Theoretical Study of Cytosine−Al, Cytosine−Cu and Cytosine−Ag (Neutral, Anionic and Cationic)

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The binding of cytosine to Al, Cu and Ag has been analyzed using the hybrid B3LYP density functional theory method. The three metals all have open shell electronic configuration, with only one unpaired valence electron. Thus it is possible to study the influence of electronic configuration on the stability of these systems. Neutral, cationic and anionic systems were analyzed, in order to assess the influence of atomic charge on bond formation. We argue that in the case of anions, nonconventional hydrogen bonds are formed. It is generally accepted that the hydrogen bond A-H···B is formed by the union of a proton donor group A-H and a proton acceptor B, which contains lone-pair electrons. In this study, we found that in the case of (Cu−cytosine)$^{-1}$ and (Ag−cytosine)$^{-1}$, N−H···Cu and N−H···Ag bonds are geometrically described as nonconventional hydrogen bonds. Their binding energies fall within the range of −20.0 to −55.4 kcal/mol (depending on the scheme of the reaction) and thus they are classified as examples of strong (>10 kcal/mol) hydrogen bonds.

Introduction

It is well-known that metals in their ionic states play a major role in the biochemical processes which sustain life. They also act as causal factors in a number of pathologies, possibly influencing enzyme-specificity, by binding to specific positions in the DNA molecule.[1−7] Generally, the structure and function of DNA is dependent on hydrogen bonds, short range interactions (such as van der Waals) and metal ions. In particular, metal ions are able to interact with three sites in DNA: sugar moiety, phosphate groups and DNA bases.[8] Alkaline and alkaline-earth metal cations usually interact with the phosphate group, whereas transition metal cations often attach themselves directly to nitrogen bases.[9] It is likely that cation−base interactions are involved in several biophysical processes, for example certain stabilization modes of DNA triple helices. Although interaction with these bases is not very common, it is however important, because it may modify the DNA structure irreversibly. Under different circumstances it is possible to stabilize a number of tautomers of DNA,[10−14] leading to the formation of anomalous base-pairs,[15,16] which are incompatible with the DNA double-helix structure.

Metal centers in biologically active systems act as fundamental constituents, which impart functionality to the molecular aggregate. Removal of these centers often results in the formation of inactive compounds. Moreover, where it is possible to retain some minimal, structural features around the metal centers, some biological activity is also maintained.[17] Thus, owing to the close relationship between the structure and biological function of biomolecules, such as DNA, processes which either stabilize or disrupt these structures, for example interaction with metal ions, are of great interest.[14,18] Likewise, the theoretical study of the tautomerism of nucleobases, produced where there is interaction with metal ions, is important, due to possible effects on base pairing, base stacking, and formation of H-bonded complexes.[19] Studies of metal−DNA and metal−ARN interactions provide valuable thermodynamic and structural information. The interaction of DNA molecule with transition, alkaline and alkaline earth metal atoms has been reported previously.[11,15,16, 20−28] In a previous work,[22] Ca−, Zn−, and Cd−cytosine in their neutral and ionic forms were studied at the B3LYP/LANL2DZ level. We reported that the most stable isomer in each group is derived from the canonical isomer of cytosine. The interaction between metal and cytosine is predominantly electrostatic, and becomes stronger as the nuclear charge of the metal increases. Besides this, the ionization energies of the metal−cytosine compounds exhibit a significant reduction (falling below 6 eV), compared to the value for cytosine (8.7 eV). Analyses of global reactions which form cationic species show that metal cations bind more strongly to neutral cytosine than they do to neutral metals. In this previous work, we analyzed the interaction of cytosine with metals which have closed shell electronic configuration.

The influence of d orbital occupation on the binding of transition metals to nucleobases has been studied previously. Due to the important role played by metal cation−nucleobase interactions in terms of the stability of DNA, this has been the focus of many experimental and theoretical investigations. The fundamental nature of M−nucleobase interactions, as well as the metal cation affinity of nucleobases, has been described previously. However, the influence of the negative metal atomic charge on bond formation has not yet been assessed. The objective of this research was to establish the influence of metal atomic charge on the binding of metal atoms to the nucleobase.

In this work, the interaction between cytosine and Al, Cu and Ag is analyzed. These three metals have an open shell electronic configuration, with only one unpaired valence electron. Neutral, cationic and ionic systems were analyzed, in order to assess the influence of the atomic charge on bond formation. Optimized geometries, Mulliken atomic charges, and

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binding energies were used to provide insights on the binding mechanism of this nucleobase. We argue that the presence of anions results in the formation of nonconventional hydrogen bonds. Crabtree et al.[28a] concluded that "unconventional hydrogen bonds are formed between proton donors with OH and NH bonds and a variety of metal hydrides as proton acceptors". Also, Kryachko and Remacle[28b] reported nonconventional hydrogen bonds between gold clusters and nitrogen bases. It is well accepted that the hydrogen bond A−H···B results from the union between a proton donor group A−H and a proton acceptor B, which contains lone-pair electrons. In this study, we found that in the case of (Cu−cytosine)$^{-1}$ and (Ag−cytosine)$^{-1}$, N−H···Cu and N−H···Ag bonds are geometrically described as nonconventional hydrogen bonds, similar to those described previously.[28]

Computational Details

Density functional theory[29−31] as implemented in the suite of programs *Gaussian 03*[32] was used for the purpose of all calculations. The hybrid three parameter B3LYP[33−35] functional and the LANL2DZ[36−38] basis set were used to calculate complete optimizations of molecular geometries, without symmetry constraints for the several M−cytosine isomers (M = Al, Cu, Ag) in their neutral and ionic forms, included in this study. Harmonic frequency analyses allowed us to verify optimized minima.

Previous studies show that DFT reproduces equilibrium geometries and relative stabilities with hybrid functionals, which partially include the Hartree−Fock exchange energy. These results are largely consistent with those obtained using the Møller−Plesset perturbational theory at second order and basis sets of medium quality, such as 6-31G(d,p), and cc-pVDZ.[39−41]

An adequate number of isomers used during the initial stage of the study provided several initial geometries, which allowed us to extensively explore the potential surface energy, in search of the global minimum. Notwithstanding the difficulties associated with identifying ground states, it is also possible that the global minimum might not be recognized. Nonetheless, the number of initial geometries examined here is large enough to reliably identify the global minima pertaining to each system. In order to compute the vertical electron detachment energies (VEDE) of anionic species, further single-point calculations were required. Formation energies for neutral and cationic species were calculated using zero-point corrected energies. The M−cytosine compounds will be considered to be at their lowest electronic states, singlets (ionic species) and doublets (neutral species), since optimized triplet states were found to be less stable for more than 10 kcal/mol.

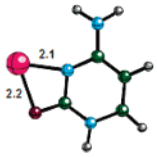
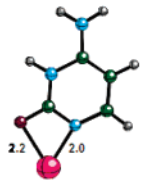
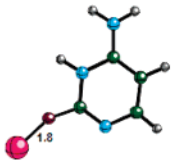
Although there is no universally accepted method for assigning electrostatic charges to atoms, and no experimental technique is currently available for directly measuring these, in a previous study, de Oliveira et al.[42] reported having tested the quality of charges obtained, using the Mulliken and Bader population analysis methods. They found ample correlation between both of these, having taken into account the qualitative description of the atomic charges. Thus in this paper, Mulliken atomic charges are used in the discussion of the qualitative behavior involved in the charge-transfer process.

Results were analyzed, using the Molekel[43,44] and the Ball&Stick[45] packages.

Results and Discussion

Al−Cytosine (Neutral). Table 1 shows neutral Al−cytosine optimized structures. Energy differences, Mulliken atomic charges on selected atoms (see Figure 1 to verify the number of the atoms), adiabatic ionization energies (IE) and electron affinities (EA) are shown, along with the most significant interatomic lengths for the metal atom. The three most stable isomers, lying at an interval of 10 kcal/mol from the ground-state isomer, are indicated. The second and third structures are 3.7 and 8.8 kcal/mol less stable. Al−cytosine (neutral) is essentially a planar molecule. The ground state isomer is related to Watson−Crick's canonic tautomer for cytosine, while the other two are derived from a different tautomer. The interatomic lengths, measured from the metal atom to the nearest atoms in the six-membered ring, are greater than the sum of their covalent radii, discouraging any interaction of covalent character as this was later confirmed by the absence of bonding interactions in the molecular orbitals. Nonetheless the formation energy of these compounds (−41.2 kcal/mol for the ground state) makes the metal−cytosine interaction significantly strong, due chiefly to the significant differences between the atomic charges of Al, O and N (see Table 1), which are thus electrostatic in nature. The aluminum Mulliken atomic charge is positive and equal for all the isomers, while O and N are negatively charged. These values

TABLE 1: Optimized Al−Cytosine (Neutral) Structures[a]

ΔE (kcal/mol)	Structure	Ionization energy (IE) and electron affinity (EA) [in eV]	Atomic charges
0.0		IE = 4.5 EA = -0.2	Al 0.5 N3 -0.6 C2 0.3 O -0.5 N1 -0.3
3.7		IE = 4.6 EA = 0.1	Al 0.5 N3 -0.4 C2 0.3 O -0.5 N1 -0.5
8.8		IE = 4.5 EA = -0.2	Al 0.5 N3 -0.5 C2 0.2 O -0.7 N1 0.0

[a] Atomic charges on selected atoms, adiabatic ionization energies (IE) and electron affinities (EA), in eV, are shown along with the most significant interatomic lengths (in Å) to the metal atom.

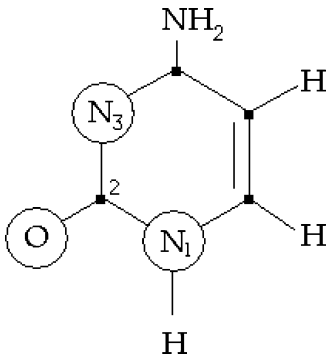
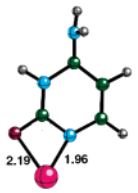
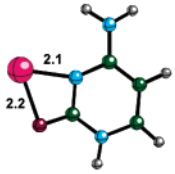
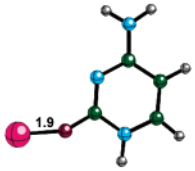


Figure 1. Watson−Crick's cytosine molecule.

TABLE 2: Interatomic Lengths (Å) and Atomic Charges (au), of Neutral and Ionic Species of the Ground State Al−Cytosine Compound in Each Case

Anion (1-)	Neutral	Cation (1+)
		
Al 0.2 N3 -0.6 C2 0.3 O -0.5 N1 -0.4	Al 0.5 N3 -0.6 C2 0.3 O -0.5 N1 -0.3	Al 0.7 N3 -0.1 C2 0.3 O -0.5 N1 -0.3

confirm the hypothesis that an electrostatic interaction takes place between the metal atom and the cytosine molecule. As shown in Table 1, these compounds have very little EA values, measuring less than 5 kcal/mol and falling below the level of uncertainty which is recognized as being inherent in the method.

The IE values of the three most stable isomers are similar. The IE of the isolated cytosine (8.7 eV), and also that of the aluminum atom (6.2 eV), is greater than the IE of Al−cytosine (4.5 eV). The diffuse nature of the HOMO in this compound is related to its low ionization energies. The low values of IE suggest that experimental determination indicating levels will be possible. However, because of the similarity in their IE values and in terms of stability, we can predict that these three isomers will be indistinguishable, when a photoelectron detachment experiment is applied. This information may be important for further experiments and could also be of interest for describing the charge-transfer process along the DNA strand.

Al−Cytosine (Cation and Anion). The optimized geometries of the Al−cytosine cations (Table 2) are structurally similar to their neutral counterparts, except that they manifest a major alteration in the Al−O interatomic length (1.9 Å for the ground state), as a consequence of atomic charge redistribution, as this promotes a major charge transfer from the metal atom to the cytosine molecule. The optimized geometries of the Al−cytosine anionic species (Table 2) show the greatest change, consisting in the pyramidalization of the amino group, but this is not matched by their neutral counterparts. In the case of the anion, another isomer also exists which is related to the canonical tautomer of cytosine, manifesting very similar energy levels (the energy difference equals 1.5 kcal/mol, see Figure 2), which is also not planar. Although aluminum has an open shell electronic configuration, and therefore a nonzero electronic affinity, it represents the cytosine molecule with the greatest charge, due to the binding of an extra electron; thus the compound which expends most energetic strain through the distortion of its geometry manifests the lowest energy level and thus becomes the ground-state isomer. For the anion, the 3 p orbital of Al participates in bonding with cytosine. Analyzing the atomic charges of aluminum present in Al−cytosine compounds (Table 2), it is possible to see that when the cation is formed, the electron is removed from the aluminum atom. The initial ionization energy present in Al (6.2 eV) is more than 2 eV lower than the initial ionization energy present in cytosine (8.7 eV). Taking these values as a reference, it is possible to predict that it will be energetically easier to remove an electron from the Al atom than from the cytosine. This conforms with Mulliken's description of the atomic charges of $(Al-cytosine)^{+1}$. On the other hand, in the case of the anion, when an electron is added, this will go to the cytosine molecule and the aluminum atom will remain almost neutral.

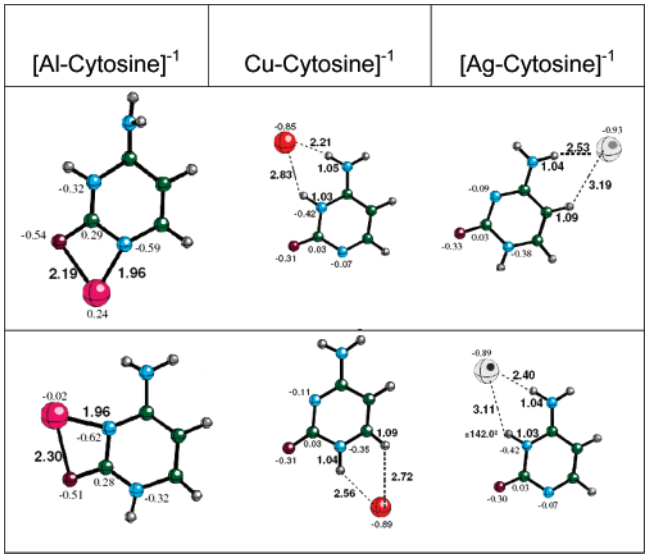


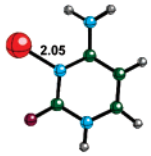
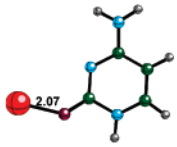
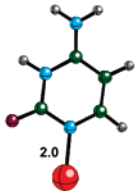
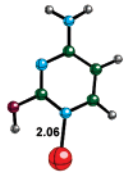
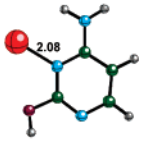
Figure 2. Most stable isomers of M−cytosine anions (ground states on the first line). Structures are almost degenerated. The biggest energy difference is 2.7 kcal/mol for $[Cu-cytosine]^{-1}$ isomers.

Cu−Cytosine and Ag−Cytosine (Neutral). Copper and silver are both isoelectronic with regard to their valence shells. For this reason, comparable chemical behavior can be expected. Neutral compounds formed from Cu and Ag with cytosine exhibit patterns similar to those found in the system previously described for Al. The ground-state compounds for each family are related to the canonic tautomer of cytosine (as shown in Tables 3 and 4), but in each system up to five isomers were found within the 10 kcal/mol from the respective ground state, where two tautomers of cytosine were involved. Interatomic lengths between Cu and Ag, respectively, and the nearest atoms in cytosine's ring are slightly shorter than the sum of the covalent radii for Cu−cytosine (2.0 Å for the Cu−N pair, and 2.1 Å for Cu−O), but the lengths for Ag−cytosine are longer (2.5 Å for Ag−N and also for Ag−O); besides, there is no other evidence from molecular orbitals which upholds the possibility that these interactions are covalent in character.

Tables 3 and 4 also present the EA and IE, for Cu−cytosine and Ag−cytosine. The EA of Cu−cytosine at ground state is less than that of Ag−cytosine at ground state. Comparing these values to those corresponding to Al−cytosine (Table 1) it is possible to conclude that the EA of Al−cytosine is less than that of the other systems. In this case, the system which shows greater EA is Ag−cytosine.

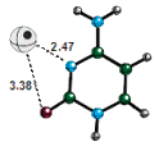
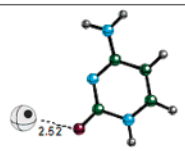
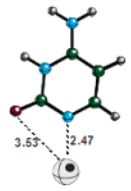
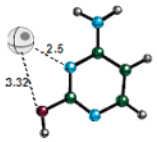
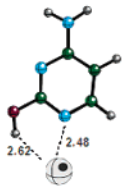
As can be seen in Tables 3 and 4, the value of IE for Cu−cytosine and Ag−cytosine is less than that of isolated cytosine (8.7 eV) and also it is less than that found in metal atoms (7.8 eV for both atoms). However it is greater in the case of Ag−cytosine than in the case of Cu−cytosine and Al−cytosine. For Cu−cytosine, two isomers exist which are less stable than the ground state and which manifest different IE. The cytosine of these two isomers contains an OH group. It may be possible to distinguish these two isomers from the others, using a photoelectron detachment experiment because of the difference in their IE. This is not the case for Ag−cytosine, because in the case of this compound, all the isomers have similar IE values, and thus it is difficult to distinguish between them in an experiment. As observed in the case of other systems[22] studied previously, it would appear that the bond between the metal

TABLE 3: Optimized Cu−Cytosine (Neutral) Structures[a]

ΔE (kcal/mol)	Structure	Ionization energy (IE) and electron affinity (EA) [in eV]	Atomic charges
0.0		IE = 4.8 EA = 0.3	Cu - 0.1 N3 -0.3 C2 0.2 O -0.3 N1 -0.4
4.9		IE = 4.6 EA = -1.2	Cu - 0.2 N3 -0.1 C2 0.2 O -0.4 N1 -0.4
7.8		IE = 4.7 EA = 0.1	Cu - 0.1 N3 -0.4 C2 0.2 O -0.4 N1 -0.4
7.9		IE = 5.7 EA = 0.7	Cu - 0.2 N3 0.0 C2 0.2 O -0.4 N1 -0.3
8.6		IE = 5.1 EA = 1.1	Cu - 0.2 N3 - 0.3 C2 0.2 O -0.4 N1 -0.1

[a] Atomic charges on selected atoms, adiabatic ionization energies (IE) and electron affinities (EA), in eV, are shown along with the most significant interatomic lengths (in Å) to the metal atom.

TABLE 4: Optimized Ag−Cytosine (Neutral) Structures[a]

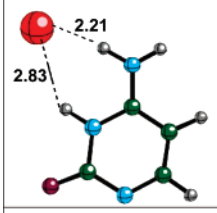
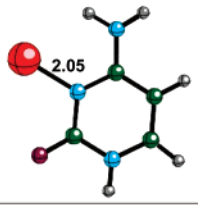
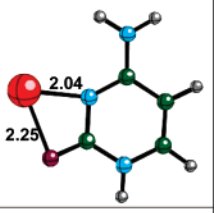
ΔE (kcal/mol)	Structure	Ionization energy (IE) and electron affinity (EA) [in eV]	Atomic charges
0.0		IE = 5.6 EA = 1.7	Ag -0.1 N3 -0.2 C2 0.2 O -0.3 N1 -0.4
2.0		IE = 5.2 EA = 1.7	Ag -0.1 N3 -0.1 C2 0.2 O -0.3 N1 -0.4
7.9		IE = 5.9 EA = -0.1	Ag - 0.1 N3 -0.4 C2 0.2 O -0.3 N1 -0.1
7.9		IE = 5.4 EA = 1.6	Ag - 0.1 N3 - 0.2 C2 0.1 O -0.4 N1 -0.1
8.1		IE = 5.9 EA = 1.2	Ag - 0.1 N3 - 0.0 C2 0.1 O -0.4 N1 -0.2

[a] Atomic charges on selected atoms, adiabatic ionization energies (IE) and electron affinities (EA), in eV, are shown along with the most significant interatomic lengths (in Å) to the metal atom.

atoms and the cytosine molecule diminishes the energy which is necessary for an electron to be removed from the system.

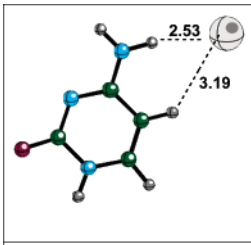
Cu−Cytosine and Ag−Cytosine (Cations and Anions). In Tables 5 and 6, the ground-state structures of neutral and ionic species of Cu−cytosine and Ag−cytosine are presented. Mulliken atomic charges are also included. For the optimized cationic species for each system, we found only two isomers, related to the cytosine canonical tautomer (the ground state) and another tautomer where the hydrogen atom is bonded to N3 (not shown, see Figure 1 in order to recognize the atom numbers). These isomers are 4.9 kcal/mol ($(Cu-cytosine)^+$) and 4.0 kcal/mol ($(Ag-cytosine)^+$) less stable than the corresponding ground state. In the case of the anions, in Figure 2 we can see that there are two stable isomers, with very similar energy. Not all optimized anions are planar. For Cu the most stable isomer includes the noncanonical tautomer of the cytosine molecule. However, there is another stable structure for the Cu−cytosine anion, which is very similar in energy (energy difference equal to 2.7 kcal/mol), which contains the canonical tautomer. These two isomers may both be present in an experiment. In both cases, the metal atom is negatively charged, and the bond between the metal and the cytosine is caused by the two hydrogen atoms present in cytosine. The results are similar for Ag−cytosine. Since the general conclusion for both isomers is similar, further discussion will refer only to the ground state, but it is important to remember that there are other isomers which manifest similar stability. The existence of distinct isomers whose stability is comparable may play a role in future experiments for determination, such as that of photoelectron spectroscopy.

TABLE 5: Interatomic Lengths (Å) and Atomic Charges (au), of Neutral and Ionic Species of the Ground State Cu−Cytosine Compound in Each Case

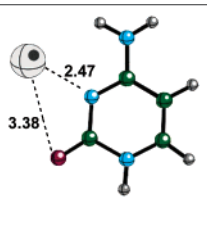
		
Anion (1-)	Neutral	Cation (1+)
Cu -0.9 N3 -0.4 C2 0.0 O -0.3 N1 -0.1	Cu -0.1 N3 -0.3 C2 0.2 O -0.3 N1 -0.4	Cu 0.6 N3 -0.4 C2 0.3 O -0.3 N1 -0.3

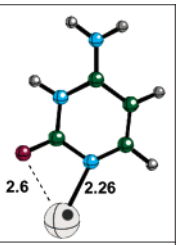
In the case of the anions, the extra electron is localized on the metal atom, as can be inferred from the Mulliken atomic charges. In the formation of a neutral molecule, this extra electron pertaining to the anions is removed from the metal

TABLE 6: Interatomic Lengths (Å) and Atomic Charges (au), of Neutral and Ionic Species of the Ground State Ag−Cytosine Compound in Each Case



Anion (1-)		Neutral		Cation (1+)	
Ag	-0.9	Ag	-0.1	Ag	0.7
N3	-0.1	N3	-0.2	N3	-0.4
C2	0.0	C2	0.2	C2	0.3
O	-0.3	O	-0.3	O	-0.3
N1	-0.4	N1	-0.4	N1	-0.3





atom. For this reason, the metal atomic charge in the neutral systems is close to zero. If we now analyze the cationic system, in both cases (that of Cu and Ag) the positive charge is localized on the metal atom. It appears that the electron pertaining to the neutral systems is detached from the metal atom.

Al versus Cu and Ag. Comparing the atomic charges of neutral and ionic species of Al−cytosine, Cu−cytosine and Ag−cytosine, it may be observed that, in the case of these three systems, the greater part of the positive charge of the cations is distributed over the metal. This might be explained in terms of the electronic configuration of the metals. Al^+, Cu^+ and Ag^+ have a closed shell electronic configuration, which is more stable than an open shell electronic configuration. For this reason, when an electron is removed from the metal atom, the system becomes more stable. In the case of the neutrals, aluminum is more positive than the other two metal atoms, while in the case of the anions, the extra electron is localized on the cytosine molecule of Al−cytosine, but, however, on the metal atom of Cu−cytosine and Ag−cytosine. This agrees with the electronic configuration stability relating to metal ions. With an extra electron, Cu and Ag have a closed shell electronic configuration which is more stable; whereas Al has an open shell electronic configuration which is less stable. This fact is reflected in the vertical electron detachment energies (VEDEs) of the anions, as presented in Table 7. In the case of the anion of Al−cytosine, the VEDEs are less than those found in the other two systems, because the electron has been removed from the cytosine molecule, whereas in the cases of Cu−cytosine and Ag−cytosine, the electron has been removed from the metal atom which has a closed shell electronic configuration. It is energetically more expensive to remove an electron from a closed shell electronic configuration, resulting in greater VEDEs. These results may be useful for further experiments or have other applications.

Several reaction schemes were examined in order to discover distinctive patterns among the metal−cytosine compounds. Two reaction schemes involved in the formation of M−cytosine (cationic and anionic) were considered, each of the reactants manifesting a different charge distribution: one consisting of a metal ion with neutral cytosine and the other an ionic cytosine with a neutral metal atom. Dissociation energies calculated for these reactions schemes are shown in Table 7. All values are positive, and thus, the reactions presented favor the formation of compounds over the separated atoms and molecules. The affinity of neutral metal atoms for neutral and cationic cytosine decreases as Al > Cu > Ag, whereas in the case of the anionic

TABLE 7: Dissociation Energies (kcal/mol) for the Most Stable Isomers in Each Case[a]

	scheme of the dissociation reaction	dissociation energy (kcal/mol)	VEDE (eV)
	Al−Cytosine		
neutral	$Al\ (cyt) \rightarrow Al + cyt$	40.1	
cation	$Al\ (cyt)^{+1} \rightarrow Al + cyt^{+1}$	137.9	
	$Al\ (cyt)^{+1} \rightarrow Al^{+1} + cyt$	79.2	
anion	$Al\ (cyt)^{-1} \rightarrow Al + cyt^{-1}$	47.2	0.52
	$Al\ (cyt)^{-1} \rightarrow Al^{-1} + cyt$	55.7	
	Cu−Cytosine		
neutral	$Cu\ (cyt) \rightarrow Cu + cyt$	16.1	
cation	$Cu\ (cyt)^{+1} \rightarrow Cu + cyt^{+1}$	107.1	
	$Cu\ (cyt)^{+1} \rightarrow Cu^{+1} + cyt$	85.5	
anion	$Cu\ (cyt)^{-1} \rightarrow Cu + cyt^{-1}$	52.3	2.21
	$Cu\ (cyt)^{-1} \rightarrow Cu^{-1} + cyt$	24.0	
	Ag−Cytosine		
neutral	$Ag\ (cyt) \rightarrow Ag + cyt$	7.8	
cation	$Ag\ (cyt)^{+1} \rightarrow Ag + cyt^{+1}$	88.7	
	$Ag\ (cyt)^{+1} \rightarrow Ag^{+1} + cyt$	65.9	
anion	$Ag\ (cyt)^{-1} \rightarrow Ag + cyt^{-1}$	55.4	2.04
	$Ag\ (cyt)^{-1} \rightarrow Ag^{-1} + cyt$	20.7	

[a] Vertical electron detachment energies (VEDEs) of the anions are also reported.

cytosine, the attraction decreases as Al < Cu < Ag. The dissociation energy is greater in the case of the cation than it is in the case of the anion, meaning that the cationic cytosine is more reactive toward the neutral atoms than the anionic cytosine. Looking at these schemes in the context of metal ions, Cu^{+1} has greater affinity for neutral cytosine than Al^{+1} and Ag^{+1}. The affinity of anion metal atoms for neutral cytosine decreases as Al > Cu > Ag. The lowest value pertains to the neutral systems, indicating that neutral cytosine is not greatly attracted to the neutral atoms. In the case of the cations, there is an electrostatic interaction and the dissociation energies are great. In the case of $Cu-(cytosine)^{-1}$ and $Ag-(cytosine)^{-1}$ the interaction is through two hydrogen bonds and the dissociation energy is less than that found in systems where an electrostatic interaction exists.

If we now compare these results with those previously reported for Ca−cytosine, Zn−cytosine and Cd−cytosine,[22] they appear to be very different. For calcium, zinc and cadmium, the metal atom of M−cytosine (anion) is almost neutral, because neutral metal atoms have a closed shell electronic configuration. An extra electron on the metals produces less stable systems. In the case of Cu and Ag, the extra electron produces a closed shell metal electron configuration, which stabilizes the systems. The metal is negatively charged while the cytosine molecule is almost neutral. The consequences of this effect are found in the structure of the compound and also in the interaction energy. Tables 5 and 6 show that, in the case of anions, the metal is bonded to two hydrogen atoms, pertaining to the cytosine. These bonds are similar to hydrogen bonds. The metal atom (Cu and Ag) is negatively charged and represents a proton acceptor containing lone-pair electrons. Whereas interaction in the case of the neutrals and the cations is electrostatic, for the anions it is similar to a hydrogen bond. The bond is formed between a proton donor group (N−H) and a proton acceptor (Cu^{-1} and Ag^{-1}), containing lone-pair electrons. Conventional hydrogen bonds are geometrically described in terms of bond lengths and angles. The distance between the bridging proton and the proton acceptor (Cu or Ag) is shorter than the sum of the van der Waals

radii of H and the metal. In each compound, we have two hydrogen bonds. For $(Cu-cytosine)^{-1}$, N−H···Cu bond angles measure 168° and 143°. Comparing these values with those previously reported,[46] measurements for the N−H···O hydrogen bond were 177° and 127° for strong and weak hydrogen bonds, respectively. These bonds can be classified as intermediate. However, in Table 7 we can see that the binding energies fall within a range of −24.0 to −52.3 kcal/mol (depending on the scheme of the reaction), therefore classifying these as examples of strong (>10 kcal/mol) hydrogen bonds. The individual hydrogen bonds are not strong (bond angles indicate this), but two hydrogen bonds exist here, and for this reason, the binding energy is large. We found similar results for $(Ag-cytosine)^{-1}$. The N−H···Ag bond angle measures 172°. This can be considered as a strong hydrogen bond. The other hydrogen bond is C−H···Ag, and this measures 140°. This is considered a weak hydrogen bond. The binding energies reported in Table 7 point to the same conclusions as those for $(Cu-cytosine)^{-1}$. In both cases, Cu and Ag, the anions show nonconventional hydrogen bonds, similar to those previously reported for other systems.[28]

Conclusions

There is a stabilizing effect on the tautomerization of the cytosine isomers due to interaction with a metal atom, which changes the order of the relative stability of M−cytosine compounds. In most of the systems, the stabilization order of cytosine tautomers with different metal atoms remains the same.

The bond between the metal atoms and the cytosine molecule decreases the amount of energy which is necessary for the removal of an electron from the system. This is related to the diffuse nature of the HOMO in neutral M−cytosine compounds.

In neutral and cationic systems, the nature of the bonding is mainly electrostatic. $(Al-cytosine)^{-1}$ also manifests electrostatic and covalent interactions. As a consequence of the electronic configuration of the metal atom, Cu and Ag are negatively charged on M−cytosine anions. The negative atomic charge on the metal atom produces nonconventional hydrogen bonds. In the case of $(Cu-cytosine)^{-1}$ and $(Ag-cytosine)^{-1}$, the N−H···Cu and N−H···Ag bonds are geometrically described as nonconventional hydrogen bonds.

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References and Notes

(1) Liang, R.; Senturker, S.; Shi, X.; Bal, W.; Dizdarogluand, M.; Kasprzak, K. S. *Carcinogenesis* **1999**, *20*, 893.

(2) Hartwig, A. *Pure Appl. Chem.* **2000**, *72*, 1007.

(3) Müller, J.; Sigel, R. K. O.; Lippert, B. *J. Inorg. Biochem.* **2000**, *79*, 261.

(4) Bidlack, W. R. *J. Am. Coll. Nutr.* **1999**, *18*, 368.

(5) Clark, P.; Eichhorn, G. L. *Biochemistry* **1974**, *13*, 5098.

(6) Arakawa, H.; Neault, J. F.; Tajmir-Riahi, H. A. *Biophys. J.* **2001**, *81*, 1580.

(7) Polyanichko *Nucleic Acids Res.* **2004**, *32*, 989.

(8) Sigel, H. *Chem. Soc. Rev.* **1993**, *18*, 32.

(9) Noguera, M.; Branchadell, V.; Constantino, E.; Ríos-Font, R.; Sodupe, M.; Rodríguez-Santiago, L. *J. Phys. Chem. A* **2007**, *111*, 9823.

(10) Barsky, D.; Colvin, M. E. *J. Phys. Chem. A* **2000**, *104*, 8570.

(11) Šponer, J. V. B. J.; Sabat, M.; Leszczynski, J.; Hobza, P. *J. Phys. Chem. A* **1998**, *102*, 5951.

(12) Dolgounitcheva, O.; Zakrzewski, V. G.; Ortiz, J. V. *J. Am. Chem. Soc.* **2000**, *122*, 12304.

(13) Alemán, C. *Chem. Phys.* **2000**, *253*, 13.

(14) Dabkowska, I.; Gutowski, M.; Rak, J. *J. Am. Chem. Soc.* **2005**, *127*, 2238.

(15) Šponer, J.; Šponer, J. E.; Gorb, L.; Leszczynski, J.; Lippert, B. *J. Phys. Chem. A* **1999**, *103*, 11406.

(16) Pedersen, D. B.; Simard, B.; Martínez, A.; Moussatova, A. *J. Phys. Chem. A* **2003**, *107*, 6464.

(17) Siegbahn, P. E. M.; Blomberg, M. R. A. *Annu. Rev. Phys. Chem.* **1999**, *50*, 221.

(18) Desfrançois, C.; Carles, S.; Schermann, J. P. *Chem. Rev.* **2000**, *100*, 3943.

(19) (a) Colominas, C.; Luque, F. J.; Orozco, M. *J. Am. Chem. Soc.* **1996**, *118*, 6811. (b) Fonseca Guerra, C.; Bickelhaupt, F. M.; Snijders, J. G.; Baerends, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4117. (c) Šponer, J. E.; Špackova, N.; Kulhánek, P.; Leszczynski, J.; Šponer, J. *J. Phys. Chem. A* **2005**, *109*, 2292. (d) Müller, A.; Frey, J. A.; Leutwyler, S. *J. Phys. Chem. A* **2005**, *109*, 5055.

(20) Martínez, A. *J. Chem. Phys.* **2005**, *123*, 024311 (9 pp).

(21) Hettich, R. L. *Int. J. Mass Spectrom.* **2001**, *204*, 55.

(22) Vázquez, M. V.; Martínez, A. *J. Phys. Chem. A* **2007**, *111*, 9931.

(23) (a) Russo, N.; Toscano, M.; Grand, A. *J. Mass. Spectrom.* **2003**, *38*, 265. (b) Russo, N.; Toscano, M.; Grand, A. *J. Comput. Chem.* **2000**, *21*, 1243.

(24) Bal, W.; Kasprzak, K. S. *Toxicol. Lett.* **2002**, *127*, 55.

(25) (a) Burda, J. V.; Sponer, J.; Hobza, P. *J. Phys. Chem.* **1996**, *100*, 7250. (b) Burda, J. V.; Sponer, J.; Leszczynski, J.; Hobza, P. *J. Phys. Chem. B* **1997**, *101*, 9670. (c) Fuentes-Cabrera, M.; Sumpter, B. G.; Sponer, J. E.; Sponer, J.; Petit, L.; Wells, J. C. *J. Phys. Chem. B* **2007**, *111*, 870. (d) Sponer, J.; Sabat, M.; Burda, J. V.; Leszczynski, J.; Hobza, P. *J. Phys. Chem. B* **1999**, *103*, 2528.

(26) (a) Rodgers, M. T.; Armentrout, P. B. *J. Am. Chem. Soc.* **2002**, *124*, 2678. (b) Rodgers, M. T.; Stanley, J. R.; Amunugama, R. *J. Am. Chem. Soc.* **2000**, *122*, 10969.

(27) Onyido, I.; Norris, A. R.; Buncel, E. *Chem. Rev.* **2004**, *104*, 5911.

(28) (a) Crabtree, R. H.; Siegbahn, P. E. M.; Eisenstein, O.; Rheingold, A. L.; Koetzle, T. F. *Acc. Chem. Res.* **1996**, *29*, 348. (b) Kryachko, E. S.; Remacle, F. *Nano Lett.* **2005**, *5*, 735.

(29) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974.

(30) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, *136*, B864.

(31) Kohn, W.; Sham, L. J. *Phys. Rev.* **1965**, *140*, A1133.

(32) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; *Gaussian 03*;Gaussian, Inc.: Wallingford, CT, 2004.

(33) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098.
(34) Mielich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200.
(35) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(36) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270.
(37) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.
(38) Wadt, W. R. *J. Chem. Phys.* **1985**, 82, 284.
(39) Shishkin, O. V.; Gorb, L.; Luzanov, A. V.; Elstner, M.; Suhai, S.; Leszczynski, J. *J. Mol. Struct.* (THEOCHEM) **2003**, *625*, 295.
(40) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 1618.
(41) Saebo, S.; Almlof, J. *Chem. Phys. Lett.* **1989**, *154*, 83.
(42) de Oliveira, A. E.; Guadagnini, P. H.; Haiduke, R. L. A.; Bruns, R. E. *J. Phys. Chem. A* **1999**, *103*, 4918.
(43) Flükiger, P.; Lüthi, H. P.; Portmann, S.; Weber, J. *Molekel*, 4.3 ed.; Swiss Center for Scientific Computing: Manno, Switzerland, 2000−2002.
(44) Portmann, S.; Lüthi, H. P. *Chimia* **2000**, *54*, 776.
(45) Müller, N.; Falk, A. *Ball&Stick*, 3.75 ed.; Johannes Kepler University: Linz, 2000.
(46) Hay, B. P.; Gutowski,M.; Dixon, D. A.; Garza, J.; Vargas, R.; Moyer, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 7925.