Fluid Phase Equilibria 556 (2022) 113389

Contents lists available at ScienceDirect

Fluid Phase Equilibria

journal homepage: www.elsevier.com/locate/fluid

Calculating the closest approach parameter for ethyl lactate-based ATPS[☆]

Pedro Velho, Elena Gómez, Eugénia A. Macedo[*]

Associate Laboratory of Separation and Reaction Engineering - Laboratory of Catalysis and Materials (LSRE-LCM), Department of Chemical Engineering, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias, s/n, Porto 4200-465, Portugal

ARTICLE INFO

Article history:
Received 30 September 2021
Revised 5 January 2022
Accepted 10 January 2022
Available online 12 January 2022

Keywords:
ATPS
Ethyl lactate
Thermodynamic modelling
Pitzer-Debye-Hückel
Closest approach parameter

ABSTRACT

Aqueous Two-Phase Systems (ATPS) is a powerful separation technique for biotechnological compounds, such as pigments, proteins and flavonoids. Nowadays, ATPS generally include dissolved salts, which cause phase immiscibility and promote solute partition. Therefore, to accurately model the liquid-liquid equilibria (LLE) of these systems, specific terms for the long-range interactions in thermodynamic models are needed. A well-known hypothesis for this purpose is the Pitzer-Debye-Hückel (PDH) term, which requires the knowledge of the closest approach parameter (ρ), i.e., an adjustable parameter. The aim of this work was calculating this parameter supposing total dissociation of the salts in ethyl lactate-based ATPS. In this new approach, ρ became specific for each chemical species and its physical meaning (related to the distance between ions of different charges) was preserved. This method was applied in the LLE modelling of 7 ethyl lactate organic or inorganic salts water systems measured by the group, using the PDH term coupled with the UNIversal QUAsi-Chemical (UNIQUAC) model, whose junction is generally known as PDH UNIQUAC, and compared with classical UNIQUAC and with previous works. The new approach accurately described the experimental liquid-liquid equilibria (LLE) data and presented smaller composition deviations than UNIQUAC.

1. Introduction

The chemical engineering industry involves several separation processes which rely on diffusional operations, i.e., the net transport of a solute through a solvent [1]. Therefore, it is crucial to accurately estimate the fluid phase equilibria of the systems and to apply this knowledge in optimizing processes and in adequately designing unit operations [1,2]. To do so, generally two different approaches can be taken: using models which express the mixture excess Gibbs energy as a function of composition, such as the UNIversal QUAsiChemical (UNIQUAC) [1] model and the Non-Random Two Liquid (NRTL) [3] model, or using equations of state, such as the Perturbed Chain - Statistical Associating Fluid Theory (PC-SAFT) [4] equation of state and the Cubic Plus Association (CPA) [5] equation of state.

Aqueous Two-Phase Systems (ATPS) constitute an efficient separation method for biotechnological materials, such as amino acids, pigments, proteins, vitamins and flavonoids [6]. It was first developed by the Swedish biochemist Per-Åke Albertsson in 1986 and has become since a very common methodology for its efficiency in extraction, simplicity, biocompatibility, which allows for preserving the activity and properties of compounds such as antioxidants and vitamins, versatility and tunability, since a wide variety of solutes can be extracted, and for its low cost and low environmental footprint [6,7], which are mostly due to the high water-content. Moreover, the ATPS technique presents some economic advantages in downstream processing, since the involved chemical species are inexpensive, since several process stages can be reduced and substituted by ATPS, and since it is performed at room temperature, making it an energy-efficient and cost-effective alternative [6].

Conventional ATPS are formed with ternary mixtures of water, salt and a polymer or water and two different polymers [8]. In recent years, ATPS with green solvents, such as poly(ethylene glycol) (PEG) [8] and ethyl lactate [7], and salts, such as potassium tartrate and sodium citrate [7], had a surge in use as replacements for other less environmentally-friendly materials. After the appearance of the two immiscible phases, which is generally promoted by a salt, the biological material preferentially diffuses into the top

---

[☆] This article was presented at the 31st European Symposium on Applied Thermodynamics (ESAT) in 2021.

[*] Corresponding author.

E-mail addresses: velho@fe.up.pt (P. Velho), elenacostas@fe.up.pt (E. Gómez), eamacedo@fe.up.pt (E.A. Macedo).

https://doi.org/10.1016/j.fluid.2022.113389

or bottom phase, which is usually referred to as liquid-liquid extraction, solvent extraction or partition.

Ethyl lactate (EL) is a monobasic ester that can be produced from corn fermentation. It has become a very relevant alternative green solvent in ATPS because of its low toxicity and eco-toxicity, non-corrosiveness and high solvent power [7]. So far, it has presented good results as extraction agent for different biomolecules, such as flavonoids, antioxidants, vitamins and hydrocarbons [7].

The modelling of ATPS is highly relevant either for academic and industrial purposes, but it is often complex due to the existence of two solvents and electrolytes in solution. In literature, different thermodynamic models and equations of state (EoS) have been applied to ATPS with salts. Amongst the most used equations of state are the Wilson EoS, the modified Wilson EoS [9,10] and the Statistical Associating Fluid Theory (SAFT) EoS [11]. Concerning excess Gibbs energy (G^E) thermodynamic models, the UNIQUAC Functional-group Activity Coefficients (UNIFAC), modified UNIFAC [12], NRTL, modified NRTL [10,13], extended UNIQUAC (with the Debye-Hückel term) [12] and the extended Pitzer model are the most preponderant [14].

The combination of the Pitzer-Debye-Hückel (PDH) equation [15] with the UNIQUAC [1] model is generally referred to as PDH UNIQUAC and has successfully been applied to describe the liquid-liquid equilibria (LLE) of different electrolytes [16]. In this model, the UNIQUAC accounts for the short-range interactions, whilst the PDH term describes the long-range interactions between ions of opposite charges, considering the solvent as a dielectric medium [16,17]. The PDH term requires the fitting of a parameter called closest approach parameter (ρ), which is related to the distance between the salt ions of opposite electronic charges. The fitting of ρ is performed from 8 to 15 [15], regardless of the electrolyte under study, so this process does not conserve the physical meaning that the parameter should have. The calculation of this parameter would preserve the specificity for each chemical compound, decrease the total number of adjustable parameters and ease the mathematical convergence of the models, which could yield better modelling results.

The aim of this work was to evaluate the modelling performance of the PDH UNIQUAC model in 7 ethyl lactate-based Aqueous Two-Phase Systems (ATPS) comprising 3 inorganic (K_2HPO_4, $(NH_4)_2SO_4$ and NaH_2PO_4) and 4 organic salts ($C_6H_5Na_3O_7$ (sodium citrate), $C_6H_5K_3O_7$ (potassium citrate), $C_4H_4Na_2O_6$ (sodium tartrate) and $KNaC_4H_4O_6$ (sodium potassium tartrate)). The novelty of this work relies on calculating the closest approach parameter (ρ) for the PDH term instead of considering it as an adjustable parameter, which is the classical practice. The results were compared with UNIQUAC and with PDH UNIQUAC with fitted closest approach parameter (ρ). Besides, the binodal curve and tie-line compositions of {ethyl lactate (1) K_2CO_3 (2) water (3)} were determined.

2. Experimental procedure

2.1. Chemicals and apparatus

The chemicals used can be seen in Table 1. All chemicals were used without further purification steps.

Mass (m) was measured using a Mettler AXE 205 Delta Range scale with an uncertainty in the measurement of ± 3 10^{-4} g. Density (ρ) was determined using an Anton Paar DSA-5000 M with an uncertainty of ± 3 10^{-5} g cm^{-3}. The refractive index (n_D) was measured using an Abbemat-HP Dr. Kernche with an uncertainty of ± 4 10^{-5}. Temperature (T) was kept at 25 °C using a PoliScience thermostatic bath and a digital temperature controller ASL F20 with an uncertainty of ± 0.1 K. pH was determined with a pHmeter Crison Basic 20 with uncertainties of ± 0.01 in the pH and ± 0.1 K in the temperature.

2.2. Phase diagram determination

2.2.1. Binodal curve

The binodal curve or coexistence curve, which describes the phase transition border in liquid-liquid equilibria (LLE), was determined following the "cloud point" method [18] for the system {ethyl lactate (1) K_2CO_3 (2) water (3)}.

In this method, first, a solution of the salt in water (50.40% wt) was prepared close to maximum solubility, ensuring complete dissolution and homogeneity. Second, this solution was titrated with pure ethyl lactate (EL) until phase separation was observed (instantaneous and persistent turbidity or "cloudiness") and the compositions were determined by gravimetry. Fourth, drops of pure water were consecutively added until the solution became clear again. This process, which can be observed in Fig. 1, was repeated until enough data were obtained to properly comprehend the binodal curve.

The obtained data were fitted using the Merchuck *et al.* [19] equation, shown by Eq. (1), which is commonly applied to describe the binodal curves in Aqueous Two-Phase Systems (ATPS) in literature [17,20].

$$[\mathrm{EL}] = A \cdot \exp\left(B[\mathrm{salt}]^{0.5} - C[\mathrm{salt}]^{3}\right) \quad (1)$$

where [EL] and [salt] are the ethyl lactate and salt compositions in weight percentage, respectively, and A, B and C are adjustable parameters.

2.2.2. Tie-lines

To experimentally determine the tie-lines, i.e., isothermal lines which connect two corresponding phases, the procedure shown in Fig. 2 was carried out. First, known ternary mixtures {ethyl lactate (1) salt (2) water (3)} in the immiscible zone were prepared in vials. After properly sealing to avoid moisture absorption, evaporation and eventual contamination, they were stirred for 6 h at 298.15 K and atmospheric pressure.

Then, they were left to settle overnight, which corresponds to about 12 h, at 298.15 K and atmospheric pressure to ensure proper phase separation of the Aqueous Two-Phase System (ATPS). From each vial, samples of the ethyl lactate-rich phase (top) and salt-rich phase (bottom) were carefully collected using a syringe and without remixing the phases. Lastly, the composition of each sample was determined by crossing previously measured density (ρ) and refractive index (n_D) isolines.

To define the property isolines, binary and ternary mixtures with known compositions were used to cover the chosen miscible region to describe the ATPS. Density and refractive index were measured at 298.15 K and atmospheric pressure and a polynomial expression following Eq. (2) was obtained for each property after fitting the experimental data.

$$PP = \sum_{i=1}^{n} \sum_{j=1}^{m} A_{ij} w_i^m \quad (2)$$

where PP is the physical property (ρ or n_D), n is the total number of species in the ternary mixtures, A_{ij} are the adjustable parameters, w_i is the mass fraction of component i and m is the polynomial degree.

3. Thermodynamic modelling

3.1. UNIQUAC

UNIversal QUAsiChemical (UNIQUAC) is a statistical mechanics-based model which comes from generalizing the Guggenheim

Table 1
Chemicals used with respective commercial suppliers, purities, Chemical Abstracts Service (CAS) number and abbreviation.

Chemical	Supplier	Purity [a]	CAS	Abbreviation
Water (H_2O)	VWR chemicals	–	7732–18–5	–
(-) ethyl L-lactate ($C_5H_{10}O_3$)	Sigma-Aldrich	> 98 wt% [b]	97–64–3	EL
Potassium carbonate (K_2CO_3)	Sigma-Aldrich	> 99 wt% [b]	584–08–7	–

[a] Provided by the supplier.
[b] wt% refers to weight percentage.

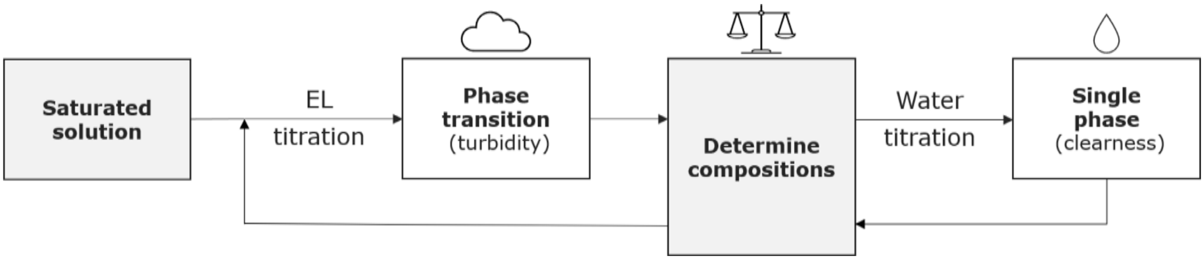

Fig. 1. Experimental procedure taken to determine the binodal curve.

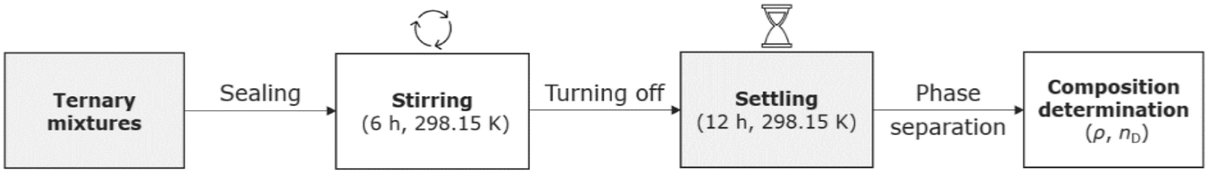

Fig. 2. Experimental procedure taken to determine the tie-lines.

method [1]. UNIQUAC is valid for polar and nonpolar solvents and is capable of properly describing very asymmetrical mixtures in size and shape. Even though it was developed to only account for non-charged species, it has been successfully used in describing a wide range of electrolytes [17,21], such as salts in Aqueous Two-Phase Systems (ATPS) [17,20,22].

Since this model is well-reported in the literature, its equations will not be discussed and can be read in a previous publication of the group [17].

3.2. PDH UNIQUAC

When dealing with charged species, long-range interactions become dominant, and it is necessary to account for their presence. To do so, when determining the activity of a species, one can consider the UNIQUAC thermodynamic model to account for the short-range interactions and the Pitzer–Debye–Hückel (PDH) equation to describe the long-range electrostatic interactions [15], as Eq. (3) shows. This junction is normally referred to as PDH UNIQUAC.

$$\ln\left(\gamma_i\right) = \ln\left(\gamma_i^{\mathrm{UNIQUAC}}\right) \quad \ln\left(\gamma_i^{\mathrm{PDH}}\right) \tag{3}$$

where $\gamma_i^{\mathrm{UNIQUAC}}$ is the UNIQUAC activity coefficient contribution and γ_i^{PDH} is the PDH equation activity coefficient contribution.

The Pitzer-Debye-Hückel activity coefficient contribution is obtained by Eq. (4), in the symmetrical convention [17,23].

$$\ln\left(\gamma_i^{\mathrm{PDH}}\right) = \; - z_i^2 A_{\mathrm{DH},x}\left[\frac{2}{\rho}\ln\left(\frac{1 \quad \rho\sqrt{I_x}}{1 \quad \rho\sqrt{I_x^{\nabla}}}\right) \qquad \sqrt{I_x}\,\frac{1 - {}^{I_x}/_{I_x^{\nabla}}}{1 \quad \rho\sqrt{I_x}}\right] \tag{4}$$

where z_i is the charge of the species and I_x refers to the mole ionic strength, obtained by:

$$I_x = 0.5\sum_{i=1}^{N_{\mathrm{ion}}} z_i^2 x_i \tag{5}$$

where N_{ion} refers to the number of different ions in solution and z_i is the ionic charge of ion i.

On the other hand, I_x^{∇} is the ionic strength of the pure salt, which is given by Eq. (5) for monocharged electrolytes [23].

$$I_x^{\nabla} = \frac{z_i^2}{2} \tag{6}$$

$A_{\mathrm{DH},x}$ is the so-called Debye-Hückel parameter, which is calculated using:

$$A_{\mathrm{DH},x} = \frac{1}{3}\frac{\sqrt{2\mathrm{N_A}}}{8\pi}\left(\frac{e^2}{{}_0\mathrm{k}}\right)^{1.5}\frac{\rho_0^{0.5}}{(\;T)^{1.5}} \tag{7}$$

where $\mathrm{N_A}$ is the Avogrado’s number, e is the electronic charge, $_0$ is the vacuum permittivity, k is the Boltzmann constant, ρ_0 is the solvent’s density and is the solvent’s dielectric constant.

Generally, for solvents, Eq. (3) is reduced to Eq. (8) since they are neutral species.

$$\ln\left(\gamma_i^{\mathrm{PDH}}\right) = A_{\mathrm{DH},x}\frac{2I_x\sqrt{I_x}}{1 \quad \rho\sqrt{I_x}} \tag{8}$$

where ρ is the closest approach parameter.

Pitzer [15] presented the closest approach parameter (ρ) in 1980 as a dimensionless adjustable parameter and its values have been assumed between 8 and 15 [15,24,25], generally being 14.9 for a wide variety of salts and for a wide range of temperatures and pressures [26].

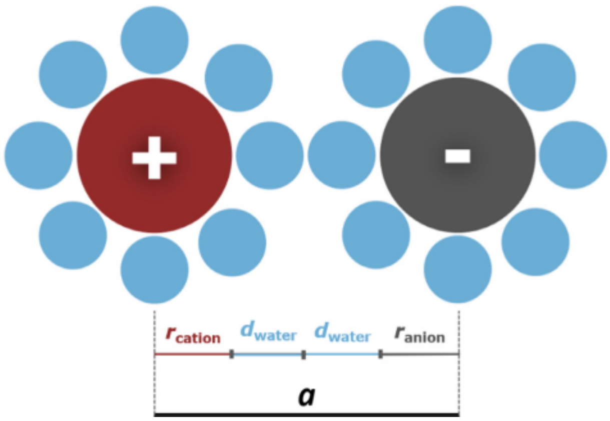

Fig. 3. Influence of solvation in the hard-core collision diameter (a). The red sphere ( ) represents the cation, the grey sphere (-) the anion and the blue ones ( ) represent the solvent (water).

Yet, in its essence, the closest approach parameter (ρ) is related to the distance between the centers of ions of opposite electronic charges, which is generally approximated by the hard-core collision diameter, so it should not be considered the same for very different particles. Being so, in this work, it will be calculated following the equation proposed by Pitzer and Simonson [27]:

$$\rho = a\left(\frac{2e^2 \mathrm{N_A} \rho_i}{M_i \ {}_0 \mathrm{k} \ T}\right)^{\frac{1}{2}} \tag{9}$$

where ρ_i is the density of the species i, M_i is molecular mass of the species i and a is the hard-core collision diameter.

The hard-core collision diameter or distance of closest approach (a) [28] is the distance between the centers of ions of opposite charges. It supposes both ions have rigid spherical shapes and accounts for the contribution of the shape and size of the solvent molecule.

The ATPS presented in this work are formed by strong organic and inorganic salts, so these are assumed to be completely dissociated. Therefore, both ions are surrounded by the present solvents, in this case, they are solvated by water and ethyl lactate. Being so, at least two solvent molecules exist between the ions, as Fig. 3 illustrates. This situation corresponds to the minimum distance in which total dissociation occurs, which was supposed for all the salts, as mentioned above. Although more than two solvent molecules could exist between the salt ions, the goal is to evaluate whether considering the PDH term would make the thermodynamic modelling more accurate and whether the ρ parameter could be effectively calculated, so it is not necessary to evaluate the results with more than two solvent molecules.

For ethyl lactate-based ATPS, and for the systems studied in this work, salt solubility in ethyl lactate is generally smaller than in water. Moreover, the composition in water is sufficient in both phases to completely dissolve the organic and inorganic salts. Hence, only water will be considered as solvating agent. Therefore, the closest approach parameter in this situation is obtained by:

$$a = \ r_{cation} \quad 2\ d_{water} \quad r_{anion} \tag{10}$$

where d_{water} is the water molecule diameter and r_{cation} and r_{anion} are the cation and anion radii, respectively.

In this work, the radius of each ion (r_{ion}) will be approximated to the van der Waals radius, which will be calculated, supposing a spherical shape, from the van der Waals volume, i.e., the volume occupied by each mole of the compound, which is considered impenetrable to other molecules at ordinary temperatures [29], using:

$$r_{ion} \cong r_w = \sqrt[3]{\frac{3V_w}{4\pi}} \tag{11}$$

where r_{ion} stands for the radius of the cation/anion, r_w for the van der Waals radius and V_w for the van der Waals volume.

The van der Waals volume will be calculated using the UNIQUAC volume structural parameter R, following equation [30]:

$$V_w = 15.17\ R \tag{12}$$

The UNIQUAC structural parameters, R and Q, for each salt were found in literature [7,22,31,32] or calculated using Bondi's method [33] and can be seen in the Supporting Materials, Table S1.

Table 2
Experimental binodal curve data for the ternary system {ethyl lactate (1) K_2CO_3 (2) water (3)} determined at T = 298.15 K and p = 0.1 MPa in weight percentage (w_i) [a].

w_{EL}	w_{salt}	w_{EL}	w_{salt}	w_{EL}	w_{salt}
86.6	0.9	44.3	8.1	3.4	28.9
79.2	1.7	35.4	10.8	1.9	34.1
69.9	2.6	29.2	13.3	1.9	49.4
63.4	3.5	25.3	14.7	1.6	49.6
59.6	4.4	15.9	19.9	1.1	38.9
53.3	5.7	9.6	23.2	1.2	44.2
51.2	6.4	5.8	26.0		

[a] Standard uncertainties, u, are: $u(T)$ = 0.1 K, $u(p)$ = 10 kPa, $u(w) = 10^{-1}$.

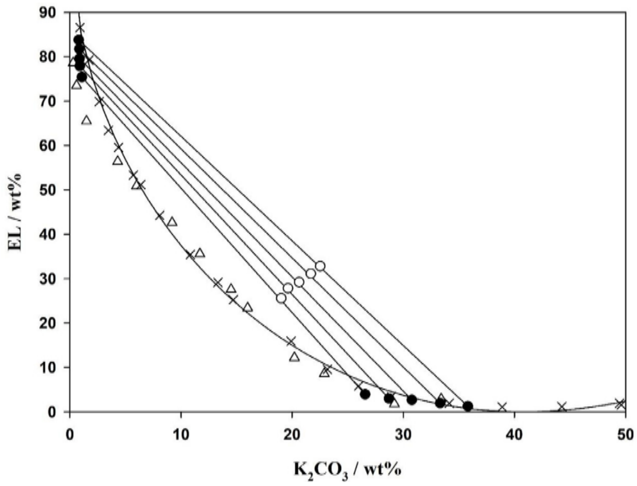

Fig. 4. Binodal curves and tie-lines for the ternary system {ethyl lactate (1) K_2CO_3 (2) water (3)} at T = 298.15 K and atmospheric pressure. (○) feed compositions, (X) binodal curve, (–) fit of the binodal data, ( ) experimental tie-line data and (Δ) literature-based binodal curve [34].

4. Results and discussion

4.1. Experimental ATPS determination

In this work, the binodal curve and the tie-line compositions for {ethyl lactate (1) K_2CO_3 (2) water (3)} were determined. The binodal curve, as mentioned earlier, was obtained following the "cloud point method" and the results can be seen in Table 2 and Fig. 4.

In Fig. 4, it can be seen that the binodal curve of this system has significant curvature and, consequently, a large biphasic area, which will make the system {ethyl lactate (1) K_2CO_3 (2) water (3)} suitable for a good phase separation.

The obtained binodal data were fitted according to Merchuck *et al.* [19], Eq. (1), which was used to represent the coexistence

Table 3
Fitting parameters obtained for the Merchuk equation, Eq. (1), and standard deviation[a] for the experimental binodal curve data for {ethyl lactate (1) K_2CO_3 (2) water (3)} at $T = 298.15$ K and $p = 0.1$ MPa.

System	A	B	C	σ [a]
EL K_2CO_3 water	121.648	- 0.342	$7.15 \; 10^{-5}$	0.899

[a] Standard deviation; $\sigma = \{\sum_{i}^{n_{\mathrm{data}}} ((z - z_{\mathrm{calc}}))^2 / n_{\mathrm{data}}\}^{1/2}$ (z and z_{calc} are the values of the experimental and calculated property and n_{data} is the number of experimental data points).

curve in Fig. 4. This equation is one of the most applied in the fitting of binodal curves and was successfully used for this system, presenting a very small deviation. The respective fitting parameters and deviation are presented in Table 3.

To determine the tie-lines composition, density and refractive index of binary and ternary mixtures with known compositions were determined at 298.15 K and atmospheric pressure, which can be seen in Table S2, in the Supporting Information. Then, polynomial expressions were obtained for each property, as Table 4 shows.

The polynomial expressions of Table 4, i.e., isolines, were crossed for each phase sample, allowing for determining the phase compositions. The composition results can be observed in Table 5 and Fig. 4, together with the respective tie-line lengths (TLL) and tie-line slopes (STL), which are two common tools for the analysis of the liquid-liquid equilibria (LLE) of the systems, as well as *p*H measurements for both phases. TLL and STL were calculated following a previous work of the group [7].

As seen in Table 5, the *p*Hs of all the studied bottom and top phases are rather different: around 9 for top and 11 for bottom phases. The *p*H of the phases is specific for each ATPS and should always be reported in the liquid-liquid equilibria (LLE) studies, since this technique is majorly applied in the partition of biomolecules such as vitamins and antioxidants, which can be very unstable and even present different chemical structures (neutral and ionic) in some *p*H values.

In future partition studies, tie-line number 5 should yield a better extraction, since it has the largest tie-line length (TLL), which implies a more significant difference between top and bottom phase compositions. Regarding the tie-line slope (STL), it can be seen that the same tie-line presents the biggest slope. Therefore, this tie-line presents the most significant difference in ethyl lactate composition between the two (top and bottom) corresponding phases.

The binodal curve data was compared with the available literature [34], and very similar results were noticed, especially for high salt mass fraction. However, in the ethyl lactate-rich region, significant deviations were visible, as shown in Fig. 4.

With the aim of comparing the results obtained in this work for {ethyl lactate (1) K_2CO_3 (2) water (3)} with previous publications of the research group on ethyl lactate-based ATPS with salts [7,17,22], Fig. 5 shows the comparison of the studied system with other ATPS with inorganic (K_2HPO_4, $(NH_4)_2SO_4$ and NaH_2PO_4) and organic salts ($C_6H_5Na_3O_7$ (sodium citrate), $C_6H_5K_3O_7$ (potassium citrate), $C_4H_4Na_2O_6$ (sodium tartrate) and $KNaC_4H_4O_6$ (sodium potassium tartrate)) reported in literature by the group [7,17,22].

From Fig. 5, it can be observed that the ATPS with $(NH_4)_2SO_4$, K_2HPO_4, Nacitrate and Natartrate present the largest miscible zones. Therefore, these systems are more favourable for extraction processes, since a better separation is obtained. On the other hand, the smallest miscible zones were noticed for Kcitrate, NaKtartrate and K_2CO_3. Being so, systems with sodium-based salts provide more efficient separation media than potassium-based salts. Moreover, organic salts are, generally, more eco-friendly than inorganic salts [7], so, from the studied salts, organic salts with sodium, such as Natartrate or Nacitrate, should be preferred.

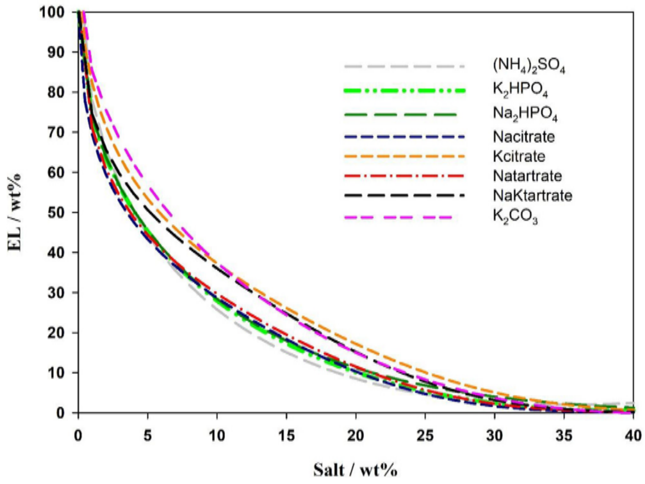

Fig. 5. Binodal curves of the ternary systems {ethyl lactate (1) organic and inorganic salts (2) water (3)} determined at $T = 298.15$ K and atmospheric pressure. Salts: line medium dash grey $(NH_4)_2SO_4$ [17]; line short-short pink K_2CO_3 (data presented in this work); line dash-dot-dot green K_2HPO_4 [17]; line long dash dark green NaH_2PO_4 [17]; line short dash dark blue Nacitrate [7]; line dash-dot red Natartrate [22]; line short dash orange Kcitrate [7] and line medium-dash black NaKtartrate [22].

4.2. Modelling ATPS

As mentioned earlier, two thermodynamic models were compared in the LLE description: UNIQUAC, which only accounts for neutral molecules, and PDH UNIQUAC, which considers both short-range and long-range interactions. Regarding the PDH UNIQUAC model, it was used following two different methodologies: one considering the closest approach parameter (ρ) as an adjustable parameter between 8 and 15, as Pitzer [26,27] defended; another calculating the ρ parameter (Eq. (9)) taking into account solvation and ionic radii (Eq. (10)).

The objective function used in the thermodynamic modelling for all the approaches is given by the following equation:

$$\mathrm{O.F.} = \sum_{j}^{m} \sum_{i}^{n} \left[\ln\left(x_{ij}^{\mathrm{I,cal}} \gamma_{ij}^{I}\right) - \ln\left(x_{ij}^{\mathrm{II,cal}} \gamma_{ij}^{\mathrm{II}}\right) \right] \tag{13}$$

where γ stands for the activity coefficients.

In this work, for the organic salts ($C_6H_5Na_3O_7$ (sodium citrate), $C_6H_5K_3O_7$ (potassium citrate), $C_4H_4Na_2O_6$ (sodium tartrate) and $KNaC_4H_4O_6$ (sodium potassium tartrate), the PDH UNIQUAC model was applied with both fitted and calculated closest approach parameters (ρ).

For the inorganic salts: $(NH_4)_2SO_4$ (ammonium sulfate), K_2HPO_4 (dipotassium phosphate) and NaH_2PO_4 (monosodium phosphate), PDH UNIQUAC with calculated ρ was applied and the results were compared with data from literature [17] for PDH UNIQUAC with fitted ρ. The UNIQUAC model results were collected from literature [7,17,22].

The thermodynamic modelling was performed after evaluating hydrolysis of the present salts. Since very small concentrations of the hydrolysed ions were obtained, only the predominant species were considered (cation and anion of the added salt). Transesterification was also disregarded because of the low temperature (298.15 K), mild *p*H values, absence of catalyst and alcohol scarceness in the studied ATPS.

The goals were to study to what extent considering the Pitzer-Debye-Hückel term would be beneficial to the description of

Table 4
Polynomial expressions (isolines) for density and refractive index as function of the composition for the ternary system {ethyl lactate (1) K_2CO_3 (2)   water (3)} at T = 298.15 K and p = 0.1 MPa.

$\rho = 0.1468\cdot w_1 + 0.9944\cdot w_1^2 - 0.1076\cdot w_1^3 + 0.4819\cdot w_2 + 1.7444\cdot w_2^2 + 0.1285\cdot w_2^3 + 0.1005\cdot w_3 + 1.0023\cdot w_3^2 - 0.1061\cdot w_3^3$
$n_D = 0.0629\cdot w_1 + 1.4335\cdot w_1^2 - 0.0822\cdot w_1^3 + 0.0508\cdot w_2 + 1.5005\cdot w_2^2 - 0.0199\cdot w_2^3 + 0.1740\cdot w_3 + 1.2470\cdot w_3^2 - 0.0894\cdot w_3^3$

Table 5
Experimental phase equilibrium compositions (in weight percentage), together with their corresponding tie-line lengths (TLL) and tie-line slopes (STL), as well as pH measurements of each phase, for {ethyl lactate (1) + K_2CO_3 (2) + water (3)} at T = 298.15 K and p = 0.1 MPa[a].

Tie-line (TL)	Feed		Top phase			Bottom phase			STL	TLL
	[EL]	[salt]	[EL]	[salt]	pH	[EL]	[salt]	pH		
TL1	25.6	19.0	75.4	1.1	9.12	3.9	26.6	10.92	−2.80	75.87
TL2	27.9	19.6	77.9	0.9	9.13	3.0	28.7	11.10	−2.69	79.90
TL3	29.2	20.6	79.6	0.9	9.12	2.7	30.8	11.14	−2.57	82.53
TL4	31.1	21.7	81.7	0.9	9.07	1.9	33.3	11.37	−2.46	86.14
TL5	32.8	22.5	83.8	0.8	9.00	1.3	35.8	11.39	−2.36	89.65

[a] Standard uncertainties, u, are: $u(T)$ = 0.1 K, $u(p)$ = 10 kPa, $u(w) = 10^{-1}$, $u(\text{pH}) = 10^{-2}$.

Table 6
Root mean square composition deviations from experimental data obtained for different ethyl lactate-based ATPS with organic/inorganic salts using UNIQUAC (σ_{UNIQUAC}) and PDH   UNIQUAC with fitted ($\sigma^{\text{fit}}_{\text{PDH \; UNIQUAC}}$) and calculated ($\sigma^{\text{calc}}_{\text{PDH \; UNIQUAC}}$) closest approach parameter.

Salt	σ_{UNIQUAC}	$\sigma^{\text{fit}}_{\text{PDH \; UNIQUAC}}$	$\sigma^{\text{calc}}_{\text{PDH \; UNIQUAC}}$	Type
Sodium citrate, $C_6H_5Na_3O_7$	0.40 [a]	0.00097 [d]	0.00062 [d]	Organic
Potassium citrate, $C_6H_5K_3O_7$	0.48 [a]	0.0024 [d]	0.00033 [d]	Organic
Sodium tartrate, $C_4H_4Na_2O_6$	0.07 [b]	0.0032 [d]	0.0013 [d]	Organic
Sodium potassium tartrate, $KNaC_4H_4O_6$	0.05 [b]	0.0053 [d]	0.0012 [d]	Organic
Ammonium sulfate, $(NH_4)_2SO_4$	0.069 [c]	0.0092 [c]	0.0064 [d]	Inorganic
Dipotassium phosphate, K_2HPO_4	0.057 [c]	0.029 [c]	0.026 [d]	Inorganic
Monosodium phosphate, NaH_2PO_4	0.041 [c]	0.029 [c]	0.018 [d]	Inorganic

[a] From ref. [7].
[b] From ref. [22].
[c] From ref. [17].
[d] From this work.

the liquid-liquid equilibria of ethyl lactate-based ATPS with organic/inorganic salts and to understand if calculating the closest approach parameter (ρ) according to its physical meaning would provide better results than adjusting it.

The composition deviations between the thermodynamic modelling results and the measured/literature experimental data were determined following Eq. (14).

$$\sigma x = \sqrt{100\left(\frac{\sum_i^m \sum_j^{n-1} \left(x_{ij}^{\text{I,exp}} - x_{ij}^{\text{I,cal}}\right)^2 \quad \left(x_{ij}^{\text{II,exp}} - x_{ij}^{\text{II,cal}}\right)^2}{2mn}\right.} \tag{14}$$

where m is the total number of tie-lines and n is the total number of components in the mixture. The superscripts I and II refer to the top and bottom phase, respectively, and x_i^{exp} and x_i^{cal} are the experimental and calculated compositions in mole fraction of component i, respectively.

Table 6 summarizes the composition deviations obtained using the different approaches. All the deviations were obtained using the same equation.

As Table 6 shows, PDH   UNIQUAC always presented smaller composition deviations than UNIQUAC, so accounting for long-range interactions, i.e., using the Pitzer-Debye-Hückel term, is required for a better modelling of these systems.

For all the systems studied, PDH   UNIQUAC with a calculated closest approach parameter presented smaller deviations than PDH   UNIQUAC with fitted ρ. The PDH   UNIQUAC model is very sensitive to variations in the value of this parameter, so calculating it allows for easier minima search of Eq. (12) and provides more reasonable values for the binary interaction parameters. The obtained UNIQUAC binary interaction parameters for all the different modelling methodologies performed in this work can be found in Table S3, in the Supporting Information. The obtained binary interaction parameters presented reasonable results for all the models used.

Table 7
Fitted (ρ_{fitted}) and calculated ($\rho_{\text{calculated}}$) closest approach parameters obtained for different salts, from experimental data, using PDH   UNIQUAC.

Salt	ρ_{fitted}	$\rho_{\text{calculated}}$
Sodium citrate, $C_6H_5Na_3O_7$	8.98	3.02
Potassium citrate, $C_6H_5K_3O_7$	11.42	3.45
Sodium tartrate, $C_4H_4Na_2O_6$	8.82	3.44
Sodium potassium tartrate, $KNaC_4H_4O_6$	8.90	3.73
Ammonium sulfate, $(NH_4)_2SO_4$	12.69	3.96
Dipotassium phosphate, K_2HPO_4	13.55	4.22
Monosodium phosphate, NaH_2PO_4	11.67	4.62

The fitted and calculated closest approach parameters are shown in Table 7.

As seen in Table 7, adjusting the closest approach parameter inside the 8 to 15 interval, as suggested by Pitzer [26,27], significantly overestimated the distance between the ions when compared to the calculated values. Since this fitting interval has been used independently of the size and shape of the molecules under study, it has lost its physical meaning and has become only a mathematical tool (an adjustable parameter). Table 7 also shows that ρ_{fitted} and $\rho_{\text{calculated}}$ do not follow a common trend, which strengthens the point that the fitting hampers the establishment of correlations between the chemical structure and the values of the closest approach parameter. Therefore, calculating the value of the

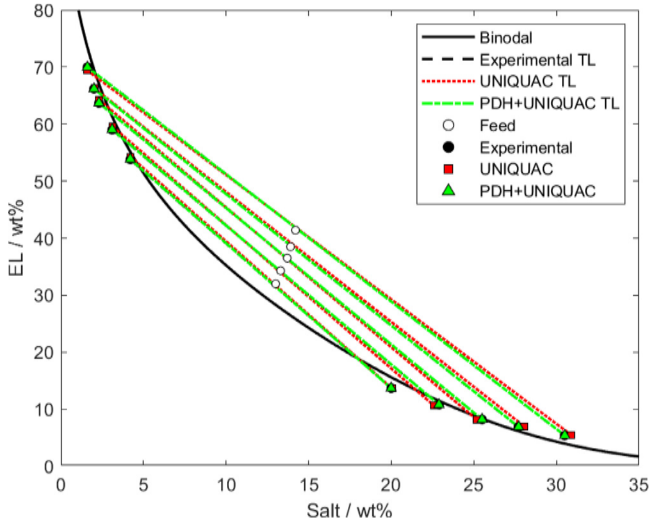

Fig. 6. Binodal curve and tie-lines for the ternary system {ethyl lactate (1) sodium potassium tartrate (2) water (3)} at $T = 298.15$ K and atmospheric pressure. (o) feed compositions [22], (–) fit of the binodal data [22], ( ) experimental tie-line data [22], (–) experimental tie-lines, (🟥) calculated tie-lines data by the UNIQUAC thermodynamic model and (...) respective tie-lines, (▲) calculated tie-lines data by the PDH UNIQUAC thermodynamic model with calculated ρ and (- -) respective tie-lines.

parameter instead of fitting provides more accurate descriptions of the systems and eases convergence.

Although the calculation of ρ only supposes two water molecules between the salt ions, the difference between the adjusted and calculated values of the closest approach parameters is too large to be explained solely by the existence of water molecules, since this would imply the presence of so many water molecules that long-range interactions would become weak. Ultimately, this decrease in electrostatic forces would contradict the relevance of the PDH term observed in Table 6.

The same results discussed above and shown in Table 6 can be observed in Fig. 6, as example, which compares the LLE modelling results of UNIQUAC and PDH UNIQUAC for {ethyl lactate (1) sodium potassium tartrate (2) water (3)}. The other figures can be observed in the Supporting Information, in Fig. S1.

5. Conclusions

The main goal of this study was to evaluate the performance of PDH UNIQUAC using a calculated closest approach parameter (ρ) in the thermodynamic modelling of ethyl lactate-based Aqueous Two-Phase Systems (ATPS) with organic/inorganic salts.

Two different methodologies were used: one considering the closest approach parameter (ρ) from the Pitzer-Debye-Hückel (PDH) term as an adjustable parameter between 8 and 15; another calculating the ρ parameter considering solvation and ionic radii. The results were compared with classical UNIQUAC.

The thermodynamic modelling was carried out supposing total dissociation of the salts and was performed for 7 ethyl lactate-based Aqueous Two-Phase Systems (ATPS) with 4 organic and 3 inorganic salts. The binodal curve and tie-lines composition of {ethyl lactate (1) K_2CO_3 (2) water (3)} were experimentally determined using the “cloud point” method and by crossing density and refractive index isolines, obtaining similar data to available literature.

The inclusion of the PDH term significantly reduced composition deviations when compared to UNIQUAC, so this additional term should be considered in the modelling of ethyl lactate-based ATPS with strong salts. It was also shown that calculating the closest approach parameter (ρ) provided more accurate modelling than fitting it and that calculating ρ maintained its physical meaning.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Pedro Velho: Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Elena Gómez:** Writing – review & editing, Conceptualization, Supervision, Validation. **Eugénia A. Macedo:** Conceptualization, Supervision.

Acknowledgments

This work was financially supported by: Base - UIDB/50020/2020 and Programmatic - UIDP/50020/2020 funding of LSRE-LCM, funded by national funds through FCT/MCTES (PIDDAC). Pedro Velho is grateful to the research grant under Base - UIDB/50020/2020 and Programmatic - UIDP/50020/2020 funding of LSRE-LCM, funded by national funds through FCT/MCTES (PIDDAC). Elena Gómez thanks funding support from Stimulus of Scientific Employment, Individual Support 2017, CEECIND/02646/2017, FCT.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.fluid.2022.113389.

References

[1] D.S. Abrams, J.M. Prausnitz, Statistical thermodynamics of liquid mixtures: a new expression for the excess Gibbs energy of partly or completely miscible systems, AIChE J. 21 (1) (1975) 116–128, doi:10.1002/aic.690210115.
[2] S. Pinho, E.A. Macedo, Representation of salt solubility in mixed solvents: a comparison of thermodynamic models, Fluid Phase Equilib. 116 (1996) 209–216, doi:10.1016/0378-3812(95)02889-7.
[3] H. Renon, J.M. Prausnitz, Local compositions in thermodynamic excess functions for liquid mixtures, AIChE 14 (1) (1968) 135–144, doi:10.1002/aic.690140124.
[4] J. Gross, G. Sadowski, Perturbed-chain SAFT: an equation of state based on a perturbation theory for chain molecules, Ind. Eng. Chem. Res. 40 (4) (2001) 1244–1260, doi:10.1021/ie0003887.
[5] G.M. Kontogeorgis, E.C. Voutsas, I.V. Yakoumis, D.P. Tassios, An equation of state for associating systems, Ind. Eng. Chem. Res. 35 (1996) 4310–4318.
[6] W.N. Phong, P.L. Show, Y.H. Chow, T.C. Ling, Recovery of biotechnological products using aqueous two phase systems, J. Biosci. Bioeng. 126 (3) (2018) 273–281, doi:10.1016/j.jbiosc.2018.03.005.
[7] P. Velho, P.F. Requejo, E. Gómez, E.A. Macedo, Novel ethyl lactate based ATPS for the purification of rutin and quercetin, Sep. Purif. Technol. 252 (2020) 117447, doi:10.1016/j.seppur.2020.117447.
[8] K. Wysoczanska, H.T. Do, C. Held, G. Sadowski, E.A. Macedo, Effect of different organic salts on amino acids partition behaviour in PEG-salt ATPS, Fluid Phase Equilib. 456 (2018) 84–91, doi:10.1016/j.fluid.2017.10.007.
[9] R. Sadeghi, H.R. Rafiei, M. Motamedi, Phase equilibrium in aqueous two-phase systems containing poly(vinylpyrrolidone) and sodium citrate at different temperatures -Experimental and modeling, Thermochim. Acta 451 (1-2) (2006) 163–167, doi:10.1016/j.tca.2006.10.002.
[10] P. Mobalegholeslam, H. Bakhshi, A new model of excess Gibbs energy for systems containing polymer–salt–water applicable to aqueous two phase systems, J. Solution Chem. 45 (2016) 1826–1841, doi:10.1007/s10953-016-0544-0.
[11] T. Reschke, C. Brandenbusch, G. Sadowski, Modeling aqueous two-phase systems: III. Polymers and organic salts as ATPS former, Fluid Phase Equilib. 387 (2015) 178–189, doi:10.1016/j.fluid.2014.12.011.
[12] M. Ketabi, M. Pirdashti, P. Mobalegholeslam, Liquid-liquid equilibrium and physical properties of aqueous mixtures of poly (ethylene glycol) 3000 with tri-potassium citrate at different pH: experiment, correlation and thermodynamic modeling, J. Korean Chem. Soc. 63 (1) (2019) 12–23, doi:10.5012/jkcs.2019.63.1.12.

[13] G.F. Muraria, J.A. Penido, P.A.L. Machado, L.R. de Lemos, N.H.T. Lemes, L.S. Virtuoso, G.D. Rodrigues, A.B. Mageste, Phase diagrams of aqueous two-phase systems formed by polyethylene glycol   ammonium sulfate   water: equilibrium data and thermodynamic modeling, Fluid Phase Equilib. 406 (2015) 61–69, doi:10.1016/j.fluid.2015.07.024.

[14] B. Perez, L.P. Malpiedi, G. Tubío, B. Nerli, P.A.P. Filho, Experimental determination and thermodynamic modeling of phase equilibrium and protein partitioning in aqueous two-phase systems containing biodegradable salts, J. Chem. Thermodyn. 56 (2013) 136–143, doi:10.1016/j.jct.2012.07.017.

[15] K. Pitzer, Electrolytes: from dilute solutions to fused salts, J. Am. Chem. Soc. 102 (9) (1980) 2902–2906, doi:10.1021/ja00529a006.

[16] C. Chang, S. Lin, Extended Pitzer−Debye−Hückel model for long-range interactions in ionic liquids, J. Chem. Eng. Data 65 (2020) 1019–1027, doi:10.1021/acs.jced.9b00368.

[17] P. Velho, P.F. Requejo, E. Gómez, E.A. Macedo, Thermodynamic study of ATPS involving ethyl lactate and different inorganic salts, Sep. Purif. Technol. 275 (2021) 119155, doi:10.1016/j.seppur.2021.119155.

[18] T.M. Letcher, S. Wootton, B. Shuttlemorth, C. Heyward, Fluid phase for (n-heptane   water   alcohol) at 298.2K, J. Chem. Thermodyn. 18 (1986) 1037–1042, doi:10.1016/0021-9614(86)90017-0.

[19] J.C. Merchuk, B.A. Andrews, J.A. Asenjo, Aqueous two-phase systems for protein separation: studies on phase inversion, J. Chromatogr. B 711 (1998) 285–293, doi:10.1016/S0378-4347(97)00594-X.

[20] S. Ghaffari, J. Shahrouzi, F. Towfighi, A. Khoshfetrat, Partitioning of cefazolin in aqueous two-phase systems containing poly (ethylene glycol) and sodium salts (citrate, tartrate, and sulphate), Fluid Phase Equilib. 488 (2019) 54–61, doi:10.1016/j.fluid.2019.01.010.

[21] M. Iqbal, Y. Tao, S. Xie, Y. Zhu, D. Chen, X. Wang, L. Huang, D. Peng, A. Sattar, M.B. Shabbir, H.I. Hussain, S. Ahmed, Z. Yuan, Aqueous two-phase system (ATPS): an overview and advances in its applications, Biol. Proced. Online 18 (2016) 1–18, doi:10.1186/s12575-016-0048-8.

[22] P.F. Requejo, P. Velho, E. Gómez, E.A. Macedo, Study of liquid−liquid equilibrium of aqueous two-phase systems based on ethyl lactate and partitioning of rutin and quercetin, Ind. Eng. Chem. Res. 59 (2020) 21196–21204, doi:10.1021/acs.iecr.0c02664.

[23] B. Sander, A. Fredenslund, P. Rasmussen, Calculation of vapour-liquid equilibria in mixed solvent/salt systems using an extended UNIQUAC equation, Chem. Eng. Sci. 41 (1986) 1171–1183, doi:10.1016/0009-2509(86)87090-7.

[24] C.C. Chen, L.B. Evans, A local composition model for the excess gibbs energy of aqueous electrolyte systems, AIChE J. 32 (1986) 444–454, doi:10.1002/aic.690320311.

[25] P.A. Barata, M.L. Serrano, Thermodynamic representation of the solubility for potassium dihydrogen phosphate (KDP)   water   alcohols systems, Fluid Phase Equilib. 141 (1997) 247–263, doi:10.1016/S0378-3812(97)00188-X.

[26] K.S. Pitzer, in: Activity Coefficients in Electrolyte Solutions, second ed., CRC Press, 1991, p. 474, doi:10.1201/9781351069472.

[27] K.S. Pitzer, J.M. Simonson, Thermodynamics of multicomponent, miscible, ionic systems: theory and equations, J. Phys. Chem. 90 (1986) 3005–3009, doi:10.1021/j100404a042.

[28] M. TaghiZafarani-Moattar, R. Majdan-Cegincara, Applicability of different equations in modeling the thermodynamic and transport properties of aqueous and non-aqueous ionic liquid solutions, Fluid Phase Equilib. 386 (2015) 82–95, doi:10.1016/j.fluid.2014.11.023.

[29] P. Velho, X. Liang, E.A. Macedo, E. Gómez, G.M. Kontogeorgis, Towards a predictive Cubic Plus Association equation of state, Fluid Phase Equilib. 540 (2021) 113045, doi:10.1016/j.fluid.2021.113045.

[30] L.B. Rockland, L.R. Beuchat, Water Activity: Theory and Applications to Food, IFT - Basic Symposium Series, first ed., 1987, pp. 7–23. pages, doi:10.1201/9780203734148.

[31] A. Haghtalab, B. Mokhtarani, The new experimental data and a new thermodynamic model based on group contribution for correlation liquid–liquid equilibria in aqueous two-phase systems of PEG and (K2HPO4 or Na2SO4), Fluid Phase Equilib. 215 (2004) 151–161, doi:10.1016/j.fluid.2003.08.004.

[32] A. Haghtalab, M. Joda, Modification of NRTL-NRF model for computation of liquid–liquid equilibria in aqueous two-phase polymer–salt systems, Fluid Phase Equilib. 278 (2009) 20–26, doi:10.1016/j.fluid.2008.12.006.

[33] A. Bondi, Physical Properties of Molecular Crystals, Liquids and Glasses, John Wiley and Sons, New York, London, Sydney, 1968.

[34] I. Kamalanathan, L. Canal, J. Hegarty, V. Najdanovic-Visak, Partitioning of amino acids in the novel biphasic systems based on environmentally friendly ethyl lactate, Fluid Phase Equilib. 462 (2018) 6–13, doi:10.1016/j.fluid.2018.01.016.