

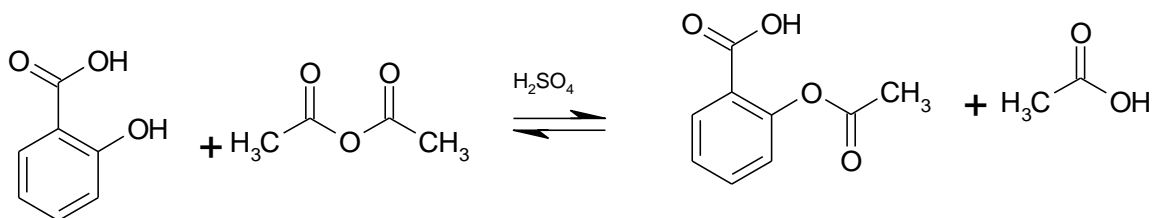
A new take on the aspirin synthesis lab: A multi-step organic synthesis laboratory for high school students

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Rationale

The use of the extracts of various plants for the treatment of pain and fever goes back several centuries. A tea made from the leaves or bark of Willow (*Saliaceae*) was found to be especially effective. By the late 19th Century, the active ingredient in these plant extracts, salicylic acid, had been identified. In 1874, the process for the commercial production of salicylic acid was perfected. The use of salicylic acid as an analgesic became widespread. However, side effects, such as gastric bleeding, made long term use of the drug impossible for many patients. In 1895, Felix Hoffman of the Fredrick Bayer Company found a method to acetylate salicylic acid, producing acetyl salicylic acid. This derivative was found to be as effective as salicylic acid as an analgesic but did not have the side effects associated with salicylic acid. The new drug was named “aspirin”, a name inspired by Saint Aspirinius, the patron saint of headaches. The introduction of aspirin marks the beginning of the modern pharmaceutical industry. The mechanism as to how aspirin alleviates pain was not elucidated until the 1970’s, when it was found that aspirin inhibits COX 1 and COX 2, enzymes that catalyze the formation of prostaglandins, substances that cause inflammation (1).

The synthesis of aspirin, acetylsalicylic acid, is a standard first year organic chemistry laboratory activity at the college level. In most protocols, salicylic acid is reacted with acetic anhydride producing aspirin and acetic acid by acid catalysis:



The reaction is refluxed for 30 minutes, and then cooled. The crude aspirin product is filtered and washed and then dissolved in hot water. Upon recrystallization, the purity of the aspirin is determined by melting point determination.

When doing this, or any laboratory activity, teachers often have as a goal the reinforcement of a chemical principle or the introduction and practice of certain

laboratory techniques. I think that sometimes we fail to give students a sense as to from where these “chemicals” we are using come. From the students’ perspective, these things simply come out of this or that jar or bottle. The sources of the ingredients are often not a concern. Parenthetically, this is the same sort of relationship that students have with food. A precious few have any sense as to the actual source of the chicken nuggets that they have had for lunch.

In accordance with the theme, “The Chemistry that Surrounds Us”, this unit gets students to synthesize aspirin from naturally occurring substances. This activity will highlight and reinforce some of the basic organic reactions that are covered in the International Baccalaureate (IB) Chemistry curriculum (2), allow the students to rehearse some standard organic chemistry laboratory techniques, and introduce the students to a multi-step organic synthesis.

Objective

North Mecklenburg High School is located in Huntersville, NC and is part of the Charlotte-Mecklenburg School System. As of the 2011-2012 school year, the student population is 1600. The student body is 60.6% African-American, 23.8% White, 11.6% Hispanic and 4% Other. Over the past two years our school has seen its free and reduced lunch participation more than double, from 23% in 2009-2010, to 48% at present.

The International Baccalaureate Program has been in place at North Mecklenburg High School for the past 20 years. Students in the ninth and tenth grades are completing the last two years of the IB Middle Years Program. As sophomores, most take the Chemistry I course, which follows the North Carolina standard course of study (2). Students electing to pursue the IB diploma begin the program in their junior year. Students are required to take two sciences. Most of those who take chemistry for the diploma take biology as their second science. This year, 2011-2012, there are 30 juniors and 15 seniors in the North Mecklenburg High School IB Chemistry Program.

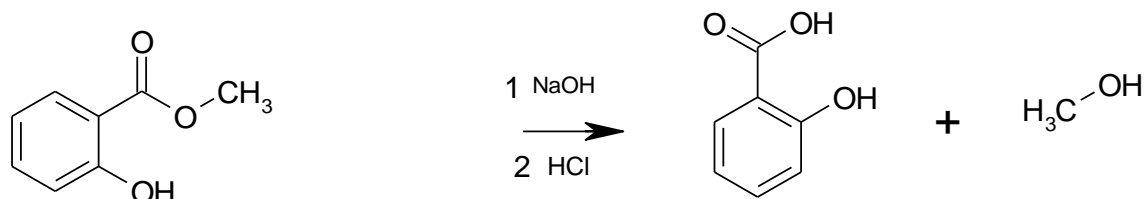
For the past 12 years I have been teaching IB Chemistry at our school. The IB Diploma Chemistry curriculum is covered over a period of two years. During the first year, juniors are taught what amounts to roughly two thirds of the curriculum. The topics covered and the depth into which the students explore these concepts very closely mirrors those of the advanced placement (AP) chemistry course. As seniors, the students focus on the organic chemistry component of the IB curriculum which, by secondary school standards, is enormous. My approach in the classroom is designed to tie together all the concepts in the curriculum using organic chemistry as the central theme. Feedback from former students indicates that this approach prepares them well for university level chemistry. Most report finding that they are far better prepared than the other students in their college chemistry courses. To date, I know of 35 former students from our program who have gone on to obtain degrees in chemistry, biochemistry, and related fields, with many going on to post-graduate work.

As part of the requirements for the IB diploma, students must complete at least 65 hours of documented laboratory work. In reality, the students in our program spend much more than that over the two years. Over the course of the program, I strive to give the students ample opportunity to practice and master basic laboratory techniques. In addition, an emphasis is placed upon open-ended laboratory activities. I include as many organic chemistry laboratory activities as possible given the constraints on equipment and reagents one deals with in the high school setting.

The goal of this unit is to augment the IB Diploma program in chemistry at North Mecklenburg High School by giving students a laboratory experience that will not only cover pertinent curriculum topics but also prepare them for college level laboratory activities.

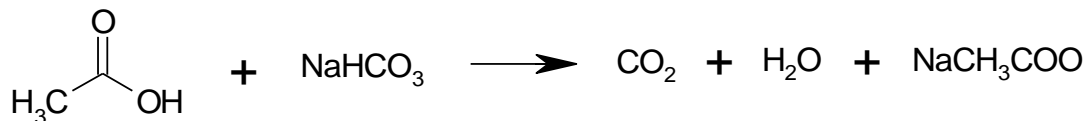
The Unit

The laboratory activity consists of three parts. In the first, the students will isolate oil of wintergreen, methyl salicylate, from its natural source, Checkerberry Wintergreen, *Gaultheria procumbens*, by steam distillation of the leaves and/or berries of the plant. The ester will be purified, hydrolyzed, and then acidified with hydrochloric acid:

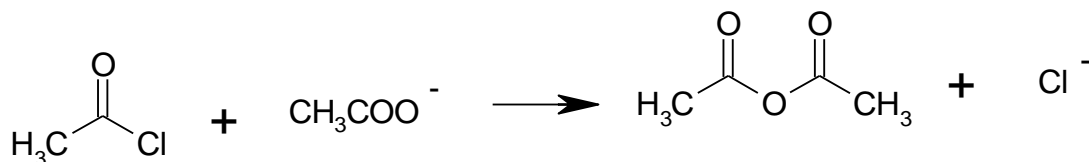


The salicylic acid product is then filtered, recrystallized and saved for Part 3.

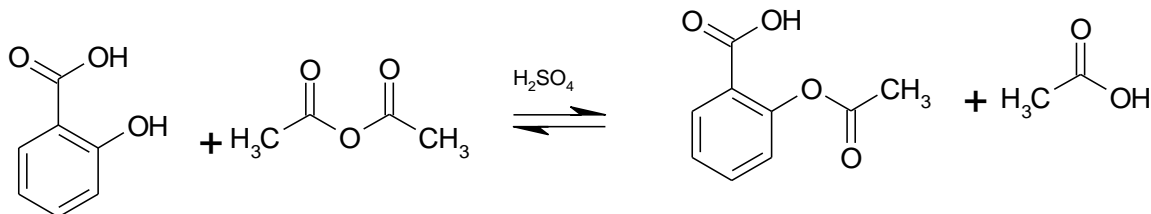
In Part 2, sodium acetate is purified from white vinegar and then converted to acetic anhydride. Sodium bicarbonate is reacted with vinegar and the resulting sodium acetate is purified and dried:



The salt is then reacted with acetyl chloride to produce acetic anhydride:



In Part 3, the salicylic acid produced in Part 1 is reacted with the acetic anhydride from Part 2 to produce aspirin:



Details of the unit

In the following sections, detailed information is given for the instructor's benefit for each of the parts of the laboratory activity, including suggestions for possible extensions of the activities. Background pertaining to the actual reactions can be gotten from any standard organic chemistry text (3).

Part 1: Isolation of methyl salicylate

The Checkerberry Wintergreen, *Gaultheria procumbens*, is a forest shrub found commonly in the northeastern United States (4). The plant was formerly the source for the industrial production of methyl salicylate (Oil of Wintergreen) (5). The methyl salicylate was obtained by the steam distillation of the leaves of the plant. The yield from leaves typically ranges from .5% to .8% (6).

Checkerberry Wintergreen is commonly sold as an ornamental ground cover, occasionally under the name Creeping Wintergreen, and can be easily obtained from most nurseries. For this laboratory activity, I purchased a single plant for \$15. Enough leaves were gotten from this plant to run the activity eight times using 20 fresh leaves, about 5 g.

For each student group 5 g of leaves is placed in a blender along with 20ml of distilled water. The mix is chopped and then transferred to a 50-ml beaker. The students will be able to detect the aroma of wintergreen at this point. The beakers are then placed in a warm spot overnight. I used an incubator set at 35° C. Allowing the mix to incubate overnight will increase the yield of methyl salicylate (5). The actual yield of ester from 5 g of leaves is quite small, 25 mg or less. Assuming the minimal yield of .05%, 800 leaves would be required to obtain 1 g of methyl salicylate. For this reason, each student sample is "salted" with 1 ml of methyl salicylate before the next laboratory session.

Many organic compounds decompose at their boiling points, making simple distillation unsuitable for the separation of many substances. Steam distillation takes advantage of the fact that for two phase systems, such as water and methyl salicylate, the

vapor pressure of the mix is the simple sum of the vapor pressures of the two substances present:

$$P_{\text{total}} = P_{\text{water}} + P_{\text{methyl salicylate}}$$

This allows the two substances to co distill at a temperature lower than that of either substance's boiling points. At 95° C, the vapor pressure of water is approximately 753 mm Hg and that of methyl salicylate 7 mm Hg (7).

(The yield of methyl salicylate by steam distillation can be predicted, as the ratio of moles of substances in the mixture is related to their respective partial pressures. Letting n_1 and P_1 represent the moles and partial pressures of the methyl salicylate and n_2 and P_2 the moles and partial pressures of water:

$$n_1/n_2 = P_1/P_2$$

$$(\text{mass 1}/\text{molar mass 1})/(\text{mass 2}/\text{molar mass 2}) = P_1/P_2$$

$$\text{mass methyl salicylate} = (\text{mass 2} \times P_1 \times \text{molar mass 1})/ (P_2 \times \text{molar mass 2})$$

If 100 ml of water is distilled, the expected mass of methyl salicylate is 9.30 g.)

For this activity, students set up the steam distillation apparatus as follows. A 500-ml Erlenmeyer flask fitted with a one hole rubber stopper was the source of the steam. A U-shaped glass tube was inserted into the 500-ml flask and ran to a one hole stopper fitted to a 125-ml distillation flask. The glass tube was cut long enough so that it reached the bottom of the distillation flask. The distillation flask was attached to a condenser. Steam is generated by heating the 500-ml flask with a hot plate set on high. See Mohrig et al. (8) for other steam distillation set ups.

Distil the sample until 100 ml of liquid is obtained. The methyl salicylate will be visible as globules on the bottom. This is transferred to a separatory funnel and the bottom layer is retained. The collected methyl salicylate is dried using anhydrous magnesium sulfate (8) and transferred to a 125-ml flask.

Part 1: Isolation of salicylic acid

To the flask containing the methyl salicylate add 25 ml of 6 M sodium hydroxide and reflux (7) for 30 minutes. Allow the solution to cool to room temperature and then add 12 M hydrochloric acid until salicylic acid precipitates. This is then vacuum filtered with a Buchner funnel (7). The crude product is then dissolved in a minimal amount of hot water (95° C) and allowed to cool. Needle-like crystals of salicylic acid will form. If they do not, adding a few pieces of ice to the solution will usually induce crystallization. The solution is then vacuum filtered and the pure salicylic acid is dried overnight in an oven at 30° C.

Part 2: Isolation of sodium acetate

The suggested amount of white vinegar for each student group is 50 ml and the reaction should be carried out in a 250-ml beaker. White vinegar is 5% acetic acid, so 50 ml of vinegar contains 2.50 ml of acetic acid. The amount of sodium bicarbonate required is 3.67 g:

$$2.50 \text{ ml acetic} \times (1.0492 \text{ g acetic}/1 \text{ ml}) \times (1 \text{ acetic}/60.05 \text{ g}) \times (1 / 1) \times (84.008 \text{ g}) = 3.67 \text{ g}$$

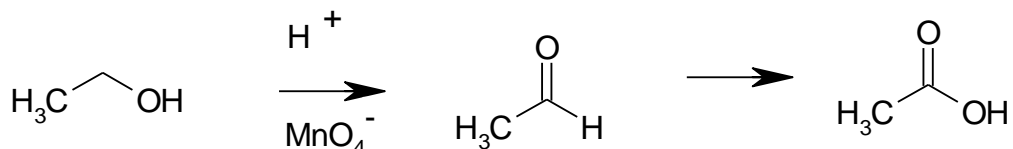
The expected yield of sodium acetate is 3.58 g:

$$3.67 \text{ g NaHCO}_3 (1 \text{ NaHCO}_3/84.008\text{g}) \times (1 \text{ NaC}_2\text{H}_3\text{O}_2/1 \text{ NaHCO}_3) \times 82.032 \text{ g} = 3.58 \text{ g}$$

The % yield of sodium acetate obtained this way is usually over 95%.

After the sodium bicarbonate has been added, the solution is heated on a hot plate and boiled down to 20 ml. The solution will have a light brown color. At this point add a thumb nail size amount of decolorizing charcoal, stir and then filter while still hot. The solution obtained will then be clear. Continue heating the sodium acetate solution until nearly dry. The beaker is then placed over night in the drying oven at 60° C. Note that it is essential that the sodium acetate be totally dry before reacting it with acetyl chloride. Any water present will react with the acid chloride to produce acetic acid.

(This portion of the activity can be extended to include more reactions and techniques. Instead of beginning with vinegar, one could start with sucrose and yeast, producing ethanol by fermentation. The ethanol is then separated by simple distillation (8). The resulting alcohol is then oxidized to acetic acid with acidified permanganate:



The resulting acetic acid is then reacted with sodium bicarbonate as above.)

Part 2: Production of acetic anhydride

The anhydrous sodium acetate is then reacted with an equimolar amount of acetyl chloride. For the expected yield of 3.58 g of sodium acetate, 3.10 ml of acetyl chloride would be required:

$$3.58 \text{ g NaC}_2\text{H}_3\text{O}_2 (1 \text{ mol}/82032 \text{ g}) (1 \text{ mol acid chloride}/1 \text{ mol acetate}) (78.494 \text{ g}/1 \text{ mol}) (1 \text{ ml acetyl chloride}/1.104 \text{ g}) = 3.10 \text{ ml acetyl chloride}$$

This reaction can be done in the beaker containing the dry sodium acetate but must be done in a fume hood. The resulting acetic anhydride is then transferred to a stoppered flask for use in Part 3.

Probably in many cases, acetyl chloride will not be available in the high school laboratory. In such cases, the laboratory activity can be modified by having the students turn in their sample of sodium acetate for an equimolar amount of acetic anhydride. For the expected yield of 3.58 g of sodium acetate, 4.12 ml of acetic anhydride would be required:

$$3.58 \text{ g NaC}_2\text{H}_3\text{O}_2 \text{ (1 mol/82.032 g) (1 mol anhydride/1 mol acetate) (102.088g/1mol) (1 ml acetic anhydride/1.082g) = 4.12 ml acetic anhydride}$$

Part 3: Synthesis of aspirin

The salicylic acid from Part 1 is placed in a 125-ml flask along with the acetic anhydride from Part 2. Five drops of concentrated sulfuric acid are added and the flask is placed in a 90° C water bath. After 20 minutes, the flask is removed from the water bath and 50 ml of cold distilled water is added. The water reacts with any excess acetic anhydride, producing acetic acid. Aspirin crystals will form as the solution cools. The aspirin is then vacuum filtered. The aspirin is then dried over night at 60° C (8). The purity of the students' sample can be determined by melting point (135° C versus 157° C for salicylic acid). In addition, the purity of the sample can be determined qualitatively by dissolving a small amount of the sample in ethanol and adding a drop of 1% ferric chloride. Ferric chloride forms a complex with phenols. The solution will turn purple in the presence of phenols. Aspirin will not react, while salicylic acid will.

Teaching strategy

This unit is intended for advanced chemistry students who have had previous experience with the laboratory techniques used in this activity. It has been designed to be used with IB Chemistry students who are in the second year of the Diploma Programme. It would also be suitable for Advanced Placement Chemistry students.

The unit can be used in its entirety, or the individual parts can be run as stand alone activities. Pre-lab preparation should include lecture material and activities that review the factors that affect the boiling point of a substance. The principles of distillation will need to be introduced, including a discussion of azeotropes and how these relate to the problem of separating mixtures of different liquids (8). This is a topic that is barely mentioned in the standard secondary chemistry curriculum.

With regard to the IB Chemistry curriculum, this laboratory activity would best be used after the students had completed the organic chemistry portion of the curriculum (Topics 10 and 20). Organic synthesis is a major theme in Option G: Further organic chemistry. This option also covers addition-elimination reactions of acid anhydrides and acyl chlorides, tying in nicely with this laboratory activity. Analgesics and their mechanism of action are covered in Option D: Medicines and drugs, and enzyme kinetics and inhibition is dealt with in Option B: Human biochemistry. This laboratory activity could be incorporated into the teaching of either of these options.

This activity can be completed within four 90 minute laboratory sessions. The preparation of the plant material can be made in advance and takes less than 30 minutes. It is important that the students actually prepare the fresh *Gaultheria* leaves themselves as the overall goal of this laboratory activity is to have them actually obtain their starting material from natural sources. The steam distillation and separation and drying of the methyl salicylate in Part 1 requires an hour. The neutralization of acetic acid in Part 2 requires 30 minutes. Up to an hour may be required to boil down the sodium acetate solution. Part 3, the synthesis of aspirin requires an hour. Determining the melting point of the purified aspirin, depending upon the type of apparatus available, would require an hour for all student groups to complete the task.

The materials required for the activity are as follows:

Part 1: *Gaultheria procumbens* leaves (20 per group); methyl salicylate (1 ml per group); distilled water; kitchen blender; anhydrous magnesium sulfate (approximately 5 g per group); hot plate; 150-ml separatory funnel; steam distillation set up as described above; 6 M sodium hydroxide (20 ml per group); 12 M hydrochloric acid (approximately 10 ml per group); Buchner funnel; balance; incubator.

Part 2: white vinegar; sodium bicarbonate; decolorizing carbon; hot plate; set up for gravity filtration; fume hood; acetyl chloride (approximately 5 ml per group); acetic anhydride (approximately 5 ml per group); drying oven.

Part 3: hot plate; 18 M sulfuric acid; melting point apparatus; drying oven; Buchner funnel; 95% ethanol (5 ml per group); 1% ferric chloride solution.

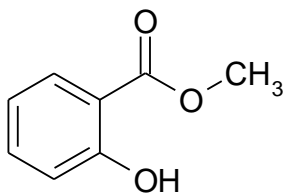
Student handouts

The following are suggested forms for the pre-laboratory quiz and the student instructions for the laboratory activity.

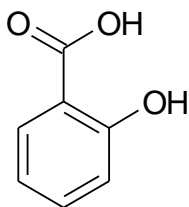
Pre-lab Questions: Multi-step synthesis of aspirin

1. Determine the molecular formula and molar mass from the following structural formulas:

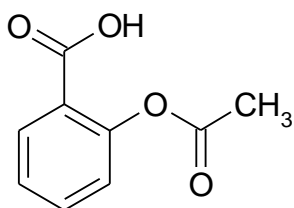
methyl salicylate



Salicylic acid



Aspirin



2. Write the balanced equation for the reaction between acetic acid and sodium bicarbonate:

3. Calculate the mass of sodium bicarbonate required to react with 2.00 ml of acetic acid. The density of acetic acid is 1.082 g/ml.

4. A mixture of water and methyl salicylate boils at 95°C . The vapor pressure of water at this temperature is 753 mm Hg. What is the vapor pressure of methyl salicylate at 95°C ?
5. The condensate from a steam distillation contains 10.0 g of compound A and 18.0 g of water. At the temperature of the distillation, the vapor pressure of water is 660 mm Hg. What is the approximate molecular weight of compound A?
6. What is the expected yield of aspirin when 2.00 g of salicylic acid reacts with an excess of acetic anhydride?
7. If 2.45 g of aspirin is actually produced, what is the % yield for this reaction?

The Synthesis of Aspirin from Naturally Occurring Substances

Aspirin, acetyl salicylic acid, is formed by the reaction of salicylic acid with acetic anhydride. In this laboratory activity we will use naturally occurring substances to produce the ingredients needed for aspirin production. The lab exercise consists of three parts.

In Part 1 you will obtain methyl salicylate (Oil of Wintergreen) from the leaves of the Checkerberry Wintergreen by the process of steam distillation. The methyl salicylate will then be hydrolyzed and the acid portion of the ester, salicylic acid, will be recovered.

In Part 2 you will obtain sodium acetate from white vinegar by reacting the vinegar with sodium bicarbonate. The purified sodium acetate is then reacted with acetyl chloride to produce acetic anhydride.

In Part 3 you will synthesis aspirin using the products that you made during the first two parts of the laboratory exercise.

Laboratory Procedure:

Part 1:

On the day before the laboratory activity obtain 20 fresh Checkerberry Wintergreen leaves. Place these in a blender and add roughly 20ml of distilled water. Chop the leaves for 1 minute, then transfer the leaf puree to a 50-ml beaker and place the beaker in an incubator set at 30° C.

Day 1: Place the leaf material in a 125-ml distillation flask and connect the flask to the steam distillation apparatus. Collect 100 ml of condensate. You should note the globules of methyl salicylate on the bottom of the collection flask.

Transfer the condensate to a 150-ml separatory funnel and remove the bottom layer, placing it in a 150-ml beaker. This is the methyl salicylate. Add 1 g of anhydrous magnesium sulfate to the crude ester. With a glass pipette transfer the ester to a 150-ml flask and stopper.

Day 2: Add 20 ml of 6 M sodium hydroxide to the ester and attach the flask to the reflux apparatus. Heat the mix gently (just under boiling) for 30 minutes. After the 30 minutes, remove the flask and allow it to cool to room temperature.

Slowly add 12 M hydrochloric acid to the flask. Do not add more than 1 ml at a time. Salicylic acid will precipitate out. Vacuum filter and rinse the salicylic acid. Transfer the crude salicylic acid to a 50-ml beaker and add just enough 90° C water to dissolve the salicylic acid. Allow the solution to cool. Fine, needle-like crystals of salicylic acid will begin to form.

Vacuum filter the pure salicylic acid and place the sample in the drying oven

Part 2:

Day 3: Place 50 ml of white vinegar in a 250-ml beaker. Gradually add 3.65 g of sodium bicarbonate, stirring as you do so. Once the reaction is complete (how do you know?), place the beaker on a hot plate. Slowly heat the sodium acetate solution to boiling and boil the solution down to around 20 ml. The solution will be a light brown color. Remove the beaker from the heat and carefully add .5 g of decolorizing charcoal to the solution and then immediately gravity filter the hot solution. Continue to gently heat the now clear solution until dry. Place the beaker in the drying oven.

Day 4: In the fume hood, add 3 ml of acetyl chloride to the beaker containing your sample of anhydrous sodium acetate. Transfer the resulting acetic anhydride to a 125-ml flask.

Part 3:

Day 4: Add your salicylic acid sample from day 2 to the acetic anhydride and add 5 drops of 18 M sulfuric acid. Heat the flask in a 75° C water bath for 20 minutes. After the 20 minutes, remove the flask and allow it to cool to room temperature. Add 50 ml of cold distilled water to the flask. This will decompose any remaining acetic anhydride as well as induce the precipitation of the aspirin. Add a bit of ice to speed up the formation of solid aspirin.

Vacuum filter the crude aspirin. Dissolve the aspirin in just enough hot (90° C) water and allow to cool. Vacuum filter the pure aspirin.

The final aspirin product can be quickly checked for purity by dissolving a small amount in ethanol and then adding a drop of 1% ferric chloride. If unreacted salicylic acid remains in the sample, the solution will turn purple, as iron(III) forms a complex with the phenol group. Aspirin lacks the phenol group and will not react with ferric chloride. Purity can also be assessed by melting point determination. The melting point for aspirin is 137° C.

Appendix: Implementing district standards

This unit has been designed to be used as a laboratory activity that incorporates some key concepts in the International Baccalaureate Programme Chemistry curriculum. These are:

Topic 1: Quantitative chemistry: The mass relationships in chemical reactions.

Topics 4 and 14: Chemical bonding. The relationship between molecular structure and physical properties. These are exploited when separating mixtures of compounds.

Topic 17: Equilibrium. Liquid-vapour equilibrium, which relates to the principles behind steam distillation. The position of the equilibrium, which relates to the dynamics of the acid catalyzed esterification reaction.

Topics 10 and 20: Organic chemistry. Reaction pathways, condensation reactions and addition-elimination reaction mechanisms.

Option B: Human biochemistry. Proteins, enzyme kinetics, enzyme inhibition.

Option D: Medicines and drugs. Pharmaceutical products, analgesics, drug action, and drug design.

Option G: Further organic chemistry. Addition-elimination reactions and reaction pathways.

Notes

- (1) Vane, J. R., and R. M. Botting. "The mechanism of action of aspirin." *Thrombosis Research* 110 (2003): 253-258.
- (2) *Diplomma Programme. Chemistry Guide*. Cardiff, Wales: International Baccalaureate Organization, 2007.
- (3) Fessenden, R. J., and J. S. Fessenden. *Organic Chemistry*. Pacific Grove, CA: Brooks/Cole, 1998.
- (4) Robinette, S. L... "Shrubs and vines for northeastern wildlife." *General Technical Reports, USDA/F&WS* 101 (1974): 20-22.
- (5) Gibbons, E... *Stalking the healthful herbs*. New York: David McKay Company, 1966.
- (6) Leung, A. Y... *Encyclopedia of common natural ingredients used in food, drugs, and cosmetics*. New York: J. Wiley and Sons, 1980.
- (7) Matthews, J. B., J. F. Sumner, and E.A. Moelwyn-Hughes. "The vapour pressures of certain liquids." *Transactions of the Faraday Society* 46 (1950): 797-803.
- (8) Olmstead, J... "Synthesis of aspirin: A general chemistry experiment." *Journal of Chemical Education* 75, no. 10 (1998): 1261-1263.

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