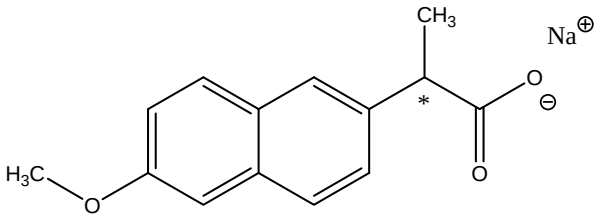
INTRODUCTION

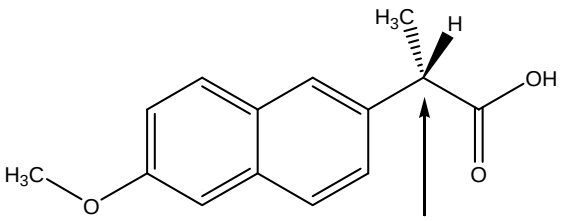
In this experiment, you will be isolating the active ingredient in the anti-inflammatory drug Naproxen Sodium. You will do this by converting it to its neutral carboxylic acid form, Naproxen (II). This will be extracted into ethyl acetate, separated, dried and the solvent removed. Its structure will be identified by IR (KBr) and NMR (^{1}H and ^{13}C). Naproxen is a chiral compound (with S absolute configuration), and if circumstances permited, you would also measure its optical rotation. However, we don't have a polarimeter.

Structure of Naproxen Sodium (I)



* = chiral center

Structure of Carboxylic acid Naproxen (II)



"S" in Naproxen

Apparati (tools)

Mortar & Pestle
Large test tube
Pipets
Small round bottom flask
Rotovap

Chemicals

Ethyl acetate
3M HCl
Brine (saturated sodium chloride solution)
$NaSO_4$

PROCEDURE:

Obtain 1 Naproxen Sodium tablet from your instructor and record the weight of the pill to the nearest milligram (use the package label to determine the mass and calculate how many moles of Naproxen Sodium are present). Use a clean "mortar & pestle" to grind the tablet to a fine powder. Transfer the powder to a large test tube.

Add 3 mL of ethyl acetate and 1 mL of 3M HCl and mix thoroughly (how many moles of HCl are there?). You can mix the tube contents by holding the test tube firmly in one hand and using a finger from your other hand to repeatedly vortex the tube. Caution: you want to be vigorous, but you don't want to flip the tube out of your grasp.

Alternatively, you can use the pipet to suck up the liquid and vigorously squirt it back into the tube. Allow the organic phase and aqueous phase to separate. As best you can, pipet out the top organic layer, leaving some behind to avoid transferring any of the blue particulate filler from the capsule or aqueous solution. Transfer the organic layer into another clean test tube.

Add in another 2 ml of ethyl acetate to the aqueous acid solution, repeat the mixing and transfer of the organic phase into the same tube as your first organic transfer. (Never use a contaminated pipet in any reagent bottle or you will contaminate the entire bottle.) Do this once more (extract 3 times for a total of about 7 mL of ethyl acetate). Each time leave the blue particulate filler behind in the aqueous layer. Save the aqueous phase in case you need to further extract it. When finished, you can dispose of the aqueous fraction in the aqueous waste container.

Wash the combined organic layers with 1 mL of brine, either by using a pipet (suck up liquid and squirt it back in) or vortex the tube contents. Pipet off the lower brine layer, taking just a bit of the organic solvent with its removal. Your goal is to leave the maximum amount of organic phase (because naproxen will stay in that phase), yet still remove all of the aqueous phase. Do not leave any visible trace of water.

Add enough anhydrous sodium sulfate for final drying. If there is still suspended particulate matter you can do a crude filtration by inserting a small plug of cotton in a pasture pipet and pipet the organic phase through that plug into a small, clean, dry preweighed round bottom flask. Avoid having any brine in the pure organic sample, which will contaminate your Naproxen with salt and will also make it very difficult to dry your material. It will also affect your yield of product.

The ethyl acetate can be evaporated at the rotovap, using warm water to help drive it off at the very end, or it can be placed on a watch glass and set under the lowered hood sash to allow air flow to help evaporate the ethyl acetate. This is slower, but it's fun to see the crystals form (preweigh your watch glass). Wait until your sample is completely dry, and record the weight. The white crystals should be pure extracted naproxen.

The theoretical mass of sodium naproxen per pill can be obtained from information on the box. When sodium is substituted out and replaced with a proton the weight will change a little bit. See if you can calculate the actual weight of naproxen (with a proton instead of sodium) that you should recover. Obtain a melting point to check its purity and an IR, ^{1}H NMR and ^{13}C NMR. Fully interpret all of your spectra to confirm the structure of Naproxen. If a polarimeter and time are available, a measurement of optical rotation can be made.

Package Label Information

Inactive Ingredients: Carnauba Wax, FD&C Blue No. 2 Aluminum Lake, Hyprobellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Povidone, Talc, Titanium Dioxide. Each caplet contains sodium (20 mg).

Active Ingredients: (in each caplet): Naproxen Sodium 220 mg (naproxen 200 mg), Nonsteroidal Anti-Inflamatory Drug (NSAID), Purpose: Pain reliever/Fever Reducer.

1. Look up the structure of Motrin. What are some similarities and differences from Naproxen?
2. Is there enough HCl added to completely neutralize the Naproxen sodium? Show all work.
3. What is the common commercial brand name of Naproxen?
4. What are the medical uses of Naproxen? What are possible side effects?
5. Propose or find a synthesis of Naproxen. You can find some on the internet (hint: Wikipedia has one). Do you know the mechanisms of the steps?
6. Naproxen is said to be the first NSAID marketed in an enantiomerically pure form. What is an enantiomer? Identify its absolute chirality.
7. Does Naproxen or Ibuprofen provide longer relief? Which has a lower risk of stomach and kidney problems?
8. Are there important advantages of NSAIDs over SIADs?