Gas-Phase Absolute Ca^{2+} and Mg^{2+} Affinity for Nucleic Acid Bases. A Theoretical Determination

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A density functional investigation of the interaction between calcium and magnesium divalent cations and nucleic acid bases was performed to determine coordination geometries, electronic features, absolute metal ion affinities, entropies, and free energies for all possible complexation stable products. Cations were allowed to interact with the canonical and noncanonical tautomers of free bases after a careful selection of several attachment sites. Magnesium ion shows a greater affinity for nucleic acid bases than calcium. All complexes are characterized by a ionic interaction between ligand and metal ions that appears slightly more pronounced for magnesium.

Introduction

The significant role of metalation on the structure, stability, and reactivity of DNA and RNA nucleic acids was widely demonstrated by a series of theoretical[1−20] and experimental works.[21−28]

Both monovalent and divalent cations usually interact with the phosphate group, but many studies[29−32] confirm that the direct cation−base interactions occur and that they are frequently involved in biological processes.[7,33−36] For example, the double charged cations can induce proton transfer between guanine N1 and cytosine N3 positions in Watson−Crick base pairs,[5] can stabilize some purine−purine−pyrimidine DNA triplexes,[37] can favor the formation of rare tautomers and mispairs,[30,32] and interact favorably with π-systems causing the bases to unstick.[13]

Cases in which a hydrated metal cation coordinates simultaneously the base and the phosphate group are also known.[38−52] In these last situations the phosphate group appears involved in an outer-sphere coordination through one of the solvent molecules.[32,53]

The inclusion of the solvation shell of cations can change the coordination type with the base especially when metal ions with small atomic radii are considered.[12] This can be explained by the increased possibility for a large ion to extend its coordination sphere in a such a way as to preserve the coordination of the bare species and simultaneously add some water molecules. So, for example, the Mg^{2+} cation presents two different coordinations depending on whether we consider its solvation sphere or not. In particular, taking as reference only the base moiety, it appears monocoordinated to the N7 atom of guanine in the first case and bicoordinated to both N7 and O6 atoms in the second one.[12] On the contrary, Ca^{2+} is always bicoordinated to N7 and O6 of guanine.

The available literature is very rich in studies concerning the magnesium cation and its interaction with DNA and RNA.[8,9,11−13,21,22,25,28,54] However, much less work has been devoted to calcium complexes.[8,9,11,12]

The aim of this paper is to evaluate the absolute Mg^{2+} and Ca^{2+} affinity for DNA and RNA nucleobases. We have considered the interactions between isolated bases and bare cations because we think that this kind of investigation represents the first step in explaining the effective role of metalation in the biophysics of nucleic acids. On the other hand, since the hydration of a cation cannot be represented simply by a fixed number of solvent molecules at their fixed coordination geometry, the results obtained considering the solvation shell would not be complete without molecular dynamics. Furthermore, because the experimental studies on this subject are often be performed in the framework of mass spectrometry (i.e. kinetic method),[55−58] the theoretical determination of metal affinities in the gas phase can find confirmation immediately and in turn be used as a guideline to interpret the measured values.

Computational Details

Computations were performed with Becke3 (B3) exchange[59] and Lee−Yang and Parr (LYP) correlation[60] potentials and the 6-311+G(2df,2p) orbital basis set as implemented in the Gaussian 98 code.[61] The choice of the basis set used here was based on our previous experience in alkali metal affinity determinations for biological systems.[14−17]

The most stable base tautomers and the possible complexes originated by the different coordinations of Mg^{2+} and Ca^{2+} ions, including also the interaction with the π electron system of the nucleobases, were fully optimized and characterized from the vibrational point of view. It is worth noting that some low-lying tautomers such as the aromatic form of uracil and thymine, where both oxygen atoms carry a H atom, were not considered in this study because of their scarce biological significance or the absence of suitable attachment sites. These same arguments cannot be applied to the cytosine for which the C1 canonical and C2 aromatic forms coexist.[62−65]

Natural bond order (NBO) analysis[61] was used to the describe the bond type involved in the formation of the complexes.

Metal ion affinity (MIA) was assumed to be the negative of the enthalpy variation (ΔH) for the dissociation process of the bases−M^+ species.

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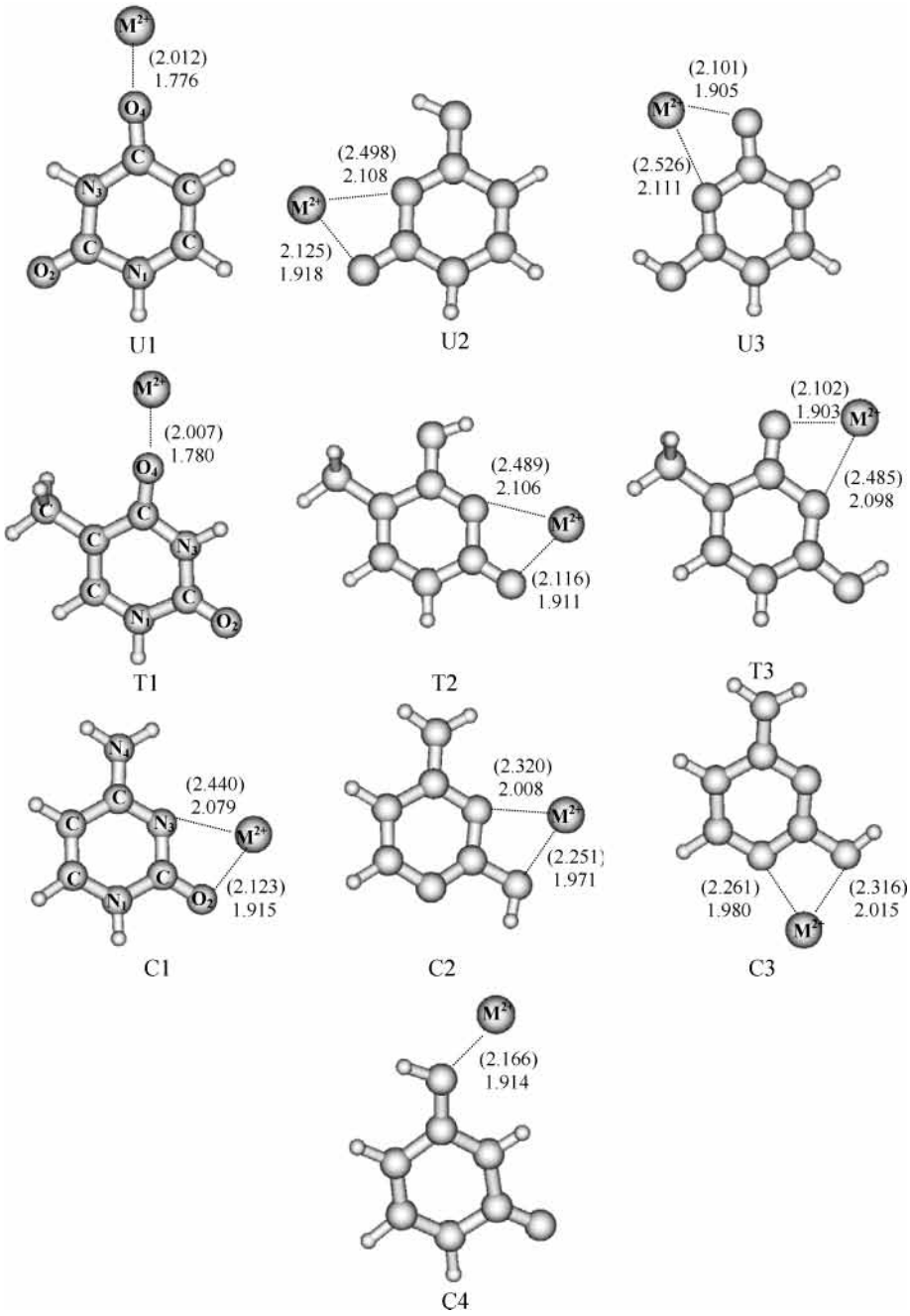

Figure 1. B3LYP/6-311+G(2df,2p) optimized structures of uracil, thymine, and cytosine complexes with M^{2+} ($M^{2+} = Mg^{2+}$ and Ca^{2+}) cations. Distances are in Å. Values in brackets are for the calcium ion.

Basis set superposition error (BSSE) computed for the most stable bases$-M^+$ species, through the counterpoise method[66] implemented in the Gaussian 98 code, was used to correct all the MIA values. The entropic ($T\Delta S$) and free energy (ΔG) variations for the above-mentioned dissociation processes were obtained by a thermochemical analysis at 298 K.

Results and Discussion

Optimization and vibrational analysis confirmed that both magnesium and calcium ions form stable complexes with DNA and RNA base tautomers.

Interaction of cations with the π electron system of bases, suggested by McFail-Isom et al.,[13] was not corroborated by our computations. In fact, all attempts to optimize the structures of these complexes failed because of energy convergence problems or because of their collapse in another minimum structure. However, it is worth noting that such a type of interaction is widely dependent on the hydration water molecules surrounding the cation.[13]

In Figures 1 and 2 are reported the most significant geometrical parameters of the stable $M^{2+}-$DNA (RNA) bases ($M^{2+}= Mg^{2+}$, Ca^{2+}) complexes obtained by B3LYP/6-311+G(2df,2p) computations. Relative energies of the various species and MIA values are collected in Table 1 for both magnesium and calcium ions.

As can be noted, uracil and thymine are able to coordinate both $Mg^{2+}$and Ca^{2+} ions.

For the magnesium ion, the complexes originating from U1 and T1 free tautomers are monocoordinated species. The $Mg^{2+}-O_4$ bond length is very similar in these two complexes and the $Mg^{2+}-O_4-C$ valence angles deviate from linearity by 10° and 20° respectively in U1$-Mg^{2+}$ and T1$-Mg^{2+}$. The relative

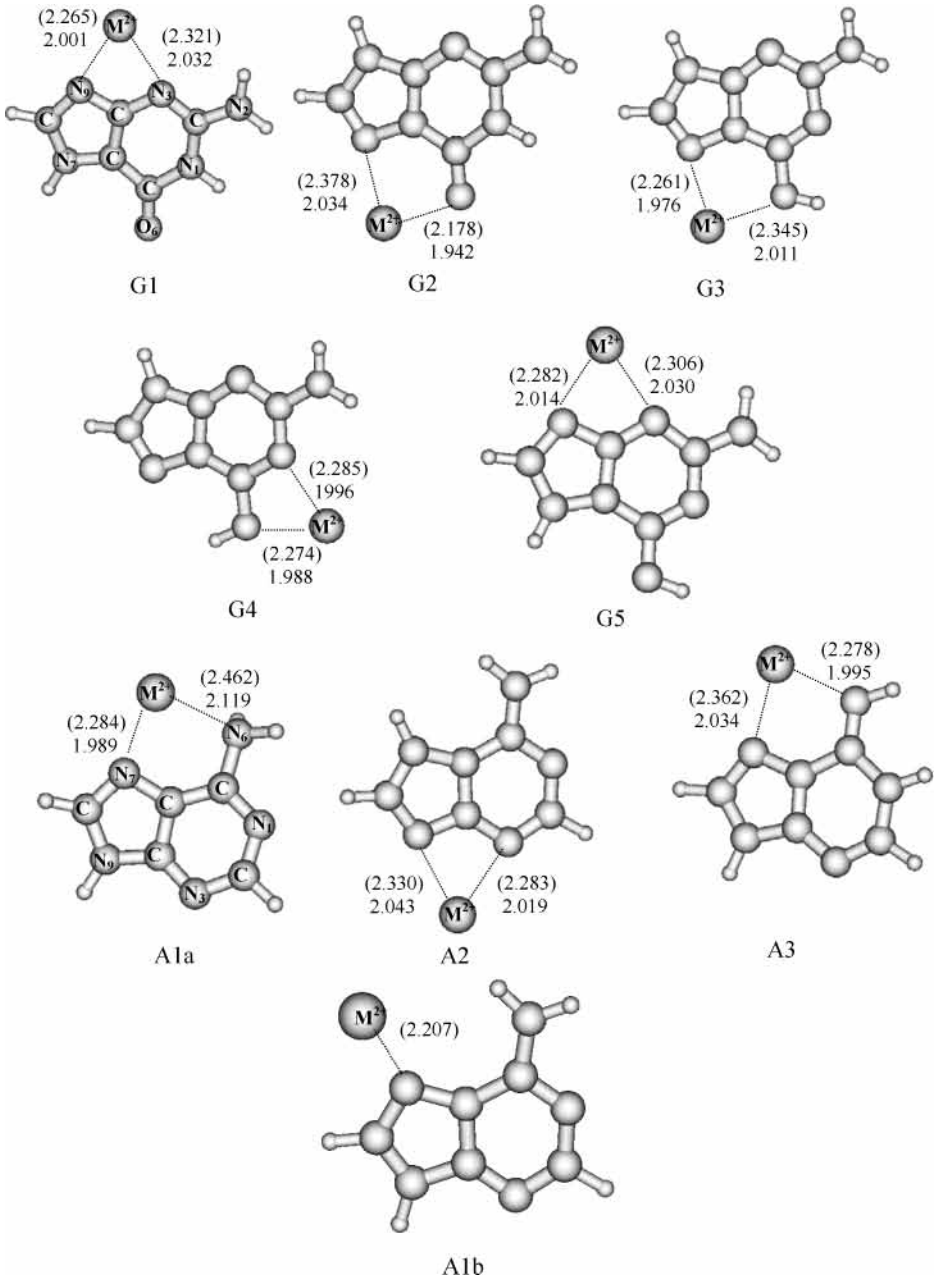

Figure 2. B3LYP/6-311+G(2df,2p) optimized structures of guanine and adenine complexes with M^{2+} ($M^{2+} = Mg^{2+}$ and Ca^{2+}) cations. Distances are in Å. Values in brackets are for the calcium ion.

energies associated with these species are quite a bit higher with respect to those of complexation forms of other tautomers that show the cation bicoordinated.

For calcium, the energetic gap between U1−Ca^{2+} and T1−Ca^{2+} and the most stable complexes of U2, U3, T2, and T3 is quite more restrained. In these species we found a Ca^{2+}−O_4 distance of 2.012 and 2.007 Å and a valence angle of 175° and 174°, respectively. In the complexes of the noncanonical tautomers of uracil and thymine, the distance between the calcium ion and the oxygen atoms becomes slightly longer than those present in the monocoordinated systems, instead, a more pronounced lengthening of the cation−nitrogen distance occurs. In this situation and being ionic the nature of both Ca^{2+}−O and Ca^{2+}−N bonds, as evidenced by the NBO analysis, is not easy to define exactly if these systems are mono- or bicoordinated.

Since the tautomerism phenomenon is not so significant for uracil and thymine, as well as for adenine,[17] as demonstrated by the ΔE values reported in Table 1, it is quite improbable that U2, U3, T2, and T3 noncanonical forms are present in any real experimental conditions and the indication that they can yield stable complexes becomes only a theoretical estimation of this possibility.

The metal ion affinity values computed for the two monocoordinated U1−Mg^{2+} and U1−Ca^{2+} species are 140.9 and 107.7 kcal/mol, respectively. For T1−Mg^{2+} and T1−Ca^{2+} the corresponding values are 142.8 and 108.9 kcal/mol.

C1−M^{2+} > C3−M^{2+} > C2−M^{2+} > C4−M^{2+} is the stability order found for the cytosine adducts with both Mg^{2+} and Ca^{2+} cations. As is evident from Table 1, the metalation process induces between complexes an energy separation greater than that existing between free tautomers. This means that the MIA values for this nucleic base depend exclusively on the stability of the metalated species also if the free tautomers can coexist.[62−65] The complexes C1−Mg^{2+}, C2−Mg^{2+}, and C3−Mg^{2+} show the bicoordinated magnesium ion, which engages

TABLE 1: B3LYP/6-311+G(2df,2p) Absolute (*E*, au) and Relative (Δ*E*, kcal/mol) Energies for Free Tautomers (B) and Magnesium (B−Mg^{2+}) and Calcium (B−Ca^{2+}) Complexes of DNA and RNA Nucleic Acids Bases[a]

	B		B−Mg^{2+}				B−Ca^{2+}			
	$E_{SCF+ZPE}$	Δ*E*	$E_{SCF+ZPE}$	Δ*E*	MIA	Δ*G*	$E_{SCF+ZPE}$	Δ*E*	MIA	Δ*G*
U1	−414.884 518	0.00	−614.347 778	17.4	140.9	133.9	−1 091.959 524	6.3	107.7	100.5
U2	−414.865 915	11.7	−614.375 458	0.0	170.0	161.8	−1 091.969 590	0.0	125.5	117.8
U3	−414.854 324	18.9	−614.374 631	0.5	176.7	168.5	−1 091.966 187	2.1	130.8	123.0
T1	−454.188 940	0.0	−653.655 240	20.7	142.8	135.2	−1 131.265 888	8.9	108.9	101.8
T2	−454.168 683	12.6	−653.688 222	0.0	176.3	168.2	−1 131.280 143	0.0	130.5	122.8
T3	−454.159 830	18.3	−653.688 146	0.1	181.8	173.8	−1 131.278 006	1.3	134.7	127.1
C1	−394.980 359	0.0	−594.517 265	0.0	187.1	178.4	−1 072.106 999	0.0	140.1	131.8
C2	−394.978 268	1.3	−594.465 659	32.4	156.1	148.1	−1 072.057 236	31.2	110.1	102.5
C3	−394.977 063	2.1	−594.482 841	21.6	167.6	159.4	−1 072.075 111	20.0	122.1	114.2
C4	−394.976 631	2.3	−594.445 573	45.0	144.5	136.2	−1 072.043 184	40.0	102.3	95.4
G1	−542.631 348	0.0	−742.161 088	21.9	182.6	174.6	−1 219.746 452	19.9	132.8	125.2
G2	−542.630 236	0.7	−742.196 038	0.0	205.3	196.7	−1 219.778 109	0.0	134.0	125.9
G3	−542.628 447	1.8	−742.146 217	31.3	175.1	166.9	−1 219.732 940	28.3	126.2	118.4
G4	−542.627 732	2.3	−742.126 014	43.9	162.9	155.3	−1 219.714 895	39.7	115.3	106.8
G5	−542.624 372	4.4	−742.163 177	20.6	188.3	180.1	−1 219.748 316	18.7	138.4	130.6
A1a	−467.369 809	0.0	−666.872 864	26.6	165.9	157.8	−1 144.450 966	24.4	111.5	104.1
A1b	−467.369 809						−1 144.479 016	6.9	129.1	121.0
A2	−467.356 929	8.1	−666.895 952	12.1	188.5	180.3	−1 144.444 613	28.4	115.6	107.7
A3	−467.340 389	18.5	−666.915 330	0.0	211.0	202.3	−1 144.489 905	0.0	154.4	146.1

[a] Metal ion affinities (MIA, kcal/mol) and free energy values (Δ*G*, kcal/mol) are given at 0 and 298 K, respectively. $E_{SCF}(Mg^{2+}) = -199.241000$ au; $H(Mg^{2+}) = -199.238640$ au; $E_{SCF}(Ca^{2+}) = -676.905785$ au; $H(Ca^{2+}) = -676.903424$ au;

with oxygen, bonds that are usually shorter than that with nitrogen atoms. The species C4−Mg^{2+} is monocoordinated. The same systems with calcium present bond lengths with nitrogens that underline a major tendency of this metal ion to approach the oxygens. The B3LYP absolute affinity values for Mg^{2+} (187.1 kcal/mol) and for Ca^{2+} (140.1 kcal/mol) indicate that the first cation reacts more favorably with cytosine than the second.

The adenine low-lying tautomers that we have considered give with magnesium and calcium cations three and four complexes, respectively. The most stable systems in both cases are obtained with the A3 imino form of the free base and show the metal ions bicoordinated. Significant differences can be observed, instead, in the stability order of the adducts that the two cations form with A2 and A1 tautomers. In particular, magnesium prefers the bicoordination with the N9 and N3 rather than with the N7 and N6 atoms of A2; furthermore, the monocoordinated complex with A1 tautomer (A1b−Mg^{2+}), proposed by previous theoretical data,[8,11] is not a minimum because, during the optimization, it collapses in the A1a−Mg^{2+} system.

With calcium the situation is different. In fact, after the most stable A3−Ca^{2+} complex, at 6.9 kcal/mol, we found the A1b−Ca^{2+} complex in which the cation is linked to the N7 atom.

The exact reason why the A1b−Mg^{2+} does not exist is not easy to understand. Perhaps the double positive charge concentrated on the smaller magnesium cation is able to force the pyramidality of the $-NH_2$ planar group to go in search of the lone pair to form the most stable A1a−Mg^{2+} complex.

The bicoordinated adducts A2−Ca^{2+} and A1a−Ca^{2+} lie at 24.4 and 28.8 kcal/mol, respectively.

Since, as mentioned before, the interconversion between the canonical A1 and noncanonical A2 or A3 forms of adenine is improbable, not only for their energy differences but also for the heights of the barriers usually involved in the proton shift mechanisms,[15] we think that the magnesium and calcium affinity values must be referred to the most stable complexes obtained starting from the A1 tautomer. For this reason, 165.9 and 129.1 kcal/mol should be the appropriate estimations for Mg^{2+} and Ca^{2+}, respectively. These two values are, however, very different from those proposed by Šponer et al.[8] and Burda et al.[11] in their study on purine bases and base pairs performed at MP2 all-electron and MP2 pseudopotential levels on HF optimized geometry.[11] These authors report for magnesium MIA values of 122.3 and 112.2 kcal/mol and for calcium values of 66.8 and 66.7 kcal/mol. The strong discrepancies, although partially ascribable to the different theoretical treatments, are mainly due to the fact that the B3LYP minima structures that we consider to compute the MIA values are different from those taken into account in the MP2/HF studies.[8,11]

This fact brings up two different problems that concern the reliability of the computational method in the research of the minima and in the reproduction of MIA.

Since, as is evident, all-electron and pseudopotential MP2 values are quite different, it is probable that the description of magnesium orbitals offered by the pseudopotential is poor. On the other hand, MP2 all-electron and B3LYP/6-311+G(2df,2p) computations validate each other, as we will show, if the comparisons are done on similar structures. Furthermore, other previous theoretical studies[14−17] on the same subject have demonstrated that the B3LYP protocol used here always yields reliable MIA values.

In any case, it is worth remembering that our computations suggest that, in the case of the magnesium cation, the only stable structure with the A1 tautomer is the bicoordinated complex A1a−Mg^{2+} (see Figure 2), whose energy was not computed at the MP2 level.

In the case of calcium interaction, the comparison with previous theoretical data[8,11] is dramatic. The MP2/HF all-electron and pseudopotential MIAs are practically the same (66.7 kcal/mol), but both are very far from our result (129.1 kcal/mol). The analysis of the B3LYP and HF[11] equilibrium structures shows features quite different particularly as far as the N7−Ca^{2+} bond length (2.207 versus 2.380 Å) and the C4−N7−Ca^{2+} valence angle (175.14° versus 134°) are concerned. Although the use of a similar argument to justify so big a difference in the MIA values can be considered hazardous, nevertheless it appears clear that the value of 134° proposed by Burda et al.[11] for the C4−N7−Ca^{2+} angle can produce a strong repulsion effect between the metal cation and one of the hydrogen atoms of the planar $-NH_2$ amino group. For this reason, we have performed a single-point B3LYP/6-311+G-

(2df,2p) calculation fixing the geometry of the A1b−Ca^{2+} complex at the reported HF values.[11] The result indicates that the energy of such a system is 69.1 kcal/mol higher than that of the fully optimized B3LYP minimum, and that in this case the MIA assumes a value of 60.0 kcal/mol, in better agreement with the MP2/HF study. Forcing the pyramidality of the $-NH_2$ group, the repulsive effect with calcium ion decreases sensibly (see the A1a−Ca^{2+} complex in Figure 2) and the MIA becomes again much higher (111.5 kcal/mol).

The discussion about the complexes that guanine tautomers form with Mg^{2+} and Ca^{2+} presents many aspects in common with that of cytosine. Also in this case we found the same stability order for the metalated species (G2−M^{2+} > G5−M^{2+} > G1−M^{2+} > G3−M^{2+} > G4−M^{2+}) with magnesium and calcium ions and the energetic gap between them greater than that between the free tautomers.

All complexes can be classified as bicoordinated systems although the G2−Ca^{2+} hardly falls into this category. In the absolute minima, the coordination sites are the O6 and N7 atoms often suggested[11,54] as the most suitable to receive the metal cations. The MIA values, obtained in correspondence with G2−Mg^{2+} and G2−Ca^{2+} species, are 205.3 and 134.3 kcal/mol, respectively. These values are quite similar to those computed at the MP2/HF level[11] in both all-electron (212.6 and 137.0 kcal/mol) and pseudopotential (206.0 and 136.6 kcal/mol) approximations for the same topological situation.

The experimental approaches[55−58] normally used to evaluate the entropic terms give results that are not ascribable unequivocally to the dissociation of the examined system because of the presence of competitive processes. This is the reason our computations were also addressed to the determination of free energy variation (see Table 1). The $T\Delta S$ values range from 7 to 9 kcal/mol and do not modify significantly the relative trends of stability.

The geometrical parameters reported in the Figures 1 and 2 underline that magnesium cation establishes shorter bonds with DNA and RNA bases than with calcium. This depend essentially on the size of the metal ion because the nature of the interaction seems to be very similar for the two cations. Natural bond orbital analysis suggests that the ligand−metal ion bond is ionic as is also evidenced by the natural net charges on atoms. In fact, in the complexes that we have considered to compute the MIA values (U1−Mg^{2+}, T1−Mg^{2+}, C1−Mg^{2+}, G2−Mg^{2+}, A1a−Mg^{2+}), the charge of the magnesium cation is 3%, 3%, 9%, 7%, and 9% smaller than the original charge, respectively. For calcium−nucleobase systems (U1−Ca^{2+}, T1−Ca^{2+}, C1−Ca^{2+}, G2−Ca^{2+}, A1b−Ca^{2+}), the positive net charge on the cation upon metalation reduces to 5%, 5%, 6%, 6%, and 6%, respectively.

The fact that the bonds have essentially ionic character also is supported by the equilibrium geometry of the nucleobases in the complexes that appears unchanged with respect to that of the free molecules.

Conclusions

Structures and energetic aspects of the complexes of calcium and magnesium with DNA and RNA nucleobases were studied at the B3LYP/6-311+G(2df,2p) density functional level with the aim of evaluating the absolute metal ion affinity values.

The results indicate the following: The computational protocol used to determine the metal ion affinity yields results that are in agreement with previous MP2 data on guanine and adenine if the comparison is done for complexes having similar structure. The binding energy values suggest that magnesium has more affinity for nucleobases than the calcium cation. The nucleic acid bases reactivity order with magnesium is uracil ≤ thymine < adenine < cytosine < guanine; except for an inversion that concerns cytosine and guanine, the same trend is found for calcium. The ionic nature of the ligand−metal ion bond is supported by the natural atomic net charge values and by the absence of any covalent contributions as suggested by natural orbital analysis. The MIA value can be associated to the complex originating from the most stable tautomer of the free bases in the case of uracil, thymine, and adenine also if this is not the most stable one. For cytosine and guanine, whose free tautomers fall in a narrow range of energy, the stability of the systems formed upon metalation determines the most reliable metal affinity value.

Our results obtained in the gas phase are the first theoretical indication that concerns the magnesium and calcium interactions with all nucleobases. They can be used with caution as a guideline for the condensed phase remembering that hydration effects can influence both the coordination sites and binding energies.

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