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Spectroscopic, Against bacteria and cancer of a new schiff base and its complex with Cu^{+2} and Co^{+2} derived from methyl 4-amino benzoate

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Abstract

In this study, Schiff-base ligand was prepared (LS1) by condensation (methyl 4-amino benzoate) with aldehyde (ortho-vanillin). The prepared schiff-base was identified by FT-IR, UV-Visible, Mass ^{1}H, and ^{13}C-NMR spectroscopy. The electronic spectra of these Azomethine ligand was investigated in terms of acid-base properties, and determination of ionization constants at various pH values (6-12). The complexes were characterized by infrared spectroscopy and measurements of the percentage of copper (II) and the percentage of cobalt (II) using flame atomic absorption spectroscopy, as well as measurements of magnetic susceptibility, molar conductivity, and thermogravimetric analysis. Through the diagnosis and measurements, the geometric shape of the complexes was proposed. Its effectiveness was studied against two types of bacteria and against lung cancer cells.

Keywords: Schiff-base ligand, Acid-Base properties, Hela cells, Antibacterial activity, complexes.

Introduction

Schiff bases (azomethines) are ligands created from an amine and a reasonably simple aldehyde or ketone. Because of their numerous uses, they have become important ligands. In coordination chemistry, it is widely used. [1], homogeneous

catalysis [2,3], drugs [4] , and its use in the preparation of organic ligands [5]. Anti-cancer [6], antioxidant [7], anti-inflammatory [8], antimicrobial [9], anticonvulsant [10], and antitubercular [11] functions of these ligands have also been demonstrated. Mean while, tetra dentate Schiff bases compensated by OH groups with delocalized π systems have good photochromic properties [12] and use organic light-emitting ligands (OLED). [13,14]. In addition, these bonds have a fundamental role in the field of developing coordination chemistry due to their ease of association with some transition metals in different oxidation states and the formation of stable complexes [15]. In a variety of heterogeneous and homogeneous reactions, transition complexes of Schiff bases have been widely used as catalysts [15,16]. Scientists were attracted to schiff bases derived from pharmaceutical benzoate amines because of their distinctive structur [17,18]. This property improved their medical, chemosensor, and biological processes applications [19,20]. These molecules also have excellent chelation properties against transition metal ions, allowing them to be used as binary or ternary chelates in industrial and biological applications [21]. Schiff bases have been used as catalysts, as well as elements of organic light emitting diodes (OLEDs) and thin-film organic solar cells [22,23].

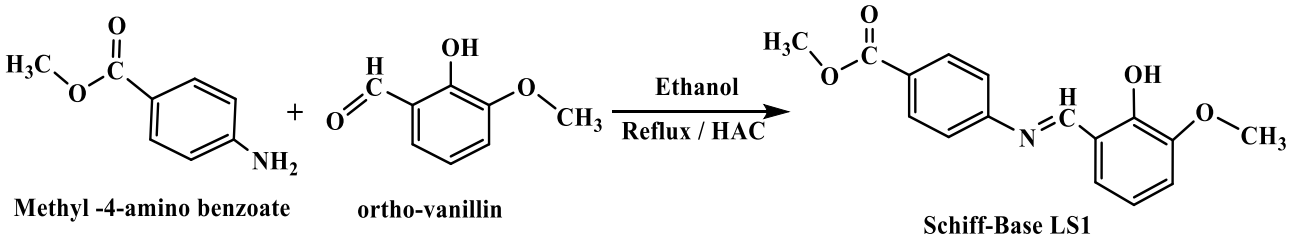
Experimental

Materials and Methods

Aldrich and Merck obtained all the reagents and solvents and used them without further purification. Infrared spectra were recorded as KBr discs using a SHIMADZU FT-IR-8400S. Melting points of ligands were determined by a thermo Scientific (9100). Ligand spectrum ^{1}H and ^{13}C-NMR was obtained on Bruker 400 MHZ and recorded at room temperature in DMSO. UV\Visible spectra measured by Shimadzu UV-1800 using ethanol as a solvent. Mass spectra were recorded by E1 Technique using Agilent Technologies spectrometers using 70 eV. Tracking the completion of the reaction using thin layer chromatography (TLC).

Preparation of Schiff base ligand, (LS1) [24]

The schiff-base ligand (LS1) is schematically showen in scheme 1. schiff base LS1 has been synthesized by reaction of hot ethanolic solution of aldehyde (ortho-vanillin) (0.9129g, 0.006 mol) and hot ethanolic solution of amine (methyl-4-amino benzoate) (0.9070 g, 0.006 mol) in ethanol in the presence of some drops of glacial acetic acid. The mixture was refluxed then cooled at room temperature. The precipitate product was filtered, dried and recrystallized from absolute ethanol. [orange color ; yield: 89 %; M.P 123-125 °C; FT-IR (ν cm^{-1}): 3346 (ν O-H), 3163 (ν C-H aliphatic), 1681 (ν C=O), 1653 (ν C=N), 1604-1438 (ν C=C), 1274 (ν C-N); ^{1}H NMR ($CHCl_3$, 400 MHz; δ ppm) δ: 13.31 (s, 1H, OH), 8.62 (s, 1H, HC=N), 8.09-6.87 (m, 7H, Ar-H), 3.91(t,6H,O-CH_3); ^{13}C NMR ($CHCl_3$, 400 MHz; δ ppm): 166.54 (C_2,C=O), 164.20(C_9,C=N), 152.14 (C_{11},C-OH), (C_{12},C-OCH_3), 148.47 (C_6,C-N), 131.04-115.25($C_{4,5,7,8,13-15}$,C=C), 56.18(C_{16},O-CH_3), 52.21(C_1,O-CH_3); MS: m/z: 285[M^+], 245[M^+], 196[M^+], 120.1[M^+], 76[M^+], 59[M^+]; Uv-Viss. in Ethanol, cm^{-1} (transition): 249, 294 (π-π*) and 347 (n-π*)].



Scheme 1. Synthesis of ligand (LS1).

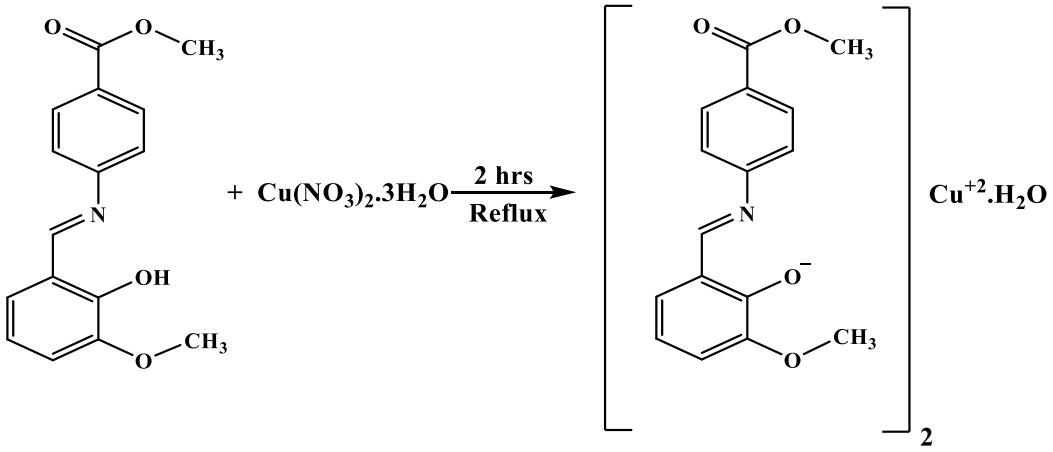
LS1: Methyl (E)-4-((2-hydroxy-3-methoxybenzylidene)amino)benzoate.

Preparation of complex ligand, $[Cu(LS1)_2].H_2O$, $[Co(LS1)_2(H_2O)_2]$[24]

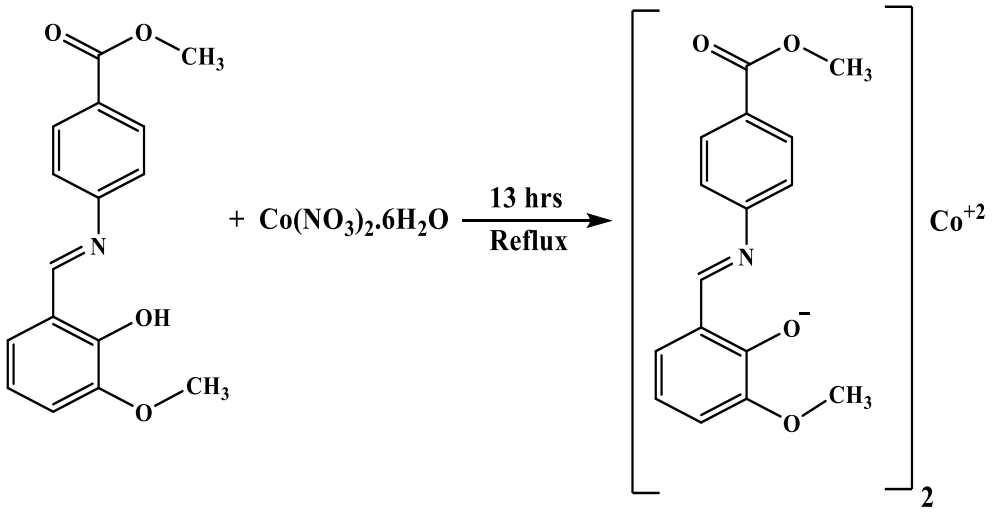
The complex $[Cu(LS1)_2].H_2O$ is schematically showen in scheme (2). (0.2416 g, 0.001 mol) of copper (II) nitrate trihydrate dissolved in (20) ml of absolute ethanol was added to (0.5706 g, 0.002 mol) with the Schiff base bond. LS1 was dissolved in (30) ml of absolute ethanol in a beaker. Circular with a capacity of (100) ml, and the mixture was thickened using the return sublimation method with continuous stirring for (2) hour (Scheme 2). The mixture was then cooled, then the

formed crystals were filtered and washed with water, hot ethanol and ether to get rid of the unreacted starting materials. [brown color ; yield: 58 %; M.P 199-203 °C; FT-IR (ν cm^{-1}): 1656 (ν C=N), 1274 (ν C-N); rato metal: ligand (1:2) respectively; the molar conductivity (20.9 $Ohm^{-1}.cm^{2}.mol^{-1}$); the magnetic susceptibility 1.32; Hybridization sp^3 or dsp^2.

The complex $[Co(LS1)_2(H_2O)_2]$ is schematically showen in scheme 3. As well as in a round flask with a capacity of (100) ml, mix (0.2910 g, 0.001 mole) of copper (II) nitrate trihydrate dissolved in (20) ml of absolute ethanol to (0.5706 g, 0.002 mole) with ligand of schiff bases LS1 dissolved in (30) ml absolute ethanol and the mixture was refluxed with continuous stirring for (13) hour. The mixture was cooled, then the formed crystals were filtered and washed with water, hot ethanol, and ether to get rid of the remaining unreacted parts [green color ; yield: 55 %; M.P dissociation at 180-185 °C; 3450 (ν O-H, water),1633 (ν C=N), 1278 (ν C-N); rato metal: ligand (1:2) respectively; the molar conductivity (16.5 $Ohm^{-1}.cm^{2}.mol^{-1}$); the magnetic susceptibility 1.83; Hybridization d^2sp^3.



Scheme 2. Synthesis of complex $[Cu(LS1)_2].H_2O$.



Scheme 3. Synthesis of complex $[Co(LS1)_2(H_2O)_2]$.

Solutions

* 1 x 10^{-3} M of schiff-base ligand LS1, $[Cu(LS1)_2].H_2O$ and $[Co(LS1)_2(H_2O)_2]$.
* Universal and solution (pH 6-12) [24].

base properties

Buffer solutions were prepared with pH values ranging from (6-12) in which the total ligand concentration was ($4.0x10^{-4}$ M) using universal buffer. The absorbance of these solutions was recorded at a range of wavelengths (350-430) nm (using the pH value as a reference solution).

Maintenance of cell cultures

cancer and normal cell lines were obtained from the IRAQ Biotech Cell Bank Unit in Basrah and maintained in RPMI-1640 supplemented with 10% Fetal bovine, 100 units.ml^{-1} penicillin, and 100 µg.ml^{-1} streptomycin. Cells were passaged using Trypsin-EDTA reseeded at 70% confluence twice to third a week and incubated at 37 C° and 5% Co_2 [25].

Cytotoxicity Assays

To determine the cytotoxic effect, the MTT cell viability assay was conducted on 96-well plates. Cell lines were seeded at 1×10^4 cells/well [26]. After 24h or a confluent monolayer was achieved, cells were treated with the tested ligand LS1,

complexes $[Cu(LS1)_2].H_2O$ and $[Co(LS1)_2(H_2O)_2]$ with concentrations (1000) $\mu g.ml^{-1}$ for each compounds. Cell viability was measured after 72 hrs [27]. Measurement was done at 620 nm (test wavelength) and the percentage of cytotoxicity was calculated from the following equations [28]:

(PR)= B/A*100 and IR= 100- PR.

Anibacterial test method

The hole diffusion method [29] was adopted to measure the biological antibacterial activity of the prepared ligands under study, where holes of equal diameters and equal dimensions were made for each dish on the surface of the culture medium. After that, the sterile dishes containing the solid culture medium were inoculated with the test bacteria by pouring (0.1 ml) of bacterial suspension on the surface in different directions and then move the dishes to ensure its spread. The plates were left for half an hour at laboratory temperature to ensure the absorption process, then (10 microliters) of ligand solutions with a concentration of (1000 ppm) were placed using a fine pipette in the holes on the media grown with the bacterial species, and after they dried, they were incubated for twenty-four hours at a temperature of (37 C^o). The areas of bacterial growth inhibition around each spot were then measured using a millimeter ruler, which appears as a halo free of bacterial growth surrounding the spot of the chemical ligand LS1, complexes $[Cu(LS1)_2].H_2O$ and $[Co(LS1)_2(H_2O)_2]$.

Result and discussion

Schiff base ligand was synthesis (LS1) by condensation (methyl-4-amino benzoate) with appropriate aldehyde (ortho-vanillin), represented in scheme (1). The structures of synthesized ligands were elucidated by ^{1}H-NMR, ^{13}C-NMR, FT-IR, and mass spectra data, and all spectral data were in accordance with assumed structures.

The spectra of ligand (LS1) exhibit band 1681 cm^{-1} due to ν(C=O) group. The infrared data of the schiff bases (LS1) show absorption band at 1653 cm^{-1}**.** Assigned to the (C=N) stretching vibrations, indicating the formation of azomethine band. Moreover, the absence of primary amine group stretching vibration in the spectra of the ligands indicates the occurrence of schiff base condensation [30,31], while appearing of ν(C=C) band occurred in the range of 1604-1438 cm^{-1}, as presented in **Fig. 1.**

The electronic spectra of the ligand appear bands belonged to π-π* and n-π* transition, as presented in **Fig. 2.**

The molecular ion peak was seen with the mass spectra of ligands at m/z = 285 with 100% abundance for LS1, which correspond to $[C_{15}H_{13}NO_3]^{+\cdot}$ Species. At m/z = 285, base peak could be seen, as presented in **Fig. 3**.

Wheres Fig3,4,……?

The H NMR spectrum of the LS1 ligand (**Fig. 4**) is characterized by a single signal with a chemical shift 13.31ppm due to the proton of the (H-O) group. A single signal appears at a chemical shift of 8.62 ppm that belongs to the proton of the azomethine group (H-C=N) [32]. As for the protons of the aromatic ring, they appear in the form of a multiple signal with a chemical shift of 8.09-6.89 ppm [33]. We note the appearance of a single signal due to the protons of the methoxy group (O-CH3) [34] attached to the aromatic ring and the methoxy group (O-CH3) attached to the aliphatic chain at the same location with a chemical shift (3.91)ppm.

It is noted in the ^{13}C NMR spectrum of the LS1(**Fig. 5**) ligand that a signal appears at a chemical shift 166.54 ppm, returning to the carbon atom of the carbonyl group (C=O), and another signal appears at a chemical shift 164.20 ppm, returning to the carbon atom of the azomethine group (HC=N). Also, a signal at a chemical shift 152.14 ppm goes back to the carbon atom attached to the hydroxyl group (C-OH). The signal at 151.47 ppm belongs to the carbon atom of the aromatic ring attached to the methoxy group (C-OCH_3). Another signal at a chemical shift 148.47 ppm goes back to the carbon atom of the (C-N) group. Also, multiple signals appear that belong to the carbon atoms of the aromatic rings with a chemical shift 131.04-115.25 ppm. We notice a signal at 56.18 ppm that belongs to the carbon atom of the (O-CH_3) group in the aliphatic chain. Either the signal of the carbon atom group (O-CH_3) attached to the aromatic ring appears at a chemical shift 52.21ppm.

The effect of pH values on the ligand of schiff bases LS1 was studied (**Fig. 6A**). A series of solutions of the compound LS1 were prepared using universal buffer solutions with different pH values (6-12). The spectrum shows intense bands (λ_{max} 390 nm.) in an alkaline medium. At the pH range (7-11) due to ionization of the

Schiff base ligand (anionic form) it forms a soluble solid in aqueous medium instead of the acidic form. The highest absorption band was observed at pH 11.

From the absorbance – pH curves of the schiff base ligand was plotted to determine the ionization constant of the schiff base ligand (LS1) at certain wavelength 390 nm. (**Fig. 6B)**.

pK_a = pH (at A1/2) where ; A1/2 = (AL+ Amin.) / 2

AL and Amin are limiting and minimum absorbencies respectively. Then the (pK_a=9.1) constant was measured using the Absorbance – pH curve. The mechanism of the ionization processe of the pure schiff bases (LS1) was suggested as shown in Scheme 4.

The spectra of complexes $[Cu(LS1)_2].H_2O$ and $[Co(LS1)_2(H_2O)_2]$ exhibit bands 3400 cm^{-1} and 3450 cm^{-1} respectively due to ν(O-H, water) group. Shift of the frequency of the azomethine group ν(C=N) towards lower or higher frequency regions with a noticeable change in its shape and intensity in the spectral range (1656 and 1633) cm^{-1} respectively. It was also observed in the spectra of the complexes that weak nine-frequency bands at the frequency (530 and 518) cm^{-1} belong to the ν(M-O) bond [35] as presented in **Fig. 7A** and **Fig. 7B**.

Flame atomic absorption spectroscopy (A.A.S.) was used to estimate the ratio of the metal to the ligand in the studied complexes. The process of digesting the complexes is carried out by dissolving approximately (0.01) g of the prepared complex in (5) ml of concentrated nitric acid, then the solution is heated until it becomes clear and is then This involves diluting the sample with ion-free distilled water and then entering the flame atomic absorption device for measurement [36]. It is evident from the values and calculations of the practical percentages that they are very close to the values and calculations of the theoretical percentages calculated for the metals involved in the composition of the complexes studied (Table-1). This confirms that the ratio of metal to ligand in all of these complexes is 1:2 (metal: ligand).

The molar conductivity of solutions of copper (II) and cobalt (II) complexes were measured respectively in dimethylformamide (DMF) solvent with a concentration of ($1x10^{-3}$ molar) and at room temperature, and the molar conductivity was calculated using equations (L=G x A) and (Λ_M=1000 x L/C) [37]. We notice from

the molar conductivity values listed in **(**Table-2**)** that all copper (II) and cobalt (II) complexes, were low, as the molar conductivity value ranged (20.9 and 16.5) respectively. The lack of ionic character indicates the absence of negative ions outside the coordination ball [38,39] for all complexes.

The results of the magnetic susceptibility technique measurements reinforce the conclusions that predict the proposed stereoforms of the studied complexes and reinforce what other diagnostic techniques have reached about structure and stereoscopic shape [40]. Additional information can also be obtained about the oxidation state of the central atom in the complex and the electronic arrangement [41]. Through the experimental values of the effective magnetic moment (μeff), we can determine whether the central atom possesses one or more single electrons, which will show the complex with paramagnetic properties, or if it does not have a single electron, which will lead to the appearance of magnetic properties [42,43]. The experimental values of the effective magnetic moment (μeff) of the studied metal complexes were calculated at room temperature (298 K), and the diamagnetic correction of the atoms in organic molecules, inorganic radicals, and metal ions was carried out using (Pascal's constants) [44] according to the following equations ($\mu_{eff} = 2.828 \sqrt{X_A T}$ B.M., $X_A = X_M - D$, $X_M = X_g$ x M.wt and $X_g = [C \times L / 10^9 m] \times (R - R_o)$). After calculating the practically calculated effective magnetic moments (μeff) values (Table-3) for all copper (II) and cobalt (II) complexes with schiff base ligand LS1, which are close to the values of copper (II) and cobalt (II) complexes (1.73, 1.80) por.magnaton respectively [45]. We can conclude from these values that copper (II) complexes possess paramagnetic properties that confirm the presence of only one electron. As for the expected geometric shape of all copper (II) complex, it is either quadrilateral or symmetrical. Sp^3 hybridized or planar square with dsp^2 hybridized**,** while the proposed geometric shape for cobalt (II) complexes is a distorted octahedron, the type of distortion is (Z-out) with d^2sp^3 hybridization, and they are considered internal orbital complex [125].

Thermogravimetric analysis measurements of the studied complexes were recorded with a temperature range of (25-1000) Cº for copper (II) and (25-550) Cº for cobalt complexes at a heating rate (10 °C.min^{-1}) in an inert arkon atmosphere, and given the great importance of thermogravimetric analysis techniques in

studying thermal behavior and verifying the ratios Organic and inorganic components in complexes, as complexes differ in their thermal stability within a certain range of temperatures and this is due to the nature of their components (the ligand or metal), and the metal oxides included in the composition of these complexes are the final products at high temperatures in an argon atmosphere, as is done Through the results of this technique, the stability of the studied complexes can be confirmed, and through these results, it is also possible to confirm the presence of water molecules in the crystal lattice of these complexes [46,47]. Studies indicate that water molecules that are outside the coordination sphere of the complex are often lost in the first stage of heating, with a range of temperatures (approximately 25-150 C°), and the range varies from one complex to another, which confirms the difference in bond strength [48,49]. Thermogravimetric analysis is shown in the **Fig. 8A** and **Fig. 8B**.

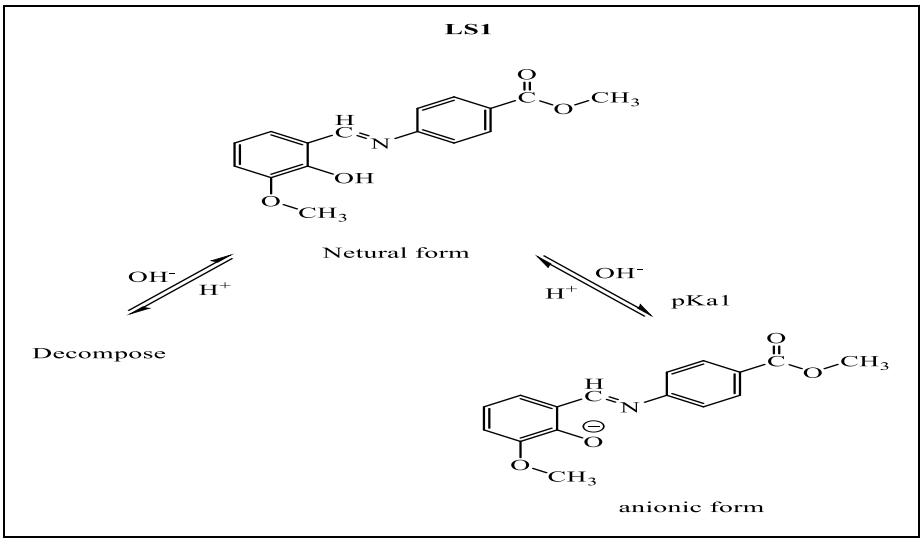
Based on the information obtained from infrared spectra, measuring the percentage of copper (II) and cobalt (II) complexes, measuring magnetic susceptibility, molar electrical conductivity, and the thermal analysis curve for all complexes, the formation of the complexes was proposed, as in Figure 9A and Figure 9B for copper (II) and cobalt (II) complexes respectively.

Applications :-

The effectiveness of schiff base ligand (LS1) and their complexes with copper (II) and cobalt (II) (Fig. 10) was studied at a concentration of (1000) $\mu g.ml^{-1}$ on lung cancer cells, and at the maximum wavelength (620 nm). The study showed the non-effectiveness of ligand (LS1) against these cells through the inhibition values (%Inhibition), as it is noted that the value is (37.86). It is noted that the effectiveness of the ligand increases in its complexes with copper (II) and cobalt (II), as the inhibitor values for (72.70, 78.68) the complexes of copper (II) and cobalt (II) with (LS1), respectively.

The biological activity of Schiff base (LS1) and its complexes with copper (II) and cobalt (II) was studied against two types of bacteria (Staphylococcus Aureuse) and (Escherichia Coli). Figure 11A shows the obvious effect of ligand (LS1) and copper(II) and cobalt(II) complexes in inhibiting the growth of bacteria (Staphylococcus Aureuse). The effect of the ligand (LS1) and its complex with copper (II) and cobalt (II) was measured by measuring the diameter of the

inhibition zone (13 mm), which did not change in the ligand from complexes with bacteria (Staphylococcus Aureuse). The study also showed that the ligand LS1 gave higher activity than its complex with cobalt (II)(15 ,12 mm) respectively, and that the ligand in its complex with copper (II) did not show any activity against the bacteria (Escherichia coli) studied (Fig. 11B).



Scheme 4. mechanism of the ionization ligand LS1.

Table-1: Proportions of copper(II) and cobalt (II) in its complexes using flame atomic absorption technology

complex	weight g	Molecular weight g.mol^{-1}	[Cu] in (A.A.S.) g x10^{-6}	Cu (II)%		Metal:Ligand
				Theoretical	Practical	
$[Cu(LS1)_2].H_2O$	0.0099	650.14	867	9.77	8.76	1 : 2
$[Co(LS1)_2(H_2O)_2]$	0.0099	650.14	867	9.77	8.76	1 : 2

Table-2: Values of electrical conductivity, molarity, and electrolyte type for copper (II) and cobalt (II) complexes.

complex	Electrical conductivity Sx10^{-6}	Molar conductivity Ohm^{-1}.cm^2.mol^{-1}	Type of electrolyte

$[Cu(LS1)_2].H_2O$	21	20.06	Non-electrolytic
$[Co(LS1)_2(H_2O)_2]$	9	8.60	Non-electrolytic

Table-3: Magnetic susceptibility data for copper(II) and cobalt (II) complexes.

complex	$-D.10^{-6}$	$Xg.10^{-6}$	$Xm.10^{-6}$	$XA.10^{-6}$	μ_{eff}	Hybridization
$[Cu(LS1)_2].H_2O$	329.34	0.61	407.58	725.92	1.32	sp^3or dsp^2
$[Co(LS1)_2(H_2O)_2]$	331.14	1.62	1074.93	1406.07	1.83	d^2sp^3

Table-4 : TGA data for copper copper(II) and cobalt (II) complexes.

complex	stage	C°	The missing part	Weight loss%	
				Theoretical	Practical
$[Cu(LS1)_2].H_2O$	1	25-120	H_2O	2.77	3.29
	2	120-275	CH_4O, $C_2H_4O_2$	14.56	14.58
	3	275-450	C_7H_7N	19.34	20.38
	4	450-820	$C_7H_8O_2$	28.12	30.37
$[Co(LS1)_2(H_2O)_2]$	1	183-292	$2H_2O$, $2(C_2H_4O_2)$	23.53	25.50
	2	292-415	C_6H_6	15.27	13.55
	3	487-550	CH_3N	7.16	6.46

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