International Baccalaureate Diploma Programme

EXTENDED ESSAY
- CHEMISTRY -

An investigation into the synthesis of Aspirin in accordance with the principles of green chemistry

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1. INTRODUCTION

Aspirin is a commonly-used medication to treat pain, fever, and inflammation. Its industrial method of synthesis involves reacting salicylic acid with acetic anhydride (Lewis), a reaction known as esterification—which is the formation of ester by reacting a carboxylic acid with an alcohol.

Acetic anhydride, however, is a chemical compound that exhibits numerous hazardous effects. Moreover, it is one of the key substances used in making heroin, a highly addictive drug frequently used for recreational purposes. If not securely controlled, its uses may even result in more negative effects than positive benefits.

Because of this—along with the current trend of steering modern manufacturing methods toward *green industry*, a term created by the United Nations Industrial Development Organization (UNIDO) that refers to the "striving for a more sustainable pathway of growth"—I have been prompted to examine alternatives in synthesizing aspirin in hope of finding a safer and greener method. This led me to form the following research question:

To what extent can the industrial method of synthesis of aspirin be altered to best comply with the principles of green chemistry?

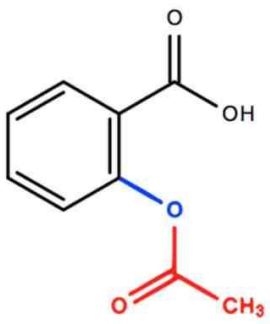
In this investigation, the standard industrial methodology in synthesising aspirin was altered whenever possible to move closer to achieving a completely green synthesis. The changes made

were determined based on the changes' consistencies with the twelve principles of green chemistry (see **1.3. Green Chemistry** and **Appendix 1**).

1.1. Acetic Anhydride Replacements

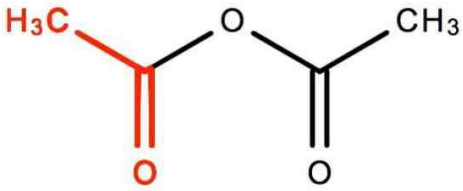
The process in which an ester is formed from alcohol and carboxylic acid in the presence of an acid catalyst is known as esterification. In aspirin's industrial method of synthesis, acetic anhydride (alcohol) and salicylic acid (carboxylic acid) undergo a condensation reaction to form aspirin (figure 1)—an ester—and produces acetic acid as a byproduct.

Figure 1: Aspirin



In *Figure 1*, the portion of aspirin in ***blue*** highlights what is left of the hydroxyl group after the condensation reaction, and the portion in **red**—also known as the acetyl group (CH_3CO)—highlights that of the carboxyl group. As acetic anhydride (*Figure 2*) contains the carboxyl group—and thus, the acetyl group (highlighted in **red**)—it is capable of undergoing esterification to form aspirin. Realizing this, I can infer as a general rule that for organic compounds to react with salicylic acid and form aspirin, it must at least contain an acetyl group.

Figure 2: Acetic Anhydride



As have discussed in the introduction, acetic anhydride exhibits numerous hazardous effects and can be used to produce heroin. Additionally, since it is a *Category IV substance*—which refers to a group of strictly regulated chemicals that can be used to produce illicit narcotics in Thailand—the compound is not an ideal candidate for a green synthesis, and thus prompted me to look for possible replacements. Observing that compounds must contain the acetyl group, I found two possible acetic anhydride replacements: acetyl chloride (*Figure 3*) and acetic acid (*Figure 4*). The acetyl groups are highlighted in **red**.

Figure 3: Acetyl Chloride

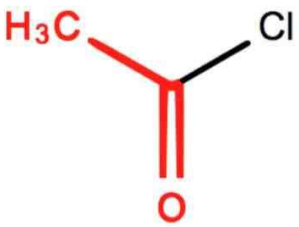
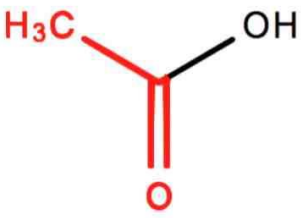


Figure 4: Acetic Acid



However, after further investigation, I found out that acetyl chloride, like acetic anhydride, is also a Category IV substance. Being category IV substances, they are illegal for normal uses in Thailand (Chaninat). While quantitative conclusions of these two substances could not be drawn

from this investigation, the fact that both substances are illegal already suggests that they are not the appropriate reactants for a green synthesis. Further evaluation of the three reactants and an explanation to why acetic acid is most preferable can be found in **5.1. Discussion**.

1.2. Acetic Acid and the Equilibrium

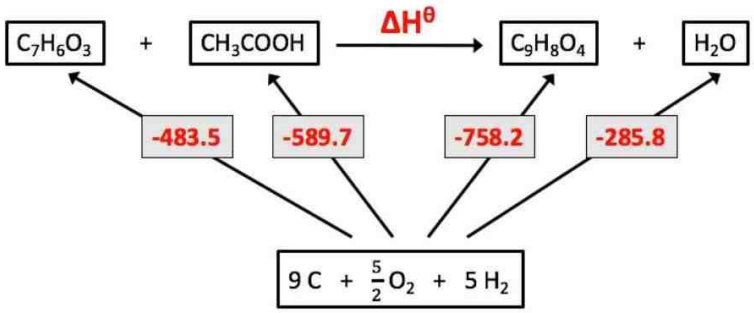
As acetic acid has a chemical structure that is different to that of acetic anhydride, the products of its reaction with salicylic acid will also be different. While the conventional synthesis would produce acetic acid as the byproduct to Aspirin, the reaction between acetic acid and salicylic acid would form water molecules as the byproduct instead. The equation for this synthesis is written below:

$$C_7H_6O_3\ (s) + CH_3COOH\ (l) \rightleftharpoons C_9H_8O_4\ (s) + H_2O\ (l)$$

(Equation 1)

Notice from the equation above that the reaction mentioned forms an equilibrium: the forward reaction is the synthesis of aspirin, and the reverse reaction is its hydrolysis. Among the modifications that can be made to the industrial method, the reaction's equilibrium nature suggests that temperature can also be changed to favor one side of the reaction (Clark). Since green chemistry is aimed at reducing waste—thus maximizing productivity—I can shift the equilibrium by changing the temperature in a manner such that the forward reaction is favored. To determine whether I should increase or decrease the temperature, I must know if the synthesis of aspirin is exothermic or endothermic. This can be calculated using the enthalpy cycle.

Figure 5: Energy cycle



Based on Hess's Law, the energy cycle above (*Figure 5)*, which uses the standard enthalpies of formation obtained from **NIST Chemistry WebBook**, can be used to calculate the standard enthalpy change when aspirin is formed

$$\Delta H_f^\ominus(C_7H_6O_3) + \Delta H_f^\ominus(CH_3COOH) + \Delta H = \Delta H_f^\ominus(C_9H_8O) + \Delta H_f^\ominus(H_2O) \quad ...1$$

$$(-483.5) + (-589.7) + \Delta H = (-758.2) + (-285.8) \quad ...2$$

$$\Delta H = 29.2 \text{ kJ mol}^{-1} \quad ...3$$

Based on the calculation above, there is a positive change in enthalpy, indicating that the reaction is endothermic. This means that the temperature of the reaction can be raised to favor the forward reaction, and thus, increase the aspirin yield. This, however, raised another question: To what extent should the temperature be increased? This investigation aimed to find the ideal temperature that balances between temperature and rate in order to obtain the method that is arguably most consistent with the principles of green chemistry.

1.3. Green Chemistry

Green chemistry is an area in chemistry geared towards developing and designing processes that minimize the use of hazardous substances, avoid producing waste, and emphasize on sustainable and renewable energy. As an attempt to establish a conventional standards of green chemistry, Paul Anastas and John Warner came up with the twelve principles of green chemistry (listed in **Appendix 1**).

For this specific investigation, the changes that I made to the standard methods are most consistent with the following principles of green chemistry: (1) waste prevention, (2) atom economy, (3) less hazardous chemical syntheses, and (4) designing safer chemicals.

First, to avoid using more-than-needed reactants, stoichiometric calculations were made to ensure that just the right ratio of both reactants were used. Secondly, using acetic acid instead of the other two options—acetic anhydride or acetyl chloride—also resulted in a higher atom economy. While acetic anhydride and acetyl chloride had the atom economy percentages of 75.0% and 83.2%, respectively, acetic acid had a percentage of 90.9%, reflecting how more reactants have been converted to the desired product ("The PubChem Project"). As have discussed in **1.1. Acetic Anhydride Replacements**, the use of acetic acid also contributed to a safer chemical synthesis. Finally, using acetic acid also allowed for a safer synthesis design. This is because the reaction between acetic acid and salicylic acid produced water as a byproduct rather than hydrochloric acid and acetic acid, both of which can be quite corrosive.

2. INVESTIGATION

2.1. Variables

Control

1. 2.00 grams of salicylic acid and 5 millimeters of glacial acetic acid were used.
2. The solution containing the reagents was heated up and cooled down for the same amount of time.
3. The room temperature was fixed at 25°C.
4. All produced aspirin was left to be dried overnight in an oven at 70°C

Independent Variable

The independent variable is the temperature of the water surrounding the solution containing the reagents. The water was heated and controlled to maintain the five different variations of temperature: 65, 75, 85, 95, and 105°C. Note that while the water in the beaker was indeed boiling at 105°C, the solution level in the erlenmeyer flask was still kept submerged under the water level throughout the whole heating process.

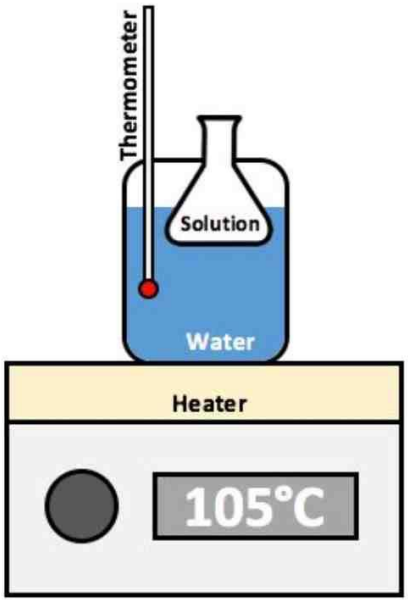


Figure 6: Lab Setup Whilst the Reagents Reacted (Left)

Clamps and stands, although used, are not included in the figure on the left.

Dependent Variable

The purity—tested using the melting point test—of the aspirin produced and the percentage yield—measured through calculating the product's mass.

2.2. Materials

Chemical

1. (30 grams) Salicylic Acid
2. (36 millimeters) Glacial Acetic Acid
3. (225 millimeters) Distilled Water
4. (5 millimeters) 18 M Sulfuric Acid
5. (225 millimeters) Ethanol
6. Water

Apparatus

1. Heater
2. 50ml Erlenmeyer Flask
3. Stirring Rod
4. Weighing Scale
5. Clamp stand
6. 250 ml Beaker
7. Watch Glass
8. Melting Point Apparatus (meter)
9. Refrigerator (or ice bath)
10. 10 ml Graduated Cylinder
11. 250 ml Beaker
12. 25 ml Graduated Cylinder
13. Pipette
14. Filter Paper
15. Buchner Funnel
16. Rubber Disk
17. Filter Flask
18. Aspirator
19. Fume Hood
20. Chromatography Plate
21. Weigh Boat
22. Thermometer

The methodologies below are modified from the standard method in synthesizing aspirin published by Professor Eddy at Louisiana Tech University (Eddy).

2.3. Preparing the Materials

1. 2.00 grams of **salicylic acid** was transferred onto a **weigh boat** to be weighed using a **weighing scale**.
2. The weighed salicylic acid was then transferred into a **50 ml Erlenmeyer flask**.
3. 5.0 millimeters of **glacial acid** was measured using a **10 ml graduated cylinder**.
4. The acid was poured into the weigh boat, and then into the Erlenmeyer flask.
5. 10 drops of **19 M sulfuric acid** were added to the flask.
6. The reagents inside were stirred using a **stirring rod**.

2.4. Reacting the Reagents

In reacting salicylic acid and acetic acid, I have modified the methodology of a standard aspirin synthesis to better suit the concept of green chemistry proposed in this investigation. Realizing that distilled water is normally added to react with the excess acetic anhydride and form acetic acid in the conventional method, I skipped this step to avoid using unnecessary resources.

1. 200.0 ml of **water** was poured into a **250 ml beaker**.
2. The temperature of the **heater** was set to the variations being tested: 65, 75, 85, 95, and 105°C).
3. A **thermometer** was placed inside the beaker, which was then laid onto the heater.

4. After reaching the water inside inside the beaker reached the desired temperature, a **clamp stand** was used to hold the erlenmeyer flask inside the flask such that the reagents in the flask were fully submerged under the water's level (see *Figure 6*).
5. The reactants were left to be heated (reacted) for 15 minutes.
6. After 15 minutes, the Erlenmeyer flask was left to be cool down at room temperature for 10 minutes.
7. The crystallization of the product was induced by scratching the liquid solution inside the Erlenmeyer flask against the wall of the flask.
8. The flask was immediately moved into the **refrigerator**, and was left there for another 10 minutes.

2.5. Filtering the Aspirin

The filtration of aspirin involves the use of a **Büchner funnel**, a **rubber ring**, a **filtering flask**, and an **aspirator**. This process, also known as *pressure assisted filtration*, creates a vacuum, thus unequal pressure inside the flask. This allows the greater atmospheric pressure above the funnel to push the liquid through the **filter paper** and the funnel's porous plate. This process follows the standard standard filtration method using the Büchner funnel. Its specific instructions can be found under **Appendix 2**.

2.6. Recrystallizing Aspirin

1. The filtrated crystal was transferred to a **250 ml beaker**.
2. 15.0 ml of **ethanol** was dissolved with the crystal.

3. 15.0 ml of **distilled water** was heated to 50°C and then added to the beaker.
4. The beaker was left to be cooled at room temperature for 10 minutes.
5. The inner wall of the beaker was scratched again to induce the crystallization.
6. The beaker was placed into a **refrigerator** for another minutes to allow recrystallisation to occur.
7. The crystal was filtered again, repeating the steps in **2.5. Filtering Aspirin**. However, in addition to the steps mentioned, the mass of the filter paper being filtration was measured.
8. The mass of a **watch glass** was measured using the **weighing scale**.
9. The final filtrated product was transferred to the watch glass, and then dried overnight to be analysed quantitatively.

2.7. Percentage Yield

1. The total mass of the watch glass was measured.
2. The mass of the product was calculated by subtracting the measured total mass with the mass of the watch glass and the mass of the filter paper.

To calculate the percentage yield, do $\frac{actual\ yield}{theoretical\ yield} \times 100\%$. This sample calculations can be found under **4.3. Sample Calculations**.

2.8. Melting Point Test

Melting point tests are used to test the purity of solid samples. Melting point, the temperature in which a substance melts, is dependent on the strength of the intermolecular forces of that substance. As each chemical compound has a unique chemical structure, it will have a unique melting point. This fact can be used to help test the purity of a sample (SRS).

Based on *Equation 1* in **1.2. Acetic Acid and the Equilibrium**, the reaction producing aspirin forms an equilibrium, thus, giving rise to four different possible products: solid salicylic acid and aspirin, and liquid acetic acid and water. However, as the crystal produced is left to be dried overnight, the only products left on the watch glass should theoretically only contain the two solids: salicylic acid and aspirin.

The table below tells the melting point, in celsius, of the two solids ("The PubChem Project"),

Substance	Melting Point (°C)
Aspirin	135
Salicylic Acid	158

Due to the presence of both aspirin and salicylic acid, the melting point of the crystal will lie between the boiling points of the two compounds: 135°C and 158°C. The closer the melting point of the crystal is to that of aspirin, the greater the aspirin yield.

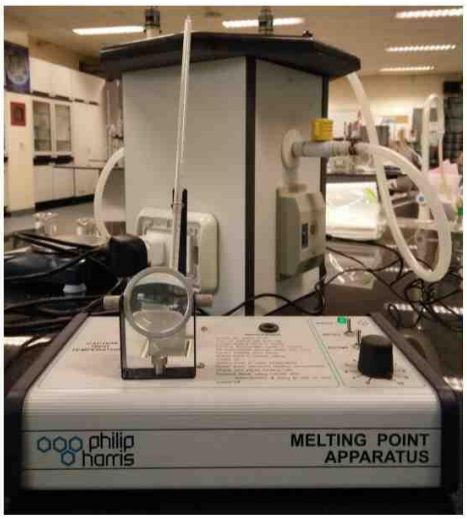
This process follows the standard procedure of a melting point test (see **Appendix 3**). Realizing that the sample would not start melting until the it reached the temperature of 135°C, I quickly heated the apparatus to 110°C. From this point on, the temperature was gradually increased.

Due to the color of aspirin's crystal, it was relatively hard to determine the exact point in which the crystal started to melt. Because of this, another capillary tube with crystal from the sample inside was used to perform a side-by-side comparison. This tube was not heated. *Figure 7* shows the difference in texture and color of the two capillary tubes, and *Figure 8* shows the picture of the melting point apparatus used.

Figure 7: Capillary Tubes Comparison

Left: Tip slightly translucent shows that the crystal has melted. Right: Crystal is still clear.

Figure 8: Melting Point Apparatus



3. SAFETY GUIDELINES

- The material preparation and reaction of aspirin were placed and done under the fume hood.
- Gloves and safety goggles were worn at all times.
- Ignition sources were removed from the area of the lab.
- When acidic wastes were disposed, baking soda was added to neutralize the acid.

4. RESULTS

4.1. Qualitative Data

- The time taken for crystals to form varied from trial to trial.
- There was an apparent increase in volume of crystal produced for the temperature variations from 65°C to 85°C.

Figure 7: Crystal Produced at 65 °C (left) vs. at 105 °C (right)

4.2. Quantitative Data

Table 1: The mass of crystal produced and its melting point at different temperature variations. *The total mass is the mass of aspirin and the filter paper on the watch glass. The mass of the watch glass and the filter paper combined was 48.78 grams.*

Temperature (°C)	Trial	Total Mass (g)	Mass of Product (g)	Melting Point (°C)
65	1	49.61	0.83	145
	2	49.66	0.88	146
	3	49.72	0.94	147
75	1	49.75	0.97	143
	2	49.80	1.02	143
	3	49.72	0.94	141
85	1	49.88	1.10	139
	2	49.83	1.05	140
	3	49.84	1.06	140
95	1	49.91	1.13	138
	2	49.93	1.15	140
	3	49.95	1.17	137
105	1	49.98	1.20	135
	2	49.96	1.18	136
	3	49.95	1.17	136

Table 2: Processed Data and Uncertainties. *The uncertainties displayed above are procedural uncertainties. They are rounded to one significant figure.*

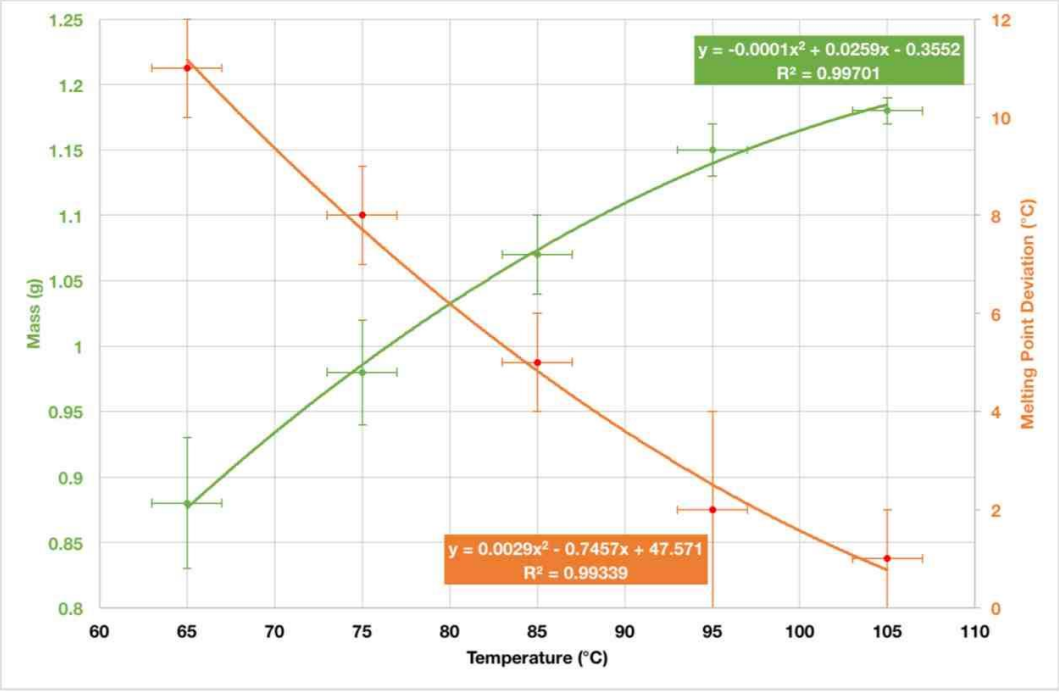
Temperature (± 2 °C)	Avg. Mass of Product (g)	Uncertainty (± g)	Avg. Melting Point (°C)	Uncertainty (± °C)
65	0.88	0.05	146	1
75	0.98	0.04	143	1
85	1.07	0.03	130	1
95	1.15	0.02	138	2
105	1.18	0.01	136	1

4.3. Data Analysis

Table 3: Melting Point Deviations from the Actual Value

Temperature (± 2 °C)	Avg. Melting Point (°C)	Deviation from the Actual Value (°C)	Uncertainty (± °C)
65	146	11	1
75	143	8	1
85	140	5	1
95	138	2	2
105	136	1	1

Figure 9: *Graph comparing the mass of crystal produced and melting point deviation at different temperatures.*



The graph in *Figure 9* shows the relationship between the mass of crystal produced (**green**) and the magnitude (in celsius) in which the measured melting point deviated from the actual value (**orange**). The trend lines in both relationships display a quadratic relationship, both of which also pass through all the error bars.

4.4. Interpretation

From the graph, it can be seen that as temperature increases, the mass of crystal produced also increases and the melting point deviation decreases. Note that the mass of the crystal produced is not equivalent to the mass of aspirin. This is due to the fact that the crystals have deviations from the melting point of aspirin, thus indicating that they are impure.

As evident from *Figure 9*, there is a negative correlation between temperature and melting point deviation, suggesting that at higher temperature, the ratio of aspirin to salicylic acid in the crystal sample increases. This is more preferable as it gives rise to more useful products, thus adhering to the first principle of green chemistry: waste prevention. The positive trend between temperature and mass of crystal produced, like that of temperature and melting point deviation, also results in a more preferable outcome when temperature increases as there is a greater amount of product produced despite using the same amount of reactants.

Collectively, they indicate that at higher temperatures, aspirin yields increases. This is consistent with the goal of a green synthesis, that is to maximize productivity.

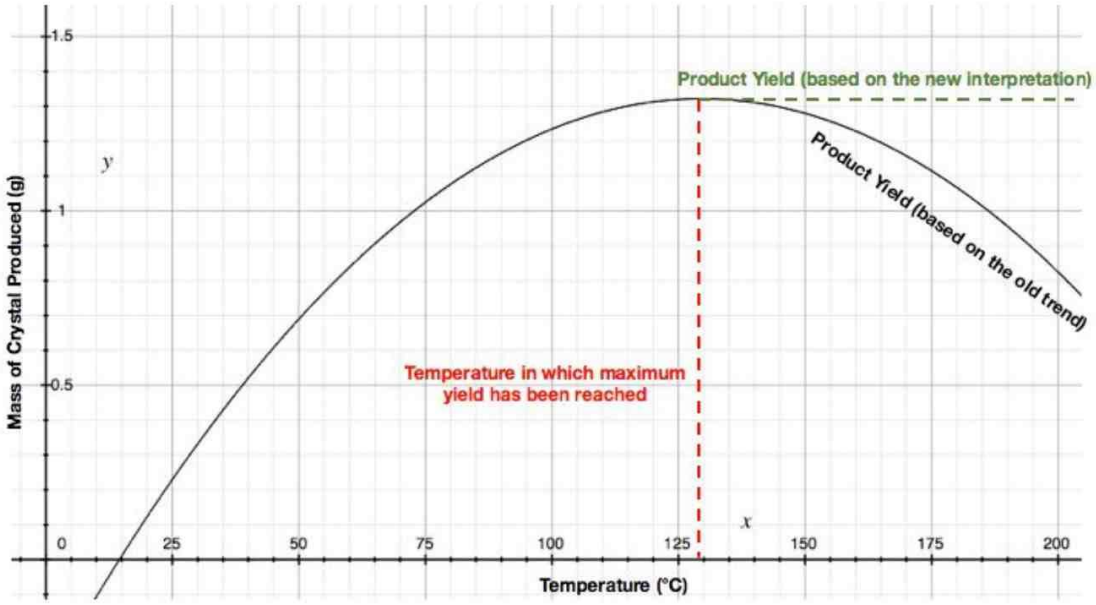
However, at the same time, the quadratic nature of both trends also present a limitation. If extrapolated, the mass-of-crystal-produced trend will eventually slope downward and the melting-point-deviation trend upward, implying that the aspirin yield will decrease after the temperature has increased beyond a certain point. This is not supported by current chemistry theories since increases in temperature, as I have discussed in **1.2. Acetic Acid and the Equilibrium**, should favor endothermic reactions in equilibriums, subsequently increasing aspirin yield.

Despite this error, using a positive linear line-of-best-fit will not necessarily provide a more accurate prediction either; this is because a linear trend suggests that the mass of crystal produced will continue to increase indefinitely when temperature increases. This, however, is not true as the amount of aspirin produced will be limited by the amount of reactants used.

Hence, the quadratic trends are still used as they are more representative of the collected data. This is reflected through the close-to-one R^2 *value* and the intersection of the trend lines through all the error bars. As for the trends' maximum and minimum points, they will be interpreted as limits instead. This is logical as the amount of crystal produced can only be as much as the moles of reactants used.

This new interpretation suggests that after a certain temperature, all of the reactants will be completely used up, and the products will reach its maximum yield. The new trend illustrating this interpretation can be seen in *Figure 10.*

Figure 10: *Graph illustrating the new interpretation of the mass-of-crystal-produced trend.*



The specific temperature in which the aspirin yield stops increasing, as evident in *Figure 10*, correspond with the maximum and minimum of the trends, which can be calculated using the vertex formula of a quadratic function $x = -\frac{b}{2a}$. The values of these temperatures are calculated to be 129.5 °C for the mass-of-crystal-produced trend, and 128.6 °C for the melting-point-deviation trend.

At 129.5 °C, the mass of crystal produced is calculated to be 1.322 grams, and at 128.6 °C, the melting point deviation is calculated to be -0.3659. As negative deviation values are theoretically impossible because the crystal sample only contained aspirin and salicylic acid, it can be inferred that at temperature higher than 128.6 °C, the deviation has already reached the limit of 0. This implies that the produced crystal is pure aspirin.

Based on stoichiometric calculations, 2.00 grams of salicylic should produce 2.61 grams of aspirin. Thus conclusively, the aspirin yield from the reaction between salicylic acid and acetic acid increases at higher temperature, and is highest at 129.5 °C, producing 1.322 grams of aspirin and a percentage yield of 50.7%.

4.5. Sample Calculations

Mass of Product – 65 °C (Trial 1)

$$Total\ Mass - Mass\ of\ Watch\ Glass\ and\ Filter\ Paper = 49.61 - 48.78 = 0.83\ \text{g}$$

Average Mass of Product – 65 °C

$$\frac{Mass\ of\ Aspirin\ in\ Trial\ 1 + Trial\ 2 + Trial\ 3}{3} = \frac{0.83 + 0.88 + 0.94}{3} = 0.88\ \text{g}$$

Average Melting Point – 75 °C

$$\frac{Melting\ Point\ in\ Trial\ 1 + Trial\ 2 + Trial\ 3}{3} = \frac{143 + 143 + 141}{3} = 143\ °\text{C}$$

Uncertainty of Average Mass – 85 °C

$$\frac{Maximum\ Mass - Minimum\ Mass}{2} = \frac{1.10 - 1.05}{2} = 0.25\ \text{g} \approx 0.3\ \text{g}$$

Uncertainty of Average Melting Point – 95 °C

$$\frac{Maximum\ Melting\ Point - Minimum\ Melting\ Point}{2} = \frac{140 - 137}{2} = 1.5\ °\text{C} \approx 2\ °\text{C}$$

Deviation from the Actual Value – 105 °C

$$Average\ Melting\ Point - Actual\ Value = 136 - 135 = 1\ °\text{C}$$

***x*-Coordinate of the Vertex** – Mass-of-Crystal-Produced Trend

$$Temperature = -\frac{b}{2a} = -\frac{0.0259}{2(0.0001)} = 129.5\ °\text{C}$$

***y*-Coordinate of the Vertex** – Melting-Point-Deviation Trend

$$Deviation = 0.0029x^2 - 0.7457x + 47.571 = -0.3659\ °\text{C}$$

5. CONCLUSION AND DISCUSSION

To argue why acetic acid is most preferable reagent over the other two mentioned in **1.1. Acetic Anhydride Replacements**—acetic anhydride and acetyl chloride—for the synthesis of aspirin to be green, I will delve into each of the synthesis and evaluate its consistency with the principles of green chemistry.

5.1. Acetic Anhydride

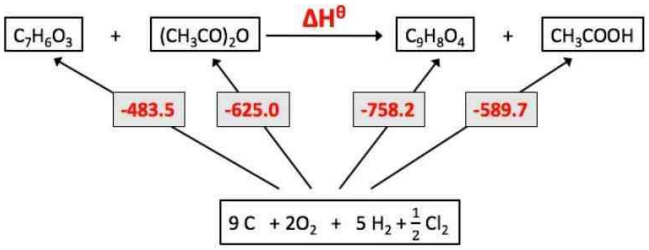
Acetic anhydride reacts with salicylic acid to form aspirin and acetic acid. This reaction can be represented by the following equation:

$$C_7H_6O_3\ (s) + (CH_3CO)_2O\ (l) \rightarrow C_9H_8O_4\ (s) + CH_3COOH\ (l)$$

(Equation 2)

This synthetic procedure is the most common method used in manufacturing aspirin as the use of an anhydrous compound does not lead to production of water, but the production of carboxylic acid instead. This helps prevent the reverse reaction—the hydrolysis of aspirin—from occurring, and thus, allows the the synthesis to proceed at a higher rate and produce a greater yield of aspirin due to the absence of an equilibrium. Additionally, as the reaction between acetic anhydride salicylic and salicylic acid is extremely exothermic (see *Figure 11*), the heat given off by the reaction is also sufficient enough to facilitate the reaction without the need of external heating (Handal-vega). This is supported by the gibbs free energy equation, $\Delta G = \Delta H - T\Delta S$. The very negative ΔH helps lower ΔG, thus making the reaction more spontaneous (Bodner).

Figure 11: Enthalpy Change in Synthesising Aspirin Using Acetic Anhydride



*Based on the energy cycle above, the change in enthalpy is calculated to be -239.4 kJ mol^{-1}. The enthalpy of formation values are obtained from the **NIST Chemistry WebBook**.*

This, however, comes with a cost: while this method offers aspirin manufacturers a more economically viable option, it involves the use of a much more hazardous substance. As have discussed in **1. INTRODUCTION**, acetic anhydride exhibits numerous hazards: as the liquid is extremely harmful and toxic—it can cause respiratory irritation if inhaled and severe burns on contact—its volatility makes the compound only more dangerous. Furthermore, as this synthetic procedure forms pure acid (glacial acetic acid) as the byproduct, it can dissociate into H^+ and CH_3COO^-. This increases the concentration of H^+, making the solution more acidic. Consequently, the disposal of this synthesis' waste entails further treatment—that is the neutralization of the acid.

Therefore, even though the use of acetic anhydride does not need any external supply of energy—thus adhering to the sixth principle, design for energy efficiency—the methodology involves the use of a more hazardous substance, produces more waste due to the need of neutralization, and has greater potential risks, all of which are inconsistent with the principles of green chemistry.

5.2. Acetyl Chloride

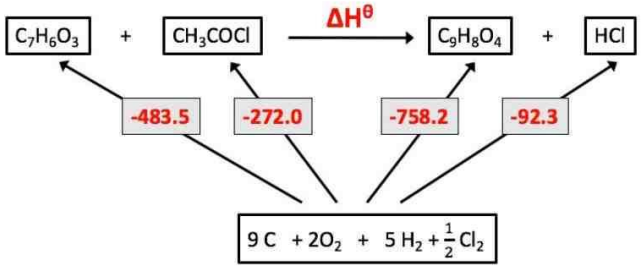
Acetyl chloride, similarly, has negative consequences that outweigh the positive. Acetyl chloride and salicylic acid react to form aspirin and hydrogen chloride. This reaction can be represented by the following equation:

$$C_7H_6O_3\ (s) + CH_3COCl\ (l) \rightarrow C_9H_8O_4\ (s) + HCl\ (g)$$

(Equation 3)

The reaction between salicylic acid and acetyl chloride, like that with acetic anhydride, does not form an equilibrium as the reaction does not form water. Instead, it initially forms the gaseous byproduct hydrogen chloride (*HCl*). As this reaction is also exothermic (see *Figure 12*), this means that this synthesis, too, exhibits the benefits of being a fast reaction and giving a high product yield.

Figure 12: Enthalpy Change in Synthesising Aspirin Using Acetyl Chloride

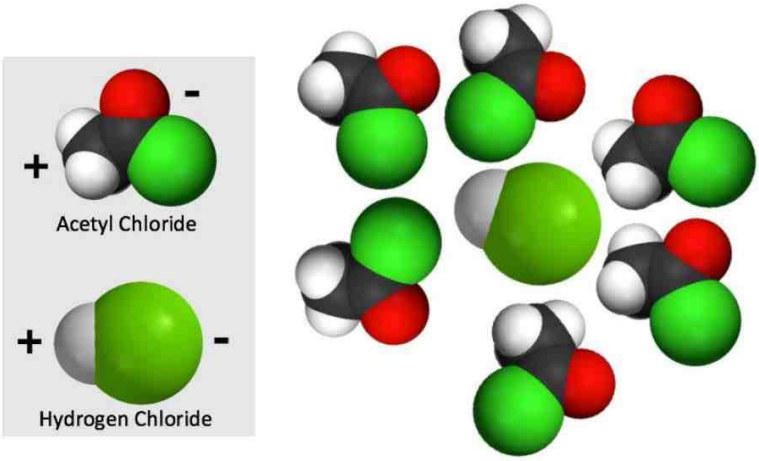


Based on the energy cycle above, the change in enthalpy is calculated to be -95.0 kJ mol^{-1}. The enthalpy of formation values are obtained from the ***NIST Chemistry WebBook****.*

Nonetheless, the formation of hydrogen chloride, a hazardous gas, poses much greater negative consequences. As this synthesis procedure takes place in a liquid environment, hydrogen

chloride, a strong electrolyte, is susceptible to being dissolved by the liquid polar molecules into hydrogen ions and chloride ions (Bertrand). This process is illustrated in *Figure 12*.

Figure 12*: *Dissolving Hydrogen Chloride



The slight negative charge near chlorine in acetyl chloride attracts the slight positive charge near hydrogen in hydrogen chloride, and the slight positive charge near hydrogen in acetyl chloride attracts the slight negative charge near chloride in hydrogen chloride. With enough acetyl chloride molecules around the hydrogen chloride molecule, the attraction between them may be powerful enough to overcome the covalent bond in hydrogen chloride, thus resulting in the molecule's dissociation. This gives rise to hydrogen ions, which causes the solution to become acidic. This means that a waste treatment to neutralize the waste product before it can be disposed is also needed.

Ultimately, the synthesis of aspirin using acetyl chloride produces gaseous hydrogen chloride. However, as the reaction takes place in a liquid environment, the gaseous byproduct partially dissolves, thus resulting in both an acidic solution and the production of hydrogen chloride gas.

When compared to the conventional method—the synthesis using acetic anhydride—the use of acetyl chloride is arguably much weaker in many ways. In addition to the flaws that the synthesis using acetic anhydride has, this method also requires much greater care due to the production of hydrogen chloride. Moreover, additional treatment is needed to get rid of the hazardous gas. One possible option is through reacting the gas with hydrogrossular, a calcium aluminium garnet (Fujita), thus resulting introducing greater waste. The reaction's less negative enthalpy change, -95 kJ mol^{-1}, that that using acetic anhydride, -239.4 kJ mol^{-1}, also suggests a lower spontaneity. Altogether, the use of acetyl chloride poses much more consequences that are inconsistent with the principles of green chemistry that the other two syntheses.

5.3. Conclusion

Conclusively, based on the discussions about the use of acetic anhydride and acetyl chloride, it is justifiable to use acetic acid as the reagent in order to develop a greener synthesis. *Table 4* in the next page summarizes each method's consistency with the principles of green chemistry.

Table 4: *Comparison of the three syntheses' consistency with the principles of green chemistry.*

Boxes highlighted in **green** reflect on the chosen reagent being most consistent with the principles of green chemistry, **yellow** being mediocre, and **red** being the least.			
Principle	**Acetic Acid**	**Acetic Anhydride**	**Acetyl Chloride**
Waste Prevention			
Atom Economy			
Less Hazardous Syntheses			
Designing Safer Chemicals			
Design for Energy Efficiency			
Inherently Safer Chemistry for Accident Prevention			
Not Applicable			
Safer Solvents and Auxiliaries		Use of Renewable Feedstocks	
Reduce Derivatives		Catalysis	
Design for Degradation		Real-time analysis for Pollution Prevention	

As apparent in the table above, acetic acid has the most amount of green boxes, indicating it is the greenest reagent. The compound's only weakness—as reflected by the red box under the principle "Design for Energy Efficiency"—arises due to the formation of an equilibrium, which hinders the forward reaction. However, as evident from this investigation's quantitative result, this can be countered by increasing the temperature in order to facilitate the rate of reaction and the amount of aspirin yield. Based on the interpretation of the line of best fit in *Figure 10*, reacting the reagents at 129.5 °C will give the best yield. Decreasing the temperature will lead to a reduction in yield, and increasing the temperature will not increase the yield any further.

6. EVALUATION

1. As the solution was left alone to recrystallize, some trials took much longer than the other before recrystallization started. This would have definitely affected the amount of crystal formed as solutions. A solution to solving this inconsistency is to manually induce recrystallization myself by scratching onto the side of the solution, and then leave the solution inside the refrigerator (or the ice bath) for an extended amount of time.
2. A test run to measure the amount of time it takes for the reaction between salicylic acid and acetic acid to reach equilibrium was never done. This means that the reaction may have not necessarily reached equilibrium yet when the reaction was quenched in cold water. This error can be fixed by performing multiple test synthesis using the lowest temperature to determine the concentration at different time period. By plotting the time versus concentration graph, I will be able to determine the approximate of time needed for equilibrium to be achieved.

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8. APPENDICES

8.1. Appendix 1

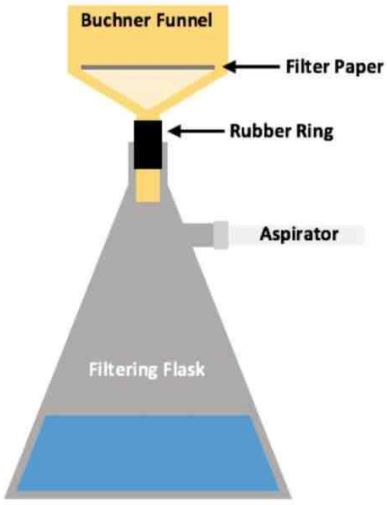
1	**Waste Prevention**
	Instead of designing ways to treat waste that is produced, try to design a process that would not produce waste at all.
2	**Atom Economy**
	Avoid using more than enough chemicals, meaning that the process completely use up all the reagents involved in the process to reduce the amount of leftover.
3	**Less Hazardous Chemical Syntheses**
	Both during and after the synthesis, the process should be designed to use and produce chemical compounds that are least hazardous to both the environment and human health.
4	**Designing Safer Chemicals**
	The chemical produced should be designed to exhibit the least hazardous effects.
5	**Safer Solvents and Axillaries**
	Attempt to minimize the use of solvents. Additionally, safe solvents should be used as these chemicals become wastes after the synthesis.
6	**Design for Energy Efficiency**
	Process should avoid using extreme temperatures or pressure; use of energy should be minimized.
7	**Use of Renewable Feedstocks**
	The chemicals used in the process should be renewable.
8	**Reduce Derivatives**
	Avoid using derivatives to shorten length of reaction, and reduce the resources needed and waste produced.
9	**Catalysis**
	A catalyst is always preferred as it can reduce both the reaction time and the amount of energy needed to start the reaction.
10	**Design for Degradation**
	The chemicals produced should be able to degrade into compounds harmless to the environmental and human health after use.
11	**Real-time analysis for Pollution Prevention**
	The chemicals engaged in the reaction should be monitored at all times to ensure that hazardous or polluting products are not produced.
12	**Inherently Safer Chemistry for Accident Prevention**
	The process should minimize the risk of accidents.

8.2. Appendix 2

Methodology to how the aspirin was filtrated using a Büchner funnel.

1. The equipment was set to up similar to that shown in *Figure 14*.
2. One end of the aspirator was attached to a faucet.
3. A filter paper was dampened with **distilled water** to create adhesion with the funnel.
4. The faucet was turned on.
5. The content inside the Erlenmeyer flask from **2.4. Reacting the Reagents** was transferred to the funnel.
6. Distilled water was sprayed into the flask to help transfer the remaining crystal inside the residue.
7. The faucet was left on until the liquid droplets stopped dripping out of the funnel.

Figure 14: Aspirin Filtration Setup



8.3. Appendix 3

Methodology to how the melting point test was conducted.

1. The opened end of the **capillary tube** was pushed into the crystal sample.
2. The tube was flipped such that the opened end is now at the top, and the bottom at the bottom.
3. The closed end was tapped repetitively against the table until the crystal inside fell to the bottom of the tube.
4. The tube was inserted into the **melting point apparatus'** tube channel, the closed end going in first.
5. The **mercury thermometer** was inserted into the neighboring tube channel.
6. The heater and the "heat boost" were turned on until the thermometer read 110 °C.
7. After the temperature reached 110 °C, the temperature was gradually increased.
8. The sample was observed continuously to avoid missing the point in which the sample started to melt.
9. After the sample started to melt, the temperature reading on the mercury thermometer was recorded.