Electronic Supplementary Material (ESI) for Chemical Communications


# The role of thermodynamics and kinetics in ligand binding to G-quadruplex DNA

Ben Corry*[a] and Nicole M. Smith[b]

[a]*Research School of Biology, Bldg 134, The Australian National University, Canberra ACT 0200, Australia.*

[b]*Research School of Chemistry, Bldg 35, The Australian National University, Canberra ACT 0200, Australia.*

* To whom the correspondence should be addressed. E-mail: ben.corry@anu.edu.au

## SUPPORTING INFORMATION

### Contents

## 1.0 Computational Analysis

**Supplementary Table 1. Average interaction energies** (kcal/mol) of each compound with HTelo DNA. Electrostatic (ES) and van der Waals (VdW) interactions are shown for each part of the compounds as well as the total interaction energy of the entire molecule when bound in the lowest energy conformation found in the study. Compound **5** refers to a dimethylamino functionalised 4'-aryl-2,6-bis(4-aminophenyl)pyridine studied previously (N. M. Smith et al, *Lab Chip,* 2009, **9,** 2021–2025.) that lacks the charged side chains.

| | Core | | 4-aryl substituent | | Side Chain 1 | | Side Chain 2 | | All |
|---|---|---|---|---|---|---|---|---|---|
| | ES | VdW | ES | VdW | ES | VdW | ES | VdW | Total |
| **1** | -0.5 | -42.4 | -3.8 | -23.1 | -114.2 | -7.5 | -56.8 | -3.9 | -252.2 |
| **2** | 1.9 | -48.9 | -0.8 | -11.1 | -85.6 | -11.3 | -26.1 | -4.7 | -186.5 |
| **3** | 3.9 | -50.7 | -1.4 | -8.8 | -51.0 | -12.2 | -42.6 | -4.9 | -167.7 |
| **4** | 7.4 | -41.6 | -9.0 | -14.9 | -105.9 | -10.7 | -42.8 | -3.9 | -226.3 |
| **5** | -4.2 | -41 | 0.2 | -16.6 | - | - | - | - | -61.7 |

## 2.0 Computational Experimental

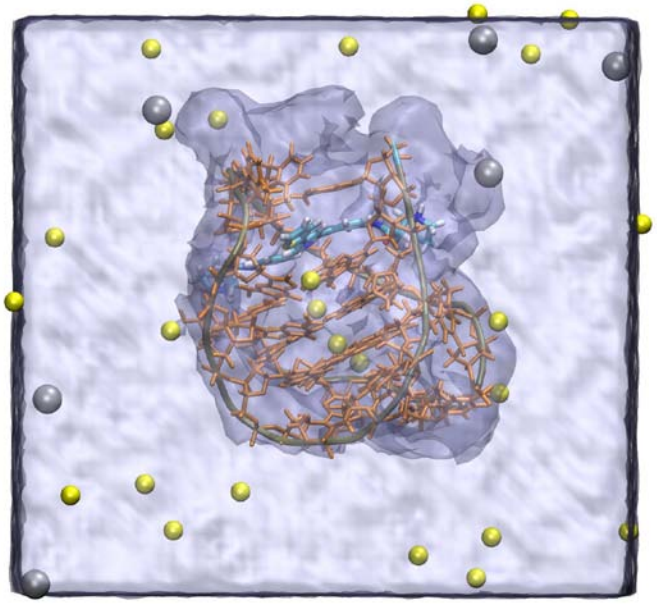
### 2.1 Optimization of compounds

Before conducting molecular dynamics simulations, each compound to be studied was parameterised using ab initio calculations. Partial charges were calculated using the Merz-Kollman electrostatic fitting method in the program GAUSSIAN03[14] after optimizing the structure with Hartree-Fock theory and a 6-31+G* basis set. Force constants for bond stretching, angle bending, and dihedral torsions as well as Lennard-Jones parameters were taken from similar atoms in the CHARMM27 force field.

### 2.2 Molecular dynamics simulations

The NMR solution structure of the HTelo repeat (PDB 143D, model 1)[15] was used as a starting conformation of the DNA and the compounds were initially positioned within it based upon the position of 3,6-bis-[3-pyrrolidino-propionamide] acridine (BSU6039) in a crystal structure bound to the telomeric sequence of Oxytrichia nova d(GGGGTTTTGGGG) (PDB 1L1H).[16] To do this the Htelo DNA was first aligned to the Oxytrichia nova structure and then the pyridine core of the compounds were given their best alignment to the acridine. Each compound was also rotated in the plane of the upper G quartet to create alterative binding modes in which the side chains of the compound extend through different gaps in the DNA. Binding free energies were calculated for each as described below and only the mode with the most negative binding energy is discussed. The compound-DNA complexes were solvated in a 57x57x57Å TIP3P water box and neutralized with 100mM NaCl (Supplementary Figure 1). Simulations were conducted at a pressure of 1atm and temperature of 300K using a 1fs timestep using the program NAMD[17] with the CHARMM27 force field for nucleic acids.[18-20] Equilibrium simulations lasting 15ns were conducted for each compound with data extracted only from the last 5ns. Binding free energies of each complex with the DNA quadruplex were determined by conducting alchemical free energy perturbation simulations[20] in which the compound bound to the DNA slowly disappeared and was replaced by a copy appearing in the aqueous medium in 35 steps (with □ values $10^{n}$, for

n=-9,-8,.. -2 then 0.05 incrementing by 0.05 to 0.95, then 1-$10^n$, for n=-2,-3,.. -9), totaling 9ns for each compound. Repeat simulations on two of the compounds showed agreement for the binding free energy to be within 1kcal/mol.



**Supplementary Figure 1:** Simulation system used in molecular dynamics simulations. The compound (coloured by atom type) is inserted into the Htelo quadruplex DNA (orange) and solvated in water with $Na^+$ (yellow) and $Cl^-$ (grey).

### 2.3 Metadynamics simulations

The pathway and energetics of unbinding of compounds **2** and **4** were studied using metadynamics simulations, a method for simulating rare events and obtaining free energies.[21,22] In this, a history dependent biasing potential is added to the system, constructed as a sum of Gaussians centred along the trajectory of the simulation described by a set of collective variables. In this case, the collective variables were chosen to be the distance of the pyridine core of the compound from the axis running through the centre of the guanine tetrad and the distance of the compound above the plane of the top tetrad. This potential, in time, fills the minima in the free energy surface forcing the system to adopt new configurations and allowing an estimate of the free energy surface. It should be noted that due to the complexity of the conformational space, and the difficulties in the compound moving many times between the bound and unbound states, the energies should only be taken as a rough estimate. Each metadynamics simulation lasted 35 ns. In total more than 500 ns of simulations were conducted for this study.

### References

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