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Association of alkanes with the aqueous liquid-vapor interface: a reference system for interpreting hydrophobicity generally through interfacial fluctuations

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Abstract

We report free energy calculations and fluctuation profiles of single alkanes (from methane to pentane) along the direction normal to the air-water interface. The induced fluctuations and alkanes' interfacial stabilities are found to be correlated and similar with the results regarding inorganic monovalent ions (Ou *et al.*, *J. Phys. Chem. B*, 2013, 117, 11732). This suggests that hydrophobic solvation of solutes and ions is important in determining the adsorption behavior.

1 Introduction

Phenomena at aqueous interfaces continue to garner attention ^{1,2}. Experimental techniques such as second-harmonic generation (SHG) ³⁻⁷ and vibrational sum frequency generation (VSFG) ^{8,9} enable the studies of the responses of aqueous interfaces to added impurities. Of particular interest has been the different adsorption behaviors of solutes/ions at the aqueous interface ¹⁰⁻¹³. These different adsorption behaviors are important to a variety of physico-chemical and biological processes ¹⁴⁻¹⁶. However, solute adsorption behaviors at interfaces continue to defy a unified theory. For the scale of an ion merging with an extended interface, it has been proposed that the total entropic contribution disfavors the adsorption of ions at the interfaces ¹⁷⁻²⁰. Recent work illuminated the connection between air-water interfacial stability of chemical species (i.e. a free energy minimum state with the ion at the interface) and the extent to which the presence of these molecular species in the vicinity of the interface induces collective fluctuations of the interface in addition to the level inherent in pure water due to thermal motion ^{18,20-24}. These studies further concluded that the malleability of the solvation shell (primarily first shell) around the larger, less charge-dense anions is a critical behavior associated with correlation of anion interface stability and induced interface fluctuations. This malleability of the solvation shell is more specifically the ability of vicinal solvent to exchange with solvent further from the anion, thus behaving collectively as a loosely-held, adaptable environment that can facilitate communication with solvent beyond the vicinal solvation shells. The importance of the properties of the first

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solvation shell of ions has been recently emphasized in the context of large-scale DFT studies by Mundy and coworkers^{10,25-27}. These results suggest that the formation of the hydrophobic cavity along with the partial hydration of the solute is central to the adsorption process, although the balance between short-ranged and long-ranged interactions between the interface and the bulk phase is very subtle²⁸⁻³¹. The notion of “hydrophobic ions” along with the cavity energy has also come to attention within continuum theories in the last decade³²⁻³⁵. The interfacial stability of ions (particularly larger, less charge-dense anionic inorganic monovalent ions) has given reason to consider the prospect of some hydrophobic nature of these ions relative to the smaller, more charge dense, and chemically “hard” anions (such as F^- , Cl^- etc.). It seems appropriate and timely to compare and contrast the interfacial stability properties of these ions with those of simple model hydrophobes, such as linear alkanes. While vast studies focus on the ion-specific adsorption using various force fields, however, to the best of our knowledge, the free energetics for realistic, hydrophobic alkanes reported are relatively limited and concentrated on the adsorption of methane-like solutes and *n*-alkanes^{28,36-40}. We therefore consider a detailed analysis regarding the free energetics and interfacial response to the presence of a hydrophobic solute approaching the aqueous air-water interface. In this article, we calculate free energies as functions of the position of single alkanes along a direction normal to the air-water surface (potentials of mean force, PMF), using nonpolarizable and polarizable force fields (acknowledging these force fields have been carefully parametrized and validated), as well as the corresponding induced surface fluctuation profiles. We will present both *n*-alkanes and isomers with less than 6 carbon atoms, considering their sizes comparable to the scale of spherical ions. We hope to demonstrate some similarities between what are commonly considered canonical hydrophobic species and simple ions. We attempt to explore the idea that the fundamental physical connection between canonical hydrophobes (alkanes in this case) and large interfacially-stable anions lies in the malleability, adaptability, flexibility of their solvation shells. This character of the immediate solvation shells of both types of species leads to greater ability for water to leave the immediate vicinity of the solute. This environment of greater solvent density fluctuation can then couple with other similar environments (eg. extended, significantly hydrophobic interfaces such as the liquid-vapor interface) and allow for solute association with the interface. Thus, we attempt to draw attention to more general aspects of the solvation shells that transcends the underlying mechanisms that give rise to the structure or dynamics of these shells.

This study is organized as follows. In Section 2 we outline the methods, force fields, and related issues. We next present our results and discussions in Section 3, including the PMF of single alkanes and corresponding induced liquid-vapor surface height fluctuations. We conclude our study in Section 4 with a summary of our findings.

2 Method

2.1 Simulation Details

Molecular dynamics simulations were performed with NAMD 2.9b3^{41,42}. Simulations of liquid-vapor interfaces were performed in the *NVT* ensemble. Temperature is fixed at 300 K via a Langevin friction force with damping coefficient of 5ps^{-1} . A rectangular bulk slab (40

($40 \text{ \AA} \times 40 \text{ \AA} \times 150 \text{ \AA}$) consisting of 1977 TIP3P/SWM4-NDP water molecules with a single alkane (methane, ethane, propane, *n*-butane, isobutane, *n*-pentane, and neopentane) was positioned in the center of the simulation cell. We use the CHARMM36 all-atom force field⁴³ for simulations with rigid SHAKE⁴⁴-restrained TIP3P water⁴⁵; parameters for simulations using Drude Oscillator Model are from Reference^{46,47}. Three-dimensional periodic boundary conditions are applied. Particle Mesh Ewald (PME)⁴⁸ was implemented to treat conditionally convergent long-range electrostatic interactions using a grid of $40 \times 40 \times 150$ points. Lennard-Jones interactions were gradually switched off over the range $10 \text{ \AA}$ to $12 \text{ \AA}$.

PMFs as single alkanes approach the aqueous air-water interface are computed to characterize the interfacial stability of the alkane. We consider single alkane potentials of mean force for several reasons. First, since we compare directly to the behaviors of single ions as they approach the liquid-vapor interface, we maintain that a similar analysis be applied for the alkanes. Second, if one considers that the liquid-vapor interface is indeed a limiting case of a hydrophobic interface, then the consideration the present PMF's make is one of association of two hydrophobes; in effect, this is the association of ions-with a hydrophobic interface as well as of hydrophobes with a hydrophobic interface. The hydrophobic effect is often considered in the context of multiple hydrophobic species associating, thus the present computational scenario contains some value. Finally, by considering the behaviors of single alkanes, much as we do for single ions, we can systematically decompose underlying similarities between the species.

To calculate PMFs, alkanes are restrained to z -positions from 0 - $40 \text{ \AA}$ relative to the water slab center of mass using a harmonic potential with force constants $4 \text{ (kcal/mol)/\AA}^2$; this encompasses a range approximately $18 \text{ \AA}$ below the Gibbs Dividing Surface (GDS) to approximately $22 \text{ \AA}$ above it. For discussions in this manuscript, we use the position of GDS as 0 and therefore simulation windows are translated between -18 and $22 \text{ \AA}$. PMF's were then calculated using the Weighted Histogram Analysis Method (WHAM)⁴⁹. Total sampling time for each window was 11 - 16 ns ; properties were calculated from all but the first nanosecond, which was treated as equilibration.

2.2 Instantaneous Interfaces and Surface Fluctuations

Interfacial fluctuations are computed relative to a mean surface, obtained as an average of instantaneous surfaces. We obtain coarse-grained, continuous instantaneous surfaces by Gaussian smoothing discrete, atomically-resolved surfaces⁵⁰. In practice, we compute coarse-grained densities $\rho_{\text{oxygen}}(x, y, z)$ at points on a grid (x, y, z) . The resolution for the grid is $1 \text{ \AA}$ in x and y -dimensions, and $0.5 \text{ \AA}$ in z -dimension. The instantaneous surface is obtained as the manifold by setting $\rho_{\text{oxygen}}(x, y, z) = \frac{1}{2} \rho_{\text{oxygen, bulk}}$. Averaging these instantaneous surfaces ($h_t(x, y)$) one obtains the mean surface ($\bar{h}(x, y)$). Subtracting the mean values from instantaneous $h_t(x, y)$, yields $\delta h_t(x, y)$ and the height fluctuations $\delta h_t^2(x, y)$; by construction, $\langle \delta h_t(x, y) \rangle = 0$. Detailed analyses for convergences and uncertainties for surface fluctuations can be found in Supplemental Material⁵¹. Using this framework to characterize interface fluctuations, we can probe the magnitudes of interface fluctuations when the ions reside at various positions along the reaction coordinate.

3 Results

Figure 1 and Figure 2 show the PMF's as functions of the restrained single alkane at z using CHARMM36 and Drude force fields, respectively. The uncertainties in PMF's are determined using the approach of Zhu and Hummer⁵².

$$\text{var}[G(\xi_N)] \approx \sum_{i=1}^N \text{var}[K\Delta\xi z_i] \quad (1)$$

where z_i is the mean position of z in the i_{th} window, which can be obtained from block averages⁵³. K is the force constant. The corresponding standard deviation $\sigma[G(\xi_N)]$ is then the square root of $\text{var}[G(\xi_N)]$. Uncertainties at the PMF minima are approximately 0.06 kcal/mol; the largest uncertainties for the systems are less than 0.15 kcal/mol (discussed in Supplemental Material⁵¹). The free energy differences between bulk/vapor state ($z = -18$ or $22 \text{ \AA}$) and the global minimum, marked as $G_{\text{bulk}}/G_{\text{vapor}}$, are presented below each PMF. In general, all alkanes exhibit free energy minima in the interfacial water region (slightly in the vapor side of the interface); the minimum becomes deeper as the number of carbon increases. For the same molecule, deeper minima are found using Drude polarizable force fields; however, the values of $G_{\text{vapor}} - G_{\text{bulk}}$ (hydration free energy) are similar. We include the calculation of number of water molecules around the carbon atoms throughout the simulation windows in Figure 3; within the radius of $5 \text{ \AA}$ from all the carbon atoms, alkanes are still surrounded by more than six water molecules at the state of free energy minimum.

We next address the air-water interface fluctuation profiles as the single alkanes move from water bulk to the vapor. Figure 4 displays the height fluctuations induced by single n -pentane at the simulation window $z = 12.0 \text{ \AA}$. Although n -pentane is the most chain-like and least spherical in the current study, we still see a radial symmetry for the fluctuation profile $r = \sqrt{x^2 + y^2}$ and consequently present data as a function of the lateral distance $\langle \Delta h^2(x=0, y=0) \rangle$. This is true for all the simulation windows and all the solutes in this study (refer to Supplemental Material for the fluctuation profiles of other windows⁵¹), hence $\langle \Delta h^2 \rangle$ is considered as the characteristic value to help illustrate the fluctuation profile as a function of the alkane's z -position. In the case of pure water (in the absence of solutes), $\langle \Delta h_L^2 \rangle$ for the current system size for the current force fields are 1.30 (TIP3P) and 1.05 (SWM4-NDP). This difference is most likely a manifestation of the higher surface tension of the SWM4-NDP water model compared to that of TIP3P. Therefore, in order to demonstrate and compare the fluctuations induced from the alkanes in different force fields, we define $\{\Delta h^2\}$ as the fluctuations normalized by the value of pure water fluctuation in the corresponding force field. Here we would like to address that, although the surface fluctuation of pure water for the same force field does change according to the size of the simulation cell (basically, the larger the x, y dimensions, the larger the fluctuation value), the normalized $\{\Delta h_L^2(0, 0)\}$ remains the same for the same solute at the same relative position

along the reaction coordinate, which indicates that the solute-induced fluctuation is indeed a characteristic of the solute and is system size independent (for the range of system sizes we consider). The results of alkane-induced fluctuation profiles using non-polarizable force fields are displayed in Figure 5.

Generally, when the solute is 4-6 Å below the GDS, the fluctuation shows a maximum. As the molecule moves closer to the GDS, the fluctuation is reduced; when the alkane resides at the GDS, the fluctuations are suppressed relative to the inherent fluctuation of pure water. The enhancement of fluctuations is related to the solvent spatial perturbations by the alkane. As an alkane approaches the air-water interface, its solvation shell water couples with interfacial water; the surface fluctuation is amplified to a maximum when the edge of the first hydration shell of the alkane coincides with the GDS. This process can be demonstrated by employing the 360° angle-averaged radial water density around the solute as it resides at different z -position, as shown in Figure 6. This figure demonstrates the different manners in which the hydration shells of the single methane couple with the solvent at the interface at $z = -18.0, -6.0, -4.0$ and 0.0 Å. At $z = -6.0$ Å, the methane retains its first hydration shell, sheds its outer hydration layers in the sense that these shells intermingle with the interfacial solvent. At $z = -4.0$ Å, the first hydration shell breaks; solvent redistribution and exchange occurs and thus induces more interfacial fluctuations. This behavior is in general reminiscent of the I^- anion shown in Figure 6A of reference ²¹. Furthermore, there is evidence of water residence times in first hydration shells of various anions (based on Grote-Hynes and reactive flux approaches incorporating quantum nuclear effects) suggesting that for larger anions such as I^- , water is not as persistent in the first hydration shell as it is for smaller ions such as Cl^- and F^- ⁵⁴. This suggests a “hydrophobic” nature of the anions, and in particular, those with relatively low charge density as modeled in a classical point-charge plus Lennard-Jones type of force field.

Previously, we reported that near the (hydrophobic) interfaces, ions can be differentiated depending on the associated induced interfacial fluctuations ^{21,23}. By plotting the maximum interfacial fluctuation (ΔG) versus the value of the PMF at the position of the minimum (G) for various spherical monovalent ions, we found a force-field-independent best-fitting line, indicating a threshold of $\Delta h_L^2 \approx 1.5$ dividing those ions that are interfacially stable and those that are not ²¹. The same analysis is performed here as the main focus of this study is on the correlation of the behaviors of hydrophobic solutes and ions with respect to induced interface fluctuation and interfacial stability, as presented in Figure 7.

We note that for the case of alkanes, the vapor state is chosen as the reference to define our G , which may seem unorthodox since the maximum fluctuation of the liquid-vapor interface happens at a position on the bulk-side of the GDS. Since our attempt is to correlate free energetic behavior of ions approaching a liquid-vapor interface with that for alkanes approaching the same interface, the fluctuations used in a correlative analysis should be at similar points. Furthermore, alkanes are essentially desolvated in the vapor phase, making the analysis of induced fluctuations of the liquid-vapor interface difficult from the vapor side of the GDS. The difficulty arises because the induced interfacial fluctuations are mediated by the solvation shell (at least first and second) water molecules surrounding the solutes.

Towards the vapor side of the GDS and beyond, the alkanes as modeled with all-atom force fields are completely desolvated, and thus a reference position for the maximum fluctuation toward the vapor side of the GDS is not amenable nor tractable for use in the present type of analysis. On the other hand, the positions of the PMF minima between ions and alkanes have a subtle but significant difference. While surface-stable ions happen to show PMF minima at the bulk side of GDS, on the contrary, the PMF minima of alkanes tend to be reside at the vapor side of the GDS. These observations combined with the fact that alkanes have a lower free energy state being at the vapor than at the bulk (while ions are totally reversed, as shown in the Supplemental Material ⁵¹), we believe that the choice of using vapor state to define our G for alkanes is reasonable.

From Figure 7, we observe that alkanes inducing more fluctuations show stronger interfacial stabilities. Included are results of spherical monovalent ions adapted from Reference ^{21,23}

for comparison. A linear relationship between $\langle \Delta h_{L,max}^2 \rangle$ and G is found with a best-fit intercept of 1.51, which is very close to the result obtained for spherical monovalent ions (1.53). The intercept value of 1.5 is not necessarily an absolute threshold; this may be sensitive to the parameters of the calculation protocol (eg., width of Gaussian for coarse-graining water density) used to compute instantaneous interfaces and fluctuations; nevertheless, the qualitatively similar behavior between alkanes and spherical ions should be robust. Analogous to enhanced solvent density fluctuations seen for molecular hydrophobic solutes in water ^{55,56}, as the solute becomes more hydrophobic, it perturbs solvent structure and dynamics leading to more fluid, dynamic, and fluctuating solvent structure. These results recapitulate the idea put forth by Noah-Vanhoucke *et al.* that there exists an interface-based entropic benefit for moving a volume-excluding solute from bulk to a position within the interface below the water surface; the free energy penalty for loss of electrostatic water-solute interactions becomes dominant after the passage of the solute through the water surface and into the vapor-like regions ⁵⁷. In that work, the interface entropy derived from fluctuations of the interface height is determined using analytics derived from information theory. Due to the significant dependence of this entropy on the parameters of the algorithm, only qualitative trends are extractable from such an analysis as a function of the position of the solute relative to the liquid-vapor interface. The estimation of this interface-derived entropy (as a function of several solute positions relative to the interface for methane and pentane) along with its convergence in this adsorption process based on our surface height fluctuation analysis is included in the Supplemental Material ⁵¹. The difference of interface entropy relative to the solute positioned in the bulk solvent is calculated as $S_{largest} = S(z = -4) - S(z = -18) = 82.5k_B$, $S_{interface} = S(z = 0) - S(z = -18) = -34.7k_B$, while $S_{largest}$ and $S_{interface}$ refer to the increment/reduction of entropies when the methane is placed at the position that generates the largest fluctuation or at the interface. For the case of pentane, these values are $S_{largest} = 184.1k_B$ and $S_{interface} = -37.1k_B$, respectively.

We also observe different slopes for alkanes and ions in Figure 7. This may be related to differences in the inherent hydrophobicity of alkanes and ions. Solvent density fluctuation is enhanced in the vicinity of a hydrophobic solute, implying relatively malleable hydration shells with more frequent exchange of water between shells. However, in the case of ions,

solvated water molecules are held with preferred orientations due to the presence of net charge, thus suppressing the possible exchange/redistribution of solvent around the ion, and thereby suppressing more distal perturbations/fluctuations of the solvent density (i.e., the rippling, or density fluctuations around the solute, as seen in Figure 6, is diminished). Furthermore there is a geometrical difference between alkanes and ions. Although in this study we chose small hydrophobic solutes to accommodate the scale of ions, alkanes still have more structural configurations than simple spherical ions. Some configurations may induce more surface fluctuations during the alkanes' adsorption processes. When the long axis of the alkane is perpendicular to the interface, the alkane's effect to the fluctuations may be close to an ion; however, when the long axis of the alkane is parallel to the interface, the induced fluctuation may be larger. Further studies regarding these two aspects are needed and still continuing.

4 Summary and Conclusions

The calculations of free energy profiles of single alkanes imply that the adsorption of alkanes at the air-water aqueous interface is thermodynamically favored based on classical force field models of interactions between aqueous solvent and simple short-chain alkanes. By computing the surface fluctuations induced by a series of alkanes, we find a relationship between the induced fluctuations and alkanes interfacial stabilities; the more favorable an alkane is to reside at the interface, the larger possible fluctuation it generates due to solvent redistribution. Overall, results combined with our previous studies of ion-specific surface adsorption of inorganic monovalent anions may be discussed in the context of increasing solute hydrophobic character as recently suggested^{19,58}. Based on Figure 7, we observe that considering the correlation between induced interfacial fluctuations and solute adsorption free energy (PMF minimum), there emerges a continuum of behaviors that appear to be related, particularly for those solutes displaying inherent abilities to adsorb to the aqueous liquid-vapor interface. Larger anions, particularly those that are modeled classically with low charge-density, behave as canonical hydrophobic solutes with respect to their solvent-mediated interactions with soft interfaces such as the aqueous liquid-vapor interface. Underlying this phenomenon is the fundamental nature of the solvation shell structure, dynamics, and rigidity around the solutes. These ideas call for further study regarding specific details about the nature of the relationship between fluctuations, degree of solute hydrophobicity, solute solvation/hydration shell properties, and interfacial stability.

Regarding the idea of trying to connect the natures of true hydrophobes such as alkanes to larger ions (less charge dense) we are borrowing from the work of Garde *et al.* over the recent years^{56,59-62} shedding light on further signatures of hydrophobic solutes. This work has shown that fluctuations of water density around what are known as canonical hydrophobic molecules and surfaces are enhanced in comparison to polar or high charge-density surfaces. In connecting the induced interfacial fluctuations of the water liquid-vapor interface (effectively what amounts to a density fluctuation in the vicinity of the solute) of ions and alkanes, we see that there is a degree of hydrophobic signature displayed by ions that demonstrate interfacial stability as do alkanes. Since the interface is between water and an ideal hydrophobe (vapor), we find it interesting that both the alkanes (naturally preferring to reside at such an interface) and the larger ions (less charge dense) show interfacial

stability that correlates with the ability to induce enhanced interfacial fluctuations (or water density fluctuations). Thus, since the larger anions prefer to associate with the interface (which has an ideal hydrophobe adjacent to the polar water) as evidenced by a negative free energy, we think that drawing an analogy between ions and alkanes with regard to this observable is warranted. Furthermore, we are trying to indicate that regardless of the mechanism that underlies the solute-solvent interactions (i.e., dipole-charge versus dispersion only), the final/ultimate physical manifestation of the combination of interactions and forces must lead to an enhancement of solvent density / interfacial fluctuations in order for so-called hydrophobic behavior to be observed. The hydrophobic behavior that we are concerned with is the tendency for a solute to prefer to some extent, an interfacial state relative to a purely solvated state. Finally, Patel *et al.*⁵⁶ have recently put forth the idea of how biophysical systems “sit at the edge” of what are ostensibly phase transitions that are fundamentally characterized by enhanced fluctuations in relevant order parameters, the solvent density and interfacial fluctuations being relevant order parameters in this work. This suggests a complementary view of hydrophobic nature of solutes in which the solvent environment is typical of one at a phase transition which in this case would be the “dewetting” or “drying” of the solvation shell in order to accommodate association of hydrophobes. With a malleable solvent shell around themselves, such solutes can facilely associate, the hallmark signature of the hydrophobic effect.

We can further say that there is a thermodynamic consequence arising from a “more-or-less universal” situation established by various/different mechanisms. In the case of ions, a “loose” or “malleable” hydration shell (solvation shell) provides a way for the system to discern the position of most favorability of the ion. Likewise, a similar characteristic of the solvation shell for alkanes is at play. The specific approaches used by the ion or the alkane to realize/effect/induce/establish a situation that causes a malleability of the solvation/hydration shell are different (ion-dipole versus water-water interactions, i.e.), but the point of focus is the general necessary (though perhaps not sufficient) condition of solvation shell malleability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1. Potential of mean force as a function of the z -position of a single alkane along the direction normal to the TIP3P water surface. An offset of 2 kcal/mol is added at the minimum state for clarity. Numbers below the PMF's indicate the free energy difference between bulk/vapor state ($z = -18$ or $22 \text{ \AA}$) and the global minimum, which are marked as $G_{\text{bulk}}/G_{\text{vapor}}$.

Fig. 2.

Potential of mean force as a function of the z -position of a single alkane along the direction normal to the SWM4-NDP water surface. An offset of 2 kcal/mol is added at the minimum state for clarity. Numbers below the PMF's indicate the free energy difference between bulk/vapor state ($z = -18$ or 22 Å) and the global minimum, which are marked as $G_{\text{bulk}}/G_{\text{vapor}}$.

Fig. 3. Average number of water molecules within the sphere of radius of 5 $\text{\AA}$ from carbon atoms of single alkanes in CHARMM36 force field.

Fig. 4.

Average surface fluctuation $\{\Delta h^2\}$ for single pentane, for the simulation window that induces the largest fluctuation.

Fig. 5.

$\{\Delta h_L^2(0, 0)\}$ for single alkanes at different restrained window relative to the Gibbs dividing surface.

Fig. 6. Average water oxygen density ($\text{\AA}^{-3}$) relative to single methane at the position of -18.0 , -6.0 , -4.0 and 0.0 $\text{\AA}$.

Fig. 7.

Largest normalized fluctuation for alkanes and ions as a function of corresponding free energy of adsorption. The legend shows the linear fitting results using only the data for alkanes or ions. In general, the uncertainties of ΔG and $\langle \delta h^2 \rangle$ are less than 0.15 kcal/mol and 0.1 Å², thus the error bars are not shown for clarity. Black circles and red rectangular mark the results of alkanes in TIP3P and SWM4-NDP. Blue triangles and purple diamonds mark the results of ions using TIP3P and SWM4-NDP, while are adapted from Reference^{21, 23}