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Coordination properties of glycylglycine to Cu^+, Ni^+ and Co^+. Influence of metal cation electronic configuration

Erika Constantino, Albert Rimola, Luis Rodríguez-Santiago and Mariona Sodupe*

Departament de Química, Universitat Autónoma de Barcelona, 08193 Bellaterra, Spain. E-mail: mariona@klingon.uab.es

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The structure, vibrational frequencies and binding energies of the complexes formed by the interaction of $Cu^+(d^{10}, {}^1S)$, $Ni^+(d^9, {}^2D)$ and $Co^+(d^8, {}^3F$ and $ {}^1G)$ with glycylglycine have been theoretically determined. The most stable structure of Cu^+–glycylglycine is bicoordinated with the Cu^+ cation interacting with the terminal carbonyl oxygen and the amino group. However, for Ni^+–glycylglycine and Co^+–glycylglycine the lowest energy structures are tricoordinated, the interaction of the metal cation given by the same groups of Cu^+-glycylglycine plus the nitrogen or oxygen atoms of the peptide bond. As for glycine, D_e values follow the order $Ni^+ > Co^+$ (triplet) $\sim Cu^+$, but the interaction energies are about 11–13 kcal mol^{-1} larger. Differences on the coordination properties of the metal cations are discussed and interpreted according to their electronic structure.

Introduction

The study of the interaction of metal cations with amino acids and peptides has attracted considerable attention during the last three decades, due to the importance of metal cations in many biochemical processes,[1] such as respiration, much of metabolism, and nerve transmission.[2] Metal cation binding to amino acid residues determines the structure and function of biomolecules and thus a detailed understanding of the fundamental nature of this kind of interaction is of great importance. On the other hand, the coordination of metal cations to peptides implies an electron density reorganization of the ligand and, as a consequence, the activation of some particular bonds that under mass spectrometry conditions can produce specific fragmentations[3] and provide useful information for peptide sequencing.[4–15]

At present, quantum chemical studies can provide an accurate description of this type of M^+–L system and determine the preferred modes of coordination, the metal-specific binding sites and the metal cation affinities. Furthermore, theoretical calculations can provide trends and insights on the nature of the bonding as a function of the electronic structure of the metal cation.[15–36,9] However, until now, most of the reported studies have dealt with the interaction of glycine or other amino acids and small peptides with alkali, alkaline-earth[32–34,9,15,17,20,24,25,27] and closed-shell transition metals cations,[21–23,16,18,19,34,36] and only a few works have analyzed the interaction of open-shell transition metal cations.[18,19,22,26,28,35,36] In particular, for the simplest glycylglycine peptide molecule, only the interactions of Na^+, K^+, Cu^+ and Ag^+ have been considered.[9,15,21,24] For Na^+ and K^+, two structures were found to be the lowest energy isomers. One of them has the metal ion ligated in a tridentate fashion by the two carbonyl oxygens and the amino group, and the other one is coordinated by the two carbonyl groups, whereas the N-terminus is involved in a hydrogen bond with amide nitrogen. For K^+ the latter structure is the most stable one, but for Na^+ the two structures are nearly degenerate and the global minimum depends on the level of theory used.[9,15,24] In contrast, for Cu^+, the lowest energy structure found by Shoeib *et al.* is dicoordinated with the terminal nitrogen and the carbonyl oxygen of the amide, and no tricoordinated structures are found to be minima on the potential energy surface.[21] From these results it is clear that the nature of the metal cation, its size and electronic structure are important factors to determine the optimal conformation of the peptide upon metal binding. For transition metal ions, the nature of the M^+–L interaction is particularly complex because, in addition to the obvious electrostatic terms, other effects such as the metal–ligand repulsion, the s–d promotion and hybridization or dative interactions can significantly influence the mode of binding.

The aim of this work is to provide a detailed analysis of the gas phase binding chemistry between Cu^+, Ni^+, and Co^+ and glycylglycine, the simplest peptide. Polyglycines can be considered as peptide backbones and therefore glycylglycine is a logical choice for initial studies to analyze the interaction of transition metal cations with peptides. Cu^+ has a closed shell $^1S(d^{10})$ ground state, and Ni^+ and Co^+ are open shell systems with a $^2D(d^9)$ and $^3F(d^8)$ ground states, respectively. Co^+ also has a quintet $^5F(4s^13d^7)$ and a singlet $^1G(3d^8)$ low excited states. In a previous study of the interaction of Co^+ with glycine developed in our group,[28] it was shown that the binding of Co^+ to glycine leads to an increase of the quintet–triplet difference and to a decrease of the singlet–triplet difference with respect to the naked atom. Thus, in addition to the triplet ground state of Co^+, we have considered only the singlet excited state of Co^+. To the best of our knowledge, the interaction of open shell cations with glycylglycine has not been considered from a theoretical point of view. It is thus interesting to analyze both the differences found among the conformers formed with glycylglycine and the metal cation affinity as a function of the electronic configuration of the metal cation.

Methods

Molecular geometries and harmonic vibrational frequencies of the considered structures have been obtained using the non-local hybrid three-parameter B3LYP density functional approach,[37–40] as implemented in the Gaussian 03 set of programs package. Previous theoretical calculations have shown that the B3LYP approach is a cost-effective method for study-

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ing transition metal ligand systems.[41–45] Even in difficult cases such as the M^+=CH_2 systems, B3LYP results compare well with the highly correlated CCSD(T) or multireference ACPF methods, as well as with the experimental values.[46] Moreover, a comparison of B3LYP with CCSD(T) concerning the interaction between Cu^+, Ni^+, Co^+ and the glycine molecule, confirm that B3LYP is sufficiently accurate for studying these kinds of system.[18,28] For the computation of the binding energies, atomic calculations have been performed assuming adequate d occupations, which correspond to a single determinantal representation of the desired atomic term.[45]

In order to explore the conformational space of this kind of system a previous conformational search of M^+-glycylglycine complexes has been done using the Monte Carlo Multiple Minimum (MCMM) procedure,[47] with the AMBER* force field,[48,49] as implemented in the Macromodel 7.0 package.[50] In a first approach Li^+ has been considered to model the electrostatic interactions of the metal cation with glycylglycine, because of the non existence of parameters for Cu^+, Ni^+ and Co^+. Among all the possible structures obtained only those lying within a range of 10 kcal mol^{-1} have been calculated at the B3LYP level. Moreover, some structures not obtained in the conformational search but chemically important and derived from experience and chemical intuition have also been computed.

Geometry optimizations and frequency calculations have been performed using the following basis sets. The metal basis is derived from (14s9p5d) primitive set of Wachters[51] supplemented with one s, two p, one d diffuse functions[52] and one f polarization function, the final contracted basis set being [10s7p4d1f]. For C, N, O and H we have used the 6-31++G(d,p) basis set. Thermodynamic corrections have been obtained assuming an ideal gas, unscaled harmonic vibrational frequencies and the rigid rotor approximation by standard statistical methods.[53] Net atomic charges and spin densities have been obtained using the natural population analysis of Weinhold *et al.*[54] Open shell calculations have been performed using an unrestricted formalism. For all calculations Gaussian 03 package has been employed.[55]

Results and discussion

Glycylglycine is known to exist in neutral form in the gas phase, the zwitterionic form not being a minimum.[56] However, since this form can be stabilized through the interaction with metal cations,[57] we have considered the coordination of the metal cation to both forms of glycylglycine. There exist five different basic sites on the ligand suitable for metal cation coordination: the terminal amino nitrogen (N), the terminal carbonyl oxygen (O), the hydroxyl oxygen (O_H), the carbonyl oxygen of the amide (O_a) and the amide nitrogen (N_a). The starting structures for the geometry optimizations of the neutral forms involve different coordination to the basic sites and were selected in order to maximize the metal cation–glycylglycine interaction. Some of them come from the molecular mechanics conformational search with Li^+ whereas some other chemical interesting structures, not found in this previous analysis, have been built from chemical intuition. For the zwitterionic form only the interaction of the metal cation with the terminal CO_2^- group has been considered.

The relative energy of the different coordinations is determined by several factors, the main ones being the electrostatic interaction between the ligand and the metal cation, the ligand polarization, the closed shell metal–ligand repulsion, the charge transfer and the deformation of the ligand in the complex. It should be noted that, contrary to what happens with alkali metal cations, different transition metal cations can adopt different coordination environments in order to maximize the attractive factors while minimizing the repulsive ones. This ability of transition metal cations is conferred by their varied electronic structures. As a result, a very diverse behavior of the different transition metal cations in front of the same ligand can be found.

We will first analyze in detail the minima obtained when $Cu^+(d^{10})$ ^1S is the metal cation. Then, we will present the structures found for $Ni^+(d^9)$ ^2D and $Co^+(d^8)$ ^3F and ^1S, and the differences observed on structural and energetic parameters will be discussed.

A. Cu^+–glycylglycine

Fig. 1 displays the minima obtained for Cu^+–glycylglycine system. The computed relative energies are shown in Table 1 and the variation of the peptide bond length and the deviation of the dihedral angle from planarity for each conformer are given in Table 2.

The most stable structure of the Cu^+–glycylglycine system is Cu1, in which Cu^+ is coordinated to the terminal amino and carbonyl oxygen groups, and the peptide bond adopts a *trans* conformation. This structure was not found by Shoeib *et al.*,[21] who gave as global minimum our second most stable structure, Cu2 (4.7 kcal mol^{-1} above Cu1). The metal cation in Cu2 is chelated to the terminal amino group and to the carbonyl oxygen of the amide, and a stabilizing hydrogen bond is established between terminal carbonyl group and the amide hydrogen. It should be mentioned that Cu2 is similar to the most stable structure of Cu^+–glycine.[16,18]

Cu3 structure, which lies 6.5 kcal mol^{-1} above Cu1, shows the same coordination as Cu2, but the terminal carboxyl group points towards the terminal amino, and so the hydrogen bond present in Cu2 is broken. The energy difference between Cu3 and Cu2 is about 1.8 kcal mol^{-1} and can be considered as an estimation of the hydrogen bond energy between the terminal carbonyl oxygen and the hydrogen amide. Cu4 is 6.9 kcal mol^{-1} above Cu1 and corresponds to the same structure as Cu1 but with the peptide bond in *cis* conformation.

Cu5 (7.2 kcal mol^{-1} above Cu1) structure presents a different mode of coordination, where both carbonyl oxygens, amide and terminal, are involved, and a hydrogen bond between the amide hydrogen and the terminal nitrogen is established. This structure was found to be the global minima when glycylglycine interacts with Na^+, and K^+,[9,15,24] showing that the nature of the interaction of glycylglycine with Cu^+ is rather different than that with alkali metal cations.

Cu6 and Cu7 structures (8.6 and 8.8 kcal mol^{-1} above Cu1, respectively) show the same coordination modes as Cu2 and Cu3 but the peptide bonds are in *cis* conformation. The remaining structures lie more than 13 kcal mol^{-1} above the most stable one and their instability is due to different reasons. Some of these structures correspond to the metal cation interacting with the hydroxyl oxygen instead of the terminal carbonyl oxygen (Cu8, Cu10 and Cu11). Other structures (Cu12 and Cu14) are either monocoordinated or correspond to zwitterionic conformations of the ligand (Cu9, Cu13 and Cu15).

Although zwitterionic structures lie high in energy, it is worth devoting a paragraph to them. If zwitterionic forms of peptides are understood as any structure with a charge separation due to an intramolecular proton transfer, Cu9 is the most stable zwitterionic form of Cu^+–glycylglycine system on this potential energy surface. This structure was found after the optimization of a structure in which Cu^+ was initially coordinated to the carboxylic group; that is, during the optimization process a spontaneous proton transfer from the OH of carboxylic group to CO of amide occurred and the final structure collapsed to Cu9. As a result a strong hydrogen bond between the protonated amide oxygen and the carboxylate group is formed. The relative short distance (1.389 Å) and the O–H–O angle (167°) close to linearity contribute to the stability of this form. Furthermore, due to this new hydrogen bond the interaction of Cu^+ with the carboxylate group becomes unsymme-

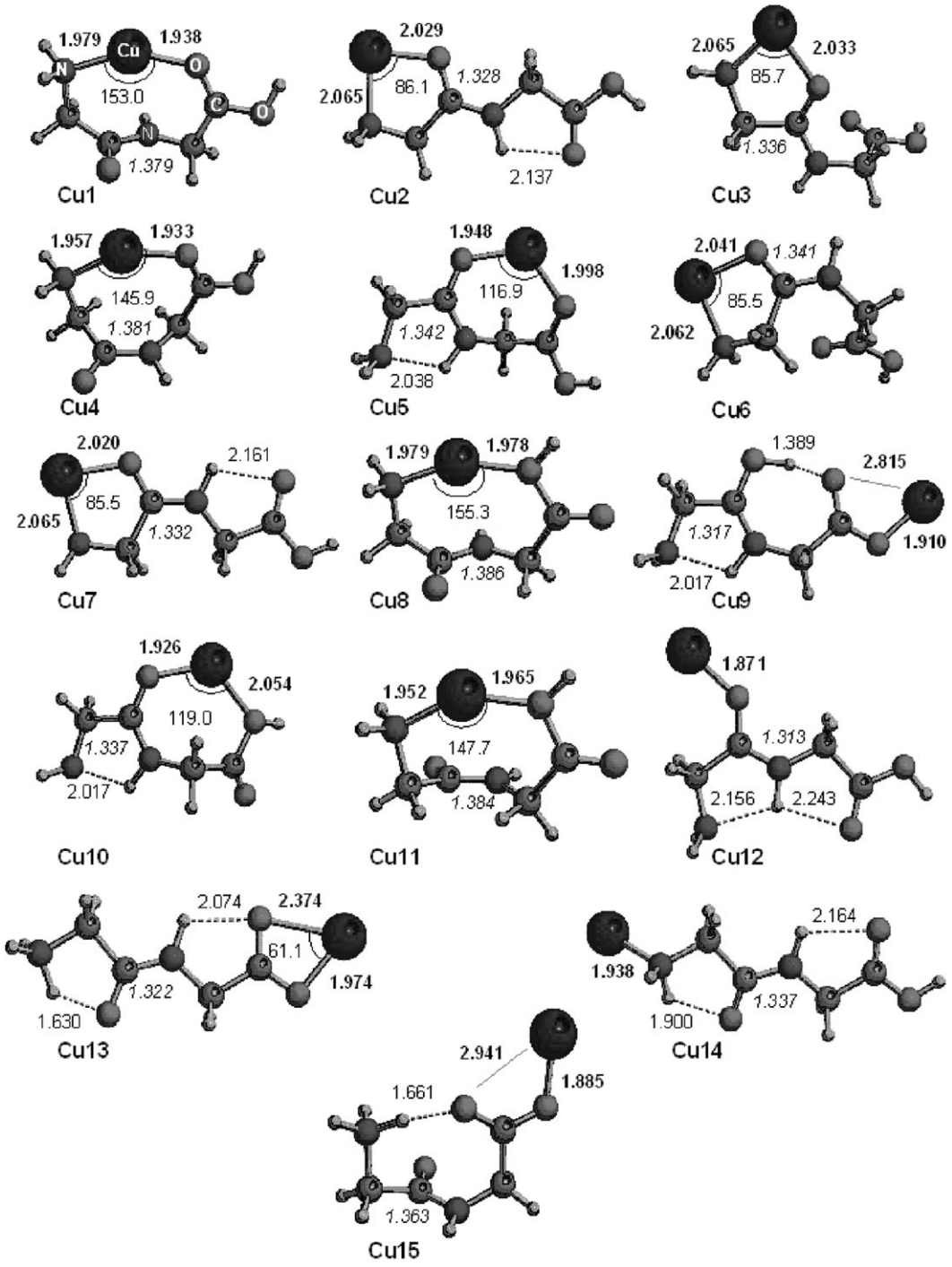

Fig. 1 B3LYP optimized geometries for the different minima of Cu^+–glycylglycine. Distances are in Ångstroms and angles are in degrees.

trical (1.910 and 2.816 Å). The other zwitterionic structures correspond to forms in which the protonated group is the amino one. Cu13 (20.8 kcal mol^{-1} relative to Cu1) is more stable than Cu15 (24.3 kcal mol^{-1}) basically due to the presence of an additional hydrogen bond and to the fact that the complex is bicoordinated and not monocoordinated as in Cu15.

After describing all the optimized structures it is possible to establish some trends related to the stability of the complexes. First of all, structures with peptide bond in *trans* conformation are more stable than those homologous structures having the peptide bond in *cis* conformation. See, for example, the pairs Cu1 and Cu4, structures Cu2 and Cu7, Cu3 and Cu6, or Cu8 and Cu11. Moreover, the zwitterionic and monocoordinated conformers are only found with the peptide bond in *trans* conformation.

Another interesting feature to analyze is which groups does Cu^+ prefer to interact with. In general, Cu^+ prefers those centers which show larger basicity, that is, the terminal amino nitrogen and the carbonyl oxygens. Among all the possibilities, the most stable structure (Cu1) corresponds to the Cu^+ cation coordinated to the two terminal groups forming an eight-member ring. This configuration allows a coordination environment around Cu^+ that approaches to linearity (α(NCuO) = 153.0°), which minimizes metal–ligand repulsion. As can be observed in Fig. 2, the highest d orbital of Cu in Cu1 is the d_{z^2} orbital which hybridizes with the 4s orbital in order to reduce the repulsion along the metal–ligand axis. In contrast, the electron density increases in the direction perpendicular to the z axis making difficult the interaction with a third basic center. Cu2 corresponds to the interaction with the amino nitrogen and the amide carbonyl oxygen (α(NCuO) = 86.1°).

Table 1 Relative potential energies (including ZPE) of M^+–glycylglycine structures (M = Cu, Ni, Co) in kcal mol^{-1}. In parenthesis, relative free energies

Structure	Coordination[a]		ΔE + ZPE (kcal mol^{-1})			
			Cu^+	Ni^+	Co^+(T)	Co^+(S)
M1	O,N	*trans*	0.0(0.0)	—	—	—
M1a	O,N,N_a	*trans*	—	0.0(0.0)	2.0(1.6)	0.7(0.0)
M1b	O,N,O_a	*trans*	—	2.5(2.7)	0.0(0.0)	0.0(0.1)
M2	O_a,N	*trans*	4.7(3.6)	2.2(0.8)	3.3(1.4)	9.6(7.4)
M3	O_a,N	*trans*	6.5(5.2)	4.1(2.5)	5.1(3.7)	11.7(9.4)
M4	O,N	*cis*	6.9(6.7)	—	—	—
M4a	O,N,N_a	*cis*	—	9.1(9.0)	8.3(7.9)	—
M5	O,O_a	*trans*	7.2(6.5)	5.5(4.6)	5.0(4.0)	14.0(12.4)
M6	O_a,N	*cis*	8.6(7.5)	6.0(4.7)	7.2(5.8)	13.2(11.1)
M7	O_a,N	*cis*	8.8(7.6)	6.1(4.5)	7.3(5.9)	13.2(11.0)
M8	O_H,N	*trans*	13.1(12.7)	—	—	—
M8a	O_H,N,N_a	*trans*	—	10.9(10.5)	12.5(12.0)	12.4(11.3)
M8b	O_H,O_a,N	*trans*	—	14.4(14.2)	11.6(11.2)	14.1(13.7)
M9	O,O(CO_2^-)	*trans*	15.8(14.2)	17.9(16.6)	16.2(14.9)	30.5(28.5)
M10	O_H,O_a	*trans*	16.4(15.4)	16.5(15.1)	15.3(13.8)	27.5(25.6)
M11	O_H,N	*cis*	18.9(18.4)	—	—	—
M11a	O_H,N,N_a	*cis*	—	18.5(18.0)	18.3(17.8)	—
M12	O_a	*trans*	19.8(17.1)	—	—	—
M13	O,O(CO_2^-)	*trans*	20.8(19.1)	20.7(19.1)	20.4(18.8)	31.1(28.1)
M14	N	*trans*	21.7(19.6)	—	—	—
M15	O,O(CO_2^-)	*trans*	24.3(23.4)	26.3(25.3)	25.3(24.4)	36.9(35.1)

[a] See text.

In this case, the highest d orbital (assuming N–Cu–O in the *xz* plane) is the d_{xz} one hybridized with the p_z orbital to reduce repulsion. Since the 4p orbitals of the metal cation are higher in energy than the 4s one, the polarization in the second structure is somewhat less effective. Note that metal–ligand distances are shorter in Cu1 than in Cu2.

According to the previous paragraph, the mechanism used by Cu^+ to reduce metal–ligand repulsion is related to the coordination angle and can be useful to classify the different conformers. First, four structures (Cu1, Cu4, Cu8, and Cu11) with a coordination angle around 150 degrees are found. The Cu–N bond lengths are the shortest for these eight-membered ring structures (1.95–1.98 Å), and the peptide bond length is increased compared to neutral glycylglycine (Δd_{pb} ranges from 0.033 to 0.040 Å). Furthermore, a significant charge transfer is observed, the net metal charge of Cu being 0.79. In a second group we can find five-membered ring complexes with a coordination angle of 85–86° (Cu2, Cu3, Cu6, and Cu7). These structures show Cu–N bond distances about 2.06 Å, and the peptide bond is slightly shortened compared to neutral glycylglycine (Δd_{pb} lies between −0.005 and −0.018 Å). This shortening is due to the interaction of the metal cation with the amide carbonyl oxygen, which stabilizes the –$(H)^+$N=C–(O^-)– resonant form of the peptide bond. In all these conformations a similar charge transfer takes place, the charge of Cu being 0.88. Finally, there is a third group that involves seven-membered rings structures with a coordination angle around 117–119° (Cu5 and Cu10). Cu–O_a distances are

Table 2 Variation of the peptide bond distance with respect to the most stable glycylglycine form (1.346 Å) and deviation of the peptide dihedral angle with respect to the planarity (in degrees)

Structure	Δpept. bond (C–N_a)				Δpept. dihedral angle (O_a–C–N_a–H)			
	Cu^+	Ni^+	Co^+(T)	Co^+(S)	Cu^+	Ni^+	Co^+(T)	Co^+(S)
M1	0.033	—	—	—	6.3	—	—	—
M1a	—	0.084	0.074	0.117	—	39.6	35.2	52.5
M1b	—	0.013	0.014	0.027	—	4.9	5.0	6.3
M2	−0.018	−0.020	−0.018	−0.023	0.9	1.0	0.8	0.8
M3	−0.010	−0.012	−0.010	−0.015	7.4	7.4	7.4	7.2
M4	0.035	—	—	—	3.6	—	—	—
M4a	—	0.105	0.086	—	—	13.9	1.5	—
M5	−0.004	−0.008	−0.006	−0.011	0.3	0.2	0.2	0.4
M6	−0.005	−0.008	−0.005	−0.012	2.0	2.8	2.2	3.1
M7	−0.014	−0.016	−0.013	−0.020	0.8	0.8	0.9	0.7
M8	0.040	—	—	—	15.9	—	—	—
M8a	—	0.091	0.082	0.120	—	42.3	38.4	53.0
M8b	—	0.006	0.008	0.017	—	3.3	3.0	4.1
M9	−0.029	−0.031	−0.030	−0.033	0.3	0.2	0.2	0.3
M10	−0.009	−0.011	−0.011	−0.015	0.5	0.9	0.5	1.6
M11	0.038	—	—	—	5.8	—	—	—
M11a	—	0.111	0.095	—	—	14.7	2.7	—
M12	−0.033	—	—	—	0.0	—	—	—
M13	−0.024	−0.022	−0.023	−0.020	0.1	0.0	0.1	0.1
M14	−0.009	—	—	—	0.9	—	—	—
M15	0.017	0.014	0.014	0.012	3.6	3.6	3.4	4.5

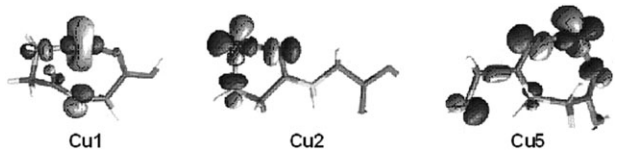

Fig. 2 HOMO orbitals of different Cu^+–glycylglycine structures.

shorter than the second group structures (1.93–1.95 Å *versus* 2.02–2.04 Å, respectively), while Cu–O_C and Cu–O_H distances are longer than in structures of the first group (2.00 Å *versus* 1.93–1.94 Å, and 2.05 Å *versus* 1.96–1.98 Å, respectively). The peptide bond length results also slightly decreased by the effect of coordination of Cu to carbonyl oxygen of the amide (Δd_{pb} lies between −0.004 and −0.009 Å) and metal charge (0.90) is similar to the second group.

For the zwitterionic forms, the two lowest conformations in energy (Cu9 and Cu13) show a shortening of the peptide bond length (−0.029 and −0.024 Å, respectively), whereas in Cu15 there is an enlargement of this bond length (Δd_{pb} = 0.017 Å). Note, however, that in Cu9 the carbonyl oxygen of the amide is protonated and in Cu13 this oxygen is involved in a hydrogen bond. Despite this difference, there is a similar charge transfer for these three structures and the net metal charge value lies between 0.85 and 0.88.

B. Ni^+–glycylglycine

Fig. 3 shows the optimized structures of Ni^+–glycylglycine. Ni^+ is a d^9 cation and the highest d orbital is monooccupied. In these conditions, the repulsion between the metal atom and the ligand is lower than for a d^{10} cation like Cu^+. In particular, if we take as a starting point the Cu1 eight-member ring

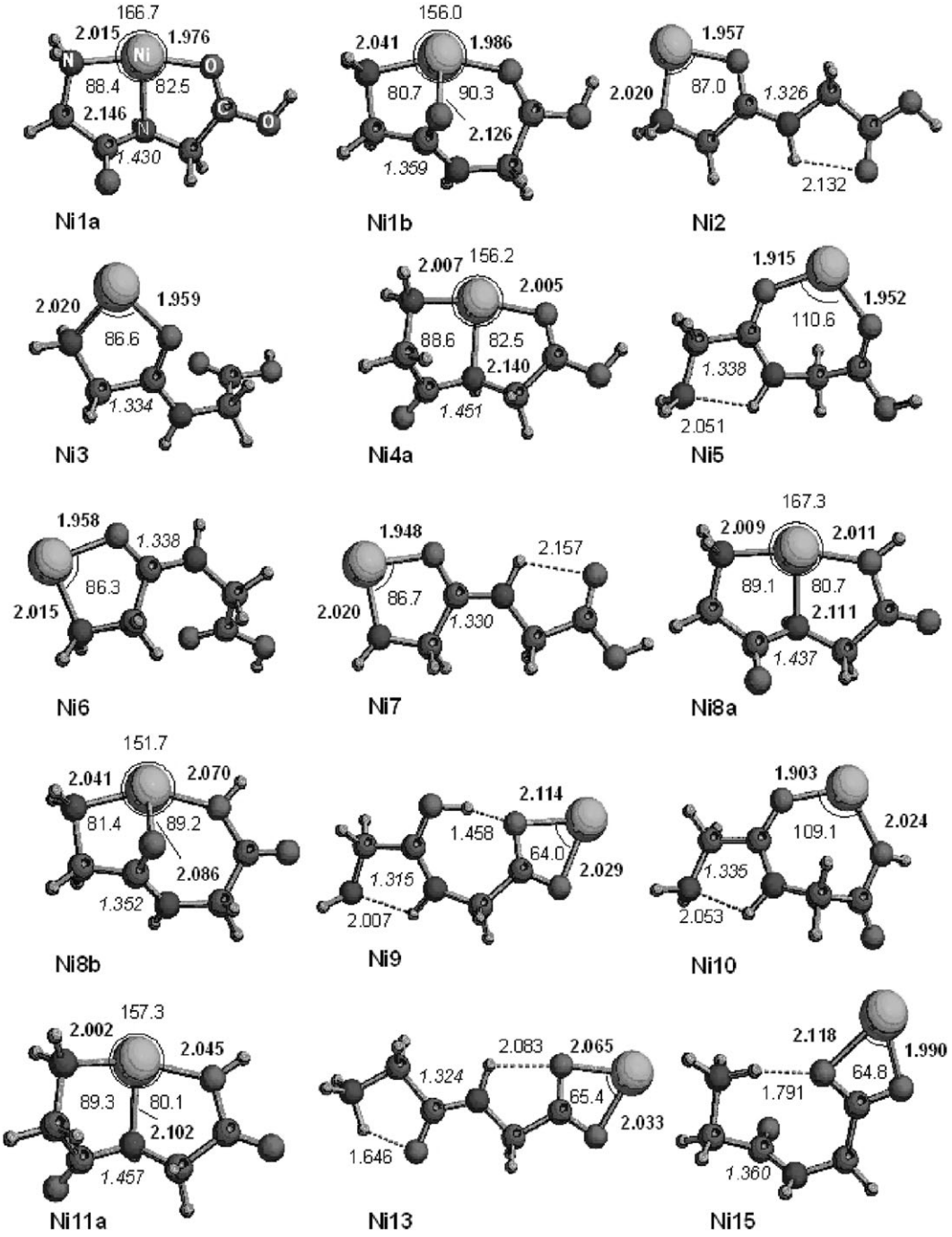

Fig. 3 B3LYP optimized geometries for the different minima of Ni^+–glycylglycine. Distances are in Ångstroms and angles are in degrees.

structure, the d_z^2 orbital of Ni is now monooccupied and the electron density in the perpendicular direction is much lower than in the case of Cu. This permits the attachment of another basic site, which can either be the amide nitrogen, resulting in the lowest energy conformer Ni1a, or the amide carbonyl oxygen (Ni1b, 2.5 kcal mol^{-1} higher than Ni1a). In general, it can be observed in Fig. 3 that all the eight-member ring type structures that were dicoordinated with Cu^+ present a third metal–ligand interaction when the metal cation is Ni^+. Therefore, the most important change observed in Ni^+–glycylglycine compared to Cu^+–glycylglycine is that tricoordinated structures are formed.

The structures equivalent to Cu8 also present both possibilities, coordination to the nitrogen or carbonyl oxygen of the amide bond (Ni8a and Ni8b, 10.9 and 14.4 kcal mol^{-1} above Ni1a, respectively). Again, the structure having the amide nitrogen coordinated to the metal cation is more stable than that coordinated by the amide oxygen. However, in the case of structures 4 and 11 only the coordination to the amide nitrogen is found (Ni4a and Ni11a, 9.1 and 18.5 kcal mol^{-1} above to Ni1a). This fact can be explained considering that now the peptide bond is in *cis* conformation, whereas the previous structures present a *trans* conformation. That is, the peptide bond in *cis* conformation hinders the interaction between the amide oxygen and Ni^+, since such an interaction would imply too large a deformation energy of the peptide.

As a general trend, it can be observed that the relative energies of Ni^+–glycylglycine conformers are smaller than those of Cu^+–glycylglycine. For example, the energy difference between Ni1a and Ni2 is 2.2 kcal mol^{-1}, while that between Cu1 and Cu2 is 4.7 kcal mol^{-1}. This reduction is observed for those structures in which coordination to Ni^+ is given by the amino terminus and the carbonyl oxygen of amide: Ni2, Ni3, Ni6, and Ni7 (2.2, 4.1, 6.0, and 6.1 kcal mol^{-1} higher in energy than Ni1a, respectively) in front of Cu2, Cu3, Cu6, and Cu7 (4.7, 6.5, 8.6, and 8.8 kcal mol^{-1} with respect to Cu1, respectively), and is due to the smaller metal–ligand distances when the metal ion is Ni^+.

As for Cu^+–glycylglycine, the Ni^+–glycylglycine neutral conformations can be classified according to the coordination angles. As mentioned, one should notice that some of the bicoordinated structures of Cu^+ (in particular those with the terminal NH_2 and COOH groups) become tricoordinated due to an additional interaction with the peptide bond. The structures of this group coordinated to the amide nitrogen show two five-membered rings. Furthermore, the coordination to the amide nitrogen results in a significant lengthening of the peptide bond (Δd_{pb} ranges from 0.084 to 0.111 Å), essentially due to the polarization of the electron density towards the metal cation. However, the structures coordinated to the amide carbonyl oxygen as a third site, show a five- plus a seven-membered ring structure. The characteristics of the other two groups are very similar to those found for the Cu^+–glycylglycine system.

For the zwitterionic conformations, the most remarkable difference compared to Cu^+ is the almost symmetrical coordination of Ni^+ to both oxygens of the CO_2^- group. This is due to the monoocupation of the highest d orbital of Ni^+, which results in a lower repulsion of the metal with the lone pairs of the coordinating oxygens. Monocoordinated structures have not been computed due to the fact that they remain quite high in energy for Cu^+–glycylglycine and do not contribute any additional information. Finally, it is worth noting that the spin density of Ni is similar for all conformers, and lies between 0.91 and 0.95, as expected for a d^9 metal cation.

C. Co^+–glycylglycine

Co^+ has a d^8 metal configuration, which implies that both triplet and singlet states may exist. Although the triplet spin state is the lowest one with small ligands, the singlet–triplet energy gap decreases as the metal coordination number is increased.[28] Thereby for each complexation structure both spin states have been computed. The open shell nature of Co^+ cations makes necessary to consider different electronic states arising from the 3d metal orbital occupation. However, a previous Co^+–glycine study showed that the most stable electronic metal occupation is that which minimizes the metal ligand repulsion.[28]

Fig. 4 shows the obtained minima for Co^+–glycylglycine whereas the computed relative energies are given in Table 1. As for Ni^+–glycylglycine, the monocoordinated complexes found in Cu^+–glycylglycine have not been considered as they remain high in energy on the potential energy surface. At first glance we can observe three basic modes of coordination of Co^+ cations interacting with neutral glycylglycine, as occurred with Ni^+: one involving three donor centers and two modes involving only two donor atoms. As for free glycylglycine, the comparison between analogous structures differing only in the *cis*/*trans* peptide bond conformation makes evident the preference to adopt a *trans* conformation.

For both spin multiplicities the most stable structure of Co^+–glycylglycine is Co1b, the triplet spin state being more stable by 17.9 kcal mol^{-1}. This structure arises from Cu1 but with an additional interaction with the peptide bond, more concretely with the amide oxygen. The tricoordinated structure with the amide nitrogen, Co1a, is the second most stable conformation for both spin states and lies only 2.0 kcal mol^{-1} (triplet state) and 0.7 kcal mol^{-1} (singlet state) higher in energy. This is in contrast to Ni^+ for which the most stable structure was Ni1a, with Ni^+ bound to the amide nitrogen. As for Ni^+ complexes, other tricoordinate structures arising from the bicoordinated Cu4, Cu8 and Cu11 of Cu^+ have been found to be stable. For Co4 and Co11, with the peptide bond in a *cis* conformation, we have only located the tricoordinated structure in which Co^+ interacts with the amide nitrogen ("a" forms). Moreover, these structures only exist in the triplet state. The relative energies of the remaining structures vary depending on the spin state.

Triplet States. As a general trend, the relative energies of the different minima of Co^+–glycylglycine are slightly smaller than those computed for Cu^+. Compared to Ni^+, results are quite similar except for a few cases. The most noticeable difference is that the "b" forms (interaction through the amide O) become more stable than the "a" ones (interaction with the amide N). This is in agreement with the fact that the difference between the N and O metal cation affinity decreases from Ni^+ to Co^+. Note for example that the interaction energy of M^+–NH_3 is larger than that of M^+–H_2O by 14.7 kcal mol^{-1} in the case of Ni^+ whereas it is 13.3 kcal mol^{-1} for Co^+. This fact makes the conformations Co5 and Co10, both involving two oxygen atoms, to appear slightly more stabilized in comparison to their Ni^+ analogues.

With respect to the zwitterionic forms, the obtained structures are similar to those of Ni^+, the metal cation interacting almost symmetrically with both oxygen atoms of CO_2^-. Furthermore, among this kind of conformation Co9 is the most stable one, lying 16.2 kcal mol^{-1} above Co1b. It should be noted that, for all metals, the zwitterionic structures of M^+–glycylglycine are less stable than the corresponding M^+–glycine complexes.

The natural population analysis shows that for almost all structures the metal charge ranges between 0.86 and 0.91, following a similar behavior as Cu^+ and Ni^+. However, these values decrease to about 0.77 when the amide N takes part in the M–L interaction, denoting a slight charge transfer from the glycylglycine moiety to the metal cation. For all the computed conformations the spin density is almost entirely located over

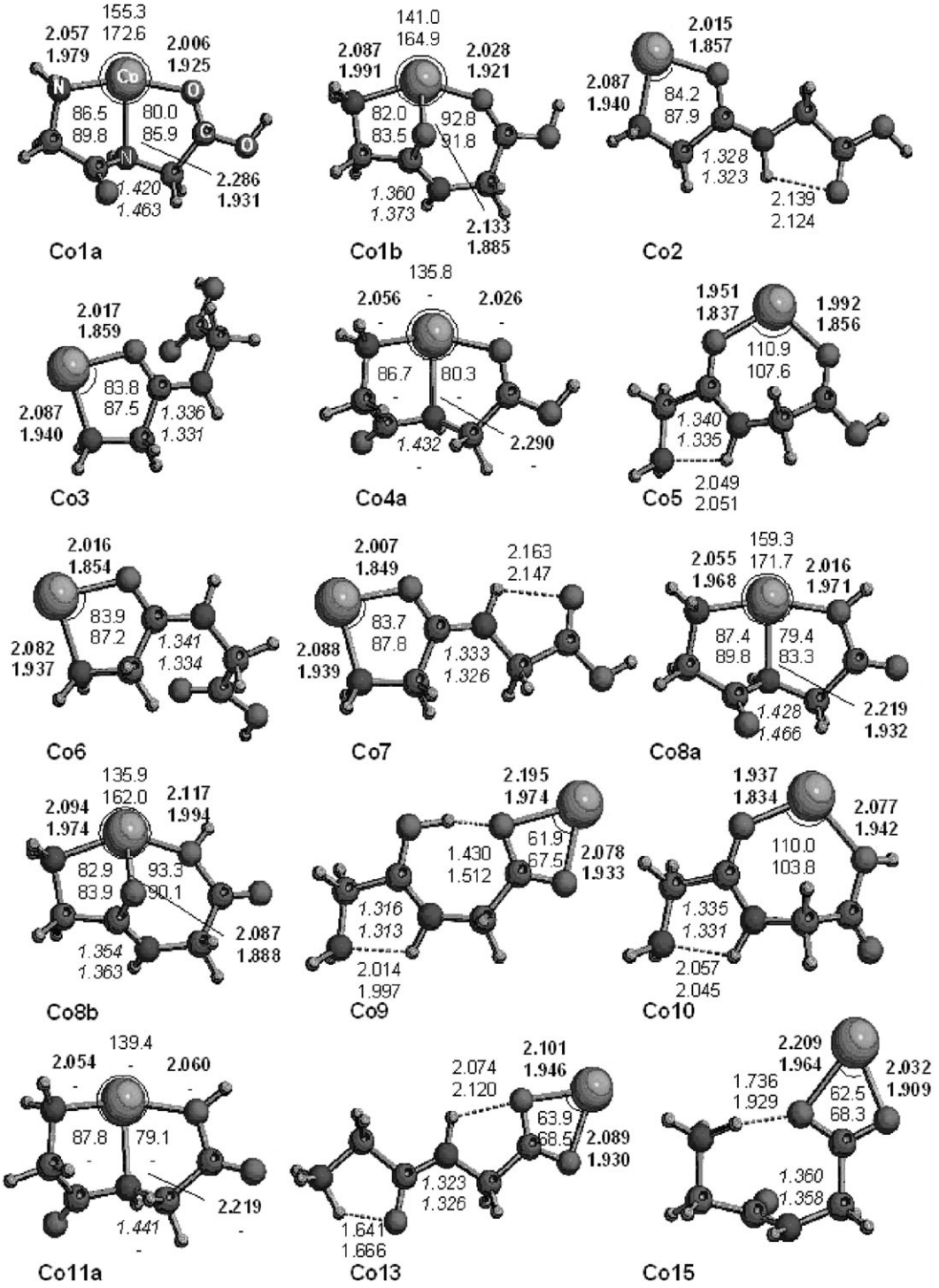

Fig. 4 B3LYP optimized geometries for the different minima of Co^+–glycylglycine, where the upper number stands for the triplet state and the lower for the singlet. Distances are in Ångstroms and angles are in degrees.

the Co atom, presenting values between 1.92 and 1.96. As expected, the highest monooccupied orbital in Co1a corresponds to the antibonding combination of the $d\sigma$ metal orbital with the nitrogen and amide oxygen lone pairs of glycylglycine. As found for Co^+-glycine systems, this orbital is slightly polarized through *sd* or *pd* hybridization in order to reduce the Pauli repulsion.

Singlet states. For singlet spin states Co1b and Co1a are also the most stable conformations (as found for triplets), but both forms are now nearly degenerate (0.0 and 0.7 kcal mol^{-1}, respectively). The ordering of the rest of the structures presents significant differences compared to the triplet state. An important difference is that tricoordinated forms having a *cis* peptide bond conformation, Co4 and Co11, do not exist in the singlet state. Moreover, it can be observed in Table 1 that, with the exception of tricoordinated structures Co8a and Co8b, relative energies are significantly larger than in the triplet states or those computed for Cu^+ and Ni^+ analogues. This fact is especially remarkable in the case of Co5 and Co10 structures, both of them coordinated to carbonyl oxygens, which shows the preference of ^1G state of Co^+ to bind to other basic centers, such as the amino group or the amide N.

Another important difference is the huge destabilization of the zwitterionic forms Co9, Co13 and Co15 (between 10.7 and 14.3 kcal mol^{-1}) compared to the other M^+–glycylglycine studied systems. In the singlet state, one d orbital is empty

and so, a larger L → M charge transfer is expected. In fact, the natural population analysis shows that this is the situation and, except for Co1b (0.86), the metal net charge varies between 0.58 and 0.76. As found previously, those structures involving the metal interaction with the amide N present more charge transfer from the ligand to the d empty Co^+ orbital. Therefore, it is not surprising that O,O coordinated structures become less stable in this spin state.

The unoccupied d orbital in Co1b corresponds to the highest singly-occupied orbital in the triplet state. This empty $d\sigma$ orbital allows a better L → M charge transfer and, as a consequence, the M–peptide bond interaction becomes much stronger than in the other cases. Therefore the cation can adopt a coordination environment closer to the square-planar (the angles present values of about 162.0–172.6) than in triplets (135.8–155.3) or than in the Ni^+ analogues (156.2–167.3), which is an important factor to stabilize this kind of structures.

D. Comparison of the three metal cations

For the set of the studied cations the atomic radii decrease following the order $Co^+(^3F)$ > $Ni^+(^2D)$ > $Cu^+(^1S)$ > $Co^+(^1G)$. So, the expected trend in M^+–L distances should parallel the decrease from Co^+ (triplets) to Co^+ (singlets). However, some divergences can be found. For example, in N,O bicoordinated structures such as Cu2 or Cu6, the Cu^+–L distances can be larger than Ni^+–L ones (see M^+–O distances as example) and even, in some cases, larger than Co^+ (triplet state). In fact, these trends were already found when comparing Cu^+, Ni^+, Co^+–glycine systems,[18,28,35] and can be explained considering that in Cu^+ all the d orbitals (see Fig. 2) are doubly occupied, which increases the M–L repulsion, the Cu^+–L distances increasing compared to Ni^+–L. On the other hand, from Fig. 4 it can be observed that Co^+–L distances are shorter in the singlet structures. This is due to the smaller size of the singlet Co^+ cation and to the d empty orbital.

The interaction of metal cations with neutral glycylglycine induces activation of the ligand moiety, especially of the peptide bond skeleton. Except for the structures of the first group (tricoordinated structures in the case of Ni^+ and Co^+), the M–L interaction leads to a shortening of the peptide bond ($C–N_a$ distance). However, this does not hold true for the first group structures, where an enlargement of this bond is observed. This variation is more pronounced in the "a" forms, when the interaction occurs with the amide N. Moreover, in these cases the values of the peptide dihedral angle deviate significantly from planarity. Both effects manifest in a greater distortion of the peptide skeleton, which in turn is a consequence of the larger charge transfer from the ligand to the metal in these conformations. Thus, the largest variations are observed for Co^+ in the singlet state.

Interaction energies. Table 3 shows the computed D_e, D_0, ΔH^0_{298} and ΔG^0_{298} values for the most stable M^+–glycylglycine structures, Cu1, Ni1a, Co1b (for both triplet and singlet). Considering that the bonding is mainly electrostatic and that ionic radii decrease from left to right in the row, one would expect an increase of the M–L interaction energy values as the atomic number increases. However, when comparing the D_e values of these complexes, it can be observed that the binding energy increases from Co^+ (triplet) to Ni^+ and then it decreases from Ni^+ to Cu^+, the Co1b and Cu1 interaction energies being very similar. In fact, this trend has been already described for glycine and other ligands such as H_2O,[58–63] NH_3,[63,64] or adenine[65] and is correlated with the size of the metal cation and the metal–ligand repulsion. As commented previously, although $Cu^+(d^{10})$ has the smallest ionic radius of the three, the metal *3d* orbital interacting with the ligand becomes doubly occupied, which significantly increases the metal ligand repulsion and consequently, the interaction energy decreases. On the other hand, it should be noted that the binding energies of M^+–glycylglycine are about 11–13 kcal mol^{-1} larger than those of M^+–glycine. This is due to the existence of more basic centers and additional metal–ligand interactions (for Ni^+ and Co^+) and to the fact that the ligand is larger, which allows a better ligand disposition to interact with the metal (for Cu^+). Previous results have shown that linear bisligated Cu^+ complexes are specially stable due to an efficient $sd\sigma$ hybridization of Cu^+ which allows decreasing the electron density (and thus, M–L repulsion) along the coordination axis.

Table 3 Interaction energies (D_e, D_0, ΔH°_{298} and ΔG°_{298}) in kcal mol^{-1} of M^+–glycylglycine and M^+–glycine

	M^+–glycylglycine			
	Cu^+ ^1A	Ni^+ ^2A	Co^+ ^3A	^1A
D_e	87.5	95.3	87.2	61.5
D_0	85.6	93.4	85.7	59.4
ΔH^0_{298}	86.4	94.3	86.5	60.7
ΔG^0_{298}	76.8	84.2	76.8	48.6
	M^+–glycine			
D_e	75.4[a] (68.1)[d]	84.6[b]	74.2[c] (72.4)[d]	

[a] Ref. 18. [b] Ref. 29. [c] Ref. 28. [d] Determined at the CCSD(T) level using the B3LYP geometries.

Conclusions

This paper presents a computational study of the binding of $Cu^+(d^{10})$, $Ni^+(d^9)$ and $Co^+(d^8)$ cations to neutral and zwitterionic glycylglycine. For both open-shell metal cations only the most stable electronic states arising from the doublet ($3d^9$) state of Ni^+ and the triplet and singlet ($3d^8$) states of Co^+ have been considered. Neutral structures can be divided into three groups depending on the coordination angles, which are related to the size of the rings formed. The comparison of the relative energies manifests different trends in the stabilization of the studied conformations depending on the cation and on the peptide conformation. The most relevant one is that Cu^+ only binds up to two atoms, the lowest energy conformer being that in which the metal cation adopts a nearly linear coordination with the terminal carbonyl oxygen and the amino group (Cu1). In contrast, Ni^+ and Co^+ present three-coordinated structures. Both for Ni^+ and singlet and triplet Co^+, the most stable structures arise from Cu1 but present a third M–L interaction through the peptide bond, which can either take place through the N or the O atom. Although both tricoordinated structures are close in energy ~ 2 kcal mol^{-1}, results seem to suggest that Ni^+ prefers interacting with the amide N (Ni1a), whereas Co^+ prefers binding to the amide O (Co1b).

The metal interaction with the peptide skeleton induces structural changes. Except for the tricoordinated structures, the interaction of the metal cation to the amide oxygen shortens the peptide bond. However, this bond is significantly elongated when the metal interaction takes place through the amide nitrogen. In these latter cases the weakening is accompanied by a charge transfer from the glycylglycine moiety to the metal cation. As for glycine, the binding energy (D_e) follows the order Ni^+ > Co^+ (triplet) ~ Cu^+, but the interaction energies are about 11–13 kcal mol^{-1} larger.

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