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Free energy calculations of counterion partitioning between DNA and chloride solutions

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Experimental

MD simulation protocol. We focused on the competitive Na^+ vs. K^+ ionic distribution around canonical B-form of a 16-base-pair DNA oligomer $[d(CGAGGTTTAAACCTCG)]_2$,[1] in an aqueous/salt solution. We built an ideal DNA chain model and carried out all-atom MD simulations in explicit, TIP3P water[2] using the AMBER 8.0 suite of programs[3] and the Amber Parm99 force field.[4] To compute the free energy cost of moving a K^+ ion from a DNA solution to a bulk solution, and simultaneously, bringing a Na^+ ion from the bulk solution to the DNA solution we prepared the following two starting systems: 1) the DNA oligomer in a mixture of 15 neutralizing Na^+ and 15 neutralizing K^+ ions and additional 0.06 M of both NaCl and KCl salts (7 additional Na^+ ions, 7 additional K^+ ions, and 14 Cl^- ions); and 2) the bulk system comprised of 7 Na^+ ions, 7 K^+ ions, and 14 Cl^- ions. Both systems were further solvated in more than 6000 TIP3P water molecules in a rectangular box, having dimensions 50, 50 and 86 A. In the main text we refer to the above systems as **1** and **2**, respectively. Two DNA segments from neighboring periodic images in **1** were at least 30 A apart. The overall number of atoms in each system was ~19500 in the periodic box. We used a multistage equilibration process, reported by Orozco and coworkers,[5] to equilibrate all starting structures. The subsequent production runs for each MD in **1, 2** were carried out at constant temperature (300 K) and pressure (1 bar) using the Langevin temperature equilibration scheme (see AMBER 8 manual), the "weak-coupling" pressure equilibration scheme, [6] and periodic boundary conditions.

Harmonic positional restraints of $5 \cdot 10^{-5}$ kcal/mol/A^2 were applied to all DNA atoms in **1** to prevent a large angle rotation of the macromolecule in the anisotropic simulation box, which, in turn, would have lowered the separation among DNA segments in neighboring

periodic cells. These restraints were extremely weak, allowing atomic thermal fluctuations on the order of 10 A around the reference atomic positions, thus, they did not influence the conformational dynamics of the stiff DNA oligomer.

The translational center-of-mass motion was removed every 2 ps. We used the SHAKE algorithm[7] to constrain all bonds involving hydrogens, allowing to perform all MD simulations with an increased time step of 2 fs without any instability. Particle Mesh Ewald method[8] was used to treat long-range interactions with a 9 A nonbonded cutoff. The production runs for simulations **1** and **2** were carried out for 60 ns and 30 ns, respectively, to ensure the equilibration of ions. It was shown in prior works[9,10] that 50 ns MD was enough to equilibrate the Na^+ atmosphere around DNA in a smaller system comprised of ~16000 atoms. Given the slightly larger size of our system (~ 19500 atoms), we used extra 10 ns of MD to ensure equilibration. A twice as shorter simulation run in **2** was carried out, since the absence of polyion allows much faster ionic equilibration.

As indicated in the main text, we also prepared and simulated system **1**, according to the above described MD protocol, using Charmm27 force-field.[11,12] We used VMD, a graphical program,[13] for simulation setup and NAMD,[14] a MD simulation package, to carry out the simulations. The obtained results were then compared to the results obtained from the corresponding Amber simulations.

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