Simulation of *Eco*RI Dodecamer Netropsin Complex Confirms Class I Complexation Mode

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Abstract: The knowledge of the exact positions of ligands complexed to DNA is essential for systematic modeling of new antitumor drugs controlling transcription. In the case of the *Eco*RI dodecamer netropsin complex (= Nt/(CGCGAATTCGCG)$_2$ complex), experimental techniques yield contradicting results about the drug position. Hence, we have investigated the Nt/(CGCGAATTCGCG)$_2$ complex by a 5 ns molecular dynamics simulation to shed light onto the binding mode. Analysis of the simulation confirms in agreement with NMR data and X-ray results that the Nt/(CGCGAATTCGCG)$_2$ complex exists as a class I complex, although the simulation was started from class II conformation suggested by alternative X-ray investigations. Additionally, the simulation revealed stable conformations of the complexed netropsin molecule, providing new contact information that may be important for the design of new potential ligands.

Introduction

The interactions of small molecules bound to B-DNA have been under intense study for many years.[1−5] For the development of these molecules and for the design of other new ligands, the precise position and contacts of the drug in the complex has to be known. Currently there exists a wealth of high-resolution data for a variety of such drug DNA complexes out of which over 100 are freely available via the Nucleic Acid Data Base (NDB).[6] Drugs interact with DNA either by binding to the minor or major groove,[2,7−11] by intercalation,[12,13] through covalent attachments/cross-linking,[14] or by combinations[15−17] of these interactions. Structural data indicate that the small drug molecules act in most cases as rigid bodies with little conformational change[4].

Although in contrast to intercalation groove binding does not induce major alteration of the DNA structure, minor groove binding can inhibit expression of specific genes.[18−21] Thus sequence-specific binding drugs[22−32] are of great interest as antitumor agents.

The majority of small molecules binds to the minor groove of B-DNA. One of the best studied minor groove binders so far is netropsin (Figure 1),[12,33−43] which has a binding preference for AT-rich regions.

This sequence specificity is explained by the better electrostatic interaction[9,35] of the positively charged ligand with the highly negative electrostatic potential of B-DNA in the minor

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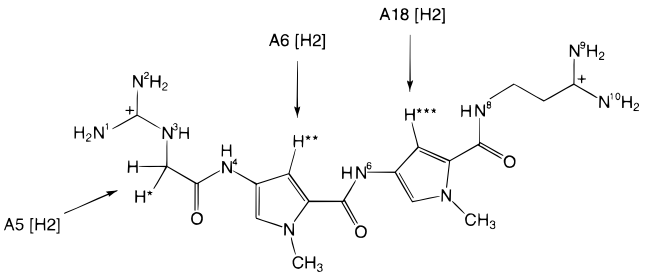

Figure 1. Chemical structure of the minor groove binder netropsin with nitrogen atoms numbered according to Goodsell et al.[8] The arrows indicate NMR-derived hydrogen bond interactions proposed by Patel et al.[38] suggesting a class I binding mode for the complex.

Table 1. X-ray Structures of B-DNA Complexes with Netropsin[a].

complex	resolution, Å	*R* factor	author
class I			
Nt/(CGCGAATT^{5Br}CGCG)$_2$	2.25	0.163	Goodsell et al.[8]
Nt/(CGCGAATT^{5Br}CGCG)$_2$	2.2	0.211	Kopka et al.[41]
Nt/(CGCAAATTTGCG)$_2$	2.2	0.198	Tabernero et al.[40]
Nt/(CGCAATTGCG)$_2$	2.4	0.246	Nunn et al.[43]
class II			
Nt/(CGCGATATCGCG)$_2$	2.4	0.200	Coll et al.[39]
Nt/(CGCGAATTCGCG)$_2$	2.2	0.164	Sriram et al.[46]
Nt/(CGC[e^6G]AATTCGCG)$_2$	2.5	0.156	Sriram et al.[46]

[a]The X-ray analyses indicate the existence of two different binding modes.

groove of A·T base pairs, by the greater propeller twist of A·T regions resulting in a narrower minor groove[3] and thus better van der Waals contacts, and by the concave shape of netropsin, which fits exactly in the convex minor groove of DNA and is only disturbed by the exocylic amino N2 group of guanine. In addition, the drug can form hydrogen bonds[38] to O2 of thymine and N3 of adenine. On the basis of this knowledge about sequence-specific binding, the lexitropsins,[44,45] which are netropsin analogues, have already been developed.

Available X-ray studies reveal the existence of two different binding modes for netropsin−DNA 1:1 complexes (cf. Table 1).

Class I complexes are found for the sequences (CGCGAATT^{5Br}CGCG)$_2$, (CGCAAATTTGCG)$_2$, and (CGCAATTGCG)$_2$.[8,40,41,43] In these complexes, the netropsin molecule is located exactly in the middle of two successive base pairs enabling the amide hydrogens of netropsin to build hydrogen bonds with both strands of the DNA. In class II complexes, netropsin is shifted in the minor groove by about half a base step[8] (Figure 2). Although in this binding mode the amide groups cannot build three centered hydrogen bonds to both DNA strands, X-ray studies of (CGCGATATCGCG)$_2$ and (CGCGAATTCGCG)$_2$ suggest that netropsin binds to DNA as a class II complex,[39,46] in contrast to the above-mentioned results.

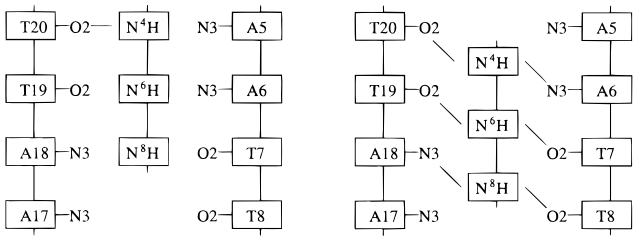

Figure 2. Schematic representation of the two different binding modes of netropsin: (right) the class I binding mode and (left) the class II binding mode (the lines indicate hydrogen bonds between DNA and netropsin).

NMR data by Patel[38] show the existence of hydrogen bond interactions (cf. Figure 1) between the pyrrole H** and A6[H2], between H*** and A18[H2], and between the terminal methylene H* and A5[H2], thus indicating that netropsin occupies a class I binding mode, supporting the class I X-ray results.

To clarify the problem of the different experimental results concerning the binding mode, a 5 ns molecular dynamics simulation was carried out. Analysis of the resulting interaction patterns throughout the simulation suggests the class I binding mode for the Nt/(CGCGAATTCGCG)$_2$ complex, which is in agreement with mentioned experimental data.[8,38,40,41,43] This result is also supported by chemical intuition, as in class I complexation netropsin is able to build a higher number of hydrogen bonds (cf. Figure 2) with DNA, allowing an explanation of binding specificity.

Methods and Computational Details

Molecular dynamics simulations are an excellent tool for the examination of the structure and dynamics of biological interesting molecules such as DNA[47−50] and DNA−ligand complexes. The most important advantage of simulations is the nearly unlimited resolution of space, energy, and time. Although a description of B-DNA with older force fields was problematic, nowadays better force fields and the inclusion of the long-range interactions via the Ewald summation in form of the so-called particle mesh Ewald method[51,52] allow the calculation of stable B-form-DNA trajectories.[52−54]

As starting point, the crystal structure of the underivated Nt/(CGCGAATTCGCG)$_2$ complex was used. The structure has the PDB code 1D86. It represents a class II complex. Each strand of the DNA

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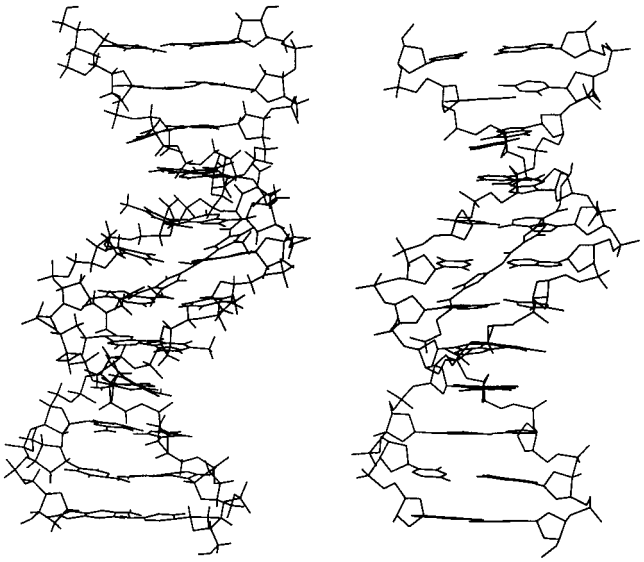

Figure 3. Comparison between the structure after equilibration (left) and the X-ray structure[46] (right).

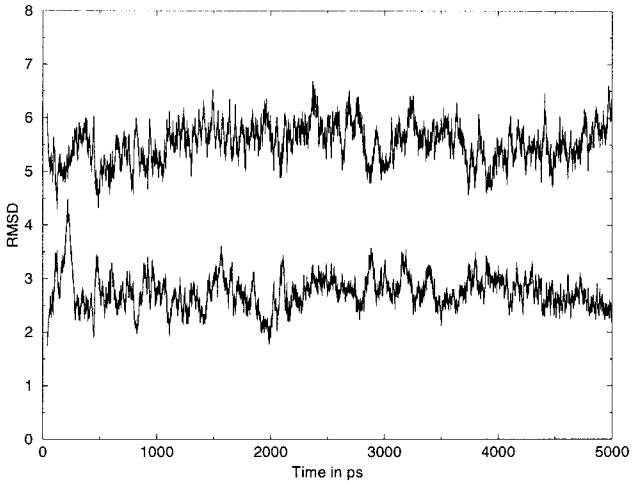

Figure 4. Rms deviation (Å) of the simulation with respect to canonical A-DNA (top) and with respect to canonical B-DNA (bottom).

has 11 PO_4^- anions. The netropsin molecule has two positive charges. To achieve electroneutrality, 20 Na^+ counterions were added using the program CION of the AMBER[55] package. Subsequently solvation of the DNA with TIP3P Monte Carlo water boxes requiring a 12 Å solvent shell in all directions resulted in a system with the dimension 67.1 × 50.6 × 48.7 $Å^3$ containing 4642 water molecules. The corresponding Γ value (water/nucleotide) is 193.4. The simulation was carried out using the AMBER5[55] package with the all-atom force field of Cornell et al.[56] The force field parameters of netropsin were selected in analogy to existing parameters in the force field of Cornell et al.[56] Charges were derived using the RESP[57] charge-fitting procedure. The ab initio electrostatic potential for RESP was calculated using GAUSSIAN94[58] at the HF/6-31G* level of theory. The complete set of additional parameters is available as Supporting Information.

To obtain the best possible description, previously described simulation protocols[59−63] were adapted for our needs. At the beginning,

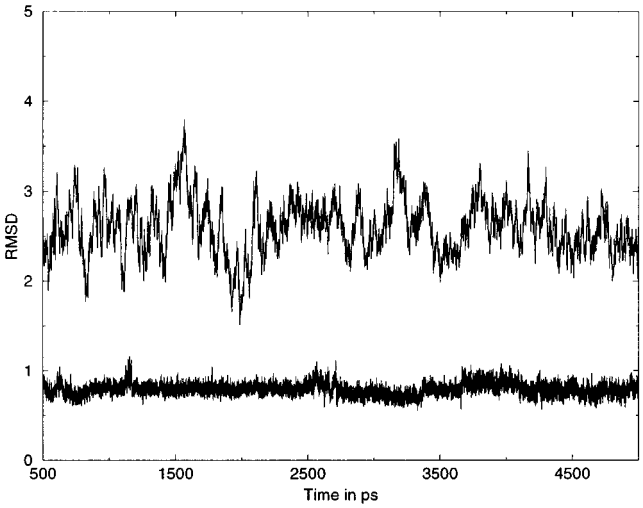

Figure 5. Rms deviations (Å) of the whole complex and of the DNA alone with respect to the starting structure (both nearly identical; both curves coincide in the top) and rms deviation of the ligand with respect to the starting structure (bottom).

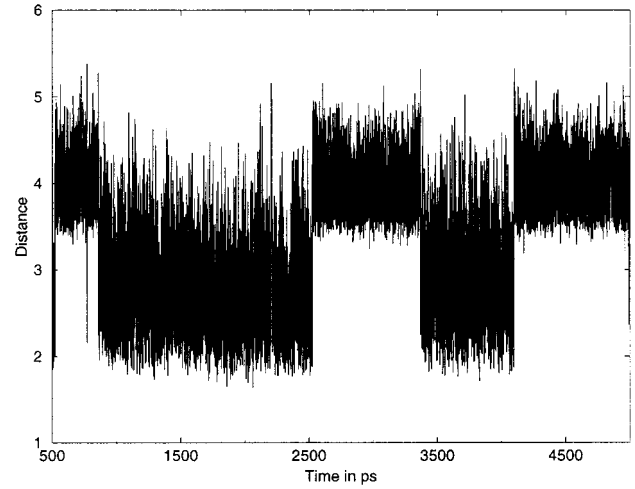

Figure 6. Distance (Å) between A5[H2] and netropsin H*. The plot shows the existence of two stable netropsin conformations and the occurrence of conformational transitions.

minimizations were carried out with harmonic restraints on DNA and counterion positions. The restraints were stepwisely relaxed, and at the end a 500-step minimization without restraints was performed. A similar procedure was applied for the equilibration. The system was heated from 50 to 300 K during 10 ps under constant-volume conditions and harmonic restraints. Subsequently, the restraints were once again relaxed and finally an unrestrained 5 ps equilibration was carried out. After this procedure, the system was switched to constant temperature and pressure.

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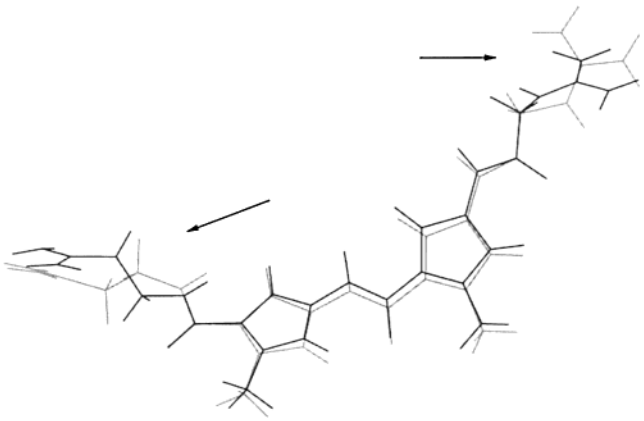

Figure 7. Superposition (rms deviation 1.3 Å) of the different netropsin conformations. The left arrow indicates the conformational transition in the propylamidinium group and the right arrow indicates the changes of the guanidinium tail.

Table 2. Contact Distances (Å) between $(CGCGAATTCGCG)_2$ and Netropsin for Class I and Class II Complexes and the Average Distance Derived from the Simulation]

distance	class I	class II	simulation
Nt-N4 to T20-O2	2.8	3.3	2.9
Nt-N6 to T19-O2	3.2	4.4	3.1
Nt-N8 to T8-O	2.6	3.8	3.0
Nt-N6 to T7-O2	3.6	4.2	3.5
Nt-N4 to A6-N3	3.3	3.8	3.3
Nt-N8 to A18-N3	2.6	4.3	3.8

Results

After switching from isochor to isobar conditions, the energy reaches a stable value for the rest of the simulation. The X-ray structure and the structure after equilibration are shown in Figure 3 exhibiting a close resemblance to each other.

The rms value indicates that the simulation reached equilibrium after 250 ps (cf. Figure 4). Hence 0.5 ns was chosen as starting point for the analysis of the simulation. Figure 4 also demonstrates that the DNA is in B-DNA form during the whole simulation.

The rms values with respect to the starting structure were used to investigate whether the netropsin molecule moves in the minor groove. We calculated the rms values of the whole complex, of DNA, and of netropsin with respect to the starting structure. The rms deviations of DNA and of the whole complex are very similar throughout the whole simulation and so the two curves conincide in the plots (Figure 5). This indicates that the netropsin molecule does not move substantially in the minor groove. The rms value of netropsin is ~0.79 Å, indicating that the ligand is very rigid and supporting the well-known lock and key mechanism.

An analysis of the contact distances between the netropsin molecule and DNA confirms these results as all but two contacts remain in a small region and no shift of the drug occurs. The fact that the ligand does not move along the DNA is a first indication that the complex is a class I complex.[8] A precise investigation of the distances further supports this assumption (cf. Table 2).

Remembering that the starting structure was a class II complex, these results are rather surprising. In solution, the class I complexation seems to be preferred. The occurrence of the class I complexation is in agreement with the NMR results for the $Nt/(CGCGAATTCGCG)_2$ complex and X-ray experiments for $Nt/(CGCGAATT^{5Br}CGCG)_2$ as well $Nt/(CGCAAATTTGCG)_2$ and $Nt/(CGCAATTGCG)_2$.[8,40,41,43]

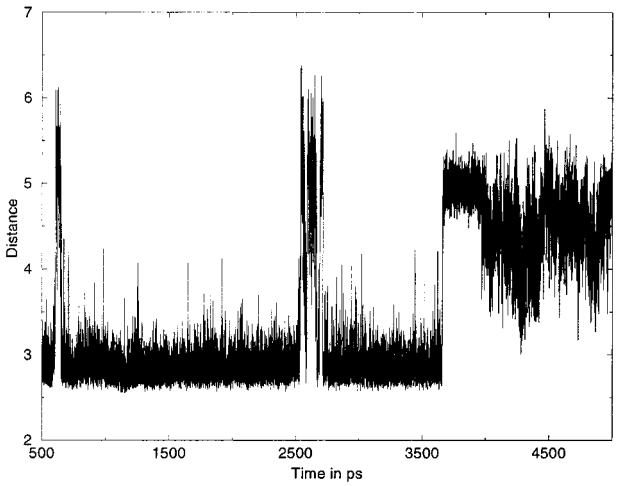

Figure 8. Distance (Å) between the C21[O2] and the N^2 of netropsin. The first two transitions are different compared to the transition at 3600 ps, indicating the existence of two distinct types of transition.

The rather small rms values of the netropsin molecule (Figure 5) indicate that the formed contacts stabilize the drug in the minor groove. All but two contacts fluctuate little around their contact distances, indicating that the molecule does not move in the minor groove. Two contacts can be assigned (via visual analysis) to conformational transitions localized on the flexible guanidinium and amidinium termini. Figure 6 shows the distance plot of A5[H2] to H* of netropsin. There are two stable conformations which are equally occupied; i.e., no substate seems to be preferred. The conformational transition is extremely fast.

Visual analysis with gOpenMol[64] reveals two conformations which are characterized by two different torsion angles within the propylamidinium group. The contacts of the amidinium group with the DNA and the relative orientation of the methylene groups with respect to each other remain almost unchanged (Figure 7).

The second conformational transition occurs on the other end of the molecule (guanidinium tail) and is represented by the distance plot between C21[O2] and netropsin N^2 (Figure 8). In this case, the starting conformation is populated more and thus seems to be thermodynamically preferred. Analysis of the three transitions reveals that the system relaxes very fast after the first two transitions, whereas it interconverts into another stable conformation at 3600 ps. This indicates that there are two different kinds of transitions, which is again confirmed by visual analysis. The changes at the first two transitions cannot be assigned to conformational states, whereas after the third transition the orientation of the guanidinium group and the neighboring methylene group is changed (Figure 7) with respect to the rest of the molecule.

Summary and Conclusions

We performed a 5 ns molecular dynamics simulation of the $Nt/(CGCGAATTCGCG)_2$ complex and analyzed the structural and dynamical properties of the complex. The rms values show that netropsin does not move in the minor groove as some crystallographic studies suggested. The simulation confirms the often observed lock and key mechanism. The netropsin molecule shows only small structural deviations from the starting structure. The largest flexibility is observed at the drug's termini resulting in conformational transitions. The knowledge of these

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conformations and the associated contacts is important for the design of new ligands. In contrast to the X-ray data of Sriram et al., our simulation supports the occurrence of a class I complex in solution, which is in agreement with NMR data and X-ray experiments for derivated Nt/DNA complexes.

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Supporting Information Available: Atomic numbering scheme of netropsin; RESP charges and atomic types for the heavy atoms and the hydrogens of netropsin (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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