Ion Selectivity at the Internal Cavity Site of G-Quadruplexes: 
a Quantum-Chemical Approach

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In the telomeric part of the chromosome, which is crucial for the protection of the genetic
code,1 quadruplexes occur which are composed of stacked guanine quartets. The guanine
bases in the latter are essentially coplanar and interact through hydrogen bonds. The
quadruplexes are furthermore stabilized by the presence of monovalent ions, such as K+ and
Na+, in between the layers of quartets with a preference for K+ under physiological
conditions (see Figure).2

We report quantum-chemical calculations based on dispersion-corrected
density functional calculations (DFT-D3) of bi-layered G-quadruplex
(GQ) structures interacting in turn with K+, Na+, Rb+, Li+ or Cs+
at the channel coordination site. The model includes bi-layered GQs
provided with sugar-phosphate backbone, interacting in turn with
Li+, Na+, K+, and Rb+. The computational studies were performed
for the conditions in the gas phase and in water described with an
implicit solvent model. The simulations in water reproduced the
consolidated experimental channel site cation affinity sequence4
K+ > Na+ > Li+.

With our quantitative Kohn-Sham molecular orbital (MO) and corresponding energy
decomposition analyses (EDA), we have been able to understand the cooperativity of the
hydrogen bonds.5,6 In this study, we analyzed the interaction of the alkali cation with the
guanine bases and explain the experimental order of affinity in guanine quadruplexes.

References
1. Quadruplex Nucleic Acids, S. Neidle, S. Balasubramanian, Eds; RSC Publishing,
2. F. Zaccaria, G. Paragi, C. Fonseca Guerra, in preparation
Chem. Acc. 2010, 125, 245-252
4. F. C. Marincola, A. Virno, A. Randazzo, F. Mocci, G. Saba, A. Lai, MRC, 2009, 47, 12,
1036–42.
12612-12622.
1592