Effect of Salt on the Dynamics of Aqueous Solution of Hydrophobic Solutes: A Molecular Dynamics Simulation Study†

Niharendu Choudhury*

Theoretical Chemistry Section, Chemistry Group, Bhabha Atomic Research Centre, Mumbai 400 085, India

The effect of salt concentration on the dynamics of the aqueous solution of small hydrophobic solutes is presented. We have performed molecular dynamics simulation in an isothermal−isobaric ensemble of methane in water without and with sodium chloride of different concentrations at standard temperature and pressure. Mean square displacements of methane, water, and ions have been calculated from the analysis of simulation trajectories, and diffusion constants have been obtained from slope of the respective mean square displacement (MSD) plot. Translational mobilities of these molecules are shown to decrease with the increase of salt concentration. Whether any correlation exists between the translational dynamics and the structure of constituent particles in the solution has been investigated. Analysis of the methane−methane radial distribution function reveals that the decreasing mobility of methane molecules is a consequence of the increasing hydrophobic interaction between methane molecules as the concentration of the salt increases. For ions also, the same correlation is observed, whereas in the case of water decreasing mobility is not directly related with its structure.

Introduction

Since aqueous salt solutions form matrices for biological molecules, it is perhaps not surprising that many biological self-assembly processes such as protein folding, membrane formation, and molecular recognition, etc. are sensitive[1−4] to the nature and concentration of ions. It is believed that solvent induced interaction between hydrophobic molecules in water, known as hydrophobic interaction, is one of the dominant forces[5−9] in many self-assembly processes. The hydrophobic interaction is greatly influenced by the presence of salt in the medium.[2] Depending on the nature and concentration of the salt solution, either aggregation or dissolution of hydrophobic solutes in water takes place. Knowledge of the effect of salt on the structure and dynamics of hydrophobic solutes and other constituent particles in the medium such as ions and water is of fundamental interest for the understanding of aggregation phenomena in biological systems.

Although the importance of the hydrophobic effect is well recognized and many investigations[10−15] have been devoted to understand it, all facets of it are not yet completely understood. Even the dissolution and aggregation of a small hydrophobic solute like methane in water is not well understood, and theoretical and computational endeavors to understand methane hydration are still going on.[16−24] In particular, understanding the behavior of methane in water is of fundamental as well as industrial importance. As the methane + water system is one of the simplest system to investigate computationally, fundamental insight into hydrophobic effect and hydrophobicity induced aggregation can be achieved easily. Investigations on the behavior of hydrophobic solutes at the small lengthscale is the first step toward understanding hydrophobicity at larger lengthscales, at which manifestation of hydrophobicity is believed to be different and not well understood.[25−32] Apart from this, clathrate hydrate formation[33,34] by methane in the presence of water is of practical concern as it poses hazards in oil and natural gas drilling and explorations. Clathrate hydrate is a solid in which hydrophobic gas molecules occupy cages formed by hydrogen bonded water molecules. The investigations on the effects of temperature, pressure, and other chemicals on the formation and dissolutions of the gas hydrates are thus of immense industrial importance.

Many recent studies[21,35−40] have been devoted to understanding the role of hydrophobic effect on the aggregation−dissolution of methane in water. Theoretical studies in this respect started long ago. A true statistical mechanical description of the methane + water system has been provided by the work of Pratt and Chandler[16,17] and subsequent simulation study by Berne and co-workers.[17] Since then, many aspects of hydrophobic hydration at the small lengthscale have been studied thoroughly. Many theoretical investigations involving integral equation theory,[16] scaled particle theory,[8] information theory,[18] and simulations[19−21,41] have been reported. The thermodynamics of hydrophobic hydration and aggregation of methane in water have been studied in detail by many research groups.[13,42−46] The pressure dependence of the potential of mean force between two methane molecules in water has also been investigated[36,47] and its connection to pressure induced denaturation of protein has been discussed. The effect of temperature on the aggregation of methane molecules in water has been studied. The solubility of methane in water is directly related to the free energy of solvation, and several studies[21,38] have focused on the development of a suitable methane + water model to reproduce experimental solubility data as a function of temperatures.

Electrolytes are naturally present in the biological systems and its effect on the self-assembly of biological molecules is significant. A large body of work[19−21,37,40,41,48,49] has therefore been devoted to understand the effect of electrolyte on the behavior of hydrophobic molecules in water. Quantification and suitable explanation of the well-known Hofmeister (solubility)

---

* To whom correspondence should be addressed. E-mail: nihcho@barc.gov.in and niharc2002@yahoo.com.

† Part of the special issue “Robin H. Stokes Festschrift”.

10.1021/je8004886 CCC: $40.75

Table 1. Number of Each Species Used in the Simulations of Aqueous NaCl Solutions of Concentration *c*

N_{Me}[a]	N_{H_2O}[a]	N_{Na^+}[a]	N_{Cl^-}[a]	c/mol·L^{-1}
20	995	0	0	0.00
20	955	20	20	1.15
20	915	40	40	2.39
20	885	55	55	3.39

[a] N_{Me}, N_{H_2O}, N_{Na^+}, and N_{Cl^-} are numbers of methanes, water molecules, Na^+, and Cl^-, respectively.

Table 2. Potential Parameters (LJ Well Depth ϵ, LJ Size Parameter σ, and Partial Charge q) for Different Species Used in the Simulation

atom	ϵ/kJ·mol^{-1}	σ/nm	q/e
Me	1.2340	0.3700	0.0000
Na	0.4184	0.2580	+1.0000
Cl	0.4184	0.4400	−1.0000
O (SPC/E)	0.6502	0.3169	−0.8476
H (SPC/E)	0.0000	0.0000	+0.4238

effect[2] in protein solutions have been the subject matter of many investigations over the decades. The effect of monovalent and divalent salts on the hydrophobic interaction of methane in water[41] as well as the nature of the salt ions on the hydrophobic interaction of methanes in water have been studied recently.[48,40] The reduction in hydrophobic interaction upon addition of NH_4Cl has been shown[48] to result from their reduction of structural fluctuations, whereas increase in hydrophobic interaction due to guanidinium chloride is attributed to its ability to make large solvation shells. Dynamics of association has also been studied, and the lifetime of the hydrophobic association has been shown to increase upon salt addition. How a basic parameter like charge density on the ion modifies the hydrophobic interaction leading to experimentally observed "salting-in" and "salting-out" phenomena has also been investigated.[40] A conceptually simple but useful effort toward understanding the salt effect is the preferential solvation/exclusion model by Timasheff and co-workers,[50] and it has been successfully used[37] to explain the effect of electrolytes on the solvation free energy as well as pair and manybody hydrophobic interactions of methane in water. In order to understand the effect of salt on hydrophobic hydration and hydrophobic interaction, most of these studies have focused on the interaction between salt and the hydrophobic solutes. Recently the Hofmeister effects of small hydrophobic solutes has been explained[49] in terms of the extent of hydrogen bonding in electrolyte solution without hydrophobic solutes. From this study, it appears that the change in water structure due to addition of salt is more fundamental to the Hofmeister effect than preferential interaction between small hydrophobic solutes and the salt.

Most of these investigations have studied the influence of salt on the structural and energetic aspects of methane hydration, and there are a few reports on the dynamics of the hydrophobic solutes in water. The effect of salt on the dynamics of small hydrophobic solutes and other constituents in the ionic solution has not been investigated so far. In the present investigation, we therefore intend to study the effect of salt on the translational diffusions of hydrophobic solutes and other constituents such as ions and water. We also try to find out whether any possible correlation exists between the dynamics and the structure of the constituent particles in the medium. In what follows, in the next section I describe the model and simulation method, followed by the results and discussion and a brief concluding remark.

Models and Methods

In order to investigate the effect of salt on the dynamics of an aqueous solution of small hydrophobic solutes, molecular dynamics (MD) simulations of 20 methane molecules in aqueous solutions of varying NaCl concentrations, namely (0, 1.15, 2.4, and 3.4) mol·L^{-1}, have been carried out. The number of species included in each simulation is given in Table 1 The methane molecule was represented as a spherically symmetric united atom Lennard-Jones (LJ) solute. The salt ions Na^+ and Cl^- were modeled as charged spherical LJ solutes with the charge located at the center. Water in the simulation was represented by the SPC/E model.[51] The potential parameters for water, methane, and ions are tabulated in Table 2. For solute−water, solute−ion, and water−ion interactions and for the interaction between positive and negative ions, cross parameters for the LJ potential were obtained by the Lorentz−Berthelot mixing rule.

All the simulations were performed at constant temperature and pressure (isothermal−isobaric (NPT) ensemble) with molecular dynamics extended system approach of Nose and Anderson.[52] Initially around 1000 SPC/E water molecules were simulated in the NPT ensemble with a target pressure of T = 298 K and P = 1 atm (760 bar) for equilibration. Twenty methane molecules were then randomly inserted into the system and all the water molecules from the vicinity of each methane molecule were removed followed by a steepest decent minimization. Depending on the concentration of electrolyte we want to consider, different numbers of NaCl molecules were then incorporated in the system in a similar manner. Periodic boundary conditions were applied in all three directions and the Ewald method was applied to compute electrostatic interactions. The bonds and angle of the water molecule were constrained by using the RATTLE algorithm.[52] Equations of motion were propagated using the velocity Verlet algorithm with a 2 fs time step. Equilibration runs of 2 ns followed by a production run of 2 ns have been performed. Mean square displacement (MSD) for different species and radial distribution functions for different pair of species have been calculated from the 2 ns simulation trajectory. The diffusion constant has been calculated from the slope of the MSD using the Einstein relation:

$$D = \frac{1}{6}\lim_{t\to\infty}\frac{\langle|r(t+\Delta t) - r(t)|^2\rangle}{\Delta t} \tag{1}$$

where $r(t)$ is the displacement at time t. The diffusion constant can also be obtained from the integral of the velocity autocorrelation function.

Results and Discussions

As stated earlier, in this investigation, we have considered aqueous solution of methane molecules with varying concentrations of NaCl salt to investigate translational dynamics of methane molecules, ions, and water molecules. The structural analysis of the solution has also been performed. The dynamical aspects of methanes, ions, and water molecules have been presented in the following subsection, while the structural aspects of those species in solution have been presented subsequently.

Dynamical Behavior of Various Species in Aqueous Electrolyte Solution of a Small Hydrophobic Solute. The translational dynamics of methane, ions, and water as obtained from the mean square displacements have been presented here. In Figure 1, we plot mean square displacements of methane molecules at different salt concentrations. The MSD of methane molecules decreases with increasing salt concentration indicating slower translation mobility of the small hydrophobic particle.

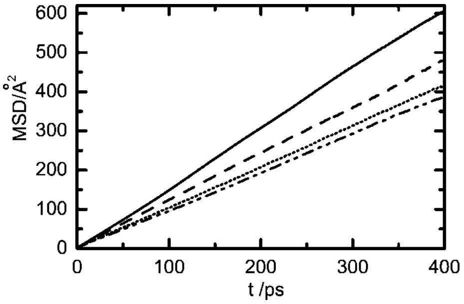

Figure 1. Mean square displacements (MSD) of methane in aqueous solution without and with added NaCl salt at varying concentrations. The solid line represents the MSD of methane without any salt, while the dashed line is for 1.15 $\text{mol}\cdot\text{L}^{-1}$, the dotted line is for 2.4 $\text{mol}\cdot\text{L}^{-1}$, and the dash double dot line is for 3.4 $\text{mol}\cdot\text{L}^{-1}$ NaCl concentrations.

Table 3. Diffusion Constants (*D*) of Methane and Fitting Parameters *P* and α (cf. Equation 2) of Methane MSDs in Various Aqueous NaCl Solutions of Concentration *c*

$\frac{c}{\text{mol}\cdot\text{L}^{-1}}$	$\frac{10^{-5}D}{\text{cm}^2\cdot\text{s}^{-1}}$	P	α
0.00	2.60 ± 0.09	1.48	1.006
1.15	1.97 ± 0.09	1.42	0.971
2.39	1.76 ± 0.04	1.42	0.971
3.39	1.64 ± 0.06	0.90	1.014

The diffusion constants as calculated from the MSD plots using eq 1 have been shown in Table 3. It is clear that diffusion constant of methane decreases as the concentration of the salt increases. There is almost 37 % decrease of the diffusion constant of methane in 3.4 $\text{mol}\cdot\text{L}^{-1}$ NaCl solution as compared to the same in the solution without any salt. To examine whether methane molecules follow any anomalous diffusion, as observed in many studies on hydration water of fullerenes[53,54] and proteins,[55] we have fitted each of the MSD curve with the equation

$$\langle |r(t) - r(0)|^2 \rangle = Pt^{\alpha} \tag{2}$$

where P and α are two parameters. In Table 3, we have tabulated the values of P and α for all the four solutions studied here. The value of α is 1 in an ideal case of 3-D Brownian diffusion, and any deviation from unity indicates the presence of anomalous diffusion, which is shown to be related to a change in effective dimensionality in some cases or dynamical and spatial heterogeneity in others. Deviation is observed in case of hydration water of a protein or a fullerene molecule. Subdiffusive behavior of hydration water has been observed in these cases. In the present case of methane diffusion, however, minimal deviation from linearity has been observed.

The MSDs of Na^+ and Cl^- ions have been shown in Figure 2a and b, respectively. For the Na^+ ion, it has been observed that although the slope of MSD decreases with increasing salt concentration, there is not much changes in the slope, where as for Cl^- ions there is a significant change in the slope of MSD in going from (1.15 to 2.39) $\text{mol}\cdot\text{L}^{-1}$. The diffusion constants as calculated from the MSD for both the ions at different salt concentrations are displayed in Table 4. It is clearly seen for the Na^+ ion that the change in D from the 1.15 $\text{mol}\cdot\text{L}^{-1}$ solution to the 2.39 $\text{mol}\cdot\text{L}^{-1}$ solution is only 11 %. On the other hand, the change in D for the Cl^- ion is significant, and it is about 30 % in the 2.39 $\text{mol}\cdot\text{L}^{-1}$ electrolyte solution as compared to 1.15 $\text{mol}\cdot\text{L}^{-1}$ solution. It is interesting to observe that a Cl^- ion has greater translational mobility as compared to a Na^+ ion in 1.15 $\text{mol}\cdot\text{L}^{-1}$ solution. It is not surprising because a Na^+ ion is more hydrated than a Cl^- ion, and it is evident from the ion−water radial distribution functions (not shown). Similar behavior has been observed in many earlier studies for infinitely dilute solution. The difference in diffusivities between Na^+ and Cl^- ions decreases as salt concentration increases, which may be a consequence of ion-pair formation.

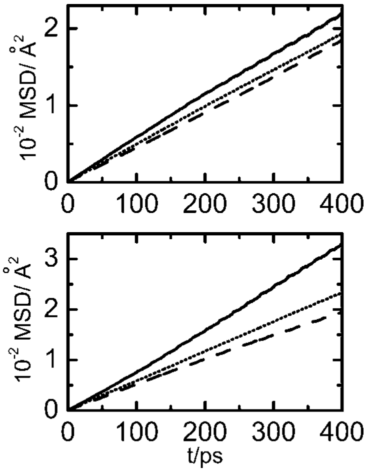

Figure 2. Mean square displacements of (top) sodium ions and (bottom) chloride ions in the aqueous electrolyte solution of methane at different NaCl concentrations (c): solid line, c = 1.15 $\text{mol}\cdot\text{L}^{-1}$; dotted line, c = 2.39 $\text{mol}\cdot\text{L}^{-1}$; dashed line, c = 3.39 $\text{mol}\cdot\text{L}^{-1}$ NaCl concentrations.

Table 4. Diffusion Constants of Na^+ (D_{Na^+}) and Cl^- (D_{Cl^-}) Ions in Various Aqueous NaCl Solutions of Concentration *c*

$\frac{c}{\text{mol}\cdot\text{L}^{-1}}$	$\frac{10^{-5}D_{\text{Na}^+}}{\text{cm}^2\cdot\text{s}^{-1}}$	$\frac{10^{-5}D_{\text{Cl}^-}}{\text{cm}^2\cdot\text{s}^{-1}}$
1.15	0.8923	1.4172
2.39	0.7865	0.9861
3.39	0.7739	0.7903

Table 5. Diffusion Constants of Water $D_{\text{H}_2\text{O}}$ and Fitting Parameters, P and α (cf. Equation 2), of Water MSD in Various Aqueous NaCl Solutions of Concentration *c*

$\frac{c}{\text{mol}\cdot\text{L}^{-1}}$	$\frac{10^{-5}D_{\text{H}_2\text{O}}}{\text{cm}^2\cdot\text{s}^{-1}}$	P	α
0.00	2.35	1.4689	0.994
1.15	2.08	1.2285	1.002
2.39	1.72	1.1071	0.990
3.39	1.48	0.9755	0.986

In order to investigate the effect of electrolyte concentration on the dynamical behavior of water in the methane + water system, the MSD of water for different solutions with varying salt concentrations have been displayed in Figure 3. Here too, the slope of the MSD plot decreases with increase in ion concentration. It is consistent with earlier simulation study,[56] which shows that the translational mobility of water at normal

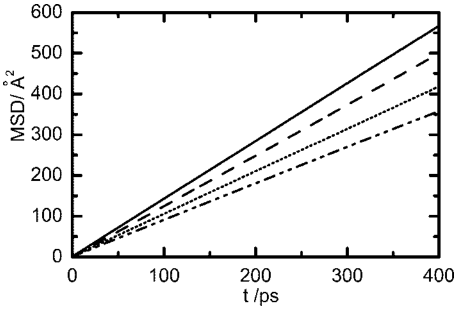

Figure 3. Mean square displacements (MSD) of water in aqueous solution without and with added NaCl salt at varying concentrations. The lines represent the same concentrations as in Figure 1.

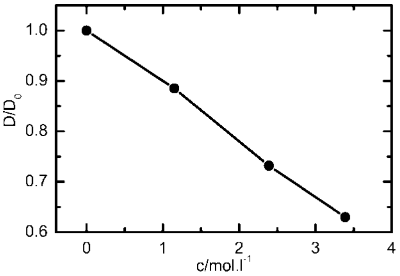

Figure 4. Diffusion constant of water in the methane + water solution relative to the diffusivity (D_0) of water in the methane + water solution without added salt as a function of salt concentration.

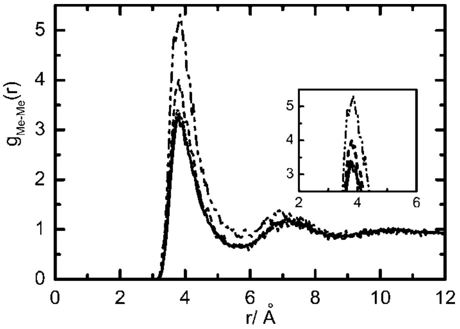

Figure 5. Methane−methane radial distribution functions ($g_{\mathrm{Me-Me}}(r)$) at various concentrations (c) of NaCl: solid line, no salt; dotted line, c = 1.15 mol·L^{-1}; dashed line, c = 2.39 mol·L^{-1}, and dash double dot, c = 3.4 mol·L^{-1}.

temperature and pressure decreases with increasing concentration of sodium ion. The diffusion constants of water as calculated from the slopes of the MSD plots have been shown in Table 5. It is of note that the diffusion constant can also be obtained from the velocity autocorrelation function and the values of the diffusion constant as obtained from the two methods are close to each other.[53,54] The diffusivity of water also follows the same trend that it decreases with increase in salt concentration. The analysis of the MSD plot using eq 2 for any anomalous diffusion of water in the medium shows no significant deviation from the usual linear behavior. In Figure 4, the diffusivity of water in different solutions with varying salt concentration relative to the same at salt free solution has been shown as a function of salt concentration. The decrease in $D_{\mathrm{H_2O}}$ with increasing salt concentration as shown in Figure 4 is linear. Similar effect of salt on water diffusion constant has been observed in electrolyte solution near and above freezing point. The reason for this decrease has been analyzed in a recent investigation, and it is found[56] that increase in the number of the long-lived water molecule residing in the solvation shells contributes to the slowness of the translational mobility of water.

Structural Aspects of Various Species in the Aqueous Electrolyte Solution of Small Hydrophobic Solutes. In this subsection, structural aspects of methanes, ions, and water have been presented. Possible correlations, if any, between the dynamic behavior and the liquid structure have been discussed. In order to monitor the effect of salt concentration on the methane−methane aggregation, which is related to the potential of mean force between the methane molecules in water, we have shown in Figure 5 the Me−Me radial distribution function at different salt concentrations. It is clearly seen that the first peak of $g(r)$ increases with increasing salt concentration indicating increasing hydrophobic interaction between methane molecules. Thus, the slower diffusion of the methane with increasing salt concentration is a consequence of the increasing tendency of the methane molecules for aggregation. We have already shown that ion diffusion, in general, becomes slower with increasing salt concentration. In order to investigate whether there is any correlation of the decrease in D with the ion−ion radial distribution functions, we have calculated $g_{\mathrm{Na^+-Na^+}}(r)$ and $g_{\mathrm{Cl^--Cl^-}}(r)$, and these are shown in Figure 6a and b, respectively. In both the cases, there is increasing correlation with increasing salt concentration as evident from the increasing height of the first peak in the ion−ion $g(r)$. So, the decreasing nature of the diffusion constants of the ions with increasing salt concentration is a consequence of increasing effective interaction between the ions.

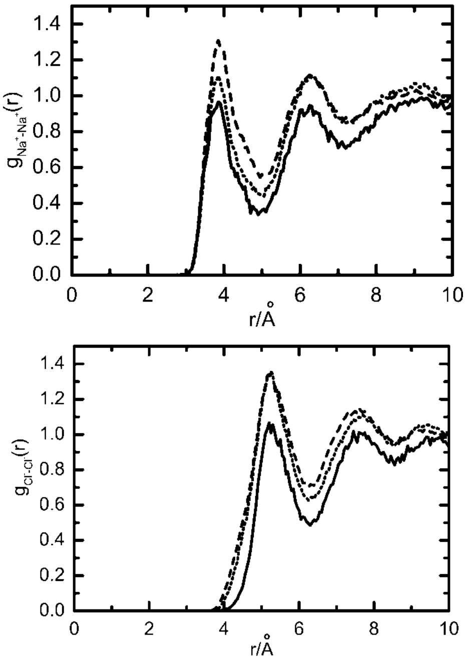

Figure 6. (a) Na$^+$−Na$^+$ radial distribution functions ($g_{\mathrm{Na^+-Na^+}}(r)$) at various salt concentrations: solid line, c = 1.15 mol·L^{-1}, dotted line, c = 2.39 mol·L^{-1}; dashed line, c = 3.39 mol·L^{-1}. (b) Cl$^-$−Cl$^-$ radial distribution functions ($g_{\mathrm{Cl^--Cl^-}}(r)$) at various salt concentrations. The lines represent the same concentrations as in part a.

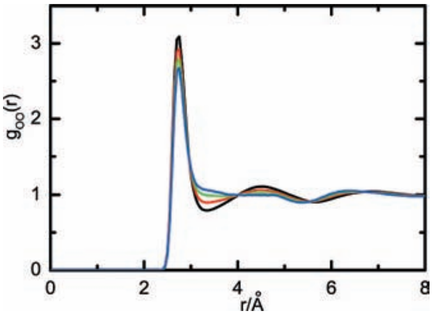

Figure 7. Oxygen−oxygen radial distribution functions ($g_{\mathrm{OO}}(r)$) of water at various NaCl concentrations (c): black line, no salt; red line, c = 1.15 mol·L^{-1}, green line, c = 2.39 mol·L^{-1}; blue line, c = 3.39 mol·L^{-1}.

We have seen that the decrease in diffusivity of methane molecules and ions with increasing electrolyte concentration is related to their respective radial distribution function, which is a measure of the effective interaction among the particles. Whether decrease in diffusivity of water is related to its structure in the same way, we have calculated the oxygen−oxygen radial distribution function of water and it is shown in Figure 7 for different salt concentrations. Contrary to the previous two cases, the first peak of $g(r)$ here decreases with increasing salt concentration, indicating disruption of water structure. Sodium chloride is known to be a water structure breaker at normal temperature and pressure. Thus, the decrease of diffusivity of water can not be explained by considering the water radial distribution. This issue has been recently discussed and the reason for the decrease in *D* in electrolyte solution is shown to be a consequence of the long residence time of some of the solvation shell water molecules.

Concluding Remarks

We have investigated structure and dynamics of aqueous solution of methane with and without added salt. The effect of increasing salt concentration on the dynamics of methane, ions, and water has been analyzed. It is shown that translational mobility of each of the species (methane, + ve and − ve ions, and water) decreases with increasing salt concentration. Possible correlation of the structure with diffusion has been shown to exist in case of methane and ions. For water however, diffusion is not correlated with structure in the same way. Further studies of the dynamics of hydration water around ions, methanes, and water molecule will be useful in this respect and such studies are in progress.

Acknowledgment

The author is thankful to Dr. S. K. Ghosh and Dr. T. Mukherjee for their kind interest and encouragement. It is a pleasure to thank Computer Division, B.A.R.C., Mumbai, for providing Anupam supercomputating facilities and support.

Literature Cited

(1) Collins, K. D.; Washabaugh, M. W. The Hofmeister Effect and The Behaviour of Water at Interfaces. *Q. Rev. Biophys.* **1985**, *18*, 323–422.

(2) Hofmeister, F. *Arch. Exp. Pathol. Pharmakol.* **1888**, *25*, 1–30.

(3) Cacace, M. G.; Landau, E. M.; Ramsden, J. J. The Hofmeister Series: Salt and Solvent Effects on Interfacial Phenomena. *Q. Rev. Biophys.* **1997**, *30*, 241–277.

(4) von Hippel, P. H.; Schleich, T. In *Structure and Stability of Biological Macromolecules*; Timasheff, S. N., Fasman, G. D., Eds.; Marcel Dekker: New York, 1969; Vol. 2, pp 323−422.

(5) Tanford, C. *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*; John Wiley: New York, 1973.

(6) Kauzmann, W. Some Factors in The Interpretation of Protein Denaturation. *Adv. Protein Chem.* **1959**, *14*, 1–63.

(7) Pratt, L. R.; Pohorille, A. Hydrophobic Effects and Modeling of Biophysical Aqueous Solution Interfaces. *Chem. Rev.* **2002**, *102*, 2671–2692.

(8) Ashbaugh, H. S.; Pratt, L. R. Scaled Particle Theory and The Length Scales of Hydrophobicity. *Rev. Mod. Phys.* **2006**, *78*, 159–178.

(9) Ben-Naim, B. Hydrophobic Interactions; Plenum: New York, 1980.

(10) Jones, S.; Thornton, J. M. Principles of Protein-protein Interactions. *Proc. Natl. Acad. Sci.* **1996**, *93*, 13.

(11) Hummer, G.; Garde, S.; Garcia, A. E.; Paulaitis, M. E.; Pratt, L. R. Hydrophobic Effects on a Molecular Scale. *J. Phys. Chem.* **1998**, *102*, 10469–10482.

(12) Southall, N. T.; Dill, K. A.; Haymet, A. D. J. A. View of The Hydrophobic Effect. *J. Phys. Chem. B* **2002**, *106*, 521.

(13) Smith, D. E.; Haymet, A. D. J. Free Energy, Entropy, and Internal Energy of Hydrophobic Interactions: Computer Simulations. *J. Chem. Phys.* **1993**, *98*, 6445.

(14) Perkyns, J. S.; Pettitt, B. M. Dependence of Hydration Free Energy on Solute Size. *J. Phys. Chem.* **1996**, *100*, 1323–1329.

(15) Southall, N. T.; Dill, K. A. Potential of Mean Force Between Two Hydrophobic Solutes in Water. *Biophys. Chem.* **2002**, *101*, 295–307.

(16) Pratt, L. R.; Chandler, D. C. Theory of The Hydrophobic Effect. *J. Chem. Phys.* **1977**, *67*, 3683–3704.

(17) Pangali, C.; Rao, M.; Berne, B. J. A Monte Carlo Simulation of The Hydrophobic Interaction. *J. Chem. Phys.* **1979**, *71*, 2975–2981.

(18) Hummer, G.; Garde, S.; Garcia, A. E.; Pohorille, A.; Pratt, L. R. An Information Theory Model of Hydrophobic Interactions. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 8951–8955.

(19) Mancera, R. L. Does Salt Increase The Magnitude of The Hydrophobic Effect? A Computer Simulation Study. *Chem. Phys. Lett.* **1998**, *296*, 459–465.

(20) Guillot, B.; Guissani, J. A computer Simulation Study of The Temperature Dependence of The Hydrophobia Hydration. *J. Chem. Phys.* **1993**, *99*, 8075–8094.

(21) Docherty, H.; Galindo, A.; Vega, C.; Sanz, E. A Potential Model for Methane in Water Describing Correctly The Solubility of The Gas and The Properties of The Methane Hydrate. *J. Chem. Phys.* **2006**, *125*, 074510.

(22) Lyubartsev, A. P.; Forrisdahl, O. K.; Laaksonen, A. Solvation Free Energies of Methane and Alkali Halide Ion Pairs: An Expanded Ensemble Molecular Dynamics Simulation Study. *J. Chem. Phys.* **1998**, *108*, 227–233.

(23) Moghaddam, M. S.; Shimizu, S.; Chen, H. S. Temperature Dependence of Three-body Hydrophobic Interactions: Potential of Mean Force, Enthalpy, Entropy, Heat Capacity, and Nonadditivity. *J. Am. Chem. Soc.* **2005**, *127*, 303–316.

(24) Zhang, J.; Piana, S.; Freij-Ayoub, R.; Rivero, M.; Choi, S. K. Molecular Dynamics Study of Methane in Water: Diffusion and Structure. *Mol. Sim.* **2006**, *32*, 1279–1286.

(25) Hummer, G.; Rasaiah, J. C.; Noworyta, J. P. Water Conduction Through the Hydrophobic Channel of a Carbon Nanotube. *Nature* **2001**, *414*, 188–190.

(26) Choudhury, N.; Pettitt, B. M. On the Mechanism of Hydrophobic Association of Nanoscopic Solutes. *J. Am. Chem. Soc.* **2005**, *127*, 3556–3567.

(27) Choudhury, N.; Pettitt, B. M. The Dewetting Transition and The Hydrophobic Effect. *J. Am. Chem. Soc.* **2007**, *129*, 4847–4852.

(28) Lum, K.; Chandler, D.; Weeks, J. D. Hydrophobicity at small and large length scales. *J. Phys. Chem. B* **1999**, *103*, 4570–4577.

(29) Chandler, D. Interfaces and The Driving Force of Hydrophobic Assembly. *Nature* **2005**, *437*, 640–647.

(30) Choudhury, N. On the Manifestation of Hydrophobicity at the Nanoscale. *J. Phys. Chem. B* **2008**, *112*, 6296–6300.

(31) Ball, P. Water as an Active Constituent in Cell Biology. *Chem. Rev.* **2008**, *108*, 78–108.

(32) Ball, P. How to keep dry in water. *Nature* **2003**, *423*, 25–26.

(33) Van der Waals, J. H.; Platteeuw, J. C. Clathrate Solutions. *Adv. Chem. Phys.* **1959**, *2*, 1–57.

(34) Sloan, E. D. Fundamental Principles and Applications of Natural Gas Hydrates. *Nature* **2003**, *426*, 353–359.

(35) Ghosh, T.; Garcia, A. E.; Garde, S. Water-mediated Three-particle Interactions Between Hydrophobic Solutes: Size, Pressure, and Salt Effects. *J. Phys. Chem. B* **2003**, *107*, 612–617.

(36) Ghosh, T.; Garcia, A. E.; Garde, S. Molecular Dynamics Simulations of Pressure Effects on Hydrophobic Interactions. *J. Am. Chem. Soc.* **2001**, *123*, 10997–11003.

(37) Ghosh, T.; Kalra, A.; Garde, S. On the Salt-induced Stabilization of Pair and Many-body Hydrophobic Interactions. *J. Phys. Chem. B* **2005**, *109*, 642–651.

(38) Docherty, H.; Galindo, A.; Sanz, E.; Vega, C. Investigation of The Salting Out of Methane from Aqueous Electrolyte Solutions Using Computer Simulations. *J. Phys. Chem. B* **2007**, *111*, 8993–9000.

(39) Raschke, T. M.; Tsai, J.; Levitt, M. Quantification of The Hydrophobic Interaction by Simulations of The Aggregation of Small Hydrophobic Solutes in Water. *Proc. Natl. Acad. Sci.* **2001**, *98*, 5965–5969.

(40) Zangi, Z.; Berne, B. J. Aggregation and Dispersion of Small Hydrophobic Particles in Aqueous Electrolyte Solutions. *J. Phys. Chem. B* **2006**, *110*, 22736–22741.

(41) Jonsson, M.; Skepo, M.; Linse, P. Monte Carlo Simulations of The Hydrophobic Effect in Aqueous Electrolyte Solutions. *J. Phys. Chem. B* **2006**, *110*, 8782–8788.

(42) Smith, D. E.; Zhang, L.; Haymet, A. D. J. Entropy of Association of Methane in Water: A New Molecular Dynamics Computer Simulation. *J. Am. Chem. Soc.* **1992**, *114*, 5875–5876.

(43) Shimizu, S.; Chan, H. S. Configuration-Dependent Heat Capacity of Pairwise Hydrophobic Interactions. *J. Am. Chem. Soc.* **2001**, *123*, 2083–2084.

(44) Rick, S. W.; Berne, B. J. Free Energy of The Hydrophobic Interaction From Molecular Dynamics Simulations: The Effects of Solute and Solvent Polarizability. *J. Phys. Chem.* **1997**, *101*, 10488–10493.

(45) Rick, S. W. Free Energy, Entropy and Heat Capacity of The Hydrophobic Interaction As a Function of Pressure. *J. Phys. Chem. B* **2000**, *104*, 6884–6888.

(46) Ghosh, T.; Garcia, A. E.; Garde, S. Enthalpy and entropy contributions to the pressure dependence of hydrophobic interactions. *J. Chem. Phys.* **2002**, *116*, 2480–2486.

(47) Hummer, G.; Garde, S.; Garcia, A. E.; Paulaitis, M. E.; Pratt, L. R. The Pressure Dependence of Hydrophobic Interactions is Consistent With The Observed Pressure Denaturation of Proteins. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 1552–1555.

(48) Fujita, T.; Watanabe, H.; Tanaka, S. Effects of Salt Addition on Strength and Dynamics of Hydrophobic Interactions. *Chem. Phys. Lett.* **2007**, *434*, 42–48.

(49) Thomas, A. S.; Elcock, A. H. Molecular dynamics simulations of hydrophobic associations in aqueous salt solutions indicate a connection between water hydrogen bonding and the hofmeister effect. *J. Am. Chem. Soc.* **2008**, *129*, 14887–14898.

(50) Timasheff, S. N. Control of Protein Stability and Reactions by Weakly Interacting Cosolvents: The Simplicity of The Complicated. *Adv. Protein Chem.* **1998**, *51*, 355–432.

(51) Berendsen, H. J. C.; Grigera, J. R. The Missing Term in Effective Pair Potentials Straatsma T. P. *J. Phys. Chem.* **1987**, *91*, 6269–6271.

(52) Allen, M. P.; Tildesley, D. J. *Computer Simulation of Liquids*; Oxford University: New York, 1987.

(53) Choudhury, N. Dynamics of Water in the Hydration Shells of C60: Molecular Dynamics Simulation Using a Coarse-Grained Model. *J. Phys. Chem. B* **2007**, *111*, 10474–10480.

(54) Choudhury, N. Dynamics of Water in Solvation Shells and Intersolute Regions of C60: A Molecular Dynamics Simulation Study. *J. Phys. Chem. C* **2007**, *111*, 2565–2572.

(55) (a) Rocchi, C.; Bizzarri, A. R.; Cannistraro, S. Water Dynamical Anomalies Evidenced by Molecular-dynamics Simulations At The Solvent-protein Interface. *Phys. Rev. E* **1998**, *57*, 3315–3325. (b) Bizzarri, A. R.; Paciaroni, A.; Cannistraro, S. Glasslike Dynamical Behavior of The Plastocyanin Hydration Water. *Phys. Rev. E* **2000**, *62*, 3991–3999.

(56) Kim, J. S.; Yethiraj, A. A Diffusive Anomaly of Water in Aqueous Sodium Chloride Solutions at Low Temperatures. *J. Phys. Chem. B* **2008**, *112*, 1729–1735.

Received for review June 30, 2008. Accepted August 28, 2008.

JE8004886