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High propeller twist and unusual hydrogen bonding patterns from the MD simulation of $(dG)_6 \cdot (dC)_6$

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A molecular dynamics (MD) study of $(dG)_6 \cdot (dC)_6$ including counter ions and 292 water molecules was made. The hydrogen bonding pattern and propeller twist angles for the mini-helix are reported as averages for times spanning 21–30, 31–40, 41–50, and 51–60 ps. The propeller twist angles range from 18° to 38°. Bifurcated and interstrand neighboring base (twisted) hydrogen bonding patterns were found.

Molecular dynamics; Hydrogen bonding; Propeller twist; $(dG)_6 \cdot (dC)_6$; Poly(dG) · poly(dC)

1. INTRODUCTION

The interest in homopurine · homopyrimidine tracts in DNAs has been increasing because of their distinct properties. For example, poly(dA) · poly(dT) and poly(dG) · poly(dC) cannot be reassociated into nucleosomes [1,2] and are resistant to DNase I digestion [3]. Also, the structure of poly(dA) · poly(dT) is different from generic B-DNA and resists the B to A transition as relative humidity is decreased [4].

Recently, the α-form poly(dA) · poly(dT) X-ray fiber diffraction study has been reported [4]. In this structure both polynucleotide chains are conformationally similar (C2′-endo furanose rings on both strands) and yet different enough to be distinct from B-DNA. The significant features of the structure are the intrastrand base stacking, which may be responsible for the observed somewhat heteronomous chains, and the propeller twist, θ_P, which for the poly(dA) · poly(dT) was large (22.0°) compared to that found in standard B-DNA (13.0°). The conformational features and the large θ_P of the poly(dA) · poly(dT) were attributed to the extra freedom in AT base-pairs which are linked by only two hydrogen bonds while the optimal stacking in the poly(dA) · poly(dT) structure accounts for its robustness compared to B-DNA.

A recent single crystal X-ray diffraction study of a dodecamer containing a six base-pairs oligo(dA) · oligo(dT) tract also finds a large θ_P (20° average) for the oligo(dA) · oligo(dT) region [5]. This large propeller twist maximizes the purine-purine stacking interactions while creating the potential for additional non-Watson-Crick interstrand hydrogen bonds diagonally across the major groove. The net result is a conformational rigidity in accord with the properties of the poly(dA) · poly(dT) polymer. A similar cross strand next step hydrogen bonding stabilization of an oligo(dA) · oligo(dT) sequence with a high θ_P region has been reported [6].

Even though a recent fiber diffraction study for poly(dG) · poly(dC) is not available in the literature, a model of poly(dG) · poly(dC) was developed from a single crystal X-ray diffraction study of the dG_4C_4 duplex [7]. This model with a roll of 5°, tilt of 12°, rise per residue of 0.288 nm and a propeller twist of 8° is similar but not identical to standard A-DNA. Other studies [8–10] on GC-rich oligomers report θ_P of approx. 10°–12°.

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Raman spectroscopy of the polymer poly(dG)·poly(dC) as a fiber and in solution indicates that the polymer is predominantly A-DNA in a concentrated solution, but displays a predominantly B-DNA form in dilute solution [11]. The fiber polymer, interestingly, is an intermediate case with a non-A-DNA structure that departs significantly from that expected for a typical B-DNA structure. Clearly the conformation of oligo(dG)·oligo(dC) needs further investigation.

Similarity for some properties indicates that some structural features can be expected to be the same for the two homopurine·homopyrimidine polymers. To address this issue a molecular mechanics and molecular dynamics study of $(dG)_6 \cdot (dC)_6$ as a model for poly(dG)·poly(dC) has been initiated. MD has been shown to be useful for elucidating the structural features of oligonucleotides in vacuum and in solution [12–15]. In this paper the propeller twist and hydrogen bonding patterns obtained by MD simulation of $(dG)_6 \cdot (dC)_6$ are reported.

2. MATERIALS AND METHODS

The starting geometry for the hexamer was a standard B-DNA [16] structure, step height of 0.34 nm and helix twist of 36.0°, with 5′- and 3′-terminals ending in deoxyribose groups. Octahedrally hydrated sodium ions were placed at the ten phosphate positions. The resulting complex was immersed in a box of SPC water [17] and only the 292 water molecules within 0.5 nm of a solute atom were kept to model at least the first hydration shell for the complex.

Results were obtained using the Gromos [15,18] (Groningen molecular simulation system) programs without modification. Non-bonded pair interactions and electrostatic interactions were cut off at 0.8 nm and 1.8 nm, respectively.

The initial structure was relaxed using molecular mechanics. Dynamics were initiated with velocities from a 300 K Maxwellian distribution. The system was weakly coupled to a 300 K thermal bath. No pressure effects were included. The central hydrogen bond of the top and bottom base-pairs was restrained to its initial length to prevent fraying of the ends of the helix. Trajectories from the 60 ps MD run were created with coordinates saved every 0.050 ps. Only the final 40 ps were used for analysis. Average structures for the time spans T21–30, T31–40, T41–50, and T51–60 were obtained from the corresponding ten individual one picosecond averages.

3. RESULTS AND DISCUSSION

During the MD simulation the water molecules around the mini-helix rearranged forming a distinctly spherical droplet. Most of the water was observed to concentrate in the grooves and along the backbone of the mini-helix. Only a few water molecules remained at the top and bottom hydrophobic regions of the helix. Over the course of the simulation one water molecule evaporated from the surface of the droplet. The sodium ions drifted from their original positions but remained hydrated. Detailed analysis of the water structure and sodium ion distribution will be presented elsewhere.

Two important features of the conformation of the $dG_6 \cdot dC_6$ model, which retained its B-DNA form, became apparent during the dynamics study. The first of these was the large θ_P for each base-pair which appeared in the first picoseconds of the simulation (fig.1). The second was the appearance of the potential for bifurcated and unusual hydrogen bonding between the strands of the mini-helices (figs 2 and 3).

The large fluctuating θ_P found during the MD simulation is illustrated in fig.1 where the average θ_P for each picosecond of the trajectory computed from the 20 snapshots for the first base-pair, bases G1 and C12, as a function of time is presented. Similar behavior was observed for all base-pairs in the mini-helix. The θ_P was calculated as the angle between the normals to the least square planes of a base-pair. The numerical values for θ_P, for each base-pair step for four 10 ps average conformations are presented in table 1. These averages accurately represent the θ_P found in fig.1. These average values are slightly larger, 24–33°, than those recently reported for poly(dA)·poly(dT), (15–20°) [4,5]. Even though each column represents the average over 200 individual conformations some indication of oscillatory behavior along the oligomer strand as a function of time can still be seen.

The hydrogen bonding pattern for the $(dG)_6 \cdot (dC)_6$ hexamer is represented schematically in fig.2. These bonds were located with the PROCHB program of the Gromos [18] library with a maximum hydrogen to hydrogen-acceptor distance and a minimum hydrogen bond angle cutoff set at 0.25 nm and 135.0°, respectively. Fig.2 clearly conveys the dynamic state of the hexamer model even though 10 ps average conformations were used. The number of hydrogen bonds can clearly be seen to vary as time proceeds from left to right in the diagram.

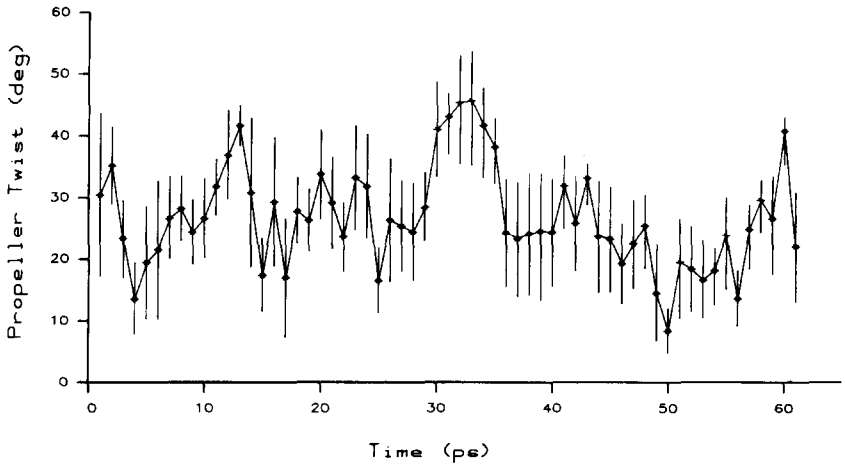

Fig.1. Propeller twist, θ_P, for the first base-pair in the mini-helix. Each point is an average of the 20 snapshot configurations within 1 ps of the trajectory. Error bars indicate the standard deviation for each picosecond.

The interstrand hydrogen bonding between neighboring base planes (diagonals in fig.2) is very interesting. These bonds, between N4 of a cytosine and O6 of a guanine in the next base-pair, have an average hydrogen-hydrogen-acceptor distance of 0.226 (0.012) nm and a hydrogen bond angle of 149.4° (10.6°). These compare favorably with average values for two center bonds (161.4° (13.7°) and 0.190 (0.013) nm) [19]. The hydrogen bond length reported here is a little longer than the average value. This is not unexpected since the structures analyzed are averages over 10 ps of the trajectory. The bifurcated hydrogen bond (three-center bond) [19] formed by the N1 hydrogen of the guanine and the N3 and O2 of the cytosines is another interesting feature of this diagram. For the sixteen entries of this type the following mean distances and angles were obtained: r(G)N1-H--N3(C) is 0.209 (0.016) nm; ∠ (G)N1-H--N3(C) is 159.4° (4.7°); r(G)N1---N3(C) is 0.302 (0.015) nm; r(G)H--O2(C) is 0.226 (0.013) nm; ∠ (G)N1-H--O2(C) is 141.1° (4.3°); r(G)N1---O2(C) is 0.308 (0.010) nm. Again the angle reported here for the (G)N1-H--O2(C) bond falls in the average range given by Taylor et al. [19] while the (G)N1---O2(C) distance is a bit long. The (G)N1-H--N3(C) bond angle and length, on the other hand, are near the values used for normal two center hydrogen bonds. This means that though the central hydrogen bond for each GC base-pair remains essentially intact during the MD simulation there is sufficient flexibility in the base-pair to permit a bifurcated bond to form. In fact for the T41-50 time slice on GC base-pair has opened out into the major groove so that only the unusual (G)N1-H--O2(C) hydrogen bond remains. This bond, r(G)N1-H--O2 = 0.195 nm and ∠ (G)N1-H--O2(C) = 165.0° and r(G)N1---O2(C) = 0.290 nm, is clearly a standard two center hydrogen bond. At T51-60 this base-pair has closed up to a more normal hydrogen bonding pattern.

Table 1

Propeller twist (θ_P degrees) in $(dG)_6 \cdot (dC)_6$

Bases	Time slice (ps)				
	T21-30	T31-40	T41-50	T51-60	Av. (rms)
1-12	25.3	30.6	18.4	20.3	23.7 (4.7)
2-11	23.8	29.5	20.4	20.5	23.6 (4.0)
3-10	27.2	33.4	25.7	29.6	29.0 (3.0)
4- 9	27.3	37.5	30.0	36.5	32.8 (4.3)
5- 8	17.2	13.8	27.5	34.9	23.4 (8.4)
6- 7	18.3	17.6	21.4	30.6	22.0 (5.2)
Av. (rms)	23.2 (4.0)	27.1 (4.0)	23.9 (4.1)	28.7 (6.3)	

The overall picture emerging from our study of $(dG)_6 \cdot (dC)_6$ is that this oligomer in a droplet of water displays a dynamic conformation involving a propeller twisting of the bases which varies up and down the helix fragment about a mean value of 24°. This large propeller twist gives rise to interesting hydrogen bonding patterns in the model.

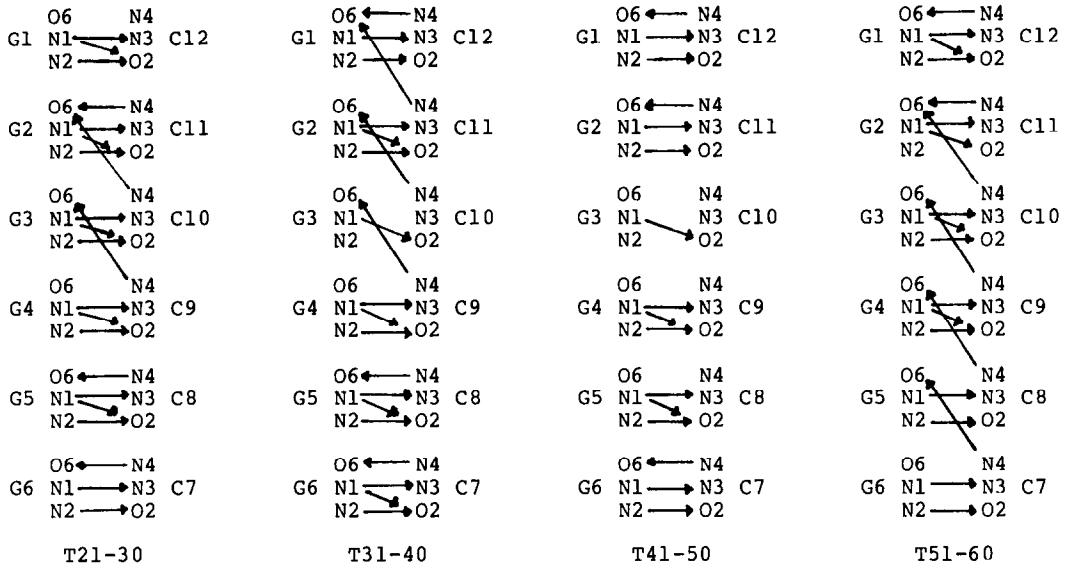

Fig.2. Schematic representation of base-pair hydrogen bonding patterns observed in the 10 ps time average structures from the MD simulation of $(dG)_6 \cdot (dC)_6$. The arrows point from donor to acceptor atoms of the hydrogen bond.

From these hydrogen bonding patterns an additional type of motion, involving an opening and closing of the base-pairs into the major groove, is superimposed on the propeller twist variability. Nothing equivalent to this was reported for available crystallographic studies on related systems, such as the d(GGGGCCCC) [7] and d(CCCCGGGG) [8] systems where normal hydrogen bonding patterns and small propeller twists were reported. In both of these cases it was clearly shown that the terminal base-pairs are flush against the shallow minor groove of another duplex in the crystal. This gives rise to considerable crystal packing forces between the mini-helices making a direct comparison of our model to crystal models impossible. Spectroscopic studies [11,20]

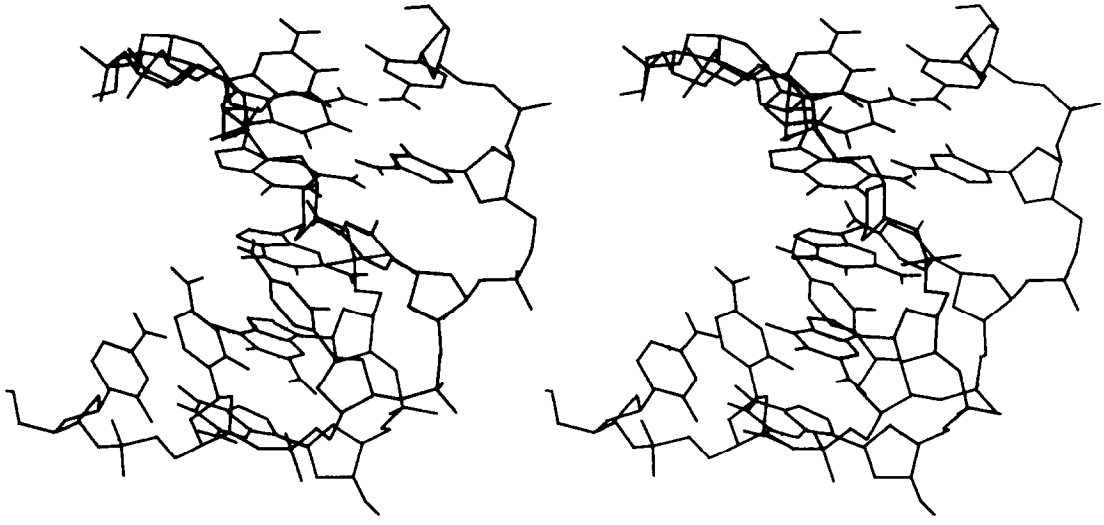

Fig.3. Stereo-view of the T51-60 conformation showing the high propeller twist and unusual hydrogen bonding for $(dG)_6 \cdot (dC)_6$.

also indicated that the structure of poly(dG)·poly(dC) in solution depends on the various environmental factors including solute concentration, salt concentration, methylation and sequence. Additional theoretical studies to elucidate the possible causes of the unusual structural features found in this study are in progress. Particular attention is being given to the above mentioned factors and their influence on the fine structure of DNA.

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