Hydrophobic hydration of small apolar molecules and extended surfaces: A molecular model

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Hydrophobic hydration of small apolar molecules and of extended hydrophobic surfaces is analysed applying a statistical thermodynamical lattice-gas model. This model, in which the orientation-dependent interactions between water molecules (e.g. hydrogen bonds) are accounted for, reproduces the anomalous thermodynamic behaviour of water. Moreover, in this model these macroscopic phenomena can be related to underlying molecular behaviour. The temperature dependencies of the density of pure water and of the solubility of small apolar molecules in water share a common molecular basis. Dissolution of small apolar molecules leads to a relatively small enhancement of the pronounced structuring that is intrinsically present in water. Formation of special "iceberg-like" structures around apolar solutes does not occur. The negative solvation entropy is related to changes of the local ordering of the water molecules similar to those occurring upon expansion of pure water. Hydrogen bonding hardly decreases for these cases. The small, at lower temperatures even negative value of the solvation enthalpy is due to a reduction of the number of repulsive water-water interactions. Calculations on an extended flat hydrophobic surface indicate that the anomalous aspects of the solvation thermodynamics do not occur with bulky apolar particles. With these, a decrease of hydrogen bonding cannot be avoided and water tends to be depleted from such surfaces.

Introduction

The thermodynamic behaviour of water is special as compared to most other liquids. Its density passes a maximum with varying temperature at constant pressure whereas for other fluids and also for solids the isobaric density is a monotonously decreasing function of temperature. The isothermal compressibility passes a minimum with varying temperature. Ice contracts upon melting into liquid water. Water has a large heat capacity and a high melting and boiling point as compared to other compounds of similar molecular mass. The surface tension, γ, of water is relatively high and surface entropy, $-d\gamma/dT$, passes through a maximum with varying temperature (1-3). whereas for simple fluids, such as argon, both γ and $-d\gamma/dT$ are monotonously decreasing functions (3).

The most intriguing properties of water, especially with regard to its role in biological systems, are referred to by the term *hydrophobic effect*. This term is used to denote the anomalous behaviour of water as it interacts with apolar material. This is relevant, not only for the behaviour of simple aqueous solutions, but e.g. also for the conformation of proteins, the formation of micelles and biological membranes and for adsorption of surfactants at interfaces (4-11).

Since the typical features emerge most clearly in aqueous solutions of low molecular weight apolar compounds we will first analyse these. The solubility of apolar compounds in water is low and passes a minimum at about room temperature upon varying temperature (12-14). This implies that the roles of entropy and enthalpy are unusual as compared to other mixtures. The precise value of the temperature of minimum solubility is somewhat different for each apolar compound. The solubility of apolar molecules

in water is related to the Gibbs energy of transfer of an apolar molecule from a fixed position in an apolar medium to a fixed position in water (15). This transfer is indicated by Δ_s. The Gibbs-Helmholtz relation

$$\Delta_s H = -T^2 \left(\frac{\partial (\Delta_s G/T)}{\partial T} \right)_p \tag{1}$$

implies that the solvation enthalpy changes sign, from negative to positive, at the temperature of minimum solubility. Combining this with

$$\Delta_s G = \Delta_s H - T\Delta_s S \tag{2}$$

it is inferred that the high positive value of $\Delta_s G$, that leads to the low solubility, is due to a strongly negative entropy of dissolution. Both enthalpy and entropy of solvation are markedly temperature dependent but these temperature dependencies compensate in such a way that the Gibbs energy is not very temperature-sensitive. The strong temperature dependence of $\Delta_s H$ implies that the partial heat capacity of the solute $\Delta_s C = (\partial \Delta_s H / \partial T)_p$ is large (16, 17). The trends of the temperature dependencies of $\Delta_s G$ and its enthalpic and entropic contributions are usually more or less as shown in Fig. 5. This behaviour is quite unusual as compared to non-aqueous solutions. Usually, $\Delta_s H$ is positive as expected from Berthelot's principle ("geometric-mean rule") for the attractive interactions between unlike molecules (5, 18). In most cases, poor compatibility of different compounds is mainly due to a high value of $\Delta_s H$.

The explanation of these phenomena has been a subject of debate for about sixty years now. Most current molecular interpretations, postulate a variant of "iceberg formation" (more modern terms such as "clathrate cage" refer to a similar physical picture). Water surrounding an apolar molecule is in this picture stronger structured than in the bulk of the liquid (10, 19-21). In this way, the negative entropy of solution is explained. The low value of the solvation enthalpy is often explained by an increase of the number of hydrogen bonds upon addition of an apolar molecule (10, 20) or by assuming that hydrogen bonds in the "solvation shell" are stronger than in bulk water (22). The same mechanism is believed to operate with the solvation of extended surfaces. Hence, the solvation of small apolar molecules is often supposed related to the surface tension of water.

The notion of an enhancement of hydrogen bonding upon introduction of apolar compounds appeared to us as unsatisfactory. It will be shown that an alternative molecular interpretation can be obtained that also consistently explains many other aspects of aqueous behaviour. It is our goal to interpret the above mentioned phenomena in terms of a molecular picture. To that end, we present an analysis, based on a detailed statistical-thermodynamic treatment that accounts for orientation-dependent intermolecular interactions (23, 24). This model is admittedly somewhat coarse grained in order to be mathematically tractable for a large variety of situations. Still it captures in our opinion the essential physics. This is confirmed by the fact that the anomalous behaviour of water is reproduced by the model.

A Lattice Model for Water

To facilitate the configurational analysis, the molecules are confined to a body-centred cubic lattice (see Fig. 1). Each site is surrounded by eight nearest neighbours. A site can be vacant or occupied by a water molecule or a small apolar molecule. Vacant lattice sites are indicated by subscript v, water molecules by w and apolar molecules by a. A value for the volume per lattice site, $v = 1.632 \ 10^{-29} \ \text{m}^3$ is obtained by equating the density of ice to that of a half-filled bcc lattice. It will be convenient to express the density of a certain component A (either w, a or v) in terms of the fraction of sites occupied by A: $\phi_A = n_A/N = v\rho_A$, $\rho_A = n_A/V$ is the number density. As we will also study heterogeneous systems, the lattice is divided into parallel layers that are allowed to be differently occupied. The composition can be different for each layer and we will use the notation $\phi_A(z)$ for the site fraction of component A in layer z. For homogeneous systems the index z can be omitted.

It has been understood for a long time that the directionality of the intermolecular interactions (e.g. hydrogen bonds) plays an important role in water. To account for this, we distinguish different faces on
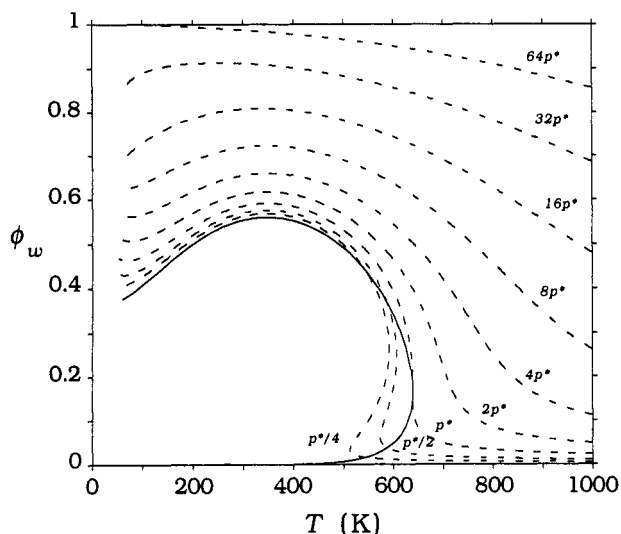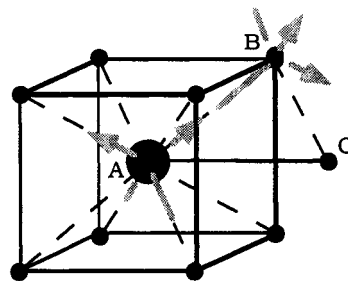
Fig. 1. Ten sites of a bcc lattice. Site A is surrounded by its eight nearest neighbours. One of the next-nearest neighbours is drawn (C). Two water molecules are indicated by solid balls bearing arrows and sticks, indicating respectively the protons and the lone pairs of electrons. The molecules, interact through a hydrogen bond.

Fig. 2. Theoretical isobaric density at various pressures ------, p^* is the theoretical critical pressure ($1.7423 \ 10^7$ Pa). The liquid-vapour coexistence curve ——— encloses the two-phase region where the isobars exhibit a Van der Waals loop.

the water molecules. Two of these represent protons; two others lone pairs of electrons. These four faces are arranged tetrahedrally on the surface of the molecule. In addition, a water molecule has four "indifferent" faces. Not only are the molecules confined to lattice sites, also their faces are confined to be directed towards nearest-neighbour sites. Consequently, in the present model a water molecule has 12 orientations. A contact between a proton and a "lone pair" is identified as a hydrogen bond. If two nearest-neighbour sites are occupied by water molecules, only in 18 out of the 144 viable configurations of this pair a hydrogen bond exists. To a hydrogen bond, an energy of u_{Hb} is attributed. To all non-hydrogen bonding contacts between water molecules, an energy $u_{\neq Hb}$ is assigned.

Applying expressions for the equilibrium configuration and for the thermodynamic properties that will be discussed hereafter, these parameters were determined by fitting the density and pressure of the liquid at coexistence with vapour, at 0 °C. In this way values $u_{Hb} = -20.1$ kJ/mol and $u_{\neq Hb} = 1.75$ kJ/mol are obtained (23, 24). These values are used throughout all calculations of the present paper. Our value of the hydrogen bond energy is close to the experimental value (25). It is important to note that the non-hydrogen bonded contacts are repulsive. According to our calculations, this repulsion is the origin of the open, low coordinated structure of water. Such a repulsive interaction is usually not considered in discussions on the properties of water. Considering the distribution of electrical charge within the water molecule (as discussed e.g. in ref. (10)), it is not unexpected that the interaction between two water molecules that have the proper separation, but not the relative orientation required to form a hydrogen bond is, on the average, repulsive.

To analyse this model, we apply the Bethe-Guggenheim approximation (also called quasi-chemical). Contrary to the well known Bragg-Williams type of mean-field approximation, local ordering (correlations in the occupation of neighbouring sites) is accounted for. This is particularly important in systems with directional interactions. The distribution of contacts is given by mass-action like relations (23, 24, 26, 27):
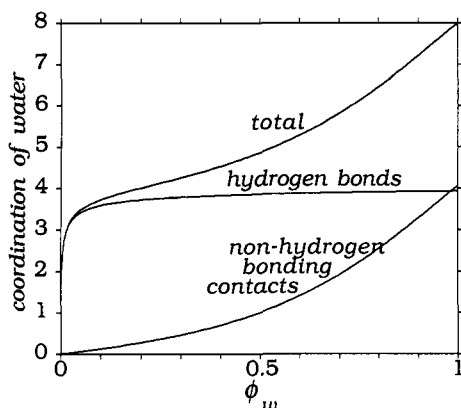
Fig. 3. Coordination of water molecules as a function of water density at 300 K and the contributions of hydrogen bonds and non-hydrogen bonded contacts.
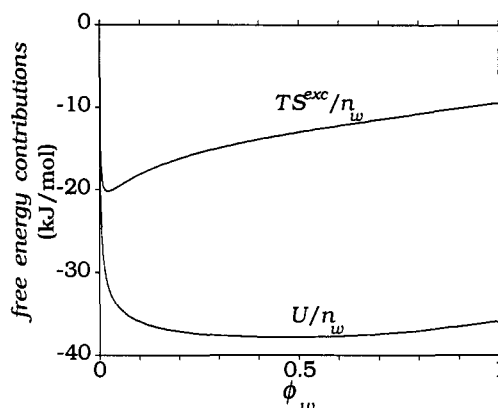
Fig. 4. Excess entropy and cohesive energy per mole of water as a function of water density at 300 K. The density of liquid water corresponds to $\phi_w \approx 0.55$. In this, and the previous figure, densities that are unstable with respect to liquid-vapour phase separation are included.

$$\frac{n_\alpha^d(z)_\beta n_\beta^d(z)_\alpha}{n_\alpha^d(z)_\alpha n_\beta^d(z)_\beta} = \exp\left(\frac{u_{\alpha\alpha} + u_{\beta\beta} - 2u_{\alpha\beta}}{k_B T}\right) \tag{3}$$

where α, β can indicate any of the face-types of any of the components (vacancy included); superscript d indicates one of the eight directions of the lattice (e.g. $n_\alpha^d(z)_\beta$ should be read as the number of contacts between α-faces located at layer z, having direction d, with faces of type β; $u_{\alpha\beta}$ is the energy of a contact between an α-, and a β-face).

The total configurational energy can be written in terms of numbers of contacts and interaction-energy parameters as

$$U = \tfrac{1}{2} \sum_{\alpha,\beta,d,z} n_\alpha^d(z)_\beta u_{\alpha\beta} \tag{4}$$

The distribution of contacts reflects the local ordering in the system that is related to the preferred formation of low energy contacts. Within the Bethe-Guggenheim approximation, the configurational entropy is given by (23, 24)

$$\frac{S}{k_B} = -\sum_{A,o,z} n_A^o(z) \ln \phi_A^o(z) - \tfrac{1}{2} \sum_{\alpha,\beta,d,z} n_\alpha^d(z)_\beta \ln g_\alpha^d(z)_\beta \tag{5}$$

The first term on the right-hand side can be recognized as the ideal entropy of mixing the vacancies and the molecules, that have a certain distribution over orientations and layers. The second term, S^{exc}/k_B, accounts for the entropy lowering due to local ordering, $g_\alpha^d(z)_\beta = n_\alpha^d(z)_\beta / n_\alpha^{*d}(z)_\beta$ with $n_\alpha^{*d}(z)_\beta$ indicating the value of $n_\alpha^d(z)_\beta$ that would occur if the contacts would form randomly. Note that in the sum over all contacts, "contacts" involving vacancy are included.

From the expressions for the energy and entropy, all other thermodynamic functions can be derived as well as a set of self-consistent field equations for the equilibrium distributions of molecules over orientations and layers and for the distributions of contacts (23, 24). In the subsequent sections we will not go into these derivations but instead concentrate on the discussion of a selection of results.

Solvation of Small Apolar Molecules in Relation to the Properties of Pure Water

The isobaric densities and liquid-vapour coexistence curve, calculated from this model are shown in Fig. 2. These results resemble at least qualitatively the experimental findings. The anomalous maximum

isobaric density is reproduced. This supports the view that the essential physics is captured in the present model.

To interpret the anomalous behaviour of water from a molecular point of view, we have to look at the distribution of contacts. Due to the strong directional interactions between water molecules, a pronounced local ordering occurs. The number of hydrogen bonds (see Fig. 3) exceeds by large its random value (which would be equal to ϕ_w). Simultaneously, the frequency of non-hydrogen bonded water-water contacts is smaller than its random value $7\phi_w$. Further, the number of water-vacancy "contacts" is lower than its random value. This ordering is most pronounced at low water density where the fluid preserves a large number of hydrogen bonds. Hence, the configurational freedom of the molecules is more severely restricted at low density. According to eq. (5), this is reflected in the excess entropy per water molecule which has a minimum at low ϕ_w. The calculated excess entropy per water molecule as a function of water density is plotted in Fig. 4 for 300 K. At liquid density, the excess entropy per water molecule decreases upon decreasing water density. This behaviour is quite unusual and does not occur in simple fluids. It is the origin of the negative solvation entropy of small apolar molecules and vacancies. Addition of an apolar molecule reduces ϕ_w. At ambient conditions this leads to a decrease of S^{exc}/n_w.

Hydrogen bonds contribution negatively to the cohesive energy and the non-hydrogen bonding water-water contacts contribute positively. As can be seen in Fig. 4 the molecular cohesive energy, U/n_w, of water at first decreases steeply upon increasing the density of water from $\phi = 0$. This is due to hydrogen-bond formation (see Fig. 3). If the temperature is not too high, the number of hydrogen bonds per molecule has reached a plateau value at liquid density. Then the cohesive energy per molecule corresponds to about two hydrogen bonds. Upon further increase of the density the number of hydrogen bonds per water molecule increases slightly. Mainly the number of repulsive contacts increases (see Fig. 3) and hence the molecular energy (Fig. 4). Isothermal expansion of liquid water is predicted to be exothermic (if not the pressure is reduced to the extent that boiling occurs). More importantly, the exothermic effect upon dissolving apolar molecules in water can be explained by a decrease of repulsive non-hydrogen bonding water-water contacts. Upon addition of an apolar molecule, the water density decreases and hence the cohesive energy.

The attractive 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, no qualitative change of structure upon addition of a small apolar molecule is expected. Rather, the change of water structure will be similar to changes due to expansion of pure water at which additional cavities are created (this has been suggested before in ref. (28)). Obviously this only holds for apolar molecules that are of approximately the same size as the cavities that spontaneously exist in pure liquid water.

Since we are, for the moment, not interested in quantitative results on specific apolar compounds but in the qualitative aspects that all apolar solutes have in common, we examine a (in our model simplest possible) model-apolar molecule that is similar to vacancies. Such a molecule occupies one lattice site and does not interact with other molecules.

The Gibbs energy of transfer of such a model molecule a from a fixed position in an a-phase, consisting of a-molecules and vacancies, to a fixed position in water of the same pressure, is the same as that of a similar transfer of a vacancy. It is related directly to the isobaric density of pure water as plotted in Fig. 2. In the terminology of our lattice model, $\Delta_s G$ equals $-kT \ln \phi_v - pv$, where p is the pressure (23, 24). The vacancy content (free volume) in water is related to this Gibbs energy of solvation. The maximum in the isobaric density can be regarded as a minimum of the "solubility of vacancy", and has the same physical origin as the minimum in the solubility of small apolar molecules. It is clear that this similarity will not hold quantitatively for real apolar molecules. Small differences between properties (molecular size, interactions) of apolar compounds will have some quantitative effects but the behaviour will be qualitatively the same.

The isobar for the lowest pressure in Fig. 2 is for $\frac{1}{4} p^*$ which corresponds to about forty atm. The liquid branch of the isobars at lower pressures falls between the liquid branch of the binodal and the $\frac{1}{4} p^*$-isobar. Hence qualitatively these isobars and also $\Delta_s G$ as a function of temperature will be similar at lower temperatures whereas the liquid-vapour phase transition (boiling) is shifted to a higher
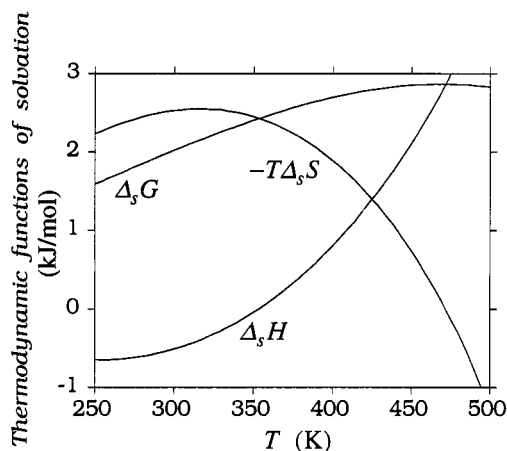
Fig. 5. Temperature dependence of the Gibbs energy of solvation of vacancies or model apolar molecules and its enthalpic and entropic contributions at $\frac{1}{4}p^*$.

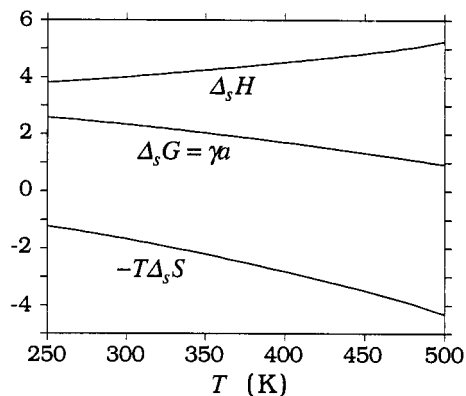Fig. 6. Temperature dependence of the Gibbs energy of solvation per site of an inert surface at $\frac{1}{4}p^*$, and its entropic, and enthalpic contribution.

temperature. This enables us to examine $\Delta_s G$ and its enthalpic and entropic contributions over a larger temperature range than at atmospheric pressure. For a pressure $\frac{1}{4}p^*$, $\Delta_s G$ and its enthalpic and entropic contributions are plotted in Fig. 5. At least qualitatively, all aspects of the anomalous temperature dependence of the Gibbs energy of solvation as discussed in the introductory section are reproduced. Recently, attention was drawn to the occurrence of a maximum of $\Delta_s G$ at elevated temperature (4), indicating that there the solvation entropy, for which we can write $\Delta_s S = -\left(\partial \Delta_s G / \partial T\right)_p$, changes sign from positive to negative (see also Fig. 5). This is also reproduced by our model.

Solvation of an Extended Hydrophobic Surface

Above, we discussed the solvation of small apolar molecules. These are accommodated in fluid water in such a way that the number of hydrogen bonds is reduced only slightly. As a consequence, the enthalpy of solvation is small but, due to the loss of configurational freedom of the water molecules, the associated entropy loss is considerable. Obviously, bulky particles can not be accommodated in this way. To indicate what consequences this has for the solvation of bulky particles and macroscopic apolar surfaces, we present some theoretical results on liquid water adjoining an extended planar hydrophobic surface.

To be able to compare with the "vacancy-like" solute molecules of the previous section, we will examine a surface that does not interact with water molecules. The solvation of single vacancies, having a size of one lattice site, and of a flat non-interacting 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.

In Fig. 6, which should be compared with Fig. 5, the Gibbs energy of solvation of this model surface is plotted together with its entropic and enthalpic contributions. The Gibbs energy of solvation of a mole of sites of the surface equals the surface tension of the solid-liquid surface times the surface area of a mole of surface sites: $\Delta_s G = \gamma a$, with a the cross-sectional surface area per mole of sites. This interfacial tension nearly equal to that of the aqueous liquid-vapour interface, as can be calculated within the same theory (23, 24).

Each site of the model surface exposes two faces to the liquid. At 300 K the solvation Gibbs energy per unit of surface is about four times higher for the extended flat surface. This agrees qualitatively with the results from molecular-dynamics simulations (on a different model for water) by Postma et all. who studied the solvation of cavities of different sizes (29, 30). Unfortunately, they did not obtain the temperature dependencies nor separate entropy and enthalpy contributions.
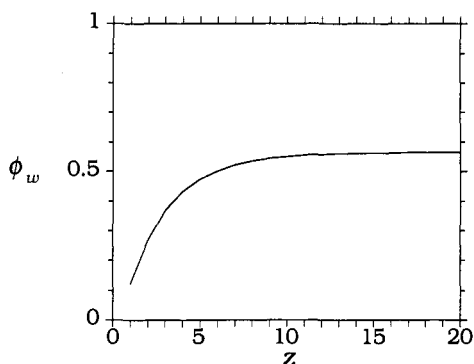
Fig. 7. Density profile of water at a non-interacting surface. The surface is located at $z = 0$. To guide the eye, calculated values, at the centres of the lattice layers (integer values of z), are connected by straight lines.

It is remarkable that the entropic and enthalpic contributions are very different as compared to solvation of a small molecule. Over the temperature range examined, the entropy and enthalpy of hydration are both positive. These results indicate that the anomalous temperature dependence that is characteristic for the hydrophobic effect, is absent for bulky particles. This is due to a very different molecular mechanism. Adjoining the extended surface, it is impossible to maintain a high value of hydrogen bonding between water molecules. The equilibrium density distribution at a model surface is shown in Fig. 7. The density of water decreases towards the surface as it does at the liquid-vapour interface (see refs. (23, 24)).

Concluding Remarks

The balance between orientation-dependent attractive (hydrogen bonds) and repulsive interactions (non-hydrogen bonding contacts) leads to the open, approximately four-coordinated structure of water at ambient conditions, to the anomalous temperature dependencies of the isobaric density and of the solubility of apolar molecules (as well as to other properties that are not discussed here). The energy and entropy changes upon dissolution of small apolar molecules are related to changes of the distribution of intermolecular contacts. The molecular mechanism underlying the maximum of isobaric density of pure water is the same as for the minimum of the solubility of small apolar molecules as a function of temperature. We reject the idea that a region of specially structured water is present around a dissolved small apolar molecule. With regard to the structural changes incurred, the introduction of a small apolar solute is not very different from adding another vacancy. Upon adding a small apolar molecule in water, the number of hydrogen bonds decreases slightly, but the possibilities for realisation of these hydrogen bonds decreases strongly. Hence the entropy decrease. The low, for low temperatures even negative value of the enthalpy change is due to a reduction of repulsive non-hydrogen bonding interactions between water molecules. These changes are merely an enhancement of the kind of structuring that is intrinsically present in water. Similar changes occur upon expansion of pure water.

As an additional argument, we note that there is a certain analogy between the swelling of polymer networks and expansion of water (28). 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 upon expansion of the network and hence the entropy. Upon expansion of pure liquid water, or by uptake of small apolar molecules, the number of hydrogen bonds between water molecules does not decrease much and consequently the configurational freedom of the water molecules decreases. Water can in some respects be considered as a network of molecules connected by hydrogen bonds. However, the lifetime of a hydrogen bond is short and the hydrogen bonds are reshuffling all the time.

This mechanism will hold for small solutes of similar size as the water molecules and for slender apolar chains. It will break down for bulky solutes and for the hydration of extended surfaces. The latter will inevitably lead to *qualitative* changes of adjacent water as compared to the bulk, and to more substantial reduction of the number of hydrogen bonds. According to our calculations, both the thermodynamics and the changes of water structure differ qualitatively from the case of small apolar

molecules. Adjacent to the apolar surface water is depleted. The resulting temperature dependencies of the enthalpy and entropy of solvation do not exhibit the behaviours typical for "hydrophobic effect".

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