



**HAL**  
open science

**Channeling Through Two Stacked Guanine Quartets of One and Two Alkali Cations in the Li + , Na + , K + and Rb + Series. Assessment of the Accuracy of the SIBFA Anisotropic Polarizable Molecular Mechanics Potential**

Nohad Gresh, Sehr Naseem-Khan, Louis Lagardère, Jean-Philip Piquemal, Judit E. Sponer, Jiri Sponer

► **To cite this version:**

Nohad Gresh, Sehr Naseem-Khan, Louis Lagardère, Jean-Philip Piquemal, Judit E. Sponer, et al.. Channeling Through Two Stacked Guanine Quartets of One and Two Alkali Cations in the Li + , Na + , K + and Rb + Series. Assessment of the Accuracy of the SIBFA Anisotropic Polarizable Molecular Mechanics Potential. Journal of Physical Chemistry B, 2017, <10.1021/acs.jpcc.7b01836>. <hal-01502376>

**HAL Id: hal-01502376**

**<https://hal.sorbonne-universite.fr/hal-01502376v1>**

Submitted on 5 Apr 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

1  
2  
3  
4  
5 **Channeling Through Two Stacked Guanine Quartets of One and Two Alkali**  
6 **Cations in the Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup> and Rb<sup>+</sup> Series. Assessment of the Accuracy of the SIBFA**  
7 **Anisotropic Polarizable Molecular Mechanics Potential.**  
8  
9

10  
11 <sup>1</sup>Nohad Gresh\*, Sehr Naseem-Khan, Louis Lagardère, Jean-Philip Piquemal

12 <sup>2</sup>Judit E. Sponer,<sup>2,3</sup> Jiri Sponer\*<sup>2,3</sup>  
13  
14  
15  
16  
17

18 <sup>1</sup>Laboratoire de Chimie Théorique, Sorbonne Universités, UPMC, UMR7616 CNRS, Paris,  
19 France  
20

21 <sup>2</sup>Institute of Biophysics, Academy of Sciences of the Czech Republic, Kralovpolska 135, 612  
22 65 Brno, Czech Republic  
23

24 <sup>3</sup> CEITEC – Central European Institute of Technology, Masaryk University, Campus  
25 Bohunice, Kamenice 5, 625 00 Brno, Czech Republic  
26  
27  
28

29 e-mail addresses: [gresh@lct.jussieu.fr](mailto:gresh@lct.jussieu.fr) (NG); [sponer@ncbr.muni.cz](mailto:sponer@ncbr.muni.cz) (JS).  
30  
31

32 **Abstract.**

33 Stacking of guanine quartets (GQ) can trigger the formation of DNA or RNA quadruple  
34 helices, which play numerous biochemical roles. The GQs are stabilized by alkali cations,  
35 mainly K<sup>+</sup> and Na<sup>+</sup>, which can reside in, or channel through, the central axis of the GQ stems.  
36 Further, ion conduction through GQ wires can be leveraged for nanochemistry applications.  
37 G-quadruplex systems have been extensively studied by classical molecular dynamics (MD)  
38 simulations using pair-additive force fields or by quantum-chemical (QC) calculations.  
39 However, the non-polarizable force fields are very approximate while QC calculations lack  
40 the necessary sampling. Thus, ultimate description of QG systems would require long-enough  
41 simulations using advanced polarizable molecular mechanics (MM). However, to perform  
42 such calculations, it is first mandatory to evaluate the method's accuracy using benchmark  
43 QC. We report such an evaluation for the SIBFA polarizable MM, bearing on the channeling  
44 (movement) of an alkali cation (Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, or Rb<sup>+</sup>) along the axis of two stacked G quartets  
45 interacting with either one or two ions. The QC energy profiles display markedly different  
46 features depending upon the cation but can be retrieved in the majority of cases by the SIBFA  
47 profiles. An appropriate balance of first-order (electrostatic and short-range repulsion) and  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 second-order (polarization, charge-transfer and dispersion) contributions within  $\Delta E$  is  
6 mandatory. With two cations in the channel, the relative weights of the second-order  
7 contributions increase steadily upon increasing the ion size. In the G8 complexes with two  $K^+$   
8 or two  $Rb^+$  cations, the sum of polarization and charge-transfer exceeds the first-order along  
9 terms for all ion positions.  
10  
11  
12  
13  
14  
15  
16  
17

### 18 **Introduction.**

19 The present study bears on the channeling of one and two alkali cations between two stacked  
20 guanine quartets (GQ). It is motivated by the growing evidence for the involvement of G  
21 quartets in a wealth of biological events [for a recent review, 1]. Thus GQs promote the  
22 formation of quadruple helices in telomeric DNA<sup>2</sup> and in G-rich sequences in the genome<sup>3,4</sup>  
23 Evidence is mounting for the involvement in GQs in human genome regions that are essential  
24 for replication, such as *c-myc*<sup>5</sup>, *bcl-2*<sup>6</sup>, *c-kit*<sup>7</sup>, VEGF<sup>8</sup>, and Refs. therein] but also in viruses<sup>9</sup>,  
25 <sup>10</sup>. GQs thus constitute an emerging target for the design of novel chemotherapeutic molecules  
26 which can stabilize the quadruple helix and inhibit telomerase or interfere with transcription  
27 <sup>11-15</sup>. GQs are endowed with electron transport<sup>16, 17</sup>, photoelectronic properties of potential  
28 interest in nanochemistry<sup>18, 19</sup> while GQ-based nanowires are endowed with ion-conducting  
29 properties<sup>20, 21</sup>.  
30  
31

32 GQ quadruple helices have been investigated by X-ray crystallography<sup>22, 25</sup> and Refs. therein,  
33 high-resolution NMR<sup>23, 24, 26</sup>, and molecular dynamics<sup>27-30</sup>; for a review, see Ref. 31. G-  
34 quartets have been studied in several high-level ab initio quantum chemistry (QC)  
35 calculations bearing on their electronic and cation-binding properties<sup>32, 33</sup>, the ranking of  
36 competing conformers<sup>34</sup> and the cooperativity of their self-associations<sup>35, 36</sup>. Extensions of  
37 QC analyses to novel halogenated derivatives of deazaguanine and their complexes with  $Na^+$   
38 and  $K^+$  were recently reported<sup>32</sup>.  
39  
40  
41

42 The alkali cations  $Na^+$  and  $K^+$  can act as important contributors to the stability of stacked G  
43 quartets, owing to their propensity to bind in-between two successive GQs. GQ-containing  
44 quadruple helices can interconvert between several alternative forms with short-lived  
45 intermediates, the detection of which can evade direct experimental measurements. Long-  
46 duration molecular dynamics could be ideally suited for such explorations and have already  
47 provided insight to unravel candidate interconversion pathways<sup>30</sup>. There are, however  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 acknowledged limitations to ‘classical’ molecular mechanics (MM) force-fields for such  
6 applications, which could be magnified in the presence of metal cations. Thus a recent study  
7 investigated the channeling of a monovalent cation along the Z axis of two and three stacked  
8 G quartets, in the presence of another cation fixed along this axis at 1.1 Å above the topmost  
9 quartet<sup>37</sup>. The MM energy profile differed significantly from the DFT-D3 one upon moving  
10 the cation closer to the fixed one. This was ascribed to the lack of an explicit polarization  
11 contribution ( $E_{\text{pol}}$ ): a raise of the inter-cation electrostatic repulsion ought to be, to a  
12 significant extent, compensated for by a concomitant increase of  $E_{\text{pol}}$ , since the polarizing  
13 field exerted by both cations on the G quartets increases as the two cationic charges get closer  
14 together, yet this contribution is absent from classical MM. This then raises an essential issue:  
15 how well, by contrast, would anisotropic polarizable molecular mechanics (APMM) profiles  
16 fare with respect to the QC profiles? Owing to the highly polar and polarizable nature of  
17 guanine, cation-bound G quartets constitute a very revealing benchmark for the accuracy of  
18 APMM procedures. Their stabilization involves the interplay of multiply H-bonded, stacked,  
19 and cation-ligand interaction and the onset of non-additivity of the total intermolecular  
20 interaction energies ( $\Delta E$ ). Evaluation of the APMM accuracy in light of these tests is also part  
21 of the construction of polarizable potentials for DNA and RNA<sup>38</sup> owing to the prevalence and  
22 constant interplay of such effects. The present GQ tests will bear on the SIBFA APMM  
23 procedure<sup>39</sup> and is a continuation of two preceding works. The first bore on the calibration of  
24 the alkali cation series ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Rb}^+$ ,  $\text{Cs}^+$ ) and QC validation tests of a series of their  
25 polyligated complexes<sup>40</sup>. The second bore on several stacked and H-bonded complexes of  
26 cytosine and guanine<sup>41</sup>. The first polarizable molecular mechanics study bearing on the  
27 selective entrapment of alkali cations between two G quartets was a SIBFA study published in  
28 1986<sup>42</sup>. Each quartet was then however considered as one entity, while in the present study  
29 the individual entities are the bases and the cations.

30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
A CPK representation of the two stacked G quartets and of the channeling cation in its  
successive positions are represented in Figure 1. The unmoving cation is on the top of the Z  
axis. Throughout this study we retain for both QC and SIBFA computations the idealized  
stacked GQ geometry constructed in Ref. [37]. Owing to the validation purpose of the present  
study, relaxing the geometries by energy-minimization or molecular dynamics would be  
unrealistic and untimely, as it would ignore the averaging effect of additional stacked G  
quartets, of other channeling cations and the effects of the environments: this will be very

1  
2  
3  
4  
5 continuation of the present work. Note that the geometries taken from ref. [37] are very well  
6 prepared and should be sufficient for the purpose of the benchmark computations.

7  
8 The organization of this paper is as follows. We first consider one G quartet and compare  
9 SIBFA and QC results at both HF and DFT-D3 levels. GQ is emblematic of cyclic, multiply  
10 H-bonded complexes with strong anticipated cooperativity. Energy Decomposition Analyses  
11 (EDA) performed at the HF level will enable to compare the summed values of each  
12 individual energy contribution in the six guanine dimers to its value in the quartet. We thus  
13 trace back the share of each contribution of  $\Delta E(QC)$  in the total cooperativity, and how well it  
14 is reflected in the context of the SIBFA. Another test bears on the stacking of two half-  
15 quartets. We retain in the first quartet one H-bonded guanine dimer, denoted as G1-G2, and in  
16 the second quartet one of the two H-bonded dimers with maximal overlap with G1-G2,  
17 denoted as G1'-G2'. This will enable to evaluate non-additivity in mixed H-bonded/stacked  
18 complexes: could cooperativity now possibly revert into anticooperativity? Such analyses are  
19 limited to four guanines as larger-sized complexes are not amenable to EDA with large basis  
20 sets.  
21

22 We next consider the complex of two stacked G quartets. It involves two extensive surfaces,  
23 each guanine of the first quartet being involved in non-remote stacking interactions with two  
24 guanines of the second quartet, whence a total of eight such interactions. Two stacked G  
25 quartets total twenty-eight simultaneous H-bonded or stacking guanine-guanine interactions,  
26 whether close or remote. Could an acceptable match of  $\Delta E(SIBFA)$  to  $\Delta E(QC)$  still be  
27 obtained?  
28

29 Following these preliminary validations, we consider the channeling of one alkali cation,  $Li^+$ ,  
30  $Na^+$ ,  $K^+$ , and  $Rb^+$  along the Z axis. We follow the same trajectory as in the original paper<sup>37</sup>. It  
31 starts from a  $Z = -1.1 \text{ \AA}$  position below the first quartet and ends at  $Z = 2.5 \text{ \AA}$  above it, namely  
32  $0.8 \text{ \AA}$  below the second quartet. The same trajectory is recomputed, now in the presence of a  
33 second cation, the position of which is fixed at  $1.1 \text{ \AA}$  above the second quartet. The shortest  
34  $M^+ - M^+$  distance of approach is thus  $1.9 \text{ \AA}$ . The first series of SIBFA vs. QC comparisons are  
35 reported at the HF level and with HF-derived multipoles and polarizabilities for SIBFA  
36 calculations. The second series of comparisons is at the DFT-D3 level and, for the SIBFA  
37 calculations, with DFT-derived multipoles and polarizabilities and the inclusion of an explicit  
38 dispersion contribution. We conclude with perspectives of MD applications to GQ-based  
39 channels and their alkali cation complexes.  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Procedure.**

**Quantum-Chemistry (QC) calculations.** The QC calculations used the cc-pVTZ(-f) basis set<sup>43, 44</sup> since the studied complexes on account of their sizes were not amenable to aug-cc-pVTZ(-f) calculations. A triple-dzeta basis set was used on K<sup>+</sup><sup>45</sup>. The Stuttgart effective core potential<sup>46</sup> was used on Rb<sup>+</sup>. Energy Decomposition Analyses (EDA) resorted to the RVS analysis due to Stevens and Fink<sup>47</sup> and coded in the GAMESS-US package<sup>48</sup>. Calculations at the correlated level used the B97-D3 energy functional augmented with the dispersion correction by Grimme et al.<sup>49</sup>. Some DFT calculations were also performed with the B3LYP functional<sup>50, 51</sup>. The DFT calculations were done with the G09 package<sup>52</sup>.

**SIBFA calculations.** In the SIBFA procedure<sup>39</sup>, the intermolecular interaction energy is computed as the sum of five contributions: electrostatic multipolar ( $E_{MTP*}$ ), short-range repulsion ( $E_{rep}$ ), polarization ( $E_{pol}$ ), charge transfer ( $E_{ct}$ ), and dispersion ( $E_{disp}$ )

$$\Delta E_{TOT} = E_{MTP*} + E_{rep} + E_{pol} + E_{ct} + E_{disp}$$

$E_{MTP*}$  is computed with distributed multipoles (up to quadrupoles) derived from the QC molecular orbitals precomputed for each individual molecule using the Generalized Multipole Analysis (GDMA) method by Stone<sup>53</sup>. It is augmented with a penetration term<sup>54, 55</sup>. The anisotropic polarizabilities intervening in the expression of  $E_{pol}$  are distributed on the centroids of the localized orbitals (heteroatom lone pairs and bond barycenters) using a procedure due to Garmer and Stevens<sup>56</sup>.  $E_{rep}$  and  $E_{ct}$ , the two short-range repulsions, are computed using representations of the molecular orbitals localized on the chemical bonds and on localized lone-pairs<sup>55, 57</sup>.  $E_{disp}$  is computed as an expansion into  $1/R^{**6}$ ,  $1/R^{**8}$ , and  $1/R^{**10}$ , and also embodies an explicit exchange-dispersion term<sup>58</sup>.

We have also calibrated the short-range cation-cation repulsion, as it was found that at shorter  $M^+-M^+$  distances, the sole electrostatic repulsion was insufficient. The calibration bore on the atom-pair multiplicative factor of  $E_{rep}$ , denoted  $PK_{IJ}$ , where I and J denote the atomic numbers of the two atoms concerned. It was done on the basis of EDA computations on the  $M^+-M^+$  diatomic complexes, to match the radial dependency of  $E_{rep}$  in a range of distances between 2.0 and 3.0 Å. The multiplicative factors are  $PK_{Li-Li}=1.0$ ,  $PK_{Na-Na}=9.0$ ,  $PK_{K-K}=300.0$ , and  $PK_{Rb-Rb}=685$ . Apart from this point, we use the same cation parameters as those derived in 2015<sup>40</sup>.

1  
2  
3  
4  
5 The multipoles and polarizabilities at the HF and DFT levels are those derived in the context  
6 of our above-mentioned study on the cytosine and guanine complexes <sup>41</sup>. The general  
7 parameters were those previously derived on the basis of EDA on model complexes with the  
8 aug-cc-pVTZ(-f) basis by Devereux et al. <sup>59</sup> with the automated I-NoLLS (Interactive,  
9 nonlinear least squares) procedure <sup>60</sup>. Following [El Khoury et al., submitted] we use an  
10 improved representation of the sp<sup>2</sup> lone pairs on O6 and of the sp lone pairs on N7 and N3,  
11 ‘smearing’ them partially on both sides of the guanine plane. The in-plane component of the  
12 N7 and N3 lone pairs retains an electron population of 1.45, while each out-of-plane  
13 component, extending the external bisector of the nitrogen perpendicular to the plane, has an  
14 electron population of 0.275. The in-plane component of each O6 sp<sup>2</sup> lone-pair retains an  
15 electron population of 1.70, and there are two smeared components each with an electron  
16 population of 0.30, above and below the C=O bond. Such populations, together with the  
17 internal coordinates of the smeared lone-pairs, were fit to improve the radial dependencies of  
18 E<sub>rep</sub>(SIBFA) compared to E<sub>exch</sub>(RVS) upon in- and out-of-plane variations of the approach of  
19 a Zn(II) probe to O6 and N7 [Naseem-Khan et al., to be published]. We denote as E<sub>1</sub> the sum  
20 of the two first-order contributions E<sub>C</sub> and E<sub>exch</sub> (QC) and E<sub>MTP</sub> and E<sub>rep</sub>(SIBFA), and by E<sub>2</sub>  
21 the sum of the two second-order contributions E<sub>pol</sub> and E<sub>ct</sub>.  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31

32 **Non-Covalent Interaction (NCI) analyses.** The NCI procedure <sup>61, 62</sup> is based on the study of  
33 the reduced density gradient as a function of density. It enables to visualize interaction zones  
34 between two molecules and gives access qualitatively to the magnitude of these interactions.  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Results.

### 1. Stabilization energies in the G quartet, the stacked half-quartet, and in two stacked G quartets.

a) *G quartet*. Tables 1 report the results of the QC and SIBFA intermolecular interaction energies at the HF and correlated levels respectively.

*HF results*. The RVS procedure enables to trace back the origin of cooperativity by comparing the value of each  $\Delta E$  contribution to the sum of its values in the six guanine dimers considered separately. The same comparisons are reported for SIBFA.  $\Delta E(\text{HF})$  is overestimated by  $\Delta E(\text{SIBFA})$  by 4.5 kcal/mol out of 50. This is due to both  $E_{\text{MTP}}$  and  $E_{\text{rep}}$  within  $E_1$ , each accountable for 2.1 kcal/mol out of app. 65 and 40 respectively. These overestimations occur in the four H-bonded dimers, amounting to 0.6 kcal/mol out of 16 and 10 for  $E_{\text{MTP}^*}$  and  $E_{\text{rep}}$ , respectively. These errors could appear of lesser importance, but each is multiplied by four upon passing to the quartet. Shortcomings of  $E_{\text{MTP}^*}$  could be due to instabilities in the GDMA procedure to derive distributed multipoles in the case of highly conjugated anionic ligands with diffuse functions, rendering them very sensitive to the choice of input parameters to derive them from the molecular orbital, namely the effective H radii and the switch function<sup>53</sup>. Towards deriving less sensitive multipoles, newly-emerging alternatives to GDMA are being considered, such as the Iterative Stockholder Analysis (ISA)<sup>63, 64</sup> and Gaussian Electrostatic Multipoles (GEM)<sup>65, 66</sup>. Their use will be reported elsewhere.  $E_{\text{rep}}$  is in turn impacted by the multipolar distribution as it has a prefactor which depends upon the monopolar charges of the interacting atoms. At present we move forward and leave aside these shortcomings. As shown below, upon passing to correlated levels, correlated multipoles afford a much closer match of SIBFA to QC than at the HF level. Furthermore,  $E_2(\text{SIBFA})$  gives a closer match to its RVS counterpart than  $E_1$ , and it is  $E_2$  that is responsible for the non-additivity of  $\Delta E$ ,  $\delta E_{\text{nadd}}$ , a critical element in the stacked G quartet-cation complexes. What is the amplitude of  $\delta E_{\text{nadd}}(\text{QC})$ , and could it be satisfactorily accounted for? Table 1 also reports the values of  $\Delta E$  and its contributions in each of the six guanine-guanine dimer complexes, denoted G1-G2 to G3-G4. There are four equivalent doubly H-bonded dimers, G1-G2, G1-G4, G2-G3, G3-G4, and two non H-bonded dimers, G1-G3 and G2-G4. The summed values correspond to four times the values of one H-bonded dimer plus twice that of a non H-bonded dimer. As in our previous papers, we compare  $E_{\text{pol}}(\text{RVS})$  to  $E_{\text{pol}}^*(\text{SIBFA})$ ,

1  
2  
3  
4  
5 as computed prior to iterating on the induced dipoles, and  $E_{\text{pol}}(\text{VR})$  to  $E_{\text{pol}}(\text{SIBFA})$ , after  
6 completion of the iterations.  $E_{\text{pol}}(\text{VR})$  is obtained as the difference between  $\Delta E(\text{HF})$  and  
7  $E_1(\text{RVS})$  and  $E_{\text{ct}}(\text{RVS})$ .  $\delta E_{\text{nadd}}(\text{SIBFA})$  of -9.2 kcal/mol is close to the  $\delta E_{\text{nadd}}(\text{QC})$  of -9.6  
8 kcal/mol. A close agreement is also found regarding polarization and charge-transfer. Thus  
9 for  $E_{\text{pol}}(\text{RVS})$  and  $E_{\text{pol}}^*$ ,  $\delta E_{\text{nadd}}$  amounts to -5.9 and -5.8 kcal/mol (respectively). It increases  
10 in magnitude for both  $E_{\text{pol}}(\text{VR})$  and  $E_{\text{pol}}(\text{SIBFA})$ , to -8.8 and -8.4 kcal./mol, respectively.  
11 Such increases were previously noted as signatures for cooperativity.  $E_{\text{ct}}(\text{RVS})$  is also clearly  
12 cooperative, even though its  $\delta E_{\text{nadd}}$  has a lesser magnitude (-0.8 kcal/mol in both QC and  
13 SIBFA). Such a result has precedents with the cyclic water pentamers and hexamers [57]. In  
14 these complexes, as with GQ, each monomer simultaneously acts as proton acceptor from one  
15 neighbor and a proton donor to the other.

16  
17  
18  
19  
20  
21  
22  
23  
24 *Correlated results (Table 2).*  $\Delta E_{\text{tot}}(\text{SIBFA})$  amounting to -68.8 kcal/mol has a much closer  
25 agreement with  $\Delta E(\text{B97-D3})$  amounting to -69.8 kcal/mol than with  $\Delta E(\text{B3LYP-D3})$   
26 amounting to -74.7 kcal/mol. Such closer agreements with the former functional have been  
27 previously noted<sup>70, 71</sup>.  $\delta E_{\text{nadd}}$  has similar values with both functionals (-11.5 and -11.8  
28 kcal/mol), however  $\delta E_{\text{nadd}}(\text{SIBFA})$  is smaller (-8.8 kcal/mol). We have no explanation for  
29 this reduction in magnitude of  $\delta E_{\text{nadd}}(\text{SIBFA})$  as compared to the situation at the HF level. A  
30 larger magnitude for  $\Delta E(\text{DFT})$  value of -79.1 kcal/mol was recently reported by Paragi and  
31 Fonseca Guerra<sup>36</sup> but this was possibly due to the use of different basis set and functional  
32 (BLYP-D/TZ2P) and/or stacked geometry.

33  
34  
35  
36  
37  
38  
39 *b). Stacked half-quartets.* The results are reported in Table 3 and 4 at HF/RVS and correlated  
40 levels, respectively, regarding the four-guanine complex and the six separate dimeric  
41 complexes G1-G2 till G1'-G2'.

42  
43  
44 *HF/RVS calculations.*  $\Delta E(\text{HF})$  is overestimated by  $\Delta E(\text{SIBFA})$  by 4 kcal/mol out of 8. This  
45 was unexpected, the more so, as it is due to  $E_{\text{MTP}}^*$  accountable for a 5.8 kcal/mol  
46 overestimation, only partly compensated for by the other contributions. Examination of the  
47 individual dimers shows the error in  $E_{\text{MTP}}^*$  to originate mainly from the three stacked  
48 complexes G1-G2, G2-G1', and G2-G2', namely 1.5 kcal/mol for each. This could again  
49 diagnose some shortcoming in the present derivation of the distributed multipoles, more acute  
50 in stacked arrangements where the quadrupolar contributions could be more effective than in  
51 the H-bonded complexes. Regarding the second-order contributions, we observe  $\delta E_{\text{nadd}}$  to now  
52 be positive, indicative of anticooperativity. It is slightly more pronounced in SIBFA than in  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 QC/RVS (2.2 versus 1.7 kcal/mol). It stems predominantly from  $E_{\text{pol}}$ , nevertheless  $E_{\text{ct}}$  has a  
6 small, yet beyond rounding-off error, contribution to it.  
7

8 *Correlated calculations.*  $\Delta E_{\text{tot}}(\text{SIBFA})$  of -38.0 kcal/mol now compares much more favorably  
9 to  $\Delta E(\text{B3LYP-D3})$  and  $\Delta E(\text{B97-D3})$  of -39.8 and -34.8 kcal/mol, respectively. The agreement  
10 is better with the former functional, a reverse situation to the one occurring with the H-bonded  
11 complexes. There is a significantly more uniform agreement with the six guanine dimers than  
12 was the case at the HF level. This could indicate a better balanced multipolar distribution  
13 derived at the DFT than at the HF level. But it is not precluded that the choice of the  
14 parameters used in the GDMA procedure was better adapted for the DFT-derived multipoles  
15 than those used for the HF ones.  $\delta E_{\text{nadd}}$  of 1.5 kcal/mol for SIBFA is closer to  $\delta E_{\text{nadd}}$  for  
16 B3LYP-D3 (1.6 kcal/mol) than for B97-D3 (2.2 kcal/mol).  
17

18 In the absence of metal cations, such values of  $\delta E_{\text{nadd}}$  are about five times smaller than those  
19 found with an opposite sign for each of the two quartets, so that the stacking of two G quartets  
20 should be dominated by cooperativity. However it should be noted that there are four  
21 equivalent 'half-quartets', G1-G2/G1'-G2' till G4-G1/G4'G1', each one sharing two G bases  
22 from the previous one. A complete analysis would need to be done involving all eight bases of  
23 the two stacked GQ complexes, with as well as without metal cations. It is planned in future  
24 studies. At this stage it was essential to evaluate how well the trends and magnitudes of  $\delta E_{\text{nadd}}$   
25 found in QC could be retrieved in SIBFA.  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37

38 *c). Two stacked G quartets (Table 5).* The results are fully consistent with those found at the  
39 quartet level. At the HF level),  $\Delta E(\text{SIBFA})$  is larger than  $\Delta E(\text{HF})$  by an amount nearly twice  
40 as large as with one quartet (the BSSE correction was not subtracted). At the correlated level,  
41  $\Delta E_{\text{tot}}(\text{SIBFA})$  of -169.8 kcal/mol is larger in magnitude than  $\Delta E(\text{B97-D3})$  of -168.6 kcal/mol  
42 by 1 kcal/mol out of 169, while it was smaller than it by 1 kcal/mol out of 69 in one quartet. It  
43 is smaller in magnitude than  $\Delta E(\text{B3LYP-D3})$  of -184.0 by 14 kcal/mol out of 180, an amount  
44 only slightly larger than the double of the 6 kcal/mol out of 70 found with one quartet. It is  
45 noted that the SIBFA and B97-D3 values of -169 kcal/mol are now close to the -172.4  
46 reported by Paragi and Fonseca Guerra for the stacked GQ dimer<sup>36</sup>. It is instructive to  
47 compute the amount of stabilization brought by stacking, upon comparing these  $\Delta E_{\text{tot}}$  values  
48 to twice the values found in the isolated quartets. Such values amount to -137.6, -139.6, and -  
49 149.4 in SIBFA, B97-D3 and B3LYP-D3, respectively. The stacking of the two G quartets  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 thus results into additional stabilization energies,  $\delta_{\text{stack}}$ , of -36.6, -40.8, and -30.3 kcal/mol in  
6 these respective approaches. The close  $\delta_{\text{stack}}$  values found in SIBFA and B97-D3 imply that  
7 the additional stabilization brought by stacking and its impact on cooperativity, are computed  
8 consistently by these two approaches. It is noteworthy that their difference, 4.2 kcal/mol, is  
9 smaller than the B97-D3 and B3LYP-D3  $\delta_{\text{stack}}$  difference of 10.5 kcal/mol.

10 We deem these preliminary analyses to be essential prior to studying the cation complexes of  
11 the stacked G quartets. With two cations thus ten interacting entities, there is a total of forty-  
12 five ‘dimer’ interactions, namely twenty-eight base-base, sixteen base-cation, and one cation-  
13 cation interaction. How well the H-bonded and stacked base-base interactions, modulated by  
14 the potentials and fields of the other bases and the cations, are accounted for by APMM  
15 methods, can critically impact the potential energy surfaces they generate for the stacked G  
16 quartet-cation complexes  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27

## 28 **2. Channeling of one monovalent cation ( $\text{Li}^+$ , $\text{Na}^+$ , $\text{K}^+$ , $\text{Rb}^+$ ) through two stacked G** 29 **quartets.**

30  
31 The cation is displaced along the Z axis from bottom to top in fifteen steps of 0.25 Å  
32 amplitude. We retain the coordinates adopted by Gkionis et al.<sup>37</sup>. However the atom ordering  
33 is not the same. The one used in the SIBFA library of fragments starts with H(9), N9, C8, etc.  
34 The G8 complex was reconstructed by molecular graphics to superimpose with the one given  
35 by Gkionis et al. With this construction, the planar separation between the two quartets is 3.4  
36 Å, but while each quartet is flat, there can be small deviations from the uniform Z values of -  
37 1.7 and +1.7 Å for the bottom and the top quartets. The geometries are given in Supp. Info.  
38 The cation starts at  $Z=-2.72$  Å, 1 Å below the center of the bottom quartet, and ends at  $Z=0.78$   
39 Å, 2.5 Å above that center and 0.9 Å below the center of the top quartet. The energy profiles  
40 for the channeling of each cation are reported in Figures 2a-d regarding  $\Delta E(\text{HF})$  and  
41  $\Delta E(\text{SIBFA})$  computed with HF-derived multipoles and polarizabilities, along with the  $E_1$  and  
42  $E_2$  contributions of  $\Delta E(\text{SIBFA})$ . Figures 3a-e report the corresponding profiles for  $\Delta E(\text{B97-}$   
43  $\text{D3})$  and  $\Delta E_{\text{tot}}(\text{SIBFA})$  now with correlated multipoles and polarizabilities and the dispersion  
44 contribution. The fifth point in the plot corresponds to the cation in the plane of the bottom  
45 quartet, and twelfth point to the cation at mid-distance from the two quartets. We report in  
46 Appendices I and II the Tables giving the energies plotted in Figures 2a-d and 3a-e. We do  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

not list the separate values of  $E_{\text{pol}}$  and  $E_{\text{ct}}$  within  $E_2$ .  $E_{\text{ct}}$  has shallower variations than  $E_{\text{pol}}$ , and is in the range -15 -- -20 kcal/mol.

a)  $\Delta E(\text{HF})$  and  $\Delta E(\text{SIBFA})$  profiles. The four cations display markedly different QC energy profiles, which can be closely matched by SIBFA.

$\text{Li}^+$  (Figure 2a)  $\Delta E(\text{HF})$  has two shallow minima, at  $Z=-1.47 \text{ \AA}$ ,  $0.25 \text{ \AA}$  above the first quartet, and at  $Z=0.78 \text{ \AA}$ , with values of -211.3 and -210.4 kcal/mol, respectively.  $\Delta E(\text{SIBFA})$  has minima at these two points as well, with values of -209.1 and -207.0 kcal/mol, respectively. Both  $\Delta E(\text{HF})$  and  $\Delta E(\text{SIBFA})$  have a shallow maximum at  $Z=0 \text{ \AA}$ , when the cation is in-between the two quartets, with values of -206.7 and -202.5 kcal/mol, respectively. In SIBFA,  $E_1$  has a much larger magnitude than  $E_2$ , with a ratio in the range 1.4-1.65. However, while it is  $E_1$  that confers its shape to  $\Delta E(\text{SIBFA})$  in the first half of the trajectory, namely until  $Z=-1$ , it is the reverse in the second half, and the shallow maximum at  $Z=0 \text{ \AA}$  is clearly due to  $E_2$ .

$\text{Na}^+$  (Figure 2b). Both  $\Delta E(\text{HF})$  and  $\Delta E(\text{SIBFA})$  curves are very shallow in-between  $Z=-1.22$  and  $Z=0.78 \text{ \AA}$ , where the energy variations are  $<1.5$  kcal/mol out of 205, i.e. less than 1%. The curves are actually shallower than the corresponding  $\text{Li}^+$  curve, despite the larger size of the cation. Two very flat minima can still be discerned. The first is at  $Z=-0.97 \text{ \AA}$  (HF) and at  $Z=-1.22 \text{ \AA}$  (SIBFA) with  $\Delta E(\text{HF})$  and  $\Delta E(\text{SIBFA})$  values of -205.6 and -207.2 kcal/mol, respectively. The second minimum is at  $Z=0.78$ , with virtually identical HF and SIBFA values of -206.2 kcal/mol. As was the case with  $\text{Li}^+$ , the shape of  $\Delta E(\text{SIBFA})$  is dictated by  $E_1$  in the first half of the trajectory and by  $E_2$  in the second half.

$\text{K}^+$  (Figure 2c). The HF and SIBFA energy profiles dramatically differ from the  $\text{Li}^+$  and  $\text{Na}^+$  ones, and they do so on many counts. There now is one single, well-defined minimum at  $Z=0$ , namely when the cation is in the center of the cavity ( $\Delta E(\text{HF})=-196.3$  and  $\Delta E(\text{SIBFA})=-195.8$  kcal/mol). This is a clear indication for the fact that owing to its size,  $\text{K}^+$  is the most suited cation to bridge the two G quartets at equal distances. Along the alkali cation series, it is also the cation endowed with the most favorable stacked G quartet binding affinity as recently demonstrated by QC energy balance analyses<sup>33</sup>. The relative weight of  $E_1$  to  $E_2$  fluctuates much more than with the two smaller cations: from 1.26 in the first third of the curve to 1.74 at, and close to the minimum.

$\text{Rb}^+$  (Figure 2d). The HF and SIBFA curves have much more pronounced features than the  $\text{K}^+$  curves. Both have a well-defined maximum at  $Z=-1.72 \text{ \AA}$ , namely when the cation is in the center of the first monomer, a clear indication of the fact that the cation is oversized with

1  
2  
3  
4  
5 respect to the GQ cavity size. As for  $K^+$ , the energy minima are at  $Z=0$  Å, in the center of the  
6 cavity, but are deeper than for  $K^+$ .  $\Delta E(\text{HF})$  and  $\Delta E(\text{SIBFA})$  at the minimum are numerically  
7 close (-186.7 and -190.0 kcal/mol, respectively), and this is the case for the entire trajectory,  
8 except to a limited extent (up to 4%) in the high-lying zone. The ratios of  $E_1$  to  $E_2$  are now  
9 very contrasting.  $E_1$  dictates its shape to the entire trajectory. Except for the first point, it is  
10 lesser in magnitude than  $E_2$  until  $Z=-1.2$  Å, and has the least value at  $Z=-1.72$  Å, when the  
11 cation is in the center of the first quartet.

12  
13  
14  
15  
16 *b)  $\Delta E(\text{DFT-D3})$  and  $\Delta E_{\text{tot}}(\text{SIBFA})$  profiles.*

17 We will mostly display the results found with the B97-D3 functional, which in keeping with  
18 previous results was the one giving rise to the closest agreements with  $\Delta E_{\text{tot}}(\text{SIBFA})$ <sup>67,68</sup>. The  
19  $\Delta E(\text{B3LYP-D3})$  curves, shown below for the  $\text{Li}^+$  complexes, are invariably parallel to the  
20 B97-D3 one but app. 30 kcal/mol lower. The increases in magnitude upon passing from  
21  $\Delta E(\text{HF})$  to  $\Delta E(\text{B97-D3})$  and from  $\Delta E(\text{SIBFA})$  to  $\Delta E_{\text{tot}}(\text{SIBFA})$ , are closely similar for all four  
22 cations.  $E_{\text{disp}}(\text{SIBFA})$  stems solely from the guanine-guanine interactions contributing -88.5  
23 kcal/mol for all complexes. It is not shown in the figures.

24  
25  
26  
27  
28  
29  
30  $\text{Li}^+$  (Figure 3a). While  $\Delta E_{\text{tot}}(\text{SIBFA})$  has the same shallow profile as  $\Delta E(\text{SIBFA})$  with a flat  
31 minimum at  $Z=-1.22$  Å.  $\Delta E(\text{B97-D3})$  undergoes a regular decrease until  $Z=-0.47$  Å. The  
32 decrease then becomes more accented with a minimum at  $Z=0.03$  Å, and this is observed as  
33 well for  $\Delta E(\text{B3LYP-D3})$  but had not happened with  $\Delta E(\text{HF})$ . This appears to stem from the  
34 D3 functional. Thus Figure 3b recasts the profile computed with the B3LYP functional in the  
35 absence of such correction, seen to parallel  $\Delta E(\text{HF})$ , but not  $\Delta E(\text{B3LYP-D3})$ .

36  
37  
38  
39  
40  
41  $\text{Na}^+$  (Figure 3c).  $\Delta E(\text{B97-D3})$  has a profile similar to the  $\text{Li}^+$  one, with its minimum at  
42  $Z=0.03$ , while  $\Delta E_{\text{tot}}(\text{SIBFA})$  has a shallow behavior from  $Z=-1.7$  Å throughout, with two  
43 shallow minima at  $Z=-1.22$  Å and  $Z=0.78$  Å. As a result, the relative error of  $\Delta E_{\text{tot}}(\text{SIBFA})$   
44 with respect to  $\Delta E(\text{B97-D3})$  is the smallest at  $Z=-1.72$  Å, at the center of the first quartet  
45 (2%), and is the largest at  $Z=0$  Å (6%).

46  
47  
48  
49  $K^+$  (Figure 3d).  $\Delta E(\text{B97-D3})$  and  $\Delta E_{\text{tot}}(\text{SIBFA})$  have similar shapes, as in the absence of  
50 correlation/dispersion (Figure 2c). There is a shallow increase in magnitude in the region  $Z=-$   
51  $2.72$  till  $-0.97$  Å, followed by a more accented descent to the minimum at  $Z=0$  Å. As with  
52  $\text{Na}^+$ , the minimum is deeper for  $\Delta E(\text{B97-D3})$  than for  $\Delta E_{\text{tot}}(\text{SIBFA})$ , and the relative error is  
53 the largest there (4%) while it was <1% at the HF level.

Rb<sup>+</sup> (Figure 3e).  $\Delta E(\text{B97-D3})$  and  $\Delta E_{\text{tot}}(\text{SIBFA})$  have more parallel shapes than was the case with the smaller cations, the offset never exceeding 11.3 kcal/mol out of 220, its average value being of 7.3 kcal/mol, the average energy difference amounting to 3%. As with the HF calculation, the maximum of both  $\Delta E(\text{B97-D3})$  and  $\Delta E_{\text{tot}}(\text{SIBFA})$  is at  $-1.72 \text{ \AA}$  in the center of the first quartet, and the minimum is at  $Z=0.0$ .

### 3. Channeling of two monovalent cations (Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Rb<sup>+</sup>) through two stacked G quartets.

We report in Appendices III and IV the Tables giving the energies plotted in Figures 4a-d and 5a-d. We do not list the separate values of  $E_{\text{pol}}$  and  $E_{\text{ct}}$  within  $E_2$ .  $E_{\text{ct}}$  has shallower variations than  $E_{\text{pol}}$ , and is in the range  $-18$  --  $-24$  kcal/mol.

#### a) $\Delta E(\text{HF})$ and $\Delta E(\text{SIBFA})$ profiles.

The results are reported in Figures 4a-d. For all cations, both QC and SIBFA profiles very significantly differ from the corresponding one-cation profiles.

Li<sup>+</sup> (Figure 4a). The minima of both QC and SIBFA are shifted from  $Z=-1.47$  to  $Z=-1.72 \text{ \AA}$ , namely in the center of the first quartet, after which the energy raises continuously rather than plateauing. The  $E_1/E_2$  ratio decreases progressively, until  $E_2$  becomes larger in magnitude at  $Z=-0.22 \text{ \AA}$ . This clearly translates the raise in total polarization energy of the two G quartets upon shortening the cation-cation distance, counteracting the raise in their mutual Coulomb repulsion. It is notable that the sum of  $E_1$  and  $E_2$  enables SIBFA to match  $\Delta E(\text{HF})$  with relative errors  $< 2\%$  thus accounting for the  $Z$ -dependent  $\Delta E$  magnitude increase upon passing from the one- to the two-cation G8 complexes.

Na<sup>+</sup> (Figure 4b). The profiles of  $\Delta E(\text{HF})$  and  $\Delta E(\text{SIBFA})$  both resemble the Li<sup>+</sup> ones, with a minimum shifted at  $Z=-1.72 \text{ \AA}$ , a continuous raise thereafter, and a  $E_1/E_2$  crossing at  $Z=-0.22$ . In the low-energy zone,  $\Delta E(\text{SIBFA})$  matches  $\Delta E(\text{HF})$  with relative errors of 2%, comparable to those found with Li<sup>+</sup>, but now overestimates it rather than underestimating it.

K<sup>+</sup> (Figure 4c). The  $Z=0 \text{ \AA}$  minimum has disappeared owing to the increased electrostatic repulsion undergone by the moving cation. Instead, the energy plateaus along the whole  $Z=-2.72$  --  $-0.22 \text{ \AA}$  region, undergoing  $< 2\%$  variations. Except for the first two points,  $E_2$  is now larger in magnitude than  $E_1$ , the gap increasing steeply past  $Z=0 \text{ \AA}$ . The relative error of  $\Delta E(\text{SIBFA})$  with respect to  $\Delta E(\text{HF})$  is 3%.

1  
2  
3  
4  
5 Rb<sup>+</sup> (Figure 4d). With respect to the K<sup>+</sup> curve, a shallow maximum is present at Z=-1.72 Å,  
6 when the moving cation is in the center of the first quartet, and there still does exist a  
7 minimum at Z=-0.47 Å, 0.5 Å before the center of the cavity is reached. Past this minimum,  
8 the energy raises more steeply than with K<sup>+</sup>, owing to the much larger short-range Rb<sup>+</sup>-Rb<sup>+</sup>  
9 than K<sup>+</sup>-K<sup>+</sup> short-range repulsion. Thus with both QC and SIBFA there are two well-defined  
10 minima, at the start of the trajectory (Z=-2.72 Å) and close to the center of the cavity (Z=-0.47  
11 Å). E<sub>2</sub> is now invariably larger in magnitude than E<sub>1</sub>, but the shape of ΔE is dictated by E<sub>1</sub>.  
12 The relative errors of ΔE(SIBFA) are larger than in the two K<sup>+</sup> case, and can reach 6% in the  
13 low-energy zone.  
14  
15  
16  
17  
18  
19

20 *b) ΔE(B97-D3) and ΔE<sub>tot</sub>(SIBFA) profiles.*

21 Li<sup>+</sup> (Figure 5a). Both QC and SIBFA curves closely resemble their counterparts at the HF  
22 level (Figure 4a). There is a shallow minimum at Z=-1.72 Å, in the center of the first quartet  
23 followed by a progressive rise in the energy. The E<sub>1</sub> and E<sub>2</sub> curves cross at Z=-0.72 Å, 0.30 Å  
24 earlier than at the HF level. The relative SIBFA versus QC error now averages 5%, larger  
25 than the 2% error found at the HF level.  
26  
27  
28  
29

30 Na<sup>+</sup> (Figure 5b). Again, the shapes of ΔE(B97-D3) and ΔE<sub>tot</sub>(SIBFA) are very similar to their  
31 HF counterparts. The shallow minimum in the first half of the trajectory locates Na<sup>+</sup> at Z=-  
32 1.47 Å, namely 0.25 Å above the center of the first quartet, and the E<sub>1</sub>/E<sub>2</sub> crossing occurs 0.5  
33 Å earlier than at the HF level. The relative SIBFA error averages 3% over the relevant energy  
34 zone but is lowest at the minimum.  
35  
36  
37

38 K<sup>+</sup> (Figure 5c). Both curves plateau closely similar to their HF counterparts. There is a  
39 discernible minimum for Z=-0.72 Å, and the total energies start to rise steeply as the moving  
40 cation progresses 0.5 Å past it and beyond. The crossing of the E<sub>1</sub>/E<sub>2</sub> curves now occurs at the  
41 very start of the trajectory, rather than 0.5 Å past it as with the HF curves. The relative errors  
42 in SIBFA are strikingly small (1%) over the low energy range of distances, namely in thirteen  
43 points covering a 3 Å trajectory.  
44  
45  
46  
47

48 Rb<sup>+</sup> (Figure 5d). As with the HF curves, a local maximum is located in the center of the first  
49 quartet, and for both SIBFA and QC the global minimum occurs at Z=-0.47 Å, 0.5 Å before  
50 the center of the cavity. E<sub>2</sub> has larger magnitudes than E<sub>1</sub> throughout and the gap increases  
51 along the entire trajectory except close to the energy minimum. The relative errors in SIBFA  
52 are <2% for the thirteen first points in the trajectory.  
53  
54  
55

56 **Non-Covalent Interaction (NCI) analyses.** Analyzing the sign of the second eigenvalues, λ<sub>2</sub>,  
57 of the electron density Hessian matrix shows the nature of the non-covalent interaction:  
58  
59  
60

1  
2  
3  
4  
5 attractive if  $\lambda_2$  is negative, and repulsive if positive. If  $\rho$  denotes the electronic density, a plot  
6 of the reduced gradient density,  $s$ , as a function of the product  $\lambda_2\rho$  provides information on  
7 such a nature, classified as attractive, weak, or repulsive.  
8  
9

10 A red-green-blue color scheme is chosen for the 2D and 3D plots to distinguish between  
11 strong and attractive interactions such as ionic or hydrogen bonds (in blue), weak interactions  
12 such as van der Waals or related interactions (in green), and repulsive interactions (in red).  
13  
14

15 We first consider the two stacked quartets prior to cation binding (Figure 6). The onset of  
16 stabilizing inter-quartet interactions is attested by the large, deep-green isosurfaces in the mid-  
17 plane (Figures 6a-b). Within each quartet plane, the spherical blue-green isosurfaces between  
18 H(N1) and O6, and between H(N2) and N7, attest to the onset of strong inter-molecular H-  
19 bonds. The red oval surfaces in the middle of both rings of each guanine attest to local intra-  
20 molecular repulsions (Figure 6a).  
21  
22  
23

24 We next consider the NCI plots for one  $K^+$  cation channeling along the Z axis (Figures 7a-d).  
25 When it is located beneath the first quartet ( $Z=-2.7$  Å, Figure 7a), the  $K^+ \cdots O6$  interactions are  
26 translated by downward-pointing green disk-shaped isosurfaces, with no visible perturbation  
27 of the mid-plane isosurfaces. Its in-plane location ( $Z=-1.7$  Å, Figure 7b) translates by in-plane  
28 alignments of O6,  $K^+$ , and the disk-shaped isosurfaces, with little impact on the mid-plane  
29 isosurfaces. The location of  $K^+$  in the center of the cavity ( $Z=0.0$  Å, Figure 7c) translates, on  
30 the one hand, by an upward displacement of the disk isosurfaces connecting  $K^+$  to the bottom  
31 quartet O6 and downward displacement of the disk isosurfaces connecting it to the top quartet  
32 O6. The mid-plane isosurfaces are less disjoint than with  $Z=-2.7$  and  $-1.7$  Å, or in the absence  
33 of cation altogether. When  $K^+$  is closer to the top quartet ( $Z=0.7$  Å, Figure 7d), the O6- $K^+$   
34 isosurfaces stemming from the bottom quartet have faded out, while those stemming from the  
35 top quarter have their density increased. The mid-plane isosurfaces are not significantly  
36 impacted.  
37  
38  
39  
40  
41  
42  
43  
44

45 The NCI features along the four steps of this trajectory become more accented in the presence  
46 of an additional cation held on top of the top quartet at  $Z=2.8$  Å (Figures 8a-d). Whatever the  
47 location of the channeling cation, there are four upward directed disk-shaped isosurfaces  
48 between the four O6 atoms of the top quartet and the topmost cation. As was the case with  
49 one  $K^+$ , the corresponding four isosurfaces of the bottom quartet follow the moving cation:  
50 downward-pointing for  $Z=-2.8$  Å (8a), in-plane location for  $Z=-1.8$  Å (8b), upward-pointing  
51 for  $Z=0.0$  Å (8c), and fading out for  $Z=0.8$  Å (8d). For  $Z=0.0$  Å, it is instructive to observe  
52 that each O6 atom from the top quartet contributes two disk-shaped isosurfaces: upward-  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 pointing toward the top  $K^+$ , and downward-pointing toward the central  $K^+$ . The mid-plane  
6 isosurfaces are brighter than the corresponding ones with only one  $K^+$ .  
7

8  
9 The different peaks present in the 2D plot can be analyzed for a better understanding of the  
10 features of the 3D isosurfaces. We can detect first the signature peak of the guanines, prior to  
11  $K^+$  binding (Figure 6c). There is a neat peak in the attractive region ( $\lambda_{2\rho} = -0.02$  au). It  
12 corresponds to the inter-molecular H1-O6 and H2-N7 bonds. The two green peaks ( $\lambda_{2\rho} = -$   
13  $0.005$  and  $0.0$  au) correspond to the mid-plane isosurfaces. The red peak at  $\lambda_{2\rho} = 0.025$  au  
14 corresponds to the repulsive intra-ring interactions in each guanine.  
15  
16  
17

18 We next consider the evolutions of these peaks in the presence of one and two  $K^+$  cations.  
19 When  $K^+$  is below the bottom quartet ( $Z = -2.8$  Å, Figure 7a), an additional blue peak appears  
20 at  $\lambda_{2\rho} = -0.015$  au. When  $K^+$  is in the center of this quartet ( $Z = -1.8$  Å, Figure 8b), the peak is  
21 shifted to a more attractive region with  $\lambda_{2\rho} = -0.03$  au. When  $K^+$  moves to the center of the  
22 cavity ( $Z = 0.0$  Å, Figure 7c), or closer to the topmost quartet ( $Z = -0.8$  Å, Figure 7d), this blue  
23 peak disappears. For the first two points ( $Z = -2.8$  and  $-1.8$  Å) and for the last one ( $Z = +0.8$  Å,  
24 Figure 7d), the two central green peaks on both sides of  $\lambda_{2\rho} = 0$  have the same features as in  
25 the absence of  $K^+$ . When  $K^+$  is in the center of the cavity ( $Z = 0.0$  Å), the left-most peak  
26 becomes wider, consistent with the increase of the mid-point isosurfaces in the 3D plots  
27 (Figure 7c).  
28  
29  
30  
31  
32  
33

34 We next consider the two  $K^+$  complexes. There are no marked differences for the first two  
35 points ( $Z = -2.8$  and  $-1.8$  Å, Figures 8a-b) with respect to the one-cation case. When  $K^+$  is in  
36 the center of the cavity, on the other hand, both left and right green peaks around  $\lambda_{2\rho} = 0.0$  au  
37 are enlarged with respect to the one-cation case. At  $Z = 0.8$  Å, an additional red peak appears at  
38  $\lambda_{2\rho} = 0.015$  au. It translates the onset of short-range repulsive interactions between the two  
39 cations which are at  $2.0$  Å from one another.  
40  
41  
42  
43

44 For both  $Na^+$  and  $Rb^+$  complexes, both 2D and 3D plots present very similar features as with  
45  $K^+$  (not shown). The most conspicuous feature which differentiates between them is found  
46 with the two-cation complexes at  $Z = 0.7$  Å. It relates to the repulsive peak at  $\lambda_{2\rho} = 0.015$  au,  
47 more spread-out with  $Rb^+$  than with  $K^+$ , and virtually undetectable with  $Na^+$ .  
48  
49

50 In conclusion, the NCI analysis demonstrates that both the guanine-guanine and guanine-  
51 metal key interactions are in a van der Waals regime. The strength of guanine-metal  
52 interactions clearly depends on the cation position, being maximized when the metal is  
53 located at the center of the cavity. The relative selectivity of the various cations therefore  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 relies on subtle variations of van der Waals interactions that can be highlighted by the  
6 presented supermolecular interaction energies.  
7  
8

### 9 10 **Discussion.**

11 We have carried out benchmark comparisons of the SIBFA APMM procedure against QC  
12 results in a demanding test case, the complex of two stacked guanine quartets (GQ) with one  
13 or two alkali cations  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Rb}^+$ , and the energy profile for the channeling of one  
14 cation along the Z axis with or without another one set above the topmost quartet. These tests  
15 are motivated by the emerging importance of GQs in molecular biology, in drug design, and  
16 in nanoscience. The alkali cations  $\text{K}^+$  and  $\text{Na}^+$  inside their cavity can play a major role in their  
17 stabilization. Stacked GQ's in a wealth of settings clearly constitute a privileged avenue for a  
18 manifold of future large-scale APMM applications. They are stabilized by the simultaneous  
19 interplay of multiply H-bonded interactions, stacking interactions between extended and polar  
20 surfaces, and cation-ligand interactions. Non-additivity effects strongly come into play, and  
21 have to be correctly quantified by APMM procedures. It is thus mandatory to objectively  
22 benchmark their expectable accuracy against high-level QC, and how well they perform  
23 compared to non-polarizable potentials<sup>37</sup>. We have adopted a staged approach comparing first  
24  $\Delta E(\text{SIBFA})$  to  $\Delta E(\text{HF})$  and then  $\Delta E_{\text{tot}}(\text{SIBFA})$  to  $\Delta E(\text{DFT-D3})$ . An essential motivation for  
25 this is the fact that all  $\Delta E(\text{SIBFA})$  parameters were derived beforehand on the basis of RVS  
26 EDA's done at the HF level with the aug-cc-pVTZ(-f) level<sup>59</sup>, then extended to alkali cations  
27<sup>40</sup> and to cytosine and guanine<sup>41</sup>. The passage to correlated tests is done solely upon replacing  
28 the HF-derived multipoles and polarizabilities by those derived at the DFT level, and adding  
29 an appropriately rescaled  $E_{\text{disp}}$  contribution. Can we, then, be equally successful, if at all, in  
30 reproducing in succession both HF and DFT-D calculations?  
31  
32

33 We considered the stabilization energies of one, then of two stacked quartets prior to cation  
34 binding, and then the complexes of two stacked GQ's with one and with two cations.  
35

36 *-In-plane G quartet.* At the HF level, in each of the four doubly H-bonded dimers G1-G2 till  
37 G4-G1,  $E_{\text{MTP}}$  and  $E_{\text{rep}}$  were each accountable for overestimations of 0.5 kcal/mol out of 16  
38 ( $E_{\text{C}}$ ) and 11 ( $E_{\text{exch}}$ ). This indicates that improvements to  $E_{\text{MTP}}$  could be sought for, such as  
39 GEM or ISA. These could impact  $E_{\text{rep}}$ , as well, since  $E_{\text{rep}}$  embodies a dependence upon  
40 electrostatics in its prefactor. The second-order contributions,  $E_{\text{pol}}$  and  $E_{\text{ct}}$  gave close matches  
41 to their QC counterparts. Cooperativity was correctly accounted for,  $\delta E_{\text{nadd}}$  amounting to -9.6  
42 and to -9.2 kcal/mol in HF and SIBFA, respectively. At the correlated level,  $\Delta E_{\text{tot}}(\text{SIBFA})$  of -  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

68.8 kcal/mol was found to have a closer agreement to  $\Delta E(\text{B97-D3})$  of -69.8 kcal/mole than to  $\Delta E(\text{B3LYP-D3})$  of -74.7.

*-Two stacked half-quartets.* Such an arrangement involves a doubly H-bonded dimer of the first quartet and one of the two most overlapping H-bonded dimers of the other quartet.  $\delta E_{\text{nadd}}$  now has a positive sign, indicative of local anticooperativity, and its QC value is satisfactorily accounted for in SIBFA: 1.5 vs. 2.2 kcal/mol at the HF level, and 1.5 versus 1.6 and 2.2 kcal/mol at the B3LYP-D3 and 2.2 levels, respectively. As with the in-plane G quartet, better agreements are found between  $\Delta E_{\text{tot}}(\text{SIBFA})$  and  $\Delta E(\text{DFT-D3})$  than at the HF level. Thus  $\Delta E_{\text{tot}}(\text{SIBFA})$  amounts to -38.0 kcal/mol as compared to -39.8 and -34.8 kcal/mol with the B3LYP-D3 and B97-D3 functionals.

*-Two-stacked GQ complex.* The best agreement was between  $\Delta E_{\text{tot}}(\text{SIBFA})$  and  $\Delta E(\text{B97-D3})$ , namely -169.8 vs. -168.6 kcal/mol. This value is smaller than the -184 kcal/mol  $\Delta E(\text{B3LYP-D3})$  one. The agreement between SIBFA and B97-D3 is again closer than that of the two DFT-D3 procedures between themselves. This was observed previously in a Zn(II)-metalloprotein recognition site [68], and is also found in all mono- and dication curves.

*-Cation channeling.* We next compared the  $\Delta E(\text{SIBFA})$  and  $\Delta E(\text{HF})$  profiles for one cation channeling in the absence of the other. SIBFA could closely match the QC profiles for all four cations, the relative  $\Delta E$  error being always <2% in the low-energy zones.  $\text{Li}^+$  and  $\text{Na}^+$  had similar, very flat profile, nevertheless two minima were discernible for both: the first, about 0.50 Å above the center of the first quartet, and the second, at the end of the trajectory. A flat maximum was at the center of the cavity, found by both QC and SIBFA. In SIBFA, the magnitude of  $\Delta E$  was mostly due to  $E_1$  accounting for its two thirds, yet it was  $E_2$  that conferred to  $\Delta E$  its shape in the last part of the trajectory.  $\text{K}^+$  had a starkly different profile, increasing regularly in magnitude until it reached the center of the cavity. The  $E_1/E_2$  ratio was much more strongly variable than with the two cations, from 1.25 till 1.80 in the center of the cavity. The contrasted  $E_1$  and  $E_2$  profiles from  $Z=-1.47$  Å and beyond are noteworthy, yet they sum up to confer the right profile to  $\Delta E(\text{SIBFA})$  as compared to  $\Delta E(\text{HF})$ . A significant reshape of the energy profile, imposed by  $E_1$ , occurred with  $\text{Rb}^+$ , with an accented maximum in the center of the first quartet, and a minimum in the center of the cavity.

There are lesser agreements upon comparing  $\Delta E_{\text{tot}}(\text{SIBFA})$  and  $\Delta E(\text{B97-D3})$  for the two lighter cations,  $\text{Li}^+$  and  $\text{Na}^+$ .  $\Delta E(\text{B97-D3})$  and  $\Delta E(\text{B3LYP-D3})$  contrary to  $\Delta E(\text{HF})$  now have a minimum at  $Z=0$  Å. It is not found for  $\Delta E_{\text{tot}}(\text{SIBFA})$ , which behaves exactly as  $\Delta E(\text{HF})$  and

1  
2  
3  
4  
5  $\Delta E(\text{SIBFA})$ , but also as  $\Delta E(\text{B3LYP})$ . The reasons for the different B3LYP and B3LYP-D3  
6 shapes remain to be clarified.  $\Delta E_{\text{tot}}(\text{SIBFA})$  compares much more favorably to  $\Delta E(\text{B97-D3})$   
7 with  $\text{K}^+$ , the  $Z=0$  Å minimum at the center of the cavity being the ‘natural’ one. Nevertheless  
8 the relative SIBFA error is still the largest at this point: 4% as compared to 2% in the first half  
9 of the trajectory. There is a more regular SIBFA/QC parallelism with  $\text{Rb}^+$ , the relative error  
10 being contained to <3% throughout.

11  
12  
13  
14  
15 The energy profiles in the presence of a second cation are markedly different. Could, upon  
16 decreasing the cation-cation distance, the increase of magnitude of  $E_2$  due to increased  
17 polarization correctly compensate for the decrease of  $E_1$  magnitude due to increased cation-  
18 cation electrostatic repulsion, and also, for the larger cations close to the end of their  
19 trajectory, the increase of their short-range repulsion? Any  $E_2/E_1$  imbalance, that could be  
20 further magnified by the non-additivities of  $E_{\text{pol}}$  and  $E_{\text{ct}}$  in the presence of the second cation,  
21 could severely downgrade the SIBFA versus QC parallelism. Regarding  $\Delta E(\text{SIBFA})$  and  
22  $\Delta E(\text{HF})$ , the lighter two cations had closely similar energy profiles, their minima now  
23 occurring in the center of the first quartet, rather than above it. The relative error is for both  
24 <2% over the whole low-energy zone. A cross-over of the  $E_1$  and  $E_2$  curves occurs at 0.25 Å  
25 before reaching the center of the cavity. A close parallelism is also found for  $\text{K}^+$ . With both  
26 QC and SIBFA, the energy minimum is considerably shallower than in the one-cation case,  
27 and is displaced 0.75 Å beneath the center of the cavity. The  $E_1/E_2$  crossover now occurs  
28 already at 0.5 Å after the start of the trajectory. The relative SIBFA/QC error is < 3% in the  
29 low-energy range. The shape of the  $\text{K}^+$  energy profile is further accented with  $\text{Rb}^+$ . While the  
30 first maximum is still in the center of the first quartet, the minimum is displaced 0.5 Å  
31 beneath the center of the cavity.  $E_2$  is larger in magnitude throughout the entire trajectory, the  
32 gap increasing upon  $\text{Rb}^+$  progression along the  $Z$  axis.  $\Delta E(\text{SIBFA})$  very closely reproduces  
33  $\Delta E(\text{HF})$  in the first part of the trajectory, the relative error being <2%, increasing slowly to  
34 5% at the energy minimum. Closely similar conclusions can be reached regarding  $\Delta E(\text{B97-}$   
35  $\text{D3})$  and  $\Delta E_{\text{tot}}(\text{SIBFA})$ . For both  $\text{Li}^+$  and  $\text{Na}^+$ , the two curves display good parallelism, with  
36 relative SIBFA errors < 4% ( $\text{Li}^+$ ) and <3% ( $\text{Na}^+$ ). The energy minima are in the center of the  
37 first quartet. The  $E_1/E_2$  crossover occurs for  $\Delta E_{\text{tot}}(\text{SIBFA})$  0.50 Å earlier than for  $\Delta E(\text{SIBFA})$ ,  
38 translating the larger relative weight of  $E_2$  with respect to  $E_1$  with correlated multipoles and  
39 polarizabilities. For  $\text{K}^+$  and  $\text{Rb}^+$ , there is a rather remarkable overlap of the SIBFA and QC  
40 trajectories throughout. The relative errors are now 1%. Nevertheless the fact that we recover  
41 a better agreement with two than with one cation implies there are some compensations of  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5 errors that we will seek to unravel in future work. The  $E_1/E_2$  crossover now occurs at the very  
6 start of the trajectories. For  $K^+$ , the energy minimum is at  $Z=-0.72 \text{ \AA}$ , consistent with its  
7  $\Delta E(\text{HF})$  location. For  $Rb^+$ , with both  $\Delta E(\text{B97-D3})$  and  $\Delta E_{\text{tot}}(\text{SIBFA})$ , it is shifted  $0.25 \text{ \AA}$   
8 upward compared to  $K^+$ , and is more accentuated.  
9

10 The present results could be used to benchmark other polarizable potentials<sup>69-72</sup> or semi-  
11 empirical QC methods. For this purpose we give as Supp. Info S1-S4 the G09 input data used  
12 for the G8 complexes with two cations. The moving cation is given its coordinates at the start  
13 of the trajectory ( $Z=-2.72 \text{ \AA}$ ), the  $Z$  coordinate of the fixed cation being set at  $2.80 \text{ \AA}$ .  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29

### 30 **Concluding remarks.**

31 The present SIBFA benchmarks appear convincing and should lend credence to prospective  
32 simulations of stacked G quartets and their metal cation complexes. Long-duration molecular  
33 dynamics (MD) on periodic GQ stacks and their complexes with metal cations are thus  
34 envisaged. They will benefit from the recent integration of the SIBFA potential and its  
35 gradients into the massively parallel Tinker-HP package<sup>73</sup>. This should enable to study their  
36 ion transport properties, the impact of molecular environment in different phases, such as  
37 liquid, gel, solid, or close to a conducting surface, etc. MD could also provide poses for post-  
38 processing by QC to calculate their most salient electronic properties. GQs could be  
39 connected together by variable linkers, to yield supramolecular complexes of tunable  
40 properties. We are also pursuing the refinements of the SIBFA potential. On the one hand,  
41 alternatives to GDMA multipoles are being tested. On the other hand, in line with our  
42 previous work<sup>41</sup>, additional SAPT calculations<sup>74-76</sup> on the complexes of nucleic acid bases  
43 with cation and water probes are being performed. This should enable a finer-tuning, now at  
44 the correlated level, of each of the five SIBFA contributions against its QC counterpart. There  
45 are simultaneous ongoing SIBFA refinements of the sugar-phosphate backbone of DNA and  
46 RNA which should pave the way for future APMM simulations of quadruplex DNA and their  
47 ligand complexes. These will be reported subsequently.  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Appendices 1-4.** Channeling of one cation ( $\text{Li}^+$ -  $\text{Rb}^+$ ) along the Z axis of two stacked G4 tetramers. Comparison of  $\Delta E(\text{QC})$  and  $\Delta E(\text{SIBFA})$  values. Consistent with Figures 2-5, the Z values (first column) are multiplied by a factor of 100 for clarity.

**Appendix 1.** Channeling of one cation along the Z axis of two stacked G4 tetramers. Comparison of  $\Delta E(\text{HF})$  and  $\Delta E(\text{SIBFA})$  values (in kcal/mol).

	$\text{Li}^+$		$\text{Na}^+$		$\text{K}^+$		$\text{Rb}^+$	
	$\Delta E(\text{HF})$	$\Delta E(\text{SIBFA})$	$\Delta E(\text{HF})$	$\Delta E(\text{SIBFA})$	$\Delta E(\text{HF})$	$\Delta E(\text{SIBFA})$	$\Delta E(\text{HF})$	$\Delta E(\text{SIBFA})$
-272	-187.94	-185.48	-184.18	-184.91	-170.95	-172.78	-156.73	-159.00
-247	-195.25	-192.88	-190.14	-191.72	-172.08	-174.75	-153.32	-153.96
-222	-201.51	-199.33	-195.1	-197.52	-172.13	-175.69	-149.11	-147.52
-197	-206.37	-204.36	-198.99	-202.01	-172.32	-176.44	-146.02	-142.35
-172	-209.64	-207.64	-201.88	-205.09	-173.65	-177.92	-146.02	-141.33
-147	-211.32	-209.12	-203.90	-206.78	-176.68	-180.65	-149.63	-145.87
-122	-211.13	-208.98	-205.12	-207.2	-181.11	-184.39	-157.34	-155.02
-97	-210.78	-207.68	-205.61	-206.61	-186.02	-188.34	-166.25	-166.16
-72	-209.49	-205.81	-205.52	-205.39	-190.44	-191.71	-174.77	-176.47
-47	-207.95	-203.99	-205.13	-204.06	-193.74	-194.08	-181.43	-184.17
-22	-206.94	-202.77	-204.75	-203.11	-195.71	-195.4	-185.48	-188.66
3	-206.69	-202.49	-204.68	-202.9	-196.30	-195.83	-186.67	-189.95
28	-207.32	-203.24	-205.03	-203.53	-195.55	-195.42	-184.97	-188.09
53	-208.67	-204.88	-205.64	-204.84	-193.45	-194.1	-180.46	-183.03
78	-210.36	-207.00	-206.20	-206.43	-190.10	-191.73	-173.50	-174.83

**Appendix 2.**

Channeling of one cation along the Z axis of two stacked G4 tetramers. Comparison of  $\Delta E(\Delta E(\text{B97-D3}))$  and  $\Delta E(\text{SIBFA})$  values (in kcal/mol).

	$\text{Li}^+$		$\text{Na}^+$		$\text{K}^+$		$\text{Rb}^+$	
	$\Delta E(\text{QC})$	$\Delta E_{\text{tot}}(\text{SIBFA})$	$\Delta E(\text{QC})$	$\Delta E_{\text{tot}}(\text{SIBFA})$	$\Delta E(\text{QC})$	$\Delta E_{\text{tot}}(\text{SIBFA})$	$\Delta E(\text{QC})$	$\Delta E_{\text{tot}}(\text{SIBFA})$
-272	-271.74	-256.79	-265.75	-255.82	-250.46	-243.78	-232.92	-230.18
-247	-276.48	-264.35	-270.44	-262.68	-250.82	-245.82	-231.08	-225.29
-222	-281.91	-270.94	-274.47	-268.51	-250.45	-246.84	-226.75	-219
-197	-286.17	-276.10	-277.8	-273.07	-250.48	-247.68	-223.98	-213.99
-172	-289.17	-279.56	-280.57	-276.30	-252.05	-249.33	-224.43	-213.15
-147	-291.05	-281.25	-283.02	-278.23	-255.67	-252.29	-229.10	-217.9
-122	-291.93	-281.37	-285.21	-278.98	-261.08	-256.33	-237.11	-227.31
-97	-292.05	-280.35	-287.12	-278.78	-267.37	-260.65	-247.40	-238.73
-72	-292.21	-278.78	-288.94	-277.98	-273.23	-264.4	-256.94	-249.35
-47	-295.15	-277.29	-290.76	-277.07	-277.7	-267.16	-264.26	-257.39
-22	-300.27	-276.41	-292.14	-276.53	-280.09	-268.87	-268.93	-262.23
3	-301.07	-276.50	-292.61	-276.71	-280.73	-269.68	-270.46	-263.89
28	-299.39	-277.65	-292.07	-277.70	-279.85	-269.64	-268.25	-262.42
53	-294.47	-279.69	-290.71	-279.33	-277.15	-268.66	-260.92	-257.73
78	-292.62	-282.20	-289.04	-281.20	-272.93	-266.59	-255.41	-249.91

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### Appendix 3.

Channeling of one cation along the Z axis of two stacked G4 tetramers in the presence of a fixed cation above the top tetramer. Comparison of  $\Delta E(\text{HF})$  and  $\Delta E(\text{SIBFA})$  values (in kcal/mol).

	$\text{Li}^+$		$\text{Na}^+$		$\text{K}^+$		$\text{Rb}^+$		
	$\Delta E(\text{HF})$	$\Delta E(\text{SIBFA})$	$\Delta E(\text{HF})$	$\Delta E(\text{SIBFA})$	$\Delta E(\text{HF})$	$\Delta E(\text{SIBFA})$	$\Delta E(\text{HF})$	$\Delta E(\text{SIBFA})$	
	-272	-239.74	-234.17	-232.48	-233.21	-207.03	-210.38	-179.99	-184.88
	-247	-245.78	-240.49	-237.13	-238.94	-206.66	-211.25	-175.07	-178.75
	-222	-250.63	-245.73	-240.61	-243.5	-205.2	-210.97	-169.2	-171.08
	-197	-253.88	-249.37	-242.82	-246.58	-203.62	-210.31	-164.27	-164.52
	-172	-255.28	-251.03	-243.76	-248.01	-202.98	-210.15	-162.17	-161.87
	-147	-254.73	-250.57	-243.46	-247.74	-203.74	-210.94	-163.76	-164.47
	-122	-252.33	-248.13	-241.93	-245.84	-205.47	-212.34	-168.26	-171.28
	-97	-248.34	-244.08	-239.15	-242.47	-206.97	-213.48	-173.71	-179.51
	-72	-243.13	-238.90	-235.17	-237.92	-207.61	-213.38	-177.75	-186.08
	-47	-237.10	-233.09	-230.15	-232.55	-205.56	-211.32	-178.36	-188.59
	-22	-230.54	-226.99	-224.38	-226.65	-200.92	-206.67	-173.45	-184.99
	3	-223.50	-220.64	-216.86	-220.25	-192.23	-198.13	-159.44	-171.71
	28	-215.63	-213.67	-208.18	-212.94	-176.75	-182.29	-128.61	-139.43
	53	-206.14	-205.23	-196.98	-203.75	-147.18	-149.92	-63.27	-63.05
	78	-193.62	-193.85	-181.06	-190.95	-85.05	-75.84	75.55	126.08

### Appendix 4.

Channeling of one cation along the Z axis of two stacked G4 tetramers in the presence of a fixed cation above the top tetramer. Comparison of  $\Delta E(\text{B97-D3})$  and  $\Delta E_{\text{tot}}(\text{SIBFA})$  values (in kcal/mol).

	$\text{Li}^+$		$\text{Na}^+$		$\text{K}^+$		$\text{Rb}^+$	
	$\Delta E(\text{QC})$	$\Delta E_{\text{tot}}(\text{SIBFA})$	$\Delta E(\text{QC})$	$\Delta E_{\text{tot}}(\text{SIBFA})$	$\Delta E(\text{QC})$	$\Delta E_{\text{tot}}(\text{SIBFA})$	$\Delta E(\text{QC})$	$\Delta E_{\text{tot}}(\text{SIBFA})$
-272	-327.72	-309.20	-317.50	-307.44	-288.21	-284.77	-259.11	-259.59
-247	-332.32	-315.79	-321.04	-313.30	-287.36	-285.81	-253.71	-253.69
-222	-336.50	-321.28	-323.81	-318.00	-285.65	-285.69	-247.81	-246.26
-197	-339.33	-325.19	-325.72	-321.26	-284.13	-285.24	-243.16	-239.96
-172	-340.66	-327.17	-326.85	-322.97	-283.81	-285.36	-241.43	-237.61
-147	-340.58	-327.11	-327.32	-323.09	-285.12	-286.53	-243.54	-240.58
-122	-338.98	-325.13	-327.02	-321.69	-287.71	-288.41	-248.87	-247.80
-97	-335.82	-321.58	-325.79	-318.89	-290.62	-290.09	-255.40	-256.49
-72	-331.35	-316.92	-323.73	-314.93	-292.47	-290.54	-260.86	-263.54
-47	-326.14	-311.64	-320.85	-310.14	-292.27	-289.03	-262.92	-266.54
-22	-320.40	-306.06	-316.51	-304.74	-288.85	-284.86	-259.13	-263.39
3	-313.96	-300.22	-309.96	-298.75	-280.67	-276.73	-246.18	-250.49
28	-306.29	-293.73	-300.67	-291.74	-265.66	-261.19	-216.46	-218.52
53	-296.61	-285.70	-288.15	-282.72	-237.32	-228.99	-153.92	-142.35
78	-283.64	-274.66	-269.87	-269.97	-178.80	-154.97	-21.58	46.69

Supporting Information available for publication.

G09 input data used for the G8 complexes with two cations ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ , or  $\text{Rb}^+$ ). The moving cation is given its coordinates at the start of the trajectory ( $Z=-2.72 \text{ \AA}$ ) the  $Z$  coordinate of the fixed cation being set at  $2.80 \text{ \AA}$ .

### Acknowledgments.

We wish to thank the Grand Equipement National de Calcul Intensif (GENCI), Institut du Développement et des Ressources en Informatique Scientifique (IDRIS), Centre Informatique de l'Enseignement Supérieur (CINES, France, project No. x2009-075009), and the Centre de Ressources Informatiques de Haute Normandie (CRIHAN, Rouen, France, project 1998053). JES and JS acknowledge support by the Czech Science Foundation [grant number 16-13721S]. Their research has also been financially supported by the Ministry of Education, Youth and Sports of the Czech Republic under the project CEITEC 2020 (LQ1601).

### References.

1. Rhodes, D.; Lipps, H. J., G-Quadruplexes and their Regulatory Roles in Biology. *Nucleic Acids Research* **2015**, *43* (18), 8627-8637.
2. Williamson, J. R., G-Quartet Structures in Telomeric DNA. *Annual Review of Biophysics and Biomolecular Structure* **1994**, *23* (1), 703-730.
3. Rodriguez, R.; Miller, K. M.; Forment, J. V.; Bradshaw, C. R.; Nikan, M.; Britton, S.; Oelschlaegel, T.; Xhemalce, B.; Balasubramanian, S.; Jackson, S. P., Small Molecule-Induced DNA Damage Identifies Alternative DNA Structures in Human Genes. *Nature chemical biology* **2012**, *8* (3), 301-310.
4. Biffi, G.; Tannahill, D.; McCafferty, J.; Balasubramanian, S., Quantitative Visualization of DNA G-Quadruplex Structures in Human Cells. *Nature chemistry* **2013**, *5* (3), 182-186.
5. Siddiqui-Jain, A.; Grand, C. L.; Bearss, D. J.; Hurley, L. H., Direct Evidence for a G-Quadruplex in a Promoter Region and its Targeting with a Small Molecule to Repress *c-Myc* Transcription. *Proceedings of the National Academy of Sciences of the United States of America* **2002**, *99* (18), 11593-11598.
6. Dexheimer, T. S.; Sun, D.; Hurley, L. H., Deconvoluting the Structural and Drug-Recognition Complexity of the G-Quadruplex-Forming Region Upstream of the *bcl-2* P1 Promoter. *Journal of the American Chemical Society* **2006**, *128* (16), 5404-5415.
7. Wei, D.; Parkinson, G. N.; Reszka, A. P.; Neidle, S., Crystal Structure of a *c-Kit* Promoter Quadruplex Reveals the Structural Role of Metal Ions and Water Molecules in Maintaining Loop Conformation. *Nucleic Acids Research* **2012**, *40* (10), 4691-4700.
8. Agrawal, P.; Hatzakis, E.; Guo, K.; Carver, M.; Yang, D., Solution Structure of the Major G-Quadruplex Formed in the Human VEGF Promoter in  $\text{K}^+$ : Insights into Loop

- Interactions of the Parallel G-Quadruplexes. *Nucleic Acids Research* **2013**, *41* (22), 10584-10592.
9. Métifiot, M.; Amrane, S.; Litvak, S.; Andreola, M.-L., G-Quadruplexes in Viruses: Function and Potential Therapeutic Applications. *Nucleic Acids Research* **2014**, *42* (20), 12352-12366.
10. Amrane, S.; Kerkour, A.; Bedrat, A.; Vialet, B.; Andreola, M.-L.; Mergny, J.-L., Topology of a DNA G-Quadruplex Structure Formed in the HIV-1 Promoter: A Potential Target for Anti-HIV Drug Development. *Journal of the American Chemical Society* **2014**, *136* (14), 5249-5252.
11. Alcaro, S.; Musetti, C.; Distinto, S.; Casatti, M.; Zagotto, G.; Artese, A.; Parrotta, L.; Moraca, F.; Costa, G.; Ortuso, F.; Maccioni, E.; Sissi, C., Identification and Characterization of New DNA G-Quadruplex Binders Selected by a Combination of Ligand and Structure-Based Virtual Screening Approaches. *Journal of Medicinal Chemistry* **2013**, *56* (3), 843-855.
12. Teulade-Fichou, M.-P.; Carrasco, C.; Guittat, L.; Bailly, C.; Alberti, P.; Mergny, J.-L.; David, A.; Lehn, J.-M.; Wilson, W. D., Selective Recognition of G-Quadruplex Telomeric DNA by a Bis(quinacridine) Macrocycle. *Journal of the American Chemical Society* **2003**, *125* (16), 4732-4740.
13. Castor, K. J.; Liu, Z.; Fakhoury, J.; Hancock, M. A.; Mittermaier, A.; Moitessier, N.; Sleiman, H. F., A Platinum(II) Phenylphenanthroimidazole with an Extended Side-Chain Exhibits Slow Dissociation from a c-Kit G-Quadruplex Motif. *Chemistry. A European Journal* **2013**, *19* (52), 17836-17845.
14. Balasubramanian, S.; Hurley, L. H.; Neidle, S., Targeting G-Quadruplexes in Gene Promoters: a Novel Anticancer Strategy? *Nature reviews. Drug discovery* **2011**, *10* (4), 261-275.
15. Rajendran, A.; Endo, M.; Hidaka, K.; Teulade-Fichou, M.-P.; Mergny, J.-L.; Sugiyama, H., Small Molecule Binding to a G-Hairpin and a G-Triplex: a New Insight into Anticancer Drug Design Targeting G-Rich Regions. *Chemical Communications* **2015**, *51* (44), 9181-9184.
16. Livshits, G. I.; Stern, A.; Rotem, D.; Borovok, N.; Eidelstein, G.; Migliore, A.; Penzo, E.; Wind, S. J.; Di Felice, R.; Skourtis, S. S. et al. Long-Range Charge Transport in Single G-Quadruplex DNA Molecules. *Nat Nano* **2014**, *9* (12), 1040-1046.
17. Ma'ani Hessari, N.; Spindler, L.; Troha, T.; Lam, W.-C.; Drevenšek-Olenik, I.; Webba da Silva, M., Programmed Self-Assembly of a Quadruplex DNA Nanowire. *Chemistry. A European Journal* **2014**, *20* (13), 3626-3630.
18. Jissy, A. K.; Ashik, U. P. M.; Datta, A., Nucleic Acid G-Quartets: Insights into Diverse Patterns and Optical Properties. *The Journal of Physical Chemistry C* **2011**, *115* (25), 12530-12546.
19. Hua, Y.; Chaugenet-Barret, P.; Improtta, R.; Vayá, I.; Gustavsson, T.; Kotlyar, A. B.; Zikich, D.; Šket, P.; Plavec, J.; Markovitsi, D., Cation Effect on the Electronic Excited States of Guanine Nanostructures Studied by Time-Resolved Fluorescence Spectroscopy. *The Journal of Physical Chemistry C* **2012**, *116* (27), 14682-14689.
20. Liu, S.-P.; Weisbrod, S. H.; Tang, Z.; Marx, A.; Scheer, E.; Erbe, A., Direct Measurement of Electrical Transport Through G-Quadruplex DNA with Mechanically Controllable Break Junction Electrodes. *Angewandte Chemie International Edition* **2010**, *49* (19), 3313-3316.
21. Trajkovski, M.; Plavec, J., Assessing Roles of Cations in G-Quadruplex-Based Nanowires by NMR. *The Journal of Physical Chemistry C* **2012**, *116* (44), 23821-23825.
22. Parkinson, G. N.; Lee, M. P. H.; Neidle, S., Crystal Structure of Parallel Quadruplexes from Human Telomeric DNA. *Nature* **2002**, *417* (6891), 876-880.

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
23. Bouaziz, S.; Kettani, A.; Patel, D. J., A K Cation-Induced Conformational Switch within a Loop Spanning Segment of a DNA Quadruplex Containing G-G-G-C Repeats. *Journal of Molecular Biology* **1998**, *282* (3), 637-652.
24. Lim, K. W.; Amrane, S.; Bouaziz, S.; Xu, W.; Mu, Y.; Patel, D. J.; Luu, K. N.; Phan, A. T., Structure of the Human Telomere in K(+) Solution: a Stable Basket-Type G-Quadruplex with only two G-Tetrad Layers. *Journal of the American Chemical Society* **2009**, *131* (12), 4301-4309.
25. Campbell, N. H.; Parkinson, G. N.; Reszka, A. P.; Neidle, S., Structural Basis of DNA Quadruplex Recognition by an Acridine Drug. *Journal of the American Chemical Society* **2008**, *130* (21), 6722-6724.
26. Agrawal, P.; Lin, C.; Mathad, R. I.; Carver, M.; Yang, D., The Major G-Quadruplex Formed in the Human BCL-2 Proximal Promoter Adopts a Parallel Structure with a 13-nt Loop in K(+) Solution. *Journal of the American Chemical Society* **2014**, *136* (5), 1750-1753.
27. Ren, J.; Qu, X.; Trent, J. O.; Chaires, J. B., Tiny Telomere DNA. *Nucleic Acids Research* **2002**, *30* (11), 2307-2315.
28. Fadrná, E.; Špačková, N. a.; Sarzyńska, J.; Koča, J.; Orozco, M.; Cheatham, T. E.; Kulinski, T.; Šponer, J., Single Stranded Loops of Quadruplex DNA As Key Benchmark for Testing Nucleic Acids Force Fields. *Journal of Chemical Theory and Computation* **2009**, *5* (9), 2514-2530.
29. Islam, B.; Stadlbauer, P.; Krepl, M.; Koca, J.; Neidle, S.; Haider, S.; Šponer, J., Extended Molecular Dynamics of a *c-kit* Promoter Quadruplex. *Nucleic Acids Research* **2015**, *43* (18), 8673-8693.
30. Stadlbauer, P.; Mazzanti, L.; Cragolini, T.; Wales, D. J.; Derreumaux, P.; Pasquali, S.; Šponer, J., Coarse-Grained Simulations Complemented by Atomistic Molecular Dynamics Provide New Insights into Folding and Unfolding of Human Telomeric G-Quadruplexes. *Journal of Chemical Theory and Computation* **2016**, *12* (12), 6077-6097.
31. Šponer, J.; Bussi, G.; Stadlbauer, P.; Kührová, P.; Banáš, P.; Islam, B.; Haider, S.; Neidle, S.; Otyepka, M., Folding of Guanine Quadruplex Molecules—Funnel-Like Mechanism or Kinetic Partitioning? An Overview from MD Simulation Studies. *Biochimica et Biophysica Acta (BBA) - General Subjects*, in press. <http://dx.doi.org/10.1016/j.bbagen.2016.12.008>
32. Bazzi, S.; Novotný, J.; Yurenko, Y. P.; Marek, R., Designing a New Class of Bases for Nucleic Acid Quadruplexes and Quadruplex-Active Ligands. *Chemistry. A European Journal* **2015**, *21* (26), 9414-9425.
33. Zaccaria, F.; Paragi, G.; Fonseca Guerra, C., The Role of Alkali Metal Cations in the Stabilization of Guanine Quadruplexes: why K<sup>+</sup> is the Best. *Physical Chemistry Chemical Physics* **2016**, *18* (31), 20895-20904.
34. Šponer, J.; Mládek, A.; Špačková, N.; Cang, X.; Cheatham, T. E.; Grimme, S., Relative Stability of Different DNA Guanine Quadruplex Stem Topologies Derived Using Large-Scale Quantum-Chemical Computations. *Journal of the American Chemical Society* **2013**, *135* (26), 9785-9796.
35. Fonseca-Guerra, C.; Zijlstra, H.; Paragi, G.; Bickelhaupt, F. M., Telomere Structure and Stability: Covalency in Hydrogen Bonds, Not Resonance Assistance, Causes Cooperativity in Guanine Quartets. *Chemistry – A European Journal* **2011**, *17* (45), 12612-12622.
36. Paragi, G.; Fonseca-Guerra, C., Cooperativity in the Self-Assembly of the Guanine Nucleobase into Quartet and Ribbon Structures on Surfaces. *Chemistry – A European Journal* **2017**, *23*, (13) 3042-3050.
37. Gkionis, K.; Kruse, H.; Platts, J. A.; Mládek, A.; Koča, J.; Šponer, J., Ion Binding to Quadruplex DNA Stems. Comparison of MM and QM Descriptions Reveals Sizable

1  
2  
3  
4  
5 Polarization Effects Not Included in Contemporary Simulations. *Journal of Chemical Theory and Computation* **2014**, *10* (3), 1326-1340.

6  
7 38. Gresh, N.; Šponer, J. E.; Špačková, N. a.; Leszczynski, J.; Šponer, J., Theoretical  
8 Study of Binding of Hydrated Zn(II) and Mg(II) Cations to 5'-Guanosine Monophosphate.  
9 Toward Polarizable Molecular Mechanics for DNA and RNA. *The Journal of Physical*  
10 *Chemistry B* **2003**, *107* (33), 8669-8681.

11 39. Gresh, N.; Cisneros, G. A.; Darden, T. A.; Piquemal, J.-P., Anisotropic, Polarizable  
12 Molecular Mechanics Studies of Inter- and Intramolecular Interactions and  
13 Ligand-Macromolecule Complexes. A Bottom-Up Strategy. *Journal of Chemical Theory and*  
14 *Computation* **2007**, *3* (6), 1960-1986.

15 40. Dudev, T.; Devereux, M.; Meuwly, M.; Lim, C.; Piquemal, J.-P.; Gresh, N., Quantum-  
16 Chemistry Based Calibration of the Alkali Metal Cation Series (Li<sup>+</sup>-Cs<sup>+</sup>) for Large-Scale  
17 Polarizable Molecular Mechanics/Dynamics Simulations. *Journal of Computational*  
18 *Chemistry* **2015**, *36* (5), 285-302.

19 41. Gresh, N.; Sponer, J. E.; Devereux, M.; Gkionis, K.; de Courcy, B.; Piquemal, J.-P.;  
20 Sponer, J., Stacked and H-Bonded Cytosine Dimers. Analysis of the Intermolecular  
21 Interaction Energies by Parallel Quantum Chemistry and Polarizable Molecular Mechanics.  
22 *The Journal of Physical Chemistry B* **2015**, *119* (30), 9477-9495.

23 42. Gresh, N.; Pullman, B. A Theoretical study of the Selective Entrapment of Alkali and  
24 Ammonium Cations Between Guanine Tetramers. *Int. J. Quantum Chem. Quantum Biol.*  
25 *Symp.* **1986**, *12*, 49-56.

26 43. Dunning, Jr., T. H. D., Gaussian Basis Sets for Use in Correlated Molecular  
27 Calculations. I. The atoms boron through neon and hydrogen. *The Journal of Chemical*  
28 *Physics* **1989**, *90* (2), 1007-1023.

29 44. Feller, D., The Role of Data Bases in Support of Computational Chemistry  
30 Calculations. *Journal of Computational Chemistry* **1996**, *17* (13), 1571-1586.

31 45. Machado, S. F.; Camiletti, G. G.; Neto, A. C.; Jorge, F. E.; Jorge, R. S., Gaussian  
32 Basis Set of Triple Zeta Valence Quality for the Atoms from K to Kr: Application in DFT and  
33 CCSD(T) Calculations of Molecular Properties. *Molecular Physics* **2009**, *107* (16), 1713-  
34 1727.

35 46. Bergner, A.; Dolg, M.; Küchle, W.; Stoll, H.; Preuß, H., Ab Initio Energy-Adjusted  
36 Pseudopotentials for Elements of Groups 13-17. *Molecular Physics* **1993**, *80* (6), 1431-1441.

37 47. Stevens, W. J.; Fink, W. H., Frozen Fragment Reduced Variational Space Analysis of  
38 Hydrogen Bonding Interactions. Application to the Water Dimer. *Chemical Physics Letters*  
39 **1987**, *139* (1), 15-22.

40 48. Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J.  
41 H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.;  
42 Montgomery, J. A., General Atomic and Molecular Electronic Structure System. *Journal of*  
43 *Computational Chemistry* **1993**, *14* (11), 1347-1363.

44 49. Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H., A Consistent and Accurate Ab Initio  
45 Parametrization of Density Functional Dispersion Correction (DFT-D) for the 94 Elements H-  
46 Pu. *The Journal of Chemical Physics* **2010**, *132* (15), 154104.

47 50. Lee, C.; Yang, W.; Parr, R. G., Development of the Colle-Salvetti Correlation-Energy  
48 Formula into a Functional of the Electron Density. *Physical Review B* **1988**, *37* (2), 785-789.

49 51. Becke, A. D., A New Mixing of Hartree-Fock and Local Density-Functional Theories.  
50 *The Journal of Chemical Physics* **1993**, *98* (2), 1372-1377.

51 52. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.;  
52 Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A. et al. Gaussian  
53 09, Revision B.01 Wallingford CT, 2009.

- 1  
2  
3  
4  
5 53. Stone, A. J., Distributed Multipole Analysis: Stability for Large Basis Sets. *Journal of*  
6 *Chemical Theory and Computation* **2005**, *1* (6), 1128-1132.
- 7 54. Piquemal, J.-P.; Gresh, N.; Giessner-Prettre, C., Improved Formulas for the  
8 Calculation of the Electrostatic Contribution to the Intermolecular Interaction Energy from  
9 Multipolar Expansion of the Electronic Distribution. *The Journal of Physical Chemistry A*  
10 **2003**, *107* (48), 10353-10359.
- 11 55. Piquemal, J.-P.; Chevreau, H.; Gresh, N., Toward a Separate Reproduction of the  
12 Contributions to the Hartree-Fock and DFT Intermolecular Interaction Energies by  
13 Polarizable Molecular Mechanics with the SIBFA Potential. *Journal of Chemical Theory and*  
14 *Computation* **2007**, *3* (3), 824-837.
- 15 56. Garmer, D. R.; Stevens, W. J., Transferability of Molecular Distributed Polarizabilities  
16 from a Simple Localized Orbital Based Method. *The Journal of Physical Chemistry* **1989**, *93*  
17 (25), 8263-8270.
- 18 57. Gresh, N., Model, Multiply Hydrogen-Bonded Water Oligomers (N = 3-20). How  
19 Closely Can a Separable, ab Initio-Grouped Molecular Mechanics Procedure Reproduce the  
20 Results of Supermolecule Quantum Chemical Computations? *The Journal of Physical*  
21 *Chemistry A* **1997**, *101* (46), 8680-8694.
- 22 58. Creuzet, S.; Gresh, N.; Langlet, J. Adjustment of the SIBFA Method for Potential  
23 Maps to Study Hydrogen Bonding Vibrational Frequencies. *J. Chim.-Phys.*, **1991**, *88*, 2399-  
24 2409.
- 25 59. Devereux, M.; Gresh, N.; Piquemal, J.-P.; Meuwly, M., A Supervised Fitting  
26 Approach to Force Field Parametrization with Application to the SIBFA Polarizable Force  
27 Field. *Journal of Computational Chemistry* **2014**, *35* (21), 1577-1591.
- 28 60. Law, M. M.; Hutson, J. M., I-NoLLS: A Program for Interactive Nonlinear Least-  
29 Squares Fitting of the Parameters of Physical Models. *Computer Physics Communications*  
30 **1997**, *102* (1-3), 252-268.
- 31 61. Johnson, E. R.; Keinan, S.; Mori-Sánchez, P.; Contreras-García, J.; Cohen, A. J.;  
32 Yang, W., Revealing Non-Covalent Interactions. *Journal of the American Chemical Society*  
33 **2010**, *132* (18), 6498-6506.
- 34 62. Contreras-García, J.; Johnson, E. R.; Keinan, S.; Chaudret, R.; Piquemal, J.-P.;  
35 Beratan, D. N.; Yang, W., NCIPLLOT: a program for plotting non-covalent interaction regions.  
36 *Journal of chemical theory and computation* **2011**, *7* (3), 625-632.
- 37 63. Misquitta, A. J.; Stone, A. J.; Fazeli, F., Distributed Multipoles from a Robust Basis-  
38 Space Implementation of the Iterated Stockholder Atoms Procedure. *Journal of Chemical*  
39 *Theory and Computation* **2014**, *10* (12), 5405-5418.
- 40 64. Lillestolen, T. C.; Wheatley, R. J., Atomic Charge Densities Generated Using an  
41 Iterative Stockholder Procedure. *The Journal of Chemical Physics* **2009**, *131* (14), 144101.
- 42 65. Elking, D. M.; Cisneros, G. A.; Piquemal, J.-P.; Darden, T. A.; Pedersen, L. G.,  
43 Gaussian Multipole Model (GMM). *Journal of Chemical Theory and Computation* **2010**, *6*  
44 (1), 190-202.
- 45 66. Cisneros, G. A., Application of Gaussian Electrostatic Model (GEM) Distributed  
46 Multipoles in the AMOEBA Force Field. *Journal of Chemical Theory and Computation* **2012**,  
47 *8* (12), 5072-5080.
- 48 67. El Hage, K.; Piquemal, J.-P.; Hobaika, Z.; Maroun, R. G.; Gresh, N., Substituent-  
49 Modulated Affinities of Halobenzene Derivatives to the HIV-1 Integrase Recognition Site.  
50 Analyses of the Interaction Energies by Parallel Quantum Chemical and Polarizable  
51 Molecular Mechanics. *The Journal of Physical Chemistry A* **2014**, *118* (41), 9772-9782.
- 52 68. Gresh, N.; Perahia, D.; de Courcy, B.; Foret, J.; Roux, C.; El-Khoury, L.; Piquemal, J.-  
53 P.; Salmon, L., Complexes of a Zn-Metalloenzyme Binding Site with Hydroxamate-  
54 Containing Ligands. A Case for Detailed Benchmarkings of Polarizable Molecular  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5 Mechanics/Dynamics Potentials when the Experimental Binding Structure is Unknown.  
6 *Journal of Computational Chemistry* **2016**, *37* (32), 2770-2782.
- 7 69. Ponder, J. W.; Wu, C.; Ren, P.; Pande, V. S.; Chodera, J. D.; Schnieders, M. J.;  
8 Haque, I.; Mobley, D. L.; Lambrecht, D. S.; DiStasio, R. A. et al. Current Status of the  
9 AMOEBA Polarizable Force Field. *The Journal of Physical Chemistry B* **2010**, *114* (8), 2549-  
10 2564.
- 11 70. Zhang, C.; Bell, D.; Harger, M.; Ren, P., Polarizable Multipole-Based Force Field for  
12 Aromatic Molecules and Nucleobases. *Journal of Chemical Theory and Computation* **2017**,  
13 *13*, 666-676.
- 14 71. Lemkul, J. A.; MacKerell, A. D., Balancing the Interactions of Mg<sup>2+</sup> in Aqueous  
15 Solution and with Nucleic Acid Moieties For a Polarizable Force Field Based on the Classical  
16 Drude Oscillator Model. *The Journal of Physical Chemistry B* **2016**, *120* (44), 11436-11448.
- 17 72. Harder, E.; Anisimov, V. M.; Vorobyov, I. V.; Lopes, P. E. M.; Noskov, S. Y.;  
18 MacKerell, A. D.; Roux, B., Atomic Level Anisotropy in the Electrostatic Modeling of Lone  
19 Pairs for a Polarizable Force Field Based on the Classical Drude Oscillator. *Journal of*  
20 *Chemical Theory and Computation* **2006**, *2* (6), 1587-1597.
- 21 73. Tinker HP\_Team, Tinker-HP, <http://www.ip2ct.upmc.fr/tinkerHP>, 2016. Accessed March  
22 29, 2017.
- 23 74. Jansen, G.; Hesselmann, A., Comment on “Using Kohn–Sham Orbitals in Symmetry-  
24 Adapted Perturbation Theory To Investigate Intermolecular Interactions”. *The Journal of*  
25 *Physical Chemistry A* **2001**, *105* (49), 11156-11157.
- 26 75. Jeziorski, B.; Moszynski, R.; Szalewicz, K., Perturbation Theory Approach to  
27 Intermolecular Potential Energy Surfaces of van der Waals Complexes. *Chemical Reviews*  
28 **1994**, *94* (7), 1887-1930.
- 29 76. Misquitta, A. J.; Jeziorski, B.; Szalewicz, K., Dispersion Energy from Density-  
30 Functional Theory Description of Monomers. *Physical Review Letters* **2003**, *91* (3), 033201.
- 31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55

56 **Figures captions:**  
57  
58  
59  
60

**Figure 1.** Complex of two stacked G quartets with two monovalent cations. Representation of the trajectory followed by the moving cation. The fixed cation is located on top of the upper quartet.

**Figures 2.** Complex of two stacked G quartets with one monovalent cation.  $\Delta E(\text{HF})$ ,  $\Delta E(\text{SIBFA})$ , and  $E_1/E_2(\text{SIBFA})$  profiles for cation channeling along the Z axis.

2a:  $\text{Li}^+$ ; 2b:  $\text{Na}^+$ ; 2c:  $\text{K}^+$ ; 2d:  $\text{Rb}^+$ .

**Figures 3.** Complex of two stacked G quartets with one monovalent cation.

3a:  $\Delta E(\text{B97-D3})$ ,  $\Delta E(\text{B3LYP-D3})$ ,  $\Delta E_{\text{tot}}(\text{SIBFA})$  and  $E_1/E_2(\text{SIBFA})$  profiles for  $\text{Li}^+$  channeling along the Z axis.

3b:  $\Delta E(\text{HF})$ ,  $\Delta E(\text{B3LYP})$  and  $\Delta E(\text{SIBFA})$  profiles for  $\text{Li}^+$  channeling.

3c-3d:  $\Delta E(\text{B97-D3})$ ,  $\Delta E(\text{B3LYP-D3})$ ,  $\Delta E_{\text{tot}}(\text{SIBFA})$  and  $E_1/E_2(\text{SIBFA})$  profiles for cation channeling along the Z axis.

3c :  $\text{Na}^+$  ; 3d :  $\text{K}^+$  ; 3e:  $\text{Rb}^+$ .

**Figure 4.** Complex of two stacked G quartets with two monovalent cations with one moving cation.  $\Delta E(\text{HF})$ ,  $\Delta E(\text{SIBFA})$ , and  $E_1/E_2(\text{SIBFA})$  profiles for cation channeling along the Z axis.

4a:  $\text{Li}^+$ ; 4b:  $\text{Na}^+$ ; 4c:  $\text{K}^+$ ; 4d:  $\text{Rb}^+$ .

**Figure 5.** Complex of two stacked G quartets with two monovalent cations with one moving cation.  $\Delta E(\text{B97-D3})$ ,  $\Delta E_{\text{tot}}(\text{SIBFA})$ , and  $E_1/E_2(\text{SIBFA})$  profiles for cation channeling along the Z axis.

5a:  $\text{Li}^+$ ; 5b:  $\text{Na}^+$ ; 5c:  $\text{K}^+$ ; 5d:  $\text{Rb}^+$ .

**Figures 6a-b.** 3D plot NCI analysis of the two guanine quartets without cation: (a) in the XZ plane; (b) in the XY plane; and (c) corresponding 2D plot. In the 3D plots, the NCI surfaces correspond to  $s = 0.50$  isosurfaces.

**Figures 7a-d.** 2D and 3D plot NCI analyses of the two guanine quartets with  $\text{K}^+$  along the Z axis: (a):  $Z = -2.7 \text{ \AA}$ , (b):  $Z = -1.7 \text{ \AA}$ , (c):  $Z = 0.0 \text{ \AA}$ , (d):  $Z = 0.8 \text{ \AA}$ . In the 3D plots, the NCI surfaces correspond to  $s = 0.50$  isosurfaces.

**Figures 8a-d.** 2D and 3D plot NCI analyses of the two guanine quartets with a fixed  $\text{K}^+$  cation at  $Z = 2.8 \text{ \AA}$  and a mobile  $\text{K}^+$  cation along the Z axis : (a):  $Z = -2.7 \text{ \AA}$ , (b):  $Z = -1.7 \text{ \AA}$ , (c):  $Z = 0.0 \text{ \AA}$ , (d):  $Z = 0.8 \text{ \AA}$ . In the 3D plots, the NCI surfaces correspond to  $s = 0.50$  isosurfaces.

**Table 1. Intermolecular interaction energies (kcal/mol) and their contributions in a G4 tetramer and evaluation of non-additivities. Comparisons between  $\Delta E(\text{RVS})$  and  $\Delta E(\text{SIBFA})$ .**

<i>G4 tetramer</i>	QC	SIBFA
$E_{\text{c}}/E_{\text{MTP}}$	-65.8	-67.9
$E_{\text{exch}}/E_{\text{rep}}$	44.2	42.4
$E_1$	-21.7	-25.5
$E_{\text{pol}}(\text{RVS})/E_{\text{pol}}^*$	-17.5	-17.0
$E_{\text{pol}}(\text{VR})/E_{\text{pol}}$	-23.8	-21.8
$E_{\text{ct}}$	-8.1	-9.2
$E_{\text{ct}}^*$	-6.5	
$\Delta E$	-52.0	-56.5
<i>Dimers</i>	QC	SIBFA
G1-2, G1-4, G2-3, G3-4		
$E_{\text{c}}/E_{\text{MTP}}$	-15.8	-16.4
$E_{\text{exch}}/E_{\text{rep}}$	11.1	10.6
$E_1$	-4.7	-5.8
$E_{\text{pol}}(\text{RVS})/E_{\text{pol}}^*$	-2.9	-2.8
$E_{\text{pol}}(\text{VR})/E_{\text{pol}}$	-3.7	-3.3
$E_{\text{ct}}$	-1.8	-2.2
$E_{\text{ct}}^*$	-1.5	
$\Delta E$	-9.9	-11.3

<i>Dimers</i> G1-3, G2-4	QC	SIBFA
$E_{\circ}/E_{MTP}$	-1.3	-1.3
$E_{\text{exch}}/E_{\text{rep}}$	0.0	0.0
$E_1$	-1.3	-1.3
$E_{\text{pol}}(\text{RVS})/E_{\text{pol}}^*$	-0.1	-0.1
$E_{\text{pol}}(\text{VR})/E_{\text{pol}}$	-0.1	-0.1
$E_{\text{ct}}$	0.0	0.0
$E_{\text{ct}}^*$	0.0	
<b><i>Summed values.</i></b>		
	-65.8	-67.8
$E_{\circ}/E_{MTP}$		
$E_{\text{exch}}/E_{\text{rep}}$	44.4	42.4
$E_1$	-21.4	-25.5
$E_{\text{pol}}(\text{RVS})/E_{\text{pol}}^*$	-11.6	-11.4
$\delta E_{\text{nadd}}$	-5.9	-5.8
$E_{\text{pol}}(\text{VR})/E_{\text{pol}}$	-15	-13.4
$\delta E_{\text{nadd}}$	-8.8	-8.4
$E_{\text{ct}}$	-7.3	-8.8
$\delta E_{\text{nadd}}$	-0.8	-0.8

**Table 2. Intermolecular interaction energies (kcal/mol) and their contributions in a G4 tetramer and evaluation of non-additivities. Comparisons between  $\Delta E(\text{DFT-D3})$  and  $\Delta E_{\text{tot}}(\text{SIBFA})$ .**

<b>B3LYP-D3</b>			
<i>G4 tetramer</i>	QC	SIBFA	
$\Delta E$	-74.7	-68.8	
$\Delta E(\text{MP2})$	-73.0		
<i>Dimers</i>			
	QC	SIBFA	
G1-2, G1-4, G2-3, G3-4	-15.1	-14.3	
G1-3, G2-4	-1.4	-1.4	
<i>Summed values</i>			
	-63.2	-60.0	
$\delta E_{\text{nadd}}$	-11.5	-8.8	

<b>B97-D3</b>			
<i>G4 tetramer</i>	QC	SIBFA	
$\Delta E$	-69.8	-68.8	
<i>Dimers</i>			
	QC	SIBFA	
G1-2, G1-4, G2-3, G3-4	-13.8	-14.3	
G1-3, G2-4	-1.4	-1.4	
<i>Summed values</i>			
	-58.0	-60.0	
$\delta E_{\text{nadd}}$	-11.8	-8.8	

**Table 3. Intermolecular interaction energies (kcal/mol) and their contributions in a stacked complex of bases G1-2 and G1'-2' of the first and second G4 tetramers and evaluation of non-additivities. Comparisons between  $\Delta E(\text{RVS})$  and  $\Delta E(\text{SIBFA})$ .**

<i>G4 tetramer</i>	QC	SIBFA
$E_C/E_{\text{MTP}}$	-26.4	-32.0
$E_{\text{exch}}/E_{\text{rep}}$	30.4	31.5
$E_1$	4.0	-0.5
$E_{\text{pol}}(\text{RVS})/E_{\text{pol}}^*$	-6.4	-6.0
$E_{\text{pol}}(\text{VR})/E_{\text{pol}}$	-9.4	-6.7
$E_{\text{ct}}$	-4.8	-4.6
$E_{\text{ct}}^*$	-2.5	
$\Delta E$	-7.8	-11.8
<i>Dimers</i>	QC	SIBFA
G1-G2, G1'-G2'		
$E_C/E_{\text{MTP}}$	-15.8	-16.4
$E_{\text{exch}}/E_{\text{rep}}$	11.1	10.7
$E_1$	-4.7	-5.7
$E_{\text{pol}}(\text{RVS})/E_{\text{pol}}^*$	-2.9	-2.7
$E_{\text{pol}}(\text{VR})/E_{\text{pol}}$	-3.8	-3.3
$E_{\text{ct}}$	-1.8	-2.2
$E_{\text{ct}}^*$	-1.4	
$\Delta E$	-9.9	-11.2
G1-G1'		
$E_C/E_{\text{MTP}}$	-1.3	-1.3
$E_{\text{exch}}/E_{\text{rep}}$	0.0	0.0
$E_1$	-1.3	-1.3
$E_{\text{pol}}(\text{RVS})/E_{\text{pol}}^*$	-0.1	-0.1
$E_{\text{pol}}(\text{VR})/E_{\text{pol}}$	-0.1	-0.1

1			
2			
3			
4			
5	$E_{ct}$	0.0	0.0
6	$E_{ct}^*$	0.0	
7			
8			
9	$\Delta E$	-1.4	-1.3
10			
11			
12	G1-G2'		
13	$E_c/E_{MTP}$	2.0	0.5
14	$E_{exch}/E_{rep}$	3.0	3.6
15	$E_1$	5.0	4.1
16			
17			
18	$E_{pol}(RVS)/E_{pol}^*$	-0.6	-0.7
19	$E_{pol}(VR)/E_{pol}$	-0.6	-0.7
20			
21			
22	$E_{ct}$	-0.5	-0.2
23	$E_{ct}^*$	-0.1	
24			
25			
26	$\Delta E$	3.9	3.2
27			
28			
29	G2-G1'		
30	$E_c/E_{MTP}$	2.0	0.4
31	$E_{exch}/E_{rep}$	3.1	3.7
32	$E_1$	5.1	4.1
33			
34			
35	$E_{pol}(RVS)/E_{pol}^*$	-0.6	-0.7
36	$E_{pol}(VR)/E_{pol}$	-0.6	-0.7
37			
38			
39	$E_{ct}$	-0.4	-0.2
40	$E_{ct}^*$	-0.1	
41			
42			
43	$\Delta E$	4.0	3.2
44			
45			
46	G2-G2'		
47	$E_c/E_{MTP}$	2.5	1.0
48	$E_{exch}/E_{rep}$	2.3	2.9
49	$E_1$	4.8	3.9
50			
51			
52	$E_{pol}(RVS)/E_{pol}^*$	-0.6	-0.6
53	$E_{pol}(VR)/E_{pol}$	-0.6	-0.6
54			
55			
56	$E_{ct}$	-0.2	-0.1
57	$E_{ct}^*$	-0.1	
58			
59			
60			

$\Delta E$	3.8	3.2
<hr/>		
<i>Summed dimer interactions</i>	QC	SIBFA
<hr/>		
$E_{\text{pol}}/E_{\text{MTP}}$	-26.5	-32.0
$E_{\text{exch}}/E_{\text{rep}}$	30.6	31.5
$E_1$	4.1	-0.5
$E_{\text{pol}}(\text{RVS})/E_{\text{pol}}^*$	-7.7	-7.7
$\delta E_{\text{nadd}}$	1.3	1.7
$E_{\text{pol}}(\text{VR})/E_{\text{pol}}$	-9.5	-8.7
$\delta E_{\text{nadd}}$	1.3	2.0
$E_{\text{ct}}$	-5.1	-4.8
$\delta E_{\text{nadd}}$	0.3	0.2
$E_{\text{ct}}^*$	-3.1	
$\delta E_{\text{nadd}}$	0.6	0.2
$\Delta E$	-9.5	-14.0
$\delta E_{\text{nadd}}$	1.7	2.2

**Table 4. Intermolecular interaction energies (kcal/mol) and their contributions in a stacked complex of bases G1-2 and G1'-2' of the first and second G4 tetramers and evaluation of non-additivities. Comparisons between  $\Delta E(\text{DFT-D3})$  and  $\Delta E_{\text{tot}}(\text{SIBFA})$ .**

**B3LYP-D3**

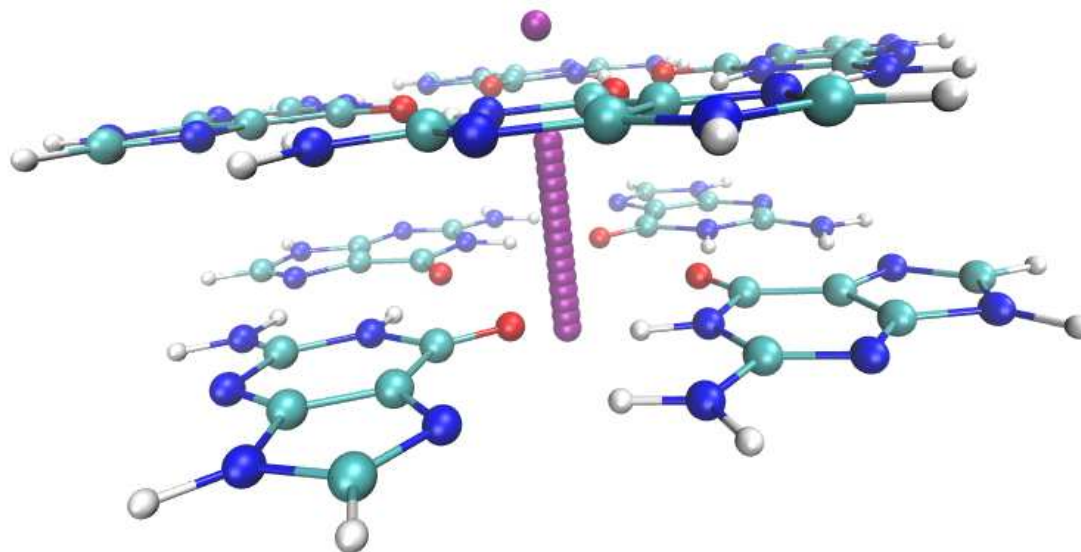
<i>G4 tetramer</i>	QC	SIBFA
$\Delta E$	-39.8	-38.0
<i>Dimers</i>		
	QC	SIBFA
G1-G2	-15.2	-14.3
G1-G1'	-1.3	-1.3
G1-G2'	-3.6	-3.3
G2-G1'	-3.4	-3.3
G2-G2'	-3.1	-3.0
G1'-G2'	-14.9	-14.3
<i>Summed values</i>	-41.4	-39.5
$\delta E_{\text{nadd}}$	1.6	1.5

**B97-D3**

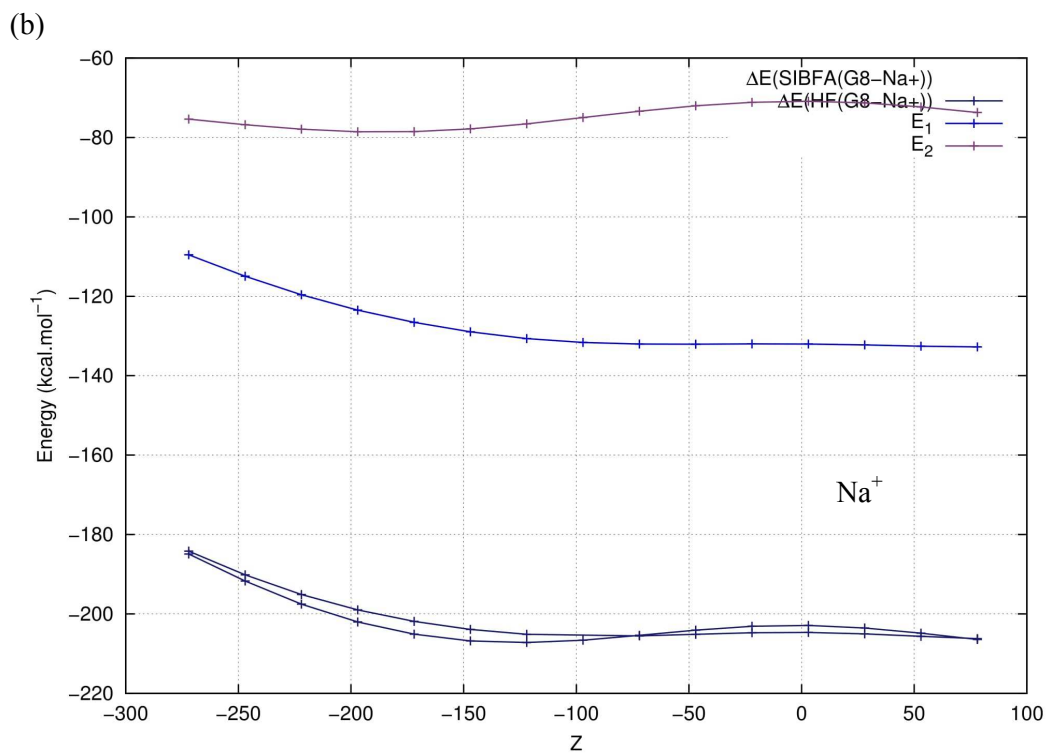
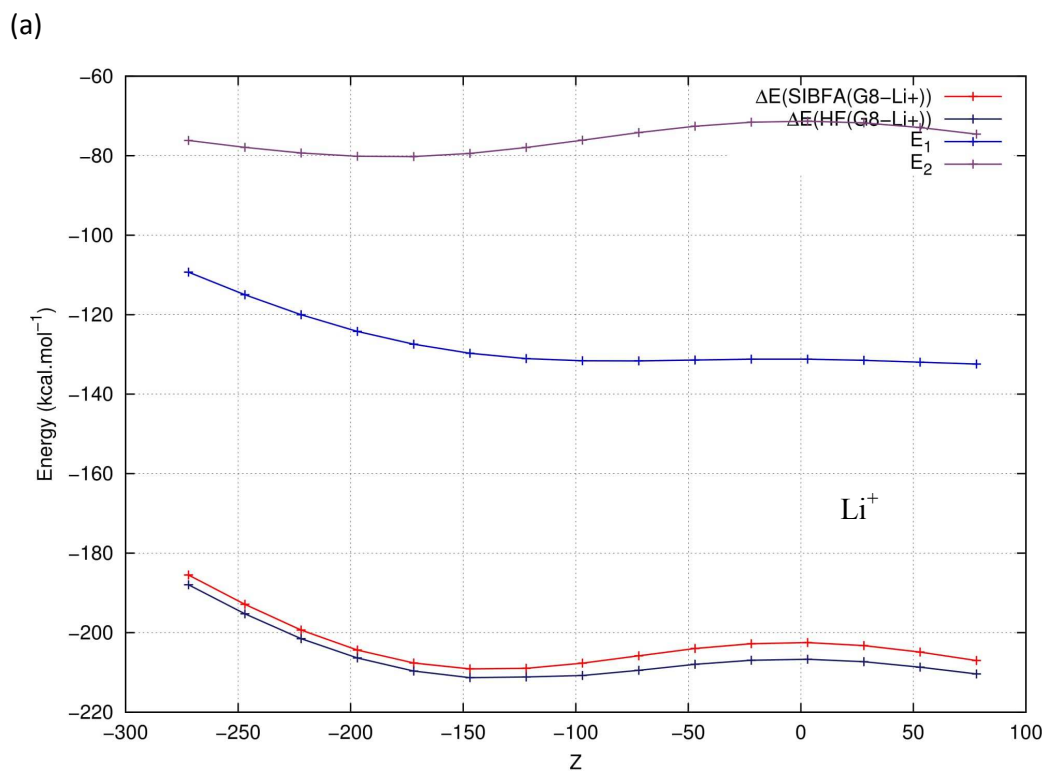
<i>G4 tetramer</i>	QC	SIBFA
$\Delta E$	-34.8	-38.0
<i>Dimers</i>		
	QC	SIBFA
G1-G2	-13.8	-14.3
G1-G1'	-1.2	-1.3
G1-G2'	-3.1	-3.3
G2-G1'	-2.8	-3.3
G2-G2'	-2.5	-3.0
G1'-G2'	-13.5	-14.3
Summed values	-37.0	-39.5
$\delta E_{\text{nadd}}$	2.2	1.5

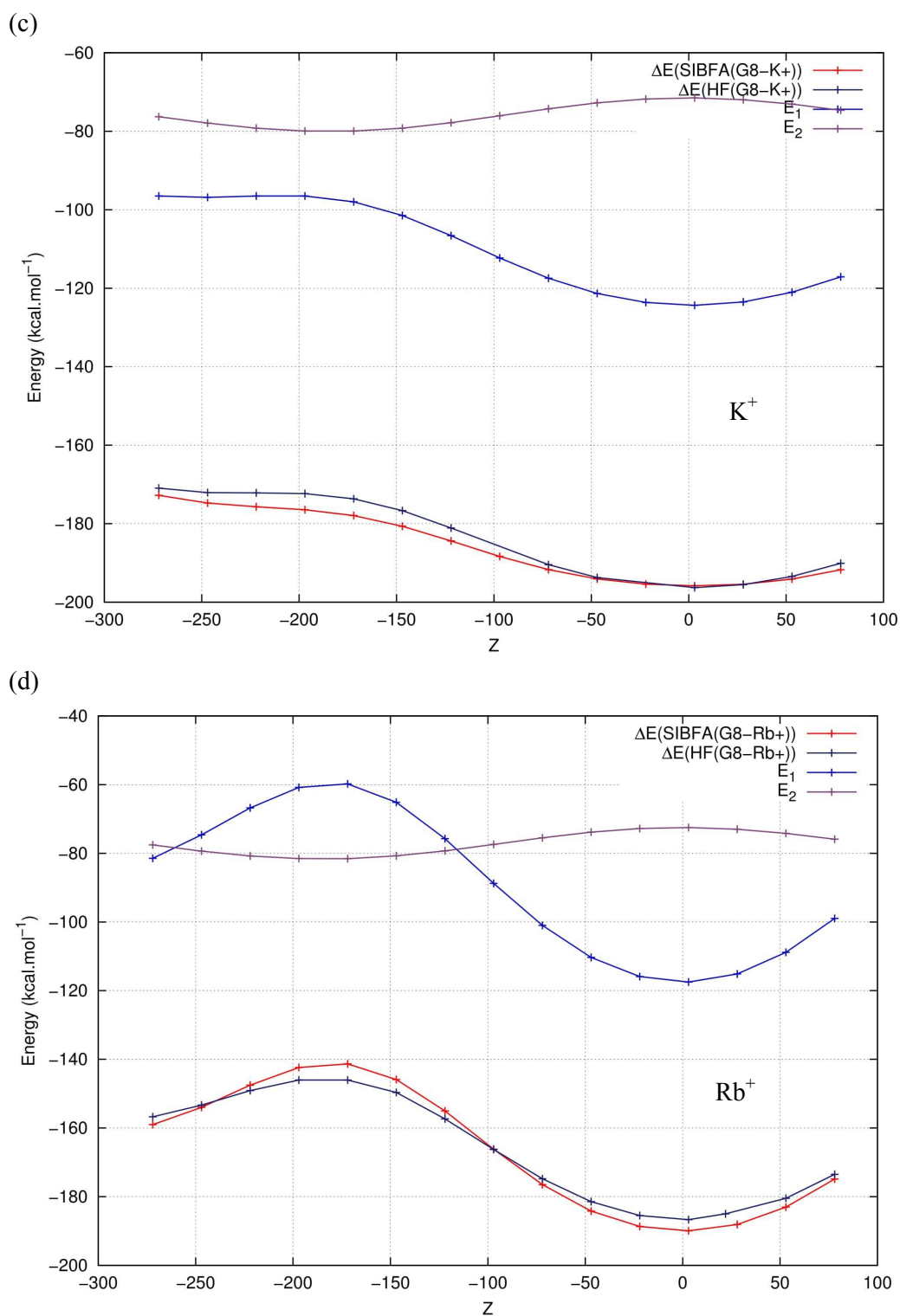
**Table 5. Intermolecular interaction energies (kcal/mol) in two stacked G4 tetramers.**

	QC(HF)	SIBFA	
$\Delta E$	-89.5	-94.8	
	QC(B3LYP-D3)	QC(B97-D3)	$\Delta E_{\text{tot}}(\text{SIBFA})$
$\Delta E$	-184.0	-168.6	-169.8



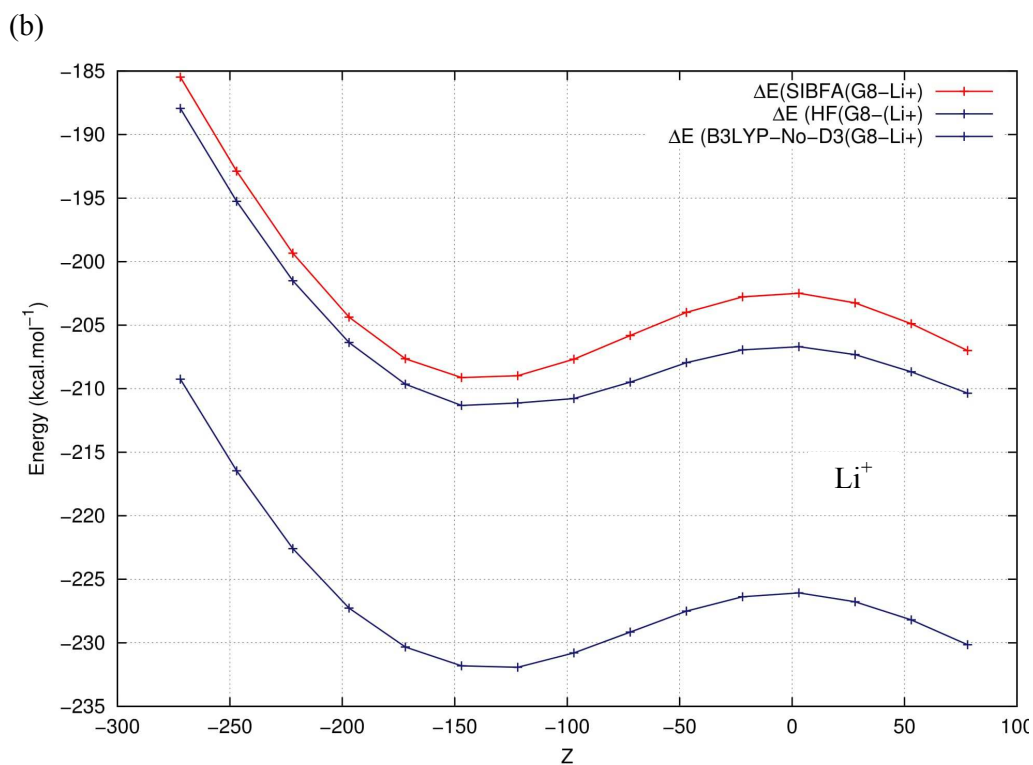
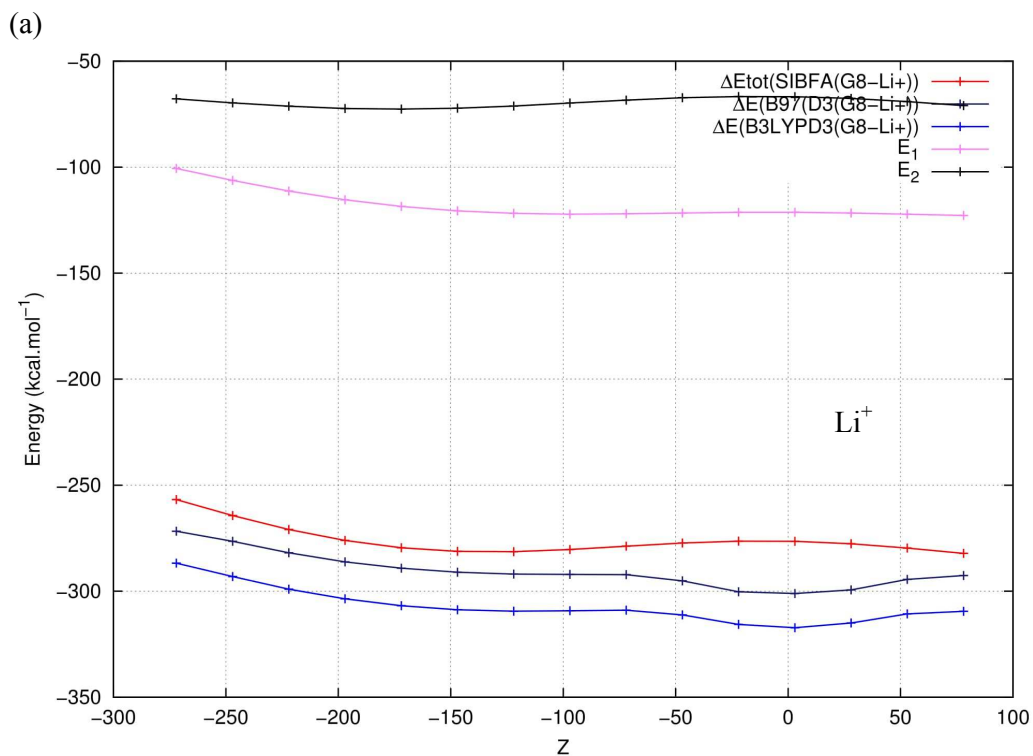
**Figure 1.** Representation of the complex of two stacked guanine quartets with one monovalent cation channeling along the Z axis and a fixed cation set on top of the upper quartet.

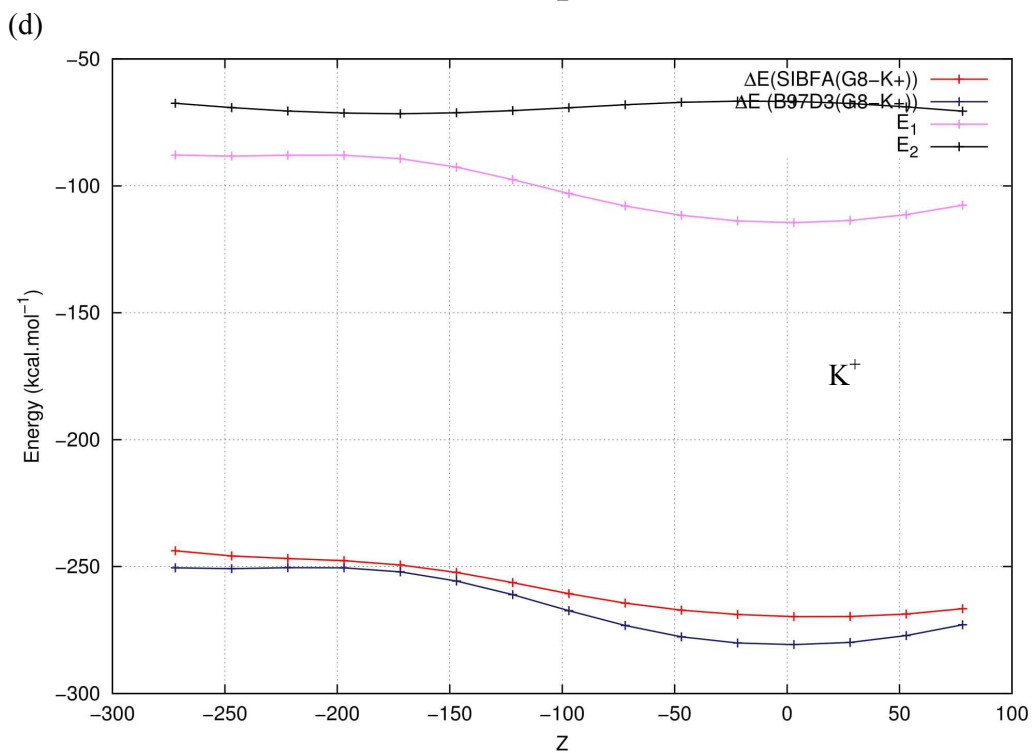
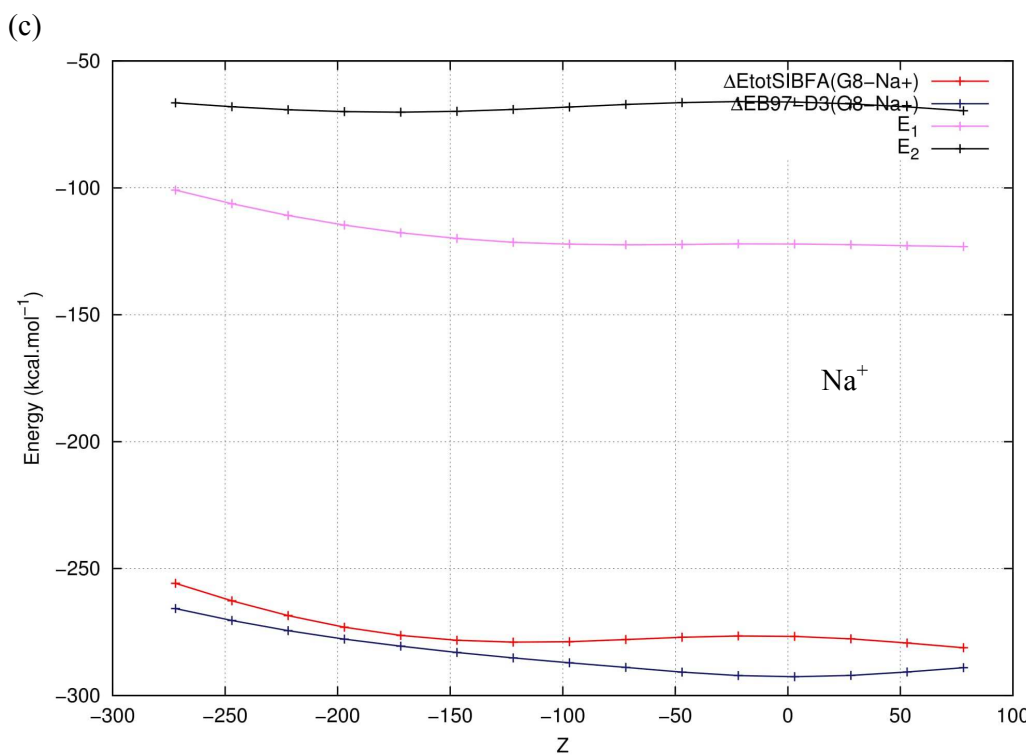


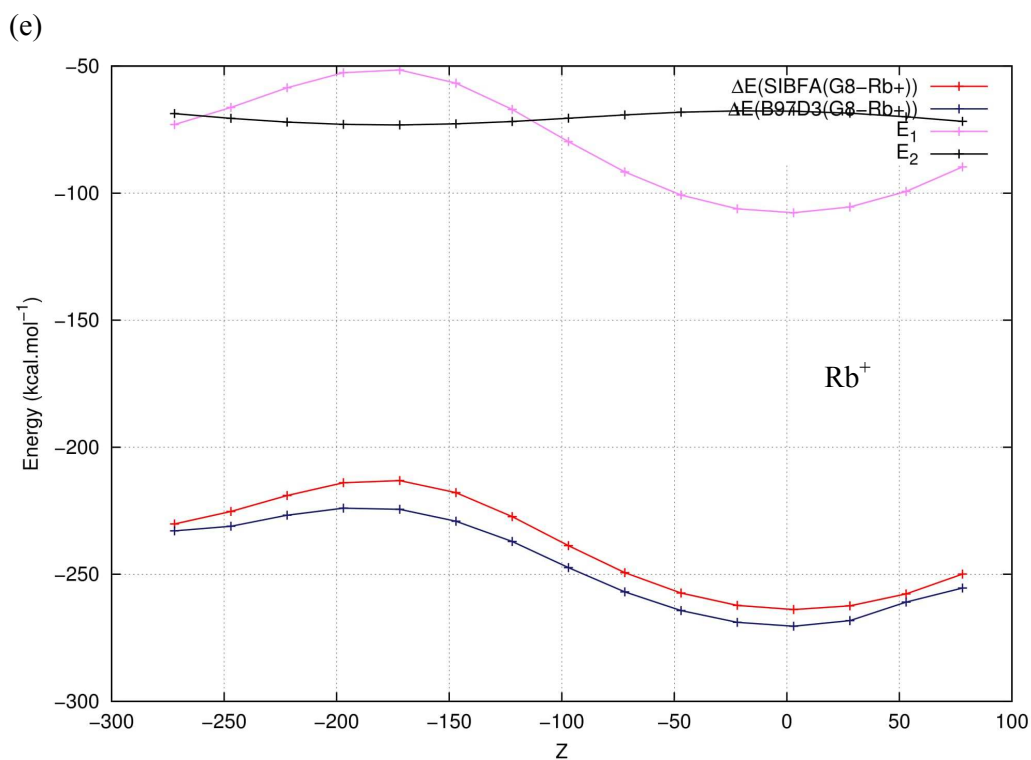


**Figure 2.** Complex of two stacked G quartets with one monovalent cation.  $\Delta E(\text{HF})$ ,  $\Delta E(\text{SIBFA})$ , and  $E_1/E_2(\text{SIBFA})$  profiles for cation channeling along the Z axis. 2a:  $\text{Li}^+$ ; 2b:

Na<sup>+</sup>; 2c: K<sup>+</sup>; 2d: Rb<sup>+</sup>. For clarity, the Z values along the abscissa (Å) were multiplied by a factor 100.





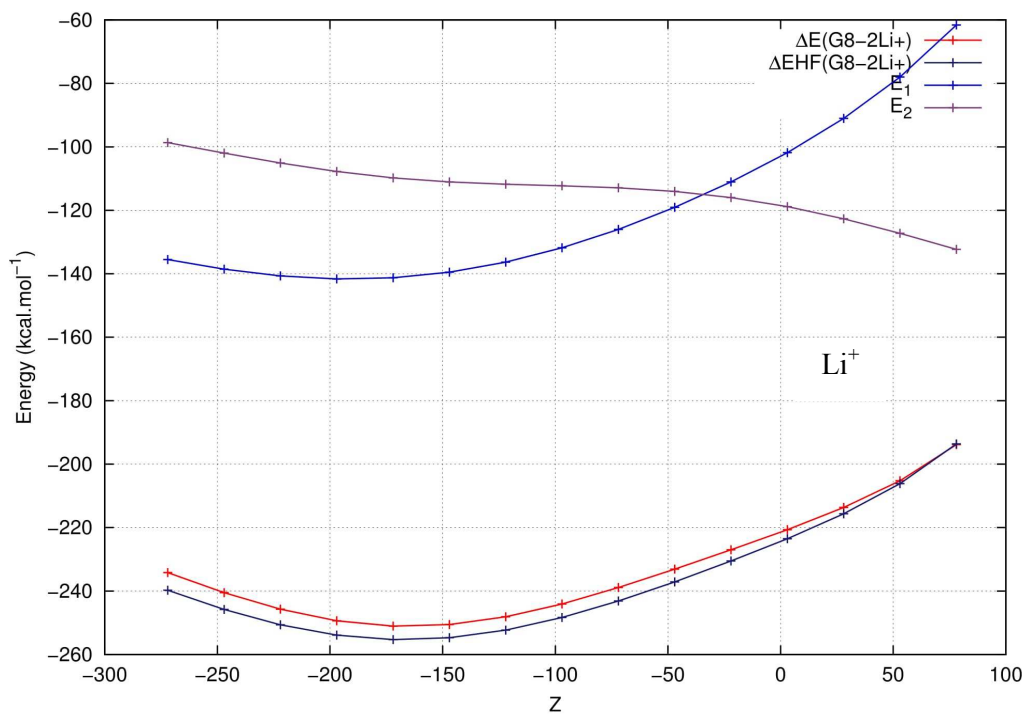


**Figure 3.** 3a:  $\Delta E(\text{B97-D3})$ ,  $\Delta E(\text{B3LYP-D3})$ ,  $\Delta E_{\text{tot}}(\text{SIBFA})$  and  $E_1/E_2(\text{SIBFA})$  profiles for  $\text{Li}^+$  channeling along the Z axis. 3b:  $\Delta E(\text{HF})$ ,  $\Delta E(\text{B3LYP})$  and  $\Delta E(\text{SIBFA})$  profiles for  $\text{Li}^+$  channeling.

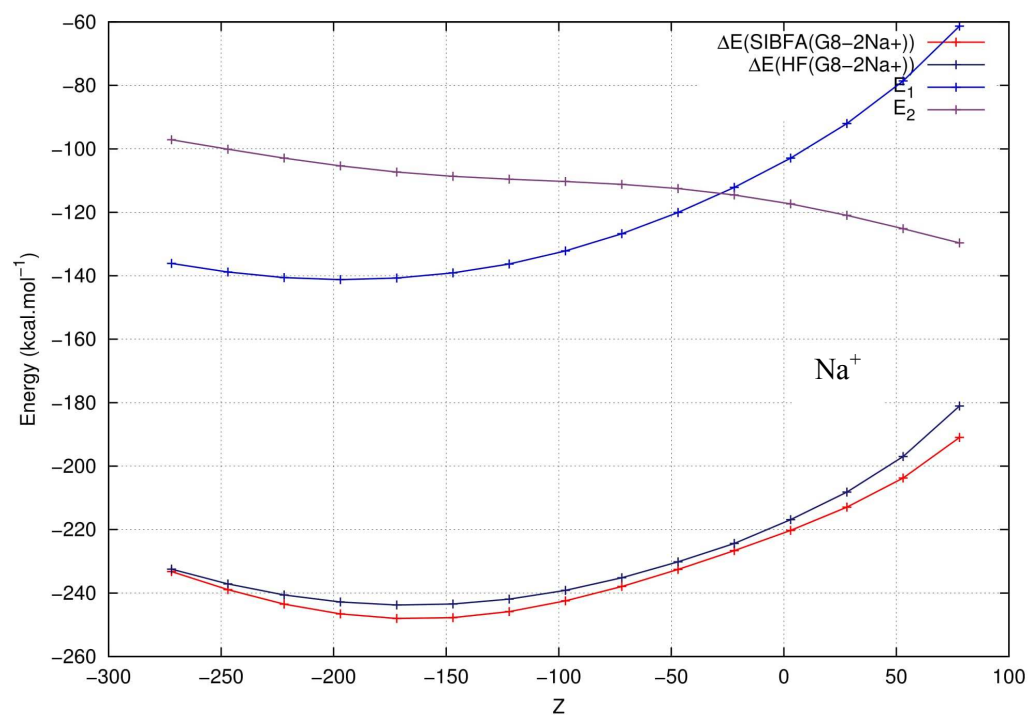
3c-3d:  $\Delta E(\text{B97-D3})$ ,  $\Delta E(\text{B3LYP-D3})$ ,  $\Delta E_{\text{tot}}(\text{SIBFA})$  and  $E_1/E_2(\text{SIBFA})$  profiles for cation channeling along the Z axis. 3c:  $\text{Na}^+$ ; 3d:  $\text{K}^+$ ; 3e:  $\text{Rb}^+$ .

For clarity, the Z values along the abscissa ( $\text{\AA}$ ) were multiplied by a factor 100

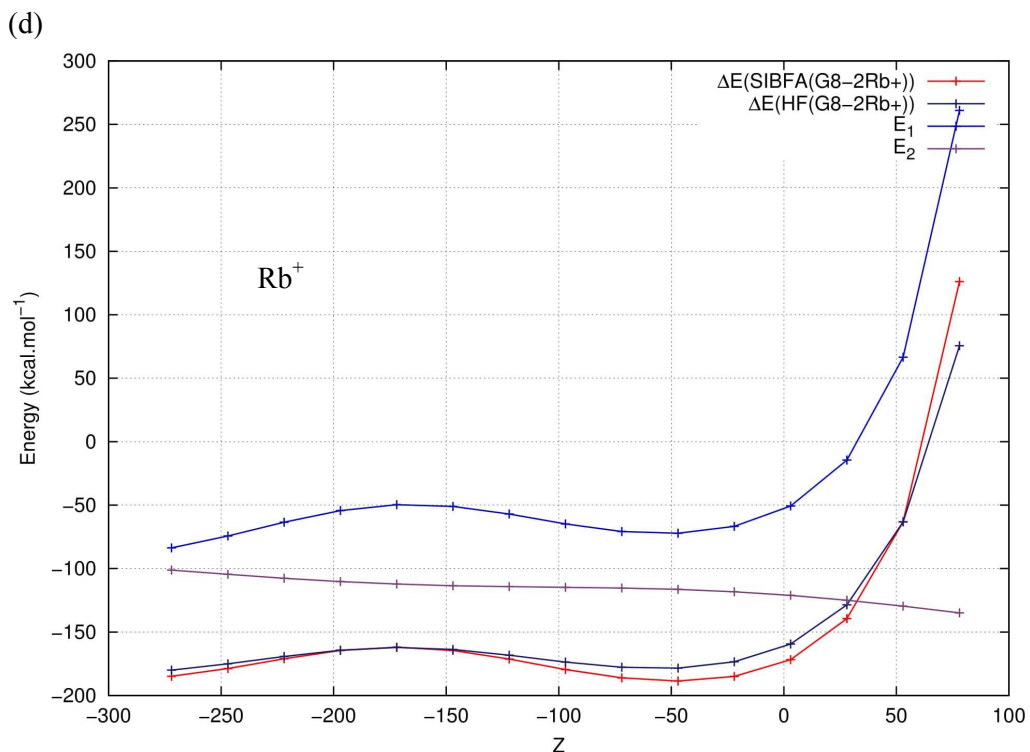
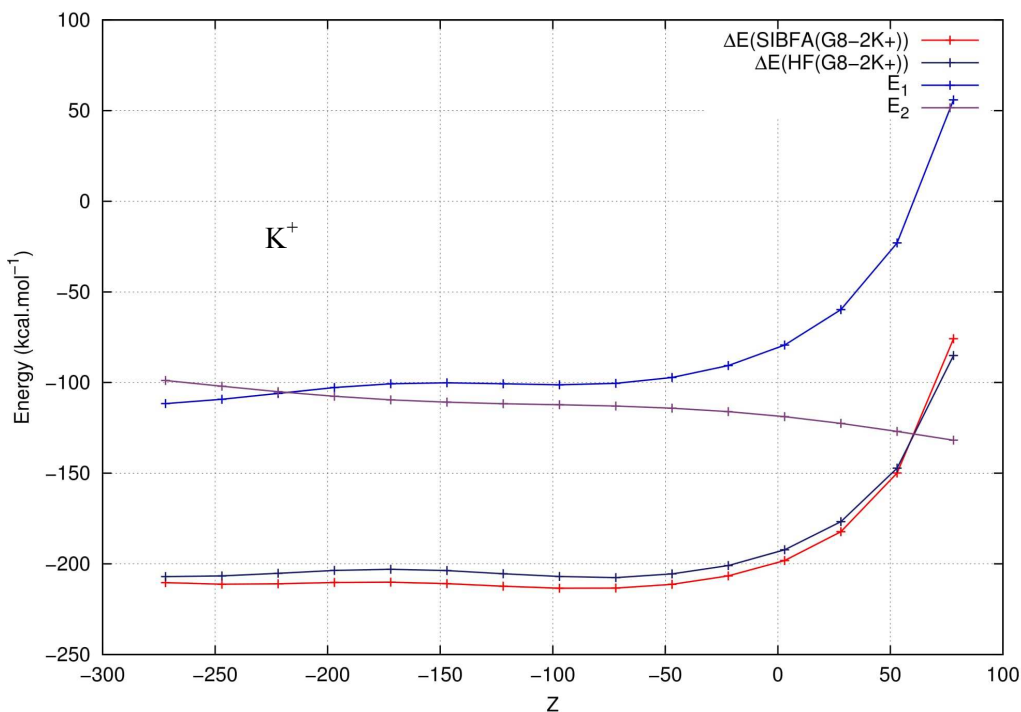
(a)



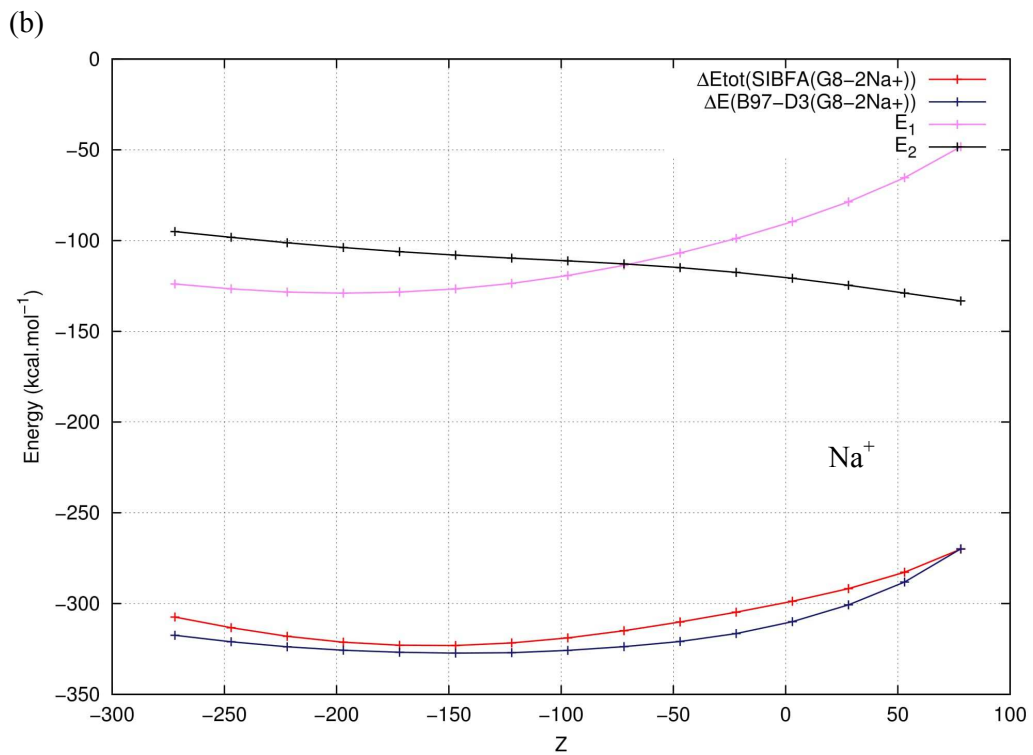
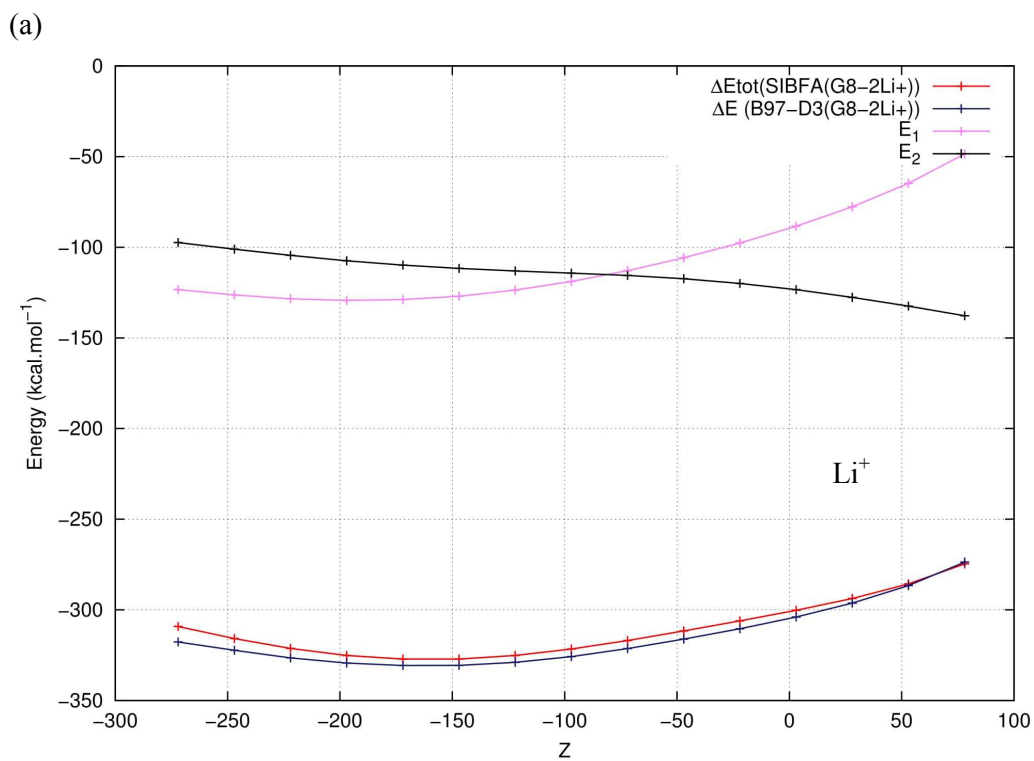
(b)

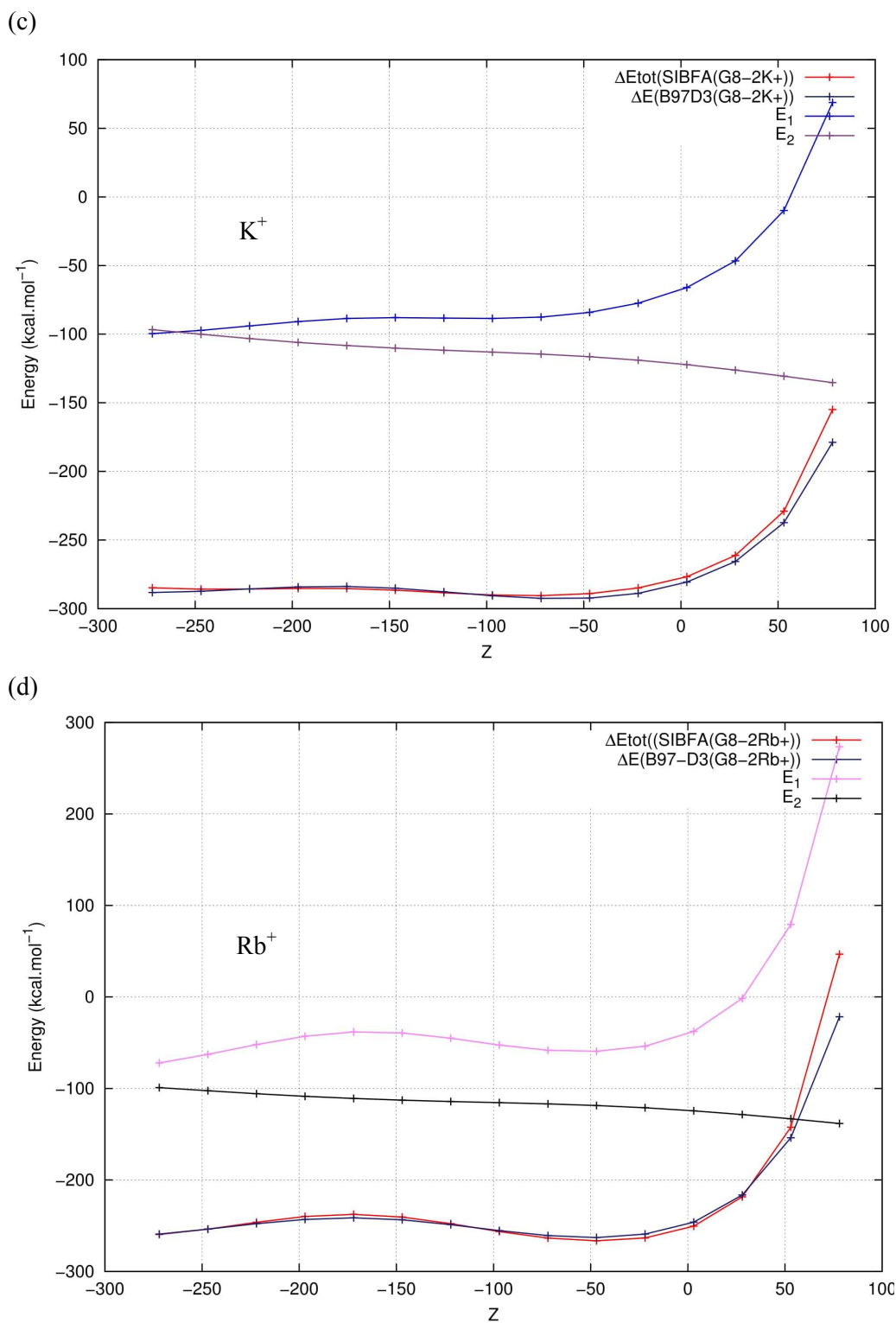


(c)



**Figure 4.** Complex of two stacked G quartets with two monovalent cations with one moving cation.  $\Delta E(\text{HF})$ ,  $\Delta E(\text{SIBFA})$ , and  $E_1/E_2(\text{SIBFA})$  profiles for cation channeling along the Z axis. 4a:  $\text{Li}^+$ ; 4b:  $\text{Na}^+$ ; 4c:  $\text{K}^+$ ; 4d:  $\text{Rb}^+$ . For clarity, the Z values along the abscissa ( $\text{\AA}$ ) were multiplied by a factor 100.

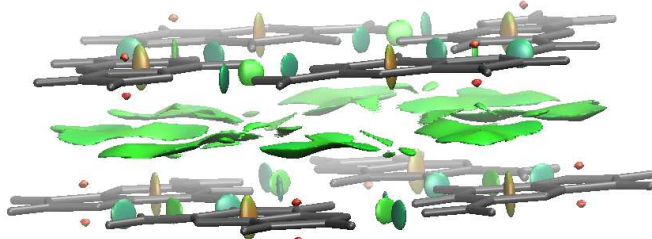




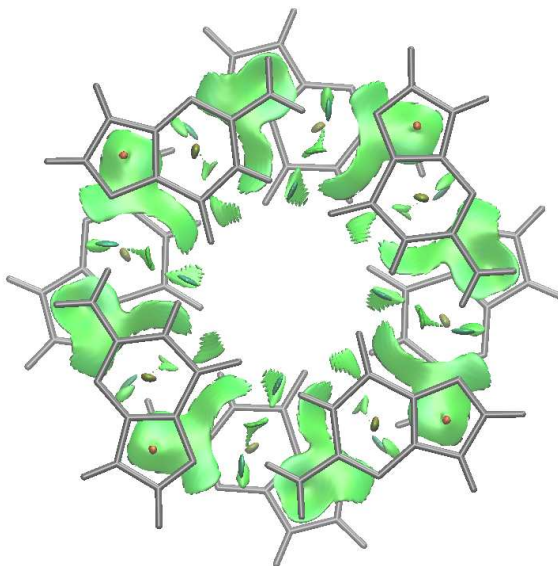
**Figure 5.** Complex of two stacked G quartets with two monovalent cations with one moving cation.  $\Delta E(B97-D3)$ ,  $\Delta E_{tot}(SIBFA)$ , and  $E_1/E_2(SIBFA)$  profiles for cation channeling along

the Z axis.. 5a:  $\text{Li}^+$ ; 5b:  $\text{Na}^+$ ; 5c:  $\text{K}^+$ ; 5d:  $\text{Rb}^+$ . For clarity, the Z values along the abscissa ( $\text{\AA}$ ) were multiplied by a factor 100.

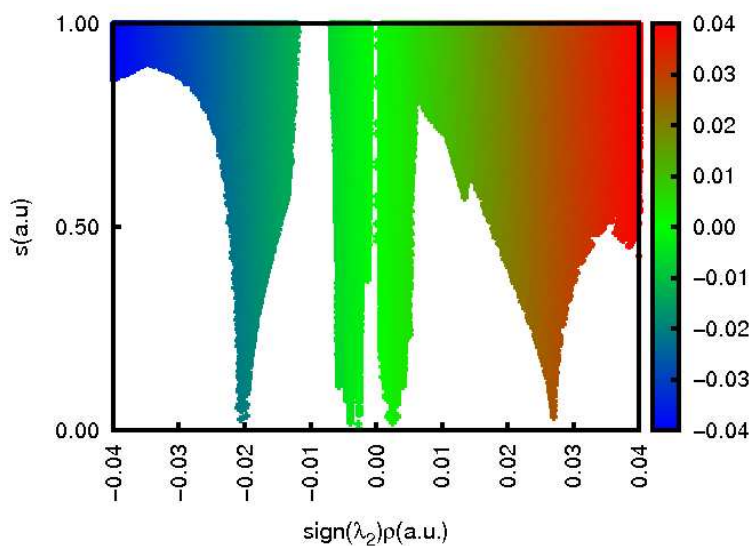
(a)



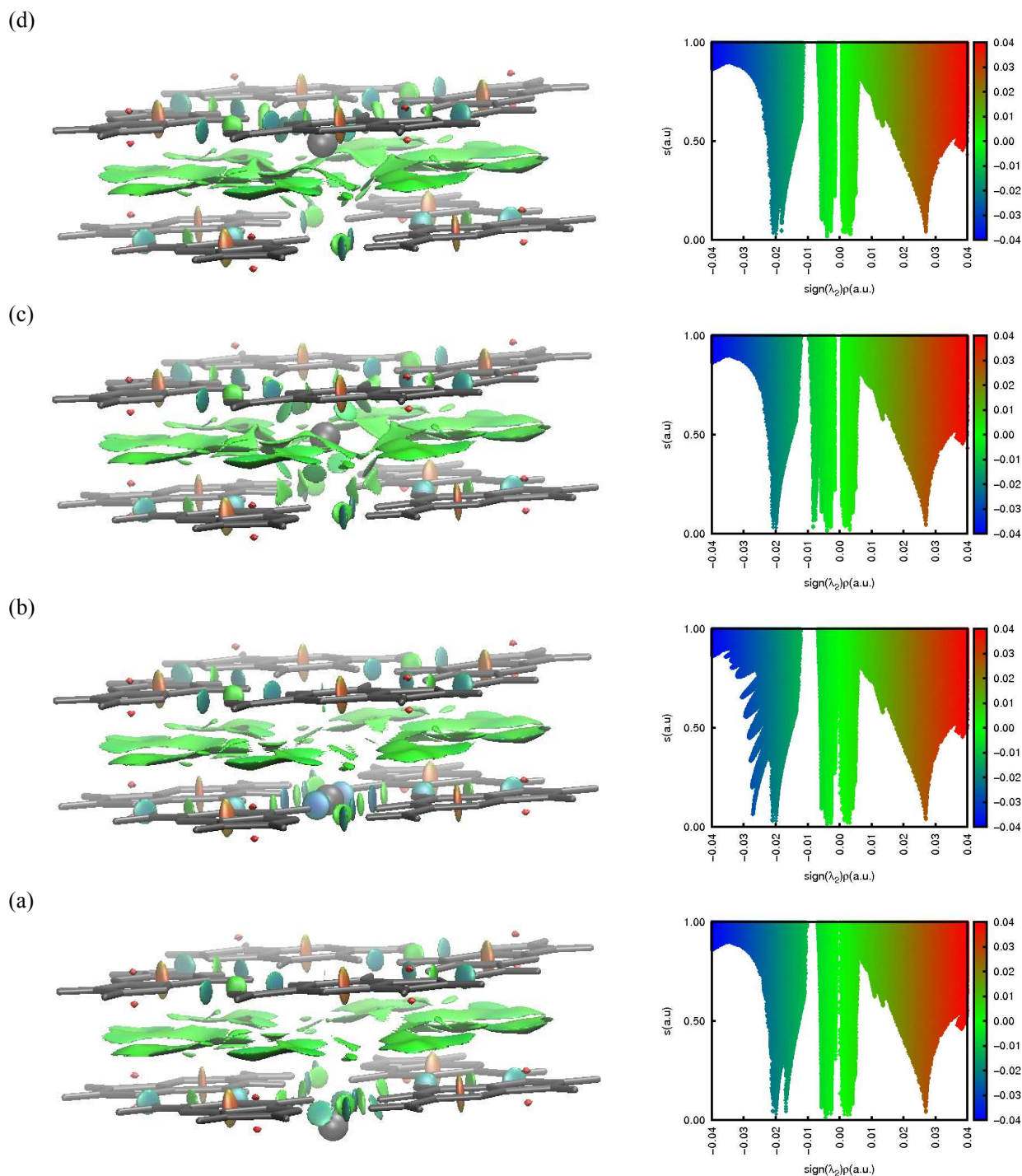
(b)



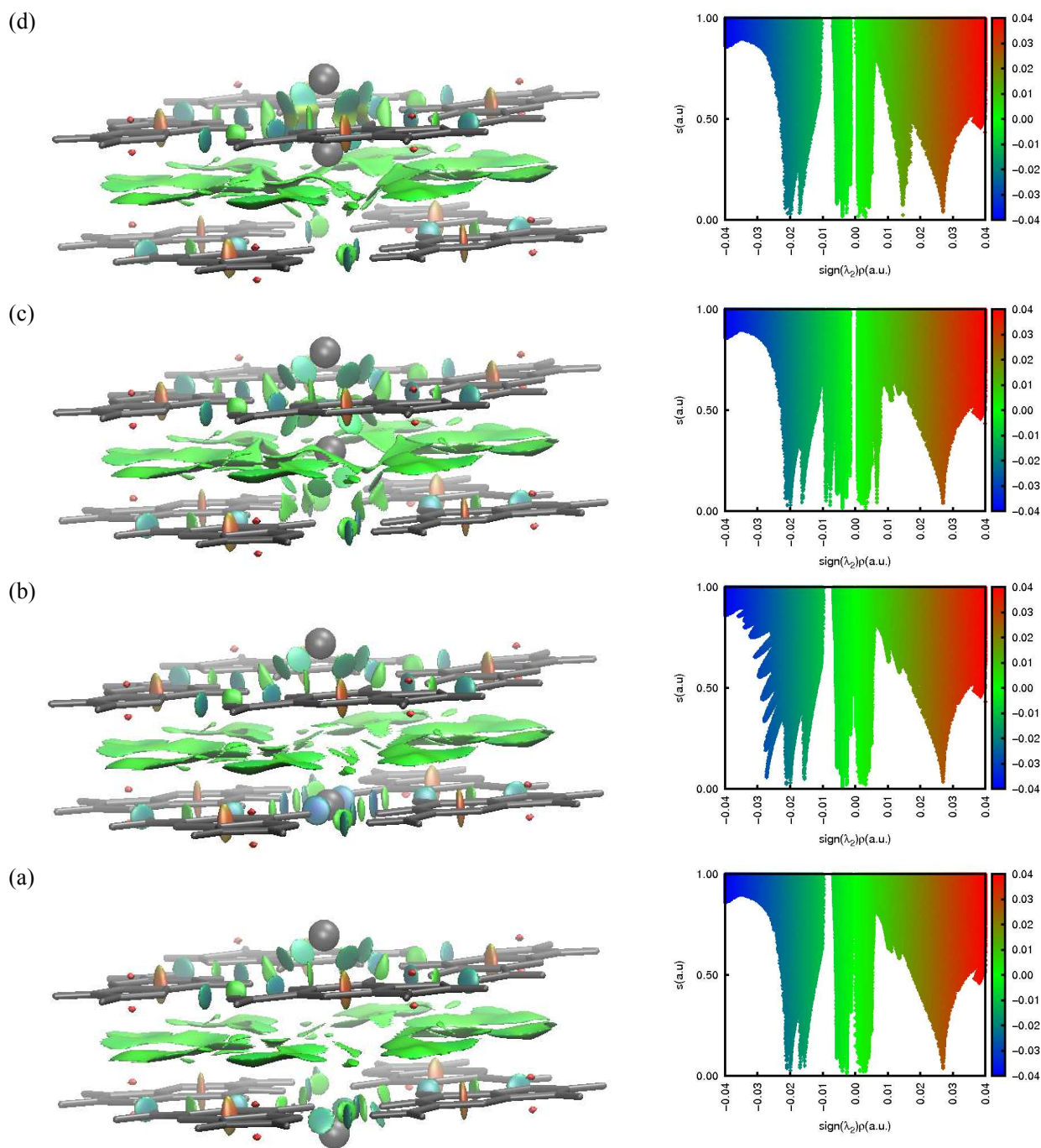
(c)



**Figure 6.** 3D plot NCI analysis of the two guanine quartets without cation: (a) in the XZ plane; (b) in the XY plane; and (c) corresponding 2D plot. In the 3D plots, the NCI surfaces correspond to  $s = 0.50$  isosurfaces.

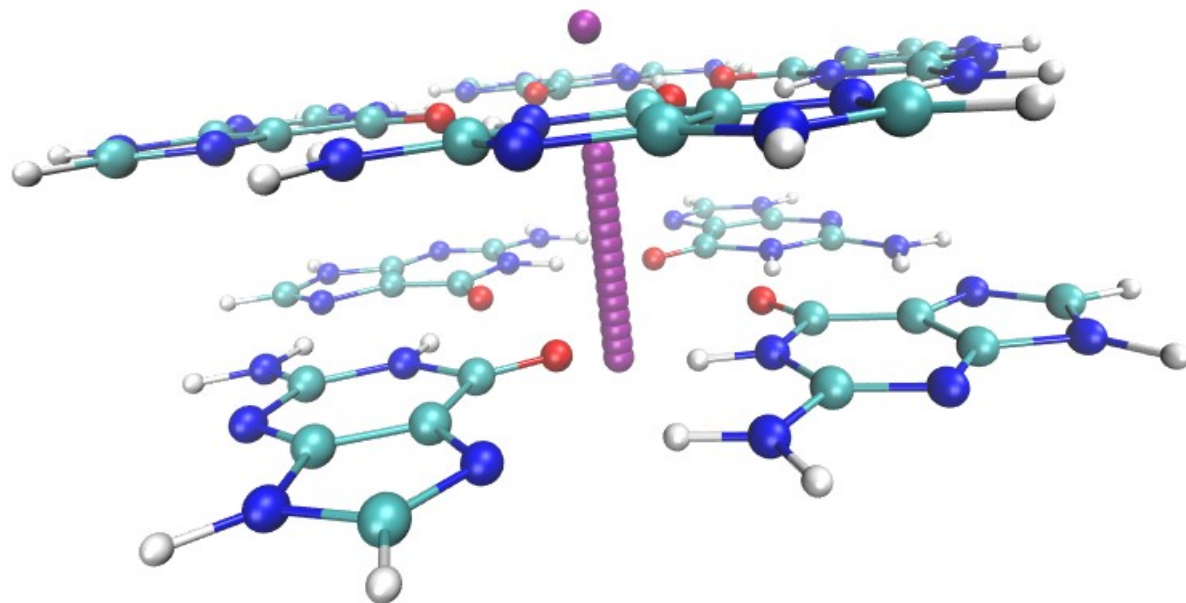


**Figures 7a-d.** 2D and 3D plot NCI analyses of the two guanine quartets with  $K^+$  along the Z axis: (a):  $Z = -2.7 \text{ \AA}$ , (b):  $Z = -1.7 \text{ \AA}$ , (c):  $Z = 0.0 \text{ \AA}$ , (d):  $Z = 0.8 \text{ \AA}$ . In the 3D plots, the NCI surfaces correspond to  $s = 0.50$  isosurfaces.



**Figures 8a-d.** 2D and 3D plot NCI analyses of the two guanine quartets with a fixed  $\text{K}^+$  cation at  $Z = 2.8 \text{ \AA}$  and a mobile  $\text{K}^+$  cation along the  $Z$  axis : (a):  $Z = -2.7 \text{ \AA}$ , (b):  $Z = -1.7 \text{ \AA}$ , (c):  $Z = 0.0 \text{ \AA}$ , (d):  $Z = 0.8 \text{ \AA}$ . In the 3D plots, the NCI surfaces correspond to  $s = 0.50$  isosurfaces.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60