Enantiomeric Resolution of (±)-Mandelic Acid by (1*R*,2*S*)-(–)-Ephedrine

An Organic Chemistry Laboratory Experiment Illustrating Stereoisomerism

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Racemic thalidomide was administered to pregnant women in the 1960s with a devastating effect *(1).* The (*R*) enantiomer exhibited the desired analgesic properties, but the (*S*) enantiomer induced fetal malformations or deaths. As a result of this tragedy, marketing regulations for synthetic drugs became significantly more stringent. Racemates can no longer be sold as commercial drugs without characterization of each enantiomer and proof that the nonpotent stereoisomer is devoid of any harmful side effects. Thus pharmaceutical companies have focused on developing technologies that produce single-isomer drugs. These chiral technologies include (i) utilization of chiral starting material whose configuration is maintained throughout the synthesis, (ii) resolution of a racemic mixture to give the desired stereoisomer, and (iii) asymmetric synthesis where asymmetry is introduced directly into a nonchiral material *(2).*

Because of the critical, and rapidly expanding, contribution that chiral technology is playing, we wished to incorporate an illustrative experiment into the undergraduate organic lab curriculum. Enantiomeric resolution is an excellent example of chiral technology appropriate for the introductory organic chemistry lab. The chemistry involved is covered early in lecture and requires several techniques to effect the resolution. Thus this separation problem provides the opportunity to apply vacuum filtration, recrystallization, extraction, rotary evaporation, melting point, and polarimetry analyses as well as to review acid–base chemistry.

Enantiomeric resolution is not new to the organic chemistry lab. Several organic chemistry lab texts include an experiment using this method and a few have been published in this *Journal (3, 4).* The most frequently cited one is Ault's resolution of racemic α-phenylethylamine (α-methylbenzylamine) by (*R,R*)-(+)-tartaric acid, which was published in this *Journal* and later in *Organic Synthesis (4a, 5).* We have repeatedly performed this resolution, but typically obtained an optical purity for the high boiling (–)-α-phenylethylamine of 70%, not 95% cited by Ault.[2] With the desire to improve optical purity, we reviewed Ault's original work as well as other enantiomer resolutions in seminal articles *(6, 7).*

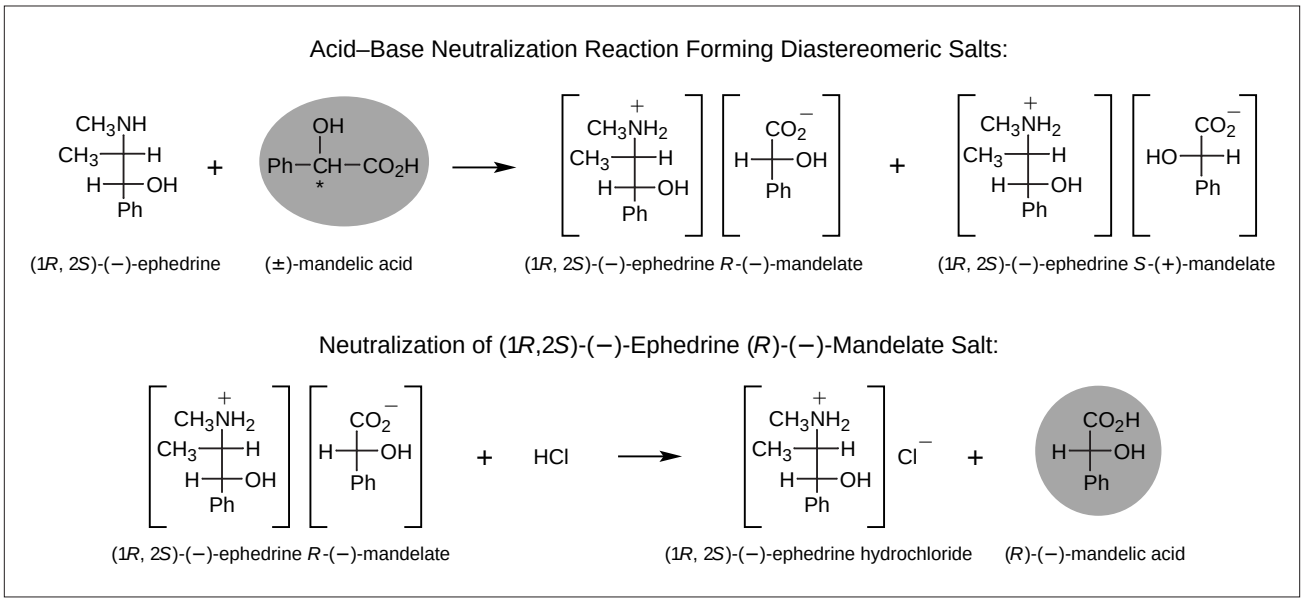
In all classical resolutions, the initial diastereomeric salt collected was subjected to recrystallization, if not multiple recrystallizations, to improve purity. Ault described a recrystallization of the diastereomeric ammonium tartrate salt in *Organic Synthesis*, but he indicated that it required a large volume of methanol (450–500 mL for ~22 g of tartrate salt) and required sitting at room temperature overnight for crystals to reform *(5).* We repeated the resolution, on 0.25 scale, isolating ~5 g of diastereomeric salt that required 110 mL of methanol for a recrystallization. Although the recrystallization improved the quality of the salt, the combination of the solvent volume and time commitment for this purification was prohibitive.[3] Perhaps this is why Ault does not include a recrystallization step in either his *J. Chem. Educ.* article or lab text *(3a, 4a).*

A literature review indicated that there was not a great difference in the solubility of the ammonium tartrate salts in the α-phenylethylamine–(+)-tartaric acid system, thus a significant quantity of both diastereomers co-precipitated from methanol *(7).* We looked for a resolution system in which the selective precipitation of one diastereomer was greater so that recrystallization would be either unnecessary or easy to accomplish if necessary. The combination of the chiral amine, (–)-ephedrine, and (±)-mandelic acid yielded diasteromeric salts that had a very attractive precipitation ratio (Scheme I) *(7).* Additional advantages to this combination were that the diasteromeric salts underwent a facile recrystallization and the resolved product is a solid, not a high-boiling liquid amine, so melting point, as well as polarimetry, could be used to analyze the product's optical purity.[4]

Results and Discussion

We evaluated the success of the enantiomer resolution performed with and without a recrystallization. A solution of (1*R*,2*S*)-(–)-ephedrine and (±)-mandelic acid was prepared in 95% ethanol and allowed to sit at room temperature for 4 hours in a sealed flask. A white precipitate was collected and identified as an 80% yield of crude (1*R*,2*S*)-(–)-ephedrine (*R*)-(–)-mandelate salt by its melting point of 160–165 °C (cor); lit value 170 °C *(8).* This crude salt was neutralized with 6 M HCl and the reaction mixture was extracted with *tert*-butyl methyl ether (TBME). Rotary evaporation of the ether produced a white solid whose melting point of 128–132 °C identified it as the (*R*)-(–)-mandelic acid with a specific rotation of –144° (*c* 0.4167, abs EtOH), which corresponds to a 90% optical purity.[5] When a recrystallization step was inserted, it required only 25 mL of ethanol and 10 minutes of cooling in an ice bath. The melting point of the diastereomeric salt improved to 168–170 °C, and the (*R*)-(–)-mandelic acid's purity also improved as indicated by its melting point of 133.0–134.5 °C and specific rotation of –155° (*c* 0.4973, abs EtOH), which corresponds to a 96% optical purity.

Beginning organic chemistry students, performing these techniques for the first time, would probably not match these results, so a recrystallization was incorporated into the organic chemistry lab sequence to ensure the highest optical



Scheme I. Enantiomeric resolution of (±)-mandelic acid using (1*R*,2*S*)-(–)-ephedrine.

purity. The following results are the averages from the two current lab sections (33 students) and are reflective of typical results from previous years' classes (85 students) taught by several different faculty. The crude mass of the diastereomeric salt was 86%; after recrystallization the mass was 52%. The salt's purity was excellent as indicated by the expected lustrous quality of the crystals and a mp of 168–170 °C. Neutralization followed by purification gave a 32% yield of (*R*)-(–)-mandelic acid, which melted at 132–134 °C (cor). Specific rotations generally ranged from -135° to -160°, which corresponded to optical purities of 85–100%.[6]

Summary

The incorporation of an experiment involving enantiomeric resolution, as an illustration of chiral technology, is an excellent early organic chemistry lab experiment because it involves familiar acid–base chemistry and reinforces stereochemistry concepts covered at the beginning of an organic chemistry course. It is an excellent framework in which to teach fundamental laboratory techniques such as recrystallization, extraction, rotary evaporation, polarimetry, and melting point analyses. The experiment we describe here has been performed by 118 students with consistently excellent optical purities. In addition to polarimetry, the success of the enantiomer resolution can be judged by melting point. Although (1*R*,2*S*)-(–)-ephedrine is a more expensive chiral resolving agent, in our opinion, the improved separation and the ability to evaluate the resolved (*R*)-(–)-mandelic acid's optical purity by both polarimetry and melting point, justifies the use of the (±)-mandelic acid–(1*R*,2*S*)-(–)-ephedrine system to demonstrate enantiomeric resolution. The entire sequence requires two full lab periods and 0.5 hour of an earlier period in which the initial diastereomeric salt solution is prepared.

Hazards

(1*R*,2*S*)-(–)-ephedrine, (±)-mandelic acid, ethanol, and *tert*-butyl methyl ether are irritants, with the solvents being flammable as well. The 6 M HCl is corrosive, therefore, throughout all operations, gloves were worn, students worked in hoods, and hotplates served as the heat source. Ephedrine is a regulated substance that requires the submission of a vendor's short form describing its intended use before shipping.

[w]Supplemental Material

Instructions for the students and notes for the instructor are available in this issue of *JCE Online*.

Notes

1. Andrea L. Cerrone-Szakal (biochemistry major, Muhlenberg College class of 2002) is currently a graduate student at The Pennsylvania State University.

2. Optical purity, 70%, was typical for the hundred students who performed Ault's resolution at our institution. Landgrebe *(3d)* also indicated similar results. Needlelike crystals corresponding to the other diastereomeric salt always contaminated the desired prismatic salt crystals. Rewarming to dissolve the needles, as Ault suggests, did not prevent their reformation with cooling.

3. Our recrystallized salt melted at 190.0–192.0 °C dec (cor) whereas Ault cites 179–182 °C.

4. The literature melting points for (±)-mandelic acid and (*R*)-(–)-mandelic acid are 120–122 °C and 131–133 °C, respectively. (Aldrich).

5. We based our optical purity on polarimetry analysis of commercial (*R*)-(–)-mandelic acid, which gave a specific rotation of -160° (*c* 0.5110, abs EtOH). This differs from the value of -173°

reported by Jarowski and Hartung *(8),* but it is not clear whether they used 95% or absolute ethanol as their solvent.

6. A range of optical purities was observed, despite excellent melting point values. We believe this was primarily due to an easily corrected technical error. Some students failed to reweigh their samples after removing a quantity for melting point. Thus the subsequent experimental optical rotations reflected the drop in mass, but the students still utilized the original, higher mass in their specific rotation calculations, which leads to an artificially decreased value. Also ~10% of our students' results showed lower optical purities with a corresponding depressed melting point.

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