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Preparation of Acetylsalicylic acid

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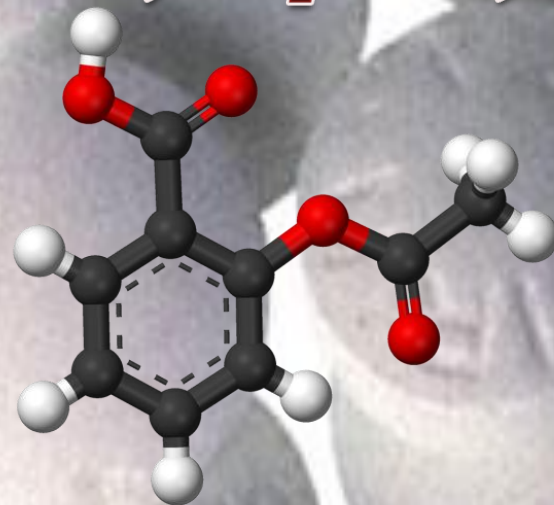
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Ali Basim

Properties of Acetylsalicylic acid, Aspirin,

1- Aspirin occurs as white crystals or as a white crystalline powder.

2- It is slightly soluble in water (1:300), soluble in alcohol (1 :5), chloroform (1:17) & ether (1:15). It dissolves easily in glycerin.



Molar mass 180.15 g/mol

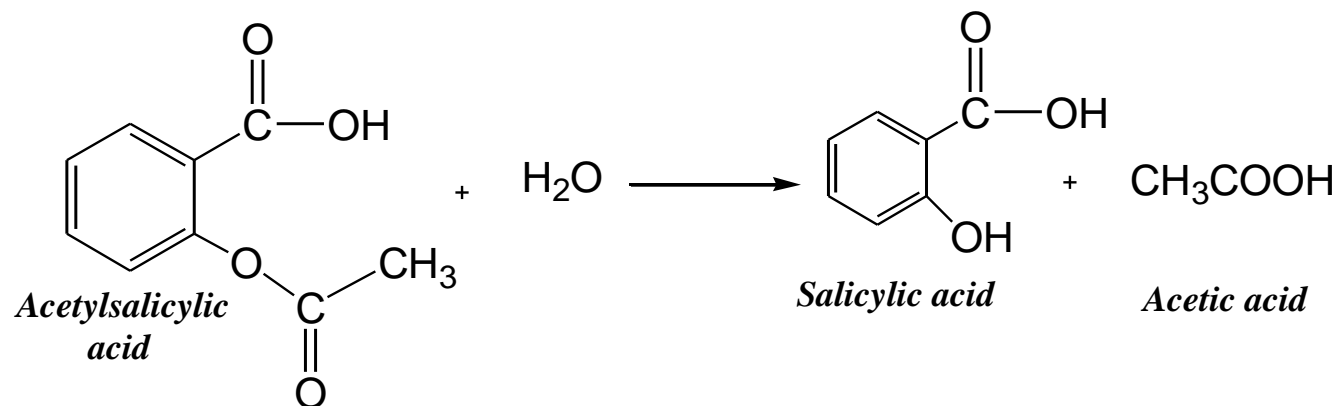
Melting point 135 °C

3- Practically all salts of aspirin (soluble in aqueous media) , except those of aluminum and calcium (insoluble in aqueous media), are unstable for pharmaceutical use.

4- Aspirin gives No color with FeCl_3 solution.

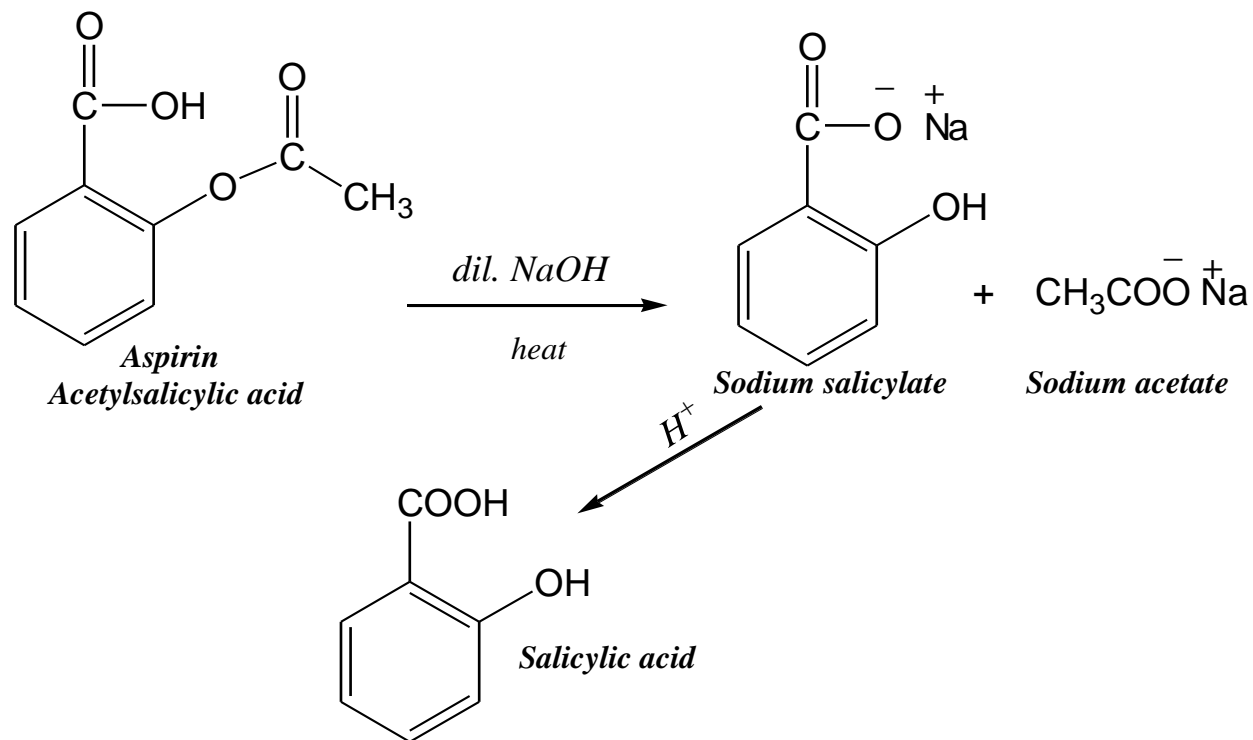
5- It's used as antipyretic, analgesic & antirheumatic in tablets, suppositories, vials, ...etc. dosage form.

6- Aspirin is stable in dry air, but in the presence of moisture, it slowly hydrolyzes into **acetic acid** and **salicylic acid**.



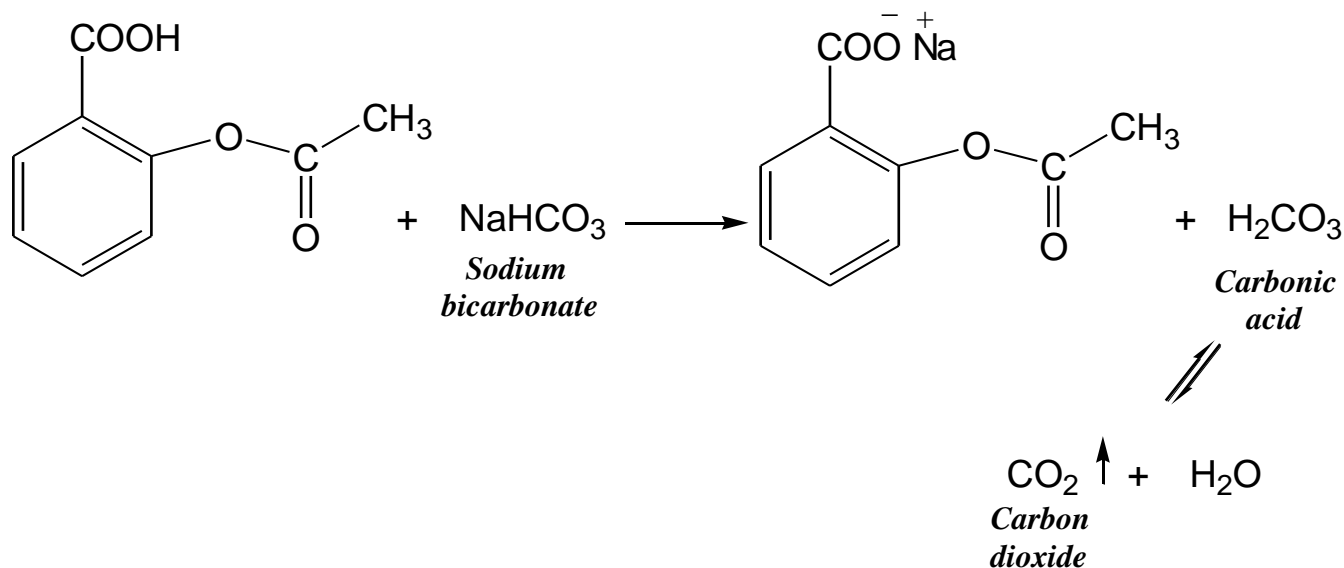
So old aspirin tablets may have a smell like vinegar as a result of the hydrolysis reaction that produces acetic acid (Ethanoic acid).

7- Salicylic acid will crystallize out when an aqueous solution of aspirin and NaOH is boiled and then acidified.



So , Aspirin decomposes in the presence of alkaline hydroxides & carbonates.

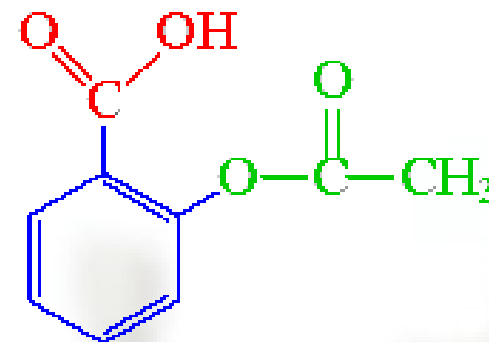
8- Aspirin itself is acidic enough to produce effervescence with carbonates.



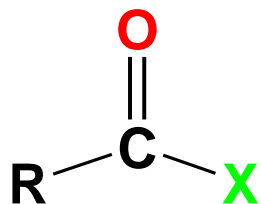
Acetylsalicylic acid:

Aspirin contains three groups:

- Carboxylic acid functional group (R-COOH)
- Ester functional group (R-O-CO-R')
- Aromatic group (benzene ring)

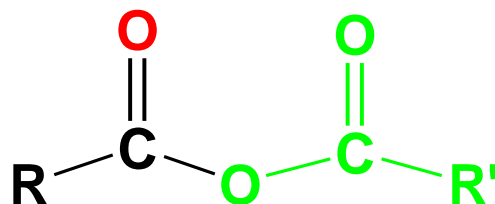


Carboxylic acid derivatives:

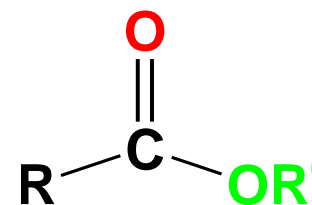


Acid halide

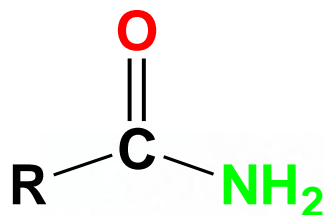
$\text{X}=\text{Cl}, \text{Br}$



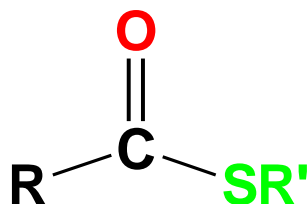
Acid anhydride



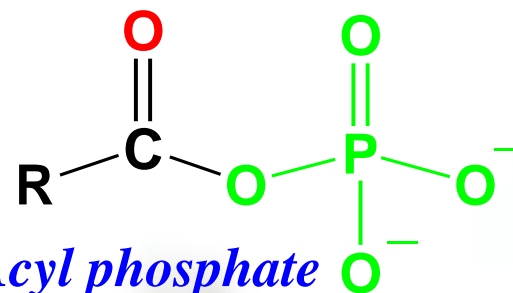
Ester



Amide



Thioester



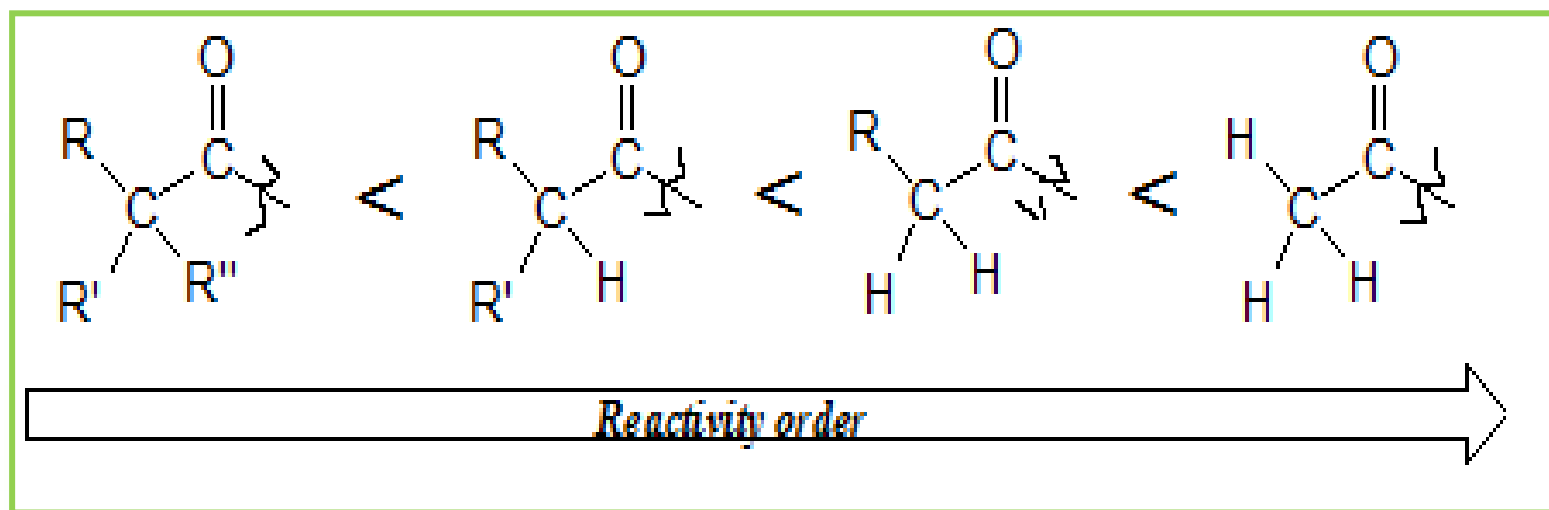
Acyl phosphate

Relative reactivity of carboxylic acid derivatives:
Steric and **electronic** factors are both important in determining reactivity.

Sterically,

Within series of similar acid derivatives that unhindered, accessible carbonyl groups react with nucleophiles more readily than do sterically hindered groups.

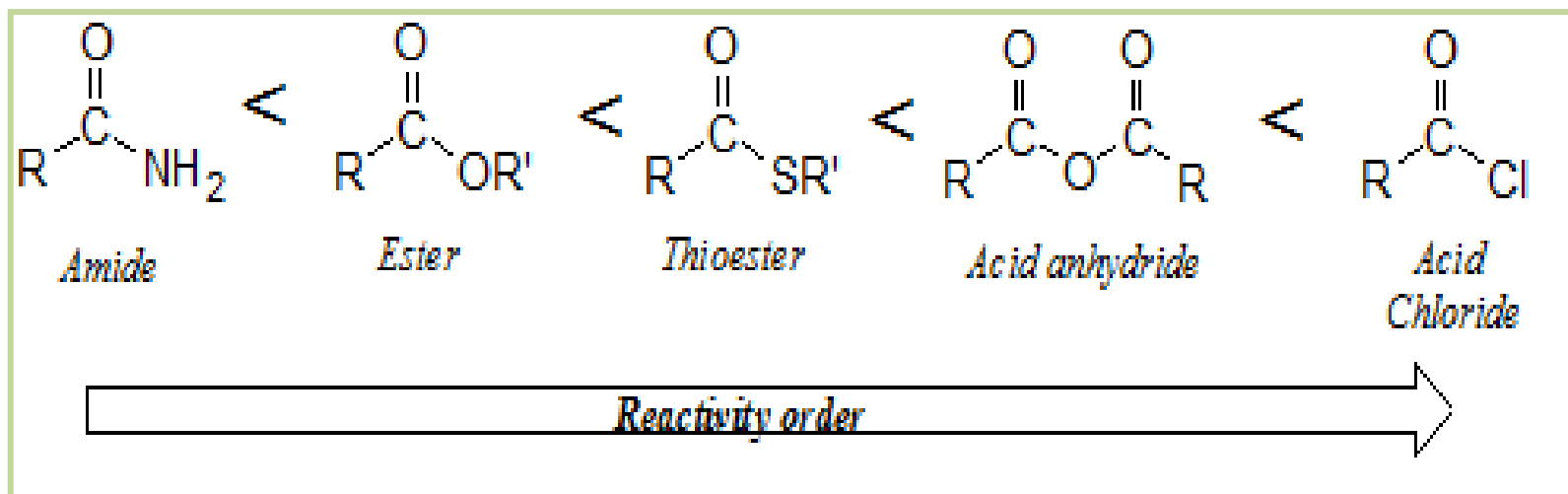
The reactivity order is;



Electronically,

strongly polarized acyl compounds react more readily than less polar ones.

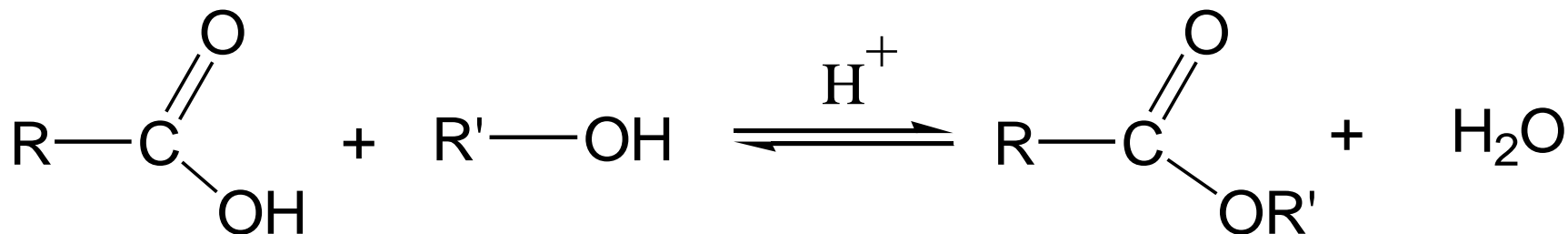
Thus, acid chlorides are the most reactive because the electronegative chlorine atom withdraws electrons from the carbonyl carbon, whereas amides are the least reactive.



PREPARATION OF ESTER:

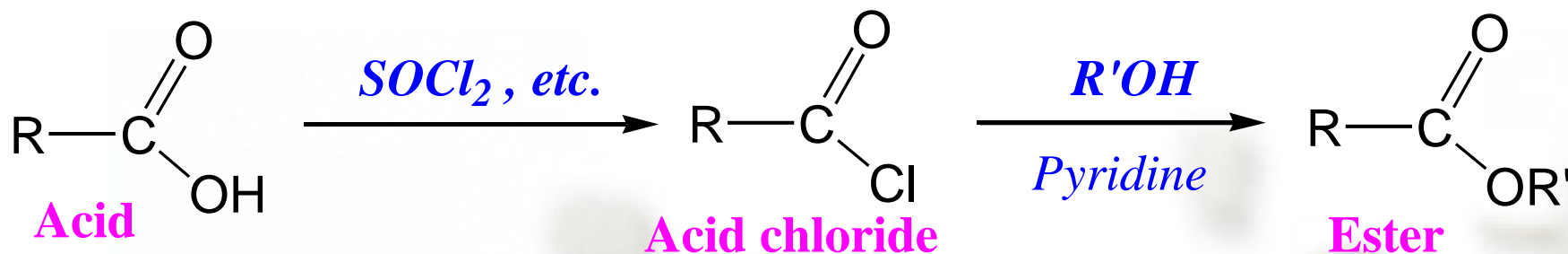
1- Direct esterification procedure:

The interaction between a carboxylic acid & an alcohol is: **(a) Reversible.** **(b) Proceeds very slowly.**



2- Esterification using acid chlorides:

Acid chlorides reacts readily with primary & secondary alcohols to give esters in **very good yields**.



The reaction is fast but it's **not safe** and it **produces HCl gas** so **pyridine** should be used as a base to pick up a proton (H^+) and gives **pyridinium chloride**.

Pyridine is teratogenic and air pollutant.

3- Esterification using acid anhydrides:

Esterification can be carried out with acid anhydrides in the presence of a suitable catalyst either an acidic catalyst such as sulphuric acid, or a basic catalyst.

- The order of acetylating power:***

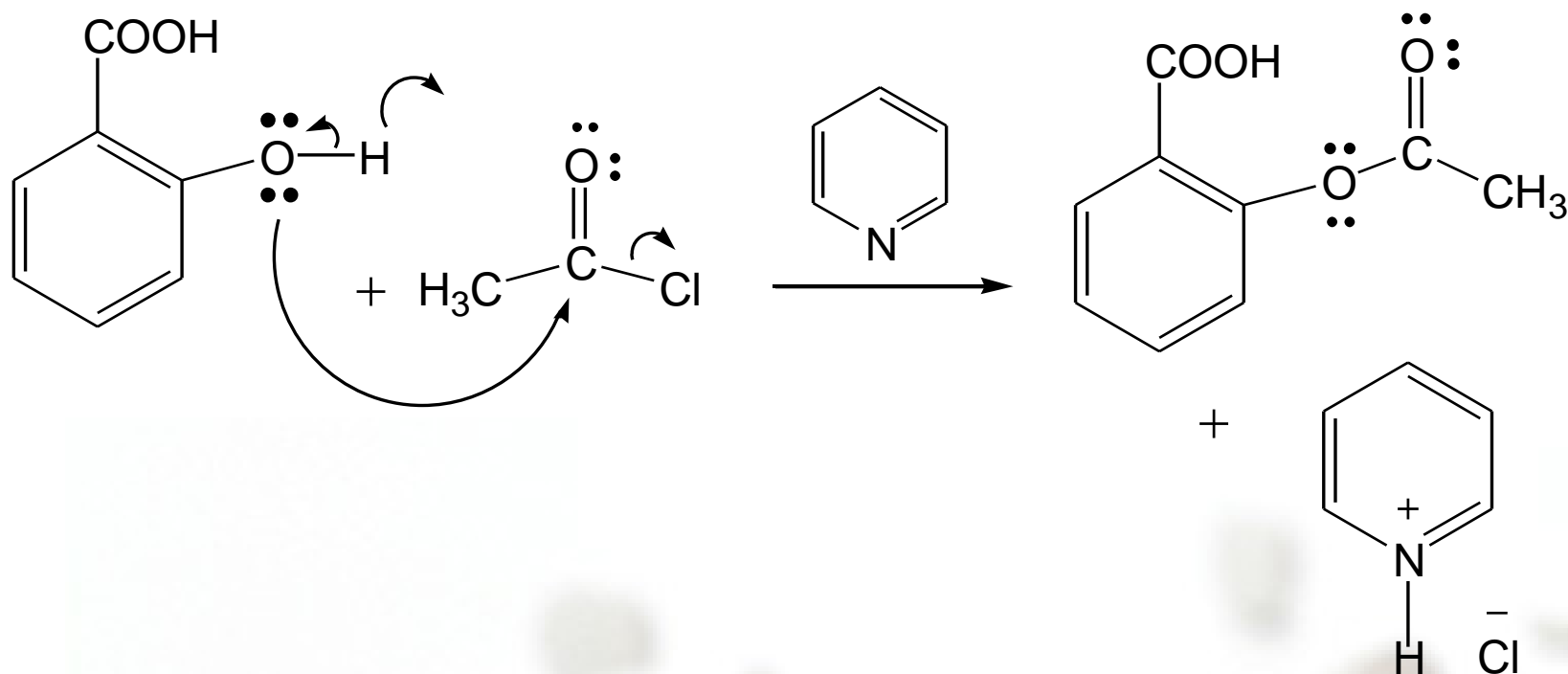
Acetyl chloride > Acetic anhydride > Acetic acid

Preparation of acetyl salicylic acid:

Method I:

Preparation of aspirin by using acetyl chloride with salicylic acid

Acetyl chloride is an acyl chloride, is very reactive it reacts vigorously with Salicylic acid to form aspirin.



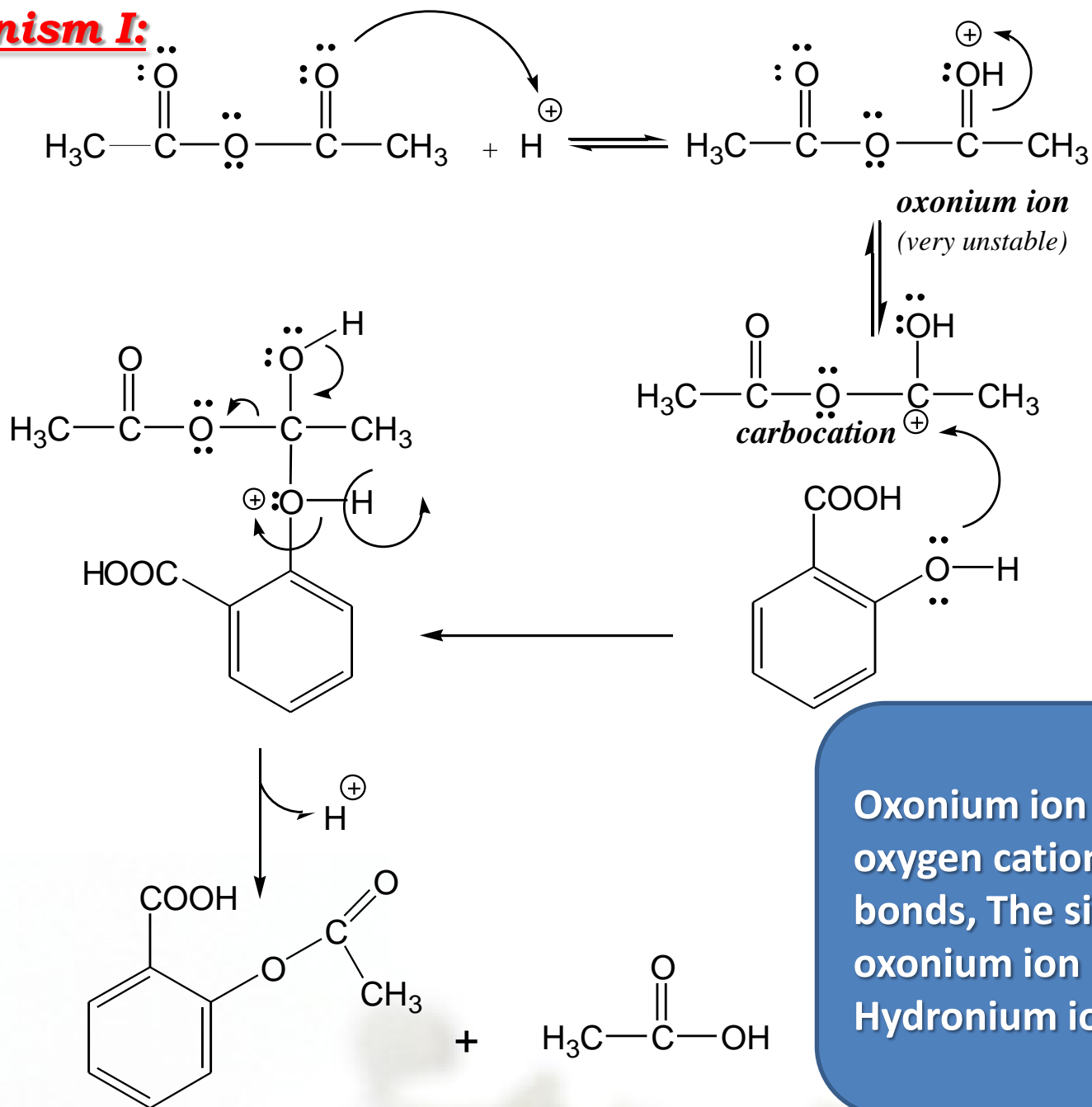
Method II:

Preparation of aspirin by the reaction of S.A. and acetic anhydride :

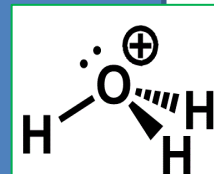
Acetic anhydride, Ac_2O , is an acid anhydride which is used chiefly to make esters that cannot be made by direct esterification with acetic acid.

Acetic anhydride is cheap , readily available, easily handled and not forming corrosive HCl gas , with moderate reactivity , the acetylating reaction is moderate but safer than that of acid chloride.

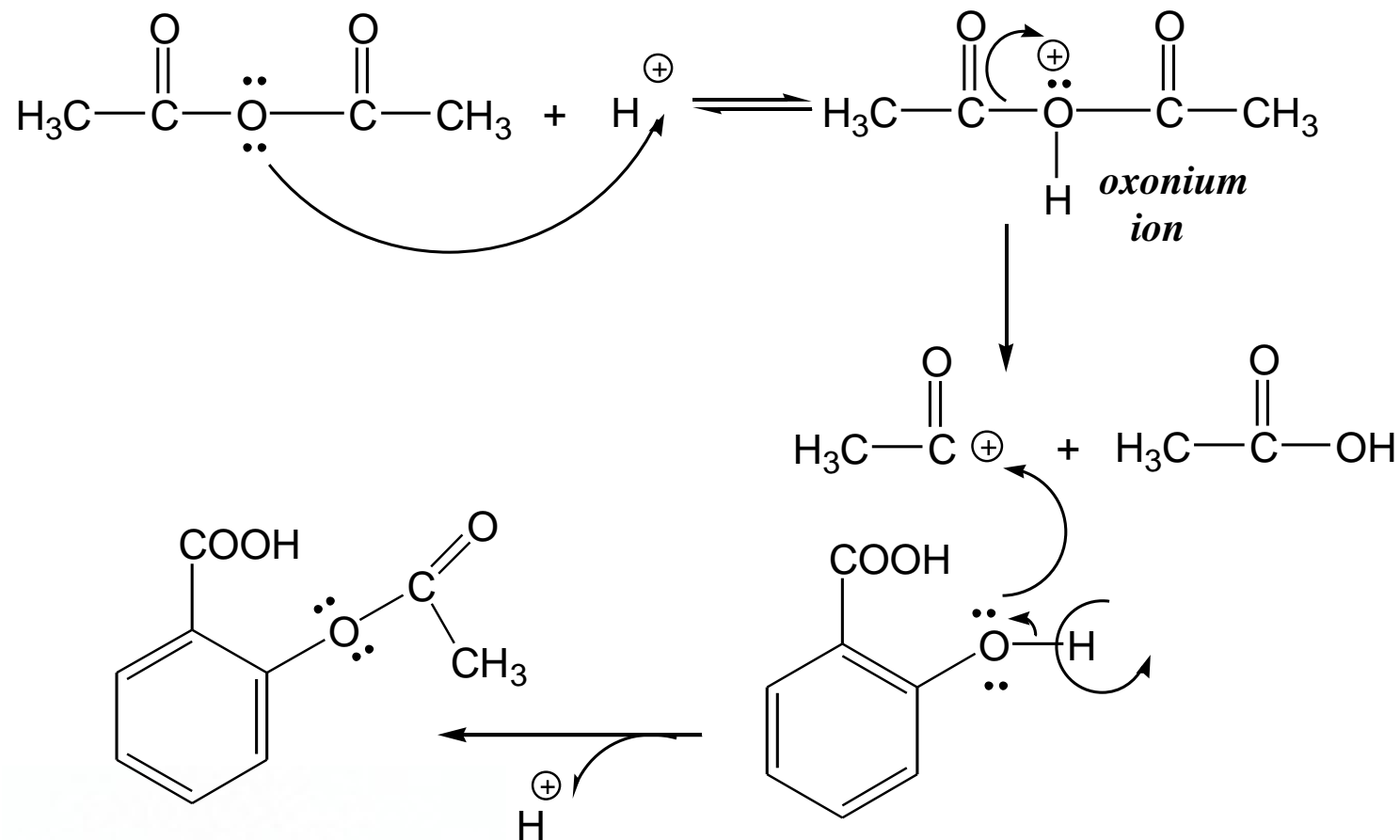
Mechanism I:



Oxonium ion is any oxygen cation with 3 bonds, The simplest oxonium ion is Hydronium ion.



Mechanism II:



Name of Experiment: **Esterification using acid anhydride.**

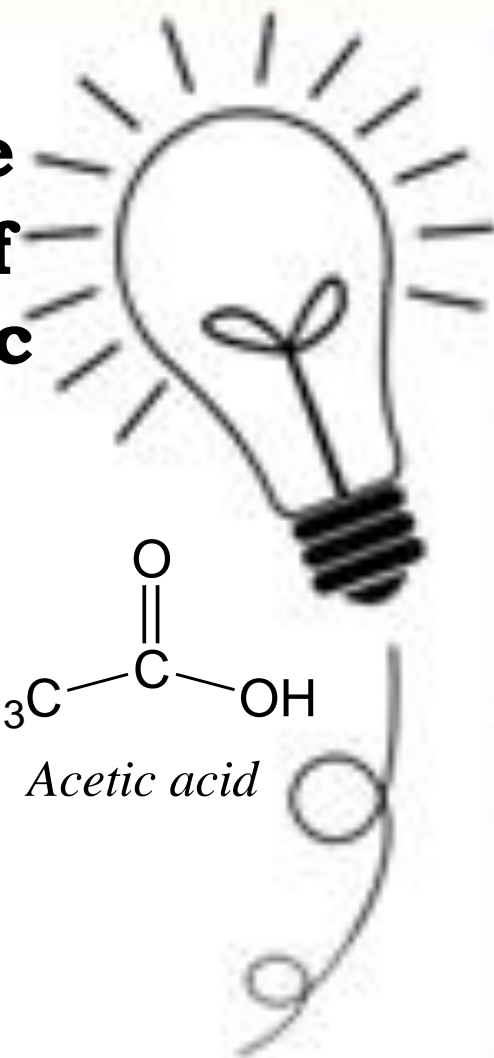
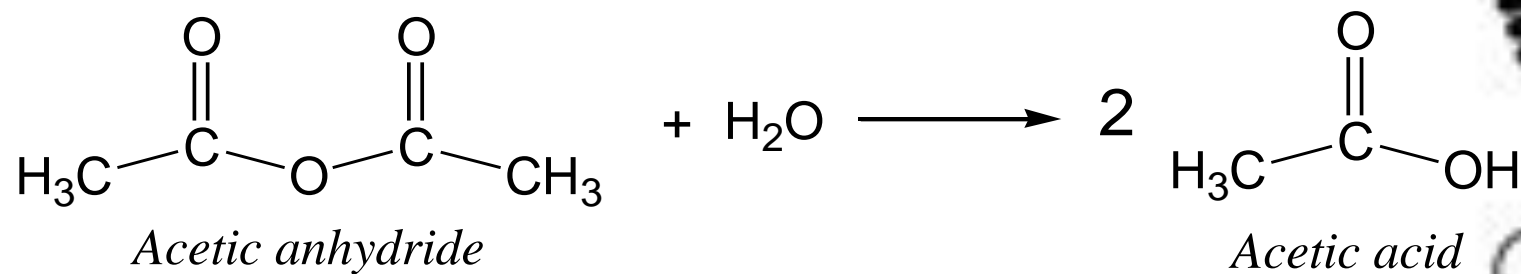
Aim of experiment: **Preparation of Aspirin.**

Procedure:

- 1) Put 2.5 gm of S.A in a dry conical flask*.**
- 2) Add 5 ml of acetic anhydride**.**
- 3) Shake well.**
- 4) Add 3-5 drops conc. H_2SO_4 ***.**
- 5) Warm on water bath to (50-60) °C for about (10-15) min****.**
- 6) Stirring, cooling (ppt. of aspirin) then add 75 ml D.W.***** .**
- 7) Filtration, wash the ppt. with cold D.W. and collect the product (aspirin).**

Notes:

* The conical flask should be dried well since the presence of moisture could hydrolyze acetic anhydride to acetic acid .



**** The 1st step in this esterification is to create a suspension of Salicylic acid (a solid at r.t.) in an excess of Acetic anhydride (a liquid at r.t.).**

So, Acetic anhydride serves as both a reactant and a solvent.

***** A catalyst is required for this reaction.**

Conc. H_2SO_4 , donates a proton which binds to the reaction complex.

As a catalyst, H^+ is regenerated, not consumed by the end of the reaction.

******** As the reaction proceeds , the solid S.A. disappears and the Acetylsalicylic acid product remains dissolved in the hot solution.

Once all solid has disappeared (all the S.A. has been consumed) the reaction is completed.

Avoid very high temperature or prolonged heating period *since* the synthesized acetylsalicylic acid may decompose.

***** At this point the **excess unreacted** Acetic anhydride must be hydrolyzed (split apart by the addition of water) to acetic acid. Acetic anhydride is **very reactive** toward water, so the hydrolysis must be done slowly, water should be added drop-wisely. More water is then added and the flask is placed in an ice bath to lower the solubility and precipitate the prepared aspirin.

The collected ASA is then recrystallized by using mixed solvents to further purify the product.



Percent yield :

It serves to measure the effectiveness of a synthetic procedure.

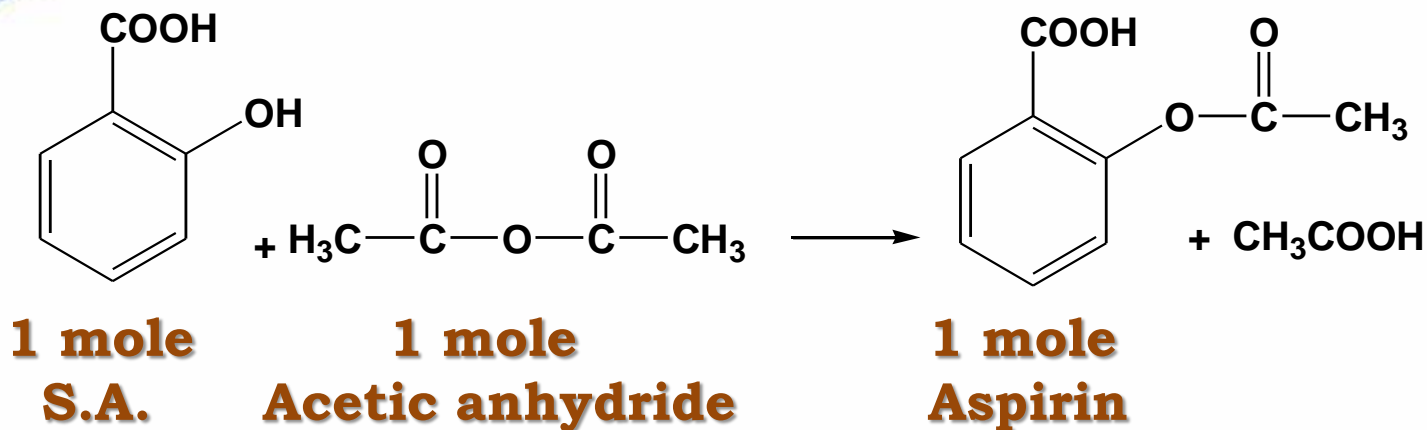
To calculate the percent yield of a reaction:

- 1- Write a balanced equation for the reaction.**
- 2- Finding the limiting reagent.**
- 3- Determination of the theoretical yield.**
- 4- Determination of the actual yield.**
- 5- Calculation of the percent yield.**

$$\text{Percent yield} = \frac{\text{Actual yield}}{\text{Theoretical yield}} * 100 \%$$

EXAMPLE

In our experiment today



- We used acetic anhydride in excess so salicylic acid is the limiting reagent.
- Use salicylic acid to calculate the theoretical yield.

$$1 \text{ mol S.A.} = 1 \text{ mol ASA}$$

$$\frac{\text{wt. S.A.}}{\text{m.wt. S.A.}} = \frac{\text{wt. ASA}}{\text{m.wt. ASA}}$$

$$\frac{2.5 \text{ g}}{138 \text{ g/mol}} = \frac{\text{wt.}}{180 \text{ g/mol}}$$

**Wt . = 3.25 g of the ASA
theoretically**

The wt. of ASA synthesized in the experiment = 2.7 g
"for example"

**Wt. = 2.7 g of the ASA
Actual**

$$\text{Percent yield} = \frac{2.7 \text{ g}}{3.25 \text{ g}} * 100 \% = 83 \%$$