Preparation of Aspirin (10A/PA)

Sam White

28/11/2017

1 Reaction Mechanism and Overall Equation
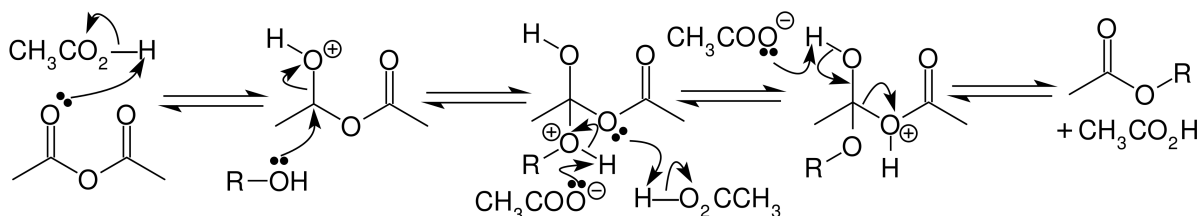

Figure 1: Mechanism for the reaction where ROH is salicylic acid.
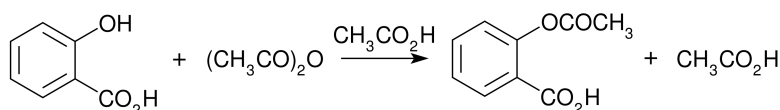

Figure 2: Equation for the reaction.

2 Summary of Method

Salicylic acid ($3.50\,\mathrm{g}$), glacial acetic acid ($5\,\mathrm{cm}^3$) and acetic anhydride ($3\,\mathrm{cm}^3$) were boiled under reflux for 10 minutes. The product was precipitated by pouring into ice-cold water ($75\,\mathrm{cm}^3$) and then recrystallised in a water and glacial acetic acid mixture (1:1 by volume) using ice to cool the mixture. The crude product, recrystallised product, salicylic acid and a sample of pure aspirin (each in $0.5\,\mathrm{cm}^3$ dichloromethane) were then analysed using thin-layer chromatography (TLC) with light petroleum ether and ethyl acetate (70:30 by volume) as the TLC solvent. The melting point of the purified product was then determined.

3 Results and Analysis

Mass of purified product: $3.99\,\mathrm{g}$

3.1 Thin-Layer Chromatography (TLC) Results

Substance	R_f Value of First Spot	R_f Value of Second Spot
Salicylic acid	0.64	N/A
Pure aspirin	0.32 (Diffuse)	N/A
Crude product	0.42	0.58
Purified product	0.43	N/A

The crude product gave two distinct spots on the TLC plate indicating the presence of two substances in the sample. The R_f value for the first spot (at 0.42) is different to that for the aspirin, however the aspirin produced a diffuse mark on the plate (possibly since too much solution was added to the plate) with the R_f values for the bottom and top of the mark being 0.18 and 0.45 respectively. The R_f value for the first spot from the crude product is within this range, hence suggesting that the crude product contains aspirin. The R_f value of 0.58 for the second spot of the crude product is close to the R_f value of the salicylic acid which suggests the presence of salicylic acid as an impurity in the product. This indicates that the reaction did not proceed to completion since the salicylic acid was the limiting reagent (see the percentage yield calculation in section 3.3). This is expected since the reaction is reversible (see figure 1), hence an equilibrium between the reactants and products will be established.

The TLC result for the purified product only shows a single spot at almost the same position as that for the spot assigned to aspirin in the crude product. This suggests that the recrystallisation was effective at removing the salicylic acid impurity since the spot due to this impurity is no longer present.

3.2 Melting Point Determination

Table 1: Melting Point Determination Results.

Run	Melting Started / °C	Melting Finished / °C
1	95.1	101.9
2	88.7	112.0
3	91.1	100.4

The expected melting point for aspirin is $136\,°C$.[1] The melting temperature results show a wide temperature range of over $10\,°C$ for the melting of the product and the temperature at which the product melted is much lower than the expected value. This is likely to have occurred since the product was not completely dry (the product consisted of clumps and upon grinding with a pestle and mortar some of the product formed a thin paste instead of forming a fine powder).

To reduce the amount of solvent contaminating the product it could have been left in the Büchner funnel for a longer period of time after the final filtration, however it is unlikely that this would result in a fully dried product since the solvent used was not particularly volatile (the boiling temperature of water is $100\,°C$ and that of acetic acid is $117.9\,°C$[2]). A more effective way to dry the product would have been to leave it in a vacuum desiccator overnight, since then the ambient pressure would be reduced below the vapour pressure of the solvent, hence causing it to evaporate much faster and leave a drier product.

3.3 Yield Calculation

The density of acetic anhydride is $1.082\,\mathrm{g\,cm^{-3}}$.[3]

$$\text{Moles of salicylic acid at start of reaction} = \frac{3.50\,\mathrm{g}}{(7(12.011) + 6(1.008) + 3(15.999))\,\mathrm{g\,mol^{-1}}}$$

$$= \frac{3.50\,\mathrm{g}}{138.122\,\mathrm{g\,mol^{-1}}} = 0.0253\,\mathrm{mol}$$

$$\text{Moles of acetic anhydride at start of reaction} = \frac{3.00\,\mathrm{cm^3} \times 1.082\,\mathrm{g\,cm^{-3}}}{(4(12.011) + 6(1.008) + 3(15.999))\,\mathrm{g\,mol^{-1}}}$$

$$= \frac{3.246\,\mathrm{g}}{102.089\,\mathrm{g\,mol^{-1}}} = 0.0318\,\mathrm{mol}$$

From the equation (see figure 2) there is a 1:1 molar ratio between salicylic acid and acetic anhydride, hence the acetic anhydride is in excess. The equation also shows a 1:1 molar ratio between the salicylic acid and aspirin, hence the theoretical amount of aspirin produced is $0.0253\,\mathrm{mol}$.

$$\therefore \text{Theoretical yield of aspirin} = 0.0253\,\mathrm{mol} \times (9(12.011) + 8(1.008) + 4(15.999))\,\mathrm{g\,mol^{-1}}$$

$$= 0.0253\,\mathrm{mol} \times 180.159\,\mathrm{g\,mol^{-1}} = 4.57\,\mathrm{g}$$

$$\therefore \text{Percentage yield} = \frac{3.99\,\mathrm{g}}{4.57\,\mathrm{g}} \times 100\,\% = 87.4\,\%$$

This is very high: this is because the aspirin was not fully dry before the mass was determined (see section 3.2). This yield value is much higher than expected since the reaction is reversible and hence will not proceed to completion (as shown in section 3.1 with the TLC results of the crude product).

In addition there were significant transfer losses at all transfers since the product was difficult to completely remove the sides of the vessels and while washing with ice-cold water aided in the transfer of product this would have also reduced the yield since some of the product would have dissolved in the water.

[1] W. M. Haynes, ed. *CRC Handbook of Chemistry and Physics*. 97th ed. Boca Raton: CRC Press, 2016, Physical Constants of Organic Compounds, 3-8.
[2] Haynes, *CRC Handbook of Chemistry and Physics*, Physical Constants of Organic Compounds, 3-4.
[3] Haynes, *CRC Handbook of Chemistry and Physics*, Physical Constants of Organic Compounds, 3-4.

3.4 Spectra

Table 2: IR Spectrum of Salicylic Acid.

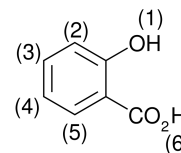| Wavenumber / cm^{-1}	Strength	Assignment
1609.7	Moderate	C=C Absorption.
1651.5	Moderate	C=O Absorption.
2850.8	Weak and Broad	O−H Absorption in hydroxyl group.

Figure 3: Salicylic acid.

Table 3: ^{1}H NMR Spectrum of Salicylic Acid in DMSO.

Chemical Shift / ppm	J-Coupling	Integral Area	Summary
9.6	Broad Singlet	Not Integrated	Proton in (6) (carboxyl group).
7.6	Doublet of Doublets	4.00	Proton in (5), coupling with (4) and (3).
7.2	Doublet of Doublets		Proton in (2), coupling with (3) and (4).
6.6	Triplet of Doublets (Considerable Roofing)	(Integrated together)	One proton in (3) and one in (4), coupling with (2) and (5) (and with each other).
2.4	Singlet	0.17	Characteristic of DMSO (solvent).

Table 4: IR Spectrum of Acetic Anhydride.

Wavenumber / cm^{-1}	Strength	Assignment
1751.0	Strong	C=O Absorption.
1821.9	Strong	C=O Absorption.

Table 5: ^{1}H NMR Spectrum of Acetic Anhydride.

Chemical Shift / ppm	J-Coupling	Integral Area	Summary
2.3	Singlet	1.00	Six protons in equivalent environment (from the two methyl groups).

Table 6: IR Spectrum of Product.

Wavenumber / cm^{-1}	Strength	Assignment
1602.5	Moderate	C=C Absorption.
1681.7	Strong	C=O Absorption.
1750.4	Moderate	C=O Absorption.
2835.7	Weak and Broad	O−H in hydroxyl group.
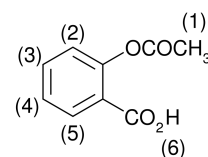
Figure 4: Aspirin.

Table 7: ^{1}H NMR Spectrum of Product.

Chemical Shift / ppm	J-Coupling	Integral Area	Summary
8.4-6.8	Complex Multiplet	16.21	Protons (2), (3), (4) and (5) from aspirin and salicylic acid impurity.
2.4	Singlet	7.40	Six protons from acetic anhydride impurity.
2.2	Singlet	3.00	Three protons in (1) from aspirin.

The product used for the ^{1}H NMR spectra was not pure since the spectrum contains a singlet peak from the two methyl groups in acetic anhydride and the relative area for the aromatic peaks is greater than four with a poorly defined splitting patten, hence indicating the presence of salicylic acid. Some aspirin can be seen to have been produced by the presence of the additional peak at 2.2 ppm due to the three protons in (1). The composition of the product can be determined by comparing the areas of the peaks sue to each substance and is 1.00:1.23:3.05 (aspirin:acetic anhydride:salicylic acid). This indicates that the purification steps were not very successful since the sample mostly consisted of impurities. The IR spectrum shows that aspirin was produced since the number of peaks due to carbonyl bonds increased from the one in salicylic acid to two in the product: is expected for an acylation.