J. Phys. Chem. A **1998,** *102,* 5951−5957

Interaction between the Guanine−Cytosine Watson−Crick DNA Base Pair and Hydrated Group IIa (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) and Group IIb (Zn^{2+}, Cd^{2+}, Hg^{2+}) Metal Cations

Jiří Šponer,*[†,‡] Jaroslav V. Burda,[§] Michal Sabat,*[||] Jerzy Leszczynski,[⊥] and Pavel Hobza[†]

J. Heyrovský Institute of Physical Chemistry, Academy of Sciences of the Czech Republic, Dolejškova 3, 182 23, Prague, Czech Republic, Institute of Biophysics, Academy of Sciences of the Czech Republic, Královopolská 135, 612 65 Brno, Czech Republic, Department of Chemical Physics, Faculty of Mathematics and Physics, Charles University, Ke Karlovu 2, Prague, Czech Republic, Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901, Department of Chemistry, Jackson State University, Jackson, Mississippi 39217

Received: January 13, 1998; In Final Form: April 13, 1998

Structures and energetics of complexes between the guanine−cytosine Watson−Crick DNA base pair and pentahydrated Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Zn^{2+}, Cd^{2+}, and Hg^{2+} metal cations were studied. Comparison has been made with the data for the unsolvated cations. The complexes were fully optimized within the Hartree−Fock approximation applying the 6-31G* basis set of atomic orbitals, while relativistic pseudopotentials were used for the cations except magnesium. The energetics have been studied with the inclusion of electron correlation using the full second-order Møller−Plesset perturbation theory. The cation with its hydration sphere has been considered as one subsystem in the calculations of interaction energy. Thus, the complete system for a calculation would include the hydrated cation−guanine−cytosine trimer. The interaction between hydrated cation and guanine is significantly reduced compared to the guanine−unsolvated cation interaction. Though the stabilizing three-body contribution has been reduced by almost 50% by hydration, it still remains significant. The stability of the guanine−cytosine Watson−Crick base pair is enhanced by ca. 20−30% due to the coordination of the hydrated cation. All the transition metal and Mg^{2+} cations are tightly bound to the N7 atom of guanine, constituting an octahedral coordination sphere. The Ca^{2+}, Sr^{2+}, and Ba^{2+} cations are coordinated simultaneously to the N7 and O6 atoms of guanine and the base−cation distance increases with the row number in this series. However, the energy difference between the N7 and N7−O6 types of coordination is rather small. The calculations show a different balance between the transition metal and alkaline earth cations with respect to the cation−base and cation−water interactions. Zn^{2+} compared to Mg^{2+} is bound more tightly to the base, and the hydration shell around Zn^{2+} is more flexible. The replacement of Mg^{2+} by Zn^{2+} can be viewed, to some extent, as a shift from the interaction between nucleobase and a hydrated cation toward hydration of a metalated base. This is likely to contribute to the different biological role of Zn^{2+} and Mg^{2+}.

1. Introduction

High-level ab initio calculations carried out since 1994 have provided a basic physical characterization of various hydrogen-bonding and stacking interactions of nucleic acid bases.[1−4] The recent studies were based on the use of the second-order Møller−Plesset perturbation method (MP2) with medium-sized diffuse polarized basis sets of atomic orbitals. The reliability of the MP2 estimation of base−base interactions was verified by preliminary calculations utilizing the coupled-cluster method with noniterative triple excitations (CCSD(T)).[5]

However, quantum chemistry faces yet another challenging task involving nucleic acid base pairs: their interactions with various metal cations. Such interactions are important for some aspects of nucleic acid structure.[6] Empirical potentials can hardly explain many important features in metal complexes with the bases[7−9] mainly due to their inability to describe the electron transfer between bases and metal ions. Thus, ab initio methods remain the only feasible technique to study this phenomena.

Preliminary calculations on the interactions between bases, base pairs or model complexes, and metal cations were carried out in the 1980s.[10−15] These calculations were aided by the use of the Hartree−Fock approximation (at best), mostly with a minimal basis set of atomic orbitals. The gradient geometry optimization was not available, the calculations were usually not corrected for the basis set superposition error, and the number of metal cations considered was very limited. The most important conclusion from the early studies was the observation of the enhancement of base pairing caused by polarization effects due to the metal coordination.[13−15] A significant effort has also been devoted to parametrize a force field for platinated nucleobases.[16]

Recent developments in computer power together with more efficient codes allow application of higher level ab initio methods to the complexes of base pairs with metal cations.[7−9,17,18] One possibility is to rely on the density functional theory techniques, as applied by Carloni and Andreoni to the platinated

---

* Correspondence to Jiří Šponer, Institute of Physical Chemistry, Prague; fax 420 2 858 2307; e-mail sponer@indy.jh-inst.cas.cz or Michal Sabat, Department of Chemistry, University of Virginia; fax (804) 924-3710; e-mail sabat@virmod.chem.virginia.edu.

[†] J. Heyrovský Institute of Physical Chemistry.

[‡] Institute of Biophysics.

[§] Charles University.

[||] University of Virginia.

[⊥] Jackson State University.

S1089-5639(98)00769-5 CCC: $15.00

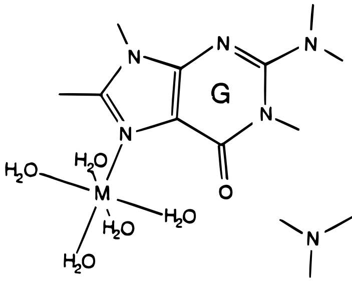

Figure 1. Schematic diagram of the hydrated metal ion−GC (WC) base pair complex.

adenine−thymine base pair in the solid state.[17] An alternative is to use the conventional correlated ab initio techniques combined with relativistic pseudopotentials.[7−9,18] Recently we have studied[7−9] interactions between 15 mono- and divalent metal cations and nucleobases, as well as the Watson−Crick (WC) and reverse Hoogsteen (rH) base pairs. These calculations demonstrated that every cation has a rather unique interaction with the DNA bases and base pairs. The binding energies and geometries are determined not only by the charges and atomic radii but also by the electronic structure of the cation and by the relativistic effects.[8,9] In addition, the metal complexes are characterized by pronounced polarization and charge-transfer effects. Empirical potentials used in biomolecular modeling are not able to describe the interactions between bases and cations and the many-body effects in the cation−base pair complexes properly.[7,9] The calculations also showed a large polarization enhancement of the base pairing in the M•••GC (WC)[9] (M-metal cation) and especially in the M•••GG (rH) complexes.[7] It is very likely that this enhancement of base pairing due to the metal coordination can be important in Purine•PurinePyrimidine (Pu.PuPy) triplexes.[19−21] On the other hand, only a small polarization enhancement of the base pairing has been found for the AT (WC) and AA (rH) base pairs.[7,9] There was a strengthening of the AT (WC) complex due to the cation binding caused by the long-range electrostatic interaction between the cation and thymine.[9] In these two systems, the pairing can be strongly destabilized by the ability of the cation to be simultaneously coordinated to the N7 atom and the amino group N6 atom of adenine.[7]

The previous calculations were carried out without the consideration of solvent effects. Here, we present the first systematic study of the interaction between fully solvated (hydrated) divalent metal cations with an octahedral coordination sphere consisting of N7 of guanine and five water molecules (for the explanation see below) and the guanine−cytosine Watson−Crick base pair (Figure 1). The calculations were performed for Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+} (group IIa) and Zn^{2+}, Cd^{2+}, and Hg^{2+} (group IIb) cations. In addition, the effect of replacement of one neutral water molecule by OH^- ion was investigated. We think that the presence of OH^- in the hydration sphere cannot be ruled out in real systems,[14] although it is very difficult to prove it experimentally. The later model system gives us also an upper estimate of the influence of a negatively charged phosphate group in nucleic acids. (The negatively charged phosphate group can interact with the hydration shell of the cation, but not directly with the cation. The phosphate group has been found to be involved in an outer-sphere coordination through one of the aqua ligands.)[20]

In contrast to metal−nucleobase interactions, hydration of divalent cations has been analyzed in numerous theoretical studies using explicit and continuous models of solvent.[22−36] Ab initio quantum chemical, empirical potential, and hybrid techniques were used. Among other phenomena, significant nonadditivity of molecular interactions within the hydration shell has been revealed.[22] Also, the difference between various cations with respect to the hydration was studied, and it has been shown that the hydration shell of Zn^{2+} is more flexible than that of Mg^{2+}, which allows a reduction of the coordination number of six for Zn^{2+} without a substantial energy penalty.[30]

2. Methods

The system studied by using gradient geometry optimization within the Hartree−Fock (HF) approximation consisted of the GC (WC) base pair interacting with a divalent metal cation surrounded by a water shell (Figure 1) (five water molecules were used to achieve the most likely coordination numbers of six or seven; see below).[6,20,22,30] The cations were initially placed near the N7 atom of guanine; however, no constraints were applied in the optimization. The standard split-valence 6-31G* basis set of atomic orbitals was used for Mg^{2+}, O, N, C, and H. The other cations (Ca^{2+}, Sr^{2+}, Ba^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}) were described by using the Christansen relativistic pseudopotentials[37] as in our previous studies.[7−9] In addition, the effect of substitution of one of the water molecules by the OH^- group was studied for the Mg complex designated as "$MgOH^+$".

The use of relativistic pseudopotentials instead of the conventional all-electron approach has several advantages. First, only valence electrons are considered explicitly for atoms for which the pseudopotential is used. The effect of core electrons is included via effective core pseudopotential. This results in a reduction of the number of electrons and thus the dimension of the Hamiltonian matrix. The calculations are in principle faster and the convergency is improved. Second, the pseudopotentials allow one to consider part of the relativistic effects (Darwin and mass-velocity terms) in a relatively simple way using scalar wave function and standard nonrelativistic methodology. No relativistic effects could be included using the all-electron approach.[37]

The interaction energies were evaluated for the HF-optimized geometries by applying the full second-order Møller−Plesset perturbation method (MP2) with the same basis sets and pseudopotentials as specified above (abbreviated as MP2/6-31G*//HF/6-31G* level). In contrast to many of our previous studies,[1,4,5] we did not modify the exponent of d-polarization functions because this modification does not influence the H-bonding energies significantly.[5] Since we were interested in the influence of the full solvation shell around the cation on the base pairing, the interaction energies were mostly evaluated for the following trimer: solvated cation•••guanine•••cytosine. In other words, the cation plus the five water molecules were considered as one subsystem in the interaction energy calculations. The interaction energy of a trimer, ΔE_{ABC}, can be expressed in two ways:[7,9]

(i) as a difference of the electronic energy of the complex and the monomers:

$$\Delta E_{ABC} = E_{ABC} - (E_A + E_B + E_C) \tag{1}$$

or

(ii) as a sum of three pairwise dimer interaction energies and the three-body term ΔE_3:

$$\Delta E_{ABC} = \Delta E_{AB} + \Delta E_{AC} + \Delta E_{BC} + \Delta E_3 = E_{AB} - (E_A + E_B) + E_{AC} - (E_A + E_C) + E_{BC} - (E_B + E_C) + \Delta E_3 \tag{2}$$

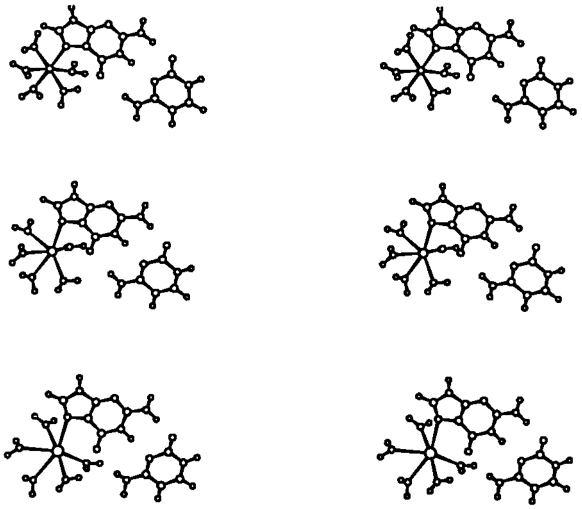

Figure 2. Stereoviews of the optimized complexes between the GC Watson−Crick base pairs and a hydrated cation: Mg^{2+} (top), Ca^{2+} (middle), Ba^{2+} (bottom).

Thus, the three-body term can be evaluated as

$$\Delta E_3 = E_{ABC} - E_{AB} - E_{AC} - E_{BC} + E_A + E_B + E_C \quad (3)$$

These equations can be easily extended for complexes consisting of N subsystems. (ΔE stand for the interaction energies, E for the total electronic energies.)

All interaction energies were calculated by using the optimized geometries of the complex and were corrected for the basis set superposition error[38] in the trimer-centered basis set.[7,9] Because of the use of trimer-centered basis sets, the ΔE_3, which is a genuine three-body term defined only for the trimer, is defined unambiguously. The deformation energies of the monomers were neglected since they are an order of magnitude smaller than the interaction energies.[7,9] (The deformation energy of a monomer is a repulsive contribution. It is caused by deformation of a monomer upon formation of the complex and is evaluated as the difference of total electronic energy of the monomer having the geometry in the complex compared to the optimized isolated monomer.) The deformations concern mainly the guanine residue due to its direct interaction with the cation. Nevertheless, we have checked the deformation energies in all the complexes under consideration. These deformation energies of guanine were within the range of 5−8 kcal/mol. This is a reduction of deformation energies compared to those previously obtained for unsolvated cations.[7] The deformation of guanine by the cation reduces the stability of the whole complex, but it does not directly influence the base pairing enhancement.[7]

All calculations were done by employing the Gaussian94 suite of programs.[39]

3. Results

3.1. Structures. *Coordination Spheres.* All previous calculations carried out for unsolvated cations resulted in structures showing a simultaneous coordination of the cation to both the N7 and O6 sites of guanine. The inclusion of the solvation shell protects the O6 site from a direct contact with the cation in the case of all group IIb elements and Mg^{2+} (Figure 2). On the other hand, Ca^{2+}, Sr^{2+}, and Ba^{2+} are coordinated to both the N7 and O6 atom. This reflects the increased ionic radii of the alkali metal cations and higher coordination numbers preferred. Including the O6 group of guanine, the coordination number increases from six to seven. In the case of the largest, Ba^{2+}, the coordination number could be even higher, since it is known from several experimental data that it prefers a coordination number of eight. For example, in the $d(CGCGCG)_2$ Z-DNA crystal structure, the barium atom is shared between N7 and O6 atoms of two guanines of adjacent helices and hydrated by four water molecules.[40]

We are aware that inclusion of five water molecules (coordination numbers six or seven) may not represent an optimal coordination number for all the cations studied. However, we could not investigate all possible coordination patterns due to the computer requirements. Further, the main aim of this study was to qualitatively understand how the hydration of a cation influences the base pairing. For this purpose the present set of data seems sufficient. Let us note that the actual hydration of a cation is characterized by a dynamical coexistence of various coordination modes.[36]

Amino Group−Acceptor Interaction in the Ba^{2+} Complex. Although our calculations have been carried out without any geometrical constraints, the GC WC base pairs remained planar. The only exception is the pair interacting with the large Ba^{2+} cation. Barium causes a significant nonplanarity (buckling) of the base pair. Figure 2 shows the differences in geometries of the complexes with hydrated Mg^{2+}, Ca^{2+}, and Ba^{2+} cations. The buckled structure obtained for the Ba^{2+} cation is a consequence of a direct interaction between one of the water molecules and the cytosine amino group. The amino group nitrogen atom serves as a hydrogen acceptor with the $N\cdots H(H_2O)$ distance of 2.40 Å. The other aqua ligand close to the cytosine has a different orientation (see Figure 2), and the hydration shell is very asymmetric relative to the guanine plane. The cation is shifted away from the guanine plane by 0.5 Å. In other words, due to the activation of the cytosine amino group, the system is deviating from the C_s symmetry significantly. The cytosine amino group has partially pyramidal arrangement with dihedral angles between the hydrogen-bonded H atom and the cytosine ring of 17°. The analogous dihedral angle involving the non H-bonded H atom is 25°. The pyramidalization of amino groups of nucleobases is important in many interactions involving nucleic acid bases[1,41,42] and is frequently associated with perturbation of symmetry.[41] A very weak nonplanarity of the amino H atoms of cytosine (ca. 4°) is also observed for the Sr^{2+} complex, although in this case the pair remains essentially planar and the cation is coplanar with guanine, because the water shell is not close enough to the amino group. It should be noted that the present result for Ba^{2+} cannot be considered as an ultimate prediction that barium induces the nonplanarity of the GC (WC) base pair. Our calculations for example neglect the second hydration shell and those water molecules could accept H-bonds from the first hydration shell of the cation instead of the amino group nitrogen atom. Nevertheless the calculations show a certain potential of the polarized water molecules around the barium cation to activate the cytosine amino group. On the other hand, much stronger cation−amino group or cation−polarized water−amino group interactions occur in case of coordination of a cation to the N7 position of adenine. This will be analyzed in a subsequent study.

Interatomic Distances. Table 1 compares selected interatomic distances in the complexes studied: the cation−base distances, the cation−water separations, and the base−base H-bonds. The closest cation−base distance was found for Zn^{2+} (2.08 Å), followed by Mg^{2+} (2.19 Å), in agreement with the data obtained for the unsolvated cations.[8] However, the $Mg^{2+}\cdots O$(water) distances are slightly shorter than those between Mg^{2+} and N7, whereas an opposite trend has been found for Zn^{2+}. This

TABLE 1: Optimized (HF/6-31G*) Geometries of the GC WC Base Pair Interacting with a Solvated Cation (M)[a]

	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Zn^{2+}	Cd^{2+}	Hg^{2+}	$MgOH^{+}$
M···N7	2.19	2.60	2.74	2.96	2.08	2.32	2.28	2.24
M···O6	3.47	2.57	2.70	2.77	3.44	3.47	3.44	3.62
M···W	2.09−14	2.46−49	2.62−65	2.80−87	2.11−17	2.34−39	2.43−50	2.11−19
N4(H)···O6	3.25	3.27	3.26	3.17	3.24	3.25	3.26	3.11
N3···(H)N1	3.05	3.05	3.06	3.07	3.05	3.06	3.05	3.04
O2···(H)N2	2.81	2.84	2.84	2.89	2.81	2.81	2.81	2.88

[a] M···N7 and M···O6, Cation−Base Distances. M···W, the range of cation−water oxygen distances. The last three rows summarize the base-pair hydrogen bonds. Some other important geometry features are discussed in the text. All distances are in angstroms.

indicates that the balance between the cation−base and cation−water interactions is different for these two cations and that the transition metal cation prefers to interact with the base. These will be further discussed below. The difference between members of groups IIa and IIb becomes even more evident for the elements with higher atomic numbers. Starting with Ca^{2+}, the IIa cations are coordinated to both N7 and O6 of guanine. The cation−base and cation−water distances increase gradually with the increasing atomic number for the IIa elements, and the cation−base distances are always larger than the cation−water distances. On the other hand, the two other group IIb elements, Cd^{2+} and Hg^{2+}, remain coordinated to N7. The cation−base distances are short, and the cation−water distances are always longer that the cation−N7 distances. In addition, the cation−base distance decreases when going from Cd^{2+} to Hg^{2+}, while the cation−water separations become even larger. The difference between the IIa and IIb elements has previously been noticed in the studies of interactions between unsolvated cations and bases and has been attributed to the high covalent d-orbital (cation)−lone pair (base) bonding interaction characteristic for the transition elements of group IIb.[8,9] The anomalous differences observed in the series Zn^{2+}, Cd^{2+}, Hg^{2+} can be attributed to the relativistic effects, well pronounced for mercury.[8,9] The cation···water oxygen distances obtained in the present study are in a very good agreement with the available experimental values for all cations, which provides additional support for the reliability of our methodology (cf. ref 43, Table 13).

We will now discuss geometry of the base pairs. In general, all the hydrated cations have the same effect on the base pair geometry. The cytosine is slightly counter-rotated in the electric field of the solvated cation (optimization of the ion−molecular dipole interaction), which leads to an elongation of the O6(G)···N4(C) H-bond by about 0.3−0.35 Å with respect to the optimized isolated base pair. Similar effects have been observed for the unsolvated cations,[9] where the elongation of the O6(G)···N4(C) H-bond was even larger (ca. 0.55 Å). The screening effect of the water shell is thus quite evident. As already discussed, the base pair geometry is quite significantly changed in the presence of Ba^{2+}.

Influence of OH^-. Some interesting changes have also been observed while replacing one of the hydration sphere water molecules (the outer one) by an OH^- ion. The calculations, carried out for Mg^{2+} and presented in the last column of Table 1, show that the resulting changes in geometry of the complex were small. The cation−base and cation−water distances increased by ca. 0.05 Å. The Mg···OH distance was reduced by 0.2 Å. Also, due to the reduction of charge, the orientation of cytosine with respect to guanine is closer to that in the isolated GC WC base pair, as evidenced by a shortening of the O6···N4 distance by about 0.15 Å relative to the Mg^{2+} complex.

N7 vs N7−O6 Coordination. Two important problems should be addressed: (i) to what extent can the present data predict the actual coordination sites in nucleic acids and (ii) how different are the effects exerted on the base pairing and DNA structure by the “N7-only” and “N7-O6” coordination modes. We first tested the importance of these differences in geometry for the unsolvated Ca^{2+} cation interacting with the GC WC base pair. We carried out an optimization with the unsolvated cation constrained to interact with the N7 site only (the C5−N7−M angle was constrained to be 127°). The subsequent calculations of interaction energy revealed no significant differences in the energetics with respect to the fully optimized structure; only the direct cation−guanine interaction has been reduced by about 15 kcal/mol, i.e., by ca. 10%.[8,9] The three-body term did not change, which means that the base pair stability did not change. Therefore, it seems that the precise position of the cation relative to the N7 and O6 atoms does not significantly influence the base-pairing and polarization effects. We then repeated the same constrained calculation with a hydrated cation. Here, the difference between the total HF energy for the fully optimized “N7−O6” and constrained “N7” solvated structures was only 1.5 kcal/mol. This indicates that the energies of the “N7” and “N7−O6” systems are close to each other. We believe that, under appropriate circumstances, all cations can adopt both types of coordination, although the larger cations of group IIa show a more pronounced ability to interact with O6 than the IIb elements or Mg^{2+} due to the higher coordination number.

3.2. Energetics. Tables 2 and 3 summarize the energies of interactions in the hydrated cation−guanine−cytosine complexes. Table 2 shows the data obtained within the Hartree−Fock approximation, and Table 3 presents the more accurate data with inclusion of electron correlation effects at the MP2 level of theory. In general, both approximations mostly provide a very similar picture. The values in parentheses show the data obtained earlier for the unsolvated cations.[9]

Pairwise Contributions. The interaction between the hydrated cation and guanine (evaluated as a pairwise additive contribution) has been sharply reduced compared to the analogous interaction between the unsolvated cation and the base. Furthermore, the differences between various cations have been substantially reduced by the hydration shell. The energies of interaction between guanine and the bare cation vary within the range −118 (Ba^{2+}) to −237 (Zn^{2+}) kcal/mol,[8,9] while the hydrated cation···guanine interaction energies range from −71 (Ba^{2+}) to −94 (Zn^{2+}, Hg^{2+}) kcal/mol. It should be noted, however, that this concerns the interaction energy evaluated as (hydrated cation)···base contribution. It will be shown below that when this energy is further decomposed, differences among the cations reappear. The pairwise base−base interaction energies are basically unaffected by the water shell; the hydrated cation−cytosine interaction is weakly attractive.

Polarization Enhancement of the Base Pairing. Perhaps, the most interesting energy term is the three-body contribution, which, as expected, has been reduced relative to the complexes with unsolvated cations. However, this reduction is moderate (only 40−50%, except for the Ba^{2+} complex). Therefore, this term is still very significant and represents an important

TABLE 2: Interaction Energies in the Solvated Cation (M)−Guanine (G)−Cytosine (C) Complexes Evaluated by the Hartree−Fock Method (HF/6-31G*//HF/6-31G* level)[a]

	ΔE_{GM}	ΔE_{CM}	ΔE_{GC}	ΔE_3	ΔE^T
Mg^{2+}	−89.8(−209.7)	−1.6(−)	−25.6(−25.9)	−7.1(−)	−124.2(−252.9)
Ca^{2+}	−86.5(−143.5)	−1.5(−3.0)	−25.5(−25.5)	−4.6(−8.8)	−118.1(−180.8)
Sr^{2+}	−80.1(−)	−1.9(−)	−25.0(−)	−3.9(−)	−110.9(−)
Ba^{2+}	−70.8(−120.6)	−6.4(−1.9)	−22.4(−25.3)	−1.9(−8.3)	−101.4(−156.0)
Zn^{2+}	−93.6(−234.9)	−1.6(−4.6)	−25.6(−26.0)	−7.6(−15.0)	−128.5(−280.6)
Cd^{2+}	−87.7(−190.5)	−1.2(−4.3)	−25.5(−25.7)	−7.0(−12.1)	−121.4(−232.6)
Hg^{2+}	−91.9(−196.7)	−1.4(−4.3)	−25.4(−25.7)	−7.6(−13.0)	−126.2(−239.6)
$MgOH^+$	−58.0(−)	+0.4(−)	−26.1(−)	−4.2(−)	−88.0(−)

[a] ΔE_{GM}, pairwise interaction energy between the guanine and the solvated cation; ΔE_{CM}, pairwise interaction energy between the cytosine and the solvated cation; ΔE_{GC}, the pairwise base pair interaction energy; ΔE_3, the three-body term; ΔE^T, the total interaction energy, i.e., the sum of the previous contributions. All energies are in kcal/mol; deformation energies of monomers were not included. The values in parentheses were obtained for the GC base pair interacting with the unsolvated cation.[9]

TABLE 3: Interaction Energies in the Solvated Cation (M)−Guanine (G)−Cytosine (C) Complexes Evaluated with Inclusion of the Electron Correlation (MP2/6-31G*//HF/6-31G* level)[a]

	ΔE_{MG}	ΔE_{CM}	ΔE_{GC}	ΔE_3	ΔE^T
Mg^{2+}	−89.3(−198.7)	−1.5(−)	−26.4(−26.0)	−8.1(−)	−125.4(−243.8)
Ca^{2+}	−82.6(−133.9)	−1.7(−3.0)	−26.3(−25.8)	−5.2(−10.1)	−115.8(−172.7)
Sr^{2+}	−76.0(−)	−2.1(−)	−25.8(−)	−4.4(−)	−108.5(−)
Ba^{2+}	−71.2(−118.3)	−7.7(−2.0)	−23.2(−25.6)	−2.1(−9.6)	−104.1(−156.1)
Zn^{2+}	−93.8(−237.2)	−1.5(−)	−26.4(−)	−8.7(−)	−130.4(−285.4)
Cd^{2+}	−87.9(−192.6)	−1.1(−)	−26.3(−26.0)	−8.0(−)	−123.3(−237.2)
Hg^{2+}	−94.3(−208.0)	−1.3(−)	−26.2(−25.9)	−8.7(−)	−130.5(−253.9)
$MgOH^+$	−57.6(−)	+0.4(−)	−27.0(−)	−4.8(−)	−89.0(−)

[a] ΔE_{GM}, pairwise interaction energy between the guanine and the solvated cation; ΔE_{CM}, pairwise interaction energy between cytosine and the solvated cation; ΔE_{GC}, the pairwise base pair interaction energy; ΔE_3, the three-body term; ΔE^T, the total interaction energy, i.e., the sum of the previous contributions. All energies are in kcal/mol; deformation energies of monomers were not included. The values in parentheses were obtained for the GC base pair interacting with the unsolvated cation.[9]

additional stabilization of the base pairing due to polarization effects. Let us point out that the base pairing enhancement (the difference of energies that are necessary to separate the two bases without and with the presence of a cation) consists basically of two terms: the three-body term, which includes the polarization effects, and the classical electrostatic attraction between the hydrated cation and cytosine.

Influence of OH^-. The preliminary calculations for the $MgOH^-$ system can be summarized as follows. The energy of interaction between the hydrated cation and guanine and the three-body term were further reduced with respect to the neutral hydration shell. Nevertheless, the many-body term is still significant (−5 kcal/mol) so that the stability of the H-bonded base pair is enhanced compared to the isolated base pair. We should keep in mind that the effect of the OH^- anion can be considered as the upper limit of the reduction of the base-pairing enhancement, which might be caused by negatively charged phosphate groups interacting through a water molecule with the cation. Therefore, the present calculations indicate that the full hydration shell and a proximal negatively charged group do not fully eliminate the base-pairing enhancement caused by coordination of the divalent metal cation to guanine.

3.3. Difference between the Zn^{2+} and Mg^{2+} Cations. The previous paragraphs dealt mainly with the influence of a hydrated metal cation on the base pairing. Let us now analyze another important phenomena. It is well established that divalent zinc and magnesium cations play different roles in some biochemical processes, while their effect is identical in some others.[6,30] The hydrated cation−guanine complex has been further explored, and we think that the calculations provide a rationalization for this seemingly ambiguous behavior. Zn^{2+}···purine interaction is much stronger than the Mg^{2+}···purine one due to the additional metal d-orbital−guanine MO donating/back-donating interaction,[8,9] while the water···cation interaction energies and the hydration energies are very similar for these two cations.[22] The trends in water···cation and base···cation distances reported in Table 1 support the idea of a different balance of interaction between the cation and base and the hydration of the cation for Zn^{2+} and Mg^{2+}. We carried out additional calculations in order to understand this difference better.

Decomposition of the Guanine−Hydrated Cation Interaction. First, we made a decomposition of the guanine···hydrated cation interaction energies into the individual pair components (pairwise cation···base interaction, five pairwise water···base contributions, and the many-body term). The pairwise cation···guanine interaction is much stronger for Zn^{2+} (−186 kcal/mol at the MP2 level, −174 kcal/mol at the HF level) than for Mg^{2+} (−149 kcal/mol at the MP2 level, −151 kcal/mol at the HF level).[44] The sum of the five pairwise water···base contributions is similar (ca. +12.5 kcal/mol, MP2 level) for both complexes, since the geometries are very similar. On the other hand, the many-body term is very different, +46 kcal/mol for the Mg^{2+} complex and +77 kcal/mol for the Zn^{2+} complex at the MP2 level, while the corresponding HF values are +46 and +65 kcal/mol.[45] This many-body term mainly includes screening of the cation···base interaction by the hydration shell and the change of the base···water contributions due to nonadditive polarization effects. Due to the nature of the many-body term, it is not possible to separate them. Nevertheless, the similarity of energetics of the hexahydrated complexes of Zn^{2+} and Mg^{2+} [22] indicates that the reduction of the cation...base interaction upon hydration is the contribution that can be considered very different for these two cations.

Balance of the Water−Cation and Base−Cation Interactions. Table 4 compares several different ways of evaluation of the interaction energies in the studied complexes. The first two rows compare the interactions between cation and guanine and between cation and a single water molecule. Zinc has a stronger interaction with both water and the nucleobase; however, the

TABLE 4: Selected Interaction Energies (kcal/mol) Obtained at the MP2/6-31G* Level. HF/6-31G* Values Are in Parentheses. All Interaction Energies Were Corrected for the Basis Set Superposition Error; Deformation Energies of Monomers Are Not Included. The Last Column Shows the Difference between Zinc and Magnesium

	Zn^{2+}	Mg^{2+}	$Zn^{2+} - Mg^{2+}$
$G\cdots M^{2+}$	−185.1(−174.0)	−148.9(−151.2)	−36.2(−22.8)
$H_2O\cdots M^{2+}$ [a]	−94.9(−90.0)	−82.9(−82.4)	−12.0(−7.6)
$M^{2+}\cdots 6H_2O$ [a,b]	−339.8(−328.0)	−329.6(−325.5)	−10.2(−2.5)
$G-M^{2+}\cdots 5H_2O$ [c]	−203.2(−201.8)	−220.3(−218.0)	+17.1(+16.2)
$G\cdots(M^{2+} + 5H_2O)$ [d]	−94.4(−94.0)	−89.9(−90.3)	−4.5(−3.7)
$G\cdots M^{2+}\cdots 5H_2O$ [e]	−388.4(−375.7)	−373.7(−369.8)	−14.7(−5.9)

[a] This system has been optimized at the HF/6-31G* level; all other energies in the table were obtained for the complexes reported in Tables 1−3. [b] Hydration of the cation (seven subsystems). [c] Hydration of the $G-M^{2+}$ complex (subsystems: five water molecules and the metalated base). [d] Interaction between the hydrated cation and base (two subsystems). [e] Interaction energy of the whole complex (seven subsystems).

zinc/magnesium difference is much more pronounced for the cation···nucleobase complex.[46] This difference influences all the other contributions. The next row provides the hydration energies of zinc and magnesium in hexahydrated complexes. The hydration energies are rather similar; the difference of 10 kcal/mol in favor of Zn^{2+} is in accord with the cation−water interaction energy values. (The previously reported difference by Probst for hexahydrated Zn^{2+} and Mg^{2+} cations was even smaller[22] because of the neglect of electron correlation). The next row presents a hydration energy of the cations bound to a nucleobase (hydration of a metalated base), indicating that the difference between Zn^{2+} and Mg^{2+} is sharply (by almost 30 kcal/mol) reversed. The reason is the repulsive contribution originating in the weakening of the cation−base attraction upon hydration. This contribution is much larger in the case of Zn^{2+}. This leads to similar interaction energies when the interaction is treated as an interaction between base and a hydrated cation (fifth row of Table 4). The last row of Table 4 shows the total interaction energies of the guanine−metal−hydration shell complex. Here the energy difference between zinc and magnesium complexes increases only slightly with respect to the corresponding value for hexahydrated cations (row 3), again because of the larger reduction of Zn^{2+}-base interaction by hydration.[49]

Let us briefly summarize the difference between the Mg^{2+} and Zn^{2+} ions. The complex consisting of the guanine molecule and a hydrated cation can be viewed following two approaches: (i) as a complex between the hydrated cation and a base (the hydrated cation is taken as one subsystem), and (ii) as hydration of a metalated base ($G-M^{2+}$ is taken as one subsystem). The calculations show that the complex with Zn^{2+} is shifted significantly more toward the second interpretation with respect to Mg^{2+}. The key energy contribution is the more covalent nature of the N7(base)···Zn^{2+} interaction. This is also fully consistent with the database search showing that Zn^{2+} interacts with nitrogen more frequently than with oxygen, compared to magnesium.[30]

To further illustrate the difference, we carried out an additional set of calculations. First, we have optimized (HF/6-31G* level) the complex of guanine with the hydrated cation (cytosine has been removed from the base pair). Then, we have fixed the N7−M distance to be by 0.1 and 0.2 Å longer (shorter) with respect to the optimized structure while the system has been fully optimized, which corresponds to a variation of the cation−base distance upon full relaxation of the hydration shell. It is easier to increase the N7−Mg^{2+} distance (the energy penalty of an increase of 0.2 Å is +0.7 kcal/mol only) than the guanine−Zn^{2+} distance (+1.7 kcal/mol). Thus, it is easier to separate the Mg^{2+} cation away from the base into the solvent. On the other hand, a compression of the cation−base distance by 0.2 Å requires +5.8 kcal/mol for Mg^{2+}, but only +3.9 kcal/mol for Zn^{2+}. This observation is probably also related to the finding by Bock et al. for hydrated cations.[30] They reported that the hydration shell around Zn^{2+} is more flexible, compared to Mg^{2+}, so that the energy penalty for changing the water shell structure around Zn^{2+} is smaller.[30] This means, together with our results, that once the Zn^{2+} cation approaches the N7 position of guanine, it tends to be bound there while the hydration shell is very flexible. On the other hand, Mg^{2+} can be more easily released back to solvent and its hydration shell is less flexible with respect to the cation.

4. Conclusions

Structures and energetics of complexes between the guanine−cytosine Watson−Crick DNA base pair and hydrated Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Zn^{2+}, Cd^{2+}, and Hg^{2+} metal cations were studied at the MP2/6-31G*//HF/6-31G* level using relativistic pseudopotentials for the description of the cations.

The interaction between hydrated cation and guanine is significantly reduced compared to the guanine−unsolvated cation interaction.

The stabilizing three-body contribution has been reduced by less than 50% and remains significant. The strength of the guanine−cytosine Watson−Crick base pair is enhanced by ca. 20−30% due to the coordination of the hydrated cation.

The group IIb metals and Mg^{2+} cations are tightly bound to the N7 atom of guanine. The Ca^{2+}, Sr^{2+}, and Ba^{2+} cations are coordinated simultaneously to the N7 and O6 atoms of guanine and the base−cation distance increases with the row number. However, the energy difference between the N7 and N7−O6 types of coordination is rather small. Relativistic effects are apparent for Hg^{2+}, changing the trend in interatomic distances.

Zn^{2+} and Mg^{2+} cations show different balance of the cation−base and cation−water interactions. Zn^{2+} is bound more tightly to the base and its water shell is more flexible than that around Mg^{2+}. The situation can be partly described as a shift from the interaction between nucleobase and hydrated cation toward the hydration of a metalated base. This may likely account for the differences in biological behavior of Zn^{2+} and Mg^{2+}.

Acknowledgment. This study was supported by Grant 203/97/0029 from GA CR, by Grant 204/96/1680 from GA CR, by ONR Grant N00014-95-1-0049, and by NIH Grant 332090. We would like to thank the Supercomputer Center, Brno, Supercomputer Center, Prague, and the Mississippi Center for Supercomputing Research for a generous allotment of computer time. M.S. thanks the Department of Chemistry, University of Virginia, for continuous support.

Supporting Information Available: Cartesian coordinates of the relevant optimized structures (8 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Šponer, J.; Leszczynski, J.; Hobza, P. J. *Biomol. Struct. Dyn.* **1996**, *14*, 117 and references therein.
(2) Alhambra, C.; Orozco, M.; Luque, F. J. *J. Phys. Chem. B* **1997**, *101*, 3846.
(3) Brameld, K.; Dasgupta, S.; Goddard, W. A., III. *J. Phys. Chem. B* **1997**, *101*, 4851.
(4) Šponer, J.; Gabb, H. A.; Leszczynski, J.; Hobza P. *Biophys. J.* **1997**, *73*, 76 and references therein.
(5) Šponer, J.; Hobza, P. *Chem. Phys. Lett.* **1997**, *267*, 263.

(6) *Metal Ions in Biological Systems*, Vol. 32; Sigel, A., Sigel, H., Eds.; Marcel Dekker Inc.: New York, 1996.

(7) Šponer, J.; Burda, J. V.; Mejzlik, P.; Leszczynski, J.; Hobza, P. *J. Biomol. Struct. Dyn.* **1997**, *14*, 613.

(8) Burda, J. V.; Šponer, J.; Hobza, P. *J. Phys. Chem.* **1996**, *100*, 7250.

(9) Burda, J. V.; Šponer, J.; Leszczynski, J.; Hobza, P. *J. Phys. Chem. B* **1997**, *101*, 9670.

(10) Del Bene, J. *J. Mol. Struct (THEOCHEM)* **1985**, *124*, 201.

(11) Sagarik, K. P.; Rode, B. M. *Inorg. Chim. Acta* **1983**, *78*, 177.

(12) Lipinski, J. *J. Mol. Struct. (THEOCHEM)* **1989**, *201*, 87.

(13) Hobza, P.; Sandorfy, C. *J. Biomol. Struct. Dyn.* **1985**, *6*, 1245.

(14) Basch H.; Krauss, M.; Stevens, W. J. *J. Am. Chem. Soc.* **1985**, *107*, 7267.

(15) Anwander, E. H. S.; Probst, M. M.; Rode, B. M. *Biopolymers* **1990**, *29*, 757.

(16) Kozelka, J. In *Metal Ions in Biological Systems*, Vol. 33; Sigel, A., Sigel, H., Eds.; Marcel Dekker Inc.: New York, 1996; p 1 and references therein.

(17) Carloni, P.; Andreoni, W. *J. Phys. Chem.* **1996**, *100*, 17797.

(18) Stewart, G. M.; Tiekink, E. R. T.; Buntine, M. A. *J. Phys. Chem. A* **1997**, *101*, 3368.

(19) Potaman, V. N.; Soyfer, V. N. *J. Biomol. Struct. Dyn.* **1994**, *11*, 1035.

(20) Soyfer, V. N.; Potaman, V. N. *Triple-Helical Nucleic Acids*; Springer-Verlag Inc.: New York, 1996.

(21) Sabat, M.; Lippert, B. In *Metal Ions in Biological Systems*, Vol. 33; Sigel, A., Sigel, H., Eds.; Marcel Dekker Inc.: New York, 1996; p 143.

(22) Probst, M. M. *J. Mol. Struct. (THEOCHEM)* **1992**, *253*, 275 and references therein.

(23) Stromberg, D.; Sandstrom, M.; Wahlgren, U. *Chem. Phys. Lett.* **1990**, *172*, 49.

(24) Hartman, M.; Clark, T.; van Eldik, R. *J. Am. Chem. Soc.* **1997**, *119*, 7843.

(25) Garmer, D. R.; Krauss, M. *J. Am. Chem. Soc.* **1992**, *114*, 6487.

(26) Kitchen, D. B.; Allen, L. C. *J. Phys. Chem.* **1989**, *93*, 7265.

(27) Pullman, A.; Demoulin, D. *Int. J. Quantum Chem.* **1979**, *16*, 641.

(28) Marcos, E. S.; Pappalardo, R. R.; Barthelat, J.; Gadea, F. X. *J. Phys. Chem.* **1992**, *96*, 516.

(29) Akesson, R.; Petterson, L. G. M.; Sandstrom, M.; Wahlgren, U. *J. Am. Chem. Soc.* **1994**, *116*, 8705.

(30) Bock, C. W.; Katz, K. A.; Glusker, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 3754.

(31) Gresh, N. *J. Comput. Chem.* **1995**, *16*, 856.

(32) Lee, S.; Kim, J.; Park, J. K.; Kim, K. S. *J. Phys. Chem.* **1996**, *100*, 14329.

(33) Rotzinger, F. P. *J. Am. Chem. Soc.* **1996**, *118*, 6760.

(34) Furuki, T.; Sakurai, M.; Inoue, Y. *J. Comput. Chem.* **1995**, *16*, 378.

(35) Pappalardo, R. R.; Marcos, E. S. *J. Phys. Chem.* **1993**, *97*, 4500.

(36) Tongraar, A.; Liedl, K. R.; Rode, B. M. *J. Phys. Chem. A* **1997**, *101*, 6299.

(37) (a) Pacios, L. F.; Christiansen, P. A. *J. Chem. Phys.* **1985**, *82*, 2664. (b) Hurley, M. M.; Pacios, P. A.; Christiansen, P. A.; Roos, R. B.; Ermler, W. C. *J. Chem. Phys.* **1986**, *84*, 6840. (c) LaJohn, L. A.; Christiansen, P. A.; Roos, R. B.; Atashroo, T.; Emler, W. C. *J. Chem. Phys.* **1987**, *87*, 2812. Roos, R. B. Powers, J. M.; Atashroo, T.; Emler, W. C.; LaJohn, L. A.; Christiansen, P. A. *J. Chem. Phys.* **1990**, *93*, 6654.

(38) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553.

(39) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, W. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, L. J.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*; Gaussian, Inc., Pittsburgh, PA, 1995.

(40) Egli, M.; Williams, L. D.; Fredericks, C. A., Rich A. *Biochemistry* **1991**, *30*, 1364.

(41) Šponer, J.; Hobza, P. *J. Am. Chem. Soc.* **1994**, *116*, 709.

(42) Luisi, B.; Orozco, M.; Šponer, J.; Luque, F. J.; Shakked, Z. *J. Mol. Biol.*, in press.

(43) Marcus, Y. *Chem. Rev.* **1988**, *88*, 1475.

(44) Comparison of the last four numbers shows the role of 3d-electron polarization. While for Mg^{2+} attractive dispersion effect is canceled out by the reduction of the Coloumb term, polarizability of the Zn^{2+} cation is larger, and this results in higher MP2 stability.[8,9]

(45) Note the importance of the electron correlation for this contribution.

(46) The nitrogen atom is more sensitive to polarization effects than oxygen. Atomic polarizabilities[47] $\alpha_N = 1.09$ au and $\alpha_O = 0.46$ au, for the affinity of Co^+/Ni^+ to oxygen or nitrogen atom, cf. ref 48.

(47) Kang, Y. K.; Jhon, M. S. *Theor. Chim. Acta* **1982**, *61*, 41.

(48) Burda, J. V. *Chem. Phys.*, in press.

(49) The difference between zinc and magnesium would be very important when changing the local environment around the metal; for example, reduction of the hydration would be associated with larger increase of the base−hydrated cation interaction for zinc, since it should converge to the binding energy difference of ca. 35 kcal/mol in favor of zinc for unsolvated cations.