I. Introduction

Sulfanilamide, or \( p \)-aminobenzenesulfonamide, was first synthesized in 1908. It was discovered that sulfanilamide has antibacterial properties, and the mode of action has been determined. Bacteria must synthesize folic acid in order to grow. Sulfanilamide inhibits the formation of folic acid, and therefore, stops the growth of bacteria. Since humans do not synthesize folic acid (must be acquired in food), only bacteria are affected by the use of sulfanilamide. Thus, there is no negative side effect to taking sulfanilamide since it does not disrupt any critical biological action in the body.

This experiment focuses on the three-step synthesis of sulfanilamide, starting with acetonilide. The synthetic scheme is shown below. In this three-step route, acetonilide is subjected to chlorosulfonation, which is then followed by sulfonamide formation, and finally, reduction of the acetyl amide to yield sulfanilamide. The final product, sulfanilamide, is then crystallized and weighed to determine the percent yield of the pure product. The melting point and IR spectrum are used to verify the purity and identity of sulfanilamide.
II. Procedure and Data/Observations

Construction of a hydrogen chloride vapor trap.

A 25-mL Erlenmeyer flask was fitted with a septum, which was connected to a short length of polyethylene tubing that led into a reaction tube containing a small piece of damp cotton.

Synthesis of p-Acetaminobenzenesulfonyl chloride.

Acetanilide (0.25 g) was added to the 25-mL Erlenmeyer flask. Chlorosulfonic acid (0.625 mL) was added (a few drops at a time) to acetanilide; the flask was re-connected to the gas trap between additions. Upon addition of chlorosulfonic acid to acetanilide, a reaction was observed,
and a yellow reaction mixture resulted. After ~7 minutes, the reaction subsided, and only a few small pieces of acetanilide remain undissolved. This resulting reaction mixture was then heated on a sand bath for 10 minutes to complete the reaction. The flask was cooled in ice, and the oily product was transferred to a 10-mL Erlenmeyer, which contained 3.5 mL of ice water; caution was used during this transfer as unreacted chlorosulfonic acid (if present) produces acidic gases upon addition to water. Upon transferring the oil to the ice water, a white granular solid resulted and was collected via vacuum filtration with a Hirsch funnel. The wet solid was pressed and drained and then transferred back to the reaction flask.

_Synthesis of p-Acetaminobenzenesulfonyl acid._

Concentrated aqueous ammonia solution (0.75 mL) and distilled water (0.75 ml) were added to _p_-acetaminobenzenesulfonfonyl chloride in the reaction flask. The mixture was heated in a sand bath to just below boiling for 5 minutes with occasional swirling. Upon reaction, the mixture turned into a pasty suspension. The suspension was cooled in an ice bath, and the _p_-acetaminobenzenesulfonyl chloride was collected by vacuum filtration. The light yellow solid was pressed and drained.

_Synthesis of Sulfanilamide._

The sulfonamide was transferred to the reaction flask, and concentrated hydrochloric acid (0.25 mL) and distilled water (0.5 mL) were added to the flask. The mixture was heated to a boil until the solid had dissolved (~8 minutes) and then heating continued for 10 minutes longer. The resulting light yellow solution was cooled to room temperature and shaken with granulated decolorizing charcoal, which was filtered by removal of the solution with a pipette. The
resulting colorless solution was placed in a 30-mL beaker, and an aqueous solution of sodium bicarbonate (0.25 g) was added to neutralize the hydrochloride; foam resulted upon this addition. The suspension’s pH was tested with indicator paper, which revealed that the suspension was still slightly acidic. Additional sodium bicarbonate solution was added until the suspension reached a neutral pH. The suspension was cooled in ice, and the resulting white, granular solid was collected via vacuum filtration. The melting point of the crude product of sulfanilamide was taken and found to be 161–163°C. The crude product (213 mg) was recrystallized from water (10 mL) to afford pure sulfanilamide (mp 163-164°C) in 174 mg yield (82% recovery from recrystallization; 55 % yield for the overall reaction – starting from acetanilide).

**III. Results/Discussion/Conclusions**

The overall outcome of this experiment was successful considering the overall percent yield was a 55% for a three-step procedure; this percent yield translates to nearly an 80% yield per step. The percent recovery of recrystallized sulfanilamide (82%) is not as high as the expected, reported percent recovery. (The calculations for percent yield and recovery are shown below). Perhaps, if a second crop of sulfanilamide was collected, this percent recovery may have increased. The purity of the recrystallized sulfanilamide was satisfactory; the melting point of the pure product had a narrow range of 163-164°C while the theoretical melting point is 165-167°C (as reported by *Aldrich*). A second recrystallization would possibly increase the purity of this “pure” product, and a melting point equivalent to the theoretical may then be observed.

Percent yield of sulfanilamide starting from acetanilide, the limiting reagent:

\[
\% \text{ yield} = \frac{174 \text{ mg}}{316 \text{ mg}} \times 100\% = 55\% \text{ yield}
\]

Percent recovery of the recrystallized sulfanilamide:
174 mg/213 mg x 100% = 82% recovery

In summary, the synthesis of sulfanilamide was successful. The HCl gas trap for the chlorosulfonation step was found to be trivial. Minimal transfer losses were made which translated into a decent percent yield for the overall reaction.

**IV. PostLab Exercise**

1. What happens when \( p \)-acetaminobenzenesulfonyl chloride is allowed to stand for some time in contact with water?

   The sulfonyl chloride functionality (an electrophilic entity) will react with water (a nucleophile) to produce \( p \)-acetaminobenzenesulfonic acid; SO_2Cl will be converted to SO_3H.

2. What happens when chlorosulfonic acid comes in contact with water?

   The following reaction occurs:

   \[
   \text{HSO}_3\text{Cl} + \text{H}_2\text{O} \rightarrow \text{H}_2\text{SO}_4 + \text{HCl}
   \]

   Produce two acids
V. Reference