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Toward Thermodynamic Predictions of Aqueous Vitamin Solubility: An Activity Coe cient-Based Approach

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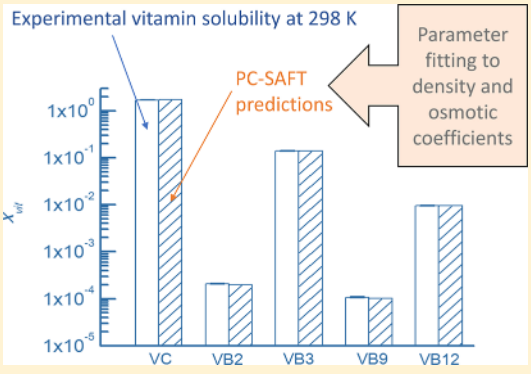
Supporting nformation

ABSTRACT: Research on water-soluble vitamins is still required, especially due to the diversity of their structures that in uence strongly physicochemical properties of water vitamin mixtures. Such in uences are still underexplored. Further, solubility of vitamins in aqueous environment is of crucial importance for life sciences and process design, but still experimental data of vitamin solubility is rather limited in literature. In this work, solubilities of the vitamins ascorbic acid, ribo avin, nicotinic acid, folic acid, and cyanocobalamin were predicted with Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT). PC-SAFT parameters for vitamins were estimated by fitting them to solubility-independent data, namely experimental liquid-density data and osmotic-coefficient data of aqueous vitamin solutions measured in this work. PC-SAFT predicted solubilities were validated by new experimental solubility data at T = 298.15 K and p = 1 bar. PC-SAFT predictions were in quantitative agreement to experimental vitamin solubility in water. Further, PC-SAFT allowed predicting the temperature in uence on the solubility of vitamins in water with reasonable accuracy.



1. INTRODUCTION

Vitamins play important roles in human s metabolism. Unfortunately, most vitamins are not synthesized in the body at all, while only few (vitamins B3 and D) are synthesized in inadequate quantities.[1,2] In contrast to fat-soluble vitamins (A, D, E, K), water-soluble vitamins (C, complex B) dissolve in aqueous body uids. Further, excess amounts of water-soluble vitamins cannot be stored in the body for later use due to the constant physiological excretion of body liquids. For these reasons, past research works from literature mainly focused on deeper understanding of the biological functions of water-soluble vitamins and on the design of different methods of their supply. These studies have been mostly carried out for the prevention of various diseases, as several body dysfunctions are caused by vitamin deficiencies.[3,4]

More recent publications have significantly broadened the scope of the research on water-soluble vitamins by showing a high interest of using them, e.g., as precursors for sensing materials, which are readily applied in the field of environmental protection[5] or as model compounds and ligands in new controlled-release and targeting drug delivery systems.[6] The latter are often evaluated from the anticancer treatment standpoint.[7 9] However, the applicability of water-soluble vitamins requires knowledge on physicochemical properties, and solubility in water is one of the most important.[10] It is obvious that the effort needed to obtain accurate experimental data is huge, which is related to the number of required measurements caused by the diverse in uencing factors (e.g., pH, temperature, presence of additives) on solubility. Thus, to fully characterize aqueous vitamin solutions, the availability of predictive thermodynamic models for these organic solutions is an urgent need.

So far, different thermodynamic approaches have been proposed for the correlation, modeling, and prediction of the properties of organic substances in aqueous solutions. These are mainly the Gibbs energy (g^E) models and equations of state (EOS). Solid liquid equilibria can be described through melting properties and activity coefficients. The latter might be estimated using different models, e.g., UNIFAC, NRTL, CPA, COSMO, and SAFT.[11 15] Among them, CPA EOS has already been evaluated for the prediction of the solubilities of ascorbic acid and nicotinic acid in organic solvents, whereas COSMO-RS has been used for calculations of solubilities of these vitamins in water.[16 18] SAFT-based models are recommended due to their predictive nature and physical background they are based on. According to studies reported in literature, Perturbed-Chain (PC-SAFT) is suitable for the prediction of

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the aqueous solubilities of nicotinamide[19 21] and many different organic components, sugars, amino acids, and APIs,[22 24] in very good agreement to experimental data. Pure-component parameters for the system components and binary parameters must be determined.

In this work, the five PC-SAFT pure-component parameters and one binary interaction parameter (k_{ij}) were estimated by fitting them to solubility-independent experimental liquid-density data and osmotic-coefficient data of binary water + vitamin mixtures. The association schemes of the vitamins were set according to the molecular structure. The vitamins under investigation are ascorbic acid (VC), ribo avin (VB2), nicotinic acid (VB3), folic acid (VB9), and cyanocobalamin (VB12). Thus far, there are just a few publications in the literature that contain physicochemical data of aqueous vitamin solutions such as density or osmotic coefficients. Additionally, in these articles, just two moderately soluble vitamins were considered, namely VC and VB3.[25,26] Therefore, densities and osmotic coefficients were measured in this work to provide the experimental data basis for the parameter estimation.

The three amphoteric vitamins considered in this work (VB2, VB9, and VB12) are structurally more complex and less soluble compared to acidic VC and amphoteric VB3. Because of this and many other limitations, there are much less studies in literature on the solubility of VB2, VB9, and VB12. Furthermore, the temperature-dependent solubilities have been reported in literature just for VC and VB3. In this work, aqueous solubilities of the vitamins were predicted using activity coefficients obtained with PC-SAFT. To validate the PC-SAFT predictions, sets of solubility experiments at T = 298.15 K and p = 1 bar, have been prepared. The melting properties of all vitamins were taken from the literature or estimated. Further, for the two vitamins, VC and VB3, PC-SAFT was validated using solubility data in a broad temperature range from literature.[27,28]

It should be noted that pH plays a major role for solubility of vitamins.[29] In many published studies, aqueous solubilities are given without corresponding pH values, what makes such data unusable and significantly reduces the number of data available for evaluation of predictions. This is especially big disadvantage in terms of future application of the predictions in different systems. Thus, all solubility results measured in this work are given with the corresponding pH of each vitamin saturated solution.

2. PC-SAFT MODELING

Water + vitamin binary systems were modeled in this study using PC-SAFT, which is based on the reference hard-chain system and perturbations to that. The energy contributions caused by hard-chain forces ($a^{\text{hardchain}}$), dispersive van der Waals attraction ($a^{\text{dispersion}}$), and hydrogen bonding ($a^{\text{association}}$) are summed in order to yield the residual Helmholtz energy (a^{residual}).[19]

$$a^{\text{residual}} = a^{\text{hardchain}} + a^{\text{dispersion}} + a^{\text{association}} \tag{1}$$

To characterize a nonassociating compound i, PC-SAFT requires three pure-component parameters, namely the segment number (m_i), the segment diameter ($_i$), and the dispersion-energy parameter (u_i/k_B). The latter involves normalization to Boltzmann constant (k_B). In the case of an associating uid, two additional parameters are introduced, i.e., the association-energy parameter ($\varepsilon^{A_iB_i}/k_B$) and the association-volume parameter ($k^{A_iB_i}$). Besides these two fitting parameters, additionally the number of association sites ($N^{\text{association}}$) must be defined according to the possible molecular interactions. This was done in the present work before parameter estimation.

To apply PC-SAFT for mixtures, the Berthelot Lorentz[30,31] and Wolbach Sandler[32] combining and mixing rules were applied (eqs 2 4). They are used for the calculations of the mean segment diameter, mean dispersion-energy parameter, and mean association-energy parameter. Implementation of only one additional parameter between components i and j, namely the binary interaction parameter (k_{ij}), can be meaningful for the modeling of mixtures.

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

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

$$\epsilon^{A_iB_j} = \frac{1}{2}\cdot(\varepsilon^{A_iB_i} + \varepsilon^{A_jB_j}) \tag{4}$$

In this work, the PC-SAFT parameters were fitted to solubility independent data using a Levenberg Marquardt algorithm (DLS: damped least-squares). DLS method has been implemented to PC-SAFT to minimize the objective function (OF) in eq 5, in which y^{mod} and y^{exp} are modeled and experimental values for a certain number of data points NP, respectively.

$$\text{OF} = \sum_{k=1}^{\text{NP}} \left(1 - \left(\frac{y^{\text{mod}}}{y^{\text{exp}}}\right)_k\right)^2 \tag{5}$$

eq 6 allows the calculation of activity coefficient (γ_i) of a component i. Fugacity coefficient in the mixture φ_i is divided by fugacity coefficient of the pure component φ_{0i}.

$$\gamma_i = \frac{\varphi_i}{\varphi_{0i}} \tag{6}$$

Once an expression for γ_i is available by PC-SAFT, the mole-fraction based solubility $x_i^{L,\text{pred}}$ can be predicted according to eq 7.[33]

$$x_i^{L,\text{pred}} = \frac{1}{\gamma_i^L}\exp\left[-\frac{\Delta_{\text{cr}}^L H_m^0}{RT}\left(1 - \frac{T}{T_{m,i}}\right) - \frac{\Delta_{\text{cr}}^L Cp_m^0}{R}\left(\frac{T_{m,i}}{T} - 1 - \ln\left(\frac{T_{m,i}}{T}\right)\right)\right] \tag{7}$$

Prior to the solubility predictions, the melting properties of the component i, such as melting temperature ($T_{m,i}$), melting enthalpy ($\Delta_{\text{cr}}^L H_m^0$), and the difference of its liquid and solid heat capacities ($\Delta_{\text{cr}}^L Cp_m^0$) must be known. Solubility of vitamins in water expressed by $x_i^{L,\text{pred}}$ can be converted to $m_i^{L,\text{pred}}$ using eq 8.

$$m_i^{L,\text{pred}} = \frac{x_i^{L,\text{pred}}\cdot 1000}{(1 - x_i^{L,\text{pred}})\cdot M_{\text{water}}} \tag{8}$$

The deviation between experimental ($m_i^{L,\text{exp}}$) and predicted solubility ($m_i^{L,\text{pred}}$) is given by the average relative deviation (ARD) and was obtained with eq 9.

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$$\mathrm{ARD} = 100 \cdot \frac{1}{\mathrm{NP}} \cdot \sum_{k=1}^{\mathrm{NP}} \left| 1 - \left(\frac{m_i^{L,\mathrm{pred}}}{m_i^{L,\mathrm{exp}}} \right)_k \right| \quad (9)$$

3. MATERIALS AND EXPERIMENTAL METHODS

3.1. Materials. The water-soluble vitamins under consideration in this work are ascorbic acid (VC), ribo avin (VB2), nicotinic acid (VB3), folic acid (VB9), and cyanocobalamin (VB12). For dilution purpose and to prepare vitamin stock solutions, deionized Millipore water (Merck KGaA) was used. For measurements of the density (water VB2 and water VB9) and osmolality (water VB12), the stock solutions of vitamins were prepared with addition of negligible amount of potassium hydroxide. The CAS registry numbers, purities, and suppliers of the chemicals are listed in Table 1. All products were used as received without any further purification. Weighing was carried out on a Mettler Toledo analytical balance (XS205 Dual Range) with an uncertainty of ±0.01 mg.

Table 1. Sample Provenance Table

component[a]	CAS	supplier	mole fraction purity
VC	50-81-7	PanReac	≥0.99
VB2	83-88-5	Sigma	≥0.98
VB3	59-67-6	Sigma-Aldrich	≥0.98
VB9	59-30-3	Sigma	≥0.97
VB12	68-19-9	Sigma	≥0.98
KOH	1310-58-3	Merck	≥0.99

[a]VC = ascorbic acid. VB2 = ribo avin. VB3 = nicotinic acid. VB9 = folic acid. VB12 = cyanocobalamin. KOH = potassium hydroxide.

3.2. Measurement of Density and Osmotic Coefficients. The PC-SAFT parametrization of vitamins (e.g., with the intention of afterward solubility predictions) requires experimental data on binary systems water vitamin that are independent of solubility itself. In this work, liquid mixture densities and osmotic coefficients of water vitamin mixtures have been measured. All samples were prepared at least in triplicate, and the mean values have been considered. Liquid densities (ρ) of water vitamin mixtures were measured at T = 298.15 K and p = 1 bar, using Anton Paar density meter (DMA 4200 M). The technique is based on the oscillating U-tube principle. Through the differences in frequencies of oscillation, the densities of binary systems water vitamin were determined. The osmotic coefficients (ϕ) of binary systems water vitamin were obtained using a freezing-point depression Gonotec osmometer (FP Osmomat 010, Germany). They were calculated from experimental osmolalities (osm), according to eq 10. It involves initial molality of vitamin in each solution (m) and number of species, into which the components present in solution can dissociate (ν). In this work, all the vitamins were modeled as molecular nondissociated species (ν = 1). The equipment was calibrated using standard sodium chloride solutions (ν = 2), and the baseline was set by measuring the osmolality of pure water. These calibrating procedures were repeated also in between the measurements to ensure the highest accuracy, as well as to exclude any baseline drifts of the equipment.

$$\phi = \frac{\mathrm{osm}}{\nu_i \cdot m_i} \quad (10)$$

The properties of VB3 and VC solutions have been measured without using KOH. For VB2, VB9, and VB12, KOH was added to measure density and osmotic coefficient of these vitamin solutions. A negligible amount of KOH used in this work was used to slightly increase vitamin solubility to reach the detection limit for density and osmolality measurements without changing the species distribution by more than 5 . Following this rule, KOH has been added just to one sample (containing VB12) for osmolality measurement.

3.3. Solubility Measurements. The equilibrium solubilities of vitamins in water studied in this work were measured at T = 298.15 K and p = 1 bar, using the experimental shake- ask method. Each sample was prepared by adding a solid (vitamin) into a sealable tube and filling it with water. After that, all tubes were shaken on a Vortex mixer for 15 min. If heterogeneous systems were observed (solid and liquid), they were placed inside a thermomixer (Thermomixer Comfort, Eppendorf) with constant stirring of 800 rpm, at T = 298.15 ± 0.1 K, for a minimum of 72 h. During incubation time, samples were constantly protected from the light and well-sealed. Afterward, tubes were centrifuged for 20 min (refrigerated centrifuge 5418 R, Eppendorf) at 13 × 10^3 rpm, T = 298.15 K. To ensure complete phase separation, they were then placed back into the thermomixer and incubated at T = 298.15 K, without stirring. After about 6 h, pH values of the upper liquid phase were measured (glass electrode QpH 70, VWR). The entire procedure, starting from the incubation with stirring, through centrifugation, until total phase separation was repeated until the change in the pH value was measured to be $\Delta\mathrm{pH} \leq 0.1$. If this condition was fulfilled, small aliquots of supernatant (in duplicate) were taken out with a micropipette from the saturated solution and diluted with water, respectively. All the dilutions were prepared gravimetrically on an analytical balance. The concentrations of vitamin in each sample were determined using UV vis spectrophotometry (Tecan microplate reader Infinite M200 Pro). Prior to this, wavelengths were chosen: λ_{max}(VC, VB2, VB3) = 270 nm, λ_{max}(VB9) = 280 nm, and λ_{max}(VB12) = 360 nm, and calibration curves for each

Table 2. Experimental Solubilities of Vitamins at T = 298.15 K, p = 1 bar, Measured in This Work, along with pH of the Saturated Solutions and p $_a$ Values at 293.15 K

		pK_a[b]						
component	pH[a]	pK_{a1}	pK_{a2}	pK_{a3}	pK_{a4}	$m_i^{L,\mathrm{exp}}$ [mol/kg]	$ARD_{m_i^{L,\mathrm{exp}}}$	$ARD_{m_i^{L,\mathrm{pred}}}$
VC	1.94	4.17	11.57			1.8262	0.59	2.57
VB3	3.42	2.07	4.81			0.1401	1.20	1.62
VB2	5.68	1.7	6.1	10.2		0.2058 × 10 ^{3}	1.05	3.28
VB9	4.28	2.38	3.34	4.7	8.1	0.1069 × 10 ^{3}	1.26	4.56
VB12	5.55	1.82	13.99			9.6449 × 10 ^{3}	0.95	0.20

[a]pH uncertainty: ±0.03. [b]References for pK_a: VC,[36] VB3,[37] VB2,[38 42] VB9,[43,44] VB12[42]

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vitamin were determined. To ensure that the equilibrium state of binary systems water vitamin was reached, the tubes with supersaturated solutions were stirred for at least one more day. After complete phase separation, new aliquots were withdrawn and diluted with water, and the concentrations were determined. Equilibrium was ascertained, if for different samples measured in time intervals, differences in vitamin solubilities were lower than 6 . As vitamin solubility data are strongly pH dependent, the reported solubility data in this work are only valid at the pH which was recorded and is given along with the solubility data.

4. RESULTS AND DISCUSSION

4.1. Experimental Solubility Data. Experimental aqueous solubility data for all vitamins, which were measured in this work at T = 298.15 K and p = 1 bar, and corresponding pH of the saturated solutions are given in Tables 2 3 along with the

Table 3. Temperature-Dependent Solubility of Water-Soluble Vitamins, p = 1 bar, along with pH of the Saturated Solutions

component	T [K]	pH	$m_i^{L,\mathrm{exp}}$ [mol/kg]	ref[a]	ARD $m_i^{L,\mathrm{pred}}$
VC	298.15	1.94	1.8262	TW	
	293	na	1.6555	27	
	298	na	1.8984		
	303	na	2.1800		
	308	na	2.5414		29.24
	313	na	2.9443		
	318	na	3.4140		
	323	na	3.9434		
VB3	298.15	3.42	0.1401	TW	
	283.59	3.60	0.0957	28	
	293.41	3.45	0.1214		
	303.03	3.37	0.1561		2.82
	312.97	3.27	0.2036		
	322.83	3.22	0.2593		
	332.01	3.12	0.3271		

[a]Reference: TW = this work.

pK_a values of the vitamins. More detailed results are included in Supporting Information (SI), Tables S3 S4. Table 3 also contains additional data taken from literature.[27,28] According to common terms used in literature to describe the solubility levels in water, just one vitamin studied in this work (VC) is freely soluble. While VB3 and VB12 can be still classified as sparingly soluble, VB2 and VB9 are already considered as practically insoluble.

Incomplete and possibly inconsistent data on aqueous solubility of vitamins is the biggest problem emerging in literature (deviations in solubility of even 30 if comparing different works).[34] For this reason, the experimental data measured in this work could be properly compared just with one study from literature and for one water-soluble vitamin. The report, which can be used for this comparison, provides data on aqueous VB9 solubility, at T = 298.15 K and p = 1 bar, and the pH values of equilibrated solutions.[35] The deviations of pH and solubility, calculated from data found in literature and obtained here, are about 6 and 9 , respectively. This difference in solubility might be related to experimental uncertainty, but additionally can be caused by pH effect. A detailed explanation on the pH-solubility relations has been included elsewhere.[29] Only slightly different pH values of equilibrated solution of amphoteric VB9 (in region of pH ≈ 4) will already impact solubility.

4.2. PC-SAFT Parameters. PC-SAFT pure-component parameters and binary interaction parameters were fitted to solubility-independent experimental densities (SI, Table S1) and osmotic coefficients (SI, Table S2) of binary systems water vitamin. The results of this modeling are presented in Figure 1a c. For better visibility, the densities of aqueous solutions containing VC were plotted in separate diagram (Figure 1b). The highest average relative deviation (SI, Table S4) among experimental and PC-SAFT modeled densities was 0.16 (VC). This result is still of high accuracy. Among all vitamins studied in this work, VC is the most soluble and liquid densities of water + VC have been already reported in literature for wide range of concentrations.[25] It can be observed from Figure 1b that literature data and data from this work are in good agreement. The lowest ARD between PC-SAFT and experimental liquid densities was calculated for water + VB2 (0.0007). This is because the PC-SAFT parameters for VB2 were fitted solely to densities of binary systems water VB2. Osmotic coefficients of water VB2 were not accessible experimentally due to the very low solubility of VB2. The same procedure was applied to the other practically insoluble vitamin VB9. Nevertheless, at very low concentrations, osmotic coefficients of aqueous solutions containing uncharged components are very close to one. For this reason, ϕ_{VB2} and ϕ_{VB9} were assumed to be one at maximum VB2 and VB9 molality (i.e., at the solubility limit at 298.15 K); this assumption was an additional condition in the parameter fit for VB2 and VB9. Even addition of KOH to VB2 and VB9 solutions did not allow for reliable experimental osmotic coefficients. The lowest ARD of modeled osmotic coefficients (0.9) was observed for the most soluble vitamin studied in this work (VC).

Table 4 contains an overview of all PC-SAFT pure-component parameters and binary interaction parameters determined in this work. For water, the 2B association model has been used.[45] Even though the 2B model is less realistic than the 4C model, the 2B model has been recommended in the literature for modeling thermodynamic properties of biological solutions.[23,46] The association schemes of the vitamins were set as a compromise between the best modeling result (density and osmotic coefficients of water vitamin mixtures) and the counted numbers of possible acceptor and donor sites. Because of high structural diversity of the vitamins, a high number of different kinds of interactions exists for every vitamin, and the association sites were set for each vitamin individually. For this purpose, available online tools were applied, which characterize the molecules through chemical structure analyses, e.g., Chemicalize[47] or PubChem. Analyzing the vitamins using these tools yielded the number of association sites as listed in Table 4. For VB12, the molecule was too complex for the molecular structure analysis and a result was not obtained with Chemicalize. Overall, it can be observed that the association sites that were set to the vitamins are generally in good agreement to the association sites obtained by counting the theoretically maximal acceptor and donor sites using Chemicalize or PubChem.

As vitamins in the aqueous solutions considered in this work are mainly presented as neutral species, in this study they were treated as uncharged molecules. Most of the vitamins studied in this work are uncharged (VC, VB3, VB12) at the pH values

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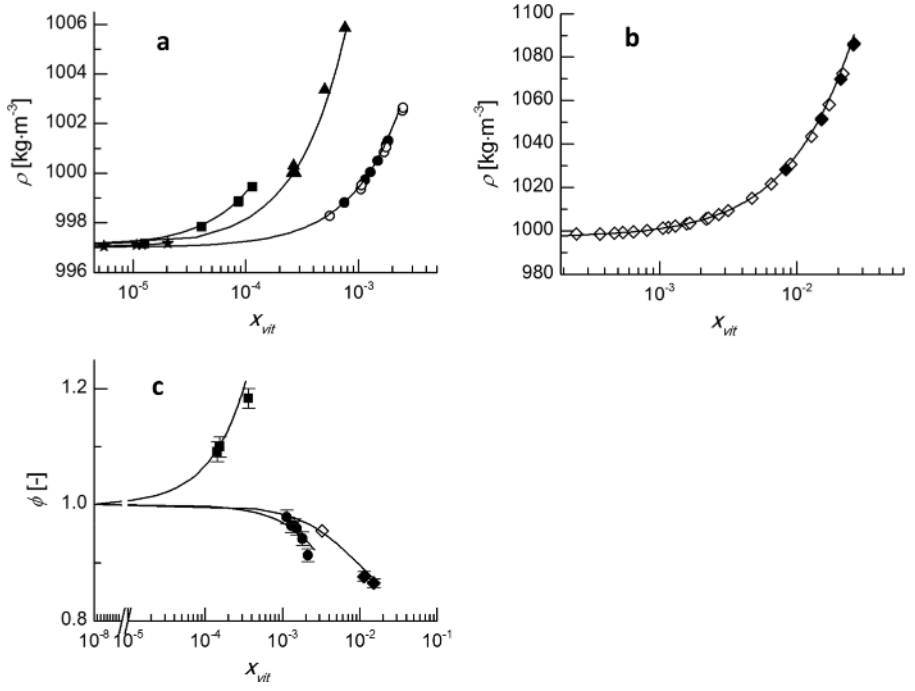

Figure 1. Densities ρ (a,b) and osmotic coefficients ϕ (c) of binary systems water vitamin vs vitamin mole fraction x_{vit}, at T = 298.15 K, p = 1 bar. Full symbols: data from this work: VC ( ), VB2 ( ), VB3 (●), VB9 (▲), and VB12 (■). Open symbols: data from literature VC (◇), VB3 (○), refs 25,26 Lines: PC-SAFT modeling using parameters from Table 4.

Table 4. PC-SAFT Pure-Component Parameters and Binary Interaction Parameters for Neutral Species of Water-Soluble Vitamins Studied in This Work TW) and Water, as Well as Association Schemes

										association scheme[a]	
component	M [g/mol]	m_i^{seg} [ ]	$_i$ [Å]	u_i/k_B [K]	ε^{AiBi}/k_B [K]	κ^{AiBi} [ ]	association scheme[a]	$k_{ijwater\ vitamin}$	ref	PubChem[48]	CH[47]
VC	176.13	11.7082	2.3670	353.44	2600.68	0.039	4/1	1.80 × 10 ^{2}	TW	6/4	5/4
VB2	376.36	15.9238	2.6300	150.32	2548.11	0.034	5/5	4.70 × 10 ^{2}	TW	7/5	9/5
VB3	123.11	8.0883	2.3522	209.04	1088.56	0.002	3/1	3.90 × 10 ^{2}	TW	3/1	3/1
VB9	441.40	16.7167	2.6907	152.02	2379.47	0.034	8/4	1.40 × 10 ^{2}	TW	9/6	12/6
VB12	1355.37	21.8544	4.0500	346.45	2136.56	0.010	23/6	2.11 × 10 ^{2}	TW	21/9	na
water	18.02	1.2047	[b]	353.95	2425.67	0.045	1/1		45		

[a]Association scheme: acceptor/donor, CH = Chemicalize. [b] $_i$ = 2.7927 + 10.11·exp(0.01775·T[K]) 1.417·exp(0.01146·T[K]).

considered in this work, or they are slightly charged in their saturated aqueous solutions (VB2). For VB2, the deviation between intrinsic solubility of VB2 (experimental: 0.0002 mol/kg) and the solubility measured in saturated solution without pH modification (this work): 0.00021 mol/kg is lower than the experimental error. Besides VC, all vitamins studied in this essay were amphoteric. The PC-SAFT pure-component parameters for amphoteric components, namely amino acids, have been already estimated in literature[23] using the same binary systems properties as measured in this study, i.e., density and osmolality. On the basis of excellent results of the modeling of amino acids, the water vitamin solutions were prepared and modeled according to procedures, which have been previously published for amino acids. For better modeling result, the properties of water vitamin solutions were studied in wide range of vitamin concentrations, approaching the last point at maximum vitamin concentration, which was possible to reach at the time of sample preparation. More precisely, these were the concentrations of vitamins, which led to formation of homogeneous aqueous solutions.

4.3. Solubility Predictions. In this study, the aqueous solubilities of acidic (VC) and amphoteric (VB2, VB3, VB9, VB12) vitamins were predicted according to eq 7. Melting properties needed for these predictions are given in Table 5.

Table 5. Melting Properties of Water-Soluble Vitamins

component	$T_{m,i}$ [K]	$\Delta^L_{cr}H^0_m$ [kJ/mol]	$\Delta^L_{cr}Cp^0_m$ [J/mol]	ref
VC[a]	465.15	29.12	43.00	18
VB2[b]	553.15	31.25	na	50
VB3	509.91	28.20	38.00	28,51
VB9[b]	523.15	29.56	na	52
VB12[b]	665.15	37.58	na	53

[a]$\Delta^L_{cr}Cp^0_m$ estimated using solubility data in T = 293.15 323.15 K. [b]$\Delta^L_{cr}H^0_m$ calculated with Walden Rule ($\Delta^L_{cr}H^0_m = \Delta^L_{cr}S^0_m \cdot \Delta^L_{cr}T^0_m$ using an established value $\Delta^L_{cr}S^0_m$ = 56.5 J/(mol K).[49]

Among all melting properties needed to be introduced to eq 7, just melting temperature $T_{m,i}$ was available for all five vitamins. The rest of properties, i.e., change of melting enthalpy $\Delta^L_{cr}H^0_m$ and change of heat capacity $\Delta^L_{cr}Cp^0_m$, if not found in literature, had to be estimated or calculated.[49] VB3 was the only vitamin for which a complete set of melting data ($T_{m,i}$, $\Delta^L_{cr}H^0_m$, $\Delta^L_{cr}Cp^0_m$) was available in literature. For VC, it was possible to find both

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$T_{m,i}$ and $\Delta^{L}_{cr}H^{0}_{m}$, but $\Delta^{L}_{cr}Cp^{0}_{m}$ had to be estimated. However, in this case, introducing $\Delta^{L}_{cr}Cp^{0}_{m}$ led to just a slight change in VC solubility and it was applied to keep consistent number and type of input data to predict temperature dependent solubilities of VC and VB3. For VB2, VB9, and VB12 only $T_{m,i}$ was provided in the literature and $\Delta^{L}_{cr}H^{0}_{m}$ values were calculated using Walden Rule.[49]

Focus of this work was to predict solubility of vitamins with PC-SAFT and using the melting properties listed in Table 5. These solubility predictions have been divided into predictions of solubilities at constant temperature, T = 298.15 K and predictions of temperature-dependent solubilities (VC, VB3). Results of these predictions are given in Figures 2 3, respectively.

4 3 1 Solubility of Vitamins at 298 15 K First, the aqueous solubilities of one acidic (VC) and four amphoteric vitamins (VB2, VB3, VB9, and VB12) were predicted at constant temperature, T = 298.15 K. The results of PC-SAFT predictions, accompanied with experimental data, are given in Table 2 and are presented in Figure 2. Experimental

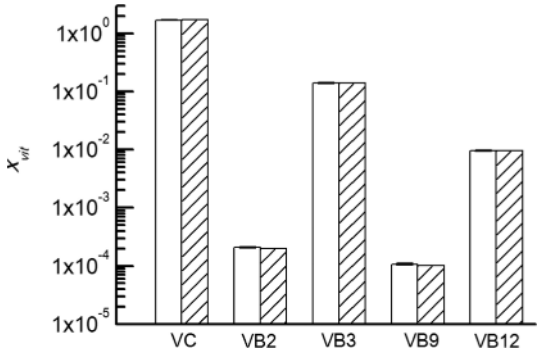

Figure 2. Solubility of vitamin expressed as mole fraction x_{vit} at T = 298.15 K and p = 1 bar. PC-SAFT predictions (striped bars) and experimental data from this work (nonpatterned bars).

solubilities were reported together with pH of equilibrated solutions. For all vitamins considered in this study, PC-SAFT allowed quantitative predictions of their aqueous solubilities at T = 298.15 K. The highest deviation between measured and predicted solubility (ARD = 4.13) was observed for the least soluble vitamin (VB9). However, this deviation is still very small and leads to the conclusion that PC-SAFT can excellently predict the solubilities of even such complex components at T = 298.15 K. This is a very promising result for the very complex vitamin molecules, especially as solubility data have not been used for the PC-SAFT parameter estimations.

4 3 2 Temperature Dependence of Vitamin Solubility The temperature dependence on solubilities of two most soluble vitamins considered in this work has been studied. According to Figure 3, and as expected, the solubility of VC and VB3 increases with increasing temperature. PC-SAFT allows accurately predicting the solubility of VB3 within the range of 283.59 332.09 K (ARD = 2.82). VB3 is one of the most stable molecules against air, light, acids and alkalis, among other water-soluble vitamins.[2] VC is a very unstable compound concerning air and light, and thus thermo-induced degradation could occur at higher temperatures during solubility experiments. For VC, PC-SAFT overpredicted experimental solubility at temperatures higher than 298.15 K.

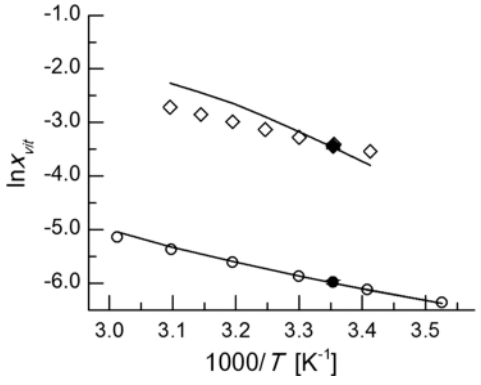

Figure 3. Temperature-dependent aqueous vitamin solubilities x_{vit}. PC-SAFT predictions are represented by lines, experimental validation are symbols. Black symbols: this work (VC ( ), VB3 (●)). Open symbols: literature data (VC (◇), VB3 (○)[27,28]).

This might be caused by decomposition and questionable solubility data which cannot be described by the model (e.g., decomposition),[54] or by the need of temperature-dependent binary interaction parameters. Although an effective method, use of the latter is not within the scope of this work. In sum, these deviation might be due to model inaccuracies or due to the use of harmful experimental conditions (nonharmful: pH ∼ pH of uncharged vitamins, stable around room temperature, protection from light, protection from air by using well-sealed vials). Most probably, deviations between predicted and experimental solubilities might be caused by pH effects, which were not considered by the PC-SAFT model as pH values, were not given (cf. Table 3). The pH in uence on solubility of different natural components (acidic, basic, amphoteric) have been discussed in literature.[29] The pH of VC solutions is expected to decrease for higher solubility, which forces the total solubility of VC to decrease. It can be seen in Figure 3 that the deviation between measured and predicted solubilities of VC increases gradually with increasing solubility. To include this effect into the PC-SAFT predictions, dissociation equilibria are required. Unfortunately, the pH values of equilibrated solutions are not known, which does not allow fully unravelling the reasons of VC solubility deviations of PC-SAFT predictions. Nevertheless, knowledge on the pH in uence of vitamin solutions on solubility data is of high importance, and this will be addressed in a following work.

5. CONCLUSIONS

In this work, physicochemical properties such as densities and osmotic coefficients of aqueous solutions containing one of the water-soluble vitamins (VC, VB2, VB3, VB9, VB12) were measured. These data served as input to estimate PC-SAFT pure-component parameters and one binary interaction parameter between water and each vitamin. These parameters and literature melting properties were used to predict the activity coefficients needed for PC-SAFT predictions of aqueous vitamin solubilities. It has been observed that PC-SAFT allows quantitative prediction of the vitamin solubilities in water at T = 298.15 K. The temperature dependence of the solubility of VB3 could be successfully predicted between 283.59 and 332.09 K. No parameters were fitted to any solubility data. Besides this success, deviations were observed between PC-SAFT and experimental VC solubility at increased temperatures. Among all vitamins studied in this work, VC is

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the least stable against air and light and it is the most acidic vitamin. Thus, the observed deviations might be caused by different effects that are not included in the model (e.g., decomposition, pH effect). pH effect on solubility is especially important and is addressed in an ongoing work.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.iecr.9b00742.

Experimental data on densities and osmotic coefficients of vitamin solutions at 298 K and 1 bar, as well as experimental solubilities vitamins in water and the respective pH values; deviations between PC-SAFT and the experimental data (densities, osmotic coefficients, solubility) (PDF)

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Notes

The authors declare no competing financial interest.

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