

Synthesis of Aspirin

A General Chemistry Experiment

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In recent years, examples from organic chemistry have come to play increasingly prominent roles in the first-year university general chemistry course. The American Chemical Society has recommended more integration of biological concepts into college-level introductory general chemistry courses. Following this recommendation, at least two current general chemistry textbooks make liberal use of organic examples (1), and some universities are bringing organic chemistry much more into the forefront of the introductory course (2).

At California State University, Fullerton, the first-semester general chemistry laboratory has been redesigned over the past several years. The redesign has added an organic component and provided students with explicit examples of several types of operations in which chemists engage: observation, synthesis, quantitative measurements, construction of apparatus, and chemical analysis. Our experiment that accentuates accurate quantitative measurements was reported earlier (3).

Over the course of the first semester and the beginning of the second, our general chemistry students synthesize two organic substances (aspirin and methyl orange) and two inorganic substances (alum and potassium ferrioxalate). An earlier paper described our ferrioxalate synthesis experiment (4). This paper describes the first of our organic synthesis experiments, the synthesis, purification, and qualitative spectroscopic characterization of aspirin.

Aspirin (acetylsalicylic acid) is a pain-relieving compound familiar to virtually all students. The synthesis of aspirin from oil of wintergreen is an example of one of the most prevalent, profitable, and honored activities of chemists: the conversion of a naturally occurring substance into one with therapeutic value. Simple enough to be accomplished and understood by beginning students, this synthesis nevertheless serves as a paradigm for the pharmaceutical industry, from tranquilizers and antibiotics to yet-undiscovered agents for treating cancer, heart disease, and AIDS.

Rationale

The two-step conversion of oil of wintergreen (methyl 2-hydroxybenzoate) into salicylic acid (5) and then into aspirin (6) serves as an introductory example of multistep sequential synthesis. It also provides practice in molecular pattern

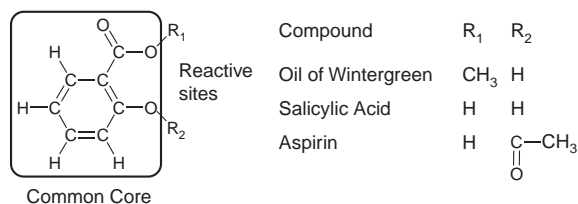
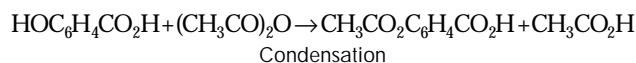
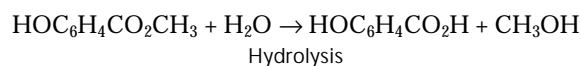


Figure 1. The structural core common to oil of wintergreen, salicylic acid, and aspirin.

recognition, as the reactions modify the periphery of a structural core common to the starting material, intermediate product, and final product (Fig. 1).

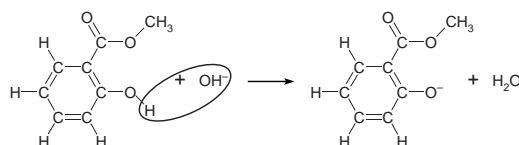
Viewed from another perspective, this sequence exemplifies two of the most common types of chemical reaction, hydrolysis and condensation:



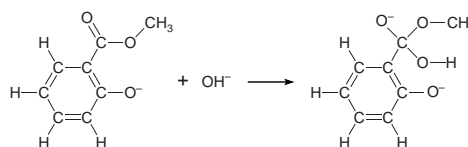
As illustrated in Figure 2, the hydrolysis reaction proceeds in several steps involving deprotonation and protonation as well as cleavage of a C–O bond (7). These encompass examples of Brønsted acid–base proton transfer, another major class of chemical reactions.

These structural changes manifest themselves through readily observed macroscopic changes as the synthesis proceeds. Addition of aqueous base to syrupy, fragrant oil of wintergreen yields a white odorless solid. Upon heating, this

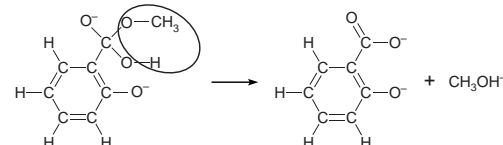
I. Deprotonation of oil of wintergreen



II. Attack by hydroxide anion



III. Elimination of methanol



IV. Protonation of dianion

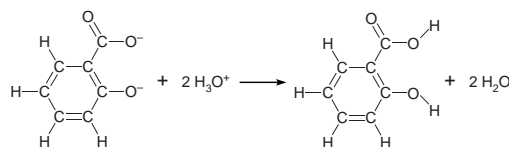


Figure 2. Reaction mechanism for the conversion of oil of wintergreen into salicylic acid.

solid reacts further to yield a solution, from which a different white solid precipitates upon acidification. On heating with acrid liquid acetic anhydride, salicylic acid reacts and dissolves. Dilution with water and cooling results in precipitation of aspirin, yet another white solid.

Synthesis must always be accompanied by isolation and purification of the product. Both salicylic acid and aspirin are sparingly soluble in water, making these procedures readily accessible to the general chemistry student. Isolation is easily accomplished by suction filtration using a Büchner funnel apparatus, and purification is equally easily accomplished by dissolving the crude product in hot water and chilling to recrystallize the pure product.

A newly synthesized chemical substance must be appropriately characterized before the synthesis can be judged a success. While characterization is multifaceted and typically involves techniques well beyond the scope of general chemistry, FTIR spectrophotometry is well suited to characterization of aspirin and its precursors. By taking FTIR spectra of their products, our students not only “see” that their white solids are distinctly different but also become familiar with one of the most prevalent instruments of the contemporary laboratory. Figure 3 shows actual FTIR spectra taken under the same conditions that are used by our students. The three compounds share spectral features due to their common framework, for example the aromatic C–H bending vibrations in the 600–800 cm^{-1} region. They differ substantially in the absorptions arising from the CO_2H , CO_2 , and OH groups. Aspirin lacks the broad hydrogen-bonded OH absorption that is prominent in oil of wintergreen and salicylic acid between 3000 and 3500 cm^{-1} . On the other hand, whereas oil of wintergreen and salicylic acid have a single C=O absorption at about 1700 cm^{-1} , aspirin has two distinct peaks arising from its ester and acid C=O groups.

Procedure

Outlined here is a compact version of the procedure carried out by our students and the instructions for their laboratory report. The procedure given to the students includes more detailed specifications for standard techniques with which they may not be sufficiently familiar. Pan balances provide sufficient accuracy for all weighings, and graduated cylinders provide sufficient accuracy for volume measurements. Glassware can be cleaned by rinsing with deionized water and need not be dry except when explicitly noted. Isolation of solids is accomplished by cold suction filtration using a Büchner funnel.

The filtrate from the first synthesis procedure is substantially acidic and should be disposed of properly following procedures for acidic aqueous waste. All other liquid waste is relatively benign and can be rinsed down the sink.

Conversion of Oil of Wintergreen to Salicylic Acid

Transfer 4 ± 0.2 mL of oil of wintergreen to a previously weighed clean, dry 250-mL beaker and reweigh. Add, with stirring, 40 mL of 6 M NaOH (precipitate forms). Heat with occasional stirring to a gentle boil, reduce the heating rate to avoid “bumping”, and continue boiling gently for 15 minutes. Midway through heating, rinse any solids adhering to the beaker walls into the solution with a small quantity of

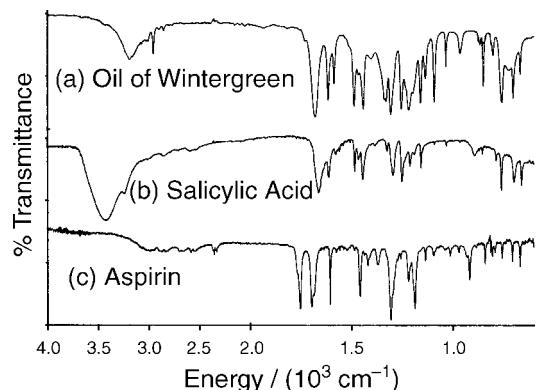


Figure 3. FTIR spectra of oil of wintergreen, salicylic acid, and aspirin.

deionized water. Cool the beaker in an ice bath until it is just warm to the touch. Without removing the beaker, slowly add, with continuous stirring, 50 mL of 8 M H_2SO_4 (precipitate forms). After chilling in the ice bath, isolate the product. Rinse the beaker with iced deionized water, pour over the precipitate, and continue suction for about 10 minutes.

Transfer the crude solid to a 250-mL beaker containing 100 mL of deionized water. Heat to a gentle boil until the solid dissolves completely. Allow the beaker to cool (crystals form), then transfer the beaker to an ice bath and chill thoroughly. Isolate the product. Rinse the beaker with 50 mL of iced deionized water, pour over the precipitate, and continue suction for 15 minutes. Spread the solid on a watch glass, cover with filter paper, and store overnight until dry.

Conversion of Salicylic Acid into Aspirin

Weigh 1.4 g of salicylic acid and transfer to a clean, dry 125-mL Erlenmeyer flask. Add 3.0 mL of acetic anhydride (CAUTION: caustic vapors: use a hood) and 5 drops of concentrated H_3PO_4 . Stopper with a one-hole rubber stopper fitted with 2 cm of plastic tubing. Float the Erlenmeyer flask in an 800-mL beaker containing 250 mL of water. Heat this beaker to 85 °C and maintain between 85 and 90 °C for five minutes (CAUTION: do not boil; steam baths may be used if available). Discontinue heating and immediately use a Pasteur pipet to deliver 2 mL of deionized water through the plastic tubing (CAUTION: hot acid vapors). When the flask is sufficiently cool, remove it using a towel, remove the stopper, and add 20 mL of deionized water. Allow to stand at room temperature until crystals begin to form. Then add 10 mL of deionized water, swirl, and place the flask in an ice bath. After chilling, isolate the product. Rinse the flask with 15 mL of iced deionized water, pour over the precipitate, and continue suction for about 10 minutes.

Weigh the solid in a clean, dry 50-mL beaker and add to the beaker 10 mL of deionized water per gram of solid. Heat with continuous stirring until all solid dissolves. Transfer the beaker to an ice bath and chill (crystals form) until precipitation appears complete. Isolate the product and continue suction for an additional 10 minutes. Then transfer the solid to a clean, dry 50-mL beaker and oven-dry at 80 °C (CAUTION: aspirin melts and decomposes at 100 °C) for one hour. Remove, cool, and weigh the final product.

Infrared Characterization

Prepare a solution of each solid (salicylic acid and aspirin) by placing about 1 mL of ethyl acetate in a clean, dry test tube, adding a spatula-tip amount of solid, and stirring to dissolve. Using a Pasteur pipet, transfer 4–5 drops of this solution to a salt plate and allow the solvent to evaporate. Place the salt plate on the mount in the sample compartment of an FTIR spectrophotometer. Scan the spectrum and print a copy. Clean the salt plate three times by placing several drops of ethyl acetate on its surface and wiping thoroughly with a clean lint-free tissue.

Include in your report for this experiment a one-paragraph abstract, brief procedure, data and results, and discussion. In the procedure, describe the details of what *you* did and observations you made, but do not reproduce the procedure from the laboratory manual. Data and results should include all masses used, the theoretical yields of products, and the percent yields of products. In the discussion, answer the question “What explains why my yields are different from theoretical yields?” Also compare the IR spectra of oil of wintergreen and your two products and identify the peaks that are unique to each of the products.

Discussion

The one-step synthesis of aspirin from salicylic acid is described in many general chemistry laboratory manuals (8) and may be traced to a report by Brown and Friedman (6). The experiment described here differs from these typical syntheses in three respects. First, it is a more elaborate two-step synthesis that starts from a common natural substance. Second, it is designed to be carried out early in the general chemistry laboratory rather than toward the end, where more typical organic syntheses are placed. Third, it incorporates the use of FTIR spectroscopy for qualitative identification of the chemical changes that have occurred.

The two-step synthesis requires more than one laboratory period. This is in keeping with our laboratory design, in which students perform a small number of extended experiments with a thread of continuity that reflects actual laboratory practice. However, the synthesis/characterization experiment can easily be segmented into three single-period experiments: the conversion of oil of wintergreen into salicylic acid, synthesis of aspirin from salicylic acid, and IR characterization of these substances. Such segmentation would allow simple air-drying of the aspirin product in place of the oven-dry procedure described here. In addition, melting point characterization of salicylic acid and aspirin can easily be added to the characterization procedure (8).

Placing an organic synthesis experiment early in the general chemistry laboratory emphasizes that the principles of chemical reactivity and stoichiometry apply equally to organic and inorganic materials. Additionally, this synthesis has a strong practical appeal. Students enjoy the fragrance of oil of wintergreen (which may remind them of the kitchen, the athletic locker room, or both) as well as the production of a staple pharmaceutical product. While they are unlikely to appreciate the nuances of organic functional groups early in their course, the simplicity of the reaction mechanisms makes it possible for them to understand the chemistry taking place during the synthesis.

The use of FTIR in undergraduate laboratories is becoming increasingly prevalent as this technique becomes routine and instruments are more affordable. Others have described experiments using FTIR spectroscopy in general chemistry for smog analysis (9) and for exploring Lewis structures (10). The technique also finds applications in the organic laboratory (11) and throughout the undergraduate curriculum (12). At Fullerton we make use of FTIR not only in general chemistry laboratory but also in our undergraduate organic, analytical, and physical chemistry laboratories; and our students often use the instruments in the course of their undergraduate research projects.

The use of FTIR spectroscopy to differentiate aspirin from other substances is not unique to this instructional exercise in chemical synthesis. Procedures for quantitative analysis of aspirin using FTIR have been reported for pharmaceutical preparations (13) and drug testing (14). Furthermore, contemporary research utilizes FTIR to study aspirin–DNA (15) and aspirin–RNA interactions (16). Thus, the qualitative identification of aspirin by FTIR serves as a representation of how modern spectroscopic techniques facilitate analytical and physical research work.

Acknowledgments

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