THE ROLE OF ATTRACTIVE FORCES ON THE DEWETTING OF LARGE HYDROPHOBIC SOLUTES

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1. Introduction

The hydrophobic effect[1,2,3] between solutes in aqueous solutions plays a central role in our understanding of recognition and folding of proteins[4,5], and association of lipids[6,7]. This effect has recently been restudied and new mechanisms proposed for its origins.[8] Central to the debate is whether dewetting of the hydrophobic surfaces occurs prior to contact or at distances where water would not be allowed to intervene sterically.[8] Small hydrophobic solutes have been well studied.[9,10,11,12,13,14,15,16] The mechanism by which small solutes are accommodated into the natural cavities of water within the hydrogen bond network is well understood. Solvation of a large hydrophobic solute in water is thought to be associated with an energy cost due to partial disruption of hydrogen bond networks.[8] This mechanism leads to dewetting for specific cases and thus a particular mechanism for the hydrophobic effect. The question then is whether there are other energetic compensations which dictate a differing mechanism.

The energetic imbalance required for dewetting would be maximal when considering a purely repulsive model for nonpolar solutes in water, where incomplete hydrogen bonding might occur near such a repulsive solute with a large radius of curvature. Low dimensional networks of water might not be expected to have sufficient cohesion to be stable near such solutes. The imbalance in forces would cause an effective potential-cavity expulsion potential(CEP) to be generated. The effect of the CEP should increase[17] with increasing size of the solute due to an increasing interfacial region.

According to this picture,[8,18] for a large solute of nanometer size and above, the CEP causes water to be pushed away from the solute surface forming a thin vapor layer around it. When two such solutes come closer to each other, the fluctuations in the vapor-liquid interface between the individual solutes aids in growing the vapor layer and finally create a vacuous or dewetted region between the two solutes. Once the intersolute region is a vacuum, the solutes would then aggregate due to the solvent induced forces on them.

This theoretical picture of dewetting induced collapse [8,19,20,21,22] of large hydrophobic solutes has been supported by simulations[23,24,25,26] using purely repulsive or weakly attractive solute potentials. Theoretical works by Chandler and coworkers,[8,19,20,21] based on a mesoscopic square gradient theory for the liquid-vapor interface imply that hydration behavior interpolates between the traditional view of a small hydrophobic solute to this quite different picture for a large hydrophobic solute for such models.

Recent simulation studies[27,28] on the behavior of water inside an atomistically

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modeled carbon nanotube (CNT) with realistic potentials have observed a one dimensional hydrogen-bonded chain of water molecules inside the hydrophobic nanotube. From the perspective of the theoretical arguments given above this would be unexpected. Earlier simulation studies by Rossky and coworkers[29,30] did not find any water density depression near an infinite repulsive wall.

Differing behavior in other systems has been seen. Further studies on the behavior of water near hydrophobic materials from the recent experimental literature,[31,32] indicate that water may wet a graphite surface and therefore may act as a lubricant between two layers of graphite like other gases. A number of recent experimental investigations[33,34,35,36] indicating contrasting results on the wetting/dewetting of large hydrophobic surfaces by water have made the study of hydrophobic hydration more interesting[37]. Although some recent computational studies[38,39,40] have attempted to elucidate the microscopic mechanism behind the strong attractive interaction between two large plates as observed in some surface force measurements,[41,42,43,44] it is clear that the fairly long ranged attraction, which may extend over several thousands of angstroms[43] to a few hundred angstroms[45] are computationally not feasible at present.

The role of the solute details in governing system behavior is thus apparent from both the theoretical and experimental sides. The role of simulation artifacts like boundary conditions have been explored by Patey and coworkers[46]. That group also explored the role of attractions in simple fluids near plates and found a strong dependence[47]. Observations from Hummer and coworkers[27,48,49] and from the recent studies by Berne and coworkers[25,50] lead one to question the role of the small attractive component of the usual van der Waals interaction, which is often thought[10,51] to have only a minor influence in determining the liquid structure and hence on the hydration phenomena. Although effects of attractive solute-solvent interactions on the hydration water structure around spherical solutes have been studied,[9,10,17,21] conclusions from such studies still show contradictions.

In a series of recent studies[52,53] we have demonstrated how the features of hydrophobic hydration of large solutes dramatically changes with the addition of normal attractive dispersion interaction to its usual purely repulsive counterpart. Here, we review that work and we demonstrate the importance of attractive solute-solvent interaction on the hydration behavior of large hydrophobic solutes and the mechanism of the hydrophobic effect.

2. Methods

We consider here the results from our recent isothermal isobaric (NPT) simulation studies on the solvation behavior of nanoscopic solutes in water. Water was represented by the standard SPC/E[54] model and each of the hydrophobic solutes was modeled as a graphene sheet with carbon-carbon bond lengths of 1.4 Å. The solute was kept fixed and rigid during simulation. The carbon atoms of the solute were modeled as uncharged particles interacting with a Lennard-Jones (LJ) potential with diameter $\sigma_{CC} = 3.4$ Å. The well depth of the LJ potential was varied from $\varepsilon_{CC} = 0.086$ kcal mol^{-1} (or 0.3598 kJ mol^{-1}), corresponding to the sp^2 carbon atom of the AMBER 96 force field,[27,55] to a purely repulsive potential as obtained by the Weeks-Chandler-Andersen (WCA) truncation of the above LJ potential.

The potential of mean force between two solutes in water was calculated from thermodynamic perturbation theory.[56] Details of the simulation methods and other computational procedures have been given elsewhere.[52,53]

3. Results

Potential of Mean Force and Hydration Structure of Nanoscopic Nonpolar Solutes

Let us first discuss the importance of considering solute attraction, which may be small at the atomic scale, on the large solute correlation by comparing the PMFs between two large plates in water with and without attractive dispersion interactions. We specifically compare the PMF between two 60 atom plates with the usual LJ interaction having parameters from the AMBER force field (type I) to that of geometrically equivalent but
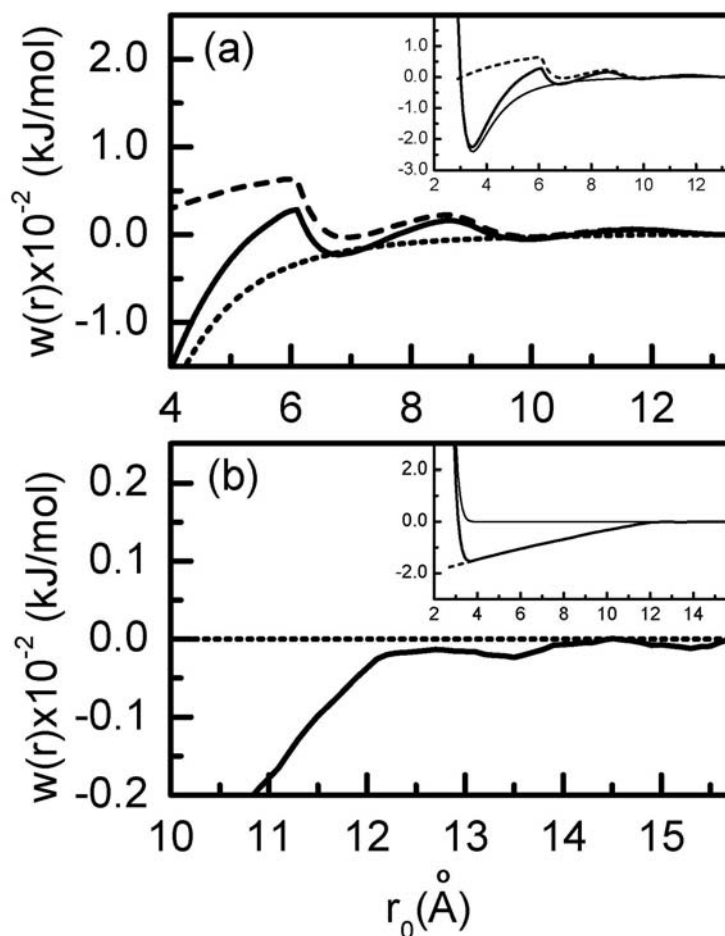

Figure 1. *Solute-solute potential contribution (dotted line) and solvent contribution (dashed line) to the potential of mean force (solid line) for (a) type I solute-water system and (b) for type II solute-water system. The inset in each figure shows the same over the entire range of r_0.*

purely repulsive analogues (type II) of the above LJ solutes. The potential of mean force, $w(r)$, as a function of the separation between the two large parallel plates of type I, is shown in Fig.1(a) and for type II in (b).Although at large separations, the undulating nature of the PMF corresponding to the solvent separated states with varying numbers of intervening water layers, has been observed in both the cases, at shorter separations a remarkable difference between the two PMFs can be seen.

From the decomposition of the PMFs into direct and solvent induced contributions, it was found that the difference in the mechanism of contact pair formation in these two types of solute is striking. For the repulsive solute-solvent system (type II) we find a

large, purely solvent induced stabilization near contact, the direct contribution being zero. This result is consistent with earlier results[24] on the PMF of purely repulsive ellipsoidal solutes and thus eliminates several doubts raised in the literature about the specific water potential[25] and the effect[48] of curvature of the solute used in that study on their results. For the attractive solute plates (type I), however, we find a small solvent stabilization near contact with the overall PMF dominated by the solute-solute attractive potential. Beyond the contact minimum we also find a solvent separated minimum at around an intersolute distance of 6.8 Å, separated by a barrier between the contact and first solvent separated states. For repulsive solutes there is no barrier or solvent separated state around this distance.
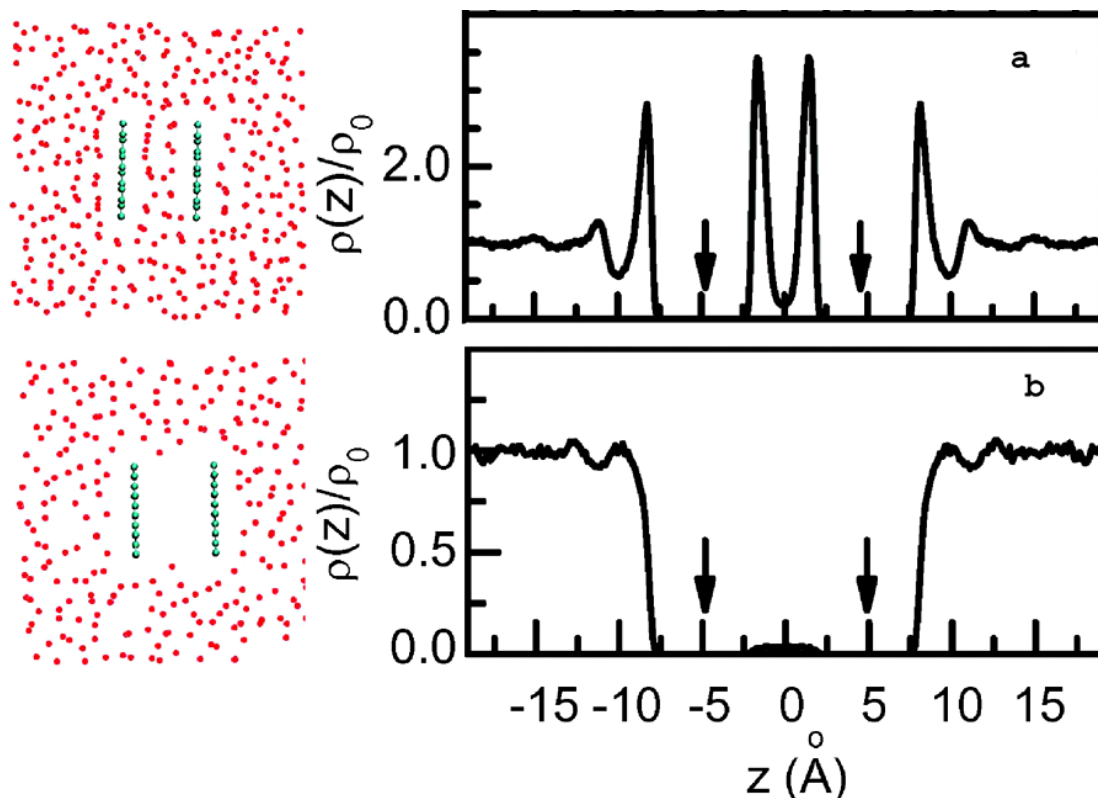

Figure 2. *Solute-solvent distributions. (a) Plot of a configuration for the system with full attractions. Red circles are the positions of the water oxygen atoms and blue circles are the carbon atoms on the solute plates for a slab through the sample. Right: Plot of the normalized single particle density* $\rho(z)/\rho_0$ *as a function of* z, *the distance perpendicular to the plates. Two arrows on the x-axis have been drawn to indicate the position (z-coordinate) of the two plates. (b) same as (a) but without attractions.*

The influence of attractive interaction on both solute-solute and solute-water correlation with simple small spherical solutes has been studied some time ago by Pratt and Chandler[10]. Although using previously used models for solute-water and solute-solute interactions, they found only a weak effect of attraction on the solute-water correlation, with a realistic methane potential, they found a 40 % change in the solute-solvent correlation. Thus, our observation that the solute correlation and PMF are entirely different for the cases of a purely repulsive solute and a LJ solute, is not surprising if we note that the size of the solute considered here is much larger than those used in that study[10].

For the type I system well outside of contact, Fig. 1(a) shows shallow minima in the PMF at separations (r_0) of 6.8 Å, 10 Å and 13 Å. In order to visualize the solvent structure near the solute plates corresponding to the minimum in the PMF, we have shown in Fig. 2(a) the coordinates (single configuration) and the number density profile

corresponding to the minimum at $r_0 = 10$ Å that corresponds to two intervening water layers between the two solutes. The system without attractions (type II) is shown in 2(b). The lack of attractive forces expels the layer of water molecules from the intersolute region.

This shows the importance of taking into account solute attraction in determining the solute-solute correlation and hence predicting the dewetting induced collapse of large hydrophobic particles. Our results are consistent with the observation of a stable water chain inside a CNT[27] and nano cavity[49] as well as the results of Ashbaugh et al.[17] that found enhanced hydration (wetting) of a large single methane cluster in water with the full LJ interactions.

In order to test the stability of the configuration corresponding to the barrier in the PMF at $r_0 = 6.2$ Å that contains a highly strained water layer in the inter solute region, we have calculated (not shown) water occupancy in the intersolute region at this separation as a function of time, for a total simulation time of 2.5 nano seconds. It reveals that the number of water molecules confined between the two plates fluctuates around 14 for most of the time, indicating that the configuration is stable. Although once in that period a large fluctuation made the confined region empty for around 30ps, water molecules again entered the region and within 100ps, the number of water molecules continued to fluctuate around 14, where the average remained for rest of the time.

In order to investigate whether the solute-solvent configuration corresponding to the barrier observed in the solvent induced PMF at $r_0 = 6.2$ is metastable, we also performed a 1.2 ns simulation at this r_0 starting from a dry initial state where the inter plate region is initially empty. This test showed that an empty inter solute cavity is filled by around 14 water molecules within 120ps and thereafter the average number of water molecules remains the same. It is important to mention at this point that there is no first solvent separated state and hence barrier connecting that with the contact pair state in case of purely repulsive solutes (compare PMF of solute I with that of solute II). For the purely repulsive case, the PMF is monotonically decreasing with decreasing intersolute distance below 12 Å. This is due to the fact that all the water molecules are expelled from the intersolute region (see Fig.2(b)) even when the available space from geometric consideration can easily accommodate one to two layers of water. In fact the essentially linear decrease in the PMF (ΔG) with the decrease in the area ΔA of the liquid vacuum interface of the cavity makes it possible to calculate the liquid-vapor surface tension γ_{lv} from the relation $\Delta G = \gamma_{lv} \Delta A$. The liquid-vapor surface tension γ_{lv} obtained[52] in this way for SPC/E water is about 71.7 mJ/m^2. This is in good agreement with that calculated recently[20] from a simulation study of the liquid-vapor interface of the same water model. This indicates that the bubble has been formed in the intersolute region of repulsive plates with a center to center separation of around 10 Å and below and the free energy cost of maintaining the interface strongly resembles that of a free, planar water-vapor interface[52].

In contrast, for the attractive solute, not only is the loss of hydrogen bonds less, there is compensation from the solute-solvent attractive interaction as well. Therefore, in this case we do not observe any dewetting as long as there is steric space available for physically accommodating water in between the two solutes.
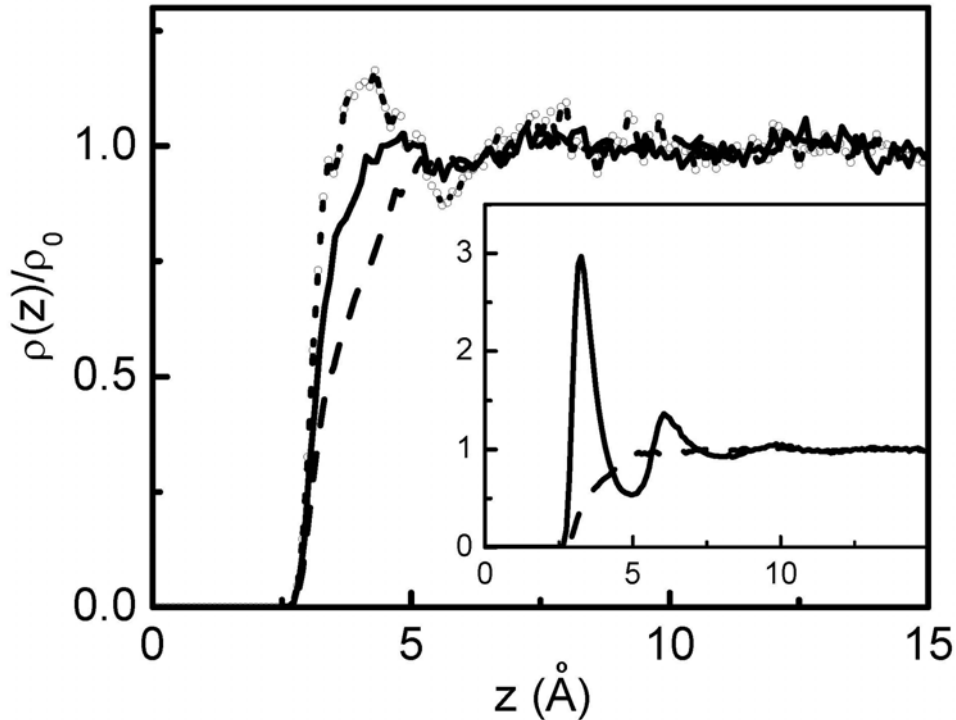
Effect of solute size on hydration

Figure 3. *Plot of the normalized single particle density $\rho(z)/\rho_0$ of water oxygen as a function of the distance perpendicular to the solute plate with solute atoms interacting with repulsive potential (type II) for three different solute sizes (half of the box is shown). The smallest one with 28 atoms shown by an open circle with a line, 60 atoms by a solid line and 178 atoms by a dashed line. In the inset the density profile of water around the largest solute with a purely repulsive interaction (dashed line) is compared with that including the LJ interaction (solid line).*

In order to investigate the effect of solute sizes, we have performed several MD simulation runs in the NPT ensemble with single flat planar solutes of various sizes immersed in water with the same two types of solute-solvent interaction: one with normal attractions and a purely repulsive potential obtained using the WCA approximation[51]. We show the results for the density profiles for three different solute sizes with the repulsive interactions in Fig.3 and with LJ interactions in Fig.4. The nature of density profiles for the repulsive solutes is distinctly different from that of their LJ counter parts. The LJ solutes are significantly wetted as indicated by the sharp well defined density peaks with a contact value or peak height considerably above the bulk density. Moreover, no significant change is observed in this feature with a change in solute size. In the case of the repulsive solute, however, the water density profile is drastically changed from its LJ analogue, with no strong layering around the solute (see the comparison in the inset of Figure 3). Most importantly, we observe a significant change in the water density profile when we change the solute size. The contact peak not only decreases with increasing sizes of the solutes, it rises from zero more slowly over a wide range as well (see the increase in the position of the first peak with increasing solute size).

The water density profile in Figure 3 around the largest repulsive solute plate considered here (21 Å × 21 Å) has been interpreted as showing a vapor-liquid like interface in the vicinity of the solute.[8,20,25] However if one compares (See inset of

Fig 3) this density profile with the one for the same solute size but with LJ interactions, the difference is apparent.
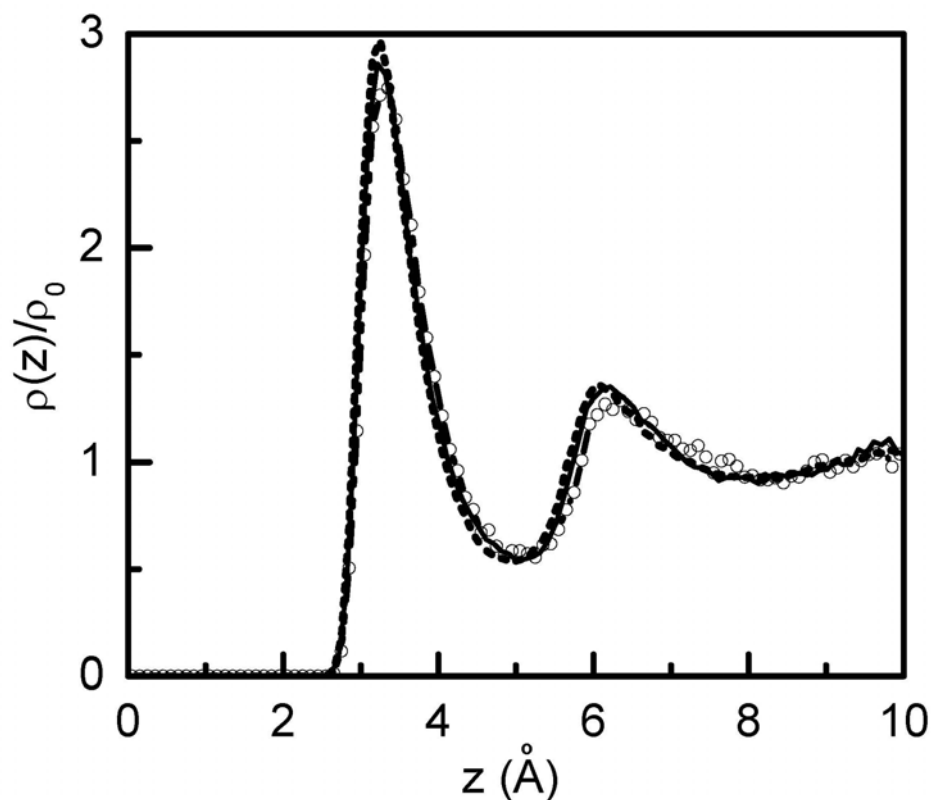

Figure 4. *Same as Fig.3 but the potential of the solute atoms modeled with full LJ interaction.*

This difference in size dependence of the water accumulation around large nonpolar solutes with and without attraction can be well understood in terms of the CEP[48]) that arises due to the imbalance in the attractive forces in water near a large repulsive surface. An increase in solute size causes the CEP to increase[17] due to the imbalance in the attractive interactions and thus water accumulation near the solute decreases with the increase in solute size. However, when an attractive dispersion interaction of the solute is taken into account, the cumulative attractive interaction between the solute and the solvent compensates for this CEP and thus we observe a significant hydration of the nanoscopic solutes without much solute size effect.

4. Conclusion

The results from a series of investigations[52,53] from our laboratory demonstrate the importance of the weak dispersion interactions naturally present in essentially all nonpolar substances to study hydration behavior of such solutes in general and dewetting in the intersolute region in particular. Our results indicate that the dewetting induced collapse of large hydrophobic solutes as predicted by many recent investigations[8,19,22,24,25] based on either purely repulsive or weakly attractive solute potential may not apply to hydrophobic solutes like protein interfaces which have significant polarity and dispersion interactions. These results should be considered when interpreting the mechanism of aggregation phenomena observed in many areas of chemistry and biology.[50]

References

[1] W. Kauzmann, *Adv. Protein Chem.*, 1959, , 1.

[2] Tanford, C. *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*; John Weiley: New York, 1973.

[3] L. R. Pratt and A. Pohorille, *Chem. Rev.*, 2002, , 2671.

[4] C. L. Brooks, J. N. Onuchic and D. J. Wales, *Science*, 2001, , 612.

[5] J. Shea and C. L. Brooks, *Annu. Rev. Phys. Chem.*, 2001, , 499.

[6] G. Hummer, S. Garde, A. E. Garcia and L. R. Pratt, *Chem. Phys.*, 2000, , 349-370.

[7] L. Lu and M. L. Berkowitz, *J. Am. Chem. Soc.*, 2004, , 10254.

[8] K. Lum, D. Chandler and J. D. Weeks, *J. Phys. Chem. B*, 1999, , 4570.

[9] L. R. Pratt and D. Chandler, *J. Chem. Phys.*, 1977, , 3683.

[10] L. R. Pratt and D. Chandler, *J. Chem. Phys.*, 1980, , 3434.

[11] C. Pangali, M. Rao and B. J. Berne, *J. Chem. Phys.*, 1979, , 2975.

[12] D. E. Smith and A. D. J. Haymet, *J. Chem. Phys.*, 1993, , 6445.

[13] G. Hummer, S. Garde, A. E. Garcia, A. Pohorille and L. R. Pratt, *Proc. Natl. Acad. Sci. U.S.A.*, 1996, , 8951.

[14] N. T. Southall and K. A. Dill, *Biophys. Chem.*, 2002, , 295.

[15] J.S. Perkyns and B.M. Pettitt, *J. Phys. Chem.*, 1996, , 1323-1329.

[16] N. M. Cann and G. N. Patey, *J. Chem. Phys.*, 1997, , 8165.

[17] H. S. Ashbaugh and M. E. Paulaitis *J. Am. Chem. Soc.*, 2001, , 10721-10728.

[18] F. H. Stillinger, *J. Solution Chem.*, 1973, , 141.

[19] D. M. Huang and D. Chandler, *Proc. Natl. Acad. Sci. U.S.A.*, 2000, , 8324.

[20] D. M. Huang, P. L. Geissler and D. Chandler, *J. Phys. Chem. B*, 2001, , 6704.

[21] D. M. Huang and D. Chandler, *J. Phys. Chem. B*, 2002, , 2047.

[22] P. R. ten Wolde and D. Chandler, *Proc. Natl. Acad. Sci. U.S.A.*, 2002, , 6539.

[23] A. Wallqvist and B. J. Berne, *J. Phys. Chem.*, 1995, , 2885.

[24] A. Wallqvist and B. J. Berne, *J. Phys. Chem.*, 1995, , 2893.

[25] X. Huang, C. J. Margulis, and B. J. Berne, *Proc. Natl. Acad. Sci. U.S.A.*, 2003, , 11953.

[26] A. Walqvist, E. Gallicchio and R.M. Levy, *J. Phys. Chem.*, 2001, , 6745-6753.

[27] G. Hummer, J. C. Rasaiah and J. P. Noworyta, *Nature*, 2001, , 188.

[28] M. S. P. Sansom and P. C. Biggin, *Nature*, 2001, , 156.

[29] C. Y. Lee, J. A. McCammon and P. J. Rossky, *J. Chem. Phys.*, 1984, , 4448.

[30] S. H. Lee and P. J. Rossky, *J. Chem. Phys.*, 1994, , 3334.

[31] M. E. Schrader, *J. Phys. Chem.*, 1980, , 2774.

[32] M. Luna, J. Colchero and A. M. Baro, *J. Phys. Chem. B*, 1999, , 9576.

[33] R. Steitz, T. Gutberlet, T. Hauss, B. Klosgen, R. Krastev, S. Schemmel, A. C. Simonsen, G. H. Findenegg, *Langmuir*, 2003, , 2409.

[34] T. R. Jensen, M. O. Jensen, N. Reitzel, K. Balashev, G. H. Peters, K. Kjaer and T. Bjornholm, *Phys. Rev. Lett.*, 2003, , 086101.

[35] D. Schwendel, T. Hayashi, R. Dahint, A. Pertsin, M. Grunze, R. Steitz and F. Schreiber, *Langmuir*, 2003, , 2284.

[36] V. Yaminsky and S. Ohnishi, *Langmuir*, 2003, , 1970.

[37] P. Ball, *Nature*, 2003, , 25.

[38] J. Forsman, B. Jonsson and C. E. Woodward, *J. Phys. Chem.*, 1996, , 15005.

[39] D. Bratko, R. A. Curtis, H. W. Blanch and J. M. Prausnitz, *J. Chem. Phys.*, 2001, , 3873.

[40] T. Hayashi, A. J. Pertsin and M. Grunze, *J. Chem. Phys.*, 2002, , 6171.

[41] P. M. Claesson and H. K. Christenson, *Science*, 1988, , 390.

[42] H. K. Christenson, In *Modern Approaches to wettability: Theory and Applications*; M. E. Schrader, G. Loeb, Eds.; Plenum: New York, 1992.

[43] J. L. Parker, P. M. Claesson and P. Attard, *J. Phys. Chem.*, 1994, , 8464.

[44] R. M. Pashley, P. M. McGuiggan, B. W. Ninham and D. F. Evans, *Science*, 1985, , 1088.

[45] J. Wood and R. Sharma, *Langmuir*, 1995, , 4797.

[46] J.C. Shelley and G.N. Patey, *Molecular Physics* , 1996, , 385.

[47] D. R. Berard, Phil Attard, and G. N. Patey,*J. Chem. Phys.*, 1993, , 7286.

[48] G. Hummer and S. Garde, *Phys. Rev. Lett.*, 1998, , 4193.

[49] S. Vaitheeswaran, H. Yin, J. C. Rasaiah and G. Hummer, *Proc. Natl. Acad. Sci. USA*, 2004, , 17002-17005.

[50] R. Zhou, X. Huang, C. J. Margulis and B. J. Berne, *Science*, 2004, , 1605.

[51] D. Chandler, J. D. Weeks and H. C. Andersen, *Science*, 1983, , 787; J. D. Weeks, D. Chandler and H. C. Andersen, *J. Chem. Phys.*, 1971, , 5237.

[52] N. Choudhury, and B. M. Pettitt, *J. Am. Chem. Soc.*, 2004, , 3556.

[53] N. Choudhury, and B. M. Pettitt, *Mol. Sim.*, 2004, , 457.

[54] H. J. C. Berendsen, J. R. Grigera and T. P. Straatsma, *J. Phys. Chem. B*, 1987, , 6269.

[55] D. W. Cornell, W. D. Cornell, P. Cieplak, C. I. Bayly, I. R. Gould, K. M. Merz, D. M. Ferguson, D. C. Spellmeyer, T. Fox, J. W. Caldwell and P. A. Kollman,*J. Am. Chem. Soc.*, 1995, , 5179.

[56] R. W. Zwanzig, *J. Chem. Phys.*, 1954, , 1420.