Isolation of Optically Pure (S)-(+)–Ibuprofen

In this laboratory exercise we will isolate (S)-(+)–Ibuprofen from a racemic mixture of both enantiomers of this compound.

This will be accomplished by treating the racemic mixture of Ibuprofen with (S)–(-)-α-Phenethylamine, whose molecules are themselves chiral, to form (S,S) and (R,S) Ibuprofen/Phenethylamine diastereomeric salts. Because the (S,S) salt is much less soluble than the (R,S) salt, the (S,S) salt can be separated from the (R,S) salt by simple filtration. Subsequently the (S,S) Ibuprofen/Phenethylamine salt can be recrystallized to increase its purity and then acidified to recover pure (S)-(+)–Ibuprofen. The (S)-(+)–Ibuprofen can be extracted from the acidic solution and solidified after removal of the extraction solvent.

Although alike in almost all of their chemical and physical properties, enantiomers can behave very differently in biological systems. This is because the enzymes that act on biomolecules and other bioreceptors have active sites that are chiral. In the present case, (S)-(+)–Ibuprofen is found to be a much more effective analgesic than is a racemic mixture of the Ibuprofen enantiomers. Thalidomide provides another example of how different enantiomers of a compound can behave quite differently.
Thalidomide, as a racemic mixture, was the active ingredient in a prescription to relieve the symptoms of morning sickness in pregnant women. The drug was widely used in the late 1950’s and early 1960’s, until it was linked to severe birth-defects in the children born to women using the medication. It turns out, the (R) enantiomer is effective against morning sickness, but the (S) isomer causes birth defects.

Resolution of racemic mixtures is typically very difficult because, as mentioned, enantiomeric substances are alike in most of their chemical and physical properties. Louis Pasteur was able to resolve a racemate of Tartrate salts by mechanically separating physically distinct crystals of the enantiomers.

Tarter, or crude potassium acid tartrate, had long been known to vintners as a solid which separates as a sludge from wine during fermentation; it is poorly soluble in alcohol. Tartaric acid, a normal constituent of grapes, was first isolated and studied by Scheele and subsequently was produced commercially. This was the dextro-rotatory form of the acid. Around 1820 Charles Kestner, a manufacturer of chemicals in Than in the Haut-Rhin, encountered a new form of tartaric acid which behaved differently than the usual product; he was unable to produce more of it. The unique acid was studeied by Johann Friedrich John of Berlin, later by Gay-Lusac, who named it racemic acid (L. racemus, grape), and still later by Berzelius, who called it paratartaric acid. Biot showed that racemic acid and its salts do not influence polarized light.

In a careful study of the sodium ammonium salts of tartaric and racemic acids, Mitscherlich in 1844 reported that the salts have the same crystalline form, their only difference being that tartaric acid is dextro-rotatory and racemic acid is inactive.

Pasteur suspected that Mitscherlich and other crystallographers might have overlooked a dissymmetry in the crystals. His own painstaking investigation of the crystals of these salts showed that the tartrate crystals were truly hemihedral. The racemic crystals, which he expected to be symmetrical, he found were also hemihedral. Closer examination revealed that in the tartrate crystals the hemihedral faces were all oriented in the same way, but that in the racemic crystals the faces of some were oriented toward the right whereas the faces of others were oriented toward the left.

Pasteur laboriously separated the right-handed and left-handed crystals and dissolved each kind in water. He noted that one solution rotated polarized light toward the right and that the other solution rotated the light to the left. ...

No one realized until later that Pasteur had been exceedingly fortunate in preparing his crystals, in the choice of both compound and of working conditions. When sodium ammonium tartrate crystallizes from a hot concentrated solution, the crystals are fully symmetrical and the monohydrate contains equal proportions of the dextro- and levo-rotatory molecules. But there is a transition point at 28°C. When the tartrate crystallizes below this temperature it forms the tetrahydrate and half the crystals are pure dextro- and the other half pure levo-rotatory molecules.

Our resolution of racemic Ibuprofen will involve adding a Resolving Agent, (S)-(−)-α Phenethylamine, to the racemic mixture. This Resolving Agent will undergo an acid-base reaction with Ibuprofen, producing two salts that are diastereomers.
Unlike enantiomers, diastereomers have very different chemical and physical properties. In this case, the (S,S) salt is much less soluble in Water than the (R,S) salt and can be separated out by simply filtering the reaction mixture.

Once isolated, the (S,S) salt can be acidified to regenerate (S)-(+) Ibuprofen in its unionized form.
The unionized Ibuprofen has a low Water solubility and can be extracted into an organic solvent like MTBE (Methyl tert-Butyl Ether). Once extracted, the extraction solvent can be dried and stripped off. The resulting (S)-(+) Ibuprofen then tends to solidify.

In another laboratory, our (S)-(+) Ibuprofen will be tested for optical purity using polarimetry; a difference in the rotation of plane polarized light is one of the few physical properties that distinguishes enantiomers.

(Reaction schemes adapted from “The Resolution of Ibuprofen, 2-(4’-Isobutylphenyl)propionic Acid” by James V. McCullagh reported in The Journal of Chemical Education, Vol. 85 (2008).)
Pre-Lab Questions

1. Identify the assymetric carbon(s) in Menthol. How many stereoisomers are possible for Menthol? Sketch them using a wedge-and-dash notation.

2. If (S)-Ibuprofen is more active pharmacologically, why are Ibuprofen prescriptions still prepared from a racemic mixture of the enantiomers?

3. Besides optical rotation, what is a physically distinct difference between (+)-Carvone and (-)-Carvone?

4. Tartaric acid occurs in two forms; naturally occuring l-(+)-Tartaric Acid and d-(−)-Tartaric Acid.

![Diagram of Tartaric Acid](image)

Why is d-Tartaric Acid levo-rotatory? Provide (R),(S) designations for the number 2 and number 3 carbons in d-(−)-Tartaric Acid and l-(+)-Tartaric Acid.
Procedure


Generation of the Diastereomeric Salts

To a 100 mL round bottom flask, add a stir bar, 3.0g of racemic Ibuprofen and 30 mL of 0.24 M KOH. Clamp the flask into a heating mantle and insert a thermometer. Initiate stirring. Heat the solution to a temperature between 75°C-85°C. Most but not all of the Ibuprofen will dissolve at this temperature. Next, add 0.9 mL of (S)-(−)-α Phenethylamine dropwise and slowly to the flask. (Wear gloves when handling this compound as it is irritating to the skin. Recap the bottle immediately after use as the compound reacts with the Carbon Dioxide in the Air.) Precipitate will form within a few minutes. Keep the solution at this temperature for 1 hour. Remove the flask from the sand bath and allow it to cool to Room Temperature. Collect the precipitated salt by vacuum filtration. Wash the solid with a small amount (~2-3 mL) of ice cold Water. Weigh the solid.

Recrystallization of the (S,S) Ibuprofen/Phenethylamine Salt

Place the salt in a 50 mL beaker that contains a boiling stone. Add 2-Propanol (16 mL per gram, dry weight, of salt. If the salt was not dried before weighing use 30 mL of 2-Propanol.). Place a watch glass on top of the beaker and heat the solution to a boil. At this point all the solids should dissolve. (If all the solid does not dissolve, remove from heat and add 1-2 mL 2-Propanol. Bring back to reflux.) Remove the solution from the heat source and allow it to cool to Room Temperature; 1-15 minutes. Filter the resulting crystals. Wash the crystals with 2-3 mL of ice cold Water. Weigh the crystals after they are dry. Set aside enough for a melting point determination.

Recovery of (S)-(+)–Ibuprofen

Place the recrystallized salt into a 50 mL beaker. Add a stir bar and 25 mL of 2M H₂SO₄. Stir the solution for 5 minutes. The crystals will quickly dissolve and will leave behind thick oily droplets suspended in the solution. Extract the aqueous layer with 15 mL of MTBE three times. Combine the organic layers together and extract them once with 15 mL of Water and the once with 15 mL of sat’d aqueous NaCl. Dry the organic layer over anhydrous Sodium Sulfate. Transfer the MTBE solution to a pre-weighed beaker with a boiling chip. Boil off all the ether on a sand bath set to a temperature of 100°C. The product at first will be a thick, clear oil but it usually solidifies on standing. Weigh the product. If solid, take a melting point. Determine your percentage recovery. (What should this value be?)
Post Lab Questions

1. What is the pH of the 0.24 M KOH solution used in the first part of the lab procedure? What is the purpose of using a basic solution for this reaction mixture?

2. How do the melting points of enantiomers compare to each other? How does the melting point of a racemate compare to that of the enantiomers? (There are a couple of cases here.) How do the melting points of diastereomers compare to each other?

3. Why do we not try to recover (R)-(-)-Ibuprofen from the filtrate at the end of the first procedure?

4. What is the purpose of “washing” the MTBE with sat’d aqueous NaCl? (You may wish to consult your laboratory instructor about this.)