Interaction Energies and Dynamics of Alkali and Alkaline-Earth Cations in Quadruplex-DNA-Structures

Jutta Töhl, Wolfgang Eimer

Universität Bielefeld, Physikalische Chemie I, D - 33615 Bielefeld, Germany. (jutta@chep122.uni-bielefeld.de)

Abstract

We have investigated the nonbonded interaction energies and dynamical properties of different types of cations in quadruplex DNA structures using the GROMOS force field [1]. Quadruplex structures consist of planar guanine-quartets stacking together and causing the formation of a chan-nel, large enought to enclose several cations (Figure 1). In recent years many experimental studies have indicated a prefered formation of this unusually stabel complexes with K^+-ions. However, the high selectivity of this cation has not yet been understood [2].

To determine the most stable coordination sites and the mobility of cations, we have calculated the pair potential energy of alkali and alkaline-earth cations along the heli-
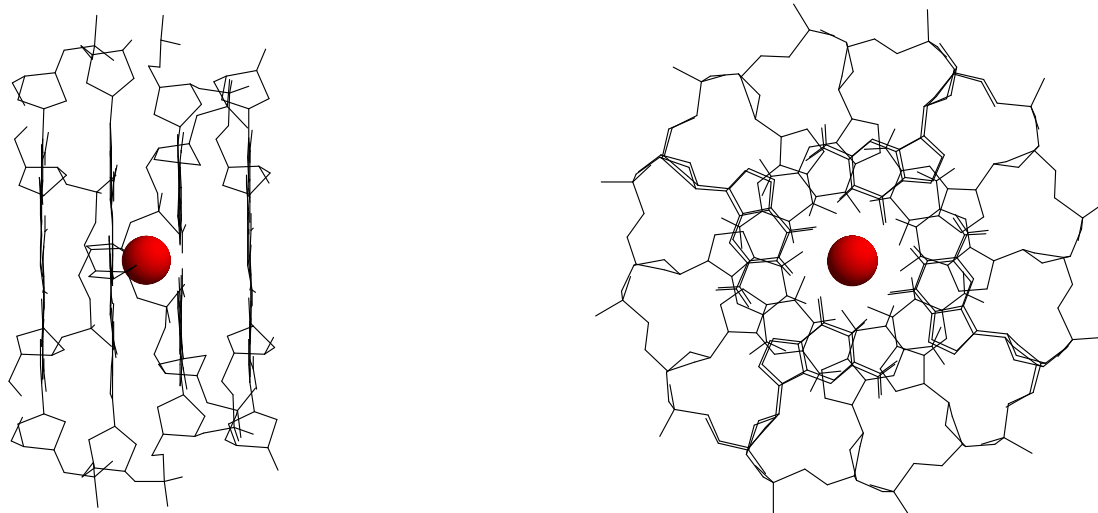

Figure 1. *Wireframe presentations of the d[GGGG]$_4$ quadruplex structure. View perpendicular to the helical axis (left) and in the helical axis (right).*
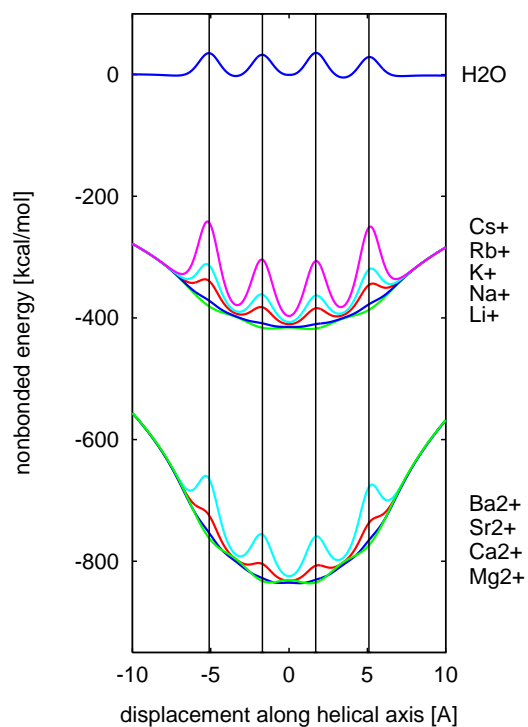
Figure 2. *Pairwise interaction of alkali, alkaline-earth metal ions, and water with all DNA-atoms, along the helical axis.*

Figure 3. *Pairwise interaction of K⁺ (red sphere) of different water configurations (1 to 4). Two additional potassium cations in the neighbouring cages were considered (black spheres). Simulation-period: ca. 2ps.)*

cal axis of a model quadruplex structure (Figure 2). Our force field calculations indicate that small ions like Li⁺, Na⁺, Mg²⁺ and Ca²⁺ are free to move throught the channel. In contrast, for K⁺ and larger ions a high potential barrier appears, located in the plane of the tetramer unit. These findings are in agreement with data from X-ray crystallography, indicating that K⁺ cations are located between two planes while Na⁺ ions also can occupy coordination sites in the G-quartet plane.
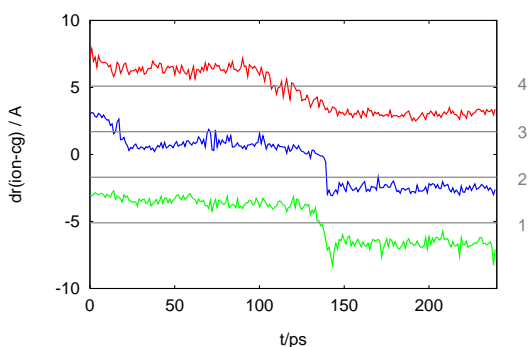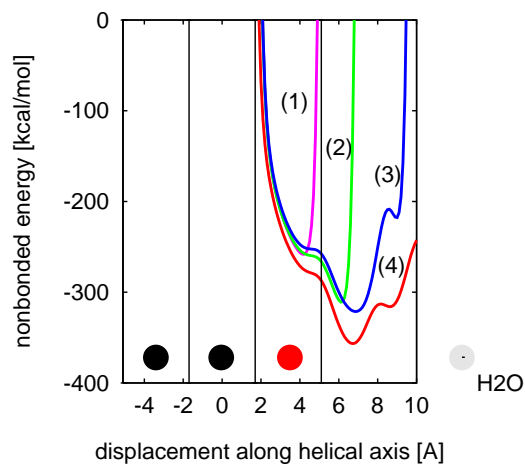
Considering solvent atoms in our calculations leads to the observation that a cation at the end of the quadruplex strongly interacts with one water molecule located near the entrance of the cage. Snapshots taken at different times of the MD simulation provide configurations which differ mainly in the position of this complexing water molecule. Moving away from the entrance of the cage causes a significant decrease of the potential barrier for K⁺ and smaller 'cage cations' (Figure 3). For the larger ions the potential barrier is much higher than the thermal energy (not shown), preventing the cations from leaving and entering the cage.

This conclusion is in agreement with results from our MD simulations. We followed the dynamics of different cations. While K⁺ is able to leave as well as to re-migrate into the channel (movie I), this was not observed for other
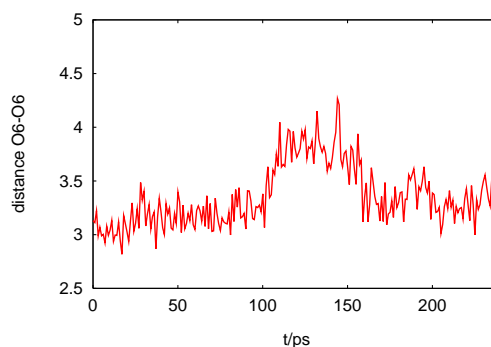

Figure 4. *z-component of the ion fluctuation about the center of geometry. The horizontal lines indicates the tetrameric planes.*

Figure 5. *Averages distance of O6 atoms in the fourth plane*

types of cations. Figure 4 shows the time history of the positional fluctuations of potassium along the helical axis, and in Figure 5 we have monitored the distance between the O6-oxygen atoms of the outer G-quartet. It becomes clearly evident that the cation movement through the planes is correlated with the dynamic behaviour of the tetrameric planes. When the K^+-ion penetrates the tetrameric unit to enter the quadruplex, the O6-O6-distance - a measure of size of the hole of the plane - increases. After a while the cation has reached the cage position and the G-quartet contracts to the initial value. That means the tetrameric planes perform a kind of breathing motion.

For lithium ions we find a much higher mobility of the cation within the quadruplex channel. Two of three ions are leaving the cage instantaniously (not shown).

Another indication of the experimentally observed much weaker complexation tendency of quadruplexes with lithium is the change in the distances of planes (a measure for the cage size) with time. While in the case of potassium the distance of planes is nearly the same for all three cages, for lithium the central occupied cage is much smaller than the cage in the starting structure, indicating that the DNA structure has to adjust its conformation to the cation size. On the other side the outer unoccupied cages are much greater and less stable. Due to this cation induced

quadruplex deformation we observe an unwinding of the DNA-structure in the presens of lithium ions at longer simulation periods (400 ps).

Movie

The movie shows the dynamics of the model quadruplex $d[GGGG]_4$ and the potassium ions (yellow) over a simulation period of 11 ps. Two water molecules at the ends of the channel are considered (dots indicates the van der Waals radii). At the end of the movie one ion is leaving the channel (see Figure 4), while the water molecule is displaced from the channel exit. Then the ion, which occupies the central cage jumps into the empty outer cage.

References

1. van Gunsteren, W.F.; Berendsen, H.J.C. Groningen Molecular Simulation (GROMOS) Library Manual; University of Groningen, Groningen **1986**.
2. Williamson, J.R. *Ann. Rev. Biophys. Biomol. Struct.* **1994**, *23*, 703 - 730.