

SUPPORTING INFORMATION

Enantiospecific kinking of DNA by partially intercalating metal complex

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Material and Methods

Molecular Dynamic: Preparation and Simulation protocols

All Molecular Dynamics (hereafter MD) simulations were performed with Amber11 software package [1]. FF-10 (in particular ff99bsc0 [2]) parameters were used for DNA, GAFF parameters [3] – for Λ and Δ -[Ru(phen)₃]²⁺, excluding parameters of the ruthenium(II) ion coordination sphere: Ru-N bonds, Ru-N-C and N-Ru-N angles, and all torsion angles, which involve ruthenium. These additional parameters, compatible with GAFF force fields to be used with AMBER energy functional form, were calculated analogously to the procedure described in [4, 5], values given in the table S1. RESP charges [6] and geometry optimization of [Ru(phen)₃]²⁺, as well as Ru(II)-coordinating sphere parameters were obtained with Gaussian09 software package [7] using B3LYP functional [8-10] with LANL2DZ basis set [11], phenanthroline ligands were also calculated with B3LYP/6-31G* for comparison. The prep files of Λ and Δ -[Ru(phen)₃]²⁺ are available upon request.

Unrestrained MD simulations, aiming to find stable geometries of DNA-[Ru(phen)₃]²⁺ complexes, starting from the “pre-intercalated” state at the DNA minor groove: peripheral hydrogen atoms of the interacting phen-ligand were overlapping, when viewed from top, with the O2 and C2 atoms of A-T base pairs, or O2 and N2 atoms of G-C base pairs, forming potential intercalation pocket, were performed according to the following protocol. The system (DNA-[Ru(phen)₃]²⁺ complex, neutralized by sodium ions and solvated by 10 Å octahedron of explicit TIP3P waters [12]) was initially minimized by 1000 steps of steepest descent followed by 1000 steps of conjugate gradient, followed by fast heating (50 ps) from 0 to 300 K with the Langevin thermostat [13] temperature control scheme with collision frequency of 2 ps⁻¹, with harmonic restraints of 20 kcal/mol/Å² on the heavy atoms of the solutes, performed in constant volume. The restraints then were gradually reduced to zero in a series of equilibration runs of 100 ps each, at constant pressure (1 bar) and temperature (300 K) sustained using Langevin thermostat but with collision frequency of 1 ps⁻¹. Productive MD trajectories were recorded at constant pressure and various temperatures. An integration time step of 2 fs was used and all bond lengths involving hydrogen atoms were constrained using SHAKE [14]. Long-range interactions were treated using the PME approach with a 9 Å direct space cut-off.

Table S1. MD parameters (to be used with AMBER GAFF force fields) of Ru(II)-coordinating sphere, atom types: ru, n_x, n_y and n_z correspond to the atom names given on the figure S1, “c_a” – aromatic carbon atom type, “h_a” – hydrogen atom attached to aromatic carbon.

Bond parameters: force constant in kcal/mol*Å ² and equilibrium bond length in Å				
[n _x n _y n _z]-ru	180.0	1.96		
[n _x n _y n _z]-c _a	440.0	1.34		
Angle parameters: force constant in kcal/mol*rad ² and equilibrium bond angle in degrees				
[n _x][n _y][n _z]-ru-[n _x][n _y][n _z]	16.4	180		
[n _x n _z]-ru-[n _y]; [n _x n _y]-ru-[n _z]; [n _y n _z]-ru-[n _x]	52.4	91		
ru-[n _x n _y n _z]-c _a	66.9	123		
Torsion parameters: 1 st position – multiplication factor, 2 nd – barrier height (kcal/mol) divided by a factor of 2; 3 rd – phase shift angle in the torsional function; 4 th – periodicity of the torsional barrier.				
ru-[n _x n _y n _z]-c _a -c _a	1	1.205	180.0	-2.0
ru-[n _x n _y n _z]-c _a -c _a	1	-1.405	180.0	1.0
[n _x n _z]-ru-n _y -c _a	1	-0.125	180.0	4.0
ru-[n _x n _y n _z]-c _a -h _a	1	5.269	180.0	2.0
ru-[n _x n _y n _z]-c _a -c _a	1	5.205	180.0	-2.0
A and B parameters of the van der Waals term				
ru		2.34	0.438	

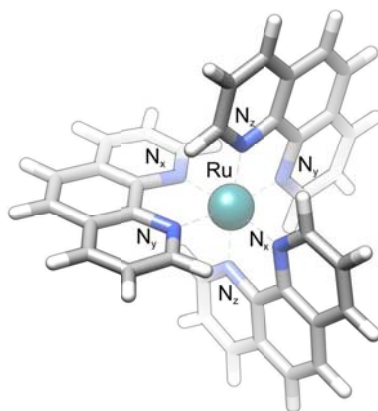


Fig S1. 3-D structure of Δ -[Ru(phen)₃]²⁺, opposite, “cross-ruthenium”, nitrogen atoms of the phenanthroline ligands were assigned to N_x, N_y and N_z atom types.

Subsequent set of MD simulations, aimed to explore conformational space of binding associations of [Ru(phen)₃]²⁺ to DNA by testing 4 different sequences: (GC)₆, (GC)₂GTAC(GC)₂, (GC)₂ATAT(GC)₂ and GCG(AT)₃CGC, performed with a steered MD approach coupled to Replica-exchange MD. During the 1st nanosecond, using steered MD setup, [Ru(phen)₃]²⁺ was softly pulled to DNA (force constant of 0.05 kcal/mol/Å²). The pulling condition was the distance between the Ru(II) and C4* (of the sugars of DNA bases forming potential intercalation pocket) to be 9 Å. This criterion would be satisfied for both association geometries: groove binding and intercalative binding, and thus does not bias the final complex geometries to any of the binding configurations. Subsequent

6 ns were recorded at unrestrained MD conditions coupled to replica exchange MD for better sampling of the conformational space, allowing the metal complex to “choose” by itself the mode of binding. Taking into account the properties of DNA, as well as that all simulations were performed with explicit solvent model, the temperature span was only 9 degrees, from 300 to 309.5 K with a temperature step of 0.5 K, resulting in total 20 replicas for each of combinations of the DNA sequence and the Ru(II)tris(phen) enantiomer.

Those of trajectories that resulted in stable association of $[\text{Ru}(\text{phen})_3]^{2+}$ were subjected to the MMPBSA analysis [15] of association free energies, performed with MMPBSA.py utility of AmberTools [1]. For the Λ - $[\text{Ru}(\text{phen})_3]^{2+}$ the percentage of stable trajectories was evenly distributed among the 4 DNA sequence resulting in 50-60% of “successful” trajectories, while for the Δ - $[\text{Ru}(\text{phen})_3]^{2+}$ the distribution was uneven: $(\text{GC})_6$ – 45%, $(\text{GC})_2\text{GTAC}(\text{GC})_2$ – 25%, $(\text{GC})_2\text{ATAT}(\text{GC})_2$ – 30% and $\text{GCG}(\text{AT})_3\text{CGC}$ – 45%. The results presented in the Table 1 (main text) were averaged for each of the enantiomers over all stable trajectories for all 4 DNA sequences. The resulting association energies were calculated according to the formulas:

$$\Delta G_{\text{bind}} = \Delta H - T\Delta S \approx \Delta E_{\text{MM}} + \Delta G_{\text{solvation}} - T\Delta S$$

$$\Delta E_{\text{MM}} = \Delta E_{\text{internal}} + \Delta E_{\text{Electrostatic}} + \Delta E_{\text{VDW}}$$

$$\Delta G_{\text{solvation}} = \Delta G_{\text{PB}} + \Delta G_{\text{SA}}$$

MMPBSA Calculations

The gas-phase interaction energy between the DNA and $[\text{Ru}(\text{phen})_3]^{2+}$, ΔE_{MM} , is the sum of electrostatic and van der Waals interaction energies. The solvation free energy $\Delta G_{\text{solvation}}$ is the sum of polar (ΔG_{PB}) and nonpolar (ΔG_{SA}) parts. The ΔG_{PB} term was calculated by solving the finite-difference Poisson-Boltzmann equation using the grid spacing of 0.5 Å. For Ru(II) compound as well as DNA the van der Waals radii, specified by corresponding force field were used. The value of the exterior dielectric constant was set to 80, and the solute dielectric constant was set to 2. For the calculations of ΔE_{MM} , ΔG_{PB} , and ΔG_{SA} , 1200 snapshots evenly extracted from the “successful” MD trajectory of complex from 1 to 7 ns of unrestrained REMD were used.

The Entropy Calculations

The normal-mode analysis was performed to evaluate the conformational entropy change upon Ru(II)tris(phen) binding ($-T\Delta S$) using the nmode program in Amber11 [1]. The normal-mode analysis is more computationally expensive than the actual MMPBSA calculation, we only considered the residues within a 10 Å sphere centred at the intercalation, corresponding residues were retrieved from each of the MD snapshots, all open valences were saturated by adding hydrogen atoms using tleap utility of AmberTools. Then, each structure was minimized for 5000 steps using a distance-dependent dielectric of $4r_{ij}$ (r_{ij} is the distance between two atoms) to mimic the solvent dielectric change from the solute to solvent until the root-mean-square of the elements of the gradient vector was less than 10^{-2} kcal/mol*Å. To reduce the computational demand, 125 snapshots were taken from 1 to 7 ns to estimate the contribution of the entropy to binding. The final

conformational entropy was obtained from the averaging over all snapshots. It should be noted that, different from the other energy terms, the entropy contribution is computed in a way independent of the internal dielectric constant.

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