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Insight into the Gas-Phase Structure of a Copper(II) L-Histidine Complex, the Agent Used To Treat Menkes Disease

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Supporting Information

ABSTRACT: Copper(II) L-histidine is used in the treatment of a rare neurological disease called Menkes disease. An infrared multiple photon dissociation (IRMPD) vibrational spectrum of the gas-phase copper(II) L-histidine complex has been obtained. This spectrum was compared to lowest-energy computational spectra obtained at the B3LYP/6-311+G** level of theory. Two species, CuHis1 and CuHis2, are very close in Gibbs free energy, and both have computed vibrational spectra in good agreement with the experimentally observed IRMPD spectrum. The first structure exhibits four histidine−copper interactions in the same plane and a fifth out-of-plane interaction. The second structure exhibits four histidine−copper interactions in the same plane. The fact that the experimental and computational spectra are found to be in good agreement adds considerable insight into the gas-phase structure of the copper(II) L-histidine complex.

Copper is an important metal for the maintenance of human health.[1] It is involved in many enzymatic reactions, such as those catalyzed by cytochrome *c* oxidase as part of the electron-transport chain, by superoxide dismutase in the detoxification of free radicals, by tyrosinase in the production of melanin for skin pigmentation, and by dopamine-β-hydroxylase in the production of catecholamines.[1] Copper may also exist in complexes with various amino acids in the blood for the purpose of copper transport. Copper histidine, one of the important complexes of copper with amino acids, is used as a treatment for Menkes disease. Menkes disease is a rare genetic disorder seen in childhood that results in progressive neurodegeneration if left untreated.[2] It is thought to be a result of impaired intestinal copper absorption, leading to decreased levels of developmental enzymes that require copper to function.[3,4] Therefore, much effort has been made in order to characterize the structure of the copper(II) bis(L-histidinato) complex.[3,5−11] An X-ray crystallographic study by Deschamps et al. determined the structure of physiologic copper histidine[12] to be a neutral five-coordinate complex with a distorted square-pyramidal geometry. Two L-histidine ligands exist in both bidentate and tridentate orientation with respect to the copper ion. The structure of the copper histidine complex has also been investigated using the technique of electron paramagnetic resonance/electron nuclear double resonance with supporting density functional theory (DFT) calculations by Goldfarb and colleagues.[5] The structure determined, from frozen solutions, exhibited a square-pyramidal geometry in which both L-histidine molecules were bound to copper through interactions with imidazole and amino moieties. Here we report a structural study of the copper(II) bis(L-histidinato) complex using infrared multiple photon dissociation (IRMPD) with supporting quantum-chemical calculations.

In this work, IRMPD spectroscopy has been used to obtain the gas-phase vibrational signature of $[Cu(His)_2H]^+$. IRMPD spectroscopy is a technique that allows for the generation of infrared absorption consequence data from mass-selected gas-phase molecular ions, which has been described in detail elsewhere.[13−16] Additionally, electrospray ionization is thought to often conserve solution-phase structures.[17] IRMPD experiments were carried out at the Centre de Laser Infrarouge d'Orsay (CLIO) at the University of Paris XI. The copper(II) L-histidine complex was generated as described previously.[4] Solutions containing the copper(II) L-histidine complex were prepared with concentrations of $\sim 10^{-5}-10^{-6}$ M in 50:50 acetonitrile/water with 0.1% formic acid. Ionic species of interest were generated using electrospray ionization, and the ions were subsequently transferred to a Bruker Esquire ion-trap mass spectrometer, where the desired ionic species is mass-isolated, trapped, and irradiated by the tunable infrared beam of the free electron laser. Sequential multiple photon absorption, followed by fragmentation, thus generates a consequence spectrum, which, as a function of the wavelength, gives the IRMPD vibrational spectrum. The fragmentation of the $[Cu(His)_2H]^+$ complex proceeds via successive losses of one and two molecules of CO_2, which might suggest that the complex indeed involves a dicarboxylate interaction with a Cu^{2+} center in which migration of a carboxylic acid proton to a basic nitrogen center has occurred.

Electronic structure calculations were performed using the *Gaussian 09* program package.[18] Structural optimizations and frequency calculations were obtained at the B3LYP/6-311+G** level of theory.[19] This level of theory was used for all atoms, including copper. This level of theory has been shown to be a relatively low-computational-cost yet high-accuracy method of calculating vibrational frequencies[20,21] and optimized structures for gaseous ionic complexes that exhibit hydrogen bonding.[22] Computed vibrational spectra were generated using a Lorentzian line shape with a full width at half-maximum of 12 cm^{-1}. A vibrational-frequency scaling factor of 0.995 for calculated spectra using the B3LYP method was employed.[23]

Various structural possibilities of the copper(II) L-histidine complex were investigated computationally, and the two structures determined to be the most energetically favorable in

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terms of the Gibbs free energy by DFT calculations are shown in Figure 1. The first complex, CuHis1, exhibits a distorted square-

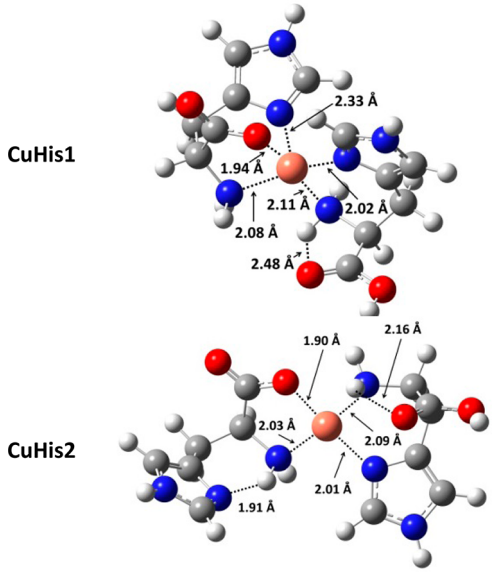

Figure 1. Structures of CuHis1 and CuHis2 obtained at the B3LYP/6-311+G** level of theory.

pyramidal geometry. Four L-histidine–copper contacts exist in the same plane. Two of these contacts involve amino and carboxylate contacts of one L-histidine molecule. The amino contact exhibits a N···Cu distance of 2.08 Å, and the carboxylate contact displays an O···Cu distance of 1.94 Å. The remaining two contacts involve amino and imidazole contacts of the second L-histidine molecule. The amino contact shows a N···Cu distance of 2.11 Å, and the imidazole contact has a N···Cu distance of 2.02 Å. An additional out-of-plane contact exists between the imidazole of the initial L-histidine molecule described and copper with a N···Cu distance of 2.33 Å. It is also worthwhile to note that a contact exists between the carboxyl carbonyl oxygen and the amino hydrogen of the second L-hisitidine molecule described. This interaction has a length of 2.48 Å and contributes to the basicity of the amino nitrogen, thereby strengthening the interaction between the amino nitrogen and the copper ion.

The second complex shown in Figure 1, CuHis2, is 3.3 kJ mol^{-1} higher in Gibbs free energy compared to CuHis1. The structures also differ by the fact that there are only four copper contacts instead of five. The four contacts are in the same plane, with two contacts of one L-histidine being a carboxylate and an amino and the other two contacts from the second L-histidine being an amino and an imidazole. The carboxylate and amino contacts of the first L-histidine have O···Cu and N···Cu distances of 1.90 and 2.03 Å, respectively. The amino and imidazole contacts of the second L-histidine have N···Cu distances of 2.09 and 2.01 Å, respectively. Interestingly, this complex exhibits additional intramolecular interactions. The first L-histidine displays an imidazole nitrogen interacting with an amino hydrogen with a N···H contact distance of 1.91 Å. This contributes to the basicity of the amino nitrogen, again strengthening the interaction between the amino nitrogen and the copper ion. The second L-histidine exhibits an interaction between the carboxyl oxygen and the amino hydrogen with an O···H contact distance of 2.16 Å. As previously noted, this interaction also strengthens the nitrogen–copper interaction of the corresponding amino group.

A comparison of the IRMPD spectrum of the copper(II) L-histidine complex and the vibrational spectra of the two lowest-energy computational structures is shown in Figure 2. These

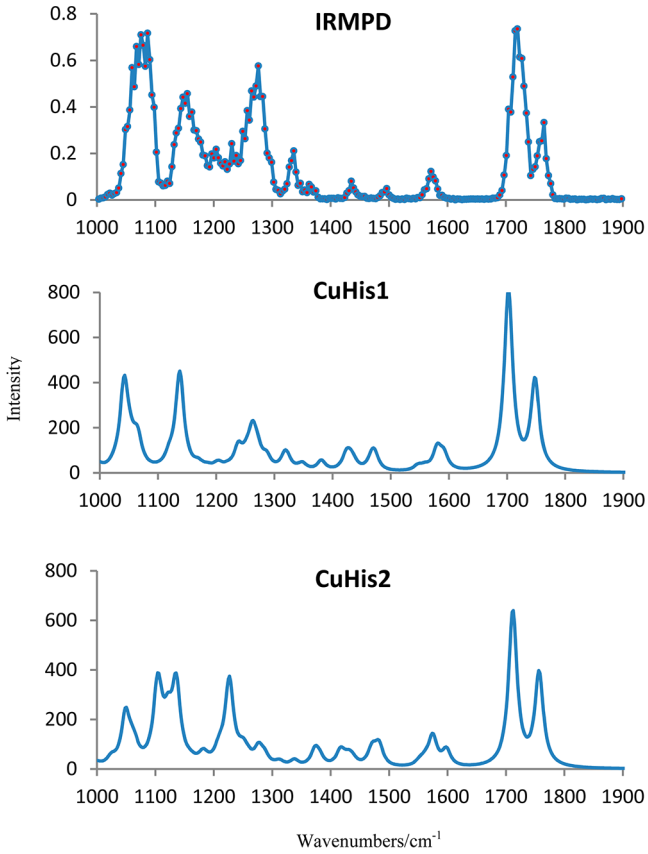

Figure 2. Comparison of the experimental IRMPD spectrum and the computational vibrational spectra of CuHis1 and CuHis2 obtained at the B3LYP/6-311+G** level of theory.

structures have similar spectra with some minor differences, and both match the IRMPD spectrum quite well. Consequently, it is quite possible that both are present in the gas phase and, if a statistical mixture were present, they would be in roughly equal amounts.

A wide variety of other structural possibilities were also investigated including, as noted above, those involving dicarboxylate interaction. However, all other structures were found to be at least 30 kJ mol^{-1} higher in Gibbs free energy than the lowest-energy conformer and, as expected, their spectra did not match the experimental spectrum. The spectra, structures, and energetics of these next-lowest-energy species found are shown in the Supporting Information (SI). Notably, structure CuHis5, with the most energetically favorable dicarboxylate interaction, is found to lie 72.9 kJ mol^{-1} higher in Gibbs energy than CuHis1. CuHis4, which is also a dicarboxylate species, differs from CuHis5 primarily by the endothermic transfer of the proton from the imidazole nitrogen of one histidine unit to the amino nitrogen of the other histidine unit.

The major bands from the IRMPD spectrum and comparable bands from the computational spectra of CuHis1 and CuHis2 are listed in Table 1.

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Table 1. List of Major Vibrational Frequencies (cm^{-1}) for IRMPD, CuHis1, and CuHis2 at B3LYP/6-311+G**

IRMPD	CuHis1	CuHis2	IRMPD	CuHis1	CuHis2
1075	1040	1050	1435	1430	1420
		1100	1500	1470	1480
1150	1140	1135	1570	1580	1580
		1225	1715	1700	1710
1275	1260	1280	1765	1750	1755
1340	1320	1370			

The band at 1075 cm^{-1} of the experimental spectrum is noticeable at 1040 and 1050 cm^{-1} in the computational spectra of CuHis1 and CuHis2, respectively. This band represents NH_2 wagging. A band at 1100 cm^{-1} of the CuHis2 spectrum is not visible in the CuHis1 and IRMPD spectra and similarly represents a NH_2 wag. A band at 1150 cm^{-1} of the IRMPD spectrum appears at 1140 and 1135 cm^{-1} in the computational spectra of CuHis1 and CuHis2, respectively, and represents a COH bend with a NH_2 wag. A further band at 1225 cm^{-1} of the CuHis2 spectrum is not visible in the CuHis1 and IRMPD spectra and represents NH_2 and CH bending motions. Another band appears at 1275 cm^{-1} in the experimental spectrum, corresponding to the bands at 1260 and 1280 cm^{-1} in the spectra of CuHis1 and CuHis2, respectively, and represents imidazole breathing motions. The band at 1340 cm^{-1} in the experimental spectrum corresponds to the bands at 1320 and 1370 cm^{-1} in the spectra of CuHis1 and CuHis2, respectively, and represents CH and NH_2 twisting motions. The band at 1435 cm^{-1} in the experimental spectrum is consistent with the bands at 1430 and 1420 cm^{-1} in the spectra of CuHis1 and CuHis2, respectively, and represents imidazole NH bending and NH_2 scissoring motions. The band that appears at 1500 cm^{-1} in the experimental spectrum corresponds to the bands at 1470 and 1480 cm^{-1} in the spectra of CuHis1 and CuHis2, respectively, and represents the imidazole breathing motion. The band at 1570 cm^{-1} in the experimental spectrum corresponds to the band at 1580 cm^{-1} in both the CuHis1 and CuHis2 spectra, respectively, and represents NH_2 scissoring. A further band appearing at 1715 cm^{-1} in the experimental spectrum is consistent with the bands at 1700 and 1710 cm^{-1} in the spectra of CuHis1 and CuHis2, respectively, and represents the carbonyl stretch of the carboxylate group. Finally, a band appearing at 1765 cm^{-1} in the experimental spectrum corresponds to the bands at 1750 and 1755 cm^{-1} in the spectra of CuHis1 and CuHis2, respectively, and represents the carbonyl stretch of the carboxyl group, slightly higher than that of the carboxylate group.

Taken together, these data suggest that IRMPD is a useful tool for investigating the gas-phase structure of copper(II) L-histidine. In addition, the results indicate that a mixture of both CuHis1 and CuHis2 could be present in the gas phase. This study adds further insight into the gas-phase structure of copper(II) L-histidine.

■ ASSOCIATED CONTENT

Supporting Information

Computational vibrational spectra of additional species discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written by B.E.Z. and T.B.M. All authors contributed equally to data generation. The experiment was conceived by B.E.Z.

Notes

The authors declare no competing financial interest.

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