

Short Communication

Phase Diagrams for Mixtures of (S)-1-Phenylethylammonium (S)-Mandelate and (R)-1-Phenylethylammonium (S)-Mandelate

Heidi Lopez de Diego

Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen Ø, Denmark

Lopez de Diego, H., 1995. Phase Diagrams for Mixtures of (S)-1-Phenylethylammonium (S)-Mandelate and (R)-1-Phenylethylammonium (S)-Mandelate. – Acta Chem. Scand. 49: 459–463 © Acta Chemica Scandinavica 1995.

The separation of enantiomers from a racemic mixture of a base (acid) is often achieved by reaction with an enantiomerically pure acid (base):¹



If the difference in solubility of the diastereomeric salts is sufficiently large, the less soluble salt can be isolated by precipitation provided that no cocrystallization of the two salts occurs. The enantiomer can then be recovered by chemical separation.

In the present investigation the resolution of racemic 1-phenylethylamine by (S)-mandelic acid has been examined. The difference in solubility of the diastereomeric salts (S)-1-phenylethylammonium (S)-mandelate (S-PEA)(S-MA) and (R)-1-phenylethylammonium (S)-mandelate (R-PEA)(S-MA) is very large,² indicating that an efficient resolution should be possible if the two salts do not cocrystallize.

Ingersoll *et al.* mention three stable salts made of 1-phenylethylamine and (S)-mandelic acid,³ (S-PEA)(S-MA), (R,S-PEA)(S-MA) and (R-PEA)(S-MA), but they report the melting point of (R,S-PEA)(S-MA) as 176 °C, which is the melting point of the less soluble salt (S-PEA)(S-MA). In most of their precipitations the exact amount of each enantiomer is not given, which makes a comparison difficult, but they report the relative solubility order, (S-PEA)(S-MA) < (R,S-PEA)(S-MA) < (R-PEA)(S-MA), in agreement with the results presented here. The crystal structures of the three salts have been determined and described.^{4–6} (R,S-PEA)(S-MA) contains equal amounts of the two enantiomers of the cation, and no disorder in the crystal structure was observed. Similarities were found in the hydrogen-bond patterns of the three salts.

On the other hand it has been stated that the salts form solid solutions in all ratios, making the resolution impossible.^{2,7–9} All these papers refer to Leclercq and Jacques,

who published the ternary diagram at 283 K with (S-PEA)(S-MA), (R-PEA)(S-MA) and H₂O as the three components.² They used the optical rotation of the mixtures to determine the composition, and their measured tie lines show that the salts form solid solutions.

The present study of the phase diagram at room temperature was initiated because pure (S-PEA)(S-MA) was obtained as the first precipitate when racemic 1-phenylethylamine and (S)-mandelic acid was mixed in equimolar amounts in water. This is not in accordance with the formation of solid solutions.

In this paper the binary phase diagram of the two diastereomeric salts and a ternary phase diagram with water as the third component are reported. The construction of the diagrams is based on the results obtained from a combination of X-ray diffraction (powder and single crystal), solubility determination, DSC and ¹H NMR measurements made on mixtures of the salts.

Experimental

Preparations. The two pure diastereomeric salts were made by mixing equimolar amounts of enantiomerically pure base and (S)-mandelic acid in aqueous solution, and subsequent recrystallization from water.

For the resolution, racemic 1-phenylethylamine was mixed with enantiomerically pure (S)-mandelic acid in an equimolar ratio in aqueous solution. The solution was filtered, and the precipitate, called first fraction, was dried. The mother liquor was left for further evaporation of the water, filtered and the procedure was continued until the mixture was divided into 5–7 fractions. The fractions were then analyzed by DSC, X-ray diffraction and ¹H NMR.

Mixtures containing solid and liquid phases in equilibrium with known overall composition were prepared as

follows. (*S*)-Mandelic acid, racemic 1-phenylethylamine, enantiomerically pure 1-phenylethylamine and water were mixed in weighed amounts to give the decided overall composition. The mixture was covered with parafilm to avoid evaporation and stirred for 3 h. It was then shaken thoroughly 5–6 times a day for three days. The solution was filtered, and the water content of the separated phases was determined by weighing before and after evaporation of the solvent to dryness. The remaining solid was pounded and analyzed by ^1H NMR to determine the relative content of each diastereomeric salt in the two phases, and finally the composition of the liquid phase and the wet residue was calculated. The compositions are given as points in the triangular diagram Fig. 4 (see later). The melting behavior of these dried samples was determined with DSC.

DSC. The melting behavior was determined with a Polymer Laboratories PL-DSC instrument, calibrated with indium and tin. Samples of ca. 4 mg, weighed with a precision of 0.001 mg, were encapsulated in aluminium crucibles with an empty crucible as reference. The encapsulation was necessary to avoid decomposition of the samples. The heating rate was 5 K min^{-1} , and sampling was made every 1.25 s. The error in the melting points of the pure salt is $\pm 0.5\text{ K}$, and the heat of fusion could be reproduced within 5%. The melting curves for the mixtures showed very broad peaks. Therefore the eutectic, peritectic and end of melting points are given as the temperatures corresponding to the top of the peaks.

NMR. The relative amount of the two diastereomeric salts in samples of unknown composition was determined by ^1H NMR, 400 MHz, using a Varian Unity 400 spectrometer. The salts were dissolved in pyridine to a concentration of 1 mg mL^{-1} . In these solutions the chemical shift of the doublet from the methyl hydrogens in the two bases differed by about 0.012 ppm. This was sufficient to determine the relative composition by integration. To check the accuracy of the results, the method was used on five mixtures of known composition covering the range 0–1 of $x_{(\text{S-PEA})(\text{S-MA})}$. The results agreed with the known composition within 3%.

X-Ray diffraction. The fractions isolated during the resolution experiments were analyzed with powder- and single crystal X-ray diffraction. A Guinier–Hägg camera with $\text{Cu K}\alpha$ radiation using silicon as internal standard was used for the powder diffraction measurements, and Weissenberg methods were used to examine single crystals.

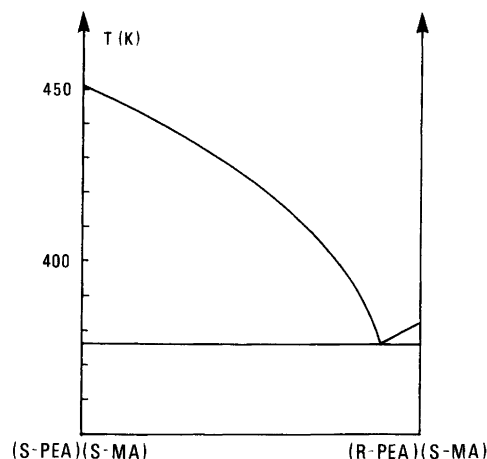


Fig. 1. Binary phase diagram if no cocrystallization occurs, calculated from the melting points and enthalpies of fusion for the pure salts using eqn. (1).

Details of the crystal structure determination of (*R,S*-PEA)(*S*-MA) are described Ref. 5.

Results and discussion

Binary phase diagram. If no intermediate compounds nor solid solutions are formed between (*R-PEA*)(*S-MA*) and (*S-PEA*)(*S-MA*), the shape of the binary phase diagram would be as in Fig. 1, which is calculated from the melting points and enthalpies of fusion of the pure salts using the Schröder–Van Laar equation:^{10,11}

$$\ln x = \frac{\Delta H_f}{R} \left(\frac{1}{T_m} - \frac{1}{T} \right) \quad (1)$$

The melting points and enthalpies of fusion, determined by DSC, are given Table 1.

Melting curves for some of the fractions from a resolution experiment are shown in Fig. 2. The first two fractions are pure (*S-PEA*)(*S-MA*). NMR showed no signal from (*R-PEA*)(*S-MA*), and X-ray film methods showed the same pattern as (*S-PEA*)(*S-MA*). The small lowering of the melting compared to the pure salt is therefore caused by contamination with mother liquor on the crystals. On the melting curve of the third fraction a small bump is observed at ca. 393 K. This is not in agreement with either Fig. 1 or with formation of solid solutions. In the fifth fraction a large melting peak is found at this temperature, and the melting ends at 428 K. The fifth

Table 1. Physico-chemical properties of the pure diastereomers.

Salt	Melting point, T_m/K	$\Delta H_{\text{fus}}^\ominus$ at T_m/kJmol^{-1}	Solubility (295 K, g/100 g soln)
(<i>S-PEA</i>)(<i>S-MA</i>)	450.5 ± 0.5	41.0 ± 1.4	4.6 ± 0.1
(<i>R-PEA</i>)(<i>S-MA</i>)	382.5 ± 0.5	26.0 ± 0.8	≈ 41

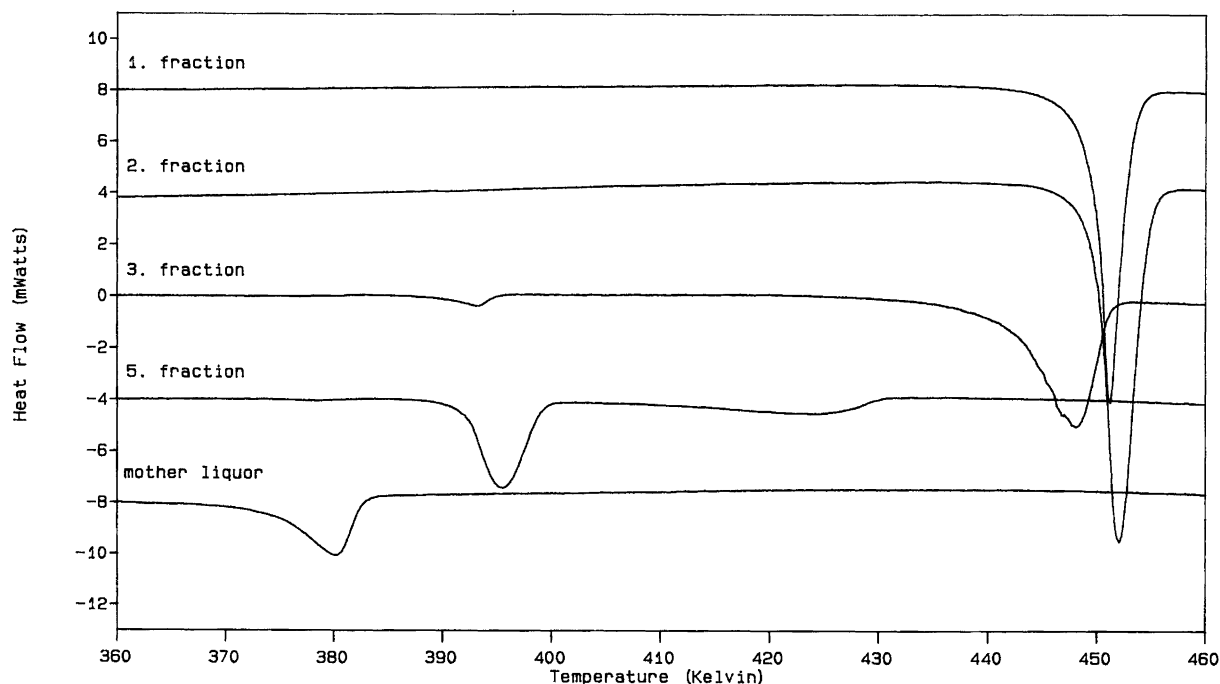


Fig. 2. Melting curves for five fractions of a resolution.

fraction was analyzed, NMR showed a composition of 50% of each salt, and X-ray diffraction measurements revealed a crystal structure containing equal amounts of the two enantiomers of the cation.⁵ Even though the crystal structure of this compound is quite similar to the crystal structure of the less soluble salt (S-PEA)(S-MA),⁴ there is no disorder in the structure. In the case of formation of solid solutions, some disorder would be expected in the cation. Some crystals of equal size and shape were picked up one by one under the microscope in order to obtain the melting point of this pure compound, but the melting curve showed the same double melting as the fifth fraction curve (Fig. 2). The end of melting at around 428 K agrees with the calculated binary phase diagram (Fig. 1) at a molar fraction of 0.5. The only explanation for this behavior is incongruent melting; thus it melts at 393 K, but part of the melt recrystallize as (S-PEA)(S-MA) and then melts slowly according to Fig. 1. The resulting binary phase diagram of the system is shown in Fig. 3. The melting curve of the mother liquor (Fig. 2) agrees with the eutecticum. Melting curves were made for samples with compositions 5, 6, 14, 20, 30, 42, 50, 63 and 78% (S-PEA)(S-MA) (known from NMR measurements). The results are shown as circles in Fig. 3.

Ternary phase diagram. The results from the measurements of liquid and wet-residue composition in mixtures with known overall composition are shown in the ternary diagram (Fig. 4). The solubilities determined for the pure salts are given in Table 1. The tie lines through the points show that three solid phases exist. DSC traces of the samples and the ordered crystal structures further em-

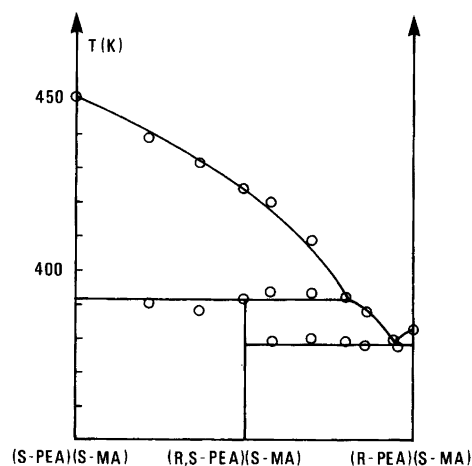


Fig. 3. Binary phase diagram for (S-PEA)(S-MA) and (R-PEA)(S-MA).

phasize that no solid solutions are formed.

The shape of the diagram explains the results from the resolutions. When equimolar amounts of racemic 1-phenylethylamine and (S)-mandelic acid are dissolved in water at room temperature, and the solvent is allowed to evaporate, the first region entered contains solid pure (S-PEA)(S-MA) in equilibrium with a liquid of changing composition. (R,S-PEA)(S-MA) will not begin to precipitate until the water content of the mixture is lowered to 66%. At this point 15% of the mixture is solid, corresponding to precipitation of 88% of the total amount of (S-PEA)(S-MA). This means that in theory 88% of the (S)-1-phenylethylamine can be obtained in the resolution by formation of diastereomeric mandelate salts. It is thus

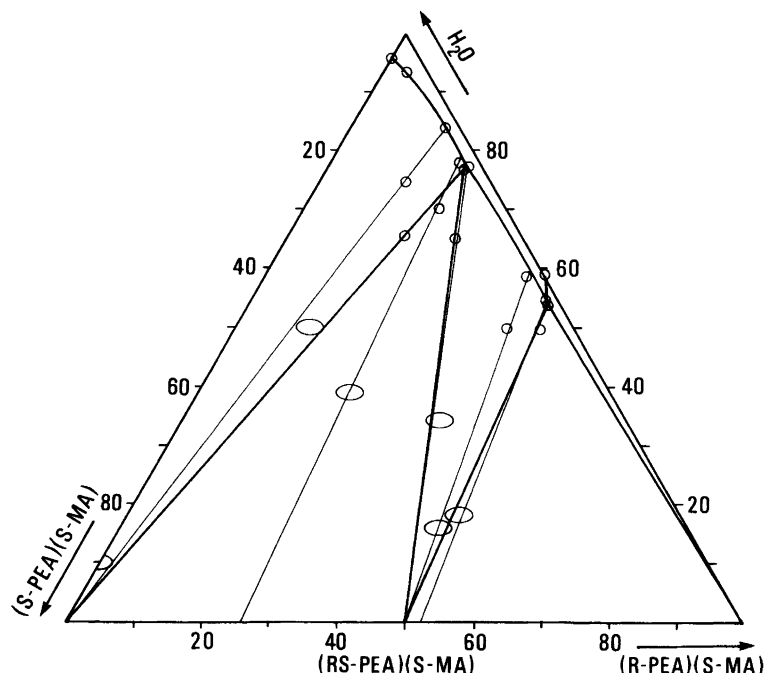


Fig. 4. Ternary phase diagram showing the solubility in water of mixtures at 295 K.

possible to resolve racemic 1-phenylethylamine through formation of diastereomeric mandelate salts, although the resolution seems less efficient than the opposite resolution of mandelic acid by formation of diastereomeric 1-phenylethylammonium salts. This is due to the formation of the salt (*R,S*)-1-phenylethylammonium (*S*)-mandelate containing both enantiomers of the cation, and the

formation of this salt might explain why solid solutions between the diastereomers were assumed.

Similar behavior is reported for the resolution of the bis(ethylenediamine)oxalatocobalt(III) ion with (*1R,3S,4S,7R*)-3-bromocamphor-9-sulfonate as resolving agent.¹² The resolution is reported to be impossible at 298 K owing to the formation of a partially racemic salt.¹³

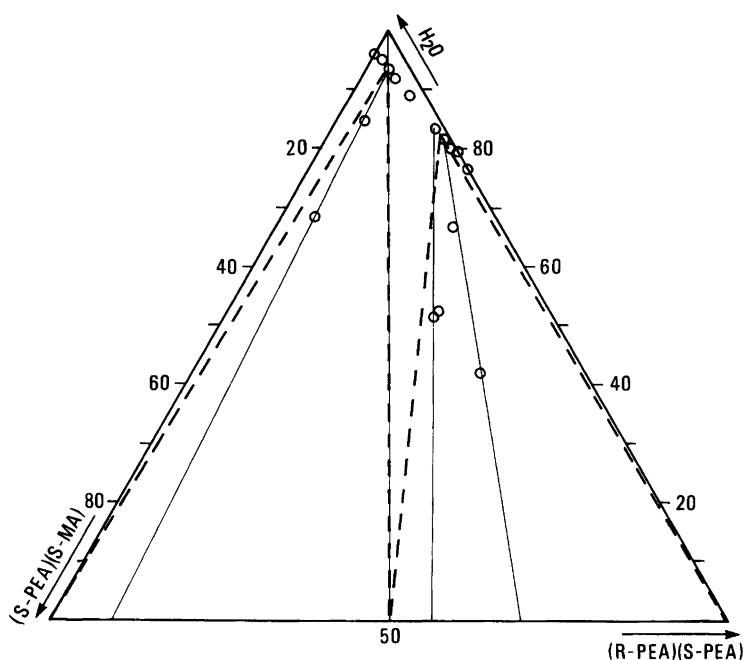


Fig. 5. Ternary phase diagram at 283 K showing an alternative interpretation to that given by Leclercq and Jacques.² The points and tie lines (thin lines) are those reported in Ref. 2.

However, determination of the solubility isotherm at lower temperatures¹² revealed that the resolution is possible below 292 K despite the formation of the partially racemic salt. By lowering the temperature, the point in the ternary diagram that corresponds to the composition of liquid in equilibrium with a mixture of a solid, less soluble compound and a solid, partially racemic compound, moves upward in a direction parallel to the less soluble compound – water line. At 292 K this point crosses the line of racemic composition; thus at temperatures lower than 292 K the entire two-phase region with solid partially racemic salt in equilibrium with liquid is at one side of the line of racemic composition. The first precipitate in the resolution is then the less soluble diastereomer, and the diagram resembles the ternary diagram described in the present paper.

Similar behavior of the diastereomeric 1-phenylethylammonium (*S*)-mandelates may explain the difference between the ternary diagram at 295 K and the one reported at 283 K,² although the opposite temperature dependence of the resolution efficiency is observed. Figure 5 shows the triangular diagram at 283 K with the points reported by Leclercq and Jacques.² In the light of the discussion above, instead of formation of solid solutions, it could be interpreted as shown by the dotted lines. In this case all three equilibrium solutions were selected in three-phase regions, which explains why formation of a solid solution was assumed. The point corresponding to the composition of liquid in equilibrium with a mixture of solid (**S-PFA**)(**S-MA**) and (**R,S-PEA**)(**S-MA**) moves upward parallel to the (**R-PEA**)(**S-MA**)–water line when the temperature is lowered and crosses the racemic composition at 283 K; accordingly resolution should be possible at temperatures above 283 K. To determine if this is the correct interpretation, more data points are needed, for which the precipitates are analyzed in order to distinguish between solid solutions and mechanical mixtures.

Acknowledgements. I am grateful to Dr. Sine Larsen and Mrs. Katalin Marthi for valuable discussions, and thank Mrs. Jette Cohr and Mrs. Kirsten Dayan for the NMR measurements and Mrs. Jette Eriksen for the powder diffraction measurements. The DSC equipment was made available through a grant from the Lundbeck Foundation. Support from The Carlsberg Foundation is gratefully acknowledged.

References

1. Jacques, J., Collet, A. and Wilen, S. H. *Enantiomers, Racemates and Resolutions*, J. Wiley, New York 1981, pp. 253–254.
2. Leclercq, M. and Jacques, J. *Bull. Soc. Chim. Fr.* (1975) 2052.
3. Ingersoll, A. W., Babcock, S. H. and Burns, F. B. *J. Am. Chem. Soc.* 55 (1933) 411.
4. Larsen, S. and Lopez de Diego, H. *Acta Crystallogr., Sect. B* 49 (1993) 303.
5. Lopez de Diego, H. *Acta Crystallogr., Sect. C* 50 (1994) 1995.
6. Lopez de Diego, H. *Acta Chem. Scand.* 48 (1994) 306.
7. Jacques, J., Collet, A. and Wilen, S. H. *Enantiomers, Racemates and Resolutions*, J. Wiley, New York 1981, pp. 300–301.
8. Van der Haest, A. D. *Classical Resolutions; Design of Resolving Agents and Studies of Diastereomeric Salts (PhD Thesis)*, Drukkerij van Denderen, Groningen 1992, p. 9.
9. Brianso, M. C., Leclercq, M. and Jacques, J. *Acta Crystallogr., Sect. B* 35 (1979) 2751.
10. Schröder, I. *Z. Phys. Chem.* 11 (1893) 449.
11. Van Laar, J. *J. Arch. Neerl.* II 8 (1903) 264.
12. Fuyuhiro, A., Yamanari, K. and Shimura, Y. *Bull. Chem. Soc. Jpn.* 52 (1979) 1420.
13. Shimura, Y. and Tsutsui, K. *Bull. Chem. Soc. Jpn.* 50 (1977) 145.

Received October 25, 1994.