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Traditional Undergraduate Experiment: Synthesis of Aspirin

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Contents

Manuscript prepared by Sarah Moore.

Objectives

The aim of the experiment is to introduce NMR spectroscopy into a traditional undergraduate organic chemistry experiment. Students synthesise aspirin and evaluate the purity of their product using ^{1}H-NMR spectroscopy. This laboratory introduces students to aspects of practical organic chemistry including synthesis, crystallization, stoichiometry, and percent yield.

Introduction

Aspirin is a pain relieving compound that most students will be familiar with, thus its synthesis gives students an insight into how chemistry is used in real-life applications. The synthesis of aspirin may be achieved in one simple step, O-acetylation of salicylic acid (Figure 1), which is incorporated into many undergraduate synthetic chemistry laboratory courses. The purity of the product as a pharmaceutical is crucial, and therefore students must determine the purity of their product. Typically this is done using thin layer chromatography (TLC), and here we introduce ^{1}H-NMR spectroscopy as a means of determining the purity of their sample and giving students experience in reporting the chemical shifts of a synthetic product. To do this, students obtain ^{1}H-NMR spectra of their starting materials, crude and purified products.

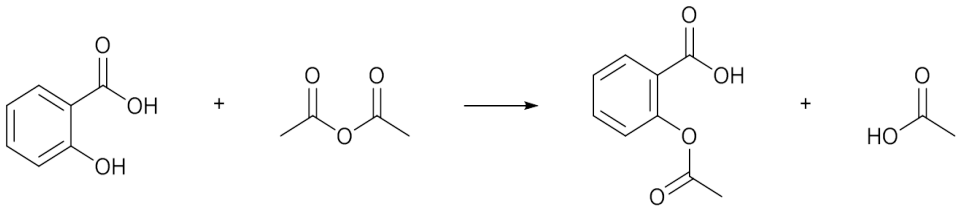


Figure 1: O-Acetylation of salicylic acid to give acetylsalicylate (aspirin).

An additional step may be added to the synthesis of aspirin: conversion of oil of wintergreen (methyl salicylate) to salicylic acid (Figure 2). This serves as an introduction to multi-step synthesis and the concept of converting a naturally occurring substance into one with therapeutic value. This also gives students an additional compound to isolate, purify, determine yield and characterise by ^{1}H-NMR spectroscopy.

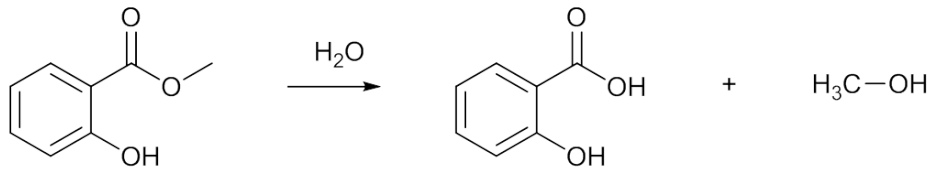


Figure 2: Hydrolysis of methyl salicylate (oil of wintergreen) to give salicylic acid.

Synthesis of salicylic acid from oil of wintergreen

	Methyl Salicylate	Salicylic Acid
Molecular Mass	152.15 g mol^{-1}	138.12 g mol^{-1}
Stoichiometry	1	1
Density	1.17 g mL^{-1}	Solid
Moles	0.03 mol	Theoretical: 0.03 mol
Mass	4.68 g (4 mL)	Theoretical: 4.14 g

Procedure

Add methyl salicylate (4 mL) and 6 M sodium hydroxide (40 mL) to a beaker and stir. Heat with occasional stirring until mixture reaches a gentle boil. Continue gentle boil for 15 minutes. During heating, wash solid from the sides of the beaker with a little distilled water. After heating, cool the reaction mixture in an ice bath until warm to touch. Leaving the beaker in the ice bath, add 8 M sulphuric acid (50 mL) to the reaction mixture with stirring. Leave mixture in the ice bath until chilled and crystals form. Isolate the precipitate using Buchner filtration and rinse the solid with a little cold distilled water. Obtain a yield and ^{1}H-NMR spectrum (in chloroform-d) of the crude product. Recrystallise the crude product from distilled water and dry crystals in a desiccator. Obtain a yield and ^{1}H-NMR spectrum (in chloroform-d) of the purified product. Also record the ^{1}H-NMR spectrum (in chloroform-d) of methyl salicylate.

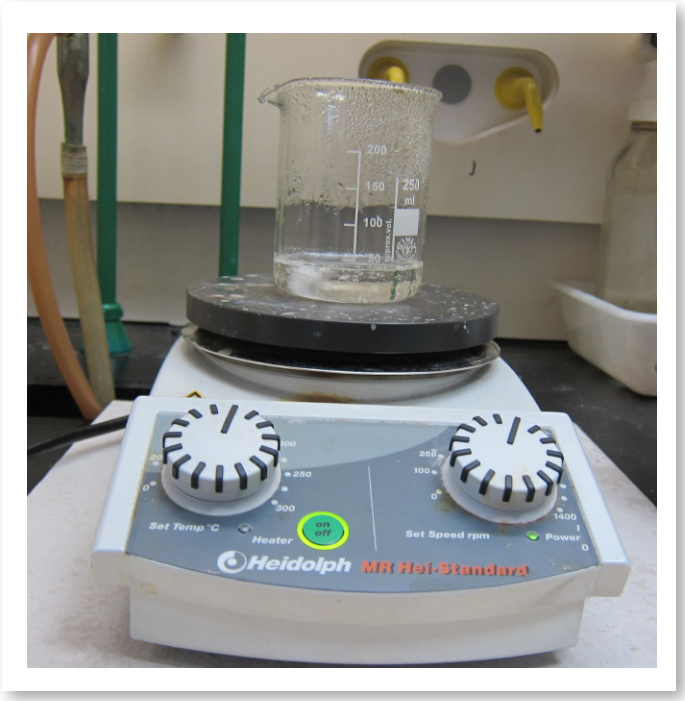


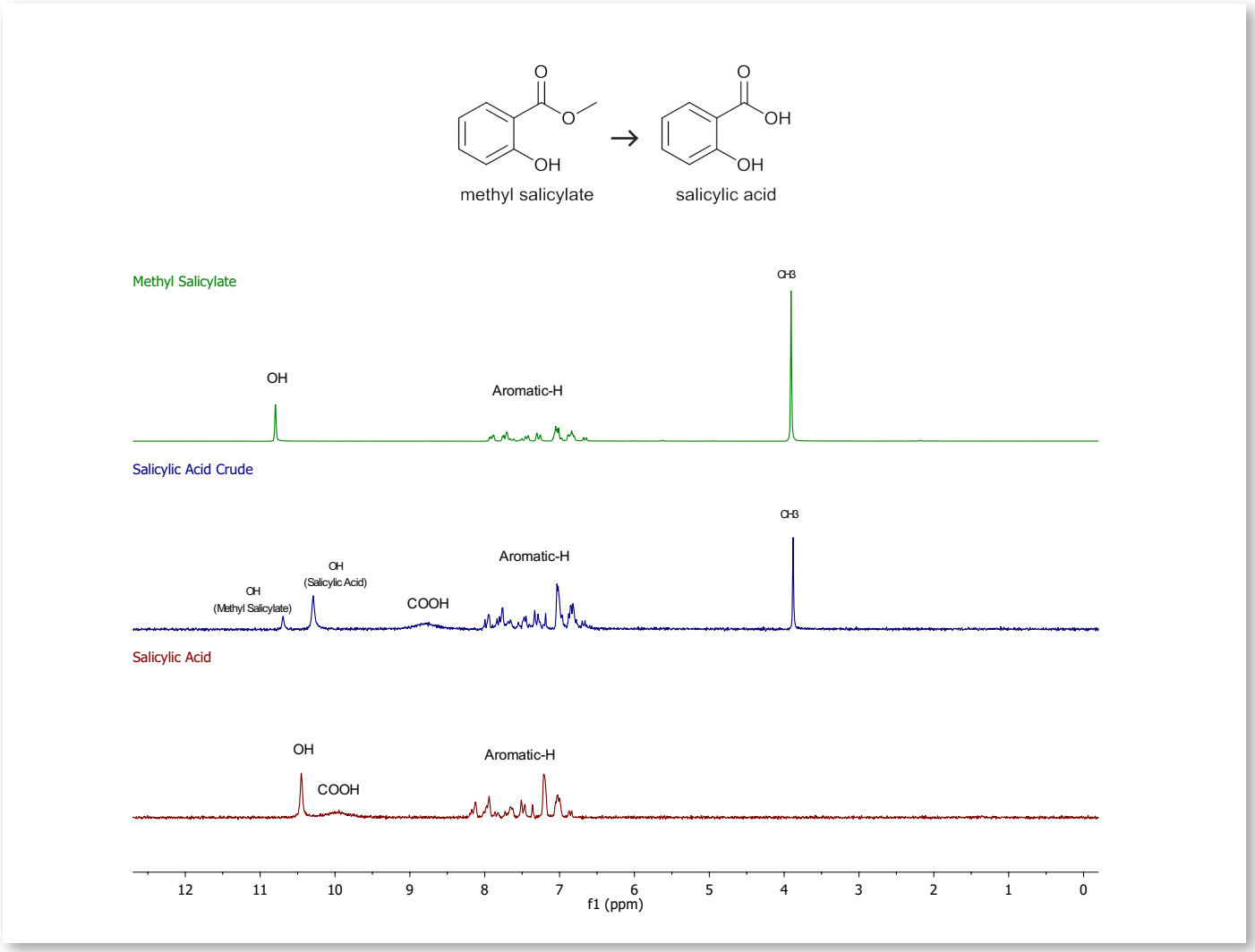
Figure 3: Hydrolysis of oil of wintergreen.

Risk Assessment

Methyl salicylate and salicylic acid are combustible and harmful if swallowed. Sodium hydroxide is corrosive, alkaline and causes severe burns. Care must be taken when making up the 6 M solution as dissolving sodium hydroxide pellets is exothermic and can become very hot. Sulfuric acid is corrosive, acid and causes severe burns. Care must be taken if the 8 M solution is prepared from concentrated sulfuric acid that the acid is added to the water, and not the other way around.

Figure 4: Crude and recrystallized salicylic acid.

^{1}H-NMR Spectra



Synthesis of aspirin from salicylic acid

	Salicylic Acid	Acetic Anhydride	Sodium Acetate	Acetylsalicylic Acid	Acetic Acid
Molecular Mass	138.12 g mol^{-1}	102.09 g mol^{-1}	82.03 g mo^{l-1}	180.16 g mol^{-1}	60.05 g mol^{-1}
Stoichiometry	1	1 (3, excess)	(Catalyst)	1	1
Density	Solid	1.08 g mL^{-1}	Solid	Solid	1.05 g mL^{-1}
Moles	0.014 mol	0.042 mol	0.0047 mol	Theoretical: 0.014 mol	Theoretical: 0.014 mol
Mass	2 g	4 g (4.4 mL)	0.4 g	Theoretical: 2.52 g	Theoretical: 0.84 g (0.8 mL)

Procedure

To a suspension of salicylic acid (2 g) in acetic anhydride (4.5 mL) in a conical flask add anhydrous sodium acetate (0.4 g) with stirring. Heat the reaction mixture for approximately 15 minutes. When the solid has dissolved, remove from the heat and add distilled water (20 mL). Place the flask in an ice bath until the mixture has chilled and crystals have formed. Collect the precipitate by Buchner filtration and rinse the solid with cold distilled water. Obtain a yield and ^{1}H-NMR spectrum (in chloroform-d) of the crude product. Recrystallise the crude product from distilled water and dry crystals in a desiccator. Obtain a yield and ^{1}H-NMR spectrum (in chloroform-d) of the purified product. Also record the ^{1}H-NMR spectra (in chloroform-d) of acetic anhydride and salicylic acid (if the first step of the synthesis was not carried out).

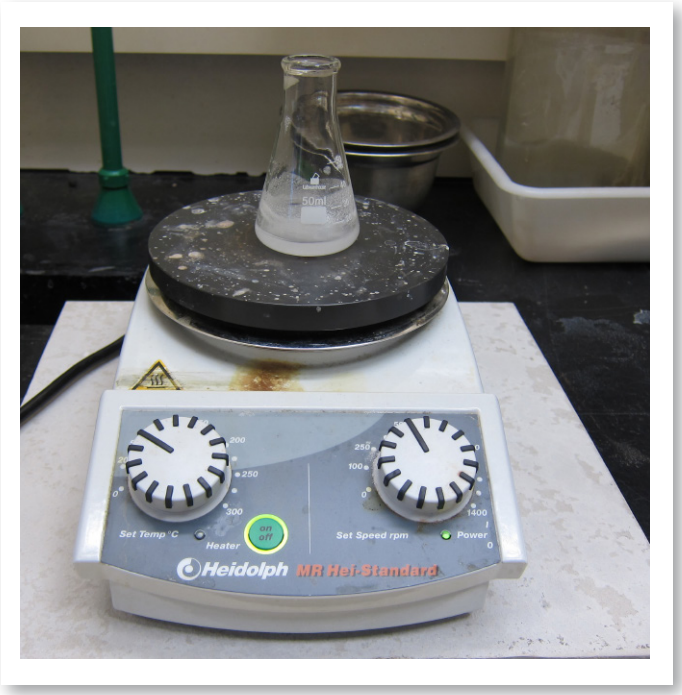


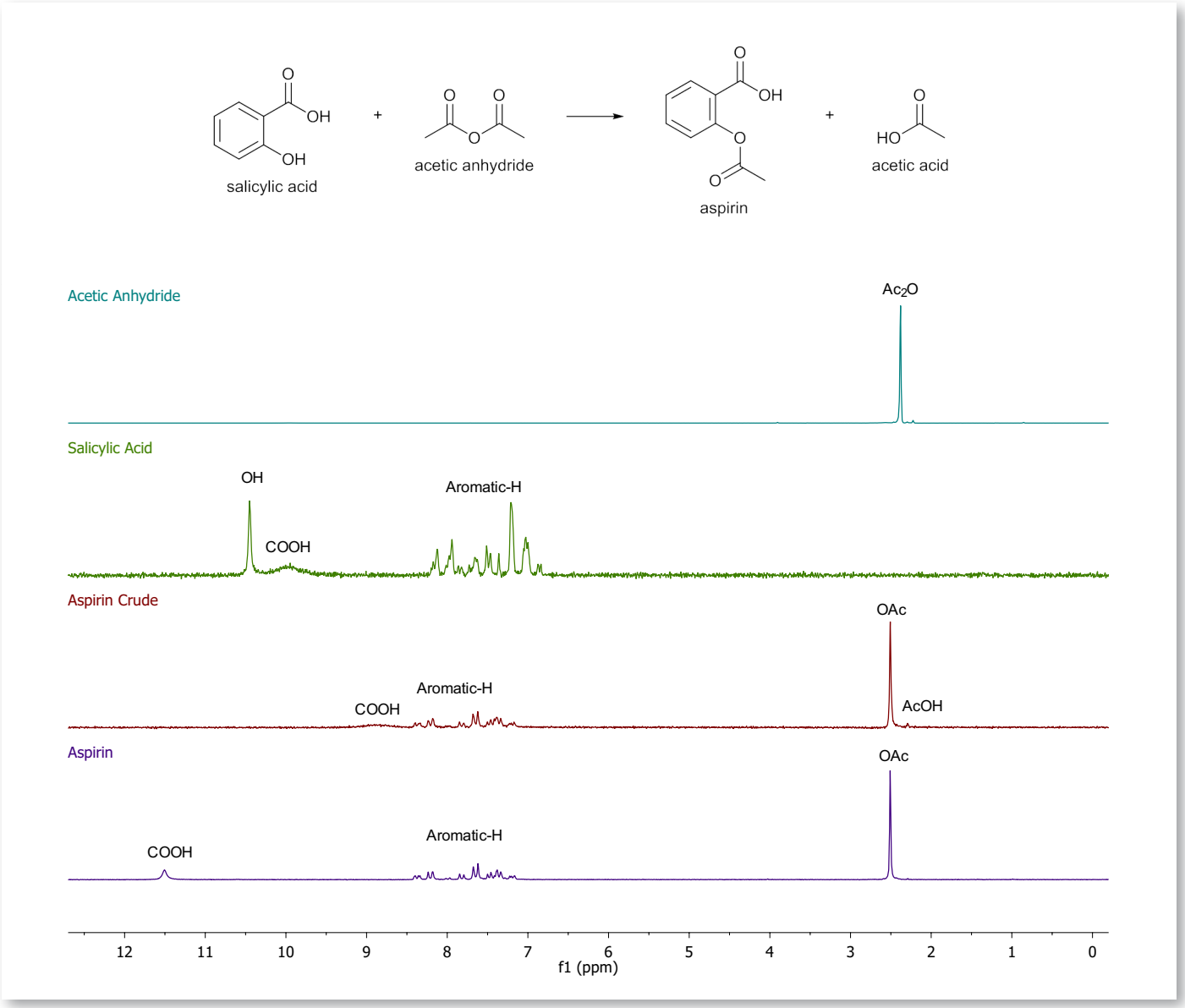
Figure 5: Acetylation of salicylic acid.

Risk Assessment

Acetylsalicylate and salicylic acid are combustible and harmful if swallowed. Acetic anhydride is corrosive, acid, can cause severe burns and is highly flammable. Ethanol is highly flammable.

Figure 6: Crude and recrystallized aspirin.

^{1}H-NMR Spectra



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Tasks and Questions

1. Calculate % yield for each step of the synthesis.
2. Assign the peaks in the ^{1}H-NMR spectra of all starting materials and products, and identify functional groups that are unique in each sample.
3. Identify the impurities in the crude products. Did recrystallization remove these impurities?

References

1) J. Olmsted III, Synthesis of Aspirin – A General Chemistry Experiment, *Journal of Chemical Education*, 75 (1998), 1261.

2) Royal Society of Chemistry. (2007). *Aspirin- the wonder medicine*. Retrieved from http://www.rsc.org/learn-chemistry/resource/res00000287/aspirin.

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