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# Enantiomeric Mandelic Acid System—Melting Point Phase Diagram and Solubility in Water

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A systematic study of the binary melting point phase diagram and ternary solubility phase diagram of the enantiomeric mandelic acid species in water has been undertaken. The melting point phase diagram of the system (+)-/(−)-mandelic acid was determined by means of thermal analysis. In agreement with previous observations mandelic acid was found to belong to the compound forming systems. The solubilities of three fixed enantiomeric mixtures in water (pure enantiomer, racemic, and eutectic compositions) were measured in the temperature range between 0 °C and >90 °C. The results revealed that the solubility is strongly affected by temperature in a medium-temperature range. The ideal solubility curves of the three enantiomeric mixtures were calculated and the activity coefficients derived. An empirical three-step model is suggested to describe these activity coefficients.

## Introduction

Chiral compounds have a broad application as drugs and are relevant for the pharmaceutical industry. The increasing demands for enantiopure pharmaceuticals require efficient methods to separate the racemic mixtures that are the common product of chemical synthesis. Enantioselective crystallization from solution is considered to be a suitable approach for separation of systems forming conglomerates or systems already enriched in one enantiomer. With this background, the study of the fundamental thermodynamic parameters of relevant chiral substances is of special interest for design and optimization of crystallization processes.

Racemic mandelic acid is applied in different esterified forms (mandelates) as a pharmaceutical component because of its analgesic, antirheumatic, and spasmolytic effects (e.g., Spasmocyclon, Mandropine).[1] The (+)- and (−)-enantiomers of mandelic acid are widely used as resolving agents in enantioseparation of various other racemates (via salt formation).

However, only limited thermodynamic data of mandelic acid are available, and they are partly inconsistent. Measurements of melting points in the binary (+)-/(−)-mandelic acid system are reported by Angus and Owen,[2] referring to further values from Centnerszwer[2] and Adriani.[2] More recent pure component data are given by Leclercq et al.[3] and Li et al.[4] Solubility data of pure enantiomeric and racemic mandelic acid in water have been published by Angus and Owen,[5] Stephen and Stephen,[6] and Nishiguchi et al.[7]

In the present work, the results of a systematic study of solid−liquid equilibria of mandelic acid are reported. At first the melting equilibria in the binary system (+)-mandelic acid/(−)-mandelic acid were determined experimentally. Subsequently, solubility equilibria in ternary (+)-mandelic acid/(−)-mandelic acid/water mixtures were measured. The results are compared to literature data, and the deviation from ideal solution behavior is discussed.

## Experimental Section

***Substances.*** The chiral substances used were DL-mandelic acid (Merck, >99%), *S*-(+)-mandelic acid (Aldrich, 99%), and *R*-(−)-mandelic acid (Merck, >99%). The water was deionized.

***Melting Point Phase Diagram.*** To determine the phase diagram of the mandelic acid enantiomers, a heat flux calorimeter of the Calvet type (differential scanning calorimeter DSC 111, Setaram, France) was used. Temperature calibration took place regularly using the melting temperatures of highly pure indium, tin, and lead in a medium-temperature range, and aluminum and water for high and low temperatures, respectively. All measurements were carried out at a heating rate of 0.5 K/min. A continuous purge gas flow of about 8 mL/min pure helium (99.999%) was used. Measurement samples were between 8 and 20 mg. The enantiomeric mixtures were prepared by previously weighing and mixing larger samples of the pure enantiomers and crushing them together in a mortar. Measurements using different samples of the same mixture confirmed sufficient mixing. The resolution of the analytical balance was 0.001 mg.

The reproducibility of the DSC technique was determined by repeating measurements of different samples of the pure enantiomer and the racemate. The error in the determination of the melting temperature was ±0.24 K (i.e., <±0.2% in the temperature range applied); the error in measuring the melting enthalpy was below ±1.4%. The latter one is related to a significant decomposition of mandelic acid during melting, making it impossible to measure a “true” melting enthalpy. The decomposition process affects the entire melting peak but only slightly affects the onset temperature used for determination of the melting point. A coupled thermogravimetry−DSC experiment using a TG-DSC 111 unit (Setaram, France) showed a mass loss of 2.8 mass % of the mandelic acid sample until melting was completed under the conditions mentioned

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**Table 1. Error Analysis of the Classical Isothermal Method for Solubility Determination ($n$, number of experiments; s.d., standard deviation;[a] error, error of solubility data)**

| $t$/°C | $n$ | s.d. | error/% |
|---|---|---|---|
| 25 | 9 | 0.23 | 1.34 |
| 40 | 10 | 1.23 | 2.40 |

[a] $\text{s.d.} = \left[\left(\Sigma X_i^2 - \frac{1}{n}(\Sigma X_i)^2\right)\Big/(n-1)\right]^{1/2}$

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above. This error must be kept in mind when evaluating the data presented below.

***Solubility Measurements.*** Solubility data in water were obtained by means of two different techniques: a classical isothermal method in an equilibrium apparatus for measuring solubilities in the entire ternary system and a nonisothermal DSC method for measuring solubilities of the pure enantiomers and the racemic mandelic acid only. Measurements were performed in the temperature range between 0 °C and >90 °C.

The DSC technique applies the heat effect caused by the dissolution of a definite amount of solute. A solute/solvent mixture of known composition with an excess of undissolved solute is subjected to a linear heating program. If the heating rate is low enough to ensure equilibrium conditions, the solubility temperature can be derived from the resulting heat flow−temperature curve. Samples used were between 50 mg and 110 mg in 150 $\mu$L gastight stainless steel crucibles. The optimal heating rate was 1 K/min. More detailed information about the method has been published previously.[8]

For solubility determinations using the classical isothermal method, measurements in a solubility apparatus were made. The experimental setup consisted of a thermostated double or triple walled glass apparatus, where a vial with the mixture to be studied was placed. The temperature of the mixture was measured with a Pt-100 resistance thermometer (resolution 0.01 K, uncertainty 1/3 DIN). The preparation of the sample included putting water with a syringe (2−10 mL) into the vial and adding a weighed amount of the mandelic acid mixture. The sample was first heated to a temperature approximately 4 K above the desired value, held at that temperature until just single crystals remained in the solution, and, subsequently, cooled to the equilibrium temperature. Afterward, the solution was electromagnetically stirred for 5−6 h at constant temperature (within ±0.05 K). In a separate preliminary experimental study, this was found sufficient for the establishment of solid−liquid equilibrium. For analysis the saturated solution was filtered (thermostated glass filter P16, max. pore width 10−16 $\mu$m) and samples of 2−3 mL were withdrawn from the clear solution into two flasks for double analysis. The mass of the samples, $m_{\text{sol}}$, and, after completely removing the solvent in a rotary evaporator, the mass of the remaining solid, $m_{\text{dr}}$, were determined. Its enantiomeric composition was analyzed by HPLC (Column: 250 mm × 4.6 mm Chirobiotic T, 5 $\mu$m, Astec/USA. Eluent: 1% TEAA/methanol (80/20, v/v). pH = 4). The solubility, $S$, expressed in mass percent (mass %), is then given by

$$S = 100(m_{\text{dr}}/m_{\text{sol}}) \tag{1}$$

To evaluate the error of the solubility data obtained with the isothermal method, repeated measurements were made at temperatures of 25 °C and 40 °C using racemic mandelic acid. Results are shown in Table 1.

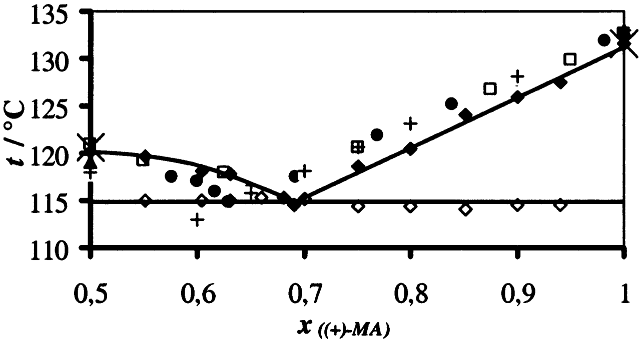

**Figure 1.** Binary melting point phase diagram of the mandelic acid enantiomers: ◆, $t_{\text{m}}$ present work; ◇, $t_{\text{eu}}$ present work; ●, Angus/Owen;[2] +, Adriani;[2] □, Centnerszwer;[2] ▲, Leclercq et al.;[3] ×, Li et al.[4] (lines are guides to the eye).

**Table 2. Solidus and Liquidus Temperature, $t_{\text{eu}}$ and $t_{\text{m}}$, in the Melting Point Phase Diagram of Mandelic Acid as a Function of the (+)-Mandelic Acid Mole Fraction, $x_{((+)\text{-MA})}$**

| $x_{((+)\text{-MA})}$ | $t_{\text{eu}}$/°C | $t_{\text{m}}$/°C | $x_{((+)-\text{MA})}$ | $t_{\text{eu}}$/°C | $t_{\text{m}}$/°C |
|---|---|---|---|---|---|
| 1.0000 |  | 131.5 | 0.6310 | 115.0 | 117.8 |
| 0.9406 | 114.5 | 127.5 | 0.6050 | 115.1 | 118.2 |
| 0.9002 | 114.6 | 126.0 | 0.5514 | 115.0 | 119.7 |
| 0.8504 | 114.1 | 124.0 | 0.5000 |  | 120.2 |
| 0.7997 | 114.3 | 120.5 | 0.4000 | 114.6 | 118.2 |
| 0.7508 | 114.4 | 118.6 | 0.3192 |  | 114.4 |
| 0.7008 | 115.2 | ncd[a] | 0.3096 | 115.2 | ncd |
| 0.6902 |  | 114.6 | 0.1994 | 115.1 | 120.5 |
| 0.6807 |  | 115.2 | 0.0000 |  | 131.6 |
| 0.6604 | 115.2 | ncd |  |  |  |

[a] ncd = not clearly determinable.

**Table 3. Melting Enthalpy, $\Delta_{\text{fus}}H$, of the Mandelic Acid Enantiomers, the Racemic Mandelic Acid, and the Eutectic Mixture in kJ/mol (Present Work and Literature Data)**

|  | enantiomer | racemic compound | eutectic mixture |
|---|---|---|---|
| present work | 24.5 | 25.6 | 24.9 |
| Leclercq et al.[3] | 26.4 | 25.1 |  |
| Li et al.[4] | 25.7 | 26.8 |  |

## Results and Discussion

***1. Binary Melting Point Phase Diagram.*** Tables 2 and 3 contain the results of DSC measurements using mandelic acid mixtures of different enantiomeric composition. Solidus and liquidus temperatures (t$_{\text{eu}}$ and t$_{\text{m}}$) were determined from the extrapolated onset temperature of the eutectic effect and the peak temperature of the subsequent dissolution effect of the excess component in the melt. The resulting melting point phase diagram, reduced to the range between the racemic composition ($x_{((+)\text{-MA})} = 0.5$) and the (+)-enantiomer ($x_{((+)\text{-MA})} = 1$), is shown in Figure 1. The symmetry of the diagram around the racemic composition was confirmed by additional data ($x_{((+)\text{-MA})} < 0.5$) included in Table 2.

The presence of an eutectic at an intermediate composition and the rounded shape of the liquidus curve at the racemic composition indicate that the mandelic acid enantiomers form a 1:1 compound in the solid state, which dissociates in the liquid (melt) phase. As derivable from data in Table 2, the exact eutectic composition was difficult to access. Sharp melting effects characterizing the eutectic were obtained at enantiomeric compositions of 0.6807, 0.6902, and 0.3192. The heat flow curves measured for mixtures of composition 0.68 ± 0.02 (or 0.32 ± 0.02) could not be resolved to estimate the liquidus temperature (which

**Table 4. Solubility, *S*, of the Mandelic Acid Enantiomer, the Racemic Compound, and the Eutectic Composition in Water**

| | (+)-enantiomer | | racemic compound | | eutectic[b] | |
|---|---|---|---|---|---|---|
| *t*/°C | *S*/mass % | Tech[a] | *S*/mass % | Tech | *S*/mass % | Tech |
| 0.00 | 4.94 | 1 | 6.91 | 1 | 8.62 | 1 |
| 5.00 | 5.42 | 1 | 8.10 | 1 | 9.28 | 1 |
| 10.00 | 6.30 | 1 | 9.32 | 1 | 10.81 | 1 |
| 15.00 | 7.40 | 1 | 10.70 | 1 | 13.30 | 1 |
| 18.94 | | | 15.29 | 2 | | |
| 20.00 | 8.44 | 1 | 13.30 | 1 | 15.63/15.81[c] | 1 |
| 25.00 | 9.94 | 1 | 17.20 | 1 | 22.20/21.70[c] | 1 |
| 29.53 | | | 20.25 | 2 | | |
| 30.00 | 11.90 | 1 | 24.79 | 1 | 33.90/34.10[c] | 1 |
| 33.30 | | | 30.60 | 2 | | |
| 35.00 | 15.83 | 1 | 36.20 | 1 | 48.50/48.90[c] | 1 |
| 35.73 | | | 42.91 | 2 | | |
| 40.00 | 22.56 | 1 | 51.33 | 1 | 60.18 | 1 |
| 42.50 | | | 60.11 | 2 | | |
| 45.00 | 35.30 | 1 | | | | |
| 47.30 | | | 62.32 | 2 | | |
| 50.00 | 49.19 | 1 | 68.47 | 1 | 73.76 | 1 |
| 50.80 | 40.07 | 2 | | | | |
| 52.80 | | | 69.14 | 2 | | |
| 55.50 | 60.32 | 2 | | | | |
| 60.00 | 66.90 | 1 | 78.75 | 1 | 80.47 | 1 |
| 61.80 | | | 78.44 | 2 | | |
| 74.10 | 80.00 | 2 | 88.18 | 2 | | |
| 80.20 | | | 90.36 | 2 | | |
| 97.00 | 88.63 | 2 | | | | |
| 99.00 | 90.06 | 2 | | | | |

[a] Technique: 1, classical isothermal method; 2, DSC method. [b] Eutectic composition: $x_{((+)\text{-MA})} = 0.69$. [c] Eutectic composition: $x_{((+)\text{-MA})} = 0.31$.

is related to the instruments time constant). The position of the eutectic was found previously to vary between $x = 0.6$ and $x = 0.7$.[2,9] The presence of partial miscibility in the solid state (formation of a solid solution close to the mandelic acid enantiomers) could be excluded by means of a Tammann plot not presented here. The results obtained for the melting point phase diagram are in good agreement with data published by Li et al.[4] but show deviations from older data reported by Angus and Owen[2]. However, except for the case of one point measured by Adriani,[2] this deviation is within ±3 K.

Table 3 contains melting enthalpies determined for the enantiomer, the racemic compound and the eutectic mixture of mandelic acid along with literature values. When comparing these data, the thermal instability of mandelic acid during melting has to be taken into account. The extent of decomposition depends on the duration of thermal treatment in the experiments performed.

***2. Solubility of the Mandelic Acid Species in Water.*** Experimental data for solubility obtained in this work are summarized in Tables 4 and 5. According to their relevance, mainly three typical enantiomeric mixtures of mandelic acid in water were studied—the enantiomer, the racemic compound, and the eutectic mixture. The appropriate solubility data are given in Table 4. Table 5 contains data for mixtures with deviating compositions.

The resulting ternary phase diagram of the mandelic acid enantiomers in water is presented in Figure 2. As expected, the diagram shows mirror image symmetry with respect to the racemic axis. Solubility isotherms having the same shape as the liquidus curves in the melting point phase diagram independently confirm the compound-forming character of mandelic acid. The composition of the eutectic in the binary (+)-/(−)-mandelic acid system is not affected by the presence of the solvent (ideal behavior); that is, the enantiomeric composition of the monovariant "eutectic curve" in the ternary system (characterizing an invariant (doubled saturated) solution at constant temperature) remains unchanged. The obtained values of approximately 0.69 and 0.31 correspond to literature data.[7]

**Table 5. Solubility, *S*, of Further Mixtures of the Mandelic Acid Enantiomers in Water[a]**

| *t*/°C | *S*/mass % | $w_{(\text{water})}$ | $w_{((-)\text{-MA})}$ | $w_{((+)\text{-MA})}$ |
|---|---|---|---|---|
| 15 | 10.30 | 0.897 | 0.019 | 0.084 |
| | 12.30 | 0.877 | 0.038 | 0.085 |
| | 11.30 | 0.887 | 0.043 | 0.070 |
| 25 | 14.30 | 0.857 | 0.029 | 0.114 |
| | 16.50 | 0.835 | 0.039 | 0.126 |
| | 20.10 | 0.799 | 0.057 | 0.144 |
| | 22.20 | 0.778 | 0.066 | 0.156 |
| | 19.00 | 0.810 | 0.071 | 0.119 |
| 30 | 14.80 | 0.852 | 0.021 | 0.127 |
| | 23.80 | 0.762 | 0.057 | 0.181 |
| | 27.00 | 0.730 | 0.079 | 0.191 |
| | 28.10 | 0.719 | 0.104 | 0.177 |
| | 25.00 | 0.750 | 0.100 | 0.150 |
| 35 | 18.10 | 0.819 | 0.027 | 0.154 |
| | 22.10 | 0.779 | 0.025 | 0.196 |
| | 47.30 | 0.527 | 0.142 | 0.331 |
| | 41.70 | 0.583 | 0.155 | 0.262 |

[a] The composition of the ternary mixtures is given in weight fraction, $w_{(i)}$ (technique: classical isothermal method).

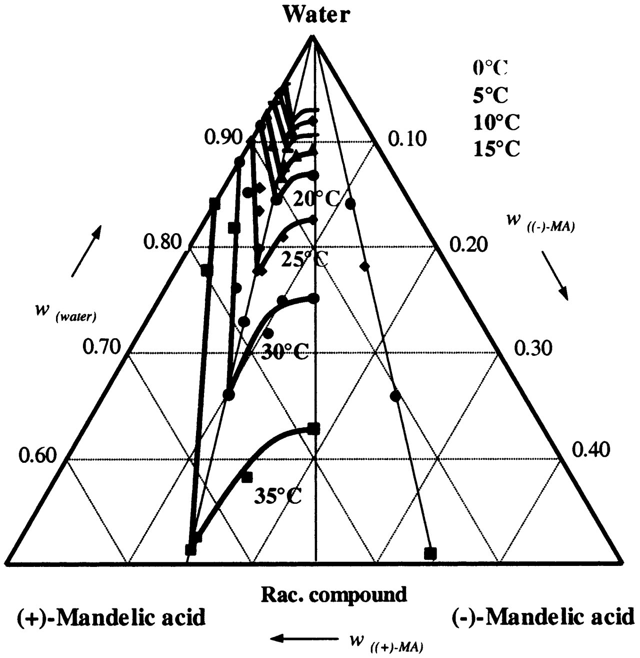

**Figure 2.** Ternary phase diagram of the mandelic acid enantiomers in water including solubility isotherms for $w_{((+)\text{-MA})}$ and $w_{((-)\text{-MA})} \le 0.5$ (axes in weight fraction; lines are guides to the eye).

Solubilities of racemic and pure enantiomeric mandelic acid as a function of temperature are presented in Figure 3. The solubility curves increase steadily with temperature, exhibiting a steep slope in the medium-temperature range between approximately 30 and 50 °C for the racemic compound and between approximately 40 and 60 °C for the enantiomer. The results are in good agreement with literature. However, there is a discrepancy to the higher racemate solubility data from Angus and Owen[5] above 35 °C, which cannot be explained. Recently, Profir and Rasmuson[11] discussed the possible existence of a metastable mandelic acid conglomerate, which might account for higher solubility.

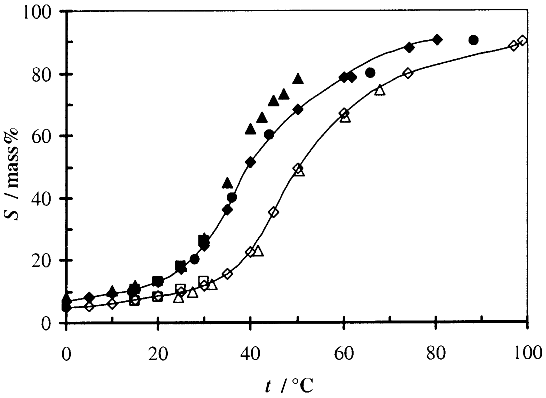

**Figure 3.** Solubility, *S*, of racemic mandelic acid (rac) and (+)-mandelic acid in water as a function of temperature: ◆, rac, present work; ◇, (+)-MA, present work [$t \leq 60$ °C, classical method; $t > 60$ °C, DSC method]; ▲, rac, Angus/Owen;[5] △, (+)-MA, Angus/Owen;[5] ■, rac, Nishiguchi et al.;[7] □, (+)-MA, Nishiguchi et al.;[7] ●, rac, Rauls[10] (lines are guides to the eye).

**3. *Estimation of Activity Coefficients.*** In an equilibrated saturated solution, the chemical potential of the solute in solution is equal to that of the solute in the pure solid state. As a suitable standard state, the solute as a pure subcooled liquid at the same temperature as that of the solution in question can be chosen. On the basis of classical thermodynamics, the activity of the dissolved solid ($a_s$) can be expressed by[12]

$$\ln a_s = \frac{\Delta_{fus}H}{RT}\left(\frac{T}{T_m} - 1\right) + \frac{\Delta c_p}{R}\left(\frac{T_m}{T} - 1\right) - \frac{\Delta c_p}{R}\ln\frac{T_m}{T} \qquad (2)$$

where $\Delta_{fus}H$ is the enthalpy of fusion at the melting temperature $T_m$, $R$ is the universal gas constant, and $\Delta c_p$ is the difference in the heat capacities ($\Delta c_p = c_{p,liquid} - c_{p,solid}$). The three terms on the right-hand side of eq 2 are not equally relevant. The first term is dominant whereas the other two terms tend to compensate each other, particularly when $T$ approaches $T_m$. Therefore, in many cases it is sufficient to consider only the term which includes $\Delta_{fus}H$ and to neglect the $\Delta c_p$-containing terms. Jacques et al.[13] determined, for example, the liquidus curves in the binary system of the hydrobenzoin enantiomers both including and neglecting the heat capacity terms. The deviation of the melting temperature was 1.5 K at the eutectic and clearly smaller at high enantiomeric purities.

Thus, eq 2 can be rewritten in the often used simplified form

$$a_s = \exp\left[\frac{\Delta_{fus}H}{RT}\left(\frac{T}{T_m} - 1\right)\right] = x_s\gamma \qquad (3)$$

where $x_s$ is the mole fraction of the solute in the solution at saturation temperature $T$ and $\gamma$ is the activity coefficient quantifying the real behavior of the system. For $\gamma = 1$, eq 3 allows to calculate the ideal solubility curve as a function of temperature using only the values for $\Delta_{fus}H$ and $T_m$. The activity coefficient $\gamma$ for a real solution can be determined by comparing the ideal and the experimentally observed solubility data.

In Figure 4 activity coefficients calculated for (+)-mandelic acid, the racemic compound, and the eutectic mixture in water are presented as a function of temperature. In each case, the temperature dependency of $\gamma$ can be described by three characteristic regions. Since it is not the intention of this paper to analyze the activity coefficients in detail, here only a simple empirical three-step model for correlating these coefficients is suggested. For the three temperature regions, separated by $t_1$ and $t_2$, different $\gamma = f(t)$ functions can be used for the three characteristic enantiomeric compositions. At low temperatures ($t < t_1$), the activity coefficient is maximum and approximately constant, $\gamma = \gamma^*_{max}$. Between $t_1$ and $t_2$, the activity coefficient decreases almost linearly with temperature, and at high temperatures ($t > t_2$), ideal behavior is observed, that is, $\gamma = 1$. The corresponding relationships are given in Table 6.

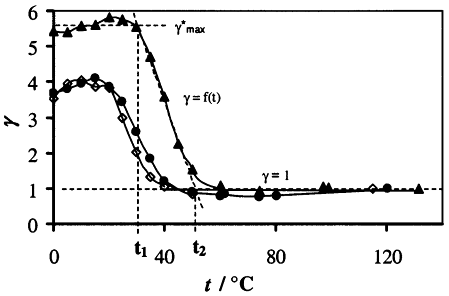

**Figure 4.** Activity coefficients, $\gamma$, versus temperature: ▲, (+)-MA; ●, rac MA; ◇, eutectic mixture (lines are guides to the eye).

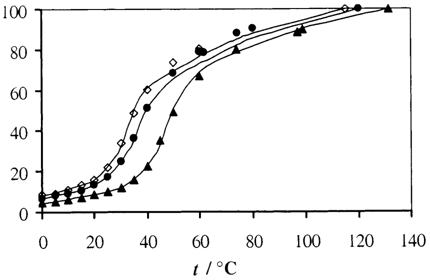

**Figure 5.** Calculated and experimentally determined solubility data of mandelic acid species in water: ▲, (+)-MA, exp; ●, rac MA, exp; ◇, eutectic mixture, exp; lines, empirical model.

**Table 6. Empirical Three-Step Model for Describing the Activity Coefficients in the Ternary System of the Mandelic Acid Enantiomers in Water**

| substance | $t_1$/ °C | $t_2$/ °C | $t < t_1$ | $t_1 < t < t_2$ | $t > t_2$ |
|---|---|---|---|---|---|
| (+)-MA | 30 | 52 | $\gamma^*_{max} = 5.59$ | $\gamma = -0.2083t + 11.861$ | $\gamma = 1$ |
| rac compd | 20 | 41 | $\gamma^*_{max} = 3.89$ | $\gamma = -0.1381t + 6.7279$ | $\gamma = 1$ |
| eutectic | 20 | 37 | $\gamma^*_{max} = 3.85$ | $\gamma = -0.1697t + 7.2091$ | $\gamma = 1$ |

In Figure 5 the solubilities calculated by means of the described empirical model are compared with the experimental values. As can be seen, the agreement is satisfying in the entire temperature range with the best results for the enantiomer. The average errors of the solubilities were found to be 2.1% for the enantiomer, 3% for the racemic compound, and 3.2% for the eutectic mixture.

## Literature Cited

(1) Elvers, B., Ed. *Ullmann's Encyclopedia of Industrial Chemistry*; VCH: Weinheim, 1989.

(2) Angus, W. R.; Owen, R. P. The Stability of Racemates. Mandelic Acid and Some of its Derivatives. *J. Chem. Soc.* **1943**, 227−230.

(3) Leclercq, M.; Collet, A.; Jacques, J. Etude des melanges d'antipodes optiques-XII; Mesure de la stabilite des racemiques vrais. *Tetrahedron* **1976**, *32*, 821−828.

(4) Li, Z. J.; Zell, M. T.; Munson, E. F.; Grant, D. J. W. Characterization of Racemic Species of Chiral Drugs Using Thermal Analysis, Thermodynamic Calculation, and Structural Studies. *J. Pharm. Sci.* **1999**, *88*, 337−346.

(5) Angus, W. R.; Owen, R. P. Aqueous Solubilities of r- and l-Mandelic Acids and Three O−Acyl-r-mandelic Acids. *J. Chem. Soc.* **1943**, 231−232.

(6) Stephen, H., Stephen, T., Eds. *Solubilities of Inorganic and Organic Compounds*; Pergamon Press: Oxford−London−New York−Paris, 1963.

(7) Nishiguchi, N.; Moritoki, M.; Shinohara, T.; Toyokura, K. In *Separation and purification by crystallisation;* Botsaris, G. D., Toyokura, K., Eds.; American Chemical Society: Washington, DC, 1997; pp 73−82.

(8) Lorenz, H.; Seidel-Morgenstern, A. Binary and ternary phase diagrams of two enantiomers in solvent systems. *Thermochim. Acta* **2002**, *382*, 129−142.

(9) Fouquey, C.; Leclercq, M. Détermination de la pureté optique d'un corps cristallin par calorimétrie-II; Validité de la méthode et précision des résultats. *Tetrahedron* **1970**, *26*, 5637−5651.

(10) Rauls, M. (BASF Ludwigshafen, Germany). Personal information, 2000.

(11) Profir, V.; Rasmuson, Å. C. In *BIWIC 2001, 8th International Workshop on Industrial Crystallisation*; Jansens, P., Kramer, H., Roelands, M., Eds.; Delft University of Technology: Delft, The Netherlands, 2001; pp 71−73.

(12) Prausnitz, J. M.; Lichtenthaler, R. N.; Gomes de Azevedo, E. *Molecular Thermodynamics of Fluid-Phase Equilibria*; Prentice Hall: Upper Saddle River, NJ, 1986.

(13) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Krieger Publishing: Florida, 1994.

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