

## SPONTANEOUS ENANTIOMERIC ENRICHMENT OF CHIRAL 1- (1-NAPHTHYL) ETHYLAMINE

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### Abstract

An aqueous solution of the reaction product R-(+)-1-(1-naphthyl)ethylamine hydrochloride, having high enantiomeric excess, was spontaneously resolved into the two enantiomers by simple crystallization to afford the product in nearly 100% ee.

**Keywords:** enantiomers, diastereomeric pairs, chiral resolving agents, chiral amines, chiral carboxylic acids, aminolysis and active pharmaceutical ingredients.

### Introduction

In an article published in this journal<sup>1</sup> the preparation is described of chiral carboxylic acid compounds that are useful as intermediates in the synthesis of active pharmaceutical ingredients (APIs).

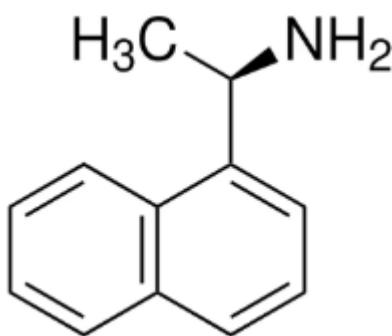
Molecules that have chiral center and are not superimposable on their mirror images are regarded as enantiomers, so chirality is the sufficient condition for their existence.

Chiral amines are useful as intermediates in the synthesis of drugs and also as chiral resolving agents for the preparation of chiral carboxylic acids in a two-step method for separating enantiomers, which is traditionally carried out by converting a mixture of R and S enantiomers with one chiral center into a diastereomeric pair by salt formation or via covalent bond formation, with the enantiopure resolving agent and separating the diastereomers by using recrystallisation, which is feasible because enantiomers have shared physical properties such as melting point and boiling point, but diastereomers have different chemical properties, so they can be separated like any two different molecules.

Owing to the importance of this class of compounds, many optically active amines have been the targets of an increasing number of synthetic efforts<sup>2</sup>. Practical methods for their synthesis usually involve multistep transformations starting from chiral natural amino acids, or resolution of racemic mixtures via reaction with a chiral carboxylic acid to form a diastereomeric mixture of salts followed by consecutive fractional crystallizations and recovery of the amine. Enzyme catalyzed aminolysis in organic solvents can provide an alternative method for the preparation of optically active amines such as chiral 1-(1-naphthyl)ethylamine<sup>3,4</sup>.

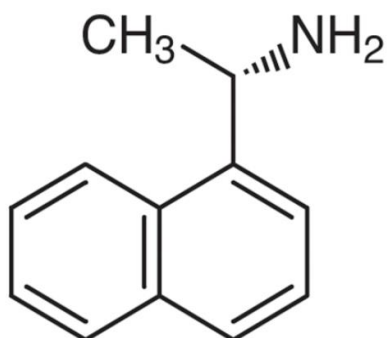
### Materials and methods

In the case of chiral 1-(1-naphthyl)ethylamine, the two enantiomers, which are mirror images, are the following:



R-(+)-1-(1-naphthyl)ethylamine

and



S-(-)-1-(1-naphthyl)ethylamine

Both enantiomers of a molecule have the same chemical and physical properties except for rotation of polarized light whereas enantiomer that rotates plane-polarized light in

the positive direction, or clockwise, is called dextrorotary [(+), or d], while the enantiomer that rotates the light in the negative direction, or counterclockwise, is called levorotary [(-), or l]. In the case of S-(-)-1-(1-naphthyl)ethylamine, the compound is levorotary<sup>5</sup>.

The enantiomeric excess was determined by HPLC chromatographic analysis using Crownpak CR(+) chiral column, solvent mixture of 85% aqueous HClO<sub>4</sub> solution (pH 2) and 15% methanol at flow rate of 0.6 ml/minute and detection at 210 nm.

The % of enantiomeric excess (ee) was calculated according to the following equation:

$$\% ee = \frac{\text{Concentration of the R-enantiomer} - \text{Concentration of the S-enantiomer}}{\text{Concentration of the R-enantiomer} + \text{Concentration of the S-enantiomer}} \times 100$$

## Results and Discussion

Although both enantiomers of 1-(1-naphthyl)ethylamine hydrochloride are supposed to have the same crystallization behavior, while carrying out experiments with aqueous solutions of R-(+)-1-(1-naphthyl)ethylamine hydrochloride, it was surprisingly discovered that in a vessel, which was left aside at room temperature overnight, containing an aqueous solution of R-(+)-1-(1-naphthyl)ethylamine hydrochloride, having enantiomeric excess (ee) of 82%, white crystals were spontaneously floating above the solution surface. The crystals were collected, washed, dried and a sample was withdrawn for HPLC analysis, showing that the product was R-(+)-1-(1-naphthyl)ethylamine hydrochloride in about 100% ee.

The chemical purity of the obtained product was over 99%, as determined by HPLC analysis using RP-18 column, solvent mixture of 75% acetonitrile and 25% of aqueous HClO<sub>4</sub> solution (pH 2.7) at flow rate of 1.1 ml/minute and detection at 222 nm. The concentration of the sample was 0.01 molar.

The optical rotation of R-1-(+)-(1-naphthyl)ethylamine hydrochloride was  $[\alpha]_{D,25} (10.0, \text{MeOH}) = + 60.4$ .

The enantiomerically enriched R-1-(+)-(1-naphthyl)ethylamine hydrochloride was produced, e.g., by dissolving 1.5L (1600 g, 9.3 mol) of the racemic 1-(1-naphthyl)ethylamine in 3L of the solvent 3-methyl-3-pentanol and reacting with 5425 g (32 mol) of 2,2,2-trifluorethyl butyrate dissolved in 3-methyl-3-pentanol in a preparative column containing 5.7g of immobilized subtilisin at a temperature of 38°C. The effluent was collected into a reservoir containing 1M hydrochloric acid. The layers were separated and the organic layer was distilled to afford a "cake" containing S-N-1-(1-naphthalenyl)butanamide and small quantity of R-1-(+)-(1-naphthyl)ethylamine hydrochloride. The solid was partitioned in a mixture of dichloromethane and water

and the layers were separated. The dichloromethane layer was evaporated to afford S-N-1-(1-naphthaleny1)ethyl butanamide (1114 g, 50%). Hydrolysis of the amide yielded S-1-(-)-(1-naphthyl)ethylamine.

The aqueous layers, containing R-(+)-1-(1-naphthyl)ethylamine hydrochloride, were combined, a sample was withdrawn for HPLC analysis showing that the obtained product had an enantiomeric excess of 82%. The aqueous phase was concentrated by evaporation and crystals were formed of optically pure R-(+)-1-(1-naphthyl)ethylamine hydrochloride (695 g). The free amine was obtained by treatment with solution of gaseous ammonia dissolved in chloroform. The solvent was dried over sodium sulfate and evaporated to afford an oil, which was distilled at 85°C, 0.1 mm Hg. The yield was 560 g of the free amine, (35%)<sup>6</sup>.

This research was conducted in the years 1990-1991.

## Conclusion

In some cases, as described hereinabove, it is possible to obtain enantiomerically pure R-(+)-1-(1-naphthyl)ethylamine hydrochloride by simple spontaneous crystallization and thus avoiding the need to carry out resolution of racemic mixtures via reaction with a chiral carboxylic acid to form a diastereomeric mixture of salts followed by consecutive fractional crystallizations and recovery of the free amine.

## References

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