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Gas-phase theoretical prediction of the metal affinity of copper(I) ion for DNA and RNA bases

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The most stable tautomeric forms of free DNA and RNA bases were considered as substrates for the interaction of Cu^+ ion. Several suitable attachment sites were selected that involved mono- and bi-coordination of the cation. B3LYP/6–311 + *G*(2df,2p) bond energies showed that copper ion has the major affinity for guanine and cytosine bases. The proposed values of Cu^+ ion affinity are 59.9, 60.0, 80.2, 88.0 and 69.0 kcal mol^{-1} for uracil, thymine, cytosine, guanine and adenine, respectively. The preference for the mono- or bi-coordination depends on the particular tautomer for each base. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: metal ion affinity; nucleic acid bases; density functional computations

INTRODUCTION

Metal ions interact with many groups in different sites of nucleic acids influencing the canonical DNA structures.[1–7] They are essential in the formation of non-canonical forms.[2,5,6] It has recently been demonstrated that inter-base copper coordination can replace the hydrogen bonding schemes found in the natural base pairs.[8] Among the elements present in plants, animals and bacteria, copper is one of the most abundant transition metals.[9] Its role in biochemistry is significant because it takes part in the metabolism of iron and zinc and is the cofactor of several redox reactions involving molecular oxygen. Copper also participates in the action mechanism of some enzymes and is involved in the immune system resistance and in antibody production. Furthermore, it has been found that in aqueous solution copper interacts with N7 and N1 sites of purine rings.[10]

Although both Cu^+ and Cu^{2+} complexes play an important role in chemistry and in biochemistry, studies of the interactions of the divalent cation with biological systems are limited to very few cases[8,11–14] and none of these investigations concerns explicitly the DNA or RNA bases. In contrast, the Cu^+ complexes of DNA/RNA have received more attention.[15,16] In particular, two *ab initio* studies on Cu^+–guanine (–adenine)[15] and Cu^+–base pair[16] interactions, appeared in the literature a few years ago. Although the interaction of Cu^+ with some amino acids has been studied by mass spectrometry,[17] to our knowledge, no experimental information about the Cu^+ affinity for nucleic acid bases is available.

Two recent reviews[18,19] demonstrated the fruitful links between theory and mass spectrometry in several fields of gas-phase chemistry, so information coming from quantum mechanical investigations can help and/or stimulate future experimental determinations especially in some difficult cases such as the metal evaluation of ion affinities.

Although it is known that most of the phenomena involving nucleic acid bases and metal ions occur in the condensed phase, to understand the role of metal cations in the biochemistry of DNA and RNA, it is useful to consider first their interaction with isolated bases. For this reason, in this paper, we have studied the interaction of adenine, guanine, cytosine, thymine and uracil free nucleic acid bases with copper(I) ion in order to determine the metal ion affinity values and the preferred coordination sites of the cation. In the gas phase, solvent molecules and counterions are absent hence, the intrinsic bonding characteristic is revealed. Furthermore, it is worth noting that this investigation represents the first study in which Cu^+ interaction with all DNA and RNA bases has been treated at the same high level of theory.

COMPUTATIONAL METHOD

Full geometry optimization and vibrational analysis of the considered nucleic acid bases and their copper(I) complexes were carried out using the hybrid Becke3 (B3) exchange[20] and Lee, Yang and Parr (LYP) correlation[21] potentials. The 6–311 + G(2df,2p) orbital basis set, implemented in the Gaussian 94 code,[22] was chosen on the basis of the

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reliable results obtained in some of our previous studies on similar subjects.[23–25] All possible complexes originating from the interaction of copper cation with the different coordination sites present on the most stable free base tautomers were considered.

Following a consolidated procedure, copper ion affinity (CuIA) (i.e. the negative of the enthalpy variation (ΔH) of the metalation process) was computed by subtracting the sum of the absolute energies of the Base and Cu^+ fragments from the absolute energy of the Base–Cu^+ generic complex.

Basis set superposition errors (BSSE) were estimated for the most stable Base–Cu^+ complexes through the counterpoise method[26] implemented in the Gaussian 94 code, and were used to correct all the CuIA values. The variations in zero point energies were computed using the harmonic vibrational frequencies obtained by the analytical second derivatives. The entropic ($T\Delta S$) and free energy (ΔG) terms for the considered processes arose from thermochemical analysis at 298 K.

RESULTS AND DISCUSSION

Detailed information on the gas-phase tautomeric equilibria of DNA and RNA bases can be found in a series of previous experimental and theoretical papers.[27–37] From all these studies it is possible to conclude that the various non-canonical tautomeric forms of uracil, thymine and adenine lie so far apart in energy from the oxo tautomer that their spontaneous interconversion even at high temperature is unlikely. For cytosine and guanine the situation seems to be different because a good number of their tautomers fall in a narrow range of energy values, but except for some cases,[24] also for the above two bases, the tautomerization processes involve very high energy barriers. However, the contemporary occurrences of more than one tautomeric form of cytosine and guanine are now experimentally confirmed.[38–41]

Density functional and *ab initio* correlated methods sometimes give different stability orders of tautomers, but this is normal, especially in the presence of very small energy differences. We have already demonstrated in previous work[23–25] that eventual small stability inversions do not influence significantly the values of CuIA which, instead, depend strongly on the stability and structure of the different complexes originating from the different tautomers.

The B3LYP/6–311 + G(2df,2p) absolute and relative energies (corrected by the zero point energies) of the selected tautomers of DNA and RNA bases are reported in Table 1 together with those concerning the corresponding most stable optimized complexes with Cu^+, CuIA and ΔG values. Figures 1 and 2 show the equilibrium geometries and the main structural parameters of the most stable systems obtained upon metalation of the various tautomers.

In the three complexes of uracil, the Cu^+ ion is always mono-coordinated to the oxygen atoms. In the most stable U1–Cu^+ system, the O4–Cu^+ bond length measures 1.866 Å. In this same tautomeric form, the O2 atom appears to be a less favourable site for the Cu^+ attachment the energy value (−2055.145864 au) associated with the obtained

Table 1. Relative energies (ΔE) and copper(I) ion affinity (CuIA) at 0 K for DNA and RNA bases computed at the B3LYP/6–311 + G(2df,2p) level, with entropic contribution ($T\Delta S$) and free energies (ΔG) given at 298 K (all data are in kcal mol^{-1})[a]

Base		Base-Cu^+			
	ΔE	ΔE	CuIA	$T\Delta S$	ΔG
U1	0.00	0.0	59.9	7.7	52.8
U2	11.7	0.3	71.3	8.0	63.9
U3	18.9	2.7	76.1	8.1	68.5
T1	0.0	1.2	60.0	8.4	52.1
T2	12.6	0.0	73.9	7.9	66.6
T3	18.3	2.2	77.3	8.1	69.8
C1	0.0	0.0	80.2	8.3	72.4
C2	1.3	12.6	68.9	7.8	61.6
C3	2.1	6.0	76.2	8.2	68.6
C4	2.3	9.3	73.2	7.9	65.8
G1	0.0	9.5	77.9	8.5	69.9
G2	0.7	0.0	88.0	7.2	81.4
G3	1.8	12.6	76.6	7.9	69.3
G4	2.3	18.2	71.5	8.4	63.6
G5	4.4	12.6	79.1	7.4	72.3
A1	0.0	9.8	69.0	8.3	61.2
A2	8.1	5.4	81.4	7.8	74.2
A3	18.5	0.0	97.3	8.6	89.3

[a] Absolute energy values for the most stable free tautomer of each base at 0 K are: −414.884518 (U1), −454.188940 (T1), −394.980359 (C1), −542.631348 (G1) and −467.369809 (A1) a.u.; absolute energy values for the most stable complex of each base at 0 K are: −2055.154507 (U1–Cu^+), −2094.461036 (T2–Cu^+), −2035.282669 (C1–Cu^+), −2182.945155 (G2–Cu^+) and −2107.669944 (A1–Cu^+) a.u.

complex being higher of 5.4 kcal mol^{-1} (1 kcal = 4.184 kJ) with respect to the absolute minimum. As a distinctive characteristic compared with the interaction of nucleic bases with alkali metal ions,[23,24] we emphasize that copper induces a considerable decrease in the C—O4—M^+ valence angle (139.4° in Cu^+ versus 180° in Li^+, Na^+ and K^+ complexes). Only 0.3 kcal mol^{-1} higher in energy, we found the U2–Cu^+ species in which the O2 atom represents the coordination site. The O2—Cu^+ distance is 1.896 Å. The less stable U3–Cu^+ complex follows at +2.7 kcal mol^{-1} and exhibits an O4—Cu^+ length of 1.888 Å. The metalated species of uracil are less separated in energy than the free tautomers and the values of CuIA range from 59.9 to 76.1 kcal mol^{-1}. As mentioned at the beginning of this section, it is improbable that the U2 and U3 tautomers are populated, also at high temperature; for these reasons, the U1 tautomer dominates under any conditions and the most reliable CuIA value is derived from the U1–Cu^+ system.

As expected, the structural features of the thymine complexes are similar to those of uracil. All species are mono-coordinated and again the copper ion interacts with oxygen atoms. The distances between Cu^+ and the attachment site are 1.875, 1.892 and 1.895 Å, in T1–Cu^+, T2–Cu^+ and T3–Cu^+, respectively. In the T1–Cu^+ complex, we

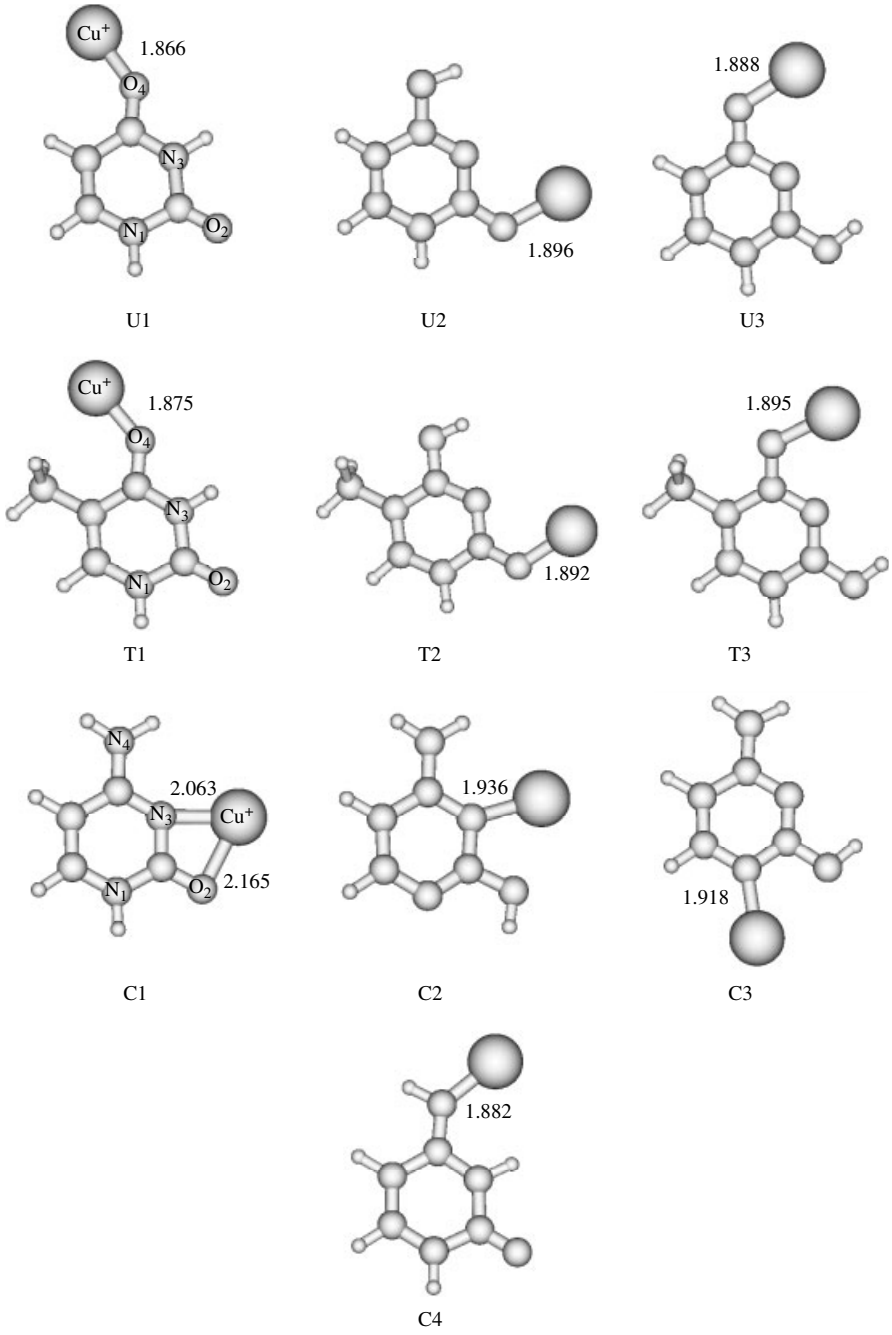

Figure 1. B3LYP/6–311 + G(2df,2p) optimized structures of the most stable complexes of uracil, thymine and cytosine tautomers with copper(I) cation. Distances are in Å.

found a C—O4—Cu^+ angle of 135.5° instead of the linear situation occurring in the thymine–alkali ions systems.[23,24] The metalation of the O2 site in T1 gives rise to a complex with an energy (−2094.454133 au) that lies at 4.3 kcal mol^{-1} above the T2–Cu^+ absolute minimum. A slight difference for thymine with respect to uracil is the stability order of the three metalated systems. Although the energy difference is very small, the T2–Cu^+ complex appears to be more stable (by 1.2 kcal mol^{-1}) than T1–Cu^+. Also in this case we note the stabilizing effect of the metal ion because the complexes fall in an energy range of only 2.2 kcal mol^{-1}. The lowest CuIA value (60.0 kcal mol^{-1}) corresponds to T1–Cu^+ and it is certainly the most reliable one in view of the energy differences between the free tautomers.

The four free cytosine isomers considered fall within 2.3 kcal mol^{-1}. Their interaction with Cu^+ yields many complexed species whose relative energy values cover a range of about 12 kcal mol^{-1}. The stability trend of copper(I) complexes is similar to that of alkali metal and manganese ion complexes except for the C4—Cu^+ system which, in contrast to the corresponding Li^+,[23] Na^+, K^+[24] and Mn^{2+}[25] systems, appears to be more stabilized than C2–Cu^+. The most important difference between the Cu^+ and the other above-mentioned metal ion complexes is the coordination type. Generally, the cytosine–M^+ (M^+ = Li^+, Na^+, K^+) species are bi-coordinated systems;[23–25] instead, for Cu^+, only the most stable C1–Cu^+ complex is bi-coordinated, while C2–Cu^+, C3–Cu^+ and C4–Cu^+ appear to

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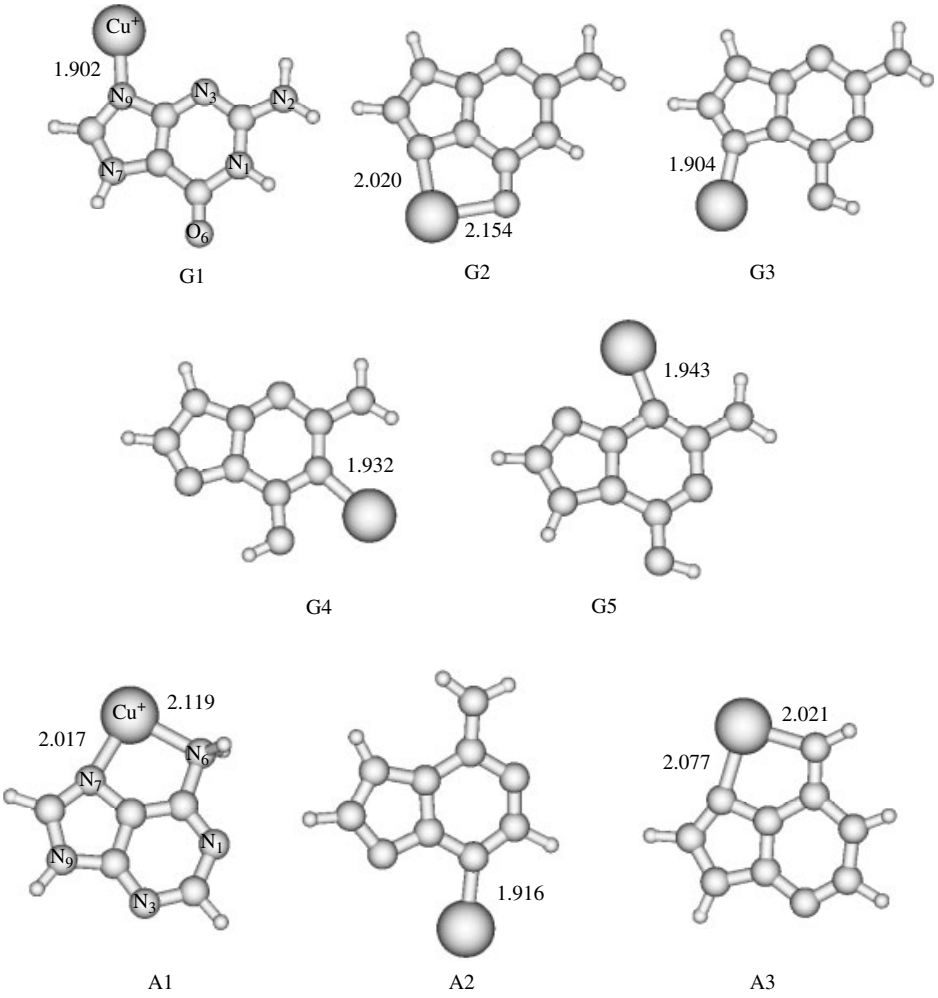

Figure 2. B3LYP/6–311 + G(2df,2p) optimized structures of the most stable complexes of guanine and adenine tautomers with copper(I) cation. Distances are in Å.

be mono-coordinated with the metal ion linked to N3, N1 and N4 atoms, respectively. In the C1–Cu^+ global minimum, the N3–Cu^+ and O2—Cu^+ bond lengths are 2.063 and 2.165 Å, respectively. A comparison between the structural features of the thymine, uracil and cytosine complexes reveals that only cytosine is able to form a bi-coordinated system (C1–Cu^+) whereas uracil and thymine always prefer mono-coordinated situations also in their T2–Cu^+ and U2–Cu^+ complexes that show an arrangement very similar to that of C1–Cu^+. The explanation for this different behaviour can be derived by Fukui indices analysis. The highest Fukui index in all pyrimidine bases is associated with the O2 site (0.2206, 0.2111 and 0.1932 for C1, U2 and T2, respectively). The N3 atom has a Fukui index value that decreases on going from C1 (0.0910) to U2 (0.0861) to T2 (0.0720). Consequently, electrophilic attack occurs preferentially at the O2 site involving the N3 atom only in the cytosine.

The highest CuIA value (80.2 kcal mol^{-1}) is associated with the C1–Cu^+ complex and is probably the most reliable one because, although the C1 and C2 tautomers co-exist,[38–40] the C2–Cu^+ system is significantly less stable than C1–Cu^+ system and hence should not be formed.

For guanine there are five low-lying tautomers that range from 0.0 to 4.4 kcal mol^{-1}. In the most stable G2–Cu^+ complex, the cation is bi-coordinated to the N7 and O6 atoms with distances of 2.020 and 2.154 Å, respectively. The stability order of the complexes (see Table 1), together with the proven co-existence of G1 and G2 tautomers,[41] suggests that the isoenergetic G3–Cu^+ and G5–Cu^+ and the G4–Cu^+ species, all of which are mono-coordinated, are difficult to form. G1–Cu^+, lying at 9.5 kcal mol^{-1} above the absolute minimum, is further thermodynamically unfavourable. For the same reasons as presented in the case of cytosine–M^+ complexes, the reliable CuIA value should correspond to the binding energy (88.0 kcal mol^{-1}) of the G2–Cu^+ system. Our B3LYP/6–311 + G(2df,2p) value lies near that computed for the same complex by a single point calculation (on HF optimized geometry) at the MP2 level[15] (80.3 kcal mol^{-1}), taking into account that the MP2 determination was performed using a pseudo potential for Cu^+ cation and a smaller basis set (6–31G**) for the guanine atoms, and was given in terms of $\Delta E + \mathrm{BSSE}$ rather than ΔH. Comparison of our B3LYP with the HF structural parameters evidences a large difference (0.134 Å) between the two N7—Cu^+ bond distances. On the other hand, the HF O6—Cu^+ bond is longer than the B3LYP bond by only 0.030 Å. Because of the well known differences in the performances of the two methods, an explanation of the

possible causes of the discrepancies is unnecessary. The only relevant fact is that both methods suggest a bi-coordination of the copper ion.

The three stable complexes of adenine arise from three tautomers whose energies are different (see Table 1). As previously found for the Li^+–[23] and Mn^{2+}–adenine[25] interaction, the most stable system is obtained if the A3 free isomer is linked with Cu^+ ion at atoms N6 and N7. The N6–Cu^+ and N7–Cu^+ distances are 2.021 and 2.077 Å, respectively. Computations performed starting from the copper ion bi-coordinated to the N9 and N3 atoms of the A2 tautomer yield a mono-coordinated complex (A2–Cu^+ at +5.4 kcal mol^{-1} above A3–Cu^+) in which the metal ion is linked to the N3 site. This result allows us to discard the possibility of having a stable species in which Cu^+ coordinates the N9 atom, or rather if this complex exists it probably will lies at an energy value higher than that referred to the reported A2–Cu^+ system. The optimization of the bi-coordinated species involving the N6 and N1 atoms, in the A2 tautomer, leaves the copper ion only on the N1 nitrogen. The complex obtained is characterized by a high value of energy (−2107.634437 au) and lies at 22.3 kcal mol^{-1} with respect to the A3–Cu^+ most stable form.

Finally, the A1–Cu^+ species, which originates from the most stable A1 tautomer, is found at +9.8 kcal mol^{-1} above the absolute minimum.

The possible values of the CuIA for adenine complexes cover a wide range, varying from 69.0 (for A1–Cu^+) to 81.4 (for A2–Cu^+) to 97.3 kcal mol^{-1} (for A3–Cu^+). However, although the A3–Cu^+ system is thermodynamically very stable, it is difficult to obtain because the A3 tautomer is 18.5 kcal mol^{-1} less stable than A1. A1 should dominate under any experimental conditions, giving rise to the A1–Cu^+ metalated species alone. The best CuIA value must therefore be associated with this last complex (69.0 kcal mol^{-1}). As in the case of guanine, also for adenine an *ab initio* CuIA exists.[15] The MP2 value[15] of 56.6 kcal mol^{-1} is very different from the B3LYP value, but refers to a mono-coordinated complex that we have not taken into account or, more precisely, a complex for which HF optimization leads to a coordination very different from that obtained by us.

The behaviour of adenine and guanine nucleic acid bases in the metalation processes can be rationalized by means of the DFT chemical descriptors theory. In a recent study, Cadet *et al*.[42] computed the local Fukui indices for all guanine and adenine tautomers considered here. Their investigation showed that the highest Fukui index (f^-) for an electrophilic attack is ascribable to the N6 atom in the A3 tautomer of adenine (0.1657). The site N6 retains the most favorable reactivity also in the A1 (0.1373) and A2 (0.1334) tautomers, albeit with slightly smaller values. This means that the cation species approaches preferentially the N6 atom in A3 but, because the other nearest nitrogen atom (N7) is also prone to an electrophilic attack, the resulting most stable structure has the metal ion bi-coordinated. In the same topological situation, the A1 tautomer gives a less stable complex since the two active electrophilic nitrogens (N6 and N7) have lower Fukui indices. In the A2 tautomer, the presence of a hydrogen atom on N7 does not allow the bi-coordination of the cation which, instead, goes towards the N3 atom characterized by a high value of f^- (0.0973), thereby giving rise to a mono-coordinated complex.

The availability of Fukui indices help us to rationalize also the stability of the guanine complexes. In the G1 and G2 tautomers, the O6 atom is the site having the highest probability to be attached by the cation, with f^- values of 0.1317 and 0.1338, respectively. The bi-coordinated complex arising from G2 is favoured with respect to G1–M^+ because of the presence of another electrophilic center (N7 with $f^- = 0.0552$). Both O6 and N7 sites on G2 are exposed and do not suffer from steric hindrance problems.

Although it is well known that Mulliken analysis gives qualitative information on the charge distribution, our study suggests that in all complexes a charge transfer of about 0.5 $|e|$ occurs from the ligand to the cation, which appears to be more pronounced in the case of the purine bases and in the bi-coordinated systems.

Because of the presence of competitive processes, the extended kinetic method, which can be employed to obtain entropies,[43–46] may not produce adequate ΔS data; hence the computational approach represents the best way for the explicit evaluation of ΔS. For this reason, we determined also the free energy variation for the metalation processes. The results, obtained by thermochemical analysis at 298 K, are reported in Table 1. The ΔS values are similar for all tautomers, ranging from about 24.0 to 29.0 cal $mol^{-1}K^{-1}$. The relative differences between the ΔG values remain almost the same as those between ΔH values; the set of $T\Delta S$ values provided would be useful in future experimental measurements of the interaction between copper(I) and DNA or RNA bases.

CONCLUSIONS

The interaction of DNA and RNA bases with copper(I) ion was investigated at the density functional level using the hybrid B3LYP exchange-correlation potential and the extended basis set 6–311 + G(2df,2p). On the basis of the present and other previous computations of similar subjects performed at the same level of theory, the following conclusions can be drawn:

- Copper(I) ion forms a number of stable complexes with nucleic acid base tautomers in which it appears most frequently mono-coordinated. The only cases of bi-coordination that can influence the metal affinity values were found for the C1 tautomer of cytosine, G2 tautomer of guanine and A1 tautomer of adenine.
- In the mono-coordinated complexes of uracil and thymine, the cation is always linked to oxygen atoms, whereas in cytosine, guanine and adenine it prefers to bind at nitrogens.
- As in the case of alkali metal and manganese ions, the most stable complexes of adenine, guanine and thymine can be obtained by interaction with free tautomers that are not the most stable ones.
- The stability order of the complexes can be rationalized in terms of reactivity descriptors such as local Fukui indices.

- The values of metal affinities proposed as the most reliable ones have been selected on the basis of the stability of the free and metalated tautomers and follow the order guanine > cytosine > adenine > thymine > uracil.

Since no experimental studies are available on Cu^+–DNA or –RNA base complexes, comparison of the results obtained by the B3LYP/6–311 + G(2df,2p) computational scheme with experimental data is not possible; however, previous investigations, performed on alkali metal ion–nucleic base complexes, have proved that the level of theory used provides reliable equilibrium geometries and energetics, so we can treat the data arising from this study with confidence, waiting for future measurements.

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