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REGULAR ARTICLE

Hydrophobic Hydration: A Theoretical Investigation of Structure and Dynamics

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Abstract. The presence of external solutes alters the local structures, and dynamics of water. The nature and extent of these structural modifications depend on several factors. Particularly, the chemical nature of the solute is very crucial. The alteration of water structure and dynamics in the presence of hydrophobic substances draws considerable attention in biological systems. The present work is focused on exploring the microscopic arrangement of solvation shells of tiny hydrophobic solute methane. We explore the tetrahedral order, local structural index, and van Hove self-correlation function to get a quantitative understanding. We observe a slight increase in the structural order of water molecules in methane's first solvation shell, similar to that of the low-temperature water. We also find that water facing the methane have lower structural order than bulk water. Furthermore, the water molecules in the first solvation shell around methane show relatively slower orientational relaxation.

Keywords. Hydrophobic Hydration; Local Structure; Tetrahedral Order.

1. Introduction

Water is one of the unique and ubiquitous liquids in nature that is a part of various processes and systems we see around us.[1] Despite several conclusive experimental and theoretical studies,[2–7] water structure and dynamics in the presence of non-polar solutes remain exciting research areas, and its microscopic details are still unclear. Hydrophobic solutes are known to strongly affect the structural and dynamic properties of surrounding water.[8–10] It depends on the solute behaviour or the relaxation of the hydrogen bond network.[10] Hydrophobic hydration is essential in many biological processes like protein folding-unfolding, enzyme activity, bio-molecular transportation, etc.[11–13] Water accommodates small hydrophobic solutes with minor alterations in its hydrogen bond network. These alterations of the water hydrogen bond network is called hydrophobic hydration. Hydrophobic hydration is extremely sensitive to the nature of the hydrophobe and its interaction with water.[14] The free energy cost of solvating hydrophobic solutes in water depends on the solute size as described in the Lum-Chandler-Weeks (LCW) theory.[15] Water in the presence of the small hydrophobic solute methane (CH_4) was investigated by several theoretical,[16–21] molecular dynamics(MD),[22–26] and *ab-initio* molecular dynamics (AIMD) studies.[27,28] As methane is sparingly soluble in water, it is challenging to study such systems experimentally. Nevertheless, previous experimental studies showed contrasting results. Some studies found strengthening hydrogen bonds of water around the hydrophobic solutes, resulting in ice-like and clathrate cages structure.[28–30] In contrast, neutron scattering measurements[31] did not show any such structural enhancement. Previous IR[32,33] and NMR[34,35] experimental studies and other theoretical[21,22] studies showed slower water dynamics near the hydrophobe, but didn't show any evidence for the presence of ice like structure.

Recent IR and *ab-initio* molecular dynamics studies identified the presence of strengthened water hydrogen bonds near the hydrophobic solutes.[36–38] In one of our recent studies, in addition to the strengthened water,

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we also found some dangling water among the water molecules that are directly facing the hydrophobic solute.[8] In one of the earlier studies, Duboué-Dijon and Laage showed that the use of a single order parameter might lead to ambiguous conclusions for the investigation of the local order of aqueous systems.[39] Quantifying the structural order in liquids and glasses is challenging since such systems have short-range order and they are in a continuous dynamical state.

In the present work, we aim to analyze the effect of hydrophobicity on water structure and dynamics by utilizing computer simulations. We analyse the system in depth by focusing on different structural order parameters and time-correlation functions. The rest of this article is structured as follows. We elaborate on simulation details in Section 2, data analyses and results are discussed in Section 3, and conclusions are given in Section 4.

2. Simulation details

We perform classical molecular dynamics simulations using GROMACS 2019.3.[40] We chose three systems for this study. The first system contains 256 water molecules, the second system includes one methane and 255 water, and the third system has 10 methane and 246 water. To describe methane molecule, we use all-atom 'Optimized Potentials for Liquid Simulations' (OPLS-AA)[41] force field and extended simple point charge (SPC/E)[42] model for water molecules. Periodic boundary conditions are applied in all three directions. We employ the steepest descent method to perform energy minimization, followed by 1 ns equilibration in the NPT ensemble. Finally, the data acquisition is made in the NVT ensemble for 1 ns. We use the Nosé-Hoover[43] thermostat to control the temperature with a relaxation time of 0.1 ps. The Parinello-Rahman[44] barostat is used to control the pressure with a relaxation time of 1.0 ps. We use a cutoff radius of 9Å for neighbor search interactions. For bond constraints, we use the LINCS[45] algorithm. Long-range electrostatic interactions are calculated by using Particle Mesh Ewald (PME)[46] with an FFT grid spacing of 1.6 Å.

3. Results and Discussion

To analyze the effect of hydrophobic solute methane on water structure and dynamics, we simulate the methane-water system at 300 K and bulk water at 270, 300, and 370 K temperatures. In methane-water system, we select one water molecule that stays longer duration in the first solvation shell of methane. This will amplify the effect of methane on the properties of water. Figure S1 (SI) shows the probability of distance between the carbon of methane and oxygen of one such tagged water molecule. This tagged water molecule stays 77.77% of the time in the first solvation shell over one ns trajectory. We perform the following analysis using this tagged water trajectory. To characterize the dynamics of bulk water and methane-water, we calculate the frequency fluctuation correlation function (FFCF), the orientational time correlation function (OTCF), and Van Hove self-correlation function. To quantify local structural order in the presence of methane, we compute the probability distribution of two structural order parameters: tetrahedral order parameter (q) and local structure index (LSI).

3.1 *Frequency Fluctuation Correlation Function (FFCF)*

In one of our earlier works, we developed the mixed quantum-classical theoretical spectroscopy map based approach to obtain the O-H vibrational frequencies in the case of methane-water system.[8] We utilize this approach to get the vibrational frequency trajectories for the selected water molecules. We analyze the spectral diffusion in terms of amplitudes and time scales of the dynamics by computing the FFCF. The equation of FFCF can be expressed as follows:

$$c_\omega(t) = \langle d\omega(0) d\omega(t) \rangle, \tag{1}$$

where $d\omega = \omega - \bar{\omega}$.

In Figure 1, we plot the FFCF for the bulk water and a water molecule from methane-water simulation selected as per the criteria mentioned previously. The FFCF of methane-water shows slow relaxation compare to that of bulk water. The curve is fitted by using a fitting function introduced by Hynes and co-workers.[47]

$$c(t) = a_1 cos(\omega_{OO} t) e^{\frac{-t}{\tau_1}} + a_2 e^{\frac{-t}{\tau_2}} + a_3 e^{\frac{-t}{\tau_3}} \tag{2}$$

The fitting parameters provide the estimate of the relaxation times in the case of both bulk and methane-water systems. Table 1 presents the fitting parameters of bulk water and ten methane-water systems. It is clear from the table that the hydrophobic methane molecule indeed slows down water dynamics. This observation is similar to the findings of many earlier works.[21,22,32–35] Further investigation of the slow

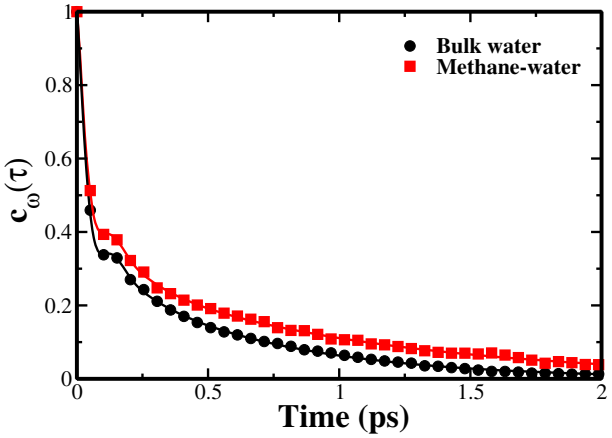

Figure 1. FFCF of the bulk water (Black) and the selected water molecule which is staying longer time in the first solvation shell of methane in ten methane-water system (Red). The symbols represent the raw data and solid lines represent the fitting.

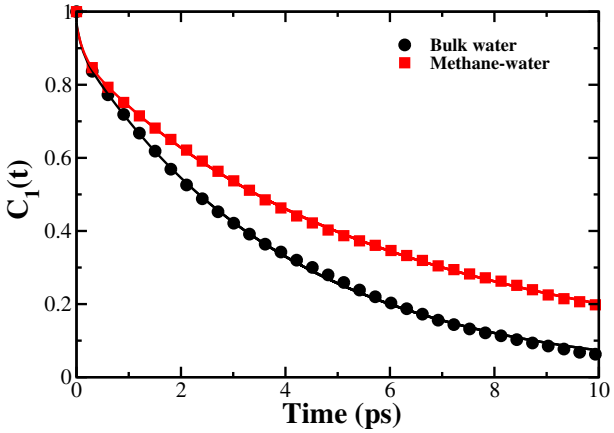

Figure 2. First rank OTCF of the bulk water (Black) and the selected water molecule which is staying longer time in the first solvation shell of methane in ten methane-water system (Red). The symbols represent the raw data and solid lines represent the fitting.

dynamics of water in the presence of methane is showed in the latter part of this article.

3.2 *Orientational Time Correlation Function (OTCF)*

The rotational correlation time is an useful probe of the hydration shell because of its strong dependence on the local hydrogen bond configuration. The rotational motion of a molecule can be calculated by using the orientational time correlation function (OTCF). The first and second rank OTCFs can be expressed as follows.

$$c_1(t) = \left\langle P_1[\vec{\mu}(0) \cdot \vec{\mu}(t)] \right\rangle \tag{3}$$

$$c_2(t) = \left\langle P_2[\vec{\mu}(0) \cdot \vec{\mu}(t)] \right\rangle \tag{4}$$

where $P_1(x)$ and $P_2(x)$ is the first and second order Legendre polynomial and $\vec{\mu}$ is a dipole vector along the molecular dipole moment. Orientational correlation functions can be probed by different experimental techniques. For example, the first-order orientational correlation function decay was investigated using dielectric relaxation (DR) and terahertz (THz) time-domain spectroscopy, whereas the $c_2(t)$ decay was investigated using fs-IR, NMR, and optical Kerr effect spectroscopy.[48]

In Figures 2 and 3, we plot $c_1(t)$ and $c_2(t)$ of bulk water and methane-water at 300 K. It is clear from the figures that indeed water orientational relaxation is much slower in the methane-water system when compared with bulk water. It is similar to the experimental femtosecond midinfrared spectroscopic[49] study and some of the earlier theoretical investigations.[22] To extract the different relaxation times, we fit the OTCFs with a tri-exponential fitting function, and the fitting parameters are shown in Tables 2 and 3.

3.3 *Van Hove self-correlation function*

To analyse the transnational-rotational coupling on the rotational dynamics of water molecules in the bulk water and, methane-water systems, we use Van Hove self-correlation function (VHCF). The angular Van Hove self-correlation function[50] can be expressed as follows:

$$G(\theta, t) = \left\langle \delta[\theta - \theta(t)] \right\rangle \tag{5}$$

where $\theta = cos^{-1}[\hat{u}(t) \cdot \hat{u}(0)]$ and $\hat{u}(t)$ is the unit vector of O-H bond at time t (Figure 4).

Table 1. FFCF fitting parameters using Eq. 2 in the case of bulk and methane-water systems.

System	$\omega_{OO}(ps^{-1})$	a_1	τ_1 (ps)	a_2	τ_2 (ps)	a_3	τ_3 (ps)	$\langle \tau \rangle$ (ps)
Bulk water	35.85	0.37	0.05	0.33	0.61	0.31	0.10	0.25
Methane-water	35.13	0.34	0.05	0.31	0.97	0.36	0.12	0.36

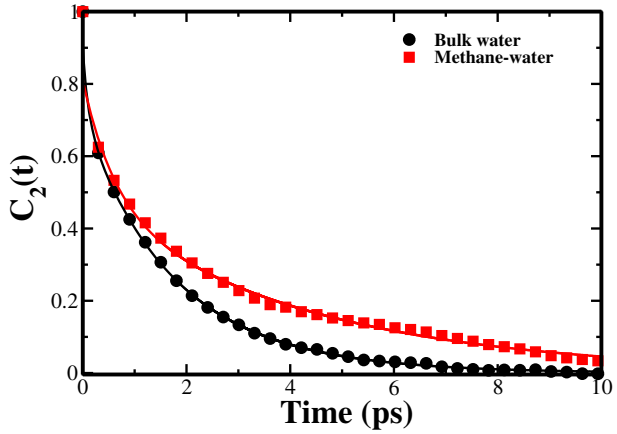

Figure 3. Second rank OTCF of the bulk water (Black) and a tagged water molecule which is staying longer time in the first solvation shell of methane in 10 methane-water system (Red). The symbols represent the raw data and solid lines represent the fitting.

If the system contains translationally immobile water molecules that cause large angular jump. It will form two well-separated peaks in the angle distribution.[51] In other cases, the translationally mobile water show a continuous angle distribution for a sufficiently longer trajectory over the entire θ range. It indicates in addition to the large angular jump translationally mobile molecules also perform the small-angle rotational diffusion. In Figure 4, we plot Van Hove self-correlation function of bulk water at different temperatures and selected water molecules for methane-water systems. For shorter τ values, we observe there exist reasonable differences in translational and rotational dynamics of the methane-water system compared to bulk water. The methane-water system behaves more like a bulk water at lower temperature. However, in case of $\tau = 50$ps all the VHCF are converging to similar behaviour. Although the orientational dynamics is slower in case of hydration shell water of methane, the VHCF leads us to the conclusion that the hydration water of methane does not behave like an ice. To further confirm, we perform tetrahedral and local structure index order parameter calculations for both the systems.

3.4 *Tetrahedral order parameter*

Tetrahedral order parameter (q) is used to study the local structure of bulk water and water in presence of hydrophobic solute. Tetrahedral parameter (q) lies in between 0 and 1. If perfect tetrahedron shape is present in system, q value becomes 1. The tetrahedral parameter is expressed as[52]

$$q_k = 1 - \frac{3}{8}\sum_{i=1}^{3}\sum_{j=i+1}^{4}\left[cos\psi_{ikj} + \frac{1}{8}\right]^2 \tag{6}$$

where ψ_{ikj} is the angle form by the molecule k and its nearest neighbors i and j. Then the average q can be expressed as

$$\langle q \rangle = \frac{1}{N}\sum_{N} q_k \tag{7}$$

where N is the total number of molecules.

In Figure (S2, SI), we plot the tetrahedral parameter for the bulk water and the methane-water systems. The slight enhancement in q parameter confirms the presence of more structural order in ten methane-water system. To quantify the microscopic structures, we calculate q for different solvation shells in case of one methane-water system. We select the first solvation shell water based on distance criteria by taking into consideration of radial distribution function of carbon

Table 2. Fitting parameters for first rank OTCF obtained by using fitting equation $c_1(t) = a_1 e^{\frac{-t}{\tau_1}} + a_2 e^{\frac{-t}{\tau_2}} + a_3 e^{\frac{-t}{\tau_3}}$.

System	a_1	τ_1 (ps)	a_2	τ_2 (ps)	a_3	τ_3 (ps)	$\langle\tau\rangle$ (ps)
Bulk water	1.11	3.68	0.07	0.19	-0.23	2.35	3.56
Methane-water	0.69	7.98	0.20	2.68	0.08	0.14	6.05

Table 3. Fitting parameters for second rank OTCF obtained by using fitting equation $c_2(t) = a_1 e^{\frac{-t}{\tau_1}} + a_2 e^{\frac{-t}{\tau_2}} + a_3 e^{\frac{-t}{\tau_3}}$.

System	a_1	τ_1 (ps)	a_2	τ_2 (ps)	a_3	τ_3 (ps)	$\langle\tau\rangle$ (ps)
Bulk water	0.43	2.11	0.28	1.33	0.19	0.10	1.30
Methane-water	0.43	4.56	0.31	0.91	0.17	0.08	2.26

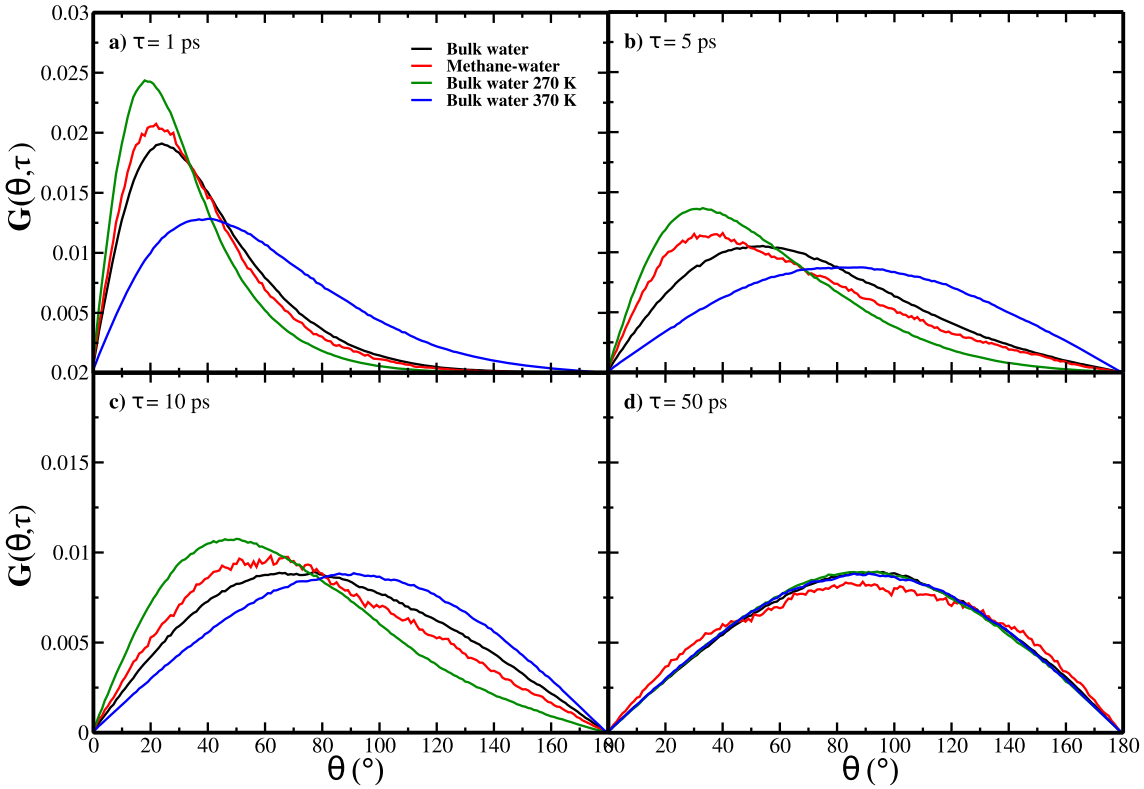

Figure 4. Van Hove self-correlation function of bulk water at different temperatures and ten methane-water for different waiting times.

of methane and oxygen of water (Figure S4, SI). We further isolate the water molecule nearest to the methane molecule and consider that as water-facing methane. In case of ten methane system, the solvation shells of methane overlaps and it is very difficult to examine the spatial propagation of the hydrophobic effect. To avoid this, we perform the solvation shell-wise analysis by using the trajectory of one methane-water system.

The comparison of q for the methane-water system with bulk water at different temperatures helps us to understand the water structural order in rather quantitative way. The tetrahedral order parameter of methane-water for different solvation shells are shown in Figure 5. We observed low tetrahedral ordering near the methane surface. This result is similar to our previous work.[8] The structure of water molecules in the first, second, and third solvation shells are almost similar and show little structural enhancement than compared to bulk. Even, at the third solvation shell, the water molecules do not behave completely bulk like. Furthermore, the temperature dependent data helps us to realize that the structure of methane solvation shells are similar to the low temperature bulk-water. In addition, we also observe that the water molecules near the methane surface behave similar to the water at higher temperature.

3.5 *Local Structural Index (LSI)*

The local microscopic structure of liquid water can be characterized by the probability density distribution of the local structure index (LSI) order parameter. The extent of gap between 1st and 2nd hydration shell measured by using LSI parameter. It can be expressed as follows:

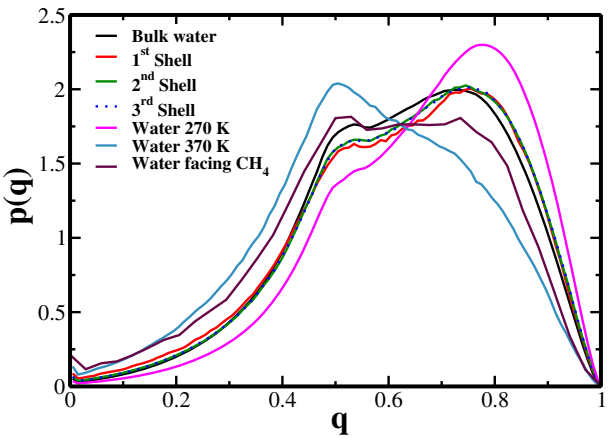

Figure 5. Tetrahedral order parameter (q) of bulk water at different temperatures and solvation shell wise decomposition of one methane-water system.

$$I(k,t) = \frac{1}{n(k,t)} \sum_{i=1}^{n(k,t)} \left[\Delta(i;k,t) - \overline{\Delta}(k,t)\right]^2 \quad (8)$$

where $\Delta(i;k,t) = r_{i+1} - r_i$ and $\overline{\Delta}(k,t)$ is the average of $\Delta(i;k,t)$, r_i is the distance between center molecule k and i^{th} molecule, and in ascending order of distance from the center molecule, $r_1 < r_2 < r_3 < r_4$ .....$< r_{n(k,t)} < r_{n(k,t)+1}$. The $\overline{\Delta}(k,t)$ is defined as

$$\overline{\Delta}(k,t) = \frac{1}{n(k,t)} \sum_{i=1}^{n(k,t)} \Delta(i;k,t). \quad (9)$$

When molecules are randomly distributed without forming the tetrahedral order, then $I(k,t) = 0$. The tetrahedral structure is locally developed, when molecules are concentrated in the region 2.7 Å < r < 3.2 Å and are excluded out from the region 3.2 Å < r < 3.8 Å, which results in the large value of LSI.[53] The local structure index calculated by using equation 8.

In Figure S3 (SI), we plot the LSI of bulk water and ten methane-water systems. We observe structural enhancement and a structural collapse in the methane-water system. To understand microscopically, we further analyze LSI parameters for different solvation shells in the methane-water system and bulk water at different temperatures.

In the first solvation shell of methane-water, the LSI value is more probable at zero. That means-water molecules that stay near the methane have less structural order. This finding indicates that most molecules are situated in high-density-like locally disordered environments in the first shell of methane-water. We also observe bimodal peak nature in both low-temperature water and the first solvation shell of methane-water. Based on that, we conclude first solvation shell water molecules are similar to low-temperature water molecules. From Figure 6, we find similarities between water molecules staying near the methane and high-temperature water are the same. Our earlier work showed that the first shell water molecules are identical to the low temperature, and water near the methane is similar to the high-temperature water. The LSI and tetrahedral order parameters also suggest similar interpretations.

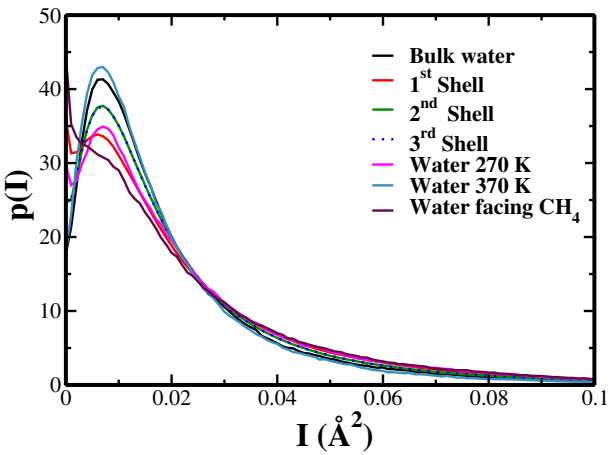

Figure 6. Local structure index (LSI) of bulk water at different temperature and for different solvation shells in the case of one methane-water system.

4. Conclusions

The understanding of the structural modifications of water by the external solute is extremely crucial, particularly in the context of biological systems. This work focuses on exploring the microscopic arrangement of the solvation shells of tiny hydrophobic solute methane. We explore the local structural alteration by using the tetrahedral order (q), local structural index (LSI), and Van Hove self-correlation function (VHCF). We find a slight increase in structural order in the first solvation shell of methane, similar to the low-temperature water. In addition, part of the first shell waters, particularly those directly facing the methane, have lower structural order. In one of our previous works, we showed that the water-water hydrogen bonds have a wide distribution in the first solvation shell.[8] Some water molecules surrounding methane contain two types of O-H bonds, one towards and one away from methane. Because of the lack of water molecules, the O-H bond towards methane has fewer hydrogen bonds. In contrast, the distant O-H bond tries to compensate for this deficiency by forming relatively stronger H-bonds or, in some cases, more H-bonds. This influences the structure and dynamics of the waters in different hydration shells.

We also probe the influence of the hydrophobic solute on the dynamics by using frequency fluctuation correlation function (FFCF) and orientational time correlation functions (OTCFs). It is clearly shown from FFCF and OTCFs that water becomes slower in the methane-water system than compared to bulk water. The water molecules in the methane first solvation shell have relatively slower orientational relaxation. This leads to the conclusion that the first shell water behaves more orderly and rigid similar to that of low-temperature water. From the solvation shell-wise analyses of bulk water and methane-water systems, we find water molecules near the hydrophobic surface have less structural order, and other first solvation water molecules have more

structural order. Furthermore, the temperature-dependent structural orders of methane-water with bulk water conclude that the first shell water molecules are similar to the low-temperature water. The dangling waters facing the methane molecule behave like high-temperature water.

Supplementary Information (SI)

The supplementary information about the probability distribution of the distance between the carbon of methane and oxygen of the tagged water molecule in ten methane water systems; probability distribution of tetrahedral order parameter (q), and local structure index (LSI) of bulk water and ten methane-water systems; The Solvation shell wise decomposition based on radial distribution function (RDF) of methane carbon and water oxygen. Supplementary Information is available at www.ias.ac.in/chemsci.

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