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Solubility of drug-like molecules in pure organic solvents with the CPA EoS

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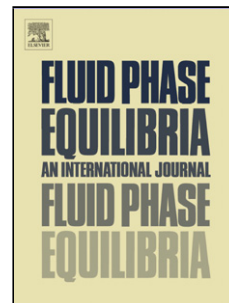
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1 **Solubility of Drug-like Molecules in Pure Organic**

2 **Solvents with the CPA EoS**

3

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1 **Abstract**

2 Solubility data in different solvents are an important issue for separation
3 processes involving complex molecules such as natural products and pharmaceutical
4 drugs. Nonetheless, solubility data are in general scarce and difficult to obtain, and so
5 models are important tools to generate the necessary estimates.

6 Different correlative, statistical and thermodynamic models have been proposed
7 to evaluate solubilities. From these, the more theoretically sound thermodynamic
8 models allow to generate estimates at broader temperature, pressure and composition
9 conditions while using a smaller amount of experimental information. Among these, the
10 Cubic-plus-Association equation of state that combines the simplicity and robustness of
11 a cubic equation of state with the Wertheim's association contribution has been under
12 attention. In this work, this EoS is for the first time proposed to model organic phase
13 solubilities of drug-like molecules in a wide range of temperatures.

14 Solubilities of acetanilide, acetylsalicylic acid, adipic acid, ascorbic acid,
15 hydroquinone, ibuprofen, paracetamol and stearic acid were estimated in alcohols,
16 ketones, alkanes, esters, acids, aromatics, chlorinated solvents, as well as in other
17 common solvents. The hydrogen bonding behaviour was explicitly accounted for with
18 each associating group being treated individually, as well as multiple group
19 substitutions.

20 Accurate correlations were obtained using a single binary interaction parameter
21 (global AAD of 24.2%), while considering the complexity of the studied systems
22 predictions were generally also satisfactory.

23

24 **Keywords: CPA, drug-like, modelling, solubility, organic solvents.**

1 **1. Introduction**

2 The first step in the physicochemical characterization of a pharmaceutical drug
3 candidate involves solubility studies. In general, solubility data in several solvents at
4 various temperatures are important during pre-formulation steps [1].

5 Given the complexity of most drug and drug-like molecules, and the variety of
6 their solvent interactions, many thermodynamic tools have been proposed for modelling
7 such equilibrium data. Reviews on the most commonly used models in the
8 pharmaceutical industry can be found elsewhere [2, 3]. However, the readily application
9 of these theoretical methods is commonly hampered by the lack of information about
10 the molecules under study, and therefore empirical or semiempirical models are usually
11 used, showing good agreement between experimental and correlated data [4-11].

12 One of the most widely used thermodynamic approaches in the pharmaceutical
13 industry is the regular solution theory [12], which is still being used [13]. The solubility
14 is a function of the solvent and solute solubility parameters, and the determination of
15 solubility parameters has been subject of many studies [14-16]. As a drawback,
16 solubilities higher than the ideal solubility cannot be described, as the minimum activity
17 coefficient is one. In spite of some poor results were obtained and temperature
18 dependence cannot be described accurately, this model became very popular for solvent
19 screening due to its higher predictive character.

20 On the other hand, models based on the excess Gibbs energy have been widely
21 used and proved to be able to describe properly the experimental data [6, 7, 13, 17-19].
22 However, the application of these models is limited to the availability of interaction
23 parameters or, when not available, to the existence of data for their fitting. In this sense,
24 the application of predictive group-contribution methods, such as UNIFAC, has been
25 increasing [13, 19, 20], but the description of the solubility temperature-dependence of

1 high molecular weight compounds are still a weakness of this model [21], as well as the
2 necessary group-interaction parameters can sometimes be unavailable. A successful and
3 quite recent model is the Non-random Two Liquid Segment Activity Coefficient
4 (NRTL-SAC) model [22, 23], which has been widely applied to correlate and predict
5 phase equilibria of non-ideal systems, like those containing complex pharmaceuticals
6 [2, 24]. One advantage is that it only requires a set of well-chosen data to fit a small
7 number of parameters. Despite its suitability, this model has a correlative nature since
8 the solute parameters have to be estimated from mixture data. Other models applied for
9 pharmaceuticals are based on statistical mechanics, especially COSMO and its
10 derivatives, where only data from quantum chemical calculations are used [20]. Some
11 attempts were done to use these models for complex pharmaceuticals, but their
12 capabilities for solid-liquid equilibria have not yet been proven [20, 21, 25].

13 The increasing interest on the high pressure processing of pharmaceuticals
14 suggests the use of equations of state for modeling their phase equilibria. Some
15 equations of state have already been applied for that purpose, not so widely to
16 pharmaceutical compounds, but to more simpler drug-like molecules.

17 Ruether and Sadowiski [26] investigated the use of the Perturbed-Chain
18 Statistical Associating Fluid Theory (PC-SAFT) to predict the solubility of five typical
19 drug substances and intermediates in pure and mixed solvents. The model allowed an
20 accurate description of the temperature dependence of the solubility applying a linear
21 temperature-dependent binary interaction parameter per system. The solubility in mixed
22 solvents was reliably predicted without any additional fitted parameter. Tsivintzelis et
23 al. [27, 28] applied the nonrandom hydrogen-bonding (NRHB) EoS to model the phase
24 behaviour of several mixtures of pharmaceuticals. Very satisfactory correlations were
25 obtained using only one optimized binary interaction parameter, even in supercritical

1 CO₂ and ethane. This model was also able to predict accurately the solubility in mixed
2 solvents based on interaction parameters fitted to the corresponding single solvent data.
3 Recently, our group successfully used the CPA EoS for modeling the aqueous solubility
4 of drug-like molecules [29].

5 The aim of this work is to evaluate the CPA EoS for modeling drug-like
6 solubilities in organic solvents in a wide temperature range. The solubilities of
7 acetanilide, acetylsalicylic acid, adipic acid, ascorbic acid, hydroquinone, ibuprofen,
8 paracetamol and stearic acid were studied in solvents covering several alcohols,
9 ketones, alkanes, esters, benzene derivatives and carboxylic acids. The molecular
10 structures of the compounds under study are presented in Figure 1.

11 As observed before for the aqueous solubilities [29], there is a good agreement
12 between the experimental and calculated data using a single temperature independent
13 binary interaction parameter.

14
15

16 **2. Thermodynamic framework**

17

18 The solubility of a solid in a liquid solvent is calculated by solving the
19 thermodynamic equations of equilibrium [12]. Assuming a pure solid phase, no
20 significant temperature dependence on the difference between the heat capacity of the
21 pure liquid and solid (ΔC_p), and neglecting the effect of pressure on melting temperature
22 (T_m), solute enthalpies of solid-solid and melting transition ($\Delta_{tr}H$), and ΔC_p , the
23 following expression for the mole fraction solubility is obtained [12]:

$$x_s = \frac{\varphi_s^{liq_0}}{\varphi_s^{liq}} \exp \left\{ - \sum_{tr} \frac{\Delta_{tr} H}{R} \left(\frac{1}{T} - \frac{1}{T_{tr}} \right) + \frac{\Delta C_p}{R} \left[\frac{T_m}{T} - 1 - \ln \left(\frac{T_m}{T} \right) \right] \right\} \quad (1)$$

2

3 where x_s is the solute mole fraction solubility, R is the ideal gas constant, T is the
4 absolute temperature, φ is the fugacity coefficient and subscripts 0 refers to a pure
5 component, tr for a pure solute phase transition and m for melting. The different solid-
6 solid and fusion phase transitions of the solute are concerned in the summation.

7 The CPA-EoS [30] combines a cubic contribution accounting for physical
8 interactions, and a chemical term from the Wertheim theory, taking into account the
9 association due to hydrogen bonding between like molecules (self-association) and
10 unlike molecules (cross-association or solvation). The activity of each bonding site is
11 assumed independent of the other bonding sites on the same molecule being steric
12 hindrance and cooperativity effects neglected. This model has already been successfully
13 employed for mixtures of water with other associating compounds [29, 31-32]. The
14 cubic and association contributions to the Helmholtz energy (A) are the following [31,
15 33, 34]:

$$A^{cubic} = \frac{an}{b(\delta_2 - \delta_1)} \ln \left(\frac{1 + b\rho\delta_1}{1 + b\rho\delta_2} \right) - nRT \ln(1 - b\rho) \quad (2)$$

$$A^{assoc} = RT \sum_i n_i \sum_{A_i} \left[\ln(X_{A_i}) - \frac{X_{A_i}}{2} + \frac{1}{2} \right] \quad (3)$$

18

19 where i is a component index, b is the co-volume parameter, a is the energy parameter,
20 ρ is the molar density, n is the number of moles, and X_{A_i} is the mole fraction of
21 component i not bonded at site A . As the Soave-Redlich-Kwong cubic term is used in

1 this work, δ_1 is set equal to 1 and δ_2 to 0. The pure-component energy parameter a is
 2 given by a Soave-type temperature dependency, while b is constant:

$$3 \quad a(T) = a_0 \left[1 + c_1 \left(1 - \sqrt{T_r} \right) \right]^2 \quad (4)$$

4 where a_0 and c_1 are pure component parameters and T_r is the reduced temperature. For
 5 mixtures, classical van der Waals one-fluid mixing rules are employed, where a binary
 6 interaction parameter k_{ij} is introduced on the cross-energy parameter. X_{A_i} is the key
 7 element of the association term and is related to the association strength, Δ^{A,B_j} , between
 8 two sites belonging to two different molecules, site A on molecule i and site B on
 9 molecule j by:

$$11 \quad X_{A_i} = \frac{1}{1 + \rho \sum_j x_j \sum_{B_j} X_{B_j} \Delta^{A,B_j}} \quad (5)$$

12 For cross-associating systems, the computationally simpler Elliot rule is adopted
 13 for the cross-association strength [35].

14 Experimental solubility data are used for the regression of the k_{ij} parameters with
 15 the objective function (OF):

$$16 \quad OF = \sum_i^{NP} \left(\frac{x_i^{\text{exp}} - x_i^{\text{calc}}}{x_i^{\text{exp}}} \right)^2 \quad (6)$$

17 where NP is the number of available solubility points, and the superscripts exp and $calc$
 18 refer to experimental and calculated values, respectively.

19 The absolute average deviations (AAD) were used to compare experimental and
 20 calculated results:

$$AAD (\%) = \frac{1}{NP} \sum_i \frac{|x_i^{\text{exp}} - x_i^{\text{calc}}|}{x_i^{\text{exp}}} \times 100 \quad (7)$$

1

2

3

4 **3. Results and Discussion**

5

6 In a previous work, the nature and number of associating groups in each of the
7 studied solutes were established [29], following the associating schemes proposed by
8 Huang and Radosz [36]. The one-site (1A) scheme was used for carboxylic acid groups;
9 the two-site (2B) for alcohols and the three-site (3B) and two-site (2B) schemes for
10 primary and secondary amines, respectively [34]. Solvents like chloroform, alkanes,
11 1,4-dioxane, ketones, toluene, acetonitrile and esters are considered to be non-self-
12 associating.

13 The pure component parameters were obtained regressing experimental vapor
14 pressure and liquid density data compiled from the DIPPR database [37], where the
15 critical properties and van der Waals volume, as well as property correlations as a
16 function of temperature, were also collected. These properties and parameters were
17 presented by Mota et al. [29]. Regression of all the CPA parameters was performed in
18 the reduced temperature range from 0.45 up to 0.85 where, in general, the DIPPR
19 correlations are in agreement with the experimental data. Only for hydroquinone and
20 paracetamol liquid density data are not available, and like that just the correlations are
21 used. The AAD's found for vapor pressure and liquid density were 2.5 and 1.8%,
22 respectively, which are good results given the complexity of the studied molecules.
23 Parameters for the various solvents are well established and were collected from the

1 literature [33,38] or whenever unavailable were estimated for this work. The used
2 parameters and respective associating schemes are presented in Table 1. The thermal
3 properties, melting temperature (T_m), enthalpy of fusion ($\Delta_{fus}H$) and heat capacity
4 difference (ΔC_p) are also presented in Table 1 for all the drug molecules [29].

5 Following a previous work where the aqueous solubilities of the same drug-like
6 molecules were studied [29], in this work the same set of CPA parameters for
7 describing the solubility in organic solvents are evaluated. Results of the model
8 predictions (without fitting any parameter) and correlations (with a temperature
9 independent binary interaction parameter k_{ij}) are given in Tables 2 to 5.

10 All the investigated solutes are associating molecules, while some solvents such
11 as ketones, esters, cyclic ethers and toluene, although not explicitly forming solute-
12 solvent hydrogen bonds, can present increased solubilities due to stronger solvating
13 interactions. To account for this issue, Folas et al. [38] proposed to use a cross-
14 association energy half of that of the associating component and left the cross-
15 association volume as an adjustable parameter, to be fitted from equilibrium data. This
16 was initially done in this work but it was found that in most of the cases, this fitting was
17 not necessary, as the fit of a single and small k_{ij} already provided excellent results.
18 Whenever higher k_{ij} values were found for a particular solute it was also observed that
19 this also occurred for associating solvents. So to keep a higher predictive character of
20 the model, only the k_{ij} values were fitted from binary data.

21 The results for acetanilide are presented in Table 2. Except for the alkane
22 solvents (n-hexane and cyclohexane), where CPA overpredicts the experimental data,
23 the model is able to represent the data with small k_{ij} 's. In the alkane solvents the
24 solubilities are, unexpectedly, very low, considering that the solvent with the maximum
25 solubilities is octanol. For this same solvent the model is able to correctly estimate the

1 solubilities. In Figure 2, the solubility of acetanilide in the studied alcohols is presented
2 and it can be seen that as long as the molecular weight of the alcohol increases, the
3 solubility increases, but the model reverses the order between methanol and ethanol.
4 The results obtained by Tsivintzelis et al. [27] with the NRHB EoS in chloroform are
5 better (AAD of 1.5%). Only one parameter was used in both works, but these authors
6 investigated a narrower temperature range. However, if the regression of k_{ij} is made in
7 the same temperature range as Tsivintzelis et al. [27], a higher value is found and the
8 results have almost the same accuracy. In octanol, the results found in this work are
9 better than those found by Tsivintzelis et al. [27] with the NRHB EoS.

10 Acetylsalicylic acid has the associating group $-\text{COOH}$ and the ester group ($-\text{COO}$),
11 which are able to cross associate with alcohol molecules. Thus, the associating
12 behaviour in the corresponding solutions is rather complicated. The correlation results
13 showed that all the interaction parameters are small and negative (Table 3), proving that
14 the interactions are stronger than expected by the model. Nevertheless the model is still
15 able to adequately correlate the data. For this solute, the solubility values are similar,
16 except in acetone where they are slightly higher. Indeed, acetone is the solvent where
17 the model gives the best estimates, both for prediction and correlation. The results in
18 alcohols are in the same accuracy range of those obtained before for aqueous solubilities
19 (AAD of 15.5%) [29], but the k_{ij} values were significantly more pronounced for the
20 water binaries.

21 Excluding the adipic acid/toluene system where the solubilities are very low, the
22 correlation results found with CPA are very good, with small interaction parameters
23 (Table 3). The results are in the same order of accuracy of those found before by Mao et
24 al. [7] with the UNIFAC method, and not much worse than those found with the λh and
25 Apelbat correlative equations. Comparing with the results obtained for aqueous

1 solubilities in a previous work [29], only for the toluene system poorer results were
2 obtained. As presented in Figure 3, very good correlative results were found for the
3 systems acetylsalicylic acid/acetone and adipic acid/acetone at the expense of a small
4 binary interaction parameter.

5 Ascorbic acid is a complex chiral molecule containing as much oxygens as
6 carbons in its molecular structure. It has four hydroxyl groups located in different
7 environments that for modelling purposes were divided into two classes: ring and
8 aliphatic, having different associating parameters [29]. The solubilities are low in all the
9 solvents studied and probably the high melting point is a reason for that. In Table 3 it
10 can be seen that the model results are rather satisfactory. If a comparison is made with
11 the previous solutes, the interaction parameters are more pronounced, except in the case
12 of acetonitrile where the model is satisfactory even in pure prediction. A great
13 improvement is achieved after estimating a single temperature independent binary
14 interaction parameter: in average, from 87.1 to 18.1%. In Figure 4 a comparison of the
15 correlated solubilities in several solvents is presented. Among the solvents studied in
16 this work and the previous results in water [29], it can be concluded that the results here
17 are much better than for the water solubilities.

18 Hydroquinone is the solute showing more pronounced corrections (Table 4),
19 except in acetic acid where the predictions are excellent. The solubility values in this
20 solvent are the lowest, in the order of 10^{-2} (mole fraction) and, like that, do not
21 contradict some indications from the other solutes that showed larger deviations in
22 solvents where the solubilities were very low. Excluding esters, where the correlated
23 solubilities are overestimated, the values in the other solvents are underestimated. In
24 Figure 5, the results for the solubility in ethyl acetate are presented. Once again, the

1 studied solvents in this work presented better results than the aqueous solubilities [29],
2 but in this case the k_{ij} were in the same order of magnitude.

3 Among the studied compounds, ibuprofen has in general the higher solubilities
4 and also the lowest melting point. Figure 6 shows a comparison for the solubility of
5 ibuprofen in ethanol and ethyl acetate. The results for ibuprofen are presented in Table 5
6 where it can be seen that the higher interaction parameters were found for the simplest
7 alcohol solvents. In the systems ibuprofen/acetone, 4-methyl-2-pentanone or propylene
8 glycol, the interaction parameters and the results found in this work are very close to
9 those by Tsivintzelis et al. [28] with the NRHB EoS. For the other systems, the results
10 reported by these authors are slightly better. Among the solvents studied, only in 2-
11 propanol and cyclohexane the AAD's were higher than those obtained for aqueous
12 solubilities, but in this last case the k_{ij} (absolute value) was higher [29].

13 Good correlation results were also obtained for paracetamol in 16 solvents with
14 an average deviation of 28% (Table 2) and a maximum deviation of 65% in
15 cyclohexane where the solubilities are especially low. However, even in this solvent, the
16 improvement was significant between prediction and correlation, using a small
17 interaction parameter. It must be noted that the presence of the $-ACOH$ group renders
18 the hydrogen-bonding behaviour of paracetamol much more complicated compared to
19 that of acetanilide, but the results are similar, what shows the importance of explicitly
20 considering association. A comparison between several prediction and correlation
21 results is presented in Figure 7, showing the importance of fitting a k_{ij} parameter. In 2-
22 propanol, the results are almost similar to those obtained by Hojjati and Rohani [13]
23 with the UNIQUAC model, what is very good since this model has two adjustable
24 parameters from experimental binary data. The interaction parameters found in this
25 work for alcohols are all negative, except for propylene glycol, where those found

1 previously with the NRHB EoS [27] are mostly positive. So, in prediction, CPA
2 considers the solute-alcohol interactions to be weaker, while the NRHB EoS considers
3 them to be stronger. Generally, the results found by these authors are slightly better.

4 The predictions of the mole fraction solubilities of stearic acid are surprisingly
5 good (average AAD of 61.4%) and, after regressing small binary interaction parameters,
6 the deviations are further reduced being specially good for the alkanes, as can be seen in
7 Table 3. The solubility results for n-heptane are presented in Figure 8.

8 Ethanol systems were studied for all the solutes and, in all of them, CPA
9 estimates were good. The maximum AAD found was 39% in paracetamol and the
10 average AAD was 22%. Except for paracetamol in propylene glycol, all the binary
11 interaction parameters for these solutes in alcohols are negative, showing that the
12 interactions are stronger than that estimated by the model.

13 In acetone, the results are also good with an average AAD of 21%, as well as in
14 the esters where the deviations did not exceed 41%. However, for the esters it must be
15 focused that the group $-\text{COO}$ is considered non-self-associating, and its effects to
16 increase the solvation are not explicitly taken into account by the model.

17 Many pharmaceutical solids and molecular crystals show polymorphism, which
18 is the ability to exhibit more than one crystalline form, displaying different
19 thermodynamic properties [39]. In fact, each polymorph should be regarded as a
20 different solid material and the control of polymorphism provides a way to tune the
21 properties of a product. As referred in the previous work [29], some of the compounds
22 studied in this assay were reported to show polymorphic forms.

23 Solubility data of stearic acid polymorphs were available in n-hexane and
24 methanol [18]. In the n-hexane system, good predictions were obtained in the case of
25 form *B* (AAD 13.0%), while for form *C* the use of the corresponding k_{ij} value (Table 3)

1 was required, leading to an AAD of 49.2%. In the case of methanol, better estimates
2 were obtained for the solubility of form *C* (AAD of 19.9% with $k_{ij} = -0.037$) than for
3 form *B* (AAD of 46.8% with $k_{ij} = -0.031$). No polymorph solubility data for the other
4 solutes were found, and so, only the effect of the melting properties could be evaluated.
5 For paracetamol, the results considering the melting data of form *I* [40] were better
6 (AAD of 26.0%). For example in methanol, the AAD is 0.64% with the melting data of
7 form *I*, while with the DIPPR properties or form *II*, the AAD's are 14.9 and 33.5%,
8 respectively. Ibuprofen is one of the most widely known chiral compounds, and also no
9 solubility data were found for the racemate and enantiomers [41]. But, analyzing in
10 terms of different thermal data, different values of binary interaction parameters were
11 obtained for the (+)-enantiomer and the racemic mixture, leading to different correlation
12 results. The use of the racemic properties gave in general better results.

13

14 **4. Conclusions**

15

16 Given the previous success of the CPA EoS to model complex molecules in
17 aqueous systems, its performance for organic systems of complex molecules was
18 investigated in this work. The CPA EoS was applied to model the solubility of several
19 drug-like molecules, namely acetanilide, acetylsalicylic acid, adipic acid, ascorbic acid,
20 hydroquinone, ibuprofen, paracetamol and stearic acid in liquid solvents: such as
21 alcohols, alkanes, acetone, acids and esters. The complex associating behavior was
22 explicitly accounted for in the association energy and volume parameters, where the
23 corresponding parameters were estimated from vapor pressure and liquid density data.
24 Each associating group is treated individually as well as multiple group substitutions
25 were considered in the association term.

1 In the solvents studied, a rather good representation of the solubility data is
2 obtained: AAD's of 66.7 and 24.2%, respectively for model predictions and correlations
3 (using only one temperature independent binary interaction parameter per system). In
4 general the results obtained are better than those for the aqueous systems of the same
5 complex molecules. Very good results were obtained in some acetone systems where
6 the solubilities were the highest, as well as in some alcohols. In general, the binary
7 interaction parameters were small and, in the majority of the cases, negative, showing
8 that the real interactions are stronger than those estimated by the model. Often the
9 predictions are poor for very insoluble materials, but after correlating relatively small
10 and temperature independent binary interaction parameters good estimates were
11 obtained. Using thermal properties of different polymorphic forms, solubility results
12 showed quite the same quality. Even the solubility of ibuprofen, considering its
13 enantiomer or racemic properties was successfully correlated.

14 In general, the CPA EoS showed to be able to represent the solid-liquid
15 equilibrium data of drug-like molecules, proving the importance of taking into account
16 association effects. The results obtained so far in pure solvents suggest further work
17 concerning mixed solvent systems, as well as supercritical solvents.

18
19

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2

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8

9

10 **Nomenclature**

11 a = energy parameter

12 a_0 = parameter in the CPA EoS cubic term ($\text{Pa}\cdot\text{m}^6/\text{mol}^2$)

13 A = Helmholtz energy (J)

14 b = co-volume parameter (m^3/mol)

15 c_l = parameter in the CPA EoS cubic term

16 k_{ij} = binary interaction parameter

17 n = number of moles

18 NP = number of data points

19 R = gas constant (8.314 J/(mol.K))

20 T = absolute temperature (K)

21 x = mole fraction

1 X_{A_i} = mole fraction of component i not-bonded at site A

2

3 *Greek Symbols*

4 δ = specific parameters in each cubic equation

5 β = association volume

6 β_{ij} = solvation parameter

7 Δ^{A,B_j} = association strength between site A on molecule i and site B on molecule j

8 ΔC_p = difference between the heat capacity of the solute pure liquid and solid (J/mol.K)

9 $\Delta_{fus}H$ = fusion enthalpy (J/mol)

10 ε = association energy (J/mol)

11 ρ = molar density (mol/m³)

12 φ = fugacity coefficient

13

14 *Subscripts*

15 0 = pure component

16 c = critical

17 i, j, k = component index

18 m = melting

19 r = reduced

20 s = solute

1 *tr* = transition

2

3 *Superscripts*

4 *assoc* = association term

5 *calc* = calculated

6 *cubic* = cubic term

7 *exp* = experimental

8

9 *List of Abbreviations*

10 *AAD* = absolute average deviation (%)

11 *CPA* = cubic-plus-association

12 *EoS* = equation of state

13 *NRHB* = Non-Random Hydrogen Bonding

14 *OF* = objective function

15

1 **References**

2

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- 15

1 **Table 1. Pure component properties and CPA parameters.**

Compound	T_m (K)	$\Delta_{fus}H$ (kJ/mol)	ΔC_p (J/mol.K)	a_0 (Pa m ⁶ /mol ²)	c_1	$b \times 10^5$ (m ³ /mol)	Group	ϵ (kJ/mol)	β
Acetanilide [29]	388	21.65	1.92	4.37	1.17	12.25	NH	3.74	1.00 x10 ⁻¹
Acetylsalicylic acid [29]	408	25.60	26.55	4.62	1.48	13.56	COOH	11.4	1.68 x10 ⁻⁴
Adipic acid [29]	426	34.85	108.07	4.80	1.49	12.48	COOH	18.5	3.45 x10 ⁻⁴
Ascorbic acid [29]	465	29.20	81.40	3.79	2.96	11.94	OH ring	14.9	9.08 x10 ⁻³
							OH aliphatic	14.7	4.10 x10 ⁻⁵
Hydroquinone [29]	445	27.11	55.19	2.20	1.27	10.37	OH	19.2	2.38 x10 ⁻²
Ibuprofen [29]	349	25.61	149.74	7.33	1.37	20.47	COOH	1.10	9.61 x10 ⁻⁴
Paracetamol [29]	441	27.70	32.14	3.45	1.76	15.96	NH	6.45	5.48 x10 ⁻²
Stearic acid [29]	343	61.21	116.84	12.2	1.58	33.47	OH	17.9	2.06 x10 ⁻²
methanol [33]				0.405	0.431	3.09	OH	2.46	1.61 x10 ⁻²
ethanol [33]				0.867	0.737	4.91	OH	2.15	8.00 x10 ⁻³
1-propanol [33]				1.19	0.917	6.41	OH	2.10	8.1 x10 ⁻³
2-propanol [33]				1.06	0.947	6.41	OH	2.10	9.1 x10 ⁻³
1-butanol [33]				1.57	0.978	7.97	OH	2.10	8.2 x10 ⁻³
1-octanol [33]				4.16	1.15	14.9	OH	2.68	1.40 x10 ⁻⁴
propylene glycol [33]				1.38	0.937	6.75	OH	1.74	1.90 x10 ⁻²
acetic acid [33]				0.912	0.464	4.69	COOH	4.03	4.5 x10 ⁻³
n-hexane [38]				2.37	0.831	10.8			
n-heptane [38]				2.92	0.914	12.5			
cyclohexane*				2.11	0.771	9.09			
acetone*				1.39	0.788	6.14			
4-methyl-2-pentanone*				2.41	0.856	8.72			
ethyl acetate*				1.87	0.957	8.31			
butyl acetate*				2.92	1.03	11.7			
isopropyl myristate*				10.5	1.57	32.1			
1,4-dioxane*				1.85	0.825	7.39			
chloroform*				1.50	0.782	6.64			
toluene*				2.34	0.804	9.24			
acetonitrile*				1.28	0.605	4.68			
tetrahydrofuran*				1.56	0.771	6.80			
trichloroethylene*				1.85	0.771	7.60			

2 *Obtained in this work.

3

1 **Table 2. CPA Modelling Results for Acetanilide and Paracetamol, and Respective**
 2 **Binary Interaction Parameter.**

3

Compound	Solvent	Temperature (K)	Prediction	Correlation	
			AAD (%)	k_{ij}	AAD (%)
acetanilide	methanol [42]	273.15 – 333.15	73.1	-0.0728	53.0
	ethanol [42]	273.15 – 333.15	90.0	-0.0145	26.5
	1-octanol [43]	293.15 – 315.15	72.1	-0.0472	2.01
	1,4-dioxane [44]	273.15 – 313.15	35.3	-0.00124	32.7
	isopropyl myristate [45]	283.15 – 333.15	44.4	-0.0100	41.0
	chloroform [42]	293.15 – 333.15	29.6	-0.00244	26.1
	n-hexane [43]	293.15 – 315.15	49026	0.235	44.9
	cyclohexane [43]	298.15 – 313.15	10429	0.180	42.1
			57.4 ^a		24.2
paracetamol	methanol [46]	268.15 – 298.15	75.3	-0.0647	14.9
	ethanol [46, 47]	268.15 – 313.15	60.9	-0.0490	39.2
	1-propanol [46]	268.15 – 298.15	35.8	-0.0193	11.2
	2-propanol [46, 48]	268.15 – 313.15	65.3	-0.0332	14.9
	1-butanol [46]	268.15 – 298.15	55.6	-0.0207	11.7
	1-octanol [43, 45]	293.15 – 313.15	37.8		
	propylene glycol [47, 49]	293.15 – 313.15	56.8	0.00830	30.4
	toluene [46, 50]	273.15 – 303.15	34.9		
	acetone [46, 50]	268.15 – 303.15	99.7	-0.181	29.1
	1,4-dioxane [44]	293.15 – 313.15	98.6	-0.0700	51.4
	ethyl acetate [46]	268.15 – 298.15	95.7	-0.0722	34.0
	isopropyl myristate [45]	298.15 – 313.15	59.0	-0.0428	22.9
	acetonitrile [46]	268.15 – 298.15	99.6	-0.0955	39.0
	chloroform [45]	298.15 – 313.15	42.7	0.0112	5.87
n-hexane [43]	298.15 – 315.15	6799	0.174	15.1	
cyclohexane [45]	298.15 – 313.15	1297	0.0748	64.8	
			65.5 ^a		27.5

4 ^aWithout outliers: AAD > 150%.

5

1 **Table 3. CPA Modelling Results for the Acids, and Respective Binary Interaction**2 **Parameter.**

Compound	Solvent	Temperature (K)	Prediction	Correlation	
			AAD (%)	k_{ij}	AAD (%)
acetylsalicylic acid	methanol [51]	293.15 – 333.15	91.8	-0.0903	23.0
	ethanol [4]	276.30 – 336.60	87.2	-0.0683	21.8
	2-propanol [4]	291.80 – 330.20	70.1	-0.0319	24.5
	propylene glycol [4]	295.70 – 333.90	50.9	-0.0197	31.4
	acetone [4]	281.90 – 326.30	45.3	-0.0246	8.00
			69.0		21.7
adipic acid	ethanol [7, 52]	299.95 – 340.95	84.1	-0.0588	12.2
	n-butanol [7]	298.85 – 358.15	87.3	-0.0684	9.92
	chloroform [7,8]	298.15 – 331.55	65.2	0.0137	18.9
	acetic acid [6]	297.93 – 347.65	64.5	-0.0361	19.3
	toluene [8]	298.15 – 333.15	1575	0.0652	85.6
	acetone [7,8]	288.05 – 325.85	79.6	-0.0417	6.40
			76.2 ^a		25.4
ascorbic acid	methanol [53]	293.15 – 323.15	99.9	-0.167	19.3
	ethanol [53]	293.15 – 323.15	98.9	-0.106	6.50
	2-propanol [53]	293.15 – 323.15	71.8	-0.0225	17.3
	ethyl acetate [53]	293.15 – 323.15	98.9	-0.110	19.9
	tetrahydrofuran [53]	293.15 – 323.15	99.1	-0.113	11.9
	acetone [53]	293.15 – 323.15	96.5	-0.0781	21.4
	acetonitrile [53]	293.15 – 318.15	44.4	0.0126	30.1
			87.1		18.1
stearic acid	ethanol [19]	391.45 – 323.65	79.0	-0.0166	29.1
	2-propanol [19]	292.35 – 321.95	97.5	-0.0411	41.8
	acetone [19]	291.95 – 322.55	50.1		
	trichloroethylene [19]	292.75 – 323.25	67.2	-0.0183	21.1
	n-hexane [19]	293.75 – 323.55	27.8	0.00247	10.9
	n-heptane [19]	293.45 – 324.85	46.6	0.00723	9.74
			61.4		22.5

3 ^aWithout outliers: AAD > 150%.

4

1 **Table 4. CPA Modelling Results for Hydroquinone, and Respective Binary**
 2 **Interaction Parameter.**

3

Compound	Solvent	Temperature (K)	Prediction	Correlation	
			AAD (%)	k_{ij}	AAD (%)
hydroquinone	methanol [9]	281.65 – 343.40	86.5	-0.164	6.27
	ethanol [9]	276.65 – 342.15	87.2	-0.145	22.6
	2-propanol [9]	279.45 – 342.55	85.5	-0.131	8.63
	acetic acid [9]	289.45 – 341.25	8.32		
	ethyl acetate [9]	278.70 – 345.10	98.3	-0.196	23.0
	butyl acetate [9]	279.55 – 344.70	98.9	-0.231	22.2
			77.5		16.5

4

5

1 **Table 5. CPA Modelling Results for Ibuprofen, and Respective Binary Interaction**2 **Parameter.**

3

Compound	Solvent	Temperature (K)	Prediction	Correlation	
			AAD (%)	k_{ij}	AAD (%)
ibuprofen	methanol [25]	283.15 – 308.15	97.8	-0.189	18.1
	ethanol [25,54,55]	283.15 – 313.15	91.2	-0.121	15.2
	2-propanol [25]	283.15 – 308.15	91.9	-0.0932	25.5
	1-octanol [25]	298.15 – 313.15	66.6	-0.0585	18.4
	propylene glycol [55]	293.15 – 313.15	64.7	-0.0236	17.5
	toluene [25]	283.15 – 308.15	31.7	0.0151	14.8
	acetone [25]	283.15 – 308.15	14.0	0.00229	12.7
	4-methyl-2-pentanone [25]	283.15 – 308.15	17.8	0.00821	10.6
	chloroform [25, 56]	283.15 – 313.15	28.7		
	ethyl acetate [25]	283.15 – 308.15	21.6	0.0116	14.3
	isopropyl myristate [25]	298.15 – 313.15	26.1	-0.00616	10.9
	cyclohexane [25]	298.15 – 313.15	87.7	0.0199	37.6
			53.3		17.8

4

1 **Figure Captions:**

2

3 **Figure 1.** Molecular structure of: (a) acetanilide, (b) acetylsalicylic acid, (c) adipic acid,
4 (d) ascorbic acid, (e) hydroquinone, (f) ibuprofen (g) stearic acid and (h) paracetamol.

5

6 **Figure 2.** Solubility of acetanilide in methanol [42] (\diamond), ethanol [42] (\bullet) and 1-octanol
7 [43] (\blacksquare), and CPA correlations (—, methanol and 1-octanol; ---, ethanol).

8

9 **Figure 3.** Solubility of acetylsalicylic acid [4] (\bullet) and adipic acid [7] (\blacksquare) in acetone,
10 and CPA correlation results.

11

12 **Figure 4.** Summarized results for ascorbic acid solubility in several solvents:
13 experimental data [53] versus CPA correlations: ethanol (\bullet), methanol (o), 2-propanol
14 (\blacklozenge), acetone (\diamond), acetonitrile (\blacksquare), ethyl acetate (\square), and tetrahydrofuran (\blacktriangle).

15

16 **Figure 5.** Solubilities of hydroquinone as a function of temperature in ethyl acetate [9],
17 and CPA modelling results: correlation (—) and prediction (---).

18

19 **Figure 6.** Solubilities of ibuprofen as a function of temperature in (a) ethanol [25] and
20 (b) ethyl acetate [25], and CPA modelling results: correlation (—) and prediction (---).

21

22 **Figure 7.** Summarized results for paracetamol in several solvents: experimental data
23 versus CPA (a) predictions and (b) correlations: ethanol [46, 49] (\bullet), methanol [46] (o),
24 2-propanol [46, 48] (\blacklozenge), acetone [46, 50] (\diamond), acetonitrile [46] (\blacksquare), ethyl acetate [46] (\square),
25 propylene glycol [47, 49] (Δ), 1-propanol [46] (\oplus), and 1-butanol [46] (x).

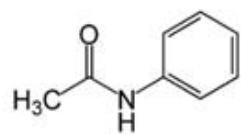
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27 **Figure 8.** Solubilities of stearic acid as a function of temperature in n-heptane [19] and
28 CPA results: correlation (—) and prediction (---).

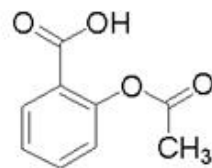
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1 **Figure 1:**

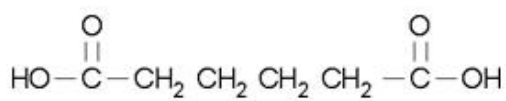
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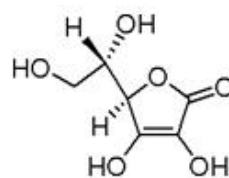
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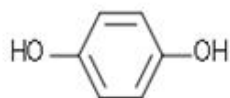
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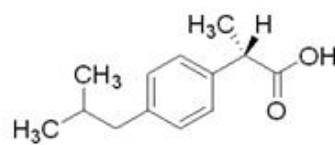
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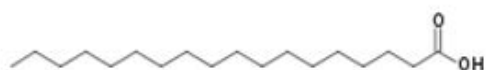
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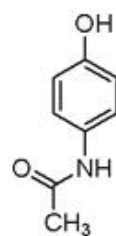
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(f)



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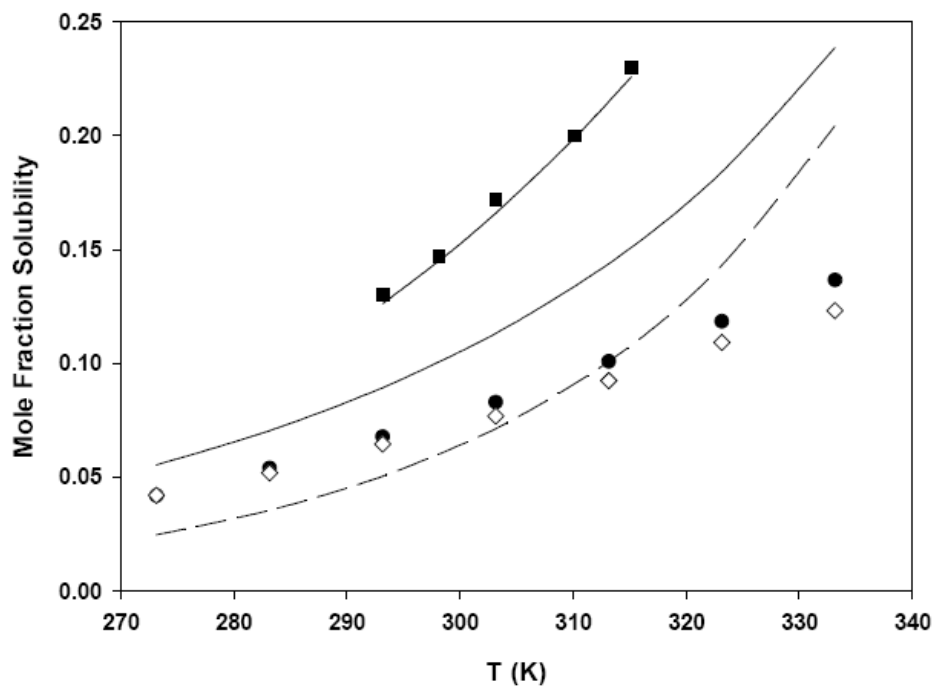


(h)

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1 Figure 2:



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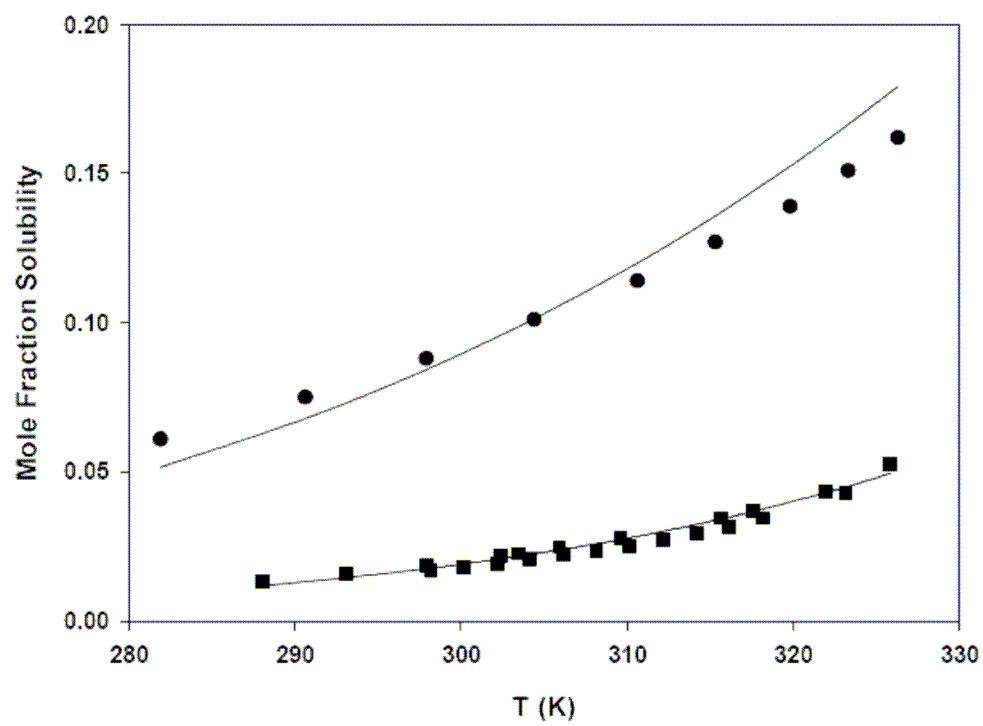
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1 **Figure 3:**

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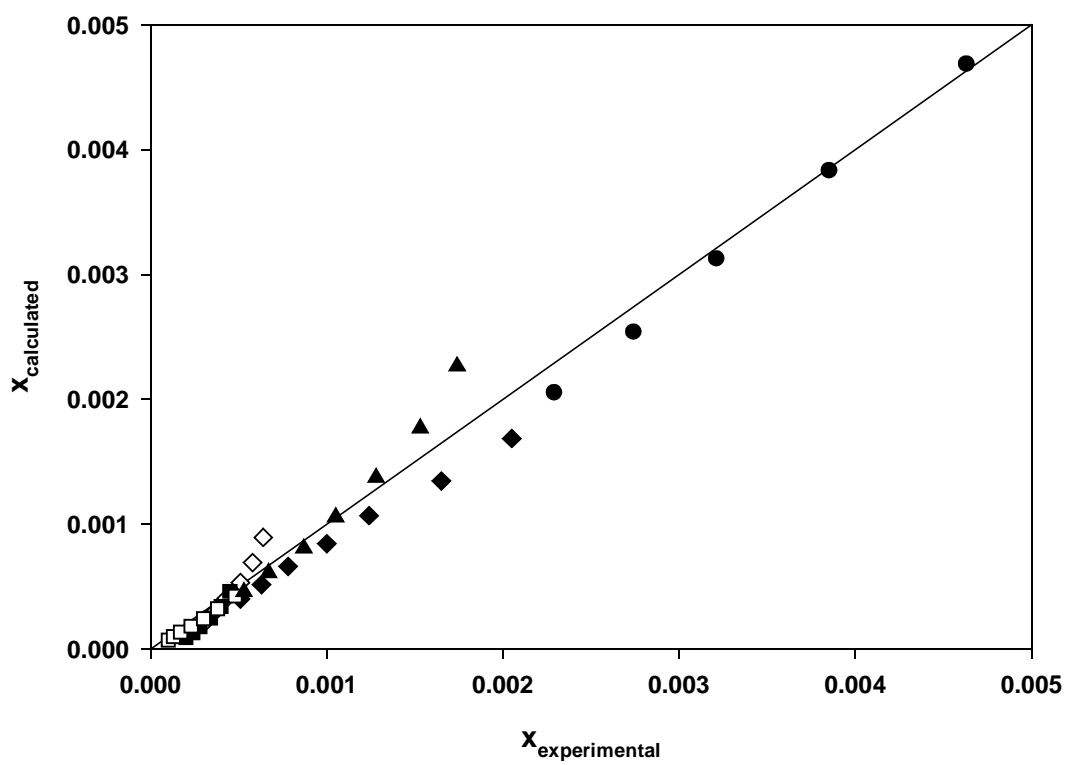
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Accepted

1 Figure 4:



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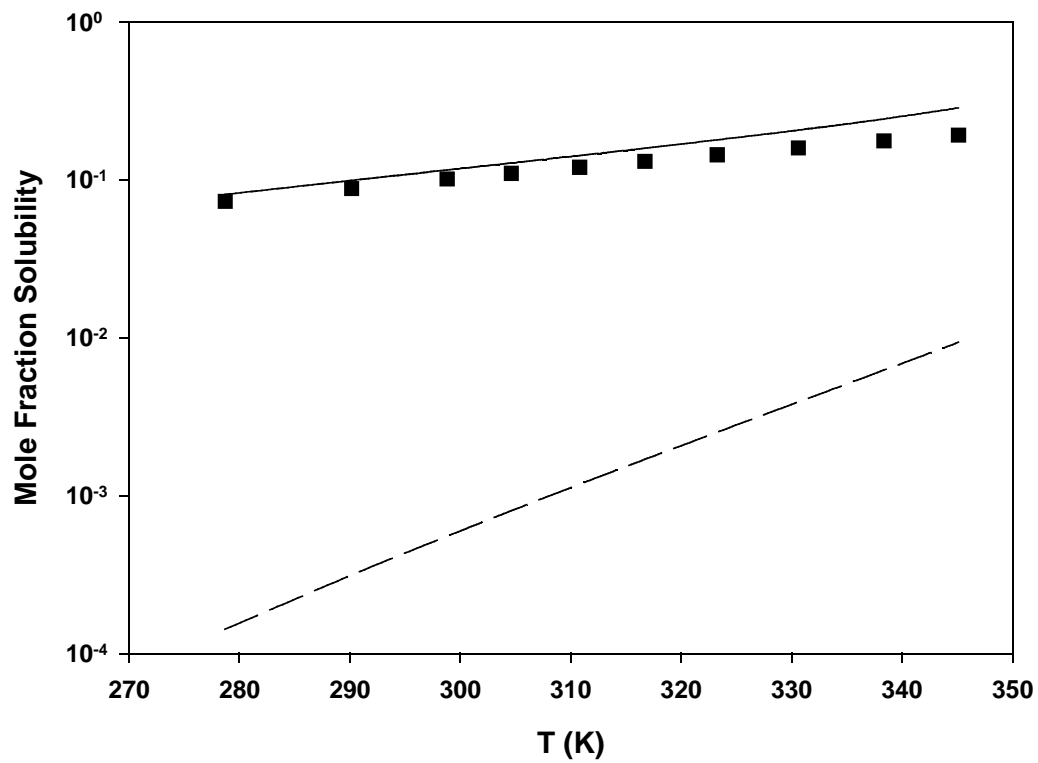
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ACCEPTED MANUSCRIPT

1 Figure 5:

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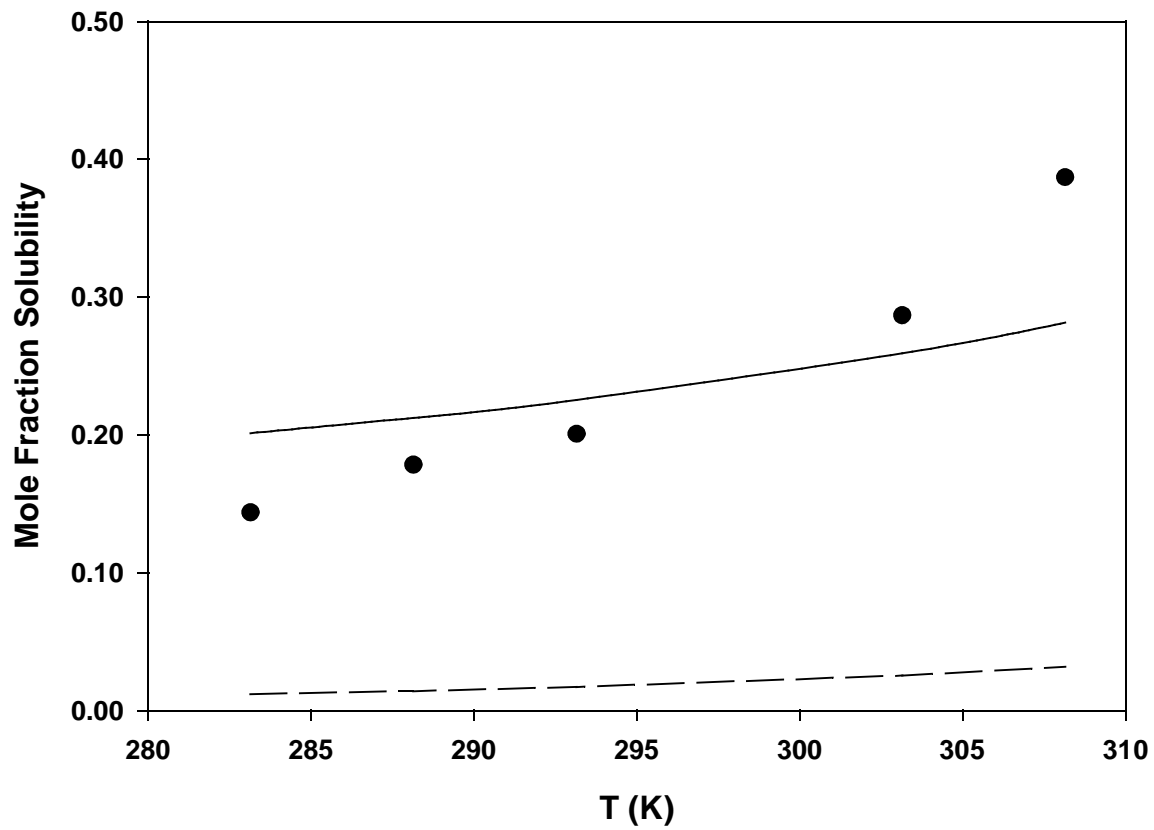


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1 **Figure 6:**

2 **(a)**

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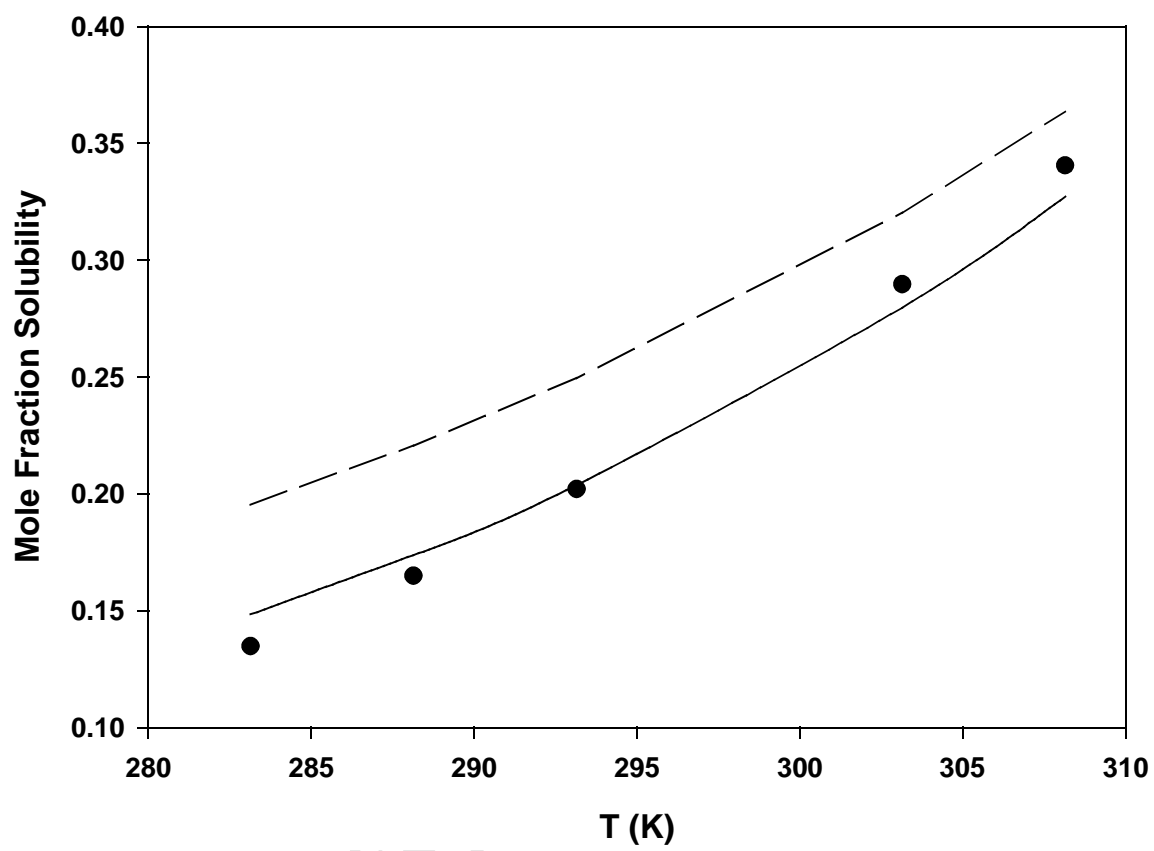
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7

1 (b)

2



3

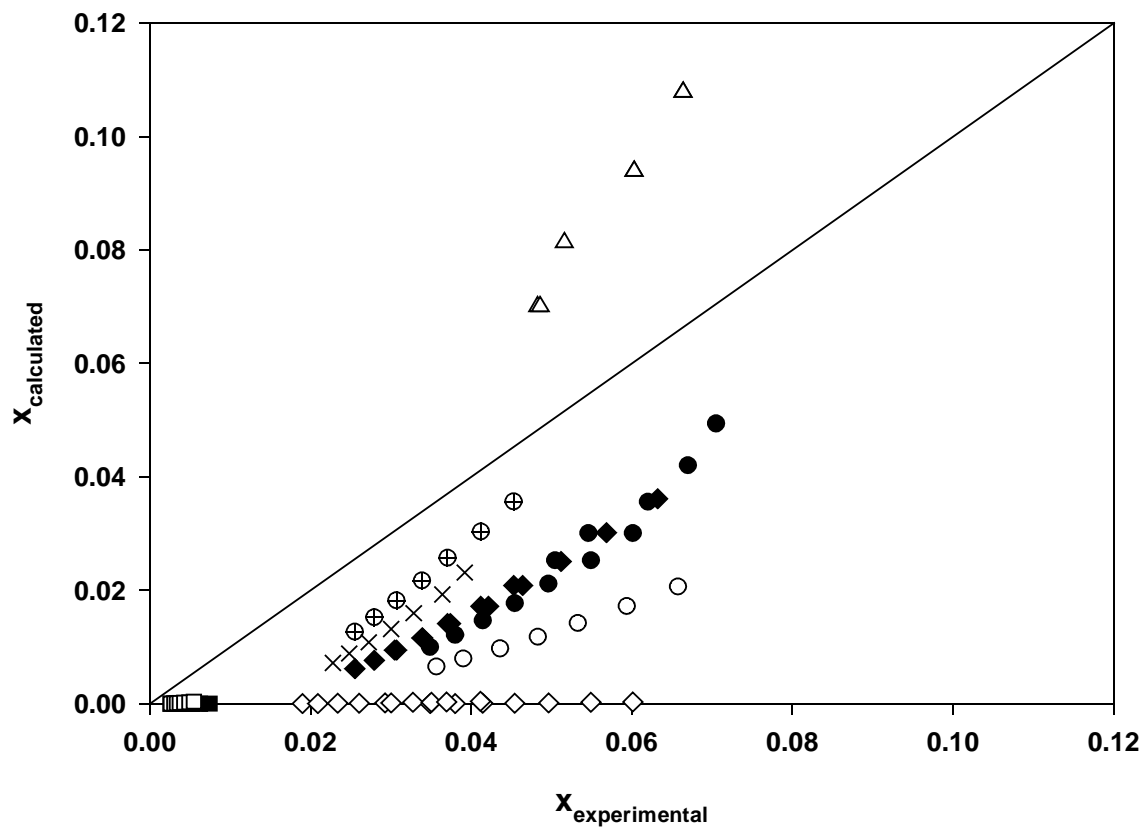
4

Accepted

1 **Figure 7:**

2 **(a)**

3



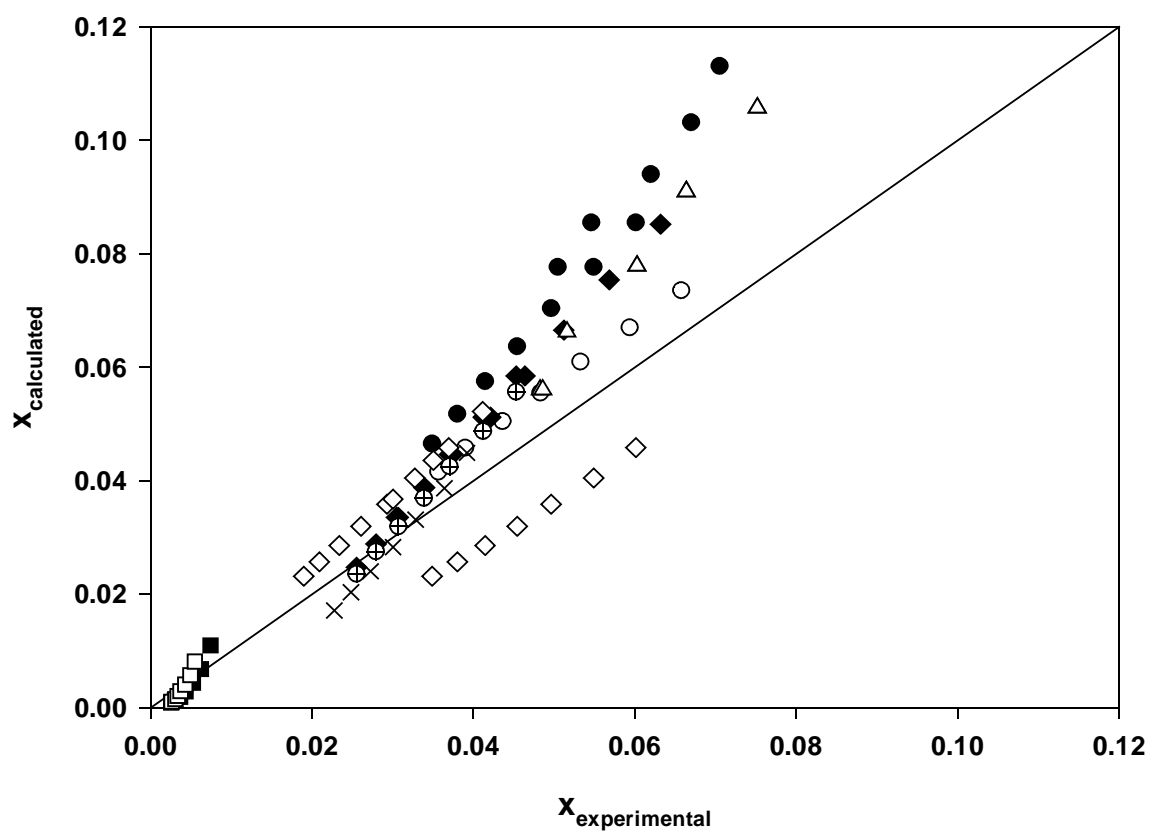
4

5

ACCEPTED

1 (b)

2



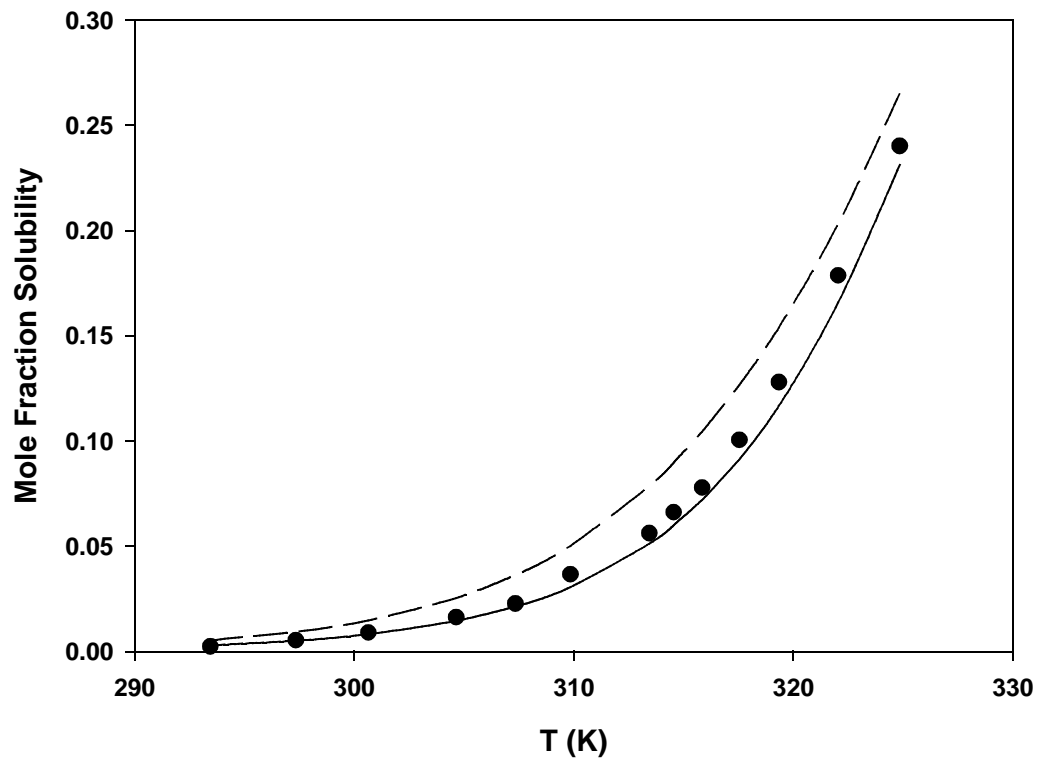
3

4

Accepte

1 **Figure 8:**

2



3

4

Accepted

1 Highlight

- 2 • The CPA EoS is applied for drug-like solubility calculations in organic solvents.
3
4 • Only a single, small and temperature independent k_{ij} parameter is required.
5
6 • Each associating group as well as multiple group substitutions are explicitly
7 considered.
8
9 • Accurate correlations are obtained (global AAD of 24 %)

10
11
12

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