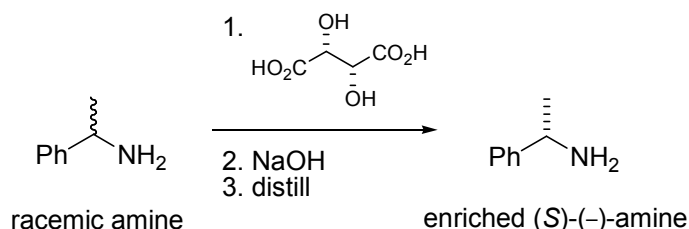


## Resolution of $\alpha$ -Methylbenzylamine

### Overall Reaction



### Purpose

This experiment has the following goals:

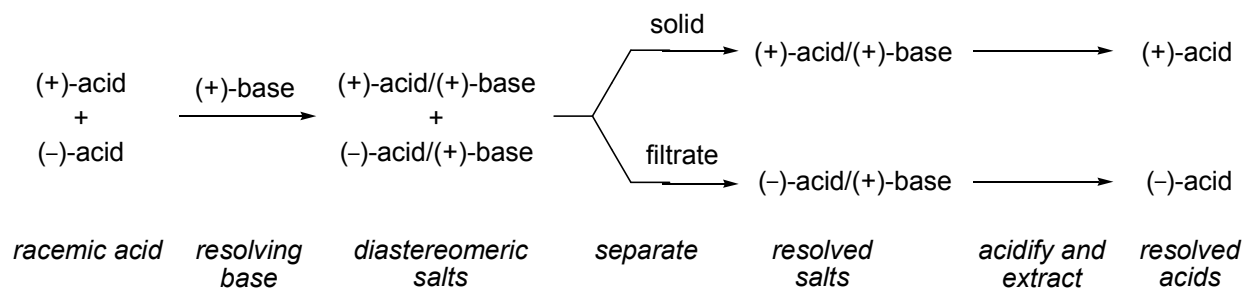
- (1) demonstrate the principle of resolution of a racemic mixture
- (2) perform a purification by reduced pressure distillation
- (3) use a chiral shift reagent to determine optical purity by NMR.

### Background

Obtaining chiral molecules in high optical purity is a significant synthetic challenge. This problem has two potential solutions: (1) make molecules as single enantiomers (asymmetric synthesis) and (2) separate individual enantiomers in a racemic mixture (resolution). Both approaches have their drawbacks. Asymmetric synthesis can be extremely challenging, but the yields of such a reaction (if you can get it to work) are theoretically 100%. Resolutions are easy and use simple technology, but the yields are limited to 50% at best. Which method is better depends on the availability and cost of the starting materials, among many other factors.

Resolutions are the “old school” method for obtaining optically pure compounds. The process is conceptually very simple. Enantiomers have identical physical properties, so standard separation techniques (chromatography, recrystallization, distillation) will not distinguish between the isomers. Diastereomers, on the other hand, do have different properties. Therefore, in a resolution, a starting material as a mixture of enantiomers (+ and -) is reacted with a single enantiomer (only +) molecule to afford two diastereomers (+/+ and -/+). Normally, one diastereomer has a lower solubility than the other, so they may be crystallized apart. Another step is needed to remove the resolving enantiomer (+) and isolate just the desired pure enantiomer of the original starting material. Since the original material was racemic, at most 50% of a single enantiomer is available. The real cost is that half of the starting material will be considered garbage at the end of the process.

Traditionally, racemic amines and acids are excellent candidates for resolution. For example, a racemic acid (+ and -) can react with a chiral base (only +) to form a pair of diastereomeric salts (+/+ and -/+) (Scheme 1). Crystallization and filtration will give a solid that is enriched in one diastereomer (assume +/+). Concentration of the filtrate will give the other enriched diastereomer (assume -/+). If either solid is not sufficiently pure, it can be further recrystallized. Reaction of either diastereomer with excess acid, such as HCl or H<sub>2</sub>SO<sub>4</sub>, will remove the chiral base resolving group and leave an enantiomerically pure (or at least enriched) chiral acid. Through the same process, racemic bases can be resolved with chiral acids. The “art” of performing a good resolution is choosing an appropriate chiral resolving agent that will give diastereomers that have very different solubilities. Finding a good resolving agent can involve a considerable amount of experimentation.



Scheme 1. Outline of a resolution of a racemic acid with a chiral base

In our experiment, we will resolve racemic  $\alpha$ -methylbenzylamine with (+)-tartaric acid, a very inexpensive optically pure acid. The (–)-amine (same as (*S*)- $\alpha$ -methylbenzylamine) forms the less soluble complex. This resolution is notoriously finicky and rarely gives outstanding results. This means that our “resolved” amine will have low optical purity – mostly (–)-amine with some (+)-amine. For us, this is not a problem because we are after the exercise of performing a resolution and not an optically pure amine.

The amine we obtain from the resolution will be purified by distillation and examined by NMR to determine the enantiomeric excess. Because enantiomers have identical properties (including chemical shifts), we will need to react the amine with a chiral acid, (*S*)-(+)-*O*-acetylmandelic acid to form a diastereomeric complex with the amine (Figure 1). In this complex, some of the  $^1\text{H}$  NMR signals on the diastereomeric complexes will be different enough for us to integrate and determine their ratio and ultimately the enantiomeric excess (e.e.) of the resolved amine.

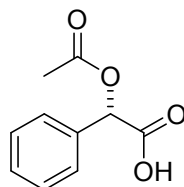


Figure 1. (*S*)-(+)-*O*-acetylmandelic acid

It may seem odd to use NMR to determine the e.e. of a compound. In 201/202, optical rotation is presented as the standard method. Unfortunately, accurate optical rotations are a challenge for us. They require a research-grade polarimeter, not the simple “instruments” that you used in 201. The standard method for determining e.e. is through chiral HPLC. An HPLC column loaded with a chiral stationary phase can differentiate between two enantiomers, which will have different retention times on the chiral column. Integration of the two peaks gives the e.e. of the mixture. While both the HPLC and NMR approaches rely on integration, HPLC peak integrations are more accurate, making HPLC the preferred method for e.e. determinations.

**Experiment** (procedure modified from Krumpole *J. Chem. Ed.* **1991**, *63*, A176-A178)

Friday (week 0): In a 500 mL flask with methanol (250 mL) add (+)-tartaric acid (125 mmol).

Heat the solution to near boiling in a sand bath to dissolve the acid. While the solution is

heating, weigh racemic  $\alpha$ -methylbenzylamine (125 mmol) in a 20 mL scintillation vial. Add the amine by pipet until you reach the desired mass. Once the acid has dissolved and the solution is

near boiling, remove the solution from the sand bath. Add the amine dropwise by Pasteur pipet while still stirring the mixture. Remove the stir bar and allow the reaction to stand at room temperature until the next lab period. Cover the top of the flask with Parafilm to minimize solvent evaporation.

Monday/Wednesday (week 1): Filter the solid on a Buchner funnel (5.5 cm paper). Collect the filtrate in a 500 mL side-arm flask. Dissolve the acid-base complex in 10% NaOH (100 mL) in a 250 mL flask with stirring. Pour the mixture into a 250 mL separatory funnel. Extract the aqueous layer with  $\text{CH}_2\text{Cl}_2$  (3×50 mL), dry the combined extracts over  $\text{MgSO}_4$ , gravity filter the mixture, and concentrate the solution in vacuo in a 500 mL round-bottom flask. Transfer the residue into a 25 mL round-bottom flask. Distill the mixture through a short-path distillation head under reduced pressure. Heat the flask with a heat gun. The boiling point should be between 70 and 100° (may be higher if the aspirator cannot achieve a low pressure). Be sure to collect the distillate in a tared flask. Determine the percent recovery from the starting racemic amine and record the boiling range of the distilled product. Obtain a  $^1\text{H}$  NMR spectrum of the distillate. Seal the amine well for storage.

(Monday/Wednesday (week 2): In a vial weigh between 0.10 and 0.15 mmol of the distilled amine. Weigh out a corresponding amount of *O*-acetylmandelic acid. Add  $\text{CDCl}_3$  (~1 mL) to the amine followed by the chiral acid. Mix well. Take a  $^1\text{H}$  NMR spectrum of the solution. Be sure to determine the ratio of the diastereomeric salts to calculate the e.e. of the distillate.

### Lab Report

Aside from the standard lab report items, your report should include the following items in the Discussion Section.

- Go into a little more detail than usual on interpreting the NMR spectrum to determine the e.e. of the product.