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Aspirin (Part 1)

Aspirin synthesis

WHAT IS ASPIRIN?!!

It is 2-acetoxybenzoic acid, which is also called acetyl salicylic acid, aspirin is a salicylate drug.

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Aspirin properties

M.F. $C_9H_8O_4$

M.Wt. 180

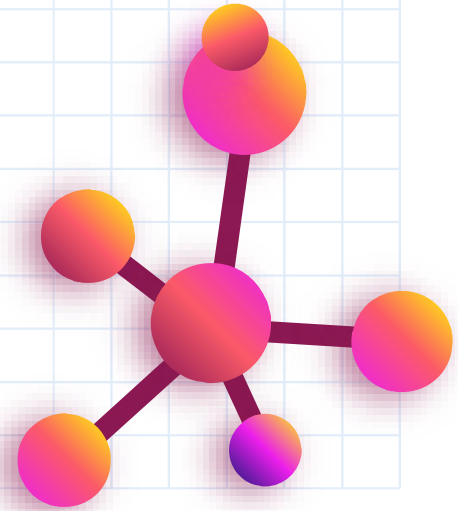
M.P. 135 °C

Physical state: crystals or crystalline powder

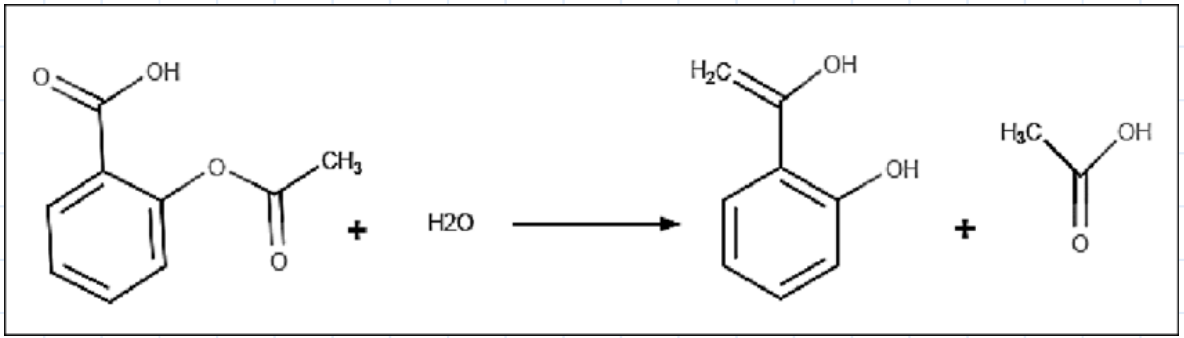
Odor: odourless

pH: 3.5

Solubility: slightly soluble in water (1:300) and readily soluble in organic solvents

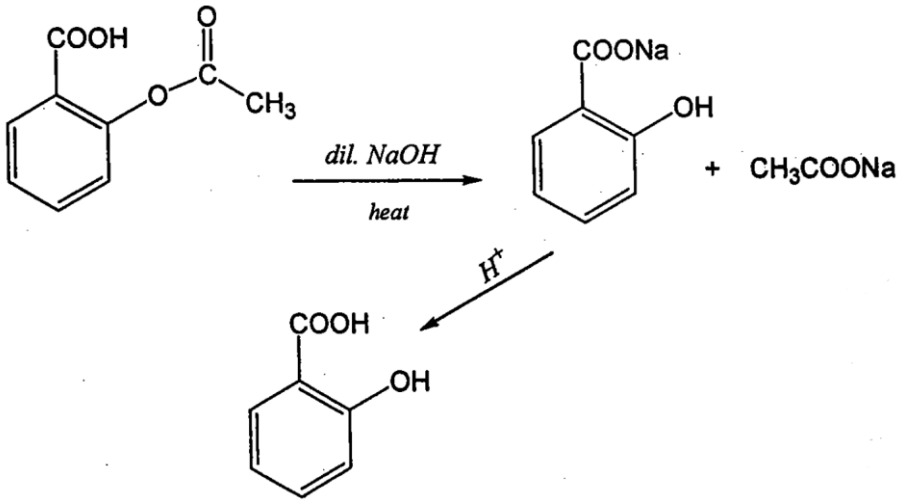


Aspirin is stable in dry air, but in the presence of moisture, it is slowly hydrolysed to into salicylic acid and acetic acid.



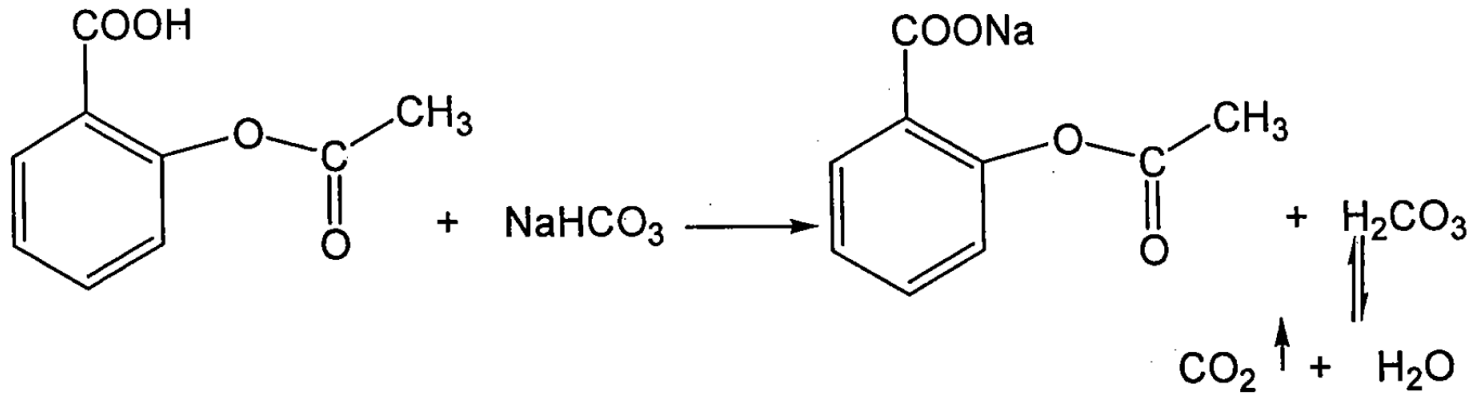
So, old aspirin tablets mat have a smell like vinegar as a result of hydrolysis reaction that produces acetic acid (ethanoic acid)

Salicylic acid will crystalize out when an aqueous solution of aspirin and sodium hydroxide is boiled and then acidified.



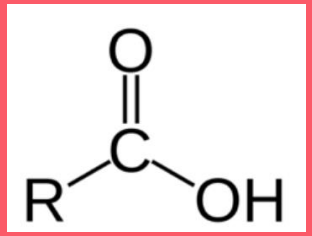
So, it decomposes in the presence of alkaline hydroxides .

Aspirin itself is acidic enough to produce effervescence with carbonates .

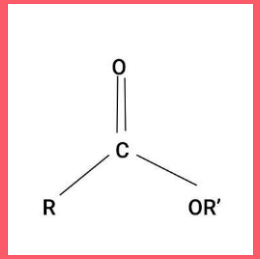


- Practically, all salts of aspirin (soluble in aqueous media), except those of aluminium and calcium (insoluble in aqueous media), are unstable for pharmaceutical use.
- Aspirin gives no colour with $feCl_3$ solution.
- It is used as antipyretic, analgesic, and anti-platelet in different doses of different dosage forms.

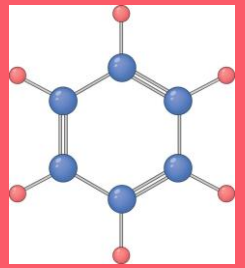
Aspirin functional groups



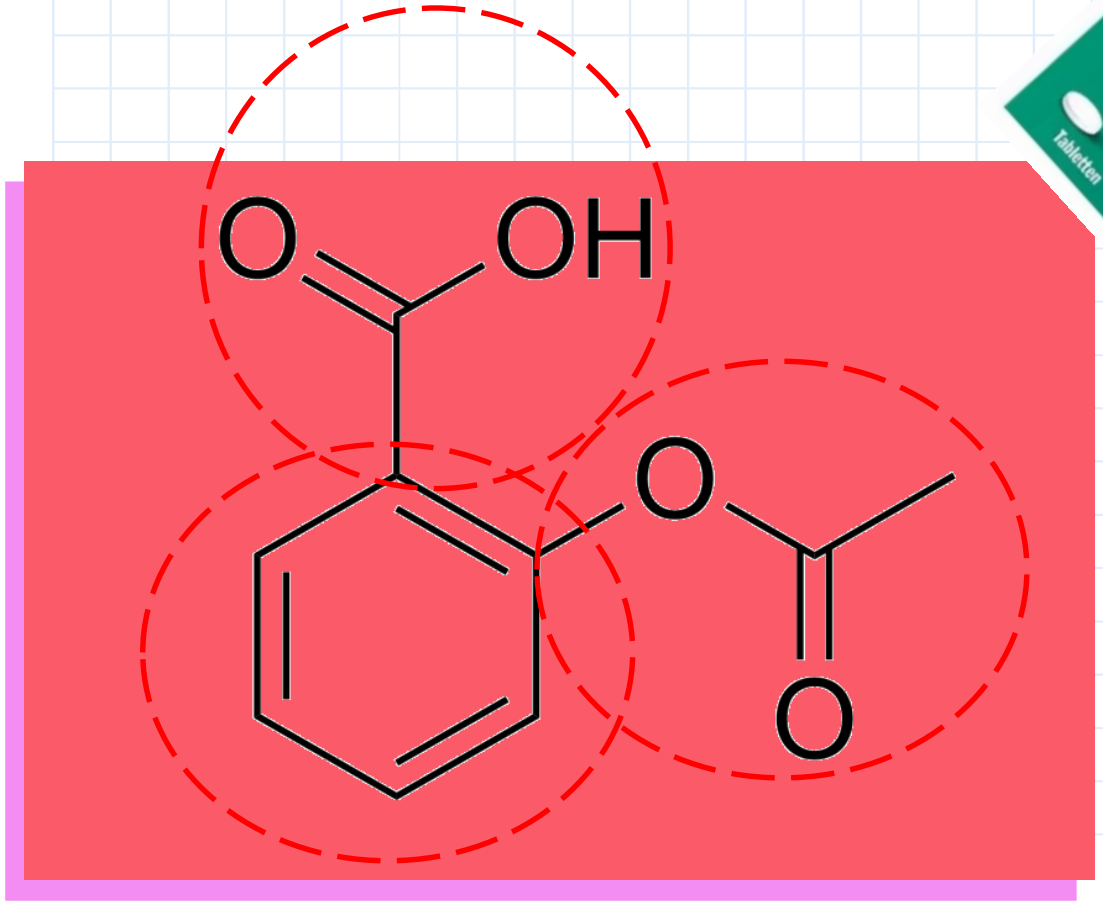
Carboxylic acid functional group



Ester functional group



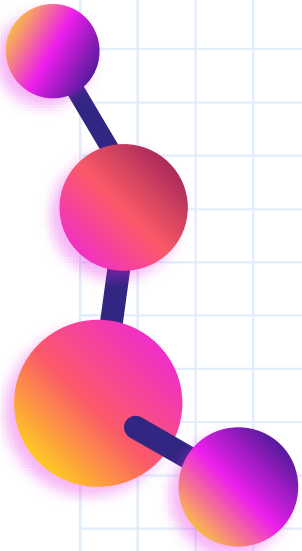
Aromatic group

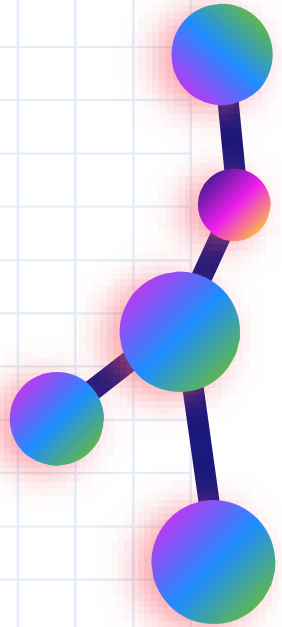

O
OH
O
O


ASPIRIN®
PROTECT 100 mg
Magensaftresistente Tabletten mit 100 mg Acetylsalicylsäure
Zur Hemmung des Zusammenklumpens der Blutplättchen
Tabletten

02

Aspirin preparation





Aspirin is synthesised by reacting S.A. with either acetyl chloride or acetic anhydride

Method I

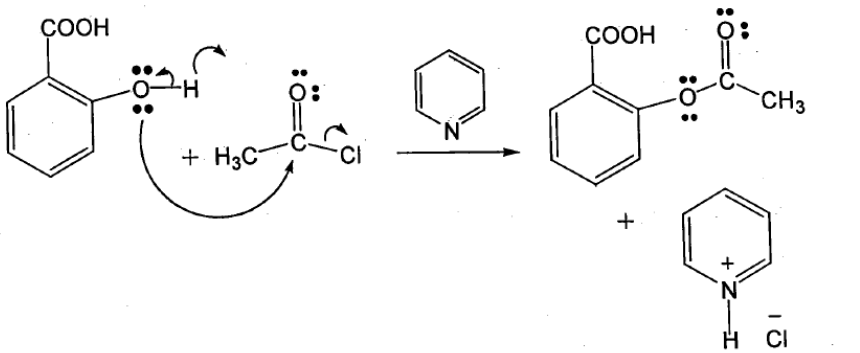
Using acetyl chloride with salicylic acid

Method II

Using acetic anhydride with salicylic acid

Method I

Acetyl chloride is an acyl chloride, is very reactive and reacts vigourously with salicylic acid to form aspirin. The reaction is fast but not safe since it produces HCl gas, so pyridine should be used as a base to pick up (H^+) proton and gives pyridinium chloride.



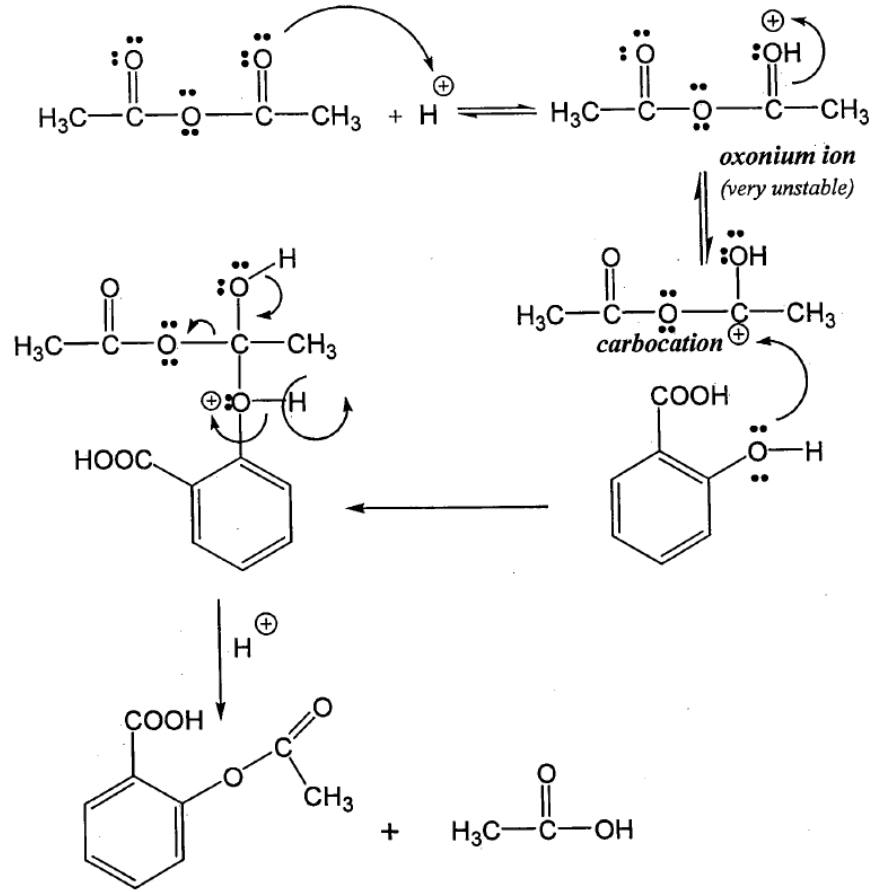
Pyridine is teratogenic and air pollutant

Method II

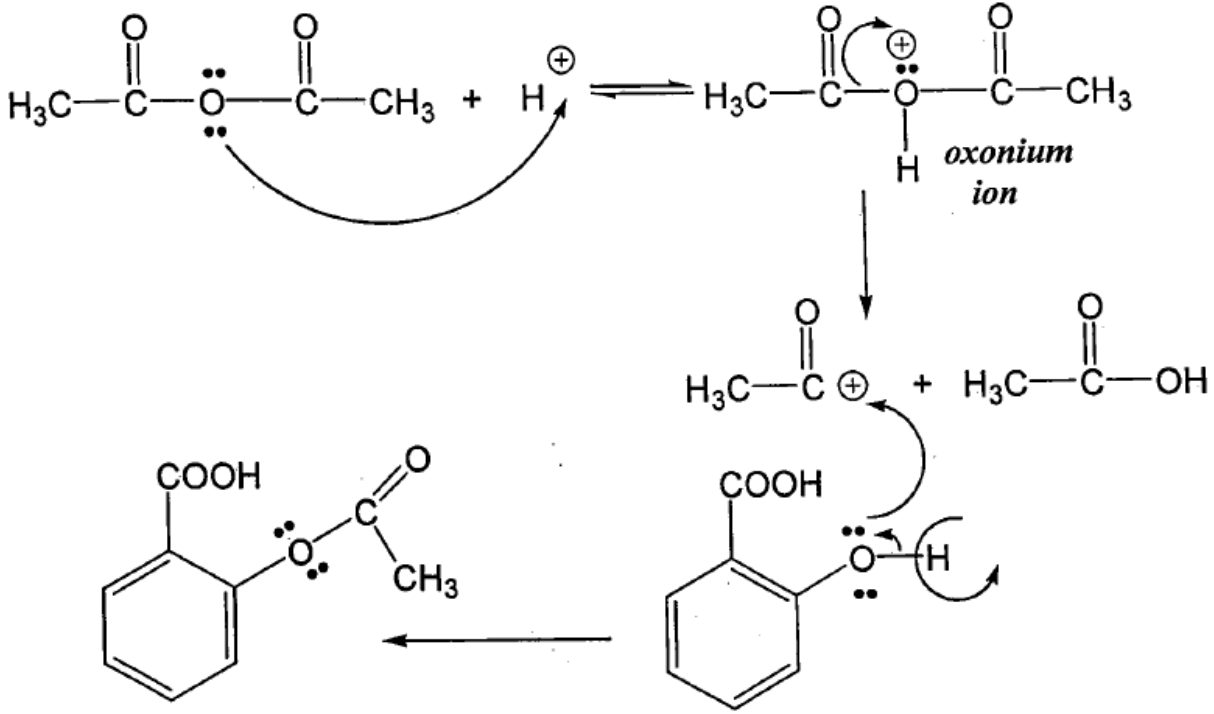
Acetic anhydride (Ac_2O) is an acid anhydride which is used chiefly to make esters that can not be made by direct esterification with acetic acid. It is cheap, readliy available, easily handled, and not forminng corrosive HCl gase, with moderate reactivity, the acetylating reaction is moderate but safer than that of acetyl chloride

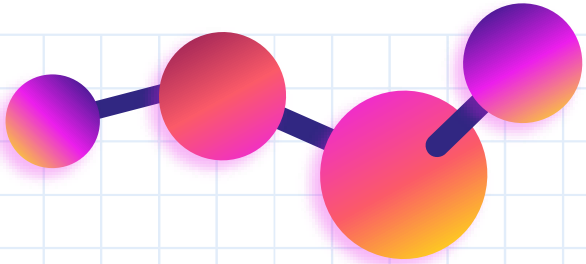
Below are the two proposed mechanisms of this reaction:

Mechanism I:



Mechanism II:





Check point!

Chemically, what are the main differences between method I and method II in the preparation of ASA.?

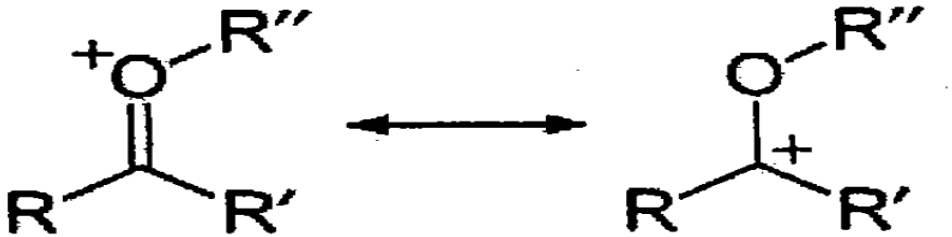
What are oxonium ion and carbocation ?

Oxonium ion

Is any oxygen cation with three bonds. The simplest oxonium ion is the hydronium ion H_3O^+.

Carbocation

Is an oxonium ion obtained by protonation or alkylation of a carbonyl group which forms a resonance structure.



Aspirin synthesis procedure

Step 01

Put 2.5 gm of S.A. in dry conical flask

Step 02

Add 5 ml of acetic anhydride

Step 03

Shake well, then add 3-5 drops of conc. H_2SO_4

Step 04

Warm on water bath to (50-60 °C) for (10-15 min)

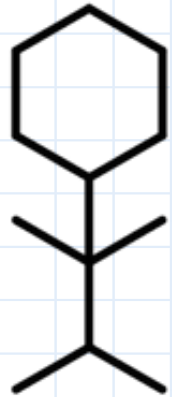
Step 05

Stirring, cooling (ppt. of aspirin) then add 75 ml of D.W.

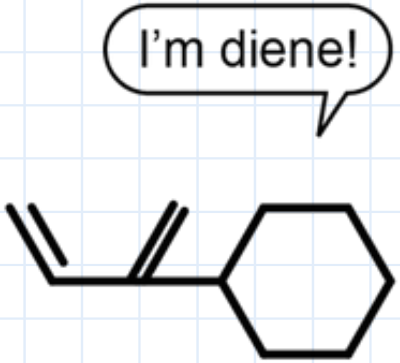
Step 06

Filtration, wash the ppt. with cold D.W. and collect the product (aspirin).

Have a break !

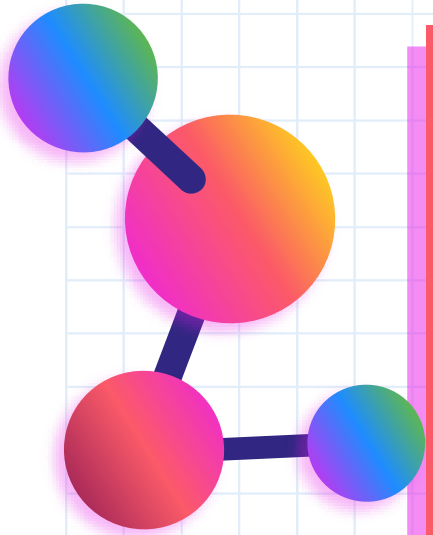


Before Organic Exam



After Organic Exam

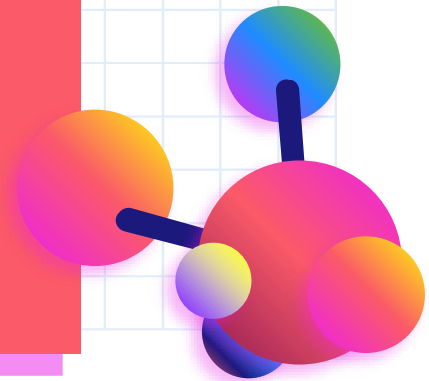
General notes



1. The conical flask should be dried well since the presence of moisture could hydrolyse acetic anhydride.

2. The first step in the purification is to create a suspension of salicylic acid (a solid at room temperature) in an excess of acetic anhydride Ac_2O, (a liquid in room temperature).

3. Acetic anhydride serves as both reactant and solvent.



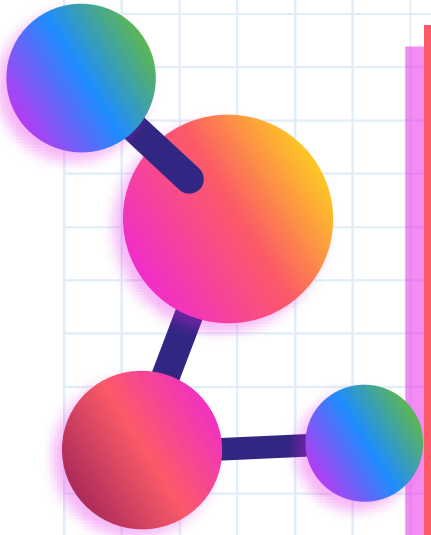
General notes

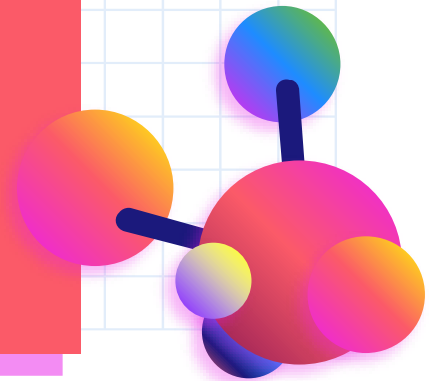
4. A catalyst required for this reaction (Conc. H_2SO_4) donates a proton which binds to the reaction complex.

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

6. As the reaction proceed, the solid S.A. disappear and the product acetyl salicylic acid remains dissolved in the hot solution.

7. Once all solid has disappeared (all S.A. have consumed) the reaction is complete.



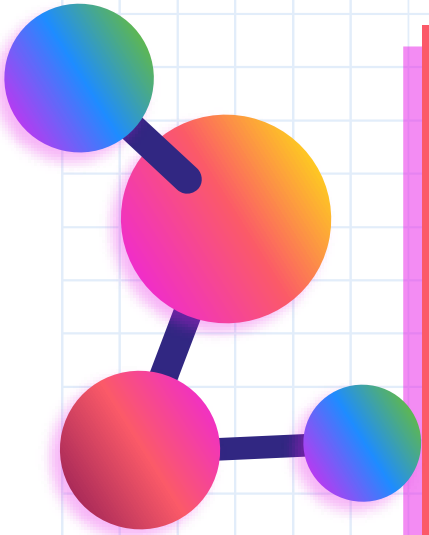


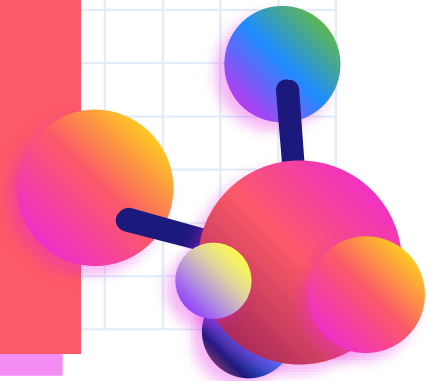
General notes

8. Avoid very high temperature or prolonged heating periods since aspirin may decompose.

9. At this point, the excess unreacted acetic anhydride must be hydrolysed (split apart by the addition of water) to acetic acid.

10. Acetic acid is very reactive towards water, so the hydrolysis must be done slowly – water should be added drop wise.





General notes

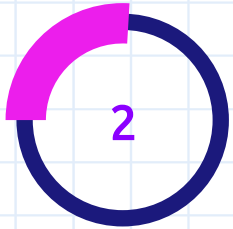
11. More water is then added and the flask is placed in an ice bath to lower the solubility and precipitate the prepared aspirin.

12. The crude product (ASA) is then collected by filtration and recrystallized to further purify the product.

The purity of the product is determined by three ways

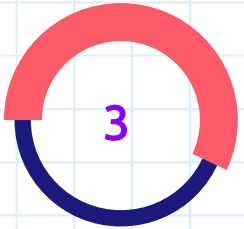
M.P.

The smaller melting range is a purer compound (sharp M.P. = pure compound)



TLC

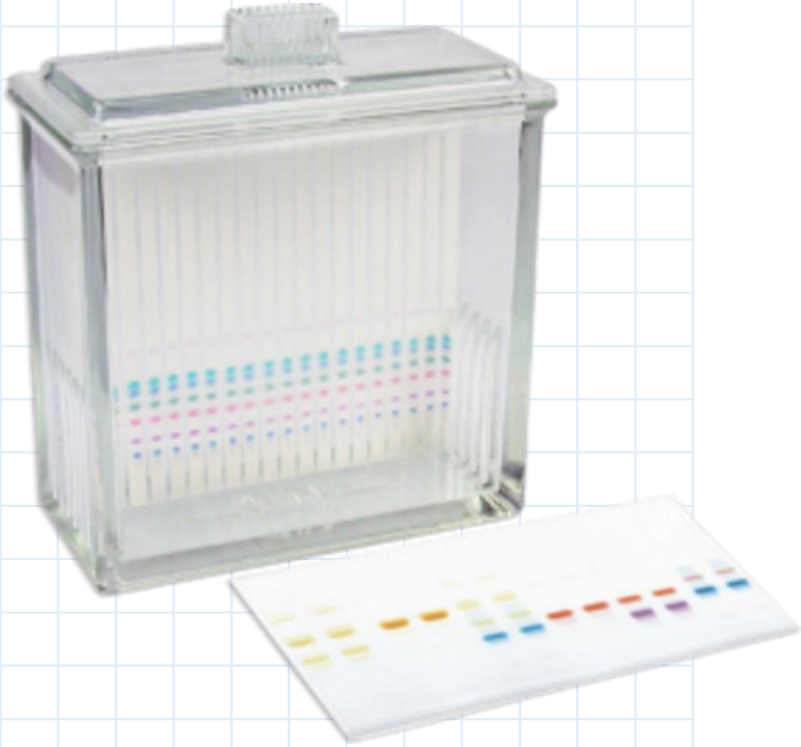
Single new spot = pure product



FeCl3

Unreacted S.A. complex with FeCl3 to create purple complex

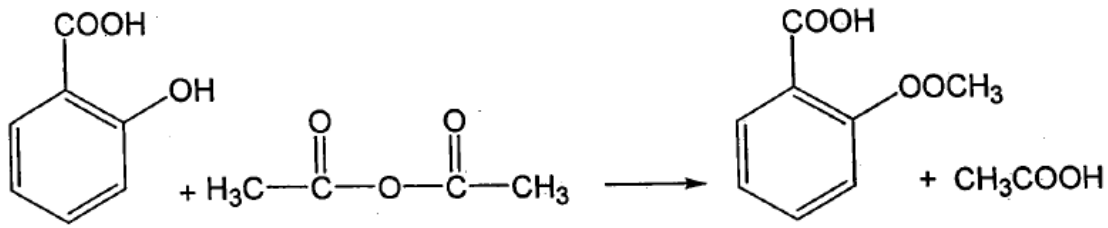

heating
plateau
ramping
HOLD
Cole-Parmer
MP-200



Samples with unreacted salicylic acid complex with $FeCl_3$ to create purple to violet complex in the aqueous solution. Pure ASA product will remains colorless.

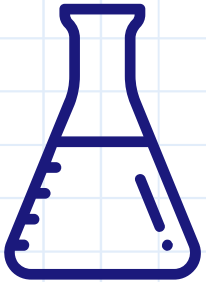
The percent yield of the reaction

The balanced equation of the reaction is:



Calculation of the percentage yield

Wight the aspiring and calculate the theoritical (maximum) yield.



1 mole ASA = 1 mole S.A.

$\frac{Wt.}{M.Wt.}$ of ASA = $\frac{Wt.}{M.Wt.}$ of S.A

* no. of moles = $\frac{Wt.(g)}{M.Wt.}$

Note: the acetic anhydride is in excess and the salicylic acid is the limiting reagent. So, the salicylic acid is used to calculate the theoretical yield.

$$\%\ of\ yield = \frac{wt.of\ the\ product\ practically}{wt.of\ the\ product\ theoretically} * 100\%$$

In our experiment today, we used 2.5 g of S.A.

$$\frac{2.5\ g}{138} = \frac{Wt.}{180} \rightarrow Wt. = 3.25\ g\ of\ ASA\ theoretically.$$

$$\%\ yiled = \frac{Wt.\ of\ ASA\ practically}{Wt.\ of\ S.A.\ theoretically} * 100$$

$$\%\ yiled = \frac{2.7\ g\ "for\ example"}{3.25\ g} * 100$$

$$\%\ yield = 83\%$$

Excercices

- A student's theoretical yield was 12.0 g aspirin, but he only obtained 7.5 g. What was his percent yield?
- What would happen to your percent yield if the aspirin you prepared was not dried completely?
- Calculate the theoretical yield of aspirin to be obtained when 2.0 g of salicylic acid and 5.0 ml of acetic anhydride (density = 1.08 g/ml) are mixed together (Molar masses: acetic anhydride = 102.1 g/mol, salicylic acid = 138 g/mol, and aspirin = 180 g/mol)?

Excercices

- In preparation of aspirin using acetic anhydride, we should use dry conical flask, why?
- In our experiment, the temperature should be between 55-60 °C, why?
- If 0.150 moles of salicylic acid and excess acetic anhydride are used during the synthesis of aspirin. How many grams of aspirin will be obtained if the reaction gives a 38% yield?

Thanks!