A Heuristic Molecular Model of Hydrophobic Interactions

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Abstract

Hydrophobic interactions provide driving forces for protein folding, membrane formation, and oil-water separation. Motivated by information theory, the poorly understood nonpolar solute interactions in water are investigated. A simple heuristic model of hydrophobic effects in terms of density fluctuations is developed. This model accounts quantitatively for the central hydrophobic phenomena of cavity formation and association of inert gas solutes; it therefore clarifies the underlying physics of hydrophobic effects and permits important applications to conformational equilibria of nonpolar solutes and hydrophobic residues in biopolymers.

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Protein folding and formation of lipid membranes and micelles are driven by hydrophobic interactions. Understanding the nature of these interactions of nonpolar solutes in water and quantitatively describing them has been the topic of numerous experimental and theoretical studies (1). Despite these efforts, a general, quantitative, molecular scale theory is not available. Motivated by information theory, we study molecular scale hydrophobic effects by exploring the thermodynamics of hydration and association of model hard core solutes (2) where otherwise the only reliable calculational tools are elaborate computer simulations. As we will show, a simple theory based upon local density fluctuations proves sufficient to describe qualitatively and quantitatively the central hydrophobic phenomena. The theory can be applied easily to solutes of arbitrary shape and size, and permits study of structural equilibria of nonpolar molecules and residues.

Among the previous theories of hydrophobic hydration, the scaled particle model (3,4) initiated an important line of development. It utilizes asymptotic results in the small and large solute limits where direct information on solvent correlations is not required. In the intermediate region and for phenomena such as solvent separated hydrophobic interactions, (5,6) molecular correlations are important. Stillinger (7) and others (8) partly filled these gaps, but much remains missing in our knowledge of hydrophobic effects. Our understanding of hydrophobic interactions is particularly meager. The available solubility or “hydrophobicity” models have not encompassed the molecular structural features that give rise to stable free energy minima with water separating hydrophobic groups — the so-called solvent separated hydrophobic interactions. Thus, the hydrophobicity models have not been justified by reproducing these interactions and to this extent must be regarded as of unproven validity for conformational analysis of biomolecular structure in solution.

Chemical potentials of nonpolar solutes in water are the quantities of ultimate interest in the theory of hydrophobic hydration. We shall mainly be concerned with the excess chemical potential \( \Delta \mu^{ex} \) of a hard core solute in water. Statistical mechanics relates \( \Delta \mu^{ex} \) to the probability \( p_0 \) of finding an empty volume, or cavity, of given size and shape in water at
equilibrium, $\Delta \mu^{ex} = -k_B T \ln p_0$. However, $p_0$ becomes exceedingly small for larger cavities, and direct calculations of $p_0$ (e.g., by computer simulations using test particle insertion (8)) become impractical. Our goal here is to provide a model to access this region of cavity sizes based upon accessible, even if indirect, information. The model we seek should not only extend the range of sizes but also apply to non-spherical cavity shapes. Complete information on the binomial moments of the occupancy of a volume identical to the cavity of interest would permit a construction of $p_0$ based upon the well known expression (4,8,9) that exactly relates $p_0$ to the fluctuations in the number $n$ of solvent molecules in the cavity region:

$$p_0 = 1 + \sum_{j=1}^{\infty} (-1)^j \left\langle \frac{n!}{j!(n-j)!} \right\rangle.$$  

This formula is useful in guiding the analysis of theories (7) but becomes impractical for larger cavities because of its sensitivity to missing information. In those instances, higher binomial moments cannot be neglected and that information is unavailable. We require an approach that is less sensitive to missing information while exploiting information readily available for cavities of all sizes and shapes. These are the low order moments of the number $n$ of solvent molecules in the cavity volume $\Delta V$,

$$\langle n \rangle = \rho \Delta V,$$

$$\langle n(n-1) \rangle = \rho^2 \int_{\Delta V} \int_{\Delta V} \, dr \, dr' g(|r - r'|),$$

where $g(r)$ is the water oxygen pair correlation function and $\rho$ is the water density. Information theory (10) provides a paradigm for exploiting such quantities. We consider the set of probabilities $p_n$ of finding exactly $n$ solvent molecules in the cavity volume, $\sum_{n=0}^{\infty} p_n = 1$. Observation of no solvent molecules in the cavity region is then just one of the elementary events, and $p_0$ is just one of the desired probabilities. We formulate models of the distribution $p_n$ that satisfy known moments, Eqs. 2 and 3. Minimizing an information measure permits the inference of probabilities of maximum likelihood in a sampling experiment.
that satisfies the moment information (10). However, the accurately parabolic character of \( \ln p_n \) for cavity volumes of small molecular size, observed in computer simulations of water (11), suggests an even simpler model: We adopt the form 

\[
p_n = \exp(\lambda_0 + \lambda_1 n + \lambda_2 n^2)
\]

with “Lagrange multipliers” \( \lambda_0, \lambda_1, \lambda_2 \) to be determined by the three moment conditions 

\[
\sum_{n=0}^{\infty} p_n = 1, \quad \sum_{n=0}^{\infty} np_n = \langle n \rangle, \quad \sum_{n=0}^{\infty} n^2 p_n = \langle n^2 \rangle.
\]

From this we extract the \( p_0 \) that provides the desired thermodynamic result.

Figure 1 shows the chemical potential for a spherical cavity in water calculated from the model as well as from direct cavity statistics. We find excellent agreement in the range considered. This simple theory based entirely on the pair correlation function of water is capable of reproducing the thermodynamics of cavity formation in the region that is accessible to direct computer simulations (8,12–14).

So far, we considered the hydrophobic hydration of a single cavity. We now proceed to study hydrophobic interactions. The free energy associated with bringing together two hydrophobic solutes corresponds to a distance dependent potential of mean force (PMF). The developed methodology provides us with the means of calculating this PMF. Given the first and second moment of the particle number distribution, an approximate chemical potential \( \Delta \mu^{ex}(r) \) can be determined for forming a cavity made of two spheres with given radius \( R \) and distance \( r \) using the model. The PMF is then defined as 

\[
W(r) = \Delta \mu^{ex}(r) - \lim_{s \to \infty} \Delta \mu^{ex}(s).
\]

In the following, we study the association of two cavities of methane size in water. For the radius of the spheres, we have chosen a value of \( R = 0.33 \) nm. This radius corresponds to the smallest distance where methane-water pair correlations reach 1.0 in commonly employed models (15). The cavity PMF is shown in Fig. 2. As a reference, the cavity potential produced by the molecular dynamics simulation of Smith and Haymet (16) is included. We obtained this by subtracting the bare potential from the PMF of methane association. Again, we find qualitative and quantitative agreement between our simple model and elaborate computer simulations. Our cavity PMF shows a strongly favored region with overlapping cavities, separated by a distinct barrier from a solvent separated, stable minimum at about
0.7 nm distance, in agreement with the computer simulations for methane association. In addition, we observe a very shallow third minimum at 1.1 nm distance.

As a last example, we study the torsional equilibrium of $n$-butane. Figure 3 shows the cavity PMF as a function of the torsional angle $\phi$, which is compared to explicit computer simulation results of Beglov and Roux (17). In complete agreement with the computer simulations, we find that the more compact cis ($\phi = 0$) and gauche structures ($\phi = \pi/3$) are favored over the extended trans conformation ($\phi = \pi$) by about 1.8 kJ mol$^{-1}$ and 0.7 kJ mol$^{-1}$, respectively.

When the cavities of interest are much larger than the size of the solvent molecules, other physical considerations intrude, as is well known in the scaled particle developments (4). We expect this two moment model to become unsufficient as a sole description in those cases. Nevertheless, a broad range of problems of biological interest, such as interactions of ligands with binding sites, effects of point mutations on protein-solvent interactions, and conformational equilibria of side chains, is within the range of applicability of this model.

The present theory permits a sound, quantitative understanding of hydrophobic hydration and association processes. This view is based upon (i) the simplicity of the present theory involving only particle number fluctuations, (ii) the small amount of input information required [$g(r)$] that is experimentally accessible, (iii) the computational ease of evaluating the theory permitting application to realistically large and complex shaped solutes, (iv) the unified and consistent treatment of hydrophobic hydration and interaction phenomena, (v) the clear connection of information theory to basic statistical thermodynamics, and (vi) the qualitative and quantitative accuracy of the theoretical predictions in a range that is otherwise inaccessible to direct theoretical treatment.

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FIGURES

FIG. 1. Hydrophobic hydration: Comparison of the chemical potential calculated from simulation (symbols) and the fluctuation model (line) for spherical cavities with radius $R$, the distance of closest approach of a water oxygen to the solute. The fluctuation integral Eq. 3 required by the information theory was reduced to one-dimensional integration (18). The simulation results were gathered from test-particle insertion, where 8000 configurations (separated by 50 passes each) of a Monte Carlo simulation of SPC water (19) were used. The same simulation was used to calculate the water-oxygen pair correlation $g(r)$.

FIG. 2. Hydrophobic interaction: PMF of cavity association. $r$ is the distance of two spherical cavities with radius $R = 0.33$ nm. The result of the fluctuation model (solid line) is compared with the cavity PMF of Smith and Haymet (dotted line; from Fig. 4 of Ref. (16)). The inserts illustrate the size of the excluded volume. At the solvent-separated PMF minimum (0.7 nm), a water molecule barely fits between the two hard-sphere solutes.

FIG. 3. Torsional PMF of $n$-butane. Butane was modeled as four spheres with radius $R = 0.33$ nm, bond length 0.153 nm and tetrahedral bond angle. The result of the fluctuation model (solid line) is compared with the cavity PMF of Beglov and Roux (dotted line; from Fig. 8 of Ref. (17)). The cis, gauche, and trans rotational states are shown as inserts.
\[ \Delta \mu (\text{kJ mol}^{-1}) \]

versus

\[ R \text{ (nm)} \]

Legend:
- Simulation
- Fluctuation model
fluctuation model simulation (Smith & Haymet)
$W(\phi)$ (kJ mol$^{-1}$) vs $\phi$ (rad)

- **cis**
- **gauche**
- **trans**

Fluctuation model simulation (Beglov & Roux)