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SYNTHESIS, SPECTROSCOPIC, THERMAL STUDIES AND BIOLOGICAL ACTIVITY OF A NEW SULFAMETHOXAZOLE SCHIFF BASE AND ITS COPPER COMPLEXES

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ABSTRACT

A new Sulfamethoxazole Schiff base (E)-4-(4-methoxybenzylideneamino)-N-(5-methylis-oxazol-3-yl) benzenesulfonamide ($C_{18}H_{17}N_3O_4S$), and its copper complex were synthesized and the structures elucidated on the basis of Physiochemical methods. The studies indicate an octahedral structure for the complexes with the ($C_{22}H_{27}N_3O_{10}SCu$) formula. The IR spectra suggest that the ligand act as tridentate (from oxygen and two nitrogen atoms) donor. Also the biological activity of the Schiff base and its Cu complex were studied.

INTRODUCTION: Schiff base compounds which contain the azomethine (imine) group (–RC=N–) are usually prepared by the condensation of a primary amine with an active carbonyl compound [1]. It has been often used as chelating agents (ligands) in the field of coordination chemistry and Schiff base metal complexes were of great interest for many years. It is well known that O and N atoms play a key role at the active sites of numerous metallo biomolecules in the coordination with metals [2].

Later, a great number of sulfanilamide derivatives were synthesized, characterized and tested as antibacterial agents, with many derivatives currently used for the treatment of bacterial infections.

Such sulfonamide derivatives widely used in clinical medicine as pharmacological agents with a wide variety of biological actions, were designed from the simple sulfanilamide lead molecule [3], also Schiff base known as anticancer and antiviral agents [4], and its metal complexes have been widely studied because they have industrial, anti-fungal, anti-bacterial, anticancer herbicidal applications [5], anti-tubercular activities [6] and chelating abilities which give it attracted remarkable attention [7]. Sulfa drugs had attracted special attention from their therapeutic importance as they were used against a wide spectrum of bacterial ailments [8].

Experimental:

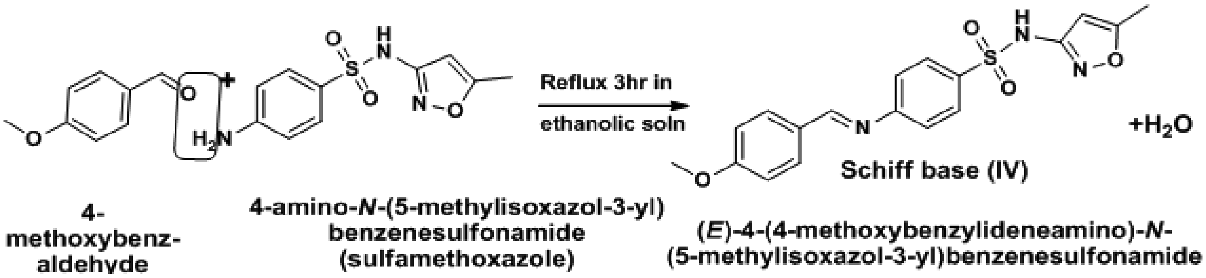
Materials: Sulfamethoxazole was obtained from Memphis Co. for Pharm. & Chemical Ind., Egypt, and p-methoxybenzaldehyde was obtained from Morgan chemical IND, Co, Egypt. Glacial acetic acid was obtained from El-Nasr pharmaceutical chemicals Co, Egypt, ethanol 99% was obtained from Technolgene. Corp, Dokki, Egypt, diethyl ether and N, N-dimethyl formamide (DMF) was obtained from SD Fine Chem. limited India, copper acetate were chemically pure of grade, Merck, Germany.

Instruments: IR spectra were obtained as KBr disc on a Pelkin Elmer FTIR spectrophotometer 57928 RXIFT-IR system. The electronic spectra were recorded by Perkin Elmer Lambda 35 Spectrophotometer using DMF as solvent. The mass spectra were performed by Hewlett Packard mass spectrometer model MS 5988.

Metal analyses were determined by atomic absorption (AAS Vario6). Conductance TDS Engineered system, U.S.A, was employed for the conductometric titration at Al-Azhar university, Cairo, Egypt.

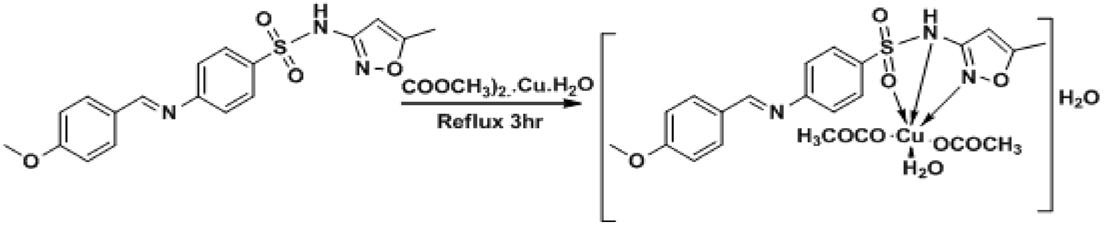
While Elemental analysis, ^{1}HNMR spectra which recorded by a Varian, USA, Gemini 200 MHz Spectrometer in DMSO-d6 were taken at Micro-analytical Center, Cairo University, Cairo, Egypt and Magnet susceptibility measurement of the complexes were determined at room temperature by the Faraday method and at Faculty of Science, Cairo University.

Synthesis of Schiff base (I): The Schiff-bases **(I)** was prepared as in **Scheme 1** by the usual condensation reaction [9], in which p-methoxybenzaldehyde (0.1 mol) was drop wisely added to the amine (Sulfamethoxazole) (0.1 mol) with continuous stirring, (drops of triethylamine [10], was added). After complete addition the reaction mixture was heated under reflux for about four hours. The product (imine) was separated after cooling at room temperature by filtration. The isolated compound was purified by recrystallization from ethanol. After one week orange prisms of Schiff base (I) was obtained, and the melting point was found to be 202°C.



SCHEME 1: SYNTHESIS OF SCHIFF BASE (I)

Synthesis of Schiff base Metal Complexes: A solution of the copper acetate $(CH_3COO)_2.Cu.\ H_2O$ (0.01 mol) in absolute ethyl alcohol was added drop wise to equimolar amounts of Schiff base (0.01 mole) (I). After complete addition of the metal salt the reaction mixture was heated under reflux for six hours, the product separated after cooling, by filtration and recrystallization from ethanol to give solid products (I_a) (**Scheme 2**). Yield = 59.50 % (0.35g), and the m.p., of the complex is >300 º C.



SCHEME 2: SYNTHESIS OF CU COMPLEX (I_a)

RESULTS AND DISCUSSION:

The structures of Schiff base (I) ($C_{18}H_{17}N_3O_4S$); was elucidated on the bases of:

- **Elemental Analysis** shows that the C, H and N of Schiff base (I) were (57.06, 6.03 and 11.53 respectively) which is compatible with that required (58.21, 4.61 and 11.31 respectively).
  - **The ^{1}H-NMR spectrum** of Schiff base (I), using DMSO d_6 as solvent, showed the multiplet signals of the aromatic protons at δ 7 - 8.2 ppm. The chemical shift of methoxy group appears at 3.9 ppm. The chemical shift of methyl group (CH_3) appears at 2.5 ppm. The signal noticed at δ 9 ppm can be assigned for the azomethine proton and the single noticed at 9.7 ppm represent NH group.
  - **The electronic spectrum** of Schiff base (I); exhibits the absorption band structure at λ_{max}= 204-228 nm corresponding to π-π^* transitions of the phenyl ring, the band at λ_{max}= 267 nm corresponds to π-π* transitions of the C=N group, while the broad band at λ_{max}= 337 nm corresponds to π-π^* transitions of the azomethine and S=O bonds [11].
  - **The IR spectrum** of Schiff base (I); exhibits a strong band in the region 3386 cm^{-1} characteristic to the stretching mode of vibrations of NH group. The band at 1604 cm^{-1} assigned to the υ C=N stretching mode of vibration of the azomethine group.

Finally, the bands at 1336 and 1162cm^{-1} represent the asymmetric and symmetric stretching frequencies, respectively, of the sulfonyl group (S =O str) [12, 13]**.**

- **The mass spectrum** of Schiff base (I); Shows a molecular ion (M^+) peak at = 371.55 (47.02%) corresponding to species $[C_{18}H_{17}N_3O_4s]^+$, which confirms the proposed formula, the ion peak at m/e = 289.95 (82.92%) is due to ($C_{14}H_{13}N_2O_3S$). The ion peak at m/e = 210.4 (100%) which is the base peak corresponds to ($C_{14}H_{12}NO$). The ion peak at m/e = 180.3 (2.05%) is due to ($C_{13}H_{10}N$), and the ion peak at m/e = 104.75 (4.94%) corresponds to (C_7H_6N).

The structure of Schiff base Copper complex (I_a) was elucidated on the bases of:

- **Molar Ratio:**
    - **Conductometric Titration:** The conductometric titration is performed by titrating 10 ml of 1x10^{-3} M metal ion solution with increasing volume of 1x10^{-3} M complexing agent solution of Schiff base, using DMF as solvent, and the conductivity was then recorded after stirring the solution for about 2 minutes. Then, by plotting the conductance values vs milliliter of the reagent added, and applying the least square equation [14], **Figure 1** show 1L:1M molar ratio.

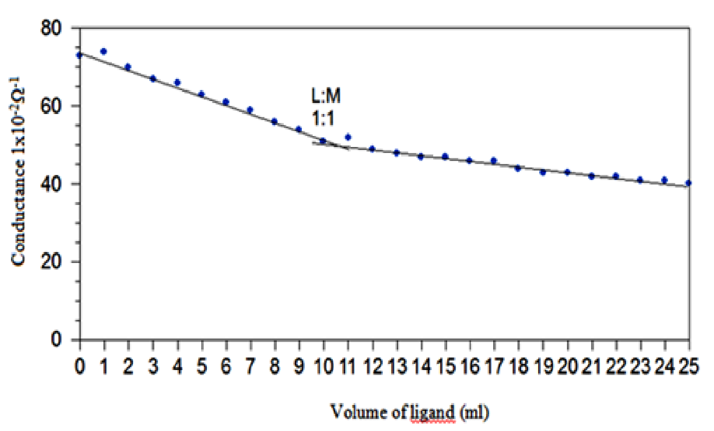


FIG. 1: CONDUCTOMETRIC TITRATION OF SCHIFF BASE (I) (1x10^{-3}M) $(CH_3COO)_2$.Cu. H_2O (1x10^{-3}M) SYSTEM

- **Spectroscopic Molar Ratio Testing:** In the present investigation, the concentration of the metal ion was kept constant, while that of the ligand was varied, a two ml of Cu^{+2} ion concentration were kept constant at 1x10^{-3} M, while that the ligands were regularly varied from 0.2x10^{-3} to 2x10^{-3} M using DMF as solvent. The absorbance of the mixed solutions was measured. A plot of the absorbance as a function of molar ratio [ligand/ metal] is represented the formation of 1:1 ligand: metal complex.

- **Elemental Analysis**: The element analysis show that the percent of N= 8.10 % and Cu= 11.95% which were compatible with required (N= 7.13 % and Cu =10.70%.

- **Electronic spectra:** The electronic spectra of the Schiff base complex were carried out in DMF solutions at a concentration of 10^{-5} M. The spectrum of the complex exhibits the absorption band structure at λ_{max}= 400 and 231 nm corresponds to π-π^* transitions of the C=O and C=N groups respectively. The sharp band at λ_{max}= 287 nm corresponds to n- π^* transitions of the acetate group. The sharp band at λ_{max}= 330 nm corresponds to n- π^* transitions of the azomethine group. Where the band at λ_{max}= 615 nm corresponds to d→d transitions of the copper metal. The assignments are in conformity with the proposed octahedral geometry for the complex [15].

Magnetic Measurements: Magnetic susceptibility was measured by the Faraday method at room temperature , the effective magnetic moment μ_{eff} , of complex I_a found to =1.92 BM; which confirms the octahedral geometric of the complex as expected [16].

IR Spectra: Comparing the IR spectra of the complexes and the free ligand, the following differences were observed:

(i) The strong band at 3386 cm^{-1} in the ligand is assigned to NH group [17], was shifted to lower frequency on chelating with metal ion indicating the NH group can act as coordinating site.

(ii) The shift of the two sulfonamide vibration (symmetric as well as the asymmetric one) toward lower wave numbers in the spectra of the complexes, as compared to the spectrum of the corresponding ligand (**table 1**) further support M-O bonding.

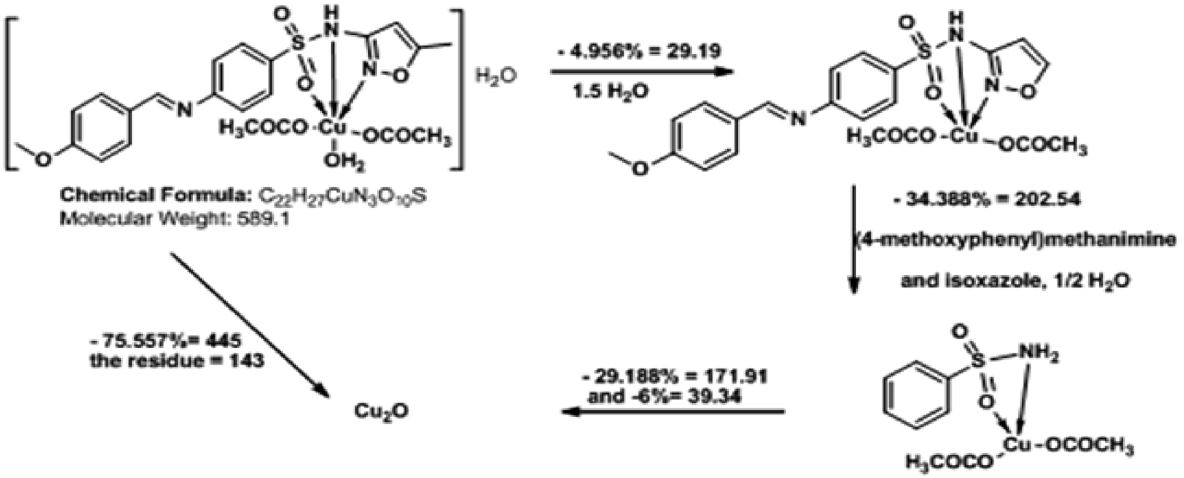
TABLE 1: IR DATA OF SCHIFF BASE AND ITS COMPLEX

Complex	Molecular mass	DTG$_{max}$/C	Decomposition step/C	Mass loss/%	M.wt found	Eliminated species	Solid residue/%
[Cu(Ac)$_2$L].H$_2$O (I$_a$)	589.07	180	141-250	4.918	28.97	1.5 H_2O	Cu$_2$O
		338	250-420	33.99	200.27	(4-methoxy phenyl) methanimine and isoxazole, 1/2 H2O	
		527	420-994	36.13	212.87	2Ac, benzene, O and NH_2	

(iii) The strong band at 3448 cm^{-1} assigned to N-O in heterocyclic exhibit lower shift as support M-N bonding, so the complexes were tridentated.

(iv) The complexes I$_a$ exhibit a broad band at (3470 cm^{-1} simultaneously appeared with a bands at (832 cm^{-1}) attributed to lattice held and/or coordinated water molecules [18]. The presence of coordinated water was also established and supported by TG/DT analysis of these complexes. (v) New bands appear in the region 552 cm^{-1} and 480 cm^{-1} in the complexes (I$_a$) spectra can be attributed to the vibrations of M← N and M ←O respectively.

Thermal Analysis: The thermal studies of Cu (II) metal complex was carried out using the thermogravimetric (TG) and differential thermal analysis (DTA) techniques represented in **Fig. 2**; to obtain information about their thermal properties as well as about the nature of intermediate and final products. The heating rate was suitably controlled at 10°C under nitrogen atmosphere and the weight loss was measured from the ambient temperature up to 1000°C, using α-Al_2O_3 as the reference. The temperature ranges of decompositions and the corresponding mass loss of species are given in **scheme 3; table 2**.



SCHEME 3: TG SUGGESTED FRAGMENTATION OF COMPLEX I$_a$

TABLE 2: THERMAL ANALYSIS DATA OF COMPLEX (I$_a$)

Complex	Molecular mass	DTG$_{max}$/C	Decomposition step/C	Mass loss/%	M.wt found	Eliminated species	Solid residue/%
[Cu(Ac)$_2$L].H$_2$O (IV,d)	589.07	180	141-250	4.918	28.97	1.5 H_2O	Cu$_2$O
		338	250-420	33.99	200.27	(4-methoxy phenyl) methanimine and isoxazole, 1/2 H2O	
		527	420-994	36.13	212.87	2Ac, benzene, O and NH_2	

Thermogram of Cu- complex indicated a total weight loss of 75.56% up to 1000°C, which is observed in four successive decomposition steps. The 1st decomposition step with an estimated mass loss of 4.956 % (=29.19 g/mol) within the temperature range 159- 181°C may be attributed to the liberation of 1.5 coordinated water molecule. The 2nd decomposition step within the temperature range 181-337°C, with an estimated mass loss of 34.388 % (=202.54 g/mol), which is reasonably accounted for the removal of (4-methoxyphenyl) methanimine, ½ H_2O and isoxazole.

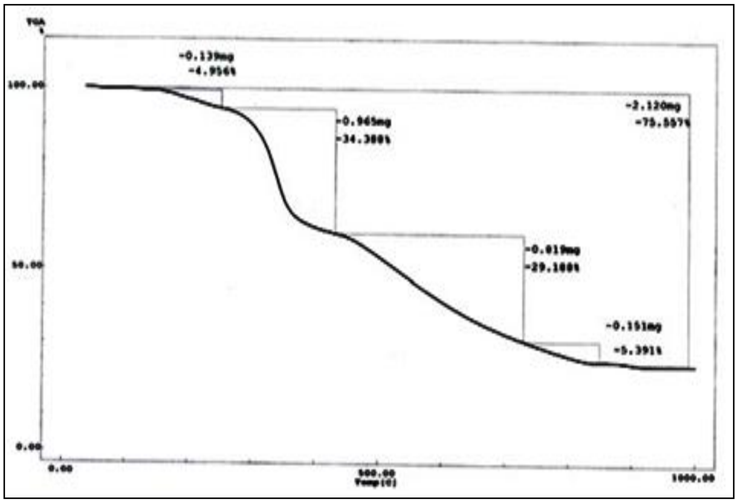


FIG. 2: THERMOGRAM OF Ia COMPLEX

The 3rd step found within the temperature range 337–720°C with an estimated mass loss of 29.188 % (= 166.68 g/mol), which is reasonably accounted for by the removal of acetate group and benzenethiol. Finally, it is found within the temperature range 720-898°C with an estimated mass loss of 5.391% leaving the final product monocopper oxide Cu_2O.

Kinetics of thermal decomposition of some prepared complexes: The calculated values of ΔE, ΔS, ΔH and ΔG for the decomposition steps are given in **Table 3**. The values were obtained, by using Excel computer program by Prof. A. Soliman *et al.*, [19]. $C_{22}H_{27}N_3O_{10}SCu$ complex showed considerable thermal stability which is reflected from the moderately high values of the activation energy averaged to 50.17 kJ mol^{-1}, the entropy change, ΔS, for the formation complex is in negative values.

The negative sign of the ΔS suggests that the degree of structural complexity (arrangement) of the activated complex was lower than that of the starting reactants and the decomposition reactions are slow reactions. The ΔH^o value and its sign, is dependent on the heat of formation of the complex and the solvent effect [20], in all cases, it is found that the ΔHº values are positive, so the Reactions are endothermic.

TABLE 3: THE KINETIC AND THERMODYNAMIC DATA OF THE THERMAL DECOMPOSITIONS OF (I_A)

Complex	D.T** (K)	ΔE* kJ mol-1	R2***	A/s-1	ΔS* kJ mol-1	ΔH* kJ mol-1	ΔG* kJ mol-1
$C_{16}H_{23}Cl_3FeNO_7{}^{3-}$	411-526	50.17	0.98	$2.83.10^5$	-155.60	46.38	117.40
(I_a)	532-693	150.45	0.99	$2.61.10^{13}$	-27.13	144.97	162.83
	698-1269	169.14	0.98	$3.77.10^{11}$	-57.15	162.49	208.19

Mass Spectroscopy: The mass spectrum of copper complex ($C_{22}H_{27}CuN_3O_{10}S$), show a characteristic molecular ion (M+) peak at m/e 589 represents the molecular ion peak of the complex [$C_{22}H_{27}N_3O_{10}SCu$]. The primary fragmentation of the complex take place due to the loss of -OCH_3, $2H_2O$ and C_2H_3O groups with peak at m/e 468. Further, degrades with the subsequent loss of -$C_6H_5CH=N$ species forming peak at m/e 365.

Further, degrades with the subsequent loss of (benzene ring) species forming species with peak at m/e= 290. Then two acetate group leaving a peak at 172 finally all atoms evaporate leaving copper oxide with peak at m/e 78 represents the stable species with 33.31% abundance. The mass spectra data confirm that the complexes were present, when supported by our additional analyses. The formula is in agreement with the mass spectral data.

Biological Activity: The antibacterial and antifungal activity [21] of the Schiff base (I) and its Cu complex (I_a) was done in comparison with Penicillin G and Streptomycin for anti-bacterial Clotrimazole and Itraconazole for antifungal as standard. All the selected strains two of bacteria and four of fungi namely; {*Staphylococcus aureus* and *Bacillus* (Gram +ve) and *Pseudomonas aeruginosa* and *Escherichia coli* (Gram -ve) and *Aspergillus fumigates*, *Geotrichum candidum*, *Candida albicans* and *Syncephalastrum racemosum*} showed sensitivity to all derivatives and compound I and I_a had shown good activity against all the tasted bacterial and fungal except *Syncephalastrum racemosum*.

CONCLUSION:

1. {(E)-4-(4-methoxybenzylidene-amino)-N-(5-methyl isox-azol-3-yl)benzenesulfonamide} (Schiff base (I)) was synthesized from reaction between a mixture of Sulphamethoxazole and p-methoxybenzal dehyde, the Schiff base (I) reacted with copper acetate monohydrate, and the result of all previous physiochemical measurements show that the structure of 1:1 complex may be represented as in scheme 2

2. The Schiff base Behaves as tridentate ligand one from oxygen of carbonyl, one from NH and the other from nitrogen from heterocyclic nitrogen to form distorted octahedral structure. Finally, the tow compounds I and I_a show more effected on both bacterial and fungal than the basic drug (sulphamethoxazole).

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