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The Mechanism of Hydrophobic Solvation Depends on Solute Radius

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We model the aqueous solvation of a nonpolar solute as a function of its radius. We use a simplified statistical mechanical model of water, the Mercedes Benz (MB) model, in NPT Monte Carlo simulations. This model has previously been shown to predict qualitatively the volume anomalies of pure water and the free energy, enthalpy, entropy, heat capacity, and volume change for inserting a nonpolar solute into water. We find a very different mechanism for the aqueous solvation of large nonpolar solutes (much larger than a water) than for smaller solutes. Small solute transfer involves a large hydrophobic heat capacity; its disaffinity for cold water (room temperature or below) is due to the ordering of the neighboring waters (entropic), while its disaffinity for hot water is due to the breaking of hydrogen bonds among the neighboring waters (enthalpic). In contrast, transferring large nonpolar solutes into water involves no such large changes in heat capacity or entropy. In this regard, large nonpolar solutes are not “hydrophobic”; their solvation follows classical regular solution theory. Putting a large nonpolar surface into water breaks hydrogen bonds at all temperatures. Therefore, the traditional “iceberg” model that first-shell water structure melts out with temperature should not apply to large solutes. These results also explain why the free energy of creating an oil/water interface ($75 \text{ cal } \text{\AA}^{-2} \text{ mol}^{-1}$) is greater than threefold for small molecule transfers ($25 \text{ cal } \text{\AA}^{-2} \text{ mol}^{-1}$). A key conclusion is that hydrophobicity depends not only on the surface area of a solute but also on its shape and curvature.

Introduction

The hydrophobic effect is often characterized by three experimental fingerprints: (1) a large positive free energy for transferring a nonpolar solute into water, (2) a large negative entropy at about 25 °C, and (3) a steep temperature dependence of the enthalpy and entropy of transfer, i.e., a large positive heat capacity of transfer. The microscopic basis for these behaviors remains a subject of active study.^{1–17}

These three properties are generally assumed to grow in proportion to the surface area of the solute.^{7,18–24} The first evidence that the hydrophobic effect depends on the surface areas of nonpolar solutes was based on the solubilities of hydrocarbons in water.^{25,26}

But a simple proportionality with the surface area of the solute is not sufficient to explain certain puzzles. First, the transfer free energy per unit surface area for cyclic alkanes is different than for linear alkanes.²⁷ Second, the interfacial tension between oil and water is $-75 \text{ cal } \text{\AA}^{-2} \text{ mol}^{-1}$ whereas the free energy of solvation for linear alkanes is $-25 \text{ cal } \text{\AA}^{-2} \text{ mol}^{-1}$.^{8,28–31} Third, the oil/water interfacial tension is dominated by enthalpy,²⁸ whereas the transfer of small nonpolar solutes is dominated by entropy.¹³ Fourth, the interfacial tension at oil–water interfaces has an enthalpy and entropy that are nearly temperature independent, while the enthalpy and entropy for small molecule transfer is highly temperature dependent (a large heat capacity).^{28,32} Since the geometries of hydrogen-bonded networks play an important role in the properties of water, it is natural to expect that solutes of different sizes and shapes might affect water structure differently.

There have been many models for how hydrophobic solvation depends on solute size. Among the first, scaled particle theory (SPT) estimates the work necessary to create a spherical cavity in water.^{33–36} It successfully predicts the free energy of small cavity formation³ and was constructed to give the surface tension of water in the planar limit. It was later shown that SPT predicts nearly the same result as Tolman’s thermodynamic treatment of the curvature dependence of surface tension, implying that there is a direct relationship between the macroscopic (interfacial tension) and microscopic (alkane solubility) measures of the hydrophobic effect.⁸ However, SPT has been criticized for predicting a monotonic increase in the entropy penalty of transfer with increasing cavity size³ and an incorrect temperature dependence in the surface tension.³⁵ Stillinger was perhaps the first to suggest that water solvates large nonpolar molecules differently than small molecules.³⁵

In a key early treatment, Pratt and Chandler developed an integral equation method that used pair correlations of bulk waters to predict the solubilities of small solutes.³⁷ Chandler has since shown that the Pratt and Chandler model can be interpreted in terms of a Gaussian distribution of density fluctuations in the bulk fluid.³⁸ A simple and illuminating information theory approach also predicts a Gaussian distribution.³⁹ But recently, Lum, Chandler, and Weeks have shown that larger solutes are not well-described by such Gaussian statistics, owing to long length scale inhomogeneities. The theory of Lum, Chandler, and Weeks reduces to Pratt–Chandler theory for small solutes but predicts large-scale drying as predicted by Stillinger near larger nonpolar surfaces.⁴⁰

Hummer and Garde modeled the free energies of transfer and radial distribution functions from simulations using perturbation theory^{1,2} and found good agreement between their results and simulations for small solutes ($r_{\text{solute}} \leq 3.6 \text{ \AA}$).

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Hydrophobic solvation as a function of solute size has also been studied in all-atom simulations.^{3–6,12,41–43} A key conclusion from such simulations is that at planar nonpolar surfaces water will “waste” a hydrogen bond by pointing the bond directly at the surface, in contrast to small nonpolar surfaces, where water conserves hydrogen bonds by pointing those bonds in directions that straddle the solute.^{44–46} Experimental evidence supporting this prediction has come from surface vibrational spectroscopy experiments showing that waters near a hydrophobic surface do not make a full one-fourth of their hydrogen bonds.⁴⁷

It is challenging to compute subtle properties such as entropies and heat capacities from all-atom simulations. Simulations often do not converge using Widom insertion or free energy perturbation if a solute has a radius larger than about $r_{\text{solute}} = 5 \text{ \AA}$, which is roughly three to four times the size of water. While such models can predict transfer free energies for small cavities and molecules, it is difficult or impossible to get converged heat capacities. And entropies of transfer are often model-dependent. Some water models (SPC and SPC/E) predict a monotonic increase in the unfavorable entropy of transfer as a function of solute or cavity size,^{4,5,41} while others (TIP4P) suggest a change in the entropy of transfer.^{3,12}

Thus few studies have yet explored the structural basis for the full thermodynamics—free energy, enthalpy, entropy, and heat capacity—of partitioning of nonpolar solutes over the full range of solute radii and temperatures. To do this, we resort to a simplified statistical mechanical model that can explore such principles and trends, but at the expense of atomic detail and quantitative accuracy.

The Model

We use the Mercedes Benz (MB) model of water,¹⁴ originally developed by Ben-Naim.⁴⁸ Each MB water molecule is a two-dimensional disk having three hydrogen-bonding arms, arranged as in the Mercedes Benz logo. There are two types of interactions between any two water molecules. First, there is a hydrogen-bonding interaction that favors the collinear alignment of one arm of one water molecule with one arm of another water. The hydrogen-bonding energy is a Gaussian function of the distance between the two water centers, and a Gaussian function of the orientation of the hydrogen-bonding arms, i and j , on two different waters with respect to the vector connecting the two water centers, \mathbf{u} :

$$U_{\text{HB}} = \epsilon_{\text{HB}} G(r_{ij} - l_{\text{HB}}) G(\mathbf{i} \cdot \mathbf{u}_{ij} - 1) \cdot G(\mathbf{j} \cdot \mathbf{u}_{ij} + 1) \quad (1)$$

where $G(x) = \exp(-x^2/2\sigma^2)$ is a Gaussian function, the optimal hydrogen bond length is $l_{\text{HB}} = 1$, the optimal hydrogen bond energy is $\epsilon_{\text{HB}} = -1$, r_{ij} is the distance between the two molecular centers, and $\sigma = 0.085$. Hydrogen bonding is strongest when the arms of two different water molecules are pointed directly at each other. The width, σ , of the Gaussian functions are chosen to be narrow enough to disfavor the formation of bifurcated hydrogen bonds.

Second, water molecules also interact through a Lennard-Jones (LJ) potential

$$U_{\text{LJ}}(r_{ij}) = 4\epsilon_{\text{LJ}} \left(\left(\frac{\sigma_{\text{LJ}}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{\text{LJ}}}{r_{ij}} \right)^6 \right) \quad (2)$$

where ϵ_{LJ} and σ_{LJ} are the Lennard-Jones well-depth and radius. We use $\sigma_{\text{LJ}} = 0.7A l_{\text{HB}}$ and $\epsilon_{\text{LJ}} = 0.1\epsilon_{\text{HB}}$.

Nonpolar solutes are modeled as LJ disks that have no hydrogen-bonding arms. The solute is dilute so it interacts only

with water molecules. A nonpolar solute therefore is represented by two parameters, σ_{LJ} , which defines the radius of the solute, and ϵ_{LJ} , which defines the solute's intermolecular potential with water molecules. Solutes have the same LJ well-depth as the MB waters, $\epsilon_{\text{LJ}} = 0.1\epsilon_{\text{HB}}$. The standard Lorentz–Berthelot geometric combining rules are assumed in calculating the solute–water interaction energy as solute radius changes.⁴⁹

The limitations of the model are obvious: it is two-dimensional, hydrogen bond donors are not distinguished from acceptors, and electrostatics is not included. Nevertheless, we believe this model captures the main physics of nonpolar solvation, namely Lennard-Jones attractions and repulsions, and an orientation-dependence that stems from hydrogen bonding. Because the model is two-dimensional, we have less configurational space to sample, which allows us to get good convergence for subtle properties such as heat capacities. Despite these simplifications, the MB model has previously been shown to qualitatively predict the volume anomalies for pure water—a density minimum, a negative thermal expansion coefficient, and a minimum in the isothermal compressibility. The MB model also predicts the trends for the temperature dependence of the free energy, entropy, enthalpy, heat capacity, and volume change of hydrophobic solute transfer.¹⁴

Methods

We explore the properties of a single nonpolar solute in MB water using NPT Monte Carlo simulations with periodic boundary conditions and the minimum-image convention.¹⁴ Each simulated insertion process involves 60 MB waters (which is equivalent to a 3D simulation having about 500 particles). The move set was adjusted to yield a 50% move acceptance ratio. To hold pressure constant, every five passes the program attempts to rescale the box length and component particles. A distance cutoff eliminated hydrogen-bonding energies smaller than $1 \times 10^{-10}\epsilon_{\text{HB}}$. Since the model hydrogen bonds have a narrow angular distribution, only the two closest arms on two neighboring waters need to be sampled to calculate hydrogen bonding between two molecules (this still allows for the formation of bifurcated hydrogen bonds, although they are not common). Errors shown in the figures represent 1 standard deviation of the block averages. Most simulations were done at a reduced temperature of $t^* = 0.18$ ($t^* = k_{\text{B}}T/|\epsilon_{\text{HB}}|$). We take this to correspond to a cold liquid state. MB water undergoes a freezing transition at about $t^* = 0.16$.⁵⁰ The temperature range we explored as being representative of liquid water was $t^* = 0.18$ – $t^* = 0.28$.

We also simulated MB water adjacent to a two-dimensional hydrophobic LJ plane. The width of the plane was $1.0l_{\text{HB}}$. Periodic boundary conditions create an infinite plane. The simulation was done at constant pressure. The average size of the plane at each integration point was used to calculate thermodynamic quantities per unit area.

We used three different types of Monte Carlo procedures. First, we simulate the solute particle solvated by 120 MB water molecules, typically for 10^8 steps, 2×10^7 of which were equilibration. In these simulations, we define the first solvation shell as the first minimum in the solute–water pair correlation function. The angular orientation of the shell waters was found as the angle between the vector for the water's hydrogen-bonding arm and the vector connecting the solute and water centers.

Second, to determine the free energy, entropy, enthalpy, and heat capacity of transfer, we used the Widom insertion process.⁵¹ For these simulations, we usually used 60 MB waters and a

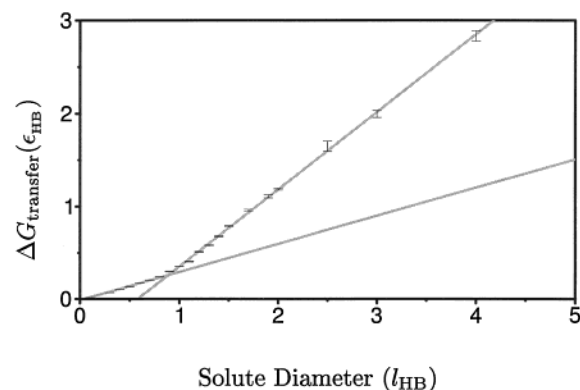


Figure 1. MB free energy of transfer as a function of solute diameter at $t^* = 0.18$, shown with error bars. In gray are the two linear regressions of the free energy data.

test particle, which were run for about 10^8 steps, depending on the size of the solute and the number of particles. Third, a thermodynamic integration procedure was used for larger particle insertions. Our multi-stepped thermodynamic integration converges well for the free energies of transfer, but not quite as well for the heat capacities.

To check whether we included sufficient solvent in the large solute transfers, we ran additional simulations with different numbers of waters. Increasing the number of waters affects the transfer thermodynamics, especially for the larger solutes, but these effects are small. This is because the excess entropy and enthalpy of transfer in a constant pressure simulation are localized to the immediate area of the solute.⁵²

Solute-Transfer Thermodynamics Depends on the Solute Radius

Large Nonpolar Solutes Have a Different Transfer Mechanism than Small Solutes. Figure 1 shows the free energy of transfer for a solute into MB water at temperature $t^* = 0.18$, which we take as a model for cold liquid water. We find that for small solutes (up to around the size of a water molecule), the free energy grows in proportion to the solute radius. In a two-dimensional model like ours, a free energy that is linear with solute radius is linear with circumference. In a 3D model, this would correspond to a free energy that is linear with surface area. Hence a straight line in Figure 1 is anticipated by conventional wisdom.

What is unexpected, however, is that for large solutes the free energy of transfer grows faster with the solute radius than it does for the solvation of small solutes. This indicates a different solvation mechanism for large solutes than for small ones. Below, we explore the thermodynamic and structural bases for these two mechanisms.

The Entropy and Enthalpy Reversal with Solute Radius. The enthalpy and entropy of transfer are more interesting than the free energy for two reasons: (1) they are more directly related to the microscopic driving forces, and (2) their slopes do not merely steepen with solute radius; both slopes change sign. Below a certain reduced solute diameter, $d_{\text{solute}} = l_{\text{HB}}$, the MB model shows the classical hydrophobic behavior: as solute size grows, $\Delta G_{\text{transfer}}$, $\Delta C_{p,\text{transfer}}$ and $-T\Delta S_{\text{transfer}}$ become more positive (see Figure 2).

In contrast, for solutes larger than $d_{\text{solute}} = l_{\text{HB}}$, insertion into water is *opposed* by $\Delta H_{\text{transfer}}$ and *avored* by $T\Delta S_{\text{transfer}}$. Because the slopes of both the enthalpy and entropy change signs for large solute radii, they compensate: the slope of the free energy

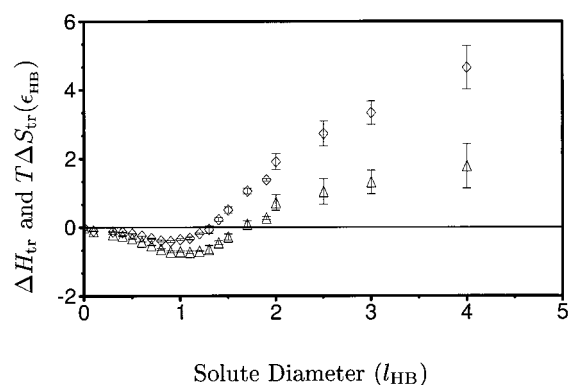


Figure 2. MB (Δ) entropy and (\diamond) enthalpy of transfer as a function of solute diameter at $t^* = 0.18$, shown with error bars.

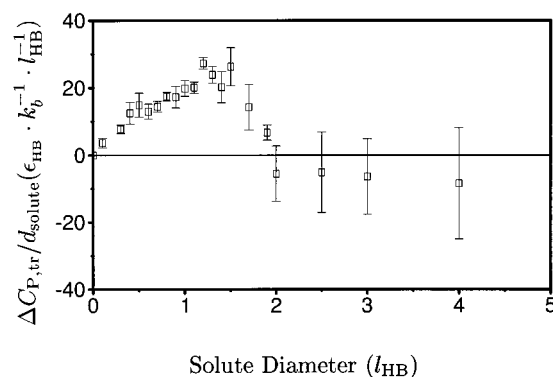


Figure 3. MB (\square) heat capacity of transfer as a function of solute diameter at $t^* = 0.18$, shown with error bars.

also changes, but the sign of its slope does not. Similar compensations have been found in other simulations.^{12,53}

Our simulations on planar nonpolar surfaces give the same values for the free energy, entropy, enthalpy, and heat capacity of transfer per unit surface area as the results from our spherical solutes extrapolated to infinite radii. For example, the slope of the free energy of transfer versus large solute radius gives $0.265\epsilon_{\text{HB}}/l_{\text{HB}}$, while for planes we find $((0.260 \pm 0.004)\epsilon_{\text{HB}}/l_{\text{HB}})$.

A prediction of a changeover in physics for large hydrophobic surfaces is consistent with experiments on planar interfaces. Experimental measurements show that interfacial tension (γ) has a favorable entropy ($-\partial\gamma/\partial T > 0$) and a large unfavorable enthalpy ($\gamma - T(-\partial\gamma/\partial T) > 0$).²⁸

The Heat Capacity of Transfer Depends on Solute Radius.

Figure 3 shows how the heat capacity of transfer depends on solute size. Large solutes (left side of the figure) have $\Delta C_{p,\text{transfer}} \approx 0$. This prediction is consistent with interfacial tension experiments, from which a negligible heat capacity change is inferred.⁵⁴ The largest heat capacity of transfer is predicted to occur at roughly $d_{\text{solute}} = 1.5l_{\text{HB}}$, unlike the free energy which peaks at about $d_{\text{solute}} = 1.0l_{\text{HB}}$, although both these values may be different in 3D models.

There is a large universe of molecules that do not mix with others, so a positive free energy of mixing does not require the kind of special terminology that is invoked by the term "hydrophobic". One of the most important thermodynamic fingerprints of the hydrophobic effect is the large $\Delta C_{p,\text{transfer}}$ that is observed for small nonpolar solutes in water. One of the main conclusions from the present paper is that $\Delta C_{p,\text{transfer}}$ is predicted to be approximately zero for the aqueous solvation of large nonpolar solutes. In that regard, if hydrophobicity is defined

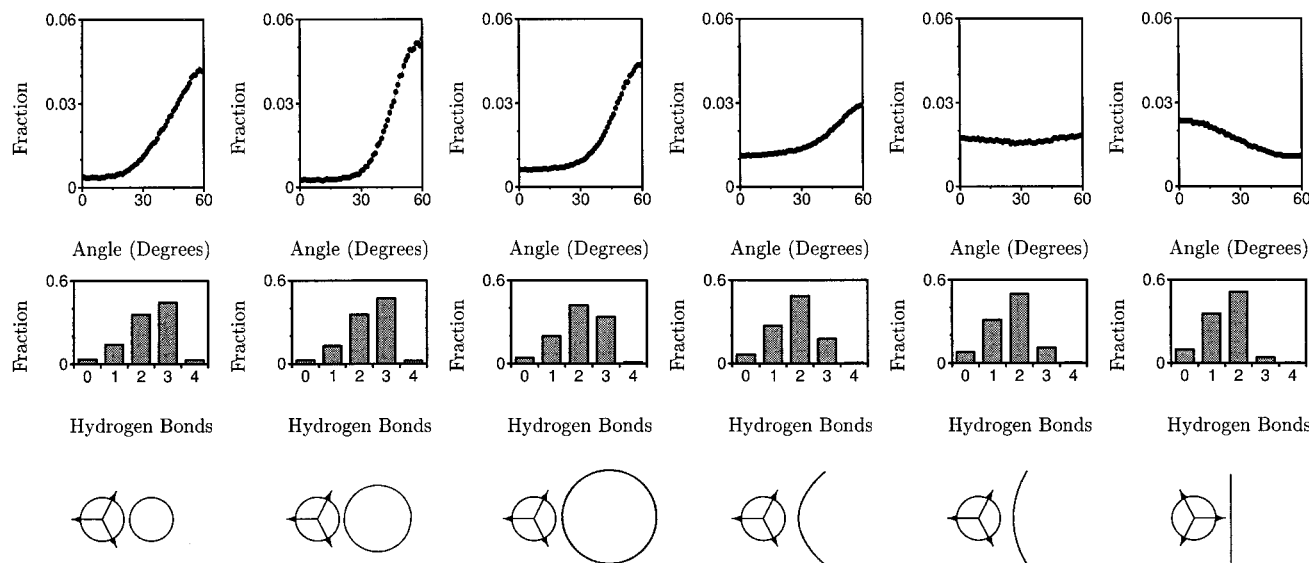


Figure 4. Angular preference for first-shell waters, percentage of hydrogen bonds made, and the size of solutes relative to an MB water for solutes of size $0.70l_{\text{HB}}$, $1.07l_{\text{HB}}$, $1.50l_{\text{HB}}$, $2.00l_{\text{HB}}$, $3.00l_{\text{HB}}$, and a planar solute, at $t^* = 0.18$. The MB model allows for a continuum of particle separations and hydrogen bond angles. Nevertheless, we find that the Monte Carlo simulation data can often be well-captured using a long-standing simplification, namely, that hydrogen bonds among first-shell water molecules fall into two categories, made and broken.^{55,56} We use a cutoff energy of $0.33\epsilon_{\text{HB}}$ to distinguish between made and broken hydrogen bonds. The results of this analysis are insensitive to the exact cutoff used.

by this particular thermodynamic signature, then large nonpolar solutes are not “hydrophobic”. Of course, if “hydrophobic” is instead defined as “nonpolar”, then solute size is irrelevant to the terminology.

The Structural Basis for the Mechanisms of Aqueous Solvation

A large nonpolar solute imposes a different geometric constraint than a small molecule does on neighboring waters. While 2D is clearly different than 3D, nevertheless the principles of geometric constraints readily generalize. Figure 4 shows the distribution of orientations of first-shell waters around solutes of different diameters. Around small solutes, waters tend to straddle the solute (an angle of 60°) to avoid wasting hydrogen bonds. This tendency is more pronounced for water-sized solutes than for very small solutes. For very large solutes, MB waters tend to point a hydrogen bond directly at the surface (an angle of 0°), in agreement with the results of Rossky et al.^{44,45} Remarkably, for solutes having radii between these two extremes, the MB model predicts much less angular preference than in either of these limits, indicating that in those cases the angular preferences of waters contribute little to solvation thermodynamics.

The problem encountered by a first-shell water molecule around a small solute is how it can orient properly to make all of its hydrogen bonds (see Figure 4) in the presence of the nonpolar obstacle. First-shell waters can make all three hydrogen bonds by straddling the solute. At low temperatures, this is mainly an entropy problem: the water loses orientational entropy to achieve maximal hydrogen bonding.

But around a large solute, a first-shell water is subjected to a very different constraint than around a small solute. A first-shell water molecule cannot straddle a large surface to form three hydrogen bonds (see Figure 4). At most, a surface water can form two hydrogen bonds. This is mainly an enthalpy problem because transferring a water from the bulk to the first shell results in the loss of one hydrogen bond. There is not much entropy loss because “wasting” a hydrogen bond by pointing it

at a large nonpolar surface can be done in different ways via various water orientations.

In cold water, the disaffinity of small solutes for water is described by $\Delta S \ll 0$ and $\Delta C_p \gg 0$ while the disaffinity of large solutes for water is described by $\Delta H \gg 0$ and $\Delta C_p \approx 0$. The explanation is that small solutes cause ordering among the first-shell waters (accounting for the $\Delta S \ll 0$), to avoid breaking hydrogen bonds, but that this first-shell ordering “melts out like an iceberg” (accounting for the $\Delta C_p \gg 0$). In contrast, a large nonpolar solute forces first-shell waters to break hydrogen bonds (accounting for the $\Delta H \gg 0$), which undergo very little additional breakage with temperature (hence $\Delta C_p \approx 0$). Figure 5 shows this comparison.

Because these are different physical mechanisms, there is no particular reason to expect the slopes of the free energy of transfer to grow with solute size in the same way for small and large solutes. We find in the model that the ratio of slopes of the free energy of transfer against size for large and small solutes is 2.4, which is to be compared to the factor of 3 obtained from the experimentally determined ratio of interfacial tensions ($75 \text{ cal } \text{\AA}^{-2} \text{ mol}^{-1}$) to small solute transfers ($25 \text{ cal } \text{\AA}^{-2} \text{ mol}^{-1}$). A three-dimensional model might lead to a factor different than 2.4. However, we believe that in three dimensions, the same principle applies, namely, that the higher cost for large interfaces than for small interfaces is the difference between hydrogen bond breakage enthalpies and water-ordering entropies.

Comparison to Experiments and Simulations

There are many experiments on small nonpolar solutes, but very few on large solutes. However, experiments show that the enthalpic component of the oil/water interfacial tension is large and unfavorable and that the entropic component is smaller and favorable,²⁸ consistent with the MB model predictions. Other large nonpolar surfaces include those on proteins and surfactant micelles. Micellization experiments are often best modeled assuming a large enthalpy and a smaller entropy, for example, in the sphere-to-rod transition of SDS micelles,^{54,58} the association of bile salt micelles,⁵⁹ and other studies of alkyl sulfate micelles.⁶⁰

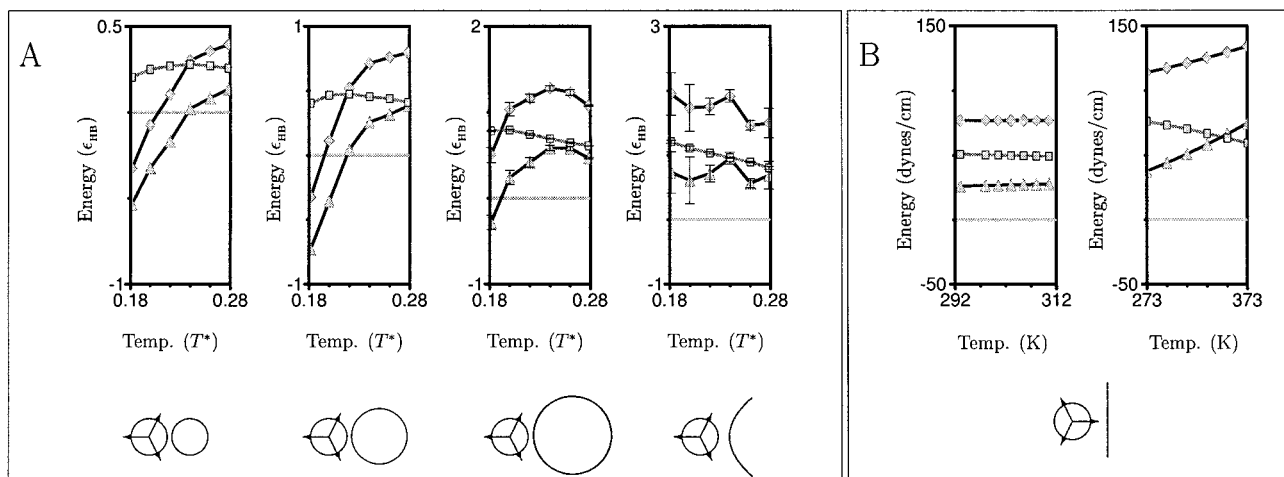


Figure 5. (A) MB (\square) free energy, (\diamond) enthalpy, and (Δ) entropy of transfer as a function of temperature and solute diameter, shown with error bars. Results presented are for solutes with diameters (from left to right): $0.70l_{HB}$, $1.07l_{HB}$, $1.50l_{HB}$, $2.00l_{HB}$. (B) The experimental (\square) interfacial tension ($\gamma = \partial G/\partial A$), (\diamond) interfacial energy ($\gamma - T\partial\gamma/\partial T$), and (Δ) interfacial entropy ($-T\partial\gamma/\partial T$) for a hexane–water interface (on the left)²⁸ and an air–water interface (on the right).⁵⁷

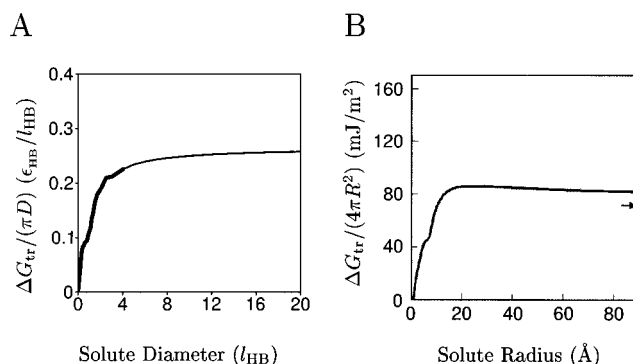


Figure 6. Free energy of transfer per unit surface. (A) MB simulation data is shown. The free energy linear regression was used to extrapolate to very large solute sizes. (B) The excess chemical potential for a hard sphere of radius R in water predicted by the theory of Lum, Chandler, and Weeks. The arrow indicates the value for the surface tension of water. Data taken from ref 40.

If planar nonpolar surfaces disrupt some hydrogen bonding of first-shell waters, then this enthalpy problem should be even worse inside concave nonpolar cavities. The complexation of benzene or arene with cyclophane results in the desolvation of a large hydrophobic cavity. This reaction is enthalpically driven.^{61,62} Similar thermodynamics are seen in the binding of aromatic substrates to hydrophobic pockets in enzymes, antibodies, cyclodextrins, and DNA.⁶²

Lum, Chandler, and Weeks have also recently predicted a substantial change in the physics of the hydrophobic effect as the solute size increases.⁴⁰ Figure 6 compares the free energy of transfer from the simulations of MB water with the predictions of their theory for water. Both approaches show a similar changeover in behavior, and, for very large solutes, a free energy of transfer that scales linearly with the amount of surface. As Lum et al. have noted, this means that for small solutes the free energy of transfer is not directly proportional to surface area. We have not explored the drying predicted by Lum, Chandler, and Weeks⁴⁰ or Stillinger.³⁵ We do not see a dramatic lowering of the density of water adjacent to large nonpolar solutes. However, our time and space scales for the simulation may be too short to see it.⁶³ Also, the phase diagram for MB model water is not yet known. We also would not see drying if the pressures in our model simulations are high.

Conclusions

What is the hydrophobic effect, and what drives it? Hydrophobicity is usually defined as the unusual thermodynamics that results from transferring a nonpolar solute into water: a large positive heat capacity, which results in a large positive free energy—a large negative entropy in cold water, and large positive enthalpy in hot water. These properties have been explained in various models, including the present MB study, in terms of the geometric constraint imposed by the nonpolar solute mainly on first-shell water molecules. Inserting a solute into cold water orders waters, costing entropy. Inserting a solute into hot water breaks water hydrogen bonds, costing enthalpy.

Here we also study how hydrophobic solvation depends on the solute radius. We find that the disaffinity of large nonpolar solutes for water has a different physical basis than for small solutes. For large solutes, the disaffinity is mainly enthalpic. Transferring large nonpolar solutes should not involve any of the classical large entropy or heat capacity that is usually taken to define the hydrophobic effect. The structural basis for the mechanism we find in the MB model is the same as has been found by Rossky et al.:^{44,45} water molecules must break hydrogen bonds to come into contact with large nonpolar surfaces. In addition, the MB model gives an explanation for why interfacial tensions at oil/water interfaces have free energies per unit surface area that are about threefold higher than small molecule transfer experiments. More broadly, a main conclusion is that the energetics of nonpolar solvation depend not only on the solute surface area but also on its shape and curvature.

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