

Supporting information

Salt Effects on the Solubility of Aromatic and Dicarboxylic Amino Acids in Water

Mehriban Aliyeva^{1,2}, Paula Brandão², José R. B. Gomes², João A. P. Coutinho², Christoph Held^{3,*}, O. Ferreira^{1,*}, Simão P. Pinho¹

¹Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, Campus de Santa Apolónia, 5300-253 Bragança, Portugal

²CICECO – Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal

³Laboratory of Thermodynamics, Department of Biochemical and Chemical Engineering, TU Dortmund University, Emil-Figge-Str. 70, 44227 Dortmund, Germany

*To whom correspondence should be addressed:

Olga Ferreira, Tel.: +351273303087, E-mail: oferreira@ipb.pt

Christoph Held, Tel.: +49 (0)231/755-2086, E-mail: christoph.held@tu-dortmund.de

Table S1. Summary of the literature solubility data of the studied amino acids in aqueous solutions containing inorganic salts.

Amino acid	Salts	<i>T</i> range/K	Salt concentration range	Reference
D-aspartic acid	NaCl KCl	293 – 344	0 - 1.8251 mol/(kg of solution) 0 – 1.4360 mol/(kg of solution)	[1]
L-aspartic acid	NaCl	293 – 338	0 - 3.0446 mol/(kg of solution)	[1]
	NaCl	298.15	0 - 5.556 mol/(kg of H ₂ O)	[2]
	NaCl KCl, NaNO ₃ KNO ₃ NH ₄ Cl NH ₄ NO ₃	298.2	0 - 2 mol/(kg of H ₂ O)	[3]
L-glutamic acid	NaCl	298.15	0.001 - 5.246 mol/(kg of H ₂ O)	[2]
	NaCl KCl	298.15- 323.15	0 – 3 mol/(kg of H ₂ O)	[4]
DL-tyrosine	NaCl	298.15	0 - 4.999 mol/(L of solution)	[5]
L-tyrosine	NaCl	298.15	0; 1 and 3 mol/(dm ³ of solution)	[6]
	NaCl	298	0 - 3 mol/(dm ³ of solution)	[7]
	NaCl	298.15	0 - 3 mol/(kg of H ₂ O)	[8]
DL-tryptophan	NaCl	298.15	0 - 5.005 mol/(L of solution)	[5]
tryptophan ^a	CuCl ₂ ZnCl ₂ NiCl ₂	Room <i>T</i>	0 – 0.5 mol/(L of solution)	[9]

^a Isomer not specified.

Table S2. PC-SAFT pure-component parameters of water and AA, the binary interaction parameters between AA and water, and melting properties from Do *et al.* [10].

	m_i^{seg}	σ_i	$\frac{u_i}{k_B}$	$\frac{\varepsilon^{AiBi}}{k_B}$	κ^{AiBi}	N	k_{ij}	T_{0i}^{SL}	Δh_{0i}^{SL}	Δa^{L-S}	Δb^{L-S}
	[-]	[Å]	[K]	[K]	[-]	[-]	[10 ⁻²]	[K]	[kJ·mol ⁻¹]	[J·mol ⁻¹ ·K ⁻²]	[J·mol ⁻¹ ·K ⁻¹]
H ₂ O	1.2047	^a	353.94	2425.67	0.045	-	-	-	-	-	-
Gly ^c	4.850	2.327	216.960	2598.060	0.039	2	-5.85 ^c	569	24.96	-0.041	41.648
Ala ^c	5.465	2.522	287.590	3176.600	0.082	2	-6.12 ^c	608	25.99	-0.057	39.923
Val ^b	7.485	2.589	306.410	3183.800	0.039	2	-7.57 ^b	529	46.72	-0.102	73.915
Leu ^b	8.304	2.700	330.000	3600.000	0.020	2	-6.39 ^b	518	49.09	-0.052	47.3
Ile ^b	8.241	2.586	281.884	2207.529	0.001	2	-8.75 ^b	595	47.11	-0.053	51.604
Pro ^b	6.981	2.548	289.720	5527.750	0.036	2	-6.99 ^b	527	16.30 ^e	-0.05987 ^e	40.417 ^e
Ser ^b	7.024	2.284	236.920	2671.930	0.039	3	-2.57 ^b	519	32.98	-0.079	90.29
Thr ^b	6.329	2.606	325.370	2519.410	0.039	3	-2.78 ^b	587	36.64	-0.027	78.257
Asp ^d	5.827	2.522	287.625	2544.234	0.041	3	1.45 ^d	610	35.73	-0.221	176.159
Glu ^d	6.831	2.560	227.192	2544.234	0.041	3	-4.45 ^d	566	48.24	-0.16	115.101
Phe ^d	9.310	2.690	391.827	3206.094	0.010	2	-5.18 ^d	579	60.66	-0.139	265.092
Tyr ^b	8.139	2.280	289.370	2500.000	0.040	3	-0.0277 ^f	678	49.77	-0.017	74.282
Trp ^d	10.577	2.825	260.641	2563.249	0.024	3	-7.68	620	65.55	-0.407	273.799

^a Temperature-dependent segment diameter $\sigma = 2.7927 + 10.11 \exp(-0.01775T) - 1.417 \exp(-0.01146T)$ and parameters from Cameretti and Sadowski [11]; ^b pure-component parameters from Held *et al.* [12]; ^c pure-component parameters from Chua *et al.* [13]; ^d pure-component parameters from Do *et al.* [10]; ^e determined in this work; ^f this value is a correction of the misprinted value presented in the original reference [10].

Table S3. PC-SAFT pure-component parameters of ions, and k_{ij} between ion and water and between anion and cation. All parameters inherited from Held *et al.* [14].

	m_{ion}^{seg}	σ_{ion}	$\frac{u_{ion}}{k_B}$	k_{ij}	k_{ij}
	[-]	[Å]	[K]	ion-water	anion-cation
	[-]	[Å]	[K]	[-]	[-]
K ⁺	1.000	3.3417	200.00	0.20	0.064 (K ⁺ -Cl ⁻)
NH ₄ ⁺	1.000	3.5740	230.00	0.064	-1.000 (NH ₄ ⁺ - SO ₄ ²⁻)
SO ₄ ²⁻	1.000	2.6491	80.00	0.25	-1.000 (NH ₄ ⁺ - SO ₄ ²⁻)
Cl ⁻	1.000	2.7560	170.00	-0.25	0.064 (K ⁺ -Cl ⁻)

Table S4. Summary of the literature solubility data of the amino acids in pure water, studied in this work.

Amino acid	Solubility of AAs/ (g of AA)/(1000 g of water)	Reference	Literature average \pm standard deviation
L-aspartic acid	5.235	[1]	5.22 \pm 0.31
	5.00	[15]	
	5.393	[16]	
	4.95	[17]	
	4.99	[18]	
	5.744	[2]	
	5.09	[19]	
	4.9	[20]	
	5.73	[10]	
	5.140	[3]	
L-glutamic acid	8.502	[21]	8.90 \pm 0.69
	8.683	[22]	
	8.61	[17]	
	8.5434	[23]	
	10.8	[19]	
	8.7	[20]	
	8.58	[24]	
	8.62	[4]	
	9.072	[2]	
	8.88	[10]	
	8.568	This work	
L-tryptophan	13.8	[25]	13.5 \pm 1.2
	12.8	[26]	
	12.9	[27]	
	11.73	[28]	
	15.6	[29]	
	13.8	[19]	
	13.99	[10]	
	12.639	This work	
L-tyrosine	0.451	[25]	0.472 \pm 0.081
	0.453	[15]	
	0.475	[26]	
	0.5026	[30]	
	0.35	[28]	
	0.6	[10]	
	0.427	This work	

Table S5. The average ARD between ePC-SAFT and experimental solubility for N data points.

		ARD Solubility												
		Asp	Glu	Trp	Tyr	Gly	Ala	Ile	Ser	Thr	Val	Pro	Leu	Phe
KCl	ARD (%)	9.6	7.8	21.5	11.8	2.7	4.0	3.2	8.2	2.3	7.4	9.3	10.6	2.9
	N	3	5	5	5	3	2	7	7	7	2	2+6	3	3
	Ref.	[3]	^a	^a	^a	[3]	[31]	[32]	[32]	[32]	[32]	[31]	[31,33]	[3]
(NH ₄) ₂ SO ₄	ARD (%)	14.2	14.6	17.2	14.2	1.8	5.8	8.1	10.2	6.1	10.4	7.1	-	-
	N	5	5	5	5	8	2	8	8	8	4+2	2		
	Ref.	^a	^a	^a	^a	[34]	[31]	[34]	[34]	[34]	[34]	[31,35]	[31]	

^a Measured in this work.

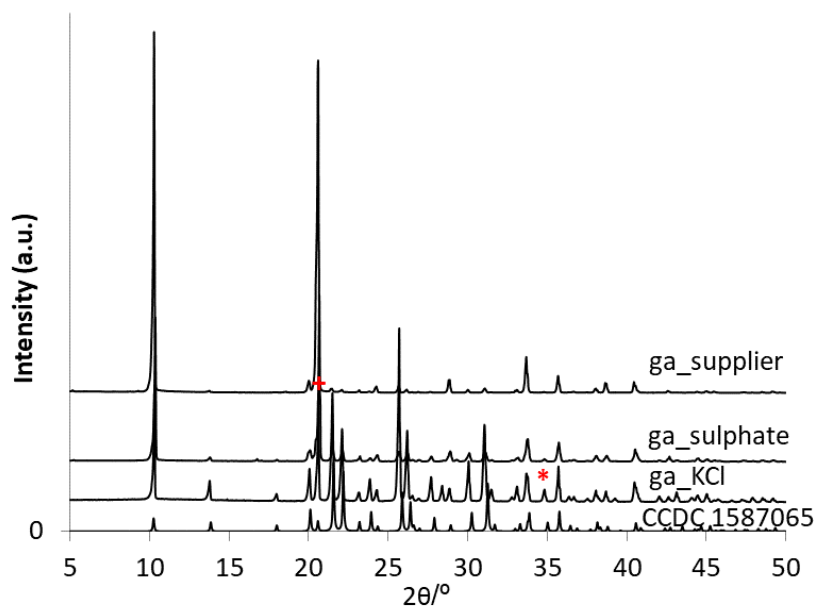


Figure S1. Comparison of the experimental X-ray powder diffraction pattern of the solid phase samples of L-glutamic acid (from supplier and filtrated from the ternary saturated solutions containing a 2 molal salt concentration) with the powder pattern calculated from the single-crystal X-ray diffraction data CCDC 1587065 [36]. The symbols * and + locate the strong peaks of KCl (at around 35 $2\theta^\circ$, [37]) and $\text{NH}_4(\text{SO}_4)_2$ (at around 21 $2\theta^\circ$, [38]), respectively.

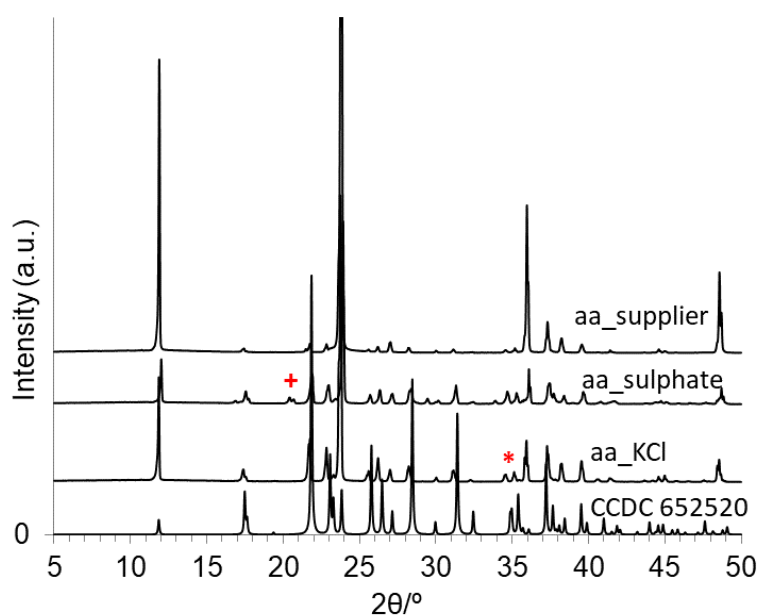


Figure S2. Comparison of the experimental X-ray powder diffraction pattern of the solid phase samples of L-aspartic acid (from supplier and filtrated from the ternary saturated solutions containing a 2 molal salt concentration) with the powder pattern calculated from the single-crystal X-ray diffraction data CCDC 652520 [39]. The symbols * and + locate the strong peaks of KCl (at around 35 $2\theta^\circ$, [37]) and $\text{NH}_4(\text{SO}_4)_2$ (at around 21 $2\theta^\circ$, [38]), respectively.

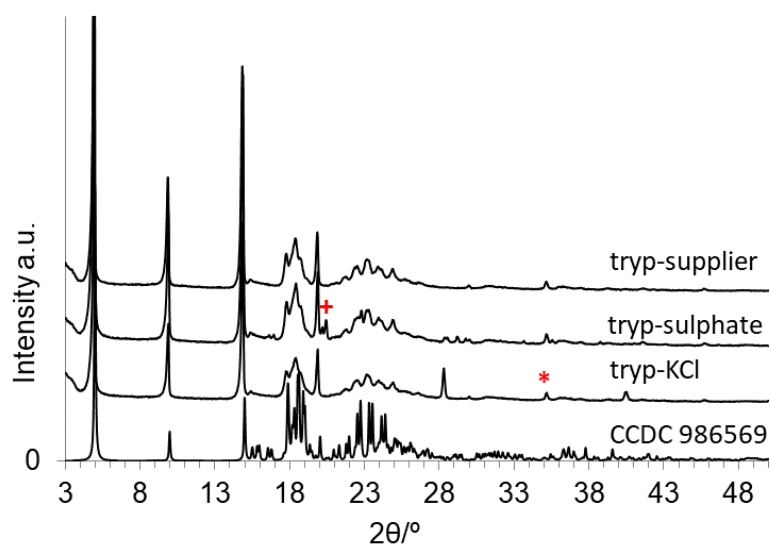


Figure S3. Comparison of the experimental X-ray powder diffraction pattern of the solid phase samples of L-tryptophan (from supplier and filtrated from the ternary saturated solutions containing a 2 molal salt concentration) with the powder pattern calculated from the single-crystal X-ray diffraction data CCDC 986569 [40]. The symbols * and + locate the strong peaks of KCl (at around 35 $2\theta^\circ$, [37]) and $\text{NH}_4(\text{SO}_4)_2$ (at around 21 $2\theta^\circ$, [38]), respectively.

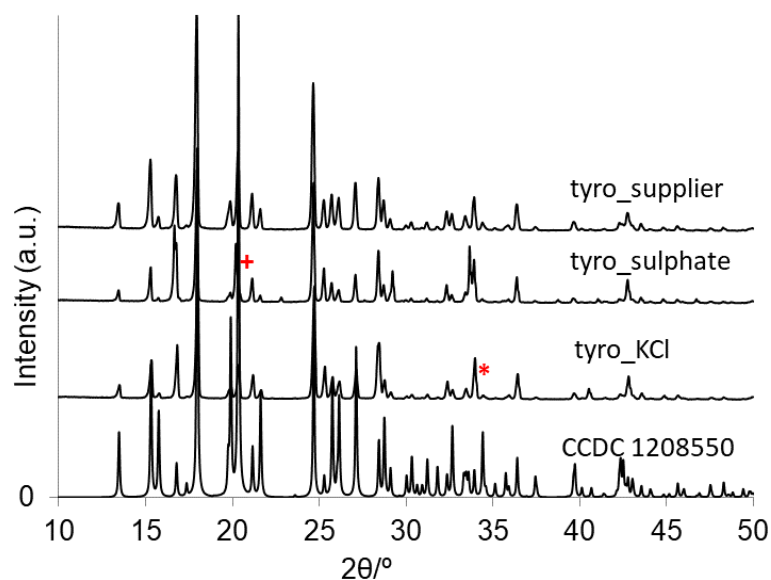


Figure S4. Comparison of the experimental X-ray powder diffraction pattern of the solid phase samples of L-tyrosine (from supplier and filtrated from the ternary saturated solutions containing a 2 molal salt concentration) with the powder pattern calculated from the single-crystal X-ray diffraction data CCDC 1208550 [41]. The symbols * and + locate the strong peaks of KCl (at around 35 $2\theta^\circ$, [37]) and $\text{NH}_4(\text{SO}_4)_2$ (at around 21 $2\theta^\circ$, [38]), respectively.

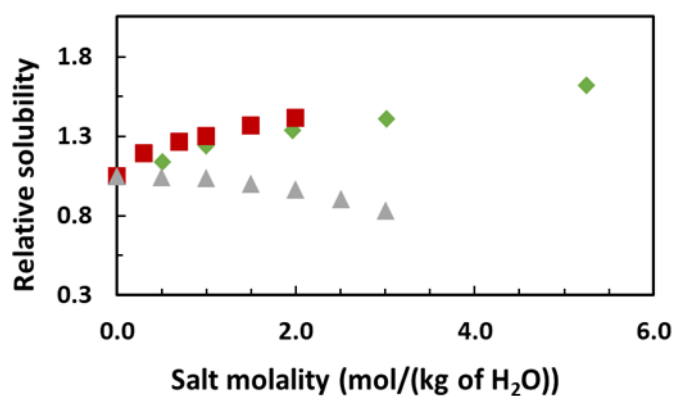


Figure S5. Relative solubility of L-glutamic acid as a function of salt molality at 298.2 K: ◆, NaCl [2]; ■, KCl (this work); ▲, KCl [4].

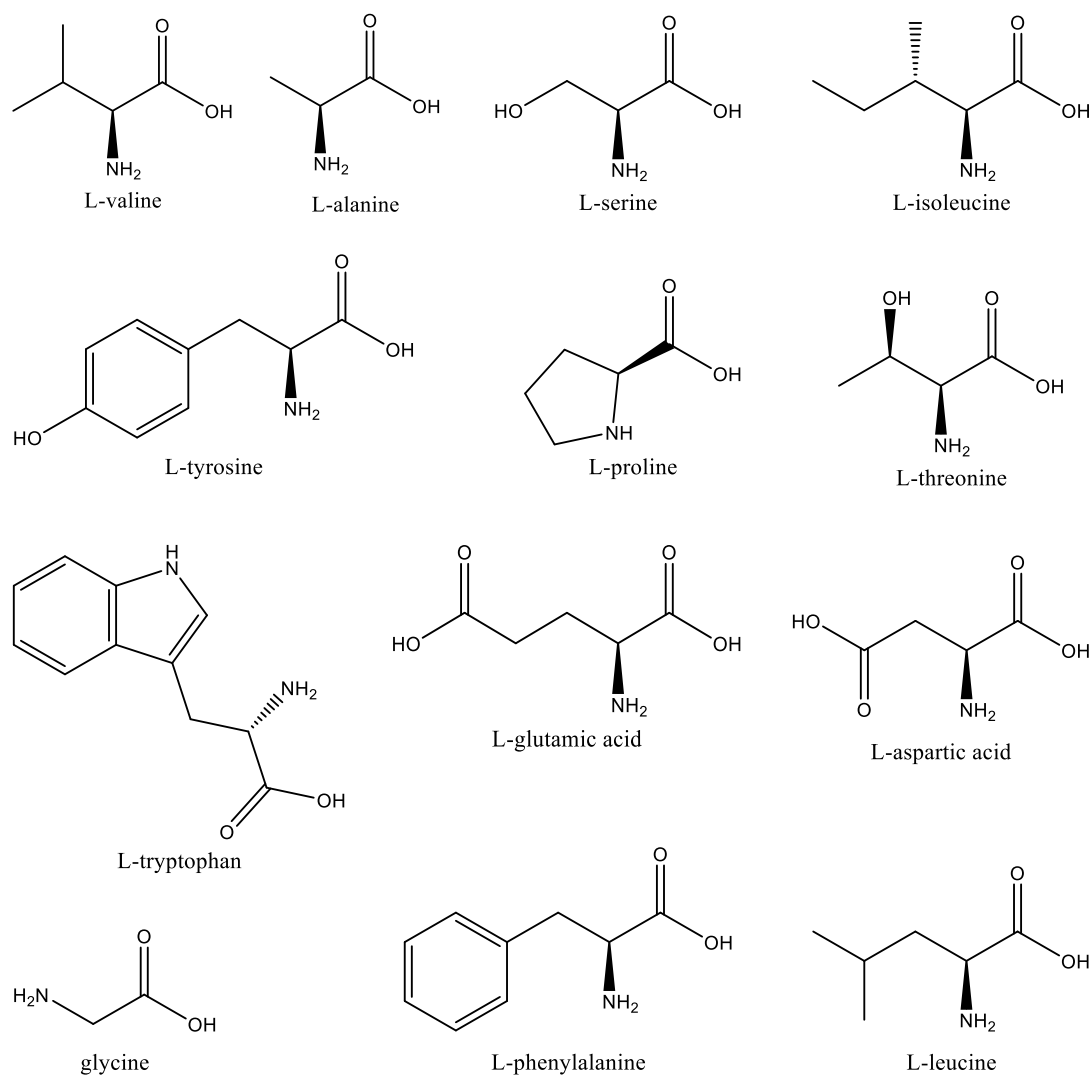


Figure S6. Chemical structures of the AA studied in this work.

References

- [1] J. Wang, J. Wang, J. Liu, S. Wang, J. Pei, Solubility of D-aspartic acid and L-aspartic acid in aqueous salt solutions from (293 to 343) K, *J Chem Eng Data*. 55 (2010) 1735–1738.
- [2] C. Bretti, R.M. Cigala, O. Giuffrè, G. Lando, S. Sammartano, Modeling solubility and acid-base properties of some polar side chain amino acids in NaCl and (CH₃)₄NCl aqueous solutions at different ionic strengths and temperatures, *Fluid Phase Equilib*. 459 (2018) 51–64.
- [3] M. Aliyeva, P. Brandão, J.R.B. Gomes, J.A.P. Coutinho, O. Ferreira, S.P. Pinho, O. Ferreira, Electrolyte Effects on the Amino Acid Solubility in Water: Solubilities of Glycine, L-Leucine, L-Phenylalanine, and L-Aspartic Acid in Salt Solutions of (Na⁺, K⁺, NH₄⁺)/(Cl⁻, NO₃⁻), *Ind Eng Chem Res*. (2022).
- [4] M.J. Abualreish, A. Noubigh, Evaluation of thermodynamic properties and correlation of L-glutamic acid solubility in some aqueous chloride solutions from 298.15 to 323.15 K, *Can J Chem*. 97 (2019) 615–620.
- [5] C. Bretti, F. Crea, C. de Stefano, S. Sammartano, G.V. Dipartimento, Some thermodynamic properties of DL-tyrosine and DL-tryptophan. Effect of the ionic medium, ionic strength and temperature on the solubility and acid-base properties, *Fluid Phase Equilib*. 314 (2012) 185–197.
- [6] R. Carta, G. Tola, Solubilities of L-cystine, L-tyrosine, L-leucine, and glycine in aqueous solutions at various pHs and NaCl concentrations, *J Chem Eng Data*. 41 (1996) 414–417.
- [7] R. Carta, Solubilities of L-cystine, L-tyrosine, L-leucine, and glycine in sodium chloride solutions at various pH values, *Journal of Chemical Thermodynamics*. 30 (1998) 379–387.
- [8] S. Roy, P.S. Guin, K. Mahali, B.K. Dolui, Amino acid solubility under the influence of NaCl at 298.15 K, *J Mol Liq*. 218 (2016) 316–318.
- [9] G. Shi, Y. Dang, T. Pan, X. Liu, H. Liu, S. Li, L. Zhang, H. Zhao, S. Li, J. Han, R. Tai, Y. Zhu, J. Li, Q. Ji, R.A. Mole, D. Yu, H. Fang, Unexpectedly enhanced solubility of aromatic amino acids and peptides in an aqueous solution of divalent transition-metal cations, *Phys Rev Lett*. 117 (2016) 1–6.
- [10] H.T. Do, Y.Z. Chua, A. Kumar, D. Pabsch, M. Hallermann, D. Zaitsau, C. Schick, C. Held, Melting properties of amino acids and their solubility in water, *RSC Adv*. 10 (2020) 44205–44215.
- [11] L.F. Cameretti, G. Sadowski, Modeling of aqueous amino acid and polypeptide solutions with PC-SAFT, *Chemical Engineering and Processing: Process Intensification*. 47 (2008) 1018–1025.
- [12] C. Held, L.F. Cameretti, G. Sadowski, Measuring and modeling activity coefficients in aqueous amino-acid solutions, *Ind Eng Chem Res*. 50 (2011) 131–141.
- [13] Y.Z. Chua, H.T. Do, C. Schick, D. Zaitsau, C. Held, New experimental melting properties as access for predicting amino-acid solubility, *RSC Adv*. 8 (2018) 6365–6372.
- [14] C. Held, T. Reschke, S. Mohammad, A. Luza, G. Sadowski, EPC-SAFT revised, *Chemical Engineering Research and Design*. 92 (2014) 2884–2897.
- [15] J.B. Dalton, C.L.A. Schmidt, The solubilities of certain amino acids and related compounds in water, the densities of their solutions at twenty-five degrees, and the calculated heats of solution and partial molal volumes, *J Biol Chem*. 103 (1933) 549–578.

- [16] M.S. Dunn, F.J. Ross, L.S. Read, The solubility of amino acids, *J Biol Chem.* 103 (1933) 579–595.
- [17] X.Z. Jin, K.-C. Chao, Solubility of four amino acids in water and of four pairs of amino acids in their water solutions, *J Chem Eng Data.* 37 (1992) 199–203.
- [18] A. Apelblat, E. Manzurola, Solubilities of L-aspartic, DL-aspartic, DL-glutamic, p-hydroxybenzoic, o-anisic, p-anisic, and itaconic acids in water from T=278 K to T=345 K, *J Chem Thermodyn.* 29 (1997) 1527–1533.
- [19] K. Gekko, E. Ohmae, K. Kameyama, T. Takagi, Acetonitrile-protein interactions: amino acid solubility and preferential solvation, *Biochim. Biophys. Acta, Protein Struct. Mol. Enzymol.* 1387 (1998) 195.
- [20] C.-Y. Lee, J.-T. Chen, W.-T. Chang, I.-M. Shiah, Effect of pH on the solubilities of divalent and trivalent amino acids in water at 298.15K, *Fluid Phase Equilib.* 343 (2013) 30–35.
- [21] Y. Mo, L. Dang, H. Wei, Solubility of α -form and β -form of L-glutamic acid in different aqueous solvent mixtures, *Fluid Phase Equilib.* 300 (2011) 105–109.
- [22] S. Pabba, A. Kumari, T. Narra, P.K. Thella, B. Satyavathi, K. Shah, S. Kundu, S.K. Bhargava, Measurement and modeling of solid–liquid equilibria of L-glutamic acid in pure solvents and aqueous binary mixtures, *J Chem Eng Data.* 64 (2019) 1155–1165.
- [23] M.W. Hermanto, N.C. Kee, R.B.H. Tan, M.-S. Chiu, R.D. Braatz, Robust Bayesian estimation of kinetics for the polymorphic transformation of L-glutamic acid crystals, *AIChE Journal.* 54 (2008) 3248–3259.
- [24] E. Manzurola, A. Apelblat, Solubilities of L-glutamic acid, 3-nitrobenzoic acid, p-toluic acid, calcium-L-lactate, calcium gluconate, magnesium-DL-aspartate, and magnesium-L-lactate in water, *J Chem Thermodyn.* 34 (2002) 1127–1136.
- [25] Y. Nozaki, C. Tanford, The solubility of amino acids and related compounds in aqueous urea solutions, *J Biol Chem.* 238 (1963) 4074–4081.
- [26] Y. Nozaki, C. Tanford, The solubility of aminoacids, diglycine, and triglycine in aqueous guanidine hydrochloride solutions, *J Biol Chem.* 245 (1970) 1648–1652.
- [27] K. Sasahara, H. Uedaira, Solubility of amino acids in aqueous poly (ethylene glycol) solutions, *Colloid Polym Sci.* 271 (1993) 1035–1041.
- [28] N.A. Bowden, J.P.M. Sanders, M.E. Bruins, Solubility of the proteinogenic α -amino acids in water, ethanol, and ethanol–water mixtures, *J Chem Eng Data.* 63 (2018) 488–497.
- [29] W. Zhu, Y. Fan, Q. Xu, X. Liu, B. Heng, W. Yang, Y. Hu, Saturated solubility and thermodynamic evaluation of L-Tryptophan in Eight Pure Solvents and Three Groups of Binary Mixed Solvents by the Gravimetric Method at T = 278.15-333.15 K, *J Chem Eng Data.* 64 (2019) 4154–4168.
- [30] Q. He, Y. Cong, M. Zheng, A. Farajtabar, H. Zhao, Solubility of L-tyrosine in aqueous solutions of methanol, ethanol, n-propanol and dimethyl sulfoxide: Experimental determination and preferential solvation analysis, *J Chem Thermodyn.* 124 (2018) 123–132.

- [31] C. Held, T. Reschke, R. Müller, W. Kunz, G. Sadowski, Measuring and modeling aqueous electrolyte/amino-acid solutions with ePC-SAFT, *Journal of Chemical Thermodynamics*. 68 (2014) 1–12.
- [32] L.A. Ferreira, E.A. Macedo, S.P. Pinho, KCl effect on the solubility of five different amino acids in water, *Fluid Phase Equilib.* 255 (2007) 131–137.
- [33] S. Roy, P.S. Guin, K. Mahali, B.K. Dolui, Role of electrolytes in the solubility of L-proline and its transfer free energetics, *J Mol Liq.* 223 (2016) 927–933.
- [34] L.A. Ferreira, E.A. Macedo, S.P. Pinho, The effect of ammonium sulfate on the solubility of amino acids in water at (298.15 and 323.15) K, *Journal of Chemical Thermodynamics*. 41 (2009) 193–196.
- [35] L.I.N. Tome, S.P. Pinho, M. Jorge, J.R.B. Gomes, J.A.P. Coutinho, Salting-in with a salting-out agent: Explaining the cation specific effects on the aqueous solubility of amino acids, *J Phys Chem B*. 117 (2013) 6116–6128.
- [36] M.T. Ruggiero, J. Sibik, J.A. Zeitler, T.M. Korter, Examination of L-Glutamic Acid Polymorphs by Solid-State Density Functional Theory and Terahertz Spectroscopy, *J Phys Chem A*. 120 (2016) 7490–7495.
- [37] Will G., Energiedispersion und Synchrotronstrahlung: eine neue Methode und eine neue Strahlenquelle für die Röntgenbeugung, *Fortschritte Der Mineralogie*. 59 (1981) 31–94.
- [38] E.O. Schlemper, W.C. Hamilton, Neutron-diffraction study of the structures of ferroelectric and paraelectric ammonium sulfate, *J Chem Phys*. 44 (1966) 4498–4509.
- [39] E.E. Bendeif, C. Jelsch, The experimental library multipolar atom model refinement of L-aspartic acid, *Acta Crystallogr C*. 63 (2007) o361–o364.
- [40] C.H. Görbitz, K.W. Törnroos, G.M. Day, Single-crystal investigation of L-tryptophan with $Z' = 16$, *Acta Crystallogr B*. 68 (2012) 549–557.
- [41] M.N. Frey, T.F. Koetzle, M.S. Lehmann, W.C. Hamilton, Precision neutron diffraction structure determination of protein and nucleic acid components. X. A comparison between the crystal and molecular structures of L-tyrosine and L-tyrosine hydrochloride, *J Chem Phys*. 58 (1973) 2547–2556.