Solubility of Chiral Threonine Species in Water/Ethanol Mixtures

Dragomir Sapoundjiev,*,† Heike Lorenz,† and Andreas Seidel-Morgenstern†,‡

Max-Planck-Institut fuer Dynamik Komplexer Technischer Systeme, Sandtorstrasse 1, D-39106 Magdeburg, Germany, and Otto-von-Guericke-Universitaet, PSF 4120, D-39016 Magdeburg, Germany

Solubility equilibria of threonine in water/ethanol mixtures were measured in the temperature range between (10 and 46) °C. Threonine exhibits good solubility in water and is hardly soluble in ethanol. The ternary-phase diagram of the threonine enantiomers in the solvents used reveals the presence of a conglomerate-forming system. Threonine shows ideal solution behavior (i.e., heterochiral interactions do not occur in solution). To correlate the measured data with regard to temperature and solvent composition, a simple empirical approach is proposed. The correlation presented is of interest for calculation of solubilities when designing crystallization or chromatography-based processes to separate the threonine enantiomers.

Introduction

Chemical synthesis of chiral substances provides usually 50:50 mixtures of the two enantiomers[1] that are generally called racemates or racemic mixtures. Often the enantiomer with the desired characteristics has to be retrieved subsequently in pure form. For the pharmaceutical industry, the production of the so-called optically pure substances is of particular importance. Crystallization presents a feasible approach for separation and purification of mixtures offering a comparably cheaper alternative to chromatographic techniques that are frequently used. In a crystallization process, different phases are in contact with each other making knowledge of the corresponding phase equilibria mandatory.[2] A literature survey on available solubility data of organic fine chemicals reveals existing deficits.

The amino acid threonine occurs in nature as the (2*S*,3*R*)-form designated as L-threonine. The (2*R*,3*S*)-form (D-threonine), the racemic mixture, as well as other isomers (allothreonine) are available from the chemical synthesis. Threonine was the first amino acid recognized as an essential amino acid; the recommended daily dose is 0.5 g. It can be found in proteins of eggs, meat, and milk in contents up to 5 % and in flour, rice, potatoes, legumes, and cabbage in contents of (3 to 4) %. It is generally required for growth, uric acid metabolism, and the immune system. Threonine is an important component in the protein metabolism chain and contributes to the formation of enzymes and hormones. It is included in the formation of immunglobines and antibodies.[3−5]

Solubility data of threonine (thr) are limited to discrete measurements of the racemic mixture (DL-thr) and the enantiomer (L-thr) in water.[6−8] Profir and Matsuoka[9] provided polynomials to approximate the solubility curves of both characteristic species in water.

Chromatographic separations of amino acids are often performed on chiral columns with water/alcohol (methanol, ethanol, or 2-propanol) mixtures as solvent.[10,11] Since threonine is only sparingly soluble in alcohols, problems with recrystallization on the column might occur. Thus, solubility data are required (e.g., in water/ethanol mixtures).

* Corresponding author. E-mail: dragomir@mpi-magdeburg.mpg.de. Tel: +49 391 6110 287. Fax: +49 391 6110 635.
† Max-Planck-Institut fuer Dynamik Komplexer Technischer Systeme.
‡ Otto-von-Guericke-Universitaet.

On that basis, the present article is concerned with a systematic study of solubility equilibria in the system L-thr/D-thr/water/ethanol mixtures in the temperature range between (10 and 46) °C. The ternary solubility diagrams are constructed as a function of the solvent composition. A simplified empirical approach is proposed to correlate the measured solubility data.

Experimental Section

Materials. DL-Threonine und D-threonine were obtained from Aldrich with purity > 98 %. L-Threonine was provided by Merck with purity > 99 %. The water used was deionized, and ethanol was of HPLC grade (Merck).

Apparatus and Procedure. Solubility data of threonine in water/ethanol mixtures were obtained in a temperature range between (10 and 46) °C. The method applied to study solubility equilibria was published in a previous article.[12] It represents an isothermal procedure where a vial containing the mixture of the solid and the solvent is put into a thermostated glass apparatus and electromagnetically stirred at constant temperature (within ± 0.05 K) until equilibrium is established. Subsequently, the solid and liquid phases are separated and analyzed. The total concentration of the saturated mother liquor (corresponding to the solubility of the given enantiomeric mixture at the temperature used) was determined gravimetrically. For the enantiomeric composition in both phases, chiral HPLC was employed (column: 150 × 4.6 mm Chirobiotic T, 5 μm, Astec/USA; eluent: water/ethanol = 40/60 v/v).

The time required to attain equilibrium was studied for DL-thr in a water/ethanol mixture (40/60 v/v) at 20 °C. For this, at certain time intervals during the solubility measurements liquid-phase samples were taken, and the concentrations were determined gravimetrically. The results show that equilibrium in the solution was already attained after 5 min. However, to guarantee equilibration, the time was fixed to at least 4 h.

The reproducibility of the solubility measurements was studied carrying out 12 experiments under the same conditions. The measurements were performed with DL-thr in a water/ethanol mixture (60/40 v/v) as solvent at 20 °C. The standard deviation [$SD = \sqrt{\sum(S_i^2 - n\bar{S})/(n-1)}$] was estimated to be 0.08, thus an error of 2.5 % must be taken into account. In addition, the liquid-phase concentration was determined by HPLC under

10.1021/je060053h CCC: $30.25
Published on Web 08/15/2006

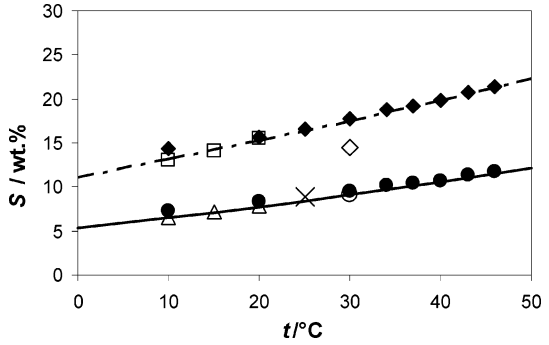

Figure 1. Solubility data of L-thr and DL-thr in water (gravimetrical determination). Literature data are also considered: ●, ◆, L-/DL-thr, this work; △, □, L-/DL-thr, ref 6; ○, ◇, L-/DL-thr, ref 7; ×, L-thr, ref 8; solid line/dashed line, L-/DL-thr, ref 9.

Table 1. Solubility Data (in wt %) of L-thr and DL-thr in Water/ Ethanol Mixtures Measured by Gravimetry

t	20/80 v/v	40/60 v/v		60/40 v/v		80/20 v/v		100/0 v/v	
°C	DL-thr	DL-thr	L-thr	DL-thr	L-thr	DL-thr	L-thr	DL-thr	L-thr
10		0.76	0.37		1.01	6.18	2.90	14.34	7.34
15				2.82					
20	0.28	1.13	0.51	3.18	1.46	7.80	3.70	15.69	8.31
25				3.54				16.62	
30		1.51	0.67	4.18	1.92	9.60	4.57	17.70	9.49
34								18.74	10.12
37								19.70	10.38
40	0.35	2.01	0.73	5.55	2.55	11.56	5.60	19.84	10.78
43								20.79	11.29
46								21.38	11.79

the conditions mentioned above. These data served only for comparison.

The solubility, *S*, expressed in weight percentage is given as

$$S = (m_{\text{solute}}/m_{\text{solution}})\cdot 100, \text{ wt \%} \quad (1)$$

where m_{solute} and m_{solution} are the masses of the solute and the entire solution, respectively. Alternatively, the solubility, S_n, can be expressed in mole fraction according to

$$S_n = n_{\text{solute}}/(n_{\text{solute}} + n_{\text{solvent}}) \quad (1a)$$

with n_{solute} and n_{solvent} as the number of moles of the solute and solvent, respectively.

Results and Discussion

Solubility of Pure Enantiomers and Racemate in Water. Threonine was identified to be a conglomerate-forming chiral system.[13] Therefore, the solubility study was mainly focused on the two characteristic species—enantiomer and racemic mixture. Figure 1 shows the solubilities of L-thr and DL-thr in water measured gravimetrically in this study compared to literature values. The obtained data are given in Table 1. As can be seen, the solubilities in the literature are limited to discrete measurements for both the enantiomer and the racemic mixture. Profir and Matsuoka[9] used linear functions to describe the solubilities. The increase in solubility for the enantiomer and the racemic mixture in the temperature region studied (10 to 46 °C) is 4.5 wt % and 7 wt %, respectively. As expected, the higher solubilities can be assigned to the racemic mixture. The maximum deviation between the results presented here and data from Shiraiwa et al.[6] and Profir and Matsuoka[9] appears at the lowest temperature (10 °C), where the difference for the racemic mixture is approximately 9.5 % and for the enantiomer is 12 %. The agreement with the polynomials of Profir and Matsuoka[9] proposed for the description of the solubility is excellent at temperatures > 25 °C (Figure 1). The data reported by Jacques and Gabard[7] and Nozaki and Tanford[8] refer only to a few specific conditions.

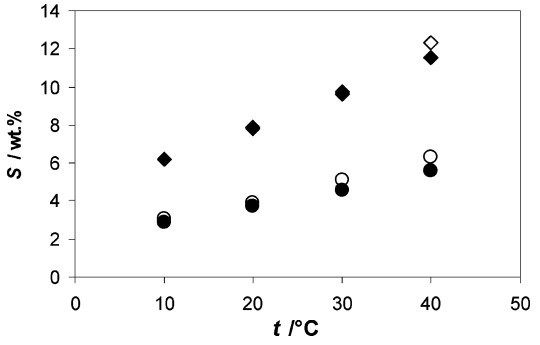

Figure 2. Comparison between gravimetrically and HPLC based solubility determinations in water as solvent: ◇, DL-thr, HPLC; ◆, DL-thr, gravimetry; ○, L-thr, HPLC; ●, L-thr, gravimetry.

Table 2. Solubility Data (in wt %) of L-thr and DL-thr in Water/ Ethanol Mixtures Measured by HPLC

t	40/60 v/v		60/40 v/v		80/20 v/v		100/0 v/v	
°C	DL-thr	L-thr	DL-thr	L-thr	DL-thr	L-thr	DL-thr	L-thr
10	1.00	0.59		1.18	6.16	3.07	14.45	7.74
20		0.79	2.97	1.63	7.88	3.93	16.32	9.03
30	1.68	0.91	4.20	2.06	9.76	5.10	18.24	10.70
40	2.13	1.23	5.86	2.60	12.33	6.29	21.88	12.18

Table 3. Comparison of Solubility Measurements for L-thr and D-thr (gravimetrically analyzed)

t	*S*/wt %	
°C	L-thr	D-thr
10	7.34	7.29
20	8.31	8.34
30	9.49	9.52
40	10.78	10.71

A comparison between the experimentally obtained and the calculated ideal solubility values can be used to derive activity coefficients, which could be applied to predict solubilities.[12] Unfortunately, due to the thermal decomposition of L-thr and DL-thr, it is impossible to obtain the melting temperature and melting enthalpy data required to predict ideal solubilities. Consequently, an estimation of activity coefficients is not feasible.

The measurements obtained by means of HPLC are summarized in Table 2. Figure 2 considers a comparison of solubility data in water measured by gravimetry and HPLC. Obviously, both methods provide similar results. The solubilities determined based on HPLC are negligibly higher than the gravimetrical data. That difference becomes slightly larger with increasing temperature. The average deviation [$\text{AD} = \sum_i^n [100\cdot(S_i^{\text{HPLC}} - \bar{S}_i)/\bar{S}_i]$] was estimated to be 5.5 %. Similar trends are found for all other solvent compositions, indicating a constant deviation between both analytical techniques. An evaluation of different analytical methods (IR spectroscopy, density measurements, refractometry, gravimetry, and HPLC) applied for solubility determinations of nitramines is given by Teipel et al.[14] For the temperature range (20 to 80) °C, the average deviation among the different approaches is reported to be 15 % at lower temperatures and 20 % at higher temperatures.

The symmetry in the physical—chemical characteristics of the two enantiomers is corroborated when considering their solubilities (Table 3). Both data sets can be regarded as identical within the error range.

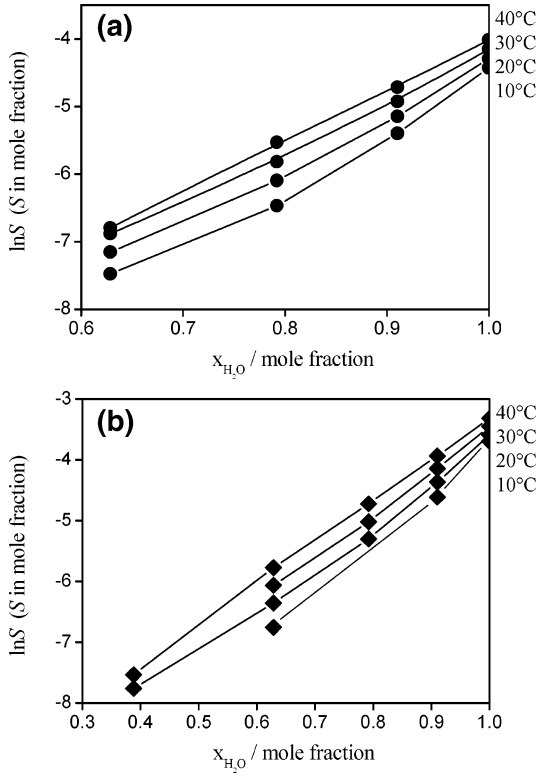

Figure 3. Logarithmic representation of solubility isotherms of L-thr (●) and DL-thr (◆) in water/ethanol mixtures as function of solvent composition.

Impact of the Solvent Composition on Solubility. The complete data set obtained for different water/ethanol mixtures as solvent is summarized in Table 1. The water content in the solvent ranged from (20 to 100) vol %. In Figure 3, the solubilities of L-thr (Figure 3a) and DL-thr (Figure 3b) are presented at different temperatures as a function of the solvent composition. Since threonine belongs to the polar hydrophilic amino acids, it is well-soluble in water and hardly soluble in ethanol. The hydroxyl group of the threonine molecule is mainly responsible for its polarity and reactivity. Figure 3 shows how the solubility of the L- and DL-species is influenced by the fraction of ethanol. With decreasing water/ethanol ratio, the solubility isotherms decline significantly. Almost linear functions are obtained for the logarithmic representation of the solubilities. Moreover, the linear approximation indicates a similar slope of the different curves for both threonine species. The similar gradients can be attributed to the temperature independence of the intermolecular interactions between solvent and solute and to the lack of heterochiral interactions (one enantiomer is not influenced by the presence of the other enantiomer in solution). The obtained solubility behavior of threonine in water/ethanol mixtures reveals the possibility of creating supersaturation (i.e., to induce crystallization) by a specific change of the solvent composition in the solution.

Solubility Phase Diagram of Threonine Enantiomers in a Solvent. In Figure 4, the solubility phase diagram of the threonine enantiomers in water is shown. Four isotherms between (10 and 40) °C are considered. Except for the 20 °C isotherm, solubility measurements in the ternary system were limited to obtain data of the enantiomers (to prove the symmetry in the system) and of the racemic mixture. As expected, the phase diagram exhibits the typical shape of a conglomerate-forming chiral system with a maximum solubility at the racemic composition. The solubility ratio α (i.e., the ratio between the solubilities of the racemic mixture and the enantiomer, with the

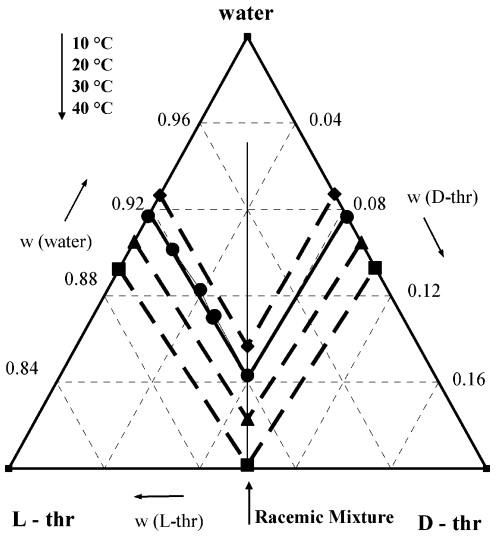

Figure 4. Ternary-phase diagram of the threonine enantiomers in water including solubility isotherms between (10 and 40) °C (axes in weight fraction; $w_{(L-thr)}$; $w_{(D-thr)} \leq 0.2$; lines only to guide to the eye).

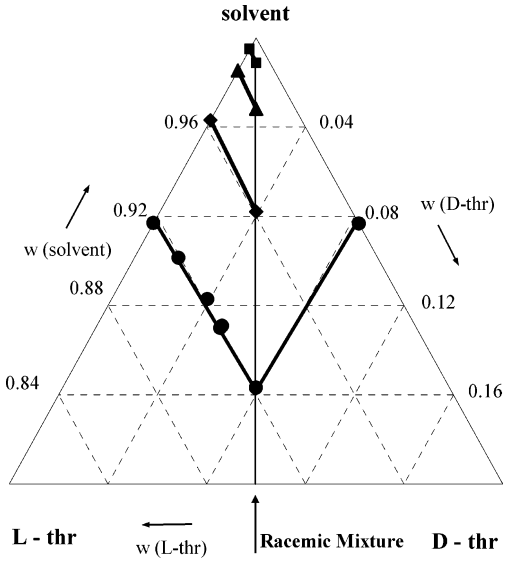

Figure 5. Position of the 20 °C solubility isotherms for different solvent compositions in the ternary-phase diagram of threonine (symbols: water/ethanol fraction in the solvent in volume percent: ■, 40/60; ▲, 60/40; ◆, 80/20; ●, 100/0; axes in weight fraction; $w_{(L-thr)}$; $w_{(D-thr)} \leq 0.2$; lines only to guide to the eye).

solubility expressed in mole fraction) was calculated to be $\alpha = 2$ in water. The ratio increases only slightly with rising ethanol fraction up to $\alpha = 2.3$ in water/ethanol = 40/60 v/v. This indicates an ideal behavior of the threonine species (i.e., the solubility of one enantiomer is not influenced by the presence of the other one); therefore, the solubility of the racemic mixture results from the superimposition of the enantiomer solubilities ("double solubility rule"[13]). The ideal behavior is further corroborated by the course of the 20 °C isotherm in Figure 4. The measured data points lie on an isoplethal in the phase diagram indicating a linear increase of the overall solubility toward the racemic mixture.

Figure 5 illustrates the impact of the solvent composition on the solubility isotherms in the ternary phase diagram using the 20 °C isotherm as an example. Apparently, the increasing ethanol content significantly affects the position of the saturation curves, which correspondingly move toward lower solute concentrations (i.e., toward the solvent corner). The almost

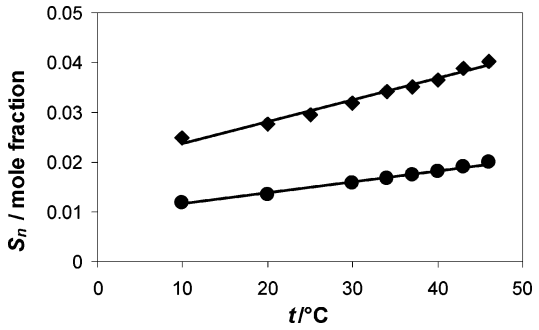

Figure 6. Solubility data in water gravimetrically determined for L-thr and DL-thr expressed in mole fraction: ◆, DL-thr, experiment; ●, L-thr, experiment; —, linear approximation (see also Table 4 and eq 2).

Table 4. Derived Coefficients (*a*, *b*) of Equation 2 for L-thr and DL-thr[a]

	a/K^{-1}	b	R
L-thr	0.0002	0.0093	0.9902
DL-thr	0.0004	0.0195	0.9832

[a] R, regression coefficient.

Table 5. Slope Coefficients (δ) of Equation 3 Used To Describe the Solubility Data in Figure 3

	10 °C	20 °C	30 °C	40 °C
L-thr	8.15	7.64	7.30	7.40
DL-thr	8.09	6.75	7.03	6.85

parallel course of the solubility isotherms again indicates a similar solubility ratio of $\alpha \approx 2$ and, thus, ideality in the system.

Correlation of Solubility Data. Figure 6 considers the gravimetrically measured solubility data in water for L- and DL-thr expressed in mole fraction. (The presentation in mole fraction is used here to simplify the correlation procedure below.) Both curves exhibit almost linear temperature functions of the solubility in water within the interval studied. Thus, for interpolation of solubility data of threonine in water with regard to temperature, $S_n^{H_2O}(T)$, a simple linear function can be used:

$$S_n^{H_2O}(T) = a \cdot T + b \tag{2}$$

The coefficients a and b of eq 2 estimated for the threonine enantiomer and the racemic mixture are summarized in Table 4.

Furthermore, similar polynomials of the first order can be applied to describe the solubility of the threonine species as function of the solvent composition shown in Figure 3. For the logarithm of the solubility at a given temperature T, $\ln S_{n,T}$, with respect to the mole fraction of water in the solvent, x_{H_2O}, can be written as

$$\ln S_{n,T}^{H_2O/EtOH} = \delta \cdot x_{H_2O} + B \tag{3}$$

The experimentally derived slope coefficients, δ, are listed in Table 5. The values of δ vary by ± 5.7 %; the mean value is $\bar{\delta} = 7.4$.

With respect to the solubility in pure water eq 3 provides

$$\ln S_{n,T}^{H_2O} = \delta + B \tag{4}$$

The solubility value in eq 4, $S_{n,T}^{H_2O}$, can be obtained from eq 2. Combination of eqs 3 and 4 yields

$$\ln S_{n,T}^{H_2O/EtOH} = \delta \cdot (x_{H_2O} - 1) + \ln S_{n,T}^{H_2O} \tag{5}$$

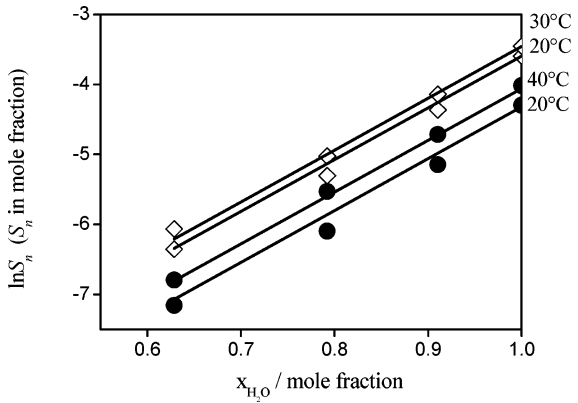

Figure 7. Comparison between correlated and experimentally determined solubility data for L-thr and DL-thr. The complete curves as function of the solvent composition result from eq 6; ◇, DL-thr, experiment; ●, L-thr, experiment; —, correlated data.

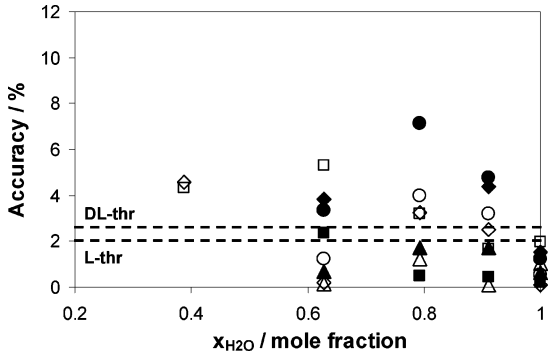

Figure 8. Accuracy of the correlated solubility data for the threonine enantiomer and racemic mixture at different temperatures and solvent compositions (data refer to results in Figure 7: ◆, DL-thr, 10 °C; ◇, DL-thr, 20 °C; ■, DL-thr, 30 °C; □, DL-thr, 40 °C; ●, L-thr, 10 °C; ○, L-thr, 20 °C; ▲, L-thr, 30 °C; △, L-thr, 40 °C; dashed lines, average deviation for DL/L-thr, respectively).

Using the average value for δ and considering eq 2, eq 5 can be transformed to

$$\ln S_{n,T}^{H_2O/EtOH} = \bar{\delta} \cdot (x_{H_2O} - 1) + \ln(a \cdot T + b) \tag{6}$$

Equation 6 allows the interpolation of solubility data with respect to temperature and solvent composition in water/ethanol mixtures.

As an example, correlated and experimentally obtained data are compared in Figure 7. Figure 8 illustrates the accuracy of the proposed correlation approach. As a result, solubility data for the threonine species can be predicted for different solvent compositions with an average deviation from the experiment < ± 2.2 %. The best fit of the measured data is achieved for the solubilities in pure water. The deviations from experimental values calculated for different temperatures and solvent compositions are summarized in Table 6.

The distinctly pronounced dependence of the threonine solubility on the water/ethanol ratio can be applied (e.g., in a so-called "drowning-out" or "antisolvent" crystallization process). By changing the solvent composition, a defined supersaturation can be created to induce crystallization. The interpolation approach proposed above can then provide the required solubility data in order to choose optimal conditions for the crystallization process.

Moreover, solubility data as a function of solvent composition are relevant in the case of chromatographic separation and

Table 6. Average Deviation (in %) between Experimental and Correlated Solubilities for L- and DL-Threonine at Different Temperatures and Solvent Compositions[a]

x_{H_2O}	L-thr				DL-thr			
mole fraction	10 °C	20 °C	30 °C	40 °C	10 °C	20 °C	30 °C	40 °C
0.3883						4.57		4.3
0.6286	3.35	1.23	0.68	0.15	3.86	0.20	2.35	5.31
0.7920	7.14	3.96	1.72	1.21		3.25	0.47	3.21
0.9103	4.76	3.22	1.73	0.11	4.37	2.49	0.46	1.65
1.0000	1.21	0.55	0.66	1.04	1.52	0.07	0.21	1.95

[a] The data are shown in Figure 8.

purification of the threonine enantiomers. Chiral resolution of racemic threonine can be performed (e.g., by liquid chromatography using chiral stationary phases). Since water/ethanol mixtures are used as eluent, both solubilities of the racemic mixture and the enantiomer at the actual eluent composition must be known to prevent crystallization on the usually expensive stationary phase.[15]

Since threonine belongs to the conglomerate-forming chiral systems, the racemic mixture might be resolved via the so-called preferential crystallization technique[13] as well. This technique is based on the possibility of selectively crystallizing (kinetically driven) only the desired enantiomer from supersaturated racemic solutions in the three phase domain of the ternary-phase diagram. The knowledge of the ternary solubility equilibria is mandatory for designing such a delicate process. Results concerning different fundamental and also engineering aspects of preferential crystallization of threonine have been recently published.[16−18]

Conclusions

The system L-/D-threonine is a conglomerate-forming chiral system. The temperature dependence of the solubility of the threonine species is not strongly pronounced. An evidence of ideal solution behavior in water/ethanol mixtures are the missing heterochiral interactions between both counter enantiomers (i.e., the solubility of the one enantiomer is not affected by the presence of the other one in solutions). Threonine exhibits good solubility in water and is in contrast hardly soluble in ethanol. This feature can be applied (e.g., for the realization of a "drowning-out" crystallization). In such crystallization processes, supersaturation in the solution is created through changing the solvent composition. Moreover, the knowledge of the solubility limit is of interest for chromatographic resolutions of threonine as well. An increase of the ethanol fraction in the eluent and/or a change of the enantiomer composition toward the pure enantiomers during the chromatographic separation can entail a significant decrease of the solubility and consequently can induce spontaneous crystallization on the chromatographic column. The almost linear functions obtained for the measured solubilities with regard to temperature and solvent composition allow a relatively simple correlation of the data. The prediction of solubilities with the proposed approach provides acceptable results in the temperature/concentration interval studied.

Literature Cited

(1) Ahuja, S. *Chiral Separations*: *Applications and Technology*; American Chemical Society: Washington, DC, 1997.
(2) Mullin, J. W. *Crystallization*, 3rd ed.; Butterworth-Heinemann: Oxford, 1997.
(3) Hoppe, B.; Martens, J. aminosäuren—herstellung und gewinnung. *Chem. Unserer Zeit* **1984**, *18*, 73−86.
(4) Izumi, Y.; Chibata, I.; Itoh, T. Production and utilization of amino acids. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 176−183.
(5) Soukup, M.; Wipf, B.; Hochuli, E.; Leuenberger, H. G. W. Enantioselektive synthese des L-threonins. *Helv. Chim. Acta* **1987**, *70*, 232−236.
(6) Shiraiwa, T.; Yamauchi, M.; Yamamoto, Y.; Kurokawa, H. Optical resolution by replacing crystallization of DL-threonine. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3296−3299.
(7) Jacques, J.; Gabard, J. Study of optical antipodal mixtures. *Bull. Soc. Chim. Fr.* **1972**, *1*, 342−350 (in French).
(8) Nozaki, Y.; Tanford, C. The solubility of amino acids and related compounds in aqueous ethylene glycol solutions. *J. Biol. Chem.* **1965**, *240*, 3568−3573.
(9) Profir, V. M.; Matsuoka, M. Processes and phenomena of purity decrease during the optical resolution of DL-threonine by preferential crystallization. *Colloids Surf., A* **2000**, *164*, 315−324.
(10) Wallworth, D.; Beesley, T. E. New chromatographic techniques for amino acid analysis and purification. *Specialty Chem. Mag.* **2002**, *December*, 10−12.
(11) Berthod, A.; Liu, Y.; Bagwill, C.; Armstrong, D. W. Facile liquid chromatographic enantioresolution of native amino acids and peptides using a teicoplanin chiral stationary phase. *J. Chromatogr., A* **1996**, *731*, 123−137.
(12) Lorenz, H.; Sapoundjiev, D.; Seidel-Morgenstern, A. Enantiomeric mandelic acid system—melting point phase diagram and solubility in water. *J. Chem. Eng. Data* **2002**, *47*, 1280−1284.
(13) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Krieger Publishing Company: Malabar, FL, 1994.
(14) Teipel, U.; Kroeber, H.; Leisinger, K.; Hartlieb, K. Measurement of solubilities of nitramines: a comparison of different methods; 15th International Symposium on Industrial Crystallization (ISIC 15), 2003, Sorrento (Italy). *Chem. Eng. Trans.* **2002**, *1*, 227−232.
(15) Lorenz, H.; Sapoundjiev, D.; Seidel-Morgenstern, A. Solubility equilibria in chiral systems and their importance for enantioseparation. *Eng. Life Sci.* **2003**, *3*, 132−136.
(16) Alvarez Rodrigo, A.; Lorenz, H.; Seidel-Morgenstern, A. Online monitoring of preferential crystallization of enantiomers. *Chirality* **2004**, *16*, 499−508.
(17) Elsner, M. P.; Fernández Menéndez, D.; Alonso Muslera, E.; Seidel-Morgenstern, A. Experimental study and simplified mathematical description of preferential crystallisation. *Chirality* **2005**, *17*, S183−S195.
(18) Lorenz, H.; Perlberg, A.; Sapoundjiev, D.; Elsner, M.; Seidel-Morgenstern, A. Crystallization of enantiomers. *Chem. Eng. Process.* **2006**, *45*, 863−873.

Received for review February 9, 2006. Accepted July 8, 2006. The authors gratefully acknowledge the financial support of FCI, Fonds der Chemischen Industrie.

JE060053H