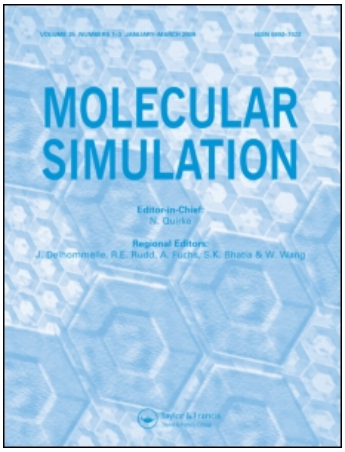

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A Study of the Hydrogen-bonded Network Around the Left-handed and Right-handed DNA in an Ionic Solution

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A Study of the Hydrogen-bonded Network Around the Left-handed and Right-handed DNA in an Ionic Solution

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Molecular dynamics simulations were carried out for a right-handed and left-handed DNA heteropolymeric fragment, in which four different types of nucleotides constituted the sequence. The average structures obtained from the simulation converged to within ~1.4 Å rms fluctuation for the left-handed and for the right-handed DNA. The distribution of hydration sites and the hydrogen-bonded circular network of water molecules around guanine and cytosine bases were distinctively different in two DNA conformations. The hydrogen-bonded circular network, ring structure, of water molecules within 4.0 Å around two DNA molecules was better formed in the right-handed DNA than in the left-handed DNA, showing a higher ratio of hexameric ring to pentameric ring (R_6/R_5).

Keywords: Molecular dynamics simulation; B-DNA; Z-DNA; Hydration

INTRODUCTION

It is well known that water has a dominant influence on the conformation and activities of biological molecules such as DNA, RNA, and proteins [1–7]. To illuminate the role of water in DNA structure, both experimental and theoretical studies on DNA hydration have been carried out [8–12]. To describe the hydration pattern around bases of DNA, several methods have been developed. Particularly interesting is a statistical analysis of crystallographic hydration sites around the four different types of bases in right-handed DNA, A- and B-DNA conformations, and in left-handed DNA, Z-DNA conformation [13]. The study on the clear hydration sites at the base amino groups and carbonyl groups in the minor and major grooves suggested that DNA hydration is mostly local, irrespective of the various base sequences of the DNA fragments used in the analysis. Also, another experimental method measuring molar volume and compressibility as a function of base composition concluded that C/G base pairs are more strongly hydrated than A/T base pairs [14]. In addition, mixed base sequences were found to be less hydrated than either C/G or A/T homopolymers. From previous studies, it is well established that there is a different hydration pattern around bases in A-, B-, and Z-DNA conformation. Although there have been many experimental and theoretical studies on DNA hydration, the role of water in DNA conformational transitions is not yet understood. In addition, such studies have some limits in studying hydration patterns. Water molecules in the first solvation layer around DNA remain unrefined and thus invisible through experimental tools such as X-rays. Also, localized ions around DNA cannot be easily distinguished from water oxygen atoms.

Recently, theoretical approaches through computer simulation methods have been used to surmount the above-mentioned limit. Early computer simulations [15,16] were mainly carried out on systems including explicit solvent around a rigid right-handed DNA fragment. Recently, fully flexible DNA homopolymeric fragments in explicit solvents for right-handed and left-handed DNA have been studied using different force fields [17]. Also, Z-DNA was identified in 1972 [18] and many structures of Z-DNA were determined [19–21]. Since then, studies on the difference in hydration pattern between the right-handed and the left-handed

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DNA through semi-empirical tools have been more and more important to understand the differences of the conformations and functions of the two kinds of DNA.

In this study, we carried out a molecular dynamics simulation for right-handed and left-handed DNA heteropolymeric fragments in which the sequence is constituted by mixing the four base types. We discuss the differences of the conformations of DNA itself and of the hydration patterns in two DNA conformations.

CALCULATION METHOD

B-DNA hexamer, d(CGTACG), and Z-DNA hexamer, d(CGTACG), are obtained from Nucleic-acid Data Base (NDB). The DNA duplexes consist of two symmetric strands. For simplicity, we will arbitrarily number one strand from 1 to 6 and refer to the other strand as the primed number with the reversed order, i.e. in B-DNA, 1C:6′G, 2G:5′C, 3T:4′A, 4A:3′T, 5C:2′G and 6G:1′C base pairs exist as shown in Fig. 1. They were simulated with the CHARMM force fields [22]. All hydrogen model with solvent of 1529–1536 explicit TIP3P [23] water molecules and 10 Na^+ counter-ions were used. First, the system including the DNA hexamer within water molecules underwent the steepest descent minimization and initial normal NVE dynamics fixing DNA fragment in order to remove close contact. Then, Na^+ counterions were located at 5 Å from the phosphorous atom by replacing water molecules throughout the simulation box.

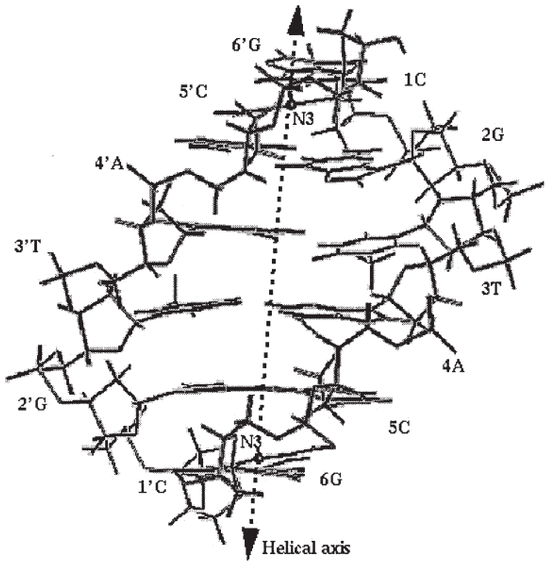

FIGURE 1 DNA configuration with abbreviations for each sequence and with the helical axis *lied* in the direction from N3 in 1C to N3 in 1′C are shown.

All simulations were performed in the NPT ensemble using a leapfrog integration algorithm, which is considered to be the most stable in molecular dynamics. The temperature and pressure of the system were controlled by the Langevin piston method [24], which can avoid the formation of a temperature gradient in an inhomogeneous system. For the pressure and temperature mass, we used a 225 atomic mass unit (amu) and 1000 Kcal ps^2, respectively. Also, for the collision frequency, 20 ps^{-1} was used. For treating long-range interactions, Ewald summation method [25], which gives more stable trajectories in simulations [26,27], was used to avoid cutoff effects. The time step was 1 fs. The non-bonded interactions were spherically truncated at 10.5 Å. The non-bonded list was generated with 11.5 Å cutoff. For the non-bonded list update, a heuristic test was performed every time. In heuristic test, the energy calculation was called for and a non-bonded list update was done if necessary.

Conventional periodic boundary conditions were applied during the simulations. The system was warmed up to 298 K under 1 bar for 20 ps and equilibrated for 1.2 ns. The production run was continued for 0.2 ns. For the analysis of the hydrogen-bonded circular network, ring, of water molecules, the energetic criterion was used. Detailed explanations for selecting ring structure are given in the work of Yu *et al.* [28].

RESULTS AND DISCUSSIONS

Structural Analysis of DNA Itself

As judged by rms deviations, average structures converge to within ~1.4 Å for the left-handed and the right-handed DNA, respectively. In general, it is known that the nucleotides along the double helix of left-handed DNA are in the *syn* conformation at purine ($\chi \approx 70.0°$) and in the *anti* conformation at pyrimidine (χ ranging from $-145°$ to $-180°$), whereas in right-handed DNA the bases are only in the *anti* conformation (χ ranging from $-100°$ to $-145°$) [29]. In our studies, the χ values of Z-DNA are well maintained at both purine ($\chi \approx 60–70°$) and pyrimidine ($\chi \approx -150$ to $-160°$), and those of B-DNA also remain at *anti*-conformation for all bases ($\chi \approx -110$ to -130).

To confirm the right-handed DNA conformation, furanose ring pseudorotations for each base type of the strand are shown in Fig. 2. A- and B-type backbones of the right-handed DNA are characterized by a sugar pseudorotation angle. For the typical A conformation, the pseudorotation angle is found around ~0°–10°, and for B-DNA conformation it is between 100° and 180° [29]. In our simulation for the right-handed DNA with CHARMM force field, all

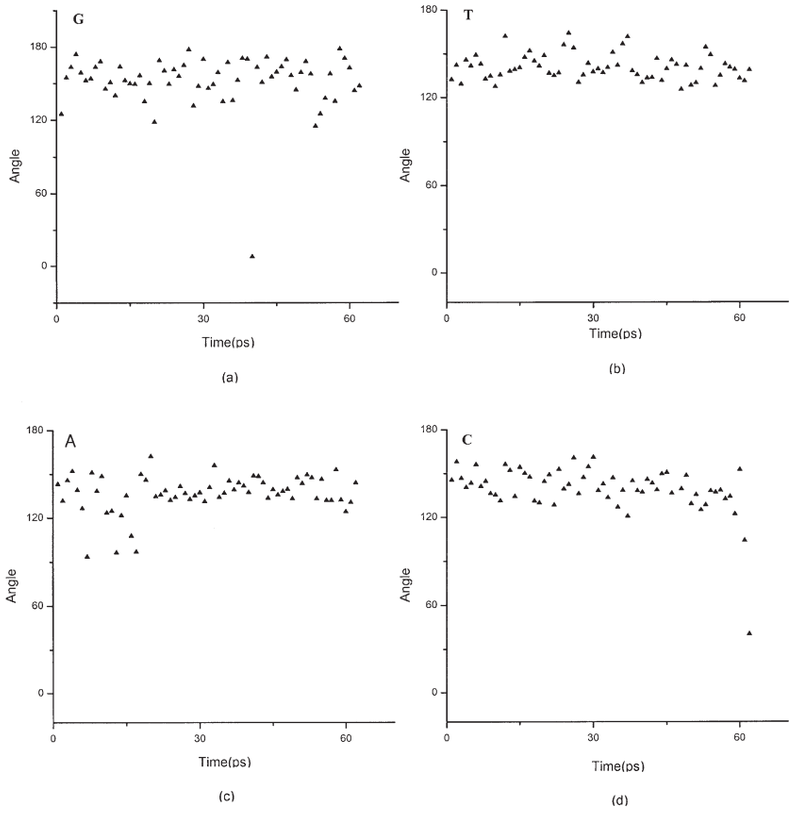

FIGURE 2 Furanose ring pseudorotations for each base type of the right-handed DNA: (a) guanine (b) thymine (c) adenine (d) cytosine.

bases show B-philic sugar puckering. Therefore, the resulting right-handed DNA duplex finally takes the conformation of B-DNA.

Hydration around Bases

Now, we focus on the comparison of hydration between the left-handed and the right-handed DNA duplex.

In Table I, we reported the averaged number of water molecules positioned 3.8 Å closer around each residue for the left-handed and the right-handed DNA. Atoms that participate in the central base-pairing hydrogen bond (N1 for purine, N3 for pyrimidine) are greatly screened from the contact to water molecules, excluding N3 in guanine. Also, the hydration of the base atoms in each DNA conformational type is shown in Figs. 3–6. The difference of hydration around base pairs in two DNA conformations is more profound in the C/G base pair than in the A/T base pair.

Especially, guanine hydration greatly differs for the left-handed and the right-handed DNA. The right-handed DNA N3 atom is more hydrated than the left-handed DNA N3 atom, which remains nearly inaccessible to solvent, since guanine in the left-handed DNA is in the *syn* conformation with respect to the sugar ring. N3 has a single hydrogen-bonding

TABLE I The averaged number of water molecules positioned 3.8 Å closer around phosphate groups and base atoms for two DNA conformations

	Right-handed DNA	*Left-handed DNA*
A		
Phosphate group	4.78*	3.72
N1	0.08	0.01
N3	1.01	0.42
N6	0.86	0.91
N7	0.98	1.49
N9	0.38	0.30
C		
Phosphate group	4.23	3.49
N1	1.48	0.09
N3	0.55	0.21
N4	3.52	1.79
O2	1.67	1.33
G		
Phosphate group	8.97	5.73
N1	0.52	0.27
N2	2.89	1.87
N3	1.43	0.73
N7	2.64	2.40
N9	0.64	0.72
O6	2.34	1.61
T		
Phosphate group	3.85	3.67
N1	0.14	0.00
N3	0.11	0.00
O2	0.93	1.06
O4	0.78	0.47

* The averaged number of water molecules.

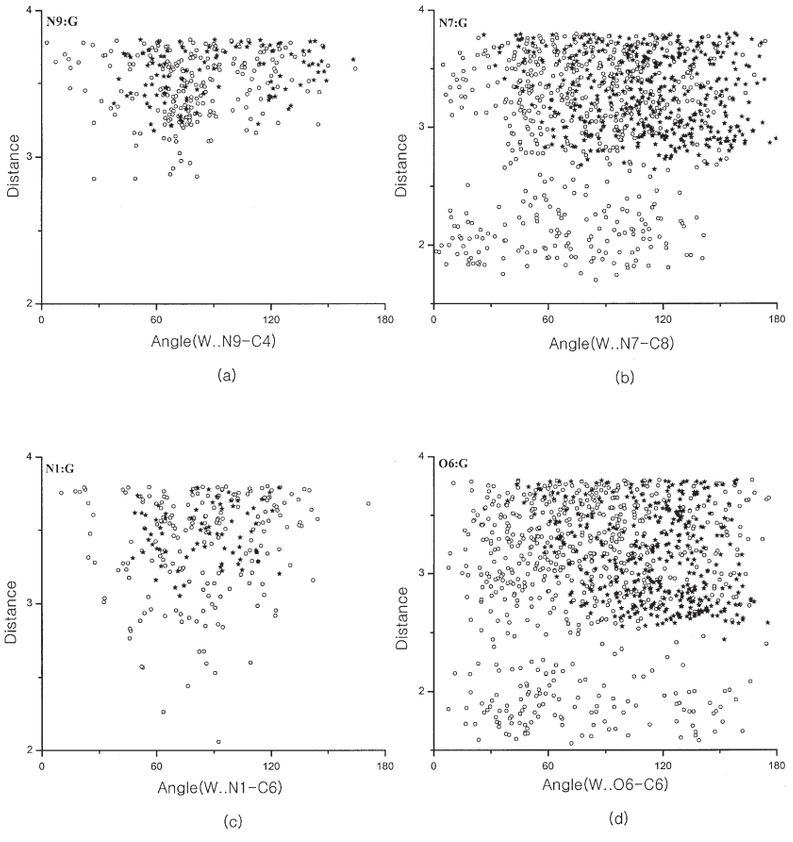

FIGURE 3 The distribution of water molecules around guanine base atoms is shown with distance, W···A, and bond angle, W···A–B in the scattergrams for two DNA conformations: (a) N9 atom (b) N7 atom (c) N1 atom (d) O6 atom

site slightly out of the base plane. The hydration number of the right-handed DNA N2 atom is greater than the right-handed DNA N3 atom. Generally, it is thought that the N2 atom is engaged in the crystal packing of the right-handed DNA. But in our simulation, since hexamer is analyzed, the hydration number of these atoms is very similar. Also, results of the hydration number of N2 and N3 atoms agree well, not with the crystal analysis [5,30], but rather with the simulated results by Feig and Pettitt [17]. In our simulation, N3 atoms also occupy some of the hydration sites of N2 atoms. All of the hydration at the N2 atom is closer to the base plane.

In the right-handed DNA (Table I, Fig. 3), guanine N7 atoms are slightly more hydrated than guanine O6 atoms. The angular distribution of N7 atoms is

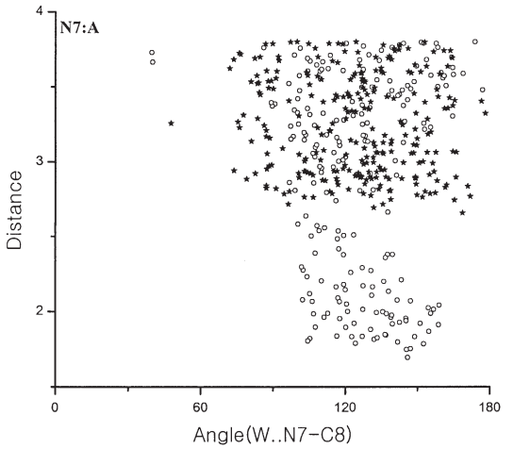

FIGURE 4 The distribution of water molecules around adenine N7 atom as shown in Fig. 3.

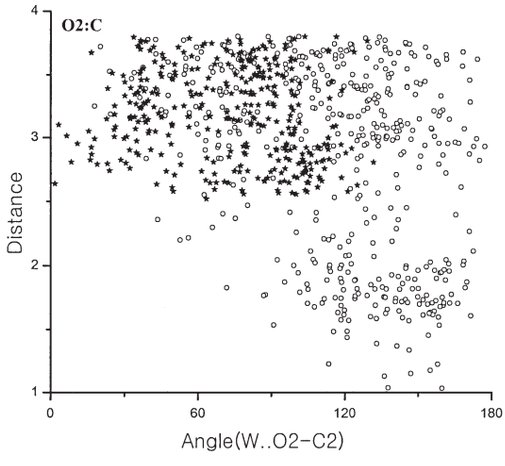

FIGURE 5 The distribution of water molecules around cytosine O2 atom as shown in Fig. 3.

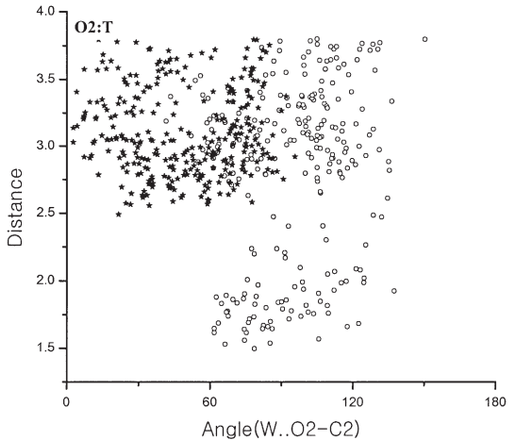

FIGURE 6 The distribution of water molecules around thymine O2 atom as shown in Fig. 3.

slightly narrower than that of O6 atoms in the short distance ranges. On the other hand, in the left-handed DNA, guanine O6 atoms are hydrated less than guanine N7 atoms. These atoms have narrower angular distribution than in the right-handed DNA, as shown in Fig. 3.

For adenine, it is noticeable that N7 atoms in the left-handed DNA have the greatest hydration number. In the geometrical distribution of N7 atoms, as shown in Fig. 4, the range of distance is above 2.8 Å in the left-handed DNA, while it is found below 2.8 Å in the right-handed DNA. It is expected that N7 atoms in the right-handed DNA will have more hydrogen bond contact in a narrow distribution, that is, less than 2.8 Å.

For cytosine in the right-handed DNA, N4 atoms have a slightly greater hydration number than the O6 atoms in guanine forming base-pairing hydrogen bonds, and are significantly more hydrated than the cytosine O2 atoms. In the left-handed DNA, N4 atoms have a similar hydration number to the O2 atoms. This aspect shows that the space around N4 in the right-handed DNA is more open to nonspecific contacts. Also, the geometrical distribution in the two DNA conformations is greatly different, as shown in Fig. 5.

For thymine, all base atoms have similar hydration numbers in both DNA conformations. Especially, O2 atoms in the right-handed DNA have a larger portion below 3.0 Å than O2 atoms in the left-handed DNA, as shown in Fig. 6. The bond angle range of O2 atoms is relatively narrow in two DNA conformations. The hydration pattern of O2 atoms in thymine is similar to that in cytosine.

The above results demonstrate that there are distinctive differences in the distribution of hydration sites around guanine and cytosine in the left-handed and the right-handed DNA. All DNA conformations show a greater extent of hydration of C/G base pairs. This is confirmed from experiment [14]. Although it has been found that the bases of nucleic acid molecules are 80% buried [31], we have also found that the base atoms are still well hydrated. Of course, the backbone is more exposed.

We next represent the distribution of water molecules around the helical axis in both DNA conformations in Table II. The helical axis vector lies in the direction of N3 atoms (1C:N3, 1′C:N3) in the first base of one DNA strand and the other DNA strand. In the two DNA conformations, occupancies and distances of water molecules around the helical axis are greatly different. For the right-handed DNA, water molecules are positioned around all bases at nearly the same distance. On the other hand, for the left-handed DNA, only 4A:3′T and 3T:4′A base pairs have water molecules around helical axis. This result demonstrates that the spine of hydration can be formed only in the right-handed DNA conformation.

Water Structures Around DNA

Table III, shows the interaction energies between water molecules around DNA and between water and DNA molecules and also an averaged, hydrogen-bonded circular network, a ring structure, of water molecules around two DNA conformations within 4.0 and 7.0 Å, respectively. To calculate

TABLE II The distribution of water molecules around helical axis in two DNA molecules.

Right-handed DNA			*Left-handed DNA*		
*Water**	*Occ.†*	*Distance‡*	*Water*	*Occ.*	*Distance*
42:W(6G:1′C)	0.73	2.01	27:W(4A:3′T)	0.99	2.23
59:W(3T:4′A)	0.70	1.80	423:W(4A:3′T)	0.82	1.91
93:W(4A:3′T)	0.76	1.83	1140:W(4A:3′T)	0.94	2.99
213:W(2G:5′C)	0.95	1.88	1445:W(4A:3′T)	0.72	2.21
713:W(6G:1′C)	0.74	1.17			
938:W(2G:5′C)	0.73	1.73			
1112:W(6G:1′C)	0.95	2.31			
1243:W(5C:2′G)	0.98	1.84			
1335:W(3T:4′A)	0.61	1.38			
1505:W(5C:2′G)	1.00	1.51			

*The water molecules positioned around helical axis of base pairs in two DNA molecules. †The occupancies of water molecules around helical axis; full occupancy = 1.0. ‡The averaged distance between water and helical axis.

TABLE III Interaction energies and ring structures (hydrogen-bonded circular network) of water molecules around two DNA conformations within the specified range.

Range			*Right-handed DNA*	*Left-handed DNA*
	W–W energy*		−1073.695	−1047.135
<4.0 Å	W–S energy†		−1328.241	−1219.408
	Ring	3-ring	27.78	26.67
	Structure (%)	4-ring	38.89	33.33
		5-ring	11.11	26.67
		6-ring	22.22	13.33
	W–W energy		−4575.668	−3359.167
	W–S energy		−1606.337	−1449.217
<7.0 Å	Ring	3-ring	15.68	22.98
	Structure (%)	4-ring	22.03	19.26
		5-ring	26.27	27.33
		6-ring	36.01	30.43

*The interaction energy between water and water molecules in Kcal/mol.
†The interaction energy between water and DNA molecules in Kcal/mol.

the hydrogen-bonded circular network, we used an energetic criterion of −2.25 Kcal/mol or less, corresponding to the minimum of the pair energy distribution of the TIP3P potential. As shown in Table III, within 4.0 Å around DNA molecules, water molecules are better ordered around right-handed DNA than around left-handed DNA, showing a higher ratio of hexamer to pentamer (R_6/R_5). However, within 7.0 Å around DNA molecules, the hydrogen-bonded network including water molecules that have no direct interactions with DNA molecules show a slightly different pattern. Water molecules around the left-handed DNA have an increasing ratio of hexamer to pentamer (R_6/R_5).

These results mean that in the first hydration shell the structure of water molecules is greatly influenced by the characteristic of DNA conformation, as we expected in our study [32]. In particular, as shown in Table IV, the hydrogen-bonded network of water molecules around each base within 4.0 Å clearly represents the ordered structure of the surrounding water molecules. It is noticeable that the structure of water molecules around all bases is better organized in the right-handed DNA than in the left-handed DNA. The differences in the structure of water molecules are greater for cytosine and thymine bases than for adenine and guanine bases. In the right-handed DNA, water molecules are slightly better ordered around C/G base pairs than around A/T base pairs, while in the left-handed DNA, water molecules are greatly better ordered around AT base pairs than around C/G base pairs. Thus, from these results, we know that the structure of water molecules deeply depends on conformational differences in DNA molecules.

CONCLUSIONS

To examine the question of how the structure of water molecules differs around DNA molecules with different conformations, we calculated the hydrogen-bonded circular network of solvent molecules around a left-handed and a right-handed DNA using a NPT molecular dynamics simulation with a CHARMM force field. In analyzing the structure of DNA itself, the left-handed DNA and the right-handed DNA remained well around its X-ray structure. Results of the hydration around the bases showed that hydration sites of guanine and cytosine are distinctively different in the two DNA conformations. The hydration around phosphate groups is greater in the right-handed DNA than in the left-handed DNA. The number of water molecules contacted by DNA molecules is slightly larger in the right-handed DNA than in the left-handed DNA. The water molecules in the right-handed DNA are better ordered than in the left-handed DNA. In the right-handed DNA, water molecules around C/G base pairs are better stabilized than water molecules around A/T base pairs, but in the left-handed DNA, these findings are reversed. These results indicate that the structure and distribution of water molecules around nucleic acid is greatly different according to the conformational differences of DNA molecules.

TABLE IV Ring structure (hydrogen-bonded circular network) of water molecules around bases of two DNA molecules within 4.0 Å. The values of clustering energy of water molecules consisting hydrogen-bonded circular network is shown in parenthesis.

Left-handed DNA		*Right-handed DNA*	
	G		G
6-ring	1.0 (−36.109 Kcal/mol)	6-ring	1.0 (−29.884 Kcal/mol)
	A		C
4-ring	1.0 (−26.309 Kcal/mol)	6-ring	2.0 (−35.690 Kcal/mol)
6-ring	1.0 (−33.755 Kcal/mol)		
	T		A
4-ring	2.0 (−22.470 Kcal/mol)	3-ring	1.0 (−13.002 Kcal/mol)
5-ring	1.0 (−27.534 Kcal/mol)		
			T
		4-ring	1.0 (−20.428 Kcal/mol)
		6-ring	1.0 (−35.637 Kcal/mol)
		6-ring	1.0 (−32.950 Kcal/mol)

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