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## Water solubility of drug-like molecules with the cubic-plus-association equation of state

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► **To cite this version:**

Fátima L. Mota, António J. Queimada, Simão P. Pinho, Eugénia A. Macedo. Water solubility of drug-like molecules with the cubic-plus-association equation of state. *Fluid Phase Equilibria*, 2010, 298 (1), pp.75-82. 10.1016/j.fluid.2010.07.004 . hal-01637114

**HAL Id: hal-01637114**

**<https://hal.science/hal-01637114v1>**

Submitted on 26 Oct 2018

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1 **Water Solubility of Drug-Like Molecules with the Cubic-**  
2 **Plus-Association Equation of State**

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1 **Abstract**

2

3 Although of extreme importance for evaluating the effective therapeutic action,  
4 aqueous solubility data involving drug-like molecules are scarce. Thermodynamic models  
5 can be used to estimate these solubilities, and different models, namely activity coefficient  
6 models, have been applied for that purpose. Still, these frequently cannot describe with  
7 accuracy broad temperature and pressure ranges, various solvent compositions or  
8 multifunctional molecules.

9 Despite the success of the cubic-plus-association (CPA) equation of state (EoS) in  
10 modeling complex systems, it has never been used for modeling the phase equilibria of  
11 drug-like molecules, explicitly accounting for the number and nature of associating sites. In  
12 this work, aqueous solubilities of different complex solutes, like acetamide, acetanilide,  
13 acetylsalicylic acid, adipic acid, ascorbic acid, bisphenol A, camphor, dibenzofuran,  
14 hexachlorobenzene, hydroquinone, ibuprofen, nicotinic acid, paracetamol, piperazine,  
15 stearic acid, sorbitol, terephthalic acid and vanillin are estimated in a wide temperature  
16 range with the CPA EoS. Generally, the modeling results are within the experimental  
17 uncertainties using a single temperature independent binary interaction parameter, or a  
18 solvation parameter for some non-associating solutes. Globally, an average absolute  
19 deviation of 39% was obtained.

20

21 **Keywords: CPA, drug-like, modeling, solubility, water.**

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## 1 **1. Introduction**

2

3           Classical chemical engineering thermodynamic models such as equations of state  
4 are seldomly used to obtain the aqueous solubility of drugs or drug-like molecules, either  
5 because these are typically highly non-ideal systems, or the solute complexity is so high  
6 that it is often impractical to determine the model parameters from the reduced data sets  
7 available.

8           Pharmaceutical compounds are medium-size molecules from different chemical  
9 families, with diverse molecular structures, typically composed of several interlinked  
10 aromatic cores and multiple substituents containing heteroatoms as N, P, O, S, and  
11 halogens. The presence of aromatic groups and electronegative heteroatoms makes these  
12 molecules highly polarizable, and sometimes, conformationally flexible [1]. That flexibility  
13 may affect the reactivity and solvation of the molecule, as well as possible polymorph  
14 formation. This high complexity makes the prediction of their phase behavior a challenging  
15 task. Thus, the thermodynamic behavior of pharmaceutical compounds is a key property in  
16 drug design, as well as in the development and optimization of manufacturing processes.

17           Solubility is required in many stages of drug development. In recent years, efforts  
18 have been made towards the development of predictive models to calculate the physical  
19 properties and phase behavior of newly discovered active ingredients, as well as for the  
20 existing ones, as available experimental data is nowadays still scarce. A brief review of the  
21 excess Gibbs energy based thermodynamic models most commonly used in the  
22 pharmaceutical industry was recently presented by Mota et al.[2].

1           The limitations of that type of models for high pressure and temperature phase  
2 equilibria, non-ideal vapor phases as well as their need of mixture data, suggests further  
3 research on the application of EoS for these systems. EoS can be used to predict solubilities  
4 of complex molecules, but aqueous solubilities require that hydrogen bonding and solvation  
5 effects are explicitly taken into account. The statistical associating fluid theory (SAFT) [3]  
6 and the cubic-plus-association (CPA) [4-6] are two of the most successful associating EoSs.  
7 These are relevant to multicomponent, multiphase equilibria of systems containing  
8 associating components, but so far only PC-SAFT has been applied to pharmaceuticals [7],  
9 where paracetamol, ibuprofen, sulfadiazine, *p*-hydroxyphenylacetic acid, and *p*-  
10 aminophenylacetic acid data in pure and mixed solvents were examined, as well as their  
11 solubility temperature dependence. Ruether and Sadowski [7] obtained the pure component  
12 and binary interaction parameters simultaneously from mixture data, and to quantitatively  
13 describe the temperature dependence of the solubilities a temperature dependency on the  
14 binary interaction parameter was introduced. Also, for simplicity, the heat capacity term in  
15 the solid-liquid-equilibrium equation [8] was ignored, what is not always a good  
16 approximation as discussed by Pappa et al. [9].

17           A recent and successful EoS is the nonrandom hydrogen bonding (NRHB) model  
18 [10-11], a comprehensive lattice model combined with an EoS theory, where holes are used  
19 to account for density variation as a result of temperature and pressure changes. This  
20 methodology accounts explicitly for the nonrandom distribution of molecular sites, being  
21 the model useful for property calculations of highly non-ideal fluids. Tsivintzelis et al. [12-  
22 13] applied it to represent the phase behavior of mixtures of pharmaceuticals, namely:

1 ibuprofen, ketoprofen, naproxen, benzoic acid, methyl paraben, ethyl paraben, N-methyl  
2 aniline, acetanilide, paracetamol and phenacetin. Very satisfactory correlations were  
3 obtained both in liquid or supercritical solvents, using only one regressed binary interaction  
4 parameter.

5         Despite the success of the CPA EoS in predicting the phase equilibria of mixtures  
6 containing a wide range of compounds, among others, hydrocarbons [14], polycyclic  
7 aromatic hydrocarbons [15], fatty acids [16], and phenolic compounds [17-18], its  
8 application to drug and drug-like molecules has not yet been evaluated. The model seems to  
9 be promising for such molecules as many of the EoS pure component parameters can be  
10 obtained from available pure component constants, such as the critical temperature and  
11 pressure, and the van der Waals volume [17-18], that if not available can be accurately  
12 estimated from well established group-contribution models, some of them able to  
13 distinguish among isomers [19]. Additionally, some studies suggest that the cubic term  
14 parameters of CPA can be correlated with the component chain length, and that similar  
15 molecules present similar parameters [15-16, 20-21]. More recently, studies on  
16 polifunctional phenolics solubility indicated that a group-contribution scheme can be  
17 applied for the association term [17-18].

18         The aim of this work is to use CPA to model water solubilities of drug-like  
19 molecules. The solubilities of acetamide, acetanilide, acetylsalicylic acid, adipic acid,  
20 ascorbic acid, bisphenol A, camphor, dibenzofuran, hexachlorobenzene, hydroquinone,  
21 ibuprofen, nicotinic acid, paracetamol, piperazine, stearic acid, sorbitol, terephthalic acid  
22 and vanillin in water were studied. Particularly, the existence of solid-solid phase

1 transitions and the existence of polymorphic forms were also analyzed. The molecular  
2 structures of the compounds under study are presented in Fig. 1.

3 It is shown that CPA provides a good description of the aqueous solubilities for the  
4 tested molecules in the complete temperature range of the available data, using a single  
5 temperature independent binary interaction parameter for the majority of the systems. A  
6 few non-associating compounds require an additional solvation parameter that takes into  
7 account the cross-association phenomena with water.

8

## 9 **2. Thermodynamic framework**

10 The solubility of a solid solute in a liquid solvent is calculated by solving the  
11 thermodynamic equations of equilibrium [8]. Assuming a pure solid phase, no significant  
12 temperature dependence on the difference between the heat capacity of the pure liquid and  
13 solid ( $\Delta C_p$ ), and neglecting the effect of pressure on melting temperature ( $T_m$ ), solute  
14 enthalpies of phase transition ( $\Delta_{tr}H$ ), and  $\Delta C_p$ , the following expression is obtained:

15

$$16 \quad x_s = \frac{\varphi_s^{liq_0}}{\varphi_s^{liq}} \exp \left\{ - \sum_{tr} \frac{\Delta_{tr}H}{R} \left( \frac{1}{T} - \frac{1}{T_{tr}} \right) + \frac{\Delta C_p}{R} \left[ \frac{T_m}{T} - 1 - \ln \left( \frac{T_m}{T} \right) \right] \right\} \quad (1)$$

17

18 where  $x_s$  is the solute mole fraction solubility,  $R$  is the ideal gas constant,  $T$  is the absolute  
19 temperature,  $\varphi$  is the fugacity coefficient, and subscripts  $0$ ,  $tr$  and  $m$  refers to a pure  
20 component, a pure solute phase transition and melting, respectively. The summation in  
21 equation 1 stands for the different solid-solid and fusion phase transitions of the solute.

1           The CPA-EoS [6] combines the robustness and simplicity of a cubic EoS, the  
2 Soave-Redlich-Kwong (SRK) or the Peng-Robinson (PR) equations, accounting for  
3 physical interactions, and a chemical term from the Wertheim theory [22-23], taking into  
4 account the association due to hydrogen bonding between like molecules (self-association)  
5 and unlike molecules (cross-association or solvation). Polar and quadrupolar interactions  
6 are not explicitly taken into consideration. The activity of each bonding site is assumed  
7 independent of the other bonding sites on the same molecule. Thus, steric hindrance and  
8 cooperativity effects are neglected. This association contribution, which depends on the  
9 number and type of association sites, was used in other associating EoS such as SAFT [24-  
10 25], and their subsequent versions [3].

11           Using a generalized cubic term, the cubic and association contributions to the  
12 Helmholtz energy ( $A$ ) are the following [4-5, 18]:

$$13 \quad A^{cubic} = \frac{an}{b(\delta_2 - \delta_1)} \ln\left(\frac{1 + b\rho\delta_1}{1 + b\rho\delta_2}\right) - nRT \ln(1 - b\rho) \quad (2)$$

$$14 \quad A^{assoc} = RT \sum_i n_i \sum_{A_i} \left[ \ln(X_{A_i}) - \frac{X_{A_i}}{2} + \frac{1}{2} \right] \quad (3)$$

15  
16 where  $i$  is a component index,  $b$  is the covolume parameter,  $a$  is the energy parameter,  $\rho$  is  
17 the molar density,  $n$  is the number of moles, and  $X_{A_i}$  is the mole fraction of component  $i$  not  
18 bonded at site  $A$ . If the SRK cubic term is used,  $\delta_1$  is set equal to 1 and  $\delta_2$  to 0; if, instead,  
19 PR is used,  $\delta_1$  is set equal to  $1 + \sqrt{2}$  and  $\delta_2$  to  $1 - \sqrt{2}$ . The pure component energy parameter  $a$   
20 is given by a Soave-type temperature dependency, while  $b$  is constant:



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

2

3 where  $a_0$  and  $c_1$  are pure component parameters and  $T_r$  is the reduced temperature. For  
 4 mixtures, classical van der Waals one-fluid mixing rules are employed, where a binary  
 5 interaction parameter  $k_{ij}$  is introduced on the cross-energy parameter. For some cases, a  
 6 fitted cross-association volume  $\beta_{ij}$  is also required in the association term, as will be  
 7 explained later.  $X_{A_i}$  is the key element of the association term and is related to the  
 8 association strength,  $\Delta^{A_i B_j}$ , between two sites belonging to two different molecules, site  $A$   
 9 on molecule  $i$  and site  $B$  on molecule  $j$ , by:

10

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

12

13 For cross-associating systems, combining rules for the cross-association energy  $\epsilon^{A_i B_j}$   
 14 and cross-volume  $\beta^{A_i B_j}$  parameters (or alternatively, for the association strength) are  
 15 required. Different sets of combining rules have been proposed [26-29] but, in this work,  
 16 only the computationally simpler Elliot rule is adopted [29]:

17

18 
$$\Delta^{A_i B_j} = \sqrt{\Delta^{A_i B_i} \Delta^{A_j B_j}} \quad (6)$$

1

2           The three cubic parameters  $a_0$ ,  $c_1$  and  $b$ , and the associating parameters  $\varepsilon^{A_i B_i}$  and  
 3  $\beta^{A_i B_i}$  are the pure compound parameters of the model. Like in most EoS, these are usually  
 4 optimized fitting vapor pressure and liquid density data. If the compound is non-  
 5 associating, only the three parameters of the cubic term are required. When fitting the pure  
 6 component parameters, the objective function (OF) used is:

7

$$8 \quad OF = \sum_i^{NP} \left( \frac{P_i^{\text{exp}} - P_i^{\text{calc}}}{P_i^{\text{exp}}} \right)^2 + \sum_i^{NP} \left( \frac{\rho_i^{\text{exp}} - \rho_i^{\text{calc}}}{\rho_i^{\text{exp}}} \right)^2 \quad (7)$$

9

10 where  $NP$  is the number of points,  $P$  is the pressure, and the superscripts *exp* and *calc* refer  
 11 to experimental and calculated values, respectively.

12           For systems where solvation can occur between an associating component and a  
 13 non-associating one, Folas et al. [30] proposed to use the cross-association energy as half  
 14 the associating component association energy, and the cross-association volume as an  
 15 adjustable parameter, to be fitted from equilibrium data. This scheme has been successfully  
 16 used by several authors [14-15, 30-31].

17           For the estimation of the  $k_{ij}$  and  $\beta_{ij}$  parameters, experimental solubility data was  
 18 used with the objective function:

19

$$OF = \sum_i^{NP} \left( \frac{x_i^{\text{exp}} - x_i^{\text{calc}}}{x_i^{\text{exp}}} \right)^2 \quad (8)$$

In order to compare the experimental and calculated results, absolute average deviations (AAD) were used:

$$AAD (\%) = \frac{1}{NP} \sum_i \frac{|x_2^{\text{exp}} - x_2^{\text{calc}}|}{x_2^{\text{exp}}} \times 100 \quad (9)$$

### 3. Results and Discussion

From all the compounds studied in this work, only compounds g-i in Fig. 1 are not self-associating. For the other molecules, the association term in CPA was characterized by the nature and number of associating groups, each of these being defined by an association scheme, as proposed by Huang and Radosz [25]. The one-site (1A) scheme was used for carboxylic acid groups. The two-site (2B) was used for alcohols. The three-site (3B) and two-site (2B) schemes were used for primary and secondary amines, respectively. Furthermore, the hydroxyl groups of ascorbic acid and sorbitol were divided into two classes: in ascorbic acid they were separated into ring and aliphatic hydroxyl groups, while in sorbitol the two terminal –OH groups were considered to be different from the other 4. Acetanilide, piperazine and paracetamol have secondary amine groups, whereas acetamide has a primary amine group. The four-site (4C) association scheme was used for water [5].

1           The pure component parameters were obtained regressing vapor pressure and liquid  
2 density data collected from the DIPPR database [32], from where the critical properties and  
3 van der Waals volumes were also collected (Table 1). The regression was made in the  
4 reduced temperature range between 0.45 and 0.85, being also required the critical  
5 temperature ( $T_c$ ) and pressure ( $P_c$ ), and the acentric factor ( $\omega$ ), the first to calculate the  $a$   
6 parameter in Eq. (4), while the others were used (simultaneously with  $T_c$ ) to generate initial  
7 estimates of the cubic term parameters. The regressed parameters are presented in Tables 1-  
8 2 together with the water parameters from a previous work [17]. The AAD's found for  
9 liquid density and vapor pressure were 1.7 and 1.8%, respectively, which are good results  
10 since the molecules studied are substantially more complex than those usually modeled by  
11 CPA. In Fig. 2, an example of the parameter fitting to the experimental data is presented for  
12 acetamide and bisphenol. Regressing the cubic parameters with  $T_c^2/P_c$  ( $a_0$ ) and the van der  
13 Waals volume vdWV ( $b$ ), like in previous works [17-18], a perfect linearity was not  
14 obtained, but a correlation could be proposed for each of the parameters. In this way, the  
15 cubic parameters estimated by those correlations were used as first estimates. However, the  
16 results obtained turned out to be the same as without using these values as first estimates.

17           Concerning the association contribution, the association energy and volume for the  
18 different associating groups involved in each molecule are presented in Table 2. No  
19 tendency can be explicitly observed in these pure component parameters, since the  
20 compounds do not pertain to the same family, having different structures and functional  
21 groups in the same molecule.

1           Some of the CPA parameters can be compared with literature values for similar  
2 molecules. In Fig. 3 a comparison is made: the values obtained for acetamide, acetanilide,  
3 paracetamol and piperazine are compared with those presented by Kaarsholm et al. [33] for  
4 primary and secondary amines; vanillin with those of an hydroxyl group in an aromatic ring  
5 in a *ortho* position (in relation to the aldehyde group) [17]; bisphenol A, hydroquinone and  
6 paracetamol hydroxyl with phenol parameters [17]; nicotinic and terephthalic acid to those  
7 of benzoic acid [17]; and the adipic and stearic acids with those published by Oliveira et al.  
8 [16] for fatty acids. In general, the  $\varepsilon$  values are in better agreement than the  $\beta$ .  
9 Discrepancies in the  $\beta$  parameter are expectable, since it depends more strongly on the  
10 overall molecular structure, while the association energy is related to the localized  
11 hydrogen bonding formation. The non-agreement found in  $\varepsilon$  can be related with ring  
12 substitutions that although not forming hydrogen bonds contribute for changing the polar  
13 interactions.

14           Once the CPA pure component parameters are estimated, it is possible to describe  
15 binary mixture properties, in this study, aqueous solubilities. Several works have been  
16 published on the aqueous solubility of the studied compounds at ambient pressure, in the  
17 full liquid range of water, between 273 and 373 K [34-49]. The required pure component  
18 properties for solubility calculations (Eq. (1)) are also presented in Table 1. The fusion  
19 enthalpy for nicotinic and terephthalic acids were not available in the DIPPR tables[32] and  
20 so, they were obtained from the open literature [50-52]. The molar heat capacity is assumed  
21 to be temperature independent, and so the presented values are calculated at 298 K.

1           Aqueous solubility data frequently presents considerable scatter [49]. Whenever  
2 several points are available for each solute at the same temperature, van't Hoff plots [ $\ln(x)$   
3 vs.  $1/T$ ] were analyzed and the outlier points rejected. The correlations of the aqueous  
4 solubility for each compound are presented in Table 3, and they were the basis to estimate  
5 the  $k_{ij}$  and  $\beta_{ij}$ . For piperazine and terephthalic acid, S-type solubility curves were found, and  
6 more than one correlation equation were required.

7           The modeling studies of this work started in a completely predictive way, where  $k_{ij}$   
8 and  $\beta_{ij}$  were set equal to zero. Unfortunately, only in the case of dibenzofuran acceptable  
9 solubility predictions were obtained (AAD = 59%). For all the other compounds, the  
10 deviations were higher than 90%. These deviations are not impressive because these are  
11 complex molecules, with multiple functional groups, that in some cases contain ether,  
12 carbonyl or ester groups that are not explicitly considered by the CPA EoS.

13           In order to obtain a better description of the experimental solubility data, a binary  
14 interaction parameter  $k_{ij}$  is required, and eventually, in the case of implicit cross-associating  
15 systems (where the 2<sup>nd</sup> component is not associating but cross-associates with water), a  
16 solvation parameter  $\beta_{ij}$  is also employed. Camphor, dibenzofuran and hexachlorobenzene  
17 are non-self-associating, but dibenzofuran and hexachlorobenzene are able to cross-  
18 associate with water. So, for these compounds, both  $k_{ij}$  and  $\beta_{ij}$  were estimated  
19 simultaneously. For camphor, a  $\beta_{ij}$  was also estimated ( $k_{ij} = -0.19$  and  $\beta_{ij} = 0.39$ ), but the  
20 correlation results worsen, and the  $\beta_{ij}$  value was too high. The estimated parameters are  
21 presented in Table 4, together with the CPA deviations. An overall good description of the  
22 data was obtained: an average AAD around 39 % was found, with a maximum deviation of

1 68 % for vanillin, where the  $-O-CH_3$  group was not taken into account for associating  
2 interactions. It is important to mention that for ascorbic acid the datasets presented by  
3 Yalkowsky [49] and Shalmashi and Eliassi [46] show differences between 16 and 175%,  
4 proving the inherent complexities to describe such data, and thus supporting the conclusion  
5 that the CPA estimates are much within the limits of the reported data. The good results  
6 found for some compounds under study are presented in Fig. 4. Except for  
7 hexachlorobenzene, all the  $k_{ij}$ 's are negative, indicating that the water-solute interactions  
8 are stronger than described by the model. The data rejected when the van't Hoff plots were  
9 obtained are also plotted. This enables a better understanding about the difficulties to  
10 determine these solubilities not only when modeling, but also for experimental  
11 measurements.

12 To further support the importance of considering the non-ideality of these systems  
13 through the use of the CPA EoS, we have also determined the ideal solubilities, where the  
14 ratio of fugacity coefficients in Eq. (1) is set equal to one. Whenever ideal solution was  
15 considered, extremely bad solubility predictions were obtained, with minimum deviations  
16 of 70%, supporting the importance of the non-ideality on the aqueous solubility estimation.

17 CPA was applied before in the description of aqueous solubilities of much simpler  
18 molecules such as polycyclic aromatic compounds [15], phenolic compounds [17-18],  
19 hydrocarbons [14] and fatty acids [16]. Satisfactory predictions were obtained based on a  
20 single temperature independent binary parameter, with a maximum AAD of 66% for a  
21 phenolic compound and, in the case of polycyclic aromatic compounds in a totally  
22 predictive scheme, in average, below 60%. Wide temperature and pressure ranges were

1 tested, proving the applicability of this EoS. If a comparison is made between these results  
2 and those found in this work for much more complex molecules, it can be concluded that  
3 here good results were found.

4 Comparing the results obtained in this work for paracetamol with those by Mota et  
5 al. [2] with the NRTL-SAC model, it can be seen that the results are of similar quality,  
6 which is very good since NRTL-SAC is a correlative model based in four parameters  
7 estimated from experimental data in a wide set of solvents. Excluding the acetanilide–water  
8 system, for which the results are similar, the correlations found in this work are better than  
9 those found with the NRHB [12-13].

10 If solid-solid transitions occur before fusion, these need to be considered in Eq. (1).  
11 For nicotinic acid, there is a solid–solid transition at 452 K, while its normal melting point  
12 is 510 K [52]. The enthalpy of that transition is not so high (0.8 kJ/mol), but considering it,  
13 the results in the AAD are reduced, from 30% to 29%. As the experimental uncertainties of  
14 both enthalpies of transition are in the same order, even if the improvement in the results is  
15 not so great, it can be said that the model correctly incorporates these solid–solid  
16 transitions.

17 Many pharmaceutical solids and molecular crystals show polymorphism, which is  
18 the ability to exhibit more than one crystalline form, displaying different thermodynamic  
19 properties [53]. In fact, each polymorph should be regarded as a different solid material and  
20 the control of polymorphism provides a way to tune the properties of a product. Some of  
21 the compounds studied in this work were reported to have polymorphic forms. For  
22 example, stearic acid has four polymorphic forms, *A*, *B*, *C* and *E*. Form *C* can be obtained



1 by solidification of the melt and/or by recrystallization from a nonpolar solvent. Forms *A*  
2 and *B* when heated are transformed irreversibly into form *C*, before melting. The thermal  
3 properties of polymorphic forms *B* and *C* were presented by Mirmehrabi and Rohani [54]:  
4 the melting temperature and enthalpy of fusion of form *C* are, respectively, 342 K and 68.3  
5 kJ/mol; while the transition of polymorph *B* to *C* occurs at 322 K with an enthalpy of  
6 transition of 5.7 kJ/mol. Although many solid phase studies on the polymorphism of this  
7 molecule have been reported, no water solubility data of each polymorph is available as a  
8 function of temperature. So, only the effect of the thermal properties on the solubility  
9 calculation could be evaluated, being the results only slightly different. In fact the AAD's  
10 and regressed  $k_{ij}$  values were not changed significantly with respect to the more stable solid  
11 form *C*.

12 To extend the knowledge for other equilibrium calculations, CPA is also used for  
13 estimating water activity in sorbitol + water mixtures at temperatures ranging from 283 to  
14 308 K [55]. Both with prediction and correlation ( $k_{ij} = -0.19$ , the same as for solubility  
15 calculations), very good results were obtained when using CPA to calculate water activities.  
16 In Figure 5 is presented the results at 298 K where AAD of 11 and 7% were found,  
17 respectively for prediction and correlation, and can be seen that estimates are improved  
18 especially at lower solute concentrations.

19

20

21 **4. Conclusions**

1

2           The compounds studied in this work are complex drug-like molecules with different  
3 structures and functional groups, and different abilities to associate. The CPA EoS was  
4 used, for the first time, to model the aqueous solubilities of 18 of these complex molecules  
5 in a wide range of temperatures. The CPA pure compound parameters were estimated  
6 through a simultaneous regression of vapor pressure and liquid density data. The global  
7 deviations in vapor pressures and liquid densities were 1.8% and 1.7%, respectively. The  
8 hydrogen bonding behavior was also explicitly accounted for in the energy and volume  
9 association parameters, with each associating group being treated individually as well as  
10 multiple group substitutions considered in the association term.

11           Once the CPA parameters were obtained, phase behavior calculations could be  
12 made. Pure predictions were inaccurate but if a temperature independent binary interaction  
13 parameter  $k_{ij}$  is estimated from experimental solubility data, the quality of the correlations  
14 improve significantly. For dibenzofuran and hexachlorobenzene a solvation parameter  $\beta_{ij}$ ,  
15 is additionally required. Based on 246 experimental points, a correlation with a global AAD  
16 of 39% was obtained. The CPA EoS is able to represent the solid–liquid equilibrium data of  
17 drug-like molecules, proving the importance of taking into account association effects.

18           Using thermal properties of different polymorphic forms, solubility results showed  
19 quite the same quality and using the same interaction parameter it was possible to represent  
20 simultaneously water activity data in water + sorbitol mixtures.

21

22   **Acknowledgement**

1

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

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7

## 8 **List of symbols**

9  $a$  = energy parameter

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

11  $A$  = Helmholtz energy (J)

12  $b$  = covolume parameter ( $\text{m}^3/\text{mol}$ )

13  $c_1$  = parameter in the cubic term

14  $k_{ij}$  = binary interaction parameter

15  $n$  = number of moles

16  $NP$  = number of data points

17  $P$  = pressure (Pa)

18  $R$  = ideal gas constant ( $8.314 \text{ J}/(\text{mol}\cdot\text{K})$ )

19  $T$  = absolute temperature (K)

- 1  $vdW$  = van der Waals volume ( $m^3/mol$ )
- 2  $x$  = mole fraction
- 3  $X_{A_i}$  = mole fraction of component  $i$  not bonded at site A
- 4
- 5 *Greek symbols*
- 6  $\delta$  = specific parameters in each cubic equations
- 7  $\beta$  = association volume
- 8  $\beta_{ij}$  = solvation parameter
- 9  $\Delta^{AiBj}$  = association strength between site A on molecule  $i$  and site B on molecule  $j$
- 10  $\Delta C_p$  = difference between the heat capacity of the pure liquid and solid (J/mol.K)
- 11  $\Delta_{fus}H$  = fusion enthalpy (J/mol)
- 12  $\varepsilon$  = association energy (J/mol)
- 13  $\rho$  = molar density ( $mol/m^3$ )
- 14  $\varphi$  = fugacity coefficient
- 15
- 16 *Subscripts*
- 17  $0$  = pure component
- 18  $c$  = critical

- 1  $i, j, k$  = component index
- 2  $m$  = melting
- 3  $r$  = reduced
- 4  $s$  = solute
- 5  $tr$  = transition
- 6
- 7 *Superscripts*
- 8  $assoc$  = association term
- 9  $calc$  = calculated
- 10  $cubic$  = cubic term
- 11  $exp$  = experimental
- 12
- 13 *List of abbreviations*
- 14  $AAD$  = absolute average deviation (%), Eq. (9)
- 15  $CPA$  = cubic-plus-association
- 16  $EoS$  = equation of state
- 17  $OF$  = objective function
- 18

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2

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3  
4  
5



1 **Table 1. Pure component properties [32, 50-52], cubic CPA parameters and AAD's**  
 2 **for vapor pressure and liquid densities.**

3

Compound	T <sub>c</sub> (K)	T <sub>m</sub> (K)	Δ <sub>fus</sub> H (kJ/mol)	ΔC <sub>p</sub> (J/mol K)	vdW x 10 <sup>5</sup> (m <sup>3</sup> /mol)	CPA cubic term parameters			AAD (%)	
						a <sub>0</sub> (Pa m <sup>6</sup> /mol <sup>2</sup> )	c <sub>1</sub>	b x 10 <sup>5</sup> (m <sup>3</sup> /mol)	P	ρ
Acetamide	761	354	15.71	51.58	3.57	1.92	0.91	5.54	1.3	2.2
Acetanilide	825	388	21.65	1.92	7.93	4.37	1.17	12.25	3.8	1.9
Acetylsalicylic acid	765	408	25.60	26.55	9.17	4.62	1.48	13.56	0.1	2.3
Adipic acid	809	426	34.85	108.07	8.00	4.80	1.49	12.48	1.3	2.4
Ascorbic acid	783	465	29.20	81.40	8.10	3.79	2.96	11.94	3.4	2.2
Bisphenol A	849	430	29.29	170.22	13.5	6.14	2.19	20.06	2.0	1.2
Camphor	709	452	6.82	92.78	9.69	4.49	0.87	14.64	0.6	0.1
Dibenzofuran	824	355	19.29	39.74	8.66	5.14	0.94	14.28	1.1	1.7
Hexachlorobenzene	825	502	25.52	111.79	10.7	4.84	1.42	14.13	1.3	0.7
Hydroquinone	823	445	27.11	55.19	5.94	2.20	1.27	10.37	3.7	0.7
Ibuprofen	765	349	25.61	149.74	12.8	7.33	1.37	20.47	3.9	2.1
Nicotinic acid	760	510	26.70	32.93	6.27	3.38	1.25	10.33	0.2	1.3
Paracetamol	736	441	27.70	32.14	8.44	3.45	1.76	15.96	0.4	0.5
Piperazine	638	379	11.70	5.24	5.71	2.25	1.29	10.61	0.5	1.6
Stearic acid	804	343	61.21	116.84	19.7	12.22	1.58	33.47	3.2	2.1
Sorbitol	868	365	32.00	28.08	9.58	4.82	2.34	12.72	3.7	2.7
Terephthalic acid	1113	700	63.43	44.23 <sup>a</sup>	8.28	5.16	1.33	10.91	0.7	3.6
Vanillin	777	355	15.60	50.72	8.14	4.12	1.43	12.63	0.3	1.7
Water	647	273	6.00		1.24	0.12	0.67	1.45	1.3	0.6
									1.8	1.7

4

5 <sup>a</sup> Calculated using a group-contribution method for the estimation of the heat capacities of  
 6 liquids [56] and a correlation based on molecular structure for the heat capacity of solids  
 7 [57].

1 **Table 2. Association parameters in the CPA EoS.**

Compound	$\varepsilon$ (kJ/mol)	$\beta$	Group
Acetamide	13.4	$2.99 \times 10^{-3}$	NH <sub>2</sub>
acetanilide	3.74	$1.00 \times 10^{-1}$	NH
Piperazine	3.57	$1.00 \times 10^{-1}$	NH
Acetylsalicylic acid	11.4	$1.68 \times 10^{-4}$	COOH
Adipic acid	18.5	$3.45 \times 10^{-4}$	COOH
Ibuprofen	1.10	$9.61 \times 10^{-4}$	COOH
Nicotinic acid	4.40	$7.33 \times 10^{-3}$	COOH
Stearic acid	42.2	$4.10 \times 10^{-5}$	COOH
Terephthalic acid	35.4	$9.20 \times 10^{-3}$	COOH
Ascorbic acid	14.9	$9.08 \times 10^{-3}$	OH ring
	14.7	$4.10 \times 10^{-5}$	OH aliphatic
Bisphenol A	19.2	$1.54 \times 10^{-3}$	OH
Hydroquinone	19.2	$2.38 \times 10^{-2}$	OH
	18.6	$1.68 \times 10^{-5}$	OH aliphatic
Sorbitol	21.4	$5.54 \times 10^{-3}$	OH terminal
Vanillin	7.82	$3.87 \times 10^{-2}$	OH
	6.45	$5.48 \times 10^{-2}$	NH
Paracetamol	17.9	$2.06 \times 10^{-2}$	OH
Water	16.6	$8.90 \times 10^{-2}$	OH

2

3

1 **Table 3. Correlations of the experimental aqueous solubility data for the compounds**  
 2 **under study:  $\ln(x) = A/T + B$ .**

3

Compound	A	B	R <sup>2</sup>	Refs.
Acetamide	-552.1	0.140	0.989	[49]
Acetanilide	-3232.3	3.703	0.988	[35-36, 42, 45, 49]
Acetylsalicylic acid	-2948.9	2.171	0.994	[49]
Adipic acid	-4800.4	10.303	0.987	[37, 49]
Ascorbic acid	-1773.3	2.240	0.994	[46, 49]
Bisphenol A	-2613.9	-1.598	0.984	[40, 49]
Camphor	-992.2	-5.494	0.941	[49]
Dibenzofuran	-4074.7	-0.817	0.992	[47, 49]
Hexachlorobenzene	-4359.3	-7.185	0.969	[47, 49]
Hydroquinone	-3916.6	8.803	0.987	[41]
Ibuprofen	-3672.4	-1.326	0.952	[38, 49]
Nicotinic acid	-2458.5	2.329	0.982	[48-49]
Paracetamol	-3142.5	4.252	0.983	[35-36, 39, 49]
Piperazine	-3238.2 <sup>a</sup> ; -418.59 <sup>b</sup>	7.532 <sup>a</sup> ; -0.770 <sup>b</sup>	0.953 <sup>a</sup> ; 0.991 <sup>b</sup>	[49]
Stearic acid	-1540.2	-10.296	0.988	[49]
Sorbitol	-537.7	-0.923	1.000	[49]
Terephthalic acid	3961.8 <sup>c</sup> ; -964.6 <sup>d</sup> ; -2458.2 <sup>e</sup>	-25.442 <sup>c</sup> ; -8.616 <sup>d</sup> ; -3.978 <sup>e</sup>	0.983 <sup>c</sup> ; 0.919 <sup>d</sup> ; 0.986 <sup>e</sup>	[34, 49]
Vanillin	-4522.2	8.413	0.965	[43-44, 49]

4

<sup>a</sup> T < 298.15 K.

5

<sup>b</sup> T ≥ 298.15 K.

6

<sup>c</sup> 278.15 < T < 293.15 K.

7

<sup>d</sup> 293.15 ≤ T < 312.15 K.

8

<sup>e</sup> 312.15 ≤ T < 332.15 K.

9

10

1 **Table 4. CPA modeling results and respective binary interaction and cross-volume**  
 2 **parameters.**

3

Compound	$k_{ij}$	$\beta_{ij}$	AAD (%)	RMSD <sup>a</sup>
Acetamide	-0.079	-	44.1	0.24
Acetanilide	-0.099	-	12.9	0.08
Acetylsalicylic acid	-0.151	-	15.8	0.08
Adipic acid	-0.110	-	60.7	0.63
Ascorbic acid	-0.184	-	45.4	0.32
Bisphenol A	-0.111	-	34.8	0.21
Camphor	-0.252	-	19.5	0.10
Dibenzofuran	-0.025	0.001	25.6	0.10
Hexachlorobenzene	0.144	0.014	38.8	0.23
Hydroquinone	-0.209	-	43.2	0.34
Ibuprofen	-0.140	-	18.7	0.10
Nicotinic acid	-0.197	-	35.5	0.17
Paracetamol	-0.210	-	32.8	0.12
Piperazine	-0.248	-	55.8	0.48
Stearic acid	-0.267	-	63.9	0.47
Sorbitol	-0.190	-	34.6	0.23
Terephthalic acid	-0.197	-	52.5	0.53
Vanillin	-0.091	-	68.0	0.25
			39.0	0.26

4 <sup>a</sup>  $RMSD = \sqrt{\frac{\sum_{i=1}^n (\ln x_{i,calc} - \ln x_{i,exp})^2}{n}}$

1 **Figure Captions:**

2

3 **Fig. 1.** Molecular structure of: (a) acetamide, (b) acetanilide, (c) acetylsalicylic acid, (d)  
4 adipic acid, (e) ascorbic acid, (f) bisphenol A, (g) camphor, (h) dibenzofuran, (i)  
5 hexachlorobenzene, (j) hydroquinone, (k) ibuprofen, (l) nicotinic acid, (m) paracetamol, (n)  
6 piperazine, (o) stearic acid, (p) sorbitol, (q) terephthalic acid and (r) vanillin.

7

8 **Fig. 2.** Performance of the CPA EoS in the correlation of (a) liquid density and (b) vapor  
9 pressure of acetamide (●) and bisphenol (▲): —, CPA; ---, DIPPR correlation.

10

11 **Fig. 3.** Comparison between associating parameters obtained for the molecules under study  
12 ( $\Delta$ , acetamide; x, acetanilide; ☆, adipic acid;  $\circ$ , acetylsalicylic acid;  $\circ$ , bisphenol A; +,  
13 hydroquinone; •, ibuprofen; -, nicotinic acid; ◆, paracetamol; ■, piperazine; ▲, stearic  
14 acid; ◇, terephthalic acid; □, vanillin) and similar molecules: (a)  $\varepsilon$  and (b)  $\beta$ . The  
15 superscript \* refers to the same associative group in different molecules.

16

17 **Fig. 4.** Aqueous solubilities of some compounds under study: experimental (•, acetamide;  
18  $\circ$ , acetylsalicylic acid; ◇, bisphenol A; +, camphor; x, dibenzofuran; □, hydroquinone; ▼,  
19 hexachlorobenzene; ◆, nicotinic acid; ■, terephthalic acid) and CPA results (—).

20

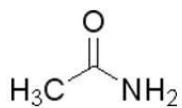
21 **Fig. 5.** Water activity in aqueous sorbitol solutions at 298.15 K (◆, experimental [55]; and  
22 CPA results: ---, prediction; —, correlation).

23

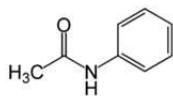
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1 **Figure 1:**

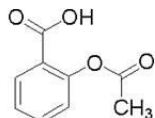
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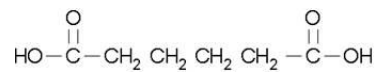
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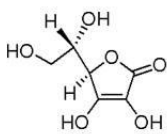
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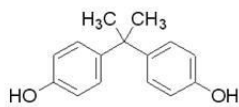
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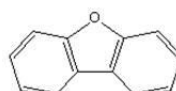
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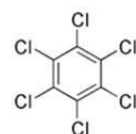
**(f)**



**(g)**



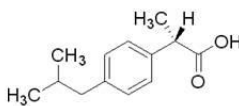
**(h)**



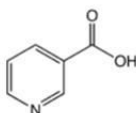
**(i)**



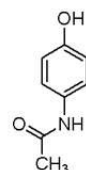
**(j)**



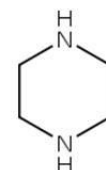
**(k)**



**(l)**



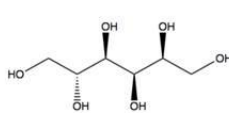
**(m)**



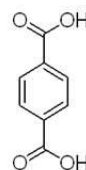
**(n)**



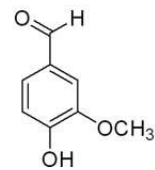
**(o)**



**(p)**



**(q)**

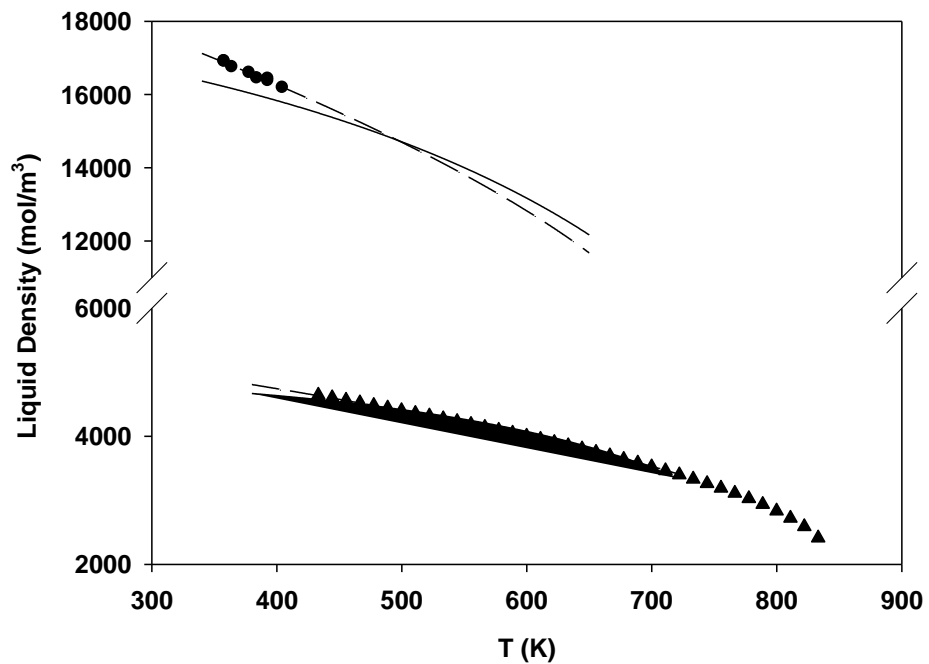


**(r)**

3

1 **Figure 2:**

2 (a)

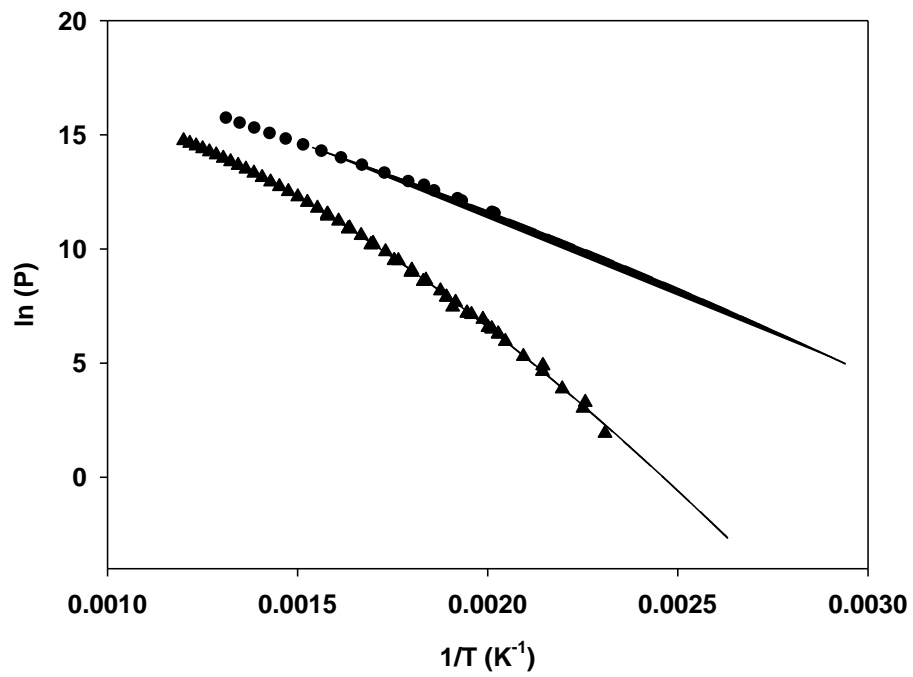


3

4

5

(b)

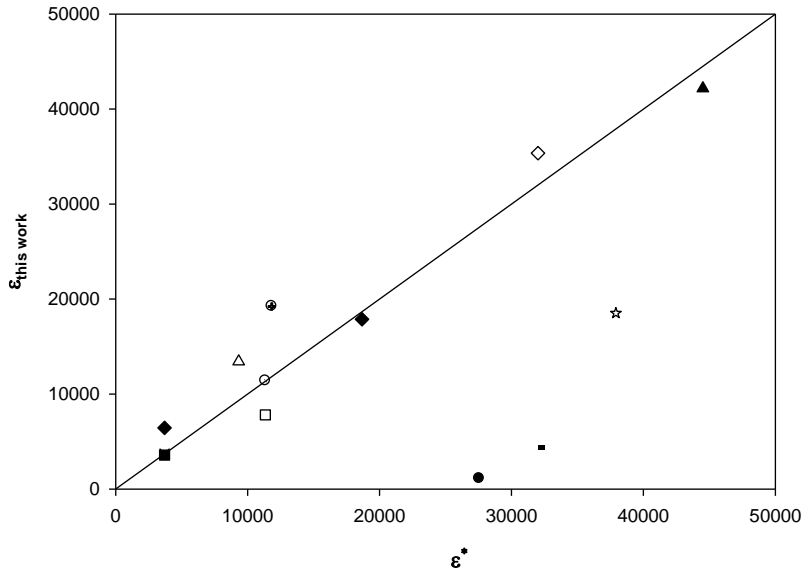


6

7

1

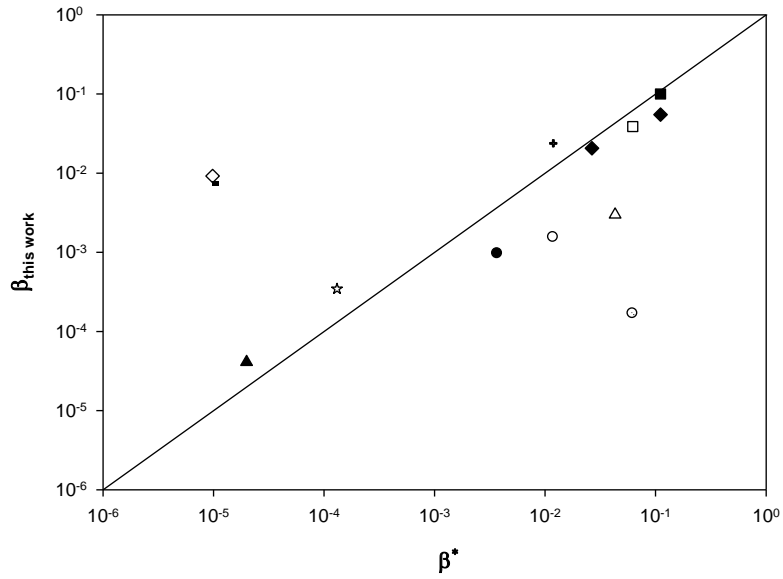
2 **Figure 3:**



3

4

(a)



5

6

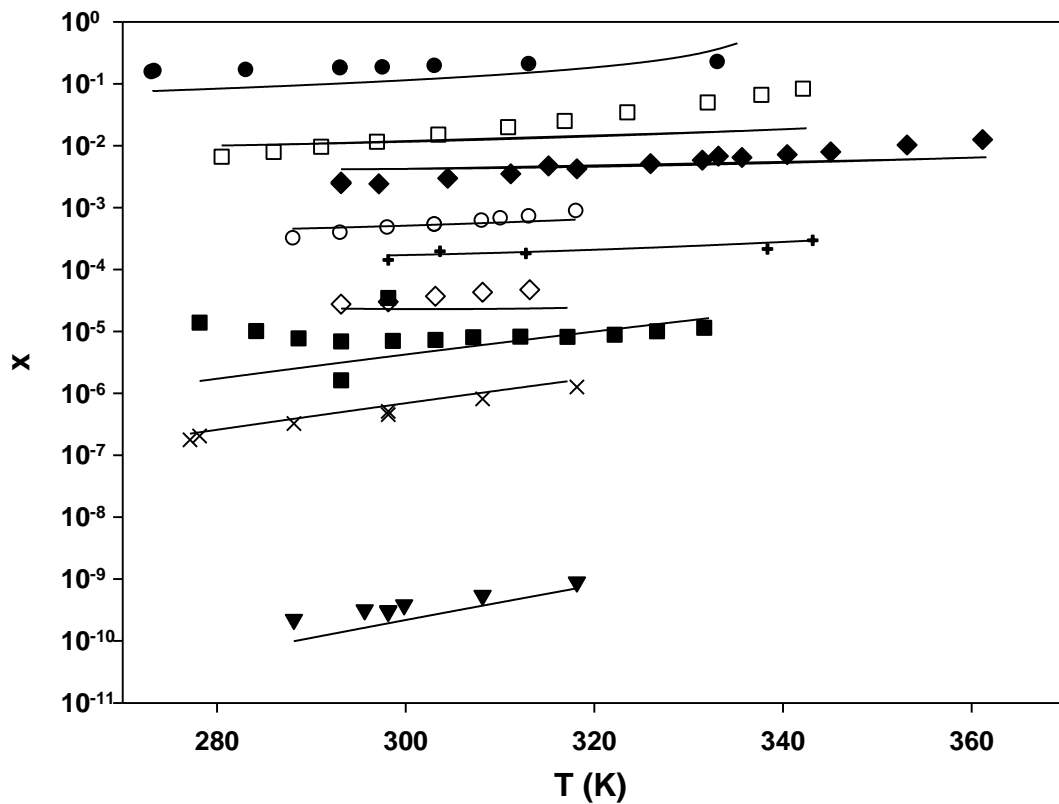
7

(b)



1 **Figure 4:**

2



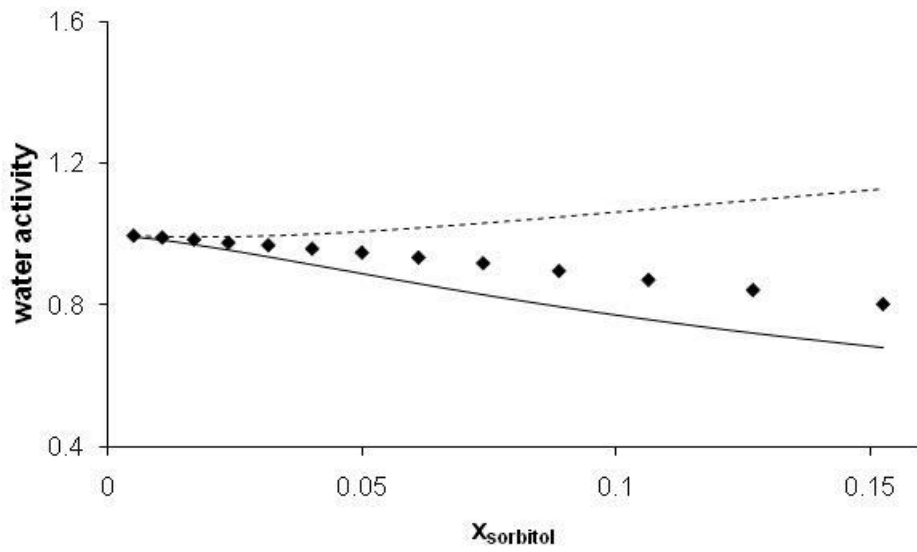
3

4

5

1 **Figure 5:**

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