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Water-Mediated Magnesium-Guanine Interactions

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Divalent cations, particularly magnesium, play an important role in the stabilization of nucleic acids and in their biochemistry. Of special interest is the strong affinity of a hydrated magnesium ion for guanine. To investigate the nature of this interaction, we calculated the interaction energy (IE) for eight optimized complexes in which tetra-, penta-, and hexahydrated magnesium ions were initially placed in the plane of guanine near the O6 and N7 binding sites. Results at the RHF/6-311G**//RHF/6-311++G** level indicate that the guanine-tetrahydrated magnesium ion complex has the highest value of the IE. However, the formation of the tetrahydrated magnesium ion from a hexahydrated ion decreases the energy of this complex and, overall, the hexahydrated ion is considered to be more stable. We also investigated the binding site of a hexahydrated magnesium ion located in a high-resolution crystal structure of the dodecamer [d(CGCGAATTCGCG)]₂. Complexes of the hexahydrated magnesium ion with the individual and combined G2 and G22 bases extracted from the crystal structure were also considered and Natural Energy Decomposition Analysis used to partition the IEs. The results show that water-mediated charge transfer from guanine to magnesium plays an important role in the stabilization of these guanine-water-magnesium complexes and occurs by a cooperative mechanism.

Introduction

The structure and function of DNA and RNA strongly depend on their interactions with divalent cations.^{1–4} These cations are found to interact with different sites at the surface of nucleic acids: phosphate oxygens, sugar oxygens and nucleotides. Besides the fact that the presence of magnesium ions in solution leads to a decrease in the persistence length of DNA⁵ and increases the melting temperature of DNA double-helices,^{6,7} magnesium is also involved in the site-specific hydrolysis of the polyester bond of DNA, both enzymatically^{8–10} and in protein-free systems,^{11,12} and in RNA.^{13,14} It has also been reported that divalent metal cations stimulate the formation of DNA and RNA triple helices^{15,16} and stabilize other noncanonical structures such as quadruple helices.¹⁷

To understand the nature of the interaction between nucleic acids and metal cations, a number of computational investigations have recently been made. Continuum models that use the Poisson–Boltzmann (PB) equation^{18–20} and other techniques^{21,22} of statistical mechanics are very useful for properties that do not involve specific interactions with water molecules. Molecular dynamics (MD)^{23–27} and Monte Carlo (MC)^{20,28,29} simulations are individual particle approaches and require a good description of the potential energy surface, generally approximated by the interaction potentials among all species in the system. However, the explanation of the effect of cations based on these empirical potentials does not provide a complete picture of cation-nucleotide interactions because the stabilizing effects of electronic polarization and charge transfer between interacting units are not included. The majority of the specific phenomena mentioned above that occur in biologically relevant systems can be understood only if detailed information is available about the behavior of divalent cations near the surface of nucleic acids.

X-ray studies provide the position of hydrated magnesium ions in crystal structures of nucleic acids and reveal several characteristic modes of binding. One mode corresponds to the direct interaction between a magnesium ion and a particular atom of the nucleic acid (inner-sphere coordination).^{30,31} Hydrated magnesium ions have been observed to form inner-sphere contacts with either O6 or N7 atoms of guanine, but not simultaneously with both.³⁰ In contrast, calcium ions, considered to be softer than magnesium, can exhibit inner-sphere coordination with both O6 and N7 atoms.³² A second binding mode represents the case in which magnesium-guanine interactions are mediated by the cation hydration shell (outer-sphere coordination).^{30,32–34} This type of contact is found in both the major and the minor grooves of DNA: hydrated magnesium ions interact with the O6 and N7 atoms of guanine and adenine³⁰ and with cross-strand base and O2' atoms of adjacent base pairs.³² The interaction of hydrated magnesium ions with guanine bases of RNA has also been reported. Juneau et al.³⁰ analyzed the positions of 27 hydrated magnesium ions in an RNA crystal structure and found that there were 21 outer-sphere coordination contacts with the binding sites of guanine, whereas only 3 inner-sphere contacts were observed. These data confirm the preference of water-mediated outer-sphere interactions for magnesium-guanine complexes. We should also mention that a particular magnesium ion may form both inner- and outer-sphere coordination contacts simultaneously, which we refer to below as mixed-sphere coordination.

The details of cation-base interactions can be investigated by high level quantum chemical calculations. Spomer's group has studied the interactions between several divalent metal cations and the O6 and N7 binding sites in guanine-cytosine base pairs at the MP2/6-31G**//HF/6-31G* level by doing a full optimization of the structures.^{35–40} They found that the majority of divalent ions coordinate N7 directly and, being octahedrally coordinated, are surrounded by five water molecules. However, Famulari et al., in calculations at the RHF/3-21G level, showed

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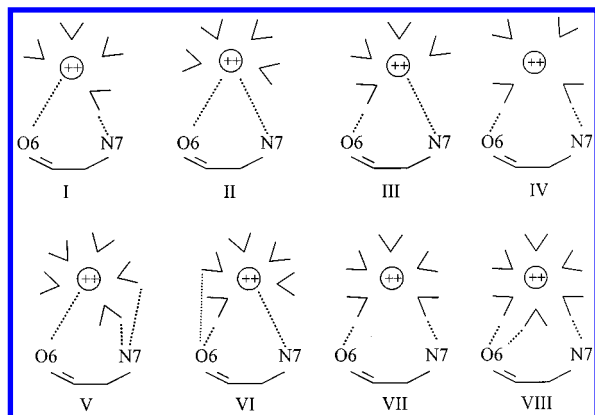


Figure 1. Schematic representation of guanine-Mg(H₂O)_n²⁺ complexes (*n* = 4–6). Only the binding sites of guanine are shown.

that a pentahydrated magnesium ion prefers inner-sphere coordination to O6 of guanine over N7.⁴¹ The Mg–N7 bond has been found to be much weaker than those formed between divalent cations group of IIb and guanine.⁴² This has also been confirmed experimentally by measurements of the stability of guanoside 5'-triphosphate-hydrated magnesium complexes with a guanine N7 back-bond.⁴³

X-ray analysis and *ab initio* methods are powerful techniques that help explain the nature of interactions between solvated cations and nucleic acids. In this respect, the aim of the present paper is 3-fold. First, we investigate inner- and outer-sphere coordination of a magnesium ion hydrated with 4 to 6 water molecules to the O6 and N7 binding sites of guanine. Second, we consider interactions between the hexahydrated magnesium ion and guanine bases that occur in the crystal structure of Shui et al.³³ Third, by applying NBO theory⁴⁴ and Natural Energy Decomposition Analysis,^{45,46} we look into the details of these interactions and, particularly, investigate the charge-transfer mechanism stabilizing the complexes.

Methods

Gaussian 98 software⁴⁷ was used to optimize the geometry of all guanine-magnesium ion complexes. Complexes I–VIII, shown in Figure 1 (a description is given below), were fully optimized at the restricted Hartree–Fock level with the extended 6-311++G** split-valence, triple- ζ basis set with one set of polarization and two sets of diffuse functions on all atoms, including hydrogens. In complexes IX–XV, the heavy atoms were fixed in the positions given by the published crystal structure³³ (NDB ID: BDL084) but all hydrogen atoms were optimized.

The calculation of the interaction energy between monomers A and B of the complexes were performed, A represents all the bases consisting in a given complex and B represents a hydrated magnesium ion; single point energy calculations were done using the SCF = tight option. Preliminary calculations carried out on complex XIV gave values of the interaction energy at the RHF/6-31G**//RHF/6-31G*, B3LYP/6-31G**//B3LYP/6-31G* and MP2/6-31G**//RHF/6-31G* levels of –57.0, –54.3, and –57.2 kcal/mol, respectively. Because these values differed by no more than 5%, to save computational time all further calculations of the interaction energy were performed at the RHF/6-311G** level with optimization carried out at the RHF/6-31G level or greater. The basis set superposition error (BSSE) was obtained by applying the counterpoise (CP) correction method of Boys and Bernardi.⁴⁸ ESP charges were calculated from the electrostatic potentials of guanine-magnesium complexes derived using

the Singh–Merz–Kollman scheme^{49,50} as implemented in Gaussian 98.⁴⁷ The electrostatic term of the interaction energy in kcal/mol based on ESP charges was computed according to the equation

$$ES^{\text{ESP}} = 331.5 q_{\text{Mg}} \sum_i^{\text{All atoms of guanine}} \frac{q_i}{r_{i-\text{Mg}}} \quad (1)$$

where $r_{i-\text{Mg}}$ is the distance in angstroms, and q is the atomic charge in units of the proton charge.

The electrostatic energy in kcal/mol based on representing guanine by a classical dipole interacting with a point charge is

$$ES^{\text{C-D}} = 69.02 \frac{q_{\text{Mg}} \mathbf{D} \cdot \mathbf{r}}{r^3} \quad (2)$$

where \mathbf{D} is the dipole vector of guanine (in Debyes), and \mathbf{r} is the vector (in angstroms) between the origin of the dipole moment (the center of mass of guanine) and the magnesium ion.

The charges of atoms in the optimized structures were computed using natural bond orbital (NBO) theory⁴³ at the RHF/6-311G** level and the energy lowering due to the charge-transfer interactions was estimated by second-order perturbation theory. These calculations were performed using the NBO 4.M program⁵¹ linked to the GAMESS package.⁵² To obtain the different contributions of the interaction energy, we applied Natural Energy Decomposition Analysis (NEDA) proposed by Glendening.^{45,46} This scheme decomposes the CP-corrected value of the interaction energy (IE) into electrostatic (ES), polarization (PL), charge transfer (CT), exchange (EX), and deformation (DEF) components

$$\text{IE} = \text{ES} + \text{POL} + \text{CT} + \text{EX} + \text{DEF} \quad (3)$$

Such a partition differs somewhat from the scheme proposed by Kitaura and Morokuma (KM),^{53,54} and we have chosen NEDA for the energy analysis for two reasons. First, the lack of wave function antisymmetry in the computation of the polarization term in the KM scheme may lead to the collapse of the valence electrons of one part of the complex into the core orbitals of its complementary part.⁴⁶ This phenomenon was observed using the KM scheme in some preliminary studies. Second, to analyze the charge-transfer mechanism, we used NBO theory, which also serves as a basis for NEDA.

Results

(A) Study of the Guanine Binding Site of a Hydrated Magnesium Ion. It has been established that a hydrated magnesium ion preferentially binds to guanine.^{30–32} To investigate the nature of the contacts, we modeled complexes in which tetra-, penta-, and hexahydrated magnesium ions were initially placed in the plane of guanine near the O6 and N7 binding sites in all possible inner-, outer-, and mixed-sphere coordination modes. The eight initial complexes are represented in Figure 1. Complexes I–IV contain four hydration shell water molecules, V–VII five waters, and in VIII, the magnesium ion is hexahydrated. The magnesium ion has only inner-sphere contacts with guanine in II, only outer-sphere contacts in IV, VII, and VIII, and both types of coordination exist in I, III, V, and VI.

Full optimization of the geometries was carried out at the RHF/6-311++G** level. Frequency calculations confirm that all these complexes are stationary states. The interaction energies

TABLE 1: Hydration Number of Magnesium, Coordination Number of Magnesium, Number of Inner- and Outer-Sphere Contacts, NBO Charge of Magnesium, Electronic Energies (Hartrees), and Interaction Energies (kcal/mol) Calculated at the RHF/6-311++G//RHF/6-311G** Level for the Guanine–Water–Magnesium Complexes Displayed in Figure 1**

complex	hydration No.	coord. No.	inner contacts	outer contacts	NBO Mg charge	electronic energy	IE ^a	IE ^b
I	4	5	1	1	1.813	−1043.1251	−104.6	−88.9
II	4	6	2	0	1.781	−1043.1245	−110.1	−88.5
III	4	5	1	1	1.800	−1043.1079	−93.4	−78.1
IV	4	4	0	2	^c	^c	^c	^c
V	5	6	1	2	1.783	−1119.2121	−91.8	−77.5
VI	5	6	1	1	1.774	−1119.2012	−85.5	−70.9
VII	5	5	0	2	1.812	−1119.1880	−65.1	−61.9
VIII	6	6	0	3	1.781	−1195.2852	−68.7	−60.2

^a Deformation of monomers is neglected, CP-correction is applied. ^b Deformation of monomers is taken into account. ^c Complex IV evolved into complex I during preliminary optimization at the RHF/6-31G level.

TABLE 2: Selected Bond Distance Ranges for Guanine–Water–Magnesium Complexes Obtained at the RHF/6-311++G//RHF/6-311G** Level**

complex	Mg–O6	Mg–N7	Mg–O _w ^a	Mg–O _w ^b	H _w –O6	H _w –N7
I	1.99		2.06–2.14	2.01		1.78
II	2.12	2.29	2.10–2.12			
V	2.02		2.11–2.13	2.10–2.12		2.09–2.25
VIII			2.12–2.13	2.07–2.09	1.85	1.85

^a Nonbridging water molecules. ^b Bridging water molecules.

between guanine and the hydrated magnesium ion calculated at RHF/6-311G** are presented in Table 1. Complex IV was found to be unstable and during optimization at the RHF/6-31G level evolved into complex I. Within each group containing tetra-, penta-, or hexahydrated magnesium ions the largest interaction energies were found for the octahedrally coordinated structures II, V, and VIII. However, if one takes into account the deformation of monomers that form these complexes, the list of the most stable structures according to their interaction energies is I, V, and VIII. Selected geometrical parameters for these structures are given in Table 2. The distances between magnesium and the oxygens of nonbridging water molecules are in the range 2.06–2.14 Å for all three structures. However, contrary to the findings of Famulari et al.⁴¹ at the HF/3-21G level, according to which the Mg–O₆ bond length in structure V equals that of Mg–O_w (water), our calculations performed at a higher level of theory showed that the two lengths differ by 0.08–0.11 Å. Moreover, in VIII, the distances between magnesium and bridging and nonbridging water molecules are not identical.

(i) *Interaction Energies and Stability of the Optimized Complexes.* As seen in Table 1, complex II is the most stable structure and the magnesium ion prefers inner-sphere contacts over outer-sphere contacts with guanine. Numerous experimental data demonstrate that in solution the first hydration shell of a single magnesium ion contains six water molecules. Markham et al.⁵⁵ performed calculations of the hydration energies of a magnesium ion at the MP2(FULL)/6-311++G**//RHF/6-31 level showing that it costs 46.6 kcal/mol to remove two waters from Mg(H₂O)₆²⁺. The value of the free energy of hydration for the reaction Mg(H₂O)₄²⁺ + H₂O → Mg(H₂O)₅²⁺ is −27.4 kcal/mol and that for Mg(H₂O)₅²⁺ + H₂O → Mg(H₂O)₆²⁺ is −19.0 kcal/mol. A possible explanation for the observed predomination of outer-sphere contacts may be proposed based on the fact that the hexahydrated complex (−68.7 kcal/mol) remains more stable than the tetrahydrated one (−110.1 kcal/mol): the difference in their interaction energies of 41.4 kcal/mol does not compensate for the energy of 46.4 kcal/mol required for removal of two water molecules from the hydration shell of the ion. (We present this explanation based on the values of the interaction energies calculated when the deformation of

monomers was neglected. The same analysis applies if one takes into account these deformations; however, in this case, the compensation for the dehydration of two water molecules from complex VIII (−60.2 kcal/mol) to complex I (−88.9 kcal/mol) is even smaller and consists of 28.7 kcal/mol.)

(ii) *Dependence of the Magnesium Ion Charge on its Coordination Number.* On the basis of their optimized geometries, we performed NBO analysis of complexes I–VIII. The charge of the magnesium ion in each complex is presented in Table 1. It is seen that the charge on magnesium depends on its coordination number (1.80–1.81 e₀ for penta- and 1.77–1.78 e₀ for hexacoordinated ions); however, it does not matter whether magnesium has inner-, outer-, or mixed-sphere contacts with guanine. The difference between these cases exactly corresponds to the amount of charge transferred to magnesium by each coordination site, which is about 0.035 e₀. In complexes III and VI, in which magnesium has inner-sphere contacts with N7 of guanine, the charge on magnesium is lower by 0.01 e₀ in comparison with complexes I and V, respectively, in which there is inner-sphere coordination to O6 of guanine. This is expected because the strength of an electron donor is proportional to its electropositivity and nitrogen is the more electropositive atom.

(B) *Investigation of a High-Resolution Crystal Structure.* In this paper, we also describe calculations based on the [d(CGCGAATTCGCG)]₂-hexahydrated magnesium crystal structure of Shui et al.³³ In this complex the magnesium ion was observed to be bound through its first hydration shell to O6 and N7 of guanine (G2) and to O6 of guanine (G22).

(i) *Analysis of the Interaction Energies.* In its crystal location, the hexahydrated magnesium ion may interact with numerous bases: C1, G2, C3, C21, and G22. To reduce computational effort, we performed optimization of all hydrogen atoms in a complex containing the hexahydrated magnesium ion and two base pairs G2–C23 and G22–C3 extracted from the crystal structure (IX; shown in Figure 2). Selected bond distances and angles of this complex obtained at the RHF/6-31G level are presented in Table 3.

By analyzing the geometrical arrangement of the ion with respect to the bases of the dodecamer, McFail–Isom and co-workers⁵⁶ proposed the possibility of cation– π interactions between the cytosines and the hexahydrated magnesium ion.

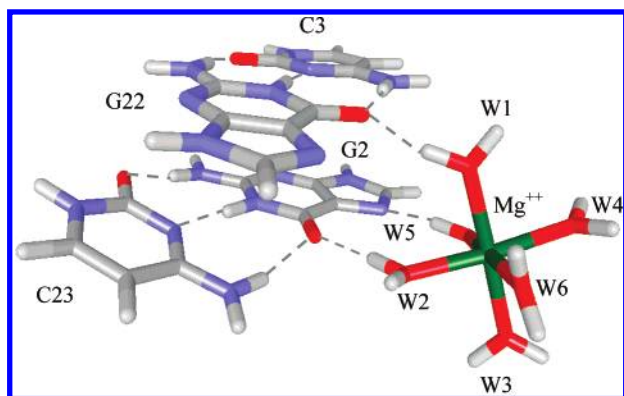


Figure 2. Complex IX containing a hexahydrated magnesium ion and two G–C base pairs extracted from a high-resolution crystal structure.³³

TABLE 3: Selected Parameters for Complex IX (Figure 3) Obtained at RHF/6-311G// RHF/ 6-31G Level**

bond	length (Å)	angle	degrees
O(W1)–H1(W1)	0.980	O(W1)–H1(W1)–O6(G22)	166.1
O(W2)–H1(W2)	0.981	O(W2)–H1(W2)–O6(G2)	163.5
O(W5)–H1(W5)	0.986	O(W5)–H1(W5)–N7(G2)	170.1
O6(G2)–H1(W2)	1.676		
N7(G2)–H1(W5)	1.781		
O6(G22)–H1(W1)	1.766		
N7(G22)–H1(W1)	3.454		

Calculations performed at the MP2/6-31G* level by Sponer et al.⁵⁷ for the $\text{Mg}(\text{H}_2\text{O})_6^{2+}$ -C1 and $\text{Mg}(\text{H}_2\text{O})_6^{2+}$ -C21 complexes give values for the interaction energy of -13.5 and -8.1 kcal/mol, respectively, and essentially rule out the presence of cation- π interactions in the crystal. In these calculations, magnesium was frozen with respect to the cytosine rings, whereas all atoms of the six waters were free to move. However, these calculations do not give a totally consistent picture of the interacting systems because the positions of the water oxygens in the crystal with respect to both the cytosine rings and the magnesium ion are well determined and are affected by their interactions with the rest of the crystal. Previous results by our group⁵⁸ showed that application of these constraints and optimization of only the hydrogen atoms substantially decreases the values of the interaction energy in comparison with those obtained by Sponer et al.,⁵⁷ and, at the same level of theory, gives values of -4.4 and -4.2 kcal/mol, respectively. These data confirm the insignificance of cation- π interactions in this system compared to the guanine-Mg $(\text{H}_2\text{O})_6^{2+}$ interactions. In the following, we describe these strong interactions with guanine that play an important role in stabilizing the position of magnesium in the crystal.

The total interaction energy (CP-corrected values follow in parentheses) for complex IX is -97.3 (-95.6) kcal/mol (Table 4). In the crystal structure of Shui et al.,³³ magnesium binds to guanine through its hydration shell, but not directly. The explanation of this is the same as given above: it is more favorable energetically for a magnesium ion to form a complex with two guanines through outer-sphere coordination (Figure 3a) than to lose two water molecules from the first hydration shell and form inner-sphere contacts (Figure 3b).

To independently investigate the interactions between the hexahydrated magnesium ion and the G2–C23 and G22–C3 base pairs, we constructed complexes X and XI, respectively, by extracting the hexahydrated magnesium ion with the corresponding base pair from complex IX and calculated the values of the IE. These data are also presented in Table 4. The interaction energies for X and XI were found to be somewhat nonadditive at the RHF level in comparison with that obtained

for complex IX: -107.6 (-106.2) kcal/mol (row 2 plus row 3) compared to -97.3 (-95.5) kcal/mol obtained for the full complex (IX). The MP2 level of theory provides qualitatively similar results: -115.6 and -105.3 kcal/mol, respectively.

Because the O6 atoms of guanine form hydrogen bonds not only with hydration shell of magnesium ion but also with hydrogen atoms of complementary cytosines C2 and C23, we examined the influence of the presence of these cytosines on guanine-magnesium interactions. For this purpose we deleted these cytosines from complexes X and XI to obtain complexes XII and XIII, respectively, and found that the values for the IE of the latter pair of complexes do not change significantly (only by -0.6 (0.0) and 2.5 (2.1) kcal/mol) in comparison with those calculated for the former pair of structures in which cytosine was included.

It was pointed out above that interactions between cytosines in the dodecamer and the hexahydrated magnesium ion are relatively weak. The major component of the IE appears as a result of magnesium hydration shell contacts with G2 and G22. To study these interactions in detail we constructed complexes XIV and XV in which the hexahydrated magnesium ion was situated with G2 and G22 bases, respectively. However, in contrast to XII and XIII, we optimized all hydrogen atoms in complexes XIV and XV at the RHF/6-311G** level. The interaction energies for these systems, also presented in Table 4, are -61.6 (-59.3) and -47.6 (-46.9) kcal/mol, respectively. The small difference between these energies and those obtained for the corresponding structures XII and XIII (-62.4 (-60.8) and -48.6 (-47.5) kcal/mol, respectively) is yet another indication that magnesium-cytosine interactions do not play an important role in stabilizing this crystal structure.

The strongest interactions that stabilize the solvated magnesium ion at its position in the crystal structure appear to be with the G2 and G22 bases. The factors that explain such high values of the IE are the favorable geometrical arrangement of the units in the guanine-hexahydrated magnesium complexes and, as a consequence, some specific interactions occurring between the units. The dipole moment of each guanine is pointing almost directly toward the magnesium ion (Figure 4). The angle between the dipole moment and the vector connecting the guanine center of mass and the magnesium ion is 7.7° for G2 and 25.2° for G22. To demonstrate the significance of such charge dipole interactions we calculated the interaction energy of the guanine-bare magnesium complexes in various ways: (a) classically, treating guanine as a dipole interacting with a point charge; (b) using the Merz–Singh–Kollman scheme to obtain the atomic charges that represent the electrostatic potential of the guanine (ESP charges) and calculating the pairwise electrostatic interactions between these charges and the magnesium ion; and (c) applying the Natural Energy Decomposition Analysis scheme and extracting the electrostatic components of the interaction energies; these values are presented in Table 5. The second and the third methods quantitatively agree, whereas representation of guanine by a dipole accounts for only about 70% of the energy, which can be explained by the fact that the dipole moment is the second term in the potential moment expansion and the interaction energy between guanine and the magnesium ion is valid only when the two components are separated by large distance. Overall, as seen from Table 6, the electrostatic interaction is a major contributor to the total value of the interaction energy for complexes XIV and XV and their water-free derivatives. Another component of the interaction energy that significantly stabilizes the complexes is charge transfer. Below we describe the detailed mechanism of charge

TABLE 4: Interaction Energies (kcal/mol, deformation of monomers is neglected) of Complexes IX–XV

complex	composition	IE CP-uncorrected at RHF/6-311G**	IE CP-corrected at RHF/6-311G**	IE CP-uncorrected at MP2/6-31G**
IX ^a	G2C23G22C3–Mg(H ₂ O) ₆ ²⁺	–97.3	–95.6	–105.3
X ^b	G2C23–Mg(H ₂ O) ₆ ²⁺	–61.8	–60.8	–67.8
XI ^b	G22C3–Mg(H ₂ O) ₆ ²⁺	–45.8	–45.4	–47.8
XII ^b	G2–Mg(H ₂ O) ₆ ²⁺	–62.4	–60.8	–66.3
XIII ^b	G22–Mg(H ₂ O) ₆ ²⁺	–48.3	–47.5	–48.2
XIV ^c	G2–Mg(H ₂ O) ₆ ²⁺	–61.6	–59.3	—
XV ^c	G22–Mg(H ₂ O) ₆ ²⁺	–47.6	–46.9	—

^a Complex IX was optimized at the RHF/6-31G level. ^b Geometries of X–XIII were taken from complex IX. ^c Geometries of XIV and XV were obtained by performing an optimization of all hydrogen atoms at the RHF/6-311G** level.

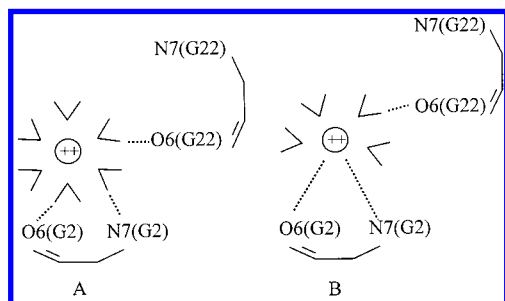


Figure 3. Schematic representation of two guanine–Mg(H₂O)₆²⁺ complexes: (A) crystal structure bonding pattern, (B) hypothesized higher energy structure. Only the binding sites of guanine are shown.

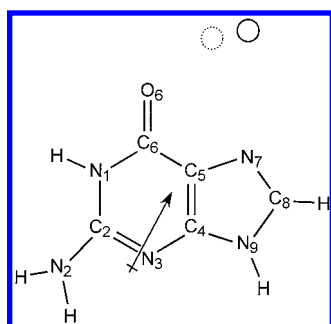


Figure 4. Direction of the dipole moment of guanine (7.88 D for G2 and 7.85 D for G22 calculated at the RHF/6-311G** level for corresponding guanine–magnesium complexes based on the geometries extracted from complex IX). The solid sphere indicates the position of a magnesium ion with respect to G2; the dashed sphere indicates the position of a magnesium ion with respect to G22. In both cases the projection in the plane of guanine is shown.

TABLE 5: Electrostatic Component of the Interaction Energy (kcal/mol) of Guanine–Magnesium Ion Complexes Calculated by Different Approaches

complex	classical dipole-ion ^a	ESP charges-ion ^b	NEDA (ES)
G2–Mg ²⁺	–30.3	–39.7	–41.2
G22–Mg ²⁺	–24.8	–34.3	–34.8

^a Based on a dipole moment of 7.88 D for G2 and 7.85 D for G22 obtained at the RHF/6-311G** level for corresponding guanine–magnesium complexes based on the geometries extracted from complex IX and a magnesium ion charge of +2 e₀. ^b Based on ESP charges of guanine obtained at the RHF/6-311G** level and a magnesium ion charge of +2 e₀.

transfer from guanine through the water molecules of the hydration shell to the magnesium ion.

(ii) *Mechanism of the Charge Transfer.* Charge transfer is one of the key components that stabilizes guanine–magnesium complexes. According to Weinhold,⁵⁹ charge transfer in any ternary cluster will be cooperative if the central monomer is electrically neutral with respect to CT or, in other words, if the

central unit serves simultaneously as electron donor and acceptor.

Not all the waters in complexes XIV and XV are located in equivalent positions with respect to the guanines. We can single out those waters situated between the central ion and the guanine bases. G2 forms hydrogen bonds between the lone pairs of both the O6 and N7 atoms and two bridging waters (W2 and W5) of the magnesium hydration shell, whereas there is only one hydrogen bond between O6 of G22 and water molecule W1 (Figure 2.). To see the effect of the hydration shell, we calculated the interaction energy of the guanine–dihydrated magnesium ion complex obtained from complex XIV by deleting the four nonbridging waters: the energy was found to be –78.8 kcal/mol (Table 6). This destabilization by 19.5 kcal/mol compared to XIV is due to the presence of four additional water molecules that decrease the charge of the magnesium ion from 1.92 e₀ to 1.78 e₀ (here and below, NBO natural atomic charges in units of the proton charge e₀ calculated at the RHF/6-311G** level are given). The nonbridging water molecules affect not only the electrostatic component of the interaction energy, but also the polarization and charge-transfer terms (Table 6). Thus, the bridging water molecules stabilize complexes XIV and XV; the other water molecules destabilize them.

In XIV, a charge of –0.08 e₀ is transferred from guanine to the two intermediate water molecules W2 and W5 (Table 7). However, this charge is not accumulated by them and is further transferred to the magnesium ion. W2 bears a charge of only 0.001 e₀ and the charge on W5 is –0.001 e₀. These two waters coordinate the O6 and N7 atoms of guanine, respectively. The charges on W2 and W5 are small compared with –0.035 e₀ that each of the other four water molecules transferred to magnesium. In XV, the bridging water molecule W1, bound to O6 atom of G22, is not completely neutral; it bears a net charge of 0.01 e₀. In comparison with W2 in complex XIV, such a difference can be explained if one considers the geometry of these complexes in more detail as follows.

The angle between the O6 atom of G2 (or G22), the oxygen of the bridging water molecule W2 (or W1) and the magnesium ion is 135.3° (or 127.3°). Because these values are close to each other the charge of W1 in XV cannot be explained by the difference in the angles of the charge-transfer pathways. However, a significant difference in the geometries is seen when comparing the bond distances between O6 atoms of G2 and G22 and the closest hydrogen atom of a bridging water molecule: 1.674 Å vs 1.766 Å. Using the NBO 4.M program we calculated the energy lowering due to charge transfer ($E_{n \rightarrow \sigma^*}$) from the two lone pairs of each of the two O6 atoms (n_O) to the vacant σ_{OH}^* orbital of the bridging water molecules. These values were found to be –29.4 kcal/mol and –19.5 kcal/mol for G2 and G22, respectively. This indicates that the amount of charge being transferred depends on the distance. To eliminate any questions that might arise about the influence of the

TABLE 6: Natural Energy Decomposition Analysis of Guanine-Magnesium Complexes Performed at the RHF/6-311G Level. Energy Components Are Given in Kcal/Mol**

complex	ES ^a	EX ^b	PL ^c	CT ^d	DEF ^e	IE ^f
G2-Mg(H ₂ O) ₆ ²⁺ (XIV)	-64.0	-4.1	-26.5	-49.2	84.5	-59.3
G2-Mg ²⁺ (Based on XIV)	-41.2	0.0	-11.7	-42.0	17.00	-77.9
G2-Mg(H ₂ O) ₂ ²⁺ (Based on XIV)	-73.5	-3.6	-32.1	-54.7	85.2	-78.8
G22-Mg(H ₂ O) ₆ ²⁺ (XV)	-43.5	-1.5	-19.4	-19.1	36.5	-46.9
G22-Mg ²⁺ (Based on XV)	-34.8	0.0	-8.6	-48.6	16.6	-75.4

^a Electrostatic. ^b Exchange. ^c Polarization. ^d Charge transfer. ^e Deformation. ^f Total value of the interaction energy (deformation of monomers is neglected).

TABLE 7: NBO Charges Calculated at the RHF/6-311G Level**

unit	G2-Mg(H ₂ O) ₆ ²⁺ ^a	G22-Mg(H ₂ O) ₆ ²⁺ ^b	Mg(H ₂ O) ₆ ²⁺ ^c
Guanine	0.082	0.032	
Mg	1.777	1.777	1.779
W1	0.035	0.011	0.037
W2	0.001	0.035	0.036
W3	0.035	0.036	0.036
W4	0.036	0.036	0.037
W5	-0.001	0.036	0.038
W6	0.035	0.035	0.036

^a Complex XIV. ^b Complex XIV. ^c Based on the geometry of complex XIV.

magnesium ion because its position with respect to each guanine is different, we repeated the NBO calculation using the fragments of XIV and XV that contain the corresponding guanines and bridging water molecules only (we assume that this is a natural state of guanine in solution). This gives values for $\Delta E_{n \rightarrow \sigma^*}$ of -21.0 kcal/mol and -13.2 kcal/mol. Because it is reasonable to assume that the value of $\Delta E_{n \rightarrow \sigma^*}$ is proportional to the amount of charge transferred, we conclude that the amount of charge depends only on the length of the hydrogen bond and not on the position of magnesium with respect to guanine. Thus, the presence of magnesium does not change the relative amount of charge transferred (a factor of two) from guanine to bridging water molecules, but does enhance its absolute magnitude from 0.043 e_0 to 0.083 e_0 for G2 and from 0.016 e_0 to 0.032 e_0 for G22. These data clearly illustrate the cooperative nature of charge transfer within the guanine-water-magnesium ion fragment.

On the other hand, considering the influence of guanine on the hexahydrated magnesium ion, we point out that the presence of guanine does not affect the amount of charge transferred from water molecules to magnesium. Independent of the composition of the complex (Table 7), the charge borne by magnesium was found to be 1.78 e_0 for each structure, which means that it does not matter whether the charge was transferred from guanine through the bridging waters and the other nonbridging water molecules or directly from all six waters. This is also consistent with the fact that values of the energy lowering ($\Delta E_{n \rightarrow n^*}$) due to charge transfer from the lone pair of a water oxygen to a vacant Rydberg orbital of magnesium were found to be nearly identical (± 0.5 kcal/mol) in the presence and in the absence of guanine. Note also that the magnesium ion in each complex in Table 7 is octahedrally coordinated. This is consistent with the hypothesis proposed at the end of the first part of this paper that the charge on a magnesium ion mainly depends on its coordination number.

Conclusions

A tetrahydrated magnesium ion forming inner sphere contacts with both the O6 and the N7 atoms of guanine is the most stable complex among structures I–VIII (Figure 1) investigated here.

Because of the high energy cost of dehydration of Mg(H₂O)₆²⁺, for example, in comparison with that of a hydrated calcium ion, the formation of a guanine-tetrahydrated magnesium ion complex with two inner-sphere contacts from a hexahydrated ion is not favorable. Among guanine-pentahydrated magnesium complexes, the most stable structure has inner-sphere coordination with the O6 atom of guanine. Overall, outer-sphere coordination was found to be preferable in both the theoretical models and the crystal structures.

The values of the interaction energy between the hexahydrated magnesium ion and base pairs G2C23 and G22C3 in the crystal structure of Shui et al. (complexes X and XI) were found to be slightly nonadditive (~10%) in comparison with that obtained for the G2C3G22C23-Mg(H₂O)₆²⁺ complex (IX). By analyzing the values of the interaction energies calculated for the complexes extracted from complex IX (structures X, XI, XII, and XIII), we conclude that cytosines C3 and C23 do not significantly affect the interaction energies between guanines G2 and G22 and the hexahydrated magnesium.

We have shown that stabilization of the guanine-water-magnesium ion complexes mainly occurs due to electrostatic interactions between units and the cooperative enhancement of charge transfer from guanine to magnesium through the hydration shell of the ion. The amount of charge transferred from guanine strongly depends on the length of the bond. The main determinant of the charge of the magnesium ion is its coordination number. We also demonstrated that the magnesium charge decreases slightly with increasing electropositivity of the electron donor.

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