I
X = + M

δ^+ increase
δ^+ decrease
δ^+ strong decrease

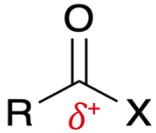
Let's start with the easy one: **Induction Effects (+/- I)**



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

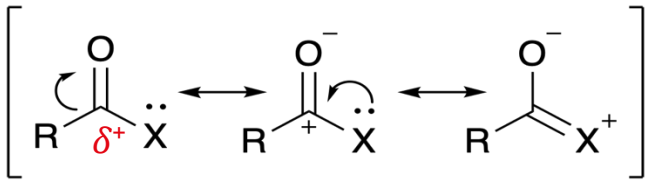
In all cases, the carbonyl carbon is electrophilic. However, the reactivity of carboxlic acid derivatives depends on the properties of the substituent (X). Think about how “electrophile” (partial positive charge) the carbonyl carbon is.



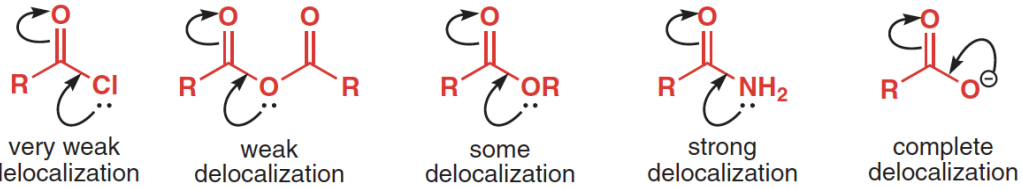
X = – I
X = + I
X = + M

δ^+ increase
δ^+ decrease
δ^+ strong decrease

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

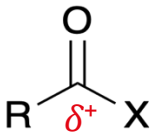


Lone pair of electrons on X atom can resonate to create a C=X double bond and a C-O single bond, stabilizing the carbonyl. The degree of delocalization depends on the electron-donating power of the substituent



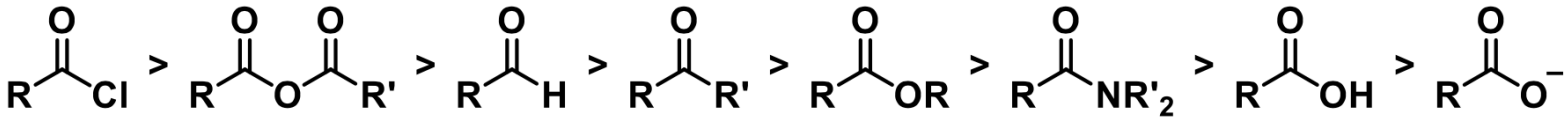
Carboxylic acid derivatives – Reactivity

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.

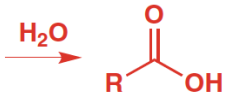
General reactivity:

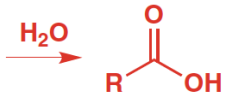


fast at 20 °C slow at 20 °C

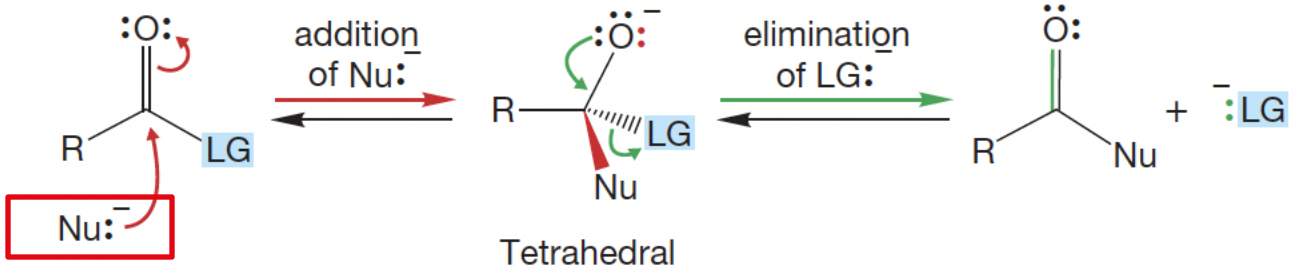
only on heating with acid or base catalyst

prolonged heating needed with strong acid or base catalyst





Substitutions at the carbonyl group



Can be activated by base if needed

Step 1: Nucleophilic attack

A nucleophile (Nu^-) attacks the electrophilic carbon of the carbonyl group (C=O).

The π electrons of the C=O bond shift to the oxygen, forming a negatively charged oxygen (tetrahedral intermediate).

Step 2: Formation of the tetrahedral intermediate

The carbon is now bonded to four groups: the original R group, the nucleophile (Nu), the leaving group (LG), and a negatively charged oxygen.

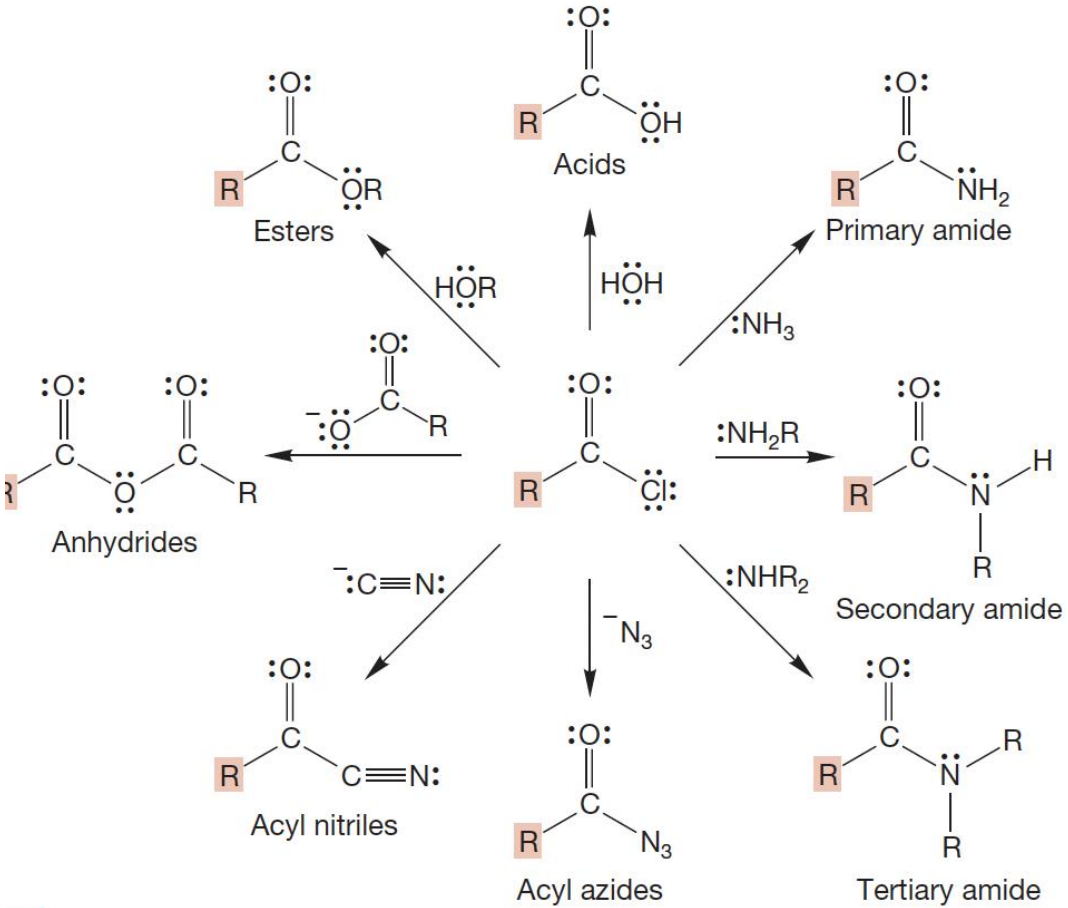
This intermediate is unstable and sets up for elimination.

Step 3: Elimination of the leaving group

The lone pair on the negatively charged oxygen reforms the C=O double bond.

This results in the expulsion of the leaving group (LG^-) from the carbon.

Substitutions at the carbonyl group

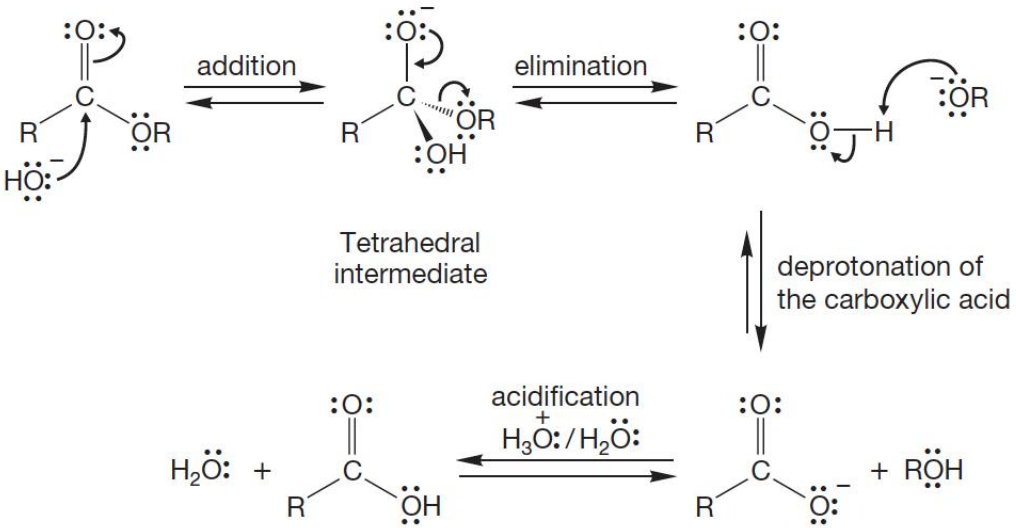


Esters can be hydrolyzed in acidic or basic conditions

Esters are **less reactive** than **acid chlorides** and **acid anhydrides**.
Esters are **more reactive** than **amides**.
Reactivity trends relate to how easily the leaving group can depart and how electrophilic the carbonyl carbon is. Esters undergo **hydrolysis** under either **acidic** or **basic aqueous conditions**. The product of hydrolysis is the **parent carboxylic acid** (after acid work-up in basic conditions).

Saponification

Not catalytic!
OH- is used up



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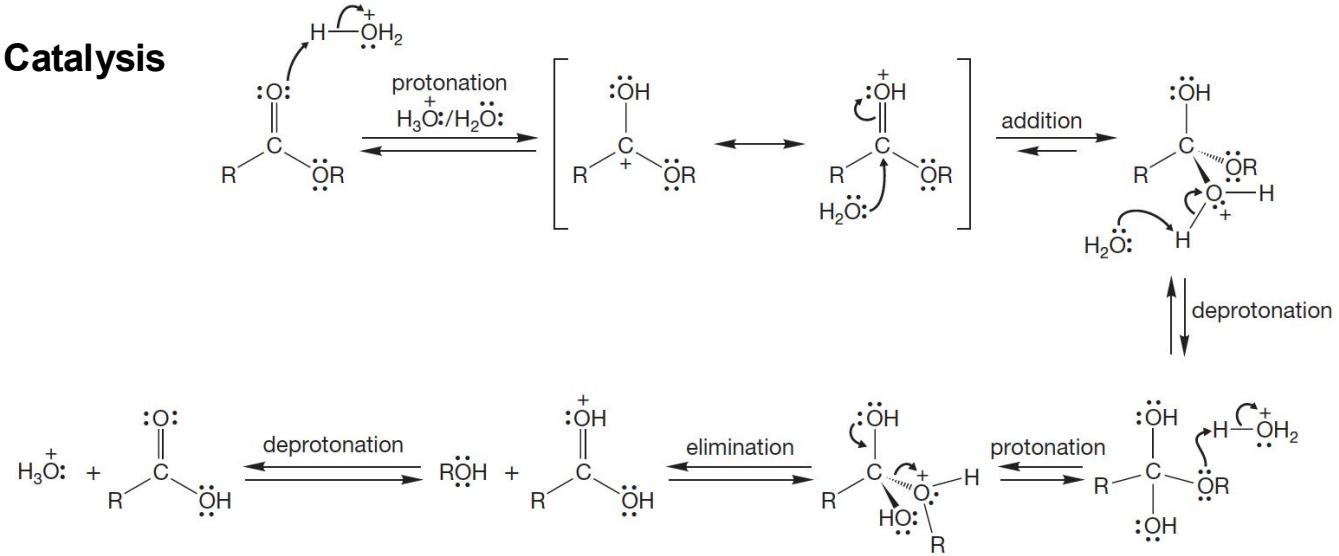
Acidic Catalysis

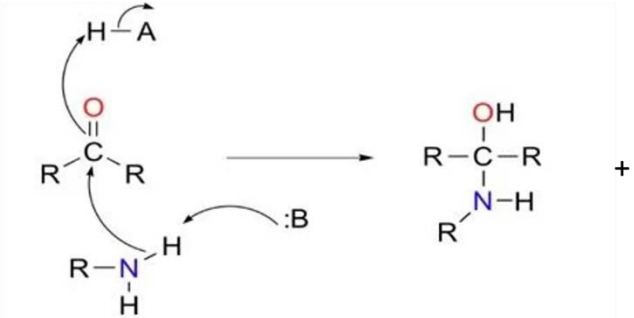


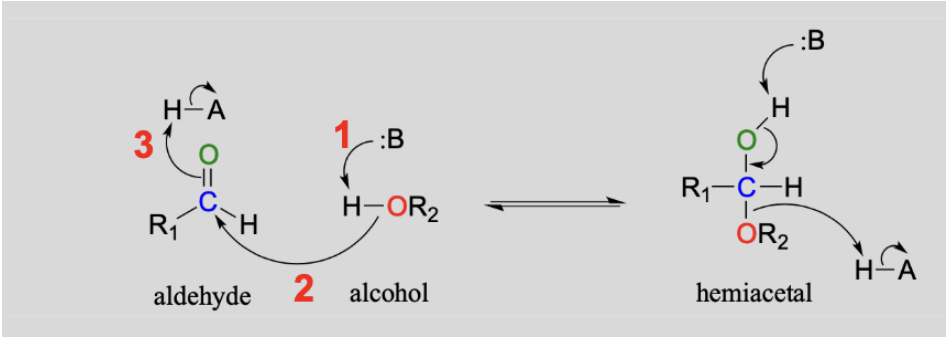
Exercises 10

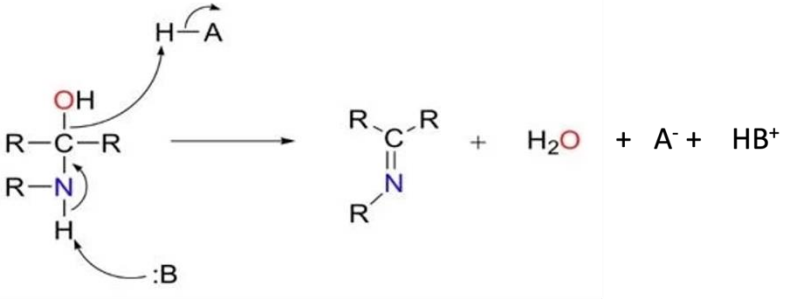
Solutions

10.1 Imine formation

1. Draw the enzymatic mechanism of imine formation.
Which step is different to the formation of acetal/ketals?

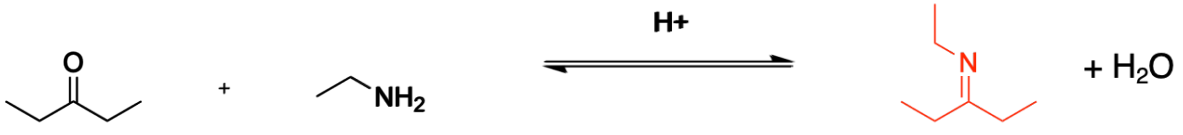


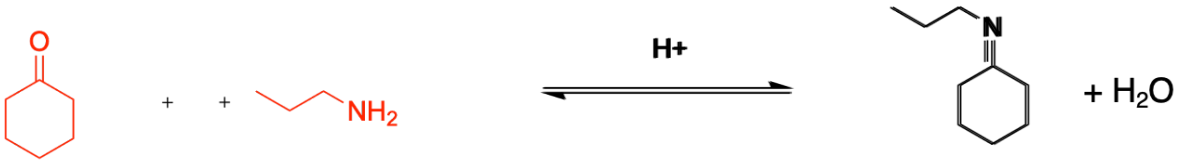


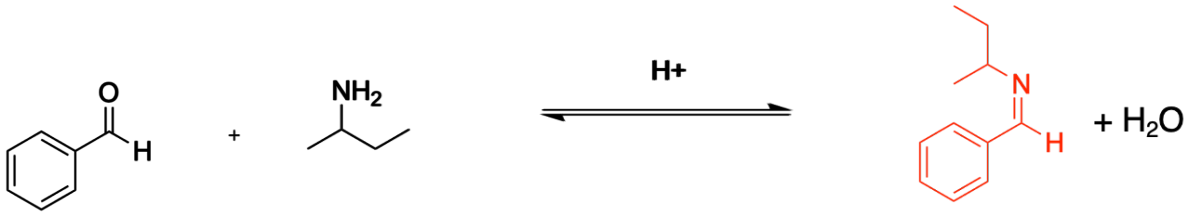


10.1 Imine formation

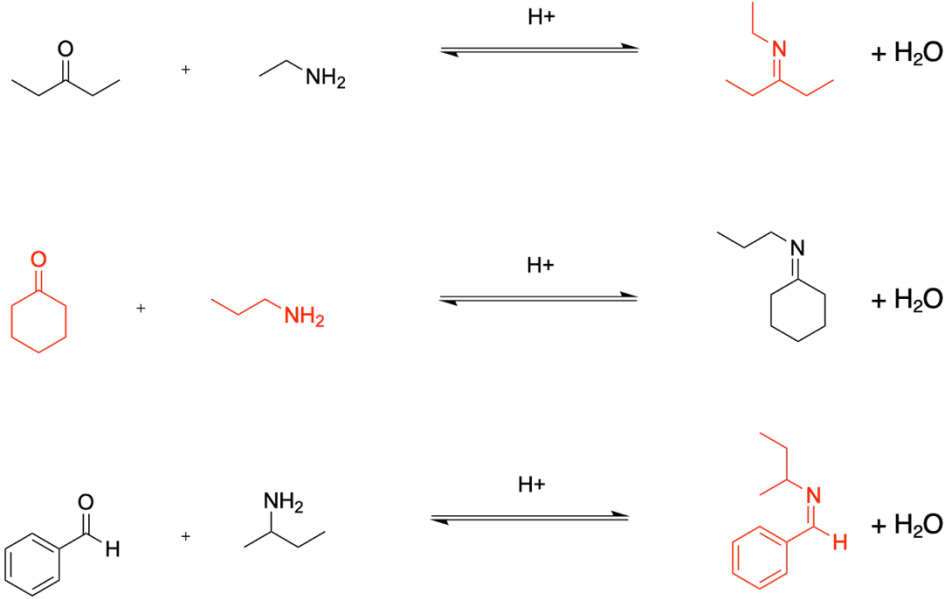
Fill in the blanks in the reactions below. Explain which reaction step requires acid-catalysis during imine formation.

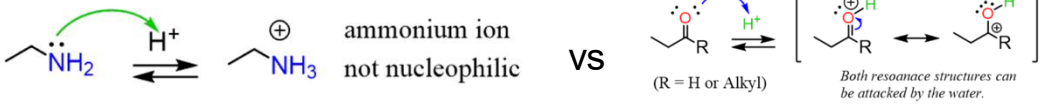




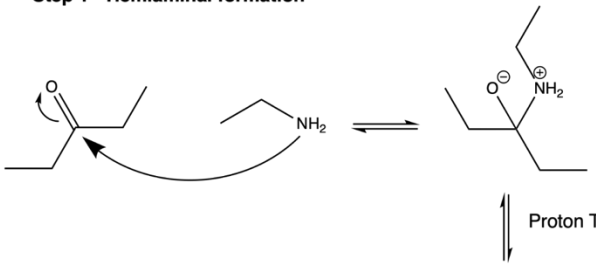


10.1 Imine formation



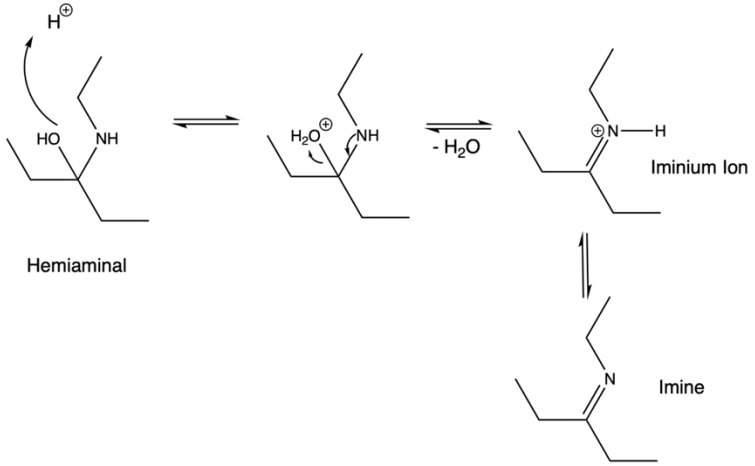


Step 1 - Hemiaminal formation



Hemiaminal

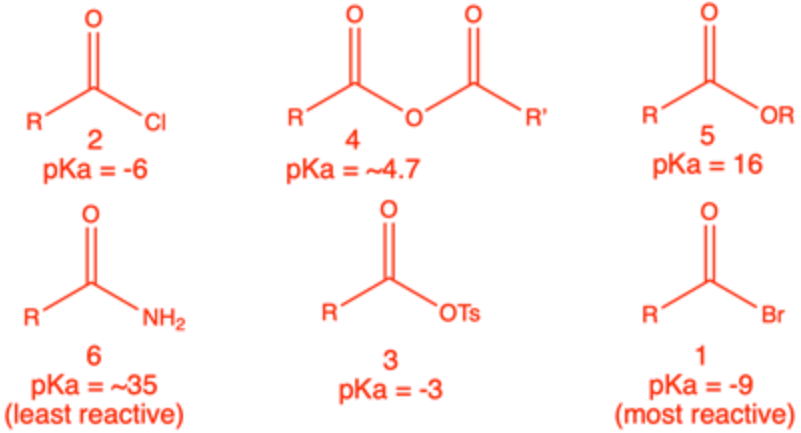
Step 2 - Imine Formation



Hemiaminal

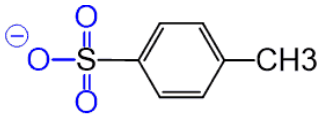
10.2 Nucleophilic acyl substitutions: Reactivity

Rank the following carboxylic acid derivatives by their reactivity with the nucleophile water and hypothesize about the required reaction conditions.

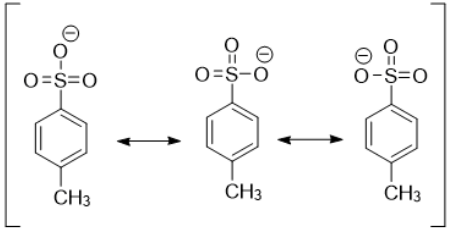


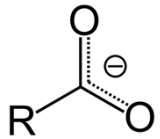
More reactive :
better leaving group – weaker base – stronger acid

Stronger acid – more willing to donate H!
So stable without H!



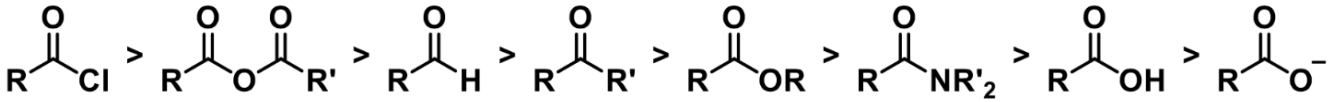
Tosylate





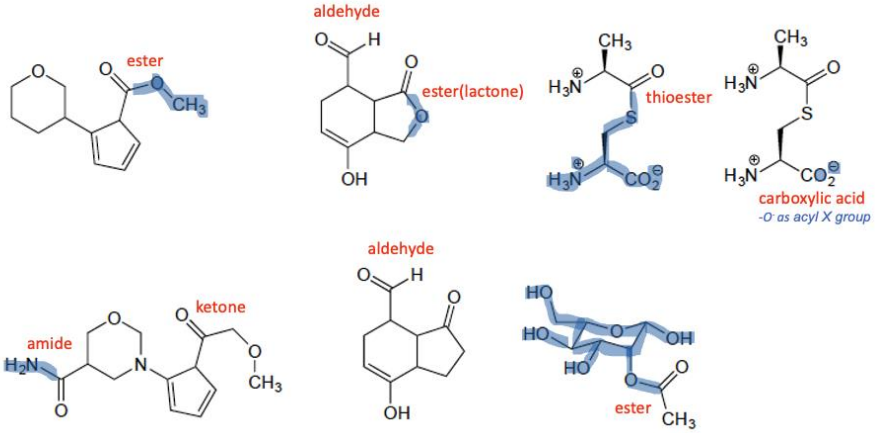
Carboxylate

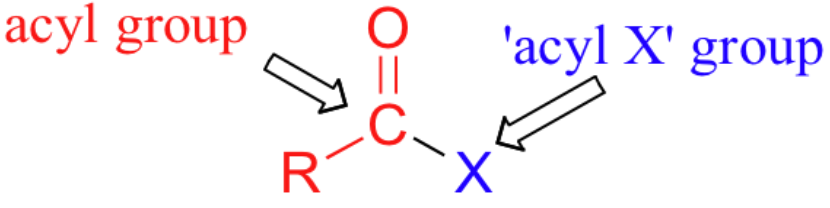
General reactivity:



10.3 Nucleophilic acyl substitutions: Carboxylic acid derivatives

Name all aldehydes, ketones and carboxylic acid derivative groups in the molecules below and indicate which part is the “acyl X group” (the acyl X group corresponds to the leaving group in an acyl substitution).



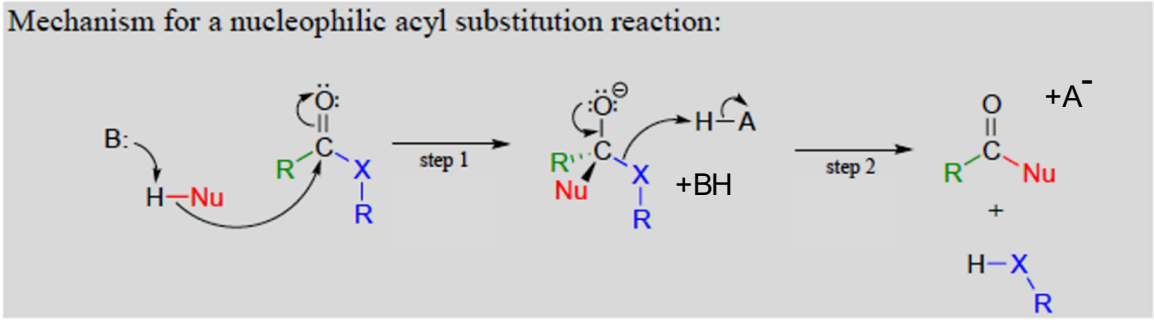


R - alkyl or C containing group

X - heteroatom-containing group

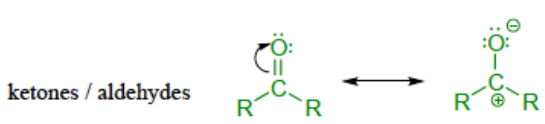
10.4 Nucleophilic acyl substitutions: Carboxylic acid derivatives

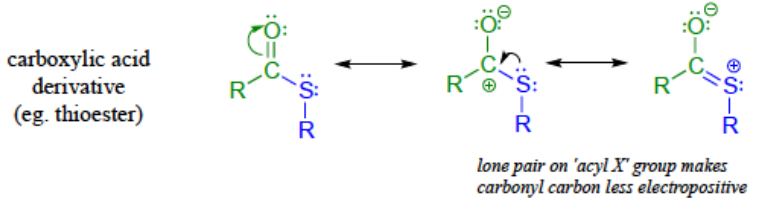
a) Draw the 2 steps of a nucleophilic substitution to a carbonyl. Use arrows to indicate the movement of electrons.



b) The **first mechanistic step** is the same as in nucleophilic additions to carbonyls. Explain why this step is faster for aldehydes and ketones compared to carboxylic acid derivatives.

More stable carbonyl carbon – less reactive – slower the reaction

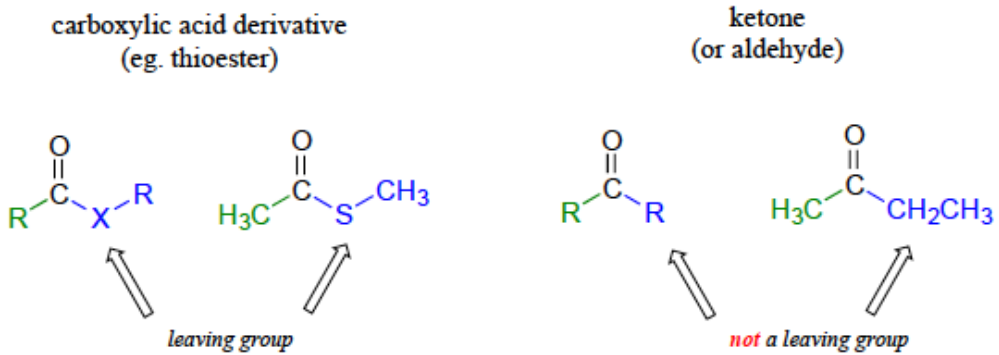




10.4 Nucleophilic acyl substitutions: Carboxylic acid derivatives

Explain why carboxylic acid derivatives undergo nucleophilic acyl substitutions and aldehyde and ketones do not.

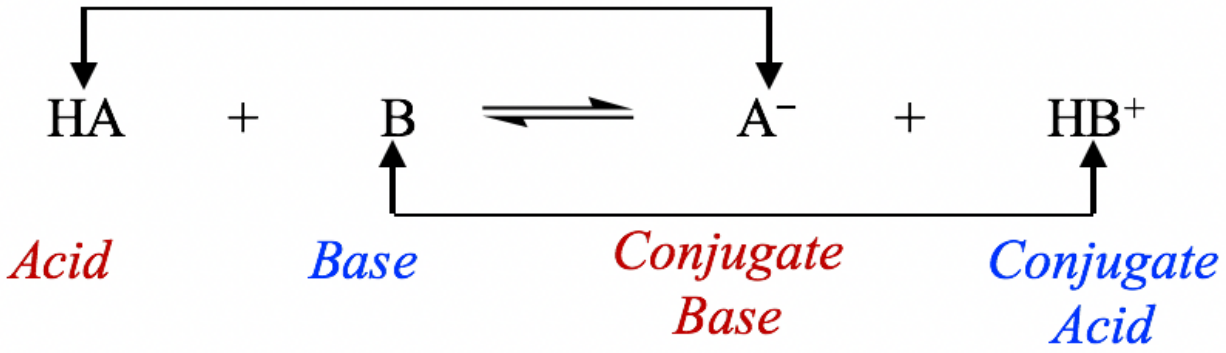
The carbonyl carbon of aldehydes and ketones **do not contain suitable leaving groups (R- or H- are too unstable)**.
Aldehydes and ketones tend to undergo **nucleophilic addition** to form a tetrahedral alkoxide intermediate.



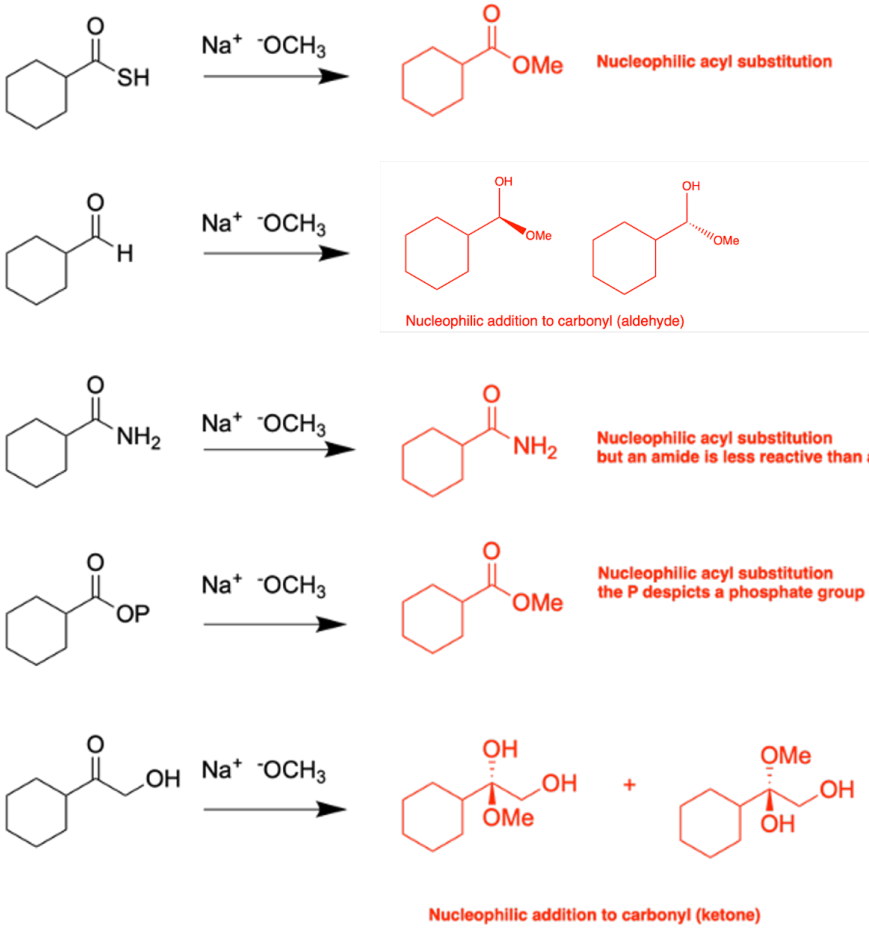
10.4 Nucleophilic acyl substitutions: Carboxylic acid derivatives

Repetition question/Important to understand concept: How does the strength of a leaving group (Y) correspond to the stability of the negative charge, basicity and the pKa of its corresponding conjugate acid (HY)?

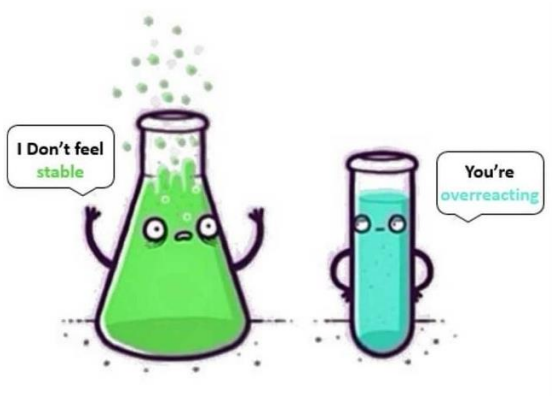
The better the negative charge is stabilized on the leaving group, the weaker it is as a base (A-), the lower is the pKa of its corresponding conjugate acid (HA).



10.5 Draw the products of following reactions

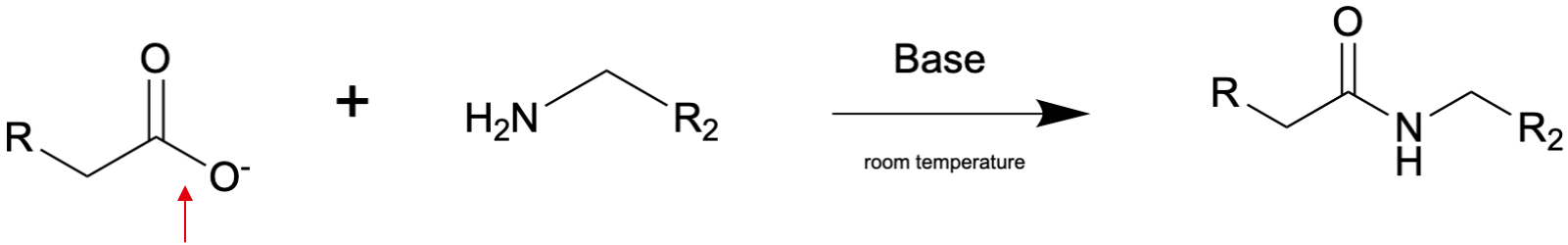


It is possible to convert a reactive acid derivative to a less reactive acid derivative, but not the other way round.



10.6 Activation of Carboxylic acid derivatives

a) Why does the following reaction not happen spontaneously?



carboxylate - highly unreactive carboxylic acid derivative

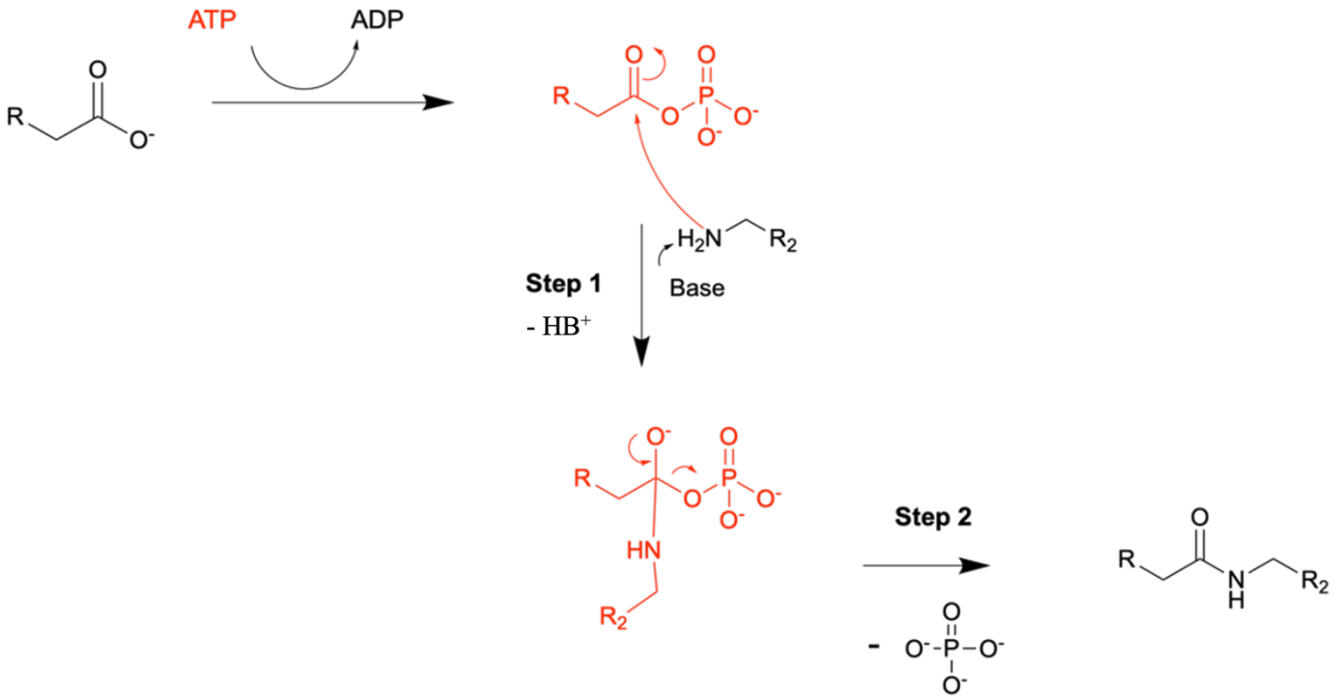
O-, is no leaving group, as the additional negative charge would be very badly stabilized). Formation of an amide bond would therefore require energy (uphill reaction).

b) How, then, does a living system accomplish a reaction such as the one shown above? To what other, highly reactive carboxylic acid derivative are carboxylates mostly converted to in biological systems in order to become activated?

Needed a linked reaction which 'gives' energy - hydrolysis of ATP.
Enzymes activate the carboxylate by converting it to an **acyl phosphate,** while ATP gets converted to ADP

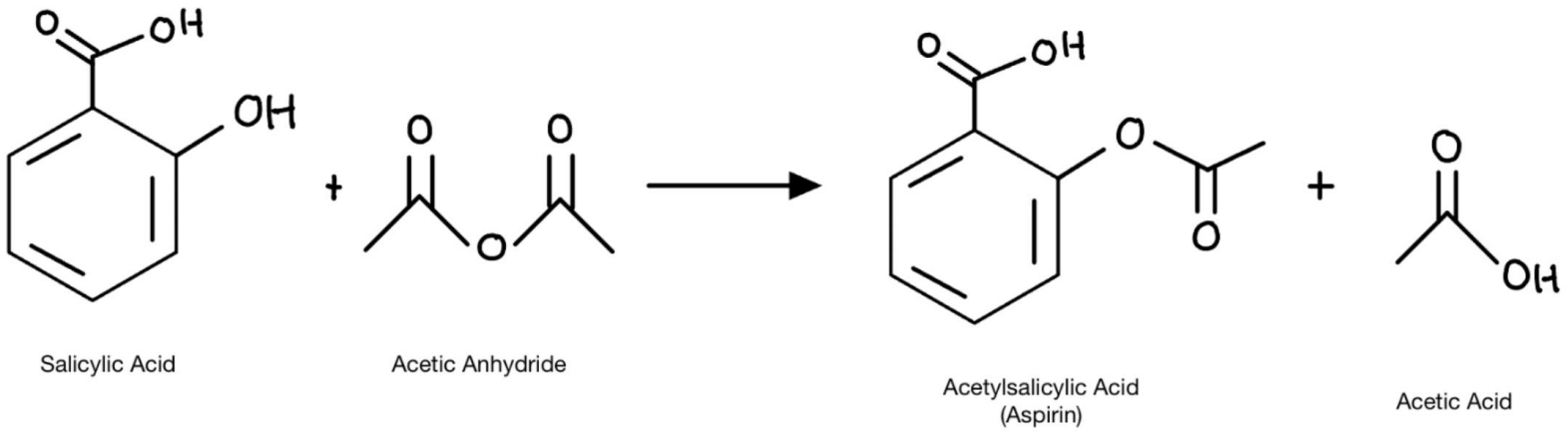
10.6 Activation of Carboxylic acid derivatives

c) Fill in the blank in following reaction scheme



10.7 Aspirin Synthesis

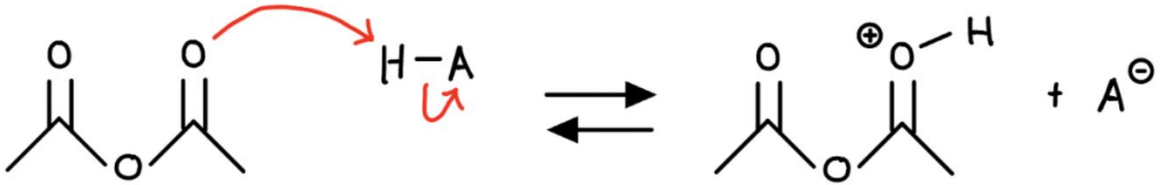
The commercial preparation of Aspirin involves the following reaction of a benzene derivative with an anhydride. Draw a complete mechanism for this reaction:



10.7 Aspirin Synthesis

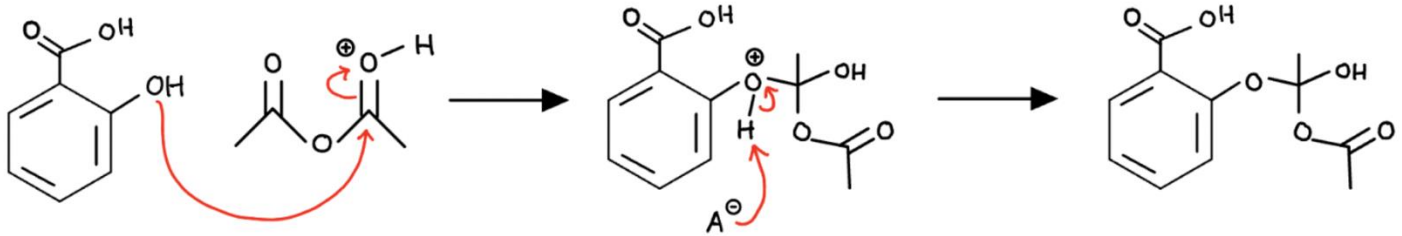
The commercial preparation of Aspirin involves the following reaction of a benzene derivative with an anhydride. Draw a complete mechanism for this reaction:

1. Activation of Acetic Anhydride: Acetic anhydride is activated in the presence of an acid catalyst, protonating the carbonyl oxygen and making it more electrophilic.



Acetic Anhydride

2. Nucleophilic attack by Salicylic Acid: the hydroxyl group on the benzene of salicylic acid acts as a nucleophile and attacks the electrophilic carbon of the acetic anhydride. This forms a tetrahedral intermediate

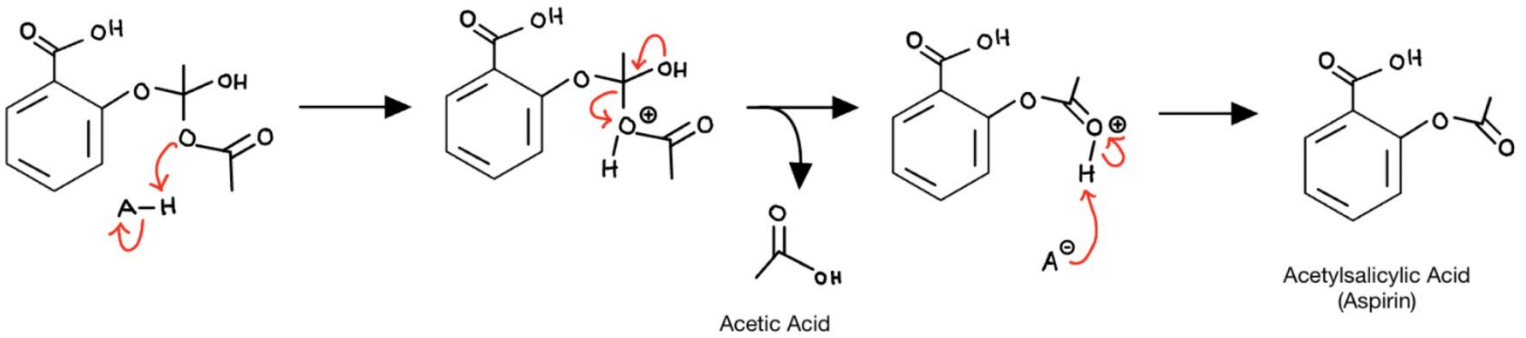


Salicylic Acid

10.7 Aspirin Synthesis

The commercial preparation of Aspirin involves the following reaction of a benzene derivative with an anhydride. Draw a complete mechanism for this reaction:

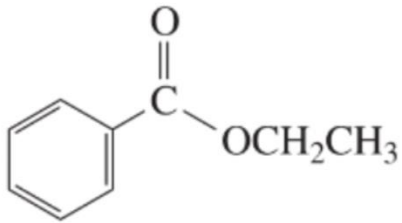
3. Formation of Acetylsalicylic acid: the tetrahedral intermediate collapses expelling acetic acid as a leaving group and forming aspirin.

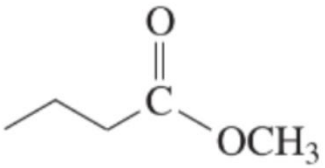


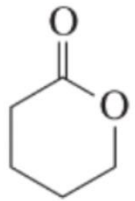
10.8 Ester Hydrolysis

You have learned about ester hydrolysis under basic conditons. Try to reason from your previous experience of how acids react with carbonyl groups how hydrolysis works under acidic conditions.

a) What products are formed from an acid-catalyzed hydrolysis of the following esters.

a. 

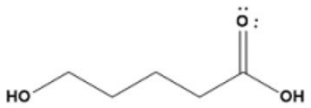
b. 

c. 

Hydrolysis products:

a.
Benzoic acid (C_6H_5COOH)
Ethanol (CH_3CH_2OH)

b.
Butanoic acid ($CH_3CH_2CH_2COOH$)
Methanol (CH_3OH)

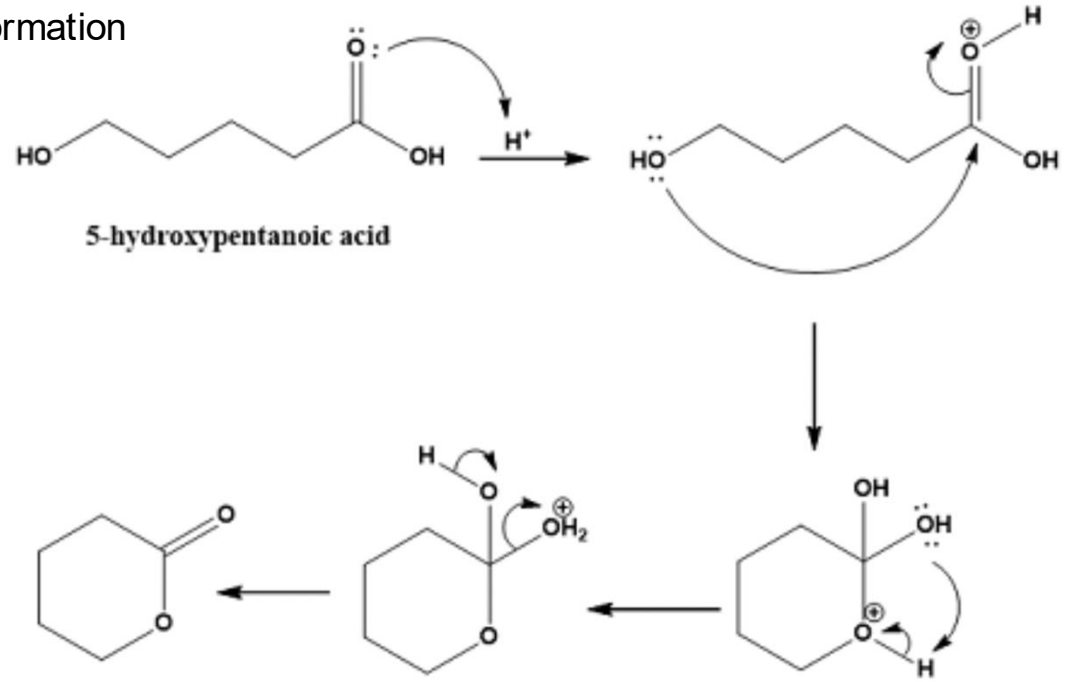
c. 

5-hydroxypentanoic acid

10.8 Ester Hydrolysis

a) Show the mechanism of the ester-hydrolysis under acidic conditions for c.

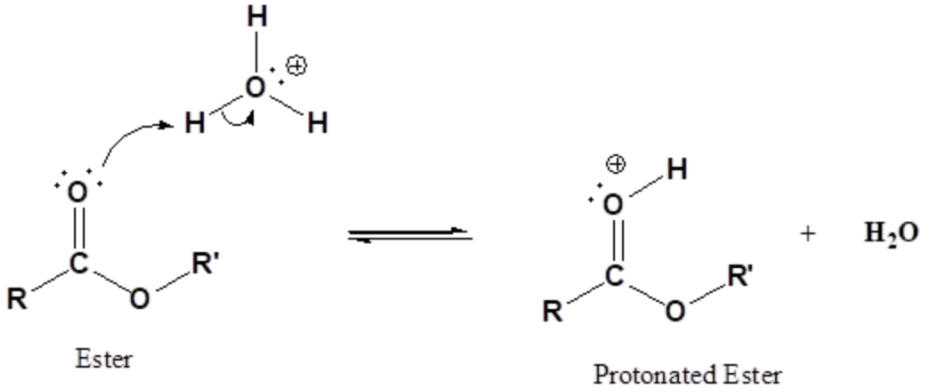
Ester Formation



10.8 Ester Hydrolysis

Ester Hydrolysis (reverse ester formation)

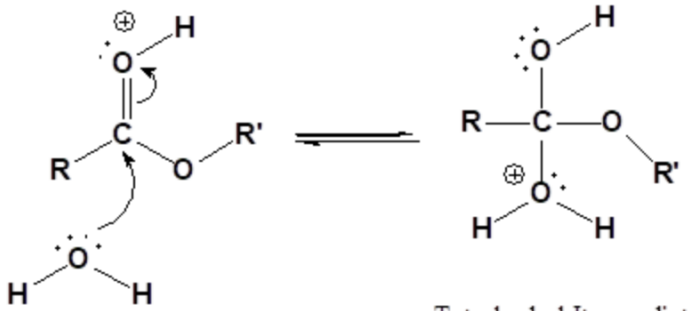
1) Protonation of the carbonyl



Ester

Protonated Ester

2) Nucleophilic attack by water

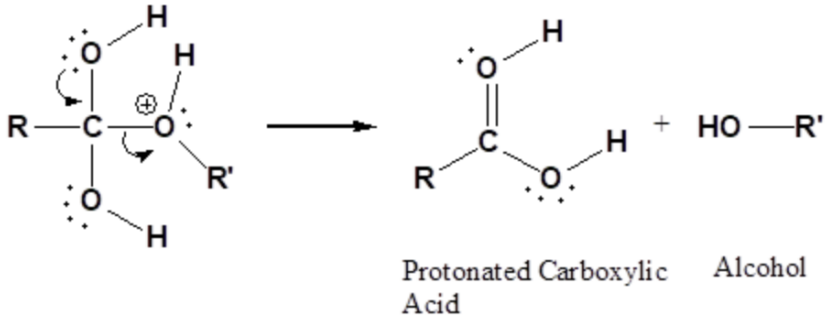


Tetrahedral Itermediate

10.8 Ester Hydrolysis

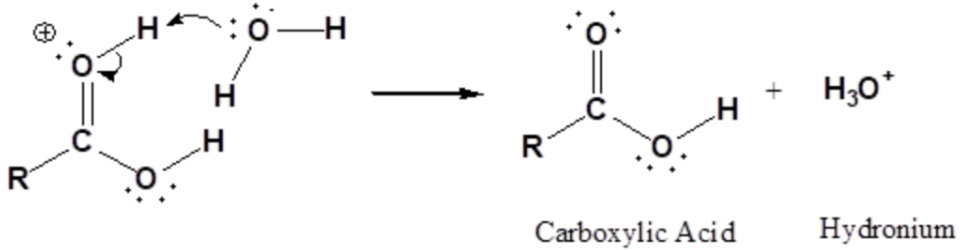
3) Proton transfer

4) Leaving group removal



10.8 Ester Hydrolysis

5) Deprotonation




Questions?