Modeling Hydration Water and its Role in Polymer Folding

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Abstract. The hydrophobic effect is the dominant force which drives a protein towards its native state, but its physics has not been thoroughly understood yet. We introduce an exactly solvable model of the solvation of non-polar molecules in water, which shows that the reduced number of allowed configurations of water molecules when the solute is present is enough to give rise to hydrophobic behaviour. We apply our model to a non-polar homopolymer in aqueous solution, obtaining a clear evidence of both ‘cold’ and ‘warm’ collapse transitions that recall those of proteins. Finally we show how the model can be adapted to describe the solvation of aromatic and polar molecules.

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1. Introduction

The hydrophobic effect, namely, the free energy cost that non-polar solutes pay when transferred into water, is believed to be the dominant driving force of protein folding [1]. In the native state of real proteins, in fact, non-polar residues are buried in the interior of the structure, thus minimizing the exposure to water and the subsequent free energy cost.

Nonetheless, the physical properties of liquid water underlying the phenomenon of hydrophobicity and giving rise to the characteristic behaviour of the change of the thermodynamic functions upon solvation of a non-polar compound (not only the free energy increase, but also the characteristic temperature-dependence of the excess specific heat, of the internal energy and of the entropy) are not yet completely understood, despite the extensive studies devoted to their investigation, ranging from simplified models [2] to numerical simulations (see Reference [3] and references therein). In many studies hydrophobicity has been related to the ordering of water molecules around the solute [4, 5], but the question is still controversial,

since this behavior, indeed detected in simulations [5], could be a by-product and not the origin of hydrophobicity. An alternative explanation suggests that hydrophobic behaviour is related to the process of opening a cavity in water to insert the nonpolar solute, and to the interaction between water and solute [6]. The decrease in entropy would not be related to bond-induced ordering of water molecules, but to the opening of the cavity.

Here we discuss a model of hydrophobic solvation which is able to test the ‘ordering’ hypothesis *directly*. First, we show that the smaller number of allowed configurations of water molecules around a non-polar compound is enough to produce hydrophobic behaviour. Then we apply our model, which we keep as simple as to be analytically integrable, to the case of polymer solvation, and recover for a nonpolar homopolymer both ‘cold’ and ‘warm’ collapse transitions that recall those of proteins [7], thus strengthening the idea, already put forward in References [8, 9], that an explicit, though simplified, description of water molecules around non-polar solutes can provide a framework for a unified treatment of both the ‘warm’ and the ‘cold’ collapse transitions of polymers and proteins in aqueous solution. We recall that most treatments of protein folding, where water is not taken into account explicitly and hydrophobicity is described through effective potentials, do not allow a description of cold unfolding. Thus the model introduced here might well be relevant to the problem of protein folding. Finally we show how our model can be adapted to describe not only the solvation of purely non-polar (aliphatic) molecules, but also aromatic and polar ones. This opens the road towards a definition of a model of the solvation of a real protein.

2. Modeling hydration water

Let us now introduce our model. Consider the water molecules belonging to the hydration shell around an isolated solute: the solute will affect their geometric arrangement, causing a stronger spatial correlation than in the bulk case. We describe water at the scale of the cluster of molecules which are spatially correlated in the presence of a nonpolar solute: interactions between clusters are not explicitly considered and correlations are lost above this scale. This is consistent with the observation [7] that the contributions to thermodynamic functions from the different chemical groups of a residue’s side chain are to a good extent additive, suggesting the existence of a length scale up to which molecules are spatially correlated due to the solute, while correlation is small and can be neglected on larger scales.

For the sake of simplicity we describe water molecules as two-dimensional objects with three hydrogen-bonding arms [10, 5], representing the projection on a plane of the tetrahedral coordination of a real water molecule. The three arms are equivalent: no distinction is done between hydrogen donors and acceptors. A schematic picture of a hydration water shell according to our model is presented in Figure 1. Given a cluster of m molecules, we assume that its ground state is characterized by a completely formed hydrogen-bond network, not only in the bulk

Figure 1. Schematic picture of a hydration water cluster according to the model described in the text. The cluster molecules form bonds that can be divided into external (e), on-shell (s) and internal (i) bonds. In the external region molecules of other clusters can be found, while the internal region contains either a solute (shell case) or other water molecules (bulk case). Bonds can be broken (with probability p_1 : see text) if their energy is larger than a given threshold.

case, but also when a solute is present (this involves geometric conditions on the solute's shape and size, which we take for granted). Thus each molecule in the ground state has $3/2$ hydrogen bonds, but their energy can be different in the 'bulk' and 'shell' cases: namely, the energy difference per molecule, normalized to a bulk hydrogen-bond energy h_b , is:

$$K = \frac{3}{2} \left(1 - \frac{h_s}{h_b} \right) + J, \quad (1)$$

where h_s is the bond energy for shell molecules, and J takes into account all the contributions not related to hydrogen bonds (Van der Waals and so on). Here $h_\bullet$ are positive quantities, while J and K can be positive or negative.

Our goal is to evaluate the partition function for the cluster in both cases:

$$\mathcal{Z}_\bullet^{\text{clu}} = \int_0^\infty d\varepsilon g_\bullet(\varepsilon) e^{-\beta \mathcal{H}_\bullet^{\text{clu}}(\varepsilon)} \quad (2)$$

where $\bullet = b, s$ in the bulk and in the shell case, respectively, $g_\bullet(\varepsilon)$ is the density of states of the cluster at the energy $E = h_b \varepsilon$ above its ground state and $\mathcal{H}_\bullet^{\text{clu}}$ is

$$\mathcal{H}_\bullet^{\text{clu}} = h_b(\varepsilon + Km\delta_{\bullet,s}). \quad (3)$$

In the above framework, all the important features determining the system thermodynamics are encoded in the density of states $g_\bullet(\varepsilon)$ (rather than in the Hamiltonian, which has been substituted by its value). To evaluate $g_\bullet(\varepsilon)$, we assume that each

bond in the system can be broken or formed independently of the others, and that every formed one can be described by a harmonic potential. A bond is broken if its energy* exceeds $h_\bullet$, while to form a bond one needs also to have a bonding partner whose arms are correctly oriented. In other words, all the configurations with a given number of broken bonds are degenerate in energy, and this degeneracy depends on geometrical constraints, which can be different in the bulk and shell cases. Thus, at a given energy ε there will be a probability $p_\bullet(\lambda, \varepsilon)$ to break λ bonds, and a given number of broken bonds can be obtained with a set of configurations of water molecules whose number depends on the presence or absence of a nonbonding solute (see Figure 2). The important point is that when few bonds are broken the available number of configurations is *smaller* in the shell case rather than in the bulk one, i.e., the solute indeed forces an ‘ordering’ of the water cluster. We shall see in the following that this fact, together with a different value for h_s and h_b , is enough to get hydrophobic behaviour.

Hence, a reasonable ansatz for the functional form of $g_\bullet(\varepsilon)$ appears to be:

$$g_\bullet(\varepsilon) = \sum_{\lambda=0}^{\frac{3}{2}m} p_\bullet(\lambda, \varepsilon) \omega(\lambda, \varepsilon) \gamma_\bullet\left(\frac{3}{2}m - \lambda\right), \quad (4)$$

where $\omega(\lambda, \varepsilon)$ is the density of states of the system of harmonic oscillators resulting when λ bonds are broken, and $\gamma_\bullet(v)$ is the number of geometric arrangements of the water molecules allowing v unbroken bonds. Assuming independence of the bonds, we can write:

$$p_\bullet(\lambda, \varepsilon) = \binom{\frac{3}{2}m}{\lambda} p_1^\lambda (1 - p_1)^{\frac{3}{2}m - \lambda} \quad (5)$$

where p_1 is the probability that a bond acquires an energy larger than $h_\bullet$ and breaks, when the cluster energy $h_b \varepsilon$ is equipartitioned on D degrees of freedom, so that $p_1 = e^{-h_\bullet/\tilde{T}}$ and $\tilde{T} = \frac{2\varepsilon h_b}{D}$. Notice that in principle $D = D(m, \lambda)$ also depends on λ , as well as $\omega(\lambda, \varepsilon)$ does: the density of states of interacting molecules depends on how many molecules are bonded and how many are free, which in turn is a function of λ . Yet, for the sake of simplicity, we assume the degrees of freedom to be always those of bonded molecules, so that $D = 2mf$ and

$$\omega(\lambda, \varepsilon) \simeq \omega(\varepsilon) = \mathcal{C} \varepsilon^{\frac{D}{2}-1}, \quad (6)$$

where f are the degrees of freedom of one molecule ($f = 3$ for the 2-dimensional case), and $\mathcal{C}$ is a constant.

To estimate $\gamma_\bullet(v)$ in the 2-dimensional case we consider a cluster and divide the space in three regions: the cluster’s molecules are aligned in the shell region, that separates the external one, where water molecules of other clusters are found, from

* Considering independent bonds allows one to speak of the ‘energy of a bond’, even if in principle one can only speak of a mean energy per molecule.

Figure 2. An example showing the dependence of the ‘geometric’ contribution to the density of states $g_{\bullet}$, $\gamma_{\bullet}$ in Equation (4), on the presence of the solute. To keep the correct number of bonds per molecule we fictitiously split water molecules in the cluster in two groups: molecules of group a will be able to form only one bond (one black arm), while two bonds will be attributed to group b ones. Assuming that bonds can be broken independently, in the situation (a) depicted on the left, where both molecules are in state 1 (with two on-shell and one external arm; see text), every bond may be broken or formed. If we want to evaluate the number of configurations allowing ν intact bonds, this particular arrangement will be counted for every value of ν ranging from 0 to $\frac{3}{2}m$ (three, in this case). But if we rotate one of the molecules (right picture) to state 2 (with one internal arm), the shell bond is always broken for geometric reasons. The missing bond is definitely lost in the shell case (b), but might be recovered by the internal arm in the bulk water case (c). This means that this configuration will contribute to the $\nu = \frac{3}{2}m$ case just in bulk water. When the solute is present, at least one bond is broken, so this configuration will contribute to the $\nu = \frac{3}{2}m - 1$ case (1 bond broken) down to the all-broken case $\nu = 0$, but not to the completely bonded $\nu = \frac{3}{2}m$. This example helps one to understand why $\gamma_s < \gamma_b$ when few bonds are broken.

the internal one, which contains either the nonbonding solute or other water molecules in the ‘s’ or ‘b’ cases, respectively. Thus, we talk about ‘external’, ‘on-shell’ and ‘internal’ bonds, according to the region they point towards (see Figure 1). Moreover, we classify the orientation of a molecule of the cluster according to the direction of its arms, considering, for the sake of simplicity, only two states: state 1, with two on-shell arms and the third pointing outside, and state 2, with two external and one internal arms. In the latter, the internal bond will always be broken when the solute is present, while in the bulk water case it can be formed with a probability accounting for geometric restrictions on the orientation of the internal water. We assume no restriction on external bonds: they can always be formed. In this framework, $\gamma_{\bullet}(\nu)$ is related to the number of arrangements of the m molecules in the two states allowing for ν bonds to be formed, and in the end one gets:

$$\gamma_{\bullet} = \sum_{v_s=0}^v \sum_{v_e=0}^{v-v_s} \delta_{\bullet}(v_e, v_s, v_i), \quad (7)$$

where $v_i = v - v_s - v_e$,

$$\delta_{\bullet}(v_e, v_s, v_i) = \sum_{s=0}^m \sum_{k=0}^{k_{\max}} \sum_{j=0}^s \sum_{i=0}^j \xi_{\bullet}(s, k, j, i, v_e, v_s, v_i), \quad (8)$$

with $k_{\max} = \min(s, m - s - v_s)$ and

$$\begin{aligned} \xi_{\bullet}(s, k, j, i, v_e, v_s, v_i) &= \pi(s, k) \pi_h\left(j; s, \frac{m}{2}, m\right) \pi_h(i; j, q_{\bullet}, m) \\ &\times \pi_b\left(v_i, i, \frac{1}{2}\right) \pi_b\left(v_e, \frac{m}{2} + s - j, \frac{1}{2}\right) \pi_b\left(v_s, m - s - k, \frac{1}{2}\right). \end{aligned} \quad (9)$$

In the above equation the following definitions hold:

$$\pi(s, k) = \frac{1}{2^m} \left[\binom{s}{k} \binom{m-s}{k} (1 - \delta_{sm}) + \delta_{sm} \delta_{k0} \right], \quad (10a)$$

$$\pi_h(s; n, S, N) = \binom{S}{s} \binom{N-S}{n-s} \left[\binom{N}{n} \right]^{-1}, \quad (10b)$$

$$\pi_b(j, n, p) = \binom{n}{j} p^j (1-p)^{(n-j)}. \quad (10c)$$

Let us now explain how these expressions can be derived. To keep the right number of bonds per molecule (i.e., $3/2$), let us fictitiously split the m molecules into two groups of $m/2$ each. Group a -molecules will be able to form one bond: a shell one when in state 1 and an external one when in state 2. Group b -molecules will be able to form two bonds: a shell one and the external one in state 1, an external and the internal one in state 2 (see Figure 2). Hence, state 1 of both groups is able to form shell bonds, while internal bonds are possible only in the $(b, 2)$ state. Given the number s of molecules in the state 2 (not shell-bonding) and the number k of groups of state 1-molecules between state 2-ones, the probability of making $\chi = m - s - k$ shell bonds is $\pi(s, k)$ given in Equation (10a). The probability that one of these configurations also has i internal bonds depends, first of all, on the probability of fishing out j $(b, 2)$ -molecules among the total of s in state 2, given the total number of molecules m and the total number of b -molecules $m/2$, so that one gets a hypergeometric probability – defined in Equation (10b) – $\pi_h(j; s, \frac{m}{2}, m)$. This is not enough, though, because, for geometrical reasons, some of the internal arms will not find a bonding partner. Indeed, we assume that there are just $q_{\bullet}$ (out of m) positions where internal bonds may actually be formed. Their number distinguishes the bulk from the shell-water case: $q_s = 0$ with a non-bonding solute,

while in the bulk case $0 < q_b \leq m$. Again we have a hypergeometric probability of placing i of the j molecules with internal arms, in the $q_\bullet$ good positions for bond formations, on a total of m possibilities: $\pi_h(i; j, q_\bullet, m)$. The product of the above probabilities gives the fraction of the total number of conformations that is able to form χ shell bonds, i internal ones and $m/2 + s - j$ external ones, assuming that all the molecules with external arms – i.e., group b and state $(a, 2)$ – form external bonds. If we now let the bonds be also broken, any geometric arrangement of the m molecules allowing ν bonds also contributes to the cases where fewer bonds are formed. Indeed, given a geometric arrangement, we can choose to keep or break the external, internal and shell bonds with the binomial probability π_b defined in Equation (10c), whence the expression of $\xi_\bullet$ in Equation (9). Upon summing over all the geometric arrangements that can contribute to a pattern with ν bonds, we obtain the expression (7) for $\gamma_\bullet(\nu)$.

Upon substituting Equations (5, 6, 7) into Equation (4) and then into Equation (2), we get:

$$\mathcal{Z}_\bullet^{\text{clu}} = A_\bullet e^{-\beta h_b K m \delta_{\bullet,s}} \quad (11)$$

where

$$A_\bullet = \mathcal{C} \sum_{\lambda=0}^{\frac{3}{2}m} \binom{\frac{3}{2}m}{\lambda} \gamma_\bullet \left(\frac{3}{2}m - \lambda \right) I_\bullet(\lambda), \quad (12)$$

$\mathcal{C}$ is a constant and

$$I_\bullet(\lambda) = \frac{(D-1)!}{(\beta h_b)^D} \delta_{\lambda,0} + \sum_{j=1-\delta_{\lambda,0}}^{3m/2-\lambda} \binom{\frac{3m}{2}-\lambda}{j} (-1)^j 2\sigma_\bullet^{D/2} K_D(\tau_\bullet), \quad (13)$$

where $K_n(z)$ is the Bessel- K function and the following definitions hold:

$$\sigma_\bullet = \frac{h_\bullet D(j + \lambda)}{\beta h_b^2}, \quad (14)$$

$$\tau_\bullet = 2\sqrt{\beta h_\bullet D(j + \lambda)}. \quad (15)$$

3. Hydrophobic solvation

Having defined a model for hydration water which should take into account the main physical ingredients relevant to the thermodynamics of solvation, let us now apply our model to two physically interesting cases which can be dealt with in a purely analytical way. To start with, we consider the solvation of a single non-polar compound, then we apply our model to a non-polar homopolymer.

Figure 3. Free energy, energy, entropy and specific heat changes upon solvation of a nonpolar solute: ΔF (dash-dotted line), ΔE , (dashed), $T\Delta S$ (dotted), $\Delta C/3$ (solid line; $1/3$ is for rendering purposes). Here $m = 4$, $q_b = m/2$ (half of the molecules can form internal bonds, in the bulk case), $h_s/h_b = 1.2$, $J = 0.3$ (so that the ground-state energy shift $K = 0$). Energies and temperatures are expressed in bulk hydrogen bonds units (h_b); Boltzmann constant k_B is set to 1 and specific heat is, accordingly, adimensional. The shaded region can be compared with numerical simulations (e.g., with Figure 5 of Reference [5]) and experimental results like those reported in Reference [7].

3.1. TRANSFER OF A NONPOLAR SOLUTE INTO WATER

Let us consider the cluster of m water molecules in the bulk case and substitute the internal water with a nonpolar solute. This describes the transfer of a nonpolar molecule from its gas (non-interacting) phase to water, i.e., hydrophobic solvation. We study the difference in thermodynamic functions. The free energy change is:

$$\Delta F = F_{\text{solution}} - F_{\text{water}} = -\frac{z}{\beta} \log x, \quad (16)$$

where

$$x = \frac{A_s}{A_b} e^{-\beta K h_b m}. \quad (17)$$

Similar expressions hold for energy, entropy and specific heat changes. The temperature dependence of these functions, reported in Figure 3, shows the hallmarks of hydrophobic behaviour, even for $K = 0$ (i.e., without any ground-state energy difference). In fact, we find a maximum in the free energy cost, a pronounced and positive peak in the specific heat difference ΔC , and minima in both ΔE and $T\Delta S$; then, as T grows, ΔE and $T\Delta S$ cross the zero – thus defining the characteristic temperatures commonly referred to as T_H and T_S – and eventually become positive. Notice that the peak in ΔC cannot be recovered within the Information Theory Approximation, usually applied together with the cavity approach [11].

3.2. POLYMER IN SOLUTION

Let us now turn to the study of a nonpolar homopolymer in solution, taking into account just the behaviour of water clusters in the vicinity of a monomer, and disregarding interactions between monomers and between water clusters. Our goal is, in fact, to understand the effect of the hydrophobic effect alone on polymer behaviour.

We model a polymer as a N -step self-avoiding walk on a two-dimensional lattice with coordination z . On each lattice site there can be either a monomer or z clusters of m water molecules, so that each monomer-water contact involves one cluster. The Hamiltonian follows from Equation (3):

$$\mathcal{H} = \sum_{j=1}^{N_W} h_b \left(\sum_{\mu=1}^z \varepsilon_{j\mu} + K m l_j \right), \quad (18)$$

where $N_W = (z - 2)/N + 2$ is the highest number of water sites that can be in contact with the polymer, and l_j is the number of contacts between the j -th water site and the monomers. The partition function of the polymer in solution reads as:

$$\mathcal{Z} = \sum_C Z(C) = \sum_{n_c} \zeta(n_c) Z(n_c) \quad (19)$$

where C are the conformations of the polymer and $Z(C)$ the restricted partition function, obtained tracing over water variables at fixed conformation C . Due to the form of the Hamiltonian given in Equation (18), $Z(C)$ depends only on the total number of water-monomer contacts n_c , and $\zeta(n_c)$ is the number of SAWs characterized by the same value of n_c . $\mathcal{Z}$ can be factorized as

$$\mathcal{Z} = \mathcal{Z}_b \mathcal{Z}_I, \quad (20)$$

where $\mathcal{Z}_b = (\mathcal{Z}_b^{\text{clu}})^{zN_W} = A_b^{zN_W}$ is the contribution of all water sites when in contact to other water, and

$$\mathcal{Z}_I = \sum_{n_c} \zeta(n_c) x^{n_c}. \quad (21)$$

In the following we shall study the specific heat of the system, that, according to the above factorization, is the sum of a bulk contribution C_b and of an interaction contribution C_I . We shall also study the average number of water-monomer contacts:

$$\langle n_c \rangle = x \frac{\partial}{\partial x} \log \mathcal{Z}_I, \quad (22)$$

which is a measure of the compactness of the polymer. To exactly evaluate the above quantities, an exhaustive enumeration of the SAWs should be performed, in order to obtain $\zeta(n_c)$. However, if we restrict ourselves to a square lattice, the numerical estimates reported in [12] allow us to write

Figure 4. Excess specific heat C_I/N_W of the nonpolar homopolymer in solution, for different lengths: $N = 2 \times 10^2$ (dashed), $N = 10^4$ (dash-dotted), $N = 10^6$ (solid line). Parameters as before.

$$\zeta(n_c) \simeq \zeta_0 \frac{1}{w(n_c)!} (\alpha_0 N)^{w(n_c)} \exp(\alpha_0 N), \quad (23)$$

where $w(n_c) = (N_W - n_c)/2$ is the number of monomer-monomer contacts, ζ_0 is the number of SAWs of length N and $\alpha_0 = 0.164$. Such an estimate is expected to be very good if N is large [12]. Hence, an analytical expression can be found for $\mathcal{Z}_I$:

$$\mathcal{Z}_I = \frac{1}{w_{\max}!} x^{N_W} \Gamma\left(w_{\max} + 1, \frac{\alpha_0 N}{x^2}\right) e^{-\alpha_0 N(1 - \frac{1}{x^2})}, \quad (24)$$

where $\Gamma(n, x)$ is the incomplete Γ -function and $w_{\max} = (N_W - n_c^{\min})/2$ ($n_c^{\min}$ accounts for the fact that the smallest number of water-monomer contacts is determined by the length of the perimeter of the globule: $n_c^{\min} \simeq 2\sqrt{N\pi}$).

The results obtained C_I and $\langle n_c \rangle$ stemming from Equation (24) are reported in Figures 4 and 5, for different lengths of the polymer.

The presence of both ‘cold’ and ‘warm’ collapse transitions, signalled by the drop of the number of contacts and by the jumps in the specific heat is strikingly evident from our results. As N grows both transitions get sharper, thus suggesting the existence of a true phase transition in the thermodynamic limit. This phenomenology is very close to that of proteins in solution: our results confirm that, as already suggested in References [8, 9], the explicit treatment of the solvent – though in an extremely simplified way – is a natural and powerful way to get a unified modeling of both the cold and the warm unfolding transitions in proteins. Moreover, it is worth noticing that a cold collapse qualitatively very similar to that predicted by our model has been experimentally observed also in homopolymers like the poly(N-isopropylacrylamide) [13].

Figure 5. Normalized average number of water-monomer contacts, $f_c = \langle n_c \rangle / N_W$, for different polymer lengths (the same as before). Parameters and rendering conventions as before.

4. Solvation of aromatic and polar compounds

Proteins are heteropolymers whose monomers are aminoacids. The aminoacid residues (i.e., those parts of the aminoacids which can be exposed to water once they are linked with other aminoacids in a protein chain) can be roughly split into two classes: polar (or even charged) and non-polar. However, as far as the qualitative features of their interaction with water is concerned, not all the non-polar molecules behave in the same way. One can identify two families, aliphatic and aromatic residues [7], with different thermodynamic behavior. Aliphatic compounds are ‘purely’ hydrophobic, i.e., show a positive jump in both the specific heat and the free energy upon solvation. On the contrary, when an aromatic residue is transferred into water from the gas phase there is a positive jump in the specific heat but there is a free energy gain too, i.e., $\Delta F < 0$. Aromatic molecules show, in a way, an intermediate behaviour between hydrophobic and hydrophilic. Moreover, also in the case of polar molecules there is a change in the thermodynamic functions: $\Delta F < 0$ and $\Delta C < 0$, so that they can be reasonably called hydrophilic.

The model of solvation discussed so far works very well when applied to purely hydrophobic solvation, i.e., to the solvation of aliphatic monomers or homopolymers. However, in view of a generalization of the approach presented here to heteropolymers and especially to proteins, one should devise a way to model also the solvation of aromatic and polar residues. As we are going to show in the following, our model is able to accomplish both tasks, provided one chooses the parameters according to the physical requirements of these situations. This is not only very promising for future applications to proteins, but also tells us that our model grasps, though in a very simplified way, some of the basic physics of water-solute interaction.

Figure 6. Free energy, energy, entropy and specific heat changes upon solvation of an aromatic solute: rendering conventions as in Figure 3. Here $m = 4$, $q_b = m/2$, $h_s/h_b = 0.98$, $J = -0.07$. The shaded region can be compared with experiments reported in Reference [7].

Figure 7. As in Figure 6 for a polar solute. Here $m = 4$, $q_b = m/2$, $h_s/h_b = 0.4$, $J = -0.95$.

4.1. AROMATIC MOLECULES

Figure 6 presents trends in the changes in thermodynamic functions upon solvation that qualitatively recall those obtained experimentally for aromatic residues [7]. The plots are obtained with $h_s/h_b = 0.98$, $J = -0.07$, $q_s = 0$, $q_b = m/2$; more in general, $h_s/h_b \simeq 1$ and $q_b = m/4$ would provide similar results, as far as the experimental temperature window is concerned (data not shown). In the framework of the model, this implies that hydrogen bonds for bulk and hydration water are more or less equivalent, and that shell molecules are less likely to form internal bonds than in the bulk case (or cannot at all). At the same time there is a small gain, related to J , in hydrating the solute, suggesting that other interactions than hydrogen bond could favour the aromatic hydration. A clear interpretation of this fact is not straightforward: it is unlikely that a negative J could come from Van der Waals contributions prevailing over the electrostatics of bulk water: electrostatics

interactions between solute and solvent should come into play, instead. It is difficult to say if their effect could be described by an isotropic term J ; we cannot exclude also that a negative J compensates the fact that in the model internal bonds have the same energy as external and on-shell. Even if the precise scenario could be determined only by all-atoms simulation, the hypothesis that electrostatic interactions between solute and water are more important for aromatic than for aliphatic compounds is supported by the experimental evidence that aromatic residues present a partial polar nature, with an excess negative charge on the faces of the aromatic ring and a partial positive charge of the hydrogen atoms at the border [7, 14, 4].

4.2. POLAR MOLECULES

Figure 7 presents thermodynamic trends which are in a good qualitative agreement with experimental findings for polar residues [7]. Again, the choice of the parameters is not unique, since the region to be compared to experiments is not as sensitive as the low T one to parameters changes, and a comparison of a two-dimensional model to real experiments cannot be made truly quantitative. Nevertheless, there are some crucial aspects characterizing polar behavior: a low value of h_s/h_b (i.e. less than 0.6) is required to produce the correct trend in ΔC together with a low value for T_s , whence the relation $\Delta E < \Delta F$. On the other hand, a low ratio h_s/h_b would yield a positive energy shift K ; thus, it must be compensated by a large and negative J , favouring solvation, if the experimental values for a large and negative ΔF are to be recovered. It is important to notice that, for low values of h_s/h_b , the different degeneracies $g_b(\varepsilon)$, $g_s(\varepsilon)$ in bulk and shell water come essentially from the different probabilities of breaking bonds: the geometric arrangement of the molecules almost plays no role.

The need for a low ratio h_s/h_b and $J < 0$ suggests a possible physical explanation of the parameters: the presence of a polar compound hinders the formation of hydrogen bonds between water molecules by competing with it; a strong direct solute-water interaction (J is almost equal to h_b) results in weakened hydrogen bonds among shell water molecules.

5. Concluding remarks and future developments

We have introduced and discussed a statistical-mechanical model of non-polar solvation in water. In our model the water degrees of freedom are explicitly considered, though in a very simplified way: water molecules are modeled as planar objects with three equivalent bonding arms (roughly speaking, the projection of water's tetrahedral coordination into a plane) and all the treatment is for a two-dimensional system. Nonetheless, this allows us to obtain an exact analytic solution of the model, which unambiguously shows that hydrophobic behaviour can be related to a combination of the strengthening of hydrogen bonds together with the reduction of available configurations for water molecules when the solute is

present. Our model thus supports the conjecture that the physical origin of hydrophobicity is the formation of 'ordered' cages of water around the solute, with stronger hydrogen bonds than in bulk, even if we cannot say which one of the two ingredients above is more determinant. Applying our model to a hydrophobic homopolymer we have clearly shown that it is swollen at low temperatures, then becomes maximally compact and eventually unfolds again at higher temperatures. This behaviour closely reminds that of proteins, which undergo both a cold and a warm unfolding transition.

In view of the application of our model to proteins, we have shown that it can be adapted to describe also the solvation of aromatic and polar molecules. To study the behaviour of a model of a real protein along these lines, however, it will be necessary to extend the model to the three-dimensional case and to determine, by means of a comparison with experiments, the right parameters for all the aminoacids. Work is in progress in these directions.

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