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Hydrophobic hydration: Inhomogeneous water structure near nonpolar molecular solutes

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A potential of mean force (PMF) expansion is used to predict the water structure near nonpolar solutes having different shapes and molecular conformations. The decomposition of n-particle PMFs into pair and triplet contributions describes well the hydration of those solutes consisting of nonbonded clusters, but not covalently bonded molecules. Alternative proximity approximations are devised based on the local dependence of the water structure on solute shape and excluded volume. Accurate predictions obtained using these proximity approximations demonstrate that water organization is only locally sensitive to structural details of nonpolar solutes. [S1063-651X(96)50905-0]

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Current theoretical approaches, viz., integral equation or density functional theories, have met with only limited success in describing the structure of water surrounding molecular hydrophobic solutes. This is a consequence of the complexities involved in treating inhomogeneous molecular fluids [1], such as the high dimensionality of molecular potential functions. Molecular simulations can provide exact structural information on model solute-water correlations, but are seriously limited by the computational effort needed to obtain satisfactory statistical precision. We present here an alternative approach to predicting the inhomogeneous water structure around molecular hydrophobic solutes, in which the potential of mean force (PMF) between the solute and a water molecule is decomposed in terms of lower-order PMFs. The PMF expansion has been successfully applied to strongly associating inhomogeneous systems, such as ion density distributions near nucleic acids [2], the ice-water interface [3], and biomolecular hydration [4–6]. In the present study of hydrophobic solutes, we identify important limitations of the PMF expansion which lead to alternative descriptions of water structure when volume exclusion is the dominant interaction.

The central quantity in our formal development is the inhomogeneous one-particle density of water molecules, where the inhomogeneity is induced by an external field that describes the nonpolar molecular solute fixed at an arbitrary position and in a given conformation in space. The one-particle water density or conditional probability of finding a water molecule at $\mathbf{r}_W$, given that the n different sites defining the solute are fixed at $(\mathbf{r}_1,\ldots,\mathbf{r}_n)$, can be written as [3,4]

$$\rho^{(n,1)}(\mathbf{r}_W|\mathbf{r}_1,\ldots,\mathbf{r}_n)=\rho_0\prod_{i=1}^{n} g^{(2)}(\mathbf{r}_W,\mathbf{r}_i)\prod_{j=1}^{n-1}\prod_{k=j+1}^{n}\frac{g^{(3)}(\mathbf{r}_W,\mathbf{r}_j,\mathbf{r}_k)}{g^{(2)}(\mathbf{r}_W,\mathbf{r}_j)g^{(2)}(\mathbf{r}_j,\mathbf{r}_k)g^{(2)}(\mathbf{r}_k,\mathbf{r}_W)}\cdots, \tag{1}$$

where $g^{(n)}$ is the n-particle correlation function and ρ_0 is the bulk water density. Equation (1) corresponds to decomposing the $(n+1)$-particle PMF into two-particle, three-particle, and higher-order contributions. Retaining terms up to two- and three-particle correlations corresponds to the Kirkwood (KSA) [7] and Fisher-Kopeliovich (FKSA) [8] superposition approximations for $g^{(3)}$ and $g^{(4)}$, respectively. We have applied Eq. (1) truncated at the FKSA level to calculate one-particle water oxygen and hydrogen densities around nonpolar molecular solutes defined in terms of individual methane (Me) sites. This calculation requires Me-O and Me-H pair, and Me-Me-O and Me-Me-H triplet correlation functions, which we have obtained from simulations of Me monomers and dimers at fixed separations in water [4]. Once this database of correlation functions has been generated, the prediction of inhomogeneous water densities around molecular solutes of arbitrary shape and size, and in different molecular conformations, is straightforward. The relative ease with which these correlation functions can be determined using simple nonpolar solutes, and then applied to more complex solutes, makes the truncated PMF expansion well suited for characterizing solvent structure around complex hydrophobic solutes.

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Monte Carlo simulations [9] of Me monomers and dimers in 256 water molecules were performed at a temperature of 298 K and a constant density of 33.33 molecules/nm^3. The united-atom representation was used for Me, which was treated as a spherically symmetric Lennard-Jones particle with $\sigma_{\text{Me-Me}}=0.373$ nm and $\epsilon_{\text{Me-Me}}=1.23$ kJ/mol [10,11]. The simple point charge (SPC) model [12] was used for water. Me-water Lennard-Jones parameters were calculated using Lorentz-Berthelot mixing rules [9]. The Ewald summation technique was used for Coulomb interactions [9]. The Me-O and Me-H pair correlation functions were obtained from a simulation of a single Me in water. The Me-Me-O and Me-Me-H triplet correlation functions were obtained from simulations of Me-Me dimers over a range of Me-Me separations from 0.12 to 0.66 nm at an interval of 0.02 nm. Equilibration consisted of 50–60 K passes (one pass corresponds to one attempted move for each of the water molecules), and production runs following equilibration amounted to 60–100 K passes, with averaging done once every 5 passes.

The accuracy of Eq. (1) was evaluated by comparing predicted inhomogeneous density profiles of water oxygens with profiles obtained directly from simulations for several different solutes in water. In all cases, similar results were obtained when comparing the water-hydrogen density profiles. The following solutes were chosen to reflect increasing molecular complexity in terms of the number of solute sites and molecular conformations: (1) C3 solute consisting of three Me sites in an equilateral triangle separated by 0.419 nm, the distance corresponding to the minimum in the Me-Me potential; (2) C4 solute consisting of four Me sites in a tetrahedral configuration separated by 0.419 nm; (3) n-butane in the *trans*-conformation; and (4) benzene. Both *trans*-butane and benzene were simulated using the united-atom Me parameters for the carbons as listed above; carbon–carbon bond distances were taken from Jorgensen *et al.* [11].

Comparison of the density profiles was facilitated by an expansion in terms of spherical harmonics,

$$\frac{\rho(\mathbf{r})}{\rho_0}=\sum_{n=0}^{\infty}\sum_{m=0}^{n}\left[C_{nm}(r)Y^e_{nm}(\theta,\phi)+S_{nm}(r)Y^o_{nm}(\theta,\phi)\right],$$

where $Y^e_{nm}(\theta,\phi)=P^m_n(\cos\theta)\cos(m\phi)$ and $Y^o_{nm}(\theta,\phi)=P^m_n(\cos\theta)\sin(m\phi)$. We restrict this comparison to the dominant features of the density profile that are captured in the lowest-order coefficients, independent of truncation of the expansion. The spherical-harmonic coefficients, $C_{nm}(r)$ and $S_{nm}(r)$, give the angular dependence of the one-particle density as a function of the distance, r, from the center of mass of the solute molecule. The symmetry of the solute in the polar and azimuthal direction allows us to infer which of these coefficients are nonzero. For example, if the C3 solute is placed in the x-y plane, the density profile is symmetric about this plane and exhibits a threefold rotation symmetry about the z axis. Thus, only coefficients with $n+m$ even and m a multiple of 3 can be nonzero. The spherical-harmonic coefficients for the PMF-predicted density profiles were calculated using Monte Carlo integration and compared to the simulation results.

Nonzero spherical-harmonic coefficients for the one-particle density of water oxygens around the C3 solute are shown in Figs. 1 and 2. The coefficient C_{00} (Fig. 1) gives the spherically averaged density at a distance r from the center of mass of the solute, normalized by the bulk density of water. The PMF-predicted values reproduce the essential features of the density profile, including the positions of the maxima and the shoulder on the first peak, but the height of the first peak is slightly overestimated. Comparable or better agreement is obtained for C_{20} and C_{40} (Fig. 1 inset), reflecting an accurate description of the two-fold planar symmetry of this solute. Subtle details in the density profile are captured as well in the predicted S_{33} and S_{53} coefficients (Fig. 2). The PMF-predicted density profile of water oxygens around the C4 solute (not shown) shows equally good agreement with simulation results. Therefore, we conclude that two- and three-particle PMFs make the major contributions to the $(n+1)$-particle conditional PMF, and as such, contain the information needed to represent the inhomogeneous structure of water around these solutes.

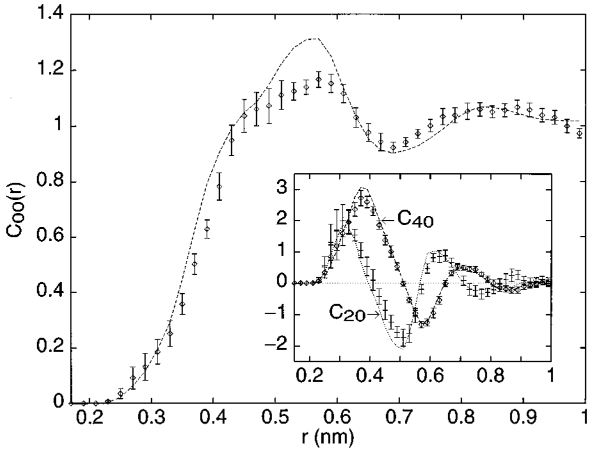

FIG. 1. C_{00} for the water-oxygen density around the C3 solute calculated from simulation (symbols) and the truncated PMF expansion (dashed line). Inset: coefficients C_{20} and C_{40}.

The coefficient C_{00} for water-oxygen densities around benzene is shown in Fig. 3. Although the shape of the den-

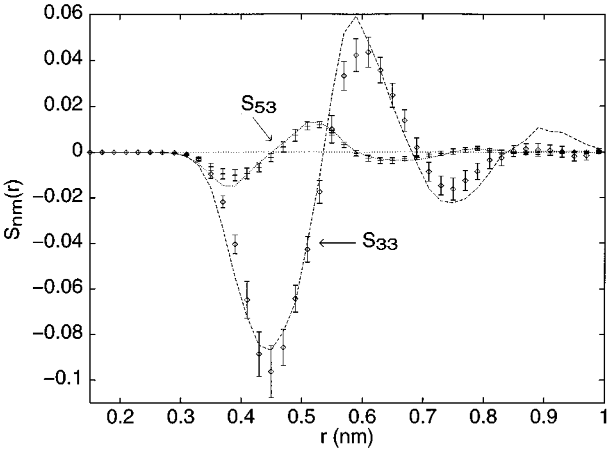

FIG. 2. S_{33} and S_{53} for the water-oxygen density around the C3 solute calculated from simulation (symbols) and the FKSA-PMF expansion (dashed lines).

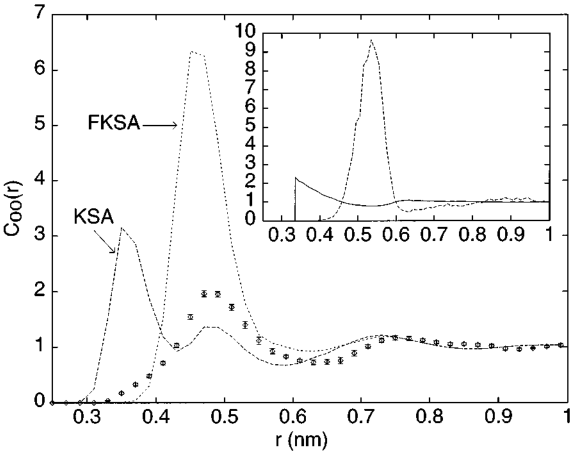

FIG. 3. C_{00} for the water-oxygen density around benzene calculated from simulation (symbols), the KSA- and FKSA-PMF expansions (dashed lines). Inset: $g_{\mathrm{HS,O}}(r)$ (solid line) and C_{00} (dashed line) for the water-oxygen density around a solute consisting of six hard-sphere sites calculated from the FKSA in the limit of complete site overlap.

sity profile and the peak positions are reproduced by the truncated PMF expansion, the first peak is much higher than that obtained from the simulation. Similar observations are made for C_{20} and C_{40} (not shown). Therefore, contrary to our previous conclusions for nonbonded hydrophobic solutes, it appears that pair and triplet conditional PMFs alone do not accurately approximate the $(n+1)$-particle conditional PMF for benzene. The PMF-predicted peaks of the nonzero coefficients for *trans*-butane (not shown) are also more pronounced than the simulation results, although the discrepancies were significantly less than those for benzene. Similar overestimates were also observed by Pellegrini and Doniach [13] for water densities around alanine dipeptide. Separate PMF calculations using the KSA are also presented in Fig. 3 and show that including Me-Me-O triplet correlations in the FKSA corrects for overestimates of the density in the contact region of benzene, but results in too high densities at larger distances.

The individual Me sites in benzene overlap considerably (0.14 nm Me-Me separation). A qualitative estimate of the consequences of this overlap can be made by considering the limit of complete site overlap, assuming for simplicity that the individual solute sites are hard spheres (HS). In this limit, the hard n-site solute approaches a single HS, and the water structure is determined by the presence of only a single HS site. From the FKSA-PMF expansion, the one-particle water-oxygen density around this solute placed at $r=0$ is $\rho^{(n,1)}(r)=\rho_0[g_{\mathrm{HS,O}}(r)]^{n-n(n-1)/2}$. The inset of Fig. 3 shows the FKSA-PMF result for six perfectly overlapping hard spheres, $[g_{\mathrm{HS,O}}(r)]^{-9}$. The FKSA-PMF result differs substantially from the exact curve, $g_{\mathrm{HS,O}}(r)$, where the HS-oxygen pair correlation function was calculated from a Monte Carlo simulation, but closely resembles the FKSA-PMF result for benzene; that is, the water-oxygen density is too low at contact and too high at the first minimum of $g_{\mathrm{HS,O}}(r)$. This clearly reveals the problems of low-level truncations of the PMF expansion for covalently-bonded, nonpolar molecules. All terms are needed in the PMF expansion if the volumes of individual sites overlap and the dominant interaction with water is volume exclusion.

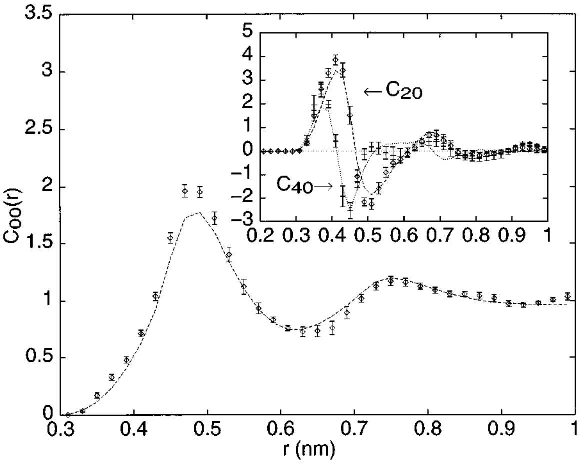

FIG. 4. C_{00} for the water-oxygen density around benzene calculated from simulation (symbols) and the two-site proximity approximation (dashed line). Inset: C_{20} and C_{40}.

Successful approaches to the treatment of hydrophobic hydration—namely, cavity statistics [14,15] and scaled particle theory [16]—provide the insights needed to devise alternative approximations. In these approaches, the formation of a cavity of an appropriate size and shape constitutes the major contribution to the solvation thermodynamics of a nonpolar molecular solute. Thus, a successful theory of hydrophobic hydration must necessarily capture the effects of solute shape and excluded volume. In fact, for the solvation of nonpolar solutes, lower order structural information might suffice if the shape and excluded volume of the solute are correctly included in the treatment. To this end, we assume that water organization is only *locally sensitive* to the structural details of the nonpolar molecular solute. Thus, in the first approximation, the inhomogeneous structure of water is determined by water correlations with only the nearest solute site. In the next higher level of approximation, $\rho^{(n,1)}$ is determined by site-site-water triplet correlations involving the two nearest solute sites,

$$\rho^{(n,1)}(\mathbf{r}_W|\mathbf{r}_1,\ldots,\mathbf{r}_n)\approx\rho_0 g(\mathbf{r}_W,\mathbf{r}_j), \tag{2a}$$

$$\rho^{(n,1)}(\mathbf{r}_W|\mathbf{r}_1,\ldots,\mathbf{r}_n)\approx\rho_0 g(\mathbf{r}_W|\mathbf{r}_j,\mathbf{r}_k), \tag{2b}$$

with j and k such that $|\mathbf{r}_W-\mathbf{r}_j|=\min_{l=1,\ldots,n}|\mathbf{r}_W-\mathbf{r}_l|$ and $|\mathbf{r}_W-\mathbf{r}_k|=\min_{m=1,\ldots,n;m\neq j}|\mathbf{r}_W-\mathbf{r}_m|$, assuming solute sites of equal size. Eqs. (2a) and (2b) are defined, respectively, as one- and two-site proximity approximations. The n-site proximity approximation would be exact. If we consider a Me-Me-O triangle where the two Me sites are covalently bonded, the Me-Me bond length corresponds to the minimum separation in all physical situations. The one-site proximity approximation in that case, is equivalent to a *modified* Kirkwood approximation [1,17], in which the triplet correlation is calculated as the product of pair correlations corresponding to the Me-Me and shortest Me-O sides of the triangle. This approximation is exact for hard rods in one dimension [18].

The coefficients C_{00}, C_{20}, and C_{40} for the density of water oxygens around benzene, predicted on the basis of the two-site proximity approximation, are now well reproduced as shown in Fig. 4. Differences between the one-site (not shown) and the two-site approximations are small, although the two-site proximity approximation is expected to perform better. We also calculated one-particle water oxygen densities around the C3 and C4 solutes using the two proximity approximations, and found that both approximations work as well as the truncated PMF expansion. Thus, the results for all four solutes support our hypothesis that water organization is sensitive only to the local details of solute structure embodied in the shape and excluded volume of nonpolar solutes, contrasting the findings for solutes with strong charge or hydrogen-bond interactions [2–6]. A similar proximity approximation has also been successfully applied to calculating water-solute pair correlation functions and entropies of hydration of normal alkanes [19].

In this study, we utilized the PMF expansion to predict the inhomogeneous water structure around nonpolar molecular solutes. For solutes consisting of clusters of nonbonded sites, the two- and three-particle PMFs make the major contributions to the $(n+1)$-particle PMF. However, for solutes consisting of bonded sites, there is a combinatorial explosion of terms in the PMF expansion in the limit of complete site overlap. Application of the PMF expansion to molecular solutes consisting of covalently bonded sites, therefore, requires knowledge of higher-order correlations to make correct predictions of the water structure. An alternative approach is to approximate the $(n+1)$-particle PMF using only lower-order, *local* water-solute PMFs that are capable of capturing the shape and excluded volume of the solute. The resultant density profiles obtained from proximity approximations constitute important input information to perform quantitative calculations of entropies of hydration [20]. Although sensitive to the details of the long-range part of the density profiles, Kirkwood-Buff integrals [21] can be used to calculate partial molar volumes.

Predictions of solvent structure using the truncated PMF expansion or the proximity approximations are 10^2 to 10^4 times faster than conventional simulation methods. The local nature of the density predictions makes these methods attractive for practical applications in which the solvation of only local regions of a macromolecular solute is of interest. The methods are flexible and can be readily applied to predicting solvent structure around complex solutes, such as biological macromolecules [4–6].

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