EXPERIMENT 18
PREPARATION OF ASPIRIN AND ANALYSIS OF A COMMERCIAL SAMPLE OF ASPIRIN.

Structure

18.1 INTRODUCTION

In the previous eight experiments you have learnt about the organic and inorganic quantitative analysis. In this and the forthcoming experiments you will be preparing certain molecules which have applications in our day to day life . The present experiment deals with preparation of a common drug , aspirin .

Aspirin is an antipyretic,an analgesic, and an anti inflammatory drug. It is probably the most extensively used analgesic drug. As an anti–inflammatory agent aspirin is used extensively in the treatment of arthritis. Now a day it is universally being recommended as a medicine which may prevent heart attack by checking blood clotting in the arteries. It is attributed to the fact that it effects platelets which are important for clotting of blood. On the negative side in excess doses it causes gastric problems like irritation of mucous membrane. It is also said to be responsible for brain disorder (Reye's syndrome) in people below age of 18 years.

In this experiment you will learn about preparation of aspirin from salicylic acid and also about the analysis of a commercial sample of aspirin .This experiment has two parts one for preparation and other for the analysis. However, the principle and procedure etc. for the two parts are given seperately. In the preparation part (section 18.2) you will learn how to perform " acetylation", an important organic reaction. As you will see later , acetylation reaction can be carried out in a number of ways. We are giving procedures for two methods. Depending upon the convenience of time and availability of chemicals, your counsellor can choose any of these. The analysis part (section 18.3) may be carried out with any of the available nonbuffered

commercial preparation of aspirin. In the next experiment you will learn about preparation of azo dyes.

Objectives

After studying and performing this experiment you should be able to :

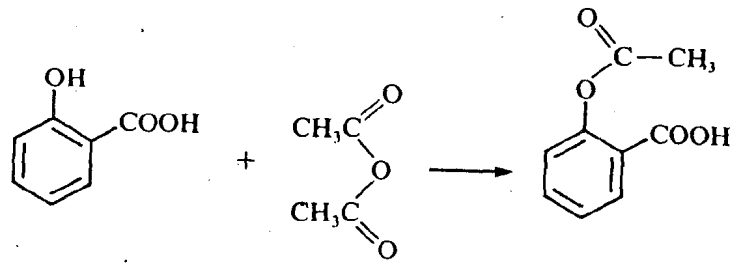
- prepare sparin from salicylic acid,
- explain the acetylation reaction and its mechanism, and
- analyse a commercial sample of aspirin and outline the uses of aspinin as a drug.

18.2 PREPARATION OF ASPIRIN

As said above, this experiment has to parts. In the first part, related to preparation of aspirin, you will learn about procedure and mechanism of acetylation of salicylic acid.

18.2.1 Principle

As the name, acetylsalicylic acid suggests, aspirin is acetyl derivative of salicylic acid. It is prepared by acetylation reaction of salicylic acid.



Salicylic acid Acetic anhydride Acetylsalicylic acid

Generally in an acetylation reaction the reactive hydrogen of hydroxy (alcohol or phenols) or amino (primary and secondary amines) functional group is replaced by $-COCH_3$ group.

$$\begin{matrix} R-OH \\ \text{or} \\ RNH_2 \end{matrix} \xrightarrow{\text{acetylation}} \begin{matrix} R-OCOCH_3 \\ \text{or} \\ RNHCOCH_3 \end{matrix}$$

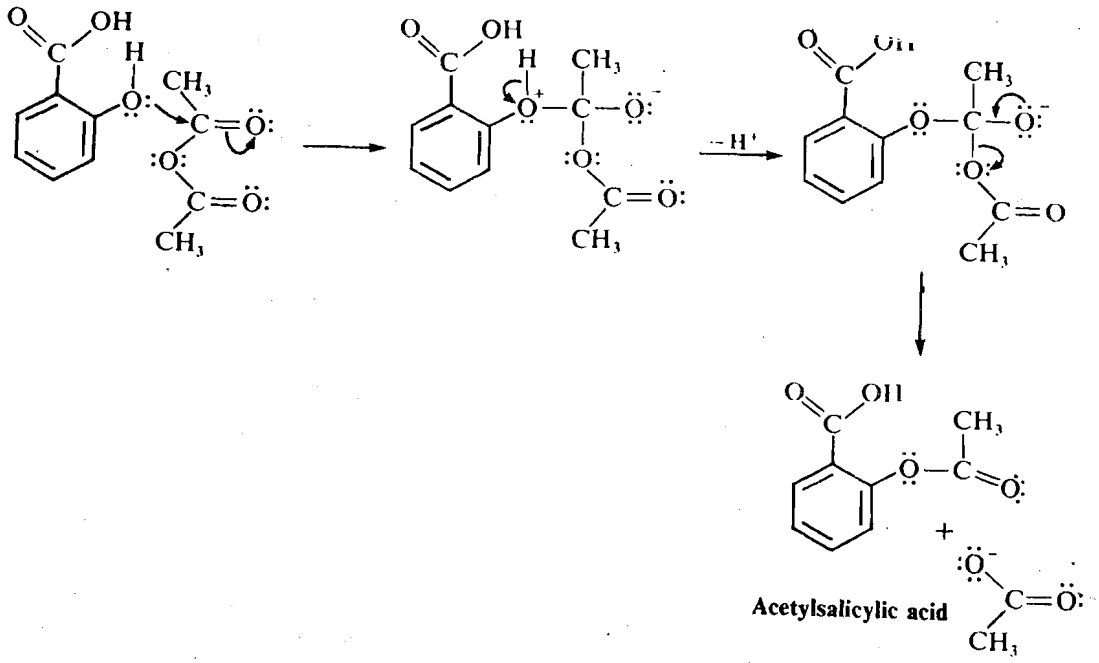
The acetylation of —OH group is equivalent to the esterification of acetic acid. It is so because the product obtained, R—$OCOCH_3$ is essentially an alkyl/aryl ester of acetic acid depending on whether R is alkyl or aryl group. Acetylation reaction can be accomplished in a number of ways. These are:

(i) with acetic anhydride in presence of a catalyst.

(ii) with acetyl chloride in presence of a base, like pyridine.

(iii) with a mixture of acetic acid and acetic anhydride.

Commercially, aspirin is prepared by method (i). We are giving procedure for both methods(i) and (ii), you may use any method as said above. The mechanism for acid catalyses acetylation of salicylic acid which may be represented as follows.



18.2.2 Requirements

Apparatus		Chemicals
Conical flask (100 cm^3)	2	Salicylic acid
Water bath	1	Acetic anhydride
Beakers (100 cm^3)	2	Sulphuric acid
		Acetyl chloride
Glass rod	1	Pyridine
		Alcohol

18.2.3 Procedure

Method i

1. Take 2.75 g (0.02 mole) of salicylic acid in a 100 cm^3 conical flask and to this add about 6 cm^3 of acetic anhydride (0.06 mol) and a few drops of conc. sulphuric acid.

   In this method acetic anhydride is taken in excess. It acts as acetylating agent as well as the solvent.

2. Swirl this flask in a water bath (temp = 50 - 60) for a few minutes till the solid material dissolves.

3. Leave the flask in water bath for about 10 minutes with occasional swirling.

4. Allow the solution to come to room temperature and then add about 50 cm^3 of ice cold water to it. You may even add crushed ice.

   Water is added to destroy the excess acetic anhydride, which gets converted to acetic acid.

5. Scratch the sides of flask with glass rod to induce crystallisation and filter the solid, so obtained.

6. Take about 10--15 mg (a speck) of the crude aspirin in a test tube and dissolve it in about 1cm^3 of alcohol. Add a drop of 1 % ferric chloride solution to it and observe the colour. Formation of intense colour indicates the presence of unreacted salicylic acid.

7. Recrystallise about half of the crude sample by ethanol\water solvent system. For this dissolve aspirin in minimum quantity of hot alcohol and to this add warm (50 - 60) water with constant swirling of the solution till a turbidity persists. If some crystals do form at this stage dissolve them by gently heating the solution.

8. Allow the solution to cool till the crystallisation is complete. Collect the crystals by vacuum filter and wash them with cold water and dry the crystal in the folds of filter paper and weigh them.

9. Determine the melting point of the recrystalised sample and report it.

Method ii

1. Dissolve 2.75g of salicylic acid to about 2 cm^3 of dry pyridine in a 100 cm^3 conical flask.

2. Quickly add about 2.5 ml of acetyl chloride to the above solution in small lots with constant swirling\shaking.

   Caution : This reaction is highly exothermic and the temperature of reacting mixture rises rapidly. Don't let the temperature go beyond about 60°C (unbearable to touch). You may cool the flask occasionally in cold water\under the tap.

3. Heat the mixture on a water bath for about 5 minutes.

4. Proceed exactly as in method 1 from step 4 onwards.

18.2.4 Results:

1. ..... g of acetylsalicylic acid was obtained from 2.75 g of salicylic acid.

   Theoretical yield = 3.6 g

$$\% \text{ yield} = \frac{\text{yield obtained} \times 100}{\text{theoretical yield}}$$

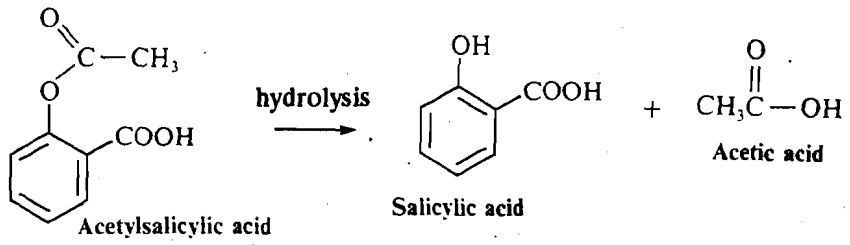
$$= \text{.....}$$

2. The melting point of aspirin was found to be = ... °C.

18.3 ANALYSIS OF ASPIRIN

Purity of any compound is important for its action. It is all the more important if the compound happens to be a drug. The purity of aspirin prepared above can be checked qualitatively by the colour test given above. Development of colour with $FeCl_3$ indicates the presence of salicylic acid in the preparation but the question arises about the amount or percentage of salicylic acid in it. We need to undertake a quantitative examination for the purpose.

Similarly a commercial sample of aspirin may also have some amount of salicylic acid. This salicylic acid originates from the hydrolysis of acetylsalicylic acid. This hydrolysis brings in another impurity - acetic acid .You may have noticed a smell of vinegar on opening an old bottle of aspirin tablets. This is due to acetic acid formed during hydrolysis.



The presence of salicylic acid, whether as an impurity in the preparation or consequence of hydrolysis, is not desirable. Incidentally salicylic acid also is an analgesic but is not as safe as aspirin, because the free —OH group causes severe mucousal irritation and gastric problems. Excessive use may even cause gastric ulcers. Further, you know that the effectiveness of a drug depends on its proper dosage besides the purity. The amount of aspirin per tablet is normally marked on the packing. You would like to know that whether the tablet you are consuming for curing your headache has enough of aspirin in it. Let us learn how do we make such determination for any laboratory/ commercial preparation of aspirin.

18.3.1 Principle :

The amount of aspirin in any preparation can be determined by a number of methods. These include simple titrimetry, conductormetry, potentiometry and colorimetry etc. . We are providing the detailed principle and procedure for the titrimetric method.

To determine aspirin titrimetrically it is first hydrolysed with an excess but known amount of strong alkali solution, which generates equivalent amounts of salicylic and acetic acid(eq.) These neutrlise part of the alkali and the remaining alkali is back titrated with a standard solution of an acid.

Normally in a titration we add the standard solution of the titrant (from the burette) to the titrand (in the conical flask) till the two react stoichiometrically ; marked by a colour change of the indicator. In certain situations excess of the titrant is added to the titrand. After the reaction is over the excess of the titrant is titrated with another reagent. This arrangement of performing the titration is called as **residual or back titration.**

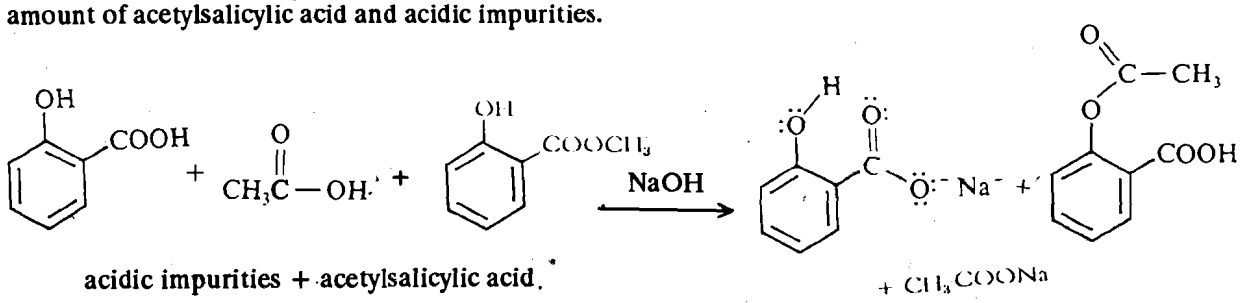
As we can see from the above equation, each mole of acetylsalicylic acid would neutralise 2 moles of NaOH. We can represent the overall chemical equation as;

$$COOHC_6H_4OCOCH_3 + 2NaOH \longrightarrow NaOOCC_6H_4OH + CH_3COONa$$

Knowing the amount of NaOH consumed by acetylsalicylic acid we can estimate the amount of acetylsalicylic acid. It would be half the amount (in moles) of NaOH consumed. You may raise a question here that the impurity of salicylic acid and/or acetic acid (if present) would also react with NaOH and consume some of it. Your question is quite valid and in fact the mols of NaOH consumed is equal to the moles of acidic impurities plus twice the moles of acetylsalicylic acid . If a given sample contains 'a' moles of acetylsalicylic acid and 'b' moles of acidic impurities, then ;

the moles of NaOH consumed in back titration = 2a + b moles

But, we need to know 'a', the moles of acetylsalicylic acid. How do we get over this problem ? To come out of this problem we have to perform yet another titration of aspirin with alkali in alcoholic medium. Under alcoholic conditions the alkali does not hydrolye the acetyl group significantly (the reaction is too slow).We can directly titrate the -COOH groups. Such a direct titration would provide an estimate of total amount of acetylsalicylic acid and acidic impurities.



You may note here that in this titration each mole of acetyl salicylic acid would

consume only one mole of NaOH. That is ,

the moles of alkali consumed in direct titration = a + b moles

From the results of the two titration we can eleminate"b" and get the value of 'a', the amount of acetylsalicylic acid.

amount of acetylsalicylic acid	=	amount of NaOH used in titration 1 (back titration)	–	amount of NaOH used in titration 2 (direct titration)
		= (2a + b) – (a + b)		= a moles

Commonly, starch is employed as binder. The use of commercial proparation containg buffers is not recomended for this experiment.

This may be sounding quite tedious an excercise. You may relax because unexposed commercial preparation normally do not have appreciable amount of acetic / salicylic acid. But they do have impurities of binders and buffers. Actually the manufacturers use some kind of binder to keep the tablet intact. These binders are usually inert and do not interfere in the titration. However, the impurity of buffer is not desirable in this experiment. This means that 'b' in the above formula is negligible for commercial tablets and we can quite a good estimate of the amount of acetyl salicylic acid found by method of back titration. This will provide you the amount of aspirin in the given commercial tablet. However, if you are using your own preparation then you will have to perform both, the direct as well as back titration.

The British pharmacopia, also recomands aspirin assay by back titration.

In fact you are going to perform experiment involving hydrolysis and back titration and in this

$$\text{amount of acetylsalicylicacid} = \frac{\text{amount of NaOH used in back titration}}{2}$$

18.3.2 Requirements:

Apparatus		Chemicals
Apparatus Burette (50 cm^3)	1	NaOH
Pipette (25 cm^3)	1	H_2SO_4
Conical flask (100 cm^3)	3	Phenol red (indicator)
Measuring flask 250 cm^3	2	Aspirin sample
Conical flask 250 cm^3	1	

Solution Provided.

1. 1*M* **NaOH solution :** It can be prepared by dissolving 4 g NaOH in water in 100 cm_3 volumetric flask

2. **0.05** *M* H_2SO_4 **solution.** This is prepared by taking 2 cm^3 sulphuric acid in water in 1 dm^3 volumetric flask.

18.3.3 Procedure :

1. Weigh accurately 3-4 tablets of aspirin (about 1.5 g) and transfer them to a 250 cm^3 conical flask.

2. Add 25.0 cm^3 of 1*M* NaOH solution and 25cm^3 of distilled water to it and gently heat the mixture for about 10-15 minutes.

This is done so as to hydrolyse the aspirin. Do not boil the solution and avoid spilling.

3. Allow the reaction mixture to cool and transfer it to a 250 cm^3 standard flask.Rinse the conical flask twice with distilled water and transfer the washings also to the standard flask. Ensure that whole of the reaction mixture is transferred to the standard flask.

4. Make up the volume to the calibration mark by adding more of distilled water and thoroughly mix the solution.

5. Transfer 25 cm^3 of this solution with help of a pipette to a 100 cm^3 conical flask and add a 2-3 drops of phenol red indicator.

6. Titrate this against 0.05 *M* sulphuric acid solution (taken in burette). The titration is marked by the change of colour from pink to orange. Record your observations in Observation Table I.

7. Repeat step no. 6 till you get at least two concordant readings.

8. Take 25 cm^3 of 1*M* sodium hydroxide solution with the help of a pipette and transfer it to another 250 cm^3 measuring flask. Dilute the solution to calibration mark with distilled water.

9. Transfer 25 cm^3 of this solution with a pipette to a 100 cm^3 conical flask. Add 3 drops of phenol red indicator and titrate against 0.05*M* H_2SO_4 solution (taken in burette). Record your observations in Observation Table II.

10. Repeat step 9 till you get two concordant readings.

18.3.4 Observations

mass of weighting tube $= m_1$ =.....g

mass of weighting tube + 3 tablets of aspirin $= m_2$ =.....g

mass of aspirin taken $= m_2 - m_1 = m$ g

Observation Table I
Titration of reaction mixture Vs 0.05*M* H_2SO_4 solution

Sl. No.	Volume of reaction mixture in cm^3	Burette reading initial	final	Volume of 0.05*M* H_2SO_4 used in cm^3 (final–initial)

Concordent reading =.....

Observation Table II
Titration of NaOH solution Vs 0.05 *M* H_2SO_4 solution

Sl. No.	Volume of NaOH solution in cm^3	Burette reading initial	final	volume of 0.05*M* H_2SO_4 used in cm^3 (final–initial)

Concordent reading = ...

18.3.5 Calculations:

Reaction involved in the titration

$$2NaOH + H_2SO_4 \longrightarrow Na_2SO_4 + 2H_2O$$

Let, molarity of acid, H_2SO_4 $= M_A$ (Provided)

molarity the of base, NaOH $= M_B$

volume of the base, NaOH $= V_B$

volume of the acid, H_2SO_4 $= V_A$

Molarity equation $= \frac{M_A \times V_A}{M_B \times V_B} = \frac{1}{2}$

$= 2M_AV_A = M_BV_B$

For titration of NaOH (standard) Vs sulphuric acid

Molarity of acid, M_A =..... (Provided)

Volume of acid used, V_A = ... (from Observation Table II)

Volume of NaOH taken, V_B = 25.0 cm^3

Molarity of NaOH, $M_B = 2M_AV_A/25$ = ... mole

For titration of reaction mixture Vs sulphuric acid

Molarity of sulphuric acid solution, M_A =..... (Provided)

Volume of sulphuric acid used, V_A =..... (from Observation Table I)

Volume of NaOH taken, V_B = 25.0 cm^3

Molarity of NaOH, $M_B = 2M_AV_A/25$ =..... mole

⇒ Amount of NaOH (in mole) consumed for neutralizing the hydrolysis products of aspirin

⇒ $(M_B - M'_B)$ moles

⇒ Amount of aspirin (in mole) $= \frac{M_B - M'_B}{2}$ moles

Amount of aspirin (in g) $= \frac{M_B - M'_B}{2} \times 180.16\ g = Z\ g$

M_m of aspirin = 180.16 g mol^{-1}

mass of aspirin (from titration) $= Z$ g

mass of aspirin (weighed from tablet) $= m$ g

percentage of aspirin in the given sample $= (Z/m) \times 100$

17.3.6 Result

The given sample contains ..... percent of aspirin.