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Water Structuring Above Solutes with Planar Hydrophobic Surfaces

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Abstract

Many important biological solutes possess not only polar and hydrogen bonding functionalities, but also weakly-hydrating, or hydrophobic, surfaces. Theories of the hydration of such surfaces predict that their solvent interactions will change from a wetting type interaction to a dewetting regime as a function of the solute size, with a gradual transition in behavior taking place around characteristic lengths of ~ 1 nm. Aggregations of non-polar species over this size range will undergo a transition from being dominated by entropy to being dominated by enthalpy. These transitions can be understood in part in terms of the geometries required of the solvating water molecules. We report here a series of simulations in aqueous solution of organic molecules with planar faces of increasing size, ranging from cyclopropane to circumcircumcoronene, in order to explore the transition in behavior for such solutes as their size increases. For this series, the dewetting transition occurred gradually, converging asymptotically to a limiting separation value for first layer water molecules of around $3.3 \text{ \AA}$, while the transition in hydrogen bonding orientational structure occurred between cyclopropane and cyclopentadene. Water immediately adjacent to the largest planar hydrophobic surfaces oriented in ways that resembled on average the structural organization of the basal planes of ice.

Graphical abstract

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Keywords

caffeine; molecular dynamics simulations; aqueous solution; water hydration; self-association

Introduction

Theories of the hydration of nonpolar species have found that extended planar surfaces should hydrate differently than smaller hydrophobic molecules.^{1–5} For hydrophobic solutes with a small spatial extent and a high curvature, such as methane or methylene, water molecules in the first “hydration shell” can straddle the solute to make hydrogen bonds to other water molecules, with neither their protons nor lone pairs directly pointing at the solute, which would involve the loss of a hydrogen bond.⁶ The cost of this structuring is entropic, since the rotational freedom of the water molecules is restricted. As a result, such species are driven to aggregate in aqueous solutions,⁷ which liberates water molecules to regain their rotational freedom. The calorimetric signature of this type of hydrophobic aggregation at room temperature is that it is entropy-driven, with a heat capacity change that is negative, since the initial solvation of such hydrophobic species is accompanied by an increase in solvent structuring and thus the heat capacity. This hydration is considered a wetting interaction, since there is a maximum in the radial distribution function for the water molecule oxygen atoms from the central carbon atom of the hydrophobic group at the van der Waals contact distance of around 3.4 Å (in a truly wetting interaction involving hydrogen bonding, this distance would be much less, around 2.8 Å). However, as the spatial dimensions of hydrophobic species grow larger, it becomes impossible for water molecules to straddle the hydrophobic surface and still make hydrogen bonds to other water molecules off to its sides.^{8–12} Under these conditions, the water molecules point one hydrogen atom or lone pair directly at the non-hydrogen-bonding surface, since the resulting loss of one hydrogen bond is nevertheless energetically better than the loss of the two to three hydrogen

bonds that would result if they adopted the orientation of waters adjacent to a methane molecule.^{3,8,9,12,13} The aggregation of such extended surfaces in aqueous solution would then be enthalpically-dominated, since the pairing of two such surfaces would allow the liberated water molecules to regain their lost hydrogen bonds. Orientational structuring of this type has been observed in molecular simulation studies of extended featureless surfaces as well as of benzene and silica.^{5,7,8,10,14} Field theories predict a gradual transition from entropic domination of the solvation free energy to enthalpic as a function of size for the case of a spherical cavity, with a characteristic length scale for the transition of ~ 1 nm.^{2,3} This type of hydration also results in a depletion of water molecule density close to the hydrophobic surface, unlike the case for the small spherical solutes such as methane, where there is a peak in water density at approximately the contact distance,¹³ so that the hydration of these surfaces is characterized by a dewetting, with a more extended zone from which water is excluded.^{3,5}

Recently we demonstrated that this type of water structuring over extended flat surfaces is a dominant factor in the aggregation of caffeine in aqueous solution.¹¹ Although the caffeine molecule is smaller than 1 nm, in a narrow volume over the hydrophobic center of the molecular plane, water molecules indeed are unable to straddle the plane and make hydrogen bonds to water molecules around the periphery of the ring. Solvent molecules in this volume point one hydrogen atom or lone pair directly at the center of the caffeine solute, even though this entails the loss of a hydrogen bond. The liberation of this structured water molecule when the face of caffeine binds to another molecule drives the association of caffeine with hydrophobic solutes, including other caffeine molecules, and from calorimetry it is known that such aggregation is enthalpically-dominated.^{15,16} As a purine, caffeine serves as a model for the interaction of other chemically-similar species in water. Such purine stacking in the double-helical structure of DNA has been known for more than half a century.^{17,18} In another study we showed that in molecular dynamics simulations of glucose interacting in aqueous solution with indole, the side chain group of the amino acid tryptophan, which is qualitatively similar to caffeine in structure, the triad of H1–H3–H5 hydrophobic protons in glucose exhibited a pronounced tendency to bind to the indole face, with an association energy of approximately 1.2 kcal/mol.¹⁹ Similar binding of glucose to caffeine was also observed, with a very similar binding energy.²⁰ Thus, the hydration of planar surfaces such as these in tryptophan, phenylalanine, and tyrosine may play an important part in molecular recognition involving protein-ligand or enzyme-substrate interactions, and has been shown to be involved in protein folding and assembly as well.^{21,22} Ligand and substrate binding sites in proteins that bind glucose often contain tryptophan side chains.^{23–25}

We report here molecular dynamics (MD) simulation studies of the hydration of a series of hydrophobic cyclic organic molecules with planar faces to examine the water structuring behavior as a function of surface extent. Similar studies have been reported previously of large non-planar molecules such as bicyclooctane, adamantane, and fullerene,^{26,27} but the transition as a function of size between entropic and enthalpic-dominated solvation and between wetting and dewetting behavior has not been fully explored for planar molecules, as opposed to model systems such as a sphere. Zangi has reported free energy calculations for

graphene plates as a function of size, but did not report a structural analysis of the solvent ordering contributing to the energies.²⁸

The series of solutes reported here included cyclopropane, cyclobutadiene, cyclopentadiene, benzene, indene, azulene, naphthalene anthracene, pyrene, coronene, ovalene, circumcoronene, and circumcircumcoronene. These species span a range of linear dimensions running from approximately 1.5 Å for cyclopropane up to 15.0 Å for circumcircumcoronene. The structures of the larger of these molecules are shown in Figure 1. Due to their planarity and all-carbon interior structure, the molecules in this series resemble the 28-, 60-, and 180-carbon graphene plates modeled by Choudhury and Pettitt, which ranged in size from 10 Å to 24 Å,⁴ and the 28- and 104-carbon graphene plates studied by Zangi,²⁸ whose largest plate, with 249 carbon atoms and dimensions of 24.1×23.4 Å, was substantially larger.

Most of the cyclic molecules in this series are aromatic, and are thought to exhibit a stronger interaction with water than might be expected for a corresponding saturated ring as the result of O–H/ π interactions between the π orbitals of the ring and the water molecules.^{29,30} Such interactions are present in molecular mechanics simulations only indirectly through the initial choice of force field parameters,³¹ and thus may be under-represented in the type of calculations reported here. However, the goal in the present case is not the quantitative calculation of hydration energies, since these solutions are largely artificial, due to the insolubility of such highly nonpolar solutes, but rather to characterize the structural nature of their interactions with water, and trends in these interactions as a function of surface size. For this purpose general MM force fields and standard water models should be adequate.

Procedures

Simulation Protocols

For each of the molecules studied, MD simulations were performed for a single solute molecule in a periodic cubic box of water. The simulations were carried out in the NPT ensemble using the CHARMM molecular mechanics program,^{32,33} with the general CHARMM36 energy parameters. The starting atomic coordinates for each solute molecule were generated as the ideal structures for their geometric topology and bond type. Water molecules were simulated using the rigid TIP4P water model.^{34,35} The lengths of the covalent bonds involving hydrogen atoms were kept fixed using the general constraint algorithm SHAKE.^{36,37} The various simulations, with their box sizes and numbers of explicit water molecules are summarized in Table 1.

All van der Waals interactions were smoothly truncated on an atom-by-atom basis using switching functions³² from 9.0 to 11.0 Å, while electrostatic interactions were treated using the Particle Mesh Ewald method^{38,39} with a real space cutoff of 12.0 Å and $\kappa = 0.454 \text{ Å}^{-1}$. The simulation was run at a constant temperature of 300 K, using a Hoover constant pressure/temperature algorithm, at a constant pressure of 1 atm, maintained using a Hoover piston with a mass of 2000 amu.⁴⁰ The equations of motions were integrated using a time step of 1 fs. Initial velocities were assigned from a Boltzmann distribution and each system was heated from 0 K to 300 K over a period of 10 ps before the production run. The lengths

of the various simulations are given in Table 1. In each case the final 3 ns were used for analysis, which was deemed sufficient considering the fast rotational relaxation rate and self-diffusion coefficient for water.

Atomic density analyses of the trajectories were carried out using the Visual Molecular Dynamics (VMD) graphics program.⁴¹ For each saved frame of the trajectory, a coordinate transformation was carried out so that the positions of the water molecules could be specified relative to the solute in a coordinate frame fixed on its center of mass. The solvent density was then contoured relative to bulk solvent density. Average orientational and distributional properties were analyzed for those water molecules located in parallelepipeds above and below the solute molecules with shapes defined by the outer edge of the carbon skeleton of each solute (Figure 2).

For those water molecules within the defined parallelepipeds, the normalized trajectory-averaged density, $g(h)$, was calculated as a function of height h above the molecular plane for both faces and averaged together since they are symmetric. For those water molecules within a sub-volume of the parallelepipeds with an outer boundary defined as the position of the first minimum in the density distribution function, the orientational distribution function for the O-H bonds of the water molecules was calculated as the probability of observing an angle θ between the bond vector and the normal to the surface from the oxygen atom.

Results and Discussion

As expected, a change in orientational behavior for neighboring water molecules was observed as the solute size increased, with the transition coming at the small end of the size range considered here, between cyclopropane and cyclopentadiene. Figure 3 illustrates typical configurations for water molecules over the faces of cyclopropane and cyclopentadiene. As expected, cyclopropane is sufficiently small such that solvent molecules over its face are able to structure as they would around methane or the methylene groups of a lipid, with one O-H bond tending to point directly away from the solute, and making hydrogen bonds to other adjacent water molecules off to its side. Water molecules over the planar face of cyclopentadiene tend to structure in the opposite fashion, with one O-H bond pointing directly at the hydrophobic surface, since a straddling-type arrangement would not succeed in actually straddling the surface and making hydrogen bonds to other peripheral water molecules, and would thus result in the loss of two to three hydrogen bonds, rather than the one lost by pointing one proton directly at the surface. Interestingly, this transition occurs at a much shorter characteristic length than the approximately 1 nm predicted for the transition to dewetting behavior.^{3,5}

Figures 4–6 display, for cyclopropane, cyclobutadiene, and cyclopentadiene, the normalized solvent water density profile $g(h)$ as a function of distance h from the planar surface in 0.1 Å-thick slabs of a parallelepipedal volume centered over the face for each of the molecules in the series, and an orientational distribution function $P(\cos(\theta))$ for those water molecules within the volume element directly over the surface up to first minimum of the density distribution function. In these functions, θ is defined as the angle between the O-H bond vectors and the surface normal. As can be seen, the density distribution profile for the

cyclopropane (Figure 4) closely resembles that for methane or a rare gas,¹³ with a broad peak centered at approximately 3.5 Å and with a shallow first minimum around 5.5 Å. Consistent with the example configuration shown in Figure 3, the orientational distribution $P(\cos(\theta))$ exhibits a strong peak at $\cos(\theta) = 1$, corresponding to an O–H bond pointing directly away from the surface. The broad peak centered around $\cos(\theta) = -0.33$ arises because, when one proton or lone pair is pointing directly away from the surface, the others are making approximately the tetrahedral angle with respect to it due to the quasi-tetrahedral geometry of the water molecule.⁴²

However, for cyclopentadiene, the exact opposite orientational distribution is observed (Figure 6), with a strong peak at $\cos(\theta) = -1$, corresponding to a “dangling”¹⁰ O–H bond pointing directly at the surface, again consistent with the representative configuration illustrated in Figure 3, and with a broad secondary peak centered around 0.33. The first peak in the density distribution is located at approximately 3 Å, but unlike the peak usually associated with the hydration of small hydrophobic species like methane or xenon, this peak is narrow and sharp, with a higher intensity, similar to that for a hydrogen-bonded neighbor, as in the first peak in the pure water radial distribution function.^{43,44} This orientational behavior subsequently applies for all of the larger planar molecules in the series up to azulene, as can be seen from Figures S1–S3 of the Supporting Information material, consistent, for example, with previous studies of benzene in water.^{5,7,8,14} However, the nature of the first peak in the density distribution changes, with a lower maximum height and a broader width at half maximum as the surface area increases (Figures 11 and 12).

Interestingly, cyclobutadiene is intermediate between these two behaviors (Figure 5). The water density profile $g(h)$ for this molecule is very similar to that of cyclopropane, with a broad peak centered around 3.4 Å, as would be expected for a small hydrophobic molecule, but the orientational distribution $P(\cos(\theta))$ exhibits a bimodal character. This function again has a peak at $\cos(\theta) = 1$, but with a lower magnitude, and instead also exhibits a peak of similar magnitude at -1 , indicating that some of the time the water molecules hydrating its face point hydrogen atoms directly at it, while some of the time they point them directly away, implying that its nonpolar face is almost large enough to make it difficult for the solvent to straddle it and hydrogen bond to other water molecules.

Beyond azulene, starting with naphthalene, the orientational ordering above the larger surfaces again begins to display the mixed character of cyclobutadiene, with peaks at both -1 and $+1$ (Figure 7), with the peak at $+1$ growing stronger as the surface area increases (Figures 8 and 9). Figure 7 illustrates these functions for ovalene, with the functions for the other solutes shown in the Supporting Information materials as Figures S4–S9. Figure S10 displays a representative instantaneous configuration for five water molecules over the center of the solute for the circumcircumcoronene case. This dual orientational character for these larger solutes is due to the fact that the water molecules in the first layer cannot all be pointing in the same direction and still be optimally hydrogen-bonded to adjacent molecules. This type of alternating orientational structuring was described by Lee et al.⁸ as resembling an ice-like arrangement in the first hydration layer, with water molecules with dangling O–H bonds or hypothetical lone pairs directed at the surface at a slightly closer distance, alternating with those with their O–H bonds pointing in the tetrahedral direction at a slightly

larger distance, as in the basal plane face of ice I_h , in order to maintain approximately three hydrogen bonds to the closest molecules. This effect becomes progressively more important as the surface area becomes larger in the series.⁸ As the solute surface area increases, the peak at -1 gradually decreases while the peak at $+1$ increases.

In the chosen series, all of the species larger than benzene are fused rings (it would of course also be possible to consider rings with larger numbers of atoms than six, but not all would be planar, and as the rings grew in size, the structuring of the waters above the middle would come to be dominated by the “hole” in the donut). For the fused rings, however, the introduction of geometric asymmetry of course complicates the specific details of the water structuring in response, so that such an increasing series does not exactly mimic the regular growth of a perfect sphere as in the formal field theories.^{1-3,5}

The indene molecule (Figure 1) is an interesting example of such fused rings, not only because it is the simplest one considered here, but also because it is the all-carbon architectural template for a number of important biological molecules such as the purines like caffeine and the nucleic acids. In our previous study of caffeine, only the area directly above the shared bond of the two rings behaved as an extended hydrophobic surface, due to the presence of hydrogen bonding functional groups in the ring. However, as might be expected, for the completely hydrophobic indene molecule, the density clouds representing the location of structured water molecules are spread over the ring surfaces, and not just over their intersection as in the caffeine case.

Figures 8 and 9 illustrate the transitions in orientational structuring with increasing surface area, with Figure 8 focusing on the smaller end of the size range. As can be seen in Figure 8, the transition is gradual, indicating that for the smaller intermediate solutes, some of the water molecules can deviate from the expected behavior, at least transiently, but that this tendency decreases as one moves away from the intermediate behavior of cyclobutadiene. In addition, as can be seen from Figure 9, the transition back to bimodal behavior for the largest solutes is also gradual. There is also a slight shift of the broad -0.33 peak toward 0 for the largest solutes, which apparently results from the overlap of the tails of the broad distribution centered around $+0.33$ in these examples.

An important feature of the hydration of such extended surfaces is a predicted dewetting due to water molecules backing away from the surface as they are drawn into the bulk due to interfacial tension, as also occurs at an air/water interface. As the solute molecules increase in size toward colloidal dimensions, the difference in characteristic lengths between the hydrophobic solute and the individual solvent molecules becomes such that it is progressively more appropriate to use continuum thermodynamic descriptions. Figure 10 displays the position of the first peak in the density distributions above the surface, $g(h)$, as a function of the surface area of the planar molecules, for all of the solute molecules except cyclopropane. This surface area could be calculated in several ways, for example as the normal projection of the van der Waals footprint, but in Figure 10 it is plotted as a function of the simple geometric footprint defined by the C–C bonds (Figure 2). As can clearly be seen, the position of this first peak characterizing the mean position of the nearest solvating water molecules grows with size, asymptotically approaching a limit of around $3.3 \text{ \AA}$,

consistent with the predicted values for surface dewetting,^{2,3} although none is as far out as for cyclopropane (3.51 Å, see Table 2).

For the larger solutes, the shape of the first peak in the density distribution $g(h)$ converges to a broad peak with a significantly lower maximum height than for the smaller solutes, as can be seen from Figures 11 and 12, which display the height of the first peak in $g(h)$ as a function of surface area and the full width of this peak at half maximum. Beyond coronene this feature is essentially converged, and its shape is qualitatively similar for all of the solutes larger than anthracene. This would be consistent with the model of Lee et al.,⁸ since this single broad peak would encompass the oxygen positions of both the alternating “up” and “down” positions in the basal plane of the ice-like structuring above the surface. Presumably the structuring of water over the extended (nearly 200 Å²) surface of circumcoronene also resembles the air-water interface, and would not change qualitatively for larger surfaces.

The orientational data displayed in Figures 8 and 9 suggests that for the larger planar surfaces the adjacent water molecules are organized in an ice-like fashion. However, at the elevated temperature studied here this average structuring does not mean that a stable I_h lattice develops, as becomes immediately apparent from inspection of individual “snapshots” of the instantaneous configurations of these molecules, which possess sufficient energy for significant positional and orientational fluctuations. Nevertheless, ice-like structure implies longer-range structural correlations of a more regular nature than are found in liquid water, as illustrated in Figure 13. A basal plane of actual ice on the surface of these planar nonpolar solutes would have three molecules of each six-molecule hydrogen bonded ring pointing either their protons or lone pairs directly at or directly away from the surface, in an alternating sequence, with the other three making tetrahedral angles with the plane. First neighbors would all be at a distance of ~2.7 Å and making a tetrahedral angle with respect to the plane of their nearest neighbors. Second neighbors would all be at a distance of ~4.5 Å and aligned parallel to their next nearest neighbors, while molecules on opposite ends of the 6-atom puckered chair-shaped rings (for example, atoms 1 and 4 in Figure 13) would be ~5.3 Å apart.

Figure 14a displays orientational correlation functions for water molecules in the first layer adjacent to the solute faces for the circumcoronene simulation, illustrating how geometrically correlated neighboring water molecules are, compared to a similar volume of water furthest away from the solute (Figure 14b), approximating pure bulk water. In this figure, the water molecule located closest to the geometric center of each of the solute’s faces is identified in each saved coordinate set, and then the angle between the normal vector of that molecule and those of every other molecule in a cylindrical disk 5 Å high and centered over the geometric center is calculated and averaged over all frames as a function of radial projection distance from the center of the cylinder. The same procedure was also applied to an exactly similar disk of water located as far as possible from the solute, using a randomly selected water molecule to serve as a center, as an approximation of the structuring behavior expected in pure bulk water.

In ice-like structuring, significantly more long-range correlation would be expected between neighboring water molecules than in pure liquid water,⁴⁴ and with peaks at positions dictated by the ice I_h lattice positions. Since liquid water retains considerable hydrogen bonding dominated by tetrahedral symmetry,⁴⁴ it is not surprising that both distributions exhibit significant probability for distances of around 2.7 Å, regardless of the angle, and a high probability for the tetrahedral angle ($\cos(\theta) = \pm 0.33$) and a strong peak at 2.7 Å and $\cos(\theta) = 0$, indicating an orthogonal arrangement. However, consistent with a somewhat more ice-like average organization, the structural correlations for the water molecules on the surface are indeed different from bulk liquid water, and exhibit stronger long-range correlations. In particular, note that the first neighbor waters adjacent to the surface exhibit a probability peak at around 2.7 Å and an angle of around 180° ($\cos(\theta) = \pm 1$), which is completely absent for the liquid water. This peak is due to anti-correlation of bond vectors and lone pairs in adjacent positions, as can be seen from Figure 13 (for example, the notional lone pair of the water molecule labeled “1” and one of the protons of water “2”), and is apparently very rare in liquid water, while the average structure near the surface seems to favor this orientation, as would be seen in the ice I_h basal plane. It can also be seen that between ~3 and 5 Å there is a much deeper first minimum at all angles and over a much broader extent for the surface water molecules than for bulk liquid water. In addition, for the surface water molecules there is a significant but very broad second peak or cluster of probability density centered around distances between ~4.5 and 6.0 Å and $\cos(\theta) = \pm 1$, and peaking around 5.2–5.4 Å, which is due to antiparallel or parallel alignments for 1-4 positions, also as would be expected for an ice-like organization, with yet another significant minimum developing at distances greater than 5.6 Å for lower values of $\cos(\theta)$. This peak is absent for the bulk-like liquid water map, but is part of a weak band of higher probability around 4.5 Å, corresponding to the second peak in the radial distribution function, for all angles, but with a shallow minimum around $\cos(\theta) = 0$. For distances greater than 6 Å from the water molecule closest to the solute center, the neighboring molecules are no longer over the solute plane for circumcircumcoronene, which has a radius of ~7.5 Å. It should be emphasized again that individual frames do not generally exhibit a static ice-like lattice structure, and that these ice-like structural correlations develop as averages over the long time behavior of the water molecules in the first solvation layer.

Conclusions

The stacking of the planar faces of purines and pyrimidines has long been known to be important for the structures of nucleic acids, and the planar faces of the side chains of tryptophan, phenylalanine, tyrosine, and histadine are important as recognition sites for carbohydrate binding in proteins such as glycosidases and sugar binding proteins.^{23–25} Similarly, purines like caffeine and the planar anthocyanins are known to aggregate extensively by face-to-face stacking in aqueous solution.^{15,45,46} Even ionic species like the planar guanidinium ion, which has a less polar center, are known to exhibit a tendency to pair by face-to-face stacking in water, in spite of their charge repulsion.^{47,48} All such interactions in an aqueous environment require the removal of the water molecules hydrating the planar faces of the solutes, which demonstrates the potential importance of the sort of water structuring observed in the present series of hydrophobic molecules.

As expected, in these simulations smaller solutes with planar hydrophobic surfaces structured water in the same manner as methane or xenon,^{13,49} with a water O–H bond pointing directly away from the solute. The cost of this structuring and its corresponding increase in heat capacity is in decreased entropy, and the disruption of this structure is conventionally believed to be the driving force behind the entropy-dominated aggregation of fats in water environments and the folding of globular proteins. Also as expected, somewhat larger planar molecules interact with water in the manner that has been predicted for extended hydrophobic surfaces, with the first hydration layer of solvent molecules tending to point an O–H bond directly at the surface, the opposite of the behavior around hydrophobic species with small extents or high surface curvatures. The transition between these two different types of behavior occurred at the small end of the series of molecules studied here, between cyclobutadiene and cyclopentadiene. The largest solutes display a mixed orientational structuring since it is not possible to have all water molecules in an extended layer pointing in the same direction and still have optimized hydrogen bonding to their neighbors. The average structuring thus resembles the basal plane of ice, as demonstrated by the long range extent of structural correlations in the first layer water molecules. This type of ice-like orientational structuring at an extended hydrophobic interface was first characterized by Lee et al.,⁸ and demonstrates the importance of hydrogen bonding rather than dipole orientations.²⁷

A small dewetting behavior was observed, which did not converge until the largest molecules studied, in agreement with the results predicted from field theories for featureless spheres. The lack of curvature in the present series of planar solutes is almost certainly the reason for the early onset of the transition to enthalpy-dominated structuring at shorter length scales than expected. It is interesting that this transition in wetting/dewetting behavior increased gradually and continuously over the entire size range studied (but with the largest changes occurring at the small end of the spectrum), while the qualitative change in orientational behavior occurs between the C3 and C5 species. It is also interesting to note that this transition to a dewetting behavior occurred even though the atoms in these solutes were not treated as hard spheres but rather as van der Waals spheres.^{1,2,50} Since the hydration behavior has been shown to be dependent on the interaction potential between the water and the solute, it should also be remembered that the force fields employed here incorporated any O–H/ π interactions in only a general manner, and probably underestimate the effects of such contributions. This underestimation may be greater in the case of the larger solutes studied as their polarizability will be greater as well.

As already noted, in the water-soluble planar molecules important in biology such as the purines, polar and hydrogen bonding groups around the periphery of the molecule result in very complex interactions with water.¹¹ As was seen in the case of caffeine, these groups significantly reduce the effective hydrophobic surface area of the solute. However, also as was seen for caffeine, these solutes may well be large enough for the unique hydration of extended surfaces to affect their interactions with other species, as in the interaction of sugars with tryptophan side chain indole groups in protein binding sites.⁵¹ For this reason, such interactions in various series of water-soluble planar analogs, such as the coal tar dyes, dioxins, and purines, should be examined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Ashbaugh HS, Paulaitis ME. Effect of Solute Size and Solute-Water Attractive Interactions on Hydration Water Structure around Hydrophobic Solutes. *J Am Chem Soc.* 2001; 123:10721–10728. [PubMed: 11674005]
2. Huang DM, Chandler D. The Hydrophobic Effect and the Influence of Solute-Solvent Attractions. *J Phys Chem B.* 2002; 106:2047–2053.
3. Chandler D. Interfaces and the driving force of hydrophobic assembly. *Nature.* 2005; 437:640–647. [PubMed: 16193038]
4. Choudhury N, Pettitt BM. The Dewetting Transition and The Hydrophobic Effect. *J Am Chem Soc.* 2007; 129:4847–4852. [PubMed: 17385863]
5. Zangi R, Berne BJ. Temperature Dependence of Dimerization and Dewetting of Large-Scale Hydrophobes: A Molecular Dynamics Study. *J Phys Chem B.* 2008; 112:8634–8644. [PubMed: 18582012]
6. Stillinger FH. Water Revisited. *Science.* 1980; 209:451–457. [PubMed: 17831355]
7. Raschke TM, Tsai J, Levitt M. Quantification of the Hydrophobic Interaction by Simulations of the Aggregation of Small Hydrophobic Solutes in Water. *Proc Natl Acad Sci USA.* 2001; 98:5965–5969. [PubMed: 11353861]
8. Lee CY, McCammon JA, Rossky PJ. The Structure of Liquid Water at an Extended Hydrophobic Surface. *J Chem Phys.* 1984; 80:4448–4455.
9. Lee SH, Rossky PJ. A Comparison of the Structure and Dynamics of Liquid Water at Hydrophobic and Hydrophilic Surfaces - a Molecular Dynamics Simulation Study. *J Chem Phys.* 1994; 100:3334–3345.
10. Stirnemann G, Rossky PJ, Hynes JT, Laage D. Water reorientation, hydrogen-bond dynamics and 2-D-IR spectroscopy next to an extended hydrophobic surface. *Faraday Discussions.* 2010; 146:263–281. [PubMed: 21043427]
11. Tavagnacco L, Schnupf U, Mason PE, Saboungi M-L, Cesàro A, Brady JW. Molecular Dynamics Simulation Studies of Caffeine Aggregation in Aqueous Solution. *J Phys Chem B.* 2011; 115:10957–10966. [PubMed: 21812485]
12. Brady JW, Tavagnacco L, Ehrlich L, Chen M, Schnupf U, Himmel ME, Saboungi M-L, Cesàro A. Weakly-hydrated surfaces and the binding interactions of small biological solutes. *European Biophysics Journal.* 2012; 41:369–377. [PubMed: 22124617]
13. Tsunekawa N, Miyagawa H, Kitamura K, Hiwatari Y. A study of water-water interactions in hydrophobic association by a molecular dynamics simulation with an optimized umbrella sampling method. *J Chem Phys.* 2002; 116:6725–6730.
14. Schravendijk P, van der Vegt NFA. From Hydrophobic to Hydrophilic Solvation: An Application to Hydration of Benzene. *J Chem Theory Comput.* 2005; 1:643–652. [PubMed: 26641686]
15. Cesàro A, Russo E, Crescenzi V. Thermodynamics of Caffeine Aqueous Solutions. *J Phys Chem.* 1976; 80:335–339.
16. Stoesser PR, Gill SJ. Calorimetric Study of Self-Association of 6-Methylpurine in Water. *J Phys Chem.* 1967; 71:564–567. [PubMed: 6044492]
17. Record MT Jr, Mazur SJ, Melancon P, Roe JH, Shaner SL, Unger L. Double helical DNA: conformations, physical properties, and interactions with ligands. *Annu Rev Biochem.* 1981; 50:997–1024. [PubMed: 7023371]

18. Kabelac M, Hobza P. Hydration and stability of nucleic acid bases and base pairs. *Phys Chem Chem Phys*. 2007; 9:903–917. [PubMed: 17301881]
19. Mason PE, Lerbret A, Saboungi ML, Neilson GW, Dempsey CE, Brady JW. The Interactions of Glucose with a Model Peptide. *Proteins: Structure, Function, and Bioinformatics*. 2011; 79:2224–2232.
20. Tavagnacco L, Engström O, Schnupf U, Saboungi M-L, Himmel M, Widmalm G, Cesàro A, Brady JW. Caffeine and Sugars Interact in Aqueous Solutions: A Simulation and NMR Study. *J Phys Chem B*. 2012; 116:11701–11711. [PubMed: 22897449]
21. Hua L, Huang X, Liu P, Zhou R, Berne BJ. Nanoscale Dewetting Transition in Protein Complex Folding. *J Phys Chem B*. 2007; 111:9069–9077. [PubMed: 17608515]
22. Liu P, Huang X, Zhou R, Berne BJ. Observation of a Dewetting Transition in the Collapse of the Melittin Tetramer. *Nature*. 2005; 437:159–162. [PubMed: 16136146]
23. Quiocho FA. Protein-Carbohydrate Interactions: Basic Molecular Features. *Pure and Applied Chemistry*. 1989; 61:1293–1306.
24. Lis H, Sharon N. Lectin-Carbohydrate Interactions. *Current Opinion in Structural Biology*. 1991; 1:741–749.
25. Quiocho FA, Vyas NK, Spurlino JC. Atomic Interactions Between Proteins and Carbohydrates. *Transactions of the American Crystallographic Association*. 1991; 25:23–35.
26. Makowski M, Czaplewski C, Liwo A, Scheraga HA. Potential of Mean Force of Association of Large Hydrophobic Particles: Toward the Nanoscale Limit. *J Phys Chem B*. 2010; 114:993–1003. [PubMed: 20039620]
27. Weiss DR, Raschke TM, Levitt M. How Hydrophobic Buckminsterfullerene Affects Surrounding Water Structure. *J Phys Chem B*. 2008; 112:2981–2990. [PubMed: 18275178]
28. Zangi R. Driving Force for Hydrophobic Interaction at Different Length Scales. *J Phys Chem B*. 2011; 115:2303–2311. [PubMed: 21332173]
29. Atwood JL, Hamada F, Robinson KD, Orr GW, Vincent RL. X-Ray Diffraction Evidence for Aromatic π Hydrogen-Bonding to Water. *Nature*. 1991; 349:683–684.
30. Reyes A, Fomina L, Rumsh L, Fomine S. Are Water–Aromatic Complexes Always Stabilized Due to π –H Interactions? LMP2 Study. *Int J Quantum Chem*. 2005; 104:335–341.
31. MacKerell AD, Bashford D, Bellott M, Dunbrack RL, Evanseck JD, Field MJ, Fischer S, Gao J, Guo H, Ha S, Joseph-McCarthy D, Kuchnir L, Kuczera K, Lau FTK, Mattos C, Michnick S, Ngo T, Nguyen DT, Prodhom B, Reiher WE, Roux B, Schlenkrich M, Smith JC, Stote R, Straub J, Watanabe M, Wiorkiewicz-Kuczera J, Yin D, Karplus M. All-Atom Empirical Potential for Molecular Modeling and Dynamics Studies of Proteins. *J Phys Chem B*. 1998; 102:3586–3616. [PubMed: 24889800]
32. Brooks BR, Bruccoleri RE, Olafson BD, Swaminathan S, Karplus M. CHARMM: A Program for Macromolecular Energy, Minimization, and Dynamics Calculations. *J Comput Chem*. 1983; 4:187–217.
33. Brooks BR, Brooks CL, MacKerell JAD, Nilsson L, Petrella RJ, Roux B, Won Y, Archontis G, Bartels C, Boresch S, Caflisch A, Caves L, Cui Q, Dinner AR, Feig M, Fischer S, Gao J, Hodoseck M, Im W, Kuczera K, Lazaridis T, Ma J, Ovchinnikov V, Paci E, Pastor RW, Post CB, Pu JZ, Schaefer M, Tidor B, Venable RM, Woodcock HL, Wu X, Yang W, York DM, Karplus M. CHARMM: The Biomolecular Simulation Program. *J Comput Chem*. 2009; 30:1545–1614. [PubMed: 19444816]
34. Jorgensen WL, Chandrasekhar J, Madura JD, Impey RW, Klein ML. Comparison of Simple Potential Functions for Simulating Liquid Water. *J Chem Phys*. 1983; 79:926–935.
35. Durell SR, Brooks BR, Ben-Naim A. Solvent-Induced Forces Between Two Hydrophilic Groups. *J Phys Chem*. 1994; 98:2198–2202.
36. Miyamoto S, Kollman PA. SETTLE: An Analytical Version of the SHAKE and RATTLE Algorithms for Rigid Water Models. *J Comput Chem*. 1992; 13:952–962.
37. van Gunsteren WF, Berendsen HJC. Algorithms for Macromolecular Dynamics and Constraint Dynamics. *Molecular Physics*. 1977; 34:1311–1327.
38. Darden T, York D, Pedersen L. Particle Mesh Ewald: An $N \log(N)$ Method for Ewald Sums in Large Systems. *J Chem Phys*. 1993; 98:10089–10092.

39. Essmann U, Perera L, Berkowitz ML, Darden T, Lee H, Pedersen LG. A Smooth Particle Mesh Ewald Method. *J Chem Phys.* 1995; 103:8577–8593.
40. Hoover WG. Canonical Dynamics - Equilibrium Phase-Space Distributions. *Physical Review A.* 1985; 31:1695–1697.
41. Humphrey W, Dalke A, Schulten K. VMD-Visual Molecular Dynamics. *Journal of Molecular Graphics.* 1996; 14:33–38. [PubMed: 8744570]
42. Rossky PJ, Karplus M. Solvation. A Molecular Dynamics Study of a Dipeptide in Water. *J Am Chem Soc.* 1979; 101:1913–1937.
43. Eisenberg, D., Kauzmann, W. *The Structure and Properties of Water.* Oxford University Press; Oxford: 1969.
44. Mason PE, Brady JW. “Tetrahedrality” and the Relationship between Collective Structure and Radial Distribution Functions in Liquid Water. *J Phys Chem B.* 2007; 111:5669–5679. [PubMed: 17469865]
45. Lilley TH, Linsdell H, Maestre A. Association of Caffeine in Water and in Aqueous Solutions of Sucrose. *J Chem Soc Faraday Trans.* 1992; 88:2865–2870.
46. Goto T, Kondo T. Structure and Molecular Stacking of Anthocyanins - Flower Color Variation. *Angewandte Chemie International Edition.* 1991; 30:17–31.
47. Mason PE, Neilson GW, Enderby JE, Sabounji ML, Dempsey CE, MacKerell AD, Brady JW. The Structure of Aqueous Guanidinium Chloride Solutions. *J Am Chem Soc.* 2004; 126:11462–11470. [PubMed: 15366892]
48. Soetens J-C, Millot C, Chipot C, Jansen G, Ángyán JG, Maigret B. Effect of Polarizability on the Potential of Mean Force of Two Cations. The Guanidinium-Guanidinium Ion Pair in Water. *J Phys Chem B.* 1997; 101:10910–10917.
49. Paschek D. Temperature dependence of the hydrophobic hydration and interaction of simple solutes: An examination of five popular water models. *J Chem Phys.* 2004; 120:6674–6690. [PubMed: 15267560]
50. Lum K, Chandler D, Weeks JD. Hydrophobicity at small and large length scales. *J Phys Chem B.* 1999; 103:4570–4577.
51. Wohllert J, Schnupf U, Brady JW. Free Energy Surfaces for the Interaction of Glucose with Planar Aromatic Groups in Aqueous Solution. *J Chem Phys.* 2010; 133:155103. [PubMed: 20969429]

coronene

ovalene

circumcoronene

anthracene

pyrene

naphthalene

indene

azulene

circumcircumcoronene

Figure 1.

The structures of indene, azulene, naphthalene, anthracene, pyrene, coronene, ovalene, circumcoronene, and circumcircumcoronene.

Figure 2. Selected examples of the areas forming the bases of the parallelepipeds used in the analysis of the properties of water molecules above the solute faces. From left to right: cyclobutadiene, indene, ovalene.

Figure 3.

Left, cyclopropane showing solvent water density contoured at 1.7 times bulk density, and right, cyclopentadiene, with surrounding water density contoured at 1.9 times bulk density. For each case, a representative example of a single water molecule contributing to this density is displayed, showing that for cyclopropane the protons tend to point away from the surface, while for cyclopentadiene, they tend to point directly toward the surface.

Figure 4.

The normalized density profile as a function of distance from the surface, $g(h)$ (left), and the orientational distribution function $P(\cos(\theta))$ for water molecules closer to the surface than the first minimum of the density distribution function (right), for the cyclopropane simulation.

Figure 5.
The functions $g(h)$ (left) and $P(\cos(\theta))$ (right) for cyclobutadiene.

Figure 6.
The functions $g(h)$ (left) and $P(\cos(\theta))$ (right) for cyclopentadiene.

Figure 7.
The functions $g(h)$ (left) and $P(\cos(\theta))$ (right) for ovalene.

Figure 8. The superpositioning of the $P(\cos(\theta))$ functions for the smaller solutes (up to azulene and naphthalene).

Figure 9.
The superposition of the $P(\cos(\theta))$ functions for all of the solutes studied.

Figure 10.

The position of the first maximum in the positional distribution as a function of height above the surface, $g(h)$, as a function of surface area, for all of the solutes except cyclopropane and cyclobutadiene (C5-C94).

Figure 11.

The height of the first maximum in the positional distribution function $g(h)$ as a function of surface area, for the solutes C5-C94.

Figure 12.

The full width at half maximum (in $\text{\AA}$) of the first peak in the positional distribution function $g(h)$ as a function of surface area, for the solutes C5-C94.

Figure 13.

A schematic representation of two basal planes of the hexagonal ice I_h crystal structure. Hydrogen bonds are indicated by gray lines.

Figure 14.

Left: probability contour map for water molecules in the first layer above the faces of the solute in the circumcoronene simulations, plotting probability averaged over the simulation versus radial distance from a center molecule and angle between the normal vectors of water molecules at that distance and the molecule closest to the center of the solute. Right: a similar plot for a disk of the same dimensions located far from the solute, the bulk-like region characteristic of pure water. Contours are in counts/Å, with bulk density being 0.033 in these units.

Table 1

Details of the simulations performed.

#C's	Name	Simulation		#H ₂ O's
		Simulation Time (ns)	Box Size Å	
3	Cyclopropane	10	24.863	510
4	Cyclobutadiene	10	24.863	507
5	Cyclopentadiene	10	24.863	507
6	Benzene	10	24.863	505
9	Indene	10	24.863	505
10	Azulene	10	24.863	504
10	Napthalene	10	24.863	505
14	Anthracene	10	24.863	503
16	Pyrene	6	31.079	988
24	Coronene	6	31.079	983
32	Ovalene	6	31.079	978
54	Circumcoronene	4	43.511	2714
94	Circumcircumcoronene	4	43.511	2699

Table 2

General Information.

#C's	Name	Surface Area ² Å ²	$G(h)I$				
			1 st min Å	1 st max Å	1 st peak height	Width at 1/2 max (Å)	Integration to 1 st min
3	Cyclopropane ³	1.00	5.51	3.51	2.5	1.14	3.38
4	Cyclobutadiene ³	2.11	4.99	3.28	2.63	0.98	3.08
5	Cyclopentadiene ³	3.46	4.16	2.97	8.88	0.48	4.82
6	Benzene	5.11	4.61	3.00	5.29	0.55	3.75
9	Indene	8.76	4.74	2.87	5.55	0.54	3.95
10	Naphthalene	10.37	4.72	3.04	3.56	0.69	3.22
10	Azulene	10.23	4.33	2.88	4.69	0.63	3.52
14	Anthracene	15.35	4.90	3.01	2.64	0.95	3.11
16	Pyrene	20.45	4.95	3.09	2.96	0.77	3.13
24	Coronene	35.83	4.88	3.14	2.55	0.92	2.84
32	Ovalene	50.20	4.91	3.19	2.54	0.95	2.91
54	Circumcoronene	97.38	4.89	3.25	2.35	1.06	2.89
94	Circumcircumcoronene	189.84	4.84	3.27	2.48	1.07	3.02

¹ $g(h)$ for a surface perpendicular to the planar surface centered at listed locations. Integration for $g(h)$ where carried out to the 1st minimum.

² Surface areas were estimated from average C-C bond distances obtained from the analyzed 3 ns trajectories.

³ Non aromatic.