Prediction of Phase Equilibria for Binary Mixtures by Molecular Modeling

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Two new procedures based on quantum/COSMO calculations and on molecular mechanics/dynamics simulations, respectively, for estimating the PHSCT EOS parameters and to predict VLE behavior for binary mixtures are presented. The quality of the predictions achieved with both methods, in conjunction with the confined computational time aspects involved, can be considered satisfactory so that these strategies can be judged as promising routes toward an on-line coupling between molecular and process simulation.

Introduction

Modern industry faces the challenge of designing, and hence producing, molecules (or molecular ensembles) having well-defined chemico-physical characteristics (such as pharmaceuticals, polymers, and additives) by fast and economical processes. The recent progress in computer architecture and molecular-simulation software have transformed the theoretical models from topics of exquisite academic interest into practical tools for molecular and process design, and thus of industrial relevance. Notwithstanding the progressively increasing importance of molecular simulation in several industrial sectors, still very few articles can be found in the current literature documenting the potential of such applications in chemical engineering (Gubbins and Quirke, 1996; Vv. Aa., 1998).

In our previous articles (Belloni et al., 2000; Fermeglia and Pricl, 1999a,b,c), we reported some examples on how molecular and process simulations can be successfully bridged via recourse to the equation-of-state (EOS) theory, both for simple and long-chain molecules. The problem of estimating parameters for EOSs is an important issue in the analysis and synthesis of chemical processes, and in the use of process simulators. Indeed, once we realize that, in modern process simulators, more than 75% of the code implemented is dedicated to physical-property calculations and predictions and that the data banks storing pure-component as well as binary interaction parameters are continuously used, the important role physical-property availability plays in process simulation becomes evident. Nonetheless, there are cases in which chemical engineers need to input EOS parameters for small molecules that have not yet been synthesized, for compounds that may be highly toxic or explosive under the current testing conditions, or for long-chain polymers for which experimental data cannot be easily obtained. Furthermore, in the calculation of rate-controlled processes, it is sometimes necessary to estimate the equilibrium condition with a high degree of accuracy, and again experimental evidence in such conditions may not be available.

The basic machinery of the procedure for bridging molecular and process simulation via EOS theory we proposed consists of the application of molecular mechanics/dynamics techniques for the determination of physically based EOS parameters. Thus, we developed a strategy to calculate the perturbed hard-sphere chain (PHSCT) EOS parameters A^*, V^*, and E^* (Fermeglia et al., 1997, 1998) and the lattice fluid (LF) EOS parameters P^*, ρ^*, and T^* (Sanchez and Lacombe, 1976). In the case of the PHSCT EOS, the proposed method essentially consists of the rough estimation of the molecular surface areas and volumes, related to the corresponding EOS parameter A^* and V^*, by a combination of molecular mechanics (MM) and graphical algorithms, whereas the third, energetic parameter E^* can be obtained from molecular dynamics simulations (MD) in the gas state. For the LF EOS, the procedure consists in determining *PVT* data sets via MD simulations at different decreasing tempera-

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Part of these results were presented at the AIChE Annual Meeting, Los Angeles CA, November 2000.

tures. The two EOS parameters P^* and ρ^* can be directly obtained by data extrapolation to 0 K, whereas the third parameter T^* can be evaluated by inserting P^*, ρ^*, and a set of simulated *PVT* data into the EOS expression.

The aim of the present article is to extend these techniques to the prediction of phase equilibria for mixtures. To this end, we resorted once again to the PHSCT EOS, and in particular to its extended version for mixtures (Fermeglia et al., 1998), and used a set of well-known binary systems as standard tests. In detail, we propose two alternative procedures to derive the PHSCT EOS parameters. The first method is based on the description of the solvation phenomena at a molecular level using the conductor-like screening model for real solvents (COSMO-RS) (Klamt and Schüürmann, 1993). The second procedure is the natural extension of the method proposed in our previous work, and is based on molecular mechanics/dynamics experiments.

The two methods presented in this article are briefly summarized as follows:

- Method 1: DMO^3/COSMO-RS calculations can be used to predict the activity coefficients and to obtain the PHSCT EOS parameters A^* and V^* for each pure component; the third PHSCT EOS parameter E^* for the pure components can be found by fitting a single experimental vapor pressure value. Finally, the binary interactions parameters k_{ij} of the EOS can be obtained from the activity coefficients found for each binary mixture;
- Method 2: In this case, A^* and V^* can be calculated using MM/QM techniques. E^* can be found either by (a) again fitting the EOS to one single experimental vapor-pressure value, or (b) MD simulations in the gas state. In this latter case, the parameters k_{ij} are found by performing NPT simulations of equimolar mixtures of each binary in the gas state.

As we discuss later in more detail, the quality of the prediction, in conjunction with the relatively fast calculation time for the simulation, can be considered extremely satisfactory, so that the strategies proposed here can be judged as promising possible routes for the on-line coupling of molecular and process simulations.

Theory

PHSCT EOS for mixtures

The EOS considered in this work is based on the simplified PHSCT EOS (Song and Mason, 1991; Song et al., 1994a,b, 1996), in which the molecule is considered to be constituted by chains of freely jointed tangent hard spheres. All the theoretical details concerning the simplified version of the PHSCT EOS, and the relevant strategy to calculate the corresponding sets of parameters A^*, V^*, and E^* for pure components have been reported in detail elsewhere (Fermeglia and Pricl, 1999a,b). It is appropriate to recall here only the meaning and the relevant expression for the EOS parameters. First the parameter A^* represents a *characteristic surface area*, and is defined as

$$A^* = \pi r \sigma^2 N_A, \tag{1}$$

where N_A is Avogadro's constant, r is the number of effective hard spheres per molecule, and σ is the separation distance between segment centers at the minimum in the pair potential. Second, the parameter V^* is a *characteristic volume*, defined as:

$$V^* = (\pi/6) r \sigma^3 N_A; \tag{2}$$

and finally a *characteristic cohesive energy* E^* is

$$E^* = r(\epsilon/k) R_g, \tag{3}$$

where R_g is the gas constant; k is Boltzmann's constant; and E^* is constructed by multiplying the potential well depth ϵ between two nonbonded segments of the molecule by the total number of segments per molecule.

The extension to mixtures of the PHSCT EOS is straightforward, and can be obtained by applying mixing rules to the EOS parameters for the pure components; this leads to the following equation (Song et al., 1994b)

$$\frac{P}{\rho kT} = 1 + \rho \sum_{i,j}^{m} x_i x_j r_i r_j b_{ij} g_{ij}(d_{ij}^+) - \sum_{i}^{m} x_i (r_i - 1) \times [g_{ii}(d_{ii}^+) - 1] - \frac{\rho}{kT} \sum_{ij}^{m} x_i x_j r_i r_j a_{ij}, \tag{4}$$

where $x_i = N_i/N$ is the number fraction of molecules; r_i is the number of segments for the ith component; and $g_{ij}(d_{ij}^+)$ is the ij pair radial distribution function of hard-sphere mixtures at contact. The accurate statistical-mechanical expression for $g_{ij}(d_{ij}^+)$ of Boublik-Mansoori-Carnahan-Starling (BMCS) (Boublik, 1970; Mansoori et al., 1971) has been used in the model

$$g_{ij}(\eta, \xi_{ij}) = \frac{1}{1-\eta} + \frac{3}{2} \frac{\xi_{ij}}{(1-\eta)^2} + \frac{1}{2} \frac{\xi_{ij}^2}{(1-\eta)^3}, \tag{5}$$

where η is the packing fraction

$$\eta = \frac{\rho}{4} \sum_{i}^{m} x_i r_i b_i, \tag{6}$$

and ξ_{ij} is given by

$$\xi_{ij} = \left(\frac{b_i b_j}{b_{ij}} \right)^{1/3} \frac{\rho}{4} \sum_{k}^{m} x_k r_k b_k^{2/3}. \tag{7}$$

Each binary molecular pair is characterized by a set of two parameters: a_{ij} (the attractive force parameter) and b_{ij} (the second cross-virial coefficient of hard-sphere mixtures), respectively. These two parameters can be obtained by extension of the corresponding equations for pure components, as

$$a_{ij} = \left(\frac{2\pi}{3} \right) \sigma_{ij}^3 \epsilon_{ij} F_a \left(\frac{kT}{\epsilon_{ij}} \right) \tag{8}$$

$$b_{ij} = \left(\frac{2\pi}{3} \right) \sigma_{ij}^3 \epsilon_{ij} F_b \left(\frac{kT}{\epsilon_{ij}} \right), \tag{9}$$

where F_a and F_b are two empirical expressions determined from the thermodynamic properties of argon and methane over a large range of T and P (Song et al., 1996).

The proposed combining rule for σ is based on the additivity of hard-sphere diameters without any interaction parameter:

$$\sigma_{ij} = \frac{\sigma_i + \sigma_j}{2}. \tag{10}$$

For the energetic parameter ϵ, a binary interaction parameter k_{ij} is introduced in the combining rule as

$$\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j}\left(1 - k_{ij}\right). \tag{11}$$

From a practical standpoint, it is more convenient to transform Eq. 4 from a number basis to a segment basis, that is

$$\frac{P}{\rho_r kT} = 1 + \rho_r \sum_{i,j}^{m} \phi_i \phi_j b_{ij} g_{ij}\left(d_{ij}^{+}\right) - \sum_{i}^{m} \phi_i \left(1 - \frac{1}{\eta}\right) g_{ii}\left(d_{ii}^{+}\right) - \frac{\rho_r}{kT} \sum_{ij}^{m} \phi_i \phi_j a_{ij}, \tag{12}$$

where

$$\rho_r = \frac{N_r}{V} \tag{13}$$

$$\phi_i = \frac{N_i r_i}{N_r} = \frac{x_i r_i}{\sum_{j}^{m} x_j r_j} \tag{14}$$

$$N_r = \sum_{i}^{m} N_i r_i. \tag{15}$$

Further, since analytical expressions for all the thermodynamic properties can be obtained in a modular and efficient way by partial differentiation of the Helmholtz energy surface with respect to either the number of moles, the temperature, or the volume (Mollerup and Michelsen, 1992), we finally rewrite Eq. 12 in terms of Helmholtz energy, thus obtaining

$$\frac{A}{N_r kT} = \sum_{i}^{m} \frac{\phi_i}{r_i} \frac{A_i^0}{kTN_i} + \rho_r \sum_{i}^{m} \sum_{j}^{m} \phi_i \phi_j b_{ij} W_{ij} - \sum_{i}^{m} \phi_i \left(1 - \frac{1}{r_i}\right) Q_{ii} - \frac{\rho_r}{kT} \sum_{i}^{m} \sum_{j}^{m} \phi_i \phi_j a_{ij} + \sum_{i}^{m} \frac{\phi_i}{r_i} \ln\left(\rho_r kT \frac{\phi_i}{r_i}\right), \tag{13}$$

where A^0 is the pure-component ideal gas term

$$W_{ij} = W_{ij}\left(\eta, \xi_{ij}\right) = \frac{1}{\rho_r} \int_0^{\rho_r} g_{ij}\, d\rho_r = \frac{I_1}{\eta} + \frac{3}{2} \frac{\xi_{ij}}{\eta^2} I_2 + \frac{1}{2} \frac{\xi_{ij}^2}{\eta^3} I_3 \tag{14}$$

$$Q_{ij} = Q_{ij}\left(\eta, \xi_{ij}\right) = \int_0^{\rho_r} \left(g_{ij} - 1\right) \frac{d\rho_r}{\rho_r} = -\ln(1 - \eta) + \frac{3}{2} \frac{\xi_{ij}}{\eta^2} + \frac{1}{4} \frac{\xi_{ij}^2}{(1 - \eta)^2} \tag{15}$$

$$\eta = \frac{\rho_r}{4} \sum_{i}^{m} \phi_i b_i \tag{16}$$

$$\xi_{ij} = \left(\frac{b_i b_j}{b_{ij}}\right)^{1/3} \frac{\rho_r}{4} \Sigma \phi_k b_k^{2/3} \tag{17}$$

$$I_n = -I_{n-1} + \frac{1}{n-1} \frac{\eta^{n-i}}{(1 - \eta)^{n-1}} \tag{18}$$

and

$$I_1 = -\ln(1 - \eta). \tag{19}$$

The chemical potential for a component in the mixture is obtained by partial differentiation of the residual Helmholtz energy with respect to the number of moles (Fermeglia et al., 1998)

$$\frac{\mu_k}{kT} = \frac{\mu_k^0}{kT} + 2r_k \rho_r \sum_{i=1}^{m} \phi_i b_{ik} W_{ik} + \sum_{ij=1}^{m} \phi_i \phi_j b_{ij} \left(N_r \frac{\partial W_{ij}}{\partial N_k}\right) - (r_k - 1) Q_{kk} - \sum_{i=1}^{m} \phi_i \left(1 - \frac{1}{r_i}\right)\left(N_r \frac{\partial Q_{ii}}{\partial N_k}\right) - \frac{2 r_k \rho_r}{kT} \sum_{i=1}^{m} \phi_i a_{ik} + \ln\left(\frac{\phi_k}{r_k} \rho_k kT\right). \tag{20}$$

This procedure has been followed in this article for developing the model and writing the thermodynamic routines of the computer programs used for the calculations.

Determination of PHSCT EOS parameters by COSMO calculations

The first-principles quantum mechanical methods are capable of correctly describing the electronic and geometrical structures of solute molecules, including polarization effects due to the presence of the solvent. In a quantum mechanical approach, however, only a number of solvent molecules can be considered explicitly, due to the high computational cost. The use of density functional theory (DFT), as implemented for instance in the DMol^3 program, allows us to treat larger molecular systems than in *ab initio* methods such as Hartree-Fock or Møeller-Plesset perturbation theory (MP2). However, even within the framework of the DFT, a simplified model has to be used, and the most successful theories used so far are all based on the *polarizable continuum model* (PCM) proposed originally by Miertus et al. (1981). In this model, the solute molecule is embedded in a dielectric continuum of permittivity $\in$. The dielectric continuum is polarized by the charge distribution of the solute, which results in a charge distribution on the cavity surface [also called solvent accessible surface (SAS)]. For a given charge distribution within the cavity, the surface screening charges are then calculated by solving the Poisson equation, and hence used as a perturbation included in the Hamiltonian for electronic structure calculations of the solute. The new, perturbed density of the solute is used again for Poisson calculations, and the procedure is iterated until self-consistency is achieved. At costs comparable to gas-phase calculations, these methods are capable of giving a surprisingly good description of the properties and the energetics of molecules in various solvents, including water. Despite the considerable success of PCM-based models, they are hardly justifiable from a theoretical point of view, mainly because the electric fields on the molecular surfaces of fairly polar solutes are so strong that the major part of the solvent polarizability, that is, is the reorientation of static dipoles, no longer behaves linearly, as it does in the macroscopic limit, but is almost at saturation.

Starting from these considerations, quite recently Klamt and his coworkers (1993, 1995, 1998) have proposed a new theory, called the *conductor-like screening model for real solvent* (COSMO-RS), based on screening in conductors, which is non-iterative and allows for the calculation of accurate gradients without cavity shape constraints. The COSMO-RS theory takes the ideally screened molecules as starting points for the description of molecules in solution. The deviations from ideal screening, which occur in any real solvent, are described as pairwise misfit interactions of the ideal screening charges on contacting parts of the molecules in the fluid. Since COSMO-RS does not depend on experimental data or any parameterization for the solvent, it efficiently enables the calculation of the chemical potential of almost any solute in almost any solvent. Thus, it is capable of treating almost the entire equilibrium thermodynamics of fluid systems and, in our opinion, can constitute a powerful alternative to group/fragment-based methods like, for instance, UNIFAC.

In this work, we use the COSMO version as implemented in the DMol^3 suite of *Cerius*^{2} (v. 3.9 from Molecular Simulations Inc., USA). This choice relies on the fact that DFT calculations yield ground-state properties as reliable as Hartree-Fock calculations with higher-order correlation corrections, but at much lower cost. Even at the default level, these have sufficiently good tails to reliably reproduce quantities such as dipole moments and polarizabilities, which are of crucial importance for any solvation calculation.

In the new procedure proposed in this work, the entire set of parameters of the PHSCT EOS version for mixtures can be obtained from DMol^3/COSMO in the following fashion. First, from the values of the area and volume of the dielectric cavity in which the solute molecule is embedded, normalized with respect to methane ($r = 1$), the relevant r and σ values can be calculated and, accordingly, the pure component parameters A^* and V^* can be obtained by means of Eqs. 1 and 2. The third, energetic parameter of the pure component set E^* can then be evaluated by inserting A^*, V^* and the corresponding experimental vapor-pressure value into the EOS expression for pure-components (Fermeglia et al., 1998). The choice of using the experimental values of vapor pressure in determining the value of the E^* parameter is because, in this investigation, we focused on mixtures. Accordingly, by eliminating errors in the limiting value of the VLE phase diagrams, we can isolate the effect of the binary interactions and, thus, propose an effective method for calculating the binary interaction parameter, as describe hereafter.

Indeed, beside the pure-component parameter sets, the PHSCT EOS version for binary mixtures requires the knowledge of the binary interaction parameter k_{ij}. For the estimation of this last parameter, we suggest a procedure that is similar to that implemented in process simulators, in which the parameters of a given model are estimated from a known set of parameters of another model. Therefore, we regressed the simulated activity coefficient data of each binary system obtained as a result of COSMO-RS calculations, using the PHSCT and the relevant pure-component parameter sets just obtained, by means of a computer program based on the maximum-likelihood method. For both E^* and k_{ij} determination, as well as for the subsequent VLE prediction, we developed *ad hoc* in-house Fortran codes, paying particular attention to reducing CPU time and to improving the reliability of the search procedure.

Determination of PHSCT EOS parameters by MM/QM and MD calculations

The second, alternative procedure we propose is based on the application of molecular mechanics/dynamics techniques. As we reported elsewhere, these types of virtual experiments can be very effectively used for the *a priori* determination of EOS parameters, provided these have a well-defined physical meaning (Fermeglia and Pricl, 1999b,c). Accordingly, the three PHSCT EOS parameters for the pure components can be estimated as follows. The two parameters σ and r can be estimated from the values of molecular areas and volumes, calculated via a modified Connolly algorithm and normalized with respect to methane ($r = 1$). Then, A^* and V^* can be obtained again by means of Eqs. 1 and 2.

The third, energetic EOS parameter E^* for the pure components can then be calculated in two different ways. Following the first route, similar to that employed for COSMO-based calculations, E^* can be evaluated by inserting A^*, V^*, and the corresponding experimental vapor-pressure value into the EOS expression for pure components. Alternatively, the parameter ϵ/k, appearing in the expression of E^* (Eq. 3), can be obtained from MD simulations in the gas state ($T = 800$ K) as the ratio of the equilibrium value of the nonbonded contributions of the potential energy and the kinetic energy at the given temperature

$$\frac{\epsilon}{k} = \frac{E_{\text{pot}}^{\text{nonbonded}}}{E_{\text{kin}}} T. \tag{21}$$

Thus, E^* is easily calculated again via Eq. 3 (Fermeglia and Pricl, 1999b,c). In Eq. 21, $E_{\text{pot}}^{\text{nonbonded}}$ is the intermolecular component of the potential energy; simple order estimation gives that $E_{\text{pot}}^{\text{nonbonded}}$ is proportional to ϵ and E_{kin} is proportional to kT in the low-density and high-temperature limit.

Once the σ_i for the pure components are known, we can obtain the values for the combined terms σ_{ij} from Eq. 10. Further, knowing the ϵ_i and extracting the combined terms ϵ_{ij} from an MD experiment carried out on the corresponding binary mixture in the gas state, we can estimate the value of the binary interaction parameter k_{ij} directly from Eq. 11. In this second pathway we do not make use of any experimental data, and it can therefore be considered as a "pure prediction" method.

Table 1. Calculated Structural Molecular Parameters and Selected Chemicophysical Data for All the Pure Components

Compound	Bond Length (Å) Bond Angle (°)	ΔH_{form} (kcal/mol)	I.P. (eV)	μ (Debye)
Methanol		−57.03 (−57.15)	11.00 (10.85)	1.62 (1.70)
C–H	1.100 (1.0936)			
C–O	1.419 (1.424)			
O–H	0.945 (0.9451)			
HCH	108.4 (108.63)			
COH	108.5 (108.53)			
Ethanol		−64.22 (−66.34)	10.68 (10.47)	1.68 (1.69)
C–H (CH_3)	1.100 (1.10)			
C–H (CH_2)	1.092 (1.09)			
C–C	1.514 (1.512)			
C–O	1.427 (1.431)			
O–H	0.976 (0.971)			
COH	105.8 (105)			
CCO	107.9 (107.8)			
HCC	111 (110.5)			
1-Butanol		−79.95 (−78.22)	10.26 (10.06)	1.70 (1.66)
C–H	1.108 (1.107)			
C–C	1.531 (1.531)			
HCH	107.1 (107)			
CCC	113.5 (113.8)			
HCC	111.1 (111.0)			
Trichloromethane		−28.99 (−24.64)	11.70 (11.37)	1.15 (1.1)
C–Cl	1.752 (1.758)			
C–H	1.098 (1.10)			
ClCCl	110.8 (111.3)			
Cyclohexane		−38.53 (−37.38)	10.09 (9.86)	0.00
C–H	1.117 (1.119)			
C–C	1.537 (1.536)			
CCC	111.1 (111.3)			
n-Hexane		−46.82 (−47.49)	10.08 (10.13)	0.00
C–H	1.107 (1.107)			
C–C	1.530 (1.531)			
HCH	107.3 (107)			
CCC	113.7 (113.8)			
Benzene		20.0 (19.74)	9.65 (9.25)	0.00
C–H	1.100 (1.101)			
C–C	1.398 (1.399)			
Chlorobenzene		14.82	9.36 (9.06)	1.61 (1.69)
C–H	1.089 (1.083)			
C–C	1.401 (1.400)			
C–Cl	1.728 (1.737)			
CC(Cl)C	121.5 (121.7)			
CC(H)C	119.7 (120)			
Hexafluorobenzene		−231.1 (228.3)	10.4 (9.906)	0.00
C–F	1.344			
C–C	1.391			
FCC	120.0			
CCC	120.0			
Pyridine		32.02 (33.56)	9.32 (9.25)	2.17 (2.215)
C–H	1.089 (1.081)			
C–C	1.393 (1.394)			
C–N	1.340 (1.340)			
HCC	121.6 (121.3)			
CCC	118.9 (118.5)			
CNC	116.1 (116.8)			
NCC	123.9 (123.9)			
HCN	115.8 (115.9)			
1,4-Dioxane		−94.97	10.2	0.00
C–H	1.106 (1.112)			
C–C	1.510 (1.523)			
C–O	1.428 (1.423)			
COC	111.6 (112.4)			
OCC	110.4 (109.2)			

Note: Available experimental data are reported in parentheses for comparison.

Simulation Details

All simulations were performed on a Silicon Graphics Origin 200 (microprocessor MIPS RISC 10000, 64-bit CPU, 128-MB RAM). The commercial software *Cerius*^{2} (v. 3.9) from Molecular Simulation Inc. was used for MM/QM and MD simulations. The generation of accurate model structures of several pure organic substances was conducted as follows. For each compound, the molecule was built and its geometry optimized via energy minimization using the COMPASS force field, the first *ab initio* force field that has been parameterized and validated using condensed-phase properties in addition to various *ab initio* and empirical data for molecules in isolation (Sun, 1998). The bond terms of the COMPASS FF potential energy function include a quartic polynomial both for bond stretching and angle bending, a three-term Fourier expansion for torsions, and a Wilson out-of-plane coordinate term. Six cross terms up through third order are present to account for coupling between the intramolecular coordinates. The final two nonbonded terms represent the intermolecular electrostatic energy and the van der Waals interactions, respectively; the latter employs an inverse 9th power term for the repulsive part rather than the more customary 12th power term.

The molecules were modeled to have a total charge equal to zero, and the distribution of the partial charge within each molecule was determined by the charge-equilibration method of Rappé and Goddard (1991). Energy was minimized by up to 5,000 Newton-Raphson iterations. Following this procedure, the root-mean-square (rms) atomic derivatives in the low-energy regions were smaller than 0.01 kcal/mol Å. Long-range nonbonded interactions were treated by applying suitable cutoff distances, and to avoid the discontinuities caused by direct cutoffs, the cubic spline switching method was used (Brooks et al., 1985). Van der Waals distances and energy parameters for nonbonded interactions between heteronuclear atoms were obtained by the sixth-power combination rule proposed by Waldman and Hagler (1993).

The gas-phase reference energies for all the structures of the data sets were obtained from nonlocal DFT VWN-BP gas-phase optimization, applying the DNP basis (v.4.0.0) of DMol^3 as implemented in the Quantum 1 platform of *Cerius*^{2}, and a real space cutoff = 5.50 Å. All structures were then reoptimized in a continuum conductor (that is, with DMol^3/COSMO and $f(\in) = 1$, using a number of segments = 92). The values of the area and volume of the dielectric cavity in which the solute molecule is embedded can be extracted directly from the corresponding COSMO files. Finally, the phase-equilibrium properties of each binary mixture considered necessary for the determination of the EOS parameters according to the procedure reported earlier, were again obtained from the COSMO files generated by DFT calculations using the new software COSMOtherm from COSMOlogic (v. C1.0, Leverkusen, Germany).

The estimation of the molecular surface areas and volumes, required for the determination of the PHSCT EOS parameters A^* and V^* by MM/MD techniques, was performed via the Connolly dot algorithm (Connolly, 1983a,b and 1985), corrected to account for quantum effects using the method proposed by Rellick and Becktel (1997). In this way, no assumption was made about the value of the radii of individual atoms or groups of atoms (Fermeglia and Pricl, 1999b).

Table 3. PHSCT EOS Energetic Parameter E^* as Obtained by Inserting Experimental Vapor Pressure P^0, Temperature T and Corresponding Set of A^* and V^* Parameters* in the PHSCT for Pure Components

Compound	P^0 (bar)	T (K)	E^* (bar dm^3/mol)
Methanol	0.169	298	58.023
Methanol	0.445	318	57.207
Methanol	0.554	323	56.992
Methanol	3.467	373	55.070
Ethanol	0.0786	298	64.842
1-Butanol	0.00872	298	88.159
Trichloromethane	0.265	298	68.419
Trichloromethane	0.693	323	68.786
Cyclohexane	0.130	298	77.204
n-Hexane	0.444	318	78.588
Benzene	0.127	298	73.420
Benzene	0.362	323	73.799
Chlorobenzene	0.0160	298	89.528
Hexafluorobenzene	0.117	298	84.328
Pyridine	0.638	373	81.173
1,4-Dioxane	0.161	323	78.821

Note: They are listed in Table 2. Experimental data from Dechema Chemistry Data Series.

Table 2. Areas A and Volumes V of Dielectric Cavities* and Corresponding PHSCT EOS Parameters A* and V*

Compound	A (Å^2)	V (Å^3)	A^* (10^{-9} cm^2/mol)	V^* (cm^3/mol)
Methanol	68.11	48.83	4.102	25.76
Ethanol	88.24	70.22	5.314	33.03
1-Butanol	124.7	114.1	7.514	41.73
Trichloromethane	116.9	105.2	7.043	39.44
Cyclohexane	132.2	127.1	7.963	43.14
n-Hexane	157.3	146.3	9.476	52.22
Benzene	121.9	110.3	7.344	41.04
Chlorobenzene	140.9	132.8	8.488	46.43
Hexafluorobenzene	163.3	159.9	9.833	52.79
Pyridine	117.7	105.7	7.091	39.75
1,4-Dioxane	120.7	110.5	7.268	40.34

Note: As obtained from DMol^3/COSMO calculations.

Table 4. Binary Interaction Parameter k_{ij} for the Systems Considered: Corresponding VLE Prediction vs. Experimental Data*

Mixture	T (K)	k_{ij}	RMSD P	RMSD y
Methanol/ethanol	298	0.0010	0.11	0.44
Methanol/1-butanol	298	0.0250	0.52	2.49
Trichloromethane/methanol	298	0.0503	1.34	4.77
Methanol/cyclohexane	298	0.0987	3.89	8.72
n-Hexane/methanol	318	0.0765	3.90	12.5
Methanol/benzene	298	0.0605	3.46	7.92
Methanol/pyridine	373	0.0206	1.10	0.63
Methanol/hexafluorobenzene	298	0.0676	2.69	7.61
Methanol/1,4-dioxane	323	0.0252	3.99	2.37
Benzene/chlorobenzene	298	0.0013	0.012	0.14
Trichloromethane/benzene	323	0.0096	0.24	0.25

Note: Experimental data from Dechema Chemistry Data Series.

For the calculation of the ϵ_i parameters of the pure components, 256 molecules were confined in a cubic box with periodic boundary conditions; in order to minimize the artifact of periodicity for liquids and gases, a cutoff distance was set equal to half the box length. The resultant structures were relaxed via MM, again using the COMPASS FF; in this case, the Ewald technique was employed in handling nonbonded interactions. To obtain values of the mixture terms ϵ_{ij}, and hence of the binary interaction parameter k_{ij}, the same simulation conditions were used for the corresponding equimolecular binary mixtures.

Each constant pressure-constant temperature (NPT) molecular dynamics run was started by assigning initial velocity for the atoms according to a Boltzmann distribution at $2 \times T$, where T was set equal to 800 K, a value well above the critical temperature for all the compounds considered. Temperature was controlled via weak coupling to a temperature bath (Andersen, 1980), with coupling constant $\tau_T = 0.01$ ps, whereas pressure was kept constant by coupling to a pressure bath (Berendsen et al., 1984), with relaxation time $\tau_P = 0.1$ ps. The Newton molecular equations of motion were solved by the Verlet leapfrog algorithm (Verlet, 1967), using an integration step of 1 fs. Since the partial charges assigned by the charge equilibration method are dependent on structure geometry, they were updated regularly every 100 MD steps during the entire MD runs.

Each MD simulation was performed using the COMPASS force field and consisted of a system equilibration phase, during which the equilibration process was followed by monitoring the behavior of both kinetic and potential energy and the time evolution of density, and a successive data-collection phase. Since the energy components as well as density have ceased to show a systematic drift and have started to oscillate about steady mean values around 30/35 ps, equilibration phases longer than 50 ps (that is, 50,000 MD steps with time step = 1 fs) and data-acquisition runs longer than 300 ps were judged not necessary to enhance data accuracy.

Results and Discussion

The validity of any molecular simulation rests on the suitability and accuracy of the equations used for the molecular potentials. Although the accuracy of a prediction may be estimated by considering the approximations and simplifications of the model and computational procedure, the final test lies in a comparison of theoretically predicted and experimentally measured properties. Table 1 shows the results of this comparison in terms of geometrical parameters and of other general chemicophysical-properties (such as dipole moment, ionization potential, and enthalpy of formation) obtained for the pure components considered in our work. From an inspection of this table we can conclude that, for all the compounds considered, the agreement is more than satisfactory.

Results from COSMO-based calculations

Table 2 reports the values of the areas A and volumes V of the dielectric cavities, in which the solute molecules analyzed are embedded as obtained from DMol^3/COSMO calculations. The determination of the relevant values of the

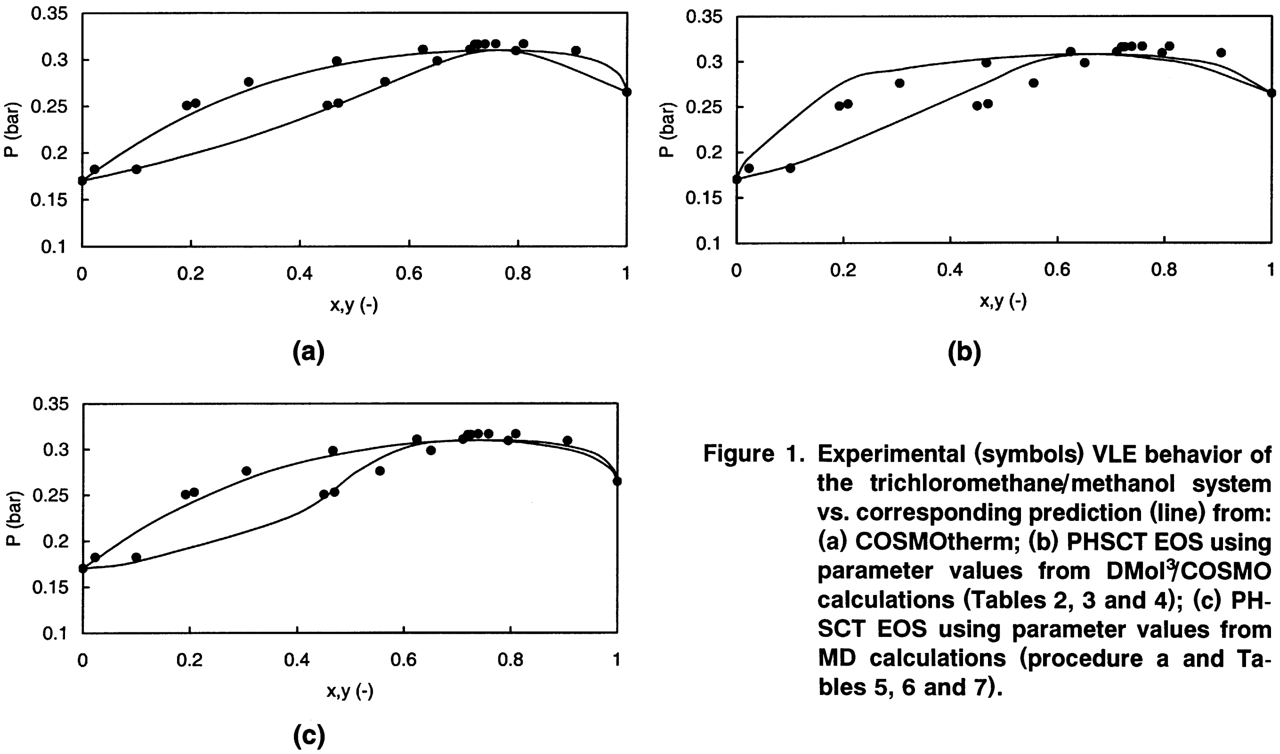

Figure 1. Experimental (symbols) VLE behavior of the trichloromethane/methanol system vs. corresponding prediction (line) from: (a) COSMOtherm; (b) PHSCT EOS using parameter values from DMol^3/COSMO calculations (Tables 2, 3 and 4); (c) PHSCT EOS using parameter values from MD calculations (procedure a and Tables 5, 6 and 7).

PHSCT EOS parameters A^* (Eq. 1) and V^* (Eq. 2) is then straightforward, and the corresponding values are also shown in Table 2. Table 3 reports the values of the third, energetic PHSCT EOS parameter E^*, as obtained by inserting the values of the corresponding A^* and V^* parameters listed in Table 2, along with the corresponding experimental vapor pressure and temperature, in the PHSCT EOS expression for pure components.

The k_{ij} values necessary to the complete characterization of any binary system were then obtained by fitting the activity coefficient data predicted from COSMO-RS calculations on the relevant mixtures performed by COSMOtherm, as described in the previous section. The pertinent values are reported in Table 4.

Once the entire sets of PHSCT EOS parameters for all pure components as well as the corresponding binary interaction parameters were available, they were inserted into the PHSCT EOS, and the corresponding VLE behavior of the systems considered were predicted. Table 4 shows the results of the comparison between experimental and predicted VLE behavior in terms of root-mean-square deviation (rmsd), defined as

$$rmsd = 100 \sum_i \sqrt{\frac{\left(M_i^{\exp} - M_i^{\mathrm{calc}}\right)^2}{N\left(M_i^{\exp}\right)^2}}, \qquad (22)$$

where $M_i^{\exp}$ is the experimental value of a generic property M, M_i^{calc} is the corresponding calculated value, and N is the total number of data points, whereas some graphical examples are given by Figures 1 to 4 for the trichloromethane/methanol, benzene/chlorobenzene, methanol/1,4-dioxane, and methanol/hexafluorobenzene systems, respectively. In particular, Figures 1a to 4a show a graphical representation of the quality of prediction obtained using COSMOtherm, while Figures 1b to 4b illustrate the quality of the calculation obtained from PHSCT (see Table 4).

In terms of rmsd, the overall quality of the results shown in Table 4 and in the pertinent figures is rather good. Nevertheless, from a detailed inspection of both Table 4 and all the graphics reported here, it is evident that the prediction of the phase behavior ranges from very good for several systems to a quality that is unsatisfactory from the standpoint of process design usability for a couple of systems considered. In particular, the virtual data predicted by COSMO are very good for all systems except for methanol/1,4-dioxane (see Figure 3a) and methanol/benzene (see Table 4). On the other hand, the PHSCT EOS nicely fits most systems (see Figures 1b to 4b) except methanol/benzene and methanol/cyclohexane, for which the model shows its inherent inability to reproduce polar–nonpolar interaction and association phenomena (see Table 4). A global comparison between these sets of figures shows the effects introduced by the EOS in the calculations.

Further, it is worthwhile noticing the computational time involved in the production of these results. The cost of collecting one vapor–liquid equilibria data point (that is, one temperature and composition for just one binary mixture) has been estimated to be about U.S. $2,600 and to take 2 days

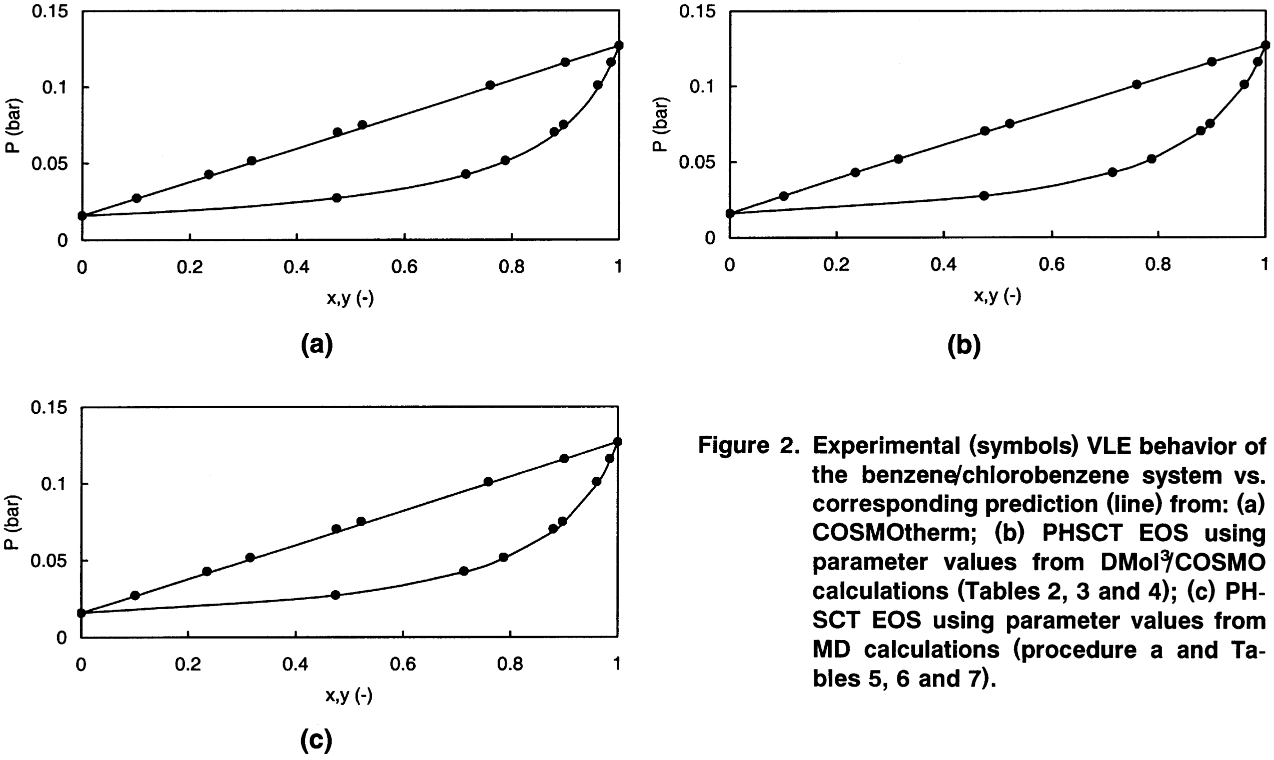

Figure 2. Experimental (symbols) VLE behavior of the benzene/chlorobenzene system vs. corresponding prediction (line) from: (a) COSMOtherm; (b) PHSCT EOS using parameter values from DMol³/COSMO calculations (Tables 2, 3 and 4); (c) PHSCT EOS using parameter values from MD calculations (procedure a and Tables 5, 6 and 7).

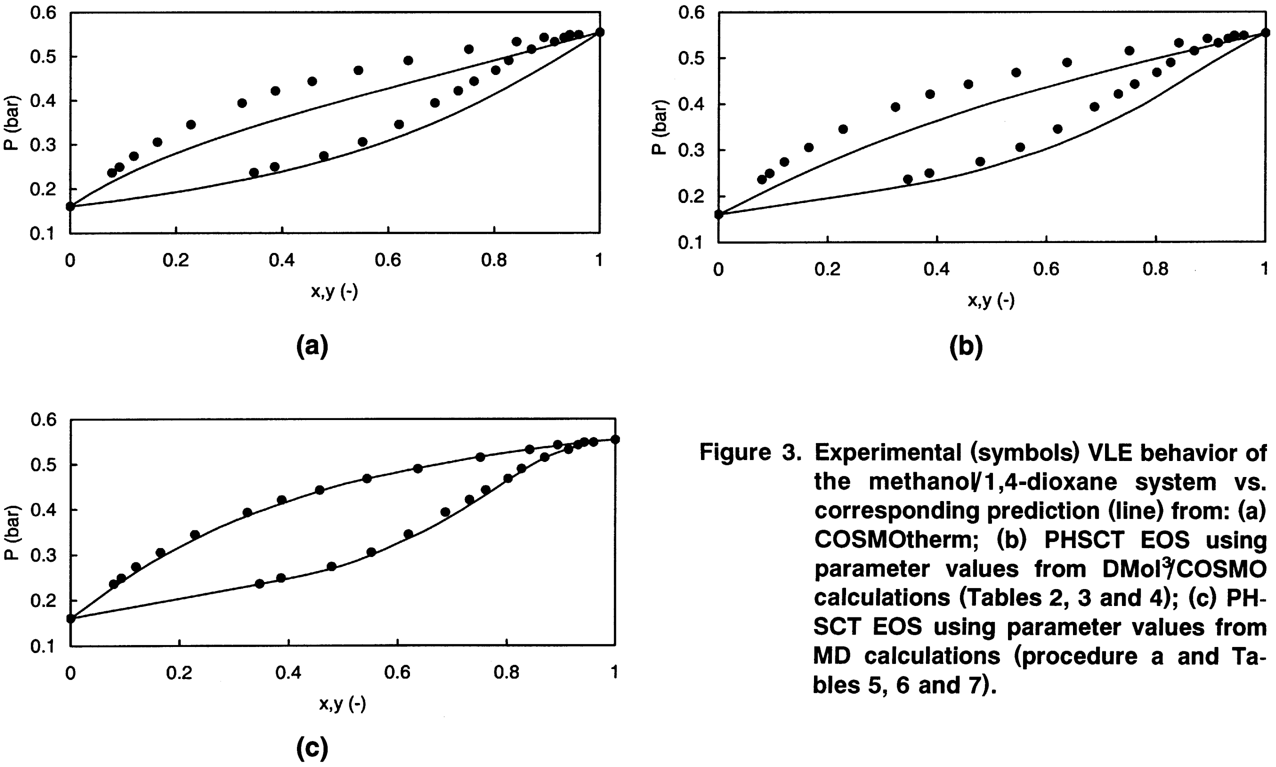

Figure 3. Experimental (symbols) VLE behavior of the methanol/1,4-dioxane system vs. corresponding prediction (line) from: (a) COSMOtherm; (b) PHSCT EOS using parameter values from DMol^3/COSMO calculations (Tables 2, 3 and 4); (c) PHSCT EOS using parameter values from MD calculations (procedure a and Tables 5, 6 and 7).

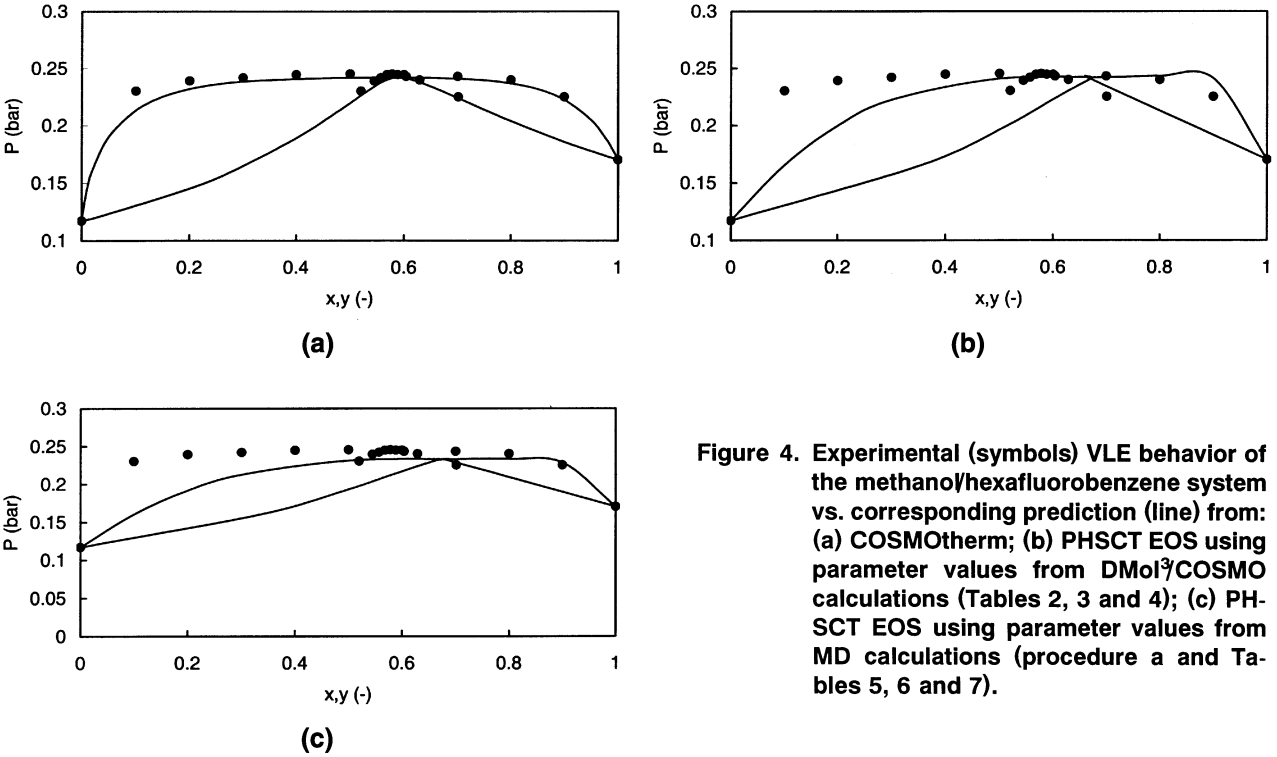

Figure 4. Experimental (symbols) VLE behavior of the methanol/hexafluorobenzene system vs. corresponding prediction (line) from: (a) COSMOtherm; (b) PHSCT EOS using parameter values from DMol^3/COSMO calculations (Tables 2, 3 and 4); (c) PHSCT EOS using parameter values from MD calculations (procedure a and Tables 5, 6 and 7).

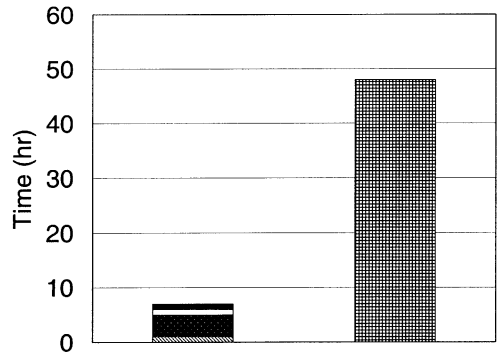

Figure 5. Time-scale comparison for global VLE prediction in the computational environment employed (left column) and one vapor–liquid data-point experimental determination.

Left column: ▨ time required for molecular modeling; ▦ time required for QM calculations; ☐ time required for EOS parameters estimation; and ■ time required for VLE prediction.

(Gubbins and Quirke, 1996), whereas the entire process, from molecule building and modeling through quantum calculations to EOS parameter estimation and VLE prediction takes less than 10 h in the computational environment described earlier and for the biggest molecules considered. In these calculations, the rate-determining step is the DMol^3 calculations (see Figure 5). Further, this time could be reduced by the availability of a database containing all the precalculated DMol^3 gas-phase and COSMO files for common compounds. In that case, the time of the molecular modeling would be of the same order of magnitude as that involved in process simulation, so that it should be possible to create an on-line liaison between the two simulation techniques.

Results from MM/MD-based calculations

The first step in our second, alternative procedure consists of the calculation of the molecular surfaces A and volumes V via a modified Connolly algorithm (Fermeglia and Pricl, 1999b). Figure 6a and 6b shows two examples of the Connolly surfaces obtained for pyridine and 1-butanol, respectively, whereas Table 5 reports the corresponding numerical values of these quantities obtained for all pure components considered. A comparison of these values with the corresponding data reported in Table 2 shows that these latter are always greater than the former; however, the difference is rather small. This is an expected result, considering the algorithm by which the A and V values of Table 5 were obtained. Indeed, we employed a method based on semiempirical molecular orbital calculations, according to which the electron density distribution of the molecule is determined using the AM1 algorithm, and the volume (and hence the surface) of the molecule is then calculated as a function of the percentage of the total calculated electronic density.

The determination of the two related PHSCT EOS parameters A^* and V^* is then straightforward, and the relevant values are also listed in Table 5.

According to the first route proposed for the calculation of the third EOS pure-component parameter E^*, the *a priori* calculated parameters reported in Table 5 were then inserted in the PHSCT EOS expression for pure components together with the corresponding experimental values of temperature T and vapor pressure P^0 (see Table 6). The third column of Table 6 shows the value of E^* thus obtained. The second path to E^* makes no use of experimental data, and consists in the determination of the ratio ϵ/k by MD simulations, as described in detail in the Theory section of this article. Once the value of ϵ/k is known for each compound, E^* is also known by virtue of Eq. 3, and the corresponding values are listed in the fourth column of Table 6.

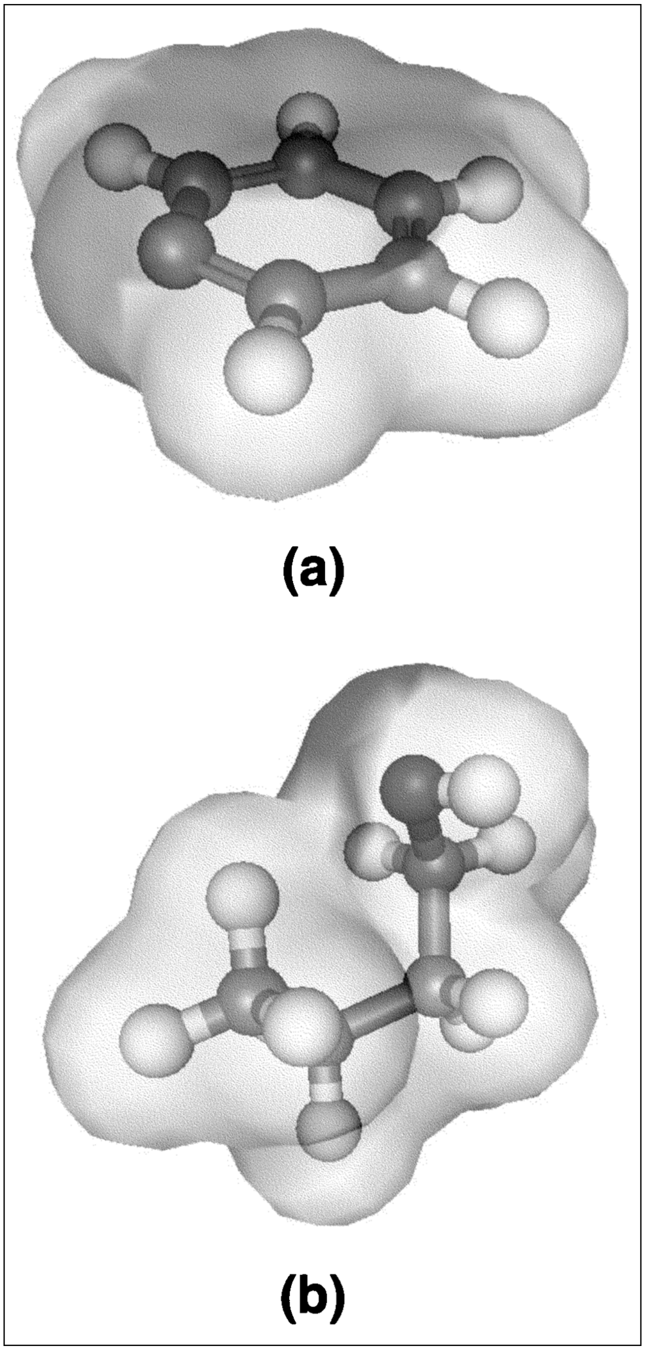

Figure 6. Example of a Connolly surface obtained for (a) pyridine; (b) 1-butanol.

Table 5. Molecular Surface Areas A and Volumes V Obtained from a Modified Connolly Algorithm and Corresponding PSHCT EOS Parameters A^* and V^*

Compound	A (Å^2)	V (Å^3)	A^* (10^{-9} cm^2/mol)	V^* (cm^3/mol)
Methanol	66.52	42.75	4.005	26.54
Ethanol	88.30	64.79	5.319	32.99
1-Butanol	115.1	72.44	6.929	46.39
Trichloromethane	112.5	92.41	6.774	39.69
Cyclohexane	131.7	124.1	7.929	43.39
n-Hexane	157.3	138.9	9.477	53.58
Benzene	121.8	109.4	7.335	41.11
Chlorobenzene	141.2	134.1	8.501	46.33
Hexafluorobenzene	160.5	145.5	9.668	53.95
Pyridine	117.7	105.4	7.087	39.78
1,4-Dioxane	118.1	97.81	7.111	41.50

Table 6. PHSCT EOS Energetic Parameter E^* (a) by Inserting Experimental Vapor Pressure P^0, Temperature T and Corresponding Set of A^* and V^* Parameters (Table 5) in PHSCT EOS for Pure Components; (b) Straight from MD Simulations

Compound	P^0 (bar)	T (K)	E^* (a) (bar dm^3/mol)	E^* (b) (bar dm^3/mol)
Methanol	0.169	298	56.253	56.193
Methanol	0.445	318	55.354	56.193
Methanol	0.554	323	55.119	56.193
Methanol	3.467	373	53.001	56.193
Ethanol	0.0786	298	64.948	65.039
1-Butanol	0.00872	298	76.019	76.101
Trichloromethane	0.265	298	64.921	65.100
Cyclohexane	0.130	298	76.411	76.586
n-Hexane	0.444	318	74.675	74.749
Benzene	0.127	298	73.216	73.113
Benzene	0.362	323	73.586	73.113
Chlorobenzene	0.0160	298	89.844	89.968
Hexafluorobenzene	0.117	298	80.891	80.945
Pyridine	0.638	373	81.058	80.940
1,4-Dioxane	0.161	323	75.175	75.344

Finally, the values of the binary interaction parameter k_{ij} for all the systems considered, again obtained from an MD calculations conducted on the mixture, using the appropriate pure-component parameter sets and Eq. 11 (see earlier for details), are reported in Table 7. This table also reports the results, in terms of rmsd (Eq. 22), of the comparison between the VLE predicted by the PHSCT EOS and the corresponding experimental data. The third and fourth columns refer to the results obtained with the EOS parameter sets calculated via the first route proposed (that is, using the experimental vapor pressure value for the determination of E^*), whereas columns 6 and 7 refer to the results based entirely on MD simulations. For the sake of comparison, some graphical examples are also reported in Figures 1c to 4c. By analyzing these figures, we can conclude that the best results are undoubtedly obtained from the application of the procedure based on MD calculations involving the experimental information on the pure-component vapor pressures. Nonetheless, if we consider the alternative procedure, and take into account the relatively short times and the low costs required to obtain the pure-component sets and the binary interaction parameter values of the PHSCT EOS for each system considered (from molecular building to MD simulations), and the fact that no single experimental data are required, the results yielded by the second route, entirely based on MM/MD simulation, are, in our opinion, to be considered more than satisfactory. The additional error introduced in this case can be sensibly ascribed to the temperature dependence of the energetic parameter E^*, which is not accounted for in this version of the PHSCT EOS (Fermeglia and Pricl, 1999).

Since the MD-based methods are effectively pure predictions, and since the COSMO virtual data are excellent for nine systems out of eleven, the slightly worse results obtained with these techniques are absolutely justifiable, since the same EOS was used in all cases.

Conclusions

This article reports the results obtained with two new procedures for estimating EOS parameters from computational chemistry, one based on COSMO solvation calculations and one on MM/MD experiments. Except for two systems, COSMO-based calculations showed satisfactory results in most cases, which is mainly ascribed to the inherent incapacity of the PHSCT EOS in treating polar/nonpolar and associated systems. The MD-based predictions show a comparable, if slightly better quality, especially in the case in which the third energetic EOS parameter E^* for the pure components was tuned on the corresponding experimental vapor-pressure values.

The new, original methods proposed in this work give good results, are relatively inexpensive, absolutely general, and can

Table 7. Binary Interaction Parameters k_{ij} and Corresponding VLE Prediction vs. Experimental Data*

Mixture	T (K)	k_{ij}	RMSD P	RMSD y	RMSD P	RMSD y
Methanol/ethanol	298	0.0891	0.15	0.25	0.15	0.50
Methanol/1-butanol	298	0.0073	0.095	1.06	0.19	1.13
Trichloromethane/methanol	298	0.0414	1.79	5.03	2.56	5.13
Methanol/cyclohexane	298	0.1084	4.66	9.60	6.33	14.2
n-Hexane/methanol	318	0.0738	5.13	14.2	5.31	14.1
Methanol/benzene	298	0.0891	2.05	6.53	2.28	6.49
Methanol/pyridine	373	0.0183	0.84	1.69	1.06	2.17
Methanol/hexafluorobenzene	298	0.0794	2.48	7.85	5.22	7.88
Methanol/1,4-dioxane	323	0.0441	0.62	2.41	6.70	2.24
Benzene/chlorobenzene	298	0.0010	0.035	0.18	0.12	0.74
Trichloromethane/benzene	323	−0.0100	0.25	0.25	3.47	0.50

*Experimental data from Dechema Chemistry Data Series.

be applied in principle to any equation-of-state, provided the parameters have a well-defined physical meaning. The overall quality of the results obtained, both in terms of VLE prediction capabilities and computational time involved, allow us to conclude that bridging between molecular and process simulation, as well as for mixture calculations, is now well established through the direct determination of the parameters of a physically based EOS model. We expect such methods, including the use of better EOS, improved intermolecular potentials, and faster quantum-mechanical methods, will be implemented in the near future.

Acknowledgments

This work was supported by the Italian Ministery for University and Scientific Research (MURST—Rome) and the University of Trieste (special grant for Scientific Research). The authors are also grateful to Dr. Andreas Klamt for the helpful and stimulating discussions, and to Prof. Stanley I. Sandler for the critical suggestions during the manuscript revision process.

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Manuscript received May 4, 2000, and revision received Apr. 16, 2001.