Acetaminophen (Tylenol®)


**Introduction:**

Acylated aromatic amines (those having an acyl group, \( \text{R} \text{CO} \), substituted on nitrogen) are important in over-the-counter headache remedies. Acetanilide, phenacetin, and acetaminophen are mild analgesics (relieve pain) and antipyretics (reduce fever) and are important, along with aspirin, in many nonprescription drugs. Today acetaminophen has replaced phenacetin and acetanilide as pain-killers; acetaminophen is marketed under the tradenames Tylenol and Datril and is used in Extra Strength Excedrin.

![Chemical structures](image)

The discovery that acetanilide was an effective antipyretic came about by accident in 1886. Two doctors, Cahn and Hepp, had been testing naphthalene as a possible vermifuge (an agent that expels worms). Their early results on simple worm cases were very discouraging, so Dr. Hepp decided to test the compound on a patient with a larger variety of complaints, including worms - a sort of "shotgun" approach. A short time later, Dr. Hepp excitedly reported to his colleague, Dr. Cahn, that naphthalene had miraculous fever-reducing properties.

In trying to verify this observation, the doctors discovered that the bottle they thought contained naphthalene had apparently been mislabeled. In fact, the bottle brought to them by their assistant had a label so faint as to be illegible. They were sure that the sample was not naphthalene since it had no odor. Naphthalene has a strong odor reminiscent of mothballs. So close to an important discovery, the doctors were nevertheless stymied; they appealed to a cousin of Hepp, who was a chemist in a nearby dye factory, to help them identify the unknown compound. This compound turned out to be acetanilide, a compound with a structure not at all like that of naphthalene. Certainly, Hepp's unscientific and risky approach would be frowned on by doctors today; to be sure, the Food and Drug Administration (FDA) would never allow human testing before extensive animal testing (consumer protection has progressed). Nevertheless, Cahn and Hepp made an important discovery.

In another instance of serendipity, the publication of Cahn and Hepp, describing their experiments with acetanilide, caught the attention of Carl Duisberg, director of research at the Bayer Company in Germany. Duisberg was confronted with the problem of profitably getting rid of nearly 50 tons of \( p \)-aminophenol, a by-product of the synthesis of one of Bayer's other commercial products. He immediately saw the possibility of converting \( p \)-aminophenol to a compound similar in structure to acetanilide, by putting an acyl group on the nitrogen. It was then believed, however, that all compounds having a hydroxyl group on a benzene ring (that is, phenols) were toxic. Duisberg devised a scheme of structural modification of \( p \)-aminophenol to get the compound phenacetin. The reaction scheme is shown here.
Phenacetin turned out to be a highly effective analgesic and antipyretic. A common form of combination pain reliever, called an APC tablet, was once available. An APC tablet contained Aspirin, Phenacetin, and Caffeine (hence, APC). Phenacetin is no longer used in commercial pain-relief preparations. It was later found that not all aromatic hydroxyl groups lead to toxic compounds, and today the compound acetaminophen is very widely used as an analgesic in place of phenacetin, thus saving the trouble of having to ethylate the phenolic OH of p-aminophenol in the manufacture of this painkiller.

Preparation of acetaminophen involves treating an amine with an acid anhydride to form an amide. In this case, p-aminophenol, the amine, is treated with acetic anhydride to form acetaminophen (p-acetamidophenol), the amide.

Acetaminophen can be found commercially in Excedrin extra strength and Tylenol.

**Caution:**

*p*-Aminophenol is a skin irritant and is toxic. It is best to use a fresh bottle (not darkly colored) of *p*-aminophenol.

**Synthesis:**

If, and only if, the *p*-aminophenol has air oxidized and is discolored to the extent that it is any darker grey than a "sweatshirt", it should be purified by the following procedure:

**PURIFICATION OF p-AMINOPHENOL**

Adjust your sand bath for a temperature of about 120 °C. Place about 0.250 g (record the actual weight in your notebook) of *p*-aminophenol in a 25-mL Erlenmeyer flask. Using a 10-mL graduated cylinder, add 7.5 mL of water to the flask. With occasional swirling, heat the mixture by partially submerging the flask in the sand bath. Heat until the solid has completely dissolved. Remove the flask from the sand bath and allow the solution to cool slowly to room temperature. Crystallization should occur during this cooling period. If it does not, scratch the inside surface of the flask with a glass rod to induce crystallization. Then place the flask in an ice-water bath. Be sure that both water and ice are present and that the beaker is small enough so there is no chance that the flask can tip over. When crystallization is complete, vacuum filter the crystals using a Hirsch funnel. Moisten the 1.3-cm filter paper disc with a few drops of water and turn on the vacuum. Swirl the mixture in the flask and pour about one-third of the mixture into the funnel. When the liquid has passed through the filter, repeat this procedure until you have transferred all the liquid to the Hirsch funnel. Using your spatula, scrape out as many of the crystals as possible from the flask. Add about 1 mL of ice-cold water to the flask. Swirl the liquid in the flask and then pour the remaining crystals and water into the Hirsch funnel. Not only does this help transfer all the crystals to the funnel, but the water also rinses the crystals on the funnel. If necessary, repeat with another 1-mL of cold methanol, making sure that all the crystals are rinsed by the cold solvent. Methanol is used instead of water because methanol is more volatile, and the crystals will dry more rapidly. Some impurities are also washed away by the methanol. Continue drawing air through
the crystals on the Hirsch funnel by suction for about five minutes. Transfer the crystals onto a watch
glass for air-drying. Separate the crystals as much as possible with a spatula. The crystals will dry in
about 10 minutes. Weigh the crystals and calculate the percentage recovery from the crystallization.
Compare the color of your purified p-aminophenol with the starting material.

Weigh about 0.100 g of purified p-aminophenol and place this in a reaction tube. Using a graduate
pipet and a syringe pipet pump, add 0.110 mL of acetic anhydride and 0.30 mL of water. Insert a boiling
stick and heat carefully so as to maintain a gentle boil. After the solid has dissolved (it may dissolve,
precipitate, and redissolve), heat the mixture for an additional 10 minutes to complete the reaction.

**Isolation and Purification:**

Remove the tube from the sand bath and allow it to cool to room temperature slowly by placing it in a
beaker. If crystallization has not occurred, scratch the inside of the tube with a glass stirring rod to initiate
crystallization. Cool the mixture in an ice bath for 15-20 minutes and collect the crystals by vacuum
filtration on a Hirsch funnel. Rinse the tube with about 1 mL of ice water and transfer this mixture to the
Hirsch funnel. Wash the crystals on the funnel with two additional 0.5-mL portions of ice water. Dry the
crystals for 5-10 minutes by allowing air to be drawn through them while they remain on the Hirsch
funnel. Transfer the product to a watch glass and allow the crystals to dry in air. It may take several hours
for the crystals to dry completely, but you may go on to the next step before they are totally dry. Weigh
the crude product and set aside a small sample for a melting point determination. Record the appearance of
the crystals in your notebook.

Crystallize the crude acetaminophen from about 0.2 mL solvent mixture composed of 50% water and
50% methanol by volume. The crystallization is performed in a tared reaction tube. The solubility of
acetaminophen in this hot (nearly boiling) solvent is about 0.2 g/mL. You can use this as a rough
indication of how much solvent is required to dissolve the solid. Add small portions (several drops) of hot
solvent until the solid just barely dissolves. Then allow the solution to cool slowly to RT. If you want
the solution to cool more slowly and possibly obtain better (purer) crystals, place about 15 mL of hot water
(about 50 °C) in a 30-mL beaker and set the reaction tube in the beaker.

When the mixture has cooled to room temperature, place the reaction tube in an ice-water bath for
several minutes. If necessary, induce crystallization by scratching. Pipet filter or vacuum filter on a
Hirsch funnel. Wash with 0.5 mL of cold 50/50:ethanol/water. Allow to dry until the next lab period or
remove solvent under vacuum by pushing the reaction tube into a piece of vacuum tubing attached to the
house or aspirator vacuum.

Weigh the purified acetaminophen and calculate the percent yield. This calculation should be based on
the weight of purified p-aminophenol used to prepare acetaminophen. Determine the melting point.
Compare the melting point and the color of the final product with that of the crude acetaminophen. Pure
acetaminophen melts at 169-170.5 °C.

**Cleaning Up:**

Filtrates from the Hirsch funnel can be discarded by flushing down the drain with water.

**Analysis:**

Analyze the product by melting point determination, by noting crystal texture and color and by the spectral
method assigned. Also, analyze by IR, 1H and 13C NMR, and GC-MS. Remember to take a 1H NMR of
the crude product.

**Final Report:**

Calculate the percentage yield and give melting points of your crude and final products. Finally answer
this question in the Discussion section of your report:

Give two possible impurities in the crude product in this reaction and discuss if they were seen in the
1H NMR of the crude product.