Dynamical Transition of Water in the Grooves of DNA Duplex at Low Temperature

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At low temperature (below its freezing/melting temperature), liquid water under confinement is known to exhibit anomalous dynamical features. Here we study structure and dynamics of water in the grooves of a long DNA duplex using molecular dynamics simulations with TIP5P potential at low temperature. We find signatures of a dynamical transition in both translational and orientational dynamics of water molecules in both the major and the minor grooves of a DNA duplex. The transition occurs at a slightly higher temperature ($T_{GL} \approx 255$ K) than the temperature at which the bulk water is found to undergo a dynamical transition, which for the TIP5P potential is at 247 K. Groove water, however, exhibits markedly different temperature dependence of its properties from the bulk. Entropy calculations reveal that the minor groove water is ordered even at room temperature, and the transition at $T \approx 255$ K can be characterized as a strong-to-strong dynamical transition. Confinement of water in the grooves of DNA favors the formation of a low density four-coordinated state (as a consequence of enthalpy−entropy balance) that makes the liquid−liquid transition stronger. The low temperature water is characterized by pronounced tetrahedral order, as manifested in the sharp rise near 109° in the O−O−O angle distribution. We find that the Adams−Gibbs relation between configurational entropy and translational diffusion holds quite well when the two quantities are plotted together in a master plot for different region of aqueous DNA duplex (bulk, major, and minor grooves) at different temperatures. The activation energy for the transfer of water molecules between different regions of DNA is found to be weakly dependent on temperature.

I. Introduction

Water in the natural world is often found under constrained and/or restricted environments: in the hydration layer of proteins and micelles, within reverse micelles and microemulsions, in the grooves of DNA duplex, and within biological cells, to name a few. Properties of water under such constrained conditions can be quite different from those of bulk, neat water.[1] However, it is likely that even under such restricted conditions water retains some of its unique properties. Study of these unique properties of water, especially in the hydration layer of biomolecules, particularly of proteins[1−6] and DNA,[1,7−12] has been a subject of great interest in recent times. A hydration layer not only provides the stability of the structure of the biomolecules, but also plays a critical role in the dynamic control of biological activity. The intercalation of antitumor drugs, such as daunomycin, into DNA involves active participation of water molecules in the grooves.[13,14]

The low temperature (near 200 K) "glasslike" transition of hydrated protein has drawn a great deal of attention in both experimental and computer simulation studies.[15−19] Above this transition temperature proteins exhibit diffusive motion, and below this temperature the proteins are trapped in localized harmonic modes. An important issue in recent times is to determine the effects of hydration water on this dynamical transition.[20−24] Recent studies have shown that dynamics of water in the hydration layer of a protein also exhibits strong temperature dependence around the same temperature, and it seems to undergo a fragile-to-strong transition that preempts an otherwise expected glass transition at a lower temperature.[24−27]

Study of the DNA hydration layer has recently indicated interesting dynamical behavior of water in the grooves.[7,8] Several recent studies have discussed the origin of the slow component of the solvation dynamics in DNA hydration layer.[11] However, a detailed discussion of this upcoming issue is beyond the scope of this paper.

A recent computer simulation study by Stanley and coworkers has shown that the liquid−liquid (L−L) transition in water induces a dynamic transition in DNA that has striking resemblance with that of the liquid-to-glass transition.[28] This study, however, did not explore the dynamics of water in the grooves of DNA.

There are many questions that have remained unanswered regarding dynamics of groove water at low temperature. For example, is there a dynamic transition in the grooves of DNA near the L−L transition of bulk water? Does it in any way resemble the one in the protein hydration layer? Note that the remarkable properties of bulk water have recently been attributed to a highly interesting L−L transition at around $T_L \approx 247$ K, that is, only 26 °C below the freezing temperature.[29−32] The effects of the bulk water L−L transition on groove water dynamics have not yet been investigated.

In this article we report our finding that water in the grooves of a DNA duplex shows a dynamical transition at a temperature (T_{GL}) slightly higher than the temperature (T_L) where the bulk water undergoes the L−L transition. The nature and manifestation of the transition in the grooves are quite stronger than those in the bulk for the same TIP5P potential.

There are several effects of confinement on the properties of liquid water. First, fluctuations with wavelength larger than that

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of the confining region are suppressed. Second, the surface can induce changes within water. For example, a hydrophobic surface can induce enhanced local order among the water molecules. A hydrophilic surface (such as a micelle or a reverse micelle) can induce frustration among water molecules in the second or third layer.[33−36] Both surfaces are expected to lower the entropy of the hydration layer.

An interesting aspect of water molecules in the DNA grooves is that they are free to exchange with the bulk. Therefore, the entropy−energy balance needs to be maintained. Because entropy of water in the hydration layer is significantly less than that in the bulk, these water molecules must be energetically stabilized by interactions among themselves and also with DNA atoms.

Arrangement of water molecules in the grooves of DNA is partly dictated by the gain in the stabilization energy due to the interaction with the charged groups of DNA and partly by the loss of entropy due to confinement. These two factors lead to a change in the preference of arrangement to lower energy states, which is the four-coordinated low density state. Thus, the dynamical (L−L) transition is expected to occur at higher temperature, which is also found by computer simulations presented here.

II. System and Simulation Details

The system we studied consists of a Dickerson dodecamer DNA duplex (CGCGAATTCGCG)[37] solvated using the LEAP module of the AMBER[39] software in a TIP5P water[38] box. The box dimensions were chosen in order to ensure a 10 Å thick solvation shell around the DNA structure. In addition, some water molecules were replaced by Na+ counterions to neutralize the negative charge on the phosphate groups of the backbone of the DNA. These procedures resulted in a solvated structure, containing around 8605 atoms that include the 758 DNA atoms, 22 counterions, and ∼1565 water molecules. The solvated structure is then subjected to 1000 steps of steepest descent minimization of the potential energy, followed by 2000 steps of conjugate gradient minimization. During this minimization the DNA molecule was kept fixed in its starting conformations using harmonic constraints. This allows the water molecules to reorganize to eliminate bad contacts with the DNA molecule. The minimized structure was then subjected to 500 ps of molecular dynamics (MD), using a 2 fs time step for integration. Subsequently, MD was performed under constant pressure and constant temperature conditions (NPT) with temperature regulation achieved using the Berendsen weak coupling method (0.5 ps time constant for heat bath coupling and 0.2 ps pressure relaxation time). This was followed by another 5000 steps of conjugate gradient. The DNA−water system is then simulated at constant pressure $P = 1$ atm, at several constant temperatures ($T = 300$, 290, 280, 270, 260, 250, 240, 230, and 220 K) with periodic boundary condition for 10 ns (for $T = 300$ K) to 30 ns (for $T = 220$ K). This ensures the equilibration of the DNA system, which has been checked by rmsd of DNA and other relevant properties. Finally, for the analysis we have carried out 30 ns of NPT simulation for each case with 2 fs time step. Statistical errors have been calculated using four independent trajectories.

We have identified the groove water by using the following procedure. We have calculated the radial distribution function ($g(r)$) of water molecules in the system from the major and minor groove atoms. On the basis of this $g(r)$, a cutoff distance of 3.5 Å (the first minima of $g(r)$) from the groove atoms is used for the selection. For bulk water analysis, we have considered those water molecules that are beyond 10 Å from any DNA atoms. We have checked that at 10 Å away, water indeed regains bulk-like behavior.

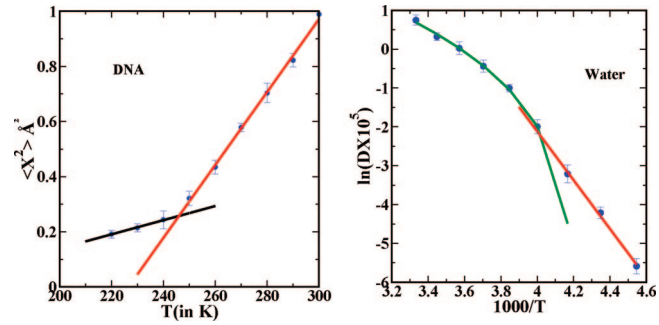

Figure 1. MSF of DNA duplex (left panel) and diffusivity (right panel) of the oxygen atoms of all water in the system. In the left (DNA) panel, MSF of DNA shows a dynamic transition at $T \approx 247$ K. We have fitted two straight lines, one using $T = 300-250$ K data and the other using $T = 240-220$ K data, to show the transition. In the right (water) panel, water shows dynamical crossover around the same temperature from a high temperature power law (fitted using $T = 300-250$ K data) behavior (cyan) to a low temperature Arrhenius (fitted using $T = 240-220$ K data) behavior (red).

III. Results and Discussions

A. Mean Square Fluctuation of DNA and Translational Diffusivity of Water. We first report the calculated mean square atomic fluctuation (which measures the variance of the position of atoms at equilibrium) $\langle X^2 \rangle$ of the DNA atoms starting from 300 to 220 K in order to characterize the macromolecular "glass" transition temperature (T_{DNA}). The left panel of Figure 1 displays the same. We find that the mean square fluctuation (MSF) of DNA slows down dramatically around 247 K and continues to remain slow for the lower temperatures. The onset of the change in slope (near $T_{DNA} \approx 247$ K) of MSF indicates a macromolecular dynamic transition. The right panel of Figure 1 shows temperature dependence of the diffusivity (obtained from the slope of the mean square displacement of water molecules at long time) for all water molecules in the system. It shows a crossover around the same temperature ($T_L \approx 247$ K) from a high temperature power law form to a low temperature Arrhenius form. From the power law fit to the high temperature region we get a glass transition temperature of 231 K, which is in agreement with the earlier simulation study by Stanley and coworkers.[28]

B. Intermediate Scattering Function. We next discuss the self-intermediate scattering function (ISF) of the oxygen atoms of the water molecules in the grooves of DNA for a set of temperatures starting from 300 to 220 K. The self-intermediate scattering function is defined as

$$F_S(k,t) = \langle \exp(-ik(r(t) - r(0))) \rangle = \left\langle \frac{\sin|k||r(t) - r(0)|}{|k||r(t) - r(0)|} \right\rangle \quad (1)$$

where k is the wave vector, and $r(t)$ is the position of the oxygen atom of the water molecules. The $|k|$ value taken here is 2.5 Å^{-1}. The translational relaxation time (τ_T) is obtained by fitting the two step relaxation of ISF at different temperatures using the relaxing cage model (RCM).[40] The fitting equation used here is given by eq 2

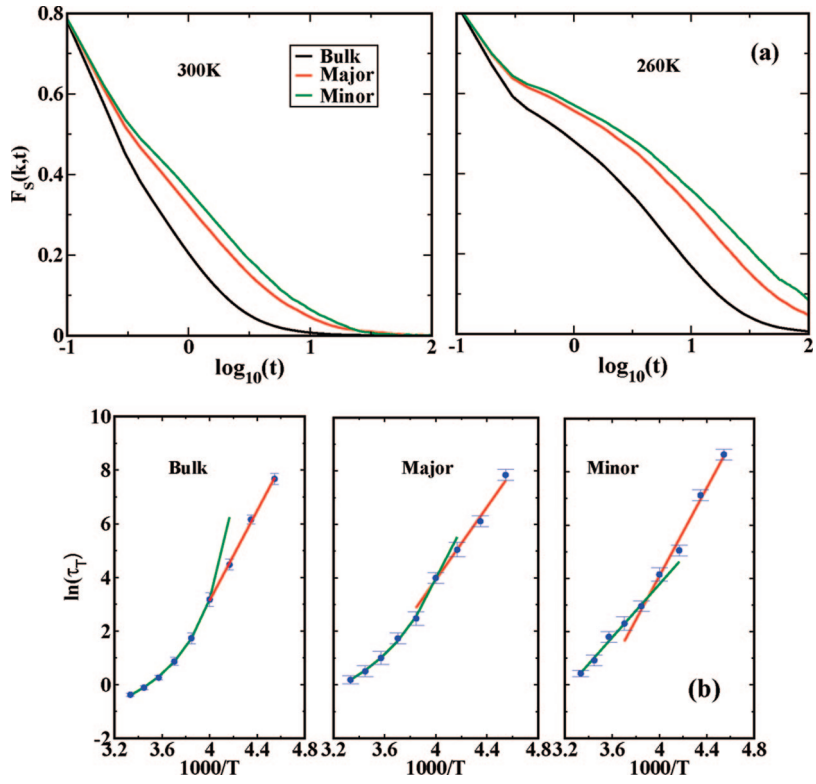

Figure 2. (a) Intermediate scattering functions ($F_S(k,t)$) of the oxygen atoms of the water molecules in bulk, major, and minor grooves of DNA duplex at two different temperatures, $T = 300$ K (left panel) and $T = 260$ K (right panel) for $|k| = 2.5$ Å^{-1}.(b) Translational relaxation time (τ_T) for bulk (left panel), major groove (middle panel), and minor groove (right panel) water. Bulk and major groove water shows dynamical crossover between high temperature VFT behavior (cyan) and low temperature Arrhenius behavior (red). Minor groove water shows a transition between two Arrhenius behaviours. For bulk water, VFT fitting has been done using $T = 300-250$ K data, and Arrhenius fitting has been done using $T = 240-220$ K data. For major groove water, VFT fitting has been done using $T = 300-260$ K data, and Arrhenius fitting has been done using $T = 250-220$ K data. For minor groove water, two Arrhenius fittings have been done using $T = 300-260$ K data and $T = 250-220$ K data.

$$F_S(k,t) = [1 - A(k)]e^{-(t/\tau_S)^2} + A(k)e^{-(t/\tau_T)^\beta} \qquad (2)$$

Here, $A(k)$ is the Debye−Waller factor, τ_T is the translational relaxation time, and β is the stretched exponent.

Figure 2a shows the ISF of oxygen atoms for the water molecules in bulk, major groove, and minor groove at 300 and 260 K. It is evident from both figures that water molecules in both the major and the minor groove tend to behave like a liquid at a temperature lower than the bulk. The behavior is more prominent for water molecules in the minor groove. This can be ascribed to the fact that translational motion of water molecules in the minor groove is more constrained owing to the more ordered structure in the minor groove than water molecules in the major groove of DNA. Water molecules in a major groove are, in turn, translationally more constrained than bulk water. Figure 2b shows the temperature dependence of τ_T for water molecules in bulk, major, and minor grooves. For both bulk and major groove water the temperature dependence at high temperature region can be fitted to the Vogel−Fulcher−Tammann (VFT) law, $\tau_T = \tau_0 \exp[DT_0/(T - T_0)]$, where D is a constant measuring fragility, and T_0 is the ideal glass transition temperature at which relaxation time diverges. In reality, however, the divergence is avoided because below a certain characteristic temperature the functional dependence of relaxation time switches over to an Arrhenius form, which is a signature of a strong liquid. The crossover temperatures for bulk water and major groove water are found to be $T_L \approx 247$ K and $T_{GL} \approx 255$ K, respectively. The dynamical transitions are of fragile-to-strong type, although the fragility of major groove water is the smaller of the two.

The minor groove water molecules, however, show a remarkably different translational dynamics. Minor groove water does not show any signature of a fragile liquid in the temperature range studied. Instead, temperature dependence of translational relaxation time for minor groove water fits well into two Arrhenius forms of different slopes with a crossover temperature around $T_{GL} \approx 255$ K (same as major groove water). This can be understood in the context of difference in the structure of hydration layer in the grooves of DNA. Hydration in the minor groove is more extensive and regular with a zigzag spine of first and second shell of hydration, whereas hydration in a major groove is restricted to a single layer of water molecule.[41] Water molecules in a minor groove are thus more structured in comparison with major groove water, which results in a strong liquid type of behavior for water molecules in minor groove even in the high temperature region. This explains why, in contrast to bulk and major groove water, minor groove water shows a strong-to-strong type of dynamical transition.

C. Orientational Dynamics. We next analyze orientational (dipole−dipole) time correlation function (TCF) of water molecules in the different regions of aqueous DNA, and the TCF calculated is defined as

$$C_\mu(t) = \frac{\langle \mu(0)\mu(t) \rangle}{\langle \mu(0)\mu(0) \rangle} \qquad (3)$$

where $\mu(t)$ is the dipole moment unit vector of the water molecule at time t, and the angular bracket corresponds the ensemble averaging.

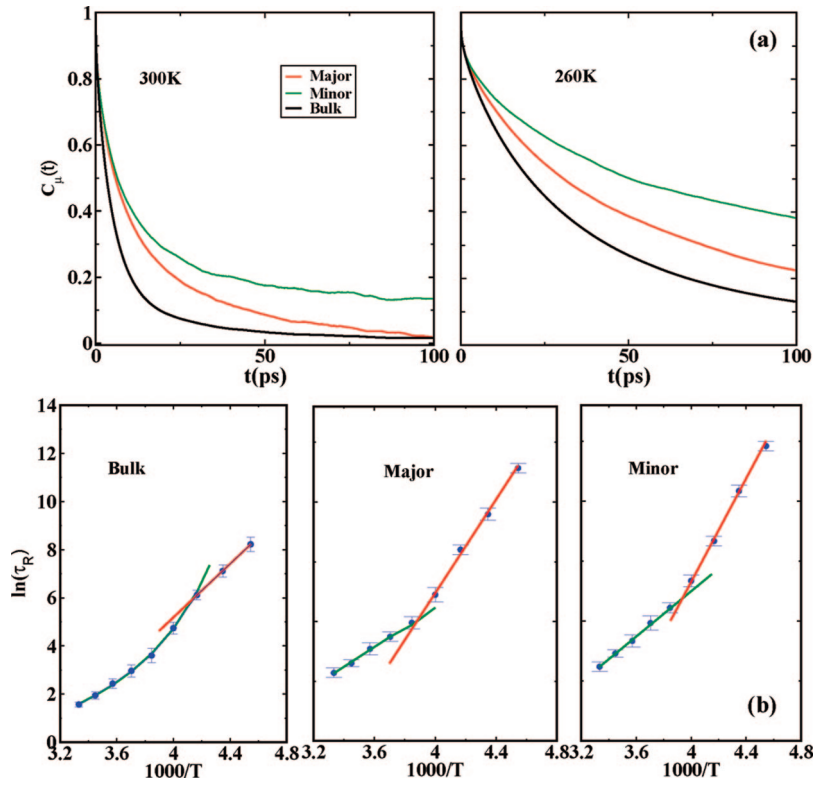

Figure 3. (a) Dipole−dipole time correlation functions ($C_\mu(t)$) of water molecules in bulk, major groove, and minor groove of DNA duplex at two different temperatures, $T = 300$ K (left panel) and $T = 260$ K (right panel). (b) Rotational relaxation time (τ_R) for bulk (left panel), major groove (middle panel), and minor groove (right panel) water. Bulk water shows a crossover between high temperature VFT behavior (cyan) and low temperature Arrhenius behavior (red). Major groove and minor groove water show transition between two Arrhenius behaviors. For bulk water, VFT fitting has been done using $T = 300-250$ K data, and Arrhenius fitting has been done using $T = 240-220$ K data. For major and minor groove waters, two Arrhenius fittings have been done using $T = 300-260$ K data and $T = 250-220$ K data in each case.

Figure 3a displays $C_\mu(t)$ for water molecules in bulk, major, and minor grooves at 300 and 260 K, respectively. Similar to the translational motion, rotation of the minor groove water molecules is found to be the most constrained. Figure 3b shows the temperature dependence of orientational relaxation time (τ_R) as obtained from stretched exponential fitting at long time of dipole−dipole TCF for bulk, major, and minor groove water. Bulk water shows a fragile-to-strong transition around the same temperature ($T_L \approx 247$K) as observed for translational relaxation time. However, unlike translational relaxation, orientational relaxation shows a transition between two Arrhenius forms of different slopes with a crossover temperature $T_{GL} \approx 255$ K for both major and minor groove water. The strong-to-strong transition observed in the minor groove (both translational and orientational dynamics) can be attributed to the effect of confinement in the minor groove (higher depth and lower width). It is known that a confined liquid is comparatively less fragile than in the bulk,[42,43] and this eventually gives rise to a Arrhenius temperature dependence of the relaxation times (signature of strong liquids) even at the higher temperature region. The reason for the different behavior of major groove water is thus probably due to the fact that rotation probes local environment more faithfully than translation.

IV. Microscopic Characterization: O−O−O Angle Distribution

To understand how the structure of groove water changes across the dynamical transition, we have calculated the O−O−O angle distribution inside the first coordination shell of a water molecule. Angle distributions at three different temperatures

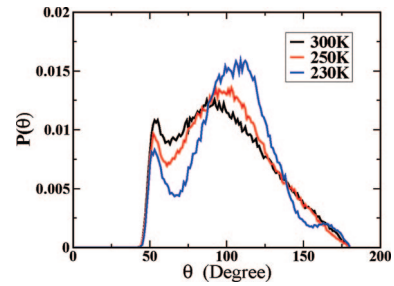

Figure 4. O−O−O angle distribution of the groove water molecules inside the first coordination shell at 300, 250, and 230 K. Note the decrease of lower angle (interstitial) peak and increase of higher angle (degree of tetrahedrality) peak height with decreasing temperature.

(300, 250, and 230 K) for groove water molecules are displayed in Figure 4. At all the temperatures, the distribution has a two-peak character. Although the peak at lower angle is the signature of the presence of interstitial water molecules inside the first coordination shell, a higher angle peak characterizes the degree of tetradehrality present. As it is evident from Figure 4, with decreasing temperature the degree of tetrahedrality increases (higher angle peak height increases) with the removal of interstitial water molecules (lower angle peak height decreases) from the first coordination shell. A structural change of this kind (increase in order with decrease in temperature) is responsible for the dynamical transition for groove water molecules.

Bulk water also exhibits a dynamical transition near 250 K. The signatures are, however, weaker in the case of bulk water than what are observed in the grooves. The role of confinement

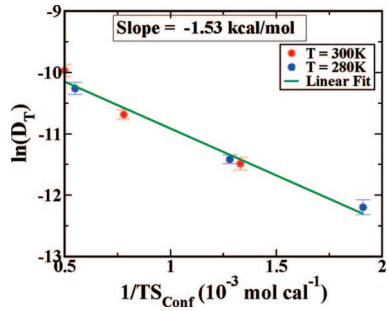

Figure 5. Adam-Gibbs plot of translational diffusivity ($\ln(D_T)$) vs $1/TS_{Conf}$ for water molecules in the different regions of DNA duplex (major groove, minor groove, and bulk) at two different temperatures, $T = 300$ K and $T = 280$ K. At a particular temperature, the points representing the bulk, major groove, and minor groove are in the downward direction of the y-axis.

in fostering the transition of tetrahedral water can be understood in the following fashion. In the confined state, water molecules gain in energy but lose entropy (see next section). The tetrahedrally coordinated water is a low entropy state of the system. Confinement thus favors the crossover/transition to the tetrahedral state.

V. Entropy Calculation

To understand the origin of the large observed differences between the dynamics of water molecules in the minor groove and in the bulk, we have calculated the entropy of water molecules in the respective regions[8,44] at two different temperatures (300 and 280 K). We have used the 2PT method[8,44] to calculate the entropy. In this scheme the total entropy is decomposed into four parts as $S = S_{vib} + S_{Conf} + S_{rot} + S_{b-vib}$. S_{b-vib} is negligible compared to other parts, and S_{rot} has been considered to be constant for each region. To calculate the other two parts of the total entropy, the method requires the translational velocity autocorrelation (VAC) function as input. We have obtained the total density of states (DOS) by taking the Fourier transform of the translational velocity autocorrelation function. Now, one can decompose the total DOS into a solid-like nondiffusive DOS ($g^s(\omega)$) and a gas-like diffusive DOS ($g^g(\omega)$) using the 2PT method.[8,44] Under the harmonic approximation, the vibrational entropy (S_{vib}) can be written as

$$S_{vib} = \int_0^\infty d\omega g^s(\omega) W_S^{HO}(\omega) \quad (4)$$

Here, $W_S^{HO}(\omega)$ is the well-known weight function for the entropy of a harmonic oscillator. Now, the configurational entropy (S_{Conf}) can be written as

$$S_{Conf} = \int_0^\infty d\omega g^g(\omega) W_S^{HS}(\omega) \quad (5)$$

Here, $W_S^{HS}(\omega)$ is the weight function for the entropy of the hard sphere gas. At both temperatures, minor groove water molecules have substantially lower entropy than bulk. At 300 K the difference is ~60% of the latent heat of fusion of bulk water. Entropy is usually found to be closely correlated with diffusion coefficient and structural relaxation time. In Figure 5 we show the correlation between TS_{Conf} and translational diffusivity and show that the Adam-Gibbs relation remains valid for the different regions of DNA. Interestingly, we find that the Adam-Gibbs plot for the two different temperatures collapse on a single curve, which can be fitted to a straight line. This seems to indicate that the activation energies for the transfer of water molecules between different regions of aqueous DNA are at most weakly dependent on temperature above the L−L transition. Dynamics below the L−L transition is too slow to allow a comprehensive study. The present calculation of entropy is semiquantitatively reliable as the entropy of bulk water is correctly (within 5%) reproduced and also the chemical potentials of bulk water and groove water are found to be the same, as expected for systems in equilibrium.

In a thermodynamic coexistence between two phases, a discontinuous change in entropy signals the presence of latent heat and a first-order phase transition. However, in the present case, the large difference in entropy between bulk and minor groove water molecules should be regarded as a signature in the difference in structure between the two phases. Because of the small number (~120 for major groove and ~80 for minor groove) of water molecules present in the groove region, a detailed quantification of microscopic structural arrangement is hard to perform.

Because the numbers of water molecules in the two grooves of the dodecamer are rather small, we have also simulated a large system with a standardized 38 base pair DNA and 8000 water molecules interacting with TIP3P potential.[45] This system is known to sustain a stable double helix over a long time period.[45] Interestingly, we obtained qualitatively similar results for the groove water molecules, but transitions (around 245 K in the grooves) are not as prominent since TIP3P is known not to be a good network forming liquid and the L−L transition is largely suppressed in the bulk phase. Nevertheless, we do find a similar kind of transition in the grooves of two different systems with two different water models, which strengthens the generality of the results obtained in the present study.

VI. Conclusions

We have studied both translational and rotational motions of water in the grooves of a DNA duplex. We find that groove water shows a remarkable dynamical transition that can explain the transition observed in DNA duplex itself. The fact that this transition occurs at not too deeply supercooled water ($T_{GL} \approx$ 255 K) suggests that this can be of importance in the natural world. The effects of confinement of water in the grooves of DNA are dictated partly by the loss of entropy and by the gain of enthalpy. Both of these factors favor formation of the low density four-coordinated state. This not only increases the temperature of the L−L transition, but makes it also stronger, as observed in simulations here.

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