Solid−Liquid Equilibria of *N*-Methylephedrine Enantiomers and Their Mixtures in Three Chiral Solvents Distinguished by Chain Length

Samuel Kofi Tulashie,[†] Heike Lorenz,*[,†] and Andreas Seidel-Morgenstern[†,‡]

Max Planck Institute for Dynamics of Complex Technical Systems, Sandtorstrasse 1, D-39106 Magdeburg, Germany, and Otto von Guericke University, Magdeburg, Germany

Solubility equilibria of the chiral *N*-methylephedrine species in three chiral solvents, (*S*)-methyl lactate, (*S*)-propyl lactate, and (*S*)-butyl lactate, have systematically been studied. Solubility measurements were performed for enantiomeric compositions ranging from 1:1 mixtures to the pure enantiomer and at temperatures between (273 and 298) K. The influence of increasing chain length of the chiral solvents on solubility has been evaluated.

Introduction

Chemical synthesis of chiral substances provides usually 1:1 mixtures of the two enantiomers that are usually known as racemates or racemic mixtures.[1] Mostly the enantiomer with the desired characteristics has to be retrieved subsequently in pure form. For the pharmaceutical industry, the manufacture of the so-called optically pure substances is of particular significance. In our recent papers, it was already mentioned that direct enantioselective crystallization from solution is acknowledged to be a possible way for the separation of chiral systems.[2,3] Since in our previous paper[3] (*S*)-ethyl lactate and (2*R*,3*R*)-diethyl tartrate have been studied to determine and analyze the solid−liquid phase equilibria of *N*-methylephedrine enantiomers, in this work we report solubilities in three chiral solvents to evaluate the influence of chain length on the solubility of chiral *N*-methylephedrine.

N-Methylephedrine as a chosen model system belongs to the class of ephedrines. Ephedrines are prospective central nervous stimulant drugs that are extensively employed in many pharmaceutical preparations.[4] A significant plant species of Ephedra—*Ephedra sinica* (Ma Huang)—has long ago been used in traditional Chinese herbal medicine for diaphoretic, antiasthmatic, and diuretic effects.[5] The main ingredients of the alkaloids in Ma Huang are ephedrine-type compounds, for instance, (−)-ephedrine, (+)-pseudoephedrine, (−)-*N*-methylephedrine, and homologous compounds.[5] In modern medicine, it is being used for the treatment of asthma and bronchitis and also for the alleviation of symptoms associated with colds and the flu.[6,7]

The present work is concerned with the systematic determination of the ternary solid−liquid phase equilibria of *N*-methylephedrine enantiomers in the three chiral solvents (*S*)-(−)-methyl lactate, (*S*)-(−)-propyl lactate, and (*S*)-(−)-butyl lactate in a wide temperature range. The ternary solubility phase diagram will be derived from the measured data of the results for the different mixtures of the enantiomers. Predicted ideal solubilities of *N*-methylephedrine were compared with the obtained experimental data in (*S*)-butyl lactate.

* Corresponding author. Phone: (0049) 391 6110 293. Fax: (0049) 391 6110 524. E-mail: lorenz@mpi-magdeburg.mpg.de.
[†] Max Planck Institute for Dynamics of Complex Technical Systems.
[‡] Otto von Guericke University.

Experimental Section

Materials. (1*S*,2*R*)-(+)-*N*-Methylephedrine ((1*S*,2*R*)-2-(dimethylamino)-1-phenylpropan-1-ol, CAS no. 42151-56-4) (1) and (1*R*,2*S*)-(−)-*N*-methylephedrine ((1*R*,2*S*)-2-(dimethylamino)-1-phenylpropan-1-ol, CAS no. 552-79-4) (2) were purchased from Sigma-Aldrich with a mass fraction purity 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) obtained 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.

Solubility Measurements. A classical isothermal method was applied for the determination of solubilities at temperatures in the range between (273 and 298) K in (*S*)-(−)-methyl lactate, (*S*)-(−)-propyl lactate, and (*S*)-(−)-butyl lactate. The method applied to study solubility equilibria was published in our previous article.[3] It represents an isothermal procedure where a mixture consisting of 5 mL of solvent and a considerable excess of solid phase (weighed with an analytical balance (resolution of balance ± 0.1 mg)) was put into a thermostatted apparatus (thermostat, RC6 CP Lauda, Germany), which was agitated by a magnetic stirrer and kept at isothermal conditions (with an uncertainty: ± 0.01 K) until equilibrium was established. Afterward, the solid and liquid phases were separated and analyzed. The liquid phase compositions were evaluated by means of HPLC after dilution with 2-propanol. Also, the solid phases of all samples were analyzed by X-ray Powder Diffraction (XRPD) to check any crystalline modification (solvates and/or polymorphs) and to ensure that no new phases were formed. Equilibration times were at least 24 h, based on our previous studies on the dissolution kinetics.[3]

The mass fraction solubility of a component *i* (w_i) is given as

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$$w_i = \frac{m_i}{\sum_{i=1}^{z} m_i} \quad (1)$$

with m_i being the mass of the constituent *i*. In our case, the summation covers at all times the two enantiomers and either (*S*)-(−)-methyl lactate or (*S*)-(−)-propyl lactate or (*S*)-(−)-butyl lactate.

The reproducibility of the solubility measurements was studied by repeating three or four experiments under the same conditions. The measurements were conducted with the racemic mixture of *N*-methylephedrine, (1*S*,2*R*)-(+)-*N*-methylephedrine, and (1*R*,2*S*)-(−)-*N*-methylephedrine in all three chiral solvents, (*S*)-methyl lactate, (*S*)-propyl lactate, and (*S*)-butyl lactate at 298 K. The standard deviations of the solubility data (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.

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

The corresponding standard deviation (SD) analysis is summarized in Table 1. Table 1 contains only the SD for (1*S*,2*R*)-(+)-*N*-methylephedrine solubilities in the chiral solvents at 25 °C since the same measurement method was applied for the other *N*-methylephedrine species and temperatures considered. The standard deviations for (1*R*,2*S*)-(−)-*N*-methylephedrine and racemic *N*-methylephedrine solubilities are in the same range.

Table 1. Error Analysis of Solubility Determination Procedure[a]

	(1*S*,2*R*)-(+)-*N*-methylephedrine in (*S*)-methyl lactate	
T/K	*n*	SD
298	3	0.34
	(1*S*,2*R*)-(+)-*N*-methylephedrine in (*S*)-propyl lactate	
T/K	*n*	SD
298	4	0.54
	(1*S*,2*R*)-(+)-*N*-methylephedrine in (*S*)-butyl lactate	
T/K	*n*	SD
298	4	0.28

[a] Standard deviation, SD, according to eq 2; number of experiments *n*.

Table 2. Mass Fraction Solubility w_i of (1*S*,2*R*)-(+)-*N*-Methylephedrine (1) and (1*R*,2*S*)-(−)-*N*-Methylephedrine (2) in (*S*)-Methyl Lactate (3) at Different Enantiomeric Excesses ee [ee = $|w_1 - w_2|/(w_1 + w_2)$] in the Liquid Phase and for Different Temperatures as well as Identity of Solid Phases (sp) in Equilibrium

100 ee	100 ($w_1 + w_2$)	100 w_1	100 w_2	100 w_3	sp
		T = 273 K			
100.00	13.32	13.32	0.00	86.68	(1)
40.46	18.50	12.99	5.51	81.50	(1)
1.19	23.87	12.08	11.79	76.13	(1), (2)
42.22	18.80	5.43	13.37	81.20	(2)
100.00	12.99	0.00	12.99	87.01	(2)
		T = 278 K			
100.00	16.50	16.50	0.00	83.50	(1)
46.40	21.12	15.46	5.66	78.88	(1)
0.00	29.03	14.52	14.52	70.97	(1), (2)
46.84	21.22	5.64	15.58	78.78	(2)
100.00	16.56	0.00	16.56	83.44	(2)
		T = 283 K			
100.00	18.74	18.74	0.00	81.26	(1)
46.50	23.45	17.18	6.27	76.55	(1)
0.00	31.42	15.71	15.71	68.58	(1), (2)
47.00	22.98	6.09	16.89	77.02	(2)
100.00	18.79	0.00	18.79	81.21	(2)
		T = 288 K			
100.00	21.00	21.00	0.00	79.00	(1)
46.70	26.60	19.51	7.09	73.40	(1)
0.00	36.20	18.10	18.10	63.80	(1), (2)
47.70	26.40	6.90	19.50	73.60	(2)
100.00	21.15	0.00	21.15	78.85	(2)
		T = 293 K			
100.00	23.04	23.04	0.00	76.96	(1)
42.88	31.02	22.16	8.86	68.98	(1)
0.22	40.36	20.22	20.12	59.64	(1), (2)
45.94	30.95	8.37	22.58	69.05	(2)
100.00	23.11	0.00	23.11	76.89	(2)
		T = 298 K			
100.00	24.41	24.41	0.00	75.59	(1)
39.09	35.06	24.38	10.68	64.94	(1)
0.97	45.16	22.80	22.36	54.84	(1), (2)
39.40	35.06	10.62	24.44	64.94	(2)
100.00	24.50	0.00	24.50	75.50	(2)

Table 3. Mass Fraction Solubility w_i of (1*S*,2*R*)-(+)-*N*-Methylephedrine (1) and (1*R*,2*S*)-(−)-*N*-Methylephedrine (2) in (*S*)-Propyl Lactate (4) at Different Enantiomeric Excesses ee [ee = $|w_1 - w_2|/(w_1 + w_2)$] in the Liquid Phase and for Different Temperatures as well as Identity of Solid Phases (sp) in Equilibrium

100 ee	100 ($w_1 + w_2$)	100 w_1	100 w_2	100 w_3	sp
		T = 273 K			
100.00	11.19	11.19	0.00	88.81	(1)
46.57	14.68	10.76	3.92	85.32	(1)
1.19	22.25	11.26	10.99	77.75	(1), (2)
47.01	16.15	4.28	11.87	83.85	(2)
100.00	11.25	0.00	11.25	88.75	(2)
		T = 278 K			
100.00	14.00	14.00	0.00	86.00	(1)
46.50	19.00	13.92	5.08	81.00	(1)
0.00	26.00	13.00	13.00	74.00	(1), (2)
47.00	19.00	5.04	13.96	81.00	(2)
100.00	13.98	0.00	13.98	86.02	(2)
		T = 283 K			
100.00	15.25	15.25	0.00	84.75	(1)
50.30	19.80	14.88	4.92	80.20	(1)
0.00	27.62	13.81	13.81	72.38	(1), (2)
51.00	19.70	4.83	14.87	80.30	(2)
100.00	15.15	0.00	15.15	84.85	(2)
		T = 288 K			
100.00	17.51	17.51	0.00	82.49	(1)
39.09	23.69	16.47	7.21	76.31	(1)
0.97	30.80	15.55	15.25	69.20	(1), (2)
38.40	23.75	7.43	16.55	76.25	(2)
100.00	16.92	0.00	16.92	83.08	(2)
		T = 293 K			
100.00	19.25	19.25	0.00	80.75	(1)
39.09	26.00	18.08	7.92	74.00	(1)
0.97	34.00	17.16	16.83	66.00	(1), (2)
38.40	26.00	8.14	18.12	74.00	(2)
100.00	19.30	0.00	19.30	80.70	(2)
		T = 298 K			
100.00	20.18	20.18	0.00	79.82	(1)
38.85	28.88	20.05	8.83	71.12	(1)
0.84	39.34	19.84	19.50	56.93	(1), (2)
37.56	29.53	9.22	20.31	70.47	(2)
100.00	20.76	0.00	20.76	79.24	(2)

Results and Discussion

The XRPD patterns of the various solid phase samples correspond to the reflexes of the references. No additional or

Table 4. Mass Fraction Solubility w_i of (1*S*,2*R*)-(+)-*N*-Methylephedrine (1) and (1*R*,2*S*)-(−)-*N*-Methylephedrine (2) in (*S*)-Butyl Lactate (5) at Different Enantiomeric Excesses ee [ee = $|w_1 - w_2|/(w_1 + w_2)$] in the Liquid Phase and for Different Temperatures as well as Identity of Solid Phases (sp) in Equilibrium

100 ee	100 ($w_1 + w_2$)	100 w_1	100 w_2	100 w_3	sp
		$T = 273$ K			
100.00	10.08	10.08	0.00	89.92	(1)
46.19	13.86	10.13	3.73	86.14	(1)
0.00	19.42	9.71	9.71	80.58	(1), (2)
43.95	14.36	4.02	10.34	85.64	(2)
100.00	10.38	0.00	10.38	89.62	(2)
		$T = 278$ K			
100.00	12.61	12.61	0.00	87.39	(1)
40.00	16.93	11.85	5.08	83.07	(1)
0.00	22.00	11.00	11.00	78.00	(1), (2)
42.00	17.26	5.01	14.25	82.74	(2)
100.00	12.90	0.00	12.90	87.10	(2)
		$T = 283$ K			
100.00	13.74	13.74	0.00	86.26	(1)
52.30	17.40	13.25	4.15	82.60	(1)
0.00	25.00	12.50	12.50	75.00	(1), (2)
50.00	17.50	4.38	13.12	82.50	(2)
100.00	13.60	0.00	13.60	86.40	(2)
		$T = 288$ K			
100.00	15.26	15.26	0.00	84.74	(1)
53.70	19.89	15.29	4.60	80.11	(1)
0.00	29.26	14.63	14.63	70.74	(1), (2)
50.00	20.95	5.24	15.71	79.05	(2)
100.00	15.81	0.00	15.81	84.19	(2)
		$T = 293$ K			
100.00	17.50	17.50	0.00	82.50	(1)
46.30	23.90	17.48	6.42	76.10	(1)
0.00	32.00	16.00	16.00	68.00	(1), (2)
48.30	24.00	6.20	17.80	76.00	(2)
100.00	17.40	0.00	17.40	82.60	(2)
		$T = 298$ K			
100.00	18.60	18.60	0.00	81.40	(1)
40.50	27.07	19.02	8.05	72.93	(1)
1.43	37.18	18.85	19.33	62.82	(1), (2)
37.10	27.85	8.76	19.09	72.15	(2)
100.00	18.55	0.00	18.55	81.45	(2)

new phases (neither polymorphs nor solvates) differing from those of the pure enantiomers were identified from the results of the crystal lattice analysis by XRPD. The obtained solubility data are summarized in Tables 2, 3, and 4. Figures 1, 2, and 3 depict the derived ternary solubility phase diagrams of the *N*-methylephedrine enantiomers, in the solvents (*S*)-methyl lactate, (*S*)-propyl lactate, and (*S*)-butyl lactate, respectively. They show clearly that the solubility isotherms in all the phase diagrams correspond to the typical shape of conglomerate-type systems. The diagrams show symmetrical mirror images with respect to the racemic axis, rather than asymmetry which is possible in chiral solvents. As known from the binary phase diagram of the chiral system, *N*-methylephedrine enantiomers do not form a racemic compound but rather a common eutectic (conglomerate) system.[8] This was established by the derived ternary phase diagrams. The solubilities in all cases increase with temperature. The slope of the solubility isotherms is expressed by the solubility ratio and will be discussed later.

Moreover, to establish the effect of increasing and decreasing chain length on solubilities also (*S*)-ethyl lactate (data presented in ref 3) was taken into consideration. Figures 4 and 5 clearly depict the solubility of (1*S*,2*R*)-(+)-*N*-methylephedrine and racemic *N*-methylephedrine as a function of temperature in (*S*)-methyl lactate, (*S*)-ethyl lactate, (*S*)-propyl lactate, and (*S*)-butyl

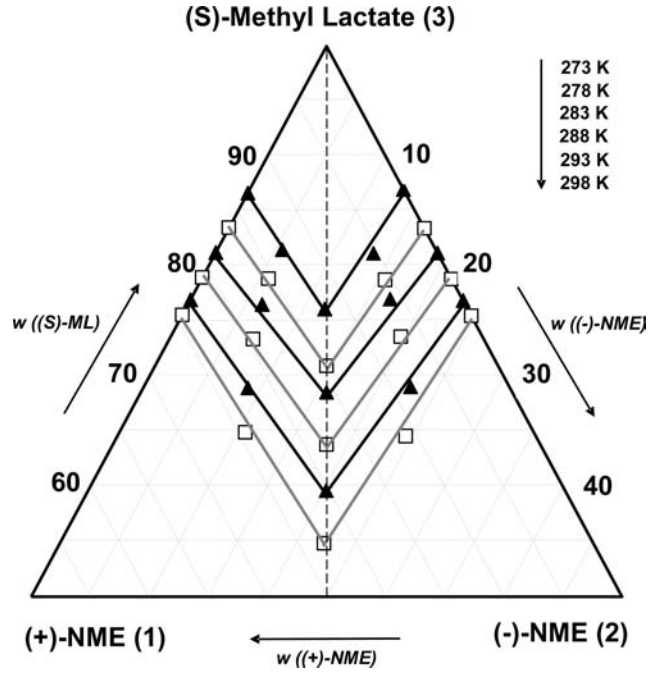

Figure 1. Ternary phase diagram of the *N*-methylephedrine enantiomers in (*S*)-methyl lactate. Just the upper section (50 %) of the phase diagram is shown for isotherms 273 K, 278 K, 283 K, 288 K, 293 K, and 298 K. The isothermal lines have been added as a visualization aid, and only the marked points show measured data.

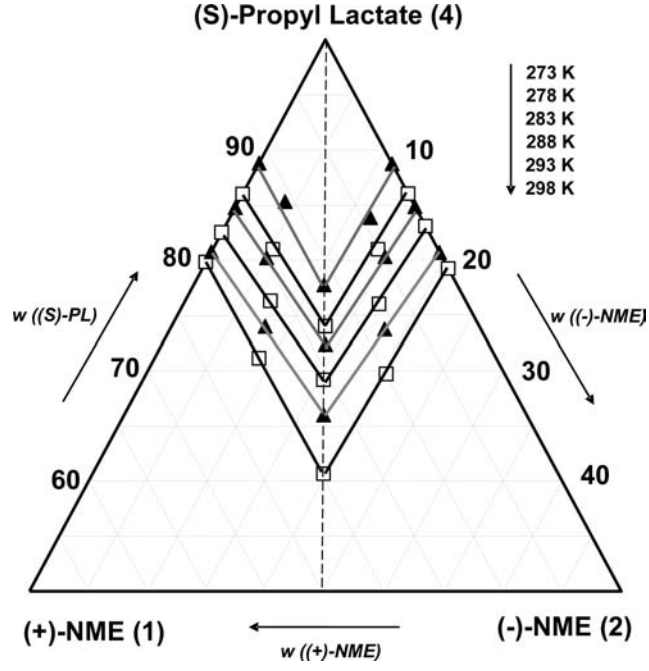

Figure 2. Ternary phase diagram of the *N*-methylephedrine enantiomers in (*S*)-propyl lactate. Just the upper section (50 %) of the phase diagram is shown for isotherms 273 K, 278 K, 283 K, 288 K, 293 K, and 298 K. The isothermal lines have been added as a visualization aid, and only the marked points show measured data.

lactate, respectively. In both figures, the solubility of *N*-methylephedrine is highest in solvent (*S*)-methyl lactate, while it decreases with an increase in solvent molecule chain length from (*S*)-methyl lactate to (*S*)-butyl lactate. Yalkowsky et al.[9] reported similar work where they demonstrated that the solubility of alkyl *p*-aminobenzoates (ester) in water is decreased as the chain length of the ester is increased. Hence, they published that solubility of the ester decreases for each methylene unit;

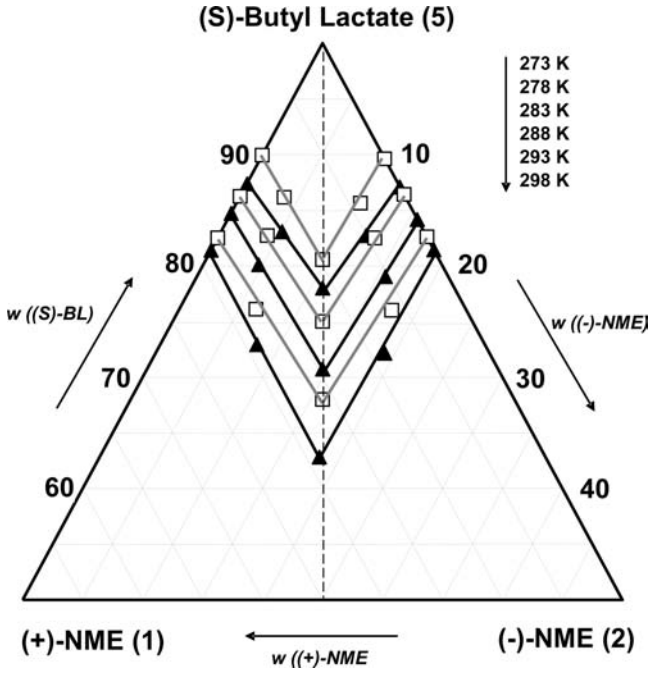

Figure 3. Ternary phase diagram of the *N*-methylephedrine enantiomers in (*S*)-butyl lactate. Just the upper section (50 %) of the phase diagram is shown for isotherms 273 K, 278 K, 283 K, 288 K, 293 K, and 298 K. The isothermal lines have been added as a visualization aid, and only the marked points show measured data.

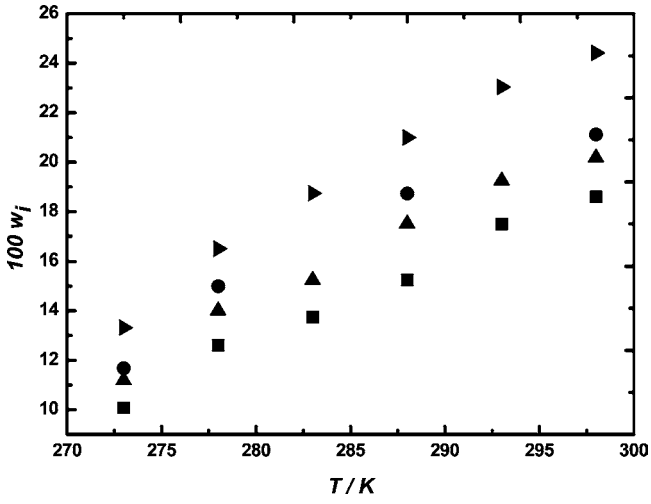

Figure 4. Solubility of (1*S*,2*R*)-(+)-*N*-methylephedrine (1) in: solid triangle pointing right, (*S*)-methyl lactate (3); ●, (*S*)-ethyl lactate (data taken from previous work);[3] ▲, (*S*)-propyl lactate (4); and ■, (*S*)-butyl lactate (5) between (273 and 298) K.

i.e., the solubility values for methyl, ethyl, propyl, and butyl esters decrease along these homologous series. A similar effect has been observed in the present work. Considering the isotherm at 25 °C for Figures 1, 2, and 3, it can be seen that the solubility data decrease from Figures 1 to 3. The decrease in solubility with increasing solvent molecule chain length can be attributed to the well-known principle of solvent−solute interactions, "like dissolves like".[10]

Relative Solubility Ratios (α_{mol} Values). The relative solubility ratio (α_{mol}) at a given temperature is defined as

$$\alpha_{mol} = \frac{x_{Racemate}}{x_{Enantiomer}} \tag{3}$$

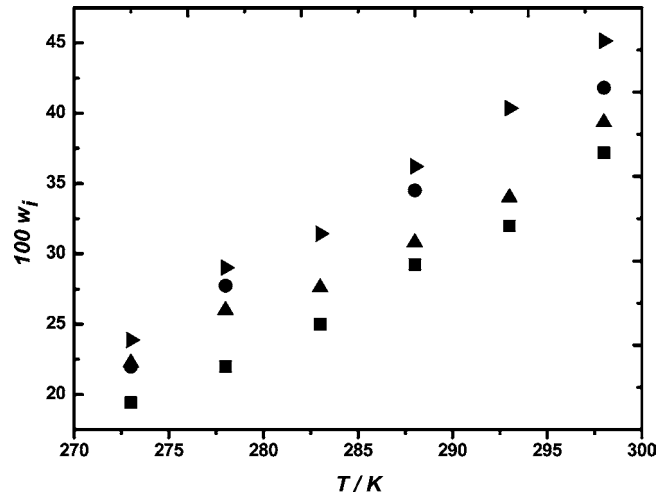

Figure 5. Solubility of racemic *N*-methylephedrine in: solid triangle pointing right, (*S*)-methyl lactate (3); ●, (*S*)-ethyl lactate (data taken from previous work);[3] ▲, (*S*)-propyl lactate (4); and ■, (*S*)-butyl lactate (5) between (273 and 298) K.

Table 5. Summary of α_{mol} of *N*-Methylephedrine in Chiral Solvents with Different Chain Lengths at Different Temperatures

solvents	α_{mol} at 273 K	α_{mol} at 278 K	α_{mol} at 288 K	α_{mol} at 298 K
(*S*)-methyl lactate	1.88	1.86	1.85	2.05
(*S*)-ethyl lactate	1.95	1.94	1.95	2.14
(*S*)-propyl lactate	2.05	1.92	1.83	2.06
(*S*)-butyl lactate	1.96	1.78	1.97	2.07

with $x_{Racemate}$ and $x_{Enantiomer}$ as the mole fraction solubilities of the racemate and the enantiomer, respectively, at that temperature. Also, the mole fraction solubility x_i is defined as

$$x_i = \frac{n_i}{\sum_{i=1}^{z} n_i} \tag{4}$$

with n_i being the molar amount of the constituent *i*. The summation covers always the two enantiomers and either (*S*)-(−)-methyl lactate or (*S*)-(−)-propyl lactate or (*S*)-(−)-butyl lactate.

Since α_{mol} is related to the slope of the metastable solubility isotherms in the phase diagram, it has a large influence on the potential productivity of a preferential crystallization.[11,12]

Table 5 gives a summary of the α_{mol} values of *N*-methylephedrine in the chiral solvents with different chain lengths for different temperatures. According to the "double solubility" rule by Meyerhoffer,[13] an ideal system should always shows α_{mol} values equal to 2. However, it is important to note that this rule is applicable only in one direction. That means, if a system behaves ideally, α_{mol} must be 2. Otherwise, if α_{mol} is found to be 2 for a system, it must not necessarily exhibit ideal behavior. For instance, the α_{mol} values derived in this work are all close to 2 (Table 5), but they do not represent ideality as illustrated in Figure 6. Figure 6 depicts the deviation of the experimentally measured solubility of the *N*-methylephedrine enantiomers in (*S*)-butyl lactate from derived ideal solubility in a temperature range between (273 and 298) K. The ideal solubilities were derived from the simplified Schröder van Laar equation (eq 5) with activity coefficient ($\gamma = 1$).

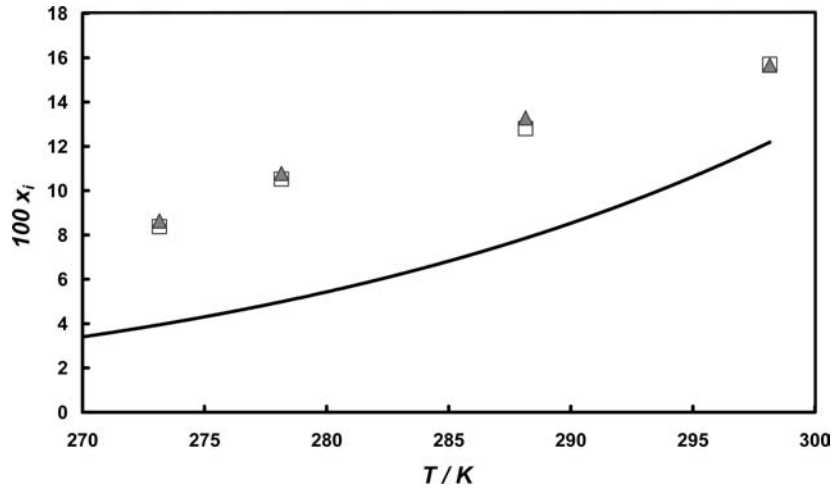

Figure 6. Experimentally measured mole fraction solubility ▲, (1*S*,2*R*)-(+)-*N*-methylephedrine (1) and □, (1*R*,2*S*)-(−)-*N*-methylephedrine (2) in (*S*)-butyl lactate (5) between (273 and 298) K compared to the ideal solubility line.

$$\ln x_s\gamma = \frac{\Delta_{fus}H}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) \quad (5)$$

where x_s is the mole fraction of the solute in the solution at saturation temperature T, i.e., the mole fraction solubility at that temperature. The enthalpy of fusion $\Delta_{fus}H = 30.531$ kJ·mol^{-1} and the melting temperature $T_m = 359.75$ K, for the *N*-methylephedrine enantiomers, have been applied in this study as determined by Wang et al.[8]

The determined experimental data in all solvents are clearly higher than the ideal solubilities of the *N*-methylephedrine enantiomers. Therefore, considerable attractive forces exist between (*S*)-(−)-methyl lactate, (*S*)-(−)-propyl lactate, (*S*)-(−)-butyl lactate, and *N*-methylephedrine molecules. A quantitative evaluation of this effect is the subject of further work.

Conclusions

We studied the solid−liquid phase equilibria of the conglomerate-forming system *N*-methylephedrine in the three chiral solvents (*S*)-methyl lactate, (*S*)-propyl lactate, and (*S*)-butyl lactate. The solubility data were measured and used to derive the ternary solubility phase diagrams. No chiral recognition was observed in terms of solubility equilibria for the three chiral solvents and chiral *N*-methylephedrine. Therefore, the ternary solubility phase diagrams are characterized by symmetric behavior. This implies that there was no quantifiable chiral discrimination in the liquid phase between the chiral solute and the chiral solvent molecules. This shows that the variation of the chain length of the chiral solvents studied in this work had no influence on chiral recognition of the chiral *N*-methylephedrine.

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