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Density functional study of isoguanine tetrad and pentad sandwich complexes with alkali metal ions

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Abstract Isoguanine tetraplexes and pentaplexes contain two or more stacked polyads with intercalating metal ions. We report here the results of a density functional study of sandwiched isoguanine tetrad and pentad complexes consisting of two polyads with Na^+, K^+ and Rb^+ ions at the B3LYP level. In comparison to single polyad metal ion complexes, there is a trend towards increased non-planarity of the polyads in the sandwich complexes. In general, the pentad sandwiches have relatively planar polyad structures, whereas the tetrad complexes contain highly non-planar polyad building blocks. As in other sandwich complexes and in metal ion complexes with single polyads, the metal ion-base interaction energy plays an essential role. In iG sandwich structures, this interaction energy is slightly larger than in the corresponding guanine sandwich complexes. Because the base–base interaction energy is even more increased in passing from guanine to isoguanine, the isoguanine sandwiches are thus far the only examples where the base–base interaction energy is larger than the base–metal ion interaction energy. Stacking interactions have been studied in smaller models consisting of two bases, retaining the geometry from the complete complex structures. From the data obtained at the B3LYP and BH&H levels and with Møller-Plesset perturbation theory, one can conclude that the B3LYP method overestimates the repulsion in stacked base dimers. For the complexes studied in this work, this is only of minor importance because the direct inter-tetrad or inter-pentad interaction is supplemented by a strong metal ion-base interaction. Using a microsolvation model, the metal ion preference $K^+ \approx Rb^+ > Na^+$ is found for tetrad complexes. On the other hand, for pentads the ordering is $Rb^+ > K^+ > Na^+$. In the latter case experimental data are available that agree with this prediction.

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Introduction

In the presence of cations, guanine(G)-rich nucleic acids may form tetraplexes containing stacked base tetrads [1–9]. Isoguanine (iG) shows a remarkable difference to this behavior. From chromatographic and electrophoretic analyses, it has been concluded that in the presence of Cs^+ pentameric complexes with stacked pentads are formed, whereas tetrameric species were claimed to exist with Na^+ and Rb^+ [10, 11]. Later, it was shown by means of NMR spectroscopy and X-ray crystallography that isoguanosine derivatives indeed form pentads with Cs^+ ions and that

these ions are located in the central cavity between two stacked pentad planes [12–14]. To the best of our knowledge, a crystallographic proof for the existence of tetrameric isoguanine complexes is still missing, however. It has recently been shown that noncovalent isoguanosine assemblies show a high Ra^{2+} selectivity even in the presence of other alkaline earth ions with smaller radii [15]. Thus, isoguanine might be used as an ionophore to extract highly toxic radioactive isotopes from solutions similar to a recently proposed waste cleanup of hazardous metal ions by siderophores [16, 17].

Quantum chemical studies can contribute to a better understanding of nucleic acid structures. Ab initio studies are very demanding and therefore they cannot be applied to complete nucleic acids, but they have contributed substantially to the analysis of building blocks [18–20]. For DNA-multiplex structures, the building blocks analyzed usually consisted of a base polyad with or without metal ions [21–29]. Recently, however, the first steps towards larger systems have been taken by calculations on two sandwiched cytosine, guanine, thymine and uracil polyads complexed with metal ions [30, 31].

Several quantum chemical studies have been directed towards isoguanine. At the semiempirical level interactions of isoguanine with the neutral and deprotonated carboxylic group have been studied to mimic the interaction with amino acids [32]. Blas and coworkers have analyzed tautomeric properties of isoguanine and the pairing with thymine in great detail using high level ab initio methods [33]. Rogstat et al. have calculated pKa-values of isoguanine at the DFT level [34]. The above-mentioned studies have shown that the environment is able to modulate the tautomeric state of iG. Recently, the first isoguanine triads, tetrads and pentads have been studied by others and by us [35–38]. We have carried out density-functional calculations on the interaction of a single isoguanine tetrad or pentad with alkali ions [38].

Here we take the next step towards a larger system and report results of density-functional calculations on the recognition of cations by two sandwiched iG-tetrads and pentads complexed with alkali ions. The results are compared with related sandwich complexes in order to take the first steps towards a complex classification. Our calculations are based on density-functional theory with medium-sized basis sets. We present a partition of the energies to compare the base–base interaction in the ligands and analyze in detail the sandwich metal ion interactions for alkaline cations in order to compare the calculated structures and energies with other sandwich complexes studied previously [31]. The properties of oligonucleotide tetraplex or pentaplex structures may also be affected by solvation. Therefore, we have considered cation solvation using a simple microsolvation approach.

The basic aim of this work is to contribute to both a better understanding of nucleic acid multiplex structures and to an improved design of cation-assisted assemblies of bioorganic ligands with isoguanines.

Materials and methods

Initial complex geometries were generated from optimized complex structures of single iG-tetrads and iG-pentads with Na^+, K^+ and Rb^+ ions calculated in our preceding study [38]. The tautomeric state has been fixed in a way to enable hydrogen bonding between each neighbor base pair of the polyads. This leads to the 6-amino keto tautomer that is also among the most stable tautomers in aqueous solutions [33, 34]. We have taken into account structures at C_{4h}-, D_4- and S_8-symmetry for complexes formed by tetrads and C_{5h}-, D_5- and S_{10}-symmetry for complexes formed by pentads. The structures were optimized with the B3LYP hybrid density functional method [39–41] and the DGauss DZVP basis sets [42] throughout using Gaussian98 and Gaussian03 [43].

The adiabatic interaction energy of the polyads was calculated according to a scheme described previously,

$$\Delta E = E(MiG_{2n}) - 2n\,E(iG) - E(M) \quad n = 4, 5 \qquad (1)$$

$E(MiG_{2n})$ denotes the total energy of the complex formed by the two iG tetrads ($n=4$) or pentads ($n=5$) and the alkali metal ion M. $E(iG)$ is the energy of a single isoguanine base and $E(M)$ is the energy of the metal ion evaluated in the full basis of the sandwich-type complex comprising the bases and the cation. All energies were evaluated at the optimized complex geometries with tight SCF convergence and counterpoise corrections for the interaction energies. The distortion of the base structures in the sandwich complexes is described by the deformation energy ΔE^{def}. The total interaction energy is given by

$$\Delta E^T = \Delta E + 2n\,\Delta E^{def} \qquad (2)$$

We neglect the changes of zero-point energy upon complex formation, since we are not interested in an absolute estimate of the interaction energy. Instead, we wish to compare sandwich complexes with different symmetries. A justification for neglecting the zero-point energy change comes from the fact that in metal ion tetrad complexes this quantity was similar for all systems studied [29]. Finally, we define the interaction energy between the

ligand L, consisting of two sandwiched tetrads or pentads, and the central metal ion M by Eq. (3).

$$\Delta E^{ML} = E(MiG_{2n}) - E(iG_{2n}) - E(M) \tag{3}$$

The difference between ΔE and ΔE^{ML} may be regarded as the sum of all base–base interaction energies ΔE^{BB}.

$$\Delta E^{BB} = \Delta E - \Delta E^{ML} \tag{4}$$

In order to estimate the reliability of the B3LYP calculations for stacking, we have selected one base from each polyad of a sandwich complex and calculated the interaction energy between these bases using various methods. In addition to the B3LYP density functional method we used the BH&H functional defined as

$$0.5^* E_X^{HF} + 0.5^* E_X^{LSDA} + E_C^{LYP} \tag{5}$$

and Møller-Plesset perturbation theory of second order (MP2). Further, the standard basis set 6-311+G(d,p) and the correlation-consistent basis set augmented by diffuse functions aug-cc-pVDZ have been used for comparison with the DZVP basis set [44, 45].

The geometrical analysis of the optimized structures including the determination of least-squares planes through the polyad heavy atoms was performed using the SYBYL modeling software version 6.9 [46]. All calculations were performed at the computing facilities of the Leibniz Institute for Age Research—Fritz Lipmann Institute (formerly known as Institute of Molecular Biotechnology—IMB) and the Konrad-Zuse-Zentrum für Informationstechnik Berlin (ZIB).

Results

Geometries and total energies

We performed geometry optimizations for tetrad sandwich complexes with Na^+, K^+ and Rb^+ ions at C_{4h}-, D_4- S_8-symmetry and for the corresponding pentad sandwich complexes at C_{5h}-, D_5- and S_{10}-symmetry. We have considered the most common cations that interact with polyads. Li^+ interacts only weakly, at least with G-tetraplexes, and has a rather small ion radius compared with the cavity size and for Cs^+ the basis set used throughout in our calculations is not defined. Results for energies and selected geometrical parameters are shown in Tables 1, 2, and 3. Figures 1 and 2 show side and top views of the sandwiched tetrad and pentad complexes with Rb^+, respectively.

Among the symmetries taken into account, iG-tetrad sandwich complexes with Na^+, K^+ and Rb^+ ions are most stable at S_8-symmetry for tetrad and at S_{10}-symmetry for pentad ligands. The energy difference between the C_{4h}- and S_8-symmetric structures decreases from the Na^+ (8.63 kcal mol^{-1}) to the Rb^+ complex. (2.05 kcal mol^{-1}). For the pentad complexes, the energy difference between the C_{5h}- and S_{10}-symmetric structures remains almost constant (Table 1). The energy difference between the D_4- and the most stable S_8-symmetric structures is quite small and decreases from the Na^+-complex (0.81 kcal mol^{-1}) to the Rb^+-complex (0.04 kcal mol^{-1}). In contrast, the energy difference of the D_5-symmetric structures relative to the most stable S_{10}-symmetic structures increases from 5.26 to 6.42 kcal mol^{-1} for the pentad sandwich complexes.

For the tetrad sandwich complexes, the distances between the cation and O2 are much smaller than for the corresponding pentad sandwich complexes (Table 3). For the latter, there is not much variation with the ion radius, whereas the distance increases from 2.68 Å in the Na^+-complex to 3.08 Å in the Rb^+-complex for S_8-symmetry. The distance $Na^+...O2$ is 2.68 Å at S_8-symmetry, whereas the corresponding distance for C_{4h}-symmetry is 2.78 Å. The distance between Rb^+ and O2 in the C_{4h}-symmetric structure is not much larger than at S_8-symmetry. In contrast to the tetrad sandwich complexes, there is a decrease in the distances between all alkali ions and O2 from S_{10}- to C_{5h}-symmetry in the pentad sandwich complexes.

In general, tetrad sandwich complexes show a high degree of non-planarity that is unfavorable for stacking interactions, whereas pentad sandwich complexes are rather planar (Figs. 1 and 2, Table 3). This holds for all symmetries taken into account.

For the pentad complexes, the D_5-symmetric structures are more planar than the other ones (Fig. 2, Table 3). For

Table 1 Total energies E_{tot} (H) and symmetries of the most stable alkali metal ion base iG-tetrad and iG-pentad sandwich complexes and relative energies ΔE (kcal mol^{-1}) between the most stable and other conformers at the B3LYP/DZVP level

	symmetry	Na	K	Rb
iG$_4$M$^+$iG$_4$				
E (H)	S_8	−4503.49877	−4941.08998	−7280.99619
ΔE (kcal mol^{-1})	D_4	0.81	0.28	0.04
ΔE (kcal mol^{-1})	C_{4h}	8.63	3.82	2.05
iG$_5$M$^+$iG$_5$				
E (H)	S_{10}	−5588.80697	−6026.42158	−8366.33804
ΔE (kcal mol^{-1})	D_5	5.26	5.87	6.42
ΔE (kcal mol^{-1})	C_{5h}	15.47	15.36	15.49

Table 2 Interaction energies ΔE and deformation energies ΔE^{def} of alkali metal ion sandwich complexes

	iG$_5$M$^+$iG$_5$	iG$_4$M$^+$iG$_4$
Symmetry	S$_{10}$	S$_8$
M=Na		
ΔE	−321.3	−302.8
ΔE^{ML}	−112.4	−147.5
ΔE^{BB}	−208.9	−155.3
ΔE^{def}	4.0	3.1
ΔE^{T}	−281.3	−278.0
$\Delta E^{\text{T}}/n$	−28.1	−34.8
M=K		
ΔE	−318.5	−264.6
ΔE^{ML}	−107.1	−124.3
ΔE^{BB}	−211.4	−140.3
ΔE^{def}	3.9	3.0
ΔE^{T}	−279.4	−240.6
$\Delta E^{\text{T}}/n$	−27.9	−30.1
M=Rb		
ΔE	−316.7	−257.4
ΔE^{ML}	−104.0	−114.9
ΔE^{BB}	−212.7	−142.5
ΔE^{def}	4.0	2.9
ΔE^{T}	−276.7	−234.2
$\Delta E^{\text{T}}/n$	−27.7	−29.3

the tetrads, on the other hand, there is no marked difference in the planarity of the C_{4h}, D_4 and S_8 complexes. The S_{10}-symmetric complexes exhibit the shortest distance between the two pentad planes (2.95 Å), the plane–plane distances of all other sandwich complexes are much larger. This value is in the range found for the helical rise of A- and B-DNA (ideal A-DNA: 2.56 Å; ideal B-DNA: 3.38 Å [47]).

Interaction energies

The interaction energies ΔE of the metal ion-tetrad and -pentad sandwich complexes decrease from Na$^+$ to Rb$^+$ (Table 2). However, this decrease is much stronger in the tetrad structures than in the pentad complexes. Also, the interaction energy between the alkali metal ions and the sandwich ligands ΔE^{ML} decreases from Na$^+$ to Rb$^+$ both for tetrad and pentad complexes (Eqs. 3 and 4). Again, the effect is much stronger in tetrad sandwich complexes than in pentad structures. The metal ion-base interaction energy ΔE^{ML} contributes 33–35% to the interaction energy ΔE of pentads and 45–49% for tetrads. Finally, the base–base interaction energy ΔE^{BB} also becomes weaker on going form Na$^+$ to K$^+$ and Rb$^+$ in the tetrad sandwich complexes. On the other hand, we find a slight increase of this energy in the pentad structures. The deformation energies ΔE^{def} are positive and decrease the total interaction energy by 1 to 2%. In the pentad complexes, ΔE^{def} is about one kcal mol^{-1} stronger. The interaction energy normalized by the

number of $\Delta E^{\text{T}}/n$ decreases from Na$^+$ to Rb$^+$ for tetrad sandwich complexes, whereas it is almost constant for the pentad complexes.

Metal ion selectivity

According to Table 2, the magnitude of interaction energies between the bases and metal ions decreases from Na$^+$ to Rb$^+$ for tetrad and pentad sandwich complexes. Experimental studies of the ion selectivity indicate, however, a preference for cations with large radii in stacked G-tetrads and iG-pentads [15]. The ion exchange reaction

$$\text{iG}_n M^+ \text{iG}_n + M'^+(\text{H}_2\text{O})_m \rightarrow \text{iG}_n M'^+ \text{iG}_n + M^+(\text{H}_2\text{O})_m \tag{6}$$
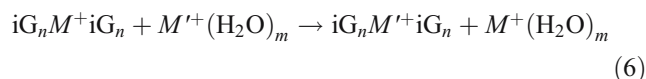
may be used to describe the relative binding affinities of alkali ions M^+ and M'^+ to the sandwich complexes in a qualitative way. To calculate the energy difference between products and reactants $\Delta E^{\text{ex},m}$ in the exchange reaction (Eq. 6) we have used a microsolvation approach with m water molecules that has been applied successfully for an analysis of the cation selectivity of crown ethers and cations by Feller and of other sandwich complexes by us [31, 48].

According to Feller, the cation preference may be estimated in a qualitatively correct sense with at least four water molecules. We have calculated the structures of water clusters with six water molecules distributed in different ways in the first and second solvation spheres for various

Table 3 Metal ion base and hydrogen bond distances, perpendicular plane distances and root-mean-square deviations (RMS plane) of atoms about the tetrad and pentad planes (Å) for alkali metal ion base sandwich complexes

|	iG$_5$M$^+$iG$_5$			iG$_4$M$^+$iG$_4$		
Symmetry	S$_{10}$	D$_5$	C$_{5h}$	S$_8$	D$_4$	C$_{4h}$
M=Na						
O2...Na	3.46	3.44	3.36	2.68	2.69	2.78
N6-H6...N1	1.92	1.82	1.90	2.12	2.12	2.10
N1-H1...O2	1.73	1.74	1.73	1.66	1.67	1.66
RMSD$_{\text{plane}}$	0.39	0.14	0.39	0.88	0.89	0.91
Plane–plane distance	2.95	3.72	4.71	5.74	5.78	6.61
M=K						
O2...M	3.48	3.51	3.39	2.90	2.91	2.98
N6-H6...N1	1.89	1.92	1.91	2.11	2.10	2.09
N1-H1...O2	1.75	1.73	1.74	1.71	1.71	1.70
RMSD$_{\text{plane}}$	0.41	0.13	0.37	0.94	0.95	0.95
Plane–plane distance	2.95	3.72	4.74	6.61	6.51	6.89
M=Rb						
O2...M	3.53	3.50	3.41	3.08	3.06	3.10
N6-H6...N1	1.92	1.90	1.92	2.09	2.09	2.08
N1-H1...O2	1.74	1.75	1.74	1.72	1.72	1.71
RMSD$_{\text{plane}}$	0.42	0.12	0.36	0.96	0.96	0.96
Plane–plane distance	2.95	3.72	4.74	7.04	7.06	7.26

Fig. 1 Structures of isoguanine tetrad complexes with Rb^+ at different symmetries
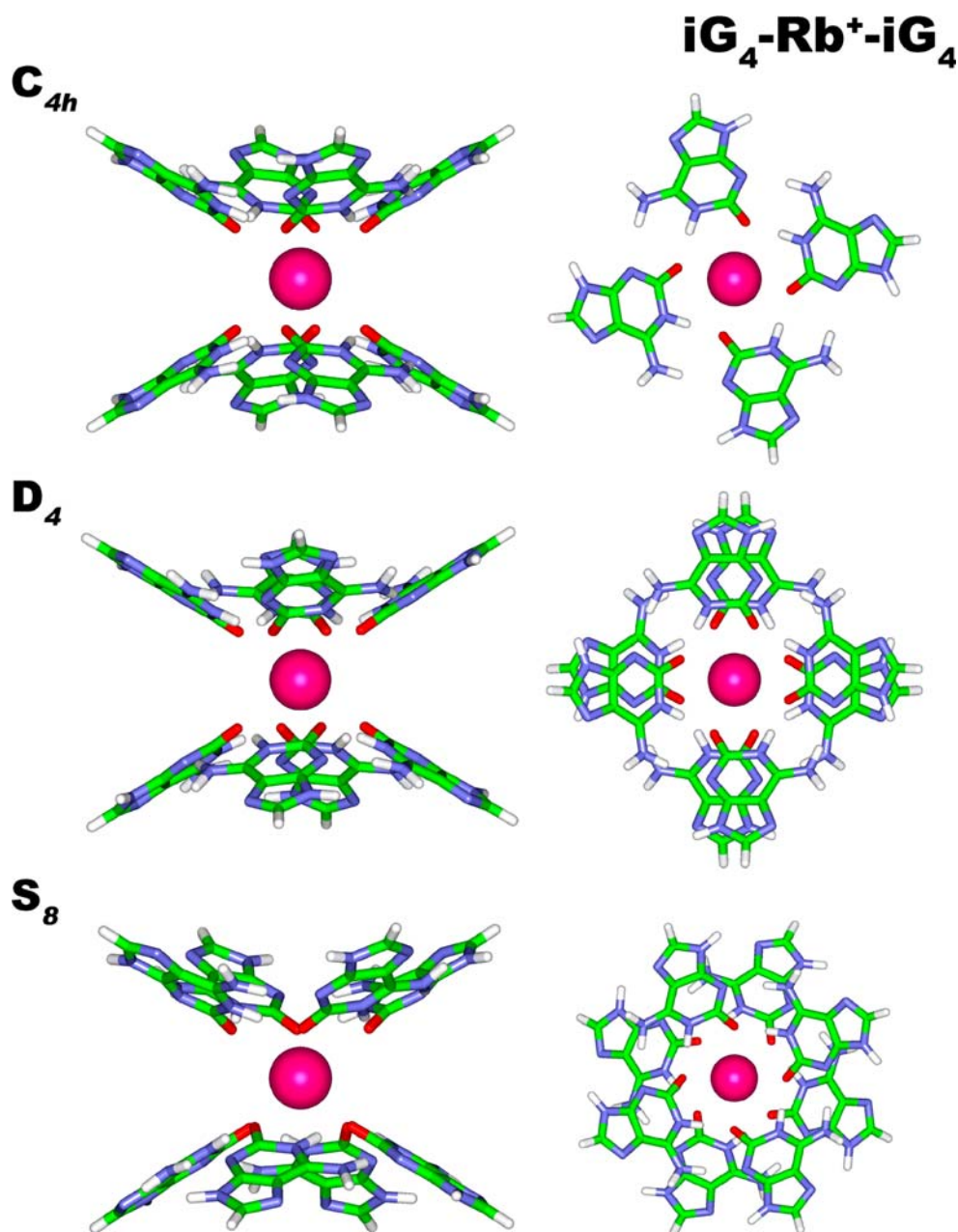
symmetries at the B3LYP/DZVP level that was also used for the iG sandwich complexes. At the B3LYP/DZVP-level, the C_2-symmetric complex with four water molecules in the first and two in the second solvation sphere turned out to be most stable (total energies: -620.88262, -1058.46661 and -3398.37489 H for the Na^+, K^+ and Rb^+ complexes). The D_{2d}-symmetric complexes are 0.4, 3.5 and 4.8 kcal mol^{-1} less stable. In general, the structures and relative energies are in close agreement with previous studies performed at the HF and MP2 levels [49]. Combining the total energies -162.06862, -599.68615 and -2939.60396 H for the bare cations Na^+, K^+ and Rb^+ and the energies of the sandwiched tetrads listed in Table 1, we obtain positive cation exchange energies $\Delta E^{ex,0}$, i. e. a preference of $Na^+>$

$K^+>Rb^+$ for tetrad and less pronounced for pentad sandwich complexes in the absence of water ($m=0$) (Table 4). With the energies of C_2-symmetric complexes consisting of cations solvated by 6 water molecules ($m=6$ in Eq. 5), however, we predict different values for $\Delta E^{ex,6}$, particularly a preference of K^+ by tetrad sandwich complexes relative to Na^+ and Rb^+. For pentad sandwich complexes, however, there is a preference of $Rb^+>K^+>Na^+$. This might be the first step to explaining the experimental formation of tetraplex structures with alkaline ions that have small radii and of pentaplex structures with ions of small size. A more rigorous analysis would also include the solvation of the nucleic acid bases, but it can be stated that the ion selectivity depends on the relative strength

Fig. 2 Structures of isoguanine pentad complexes with Rb^+ at different symmetries
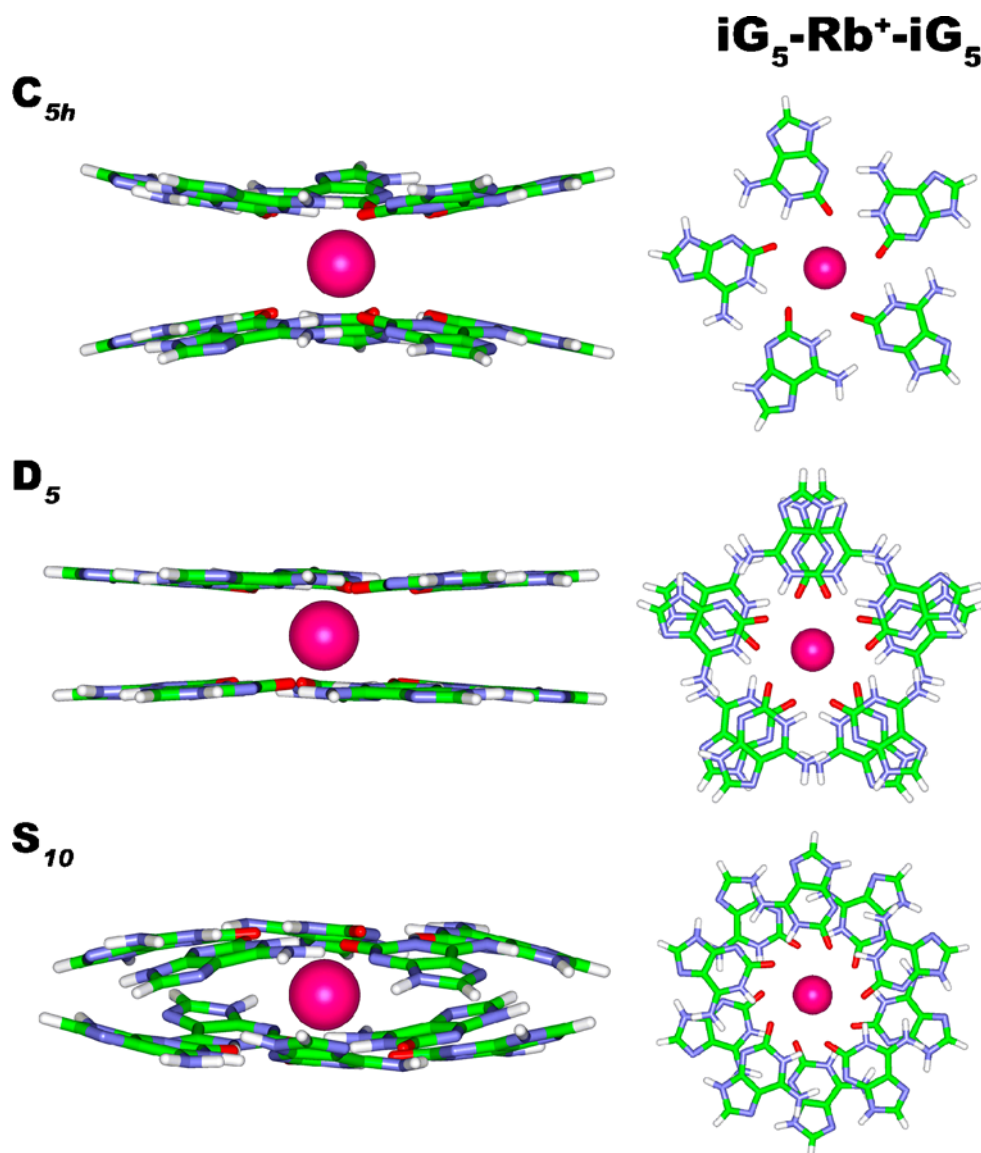
of interaction between the metal ion and the sandwich ligand on the one hand and the cation solvation energy on the other.

Discussion

Comparison of iG sandwich complexes with single iG-tetrads and pentads

Previously, iG-tetrads have been studied both with and without metal ions [36–38]. Here we present a comparison of structural features of tetrad cation complexes in order to determine the influence of the second tetrad.

In the absence of cations, planar C_{4h} and C_{5h}-symmetric structures correspond to local energy minima of iG-tetrads and pentads, respectively. Tetrad alkali ion complexes adopt non-planar C_4-symmetric structures, except for the planar

Li^+ ion structure. On the other hand, pentad alkali ion structures are planar, except for the Cs^+ complex. In this case, the cation is located 1.152 Å above the root-mean-square plane of the pentad atoms.

These different structural features of pentads and tetrads can also been seen in the sandwich complexes. The pentads are only slightly non-planar, whereas the

Table 4 Ion exchange energy of tetrad and pentad isoguanine sandwich complexes for alkali ion solvation with six water molecules ($\Delta E^{ex,6}$) and without water ($\Delta E^{ex,6}$)

$IG_nM^+iG_n$	$iG_nM'^+iG_n$	$\Delta E^{ex,0}$	$\Delta E^{ex,6}$
$IG_4Na^+iG_4$	$iG_4K^+iG_4$	16.6	−4.5
$IG_4K^+iG_4$	$iG_4Rb^+iG_4$	7.3	1.3
$IG_5Na^+iG_5$	$iG_5K^+iG_5$	1.8	−19.2
$IG_5K^+iG_5$	$iG_5Rb^+iG_5$	0.8	−5.1

tetrads deviate substantially from planarity. There is a general trend towards non-planarity of the polyad planes in passing from single tetrads or pentads to the corresponding sandwich complexes. The $iG_4Rb^+iG_4$ complex is the only exception. In this case, the plane root-mean-square deviations for the single tetrad and the sandwich tetrads are identical.

In general, the distances between the alkali ions and O2 are larger in the sandwich complexes than in the single tetrad and pentad structures. For example, the structure of Na^+iG_4 shows a distance of 2.322 Å between Na^+ and O2, [38] whereas the corresponding distance in the $iG_4Na^+iG_4$ complex at S_8-symmetry is 2.68 Å. On the other hand, there is only a very small effect of the cation type on the N6–H6...N3 H-bond distance between the iGiG pairs in each sandwich (S_8 symmetry: Na^+: 2.12 Å, Rb^+: 2.09 Å; S_{10} symmetry: Na^+ and Rb^+: 1.92 Å). In complexes of single polyads with metal ions, however, there is a decrease of this H-bond length with an increasing ion radius (Na^+: 2.266 Å, K^+: 2.098 Å) for tetrads and an increase in the pentads (Na^+: 1.891 Å, K^+: 1.941 Å).

The interaction energy ΔE^{ML} between the two sandwich ligands and the cation exceeds the corresponding interaction energy between a single polyad and the cation significantly, but the interaction energy is not doubled. The ratio between the ligand-metal ion interaction energy ΔE^{ML} of the sandwich complexes and the corresponding interaction energy in complexes consisting of a cation and a single polyad increases on going from Na^+ to Rb^+ and is generally larger for tetrads (1.30–1.55 kcal mol^{-1}) than for pentads (0.98–1.17 kcal mol^{-1}).

The interaction energy ΔE^T normalized by the number of bases in the ligand leads to similar results for sandwich complexes and for single polyad complexes with alkali ions. For pentad sandwich complexes, $\Delta E^T/10$ is almost constant for all cations investigated in this study ($\approx$28 kcal mol^{-1}), whereas $\Delta E^T/8$ decreases in magnitude from about -34.9 to -29.8 kcal mol^{-1} from Na^+ to Rb^+ tetrad sandwich complexes. This trend might indicate a preference for the formation of pentad sandwich complexes with cations that have large radii and for the formation of tetrad sandwich complexes with small cations. This is also supported by the solvation model, which indicates a preference of K^+ over Na^+ and Rb^+ in tetrad sandwich complexes and of Rb^+ over K^+ and Na^+ in pentad sandwich complexes, even though it should be taken into account that these data cannot be considered as a rigorous proof.

Comparison of iG-tetrads with other tetrads

The most stable structure of iG-tetrad sandwich complexes exhibits an S_8-symmetry, like most other tetrad sandwich complexes [31]. For the interaction energies ΔE, ΔE^{ML},

ΔE^{BB}, ΔE^T there is a decrease in the order iG>G>U>T>C (C_4-symmetry excluded) in tetrad sandwich complexes. This corresponds in a qualitative sense to the experimental observation that iG-tetraplexes are more stable than G-tetraplexes [50]. The metal ion-ligand interaction energy ΔE^{ML} is more negative than the base–base interaction energy ΔE^{BB}, as in U-, T- and C-tetraplexes [31]. But it should be noted that ΔE^{BB} is almost as high as ΔE^{ML}. In this respect, iG tetrads correspond to G-tetrads that are also stabilized by two H-bonds between two neighbor bases in each sandwich. Both the high interaction energy between the iG- and G-tetrads and the alkali metal ions and the strong base–base H-bond interactions appear to be the key feature for the unique role of the two bases in polyad formation.

Comparison with experimental data

Experimental evidence has been found both for the existence of tetrad and pentad complexes. Oligonucleotides containing iG and T, for example d($T_4iG_4T_4$), are able to form tetraplexes in the presence of Na^+ ions according to HPLC and CD spectroscopic measurements performed by Seela and coworkers [50]. Similarly, Chaput and Switzer investigated oligonucleotides such as T_4iG_4T and T_8iG_4T using electrophoretic techniques and found in general tetrameric complexes with K^+ and pentameric complexes with Cs^+ [11]. Cai and coworkers showed by X-ray crystallography that iG derivatives form a pentameric complex with Cs^+ [51]. Further, NMR studies indicated that the other alkali ions may also form pentameric complexes with iG derivatives [13]. Thus, the oligomeric state seems to be modulated by both the oligonucleotide composition and the cation type. From their geometrical features, the pentads seem to be more appropriate for stacking. However, a thorough and comprehensive elucidation of the underlying principles of tetrad and pentad formation remains to be done. From the computational point of view, this requires the analysis of extended model systems with additional bases of a different type and, in particular, a proper treatment of solvation and of entropic effects. Molecular-dynamics simulations have provided substantial information on dynamics and cation stabilization for several tetraplex structures [52–54].

Stacking interactions

The interaction energy of sandwich polyads consists of different contributions, such as H-bonding, cation-base interactions and stacking. B3LYP has provided reasonably accurate interaction energies for the first two interaction types, but its suitability for stacking has been questioned, even though the method has been used to study stacking interactions [53–59].

In order to estimate the reliability of the B3LYP calculations, we have selected base dimers consisting of next-neighbor bases from different tetrads or pentads retaining the optimized geometry of the complete sandwich complex (Fig. 3). The interaction energy between these bases has then been calculated with B3LYP, BH&H and MP2 with different basis sets. Particularly, we have selected bases related by the reflection (σ_h) for C_{4h} and C_{5h} symmetric sandwich complexes, by a rotation (C_2) for D_4 and D_5-symmetry and by an improper rotation (S_n) for S_8 and S_{10}-symmetry. The calculated interaction energy contribution complements the metal ion–base interaction energy the intra-polyad base–base interaction energy and the energy of interaction between the other bases in different polyads. For the fragments obtained from C_{4h}-, the C_{5h}- and the S_8-symmetric structures, the interaction energy is repulsive for all methods, whereas it is attractive throughout for the fragments obtained from D_4- and D_5-structures. In the S_{10} case, the B3LYP interaction energy is

repulsive for both basis sets, whereas it is attractive for BH&H and MP2. It is obvious from the structural data shown in Figs. 1 and 2 and Table 3 that the D_5-sandwich pentad complex is the only structure with approximately planar polyad planes and more or less parallel orientation of the two bases in the sandwich structures. All tetrad structures deviate strongly from planarity and therefore do not show a parallel base orientation in the dimers. The C_{5h} and S_{10} are somewhere in between the D_5 pentad sandwich complex and the tetrad sandwich structures. Usually, an approximately parallel orientation of interaction partners is assumed to be a requirement for effective stacking. Interestingly, the fragment generated from the D_5 structure shows the most marked energy differences between B3LYP on the one hand and BH&H and MP2 on the other (Fig. 4). At the B3LYP level, there is not much difference between the interaction energies obtained with the DZVP and the aug-cc-pVDZ basis set extended with diffuse functions. From the interaction energies one can conclude that for

Fig. 3 Structures of symmetry-related isoguanine dimers extracted from different planes of the tetrad and pentad sandwich complexes. The numbers indicate the distances between the O2 and H8 atom pairs in Å. These are the maximum and minimum distances between the dimer bases
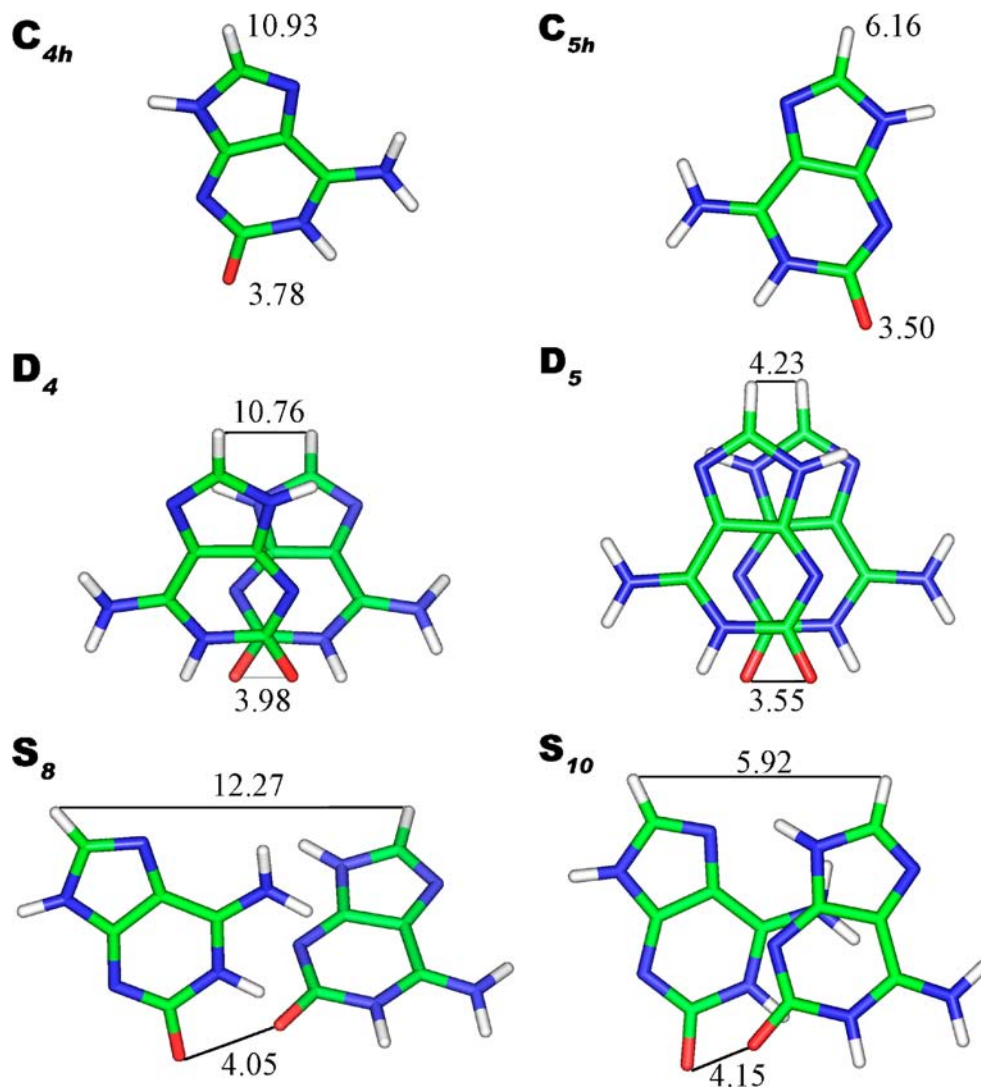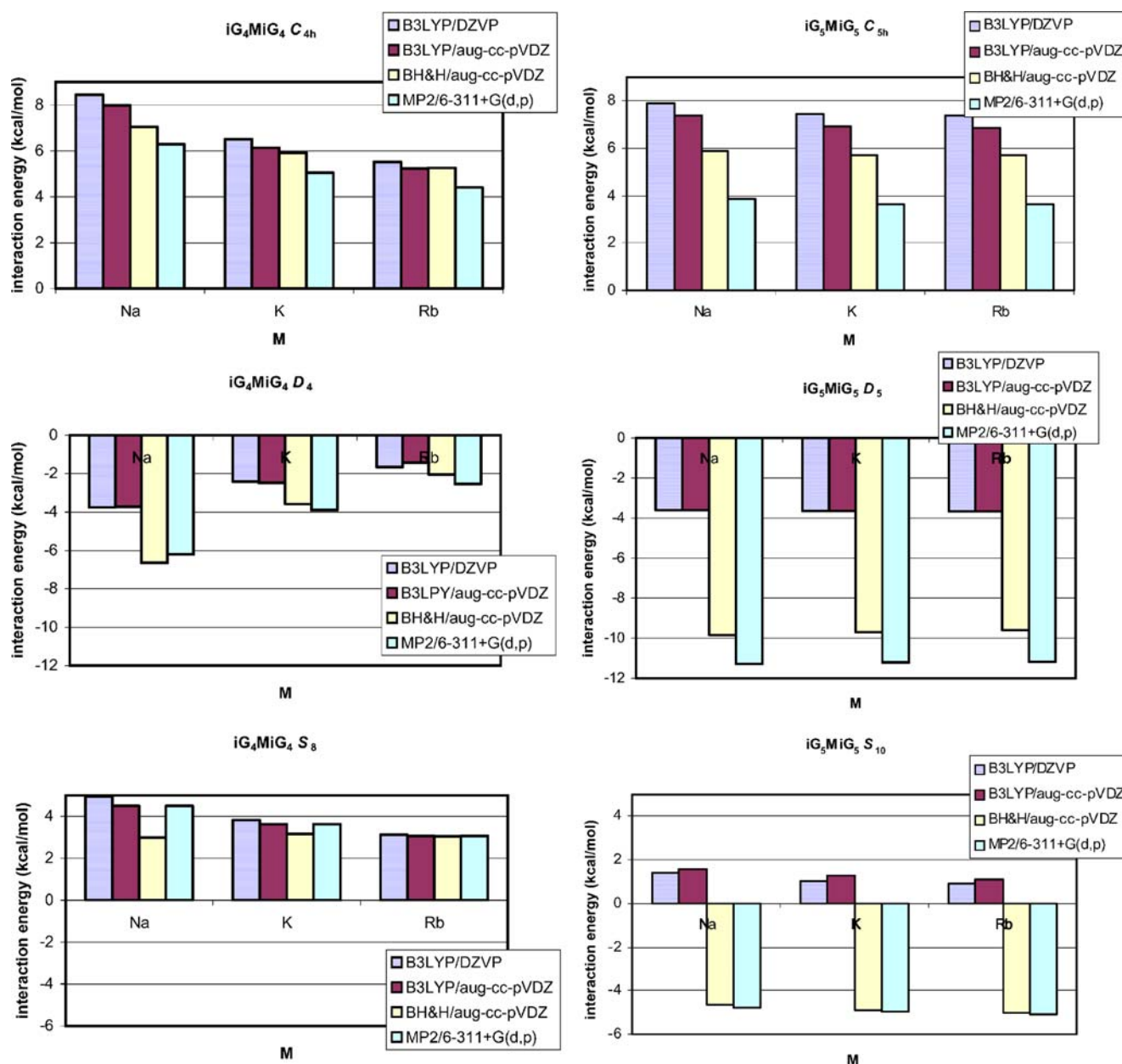
Fig. 4 Comparison of interaction energies between two isoguanine bases from different tetrads and pentads

stacked base dimers the B3LYP methods results in an overestimate of the repulsion compared to MP2 and BH&H, which can be considered to be reasonable methods for stacking interactions [58]. In our case this is less important because the direct inter-tetrad or inter-pentad interaction is supplemented by a strong metal ion-base interaction. Thus, we think that B3LYP is sufficiently accurate for our purpose, even though we are aware of examples with a much worse performance of the B3LYP hybrid functional method [59]. The BH&H functional appears to be a good choice for the investigation of stacked

bases since it has been shown recently that interaction energies obtained from more time-consuming MP2 and CCSD(T) calculations can be reproduced reasonably well [58].

Summary

We present here a systematic DFT study of sandwiched iG complexes with intercalating alkali metal ions. In general, the tetrad complexes are highly non-planar, whereas the

pentad complexes exhibit a more planar geometry. The most coplanar pentad complexes have been found for the D_5-symmetric structure. On the other hand, with 2.95 Å the shortest plane–plane distances were found for pentad structures that adopt S_{10} symmetry. This value is between the helical rise found for ideal A- and B-DNA. The S_{10}-symmetric structures are also the most stable. The distance between the metal ion and the base O2 atoms is for the tetrad structures in the range of 2.68–3.10 Å and for the pentads between 3.36 and 3.53 Å. Within the tetrads and pentads there is only a minor variability in the oxygen–metal ion distances. The interaction energy between cation and ligands decreases from Na^+ to Rb^+ and also the pentad–tetrad difference of these energies decreases in the same direction. In contrast to C-, T- and U-tetrads and to some extent also to G-sandwich complexes, the sum of the base–base interaction energies exceeds the metal ion–base interaction. From the geometric point of view, the results seem to indicate that the relatively planar pentads are more appropriate for effective stacking interactions than tetrads. On the other hand, the interaction energies per base are generally more negative for tetrads. Using a simple micro-solvation approach we have found a Rb^+ preference relative to K^+ and Na^+ in pentad sandwich complexes, whereas K^+ is preferred in tetrad complexes. Our calculations yield interesting new facts on isoguanine sandwich complexes but cannot give a definite proof of a preference for either tetrad or pentad structures. Entropic and solvation effects may lead to other preferences.

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