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Article

Study of the Cu^{II} Affinity by Three Chelating Agents of Biological Interest: TPEN, TRIEN and Et_2DTC

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Copper is an important micronutrient, and it is present in some protein structures, as well as participate in several important biological processes. Due to its importance, some ligands are used and studied like carriers of copper in the biological systems. This work has investigated the affinity of Cu^{II} by three ligands of biological interest: *N*,*N*,*N*,*N*'-tetrakis (2-pyridilmethyl) ethylenediamine (TPEN), triethylenetetramine (TRIEN), and diethyldithiocarbamate (Et_2DTC), used for this purpose. The studies were performed by evaluating the Cu^{II} d-d band when complexed with these three ligands. The Cu^{II} d-d band in aqueous solution appears around 800 nm; when in the presence of TRIEN, this band displaces to 576 nm. TRIEN ligand is substituted by TPEN ligand (d-d band at 689 nm), and finally, in the presence of the Et_2DTC ligand, the d-d band displaces to 665 nm. Theoretical calculations were used to obtain the binding energy and the values obtained were -481.85 kcal mol^{-1} for the Cu^{II}-TPEN, -417.80 kcal mol^{-1} for Cu^{II}-TRIEN and -726.72 kcal mol^{-1} for Cu^{II}-Et_2DTC. Electrochemical studies showed an oxidation peak at 0.008 V to Cu^{II}-TRIEN complex, -0.135 V to Cu^{II}-TPEN and 0.150 V to Cu^{II}-Et_2DTC. These results showed that Cu^{II} has a higher affinity by the Et_2DTC ligand compared to the other ligands studied.

Keywords: copper complexes, copper chelators, TD-DFT, UV-Vis

Introduction

Organic molecules have been widely employed as metal ions transporters in biological systems. These ligands are preferentially polydentate and give rise to compounds with different properties, which allow a better choice for their use.[1] Its functions comprise the acquisition, distribution, and availability of ions at the cellular level.[2]

Specifically, the copper ion is a micronutrient essential to living organisms due to its role as a cofactor in enzymes and as a redox catalyst in several metabolic pathways.[3] This is favored by its different oxidation states of copper: oxidized Cu^{II} and reduced Cu^{I}.[4] On the other hand, the high concentrations of copper interfere in several cellular processes including enzymatic activity, protein and pigment biosynthesis, photosynthesis, energy production, and cellular division.[3]

The copper ion's intrinsic reactivity also contributes to its toxicity. Free copper is practically inexistent in the cells at standard conditions. However, the accumulation of free copper at high cellular levels leads to the formation of hydroxyl radicals, which cause cell damage and mutagenicity by reacting with proteins, lipids, and nucleic acids.[4,5] In this sense, the maintenance of copper levels aiming at the balance between nutritional deficiency and toxicity is fundamental. This need has generated studies about specific metal chelation to achieve this clinical condition in living organisms.[6-8] An ideal chelating agent

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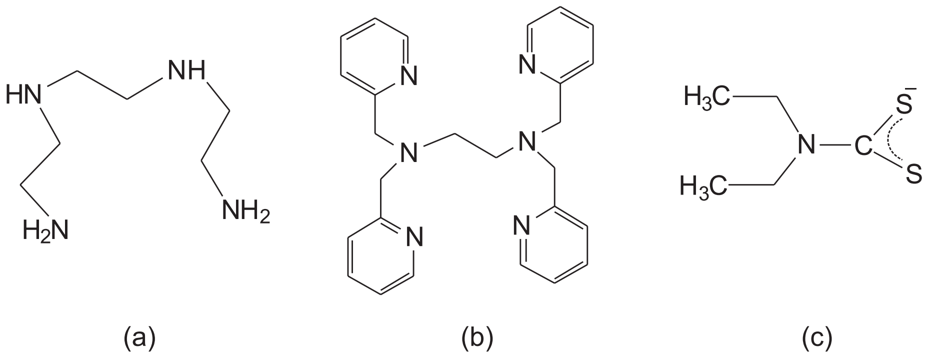


Figure 1. Molecular structure of the ligands: (a) TRIEN; (b) TPEN and (c) Et_2DTC.

with clinical applications must consider several aspects like metal affinity and selectivity, kinetic stability of the formed complex and, also, bioavailability and toxicity.[6] Besides, chelators could be employed as molecular probes of ion availability at the cellular level.[7,9]

In this context, some copper ligands as triethylenetetramine (TRIEN), *N*,*N*,*N*,*N*'-tetrakis (2-pyridilmethyl) ethylenediamine (TPEN), and diethyldithiocarbamate (Et_2DTC) have been studied (Figure 1).

TRIEN was introduced in clinical practices for the treatment of patients intolerant to penicillamine,[10] as a hydrophilic ligand able to bind copper and to promote its urinary excretion. Its use to treat Wilson's disease (a genetic disease related to copper accumulation) showed a decrease in a healthy neurological system due to the temporary increase of protein unbound copper ion.[11,12] The TPEN chelating agent shows a high affinity for Cu^{II} and Zn^{II} metal ions since the zinc chelation leads to an unbalance of reactive oxygen species (ROS) and, consequently, cell death. This fact motivated the study of TPEN use against prostate cancer.[13,14] Finally, Et_2DTC is a Cu^{II} chelating agent with Cu/Zn superoxide dismutase inhibition activity in animal and erythrocyte models. Some studies[2,15] have indicated that both pharmacological and toxic effects are related to Cu^{II} complexation with the ligand.

Therefore, understanding the behavior of Cu^{II} when in the presence of these ligands, can provide insights to new applications, as a carrier in biological or other environments. So, the main goal of this study was to evaluate the affinity of TRIEN, TPEN and Et_2DTC for Cu^{II} metal ion, employing experimental and computational techniques.

Experimental

Chemical

Analytical grade reagents were purchased from Sigma-Aldrich (São Paulo, Brazil), Vetec (São Paulo, Brazil) or Fluka (São Paulo, Brazil).

Spectrophotometric studies

The UV-Vis absorption spectra of the studied complexes were obtained using a Shimadzu-1800 UV-Vis spectrophotometer. Stock solutions of copper in water and the ligands in ethanol were prepared, both in a concentration of 1.0×10^{-2} mol L^{-1}. The remaining solutions were prepared from these ones.

To assess the affinity of the Cu^{II} by the ligands, the UV-Vis spectra were carried out in ethanolic solutions, following the protocol: first, it was placed a copper aqueous solution in a UV-Vis cell and added a solution of TRIEN. Afterward, to the solution of Cu^{II}-TRIEN complex was added a solution of TPEN, and finally, an Et_2DTC solution was added to the system. With this, it was possible to assess the behavior of the metal ion in the presence of the three ligands.

Electrochemical studies

The voltammetric measurements were carried out with an electrochemical analyzer Autolab® PGSTAT128N (Eco Chemie, Netherlands) with GPES software. A conventional cell system with three electrodes was used, consisting of: a glassy carbon electrode as a working electrode, an electrode of Ag/AgCl (3.0 mol L^{-1} KCl) as a reference electrode, and a platinum wire as an auxiliary electrode. The measurements was performed at room temperature in 10.0 mL of support electrolyte (0.1 mol L^{-1} KNO_3) containing 5.0×10^{-5} mol L^{-1} of Cu^{II} solution, and ligands solution, separately, with a final stoichiometry of 1:1 (to standardize the experiments). Before the voltammetric measurements, nitrogen gas was purged to create an inert atmosphere to avoid the oxygen influence in the analyses.

Computational details

Quantum chemistry calculations were performed for TPEN, TRIEN, and its Cu^{II} complexes. We performed calculations employing density functional theory (DFT) to optimize the structures of the ligand. The minimum energy structure was confirmed from frequencies analyses. The methodology employed to perform the geometry optimization involved Minnesota 06 (M06)[16] functional and DGauss double-zeta valence polarization (DGDZVP) basis set,[17,18] according to the previous study.[19] All DFT calculations were performed with Gaussian 09[20] package. The properties of Et_2DTC and its complex with Cu^{II} were reported in our previous study,[19] motivating us to study new ligands. Those results[19] were employed to compare to the experimental data obtained in this work. After the geometry determinations we performed the simulation of UV-Vis spectra employing time-dependent density functional theory (TD-DFT) methodology with B3LYP (Becke, 3-parameter, Lee-Yang-Parr) functional[21,22] and DGDZVP basis set in vacuum and water (aiming to simulate the biological solvation) environments using integral equation formalism-polarizable continuum model (IEF-PCM) as implicit solvation method[23-25] according to our previous work.[19] Twenty excitation states were calculated in each TD-DFT simulations.

Results and Discussion

Initially, spectroscopic profiles of the ligands in the presence of Cu^{II} were taken at the UV-Vis region after the complex formation. Figure 2 shows the UV-Vis spectra for TRIEN, TPEN, and its complexes with copper (II). Different metal complexes with dithiocarbamates, TPEN, and TRIEN, are well known in the literature.[9,26-30] The TPEN ligand (Figure 2a) shows a band on the UV region that increases in intensity after the complexation, and a new d-d band at 689 nm is observed, after the complexation. For the TRIEN ligand (Figure 2b), the d-d band is observed at 576 nm. The Et_2DTC spectroscopic profile is reported in the literature and shows two bands at the UV region and, after the complexation with Cu^{II}, two bands at the visible region: the first at 450 nm, referent to the ligand-metal charge transfer,[31,32] and a d-d band at 665 nm.[19] All complexes showed a displacement to the blue region when compared with copper salt in aqueous solution. This finding is related to a displacement to high energy regions, consistent with strong field ligands compared to water, a weak field ligand.[33]

Copper complexes frequently give rise to poorly resolved d-d bands in the visible region of the spectrum, usually from 600 to 900 nm.[34] In aqueous solution, Cu^{II} ion shows a characteristic d-d band at 800 nm.[35] The analysis of this band can provide useful insights into the complex formed. The d-d band was monitored to assess Cu^{II} affinity by the ligands.

Figure 3 shows the Cu^{II}-TRIEN spectra with successive additions of aliquots of TPEN solution. It is possible to observe the gradual displacement of d-d bands to larger wavelengths until the total complexation of copper with TPEN, in a 1:1 ratio. TPEN is a hexadentate ligand that can form a trigonal bipyramidal[36] or distorted octahedral[37] geometry complexes. Shifts to larger wavelengths are related to more easiness electronic transitions. When compared with Cu^{II}-TRIEN complex, square planar,[38,39] these results suggest that TPEN forms a more stable complex. Literature data show stability constants for the Cu^{II}-TPEN[40] and Cu^{II}-TRIEN[41] complexes of the same magnitude, with log K around 20. This can be explained by thermodynamics data: complexes with a higher number of coordination, such as TPEN, are favored by enthalpy and entropy, while the substitution by a ligand with a lower number of coordination, such as TRIEN, are favored only by entropy.[42] The data observed in this work corroborate with those found in the literature data.[40,41]

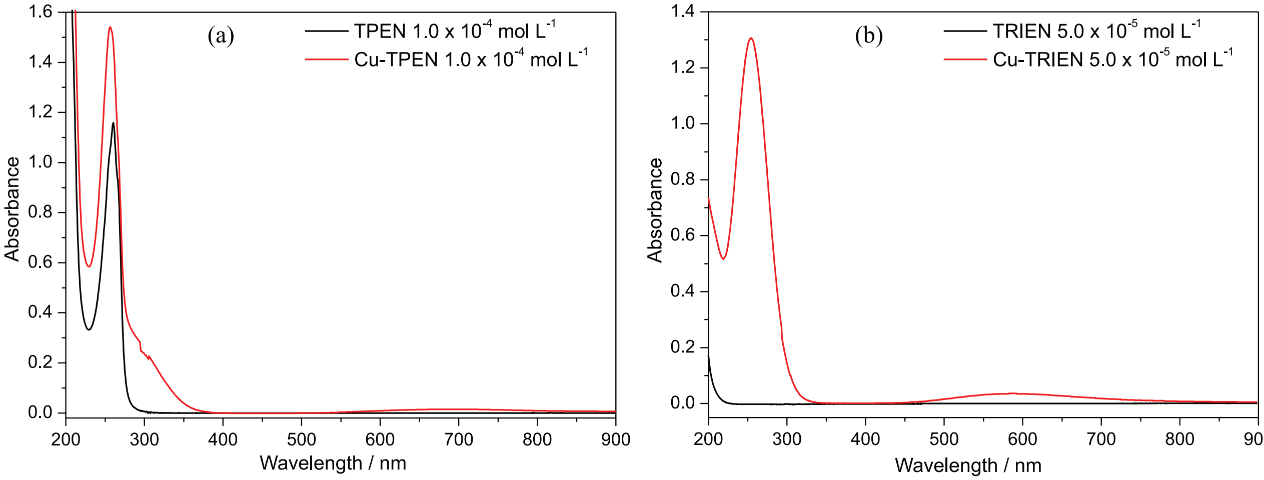


Figure 2. UV-Vis spectra for the complex formed between Cu^{II} metal ion and (a) TPEN and (b) TRIEN, in ethanol.

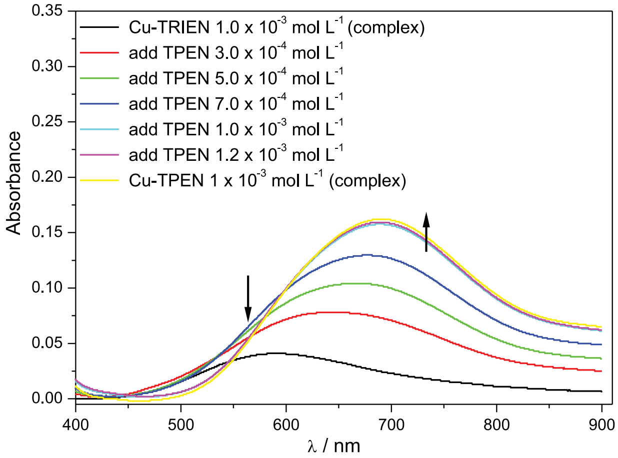


Figure 3. UV-Vis spectra of the Cu^{II}-TRIEN solution with additions of TPEN, in ethanol.

For comparison, the spectrum of Cu^{II}-TPEN in aqueous solution was added to Figure 3 (yellow spectrum). The exchange of TRIEN for TPEN occurs seconds after the addition of TPEN to Cu^{II}-TRIEN solution.

Et$_2$DTC ligand was included in this study to compare different ligands of biological interest. Although they do not present comparable structures, they are studied for similar purposes. Figure 4 shows the spectra obtained by adding Et$_2$DTC to a solution of Cu^{II}-TPEN complex. In the presence of Et$_2$DTC, the TPEN is quickly replaced, forming the Cu^{II}-Et$_2$DTC complex.

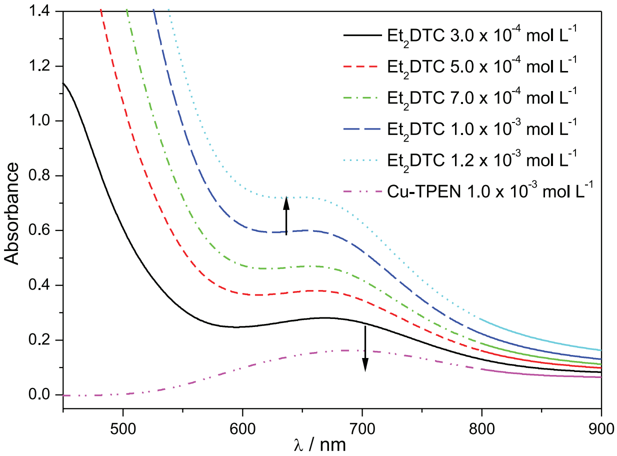
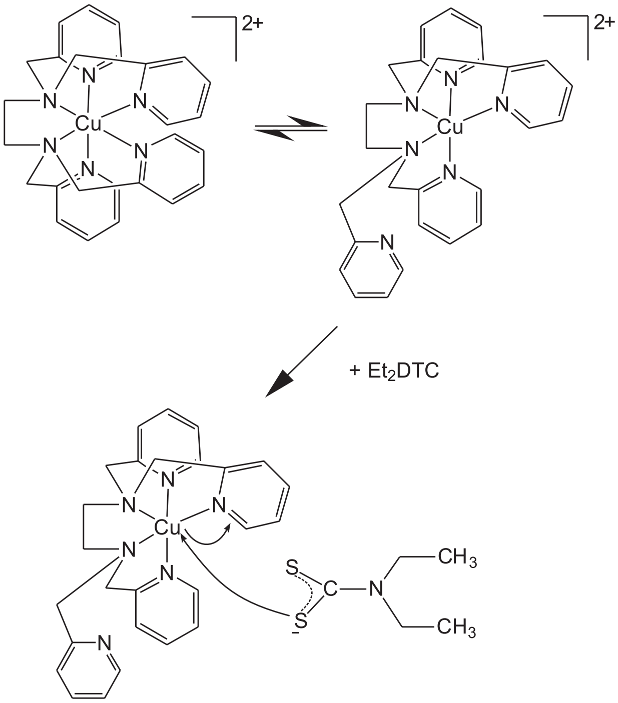


Figure 4. UV-Vis spectra of the Cu^{II}-TPEN solution with additions of Et$_2$DTC solution, in ethanol.

The formed complex shows a d-d band at 665 nm and a ligand to metal charge transfer (LMCT) band. Although the d-d band displacement occurs to smaller wavelengths (related to higher energy regions), it was observed that the formation of the Cu^{II}-Et$_2$DTC complex is favorable. Dithiocarbamates form very stable complexes with most transition metals, as already described in the literature.[43-45] The higher affinity of Et$_2$DTC, when compared to nitrogenous ligands, may be associated with the negative charge on the ET$_2$DTC ligand, acting as a nucleophile.[44] As proposed by Kaur *et al.*,[37] the Cu^{II}-TPEN complex may be in equilibrium between octahedral and trigonal bipyramidal geometries. The Cu^{II}-TPEN pentacoordinate structure can suffer a nucleophilic attack by the Et$_2$DTC, and force the TPEN withdrawal, originating the Cu^{II}-Et$_2$DTC tetracoordinate complex, according to Scheme 1.



Scheme 1. Proposed mechanism of the substitution of TPEN by Et$_2$DTC (adapted from Kaur *et al.*).[37]

To ensure these results obtained here, the study was performed in a reverse way, with the addition of TRIEN in Cu^{II}-TPEN solution, and addition of TPEN and TRIEN in Cu^{II}-Et$_2$DTC solution. As shown in Figure 5, the reverse process is not observed. According to our spectroscopic experiments, the affinity of the copper ion by the ligands presents the following order: Et$_2$DTC > TPEN > TRIEN.

Electrochemical experiments were performed to obtain more information about the studied systems. Figure 6 shows the cyclic voltammograms for the three complexes. Free copper presented an oxidation peak of 0.035 V under the studied conditions. In the presence of the TRIEN ligand, its oxidation peak appears at 0.008 V, a displacement of 30 mV to less positive region. The Cu^{II}-TPEN complex did not present a proper resolution on the glassy carbon electrode. Thus, its voltammogram was increased and inserted in the figure. Despite the low resolution, it is possible to observe a redox pair of the complex, with the

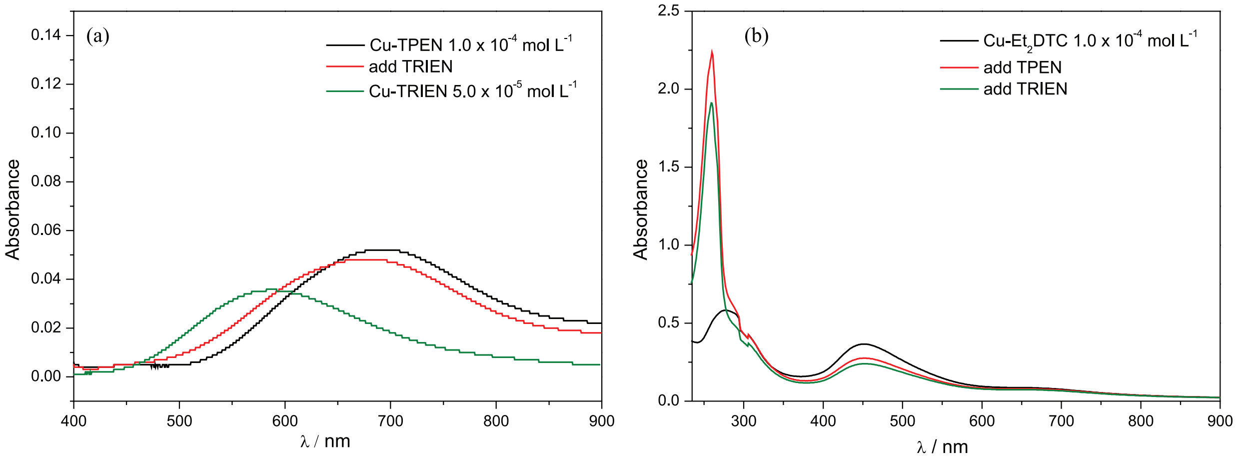


Figure 5. UV-Vis spectra of (a) Cu^{II}-TPEN solution with additions of TRIEN solutions; (b) Cu^{II}-Et$_2$DTC solution with additions of TPEN and TRIEN solutions.

oxidation peak at −0.135 V, a displacement of 100 mV with concerning the free copper. Cu^{II}-Et$_2$DTC presented an anode peak at 0.150 V, that is, 115 mV from the free copper oxidation potential. The greater the distance between the peaks (free metal and complexed metal), the greater interaction between the species. The metal ion showed different behavior in the presence of the ligands: the complexes with TPEN and TRIEN have their anodic peak shifted to the negative potential, while the Et$_2$DTC shifts to the positive potential.

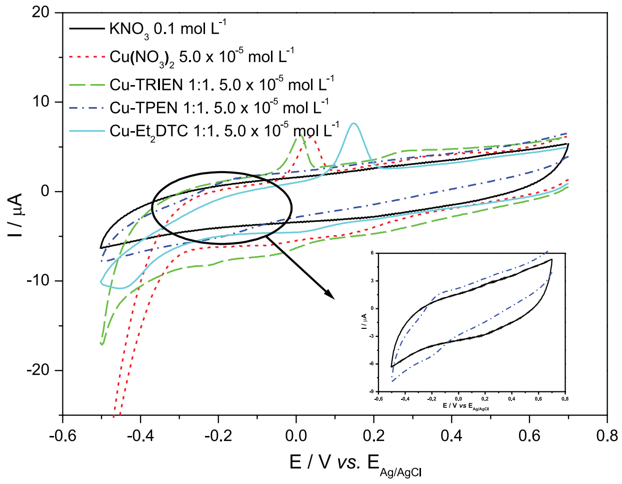
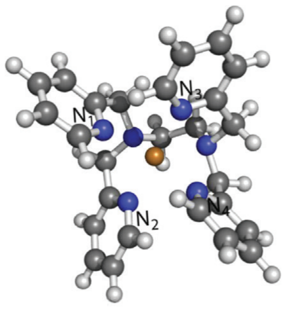
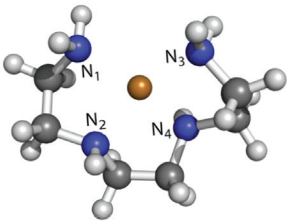


Figure 6. Cyclic voltammograms of a 5.0 × 10^{-5} mol L^{-1} Cu^{II}-TRIEN, Cu^{II}-TPEN, and Cu^{II} -Et$_2$DTC; v = 100 mV s^{-1}; 0.1 mol L^{-1} KNO$_3$.

We also used quantum mechanical calculations aiming to study the geometry of the complexes formed and their interaction energies. Table 1 displays the optimized geometries of the complexes and their N–Cu distances and angles.

As described in the literature,[47,48] Et$_2$DTC forms a 2:1 ligand:metal complex in a square planar geometry. According to our results, the TRIEN complex has a tetracoordinate structure with square planar geometry, while the TPEN complex has an octahedral geometry, corroborating the literature.[36,37] From the obtained results (Table 1), for the TPEN hexacoordinated complex with Cu^{II} ion, the distances between N$_5$ and N$_6$ with Cu^{II} atom are 0.3 Å furthermost than N$_{1-4}$ atoms and Cu^{II} atom. The different distances of N$_{1-4}$–Cu^{II} and N$_{5-6}$–Cu^{II} could be related to the difference of hybridization state of N$_{5-6}$ atoms (sp^3) in comparison to N$_{1-4}$ in which the non-ligand electron pair was located at an sp^2 orbital. These data corroborate

Table 1. Calculated structure of the Cu^{II}-TPEN and Cu^{II}-TRIEN complexes in vacuum

	Cu–N$_1$ / Å	2.1
	Cu–N$_2$ / Å	2.1
	Cu–N$_3$ / Å	2.1
	Cu–N$_4$ / Å	2.1
	Cu–N$_5$ / Å	2.4
	Cu–N$_6$ / Å	2.4
	N$_1$–Cu–N$_2$ / degree	90.4
	N$_3$–Cu–N$_4$ / degree	90.4
	N$_1$–Cu–N$_4$ / degree	147.6
E$_{binding}$ TPEN-Cu^{II} = −481.95 kcal mol^{-1}	N$_2$–Cu–N$_3$ / degree	175.5
	Cu–N$_1$ / Å	2.0
	Cu–N$_2$ / Å	2.0
	Cu–N$_3$ / Å	2.0
	Cu–N$_4$ / Å	2.0
	N$_1$–Cu–N$_2$ / degree	84.9
	N$_3$–Cu–N$_4$ / degree	84.9
	N$_1$–Cu–N$_4$ / degree	151.1
E$_{binding}$ TRIEN-Cu^{II} = −417.80 kcal mol^{-1}	N$_2$–Cu–N$_3$ / degree	151.1

E$_{binding}$ = E$_{complex}$ – (E$_{CuII}$ + E$_{ligand}$); the figures were generated with Pymol[46] 0.99c. TPEN: *N,N,N,N'*-tetrakis (2-pyridilmethyl) ethylenediamine; TRIEN: triethylenetetramine.

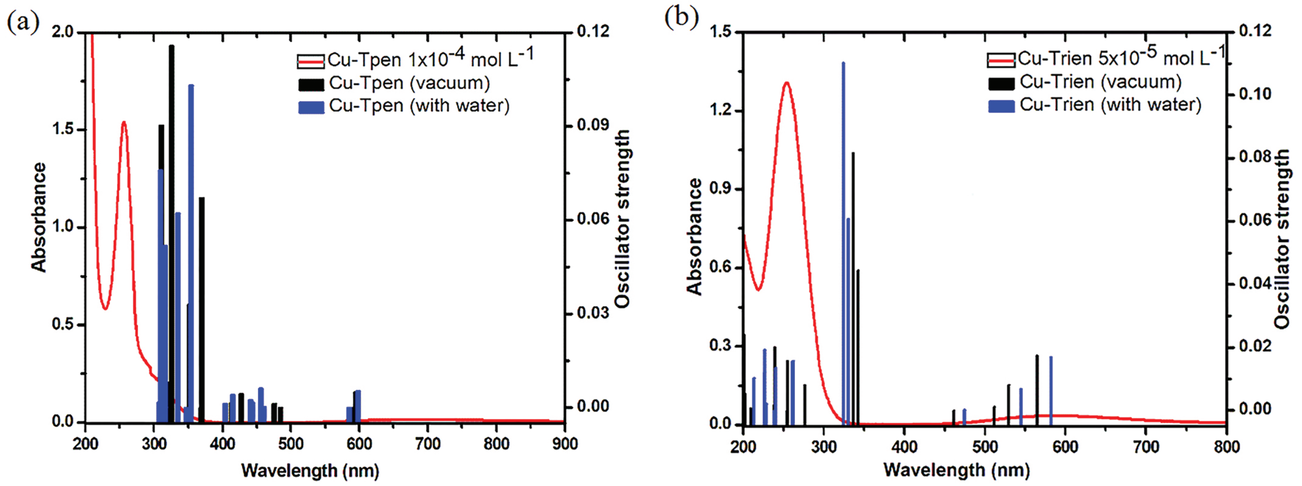


Figure 7. Experimental and calculated UV-Vis spectra for: (a) Cu^{II}-TPEN and (b) Cu^{II}-TRIEN.

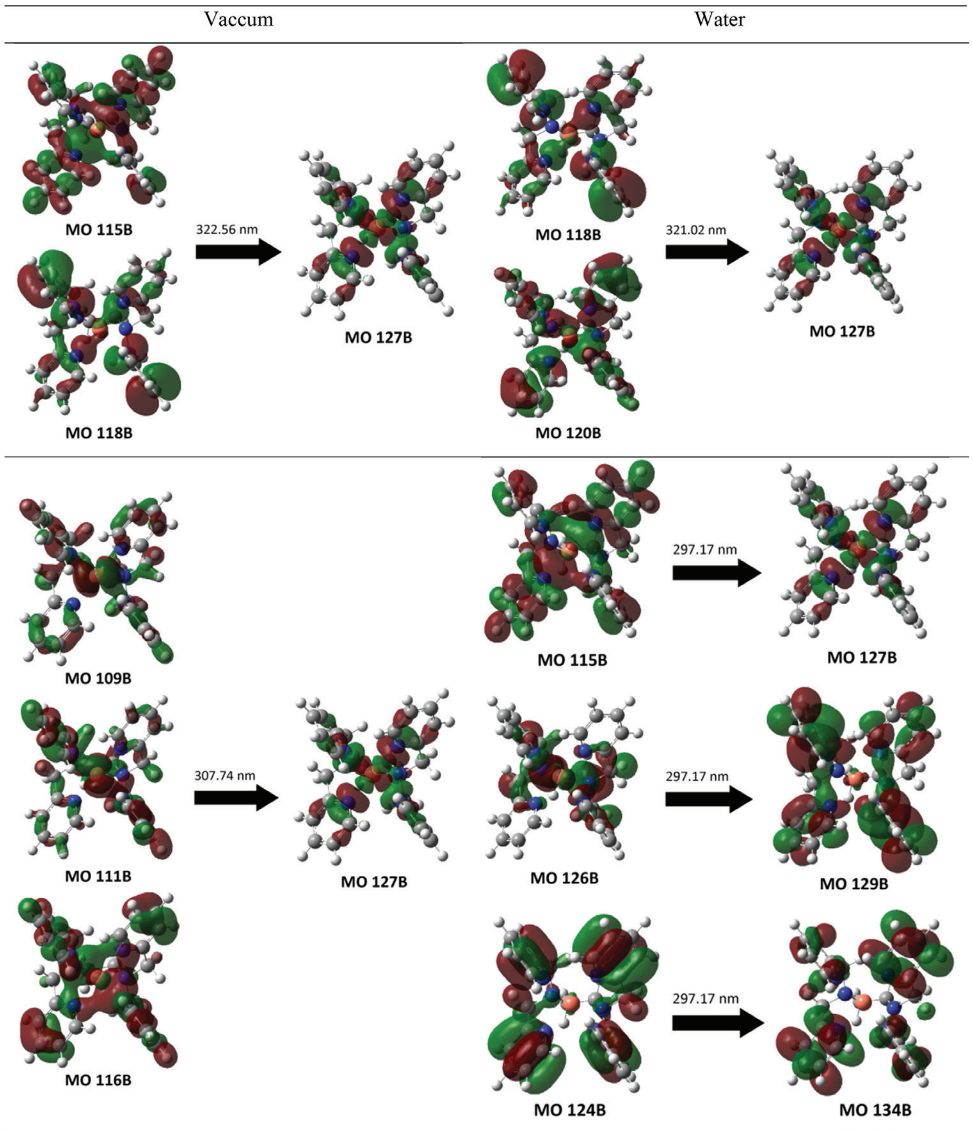


Figure 8. Plots of the molecular orbitals (MO) involved in the most intense transitions of TPEN + Cu^{II}. The occupied molecular orbital is presented before the arrow and, after, the virtual molecular orbital for which the electron is excited in the wavelength placed over the arrow. For the complex TPEN + Cu^{II}, HOMO and LUMO correspond to the molecular orbitals 126 beta (B) and 127B, respectively.

other structural information presented in the literature.[1,19] The N−Cu^{II} distances are smaller than the S−Cu^{II} distances because the atomic orbital involved in the complexation mechanism is different: the N atoms contribute with an sp^3 or sp^2 hybrid orbital and the S atom with an electronic lone pair at the 3p orbital.

The calculated values of the binding energy between Cu^{II} and Et$_2$DTC, TPEN, and TRIEN were equal to −726.72,[19] −481.85 and −417.80 kcal mol^{-1}, respectively. These results indicate a higher affinity of the copper ion for the Et$_2$DTC ligand, followed by the TPEN and, finally, the TRIEN, corroborating with the experimental results.

Figure 7 shows the theoretical spectra calculated for the Cu^{II}-TRIEN and Cu^{II}-TPEN complexes. From there, it is possible to note the similarity between theoretical and experimental spectra. A slightly difference between theoretical and experimental UV-Vis spectra can be attributed to the different environments used in the measurement. Just Cu^{II}-TPEN complex calculated spectra in vacuum and water environments are shifted to red. We selected the major wavelengths to plot molecular orbitals involved in electronic transitions, aiming to interpret the results.

Finally, the calculated molecular orbitals for both TPEN and TRIEN in complex with Cu^{II} in vacuum and water (Figures 8 and 9) indicate that the two most intense electronic transitions are related to charge transfer from ligands to copper ion.

Conclusions

From the experimental results of UV-Vis spectrophotometry, we observed the d-d bands for the

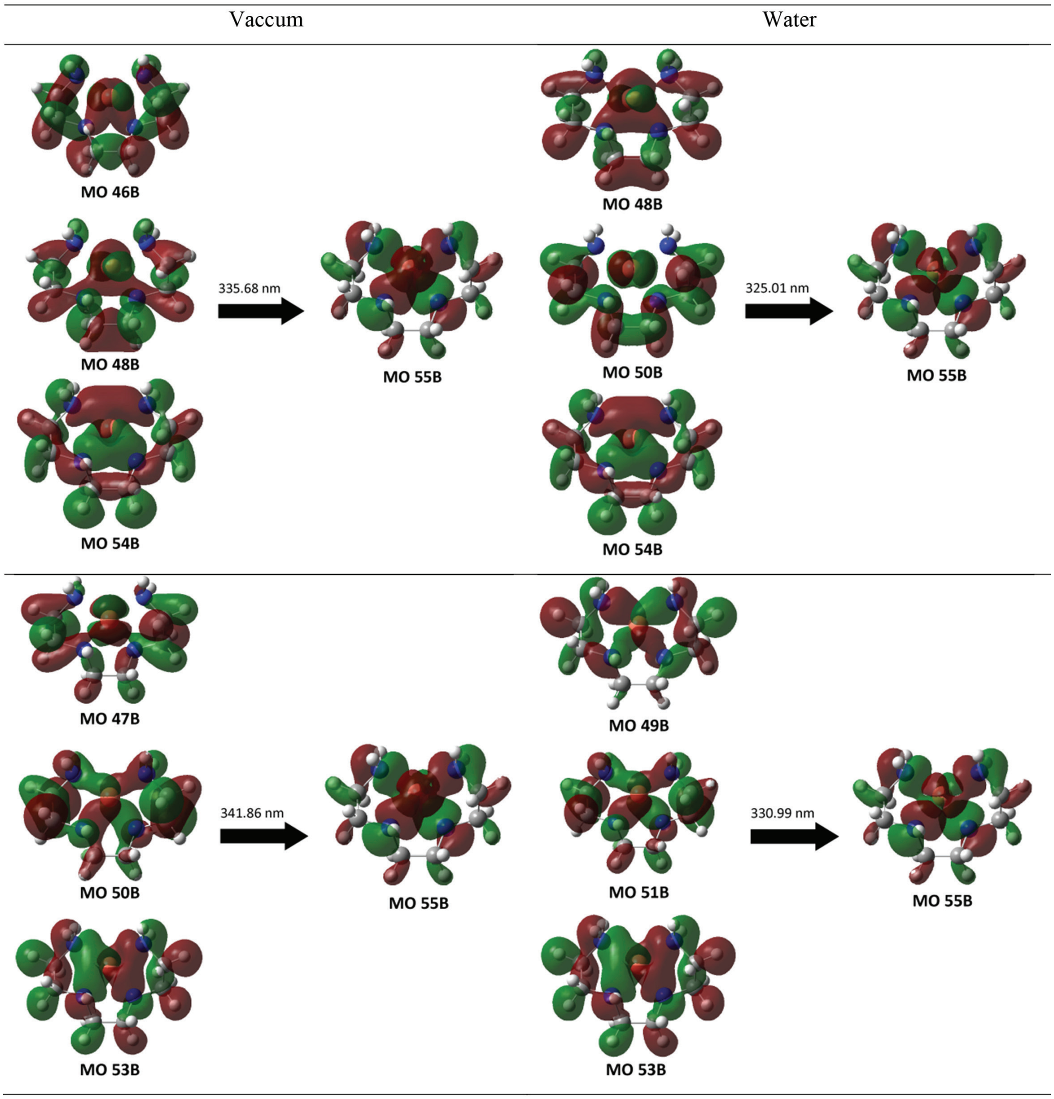


Figure 9. Plots of the molecular orbitals (MO) involved in the most intense transitions of TRIEN + Cu^{II}. The occupied molecular orbital is presented before the arrow and, after, the virtual molecular orbital for which the electron is excited in the wavelength placed over the arrow. For the complex TRIEN + Cu^{II}, HOMO and LUMO correspond to the molecular orbitals 54 beta (B) and 55B, respectively.

Cu^{II}-complexes with TPEN, TRIEN, and Et_2DTC were 689, 576, and 665 nm, respectively. Our experiments suggested that Cu^{II} has more affinity by the Et_2DTC ligand, followed by TPEN and TRIEN. Electrochemical studies indicate that the interaction between Cu^{II} is stronger with Et_2DTC ligand than with the nitrogenous ligands, due to the bigger potential displacement between the free metal and complexed metal. The same conclusion was found from theoretical calculations, with a binding energy of -417.80 kcal mol^{-1} for the Cu^{II}-TRIEN complex, -481.85 kcal mol^{-1} for the Cu^{II}-TPEN complex and -726.72 kcal mol^{-1} for the Cu^{II}-Et_2DTC complex. These values indicated that the affinity of the copper ion by the ligands presents the following order: $Et_2DTC > TPEN > TRIEN$.

Acknowledgments

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