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Synthesis and Characterization of Diranitidinecopper(II) Sulfate Dihydrate

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Abstract. The complex of ranitidine with Cu(II) has been synthesized in 1:2-mole ratio of metal to the ligand in water. The forming of the complex was indicated by shifting of maximum wavelength from 816 nm ($CuSO_4 \cdot 5H_2O$) to 626 nm (the complex). Infrared spectra indicated NO_2 and NH functional group were coordinated to Cu(II). The percentage of copper in the complex measured by Atomic Absorption Spectroscopy (AAS) analysis was 7.5% indicating that formula of the complex was $Cu(ranitidine)_2SO_4(H_2O)_n$ (n=2, 3 or 4). The electrical conductivity of Cu(II) complex in water was 71.0 Scm^2mol^{-1} corresponding to 1:1 electrolytes. Thermogravimetric/Differential Thermal Analysis (TG/DTA) showed the presence of two molecules of H_2O in the complex. UV-Vis spectra showed a transition peak on 15974 cm^{-1} indicating square planar geometry. The complex was paramagnetic with μ_{eff} 1.77 BM. The proposed formula of the complex was $[Cu(ranitidine)_2]SO_4 \cdot 2H_2O$.

1. Introduction

Study and synthesis of a metal complex with various drugs as ligands become considerable research field due to the synergistic action of both ligands and metals to improve the activity of the drugs [1-11]. The work and activity of the drug an enhancement after converted to chelate transition metals that turned out to be better than using only organic compounds [12-16]. Famotidine (fam) and cimetidine (cim) are anti-ulcer drugs and able to function as ligands because they have several free electron pairs. Famotidine and cimetidine have been reported to form complexes with Cu(II) ion [17-18]. In the tetragonal [Cu(fam)] complexes, N-guanidine (N3), N-thiazole (N9), N-amidine (N16) and S groups in the thioether are coordinated on Cu^{2+} ions [17]. Thus, the Cu^{2+} ion is coordinated by the cimetidine ligand through the -C=N group and the -CS group forming the square planar $[Cu(cim)_2]$ complex [18].

Another anti-ulcer compound that has a potentiality to form complexes with a metal ion is ranitidine. Ranitidine hydrochloride is a histamine H_2-receptor antagonist with a furan ring structure that increases its potency to inhibit gastric acid secretion induced by various stimuli while lacking the anti-androgenic and hepatic microsomal enzyme inhibiting effects [19]. The ranitidine structure showed in figure 1, has five donor atomic groups, i.e. -CN, -CS, -NH-, -CO, and $-NO_2$ which can be coordinated on metal ions.

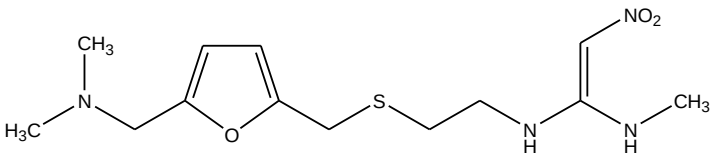

Figure 1. Structure of ranitidine

It is reported that ranitidine (ran) and glycine (gly) forming a complex with zinc. The complex of $[Zn(ran)(gly)]NO_3$ is shown in figure 2. The -NH- and $-NO_2$ groups of ranitidine together with the -COO- and $-NH_2$ groups of glycine are coordinated to Zn^{2+} ions form tetrahedral geometry [20].

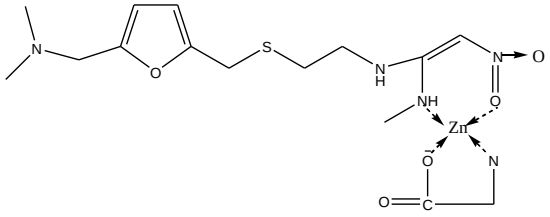

Figure 2. Structure of $[Zn(ran)(gly)]NO_3$ complex

The metal complex is one of the compounds that can be used for various applications such as science in biology, clinics, analytics and renewable science. In this paper, we use Cu(II) as metal central ions due to the effect of increasing of work activity as anti-ulcer drug compared to its free drug as ligand when complexed with Cu(II) such as in $[Cu(cim)_2]$ [21]. The Cu^{2+} ion has a $3d^9$ configuration with one unpaired electron, able to bind to a ligand that has a free electron pair. The new complex of copper with ranitidine ligand and its properties are then characterized by UV-Visible (UV-Vis) spectroscopy, Atomic Absorption Spectroscopy (AAS), molar conductivity, Thermogravimetric/Differential Thermal Analysis (TG/DTA), infrared spectroscopy, and magnetic susceptibility measurement.

2. Experimental

2.1. Materials

The chemicals and solvents were of reagent grade and used without further purification. All chemicals such as $CuSO_4 \cdot 5H_2O$, ranitidine hydrochloride, NH_4OH, $NiSO_4 \cdot 6H_2O$, $FeSO_4 \cdot 7H_2O$, $CuCl_2 \cdot 2H_2O$, $FeCl_2 \cdot 4H_2O$, $FeCl_3 \cdot 6H_2O$, $AlCl_3 \cdot 6H_2O$, and nitric acid were purchased from E. Merck.

2.2. Physical measurements

Spectra UV-VIS of metal complex and ligand was recorded in methanol solvent using UV-Vis Double Beam Shimadzu PC 1601 spectrophotometer. The copper content was determined by Atomic Absorption Spectrometer (AAS) Shimadzu AA-6650. Infrared spectra were recorded on Prestige-21 Shimadzu spectrophotometers as KBr pellets in the frequency range of 4000–450 cm^{-1}. Molar conductivity (Λ*m) of 1 mM solution in methanol was measured on Jenway CE 4071 conductivity meter at 25 ^oC. The presence or absence of H_2O molecules in the complex was estimated from the results of thermal analysis using Differential Thermal Analyzer Shimadzu 50. The magnetic moment was measured using Auto Sherwood Scientific 10169 Magnetic Susceptibility Balance.

2.3. Synthesis of Cu(II) complex

Ranitidine hydrochloride (2.10 g, 6 mmol) was dissolved in 15 ml of distilled water plus NH_4OH to reach pH 7.5 then mixed with 5 mL distilled water solution of $CuSO_4 \cdot 5H_2O$ (0.249 g, 3 mmol). The mixture was then refluxed for 2 hours while stirring. After 24 hours, obtained precipitation was filtered with filter paper and dried in a desiccator.

3. Result and Discussion

3.1. Formation of the complex

Figure 3 shows the shift of the maximum wavelength of the Cu(II)-ranitidine complex from 810 nm ($CuSO_4$ solution) to 626 nm (Cu-ranitidine complex). This large wavelength shift (185 nm) shows that ranitidine is a strong ligand.

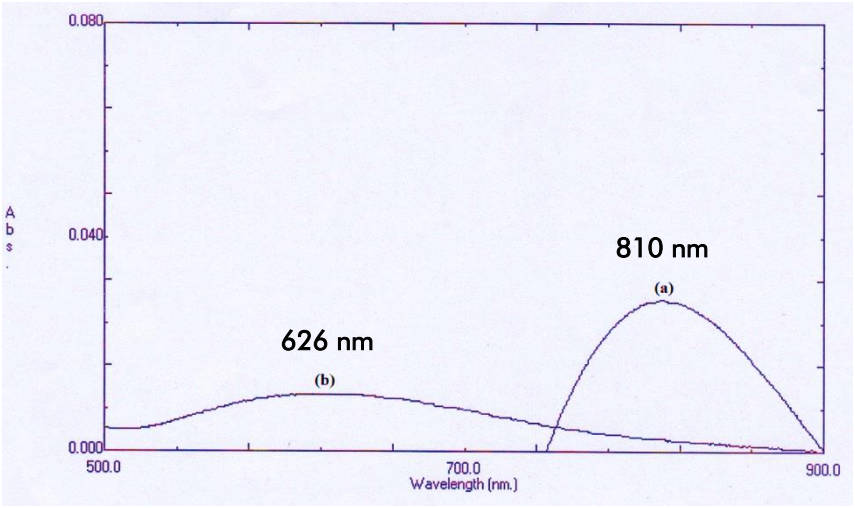

Figure 3. Electronic spectra (a) $CuSO_4 \cdot 5H_2O$ and (b) Cu(II)–ranitidine complex in water with a mole ratio of metals and ligands 1: 2.

3.2. Analysis of the amount of copper with Atomic Absorption Spectroscopy (AAS)

The copper content analyzed by AAS in the Cu(II)-ranitidine complex was 7.54 ± 0.45%. If the result of the measurement is compared with theoretical analysis shown in table 1, it can predict the formula of Cu(II)-ranitidine. The different value of copper content based on theoretic and experiment generally happen [22-24]. It needs more methods to confirm the number of presence of water molecules, such as thermogravimetry and differential thermal analysis. Therefore, the formula of the formed complex is $Cu(ranitidine)_2SO_4(H_2O)_n$ (n=2, 3 or 4).

Table 1. Percentage of copper in the complex theoretically.

Empirical Formula	Mr	% Cu
$Cu(ran)_{2(}SO_4)(H_2O)_2$	824.5	7.70
$Cu(ran)_{2(}SO_4)(H_2O)_3$	842.5	7.53
$Cu(ran)_{2(}SO_4)(H_2O)_4$	860.5	7.37

3.3. Analysis of electrical conductivity

The results of standard electrical conductivity measurements and complex in water are shown in table 2. If the electrical conductivity results of the Cu(II)-ranitidine complex compared to the standard electrical conductivity of the solution, the conductivity of the Cu(II)-ranitidine complex is close to the electrical conductivity of $CuSO_4 \cdot 5H_2O$ and $NiSO_4 \cdot 6H_2O$. The value of the measurement is consistent with the 1:1 electrolytic nature of the complex, indicating that the SO_4^{2-} ions are not coordinated to Cu^{2+}.

Table 2. Molar conductivity of metal salts and Cu(II)-ranitidine in water

Solution	Λ_m (S cm^2 mol^{-1})	Cation:anion Charge
Water	0	-
$CuSO_4 \cdot 5H_2O$	87 ± 1	1:1
$NiSO_4 \cdot 6H_2O$	81 ± 3	1:1
$FeSO_4 \cdot 7H_2O$	103 ± 1	1:1
$CuCl_2 \cdot 2H_2O$	134 ± 0.5	2:1
$FeCl_2 \cdot 4H_2O$	173 ± 1	2:1
$FeCl_3 \cdot 6H_2O$	286 ± 1	3:1
$AlCl_3 \cdot 6H_2O$	225 ± 0.3	3:1
Cu(II)-ranitidine	**71.04 ± 3**	**1:1**

3.4. Thermal analysis

TG/DTA showed the peak of endotherm at temperature 99.08 °C, shown in figure 4. Thus, at that temperature also happened the reduction of 4% compound mass at 80.05-99.72 °C showing the evaporation of two molecules of lattice water. It is reported that decomposition step at 60-100 °C is assignable to the removal of co-crystallized water molecules [25-26]. Therefore, the possible structure is $[Cu(ranitidine)_2]SO_4 \cdot 2H_2O$.

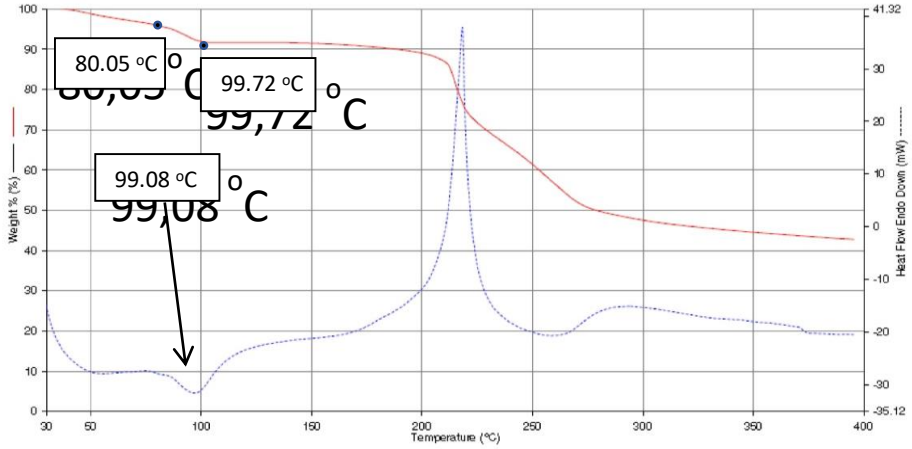

Figure 4. Thermogravimetric/differential thermal analysis spectra

3.5. Infrared analysis

Figure 5 and table 3 shows that the uptake of the -NH groups in the complex (3157 and 1519 cm^{-1}) has shifted toward a smaller wave number than the free ligand absorption of 3255 and 1568 cm^{-1}. It indicates coordination of amine group to Cu(II). The uptake of the NO_2 group in the complex (1620 and 1381 cm^{-1}) undergoes a shift from the free ligand (1631 cm-1 and 1346 cm^{-1}), indicating the presence of the coordinated NO_2 group with the metal. This case is similar to the $[Zn(ran)(gly)]NO_3$ complex which ranitidine is coordinated to Cu(II) through -NH and -NO_2 group [20]. Cu-O vibration appears at wave numbers 436 cm^{-1} and Cu-N appears at wave number 599 cm^{-1}. It is same with the complex of Cu(2-hydroxy-4-butoxy aniline) with Cu-O bonding vibrations occur in 447 cm^{-1} while Cu-N (617 cm^{-1}) [27]. No absorption band of -OH was a presence due to the overlapping of -OH and N-H absorption.

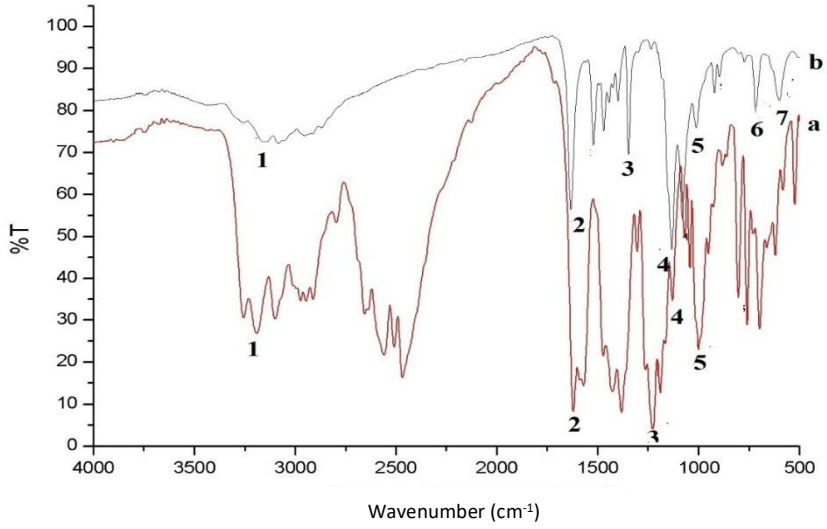

Figure 5. Infrared spectra of ranitidine hydrochloride (a) and the complex (b)

Table 3. Infrared absorption of ranitidine hydrochloride and the complex

Numbering	Functional Group	Ligand (cm^{-1}) (a)	The complex (cm^{-1}) (b)
1	-NH-	3255 1568	3157 1519
2	$-NO_2$	1620 1381	1631 1346
3	-CO	1224	1134
4	$-C-N_{ter}$	1070	1012
5	-C-S	698	700
6	Cu-O	-	599
7	Cu-N	-	435

3.6. Magnetic properties (μ_{eff})

The measurement of the effective magnetic moment (μ_{eff}) of the $[Cu(ranitidine)_2]SO_4 \cdot 2H_2O$ is 1.77±0.03 BM. The effective magnetic moment value shows the $[Cu(ranitidine)_2]SO_4 \cdot 2H_2O$ is paramagnetic with one unpaired electron. The value of the effective magnetic moment (μ_{eff}) also shows no Cu-Cu bonding, because if the Cu-Cu bond is formed the unpaired electron will be paired and the effective magnetic moment value (μ_{eff}) becomes smaller than the spin only magnetic moment value (μs) [28]. The effective magnetic moment (μ_{eff}) value of the complex is also the normal value for Cu^{2+} with an unpaired electron, which is the effective moment magnet value (μeff) of 1.70-2.20 BM [29].

3.7. Electronic spectra

The solution UV–Vis spectrum of the formed complex showed a low-intensity band at 626 nm (15974 cm^{-1}) shown in figure 3. This absorption indicates the presence of d-d transition as occurs in the Cu(II)-2-hydroxy-4-butoxy aniline complex which has a 17637 cm^{-1} uptake showing $2Eg \rightarrow 2T_2g$ transition indicating the planar square geometry complex [27].

From all the characterization analysis above, the proposed structure of the complex is shown in figure 6.

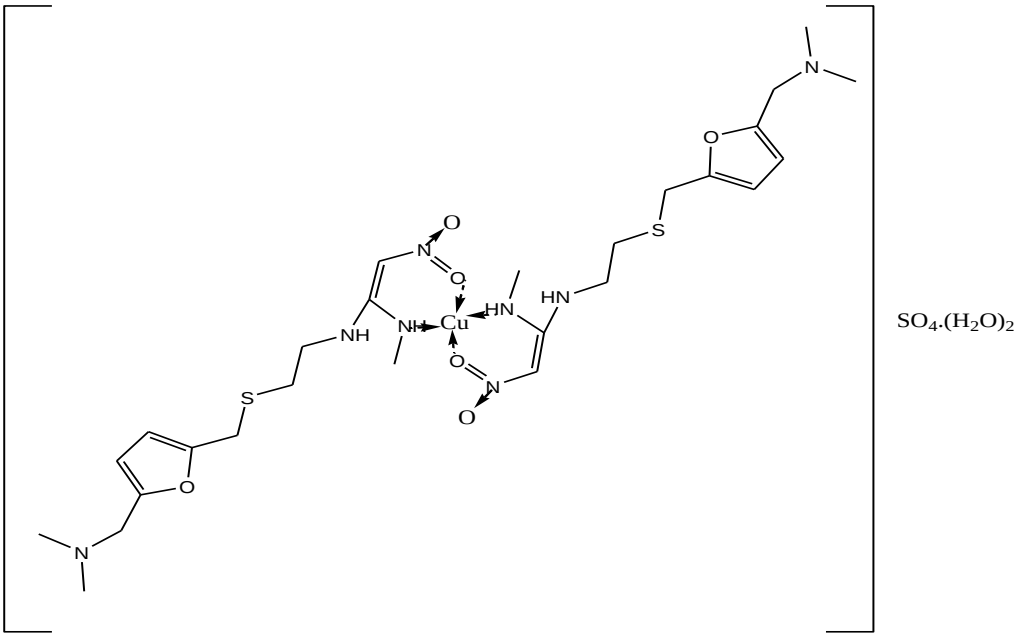

Figure 6. Suggested structure $[Cu(ranitidine)_2]SO_4 \cdot 2H_2O$

4. Conclusion

The Cu(II)-ranitidine complex can be synthesized from $CuSO_4 \cdot 5H_2O$ and ranitidine in refluxing water with mole ratio of metal to ligand = 1:2. The complex formula is $[Cu(ranitidine)_2]SO_4 \cdot 2H_2O$, namely diranitidinecopper(II) sulfate dihydrate. The coordinated groups are the O atom of -NO_2 and -NH. The complex is paramagnetic and has one peak at maximum UV-Vis absorption of 626 nm. It is indicated that the complex forming square planar geometry.

Acknowledgement

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