Supporting Information

The Influence of Dendron's Architecture on the "Rigid" and "Flexible" Behaviour in Binding DNA – a Modelling Study

Giovanni M. Pavan,[a] Andrea Danani* [a]

a: University for Applied Sciences of Southern Switzerland (SUPSI) – Mathematical and Physical Sciences Research Unit (SMF), Centro Galleria 2, Manno, CH-6928 (Switzerland)

giovanni.pavan@supsi.ch

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Simulation Procedure

The AMBER 10 suite of programs[S1] was used to conduct all the simulations presented in this work. To model the nucleic acid we used a 21 base-pair double-stranded β-DNA[S2,S3] generated with the *nucgen* module of AMBER 10. The force field parameters for the residue types of the ester-based **2b**-dendrons were obtained following a well validated procedure[S3] using the *antechamber* module of AMBER 10. The Newkome-type **3b**-dendrons were created and studied in our previous work.[S2] **G1-2b**, **G2-2b** and **G3-2b** dendrons were solvated in a TIP3P[S4] water box extending 12 Å from the solute and, in order to guarantee the neutrality of the system, a suitable number of counterions were added using the *leap* module of AMBER 10. All the systems were then minimized and equilibrated for 10 ns in NPT conditions to obtain a reliable configuration for the dendrons in solution. From the corresponding equilibrated final configurations, water molecules and counterions were removed, and **G1-2b**, **G2-2b** and **G3-2b** were placed in proximity of the DNA major groove following a validated procedure.[S5,S2,S3] Thus, three final molecular complexes were obtained. The resulting structures were again solvated in a water box extending 12 Å from the solute and the proper amount of Na^+ and Cl^- ions was added in two steps – firstly to guarantee the system neutrality and then to reproduce the relevant salt concentrations of 150 mM NaCl in the solution. Table S1 reports the details of the simulated systems.

Table S1 Details of molecular systems simulated in this work.

Complex	[NaCl] (mM)	Dendron charge	DNA charge[a]	Water box volume (Å^3)	Number of Na^+ and Cl^- atoms[b] in the system	Number of water molecules in the system	Total number of atom in the system
G1-2b	150	+6	-40	220953	46	6883	22150
G2-2b	150	+12	-40	262696	54	8209	26285
G3-2b	150	+24	-40	365676	67	11536	36485
G1-3b[c]	150	+9	-40	321840	89	7847	25149
G2-3b[c]	150	+27	-40	470895	99	11885	37843

[a] The 21 base-pair DNA has an overall charge of -40 because the terminal nucleotides do not carry a charge in the model. [b] The total amount of counterions is the sum of the Na^+ and Cl^- atoms required for system neutralization and to reproduce the experimental ionic concentration of 150 mM. [c] Data

for **G1-3b** and **G2-3b** dendrons are taken from our previous work and here reported for comparison.[S2]

Each system was initially minimized and then equilibrated 50 ps MD simulation in NVT conditions to reach the simulation temperature of 300 K. Other 50 ps of density equilibration MD run followed in NPT conditions. The production MD lasted for 10 ns in NPT periodic boundary condition at 300 K and 1 atm, using a time step of 2 femtoseconds, the Langevin thermostat and a cutoff of 10 Å. The particle mesh Ewald[S6] (PME) approach was used to treat the long-range electrostatic effects and all bonds involving hydrogen atoms were constrained using the SHAKE algorithm.[S7]

All of the molecular dynamics simulations were conducted using the *sander.MPI* and *pmemd* module of AMBER 10 and the *parm99* all-atom force field by Cornell et al.[S8] working in parallel on 128 processors of the Cray XT5 calculation cluster of the CSCS Swiss National Supercomputer Centre of Manno (Switzerland).

Free energy of binding

The energetic analysis for each dendron-DNA complex was performed for 200 snapshots taken from the equilibrated phase the MD trajectory. The binding free energy for each ligand/receptor systems, ΔG_{bind}, was calculated following the Molecular Mechanics/Poisson-Boltzmann Surface Area method (MM-PBSA)[S9] as:

$$\Delta G_{bind} = \Delta H_{bind} - T\Delta S_{bind} \quad \text{(S1)}$$

$$\Delta H_{bind} = \Delta E_{gas} + \Delta G_{sol} \quad \text{(S2)}$$

Following Eq. (S2), the average enthalpic contribution (ΔH_{bind}) was calculated as the sum of the gas-phase *in vacuo* non-bond energies ($\Delta E_{gas} = \Delta E_{ele} + \Delta E_{vdw}$) and the solvation free energies ($\Delta G_{solv} = \Delta G_{PB} + \Delta G_{NP}$).[S10]

The polar term of ΔG_{solv} (ΔG_{PB}) was calculated according to the Poisson-Boltzmann (PB) approach,[S11] and the non-polar contribution to the solvation energy was calculated as $\Delta G_{NP} = \gamma$ (SASA) + β, where $\gamma = 0.00542$ kcal/Å^2, $\beta = 0.92$ kcal/mol, and SASA is the solvent-accessible

surface calculated with the MSMS program.[S12] The normal-mode analysis approach was finally applied to 20 MD frames for the calculation of the entropic term ($-T\Delta S$).[S13] All of the enthalpic, entropic and total free energies of binding were then normalized per-charged spermine group (ΔH_{bind}, $-T\Delta S_{bind}$ and ΔG_{bind}, Table 1 in the paper) to allow a direct comparison between the different families and generations of dendrons.

Per-residue decomposition

We performed a per-residue decomposition of the receptor/ligand interaction energy to explore the uniformity of the binding interaction at the dendron-DNA interface. With this procedure it was possible to quantify the affinity of each residue of the dendron for the nucleic acid. Our previous study on Newkome-type spermine dendrons[S2] demonstrated that the binding between positive charges of the spermine units and negative charged P atoms within the DNA strands are orders of magnitude higher than the total contribution given by the other residues that compose the dendrons. All the binding affinity is consequently focussed on the surface SPM ligands. Table S2 reports contributions of each of the SPM units to the binding for the all the systems of interest (data for the **3b**-dendrons were taken from our prior publication).[S2] Each single SPM ligand is identified by a numerical index.

The energetic components reported in Table S2 can be defined by Eq. (S3). These values represent the attraction expressed by each SPM unit toward the DNA. Negative energy values indicate attraction.

$$E = E_{complex} - (E_{dendron} + E_{DNA}) \quad \text{(S3)}$$

The gas-phase energies (E_{gas}) for each residue are composed of electrostatic and van der Waals *in vacuo* interaction contributions (E_{ele} and E_{vdw}, respectively) according to Eq. (S4).

$$E_{gas} = E_{ele} + E_{vdW} \quad \text{(S4)}$$

The *in vacuo* gas-phase energy for each residue (E_{gas}) is then corrected for solvation to give the total energy E_{tot}. Since the Poisson-Boltzmann solvation methodis not supported by the *mm_pbsa.pl* script of AMBER 10 does not support for residue energy decomposition, we adopted the Generalized Born method to correct the gas-phase energies for solvation. Energy decomposition for non-polar contributions to desolvation was calculated with the LCPO method.[S14] However, the trends from the two approaches are in excellent agreement, and this deconvolution approach is particularly useful as it allows us to determine the relative binding effects of each individual residue, and from this, the level of interaction uniformity at the binding interface.

Table S2 Interaction energies (E_{tot}) determined for individual SPM residues of the **2b**- and **3b**-dendrons interacting with DNA at 150 mM NaCl. E_{tot} represents the total *in vacuo* energy after the correction for salvation and are expressed in kcal mol^{-1}.

	G1-2b	**G2-2b**	**G3-2b**	**G1-3b**[b]	**G2-3b**[b]
SPM[a]	E_{tot} (kcal mol^{-1})	E_{tot} (kcal mol^{-1})	E_{tot} (kcal mol^{-1})	E_{tot} (kcal mol^{-1})	E_{tot} (kcal mol^{-1})
1	**-23.7±2.0**	-14.5±2.4	-8.9±2.3	-11.8±2.0	**-18.3±1.7**
2	**-20.7±3.5**	-10.0±3.1	**-16.1±2.2**	**-23.1±4.0**	**-29.4±3.5**
3		**-22.3±1.3**	**-24.1±2.7**	**-20.7±3.2**	**-28.9±2.9**
4		**-18.4±2.3**	**-22.2±2.7**		**-36.1±5.5**
5			-7.9±0.4		**-23.6±2.5**
6			**-24.0±1.8**		-9.5±0.4
7			**-22.1±2.4**		**-18.1±3.4**
8			**-20.5±3.1**		-9.7±1.5
9					**-18.4±2.1**
Avg.±SD[c]	-22.2±2.1	-20.4±2.8	-21.5±3.0	-21.9±1.7	-24.7±7.7

[a] Interaction energies E_{tot} are reported for all the SPM residues (identified by numbers in column 1). [b] E_{tot} values for **G1-3b** and **G2-3b** complexes were calculated in our previous work.[S2] [c] Mean E_{tot} (Avg) and the related standard deviation (SD) are calculated over the SPMs that

actively participate to the binding (E_{tot} < -15 kcal mol^{-1} – evidenced in bold). SD values reflect the uniformity of binding.

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