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

Fátima L. Mota, António J. Queimada, Simão P. Pinho, Eugénia A. Macedo

Title: Solubility of Drug-like Molecules in Pure Organic Solvents with the CPA EoS

Authors: Fátima L. Mota, António J. Queimada, Simão P. Pinho, Eugénia A. Macedo

PII: S0378-3812(11)00019-7
DOI: doi:10.1016/j.fluid.2011.01.014
Reference: FLUID 8756

To appear in: *Fluid Phase Equilibria*

Received date: 10-11-2010
Revised date: 5-1-2011
Accepted date: 11-1-2011

Please cite this article as: F.L. Mota, A.J. Queimada, S.P. Pinho, E.A. Macedo, Solubility of Drug-like Molecules in Pure Organic Solvents with the CPA EoS, *Fluid Phase Equilibria* (2010), doi:10.1016/j.fluid.2011.01.014

Solubility of Drug-like Molecules in Pure Organic Solvents with the CPA EoS

Fátima L. Mota,[1] António J. Queimada,[1,*] Simão P. Pinho,[2] Eugénia A. Macedo[1]

[1]*LSRE/LCM - Laboratory of Separation and Reaction Engineering, Faculdade de Engenharia, Universidade do Porto, Rua Dr. Roberto Frias, 4200 - 465 Porto, Portugal*

[2]*LSRE/LCM - Laboratory of Separation and Reaction Engineering, Escola Superior de Tecnologia e Gestão, Instituto Politécnico de Bragança, Campus de Santa Apolónia, 5301-857 Bragança, Portugal*

[*]To whom correspondence should be addressed: ajq@fe.up.pt

Abstract

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

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

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

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

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

1. Introduction

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

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

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

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

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

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

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

CO_2 and ethane. This model was also able to predict accurately the solubility in mixed solvents based on interaction parameters fitted to the corresponding single solvent data. Recently, our group successfully used the CPA EoS for modeling the aqueous solubility of drug-like molecules [29].

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

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

2. Thermodynamic framework

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

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

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

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

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

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

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

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

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

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

$$X_{A_i}=\frac{1}{1+\rho\sum_j x_j\sum_{B_j} X_{B_j}\,\Delta^{A_iB_j}} \tag{5}$$

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

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

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

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

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

$$AAD\,(\%) = \frac{1}{NP}\sum_{i}\frac{\left|x_i^{\exp} - x_i^{calc}\right|}{x_i^{\exp}} \times 100 \qquad (7)$$

3. Results and Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4. Conclusions

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

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

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

Acknowledgement

The authors are grateful for the support provided by *Fundação para a Ciência e a Tecnologia* (FCT, Lisboa, Portugal) and by LSRE financing by FEDER/POCI/2010. A.J. Queimada acknowledges support from POCI/N010/2006. F.L. Mota acknowledges her FCT Ph.D. scholarship SFRH/BD/32372/2006, co-financed by the *Fundo Social Europeu* (FSE).

Nomenclature

a = energy parameter

a_0 = parameter in the CPA EoS cubic term ($Pa.m^6/mol^2$)

A = Helmholtz energy (J)

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

c_1 = parameter in the CPA EoS cubic term

k_{ij} = binary interaction parameter

n = number of moles

NP = number of data points

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

T = absolute temperature (K)

x = mole fraction

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

Greek Symbols

δ = specific parameters in each cubic equation

β = association volume

β_{ij} = solvation parameter

$\Delta^{A_iB_j}$ = association strength between site *A* on molecule *i* and site *B* on molecule *j*

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

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

ε = association energy (J/mol)

ρ = molar density (mol/m^3)

φ = fugacity coefficient

Subscripts

0 = pure component

c = critical

i, *j*, *k* = component index

m = melting

r = reduced

s = solute

tr = transition

Superscripts

assoc = association term

calc = calculated

cubic = cubic term

exp = experimental

List of Abbreviations

AAD =absolute average deviation (%)

CPA = cubic-plus-association

EoS = equation of state

NRHB = Non-Random Hydrogen Bonding

OF = objective function

References

[1] P. Kolář, J. W. Shen, A. Tsuboi, T. Ishikawa, Fluid Phase Equilib. 194 (2002) 771-782.

[2] F. L. Mota, A. P. Carneiro, A. J. Queimada, S. P. Pinho, E. A. Macedo, Eur. J. Pharm. Sci. 37 (2009) 499-507.

[3] S. P. Pinho, E. A. Macedo, Solubility in Food, Pharmaceuticals, and Cosmetic Industries,Royal Society of Chemistry, Durban, South Africa, 2003.

[4] G. D. Maia, M. Giulietti, J. Chem. Eng. Data 53 (2008) 256-258.

[5] G. L. Perlovich, A. Bauer-Brandl, Pharm. Res. 20 (2003) 471-478.

[6] L. H. Fan, P. S. Ma, Z. L. Xiang, Chin. J. Chem. Eng. 15 (2007) 110-114.

[7] Z. B. Mao, X. B. Sun, X. H. Luan, Y. Wang, G. J. Liu, Chin. J. Chem. Eng. 17 (2009) 473-477.

[8] D. W. Wei, W. J. Cao, J. Chem. Eng. Data 54 (2009) 152-153.

[9] X. N. Li, Q. X. Yin, W. Chen, J. K. Wang, J. Chem. Eng. Data 51 (2006) 127-129.

[10] A. Jouyban, O. Azarmir, S. Mirzaei, D. Hassanzadeh, T. Ghafourian, W. E. Acree, A. Nokhodchi, Chem. Pharm. Bull. (Tokyo) 56 (2008) 602-606.

[11] C. M. Wassvik, A. G. Holmen, C. A. S. Bergstrom, I. Zamora, P. Artursson, Eur. J. Pharm. Sci. 29 (2006) 294-305.

[12] J. M. Prausnitz, R. N. Lichtenthaler, E. G. Azevedo, Molecular Thermodynamics of Fluid-phase Equilibria,Third Prentice Hall PTR, New Jersey, 1999.

[13] H. Hojjati, S. Rohani, Org. Proc. Res. Dev. 10 (2006) 1110-1118.

[14] B. C. Hancock, P. York, R. C. Rowe, Int. J. Pharm. 148 (1997) 1-21.

[15] P. Bustamante, M. A. Pena, J. Barra, Int. J. Pharm. 194 (2000) 117-124.

[16] S. Romero, A. Reillo, B. Escalera, P. Bustamante, Chem. Pharm. Bull. (Tokyo) 44 (1996) 1061-1064.

[17] U. Domańska, A. Pobudkowska, A. Pelczarska, P. Gierycz, J. Phys. Chem. B 113 (2009) 8941-8947.

[18] M. Mirmehrabi, S. Rohani, Can. J. Chem. Eng. 82 (2004) 335-342.

[19] B. Calvo, E. A. Cepeda, J. Chem. Eng. Data 53 (2008) 628-633.

[20] I. Hahnenkamp, G. Graubner, J. Gmehling, Int. J. Pharm. 388 (2010) 73-81.

[21] J. Abildskov, R. Gani, P. Rasmussen, J. P. O'Connell, Fluid Phase Equilib. 181 (2001) 163-186.

[22] C. C. Chen, P. A. Crafts, Ind. Eng. Chem. Res. 45 (2006) 4816-4824.

[23] C. C. Chen, Y. H. Song, Ind. Eng. Chem. Res. 43 (2004) 8354-8362.

[24] P. B. Kokitkar, E. Plocharczyk, Org. Proc. Res. Dev. 12 (2008) 249-256.

[25] S. Gracin, T. Brinck, A. C. Rasmuson, Ind. Eng. Chem. Res. 41 (2002) 5114-5124.

[26] F. Ruether, G. Sadowski, J. Pharm. Sci. 98 (2009) 4205-4215.

[27] I. Tsivintzelis, I. G. Economou, G. M. Kontogeorgis, AlChE J. 55 (2009) 756-770.

[28] I. Tsivintzelis, I. G. Economou, G. M. Kontogeorgis, J. Phys. Chem. B 113 (2009) 6446-6458.

[29] F. L. Mota, A. J. Queimada, S. P. Pinho, E. A. Macedo, Fluid Phase Equilib. 298 (2010) 75-82.

[30] G. M. Kontogeorgis, E. C. Voutsas, I. V. Yakoumis, D. P. Tassios, Ind. Eng. Chem. Res. 35 (1996) 4310-4318.

[31] F. L. Mota, A. J. Queimada, S. P. Pinho, E. A. Macedo, Ind. Eng. Chem. Res. 47 (2008) 5182-5189.

[32] A. J. Queimada, F. L. Mota, S. P. Pinho, E. A. Macedo, J. Phys. Chem. B 113 (2009) 3469-3476.

[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] 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.

[35] E. C. Voutsas, I. V. Yakoumis, D. P. Tassios, Fluid Phase Equilib. 158 (1999) 151-163.

[36] S. H. Huang, M. Radosz, Ind. Eng. Chem. Res. 29 (1990) 2284-2294.

[37] *DIPPR Tables*, DIPPR 801 Thermophysical Properties Database,Brigham Young University, Provo, UT, 1998.

[38] G. K. Folas, G. M. Kontogeorgis, M. L. Michelsen, E. H. Stenby, Ind. Eng. Chem. Res. 45 (2006) 1527-1538.

[39] H. G. Brittain, Polymorphism in Pharmaceutical Solids,Informa Health Care, New York, 1999.

[40] M. Sacchetti, J. Therm. Anal. Calorim. 63 (2000) 345-350.

[41] G. L. Perlovich, S. V. Kurkov, L. K. R. Hansen, A. Bauer-Brandl, J. Pharm. Sci. 93 (2004) 654-666.

[42] A. Seidell, J. Am. Chem. Soc. 29 (1907) 1091-1095.

[43] G. L. Perlovich, T. V. Volkova, A. Bauer-Brandl, J. Pharm. Sci. 95 (2006) 2158-2169.

[44] P. Bustamante, S. Romero, A. Peña, B. Escalera, A. Reillo, J. Pharm. Sci. 87 (1998) 1590-1596.

[45] Y. Baena, J. A. Pinzón, H. J. Barbosa, F. Martínez, Phys. Chem. Liq. 42 (2004) 603-613.

[46] R. A. Granberg, A. C. Rasmuson, J. Chem. Eng. Data 44 (1999) 1391-1395.

[47] J. A. Jiménez, F. Martínez, J. Braz. Chem. Soc. 17 (2006) 125-134.

[48] H. Hojjati, S. Rohani, Org. Proc. Res. Dev. 10 (2006) 1101-1109.

[49] J. A. Jiménez, F. Martínez, J. Solution Chem. 35 (2006) 335-352.

[50] R. A. Granberg, A. C. Rasmuson, J. Chem. Eng. Data 45 (2000) 478-483.

[51] C. M. McLoughlin, W. A. M. McMinn, T. R. A. Magee, Powder Technol. 134 (2003) 40-51.

[52] Y. J. Yi, D. Hatziavramidis, A. S. Myerson, M. Waldo, V. G. Beylin, J. Mustakis, Ind. Eng. Chem. Res. 44 (2005) 5427-5433.

[53] A. Shalmashi, A. Eliassi, J. Chem. Eng. Data 53 (2008) 1332-1334.

[54] Y. J. Manrique, D. P. Pacheco, F. Martínez, J. Solution Chem. 37 (2008) 165-181.

[55] D. P. Pacheco, Y. J. Manrique, F. Martinez, Fluid Phase Equilib. 262 (2007) 23-31.

[56] L. C. Garzón, F. Martínez, J. Solution Chem. 33 (2004) 1379-1395.

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 x 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			

*Obtained in this work.

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

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

[a]Without outliers: AAD > 150%.

Table 3. CPA Modelling Results for the Acids, and Respective Binary Interaction 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		
	tricloroethylene [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

[a]Without outliers: AAD > 150%.

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

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

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

Compound	Solvent	Temperature (K)	Prediction AAD (%)	Correlation k_{ij}	Correlation 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

Figure Captions:

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

Figure 2. Solubility of acetanilide in methanol [42] (◊), ethanol [42] (●) and 1-octanol [43] (■), and CPA correlations (—, methanol and 1-octanol; ---, ethanol).

Figure 3. Solubility of acetylsalicylic acid [4] (●) and adipic acid [7] (■) in acetone, and CPA correlation results.

Figure 4. Summarized results for ascorbic acid solubility in several solvents: experimental data [53] versus CPA correlations: ethanol (●), methanol (o), 2-propanol (♦), acetone (◊), acetonitrile (■), ethyl acetate (□), and tetrahydrofuran (▲).

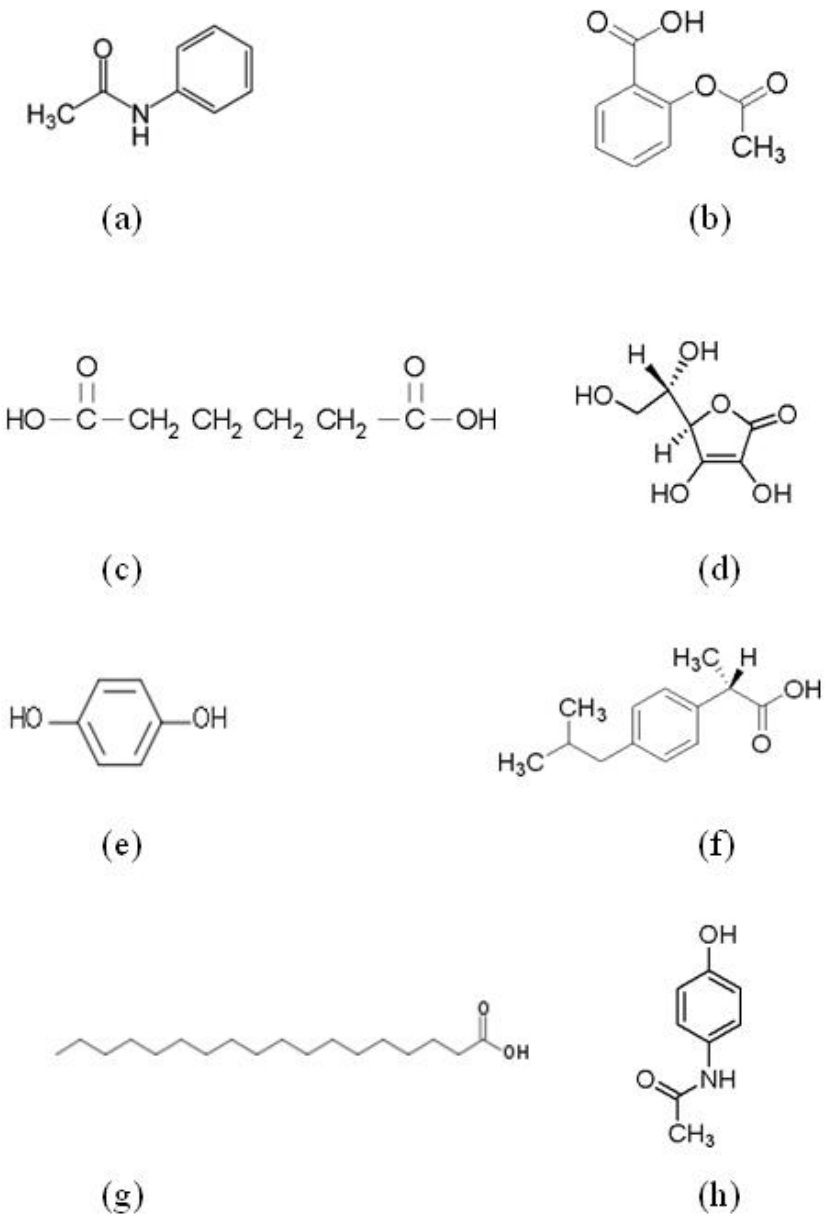
Figure 5. Solubilities of hydroquinone as a function of temperature in ethyl acetate [9], and CPA modelling results: correlation (—) and prediction (---).

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

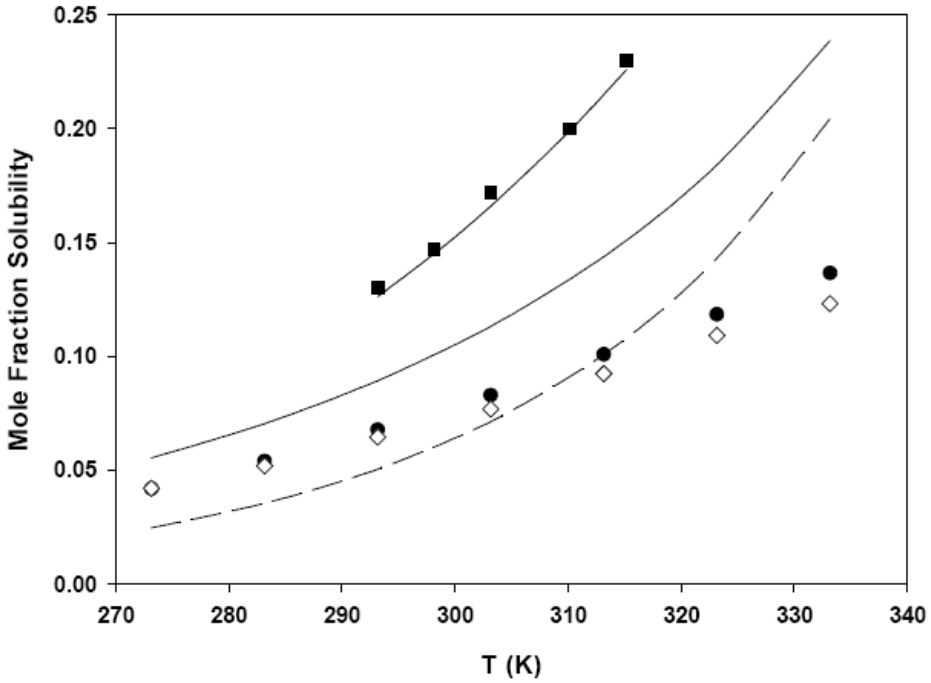
Figure 7. Summarized results for paracetamol in several solvents: experimental data versus CPA (a) predictions and (b) correlations: ethanol [46, 49] (●), methanol [46] (o), 2-propanol [46, 48] (♦), acetone [46, 50] (◊), acetonitrile [46] (■), ethyl acetate [46] (□), propylene glycol [47, 49] (Δ), 1-propanol [46] (⊕),and 1-butanol [46] (x).

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

Figure 1:



1 **Figure 2:**



2

3

4

Figure 3:

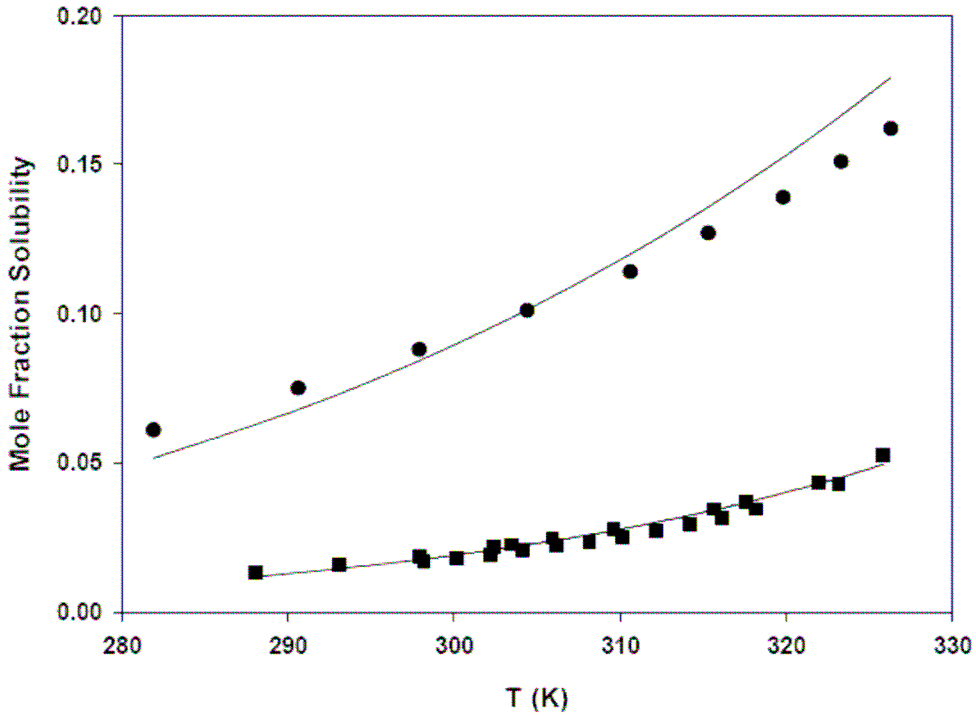


Figure 4:

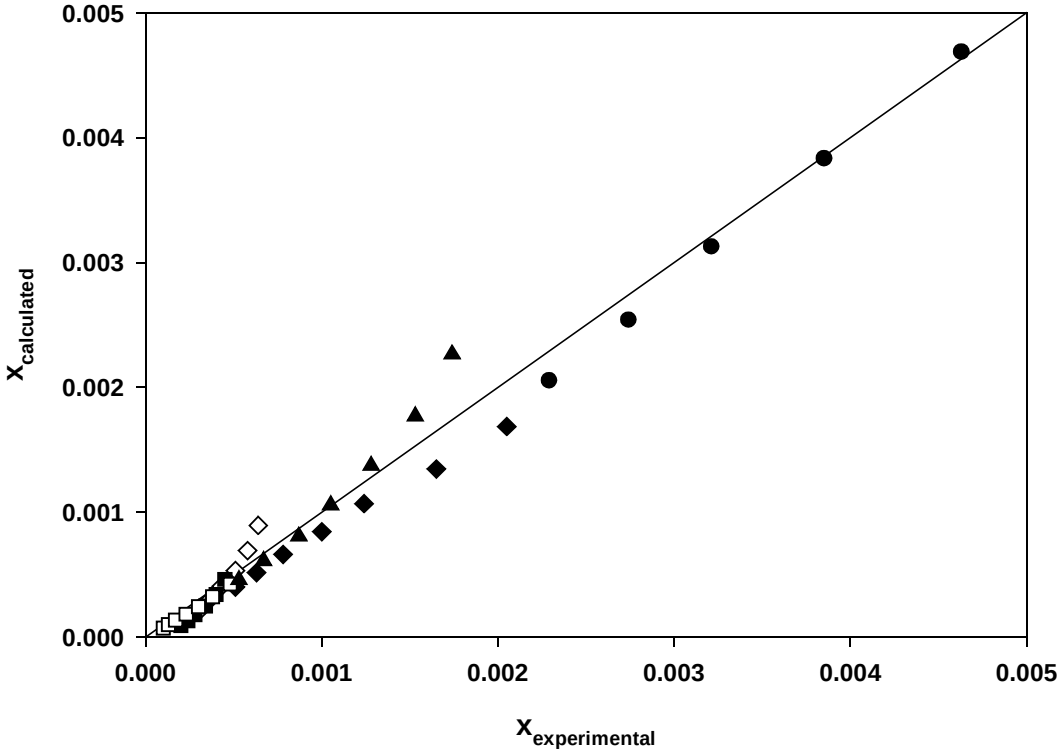


Figure 5:

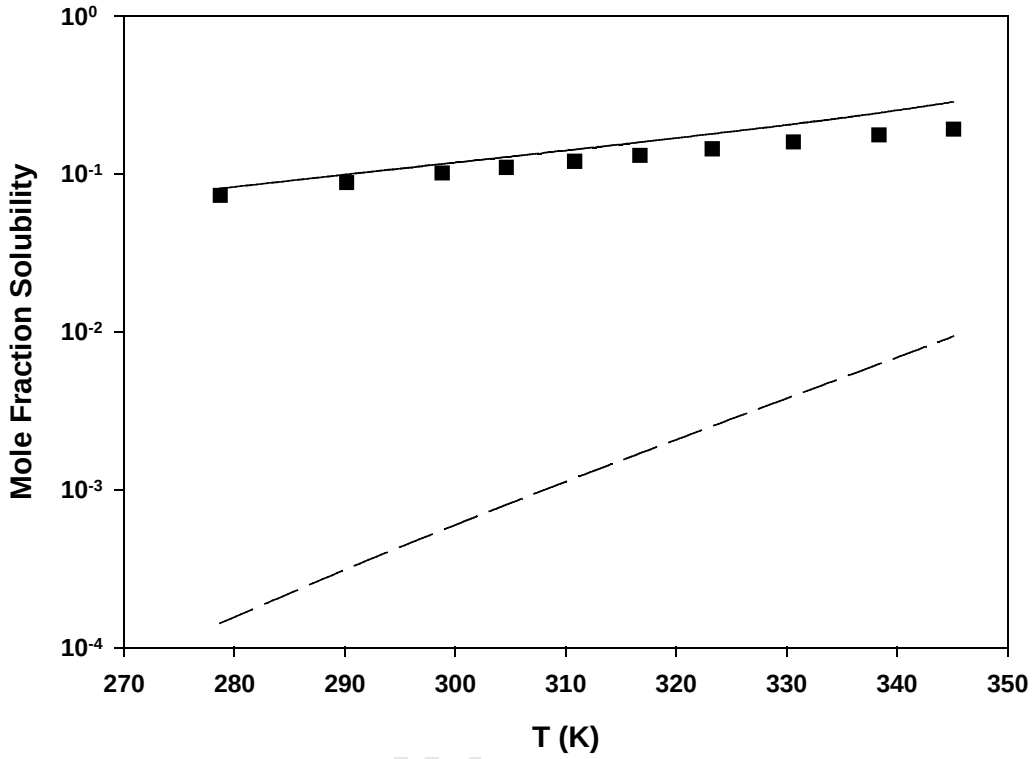
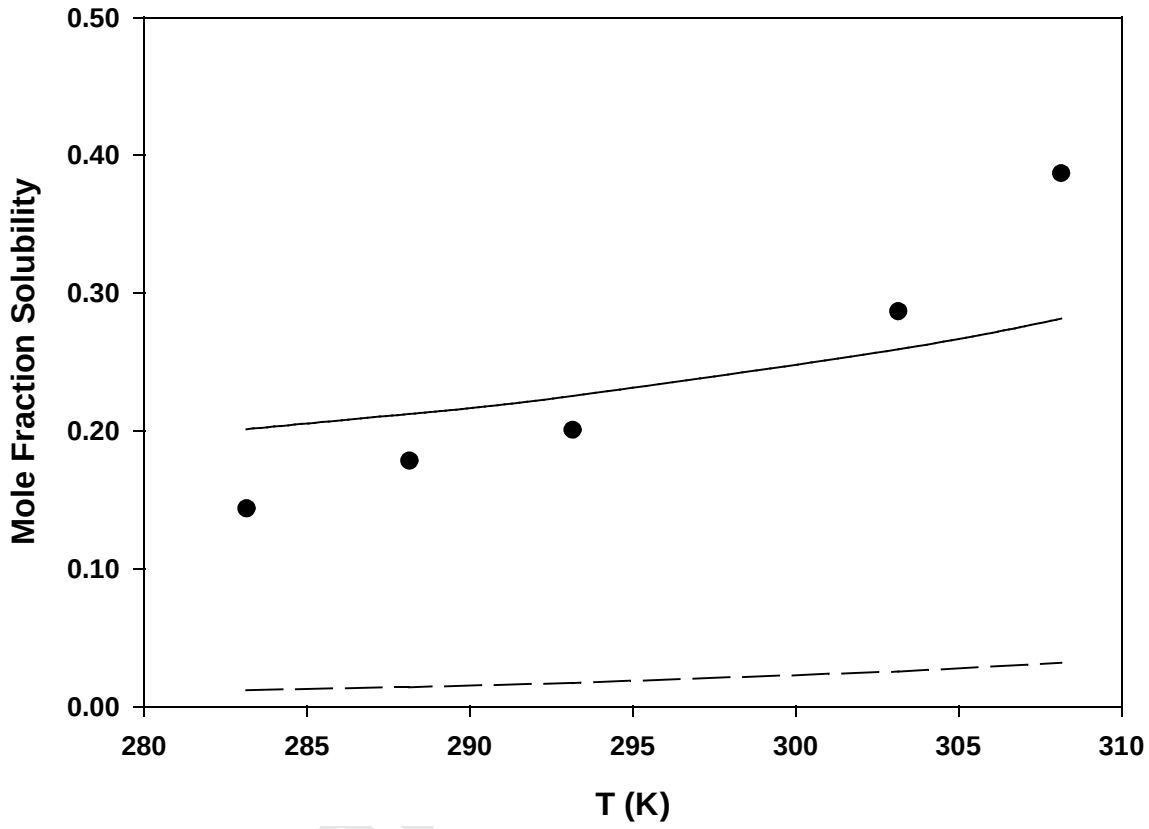


Figure 6:

(a)



(b)

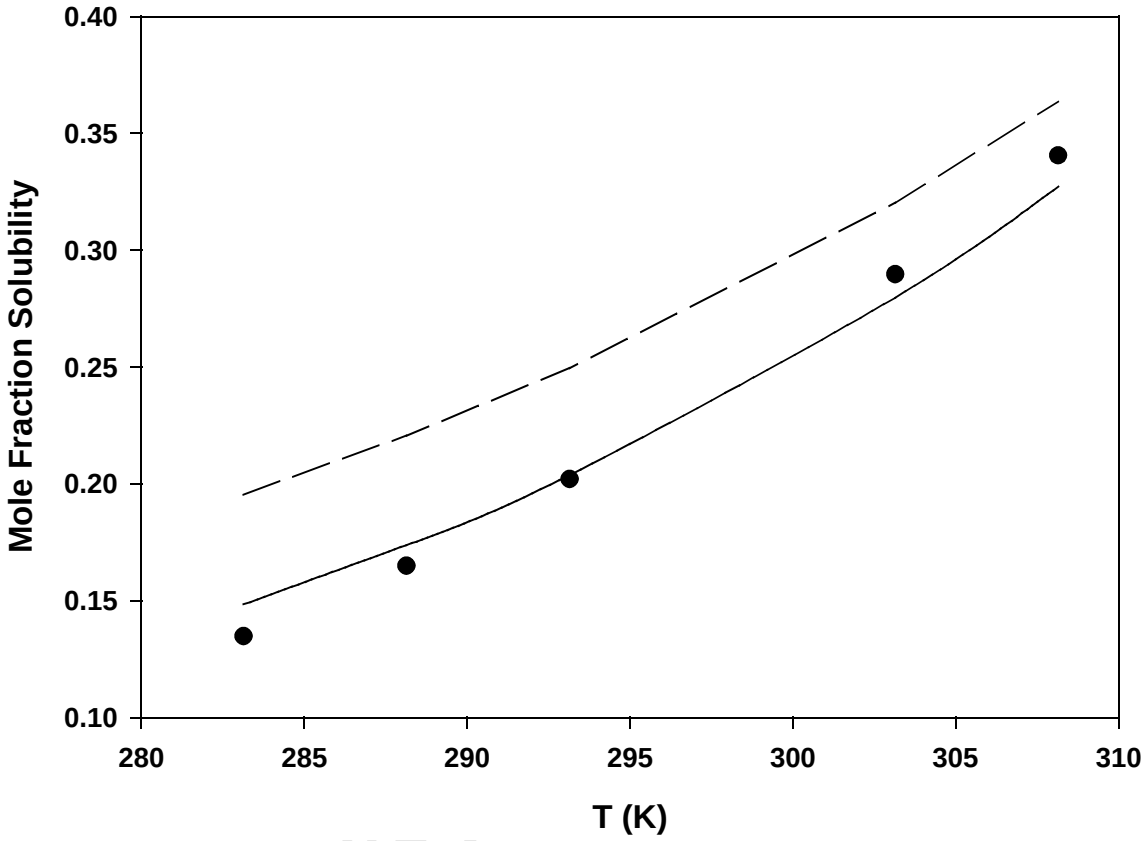
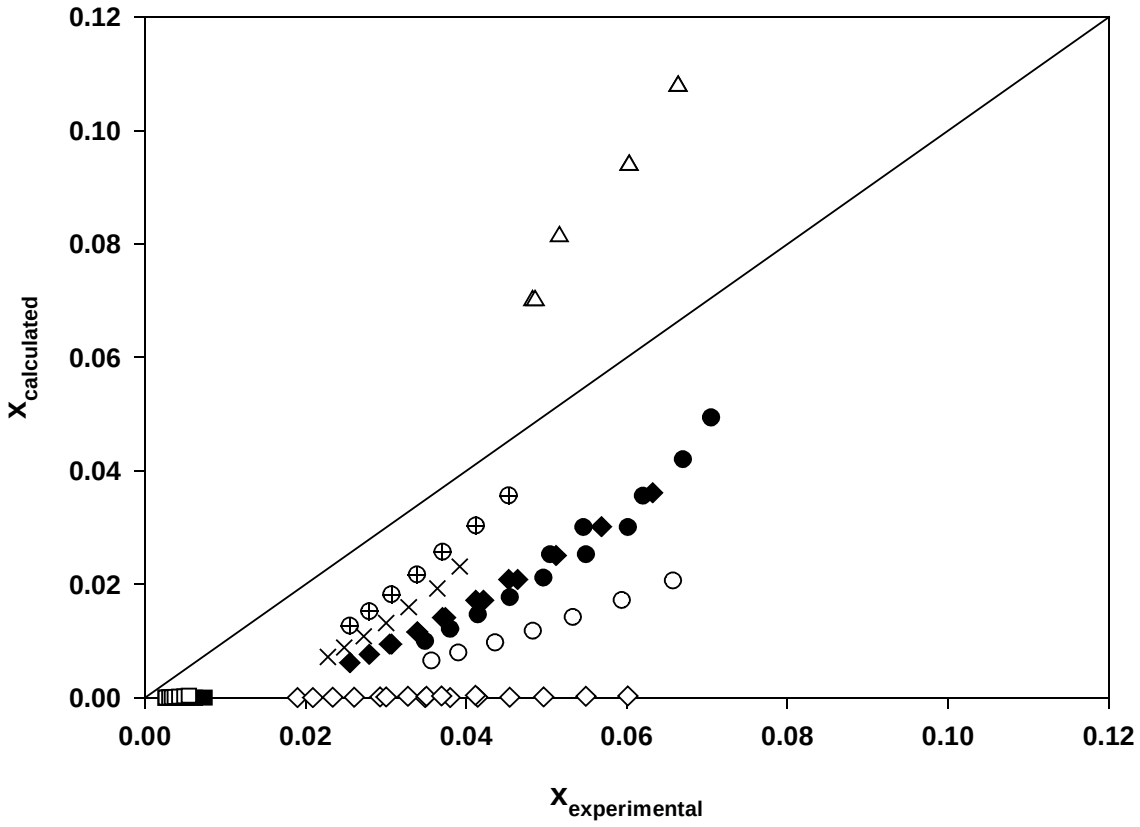


Figure 7:

(a)



(b)

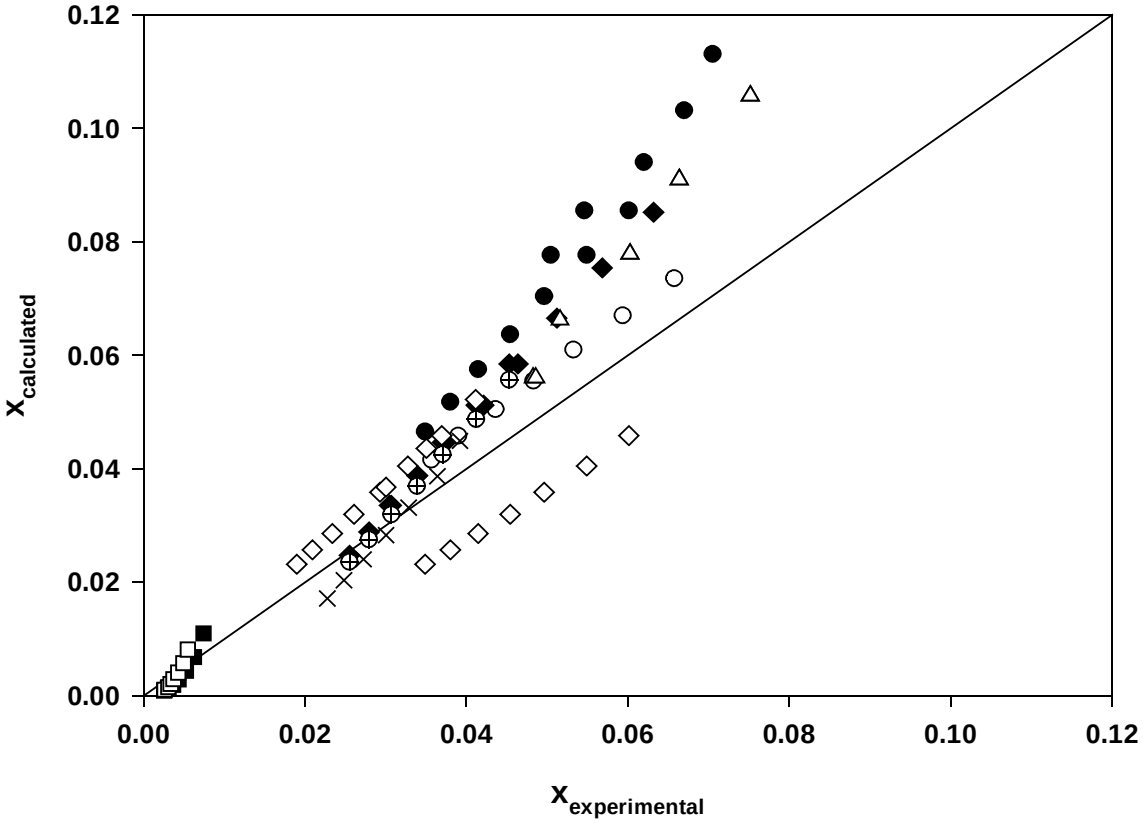
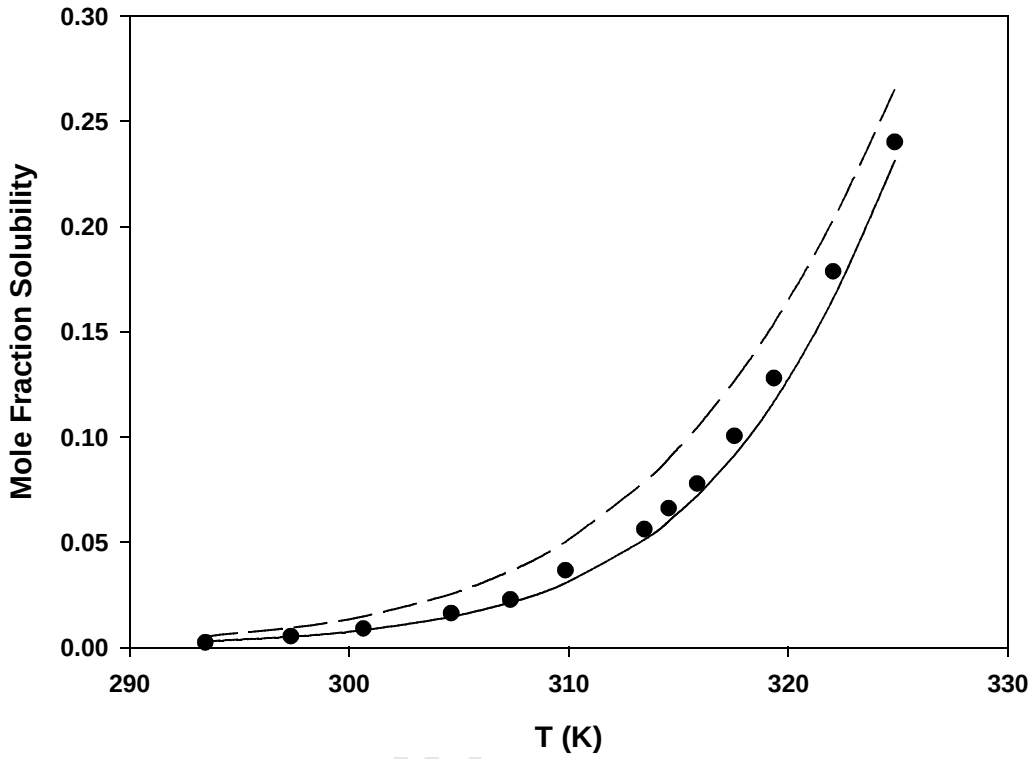


Figure 8:



Highlight

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