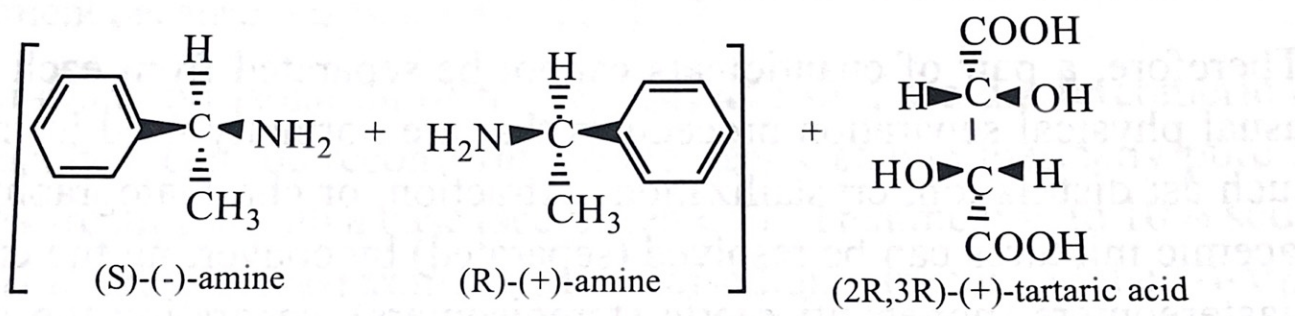
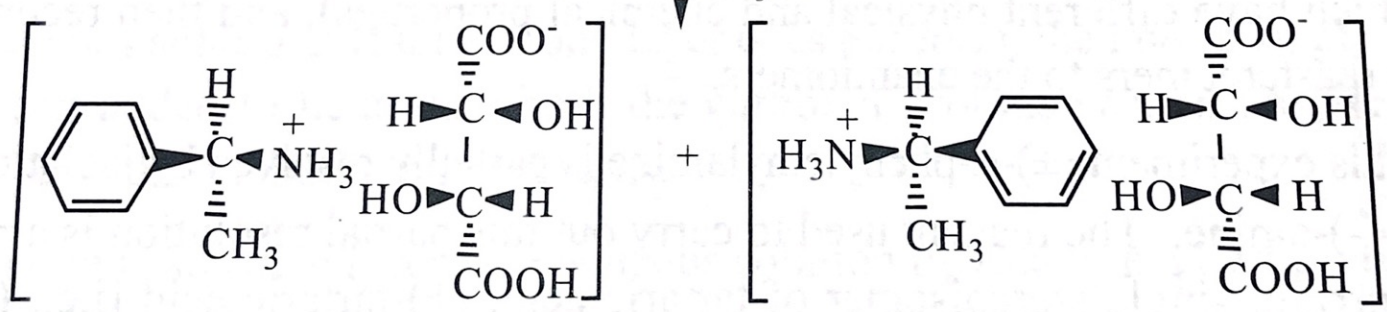
RESOLUTION OF α-PHENYLETHYLAMINE

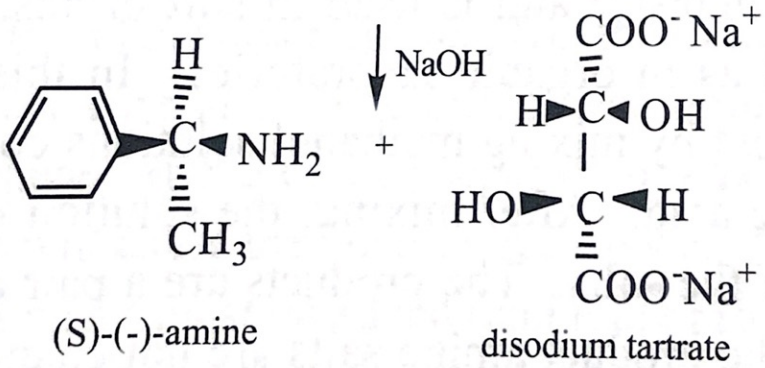
The purpose of this experiment is to enable the student to:

1. Learn about the practical and theoretical aspects involved in one of the general techniques of resolving enantiomers - via the formation and separation of diastereomeric derivatives. In an effort aimed at illustrating such a technique, the partial resolution of α-phenylethylamine will be accomplished in three steps: (1) treatment of the racemic amine with (2R,3R)-(+)-tartaric acid (a chiral reagent) - thus producing diastereomeric salts; (2) separation of the less soluble (S)-ammonium (2R,3R)-hydrogen tartrate diastereomeric salt by vacuum filtration; and (3) treatment of the isolated diasteromeric salt with excess strong base to obtain the nearly enantiomerically pure (S)-(-)-amine upon workup.
2. Learn how the specific rotation, optical purity, and %S and %R of a sample are obtained. In an effort aimed at illustrating such processes, the optical rotation of the isolated (S)-(-)-α-phenylethylamine will be measured by the use of a polarimeter; and then the specific rotation, the optical purity, and the %S and %R of the isolated amine will be determined.

SCHEME 1. Steps Involved in the Partial Resolution of α-Phenylethylamine







BACKGROUND

Reactions of racemic mixtures or achiral compounds carried out in the laboratory almost always lead to a racemic product or achiral products. Biological system, on the other hand, can synthesize a single enantiomer from achiral or racemic starting materials because the enzymes that catalyze these reactions are chiral.

A pair of enantiomers (non-superimposable mirror image isomers) exhibit the same physical and chemical properties, with two exceptions:

1. They rotate plane-polarized light in an equal, but opposite direction. The isomer that rotates the plane to the left is called the *levorotary* isomer and is designated (-) or *l*, and the one which rotates the plane to the right is called the *dextrorotary* isomer and is designated (+) or d.
2. They react at different rates with other chiral compounds. These rates may be so close together as to make the distinction practically useless, or they may be so far apart that one enantiomer undergoes the reaction at a convenient rate while the other does not react at all.

Therefore, a pair of enantiomers cannot be separated from each other by the usual physical separation procedures that are normally used in the laboratory such as: distillation, crystallization, extraction, or chromatography. However, racemic mixtures can be resolved (separated) by converting the enantiomers to diastereomers (nonenantiomeric stereoisomers), separating the diastereomers (which have different physical and chemical properties), and then reconverting the diastereomers to the enantiomers.

In this experiment (±)-α-phenylethylamine is partially resolved by isolation of the (S)-(-)-amine. The reagent used to carry out this partial resolution is a naturally occurring, single stereoisomer of tartaric acid: (+)-tartaric acid [i.e., (2R,3R)-tartaric acid], which is found in grapes and other fruit. Commercial (+)-tartaric acid is a by-product of the wine industry and is used in soft drinks, baking powder, and other foods, as well as in organic laboratories. In this partial resolution, the reaction is carried out by mixing methanol solutions containing the racemic amine and (+)-tartaric acid. After mixing, the solution becomes opaque because of precipitation of the salts. The products are a pair of amine salts (see Scheme 1). [Note that the product amine salts are not enantiomeric; the enantiomer of the (S)-(2R,3R) salt would be (R)-(2S,3S).] These amine salts are diastereomers that have different solubilities in methanol. The key to success

in this experiment is to obtain the proper crystalline form. The hydrogen tartrate salt of the (-)-amine crystallizes as dense prisms slowly from solution. Another crystalline form containing *both* diastereomers crystallizes from a rapidly cooled solution as a voluminous mass of needlelike crystals. The needles redissolve when the solution is heated; however, the prisms do not. To obtain prismatic seed crystals, the methanol solution is heated to near-boiling, rapidly cooled in an ice bath to yield both types of crystals, and then rewarmed to near-boiling to dissolve the needles (the prisms will not dissolve). The flask is then set aside and allowed to cool slowly. If the needles also recrystallize, they will redissolve slowly and be converted to prisms as long as the mixture is allowed to stand over a period of a week or more at room temperature (or the mixture can be reheated and allowed to cool).

The less soluble (prismatic) diastereomeric salt can then be separated by vacuum filtration from the other salt, which remains dissolved in the methanol solution. After the prismatic crystals are filtered, the salt of the (+)-amine could be isolated from the filtrate (by evaporation of the solvent). However, this is not done in this experiment because it is time consuming.

After separation and isolation of the less soluble salt, the diastereomeric salt (which is acidic) can be reconverted to the nearly enantiomerically pure free (-)-amine by treatment with a base (see Scheme 1). Treatment with 10% sodium hydroxide converts the diasteromeric salt to disodium tartrate and the (-)-amine. Disodium tartrate is water-soluble, but the amine is insoluble and floats on top of the aqueous solution. If this second layer does not form, then not enough NaOH has been added to neutralize both the carboxyl protons (which are the more acidic) and the ammonium ion protons.

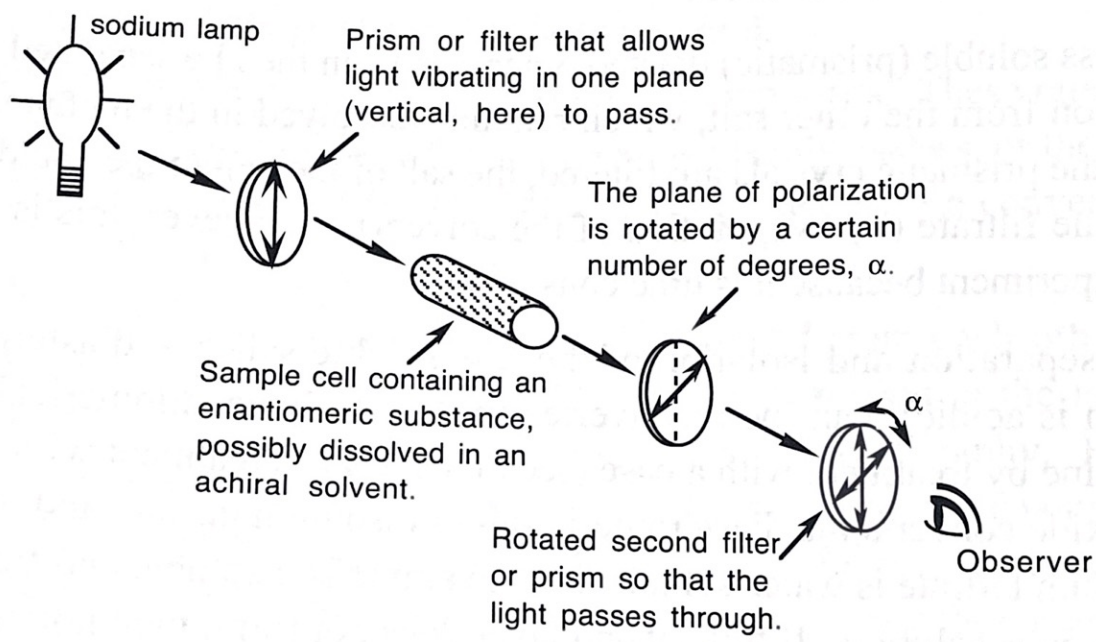
The amine is separated from the aqueous solution by steam distillation and then separated from the water via a separatory funnel. At best only 5g of the (S)-amine can be present (10 g of racemic amine were used initially - 5g of which were R and the other 5g were S); therefore, these manipulations must be carried out very carefully. The crude, wet amine is dried with anhydrous potassium carbonate. If the earlier separation was sloppy, the presence of water in the amine will cause the potassium carbonate to liquefy. If this should happen, more drying agent must be added (and more product will probably be lost).

Since the amine has a high boiling point (184-188°C), it is difficult to distill through the large-sized apparatus found in the laboratoroy; therefore the optical

rotation of the crude undistilled amine will be measured. The observed rotation in this experiment is quite small - about -8° for a typical yield of 2.1 g diluted to 7.4 mL with methanol in a 1-dm cell.

The **polarimeter** (see Figure 1) is the instrument that will be used to meausre the optical rotation of your product. A polarimeter uses a single wavelength of light [usually the D line of sodium (589.3 nm)] from a sodium lamp. In a common polarimeter, the light is passed through a *Nicol prism* ($CaCO_3$), which filters out all the light waves except those waves vibrating in a *single plane* . Light vibrating in a single plane, rather than in all planes, is called **plane-polarized light**.

Figure 1. Diagram of a Polarimeter



When plane-polarized light is passed through a single enantiomer of an organic compound, the plane of polarization is *rotated*. This phenomenon, is called **optical rotation**. One enantiomer of the pair rotates the plane of polarization of the light to the left (this enantiomer is referred to as either: levorotatory, (-), or *l*), while the other enantiomer rotates the plane of polarization of the light to the right (this enantiomer is referred to as either: dextrorotatory, (+), or d). It is important to note that: (a) separate enantiomers rotate the plane of polarized light in equal amounts but in opposite directions; (b) an equimolar mixture of two enantiomers [called a **racemic form** or **racemic mixture** and is designated as (±)- or d,*l*-] shows no rotation of plane polarized light; and (c) no obvious correlation exists between the configurations [(R)- or (S)-] and the direction [(+)- or (-)-] in which compounds rotate plane-polarized light.

The observed rotation of a substance depends on the structure of the compound and the number of molecules in the light path. The latter factor is a function of the path length and the concentration. In order to place measured rotations on a standard basis, chemists calculate a quantity called **specific rotation**, $[\alpha]_D^t$, by the following equation:

$$[\alpha]_D^t = \frac{\alpha}{l \cdot c}$$

where, α = observed rotation
l = length of sample tube in dm (1.00 dm = 10.0 cm)
c = concentration of solution in g/mL

The specific rotation also depends on the temperature (standard temperature of 20 °C) and the wavelength of light (standard wavelength of 589.6 nm, sodium D-line) employed. Specific rotations are reported so as to incorporate these quantities as well. For this particular experiment the specific rotation of (S)-α-phenylethylamine at 20°C at the D-line of sodium -> $[\alpha]_D^{20} = -40.3°$.

As was mentioned previously in this experiment a typical yield of 2.1 g dissolved in 7.4 mL of methanol would exhibit an observed rotation of about -8°. Therefore, a typical specific rotation of about -28° should be expected. The calculated experimental specific rotation of a 2.1g sample dissolved in 7.4 mL of methanol having an observed rotation of -8° is given as follows:

$$[\alpha]_{D\,(exp)}^{20} = \frac{-8°}{1.00\ dm \left(\frac{2.1\ g}{7.4\ mL} \right)} = -28°$$

The **optical purity** of a sample is the per cent excess of one enantiomer compared to the amount present in the racemic mixture. A pure enantiomer is 100% optically pure, while a racemic mixture is 0% optically pure. The equation used to calculate the optical purity is:

$$\text{optical purity} = \frac{\text{experimental } [\alpha]_D^t \text{ of the sample}}{\text{known } [\alpha]_D^t \text{ of pure sample}} \times 100$$

Since a typical specific rotation for this experiment is about -28°, the optical purity of the sample would be:

$$\text{optical purity} = \frac{-28°}{-40.3°} \times 100 = 69.\%$$

The per cent of each enantiomer (% (-)-isomer and % (+)-isomer) in a mixture can be calculated if the specific rotation for one of the enantiomers is known.

{N O T E : In this particular experiment the specific rotation for the (-)-isomer = -40.3°; therefore, the specific rotation for the (+)-isomer = +40.3°}. The fraction of the (+)- and (-)-isomers in a sample can be calculated by using the following equation:

$$[\alpha]^t_{D\,(exp)} = (f_- \cdot [\alpha]^t_{D\,-}) + (f_+ \cdot [\alpha]^t_{D\,+})$$

where, $[\alpha]^t_{D\,(exp)}$ = experimental specific rotation

f_- = fraction of (-)-isomer in sample = x

f_+ = fraction of (+)-isomer in sample = (1-x)

$[\alpha]^t_{D\,-}$ = specifc rotation of pure (-)-isomer

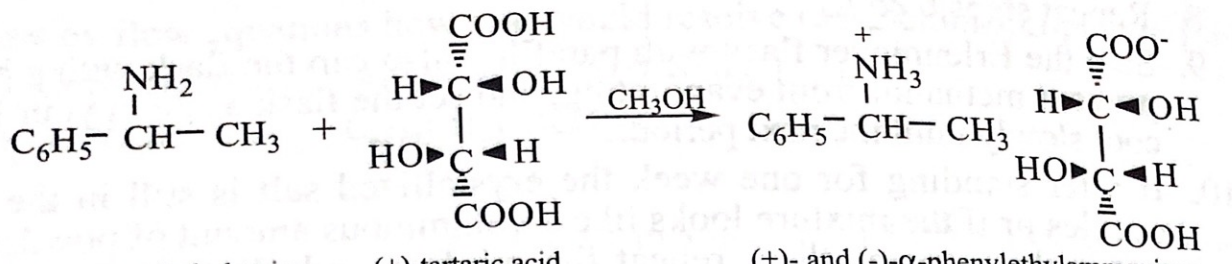
$[\alpha]^t_{D\,+}$ = specific rotation of pure (+)-isomer

Using the typical experimental specific rotation of about -28 °, $[\alpha]^{20}_{D\,-} = -40.3°$, and $[\alpha]^{20}_{D\,+} = +40.3°$, then the typical f_- and f_+ for this experiment can be calculated as follows:

$$-28 = [x \cdot (-40.3)] + [(1 - x) \cdot (+40.3)]$$
$$-28 = -40.3x + 40.3 - 40.3x$$
$$-68.3 = -80.6x$$
$$x = 0.85 = f_- \quad (\%_- = 85\%)$$
$$\therefore\ f_+ = 1 - x = 0.15 \quad (\%_+ = 15\%)$$

Since the (-)-isomer in this experiment is the (S)-isomer, then the typical %S for this experiment is 85%, while the %R would be 15%.

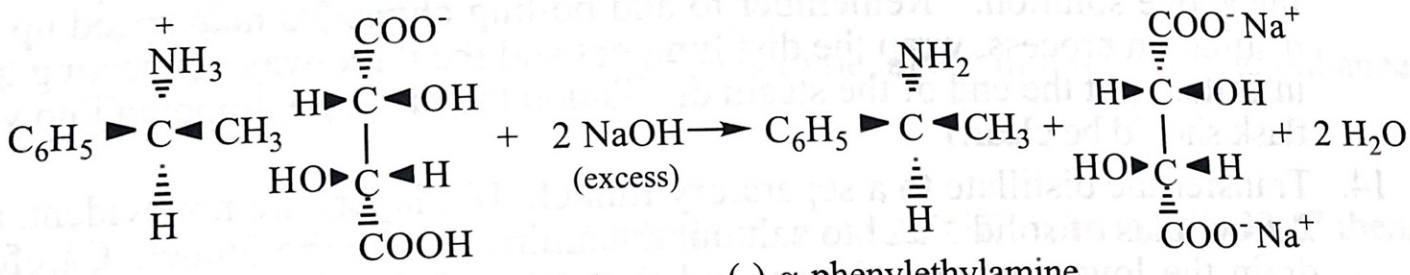
Step 1. Formation of the Diasteromers



(±)-α-phenylethylamine (+)-tartaric acid (+)- and (-)-α-phenylethylammonium (+)-hydrogen tartrate - both diasteromers

MM:	121.20	150.09	271.29
mass:	10.0 g	12.5 g	22.2 g (theory)
mL:	10.6 mL	-	-
moles:	0.082	0.083	0.082 (theory)
d (g/mL):	0.940	-	-

Step 2. Conversion of (-)-Amine Diastereomeric Salt to the Free Amine



(-)-α-phenylethylammonium (+)-hydrogen tartrate (-)-α-phenylethylamine

MM:	271.29	121.20
mass:	11.1g (theory)	5.0 g (theory)
moles:	0.041 (theory)	0.041 (theory)

EXPERIMENTAL PROCEDURE

Unless otherwise notified, you will be working with a partner.

1. Dissolve 10.0 g (10.6 mL) of (±)-α-phenylethylamine (CAUTION: α-phenylethylamine is toxic) in 75 mL of methanol (CAUTION: methanol is toxic and flammable) in a 250-mL Erlenmeyer flask and mix thoroughly.
2. In another 250-mL Erlenmeyer flask, dissolve 12.5 g of (+)-tartaric acid in 75 mL of methanol. (Tartaric acid is methanol-soluble, but the solution may remain cloudy. This cloudiness will not affect your results.)
3. Add the amine solution to the tartaric acid solution. Mix well.
4. Warm the flask (with a watch glass on top) on a hot plate almost to boiling; then cool it in an ice bath to crystallize the diastereomeric salts.
5. Inspect the crystals thoroughly. (These crystals are usually voluminous and needlelike. The needlelike crystals are a crystalline modification that contains both diastereomers.)
6. Reheat the mixture almost to boiling to dissolve the needlelike crystals. The residual prismatic crystals, that don't dissolve, act as seed crystals for the (-)-amine salt.

Laboratory Report

NAME _____ HOOD NO. _____

PARTNER(S) _____ DATE _____

A. BALANCED CHEMICAL EQUATIONS

B. RESULTS

1. Name of Limiting Reagent _____
2. Moles of Limiting Reagent Used _____
3. Name of Major Organic Product _____
4. Structure of Major Organic Product (show stereochemistry)_____
5. Theoretical Yield (moles) _____
6. Theoretical Yield (grams)* _____
7. Actual Yield (grams) _____
8. Actual Yield (moles)* _____
9. % Yield* _____

10. Observed Rotation _____

11. Literature Specific Rotation _____

12. Concentration of Sample (g/mL)* _____

13. Experimental Specific Rotation* _____

14. Typical Specific Rotation _____

15. Optical Purity* _____

16. % "S-(-)-Amine" Recovered * _____

*** Include Calculations in Provided Space**

C. CONCLUSION

Make Direct Comparisons [If your values are lower than the typical values, briefly give possible reasons for such an occurrence.]

a) experimental yield vs typical yield

b) experimental specific rotation vs typical specific rotation