

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

X. Huang, C. J. Margulis, and B. J. Berne*

Department of Chemistry and Center for Bimolecular Simulation, Columbia University, 3000 Broadway, New York, New York 10027

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In our paper, molecular dynamics was used to compute radial and orientational distribution functions of water molecules around three different molecules: argon, methane, and neopentane. In addition, the potential of mean force (pmf) between two neopentane molecules was computed. The results for the full OPLS/AA force field were compared with the solute–solvent WCA truncated OPLS/AA force field for these systems. This work addressed the question of whether a molecule of the size of neopentane is large enough to induce a hydrophobic response similar to that of large hydrophobic plates such as molecules or paraffin walls. We found that the orientational distribution of water molecules in a narrow shell proximate to the neopentane molecule was very similar to that near a paraffin wall, in contrast to argon and methane. In addition, the potential of mean force between two neopentane molecules, with the WCA truncated OPLS/AA potential, displayed a dewetting like transition much like that found between two macroscopic hydrophobic objects, albeit with the rejection of only one water molecule. On the basis of both the angular distributions and the pmf, we concluded that neopentane is already large enough to display some of the features observed around large scale hydrophobic solutes. Smaller molecules fit into a water clathrate, whereas larger molecules force the water to reorganize such that at least some fraction of proximate water molecules have dangling OH bonds pointing toward the hydrophobic surface. Graziano does not take issue with the accuracy of the data presented in our paper nor with the methodology used in it. Instead he criticizes some of the conclusions that we draw from our data. In the following, we state or where convenient paraphrase his criticism and then answer it.

1. Comments: “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.”

“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. ...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.” They then go on to say “In the present comment, we would like to reconcile the existing experimental data with the Huang et al. results.”

Answer: Nowhere in our paper do we discuss thermodynamic data for the hydrophobic hydration. In our paper, we showed

that some structural properties of the water molecules next to neopentane are very similar to those of water next to larger hydrophobic objects. In particular, the angular distribution of the OH bond and the distortion and breaking of the hydrogen bond network all show a significant similarity to what is found in the neighborhood of large hydrophobic particles. We never stated that the thermodynamics of solvation of neopentane is the same as that of large macroscopic objects in terms of ΔH , ΔS , and ΔG . With regard to the behavior of these properties we fully agree with Graziano.

2. Comment: “In particular, the large negative ΔH° value, $-22.8 \text{ kJ mol}^{-1}$, 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.’”... “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} .”

Answer: We should have said that a fraction of a hydrogen bond is broken as can be seen from our plot of the average number of hydrogen bonds vs distance (Figure 4), and it can be seen, for example in (b) for neopentane, that one goes from an average of 2.8 H bonds per water in the first shell to 3.4 far away. This is equivalent to losing 0.6 H bonds per water on average (which is consistent with Graziano’s prediction from the thermodynamic data). Clearly since this is an average, some of the time a bond is broken and some of the time it is intact.

3. Comments: “The decrease of the height of the peak of the 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 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 of water molecules in contact with the cavity is smaller than that in the bulk liquid).”

Answer: We agree with both of these comments. In fact we have stated elsewhere the second comment.

4. Comment: “Huang et al. determined also the angular distribution of water molecules in spherical shells of 1 \AA width around Ar, CH₄, and C(CH₃)₄.” Graziano points out that this shell is too narrow to include all of the water molecules in the first hydration shell of neopentane and moreover the enthalpy change for hydration for neopentane would not be qualitatively different from that of smaller solutes.

Answer: We chose a shell thickness of 1 \AA because that thickness is what was used by us and other authors in characterizing the angular distribution of water around large hydrophobic particles, next to paraffin walls,¹ or in the neighborhood of a liquid–vapor interface.² For this shell thickness, we showed that the angular distribution of water molecules around neopentane is very similar to that found around large scale hydrophobes, and we also showed that this is not true for water around Ar or methane. If larger shells were used for the larger hydrophobes or the gas–liquid interface, as Graziano would have us do for neopentane, most of the water molecules would have an angular distribution typical of bulk water as well. If large shells were used for neopentane, only a small fraction of the water molecules in such shells would lose H bonds, an observation consistent with the fact that the

* To whom correspondence should be addressed.

hydration enthalpy change for neopentane is a large negative number. We stand by our use of a small shell size for this comparison. We believe that water in a narrow shell proximate to neopentane behaves, structurally, more like water near large scale hydrophobes than water near Ar or methane. This feature gives a qualitative measure of when, that is for what solute size, one starts to see water reorganize as it does around large scale hydrophobes. It is important to note that there is no solvent depletion around neopentane as around large scale hydrophobes.

We never addressed the thermodynamics of the whole hydration shell, nor is there anything in our paper that disagrees with this.

5. Comment: Finally, Huang et al., to rationalize their results for neopentane, wrote, “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.” This statement is absolutely not precise.

Answer: We agree with this comment. What we meant to say is that water around cavities not much larger than the size of a single water molecule starts displaying an angular distribution that is different from water proximate to cavities smaller or of comparable size to a single water molecule (i.e., argon and methane).

In conclusion, we agree with Graziano that the thermodynamics of neopentane hydrophobic hydration is qualitatively similar

to that of argon and methane. In our paper, the thermodynamics of hydrophobic hydration was not addressed. We focused on structural details to show that neopentane already displays some of the characteristics seen in the hydration of large hydrophobic particles, especially when the solute–solvent potential is WCA truncated, characteristics not seen in the hydration of smaller hydrophobic particles such as argon and methane. In particular, the angular distribution of the water molecules in the near first shell of the neopentane was found to be similar to what is found near large hydrophobic surfaces, with a significant fraction of one hydrogen bond on average being broken near the neopentane molecule. In our paper, we also discussed the thermodynamics of the hydrophobic interaction between two neopentane molecules. The disappearance of the solvent-separated minimum in the neopentane–neopentane potential of mean force (pmf) when the neopentane–water interaction was WCA truncated clearly shows that neopentane is different from small solute such as argon and methane and similar to what happens with large hydrophobic solutes.

References and Notes

- (1) Lee, C. Y.; McCammon, J. A.; Rossky, P. J. *J. Chem. Phys.* **1984**, *80* (9), 4448–4454.
- (2) Taylor, R. S.; Dang, L. X.; Garret, B. C. *J. Chem. Phys.* **1996**, *100*, 11720–11725.