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Square or not Square—That’s the Question!

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Square or not Square--That's the Question!

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Abstract

Background: Most heavy metals from industrial catalysts are harmful to human body; however, to function normally, the human body *does* need traces of essential metal cofactors. Histidine is one of the nine essential amino acids to the human body, and cobalt(II) ion is cost effective and is known to be less toxic to the body. **Methods:** This project investigates the binding reactions between the cobalt(II) ion and histidine amino acids. Due to unsuccessful attempts to crystalize Cobalt(II)-Histidine complex in the lab, the quantum mechanics modeling package, G09, was employed to provide the binding mode and interaction between the metal and histidine complex. Geometric parameters were attained in order to predict the crystal structure the complex. **Results:** The data confirms that complexes between cobalt ions and deprotonated histidine will only settle into a square planar geometry, regardless of the initial geometry. However, with neutral histidine, the complex is not in square planar formation at all. Instead, the five-member ring formed among cobalt and histidine's N- and C-terminus forms an angle, where N-Co-N is almost linear (167.5°). **Conclusion:** Different reaction conditions will yield either tetrahedral and square planar geometry at the metal center, which will influence the band gap. Such influence can then be used to create a tunable and broad-spectrum solar panel materials.

Keywords: Density functional theory, cobalt(II), histidine, binding mode, electronic structure

Introduction

Proteins are very important for the wellness of humans and are the building blocks of amino acids. In fact, 20% of the human body is made of proteins, and they play crucial role in the biological processes.¹ In fact, a large proportion of protein in the human body comprises muscles, cells and tissues, all with their unique amino acid structures. Protein functions include giving cells structure, wound healing, transport and storage of nutrients and much more.² Histidine is one of the nine essential amino acids that cannot be synthesized in the human body; thus, it must be consumed. One of the critical needs of histidine is its role in the formation of hemoglobin and its assist with the formation and repair of tissues.

Certain trace metals are essential elements of well-being for human body, while some heavy metals are harmful to human body. Maximum Contaminant Levels (MCL) standards for the most hazardous heavy metals are set by the United States Environmental Protection Agency (EPA).³ Toxicity refers to the amount of the metal the body can take before being poisoned. This legal threshold toxicity limits are usually expressed as a concentration in milligrams per liter of water. The larger the concentration, the more of the metal it takes to poison the body. The transition metal cobalt is toxic at levels higher than 1.0 MCL (mg/L), and it is known to be related to cardiomyopathy, deafness, nerve conditions, tinnitus, blood thickening, and thyroid dysfunctions when found at toxic levels in the human body. Cobalt, a relatively cheap heavy metal, can bind to the amino acid histidine.⁴ Because the MCL for cobalt is so high, this reflects the low toxicity of cobalt compared to other heavy metals such as mercury, lead, or arsenic.

In this study, the binding mode between the cobalt (II) ion with histidine will be investigated through a computational modeling approach. The binding geometry and electronic structure of this binding complex will provide the insights on how the amino acid binds to the metal centers and the strength of the binding. This work has implications for both environmental and cellular biology.

Materials and Methods

All molecules and transition states are constructed using GaussView (Gaussian, Inc., Wallingford CT) optimized with the Gaussian 09 package.⁵ The popular B3LYP⁶ with hybrid exchange functional were used for all geometry optimization and frequency calculations. B3LYP is a hybrid functional that was developed in the late 1980s in order to eliminate the downsides that the other hybrid correlation functionals face when calculating electron correlation. B3LYP is used in computational molecular work, where it is used widely because of its relative versatility and speed, even when compared to more recent hybrid functionals.

All structures were fully optimized and frequency analyses were performed to ensure either a *minimum* was achieved, which had zero imaginary vibrational frequency as derived from a vibrational frequency analysis, or *transition state* was identified, which had one imaginary vibrational frequency.

The vibrational mode was visualized to confirm the expected motion of transition state. A separate intrinsic reaction coordinate (IRC) calculation was then performed on the transition state geometry to follow either the forward or reverse vibrational mode into the local minimum. The thermodynamic parameters of the reaction, such as zero point corrected energy ($[\Delta E^{ZPE}]$, enthalpies $[\Delta H^\circ]$, and Gibbs Free energies $[\Delta G^\circ]$), were calculated at 298.15 K and 1 atm.

A basis set is a set of functions that are used to calculate molecular orbitals accurately. The basis sets used were 6-31g* and LANL2DZ. The basis set 6-31g* was used for the C, N, H, and O while a split basis set LANL2DZ was used for the Ni(II) and core electrons uses LANL2DZ effective core potential.

Results

According to the Ligand Field Theory (LFT, also known as Crystal Field Theory), when ligands approach the central metal ion to form a complex, due to the electron-electron repulsion, the previous degenerate five d-orbitals will split according to the approaching

direction of ligand and orientation of the d-orbitals. This is also the foundation of group theory where the reducible and irreducible representation was generated and dissected. As shown in Figure 1, in *octahedral* geometry, when six ligands approach the central atom, the 5 d-orbitals of the central metal ion will split into two sets: one set consists of d_{z^2} and $d_{x^2-y^2}$ orbitals, while the other set consists of three orbitals: d_{xy} , d_{yz} , and d_{xz} . In the *tetrahedral* geometry, where four ligands approach the metal ion, the split pattern flips, but it still maintains two sets of splitting orbitals. However, this splitting pattern gets much more complicated when the same four ligands approach the central metal ion to form a square planar geometry. In this formation, not only the d_{z^2} and $d_{x^2-y^2}$ set of orbitals further split, but now the d_{xy} orbital is higher in energy than d_{z^2} . All of these splitting patterns are based on the amount of “imaginary” collision between the central metal ion and incoming ligand when the complex is formed. However, such “imaginary” collision shall not be confused with the coordination bond formed in the complex.

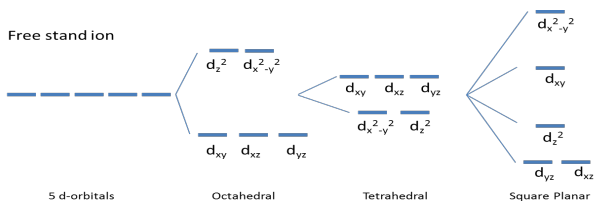


Figure 1 Five d-orbital splitting pattern in the different geometry according to the Ligand Field Theory

Splitting due to asymmetric electronic structure

One should also keep in mind that not only the geometric arrangement can distort (*aka* splitting) the electronic structure and d-electron arrangement; the unpaired electrons in the d-orbital would have the same electronic distortion on the free stand metal ion. For example, the cobalt (II) ion has seven (7) d-electrons. While the Hund's rule would like to keep the d-orbitals in degeneracy, the odd number of d-electrons would destroy the degeneracy and create a splitting pattern that depends on the electron repulsion and coupling.

The modeling results in Figure 2 demonstrates the d-orbital splitting pattern of free stand Co(II) are due to the asymmetric electronic structure. The left panel has Co(II) in doublet, where there is only one unpaired electron; meanwhile, the right panel is Co(II) in quadruplet, where there are three unpaired electrons. The modeling results show that doublet is 53.2 kcal/mol higher in Gibbs Free energy than that of quadruplet. This suggests that the free standing Co(II) would have high spin state.

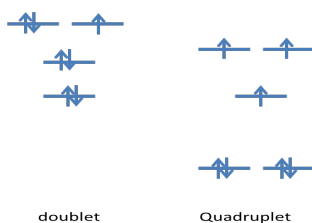


Figure 2 The d-orbital splitting pattern calculated for Co(II) due to asymmetric electronic structure

Deprotonation of histidine

Because the LFT explains the electronic structure of the complex, especially the d-orbital splitting pattern of the central metal ion, it provides an insight to the geometry around the metal center or electronic structure at the metal center. However, for any ligand to bond with metal, these ligands must have lone pairs of electrons. The histidine has a few locations that enable it to bind with metal—namely, the oxygen atoms on carboxylate portion of C-terminus, the nitrogen atom on amine group of N-terminus, and nitrogen atoms of R-group. As shown on the left in Figure 3, the neutral histidine optimized in the gas phase was not in Zwitterion (aka dipolar ion). When deprotonated (right in Figure 3) the Gibbs Free energy required is 350.6 kcal/mol. We believe the energy would be lowered when compensated by the Polarizable Continuum Model (PCM) using the integral equation formalism variant (IEFPCM) model using SCRF keyword where the charges will be solvated to further stabilize the ions.

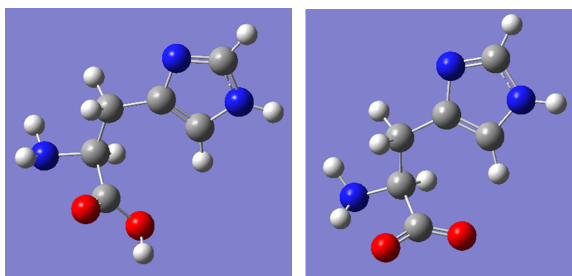


Figure 3 The optimized geometries of neutral histidine (left) and deprotonated (+1 charge) of histidine (right).

The optimized bond lengths of the neutral histidine and deprotonated histidine are listed in table 1. As one can imagine it, the only significant bond length changes would be around the carboxylate group where C1-O1 bond length significantly decreased from 1.3553 Å to 1.2588 Å upon deprotonation, while the other C1-O2 bond length slightly increased from 1.2108 Å to 1.2579 Å. The C1-C2 bond also increases from 1.5254 Å to 1.5846 Å. This suggests that upon the deprotonation, the electron lone pair used to bind the proton is re-distributed to the other C-O and C-C bonds of carboxylate group. The rest moiety of histidine does not change or shows less than hundredth Å changes.

Table 1 The geometry parameters of neutral histidine and deprotonated histidine

	Neutral Histidine	Deprotonated Histidine
O1-C1	1.35531	1.25882
C1-O2	1.21083	1.25789
C1-C2	1.52544	1.58464
C2-N1	1.46898	1.47419
C2-C3	1.545	1.55239
C3-C4	1.50336	1.50457
C4-N2	1.38424	1.3916
N2-C5	1.31349	1.31542
C5-N3	1.36479	1.36801
N3-C6	1.38185	1.38269
C6-C4	1.37611	1.37442

As mentioned earlier, there are three available binding sites on histidine: C-terminus, N-terminus, and nitrogen atoms on the R fragments. In this paper, the focus is on the C-terminus and N-terminus binding to the Co(II). For comparison, both the neutral histidine and deprotonated histidine binding to metal were investigated and presented here.

Binding Co(II) with neutral protonated histidine

When the neutral protonated histidine binds to the metal center, both form a 5-member ring that consists of the metal ion, N-terminus, α -carbon, and C-terminus forms as shown in Figure 4a. For the sake of clarity, a different view angle of same geometry is shown Figure 4b, where hydrogens are not shown. It is interesting to point out that two five-member rings are not in the same plane, instead they are angled. The N1-Co-N1' bond angle is 167.5°, O1-Co-O1' bond angle is 113.3°, and N1-Co-O1 bond angle is 76.0°. The overall geometry of this complex can be classified as boat configuration, because the Co- α C-H bond in the five-member ring is 94.1°, which is axial H on the α carbon. Relative to quadruplet state of Co(II), this binding mode has interaction energy of $\Delta G = -295.5$ kcal/mol, which suggests a strong interaction.

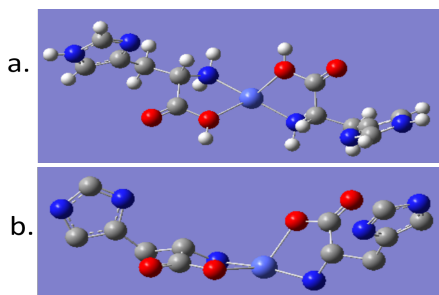


Figure 4 Optimized geometry of Cobalt (II)-neutral histidine complexes in (a). The hydrogen atoms are omitted for clarification in (b) as well as in a side-view angle

Binding Co(II) with deprotonated histidine

However, the geometry at the metal center of deprotonated histidine is drastically different than that geometry of neutral histidine complex as shown in Figure 4. As a matter of fact, the metal center of deprotonated histidine always shows a square planar geometry. Two 5-member ring that consists of the metal ion, N-terminus, α -carbon, and C-terminus of histidine are almost planar to each other. For example, the N1-Co-N1' bond angle is 179.0° , O1-Co-O1' bond angle is 178.2° , and N1-Co-O1 bond angle is 85.9° (Figure 5a). Interestingly, there are three different conformations identified for this deprotonated-Co complex as shown in Again, for the sake of clarification, all hydrogen atoms are not shown in the figure. The optimized bond lengths of these three conformations are shown in Table 2. One can see that the bond lengths of Co-N1 and Co-O1 are both longer in conformation b and c than those in conformation a. Even more interesting, the Co-N1 bond length is longer in conformation c than that in conformation b. This suggests that there is trans effect of carboxylate group that weakens the Co-N1 bond. This is evidenced that Co-O1 bond length almost identical between conformations b and c while the Co-N1 bond length is longer in conformation c (2.00506 \AA) than that of b (1.97665 \AA).

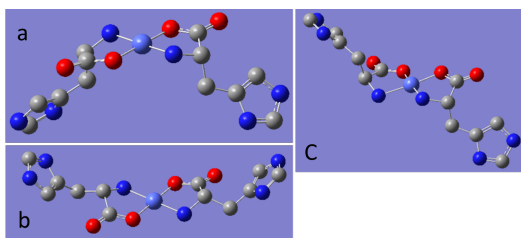


Figure 5 Three different binding modes of deprotonated histidine with cobalt (II) ion

As shown in Figure 5, the two histidine amino acids take *trans* form to each other in both conformations *a* and *b*. For example, the N-terminus of one histidine is *trans* to the N-terminus of the other histidine. However, the calculated conformation *c* has a *cis* form, where the N-terminus of one histidine is *cis* to the N-terminus of the other histidine. As a result, the conformation *c* is drastically different from those of conformations *a* and *b*. Furthermore, even the conformations *a* and *b* are slight different in their final geometry, as the R-group is slight bent up in conformation *b*. Carefully examining the optimized conformations *a* and *b* reveals that the M- α C-H bond angle may be a determining factor. For example, the M- α C-H bond angle of conformation *a* is 142° . This can be seen as an equatorial position. On the other hand, the M- α C-H bond angle of conformation *b* is 97° , which is an axial position. The M- α C-H bond angle of conformation *c* is a mixture of axial and equatorial position, which is 137 and 98 degrees.

Table 2 The optimized bond lengths of three different conformations of deprotonated Histidine complex

Conformation	a	b	c
O1-C1	1.31707	1.30885	1.30371
C1-O2	1.21919	1.22172	1.22279
C1-C2	1.55033	1.55322	1.55085
C2-N1	1.49724	1.49849	1.50395
C2-C3	1.5433	1.54092	1.54089
C3-C4	1.50435	1.50326	1.50387
C4-N2	1.38347	1.38376	1.38312
N2-C5	1.31454	1.31528	1.31504
C5-N3	1.36561	1.36637	1.36567
N3-C6	1.37945	1.37877	1.3787
C6-C4	1.37593	1.37567	1.37601
N1-Metal	1.96087	1.97665	2.00506
O1-Metal	1.85192	1.87456	1.87467
O1'-C1'	1.31708	1.30884	1.3037
C1'-O2'	1.21919	1.22172	1.2228
C1'-C2'	1.55033	1.55319	1.55084
C2'-N1'	1.49722	1.49846	1.50395
C2'-C3'	1.54331	1.54092	1.5409
C3'-C4'	1.50434	1.50326	1.50387
C4'-N2'	1.38346	1.38376	1.38312
N2'-C5'	1.31455	1.31528	1.31504
C5'-N3'	1.36561	1.36637	1.36567
N3'-C6'	1.37945	1.37877	1.3787
C6'-C4'	1.37593	1.37567	1.37601
N1'-Metal	1.96085	1.97669	2.0051
O1'-Metal	1.85186	1.8746	1.87465

Conclusions

In this study, the binding mode between the cobalt (II) ion with histidine was thoroughly investigated through computational modeling. The results demonstrated that complexes between cobalt ion and deprotonated histidine will only settle into a square planar geometry, regardless the initial geometry. However, with neutral histidine, the complex is not square planar at all. Instead, the five-member ring formed among cobalt and histidine's N- and C-terminus forms an angle, where N-Co-N is almost linear (167.5°).

These findings can assist in designing the wide spectrum solar energy materials with tunable energy gap. By modifying the reaction conditions, one can achieve a desirable geometry conformation between the histidine and metals. Such geometries such as the tetrahedral and square planar can yield specific band gap that convert the particular wavelength of sunlight into electricity.

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