Measuring and Modeling Activity Coefficients in Aqueous Amino-Acid Solutions

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The perturbed-chain statistical association theory (PC-SAFT) is applied to simultaneously describe various thermodynamic properties (density, vapor-pressure depression, activity coefficient, solubility) of aqueous solutions containing an amino acid or an oligopeptide. The 28 organic compounds considered within this work are glycine, alanine, serine, proline, hydroxyproline, valine, leucine, arginine, lysine, threonine, asparagine, tyrosine, histidine, cysteine, methionine, aspartic acid, glutamic acid, α-ABA, α-isoABA, β-ABA, γ-ABA, α-AVA, γ-AVA, diglycine, triglycine, dialanine, Gly-Ala, and Ala-Gly. If not yet available in literature, amino-acid solubility data and activity coefficients were determined experimentally. To prove the predictivity of PC-SAFT, osmotic coefficients in aqueous solutions containing two amino acids (glycine/valine and alanine/valine) were measured and predicted without applying any additional model parameters.

1. Introduction

Since the early years of the last century densities, vapor pressures, solubilities, and activity coefficients of amino acids and peptides in various solvents have been correlated, measured, and calculated. The modeling of such systems requires the availability of precise experimental data. As literature data does not cover the solubility and activity coefficients of all amino acids and peptides in water, some new data will be presented here. In the case of solubilities, the gravimetric method has already been applied and proven as a suitable tool for precise and fast determination of single-solute[1] and multisolute[1,2] solubility data.

The measurement of water activity coefficients is also well established. The oldest procedure is the isopiestic method applied for example, by Robinson and Stokes[3] to aqueous electrolyte systems. However, this method is extremely time-consuming for small solute concentrations. This makes it inappropriate for the systems considered in this work as many amino acids are very little soluble in water. Furthermore, there exist some vapor-pressure measurements which also provide activity coefficients. They are performed as measurement of absolute vapor pressures or by vapor-pressure depressions with high certainty[4] and almost no limitations with respect to concentration, solute, or solvent. However, such measurements are as difficult as they are very sensitive (e.g., to the tempering the system or to the accuracy of weighing) and additionally expensive. Recently, vapor-pressure osmometry is more and more used as an alternative possibility for the determination of activity coefficients. Because of its simplicity and reliability it has already been applied to aqueous biomolecule solutions.[5]

For the thermodynamic modeling of amino-acid and peptide solutions, two main types of models have been applied so far: Gibbs-energy (g^E) models and equations of state (EOS). Khoshkbarchi and Vera[6] give an excellent overview of the thermodynamic models—g^E models as well as EOS—applied in the recent years to calculate activity coefficients and solubilities of amino acids in aqueous solutions. For example, Kuramochi et al.[7] used the UNIFAC model combined with a Pitzer–Debye–Hückel theory to calculate activity coefficients in aqueous solutions containing amino acids, sugars, and inorganic salts. Nass[8] applied the electrolyte NRTL model to describe amino-acid solubilities of L-alanine, L-serine, and L-threonine. Xu et al.[9] and Pazuki et al.[10,11] suggested the modified Wilson model for the calculation of activity coefficients and solubilities of several amino acids in aqueous solutions that may also contain electrolytes. Both groups compared their modeling results with other g^E models like UNIQUAC or UNIFAC and perturbation models of varying complexity. The reported mean root square deviations indicate that perturbation models (equation of states) yield comparably good or even better results than g^E models.

Khoshkbarchi and Vera[6,12,13] presented a so-called primitive model based on a first-order perturbation theory for the correlation of activity coefficients and solubilities of some amino acids and oligopeptides (up to trimers) in water. In a primitive model, the solvent (in this case water) is only considered implicitly by its dielectric constant. The amino acids and peptides were modeled as Lennard-Jones spheres which also exhibit dipole–dipole interactions (Stockmayer fluid). The model of Khoshkbarchi and Vera needs three pure-component parameters, namely the molecule diameter, the dispersion energy, and the dipole moment. While the first two are fitted to experimental data, the third is calculated by means of quantum mechanics. "Simple" models like the one by Khoshkbarchi and Vera are based on a spherical shape of the molecules. However, this assumption is not even justified for molecules like small amino acids. Aiming at the description of even more complex biological systems, where the molecules exhibit a rodlike structure, segment-based models appear to be more appropriate.

The model by Liu et al.[14] is also based on a perturbation theory but it treats the solvent as a discrete molecule. Moreover, the molecules are described as chains of Lennard-Jones spheres having a dipole moment. The reference system consists of a hard-sphere mixture; chain formation, dispersion, and dipole–dipole interactions are taken into account as perturbation contributions. Four pure-component parameters (segment number, segment diameter, dispersion energy, and dipole moment) were fitted to correlate activity coefficients and solubilities of some amino acids and dipeptides in aqueous solutions. PC-SAFT has already been used to describe multisolvent and multisolute amino-acid mixtures. Fuchs et al.[15] modeled the solubility of glycine, DL-alanine, and DL-methionine in water/alcohol solutions at varying pH. Also other authors used PC-SAFT to model

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solubilities or activity coefficients of aqueous solutions in multisolvent[16] or even in multisolute systems.[1,17]

All the experimental and theoretical considerations within this work aim for broadening the basis of experimental data and model parameters as well as for a better understanding of interactions in amino-acid solutions.

2. Experimental Work

2.1. Materials and Reagents. The amino acids L-valine (Sigma, >97%), DL-valine (Sigma, >97%), L/DL-alanine (Sigma >99%), glycine (Sigma, >99%) DL-norleucine (Sigma, 98%), DL-norvaline (Sigma, >98%), L-cysteine (Sigma, 99.5%), L-methionine (Sigma, 99.5%), and diglycine (Sigma, >99%) were used without further purification. For the calibration of the vapor-pressure osmometer, a sodium chloride solution (NaCl: Merck, >99.5%) was applied. All solutions were prepared gravimetrically by weighing with an accuracy of 0.01 mg. Water from the Millipore purification system was used for the preparation of all aqueous solutions.

2.2. Measurement of Osmotic Coefficients. The measurements of osmotic coefficients were performed with a Gonotec Osmomat O70 which allows for the measurement of one-solvent solutions in the concentration range of 0.005−3.0 mol solute per kg solvent [mol/kg] up to the solvent's boiling point. The measuring cell of the Osmomat contains two thermistors placed in a tempered closed, water-saturated atmosphere. With the help of a syringe, the thermistors are wetted, one with water and the other one with the solute solution of interest. Being at the same solvent pressure, the temperature difference between the two droplets is detected. This value can be converted into the osmotic coefficient or the solvent activity coefficient.[5] Before carrying out the measurements, the Osmomat was calibrated with sodium chloride solutions between 0.05 and 1.2 mol/kg using reference values from literature.[3] After that, the experiments for the amino acids were performed at 30 °C. For each solution the measurements were repeated until a constant temperature difference could be observed. Afterward, at stable results, the measuring signal of five measurements at equal concentration were recorded and averaged. After measurement, the calibration was controlled again to exclude any baseline drifts of the apparatus. This procedure was repeated for all measured concentrations allowing for a maximum uncertainty of ±2% in experimental osmotic coefficients.

2.3. Solubility Measurements. To determine the solubility of the solutes considered in this work the gravimetrical method was applied as described, for example, in refs 1 and 2. First, the substances were filled into glass vials (20 mL) and Millipore-purified water was added. These vials were placed and rotated in an oven with a temperature deviation of ±0.3 K. After equilibration (48 h), a sample of 2 mL solution was withdrawn with a preheated syringe equipped with a syringe filter (pore size 0.45 μm). The sample was weighed with an accuracy of 0.01 mg. After solvent evaporation (drying chamber) this sample was weighed again. In order to ensure a total evaporation of the solvent, the sample was placed back into the oven and was reweighed after 24 h allowing for an uncertainty of ±3% in amino-acid solubility.

3. PC-SAFT Equation of State

3.1. The Model. One aim of this work is the calculation of various thermodynamic properties of aqueous amino-acid and oligopeptide solutions with a physically sound model and a minimal parameter set. Properties of interest are solution density, vapor-pressure depression, solute activity coefficient, and solubility. For this purpose, the PC-SAFT equation of state appears to be most appropriate. It has proved its flexibility and excellent performance in the modeling of complex systems containing polymers,[18−20] polar compounds,[21,22] associating compounds,[23] pharmaceuticals,[24] and electrolytes.[25−27] The PC-SAFT EOS is based on a perturbation theory where the hard-chain system (a chain consisting of repelling hard spheres) is used as the reference system. To obtain the residual Helmholtz energy a^{res} (the thermodynamic key quantity of the modeling) all energies deviating from the reference system (e.g., the attractive van der Waals forces) are treated as single contributions that can be considered independently:

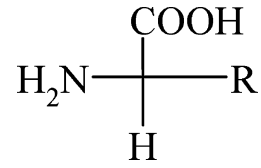

Figure 1. Amphiphilic structure of amino acids.

$$a^{res} = a^{hc} + a^{disp} + a^{assoc} \quad (1)$$

Here, a^{hc} represents the hard-chain repulsion of the reference system; a^{disp} and a^{assoc} account for the Helmholtz-energy contributions due to dispersive and associative attractive interactions which are used as in the original PC-SAFT model.[28] To describe mixed solutions, the conventional Berthelot−Lorenz combining rules are used for interactions between two components i and j (e.g., water and amino acid):

$$\sigma_{ij} = \frac{1}{2}(\sigma_i + \sigma_j) \quad (2)$$

$$u_{ij} = \sqrt{u_i u_j}(1 - k_{ij}) \quad (3)$$

The main component of almost every biological system is water which therefore is to be modeled as accurately as possible. We use the associative 2B model with temperature-dependent segment diameter as introduced by Cameretti et al.[29] In contrast to the original water parametrization by Groβ et al.[23] the temperature-dependent segment diameter allows for the correct modeling of the density anomaly at about 4 °C.

The amino acids (Figure 1) are treated as chains consisting of identical spheres. The amino group as well as the carboxylic group are assumed to have one association site each mimicking the proton donator site (acidic group) and the proton acceptor site (amino group).

If applicable, amino, hydroxyl, and carboxylic groups in the residue R are also considered. For example, serine (R = $-CH_2-OH$) exhibits one additional proton donating site. Thus, we apply a 1:2 association scheme for serine, threonine, lysine, tyrosine, and hydroxyproline, respectively. For the sake of reducing the number of adjustable parameters, both association-site types are assumed to have the same energy and volume parameters (ε_{hb}^{AiBi} and κ_{hb}^{AiBi}). When two amino acids form a peptide bond, two association sites are eliminated due to polycondensation. Thus, for example, diglycine also only possesses two association sites. For all considered cases, the number of considered association sites is given in Table 5. As amino-acid and peptide solutions (without pH adjustment) are mostly neutral (mainly consist of zwitterions), ionic charge−charge interactions between these solutes are not considered in the modeling. Although amino acids possess large dipole

Table 1. Solubilities of L-Alanine, DL-Norvaline, DL-Norleucine, DL-Valine, L-Valine, and Diglycine in Water between 291.05 and 333.45 K Determined within This Work

L-alanine		DL-norvaline		DL-norleucine		DL-valine		L-valine		diglycine	
T (K)	solubility (mol/kg)	T (K)	solubility (mol/kg)	T (K)	solubility (mol/kg)	T (K)	solubility (mol/kg)	T (K)	solubility (mol/kg)	T (K)	solubility (mol/kg)
291.05	1.711	302.55	0.724	302.55	0.084	302.55	0.618	302.55	0.160	298.15	1.791
298.65	1.828	303.85	0.728	303.85	0.086	303.85	0.628	303.85	0.165	300.95	1.893
302.55	1.896	303.85	0.738	303.85	0.095	303.85	0.622	312.15	0.170	308.05	2.029
303.85	1.919	312.95	0.755	312.95	0.097	312.95	0.686	322.15	0.186	313.05	2.142
312.95	2.164	323.25	0.787	323.25	0.114	323.25	0.770	332.05	0.204		
322.15	2.397	333.45	0.843	333.45	0.132	333.45	0.841				
332.05	2.687										

moments, numerical investigation has shown that including the dipole−dipole interactions in the EOS does not lead to a better model performance; thus they were also neglected in this work.

3.2. Calculation of Thermodynamic Properties with PC-SAFT. To calculate vapor pressures of amino-acid solutions, the equilibrium (isofugacity) condition has to be considered:

$$\varphi_i^{\mathrm{L}} x_i^{\mathrm{L}} = \varphi_i^{\mathrm{V}} x_i^{\mathrm{V}} \tag{4}$$

where φ_i^{L} and φ_i^{V} are the fugacity coefficients of component i in the liquid and the vapor phase, respectively. Since we deal with highly nonvolatile compounds (amino acids and peptides) we can assume that the vapor phase consists solely of the solvent ($x_{\mathrm{w}}^{\mathrm{V}} = 1$). Therefore, the isofugacity criterion needs to be considered only for the solvent—in our case, water.

The activity coefficients of a solute i reported in this work are normalized to the infinite dilution (rational activity coefficients) and are already converted to molality scale (for details see, e.g., ref 3). They are obtained by

$$\gamma_i^{*,\mathrm{m}} = \frac{\varphi_i^{\mathrm{m}}(T,p,m_i)}{\varphi_i^{\infty,\mathrm{m}}(T,p,m_i \rightarrow 0)} \tag{5}$$

where φ_i^{m} is the fugacity coefficient of component i in the mixture, and $\varphi_i^{\infty,\mathrm{m}}$ ($\mathrm{m}_i \rightarrow 0$) is the fugacity coefficient of the same component at infinite dilution in water. Both values can be directly obtained by PC-SAFT.

In contrast, water activity coefficients (WAC) are normalized to pure water:

$$\gamma_{\mathrm{w}} = \frac{\varphi_{\mathrm{w}}(T,p,x_{\mathrm{w}})}{\varphi_{0\mathrm{w}}(T,p,x_{\mathrm{w}} = 1)} \tag{6}$$

For the calculation of solubilities an equilibrium condition between the liquid and the solid phase is needed. Assuming a pure solid phase and neglecting the influence of different heat capacities of solid and liquid, the mole fraction of the solute in the liquid phase (its solubility) can be calculated by[30]

$$x_i^{\mathrm{L}} = \frac{\varphi_{0i}^{\mathrm{L}}}{\varphi_i^{\mathrm{L}}} \exp\left\{-\frac{\Delta h_{0i}^{\mathrm{SL}}}{RT}\left(1 - \frac{T}{T_{0i}^{\mathrm{SL}}}\right)\right\} \tag{7}$$

$\varphi_{0i}^{\mathrm{L}}/\varphi_i^{\mathrm{L}}$ is the ratio of the fugacity coefficients of component i (amino acid or peptide) as pure substance and in the mixture. $\Delta h_{0i}^{\mathrm{SL}}$ is the melting enthalpy and T_{0i}^{SL} the melting temperature of the pure amino acids, respectively.

4. Experimental Results

4.1. Amino-Acid Solubilities in Water. The solubilities of L-alanine, DL-norvaline, DL-norleucine, DL-valine, L-valine, and diglycine determined within this work are listed in Table 1. Both, the solubility of L-alanine (e.g., from ref 31−33) and the solubility of L/DL-valine (e.g., from ref 32, 34) agree with data from literature within 3%, whereas no data is available for the other amino acids. Thus, the temperature-dependence of DL-norvaline, DL-norleucine, and diglycine solubilities in water is presented here for the first time.

Table 2. Experimental Water Activity and Osmotic Coefficients in Aqueous L-Leucine Solutions at 25°C. L-Leucine Activity Coefficients Were Obtained by eq 11

x_{w} (−)	m_{leucine} (mol/kg)	Φ (−)	γ_W (−)	a_{w} (−)	$\gamma^*_{\mathrm{leucine}}$ (−)
0.9993	0.040	1.0133	0.99999	0.9993	1.0157
0.9986	0.080	1.0210	0.99997	0.9985	1.0315
0.9978	0.120	1.0209	0.99995	0.9978	1.0472
0.9971	0.160	1.0342	0.99990	0.9970	1.0629

Table 3. Experimental Water Activity and Osmotic Coefficients in Aqueous L-Methionine Solutions at 25°C. L-Methionine Activity Coefficients Were Obtained by eq 11

x_{w} (−)	$m_{\mathrm{methionine}}$ (mol/kg)	Φ (−)	γ_{W} (−)	a_{w} (−)	$\gamma^*_{\mathrm{methionine}}$ (−)
0.9991	0.050	0.9446	1.0000	0.9992	0.9242
0.9982	0.103	0.9297	1.0001	0.9983	0.8632
0.9973	0.151	0.9136	1.0002	0.9975	0.8170
0.9964	0.200	0.8925	1.0004	0.9968	0.7861

Table 4. Experimental Water Activity and Osmotic Coefficients in Aqueous L-Cysteine Solutions at 25°C. L-Cysteine Activity Coefficients Were Obtained by eq 11

x_{w} (−)	m_{cysteine} (mol/kg)	Φ (−)	γ_{W} (−)	a_{w} (−)	$\gamma^*_{\mathrm{cysteine}}$ (−)
0.9946	0.300	1.0292	0.9998	0.9945	0.8077
0.9911	0.499	0.8864	1.0010	0.9920	0.7190
0.9858	0.800	0.7531	1.0035	0.9892	0.6132
0.9823	1.000	0.7362	1.0046	0.9868	0.5493

4.2. Activity and Osmotic Coefficients in Amino-Acid Solutions. In this work the osmotic coefficients of the binary amino-acid solutions water/glycine, water/valine, water/leucine, water/methionine, and water/cysteine were measured at 25 °C. Whereas in the glycine, valine, and leucine systems such data is already available in literature, the osmotic coefficients for water/methionine and water/cysteine are presented for the first time. The respective values of the aqueous leucine, cysteine, and methionine systems measured at 25 °C are given in Tables 2 − 4. Results for glycine and valine solutions are shown in Figures 2 and 8, respectively.

The original definition of the osmotic coefficient is given in ref 35 as

$$\Phi = \frac{\ln a_{\mathrm{w}}}{\ln x_{\mathrm{w}}} \tag{8}$$

where a_{w} and x_{w} are the activity and the mole fraction of water, respectively. However, the simplified equation, which is commonly used in literature, is also applied in this work:

$$\Phi = -\frac{\ln(x_w \cdot \gamma_w)}{\nu m M_w} \quad (9)$$

with the stoichiometric factor ν being unity for the considered amino acids and peptides.

Figure 2 shows the osmotic coefficients and the water activity coefficients for aqueous glycine solutions measured within this work in comparison with literature data (obtained by different experimental methods). The results obtained in this work agree well (within 1%) with data by Romero et al.[36] and Tsurko et al.[5] However, the distinct scatter of the literature data[5,7,36,37] shows the difficulty as well as the uncertainty of such measurements.

Cysteine and methionine cause similar osmotic coefficients in water with slightly lower values in the methionine/water system. For these sulfuric amino acids, water activity/osmotic coefficients are presented for the first time. Such data is of crucial interest as many proteins (e.g., keratin) to a remarkable extent consist of these amino acids (e.g., human hair contains approximately 14% L-cysteine).

Applying the Gibbs−Duhem relation allows for the calculation of amino-acid rational activity coefficients from osmotic-coefficient data. For that purpose, the estimated osmotic coefficients are first approximated by a power series:

$$\phi - 1 = \sum_{i=1}^{n} A_i m^i \quad (10)$$

and then converted into the rational solute activity coefficients by applying (see for example ref 38) the following:

$$\ln \gamma^* = (\phi - 1) + \int_0^m \frac{(\phi - 1)}{m} \, dm \quad (11)$$

In eq 10, the A_i values are adjustable parameters and n refers to the number of parameters needed to represent the experimental osmotic coefficients. For L-methionine, A_1, A_2, and A_3 were found to be −0.83, 0.99, and 2.99, respectively.

5. Parameter Estimation for PC-SAFT

For the parameter regression of DL-methionine, Fuchs et al.[15] have used experimental sublimation pressures. However, only little of such experimental data is available for pure amino acids and peptides as they decompose before sublimation. Moreover, the relative mean deviations are fairly large since the absolute sublimation pressures are very low (down to 4 Pa). As the amino acids are solids at ambient temperature, binary (aqueous) solution data were used for the pure-component parameter estimation. In this work, the five PC-SAFT parameters (segment number, segment diameter, dispersion-energy parameter, association-energy parameter, and association volume) were fitted to experimental liquid-density and solute-activity-coefficient data of/in aqueous solutions at 25 °C.

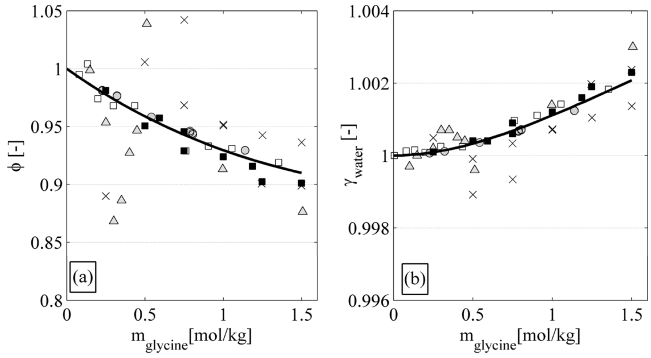

Figure 2. Experimental osmotic coefficients (a) and water activity coefficients (b) in aqueous glycine solutions at 25 °C measured within this work (full squares), by Romero and González[36] (circles), by Tsurko et al.[5] (open squares), by Pinho[37] (crosses), and by Kuramochi et al.[7] (triangles). The lines represent calculations with PC-SAFT.

Melting enthalpy and melting temperature needed for the solubility calculations were determined by the group contribution method of Marrero and Gani.[39] As these values are known to be uncertain (up to 16%), they were allowed to change within this tolerance. Thus, to describe all the different types of thermodynamic properties with only one parameter set, a binary interaction parameter k_{ij} had to be introduced. Summing up, a total of 5 PC-SAFT pure-component parameters, the binary k_{ij} parameter, and the two melting properties are necessary for modeling the above-mentioned amino acids and peptides in aqueous solution.

Since chiral molecules - such as some amino acids - reveal pronounced differences in their solubility behavior, melting enthalpy and melting temperature are given for the L as well as for the DL form, as far as experimental solubility data is available. As this difference does not influence the liquid-phase behavior, densities or activity coefficients are described by only one PC-SAFT parameter set for all chiral types of one amino acid in water.

PC-SAFT parameters for glycine, alanine, serine, proline, valine, methionine, and some oligopeptides have already been fitted by Fuchs et al.[15] to solubility data and by Cameretti et al.[29] to aqueous solution densities, vapor pressures, and solubilities. Although they achieved excellent agreement between model and experiment, the amino-acid activity coefficients cannot be described with these parameter sets. Therefore, new parameters have been adjusted to experimental solution densities and activity coefficients at 25 °C. Moreover, the association-site number has been decreased from two to one association site per type, that is, one site for both, the hydroxyl and the carboxylate group (see Figure 1). This has the advantage of reduced computation time without decreasing the accuracy of the model. Moreover, this is consistent to the modeling of water where we also used only two association sites. To additionally calculate properties at other temperatures than 25 °C, a linear temperature-dependent binary parameter k_{ij} was applied:

$$k_{ij}(T) = k_{ij,298.15\,K} + k_{ij,T}(T - 298.15\ K) \quad (12)$$

where T is the temperature in Kelvin. This procedure is commonly used (see ref 24), especially when accurate fits of solubility data are desired. It should be noted that this procedure is not necessary for all the treated amino acids in this work (see Table 5). Moreover, it is possible to apply the same k_{ij} values for all amino-acid isomers/racemates (e.g., L- and DL-serine).

For the homopolypeptides diglycine and triglycine the majority of the pure-component parameters of glycine could directly be inherited as suggested by Cameretti et al.[29] However, to reproduce activity coefficient data of the glycine-peptides, the segment number and the k_{ij}-parameter had to be refitted to experimental data. Of course, the melting properties could not be inherited, either. This approach yields reasonable results also for dialanine.

For the heteropolypeptides alanyl−glycine and glycyl−alanine the whole set of parameters had to be regressed anew. Although these peptides are different in structure, solution densities and activity coefficients are identical within measurement uncer-

Table 5. Pure-Component and Binary PC-SAFT Parameters for Aqueous Amino-Acid and Peptide Solutions[a]

amino acid/ parameter	m_{seg}	σ	ε/k_B	N	$\varepsilon_{hb}^{A_iB_i}/k_B$	$\kappa_{hb}^{A_iB_i}$	T^{SL} (K)[b]	$\Delta h^{SL}/R$[b]	$k_{ij,25\,°C}$ (H_2O)	$k_{ij,T}$ (H_2O)	ρ ARD/ AAD	N_{dp}	T (K)	ref	γ^* ARD/ AAD	N_{dp}	ref	m ARD/ AAD	N_{dp}	T (K)	ref
glycine	4.8495	2.3270	216.96	2	2598.06	0.0393	714.3	2109.3	-6.12×10^{-2}		0.05/0.55	18	298−318	41	1.6/0.01	24	7, 42	3.8/0.10	8	273−333	32
L-alanine	5.4647	2.5222	287.59	2	3176.60	0.0819	692.4	2543.7	-6.12×10^{-2}	2.91×10^{-4}	0.03/0.30	25	288−308	41	0.1/<0.01	19	7, 43	1.0/0.02	10	288−345	44
DL-alanine	5.4647	2.5222	287.59	2	3176.60	0.0819	622.2	2781.3	-6.12×10^{-2}	2.91×10^{-4}	0.03/0.30	25	288−308	41	0.1/<0.01	19	7, 43	0.3/0.01	11	273−348	45
L-serine	7.0236	2.2840	236.92	3	2671.93	0.0385	589.2	2642.0	-2.57×10^{-2}	-0.80×10^{-5}	0.02/0.20	35	278−308	46	0.7/<0.01	12	7	5.8/0.16	6	273−333	32
DL-serine	7.0236	2.2840	236.92	3	2671.93	0.0385	776.4	2865.5	-2.57×10^{-2}		0.02/0.20	35	278−308	46	0.7/<0.01	12	7	1.5/0.01	6	273−333	32
L-proline	6.9811	2.5481	289.72	2	5527.75	0.0362	562.6	1600.3	-6.99×10^{-2}		0.01/0.10	35	278−318	47	0.2/<0.01	20	41, 42	0.1/0.03	11	273−373	32
L-hydroxy-proline	1.4284	4.5000	382.73	3	2763.44	0.0231	700.0	2158.9	-0.83×10^{-2}	5.41×10^{-4}	<0.01/0.05	10	298	48	0.1/<0.01	9	49	4.2/0.13	10	273−363	50
L-valine	7.4851	2.5888	306.41	2	3183.80	0.0385	671.4	4050.7	-7.57×10^{-2}	3.85×10^{-4}	0.01/0.13	50	278−318	47	<0.1/<0.01	2	thiswork	0.45/<0.01	7	303−346	33
DL-valine	7.4851	2.5888	306.41	2	3183.80	0.0385	599.3	4324.5	-7.57×10^{-2}	3.85×10^{-4}	0.01/0.13	50	278−318	47	<0.1/<0.01	2	thiswork	4.0/0.04	11	273−373	51
L-threonine	6.3292	2.6055	325.37	3	2519.41	0.0389	500.0	3687.0	-2.78×10^{-2}	4.40×10^{-4}	0.02/0.19	32	278−308	52	<0.1/<0.01	12	42	3.5/0.05	3	298−373	33
DL-threonine	6.3292	2.6055	325.37	3	2519.41	0.0389	458.8	3659.2	-2.78×10^{-2}	4.40×10^{-4}	0.02/0.19	32	278−308	52	<0.1/<0.01	12	42	0.7/0.01	8	283−319	53
L-lysine	11.6727	2.3775	301.21	3	3787.31	0.0330	725.8	4760.5	-7.07×10^{-2}		0.03/0.33	9	298	54	4.9/0.05	22	55	6.2/0.19	3	298−373	33
L-histidine	6.0711	2.8529	316.15	3	1316.97	0.0093	500.0	2415.5	-1.95×10^{-2}	2.33×10^{-4}	0.02/0.21	21	278−308	52	<0.1/<0.01	4	5	2.8/0.01	3	298−373	33
L-arginine	9.9082	2.6572	349.71	4	2555.45	0.0393	803.7	1894.0	-1.45×10^{-2}		0.03/0.29	9	298	41	0.6/<0.01	13	55	4.2/0.09	3	298−343	33
L-leucine	8.3037	2.7000	330.00	2	3600.00	0.0200	620.9	4499.8	-6.30×10^{-2}	4.09×10^{-4}	0.04/0.36	59	278−318	47	<0.1/<0.01	4	thiswork	2.0/<0.01	10	288−346	1
DL-leucine	8.3037	2.7000	330.00	2	3600.00	0.0200	582.7	5269.9	-6.30×10^{-2}	4.09×10^{-4}	0.04/0.36	59	278−318		<0.1/<0.01	4	thiswork	8.1/0.01	11	273−373	45
L-tyrosine	8.1390	2.2798	289.37	3	2500.00	0.0400	542.5	5000.3	-2.77×10^{-4}	2.90×10^{-4}	<0.01/0.02	3	298−318	56				13.0/<0.01	11	273−373	32
L-methionine	16.0259	2.1496	220.37	3	1964.00	0.0100	780.0	8845.0	-1.43×10^{-1}	1.57×10^{-4}	0.07/0.69	67	278−318	47	<0.1/<0.01	4	thiswork	7.6/0.03	6	288−345	57
DL-methionine	16.0259	2.1496	220.37	3	1964.00	0.0100	780.0	8845.0	-1.43×10^{-1}	1.57×10^{-4}	0.07/0.69	67	278−318	47	<0.1/<0.01	4	thiswork	7.6/0.03	6	273−373	15\
L-cysteine	7.7390	2.3843	322.91	3	1964.00	0.0100	583.5	2202.9	-2.35×10^{-2}	2.77×10^{-4}	0.01/0.09	21	288−323	58	0.1/<0.01	4	thiswork	0.1/<0.01	3	298−373	33
L-asparagine	2.9998	3.3668	280.00	3	3265.67	0.0436	552.6	3838.1			0.02/0.16	20	298−328	59	0.6/<0.01	4	40	6.1/0.07	17	273−373	60
L-aspartic acid	2.9998	3.3668	207.74	3	3265.67	0.0436	619.0	2802.7	-1.92×10^{-4}		0.02/0.21	1	298	51				5.7/0.01	11	273−373	32
DL-aspartic acid	2.9998	3.3668	207.74	3	3265.67	0.0436	562.2	2790.5	-1.92×10^{-4}		0.02/0.21	1	298	51				4.6/0.01	16	273−343	61
L-glutamic acid	3.0248	3.4781	164.54	3	2536.56	0.0160	586.8	3022.6	-1.29×10^{-1}		0.02/0.17	15	293−323	1	0.1/<0.01	5	5	2.2/<0.01	8	278−342	62
α-isoABA	7.4702	2.4873	344.53	2	3481.99	0.0249			-7.44×10^{-2}		0.12/1.19	29	298	63	0.2/<0.01	15	64				
α-ABA	7.3539	2.4873	355.36	2	3481.99	0.0249	470.0	3755.8	-7.11×10^{-2}	5.10×10^{-4}	0.01/0.13	32	278−308	63	0.3/<0.01	12	36, 42	2.1/0.05	3	288−308	65 (DL)
β-ABA	7.0703	2.4873	268.01	2	3481.99	0.0249			-7.44×10^{-2}		0.01/0.05	5	298	63	1.4/0.02	23	42				
γ-ABA	6.7965	2.4873	262.38	2	3481.99	0.0249	445.0	3027.0	-7.29×10^{-2}	6.08×10^{-4}	0.03/0.25	5	298	63	2.2/0.03	14	66	0.4/0.04	2	288−298	65
α-AVA	8.8441	2.5984	339.17	2	3481.99	0.0249	550.0	3789.3	-5.99×10^{-2}	4.40×10^{-4}	0.04/0.38	9	298	67	2.2/0.02	7	42	2.3/0.02	6	304−333	this work
γ-AVA	8.5085	2.5984	262.38	2	3481.99	0.0249			-7.33×10^{-2}		0.04/0.41	9	298	68	0.1/<0.01	19	42				
diglycine	7.3374	2.3270	216.96	2	2598.06	0.0393	500.0	4452.3	-8.00×10^{-2}	5.34×10^{-4}	0.24/2.47	39	278−308	52	0.7/<0.01	8	42	0.8/0.02	4	298−313	this work
triglycine	8.8371	2.3270	216.96	2	2598.06	0.0393			-7.00×10^{-2}		0.27/2.73	27	298−318	69	0.5/<0.01	3	42				
dialanine	10.2303	2.5222	287.59	2	3176.60	0.0819			-7.35×10^{-2}		0.14/1.40	7	298	70	0.6/<0.01	10	42				
Gly−Ala	9.2047	2.4108	279.32	2	2912.22	0.0392			-7.50×10^{-2}		0.06/0.67	9	298	70	0.4/<0.01	10	42				
Ala−Gly	9.2047	2.4108	279.32	2	2912.22	0.0392			-7.50×10^{-2}		0.01/0.12	9	298	71	0.8/<0.01	10	42				

[a] The deviations AAD between modeled and experimental data are given for solution densities ρ in kg/m^3, solubilities m in mol/kg, amino-acid activity coefficients γ^* (unitless), and the ARD values in %, respectively. [b] The melting properties were estimated with the group contribution method by Marrero and Gani[39] and afterward fitted to experimental solubility data (see text).

tainty. This is not the case for the solubilities, because here the steric orientation of the peptide residues plays a predominant role for the insertion of a molecule into the crystal structure.

The PC-SAFT parameters for aminobutyric and aminovaleric acids were first fitted to the γ-form. After that, all parameters except segment number, dispersion energy, and binary interaction parameter were inherited to the β and α-types; m_{seg}, u_{ii}/k_B, and k_{ij} were readjusted to experimental data. The incentive for this procedure is 2-fold: first, the number of adjustable parameters is reduced leading to a decrease in computation time. Second, the obtained parameters may reveal physically relevant trends. Indeed, a closer look at the parameters of the aminobutyric acids shows that the segment number slightly decreases from α-ABA to γ-ABA indicating a more compact molecular structure of the γ-ABA in water.

For some of the amino acids (tyrosine, asparagine, and aspartic acid) neither solute nor water activity coefficients are available. As the solubility for aspartic acid and tyrosine is very low at ambient temperature (<0.05 mol/kg), we did not carry out osmometer measurements for these systems but adjusted their pure-component parameters only to density and solubility data. In the case of asparagine, there is only indirect data available: Cohn et al.[40] stated that (1) the interaction of glycine with glycine and of glycine with asparagine yields almost identical activity coefficients and that (2) also in other respects the physicochemical behavior of glycine and asparagine show similarities. We accounted for that by fitting the asparagine parameters to experimental glycine activity-coefficient data.

The amino acids and peptides considered in this work, as well as their chiral types and their PC-SAFT parameters are listed in Table 5.

As it can be seen from Table 5, solution densities, solute activity coefficients, and solubilities of the considered amino acids and peptides can be reproduced accurately by PC-SAFT. Moreover, vapor-pressure depressions are predicted reasonably well using the same parameter set. The respective deviations (absolute average deviations AAD and absolute relative deviations ARD) are also summarized in Table 5, calculated by

$$\mathrm{AAD} = \frac{1}{\mathrm{NP}}\sum_{k=1}^{\mathrm{NP}} |(y_k^{\mathrm{calcd}} - y_k^{\mathrm{expt}})|$$
$$\mathrm{ARD} = 100\frac{1}{\mathrm{NP}}\sum_{k=1}^{\mathrm{NP}} \left|\left(1 - \frac{y_k^{\mathrm{calcd}}}{y_k^{\mathrm{expt}}}\right)\right| \quad (13)$$

Figure 3 illustrates experimental data and the modeling of four thermodynamic properties for an aqueous glycine solution as a characteristic example.

The overall absolute relative deviations ARD between experiment and PC-SAFT modeling for the 28 considered systems are very small ($\mathrm{ARD}_{\mathrm{density}} = 0.05\%$, $\mathrm{ARD}_{\mathrm{vapor\ pressure}} = 0.46\%$, $\mathrm{ARD}_{\mathrm{activity\ coefficient}} = 0.77\%$) with the highest error in solubility data ($\mathrm{ARD}_{\mathrm{solubility}} = 3.45\%$). Presumably, this is caused by the uncertainty in experiment as well as by the simplification of the used equation (eq 7). Moreover, most of the solubility calculations were performed within a broad temperature region (0−100 °C).

In Figure 4, the temperature dependence of some amino-acid solubilities is exemplarily illustrated. Obviously, valine is the lowest-soluble molecule of this series indicating that solutes with branched instead of aliphatic CH_3 groups are harder to solubilize by the water molecules. Applying PC-SAFT, the solubility data of all amino acids in Table 5 can be modeled with the above-mentioned accuracy. The melting properties used for the modeling are given in Table 5. For the amino acids alanine,

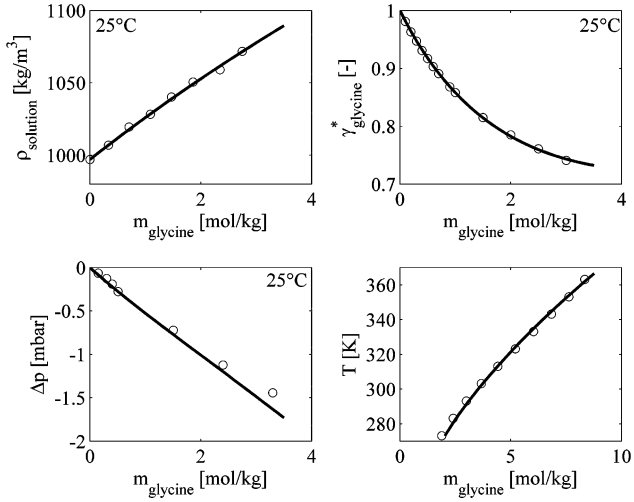

Figure 3. Solution densities, vapor-pressure depression, amino-acid activity coefficients, and solubilities of glycine in water. Circles represent experimental data, lines are calculations with PC-SAFT.

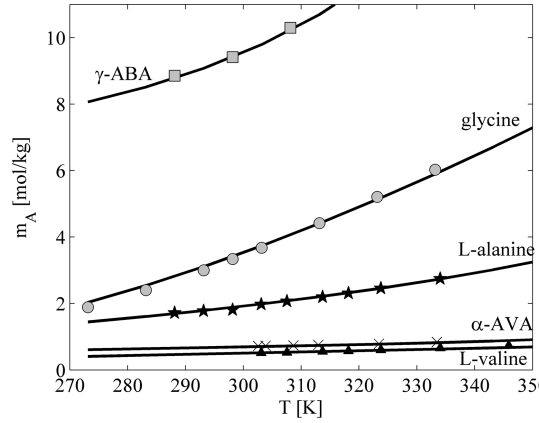

Figure 4. Amino-acid solubilities in water. Symbols represent experimental data: (squares) γ-ABA, (circles) glycine, (stars) L-alanine, (crosses) DL-α-AVA, (triangles) L-valine; lines are calculations with PC-SAFT.

valine, hydroxyproline, tyrosine, histidine, threonine, serine, leucine, methionine, cysteine, diglycine, α-ABA, γ-ABA, and α-AVA a temperature-dependent k_{ij} according to eq 12 is applied (see Table 5) especially for solubility calculations in a broad temperature range. These k_{ij} parameters are also used to simultaneously describe the temperature dependence of the other properties, e.g., solution densities (see Table 5).

Next to solubilities, activity coefficients can be precisely modeled with PC-SAFT. This is shown in Figure 5 which illustrates amino-acid activity coefficients at 25 °C. Whereas for a few amino acids (e.g., alanine, hydroxyproline) this value is close to unity over the whole concentration range, the $\gamma^*_{\mathrm{cysteine}}$ and $\gamma^*_{\mathrm{methionine}}$ values strongly decrease with increasing concentration. Cysteine and methionine have the lowest activity coefficients of all amino acids which might be caused by their sulfuric character. In contrast, leucine activity coefficients increase very strongly with increasing concentration. Note, that Kurhe et al.[38] also presented leucine activity coefficients stemming from osmotic coefficients. However, their data does not agree with our own measurements which will be discussed further down in the discussion part.

The sequence of activity coefficients within some amino-acid series is in particular considered in the next chapter.

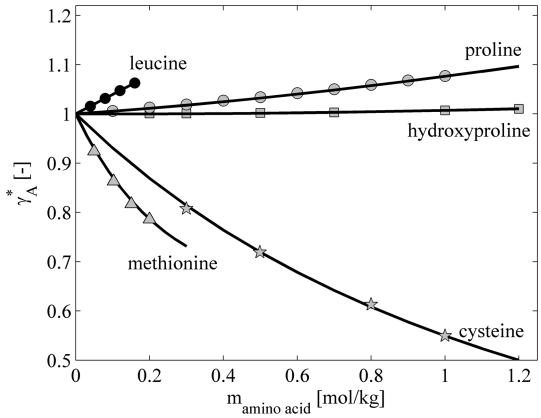

Figure 5. Amino-acid activity coefficients in aqueous solutions at 25 °C. Symbols represent experimental data: (full circles) leucine, (open circles) proline, (squares) hydroxyproline, (stars) cysteine, (triangles) methionine) obtained by Gibbs−Duhem conversion of osmotic coefficients (eq 11); lines are calculations with PC-SAFT.

6. Discussion

In general, amino acids have hydrophilic head groups (COOH and NH_2) attached to an aliphatic tail. Hence, two opposite interaction sites exist in aqueous amino-acid solutions: hydrophilic and hydrophobic ones which determine the water−water and water−solute interactions in such solutions. In the following, these interactions will be discussed by examining the trends of osmotic coefficients/WACs for various series of aqueous amino-acid and peptide solutions.

Series: Glycine/Diglycine/Triglycine. Starting from the smallest amino acid glycine, the influence of forming oligomers can be determined from the series "glycine/diglycine/triglycine". Figure 6a illustrates increasing water activity coefficients (WACs) with growing backbone length of the glycine peptides. High WACs cause high vapor pressures, that is, more water molecules pass into the vapor phase than in an ideal solution. This can be explained by investigating the partial molar excess enthalpy and excess entropy of water which are related to the WAC values by

$$\ln \gamma_{water} = \frac{\bar{h}^E_{water}}{RT} - \frac{\bar{s}^E_{water}}{R} \quad (14)$$

Experimental partial molar excess enthalpies are readily available in the literature.[70,72−74] Using experimentally determined WACs and using eq 14 one obtains the partial molar excess entropies of water. The excess enthalpies and entropies of water at 25 °C are shown in Figure 6b,c. The $-s^E$ values are all negative and decrease with increasing solute concentration. This means that the solutes disrupt the structure of water ("water-structure breakers"). This effect increases from glycine to triglycine solutions which might be due to the inserted polar peptide groups,[70] that is, substances with additional polar groups cause a more disrupted water structure. This is consistent with the fact that amino acids with other polar groups (OH or SH) also cause high positive water excess entropies.[74]

At the other hand, according to eq 14, increasing positive excess entropies for water would lead to decreasing WAC values whereas the opposite behavior is found. This means that the excess enthalpy over compensates the excess entropy and the thermodynamic behavior of the peptide solutions is thus determined by enthalpic effects. The latter becomes obvious from comparing Figures 6a and 6b which show the same trend for WAC and partial molar excess enthalpies of water.

Homologous Series: Glycine/Alanine/α-ABA/α-AVA. The amino-acid series "glycine/alanine/α-ABA/α-AVA" can also be formulated as "(Gly)-H/(Gly)-CH_3/(Gly)-CH_2-CH_3/(Gly)-CH_2-CH_2-CH_3". Here, the aliphatic tail of the amino acid is successively increased by adding one methyl group to the invariably present glycyl basis. Thus, this series allows for studying the effect of the amino-acid tail length on the interactions in aqueous solution.

Experimental and modeled WACs are shown in Figure 7a. According to the results presented in Figure 6a one would expect the lowest WAC values for the system containing glycine, the smallest molecule. However, the contrary is observed: the WAC value is the highest for the glycine system. The WACs are sequenced in the order α-AVA < α-ABA < alanine < glycine. To understand this apparent contradiction, again partial molar excess enthalpies and entropies of water are investigated in Figure 7b,c. With increasing amino-acid chain length this time decreasing water excess entropies are observed (negative values increase), that is, the larger molecules are "water-structure makers". This might be caused by hydrophobic effects as the introduction of nonpolar side groups strengthens the water network. As shown for the peptide solutions (Figure 6), WACs and excess enthalpies of water show the same trend, whereas WACs and negative excess entropies of water are oppositely directed. This again clearly points to the enthalpy-driven behavior of osmotic/activity coefficients in amino-acid solutions as already found for the series glycine/diglycine/triglycine shown in Figure 6.

From the results illustrated in Figures 6 and 7 it can be concluded that the observed series of osmotic/water activity coefficients in amino-acid and peptide solutions are caused by enthalpic effects. The latter are directly related to the polarity of the solutes: Increasing solute polarity results in increasing water excess enthalpies which cause also increasing WACs. The fact that negative water excess entropies are oppositely directed compared to WACs reveals that entropic effects play only a minor role for osmotic/activity coefficients in amino-acid solutions.

Homologous Series: α-ABA/α-iso-ABA//α-AVA/Valine//Leucine. To discuss the effect of branched methyl groups on the interactions in amino-acid systems, osmotic coefficients of two pairs of amino-acid isomers are compared. Within this series, α-ABA and α-AVA are aliphatic amino acids, whereas branched methyl groups are present within α-isoABA, valine, and leucine, respectively.

Figure 8 shows the influence of adding a methyl group to the backbone (α-ABA → α-AVA) or adding a methyl group as a branch (α-ABA → α-isoABA) on the respective osmotic coefficients. Obviously both linear and branched additions of a methyl group cause a similar increase of the osmotic coefficients. Another observation is that osmotic coefficients of α-isoABA solutions are only a little higher than α-ABA, whereas they increase stronger for the C6 amino acids (α-AVA → valine).

The knowledge of how methyl groups (branched/linear) influence osmotic coefficients allows an estimation of the qualitative correctness of experimental data. The new osmotic coefficients of leucine/water solutions determined within this work remarkably differ from the data recently presented by Kurhe et al.[38] However, due to the experience from the systems considered within this chapter, the osmotic coefficients of leucine solutions have to be higher than those of valine solutions. This is indeed observed by our own measurements (Figure 8), whereas the data by Kurhe et al. give osmotic coefficients for leucine solutions which are even below unity.

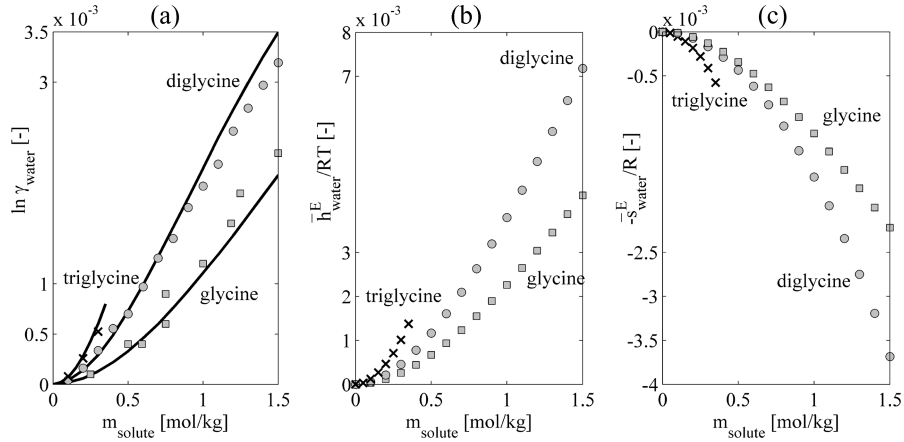

Figure 6. (a) Water activity coefficients (data see Table 5), (b) partial molar excess enthalpies, and (c) negative entropies of water[70,72] in aqueous amino-acid/peptide solutions as a nction of solute molality at 25 °C. Symbols represent experimental data: glycine (crosses), diglycine (circles), and triglycine (squares); lines are calculations with PC-SAFT.

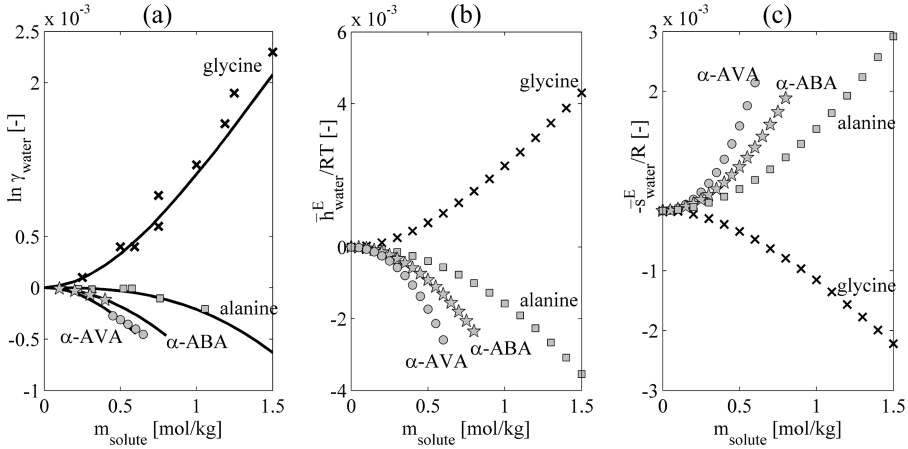

Figure 7. (a) Water activity coefficients (data see Table 5), (b) partial molar excess enthalpies, and (c) entropies of water[73,74] in aqueous amino-acid solutions as function of solute molality at 25 °C. Symbols represent experimental data: glycine (crosses), alanine (squares), α-ABA (stars), and α-AVA (circles); lines are calculations with PC-SAFT.

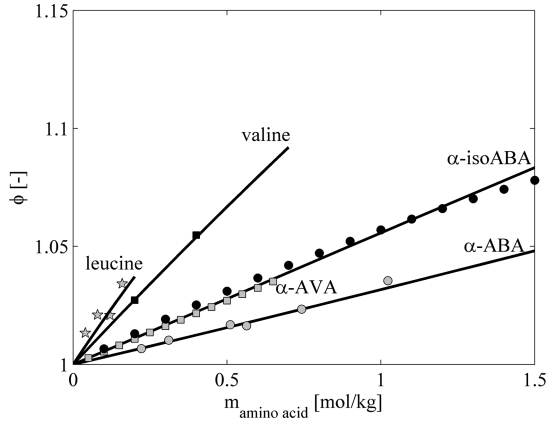

Figure 8. Osmotic coefficients (data see Table 5) of aqueous amino-acid solutions as function of solute molality at 25 °C. Symbols represent experimental data (α-ABA (open circles), α-isoABA (full circles), α-AVA (open squares), valine (full squares), leucine (stars); lines are modeled with PC-SAFT.

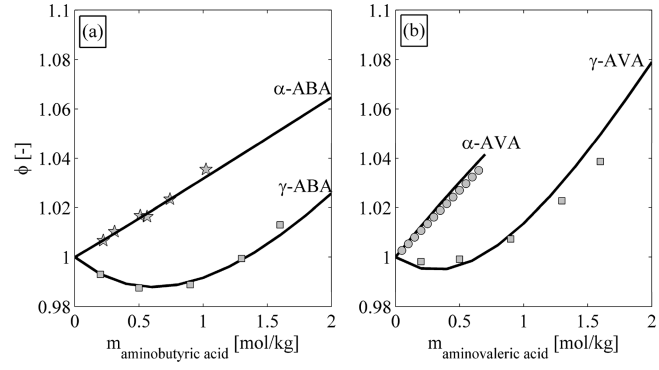

Figure 9. Osmotic coefficients of aqueous solutions as function of amino-acid molality at 25 °C. Symbols represent experimental data: (a) α-ABA (stars), γ-ABA (squares); (b) α-AVA (circles); γ-AVA (squares); lines are modeled with PC-SAFT.

Homologous Series: α-ABA/γ-ABA and α-AVA/γ-AVA. The influence of the location of the amino group on the intermolecular interactions becomes clear when investigating amino acids of the same chain length. In α-ABA both, the carboxyl group as well as the amino group are attached to the α-carbon. Hence, the dipole moment is comparatively small. In γ-ABA the position of the amino group is shifted by two carbon atoms. Therefore, the γ-ABA reveals a larger dipole moment and an effectively shorter hydrophobic tail. Just like within the series glycine/alanine/α-ABA/α-AVA the amino acid possessing the (effectively) smallest hydrophobic tail causes the lowest osmotic coefficients. These experimental observations are correctly described with PC-SAFT (see Figure 9): in the whole concentration range up to 2 mol/kg the osmotic coefficients follow the trend $\Phi_{(\alpha\text{-ABA/water})} < \Phi_{(\gamma\text{-ABA/water})}$. Also the

dispersion-energy parameters between amino acid and water are ranked in the order $u_{\gamma\text{-ABA/water}}/k_B < u_{\alpha\text{-ABA/water}}/k_B$ (see Table 5) for equal association parameters. The fact that the γ-solutes possess effectively shorter hydrophobic tails can also be found in the PC-SAFT parameter m_{seg} (number of segments) which decreases from the α- to the γ-solutes at equal segment diameters. The same conclusions are valid for the aminovaleric acids.

The osmotic coefficients of water in solutions of β-ABA, γ-ABA, and γ-AVA show a minimum at an amino-acid concentration of about 1 mol/kg. This behavior is also experimentally observed in aqueous electrolyte solutions.[26] In analogy to these systems, this behavior might be caused by long-range solute−solute interactions for the β- and γ-solutes (large dipole moments) in the low-concentration region. At higher solute concentrations, the short-range interactions become increasingly important and the osmotic coefficients are again increasing.

7. Ternary Systems Containing Two Amino Acids

Up to this point, binary aqueous mixtures have been investigated. Model parameters have been fitted for amino acids as well as for small peptides. In a previous paper[1] we have already shown that amino-acid solubilities can be predicted in multisolute aqueous solutions based on these pure-component parameters only. No additional parameters between two amino acids had to be introduced for most of the systems, for example, for aqueous solutions composed of valine/leucine or valine/alanine at temperatures between 25 and 60 °C.

In the following, the applicability of PC-SAFT for modeling osmotic coefficients of aqueous solutions containing two amino acids will be discussed briefly. As osmotic or activity coefficients for such systems are not available in literature they were measured by vapor-pressure osmometry for the systems water/alanine/valine and water/glycine/valine at 25 °C. In both systems the valine concentration varies until saturation, whereas the molalities of alanine and glycine were kept constant. The respective experimental values are given in Table 6.

As it becomes obvious from Figure 10, the addition of valine causes a remarkable increase in the osmotic coefficients for both amino-acid solutions. The influence of valine on the osmotic coefficients seems to be qualitatively the same for both systems; that is, the effect is independent of the first amino acid (alanine or glycine, respectively). The modeling results in Figure 10 show that PC-SAFT is able to predict (using only the parameters obtained from the single-amino-acid solutions) the osmotic coefficients of these mixed-amino-acid solutions. As earlier for modeling amino-acid solubilities,[1] the interaction between the two solutes does not have to be parametrized ($k_{ij} = 0$). Thus, PC-SAFT combined with the presented amino-acid parameters is expected to predict thermodynamic properties of aqueous solutions over a wide concentration range (lower concentration, osmotic coefficients; higher concentration, solubilities).

8. Conclusion

Thermodynamic properties of 28 aqueous amino-acid and peptide solutions were investigated. For solutions of the sulfuric

Table 6. Experimental Osmotic Coefficients in Aqueous Solutions Containing Alanine/Valine and Glycine/Valine at 25°C

$m_{alanine}$ (mol/kg)	m_{valine} (mol/kg)	Φ (−)	$m_{glycine}$ (mol/kg)	m_{valine} (mol/kg)	Φ (−)
0.500	0.000	1.0069	0.593	0.000	0.95188
0.500	0.199	1.0093	0.593	0.199	0.96948
0.500	0.501	1.0478	0.593	0.501	1.0057

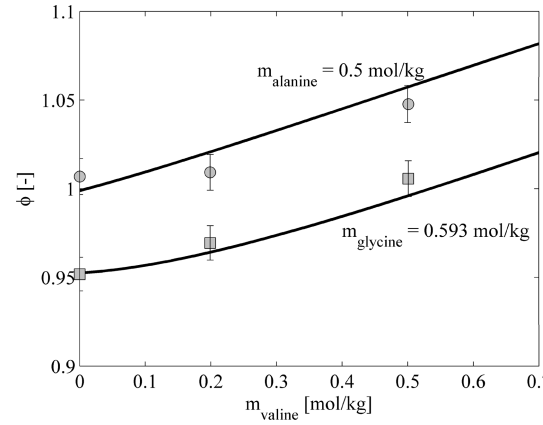

Figure 10. Osmotic coefficients of aqueous solutions containing two amino acids as a function of valine molality at 25 °C. Symbols represent experimental data: system water/alanine/valine (circles), system water/glycine/valine (squares); lines are predictions with PC-SAFT. Error bars give the estimated uncertainty of our data within ±1%.

methionine and cysteine molecules, water activity coefficients were determined for the first time. Such data is of crucial interest as many proteins (e.g., keratin) mainly consist of these amino acids. Moreover, osmotic coefficients were measured for leucine which differ remarkably from existing literature data.

Osmotic coefficients in aqueous peptide solutions decrease with increasing molecular weight of the peptide. However, this is reversed in aqueous amino-acid systems: the successive addition of one methylene group to the glycyl basis in the series from glycine to α-AVA causes increasing osmotic coefficients. This apparent contradiction is caused by the enthalpy-driven behavior in amino-acid solutions: whereas glycine and its peptides induce an increasing of the partial molar excess enthalpy of water, the addition of hydrophobic amino acids to water causes decreased enthalpies. The series of water excess enthalpies is in accordance with the series of water activity coefficients, that is, unpolar solutes cause lower water activity coefficients and therewith strengthen the water−water interaction in the liquid phase and vice versa for polar solutes. Moreover, increasing osmotic coefficients (and decreasing water activity coefficients) are observed for amino-acid isomers with (1) branched instead of aliphatic methylene groups and (2) with decreasing dipole moment (from γ- to α-amino acids).

The PC-SAFT model has been applied for modeling solution densities, activity coefficients, and solubilities of the 23 amino acids and 5 peptides in water. Using a single parameter set per solute, PC-SAFT is able to accurately describe all the considered thermodynamic properties. Moreover, PC-SAFT allows for quantitative predictions of osmotic coefficients in systems containing two amino acids without fitting additional parameters.

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Nomenclature

Roman Symbols

a = Helmholtz free energy per number of molecules (J)

a = activity (−)

A = Helmholtz free energy (J)
h = molar enthalpy (J/mol)
Δh^{SL} = melting enthalpy (kJ/kg)
k_B = Boltzmann constant, 1.38065×10^{-23} J/K (J/K)
k_{ij} = binary interaction parameter (−)
$k_{ij,T}$ = temperature-dependent binary interaction parameter (1/K)
$k_{ij,25\ °C}$ = binary interaction parameter at 25 °C (−)
m = molality (moles solute i per kg solvent) (mol/kg)
M = molecular weight (g/mol)
m_{seg} = number of segments (−)
N = number of association sites (−)
p = pressure (kPa, bar)
R = ideal gas constant (J/(mol/K))
s = molar entropy (J/(mol/K))
T = temperature (K)
T^{SL} = melting temperature (K)
x = mole fraction (−)

Greek Symbols
α, γ = α and γ amino acids (−)
γ_i = symmetrical activity coefficient of component i (related to pure component) (−)
γ_i^* = asymmetrical activity coefficient of component i (related to infinite dilution) (−)
φ_i = fugacity coefficient of component I (−)
u/k_B = dispersion-energy parameter (K)
$\varepsilon_{hb}^{AiBi}/k_B$ = association-energy parameter (K)
κ_{hb}^{AiBi}/k_B = association-volume parameter (−)
Φ = osmotic coefficient (−)
ρ = density (kg/m^3)
ν = stoichiometric factor (−)
σ_i = temperature-independent segment diameter of molecule i (Å)

Subscripts
A = amino acid
i,j = component indeces
T = function of temperature
seg = segment
W = water
0 = pure substance

Superscripts
assoc = association
disp = dispersion
E = excess
hc = hard chain
l = liquid phase
m = based on molality
res = residual
v = vapor phase
∞ = infinite dilution

Abbreviations
AAD = absolute average deviation
ABA = aminobutyric acid
isoABA = aminoisobutyric acid
ARD = absolute average relative deviation
AVA = aminovaleric acid
EOS = equation of state
g^E = excess Gibbs energy
MIAC = mean ionic activity coefficient
NRTL = non-random-two-liquid model
WAC = water activity coefficient

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