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Potential of mean force of association of large hydrophobic particles: towards the nanoscale limit

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Abstract

The potentials of mean force (PMFs) were determined, in both water with the TIP3P water model and *in vacuo*, for systems involving formation of nonpolar dimers composed of bicyclooctane, adamantane (both an all-atom model and a sphere with the radius of 3.4 Å representing adamantane), and fullerene, respectively. A series of umbrella-sampling molecular dynamics simulations with the AMBER force field were carried out for each pair, under both environmental conditions. The PMFs were calculated by using the Weighted Histogram Analysis Method (WHAM). The results were compared with our previously-determined PMF for neopentane. The shape of the PMFs for dimers of all four nonpolar molecules is characteristic of hydrophobic interactions with contact and solvent-separated minima, and desolvation maxima. The positions of all these minima and maxima change with the size of the nonpolar molecule; for larger molecules they shift toward larger distances. Comparison of the PMFs of the bicyclooctane, adamantane, and fullerene dimers in water and *in vacuo* shows that hydrophobic interactions in each dimer are different from that for the dimer of neopentane. Interactions in the bicyclooctane, adamantane, and fullerene dimers are stronger *in vacuo* than in water. These dimers cannot be treated as classical spherical hydrophobic objects. The solvent contribution to the PMF was also computed by subtracting the PMF determined *in vacuo* from that in explicit solvent. The solvent contribution to the PMFs of bicyclooctane, adamantane, and fullerene is positive as opposed to that of neopentane. The water molecules in the first solvation sphere of both adamantane and neopentane dimers are more ordered compared to bulk water, with their dipole moments pointing away from the surface of the dimers. The average number of hydrogen bonds per water molecule in the first hydration shell of adamantane is smaller compared to that in bulk water, but this shell is thicker for all-atom adamantane than for neopentane or a spherical model of adamantane. In the second hydration shell, the average number of hydrogen bonds is greater compared to that in bulk water only for neopentane and a spherical model of adamantane but not for the all-atom model. The strength of the hydrophobic interactions shows a linear dependence on the number of carbon atoms both in water and *in vacuo*. Smaller nonpolar particles interact more strongly in water than *in vacuo*. For larger molecules such as bicyclooctane, adamantane and fullerene, the reversed tendency is observed.

Keywords

hydrophobic interactions; umbrella sampling; molecular dynamics simulations; large nanoparticles

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1. Introduction

Hydrophobicity is manifested as both the low solubility of nonpolar solutes in water (hydrophobic hydration) and the strong attraction of nonpolar groups or surfaces in water (hydrophobic interactions). The nature of hydrophobicity depends both on temperature and on the size of the interacting nonpolar particles or surfaces.^{1,2}

Near room temperature, the hydrophobic hydration of small nonpolar particles is dominated by the entropy term, which results in a positive free energy of solution and accounts for the low solubility. There is a strong temperature dependence of the affinity of small nonpolar groups for water: their solubility in water decreases when the solution is heated and increases when the system is cooled near room temperature. At higher temperatures, the energetic term dominates over the entropy term.^{3,4}

For larger nonpolar particles, hydrophobicity at room temperature is dominated by energetic factors.² Additional effects are observed for mesoscopic or macroscopic size nonpolar particles, for example, planar nonpolar surfaces. Long-range hydrophobic interactions between macroscopic hydrophobic surfaces can be induced by a dewetting⁵ transition or capillary cavitation or by the formation of vicinal microbubbles.^{6,7} Direct force measurements between macroscopic surfaces are one of the most powerful methods for studying hydrophobicity. As reviewed in Meyer et al.,⁸ such measurements have thus far been focused on interactions between macroscopic or microscopic (but not nanoscopic) surfaces. The interactions between macroscopic nonpolar surfaces and those between small nonpolar solutes or molecular groups should be qualitatively the same (i.e. the force law should be “pairwise additive”), but there has been no simple way to relate these interactions quantitatively.⁸ Multibody interaction terms in hydrophobic association can account for these difficulties. For this purpose, we have studied the distance dependence of the multibody contribution to the potential of mean force for three^{9,10} and four¹¹ small nonpolar molecules.

The crossover of hydrophobic interactions from a small molecular scale to a large macroscopic scale was predicted to occur at a nanoscopic scale (about 10 Å in length) in the size of nonpolar particles.¹² The cavity solute model of Lum et al.¹² stresses that the hydrophobic effect has a significant length-scale dependence. Because of their size (about 10 Å), fullerenes have been the subject of theoretical studies of nanoscale hydrophobic interactions. The results show that they behave neither like classical nonpolar molecules nor nonpolar surfaces because of strong van der Waals interactions (due to the high density of surface atoms) between the fullerene molecules as well as between the fullerene molecules and the surrounding water molecules.^{13,14} The attraction between two fullerenes is actually weaker in water than *in vacuo*.^{13,14} Hotta et al.¹⁵ computed PMFs for a pair of fullerenes, and studied the hydration structure around a single fullerene and a pair of fullerenes using molecular dynamics simulations. For the single solute, they observed that water molecules form a fluctuating cage surrounding the solute because they are attracted to the fullerene due to the dispersion interaction. When a pair of fullerenes approached each other, the number density of water molecules in the region between the solutes showed large fluctuations described as “fluctuating drying”.¹⁵ Hotta et al. concluded that fluctuating drying and caging affect the hydrophobic interactions between two fullerenes.

Because of the low solubility of nonpolar compounds in water, hydrophobic association of model compounds cannot be measured experimentally, except for a homologous series of molecules with polar head groups and an increasing size of the nonpolar tails;^{3,4,16-18} therefore, theoretical studies remain the main source of our knowledge about this phenomenon for simple model systems. The present work is a continuation of our theoretical studies on the dependence of hydrophobic association on solute size.¹⁹ In this paper, we try to address the nanoscopic crossover region by comparing the potentials of mean force (PMFs) of hydrophobic association

of pairs of nonpolar particles with diameters close to 10 Å. Dimers of neopentane,¹⁹ and bicyclooctane (bicyclo[2.2.2]octane), adamantane (tricyclo[3.3.1.1.]decane) and fullerene (C₆₀) in water and *in vacuo* were simulated by molecular dynamics.

2. Methods

Sampling of the configurational space, necessary in the umbrella-sampling method, was carried out by using molecular dynamics (MD) simulations for the following all-atom models of nonpolar dimers, i.e., two bicyclooctane molecules, two adamantane molecules, and two fullerene (C₆₀) molecules. For comparison the results of two neopentane molecules were taken from our previous work.¹⁹ The dimers were immersed in TIP3P²⁰ water boxes with periodic boundary conditions with a box side of about 53 Å, 54 Å, and 58 Å for bicyclooctane, adamantane, and fullerene, respectively. Molecular dynamics simulations were carried out in two steps. In the first step, each system was equilibrated in the NPT ensemble (constant number of particles, pressure, and temperature) at 298 K for 100 ps. Production MD simulations were then run in the NVT ensemble (constant number of particles, volume, and temperature). In all MD simulations, the integration time step was 2 fs. A 10 Å cut-off was used for all nonbonded interactions, and the electrostatic energy was evaluated by using the particle-mesh Ewald summation.²¹ For each system, a series of 22 (for bicyclooctane, and adamantane) and 30 (for fullerene) windows of 10 ns simulations per window was run with different harmonic-restraint potentials V imposed on the distance (d) between the two atoms (one from each particle) closest to the center of the mass of each of the molecules (indicated by the stars in Figure 1), as given by Eq. (1).

$$V(d) = k(d - d_o)^2 \quad (1)$$

with the force constant $k = 2 \text{ kcal/mol/Å}^2$, and the “equilibrium” distance (d_o) for a given window equal to 3.5, 4.0, ..., 14.0 Å for bicyclooctane and adamantane dimers, for windows from 1 to 22; and 3.5, 4.0, ..., 18.0 Å for the fullerene dimer, for windows 1 to 30, respectively. Snapshots from the MD simulations were saved every 0.2 ps. A total number of 50,000 configurations were collected for each window.

The charges on the atoms of the solute molecules needed for the AMBER 8.0²² force field were determined for each system except fullerene using a standard procedure for fitting the point-charge electrostatic potential to the molecular electrostatic potential computed by using the electronic wave function calculated at the restricted Hartree-Fock (RHF) level with the 6-31 G* basis set. The program GAMESS²³ was used to carry out the quantum-mechanical calculations, while the program RESP²⁴ of the AMBER 8.0 package was used to compute the fitted charges. The molecules in this work are shown in Figure 1. The charges and the AMBER atom types are shown in Table 1. For fullerene (C₆₀), all carbon atoms had AMBER atom type of aromatic carbon (“CA”) and the charge on each of them was 0.000 e.

To determine the potentials of mean force (PMFs) for the systems studied, we processed the results from all windows of the restrained MD simulations for each system using the Weighted Histogram Analysis Method (WHAM).^{25, 26} Because the molecules studied are nearly spherical, one-dimensional histograms, dependent only on the distance between the geometric centers of the interacting molecules, were constructed. The bin dimension applied in the WHAM calculations of the PMF was equal to 0.1 Å for all systems. The calculated PMFs should tend to zero with increasing distance (after subtracting the constant factor accounting for the hydrophobic-hydration free energy of an *isolated* solute molecule). For bicyclooctane and adamantane the PMF baseline value was computed as an average of the PMFs at distances

from 12.5 to 14.0 Å, while the average PMF at distances from 16.5 – 18.0 Å was the PMF baseline value for fullerene.

To determine the PMFs for pairs of the all-atom nonpolar dimers *in vacuo*, a similar computational procedure was used as described above. The only difference was the use of shorter MD simulations, i.e., 5 ns per window.

Additionally, two spheres of zero charge and radius 3.4 Å (with values 3.4 Å for the van der Waals radius and well-depth 2.8 kcal/mol estimated based on the PMF *in vacuo* for the adamantane dimer) were immersed in a TIP3P²⁰ water box with periodic boundary conditions with a box side of about 50 Å. Molecular dynamics simulations were carried out in two steps as in the previous cases. A series of 11 windows of 2 ns simulations per window was run with different harmonic-restraint potentials imposed on the distance (d) between the two spheres, as given by Eq. (1). The “equilibrium” distance (d_o) for a given window was equal to 4.0, 5.0, ..., 14.0 Å for two spheres representing the adamantane dimer. The data were processed as for all-atom calculations, except that the PMF baseline value was computed as an average of the PMF at distances from 12.5 to 14.0 Å. A total number of 10,000 configurations were collected for each window.

Figure 2 shows the dependence of the PMF for the fullerene dimer, obtained using the umbrella-sampling/WHAM method, on the number of configurations collected from each window using the TIP3P water model calculations as an example. As seen from Figure 2, convergence is achieved as the number of configurations increases. The same convergence was observed for the remaining dimers.

We also analyzed the packing, interactions, and orientations of water molecules in the vicinity of the solutes. In the umbrella sampling simulations, only the Cartesian coordinates of the solute molecules were stored for the PMF calculations. To determine the distribution, orientation and number of hydrogen bonds of water molecules around the interacting solutes, we ran an additional 5 ns of MD simulations for adamantane; harmonic restraints were imposed to keep the monomers at selected distances (namely, the contact minimum, the desolvation barrier, and the solvent-separated minimum distances, respectively), and the Cartesian coordinates of all atoms were stored every 0.2 ps for further analysis. Because the dimer systems have cylindrical symmetry, we expressed the distributions in the cylindrical coordinates h (the axis linking the centers of the solute molecules) and r (an axis perpendicular to h) (see Figure 3a); all distributions are averaged over the azimuthal angle θ . We computed the distribution function of the water molecule density normalized to 1 for bulk water, the average number of hydrogen bonds between water molecules, and the average values of the cosine of the angle ω between the dipole moment of a water molecule and the r axis (see Figure 3) at all points of the two-dimensional grid in h and r around the dimers. Two-dimensional maps for all distributions were prepared with a 0.2 Å grid. Two water molecules were considered to be hydrogen bonded^{27,28} if the oxygen...oxygen distance was not greater than 3.5 Å and, simultaneously, the H–O · · · O angle α was not greater than 30° (see Figure 3a). In addition, we calculated the distributions of the average number of nearest water neighbors for water molecules around the adamantane, using the same 3.5 Å oxygen...oxygen distance cutoff, and the distributions of average binding energies between these nearest-neighbor water molecules, normalized per molecule or per pair of interacting molecules.

Later, we also analyzed the packing, interactions, and orientations of water molecules in the vicinity of single solute molecule. The PMF calculations for a single all-atom adamantane molecule and a single sphere with the radius of 3.4 Å representing adamantane were run using a similar procedure as for two adamantane molecules. To determine the distribution and number of hydrogen bonds of water molecules around the single solutes, we ran an additional 1.5 ns

of MD simulations for a single adamantane molecule and sphere with the radius of 3.4 Å, respectively, and the Cartesian coordinates of all atoms were stored every 0.2 ps for further analysis.

We computed the normalized distribution function of the water molecule density, the average number of hydrogen bonds between water molecules (see Figure 3b) at all points of the two-dimensional grid in h and r around the single molecules. All maps for single molecules were prepared as for the dimer simulations.

3. Results and Discussion

Figure 4a-d shows the results of the calculations of the PMF in the TIP3P water box (solid line) and *in vacuo* (dotted line) for neopentane¹⁹ (Figure 4a), bicyclooctane (Figure 4b), adamantane (Figure 4c), and fullerene (Figure 4d) dimers, using the umbrella-sampling/WHAM method.

The PMF curves (solid lines) have characteristic shapes with one deep minimum each at about 5.8 Å, 6.2 Å, 6.8 Å, and 9.7 Å, corresponding to neopentane, bicyclooctane, adamantane, and fullerene, respectively. This minimum is referred to as the contact minimum. The deepest contact minimum is observed for the fullerene (Fig. 4d) dimer with a depth of about -4.3 kcal/mol. Less deep contact-minima are observed for the remaining nonpolar dimers and are about -1.05, -1.5, and -1.75 kcal/mol, for neopentane, bicyclooctane, and adamantane, respectively.

The PMF curves shown in Figure 4 also contain the second minima at distances of about 9.2, 9.8, 10.2, and 13.0 Å for neopentane, bicyclooctane, adamantane, and fullerene, respectively. These so-called solvent-separated minima correspond to distances at which one water molecule can enter the space between the two solutes.

The first maximum in the PMF curves between the contact and solvent-separated minima is referred to as the desolvation maximum. Desolvation maxima (approximately 0.3-0.4 kcal/mol) are observed for all dimers (solid line). As seen from Figure 4, the positions and heights of these maxima change according to the size of the solute. The same variations of positions are observed for the solvent-separated minimum of the dimers investigated in this study.

Figure 4 also shows the PMFs obtained *in vacuo* (dashed-lines) for the nonpolar particles investigated in this study. All PMFs obtained *in vacuo* have the characteristic shape of the Lennard-Jones-like potential. As with the curves obtained in explicit solvent, the positions and depths of the minima change with the size of the solutes. The minimum with the smallest depth is observed for the neopentane (Fig 4a) dimer, being about -0.95 kcal/mol at position 6.0 Å. The deepest minimum *in vacuo* is observed for fullerene, being about -9.2 kcal/mol at position 9.8 Å. The positions of these minima in the PMF curves for all the dimers are shifted *in vacuo* toward greater distances with increasing size, and differ in magnitude from the positions of the contact minima obtained in water. For all dimers, the contact-minimum in water occurs at shorter distances than *in vacuo*. But for bicyclooctane, adamantane, and fullerene the difference in distance between these minima is smaller. Also bicyclooctane, adamantane, and fullerene have deeper minima *in vacuo* than in water. For the fullerene dimer the contact minimum *in vacuo* is deeper than in water about -5 kcal/mol, demonstrating that the influence of water is less important than that of van der Waals forces in hydrophobic interactions of large nanoparticles. Fullerenes (C₆₀) cannot be treated as classical hydrophobic particles. In their work^{13,14} based on PMF analysis of two fullerenes, Li and coworkers found that the interaction in water is weaker than *in vacuo*. They also concluded that, in contrast to hydrophobic particles of the same size, the effective interactions between fullerene molecules in water are diminished compared to that in vacuum. The depth of the minima of the vacuum PMFs and the depths of the contact minima of the PMFs in water are summarized in Table 2.

In Figure 5, we present the solvent contribution to the PMF determined as a difference between the PMFs in solvent and those *in vacuo*. As seen from Figure 5, the solvent has a positive contribution to the PMFs at contact distance for bicyclooctane, adamantane and fullerene dimers over the whole distance range, which is in opposition to neopentane and smaller nonpolar molecules.¹⁹ The highest solvent contribution to the PMF is observed for fullerene (the largest solute).

As follows from the discussion above, the increase in the size of a nonpolar solute results in much slower increase of the depth of the contact minimum in water than could be anticipated based on the increase of particle size (Table 2). The detailed shape of the solute does not have much effect, i.e. the contact minimum in water is less deep, for both the adamantane dimer and the dimer of van der Waals particles with adamantane size. The depth of the minimum of the vacuum PMF increases much faster. This observation is expressed quantitatively with Figure 6, in which the depth of the minima of the vacuum PMF and the depth of the contact minima of the PMF in water are plotted as functions of the number of carbon atoms. Fullerene was omitted from the plot in Figure 6 because its large size is incompatible with the scale of the abscissa. In both vacuum and in water, a good correlation between the number of carbon atoms and the depth of a minimum is observed; however, the slope is about 2 times greater for the depth of the minima of the vacuum PMF, as can be seen from eqs. (2) and (3).

$$\varepsilon = 0.298 (0.028) \cdot n - \text{carbons} - 0.248 (0.154) \quad R^2 = 0.96 \quad (2)$$

$$\varepsilon = 0.126 (0.013) \cdot n - \text{carbons} + 0.456 (0.075) \quad R^2 = 0.95 \quad (3)$$

For smaller molecules, interactions are stronger in water than in vacuum, and for larger molecules the trend is the opposite; the larger molecules interact more strongly in vacuum than in water. For isobutane (overlapping points in the plot at $n = 4$ carbon atoms) and neopentane ($n = 5$ carbon atoms) the strengths of the interactions in water and *in vacuo* are very similar. This means that neopentane can be treated as the border-line molecule between smaller and larger hydrophobic particles. For solutes larger than neopentane, the minima of the vacuum PMFs are deeper than those of the corresponding PMFs in water or, in other words, the solvent contribution to the PMF is positive.

An analysis of the structure of water in the vicinity of the solute particles can provide new physical insight about the molecular origin of hydrophobic interactions. We calculated two-dimensional distribution functions describing the water density, the average number of hydrogen bonds between water molecules, and the average value of the cosine of the angle ω of the orientation of water molecules with respect to the r axis (see Figure 3a).

Two-dimensional maps of the normalized distribution function of the water molecule density around the adamantane dimer at three selected distances between the centers of the solute molecules (6.8, 8.8 and 10.2 Å, respectively) which corresponds to the contact minimum, the desolvation barrier, and the solvent-separated minimum configurations, respectively, are shown in Figure 7. The normalized distribution function of the water density around the adamantane dimer, shown in Figure 7 (a-c), is different from those for methane and neopentane (Figure 7, d-f) at corresponding distances published in our previous paper.¹⁹ The solvation spheres around adamantane (blue and light blue) are wider and closer to the contact point than those for methane and neopentane.¹⁹ For methane and neopentane, water accumulated close to the molecular surface (green and yellow Figs 7d-f) especially at the bisector plane ($h = 0$) between the neighboring molecules (red Figs. 7d-f), where the first solvation spheres of two

monomers overlap.¹⁹ This is not observed for adamantane, for which the first solvation sphere (blue and light blue) has lower density than bulk water (Figs. 7a-c). A single adamantane molecule is larger than neopentane but it has smaller solvent excluded volume shown in light gray in Figure 7. Adamantane does not have a perfect spherical shape, and water molecules can approach closer to the center of the monomer than for neopentane.

Based on the water density maps of the adamantane and neopentane dimers at the contact minima, it can be observed that there is quite a large space at the intersection bordered by a concave surface where the motion of the water molecules will be restricted and the number of contacts with the other water molecules diminished, as happens in the neighborhood of the desolvation maximum of smaller solutes (e.g., methane¹⁹). For smaller solutes, the concave surface disappears at the contact distance. However, the area of the concave surface does not seem to be important. Based on the molecular surface area, we constructed the putative PMFs by adding the cavity contribution to a respective vacuum PMFs. The scaling coefficient of the molecular surface area was obtained by correlating the height of the desolvation maximum of the solvent contribution to the PMF with molecular surface area³⁰ and was 0.078 kcal/(mol·Å²). However, the depth of the PMF computed in such a way increased with solute size much faster than that obtained from MD simulations and the predicted solvent contribution was never positive at the contact minimum (data not shown). Therefore, the depletion of the solvent contribution at the contact minimum must be connected with unfavorable energy (decreased number of contacts) and entropy (restricted motion) of the water molecules at the intersection of the solvation spheres of the solute molecules.

Figure 8 shows the cylindrical distributions of the average number of hydrogen bonds between water molecules around the adamantane dimer. The thickness of the first solvation sphere for adamantane is greater than for neopentane dimers. The average number of hydrogen bonds between water molecules in this solvation sphere is slightly smaller (green in Figs. 8a-f) than for bulk water (white Figs. 8a-f) as in case of methane and neopentane.¹⁹ The second solvation sphere with a larger average number of hydrogen bonds (orange Figs. 8d-f) is observed only for neopentane. The average number of hydrogen bonds is not distributed uniformly within the first solvation shell of the dimer, and is always smallest in the region between the solute molecules where two solvation spheres overlap.

The average number of hydrogen bonds depends both on the average number of nearest water neighbors and on the ordering of the water orientations necessary to form hydrogen bonds. Comparison of the distributions of the average number of hydrogen bonds with the average number of nearest water neighbors around the adamantane dimer (Figure 9a), and neopentane dimer (Figure 9d), calculated using the same oxygen...oxygen distance cutoff (3.5 Å) to define a hydrogen bond, shows that ordering of the orientations has only a secondary effect for both dimers. In all layers, the distribution of the average number of hydrogen bonds always has lower values than the average number of nearest water neighbors. Figures 9b and 9e show the distribution of the average water-water interaction energy (kcal/mol) between nearest-neighbor water molecules around the adamantane and neopentane dimers, respectively. Figures 9c and 9f show the average water-water interaction energy (kcal/mol) normalized per water-water contact for both dimers. As reported for methane and neopentane,¹⁹ the pairwise water-water binding energies are more negative in the first solvation shell of a nonpolar solute, i.e., the hydrogen bonds are stronger in the first hydration shell. The first solvation sphere of the adamantane dimer is thicker than that of the neopentane dimer. The second solvation sphere, with weaker hydrogen bonds than in bulk water, is observed only for neopentane (Figure 9f).

Figure 10 displays the average value of the cosine of the angle ω between the dipole moment vector of a water molecule and the normal to the axis of the adamantane (Figs. 10a-c) and neopentane (Figs. 10d-f) dimers. It can be seen that the water molecules close to the adamantane

solutes are oriented much more at random (which would correspond to $\overline{\cos \omega} \approx 0$) than for neopentane. The maximum value of $\overline{\cos \omega}$ is ≈ 0.1 for the adamantane dimer (red), similar to that previously observed for neopentane.¹⁹ The first solvation sphere for adamantane is larger but not as ordered as the smaller first solvation sphere of neopentane dimers.

In Figure 11, we show the comparison of the PMF curves for the all-atom adamantane dimer (solid line) and a pair of spheres (dotted lines) with a radius of 3.4 Å modeling two interacting adamantane molecules. A value of the van der Waals depth for two spheres was estimated based on the PMF for the adamantane dimer *in vacuo* (Figure 4c, dotted lines), being about -2.8 kcal/mol. It can be observed that the contact minima occur at the same position but their depths are different. The depth of the contact minimum for two spheres is shallower than for adamantane because spheres interact more strongly with water (larger value of the van der Waals depth according to Lorentz-Berthelot mixing rules²⁹). According to these mixing rules, in the all-atom model of adamantane, water interacts with carbon and hydrogen atoms with much smaller values of the van der Waals depth.²²

We also calculated two-dimensional distribution functions describing the normalized water density and the average number of hydrogen bonds between water molecules (see Figure 3b) around a single molecule of adamantane and a single sphere with the radius of 3.4 Å modeling adamantane.

Two-dimensional maps of the normalized distribution function of the water molecule density around the adamantane molecule (Figure 12a) and a sphere with radius of 3.4 Å (Figure 12b) show different water density profiles in the first solvation shells. Around a sphere, we observe a maximum of the water density (yellow and red) close to the surface of a sphere about 5 Å from its center. There is a minimum around 7 Å (blue), and a much smaller maximum at 8.0 Å (light blue). For all-atom adamantane, a small maximum at 6 Å (light blue) from the center can be observed and then the density decreases at smaller distances from the center of the all-atom adamantane molecule. The solvent-excluded volume (light-grey) is much smaller for all-atom adamantane than for a sphere representing adamantane. The size of the sphere was estimated using the adamantane-adamantane interaction energy profile *in vacuo*. Water molecules can approach closer to the center of the adamantane molecule than can another adamantane molecule. A sphere is not a good model for such a molecule as adamantane.

Figure 13 shows the cylindrical distributions of the average number of hydrogen bonds between water molecules around the adamantane monomer (Figure 13a), and a sphere with radius of 3.4 Å (Figure 13b). The thickness of the first solvation sphere (green) for the adamantane monomer is greater than that around the sphere (green). The average number of hydrogen bonds between water molecules in this solvation sphere is slightly smaller than for bulk water (white in Figure 13). The second solvation sphere with greater average number of hydrogen bonds (orange Figure 13b) is only slightly visible for the sphere. The solvation pattern of the sphere with the size modeling adamantane is similar to the solvation of all-atom neopentane rather than that of all-atom adamantane.

4. Conclusions

We determined the potentials of mean force for five pairs of nonpolar solutes, i.e., neopentane, bicyclooctane, adamantane, a VdW sphere of adamantane size, and fullerene in water as functions of the distance between their geometric centers. The shape of the PMFs determined by using the TIP3P model of water is characteristic of hydrophobic interactions with contact and solvent-separated minima, and desolvation maxima. Based on our molecular dynamics simulations, we observed an increasing contribution of the Lennard-Jones term to the PMFs with the size of the solute, i.e., from neopentane to bicyclooctane, to adamantane, and to

fullerene. The minima in the PMF curves calculated *in vacuo* become deeper towards the fullerene dimer. The shape of the PMFs determined *in vacuo* is characteristic of the Lennard-Jones-like interaction for nonpolar molecules. The solvent contribution to the PMF is negative for small solute molecules, is nearly zero for isobutane and neopentane and turns positive for larger solute molecules. An analysis of the water density around the neopentane and adamantane dimers suggests that the shifting of the solvent contribution to positive values might result from the presence of a concave “cleft” close to the intersection of the solvation spheres. The water molecules trapped in this “cleft” have restricted motion (decreased entropy) and cannot form many hydrogen bonds with the neighboring water molecules. Consequently, the favorable effect of the decrease of the molecular surface area upon forming the contact dimer is overcome by the unfavorable position of the water molecules close to the intersection of the solvation spheres of the monomers.

Based on our results, we can conclude that bicyclooctane, adamantane, and fullerenes are too large to be treated as classical small hydrophobic molecules but not large enough to be considered as macroscopic hydrophobic surfaces, because the depth of the contact minima is less than the depth of the minimum of the van der Waals interactions *in vacuo*.

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Figure 1. The molecules studied in this work: (a) neopentane; (b) bicyclooctane; (c) adamantane, and (d) fullerene. The restraints during the MD simulations were imposed on the distances between the atoms labeled with stars.

Figure 2.

PMF curves for the fullerene dimer for two different numbers of configurations, obtained from the umbrella-sampling/WHAM method using the TIP3P water model at temperature 298K. The simulations were carried out at a temperature of 298 K. The dotted and solid lines refer to 50% (25,000 configurations), and 100% (50,000 configurations), respectively, of the total number of generated configurations.

Figure 3.

Schematic illustration of the definitions for the cylindrical distributions around (a) a pair of solutes at contact distance, (b) a single solute molecule. In (a), the cylindrical axis h in part links the solute molecules, and r is an axis perpendicular to it and passing through the middle of the dimer. In (b), the h axis is an arbitrary direction in space, and r is an axis perpendicular to it and passing through the center of the solute. The distribution functions of water molecules are averaged over the azimuthal angle θ . A water molecule is presented (at an arbitrary orientation) to define the angle ω between the r axis and the dipole moment vector of the water molecule. The $\text{H}-\text{O}\cdots\text{O}$ angle α used to define a hydrogen bond is presented using two water molecules in the hydrogen-bonded dimer geometry.

Figure 4.

PMF curves for the dimer systems investigated in this study, determined at temperature 298K by using the TIP3P model of water (solid lines) and obtained *in vacuo* (dotted lines): neopentane (a); bicyclooctane (b); adamantane (c); fullerene (d).

Figure 5.

The solvent contribution to the PMF determined at temperature 298K as a difference between the PMFs in solvent and *in vacuo*: neopentane (solid line); bicyclooctane (dashed line); adamantane (dot-dashed line); fullerene (dotted line).

Figure 6.

Linear regressions of the depth of the contact minima on the PMF curves *in vacuo* (solid line and full-circles) and in water (dotted line and open circles) vs. number of carbon atoms in a molecule. The values of the depth of the contact minima on PMF for methane, ethane, propane, isobutane and neopentane were taken from ref. ¹⁹, and for bicyclooctane and adamantane were obtained in this work. Fullerene is omitted from the plot because the depth of contact minimum is too large to fit on this scale.

Figure 7.

Normalized distribution functions of the water molecule density in the vicinity of the adamantane dimer (Figures a-c) and neopentane¹⁹ (Figures d-f) at monomer-separation distances Δh (a) 6.8 Å, (b) 8.8 Å, (c) 10.2 Å, (d) 5.8 Å, (e) 7.85 Å and (f) 9.2 Å, which correspond to the contact minima (a and d), the desolvation barrier (b and e), and the solvent-separated minimum configurations (c and f), respectively. The color scale is shown above the panels; and the bulk water density is displayed in white. The solute is in grey, the space between the solute and the first hydration layer is in violet, and the first hydration layer is in blue plus light blue (a-c) and green, red and yellow (d-f).

Figure 8.

Distribution of the average number of hydrogen bonds between water molecules in the vicinity of the adamantane dimer (Figures a-c) and neopentane (Figures d-f) at monomer-separation distances Δh (a) 6.8 Å, (b) 8.8 Å, (c) 10.2 Å, (d) 5.8 Å, (e) 7.85 Å and (f) 9.2 Å, which correspond to the contact minimum, the desolvation barrier, and the solvent-separated minimum configurations, respectively. The color scale is shown above the panels, and the average number of hydrogen bonds for bulk water density is displayed in white. The identification of the colored layers is described in Fig. 7.

Figure 9.

Distribution of the average number of nearest water neighbors (a and d), calculated by using the same oxygen...oxygen distance cutoff ($3.5\text{\AA}$) to define a hydrogen bond as for the average number of calculated hydrogen bonds presented in Figure 7; (b and e) the average water-water interaction energy (kcal/mol) between nearest-neighbor water molecules; (c and f) the average water-water pair energy (kcal/mol) calculated by dividing the average water-water interaction energy by the average number of nearest water neighbors, i.e., normalized per water-water contact. Distributions in Figures a-c are calculated around the adamantane dimer at $6.8\text{\AA}$ distance, and the distributions in Figures d-f are calculated around the neopentane dimer¹⁹ at $5.8\text{\AA}$ distance. The color scale is shown above the panels, and the average values for bulk water are displayed in white. The identification of the colored layers is described in Fig. 7

Figure 10.

Distribution of the cosine of the angle ω (see Figure 3) between the vector normal to the axis of the dimer and the water dipole moment vector in the vicinity of the adamantane dimer (Figures a-c), and the neopentane¹⁹ dimer (Figures d-f) at monomer-separation distances Δh (a) 6.8 Å, (b) 8.8 Å, (c) 10.2 Å, (d) 5.8 Å, (e) 7.85 Å, (f) 9.2 Å, respectively. The color scale is shown above the panels, and the value of the average cosine of the angle ω of bulk water is displayed in white. The identification of the colored layers is described in Fig. 7

Figure 11.

PMF curves for the dimers of adamantane (solid line) and two spheres (dotted line) with the radius 3.4 Å, determined by using the TIP3P model of water. The identification of the colored layers is described in Fig. 7

Figure 12.

Normalized distribution functions of the water molecule density around the single molecule of adamantane (a) and a single sphere with the radius 3.4 Å (b). The color scale is shown above the panels, and the bulk water density is displayed in white. The solute is in grey. The identification of the colored layers is described in Fig. 7

Figure 13.

Distribution of the average number of hydrogen bonds between water molecules around the single adamantane molecule (a) and a single sphere with a radius of 3.4 Å (b). The color scale is shown above the panels, and the average number of hydrogen bonds for bulk water density is displayed in white. The identification of the colored layers is described in Fig. 7

Table 1

Partial atomic charges (in electron charge units), and the AMBER atom types of the neopentane¹⁹, bicyclooctane, and adamantane molecules, calculated by using the RESP method²⁴ based on HF/6,31G* calculations carried out with GAMESS,²³ used in the calculations with the AMBER force field.²²

neopentane				Bicyclooctane				adamantane			
atom number ^a	AMBER atom type ^b	atomic charge	atom number ^a	AMBER atom type ^b	atomic charge	atom number ^a	AMBER atom type ^b	atomic charge	atom number ^a	AMBER atom type ^b	atomic charge
C1	CT	0.544	C1, C3, C4, C6, C7, C8	CT	-0.095	C1, C3, C5, C7, C9, C10	CT	-0.095	C1, C3, C5, C7, C9, C10	CT	-0.300
C2, C3, C4, C5	CT	-0.298	C2, C5	CT	-0.161	C2, C4, C6, C8	CT	-0.161	C2, C4, C6, C8	CT	-0.144
H6-H17	HC	0.054	H9, H10, H12-H15, H17-H22,	HC	0.059	H11, H12, H14, H15, H17, H18, H20, H21, H23-H26	HC	0.059	H11, H12, H14, H15, H17, H18, H20, H21, H23-H26	HC	0.138
			H11, H16	HC	0.092	H13, H16, H19, H22	HC	0.092	H13, H16, H19, H22	HC	0.180

^aThe atom numbers refer to the labels in Figure 1.

^bThe amber atom type CT denotes sp³ aliphatic carbon atom, HC denotes hydrogen atom attached to the aliphatic carbon atom.

Table 2

Depths of the contact minima in the PMF of the hydrocarbon molecules in water and *in vacuo* (in kcal/mol).

molecule	Contact-minimum depth [kcal/mol]	
	in vacuo	in water
methane ^a	−0.30	−0.75
ethane ^a	−0.45	−0.70
propane ^a	−0.43	−0.69
isbutane ^a	−0.88	−0.90
neopentane ^a	−0.95	−1.05
bicyclooctane	−2.30	−1.50
adamantane	−2.80	−1.75
fullerene	−9.2	−4.3

^aResults taken from Ref. 18.