

Solubilities of High-value Compounds in Ethyl Lactate: Measurements and Modeling

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Abstract

Solid-liquid equilibria of binary mixtures containing high-value compounds and ethyl lactate were studied. Using the gravimetric method, the solubility of various solutes such as caffeine, vanillic acid, ferulic acid, caffeic acid and thymol in ethyl lactate was measured as a function of temperature (temperature range of 298.2 – 343.2 K), at atmospheric pressure. The differences in solubility of a given solute in water-saturated and dry ethyl lactate were observed. The deviation of these binary systems from ideal mixture behaviour was discussed. In order to understand the solubilization process, melting properties of pure solutes were determined by differential scanning calorimetry (DSC). The obtained solubility data were

represented using UNIQUAC and UNIFAC-based models as well as with the Cubic-Plus-Association (CPA) equation of state. The results of the modeling indicate that these models are the appropriate tools for representing the solubility behaviour of various solutes in ethyl lactate.

Keywords: solubility, green solvents, high-value solutes, UNIQUAC, UNIFAC, cubic-plus-association equation of state

1. INTRODUCTION

High-value compounds derived from natural sources are of industrial importance due to the increased perception of their health benefits associated with their antioxidant and antimicrobial activities. Some of the examples are derivatives of hydroxycinnamic acid, such as ferulic and caffeic acids, which are the most abundant phenolic acids found in seeds of many plants: cereals, coffee, fruits and vegetables. Studies have shown their potential in the prevention of chronic illnesses such as cardiovascular diseases and cancer [1]. Free ferulic and caffeic acids presented great antioxidant activities with high scavenging effect towards hydrogen peroxide, superoxide, hydroxyl radical and nitrogen dioxide free radicals [2]. This ability has an important role associated to the anti-cancer effect of these compounds. Kaul et al. [3] reported that topical application containing caffeic and ferulic acids resulted in significant protection against anthracene-induced skin tumors while Guerriero et al. [4] showed anti-cancer activity of both acids on hepatocellular carcinoma. Ferulic acid significantly reduced the growth of oral cancer [5] as well as colon and rectal cancer [6].

Another example of phenolic compounds with high biological activity is vanillic acid which belongs to the hydroxybenzoic acid group. Recent bioactivity studies of hydroxy- and polyhydroxybenzoic acids were reviewed by Khadem and Marles [7]. Vanillic acid occurs in

many plants and it is known for its antisickling and anthelmintic activities. It reduced hepatic fibrosis in chronic liver injury [8], inhibited snake venom 5'-nucleotidase [9] and showed the protective effects in isoproterenol induced cardiotoxic rats [10].

Thymol, a compound characteristic of essential oils, has been identified as an effective antibacterial with relatively low inhibitory concentrations in vitro and somewhat higher concentration in foods [11]. In the recent study [12], thymol demonstrated dose dependent cytotoxic effects on acute promyelotic leukemia cells after 24 h of exposure.

Furthermore, one of the most widely consumed and studied natural product in history is caffeine. Although research results are controversial, it is believed that low to moderate caffeine intake is generally associated with improvements in alertness, learning capacity, exercise performance, and possibly even in mood [13]. It is also used as an additive in pain medications.

Most of high-value compounds derived from natural sources are obtained by energetically intensive vacuum distillation including several additional steps associated with the use of abundant amounts of organic solvents. As an alternative, supercritical fluid technology has been applied to extract various high-value components from natural materials [14]. Nevertheless, despite good performances, large-scale supercritical applications are burdened with bulky equipment requirements. Consequently, the search for other new alternatives – those that would be less costly, more similar by structure to the classical solvents and yet ambient friendly - continues. In that respect, ethyl lactate is a green and economically viable alternative to traditional solvents: it is fully biodegradable, non-corrosive, non-carcinogenic and non-ozone depleting. Ethyl lactate is approved by the U.S. Food and Drug Administration (FDA) as pharmaceutical and food additive and has been generally recognized as a safe (GRAS) solvent [15]. The molecular structure of ethyl lactate possess a

specific topology of hydrogen bonds present as well in other lactate alpha-hydroxyesters [16]. This allows the formation of intra- and intermolecular associations with ethyl lactate, as either proton donor or proton acceptor [17]. On the other hand, ethyl lactate is soluble in paraffin oils, which fact imposes the formation of some van der Waals interactions [18]. Thus, this ester offers diverse solvent properties that may cover a large number of solutes. Consequently, there are several attempts in the literature to use ethyl lactate as an extraction solvent. For example, Ishida and Chapman [19] reported the potential application of ethyl lactate to extract carotenoids from different sources, such as tomatoes, carrots and corn; Strati and Oreopoulou [20] studied the effect of different extraction parameters on the carotenoid recovery from tomato waste; A bioactive bicyclic diterpene, namely sclareol, was selectively extracted using ethyl lactate and recovered from the liquid solution by a CO₂ gas anti-solvent procedure [21]; Hernández et al. [22] studied the potential application of ethyl lactate to recover squalene from olive oil deodorizer distillates. Our group also reported the utilization of ethyl lactate for selective separation of α -tocopherol from triglycerides [23].

The solvent selection is one of the essential parameters to envisage any extraction process. Therefore, the knowledge of the solubility of a target component in different solvents is required. In this work, the solubility of caffeine, vanillic acid, ferulic acid, caffeic acid and thymol, in liquid ethyl lactate were measured in the temperature range of 293.2 – 343.2 K. Although experimental data on solubility are essential to provide information about a system and help to understand its behaviour, correlations and prediction models are also required for the correct design of separation processes.

Binary systems containing ethyl lactate have been described by some models, such as UNIQUAC [22],[23], UNIFAC activity coefficient models coupled with the Peng–Robinson equation of state (PR–EOS) [21] and the perturbed chain-statistical associating fluid theory (PC-SAFT) [24]. In this work, the obtained solubility data in ethyl lactate of caffeine, vanillic

acid, ferulic acid, caffeic acid and thymol, were represented using the UNIQUAC model as well as the modified (Dortmund) UNIFAC method.

In addition, for the first time we applied a simple Cubic Equation of State incorporating association, known as the CPA EoS for the description of the intermolecular physical interactions that include specific association in ethyl lactate containing systems. The CPA EoS was already successfully applied for binary mixtures water + phenolic compounds as reported by Mota et al. [25], [26] and Queimada et al.[27].

2. EXPERIMENTAL SECTION

2.1. Materials

Caffeine (99% purity), vanillic acid (97% purity), ferulic acid (99% purity), caffeic acid ($\geq 98.0\%$ purity), thymol ($\geq 99.5\%$ purity) and ethyl lactate (98% purity) were supplied by Sigma-Aldrich (Table 1). Their molecular structures are given in Figure 1. All solutes were used without further purification. We studied solubility of solutes in: a) water-saturated ethyl lactate as received and without any further treatment, and b) dried ethyl lactate. In the case of latter, vacuum at room temperature was applied to ethyl lactate for several days in order to reduce its water content. Karl-Fischer coulometric titration (Metrohm 870 KF Titrino Plus coulometer) was employed to determine the water content before and after the vacuum procedure.

2.2. Experimental procedure

2.2.1. Differential scanning calorimetry

Differential scanning calorimetry (Netzsch, model DSC 200 F3 Maia) was used in order to obtain the melting point (T_m), enthalpy of fusion (ΔH_{fus}) and differences in heat capacities

(ΔC_p) of caffeine, vanillic acid, ferulic acid, caffeic acid and thymol required for modeling the solid-liquid equilibrium. An aluminium crucible with 5 to 7 mg of sample was sealed hermetically and placed in the measuring cell of the calorimeter together with an empty crucible to be used as a reference. The sample was heated under a nitrogen stream over a large temperature range using a $3 \text{ K}\cdot\text{min}^{-1}$ heating rate. The measurements for each compound were repeated four times and average melting temperatures, enthalpies of fusion and differences in heat capacities were obtained.

2.2.2. Solid-liquid equilibria

For all the studied solutions, except the one with thymol, solid-liquid equilibrium measurements were carried out using the gravimetric method. Ethyl lactate and a solute (caffeine or vanilic acid or ferulic acid or caffeic acid) in excess were placed into a glass vessel with a stirrer. The vessels were put inside a water bath and a stirring plate was used to agitate the samples during 48 h under fixed temperature, controlled by a thermocouple (Julabo ED). The temperature was monitored by a calibrated mercury thermometer, having an accuracy of 0.1 K. After equilibrium had been reached, stirring was stopped and vessels were left still for more 48 hours to allow a complete phase separation. Samples of clear saturated liquid solution (1 cm^3) were taken by a micropipette and placed into glass vials, while both the mass of the empty vial and the mass of the sample were registered using an AAA 250L balance with the precision of $\pm 0.0001 \text{ g}$. The samples were then placed in a vacuum oven (Precision Scientific 5831) equipped with a vacuum pump (Edwards E2M1.5) for a couple of hours till constant mass of the dry samples were achieved. In order to evaporate all ethyl lactate from the samples, moderate temperature (338 K) and low pressure (0.01mbar) were applied. The vials containing dry samples were weighted and the mole fraction solubilities were finally calculated.

In the case of ethyl-lactate + thymol solutions a visual dynamic method was used to measure the solubility of thymol. Solutions were prepared gravimetrically in the glass cell using an AAA 250L balance, with the precision of ± 0.0001 g. After vigorous mixing, the cell (explained in details elsewhere [28],[29]) was placed in the glass thermostat bath and the sample was heated very slowly (less than $0.5 \text{ K}\cdot\text{h}^{-1}$ near the equilibrium temperature) with continuous stirring. The temperature at which the last crystal disappeared was taken as that of solid-liquid equilibrium.

For both methods, triplicates of each measurement were performed in order to obtain reliable solubility data. The average reproducibility in solid-liquid equilibrium temperature and compositions (mole fractions of solutes in ethyl lactate) was $\pm 0.3 \text{ K}$ and 0.0007 , respectively.

2.3. Thermodynamic modeling

The solubility of a solute i in a liquid phase can be calculated by the following equation [30]:

$$\ln \left[\frac{f_i^{\text{liq}}(T,P)}{f_i^{\text{sol}}(T,P)} \right] = \sum_{\text{tr}} \frac{\Delta_{\text{tr}}H}{R} \left(\frac{1}{T} - \frac{1}{T_{\text{tr}}} \right) - \frac{\Delta C_p}{R} \left[\frac{T_m}{T} - \ln \left(\frac{T_m}{T} \right) - 1 \right] \quad (1)$$

where $\Delta_{\text{tr}}H$, R , T and ΔC_p are the enthalpy of transition at the transition temperature (T_{tr}), the ideal gas constant, absolute temperature of solid-liquid equilibria, and difference of the liquid and solid molar heat capacities, respectively. $\sum \Delta_{\text{tr}}H$ integrates enthalpies of different solid–solid and fusion phase transitions of the solute.

In this work the experimental solubility data were described by the UNIQUAC model [30] and by the modified UNIFAC (Dortmund) method – [31] as well as by the Cubic Plus Association equation of state (CPA EoS) [32], [33].

The UNIQUAC equation [30] (an activity coefficient model) can be used to represent the solubility data and equation (1) then becomes:

$$x_i = \frac{1}{\gamma_i} \exp \left[- \sum_{tr} \frac{\Delta_{tr} H}{R} \left(\frac{1}{T} - \frac{1}{T_{tr}} \right) + \frac{\Delta C_p}{R} \left[\frac{T_m}{T} - \ln \left(\frac{T_m}{T} \right) - 1 \right] \right] \quad (2)$$

where x_i and γ_i are the mole fraction of solute i in the liquid phase and the solute i activity coefficient.

The surface area and volume fraction used in UNIQUAC were based on the volume and area parameters which were calculated using the corresponding group contribution values [34], [35]. The temperature-independent binary interaction parameters were obtained from the correlation of the SLE experimental data.

Eq. (2) was also applied using the modified UNIFAC model [31] to calculate the solute activity coefficient in the liquid phase. The ACOH – COOH interaction parameters (both groups are present in the chemical structure of the phenolic acids studied) were estimated in this work using the SLE experimental data.

The Cubic Plus Association equation of state (CPA EoS) is a combination of the simple cubic equation of state (SCEoS) and the Wertheim association term. The SCEoS term presents the description of the physical interactions, while the Wertheim association term takes into account the specific association interactions between molecules. The CPA EoS can be expressed in terms of the compressibility factor, where the pure component energy parameter (a) is given by a Soave-type temperature dependence:

$$Z = Z^{phys.} + Z^{assoc.} = \frac{1}{1-b\rho} - \frac{a\rho}{RT(1+b\rho)} - \frac{1}{2} \left(1 + \rho \frac{\partial \ln g}{\partial \rho} \right) \sum_i x_i \sum_{A_i} (1 - X_{A_i}) \quad (3)$$

$$a(T) = a_0 [1 + c_1 (1 - \sqrt{T_r})]^2 \quad (4)$$

where ρ and T_r are the molar density and reduced temperature.

X_{Ai} is related to the association strength Δ^{AiBj} between sites A and B belonging to two different molecules (i, j). Since self- and cross-association are present in the studied systems, X_{Ai} is calculating through the following set of equations:

$$X_{A_i} = \frac{1}{1 + \rho \sum_j x_j \sum_{B_j} X_{B_j} \Delta^{A_i B_j}} \quad (5)$$

$$\Delta^{A_i B_j} = g(\rho) \left[\exp\left(\frac{\varepsilon^{A_i B_j}}{RT}\right) - 1 \right] b_{ij} \beta^{A_i B_j} \quad (6)$$

$$\Delta^{A_i B_j} = \sqrt{\Delta^{A_i B_i} \Delta^{A_j B_j}} \quad (7)$$

$$g(\rho) = \frac{1}{1 - 1.9\eta} \quad (8)$$

$$\eta = \frac{1}{4} b\rho \quad (9)$$

Equation (6) is used for self-associating molecules where ε^{AiBi} and β^{AiBi} are the association energy and association volume, respectively. The Elliot combining rule (eq. 7) is used for cross-associating molecules.

The CPA EoS has been recently adopted for complex molecules in order to apply the explicit association energies and volumes for the different associating groups [25],[26],[27]. CPA EoS has five pure component parameters (a_0 , c_1 , b , ε , β) for associating compounds, which are obtained by the simultaneous correlation of experimental liquid density and vapor pressure data, taking into account the number and type of associating groups. However, these experimental data were only available for ethyl lactate and thymol and they were collected from DIPPR Database [36]. Otherwise, the pure component parameters were calculated using the following equations proposed before for phenolics [25]:

$$a_0 = 0.2267 + 24.38 \frac{T_c^2}{P_c} \quad (10)$$

$$c_1 = -3.557 + (6.289 \times 10^{-3})T_c \quad (11)$$

$$b = -2.328 \times 10^{-5} + 1.884V_w \quad (12)$$

where T_c , p_c and V_w are the critical temperature (in K), critical pressure (in Pa) and the van der Waals volume (in $\text{m}^3 \cdot \text{mol}^{-1}$), respectively.

The association energies and association volumes of ethyl lactate and thymol were as well determined using the pure component vapor pressure and liquid density data. The methodology described by Mota et al. [25] was used to obtain association energies and volumes for ferulic acid, vanillic acid and caffeic acid, since in these cases the vapor pressure and liquid density data were not available.

Finally, the solubilities of the studied solutes in ethyl lactate were obtained from the following equation:

$$x_i = \frac{\phi_i^{\text{liq}0}}{\phi_i} \exp \left[-\sum_{\text{tr}} \frac{\Delta_{\text{tr}}H}{R} \left(\frac{1}{T} - \frac{1}{T_{\text{tr}}} \right) + \frac{\Delta C_p}{R} \left[\frac{T_m}{T} - \ln \left(\frac{T_m}{T} \right) - 1 \right] \right] \quad (13)$$

in which the CPA EoS was used to calculate the fugacity coefficients. As mentioned before, the melting temperatures, enthalpies of fusion and differences in heat capacities were measured by DSC.

The experimental and modeling results were compared in terms of the absolute average deviations (AAD) of the solubilities:

$$AAD(\%) = \frac{1}{NP} \sum_i \frac{|x_i^{\text{calc}} - x_i^{\text{exp}}|}{x_i^{\text{exp}}} \times 100 \quad (14)$$

where x_i^{calc} and x_i^{exp} are the calculated and experimental mole fraction solubilities respectively, and NP is the number of available solubility points.

3. RESULTS AND DISCUSSION

Measured enthalpies of fusion and melting temperatures along with differences in heat capacities for the studied solutes (caffeine, vanillic acid, ferulic acid, caffeic acid and thymol) are given in Table 2.

A linear base line and a symmetric peak were observed for all the studied compounds, except for caffeine and caffeic acid. In the case of caffeine two phase transformations, solid-solid and solid-liquid, were detected upon heating while it was observed that caffeic acid decomposes before melting. Therefore, the melting point of caffeic acid adopted in this work was the one presented by Mota et al. [25] obtained by a third-order group-contribution method proposed by Marrero and Gani [37]. The difference in heat capacity of caffeic acid was acquired as a difference of the estimated liquid and solid heat capacities. The heat capacity of the liquid as a function of temperature was estimated by the third-order group-contribution method given by Kolska et al. [38]. The temperature dependence of the group contribution was expressed as an empirical polynomial equation which applies the group contribution parameters determined by both a non-hierarchic and a hierarchic approach. As the non-hierarchic approach showed to be slightly superior, it was used to calculate the heat capacity of liquid caffeic acid. The heat capacity of solid caffeic acid was calculated using the power-law method which has a fixed temperature functionality but applies the two-group contribution method to obtain the compound-specific constant employed in the predictive equation [39].

The observed melting point of thymol was in a good agreement with the data reported in literature [40], showing a deviation of 0.7 %. A substantially higher deviation was observed for its fusion enthalpy (20.9 %). Similarly to what was observed by Dong et al.[41], caffeine showed two phase transitions, solid-solid and solid-liquid. In the case of the fusion of caffeine, our data deviated 0.7 % and 9.9 % for melting temperature and enthalpy of fusion, respectively. The properties of the solid-solid transition of caffeine also agreed reasonably with the literature data (1.8 % and 22 % deviations for melting point and fusion enthalpy, respectively). As for thymol and caffeine, the DSC thermograms of ferulic acid showed one endothermic peak and therefore corresponds to the one of two polymorphic forms reported by Sohn and Oh [42]. Measured melting temperature was smaller for 0.7 % while the fusion enthalpy was higher for 22 %.

Table 3 and Figure 2 present the solubility data of caffeine, vanillic acid, ferulic acid, caffeic acid and thymol in ethyl lactate as a function of temperature. Since ethyl lactate is a hygroscopic compound, solubilities in both water-saturated (1.4 mass %) and dried (0.03 mass %) ethyl lactate were determined, thus permitting to understand the effect of water on solubility. To the best of our knowledge, there are no published data of the solubility of such given solutes in ethyl lactate to compare with. The relative affinity of the studied solutes to ethyl lactate follows the order: thymol >> ferulic acid > vanillic acid > caffeine > caffeic acid. As expected, solubilities of all studied solutes in ethyl lactate were moderately enhanced by temperature rise. It was observed that thymol is extremely soluble in ethyl lactate, reaching mole fraction of 0.8985 at 317.8 K which can be explained by its relatively low melting point of 322.0 K and low enthalpy of fusion of 17.4 kJ·mol⁻¹ (see Table 2). Although the chemical structures of ferulic and caffeic acids (Fig. 1) are relatively similar, their solubility in ethyl lactate were quite unlike – 0.0614 and 0.0171 in mole fraction at 333.3 K for ferulic and caffeic acid, respectively.

The substitution of one hydroxyl group of caffeic acid by a methyl ether group enhanced the solubility significantly. The solubilities of 0.0545 and 0.0614 in mole fraction at 333.3 K were observed for vanillic and ferulic acids, respectively. Thus, comparing these data it can be concluded that the presence of a longer acid alkyl chain increased the solubility only slightly.

It is interesting to note that the solubility of solutes was differently influenced by the presence of water in ethyl lactate solvent (Fig. 2). For example, the solubility of thymol was not changed by water while that of vanillic acid and caffeine was only slightly influenced. On the other hand, a significant increase of the solubility of ferulic and caffeic acids was observed when water was present in ethyl lactate. Taking into account a low solubility of ferulic and caffeic acids in water, this solubility enhancement suggests a co-solvent effect which may have implications in potential extraction processes.

According to equation (2), the calculation of the ideal solubility of a solute in a solvent at a given temperature is straightforward from the thermophysical property data (melting points, enthalpies of fusion and differences in heat capacities) of the studied compounds presented in Table 2. The ideal solubility corresponds to having an activity coefficient equal to one, meaning that the attraction forces between like-molecules (solvent-solvent and solute-solute) are the same as between unlike-molecules (solvent-solute). For the comparison of the deviation from ideal solution behavior, it is convenient to present measured (real) solubility as a function of ideal solubility (Figure 3). A straight dashed line corresponds to the ideal solution – activity coefficient $\gamma_i = 1$. On the other hand, the area above this relates to the solubility higher than ideal, indicating a tendency toward ordering between the two unlike-molecule components ($\gamma_i < 1$). Conversely, the area below the dashed line indicates a tendency toward phase separation or clustering in the solution, meaning that the attraction forces between like-molecules are superior to those of unlike-molecules ($\gamma_i > 1$). For all the

studied solutes except thymol, the activity coefficients were larger than unity, suggesting the presence of repulsive solute-solvent interactions. On the other hand, there are specific attraction forces between thymol and ethyl lactate, reflected in an activity coefficient lower than unity. Ferulic and vanillic acids showed a close to ideal behaviour at lower temperatures. As the temperature rises, solute-solvent interactions get weaker and are dominated by solute-solute and solvent-solvent cluster formations.

Calculated volume and area parameters of the UNIQUAC model (r_i and q_i) are included in Table 4 along with the temperature-independent binary interaction parameters (a_{ij} and a_{ji}) obtained from fitting the experimental solubility data. The volume and area parameters are proportional to van der Waals volume (V_w) and van der Waals area (A_w) which are presented in Table 5. As can be seen in Fig.2, the UNIQUAC equation demonstrated an excellent description of the experimental data. The absolute average deviations comparing experimental and calculated solubilities were 3.9 % for caffeine, 0.98 % for vanillic acid, 3.6 % for ferulic acid, 0.97 % for caffeic acid and 0.47 % for thymol.

Table 6 shows the group composition of the substances studied in the case of applying the modified (Dortmund) UNIFAC model. The volume parameter (R_k) for the CHCOO group (present in ethyl lactate) was considered to be 1.2700, as is for the rest of groups comprising main group 11 (ester) given by Gmehling et al. [31]. The corresponding surface area parameter (Q_k) was calculated to be 0.9901, according to Bondi [43]. The rest of group R_k and Q_k parameters together with the temperature-dependent interaction parameters (a_{ij} , a_{ji} , b_{ij} , b_{ji} , c_{ij} , c_{ji}) were obtained from the literature [31].

In the case of thymol, the calculated solubilities correspond to model predictions and give an absolute average deviation (AAD) between the experimental and calculated mole fractions of 6.9 %. As mentioned before, the ACOH-COOH group interaction was estimated in this work,

including non-zero b_{ij} and b_{ji} parameters, in order to represent the phenolic acid solubilities. The values obtained are given in Table 7 along with a comparison with those reported in literature [31]. The AAD obtained between the experimental and calculated mole fractions were 11.4 % for vanillic acid, 9.6 % for ferulic acid and 24.7 % for caffeic acid. Caffeine solubility could not be calculated due to the lack of parameter for cycl-CO group [44]. Figure 2 shows a comparison between the solubility calculations attained with the modified UNIFAC model and those obtained with the other models applied in this work.

The CPA pure component parameters for the solutes were calculated from available experimental data [25],[36],[45],[46] according to equations (10)-(12). The van der Waals volume for vanillic acid was calculated using a group contribution approach proposed in literature [34]. All calculated and adopted data are presented in Table 8.

The CPA EoS showed initially absolute average deviations (AAD) up to 72 % when the pure component parameters were calculated according to eqs. (10)-(12). A small temperature-independent binary interaction parameter (k_{ij}) was thus necessary to decrease the AAD. The CPA modeling results thus obtained are presented in Figure 2. The absolute average deviation for caffeine, vanillic acid, ferulic acid and caffeic acid are 6.05 % ($k_{ij} = -0.043$), 13.71 % ($k_{ij} = -0.213$), 14.97 % ($k_{ij} = -0.022$) and 24.21 % ($k_{ij} = -0.018$), respectively. The mixture of ethyl lactate and caffeic acid showed the highest AAD. The correlated k_{ij} 's are negative which means that the interactions between the molecules are stronger than expected by the CPA EoS. The ether group in vanillic acid was not taken into account for associative interactions which leads to the highest k_{ij} value. For the mixture of ethyl lactate and thymol, the CPA EoS gave a very small absolute average deviation (AAD = 3.17%) without adjusting the binary interaction parameter. This result leads to a conclusion that the CPA EoS is a good predictive tool for systems with self- and cross-association whenever binary interaction parameters cannot be obtained. It was also confirmed that the CPA EoS can still give

satisfactory results if the pure component parameters of the solutes are obtained only from their molecular structure, whereas a small k_{ij} is the only parameter to be determined from experimental data.

Conclusions

In this work, the solubility of caffeine, vanillic acid, ferulic acid, caffeic acid and thymol in both dry and water saturated ethyl lactate was measured as a function of temperature, at atmospheric pressure. All solubilities were found to increase with temperature. Thermophysical properties of the studied solutes, namely, enthalpies of fusion and melting temperatures along with differences in heat capacities were obtained by DSC. From the thermophysical and solubility data, activity coefficients were calculated. It was found that for all the studied solutes except thymol, the activity coefficients were larger than unity, suggesting the presence of repulsive solute-solvent interactions. On the other hand, there are specific attraction forces between thymol and ethyl lactate, reflecting in activity coefficients lower than unity.

The obtained solubility data were represented using UNIQUAC and UNIFAC as well as using the Cubic-Plus-Association (CPA) equation of state. The UNIQUAC model provided an excellent description of the solubility data, with the absolute average deviations (AAD) of 3.9 % for caffeine, 0.98 % for vanillic acid, 3.6 % for ferulic acid, 0.97 % for caffeic acid and 0.47 % for thymol,. The UNIFAC-based model showed reasonable predictive capabilities for the studied mixtures. Good agreement between the experimental and calculated mole fractions were obtained for vanillic acid (AAD of 11.4 %), ferulic acid (AAD of 9.6%), and thymol (AAD of 6.9 %) while somewhat inferior agreement was observed for caffeic acid (AAD of 24.7 %).

The CPA EoS represented very well the solid-liquid equilibrium data of the studied solutes, namely caffeine, vanillic acid, ferulic acid, caffeic acid and thymol in ethyl lactate, but only when a small binary interaction parameter was regressed from the experimental solubility data. The CPA modelling results for such complex molecules are surprisingly good, given the higher predictive character of the CPA EoS when compared with the activity coefficient models. It also clearly shows the importance of including associative effects in the model.

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Table 1. Purities of chemicals used in this work

Compound	Supplier	CAS Number	Sample purity, mass fraction
Ethyl lactate	Aldrich	687-47-8	0.98
Caffeine	Sigma-Aldrich	58-08-2	≥ 0.99
Vanillic acid	Fluka	121-34-6	≥ 0.97
Ferulic acid	Aldrich	537-98-4	0.99
Caffeic acid	Sigma	331-39-5	≥ 0.98
Thymol	Sigma	89-83-8	≥ 0.995

Table 2. Average melting points (T_m), enthalpies of fusion (ΔH_{fus}) and differences in heat capacities (ΔC_p) of the studied compounds.*

compound	T_m / K	$\Delta H_{\text{fus}} / \text{kJ}\cdot\text{mol}^{-1}$	$\Delta C_p / \text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$
Caffeine	405.8 ± 0.4^a	2.6 ± 0.2^a	
	505.4 ± 0.0	17.9 ± 0.1	12.0 ± 1.8
Vanillic acid	480.7 ± 0.2	29.1 ± 0.6	64.4 ± 2.5
Ferulic acid	444.9 ± 0.4	31.9 ± 0.9	73.7 ± 9.0
Caffeic acid	464.1^b	39.85^b	162.7^c
Thymol	322.0 ± 0.1	17.4 ± 0.6	66.6 ± 4.7

* Maximal standard uncertainties u are $u(T_m) = 0.28 \text{ K}$, $u(\Delta H_{\text{fus}}) = 0.6$, $u(\Delta C_p) = 6.4$.

^a Solid-solid transition of caffeine

^b Calculated using a group contribution method as described elsewhere[25].

^c Calculated using a group contribution method for the estimation of the heat capacities of liquids [38] and the power-law method to estimate heat capacities of organic solids[39].

Table 3. Experimental solubilities of thymol, caffeine, vanillic acid, caffeic acid and ferulic acid in ethyl lactate containing 1.40 mass % of water and dried ethyl lactate containing less than 0.03 mass %. * x stands for solute mole fraction.

T / K	x	T / K	x
1.40 mass% water in ethyl lactate		< 0.03 mass% water in ethyl lactate	
Caffeine			
298.2	0.0192	296.2	0.0144
313.2	0.0305	303.1	0.0198
328.2	0.0418	312.7	0.0253
343.2	0.0508	323.0	0.0319
		333.3	0.0414
Vanillic acid			
298.2	0.0270	296.2	0.0279
313.2	0.0355	303.1	0.0321
328.2	0.0482	312.7	0.0379
343.2	0.0584	323.0	0.0444
		333.3	0.0545
Ferulic acid			
298.2	0.0803	296.2	0.0277
313.2	0.0939	303.1	0.0349
328.2	0.1061	312.7	0.0428
343.2	0.1177	323.0	0.0526
		333.3	0.0614
Caffeic acid			
298.2	0.0129	296.2	0.0089
313.2	0.0165	303.1	0.0103
328.2	0.0203	312.7	0.0119
343.2	0.0230	323.0	0.0142
		333.3	0.0171
Thymol			
301.4	0.6975	301.0	0.6978
304.3	0.7281	303.5	0.7207
307.5	0.7653	307.5	0.7638
307.8	0.7671	308.4	0.7784
308.3	0.7717	309.3	0.7928
316.5	0.8893	311.0	0.8085
318.6	0.9137	313.3	0.8421
		317.8	0.8985

* Standard uncertainties u are $u(T) = 0.15 \text{ K}$, $u(x)$ for caffeine, vanillic acid, ferulic acid, caffeic acid equals to 0.0005, while for thymol equals to 0.0007.

Table 4. Interaction (a_{ij} , a_{ji}) and structural (r_i , q_i) parameters for the UNIQUAC model.

i	a_{ij} / K	a_{ji} / K	r_i	q_i
Ethyl lactate			4.441	3.928
Caffeine	409.11	-222.00	7.0534	5.6400
Vanillic acid	15.564	51.572	6.6638	5.6000
Ferulic acid	384.41	-207.61	5.8266	5.0040
Caffeic acid	380.93	-147.59	6.2624	5.1600
Thymol	459.35	-306.35	6.4931	4.8640

Table 5. Critical temperatures (T_c), critical pressures (p_c), van der Waals volumes (V_w) and van der Waals surface areas (A_w) used.

compound	T_c / K	p_c / MPa	$V_w \cdot 10^5 / \text{m}^3 \cdot \text{mol}^{-1}$	$A_w \cdot 10^{-6} / \text{m}^2 \cdot \text{mol}^{-1}$
Ethyl lactate [36]	607.0	3.74	6.74	0.98
Caffeine [46]	855.6	4.15	10.11 ³⁶	1.40 ³⁶
Vanillic acid [45]	905.2	3.45	8.84 ^a	1.25 ^a
Ferulic acid [25]	854.6	3.64	10.70	1.41 ^a
Caffeic acid [25]	876.2	5.11	9.50	1.29 ^a
Thymol [36]	698.3	3.41	9.85	1.22

^a Calculated using the group-contribution approach proposed by Bondy [34]

Table 6. Group composition adopted to represent the chemical structure of solutes and ethyl lactate for UNIFAC method.

	ethyl lactate	vanillic acid	ferulic acid	caffeic acid	thymol
CH3	2				2
CH2	1				
CH					1
CH=CH			1	1	
AC		2	2	1	1
ACH		3	3	3	3
ACCH3					1
ACOH		1	1	2	1
OH(s)	1				
CHCOO	1				
OCH3		1	1		
COOH		1	1	1	

Table 7. Modified UNIFAC interaction parameters between the ACOH and COOH groups: comparison between parameters regressed in this work and those reported in the literature.

i	j	a_{ij}	b_{ij}	c_{ij}	Ref.
ACOH	COOH	401.88	0.0	0.0	[31]
		415.72	-1.97	0.0	this work
COOH	ACOH	281.08	0.0	0.0	[31]
		120.50	-2.37	0.0	this work

Table 8. Pure component parameters used in the CPA EoS.

Compound	$a_0 / \text{Pa} \cdot \text{m}^6 \cdot \text{mol}^{-2}$	c_1	$b \cdot 10^4 / \text{m}^3 \cdot \text{mol}^{-1}$	OH		COOH		%AAD	
				$\varepsilon \cdot 10^{-4} / \text{J} \cdot \text{mol}^{-1}$	$\beta \cdot 10^2$	$\varepsilon \cdot 10^{-4} / \text{J} \cdot \text{mol}^{-1}$	$\beta \cdot 10^3$	p	ρ
Ethyl lactate	1.994	1.030	1.030	1.875	4.046			0.513	0.062
Caffeine	4.532	1.824	1.672						
Vanillic acid	6.017	2.136	1.432	1.837	1.185	3.201	0.010		
Ferulic acid	5.118	1.818	1.783	1.871	1.345	2.756	3.698		
Caffeic acid	3.890	1.953	1.557	1.134	6.255	2.756	3.698		
Thymol	3.113	1.140	1.418	2.242	3.796			0.396	0.019

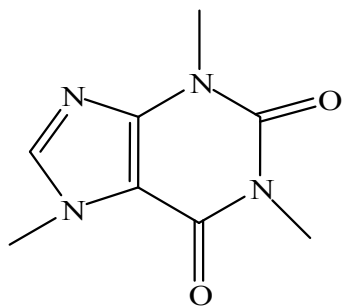
Captions to the Figures

Figure 1. Chemical structure of caffeine (a), vanillic acid (b), ferulic acid (c), caffeic acid (d) and thymol (e).

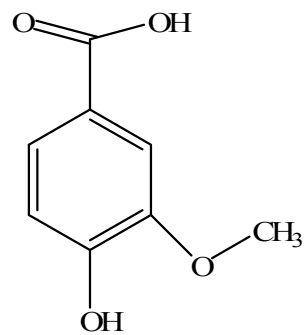
Figure 2. Solubilities of caffeine (a), vanillic acid (b), ferulic acid (c), caffeic acid (d) and thymol (e) in ethyl lactate: experimental results (empty circle stand for solute + ethyl lactate containing 1.40 mass % of water; filled circle stand for solute + dried ethyl lactate system). Lines present estimation by the UNIQUAC (round dot line), CPA (straight line) and UNIFAC (dashed line).

Figure 3. Measured solubility as a function of ideal solubility, where filled squares, filled triangles, empty circles, filled circles and asterisk stand for caffeine, vanillic acid, ferulic acid, caffeic acid and thymol, respectively. Straight dashed line corresponds to the ideal solution (activity coefficient $\gamma = 1$) calculated from equation (2), while areas above and below this line present region of $\gamma < 1$ and $\gamma > 1$, respectively.

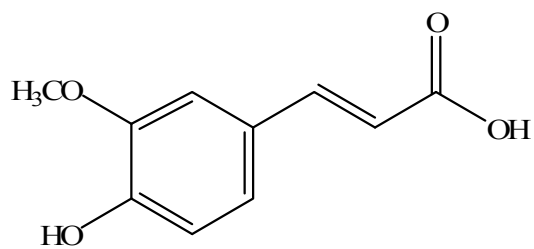
Figure 1



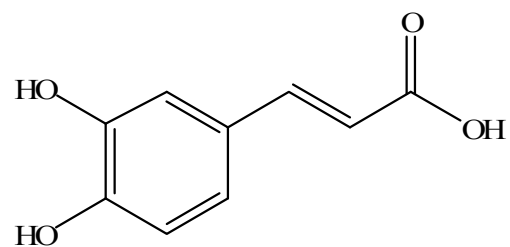
a) Caffeine



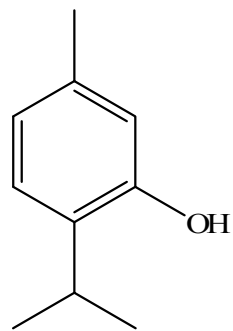
b) Vanillic acid



c) Ferulic acid



d) Caffeic acid



e) Thymol

Figure 2

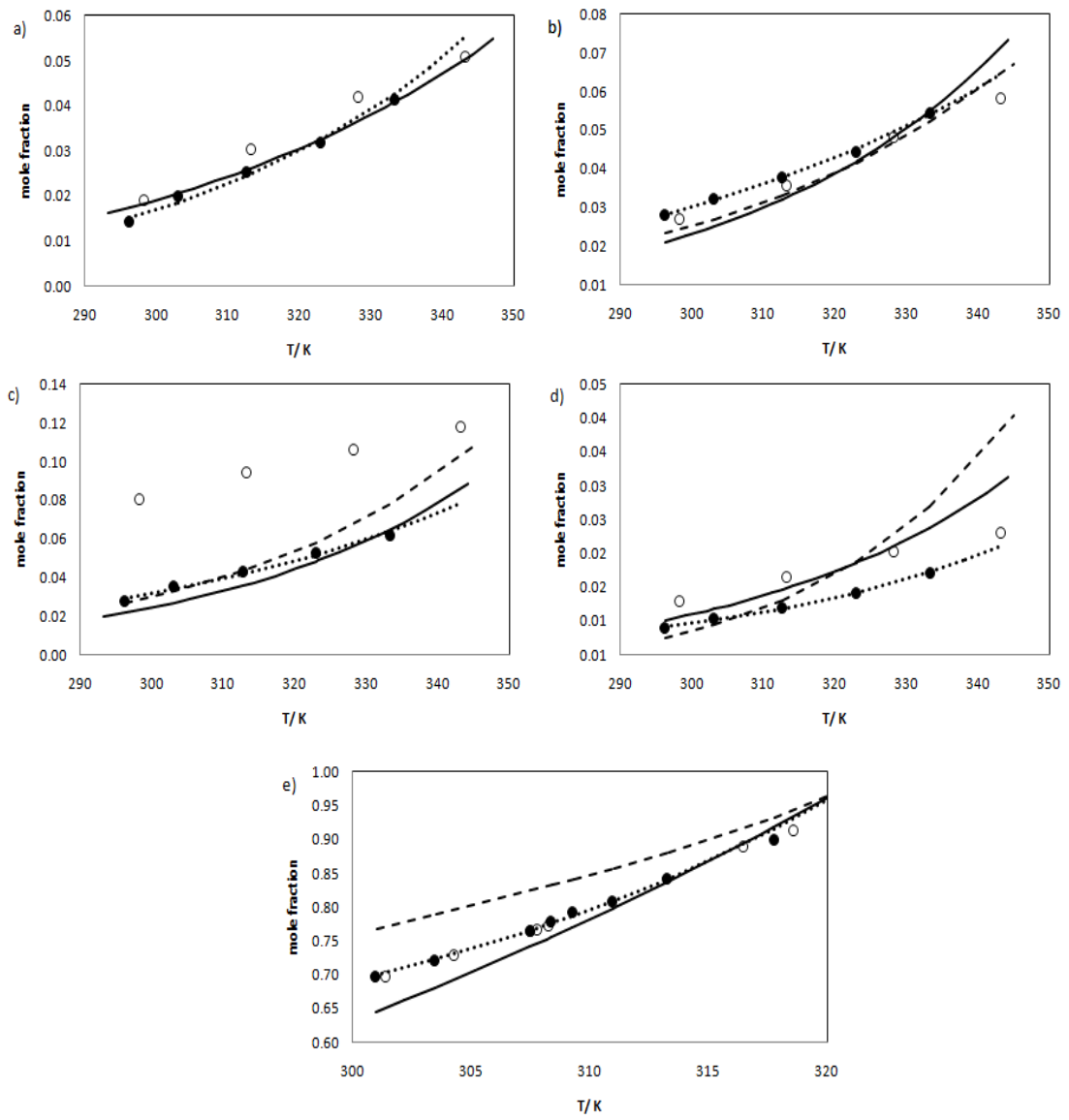
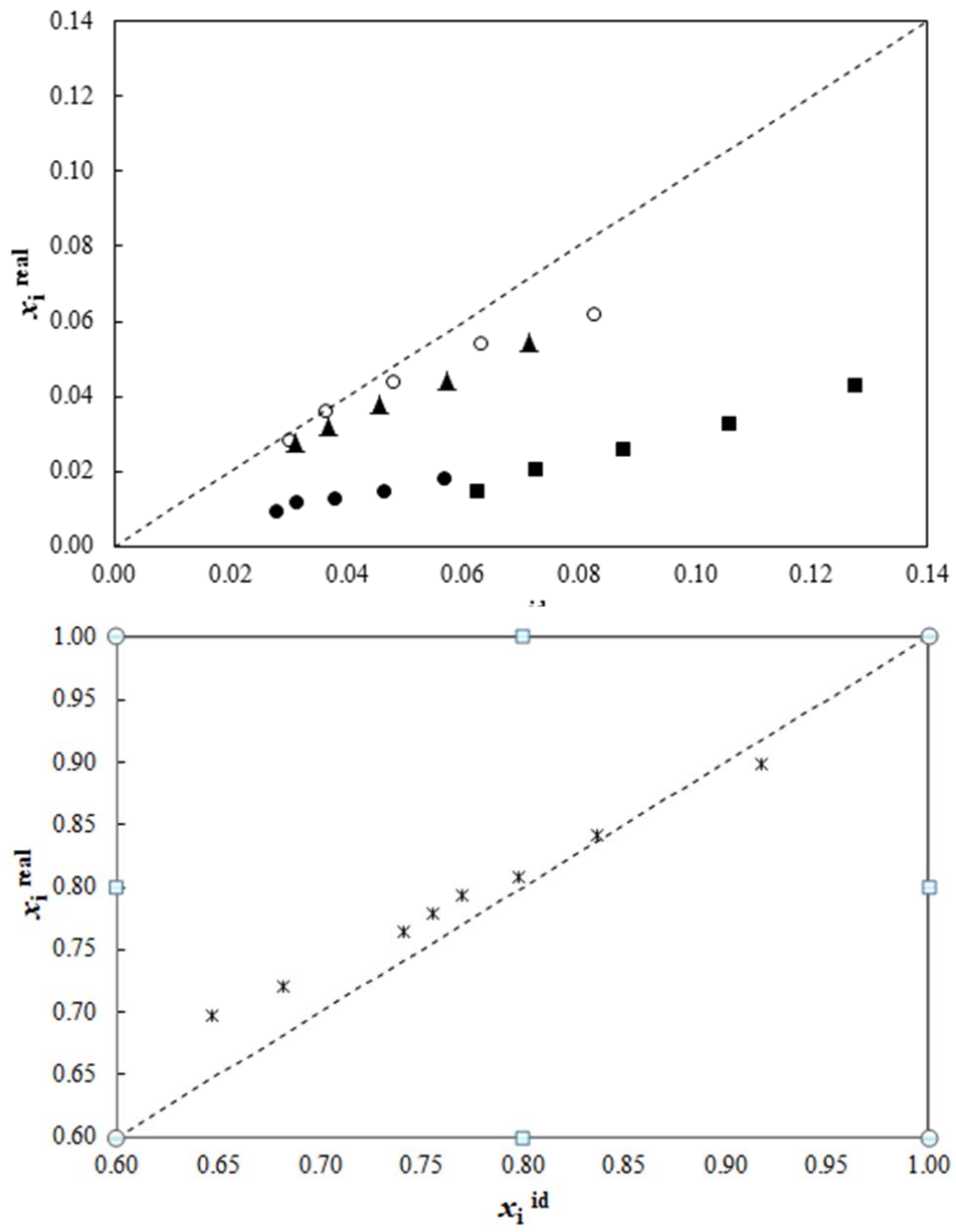


Figure 3



References

- [1] Z. Zhao, M. H. Moghadasian, *Phytochem. Rev.* 9 (2010) 133-145.
- [2] S. Ou, Y. Li, K. Gao, *Acta Nutr. Sin.* 21 (1999) 191-194.
- [3] A. Kaul, K. L. Khanduja, *Nutr. Cancer* 32 (1998) 81-85.
- [4] E. Guerriero, A. Sorice, F. Capone, S. Costantini, P. Palladino, M. D'ischia, G. Castello, *Molecules* 16 (2011) 6365-6377.
- [5] H. Mori, K. Kawabata, N. Yoshimi, T. Tanaka, T. Murakami, T. Okada, H. Murai, *Anticancer Res.* 19 (1999) 3775-3778.
- [6] K. Kawaba, T. Yamamoto, A. Hara, M. Shimizu, Y. Yamada, K. Matsunaga, T. Tanaka, H. Mori, *Cancer Lett.* 157 (2000) 15-21.
- [7] S. Khadem, R. J. Marles, *Molecules* 15 (2010) 7985-8005.
- [8] A. Itoh, K. Isoda, M. Kondoh, M. Kawase, M. Kobayashi, M. Tamesada, K. Yagi, *Biol. Pharm. Bull.* 32 (2009) 1215-1219.
- [9] B. L. Dhananjaya, A. Nataraju, C. D. R. Gowda, B. K. Sharath, C. J. M. D'Souza, *Biochem.-Moscow* 74 (2009) 1315-1319.
- [10] P. S. M. Prince, S. Rajakumar, K. Dhanasekar, *Eur. J. Pharmacol.* 668 (2011) 233-240.
- [11] P. C. Braga, M. Dal Sasso, M. Culici, T. Bianchi, L. Bordoni, L. Marabini, *Pharmacology* 77 (2006) 130-136.
- [12] D. D. Deb, G. Parimala, S. Saravana Devi, T. Chakraborty, *Chem.-Biol. Interact.* 193 (2011) 97-106.
- [13] V. Kumar, G. A. Ravishankar, *Food Rev. Int.* 25 (2009) 175-197.
- [14] M. Herrero, J. A. Mendiola, A. Cifuentes, E. Ibáñez, *J. Chromatogr. A* 1217 (2010) 2495-2511.
- [15] C. S. M. Pereira, V. M. T. M. Silva, A. E. Rodrigues, *Green Chem.* 13 (2011) 2658-2671.
- [16] S. Aparicio, R. Alcalde, *J. Phys. Chem. B* 113 (2009) 14257-14269.
- [17] S. Aparicio, S. Halajian, R. Alcalde, B. Garcia, J. M. Leal, *Chem. Phys. Lett.* 454 (2008) 49-55.
- [18] J. Drapeau, M. Verdier, D. Touraud, U. Krockel, M. Geier, A. Rose, W. Kunz, *Chem. Biodivers.* 6 (2009) 934-947.
- [19] B. K. Ishida, M. H. J. Chapman, *Agric. Food Chem.* 57 (2009) 1051-1059.
- [20] I. F. Strati, V. Oreopoulou, *Int. J. Food Sci. Tech.* 46 (2011) 23-29.
- [21] X. C. Tombokan, R. M. Aguda, D. A. Danehower, P. K. Kilpatrick, R. G. Carbonell, *J. Supercrit. Fluids* 45 (2008) 146-155.
- [22] E. J. Hernández, P. Luna, R. P. Stateva, V. Najdanovic-Visak, G. Reglero, T. Fornari, *J. Chem. Eng. Data* 56 (2011) 2148-2152.
- [23] G. Vicente, A. Paiva, T. Fornari, V. Najdanovic-Visak, *Chem. Eng. J.* 172 (2011) 879-884.
- [24] R. Ferreira, N. Pedrosa, I. M. Marrucho, L. P. N. Rebelo, *J. Chem. Eng. Data* 53 (2008) 588-590.
- [25] F. L. Mota, A. J. Queimada, S. P. Pinho, E. A. Macedo, *Ind. Eng. Chem. Res.* 47 (2008) 5182-5189.

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- [26] F. L. Mota, A. J. Queimada, S. P. Pinho, E. A. Macedo, *Fluid Phase Equil.* 303 (2011) 62-70.
- [27] A. J. Queimada, F. L. Mota, S. P. Pinho, E. A. Macedo, *J. Phys. Chem. B*, 113 (2009) 3469-3476.
- [28] C. A. S. Trindade, Z. P. Visak, R. Bogel-Lukasik, E. Bogel-Lukasik, M. Nunes da Ponte, *Ind. Eng. Chem. Res.* 49 (2010) 4850-4857.
- [29] M. S. Manic, V. Najdanovic-Visak, *J. Chem. Thermodyn.* 44 (2012) 102-106.
- [30] J. M. Prausnitz, R. N. Lichtenthaler, E. G. Azevedo, *Molecular Thermodynamics of Fluid-Phase Equilibria*, Prentice-Hall PTR: Upper Saddle River, NJ, 1999.
- [31] J. Gmehling, J. Li, M. Schiller, *Ind. Eng. Chem. Res.* 32 (1993) 178-193.
- [32] G. M. Kontogeorgis, M. L. Michelsen, G. K. Folas, S. Derawi, N. Von Solms, E. H. Stenby, *Ind. Eng. Chem. Res.* 45 (2006) 4855-4868.
- [33] G. M. Kontogeorgis, M. L. Michelsen, G. K. Folas, S. Derawi, N. Von Solms, E. H. Stenby, *Ind. Eng. Chem. Res.* 45 (2006) 4869-4878.
- [34] A. Bondy, *J. Phys. Chem.* 68 (1964) 441-451.
- [35] G. M. Kontogeorgis, G. K. Folas, *Thermodynamic Models for Industrial Application: From Classical and Advanced Mixing Rules to Association Theories*, John Wiley & Sons, Ltd, 2010.
- [36] R. L. Rowley, W. V. Wilding, J. L. Oscarson, Y. Yang, N. F. Giles, *DIPPR® Data Compilation of Pure Chemical Properties*, Design Institute for Physical Properties, AIChE, New York, 2010.
- [37] J. Marrero, R. Gani, *Fluid Phase Equilib.* 183 (2001) 183-208.
- [38] Z. Kolska, J. Kukal, M. Zabransky, V. Ruzicka, *Ind. Eng. Chem. Res.* 47 (2008) 2075-2085.
- [39] B. T. Goodman, W. V. Wilding, J. L. Oscarson, R. L. Rowley, *J. Chem. Eng. Data* 49 (2004) 24-31.
- [40] J. S. Chickos, C. M. Braton, D. G. Hesse, J. F. Liebman, *J. Org. Chem.* 56 (1991) 927-938.
- [41] X. Dong, Q. Li, Z. C. Tan, Z.-H. Zhang, Y. Liu, *J. Chem. Thermodyn.* 39 (2007) 108-114.
- [42] Y. T. Sohn, J. H. Oh, *Arch. Pharm. Res.* 26 (2003) 1002-1008.
- [43] A. Bondi, *Physical Properties of Molecular Crystalline Solids, Liquids and Glasses*, Wiley, New York, 1968.
- [44] S. Nebig, J. Gmehling, *Fluid Phase Equil.* 302 (2011) 220-225.
- [45] A. Stassi, R. Bettini, A. Gazzaniga, F. Giordano, A. Schiraldi, *J. Chem. Eng. Data* 45 (2000) 161-165.
- [46] G. Xu, A. M. Scurto, M. Castier, J. F. Brennecke, M. A. Stadtherr, *Ind. Eng. Chem. Res.* 39 (2000) 1624-1636.