

Molecular Thermodynamics of Hydrophobic Hydration[†]

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We applied a previously introduced lattice fluid theory for water to study the dissolution of apolar solutes. The treatment is based on a model for the orientation-dependent intermolecular interactions of water. It involves not only the strong directional intermolecular attraction, known as the hydrogen bond, but repulsive interactions between water molecules, which operate at a similar intermolecular separation as hydrogen bonds but at different relative orientations of the molecules, are also important. All the peculiar observations on the dissolution of apolar molecules in water, i.e. temperature dependence of solubility, the Gibbs energy of transfer from apolar medium into water, and its entropic and enthalpic contributions, are reproduced by the theory. Furthermore, the relation between these phenomena and the orientation-dependent intermolecular interactions of water is clarified. Our analysis indicates that the peculiar temperature dependence of the solubility of apolar compounds in water and of the isobaric density of pure water have a common molecular origin. Upon a small expansion of pure water or upon dissolution of small apolar molecules, a subtle enhancement occurs of the type of structuring that is characteristic for water at ambient conditions. This is sufficient to explain the negative hydration entropy of apolar molecules. The negative hydration enthalpy of small apolar molecules is due to a decrease of the number of repulsive non-hydrogen-bonding interactions between neighboring water molecules. Calculations on water adjoining a planar hydrophobic surface indicate that the characteristic features of the dissolution of small apolar solutes do not occur with bulky particles.

1. Introduction

Various macroscopic properties of water are still not very well understood from a molecular point of view. The maximum of the isobaric density as a function of temperature is one of them. Another example, which has been a subject of scientific debate for more than 60 years now, is the behavior of water as a solvent for apolar molecules. The solubility of apolar compounds in water is low. Hence, such molecules are denoted as hydrophobic. The term hydrophobic itself has become a source of confusion since many authors use it with different meanings (see e.g. the comments on terminology in refs 2 and 3). We will not enter these semantic discussions but will briefly describe the phenomena that we intend to clarify.

Obviously, poor miscibility in itself is not unusual. What is special, and in our opinion not yet satisfactorily explained in the case of apolar molecules in water, is the temperature dependence of their solubility or, equivalently, the roles of entropy and enthalpy in the hydration of such molecules. Around room temperature the solubility in water of many apolar compounds passes a minimum upon varying the temperature, indicating that the low solubility is associated with a negative entropy of hydration, whereas the hydration enthalpy is small and up to about room temperature even negative (hence promoting dissolution). The enthalpic and entropic contributions are markedly temperature dependent, but these variations cancel in such a way that the Gibbs energy of hydration is relatively insensitive to temperature.^{3–9} This behavior is different from that of most nonaqueous solutions, in which the enthalpy of mixing is positive. This is consistent with Berthelot's principle

(“geometric mean rule”) for the attractive interactions between unlike molecules.^{10–12} In those nonaqueous mixtures, (a lack of) solubility is mainly determined by the mixing enthalpy.

Over the past decades, this peculiar solvent behavior of water with respect to apolar solutes has drawn much attention, partly because of its academic interest and partly because of its major relevance in practice, not only for the behavior of simple aqueous solutions but also for more complex phenomena. These include the conformation of proteins, the formation of micelles and biological membranes, and the adsorption of surfactants at interfaces.^{3,7,8,10,12–19} In relation to these systems, the terms hydrophobic interaction, hydrophobic attraction and hydrophobic bonding are often used for the effective attraction that drives the association in water of apolar molecules or apolar parts of amphipolar molecules. Obviously, keeping in mind “Archimedes' principle” for intermolecular interactions,^{10,12} hydrophobic bonding is the counterpart of the low solubility of apolar compounds in water.

In view of its widespread occurrence and because of the challenge offered by the peculiar observations, it is not surprising that a variety of theoretical models have been proposed. Many older theories start from *ad hoc* assumptions on the intermolecular structure of water and on the effects of apolar solutes thereon. The experimentally observed negative hydration entropy has led to the idea that some special kind of structuring exists in the water layer around an apolar solute.^{3,8,12,20–23} In this context the still widely used term “iceberg” was coined by Frank and Evans about 50 years ago.²⁰ The term “clathrate cage”, when used in this context, refers to a similar molecular picture.^{12,24,25} Recent neutron diffraction results indicate that there are indeed similarities between water surrounding apolar solutes and clathrate cages.^{24,25} However, the degree of disorder in these structures in liquid water solutions is large.²⁵ It remains a problem to quantify the thermodynamic effects associated with the observed structure and disorder.

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The low and sometimes even negative value of the hydration enthalpy is often explained by an increased number of hydrogen bonds^{12,21} or by assuming that hydrogen bonds in the hydration shell are stronger than in bulk water.²³ The interpretation of the enthalpy often receives less attention than the entropy but is in our opinion at least as problematic.²⁶ The models referred to above give an *ad hoc* interpretation of the phenomena. Alternatively, statistical mechanical methods, originally developed for simple fluids,²⁷ were applied to aqueous solutions of apolar molecules.^{28,29} These methods are of a more *ab initio* nature than the earlier models. In principle they need as sole input a model for the intermolecular interactions. However, for fluids as complicated as water, it is difficult to derive thermodynamic and structural properties without resorting to additional assumptions and/or experimental input. In our opinion, a comprehensive account of the above-mentioned typical thermodynamic observations in relation to the underlying molecular behavior has not yet been given.

The advent of powerful computers made it possible to apply Monte Carlo (MC) and molecular dynamics (MD) simulations to the solvation of apolar molecules in water.^{30–40} These techniques also provide a more *ab initio* approach than the earlier models. However, computer simulations suffer from statistical inaccuracies, especially in determining thermodynamic quantities. Moreover, these techniques do not provide clear explicit relations between thermodynamic quantities and the structure of the liquid. Sometimes the latter problem was addressed by making a combination with approximate statistical mechanical expressions for thermodynamic quantities such as entropy in terms of structural aspects (correlation functions) observed in MD simulations.^{38–40}

With all this in mind, we developed a lattice fluid theory for molecules with orientation-dependent interactions,^{41,42} and applied it to water in particular.^{41,43} In this approach all properties are derived from a model for the intermolecular interactions. The theory for water requires only two adjustable parameters to quantify these. The lattice fluid (also known as lattice gas) approach is admittedly somewhat coarse-grained; e.g. intermolecular distances can only vary discretely, according to the underlying lattice, rather than continuously. However, our theory accounts well for a variety of properties of water so that we trust that it captures the essential physics. Some of these earlier results are particularly relevant for the present problem. For instance, the model reproduces the maximum in the isobaric liquid density (an alternative and in our opinion less likely model to account for this density maximum was published recently⁴⁴). Furthermore, it was found that liquid water should be considered as a macroscopic network of molecules connected by hydrogen bonds rather than as a collection of clusters of finite sizes. In the present paper, we apply this model to examine the dissolution of apolar solutes without making any additional adaptations or parameter tuning. We will not attempt to treat the hydration of a specific hydrophobic compound existing in real life. Rather, we make a comprehensive analysis of a relatively simple model in order to clarify the above-mentioned common features that recur with many different apolar compounds. As we will show, in this way an elegant interpretation is achieved in terms of water structure, accounting for all thermodynamic observations, without the necessity of postulating “icebergs” or similar structures.

In the next section, we will make some of the previous remarks more quantitative, thereby establishing the basis for the analyses in later sections. In section 3, the model for water will be reviewed as far as necessary for the present purpose. For a more complete presentation we refer to our previous publications.^{41–43} In section 4 the thermodynamics of hydro-

phobic hydration is examined and related to the isobaric density of pure water. In section 5, the thermodynamic quantities will be related to the structure of water, thereby providing a molecular interpretation for the thermodynamic properties. In section 6, hydration of an extended hydrophobic surface is examined and contrasted with that of small solutes as discussed in the earlier sections.

2. Statistical Thermodynamics of Hydration

In the regime of classical statistical mechanics, the configurational chemical potential—omitting the thermal wavelength term—of a compound A can be expressed in statistical mechanical terms as

$$\mu_A = kT \ln \rho_A - kT \ln \left\langle \exp \left(- \frac{\Psi_A}{kT} \right) \right\rangle \quad (1)$$

The first term on the right-hand side, where $\rho_A = n_A/V$ is the number density, is the ideal translational entropy term. The second term, the excess term, accounts for intermolecular interactions. The potential energy of an A-molecule due to interactions with all other molecules, Ψ_A , is a function of the positions and orientations of all molecules. The weighting factor $\langle \exp(-\Psi_A/kT) \rangle$ is the canonical average over all positions and orientations of the molecules of the Boltzmann factor $\exp(-\Psi_A/kT)$.^{45–48} We will not be concerned with internal degrees of freedom of the molecules since these are of secondary importance for the present purpose.

Equating the chemical potentials of compound A, as given by eq 1, in an aqueous phase and an apolar phase, we obtain an expression for the partitioning between the two phases.

$$\ln \frac{\rho_A^w}{\rho_A^a} = \ln \frac{\langle \exp(-\Psi_A/kT) \rangle^w}{\langle \exp(-\Psi_A/kT) \rangle^a} \equiv - \frac{\Delta_s g}{kT} \quad (2)$$

where the superscripts w and a indicate the aqueous and apolar phase, respectively. The second equality defines the Gibbs energy of hydration. It equals the change of Gibbs energy upon transfer of an apolar molecule from a fixed position in an apolar medium to a fixed position in water.⁴⁹ As was mentioned in the Introduction, the solubility of apolar compounds in water is low. This implies that $\Delta_s g$ is high and positive. The Gibbs energy of hydration can be divided in an enthalpic and an entropic contribution:

$$\Delta_s g = \Delta_s h - T \Delta_s s \quad (3)$$

What has caused much puzzlement among scientists for about 60 years now was the finding that for many nonpolar solutes the solubility in water has a shallow minimum at about room temperature. This seems to be a common feature although the precise value of the temperature of minimum solubility varies somewhat for different apolar compounds. The Gibbs–Helmholtz relation

$$\Delta_s h = -T^2 \left(\frac{\partial(\Delta_s g/T)}{\partial T} \right)_p \quad (4)$$

implies that at the temperature of minimum solubility $\Delta_s h$ changes sign from negative to positive and that around this point the absolute values of $\Delta_s h$ are small. Consequently, in combination with eq 3 it is inferred that the high positive value of $\Delta_s g$, which is the counterpart of the low solubility in water, is due to a strongly negative entropy of dissolution.

Rather recently, attention has been drawn to the occurrence of a maximum of $\Delta_s g$ at elevated temperature (above about 160 °C),⁸ indicating that there the hydration entropy, for which we

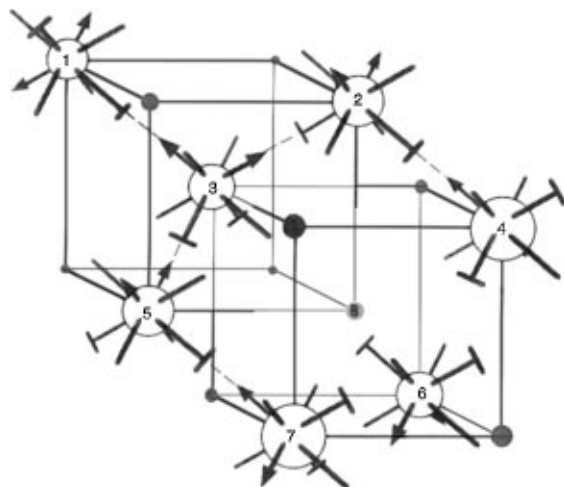


Figure 1. Sixteen sites of a body-centered cubic lattice of which seven are occupied by water molecules. These are indicated by large spheres. Outward arrows \rightarrow indicate proton donors, $\mid-$ indicate proton acceptors, and indifferent faces are indicated by plain sticks \mid . In this example there are five hydrogen bonds. The vacancy at the site indicated by 8 is coordinated by four other vacancies and by the indifferent faces of four water molecules.

can write $\Delta_s s = -(\partial \Delta_s g / \partial T)_p$, changes sign from positive to negative. Privalov and Gill state that at this temperature hydrophobic hydration disappears.⁸ Several years earlier Shinoda had drawn a similar conclusion from the experimental observation that above about 160 °C the logarithm of the solubility of several hydrocarbons in water versus $1/T$ is linear. He stated that at these elevated temperatures iceberg formation disappears.²² The way Privalov and Gill and Shinoda use the terms “hydrophobic hydration” and “iceberg formation”, respectively, merely moves the problem since they do not answer the questions, what does hydrophobic hydration or iceberg formation mean in molecular terms and how do the peculiar temperature dependencies come about.

3. A Lattice Theory for Water

The configurational statistics are analyzed on the basis of a body-centered cubic lattice (see Figure 1). A site can be vacant or occupied by a molecule. The volume per site is indicated by v . As previously, a value $v = 1.632 \times 10^{-29} \text{ m}^3$ will be used.^{1,41,43,50} This value was obtained by equating the density of ice with that of a half-filled lattice. The total volume of the system is indicated by $V = Nv$, where N is the total number of sites.

To account for the orientation dependence of the intermolecular interactions, we distinguish different “faces” on the model water molecules. Two of these faces represent protons; two others represent lone pairs of electrons. These four faces are arranged tetrahedrally on the surface of the molecule (see Figure 1). A contact between a “proton” and a “lone pair” (proton acceptor) corresponds to a hydrogen bond. The remaining four faces will be called “indifferent”. Not only are the molecules confined to lattice sites in this model but also the faces are confined to be directed toward nearest-neighbor sites. Hence, a water molecule has, in this model, a discrete number of 12 orientations. If the system is isotropic, which is the case for situations considered in this paper, all orientations are equally probable.

To a hydrogen bond, an energy of u_{Hb} is attributed. To all other (non-hydrogens bonding) contacts between water molecules, the same energy, $u_{\neq \text{Hb}}$, is assigned.⁵¹ The configurational energy of the system can be calculated from the distribution of contacts

$$U = \sum_{\alpha \leq \beta} n_{\alpha\beta} u_{\alpha\beta} \quad (5)$$

where $u_{\alpha\beta}$ and $n_{\alpha\beta}$ are the energy and the number of $\alpha\beta$ contacts, respectively. The subscripts α and β can indicate any of the face types that are present: “proton”, “lone pair”, “indifferent”, “vacancy”, and “apolar”. For pure water, this expression reduces to $n_{\text{Hb}} u_{\text{Hb}} + n_{\neq \text{Hb}} u_{\neq \text{Hb}}$ where n_{Hb} and $n_{\neq \text{Hb}}$ are the numbers of hydrogen bonds and non-hydrogen-bonded contacts between adjacent water molecules.

To derive the thermodynamic properties for this model, we have generalized the Bethe–Guggenheim approximation (also known as two-site cluster, quasi-chemical, or first-order approximation)^{52,53} for systems containing molecules with orientation-dependent interactions.^{42,43} A general derivation of the theory in terms of the partition function is presented elsewhere.⁴² In the present section we will review those aspects that are relevant for the present purpose.

Structure in fluids can only be defined in statistical terms. In the present theory we account for the structure in water in terms of correlations of the occupancies of neighboring sites, both with respect to the species (water or other molecule or vacancy) as to their relative orientations. Within the Bethe–Guggenheim approximation, these correlations can be described by mass-action type laws for contacts. Generally,

$$\frac{\left(\frac{1}{2}n_{\alpha\beta}\right)^2}{n_{\alpha\alpha}n_{\beta\beta}} = \exp\left(\frac{u_{\alpha\alpha} + u_{\beta\beta} - 2u_{\alpha\beta}}{kT}\right) \quad (6)$$

At infinite temperature ($kT \gg u_{\alpha\alpha} + u_{\beta\beta} - 2u_{\alpha\beta}$ for each α, β), contacts are formed at random. Then the number of water–water contacts is $4n_w\phi_w$, where for any species A , $\phi_A = n_A/N = \nu\rho_A$ is the fraction of sites occupied. Of these contacts, one out of eight is a hydrogen bond. The random numbers of contacts between water molecules and vacancies and between two vacancies are $8n_w\phi_v = 8n_v\phi_w$ and $4n_v\phi_v$, respectively. At finite temperatures, contacts are not formed at random. Low-energy contacts (hydrogen bonds) are preferred. Hence, certain local ordering arises. With this local ordering, a negative excess entropy contribution, S^{exc} , is associated:

$$S = S^{\text{id}} + S^{\text{exc}} \quad (7a)$$

Here, the ideal entropy of translation and orientation, that is the entropy of mixing randomly the molecules, the vacancies, and any other monomeric components, is given by

$$S^{\text{id}} = -k \sum_A n_A \ln \frac{n_A}{N\omega_A} \quad (7b)$$

where ω_A is the number of orientations of a monomer of type A . In first-order Bethe–Guggenheim approximation, the excess entropy due to correlations is given by^{42,43}

$$S^{\text{exc}} = -k \sum_{\alpha \leq \beta} n_{\alpha\beta} \ln g_{\alpha\beta} \quad (7c)$$

with the correlation function $g_{\alpha\beta} = n_{\alpha\beta}/n_{\alpha\beta}^{\infty}$ defined as the ratio of the actual number of $\alpha\beta$ contacts over its random value at the same composition of the system. If the contacts were formed at random, i.e. at infinite temperature, or if all contacts had the same energy, then $g_{\alpha\beta}$ would be equal to unity for each type of contact and the excess entropy would vanish. In principle higher order terms of S^{exc} can be derived by examining correlations within larger clusters of sites. Equations 5 and 7 provide a direct relation between the structure of the liquid as quantified by $g_{\alpha\beta}$

or $n_{\alpha\beta}$ and the thermodynamic functions. It is interesting to note that our eq 7 is quite analogous to the entropy expression used by Lazardis and Paulaitis^{38–40} for a continuous (nonlattice) model.

Equations 7 are in line with eqs 5 and 6. Equation 6 can be derived by minimizing the configurational Helmholtz energy $F = U - TS$, where the energy is given by eq 5 and the entropy by eq 7, with respect to the distribution of contacts.

Partial quantities defined as

$$f_A \equiv \left(\frac{\partial F}{\partial n_A} \right)_{T, \{n_{B \neq A}\}} \quad (8)$$

where F is the Helmholtz energy, are very convenient in a lattice model like the present one since they apply to molecular components as well as to vacancies. For f_A we can write

$$f_A = kT \ln \frac{\phi_A}{G_A} \quad (9)$$

where G_A can be interpreted as a statistical weighting factor for species A (these G s should not be confused with Gibbs energies!). This quantity can be written as the product of the orientational degeneracy factor ω_A and face weighting factors:

$$G_A = \omega_A \prod_{\alpha} G_{\alpha}^{q_{A\alpha}} \quad (10)$$

where $q_{A\alpha}$ is the number of α -faces belonging to a molecule of type A (or to a vacancy). The G_{α} 's are given by the implicit equations

$$G_{\alpha} = \sum_{\beta} \frac{\phi_{\beta}}{G_{\beta}} \exp \left(- \frac{u_{\alpha\beta}}{kT} \right) \quad (11)$$

As the interaction energies $u_{\alpha\beta}$ are defined in such a way that they vanish for "contacts with vacuum", all G_{α} 's become unity in the limit of low density.

The pressure and chemical potentials are obtained from the f_A 's as follows.

$$p \equiv - \left(\frac{\partial F}{\partial V} \right)_{T, \{n_{A \neq v}\}} = - \frac{1}{v} \left(\frac{\partial F}{\partial n_v} \right)_{T, \{n_{A \neq v}\}} = - \frac{f_v}{v} \quad (12)$$

where the subscript v indicates vacancy. For the chemical potential of molecular components we can write

$$\mu_A \equiv \left(\frac{\partial G}{\partial n_A} \right)_{p, T, \{n_{B \neq A, v}\}} \equiv \left(\frac{\partial F}{\partial n_A} \right)_{V, T, \{n_{B \neq A, v}\}} = f_A - f_v \quad (13)$$

where in the present case the subscript A can be replaced by w for water or by a for apolar solute.

From these equations, the thermodynamic properties as well as the structural features can be calculated by means of the numerical methods described in refs 41 and 42. By fitting liquid/vapor coexistence at 0 °C, the values $u_{\text{Hb}} = -20.1$ kJ/mol and $u_{\text{vHb}} = 1.75$ kJ/mol were obtained.⁴³ It is reassuring that the value for the hydrogen bond energy obtained in this way is close to experimental values.^{54,55} It should be noted that the non-hydrogen-bonded contacts in our model are repulsive. These values for the interaction parameters are the same as used previously,^{41,43} and they will be used here in all calculations. Comparison of eqs 1, 9, and 13 reveals that

$$\left\langle \exp \left(- \frac{\Psi_A}{kT} \right) \right\rangle = \frac{G_A \Lambda_v}{v} = \frac{\phi_v G_A}{v G_v} \quad (14)$$

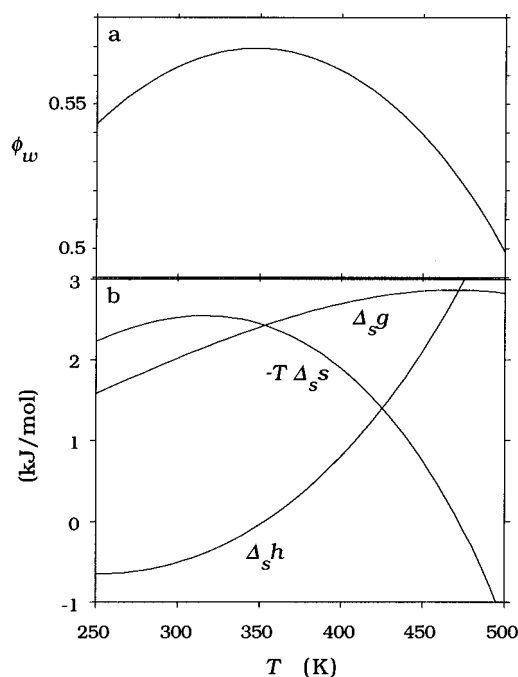


Figure 2. (a) Theoretical isobaric density of pure water at one-fourth of the theoretical critical pressure, 4.36×10^6 Pa. (b) Temperature dependence of the Gibbs energy of transfer of model apolar molecules and its enthalpic and entropic contributions at the same pressure.

where $\Lambda_v = \exp(f_v/kT)$. The Gibbs energy change of transfer of an apolar molecule a from phase a to w , which was defined in eq 2, can hence be expressed in terms of the weighting factors of eqs 9 and 10:

$$\Delta_s g = kT \ln \frac{G_a^a}{G_a^w} \quad (15)$$

The factors $\Lambda_v/v = \phi_v G_v$ in the denominator and numerator of the argument of the logarithm cancel since the pressure is the same in the two phases at equilibrium.

4. Hydration of Small Apolar Molecules and Vacancies

The isobaric density at a pressure of one-fourth of the theoretical critical pressure, calculated from this model, is shown in Figure 2a. For a more elaborate account of the isobaric densities and liquid vapor phase equilibrium we refer to earlier publications.^{1,41,43} These results agree at least qualitatively with the experimental findings. Most noteworthy, the maximum in the isobaric density is reproduced. The density of the liquid corresponds to a site fraction of water molecules, ϕ_w , that is somewhat higher than a half. In section 5 it will be shown that the water–water coordination number is somewhat above 4 and that in these water–water contacts hydrogen bonds prevail. As reproduced by our model, pure water has an open structure, containing numerous cavities that are spontaneously present. This is consistent with the experimental observation that at extremely high pressure forms of ice exist with a nearly 2-fold density as water at ambient pressure.⁵⁶ In our model the open structure is brought about by the weakly repulsive non-hydrogen-bonding interactions. Often, the open, nearly four-coordinated structure is attributed to the tendency for hydrogen bonding. This is no sufficient explanation however. Also with a dense packing and a coordination number of eight, it is possible to establish two hydrogen bonds per molecule (as e.g. in ice VII).⁵⁶ Inspecting the charge distribution in a water molecule (see e.g. ref 12), it is not surprising that the interaction between water molecules at separations similar to the hydrogen-

bond length but for non-hydrogen-bonding orientations is on average repulsive. The interaction energy between water and an apolar molecule has a purely dispersive nature and is low as compared to the energy of a hydrogen bond. Consequently, the change of water structure upon addition of a small apolar molecule is expected to be similar to changes due to expansion of pure water upon which additional cavities are created. No qualitative change of structure (as suggested by the term "iceberg") is expected.⁵⁷ Obviously, this only holds for apolar molecules of approximately the same size as the cavities that are spontaneously present in pure liquid water and possibly also for more or less flexible chains of such segments. The situation will be entirely different for bulky solutes (see section 6).

For the moment, we are mainly interested in the qualitative aspects that all small apolar solutes have in common. Hence, we examine the, in our lattice model, simplest possible model for an apolar molecule. It occupies one lattice site and excludes such a site for other molecules. Apart from this, it does not interact at all with other molecules. It will be demonstrated that this model solute exhibits all characteristic thermodynamic trends associated with hydrophobic hydration. As this model molecule is similar to a vacancy, its weighting factor G_a equals that of vacancies G_v . According to eq 14, for such a molecule

$$\left\langle \exp - \frac{\Psi_a}{kT} \right\rangle = \frac{\phi_v}{v} \quad (16)$$

where for pure water $\phi_v = 1 - \phi_w$.

Similarly, according to eqs 9, 12, and 15, the Gibbs energy of transfer of such a molecule from a fixed position in an a-phase, consisting of a-molecules and vacancies, for which $G_a^a = 1$, to a fixed position in water is related directly to the isobaric density of pure water as plotted in Figure 2a:

$$\Delta_s g = -kT \ln G_a^w = -kT \ln G_v^w = -kT \ln \phi_v^w - p v \quad (17)$$

For the same pressure as in Figure 2a, $\Delta_s g$ as obtained from eq 17 as well as its enthalpic and entropic contributions are plotted in Figure 2b. The temperature dependencies of $\Delta_s g$, $\Delta_s h$, and $\Delta_s s$ as calculated here for the "vacancy-like" solutes are very similar to what is found experimentally for the dissolution of apolar compounds in water. The temperature dependencies of both $\Delta_s h$ and $T\Delta_s s$ are rather strong, but these dependencies compensate in such a way that $\Delta_s g$ is relatively insensitive to temperature. The hydration enthalpy, $\Delta_s h$, is low. At low temperatures, hydration is even exothermic, $\Delta_s h > 0$; hence, the enthalpy change promotes dissolution in water. The entropic contribution to $\Delta_s g$, $-T\Delta_s s$, is positive and larger than $|\Delta_s h|$ and counteracts the dissolution. As $\Delta_s h$ increases with temperature, the partial heat capacity of vacancies in water, given by $\Delta_s C_p = (\partial \Delta_s h / \partial T)_p$, is positive at any T . This is also found experimentally for the heat capacity change caused by the dissolution of apolar compounds in water. For nonaqueous mixtures this effect is usually much smaller.^{58,59}

It will be clear that the similarity with vacancies will not hold quantitatively for real apolar molecules. Small differences of molecular sizes and interactions between apolar molecules will have some quantitative consequences, but the trends are qualitatively the same. For instance, a net (as compared to the reference phase) dispersion interaction between an apolar molecule and water will lead to an additional, approximately constant negative term in $\Delta_s h$ and hence in $\Delta_s g$. This will lead to a positive shift of the temperature where $\Delta_s h$ changes sign from negative to positive, which is the temperature where the solubility is minimal. Such factors explain the experimental observation that the temperature of minimum solubility varies somewhat between different apolar molecules. The isobar in

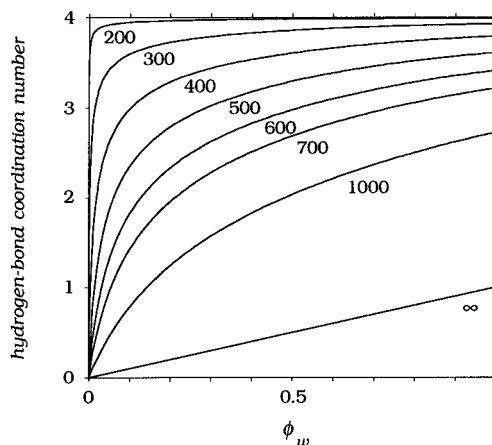


Figure 3. Coordination of water molecules by hydrogen bonds to other water molecules as a function of water density at various temperatures indicated. The random-mixing case at infinite T is indicated by the symbol ∞ . At ambient conditions, ϕ_w is about one-half. In this and the following figures the regions where the fluid is unstable with respect to liquid/vapor phase separation are included.

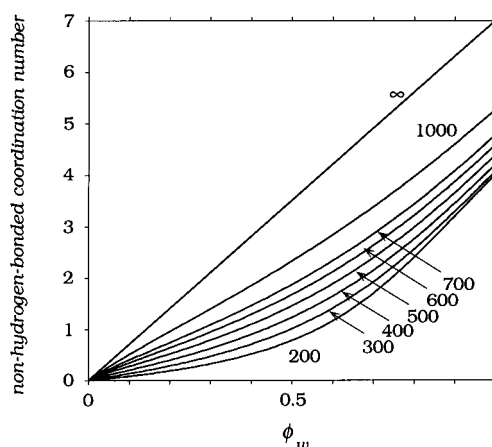


Figure 4. Non-hydrogen-bonded coordination of water molecules by water molecules as a function of water density at the same temperatures as in Figure 3.

Figure 2a was for one-fourth of the theoretical critical pressure, which corresponds to about 40 atm. As shown in ref 43, the liquid branches of isobars for this and lower pressures are very close together for not too high temperatures. According to eq 17, the same holds for the corresponding $\Delta_s g$ as a function of temperature. However, at this elevated pressure the liquid phase is stable over a larger temperature range. This enables us to examine $\Delta_s g$ and its enthalpic and entropic contributions over a larger temperature range and to include the maximum of $\Delta_s g$ that is also observed experimentally.⁸

5. Relation with Molecular Structure

We have seen in the previous section that the present theory reproduces the experimental trends on hydrophobic hydration. To obtain a molecular interpretation for these phenomena, we have to examine the distribution of contacts. The strong directional interactions between water molecules lead to a pronounced local ordering. The number of hydrogen bonds substantially exceeds its random value (see Figure 3). Simultaneously, the frequency of non-hydrogen-bonded water–water contacts and, at not too high density, the number of water–vacancy contacts are smaller than their random values (Figure 4). The vacancies are preferentially coordinated by other vacancies and by the "indifferent" faces of the water molecules. The vacancy-like apolar molecules will be coordinated in exactly the same way. For an illustration of such a configuration, see

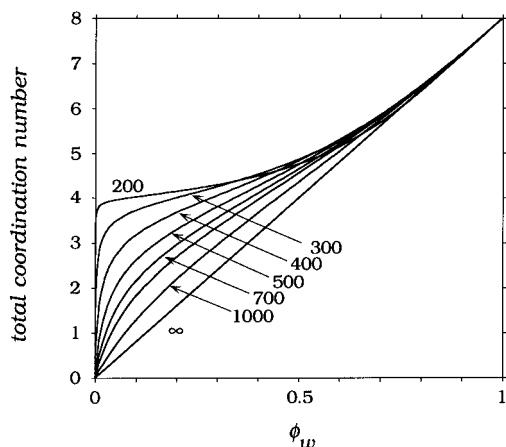


Figure 5. Total coordination of water molecules by water molecules as a function of water density at the same temperatures as in Figure 3.

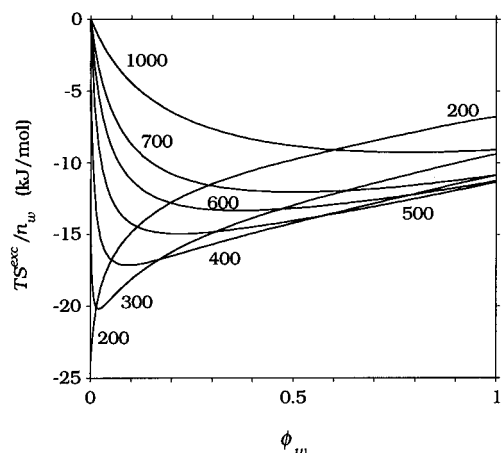


Figure 6. Excess entropy per mole of water as a function of water density at the same temperatures as in Figure 3.

Figure 1. It should be kept in mind, however, that a considerable disorder is present and that many imperfections in these “cages” are present. The ordering is most pronounced at low water density where a large number of hydrogen bonds are preserved. Hence, the configurational freedom of the molecules is more severely restricted at low density. According to eq 7 this leads to a lowering of the entropy as compared to its ideal value. The calculated excess entropy per water molecule as a function of water density is plotted in Figure 6 for several temperatures.

Especially at low temperatures, the excess entropy per water molecule as a function of density has a minimum at a density that is lower than that of the liquid at ambient pressure ($\phi_w \approx 1/2$, see Figure 2a). At ambient liquid density, the excess entropy per water molecule decreases upon decreasing the water density. This behavior is quite unusual and does not occur in simple fluids that lack the orientation-dependent interactions. It is the origin of the negative hydration entropy of small apolar molecules and vacancies. Addition of an apolar molecule reduces ϕ_w (a more exact justification for this statement is given in the Appendix), which, at ambient conditions, leads to a decrease of S^{exc}/n_w .

According to the present theory, the molecular cohesive energy of water increases with increasing density at ambient conditions (see Figure 7). This exceptional behavior is due to the orientation-dependent nature of the intermolecular interactions. For most compounds the mean molecular cohesive energy is negative and decreases with increasing density. Only at extremely high pressures, it must increase with increasing density due to the short range intermolecular repulsion that is always present.

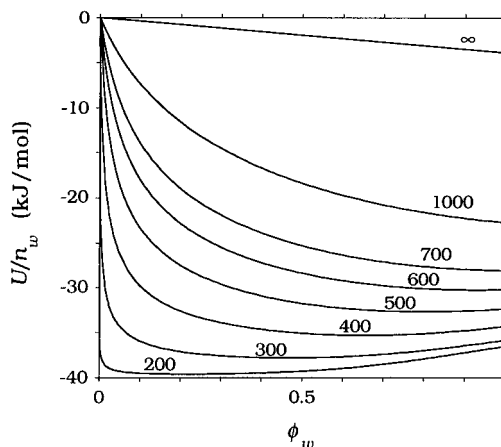


Figure 7. Cohesive energy per mole of water as a function of water density at the same temperatures as in Figure 3.

Hydrogen bonds contribute negatively to the internal energy of water, but the contribution of non-hydrogen-bonding water–water contacts is positive. As can be seen in Figure 7 the molecular cohesive energy of water initially decreases steeply upon increasing the density. This is due to hydrogen-bond formation (see Figure 3). We have seen that if the temperature is not too high, the increase of the number of hydrogen bonds per molecule levels off at intermediate density. Then the cohesive energy per molecule corresponds to about two hydrogen bonds. Upon further increase of the density, mainly the number of repulsive contacts increases (see Figure 4) and hence the molecular energy (see Figure 7), even though the number of hydrogen bonds per water molecule still increases slightly. Consequently, isothermal expansion of liquid water is predicted to be exothermic. More importantly, the exothermic effect upon dissolving apolar molecules in water can also be explained by a decrease of repulsive non-hydrogen-bonding water–water contacts. In the Appendix, it is indicated in a more exact way how the tangents of Figure 7 are related to changes upon dissolution at constant pressure.

6. Hydration of an Extended Hydrophobic Surface

The mechanism for dissolution of hydrophobic solutes in water discussed in the previous sections is expected to break down for particles that are much larger than the water molecules and the vacancies that are spontaneously present in water. To examine the consequences of size of the solute we have calculated the thermodynamic functions for the hydration of an extended planar surface that does not interact with water molecules.^{1,41} The hydration of such a surface can be compared with the hydration of the small vacancy-like solute discussed above. The small vacancy-like solute and the planar surface can be considered as limiting cases for the size of a solute particle: the smallest and the largest that are possible in the present model. We found that the Gibbs energy of hydration per unit of area is larger for the extended flat surface than for the small solute. This agrees qualitatively with the results from molecular-dynamics simulations (on a different model for water) by Postma et al. who studied the hydration of cavities of different sizes.^{30,31} Unfortunately, they obtained neither the entropic and enthalpic contributions nor the temperature dependencies. According to our calculations, the entropy and enthalpy of hydration of the surface are markedly different from those of small molecules. The temperature dependence of the Gibbs energy of hydration of the surface is similar to that of the surface tension of water that we examined earlier.^{41,43} Over the temperature range examined, the entropic and enthalpic contributions to the Gibbs energy of hydration are both positive.

These results suggest that the characteristic temperature dependencies and entropy and enthalpy effects found for small apolar molecules do not occur with bulky particles.

According to our calculations, the difference between the thermodynamic behavior of small apolar solutes and macroscopic surfaces is mainly due to a depletion of water and a reduction of hydrogen bonding in the layer adjoining the surface. Due to this depletion, the excess volume of hydration is positive for the model apolar surface. Also in this respect is hydration of a surface different from that of a small molecule. For the latter, the excess volume is close to zero (see the Appendix). In a forthcoming paper the hydration of surfaces and especially the ensuing surface forces will be examined in more detail.⁵⁰

7. Concluding Remarks

Our model reproduces the characteristic experimental trends concerning the dissolution of apolar molecules in water from first principles and provides a molecular interpretation for the thermodynamic phenomena. The peculiar thermodynamic observations are explained in terms of a subtle enhancement of the type of ordering that is intrinsically present in liquid water. Special structures around apolar molecules, such as suggested by terms like “icebergs”, do not have to be invoked.

Hydrophobic hydration is often analyzed in terms of a number of imaginary steps.^{3,7,10,19} Our results indicate that the characteristic thermodynamic features are due to the creation of a vacancy and the ensuing ordering effect upon water. The dispersion interactions will merely lead to a rather temperature independent shift of the Gibbs energy of hydration and mainly to its enthalpic term.

The balance between configurational freedom and attractive (hydrogen bonds) and repulsive (non-hydrogen-bonding contacts) interactions between water molecules leads to the open, approximately four-coordinated structure of liquid water at ambient conditions. The occurrence of a maximum isobaric density of pure water and of a minimum in the solubility of small apolar solutes are both due to a change of this balance upon temperature variation. The unusual temperature dependence of the isobaric density of pure water and the temperature dependence of the solubility of small apolar molecules share a common molecular origin. The energy and entropy changes upon dissolution of small apolar molecules are caused by a subtle enhancement of nonrandomness of the distribution of intermolecular contacts upon a decrease of water density.

By thinking of changes in density of water in terms of “dissolution of vacancies”, it is understood that the anomalous thermodynamics of dissolving apolar molecules shares a common molecular origin with the anomalous temperature dependence of the isobaric density of pure water. So the present discussion of the hydrophobic hydration also helps us to understand the behavior of pure water itself.

As an additional argument we restate that there is a certain analogy between the swelling of polymer networks and expansion of water.^{41,43,57} Upon swelling, by uptake of solvent, the entropy of a polymer network decreases. This is easily explained: since the bonds in a polymer network do not break, the configurational freedom of the polymer segments decreases and hence the entropy. Upon modest expansion or uptake of small apolar molecules, the number of hydrogen bonds between the water molecules does not decrease significantly and hence the configurational freedom of the water molecules has to decrease. For the dissolution of more or less flexible chains of small segments, dissolution thermodynamics will be similar. Although the theoretical basis for the handling of chain molecules has been laid by one of us,⁴¹ this has as yet not been applied to aqueous systems. However, as indicated in section

6, the above-mentioned mechanism does not hold for the hydration of bulky molecules and of surfaces. These will inevitably induce qualitative changes of the structure of water and a more substantial reduction of the number of hydrogen bonds. Hence, the characteristic thermodynamics associated with the hydrophobic hydration of small solutes is predicted to be absent. Hydration thermodynamics is expected to vary gradually with the “bulkiness” of the solute between that of a small single-site solute and that of an extended planar surface. It is not straightforward to generalize the present lattice theory in order to examine this in detail.

Although it is at the moment probably not (yet) possible to study by simulations on continuum (nonlattice) models all the subtle temperature dependencies that we discussed here,⁶⁰ some aspects of our results, e.g. the role of repulsive water–water interactions, could and should be examined by simulations. Its role in the overall cohesive energy and the change upon expansion of the liquid or upon introducing (isobarically) an apolar solute or vacancy could be investigated. This would be an interesting further test of our ideas.

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Appendix

The tangents of the curves in the Figures 3–6, where some property X/n_w is plotted as a function of ϕ_w , can be related to other interesting quantities. For pure water (water molecules and vacancies only) we can write

$$\left(\frac{\partial(X/n_w)}{\partial\phi_w}\right)_T = -\left(\frac{\partial(X/n_w)}{\partial\phi_v}\right)_T = -\frac{1}{\phi_w^2}\left(\frac{\partial X}{\partial n_v}\right)_{n_w,T} = -\frac{v}{\phi_w^2}\left(\frac{\partial X}{\partial V}\right)_{n_w,T} \quad (\text{A1})$$

The first identity in eq A1 holds since $\phi_w + \phi_v = 1$, and the second follows from $(\partial X/\partial n_v)_{n_w,T} = (\partial X/\partial\phi_v)_{n_w,T}(\partial\phi_v/\partial n_v)_{n_w,T}$ where $(\partial\phi_v/\partial n_v)_{n_w,T} = -(\partial\phi_w/\partial n_v)_{n_w,T} = \phi_w/N$. The third equality in eq A1 follows from $Nv = V$. Generally we are interested in changes that occur at a fixed pressure rather than at a fixed number of vacancies. For an extensive property X , we can write

$$\left(\frac{\partial X}{\partial n_a}\right)_{p,n_w,T} = \left(\frac{\partial X}{\partial n_a}\right)_{n_a,n_w,T} + \left(\frac{\partial X}{\partial n_a}\right)_{n_a,n_w,T}\left(\frac{\partial n_v}{\partial n_a}\right)_{p,n_w,T} \quad (\text{A2})$$

If X is a quantity that has the same functional dependence on n_a as on n_v then $(\partial X/\partial n_v)_{n_a,n_w,T} = (\partial X/\partial n_a)_{n_v,n_w,T}$. This holds, e.g., for the energy U , for the excess entropy, S^{exc} , and for the number of hydrogen bonds, if molecules a have similar properties as vacancies v , as in the our present model. It does not hold for S^{id} since that quantity is intrinsically related to the distinguishability between an a -molecule and a vacancy.

Now the problem is to determine $(\partial n_v/\partial n_a)_{p,n_w,T}$, the change of the number of vacancies upon isobaric addition of an a -molecule. This quantity is closely related to the partial molecular volume of a : $(\partial V/\partial n_a)_{p,n_w,T} = v(1 + (\partial n_v/\partial n_a)_{p,n_w,T})$, with v the volume per lattice site. The quantity $v(\partial n_v/\partial n_a)_{p,n_w,T}$ could be called the excess partial free volume of a . We know

$$dF|_{n_w,T} = f_a dn_a + f_v dn_v \quad (\text{A3})$$

where $f_v = (\partial F/\partial n_v)_{n_a,n_w,T} = -vp$. Applying a Legendre transform

$$d(F - f_v n_v)|_{n_w, T} = f_a dn_a - n_v df_v$$

From this, we obtain the Maxwell relation

$$\left(\frac{\partial n_v}{\partial n_a}\right)_{f_v, n_w, T} = -\left(\frac{\partial f_a}{\partial f_v}\right)_{n_a, n_w, T} = -\left(\frac{\partial f_a}{\partial n_v}\right)_{n_a, n_w, T} \quad (\text{A4})$$

Note that $-(\partial n_v / \partial f_v)_{n_a, n_w, T} = (\partial V / \partial p)_{n_a, n_w, T}$ is the isothermal compressibility. Further, $(\partial f_a / \partial n_v)_{n_a, n_w, T} = (\partial f_v / \partial n_v)_{n_a, n_w, T} - kT / n_v$ since $f_a / kT = \ln \phi_a - \ln G_a$ and $f_v / kT = \ln \phi_v - \ln G_v$ where the weighting factor G_a equals G_v since a-molecules and vacancies are similar with respect to their absence of interactions. So

$$\left(\frac{\partial n_v}{\partial n_a}\right)_{f_v, n_w, T} = -\frac{(\partial f_v / \partial n_v)_{n_a, n_w, T} - kT / n_v}{(\partial f_v / \partial n_v)_{n_a, n_w, T}} = \frac{kT}{n_v (\partial f_v / \partial n_v)_{n_a, n_w, T}} - 1 \quad (\text{A5})$$

Further we can write $(\partial f_v / \partial n_v)_{n_a, n_w, T} = (\partial f_v / \partial N)_{n_a, n_w, T} = (\partial f_v / \partial 1 / \phi_w)_{n_a, n_w, T} / n_w = -\phi_w (\partial f_v / \partial \phi_w)_{n_a, n_w, T} / N$, so that

$$\left(\frac{\partial n_v}{\partial n_a}\right)_{f_v, n_w, T} = -1 - \frac{1}{\phi_w \phi_v (\partial f_v / kT / \partial \phi_w)_{n_a, n_w, T}} \quad (\text{A6})$$

Since f_v / kT as a function of ϕ_w can be computed, all elements are now available to obtain the desired derivative of X . For liquid water in the relevant regime we found that $(\partial n_v / \partial n_a)_{f_v, n_w, T} \approx 0$. However, near the liquid/vapor critical point or near the spinodal, $(\partial f_v / \partial \phi_w)_{n_a, n_w, T}$ tends to zero and $(\partial n_v / \partial n_a)_{f_v, n_w, T}$ to infinity.

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