

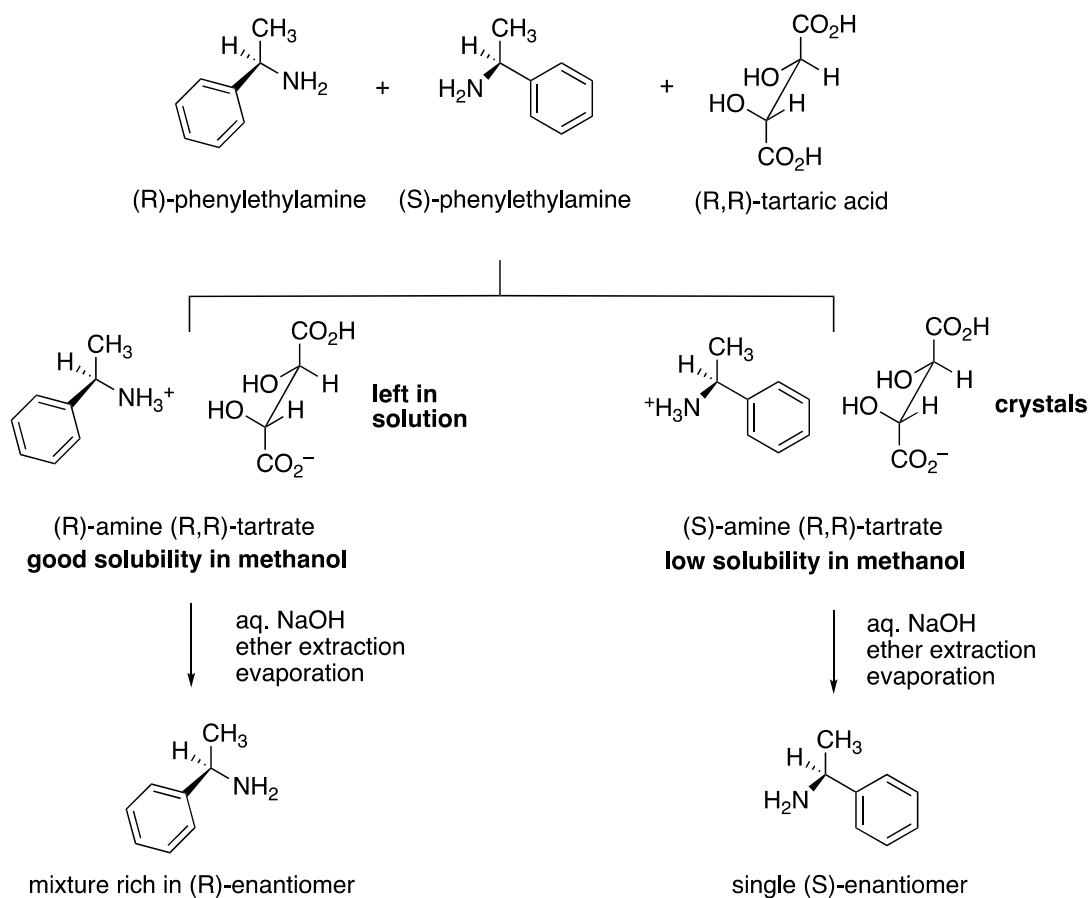
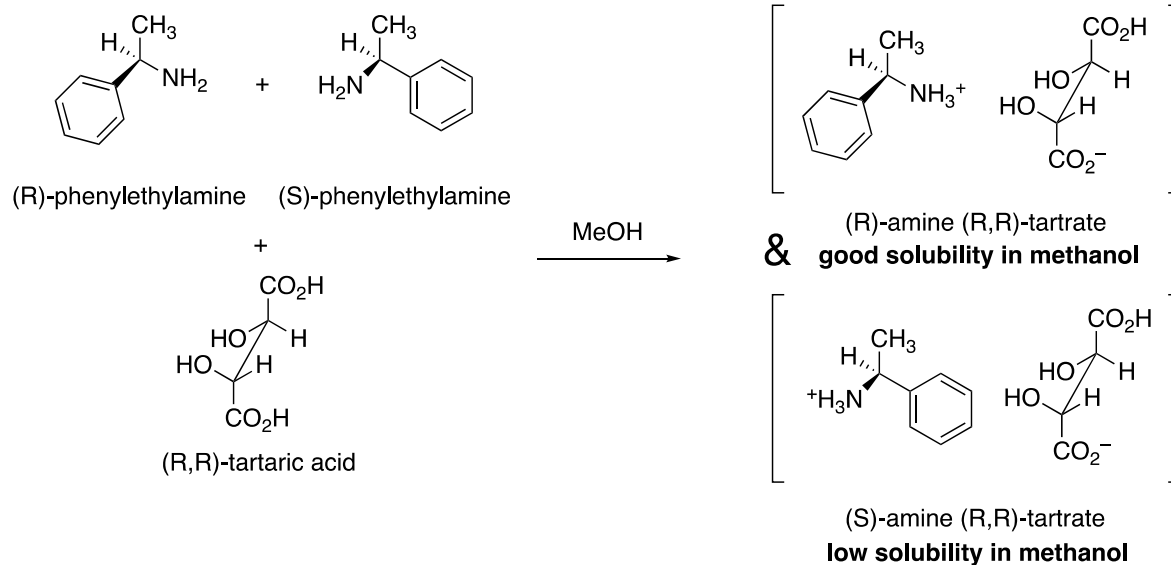
Experiment #5: Resolution of (*R,S*)-1-Phenylethylamine via Diastereoisomer formation with (*2R*),(*3R*)-Tartaric Acid

Introduction

A separation of the enantiomers of phenylethylamine can be achieved by exploiting the very different solubilities in methanol of their diastereomeric complexes with a single diastereomer of tartaric acid.

Recall that enantiomers have identical physical properties, while those of diastereomers differ. When a hot solution of *racemic* (*R,S*)-1-phenylethylamine and an equivalent amount of (*R,R*)-tartaric acid in methanol is allowed to cool, the less soluble (*S*)-amine (*R,R*)-tartrate complex crystallizes out of solution (see scheme below). Isolation of this crystalline material and treatment with excess aqueous sodium hydroxide allows liberation of the (*S*)-amine from the tartrate. Just as with the extraction experiment you have already done, we now have a situation where we can separate a relatively non-polar organic material (the amine) from a polar one (the tartrate salt). After extraction the pure (*S*)-amine is obtained by evaporating the methanol solvent on a rotary evaporator.

In theory, the more soluble diastereomeric complex that remains dissolved in the filtrate can also be isolated by treating the filtrate with sodium hydroxide solution, extracting the liberated amine into an organic solvent to separate it from tartrate, and evaporating the methanol solvent. The structures of the materials used and complexes formed are as follows. A flowchart (overleaf) details the steps involved in this resolution experiment.



In practice, it is very rare for a single crystallization of this kind to prove sufficient to fully separate two enantiomers. Invariably, the complex containing the (S) enantiomer crystallizes along with some of the complex containing the (R) enantiomer, and not all of the (S) enantiomer complex crystallizes. Thus we are left with a mixture of some of the (S) containing complex and most of the (R) containing complex in solution. If it was required to achieve absolute and complete separation of a pair of enantiomers the crystallization experiment would be performed several times, in sequence, gradually enriching the percentage of pure single enantiomer.

What you will do

Work in pairs throughout this experiment. Though the first part of this two week experiment is rather short the best results are obtained by being careful at this stage and performing the simple operations cautiously.

1st week

Care! The racemic amine mixture has a strong and irritating odor. Dispense this material and perform all your manipulations in the hood.

Weigh 6.25g (41.6mmol) of (*R,R*)-tartaric acid into a 250mL Erlenmeyer flask, add 100mL of methanol, and heat the mixture gently on a hotplate for a few minutes. To the warm solution slowly add 5g (5.3mL, 41.2mmol) of (*R,S*)-1-phenylethylamine. **Care!** too rapid addition will cause the mixture to boil over. Once the addition is complete let the solution boil very gently on the hotplate for at least 15 minutes (use a boiling stick). Let the solution cool to room temperature, seal the flask with parafilm, label it with your names and laboratory section, and place in the location indicated by your TA or instructor. **The solution must now be left to slowly crystallize until next week.**

2nd week

Care! The sodium hydroxide solution you will use will cause serious burns if it comes into contact with your skin. Wear gloves and eye protection at all times when handling this material.

Collect the crystalline product by suction filtration and wash the crystals on the filter with a little methanol. Dry the crystals on a filter paper and record the yield. DO NOT DISCARD THE FILTRATE.

Partially dissolve the product in around 50mL of water and add around 4.5mL of 50% aq. NaOH solution. Ensure that the solution is basic by testing with pH paper. Transfer the aqueous solution to a separatory funnel, add 30mL of ether, and thoroughly mix the two layers using the technique you learned in a previous experiment. Carefully return the aqueous layer to the separatory funnel and repeat the extraction with a second 30mL portion of ether. Collect the second portion of ether, combine with the ether extracts from the first extraction, and dry over anhydrous Na₂SO₄ for a few minutes. Decant the dried extracts into a round bottomed flask and remove the solvent using a rotary evaporator. Transfer the residue to a screw top vial and record the yield.

If so directed by your TA or instructor transfer the methanolic filtrate from the crystallization process to a round bottomed flask and evaporate the solvent on the rotary evaporator. Next, add 50mL of water to the residue. You are now going to follow the extract procedure from above, thus: add 4.5mL of 50% aq. NaOH solution. Ensure that the solution is basic by testing with pH paper. Transfer the aqueous solution to a separatory funnel, add 30mL of ether, and extract. Repeat the extraction with a second portion of ether (30mL), combine the ether extracts,

and dry them over anhydrous Na_2SO_4 for a few minutes. Decant the dried extracts into a round bottomed flask and remove the solvent using a rotary evaporator. Transfer the residue to a screw top vial and record the yield.

With the assistance of your instructor record the optical rotation of your two samples using the polarimeter in the central instrument room. In the same manner, also record the optical rotation of the original *racemic* mixture, (*R,S*)-1-phenylethylamine. Instructions on how to prepare the samples for this measurement will be provided when you are ready.

Cleaning Up

Your purified amines, methanol filtrate, and any ether left over from the extraction should be disposed of in the non-chlorinated waste solvent container. Your basic layers from the extraction should be placed in the aqueous waste container.

Your Report

Record the dried weight of the crystals you obtain, and the weights of the two samples of amine you isolate. Record the optical rotations of the two samples and indicate clearly which figure belongs to which enantiomer, *R* or *S*.

In your discussion section calculate a percentage recovery for the crystalline material you isolate and comment on the efficiency of this process. With reference to the optical rotations you recorded on the polarimeter discuss how effective was your attempt to separate the two amine enantiomers (optical rotations for the pure *single* enantiomers, in other words the theoretical values, are: (*S*) -38.2° and (*R*) $+38.2^\circ$).

Questions

1. The (*S*) enantiomer is isolated via a crystalline salt and, as crystals grow in a "pure" form, this enantiomer can potentially be isolated in a very pure state. Isolating the (*R*) enantiomer from the residue left in solution inevitably involves isolation of that portion of the (*S*) amine that did not crystallize. The presence of this (*S*) amine has an effect on the optical rotatory power of the sample isolated in this part of the experiment. What effect?
2. It is possible to separate the two enantiomers comprising a racemic mixture using the various forms of chromatography you have met (TLC, column, GC, HPLC). These techniques share a common operational basis, but what modification is required if separation of enantiomers is to be achieved?

Answers to Questions

1. The (S) enantiomer is isolated via a crystalline salt and, as crystals grow in a “pure” form, this enantiomer can potentially be isolated in a very pure state. Isolating the (R) enantiomer from the residue left in solution inevitably involves isolation of that portion of the (S) amine that did not crystallize. The presence of this (S) amine has an effect on the optical rotatory power of the sample isolated in this part of the experiment. What effect?

For the sake of argument let's assume that 90% of the (S) amine crystallized as its tartrate salt. The remaining 10% of the (S) amine must therefore still be in solution along with all of the (R). The optical rotatory power of the material left in solution is compromised by the presence of this 10%, i.e. for every (S) amine molecule left behind we are canceling the effect of one (R). The optical rotation recorded for the material left in solution must therefore be less than the theoretical maximum.

2. It is possible to separate the two enantiomers comprising a racemic mixture using the various forms of chromatography you have met (TLC, column, GC, HPLC). These techniques share a common operational basis, but what modification is required if separation of enantiomers is to be achieved?

All of the chromatographic techniques they've met rely on polarity differences to achieve separation. Enantiomers have identical physical properties so some change must be made to the stationary or mobile phases in order to achieve separation in this case. They've just learned that the ONLY way to discriminate between enantiomers is to have them interact with a single enantiomer of a second optically active material. Thus, a column packed with a chiral stationary phase would be employed in GC and HPLC, and there are (very expensive) forms of silica that contain embedded chiral molecules that can be used for TLC and column chromatography. The deal here is exactly the same as the experiment they have just done—formation, albeit temporarily—of diastereomeric complexes with different physical properties (polarity in this case).

Preparatory Guide

To check

Polarimeter (operation and calibration).

A balance in one of the dispensing hoods.

Reagents required

(R, R) Tartaric acid

(R), (S)-Phenylethylamine

50% NaOH solution

Methanol

Diethyl ether

Anhydrous sodium sulfate

Supplies

pH Paper.

Screw top sample vials

Pipettes

Waste

Basic aqueous waste containers. Non-chlorinated waste containers –*a few of each.*