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Synthesis, Characterization, and Biological Activitiy of Copper (II) Complexes Containing Bidentate Schiff Bases

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Abstract

Three ligands have been prepared by condensation of dithiooxamide with 2,4,5- trimethoxy benzaldehyde, 4-dimethylamino benzaldehyde and Vanailin. These ligands are named N,N′- bis(2,4,5 – trimethoxybenzalidene) dithiooxamide(LH_1), N,N′-bis(4-dimethylaminobenzalidene) dithiooxamide(LH_2) and N,N′-bis (vanaillidene) dithiooxamide(LH_3), respectively. Complexes of LH_1, LH_2 and LH_3 were prepared with 1:2 M:L molar ratio, with copper ion in the formulas $[Cu(LH_1)_2(H_2O)_2] Cl_2.H_2O.0.5CH_2Cl_2$, $[Cu (LH_2)_2(H_2O)Cl] Cl.H_2O$ and $[Cu (LH_3)_2(H_2O)_2] CL_2.H_2O$. The ligands and their complexes have been characterized by IR, UV-Vis spectroscopy Magnetic, conductivity measurements, thermal analysis and atomic absorption technique. Biological activities of the Schiff bases and their metal complexes have been evaluated against two types of pathogenic bacteria (*Escherichia coli* and *staphylococcus aureus*).

Keywords: Dithiooxamide , Schiff base, Copper(II), bidentate ligands

تحضير وتشخيص والفعالية البيولوجية لمعقدات النحاس الثنائي الحاوية على قواعد شيف ثنائية السن

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الخلاصة

حضرت ثلاث ليكندات بنسبة مول واحد من الثنائي ثايو اوكساميد ومولين من كل من ٥,٤,٢– ثلاثي ميثوكسي بنزالديهايد و ٤– ثنائي مثيل امينو بنزالديهايد وفانيلين. هذه الليكندات تشمل $N,N^/$– ثنائي(٥,٤,٢– ثلاثي ميثوكسي بنزاليدين) ثنائي ثايو اوكساميد (LH_1)، $N,N^/$– ثنائي(٤–ثنائي مثيل امينو بنزاليدين) ثنائي ثايو اوكساميد (LH_2) و $N,N^/$–ثنائي(فانلدين) ثنائي ثايو اوكساميد(LH_3) على التوالي. تم تحضيرمعقدات هذه الليكندات مع ايون النحاس الثنائي بنسبة ١:٢ مول من الليكند :الفلز بالصيغ $[Cu(LH_1)_2(H_2O)_2]Cl_2.H_2O.0.5CH_2Cl_2$، $[Cu(LH_2)_2(H_2O)Cl]Cl.H_2O$ و $[Cu(LH_3)_2(H_2O)_2]CL_2.H_2O$. شخصت الليكندات بتقنيات الأشعة تحت الحمراء والأشعة فوق البنفسجية–المرئية اما المعقدات فشخصت بتقنيات القياسات المغناطيسة وقياسات التوصيلية والتحاليل الحرارية و تقنية الأمتصاص الذري اللهبي اضافة الى تقنيات الأشعة تحت الحمراء والأشعة فوق البنفسجية–المرئية. الفعالية البايولوجية لقواعد شيف ومعقداتها قيمت ضد نوعين من البكتريا وهما *Escherichia coli* و *staphylococcus aureus* .

مفاتيح الكلمات: الثنائي ثايواوكسمايد، قاعدة شيف، النحاس ثنائي التكافؤ، ليكندات ثنائية السن

1. Introduction

Recent years have witnessed a great deal of interest in the synthesis and characterization of transition metal complexes containing Schiff bases as a ligand, due to their importance as anticancer, antibacterial, antifungal and antiviral drugs$^{(1-5)}$. Schiff bases derived from dithiooxamide and aldehydes which contain S, N atoms proved to have biological activities. Recently, anew set of Schiff bases derived from dithiooxamide and benzaldehyde, o-nitrobenzaldehyde or p- nitrobenzaldehyde have been synthesized along with their Cu(II) complexes(6,7). The present study aimed to synthesize and characterize copper (II) complexes with a new Schiff bases derived from dithiooxamide and three different aldehydes, as possible antibacterial and antitumor agents.

2. Experimental

2.1Chemicals

Ethanol(absolute),dichloromethane(98%),diethylether(99%),dimethylformamide,p-dimethylaminobenzaldehyde (99%), Vanailin, petroleum ether (40-60 ^oC), Dithiooxamide (>99%) , piperidine (99%) from Fluka company. 2,4,5-trimethoxybenzaldehyde (95%) from Pract. Copper (II) chloride from BDH company.

2.2 Instruments

The I.R spectra using CsI disc technique were recorded using FT.IR 3800 spectrophotometer of Shimadzu company. The electronic spectra were recorded using (Shimadzu UV-160A) ultraviolet spectrophotometer. Metal analysis of the complexes was performed using (Shimadzu-AA 670 G) atomic absorption spectrophotometer. Magnetic susceptibility measurements were obtained at room temperature using: Bruker B. M6 Instrument in Al-Nahrain University . Conductivity was measured by Dist WP3 conductivity/TDS meters at concentration of 1×10^{-3} M in DMF.

2.3 Preparation of LH_1

2,4,5-trimethoxybenzaldehyde (20mmole)was mixed with dithiooxamide (10 mmole) in absolute ethanol followed by (2-3) drops of piperidine. The mixture was stirred and refluxed for one hour. The orange precipitate was filtered, washed with cold ethanol several times and dried. The prepared crude product was recrystallized from dichloromethane and dried under vacuum over anhydrous $CaCl_2$.

2.4 Preparation of LH2

4-dimethylaminobenzaldehyde (20mmole) was mixed with dithiooxamide (10mmole) in absolute ethanol followed by (2-3) drops of piperidine. The mixture was stirred and refluxed For 72 hours. The precipitate was filtered, washed with cold ethanol several times. The precipitate was dried under vacuum over anhydrous $CaCl_2$.

2.5 Preparation of LH3

Vanailin (20 mmole) was mixed with dithiooxamide (10 mmole) in absolute ethanol followed by (2-3) drops of piperidine. The mixture was stirred and refluxed for 48 hours. The precipitate was filtered and washed with cold ethanol and diethylether several times, and dried under vacuum over anhydrous $CaCl_2$.

2.6 Preparation of the (Cu LH1) and (CuLH2)

To a ligand solution (20mmole) in 10ml (CH_2Cl_2), (l0mmole) of the copper chloride ($CuCl_2.2H_2O$) dissolved in (5ml) acetone was added drop wise. The mixture was refluxed for (0.5-1) hour, then the volume of the solution was reduced to about (5ml), the resultant complex was precipitate by the addition of light petroleum ether (40-60) °C and washed by appropriate solvent and then dried under vacuum.

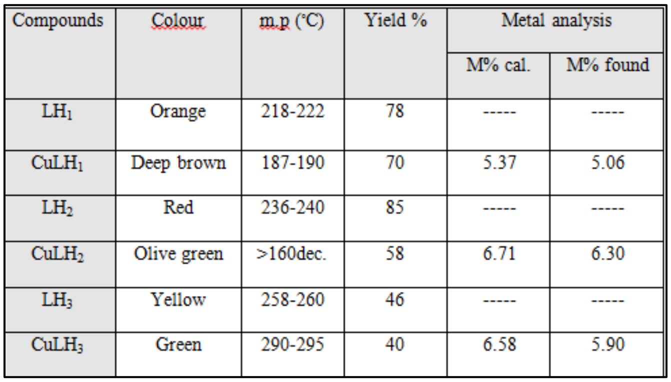
2.7 Preparation of the (CuLH3)

A similar procedure to that described in (section 2.6) was followed to prepare ($CuLH_3$) except using acetone as a solvent for both (LH_3) and the metal salt.

3. Results and discussion

Table.1 shows the physical data for the prepared compounds. The complexes showed different melting points, some of them were higher than the parent ligand; others were of lower melting points. The colors of the complexes were useful in structural determination as will be illustrated in section (3-2).The data of metal analysis were obtained using flame atomic absorption technique. The calculated values are in a good agreement with the experimental values.

Table. 1 shows the physical data for the ligands and their copper complexes



Compounds	Colour	m.p (°C)	Yield %	Metal analysis	
				M% cal.	M% found
LH_1	Orange	218-222	78	-----	-----
$CuLH_1$	Deep brown	187-190	70	5.37	5.06
LH_2	Red	236-240	85	-----	-----
$CuLH_2$	Olive green	>160dec.	58	6.71	6.30
LH_3	Yellow	258-260	46	-----	-----
$CuLH_3$	Green	290-295	40	6.58	5.90

3.1 IR spectra

The ligands (LH_1, LH_2) and (LH_3) Fig.1-3 have two important groups of bands ,these are azomethine and thioamide. In general azomethine group,(C=N-) absorption occurs in the region (1660-1570)cm^{-1} depending on nature of moieties linked to it (8,9). The I.R spectra of (LH_1, LH_2) and (LH_3) showed the azomethine have stretching vibration band at (1589) cm^{-1}, (1606) cm^{-1} and (1598) cm^{-1} , respectively. The (C=S) moiety appeared at (1213) cm^{-1}, (1157) cm^{-1} and (1188) cm^{-1}, respectively. In ($CuLH_1$) spectrum Fig.4, the azomethine frequency was shifted to (1616) cm^{-1} , indicating the coordination through azomethine nitrogen(10-12).The I.R spectrum of ($CuLH_2$) Fig.5 exhibited a shift in the azomethine bands frequency by about (2)cm^{-1} to lower region. This indicate that these metal ions coordinate with the nitrogen of the azomethine group furthermore , new bands observed at (480) cm^{-1} which was attributed to stretching vibration of (Cu-N) (13) . The spectrum of ($CuLH_3$) F.g.6 showed new bands at (550) cm^{-1} and (3360-3600) cm^{-1} due to stretching vibration of (Cu-N) (14) and lattice water (15), respectively. This indicates that copper ion coordinates via nitrogen of azomethine, which was more indicated by the change of the shape of azomethine peak. Table.2 shows the most characteristic bands of the ligands and their complexes.

Table .2 shows the most characteristic bands of (LH_1), (LH_2) and (LH_3) and their complexes

Compound	Azomethine ʋ (C=N)	Thiocarbonyl Bands	ʋ(M-N)	Lattice Water
LH_1	$1589_{(m)}$	$1213_{(s)}$	-----	-----
$CuLH_1$	$1616_{(s)}$	$1217_{(s)}$	585	3300
LH_2	$1606_{(s)}$	$1157_{(s)}$	-----	-----
$CuLH_2$	$1604_{(s)}$	$1188_{(s)}$	480	3360-3600
LH_3	$1598_{(s)}$	$1188_{(s)}$	-----	-----
$CuLH_3$	$1598_{(s)}$	$1188_{(s)}$	550	3300-3600

s=strong, m=medium

Fig. (1) FT-IR of LH1

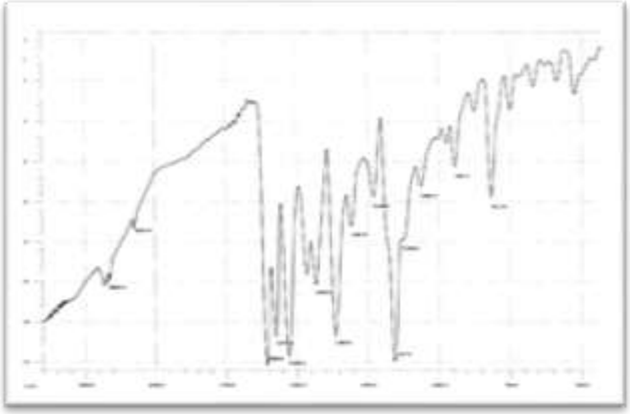


Fig. (2) FT-IR of LH2

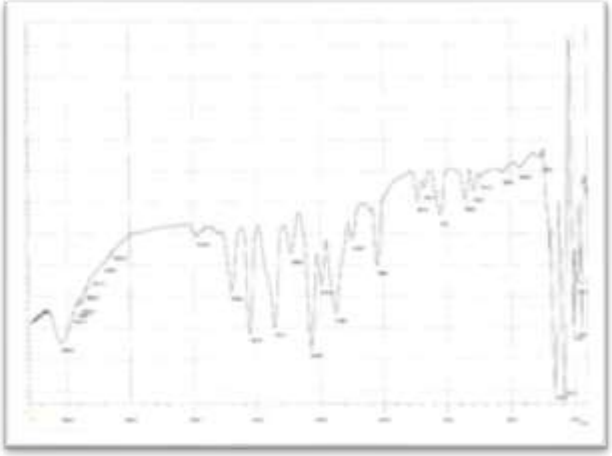


Fig. (3) FT-IR of LH3

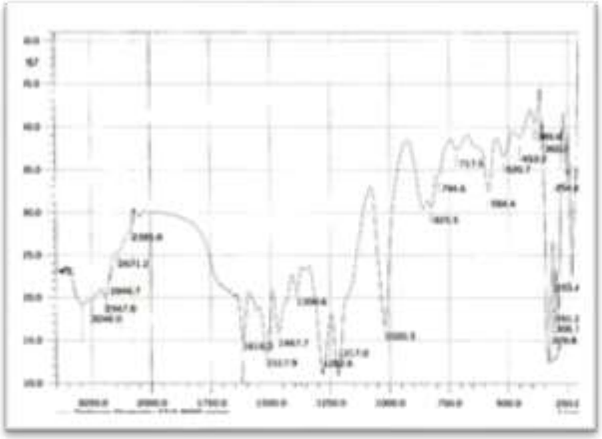


Fig. (4) FT-IR of Cu(LH1)

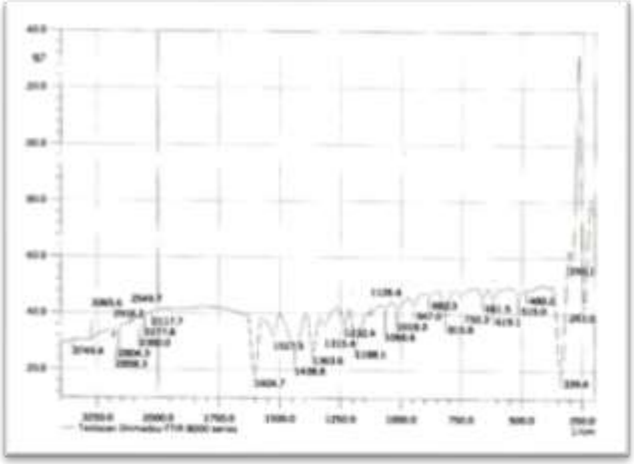


Fig. (5) FT-IR of Cu(LH2)

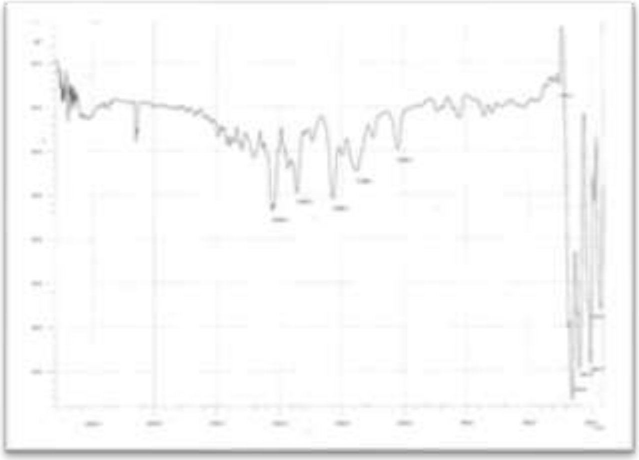


Fig. (6) FT-IR of Cu(LH3)

3.2 Electronic spectra and magnetic properties

The spectra of the ligands (Fig.7-9) showed that the first absorption band between 239 nm (41841 cm^{-1}) and 264 nm (37878 cm^{-1}) which can be attributed to (π-π*) transition for the aromatic nucleus. The second band which appeared between 392nm (25510) cm^{-1} and 437nm (22883) cm^{-1} was attributed to (n-π^*) transition of imino group(C=N)$^{(16)}$.

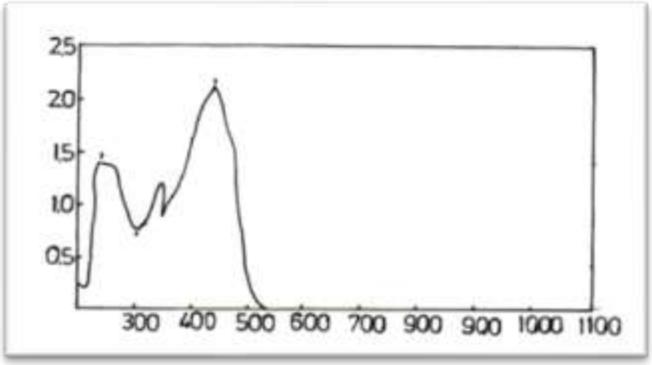


Fig. (7) Electronic Spectrum of LH_1

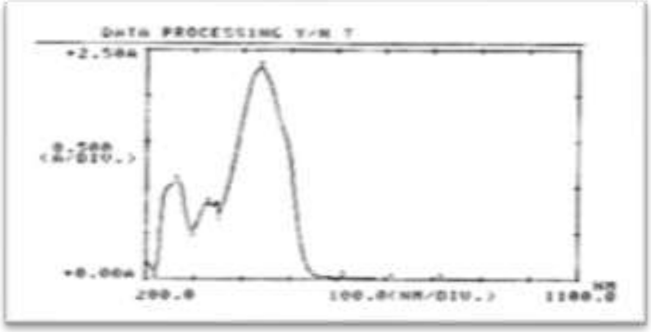


Fig.(8) Electronic Spectrum of LH2

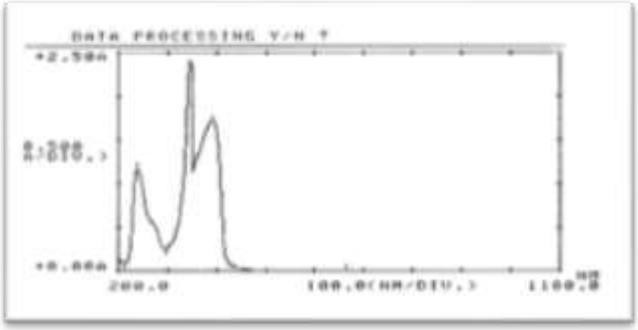


Fig. (9) Electronic Spectrum of LH3

The spectrum of ($CuLH_1$) Fig. 10 have a broad band at 725nm (13793) cm^{-1} due to a combination of two transitions, $^2B_1g\rightarrow{}^2A_1g$ and $^2B_1g\rightarrow{}^2B_2g$ respectively, and another band as a shoulder at 520nm(19230)cm^{-1}

due to $^2B_1g \rightarrow {}^2Eg$ transition. These transitions refer to distorted octahedral geometry around Cu (II) ion (17, 18).

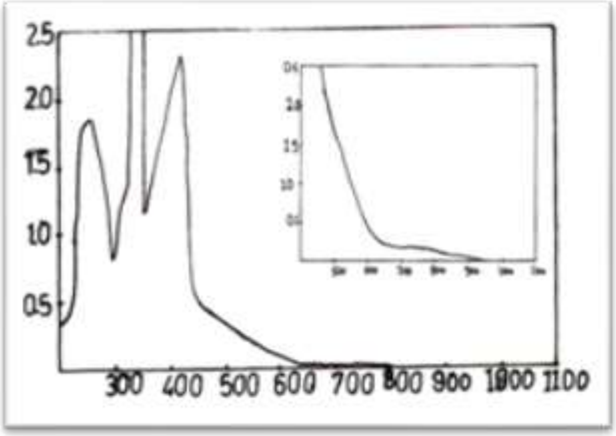


Fig. (10) Electronic Spectra of Cu(LH1)

The value of magnetic moment that have been measured at R.T was 2.19 B.M. This value came within the rang of octahedral geometry (16-19). Molar conductivity measurement showed that the complex was electrolyte. According to these data, an octahedral geometry around Cu (II) ion can be suggested, Fig.11.

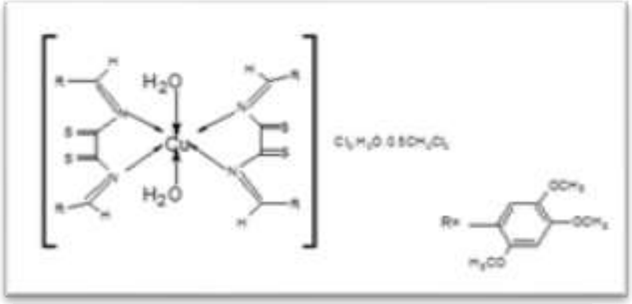


Fig.11 Proposed structure of the complex $CuLH_1$

The olive green copper complex ($CuLH_2$) Fig.12 showed abroad band at 645nm(15503) cm^{-1} due to the following three transition $^2B_1g \rightarrow {}^2A_1g$ (v_1) , $^2B_1g \rightarrow {}^2B_2g$(v_2)and $^2B_1g \rightarrow {}^2Eg$ (v_3). These transitions refer to distorted octahedral around copper complex (19-20), according to the data of magnetic measurement (2.54B.M), in addition to that I.R of and flame atomic absorption , the suggested structure of $CuLH_2$ complex is as described in Fig.13.

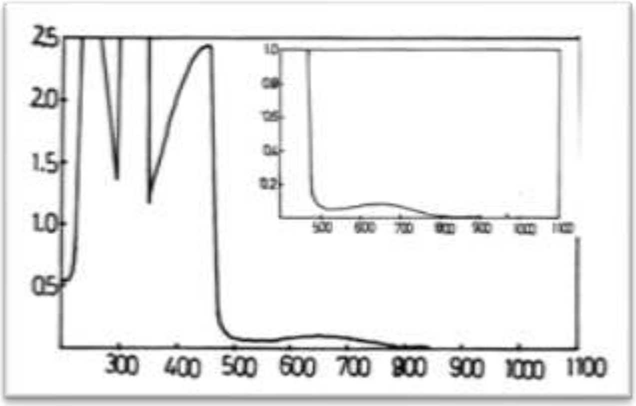


Fig. (12) Electronic Spectra of Cu(LH2)

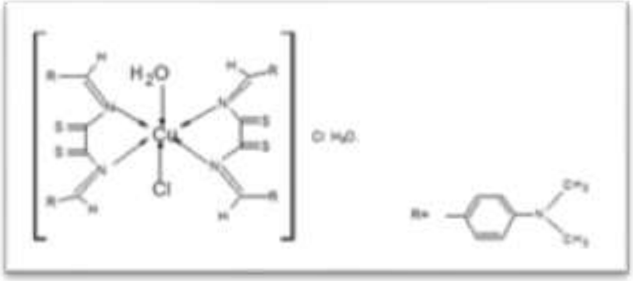


Fig.13 Proposed structure of the complex $CuLH_2$

The electronic spectrum of the green ($CuLH_3$) Fig.14 showed a broad band at 612nm (16339) cm^{-1} assigned as in $CuLH_2$ complex, which refers also to distorted octahedral coordination about copper ion (19,20). The magnetic susceptibility (2.71 B.M)and molar conductivity measurement data indicate that complex is paramagnetic and electrolyte, from these results , an octahedral geometry a round Cu(II) can be suggested, Fig.15 .

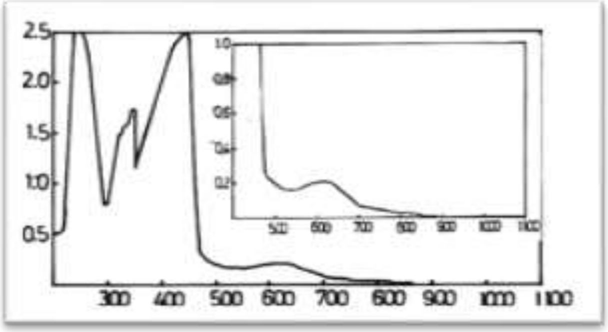


Fig. (14) Electronic Spectra of Cu(LH3)

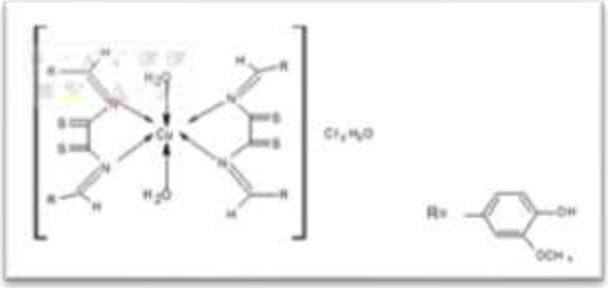


Fig.15 Proposed structure of the complex $CuLH_3$

3.3 Thermal analysis of prepared compounds

The results obtained from thermal analysis of the complexes $[Cu(LH_1)_2(H_2O)_2]\ Cl_2.H_2O.0.5CH_2Cl_2$ and $[Cu\ (LH_3)_2(H_2O)_2]\ CL_2.H_2O$ by TG and DTG techniques within the range (30-800) °C at a heating rate of 20 °C/min under nitrogen atmosphere are described in Table.3, and their thermographs are shown in Fig.16 and Fig.17. Steps of thermal decomposition at maximum temperature of DTG are recorded together with weight loss. The following points can be concluded:

- Lattice water and organic solvents that are not directly coordinated to the metal ion were found to be lost at earlier stages of lower temperatures (21).
- Stages of decomposition reflect the nature of binding between the metal and ligand atoms and the stability of the complexes (22).
- Latest steps appeared left the metal ion with sulfur atom in, which reflects the affinity of copper atom towards the sulfur according to Pearson's law (23).

- Finally, a general trend in thermolysis steps was observed in the earlier stages, where the solvent molecules were first lost followed by methoxy group.

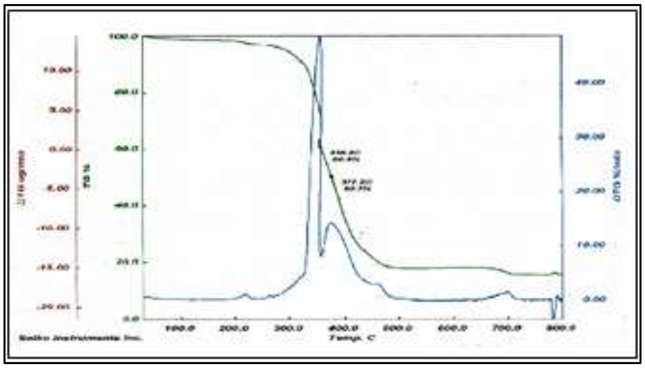


Fig. 16 TG, DTG Thermograms of $Cu(LH_1)$

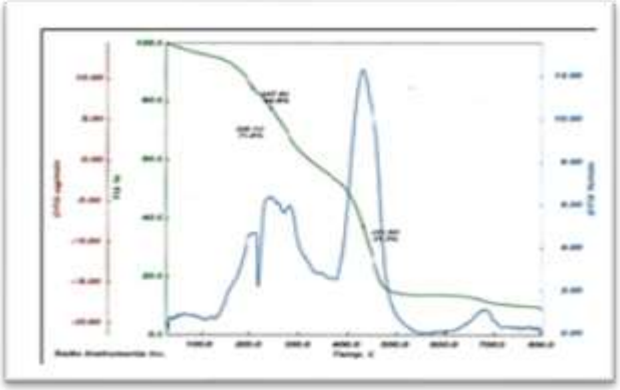


Fig. 17 TG, DTG Thermograms of Cu (LH_3)

Table.3Thermaldecompositionof $[Cu(LH_1)_2(H_2O)_2]\ Cl_2.H_2O.0.5CH_2Cl_2$ and [Cu (LH3)2(H2O)2] CL2.H2O

Stable phase of $[Cu(LH_1)_2(H_2O)_2]\ CL_2.H_2O.0.5CH_2CL_2$	Temp range of decomp. at DTG(C)	Peak temp. at DTG(C)	Weight loss% found(calc.)
$-H_2O$ ↓ $-0.5\ CH_2Cl_2$	25-130	-	5.26 (5.11)
-2Cl ↓ - 2H2O	130-216	200	11.27 (9.036)
↓ $-12\ OCH_3$	216-370	238	30.81 (31.44)
↓ -4 Ph -4 CHN, -2 CS	370-719	433	42.09 (41.54)
$-C_2S$ CuS	719-800	-	10.52 (12.79)
Stable phase of $[Cu\ (LH_3)_2(H_2O)_2]\ CL_2.H_2O$			
↓ $-H_2O$ -2 Cl	200-320	213	9.022 (9.22)
↓ $-2\ H_2O$ -4 OH, $-4\ OCH_3$, -Ph	320-356	356	30.82 (31.400)
↓ -3 Ph -4 CHN, -2 CS	356-713	377	43.60 (43.63)
$-C_2S$ CuS	-	-	15.78 (15.70)

3.4 Antibacterial activity

The antibacterial activity of the ligands and their copper(II) complexes have been tested for the in vitro growth inhibitory activity against the pathogenic bacteria *Escherichia coli* and *staphylococcus aureus* by using the disc diffusion method(24) .The bacteria were cultured in Mueller-Hinton agar medium and used as inoculums for this study. The studied compounds were dissolved in DMSO to two final concentration of 500 and 1000ppm and soaked in filter paper discs , these discs were placed on the already seeded plates and incubated at 35 ± 2 °C for 45h . The ligand LH_1 showed little activity against E-coli, while LH_1 and LH_3 did not show any activity against this bacteria. $CuLH_1$ and $CuLH_3$ complexes showed a greater activity compared to their, respective ligand. The Cu LH_2 did not show any activity against E-coli both 500 and 1000 ppm. The ligands LH_1, LH_2 and LH_3 showed a large activities against staph bacteria compared with E-coli. The $CuHL_1$ showed a similar as ligands (LH_1, LH_2 and LH_3) same activity against this bacteria while $CuHL_3$ complex had greater activity against this bacteria These activities may be explained according to tweedy's chelation theory (25), according to which chelation reduces polarity of the metal atom mainly because of the partial sharing of it's positive charge with the ligand , which favours permeation of the complexes through the lipid layer of cell membrane . Furthermore, the mode of action of the compounds may involve hydrogen bonding via the C=N group with active centers of cell constituents resulting in the interference with normal cell process.

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