

COMMENTS

Comment on “Do Molecules as Small as Neopentane Induce a Hydrophobic Response Similar to That of Large Hydrophobic Surfaces?”

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Following an observation by Kauzmann,¹ Lum et al.² developed a theoretical approach showing that the nature of hydrophobicity at room temperature is entropic for small length-scale, but becomes energetic for large length scale. The dual nature of hydrophobicity should have important consequences for the folding of globular proteins.³ What is the minimum size for which the hydrophobicity changes from entropic to energetic in character is not yet entirely defined.

In a recent article, by means of molecular dynamics, MD, simulations in SPC water, Huang et al.⁴ tried to address if a nonpolar molecule as small as neopentane would be characterized by a large length-scale hydrophobicity. Using the WCA truncated⁵ solute–water interaction potential (i.e., considering solely the repulsive part of the potential), Huang et al. showed that the height of the peak of the water radial distribution function, rdf, around Ar, CH₄, and C(CH₃)₄ decreases from 1.85 to 1.60 and 1.45, respectively. On this ground, Huang et al. suggested the onset of a dewetting-like phenomenon passing from argon to neopentane. Furthermore, Huang et al. showed that the angular distribution of water molecules in the “first” shell of C(CH₃)₄ differs from that around Ar and CH₄, resembling that of water–vapor interface. Water molecules close to a flat extended hydrophobic surface or to the water–vapor interface sacrifice a H bond by pointing a hydrogen atom toward the surface.⁶ A similar orientation would be adopted by water molecules in the “first” shell of neopentane. So Huang et al. concluded: “Neopentane is the smallest molecule so far that exhibits “large molecule” dewetting behavior and thus represents the dividing point between small and large molecule behavior”.⁴

The results of Huang et al. are very interesting because they provide direct structural information on an important topic. Nevertheless, we think that they have to be inserted in the correct well-established perspective not to mislead readers. Even though the analysis of Huang et al. was solely concerned with the structure of the hydration shell, experimental thermodynamic data cannot be ignored. An interested but not so expert reader would conclude from the Huang et al. work that neopentane hydration shows thermodynamic features that differ from those of Ar and CH₄ and resemble those of large hydrophobic surfaces. This is absolutely not true. In the present comment, we would like to reconcile the existing experimental data with the Huang et al. results.

TABLE 1: Thermodynamic Data for the Hydration Process of Argon, Methane, and Neopentane at 25 °C, Corrected for the Ben-Naim Standard State^a

	σ , Å	ΔC_p° , J K ⁻¹ mol ⁻¹	ΔH° , kJ mol ⁻¹	ΔS° , J K ⁻¹ mol ⁻¹	ΔG° , kJ mol ⁻¹
Ar	3.41	195	-9.6	-60.4	8.4
		223	-10.4	-63.1	8.4
CH ₄	3.70	218	-10.9	-64.4	8.3
		244	-11.0	-65.1	8.4
C(CH ₃) ₄	5.89	486	-22.8	-111.7	10.5
		510	-25.5	-123.1	11.2

^a For each solute, the data in the first row are from ref 8; the data in the second row are from ref 9 for Ar and CH₄ and from refs 10 and 11 for C(CH₃)₄.

The Ben-Naim standard⁷ thermodynamic quantities associated with the hydration of Ar, CH₄, and C(CH₃)₄ at room temperature^{8–11} are reported in Table 1. It is evident that for all three solutes ΔG° is large positive, ΔH° and ΔS° are very negative, and ΔC_p° is very positive. There is no qualitative distinction between neopentane and the other two smaller solutes. In particular, the large negative ΔH° value, -22.8 kJ mol⁻¹, of neopentane does contrast with the Huang et al. statement “H bonds must be broken to accommodate neopentane molecules and the energy cost paid in this process is larger than available from normal thermal fluctuations”.⁴ Consider that, according to the calculations of Jorgensen and co-workers,¹² the neopentane–water attractive energy, due to van der Waals interactions, amounts to -36.0 kJ mol⁻¹. Thus, the contribution of H bond reorganization to the hydration enthalpy should amount to 13.2 kJ mol⁻¹. The latter number indicates unequivocally that the insertion of neopentane into liquid water does not cause the breaking of H bonds, since the energy of a single H bond is around 20 kJ mol⁻¹.^{13,14} In contrast, as suggested by Kauzmann,¹ the hydration of large hydrophobic surfaces should have both ΔH° and ΔS° positive, so that ΔG° is positive due to energetic contributions.

The decrease of the height of the peak of water rdf passing from Ar to CH₄ and to C(CH₃)₄ cannot be considered a strong indication that the water structure is changing in a significant manner. In this respect, it is worth noting that the original scaled particle theory, SPT, developed by Reiss and colleagues,¹⁵ predicts that the number of water molecules in contact with the cavity surface decreases on increasing the cavity size. The SPT contact correlation function $G(R_c)$, calculated at 25 °C using as input data solely the experimental density of liquid water and the hard sphere diameter $\sigma_1 = 2.80$ Å of water molecules,¹⁶ is shown in Figure 1. The $G(R_c)$ function, defined as the ratio of the number density of solvent molecules in contact with a cavity of size $R_c = r_c + r_1$ to that in the bulk, shows a maximum of 2.1 at $R_c \approx 2$ Å and then decreases monotonically becoming smaller than 1 at $R_c \approx 7.5$ Å. The depletion of water molecules from the cavity surface is predicted by SPT without the need to introduce explicit information on the structural organization of water molecules in the liquid phase (i.e., the existence of H bonds and the tetrahedral coordination are not needed). In addition, we think that one can correctly speak of dewetting only when $G(R_c)$ is smaller than 1 (i.e., when the number density

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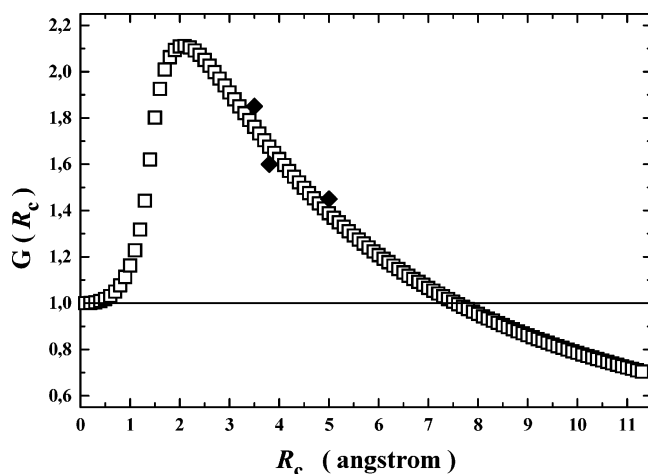


Figure 1. Contact correlation function for water at 25 °C, calculated by means of the original scaled particle theory, using the experimental density of liquid water and a hard sphere diameter of 2.80 Å for water molecules. Note that $R_c = r_c + r_1$, where r_c is the radius of the cavity (i.e., the spherical region from which any part of solvent molecules is excluded) and r_1 is the radius of solvent molecules. The filled diamonds represent the height of the rdf peaks determined by Huang et al. for Ar, CH₄, and C(CH₃)₄ from MD simulations, using the WCA truncated potential. Even though such a comparison is not strictly correct, it may be useful to gain perspective.

of water molecules in contact with the cavity is smaller than that in the bulk liquid). The effect of turning on solute–water attractive interactions on the height of the rdf peak was already investigated and clarified by other authors.^{17,18}

Huang et al. determined also the angular distribution of water molecules in spherical shells of 1 Å width around Ar, CH₄, and C(CH₃)₄. The angular distribution in the “first” shell around C(CH₃)₄ differs from that in subsequent shells and from those around Ar and CH₄, suggesting that water molecules in such a “first” shell lose one H bond. The point here is the average number of water molecules populating such a “first” shell around C(CH₃)₄, that covers the 3.2–4.2 Å range from the center-of-mass of neopentane. The most part of the ≈30 water molecules¹⁹ constituting the whole hydration shell of neopentane populates the “second” and “third” shells defined by Huang et al., as can be simply verified by comparing Figure 3c with Figures 5c and 6c of their article. The water molecules in the “second” and “third” shells have an angular distribution very similar to that of water molecules around Ar and CH₄. This should explain why the hydration thermodynamics of neopentane is qualitatively similar to that of argon and methane.

The correctness of this interpretation is confirmed by the following analysis. According to Figure 4b of Huang et al., the number of H bonds per water molecule in the “first” shell of C(CH₃)₄ is 2.85, whereas it is 3.2 for those in the “second” shell, no less than 3.3 for those around Ar, and 3.45 for those in the bulk. These numbers indicate that, if the fraction of water molecules in the “first” shell of neopentane were substantial, the hydration enthalpy change ΔH° could not be large negative, as it is.

Finally, Huang et al. to rationalize their results for neopentane wrote the following: “the crossover region between typical “small molecule” hydrophobicity and what is observed for macroscopic systems occurs when the solute molecule is much

larger than typical cavities generated by normal fluctuations in the solvent density”.⁴ This statement is absolutely not precise. Pohorille and Pratt,²⁰ by means of MD simulations, determined the cavity size distribution in water at room temperature and showed that the most probable cavity diameter is about 0.5 Å. According to the Pohorille and Pratt cavity size distribution, a cavity of 3 Å diameter, significantly smaller than that suitable to host a neopentane molecule, has a very low probability of occurrence in water. So, a cavity of 3 Å diameter should be considered larger than typical cavities generated by density fluctuations in liquid water. This implies that the Huang et al. interpretation is not correct.

In conclusion, experimental thermodynamic data indicate that the hydrophobicity of neopentane is qualitatively similar to that of small nonpolar solutes such as argon and methane, and differs from that of large hydrophobic surfaces. The structural details provided by the Huang et al. work are important for a more complete understanding but should be interpreted with care. Water molecules reorganize around a nonpolar spherical solute to avoid the loss of H bonds.²¹ This mechanism is always operative, but its complete success depends on the size of the nonpolar solute and is nearly independent of solute–water attractive interactions. On increasing the size of the nonpolar molecule, a fraction of the surrounding water molecules for simple geometric reasons is not able to form all of its potential H bonds. However, in the case of neopentane, this fraction is small and does not affect the nature of neopentane hydrophobicity.

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