Chiral Resolution of Methylbenzylamine via Fractional Crystallization

Experiment taken from “Experiments in Organic Chemistry: From Microscale to Macroscale” by Jonathon S. Nimitz and “Theory and Practice in the Organic Laboratory, 5th ed” by John A. Landgrebe

Introduction
Often during a synthesis of a compound containing a chiral center, a racemic mixture is produced. A racemic mixture is an equal mixture of two enantiomers. This situation can occur because achiral starting materials and reagents cannot induce net chirality in the molecule. To obtain one enantiomer in purified form, we must either use chiral reagents or perform a resolution of the racemic mixture.

Enantiomers have identical physical properties, such as melting point, boiling point, index of refraction, and solubility. They can be distinguished by the direction they rotate plane-polarized light and by their reactions with other chiral molecules. In this experiment, you will resolve (separate) a racemic mixture of R– and S–α–phenylethylamine (also called methylbenzylamine) by forming a salt with the chiral molecule (+)–tartaric acid. Tartaric acid is very inexpensive, being obtained as a by-product of wine making. It is used in soft drinks, baking powder, and other foodstuffs.

PreLab Exercise: Determine the salts that will be formed when (+)–tartaric acid reacts with the racemic mixture of methylbenzylamine. Are the products enantiomers or diastereomers?

Items to Consider: Do diastereomers have different physical properties? How does this experiment help achieve the separation of R– and S–methylbenzylamine?

Once the salts are formed, they will be separated via fractional crystallization on the basis of their differing solubility in methanol. [(-)–Amine–(-+)–tartrate has a lower solubility in methanol than the (+)–amine salt.] After preparation, treatment with bases regenerates the free amine. The amine is distilled, and its optical rotation is measured in a polarimeter to determine the optical activity. Please read up on polarimetry (chapter 11) and extraction/use of a separatory funnel (chapter 6) in the Chem 35 & 36 Lab Guide.

To calculate the specific optical rotation of the compound, one takes the observed rotation (in degrees) and divides by the length of the cell in decimeters (usually 1.0) and the concentration of the solute in g/mL.
Once specific rotation is known, it can be compared to the tabulated specific rotation for that compound to determine optical purity:

\[
\text{Optical purity} = \left( \frac{\text{specific rotation}}{\text{literature value of specific rotation}} \right) \times 100\% 
\]

The optical purity presents the excess of one enantiomer in the sample. A pure enantiomer has an optical purity of 100% and a racemic mixture 0%.

**Procedure**

**Resolution by Fractional Crystallization: Day One**

Add 6.3 g (42.0 mmol) of (+)-tartaric acid and 5.0 g (41.3 mmol) of (+)-\(\alpha\)-methylbenzylamine to 75 mL of methanol (room temperature) in a 125–mL Erlenmeyer flask. Stir the mixture with 2–3 boiling sticks, and heat to just below the boiling point to achieve a complete solution. Allow the solution to stand quietly for at least 24 hours.

*Note:* Prismatic crystals should form as the solution cools. If needles form, warm the mixture to dissolve the needles and use a prismatic seed crystal from another student’s experiment.

**Isolation and Purification of Amine: Day Two**

Isolate the crystals by suction filtration and wash them with a very small amount of cold methanol.

*Note:* In the following procedure, use a minimum amount of water to prepare the solution of the amine salt. Alternatively, the sodium hydroxide solution can be added directly to the solid crystals.

Treat a concentrated solution of the amine salt with enough sodium hydroxide solution (10–50% by weight) to cause the amine to oil out. Isolate the free amine by extraction with three 10–mL portions of ether in
a 125-mL separatory funnel. Dry the combined ether layers over anhydrous sodium sulfate. Filter off the sodium sulfate and rotovap the resulting solution. Transfer the oil to a 10-mL round bottom flask.

Distill the liquid residue under vacuum (house vacuum) using a short-path distillation head. Be sure to check the pressure of the house vacuum; the TA will assist you in using the Pirani gauge pressure reader. Use a nomograph (one will be given to you) and the measured pressure to estimate the boiling point of the oil at reduced pressure. (The boiling point is 184–186°C at 760 Torr). Record the weight and percent recovery of the (--)-amine.

Determine the optical rotation of your product. The reported specific optical rotation for (--)-α-methylbenzylamine at 22°C is –40.3°. Also determine the enantiomeric excess (% ee) of (--)-α-methylbenzylamine by using the following equation:

\[
% \text{ ee} = \frac{\text{specific rotation of the sample}}{\text{specific rotation of the pure enantiomer in excess}} \times 100
\]

PostLab Questions:
1. Why would calcium chloride be unsuitable for the drying of the amine solution?
2. A partially resolved mixture of (+)-B and (--)-B contains 75% of the (--)-isomer. What is the optical purity of this sample?