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Solubility Enhancement of Vitamins in Water in the Presence of Covitamins: Measurements and ePC-SAFT Predictions

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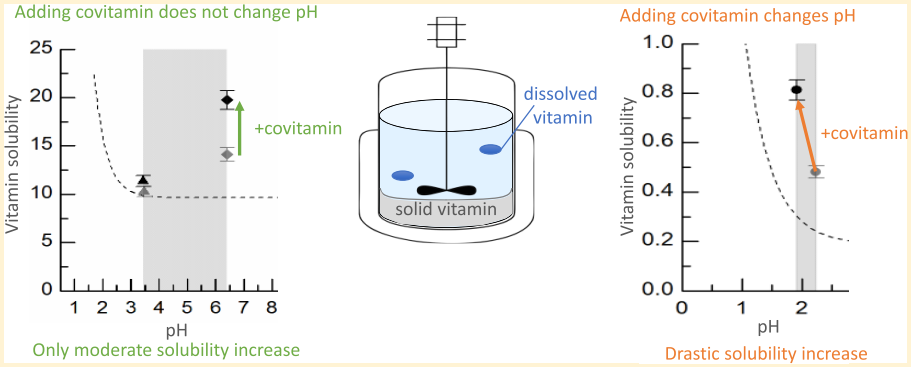
Supporting nformation



ABSTRACT: Scarce knowledge on the behavior of vitamins in aqueous solutions in the presence of additives is often a limiting factor for industrial applications such as process design and optimization. Knowing the pH-solubility pro les of vitamins is fundamental for understanding and controlling their behavior in aqueous solutions. In the present work, pH-dependent solubilities of the vitamins ascorbic acid (VC), riboflavin (VB2), nicotinic acid ($VB3^{acid}$), folic acid (VB9), and cyanocobalamin (VB12) were measured at T = 298.15 K and p = 1 bar. These results were compared to the pH-solubility pro les obtained with modi ed Henderson Hasselbalch equations using pK_a values from the literature. Further, the solubilities of poorly soluble VB2, VB9, and VB12 were increased by the addition of covitamins VC, $VB3^{acid}$, and nicotinamide ($VB3^{amide}$). As observed, $VB3^{amide}$ increases the vitamin solubility much stronger than VC and $VB3^{acid}$. These covitamins are called "hydrotropes" in several works in the literature, and they increase the solubility of other vitamins by manipulating the pH of the saturated solutions and by molecular cross-interactions. The interplay between both pH and cross-interactions depends strongly on the kind and concentration of covitamin. At low concentrations, VC and $VB3^{amide}$ (<0.2 *m*) increased solubility by pH change. At higher concentrations of VC and $VB3^{amide}$ added, mainly cross-interactions between vitamin and covitamin determine the strength of solubility increase. To separate these effects and to further reduce experimental effort, electrolyte perturbed-chain statistical association fluid theory was used to predict vitamin solubility. The pH-solubility pro les and the solubilities of vitamins in water at T = 298.15 K and p = 1 bar upon addition of covitamins were predicted with reasonable accuracy. This success resulted from accounting for different charged and neutral vitamin species according to the pH and from considering explicitly the vitamin water and vitamin covitamin interactions. It could be shown that "hydrotropic solubilization" of a vitamin is the increase of vitamin solubility caused by pH shift and by cross-interactions between the saturated species of a vitamin and the added covitamin.

1. INTRODUCTION

Understanding the mechanisms which rule the vitamin solubilization processes is crucial for unit operations and for drug-delivery studies, which nowadays are willingly reported in the literature.[1 3] Besides their vital functions, vitamins are considered as model components for drugs, and this further points to the high importance of studying interactions in their aqueous solutions. Organic components classi ed as water-soluble vitamins differ signi cantly in molecular structure and consequently also in physicochemical mixture properties, such as solubility. Some vitamins are sparingly water-soluble (e.g., cyanocobalamin VB12) or poorly soluble in water (e.g., riboflavin VB2, folic acid VB9) at T = 298.15 K and at their intrinsic pH. Low solubility drastically decreases the interest of studying their properties and leads to low

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availability of data in the literature. This is especially notable for VB12, which is difficult to characterize not just due to its limited solubility but also through its complex molecular structure.[4] A high structural complexity can lead to a huge number of possible molecular interactions in the solution and some structural changes of a vitamin, which can occur in aqueous solutions under variable conditions, and in the presence of additional components.[5 7]

The experimental procedures used to characterize the systems composed of low-soluble complex components such as vitamins are usually time-intensive and challenging. To measure the properties of vitamin solutions in a signi cant concentration range, enhancing the solubility of poorly water-soluble vitamins is of importance. The solubility is usually improved by variation of the temperature and the pH or by the addition of so-called hydrotropes. It is well known that changing the temperature can signi cantly increase the solubility of solutes in solvents.[8] Although the pH dramatically influences solubility, the information on pH is often neglected in the literature when reporting aqueous solubility data. If experimental results reported for aqueous solutions are given without corresponding pH, they are practically worthless. So far, there are a few works in which the aqueous solubility data of vitamins have been provided together with the pH of equilibrated solutions. These are mainly studies reporting the solubility of VB3 (nicotinic acid, VB3^{acid}; nicotinamide, VB3^{amide}) and VB9.[7,9,10]

The lack of information on the pH becomes even more troublesome when trying to unravel the phenomena which rule the solubilization upon addition of different solubilizers, e.g., hydrotropes. The hydrotropic solubilization is a technique used to increase the solubility of poorly water-soluble components by the addition of excess amounts of a second solute the so-called hydrotrope.[11,12] According to the literature, such a procedure can lead even to 1000- to 10 000-fold enhancement of solute solubility.[13] The phrase "hydrotropic solubilization" is often misused and applied where the same solubility increase can be achieved by pH shift upon addition of small amounts of an acid or a base (e.g., HCl or NaOH).

To date, at least two vitamins have been classi ed as hydrotropes, ascorbic acid (VC) and VB3^{amide}, and they were used to dissolve some active pharmaceutical ingredients[14] and vitamins (Table 1). In past studies, many efforts have been already devoted to unraveling the possible mechanisms which can rule the hydrotropic solubilization of solutes in their aqueous solutions.[15 18] At least several hypothetical mechanisms have been proposed. The most common conceptions are based on the molecular self-association of hydrotrope and of its cross-association toward a solute. Different hydrotrope behaviors were considered in the literature, e.g., the ability to form complexes with poorly water-soluble components, the comorbidity of donor acceptor interactions, or the possibility to form micelle-like structures with a solute.[19 21] These mechanisms, however, depend on the properties of an aqueous solution, such as pH. The addition of hydrotrope can change the pH and the species distribution of vitamin and thus modify speci c interactions.

Table 1. Aqueous Vitamin Hydrotrope Systems

poorly water-soluble vitamin	hydrotrope	ref
VB2	VB3^{amide}	22 25
	VC	26
	urea	22, 24
	caffeine	25, 27, 28
VB9	VB3^{amide}	7

Two effects influence the vitamin solubility, the pH and cross-interactions to hydrotrope. The pH dependence of solubility can be estimated by the Henderson Hasselbalch (H H) equation.[29] However, this equation requires dissociation constants (pK_a), which are uncertain, resulting in a non-negligible uncertainty of solubility estimations using the H H equation.[30,31] Due to this, the theoretical pH-solubility pro les of vitamins (obtained with pK_a values from the literature[30,32 38]) were validated using new experimental pH-solubility pro les in this work. The vitamin solubilities were determined after addition of different amounts of hydrochloric acid and sodium hydroxide at T = 298.15 K and p = 1 bar.

Some solubility data of vitamins with coexisting vitamins (so-called covitamins in refs 39, 40) are already available in the literature at high covitamin concentrations. Covitamins might show a hydrotropic behavior. To cover all of the possible effects (pH and cross-interactions), solubility data at a wide range of covitamin concentration are required in addition to the few existing literature data. For this reason, the solubilities of poorly water-soluble vitamins, VB2, VB9, and VB12, at T = 298.15 K and p = 1 bar, upon addition of covitamins: VC, VB3^{acid}, and VB3^{amide}, were determined experimentally in the present work. The effects of pH and cross-interactions on solubility were separated by using a thermodynamic model. To predict the interactions in water + vitamin + covitamin mixtures, an appropriate thermodynamic model is required that can cover important molecular interactions in these multicomponent mixtures such as Coulomb or hydrogen-bonding forces. Activity coefficients are an appropriate indicator for the interactions, and different models exist in the literature to calculate them.[41 45] Statistical Association Fluid Theory (SAFT)-based models are very often proposed because of their predictive character and physical background, and Perturbed-Chain SAFT (PC-SAFT) has already been used in the literature to model the pH and solubility of amino acid solutions; however, binary interaction parameters between amino acid and co-amino acids were required.[46] In previous works, PC-SAFT has been applied to predict the aqueous solubility of six vitamins: VC, VB2, VB3^{acid}, VB3^{amide}, VB9, and VB12 at the pH of the saturated solutions without the addition of acid or base.[47,48] In the present work, electrolyte PC-SAFT (ePC-SAFT) from Held et al.[49] was used to consider the charged vitamin species at different pH values. Recently, Bulow et al.[50] have published the influence of a concentration-dependent dielectric constant on the modeling results with ePC-SAFT. Transferring this recent method to solubility of charged vitamins in water will not impact modeling results. This is due to the fact that the vitamins considered in the present work are only poorly water-soluble; at very low concentrations, the influence of the concentration-dependent dielectric constant on modeling results is negligible. However, different modeling results are expected for conditions in which much higher vitamin concentrations are present. This is not the focus of the present work.

The nal goal of this work was to validate the ePC-SAFT predictions obtained with solubility-independent ePC-SAFT parameters. The validation of ePC-SAFT predictions was performed using solubility data measured in this work and

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reported in the literature.[7,22,26] The ePC-SAFT predictions were used to analyze the strength of the pH effect and the influence of cross-interactions on the vitamin solubility increase induced by covitamins.

2. BACKGROUND

2.1. Theoretical pH-Solubility Pro les. The aqueous solubility of ionizable organic components, such as vitamins, varies with pH. The theoretical basis of the pH-solubility pro les of ionizable components has already been discussed in the literature.[29] The principal assumptions and modi cations of the H H equation, which describe the idealized dissociation equilibria of vitamins, are included in the Supporting Information (SI) (Chapter S1). The vitamins considered in this work behave as acids and/or ampholytes. The equilibrium and solubility expressions (eqs S1 S17, SI) can help understand the pH-solubility pro les. However, deviations between the so-calculated solubilities from experimental data are frequently observed.[31] The reason behind this is that these equations do not account for solid-form changes; further, the results of the equations depend strongly on the accuracy of pK_a values.[31] Moreover, the equations neglect interactions which are intrinsically included in the experimental solubility pro les. Knowing the dissociation mechanisms and pK_a values is often not enough to determine reliable pH-solubility pro les of vitamins. Due to all of these reasons, in the following, new experimental data on the pH-solubility pro les and a thermodynamic framework to evaluate the interplay of the pH effect and molecular interactions with the vitamin solubility behavior are presented.

2.2. Model Description. The solubilities of vitamins in water and in the presence of covitamins were predicted in this work using ePC-SAFT, which is based on PC-SAFT.[51] The thermodynamic perturbation theory behind ePC-SAFT is applied to the reference hard-chain system. The residual Helmholtz energy (a^{residual}) is calculated from the sum of different energy contributions resulting from hard-chain forces ($a^{\text{hard chain}}$), dispersive van der Waals attractions ($a^{\text{dispersion}}$), hydrogen bonding ($a^{\text{association}}$), and Coulomb interactions (a^{ion})[52,53]

$$a^{\text{residual}} = a^{\text{hard chain}} + a^{\text{dispersion}} + a^{\text{association}} + a^{\text{ion}} \quad (1)$$

Any component i is characterized by three pure-component parameters: the segment number (m_i^{seg}), the segment diameter ($_i$), and the dispersion-energy parameter ($u_i k_B$). For an associating component such as water or vitamin, the number of association sites (N_i^{assoc}) is de ned before the modeling. Moreover, two additional tting parameters are implemented: the association-energy parameter ($\varepsilon^{A_iB_i}/k_B$) and the association-volume parameter ($k^{A_iB_i}$). To apply ePC-SAFT to mixtures, combining rules from Berthelot Lorentz[54,55] and Wolbach Sandler[56] are introduced (eqs 2 5). Using these expressions, the mean segment diameter, the mean dispersion-energy parameter, and the mean association-energy parameter can be determined. Involving the binary interaction parameter (k_{ij}) between components i and j can be worthwhile for the modeling of mixtures

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

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

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

$$\kappa^{A_iB_j} = \sqrt{\kappa^{A_iB_i}\cdot\kappa^{A_jB_j}}\cdot\left(\frac{2\cdot\sqrt{\sigma_i\cdot\sigma_j}}{(\sigma_i + \sigma_j)}\right)^3 \quad (5)$$

The activity coefficient of component i is calculated by dividing the fugacity coefficient of component i in the mixture φ_i by the fugacity coefficient of the pure component φ_{0i} (eq 6) at same temperature and pressure

$$\gamma_i = \frac{\varphi_i}{\varphi_{0i}} \quad (6)$$

Availability of γ_i and of the melting properties of component i, namely, melting temperature ($T_{m,i}$), melting enthalpy ($\Delta_{cr}^{L}H_m^0$), and the difference between liquid and solid heat capacities ($\Delta_{cr}^{L}Cp_m^0$), allows predicting the solubility ($x_i^{L,pred}$) according to eq 7

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

The solubility of vitamins in water expressed by $x_i^{L,pred}$ can be converted to molality $x_i^{L,pred}$ using eq 8

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

The average relative deviation (ARD) between experimental ($x_i^{L,exp}$) and predicted solubilities ($x_i^{L,pred}$) is calculated using eq 9. For the sake of simplicity, molality-based solubility is further presented as m_i

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

3. MATERIALS AND EXPERIMENTAL METHODS

3.1. Materials. In this work, six vitamins were under investigation: ascorbic acid (VC), riboflavin (VB2), nicotinic acid (VB3$^{\text{acid}}$), nicotinamide (VB3$^{\text{amide}}$), folic acid (VB9), and cyanocobalamin (VB12). Aqueous solutions were prepared using deionized Millipore water (Merck KGaA), and the pH was adjusted with hydrochloric acid and sodium hydroxide. Detailed information about each chemical used in this work is provided in Table 2. No further puri cation of purchased products has been performed. All weighting was carried out on a Mettler Toledo analytical balance (XS205 Dual Range) with an uncertainty of ±0.01 mg.

3.2. Solubility Measurements. The experimental shake-flask method was used to determine the equilibrium concentrations (i.e., aqueous solubilities) of poorly water-soluble vitamins, at T = 298.15 K and p = 1 bar. First, the solubilities of vitamins (VB2, VB3$^{\text{acid}}$, VB9, and VB12) in water were measured as a function of pH by adding HCl or NaOH. Then, a similar procedure was applied to determine the aqueous solubilities of poorly soluble vitamins (VB2, VB9, and VB12) in the presence of covitamins (VC, VB3$^{\text{acid}}$, VB3$^{\text{amide}}$).

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