Experiment 4. Reactions of Carboxylic Acids & Their Derivatives.

References: Brown & Foote, Chapters 17, 18

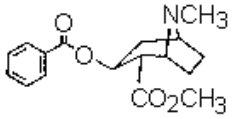
INTRODUCTION:

This experiment is in two parts. The first is a synthesis of Benzocaine, in which you convert a carboxylic acid to one of its derivatives, an ester. The second part consists of a couple of simple test tube reactions that illustrate some of the properties of carboxylic acids and various derivatives.

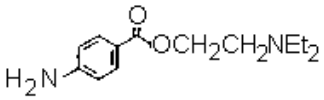
BACKGROUND:

Part A: History of Benzocaine

The scientific work that led to the discovery of the local anaesthetic "benzocaine", is typical of how many biologically active synthetic drugs have been developed from naturally occurring substances. For centuries the Amerindians of the Andes have been using the leaves of the 'Coco bush' (*Erythroxylon coca*) as a mild stimulant. They would (and still do) chew the leaves to help them cope with the exigencies of life in a harsh environment altitude, hunger, inclement weather, and a precipitous terrain make several demands on endurance. In due course, chemists investigated the components of the coco leaves, and finally the active component, the alkaloid "cocaine", was isolated pure in 1862. In the following years its properties were investigated, and by the 1880's it was in use as an anaesthetic in surgery and dentistry, one of the first such drugs to alleviate pain in medical procedures.



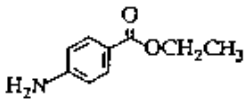
Cocaine



Novocaine

However, it was quickly realized that cocaine also had two major disadvantages, first, the lethal dose was not a great deal more than the therapeutic dose, and so safe administration of the drug in surgery was unreliable. Secondly, cocaine causes serious problems, like potentially irreversible damage to the central nervous system. Consequently, as soon as the structure of cocaine was established (in 1910), chemists began preparing analogues, in the hope of finding one that would have lower toxicity but equivalent efficiency. This search was based on the assumption that certain structural features were important for activity. As the list of successful analogues grew, it became apparent what these were: that there should be an aromatic acid derivative, with the carbonyl group separated from a tertiary amine nitrogen by a chain of two to four atoms. An example is **Novocaine**, which is one of the most successful synthetic drugs in this family in use. A simplier analogue is the ethyl ester of *para*aminobenzoic acid, called "**Benzocaine**". Clearly this lacks the tertiary amine component, so not surprisingly, it is less active as an injectable drug. Nevertheless, it retains anaesthetic properties, and is used extensively as a topical pain reliever,

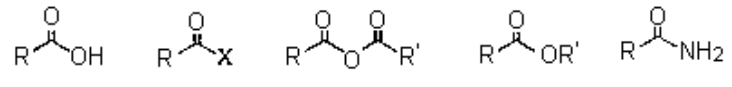
for example in medications for treating sunburn. This is the target of the synthesis part of this experiment.



Benzocaine

A similar story of discovery, investigation, and exploration lies behind the development of the synthetic antimalerial "Chloroquin" from naturally occurring quinine, and of synthetic insecticides like "Deltamethrin" from naturally occurring pyrethrins.

Part B: Tests of Carboxylic Acids, their Salts and Derivatives



carboxylic acid | acyl halide | acid anhydride | ester | amide

(a) Salt Formation

Carboxylic acids may be neutralized by strong bases to give salts. Acids which may be only slightly soluble in water can be extracted from their solutions in an organic solvent by aqueous base, as the salts are usually water soluble: RCOOH + NaOH ---> $RCOO^-Na^+ + H_2O$.

(b) Salt Hydrolysis

Most carboxylic acids are only partially dissociated in aqueous solution. Consequently, when the salt of a carboxylic acid is dissolved in water, it is partially hydrolyzed to the undissociated acid and hydroxide ion: $RCOO^-Na^+ + H_2O$ ---> RCOOH + NaOH.

(c) Acid Chlorides

The halide ion is a good leaving group making acid halides very reactive towards nucleophilic acyl substitution. Acid halides are so reactive that they are not found in nature, since they even react with water (R' = H): RCOCl + HOR' ---> RCOOR' + HCl.

Similar to carboxylic acids (R' = H), these esters products can then be converted to salts in aqueous base.

(d) Amides

Values of pK_a for amides of carboxylic acids are in the range of 15-17, which means that they are comparable in acidity to alcohols.

Amides can also be converted to salts in aqueous base, but by a slightly different mechanism: $RCONH_2 + NaOH$ ---> $RCOO^-Na^+ + NH_3$.

PRE-LAB PREPARATION:

1. Write out a mechanism for the formation of the benzocaine? (Hint: this reaction is called a fischer esterification)

2. In part **A**, a solid precipitate is formed on adding sulphuric acid. What would this solid be?

3. Write an equation which accounts for the solubility of benzoic acid in aqueous base.

4. Write out the structures of all compounds to be tested in Part B.

EXPERIMENTAL PROCEDURE:

Part A: Synthesis of Benzocaine

1. Reaction of Ethanol with *p*-Aminobenzoic Acid

a) Place 0.5 g of *p*-aminobenzoic acid in a 10 mL cylindrical vial and add approx. 6 mL of 95% ethanol, swirling gently to help dissolve the solid (not all the solid will dissolve). Cool the mixture in an ice bath and slowly add 0.5 mL of concentrated sulfuric acid (**CAREFULLY!**). A large amount of precipitate will form when the sulfuric acid is added, but this solid will slowly dissolve during the reflux that follows.
b) Attach a micro-condenser (with cooling water) and heat the mixture under reflux on a heater-stirrer for 60 min. Take care not to overheat the vial and have too violent a reflux rate. Stir the contents of the vial with a magnetic stir bar or by swirling at approximately 15 minute intervals during the first hour of the reflux.
[Note: This may be a good time to do Part B.]
c) After the 60 min reflux period and the mixture is clear, remove the heat and allow the vial to cool (you may use a beaker of cold water if you wish to hasten cooling).

2. Isolating the Benzocaine

a) When the vial is cold, transfer the contents to a 100 mL beaker and slowly add small portions of a 10% sodium carbonate solution (about 7 mL needed) to neutralize the mixture. After each addition of the sodium carbonate solution, extensive gas evolution (frothing) will be perceptible until the mixture is nearly neutralized.
b) When gas no longer evolves as you add a portion of sodium carbonate, check the pH of the solution and add further portions of sodium carbonate until the pH is 9 or above.
c) Add 15 mL of ether to the beaker and stir with a glass rod to dissolve as much of the solid benzocaine as possible - do not worry if all the solid does not dissolve.
d) Pour the mixture through *a glass funnel* (residual solids included) into a separatory funnel and rinse your beaker with a few mL of additional ether to ensure all the benzocaine has been transferred to the separatory funnel.
e) Shake the separatory funnel 3 - 4 times, releasing the ether vapour pressure after each shaking.
f) Allow the mixture to separate and save the upper ether layer.
g) Dry the ether layer with sodium sulfate (about the tip of a spatulas), and then gravity filter the ether layer into a 125 mL Erlenmeyer flask to remove the drying agent.
h) Remove the ether and ethanol by evaporating them on a steam bath until *all* of the ether (bp 35^{o}C) has been removed. About 5 to 8 mL of material should remain; some will be residual ethanol and the rest, the yellowish oily material, your ester product.

3. Purifying the Benzocaine.

The product will be recrystallized using ethanol and water as *solvent pairs* (similiar to exp. 3).
a) Add a few mL of hot ethanol and heat the mixture on the steam bath until *all* the oil dissolves.
b) Add water (*drop wise!*) to the alcohol solution until cloudiness *just* appears and then add a few drops of ethanol. Cool the mixture, with occasional VIGOROUS swirling, in an ice bath.
c) Collect the benzocaine by vacuum filtration, using a Hirsch funnel.
e) Allow the solid to dry at room temp on a *weighed* piece of filter paper, and then weigh it.
f) Calculate the percentage yield of the recrystallized product.

4. Characterization of the Benzocaine

a) Obtain and label an IR spectrum of your recrystallized product.
b) Determine the melting point of your recrystallized products, and record them.
c) The proton NMR spectra of benzocaine is shown below. Include, on the back of your IR, a table which assigns all significant peaks in the NMR (Hint: Two different peaks signals are overlapped near 4.2 ppm).
d) Dispose your product in the SOLID WASTE jar provided.

Part B: Tests of Carboxylic Acids, their Salts and Derivatives

(a) Salt Formation

In each of two test tubes, place 0.1 g of benzoic acid. To one tube add 3 mL of cold water, to the other add 3 mL of 10% sodium hydroxide solution. Shake both tubes, observe, and record the results. Then acidify salt with diluted hydrochloric acid.

(b) Salt Hydrolysis

Dissolve approximately 0.2 g of sodium acetate in 5 mL of distilled water, test the resulting solution with litmus paper, and note the result.

(c) Acid Chlorides

[These experiments MUST BE DONE IN THE HOOD.] Add drop by drop 1 mL of acetyl chloride to 1 mL of butanol. Allow to stand for about 2 minutes and then pour it carefully into 5 mL of water (acetyl chloride reacts vigorously with water). Note the odour [Recall: Smelling solutions is done by wafting the smell towards your nose]. Remove a little of the insoluble layer with a dropper and test its solubility in 5% NaOH solution.

(d) Amides

Dissolve a little acetamide in water and determine the pH of the solution using pH-paper. Compare your results with that for (i) aniline in water, and (ii) ethylamine in water. Add 0.5g acetamide to 5 mL of 10% sodium hydroxide solution in a test tube, and gently warm the solution: test any vapour evolved with moist pH paper (do not let the pH paper touch the walls of the test tube - think of why this is important!).