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Modeling the Solid–Liquid Equilibrium in Pharmaceutical-Solvent Mixtures: Systems with Complex Hydrogen Bonding Behavior

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A methodology is suggested for modeling the phase equilibria of complex chemical mixtures with an equation of state (EoS) for the case where only limited experimental data exist. The complex hydrogen bonding behavior is explicitly accounted for and the corresponding parameters are adopted from simpler molecules of similar chemical structure and/or are fitted to Hansen's partial solubility parameters. The methodology is applied to modeling the solubility of three pharmaceuticals, namely acetanilide, phenacetin, and paracetamol, using the nonrandom hydrogen bonding (NRHB) EoS. In all cases, accurate correlations were obtained. The prediction ability of the approach was evaluated against predictions from the COSMO-RS model. A thorough discussion is made for the appropriate modeling of solid solubility considering the effect of the difference of the heat capacities of the solute in liquid and solid state, $\Delta Cp = Cp_l - Cp_s$, in the determination of solid chemical potential and, also, of the polymorphism of drugs. © 2009 American Institute of Chemical Engineers *AIChE J,* 55: 756–770, 2009
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Introduction

Pharmaceuticals interact with living organisms to produce a desirable change in function. They include organic substances from different families, with different molecular struc-

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tures. Usually, many functional groups are present in these molecules, which render the prediction of their thermodynamic properties a challenging task.

Because of the complexity of pharmaceutical molecules and the variety of their interactions with solvents, mainly empirical or semiempirical models are used for modeling their thermodynamic properties.[1] The most popular predictive approach for modeling their solubility in various solvents is UNIFAC.[1,2] However, the model presents limited success in the prediction of the solubility temperature dependence and for high molecular compounds.[1] In addition, UNIQUAC and NRTL models are often used for solubility correlations. These models provide a good interpolation of experimental data, but they do not give a physical insight to the various solvent–solute interactions.

Because of lack of experimental data and of a reliable predictive model, very often the screening of solvents is performed using Hildebrand's solubility parameters.[1] This is an empirical approach and begins from the rule of thumb that "like dissolves like," which in this case is translated as "good solvents are those with similar solubility parameters to the solute." In this direction, a more sophisticated approach is the extended Hansen's model based on regular solution theory.[3] According to this, the solubility parameter can be expressed as a combination of three parameters that characterize the dispersive, the polar, and the hydrogen bonding interactions, respectively. However, this approach can only give an estimation of the ability of a solvent to dissolve a specific substance. Successful prediction of the solubility and its temperature dependence are often not possible.

Despite the limited success of the extended Hansen's model, which is mainly caused by gross simplifications,[1] the concept of solubility parameter is of much interest. The solubility parameter is defined as the square root of the cohesive energy density.[3] Recently, Stefanis et al. used an equation of state (EoS) model to predict the Hansen's partial solubility parameters for many different solvents, including nonpolar, polar, and hydrogen bonding fluids.[4]

Over the last years, many advanced thermodynamic models were developed based on statistical thermodynamics. Usually, these models are more complex than traditional approaches (e.g., empirical activity coefficient models), but result in significantly more accurate predictions for various mixtures that exhibit highly nonideal behavior, such as hydrogen bonding mixtures.

In this direction, a widely used advanced model is COSMO-RS.[5–7] The main advantage of the model is that it allows prediction of thermodynamic properties using only data from quantum chemical calculations. At the same time, the main limitations of the model are its inability to account for the supercritical state, for high-pressure and high-temperature vapor–liquid equilibrium and for the volume changes in mixing. To overcome these limitations, often the model is coupled with another model, namely a G^E-based EoS. Also, an EoS model partially based on the COSMO method has been proposed.[8,9] Free volume was incorporated by consistently combining the lattice fluid concept with the COSMO approach. It was shown that this approach and the Guggenheim's quasichemical method result in identical equations for the basic thermodynamic properties of pure fluids and mixtures.

Despite the success of other statistical thermodynamic models, such as advanced lattice and SAFT type models, they are not used often for modeling pharmaceuticals, primarily because of the lack of sufficient amount of experimental data. All models of this family use fluid-specific parameters that are usually fitted to pure fluid experimental data. In common fluids, usually experimental vapor pressures and liquid densities are used. However, for the majority of pharmaceutical complex chemicals, such extended experimental data do not exist.

An alternative approach to overcome this obstacle is to use appropriate modifications of the models that incorporate group contribution methods to predict the pure fluid parameters.[10,11] This is not always easy though. Many pharmaceutical molecules have more than one functional group capable to form hydrogen bonds. Subsequently, different types of hydrogen bonds may be formed when the fluid molecules self- or cross associate with the solvent. Parameters for these interactions are not easily obtained with group contribution methods and, subsequently, these methods often fail for complex fluids.

The aim of this study is to overcome these limitations and to suggest a methodology that allows successful modeling of complex chemicals, such as pharmaceuticals, using EoS models. We have used the nonrandom hydrogen bonding (NRHB) model,[12] which is a recent development of previous successful lattice models and showed promising results for the description of phase equilibria of various types of mixtures.[13–15] The complex hydrogen bonding behavior of the studied fluids was explicitly accounted using the flexible approach of the model. We have tried to overcome the difficulty of limited available experimental data using parameters for various hydrogen bonding interactions from simpler but similar molecules and/or optimize them using Hansen's partial solubility parameters. The solubility of acetanilide, paracetamol (acetaminophen), and phenacetin in various solvents was studied. Acetanilide is mainly used as an intermediate in the synthesis of pharmaceuticals.[16] Phenacetin has analgetic and antipyretic effects. It was used until early 1980s and then it was removed from the market because of its side effects.[16] Finally, paracetamol is one of the most common and popular nonsteroidal anti-inflammatory drugs.[16]

Theory

Solubility parameter

The solubility parameter is defined as[3]:

$$\delta = \sqrt{\frac{E_{\text{coh}}}{V}}, \tag{1}$$

where V is the volume of the system and E_{coh} is the cohesive energy, i.e., the increase of the internal energy upon removal of all intermolecular interactions. For the determination of the partial solubility parameters, the cohesive energy is assumed to be the sum of three contributions because of dispersive, E_{d}, polar, E_{p}, and hydrogen bonding, E_{hb}, interactions, respectively:

$$E_{\text{coh}} = E_{\text{d}} + E_{\text{p}} + E_{\text{hb}}. \tag{2}$$

Consequently, the total solubility parameter can be written as a function of the three partial parameters, according to the following expression:

$$\delta = \sqrt{\delta_d^2 + \delta_p^2 + \delta_{hb}^2}, \tag{3}$$

where δ is the total solubility parameter and δ_d, δ_p, and δ_{hb}, the dispersive, the polar, and the hydrogen bonding contribution, respectively. From these definitions, it is clear that the solubility parameter is a well-defined thermodynamic quantity that characterizes pure fluid intermolecular interactions.

The nonrandom hydrogen bonding model

NRHB theory is a compressible lattice model, where holes are used to account for density variation as a result of temperature and pressure changes. NRHB accounts explicitly for the nonrandom distribution of molecular sites, while Veytsman's statistics[17] is used to calculate the contribution of hydrogen bonding to the thermodynamics of the system.[12] Thus, the model is suitable for property calculations of highly nonideal fluids. According to this, N molecules are assumed to be arranged on a quasilattice of N_r sites, N_0 of which are empty, with a lattice coordination number, z. Each molecule of type i in the system occupies r_i sites of the quasilattice. It is characterized by three scaling parameters and one geometric, the surface-to-volume-ratio factor, s. The first two scaling parameters, ε_h^* and ε_s^*, are used for the calculation of the mean interaction energy per molecular segment, ε^*, according to the following equation:

$$\varepsilon^* = \varepsilon_h^* + (T - 298.15)\varepsilon_s^*. \tag{4}$$

Subscripts h and s in Eq. 4 denote an "enthalpic" and an "entropic" contribution to the interaction energy parameter, reminiscent to Flory's χ parameter contributions. The third scaling parameter, $v_{sp,0}^*$, is used for the calculation of the close packed density, $\rho^* = 1/v_{sp}^*$, as described by the following equation:

$$v_{sp}^* = v_{sp,0}^* + (T - 298.15)v_{sp,1}^*. \tag{5}$$

The hard-core volume per segment, v^*, is constant and equal to 9.75 cm^3 mol^{-1} for all fluids. Parameter $v_{sp,1}^*$ in Eq. 5 is treated as a constant for a given homologous series.[12,13] The following relation holds: $r = \mathrm{MW}\, v_{sp}^*/v^*$, where MW stands for molecular weight. Finally, the shape factor is defined as the ratio of molecular surface to molecular volume, $s = zq/zr = q/r$, and is calculated from UNIFAC group contribution method.[18] In case of mixtures, the following mixing and combining rules are used:

$$r = \sum_i x_i r_i \tag{6}$$

$$\varepsilon^* = \sum_{i=1}^{t}\sum_{j=1}^{t} \theta_i \theta_j \varepsilon_{ij}^*, \tag{7}$$

where:

$$\varepsilon_{ij}^* = \sqrt{\varepsilon_i^* \varepsilon_j^*}\left(1 - k_{ij}\right) \tag{8}$$

where t is the number of components, θ is the surface fraction and k_{ij} a binary interaction parameter.

The EoS for a fluid mixture assumes the following form[12]:

$$\tilde{P} + \tilde{T}\left[\ln(1-\tilde{\rho}) - \tilde{\rho}\left(\sum_i \phi_i \frac{l_i}{r_i} - v_{hb}\right) - \frac{z}{2}\ln\left(1 - \tilde{\rho} + \frac{q}{r}\tilde{\rho}\right) + \frac{z}{2}\ln\Gamma_{00}\right] = 0 \tag{9}$$

while the chemical potential for the component i is given by:

$$\frac{\mu_i}{RT} = \ln\frac{\phi_i}{\omega_i r_i} - r_i\sum_j \frac{\phi_j l_j}{r_j} + \ln\tilde{\rho} + r_i(\tilde{v}-1)\ln(1-\tilde{\rho}) - \frac{z}{2}r_i\left[\tilde{v} - 1 + \frac{q_i}{r_i}\right]\ln\left[1 - \tilde{\rho} + \frac{q}{r}\tilde{\rho}\right] + \frac{zq_i}{2}\left[\ln\Gamma_{ii} + \frac{r_i}{q_i}(\tilde{v}-1)\ln\Gamma_{00}\right] + r_i\frac{\tilde{P}\tilde{v}}{\tilde{T}} - \frac{q_i}{\tilde{T}_i} + \frac{\mu_{i,hb}}{RT}, \tag{10}$$

where φ_i is the site fraction of component i. The following relation holds:

$$l_i = \frac{z}{2}(r_i - q_i) - (r_i - 1) \tag{11}$$

while ω_i is a characteristic quantity for each fluid i that takes into account the flexibility and the symmetry of the molecule. This parameter cancels out in all applications of our interest. Parameters Γ_{oo} and Γ_{ii} are nonrandom factors for the distribution of empty sites around an empty site and of molecular segments of component i around a molecular segment of component i, respectively. Finally, parameters $\tilde{T} = T/T^*$, $\tilde{P} = P/P^*$, and $\tilde{v}(= 1/\tilde{\rho} = \rho^*/\rho)$ are the reduced temperature, pressure, and specific volume, respectively. The characteristic temperature, T^*, and pressure, P^*, are related to the mean intersegmental energy by:

$$\varepsilon^* = RT^* = P^* v^* \tag{12}$$

Detailed expressions for the calculation of all these parameters can be found elsewhere.[12] The expression for the chemical potential of a pure component can be obtained from Eq. 10 by setting $\varphi_i = 1$ and the number of components equal to 1.

NRHB can model properties of hydrogen-bonded fluids of any number of donor and acceptor groups. In the following equations, m is the number of proton donor types and n, the number of proton acceptor types that exist in the mixture, whereas d_α^k is the number of donor groups of type α in each molecule of type k and c_β^k the number of acceptor groups of type β in each molecule of type k. $N_{\alpha\beta}^{hb}$ is the total number of hydrogen bonds between a donor of type α and an acceptor of type β in the system.

Parameter v_{hb} is the average number of hydrogen bonds per molecular segment in the system and is given by:

$$v_{hb} = \sum_\alpha^m \sum_\beta^n v_{\alpha\beta} = \sum_\alpha^m \sum_\beta^n \frac{N_{\alpha\beta}^{hb}}{rN} \tag{13}$$

The hydrogen bonding contribution in the chemical potential of component i is given by the expression:

$$\frac{\mu_{i,\mathrm{H}}}{RT} = r_i \nu_{\mathrm{H}} - \sum_{\alpha=1}^{m} d_\alpha^i \ln \frac{\nu_{\mathrm{d}}^\alpha}{\nu_{\alpha 0}} - \sum_{\beta=1}^{n} c_\beta^i \ln \frac{\nu_{\mathrm{c}}^\beta}{\nu_{0\beta}} \tag{14}$$

where the number of donors of type α per molecular segment, ν_{d}^α, is

$$\nu_{\mathrm{d}}^\alpha = \frac{N_{\mathrm{d}}^\alpha}{rN} = \frac{\sum_k d_\alpha^k N_k}{rN}, \tag{15}$$

and the number of acceptors of type β per molecular segment, ν_{c}^β, is

$$\nu_{\mathrm{c}}^\beta = \frac{N_a^\beta}{rN} = \frac{\sum_k c_\beta^k N_k}{rN}; \tag{16}$$

while the number of the unbonded donors of type a per molecular segment, ν_{a0}, is

$$\nu_{\alpha 0} = \nu_{\mathrm{d}}^\alpha - \sum_{\beta=1}^{n} \nu_{\alpha\beta}, \tag{17}$$

and similarly the number of the unbonded acceptors of type β per molecular segment, $\nu_{0\beta}$,

$$\nu_{0\beta} = \nu_{\mathrm{c}}^\beta - \sum_{\alpha=1}^{m} \nu_{\alpha\beta}. \tag{18}$$

According to the model,[12] the $\nu_{\alpha\beta}$'s satisfy the minimization conditions:

$$\frac{\nu_{\alpha\beta}}{\nu_{\alpha 0}\nu_{0\beta}} = \tilde{\rho} \exp\left(\frac{-G_{\alpha\beta}^{\mathrm{hb}}}{RT}\right) \quad \text{for all } (\alpha, \beta). \tag{19}$$

In Eq. 19, $G_{\alpha\beta}^{\mathrm{hb}}$ is the free enthalpy of formation of the hydrogen bond of type α-β and is given in terms of the energy (E), volume (V), and entropy (S) of hydrogen bond formation by the equation:

$$G_{\alpha\beta}^{\mathrm{hb}} = E_{\alpha\beta}^{\mathrm{hb}} + PV_{\alpha\beta}^{\mathrm{hb}} - TS_{\alpha\beta}^{\mathrm{hb}} \tag{20}$$

The formalism is general and sufficient for solving phase equilibrium problems in systems of hydrogen-bonded fluids of any number of donor and acceptor groups.

For associating fluids, NRHB has three more parameters that are the energy, $E_{\alpha\beta}^{\mathrm{hb}}$, the volume, $V_{\alpha\beta}^{\mathrm{hb}}$, and the entropy change, $S_{\alpha\beta}^{hb}$, for the formation of hydrogen bonds between proton donors of type α and proton acceptors of type β in different molecules. However, usually the volume change for the formation of a hydrogen bond, $V_{\alpha\beta}^{\mathrm{hb}}$, is set equal to zero, so the number of hydrogen bonding parameters is reduced to two without compromising the performance of the model.[12]

In the NRHB model, polar and dispersive interactions are not treated separately and are characterized as physical interactions, in contrast to the hydrogen bonding or chemical interactions. Subsequently, it is not possible to estimate the polar or the dispersive partial solubility parameters. However, the partial hydrogen bonding and the total solubility parameter can be directly calculated. The corresponding equation for the cohesive energy is as follows:

$$E_{\mathrm{coh}} = E_{\mathrm{ph}} + E_{\mathrm{hb}} \tag{21}$$

where E_{ph} is the potential energy because of physical (dispersive and polar interactions) and E_{hb} is the contribution because of hydrogen bonding. For pure fluids, these quantities are calculated from the following equations:

$$E_{\mathrm{ph}} = \sum_i N_{ii}\varepsilon_{ii} = \Gamma_{11} q N \Theta_r \varepsilon^* \tag{22}$$

$$E_{\mathrm{hb}} = -\sum_a \sum_\beta N_{a\beta}^{hb} E_{a\beta}^{hb} = -rN \sum_a \sum_\beta \nu_{a\beta} E_{a\beta}^{\mathrm{hb}}, \tag{23}$$

where N_{ii} corresponds to the number of intersegmental interactions, Θ_r is the surface (contact) fraction of molecular segments with respect to the total segments (empty and occupied) of lattice, ε^* denotes the average intersegmental interaction energy, $N_{\alpha\beta}^{\mathrm{hb}}$ is the number of hydrogen bonds of type α-β in the system, while $\nu_{\alpha\beta}$ is the number of hydrogen bonds of type α-β per molecular segment, and $E_{\alpha\beta}^{\mathrm{hb}}$ is the energy change upon the formation of a hydrogen bond of the same type. The volume of the system is given by:

$$V = rN\,\tilde{v}\,v^* + \sum_a \sum_\beta N_{a\beta}^{\mathrm{hb}} V_{a\beta}^{\mathrm{hb}} \tag{24}$$

As it was mentioned earlier, usually the volume change for the formation of a hydrogen bond, $V_{\alpha\beta}^{\mathrm{hb}}$, is set equal to zero. With the above definitions, the total and partial hydrogen bonding solubility parameters are as follows:

$$\delta = \sqrt{\frac{E_{\mathrm{coh}}}{V}} = \sqrt{\frac{\Gamma_{11} q \Theta_r \varepsilon^* - r \sum_a \sum_\beta \nu_{a\beta} E_{a\beta}^{\mathrm{hb}}}{r\tilde{v}\,v^*}} \tag{25}$$

and

$$\delta_{\mathrm{hb}} = \sqrt{\frac{E_{\mathrm{hb}}}{V}} = \sqrt{\frac{-r \sum_a \sum_\beta \nu_{a\beta} E_{a\beta}^{\mathrm{hb}}}{r\tilde{v}\,v^*}}. \tag{26}$$

Solid–liquid equilibrium calculations

All the investigated pharmaceuticals of this study are crystalline solids at ambient conditions and exhibit solid–liquid equilibrium (SLE) with various liquid solvents. In SLE, the chemical potential of the solute in the liquid phase is equal to that in the crystalline solid phase:

$$\mu_2^{\mathrm{l}}(T,P) = \mu_2^{\mathrm{s}}(T,P) \tag{27}$$

where subscript 2 stands for the solute (here is the pharmaceutical species), whereas superscripts l and s refer to liquid and solid, respectively. If we make the rather accurate assumption that we have pure solute in the solid phase, this equation becomes:

$$\mu_2^{\mathrm{l}}(T,P) = \mu_{02}^{\mathrm{s}}(T,P) \tag{28}$$

where subscript 0 stands for the pure component. If as a reference state we select the pure subcooled liquid solute at the same temperature, T, and pressure, P, the previous equation becomes:

$$\mu_2^{\mathrm{l}}(T,P) - \mu_{02}^{\mathrm{l}}(T,P) = \mu_{02}^{\mathrm{s}}(T,P) - \mu_{02}^{\mathrm{l}}(T,P) = -\Delta G_{\mathrm{s-l}} \tag{29}$$

In the latter, $\Delta G_{\mathrm{s\text{-}l}}$ is the Gibbs free energy difference of pure solute converted from crystalline solid to subcooled liquid in the same temperature, T, and pressure, P. If we assume that the volume does not change with small changes in temperature and pressure (υ_{s}, υ_{L} constant) and that the triple point is very close to the normal melting point, then[19]:

$$\Delta G_{\mathrm{s-l}} = \Delta H_{\mathrm{s-l}} - T\Delta S_{\mathrm{s-l}} \tag{30}$$

$$\frac{\Delta G_{\mathrm{s-l}}}{RT} = \frac{\upsilon_{\mathrm{l}} - \upsilon_{\mathrm{s}}}{RT}(P - P_{\mathrm{tr}}) + \frac{\Delta H_{\mathrm{m}}}{RT_{\mathrm{m}}}\left(\frac{T_{\mathrm{m}}}{T} - 1\right) + \frac{1}{RT}\int_{T_{\mathrm{m}}}^{T}(\mathrm{Cp_l} - \mathrm{Cp_s})dT - \frac{1}{R}\int_{T_{\mathrm{m}}}^{T}\frac{\mathrm{Cp_l} - \mathrm{Cp_s}}{T}dT \tag{31}$$

where υ stands for the molar volume, ΔH_{m} and T_{m} are the fusion enthalpy and temperature, respectively, while $C\mathrm{p}$ is the isobaric heat capacity. For small pressure values, the first term of the right-hand side of the previous equation is negligible. According to Prausnitz at al., the second term is dominant, whereas the third and fourth terms have opposite signs and a tendency to cancel each other, approximately.[20] Consequently, usually in phase equilibrium calculations, the following approximate relation is used:

$$\frac{\Delta G_{\mathrm{s-l}}}{RT} = \frac{\Delta H_{\mathrm{m}}}{RT_{\mathrm{m}}}\left(\frac{T_{\mathrm{m}}}{T} - 1\right) \tag{32}$$

The use of the previous relation is equivalent with the consideration that the difference of the heat capacities, $\Delta C\mathrm{p} = C\mathrm{p_l} - C\mathrm{p_s}$, of the solute in liquid and solid state is zero.

Estimation of Pure Fluid Parameters

For the application of most EoS models, such as the NRHB model, the hydrogen bonding parameters are optimized using pure fluid properties. For common fluids, such as alkanols or amines, vapor pressures and liquid densities are often used.[14,15] However, for most pharmaceuticals, extended experimental data do not exist. In addition, there is another difficulty. According to the NRHB model, but also to other thermodynamic theories such as the SAFT type models, the association energy, E^{hb}, is in excess to the average van der Waals interaction energy, ε^*. Subsequently, in the absence of extended data for component fluid properties, the estimation of both physical and associating parameters is not trivial: Often there are many different sets of parameter values for E^{hb} and ε^* that can describe in an accurate way the pure fluid properties, but not all of them can be used for the successful calculation of mixture properties.

The best way to overcome this difficulty is to determine the association energy from specific experimental data, i.e., spectroscopic or calorimetric. However, such data are not always available. Panayiotou and co-workers suggested that the association energy could be estimated using data for the partial hydrogen bonding parameter.[4,21,22] An obstacle to this approach is that usually these data are based on solubility measurements and often very different values for the same fluid are reported in the literature. However, some of them are based on experimental methods, such as inverse gas chromatography, or on accurate molecular simulations.

In this work, we evaluate this suggestion for complex chemicals, for which extensive experimental data do not exist. The partial hydrogen bonding and the total solubility parameters (δ_{hb} and δ_{tot}, respectively) are used for the regression of pure fluid parameters. In addition, we claim that hydrogen bonding parameters can be adopted from simpler, but similar molecules. For example, the parameters for the $>$ NH .... NH $<$ hydrogen bonding interaction in paracetamol (Figure 1c) can be based on *N*-methyl aniline (Figure 1a), which is a simpler molecule, and extensive experimental data for pure fluid properties are available.

According to the suggested methodology, the hydrogen bonding behavior of fluids is explicitly accounted for. In molecules with many functional groups, this approach is

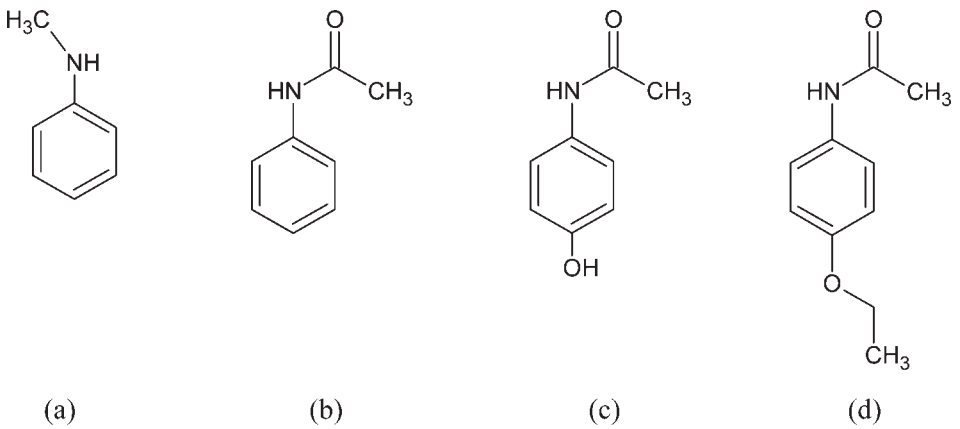

Figure 1. Molecular structure of: (a) *N*-methyl aniline, (b) acetanilide, (c) paracetamol, and (d) phenacetin.

Table 1. Summary of the Procedure used to Estimate the Pure Fluid Parameters for the Studied Pharmaceuticals

		N-methyl aniline	Acetanilide	Paracetamol	Phenacetin
		Physical parameters: ε_h*, ε_s*, and $v_{sp,0}$*			
		Regressed	Regressed	Regressed	Regressed
		Parameters for hydrogen bonding interactions: $E^{hb}_{\alpha\beta}$ and $S^{hb}_{\alpha\beta}$			
Hydrogen bonding interactions	—OH...OH—	–	–	Adopted from alkanols	–
	>NH...NH<	Regressed	Adopted from *N*-methyl aniline	Adopted from *N*-methyl aniline	Adopted from *N*-methyl aniline
	>NH...OH—	–	–	Regressed	–
	—OH...O=C<	–	–	Adopted from methanol–acetone VLE	–
	>NH...O=C<	–	Regressed	Adopted from acetanilide	Adopted from acetanilide
	>NH...—O—	–	–	–	Regressed

more complicated than the consideration of equivalent sites, but, in this way, molecules are modeled in a more physically correct way and many times there is no need for combining rules in binary mixtures. A detailed discussion on this is presented later in this article.

All of the pharmaceuticals examined here, i.e., acetanilide, phenacetin, and paracetamol, have more than one functional groups, which are able to form various types of hydrogen bonds. Their molecular structure is shown in Figure 1, while the types of self-associating interactions for each molecule and a schematic summary of the procedure used to estimate the various pure fluid parameters is presented in Table 1.

By adopting the suggested methodology, the pure fluid parameters of *N*-methyl aniline were estimated using vapor pressures and saturated liquid densities from the DIPRR compilation (based on extended experimental data).[23] Also, we used the partial hydrogen bonding and the total solubility parameter, which were predicted using van Krevelen's group contribution method.[24]

For the modeling of acetanilide, the previously estimated (from *N*-methyl aniline) parameters for the > NH....NH < hydrogen bonding interactions were used. The remaining pure fluid parameters were estimated using experimental data on sublimation pressures,[16] liquid densities (from DIPPR compilation based on limited available experimental data[23]), and partial hydrogen bonding and total solubility parameters, which were predicted using van Krevelen's group contribution method.[24] Subsequently, five parameters were simultaneously regressed for acetanilide: three physical (ε_h*, ε_s*, and $v_{sp,0}$*) and two hydrogen bonding ones (E^{hb}, S^{hb}) ones for the > NH....O=C < interaction (see Table 1).

For the modeling of paracetamol, the previously estimated parameters for the > NH....NH < and > NH....O=C < interactions were used. Furthermore, parameters for the —OH....OH— hydrogen bonding interaction were adopted from alkanols,[14] whereas the parameters for the —OH....O = C < interaction were adopted from previous VLE calculations for the methanol–acetone mixture.[14] Subsequently, again five parameters were simultaneously regressed: three physical (ε_h*, ε_s*, and $v_{sp,0}$*) and two hydrogen bonding ones (E^{hb}, S^{hb}) for the > NH....OH— interaction. The regression was performed using limited available experimental data on sublimation pressures,[16] predicted liquid densities (DIPPR compilation[23]), and partial hydrogen bonding and total solubility parameters, which were predicted using van Krevelen's group contribution method.[24]

Finally, in phenacetin the previously estimated parameters for the > NH.... NH< and >NH....O = C < interactions were used. Subsequently, again five parameters were (simultaneously) regressed: three physical (ε_h*, ε_s*, and $v_{sp,0}$*) and two hydrogen bonding (E^{hb}, S^{hb}) for the > NH.... —O— interaction. The regression was performed using limited available experimental data on sublimation pressures,[16] one liquid density datum predicted using a group contribution method[25] and partial hydrogen bonding and total solubility parameters predicted using van Krevelen's group contribution method.[24]

For the correlation of sublimation pressures, SLE calculations were performed using Eq. 31 for the evaluation of chemical potential in the solid state. The adopted values for the fusion properties are presented in Table 2. The experimental/predicted and the calculated by the model solubility parameters are presented in Table 3. The three optimized physical parame-

Table 2. Melting Temperature, Enthalpy of Fusion, and Heat Capacities in Liquid and Solid State for the Three Pharmaceuticals

Pharmaceutical	T_m (K)	ΔH_f (J mol^{-1})	Cp^l (J mol^{-1} K^{-1})	Cp^s (J mol^{-1} K^{-1})
Acetanilide	386.1*	21,200*	232.4†	208.9†
Phenacetine	407.2*	31,300*	268.1*	337.5‡
Paracetamol	443.6*	27,100*	366.3§	267.4§

*Experimental.[16]
†DIPPR correlation.[23]
‡Predicted using van Krevelen's group contribution method.[24]
§Experimental.[26]

Table 3. Partial Hydrogen Bonding and Total Solubility Parameters for Pure Compounds

	δ_{hb} (MPa$^{1/2}$)		δ_{total} (MPa$^{1/2}$)	
Compound	Literature (Experimental or Predicted)	NRHB	Literature (Experimental or Predicted)	NRHB
N-methyl-aniline	5.3*	5.4	19.3*	21.5
Acetanilide	6.5*/7.9†	6.5	21.3*/20.8†/24.8‡	24.3
Phenacetine	6.8*	6.8	18.8*/23.6‡	23.1
Paracetamol	13.9*/13.9†	13.9	24.8*/24.9†	25.5

*Predicted using van Krevelen's group contribution method.[24]
†Calculated.[3]
‡Experimental.[27,28]

Table 4. Pure Component Scaling Parameters, Percentage Average Absolute Deviation (%AAD) Between Experimental (or Predicted) Data and NRHB Correlation and Temperature Range for Parameter Regression

Component	ε_h^* (J mol^{-1})	ε_s^* (J mol^{-1}K^{-1})	$v_{sp,0}^*$ (cm^3 g^{-1})	s	% AAD in P^s	%AAD in ρ^{liq}	T/K	Ref
N-Methyl-aniline	6102.9	0.5593	0.9365	0.758	0.8	4.8	350.0–680.0	This work
Acetanilide	7243.2	1.9411	0.8955	0.780	2.6		290.0–330.0	This work
						0.7	390.0–490.0	
Phenacetin	6246.3	−0.5539	0.9333	0.827	0.7		328.0–373.0	This work
						0.4	298.0	
Paracetamol	6448.9	2.59442	1.1065	0.766	1.4		353.0–428.0	This work
						1.7	440.0–554.0	
Benzene	5148.5	−0.2889	1.06697	0.753	1.7	0.5	292.2–547.5	13
Toluene	5097.2	0.0768	1.06205	0.757	1.5	1.1	289.9–577.3	13
Methanol	4202.3	1.5269	1.15899	0.941	2.2	2.6	265.9–499.3	14
Ethanol	4378.5	0.7510	1.15867	0.903	1.8	1.1	278.4–499.9	14
1-Propanol	4425.6	0.8724	1.13923	0.881	0.2	0.6	295.6–521.8	14
2-Propanol	4103.8	0.9568	1.12381	0.881	0.7	0.5	283.1–499.3	14
1-Butanol	4463.1	1.1911	1.13403	0.867	0.2	0.5	311.6–547.3	14
1-Octanol	4532.1	1.8686	1.12094	0.839	1.2	0.5	370.5–633.7	14
Water	5336.5	−6.5057	0.97034	0.861	1.3	2.0	298.4–646.0	14
Dioxane	5590.6	−0.9959	0.91749	0.768	1.3	0.8	297.8–541.1	14
Acetone	4909.0	−1.1500	1.14300	0.908	1.4	0.9	249.9–495.7	14
Acetonitrile	6055.0	−1.7559	1.31150	0.922	1.1	5.0	263.1–521.9	14
CO_2	3468.4	−4.5855	0.79641	0.909	1.0	1.7	218.0–301.0	13

P^s and ρ^{liq} stand for vapor pressure and liquid densities, respectively.

% AAD $= \frac{1}{n}\sum_i \left|\frac{X_i^{cal} - X_i^{exp}}{X_i^{exp}}\right| \times 100$ where X stands for P^s or ρ^{liq} and n is the number of experimental data points.

ters and the shape factor s (calculated from UNIFAC group contribution method[29]) for all fluids are presented in Table 4. Finally, the hydrogen bonding sites for each functional group and the parameters for the various hydrogen bonding interactions are shown in Tables 5 and 6, respectively.

Parameter $v_{sp,1}^*$ that is used in Eq. 5 is a characteristic parameter of a given homologous series. As previously,[12,14] it was set equal to -0.412×10^{-3} cm^3 g^{-1} K^{-1} for nonaromatic hydrocarbons, -0.310×10^{-3} cm^3 g^{-1} K^{-1} for alcohols, -0.300×10^{-3} cm^3 g^{-1} K^{-1} for water, and 0.150×10^{-3} cm^3 g^{-1} K^{-1} for all the other fluids.

Binary Mixtures

The pure component parameters of Table 4 were used for the calculation of mixture phase equilibria. Parameters for the various solvents were adopted from the literature. Hydrogen bonding was explicitly accounted for and parameters for the various types of self- and cross association are presented in Table 6. When possible, the estimated hydrogen bonding parameters for solute's self-association were also used for the cross hydrogen bonding interactions with solvent molecules. For example, the parameters for the self-associating interactions of type > NH .... OH— of paracetamol were also used to describe the cross associating interactions between paracetamol and alkanols. In some cases, for which no parameters were available, they were taken from previous studies (for example parameters for HOH ....O = C < were taken from Grenner et al. and were based on VLE data for water–cyclohexanone mixture[14]). When no available parameters existed in the literature, appropriate combining rules were used. The following combining rules were used for the cross interaction between two self-associating groups[14]:

$$E_{\alpha\beta}^{hb} = \frac{E_{aa}^{hb} + E_{\beta\beta}^{hb}}{2} \tag{33}$$

$$S_{\alpha\beta}^{hb} = \left(\frac{S_{\alpha\alpha}^{hb^{1/3}} + S_{\beta\beta}^{hb^{1/3}}}{2}\right)^3 \tag{34}$$

while, for the cross interaction between one self- and one nonassociating group, the combining rules were[14]:

$$E_{\alpha\beta}^{hb} = \frac{E_{aa}^{hb}}{2} \tag{35}$$

$$S_{\alpha\beta}^{hb} = \frac{S_{aa}^{hb}}{2}. \tag{36}$$

The investigated pharmaceuticals are in solid crystalline phase at ambient temperature and have relatively high melting points. Subsequently, in all cases solid–liquid calculations were performed assuming pure pharmaceutical in the solid phase. In all cases, Eq. 31 was used for the calculation of the chemical potential of the solid solute. All calculations were performed using the fusion properties of Table 2, while the difference of the heat capacities, $\Delta Cp = Cp_l - Cp_s$, of liquid and solid solute was assumed temperature independent and equal to the difference in the melting point. Summarized results are presented in Table 7.

Table 5. Hydrogen Bonding (HB) Sites in Each Functional Group

	HB Sites	
Group	Proton Donors	Proton Acceptors
−OH	1	1
>NH	1	1
>C=O (in pharmaceuticals)	0	1
>C=O (in acetone)	0	2
−O−	0	2
HOH	2	2
−CN	0	2

Table 6. Parameters for Hydrogen Bonding (HB) Interactions

HB Groups	E^{hb} (J mol^{-1})	S^{hb} (J mol^{-1} K^{-1})	Adopted From
−OH. . . .OH−*	−24,000	−27.50	Alkanols[14]
>NH. . . .NH<	−8500	−10.25	*N*-methyl-aniline (this work)
>NH. . . .OH−	−18,100	−16.00	Paracetamol (this work)
−OH. . . .O=C<	−16,868	−13.25	Acetone–methanol VLE[14]
>NH. . . .O=C<	−9176	−6.94	Acetanilide (this work)
>NH. . . .−O−	−10,900	−6.90	Phenacetin (this work)
HOH. . .HOH	−16,100	−14.70	Water[14]
HOH. . . .OH−	Combining rule (Eq. 33)	Combining rule (Eq. 34)	
HOH. . . .NH<	Combining rule (Eq. 33)	Combining rule (Eq. 34)	
HOH. . . .O=C<	−13,412	−7.35	Water–cyclohexanone VLE[14]
HOH. . . .−O−	Combining rule (Eq. 35)	Combining rule (Eq. 36)	
−OH. . . .−O−	−10,943	−13.75	Ethanol–diethylether VLE[14]
−OH. . . .NC−	−11,466	−13.75	Ethanol–acetonitrile VLE[14]
>NH. . . .NC−	Combining rule (Eq. 35)	Combining rule (Eq. 36)	

*For methanol self-association[14] $E^{hb} = -25100$ J mol^{-1}, $S^{hb} = -26.5$ J mol^{-1} K^{-1}.

The solubility of acetanilide, phenacetine, and paracetamol in water is shown in Figure 2. Crystalline phenacetine has the highest fusion enthalpy among the examined pharmaceuticals (see Table 2) and, consequently, presents the lowest solubility in water. Its solubility is, approximately, one order of magnitude lower than the solubility of paracetamol and acetanilide. Paracetamol is the most soluble substance, despite the high fusion enthalpy of its crystalline form. The higher solubility is, mainly, due to the strong hydrogen bonding interaction between the hydroxyl group of paracetamol and water. As shown in Figure 2, model's predictions and correlations for water–acetanilide and water–phenacetin mixtures are very satisfactory. On the contrary, predictions are less accurate for paracetamol–water mixture, while the correlation does not accurately describe the temperature dependence of the solubility. Considering that the difference in the molecular structure of acetanilide and paracetamol is only the existence of one hydroxyl group in the latter molecule, the fail-

Table 7. Average Absolute Deviation (AAD) of the Calculated Mole Fractions of Pharmaceuticals Using Different Approaches

		Hydrogen Bonding Explicitly Accounted						Equivalent Hydrogen Bonding Sites in Solute		
		$\Delta Cp = \Delta Cp_m$			$\Delta Cp = 0$			$\Delta Cp = \Delta Cp_m$		
		Prediction	Correlation		Prediction	Correlation		Prediction	Correlation	
System		AAD in x_2	k_{ij}	AAD in x_2	AAD in x_2	k_{ij}	AAD in x_2	AAD in x_2	k_{ij}	AAD in x_2
Paracetamol										
Methanol–paracetamol*	268.15–303.15	0.564	−0.01609	0.007	0.880	−0.04904	0.064	0.076	−0.00200	0.014
Ethanol–paracetamol*	268.15–303.15	0.169	0.00333	0.015	0.667	−0.02536	0.087	0.161	0.00349	0.030
1-Propanol–paracetamol*	268.15–303.15	0.441	0.0074	0.031	0.573	−0.01742	0.097	0.417	0.00764	0.044
2-Propanol–paracetamol*	268.15–303.15	0.128	−0.00266	0.053	0.742	−0.02881	0.079	0.087	−0.00164	0.066
1-Butanol–paracetamol*	268.15–303.15	0.470	0.00759	0.028	0.555	−0.01612	0.111	0.429	0.00753	0.042
1-Octanol–paracetamol†	298.15–313.15	0.716	0.01154	0.042	0.243	−0.00553	0.019	0.541	0.00967	0.049
Water–paracetamol*	273.15–303.15	0.840	−0.027	0.130	0.958	−0.05018	0.031	0.333	−0.00500	0.129
Acetone–paracetamol*	268.15–303.15	0.078	−0.01775	0.007	0.730	−0.04032	0.171	0.975	−0.04500	0.270
Acetonitrile–paracetamol*	268.15–303.15	0.362	−0.0047	0.159	0.847	−0.02173	0.343	0.457	−0.00714	0.160
Toluene–paracetamol*	273.15–298.15	0.432	−0.00763	0.319	0.817	−0.02431	0.421	0.778	−0.02600	0.319
Total		0.420		0.079	0.701		0.142	0.425		0.112
Acetanilide										
Water–acetanilide‡	298.00–313.00	0.052	0.00035	0.051	0.091	−0.0001	0.087	0.558	−0.01821	0.039
1-Octanol–acetanilide†	298.15–313.15	0.333	0.00902	0.058	0.192	0.00544	0.061	0.580	−0.02171	0.068
Chloroform–acetanilide†	298.15–313.15	0.805	−0.0367	0.015	0.826	−0.04	0.014	0.701	−0.03025	0.017
Total		0.396		0.041	0.370		0.054	0.613		0.041
Phenacetin										
Water–phenacetin§	293.00–313.00	0.239	−0.00467	0.027	0.436	−0.01	0.052	0.114	0.00123	0.072
1-Octanol–phenacetin†	298.15–313.15	1.115	0.01489	0.010	0.447	0.00729	0.026	0.467	0.00751	0.017
Chloroform–phenacetin†	298.15–313.15	0.667	−0.0156	0.040	0.802	−0.02438	0.062	0.410	−0.00841	0.043
Total		0.674		0.025	0.562		0.047	0.330		0.044
Grand total		0.456		0.050	0.613		0.108	0.443		0.086

Experimental data:
*Granberg and Rasmuson.[30]
†Baena et al.[31]
‡Bustamante et al.[32]
§Bustamante and Bustamante.[33]
AAD = $\frac{1}{n}\sum_i \left|\frac{X_i^{cal} - X_i^{exp}}{X_i^{exp}}\right|$ where X stands for solubility (in mole fraction) and n is the number of experimental data points.

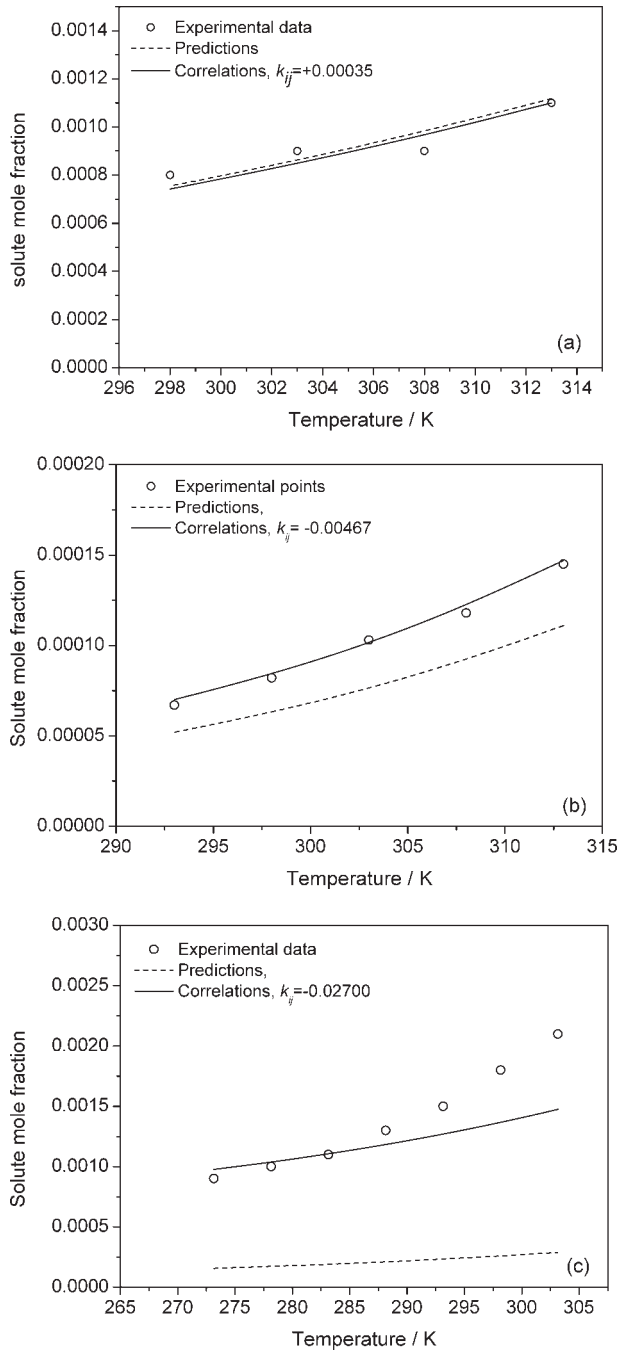

Figure 2. Solubility of (a) acetanilide, (b) phenacetin, and (c) paracetamol in water.

Experimental data, NRHB predictions, and correlations.

ure in the description of the solubility could be attributed to the parameters that were used to describe the interaction of water with paracetamol's hydroxyl group. These parameters were estimated using the combining rules of Eqs. 33 and 34.

As shown in Table 7 for various solvents, in most cases very satisfactory correlations were obtained using one temperature-independent binary interaction parameter, k_{ij}. Furthermore, predictions (k_{ij} = 0.0) were satisfactory for most of the examined mixtures, considering also the complexity of the investigated systems. The lower deviations of model's predictions from experimental data were obtained for 2-propanol–paracetamol and acetone–paracetamol systems. On the other hand, predictions for the chloroform–phenacetin and chloroform–acetanilide mixtures present high deviations from experimental data. This is expected because in these systems the cross association between chloroform and pharmaceuticals was not accounted for. In general, there is no difficulty to consider that chloroform has proton donor sites. However, the estimation of hydrogen bonding parameters for the cross associating interactions is not trivial, mainly, because no combining rule can be used for chloroform's interactions with pharmaceutical groups that have only proton acceptor sites (such as O=C < and —O—).

The aim of this study is to present a methodology to model complex chemicals in cases that only limited experimental data exist. For this reason, the same parameters were used for all molecules to characterize the interaction between the same hydrogen bonding groups. However, this is only an approximation. For example, the > NH....O=C < interaction between two paracetamol molecules is expected to be less strong than the > NH....O=C < interaction between one molecule of acetone and one molecule of paracetamol mainly because of the strong proton accepting ability of acetone and the corresponding intramolecular interactions of paracetamol. To investigate how reasonable are the values of the hydrogen bonding parameters in such approximation, the binding energy for some hydrogen bonding interactions was compared with available data from quantum chemical calculations.

Danten et al. performed density functional theory calculations to obtain the infrared absorption spectra of paracetamol complexes with ethanol and acetone.[34] On the basis of different computational levels, they estimated the binding energies between ethanol's hydroxyl and acetone's carbonyl oxygen with paracetamol functional groups (—OH, >NH, and >C=O). The calculated binding energies and the corresponding NRHB parameters that were used in this study are presented in Table 8.

The interaction energy for the ethanol...HO— association is very close to the parameter that NRHB uses for alkanols[14] and was used in this study for all hydrogen bonding interactions between hydroxyl groups. Also, the interaction energy for ethanol....NH< association is in good agreement with the parameter estimated in this work using the partial hydrogen bonding solubility parameter of paracetamol. On the other hand, the association energy for the ethanol...O=C< interaction is higher than the parameter that was used in this work to characterize all —OH....O=C < interactions. The

Table 8. Association Energies for Ethanol and Acetone Hydrogen Bonding Interactions with Paracetamol

	E^{hb} (J mol^{-1})	
Interaction	Quantum Chemistry Calculations[34]	This Work
Ethanol....HO— (Paracetamol)	25,540–29,308	24,000
Ethanol....NH< (paracetamol)	18,422–19,259	18,100
Ethanol....O=C< (Paracetamol)	23,027–24,283	16,868
Acetone....HO— (Paracetamol)	28,470–29,308	16,868
Acetone....HN< (paracetamol)	17,166–17,585	9,176

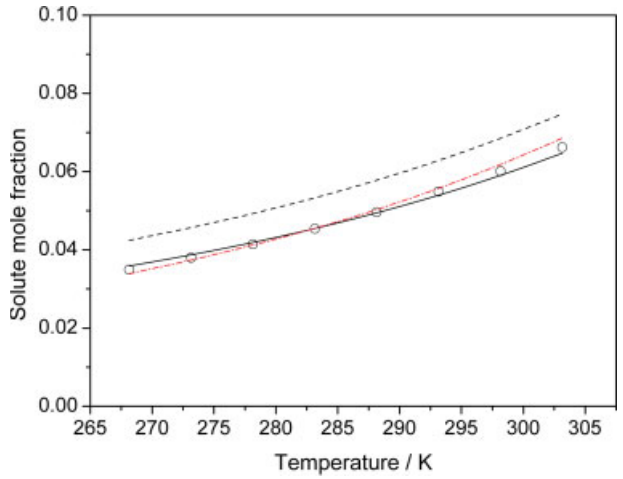

Figure 3. Solubility of paracetamol in ethanol.

Experimental data (o) and NRHB calculations using different parameters for ethanol...O=C< interactions. Predictions (----, $k_{ij} = 0$) and correlations (—, $k_{ij} = 0.00333$) using $E^{hb} = -16868$ J mol^{-1} and $S^{hb} = -13.25$ J mol^{-1} K^{-1}. Correlations (-·-·-, $k_{ij} = 0$) using $E^{hb} = -23{,}655$ J mol^{-1} and $S^{hb} = -34.0$ J mol^{-1} K^{-1}. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

latter parameter was adopted from Grenner et al. and was estimated using VLE data for acetone–methanol at only one temperature, 328 K.[14] For this reason, the association entropy was not optimized and it was set equal to the half of methanol's self-association entropy. A proper way to estimate both cross association parameters, i.e., the energy and the entropy change, for this binary system would require using data over a wide temperature range. Nevertheless, the fitting of association parameters to experimental data of binary systems was not the scope of this study. Also, the interaction energy for acetone....HN< association is higher than the parameter that was used in this work to characterize all > C=O....HN < interactions. The latter was calculated to characterize interactions of the same type in acetanilide. However, Letcher and Bricknell calculated the interaction energy for the > C=O....HN < association using a proper analysis of experimental calorimetric data for the mixing of 4-heptanone–di-*n*-propylamine.[35] They report that the association strength is −7610 J mol^{-1}, which is very close to the value that was used in this study (−9176 J mol^{-1}) to characterize all > C=O....HN < interactions.

For comparison, calculations were also made for the solubility of paracetamol in ethanol by adopting the mean value of −23,655 J mol^{-1} reported by Danten et al., based on quantum chemical calculations, for the ethanol...O=C< interactions.[34] The corresponding hydrogen bonding entropy was fitted to the experimental data and was found equal to $S^{hb} = -34.0$ J mol^{-1} K^{-1}. All other details were the same as in the previously presented calculations. The results are shown in Figure 3.

In conclusion, the use of the same values of hydrogen bonding parameters to characterize different interactions is an approximation imposed by the lack of enough available experimental data. Nevertheless, in this way, the calculations are simplified and satisfactory results are obtained in most cases, considering also the complexity of the systems and the uncertainty of the experimental data, which were used to estimate the pure component parameters for the examined pharmaceuticals.

Mixtures with supercritical fluids

Recently, various supercritical fluid processes have been developed for the production of pharmaceutical products, such as drug microparticles[36] or encapsulated drugs into biodegradable polymer matrices.[37] In this direction, modeling of the solubility of pharmaceuticals in supercritical fluids is particularly important. This kind of calculations can be performed only using EoS models. Activity coefficient models, such as UNIFAC, more sophisticated models, such as COSMO-RS, or other empirical approaches cannot be used for high pressure phase equilibria calculations if they are not coupled with another EoS model.

In this direction, NRHB model was applied to model the paracetamol's solubility in supercritical CO_2. In all cases, pure solute was assumed in the solid phase and Eq. 31 was used for the calculation of the chemical potential of the solid solute. All calculations were performed using parameters from Tables 2, 4, and 6. Results are presented in Figure 4. Unfortunately, to the best of authors' knowledge, data for the solubility of acetanilide and phenacetin in supercritical CO_2 do not exist.

Is ΔCp Important in Solid–Liquid Equilibrium Calculations?

As mentioned previously in this manuscript, for the calculation of the chemical potential of a pure solid, the second term of Eq. 31 is dominant, whereas the third and fourth terms have opposite sign and, to a first approximation, they cancel out.[20] Consequently, usually in phase equilibrium calculations, only the approximate Eq. 32 is used. This is equivalent with the consideration that the difference of the heat capacities, $\Delta Cp = Cp_l - Cp_s$, of liquid and solid solute is zero.

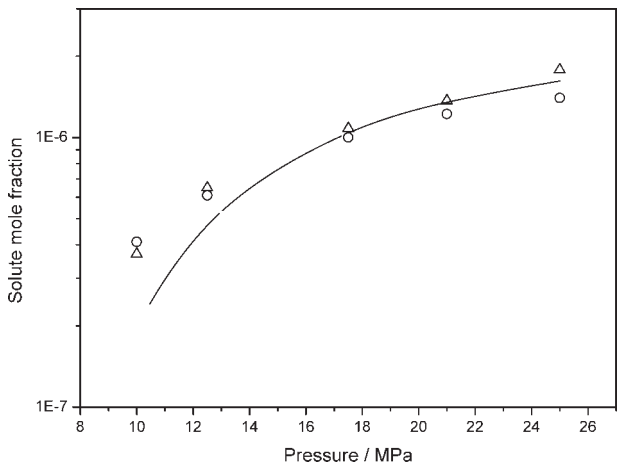

Figure 4. Solubility of paracetamol in supercritical CO_2.

Experimental data[38] at 313 K and NRHB correlations with $k_{ij} = 0.04803$.

Table 9. Pure Pharmaceutical[a] Parameters Obtained Using Eq. 32 for the Correlation of Sublimation Pressures

Pharmaceutical	ε_h^* (J mol^{-1})	ε_s^* (J mol^{-1} K^{-1})	$v_{sp,0}^*$ (cm^3 g^{-1})	s	% AAD in P^s	%AAD in ρ^{liq}
Acetanilide	7213.9	−1.60616	0.8969	0.780	2.5	0.6
Phenacetin	6246.6	−0.09439	0.9212	0.827	2.0	1.6
Paracetamol	6293.8	3.45685	1.1212	0.766	3.2	1.3

[a]Temperature range for parameter regression is as in Table 4.

To investigate how this simplification affects the calculated solubilities, calculations were also performed using the approximate Eq. 32. Initially, the pure component parameters for pharmaceuticals were estimated again using Eq. 32 for the correlation of sublimation pressures. These parameters are presented in Table 9. In all cases, they were estimated using the data described in the pure fluid section.

Furthermore, calculations for all the investigated binary systems were performed, using pure fluid parameters for solvents from Table 4 and values for the fusion properties of solutes from Table 2. Summarized results are presented in Table 7, while calculations for a characteristic binary mixture are presented in Figure 5. It is clear that the use of the full and thermodynamically consistent Eq. 31 results in much better predictions and correlations in fluids, where the difference of the heat capacities, $\Delta Cp = Cp_l - Cp_s$, is large (i.e., paracetamol and phenacetin). On the other hand, in acetanilide, which has a relatively small difference in the heat capacities compared with the aforementioned solutes, results are similar in both cases.

These findings are in agreement with Neau et al., who experimentally investigated the effect of different approximations in the ideal solubility of five high melting point solids, including paracetamol.[26] They reported that in all cases the effect of the molar heat capacity difference in the calculated ideal solubilities was not negligible. Furthermore, Gracin et al., who calculated the solubilities of various solids with UNIFAC, reported that the difference in the calculated solubilities of paracetamol is more than 100% if the heat capacity difference is considered equal to zero.[39] Finally, de Hemptinne reported that the effect of the molar heat capacity difference may become significant if the system temperature is very different from the melting temperature.[40]

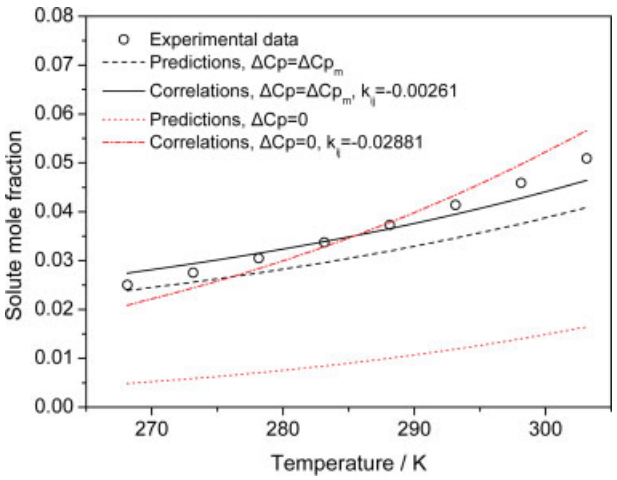

Figure 5. Solubility of paracetamol in 2-propanol.

Experimental data and NRHB predictions and correlations assuming ΔCp equal to the difference in the melting point or equal to zero. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Polymorphism of Drugs

An additional characteristic of pharmaceutical molecules that is expected to affect modeling of their solubilities is polymorphism. Solids may crystallize in many different forms. Each form has different fusion properties, which renders the experimental determination and the modeling of solubility a nontrivial procedure. It is clear that in terms of equilibrium thermodynamics, in constant temperature and pressure, the system would try to minimize the Gibbs free energy. This means that one crystalline form is the most stable and this should determine the thermodynamic equilibrium solubility. Despite this, many forms can exist simultaneously at certain temperature and pressure conditions. Furthermore, crystalline and nonequilibrium amorphous solids may exist.[47]

Three crystal forms have been reported for paracetamol: monoclinic (form I), orthorhombic (form II), and a very unstable phase, where the crystal structure has not been determined (form III).[41,42] The packing architectures of the two stable forms (I and II) are substantially different. However, the difference of the lattice energies is in the same order of magnitude as the typical experimental errors and it is difficult to estimate the enthalpy of transition $\Delta H(I \rightarrow II)$. Experimental values may even differ in sign. Nevertheless, according to Espeau et al., who collected and analyzed data from many different sources, form I is the more stable phase at ambient conditions.[42]

In many studies dealing with the experimental determination of solubilities, the crystalline structure of the materials is not investigated. To show how these peculiarities of the solid solutes affect the solubility results, calculations were performed using two different sets of fusion properties that correspond to paracetamol I and paracetamol II, respectively. Experimental fusion properties were adopted from literature[16,41] and are presented in Table 10. Pure component and association parameters of Tables 4 and 6 were used in both cases. The difference in the heat capacities, $\Delta Cp = Cp_l - Cp_s$, of a liquid and a solid solute was considered equal to

Table 10. Fusion Properties for Different Crystalline Forms of Paracetamol

Form	T_m (K)	ΔH_f (J mol^{-1})	ΔCp (J mol^{-1} K^{-1})
Paracetamol I	443.6[16]	27,100[16]	98.9[26]
Paracetamol II	430.1[41]	26,500[41]	93.9[42]

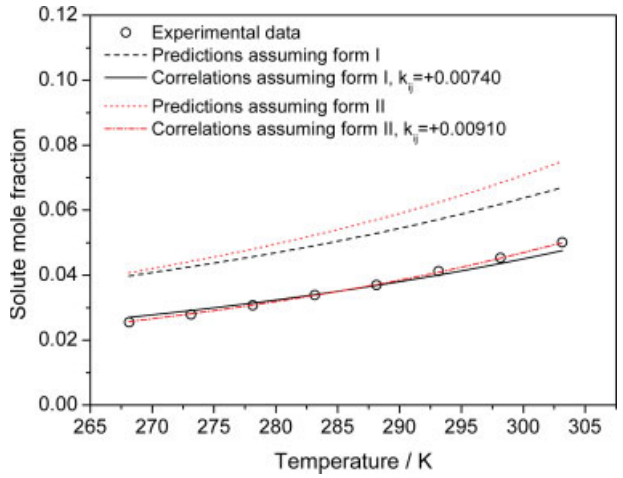

Figure 6. Solubility of paracetamol in 1-propanol.

Experimental data and NRHB predictions and correlations assuming form I or form II crystalline structure for paracetamol. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

98.9 J mol^{-1} K^{-1} for the form I,[26,42] whereas for the form II it was considered to be 5 J mol^{-1} K^{-1} lower.[42,43]

Results for the solubility of paracetamol in 1-propanol are shown in Figure 6. This very small change in the fusion properties resulted in differences between the two sets of calculations of 7% for the case of predictions and 3% for the case of correlations, respectively. This indicates that the fusion properties and, subsequently, the corresponding crystalline form of the solid should be investigated before the experimental determination of the solubility. In this way, contradictory data can be explained and the modeling of the solubility becomes more accurate.

Simplicity vs. Complexity

The suggested methodology for modeling complex chemicals, such as pharmaceuticals, explicitly accounts for the various hydrogen bonding interactions that exist in the system. Especially, in molecules with many different hydrogen bonding sites, this results in a complicated scheme with many different interactions. NRHB model uses a flexible and thermodynamically consistent hydrogen bonding approach that permits calculations in such complicated systems in a relatively easy and not time-consuming way. However, very often in modeling complex chemicals, a certain number of hypothetical equivalent sites are assumed in molecules with many functional groups resulting in much simpler calculations. In this way, Grenner et al. correlated the phase behavior of glycol solutions using simplified PC-SAFT.[44] In calculations similar to those that are presented in this study, in which many pure fluid parameters are optimized using limited experimental or predicted data, the following question arises: Are results improved when the more sophisticated scheme is adopted over a simpler and approximate hydrogen bonding scheme?

To answer this, calculations were also performed with the assumption that solute molecules only have hypothetical equivalent sites. In this direction, the investigated pharmaceuticals were modeled assuming five sites (2 proton donors − 3 proton acceptors) for paracetamol, four sites (1 proton donor − 3 proton acceptors) for phenacetin, and three sites (1 proton donor − 2 proton acceptors) for acetanilide. All hydrogen bonds between these hypothetical sites were assumed equivalent. Pure component parameters were estimated using the same data as described in the pure fluid section and are shown in Table 11.

In binary mixtures, SLE calculations were performed using Eq. 31 for the calculation of the chemical potential in the solid phase and the fusion properties of Table 2. Summarized results are presented in Table 7, while two characteristic systems are presented in Figures 7 and 8.

In general, the approach that accounts explicitly for the various hydrogen bonding interactions resulted in more accurate predictions and correlations than the simple and approximate hydrogen bonding scheme, which assumes equivalent sites in solute molecules. Furthermore, in all correlations, the more sophisticated scheme resulted in better description of the solubility temperature dependence, as shown in Figures 7 and 8.

The main disadvantage of assuming hypothetical equivalent sites in solute molecules is the use of combining rules (Eqs. 33–36) to calculate the hydrogen bonding parameters for the cross interactions with solvent molecules. This approach fails especially in systems with cross association between the solute and a nonself-associating solvent (i.e., paracetamol–acetone, paracetamol–acetonitrile). In this type of systems, the use of combining rules did not sufficiently improve phase equilibrium correlations for various binary mixtures using the simplified PC-SAFT model.[14] On the other hand, according to the methodology that is suggested in this work, if the hydrogen bonding behavior is explicitly accounted for, the need for combining rules is minimized. Parameters from Table 6 may represent a reasonable approximation and can be used for most interactions with solvent molecules.

Evaluation of the Predicting Ability (Comparison with the COSMO-RS Model)

COSMO-RS[5–7] is an advanced model, which combines an electrostatic theory for molecular surface interactions with statistical thermodynamics. Its main advantage is that the

Table 11. Pure Pharmaceutical Scaling Parameters Assuming Equivalent Hydrogen Bonding Sites and Percentage Average Absolute Deviation (%AAD) Between Experimental (or predicted) Data and NRHB Correlation

Pharmaceutical	ε^*_h (J mol^{-1})	$\varepsilon^*_{\xi_1}$ (J mol^{-1}K^{-1})	$v^{*}_{sp,0}$ (cm^3 g^{-1})	s	E^{hb} (J mol^{-1})	S^{hb} (J mol^{-1} K^{-1})	% AAD[a] in P^{vap}	%AAD[*] in ρ^{liq}
Acetanilide	7025.6	3.75419	0.91313	0.780	−11183	−20.34	1.4	0.5
Phenacetin	6317.1	−0.46926	0.93870	0.827	−12650	−20.85	1.1	0.1
Paracetamol	6248.0	2.73782	1.10434	0.766	−17478	−13.35	1.4	1.5

[a]Temperature range for parameter regression is as in Table 4.

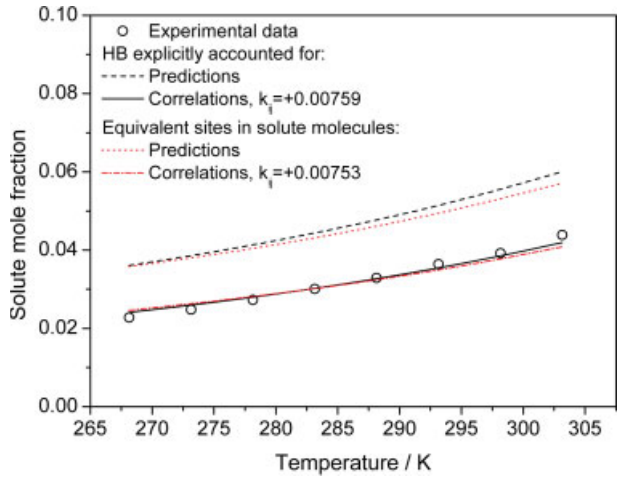

Figure 7. Solubility of paracetamol in 1-butanol.

Experimental data and NRHB predictions and correlations accounting explicitly for various hydrogen bonding interactions or assuming hypothetical equivalent sites in solute molecules. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

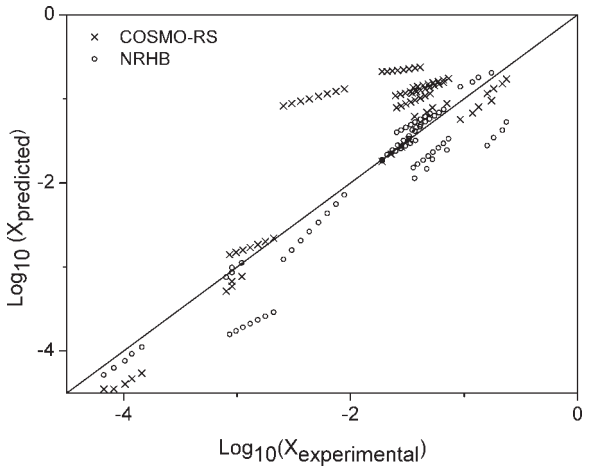

Figure 9. Summarized results for the investigated binary systems:

NRHB (o) and COSMO-RS (×) predictions.

thermodynamic properties of fluids and their mixtures can be predicted using only quantum chemical calculations. This particularity rendered the model as a very useful tool for the screening of solvents for complex chemicals, such as pharmaceuticals.[7,45]

From Table 7, it is clear that the approach that is suggested in this study results in very accurate correlations using one temperature-independent binary interaction parameter ($k_{ij} \neq 0$). In this section, calculations (predictions) using no binary interaction parameter ($k_{ij} = 0$) are compared with COSMO-RS predictions to investigate the predicting ability of the suggested methodology.

All COSMO-RS calculations were performed using COSMO*therm* software.[46] For all fluids, parameterization at the TZVP basis was applied as it is incorporated in the corresponding software database. More detailed quantum chemical calculations, which could improve COSMO-RS predictions, were not the aim of this study. In all cases, the fusion properties of Table 2 were used for the calculation of solids solubility.

The summarized results are presented in Figure 9, while characteristic calculations are shown in Figure 10. Standard deviations from experimental data are $s = 0.36$ and 0.64 in $\log_{10}$-units for NRHB and COSMO-RS, respectively. From these results, it is clear that the suggested methodology coupled with the NRHB model has a reasonably accurate predicting ability. It should be mentioned though that NRHB model uses parameters for pure fluids that are based on experimental data, while parameters for the COSMO-RS model are obtained through quantum chemical calculations.

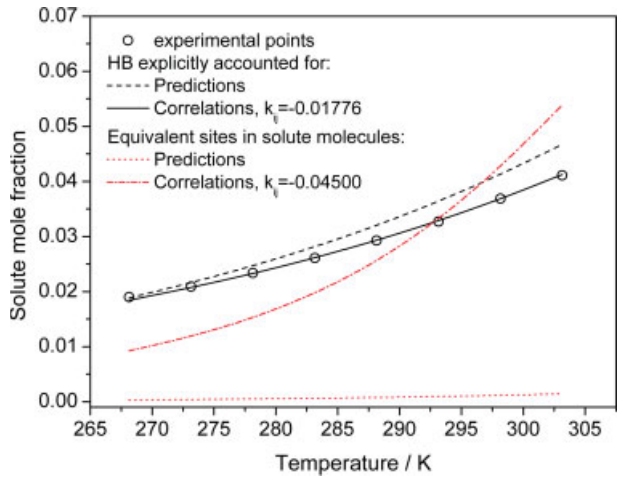

Figure 8. Solubility of paracetamol in acetone.

Experimental data and NRHB predictions and correlations accounting explicitly for various hydrogen bonding interactions or assuming hypothetical equivalent sites in solute molecules. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

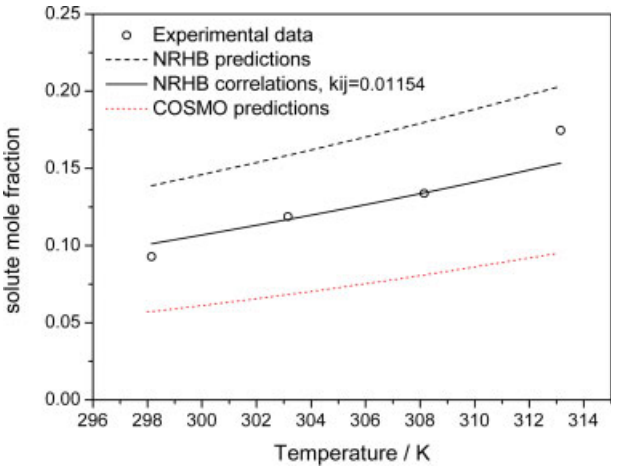

Figure 10. Solubility of acetanilide in 1-octanol.

Experimental data, NRHB calculations, and COSMO-RS predictions. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Conclusions

A methodology is proposed for modeling complex chemicals, such as most pharmaceutical substances, when only limited experimental data exist. According to this, pure fluid parameters are estimated using limited experimental or predicted data on sublimation pressures and liquid densities. The complex hydrogen bonding behavior is explicitly accounted for and corresponding parameters are adopted from simpler, but similar, molecules and/or are fitted to Hansen partial solubility parameters. The solubility of three pharmaceuticals, i.e., acetanilide, phenacetin, and paracetamol, in various solvents was modeled using the NRHB model. In all cases, very satisfactory correlations were obtained using only one optimized binary interaction parameter. Furthermore, the predicting ability of the model coupled with the suggested methodology was evaluated against COSMO-RS model predictions. In many cases, predictions were satisfactory, considering the complexity of the investigated systems and the uncertainty of the experimental data that was used to estimate the pure parameters for the examined pharmaceuticals.

Two approaches were used to model the solubility of solids in different solvents. The results revealed that using the full and thermodynamically correct equation for the chemical potential of the solid, including ΔCp, highly improved predictions and correlations especially for pharmaceuticals with high ΔCp values are obtained.

The effect of the polymorphism of crystalline solids in the calculated solubilities was discussed. Calculations were preformed for the solubility of paracetamol assuming that the drug is crystallized in two different forms.

Furthermore, calculations were performed using a simplified approach, in which hypothetical and equivalent hydrogen bonding sites were assumed in solute molecules. It was found that with this simplified approach, the temperature dependence of the solubility was not successfully correlated in many cases in contrast to the approach that explicitly accounts for the complex hydrogen bonding interactions. The main reason for this is the use of combining rules for the calculation of parameters for the cross hydrogen bonding interactions between the solute and solvent molecules.

Work is underway in, among others, extending the suggested approach to other pharmaceuticals with different functional groups, to ternary mixtures as well as in modeling inter- and intra-hydrogen bonding interactions of such systems.

Acknowledgments

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Notation

Cp = isobaric heat capacity.
c_{β}^{k} = number of acceptor groups of type β in each molecule of type k.
d_{α}^{k} = number of donor groups of type α in each molecule of type k.
E = energy.
G = Gibbs free energy change.
k_{ij} = binary interaction parameter.
N = number of molecules or hydrogen bonds.
N_r = number of molecular sites.
N_0 = number of empty sites.
l = parameter defined by Eq. 11.
MW = molecular weight.
m = number of proton donor types.
n = number of proton acceptor types.
P = pressure.
qz = average number of external contacts per molecule.
r = number of sites per molecule.
R = gas constant.
s = surface-to-volume-ratio factor.
S = entropy.
T = temperature.
T_m = melting point.
V = volume.
υ = molar volume.
v^* = average segmental volume.
v_{sp}^* = characteristic specific volume.
$v_{sp,0}^*$ = specific volume scaling parameter.
$v_{sp,1}^*$ = specific volume scaling parameter.
v_{hb} = number of hydrogen bonds per molecular segment.
$v_{\alpha\beta}$ = number of hydrogen bonds between a donor of type α and an acceptor of type β per molecular segment.
v_{z0} = number of the unbonded donors of type a per molecular segment.
$v_{0\beta}$ = number of unbonded acceptors of type β per molecular segment.
v_c^{β} = number of acceptors of type β per molecular segment.
v_d^{z} = number of donors of type α per molecular segment.
x = molar fraction.
z = lattice coordination number.
ΔH_m = fusion enthalpy.

Greek letters

Γ_{00} = nonrandom factor for the distribution of empty sites around an empty site.
Γ_{ii} = nonrandom factor for the distribution of molecular segments of component i around a molecular segment of component i.
δ = solubility parameter.
ε^* = average intersegmental interaction energy.
ε_h^* = interaction energy scaling parameter.
ε_s^* = Interaction energy scaling parameter.
θ = surface (contact) fraction.
μ = chemical potential.
ρ = density.
ϕ = segment (site) fraction.
ω = flex constant.

Superscripts

$\sim$ = reduced quantity.
* = scaling constant.
l = liquid phase.
s = solid phase.

Subscripts

α = proton donor of type α.
β = proton acceptor of type β.
$\alpha\beta$ = hydrogen bond between a donor of type α and an acceptor of type β.
hb = hydrogen bond.
i = component of type i.
j = component of type j.
coh = cohesive.
d = dispersion component.
p = polar component.
ph = physical interactions.

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