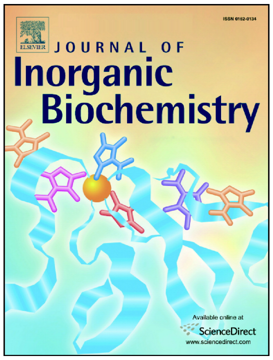

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Computational and Crystallographic Study of Hydrogen Bonds in the Second Coordination Sphere of Chelated Amino Acids with a Free Water Molecule: Influence of Complex Charge and Metal Ion

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1. Abstract

Hydrogen bonds of glycine complexes were calculated using quantum chemistry calculations at M06L-GD3/def2-TZVPP level and by analyzing the crystal structures from the Cambridge Structural Database (CSD). One hydrogen bond where amino acid plays the role of the H-donor (NH/O), and two where it plays the role of the H-acceptor (O1/HO, O1 is a coordinated oxygen atom, and, O2/HO, O2 is a non-coordinated oxygen atom) were investigated. The calculations were done on octahedral nickel(II), square pyramidal copper(II), square planar copper(II), palladium(II), and platinum(II) glycine complexes with different charges adjusted using water(s) and/or chlorine ion(s) as the remaining ligands. For NH/O hydrogen bond, interaction energies of neutral complexes are the weakest, from -5.2 to -7.2 kcal/mol for neutral, stronger for singly positive, from -8.3 to -12.1 kcal/mol, and the strongest for doubly positive complex, -16.9 kcal/mol. For O1/HO and O2/HO interactions, neutral complexes have weaker interaction energies (from -2.2 to -5.1 kcal/mol for O1/HO, and from -3.7 to -5.0 kcal/mol for O2/HO), than for singly negative complexes (from -6.9 to -8.2 kcal/mol for O1/HO, and from -8.0 to -9.0 kcal/mol for O2/HO). Additionally to the complex charge, metal oxidation number, coordination number, and metal atomic number also influence the hydrogen bond strength, however, the influence is smaller.

Keywords: hydrogen bonds, amino acids, metal complexes, crystal structures, density functional theory (DFT), Cambridge Structural Database (CSD)

1 Introduction

Hydrogen bonds are one of the most relevant noncovalent interactions in biological systems, where some of the most important roles are in the determination of the protein secondary structure and the formation of the double helix structure of DNA. [1–6] It has been shown that when a molecule coordinates to a metal, it can result in a substantial strengthening of hydrogen bonds of the coordinated molecule. [7,8] The quantum chemistry results confirmed that the interaction energy of the hydrogen bond between two free water molecules (-4.84 kcal/mol) could be increased up to -9.7 kcal/mol when a hydrogen donor (H-donor) water molecule is coordinated in the neutral complex and up to -21.9 kcal/mol when the complex is doubly positively charged. [7,8] Coordination to metal ions can also increase the NH/O hydrogen bond strengths, which was shown for interactions of ammonia and ethylenediamine with a free water molecule. [9,10] In the case of hydrogen bonds between ammonia, as a H-donor, and water molecule, the interaction energy increases from -2.3 kcal/mol for free ammonia up to -6.3 kcal/mol for neutral ammonia complexes and up to -25.0 kcal/mol for triply positively charged ammonia complex. [9] The interaction energy of ethylenediamine, as a H-donor, and water molecule ranges from -2.3 kcal/mol for free ethylenediamine up to -6.7 kcal/mol for neutral ethylenediamine complex and up to -28.0 kcal/mol for triply positive complex. [10]

The amino acids are found in different complexes, both with other ligands and as bis- and tris- amino acid complexes. [11–15] Amino acids can form many types of metal ion complexes. One of the ways in which an amino acid binds to a metal ion is via α-amino nitrogen and α-hydroxyl oxygen atom, thereby forming a five-membered chelate ring. [15,16] Introducing α-amino acids or their derivatives into catalytically active transition metal complexes offers a straightforward and cost-effective approach to obtaining chiral compounds that hold promise for applications in enantioselective catalysis. [17–22] One such example is the heterogeneous hydrogenation of prochiral olefins with rhodium(I) proline amide complexes linked to a modified zeolite through a spacer. [23–27] Numerous processes in homogeneous catalysis rely on electron-rich complexes of late transition metals, with phosphane ligands being especially valuable. This has prompted the functionalization of α-amino acids, especially the relatively inflexible proline, with phosphane groups. [20,21] Besides catalytic activity, it is known that amino acid complexes are proven to be useful antibacterial agents applied against Staphylococcus aureus, and Escherichia coli. [28]

The antitumor activity of gold(III) complexes featuring dipeptides containing L-histidine, where the N-terminal amino acids are L-alanine and L-leucine, exhibited good selectivity between cancer and normal cell lines. These complexes also demonstrated antiangiogenic effects comparable to established angiogenesis inhibitors like auranofin and sunitinib malate. Importantly, these effects were achieved without causing toxic side effects, which stood in contrast to the outcomes observed with auranofin and sunitinib malate treatments. [12] Furthermore, a glycine complex, tricarbonylchloro(glycinato)ruthenium(II), is one the so called “carbon monoxide releasing molecules” (CORMs). [29–31] The synthesis and characterization of numerous CORM molecules were encouraged by the findings that carbon monoxide has many important physiological roles as a small molecule messenger. [32] The mentioned glycine complex is used primarily as a prototype of a water-soluble CO carrier. [30]

In our previous work, the NH/O and two types of O/HO hydrogen bonds of free amino acids and amino acids complexes with a free water molecule were studied by analyzing data retrieved from the Cambridge Structural Database (CSD) for all amino acids and by quantum chemical calculations for glycine, cysteine, phenylalanine, and serine cobalt(III) complexes. [33] In the NH/O interactions, amino acids are H-donors, while in O/HO interactions, amino acids are hydrogen atom acceptors (H-acceptors). Since zwitterion amino acids were used as free species, the zwitterion-water interaction energies are quite strong, in the range for four studied amino acids (glycine, cysteine, phenylalanine, and serine): from -5.1 to -9.6 kcal/mol for NH/O, and from -6.9 to -7.6 kcal/mol for O/HO interaction. Thereby, the neutral complexes have weaker interactions than zwitterions, and singly positive complexes for NH/O and singly negative complexes for O/HO have similar to slightly stronger hydrogen bonds in comparison to free zwitterions. Additionally, NH/O interaction was calculated for doubly positive complexes where its interaction energy increased up to -16.9 kcal/mol. [33]

Considering the importance of amino acid complexes as catalysts and pharmaceuticals, investigating the hydrogen bonds of these complexes can enhance comprehension of their mechanisms of action. In this work, we studied the influence of the metal ion type and complex geometry on the hydrogen bonds between chelated amino acid and a free water molecule by quantum chemistry calculations and analysis of the results obtained from the CSD search. Quantum chemistry calculations were done on octahedral nickel(II), square pyramidal copper(II), square planar copper(II), palladium(II), and platinum(II) glycine complexes, since glycine is the simplest amino acid. The CSD search was done for cobalt and copper complexes with all amino acids. To the best of our knowledge, this is the first study of the influence of various metal atom types on the hydrogen bonds in the second coordination sphere of amino acid metal complexes.

2 Methodology

2.1 Quantum chemistry calculations

Quantum chemistry calculations on systems with a coordinated glycine and a free water molecule were performed at the M06L-GD3/def2-TZVPP level [34–36] using the Gaussian 09 program package. [37] The BSSE correction of interaction energies was taken into account using the counterpoise utility. [38] In our previous work, the good agreement of this method with the CCSD(T)/CBS values has already been confirmed. [33]

Three hydrogen bond types were investigated: between an α-amino group as a H-donor and a free water's oxygen as a H-acceptor (NH/O), between oxygen of the α-hydroxyl group (O1) as a H-acceptor and a free water as a H-donor (O1/HO), and between oxygen of the α-carbonyl group (O2) as a H-acceptor and a free water as a H-donor (O2/HO) (**Figure 1**).

Geometry optimization was performed for octahedral nickel(II), square pyramidal and square planar copper(II), square planar palladium(II), and platinum(II) glycine (Gly) complexes. All nickel(II) complexes are triplets, copper(II) doublets, and palladium(II) and platinum(II) singlets.

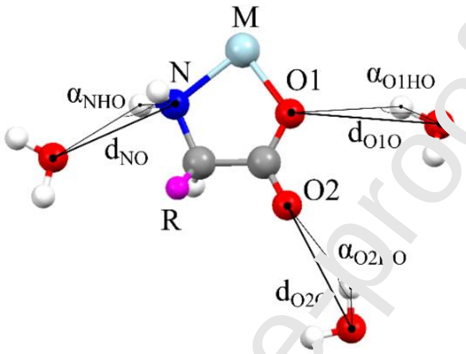

Figure 1. Graphical representation of rigid model systems used to calculate NH/O, O1/HO, and O2/HO interactions with hydrogen bond parameters.

Singly positively charged, neutral, and singly negatively charged complexes were optimized. The complex charge was adjusted using water molecule(s) and/or chlorine ion(s) as the remaining ligands. For the square pyramidal copper(II) complex, only the singly positively charged and neutral complexes were successfully optimized. The vibrational analysis was utilized to confirm that all the optimized geometries correspond to the potential energy minima.

Using optimized geometries of monomers, rigid model systems were built from a complex and a water molecule bonding via linear hydrogen bond. In the rigid systems, only the distance between a hydrogen donor and a hydrogen acceptor (hydrogen bond distance, *d*, **Figure 1**) was changed and the interaction energy was calculated for every distance. The *d* distance was changed with a 0.1 Å step in the range from 2.5 Å to 3.4 Å. After obtaining interaction energy curves, the geometries and energies at the minima of the curves were reported.

For the optimized systems, the total geometry optimization was performed starting from the minima on potential curves. The absence of negative frequencies confirmed that the optimized geometries were indeed potential energy minima. The interaction energy between a coordinated glycine and free water was calculated for these optimized geometries.

Using the M06L-GD3/def2-TZVPP method, the electrostatic potentials of coordinated glycines were computed on surfaces with 0.001 au (electronbohr^{-3}) electronic densities. [39] The value of the electrostatic potential (Vs) on the interacting glycine atom in the direction of the hydrogen bond was also calculated using the same method and electronic density.

The influence of the solvation with water was estimated on rigid systems of nickel(II) complex with water at M06L-GD3(PCM)/def2-TZVPP level. [40]

2.2 CSD search

The search of crystal structures archived in the Cambridge Structural Database (CSD, version 5.41, November 2019 release, May 2020 updated) [41] was performed using the CSD search program ConQuest (version 5.4.1, May 2020). [42] The CSD searches were done to retrieve all amino acids coordinated with different metals and interacting with a free water molecule via three types of hydrogen bonds defined above; NH/O, O1/HO, and O2/HO (**Figure 1**).

The following criteria were satisfied in every search: (a) the crystallographic R factor ≤ 0.1, (b) the error-free coordinates according to the criteria used in the CSD, (c) no polymer structures, (d) no structures with the disorder, (e) no structures solved from powder and (f) only X-Ray diffraction solved structures. The geometric criteria applied to each hydrogen bond were: the d distance between the hydrogen donor and acceptor (d_{NO}, d_{O1O}, or d_{O2O}) is less than 4.0 Å, and the hydrogen bond angle (α_{NHO}, α_{O1HO}, or α_{O2HO}) is above 110°. The corresponding geometrical parameters are denoted in **Figure 1**.

3 Results

The three types of hydrogen bonds (NH/O, O1/HO and O2/HO) were analyzed between a transition metal complex and a water molecule in the second coordination sphere. In NH/O hydrogen bonds coordinated glycine is a H-donor, while in O1/HO and O2/HO hydrogen bonds coordinated glycine is a H-acceptor (**Figure 1**). These hydrogen bonds were studied on model systems with coordinated glycine using quantum chemistry calculations to obtain optimal distance and energies of the hydrogen bonds. We also analyzed hydrogen bond geometries in crystal structures archived in the Cambridge Structural Database (CSD) [41] for metal complexes of all amino acids.

3.1 Quantum chemistry calculations

Using methods of quantum chemistry, as described in the Methodology section, the following complexes were investigated: octahedral nickel(II), square pyramidal copper(II) and square planar copper(II), platinum(II), and palladium(II) glycine complexes. These metals were chosen since they were among the most abundant in CSD for studied geometries, while glycine was selected because of its simplicity that prevents additional interactions. The previously published data for octahedral cobalt(III) glycine complexes [33] were also presented and compared with the data obtained in this work.

For NH/O hydrogen bonds (**Figure 1**), only neutral and positively charged complexes were taken into account (**Table 1**), since negative complexes as H-donors have repulsive interactions with free water molecule. For O1/HO and O2/HO hydrogen bonds (**Figure 1**), the calculations were done using neutral and negatively charged complexes (**Table 1**), since positive charge complexes as H-acceptors have repulsive interactions with free water molecule.

Quantum chemical calculations were performed on rigid and optimized systems. For the rigid systems, separated monomers, a complex and a free water molecule, were optimized, and kept rigid and bonded via a linear hydrogen bond, while only the distance between hydrogen donor and acceptor (*d*) was systemically changed from 2.5 to 3.4 Å with 0.1 Å step. For each distance, the interaction energy between monomers was calculated to find the one with the strongest hydrogen bond. The optimized systems were obtained starting from systems with the strongest rigid interactions and performing total geometry optimization. Vibrational analysis was used to confirm that the obtained optimized geometries represent potential energy minima. Interaction energy was also calculated between monomers in optimized systems.

3.1.1 Rigid systems

In the rigid systems, interaction energy was calculated for a range of hydrogen bond distances (*d*) between a coordinated glycine and a free water molecule. The potential interaction energy curves are presented in Supplementary Information (SI), Section 1. Interaction energy (ΔE), *d* distances, and electrostatic potentials on the interacting atoms (Vs) for the minima on the potential interaction energy curves of rigid systems are reported in **Table 1.** The corresponding model systems are presented in **Figures 2** and **3**.

NH/O hydrogen bonds. The NH/O interaction energy for complexes with the same geometry manifests stronger interactions with the increase of the complex charge (**Table 1**). Thus, the strongest NH/O hydrogen bond in rigid systems is calculated for the only system with a doubly positive complex, the cobalt(III) doubly positive system, which has an interaction energy of -16.9 kcal/mol (**Table 1**). In octahedral complexes with singly positive charge, the interaction energies are -8.3 and -10.8 kcal/mol, which are stronger than the interactions of neutral complexes, -5.2 and -7.2 kcal/mol (**Table 1**). With increasing cobalt(III) complex charge, the hydrogen bond distance d_{NO} shortens from 2.9 to 2.8 Å, which is in accordance with stronger interactions (**Table 1**). However, for nickel(II) complexes d_{NO} distance is 3.0 Å for both positive and neutral complexes.

Comparing octahedral cobalt(III) and nickel(II) complexes, one can anticipate that the higher metal oxidation state of cobalt(III) causes more positive electrostatic potential on all ligands, including the interacting hydrogen atom of the α-amino group. As a consequence, interactions of cobalt(III) complexes are stronger than interactions of nickel(II) complexes, while charges of the complexes are the same. Namely, for singly charged cobalt(III) and nickel(II) complexes interaction energies are -10.8 and -

8.3 kcal/mol, while for neutral complexes interaction energies are -7.2 and -5.2 kcal/mol (**Table 1**). The electrostatic potentials (Vs) for cobalt(III) complexes are higher than for nickel(II) complexes due to the higher positive oxidation state of the cobalt ion, as mentioned above (**Table 1**). Additionally, cobalt(III) complexes have shorter d_{NO} distances (2.9 kcal/mol) than nickel(II) complexes (3.0 kcal/mol) (**Table 1**).

Among square pyramidal and square planar complexes, the same influence of the complex charge can be noticed, as for the octahedral complexes (**Table 1**). Thus, square pyramidal copper(II) complex systems have -10.7 and -5.7 kcal/mol NH/O interaction energies for singly positive and neutral complex charges. The charged system also a has shorter d_{NO} distance (2.9 Å) and larger Vs values (128 kcal/mol) than the neutral (3.0 Å and 63 kcal/mol).

Square planar singly positive copper(II), palladium(II), and platinum(II) complexes have interaction energies -11.4, -11.8, and -12.1 kcal/mol, which are again stronger than the interactions of neutral systems, -6.8, -6.9, and -7.1 kcal/mol, respectively (**Table 1**). This is a consequence of the decrease in the electrostatic potential on the interacting hydrogen atom with decreasing complex charge (**Table 1**). Hydrogen bond distance is 2.9 Å for all square planar systems with NH/O interaction, except for the system with the weakest interaction energy, the neutral copper(II) system, where d_{NO} distance is 3.0 Å (**Table 1**). The interaction energy increase with the rise of metal atomic number can be noticed in both positively charged and neutral complexes. Therefore, comparing the square planar complexes, the copper(II) complex has the weakest, palladium(II) is stronger, and platinum(II) has the strongest interaction. A larger metal ion has better delocalization of the metal positive charge, which leads to stronger interactions.

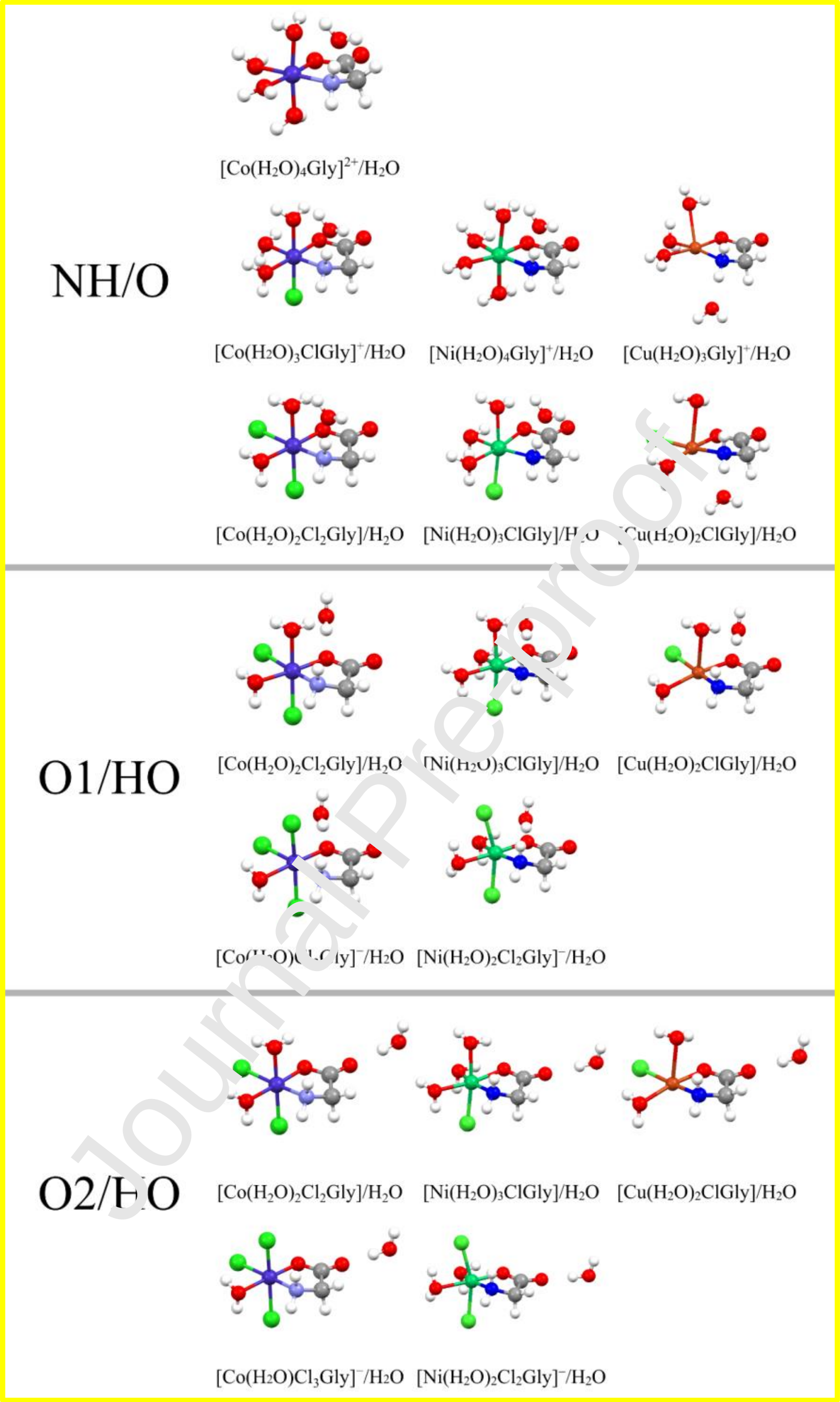

Figure 2. The rigid model systems used to calculate NH/O, O1/HO, and O2/HO interaction energies of octahedral and square pyramidal complexes with a water molecule. The structures of cobalt(III) complexes are taken from previous work [33].

Comparison of the data for different coordination numbers, six (octahedral complexes), five (square pyramidal complexes), and four (square planar complexes), indicates that a decrease of the metal coordination number of the systems with the metal oxidation number +2 and the same complex charge causes the increase in the NH/O interaction strength. Namely, the smaller the metal coordination number, the smaller the number of ligands to which the positive charge from the metal ion is dispersed, which generally results in more positive electrostatic potential on the interacting hydrogen atom of the N-H group and consequently stronger NH/O interaction. Thus, the interaction in systems with square planar complexes is stronger than for square pyramidal, which is stronger than for octahedral complex systems. Therefore, the weakest NH/O interactions for singly positive and neutral systems are found for nickel(II) complexes, and their values are -8.3 and -5.2 kcal/mol, respectively. The strongest NH/O interactions are found among square planar complex systems, more precisely for platinum(II) positive and neutral systems and their values are -12.1 and -7.1 kcal/mol, respectively (**Table 1**). Another less important consequence of the decrease in the metal coordination number is the decrease in the steric effects, which also strengthens the hydrogen bond (**Figure 2-3**). Since the neutral square pyramidal copper(II) system has Vs value of 63 kcal/mol, which is larger than the values in square planar systems (from 54 to 58 kcal/mol) (**Table 1**), it is steric effects in the square pyramidal system that decrease the interaction energy, making it weaker than the square planar systems and restoring the interaction energy order mentioned above.

<u>**O1/HO hydrogen bonds**</u>. For the systems with O1/HO hydrogen bonds, the ones with negatively charged complexes have stronger interactions than the corresponding neutral complexes. For the O1/HO hydrogen bond, the glycine complex plays the role of a H-acceptor, which explains why more negative charge on the complex increases the strength of the interaction. Hence, in octahedral systems, the negative complexes have interaction energies of -6.9 and -8.2 kcal/mol for cobalt(III) and nickel(II) complexes, while the neutral ones have weaker interactions of -2.2 and -5.1 kcal/mol (**Table 1**).

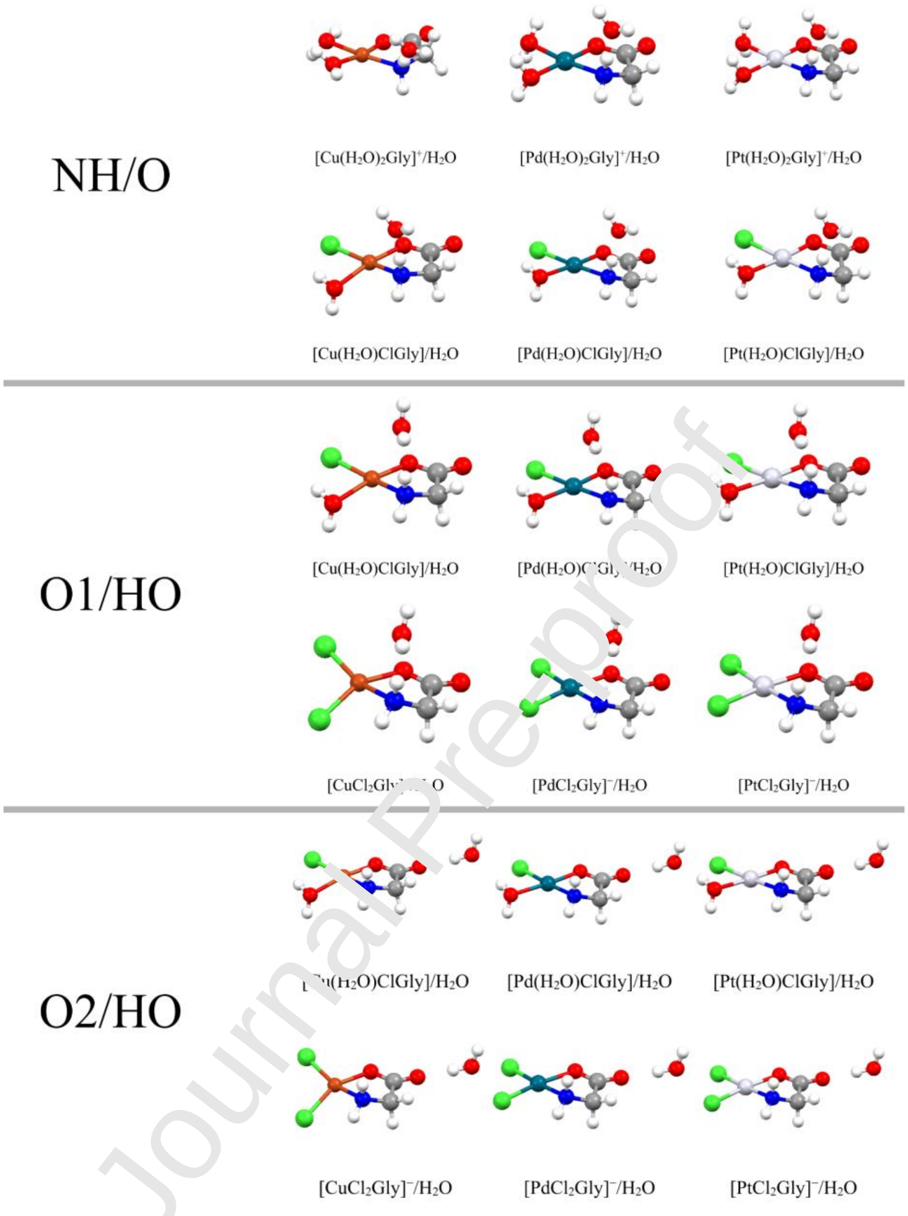

Figure 3. The rigid model systems used to calculate NH/O, O1/HO, and O2/HO interaction energies of square planar complexes with a water molecule.

Contrary to the NH/O interactions, these results show that cobalt(III) complexes have weaker O1/HO interactions than nickel(II), which suggests that a smaller metal oxidation number leads to more favorable O1/HO interaction energies (**Table 1**). It can be anticipated, since in complexes with smaller metal oxidation number less positive charge is on the ligands, what is favorable in case when complex is a H-acceptor. In accordance with that, significantly longer d_{O1O} distances are calculated for cobalt(III) negative and neutral complexes, 3.0 and 3.1 Å than for the corresponding nickel(II) complexes, 2.8 Å in both (**Table 1**). An additional hydrogen bond between coordinated water and the free water molecule could be noticed in both nickel(II) systems (**Figure 2**). These hydrogen bonds also contribute to the total interaction energies of nickel(II) systems, and therefore, it cannot be distinguished whether oxidation number decrease or additional hydrogen bond cause the increase in the total interaction energy from cobalt(III) to nickel(II) complexes with O1/HO interaction.

Only neutral square pyramidal O1/HO interaction was calculated, and interaction energy is -3.8 kcal/mol, while d_{O1O} distance is 3.0 Å (**Table 1**). According to the complex charge effect mentioned above, square planar negatively charged copper(II), palladium(II), and platinum(II) systems have stronger interactions (-7.6, -7.0, and -6.8 kcal/mol), than the neutral systems (-4.2, -3.8, and -3.6 kcal/mol) **(Table 1**). Singly negative complexes all have 3.0 Å long hydrogen bonds, while neutral ones either have the same, like copper(II) complex, or longer (3.1 Å) like palladium(II) and platinum(II) complexes, which corresponds well with weakening of the interaction for neutral complexes (**Table 1**). A steady decrease in the O1/HO interaction energy of square planar complexes with the metal atomic number rise is opposite to the increase of the NH/O strength, because of the opposite hydrogen bond role of the glycine. For O1/HO interaction, less positive charge delocalization is more favorable.

Considering the complex coordination number, as mentioned above, the smaller the coordination number, the smaller the number of ligands to which the positive charge from the metal ion is dispersed, resulting in more positive electrostatic potential on each ligand. It causes less negative electrostatic potential on the O1 oxygen atoms, thus, weaker O1/HO hydrogen bonds. Therefore, the strongest interactions are expected for octahedral, weaker for square pyramidal, and the weakest for square planar complex systems. The expected interaction energy trend is seen in singly negative complexes, where the interaction energy of -8.2 kcal/mol in nickel(II) systems is indeed stronger than the ones obtained for square planar systems, ranging from -6.8 to -7.6 kcal/mol (**Table 1**). In neutral systems, the strongest interaction of -5.1 kcal/mol is calculated in nickel(II) system, but square pyramidal interaction energy of -3.8 kcal/mol lies within the range of values obtained for square planar systems, from -3.6 to -4.2 kcal/mol. However, even though interaction energies generally follow the expected weakening with the decrease of the coordination number, the Vs values have the opposite trend: Vs values generally become more negative with the decrease in the coordination number. This indicates the importance of electrostatic potential on all groups in proximity of the free water molecule, such as chlorine ion ligands (**Figure 2-3**), and not only on the interacting O1 oxygen atom quantified by the Vs value. The influence of the electrostatic potential of other groups and ligands also explains why both neutral and singly negative nickel(II) complex systems have very short hydrogen bonds of only 2.8 Å, while in other O1/HO systems, d_{O1O} is significantly longer, from 3.0 to 3.1 Å (**Table 1**). In neutral square pyramidal copper(II) complex, the influence of other ligands is very similar to neutral square planar complexes (**Figure 2-3**). This fact, together with the similar *d* distance and Vs values, explains why there is no significant difference between the interaction energies of neutral square pyramidal and square planar systems (**Table 1**).

By taking into account the same absolute charge of the complex, NH/O and O1/HO interactions can be compared. For all complexes, the NH/O interaction is stronger than O1/HO. All the factors, complex charge, metal oxidation number, coordination number, and metal atomic number, have the opposite influence on the interaction energy, because of the reversed role of glycine in the hydrogen bond. For both NH/O and O1/HO interactions, the charge is the factor that influences the interaction energy the most, while the metal atomic number has the smallest effect.

O2/HO hydrogen bonds. For neutral octahedral cobalt(III) and nickel(II) complexes, O2/HO hydrogen bonds are 2.9 Å long and have interaction energies of -3.7 and -5.0 kcal/mol, while singly negative complexes have shorter (2.8 Å) and stronger interactions, -8.0 and -9.0 kcal/mol, respectively (**Table 1**). Similar to the O1/HO hydrogen bonds, less negative charge and higher metal oxidation number lead to weaker interaction energies. The Vs values for neutral and singly negative nickel(II) complexes are -49 and -112 kcal/mol, which is more negative than the values for neutral and singly negative cobalt(III) (-38 and -102 kcal/mol) (**Table 1**).

The d_{O2O} distance and interaction energy for neutral square pyramidal copper(II) complex are 2.9 Å and -4.4 kcal/mol (**Table 1**). For square planar systems, the interaction energies for O2/HO interaction are in the very narrow range from -4.2 to -4.3 kcal/mol for neutral and from -8.1 to -8.4 kcal/mol for singly negative complexes (**Table 1**). The strength of interaction energies of square planar complexes is decreasing as the metal atomic number is rising from copper(II) to platinum(II), because of the rise in the delocalization, as noticed in O1/HO systems as well.

The coordination number increase from 4 (square planar) to 6 (octahedral) causes the interaction energy increase for both neutral and singly negative complexes with oxidation number +2 (**Table 1**). This effect is similar to O1/HO, and opposite from NH/O interaction.

In contrast to NH/O and O1/HO hydrogen bonds, the steric effects for O2/HO interactions are relatively small, which enables the free water to approach closer and results in shorter *d* distances. It is also expected that the O2 oxygen atom, being further away from the positive metal than O1 oxygen, results in more negative Vs values and gives stronger O2/HO hydrogen bonds compared to O1/HO (**Figure 2-3**). Even though Vs electrostatic potentials are not more negative on O2 than O1 oxygen in every complex, O2/HO interactions are still generally stronger than O1/HO, because of its joint effect with the smaller steric effects and shorter hydrogen bond distances (**Table 1**). NH/O interactions are significantly stronger than both O1/HO and O2/HO interactions.

The larger distance of the O2/HO interaction from the metal ion than in NH/O and O1/HO interactions (**Figures 1-3**) explains why all four factors generally influence the O2/HO hydrogen bond less than the other two. Moreover, for O2/HO, as well as for NH/O and O1/HO interactions, the complex charge is the strongest, and the metal atomic number is the weakest factor to influence the interaction energy.

Table 1. The hydrogen bond distance *d* (Å), interaction energy ΔE (kcal/mol), and electrostatic potential Vs (kcal/mol) calculated at the M06L-GD3/def2-TZVPP level for rigid systems of coordinated glycine and a water molecule bonded via NH/O, O1/HO, and O2/HO interactions.

System	Charge	NH/O			O1/HO			O2/HO		
		d_{NO}	ΔE	Vs	d_{O1O}	ΔE	Vs	d_{O2O}	ΔE	Vs
Octahedral complexes										
$[Co(H_2O)_4Gly]^{2+}/H_2O$	+2	2.8[a]	-16.9[a]	213[a]						
$[Co(H_2O)_3ClGly]^{+}/H_2O$	+1	2.9[a]	-10.8[a]	128[a]						
$[Ni(H_2O)_4Gly]^{+}/H_2O$	+1	3.0	-8.3	109						
$[Co(H_2O)_2Cl_2Gly]/H_2O$	0	2.9[a]	-7.2[a]	56[a]	3.1[a]	-2.2[a]	-21[a]	2.9[a]	-3.7[a]	-38[a]
$[Ni(H_2O)_3ClGly]/H_2O$	0	3.0	-5.2	42	2.8	-5.1	-13	2.9	-5.0	-49
$[Co(H_2O)Cl_3Gly]^{-}/H_2O$	− 1				3.0[a]	-6.9[a]	-98[a]	2.8[a]	-8.0[a]	-102[a]
$[Ni(H_2O)_2Cl_2Gly]^{-}/H_2O$	− 1				2.8	-8.2	-98	2.8	-9.0	-112
Square pyramidal complexes										
$[Cu(H_2O)_3Gly]^{+}/H_2O$	+1	2.9	-10.7	128						
$[Cu(H_2O)_2ClGly]/H_2O$	0	3.0	-5.7	63	3.0	-3.8	-41	2.9	-4.4	-44
Square planar complexes										
$[Cu(H_2O)_2Gly]^{+}/H_2O$	+1	2.9	-11.4	132						
$[Pd(H_2O)_2Gly]^{+}/H_2O$	+1	2.9	-11.8	132						
$[Pt(H_2O)_2Gly]^{+}/H_2O$	+1	2.9	-12.1	138						
$[Cu(H_2O)ClGly]/H_2O$	0	3.0	-6.8	58	3.0	-4.2	-47	3.0	-4.3	-44
$[Pd(H_2O)ClGly]/H_2O$	0	2.9	-6.9	57	3.1	-3.8	-39	2.9	-4.2	-42
$[Pt(H_2O)ClGly]/H_2O$	0	2.9	-7.1	54	3.1	-3.6	-33	2.9	-4.2	-29
$[CuCl_2Gly]^{-}/H_2O$[b]	− 1				3.0	-7.6	-124	2.8	-8.4	-106
$[PdCl_2Gly]^{-}/H_2O$	− 1				3.0	-7.0	-115	2.8	-8.2	-100
$[PtCl_2Gly]^{-}/H_2O$	− 1				3.0	-6.8	-120	2.8	-8.1	-97

[a] Results published in ref. [33]

[b] The $[CuCl_2Gly]^{-}$ complex is distorted towards tetrahedral geometry

Correlation of interaction energies and electrostatic potentials. As mentioned above, the interaction energy is correlated to electrostatic potential; more positive potential at the NH hydrogen favors stronger interactions, while in O1/HO and O2/HO hydrogen bonds, more negative potential at the oxygen atoms favors stronger interactions. The data in **Figure 4** show the three plots of the interaction energy vs. the electrostatic potential on the interacting atom (Vs) for all three hydrogen bond types. The plots were obtained using the results presented in **Table 1** and the results reported in our previous work [33], including all investigated amino acids. The interaction energies (ΔE) are linear functions of electrostatic potentials (Vs) with high correlation coefficients (R^2) of 0.96 for NH/O, 0.96 for O1/HO, and 0.94 for O2/HO interaction. For the O1/HO interaction, the nickel(II) complexes are excluded from the linear fit analysis due to their significant deviation from the remaining results, caused by an additional hydrogen bond with coordinated water molecules (**Figure 2**).

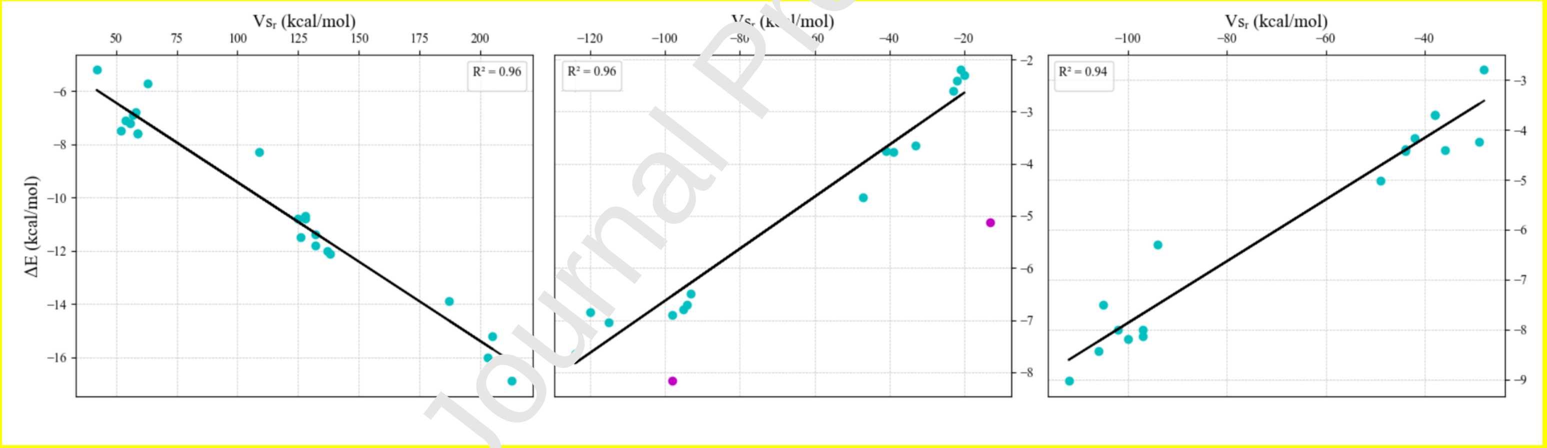

Figure 4. Interaction energy (ΔE) vs. electrostatic potential on the interacting atom (Vs) plot for NH/O, O1/HO, and O2/HO interactions in rigid systems. The plots were made using all the results for rigid systems of all amino acids reported in this (**Table 1)** and in our previous work [33]. The purple mark (●) on the O1/HO interaction represents the results for the neutral and singly negative nickel(II) systems not taken into account for the linear fit.

Solvation effect. The effect of solvation with water on the interaction energies of nickel(II) rigid systems using the PCM model is presented in SI, Section 3. Upon solvation, the interaction energies decrease for each of the three interaction types (NH/O, O1/HO, and O2/HO). Interaction energies of the charged complexes decrease significantly, by 4.0, 3.9, and 3.0 kcal/mol for NH/O, O1/HO, and O2/HO interactions, respectively (**Table 1**, **Table SI 1**). For neutral complexes, interaction energy decrease is smaller, by 1.0, 0.6, and 0.4 kcal/mol for NH/O, O1/HO, and O2/HO interactions, respectively (**Table 1**, **Table SI 1**). For both neutral and charged complexes, NH/O interaction decreases the most and O1/HO the least (**Table 1**, **Table SI 1**). This results in O2/HO interaction being stronger than NH/O, differently from the results obtained in vacuum (**Table 1**, **Table SI 1**).

3.1.2 Optimized systems

Starting from the geometries of the rigid systems, that are minima on the potential interaction energy curves (**Figure 2-3**), the total geometry optimization was performed. The data with optimized structures in **Figures 5-6** and in **Table 2** are organized by type of hydrogen bond in the starting geometries. However, after the optimization, in many systems the original hydrogen bond was absent, or significantly longer (**Table 2**). In many systems new hydrogen bonds were formed between non-coordinated water and other hydrogen bond donors or/and acceptors in a metal complex (**Figures 5-6**). In addition to factors observed in rigid systems, in these optimized systems interaction energies are strongly influenced by the position of the non-coordinated water. After geometry optimization, total interaction energies become stronger for all systems compared to rigid systems (**Tables 1-2**), which is often a consequence of multiple simultaneous interactions.

Among the results obtained after geometry optimization of the systems starting with NH/O interactions, as in rigid systems (Chapter 3.1.1) the strongest interaction was calculated in the doubly positively charged cobalt(III) complex system; -27.7 kcal/mol (**Table 2**), as a consequence of the largest charge of the complex. Same as for rigid systems, singly positive systems exhibit weaker interactions, while neutral ones display the weakest interactions. Namely, the interaction energies for singly positive cobalt(III) and nickel(II) are -22.9 and -23.4 kcal/mol, while for the neutral complexes interaction energies are -18.8 and

-18.9 kcal/mol, respectively (**Table 2**). In all neutral and singly positive octahedral complexes, the NH/O hydrogen bond is very weak, therefore, the O2/HO and the hydrogen bond with a coordinated water molecule contribute more to the total interaction energies (**Figure 5**).

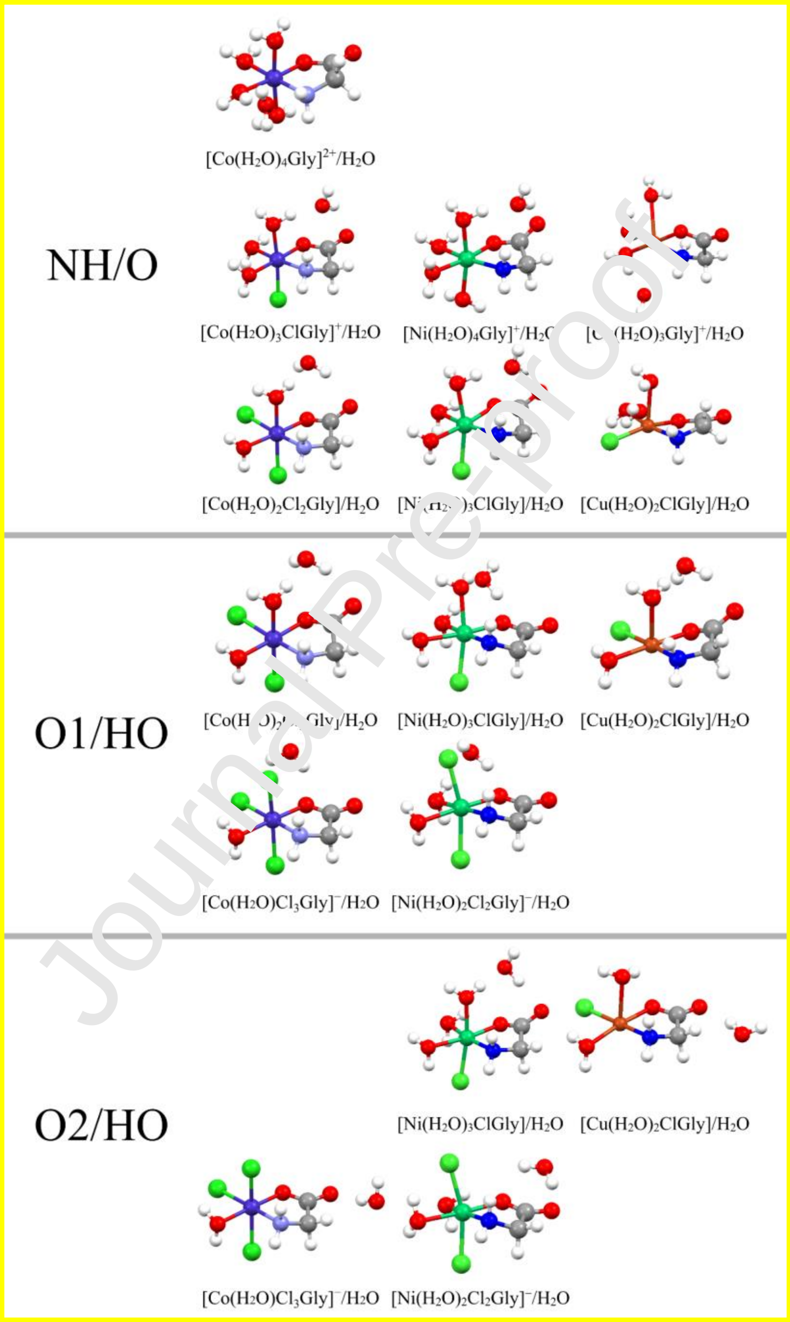

Figure 5. The optimized systems of octahedral and square pyramidal complexes with a water molecule after geometry optimization starting from the rigid system coordinates with NH/O, O1/HO, and O2/HO hydrogen bonds.

The results are organized according to the starting interaction type. The structures of cobalt(III) complexes are taken from previous work [33].

In the square pyramidal systems, the positively charged copper(II) complex has an interaction energy of -18.0 kcal/mol, while the neutral complex has a weaker interaction of -16.9 kcal/mol (**Table 2**). In both square pyramidal systems, two hydrogen bonds are present, a long NH/O and a stronger hydrogen bond with coordinated water (**Figure 5**). The interaction strengths of optimized square pyramidal complexes are generally weaker compared to those of optimized octahedral complexes (**Table 2**), opposite to rigid systems (**Table 1**), which is the consequence of the position of the non-coordinated interacting water molecule in the optimized systems.

In square planar complexes, the optimized singly positively charged copper(II), palladium(II), and platinum(II) have interaction energies of -19.1, -13.5, and -13.7 kcal/mol (**Table 2**). For all three systems, NH/O interaction is present after the optimization, but the discrepancy in interaction energies emerges because the copper(II) system has an additional hydrogen bond with a coordinated water molecule (**Figure 6**). The neutral palladium(II) and platinum(II) complexes have the weakest interactions of -11.0 and -11.1 kcal/mol (**Table 2**). Again, this is opposite to rigid systems, where square planar complexes have the strongest interactions (**Table 1**). This difference is a consequence of larger possibilities for additional interactions in the optimized systems for octahedral and square pyramidal complexes in comparison to square planar complexes. Interestingly, the geometry optimization of the neutral square planar copper(II) complex system leads to the coordination of the initially free water molecule and the formation of the square pyramidal complex (**Figure 6**).

After the geometry optimization starting from rigid systems with O1/HO interactions, the neutral octahedral cobalt(III) and nickel(II) have interaction energies of -18.8 and -24.2 kcal/mol, while negatively charged complexes have slightly weaker interactions of -11.5 and -22.3 kcal/mol (**Table 2**). This is opposite to rigid systems (**Table 1**) since for all optimized octahedral systems, interactions with other ligands, such as water and chlorine ions are present, and the larger number of interactions dictates the stronger total interaction energy. For example, the strongest interaction energy is calculated in the neutral nickel(II) system because the optimized geometry has O1/HO and two additional hydrogen bonds with coordinated water molecules (**Figure 6**, **Table 2**).

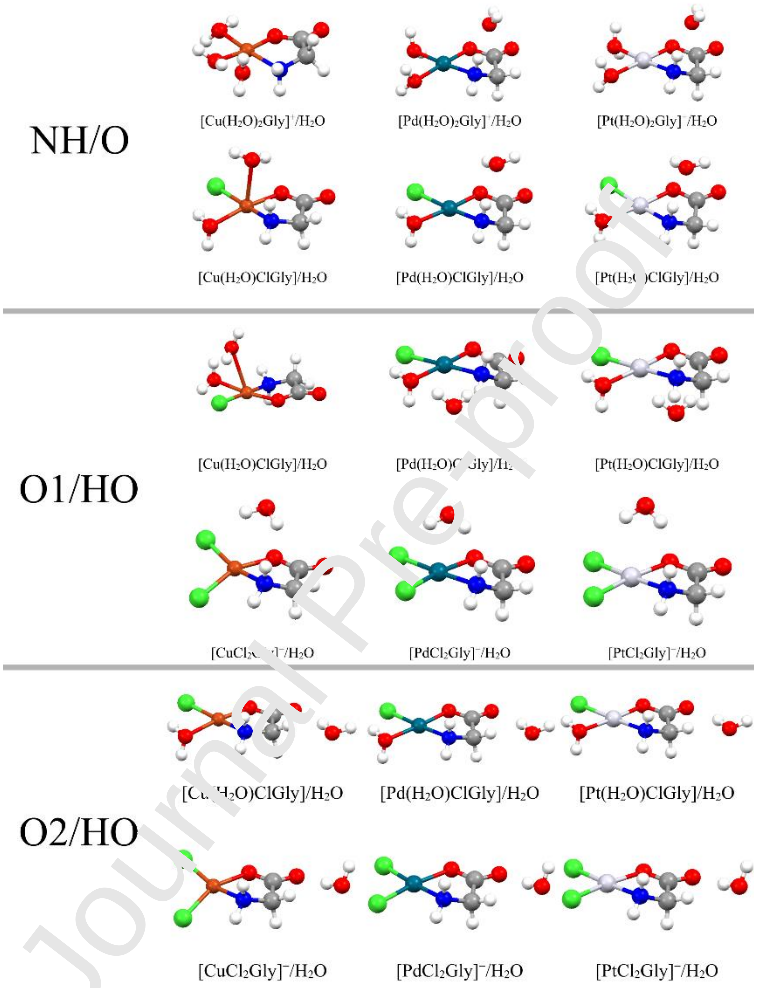

Figure 6. The optimized systems of square planar complexes with a water molecule after geometry optimization start from the rigid system coordinates with NH/O, O1/HO, and O2/HO hydrogen bonds. The results are organized according to the starting interaction type.

In the square pyramidal copper(II) system, the interaction energy of -17.7 kcal/mol is contributed by O1/HO and by an additional hydrogen bond with coordinated water (**Table 2**, **Figure 6**). Interaction energies of square planar systems are weaker than octahedral and square pyramidal, thus their values for neutral palladium(II) and platinum(II) complexes are -8.6 and -7.6 kcal/mol, while singly negative complexes have stronger interactions with interaction energies from -12.5 to -13.0 kcal/mol (**Table 2**). Again, the neutral square planar copper(II) system becomes a square pyramidal complex after the geometry optimization (**Figure 6**).

Differently from previous optimized results, after geometry optimization, systems with O2/HO hydrogen bonds tend to remain bonded via O2/HO interactions, however, the position of the interacting water is changed forming bent interactions with shorter d_{O2O} distances and stronger interactions (**Table 1-2**). For neutral octahedral nickel(II) complex, interaction energy is -19.4 kcal/mol, while for singly negatively charged complexes interactions are weaker, in spite of negative charge, interaction energies are -11.0 and -13.7 kcal/mol for cobalt(III) and nickel(II) (**Table 2**). Nickel(II) systems and the square pyramidal copper(II) are the only ones that have an additional interaction with another ligand (water or chlorine ion) (**Figure 5**). The interaction of neutral square pyramidal copper(II) complex is weaker than the ones of octahedral complexes, -8.8 kcal/mol (**Table 2**). The optimized O2/HO interactions for neutral square planar copper(II), palladium(II), and platinum(II) complexes have interaction energies of -8.9, -8.7, and -8.9 kcal/mol. Interaction becomes stronger for singly negative charged complexes, -11.7, -11.5, and -11.5 kcal/mol (**Table 2**). The O2/HO interactions in optimized complexes do not show significant variation in interaction energies with the change of geometry.

Opposite to rigid systems (**Table 1**), interactions of the optimized O2/HO systems are mostly weaker than the ones in the optimized O1/HO (**Table 2**). Namely, in the systems with O1/OH interactions, because of the close proximity of the O1 atom to the other ligands, geometry optimization enables the non-coordinated water to form several simultaneous interactions, resulting in relatively strong interactions. In the systems with O2/HO interactions, the O2 atom is significantly further away from the other ligands in the complex, therefore, geometry optimization often results in a stronger O2/HO and no additional interactions, which makes the interaction energy weaker (**Figure 5-6**).

Table 2. The hydrogen bond distance *d* (Å) and interaction energy ΔE (kcal/mol) at M06L-GD3/def2-TZVPP level after geometry optimization of systems with coordinated glycine and a water molecule. The rigid systems were used as initial coordinates for the geometry optimization, and the results are organized according to the starting interaction type. In the systems for which the starting interaction is not present after the optimization, only the interaction energy is reported ("/" sign replaces the *d* distance). The "-" sign marks the system for which the geometry optimization was not successful and the "*" sign marks the ones where the free water molecule becomes coordinated after the geometry optimization.

System	Charge	NH/O		O1/HO		O2/HO	
		d_{NO}	ΔE	d_{O1O}	ΔE	d_{O2O}	ΔE
Octahedral complexes							
$[Co(H_2O)_4Gly]^{2+}/H_2O$	+2	3.0[a]	-27.7[a]				
$[Co(H_2O)_3ClGly]^{+}/H_2O$	+1	/ [a]	-22.9[a]				
$[Ni(H_2O)_4Gly]^{+}/H_2O$	+1	/	-23.4				
$[Co(H_2O)_2Cl_2Gly]/H_2O$	0	/ [a]	-18.8[a]	/ [a]	-18.8[a]	- [a]	- [a]
$[Ni(H_2O)_3ClGly]/H_2O$	0	/	-18.9	2.6	-24.2	2.83	-19.4
$[Co(H_2O)Cl_3Gly]^{-}/H_2O$	−1			3.0[a]	-11.5[a]	2.76[a]	-11.0[a]
$[Ni(H_2O)_2Cl_2Gly]^{-}/H_2O$	−1			2.7	-22.3	2.85	-13.7
Square pyramidal complexes							
$[Cu(H_2O)_3Gly]^{+}/H_2O$	+1	3.2	-18.0				
$[Cu(H_2O)_2ClGly]/H_2O$	0	3.0	-16.9	2.8	-17.7	2.8	-8.8
Square planar complexes							
$[Cu(H_2O)_2Gly]^{+}/H_2O$	+1	3.2	-19.1				
$[Pd(H_2O)_2Gly]^{+}/H_2O$	+1	2.8	-13.5				
$[Pt(H_2O)_2Gly]^{+}/H_2O$	+1	2.8	-13.7				
$[Cu(H_2O)ClGly]/H_2O$	0	*	*	*	*	2.8	-8.9
$[Pd(H_2O)ClGly]/H_2O$	0	2.9	-11.0	/	-8.6	2.8	-8.7
$[Pt(H_2O)ClGly]/H_2O$	0	2.9	-11.1	3.1	-7.6	2.8	-8.9
$[CuCl_2Gly]^{-}/H_2O^{b}$	−1			2.9	-13.0	2.8	-11.7
$[PdCl_2Gly]^{-}/H_2O$	−1			2.9	-12.8	2.8	-11.5
$[PtCl_2Gly]^{-}/H_2O$	−1			2.9	-12.5	2.8	-11.5

[a] Results published in ref. [33]

[b] The $[CuCl_2Gly]^-$ complex is distorted

3.2 CSD search

The CSD search was done for all amino acid complexes of various metals interacting with a free water molecule via either NH/O, O1/HO, or O2/HO hydrogen bond (**Figure 1**), using criteria described in the Methodology (Chapter 2.2). Only for copper and cobalt complexes, a relatively large number of interactions was obtained. The search for copper resulted in 81 NH/O, 41 O1/HO, and 70 O2/HO contacts, while for cobalt amino acid complexes, 25 NH/O, 13 O1/HO, and 23 O2/HO contacts were found. The distribution of hydrogen bond distance d for NH/O and O2/HO interactions of copper and cobalt amino acid complexes are presented in **Figure 7**. Because of the smaller number of contacts for O1/HO interactions, these distributions for copper and cobalt complexes are shown in SI. In cobalt complexes, cobalt has oxidation number III, while in all copper complexes, copper has oxidation number II.

The distribution of d_{NO} and d_{O2O} distances in cobalt(III) complexes exhibits a peak between 2.9 Å and 3.0 Å, as depicted in **Figure 7**. The calculated d_{NO} and d_{O2O} distances for the rigid monomer are slightly lower (ranging from 2.8 to 2.9 Å, **Table 1**), while for the optimized systems, they align within the same range as observed in the crystal structures (**Table 2**). In the case of copper(II) systems, the distribution of d_{NO} and d_{O2O} distances exhibit a peak within the ranges from 3.0 to 3.1 Å and from 2.7 to 2.8 Å, respectively (**Figure 7**). The distances obtained from calculations of rigid monomers are marginally shorter for d_{NO} distances, ranging from 2.9 to 3.0 Å, and slightly longer for d_{O2O} distances averaged at 2.9 Å (**Table 1**). Similar to cobalt(III) complexes, the optimized systems demonstrate better agreement with those observed in crystal structures, since for optimized systems, the d_{NO} distance is found at 3.0 Å and 3.2 Å, while the d_{O2O} distance is 2.8 Å (**Table 2**). Better agreement with optimized structures can be anticipated, since in the crystal structures interactions of a free water molecule with amino acid complexes are the best possible in the crystal, including simultaneous interactions.

A comparison of the interactions of cobalt and copper amino acid complexes in the crystal structures shows that d_{NO} distances are shorter for cobalt complexes, while d_{O2O} distances are shorter for copper complexes. This can be explained based on the oxidation numbers of cobalt and copper. Namely, in all considered complexes cobalt has oxidation number III, while copper has oxidation number II, as was mentioned above. The larger oxidation number of cobalt(III) favors a larger number of positively charged amino acid complexes (that can be +2 and +1), in comparison to the number of positively charged complexes of copper(II) (that can be only +1). As shown above in rigid systems (Chapter 3.1.1, **Table 1**), both more positively charged complexes and larger oxidation numbers favor shorter d_{NO} distances and longer d_{O2O} distances.

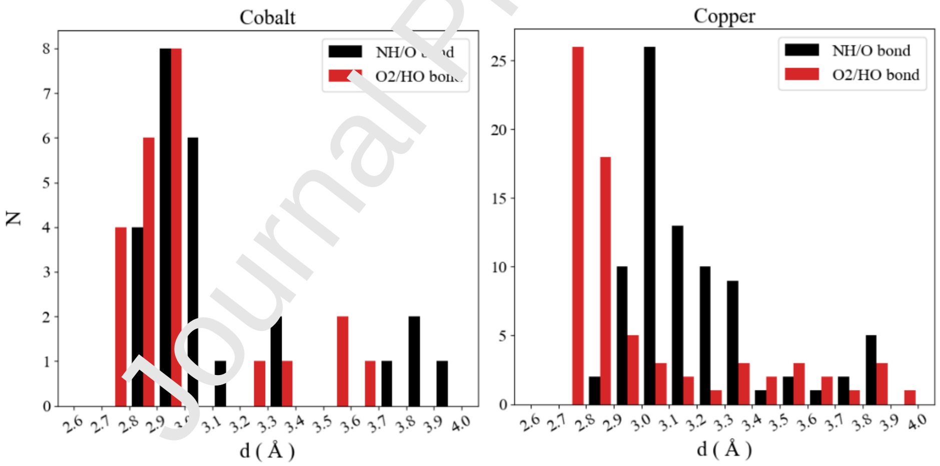

Figure 7. The distribution of donor-acceptor *d* distance for NH/O and O2/HO interactions of cobalt(III) and copper(II) coordinated amino acids with a water molecule (**Figure 1**). The geometrical parameter *d* represents d_{NO} for NH/O and d_{O2O} for O2/HO interaction.

4 Conclusions

Results of the M06L-GD3/def2-TZVPP calculations on hydrogen bonds between glycine complexes and water molecules with rigid monomers indicate a strong influence of the complex charge on the interaction energies. For the NH/O hydrogen bond, where coordinated glycine is a H-donor, the interaction energies are significantly stronger for positively charged than for neutral complexes. For O1/HO and O2/HO hydrogen bonds, where coordinated glycine is a H-acceptor, interaction energy is stronger for negatively charged than for neutral complexes. The interaction energies are also influenced by metal oxidation number, coordination number, and metal atomic number, however, these factors have a smaller influence than complex charge.

Comparison of interaction energies of the neutral complexes shows that the strongest are NH/O hydrogen bonds, followed by O2/HO, and the weakest are O1/HO. This is the consequence of the partial positive charge transferred from the metal ion to the coordinated glycine, which favors interactions where glycine is a H-donor and disfavors interactions where glycine is a H-acceptor.

After complete geometry optimization of the studied systems, the calculated strength of hydrogen bonds increases, since non-coordinated interacting water molecule forms more favorable and/or simultaneous interactions. The position of the free water significantly influences the interaction energies, however, charged complexes still form stronger interactions.

Data obtained from crystal structures from the CSD are in good agreement with the calculated data. Results for copper(III) and cobalt(II) amino acid complexes forming NH/O and O2/HO hydrogen bonds with a free water molecule, showed that the *d* distribution is in good agreement with the results for optimized systems. In addition, the data from the CSD shows that d_{NO} distances are shorter for cobalt(III) complexes, while d_{O2O} distances are shorter in copper(II) complexes. This is in agreement with the calculated influence of complex charge on interaction energies. Namely, larger oxidation numbers of cobalt(III) favor a larger number of positively charged amino acid complexes causing stronger NH/O hydrogen bonds and shorter d_{NO} distances, while copper(II) forms smaller number of positively charged complexes which favors stronger O2/HO hydrogen bonds and shorter d_{O2O} distances.

Abbreviations

CSD	Cambridge Structural Database
H-donor	hydrogen bond donor
H-acceptor	hydrogen bond acceptor
DFT	Density Functional Theory
Gly	glycine
CCSD(T)	Coupled-Cluster with Single, Double and Perturbative Triple Excitations
CBS	Complete Basis Set

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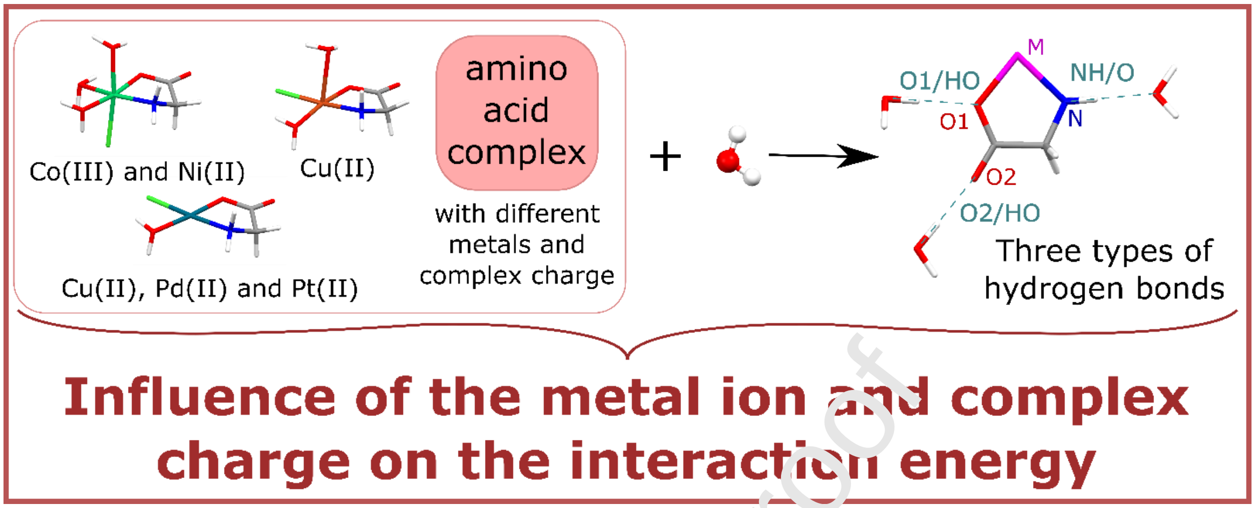
Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Graphical abstract



For NH/O interactions, neutral complexes have the weakest interaction energies, followed by singly positive, while doubly positive have the strongest. For O1/HO and O2/HO interactions, neutral complexes are again more weakly bound, while singly negative have stronger interactions. Complex geometry and metal oxidation number influence the interaction less significantly.

Highlights

- Hydrogen bonds between free water and different metal-chelated amino acids were investigated
- Nickel(II), copper(II), palladium(II), and platinum(II) glycine complexes were calculated
- Octahedral, square pyramidal and square planar glycine complexes were calculated
- The crystal structures of cobalt and copper amino acids were analyzed
- Complex charge affects the interaction energy and geometry the most