Supporting Information

Destabilisation of DNA duplexes by oxidative damage

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1 Introduction

This supporting information provides the FapydG parameterisation methodology, the atom types, the atomic charges and the modified AMBER force field for the nonplanar formamido functional group.

2 FapydG parameterisation

Since FapydG is a non-standard nucleotide, there is no available molecular parameters included in the database as is the case for standard DNA and RNA nucleotides. In order to incorporate a FapydG base into the simulations, it was first essential to assign an appropriate type and partial charge to each atom. A methyl derivative of FapydG was modelled, in which the deoxyribose moiety was substituted by a methyl group keeping the FapydG in a neutral system. Electrostatic potential on the molecular surface was calculated using Gaussian 98 [**?**], with Hartree-Fock calculations and the 6-31G* basis set. To reproduce this electrostatic potential, appropriate partial charges were then fitted at each atom using an atom-centred point charge model termed the restrained electrostatic potential (RESP) method [**?**] within the *antechamber* module. The charges were finally merged with standard AMBER charges for nucleic acid sugars and phosphates, and adjusted to give the correct total overall charge. Atom types of FapydG were assigned based on the standard AMBER parameters for organic and biomolecular molecules, parm99.dat [**?**].

The FapydG force field was calculated according to the parm99.dat with the missing torsional terms for X-C5-N5-X (see figure **??**). To analyse rotational energies around the C5-N5 bond, snapshots were generated ranging 0° to 180° with 30° increments using Insight II. A full geometry optimisation and energy calculation using the 6-31G* basis set with each torsion angle constrained was performed. The AMBER energy profile of the dihedral angles around the C5-N5 bond was also calculated and subsequently fitted with the quantum mechanically potential energy profile using different torsional parameters. Standard atom types and charges were used for the remaining nucleic acid residues.

2.1 Modified AMBER force field for FapydG

Missing force field parameters for FapydG were first reported by Perlow-Poehnelt *et al.* [**?**]. The FapydG parameters have been mostly maintained similar to the guanine nucleobase leading to the constrained formamide group in the plane with the pyrimidine ring. In contrast, the nonplanar formamide group was expected as occurred in the X-ray and the NMR structures.

Applying the new modified force field, preliminary MD simulations of a FapydG-containing oligonucleotide in the presence and absence of Fpg showed the FapydG conformation in good agreement with the crystallographic and the NMR structures. The resulting partial charges and atom type assignments are

shown in figure **??** and the modified force field for FapydG used in this study is demonstrated in table **??**.

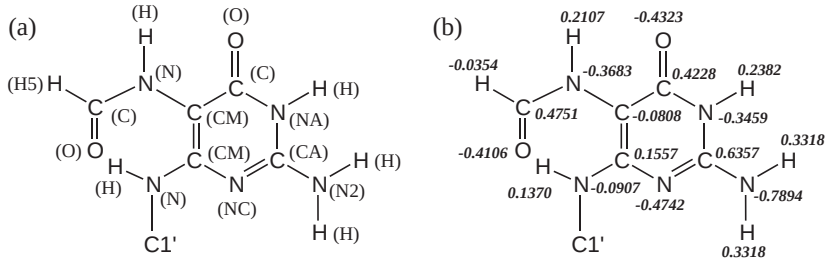

Figure 1: (a) Atom types (b) Atomic charges of FapydG.

References

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Table 1: Modified AMBER parameters added to the parm99.dat.

Bond	K_{bond}	R_{bond}	Analogy with		
N-CM	448.0	1.365	CM-N*		
NC-CM	483.0	1.339	CA-NC		
Bond angle	K_{angle}	R_{angle}	Analogy with		
C-N-CM	70.0	121.60	C-N*-CM		
N-CM-C	70.0	120.10	CM-CA-N2		
N-CM-CM	70.0	121.20	CM-CM-N*		
H-N-CM	50.0	121.20	CM-N*-H		
CM-CM-NC	70.0	121.20	CM-CM-N*		
CA-NC-CM	70.0	118.60	CA-NC-CQ		
NC-CM-N	70.0	119.30	N2-CA-NC		
N-CT-H2	50.0	109.50	N*-CT-H1		
CT-N-CM	70.0	121.20	CM-N*-CT		
OS-CT-N	50.0	109.50	OS-CT-N*		
Dihedral	Phase	$K_{dihedral}$	Phase angle	Periodicity	Analogy with
CA-NC-CM-N	1	1.10	180.0	2.	CB-NC-CA-N2
CM-CM-NC-CA	1	1.85	180.0	2.	X-CM-N*-X
H-N-CM-NC	1	1.85	180.0	2.	X-CM-N*-X
CT-N-CM-NC	1	1.85	180.0	2.	X-CM-N*-X
CT-N-CM-CM	1	1.85	180.0	2.	X-CM-N*-X
H-N-CM-CM	1	0.25	0.0	2.	New parameter
H-N-CM-C	1	0.25	0.0	2.	New parameter
C-N-CM-CM	1	0.25	0.0	2.	New parameter
C-N-CM-C	1	0.25	0.0	2.	New parameter

Notes: K is a force constant for each term and R is an ideal value.