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An Investigation on the Synthesis, Structure and Specific Properties of Zn(II) and Cu(II) Complexes with Tryptophan

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Abstract: In this work, $[Zn(Tryp)_2(H_2O)_2]$ and $[Cu(Tryp)_2H_2O]$ complexes were synthesized by using Zn^{2+} and Cu^{2+} (from $Zn(CH_3COO)_2$, $Cu(CH_3COO)_2.H_2O$, respectively) as central metal ions with tryptophan (HTryp) as ligand. The compositions and structures of the synthesized $[Zn(Tryp)_2(H_2O)_2]$ and $[Cu(Tryp)_2H_2O]$ complexes have been investigated by energy-dispersive X-ray spectroscopy (EDS), infrared (IR), nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry (MS), thermal analysis (TG, TGA/DTG), and electrical conductivity methods. The obtained results demonstrated that in the synthesized complexes, tryptophan is a bidentate ligand. The bonding between the tryptophan with central metal is with (O, N_{amino}) donor sets. The coordination number of Zn^{2+} and Cu^{2+} in the complexes is 6 and 5, respectively. The stability of synthesized complexes was also confirmed via testing in simulated gastric fluid environments.

Keywords: Zinc(II) (Zn^{2+}) complex; copper(II) (Cu^{2+}) complex; tryptophan (HTryp); metal complex; simulated gastric fluid.

1. Introduction

All amino acids are highly effective metal bonding agents and maybe the most important in transporting minerals from the intestine into mucosal cells and storing mineral components in the body of animals [1-5]. Previous reports show that the metal complexes of amino acids have higher absorption, transport, and metabolism efficiency in the body than simple inorganic forms [6-13]. Medeiros-Ventura [3] reported that the complexes of zinc(II), manganese(II), and copper (II) with an amino acid ligand could improve the performance and bone characteristics of layer-type chicks under temperatures of neutral and cold stress. In addition, the complexation with d-block metal ions can also enhance the antioxidant properties of the ligand or generate the antioxidant, anticancer, antibacterial, antifungal, or toxicity of the complexes [14-21]. Moreover, the metal-ligand bonding in coordination compounds will allow metal ions to be absorbed, transported in the blood, and across the cell membrane to bring metal ions to required locations [2,6,13,19].

In the α-amino acid family, tryptophan (HTryp), with good complexation with d-block metal ions, is widely used to prepare complexes. In these metal ion- HTryp complexes, bonding can occur at the N atom of the NH_2 group and the O atom of the COO- group from HTryp molecules [22,23]. The metal complexes of HTryp have a great potential in applications thanks

to their antibacterial activity [1,24,25], antioxidant, anticancer, toxicity, and neuroprotective [14] and increase the ability to absorb, transport, and metabolize metal minerals in the body [6-12]. Several works on synthesizing and investigating biological properties, including antioxidant, anticancer, toxicity, and neuroprotective of transition metal complex ions with organic ligands, have been reported [14,20,21]. In which the structure of complexes was usually investigated by the infrared spectroscopy (IR), ultraviolet-visible (UV-vis) spectroscopy, elemental analysis (EDX), magnetic moment, single-crystal X-ray diffraction, and nuclear magnetic resonance (NMR) spectroscopy techniques [2,4,16-19,22-28]. For example, Koppa [29] has used atomic absorption spectroscopy for analyzing the synthesized complexes of Zn^{2+} and Cu^{2+} ions with methionine, lysine, tryptophan, and isoleucine ligands.

Based on the above considering, Zn^{2+} and Cu^{2+} ions are considered as the most important microelements [14,21,23,29-32]; therefore, we report here a simple approach for the synthesis of $[Zn(Tryp)_2(H_2O)_2]$ and $[Cu(Tryp)_2H_2O]$, the Zn(II) and Cu(II) complexes of tryptophan, then following by investigation on their structure and their chemical properties for further potential applications.

2. Materials and Methods

2.1. Materials and reagents.

2,2',2",2'"-(Ethane-1,2-diyldinitrilo)tetraacetic acid ($C_{10}H_{16}N_2O_8.2H_2O$, EDTA), 1-(2-pyridylazo)-2 naphthol ($C_{15}H_{11}N_3O$, PAN), 2-hydroxy-1-(1-hydroxy-2-naphthylazo)-6-nitronaphthalene-4-sulfonic acid sodium salt ($C_{20}H_{12}N_3NaO_7S$, Eriochrome black T), $Cu(CH_3COO)_2.H_2O$ (≥ 98 wt.%), $Zn(CH_3COO)_2$ (≥ 98 wt.%), tryptophan ($C_{11}H_{12}N_2O_2$, ≥ 98 wt.%), and pepsin (≥ 250 units/mg solid) were purchased from Merck. NaOH (≥ 98 wt.%) and NaCl (≥ 99 wt.%) were purchased from Xilong Company (China). Ethanol, HCl (≥ 37 wt.%) and H_2SO_4 (98 wt.%) were purchased from Duc Giang Chemical Company (Vietnam). Deionized water was used in all the experiments.

2.2. Synthesis of $[Zn(Tryp)_2(H_2O)_2]$ and $[Cu(Tryp)_2H_2O]$ complexes.

10 mmol tryptophan (HTryp) and 5 or 8 mmol NaOH (for the synthesis of Zn(II), Cu(II) complex, respectively) were dissolved into 40 mL a mixture of water and ethanol (5:1 (v/v)) at 60°C. A solution of 5 mmol Zn(II) or Cu(II) was prepared by dissolving a corresponding amount of $Zn(CH_3COO)_2$ or $Cu(CH_3COO)_2.H_2O$) into distilled water. The first solution was added into containing metal ion solution, and the mixture was stirred at 75 °C for 4 hours. When the reaction mixture was cooled to room temperature (RT) for the crystallization process, which was allowed for 24 hours. The deposited crystalline complex was filtered and washed by cold water. Obtained complex as precipitated solid that was re-dissolved into hot distilled water (75 °C) and then cooling to RT for 24 for recrystallization. The crystalline complex was filtered, washed with cold water and acetone, respectively; then it was dried at 60°C for 24 hours to obtain of $[Zn(Tryp)_2(H_2O)_2]$ complex as a white powder and $[Cu(Tryp)_2H_2O]$ complex as a blue powder. The yield of $[Zn(Tryp)_2(H_2O)_2]$ was 91.6 wt.%, $[Cu(Tryp)_2H_2O]$ was 89.1 wt.%.

2.3. Investigation of stability of the complex in the environment simulated gastric fluid.

The simulated gastric fluid environment containing H^+, Cl^-, Na^+, pepsin, and water with pH 1 to 3, was prepared in our laboratory following previous reports [33-35]. To prepare 1 litter of simulated gastric fluid, 2 g NaCl and 3.2 g pepsin were added into a baker standing 7 mL concentrated HCl, then distilled water was added to get 1 liter of solution. For investigation of the stability of the complex in the gastric fluid simulated in the environment, an exact amount of the complex $[Zn(Tryp)_2(H_2O)_2]$ was dissolved into 10 mL of simulated gastric fluid under continuous stirring. The UV-Vis spectra of the solution sample were recorded in a range of time from 0 to 4 hours.

2.4. Methods and measurements.

Analysis of the content of elements in the complexes by chemical methods: the complex samples were dissolved by concentrated H_2SO_4, then, the concentration of metal ions were determined by titration with the standard substances and specific indicators, i.e., Cu^{2+} concentration was measured by titration with EDTA in acetate buffer (pH 4 - 5) and using the PAN indicator. Zn^{2+} was titrated with EDTA in ammonia buffer (pH 10) using the Eriochrome black T indicator. Schematic thermal analysis of complexes was recorded on a Shimadzu DTG - 60H, a heating rate of 10 °C/min, from 30 °C to 800 °C. Energy dispersive X-rays (EDS) of the complexes were recorded on the Jeol JSM 7600F. The electrical conductivity of complex solutions in distilled water was recorded on a Toledo conductivity meter. The mass spectrum of the complexes was recorded on an LC/MS/MS-Xevo TQMS, ESI method using $NaCH_3COO$ solution as solvent. Infrared spectra (IR) of the complexes were recorded on a Nicolet (Thermo - America); the complexes were pellet with KBr and spectrophotometer from 4000 to 400 cm^{-1}. UV – Vis spectra of the complexes were recorded on Agilent 8453. NMR spectra were recorded on Advance 500, 500MHz using dimethyl sulfoxide (DMSO) solvent.

3. Results and Discussion

3.1. Elemental analysis of complexes.

To verify, the obtained $[Zn(Tryp)_2(H_2O)_2]$ and $[Cu(Tryp)_2H_2O]$ complex was dissolved into hot water; then, the 0.1 M $NaHCO_3$ solution was slowly added. There was no hydroxide precipitate appeared, which implies that all Zn(II) or Cu(II) ions existed in corresponding complexes, and there were no Zn(II) or Cu(II) ions present in solution as free ions.

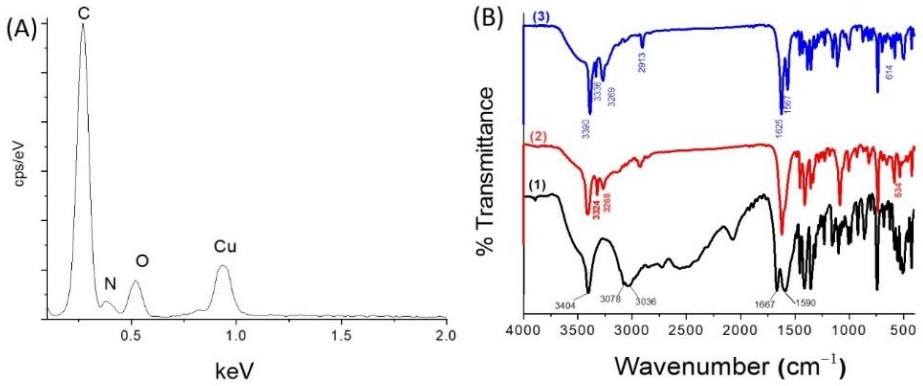

Figure 1. (A) EDS of $[Cu(Tryp)_2(H_2O)]$ complex and (B) Infrared spectra of (1) HTryp, (2) $Zn(Tryp)_2(H_2O)_2]$ and (3) $[Cu(Tryp)_2H_2O]$.

Table 1. The results of the elemental analysis of complexes.

Complex	Formula expected	% weight metal (Found /Calc.) (chemical method)	The atomic ratio of Metal:O:N (found / Calc.) (EDS method)
$[Zn(Tryp)_2(H_2O)_2]$	$[Zn(C_{11}H_{11}N_2O_2)_2(H_2O)_2]$	12.90 / 12.82	1:6.1:4.05 / 1:6:4
$[Cu(Tryp)_2(H_2O)]$	$[Cu(C_{11}H_{11}N_2O_2)_2(H_2O)]$	13.00 / 13.11	1:4.90:4.26 / 1:5:4

The composition of complexes was analyzed by chemical methods, and energy-dispersive X-ray spectroscopy (EDS), in which the main element compositions in $[Zn(Tryp)_2(H_2O)_2]$ and $[Cu(Tryp)_2(H_2O)]$ complexes are analyzed by EDS (Fig. 1A) with their ratio in proportion to the peak intensity and results are shown in Table 1. It can be seen that the obtained result of element ratios is accordingly to the composition of complexes as expected (Table 1). However, as well know that the disadvantage of the EDS method is that the determined carbon content is often inaccurate because the carbon sole is used in the measurement process. In addition, the EDS method also does not recognize too light elements like H, which causes a difference between calculation from complex formulas and EDS results.

3.2. FT-IR analysis.

IR spectra of HTryp and two synthesized complexes are shown in Fig. 1B. Strong and sharp absorption bands around 3400 cm^{-1} can be attributed to the vibration of the N-H bond in the five-membered rings of tryptophan and the O-H bonds in coordinating water molecules. The bands at 3078 cm^{-1} and 3036 cm^{-1} corresponds to the vibration of NH_3^+ and CH_2 groups in FT-IR spectrum of HTryp (curve 1) were shifted to 3324 cm^{-1} and 3268 cm^{-1}, respectively, for $[Zn(Tryp)_2(H_2O)_2]$ (curve 2), and at 3326 cm^{-1} and 3269 cm^{-1} for $[Cu(Tryp)_2(H_2O)]$ (curve 3). These changes can be attributed to the change from positive charge of $–NH_3^+$ in HTryp free ligand to neutral NH_2 group in $Tryp^-$ anion in the complexes. The COO^- group of HTryp show absorption bands around1667 cm^{-1} and 1590 cm^{-1}, but in the spectrum of $[Zn(Tryp)_2(H_2O)_2]$, they have shifted to 1621 cm^{-1} and 1600 cm^{-1}; in the spectrum of $[Cu(Tryp)_2(H_2O)]$ they have shifted to 1625 cm^{-1} and 1567 cm^{-1}. Fig. 1B (curve 2 and 3) also displays two peaks in the range of small wave numbers 450 - 620 cm^{-1}, which can be attributed to vibrations of metal-O and metal-N bonds in the complexes [17,18,22-25,27,29]. Therefore, the obtained results of IR spectroscopy confirm the complexation of HTryp and the metal ions.

3.3. NMR spectroscopy.

As shown in Fig. 2A (inserted), the HTryp molecule has 11 C atoms corresponding to 11 signals in ^{13}C-NMR spectra of $[Zn(Tryp)_2(H_2O)_2]$ (Fig. 2A and Table 2). It can be seen that there is no C signal from the COOH group, indicating a bond between Zn^{2+} and COO^- leading to a reduction in the signal intensity of the C1 atom. The signal of the C2 atom in the complex ($\delta = 54.20$) is strongly reduced compared to that of the uncoordinated ligand (57.8), indicating that there is a coordination bond between the Zn^{2+} ion and NH_2 group of the ligand. The proximity of C3 atom to the NH_2 and COO^- groups leads to the shift of the signal from 27.5 to 29.02. The remaining C atoms are less affected; therefore, their signals do not change significantly.

Table 2. Resonance signals in ^{13}C-NMR spectra of HTryp and $[Zn(Tryp)_2(H_2O)_2]$.

C number	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	$.C_{11}$
δ(HTryp)	174.5	57.8	27.5	109.7	127.4	118.8	119.8	121.7	111.1	136.5	123.0
δ(complex)	-	54.2	29.0	110.7	127.2	118.2	118.3	120.9	111.4	136.4	123.0

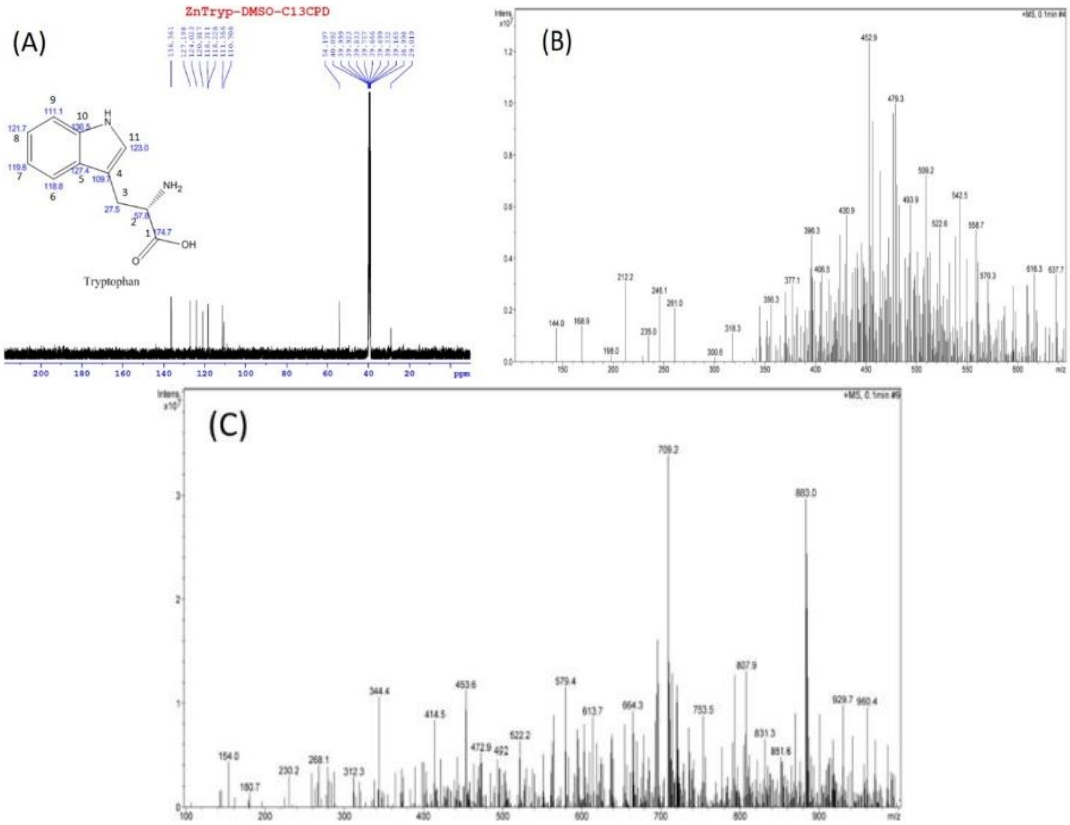

Figure 2. (A) ^{13}C-NMR spectrum of $[Zn(Tryp)_2(H_2O)_2]$ complex, (B, C) Mass spectra of $[Zn(Tryp)_2(H_2O)_2]$ and $[Cu(Tryp)_2(H_2O)]$ complexes, respectively.

3.4. MS analysis.

The molecular weight of the complexes was determined by mass spectrometry. In the mass spectrum of $[Zn(Tryp)_2(H_2O)_2]$ (Fig. 2B), there is a peak m/z = 509 (63%) with the highest intensity in the peak cluster. The value 509 is the mass of the molecule ion ($[Zn(C_{11}H_{11}N_2O_2)_2(H_2O)_2] + H^+$), so the experimental molecular mass of $[Zn(Tryp)_2(H_2O)_2]$ is 508u. Similarly, in the mass spectrum of $[Cu(Tryp)_2H_2O]$ (Fig.2C), there is a peak m/z = 492 (14%) with the most intense in the peak cluster. The value 492 is the mass of the molecule ion $([Cu(C_{11}H_{11}N_2O_2)_2] + Na)^+$, so the experimental molecular mass of $[Cu(Tryp)_2H_2O]$ is 487u. Thus, the molecular mass was in good agreement with the expected molecular formula.

3.5. Electrical conductivity of complexes.

Electrical conductivity of the $[Zn(Tryp)_2(H_2O)_2]$ 10^{-3}M solution is 6.3 $cm^2\ \Omega^{-1}\ mol^{-1}$, $[Cu(Tryp)_2H_2O]$ 10^{-3} M solution is 5.2 $cm^2\ \Omega^{-1}\ mol^{-1}$. These values are very small, implying that the molecular complexes were not dissociated.

3.6. Thermal analysis.

The thermal analysis results of the complexes are shown in Fig. 3 and Table 3. Thermal analysis diagram of $[Zn(Tryp)_2(H_2O)_2]$ complex (Fig. 3A) shows a strong endothermic effect at 284.49 ^oC accompanied by mass loss due to coordinated dehydration in the range from 30 ^oC to 300 ^oC. From 300 to 600 ^oC, there is one exothermic effect at 360.46 ^oC and endothermic at 429.75 ^oC and the significant mass reduction rate at 317.98 ^oC and 457.56 ^oC, which can be attributed to the evaporation process, the separation of gases at the same time as the oxidation-

reduction process that occurs in the sample. From 600 °C to 800 °C the sample mass is almost constant; the final product is ZnO accounting for 15.03%.

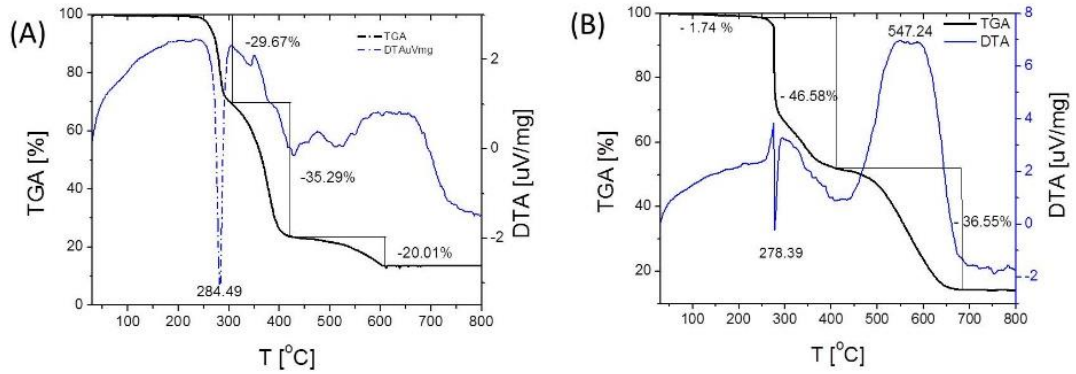

Figure 3. Thermal analysis diagram of (A) $[Zn(Tryp)_2(H_2O)_2]$ and (B) $[Cu(Tryp)_2H_2O]$.

Table 3. Thermal analysis results of complexes.

Complex	Temperature range (°C)	Mass loss (%)		Thermal effects	DrTG (°C)
		Found / Calc	Removed group		
$[Zn(Tryp)_2(H_2O)_2]$	30 - 300	84.97 / 84.03	H_2O coordination	284.49 (endothermic) 360.46 (exothermic) 429.75 (endothermic)	383.93 378.39
	300 - 600		CO_2, H_2, N_2		
	> 600	15.03 / 15.07	ZnO		
$[Cu(Tryp)_2H_2O]$	225 – 285	84.87 / 83.61	H_2O coordination	278.39 (endothermic) 547.24 (exothermic)	276.01
	285 – 675		CO_2, H_2, N_2		
	> 675	15.13 / 16.39	CuO		

Thermal analysis diagram of $[Cu(Tryp)_2H_2O]$ (Fig. 3B) shows an endothermic effect at 278.39 °C accompanied by mass loss corresponding to dehydration and an exothermic effect at 547.24 °C accompanied by the mass loss, which can be attributed to the thermal decomposition of the complex accompanied by combustion and evaporation of the products. The final product of thermal decomposition is CuO which accounts for 15.13 %. The results show that the experimental results are accordant with the expected composition. Thus, from the analytical results of the methods, it can be suggested that the formulas of the two synthesized complexes are $[Zn(Tryp)_2(H_2O)_2]$ and $[Cu(Tryp)_2H_2O]$. The coordination number of Zn^{2+} and Cu^{2+} ion is 6 and 5, respectively [28].

3.7. Investigation of the stability of the complex in the environment simulated gastric fluid.

The metal complexes of amino acids have been proven to have much higher absorption, transport, and metabolism efficiency in the body compared to that of simple inorganic forms[6-13]. Because after ingestion, metals in the simple inorganic forms are often dissociated in the stomach to produce free metal ions. These cations in the intestine can precipitate with some anions and be excreted. Metal ions in coordination compounds with amino acids in the gastric fluid environment will be transported into the intestine and to the required location in the body. Fig. 4 shows UV–Vis spectra of HTryp (curve a) and $[Zn(Tryp)_2(H_2O)_2]$ complex (curve b – g) in the environment simulated gastric fluid. It can be seen two specific peaks at 194 nm and 301 nm on the UV-Vis spectrum of HTryp.

In the UV-Vis spectra of $[Zn(Tryp)_2(H_2O)_2]$, these two peaks have shifted to 207 nm and 278 nm, respectively. Moreover, the intensity of these peaks increased throughout the survey period from 20 seconds to 150 minutes (Fig. 4, curve b to g), which implies that $[Zn(Tryp)_2(H_2O)_2]$ complex was slowly dissolved. This proves that $[Zn(Tryp)_2(H_2O)_2]$ is stable in the simulated gastric fluid.

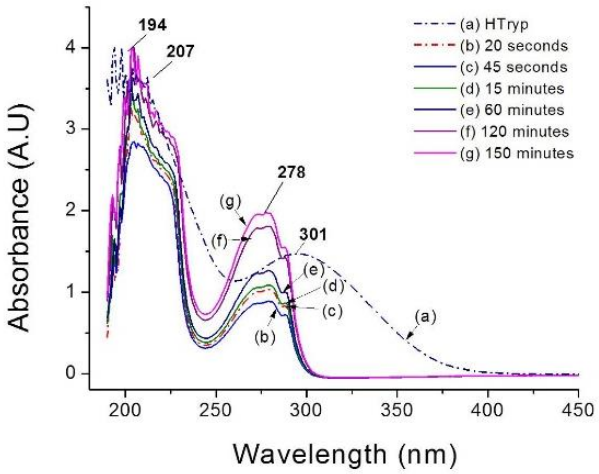

Figure 4. UV-vis spectra of $[Zn(Tryp)_2(H_2O)_2]$ in the environment simulated gastric fluid for various time.

4. Conclusions

Two complexes of Zn^{2+}, Cu^{2+} with tryptophan have been synthesized. By experimental investigation, the composition, structure, and properties of as-synthesized complexes have been studied. The formulas of the two synthesized complexes are $[Zn(Tryp)_2(H_2O)_2]$ and $[Cu(Tryp)_2H_2O]$. Among the complexes, Zn^{2+} has a coordination number of 6, and Cu^{2+} has a coordination number of 5. The $[Zn(Tryp)_2(H_2O)_2]$ complex is stable in simulated gastric, intestinal, and blood fluid. Therefore, it can be applied in the production of mineral-amino acid supplements for humans and animals.

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Conflicts of Interest

The authors declare no conflict of interest.

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