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# Hydrophobic hydration: Heat capacity of solvation from computer simulations and from an information theory approximation

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Hydrophobic hydration is studied with an information theory approximation, using the first two moments of the number of solvent centers in a cavity in liquid water, calculated from the density and the pair correlation function. The excess chemical potential, entropy, and heat capacity of solvation are determined for three cases: the two-dimensional MB model of water, in both the (i) NPT and (ii) NVT ensembles, and (iii) the central force CF1 model of water in the NPT ensemble. The results are compared with Monte Carlo simulations and experimental measurements from the literature. The information theory approximation, using only the first two moments, accurately determines the excess chemical potential and entropy of solvation but is unable to predict the excess heat capacity of solvation. Little difference is found between the results obtained using the uniform prior and the ideal gas prior. Molecular dynamics simulations are performed to calculate the excess chemical potential of solvation of soft-spheres as a function of solute size. These results are compared with the solvation of a hard sphere using the information theory approximation and previous molecular dynamics simulations of Lennard-Jones spheres in water. The information theory approximation is found to predict the free energy of solvation as a function of size accurately up to a cavity diameter of approximately 3.5 Å. © 1999 American Institute of Physics. [S0021-9606(99)50212-2]

## I. INFORMATION THEORY AND SOLVATION

Hydrophobic hydration is studied in this paper using a simple information theory approximation. We focus on the excess heat capacity of solvation for both a simple two-dimensional model<sup>1,2</sup> and a three-dimensional flexible model<sup>3</sup> of water. Advances in computer technology have improved both the efficiency and precision of computer simulations to calculate various solvation properties. Nevertheless, the measurement of properties such as the excess chemical potential of hydrophobic hydration remains a tedious task. The excess chemical potential of hydration is commonly determined from lengthy molecular dynamics or Monte Carlo calculations using a technique such as excess chemical potential perturbation theory or thermodynamic integration.<sup>3,4</sup> Such calculations consume large amounts of computer time primarily because a separate simulation (or series of simulations) is required to study each different solute. Pratt and Pohorille<sup>5,6</sup> developed a method based on scaled particle theory<sup>7</sup> in which a single simulation of pure water is used to predict the excess chemical potential of hydration of many hard sphere solutes by studying the formation of cavities in the water. In this technique, the probability that a cavity of a particular size forms spontaneously in water is expanded into various binomial moments related to the density, pair, triplet, and higher-order correlation functions. A limitation of this method is the difficulty in measuring the correlation functions beyond the pair correlation function in a computer simulation of reasonable length.

As described by Berne,<sup>8</sup> the information theory approximation<sup>9</sup> seems to overcome this deficiency. The first two moments (related to the density and pair correlation function) are extracted from a computer simulation of pure water. The least biased estimate for the other moments is determined by maximizing the information entropy. Thus, an estimate for the complete series of moments is obtained, and the excess chemical potential of hydration for the solute may be determined using the techniques of Pratt and Pohorille.<sup>5,6</sup> In earlier applications, the information theory approximation has been used to study the hydrophobic phenomena of cavity formation, association of inert gas solutes, and the conformational equilibria of nonpolar solutes.<sup>9</sup> Subsequent studies included entropy convergence and its relationship to protein folding<sup>10</sup> as well as the pressure dependence of hydrophobic interactions and how it relates to the experimentally observed denaturation of protein molecules.<sup>11</sup>

A convenient way<sup>12</sup> to summarize the anomalous properties of solvation of an inert solute in water is through the measured heat capacity of transfer, as shown in Fig. 1. The heat capacity of transfer (or, alternatively, the heat capacity of solvation) is the difference in the heat capacity of water with a dissolved solute compared to the heat capacity of pure water. Figure 1 reproduces the data of Crovetto *et al.*<sup>13–15</sup> for the transfer of gaseous argon into water. Since the information theory approximation has proved remarkably useful in predicting the excess chemical potential and entropy of solvation of hard sphere solutes in water, in this paper we attempt to determine whether the information theory approximation, using input data for only the first two moments, is

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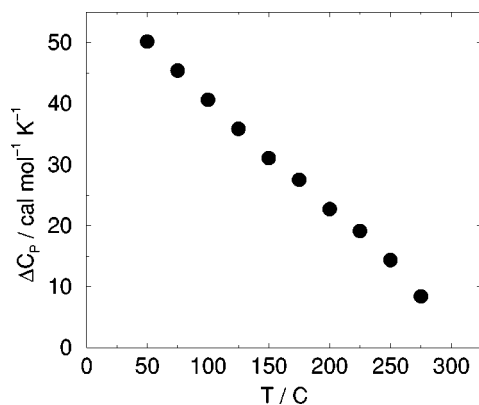


FIG. 1. Heat capacity of transfer data for solvating gaseous argon in water as reported by Crovetto *et al.* (Ref. 13).

capable of reproducing the excess heat capacity of solvation, a fingerprint for hydrophobic hydration.<sup>16,17</sup> In Sec. II of this paper we outline the basic information theory approximation and the numerical methods for implementing it. Some details are included in the Appendix. Section III lists the simulations undertaken, using the two different models of water, for comparison with the results calculated using the information theory approximation. Our results are presented and discussed in Sec. IV. The final section draws conclusions about the applicability of the information theory approximation to the study of hydrophobic hydration.

## II. APPROXIMATIONS AND METHODS

Statistical mechanics connects the excess chemical potential of hydration of a hard sphere to the probability,  $p_0$ , of finding a cavity in liquid water of appropriate size to accommodate the solute of interest. A cavity is a region of space with no oxygen atom within a certain distance of the center of that region of space. (The excess chemical potential of solvation is the standard excess chemical potential difference defined by Ben-Naim.<sup>18</sup> It is equivalent to the excess chemical potential difference measured during Monte Carlo or molecular dynamics simulations.) The excess chemical potential,  $\Delta\mu$ , is given by

$$\Delta\mu = -k_B T \ln p_0. \quad (1)$$

The quantity  $p_0$  is calculated by noting that  $p_0$  is but one of a series of probabilities  $\{p_n\}$ , where  $p_n$  is the probability of finding exactly  $n$  solvent molecules in the same sized cavity. The goal is to determine this probability distribution.

### A. Brief outline of the existing approximation

The central quantity of this approximation is  $p_0$ , the probability that zero particles are found in a cavity radius centered at a point within the water. In the approximation used to date in the literature, only oxygen atoms in the water molecules are considered. Thus the probability  $p_0$  is technically the probability that no oxygen atoms are found with the appropriate radius of the cavity. The approximation used in the literature may be extended to specifically include the

positions of the hydrogen atoms in relation to the cavity. The formalism for such a development is presented in the Appendix.

As mentioned above, the probability  $p_0$  is one element of a probability distribution  $\{p_n\}$  where  $n$  is the number of solvent molecules contained within the cavity. The probability distribution is related to the moments of the distribution<sup>19,20</sup> which, in turn, are related to quantities that can be measured in experiments or computer simulations. The relationship between the moments and the probability distribution is given by:

$$\sum_{n=0}^{\infty} p_n = 1, \quad (2)$$

$$\sum_{n=0}^{\infty} n p_n = \langle n \rangle, \quad (3)$$

$$\sum_{n=0}^{\infty} n^2 p_n = \langle n^2 \rangle, \quad (4)$$

$$\vdots \quad (5)$$

These moments can be obtained from a simulation of the pure solvent, in this case water. The first moment is related to the density of the water,

$$\langle n \rangle = \rho \Delta v, \quad (6)$$

where  $\Delta v$  is the volume excluded by the solute. The second moment relates to the oxygen–oxygen pair correlation function,

$$\langle n(n-1) \rangle = \rho^2 \int_{\Delta v} d\mathbf{r} \int_{\Delta v} d\mathbf{r}' g(|\mathbf{r}-\mathbf{r}'|). \quad (7)$$

The third (and higher) moments relate to the triplet (and higher-order) correlation functions. These latter quantities are difficult to accumulate in a computer simulation and are usually not measured.

Information theory provides a method<sup>9</sup> for using the limited information obtained from the easily calculated (low-order) moments to estimate the higher-order moments and thus determine the complete probability distribution. The information entropy of the system<sup>21</sup> is given by

$$\eta = - \sum_{n=0}^{\infty} p_n \ln p_n. \quad (8)$$

This function is maximized using the technique of Lagrange multipliers subject to the constraints in Eqs. (2)–(4). The resulting probability distribution is

$$p_n = \exp(\lambda_0 + n\lambda_1 + n^2\lambda_2), \quad (9)$$

where  $\lambda_0$ ,  $\lambda_1$ , and  $\lambda_2$  are the Lagrange multipliers determined from the constraints given by the available information. The probability,  $p_0$ , can then be extracted from this distribution and used to calculate the excess chemical potential of solvation.

The results may be improved in at least two ways. First, higher-order correlation functions can be measured during the simulation of pure water. This provides more information

on the true probability distribution and thus the estimate of the probability distribution given by the maximization of the entropy will be more accurate. Second, it is possible to calculate the cross entropy<sup>22</sup> instead of the full information entropy given in Eq. (8). The cross entropy is given by

$$\eta = - \sum_{n=0}^{\infty} p_n \ln \left[ \frac{p_n}{\hat{p}_n} \right], \quad (10)$$

where  $\{\hat{p}_n\}$  is a “default model” or “prior” distribution. The default model is an initial guess at the true probability distribution based on physical intuition. The cross entropy is the information entropy gained by changing to the new distribution,  $\{p_n\}$ . The more accurately the initial, intuitive guess reflects the true probability distribution, the more accurate the final, calculated probability distribution will be. Two commonly used choices are the ideal gas prior,<sup>9</sup> which is a Poisson distribution, and the uniform prior, which is a constant probability distribution that reduces the cross entropy expression [Eq. (10)] to the expression for the full information entropy [Eq. (8)]. For a fluid of hard spheres, Crooks and Chandler<sup>23</sup> have thoroughly examined the effect of the choice of “prior” distributions on the results predicted by the approximation.

## B. Numerical method

The following method is used to calculate the excess chemical potential of solvation of a hard sphere solute in water using the simple one-component solvent. Generalization to the two-component solvent approximation is trivial. The solute has a radius  $R_S$ . Thus it excludes water from a spherical volume of radius  $\lambda = R_S + R_W$ , where  $R_W$  is the radius of a water molecule. The radius of the water molecule can be determined from the potential function or the oxygen–oxygen pair correlation function  $g_{OO}(r)$ , where it is one half of the value of  $r$  at which the first maximum in  $g_{OO}(r)$  occurs. The excluded volume is therefore  $\Delta v = 4\pi\lambda^3/3$ .

The first moment [see Eq. (6)] is obtained by taking the number density,  $\rho$ , of oxygen atoms in the system and multiplying by the excluded volume,  $\Delta v$ . The number density is simply the number of oxygen atoms in the simulation cell divided by the average volume of the simulation cell. The second moment is obtained by numerical integration of Eq. (7). The value used in the entropy maximization is given by

$$\langle n^2 \rangle = \langle n(n-1) \rangle + \langle n \rangle. \quad (11)$$

The next step involves maximizing the information entropy [Eq. (8)] subject to the constraints given by the available information [Eqs. (2)–(4)]. Simple algebraic manipulation using the technique of Lagrange multipliers yields the expression for the probability distribution in Eq. (9). An analogous expression is achieved if the cross entropy is used in conjunction with a prior distribution.

It now remains to solve the nonlinear series of equations to determine the Lagrange multipliers. In the case where the density and the pair and triplet correlation functions are used to obtain the information required, there are four Lagrange multipliers and four nonlinear equations

$$\begin{aligned} F_1 &= \sum_{n=0}^{n_{\max}} \exp\{\lambda_0 + n\lambda_1 + n^2\lambda_2 + n^3\lambda_3\} - 1 = 0, \\ F_2 &= \sum_{n=0}^{n_{\max}} n \exp\{\lambda_0 + n\lambda_1 + n^2\lambda_2 + n^3\lambda_3\} - \langle n \rangle = 0, \\ F_3 &= \sum_{n=0}^{n_{\max}} n^2 \exp\{\lambda_0 + n\lambda_1 + n^2\lambda_2 + n^3\lambda_3\} - \langle n^2 \rangle = 0, \\ F_4 &= \sum_{n=0}^{n_{\max}} n^3 \exp\{\lambda_0 + n\lambda_1 + n^2\lambda_2 + n^3\lambda_3\} - \langle n^3 \rangle = 0. \end{aligned} \quad (12)$$

In theory  $n_{\max} = \infty$ ; but in practice the geometry of the system determines that above a certain value of  $n$  the probabilities become so small as to have no effect on the other probabilities and the final excess chemical potential of hydration. Thus the infinite sums can be truncated to  $n_{\max}$  where this is a large value, for example,  $n_{\max} = 20$ .

The Lagrange multipliers are determined using an iterative Newton–Raphson technique. (Numerical routines to perform this are found in Numerical Recipes.<sup>24</sup>) The Newton–Raphson technique solves the matrix equation

$$\mathbf{\Lambda}_{\text{new}} = \mathbf{\Lambda}_{\text{old}} - \mathbf{J}^{-1} \mathbf{F}_{\text{old}}, \quad (13)$$

where  $\mathbf{\Lambda}$  is a column vector of the Lagrange multipliers,  $\mathbf{F}$  is a column vector of nonlinear relations above, and  $\mathbf{J}$  is the Jacobian matrix

$$\begin{pmatrix} \frac{\partial F_1}{\partial \lambda_0} & \frac{\partial F_1}{\partial \lambda_1} & \frac{\partial F_1}{\partial \lambda_2} & \frac{\partial F_1}{\partial \lambda_3} \\ \frac{\partial F_2}{\partial \lambda_0} & \frac{\partial F_2}{\partial \lambda_1} & \frac{\partial F_2}{\partial \lambda_2} & \frac{\partial F_2}{\partial \lambda_3} \\ \frac{\partial F_3}{\partial \lambda_0} & \frac{\partial F_3}{\partial \lambda_1} & \frac{\partial F_3}{\partial \lambda_2} & \frac{\partial F_3}{\partial \lambda_3} \\ \frac{\partial F_4}{\partial \lambda_0} & \frac{\partial F_4}{\partial \lambda_1} & \frac{\partial F_4}{\partial \lambda_2} & \frac{\partial F_4}{\partial \lambda_3} \end{pmatrix}. \quad (14)$$

The initial guess for  $\mathbf{\Lambda}$  is determined by assuming the probability distribution will be Gaussian.

## III. APPLICATION TO MODELS OF WATER

### A. Two-dimensional MB model

In this work we examine the results of applying the information theory approximation to two different models of water. Silverstein, Haymet, and Dill<sup>1,2,25,26</sup> have recently studied the simple two-dimensional MB model of water. They have performed Monte Carlo calculations to measure numerous properties of hydrophobic hydration including the excess chemical potential, entropy, and heat capacity of solvation. Details of the simulations, model, and results can be found in the original papers.<sup>1</sup> The chemical potential has been determined by the particle insertion method whose value has been emphasized recently.<sup>27</sup> Briefly, the water molecules are treated as two-dimensional disks. Each disk has three symmetric “arms,” each 120° apart. The disks interact via a Lennard-Jones potential that determines the

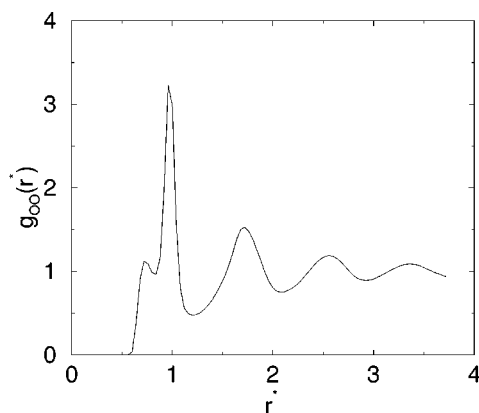


FIG. 2. The pair correlation function for the MB model of water at  $P^* = 0.19$  and  $T^* = 0.20$  as calculated by Silverstein, Haymet, and Dill (Ref. 1).

coordinates of the particles, and a hydrogen bonding term (a Gaussian function of separation and angle) that determines the orientation of the particles. A hydrogen bond forms when the arms of two neighboring particles align themselves. The inert solute is treated as a water particle without the Gaussian hydrogen bonding term. Distances are reported in units of the hydrogen-bond length, and energies (and temperatures) in units of the optimal hydrogen-bond energy. The simulations are performed at reduced temperatures from 0.16 to 0.34 in both the NPT and NVT ensembles.

Pair correlation functions of pure MB water, determined in Ref. 1 and shown in Fig. 2, are used here to implement the information theory approximation. We have used a solute-water diameter of 0.7 in reduced units, determined from the solute-water interaction potential of MB water. We have calculated the excess chemical potential of solvation of this hard sphere solute at various different temperatures in both the constant pressure and the constant volume ensemble. We have determined the excess entropy and heat capacity of solvation as a function of temperature by taking the appropriate derivatives of the excess chemical potential versus temperature data. The constant pressure results are calculated at a reduced pressure of 0.19 over a reduced temperature range from 0.16 to 0.28. The constant volume results are determined at a reduced density of 0.9 over a reduced temperature range from 0.16 to 0.34. Throughout this paper all quantities and results relating to the MB model of water are reported in reduced units.

### B. Three-dimensional CF1 water

We have calculated the pair correlation functions of the CF1 model of water<sup>28–30</sup> and used them as input into the information theory approximation. The CF1 model of water is an atom-based model of water and consists of three, spherically symmetric, potentials describing the OO, OH, and HH interactions in water. The potentials, which describe the intramolecular and intermolecular interactions, are shown in Fig. 3, and listed in Ref. 28.

We have performed molecular dynamics simulations using our locally developed program called CFW1.<sup>31</sup> Simulations of a box of 108 water molecules (composed of 108 oxygen atoms and 216 hydrogen atoms) are performed in the

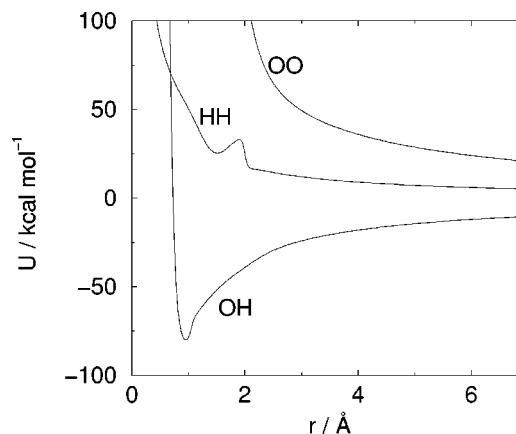


FIG. 3. The CF1 potential model of water.

NPT ensemble. The equations of motion are integrated using a fifth order Gear predictor-corrector algorithm. The time step used is 0.2 fs and the temperature and pressure are constrained using a Nosé–Hoover thermostat and barostat<sup>32</sup> with coupling constants of 0.006 ps and 0.5 ps, respectively. The Coulombic terms in the potential energies have been treated using the Ewald summation technique.<sup>33</sup> The minimum image convention has been used for the short-range terms and standard cubic periodic boundary conditions applied. Simulations are performed at various temperatures between 278 and 358 K and at a pressure of 1 atm. The pair correlation functions and average volume of the system are accumulated over 100 ps. Figure 4 shows the pair correlation functions for the CF1 model of water at 298 K and 1 atm.

In addition to the above calculations, we also performed molecular dynamics simulations to study the solvation of soft-spheres as a function of solute size for comparison with the results calculated from the information theory approximation. In this case, the simulation box consisted of one soft-sphere solute and 107 water molecules modeled by the CF1 model. The solute is modeled using an inverse-twelve potential,

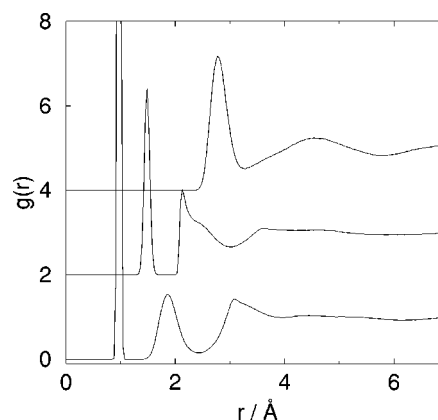


FIG. 4. The pair correlation functions for the CF1 model of water at  $P = 1$  atm and  $T = 298$  K. The  $g_{OO}$ ,  $g_{HH}$ , and  $g_{OH}$  pair correlation functions are shown from top to bottom. The  $g_{OO}$  and  $g_{HH}$  functions are offset vertically, by 4 and 2 units, respectively, for clarity.

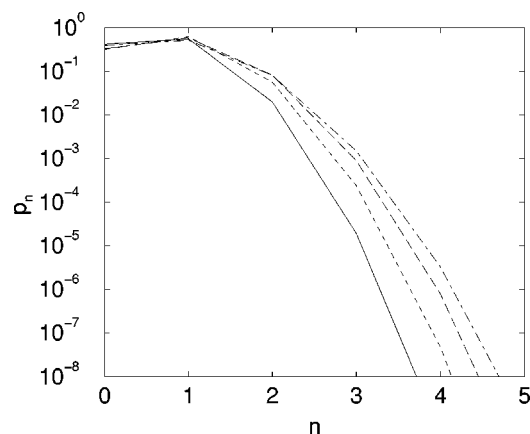


FIG. 5. Probability distributions obtained using the information theory approximation at  $T^*=0.16$  (solid line), 0.20 (dashed line), 0.24 (long-dashed line), and 0.28 (dot-dashed line) for the MB model of water at constant pressure ( $P^*=0.19$ ).

$$U(r_{SO}) = 4\epsilon \left( \frac{\sigma}{r_{SO}} \right)^{12}, \quad (15)$$

where  $r_{SO}$  is the distance between the oxygen atom of the water molecule and the solute,  $\sigma$  is the size of the solute, and  $\epsilon$  is the strength of the potential of interaction between the solute and the water molecule. There is no explicit interaction between the hydrogens of the water and the solute molecule. The excess chemical potential differences are measured using thermodynamic integration in a manner analogous to the procedure used in our previous paper where the free energy (excess chemical potential) of solvation of Lennard-Jones-like spheres is measured as a function of solute size.<sup>3</sup> A recent review of the various techniques for calculating chemical potentials has shown that thermodynamic integration is the most reliable.<sup>34</sup> For this reason, and also to maintain a link with our previous work,<sup>3</sup> we chose this method in preference to others. Except where otherwise stated in the text, the simulations used the same conditions as described above for the pure water simulations and are performed at a temperature of 298 K and pressure of 1 atm.

#### IV. RESULTS: TWO-DIMENSIONAL MODEL OF WATER

##### A. MB water at constant pressure

The information theory approximation has been used to calculate the excess chemical potential of solvation in the MB model of water at  $P^*=0.19$  and at various temperatures. Figure 5 shows the probability distributions,  $p_n$ , given by the information theory approximation using the uniform prior at various temperatures over the range of temperatures studied. As the temperature is increased the probability distribution becomes gradually broader. The value of  $p_0$  is used to determine the excess chemical potential of solvation. Figure 6 shows the excess chemical potential as a function of temperature. The information theory results have been calculated using the uniform prior. The results are compared with the excess chemical potential determined by Silverstein *et al.*<sup>1</sup> using Monte Carlo simulations. The information

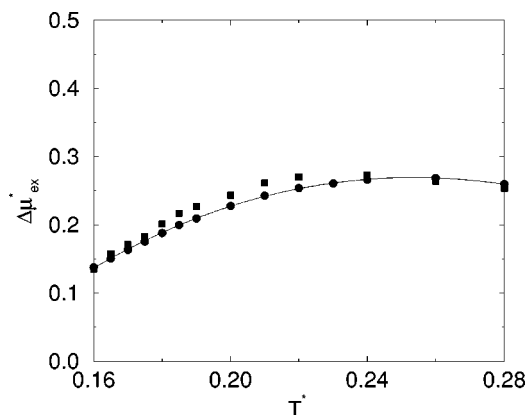


FIG. 6. Excess chemical potential of solvation as a function of temperature at constant pressure ( $P^*=0.19$ ) for MB water. The circles show the results from the information theory approximation using the uniform prior. The solid line is the line of best fit to these results. The squares are the Monte Carlo results obtained by Silverstein *et al.* (Ref. 1).

theory approximation calculates the excess chemical potential of a hard sphere solute inserted into MB water. The Monte Carlo simulations, on the other hand, calculate the excess chemical potential of solvation for a Lennard-Jones solute. In order to accurately compare the two sets of results we use a variationally determined, effective hard disk diameter. Barker and Henderson presented a method for determining the effective hard sphere diameter for any arbitrary potential function.<sup>35</sup> Henderson later applied this method to the study of two-dimensional Lennard-Jones fluids.<sup>36</sup> We have used the Barker–Henderson formalism for two-dimensional Lennard-Jones fluids to determine the correct effective hard disk diameters for use in our comparisons.

For the excess chemical potential, the results from the information theory approximation compare extremely well with the Monte Carlo simulation results of Silverstein *et al.*<sup>1</sup> This much is consistent with earlier applications of the approximation to three-dimensional models. Both simulation and approximation show a gradual increase in the excess chemical potential of solvation from a value of 0.13 at  $T^*=0.16$  to a maximum of about 0.27 at a temperature of  $T^*=0.24$ . Beyond this point there is a slight decrease in the excess chemical potential to a value of 0.25 at  $T^*=0.28$ . The Monte Carlo results display a greater degree of curvature in the temperature region around  $T^*=0.2$ ; thus the results from the information theory approximation underestimate the excess chemical potential in this region by up to 0.02 units.

The excess chemical potential of solvation has also been calculated using the information theory approximation with the ideal gas prior. There is little difference between the results of the information theory approximation calculated using the uniform prior and those calculated using the ideal gas prior. The information theory approximation predicts a very slightly higher excess chemical potential of solvation with the ideal gas prior than with the uniform prior, particularly at higher temperatures. However, this difference is small enough that it could not be seen on the scale of Fig. 6 and thus the results from the ideal gas prior are not shown. This suggests there is little difference between the two prior

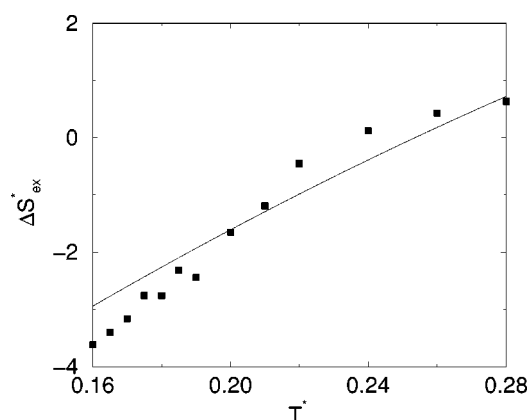


FIG. 7. Excess entropy of solvation as a function of temperature at constant pressure ( $P^*=0.19$ ) for MB water. The solid line shows in the results from the information theory approximation using the uniform prior. The symbols are the measurements from the Monte Carlo simulations of Silverstein *et al.* (Ref. 1).

distributions. Hummer *et al.*<sup>9</sup> also found that they could accurately model results from computer simulations by using the uniform prior and thus without having to use more complicated prior distributions, such as the ideal gas prior. The difference between the results obtained using the ideal gas prior and those obtained using the uniform prior is consistently small throughout all the calculations in the MB model of water. Thus we cite results only from the uniform prior for the remainder of this paper.

It is now possible to determine the excess entropy and heat capacity of solvation through differentiation of the variation of the excess chemical potential of solvation as a function of temperature. Figure 7 shows the excess entropy of solvation as a function of temperature, calculated by taking the first derivative of the data in Fig. 6. Again, Fig. 7 shows the results obtained from the information theory approximation using the uniform prior as well as the actual excess entropy of solvation measured in the Monte Carlo simulations of Silverstein *et al.*<sup>1</sup> The Monte Carlo results show that the excess entropy of solvation increases monotonically as the temperature is increased from a value of  $-0.5791$  to  $+0.1770$ . The information theory approximation predicts this behavior relatively well. It shows a similar monotonic increase in the excess entropy of solvation as the temperature increases. The agreement between the results from the Monte Carlo simulations and the results from the information theory approximation is good, but not as accurate as the modeling of the excess chemical potential as a function of temperature. The information theory approximation again does not predict the correct curvature in the Monte Carlo excess entropy data. This leads to the information theory approximation overestimating the excess entropy of solvation at the lowest temperature ( $T^*=0.16$ ) by approximately 0.8 units and underestimating the excess entropy of solvation at around  $T^*=0.23$  by the approximately same amount.

Figure 8 shows the excess heat capacity of solvation as a function of temperature, obtained from differentiating the data shown in Fig. 7. The results from the information theory approximation using the uniform prior are shown along with

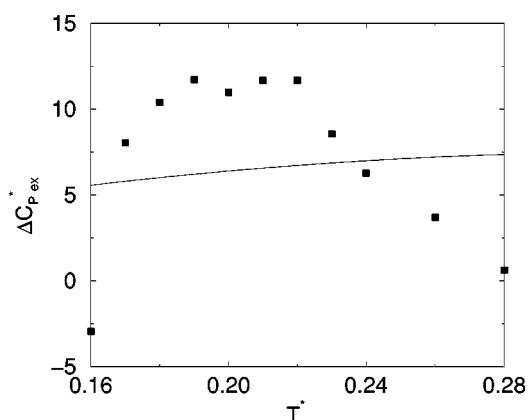


FIG. 8. Excess heat capacity of solvation as a function of temperature at constant pressure ( $P^*=0.19$ ) for MB water. The solid line is the results from the information theory approximation using the uniform prior. The symbols are the measurements from the Monte Carlo simulations of Silverstein *et al.* (Ref. 1).

a fit to the excess heat capacity of solvation calculated from the Monte Carlo simulations of Silverstein *et al.*<sup>1</sup> The results from the Monte Carlo simulations show a distinct, large maximum (of about 10 units) in the excess heat capacity at a temperature of about 0.20. As previously discussed, this maximum has been postulated as the signature of the hydrophobic effect.<sup>16,17</sup> Its experimental presence is shown in Fig. 1. It is highly desirable for any theory used to model hydrophobic hydration to be able to reproduce this feature. As seen in Fig. 8 the results from the information theory approximation (using input for only two moments) do not reproduce this maximum in the excess heat capacity of solvation. The information theory does generate values for the excess heat capacity of solvation of the right order of magnitude, but the distinct large maximum is not reproduced. This shows that the information theory approximation cannot reproduce the signature effect of hydrophobicity, at least at the level of approximation used here. Only the first two moments are used as input information.

## B. MB water at constant volume

We have also used the information theory approximation to analyze pair correlation functions obtained from the Monte Carlo simulations of pure MB water at a constant volume (density  $d^*=0.9$ ). The excess chemical potential, entropy, and heat capacity of solvation at constant volume were not calculated in the Monte Carlo simulations of Silverstein *et al.*<sup>1</sup> and thus are not available for comparison. Figure 9 shows the excess chemical potential of solvation, calculated with the information theory approximation using the uniform prior, as a function of temperature, at constant volume. The behavior differs significantly from the results obtained at constant pressure. At constant volume, there is no longer a maximum in the excess chemical potential of solvation. Instead the excess chemical potential of solvation increases monotonically and almost linearly over the temperature range studied from a value of 0.12 at  $T^*=0.16$  to 0.45 at  $T^*=0.34$ .

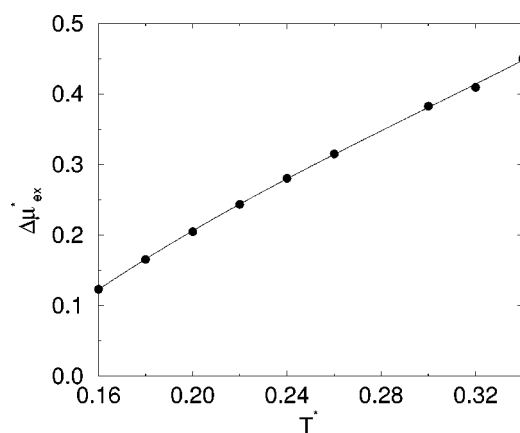


FIG. 9. Excess chemical potential of solvation as a function of temperature at constant volume ( $d^*=0.9$ ), on the same scale as Fig. 6, for MB water calculated using the information theory approximation with the uniform prior. The solid line is the curve of best fit to the calculated data (symbols).

Figure 10 shows the excess entropy of solvation as a function of temperature at constant volume. This curve is obtained, as for the constant pressure results, by taking the derivative of the excess chemical potential data in Fig. 9. At constant volume the excess entropy of solvation displays a slight maximum over the range of temperatures studied. It varies from a minimum of  $-2.24$  at  $T^*=0.16$ , through the maximum of  $-1.65$  at  $T^*=0.30$ , to finish around  $-1.75$  at  $T^*=0.34$ .

Again we may take the derivative of the excess entropy data in Fig. 10 to determine the excess heat capacity of solvation as a function of temperature. The excess heat capacity of solvation at constant volume, shown in Fig. 11, displays a slight monotonic decrease over the range of temperatures studied from an initial value of  $1.35$  to a final value of  $-0.8692$ .

Recently, Hummer *et al.*<sup>11</sup> used the information theory approximation to determine the pressure dependence of the hydrophobic interaction of two nonpolar solutes in water. They showed that the potential of mean force between the nonpolar solutes, predicted by the information theory approximation, could be used to understand the pressure dena-

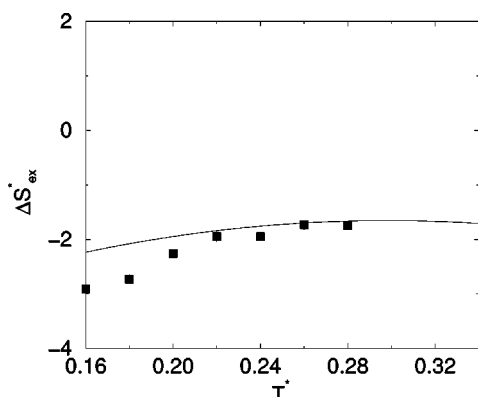


FIG. 10. Excess entropy of solvation as a function of temperature at constant volume ( $d^*=0.9$ ) for MB water using the information theory approximation with the uniform prior on the same scale as Fig. 7. The symbols are measurements from Monte Carlo simulations of Silverstein *et al.* (Ref. 26).

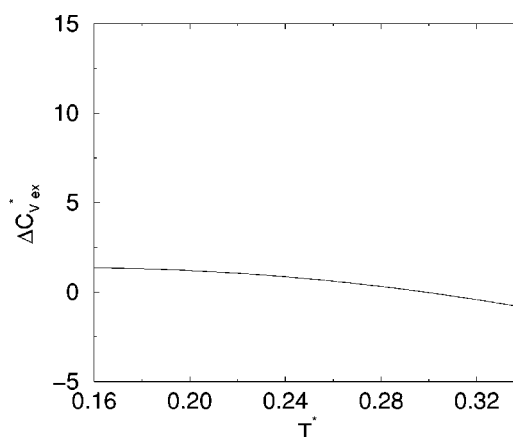


FIG. 11. Excess heat capacity of solvation as a function of temperature at constant volume ( $d^*=0.9$ ), on the same scale as Fig. 8, for MB water using the information theory approximation with the uniform prior.

turation of proteins. The results described above are an initial examination of the pressure dependence of the excess chemical potential. However, there is also a change in temperature with each point as well as pressure. We believe that the information theory approximation will not be able to adequately model the excess chemical potential as a function of temperature because it cannot reproduce the expected heat capacity behavior. Further Monte Carlo calculations and information theory approximation calculations are required to resolve this issue.

## V. RESULTS: THREE-DIMENSIONAL CF1 MODEL OF WATER

### A. The effect of solute size

The information theory approximation has been used to calculate various properties associated with hydrophobic hydration using information derived from the three-dimensional CF1 potential model of water. Figure 12 shows the excess chemical potential of solvation in CF1 water as a

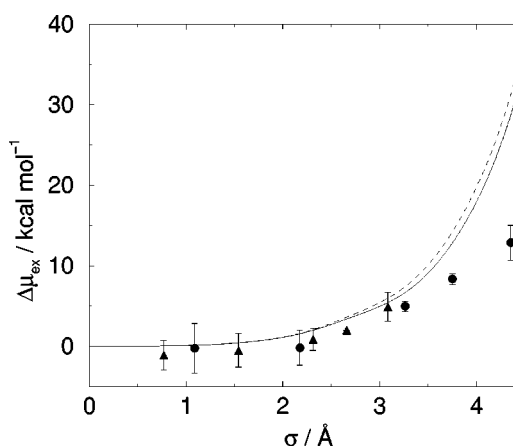


FIG. 12. Excess chemical potential of solvation as a function of solute size for CF1 water. The solid line and the dashed line are the results from the information theory approximation using the uniform and ideal gas priors, respectively. The circles and the triangles are the results from the molecular dynamics simulations using a soft-sphere potential and a Lennard-Jones potential (Ref. 3) to model the solute, respectively.



function of solute size calculated with the information theory approximation, using both the uniform and the ideal gas prior. Both results show that the excess chemical potential of solvation increases monotonically as the size of the solute increases. Moreover, the increase in the excess chemical potential of solvation with solute size is nonlinear. There is little difference between the results obtained using the uniform prior and those obtained with the ideal gas prior. The two sets of results agree very well with each other over the range of solute sizes studied. Below 2.3 Å there is no visible difference between the two curves. Above this point the results generated with the ideal gas prior predict a slightly higher (less favorable) excess chemical potential of solvation.

Molecular dynamics simulations are performed to study the solvation of soft-spheres in water for comparison with the results calculated using the information theory approximation and results calculated in a previous paper where we studied the solvation of Lennard-Jones spheres in CF1 water.<sup>3</sup> The excess chemical potentials of solvation at various solute sizes are calculated by thermodynamic integration, relative to a reference point. The reference point is the excess chemical potential of solvation of methane, taken as 2.0 kcal mol<sup>-1</sup> exactly; based on our own calculations, experimental measurements, and the estimates of this quantity in simulations of other groups. A justification for this choice is found in Ref. 3. The relative excess chemical potential of each solute studied is added to the excess chemical potential of solvation of methane to give the absolute excess chemical potential of solvation for each solute. The partial derivative of the relative excess chemical potential is calculated at eight intermediate points, determined by the eighth-order Gauss-Legendre integration methodology. Each intermediate point is equilibrated for 4 ps prior to the accumulation of the ensemble averages over another 4 ps. Hence the total simulation time for each solute is 64 ps. The soft-sphere solutes are modeled with the potential in Eq. (15). The parameter measuring the strength of the potential of interaction,  $\epsilon$ , is set to a value of 0.2134 kcal mol<sup>-1</sup>. The solute sizes,  $\sigma$ , are chosen to be 1, 2, 3, 3.4475, and 4 Å. These choices correspond to similar choices in our previous work studying the solvation of Lennard-Jones solutes.

The results from the molecular dynamics simulations studying the solvation of soft-spheres are also shown in Fig. 12, as are the results from a previous study of the solvation of Lennard-Jones solutes. As in the case of MB water the information theory approximation shows the excess chemical potential of solvation of hard sphere solutes, while the molecular dynamics simulations predict the excess chemical potentials of solvation of soft-spheres and Lennard-Jones solutes. In order to accurately compare the soft-sphere and Lennard-Jones simulation results to the results calculated using the information theory approximation it is necessary to adjust the solute-water interaction diameters to their effective hard sphere diameters. The effective hard sphere diameters are variationally determined, as before, with the perturbation theory of Barker and Henderson.<sup>35</sup>

The results from the calculation of the excess chemical potential of solvation of the soft-spheres agree well with the

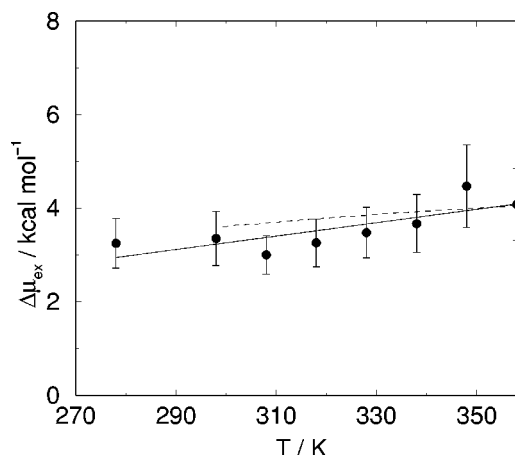


FIG. 13. Excess chemical potential of solvation as a function of temperature for CF1 water at  $P = 1$  atm, calculated with the information theory approximation using the uniform prior. The solid line is the line of best fit to the results. The dashed line is the results of Garde *et al.* (Ref. 10) for a similar system.

results from the information theory approximation. The same trend in the excess chemical potential of solvation as a function of solute size is evident; namely as the size of the solute increases, so the excess chemical potential of solvation increases nonlinearly. The results from the soft-sphere simulations are slightly lower than those calculated using the information theory approximation, although, at least for the small solutes, the results from the information theory agree with those from the soft-sphere simulations within the error associated with the simulation results. At larger solute sizes (above 3.5 Å), the difference between the information theory results and the soft-sphere simulations becomes increasingly large. This is most likely due to the information theory approximation, using only two moments, becoming increasingly less reliable for larger solutes. As the size of the cavity to accommodate the solute increases, the terms in the information theory approximation relating to the triplet and higher-order correlation functions become increasingly important. The “best guess” at these terms, generated by maximizing the information entropy, becomes increasingly less accurate.

The results from the calculation of the excess chemical potential of solvation of the Lennard-Jones solutes also agree very well with the results from the information theory approximation. Again the same trend of increasing the excess chemical potential of solvation with increasing solute size is seen and the information theory results, while slightly higher than those calculated from the simulations of the solvation of Lennard-Jones spheres, it agrees within the error bars associated with the statistical errors of the simulations.

## B. The effect of temperature

Figure 13 shows the excess chemical potential of solvation as a function of temperature, calculated using the information theory approximation with the uniform prior, with information gathered from simulations of pure CF1 water at a range of temperatures. We chose as the solute the Lennard-Jones model of methane, with the same parameters as in our

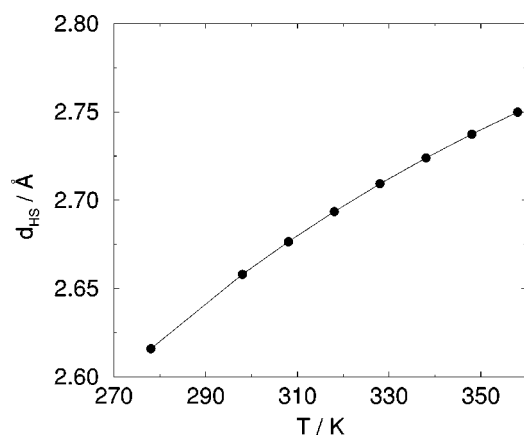


FIG. 14. Effective hard sphere diameter as a function of temperature for a solute modeled by the Lennard-Jones potential with  $\sigma=3.4475 \text{ \AA}$  and  $\epsilon=0.2134 \text{ kcal mol}^{-1}$ .

previous paper.<sup>3</sup> The solute size of  $3.4475 \text{ \AA}$  is variationally determined, as before, using the perturbation theory of Barker and Henderson.<sup>35</sup> (Figure 14 shows the effective hard sphere diameter as a function of temperature.) The effective hard sphere diameter thus calculated varied according to temperature from  $2.62 \text{ \AA}$  at  $278 \text{ K}$  to  $2.75 \text{ \AA}$  at  $358 \text{ K}$ . The error associated with each of the points is also reported. The error in the information theory calculation derives from the error in the input information; namely, the error in the average volume of the simulation box (and hence the number density) and the temperature of the simulation. A line of best fit to the points is also shown in Fig. 13. The excess chemical potential of solvation increases as the temperature is increased, from about  $3.25 \text{ kcal mol}^{-1}$  at  $278 \text{ K}$  to  $4.47 \text{ kcal mol}^{-1}$  at  $348 \text{ K}$ . The trend in the excess chemical potential of solvation as a function of temperature is as expected for the solvation of nonpolar solutes, as typified by the plot of excess chemical potential as a function of temperature in the MB model of water. Furthermore, our results also agree remarkably well with those of Garde *et al.*<sup>10</sup> for a hard sphere solute of similar size in SPC water. They used the information theory approximation to calculate the excess chemical potential as a function of temperature using information from the pair correlation function calculated in the SPC model of water. Their results use a hard sphere diameter of  $2.8 \text{ \AA}$ , slightly higher, but comparative, to the value we used. They did not variationally adjust the hard sphere diameter for the change in temperature. Their results are also plotted in Fig. 13. We expect our results to show a similar maximum in the excess chemical potential of solvation at a temperature outside the range of temperatures we have studied here.

The difference between the results calculated using the uniform and ideal gas priors is again small. As we found for the MB model of water, the information theory approximation using the ideal gas prior predicts consistently higher excess chemical potentials of solvation than when using the uniform prior. In this case the difference between the two is about  $0.3 \text{ kcal mol}^{-1}$  at all the temperatures studied, becoming very slightly larger as the temperature increases. While the difference is more substantial than seen in the results for

the information theory approximation applied to the MB model of water, it is within the error in the calculations. Thus, we have not shown the results for the ideal gas prior in Fig. 13.

Taking the derivative of the curve fitted to the points in Fig. 13, as we did for the results from the MB model of water, yields a constant value for the excess entropy of  $-0.0143 \pm 0.0122 \text{ kcal K}^{-1} \text{ mol}^{-1}$ . The error is determined by approximating the maximum and minimum of the line of best fit. As expected the error in the derivative is reasonably large. The value for the excess entropy of solvation is again consistent with that expected for the solvation of nonpolar solutes, as shown in the results for the simple MB model of water, namely a negative (unfavorable) excess entropy of solvation at low temperatures. Taking the derivative of the excess entropy as a function of temperature yields a heat capacity of solvation of zero. From the experimental data in Fig. 1, and the Monte Carlo and information theory approximation results for MB water, we know that the heat capacity is large and positive. This is not evident from this approximation. Hence, within the statistical uncertainty of the input data, we find a conclusion consistent with the conclusion above from the much more statistically precise data from the MB model of water. While the information theory approximation adequately predicts the excess chemical potential as a function of temperature, and captures the basic behavior of the excess entropy of solvation, it fails to predict the excess heat capacity of solvation, the fingerprint of hydrophobicity. Since the excess entropy and chemical potential are just one and two integrals, respectively, over the excess heat capacity, the adequate predictions of the information theory approximation for these latter two quantities must result, in this view, from a cancelation of errors. Further simulations in three dimensions, of comparable statistical accuracy to the model two-dimensional simulations, will contribute to deeper understanding of this behavior. To our knowledge, no reliable calculation of the heat capacity of solvation has yet been obtained from computer simulations in three dimensions.

## VI. CONCLUSIONS

The information theory approximation has been shown<sup>8-11</sup> to be a convenient and useful tool for studying the solvation of nonpolar solutes. It has a distinct advantage over traditional molecular dynamics or Monte Carlo simulations because it allows the calculation of various properties, for a range of different solutes, from information gained in one molecular dynamics simulation. Our calculations show that in the two-dimensional MB model of water, the information theory approximation predicts well the excess chemical potential of solvation as a function of temperature. The excess entropy of solvation is also predicted adequately by the information theory approximation, although not as accurately as the excess chemical potential. In the three-dimensional CF1 model of water, the excess chemical potential as a function of solute size is also predicted well. Comparison between the results calculated using the information theory approximation and the results from molecular dynamics simulations of the solvation of soft spheres and Lennard-

Jones spheres show very good agreement. The excess chemical potential of solvation as a function of temperature in the CF1 model of water depicts similar trends to those seen in the MB model of water, although the range of temperatures studied is limited. Free energies and entropies have also been successfully measured using the information theory approximation with other models of water.<sup>9,10</sup> Thus we conclude that the information theory approximation is an effective and quick method of calculating free energies and entropies of solvation in various models of water. For these quantities the information theory approximation presents an economical way to get reliable results in the study of the solvation of nonpolar solutes.

However, a comparison of the excess heat capacity of solvation calculated from Monte Carlo simulations and the information theory approximation shows that the information theory approximation is unable to reproduce the Monte Carlo results. Since the large maximum in the excess heat capacity of solvation is regarded as a signature of the hydrophobic effect, the failure of the simple information theory approximation, at least at the level of approximation used here and in previous papers, to reproduce this important indicator is an important property of the approximation. At present the information theory approximation is unable to measure all of the important quantities related to hydrophobic hydration and other, more expensive, simulation techniques must still be used to calculate these properties.

The difference between the results generated by using the uniform prior and the ideal gas prior with the information theory approximation has also been studied for the two-dimensional model of water, in both NPT and NVT ensembles, and for the three-dimensional CF1 model of water in the NPT ensemble, examining the change in excess chemical potential with both solute size and temperature. In all cases, the difference between the results obtained by using the two prior distributions is small. In the MB model of water the difference has been shown to be negligible with the two sets of results almost perfectly overlaying each other. In CF1 model of water the difference is slightly larger but within the error associated with the information theory approximation calculation. The ideal gas prior generally predicts slightly higher free energies of solvation. As a function of solute size, the difference between the results calculated from the two prior distributions increases as the size of the solute increases. As a function of temperature the difference in free energies is almost constant over the range of temperatures studied and within the error in the calculations. This shows that the ideal gas prior does not present any significant improvement in the values of the quantities we have calculated.

The physical effect missing from the information theory approximation is clear in our view, namely the solute is not allowed to affect the hydrogen-bond (and perhaps other) properties of the solvent, a perturbation exhibited plainly in two-dimensional simulations.<sup>1,2</sup> Hence hybrid theories are likely to be needed in three dimensions.<sup>12</sup> To improve the predictions of the information theory part of the approximation, there are at least three possible avenues. The first is to use an alternative prior distribution. We have shown that the

use of the two prior distributions that have been proposed previously result in little or no difference to the calculated results. Thus a new prior distribution would have to be significantly different, and incorporate a much more thorough picture of the cavity distribution in water than the previous choices, and the search is underway.<sup>37</sup> The second approach is to input more information in the form of triplet and possibly higher-order correlation functions. This requires a large amount of computer time, and previous work<sup>23,37</sup> has cast doubt on the efficacy of this approach. A third method, outlined in the Appendix, is to utilize more pair information. These and other approaches will surely be implemented in an effort to understand hydrophobic hydration.

## ACKNOWLEDGMENTS

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## APPENDIX: GENERALIZATION TO A TWO-COMPONENT SOLVENT

For completeness we summarize a third method for improving the accuracy of the information theory approximation by using additional pair correlation functions. In the basic method the water molecules forming the solvent are effectively treated as single spheres. The distribution of oxygen atoms in the system is the only information used to calculate the required probability distribution. However, the water molecules can be considered as a two component solvent comprised of hydrogen and oxygen atoms. By expanding the existing approximation in this way we utilize extra information available in the oxygen-hydrogen and hydrogen-hydrogen pair correlation functions as well as the oxygen-oxygen pair correlation function. This development of the method also has potential applications for studying solvation in other solvent systems, for example, metal alloys and krypton and argon solvent mixtures.

Consider a solvent comprised of two particles of type A and type B. Our aim is to determine the excess chemical potential of inserting a solute into this mixed solvent system. We generalize the probability distribution used in the original information theory by defining the probability  $p_{n,m}$  as the probability of finding a cavity in the solvent, of correct size to contain the solute of interest, with  $n$  type A molecules and  $m$  type B molecules inside it. The probability that the cavity is empty is then  $p_{0,0}$  and the excess chemical potential of solvation is given by

$$\Delta\mu = -k_B T \ln p_{0,0}. \quad (\text{A1})$$

In a similar manner to that outlined above for the existing approximation we can relate the probability distribution

to various moments of the probability  $p_{0,0}$ . In turn, these moments are related to properties measured in the simulation of the two-component system. The probabilities of the form  $p_{n,0}$  and  $p_{0,m}$  are treated exactly as the probabilities in the original one-component model. These give rise to integrals over the density, pair, and higher-order correlations of each of the two different components in the system. As in the existing approximation, the integrals over the higher-order correlation functions are ignored. The probabilities of the form  $p_{n,n}$  can similarly be applied to the “cross” correlation functions between the two components. The first term will relate to an integral over the pair correlation function  $g_{AB}$ . The other terms relate to higher-order correlation functions and are thus ignored. Similarly, all the other probabilities involve at least three particles. They therefore relate to correlation functions beyond the level of the pair correlation function and are thus ignored. This leaves us with the following relationships for the probability distributions:

$$\sum_{n=0}^{\infty} \sum_{m=0}^{\infty} p_{n,m} = 1, \quad (\text{A2})$$

$$\sum_{n=0}^{\infty} n p_{n,0} = \langle n \rangle = \rho_A \Delta v_A, \quad (\text{A3})$$

$$\sum_{m=0}^{\infty} m p_{0,m} = \langle m \rangle = \rho_B \Delta v_B, \quad (\text{A4})$$

$$\sum_{n=0}^{\infty} n^2 p_{n,0} = \langle n^2 \rangle = \rho_A^2 \int_{\Delta v_A} d\mathbf{r} \int_{\Delta v_A} d\mathbf{r}' g_{AA}(\mathbf{r}-\mathbf{r}'), \quad (\text{A5})$$

$$\sum_{m=0}^{\infty} m^2 p_{0,m} = \langle m^2 \rangle = \rho_B^2 \int_{\Delta v_B} d\mathbf{r} \int_{\Delta v_B} d\mathbf{r}' g_{BB}(\mathbf{r}-\mathbf{r}'), \quad (\text{A6})$$

$$\sum_{n=0}^{\infty} \sum_{m=0}^{\infty} n m p_{n,m} = \langle n m \rangle = \rho_A \rho_B \int_{\Delta v_A} d\mathbf{r} \int_{\Delta v_B} d\mathbf{r}' g_{AB}(\mathbf{r}-\mathbf{r}'). \quad (\text{A7})$$

The information entropy for the two-component system is given by:

$$\eta = - \sum_{n=0}^{\infty} \sum_{m=0}^{\infty} p_{n,m} \ln p_{n,m}. \quad (\text{A8})$$

By using the Lagrange minimization technique subject to the constraints given in the equations above it is possible to determine a form for the probability distribution in a manner similar to that for the existing approximation.

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