*Journal of Thermal Analysis, Vol. 44 (1995) 339-344*

# PHYSICO-CHEMICAL INVESTIGATION OF THE DIASTEREOISOMERIC SALT PAIR FORMED BY α-PHENYL-ETHYL-AMINE AND R-1-PHENYLETHYL-SUCCINAMIC ACID

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(Received November 15, 1993)

## Abstract

The diastereoisomeric salt pair formed between α-phenyl-ethyl-amine and R-1-phenylethyl-succinamic acid were investigated by physico-chemical methods. Melting and solubility phase diagrams were determined, the coincidence of the eutectic points of the two phase diagrams were demonstrated. The large difference in physico-chemical properties of the salt pair explains the efficient enantiomer separation.

**Keywords:** diastereoisomeric salts, optical resolution, α-phenyl-ethyl-amine, phase diagram

## Introduction

The optical resolution via diastereoisomeric salt formation is the most important industrial route for preparing optically pure isomers [1]. The process has not really changed since Pasteur's first resolution in 1853, for a given racemate the resolving agent and the solvent are still chosen by the trial and error method [2].

For the recognition of the governing rules of separations, detailed physico-chemical data for a large number of diastereoisomeric salts are needed. Unfor-

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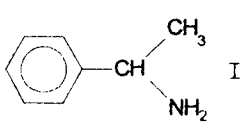
tunately most of the articles dealing with optical resolutions fail to report comparable data of both diastereoisomeric salts.

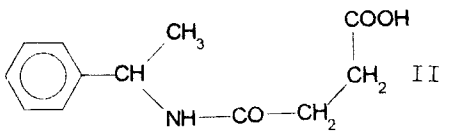
Jacques and his co-workers [3] started systematic data collections of diastereoisomeric salt pairs about 20 years ago. According to our knowledge, for the interpretation of separation results the following data are the most important: melting points, enthalpy and entropy of fusion, melting (binary) and solubility (ternary) phase diagrams.

In the present paper we investigate the physicochemical properties (melting temperature, heat of fusion, solubilities) of a diastereoisomeric salt pair for which an efficient resolution has been worked out.

The optically active α-phenyl-ethyl-amine (I) is one of the most widely used basic resolving agents. The optical isomers of the synthetically produced base can be separated by several resolving agents, one of the most effective is an acidic derivative of the base, the phenylethyl-succinamic acid (II) [4, 5]*.




I




II

## Experimental

All chemicals were purchased from Merck, except II which was prepared according to Felder and Pitre method [4, 5]. The optical resolution was also reproduced according to their patent.

The optically pure salts were prepared from molar equivalent amounts of optically pure compounds in methanol. The salt mixtures were made from calculated amounts of methanolic solutions of pure diastereoisomeric salts. From the solutions the solvent was evaporated entirely.

The DSC curves were recorded and integrated with the aid of a DuPont 1090B Thermal Analysis System. Samples of 1–3 mg were run in hermetically sealed aluminium pans with a heating rate of 5 deg·min$^{-1}$. The temperature range of thermal decomposition was determined by thermogravimetric measurements (carried out on the same system).

The solubilities were measured at 30±0.5°C and 61±0.5°C. 0.1–0.3 g samples were shaken in closed glass vessels with 10 ml of pure ethyl acetate in a thermostat. Every 30 minute 0.5 ml portions of the solvent were added to the

* We also tried to prepare appropriate size single crystals for single crystal X-ray diffraction studies of the molecular structures without success. We were able to determine the structure of II.[6]

systems. The solutions were considered saturated when all the crystals were dissolved.

## Results and discussion

The binary melting phase diagrams supply very valuable information about optical resolutions. They can reveal whether the salt pair forms conglomerate (both diastereoisomeric salts crystallize separately and the product is a physical mixture of the crystals), molecular compound or solid solution. Efficient resolution can only be achieved if the diastereoisomeric salt pair forms conglomerate. In a recent paper [7] we demonstrated how we can calculate the efficiency of a resolution from the eutectic point of the binary phase diagram (1):

$$S = \frac{1 - 2x_e}{1 - x_e} \tag{1}$$

where $S^*$: the efficiency of the resolution; $x_e$: molar fraction of the higher melting salt in the eutectic.

The liquidus curves of the binary phase diagrams can be calculated by the simplified Schröder-Van Laar equation [9] (2). The intersection of the liquidus curves determines the eutectic composition.

$$\ln x = \frac{\Delta H_i}{R}\left(\frac{1}{T_i} - \frac{1}{T}\right) \tag{2}$$

$x$: is the molar fraction of the diastereoisomers; $\Delta H_i$: the enthalpy of fusion of the pure diastereoisomers; $T_i$: the melting point the diastereoisomers; $T$: the melting point, i.e. end of fusion of a mixture with a molar fraction of $x$; $R$: the ideal gas constant.

The data required for the construction of the phase diagrams were determined by DSC. Both pure diastereoisomeric salts melt before the thermal decomposition starts, none of them form crystal solvates. The $n$ salt melts at 413 K, $\Delta H$=52.7 kJ/mol, the $p$ salt melts at 380 K, $\Delta H$=33.5 kJ/mol.

The binary phase diagrams were calculated with these data using Eq. (2). Calculated curves were verified by measuring some mixtures of the diastereoisomeric salts with DSC. The results are summarised in Table 1, the phase diagram is plotted on Fig. 1. It can be seen that the salt pair forms a conglomerate.

* The efficiency ($0<S<1$) of the resolution has been defined as the multiplication of the optical purity ($0<OP<1$) by the yield ($0<Y<1$) of the precipitated salt: $S = OP \times Y$

**Table 1** Measured and calculated eutectic and melting temperatures of the diastereoisomeric salt mixtures of α-phenyl-ethyl-amine and R-1-phenylethyl-succinamic acid

| Molar fraction | Calculated data | | Measured data | |
|---|---|---|---|---|
| $x$ | $T_{eu}/K$ | $T/K$ | $T_{eu}/K$ | $T/K$ |
| 0.2 | 372 | 373 | – | 370 |
| 0.5 | 372 | 395 | 372 | 398 |
| 0.8 | 372 | 407 | 371 | 405 |

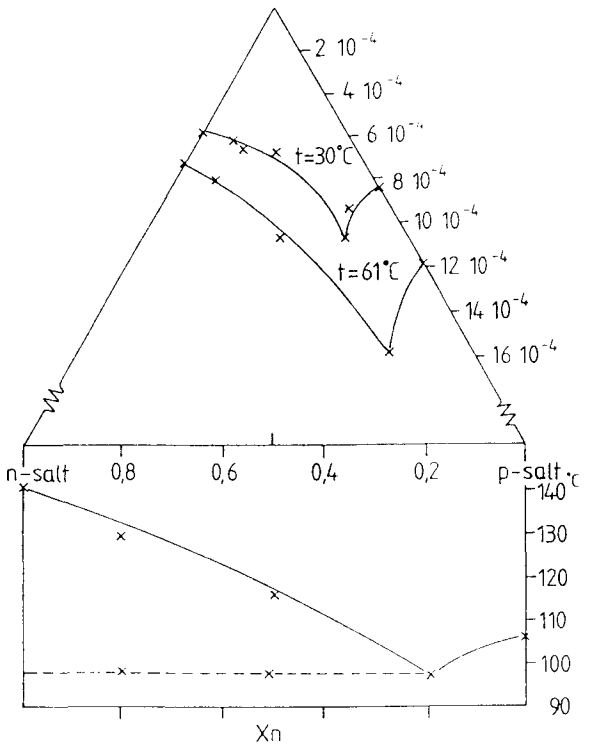



**Fig. 1** Melting and solubility phase diagram of the diastereoisomeric salt pair formed between α-phenyl-ethyl-amine and R-1-phenylethyl-succinamic acid

The measured data of the salt mixtures support the calculated melting phase diagram.

The eutectic composition is $x=0.19$, the efficiency of the resolution calculated from this by Eq. (1) ($S=0.76$) correlates well with the experimental efficiency ($S=0.72$).

Leclercq and his co-workers [10] noticed that eutectic compositions of the ternary solubility diagrams of a conglomerate forming diastereoisomeric salt

pair are approximately the same at different temperatures, and nearly identical with the eutectic composition of the melting phase diagram.

Though this is the basis of the calculation of the efficiency of resolutions by Eq. (1), this coincidence has been demonstrated still only on a few examples [10–14].

The solubilities determined at 30 and 61°C in ethylacetate are presented on Fig. 1 together with the binary phase diagram. The isotherms run nearly parallel, the eutectic compositions of the isotherms are nearly identical and agree with the eutectic composition of the binary phase diagram.

## Conclusions

The large difference in physico-chemical properties of the investigated diastereoisomeric salt pair (33°C in melting point, 19.2 kJ/mol in heat of fusion) result in a very efficient optical resolution. The calculated efficiency of the resolution from the thermal data agree well with the experimental results. Our measurements supply an other example of the coincidence of the eutectic points of binary and ternary phase diagrams of a diastereoisomeric salt pair which forms a conglomerate.

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The authors are grateful for financial support to OTKA foundation (grant numbers: F7386, T4183) and the József Varga foundation.

## References

1 P. Newman, Optical Resolution Procedures for Chemical Compounds, Vols 1–3, Optical Resolutions Information Center, Manhattan Colege, Riverdale, New York, 1978–84.
2 S. H. Wilen, A. Collet and J. Jacques, Tetrahedron, 33 (1977) 2725.
3 J. Jacques, A. Collet and S. H. Wilen, Enantiomers, Racemates and Resolutions, Wiley and Sons, New York 1981.
4 3576854. US patent (1971).
5 E. Felder, D. Pitrč and S. Boveri, Helv. Chim. Acta, 52 (1969) 329.
6 D. Kozma, S. Larsen and M. Ács, Acta Cryst., C48 (1992) 2182.
7 D. Kozma, Gy. Pokol and M. Ács, J. Chem. Soc., Perkin Trans.2, (1992) 435.
8 E. Fogassy, A. Lopata, F. Faigl, F. Darvas, M. Ács and L. Tőke, Tetrahedron Lett. 21 (1980) 647.
9 (a) I. Schroeder, Z. Phys. Chem., 11 (1893) 449; (b) J. J. Van Laar, Arch. Nederl., (1903) 264.
10 M. Leclercq and J. Jacques, Bull. Soc. Chim. Fr., (1975) 2052.
11 J. Jacques and J. Gabard, Bull. Soc. Chim. Fr., (1972) 342.
12 Y. Shimura and K. Tsutsui, Bull. Chem. Soc. Jpn., 50 (1977) 145.
13 M. Ács, F. Faigl, G. Réti, E. Fogassy, Gy. Pokol, M. Czugler and K. Simon, Proc. of 41st Int. Meeting on Phys. Chemistry: Dynamics of Molecular Crystals, Elsevier, Amsterdam 1987.

14 E. Fogassy, F. Faigl, M. Ács, K. Simon, É. Kozsda, B. Podányi, M. Czugler and G. Reck, J. Chem. Soc., Perkin Trans., 2 (1988) 1385.

**Zusammenfassung** — Mittels physikalisch-chemischen Methoden wurde das aus α-Phenylethylamin und R-1-Phenylethylbernsteinsäuremonoamid gebildete diastereoisomere Salzpaar untersucht. Es wurden die Schmelz- und Löslichkeitsphasendiagramme ermittelt und der Zusammenfall der eutektischen Punkte der zwei Phasendiagramme gezeigt. Der große Unterschied in den physikalisch-chemischen Eigenschaften des Salzpaares erklärt die effiziente Enantiomerentrennung.