Bond Energies and Attachments Sites of Sodium and Potassium Cations to DNA and RNA Nucleic Acid Bases in the Gas Phase

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Abstract: Gas-phase metal affinities of DNA and RNA bases for the Na^+ and K^+ ions were determined at density functional level employing the hybrid B3LYP exchange correlation potential in connection with the 6-311+G(2df,2p) basis set. All the molecular complexes, obtained by the interaction between several low-lying tautomers of nucleic acid bases and the alkali ions on the different binding sites, were considered. Structural features of the sodium and potassium complexes were found to be similar except in some uracil and thymine compounds in which the tendency of potassium ion toward monocoordination appeared evident. B3LYP bond energies for both metal ions were in agreement with the available experimental results in the cases of uracil and thymine for which the most stable complex was obtained starting from the most stable tautomer of the free nucleic acid base. For adenine, although the interaction of the ions with the most stable free tautomer generated the least stable molecular complex, the best agreement with experiment was found in just this case. For the remaining cytosine and guanine bases, our calculations indicated that the metal ion affinity value closest to experiment should be determined taking into account the role played by the different tautomers of the free bases with similar energy and all the possible complexes obtained by them.

Introduction

The conformational behavior and function of DNA are often influenced by the presence of metal ions.[1−6] In fact, cation−base interactions are involved in many important biophysical processes such as the stabilization of DNA triple and quadruple helices and stabilization of the ribose−base stacking in Z-DNA.[7,8] Alkali cations have a low tendency to form covalent bonds, so, they should be considered nonspecific binders. They interact mostly with phosphate groups, neutralizing the negative charges and stabilizing the double helix, but their interactions with bases, rather than phosphate groups, also neutralize the negative charges on the phosphate in a zwitterion effect.

The interaction of a specific alkali metal ion with a nucleic acid is controlled by the bond strength between the metal ion and the possible donor centers on the bases. The known sites for cation coordination are mainly the N7, N9, and O6 atoms of guanine and adenine, the O4 atom of uracil and thymine, and the N3 and O2 (when they are not involved in hydrogen bonding) atoms of cytosine. The existence of metal−N7 binding in guanine has been confirmed by variuos spectroscopic methods[9−11] and in some cases involves essentially divalent cations.

In a recent HF-SCF and B3LYP study by Gu and Leszczynski,[12] it was found that the interaction with a metal ion is essential in the formation of the guanine−tetrad complexes. In particular, the authors attribute the change in the stability trends of the monovalent cation−guanine tetrad complexes on going from the gas phase to the aqueous phase and, hence, the ion selectivity exhibited by the guanine tetraplex in water solutions, to the different relative free hydration energies rather than to a

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better fit of one cation with respect to another. The effect of the metal on the formation of guanine quartet−metal ion complexes was also investigated at density functional B3LYP level by Meyer et al.[13]

Additionally, the alkali metal ions have an inhibitory effect on the chain initiation process by RNA polymerases which may in turn alter the extent and fidelity of the RNA synthesis.[14,15]

Detailed studies of the interactions of metal ions with isolated bases are necessary for understanding the role of cations in the biophysics of DNA, because, despite the fact that biological processes occur in solution, a good knowledge of the geometry and free energy of ion complexation in the gas phase can be useful before attempting condensed-phase modeling by computational techniques.

Until now, studies in which the DNA nucleobases interact with alkali metal cations in an environment simulating the aqueous solution were essentially performed by empirical methods.[16,17] In one of these studies,[16] the molecular dynamic results were put together with ab initio computations and the comparison demonstrated that the problems concerning the reliability of the empirical force fields in representing the guanine−metal interaction energy can be alleviated using the quantum mechanical approach. The potential of high-level ab initio methods in the improvement and verification of the empirical force fields has been, however, previously underlined by Cornell et al.,[18] Halgren,[19] and Hobza et al.[20]

Several previous experimental[21−32] and theoretical works[21,33] were, instead, devoted to the gas-phase interaction of alkali metals with nucleic acid bases. In the most recent experimental/theoretical investigation, Rodgers and Armentrout[21] reported an exhaustive study of the Li^+, Na^+, and K^+ cation interactions with uracil, thymine, and adenine and compared their experimental and MP2 binding enthalpies with those previously obtained by Cerda and Wesdemiotis[31] adjusted on the basis of some considerations concerning the limitations on the absolute accuracy of the metal affinity values achievable by the kinetic method.

The present investigation is, to our knowledge, the first theoretical work in which the gas-phase interactions between the Na^+ and K^+ alkali metal ions and all nucleic acid bases are considered. The work concerns the determination of the preferred coordination sites of the cations on the nucleic acid bases, the elucidation of the influence of the tautomers on the metal ion affinity values with the aim of suggesting a new scale of affinities, to contribute to the interpretation of experimental results, and to yield some useful elements for the improvement of empirical force fields.

Computational Method. Becke3 (B3) exchange[34] and Lee, Yang, and Parr (LYP) correlation[35] potentials, in connection with the 6-311+G(2df,2p) orbital basis set as implemented in the Gaussian 94 code,[36] were used for the full geometry optimization and the vibrational analysis of all the considered nucleic acid bases and their complexes. The possible complexes were selected by considering the different coordination modes of the ions on the most stable free base tautomers including also the interaction with the π electron system of the nucleic acids. These last were found at very high energy with respect to the in-plane coordination of cations in agreement with the previous findings of an MP2 study;[21] for this reason, we have not reported these results here.

The choice of the basis set used was based on both previous experience in alkali metal affinity determinations for biological systems[21,37−39] and the tests performed for the evaluation of the sodium and potassium ion affinity for H_2O and NH_3 molecules. The small dimension of these molecules, previously used as benchmarks in some ab initio studies,[40,41] allowed easy evaluation of the influence of a sufficient number of exchange correlation potentials and basis sets on the metal affinity.

Metal ion affinity (MIA) was assumed to be the negative of the enthalpy variation (ΔH), namely, the dissociation energy of the $B-M^+$ bond, for the process

$$B + M^+ \rightarrow BM^+$$

where B represents the particular DNA or RNA bases and M^+ is the particular metal ion.

Basis set superposition error (BSSE) was computed, through the counterpoise method[42] implemented in the Gaussian 94 code, for the most stable complexes BM^+ and then used to correct all the MIA values. Harmonic vibrational frequencies were obtained by the analytical second derivatives and employed to

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Table 1. Sodium and Potassium Ion Affinities for Water and Ammonia at 0 K from Different Levels of Theory and from Experiment (All values in kcal/mol).

	H_2O		NH_3	
basis set	Na^+	K^+	Na^+	K^+
B3LYP/6-31G	34.1	23.2	35.4	23.1
B3LYP/6-311G(2df,2p)	28.3	20.2	30.5	21.3
B3LYP/6-311+G(2df,2p)	23.4	16.4	26.8	17.9
B3LYP/6-311+G(2df,2p) +BSSE	22.9	16.2	26.5	17.8
B3LYP/6-311++G(d,p)	24.4	17.5	27.6	18.8
B3LYP/6-311++G(2df,2p)	23.4	16.4	26.8	17.8
B3LYP/TZV	29.8	20.5	30.7	19.5
EXP[a]	22.6 ± 1.8		24.4 ± 1.3	
EXP[b]	23.3 ± 2.4	17.0	28.1 ± 0.4	
EXP[c]		17.9		17.9
EXP	20.1 ± 4.3[e]		27.5 ± 4.3[e]	20.1[d]
EXP	23.2[f]		24.6 ± 0.2[g]	
EXP			31.5[i]	
CBS-4[a]	20.3		24.8	
CBS-4M[a]	20.5		24.8	
CBS-Q[a]	21.2		23.3	
MP2[g]	21.3		24.5	
B3LYP/6-31G*//6311+G(2d,2p)[a]	22.6		26.0	
B3P86/6-31G*//6-311+G(2d,2p)[a]	21.8		25.2	
G2[h]	21.2		24.4	
G3[a]	23.5		26.8	

[a] From ref 41. [b] From ref 43; the value for the K^+-H_2O system is at 298 K. [c] From ref 44. [d] From ref 45. [e] From ref 46. [f] From ref 47. [g] From ref 48. [h] From ref 49. [i] From ref 50.

compute the variation in zero point energies. The entropic ($T\Delta S$) and free energy (ΔG) variations for the considered processes were obtained by a thermochemical analysis at 298 K.

Results and Discussion

The computed sodium and potassium ion affinities for H_2O and NH_3 molecules are reported in Table 1 together with the available experimental and previous high-level theoretical data.[41,43−53] From the table it is clear that the introduction of a first diffuse function, as well as the polarization functions, notably improves the value obtained by the simpler 6-31G set. In fact, the 6-311+G(2df,2p) basis set gives the results closest to the most recent experimental counterparts for both the sodium and potassium ions. The BSSE computed at the B3LYP/6-311+G(2df,2p) level modify slightly the MIA values, and the agreement with experimental data becomes still more satisfactory.

The energy of complexation for the Na^+-NH_3 system, computed at the B3LYP/6-311+G(2df,2p) level and given in terms of ΔG ($\Delta G = 20.0$ kcal/mol, obtained subtracting a $T\Delta S$ of 6.9 kcal/mol, computed at the same level of theory, by the value of $\Delta H = 26.8$ kcal/mol reported in Table 1), can be compared with a very recent Fourier transform ion cyclotron resonance value[53] of 18.6 kcal/mol at 298 K. The two values differ by 1.3 kcal/mol. The comparison with G2 and G3 MIA appears to be good especially with the G3 values from which our results differ by 0.6 and 0.3 kcal/mol for the Na^+-H_2O and Na^+-NH_3 systems, respectively.

Although these tests are encouraging, they refer nevertheless to molecules whose difference from the nucleic acid bases is quite large. For this reason, further validation of the reliability of our method was sought in the recent literature. Similar basis sets were used in the reproduction of metal affinities in a series of studies devoted to the investigation of alkali ion−amino acid or −nucleobase interactions at both density functional and ab initio correlated levels.[21,37−39] From these studies, it is possible to conclude that, although the density functional methods do not show a proper basis set saturation trend in contrast to the conventional electron correlation methods, the MIA values obtained at both B3LYP and MP2 levels are generally affected by an average error of about 2−3 kcal/mol with respect to experimental values.

Before discussing the alkali metal affinity for DNA and RNA nucleobases, it should be remembered that their gas-phase tautomeric equilibria were extensively studied at theoretical level[54−64] and the results demonstrated that for the cytosine and guanine the stability order of tautomers, obtained through the density functional methods, sometimes differs from those derived from ab initio correlated methods whose trends, in turn, can often show small disagreements between them. This is not surprising because, in the presence of very small energy differences, the reliability of the results depends strongly on the computational approach and on its accuracy. However, our objective is not so much the individuation of the most stable tautomers as their explicit consideration, because despite the fact that their small energy differences have only a modest influence on the values of MIA, the different stable complexes that they produce can, on the contrary, play a decisive role.

The full geometry optimization of the complexes formed by Na^+ and K^+ ions with the free tautomers of nucleobases gave rise to the minimum energy structures depicted in Figures 1 and 2. Absolute, relative energies and metal ion affinities are reported in Table 2.

Uracil. The free uracil tautomers U2 and U3 are separated by 11. 7 and 18.9 kcal/mol from U1 taken as reference. The most stable complexes for both the sodium and potassium cations are formed starting from the U1 tautomer. In these compounds, the ions are coordinated to the O4 atom with a distance of 2.098 Å for Na^+ and 2.463 Å for K^+.

U2−Na^+ and U2−K^+ complexes lie at 3.2 and 5.1 kcal/mol, respectively, above the global minimums U1−Na^+ and U1−K^+. The sodium cation, although quite far from the N3 atom (2.563 Å), can be still considered bicoordinated, the distance from the O2 center being 2.203 Å. For potassium, the corresponding bond lengths of 3.109 and 2.531 Å indicate its slight

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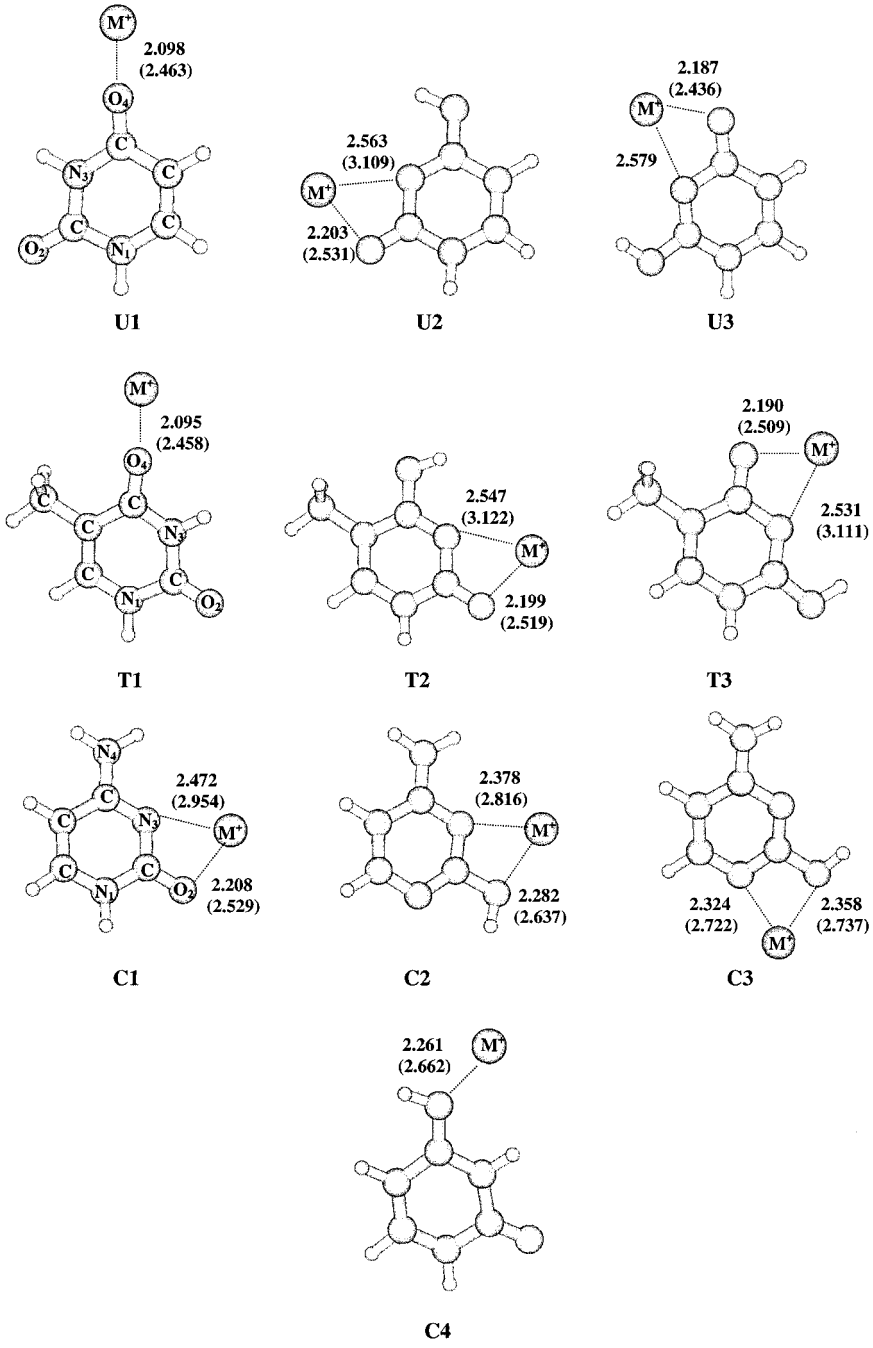

Figure 1. B3LYP/6-311+G(2df,2p) optimized structures of the uracil, thymine, and cytosine complexes with M^+ ($M^+ = Na^+$ and K^+) cations. Distances are in angstroms.

preference for monocoordination. This preference is more obvious in the U3−K^+ complex, lying at 9.4 kcal/mol above U1−K^+, in which the N3−K^+ distance measures more than 4.000 Å, while the O4−K^+ length is 2.436 Å. In the U3−Na^+ complex, separated from the U1−Na^+ by 7.8 kcal/mol, the N3−Na^+ and O4−Na^+ bond lengths are 2.579 and 2.187 Å, respectively.

The B3LYP/6-311+G(2df,2p) MIA values reported in Table 2, inclusive of BSSE and computed at 0 K, for the most stable complexes U1−Na^+ and U1−K^+ are 34.1 and 25.3 kcal/mol, respectively. For the sodium cation, the comparison with the available experimental data[21,31] shows the best agreement with the result of Cerda and Wesdemiotis[31] (33.7 ± 1.0 kcal/mol). Our value differs by 3.3 and 1.9 kcal/mol with respect to the adjusted value (30.8 ± 6.0 kcal/mol) and the threshold collision-induced dissociation (TCID) measurement (32.2 ± 0.8 kcal/mol) of Rodgers and Armentrout,[21] respectively. The MP2 value[21] agrees very well with the TCID one and is lower by 2.0 and 1.6 kcal/mol than our B3LYP and the experimental estimations of Cerda and Wesdemiotis.[31]

In the case of potassium, the comparison of the MIA obtained at the B3LYP level with the literature data reveals a good agreement with the TCID value[21] (24.9 ± 0.7 kcal/mol) and with the MP2 computation[21] (24.8 kcal/mol). The differences become slightly larger with respect to the determination of Cerda ad Wesdemiotis[31] (24.1 ± 1.0) kcal/mol) and the adjusted value proposed by Rodgers and Armentrout[21] (22.9 ± 2.9 kcal/mol).

The sodium and potassium ion affinities for uracil seem to be reproduced well at the B3LYP level and the values, which fall in the range of the experimental uncertainties, suggest that the prevalent species under the experimental conditions are the U1−Na^+ and U1−K^+ systems deriving from the most stable

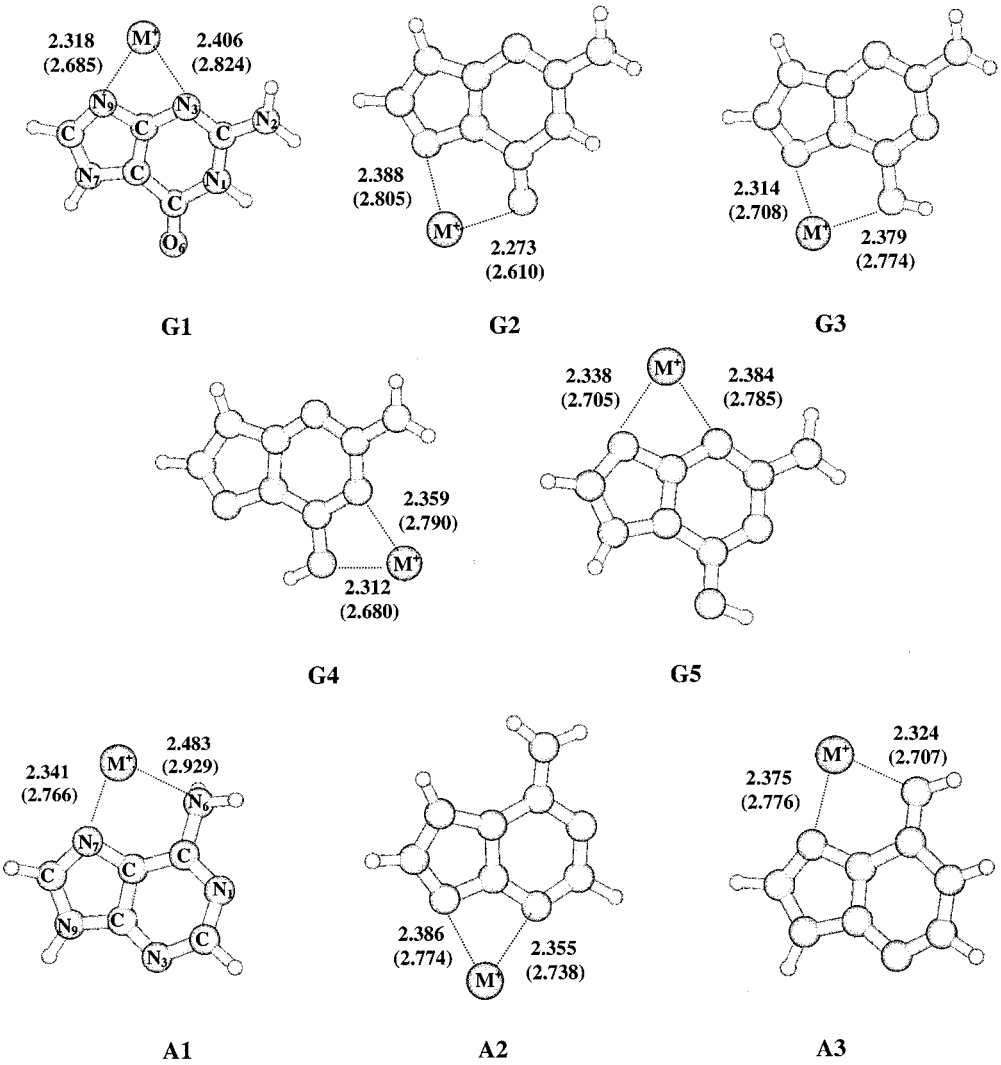

Figure 2. B3LYP/6-311+G(2df,2p) optimized structures of the guanine and adenine complexes with M^+ ($M^+ = Na^+$ and K^+) cations. Distances are in angstroms.

Table 2. Absolute (E in au), Relative (ΔE in kcal/mol) Energies, and Sodium and Potassium Metal Affinities (MIA in kcal/mol), at 0 K and Corrected by the BSSE, for the DNA and RNA Bases Computed at the B3LYP/6-311+G(2df,2p) Level.[e]

	B		B−Na^+					B−K^+				
	E_{SCF}	ΔE	E_{SCF}	ΔE	MIA	MIA[d]	ΔH_{exp}	E_{SCF}	ΔE	MIA	MIA[d]	ΔH_{exp}
U1	−414.971 535	0.0	−577.118 507	0.0	34.1	32.1	33.7,[a] 30.8,[b] 32.2[c]	−1014.776 236	0.0	25.3	24.8	24.1,[a] 22.9,[b] 24.9[c]
U2	−414.952 629	11.7	−577.113 469	3.2	42.7			−1014.768 059	5.1	31.9		
U3	−414.940 608	18.9	−577.105 707	7.8	45.4			−1014.760 823	9.4	34.9		
T1	−454.303 544	0.0	−616.450 266	0.0	34.2	32.3	34.4,[a] 32.5,[b] 32.3[c]	−1054.107 796	0.0	25.0	24.7	24.4,[a] 23.2,[b] 24.9[c]
T2	−454.283 101	12.6	−616.446 907	2.1	44.8			−1054.101 111	4.2	33.4		
T3	−454.273 749	18.3	−616.440 752	5.7	46.8			−1054.094 168	8.3	35.0		
C1	−395.078 564	0.0	−557.251 208	0.0	50.1		42.3[a]	−994.903 221	0.0	37.5		26.3[a]
C2	−395.076 865	1.3	−557.227 959	14.3	39.0			−994.882 528	12.9	26.0		
C3	−395.075 619	2.1	−557.235 205	9.8	42.2			−994.889 601	8.8	31.1		
C4	−395.075 776	2.3	−557.219 768	19.9	32.3			−994.875 547	18.0	22.0		
G1	−542.748 120	0.0	−704.911 877	9.1	44.9		43.5[a]	−1142.564 301	8.6	32.8		28.0[a]
G2	−542.746 912	0.7	−704.926 796	0.0	54.4			−1142.578 270	0.0	42.2		
G3	−542.745 155	1.8	−704.906 229	12.9	42.8			−1142.559 715	11.8	31.2		
G4	−542.744 504	2.3	−704.896 394	18.5	37.8			−1142.550 739	17.00	26.7		
G5	−542.740 761	4.4	−704.909 231	11.0	47.1			−1142.561 568	10.4	34.9		
A1	−467.481 162	0.0	−629.622 775	10.4	29.7	30.7	41.1,[a] 38.2,[b] 33.4[c]	−1067.276 332	10.2	18.2	19.8	25.3,[a] 25.1,[b] 22.7[c]
A2	−467.468 537	8.1	−629.638 594	0.0	48.1			−1067.291 562	0.0	36.3		
A3	−467.452 252	18.5	−629.635 884	2.5	56.3			−1067.284 823	5.1	42.0		

[a] From ref 31. [b] From ref 21 (adjusted values of ref 31). [c] From ref 21. [d] MP2 values from ref 21. [e] Experimental (ΔH_{exp}) values are in kcal/mol and the corresponding uncertainties are given in the text.

tautomer of free uracil. The MIA values corresponding to U2−Na^+,U3−Na^+,U2−K^+, and U3−K^+ species are sensibly higher than those discussed above; thus, because the possibility of interconversion between the various complexes should be practically negligible, the experimental measurements should not be influenced by them.

Thymine. The most stable monocoordinated complexes T1-Na^+ and T1-K^+ are obtained starting from the lowest lying tautomer T1 of the free amino acid. The metal ions interact with the O4 atom with a bond length of 2.095 Å for Na^+ and 2.458 Å for K^+. The energy differences between T1 and T2 and T1 and T3 are 12.6 and 18.3 kcal/mol, respectively. The T2−Na^+ and T3−Na^+ complexes appear to be bicoordinated systems and lie at 2.1 and 5.7 kcal/mol above the T1−Na^+ absolute minimum. The N3−Na^+ and O2−Na^+ distances in the T2−Na^+ complex measure 2.547 and 2.199 Å, while, the N3−Na^+ and O4−Na^+ bond lengths in T3−Na^+ are 2.531 and 2.190 Å, respectively.

The corresponding systems T2−K^+ and T3−K^+ lie at 4.2 and 8.3 kcal/mol above the most stable T1−K^+ complex, respectively. They cannot be defined as properly bicoordinated because the distance to the N3 atom in both T2 and T3 tautomers is sensibly longer than that expected for a double−center ion interaction. The O2−K^+ and O4−K^+ bond lengths in T2−K^+ and T3−K^+ complexes are of the order 2.591 and 2.509 Å.

The B3LYP MIA value, obtained for the most stable T1−Na^+ complex, is, in the case of sodium, in excellent agreement with the value of Cerda and Wesdemiotis[31] (34.2 vs 34.4 ± 1.0 kcal/mol) and on average higher by ∼1.7 kcal/mol than the TCID experimental (32.3 ± 0.9 kcal/mol) and MP2 (32.3 kcal/mol) values.[21]

For potassium, the agreement with available values of MIA (24.4 ± 1.0 [21] and 24.9 ± 0.9 [31] kcal/mol) is even more convincing. The largest discrepancy (1.8 kcal/mol) is found with respect to the adjusted value of ref 21 (23.2 ± 2.9 kcal/mol). Our estimation of 25.0 kcal/mol is very near the MP2 value (24.7 kcal/mol). Again, the MIA corresponding to the complexes formed starting from the T2 and T3 tautomers are significantly higher than all the measured values, so we may hypothesize the probable absence of T2 and T3 under both sets of experimental conditions.

Cytosine. The stability of cytosine complexes with the sodium ion follows the order, C1−Na^+ > C3−Na^+ > C2−Na^+ > C4−Na^+, and the relative energy differences are sensibly higher than those corresponding to free isomers (see Table 2). The first three species are bicoordinated. The N3−Na^+ and O2−Na^+ distances in C1−Na^+ have values of 2.472 and 2.208 Å, respectively. The same bond lengths in the C2−Na^+ system measure 2.378 and 2.282 Å. In the C3−Na^+ complex, the N_1−Na^+ and O_2−Na^+ bonds are quite similar with values of 2.324 and 2.358 Å. The C4−Na^+ compound appears to be a monocoordinated species in which the N4−Na^+ distance is 2.261 Å.

For potassium, as in the case of sodium, we obtain the same stability trend and the same increase in relative energy differences between the complexes with respect to the free cytosine tautomers. The most stable C1−K^+ species presents an N3−K^+ distance too long (2.954 Å) for a bicoordinated complex, while, the O2−K^+ bond has a value of 2.529 Å. In the C2−K^+system, the hydrogen linked to the O2 atom weakens the O2−K^+ bond slightly (2.637 Å); thus, the N3−K^+ length appears to be shorter (2.816 Å) than in the absolute minimum but probably still excessive for a bicoordination. The C3−K^+ species is the only bicoordinated complex in the cytosine−potassium system: the N1−K^+ and O2−K^+ bonds measure 2.772 and 2.737 Å, respectively. Finally, in the C4−K^+ compound, we have an N4−K^+ length of 2.662 Å.

Although C1−Na^+ and C1−K^+ are the complexes favored thermodynamically, the MIA values obtained from them are quite different from the available experimental data.[31] This same result was previously found in the case of the Li^+−cytosine complexes and, as widely verified, does not depend on the level of theory[39] used.

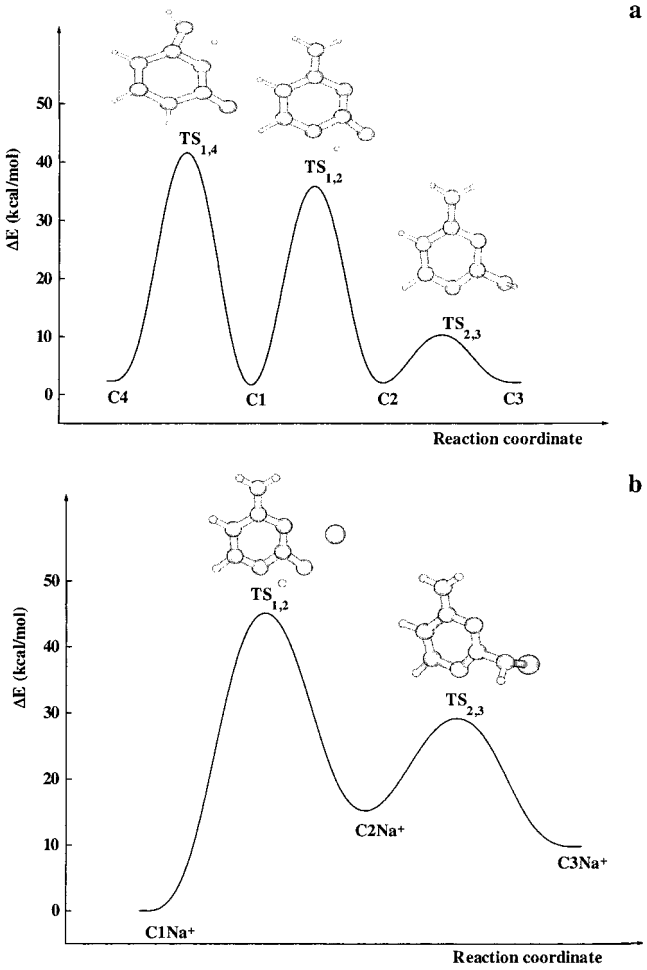

Figure 3. B3LYP/6-311+G(2df,2p) interconversion minimum energetic path for (a) the cytosine tautomers and (b) the cytosine−Na^+ complexes.

The MIA values computed by considering the complexes deriving from the C2 and C3 tautomers of the cytosine with both sodium and potassium ions are much closer to the measured values. In particular, for the Na^+ cation, the best value of MIA is the case of the C3−Na^+ species (42.2 kcal/mol) and differs by only 0.1 kcal/mol from the experimental value (42.3 ± 1.0 kcal/mol) of Cerda and Wesdemiotis.[31]

For potassium, the MIA computed for the C2−K^+ complex (26.0 kcal/mol) is in good agreement with its experimental counterpart (26.3 ± 1.0 kcal/mol).[31]

These results are difficult to rationalize because they imply the presence of some unexpected mechanism that is probably connected with the fact that this amino acid has many tautomeric forms which are very close in energy. In fact, the C1, C2, C3, and C4 tautomers are all found in a small energy range of 2.3 kcal/mol. The occurrence of these small energy differences between the tautomers suggests some interconversion process during the generation of the sample that could give rise to a mixture of complexes. To verify this hypothesis, we have explored the tautomerization path of cytosine in detail. The B3LYP/6-311+G(2df,2p) results are reported in Figure 3a. As is evident, the proton shifts involved in the C1−C4 and C1−C2 interconversions require energies of 37.4 and 43.4 kcal/mol,

respectively. The transformation C2−C3 occurs through a simple rotation around the O2−H bond and requires 9.3 kcal/mol.

Although the temperatures in the experimental preparation of the samples are generally very high, it seems quite improbable that such energetic barriers, except that for C2−C3 interconversion, can be overcome. The exclusion of this first possibility suggests a further hypothesis concerning the conversion of the most stable complex to the less favored ones. This second idea seems to be quite reasonable although in principle, the effect of the metal coordination could block the tautomerization sites as occurs for the C1−M^+ to C4−M^+ transformation. The energetic path for the interconversion between the sodium complexes is reported in Figure 3b. The system C1−Na^+ can evolve into C2−Na^+ through a proton shift that determines the transition state $TS_{1,2}$ located at 46.8 kcal/mol. The conversion of the C2−Na^+ species into C3−Na^+ occurs by a rotation of the Na^+−O_2−H group after the breaking of the N_3−Na^+ bond (see $TS_{2,3}$ in Figure 3b) and requires 15.6 kcal/mol. The height of the barrier appears to be prohibitive for the first but not for the second process, especially if high temperatures are considered.

However, these results do not solve the problem concerning the disagreement between the theoretical MIA values of the most stable complexes and the interpretation of experimental measurements. Agreement is possible only by supposing the presence of the C2 tautomer in the experimental environment. Evidence for the coexistence of the cytosine tautomers both in inert gas matrixes and in solutions can be found in the literature.[65−68] In fact, experimental infrared (IR) measurements in low-temperature inert gas matrixes show both amino−oxo (C1) and the amino−hydroxy (C2) forms to be present in appreciable concentrations.

Hence, if the C2 tautomer is present under the experimental conditions that have determined the MIA value, it is reasonable to propose the formation of C2−M^+ complexes and also their interconversion into C3−M^+ species (see Figure 3b). Consequently, we can explain the results obtained for both the sodium and potassium complexes.

Guanine. The five tautomers of guanine fall in an energy range of 4.4 kcal/mol with the G1 and G2 forms separated by only 0.7 kcal/mol. The attachment of the metal cations to the favored sites of each free tautomer gives rise to the bicoordinated complexes depicted in Figure 2. For both the Na^+ and K^+ ions, the most stable complex is obtained starting from the G2 tautomer and is characterized by a further five-membered-ring formation involving the metal species. In this species, the distances N7−Na^+ (N7−K^+) and O6− Na^+ (O6−K^+) are 2.388 (2.805) and 2.273 (2.610) Å. The remaining complexes follow the same stability order irrespective of the cation considered: G1−Na^+ (G1−K^+) > G5−Na^+ (G5−K^+) > G3−Na^+ (G3−K^+) > G4−Na^+ (G4−K^+) at 9.1 (8.6), 11.0 (10.4), 12.9 (11.8), and 18.5 (17.0) kcal/mol, respectively. The stability order of the guanine complexes is consistent with the fact that the formation of a five-membered cycle is favored with respect to that of a four-membered ring if the most negative carbonyl oxygen and imino nitrogen rather than the hydroxyl group or amino nitrogen are involved.

The best agreement between the theoretical and experimental[31] sodium ion affinity is obtained for the G3−Na^+ complex (42.8 vs 43.5 ± 1.0 kcal/mol), but the value obtained for the G1−Na^+ compound (44.9 kcal/mol) can be also taken into account.

For the potassium ion, the G4−K^+ complex yields the MIA value (26.7 kcal/mol) closest to the experimental determination (28.0 ± 1.0 kcal/mol).

Again, the mass spectrometric experimental interpretation[31] that focuses attention on the most stable complexes does not agree with theoretical predictions. But we think that this is not a coincidence because the tautomeric forms of guanine, like those of cytosine, are very similar in energy; thus, they can be contemporaneously present, as confirmed by Szczepaniak et al.,[69] and influence the experimental measurement.

Recently, particular interest has been devoted to the theoretical study of the DNA quadruplex containing guanine and cytosine nucleobases.[12,13,16,17] These studies include large-scale molecular dynamic simulation[16,17] in which one of the problems is the determination of the potential for the interaction between the alkali metal ions and the nucleobases. It was shown that the empirical potential underestimates strongly the interaction energy between Na^+/K^+ and guanine. In this context, our data as well as the other ab initio computations could be used as benchmarks for more accurate force fields.

Adenine. The most stable tautomeric form of adenine is A1 followed by A2 at 8.1 kcal/mol and A3 at 18.5 kcal/mol. The interaction with the Na^+ and K^+ metal ions generates the corresponding complexes A1−M^+, A2−M^+, and A3−M^+ (see Figure 2) that follow the same stability order. In particular, the lowest lying species is A2−M^+ in which the bond lengths N9−Na^+ (2.386 Å), N3−Na^+ (2.355 Å), N9−K^+ (2.774 Å), and N3−K^+ (2.738 Å) indicate clearly a bicoordination for both cations. At 2.5 (5.1) and 10.4 (10.2) kcal/mol, we found the A3−Na^+ (A3−K^+) and A1−Na^+ (A1−K^+) complexes, respectively. In the A3−M^+ species, the distances N7−M^+ (2.357 Å for Na^+ and 2.776 Å for K^+) and N6−M^+ (2.324 Å for Na^+ and 2.707 Å for K^+) denote a bicoordinated complex. These same bond lengths in A1−M^+ fall only just within the bounds of the bicoordination for the potassium (N7−K^+ is 2.766 Å and N_6−K^+ is 2.929 Å), while the sodium appears to be linked to both N7 (2.341 Å) and N6 (2.483 Å).

The B3LYP/6-311+G(2df,2p) MIA value closest to those measured is obtained from the less stable complex A1−M^+ for both cations (29.7 and 18.2 kcal/mol for Na^+ and K^+, respectively). This fact can be explained only by hypothesizing the absence of both the A2−M^+ and A3−M^+ complexes in the experimental determination because of the large energy differences existing between A1 and the A2 and A3 free tautomers. This assumption has been previously made by Rodgers and Armentrout[21] on the basis of their previous study.[70] Taking into account that the experimental measurements of Cerda and Wesdemiotis (41.1 ± 1.0 kcal/mol for sodium and 25.3 ± 1.0 kcal/mol for potassium) could be affected by an error larger than those admitted by the authors, as supposed in the adjusted values (38.2 ± 6.0 kcal/mol for sodium and 25.1 ± 2.6 kcal/mol for potassium) of ref 21, our results remain, however, underestimated with respect to all experimental data and, in the best case, differ by about 3.7 and 4.5 kcal/mol with respect to the TCID[21] values (33.4 ± 1.0 kcal/mol for sodium

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Table 3. Enthalpy (ΔH = MIA), Entropy ($T\Delta S$), and Free Energy (ΔG) Variations for the Formation Process of $B-Na^+$ and $B-K^+$ Complexes at 298 K (Computed at the B3LYP/6-311+G(2df,2p) Level of Theory).

	ΔH^{298K}, kcal/mol		$T\Delta S^{298K}$, kcal/mol		ΔG^{298K}, kcal/mol	
tautomer	Na^+	K^+	Na^+	K^+	Na^+	K^+
U1	34.7	25.9	6.9	6.6	27.8	19.3
U2	43.3	32.5	7.5	7.0	35.8	25.5
U3	46.0	35.5	7.6	6.4	38.4	29.1
T1	34.8	25.6	7.1	6.6	27.7	18.9
T2	45.4	34.0	7.5	7.0	37.9	27.0
T3	47.4	35.6	7.6	7.0	39.7	28.6
C1	50.8	38.0	8.0	7.3	42.8	30.7
C2	39.6	26.6	7.1	6.6	32.5	19.9
C3	42.8	31.7	7.6	7.2	35.2	24.5
C4	32.9	22.6	7.1	6.6	25.9	16.0
G1	45.5	33.4	7.9	7.5	37.6	25.9
G2	55.0	42.8	7.2	7.8	47.8	35.0
G3	43.3	31.8	7.6	7.1	35.7	24.7
G4	38.4	27.3	8.0	7.5	30.4	26.8
G5	47.7	35.5	7.3	5.8	41.8	29.7
A1	30.3	18.8	7.5	7.1	22.8	11.7
A2	48.7	36.9	7.3	6.6	41.4	30.3
A3	56.9	42.6	8.2	7.7	48.7	34.9

and 22.7 ± 0.8 kcal/mol for potassium, respectively). Whereas, a good agreement is found with MP2 computations[21] (29.7 vs 30.7 kcal/mol for sodium and 18.2 vs 19.8 kcal/mol for potassium). The B3LYP and MP2 results repropose an objective difficulty of treating adenine complexes theoretically, because, these same large discrepancies with experimental values were also found in the previous studies concerning the MIA evaluation of the Li^+-adenine system at both levels of theory.[21,39] On the other hand, the differences between all measured values and the reported uncertainties suggest some problems also at experimental level.

Entropic Contributions. A series of difficulties connected with the experimental measurement of MIA,[71] prevents the explicit evaluation of the entropic effect (ΔS) although these quantities are necessary to determine the free energy variations (ΔG) in the processes considered. Instead, from a theoretical point of view, the computation is quite easy and is carried out by a thermochemical analysis to the desired temperature.

For this reason, we have performed the calculations of ΔS and ΔG and the results, at 298 K, are reported in Table 3.

For the same bases, the ΔS values referred to the different complexes vary from about 2 to 3 cal/(mol K) for sodium and from 1 to 7 cal/(mol K) for potassium. These variations, however, have little effect on the relative differences between the various species but the agreement between theoretical MIA, in terms of ΔG rather than ΔH, and experimental data can be, in some cases, found in correspondence of a different complex.

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Conclusions

The sodium and potassium ions affinities for the DNA and RNA nucleobases were determined by the density functional method using the hybrid B3LYP exchange correlation potential and the 6-311+G(2df,2p) basis set. On the basis of the obtained results, the following conclusions can be drawn.

The level of theory used for the computations of metal ion affinity allows reliable predictions of this property with absolute mean deviations of 2.3, 0.8, and 1.8 kcal/mol with respect to the values obtained by the modified kinetic method, by the threshold collision-induced dissociation measurement, and by the adjusted experimental data.

The $B-M^+$ bond energies decrease as the size of the metal ion becomes larger.

The affinities for nucleobases increase in the order adenine < uracil < thymine < cytosine < guanine and adenine < thymine < uracil < cytosine < guanine in the cases of the sodium and potassium cation, respectively. Differences with the experimental trends concern mainly the adenine bases for which we obtain metal affinity values that appear quite a lot lower than all the measured values obtained by various techniques. The B3LYP binding energy sequences limited to adenine, thymine, and uracil are, however, very similar to those obtained at the MP2 level of theory. In particular, mean absolute deviations of 1.6 and 0.8 kcal/mol for the sodium and potassium systems, respectively, can be observed between the present density functional and previous MP2 results.

According to the experimental interpretation for uracil, thymine, and adenine, the MIA value can be associated with the most stable tautomer of the corresponding free bases. The apparent disagreement between mass spectrometric and B3LYP values in the case of the cytosine and guanine complexes can be explained by supposing the simultaneous presence of two or more tautomers of the free nucleobases of similar energy during the measurement or supposing, as is possible, some interconversion process between the complexes after their formation.

Finally, we think that our results, although calculated for the gas phase, can be used with caution as a guideline also for the condensed phase, taking into account that solvent effects can influence both the coordination sites and binding energies.

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Supporting Information Available: Center number and atomic number, type, and coordinates for the complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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