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Solubility of Mandelic Acid Enantiomers and Their Mixtures in Three Chiral Solvents

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A systematic study of the ternary solubility phase diagrams of chiral mandelic acid species in the chiral solvents (*S*)-methyl lactate, (*S*)-propyl lactate, and (*S*)-butyl lactate has been carried out. Solubility measurements were performed for different enantiomeric compositions in a temperature range between (273 and 318) K. Experimental results indicated no proof of solubility differences of the enantiomers in all three chiral solvents used. Hence, increasing chain length of the chiral solvents has no influence on chiral recognition. Besides, the eutectic composition in the chiral system in the presence of the solvent as a significant parameter for enantioseparation was determined for all the chiral solvents investigated. Also, the activity coefficients were derived for all three chiral solvents applied.

Introduction

Chiral substances have a wide application as drugs and thus are important for the pharmaceutical industry. Recently, the Food and Drug Administration (FDA) has set two guidelines for the pharmaceutical companies. The first was to alter the drug development toward the realization of single enantiomers, and the second was to stimulate the development of novel methods for asymmetric synthesis and enantiomeric separations.[1] So, the enantiomer with the preferred characteristics has to be retrieved subsequently in pure form. On the basis of these increasing demands for single drugs, the need has arisen for efficient techniques to separate the racemates that are the regular product of chemical synthesis. Crystallization provides a viable approach for separation and purification of mixtures contributing a relatively cheaper option to frequently used chromatographic techniques. As crystallization processes involve different phases which are in contact with each other, the demand for the knowledge of the corresponding phase equilibria is compulsory.[2] Enantioselective crystallization is considered to be a feasible approach for the separation of enantiomers. Recently, a crystallization-based approach was considered applying chiral solvents.[3]

Mandelic acid as the substance studied here has important medicinal applications; for example, due to its bacteriostatic properties, it is employed for the treatment of urinary tract infections, i.e., from either the calcium or ammonium salt.[4] Also, the pure form of (*R*)-mandelic acid is applied as a precursor for the synthesis of cephalosporin and penicillin.[5]

A literature survey on available solubility data of chiral systems in chiral solvents reveals no systematic studies. On the basis of this problem, we recently published a paper on solid−liquid equilibria of mandelic acid enantiomers in the chiral solvents (2*R*,3*R*)-diethyl tartrate and (*S*)-ethyl lactate.[6] However, to ascertain the effect of decreased and increased chain length in the chiral solvent molecule on solubility of mandelic acid, the three chiral solvents (*S*)-methyl lactate, (*S*)-propyl lactate, and (*S*)-butyl lactate were incorporated in this extended investigation.

Therefore, the present work is concerned with a systematic determination of the solubility of mandelic acid in three chiral solvents with different chain length, to verify the effect of the chain length in the chiral solvent molecules on solubility. Finally, ternary solubility diagrams were derived based on the determined solubility data. Activity coefficients were determined from the measured solubility data in a temperature range between (278 and 308) K.

Experimental Section

Materials. Racemic mandelic acid (racemic-2-hydroxy-2-phenylacetic acid, CAS no. 90-64-2) (rac), (*S*)-(+)-mandelic acid ((*S*)-2-hydroxy-2-phenylacetic acid, CAS no. 17199-29-0) (1), and (*R*)-(−)-mandelic acid ((*R*)-2-hydroxy-2-phenylacetic acid, CAS no. 611-71-2) (2) were supplied from Merck KGaA, Darmstadt, and Sigma-Aldrich Chemical Co. with mass fraction purities of ≥ 0.99. As solvents, (*S*)-(−)-methyl lactate (methyl-(*S*)-2-hydroxy propionate, CAS no. 27871-49-4) (3), (*S*)-(−)-propyl lactate (propyl-(*S*)-2-hydroxy propionate, CAS no. 53651-69-7) (4), and (*S*)-(−)-butyl lactate (butyl-(*S*)-2-hydroxy propionate, CAS no. 34451-19-9) (5) from PURAC Company Netherlands, with mass fraction purities of ≥ 0.98, were used. For HPLC analysis, 2-propanol from Merck KGaA, Darmstadt, with a mass fraction purity of ≥ 0.995 was applied.

Apparatus and Procedure. For the solubility measurements, a classical isothermal method was used. Evaluated excess amounts of (*S*)-mandelic acid or (*R*)-mandelic acid, racemic mandelic acid, or different mixtures of both were weighed with an analytical balance (resolution of balance was ± 0.1 mg) and filled in a glass vessel of 10 mL total volume, which was put into a thermostatted apparatus (thermostat, RC6 CP Lauda, Germany). The suspensions were magnetically stirred at a constant temperature (within ± 0.01 K) until equilibrium was attained. Afterward, the liquid and solid phases were separated and analyzed. For analysis, the saturated solution was filtered with a glass filter (pore size, 10 μm), and samples of (1 to 3)

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mL were withdrawn from the filtrate for double analysis. The concentrations were determined by means of a refractometer and chiral HPLC.

The enantiomeric compositions of the equilibrated liquid phases were analyzed by means of chiral HPLC after dilution with 2-propanol. An Agilent HP 1100 unit with a Chiralcel OD-H column (Astec, 250 × 4.6 mm/5 μm) was employed. The chromatographic separation was conducted at 298 K, and the flow rate was set to 1.0 mL·min^{-1}. A UV diode array detector was used for peak detection at a wavelength of 254 nm. The eluent fractions by volume (φ) were as follows: φ(*n*-hexane) = 0.84, φ(2-propanol) = 0.16, and φ(trifluoroacetic acid) = 0.001.

The solid phases of all samples were investigated by X-ray powder diffraction (XRPD), using a PANalytical X'Pert Pro diffractometer (PANalytical GmbH, Germany) with Cu Kα radiation. The samples were measured on Si sample holders and scanned between a diffraction angle of (3 and 40)° with step size of 0.017° and counting time of 50 s per step. These measurements were carried out to identify the solids present in equilibrium and also to check for differing solid state forms like solvates and/or polymorphs.

On the basis of our previous work, the equilibration time was set to be at least 24 h.[6]

The mass fraction solubility (w_i) according to eq 1 is used in this paper since this simplifies the graphical illustrations of, e.g., ternary solubility phase diagrams. The summation covers at all times the two enantiomers and either (*S*)-(−)-methyl lactate, (*S*)-(−)-propyl lactate, or (*S*)-(−)-butyl lactate. Herein, m_i represents the mass of the constituent *i*.

$$w_i = \frac{m_i}{\sum_{i=1}^{z} m_i} \tag{1}$$

To assess the solid−liquid equilibria of mandelic acid in the chosen solvents comprehensively, we determined the ternary phase diagram by undertaking detailed solubility measurements between (273 and 308) K for the single enantiomers and the eutectic and the racemic compositions. Additionally, to check for asymmetry in the ternary phase diagrams various compositions were measured along the 298 K isotherm ranging from the racemic compositions to the single enantiomers.

The reproducibility of the solubility measurements was studied by repeating three or four experiments under the same conditions. The measurements were conducted with racemic mandelic acid, (*S*)-mandelic acid, and (*R*)-mandelic acid in all three chiral solvents, (*S*)-methyl lactate, (*S*)-propyl lactate, and (*S*)-butyl lactate at 298 K. Standard deviations (SD) were calculated by eq 2 with *n* being the number of experiments and w_k and $\bar{w}$ being the mass fraction solubility and the mean solubility, respectively.

$$\mathrm{SD} = \sqrt{\frac{1}{n-1}\sum_{k=1}^{n}(w_k - \bar{w})^2} \tag{2}$$

The uncertainties for (*S*)- and (*R*)-mandelic acid are summarized in Table 1. The standard deviations for the racemic mandelic acid solubilities are in the same range.

Table 1. Error Analysis of Solubility Determination Procedure (Standard Deviation SD According to Equation 2, Number of Experiments *n*)

	(*S*)- and (*R*)-mandelic acid in (*S*)-methyl lactate	
T/K	*n*	SD
298	4	0.46
	(*S*)- and (*R*)-mandelic acid in (*S*)-propyl lactate	
T/K	*n*	SD
298	3	0.03
	(*S*)- and (*R*)-mandelic acid in (*S*)-butyl lactate	
T/K	*n*	SD
298	3	0.49

Table 2. Mass Fraction Solubility (w_i) of (*S*)-Mandelic Acid (1) and (*R*)-Mandelic Acid (2) in (S)-Methyl Lactate (3) at Different Enantiomeric Excesses (ee) [ee = $|w_1 - w_2|/(w_1 + w_2)$] and Temperatures as Well as Identity of Solid Phases (sp) in Equilibrium ((rac) = Racemic Mandelic Acid)

100 ee	100 (w_1 + w_2)	100 w_1	100 w_2	100 w_3	sp
		T = 273 K			
100.00	19.83	19.83	0.00	80.17	(1)
38.00	27.90	19.25	8.65	72.10	(1), (rac)
0.00	25.66	12.83	12.83	74.34	(rac)
38.00	27.97	8.67	19.30	72.03	(2), (rac)
100.00	19.80	0.00	19.80	80.20	(2)
		T = 278 K			
100.00	22.37	22.37	0.00	77.63	(1)
38.08	29.40	20.30	9.10	70.60	(1), (rac)
0.00	27.08	13.54	13.54	72.92	(rac)
38.10	29.50	9.13	20.37	70.50	(2), (rac)
100.00	22.15	0.00	22.15	77.85	(2)
		T = 288 K			
100.00	24.09	24.09	0.00	75.91	(1)
38.48	31.03	21.49	9.54	68.97	(1), (rac)
0.32	29.44	14.67	14.77	70.56	(2) (rac)
38.10	30.66	9.58	21.08	69.34	(2), (rac)
100.00	24.00	0.00	24.00	76.00	(2)
		T = 298 K			
100.00	27.57	27.57	0.00	72.43	(1)
90.90	28.46	27.17	1.29	71.54	(1), (rac)
78.42	29.79	26.58	3.21	70.21	(1), (rac)
71.32	31.34	26.85	4.49	68.66	(1), (rac)
51.78	33.93	25.75	8.18	66.07	(1), (rac)
38.08	35.04	24.19	10.85	64.96	(1), (rac)
28.60	33.93	21.82	12.11	66.07	(1), (rac)
19.20	33.26	19.82	13.44	66.74	(1), (rac)
0.00	32.89	16.44	16.44	67.11	(rac)
21.22	33.21	13.08	20.13	66.79	(2), (rac)
27.80	33.79	12.20	21.59	66.21	(2), (rac)
38.10	34.89	10.80	24.09	65.11	(2), (rac)
49.30	33.80	8.57	25.23	66.20	(2), (rac)
69.60	31.20	4.74	26.46	68.80	(2), (rac)
77.80	30.10	3.34	26.76	69.90	(2), (rac)
89.50	27.90	1.46	26.44	72.10	(2), (rac)
100.00	27.49	0.00	27.49	72.51	(2)
		T = 308 K			
100.00	30.33	30.33	0.00	69.67	(1)
38.08	38.46	26.55	11.91	61.54	(1), (rac)
0.00	35.80	17.90	17.90	64.20	(rac)
38.10	38.79	12.01	26.78	61.21	(2), (rac)
100.00	30.33	0.00	30.33	69.67	(2)

Results and Discussion

The solubility data measured are summarized in Tables 2, 3, and 4. Figures 1, 2, and 3 depict all the determined solubility data of the mandelic acid enantiomers, the racemic compound, and the different mixtures of (*S*)-methyl lactate, (*S*)-propy respectively. No extra or new

Table 3. Mass Fraction Solubility (w_i) of (*S*)-Mandelic Acid (1) and (*R*)-Mandelic Acid (2) in (*S*)-Propyl Lactate (4) at Different Enantiomeric Excesses (ee) [ee = $|w_1 - w_2|/(w_1 + w_2)$] and Temperatures as Well as Identity of Solid Phases (sp) in Equilibrium ((rac) = Racemic Mandelic Acid)

100 ee	100 ($w_1 + w_2$)	100 w_1	100 w_2	100 w_4	sp
		$T = 278$ K			
100.00	16.10	16.10	0.00	83.90	(1)
38.08	21.37	14.75	6.62	78.63	(1), (rac)
0.00	20.17	10.08	10.08	79.83	(rac)
38.10	21.21	6.56	14.65	78.79	(2), (rac)
100.00	15.70	0.00	15.70	84.30	(2)
		$T = 288$ K			
100.00	18.11	18.11	0.00	81.89	(1)
38.32	24.00	16.60	7.40	76.00	(1), (rac)
0.38	22.41	11.25	11.16	77.59	(1), (rac)
38.30	23.68	7.31	16.37	76.32	(2), (rac)
100.00	18.03	0.00	18.03	81.97	(2)
		$T = 298$ K			
100.00	20.15	20.15	0.00	79.85	(1)
90.10	21.83	20.75	1.08	78.17	(1), (rac)
79.70	23.12	20.77	2.35	76.88	(1), (rac)
69.94	24.40	20.73	3.67	75.60	(1), (rac)
49.74	26.87	20.12	6.75	73.13	(1), (rac)
38.22	27.51	19.01	8.50	72.49	(1), (rac)
30.40	26.79	17.47	9.32	73.21	(1), (rac)
19.74	25.99	15.56	10.43	74.01	(1), (rac)
0.00	25.51	12.76	12.76	74.49	(rac)
19.98	26.95	10.78	16.17	73.05	(2), (rac)
38.20	27.35	8.45	18.90	72.65	(2), (rac)
69.94	24.24	3.64	20.60	75.76	(2), (rac)
80.08	23.28	2.32	20.96	76.72	(2), (rac)
89.90	22.15	1.12	21.03	77.85	(2), (rac)
100.00	20.31	0.00	20.31	79.69	(2)
		$T = 308$ K			
100.00	24.64	24.64	0.00	75.36	(1)
38.08	32.72	22.59	10.13	67.28	(1), (rac)
0.00	30.39	15.20	15.20	69.61	(rac)
38.10	33.36	10.32	23.04	66.64	(2), (rac)
100.00	24.24	0.00	24.24	75.76	(2)

Table 4. Mass Fraction Solubility (w_i) of (*S*)-Mandelic Acid (1) and (*R*)-Mandelic Acid (2) in (*S*)-Butyl Lactate (5) at Different Enantiomeric Excesses (ee) [ee = $|w_1 - w_2|/(w_1 + w_2)$] and Temperatures as Well as Identity of Solid Phases (sp) in Equilibrium ((rac) = Racemic Mandelic Acid)

100 ee	100 ($w_1 + w_2$)	100 w_1	100 w_2	100 w_5	sp
		$T = 273$ K			
100.00	12.72	12.72	0.00	87.28	(1)
38.00	17.28	11.92	5.36	82.72	(1), (rac)
0.00	15.05	7.53	7.53	84.95	(rac)
38.00	17.45	5.41	12.04	82.55	(2), (rac)
100.00	12.63	0.00	12.63	87.37	(2)
		$T = 278$ K			
100.00	13.23	13.23	0.00	86.77	(1)
38.5	18.83	13.04	5.79	81.17	(1), (rac)
0.24	16.94	8.45	8.49	83.04	(2), (rac)
38.44	19.00	5.85	13.15	81.00	(2), (rac)
100.00	13.23	0.00	13.23	86.77	(2)
		$T = 288$ K			
100.00	15.28	15.28	0.00	84.72	(1)
38.28	21.00	14.52	6.48	79.00	(1), (rac)
0.00	19.34	9.67	9.67	80.66	(rac)
38.36	21.23	6.54	14.69	78.77	(2), (rac)
100.00	15.01	0.00	15.01	84.99	(2)
		$T = 298$ K			
100.00	16.90	16.90	0.00	83.10	(1)
84.00	19.17	17.64	1.53	80.83	(1), (rac)
74.48	20.43	17.82	2.61	79.57	(1), (rac)
68.00	21.36	17.94	3.42	78.64	(1), (rac)
48.00	23.39	17.31	6.08	76.61	(1), (rac)
46.98	24.06	17.68	6.38	75.94	(1), (rac)
45.90	23.89	17.43	6.46	76.11	(1), (rac)
38.08	23.23	16.04	7.19	76.77	(1), (rac)
24.92	24.47	15.28	9.19	75.53	(1), (rac)
0.00	21.00	10.50	10.50	79.00	(rac)
38.10	23.00	7.12	15.88	77.00	(2), (rac)
45.90	23.35	6.32	17.03	76.65	(2), (rac)
46.98	23.33	6.18	17.15	76.67	(2), (rac)
48.34	22.71	5.87	16.84	77.29	(2), (rac)
67.78	20.88	3.36	17.52	79.12	(2), (rac)
74.48	19.79	2.53	17.26	80.21	(2), (rac)
83.62	18.85	1.54	17.31	81.15	(2), (rac)
100.00	16.64	0.00	16.64	83.36	(2)
		$T = 308$ K			
100.00	20.50	20.50	0.00	79.50	(1)
38.58	27.36	18.96	8.40	72.64	(1), (rac)
0.00	26.31	13.16	13.16	73.69	(rac)
38.46	27.28	8.39	18.89	72.72	(2), (rac)
100.00	20.51	0.00	20.51	79.49	(2)
		$T = 318$ K			
100.00	22.29	22.29	0.00	77.71	(1)
37.76	30.90	21.28	9.62	69.10	(1), (rac)
0.00	28.44	14.22	14.22	71.56	(rac)
38.10	30.90	9.56	21.34	72.72	(2), (rac)
100.00	22.29	0.00	22.29	77.71	(2)

the racemic compound and the enantiomers from the crystal lattice analysis by XRPD. These results show clearly that the solubility isotherms in all the phase diagrams are of the typical shape of racemic compound-forming systems. The liquid phase is in equilibrium with the subsequent solid phase of the crystalline enantiomer for ratios of the enantiomers ranging between 0 to 0.31 and 0.69 to 1.0 (Figure 1, left upper corner, dashed tie lines), while ratios of 0.31 to 0.69 of the enantiomers in the liquid phase are in equilibrium with the crystalline racemic compound (Figure 1, left upper corner, dotted tie lines). The eutectic composition of the mandelic acid enantiomers remains unchanged (solid lines, Figure 1) compared to the previously studied case of water as solvent and also to the binary phase diagram (0.31/0.69 or 0.69/0.31).[7−10]

It is evident that in all the ternary systems investigated the solubilities of pure enantiomers, the racemate, and the eutectic mixtures increase with increasing temperature. To evaluate the effect of increasing and decreasing chain length on solubilities, the chiral solvents (*S*)-methyl lactate, (*S*)-ethyl lactate,[6] (*S*)-propyl lactate, and (*S*)-butyl lactate were taken into consideration. From Figures 1, 2, and 3, it can be concluded that the mandelic acid solubility is higher in (*S*)-methyl lactate while it decreases with an increase in the solvent molecule chain length from (*S*)-methyl lactate to (*S*)-butyl lactate. Yalkowsky et al.[11] similarly demonstrated that the solubility of alkyl *p*-aminobenzoates (esters) in water decreased as the chain length of the ester is increased. In fact, they proposed that solubility decreases per methylene unit; i.e., the solubility values for methyl, ethyl, propyl, and butyl esters decrease along these homologous series. A similar effect has been observed in this work. For instance, considering the isotherm at 298 K, the solubilities in mass fractions for (*S*)-mandelic acid in (*S*)-methyl lactate, (*S*)-propyl lactate, and (*S*)-butyl lactate were 0.2757, 0.2015, and 0.169, respectively, confirmed in Table 5 also for other temperatures.

Evaluation of Activity Coefficients

In an equilibrated condition for a saturated solution, the chemical potential of the solute in the solution is equal to the chemical potential in the pure
standard state is chosen, whe
liquid has the same temperat

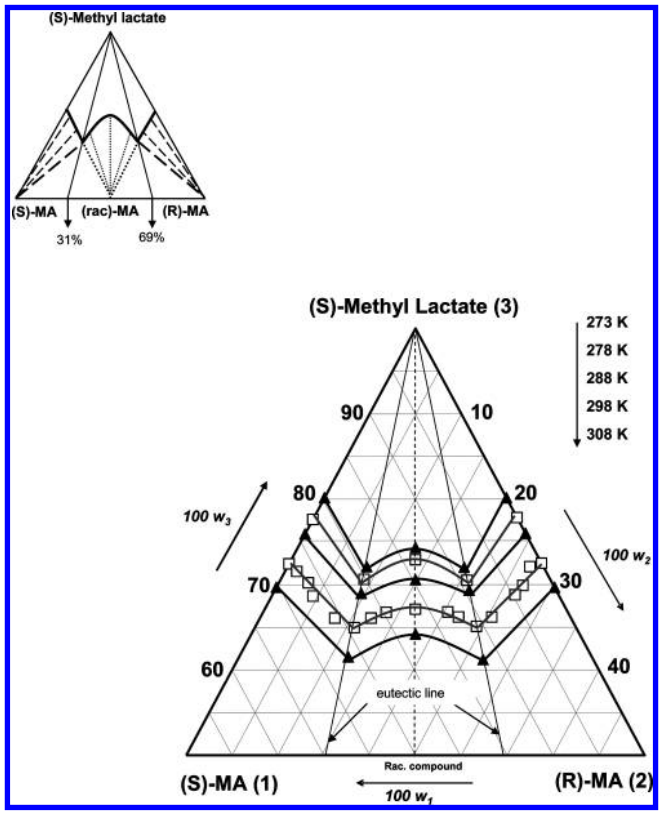

Figure 1. Ternary phase diagram of the mandelic acid enantiomers in (*S*)-methyl lactate. Just the upper section (50 %) of the phase diagram is shown for isotherms 273 K, 278 K, 288 K, 298 K, and 308 K. The isothermal lines have been added as a visualization aid, and only the marked points show measured data. Schematic overview (figure, upper left) with proposed tie lines linking the liquid phases with the corresponding solid phases.

consideration. Following classical thermodynamic approaches, the activity of the dissolved solid ($a_s = x_s\gamma$) can be expressed as[12]

$$\ln(x_s\gamma) = \frac{\Delta_{fus}H}{RT}\left(\frac{T}{T_m} - 1\right) + \frac{\Delta C_p}{R}\left(\frac{T_m}{T} - 1 - \ln\frac{T_m}{T}\right) \quad (3)$$

where T_m and $\Delta_{fus}H$ are the melting temperature of the single enantiomers and the enthalpy of fusion at $T = T_m$, respectively; R is the universal gas constant (8.314 J·mol^{-1}·K^{-1}); ($\Delta C_p = C_p^L - C_p^S$) is the difference of heat capacities of the enantiomers at the liquid and solid states; x_s is the mole fraction of the solute in the solution at saturation temperature T; and γ is the activity coefficient evaluating the real behavior of the system.

Often, instead of eq 3, the simplified form of the Schröder−van Laar equation (eq 4) is applied neglecting the contribution of the heat capacity terms as the heat capacities for the liquid and solid compensate each other. The simplified Schröder−van Laar equation for the determination of the liquidus curve is given by[13]

$$\ln x_s\gamma = \frac{\Delta_{fus}H}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) \quad (4)$$

The enthalpy of fusion ($\Delta_{fus}H = 24.5$ kJ·mol^{-1}) and the melting temperature ($T_m = 404.65$ K) of (*S*)-mandelic acid have been used in this study as determined by Lorenz et al.[8] Ideal

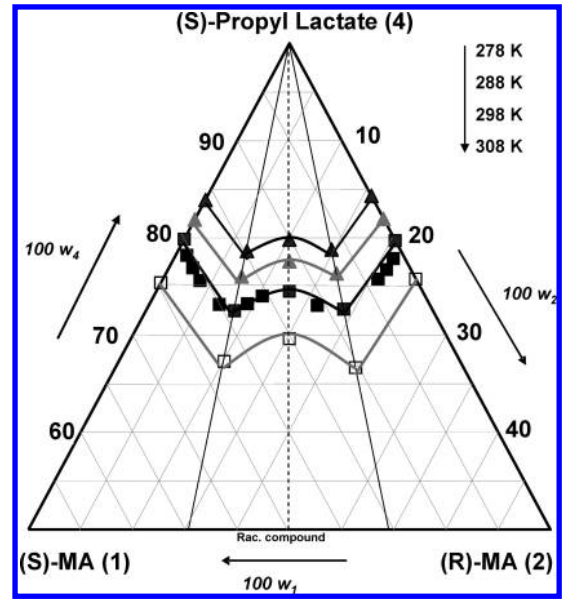

Figure 2. Ternary phase diagram of the mandelic acid enantiomers in (*S*)-propyl lactate. Just the upper section (50 %) of the phase diagram is shown for isotherms 278 K, 288 K, 298 K, and 308 K. The isothermal lines have been added as a visualization aid and only the marked points show measured data.

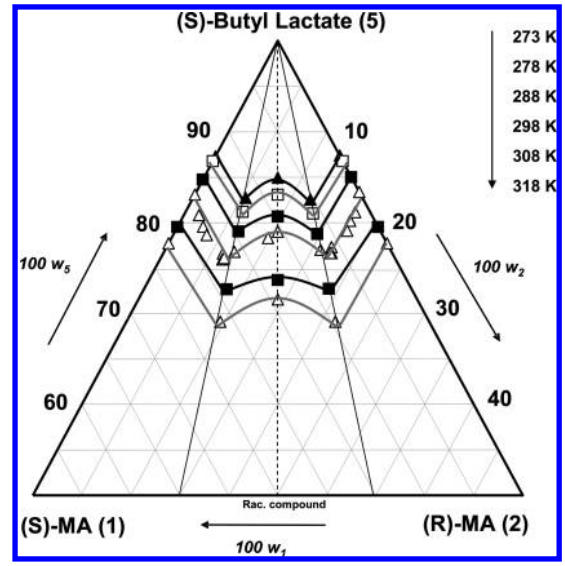

Figure 3. Ternary phase diagram of the mandelic acid enantiomers in (*S*)-butyl lactate. Just the upper section (50 %) of the phase diagram is shown for isotherms 273 K, 278 K, 288 K, 298 K, 308 K, and 318 K. The isothermal lines have been added as a visualization aid, and only the marked points show measured data.

solubilities could be calculated by using the simplified Schröder−van Laar equation (eq 4) setting the activity coefficient ($\gamma = 1$). The activity coefficient for a real solution can be determined by comparing the ideal and the experimentally observed solubility data.

The activity coefficients estimated from the experimentally determined solubility data are compiled in Table 5. Figure 4 illustrates the natural logarithm of the activity coefficients derived for (*S*)-mandelic acid in (*S*)-methyl lactate, (*S*)-ethyl lactate, (*S*)-propyl lactate, and (*S*)-butyl lactate as a function of inverse temperature. As can be seen, there is a clear trend in the activity coefficients derive
and are highest for (*S*)-butyl
lactate, (*S*)-ethyl lactate, and

Table 5. Summary of Solubilities and Activity Coefficients for (*S*)-Mandelic Acid

	solubilities in mass fractions				activity coefficients			
	T/K				*T*/K			
solvents	278	288	298	308	278	288	298	308
(*S*)-methyl lactate	0.2237	0.2409	0.2757	0.3033	0.22134	0.29512	0.35904	0.44547
(*S*)-ethyl lactate	0.1830	0.2150	0.2517	0.2790	0.24612	0.30030	0.35834	0.44262
(*S*)-propyl lactate	0.1610	0.1811	0.2015	0.2464	0.25526	0.32686	0.41281	0.46240
(*S*)-butyl lactate	0.1323	0.1528	0.1690	0.2050	0.28545	0.35667	0.45411	0.51516

temperatures, the trend is a bit altered between the activity coefficients for (*S*)-methyl lactate and (*S*)-ethyl lactate since there are slight differences in their solubility data.

Conclusions

The solid−liquid equilibria of mandelic acid in three chiral solvents, (*S*)-methyl lactate, (*S*)-propyl lactate, and (*S*)-butyl lactate, were studied. A set of solubility data in the ternary systems have been presented. The temperature dependence of the solubility of the mandelic acid species in the investigated chiral solvents is strongly pronounced. On the basis of the derived ternary solubility phase diagram, mandelic acid in the (*S*)-methyl lactate, (*S*)-propyl lactate, and (*S*)-butyl lactate system is clearly verified as a racemic compound-forming system. The measured ternary solubility phase diagrams for all chiral systems applied exhibited symmetric behavior with respect to the thermodynamic properties, which means that there was no measurable chiral recognition in the liquid state between the chiral solute and the chiral solvent molecules. This clearly shows that the chain length of the chiral solvents investigated in this work had no quantifiable enantioselective effect on solution thermodynamics of the chiral mandelic acid system. The natural logarithm of the activity coefficients derived from the solubility data for the studied chiral solvents decreases with the inverse of temperature.

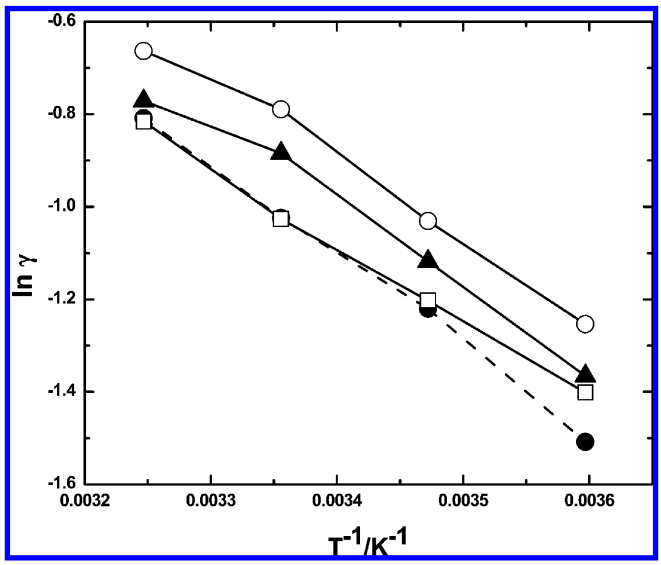

Figure 4. Plot of ln γ vs $1/T$ of (*S*)-mandelic acid (1) in ○, (*S*)-butyl lactate; ▲, (*S*)-propyl lactate; □, (*S*)-ethyl lactate*; and ●, (*S*)-methyl lactate between (278 and 308) K. *, solubility data taken from a previous article.[6]

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