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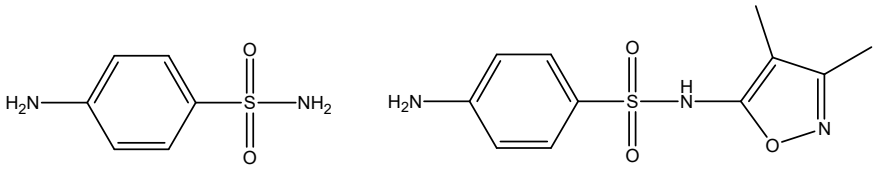
SYNTHESIS AND STRUCTURAL CHARACTERIZATION OF COPPER COMPLEXES BASED ON SULFONAMIDES

Sentot Budi Rahardjo[1,2,*], Suwarsih[1], and Husna Syaima[2]
[1]Department of Chemistry, Faculty of Mathematics and Natural Sciences, Sebelas Maret University, Surakarta, 57126, Indonesia
[2]Department of Chemistry, Graduate Program, Faculty of Mathematics and Natural Sciences, Sebelas Maret University, Surakarta, 57126, Indonesia
*E-mail: sentotbr@staff.uns.ac.id

ABSTRACT
Cu(II)-sulfanilamide and Cu(II)-sulfisoxazole were synthesized with 1:4 ratio of Cu(II) to each ligand. The complexes were characterized by Atomic Absorption Spectroscopy (AAS), UV-vis, Differential Thermal Analysis (DTA) infrared (IR), conductivity, magnetic susceptibility, and powder x-ray diffraction. Electronic spectra of Cu(II)-sulfanilamide and Cu(II)-sulfisoxazole complexes show transition peaks at 793 nm corresponding to the $^2B_{1g} \rightarrow {}^2B_{2g}$. The value of 10 Dq for Cu(II)-sulfanilamide and Cu(II)-sulfisoxazole is 150.5 kJ/mol. Infrared spectra indicate that sulfanilamide and sulfisoxazole were coordinated through primary amine. Both complexes are paramagnetic and are estimated to have orthorhombic and monoclinic, respectively.
Keywords: Synthesis, Copper(II), Sulfanilamide, Sulfisoxazole, Complexes.

INTRODUCTION

Antimicrobial resistance has become a global problem.[1-5] It also demands much effort to discover new antibiotic to deal with.[6-7] This resistance is mainly caused by the gram-positive and negative bacteria.[7-9] *Staphylococcus aureus* is a Gram-positive pathogen bacteria that cause nosocomial infections.[10-11] Gram-negative bacteria as *Escherichia coli* can cause diarrhea, meningitis, gastroenteritis, and wound infections.[12-14]. Sulfonamides are known to be effective and widely used against diseases caused by bacteria.[15-19] The antibacterial activity of sulfonamides has occurred through the inhibition of p-aminobenzoic acid (PABA). PABA are substrates for dihydropteroate synthase (DHPS), which is essential for folic acid synthesis.[20] Nowadays, treatment using sulfonamide has been reduced due to allergic reactions and many side effects.[21] Although having some effects for patients, sulfa drugs are still considered as one of the choices to cure methicillin-resistant *Staphylococcus aureus* infections.[22]
Sulfanilamide and sulfisoxazole (Fig.-1), sulfonamide derivatives are also a potential candidate as antimicrobial drug.[23-25] Sulfanilamide is an organic drug that has a sulfamoyl group is attached to aniline at the 4-position. This compound can act as a carbonic anhydrase inhibitor, an antibacterial agent, and a drug allergen. The structure is similar to p-aminobenzoic acid (PABA) with antibacterial property.[26] Sulfisoxazole is an antibacterial agent with an oxazole substituent. The compound poses antibacterial activity against Gram-negative and Gram-positive bacteria.[27] Besides, sulfanilamide and sulfisoxazole have some active groups and electron donor atoms. The feature allows these compounds to be ligands and coordinated on metal ions.



(a) (b)

Fig.-1: Sulfanilamide (a) and Sulfisoxazole (b)

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Generally, the antibacterial activity of organic compounds increases after complexing with metal ion.[28-30] According to Tweedy's chelation theory, the increasing antibacterial activity of the complexes than free ligands is caused by π electron delocalization throughout the chelate ring of ligands. The coordination of metal and ligands leads to an increase in the lipophilic character of metal center[31]. It makes the complex easier to penetrate the microbial cell membrane. One of the metals that often used is copper**.** Copper has imperative roles in biological processes.[32] In the human body, copper is needed for oxidative enzyme systems such as ascorbate oxidase, cystic C oxidase, polyphenol oxidase, and amino oxidase.[33]. Many copper complexes with sulfonamide derivatives have been synthesized. Copper complex based on sulfamerazine-Schiff base was synthesized and formed square planar geometry.[34] Radha *et al.* (2016) have been synthesized Cu(II)-sulfadiazine complex. Sulfadiazine was coordinated to Cu(II) through C=N and S=O.[35]

Copper complexes with sulfonamide ligands can form various structures and geometry with different characteristics. Due to that reason, it is also interesting for developing a novel material with antimicrobial activity and other related pharmaceutical applications. In this research, synthesis of copper(II)-sulfanilamide and copper(II)-sulfisoxazole complexes were prepared. The complexes were characterized for determining their formula and structure.

EXPERIMENTAL

Materials

The chemicals and solvents were used without further purification. The chemicals such as $CuSO_4 \cdot 5H_2O$, sulfanilamide, sulfisoxazole, nitric acid, $CuCl_2 \cdot 2H_2O$, NH_4OH, $NiSO_4 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$, and $AlCl_3 \cdot 6H_2O$ were purchased from E. Merck.

Synthesis of Cu(II)-sulfanilamide

$CuSO_4 \cdot 5H_2O$ (0.499 g; 2 mmol) in methanol (10 ml) and sulfanilamide (1.378 g; 8 mmol) in methanol (20 ml) was stirred constantly at room temperature. After 24 hours, the dark green precipitate was formed. The solid was separated by filtration, washed with methanol, and dried at room temperature.

Synthesis of Cu(II)-sulfisoxazole

$CuSO_4 \cdot 5H_2O$ (0.499 g; 2 mmol) was dissolved in methanol (10 ml). Then it was added into the solution of sulfisoxazole (2.138 g; 8 mmol) in methanol (120 ml). The mixture solution was stirred for 24 hours at room temperature to form a light green precipitate. The filtrate was separated by filtration, washed with methanol, and dried.

Physical Measurements

The percentage of copper in the complexes was calculated and the data recorded by an Atomic Absorption Spectrophotometer (AAS) of Shimadzu AA-6650. UV-vis absorption was performed using UV-Vis Double Beam Shimadzu PC 1601 spectrophotometer. Water content and thermal properties in the complex were estimated using Differential Thermal Analyzer Shimadzu 50. The electrical conductivity of the complexes was estimated using a conductometer. Calibration of the conductometer was carried out using an aqueous solution of potassium chloride (1 M) at 25° C. Molar conductivity data of the complex were compared to data of known salts solutions. Magnetic susceptibility of the complexes was calculated using Auto Sherwood Scientific 10169 Magnetic Susceptibility Balance. The effective magnetic moment (μ_{eff}) was calculated from the corrected molar magnetic susceptibility (corrected by Pascal's constant for diamagnetism effect) using formula $\mu_{eff} = 2.828 \sqrt{(\chi M.T)}$ B.M. Fourier Transform Infrared (FTIR) absorption bands of the functional groups in the complexes, sulfanilamide, and sulfisoxazole were recorded using Prestige-21 Shimadzu spectrophotometers in the frequency of 4000-450 cm^{-1}. The samples are formed as KBr pellets. Powder X-ray diffractogram of both complexes was performed using a Rigaku Miniflex Benchtop Diffractometer, Cu *K*α, λ=1.5406. The reflection data were performed in scan mode at a 2-90 degree of 2θ with a rate of 10 and an interval of 0.02. The X-ray diffractogram was analyzed using the Rietica program of the Le Bail method. To determine the space group of the complexes, diffractograms of the complex were compared to the compounds with known space group JCPDS (Joint Committee on Powder Diffraction Standards).

RESULTS AND DISCUSSION

Formation of the Complex

A mixture of $CuSO_4 \cdot 5H_2O$ with sulfanilamide resulted in a dark green solid (1.082 g). Electronic spectra of $CuSO_4 \cdot 5H_2O$ and Cu(II)-sulfanilamide complex in water are shown in Fig.-2. Cu(II)-sulfanilamide complex has a maximum wavelength of 793 nm. It shifts toward a lower wavelength than $CuSO_4 \cdot 5H_2O$ solution (808 nm). The electronic spectra of $CuSO_4 \cdot 5H_2O$ and Cu(II)-sulfisoxazole complex are shown in Fig.-3. The maximum wavelength of Cu(II)-sulfisoxazole also shifts from 802 nm for the complex to 793 nm ($CuSO_4 \cdot 5H_2O$). The shift of the maximum wavelength towards the smaller wavelength indicates the formation of the Cu(II)-sulfanilamide and Cu(II)-sulfisoxazole complex.

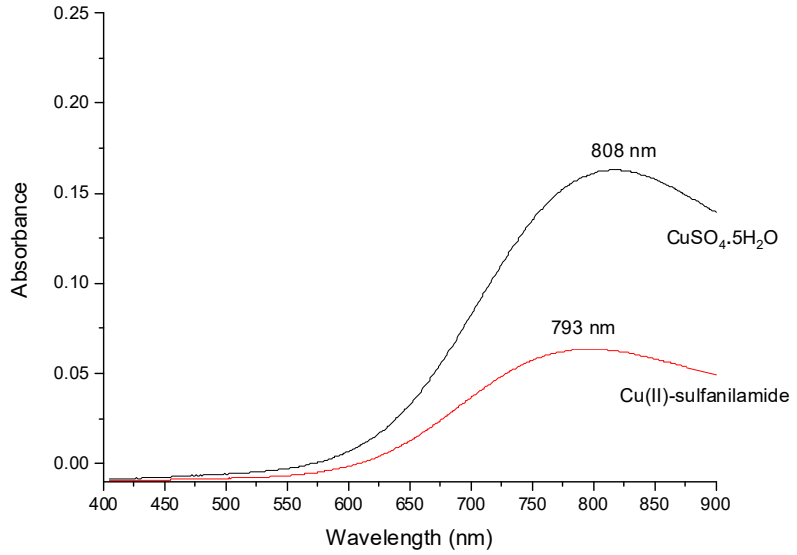

Fig.-2: Electronic Spectra of $CuSO_4 \cdot 5H_2O$ and Cu(II)-sulfanilamide Solution in Water

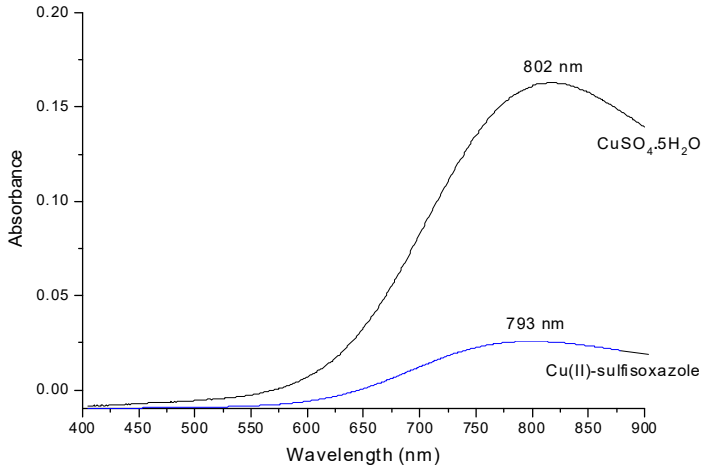

Fig.-3: Electronic Spectra of $CuSO_4 \cdot 5H_2O$ and Cu(II)-sulfisoxazole Solution in DMSO

Formula Determination of the Complexes

The empirical formula of the complex was estimated by comparing obtained AAS data to some possible formula, as shown in Table-1. By comparing the copper content in the complex with theoretical results, a possible formula of the complexes is Cu(sulfanilamide)$_3$(H_2O)$_x$$SO_4$, x=3 or 4, and Cu(sulfisoxazole)$_2$(H_2O)$_x$$SO_4$, x= 4 or 5, respectively.

Table-1: Proposed Formula of the Complex Following the Copper Content in the Complex Sample

Complex Formula	Theoretical Calculation (%)	AAS Result (%)
$Cu(sulfanilamide)_3(H_2O)_3SO_4$	8.70	8.62
$Cu(sulfanilamide)_3(H_2O)_4SO_4$	8.50	
$Cu(sulfisoxazole)_2(H_2O)_4SO_4$	8.23	8.17
$Cu(sulfisoxazole)_2(H_2O)_5SO_4$	8.10	

Thermogram of Differential Thermal Analysis (DTA) of Cu(II)-sulfanilamide and Cu(II)-sulfisoxazole complexes are shown in Fig.-4 and Fig.-5. There is a gradual thermal decomposition of the Cu(II)-sulfanilamide at 98ºC; 171ºC and 271ºC. At 98ºC and 171ºC, it is estimated to be the peak of the release of water molecules from the Cu(II)-sulfanilamide complex as hydrates and ligands. Generally, the evaporation of lattice water in the complex occurs in the range temperature of 29-160 ºC.[36] Thus, the release of coordinated water molecules can occur over that temperature. It is estimated that the process of destruction and the release of sulfanilamide begins at 271ºC.

The complex decomposition of Cu(II)-sulfisoxazole is shown in Fig.-5. The complex shows thermal decomposition at 82ºC; 119ºC and 189ºC. A peak at 82ºC; 119ºC indicates that in the complex contains water molecules, the peak at 189ºC is the process of sulfisoxazole destruction and release. From the second DTA analysis data, the complex shows that the complex contains more than one water molecule. Similar to the result of Cu(II)-sulfanilamide, Cu(II)-sulfisoxazole also contained water molecules as lattice water and coordinated-water molecules.

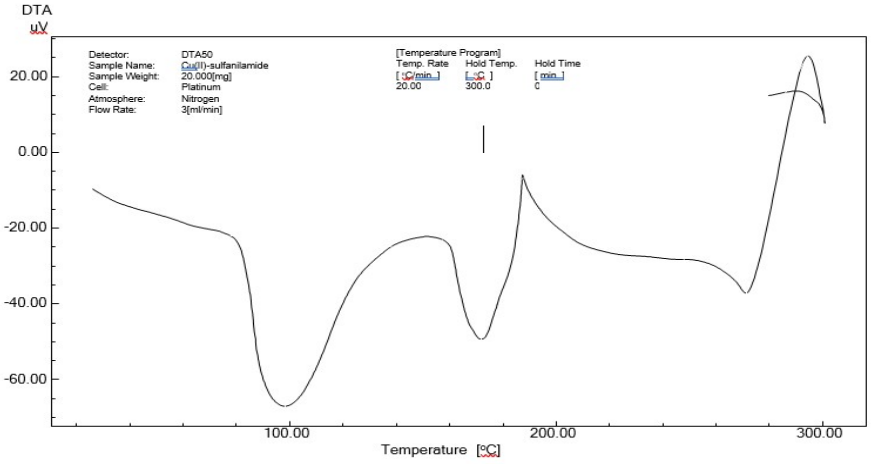

Fig.- 4: Differential Thermal Analysis (DTA) of Cu(II)-sulfanilamide

The electrical conductivity of the complexes is shown in Table-2 and Table-3. It suggests that molar conductivity value for both complexes is in the range of 1:1 cation/anion with two ions per molecule.

Table-2: Molar Conductance of Cu(II)-Sulfanilamide and Some Known Salts

Compounds	Molar Conductance Λ^*_m (μS cm^2/mol)	The Ratio of Cation/Anion	Number of Ions
Akuades	0	0	0
$CuSO_4 \cdot 5H_2O$	166	1:1	2
$NiSO_4 \cdot 6H_2O$	169	1:1	2
$CuCl_2 \cdot 2H_2O$	219	2:1	3
$NiCl_2 \cdot 6H_2O$	219	2:1	3
$AlCl_3 \cdot 6H_2O$	303	3:1	4
Cu(II)-sulfanilamide	135 ± 13.05	1:1	2

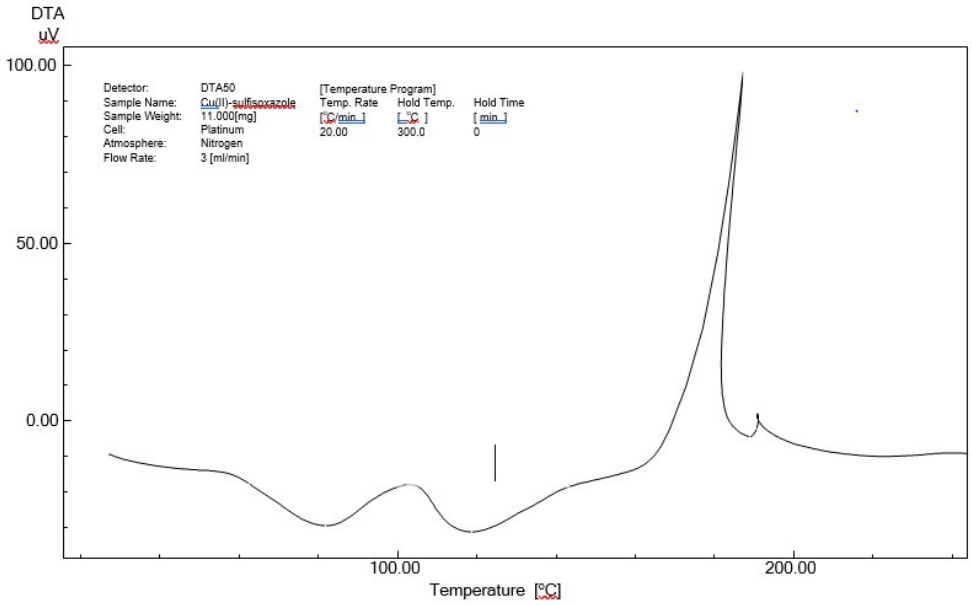

Fig.- 5: Differential Thermal Analysis (DTA) of Cu(II)-sulfisoxazole

Infrared Analysis

The infrared spectra of Cu(II)-sulfanilamide and Cu(II)-sulfisoxazole complexes are shown in Table-4. There is a slight shift in the primary amine region. Namely from 3475, 3371, and 3267 cm^{-1} on sulfanilamide to 3479, 3375, and 3267 cm^{-1} in Cu(II)-sulfanilamide. The symmetrical SO_2 group did not experience a shift. Whereas, in Cu(II)-sulfisoxazole, the same thing happens. There was also a slight shift in IR spectra in the primary amine region. The shift of functional groups of primary amine sulfanilamide also occurs in the direction of larger wavenumbers, namely from 3004 cm^{-1} to 3016 cm^{-1}.

Table- 3: Molar Conductance of Cu(II)-sulfisoxazole and Some Known Salts

Compounds	Molar Conductance Λ^*_m ($\mu S\ cm^2/mol$)	The Ratio of Cation/Anion	Number of Ions
DMSO	0	0	0
$CuSO_4 \cdot 5H_2O$	4	1:1	2
$NiSO_4 \cdot 6H_2O$	8	1:1	2
$CuCl_2 \cdot 2H_2O$	34	1:2	3
$NiCl_2 \cdot 6H_2O$	39	1:2	3
Cu(II)-sulfisoxazole	5.5±0.5	1:1	2

Table-4: FTIR Result of Ligands and Complexes

Compounds	ν primary N-H (cm^{-1})	ν secondary N-H (cm^{-1})	ν C=C (cm^{-1})	ν SO_2 (cm^{-1})	
				Symmetric	Asymmetric
Sulfanilamide	3475 3371	-	1438 1504 1596	1315	1145
Cu(II)-sulfanilamide	3479 3375	-	1438 1504 1596	1315	1149
Sulfisoxazole	3004	3217	1434 1504 1596	1346	1164.
Cu(II)-sulfisoxazole	3016	3217	1434 1504 1596	1346	1164

The shortening of the primary N-H bond in the complex causes the vibrational energy is greater than N-H in the free ligand. This shift towards larger wavenumbers also occurs in the complex $[Cu(L\text{-}Met)_2]$(L-Met=L-Methionine) with primary N-H uptake of 3298 cm^{-1} while the primary N-H uptake is ligand at 3159cm^{-1}.[37]

From infrared data, it is estimated that the primary N-H group in sulfanilamide and sulfisoxazole is coordinated to the central ion Cu(II). There are two primary amine functional groups. Coordinated amine is estimated, which is not bound to the benzene ring. It is supported by the shifting of the asymmetrical SO_2 group and the non-shifting C=C aromatic spectra. The estimated coordinated primary N-H groups from sulfanilamide and sulfisoxazole in Cu(II) are shown in Fig.-6 and Fig-7. The uncoordinated secondary N groups, O atoms to the central copper ion are indicated by the absence of asymmetric and symmetrical SO_2 wave number shifts.

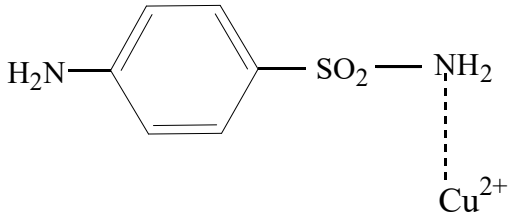

Fig.-6: Coordination Mode of Primary Amine of Sulfanilamide to Cu(II).

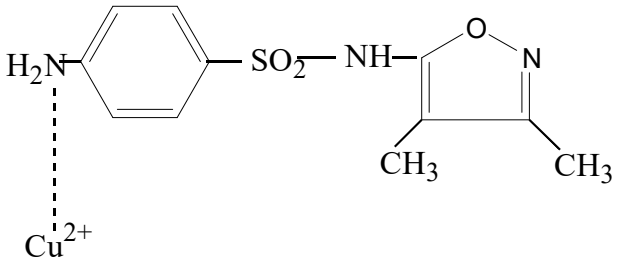

Fig.-7: Coordination Mode of Primary Amine of Sulfisoxazole to Cu(II)

Magnetic Properties (μ_{eff})

Magnetic moments observed for Cu(II)-sulfanilamide and Cu(II)-sulfisoxazole were more than 1.73 B.M., as shown in Table-5. The value is corresponding to paramagnetic copper with one unpaired electron in the d^9 electrons of Cu(II).[38-39] This result also indicates that the two complexes are paramagnetic, and there is no interaction between metals in complex compounds. Cu-Cu interaction can produce diamagnetic characteristics and have a value of μ_{ef} smaller than 1.73 B.M.

Table-5: Magnetic Susceptibility of the Complexes

Compounds	χ_g	Effective Magnetic Moment μ_{eff} (B.M.)
$Cu(sulfanilamide)_3(H_2O)_xSO_4$, x= 3 or 4	$1.31.\ 10^{-6}$ $1.19.\ 10^{-6}$ $1.22\ .10^{-6}$	1.77-1.79 ± 0.02
$Cu(sulfisoxazole)_2(H_2O)_xSO_4$, x= 4 or 5	$1.87.\ 10^{-6}$ $2.00.\ 10^{-6}$ $1.98.\ 10^{-6}$	2.13-2.15 ± 0.03

Electronic Spectra

The maximum wavelength, absorbance (A), and molar absorptivity (ε) of Cu(II)-sulfanilamide and Cu(II)-sulfisoxazole are shown in Table-6. The complex of Cu(II)-sulfanilamide has a higher molar absorptivity value than Cu(II)-sulfisoxazole. These complexes exhibit one transition due to transition from $^2B_{1g} \rightarrow {}^2B_{2g}$ of square planar geometry [40-41] and the magnitude of the transition energy is shown in Table-7. The approximate value of 10 Dq of both complexes is equal to 150.5 kJ mol^{-1}. This result indicates that sulfanilamide and sulfisoxazole have almost the same field strength.

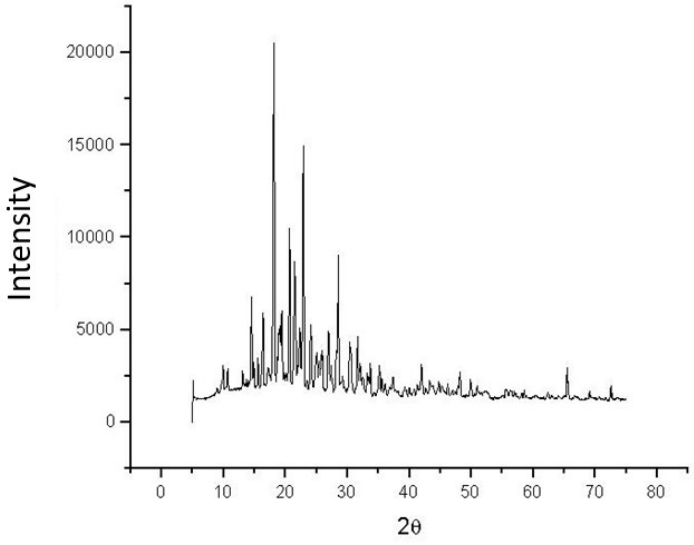

Fig.-8: Powder X-ray Diffractogram of Cu(II)-sulfanilamide

Table-6: The Maximum Wavelength, Absorbance (A) and Molar Absorptivity (ε) of Cu(II)-sulfanilamide and Cu(II)-sulfisoxazole

Complexes	A	C (M)	ε (L/mol.cm)
$Cu(sulfanilamide)_3(H_2O)_xSO_4$, x= 3 or 4	0.074	$5.18.\ 10^{-3}$	14.43-14.78
$Cu(sulfisoxazole)_2(H_2O)_xSO_4$, x= 4 or 5	0.021	$6.01.\ 10^{-3}$	3.52-3.62

Table-7: Estimated Transition Energy of the Complexes

Compounds	ν (cm^{-1})	λ_{max} (nm)	Estimated Transition Energy 10 Dq (kJ/mol)
Cu(II)-sulfanilamide	12610	793	150.5 ($d_{x2-y2} \rightarrow d_{xy}$)
Cu(II)-sulfisoxazole	12610	793	150.5 ($d_{x2-y2} \rightarrow d_{xy}$)

Powder X-ray Diffraction

The results of x-ray diffraction from Cu(II)-sulfanilamide and Cu(II)-sulfisoxazole are shown in Fig.-8 dan Fig.-9. Peaks of the complexes were different from the peaks of $CuSO_4 \cdot 5H_2O$ (Table-8). It shows that the complexes are formed. The complexes are crystalline. The crystal system can be estimated by comparing the d(Å) three strongest peaks of the complex with d(Å) the three strongest peaks of compounds known to the crystal system. According to the Miller equation, the d value is related to the values of a, b and c. If the values of a, b, and c complex are proportional to a, b, and c of the comparative compounds, then the d value will be the same. It is estimated that the crystal system of the complex is the same as the comparative compound.

Table-8: Three Strongest Peaks From X-ray Diffractrogram of Cu(II)-sulfanilamide and Cu(II)-sulfisoxazole

Compounds	d(Å)	I_o /I
$CuSO_4 \cdot 5H_2O$	4.7474	999
	3.7150	652
	3.8885	594
Cu(II)-sulfanilamide	4.9086	100
	3.8988	74
	4.3150	45
Cu(II)-sulfisoxazole	7.2710	100
	3.8733	86
	3.3238	55

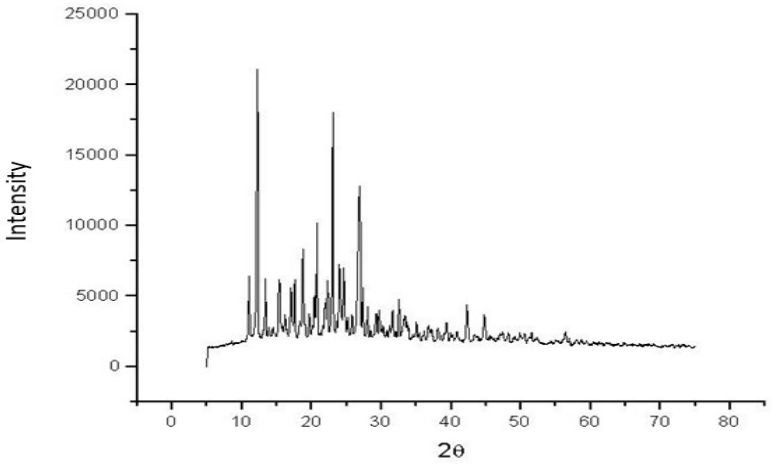

Fig.- 9: Powder X-ray Diffractogram of Cu(II)-sulfisoxazole

Absorption value, d(Å) of the three strongest complex peaks Cu(II)-sulfanilamide and Cu(II)-sulfisoxazole are similar to the value of d (Å) absorption of the three highest peaks of compounds that have orthorhombic and monoclinic crystal systems respectively. The d (Å) value of the three strongest absorption peaks of the comparative compounds for the two complexes is shown in Table-9 and Table-10.

Table-9: Strongest Absorption Peak Data of Compounds with Orthorhombic Crystal System

Compounds	d(Å)			I_o/I		
$C_{35}H_3CuNO_4S$	4.6100	3.6900	3.9800	100	67	60
$Na_2Fe(CN)_5NO(H_2O)_2$	4.7131	4.1143	2.8729	64	91	100
$K(Cu(NH_3)_5(PF_6)_3$	4.6228	3.9351	2.9475	97	100	32
$Ba(Fe(CN)_5(NO))(H_2O)_3$	4.8993	4.3200	2.8307	100	27	47
$Na_2(Fe(CN)_5NO)(H_2O)_2$	4.7131	4.1143	2.8729	63	91	100
$Zn(SCN)_2(H_2O)_2$	4.2424	4.0550	3.4125	68	66	100

Table-10: Strongest Absorption Peak Data of Compounds with a Monoclinic Crystal System

Compounds	d(Å)			I_o/I		
$C_4H_{10}CuN_4H_8.H_2O$	7.2860	3.9310	3.1540	100	75	75
$Sr(SCN)_2(H_2O)_3$	7.4844	3.9474	3.9366	55	94	100
$(CaCl_2)(OC(NH_2)_2)_4$	7.4632	3.6373	3.6272	31	91	100
$(Co(NH_3)_6(HgCl_3)Cl(HgCl_2)Cl(HgCl_2))(H_2O)$	7.9428	3.5649	3.9903	78	100	84
$(Pt(NH_3)_4)(PtBr_2(NH_3)_4(HSO_4)_4$	7.3930	3.3521	3.2622	100	65	60
$Na_4Fe(CN)_6(H_2O)_{10}$	7.3947	3.9998	3.4961	100	72	76

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