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ARTICLE *in* INTERNATIONAL JOURNAL OF QUANTUM CHEMISTRY · JANUARY 2010

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# On the Interaction of Rubidium and Cesium Mono-, Strontium and Barium Bi-Cations With DNA and RNA Bases. A Theoretical Study

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*Received 8 November 2008; accepted 23 December 2008*

*Published online 19 May 2009 in Wiley InterScience (www.interscience.wiley.com).*

*DOI 10.1002/qua.22076*

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**ABSTRACT:** We performed a density functional investigation of the interactions of the two alkaline metal ions Rb(I) and Cs(I) and two alkaline earth metal ions Ba(II) and Sr(II), with DNA and RNA nucleobases. All the possible molecular complexes, originated from the attack of these cations to the different binding sites present on some selected low-lying nucleobase tautomers, were considered to determine their relative stabilities and the preferred metal coordination geometries and sites. Absolute metal ions affinities were computed taking into account the most stable metal complex of each base with the aim to rationalize the trend of the obtained values within of and between the first and second periodic table main groups. © 2009 Wiley Periodicals, Inc. *Int J Quantum Chem* 110: 138–147, 2010

**Key words:** alkaline and alkaline earth ions; metal ion affinity; DNA and RNA nucleobases; DFT

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## Introduction

At the physiological pH, nucleic acids are polyanionic polymers hence they need cations to neutralize this charge. Non coordinating metal ions are able to neutralize only partially the total charge (about 76%) but despite this, DNA maintains a high affinity towards cations. However, metal ion coordination to nucleic acids is not only required for charge neutralization, it is also essential for their biological function [1–4]. The bonding of metal ions on different sites of DNA can influence its structure and as well as double helix stability. Usually, the neutralization of the negative charge on phosphate group through non-specific electrostatic interactions stabilizes the double helix, whereas the bonding on bases can cause the destabilization owing to the separation of two strands induced by the modification of the hydrogen bonding network between base pairs [5, 6]. Many other significant biophysical processes such as the stabilization of DNA triple helices, of quadruple helices and of ribose-base stacking in Z-DNA [7–9] are the consequence of the metal ion- bases interactions.

The different selectivity of ions towards nucleic acids depends on charge, size and electronic structures of metals. Specific ion-DNA interaction is crucial because the DNA behavior is quite different in the presence of ions also if of same valence.

Metal ions can bind to DNA directly or indirectly through hydrogen bonding with coordinated water molecules. In the case of a direct interaction, some general rules are usually followed. The sites mainly susceptible of attack are those more accessible in the major and minor grooves of DNA double helix. Furthermore, spectroscopic studies showed that the attack of metal ions occurs on sites characterized by high electronic density or on negative charge centers. Such sites can be the phosphate groups, the sugar moieties and the donor-electron atoms on bases (N7 and O6 of guanine, N7 and N6 for adenine and N3 atom for pyrimidines) [10].

In addition, previous calculations demonstrated that the stabilization or the destabilization of DNA base pairs depends on the particular cation binding sites [11]. The interactions of different metal ions on O4 atom of thymine lead to a destabilization of adenine-thymine (AT) base pair. On the other hand, the approach of cations on the other available sites, like the O2 atom of thymine or N1 and N3 atoms of adenine, leads to the stabilization of AT base pair [12].

The cations binding to phosphate group frequently are simultaneously involved in base coordination (i.e., they interact with N7 position of adenine and guanine).

Monovalent alkaline and divalent alkaline-earth cations seem to interact mainly with phosphate backbone and this involves a stabilization of DNA helix [13], but there is a strong evidence of the presence of metal ions-DNA bases adducts [14–17].

In their work, based on molecular dynamic studies, Lyubartsev and Laaksonen [18] showed the features of the behavior of alkaline ions around DNA.  $\text{Li}^+$  ion binds preferentially to phosphate group.  $\text{Na}^+$  ion is concentrated on minor groove and binds to DNA through a layer of water molecules.  $\text{Cs}^+$  ion binds to sugar O1' atom in the minor groove. Crystallographic data indicated that  $\text{Rb}^+$  ion binds to coordination inner sphere on O2 atom of thymine of opposite strands [19, 20].

Alkaline-earth ions are more reactive with respect to alkaline ones and they can exhibit mono and bi-coordination. Among the second group cations,  $\text{Mg}^{2+}$  is present in different activation processes of DNA and RNA [16]. The double charge on metal can induce proton transfer on N1 and N3 sites of Watson–Crick cytosine-guanine base pair, can favor the formation of rare tautomers and mispairs and can interact with bases  $\pi$  system preventing them to pairing.

An X-ray study of Z-DNA hexamer shows a  $\text{Ba}^{2+}$  cation bridging two side by side helices in the crystal and simultaneously coordinating to the O6 and N7 atoms of guanines. The cation is also coordinated to four water molecules [21].

A divalent cation can induce a significant polarization on base and thus can stabilize certain H-bonding base pairs and other interactions [7, 9, 11].

Most of the works present in literature are devoted to determine the role of metal ions in stabilizing or destabilizing DNA bases, base pairs and double helix. On the contrary, the goal of this density functional study is to evaluate the attachment sites, the coordination geometries preferred by  $\text{Rb}^+$ ,  $\text{Cs}^+$ ,  $\text{Sr}^{2+}$  and  $\text{Ba}^{2+}$  metal ions and their absolute affinity values for nucleic acid bases.

In fact, we think that understanding the interactions of metal ions with DNA and RNA isolated bases to a level of molecular details is necessary to know better the role played by cations on biophysics of DNA and can constitute a significant and useful complement to experiment.

## Computational Details

The calculations were performed within the framework of density functional theory (DFT) [22–24], using non local hybrid Becke3 (B3) [25] exchange Lee, Yang and Parr (LYP) [26] correlation potential, implemented in the Gaussian 03 code [27]. The triple zeta quality 6-311+G(2df,2p) basis set was employed to describe hydrogen, oxygen and nitrogen atoms, whereas Stuttgart relativistic effective core potential SDD [28], was considered for metal ions.

Harmonic vibrational frequencies were computed to characterize all conformations as minima or saddle points and to evaluate the zero-point energy (ZPE) corrections which we have included in the relative energy values.

Metal ion affinity (MIA) was evaluated as negative variation of enthalpy ( $-\Delta H$ ) for the dissociation processes of the base- $Mn^+$  most stable complexes.

## Results and Discussion

As demonstrated by several previous works [19, 20, 29–32], the problem of tautomerism of nucleobases is rather irrelevant for uracile, thymine and adenine because their various tautomeric forms are separated by a significant amount of energy. This fact entails that, despite the complexes derived from interaction of metal ions with non canonical forms of these bases can be the most stable ones, they have scarce probability to exist really.

On the other hand, even if unlikely, it could exist a mechanism able to generate them from the complexes obtained from di-cheto forms, so, looking forwards a future exploration of this possibility, we have performed calculations also for these species. However, for these three nucleobases, the discussion will concern only the most probable complexes.

### INTERACTION OF NUCLEOBASES WITH RUBIDIUM AND CESIUM IONS

The structures reported in Figure 1 represent the complexes that rubidium and cesium ions form with the selected tautomers of purine and pyrimidine DNA and RNA bases. Absolute and relative energies of free bases and complexes and metal ion affinity values are collected in Table I.

A preliminary overview of these adducts shows that irrespective of base, in the most stable complexes, both metal ions are nearly always monocoordinated to it pointing out the first significant difference with respect to the lighter metal ions belonging to the alkali group [19, 20].

Because as mentioned before it is difficult hypothesize the real existence of U2 and U3 free tautomers of uracile, the complex  $U1-M^+$  ( $M = Rb, Cs$ ) is the only one that we can consider probable.

Both rubidium and cesium ions in the  $U1-M^+$  adduct bind to O4 atom with bond lengths of 2.073 and 2.892 Å, respectively. The  $C-O4-M^+$  angles deviate from linearity of about  $177^\circ$  in both cases.

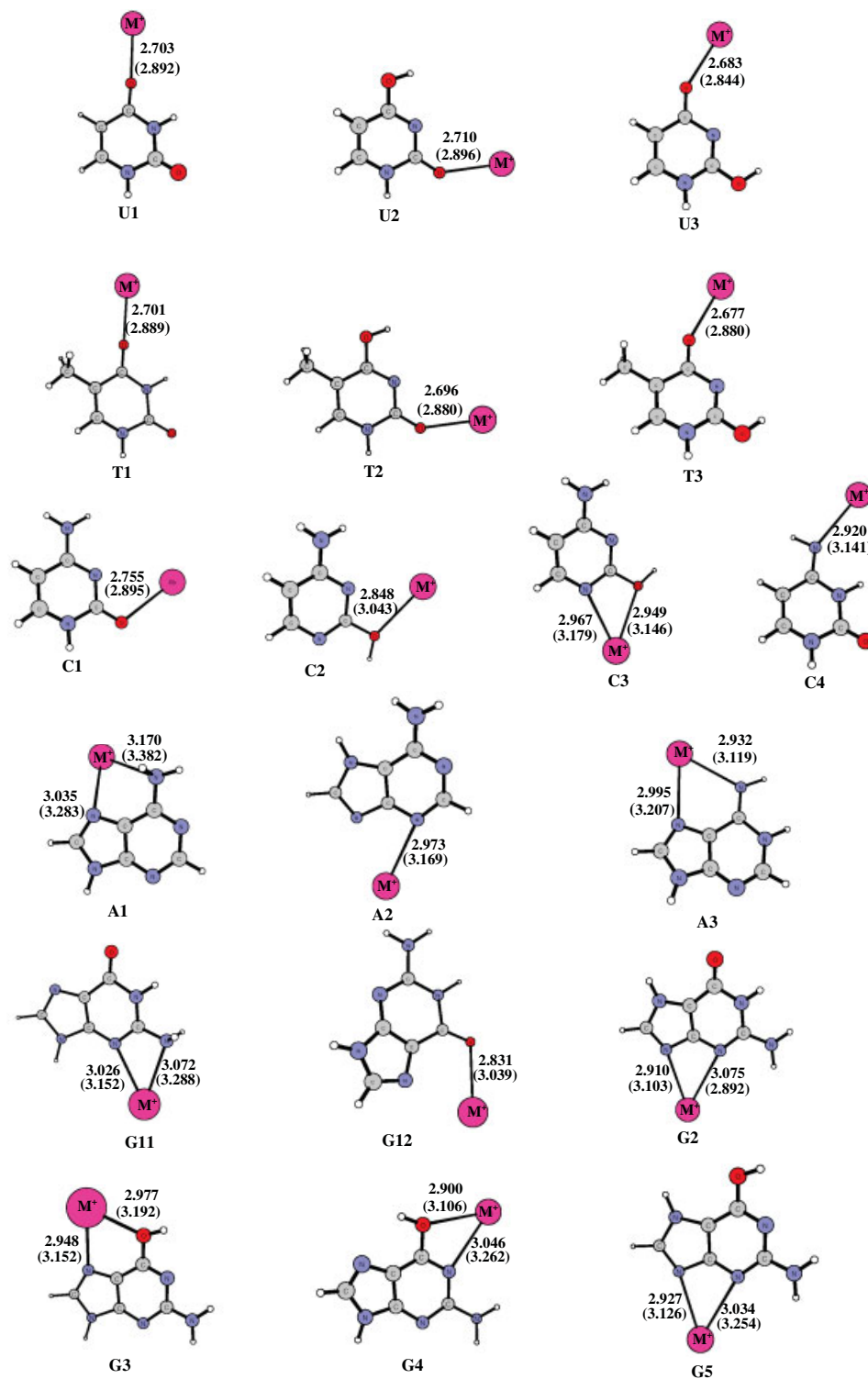
The complexes  $U1-M^+$  involving the binding of metal ions with the O2 site were proven to be less stable in the previous works concerning the alkali ions [20], nevertheless we report here also some geometric and energetic data concerning these adducts. In fact, with rubidium, the complex involving the binding to O2 ( $U1b-Rb^+$ ) site is particularly stable being at only 3.3 kcal/mol above the most stable one. Distance between metal ion and O2 is computed to be 2.721 Å and the  $C-O2-M^+$  angle is practically  $180^\circ$ .

For cesium, the analogous adduct ( $U1b-Cs^+$ ) lies at 3.2 kcal/mol above the global minimum.  $Cs^+-O2$  bond length is 2.916. The  $C-O2-M^+$  angle is again near to  $180^\circ$ .

The  $U1-M^+$  and  $U1b-M^+$  similar stability entails that both systems are probable if we consider the isolated base. However, in RNA, the ribose ring is very near to O2 hence the metalation of this site could be unfavoured for steric reasons.

The rubidium and cesium ions affinity values ( $RbIA$  and  $CsIA$ ) are 22.0 and 18.9 kcal/mol, respectively. Experimental determination of MIA stops at the first three cation of alkaline metals [33, 34], so, in the present work is not possible make direct comparisons between theoretical and measured values. However, we can be confident of the reliability of the obtained results, as the computational protocol used here is practically the same used previously for  $Li^+$ ,  $Na^+$ , and  $K^+$  interaction with DNA and RNA bases [20].

For thymine, the most stable complexes  $T1-Rb^+$  and  $T1-Cs^+$  are obtained starting from the lowest lying tautomer of free base. Also in this case, the ions interact more favorably with O4 atom of base with bond lengths of 2.701 Å for  $Rb^+$  and 2.889 Å for  $Cs^+$ . The  $C-O4-M^+$  angles are both nearer to the linearity ( $180^\circ$ ) owing to the repulsion of the methyl group.



**FIGURE 1.** Optimized structures of nucleic acid bases with  $M^+$  ( $M^+ = Rb^+, Cs^+$ ). Distances are in Å. Values in brackets are for cesium ion. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

**TABLE I**  
**Absolute (*E* in a.u.) and relative ( $\Delta E$  in kcal/mol) energies of alkaline and alkaline earth ions nucleobases complexes ( $M^{n+}$ -B).**

B	Rb <sup>+</sup> -B			Cs <sup>+</sup> -B			Sr <sup>2+</sup> -B			Ba <sup>2+</sup> -B		
	$\Delta E$	<i>E</i>	$\Delta E$	<i>E</i>	$\Delta E$	CsIA	<i>E</i>	$\Delta E$	SrIA	<i>E</i>	$\Delta E$	BaIA
U1	0.0	U1-Rb <sup>+</sup> U1b-Rb <sup>+</sup>	0.0 3.3	22.0 U1-Cs <sup>+</sup> U1b-Cs <sup>+</sup>	0.0 3.2	18.9 U1-Sr <sup>2+</sup> U1b-Sr <sup>2+</sup>	-434.891294 -445.068207	2.3 11.8	82.4 U1-Ba <sup>2+</sup> U1b-Ba <sup>2+</sup>	-439.858928	1.6 9.1	77.2
U2	12.2	U2-Rb <sup>+</sup>	6.2	U2-Cs <sup>+</sup>	6.1	U2-Sr <sup>2+</sup>		0.0	U2-Ba <sup>2+</sup>		1.4	
U3	19.4	U3-Rb <sup>+</sup>	12.7	U3-Cs <sup>+</sup>	10.8	U3-Sr <sup>2+</sup>		2.0	U3-Ba <sup>2+</sup>		0.0	
T1	0.0	T1-Rb <sup>+</sup>	0.0	T1-Cs <sup>+</sup>	0.0	T1-Sr <sup>2+</sup>	-474.193205	5.3	T1-Ba <sup>2+</sup>	-479.161802	3.2	77.7
T2	13.1	T1b-Rb <sup>+</sup>	1.5	T1b-Cs <sup>+</sup>	1.4	T1b-Sr <sup>2+</sup>		11.0	T1b-Ba <sup>2+</sup>		5.3	
T3	18.8	T2-Rb <sup>+</sup>	5.4	T2-Cs <sup>+</sup>	5.9	T2-Sr <sup>2+</sup>		0.0	T2-Ba <sup>2+</sup>		0.0	
C1	0.0	T3-Rb <sup>+</sup>	9.7	T3-Cs <sup>+</sup>	10.7	T3-Sr <sup>2+</sup>		1.9	T3-Ba <sup>2+</sup>		2.1	
C2	1.2	C1-Rb <sup>+</sup>	0.0	C1-Cs <sup>+</sup>	0.0	C1-Sr <sup>2+</sup>	-415.003834	0.0	C1-Ba <sup>2+</sup>	-419.995407	0.0	102.4
C3	1.9	C2-Rb <sup>+</sup>	11.5	C2-Cs <sup>+</sup>	11.2	C2-Sr <sup>2+</sup>		27.4	C2-Ba <sup>2+</sup>		26.8	
C4	2.4	C3-Rb <sup>+</sup>	7.4	C3-Cs <sup>+</sup>	7.2	C3-Sr <sup>2+</sup>		16.8	C3-Ba <sup>2+</sup>		16.2	
G1	0.2	C4-Rb <sup>+</sup>	16.4	C4-Cs <sup>+</sup>	15.7	C4-Sr <sup>2+</sup>		36.8	C4-Ba <sup>2+</sup>		34.2	
G2	0.0	G11-Rb <sup>+</sup>	30.7	G11-Cs <sup>+</sup>	29.9	G11-Sr <sup>2+</sup>		57.1	G11-Ba <sup>2+</sup>		55.8	
G3	1.4	G12-Rb <sup>+</sup>	0.0	G12-Cs <sup>+</sup>	0.0	G12-Sr <sup>2+</sup>	-562.650187	0.0	G12-Ba <sup>2+</sup>	-567.654376	0.0	113.6
G4	2.3	G2-Rb <sup>+</sup>	8.1	G2-Cs <sup>+</sup>	7.3	G2-Sr <sup>2+</sup>		18.6	G2-Ba <sup>2+</sup>		18.7	
G5	4.1	G3-Rb <sup>+</sup>	10.4	G3-Cs <sup>+</sup>	9.8	G3-Sr <sup>2+</sup>		25.1	G3-Ba <sup>2+</sup>		24.1	
A1	0.0	G4-Rb <sup>+</sup>	15.6	G4-Cs <sup>+</sup>	15.2	G4-Sr <sup>2+</sup>		36.6	G4-Ba <sup>2+</sup>		35.0	
A2	8.3	G5-Rb <sup>+</sup>	10.0	G5-Cs <sup>+</sup>	9.3	G5-Sr <sup>2+</sup>		17.9	G5-Ba <sup>2+</sup>		18.0	
A3	18.8	A1-Rb <sup>+</sup>	9.0	A1-Cs <sup>+</sup>	7.9	A1-Sr <sup>2+</sup>	-487.361555	22.0	A1-Ba <sup>2+</sup>	-497.552073	20.5	74.9
		A2-Rb <sup>+</sup>	0.0	A2-Cs <sup>+</sup>	0.0	A2-Sr <sup>2+</sup>		3.1	A2-Ba <sup>2+</sup>		1.5	
		A3-Rb <sup>+</sup>	6.1	A3-Cs <sup>+</sup>	7.2	A3-Sr <sup>2+</sup>		0.0	A3-Ba <sup>2+</sup>		0.0	

Metal ion affinities RbIA, CsIA, SrIA, and BaIA and relative energy of free nucleobase tautomers are given in kcal/mol.



However, the O2 site is very competitive with O4 so that the complexes  $\text{T1b-Rb}^+$  and  $\text{T1b-Cs}^+$  in which metal ions interact with O2 are practically isoenergetic with the corresponding  $\text{T1-Rb}^+$  and  $\text{T1-Cs}^+$  adducts. In both cases the difference in the stability is estimated to be about 1.5 kcal/mol. The distances of O2 from metal center are 2.709 and 2.902 Å, respectively for rubidium and cesium cations. Also in this case as for uracil, the similar stability of the complexes metalated on O4 and O2 makes them both probable. Instead in DNA, the O4 should be slightly more favorable by metal ions for the presence of sugar moiety in proximity of O2 site.

$\text{Rb}^+$  and  $\text{Cs}^+$  metal ions have for thymine an affinity comparable to that they have for uracil as can be noted by the values of  $\text{RbIA}$  and  $\text{CsIA}$  of 21.6 and 18.8 kcal/mol, respectively.

With cytosine, the phenomenon of tautomerism assumes great importance. The four isomers that we have selected show similar stabilities and are all potentially existing. Moreover, as suggested by experiment [35–38] C1 cheto- and C2 enol-forms coexist. In principle, this means that all complexes with rubidium and cesium metal ions have a concrete possibility to be formed although the final decision about their real occurrence must be taken on the basis of the relative energy values.

The stability of cytosine complexes with rubidium and cesium ions follows the order  $\text{C1-M}^+ > \text{C3-M}^+ > \text{C2-M}^+ > \text{C4-M}^+$ . These species are more separated in energy than the free corresponding tautomers.

In the most stable  $\text{C1-M}^+$  complexed form, the two cations appear to be monocoordinated to the O2 oxygen atom.  $\text{O2-M}^+$  distances are 2.755 and 2.895 Å, for  $\text{Rb}^+$  and  $\text{Cs}^+$ , respectively. The analysis of present data and of those concerning the corresponding complexes with  $\text{Li}^+$  [19],  $\text{Na}^+$ , and  $\text{K}^+$  [20] complexes, evidences starting from potassium, the gradual disappearance of the bicoordination as a function of the atomic number increase.

$\text{RbIA}$  and  $\text{CsIA}$  values for cytosine are 32.9 and 29.1 kcal/mol, respectively.

For the reasons previously explained, the less stable  $\text{A1-M}^+$  complexes that adenine forms with  $\text{Rb}^+$  and  $\text{Cs}^+$  are the most probable ones.  $\text{A1-M}^+$  complexes are bicoordinated and lie at 8.9 and 7.9 kcal/mol above  $\text{A2-M}^+$  adducts for  $\text{Rb}^+$  and  $\text{Cs}^+$ , respectively. The coordination bond lengths are quite long ( $\text{N7-Rb}^+$  and  $\text{N6-Rb}^+$  are 3.035 and 3.170 Å and  $\text{N7-Cs}^+$  and  $\text{N6-Cs}^+$  3.283 and 3.382) so that one can hypothesize weak electrostatic interactions.

This is reflected on the metal affinity values for this base that are the lowest among all other ones.

The five guanine free tautomers form six stable complexes with rubidium and cesium ions.

Also for this base as for cytosine, the tautomers are very close in energy. In fact, they fall in a range of about 4.0 kcal/mol. G1 and G2 cheto-forms are almost isoenergetic and coexist [39].

The most stable complex for both ions is  $\text{G12-M}^+$  that derives from one of the two canonical tautomers of guanine (G1).

The  $\text{M}^+\text{-N7}$  bonds are longer than those metal ions establish with O6 and keep hardly within the limit of the bicoordination (see Fig. 1).

The stability order for the remaining complexes is totally shared by both cations:  $\text{G2-M}^+ > \text{G5-M}^+ \sim \text{G3-M}^+ > \text{G4-M}^+ > \text{G11-M}^+$ .

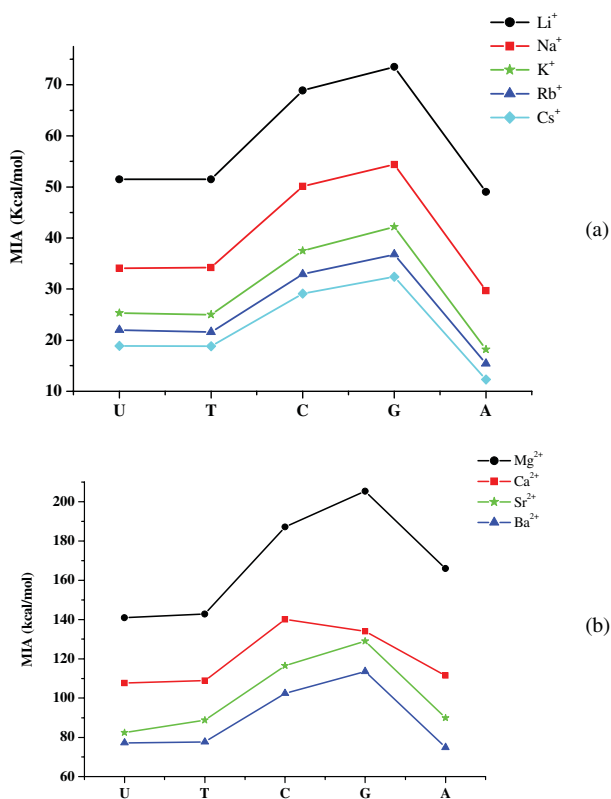
Our results for purine bases, especially as far as the coordination distances are concerned, are in good agreement with a previous Hartree–Fock and second-order Møller–Plesset study of Burda et al. [40] on the interactions of first and second group metal ions and some transition metals with guanine and adenine DNA bases. Instead, less agreement exists about the metal ion coordination type on adenine. Literature reports only cases of monocoordination on N7 atom [40, 41]. This result is the logic consequence of the fact that the amino group is usually considered in the molecular plane. Of course, this disposition prevents metal ions to coordinate contemporarily N7 and N2 sites. However, in many previous works we have suggested that [19, 20, 29–32] a simple rotation of  $\text{—NH}_2$  group out of the molecular plane, that entails a small energetic expense, can favor the bicoordination.

For both cations, the interaction with guanine nucleobase appears to be very favorable as demonstrated by the highest metal ion affinity values ( $\text{RbIA} = 36.8$  and  $\text{CsIA} = 32.4$  kcal/mol). This is a confirm of experimental suggestions for which N7 guanine atom has the major basicity among all other sites and then is the best candidate for the positive charges attach.

The Figure 2 collects the metal ion affinity values for DNA and RNA bases computed in this work for rubidium and cesium cations, and those for lithium, sodium and potassium obtained previously [19, 20] to rationalize the trend within periodic table alkali group.

The behavior of the different metal species appears to be very homogeneous.

From the Figure 2 it can be noted that the affinity for nucleobases depends on the metal atomic num-



**FIGURE 2.** (a) Alkaline and (b) alkaline earth metal ions affinity trends for nucleobases. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

ber and in particular decreases for the heavier ions. The base more susceptible to the metal ions attack is guanine, followed by cytosine, thymine, uracil and then adenine.

This result seems to be in disagreement with the data of Lyubartsev and Laaksonen [18] that, in their work concerning the interaction of alkaline ions with DNA in water solution, proposed the following order for the binding affinities:  $\text{Cs}^+ > \text{Li}^+ > \text{Na}^+ > \text{K}^+$ . This same trend was suggested also in other two older literature articles [42, 43]. However, the apparent discrepancy with our findings is certainly due to the fact that these previous investigations concern a bigger part of DNA surrounded by water molecules in which cesium binds to sugar oxygen atom.

### INTERACTION OF STRONTIUM AND BARIUM IONS WITH NUCLEOBASES

In Figure 3, we have reported the complexes of nucleobases with strontium and barium cations.

Relative energies and MIA values are reported in Table I.

Despite the incontestable similarity between the geometries of these adducts with those deriving from the interaction of bases with alkaline ions, we can see immediately substantial differences with regard to length of bonds. In fact, all complexes of Figure 3 are characterized by metal coordination distances well under 3 Å. This is a first confirmation of what we have asserted about the major reactivity of alkaline earth with respect alkaline ions corroborated, as we will show, by other significant evidences. Except for some case, metal mono- seems to be still favored than bi-coordination.

The complexes of strontium and barium originated from canonical tautomers U1 e T1 are mono-coordinated species whose stability is slightly lower than those of  $\text{U2(T2)-M}^{2+}$  and  $\text{U3(T3)-M}^{2+}$  unlikely species. We have already observed that this event occurs often on a metallation process [19, 20].

For each cation, the distances  $\text{M}^{2+}\text{-O4}$  are very similar in the two  $\text{U1-M}^{2+}$  and  $\text{T1-M}^{2+}$  complexes and  $\text{M}^{2+}\text{-O4-C}$  angles deviate from linearity by about 4°.

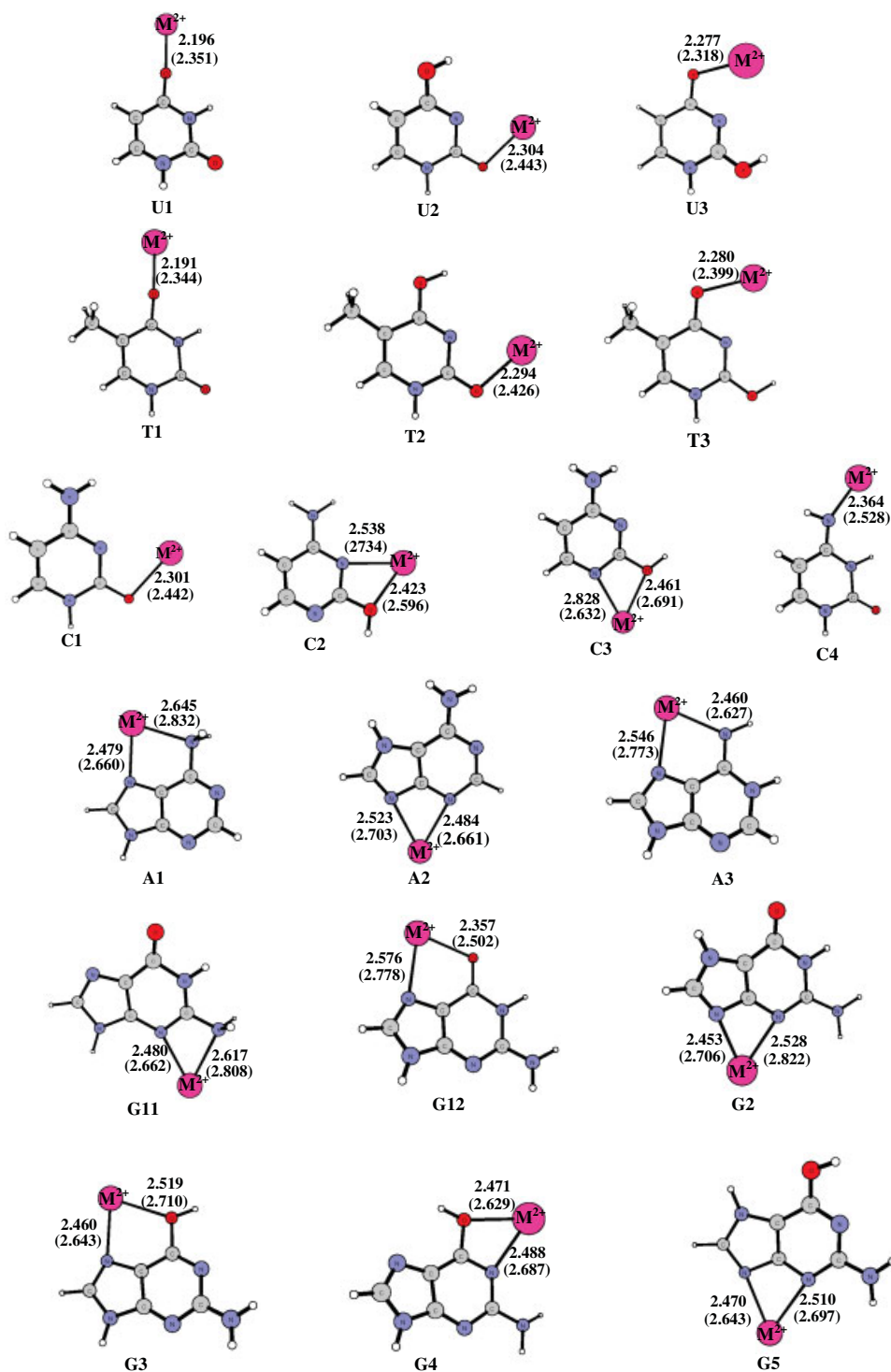
Contrary to what occurs for alkali ions, strontium and barium cations interact with the O2 site of both uracil and thymine given rise to complexes whose stability is quite different from that of the corresponding systems metalated on O4 (see Table I).

The SrIA and BaIA are 82.4 and 77.2 kcal/mol, respectively. These values compared with those obtained for rubidium and cesium ions underline that bivalent elements have greater affinity for nucleobases. No experimental determination of metal ion affinity for strontium and barium exists. This measure is missing also for other alkaline earth metals. However, as in the case of the two previous alkaline ions, we think that our results can be retained quite reliable owing to the proven goodness of the computational protocol [19, 20, 29–32] in reproducing such a type of quantities.

For cytosine, and for both cations, the complexes obtained with the C1 tautomer are the most stable and probable ones.  $\text{C1-Sr}^{2+}$  and  $\text{C1-Ba}^{2+}$  systems involve mono-coordinated ions with  $\text{M}^{2+}\text{-O}$  bond lengths of 2.302 and 2.442 Å.

The complexes of remaining cytosine tautomers are located at higher energy and exhibit both mono- and bi-coordination. Contrary to what occurs for uracil and thymine, the energetic gap between cytosine complexes is decidedly greater than that between free tautomers.





**FIGURE 3.** Optimized structures of nucleic acid bases with  $M^{2+}$  ( $M^+ = Sr^{2+}, Ba^{2+}$ ). Distances are in Angstrom. Values in brackets are for barium ion. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

The metal ion affinity values corresponding to the most stable complexes are 116.5 (SrIA) and 102.4 (BaIA) kcal/mol.

The three tautomers of adenine interact with two metal ions giving as many complexes.

Among these complexes the most stable are those obtained with A3 tautomer, as in the case of other metal ions [20, 29–32]. This is due to the presence of an imino group that is highly reactive towards positively charged species. The next A2-Sr<sup>2+</sup> and A2-Ba<sup>2+</sup> lie at 3.1 and 1.5 kcal/mol above the most stable corresponding adducts. Again, given that A2 and A3 free tautomers should not exist, the complexes obtained with A1 tautomer are the most probable ones although they lie at 22.0 (A1-Sr<sup>2+</sup>) and 20.5 (A1-Ba<sup>2+</sup>) above the most stable A3 complexes.

A1-Sr<sup>2+</sup> and A1-Ba<sup>2+</sup> present ions bi-coordinated to N7 and N6 atoms. The M<sup>2+</sup>-N6 bond lengths (2.645 for A1-Sr<sup>2+</sup> and 2.832 Å for A1-Ba<sup>2+</sup>) suggest that the interaction with N6 center is quite weaker of that involving the N7 site (M<sup>2+</sup>-N7 2.479 for A1-Sr<sup>2+</sup> and 2.660 Å for A1-Ba<sup>2+</sup>).

The SrIA and BaIA values are 89.9 and 74.5 kcal/mol, respectively.

For both cations, the most stable complexes formed with guanine are G12-Sr<sup>2+</sup> and G12-Ba<sup>2+</sup> in which metal ions are bi-coordinated with N7 and O6 atoms. Bond lengths are 2.576 and 2.357 Å for strontium and 2.778 and 2.502 Å for barium. All other strontium and barium adducts of guanine are bi-coordinated but they are much less stable than the global minima.

The SrIA and BaIA values obtained in correspondence of the two most stable structures are 129.0 kcal/mol for Sr<sup>2+</sup> and 113.6 kcal/mol for Ba<sup>2+</sup>.

In Figure 2, is reported the trend of metal ion affinity values for alkaline earth metal ions. Data concerning magnesium and calcium ions derive from a previous work [19] performed at the same level of theory used here. The general behavior is quite similar to that proposed before for alkaline ions. This means that we can draw the same conclusions about the dependence of the MIA values on the atomic number. All things considered, except for some small difference we could say that also in this case the preferential order with which the five nucleobases are attacked by these metal ions is the same than that obtained for first group ions (G > C > T > U > A). However, we must point out the anomalous behavior of the calcium ion that seems to have greater affinity for cytosine than for guanine. From literature data [19] it

emerges that the complexes that Ca<sup>2+</sup> forms with guanine and cytosine are geometrically similar to those that Mg<sup>2+</sup>, Sr<sup>2+</sup>, and Ba<sup>2+</sup> form with these bases, so, the anomaly cannot be ascribed to different structural aspects. The explanation should be searched elsewhere. We are not able at this time to solve the question but we would underline that, because of the lack of experimental support, what we define “anomaly” could not be so.

## Conclusions

In this study, we have explored in detail the gas-phase interaction of rubidium and cesium mono-, and strontium and barium bi-cations with nucleobases using a density functional based approach. Results can be summarized as follows: All examined metal ions form complexes stable with all free nucleobases tautomers. Both alkaline and alkaline earth metal ions prefer the monocoordination in almost all more likely complexes. This is very evident for the pyrimidine bases. For purines, we can observe that all considered metal ions establish bonds of different strength with the N6 and N7 sites of adenine and N6 and O6 of guanine, favoring the N7 in the first base and the O6 in the second one. The N6-M<sup>n+</sup> and N7-M<sup>n+</sup> distances in adenine and guanine, respectively, are usually so long that it results difficult to talk of bi-coordinated ions. Metal ion affinity values can be related to the given complexes originating from the most stable tautomer of free bases for uracile, thymine and adenine even if these are not the most stable metal complexes. On the contrary, for cytosine and guanine whose tautomers are very similar in energy, this same quantity should be referred to the most stable complexes. MIA trend depends on the atomic number of the ions. Small cations bind to bases more strongly than large ones. Mono- are less reactive than di-cations.

The preferential attack to the bases occurs in the order: G > C > T > U > A for both alkaline and alkaline earth metal ions. The only exception is represented by calcium ion that shows to have major affinity for cytosine.

## ACKNOWLEDGMENT

We thank the Computer Center of CENG-CEA of Grenoble and Università degli Studi della Calabria.

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