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Entropy of Water in the Hydration Layer of Major and Minor Grooves of DNA

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Transport properties (translational and rotational) of water in the two grooves of the B-DNA duplex are known to be different from those in the bulk. Here, we use a recently developed theoretical scheme to compute the entropies of water molecules in both of the grooves of DNA and compare them with that in the bulk. The scheme requires as input both translational and rotational velocity autocorrelation function ($C_V(t)$ and $C_\omega(t)$, respectively) data. These velocity autocorrelation functions were computed from an atomistic MD simulation of a B-DNA duplex (36 base pairs long) in explicit water (TIP3P). The average values of the entropy of water at 300 K in both of the grooves of DNA (the *TS* value in the major groove is 6.71 kcal/mol and that in the minor groove is 6.41 kcal/mol) are found to be significantly lower than that in bulk water (the *TS* value is 7.27 kcal/mol). Thus, the entropic contribution to the free energy change ($T\Delta S$) of transferring a minor groove water molecule to the bulk is 0.86 kcal/mol and of transferring a major groove water to the bulk is 0.56 kcal/mol at 300 K, which is to be compared with 1.44 kcal/mol for melting of ice at 273 K. We also calculate the energy of interaction of each water molecule with the rest of the atoms in the system and hence calculate the chemical potential (Helmholtz free energy per water molecule, $A = E - TS$) in the different domains. The identical free energy value of water molecules in the different domains proves the robustness of the scheme. We propose that the configurational entropy of water in the grooves can be used as a measure of the mobility (or microviscosity) of water molecules in a given domain.

I. Introduction

Water is known to play a key role in the biological activities of proteins and DNA.[1−13] From the dynamic and thermodynamic point of view, surface water molecules can be different from bulk water due to very different interactions of water molecules with proteins or DNA.[10,11,14−22] The thermodynamic properties of these surface water molecules are known to play an important role in biological processes such as recognition, intercalation, etc.[23−31] Several models such as the linear response approximation (LRA),[32] linear interaction energy (LIE),[33] protein dipole Langevin dipoles (PDLD), and its semimicroscopic version (PDLD/S)[34] have explored and demonstrated the importance of water molecules in the biological processes. However, quantification of the absolute thermodynamic properties of such surface water has proven to be rather difficult. Warshel and coworkers[35] had earlier calculated the hydration entropies of isolated hydrophobic, polar, and ionic solutes in the framework of Langevin dipole solvation model and also used the same for the calculation of hydration free energy of the DNA bases.[36] They obtained the expected decrease of entropy of water due to hydration of the solute. However, their method did not include the contribution of translational entropy toward the total hydration entropy. In several other studies,[37,38] including restraint release (RR) studies,[34,39−41] the calculation of entropy change in biological processes in solutions (such as molecular recognition, ligand binding, etc.) were carried out where the total entropy change of the system (including macromolecules and biological water) was calculated.

Here, we present a theoretical analysis of the entropy of water molecules in the grooves of aqueous DNA. We use a recently developed scheme[42,43] (the two-phase thermodynamic model, termed the 2PT method) to calculate the entropy of water molecules in various distinct regions of DNA. The scheme requires as input both translational and rotational velocity autocorrelation function data, which can be computed from molecular dynamics simulation. Lin et al.[43] applied this method for argon at different densities ($\rho^* = 1.10$ to $\rho^* = 0.05$) and different temperatures ($T^* = 1.8$ to $T^* = 0.9$) covering the whole phase diagram of argon and showed the entropy calculated using the 2PT method shows excellent agreement with that calculated using the equation of state. They also showed that a short simulation time ($\sim$20 ps) is enough to obtain good convergence of the entropy (calculated using the 2PT method) with the entropy calculated using the equation of state. Most closely related to the present work is that of Lin et al.,[42] who used this method quite successfully to calculate the entropy of water molecules in the bulk liquid and in the different domains of PAMAM dendrimers.

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The 2PT method has also been used to determine various phases of dendrimer liquid crystals[44] and stability of various forms of aggregate.[45] While the 2PT method gives excellent result for argon and liquid water, its validity for complex systems is yet to be fully demonstrated, although its application to water in dendrimer appears to lead to meaningful results. Here, we show that the method provides a reasonable measure of the entropy loss of water in the grooves of DNA. A notable merit of this method is that, unlike other quashiharmonic approaches, the 2PT method assumes harmonic vibrations only for high-frequency modes, where harmonic approximation should be valid, and explicitly corrects for the fluidicity effects in the low-frequency regime, where anharmonic effects are most prominent.[43]

In our application of the 2PT method, we calculate the translational and rotational diffusion constants of the water molecules in the different domains of DNA. We have also calculated the fluidicity factor of the water molecules in the different domains. The dynamic and thermodynamic properties that we obtain agree with those in other recent works.[15,16,42] We find that there are considerable differences in terms of dynamic and thermodynamic properties for water molecules in the different domains of DNA (major groove, minor groove, and bulk), in agreement with the recent results obtained by Lin et al.,[42] who have calculated the properties of water molecules in the different domains of PAMAM dendrimers.

We have also found that the chemical potential values (Helmholtz free energy per molecules) of water molecules in different domains of DNA (major groove, minor groove, and bulk) are identical within the uncertainty of our calculation, in contrast with the result of Lin et al.[42] This means that although the water molecules in the two grooves of DNA are dynamically and thermodynamically different from those in the bulk, they are in equilibrium with each other.

We also found that the logarithm of the translational diffusivity (D_T) as a function of the inverse of the configurational entropy (S_{conf}) shows a linear dependence, as expected from the Adam−Gibbs relation.[46] When the Stokes−Einstein relation[47] between viscosity and diffusivity is taken into account, this implies that one can consider the configurational entropy as a measure of the mobility (or microviscosity).

The organization of the remainder of the paper is as follows. In the next section, we describe the theoretical scheme used to calculate the entropy. In Section III, we describe the details of the simulation methods. The details of results and discussions are presented in Section IV, and finally, we summarize our results and conclude in Section V.

II. Theoretical Scheme

In the 2PT scheme developed by Goddard and co-workers,[43] the total entropy (S) per particle is decomposed into four parts as

$$S = S_{vib} + S_{conf} + S_{rot} + S_{b-vib} \quad (1)$$

where S_{vib} is the vibrational entropy, S_{conf} is the configurational (diffusional) entropy, S_{rot} is the rotational entropy, and S_{b-vib} is the bond-vibrational entropy (internal). The details of the scheme have been discussed by Lin et al.[43] Here, we briefly discuss the implementation of the scheme which involves the following steps.

(1) Under the harmonic approximation, the vibrational entropy (S_{vib}) can be written as[48]

$$S_{vib} = \int_0^\infty d\omega g^S(\omega) W_S^{HO}(\omega) \quad (2)$$

where $g^S(\omega)$ is the solidlike nondiffusive density of states, which can be obtained from the decomposition of the translational density of states ($g^T(\omega)$) using the 2PT decomposition[39,40] (details of the decomposition will be discussed in step 6). $W_S^{HO}(\omega)$ is the well-known weight function for the entropy of a harmonic oscillator and can be written as

$$W_S^{HO}(\omega) = \frac{\beta\hbar\omega}{\exp(\beta\hbar\omega) - 1} - \ln[1 - \exp(-\beta\hbar\omega)] \quad (3)$$

where $\beta = 1/kT$ and $\hbar = h/2\pi$,where h is the Planck's constant.

(2) The configurational entropy (S_{conf}) can be written as[42,43]

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

where $g^g(\omega)$ is the gaslike diffusive density of states, which can be obtained from the decomposition of the translational density of states ($g^T(\omega)$) using the 2PT decomposition.[42,43]

$W_S^g(\omega)$ is the weight function for the entropy of the hard sphere gas and can be written as

$$W_S^g(\omega) = \frac{1}{3}\frac{S^{HS}}{k} \quad (5)$$

where S^{HS} is the hard sphere entropy, which can be determined from the Carnahan−Starling equation of state.[49]

(3) In our calculation, the rotational entropy (S_{rot}) is assumed to have a constant value of 44.58 J $K^{-1}mol^{-1}$(or 3.2 kcal/mol in terms of TS at 300 K) because previous studies have been shown that the rotational entropy in solution can be well estimated from the ideal gas value.[50−52] These studies[50−52] estimate the entropies of the gas and liquid phases of various systems and found that the rotational entropy in both of the phases is nearly same (within 2%) for most of the systems.

The bond vibrational entropies (S_{b-vib}) are small due to the high vibrational frequencies and are ignored in our calculations.

(4) We next discuss the construction of the density of states. The density of states ($g(\omega)$) of water molecules can be written as a Fourier transform of the velocity autocorrelation function; the relation is[42]

$$g(\omega) = \frac{2}{kT}\lim_{\tau\to\infty}\int_{-\tau}^{\tau} C(t)e^{-i\omega t}\,dt \quad (6)$$

where $C(t)$ can be either the mass-weighted center of mass velocity autocorrelation function or the moment of inertia-weighted angular velocity autocorrelation function of the water molecules. In the former case, the corresponding density of states will be the translational density of states ($g^T(\omega)$). The molecular center of mass velocity autocorrelation function can be written as

$$C_V(t) = \sum_{i=1}^{N} m_i \langle \vec{v}_i^{CM}(t) \cdot \vec{v}_i^{CM}(0)\rangle \quad (7)$$

where $\vec{v}_i^{CM}(t)$ and m_i are the center of mass velocity and mass of the ith water molecule and N is the number of water molecules included in the summation. The angular velocity autocorrelation function is written as

$$C_\omega(t) = \sum_{j=1}^{3} C_{\omega j}(t) = \sum_{j=1}^{3}\sum_{i=1}^{N} I_{ij}\langle \omega_{ij}^{CM}(t)\omega_{ij}^{CM}(0)\rangle \quad (8)$$

where I_{ij} and $\omega_{ij}^{CM}(t)$ are the jth principal moment of inertia and

angular velocity of the *i*th water molecule. In this case, the density of states will be the rotational density of states ($g^R(\omega)$).

Integration of $g^T(\omega)$ or $g^R(\omega)$ over the whole frequency range ($\omega = 0-\infty$) gives the total degrees of freedom, $3N$, of the system, where N is the number of water molecules used in the summation for the respective autocorrelation function determination. The number of molecules used to determine the time correlation function is different in different regions.

(5) The zero-frequency intensity of the density of states, $g^T(\omega = 0)$ or $g^R(\omega = 0)$, corresponds to the corresponding diffusion constant of water molecules through[42]

$$D_T = \frac{kTg^T(\omega = 0)}{12mN} \tag{9}$$

and

$$D_R = \frac{kT\sum_{j=1}^{3} g^{Rj}(\omega = 0)}{4N\sum_{j=1}^{3} I_j} \tag{10}$$

where D_T and D_R are the translational and rotational diffusion constants, respectively.

(6) For the translational density of states $g^T(\omega)$, we use the 2PT decomposition method[43] to obtain the gaslike diffusive density of states ($g^g(\omega)$) and the solidlike nondiffusive density of states($g^S(\omega)$). In this decomposition method, $g^T(\omega)$ is written as[43]

$$g^T(\omega) = g^S(\omega) + g^g(\omega) \tag{11}$$

The gaslike diffusive part normalizes to $3Nf$ and the solidlike nondiffusive part normalizes to $3N$ $(1 - f)$, where N is the number of water molecules included for the summation in eq 7 and f is the fluidicity factor.

For calculating the gaslike diffusive contribution, we use the hard sphere diffusive fluid model, where the density of states can be written as[43]

$$g^g(\omega) = g^{HS}(\omega) = \frac{g_0}{1 + \left(\frac{g_0\omega}{12fN}\right)^2} \tag{12}$$

where g_0 is equal to $g^T(\omega = 0)$ and f is the fluidicity factor, now discussed.

The fluidicity factor (f) determines the conceptual partition of the system, which consists of group of water molecules between solid and gas components. As such, f needs to satisfy the following two conditions: (i) In the high temperature and/or low-density limit, the system behaves like a hard sphere gas; thus there will be no solidlike component so that $f = 1$. (ii) In the high-density limit where the system is solid, there is no gaslike component and hence we require that $f = 0$.

We can write the fluidicity factor (f) in such a way that it will satisfy the above two conditions[43]

$$f = \frac{D(T, \rho)}{D_0^{HS}(T, \rho; \sigma^{HS})} \tag{13}$$

where D is the self-diffusion constant of the system determined from eq 9 and D_0^{HS} is the hard-sphere diffusion constant in the zero pressure limit. Here, σ^{HS} is the hard-sphere diameter. Now, following the 2PT method described in ref 43, we obtain a universal expression for f in terms of Δ (the normalized diffusivity of the system) as

$$2\Delta^{-9/2}f^{15/2} - 6\Delta^{-3}f^5 - \Delta^{-3/2}f^{7/2} + 6\Delta^{-3/2}f^{5/2} + 2f - 2 = 0 \tag{14}$$

and Δ is related to g_0 by the relation

$$\Delta(T, \rho, m, g_0) = \frac{2g_0}{9n}\left(\frac{\pi kT}{m}\right)\rho^{1/3}\left(\frac{6}{\pi}\right)^{2/3} \tag{15}$$

With the use of the last two equations, we can find the fluidicity factor by knowing the value of g_0 and other parameters determined in the simulation. Once we know $g^T(\omega = 0)$ and the fluidicity factor, we can calculate $g^g(\omega)$ and also $g^S(\omega)$ [$g^S(\omega) = g^T(\omega) - g^g(\omega)$].

III. Simulation Details

The sequence of the DNA used is (GCCGCGAGGTGT-CAGGGATTGCAGCCAGCATC-TCGTCG), which has been extensively studied earlier[53,54] and found to sustain stable duplex in simulations. All MD simulations reported in this article used the AMBER7 software package[55] with the all-atom AMBER95 force field (FF).[56] AMBER95 FF has been validated for molecular dynamics (MD) simulations of B-DNA in explicit water with salt, starting from the crystal structure.[57−61] These validation studies found that the CRMS deviation from the crystal structure for a dodecamer structure is typically less than 4 Å. The electrostatics interactions were calculated with the particle mesh Ewald (PME) method[62,63] using a cubic B-spline interpolation of order 4 and a 10^{-4} tolerance set for the direct space sum cutoff. A real space cut off of 9 Å was used both for the electrostatics and van der Waals interactions with a nonbond list update frequency of 10. First, we create regular B-DNA molecule using the nucleic acid builder program Namot2[64] (version 2.2.). Using the LEAP module in AMBER, the DNA structure was immersed in a water box using the TIP3P model for water. 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 structure. This procedure resulted in solvated structures, containing approximately 25 000 atoms, which include the 2405 DNA atoms, 74 counterions, and 7534 water molecules in a simulation box of lengths of 42 Å, 42 Å, and 142 Å along the three axes. Detail of the simulations can be found elsewhere.[53,54,65]

For the present analysis, we generated three independent 100 ps long trajectories of 4 fs resolution. As observed by Lin et al.[43] and mentioned earlier, a 20 ps trajectory is usually sufficient to accurately obtain the entropy.

IV. Results and Discussion

We first describe the selection of water molecules in the different domains of DNA. In Figure 1, we show a snapshot of the part of the hydrated DNA studied here to get a clear view of the major and minor groove of the aqueous DNA. Major and minor groove atoms of two Watson−Crick base pairs are shown in Figure 2. Water molecules that are in the region within 3.5 Å from any of the atoms of a groove are selected as the respective groove water molecules for a particular snapshot. In addition, we selected the subset of those groove water molecules for our calculation, which remain in the respective grooves

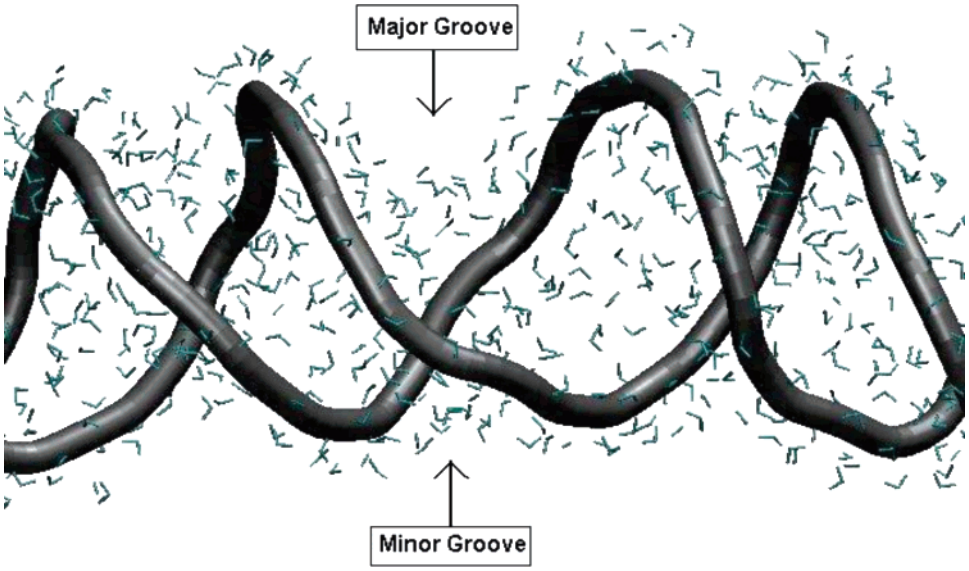

Figure 1. Water shell (3.5 Å) around the backbone of DNA. This is a two-dimensional projection.

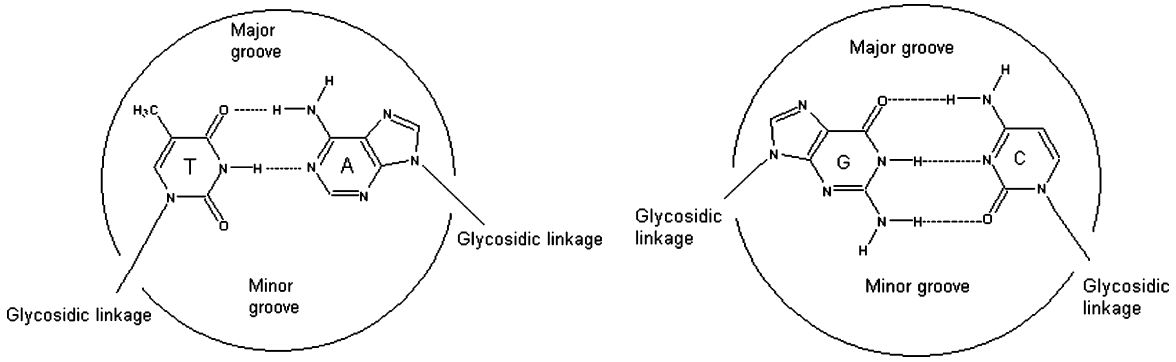

Figure 2. Atoms of the Watson−Crick base pairs in the major groove and minor groove regions.

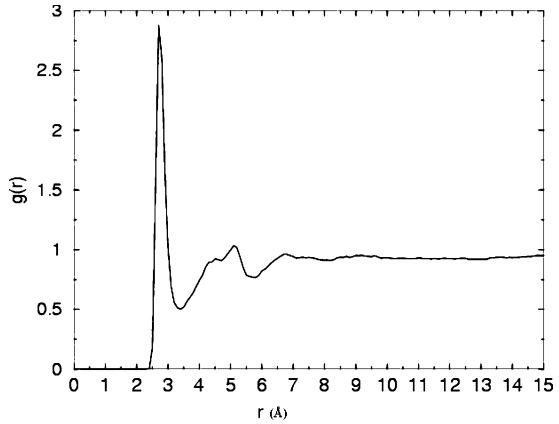

Figure 3. Pair correlation function, $g(r)$, of the oxygen atom of water molecules with respect to the oxygen atom of the phosphate residue of a 38 base pairs long B-DNA duplex at 300 K.

throughout the simulation time. The bulk water molecules are those water molecules that remain in a region beyond 10 Å away from the DNA atoms. These selections of the distances are based on the pair correlation function $g(r)$ of the oxygen atom of water molecules with respect to the oxygen atom of the phosphate residue of the B-DNA duplex, shown in Figure 3. With this approach, we selected 24 water molecules as minor groove water, 47 water molecules as major groove water, and another 47 water molecules as bulk water.

All the dynamic and thermodynamic properties that will be discussed in the next two sections are listed in Table 1 for each domain water molecules. We calculate all the dynamic and thermodynamic properties for three independent sets of simulation data to estimate the uncertainty of our analysis.

A. Dynamic Properties. The translational and rotational velocity autocorrelation functions of water molecules in different domains of DNA, shown in Figure 4, reveal that there are considerable differences in terms of dynamic properties among water molecules in the three domains of DNA. Using the velocity autocorrelation function data, we obtain the respective power spectra of water molecules in each domain with a resolution of 1.1 cm^{-1}.

The translational and rotational power spectra of water molecules in different domains of DNA are presented in Figure 5. All the spectra are normalized to one molecule so that the area under the curves is 3 (3 translational or rotational degrees of freedom). The general feature of all the translational power spectra is that there is finite intensity at $\omega = 0$, but the value of the intensity is significantly less for water molecules in the grooves of DNA (especially in the minor groove) than in the bulk. Using these $g^T(\omega = 0)$ values, we have calculated the translational diffusion constants of water in the different domains of DNA. The translational diffusion constant of bulk water (4.89×10^{-5} cm^2/s) is significantly larger than that for major groove water (2.29×10^{-5} cm^2/s) and minor groove water (1.02×10^{-5} cm^2/s). On comparing these translational diffusion constant values, it is clear that minor groove water molecules are translationally more constrained than are major groove water molecules, which in turn are more constrained than are bulk water molecules. We have calculated the rotational diffusion

TABLE 1: Dynamic and Thermodynamic Properties of Water Molecules in Different Domains of a 38 Base Pairs Long B-DNA Duplex at 300 K

properties	bulk water	major water	minor water
$g^T(\omega = 0)$ [10^{-2} cm]	1.2725 ± 0.006	0.5972 ± 0.005	0.265 ± 0.006
$g^R(\omega = 0)$ [10^{-4} cm]	7.3617 ± 0.009	6.659 ± 0.013	4.2083 ± 0.01
D_T [10^{-5} cm^2/s]	4.89 ± 0.023	2.29 ± 0.019	1.025 ± 0.023
D_R [10^{11} 1/s]	2.57 ± 0.003	2.32 ± 0.005	1.47 ± 0.004
translational librational peak [cm^{-1}]	30 ± 5	40 ± 3	65 ± 5
rotational librational peak [cm^{-1}]	445 ± 5	460 ± 3	472 ± 5
fluidicity factor (f)	0.3269 ± 0.0068	0.2259 ± 0.0072	0.1488 ± 0.008
TS_{vib} [kcal/mol]	2.06 ± 0.07	2.22 ± 0.08	2.46 ± 0.04
TS_{conf} [kcal/mol]	2.00 ± 0.04	1.28 ± 0.13	0.75 ± 0.06
TS [kcal/mol]	7.27 ± 0.03	6.71 ± 0.06	6.41 ± 0.03
interaction energy [kcal/mol]	-9.39 ± 0.09	-9.99 ± 0.06	-10.24 ± 0.15
free energy ($A = E - TS$) [kcal/mol]	-16.68 ± 0.15	-16.73 ± 0.10	-16.70 ± 0.07

constant for water molecules in each domain of the DNA and the values (see Table 1) fall in the same order as for the translational diffusion constants; minor groove water molecules are dynamically more constrained than water molecules in the major groove and in the bulk. The differing degrees of constraint discussed above are also reflected in the librational peak position of the translational and rotational power spectra of water molecules in the different domains of DNA (Figure 5 and Table 1). In the librational peak position of the translational power spectrum, there is a blue-shift of $\sim$10 cm^{-1} going from bulk water to major groove water and further a blue-shift of $\sim$35 cm^{-1} going from bulk water to minor groove water. In the librational peak position of the rotational power spectum, there is also a blue-shift, although less prominent, of $\sim$15 cm^{-1} going from bulk water to major groove water and further a blue-shift of $\sim$22 cm^{-1} going from bulk water to minor groove water. Note that the shoulder observed at $\sim$200 cm^{-1} is due to the intermolecular O- - - O vibration, present in the bulk translational power spectrum, and becomes weaker or nearly absent in the minor groove translational power spectrum. The 200 cm^{-1} band is usually attributed to hydrogen bond excitation.

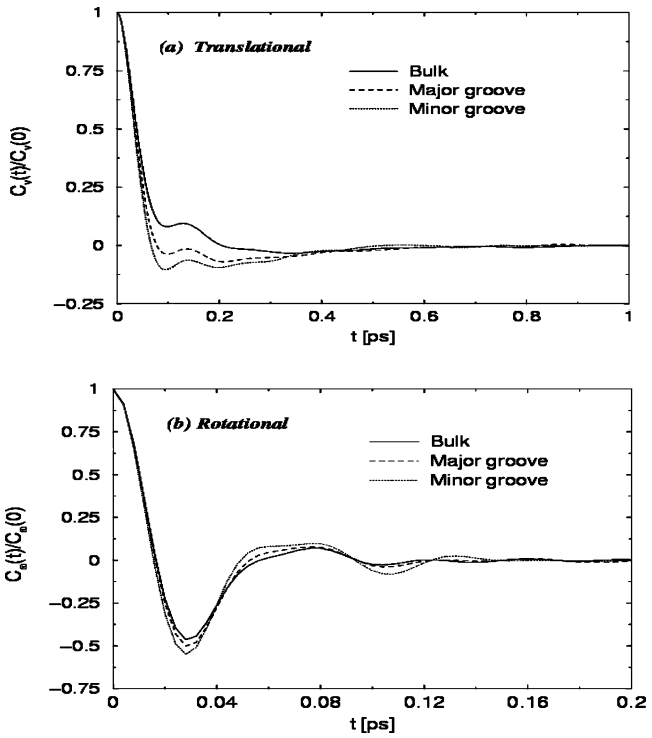

Figure 4. (a) Translational and (b) rotational velocity autocorrelation functions of water molecules in the bulk, in the major groove, and in the minor groove of a 38 base pairs long B-DNA duplex at 300 K.

We have also calculated the fluidicity factor (using eqs 14 and 15) of water molecules in each domain of DNA. The results in Table 1 show that minor groove water molecules are less diffusive than water molecules in the major groove and in the bulk.

B. Thermodynamic Properties. We calculate the entropy of water molecules for each domain of DNA using the 2PT method discussed in Section II. In particular, we calculate the vibrational entropy S_{vib}, eq 2, and configurational entropy S_{conf}, eq 4, of water molecules in each domain of DNA (recall that in eq 1 for S, the rotational entropy is constant and the bond vibrational entropy is negligible). The values of the vibrational entropies of the different domains in Table 1 increase in the sequence of going from bulk water to major groove water to minor groove water. This might seem to be puzzling in view

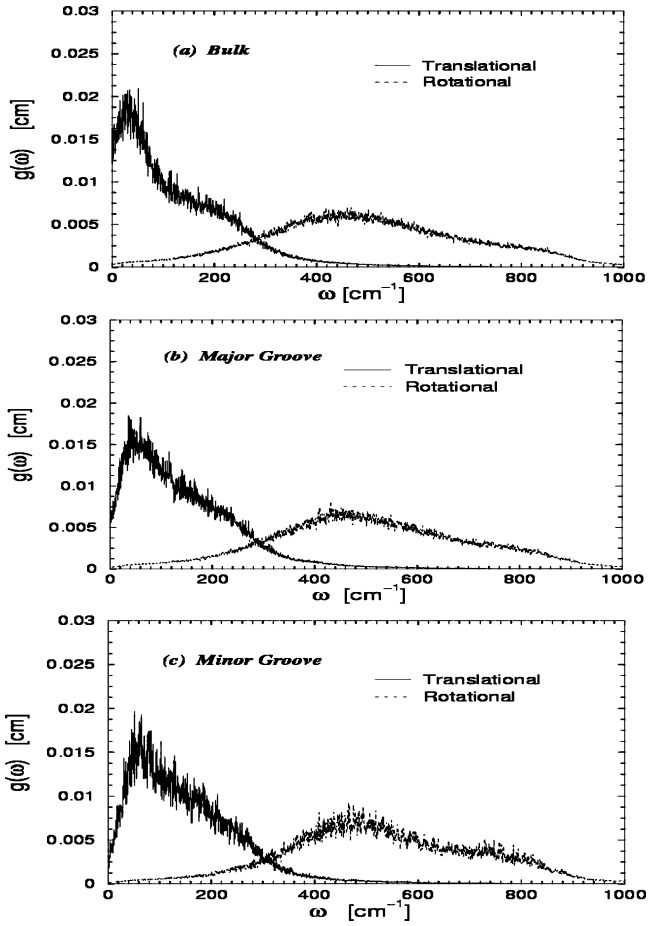

Figure 5. Averaged translational and rotational power spectra of water molecules (a) in bulk, (b) in the major groove, and (c) in the minor groove of a 38 base pairs long B-DNA duplex at 300 K.

TABLE 2: Entropic Contribution to the Free Energy Change for Some Processes

process	temperature (T), K	entropic change ($T\Delta S$), kcal/mol
release of water from minor groove of DNA to bulk	300	0.86 (± 0.03)
release of water from major groove of DNA to bulk	300	0.56 (± 0.04)
melting of ice	273	1.44

of the fact that the librational peak positions of the translational power spectra of water molecules in the different domains of DNA show a blue-shift going from bulk water to major groove water to minor groove water (Table 1 and eq 3). This unusual order of the vibrational entropies is due to the fact that the translational power spectra are becoming more and more broadened, going from bulk water to major groove water to minor groove water. This broadening may be a reflection of inhomogeneity present in the grooves. The configurational entropies S_{conf} of water molecules in the different DNA domains show a reverse order as compared to the vibrational entropies. This is quite reasonable because the fluidicity factors (f) in Table 1 show a decreasing order going from bulk water to major groove to minor groove water molecules.

The total entropy S at 300 K of the water molecules in the minor groove (the TS value is 6.41 kcal/mol) and of the water molecules in the major groove (the TS value is 6.71 kcal/mol) is significantly less than those in the bulk (the TS value is 7.27 kcal/mol). On comparing the TS values of water molecules in the different domains of DNA, it is clear that minor groove water molecules are more ordered than major groove water molecules, which in turn are more ordered than bulk water molecules.

We have also calculated the average energy of interaction (E) of water molecules in the different domains of DNA. While calculating the interaction energy, we consider the contribution coming from other water molecules, the atoms of DNA, and from the Na^+ ions. The calculated average interaction energies show minor groove water molecules (interaction energy is −10.24 kcal/mol) are energetically more stable than major groove (interaction energy is −9.99 kcal/mol) water molecules, which are also energetically more stable than bulk water molecules (interaction energy is −9.39 kcal/mol).

We have calculated the chemical potential (Helmholtz free energy, $A = E - TS$) of water molecules in the different domains of DNA. The values in Table 1 are identical within the uncertainty of our calculation for different domain water molecules. This means that the water molecules in each domain are in dynamic equilibrium with one another and provides a check on the calculation.

It is interesting to compare (Table 2) the calculated value of the entropy change ($T\Delta S$) due to the release of water molecules from the grooves of DNA to the bulk with that of the melting of ice because both involve delocalization of water molecules. While the change in entropy at 300 K due to the release of water molecules from the minor groove of DNA to the bulk is 0.86 kcal/mol and from the major groove of DNA to bulk is 0.56 kcal/mol, the entropy change due to melting of ice is 1.44 kcal/mol at 273 K. Thus, the increase of entropy due to transition of water molecules from the minor groove of DNA to bulk is significant on the scale of melting reference value.

C. Rotational Entropy Calculation. In the present scheme as described in Section II, we have added a constant value of 3.2 kcal/mol as the rotational entropy (in terms of TS at 300 K) for each domain's water molecules while calculating the total entropy of water molecules in the different DNA domains. This procedure was also adopted in the earlier application of the 2PT method.[42] Several recent studies[50−52] estimate the entropies of the gas and liquid phase of various systems and found that the rotational entropy in both of the phases is nearly the same (within 2%) for most of the systems. Therefore, an assumption of a constant value of rotational entropy for water molecules in the different domains of DNA is not expected to introduce any serious error.

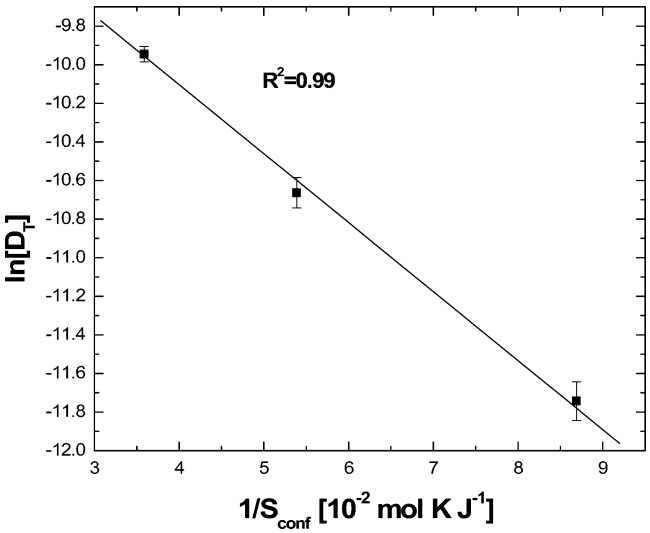

Figure 6. Plot of $\ln[D_T]$ vs $1/S_{conf}$ showing a linear dependence which is expected from the Adam−Gibbs relation (see the text).

D. Dependence of Translational Diffusivity on Configurational Entropy. Finally, we examine the dependence of the translational diffusivity of water in the different domains of DNA on the configurational entropy of the respective domains. In Figure 6, we plot the logarithm of translational diffusivity as a function of $1/S_{conf}$, which shows a linear dependence (with $R^2 = 0.99$) with a negative slope. From the plot, it is clear that there exists a relation between D_T and S_{conf}

$$D_T = A \times \exp\left(-\frac{C}{TS_{conf}}\right) \tag{16}$$

where A and C are the constants and have the values in the present case of 1.308×10^{-4} cm^2/s and 23.54 cal mol^{-1} K^{-1}, respectively. Equation 16 is the Adam−Gibbs relation between the diffusivity and the configurational entropy.[46] This can be of direct relevance to hydration dynamics of DNA and, in particular, to the dynamic exchange model,[19] i.e., bound-to-free interconversion of water with an activation entropy, as discussed below. Recently, temperature dependence of the solvation dynamics has been interpreted in terms of the dynamic exchange model. It has been shown that the entropy of activation for bound-to-free interconversion (dynamic exchange) is ∼28 cal mol^{-1} K^{-1} in cyclodextrin aggregates[66] and ∼14 cal mol^{-1} K^{-1} in a micelle.[67] Further, if one assumes a Stokes−Einstein relation, where the translational diffusion constant and the viscosity are inversely related,[47] then we have an interesting correlation between viscosity and configurational entropy. Thus, the configurational entropy of water molecules in a domain can be an empirical measure of the mobility (or microviscosity) of the respective domain.

V. Concluding Remarks

Let us first summarize the main results of this paper. We have calculated the entropy of water molecules in the major

and minor grooves of a B-DNA duplex and in the bulk using a recently developed statistical mechanical scheme developed by Goddard and co-workers.[42,43] This scheme uses computer simulation results of the translational and the rotational velocity time correlation functions to obtain the density of states of the solidlike and fluidlike modes of the liquid. This scheme is known to give a highly accurate result for a Lennard-Jones fluid[43] and, most relevant for the present work, also for bulk water.[42] The minor groove water molecules are found to have lower entropy than those in the major groove, which in turn have lower entropy than those in the bulk. The difference in entropy between the various distinct regions of DNA is found to be significant, as judged by the magnitude of the entropy changes on transferal to the bulk as compared to that for the melting of ice.

Our calculations for the water under equilibrium conditions appropriately shows that the undoubted entropy gain time T is canceled by the energetic effects in the process of transferal of water from the grooves of DNA to the bulk. We note that various authors have suggested a dominant role in ligand binding thermodynamics for the entropy gain of water[26,68,69] associated with its release from the grooves of DNA. There have been several attempts[32−34,37−41,70−71] to calculate binding free energies and to understand the explicit role of water associated with such biological processes. While the applicability of the 2PT method has been demonstrated for water in the bulk and in the restricted region of the complex system like dendrimers, the validity of the method for complex biological processes has not been demonstrated yet. In fact, the past experience of applicability of the quasiharmonic approaches has not been quite satisfactory. This is because such methods have two serious problems: (a) anharmonicity due to large amplitude motion in the low frequency domain and (b) proper sampling of the configurational space, which may require hundreds of nanoseconds to explore it. Note that both of these issues are highly nontrivial.

Although based on a series of approximations, the calculational scheme employed[43] appears to provide a reasonable quantitative estimate of the entropy of water molecules in the different distinct domains examined. The scheme allowed us to establish a correlation between the configurational entropy and the translational diffusion constant of the water molecules (Figure 6). If one assumes the Stokes−Einstein relation between the diffusion constant and the viscosity, this provides an interesting correlation between the viscosity and the configurational entropy. Such a relation is the subject of much discussion in supercooled liquids, where a decrease in configuration entropy is believed to be responsible for a large growth in the viscosity.[46,72−74] In the present case, it is perhaps more relevant to consider this correlation between viscosity and entropy as providing a thermodynamic basis of the oft-used concept of microviscosity.[75−79]

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