Ab initio Calculations for Exploring Metal Ion-(Gly-Gly-His) Complexes

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The specific interactions in metal ion-peptide systems have been studied in many research groups. It is known that the coordinated metal ions play a significant role in the biological action of peptide. Several experimental techniques have been applied to present of specific interactions in metal ion-peptide complexes.[1-8] Conformations of metal ion binding to peptides may have a critical impact on the peptide folding processes and peptide biological functions. Among metal ions, Cu^{2+} and Ni^{2+} have been widely studied and seem to have most interesting chemistry. Yang *et al.* reported that the specific interactions of peptides and metals could be applied for the fabrication of solid-state metal-ion biosensors.[4] Fisher *et al.* developed an electrode modified with the oligopeptide Gly-Gly-His with an extraordinarily low detection limit in the sub-ppt range (pM) for Cu^{2+} ions.[2]

Theoretical approaches about metal-oligopeptide structure and metal-ligand coordination geometry have been also performed by molecular dynamics simulations and ab initio calculations.[9-13] Studies have focused on the structural data of metal ion-ligand complexes. Four-coordination geometries were mainly discussed because they are most frequently encountered in the metal-binding sites of metalloproteins. Two- and six-coordination geometries were also considered.[10,11] Several groups reported the interactions between the special oligopeptides of three or four amino acid residues and metal ion because those oligopeptides are principally capable of providing the saturated (four electron donor atoms) equatorial binding site.[1,2,6,13]

In this study, our attention is focused on the interaction between the oligopeptide of three amino acid residues (Gly-Gly-His) and metal ion without solvent effect. (The response of the Gly-Gly-His modified electrode to Cu^{2+} ion was measured as a current in the solution experiment of Fisher *et al.*[2]) The interaction between Gly-Gly-His and metal ion is studied by optimized structures and stabilization energies in *ab initio* calculations. *Ab initio* calculations are performed with 6-31G(d) and 6-311+G(d,p) basis sets to determine optimized structures and stabilization energies. Density functional theory(DFT) at B3LYP level is carried out using Gaussian98[14] series of program. The optimized structures and the stabilization energies between Gly-Gly-His and metal ions (Ca^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}) are reported. Vibration frequencies are also calculated at B3LYP level to confirm that all the optimized geometries correspond to true minima on the potential energy surface. Zero-point energy

corrections are not included in stabilization energies.

The stabilization energies are calculated as the difference between the sum of the optimized energies in the reactants and the sum of the energies in the products for the reaction

$$M^{2+} + \text{Gly-Gly-His} + 3CH_3OH$$
$$\rightarrow [M^{2+}\text{-(Gly-Gly-His} - 3H^+)]^{-1} + 3(CH_3OH_2)^+$$
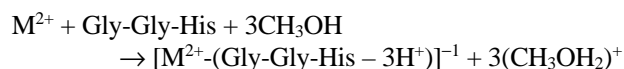
This system originated from the mass spectrum report of Fisher *et al.*.[2] The psudo-parent negative ion $[Cu^{2+}\text{-(Gly-Gly-His} - 3H^+)]^{-1}$ complex in the methanol solvent condition was observed at m/z 331.02 Da by the collision-induced dissociation using electrospray ionization Fourier transform ion cyclotron resonance mass spectroscopy (ESI-FT-ICR-MS).

The structural features of $[Cu^{2+}\text{-(Gly-Gly-His} - 3H^+)]^{-1}$ complex are shown in Figure 1. The $[Cu^{2+}\text{-(Gly-Gly-His} - 3H^+)]^{-1}$ complex is seen to possess a planar structure between Cu^{2+} and four nitrogen central atoms (4N) because the planar structure is known as the most stable structure in the four-coordination complex geometries.[2,6] The $-COO^-$ functional group of histidine could be a ligand for the four-coordination complex geometries. However, the mass spectra[2,7] supported that the Figure 1 structure (Cu^{2+}-4N) is the main structure because the most common fragment ion was observed at 287.03 Da which corresponds to decarboxylation from the histidine.

Optimized structures for metal ion complexes of Gly-Gly-His oligopeptide are shown in Figure 2. Three atoms (metal cation, N_1 and N_2) are shown to the same plane in the structures of Cu^{2+}, Ni^{2+} and Ca^{2+} complexes in Figure 2. The
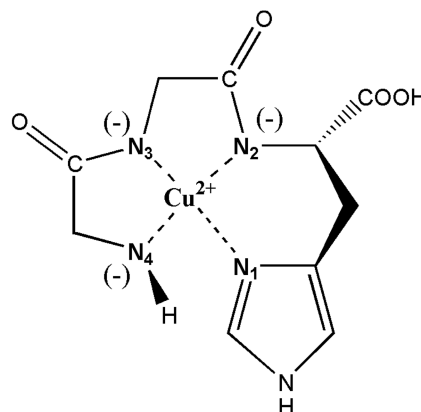
Figure 1. Structure of $[Cu^{2+}\text{-(Gly-Gly-His} - 3H^+)]^{-1}$ complex.
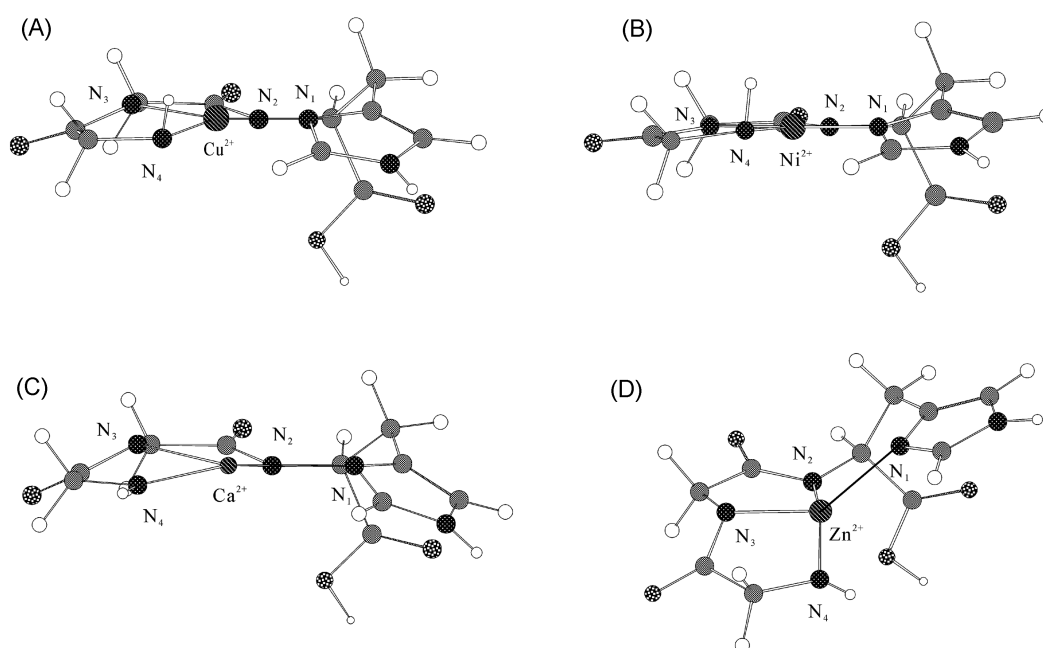
Figure 2. Optimized structures of (A) $[Cu^{2+}\text{-}(Gly\text{-}Gly\text{-}His - 3H^+)]^{-1}$ complex, (B) $[Ni^{2+}\text{-}(Gly\text{-}Gly\text{-}His - 3H^+)]^{-1}$ complex, (C) $[Ca^{2+}\text{-}(Gly\text{-}Gly\text{-}His - 3H^+)]^{-1}$ complex, and (D) $[Zn^{2+}\text{-}(Gly\text{-}Gly\text{-}His - 3H^+)]^{-1}$ complex at B3LYP/6-311+G(d,p) level.

$[Cu^{2+}\text{-}(Gly\text{-}Gly\text{-}His - 3H^+)]^{-1}$ and $[Ni^{2+}\text{-}(Gly\text{-}Gly\text{-}His - 3H^+)]^{-1}$ complexes have almost planar geometries between metal ion and 4N in the optimized structures. However, The $[Ca^{2+}\text{-}(Gly\text{-}Gly\text{-}His - 3H^+)]^{-1}$ complex has some deviation from a planar geometry and the $[Zn^{2+}\text{-}(Gly\text{-}Gly\text{-}His - 3H^+)]^{-1}$ complex does not have a planar geometry between metal ion and 4 N in the optimized structure as other results.[10,11]

The selected geometrical parameters for the optimized [metal ion-(Gly-Gly-His – $3H^+$)]$^{-1}$ complexes are summariz-ed in Table 1. Bond distances, bond angles and dihedral angles of the central part in the [metal ion-(Gly-Gly-His – $3H^+$)]$^{-1}$ complex are listed. The bond distances, and the bond angles are at the 1.834 Å-2.575Å and 72.0°-129.3° ranges respectively. From the consideration of ideal square planar bond distance (equivalent bond distance) and bond angle (90°) in the metal-ligand complex, it seems that there are geometric constraints in the [metal ion-(Gly-Gly-His – $3H^+$)]$^{-1}$ complexes. Table 1 also shows dihedral angles in the

Table 1. The selected geometrical parameters for the optimized [metal ion-(Gly-Gly-His – $3H^+$)]$^{-1}$ complexes at B3LYP/6-311+G(d,p) level

	Bond Distance (Å)				
	N_1--metal	N_2--metal	N_3--metal	N_4--metal	Average (Δ^a)
$[Cu^{2+}\text{-}(Gly\text{-}Gly\text{-}His–3H^+)]^{-1}$	2.052	2.012	1.910	1.973	1.987 (0.142)
$[Ni^{2+}\text{-}(Gly\text{-}Gly\text{-}His–3H^+)]^{-1}$	1.915	1.925	1.834	1.908	1.896 (0.091)
$[Ca^{2+}\text{-}(Gly\text{-}Gly\text{-}His–3H^+)]^{-1}$	2.575	2.402	2.239	2.240	2.364 (0.336)
$[Zn^{2+}\text{-}(Gly\text{-}Gly\text{-}His–3H^+)]^{-1}$	2.191	2.031	1.981	1.950	2.038 (0.241)
	Bond Angle (°)				
	N_1-metal-N_2	N_2-metal-N_3	N_3-metal-N_4	N_4-metal-N_1	Δ^b
$[Cu^{2+}\text{-}(Gly\text{-}Gly\text{-}His–3H^+)]^{-1}$	91.7	83.5	87.1	97.7	14.2
$[Ni^{2+}\text{-}(Gly\text{-}Gly\text{-}His–3H^+)]^{-1}$	94.1	84.8	87.4	93.7	9.3
$[Ca^{2+}\text{-}(Gly\text{-}Gly\text{-}His–3H^+)]^{-1}$	81.4	72.0	76.5	129.3	57.3
$[Zn^{2+}\text{-}(Gly\text{-}Gly\text{-}His–3H^+)]^{-1}$	88.9	83.7	89.3	107.8	24.1
	Dihedral Angle (°)				
	N_1-N_2-N_3-N_4			N_1-N_2-N_3-metal	
$[Cu^{2+}\text{-}(Gly\text{-}Gly\text{-}His–3H^+)]^{-1}$	3.8			0.0	
$[Ni^{2+}\text{-}(Gly\text{-}Gly\text{-}His–3H^+)]^{-1}$	0.4			0.3	
$[Ca^{2+}\text{-}(Gly\text{-}Gly\text{-}His–3H^+)]^{-1}$	9.8			13.1	
$[Zn^{2+}\text{-}(Gly\text{-}Gly\text{-}His–3H^+)]^{-1}$	39.6			26.3	

^{a}The difference between the longest bond and the shortest bond distance. ^{b}The difference between the biggest bond and the smallest bond angle.

[metal ion-(Gly-Gly-His – 3H$^+$)]$^{-1}$ complex. The dihedral angles (0.0°-39.6° ranges) also support that there are some geometric constraints in the [metal ion-(Gly-Gly-His – 3H$^+$)]$^{-1}$ complexes.

In case of bond distance, the [Ni^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ planar complex shows similar bond distances in the Ni^{2+}-N$_i$ (i = 1, 2, 3, and 4) bonds. The difference between the longest bond and the shortest bond distance is 0.091 Å. However, the [Cu^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ and [Ca^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ complexes show 0.142 Å and 0.336 Å bond distance differences respectively. The calculation results in the bond angles show the same tendency with those of the bond distances in Table 1. The [Ni^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ complex have similar bond angles in the Ni^{2+}-N$_i$ (i = 1, 2, 3, and 4) bonds. The difference between the biggest bond and the smallest bond angle is 9.3°. However, the [Cu^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ and [Ca^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ complexes show 14.2° and 57.3° bond angle differences respectively.

The dihedral angles in Table 1 show the planar structure for the [Ni^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ complex. The N$_1$-N$_2$-N$_3$-N$_4$ and N$_1$-N$_2$-N$_3$-metal dihedral angles are almost zero in the [Ni^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ complex because the Ni^{2+}-4N geometry has a planar structure. However, the [Cu^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ complex has 3.8° deviation from a planar geometry in the N$_1$-N$_2$-N$_3$-N$_4$ dihedral angle and the [Ca^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ complex has about 10° deviation from a planar geometry in the dihedral angles.

The stabilization energies in each of the metal ion-oligopeptide complexes are listed in Table 2. The stabilization energies are shown in the 49.0 ~ (−225.1) kcal/mol range at the B3LYP/6-311+G(d,p) level. The stabilization energy of 49.0 kcal/mol for the [Ca^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ complex shows that the sum of the reactants energies is lower than the sum of the products energies. So, it is not appropriate for Ca^{2+} ion to construct the four-coordination planar structure as it is known. This result is consistent with the result of Table S1 in the report of Fisher *et al.*.[2] (Ca^{2+} ion did not show significant interference with the Cu^{2+} measurement until the addition of 10 mM of Ca^{2+} ion to a solution of 9.8 pM of Cu^{2+} ion.)

The −161.1 kcal/mol and −225.1 kcal/mol of stabilization energies for the [Ni^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ complex and [Cu^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ complex show that four-coordination planar geometries are appropriate for Ni^{2+} and Cu^{2+} ions. These results are also consistent with the electrode experimental data that none of the other metal ions except Ni^{2+} ion showed significant interference with Cu^{2+} ion current in the report of Fisher *et al.*. So, the decrease of deviation from a planar geometry (the decrease of the dihedral angles and decrease of the differences of bond distances and angles) in the [metal ion-(Gly-Gly-His – 3H$^+$)]$^{-1}$ complex is resulted to the bigger stabilization energies for Ni^{2+} and Cu^{2+} ions. In the case of Zn^{2+}, even though the [Zn^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ non-planar structure has –115.0 kcal/mol of stabilization energy at the B3LYP/6-311+G(d,p) level, Zn^{2+} ion could not affect the Cu^{2+} ion current in the Table S1 of Fisher *et al.*.[2] It seems that the activation energy for replacing the [Cu^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ planar structure to the [Zn^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$ non-planar structure is the energy barrier in the addition experiment of Zn^{2+} ion to a Cu^{2+} ion solution.

The potential for peptide-modified electrodes to be used as metal ion sensors with extraordinarily low detection limits is seemed to depend on the geometrical structure. However, further calculations are needed for the better understanding because our calculation results did not consider the solvent effects in the optimized structures and the interaction energies.

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Table 2. Stabilization energies of [metal ion-(Gly-Gly-His–3H$^+$)]$^{-1}$ complexes (kcal/mol)

	B3LYP/6-31G (d)	B3LYP/6-311+G (d,p)
[Cu^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$	−171.2	−161.1
[Ni^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$	−236.2	−225.1
[Ca^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$	71.6	49.0
[Zn^{2+}-(Gly-Gly-His – 3H$^+$)]$^{-1}$	−133.2	−115.0