

Simple Lattice Model for Solvation of Nonpolar Molecules in Hydrogen-Bonded Liquids

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A lattice model is presented that gives closed-form expressions for solvation thermodynamic parameters in hydrogen-bonded solvents including water and alcohols. The model allows one to handle the size of solutes in a very simple way using a single parameter and accounts for the influence of the solute on the entropy of the solvent hydrogen bond network. The model suggests that the influence of solute insertion on the orientational freedom of nearby water molecules is important but not entirely responsible for the unusual entropy of the hydrophobic effect. Appeal to formal exact expressions for solvation thermodynamic parameters shows that the unusual thermodynamic descriptors of hydrophobic solvation can result from an unusual positive covariance between the energy of interaction between a solute and the solvent and the energy of interaction among solvent molecules. These effects are incorporated in the lattice model by ascribing a temperature dependence to the solute–solvent and solvent–solvent interaction parameters. When suitably parameterized, the model is consistent with the signature features of the hydrophobic effect.

Introduction

Figure 1 illustrates typical behavior for solvation of nonpolar molecules in hydrogen-bonded solvents by comparing the solvation free energy of xenon in *n*-alcohols,^{1,2} water,^{2,3} and *n*-alkanes.^{2,4–6} Xenon is less soluble in alcohols compared to alkanes, at least in part because of the presence of hydrogen bonds in the former. The qualitative chain length dependence of the two classes of solvents also differs, with the alcohols showing a minimum solvation free energy (maximum solubility) for butanol. In the case of water, the solvation free energy of xenon is anomalously high, even when compared to short-chain alcohols.² Experimental data show that at low temperatures an anomalous unfavorable entropy distinguishes solvation of nonpolar solutes in water compared to most other solvents.⁷ Thus, it appears that for alcohols and for water, the presence of hydrogen bonds has a strong influence on solvation thermodynamics.

The term *hydrophobic effect* is frequently used to describe to the unusual low solubility of nonpolar solutes in water. The hydrophobic effect is accompanied by a large unfavorable entropy of solvation near room temperature and a large positive heat capacity of solvation. As the temperature is raised, the enthalpy of solvation becomes unfavorable and the entropy of solvation becomes more favorable. These features serve to define the hydrophobic effect as considered in this report.^{8,9} The hydrophobic effect is believed to play a vital role in determining the structures of biopolymers, in ligand binding to proteins, in determining the structures of membranes and surfactant aggregates, etc. Understanding the hydrophobic effect in particular and the role of hydrogen bonding in general is therefore an important and active area of research.

Frank and Evans⁷ proposed a model of the hydrophobic effect that is now widely quoted. They described their model in terms of an analogy between the thermodynamics of ice formation and the thermodynamics of hydrophobic solvation. Like hydrophobic solvation, ice formation involves a large loss of

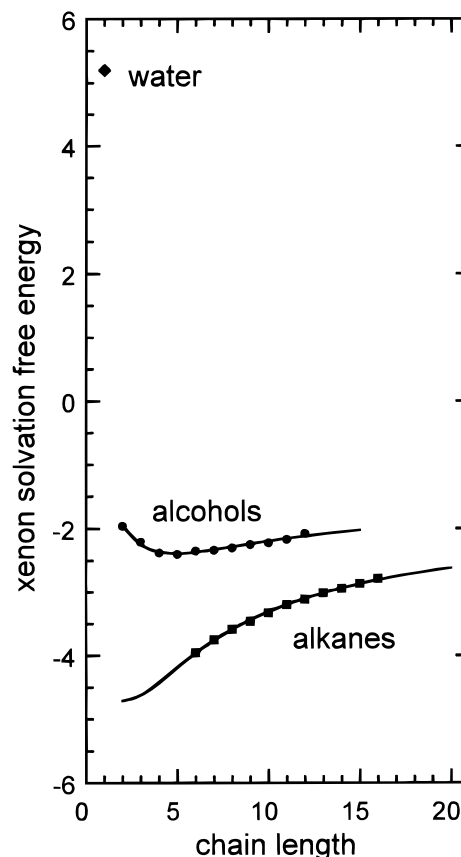


Figure 1. The solvation free energy in kJ/mol of xenon in *n*-alkanes, *n*-alcohols, and water is shown as a function of chain length. For the alcohols, the oxygen is counted as a chain segment, so water is viewed as an alcohol with a chain length of one. The alkane data are from refs 4 and 5, converted to density units as in ref 6. The alcohol data are from ref 1, converted to density units as in ref 2. The water datum is from ref 3, converted to density units as in ref 2 and extrapolated to 20 °C based on a polynomial fit to the temperature-dependent solvation free energy data. The lines through the data are based on fits of eq 35 giving parameters listed in Table 1.

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entropy and a release of heat, wherein the entropy loss is associated with an ordering of water molecules. Frank and Evans attributed the unusual thermodynamics of hydrophobic solvation to an ordering of water around nonpolar solutes, described in terms of "iceberg" formation. They were less specific about the underlying mechanism for the formation of icebergs.

Much recent progress in calculating the hydrophobic effect is based on the view that hydrophobic solvation can be calculated using the steps of forming a cavity of appropriate size, followed by insertion of the solute molecule into the cavity.¹⁰ For example, the recent information theory model¹¹ and related models¹² calculate the probability of cavity formation by extrapolating to zero the probability distribution describing the number of water molecules found in a volume equal in size to the nonpolar solute. The probability distribution, which embodies the special properties of water compared to other liquids, is obtained from experiment or simulation.

Another perspective is provided by molecular dynamics and Monte Carlo simulations carried out with realistic models of water and solutes.^{13–16} Insight into the origin of features of hydrophobic solvation has been gleaned, for example, by examining correlations of molecular orientation and position in the vicinity of nonpolar solutes in water. This type of work suggests that a significant contribution to the unusual entropy of hydrophobic solvation originates from such orientational and translational correlations.¹⁴ More primitive models of water are also occasionally used in conjunction with Monte Carlo and molecular dynamics methods to explore the special properties of water. For example, a simple two-dimensional water model, characterized by directional preference in contacts, reproduces a wide array of the anomalous aspects of water structure and solvation behavior.^{17,18} A number of additional nontraditional models for water and aqueous solvation have recently been explored.^{19–21}

Lattice models have long been used to illuminate special properties of water. These models are based on the partially filled body-centered cubic lattice introduced by Bell.²² The focus of these models has been mostly on describing the anomalous features of water itself.^{23,24} The general approach is to ascribe a low energy to tetrahedrally arranged water molecules, while ascribing a higher energy to other arrangements. There is an entropy advantage and an enthalpy penalty when nontetrahedral arrangements are adopted. Such models reproduce important properties of water including the density maximum. A related lattice model has recently been extended to treat solvation thermodynamics of nonpolar molecules in water.²⁵

The purpose of this report is to explore the influence of hydrogen bonds and other solvent properties on hydrophobic solvation using a novel lattice model. One advantage of using lattice models^{26,27} over more detailed approaches is that they often produce simple analytical expressions for thermodynamic properties. The parameters in these expressions can have simple physical interpretations that can help clarify the physics underlying the thermodynamic properties. The parameters can also often be adjusted to achieve good functional descriptors of experimental data. Unique aspects of the lattice model developed in this report are that it treats solute effects on the entropy of the solvent hydrogen bond network, it provides a simple means to handle the effect of solute size, and it gives other desirable benefits of lattice models: simple analytical expressions for solvation thermodynamics involving adjustable parameters having straightforward physical interpretation. Also, unlike other lattice models of water, the present approach is capable of dealing with more complex systems, such as alcohols or water–alcohol mixtures.

The model is constructed beginning with the assumption that both hydrogen-bonded and non-hydrogen-bonded water–water interactions are present. The types of interactions have different energies. It is assumed that the total number of hydrogen bonds does not change upon solute insertion, but non-hydrogen-bonded interactions are disrupted. The orientational contribution to the partition function for the water molecules is evaluated in a manner similar to Pauling's treatment of the residual entropy of ice,²⁸ augmented with a procedure for accounting for the influence of nonpolar solutes. A temperature dependence is ascribed to contact energies in order to obtain a nonzero heat capacity of solvation. A comparison between the lattice expressions and formal exact expressions for solvation thermodynamic quantities gives further insight into the physical content of the lattice expressions and the physical basis of the hydrophobic effect. Finally, the model is extended to treat *n*-alcohols in order to allow comparison of predictions of the model for systematically varied hydrogen bond concentrations with experiment.

Formal Exact Expressions for Solvation Thermodynamics

Pseudochemical Potential and Related Functions. As advocated by Ben-Naim based on a classical statistical thermodynamic treatment,² there are many benefits to expressing the chemical potential of a solute molecule B, μ_B , in the form

$$\mu_B = \mu_B^* + kT \ln(\rho_B \Lambda_B^3) \quad (1)$$

where ρ_B is the concentration of the solute in number density units, such as moles per liter. Λ_B is the thermal wavelength factor, and μ_B^* is called the pseudochemical potential. One advantage of this form is that the pseudochemical potential is a measure of the coupling work of a solute molecule with its surroundings when inserted in the mixture, and therefore serves as a meaningful measure of solvation thermodynamics. In this framework it is convenient to view the energy of a solute–solvent system as being divided into two parts, $\Delta E + E$. ΔE is the energy of interaction between the solute molecule and the solvent, and E is the energy of the solvent molecules among themselves. Using this terminology, the exact expression for the pseudochemical potential is

$$\mu_B^* = -kT \ln \langle e^{-\Delta E/kT} \rangle \quad (2)$$

The angled brackets denote the ensemble average of the enclosed quantity. In the canonical ensemble, this is given by

$$\langle X \rangle = \frac{\int X(\mathbf{r}) e^{-E(\mathbf{r})/kT} d\mathbf{r}}{\int e^{-E(\mathbf{r})/kT} d\mathbf{r}} = \frac{\sum_i X_i \Omega_i e^{-E_i/kT}}{\sum_i \Omega_i e^{-E_i/kT}} \quad (3)$$

Note that μ_B^* is identical to the excess chemical potential calculated using Widom sampling.²⁹

In the first form in eq 3 the average is calculated over all configurations of the system, in which a particular configuration is specified by the positions of all of the molecules, \mathbf{r} . In the second form, the configurations are sorted according to their energy, and the number of configurations with a particular energy E_i is denoted Ω_i . The latter form is more suitable for lattice models in which the system configurations are coarse-grained and will be used here. Note that the Boltzmann weights in the average do not include the energy of interaction between the solute and solvent. The Boltzmann weight of this interaction energy is the quantity being averaged in the expression for the

pseudochemical potential. In the expressions that follow, averages which do include the solute–solvent interaction term ΔE will occur. These averages will be distinguished using curly brackets:

$$\{X\} = \frac{\langle X e^{-\Delta E/kT} \rangle}{\langle e^{-\Delta E/kT} \rangle} = \frac{\sum_i X_i e^{-\Delta E_i/kT} \Omega_i e^{-E_i/kT}}{\sum_i e^{-\Delta E_i/kT} \Omega_i e^{-E_i/kT}} = \frac{\sum_i X_i \Omega_i e^{-(\Delta E_i + E_i)/kT}}{\sum_i \Omega_i e^{-(\Delta E_i + E_i)/kT}} \quad (4)$$

This report deals with very dilute solutes in hydrogen-bonded solvents, so it is worthwhile to introduce the dilute limit of the pseudochemical potential

$$\mu_B^{*0} = \lim_{\rho_B \rightarrow 0} (\mu_B - kT \ln(\rho_B \Lambda_B^3)) \quad (5)$$

The pseudochemical potential for an ideal gas is zero, so following Ben-Naim² the solvation free energy is defined in this report as

$$\Delta A_B^{*0} = RT \ln \left(\frac{\rho_{B,\text{gas}}}{\rho_{B,\text{solvent}}} \right) = \mu_{B,\text{solvent}}^{*0} \quad (6)$$

Other thermodynamic quantities of solvation are given by

$$\Delta S_B^{*0} = -\frac{\partial \Delta A_B^{*0}}{\partial T} \quad (7a)$$

$$= k \ln \langle e^{-\Delta E/kT} \rangle + \frac{\{\Delta E\}}{T} + \frac{\{E\} - \langle E \rangle}{T} \quad (7b)$$

$$\Delta U_B^{*0} = \Delta A_B^{*0} + T \Delta S_B^{*0} \quad (8a)$$

$$= \{\Delta E\} + (\{E\} - \langle E \rangle) \quad (8b)$$

$$= \{\Delta E\} + \frac{\langle E e^{-\Delta E/kT} \rangle - \langle E \rangle \langle e^{-\Delta E/kT} \rangle}{\langle e^{-\Delta E/kT} \rangle} \quad (8c)$$

$$\Delta C_B^{*0} = \frac{\partial \Delta U_B^{*0}}{\partial T} \quad (9a)$$

$$= \frac{\{(\Delta E + E)^2\} - \{(\Delta E + E)\}^2}{kT^2} - \frac{\langle E^2 \rangle - \langle E \rangle^2}{kT^2} \quad (9b)$$

$$= 2 \frac{\{E \Delta E\} - \{E\}\{\Delta E\}}{kT^2} + \frac{\{\Delta E^2\} - \{\Delta E\}^2}{kT^2} + \frac{\{E^2\} - \{E\}^2}{kT^2} - \frac{\langle E^2 \rangle - \langle E \rangle^2}{kT^2} \quad (9c)$$

Equations 7a, 8a, and 9a give definitions, while eqs 7b, 8b, and 9b show the relationships between these formal quantities and averages or fluctuations of the various interaction energies.² Equation 8c is obtained from 8b by using the definition of the average given in eq 4. This form emphasizes the role of the covariance between E , the energy of a particular solvent

configuration, with the Boltzmann weight of ΔE , which can be viewed as the probability that a solvent insertion attempt will be successful. This covariance determines the energy change of the solvent itself due to solute insertion. Similarly, eq 9c emphasizes the importance of the covariance of E_i and ΔE_i in determining the heat capacity of solvation. It will be argued that these covariance terms underlie to a large degree the unusual thermodynamic properties of the hydrophobic effect.

Lattice Model

Nomenclature. The approach for developing this lattice model for solvation in hydrogen bonded liquids follows the strategies described in a previous publication,³⁰ with slight modifications to the nomenclature. Parameters pertaining to water and solutes will be given subscripts W and B, respectively. Terms of the form w_{ij} refer to the energy of a single contact between molecules of types i and j . Terms of the form Z_{ij} refer to the maximum number of molecules of type j that can pack around a molecule of type i . The order of the subscripts is critical because of the effects of differing molecular sizes on these maximum contact numbers. It will be assumed in this report that Z_{ij} can have noninteger values. The parameter ρ is defined as the ratio Z_{BW}/Z_{WB} . ρ is important in this work because it serves as a convenient descriptor of the size of the B molecules relative to the water molecules. This parameter ρ (without a subscript) should not be confused with ρ_B , which gives the number density of solute molecules in the pseudochemical potential expressions. It is assumed that the water molecules occupy a single lattice cell each, while solute molecules are permitted to occupy more than one cell.

Simplifications for Most Probable States. Thermodynamic properties in the lattice model are calculated starting with the partition function Q for a canonical ensemble, given by

$$Q = \sum_i \Omega_i e^{-E_i/kT} \quad (10)$$

where Ω_i is the number of configurations with energy E_i , and the sum is over all possible energy levels. The free energy (A), entropy (S), internal energy (U), and heat capacity (C) are obtained from the partition function using the usual expressions: $A = -kT \ln Q$, $S = -\partial A/\partial T$, $U = A + TS$, and $C = \partial U/\partial T$. Derivatives of these with respect to the number of solute molecules give the chemical potential and other partial molar parameters.

It is common in lattice models to assume that the most probable energy level is the only energy level making a significant contribution to the overall partition function because the probability distribution function for energy level occupation is a strongly peaked Gaussian.^{26,27} It is also often assumed that the degeneracy of this most probable level is given by the total number of arrangements available to the lattice residents. The average energy of this level is approximated by calculating the average energy for a random arrangement of lattice residents.^{26,27} The expression for the partition function becomes

$$Q = \Omega e^{-E/kT} \quad (11)$$

where the symbols Ω and E without subscripts represent the number of random arrangements and the average energy of a random arrangement, respectively.

Contact Numbers. Several aspects of the treatment require counting the number of contacts among molecules or segments of different types. For example, in lattice models the energy is traditionally expressed in terms of the numbers of nearest

neighbor contacts. It will be seen below that contact numbers are also important in evaluating the orientational degeneracy available to hydrogen-bonded molecules. Expressions 12–14 have been shown to give very accurate estimates of the number of contacts, m_{ij} , between globular molecules of different sizes over the full composition range.³⁰ They are exact for dilute systems.

$$m_{WB} = \frac{Z_{WB}n_W Z_{BW}n_B}{Z_{WB}n_W + Z_{BW}n_B} = Z_{BW} \frac{n_W n_B \rho}{n_W + n_B \rho} \quad (12)$$

$$m_{WW} = \frac{1}{2}n_W Z_{WW} - \frac{1}{2} \frac{Z_{WW}}{Z_{WB}} m_{WB} \quad (13)$$

$$m_{BB} = \frac{1}{2}n_B Z_{BB} - \frac{1}{2} \frac{Z_{BB}}{Z_{BW}} m_{WB} \quad (14)$$

For dilute solutions, ρ can be viewed as a measure of the extent to which the solute molecules interfere with contacts among the solvent molecules (or solvent chain segments). This can be illustrated by considering the change in the number of water–water contacts upon addition of a single solute molecule, $\Delta m_{WW} = m_{WW}(n_B = 0) - m_{WW}(n_B = 1)$. Using eq 13 and solving for ρ gives $\rho = 2\Delta m_{WW}/Z_{WW}$. This implies that ρ is the net loss in the number of water–water contacts caused by insertion of a solute compared to the number that would be disrupted by a water-sized solute.

Average Interaction Energy. The average energy is approximated by summing all interactions expected in a random configuration after ascribing a specific interaction energy w_{ij} to each type of interaction. Water–water contacts will be subdivided into hydrogen-bonded and non-hydrogen-bonded types. In this report, the term “hydrogen bond” is used rather loosely to refer to a contact between two water molecules, one of which has an oxygen–hydrogen bond vector that is directed toward the oxygen of the other. No single pair of oxygen atoms is permitted to have more than one hydrogen bond, and no oxygen–hydrogen bond vector may be directed toward a nonpolar solute. These assumptions imply that for systems containing only water and nonpolar solutes, the number of hydrogen bonds will always be $2n_W$, while the number of non-hydrogen bond contacts is given by $m_{WW} - 2n_W$, where m_{WW} gives the total number of water–water contacts of both types according to eq 13. This implies that the energy of a water–solute mixture is given by

$$E = w_{hb}2n_W + w_{WW}(m_{WW} - 2n_W) + w_{BB}m_{BB} + w_{WB}m_{WB} \quad (15a)$$

$$= (w_{hb} - w_{WW})2n_W + \frac{1}{2}n_W Z_{WW}w_{WW} + \frac{1}{2}n_B Z_{BB}w_{BB} + m_{WB}\omega_{WB} \quad (15b)$$

where w_{hb} is the energy of a hydrogen bond, w_{WW} is the energy of a non-hydrogen-bonded water–water contact, and ω_{WB} is given by

$$\omega_{WB} = w_{WB} - \frac{1}{2} \left(\frac{Z_{WW}}{Z_{WB}} w_{WW} + \frac{Z_{BB}}{Z_{BW}} w_{BB} \right) \quad (16)$$

Configurational Degeneracy. Following previous work,³⁰ the number of ways Ω_B of arranging the globular B molecules

on a lattice containing N_L sites can be expressed using eq 17

$$\Omega_B = \frac{1}{n_B!} \prod_{i=1}^{n_B} N_L f_i \quad (17)$$

where f_i is the probability that a randomly selected location on a lattice is capable of accepting the i th B molecule, assuming that $i - 1$ B molecules are already present. Therefore, f_i is easy to calculate accurately when B molecules are dilute, as will occur in partitioning experiments. For example, an approximation used below and discussed previously is $f_i = (N_L - (i - 1)v_{B,ex})/N_L$, where $v_{B,ex}$ is the excluded volume of a B molecule. For very dilute B molecules, f_i is not significantly different from one, so the expression used is not important so long as it has the correct limit.

Once the solute molecules are arranged, there is only one way to arrange water molecules in the remaining lattice cells (ignoring for the moment the arrangements of hydrogen atoms), unless one is including empty cells to handle free volume and pressure effects. Such effects are not considered in this report.

Hydrogen Bonds and Orientational Degeneracy. The procedure for evaluating the orientational degeneracy for water molecules follows closely the procedure used by Pauling in his evaluation of the residual entropy of ice,²⁸ except noninteger coordination numbers³⁰ are permitted, and interference from the presence of solute is considered. First, the hydrogen atoms are arranged randomly on the water molecules. There are $Z_{WW}/(Z_{WW} - 1)/2$ ways to do this per water molecule. Next, one must correct for the probability that each of these donors finds itself adjacent to a water molecule. Determination of this factor begins with eq 13, which gives the number of contacts among pairs of water molecules. This expression, when divided by the number of contacts between water molecules in the absence of any solute (eq 13 with $n_B = 0$), gives the probability that a specific neighboring site contains a water molecule. This results in a correction factor of $n_W/(n_W + n_B\rho)$ for each of the $2n_W$ donors. Finally, one must account for the probability that the chosen acceptor is not already involved in a hydrogen bond with this oxygen donor. This correction is given by $(Z_{WW} - 2)/Z_{WW}$ for each of the $2n_W$ donors. The final expression for the number of ways of arranging the hydrogen bonds is the product of the number of random arrangements, the correction for solute interference, and the correction preventing multiple hydrogen bonds between oxygen pairs.

$$\Omega_{hb} = (q_{hb})^{n_W} \left[\frac{n_W}{n_W + n_B\rho} \right]^{2n_W} \quad (18)$$

where

$$q_{hb} = \frac{(Z_{WW} - 1)(Z_{WW} - 2)}{2Z_{WW}} \quad (19)$$

Note that when Z_{WW} is set to 4, this gives Pauling's result²⁸ for the number of arrangements of hydrogen atoms per water molecule in ice, $q_{hb} = 1.5$. In this model, the contact number Z_{WW} is permitted to have nonintegral values and is expected to be larger than 4 on average in liquid water. It will be seen below that the value of Z_{WW} does not appear in the expressions for hydrophobic solvation thermodynamic properties, so its precise value is not relevant in this context.

After introducing the excluded volume approximation for f_i in the expression for Ω_B and evaluating the products over the

number of water molecules, one obtains the following expression for the number of arrangements of molecules and hydrogen bonds

$$\Omega = \left[\frac{(N_L)^{N_L/\nu_{B,ex}}}{(n_B)^{n_B}(N_L - n_B\nu_{B,ex})^{(N_L/\nu_{B,ex} - n_B)}} \right] q_{hb}^{n_W} \left[\frac{n_W}{n_W + n_B\rho} \right]^{2n_W} \quad (20)$$

where Stirling's approximation, $n! = (n/e)^n$, has been used.

Expressions for Solvation Thermodynamics in Water. The partition function Q is given by eq 11, where eq 20 is used for Ω and eq 15b is used for E . The free energy is given by $A = -kT \ln Q$, giving

$$A = (w_{hb} - w_{WW})2n_W + \frac{1}{2}n_W Z_{WW}w_{WW} + \frac{1}{2}n_B Z_{BB}w_{BB} + m_{WB}\omega_{WB} + kTn_B \ln\left(\frac{n_B}{N_L}\right) + kT\left(\frac{N_L}{\nu_{B,ex}} - n_B\right) \ln\left(\frac{N_L - n_B\nu_{B,ex}}{N_L}\right) - kTn_W \ln(q_{hb}) - 2kTn_W \ln\left(\frac{n_W}{n_W + n_B\rho}\right) \quad (21)$$

The derivative of this with respect to n_B gives the chemical potential.

$$\mu_B = \frac{1}{2}Z_{BB}w_{BB} + Z_{WB}\rho\left(\frac{n_W}{n_W + n_B\rho}\right)^2 \omega_{WB} + kT \ln\left(\frac{n_B}{N_L - n_B\nu_{B,ex}}\right) + 2kT\rho\left(\frac{n_W}{n_W + n_B\rho}\right) \quad (22)$$

Taking the dilute solute limit as prescribed by eq 5 gives the desired expression for the pseudochemical potential for a dilute nonpolar solute in water:

$$\mu_B^{*0} = \rho Z_{WB}w_{WB} - \frac{1}{2}\rho Z_{WW}w_{WW} + 2kT\rho \quad (23)$$

In taking the derivative of the free energy with respect to the number of solute molecules to get the chemical potential, it was assumed that the number of solvent molecules remains constant. This is common practice in lattice models.^{26,27} This would actually lead to an increase in lattice volume by the volume of a solute particle. It is assumed here that the associated PV work makes a negligible contribution to the chemical potential.

To calculate the internal energy of solvation, the entropy of solvation, and the heat capacity of solvation, it is necessary to take derivatives of eq 23 with respect to temperature. Recall that the contact energies in this expression represent most probable energies, approximated as the average energy for random arrangements. For systems with a finite heat capacity, the average energy is a function of temperature because the addition of heat causes a redistribution of populations among the available energy levels. This effect can be introduced into the lattice model by ascribing a temperature dependence to the contact energies. This allows temperature derivatives of eq 23 to be obtained. As with the contact energies themselves, the temperature dependence of these contact energies can be viewed as empirical descriptors of the system. Such descriptors can serve as adjustable parameters for quantitative analysis, or as place holders in understanding physical aspects of the system. It will be convenient to treat the products $Z_{WB}w_{WB}$ and $Z_{WW}w_{WW}$

as descriptors of this energy, since the contact number and the interaction energy per contact contribute to the total energy, and because the number of water–water contacts may be a function of temperature.³¹

This gives the following expressions for solvation thermodynamic parameters:

$$\Delta S_B^{*0} = -\rho \frac{d}{dT} \left(Z_{WB}w_{WB} - \frac{1}{2}Z_{WW}w_{WW} \right) - \rho 2k \quad (24)$$

$$\Delta U_B^{*0} = \rho \left(Z_{WB}w_{WB} - \frac{1}{2}Z_{WW}w_{WW} \right) - \rho T \frac{d}{dT} \left(Z_{WB}w_{WB} - \frac{1}{2}Z_{WW}w_{WW} \right) \quad (25)$$

$$\Delta C_B^{*0} = \rho T \frac{\partial^2}{\partial T^2} \left[Z_{WB}w_{WB} - \frac{1}{2}Z_{WW}w_{WW} \right] \quad (26)$$

Lattice Treatment of *n*-Alcohols. The last term in the entropy of solvation (eq 24), $-\rho 2k$, arises from interference of the solute with the orientational entropy of water molecules because of the requirement that all hydrogen bond donors find acceptors. Many other liquids also have hydrogen bond donors and acceptors, and similar effects are expected in these solvents as well. It is therefore of value to carry out a similar analysis for *n*-alcohols because available data on solvation of xenon in the *n*-alcohol series provides a means to systematically vary the hydrogen bond density and evaluate its role in solvation thermodynamics. This provides an experimental check of the reasonableness of the lattice model with respect to its ability to treat the orientational entropy of hydrogen bond donors. Alcohols are also of interest in their own right and serve as simple examples of biologically and industrially important amphiphilic materials. Finally, the exercise serves to illustrate the extension of the lattice model to nonaqueous systems.

To emphasize the role of the orientational degeneracy of hydrogen bonds and to simplify and focus the analysis, the alcohol system will be treated athermally. In comparing the model to experimental data, a single term will be introduced to account for thermal contributions to the free energy of solvation, and this term will prove to be adequate to treat xenon solvation in the series of *n*-alcohols.

The notation used above for water will require a few additions to treat alcohols. Parameters pertaining to alcohol molecules will be given the subscript A, while parameters referring to individual alcohol chain segments will be given the subscript α . It will be asserted that each alcohol chain segment occupies a single lattice cell. The length of an alcohol chain molecule is denoted l_A , so $n_\alpha = n_A l_A$. Note that l_A is expressed in terms of the number of lattice cells occupied by the chain, which is not necessarily equal to the number of carbon plus oxygen atoms in the chain. Also, the oxygen atom of an alcohol is considered as (part of) a chain segment. Nomenclature is otherwise analogous to that used for water, in which the subscript α is substituted for W.

Arrangement of the solute molecules is carried out as described above for water. Accounting for the arrangements of alcohol chains follows previously published strategies developed for alkanes.³⁰ The number of ways of arranging the alcohol chain segments in the $n_\alpha = N_L - n_B\nu_B$ sites is given by eq 27.

$$\Omega_\alpha = \frac{n_\alpha!}{(n_A!)^{l_A}} C \quad (27)$$

where C is given by

$$C = \left(\frac{p_{i,i+1} n_A n_A!}{n_A n_A} \right)^{l_A-1} \quad (28)$$

Here, C corrects for the probability that randomly placed chain segments will be arranged in a manner consistent with proper covalent connectivity. Also, $p_{i,i+1}$ is the probability that an alcohol segment from position i has at least one immediate neighbor from position $i + 1$ and is given by³⁰

$$p_{i,i+1} = 1 - \left(\frac{n_\alpha + \rho n_B - n_A}{n_\alpha + \rho n_B} \right)^{Z_{\alpha\alpha}} \quad (29)$$

To calculate the correction required for the presence of hydrogen bonds, a procedure entirely analogous to that used for water is used. The hydrogen atoms are first arranged randomly on the donor atoms. Since each donor has $Z_{\alpha\alpha}$ nearest neighbors, of which one is a covalently bonded methylene, there are $(Z_{\alpha\alpha} - 1)$ ways to arrange the hydrogen atoms on each donor oxygen. Next, one must correct for the probability that each of these donors finds itself next to an acceptor. Determination of this factor begins with eq 13 (with α substituted for W), which gives the number of contacts among pairs of chain segments. This expression when divided by the number of contacts between chain segments in the absence of any solute (equation 13 with $n_B = 0$) gives the probability that a specific neighboring site contains a segment from an alcohol chain. The probability that this segment is an oxygen is the product of this ratio times the fraction of alcohol chain segments that are oxygen atoms, n_A/n_α . Thus, the probability that the cell in the chosen direction is a hydrogen bond acceptor is $n_A/(n_\alpha + \rho n_B)$. It is also necessary to correct for the probability that the chosen acceptor is not already involved in a hydrogen bond with this oxygen donor. The putative acceptor can donate in $(Z_{\alpha\alpha} - 1)$ directions, of which $(Z_{\alpha\alpha} - 2)$ are not directed at the oxygen donor. The correction preventing multiple hydrogen bonding between a single pair of oxygen atoms is therefore $(Z_{\alpha\alpha} - 2)/(Z_{\alpha\alpha} - 1)$ for each donor.

The overall correction for orientational degeneracy is therefore the product of all of these terms raised to the n_A power.

$$\Omega_{hb} = (Z_{\alpha\alpha} - 2)^{n_A} \left(\frac{n_A}{n_\alpha + \rho n_B} \right)^{n_A} \quad (30)$$

Using the expressions above for the number of arrangements for solute particles (eq 17), chain configurations (eq 27), and the number of hydrogen bond arrangements (eq 30) gives for the overall degeneracy:

$$\Omega = \left(\frac{n_\alpha}{n_A} \right)^{n_A} \left(\frac{N_L - n_B v_{B,ex}}{n_B} \right)^{n_B} \left(\frac{N_L}{N_L - n_B v_{B,ex}} \right)^{N_L/v_{B,ex}} \times \left(\frac{p_{i,i+1}}{e} \right)^{n_A(l_A-1)} q_{alc} \left(\frac{n_A}{n_\alpha + \rho n_B} \right)^{n_A} \quad (31)$$

where the products have been expanded in terms of factorials, Stirling's approximation, $n! = (n/e)^n$, has been used, and $q_{alc} = (Z_{\alpha\alpha} - 2)$.

Since we are assuming the system is athermal, the entropy is given by $S/k = \ln(\Omega)$:

$$\frac{S}{k} = -n_\alpha \ln \left(\frac{n_A}{n_\alpha} \right) - n_B \ln \left(\frac{N_L - n_B v_{B,ex}}{n_B} \right) - \frac{N_L}{v_{B,ex}} \times \left(\frac{N_L}{N_L - n_B v_{B,ex}} \right) + n_A(l_A - 1) \ln \left(\frac{p_{i,i+1}}{e} \right) + n_A \ln(q_{alc}) + n_A \ln \left(\frac{n_A}{n_\alpha + \rho n_B} \right) \quad (32)$$

In this athermal system, the chemical potential is given by the derivative of $-TS$ with respect to n_B , holding n_A constant

$$\mu_B = kT \ln \left(\frac{n_B}{N_L - n_B v_{B,ex}} \right) + kT v_B \ln \left(\frac{N_L - n_B v_{B,ex}}{N_L} \right) + kT \rho \frac{Z_{AA} n_A^2 (l_A - 1)}{(n_\alpha + \rho n_B)(n_\alpha + \rho n_B - n_A)} \left(\frac{1 - p_{i,i+1}}{p_{i,i+1}} \right) + kT \rho \frac{n_A}{n_\alpha + \rho n_B} \quad (33)$$

The desired expression for the dilute B pseudochemical potential is determined by taking the limit as prescribed by eq 5 to give

$$\mu_B^{*0} = kT \rho \frac{Z_{AA}}{l_A} \left(\frac{1 - p_{i,i+1}}{p_{i,i+1}} \right) + kT \rho \frac{1}{l_A} \quad (34)$$

The first term accounts for the loss of chain conformational degeneracy caused by the presence of the solute. The second term accounts for the reduced probability that all hydrogen bond donors will be next to acceptors. As with water, all of the terms scale with the size parameter ρ .

The physical content of the model for alcohols can be described beginning with a random arrangement of long-chain alkane molecules in the liquid state. If a terminal methyl group of each alkane is replaced with an alcohol functional group, it is very unlikely that all hydrogen bond donors will be adjacent to acceptors in this configuration. Therefore, the entropy of a long chain n -alcohol liquid will be lower compared to the corresponding alkane because some ordering is required to satisfy the hydrogen bonds. In the case of short-chain alcohols, each hydrogen bond donor will on average have several potential acceptors, giving the short-chain alcohol a higher entropy than the corresponding alkane. It was shown previously that for chain molecules, there is an increase in the pseudochemical potential due to interference of the solute with the conformational entropy of the solvent.³⁰ In the case of alcohols (which have hydrogen bonds), if a nonpolar solute is added, the probability that all hydrogen bond donors will find acceptors will be decreased, resulting in an extra entropy penalty for solvation in alcohols compared to alkanes.

Discussion

Entropy Expressions. The lattice expression for the entropy of hydrophobic solvation (eq 24) has two contributions. The first contribution involves temperature derivatives of the solute-solvent contact energy and the solvent-solvent configurational energy. By integrating the heat capacity of solvation divided by the temperature (eq 26), one can demonstrate that this term is associated with the heat transfer occurring in response to solute insertion. The second contribution is proportional to $\rho 2k$ and is a measure of the influence of solvation on the orientational degeneracy of water molecules. Within the assumptions of the lattice model this term is independent of temperature. It corresponds roughly to the influence of the solute on the residual entropy of water observed at 0 K. An important benefit of the

lattice analysis is its ability to directly estimate this contribution to the entropy.

Internal Energy Expressions. The first term in the lattice expression for the internal energy of solvation, eq 25, gives the contribution of direct interactions between the solute and solvent, and among solvent molecules. As with the lattice expression for the entropy, the second term in this expression accounts for the transfer of heat accompanying solute insertion. In fact the heat transfer terms in the lattice expressions for ΔU^{*0} and $T\Delta S^{*0}$ are identical, so there is cancellation in the expression for the chemical potential. This entropy–enthalpy compensation is observed experimentally, for example, in ligand binding studies involving series of related compounds.

The exact expression for the internal energy of solvation (eq 8b) gives the physically reasonable result that this quantity is controlled by the average interaction energy of the solute with the solvent, plus the change in the solvent energy brought about by insertion of the solute. The final form (eq 8c) shows that this difference in average solvent energy is controlled by the relation between the energy of a solvent configuration and the energy of interaction of the solute molecule with the solvent in that configuration. In particular, the covariance ($\sigma^2 = \langle e^{-\Delta E/kT} E \rangle - \langle e^{-\Delta E/kT} \rangle \langle E \rangle$) of the Boltzmann weight of the solute–solvent interaction energy with the system configuration energy determines this.

From this perspective, there are two ways in which the internal energy of solvation can be favorable. One is simply that the average energy of interaction between the solute and solvent is favorable. The other is that the solvent itself adopts a low energy configuration when a solute is present. This can happen if cavity-containing solvent structures have low energy, wherein the low-energy solvent–solvent interactions do not need to be localized. The lattice model emphasizes the consequence of the fact that either mechanism can result in a transfer of heat in to or out of the system. As will be described next, a characteristic of this latter effect is a positive heat capacity of solvation.

Heat Capacity Expressions. Finally, consider the exact expression for the heat capacity of solvation (eq 9). Since heat capacities are related to energy fluctuations, eq 9b simply gives the difference in the heat capacity in the presence and absence of the solute. The first term of eq 9c, however, shows that the heat capacity is influenced by the covariance of the solvent energy with the solute–solvent interaction energy. This implies that systems exhibiting more favorable solute–solvent interactions when the solvent is in a low energy configuration will have a positive contribution to heat capacity of solvation.

Thermodynamics of the Hydrophobic Effect. From the perspective of the exact formal expressions for solvation thermodynamic parameters, many unusual features of hydrophobic solvation can be attributed to a positive covariance between the solute–solvent interaction energy ΔE and the solvent configuration energy E . This leads to a positive heat capacity of solvation and, via the Boltzmann weight of ΔE , leads also to the favorable enthalpy and unfavorable entropy of solvation observed at low temperature. This positive covariance is reasonable for water. It is well-known that water can form low energy, open structures characterized by maintenance of hydrogen bonds around cavities.

One benefit of the lattice expressions is that they emphasize that a consequence of this unusual covariance is a transfer of heat out of the system in response to solute insertion. A view of this is that the solute locks the system in a low energy form. This heat transfer results in a favorable contribution to the

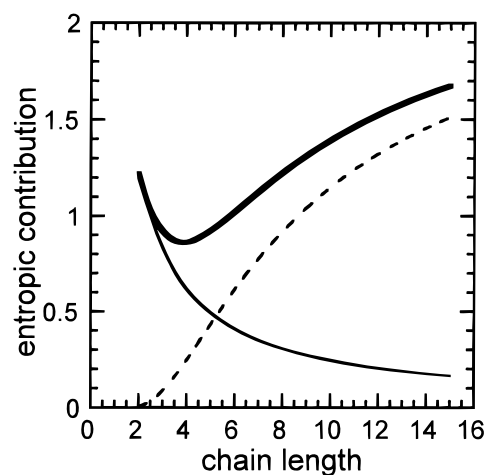


Figure 2. The athermal contribution to the solvation free energy in kJ/mol of a solute in *n*-alcohols is shown as a function of the number of chain segments calculated using eq 34. The solute is assumed to be characterized by a value of $\rho = 1$, and $Z_{\alpha\alpha}$ is fixed at 12. The broken line shows the contribution from chain entropy. The fine line shows the contribution from the hydrogen bond entropy. The heavy line shows the resulting total athermal contribution to the solvation free energy.

internal energy of hydrophobic solvation, and an unfavorable contribution to the entropy of hydrophobic solvation.

The two contributions exactly cancel in the free energy of hydrophobic solvation. The net result is that the lattice expression for the free energy of hydrophobic solvation (eq 23) is distinguished from more typical solvents mainly by the term $2\rho kT$, which is obviously quite significant compared to the thermal energy kT . This term accounts for the interference of the solute with the residual entropy of the hydrogen bond network. The lattice model therefore ascribes the low solubility of nonpolar solutes in water largely to the interference of these solutes with the hydrogen bond entropy. It ascribes the unusual compensatory contributions to entropy and enthalpy of solvation, and hence the unusual temperature dependence of the hydrophobic effect, to heat transfers that accompany solute insertion.

All of the lattice expressions for solvation properties scale linearly with the size parameter ρ . This parameter gives the number of water–water contacts that are disrupted by introduction of a solute molecule compared to the number disrupted by insertion of a water-sized solute. For solutes much larger than water, this parameter should scale closely with the solute surface area, which is in agreement with experimental water solubility data on series of related compounds such as *n*-alkanes.⁸

The entropy expression (eq 24) predicts that the entropy of solvation becomes zero at some temperature due to a cancellation between the effect of solute on the orientational degeneracy of water molecules and the contribution of heat transfer to the entropy of solvation. Since both terms scale equally with the size parameter ρ , the temperature at which the cancellation occurs should be independent of solute size. This temperature should also be fairly constant for members of the same class of molecules if the solute–water interaction energy scales with solute size. This so-called convergence temperature is observed experimentally for hydrocarbons and for thermal protein unfolding experiments.

Comparison to Data on Solvation in Alcohols. Figure 2 shows the alcohol chain-length dependence of the chemical potential of a solute characterized by $\rho = 1$ assuming $Z_{\alpha\alpha} = 12$ for an athermal system. The figure emphasizes the separate contributions from alkane chain entropy and hydrogen bond

TABLE 1: Parameters Obtained from Fits of Equation 35 to the Data in Figure 1

	alkanes	alcohols
g (kJ/mol)	-4.72	-2.87
ρ	1.22	0.57
a	1.00	0.75

entropy as described by eq 12. The chain entropy contribution, which is identical to that discussed previously for alkanes,³⁰ contributes very little for chains less than about four segments, and then increases toward a long-chain limit. The origin of this contribution is interference with the conformational entropy of the chains. The hydrogen bond entropy, on the other hand, makes a significant positive contribution only for short chains, falling off inversely with the chain length. The origin of this contribution is interference with the number of arrangements of the hydrogen bonds. For long chains, the probability of interference with hydrogen bonds is lower because the number density of hydrogen bonds in the liquid is lower. The net result of the two contributions is a minimum in the entropic contribution to the chemical potential occurring around four or five segments (three or four carbons if one assumes one carbon per segment).

As seen in Figure 1, available literature data on partitioning of xenon into alcohols exhibits the predicted behavior, including the minimum around propanol or butanol. The lines through the alcohol and alkane data are based on fits to eq 35

$$\Delta G^{*0} = g + kT\rho \frac{Z_{\alpha\alpha} \left(\frac{1 - p_{i,i+1}}{p_{i,i+1}} \right) + kT\rho \frac{1}{l_A}}{l_A} \quad (35)$$

In this expression, ΔG^{*0} is the experimental solvation free energy, g is an empirical chain length-independent part of the solvation free energy, and the final terms accounting for the chain and hydrogen bond entropy, respectively, are taken from eq 34. The final term was omitted in the fit to the alkane data. In fitting to eq 35, an additional parameter, a , is included to relate the number of chain segments to the number of carbon and oxygen atoms, n_{C+O} , in the molecules using the expression $l_A = an_{C+O}$. Optimized parameters for the data are listed in Table 1. It was assumed in these fits that $Z_{\alpha\alpha} = 12$. Results for the alkane data were published previously³⁰ and are included in Table 1 for comparison to the alcohols.

The lines through the data in Figure 1 are based on the parameters in Table 1. The functional form of eq 35 is clearly adequate for describing the data within experimental error. The value of ρ serves to scale the solute size with respect to the solvent segment size. One may speculate that the observed difference in ρ for alcohols and alkanes may be partly related to the effective number of atoms per chain segment, which is larger in alcohols than in alkanes according to the values of a in Table 1. This could lead to the relatively smaller effective size of xenon in alcohols compared to alkanes as reflected in the values of ρ . The value of the parameter g in alcohols is more positive than that in alkanes, presumably reflecting that the atom types and therefore the interaction energies should be different in the two solvents. Also, the model assumes that a single number, $Z_{\alpha\alpha}$, characterizes the orientational options for hydrogen bonding and for chain connectivity, whereas it is likely that different parameters describe the two situations. The present model makes no attempt to account for these details except as summarized by the empirical fitting parameter g .

In view of all these qualifications, it seems advisable not to take the quantitative values of the parameters too literally. The model for alcohols uses a fairly coarse-grained approach

and a small number of parameters to fit a complex array of interactions. The main point is that the model accommodates the general trends in the chain length-dependent behavior quite well, emphasizing the importance of hydrogen bond entropy and chain configuration entropy in the solvation thermodynamics of nonpolar solutes in alcohols.

The agreement indicates that an important contributor to the entropy of solvation in hydrogen-bonded solvents can be captured using the present lattice model. Considering hydrophobic solvation, this gives some support to the assertion that the reduction in solvent orientational options caused by nonpolar solutes is an important contributor to the unusual properties of hydrophobic solvation.

Summary

The present lattice model for solvation in hydrogen-bonded solvents gives simple closed-form analytical expressions for the free energy, entropy, enthalpy, and heat capacity of solvation. The model handles solute size effects on these solvation parameters in a very simple way. For dilute solutes, all terms in the expressions are proportional to the size parameter ρ . It is necessary to ascribe a temperature dependence to the contact energy parameters in the lattice model in order to obtain nonzero values of the heat capacity. By introducing this temperature dependence, the model acknowledges that the populations of energy levels change as energy is added, and that this change in populations results in a change in the average energy.

The origin of the unusual behavior of the entropy of solvation in water is due to two contributions: reduction in the orientational freedom of water molecules in order to remain hydrogen bonded, and a transfer of heat out of the system due to an unusual positive correlation between solute-solvent interaction energy and overall solvent-solvent energy. The compensatory component of the internal energy of solvation arises from the same heat transfer. Solute-independent entropy convergence is predicted by the lattice model because the cancellation of the two contributions to the entropy of solvation occurs at a temperature that is independent of solute size. A contribution to the unusually high, positive heat capacity of solvation arises from an unusual positive covariance between solute-solvent interaction energy and overall solvent-solvent energy. The exact formal solvation expressions show how this covariance influences the internal energy and entropy of solvation as well via the Boltzmann weight of the solute-solvent interaction energy. It is possible to extend the model to treat more complex solvents such as alcohols. Doing so supports the value of the lattice approach to evaluating the influence of nonpolar solutes on the degeneracy of the hydrogen bond network.

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