Activity Coefficients in Dilute Aqueous Solutions from Free Energy Simulations

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The free energy perturbation method with Monte Carlo simulations has been used to calculate relative solvation free energies and ratios of activity coefficients of organic solutes at infinite-dilution in water at 25°C. Systems studied include hydrocarbons, chlorinated hydrocarbons, and alcohols. Analysis of the free energy simulations reveals that a major limitation of current methodologies is our inability to determine a priori the electron density distribution of a molecule in a condensed, polarizing medium. Moreover, currently employed simulation lengths may be inadequate for convergence of the averages in some aqueous systems. These problems do not, however, appear to be insurmountable. In contrast to group contribution methods, free energy simulations are still rather primitive to be applied in a routine fashion for the quantitative prediction of thermodynamic properties, but dramatic improvements in the technique are still to be made.

Introduction

Aqueous mixtures are encountered in a large number of industrial operations, such as petroleum processing, coal gasification, separations and waste treatment (Newman, 1980). These mixtures can exhibit unique phase behavior, including large miscibility gaps, solubility minima with increasing temperature and lower critical solution temperatures (Franks and Reid, 1973). As a consequence, most conventional thermodynamic models either perform rather poorly (Larsen et al., 1987) or face insurmountable difficulties (Thomas and Eckert, 1984) when they are applied to aqueous systems. This difficulty has been circumvented with the development of specialized parameter sets in the group contribution approach (Hooper et al., 1988) or by the use of novel empirical mixing rules in the equation of state approach (Kabadi and Danner, 1985; Michel et al., 1989). However, even though these strategies appear to work in specific cases, the empirical nature of these models makes it difficult to extrapolate with confidence beyond the range of the experimental data used in the parameterization.

The limited success of simple engineering models in describing aqueous solutions is hardly surprising. Water is unique in both its ability to dissolve electrolytes and polar compounds and its "aversion" toward nonpolar organics (Franks, 1973). In particular, solutions of nonpolar molecules in water have attracted much attention over the past 50 years due to their unusual thermodynamic properties: favorable enthalpies of hydration, very large negative entropies of hydration and large positive heat capacity increments (Franks, 1973). Several intuitive explanations of these properties have appeared, most notably the "iceberg" hypothesis of Frank and Evans (1945), but a generally accepted interpretation is still lacking (Lazaridis and Paulaitis, 1992). The unfavorable interaction between water and nonpolar groups is thought to lead to aggregation of such groups in water (hydrophobic association) and give rise to self-assembling microstructures, such as micelles, bilayers or folded proteins (Tanford, 1980).

Molecular-level information on the microscopic structure of aqueous solutions has been obtained by Monte Carlo or Molecular dynamics computer simulations (Rossky and Karplus, 1979; Geiger et al., 1979; Postma et al., 1982). In principle, if such simulations could describe events on experimental timescales, they would allow us to determine phase behavior directly. In practice, however, limitations in computer power make this task unfeasible, at least for the foreseeable future. Instead, a more viable approach is to infer phase behavior by evaluating thermodynamic potentials in idealized, computer-simulated systems. Particularly amenable to computational studies are infinitely dilute solutions.

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Infinite-dilution activity coefficients are of fundamental importance as measures of intermolecular interactions in solution. In addition, they are useful in many practical applications (Eckert et al., 1981). For binary mixtures that exhibit moderate deviations from ideality, knowledge of the two infinite-dilution activity coefficients allows the determination of the activity coefficients over the entire concentration range (Schreiber and Eckert, 1971). Infinite-dilution activity coefficients are also directly related to Henry's constants, and in the case of sparingly soluble solutes, such as hydrocarbons in water, they readily yield the solubility. Recent advances in experimental techniques now permit accurate measurement of infinite-dilution activity coefficients (Barr and Newsham, 1987; Trampe and Eckert, 1990) but serious limitations to experimentation are frequently imposed by cost, time and safety considerations or the availability of chemicals. Moreover, no measurements can be done on molecules that do not as yet exist, such as a contemplated chemical or pharmaceutical product. Therefore, prediction of infinite-dilution activity coefficients in aqueous solutions would be of considerable practical utility.

The formalism for calculating infinite-dilution activity coefficients or Henry's constants by computer simulation has been presented in detail (Shing and Gubbins, 1982; 1983; Shing, 1985; Haile, 1986; Chialvo, 1990) and requires the calculation of the chemical potential of the solute in the solvent. To date, most applications in the chemical engineering community have been concerned with mixtures of Lennard-Jones particles with the primary goal of testing analytical statistical mechanical theories. However, a different motive for computer simulations has prevailed in the fields of organic chemistry and biochemistry, where simulations are used to obtain quantitative predictions for systems of practical interest, such as organic reactions in solution (Jorgensen, 1989b), inhibitor binding to enzymes (Fleischman and Brooks, 1990) and protein stability (Dang et al., 1989). This practical focus has brought about the development of realistic molecular models for water (Jorgensen et al., 1983), organic molecules (Jorgensen et al., 1984) and proteins and nucleic acids (Brooks et al., 1983; Weiner et al., 1984; Jorgensen and Tirado-Rives, 1988) which are thought to represent intermolecular interactions in aqueous solution with quantitative or at least semiquantitative accuracy.

In this work we examine the ability of state-of-the-art free energy simulation techniques and realistic interaction potentials to yield *quantitative results* for activity coefficients of simple organic molecules at infinite dilution in water. Specifically, we aim to answer the following questions:

(a) Given the computing power available today and reasonable interaction potentials, can we make reliable predictions of aqueous solubilities of relatively simple organic compounds without the need for experimentation?

(b) Are the results of these simulations of higher reliability than the predictions of empirical group contribution methods?

Emphasis in our calculations is placed on chlorinated compounds due to the availability of accurate experimental data (Barr and Newsham, 1987; Wright, 1991; Wright et al., 1992) and to the relevance of these chemicals to pollution abatement in industrial wastewater streams.

Thermodynamics of Infinitely Dilute Solutions

The residual chemical potential of component *i* in a mixture with respect to an ideal gas mixture (IGM) at the same temperature, T, composition, x_i, and number density, ρ, is:

$$\mu_i^V = \mu_i - \mu_i^{\mathrm{IGM}}(T,x,\rho) = kT \ln\left(\frac{f_i}{x_i \rho kT}\right) \tag{1}$$

where f_i denotes the fugacity of component i and is defined by this equation. At infinite dilution, Henry's law is valid, and the residual chemical potential of the solute is related to Henry's constant by (Shing and Gubbins, 1982):

$$\mu_i^{V,\infty} = kT \ln(H/\rho kT) \tag{2}$$

We can also define a residual or excess (Prausnitz et al., 1986, p. 518) chemical potential with respect to the IGM at the same temperature, composition, and pressure, P:

$$\mu_i^P = \mu_i - \mu_i^{\mathrm{IGM}}(T,x,P) = kT \ln\left(\frac{f_i}{x_i P}\right) \tag{3}$$

which, at infinite dilution, is related to Henry's constant by:

$$\mu_i^{P,\infty} = kT \ln\left(\frac{H}{P}\right) \tag{4}$$

Furthermore, the activity coefficient of component *i* in solution at a given T, P, and x_i is defined as:

$$\gamma_i = \left(\frac{f_i}{f_i^o x_i}\right) \tag{5}$$

where x_i is the mole fraction of this component in the mixture and f_i^o is the fugacity of pure i at the same temperature and pressure. It follows that (Haile, 1986):

$$kT \ln\gamma_i = kT \ln\left(\frac{f_i}{x_i P}\right) - kT \ln\left(\frac{f_i^o}{P}\right) = \mu_i^P - \mu_i^{P,o} \tag{6}$$

and at infinite dilution:

$$kT \ln \gamma_i^\infty = \mu_i^{P,\infty} - \mu_i^{P,o} \tag{7}$$

The ratio of infinite-dilution activity coefficients for two different solutes dissolved in the same solvent is given by:

$$\begin{aligned} kT \ln \gamma_1^\infty/\gamma_2^\infty &= (\mu_1^{P,\infty} - \mu_2^{P,\infty}) - (\mu_1^{P,o} - \mu_2^{P,o}) \\ &= (\mu_1^{P,\infty} - \mu_2^{P,\infty}) - kT \ln\left(\frac{f_1^o}{f_2^o}\right) = (\mu_1^{V,\infty} - \mu_2^{V,\infty}) - kT \ln\left(\frac{f_1^o}{f_2^o}\right) \end{aligned} \tag{8}$$

and similarly the ratio of Henry's constants is:

$$kT \ln \frac{H_1}{H_2} = (\mu_1^{P,\infty} - \mu_2^{P,\infty}) \tag{9}$$

Free Energy Simulations

Monte Carlo and molecular dynamics simulations readily yield information on the structure and the mechanical properties of a pure phase or a mixture. Thermal properties, however, such as the entropy or the free energy, which depend on the volume of phase space sampled by the system, are much more difficult to obtain and require special simulation methods. Most of the currently available methods involve the calculation of differences in free energy between systems that differ in a specific property, such as the number of molecules, the identity of a chemical group or the conformation of a polyatomic molecule. A review of such methods has recently been published by Beveridge and DiCapua (1989).

One of the first methods for calculating free energies for simple fluids is the test particle method (Widom, 1963; Adams, 1974; Shing and Gubbins, 1982, 1983). This method is based on the potential distribution theorem (Widom, 1963), which gives the free energy change upon addition of a particle to the system—that is, the chemical potential—as an ensemble average over the configurations of the original system:

$$\mu_i^V = -kT \ln\left\langle \exp - \frac{\phi_i}{kT} \right\rangle_{N-1} \tag{10}$$

where ϕ_i is the interaction energy of the added particle with all other particles in the fluid and the brackets denote an ensemble average for the original system of $N-1$ particles. In practice, this method is implemented by generating an ensemble of configurations of $N-1$ particles and calculating the interaction energy of a hypothetical ("ghost") particle inserted at random positions in the simulation box. The method has proven quite efficient but fails at high densities due to the low probability of successfully inserting a particle at these densities. Modifications to the method for applications at high densities have been proposed (Shing and Gubbins, 1982; Deitrick et al., 1989).

Another method of calculating free energy differences is thermodynamic integration implemented through the use of a coupling parameter (Kirkwood, 1935). If the free energy A of the system is a function of the coupling parameter λ, then the change in free energy upon a change in this parameter from λ_i to λ_f will be:

$$\Delta A = \int_{\lambda_i}^{\lambda_f} \frac{dA}{d\lambda}\, d\lambda \tag{11}$$

which, as can be shown (Beveridge and DiCapua, 1989; Haile, 1986), is equal to:

$$\Delta A = \int_{\lambda_i}^{\lambda_f} \left\langle \frac{dU}{d\lambda} \right\rangle_\lambda d\lambda \tag{12}$$

where U is the total potential energy of the system and $\langle\ \rangle_\lambda$ denotes a canonical ensemble average at a fixed value of λ. The residual chemical potential is obtained if the change in the coupling parameter describes the insertion of a particle in a fluid (Swope and Andersen, 1984; Shing and Chung, 1987; Shing et al., 1988). This can be achieved by defining a Hamiltonian where the interaction between the inserted particle and the rest of the system is scaled by λ; for example,

$$U(\lambda) = U_{N-1} + \lambda\phi_i, \tag{13}$$

in which case the residual chemical potential is:

$$\mu_i^V = \int_0^1 \langle \phi_i \rangle_\lambda d\lambda \tag{14}$$

This method is implemented by performing a series of simulations at different values of λ with the Hamiltonian given by Eq. 13, calculating the average $\langle\ \rangle_\lambda$ and then numerically evaluating the integral of Eq. 14. At high densities this method performs better than the test particle method since the added particle is gradually "grown," rather than inserted, into the system. However, at low values of λ the interaction energy ϕ_i can be very large leading to high statistical uncertainty in the ensemble average of Eq. 14 (Swope and Andersen, 1984). A frequently used implementation of thermodynamic integration is the "slow growth" method (Straatsma et al., 1986b). In this method a single simulation is performed while the coupling parameter is gradually changed from its initial to its final value. The ensemble average in Eq. 14 is then approximated by its instantaneous value and the integral by the sum of the integrands:

$$\Delta A = \int_{\lambda_i}^{\lambda_f} \left\langle \frac{dU}{d\lambda} \right\rangle_\lambda d\lambda \approx \int_{\lambda_i}^{\lambda_f} \frac{dU}{d\lambda} d\lambda \approx \Sigma \Delta U(\lambda - \delta\lambda) \tag{15}$$

The use of coupling parameters is also common in the free energy perturbation (FEP) method. This method uses a fundamental result of Zwanzig's perturbation theory (Zwanzig, 1954) to obtain the difference in free energy between two systems whose Hamiltonians differ by the "perturbation" potential ΔU:

$$\Delta A = -kT \ln\left\langle \exp - \frac{\Delta U}{kT} \right\rangle_o \tag{16}$$

where $\langle \ldots \rangle_o$ denotes the canonical ensemble average for the system described by the reference Hamiltonian. If ΔU corresponds to the interaction energy of a particle added to the system, then ΔA will be the residual chemical potential and Eq. 16 is equivalent to Eq. 10. If the overlap in the regions of configuration space sampled by the reference and the "perturbed" systems is small, Eq. 16 will not be of much practical utility in computer simulations, because the configurations contributing most to this average will only rarely be sampled. This is precisely the problem that arises in the test particle method at high densities. In FEP, as in thermodynamic integration, coupling parameters can be used to effect the change in ΔU of the system gradually, by making the Hamiltonian a function of the coupling parameter and allowing the latter to vary from 0 to 1:

$$U = U_o + \lambda \Delta U \tag{17}$$

Equation 16 can then be applied between any two values of λ, and the total change in free energy will be the sum of the incremental free energy differences:

$$\Delta A(\lambda_i) = -kT \ln\left\langle \exp - \frac{U(\lambda_i + \delta\lambda) - U(\lambda_i)}{kT} \right\rangle_{\lambda_i}$$

$$\Delta A = \sum_i \Delta A(\lambda_i) \tag{18}$$

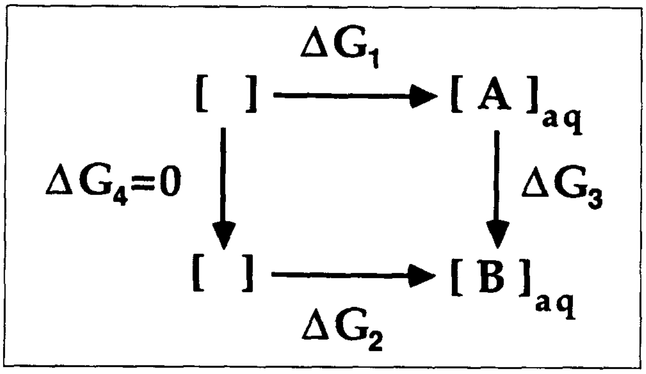

Figure 1. Thermodynamic cycle for the calculation of relative free energies of solvation.

ΔG_1 and ΔG_2 are the solvation free energies, equal to the free energy change for "growing" a solute in the solvent. ΔG_3 is the calculated free energy of "transforming" solute A to solute B in the same solvent.

The use of coupling parameters makes the FEP method quite versatile. For instance, it can be used to calculate free energies of artificial transformations, such as the "mutation" of one chemical group into another. Then, by the use of simple thermodynamic cycles (Tembe and McCammon, 1984), physically meaningful free energy increments can be extracted. For example, the difference in the free energy of solvation of two molecules A and B, $\Delta G_2 - \Delta G_1$, can be obtained through the application of the thermodynamic cycle depicted in Figure 1 by calculating the quantity ΔG_3 for the transformation of one solute into the other by computer simulation.

Critical to the success of any computational scheme to obtain quantitative thermodynamic properties from simulation is the availability of realistic interaction potentials. For water such potentials have been obtained either theoretically, through *ab initio* molecular orbital calculations (Matsuoka et al., 1976), or empirically, by adjusting the model parameters in order to reproduce specific structural and thermodynamic properties of the liquid (Jorgensen et al., 1983). While almost all potentials developed so far assume pairwise additive interactions, considerable activity has been devoted recently to the development of more sophisticated, polarizable models for water, for example, Caldwell et al. (1990).

Similar approaches have been taken to obtain interaction potential functions for simulations of organic molecules in water. One approach is to perform a large number of molecular orbital calculations of the organic molecule and a solvent water molecule at different relative positions and orientations and fit the results to an analytical potential function, for example, Swaminathan et al. (1978) and Linse et al. (1984). The other is the Transferable Intermolecular Potential Functions (TIPS) approach, taken by Jorgensen and coworkers, which associates with each atom a pair of Lennard-Jones parameters and a partial atomic charge and expresses the interaction energy as the sum of Lennard-Jones and electrostatic interactions (Jorgensen, 1981). The partial charges are obtained through molecular orbital calculations on the isolated molecule by either Mulliken population analysis or by fitting a set of partial charges to the quantum-mechanical electrostatic potential. The latter is generally considered to be the superior approach (Singh and Kollman, 1984).

Table 1. Simulations Performed and Calculated Differences in Solvation Free Energy (UC = Uncharged)

	1→2	ΔG_{calc}
A1	methane→dichloromethane	-3.56 ± 0.3
A2	methane→UC dichloromethane	-0.41 ± 0.5
A3	UC dichloromethane→dichloromethane	-2.59 ± 0.09
A4		-3.24 ± 0.1
B1	propane→dichloromethane	-4.0 ± 0.1
B2	propane→UC dichloromethane	-1.03 ± 0.03
C1	isobutane→chloroform	-2.52 ± 0.07
C2		-2.42 ± 0.07
C3		-2.32 ± 0.06
C4	UC chloroform→chloroform	-0.94 ± 0.06
D1	neopentane→carbon tetrachloride	-2.5 ± 0.08
D2		-2.09 ± 0.09
D3		-2.41 ± 0.09
D4	carbon tetrachloride→UC carbon tetrachloride	$+0.2 \pm 0.01$
E1	1,1 dichloroethane→chloroform	$+0.09 \pm 0.08$
E2		-0.15 ± 0.1
E3		-0.10 ± 0.07
E4	UC 1,1 dichloroethane→UC chloroform	-0.815 ± 0.04
E5	UC 1,1 dichloroethane→1,1 dichloroethane	-2.21 ± 0.1
F1	1,1 dichloroethane→trans-1,2 dichloroethane	-0.002 ± 0.3
F2	1,1 dichloroethane→gauche-1,2 dichloroethane	-2.3 ± 0.3
G1	toluene→phenol	-8.9 ± 0.4
G2	toluene→phenol (40 windows)	-7.78 ± 0.2
G3	toluene→UC phenol	-0.49 ± 0.07
G4	UC phenol→phenol	-7.56 ± 0.3
G5	toluene→"polar" toluene	-0.05 ± 0.01
G6	toluene→UC phenol (12-site ring)	-0.52 ± 0.1
G7	UC phenol→phenol (12-site ring)	-7.02 ± 0.3
H1	methanol→water	-2.88 ± 0.35
H2		-1.47 ± 0.37
H3		-0.96 ± 0.37

In this work, we have used TIPS-type potential energy functions in conjunction with Monte Carlo simulations and the FEP method to calculate differences in solvation free energies for organic solutes at infinite dilution in water and from these, the ratios of their infinite-dilution activity coefficients using Eq. 8. The solutes studied include hydrocarbons (methane, propane, isobutane, neopentane, and toluene), chlorinated hydrocarbons (dichloromethane, 1,1 and 1,2 dichloroethane, chloroform, and carbon tetrachloride) and alcohols (methanol and phenol). The simulations performed are listed in Table 1.

Simulation Method

The potential energy is expressed as the sum of Lennard-Jones and Coulomb potential functions (Jorgensen, 1981):

$$U = \sum_{i<j} \frac{A_i A_j}{r_{ij}^{12}} - \sum_{i<j} \frac{C_i C_j}{r_{ij}^{6}} + \sum_{i<j} \frac{q_i q_j}{r_{ij}} \tag{19}$$

where the sums are over all pairs of interaction sites, $A_i = (4\epsilon_i \sigma_i^{12})^{1/2}$, $C_i = (4\epsilon_i \sigma_i^{6})^{1/2}$, q_i is the partial electric charge of interaction site i and r_{ij} is the separation between interaction sites. The form of this equation implies that the geometric mean combining rule is used for both Lennard-Jones parameters. The interaction sites are usually atoms; however, nonpolar hydrogens bonded to carbon atoms can be combined with the carbon atom to form a single "united" atom. The TIP4P model for water (Jorgensen et al., 1983) used in this study has a total of four interaction sites: the oxygen atom, the two hydrogen atoms, and a center for the negative charge

Table 2. Interaction Potential Parameters for the Solvent and the Solutes

Molecule	(United) Atom	σ (Å)	ϵ (kcal/mol)	q (Electron Units)
TIP4P water*	O	3.15365	0.155	0.000
	H	0.000	0.000	+0.520
	M	0.000	0.000	−1.040
TIP3P water*	O	3.15061	0.1521	−0.834
	H	0.000	0.000	+0.417
methane**	CH_4	3.730	0.294	0.000
propane**	CH_3	3.905	0.175	0.000
	CH_2	3.905	0.118	0.000
isobutane**	CH_3	3.910	0.160	0.000
	CH	3.850	0.080	0.000
neopentane**	CH_3	3.960	0.145	0.000
	C	3.800	0.050	0.000
dichloromethane†	CH_2	3.800	0.118	+0.500
	Cl	3.400	0.300	−0.250
chloroform†	CH	3.800	0.080	+0.420
	Cl	3.470	0.300	−0.140
carbon tetrachloride‡	C	3.592	0.1013	+0.392
	Cl	4.0804	0.347	−0.098
1,1 dichloroethane	CH	3.800	0.080	+0.300
	CH_3	3.910	0.160	+0.100
	Cl	3.635	0.282	−0.200
1,2 dichloroethane ǂ	CH_2	3.983	0.114	+0.250
	Cl	3.635	0.282	−0.250
methanol ⧧	CH_3	3.775	0.207	+0.265
	O	3.070	0.170	−0.700
	H	0.000	0.000	+0.435
toluene	CH	3.750	0.110	0.000
	C	3.750	0.110	0.000
	CH_3	3.910	0.160	0.000
phenol	CH	3.750	0.110	0.000
	C	3.750	0.110	+0.265
	O	3.070	0.170	−0.700
	H	0.000	0.000	+0.435
12-site aromatic ring⩩	C	3.550	0.070	−0.115
	H	2.420	0.030	+0.115

*Jorgensen et al. (1983); **Jorgensen et al. (1984); †Jorgensen (1989a); ‡Rao and Singh (1991); ǂ Jorgensen et al. (1981); ⧧ Jorgensen and Ravimohan (1985); ⩩ Jorgensen and Severance (1990).

Table 3. Geometrical Parameters of the Solvent and the Solutes

	r (Å)		θ (degrees)
C(sp3)-C(sp3)	1.54	H-O-C (phenol)	109.5
C(sp3)-Cl	1.758	H-O-C (methanol)	108.5
C(arom)-C(arom)	1.39	H-O-H (water)	104.52
C-CH3 (toluene)	1.47		
C-O (phenol)	1.38		
O-H (phenol)	0.96		
C-O (methanol)	1.43		
O-H (methanol)	0.945		
O-H (water)	0.9572		
O-M (water)	0.15		
C(arom)-H(arom)	1.08		

located along the dipole vector. All parameters for the molecules studied here are listed in Table 2.

The parameters for methane, isobutane, propane, neopentane, carbon tetrachloride, 1,2 dichloroethane, and methanol were obtained from the literature (references are listed in Table 1). For dichloromethane and chloroform we used unpublished parameters suggested by Jorgensen (Jorgensen, 1989a). For 1,1 dichloroethane we used the Lennard-Jones parameters of isobutane for the CH and CH3 groups, and the Lennard-Jones parameters of 1,2 dichloroethane for the chlorine atoms. The partial charge distribution for this molecule was chosen to give a reasonable dipole moment ($\mu = 2.45$ D), somewhat higher than the experimental value ($\mu = 2.0$ D), as is the usual practice in condensed phase simulations with effective, pairwise additive potentials (Jorgensen, 1981). The parameters for the amino acid tyrosine were used for phenol (Jorgensen and Tirado-Rives, 1988). Two different models were investigated for the aromatic ring of toluene. The first consisted of six united-atom sites of zero partial charge while the second was a full, 12-site description with polar C-H bonds. The geometrical parameters for the molecules are listed in Table 3.

To calculate the free energy change for the transformation of one solute to another we performed five simulations at values of λ equal to 0.1, 0.3, 0.5, 0.7, and 0.9. In each of these simulations we calculated the difference in free energy for a change in the coupling parameter in both directions; that is, $\delta\lambda = +/-0.1$. The total free energy is obtained as the sum of the ten individual ΔGs. The transformations were performed in a way that optimizes overlap in the structures of the two solutes. For example, in the propane-to-dichloromethane simulation the two methyl groups were gradually transformed to chlorine atoms while the length of the carbon-carbon/chlorine bonds was increased from 1.54 to 1.758 Å.

The solute was initially placed at the center of a 20 Å cubic box containing 267 water molecules which had been previously equilibrated at 25°C. A number of water molecules equal to the number of heavy atoms in the solute were then deleted. This system was initially equilibrated for 500-K configurations at constant volume to relieve repulsive contacts between water molecules and the solute. Constant pressure equilibrations were then performed at each of the five values of λ for another 500-K configurations, followed by 2.5-M configurations for the production runs in the NPT ensemble.

The program BOSS was used for all calculations (Jorgensen, 1989a). Periodic boundary conditions were employed with preferential sampling of water molecules near the solute (Owicki and Scheraga, 1977). The statistical uncertainty was estimated by the standard deviation of the mean from five subsets of the production run. The water-water and water-solute interactions were cut off at 8.5 Å with a quadratic "switching" function between 8 and 8.5 Å. All simulations were carried out at 25°C and 1 atm. With these settings the transformation of one solute into another took a total of about two CPU days on a single processor of a SGI 4D-220 workstation.

Results

The calculated differences in hydration free energies for the individual simulations are reported in Table 1. For many systems replicate runs were performed in order to assess the statistical precision of the results. This approach gives a better estimate of statistical uncertainties than does the method of subaverages, since correlations between the subsets of data in the production runs can lead to an underestimation of these uncertainties by the latter method (Straatsma et al., 1986a).

Table 4. Calculated Differences in Solvation Free Energy and Ratios of Infinite Dilution Activity Coefficients at 25°C

1→2	$f_1^{\mathrm{ref}*}$ (torr)	$f_2^{\mathrm{ref}*}$ (torr)	ΔG_{calc} (kcal/mol)	$\gamma_1^\infty/\gamma_2^\infty$ (Calc.)	$\gamma_1^\infty/\gamma_2^\infty$ (UNIFAC)†	$\gamma_1^\infty/\gamma_2^\infty$ (Exp.)‡
methane→dichloromethane	204,440	429	−3.44	0.71	N/A	0.55
propane→dichloromethane	7,060	429	−3.97	50.8	1.07	16.9
isobutane→chloroform	2,675	193.4	−2.42	4.36	1.1	23.7
neopentane→carbon tetrachloride	1,287	115	−2.33	4.64	0.3	5.86
1,1 dichloroethane→1,2 dichloroethane	227	79	−1.5	4.4	1.19	1.95
1,1 dichloroethane→chloroform	227	193.4	+0.07	0.76	0.92	1.38
toluene→phenol	28.4	0.44**	−7.9	10,164	1,097	146
methanol→water	126.9	23.8	−1.77	3.8	2.24	1.3

*All are saturation vapor pressures (Boublik et al., 1973, 1984; Wilhoit and Zwolinski, 1971) except for phenol. For the aliphatic hydrocarbons the vapor pressure has been used as the reference fugacity for the γ_i^∞ reported for these gases (Mackay and Shiu, 1975). In the other cases nonideal vapor corrections are negligible.

**Fugacity of the hypothetical pure subcooled liquid, obtained from the vapor pressure of solid phenol (CRC Handbook) and the ratio f^L/f^S calculated by the method of Weimer and Prausnitz (Prausnitz et al., 1986, p. 418).

†Calculation with standard UNIFAC parameters using the program available with Sandler's textbook [Sandler, 1989].

‡All chlorinated compounds from Wright (1991, 1992); methane, propane and isobutane from Mackay and Shiu (1975); neopentane from Medir and Giralt (1982); methanol from Bergmann and Eckert (1991) by extrapolation to room temperature.

Several simulations were also performed using the so called "electrostatic decoupling" procedure (Bash et al., 1987). Here the transformation is performed in two steps: in one the Lennard-Jones parameters are changed and in the other the partial charges. This procedure allows a separate determination of the contribution of van der Waals and electrostatic interactions to the calculated free energies. The averages of free energy differences from the runs in Table 1 are listed in Table 4. These averages have also been used to calculate ratios of infinite-dilution activity coefficients which are compared to experimental values and to UNIFAC predictions in Table 4. No error bars are reported in this table, since the number of repeated runs was small. However, one can make a qualitative assessment of the statistical uncertainty by inspection of the results in Table 1.

In the methane-to-dichloromethane simulations (runs A1 to A4) the dominant contribution comes from electrostatic interactions between dichloromethane and the solvent (runs A3 and A4) with a smaller, favorable contribution coming from dispersion interactions (run A2). The difference between the two charging runs (A3 and A4) is substantially larger than the error bars calculated by the method of subaverages in both simulations. The average calculated ΔG gives a ratio of activity coefficients equal to 0.71, which is slightly higher than the experimental value of 0.55.

In the propane-to-dichloromethane simulations (runs B1, B2, A3 and A4) the van der Waals contribution is also favorable (B2) due to the more favorable dispersion interactions for the chlorine atoms with water compared to the methyl groups. This result added to the average of the results from the two dichloromethane charging runs (A3 and A4) gives a free energy change of −3.94 kcal/mol, which is close to that obtained from the one-step perturbation (B1). However, the calculated ratio of infinite-dilution activity coefficients is higher than the experimental value by a factor of 3. The largest uncertainty in this calculation is in the free energy of charging dichloromethane—the three values obtained for this free energy change are: −2.59 kcal/mol (A3), −3.24 kcal/mol (A4), and −2.97 kcal/mol (B1-B2), which can account for nearly all of this discrepancy. It should also be noted here that the error bar for run B2 is much smaller than that for the analogous run from methane (A2). This is due to the fact that, in the transformation of propane to dichloromethane, the chlorine atoms replace the methyl groups, while in the methane-to-dichloromethane transformation, the two chlorine atoms must be "grown" into and thereby displace the solvent. The much better precision obtained in run B2 indicates that it is important to achieve maximum overlap in structures of the two interconverted solutes.

Three different simulations (runs C1 to C3) for the transformation of isobutane to chloroform gave comparable results, the average of which is −2.42 kcal/mol. About 1 kcal/mol of this can be attributed to the electrostatic interactions of chloroform with water (run C4). The average value leads to a ratio of infinite-dilution activity coefficients which is significantly smaller than the experimental value and therefore is an underestimation of the free energy change for the transformation.

Three different simulations (D1 to D3) were also performed for the transformation of neopentane to carbon tetrachloride. The free energy changes from these runs agree within 0.5 kcal/mol and the average value of the free energy difference (−2.33 kcal/mol) gives a ratio of infinite-dilution activity coefficients close to the experimental value. The dominant contribution to the calculated free energy change for this transformation comes from dispersion interactions. Charging carbon tetrachloride (run D4) contributes only +0.2 kcal/mol, indicating that the partial charges chosen for this molecule do not make much difference in the calculated free energy change. The very good agreement with experiment obtained for this transformation compared to the poor agreement obtained for the propane-to-dichloromethane transformation supports the observation made above that discrepancies with experiment in the latter case are due to statistical uncertainties associated with the free energy calculations for the charging process and possibly to inaccurate values for the partial charges.

For the transformation of 1,1 dichloromethane to chloroform we performed three equivalent one-step simulations (runs E1 to E3) as well as the three-step simulation: uncharging 1,1 dichloroethane (E5), transformation to uncharged chloroform (E4), and charging chloroform (C4). The small difference in the hydration free energies for these two solutes appears to come from a balance of dispersion interactions for the hydration of chloroform (C4 + E4), which favor chloroform (it has one more chlorine atom), with electrostatic interactions (E5), favoring the hydration of 1,1 dichloroethane which is much more polar. The average free energy change for the four transformations is +0.07 kcal/mol, leading to a ratio of infinite-dilution activity coefficients equal to 0.76 vs. 1.38 from experiment. The free energy change for the three-step simulation is substantially more positive (+0.455 kcal/mol), perhaps due to uncertainties in the charging/uncharging calculations. However, the discrepancy with experiment cannot be attributed to these uncertainties alone. As noted above, the assignment of partial charges may be an additional source of error.

The transformation of 1,1 to 1,2 dichloroethane consisted of two simulations: in the first, 1,1 dichloroethane was transformed into gauche 1,2 dichloroethane and in the second into trans 1,2 dichloroethane. The free energy differences calculated from these simulations are -2.3 ± 0.3 and 0.0 ± 0.3 kcal/mol, respectively. Assuming about 33% trans population [it is about 35% in the pure liquid (Millot and Rivail, 1989)] we estimate -1.5 ± 0.3 kcal/mol for the overall transformation. This value is somewhat more negative than the experimental value (~ -1.0 kcal/mol), leading to a ratio of infinite-dilution activity coefficients of 4.4 vs. 1.95 from experiment.

For the toluene-to-phenol transformation (run G1) the calculated difference in hydration free energy is more than 2 kcal/mol greater than that obtained from experiment. Thus, the calculated and experimental ratios of infinite-dilution activity coefficients differ by almost two orders of magnitude. This transformation was also performed in 40 windows (run G2) to examine the possibility that a perturbation step of $\delta\lambda = 0.1$ was too large. The results were almost identical though. A free energy simulation transforming nonpolar toluene to "polar" toluene was also performed to determine whether the results were sensitive to the polarity of this molecule. In fact, toluene has a small dipole moment of 0.375 D (Reid et al., 1987), which will be slightly enhanced in solution. Molecular orbital calculations (George et al., 1988) have also found a surplus of positive charge (0.036 electron units) in the methyl substituent. The "polar" model of toluene was constructed by distributing the negative charge equally to the united carbon atoms of the aromatic ring. This gives a dipole moment of 0.49 D, which is a reasonable value for toluene. The free energy change for this transformation (run G5) was found to be only -0.05 kcal/mol, and hence the polarity of toluene is unable to account for the large discrepancy with experiment.

The source of the discrepancy was identified by applying the "electrostatic decoupling" procedure (runs G3 and G4) which shows that the charging phase of the simulation contributes approximately 7.5 kcal/mol of a total of 8 kcal/mol for the free energy change. Thus, it is clear that the source of the discrepancy is in the electrostatic part of the potential function. Figure 2 shows the free energy change for charging phenol as a function of the coupling parameter λ, where $\lambda = 0$ corresponds to zero partial charges and $\lambda = 1$ to the partial charges listed in Table 2. The steep slope at high values of λ is most striking and can be related to changes in the solute-water orientational correlations during the charging process. At low charge, water molecules near the hydroxyl group of phenol orient in a way characteristic of hydrophobic hydration (Lazaridis and Paulaitis, 1992; and references therein); that is, without preferential orientation of either positive or negative charges towards the neutral solute. The energy change associated with a perturbation in λ, when averaged over all "unperturbed" water configurations, will thus give a small free energy difference, as shown in Figure 2, for $\lambda < 0.5$. At high partial charge, the water molecules will orient in a way that allows them to form hydrogen bonds with the hydroxyl group. For such configurations any "perturbation" that increases the partial charges on this group will always be accompanied by a large negative change in energy. Thus, the calculated free energy will be very sensitive to the value of the partial charges. For example, the partial charges for tyrosine used in the CHARMM force field (Brooks et al., 1983) are about 93% of those in the OPLS force field used in this study. The ΔG corresponding to $\lambda = 0.93$ in Figure 2 is about -6.2 kcal/mol. A charge distribution that matches the experimental dipole moment of phenol ($\mu = 1.6$ D) would correspond to $\lambda = 0.73$, which in Figure 2 gives $\Delta G = -3.7$ kcal/mol. Clearly, a rigorous method of specifying the electron density of the solute is needed, as well as how this density is affected by a particular solvent, if reliable predictions of solvation free energies are to be made. Similar observations of the sensitivity of these free energy simulations to the choice of partial charges have also been reported in other recent publications (for example, Kuyper et al., 1991).

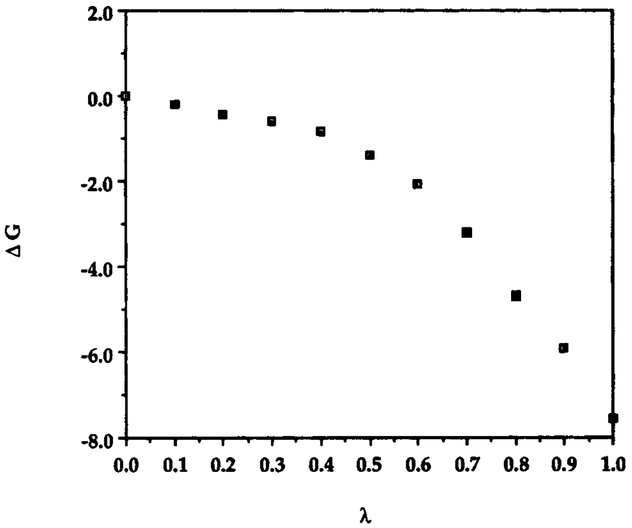

Figure 2. Calculated free energy of charging phenol as a function of the coupling parameter.

In previous work it was found that six-site models of aromatic rings do not describe adequately interactions with water (Jorgensen and Severance, 1990) and that 12-site models are superior (Randelman et al., 1989). We therefore repeated the simulation with the 12-site representation of the aromatic ring (runs G6 and G7), but found essentially the same results. In conclusion, the large discrepancy between simulation and experiment in this transformation appears to be due to the very high sensitivity of the free energy calculations to the partial charges on the hydroxyl group of phenol. The range of reasonable values that can be assigned to these partial charges can lead to calculated ratios of infinite-dilution activity coefficients that differ by several orders of magnitude. This sensitivity to the partial charges has also been noted elsewhere (Essex et al., 1992). Indeed, after submitting this manuscript, we received a preprint from Prof. Jorgensen which reports good agreement with experiment for the solvation free energies of substituted benzenes, including toluene and phenol, using much smaller partial charges for phenol (Jorgensen, 1992).

For the methanol-to-water transformation, which of course gives directly the infinite-dilution activity coefficient of methanol, three different simulations were performed (runs H1 to H3). While the calculated values for these runs differ substantially, the average ΔG of hydration (-1.77 kcal/mol) corresponds to an infinite-dilution activity coefficient for methanol that is in reasonable agreement with experiment. The wide variation in the results for these runs was also observed to a lesser extent for charging dichloromethane (runs A3 and A4) and suggests that the amount of sampling commonly reported in the literature and which was adopted in this work, can be inadequate.

Conclusions

The most widely used methods for estimating activity coefficients have been based on the group contribution approach. Current methods, such as UNIFAC (Larsen et al., 1987), use molecular thermodynamic models for the excess Gibbs free energy, but their predictive capabilities rely on formidable correlations of existing equilibrium data for binary mixtures. The general methods provide fast, reliable estimates for a wide range of simple mixtures, but perform poorly for aqueous solutions. Specialized parameter sets (Hooper et al., 1988) have been developed for such systems and do offer some improvement, but cannot be extrapolated with confidence beyond the database used in the parameterization. In contrast, free energy simulations provide a fundamentally new route to predicting thermodynamic properties of mixtures with a distinct advantage over the group contribution approach. Specifically, they are based on potential energy functions derived from pure-fluid data, such as radial distribution functions, heats of vaporization or crystal structures, and not from thermodynamic information on mixtures. In Table 4, we compare predictions of $\gamma_1^\infty/\gamma_2^\infty$ from our free energy simulations to those obtained from standard UNIFAC. For the aqueous systems studied, the two methods are in comparable, although not very good agreement with experiment.

In contrast to UNIFAC, however, significant improvements in the free energy simulations are anticipated. Specifically, it appears that a set of partial charges consistent with all the experimental data could be identified. For example, an increase in the partial charges of chloroform would give results in closer agreement with experiment for both the isobutane-to-chloroform and the 1,1 dichloroethane-to-chloroform transformations. Also, a decrease in the partial charges of dichloromethane would improve both the methane-to-dichloromethane and propane-to-dichloromethane calculations. However, making these adjustments in an empirical fashion so as to improve agreement with experiment would defeat the purpose of these simulations unless a set of partial charges truly transferable to other molecules could be found. This appears highly unlikely, and therefore, more rigorous methods of assigning partial charges must be examined.

In most applications, electrostatic interactions are described by Coulomb's law with partial charges derived from molecular orbital calculations. However, there is no generally accepted way to do this. In addition, there is no practical method of treating the effect of the solvent on the electron density distribution. For example, partial charges derived theoretically can be scaled to fit the experimental vapor-phase dipole moment or, for a condensed phase, to fit a "somewhat" larger dipole moment. However, this practice may not be satisfactory for highly polar molecules because, as we have seen in Figure 2, the free energy calculations can be sensitive to small variations in the assigned partial charges when these are large. One promising approach has been recently developed (Cramer and Truhlar, 1992) that incorporates a continuum description of the solvent into a quantum mechanical Hamiltonian for semiempirical self-consistent field calculations. A similar treatment of the solvent has been incorporated in *ab initio* calculations as well (Wong et al., 1991). Both approaches account for the polarizing effect of the solvent, but suffer from uncertainties associated with the continuum approximation.

Currently employed simulation lengths (a few million configurations with Monte Carlo or a few picoseconds for molecular dynamics) appear to be inadequate for convergence of the averages in some systems. A number of other recent publications have also recognized the difficulty of achieving convergence in free energy simulations (Mitchell and McCammon, 1991; Mazor and Pettitt, 1991; Saqi and Goodfellow, 1991). Sampling is much more severe a problem in water compared to simple fluids, since water has an extremely "structured" configurational space. However, the sampling problem is destined to be alleviated with the expected increase in computing power. Also, the methodology of free energy simulations itself is likely to accept further improvements. For example, a recent analysis of systematic sampling errors in FEP calculations would provide better detection and control of such errors (Wood et al., 1991).

In conclusion, free energy simulations appear promising, but still rather primitive to be applied in a routine fashion for the quantitative prediction of thermodynamic properties of aqueous solutions. At present, however, these simulation methods can play an important role in guiding the development of new engineering thermodynamic models for aqueous solutions by enhancing our understanding of the molecular origin of hydration phenomena. One important direction is the dissection of the free energy into components arising from specific interactions, such as van der Waals or electrostatic interactions, and also components that arise from specific molecular groups (Daggett et al., 1989; Gao et al., 1989). Another important advance would be the development of methods to separate the calculated free energies into enthalpic and entropic contributions. Current approaches for doing so suffer from high statistical uncertainty. Alternative methods that calculate the entropy, for example, Lazaridis and Paulaitis (1992) or the enthalpy alone would be an important complement to free energy simulations.

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Notation

A = Helmholtz free energy
A_i = repulsive parameter of the van der Waals interactions
C_i = attractive parameter of the van der Waals interactions
f_i = fugacity of component i in the mixture
f_i° = fugacity of pure component i at the temperature and pressure of the mixture

$f_i^{\mathrm{IGM}}(T,x,P)$ = fugacity of component i in an ideal gas mixture at the same temperature, composition and pressure
$f_i^{\mathrm{IGM}}(T,x,\rho)$ = fugacity of component i in an ideal gas mixture at the same temperature, composition, and number density
G = Gibbs free energy
H_i = Henry's constant of component i in the mixture
k = Boltzmann's constant
P = pressure
q_i = partial atomic charge
T = absolute temperature
U = potential energy
x = composition
x_i = the mol fraction of component i in the mixture

Greek letters

γ_i = activity coefficient of component i in the mixture
γ_i^{∞} = activity coefficient of component i in the mixture at infinite dilution
ϵ_i = Lennard-Jones energy parameter
λ = coupling parameter
μ_i = chemical potential of component i in the mixture
μ_i^{V} = residual chemical potential of component i in the mixture
$\mu_i^{V,\infty}$ = residual chemical potential of component i in the mixture at infinite dilution
μ_i^{P} = residual (pressure) chemical potential of component i in the mixture
$\mu_i^{P,\infty}$ = residual (pressure) chemical potential of component i in the mixture at infinite dilution
$\mu_i^{P,o}$ = residual (pressure) chemical potential of pure i
$\mu_i^{\mathrm{IGM}}(T,x,\rho)$ = chemical potential of component i in an ideal gas mixture at the same temperature, composition and number density
$\mu_i^{\mathrm{IGM}}(T,x,P)$ = chemical potential of component i in an ideal gas mixture at the same temperature, composition and pressure
ρ = density
σ_i = Lennard-Jones energy parameter
ϕ_i = interaction energy of the added particle with the system

Literature Cited

Adams, D. J., "Chemical Potential of Hard Sphere Fluids by Monte-Carlo Methods," *Mol. Phys.*, **28**, 1241 (1974).

Barr, R. S., and D. M. T. Newsham, "Phase Equilibria in very Dilute Mixtures of Water and Chlorinated Hydrocarbons I. Experimental Results," *Fluid Phase Equil.*, **35**, 189 (1987).

Bash, P. A., U. C. Singh, R. Langridge, and P. A. Kollman, "Free Energy Calculations by Computer Simulation," *Sci.*, **236**, 564 (1987).

Bergmann, D. L., and C. A. Eckert, "Measurement of Limiting Activity Coefficients for Aqueous Systems by Differential Ebulliometry," *Fluid Phase Equilibria*, **63**, 141 (1991).

Beveridge, D. L., and F. M. DiCapua, "Free Energy via Molecular Simulation: Applications to Chemical and Biomolecular Systems," *Ann. Rev. Biophys. Biophys. Chem.*, **18**, 431 (1989).

Boublik, T., V. Fried, and E. Hala, *The Vapor Pressures of Pure Substances*, 2nd ed., Elsevier, Amsterdam (1984).

Boublik, T., V. Fried, and E. Hala, *The Vapor Pressures of Pure Substances*, Elsevier, Amsterdam (1973).

Brooks, B. R., R. E. Bruccoleri, B. D. Olafson, D. J. States, S. Swaminathan, and M. Karplus, "CHARMM: A Program for Macromolecular Energy, Minimization, and Dynamics Calculations," *J. Comp. Chem.*, **4**, 187 (1983).

Caldwell, J., L. X. Dang, and P. A. Kollman, "Implementation of Nonadditive Intermolecular Potentials by Use of Molecular Dynamics: Development of a Water-Water Potential and Water-Ion Cluster Interactions," *J. Amer. Chem. Soc.*, **112**, 9144 (1990).

Chialvo, A. A., "Determination of Excess Gibbs Free Energy from Computer Simulation by the Single Charging-Integral Approach. I. Theory," *J. Chem. Phys.*, **92**, 673 (1990).

Cramer, C. J., and D. G. Truhlar, "An SCF Solvation Model for the Hydrophobic Effect and Absolute Free Energies of Aqueous Solvation," *Sci.*, **256**, 213 (1992).

CRC Handbook of Chemistry and Physics, 64th ed., CRC Press, Boca Raton (1983).

Daggett, V., F. Brown, and P. Kollman, "Free Energy Component Analysis: A Study of the Glutamic Acid 165 to Aspartic Acid 165 Mutation in Triosephosphate Isomerase," *J. Amer. Chem. Soc.*, **111**, 8247 (1989).

Dang, L. X., K. M. Merz, Jr., and P. A. Kollman, "Free Energy Calculations on Protein Stability: Thr-157→Val-157 Mutation of T4 Lysozyme," *J. Amer. Chem. Soc.*, **111**, 8505 (1989).

Deitrick, G. L., L. E. Scriven, and H. T. Davis, "Efficient Molecular Simulation of Chemical Potentials," *J. Chem. Phys.*, **90**, 2370 (1989).

Eckert, C. A., B. A. Newman, G. L. Nicolaides, and T. C. Long, "Measurement and Application of Limiting Activity Coefficients," *AIChE J.*, **27**, 33 (1981).

Essex, J. W., C. A. Reynolds, and W. G. Richards, "Theoretical Determination of Partition Coefficients," *J. Amer. Chem. Soc.*, **114**, 3634 (1992).

Fleischman, S. H., and C. L. Brooks III, "Protein-Drug Interactions: Characterization of Inhibitor Binding in Complexes of DHFR with Trimethoprim and Related Derivatives," *Proteins*, **7**, 52 (1990).

Frank, H. S., and M. W. Evans, "Free Volume and Entropy in Condensed Systems: III. Entropy in Binary Liquid Mixtures; Partial Molal Entropy in Dilute Solutions; Structure and Thermodynamics in Aqueous Electrolytes," *J. Chem. Phys.*, **13**, 507 (1945).

Franks, F., and D. S. Reid, "Thermodynamic Properties," *Water, A Comprehensive Treatise*, F. Franks, ed., Vol. 2, Chap. 5, Plenum Press, New York (1973).

Franks, F., "The Solvent Properties of Water," in *Water, A Comprehensive Treatise*, F. Franks, ed., Vol. 2, Chapter 1, Plenum Press, New York (1973).

Gao, J., K. Kuczera, B. Tidor, and M. Karplus, "Hidden Thermodynamics of Mutant Proteins: A Molecular Dynamics Analysis," *Sci.*, **244**, 1069 (1989).

Geiger, A., A. Rahman, and F. H. Stillinger, "Molecular Dynamics Study of the Hydration of Lennard-Jones Solutes," *J. Chem. Phys.*, **70**, 263 (1979).

George, P., C. W. Bock, J. J. Stezowski, T. Hildenbrand, and J. P. Glusker, "Molecular Orbital Studies of Methylation Effects in Aromatic Hydrocarbons 1. Ab Initio Calculations of Toluene etc.," *J. Phys. Chem.*, **92**, 5656 (1988).

Haile, J. M., "On the Use of Computer Simulation to Determine the Excess Free Energy in Fluid Mixtures," *Fluid Phase Equil.*, **26**, 103 (1986).

Hooper, H. H., S. Michel, and J. M. Prausnitz, "Correlation of Liquid-Liquid Equilibria for Some Water-Organic Liquid Systems in the Region 20-250°C," *Ind. Eng. Chem. Res.*, **27**, 2182 (1988).

Jorgensen, W. L., personal communication (1992).

Jorgensen, W. L., BOSS version 2.8, Yale University, New Haven, CT (1989a).

Jorgensen, W. L., and C. Ravimohan, "Monte Carlo Simulation of Differences in Free Energies of Hydration," *J. Chem. Phys.*, **83**, 3050 (1985).

Jorgensen, W. L., and D. L. Severance, "Aromatic-Aromatic Interactions: Free Energy Profiles for the Benzene Dimer in Water, Chloroform, and Liquid Benzene," *J. Amer. Chem. Soc.*, **112**, 4768 (1990).

Jorgensen, W. L., "Free Energy Calculations: A Breakthrough for Modeling Organic Chemistry in Solution," *Acc. Chem. Res.*, **22**, 184 (1989b).

Jorgensen, W. L., J. Chandrasekhar, J. D. Madura, R. W. Impey, and M. L. Klein, "Comparison of Simple Potential Functions for Simulating Liquid Water," *J. Chem. Phys.*, **79**, 926 (1983).

Jorgensen, W. L., and J. Tirado-Rives, "The OPLS Potential Functions for Proteins. Energy Minimizations for Crystals of Cyclic Peptides and Crambin," *J. Amer. Chem. Soc.*, **110**, 1657 (1988).

Jorgensen, W. L., J. D. Madura, and C. J. Swenson, "Optimized Intermolecular Potential Functions for Liquid Hydrocarbons," *J. Amer. Chem. Soc.*, **106**, 6638 (1984).

Jorgensen, W. L., J. F. Blake, and J. K. Buckner, "Free Energy of TIP4P Water and the Free Energies of Hydration of CH4 and Cl^- from Statistical Perturbation Theory," *Chem. Phys.*, **129**, 193 (1989).

Jorgensen, W. L., R. C. Binning, Jr., and B. Bigot, "Structures and Properties of Organic Liquids: n-Butane and 1,2-Dichloroethane and Their Conformational Equilibria," *J. Amer. Chem. Soc.*, **103**, 4393 (1981).

Jorgensen, W. L., "Transferable Intermolecular Potential Functions for Water, Alcohols, and Ethers. Application to Liquid Water," *J. Amer. Chem. Soc.*, **103**, 335 (1981).

Kabadi, V. N., and R. P. Danner, "A Modified Soave-Redlich-Kwong Equation of State for Water-Hydrocarbon Phase Equilibria," *Ind. Eng. Chem. Proc. Des. Dev.*, **24**, 537 (1985).

Kirkwood, J. G., "Statistical Mechanics of Fluid Mixtures," *J. Chem. Phys.*, **3**, 300 (1935).

Kuyper, L. F., R. N. Hunter, D. Ashton, K. M. Merz, and P. A. Kollman, "Free Energy Calculations on the Relative Solvation Free Energies of Benzene, Anisole, and 1,2,3-Trimethoxybenzene: Theoretical and Experimental Analysis of Aromatic Methoxy Solvation," *J. Amer. Chem. Soc.*, **95**, 6661 (1991).

Larsen, B. L., P. Rasmussen, and A. Fredenslund, "A Modified UNIFAC Group-Contribution Model for Prediction of Phase Equilibria and Heats of Mixing," *Ind. Eng. Chem. Res.*, **26**, 2274 (1987).

Lazaridis, T., and M. E. Paulaitis, "Entropy of Hydrophobic Hydration: A New Statistical Mechanical Formulation," *J. Phys. Chem.*, **96**, 3847 (1992).

Linse, P., G. Karlstrom, and B. Jonsson, "Monte Carlo Studies of a Dilute Aqueous Solution of Benzene," *J. Amer. Chem. Soc.*, **106**, 4096 (1984).

Mackay, D., and W.-Y. Shiu, "The Aqueous Solubility and Air-Water Exchange Characteristics of Hydrocarbons under Environmental Conditions," *Chemistry and Physics of Aqueous Gas Solutions*, W. A. Adams, ed., The Electrochemical Society, p. 93 (1975).

Matsuoka, O., E. Clementi, and M. Yoshimine, "CI Study of the Water Dimer Potential Surface," *J. Chem. Phys.*, **64**, 1351 (1976).

Mazor, M., and B. M. Pettitt, "Convergence of the Chemical Potential in Aqueous Simulations," *Mol. Simul.*, **6**, 1 (1991).

Medir, M., and F. Giralt, "Correlation of Activity Coefficients of Hydrocarbons in Water at Infinite Dilution with Molecular Parameters," *AIChE J.*, **28**, 341 (1982).

Michel, S., H. H. Hooper, and J. M. Prausnitz, "Mutual Solubilities of Water and Hydrocarbons from an Equation of State. Need for an Unconventional Mixing Rule," *Fluid Phase Equil.*, **45**, 173 (1989).

Millot, C., and J. L. Rivail, "Molecular Dynamics Simulation of Conformational Equilibrium of 1,2 dichloroethane," *J. Mol. Liq.*, **43**, 1 (1989).

Mitchell, M. J., and J. A. McCammon, "Free Energy Difference Calculations by Thermodynamic Integration: Difficulties in Obtaining a Precise Value," *J. Comput. Chem.*, **12**, 271 (1991).

Newman, S. A., ed., "Thermodynamics of Aqueous Systems with Industrial Applications," ACS Symposium Series, Vol. 133, ACS, Washington, D.C. (1980).

Owicki, J. C., and H. A. Scheraga, "Preferential Sampling Near Solutes in Monte Carlo Calculations on Dilute Solutions," *Chem. Phys. Lett.*, **47**, 600 (1977).

Postma, J. P. M., H. J. C. Berendsen, and J. R. Haak, "Thermodynamics of Cavity Formation in Water. A Molecular Dynamics Study," *Farad. Symp. Chem. Soc.*, **17**, 55 (1982).

Prausnitz, J. M., R. N. Lichtenthaler, and E. G. de Azevedo, *Molecular Thermodynamics of Fluid Phase Equilibria*, 2nd ed., Prentice-Hall, Englewood Cliffs, NJ (1986).

Randelman, R. E., G. S. Grest, and M. Radosz, "Monte Carlo Simulation of the Chemical Potential of Model Benzene Fluids," *Fluid Phase Equil.*, **53**, 143 (1989).

Randelman, R. E., G. S. Grest, and M. Radosz, "Monte Carlo Simulation of the Chemical Potential of Model Benzene Fluids," *Fluid Phase Equil.*, **53**, 143 (1989).

Rao, B. G., and U. C. Singh, "A Free Energy Perturbation Study of Solvation in Hydrazine and Carbon Tetrachloride," *J. Amer. Chem. Soc.*, **113**, 4381 (1991).

Reid, R. C., J. M. Prausnitz, and B. E. Poling, *The Properties of Gases and Liquids*, 4th ed., McGraw-Hill, New York (1987).

Rossky, P. J., and M. Karplus, "Solvation. A Molecular Dynamics Study of a Dipeptide in Water," *J. Amer. Chem. Soc.*, **101**, 1913 (1979).

Saqi, M. A. S., and J. M. Goodfellow, "Convergence Behavior in Free Energy Simulations," *Mol. Simul.*, **6**, 185 (1991).

Sandler, S. I., *Chemical Engineering Thermodynamics*, 2nd ed., Wiley, New York (1989).

Schreiber, L. B., and C. A. Eckert, "Use of Infinite Dilution Activity Coefficients with Wilson's Equation," *Ind. Eng. Chem. Proc. Des. Dev.*, **10**, 572 (1971).

Shing, K. S., and K. E. Gubbins, "The Chemical Potential in Dense Fluids and Fluid Mixtures via Computer Simulation," *Mol. Phys.*, **46**, 1109 (1982).

Shing, K. S., and K. E. Gubbins, "The Chemical Potential in Non-Ideal Liquid Mixtures. Computer Simulation and Theory," *Mol. Phys.*, **49**, 1121 (1983).

Shing, K. S., and S. T. Chung, "Computer Simulation Methods for the Calculation of Solubility in Supercritical Extraction Systems," *J. Phys. Chem.*, **91**, 1674 (1987).

Shing, K. S., "Infinite-Dilution Activity Coefficients from Computer Simulation," *Chem. Phys. Lett.*, **119**, 149 (1985).

Shing, K. S., K. E. Gubbins, and K. Lucas, "Henry Constants in Non-ideal Fluid Mixtures. Computer Simulation and Theory," *Mol. Phys.*, **65**, 1235 (1988).

Singh, U. C., and P. A. Kollman, "An Approach to Computing Electrostatic Charges for Molecules," *J. Comput. Chem.*, **5**, 129 (1984).

Straatsma, T. P., H. J. C. Berendsen, and A. J. Stam, "Estimation of Statistical Errors in Molecular Simulation Calculations," *Mol. Phys.*, **57**, 89 (1986a).

Straatsma, T. P., H. J. C. Berendsen, and J. P. M. Postma, "Free Energy of Hydrophobic Hydration: A Molecular Dynamics Study of Noble Gases in Water," *J. Chem. Phys.*, **85**, 6720 (1986b).

Swaminathan, S., S. W. Harrison, and D. L. Beveridge, "Monte Carlo Studies on the Structure of a Dilute Aqueous Solution of Methane," *J. Amer. Chem. Soc.*, **100**, 5705 (1978).

Swope, W. C., and H. C. Andersen, "A Molecular Dynamics Method for Calculating the Solubility of Gases in Liquids and the Hydrophobic Hydration of Inert-Gas Atoms in Aqueous Solution," *J. Phys. Chem.*, **88**, 6548 (1984).

Tanford, C., *The Hydrophobic Effect*, 2nd ed., Wiley, New York (1980).

Tembe, B. L., and J. A. McCammon, "Ligand-Receptor Interactions," *Comput. and Chem.*, **8**, 281 (1984).

Thomas, E. R., and C. A. Eckert, "Prediction of Limiting Activity Coefficients by a Modified Separation of Cohesive Energy Density Model and UNIFAC," *Ind. Eng. Chem. Proc. Des. Dev.*, **23**, 194 (1984).

Trampe, D. M., and C. A. Eckert, "Limiting Activity Coefficients from an Improved Differential Boiling Point Technique," *J. Chem. Eng. Data.*, **35**, 156 (1990).

Tsonopoulos, C., and J. M. Prausnitz, "Activity Coefficients of Aromatic Solutes in Dilute Aqueous Solutions," *Ind. Eng. Chem. Fundam.*, **10**, 593 (1971).

Weiner, S. J., et al., "A New Force Field for Molecular Mechanical Simulation of Nucleic Acids and Proteins," *J. Am. Chem. Soc.*, **106**, 765 (1984).

Widom, B., "Some Topics in the Theory of Fluids," *J. Chem. Phys.*, **39**, 2808 (1963).

Wilhoit, R. C., and B. J. Zwolinski, *Handbook of Vapor Pressures and Heats of Vaporization of Hydrocarbons and Related Compounds*, API44-TRC Publications (1971).

Wong, M. W., M. J. Frisch, and K. B. Wiberg, "Solvent Effects 1. The Mediation of Electrostatic Effects by Solvents," *J. Amer. Chem. Soc.*, **113**, 4776 (1991).

Wood, R. H., W. C. F. Mühlbauer, and P. T. Thompson, "Systematic Errors in Free Energy Perturbation Calculations Due to a Finite Sample of Configuration Space: Sample-Size Hysteresis," *J. Phys. Chem.*, **95**, 6670 (1991).

Wright, D. A. II, "Aqueous Phase Equilibria of Chlorinated Hydrocarbons," MS Thesis, University of Delaware (1991).

Wright, D. A. II, S. I. Sandler, and D. De Voll, "Infinite Dilution Activity Coefficients of Halogenated Compounds in Water," *Env. Sci. Technol.*, submitted (1992).

Zwanzig, R. W., "High Temperature Equation of State by a Perturbation Method: I. Nonpolar Gases," *J. Chem. Phys.*, **22**, 1420 (1954).

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