Quasichemical Lattice Fluid Model for Water and Hydrophobic Solvation

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A quasichemical lattice fluid model for water and mixtures of water with nonpolar solutes is presented. The model provides an analytic expression for the free energy, from which additional thermodynamic functions including the equation of state and the chemical potentials of water and solute are derived. The volumetric behavior predicted by the model is similar to that of real water. For example, it exhibits a density maximum. The model also yields the signature features of hydrophobic solvation, including low solubility, negative entropy of solvation in cold water, and positive heat capacity of solvation. Key features of water described by the model include a significant rotational contribution to the entropy resulting from the combinatorics of directed hydrogen bonding, and a temperature- and density-dependent ratio of intact vs broken hydrogen bonds. The unusual volumetric properties of water are attributed largely to the influence of free volume on the temperature-dependent rotational entropy. Similarly, the unusual thermodynamics of hydrophobic solvation are attributed largely to the influence of nonpolar solutes on the temperature-dependent rotational entropy. Parameters in the model are chosen by least-squares fitting to experimental volumetric data. The description of pure water requires four parameters: the hydrogen-bond energy, the energy of non-hydrogen-bonded water−water contacts, the lattice contact number, and the volume of a water molecule. Solutes are described by solute−water contact energies and by parameters related to molecular volume and surface area.

Introduction

The anomalous properties of water and the signature features of hydrophobic solvation are largely a consequence of the energetics and combinatorics of hydrogen bonds. For practical applications and for illustrating and understanding how these properties arise, it is useful to devise a simple conceptual framework capable of generating analytic expressions that link the properties and behavior of individual water molecules with the thermodynamic and solvent properties of bulk water. This paper presents a quasichemical directed-bond lattice fluid model that aspires to explain and link these properties within a single comprehensive conceptual framework. The model yields analytic expressions for thermodynamic descriptors of the properties of water and hydrophobic solvation. These expressions can be parametrized by fitting to experimental data.

Liquid water has a number of unique physical properties.[1,2] For example, it has a negative thermal expansion coefficient that extends throughout the supercooled temperature range up to 4 °C, it has an unusually high heat capacity, and it has unusual solvent properties. In particular, nonpolar molecules are poorly soluble in water.[3,4] The temperature dependence of this low solubility is also unusual. For a solute molecule B, a graph of the free energy of solvation at high dilution (ΔG_B^*) vs temperature has a positive first derivative and a negative second derivative within the normal liquid range of water. The positive first derivative indicates that the entropy of solvation (ΔS_B^{*0}) is negative (unfavorable). The negative second derivative indicates that the heat capacity of solvation (ΔC_{pB}^{*0}) is large and positive. As a consequence, extrapolation of the solvation free energy to high temperatures predicts that there is a temperature at which solvation of nonpolar molecules changes from being opposed

by entropy to being opposed by enthalpy.[5] This cluster of thermodynamic descriptors of solvation, $\Delta G_B^{*0}>0$, $\Delta S_B^{*0}<0$, $\Delta C_{pB}^{*0}>0$, is taken to define the hydrophobic effect.[6]

Numerous perspectives on water and on hydrophobic solvation can be found in the literature.[7,8] One class of models emphasizes the role of hydrogen bonding, as exemplified by the iceberg model of Frank and Evans.[9] According to this view, water molecules in the vicinity of a nonpolar solute form a structured shell (iceberg) because of the limited options for finding hydrogen-bonding partners and because of the enthalpically driven tendency not to waste hydrogen bonds. This solute-induced ordering of water molecules is responsible for the negative entropy of hydrophobic solvation. Because entropy is more important at higher temperatures, the hydrogen bonds in the iceberg break as the temperature is raised, leading to a high heat capacity of solvation and a switch to enthalpic opposition to solvation. This appears to be the prevalent perspective on the qualitative origin of the unusual thermodynamic signatures of hydrophobic solvation.[10]

An alternative view deemphasizes the importance of hydrogen bonding by ascribing hydrophobic solvation properties to the small size of water molecules compared to most other solvents.[11,12] The solvation process can be pictured as consisting of two steps: formation of a solute-sized cavity and insertion of the solute into the cavity. Simplistically put, formation of a cavity is less likely if there are more solvent molecules per unit volume because it is less likely that all of the solvent molecules will by chance be out of the way. According to the small size view, the low probability of finding a cavity of the appropriate size in a small solvent is responsible for the unfavorable entropy of solvation.

The information theory approach calculates the probability of cavity formation by extrapolating to zero the probability distribution describing the number of water molecules found

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in a volume equal in size to the nonpolar solute.[13-15] The probability distribution itself is determined from experimental correlation functions or from simulations. In essence the information theory approach is a powerful tool for relating solvation properties to other properties of water determined by other means. It does not seek to explain the distribution functions for water that lead to its unusual solvent properties.

Minimalist models also play an important role in the ongoing development of our understanding of water and hydrophobic solvation. For these models, a small set of essential features of the phenomenon of interest is postulated, and then the implications of these features are evaluated using computational methods, classical thermodynamics, or statistical thermodynamics. A recent example of a computational minimalist model is the two-dimensional MB ("Mercedes Benz") model.[16-18] MB water molecules are represented as Lennard-Jones disks with three hydrogen-bonding arms. A strong interaction between two adjacent molecules is achieved when arms from each molecule are aligned along the line joining the molecular centers. Metropolis Monte Carlo simulations of these objects reproduce many of the properties of water including a density maximum and the signature features of the hydrophobic effect.

Mixture models represent another minimalist approach, in which one envisions an equilibrium between water molecules in different states. For example the water molecules may be classified as participating in broken or intact hydrogen bonds. The equilibrium is treated using classical thermodynamics. By assigning entropies and enthalpies to the various states, one may parametrize the models to gain agreement with experimental data.[19-22]

Lattice statistical thermodynamics is a very powerful minimalist approach that often yields simple and physically meaningful analytic expressions for thermodynamic properties of materials and mixtures. Illustrative examples in widespread use include the regular solution theory and Flory−Huggins polymer theory. Lattice models designed to account for the unique properties of water generally involve two key features: directed bonding and use of a quasichemical approximation. In directed bonding models, molecules are ascribed different types of faces or binding arms. Interactions involving different contact types are assigned different energies. Thus, hydrogen bonds can be modeled as one specific type of contact among the various possibilities. Since hydrogen-bonded and non-hydrogen-bonded contacts are generally assigned very different energies, the populations of the contacts will differ greatly from the populations expected based on random orientations. Random mixing approximations cannot be used under these circumstances. Rather, populations and combinatorics are evaluated using a quasichemical approximation. Quasichemical approximations involve a Boltzmann weighting factor, $\exp(-\Delta G/kT)$, corresponding to a "quasi" chemical equilibrium between different contact types differing in free energy by ΔG.

Bell[23] introduced a directed bonding lattice fluid model involving a body-centered cubic (BCC) lattice. A BCC lattice can contain two interpenetrating tetrahedral lattices, and therefore serves as a good model for water. In this model water molecules have two donor and two acceptor arms arranged tetrahedrally. Low energy contacts are assigned only to donor−acceptor contacts, and a high energy is assigned to certain close-packed arrangements involving three molecules. Analysis of this model using a quasichemical treatment predicts temperature-dependent values for the isothermal compressibility, coordination number, and isobaric volume that correspond to the properties of water. Besseling and co-workers have simplified

and refined this model[24,25] and extended it to describe solvation thermodynamics for small nonpolar solutes,[26] which they model as analogues of single cell voids in the water structure. Their model reproduces several anomalous properties of water. Furthermore, key thermodynamic descriptors of hydrophobic solvation also emerge from this model, making it possible to link the directional bonding properties of water with its properties as a solvent.

This directed-bonding quasichemical lattice approach to modeling water contributes important fundamental insights into the properties of water, but it has not yet produced tools that can be used by more pragmatically oriented researchers. Biochemists, toxicologists, medicinal chemists, and formulation scientists, for example, need expressions for solvation thermodynamic properties that are both physically meaningful and quantitatively predictive for real molecules. Historically, minimalist theoretical models that provide simple analytic expressions whose parameters can be adjusted to fit experimental data have served this role well. For example, regular solution and quasichemical mixing theories along with group contribution models are widely used to predict solubilities. With these considerations in mind, recent work in this laboratory has aimed at building lattice models of structured fluids (alkanes, alcohols, etc.) with physically meaningful adjustable parameters. For example, expressions that account for differing molecular size, short chain connectivity,[27] and hydrogen bonding[28] have been developed. The resulting expressions can be accurately fit to experimental solubility data involving alkanes, alcohols, and globular nonpolar molecules. This publication extends this work by presenting a treatment that promises to allow parametrization of water properties and hydrophobic solvation by developing analytical expressions for thermodynamic descriptors of water. The scope of this communication is to describe the general properties of the model itself. The attempts to incorporate better descriptions of real molecules lead to additional physical insight, and with very little effort a quantitative description of the volumetric properties of water is achieved. A qualitative description of hydrophobic solvation is also achieved, though quantitative parametrization of hydrophobic solvation is deferred.

The manner in which solvent water is modeled in this report is similar to that used by Besseling and Lyklema.[26] For example, directed bonding and a quasichemical treatment are used to describe hydrogen bonds. Also, the intermolecular potential is characterized by an attractive hydrogen-bond interaction and a repulsive non-hydrogen-bond water−water interaction. The present model differs, however, in a few important respects. Specification of a BCC lattice is dropped, and the maximum number of nearest neighbors is treated as an adjustable parameter. The important role of solute size is handled using a contact number approach, and parameters related to the surface area and to the volume of the solute emerge from the treatment. To account for flexibility of hydrogen bonds, the two donors on a molecule are not constrained to a tetrahedral angle. A modification of Pauling's treatment of the 0 K residual entropy of ice[29] is used to handle the combinatorics of intact hydrogen bonds in a manner that accounts for the presence of broken hydrogen bonds, solute molecules, and empty space. The proportion of broken vs. intact hydrogen bonds is treated using a simplified quasichemical treatment. The combined result of these strategies is a set of analytic expressions for thermodynamic descriptors of water and hydrophobic solvation that correctly predict key experimentally observed behaviors. Because the algebra involved is relatively simple, it is straight-

forward to establish a direct term-by-term link between the description of water properties and their underlying physical basis.

Derivation of the Partition Function

The model will be evaluated using the standard expression for the lattice fluid partition function:

$$Q = \Omega e^{-E/kT} \tag{1}$$

The degeneracy Ω is determined by counting the arrangements available to objects on the lattice. The contact energy E is determined by the estimating the energy expected for the most probable arrangements of molecules. The model developed below for this partition function can be viewed as being partially quasichemical. The distribution of molecules on the lattice will be viewed as random, while a quasichemical approximation will be introduced only to evaluate the status of hydrogen bonds.

Description of the Lattice. The lattice consists of N cells, populated by n_W water molecules, n_E empty cells, and n_B nonpolar solute molecules. Water molecules (W) and empty spaces (E) occupy a single cell each, while the solute molecules (B) occupy v_B cells each, so $N = n_W + n_E + v_B n_B$. In mixtures of differently sized molecules, it is convenient to define molecular contact numbers of the form Z_{ij}. The ordered subscript indices i and j specify the maximum number of j molecules that can be packed around an i molecule. It is possible to express the total number of contacts m_{ij} between molecules of different types by introducing a weighting factor, $\rho = Z_{ij}/Z_{ji}$, where i corresponds to the larger of the two molecule types. In this work it is assumed that the solute molecules are larger or equal in size to the solvent, so $\rho = Z_{BW}/Z_{WB}$. The relevant expressions are[27]

$$m_{WB} = Z_{WB} n_W \frac{n_B \rho}{n_W + n_E + n_B \rho} \tag{2}$$

$$m_{WW} = \frac{1}{2} Z_{WW} n_W \left(\frac{n_W}{n_W + n_E + n_B \rho} \right) \tag{3}$$

$$m_{BB} = \frac{1}{2} Z_{BB} n_B \left(\frac{n_B \rho}{n_W + n_E + n_B \rho} \right) \tag{4}$$

These contact numbers are required for evaluation of the contact energy and for evaluating the probabilities of hydrogen-bond formation. Equations 2–4 are approximations that were designed to describe the contact numbers determined for randomly arranged lattices containing differently sized molecules. As described elsewhere,[27] these expressions are exact in the limit of low solute concentrations, they are reasonably accurate over the entire concentration range, and they have the correct limiting behavior when the molecules have identical sizes.

Translational Combinatorics. The number of arrangements of the water molecules, empty cells, and solute molecules will be determined first without regard for hydrogen bonds. The analysis starts with an expression for the number of ways, Ω_B, of placing the solute molecules into the lattice. This is given by the expression[27]

$$\Omega_B = \frac{\displaystyle\prod_{i=1}^{n_B} (f_i N)}{n_B!} \tag{5}$$

where f_i is the probability that a randomly selected location in a lattice already containing $i-1$ solute molecules is capable of accepting a new solute molecule without overlap with molecules that are already present. Though an exact expression for f_i is not available, an approximation that is exactly valid when the B molecules are dilute is

$$f_i = \frac{N - (i-1)v_{B,ex}}{N} \tag{6}$$

where $v_{B,ex}$ is the excluded volume of a B molecule. When B molecules are the same size as the solvent, then $v_{B,ex} = 1$ and this expression is exact at all concentrations.

The next step is to determine the number of arrangements Ω_{WE} of water molecules and empty cells in the remainder of the lattice. This is given by the usual combinatorial expression:

$$\Omega_{WE} = \frac{(n_W + n_E)!}{n_W! n_E!} \tag{7}$$

Hydrogen Bond Combinatorics. Because of the presence of OH bond vectors and hydrogen bonds, water molecules will have orientational degeneracy. Without regard for the directional constraints imposed by hydrogen bonding, the total number of orientations possible for the water molecules is given by

$$\left[\frac{Z_{WW}(Z_{WW} - 1)}{2} \right]^{n_W} \tag{8}$$

On each water molecule, the first OH vector can point to any of the Z_{WW} neighboring cells, the second to any of the $Z_{WW} - 1$ remaining, and a factor of $^1/_2$ is introduced to account for the indistinguishability of the OH vectors. The orientational degeneracy predicted by eq 8 will be reduced, however, because not all of these arrangements are consistent with constraints due to hydrogen bonds. To account for the reduction in orientational degeneracy imposed by hydrogen-bond constraints, it is convenient to introduce a correction factor, C, which is less than or equal to 1, for each OH bond vector. The contribution of hydrogen-bond orientations to the partition function is then

$$\Omega_{hb} = \left[\frac{Z_{WW}(Z_{WW} - 1)}{2} \right]^{n_W} C^{2n_W} \tag{9}$$

Quasichemical Approximation. C is defined as the probability that a randomly oriented OH vector is pointing in an acceptable direction. The model allows two situations in which the orientation of an OH vector is deemed acceptable. First, the OH bond vector can be directed toward a valid hydrogen-bond acceptor. All such contacts are classified as intact hydrogen bonds. Second, the OH bond vector can be classified as a broken hydrogen bond. All broken hydrogen bonds are directed toward sites that are unable to accept a hydrogen bond. Therefore, to develop an expression for C, it is necessary to express the probabilities for randomly oriented OH vectors to be directed toward valid acceptors and toward nonacceptors.

The probability that an OH vector is directed toward a valid acceptor is given by the probability p_W of pointing toward a water molecule,

$$p_W = \frac{n_W}{n_W + n_E + \rho n_B} \tag{10}$$

times the probability p_O that second water molecule has its two OH vectors oriented away from the potential donor. (The

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subscript is the letter "O", indicating that the putative acceptor has its oxygen atom oriented toward the putative donor.)

$$p_O = \frac{Z_{WW} - 2}{Z_{WW}} \quad (11)$$

For an OH vector that is pointing away from a hydrogen-bond acceptor, the probability that it shall be deemed acceptable depends on the number of hydrogen bonds that are intact n_i and broken n_b. To estimate these values, a quasichemical approximation is introduced.

$$\frac{n_i}{n_b} = \frac{\omega_i}{\omega_b} \exp(-w_{hb}/kT) \quad (12)$$

where w_{hb} is the energy of a hydrogen bond, and ω_i and ω_b are proportional to the number of arrangements possible for intact and broken hydrogen bonds, respectively.

The ratio ω_i/ω_b will be taken as the probability that a donor is next to a suitable acceptor compared to the probability that a donor is next to a nonacceptor. Thus, ω_i is proportional to $p_W p_O$, as described above. ω_b represents all other cases, and is proportional to $1 - \omega_i$. This gives

$$\frac{n_i}{n_b} = \frac{p_W p_O}{1 - p_W p_O} \exp(-w_{hb}/kT) \quad (13)$$

The fraction of hydrogen bonds that are broken ϵ is

$$\epsilon = \frac{n_b}{n_b + n_i} = \frac{1 - p_W p_O}{1 - p_W p_O + p_W p_O \exp(-w_{hb}/kT)} \quad (14)$$

The fraction C of randomly oriented hydrogen-bond vectors that will by chance be pointing in an acceptable direction is the fraction that are pointing at valid acceptors $p_W p_O$, plus the fraction that are considered broken ϵ.

$$C = p_W p_O + \epsilon \quad (15)$$

The temperature- and density-dependences of this expression are physically reasonable. In the high-temperature limit, $\epsilon = 1 - p_W p_O$ and $C = 1$, indicating that all OH bond orientations are acceptable. In the low-temperature limit, $\epsilon = 0$ and $C = p_W p_O$, indicating that only those orientations directed at an acceptor that is itself properly oriented are acceptable. For hexagonal ice at 0 K, where $Z_{WW} = 4$ and $p_W = 1$, eq 9 gives an expression that is identical to Pauling's estimate of the degeneracy of water molecule orientations.[29] This estimate correctly gives the residual entropy of ice. In the low-density limit, $\epsilon = 1$ and $p_W = 0$ because of the negligible chance of having water molecules in adjacent cells. As with the high-temperature limit, $C = 1$ in this dilute gas limit, indicating that all OH bond orientations are acceptable in this state.

The overall degeneracy is the product of Ω_B, Ω_{WE}, and Ω_{hb}.

$$\Omega = \left[\frac{\prod_{i=1}^{n_B} f_i N}{n_B!} \right] \left[\frac{(n_W + n_E)!}{n_W! n_E!} \right] \left[\frac{Z_{WW}(Z_{WW} - 1)}{2} \right]^{n_W} [\epsilon + p_W p_O]^{2n_W} \quad (16)$$

Contact Energy. The intermolecular contact energies that will be considered include hydrogen bonds w_{hb}, non-hydrogen-bonded water–water contacts w_{WW}, water–solute contacts w_{WB}, and solute–solute contacts w_{BB}. All contacts with empty cells

are given zero energy. Defining a single parameter for non-hydrogen-bonded water–water contacts effectively averages together HO–OH and OH–HO type contacts. These will be assumed to be unfavorable, corresponding to a positive value for w_{WW}, because they correspond to the proximal placement of like partial charges. The total energy is therefore given by

$$E = 2n_W(1 - \epsilon)w_{hb} + (m_{WW} - 2n_W(1 - \epsilon))w_{WW} + m_{WB}w_{WB} + m_{BB}w_{BB} \quad (17)$$

The first term is the number of intact hydrogen bonds times the energy of a hydrogen bond. The second term is the number of non-hydrogen-bonded water–water contacts times the energy of such contacts. The third and fourth terms depend directly on the numbers of solute–water and solute–solute contacts and their corresponding energies. It is convenient to rearrange this expression slightly to get

$$E = 2n_W(1 - \epsilon)(w_{hb} - w_{WW}) + m_{WW}w_{WW} + m_{WB}w_{WB} + m_{BB}w_{BB} \quad (18)$$

In this form, the last three terms correspond to the expression that would occur for a non-hydrogen-bonded fluid, while the first term corresponds to the influence of hydrogen bonds.

It may be noticed that there is a minor inconsistency between the energies ascribed to the hydrogen-bonded and non-hydrogen-bonded states in the quasichemical treatment compared to the treatment of the contact energy. In the quasichemical expression intact hydrogen bonds are assigned an energy of w_{hb}, whereas broken hydrogen bonds are assigned an energy of zero even if they are involved in an OH–HO type contact. In the contact energy expression such contacts are assigned an energy of w_{WW}. This approximation was introduced into the quasichemical treatment for the purpose of algebraic simplicity, and is justified by the small value of w_{WW} compared to w_{hb}.

Derivations of Molecular Thermodynamic Expressions

Helmholtz Free Energy. Combining the terms derived above, introducing Stirling's approximation, $n! \cong (n/e)^n$, and using the approximate excluded volume expression for f_i gives the following expression for the Helmholtz free energy of a mixture of water with large nonpolar solute molecules based on the expression $A = -kT \ln Q$:

$$A = kTn_B \ln\left(\frac{n_B}{N}\right) + kT\left(\frac{N - n_B v_{B,ex}}{v_{B,ex}}\right)\ln\left(\frac{N - n_B v_{B,ex}}{N}\right) + kTn_W \ln\left(\frac{n_W}{n_W + n_E}\right) + kTn_E \ln\left(\frac{n_E}{n_W + n_E}\right) - kTn_W \ln\left(\frac{Z_{WW}(Z_{WW} - 1)}{2}\right) - kT2n_W \ln(\epsilon + p_W p_O) + 2n_W(1 - \epsilon)(w_{hb} - w_{WW}) + \frac{Z_{WW}}{2}\frac{n_W^2}{n_W + n_E + \rho n_B}w_{WW} + \frac{Z_{BB}}{2}\frac{\rho n_B^2}{n_W + n_E + \rho n_B}w_{BB} + Z_{WB}\frac{n_W \rho n_B}{n_W + n_E + \rho n_B}w_{WB} \quad (19)$$

There is an obvious correspondence between terms in this expression and the model of the mixture. The first line corresponds to the translational entropy of the solute molecules, the second line corresponds to the translational entropy of the solvent and free volume, the third line corresponds to the rotational entropy of the hydrogen-bond network, the fourth line

corresponds to the energetic influence of hydrogen bonding, and the last line corresponds to the non-hydrogen-bond contact energy. All of the other thermodynamic functions of interest can be derived from this expression. Expressions for the equation of state and for the chemical potentials of water and the solute will be presented.

Equation of State. Evaluating the pressure using the expression $P = -(\partial A/\partial V)_T$ requires a relation between the volume and the number of empty cells. It is assumed that the volumes of water molecules and empty cells are identical. This volume v_W will be viewed as a scaling parameter of the model. The pressure may therefore be evaluated using the expression

$$P = -\left(\frac{\partial A}{\partial V}\right)_T = -\left(\frac{\partial A}{\partial n_E}\right)_T\left(\frac{\partial n_E}{\partial V}\right) = -\frac{1}{v_W}\left(\frac{\partial A}{\partial n_E}\right)_T \quad (20)$$

For pure water ($n_B = 0$), this gives

$$Pv_W = -kT\ln(1 - p_W) + 2kTp_W\left(\frac{\epsilon' - p_Wp_O}{\epsilon + p_Wp_O}\right) + \\ 2(w_{hb} - w_{ww})p_W\epsilon' + \frac{Z_{WW}w_{ww}}{2}p_W^2 \quad (21)$$

or

$$P\bar{V} = -kT\frac{\ln(1 - p_W)}{p_W} + \frac{Z_{WW}w_{ww}}{2}p_W + \\ 2\left[kT\left(\frac{\epsilon' - p_Wp_O}{\epsilon + p_Wp_O}\right) + (w_{hb} - w_{ww})\epsilon'\right] \quad (22)$$

where the molar volume is given by

$$\bar{V} = \frac{(n_W + n_E)v_w}{n_W} = \frac{v_w}{p_W} \quad (23)$$

and ϵ', which is related to the change in the fraction of broken hydrogen bonds with respect to change in volume, is given by

$$\epsilon' = \frac{\epsilon(1 - \epsilon)}{1 - p_Wp_O} \quad (24)$$

Chemical Potential of Water Molecules in Water. The chemical potential of water in water is

$$\mu_W = \left(\frac{\partial A}{\partial n_W}\right)_V \\ = kT\left[\ln(p_W) - \ln\left(\frac{Z_{WW}(Z_{WW} - 1)}{2}\right) - 2\ln(\epsilon + p_Wp_O) + \\ 2\frac{\epsilon' - p_Wp_O}{\epsilon + p_Wp_O}\right] + 2(1 - \epsilon + \epsilon')w_{hb} + \\ [p_WZ_{WW} - 2(1 - \epsilon + \epsilon')]w_{WW} \quad (25)$$

Chemical Potential of Nonpolar Solute. The chemical potential of the solute B is defined as

$$\mu_B = \left(\frac{\partial A}{\partial n_B}\right)_V \quad (26)$$

Substantial algebraic simplification results if the derivative is taken at constant n_E rather than constant V. Expressing A as a function of n_B and n_E, the calculus of partial derivatives gives

$$dA = \left(\frac{\partial A}{\partial n_B}\right)_{n_E} dn_B + \left(\frac{\partial A}{\partial n_E}\right)_{n_B} dn_E \quad (27)$$

Dividing by dn_B at constant volume gives the desired expression

$$\left(\frac{\partial A}{\partial n_B}\right)_V = \left(\frac{\partial A}{\partial n_B}\right)_{n_E} + \left(\frac{\partial A}{\partial n_E}\right)_{n_E}\left(\frac{\partial n_E}{\partial n_B}\right)_V \quad (28)$$

The product on the right simplifies to Pv_B, giving

$$\mu_B = \left(\frac{\partial A}{\partial n_B}\right)_{n_E} + Pv_B \quad (29)$$

Performing the prescribed derivative gives

$$\mu_B = kT\ln\left(\frac{n_B}{N}\right) + kT\frac{v_B - v_{B,ex}}{v_{B,ex}}\ln\left(\frac{N - n_Bv_{B,ex}}{N}\right) + \\ 2kT\rho\frac{p_W}{\epsilon + p_Wp_O}(\epsilon' + p_W) + \\ 2\rho p_W\epsilon'(w_{hb} - w_{ww}) - \rho p_W^2\frac{Z_{WW}w_{WW}}{2} + \\ \frac{Z_{BB}w_{BB}}{2}\left(\frac{2\rho n_B}{n_W + n_E + \rho n_B} - \left(\frac{\rho n_B}{n_W + n_E + \rho n_B}\right)^2\right) + \\ Z_{WB}w_{WB}\rho p_W\left(1 - \frac{\rho n_B}{n_W + n_E + \rho n_B}\right) + Pv_B \quad (30)$$

In Ben-Naim's standard state,[4] the solvation free energy is given by

$$\Delta G_B^{*0} = \lim_{n_B \to 0}\left(\mu_B - kT\ln\left(\frac{n_B}{N}\right)\right) \quad (31)$$

Finally, the desired expression for the solvation free energy at high dilution is

$$\Delta G_B^{*0} = Pv_B + \rho p_W\left(Z_{WB}w_{WB} - p_W\frac{Z_{WW}w_{WW}}{2}\right) + \\ 2\rho p_W\left[kT\left(\frac{\epsilon' + p_Wp_O}{\epsilon + p_Wp_O}\right) + (w_{hb} - w_{WW})\epsilon'\right] \quad (32)$$

Properties of Pure Water

The Density Anomaly of Liquid Water. Using eq 22, P vs V isotherms can be constructed for pure water. Figure 1 shows the pressure and the contributions of each term in this expression to the pressure as a function of volume at 277 K. The values of w_{hb}, w_{WW}, Z_{WW}, and v_W used to generate this figure are taken from a fit to the temperature dependence of the volume of liquid water as described below. The first two terms in eq 22 (curves T and WW, Figure 1) are consequences of translational entropy and of non-hydrogen-bonded water−water contact energies, respectively. Analogous terms occur in standard lattice and similar mean-field fluid models,[30] except the sign of the contact energy is commonly negative. Thus, for most fluid models, the first term is responsible for the outward pressure and the second term is responsible for the cohesion of the condensed phase. In the present case the second term opposes the formation of a condensed phase.

The next two terms in eq 22, grouped in square brackets, correspond to the contributions of hydrogen bonds to the

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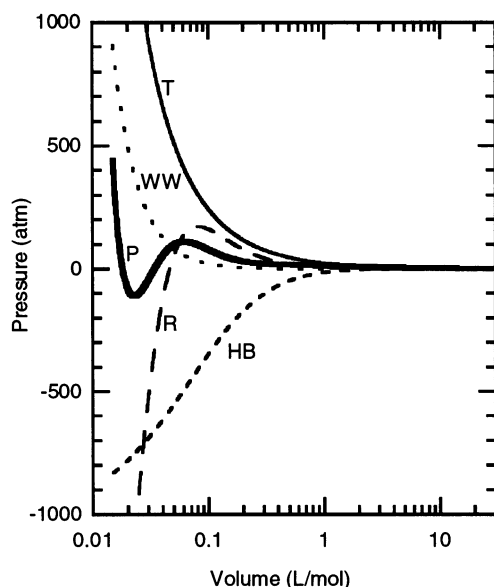## Properties of Pure Water

Figure 1. Contributions to the pressure−volume isotherm from various terms in the equation of state. P denotes the total pressure, T denotes the contribution from translational combinatorics (first term of eq 22), WW denotes the contribution from non-hydrogen-bonded water−water contacts (second term of eq 22), R represents the contribution from rotational combinatorics (third term of eq 22), and HB denotes the contribution from hydrogen-bonding energy (last term of eq 22). The curves were generated for 277 K using eq 22 and parameters described in the legend to Figure 2.

Figure 2. Plot of the molar volume of water vs temperature. Filled circles show experimental values. The line shows the predictions of eq 22 using the parameters $w_{hb} = -6.450734$ kJ/mol, $w_{WW} = 0.2569896$ kJ/mol, $Z_{WW} = 7.91005$, $v_W = 0.0129954$ L/mol/cell. The least-squares fit was performed by adjusting the parameter values to optimize agreement between the predicted volume at $P = 0$ with the experimental values.

Figure 3. Pressure−volume isotherms in the intermediate density region at low temperatures. Curves were generated in 5° increments from 220 to 260 K using eq 22 and the parameters listed in the legend to Figure 2. The metastable phase has a critical temperature near 260 K.

pressure. The factor of 2 arises from the presence of two hydrogen-bond donors per water molecule. The first of these hydrogen-bonding terms (curve R, Figure 1) is a consequence of rotational entropy. At liquidlike densities this term is strongly attractive, and is the largest contributor to the cohesion of the condensed phase. It is unusual for a combinatorial term to favor high densities, and this lies at the core of the unusual properties of water. The origin of this term is that at higher densities, each water molecule has more options for finding hydrogen-bond partners. This this leads to an increase in rotational entropy at high densities. The final term (curve HB, Figure 1) is the contribution of hydrogen-bond energy to the pressure, and behaves as a cohesive force as expected.

Figure 2 shows a plot of molar volume vs. temperature calculated from this model in the vicinity of the density maximum. Experimental values, calculated using the empirical expression of Kell,[31] are also shown. The parameters used to generate the plot were determined by a least-squares fit to the experimental data in the range 263 to 288 K. This figure shows that this model does account for the anomalous density maximum of water, providing an explanation of the phenomenon.

For temperatures and densities where most hydrogen bonds are intact, there is an energetic cost to increasing the density because of the positive sign of the non-hydrogen-bonded water−water contact energy w_{WW}. Opposing this outward pressure is the tendency to contract driven by rotational entropy. As the temperature is raised, the rotational entropy term contributes relatively more to the free energy, driving the contraction. As the temperature is raised further, hydrogen bonds begin to break as described by the quasichemical treatment. Hence, at higher temperatures the entropic advantage of high densities is reduced because when hydrogen bonds are broken there is no need to
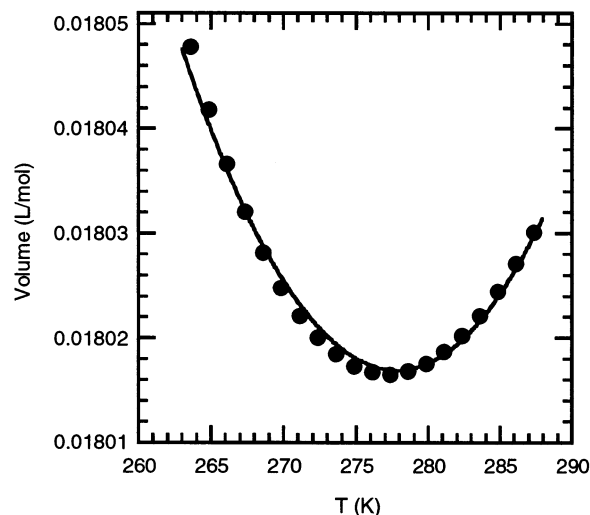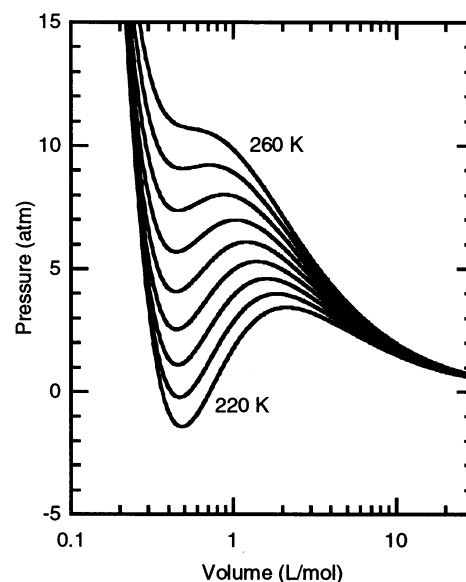
have nearby acceptors in order to have high orientational freedom. The terms contributing to expansion become more important as hydrogen bonds break. The balance between increasing the rotational entropy by increasing the density, vs increasing the rotational plus translational entropy by breaking hydrogen bonds and decreasing the density, controls the temperature of the density maximum.

Very Low Density "Bonus" Phase. Figure 3 shows a family of P−V isotherms in an intermediate-density region at low temperatures. This shows that at very moderate pressures this model exhibits a condensed state having a density about 20-fold lower than the liquid, but still much denser than the gas. This was initially unexpected and is referred to here as the bonus phase. The chemical potential of water calculated using eq 25
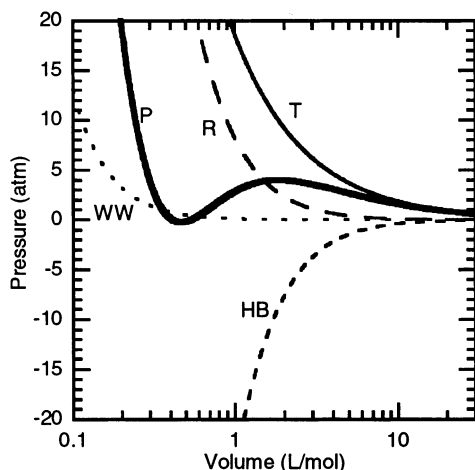
Figure 4. Contributions to the pressure in the "Bonus Phase" intermediate density region at 225° K. Symbols are the same as those used in Figure 1.

in this region is higher than that for the supercooled liquid and its associated gas phase. As a consequence, the bonus phase is metastable with respect to the already metastable supercooled liquid. It is interesting nonetheless to consider the physical factors that explain the origin of this bonus phase.

Figure 4 shows the various contributions to the $P-V$ isotherm of water under these conditions. At this density, one contribution to outward pressure is translational entropy, as expected for any fluid. In contrast to the phase at liquidlike densities (see Figure 1), in this density range the rotational entropy contributes positively to the pressure. This originates from the formation of hydrogen bonds: at this low density, the water molecules find hydrogen-bond partners, but in doing so they lose rotational entropy since they have few choices of bonding partners. On the other hand by finding hydrogen-bond partners, the molecules gain an enthalpic advantage. This decrease in enthalpy with decreasing volume acts as the cohesive force in this region. Thus, this metastable condensation is enthalpy-driven. In this sense the bonus phase is the analogue of a normal gas–liquid-phase transition for most other lattice fluid models. It differs, however, because there is an additional opposition to condensation due to the decrease in rotational freedom of the water molecules. This causes the density of this metastable phase to be low.

Hydrophobic Solvation

Classical Thermodynamic Perspective on Temperature-Dependent Solvation Parameters. It has been noted[32] that models showing water-like equations of state also show water-like solvation thermodynamic behavior. A connection between the equation of state and solvation behavior can be established using a classical thermodynamic argument. Consider the expression for the entropy of solvation, defined as

$$\Delta S_B^{*0} = -\left(\frac{\partial \Delta G_B^{*0}}{\partial T}\right)_P \tag{33}$$

Treating the free energy of solvation as a function of temperature and volume, the total derivative is

$$d\Delta G_B^{*0} = \left(\frac{\partial \Delta G_B^{*0}}{\partial T}\right)_V dT + \left(\frac{\partial \Delta G_B^{*0}}{\partial V}\right)_T dV \tag{34}$$

Dividing by $-dT$ at constant pressure gives

$$\Delta S_B^{*0} = -\left(\frac{\partial \Delta G_B^{*0}}{\partial T}\right)_P = -\left(\frac{\partial \Delta G_B^{*0}}{\partial T}\right)_V - \left(\frac{\partial \Delta G_B^{*0}}{\partial V}\right)_T \left(\frac{\partial V}{\partial T}\right)_P$$

$$= -\left(\frac{\partial \Delta G_B^{*0}}{\partial T}\right)_V - \alpha V \left(\frac{\partial \Delta G_B^{*0}}{\partial V}\right)_T \tag{35}$$

where the coefficient of thermal expansion $\alpha = (1/V)(\partial V/\partial T)_P$ has been introduced. This expression relates the entropy of solvation to the thermal contraction and expansion of water, and provides a link between solvation thermodynamics and the equation of state for the pure solvent.

Intuitively, one expects that the factor $(\partial \Delta G_B^{*0}/\partial V)_T$ in eq 35 should be negative for nonpolar solutes, because by increasing the volume and hence the amount of free volume, it should become easier to insert a solute molecule. For water in the normal liquid range, since the temperature dependence of the volume is approximately parabolic with a minimum at 277 K (Figure 2), the coefficient of thermal expansion, α, is a nearly linear increasing function of temperature that crosses zero at 277 K. Thus, the entropy of solvation in water should become more positive with increasing temperature because α is significantly temperature dependent. Furthermore, since $\Delta C_{P,B}^{*0} = T(\partial \Delta S_B^{*0}/\partial T)_P$, one expects the heat capacity of solvation to be large and positive.

Parametrization of the Model for Solvation Thermodynamics. In view of this close relationship between solvation thermodynamics and the volumetric behavior of the pure liquid, it is important for the model to describe solvation and volumetric behavior with a consistent set of parameters. It is found that fitting the model to different temperature ranges of experimental volumes results in slightly different values of the parameters, and there does not appear to be a unique best parameter set. However, a single set of parameters capable of describing the volumetric behavior at one atmosphere pressure over the entire normal liquid range is desired.

To achieve this it was found useful to augment the model by making one of the parameters explicitly temperature dependent. Since most materials, including ice itself, expand with increasing temperature, it seems appropriate to make the cell volume v_W a function of temperature. Not surprisingly, increasing the number of parameters to which a temperature dependence is ascribed increases the range and precision with which the model can be fit to experimental data. Figure 5 shows a fit of the model, augmented with a linearly temperature-dependent cell volume, to the volume of water over the normal liquid range. Close examination of Figure 5 shows that with this set of parameters, the density maximum occurs at a temperature somewhat lower than that seen in Figure 2. This parametrization is nonetheless useful in the treatment of solvation thermodynamics because the volumetric behavior is close to correct over the normal liquid range for water, as desired for the model. Parameters from this fit as listed in the legend to Figure 5 are used to predict the behavior of the solvation properties of water as described below.

Temperature Dependence of the Hydrophobic Solvation Free Energy. Figure 6 shows the solvation free energy as a function of temperature for a water-sized nonpolar solute in water. The plot was generated using eq 32 with the parameters determined from the fit to the volume of water vs temperature described in the legend of Figure 5. The *solvation* properties are predicted based on a fit to *volumetric* properties. The enthalpy and entropy of solvation are also shown. The curves are qualitatively similar to experimental results for nonpolar
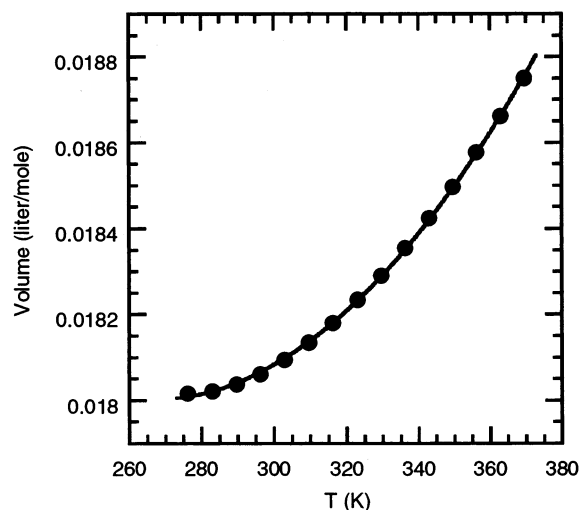
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Figure 5. Plot of the molar volume of water vs temperature in the normal liquid range. Filled circles show experimental values. The line shows the predictions of eq 22 using the parameters $w_{hb} = -8.524816$ kJ/mol, $w_{WW} = 0.2648234$ kJ/mol, $Z_{WW} = 7.367163$, $v_W = (0.01319154 + [(T - 277)(9.298768 \times 10^{-6})]$ L/mol/cell. The least-squares fit was performed as described in the legend to Figure 2.
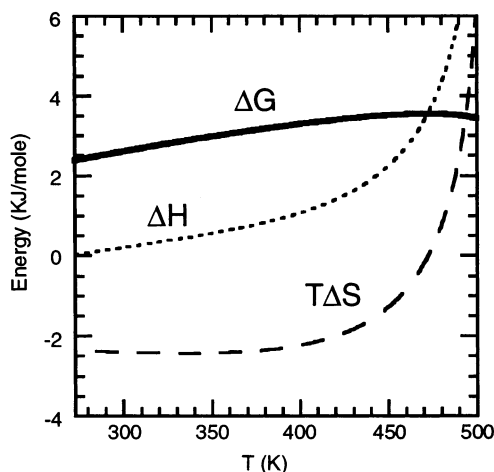

Figure 6. Solvation thermodynamics for a water-sized nonpolar solute. The solvation free energy curve was generated using eq 32 and the parameters listed in the legend to Figure 5. The solvation enthalpy and entropy were determined by taking derivatives of the free energy curve numerically. In generating this plot it was assumed that $\rho = 1.0$, and the contact energy w_{WB} was set to zero. Solutes larger than water will have larger values of ρ, which scales the entire curve. Solutes with significant contact energies with water will have lower free energies of solvation.

solutes in water. In particular, the solvation free energy is positive, consistent with a low solubility for nonpolar solutes. The entropy of solvation is negative in the normal liquid range of water, and it extrapolates to zero at a higher temperature. The free energy curve is concave down, indicating that the heat capacity of solvation is positive. Since the curve is based on a physically informative analytic expression, it is possible to identify the physical origins of all of these features for this model.

In the low-temperature limit where broken hydrogen bonds are rare ($\epsilon = 0$), the solvation free energy of nonpolar solutes in pure water is approximated by

$$\Delta G_B^{*0} = Pv_B + \rho p_W \left(Z_{WB} w_{WB} - p_W \frac{Z_{WW} w_{WW}}{2} \right) + 2\rho p_W kT$$

$$(36)$$

The first term is a pressure−volume term, negligible at atmospheric pressure. The next two terms account for the water−solute contacts that are formed, and the non-hydrogen-bonded water−water contacts that are broken, by insertion of the solute. Both of these terms contribute favorably to the solvation free energy. Under these conditions no hydrogen bonds are broken due to solute insertion. The interruption of energetically costly non-hydrogen-bonded water−water contacts and the formation of energetically favorable solute−water contacts is the origin of the negligible or even favorable heat of solvation of nonpolar solutes in cold water. The last term arises because the solute cannot accept hydrogen bonds, causing a reduction in the rotational freedom of adjacent water molecules. This term, proportional to kT, clearly increases in importance with temperature so long as large numbers of hydrogen bonds do not break. This is responsible for the initial positive slope of the plot of solvation free energy vs temperature. Thus, according to this model, the negative entropy of hydrophobic solvation is due to a reduction in the rotational entropy of water molecules in contact with the solute.

The high heat capacity of solvation is related to the concave-down feature of the temperature dependence of the solvation free energy. The solvation free energy does not continue to increase linearly with temperature as predicted with the oversimplified eq 36, because hydrogen bonds do break as the temperature is raised. When hydrogen bonds are broken, the entropic opposition to solvation is less because it is less likely that solute insertion will restrict the orientational freedom of adjacent water molecules. Since there are more ways to have broken hydrogen bonds in the presence of a solute, hydrogen bonds are broken by solute insertion at high temperatures, and there is a resulting enthalpic penalty for solvation that gradually replaces the entropic penalty. This transition from entropy to enthalpy opposition is described by a positive heat capacity of solvation.

Conclusions

The model presented here, along with the straightforward strategies described for its statistical thermodynamic analysis, provides an analytic formula for the free energy of a mixture of water with solute and free volume. The analytic expressions for the equation of state and solvation thermodynamics contain terms with clear physical interpretation, and they contain parameters that can be adjusted to obtain quantitative fits to experimental data. The expressions also provide a coherent explanation of the density maximum and the descriptors of hydrophobic solvation.

According to this model, the negative thermal expansion coefficient observed below 4 °C is a consequence of an increase in rotational entropy that occurs at higher densities. Reducing the volume by eliminating empty space results in a larger number of potential hydrogen-bond acceptors for each water molecule. This provides a larger number of directions for each water molecule to form hydrogen bonds, resulting in higher rotational entropy. The expansion at higher temperatures results from the breaking of hydrogen bonds and the corresponding increasing relative importance of translational entropy. The model can be augmented by a temperature-dependent cell volume term that accounts for the normal expansion of most materials.

Previous work with quasichemical lattice models[33] shows that greater orientational entropy can be associated with denser packing, and that this effect can drive liquid−liquid-phase transitions. The issue is of interest because of current efforts to

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understand the transitions among metastable high-density amorphous (HDA) and low-density amorphous (LDA) forms of ice.[34-36] The present model explains the density anomaly of normal liquid water on the basis of increased orientational entropy at higher densities. However, the very low-density phase predicted by the present model does not appear to be closely related to the postulated liquid−liquid phase transition that underlies HDA and LDA ices. The density of LDA is similar to other forms of condensed water, while the bonus phase is much less dense than LDA. It maintains high rotational disorder by maintaining a very low density, hence avoiding the orientational restrictions caused by hydrogen bonding. In this sense it uses a strategy that is opposite of the high-density strategy that maintains high rotational disorder by packing tightly to gain a large number of potential hydrogen-bond partners.

The predicted free energy of hydrophobic solvation exhibits the temperature dependence that is observed experimentally for nonpolar solutes. Solvation of nonpolar molecules for this model is opposed by entropy at low temperatures because the number of hydrogen-bond acceptors available to water molecules adjacent to the solute is reduced, leading to a decrease in the rotational entropy of the water molecules. The "squeezing out" of free volume or of nonpolar solutes has the same basis in cold water. At higher temperatures, solvation is opposed less by this effect because more hydrogen bonds may be broken. Nonetheless, the number of water−water contacts is reduced upon solute insertion, leading to an enthalpic opposition to solvation at high temperatures.

The physical origins of hydrophobic hydration described by the present model are very similar to the view of Besseling and Lyklema.[26] The differences are that the present model is designed to be solvable analytically, to handle solute size effects easily, and to give expressions that can be parametrized to agree with experimental solvation data. In comparison to the iceberg view, the present work does not postulate special solvation shell structuring or evoke images of crystalline structures in the vicinity of nonpolar solutes.

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