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A combined molecular dynamics/density-functional theoretical study on the structure and electronic properties of hydrating water molecules in the minor groove of decameric DNA duplex

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Abstract

A combined molecular dynamics/density-functional theoretical study was carried out to address the propensity of ambient water to form cross-strand bridging water (CSBW) and their effects on the electronic properties of a fully hydrated DNA duplex 5'-d(CCATTAATGG)₂-3'. The simulation shows ubiquitous presence of up to five CSBWs along the minor groove, each with residence time ranging from 400 ps to 750 ps. The molecular orbitals localized on these CSBWs are nearly degenerate in energy with the highest occupied molecular orbital of DNA localized on guanine bases, strongly indicating that the hole transport along the guanines is mediated by the ubiquitous CSBWs.

1. Introduction

In recent studies on nano-sized materials, DNA has attracted much attention as a primary candidate for nano-wires because of its high self-organizing capability [1] and conductivity [2–4]. While it is essential to elucidate the charge transfer (CT) mechanism in order to develop novel nano-wires based on DNA derivatives, the mechanism is not fully understood at the atomic level [5].

The mechanism for CT in duplex DNA is currently under active investigation in numerous theoretical and experimental studies. The idea of long-range charge transfer in DNA is still a matter of debate, but the experimental and theoretical evidences indicate that it does indeed occur. According to the most widely held theory [6,7], the hole migration in DNA is achieved by hopping between guanine (G) bases. This theory is supported by the experiment [8] that the hole-migration rate through DNA declines exponentially with the distance between the neighboring G-C base pairs in DNA duplex. Furthermore, it is also supported by the theoretical study [9] that the calculated ionization potential of G is the smallest among the four bases.

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On the other hand, there are other experimental studies [10,11] showing that the hole-migration rate cannot be explained solely by the DNA-base sequences. The CT reactions and conductivity measurements show a large variety of possible electronic behavior [11]. It has long been suspected that differing environment (e.g. the degree of hydration) around the DNA duplex causes the observed wide variation in the hole-migration rate. In fact, the charge conductivity through DNA was found to increase with the humidity around DNA [12]. These findings have defied a unified explanation of the hole transfer through DNA. Barnett et al. [13] pointed out that the effects of solvent water molecules and counter ions around DNA must be carefully considered to elucidate the CT mechanism in DNA.

In an earlier study [14], we investigated the electronic properties of a hydrated decameric DNA duplex 5'-d(CCATTAATGG)₂-3', whose structure was determined in a crystalline environment by neutron and x-ray diffraction studies [15,16]. The analysis revealed that a single water molecule in a cluster of five hydrating water molecules along the minor groove is hydrogen-bonded to a specific inter-strand A/T bases and acts as a cross-strand water bridge between the strands. Hereafter, we refer to the water molecule as the cross-strand-bridging water (CSBW). The calculated electronic properties [14] revealed a unique effect of CSBW on the spatial distribution of the highest occupied molecular orbital (HOMO): The MO localized on the CSBW is nearly degenerate in energy with the HOMO localized on guanine (G) bases, indicating that the CSBW would play a significant role in water-mediated hole transport along the widely separated G bases in the hydrated DNA.

The computed electronic properties of the decameric DNA with a CSBW seem to support the experimental finding [12] that the charge conductivity through a dry DNA is low but it increases with the humidity around DNA. The X-ray/neutron diffraction studies [15,16], however, revealed that in a crystalline form the hydrated decamer features only a single CSBW along its minor groove. The analysis also showed that the G-C base pairs at the opposite ends of the decameric 5'-d(CCATTAATGG)₂-3' DNA duplex are separated by as much as 24 Å by the six intervening A-T base pairs and that a single CSBW resides about half way between the G bases, too far away from either Gs to effectively mediate the hole transfer between them. In this study, we address the question of whether any other CSBWs appear on the decameric DNA at a greater degree of hydration. And if so, how would they affect the electronic properties of the hydrated DNA? Unlike the water molecules that hold a specific hydration pattern in the crystalline form [15,16], the ambient water molecules hydrating the DNA to a greater degree in a non-crystalline environment are expected to be more dynamic, and are likely to appear as CSBWs along the minor groove. In the present study, we carry out a combined classical molecular dynamic (MD)/DFT study to address these questions.

2. Methods

2.1. MD simulation on a fully hydrated decameric DNA duplex

MD simulation of the dynamics of hydrating water molecules was conducted to examine if the duplex DNA can hold any additional CSBWs along its minor groove. In addition to the 27 hydrating water molecules found in the x-ray/neutron diffraction studies [15,16], a large number of water molecules were introduced to the system to fully hydrate the DNA. The experimental structure of the DNA duplex [15,16] was held fixed during the MD simulation.

The structure of the hydrated decameric DNA duplex 5'-d(CCATTAATGG)₂-3' was determined by the neutron diffraction analysis [15] at 279 K and at 3.0 Å resolution. The analysis revealed a cluster of five hydrating water molecules along the minor groove (Fig. 1 (a)). One of these, a CSBW, resides specifically between Adenine17 and Thymine5 (Fig. 1(b)) with a long residence time [15]. This PDB structure does not provide the positions of counter ions as it is difficult to determine their positions by neutron diffraction analysis. We thus added

18 counter ions Na^+ to the PO_4 parts of DNA backbones and optimized their positions by DFT calculations [14] prior to the MD simulation (Fig. 1(c)).

The DNA was fully hydrated with a large number of water molecules to create an 8 Å-thick hydration shell, including the 18 counterions. The MD simulation was carried out at 300 K for a total simulation time of 1 nanosecond (ns), with a time-step of 1 femtosecond (fs). The MD simulation program AMBER9 [17] was employed, with the PARM99 [18] and TIP3P [19] force fields for the DNA atoms and water molecules, respectively.

2.2. DFT calculations on a fully hydrated decameric DNA duplex

DFT calculations were performed to examine the energy levels and spatial distributions of several highest HOMOs and the lowest unoccupied MO (LUMO) for a total of nine different structures obtained at various time steps in the MD simulation. In the present DFT calculations, we employed the revised PBE exchange-correlation functionals [21] and double numeric quality basis set [22] implemented in the program package Dmol³ [20]. We focus in particular on the HOMO distribution through which the hole migration takes place. From the HOMO distributions, we elucidate the pathway for hole hopping between G bases.

3. Results and discussion

3.1. Dynamics of the hydrating water molecules

In the MD simulations of the fully hydrated DNA, an initial round of equilibration was carried out for a 30 ps time span, so that the hydrated DNA system converges to a thermal equilibrium. The dynamics of the hydrating water molecules was investigated after the initial equilibration process. As we have anticipated, as many as five CSBW_s were already detected at 50 ps along the minor groove (Fig. 2(a)). Their detailed conformations and designation as CSBW_n (n=1–5) are displayed in Figs. 2(b)–(f). The figures show that all five CSBW_s reside along the minor groove, each bridging inter-strand A/T bases. In the neutron diffraction experiment [15], CSBW2 (Fig. 2(c)) was the only species identified in a crystalline environment. The MD simulations indicate that the CSBW_s form hydrogen bonds exclusively to A or T base, and not to G or C base. A Watson-Crick type G-C base pair normally forms three hydrogen bonds, whereas an A-T base pair forms only two. Consequently, both the A and T bases possess additional sites to form hydrogen bonding with ambient water molecules.

To examine if these CSBW_s appear frequently along the minor groove, we investigated the time evolution of the hydrogen-bond lengths between the CSBW and DNA bases. Figure 3 shows the change in the average bond length of the two hydrogen bonds (Figs. 2(b)–2(f)) formed between each of the five CSBW_s and DNA bases as a function of simulation time. As for the CSBW1 (Fig. 2(b)), either one of the two ambient water molecules, designated as WAT1-a and WAT1-b in the Figure, can form inter-strand hydrogen bonds. WAT1-a occupies the CSBW1 position for as long as 750 ps. WAT2 and WAT4 also reside for up to 700 ps as CSBW2 and CSBW4, respectively. The presence of such long-lived CSBW_s is comparable to the finding in neutron diffraction analysis [15]. By contrast, other ambient water molecules (WAT3-a, WAT3-b, WAT3-c and WAT5-a) have relatively short residence time as CSBW3 and CSBW5. However, Fig. 3 also illustrates the dynamical nature of the ambient water in that the CSBW3 and CSBW5 positions are kept occupied by a series of water exchange. Further, the WAT4, which resides in the CSBW4 position during the 50 – 639 ps time period, subsequently moves over to the adjacent cross-strand bridging site CSBW3. The present MD simulations reveal the dynamical nature of CSBW_s in that they can exchange sites among themselves as well as with ambient water molecules.

To compare the properties of the five CSBW, the MD trajectories were analyzed to determine their residence time and average hydrogen-bond lengths. Table 1 lists these values determined from 50 ps to 1 ns of simulation time. The CSBW1 and CSBW5, both bridging two inter-strand thymine bases, have short hydrogen-bond lengths and long residence time. By contrast, the CSBW3, which bridges two inter-strand adenine bases, has nearly half the residence time of CSBW1 and CSBW5. The CSBW2 and CSBW4 involved in the adenine-water-thymine hydrogen bonding have values in-between those of CSBW1 and CSBW3. Therefore, it is evident that CSBW, s bind more strongly to two inter-strand thymine bases than to adenine bases. This disparity in the binding strength may be explained by the difference in the atoms in DNA bases that take part in the hydrogen bonding. In the thymine-water hydrogen bonding, the oxygen atom in thymine takes part in the bonding, whereas for adenine it is the nitrogen atom that contributes to it. The former is stronger than the latter in hydrogen bonding because of greater negative charge on the oxygen. Thus, it is expected that dynamic property of the hydrating water molecules along the minor groove depends strongly on DNA base sequence and that this dependence also may cause a specific interaction between DNA and amino acids of protein through ambient water molecules.

3.2. Electronic properties of the hydrated decameric DNA duplex

To elucidate the influence of CSBW, s on the electronic properties of the DNA, we chose a total of nine MD snapshots taken every 100 ps of hydrated DNA structures and computed their electronic properties. Since the ambient water molecules in the second and more outer hydration shells have little effect on the electronic properties of the highest HOMOs, we neglect these solvation shells and investigate the electronic properties of the complex involving the DNA duplex, 18 Na⁺ counterions, and the water molecules in the first hydration shell. This complex involves a total of 794 atoms.

To investigate the hole-transfer mechanism in DNA, we focus in particular on the spatial distributions of the HOMO and HOMO-1, through which the hole transport is most likely to take place, along with the next 4 highest occupied MOs, HOMO-*n* (*n*=2–5). We attempt to examine the hole-transport pathway based on the alteration of the HOMO spatial distributions in the nine MD snapshots.

The calculated spatial distributions and orbital energies of the six highest HOMOs for the nine MD snapshots are compared in Table 2. Since the DNA duplex is held fixed during the MD simulation, Table 2 reflects solely how the conformational changes of a cluster of hydrating water molecules around the DNA alter the energies of the HOMO and HOMO-*n* (*n*=1–5). Table 2 further shows how the conformational changes alter the spatial distribution of the HOMOs. The water conformations at 200 and 800 ps give rise to rather large energy gap (0.21 – 0.28 eV) between the HOMO and HOMO-1. That gap is reduced to less than 0.1 eV at 300, 400 and 600 ps, indicating a facile hole transfer between guanine19 (G19) and CSBW1, 2, 3. At 500 ps, the gap is also very small between the HOMO localized on CSBW4, 5 and HOMO-1 localized on CSBW2, indicating a facile hole transfer among the cross-strand bridging water molecules. In addition, the HOMO energy varies in the range –2.7 and –3.4 eV with the changes in the hydrating water conformation. The results strongly suggest that the thermal change in water conformation around the DNA catalyzes the hole transport through DNA.

As shown in Table 2, the HOMO is localized on the guanine19 (G19) at 400, 600, 800 and 900 ps, in agreement with the previous experimental [6] and theoretical [9] studies, revealing the hole localization on guanine bases. The most remarkable feature in Table 2 is that the HOMO is localized on the CSBW, s in some of the MD snapshots of the hydrated DNA. In fact, the HOMO is localized on CSBW1, CSBW4-5, and CSBW1, at 300, 500, and 700 ps, respectively. Further, the nearly degenerate HOMO/HOMO-1 pair is predominantly localized on either a G/CSBW pair or on a pair of two CSBW, s in the MD snapshots of the hydrated DNA structure.

By contrast, the MOs localized on adenine bases appear at least 0.3 eV below the HOMO in energy, strongly indicating that the adenine bases would not play a role in transporting the hole along the guanine bases.

The results in Table 2 may also suggest the possibility that the ambient water molecules other than the CSBW's can ease the hole transport in DNA, since the HOMO as well as HOMO-*n* are localized at times on the water molecules bound to guanine, cytosine, and adenine. However, these water molecules are located along the major groove at the ends of the DNA duplex. At 100 ps, for instance, the HOMO is localized on GW10, a water bound to G10. Since GW10 is not in between G19 and G9, it is not likely to play any role in transporting the hole along the two guanine bases.

The MD simulation clearly indicates that the spatial distributions of the highest few HOMOs vary significantly with thermal fluctuation of water conformation around the DNA (Table 2). Moreover, the present study highlights the importance of the CSBW's in transporting the hole along the guanine bases. In a dry 5'-d(CCATTAATGG)₂-3' duplex, the G-C base pairs are separated by 24 Å by the six A-T base pairs, too far for efficient hole transfer between G19 and G9. However, the five CSBW's residing along the minor groove can ease the hole transfer by water-mediated pathway between the G bases.

The evolution of HOMO spatial distribution was mapped from the MD snapshots taken at shorter time scale to assess if the charge transport can take place via consecutive migration of hole between the CSBW's. Table 3 displays the spatial distributions and orbital energies of the HOMO and HOMO-*n* (*n*=1–5) for the nine MD snapshots taken every 10 ps between 210 and 290 ps of the MD simulation. Figure 4 displays the evolution of the HOMO between 220 and 240 ps time steps. The HOMO, initially localized on CSBW1 at 220 ps, propagates through CSBW2,3 to localize on CSBW4 by 240 ps. The results clearly indicate that the HOMO propagates consecutively from CSBW1 to CSBW4 due to dynamical conformational change of the hydrating water molecules.

Figure 5 displays a total spatial distribution of the nearly degenerate HOMO/HOMO-1 pair obtained from the nine MD snapshots taken every 100 ps of the hydrated DNA. As shown earlier, the HOMO/HOMO-1 pair tends to be spatially localized either on a guanine/CSBW pair or on a pair of two CSBW's at the same time. The total distribution was mapped by summing the spatial distributions of HOMO/HOMO-1 pair from each of the nine MD snapshots, so that it represents the distribution of hole-transporting sites in the hydrated DNA. Figure 5 highlights that a hole, or a radical cation, can be transported through a series of CSBW's, and that there is a distinct water-mediated hole-transport pathway between the widely separated guanine bases.

4. Conclusions

The MD simulations on the dynamics of hydrating water indicate that CSBW's are ubiquitous along the minor groove of the DNA duplex. The DFT calculations on the MD snapshots indicate that the MOs localized on the CSBW's are nearly degenerate in energy with the DNA's HOMO localized on G bases, strongly indicating that the ubiquitous CSBW's play a crucial role in thermally activated hole hopping between two widely separated G bases. The present study provides a framework for water-mediated hole-transport mechanism in DNA.

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Figure 1.

Structure of hydrated decameric 5'-d(CCATTAATGG)-3' DNA duplex determined by a neutron diffraction analysis [15]: (a) a cluster of five hydrating water molecules along the minor groove; (b) a water molecule involved in the cross-strand water bridge between Adenine 17 and Thymine5; (c) 18 Na⁺ counterions around the decameric DNA duplex whose positions are optimized by the DFT method [14] along with a H₂O molecule near Na16.

Figure 2.

Structures of CSBWs in the minor groove of hydrated decameric DNA duplex at 50 ps MD simulation; (a) five CSBWs in the minor groove of DNA; (b) CSBW1; (c) CSBW2; (d) CSBW3; (e) CSBW4; (f) CSBW5.

Figure 3. Time evolution of average length of two hydrogen bonds formed between the CSBW and DNA bases for each of the five CSBWs.

Figure 4. Consecutive transfer of spatial HOMO distribution from CSBW1 to CSBW4 via CSBW2,3 during the MD simulation; (a) 220 ps; (b) 230 ps; (c) 240 ps.

Figure 5.

A total spatial distribution of the nearly degenerate HOMO/HOMO-1 pair obtained from the MD snapshots of the hydrated DNA. The spatial distributions in the nine MD snapshots taken every 100 ps are superimposed.

Table 1

Residence time of CSBW and average bond length between CSBW and inter-strand bases.

CSBW _s	Binding site	Residence time (ps)	Bond length (Å)
CSBW1	Thymine18-Thymine4	870	1.83
CSBW2	Adenine17-Thymine5	524	2.00
CSBW3	Adenine16-Adenine6	416	2.09
CSBW4	Thymine15-Adenine7	527	1.96
CSBW5	Thymine14-Thymine8	724	1.88

Table 2

Spatial distributions and orbital energies (eV) of the six highest HOMOs for the MD snapshots taken every 100 ps of hydrated DNA structure. The n-th guanine and adenine are denoted as Gn and An, respectively. GWn, AWn, and CWn represent the water molecules bound to Gn, An, and Cn, respectively.

	100 ps	200 ps	300 ps
HOMO	GW10	-3.39	-2.86
HOMO-1	CSBW4	-3.54	-3.07
HOMO-2	CSBW2	-3.60	-3.24
HOMO-3	CW2	-3.75	-3.27
HOMO-4	G10	-3.76	-3.50
HOMO-5	CSBW1	-3.86	-3.67
	400 ps	500 ps	600 ps
HOMO	G19	-3.00	-3.02
HOMO-1	CSBW1	-3.10	-3.08
HOMO-2	CSBW2	-3.40	-3.18
HOMO-3	G9	-3.63	-3.22
HOMO-4	A17	-3.70	-3.29
HOMO-5	G20	-3.71	-3.39
	700 ps	800 ps	900 ps
HOMO	CSBW1	-3.07	-2.74
HOMO-1	G19	-3.17	-3.02
HOMO-2	G20	-3.28	-3.04
HOMO-3	G9	-3.32	-3.15
HOMO-4	A17	-3.33	-3.33
HOMO-5	CSBW3	-3.36	-3.48

Table 3

Spatial distributions and orbital energies (eV) of the six highest HOMOs for the MD snapshots taken every 10 ps between 210 and 290 ps of hydrated DNA structure. The n-th guanine and adenine are denoted as Gn and An, respectively. GWn, AWn, and CWn represent the water molecules bound to Gn, An, and Cn, respectively.

	210 ps	220 ps	230 ps
HOMO	CSBW2, 3	CSBW1	CSBW3, 2
HOMO-1	CSBW1, G19, (GW9)	CSBW3	GW20, (GW19)
HOMO-2	G19, GW9, CSBW1	CSBW2	G9
HOMO-3	CSBW3, 4	GW9, (G9)	CSBW2, 3, 4
HOMO-4	GW19, (G19)	CSBW4	CSBW4, (3, 2)
HOMO-5	A17	A17, (A16)	GW19, (GW20)
	240 ps	250 ps	260 ps
HOMO	CSBW4, 3	CSBW4	CSBW1
HOMO-1	CSBW2	CSBW4	CSBW2, 3
HOMO-2	CSBW1	AW16	G9, GW9
HOMO-3	A6, (A16)	AW16	CSBW3, 4
HOMO-4	CSBW5	G9	G9, GW9
HOMO-5	G9	CSBW3, (A16)	AW3
	270 ps	280 ps	290 ps
HOMO	CSBW1	G19	CSBW3, 2, 4
HOMO-1	CSBW4, 3	CSBW2, 3	CSBW4
HOMO-2	CSBW2	CSBW3, 4, (CSBW1, 2)	G10, (G9)
HOMO-3	GW20	CSBW1	G9, (G10)
HOMO-4	CSBW3, 4	CSBW3, 4	CSBW1
HOMO-5	G19	CSBW5	CSBW5