ORIGINAL PAPER

Jaroslav V. Burda · Manoj K. Shukla
Jerzy Leszczynski

Theoretical model of the aqua-copper [Cu(H$_2$O)$_5$]$^+$cation interactions with guanine

Abstract Pentaaqua complexes of Cu(I) with guanine were optimized at the DFT B3PW91/6-31G(d) level. For the most stable structures, vibration frequencies and NBO charges were computed followed by energy analyses. The order of individual conformers was very sensitive to the method and basis sets used for the calculation. Several conformers are practically degenerated in energy. The inclusion of an entropy term changes the order of the conformers' stability. Water molecules associated at the N9 position of guanine are favored by the inclusion of the entropy correction. Bonding energies of Cu–O(aqua) interactions were estimated to be about 60 kcal mol^{-1} and for Cu–N7 bonding in the range of 75–83 kcal mol^{-1}. The broad range in Cu–N interaction energies demonstrates the role of induction effects caused by water molecules associated at the various sites of guanine. The charge distribution of the guanine molecule is changed remarkably by the coordination of a Cu(I) cation, which can also change the base-pairing pattern of the guanine.

Keywords DFT calculations · Copper complexes · DNA base · Metal hydration

Introduction

Copper plays an important and very diverse role in living systems. Several theoretical investigations have been devoted to the study of the interaction of copper cations with amino acids. Recently, Sabolovic et al. [1] and

J. V. Burda (✉)
Department of Chemical Physics and Optics, Faculty
of Mathematics and Physics, Charles University, Ke Karlovu 3,
121 16 Prague 2, Czech Republic
E-mail: burda@karlov.mff.cuni.cz

M. K. Shukla · J. Leszczynski
Computational Center for Molecular Structure and Interactions,
Department of Chemistry, Jackson State University, 1325 J. R.
Lynch Street, Jackson, MS 39217-0510, USA

Sabolovic and Liedl [2] studied the structural characteristics of hydrated complexes of Cu(II) and its interaction with amino acids. Further, Rulíšek and Havalas [3–5] investigated the properties of Cu(II) complexes found in databases and compared the bonding energies of copper with respect to other metal cations. The interaction of Cu(II) with the glutamate molecule was examined by Santra et al. [6]. Bertran et al. [7] compared the similarity and differences between the bonding characteristics of Cu(I) and Cu(II) cations interacting with glycine. Several investigations have been devoted to the interactions of glycine with silver and copper monocations [8–10]. In these investigations, efforts were also made to compare the direct coordination and H-bonding possibilities in the presence of some ammonia molecules. There have also been many experimental investigations dealing with the interactions of Cu cations with biological systems in different environments. For example, the interaction of Cu(II) complexes with histidine in an ice-matrix [11] or ligand-field effects on the chemical shift in various Cu(II) complexes using the XANES spectra [12].

Theoretical investigations of the interaction of metal cations with amino acids are also important for unraveling the structural and electronic properties of the so-called blue proteins. In the blue proteins, the basic role of the copper redox Cu(I)/Cu(II) properties are utilized. Reduced blue copper proteins have such geometries that the metal coordination closely resembles its relations in the oxidized form [13–20]. The Siegbahn group studied the redox activities of the copper-amine-oxidase [21]. Some other oxidation enzymes like indophenoloxidase, which is present in the fourth cycle of the respiration chain in the so-called terminal oxidation in the function of redox center of the metalloprotein, or cytochrom c oxidase, superoxidase dismutase, tyrosinase, were also studied by the same group [22, 23]. Interesting experimental works on the charge transfer of the blue proteins were recently published [24, 25]. These enables comparison with the above theoretical studies.

Theoretical investigations have also been devoted to the interaction of copper cations with nucleic acid bases [26–30]. Recently, Yoshioka [31] applied the HF/6-31G* level of theory to determine the selectivity of the tri-aqua–Cu(I) complex with a GpGpG trinucleotide. Some experimental studies dealing with such interactions are also available, but they deal predominately with the Cu(II) cation [32–36].

The role of water as the most common environment for solvation deserves very thorough investigation. An importance of the present investigation can be seen in the number of other papers where copper hydration using either static [37, 38] or dynamic [39, 40] methods or the combination of both [41–44] was also examined. Experimental work in the gas phase confirmed the high stability of some low-coordinated Cu(II) complexes [45]. Recent efforts were also devoted to designing parameters for empirical force fields [46–48] in order to enable faster classical MD simulations for such systems. The SIFBA approach with polarizable potentials, which was successfully applied to the modeling of copper complexes, [49, 50] offers a very promising tool in this regard.

The present work is devoted to the interaction of the copper Cu(I) cation with guanine in the presence of several water molecules. Copper–N7 guanine coordination was combined with various water interactions, both Cu-bonded and H-bridged. Also, several levels of quantum chemistry were used, demonstrating the importance of individual energy and entropy contributions. This study can be considered as an extension of our previous investigations, where the interactions of the Cu(I) and Cu(II) cations with water and ammonia molecules were studied [51–53] and where the accuracy of the methods and basis sets was discussed.

Computational details

The DFT technique with the B3PW91 functional and the 6-31G(d) basis set was used to optimize the selected complexes of formula $[Cu(H_2O)_5(N7\text{-guanine})]^+$. The Cu^+ cation was described using averaged relativistic effective pseudopotentials (AREP) [54] with balanced augmentation by diffuse and polarization functions [51]. The systems were treated as closed shell complexes in the singlet electronic ground state. Frequency analyses were performed at the same computational level (also labeled later as E_1), confirming that all the configurations have character of (local) minima. These analyses were also used for obtaining thermochemical potentials—Gibbs energies for comparison of various hydrated complexes. Particularly, the very important role of entropic term derived from partition functions for ideal gas in micro-canonical ensemble will be emphasized in the discussion. Single-point energy characteristics were determined for the optimized geometries using the B3LYP functional and the extended 6-311++G(2df,2pd) basis set for N, O, and H atoms. Pseudo-orbitals on the Cu atom were augmented accordingly by s, p, d diffuse and $2f$, g

polarization functions [51]. This level of calculation is designated E_2. Stabilization energies with counterpoise corrections [55] (including BSSE and deformation corrections) were calculated according to the formula:

$$\Delta E^{\text{Stab}} = \left(E_{\text{complex}} - \sum E_{\text{monomer}} - \sum E^{\text{deform}} \right) \qquad (1)$$

Here E_{monomer} denotes the total energy of the given part calculated with the inclusion of the AOs of ghost atoms from the rest of the system. For such complexes with a relatively large number of weakly interacting molecules, there are several possibilities for the further partitioning of the space. Therefore, various interaction energies were also evaluated including the sterically corrected stabilization energy ΔE^{Stex} and the dissociation energy of the Cu–N7 bond. Based on these two values, the Cu–O(aqua) binding energy was estimated. The difference between ΔE^{Stex} and ΔE^{Stab} consists of a different partition scheme. For ΔE^{Stex} evaluation, all the cation-surrounding molecules were taken as a one part and the central Cu ion as another part of the complex. Sterical repulsions and other interactions like H-bonds between individual water molecules are not considered in this way and basically only the net Cu-coordination energy is obtained. The ΔE^{Stex} energies were also used to estimate the coordination energies E(Cu–N) and E(Cu–O). In order to be able to divide ΔE^{Stex} energies into the two different bonding contributions, another energy partition scheme (E^{CuN}) was derived, where the whole complex was divided into two parts: (1) Cu atom + the water molecules, which were localized geometrically between the Cu and the O6-guanine area; (2) guanine + the remaining water molecules associated with it. In this way, an energy of the Cu–N7 bond together with one H-bond was evaluated. This H-bond can easily be subtracted since both the water...water H-bond energy is known (about 5.7 kcal mol^{-1} obtained from similar approaches, e.g. [56–61]) or the water...O6 strength can be estimated to be roughly 4.7 kcal mol^{-1} (calculated according to the Eq. 1 for non-metalated guanine...water system). The difference between ΔE^{Stex} and ΔE^{CuN} corresponds to the Cu interaction with water molecules in its proximity and can be used to determinate the Cu–O bond energy.

Finally, the H-bond energy of waters associated with guanine was also calculated. A charge distribution analysis based on the natural population analysis (NPA) approach [62] was performed for the optimized structures in order to gain a detailed insight into the bonding relations. The program package Gaussian 98 [63] was used for ab initio quantum chemical calculations. Visualizations of geometries, MOs, and vibration modes were performed using the programs Molden 4.0 [64] and Molekel 4.3 [65, 66].

Optimized structures

The geometry optimizations of different Cu(I) complexes revealed many stable structures (local minima on

the interaction surface). It should be noted that all predicted minima represent only a static description on the hydration surfaces under the condition of isolated systems at a temperature of 0 K. In the real system, the influence of entropy results in a non-negligible part of the Gibbs energy landscape, which will be discussed later. Nevertheless, we hope that the present study can serve as a good starting point for the future development of more complex models.

In the geometry optimization, several types of complex were considered. The copper cation with all the five water molecules in its neighborhood (only one structure with the lowest energy was used for the further analyses), Cu^+ with four water molecules and the remaining molecule transferred to the guanine moiety, Cu^+ with three or two water molecules and finally the mono-aqua coordinated Cu(I) cation with the other four molecules "hydrating" the guanine. It was sometimes difficult to distinguish whether water is associated only with the O6 position of guanine (for the labeling of guanine atoms see Scheme 1) or is merged with $Cu(H_2O)^+$ and the O6 site, especially in the systems with 2 and 3 water molecules in the proximity of the metal cation. In all the cases, the copper cation exhibits only two (direct) dative bonds, which is in agreement with some other studies [51–53, 67]. The structures with a single water molecule coordinated to the Cu cation were found to be less stable than other conformers. However, entropy corrections lead to increased ΔG preference of some of these structures. Several conformers with hydrated O6, N1, N2, N9
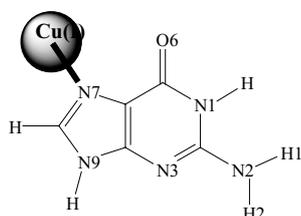
Scheme. 1 Labeling of the guanine atoms

guanine sites converged to the same or very similar structures and only the lowest structures are used here for the energy decompositions and further analyses.

The H-bond distances and coordination parameters for the complexes are shown in Table 1. It was found that the Cu–N7 bond length is always slightly shorter than the Cu–O distance (in average 1.86 Å vs 1.89 Å). Although H-bonding represents only a weak perturbation to the geometry of the $[Cu(H_2O)(N7\text{-}guanine)]^+$ complex, a small but important change in the coordination parameters was noticed when some of the water molecules were transferred from the Cu cation to the guanine moiety (Table 1). In systems with 2–4 water molecules around aqua-ligand of Cu^+, both dative bonds (Cu–O and Cu–N) are relatively shorter. Some elongation of both of these bonds occurs for the complexes with a single water molecule connected to the aqua-ligand. This water is "pulled out" by the next neighboring H_2O linked to the O6 guanine site. Also, the relatively longer (1.60 Å) H-bond between aqua-ligand and its H-bonded partner is remarkable. A distance of 1.50 Å is common for H-bonding in other comparable systems with two or more water molecules between the aqua-ligand and the O6 site of guanine. It should be noted that the H-bonds discussed above are shorter than the usual H-bond distance between water dimer due to the polarization effects of Cu(I) cation. This is also reflected by the larger (by about 0.03 e) partial charges on the H atoms of aqua ligand. In complexes where no additional water molecules are H-bonded to aqua-ligand (last three columns in Table 1), a further dilation of the Cu–O bond and shortening of the Cu–N7 bond is revealed. The elongation of the Cu–O bond is in accordance with our previous studies on the interaction of water and ammonia molecules with the Cu(I)/Cu(II) cations [51, 52]. The shortening of the Cu–N7 bond can be explained in terms of the *trans*-effect of the aqua-ligand in connection with the induction effect of water molecules associated with guanine. The dilation of the Cu–O bond is also in accordance with the fact that the

Table 1 Selected geometry parameters of the hydrated Cu-guanine complexes (distances in Å)

Label	1W	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Cu–N7	1.864	1.857	1.871	1.860	1.860	1.870	1.871	1.858	1.859	1.863	1.874	1.852	1.854	1.858	1.861	1.855
Cu–O	1.919	1.879	1.895	1.877	1.877	1.893	1.894	1.880	1.879	1.882	1.893	1.922	1.921	1.879	1.878	1.921
N7–Cu–O	168.1	177.7	170.1	177.3	176.8	171.1	169.9	178.4	178.6	177.3	170.6	179.8	176.3	177.5	178.7	173.7
H(w)...O6		1.816	1.645	1.817	1.839	1.638	1.655	1.868	1.853	1.904	1.660			1.839	1.882	
H(w)...O6					1.877							1.787	1.791	2.191		1.850
O(w)...HN1		1.971	1.745	1.953	1.718	1.904	1.737		1.950		1.744	1.814	1.806	1.749		1.709
O(w)...HN2		2.010		2.047	2.292	1.774			2.035			1.755	1.741			2.373
O(w)...H2N2				1.820							1.796				1.780	1.860
H(w)...N3		2.223		2.138		2.355					2.180		2.191		2.216	2.037
O(w)...H(N9)		1.778	1.743			1.775		1.740					1.781			1.751
H(wcu)...O(2)		1.498	1.600	1.497	1.498	1.597	1.600	1.793	1.796	1.844	1.593			1.791	1.794	
H(wcu)...O(2)								1.718	1.719	1.701				1.717	1.710	
H(w)–O6–C6		147.7	133.6	152.1	153.5	136.5	134.1	165.6	169.2	152.2	133.6	127.8	130.7	158.5	168.6	120.3
H–O6–C6–C5		81.6	179.8	102.2	48.4	178.8	178.9	35.5	45.8	75.1	179.0	160.3	168.4	14.9	43.7	164.0

Symbols h(w) and o(w) mean hydrogen and oxygen atoms in aqua ligand (directly coordinated water molecule), respectively; o(2) denotes oxygen atom from the closest water associated to aqua ligand

Table 2 Partial charges from NPA analysis at B3LYP/6-31 + G(d,p) level (in e). First two columns contain partial charges of isolated guanine and monoaqua Cu(I) complex

		Guanine	1W	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*
N	1	−0.66	−0.64	−0.65	−0.65	−0.65	−0.65	−0.65	−0.65	−0.64	−0.65	−0.64	−0.65	−0.65	−0.65	−0.65	−0.64
N	3	−0.59	−0.56	−0.60	−0.56	−0.56	−0.56	−0.56	−0.59	−0.56	−0.57	−0.56	−0.56	−0.61	−0.57	−0.56	−0.60
N	7	−0.44	−0.61	−0.61	−0.61	−0.60	−0.60	−0.60	−0.61	−0.61	−0.60	−0.59	−0.60	−0.62	−0.62	−0.60	−0.59
N	9	−0.59	−0.56	−0.57	−0.57	−0.56	−0.56	−0.57	−0.57	−0.57	−0.56	−0.56	−0.56	−0.57	−0.57	−0.56	−0.56
O	6	−0.61	−0.64	−0.68	−0.71	−0.71	−0.73	−0.72	−0.71	−0.67	−0.68	−0.66	−0.73	−0.70	−0.711	−0.71	−0.66
N	2	−0.86	−0.83	−0.84	−0.84	−0.83	−0.83	−0.83	−0.84	−0.84	−0.83	−0.83	−0.83	−0.84	−0.84	−0.83	−0.83
H N1		0.44	0.46	0.47	0.48	0.48	0.47	0.47	0.48	0.46	0.47	0.46	0.47	0.47	0.48	0.48	0.46
H N2	1	0.43	0.44	0.46	0.45	0.45	0.46	0.47	0.45	0.44	0.46	0.44	0.46	0.46	0.47	0.44	0.44
N2	2	0.45	0.46	0.45	0.46	0.46	0.46	0.45	0.45	0.46	0.46	0.46	0.46	0.47	0.45	0.46	0.48
H N9		0.46	0.48	0.50	0.49	0.48	0.48	0.48	0.50	0.49	0.48	0.48	0.48	0.49	0.49	0.48	0.48
Cu			0.77	0.74	0.76	0.74	0.74	0.76	0.76	0.74	0.74	0.75	0.74	0.76	0.75	0.74	0.74
O-ligand			−1.03	−1.08	−1.07	−1.07	−1.08	−1.07	−1.07	−1.07	−1.07	−1.07	−1.07	−1.03	−1.02	−1.07	−1.07

aqua-ligand (without additional surrounding water molecules) cannot compete with guanine, which is a substantially stronger electron donor [68–71]. It was also shown that the strength of Cu–O bond increases with the number of H-bonds of the aqua ligand. This is connected with a reduction of electron density from the H–O(aqua) bond and an increase of the negative charge on oxygen, which improves the donation ability of the aqua oxygen into vacant orbitals of the Cu atom. Further support for the above conclusion can be found in the partial-charge analysis shown in Table 2.

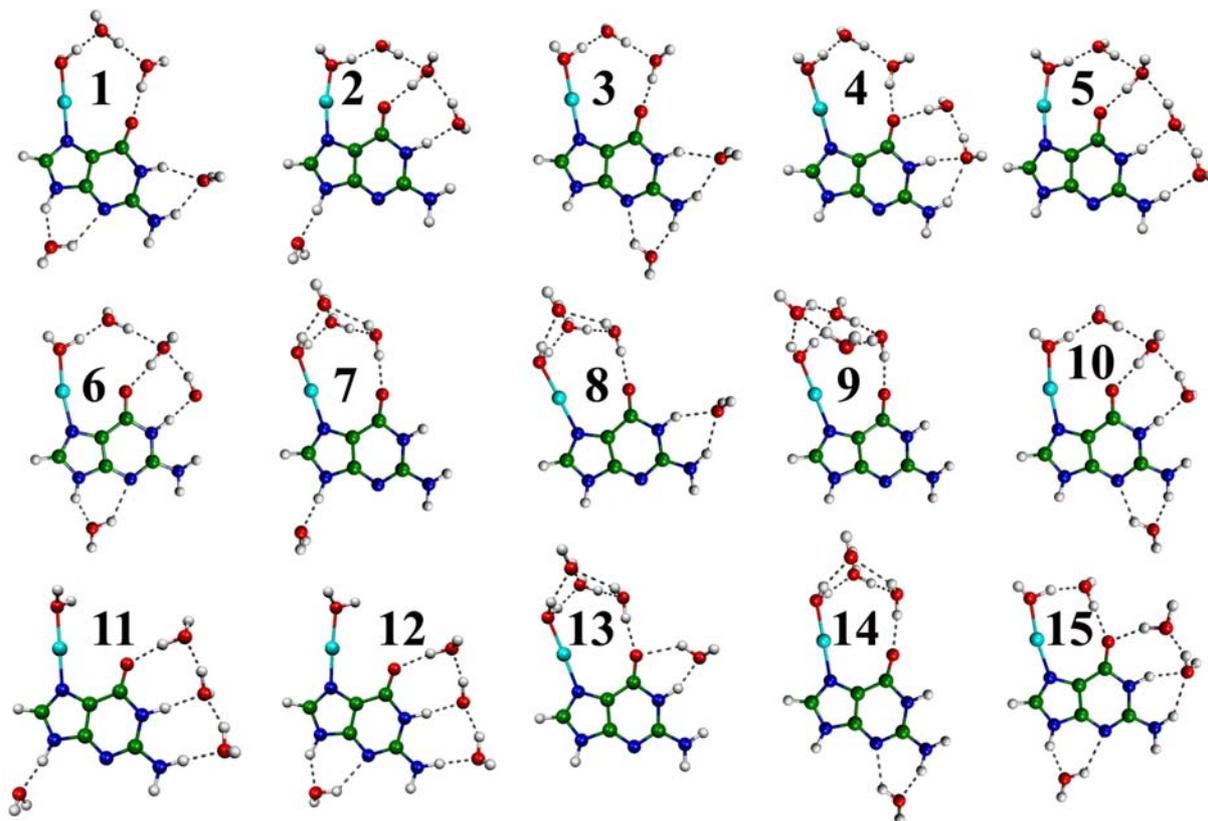The most stable structures corresponding to different pentaaqua–copper-guanine complexes are shown in

Fig. 1 The conformers of [Cu(H$_2$O)$_5$(N7-guanine)]$^+$ complex with the lowest energies

Fig. 1. The distances of coordinated ligands are in consistency with our previous studies where Cu(I)/Cu(II) cations were investigated [51–53]. The Cu–N distances are found to be smaller than the Cu–O distances in the complexes examined. However, the differences between Cu–O and Cu–N bonds are not so pronounced in comparison with some other transition metals (e.g., Co, Ni, Pd, Pt).

Hydration energies

The stabilization energies (with and without inclusion of steric repulsion computed according to Eq. 1 for the optimized geometries) together with Cu–N7 and Cu–O

bond energies are summarized in Table 3. The relative total energies calculated at the B3PW91/6-31G(d) (ΔE_1) and B3LYP/6-311++G(2df,2pd) (ΔE_2) levels, and at the B3LYP level with the inclusion of corrections for thermal and entropy contributions at 298 K obtained at the B3PW91 level (ΔG) are also shown in the Table 3.

The current investigation reveals a complex total energy profile for the complexes studied. The relative coordination energies (1), H-bond energies (2) and entropy terms (3) for the studied complexes are generally similar. (1) The maximum difference between the coordination energies obtained without steric repulsion and hydrogen-bonding corrections (ΔE^{Stex}) is about 9 kcal mol^{-1} (cf. Table 3). (2) The changes in H-bond energies are more difficult to estimate. However, since the differences between ΔE^{Stab} and ΔE^{Stex} can be considered as a consequence predominately of these weak H-bond interactions, they can be expected to differ up to 15 kcal mol^{-1}. Such large differences can be justified since the number of H-bonds varies between 6 and 8 and diverse guanine sites are involved. Moreover, the H-bond energy between the polarized coordinated water (aqua-ligand) and second shell water is about 12 kcal mol^{-1} in the $\{[Cu(H_2O)_2]^+ + 4H_2O\}$ complex [52]. A similar water arrangement also occurs in structures where more than three water molecules were in the Cu(I) neighborhood. (3) The differences in entropy terms were determined to be up to 5 kcal mol^{-1}.

At the ΔE_1 level, the global minimum is represented by a conformer with three water molecules placed in the Watson–Crick H-bond positions and the remaining water molecules are localized at the Cu cation (structure 5; for conformer numbering see Fig. 1). Based on intuition, this structure can be expected to be a very good candidate for the global minima. However, at the larger basis set, another structure (2) becomes the global minimum where the water at the N2 site is moved to the N9 position of the guanine. The third conformer (1) is similar to structure 2; the H-bond between the N1-associated water and the O6-associated water is broken

and the N1-water molecule is shifted between the N1 and N2 sites, creating bifurcated bonds in the conformer 1. The relative energies of these three structures are practically degenerate (being within 0.1 kcal mol^{-1}) at the B3LYP/6-311++G(2df,2pd) level. However, when thermal and entropy corrections are added, structure 1 was determined as the global minimum on the Gibbs energy surface, leaving the other candidates more than 1 kcal mol^{-1} higher in energy. Due to the smaller entropy contribution to the energy of complexes where water molecules are arranged in the form of H-bonded clusters (structure 9) or ordered chains (5), these complexes are relatively less stable on the ΔG free energy landscape. Further, it appears that the entropy term prefers the hydration of the N9 site of guanine, since the conformers 7, 11, 12, and 15 also become relatively more stable on the ΔG landscape. Further, among complexes 7, 8, 13, and 14, where just one water molecule is transferred from the proximity of the Cu-cation, structure 7 was found to be the most stable after the inclusion of the entropy correction.

In order to gain deeper insight into the nature of the coordination bonds, additional energy decomposition calculations were performed. The estimation of coordination energy between Cu(I)–N7 and Cu(I)–O(aqua) corresponds to ΔE^{Stex} if the remote-water...Cu interactions are subtracted properly. On the basis of our previous results [51], about 3 kcal mol^{-1} should be considered for the interaction between the copper cation and the closest water molecule(s) linked by H-bonds to an aqua ligand. On the basis of energy decompositions according to ΔE^{Stex} and ΔE^{CuN}, the coordination energy of Cu–N7 can be estimated to be within 75–83 kcal mol^{-1} and for Cu–O it is about 60 kcal mol^{-1}. Generally, a longer Cu–X bond corresponds to a weaker bonding energy. However, since the differences between different dative bonds are relatively small, this correspondence is not quite clear in the complexes studied. Moreover, the estimation of bond energies is generally approximate and depends on several factors. On going

Table 3 Relative differences of total energies for the selected conformers at several computational levels ΔE_1, ΔE_2, and ΔG and the energy characteristics of these conformers at the B3LYP/ 6-311++G(2df,2pd) level. 1 W means $[Cu(H_2O)(N7\text{-guanine})]^+$ monoaqua complex (in kcal mol^{-1}). In bold, the global minima of various computational levels are stressed

Conformer	ΔE_1	ΔE_2	ΔG	ΔE^{Stex}	ΔE^{Stab}	$E(Cu\text{–}N)$	$E(Cu\text{–}O)$	ΔE^{deform}
1W			–	−123.7	−122.3	81.2	35.2	–
1	1.8	0.1	**0.0**	−146.8	−168.4	83.4	60.4	5.8
2	0.9	**0.0**	1.1	−144.0	−167.9	81.0	59.9	7.3
3	4.4	2.6	2.6	−144.1	−165.3	80.4	60.7	7.5
4	1.0	1.1	3.5	−138.1	−166.5	74.4	60.6	8.4
5	**0.0**	0.0	3.6	−139.7	−167.7	76.5	60.1	8.2
6	1.7	1.4	3.6	−141.1	−165.7	77.9	60.1	8.5
7	3.0	3.0	4.0	−147.2	−164.9	79.7	61.5	4.5
8	0.9	1.6	4.2	−146.3	−166.1	79.1	61.1	5.2
9	1.3	2.6	5.8	−143.3	−165.0	71.2	66.0	6.1
10	3.9	3.7	6.4	−138.5	−164.1	75.6	59.8	8.4
13[a]	3.0	4.2	7.4	−141.1	−163.5	74.5	60.5	5.3
14	5.8	6.7	9.4	−141.8	−161.2	73.8	61.9	5.3

[a]Higher-laying conformers 11 and 12 shown in Fig. 1 were not used for demanding ΔE^{Stex} and ΔE^{Stex} energy analyses

from the monoaqua Cu$^+$ complex (the first column in Table 3) to penta-aqua complexes, the bond energies corresponding to the Cu–N7 bond are found to be within 10 kcal mol^{-1}. This variation mirrors the role of the water molecules associated with the guanine moiety. The strongest Cu–N7 bond occurs in complexes where a water molecule is associated to guanine either between the N1–N2 positions or at the N9 site. Water association in these positions can concur with the polarization effect of the metal cation, which strengthens both H-bonding and Cu–N7 coordination. Therefore, modulation of the Cu–N7 bond energy is more pronounced. This is also supported by the electron-distribution analysis shown in Table 2.

Interesting insight about the influence of Cu(I) cation on the H-bonding to different sites of guanine was revealed from another partitioning of the complexes. Here, water molecules directly associated with guanine are considered as one part and the rest of the complex was treated as the second part of the system. As an important subset of these calculations, four complexes were investigated. A model with the four water molecules bonded to the copper cation while the remaining water molecule was bonded at all the possible sites of the guanine was considered. Two very stable positions, namely the N1–N2 and N9 sites of guanine, were revealed for the water binding. In the first case, where water was bonded in between the N1 and N2 sites, an H-bond energy of about 12 kcal mol^{-1} was obtained. In the second case, water was bonded at the N9 site with the interaction energy of about 11 kcal mol^{-1}. The water molecule can also be placed between the N9 and N3 sites with an interaction energy of about 10 kcal mol^{-1}. It is worth mentioning that the H-bond energy of the structure 5 is about 29.1 kcal mol^{-1}, which is of the same value as the canonical GC base-pairing energy (29.1 kcal mol^{-1}) obtained in our earlier work [72, 73]. This clearly indicates that opening of the GC pair is a practically energy-free process as long as the activation barrier of the process is not considered.

The preferential binding of water molecules at different sites of guanine can be compared with other studies where hydration of guanine was examined. Poltev et al. [74] using the empirical potentials of Jorgensen (OPLS [75, 76]) and Kollman [77, 78] found that in the case of hydration of guanine with a single water molecule, the global-minimum structure has a water between the O6 and N1 sites, followed by the N1–N2 water adduct. The authors unfortunately did not consider the N9 confirmation, probably because of its biological irrelevancy. In another study [79] the mono- and diaqua–guanine systems were investigated at the ab initio RI-MP2 and MD/Q (classical molecular dynamics with quenching technique) levels. The most stable H-bonding in the 1,6 position was confirmed using both ab initio and MD approaches. Further, the MP2 method prefers the N9–N3 site (by about ΔE (2.0 kcal mol^{-1}) followed by the N2–N3 and N1–N2 positions (ΔE = 3.0 and 3.4 kcal mol^{-1}, respectively). The MD technique pre-

dicted a different order: N1–N2, N3–N9, and N2–N3 with ΔE = 1.8, 3.7, and 4.3 kcal mol^{-1} above the lowest N1–O6 conformation, respectively. The MP2/TVZPP approach is considered more reliable, since some softer polarization effects are taken into account in the process of water coordination to the various binding sites of guanine. Similar conclusions were also obtained from other studies [80–82].

From these results, it is clear that there are remarkable changes due to the polarization effects of Cu(I) cation on the guanine moiety. Obtained results can also be compared with our earlier work on metal coordination to purine DNA bases [26, 27]. Despite the fact that in our earlier investigations only bare cations were considered at the HF optimization level and 6-31G(d) basis set, the MP2 interaction energy was found to be relatively similar. Close coordination energies were also obtained for metal-bridged adenine-cytosine complexes [30]. In this study, linear coordination of Cu(I) at the O2 site of cytosine was found stronger (72 kcal mol^{-1}) than binding of Cu(I) to the N1 site of adenine (56 kcal mol^{-1}). Since these interactions are predominately of monopole–dipole moment electrostatic character, the stronger binding of Cu–O2 can be explained by the more favorable orientation of the dipole moment of the base to the copper cation.

Partial charge analysis

Electron-density distributions were explored using a natural population analysis (NPA) at the B3LYP/6-31 + G(d,p) level. Partial charges of the selected atoms, which are important in understanding the induction, polarization, and some other effects, are collected in the Table 2.

The influence of the Cu(I) cation on the distribution of the electron density of guanine is remarkable as can be seen from the comparison with isolated guanine. The magnitude of the partial charges at the O6 and N7 sites are markedly increased due to the polarization caused by the Cu cation, while at the N1, N2, and N9 sites they are generally decreased. Further, the partial charges are also affected by the presence of water molecules in the proximity of the corresponding sites. For instance, partial charge δ(N9) exhibits a increase of charge magnitude from (−0.560 to −0.570 upon hydration at the N9 site of guanine. The corresponding value for isolated guanine is −0.590e. A similar increase in the partial charge at the H(N9) atom upon hydration of guanine at the N9 site is even more significant (Table 2). Analogous changes can also be found for the other guanine positions when water associates with them. This water association also affects the strength of dative copper-guanine bond. The differences between the N1, N2, and N9 positions in comparison with N3 or O6 sites are due to the fact that the latter sites exhibit nucleophilic character. The N1, N2, and N9 atoms are bonded with protons and thereby exhibit electrophilic features. These

differences can be seen clearly on maps of electrostatic potential (not presented here). Metalation causes large changes of the electron densities due to polarization, which is connected with the increased activity of electrophilic centers suppressing the nucleophilic sites. The increased value of negative charge at the O6 atom should increase the nucleophilic activity. However, strong anisotropy of charge distribution due to the close proximity of the copper cation was observed. Therefore, the charge density is not available for O6 donation. Consequently, the H-bonded area of the O6 site, which is opposite to the Cu cation, suffers from the lack of electron density, as already mentioned in our previous work [27, 28]. On the contrary, the N1, N2, and N9 sites bind the water molecule through their hydrogen atoms and thus, some electron density is released from the corresponding N x–H bond to the N x atom.

Conclusions

The molecular structures of several Cu(I) complexes with guanine and five water molecules were optimized by the DFT technique with the B3PW91 functional and the 6-31G(d) basis set. It was found that the order of individual conformers is very sensitive to the level of calculation. Several conformers are practically degenerate in energy. In addition, the inclusion of entropy term changes the energy order of the conformers, stabilizing structures with water coordinated to the N9 position. From the NPA charge analysis, it was found that the N9 and N1 sites fit and partially enhance the polarization effect caused by Cu coordination to the N7 atom. The water associated with the polarized guanine was compared with other studies where an isolated base was hydrated by one or two water molecules and different preferences for binding were revealed.

The bonding energies of Cu–O(aqua) (about 60 kcal mol^{-1}) and Cu–N7 (75–83 kcal mol^{-1}) are in good correspondence with the results obtained for the monoaqua complex [Cu(H$_2$O)(N7-guanine)]$^+$ as well as with our previous studies where hydrated and mixed aqua-ammine Cu(I)/Cu(II) complexes were explored. The broader range in the Cu–N energies clearly demonstrates the role of induction caused by water molecules interacting at various guanine sites. When only the biologically relevant conformers are considered (excluding structures with hydration on the N9 position since the sugar is localized there in guanosides) conformers *3* and *4* are the most stable followed by form *5* (about 1 kcal mol^{-1} higher) with three water molecules in the positions of Watson–Crick pairing. This suggests that the guanine electron distribution was changed remarkably by the Cu(I) coordination and this could also change the base-pairing pattern of the guanine.

References

1. Sabolovic J, Tautermann CS, Loerting T, Liedl KR (2003) Inorg Chem 42:2268–2279
2. Sabolovic J, Liedl KR (1999) Inorg Chem 38:2764–2774
3. Rulíšek L, Havlas Z (2000) J Am Chem Soc 122:10428–10439
4. Rulíšek L, Havlas Z (2002) J Phys Chem A 106:3855–3866
5. Rulíšek L, Havlas Z (2003) J Phys Chem B 107:2376–2385
6. Santra S, Zhang P, Tan W (2000) J Phys Chem A 104:12021–12028
7. Bertran J, Rodrigues-Santiago L, Sodupe M (1999) J Phys Chem B 103:2310–2317
8. Shoeib T, Rodriquez CF, Siu KWM, Hopkinson AC (2001) Phys Chem Chem Phys 3:853–861
9. Shoeib T, Aribi HE, Siu KWM, Hopkinson AC (2001) J Phys Chem A 105:710–719
10. Shoeib T, Milburn RK, Koyanagi GK, Lavrov VV, Bohme DK, Siu KWM, Hopkinson AC (2000) Int J Mass Spectr 201:87–100
11. Manikandan P, Epel B, Goldfarb D (2001) Inorg Chem 40:781–787
12. Shimizu K, Maeshima H, Yoshida H, Satsuma A, Hattori T (2001) Phys Chem Chem Phys 3:862–866
13. Olsson MHM, Ryde U (1999) J Biol Inorg Chem 4:654–663
14. Olsson MHM, Ryde U, Roos BO, Pierloot K (1998) J Biol Inorg Chem 3:109–125
15. Randall DW, George SD, Hedman B, Hodgson KO, Fujisawa K, Solomon EI (2000) J Am Chem Soc 122:11620–11631
16. Randall DW, George SD, Holland PL, Hedman B, Hodgson KO, Tolman WB, Solomon EI (2000) J Am Chem Soc 122:11632–11648
17. Ryde U, Olsson MHM, Roos BO, De Kerpel JOA, Pierloot K (2000) J Biol Inorg Chem 5:565–574
18. Holland PL, Tolman WB (1999) J Am Chem Soc 121:7270–7271
19. Holland PL, Tolman WB (2000) J Am Chem Soc 122:6331–6332
20. Gray HB, Malmstroem BG, Williams RJP (2000) J Biol Inorg Chem 5:551–559
21. Prabhakar R, Siegbahn PEM (2003) J Phys Chem B 107:3944–3953
22. Siegbahn PEM, Wirstam M (2001) J Am Chem Soc 123:11819–11820
23. Siegbahn PEM (2001) J Comp Chem 22:1634–1645
24. Fraga E, Webb MA, Loppnow GR (1996) J Phys Chem 100:3278–3287
25. Book LD, Arnett DC, Hu H, Scherer NF (1998) J Phys Chem A 102:4350–4359
26. Burda JV, Šponer J, Hobza P (1996) J Phys Chem 100:7250–7255
27. Burda JV, Šponer J, Leszczynski J, Hobza P (1997) J Phys Chem B 101:9670–9677
28. Šponer J, Burda JV, Mejzlik P, Leszczynski J, Hobza P (1997) J Biomol Stuct Dyn 14:613–628
29. Gasowska A, Lomozik L (1995) Monatsh Chem 126:13–22
30. Šponer J, Sabat M, Burda J, Leszczynski J, Hobza P, Lippert B (1999) J Biol Inorg Chem 4:537–545
31. Yoshioka Y, Kawai H, Sato T, Yamaguchi K, Saito I (2003) J Am Chem Soc 125:1968–1974

32. Hackl EV, Kornilova SV, Kapinos LE, Andruschenko VV, Galkin VL, Grigoriev DN, Blagoi YP (1997) J Mol Struct 408/409:229–232
33. Herrero LA, Terron A (2000) J Biol Inorg Chem 5:269–275
34. Meggers E, Holland PL, Tolman WB, Romesberg FE, Schultz PG (2000) J Am Chem Soc 122:10714–10715
35. Schoentjes B, Lehn J-M (1995) Helv Chim Acta 78:1–12
36. Atwell S, Meggers E, Spraggon G, Schultz PG (2001) J Am Chem Soc 123:12364–12367
37. Tachikawa H (1996) Chem Phys Lett 260:582–588
38. Schroeder D, Schwartz H, Wu J, Wesdemiotis C (2001) Chem Phys Lett 343:258–264
39. Marini GW, Liedl KR, Rode BM (1999) J Phys Chem A 103:11387–11393
40. Schwenk CF, Rode BM (2003) Phys Chem Chem Phys 5:3418–3427
41. Berces A, Nukada T, Margl P, Ziegler T (1999) J Phys Chem A 103:9693–9701
42. Pranowo HD, Setiajin AHB, Rode BM (1999) J Phys Chem A 103:11115–11120
43. Pranowo HD, Rode BM (1999) J Phys Chem A 103:4298–4302
44. Pranowo HD, Rode BM (2001) Chem Phys 263:1–6
45. Stone JA, Vukomanovic D (2001) Chem Phys Lett 346:419–422
46. Haeffner F, Brinck T, Haeberlein M, Moberg C (1997) Chem Phys Lett 397:39–50
47. Cordeiro NMDS, Gomes JANF (1993) J Comput Chem 14:629–638
48. Subramanian V, Shankaranarayanan C, Nair BU, Kanthimathi M, Manickkavachagam R, Ramasami T (1997) Chem Phys Lett 274:275–280
49. Gresh N, Policar C, Giessner-Prettre C (2002) J Phys Chem 106:5660–5670
50. Ledecq M, Lebon F, Durant F, Giessner-Prettre C, Marquez A, Gresh N (2003) J Phys Chem B 107:10640–10652
51. Burda JV, Pavelka M, Šimánek M (2004) J Mol Struct Theochem 683:183–193
52. Pavelka M, Burda JV (2004) Chem Phys 312:193–204
53. Pavelka M, Burda JV (2004) J Comput Chem (submitted)
54. Hurley MM, Pacios LF, Christiansen PA, Ross RB, Ermler WC (1986) J Chem Phys 84:6840–6853
55. Boys SF, Bernardi F (1970) Mol Phys 19:553–566
56. Burda JV, Mrázek J (2005) (in preparation)
57. Maheshwary S, Patel N, Sathyamurthy N, Kulkarni AD, Gadre SR (2001) J Phys Chem A 105:10525–10537
58. Miyake T, Aida M (2002) Chem Phys Lett 363:106–110
59. Anick DJ (2003) J Phys Chem A 107:1348–1358
60. Hartke B (2000) Z Phys Chem 214:1251–1264
61. Kabrede H, Hentschke R (2003) J Phys Chem B 107:3914–3920
62. Reed AE, Weinstock RB, Weinhold F (1985) J Chem Phys 83:735–746
63. Frisch MJ, Tucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery Jr JA, Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Salvador P, Dannenberg JJ, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Baboul AG, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson BG, Chen W, Wong MW, Andres JL, Gonzalez C, Head-Gordon M, Replogle ES, Pople JA (2001) Gaussian 98, Revision A.1x. Gaussian Inc, Pittsburgh, PA
64. Schaftenaar G (Molden) http://www.cmbi.kun.nl/~schaft/molden/molden.html
65. Flükiger PF http://www.cscs.ch/molekel/
66. Portmann S, Lüthi HP (2000) Chimia 54:766–770
67. Feller D, Dixon DA (2002) J Phys Chem A 106:5136–5143
68. Cotton FA, Wilkinson G (1988) Advanced inorganic chemistry. Wiley Interscience, Leicester
69. Janes R, Moore E (2004) Metal-ligand bonding. Royal Society of Chemistry, Cambridge
70. Burda JV, Leszczynski J (2003) Inorg Chem 42:7162–7172
71. Zeizinger M, Burda JV, Lezczynski J (2004) Phys Chem Chem Phys 6:3585–3590
72. Burda JV, Šponer J, Leszczynski J (2001) Phys Chem Chem Phys 3:4404–4411
73. Šponer J, Hobza P (1997) Chem Phys Lett 267:263–270
74. Poltev VI, Malenkov GG, Gonzales EJ, Teplukhin AV, Rein R, Shibata M, Miller JH (1996) J Biomol Struct Dyn 13:717–725
75. Pranata J, Wierschke SJ, Jorgensen WL (1991) J Am Chem Soc 113:2810–2819
76. Jorgensen WL, Tirado-Rives J (1988) J Am Chem Soc 110:1657–1666
77. Ferguson DM, Perlman DA, Swope WC, Kollman PA (1992) J Comput Chem 13:362–370
78. Weiner SJ, Kollman PA (1986) J Comput Chem 7:230–252
79. Hanuš M, Ryjáček F, Kabeláč M, Kubař T, Bogdan TV, Trygubenko SA, Hobza P (2003) J Am Chem Soc 125:7678–7688
80. Shishkin OV, Sukhanov OS, Gorb L, Leszczynski J (2002) Phys Chem Chem Phys 4:5359–5364
81. Song B, Zhao J, Griesser R, Meiser C, Sigel H, Lippert B (1999) Chem Eur J 5:2374–2387
82. Zhanpeisov NU, Šponer J, Leszczynski J (1998) J Phys Chem A 102:10374–10379