Solvent-Induced DNA Conformational Transition

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Modified water models with scaled charges are used to investigate solvent polarity effects on DNA structure. Several intensive molecular dynamics simulations of the DNA EcoRI dodecamer d(CGCGAATTCGCG) in different model solvents are performed. When the polarity of the solvent molecule decreases, from overpolarized to less polarized, DNA experiences the conformational transitions of constrained $\rightarrow$ *B* form $\rightarrow$ (*A*-*B*)mix $\rightarrow$ *A* form. We demonstrate that one important cause of these structure changes is the competition between hydration and direct cation coupling to the free oxygen atoms in the phosphate groups on DNA backbones.

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With its unique function of storing hereditary information and regulating its expression, DNA is a hopeful fundamental building block in the fields of supramolecular chemistry, nanotechnology, and molecular computing [1–5]. These novel applications of DNA may be in environments distinct from physiological water solvents. Thus the study of the structure changes of DNA in solvent different than water is helpful for these burgeoning applications. Furthermore, as water is the most important life supporting solvent, scientists are also interested in which properties of water are sensitive for life substances such as DNA [6]. Polarity and hydrogen bonding are the distinguishing attributes of water when compared with other liquid. How DNA conformation changes in solvents with different molecular polarity and hydration strength is a challenge for us.

Most of the widely used water models, such as simple point charge (SPC) and three-point transferable intermolecular potential (TIP3P), etc., have 3-point charges, which determine molecular polarity, hydrogen bonds, and control the local orientation of solvent molecules, and a spherical Lennard-Jones core, which provides short-range intermolecule repulsion and describes the molecular size [7,8]. The intermolecular energy consists of two parts: $\phi = E_C + E_{\mathrm{LJ}}$. By modifying the ratio of E_C to E_{LJ}, i.e., the ratio of the tetrahedral part of the intermolecular potential to its spherical symmetric part [9,10], one can change the nature of water. In this Letter, the atom charges of water molecule are scaled by a factor S and the electrostatic term was scaled by S^2: $\phi = S^2 E_C + E_{\mathrm{LJ}}$. When the magnitudes of the atomic charges are less than normal water, the solvent molecules are less polarized and their hydrogen-bonding ability is decreased, and vice versa. By varying the scaling factor S, we can study how DNA conformation changes in different solvent environments with varying hydration effects and try to catch on the mechanisms behind the delicate balance of DNA structure.

Based on the flexible SPC water model, we study 5 kinds of solvent environments ranging from less polarized to overpolarized (Table I). Then we examine the conformational changes of EcoRI dodecamer d(CGCGAATTCGCG), which is frequently used in gene recombination techniques, in these solvents. The initial state of DNA is entry 171d [11] in the Protein Data Bank (PDB). We implement Amber 94 force fields [12] for their special accuracy in reflecting the effects of water activity on DNA structures [13]. One EcoRI dodecamer, 22 Na^+ counterions and 5800 solvent molecules are contained in a periodic hexagonal cell ($60 \times 60 \times 58$ Å^3, big enough to ensure the DNA does not interact with its periodic images). Molecular dynamics simulations are carried out in *NVT* ensemble at the temperature of 298 K [14]. The Ewald sum method is used to treat the electrostatic interactions and the cutoff for this long-rang interaction is 14.6 Å. After the equilibrium of the solvent and ions around constrained DNA, the resulting simulation with free DNA is 5 ns for each $S \leq 1.0$ case and 8 ns for the $S = 1.2$ case.

The order of local water structure is sensitive to the strength of dipole interaction and can be described by the tetrahedral parameter: $\langle q \rangle = \sum_i^N \{1 - \sum_{j<k}^6 3/8[\cos\theta_{ijk} + 1/3]^2\}/N$, which shows how nearly the nearest four neighbors of one molecule form a regular tetrahedron [10,15]. As shown in Table I, $\langle q \rangle$ increases monotonically from 0.368 to 0.674 when S increases from 0.6 to 1.2. This means

TABLE I. Basic parameters of the modified water solvents. S is the charge scaling relative to SPC water. μ is the dipole moment of solvent molecule. $\langle q \rangle$ is the local tetrahedral order of the solvent structure.

S	0.6	0.7	0.8	1.0	1.2
μ (Debye)	1.367	1.598	1.822	2.278	2.734
$\langle q \rangle$	0.368	0.381	0.411	0.543	0.674

the local arrangement of the solvent molecules changes from structureless random orientation to evident tetrahedral structure. For $S < 0.8$ the solvent is similar to Lennard-Jones liquid without evident local order. When S is 0.8 or 1.0, the solvent is waterlike and its local structure resembles a dynamical tetrahedron. For $S \leq 1.0$, the solvent is liquid and the potential energy of the system E_p gets convergence within 1.0 ns. When $S = 1.2$, $\langle q \rangle$ is higher than normal water. This indicates the local structure is more fixed than water by the strengthened interactions. As a result, the solvent is in glassy state and needs more than 5 ns for E_p to converge. Thus as the molecular polarity increases from less polarized to overpolarized, the solvent changes from orderless Lennard-Jones liquid to waterlike solvent with flexible tetrahedral local order, then to semiglassy state. It should be noted as shown below that the glassy dynamics for the overpolarized case of $S = 1.2$ are not comparable to the other liquid cases.

Stereo views of the averaged DNA structures during the last 2 ns simulations are given in Fig. 1. The root mean square coordinate deviation (RMSD) of the DNA trajectories with respect to canonical B, canonical A, and the starting PDB structures are given in Fig. 2. In the overpolarized solvent of $S = 1.2$, the RMSD with respect to PDB form is less than 2 Å with fluctuations less than 0.2 Å during all the simulation. This means DNA keeps its PDB form stiffly under the restriction of the surrounding glassy solvent. When $S = 1.0$ and 0.8, the RMSD with respect to standard B form fluctuates around 2.2 Å, and the DNA appears B conformation. When $S = 0.6$, in a typical Lennard-Jones liquid, the DNA changes from B form to a stable A conformation during the first 1.6 ns. After that the RMSD with respect to canonical A form remains at around 2.8 Å. While in the solvent of $S = 0.7$, the conformation has a deviation more than 4 Å from both B and A forms after 1.6 ns evolution and the fluctuation of RMSD is bigger than any other case.

To evaluate the DNA structure changes in detail, 8 distinct parameters, which are distinguishing between A and B forms, are calculated [16] and presented in Fig. 3. To avoid the thermal fluctuation of instantaneous conformation, we analyze 20 average structures of every 100 ps during the last 2 ns simulations. When S is 0.6, these parameters are close to the typical A values. When S is 0.8 and 1.0, they are all near B values. As to $S = 0.7$, MW remain close to the value of the B form, mW is near the A value, while others are located in the middle area between A and B values. This transitional state can be defined as a mixed (A-B) structure. When $S = 1.2$, all the parameters are near those of starting 171dPDB for the structure is constrained. These phenomena show that, in liquid solvent, reducing the polarity of solvent molecules changes the preferred DNA structure from B to A.

The above conformation preference of DNA can be related to the phenomenon that the right-handed DNA duplexes assume B form at high water activity and A form at reduced levels [17,18]. In the laboratory, low water activity can be induced by adding aliphatic alcohols or molar concentrations of salt solutions [17]. The molecular origin of these DNA helices changes has been suggested to be relevant to solvent accessibility, base stacking interactions, the ''economics'' of phosphate hydration, and minor groove spine of hydration [17–23]. The most commonly concerned factor should be how the repulsion between

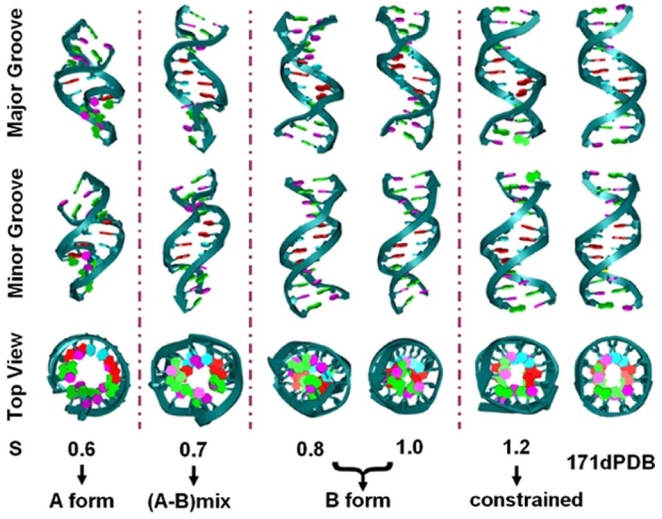

FIG. 1 (color online). Stereo views of the initial 171dPDB and the averaged resulting structures in the last 2 ns simulations. We present here three typical views from major, minor groove and top.

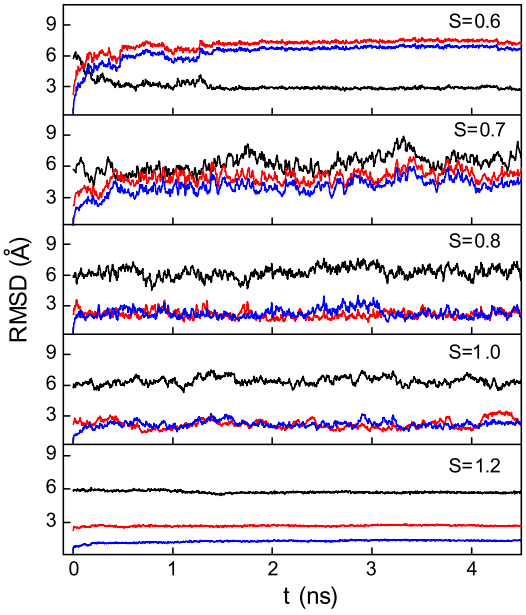

FIG. 2 (color online). RMSD of the DNA trajectories with respect to the canonical B (red or gray), A (black) forms, and the starting PDB structure (blue or dark gray).

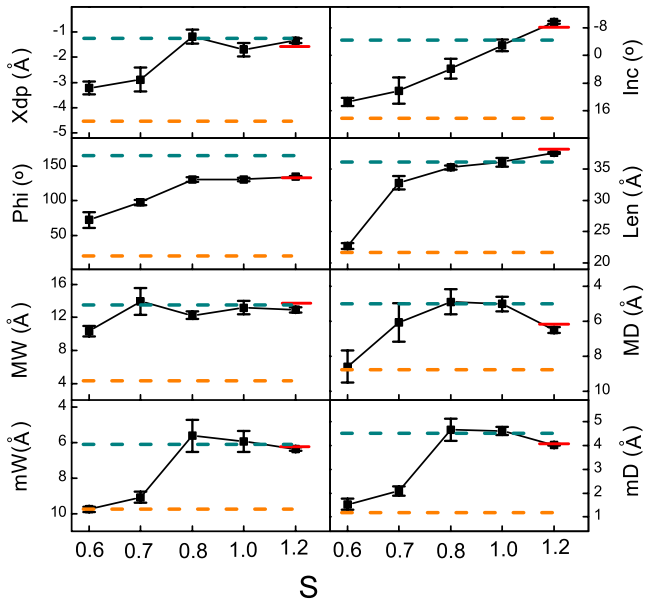

FIG. 3 (color online). Averaged DNA structure parameters during the last 2 ns simulations. They are the x-displacement (Xdp) and inclination angle (Inc) of a base pair from the helical axis, sugar pucker angle (Phi), end-to-end length (Len), width (MW and mW), and depth (MD and mD) of minor and major grooves. The horizontal dashed lines indicate the reference values of typical *A* (orange or light gray) and *B* (cyan or dark gray) forms and the short red or gray line shows the parameters of the starting PDB structure.

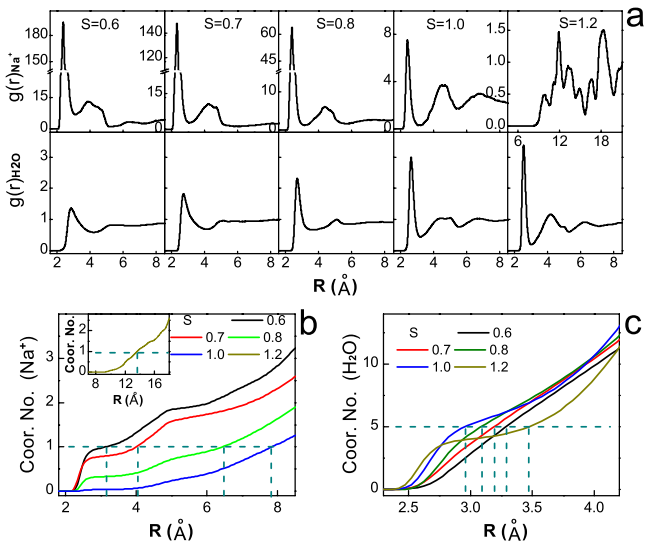

FIG. 4 (color online). RDF [part (a)] and the corresponding coordination numbers [parts (b),(c)] of Na^+ ions (the $S = 1.2$ case is shown in the inset for a longer scale) and solvent molecules around the free oxygen atoms of the phosphate groups on DNA backbones. The blue (or dark gray) dashed lines show the radii in which the coordinate number is 1 for Na^+ ions and 5 for solvent molecules.

negatively charged phosphate groups is screened [18,20,23], because the repulsion will unwind and extend the helix without screen [24] and the different screen mechanism also affects the pipeline of the electrostatic repulsion [20]. To check the underlying cause of the structural transitions induced by the solvent polarity, we evaluate the hydration and counterion distribution around the phosphate groups on DNA helix [25].

The radial distribution functions [RDF, $g(r)$] and coordination numbers of Na^+ ions and the modified H_2O molecules around the negatively charged oxygen atoms of phosphate groups are shown in Fig. 4. As to Na^+, with the decrease of the polarity of solvent molecules, the first peak of $g(r)_{Na^+}$ increases; while the radius, in which the coordination number of Na^+ reaches 1, diminishes. It shows that Na^+ ions bind to phosphate groups more and more strongly as S decreases. In contrast, the decrease of the first peak of $g(r)_{H_2O}$ from 3.3 to 1.4 suggests the trailing off of hydration effect surrounding the free oxygen atoms as S decreases. These phenomena indicate a competition between two screening mechanisms (counterion coupling and hydrogen bonding) of the negative charges on the free phosphate oxygen atoms.

In solvents of small molecular polarity ($S = 0.6$), Na^+ ions bind to the phosphate oxygen atoms in preference to solvent molecules. The first peak of $g(r)_{Na^+}$ exceeds 150 at 2.35 Å and its coordination number reaches 1 at 3.1 Å. This suggests that one Na^+ is strongly coordinated to a free phosphate oxygen atom, forming strong chemical bonds Na^+–O^-(P) and restraining the electrostatic repulsion on the backbones. Consequently, the DNA prefers the shorter and more compacted *A* form. In the solvents similar to normal water ($S = 0.8$ and 1.0), Na^+ ions are more dispersed. Thus the free phosphate oxygen atoms are mainly shielded by solvent molecules through hydrogen bonding with positively charged protons in the first hydration shell. This is realized by the reorientation of the polarized solvent molecules. The polarization effect may be transmitted through the realigned solvent molecules to neighboring hydration shells around other free oxygen atoms. In this way, there is an indirect interaction between the free oxygen atoms on DNA backbones and the DNA will take on the more extended *B* structure. When $S = 0.7$, there is a balance between the contributions of both counterion coupling and hydrogen bonding and the transitional state of an (*A*-*B*)mix appears. As to $S = 1.2$, the overpolarized case, there are some chaotic peaks in both $g(r)_{Na^+}$ and $g(r)_{H_2O}$ for the insufficient sampling of the glassy state. Because of the big polarity of solvent molecules and fewer protons needed to screen the free phosphate oxygen, the first peak of $g(r)_{H_2O}$ is a little sharper and the hydration number is less than normal water.

The dynamical properties (residence times around the free oxygen atoms t_{res} and self-diffusion coefficients D) of Na^+ ions and solvent molecules around the DNA surface (in Table II) provide further arguments for the competition

TABLE II. Dynamical properties of Na^+ ions and solvent molecules around the DNA surface. The residence time (t_{res}) of Na^+ ions and solvent molecules around oxygen atoms of phosphate group within 3.2 Å and their self-diffusion coefficients (D) are given. The data for the $S = 1.2$ case are not given here as results do not converge due to the glassy nature of the solvent.

	Na^+ ions		H_2O	
S	t_{res} (ps)	D (10^{-9} m^2/s)	t_{res} (ps)	D (10^{-9} m^2/s)
0.6	29.66	0.58	1.33	2.16
0.7	24.99	1.16	1.58	2.12
0.8	16.21	1.26	2.46	2.04
1.0	14.34	1.42	5.23	1.66

between the counterion-coupling and hydrogen-bonding effects. The t_{res} and the diffusion coefficient D of ions and the solvent molecules change monotonically as S increases: decreasing for Na^+ and increasing for solvent molecules in the case of t_{res} while increasing for Na^+ and decreasing for the solvent molecules in the case of D. When $S = 0.6$, the residence time of Na^+ is as long as 29.66 ps and its diffusion coefficient is only 0.58×10^{-9} m^2/s. This indicates the formation of Na^+–O^-(P) structure. When $S = 1.0$, the residence time of the solvent molecule rises to 5.23 ps. And for the large magnitude of the solvent molecules, the neutralization of the free oxygen is dominated by the hydration effects.

A specific structure is crucial for DNA to perform its correct biological activity or any other novel function. In solvent with counterions, when the polarity of solvent molecules changes from overpolarized to less polarized compared to normal water, the structure of EcoRI dodecamer changes in the following way: constrained → B form → (A-B)mix → A form. Although A and B forms are crucial boundary extremes for DNA, the intermediate (A-B)mix states do exist under the mildest conditions [26,27], for example, in the microenvironment when DNA combines with protein. The long range intramolecule electrostatic interactions in the nucleotide sequence can be modulated by the competition between hydration and the ion coupling to the free phosphate oxygen. In an environment with sufficiently polarized solvent molecules, the hydration is dominating and the DNA appears B form; in the less polarized Lennard-Jones-like solvents, the free oxygen atoms are mainly coupled by counterions, and the compacted A form is preferred. If these two effects are properly balanced as shown in the $S = 0.7$ case, there exist (A-B)mix states. Despite the simplicity of the charge-scaled water model, the results in this Letter are consistent with experimental phenomena and give a clear molecular-level description of the conformational preferences of DNA helices in solvents of different molecular polarity.

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