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Crystal structure, Spectroscopic Studies, DFT Calculations, Cyclic Voltammetry and Biological Activity of a Copper (II) Schiff Base Complex

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ABSTRACT

Herein we describe the chemical synthesis of a novel tetradentate Schiff base ligand (H2L), bridged with a pyridine, and its corresponding mononuclear copper complex (Cu(II)L). H2L, derived from the condensation of 2,3-diaminopyridine and 5-bromosalicylaldehyde, and Cu(II)L were structurally confirmed by routine spectral techniques, UV-Vis, FT-IR, 1H-NMR, MS and elemental analysis. Single crystal X-ray diffraction analysis of Cu(II)L complex showed a monoclinic system with P21/C space group and Z = 4 molecules per unit cell. The characterization data of the complex revealed strong coordination via azomethine nitrogen (N) and bromo-phenolate oxygen (O). Moreover, the experimental parameters were found in line with the theoretical parameters. The conductivity measurement showed a non-electrolytic nature of the complex and the electrochemical behavior exhibits two quasi reversible redox processes. In-vitro antimicrobial studies on the synthesized compounds revealed a significant activity of the complex on some bacteria strains than the free ligand. DFT calculations were fully optimized using B3LYP and confirmed practical electrochemical and antibacterial results.

Keywords: Schiff base, Copper complex, single crystal, DFT calculations, Cyclic Voltammetry, Antibacterial activity.

1. Introduction

Schiff-base ligands and their coordination compounds have attracted the researchers' attention and taken an important area in chemistry as compounds having azomethine linkage

(C=N) [1-3]. This interest is still growing due to their attractive properties, simple synthesis, stability, low toxicity, good biocompatibility [4,5] and diverse fields of applications in industry, medicine, analytic and catalysis [6-8].

The copper(II) complexes constitute an important class in chemistry not only for their proper interesting coordination chemistry, such as flexible redox properties, geometry and oxidation state [9,10] but also for their extensive application in various areas such as catalyst in oxidation, reduction and epoxidation reactions [11,12]. They are also used in many type of polymerization and as anticorrosion agents in industry [13,14]. Furthermore, the copper(II)-based compounds exhibit broad spectrum of pharmacological activities and have been largely explored in medicine for the treatment of various diseases [15-18], which are closely related to their metal complexation ability [19]. As an example, upon coordination, the lipophilicity, which controls the rate of entry into the cell, is modified thereby reducing some of the side effects and the complexes may exhibit new set of bioactive properties which are not displayed by the free ligand [20,21].

In addition, there are numerous researches reporting that Schiff base complexes containing one or more halo-atoms in their aromatic ring have been widely investigated because of their antimicrobial properties [22-26]. However, much less information is available regarding the Schiff bases derived from diamino-pyridines with other carbonyl compounds, this kind of compounds has not yet been studied systematically. There are only a few publications concerning the reactivity of 2,3-diamino-pyridine with various carbonyl compounds such as aromatic aldehydes. Thus, it is a challenge for researchers to study the reactivity of heterocyclic complexes with a pyridine ring in their structures to provide useful insight into the chemistry and biochemistry of bio-active molecules [27,28]. As an extension of these studies, we were interested in checking the behavior of a copper complex when a brome substituent on the aromatic ring moieties and a pyridine bridge were introduced,

In the current study, we highlight the synthesis and characterization of tetra-dentate Schiff base ligand derived from 5-bromosalicylaldehyde and 2.3-diaminopyridine and the corresponding copper (II) complex. The structural geometry of the complex has been determined by X-ray crystallography and the electrochemical properties have been investigated by cyclic voltammetry. In addition, and for a better understanding of the structural activity correlation, DFT calculations were performed and the antibacterial activity of prepared ligand and copper (II) complex, were studied towards some pathogenic strains of Gram positive and Gram negative bacteria.

2. Experimental

2.1. Materials and measurements

All solvents and chemicals reagents were purchased from Aldrich and Merck and used as received, without further purification. UV-Vis spectra (in DMF, 200-800 nm) were recorded on a Shimadzu UV-1800 spectrophotometer. FTIR spectra (KBr pellets, 4000-400 cm⁻¹) were obtained on a Shimadzu FTIR Affinity-1 spectrophotometer.¹H-NMR spectrum (in CDCl₃/TMS) was measured with a Bruker 300 Advance spectrometer and the mass spectrum was obtained with a Bruker Daltonics Flex Analysis spectrometer. Microanalyses were carried out using an Elementar-Vario EL III CHNOS analyzer. The molar conductance in DMF, 10⁻³ M) was determined at room temperature using a MeterLab CDM-210 conductivitymeter and the melting point was measured on a Kofler Bank 7779 apparatus.

In the electrochemical study, dimethylformamide (DMF) was employed as solvent, lithium perchlorate (LiClO₄) used as the supporting electrolyte; using a three-electrode cell in which a glassy carbon (GC) was the working electrode, a saturated calomel electrode (SCE) was the reference electrode and a platinum wire (PT) was used as an auxiliary electrode. The measurements are carried out in nitrogen atmosphere at room temperature.

The voltammograms were scanned in the potential range +1600 to -2200 mV, at a sweep rate of 100 mVs⁻¹. Ferrocene/Ferrocenium (Fc/Fc⁺) is used as an internal standard with the half wave potential $E_{1/2} = 472$ mV/ECS. All solutions were deoxygenated by passing a stream of pre-purified N₂ into the solution for at least 10 min prior to recording the voltammograms.

2.2. Synthesis of the ligand H₂L

Schema 1 shows the synthetic route of the Schiff base ligand H₂L by mixing 0.5 mmol of 2,3-diaminopyridine (0.0545 g) with 1 mmol 5-bromosalicylaldehyde (0.201 g) in 20 mL methanol with continuous stirring and reflux for 3 h at 75 °C. The yellow precipitate was washed with methanol and diethyl ether and then dried in vacuum over a night. Yield: 80 %; mp > 250 °C. Anal. calc. for C₁₉H₁₃N₃O₂Br₂: C: 48 %, H:2.7 %, N: 8.8 %, found: C: 47.7 %, H: 2.9 %, N: 8.8 %, IR (KBr pellets, \bar{v} cm⁻¹): 1622 (C=N), 1572 (C=C), 1274 (C-O), UV-Vis: DMF, λ nm, [ϵ M⁻¹ cm⁻¹]: 275 [75280], 346 [17440], ¹H-NMR: (CDCl₃, δ ppm): 6.5-8.5 (m, ArH), 13.38 (s, OH), 12.80 (s, OH), 9.47 (s, CH=N), 8.57 (s, CH=N), MS (MALDI-TOF, ditranol) [MH]⁺= 473.938.

2.3. Synthesis of the Cu(II)L complex

Cu(II)L complex Schiff base was prepared according to the literature method [29]. 1 mmol of Cu(OAc)₂ (0.0907 g) dissolved in methanol, was added drop-wise to a methanolic solution of Schiff base ligand H₂L (0.475 g) (Scheme 1). The obtained mixture was stirred at 75 °C for 2 h under nitrogen atmosphere. The obtained brown precipitate was filtered, washed with methanol and diethyl ether. Single crystals suitable for X-ray diffraction were obtained in pyridine/MeOH solvent. Yield: 78 %; mp> 250 °C. Anal.calc. for C₁₉H₁₁N₃O₂CuBr₂: C: 42.5 %, H: 2.06 %, N: 7.9 %; found: C: 42.5 %, H: 2.1 %, N: 7.8 %; MS (MALDI-TOF, ditranol): [MH]⁺ = 534.825; IR (KBr pellets, \bar{v} cm⁻¹): 1606 (C=N), 1560 (C=C), 1312 (C-O), 524 (Cu-O), 483 (Cu-N); UV-Vis: DMF, λ nm, [ϵ M⁻¹ cm⁻¹]: 271 [42560], 326 [45300], 441 [43660].



Scheme.1. Synthesis of the ligand H₂L and the copper complex Cu(II)L.

2.4. X-ray crystallography

Single crystals of Cu(II)L complex were grown by slow layer diffusion of pyridine into a MeOH solution at room temperature. A brown plate single crystal of dimensions ($0.20 \times 0.15 \times 0.10$) mm³ suitable for X-ray analysis, was used for data collection at 173(2) K on a Nonius Kappa-CCD diffractometer equipped with an Oxford Cryosystem liquid N₂ device, using graphite-monochromated Mo/Ka (k = 0.71073 Å) radiation. A semi-empirical absorption correction was applied using the MUL scan ABS routine in PLATON [30]. Transmission factors: $T_{min}/T_{max} = 0.38499/0.53425$. Atomic scattering factors and anomalous dispersion constants were taken from the International Tables for Crystallography; Volume C [31].The structure was solved by direct methods using the SHELXS-97 and SHELXL-97 programs and refined on F2 by the full-matrix least-squares methods. All of the non-hydrogen atoms were refined anisotropically and the hydrogen atoms were included in geometric positions but not refined.

2.5. Quantum calculation using Density Functional Theory (DFT) calculation

The full geometry optimization were carried out using the Gaussian 9 program, based on density functional theory (DFT) [32], using Beck's three parameter hybrid exchange functional [33], with Lee-Yang-Parr correlation functional (B3LYP) and 6-31G (d, p) basis set [34,35].

2.6. Antibacterial activity

The Schiff base ligand and the copper complex were tested *in vitro* for their antibacterial activity against *Pseudomonas aeruginosa, Klebseilla pneumoniae, Escherichia coli* and *Proteus mirabilis* as Gram negative bacteria and *Staphylococcus aureus, Methicillin resistant S.aureus (MRSA), Streptococcus pyogones* and *Micrococcus luteus* as Gram positive bacteria in Muller Hinton Agar medium (MHA) using disc diffusion method [20]. The stock solution was prepared by dissolving the compounds in DMSO to prepare two concentrations 10 and 5 mg/mL. The sterilized filter paper discs (6 mm diameter) of Watman N°1 was soaked in different test solutions and placed in the surface of sterile petri plates (9 mm diameter) previously seeded with the microorganisms. The petri plates were incubated for 24 h at 37 °C and the inhibitions zone were measured around each disc. Three standards antimicrobial agents were used in this study: Gentamicin, Amoxicillin and Ciprofloxacin; DMSO was taken as negative control which shows no inhibitory effect on bacterial growth.

3. Results and discussion

3.1. Elemental analysis and conductivity studies

Elemental analysis results of the ligand H_2L and the copper complex Cu(II)L are in good agreement with the calculated values. The molar conductance values for H_2L and Cu(II)L in 10⁻³ M DMF at room temperature are 10.38 and 5.26 Ω^{-1} cm²mol⁻¹ respectively.

These very low conductance values indicate the non-electrolytic nature of the compounds [36,37].

3.2. IR Spectroscopic Properties

The FT-IR spectrum (Table 1) of the ligand shows an absorption band at 3437 cm⁻¹, corresponding to inter and intra-molecular hydrogen bonds, which is attributed to the stretching vibrations of the hydroxyl band (O-H) [38].

The characteristic vibration of azomethine group (C=N) in the ligand appears at 1622 cm⁻¹. This absorption shifts to a lower wave number, 1606 cm⁻¹, in the case of the complex, indicating the coordination of the nitrogen atom of azomethine group to the metal [39,40]. Another broad band appearing at 1560 cm⁻¹, is assigned to (C=C) stretching absorption.

In addition the coordination of the ligand is further supported by the band around 1274 cm⁻¹, which shifts to a higher wave number of (C–O) in the complex (1312 cm⁻¹). This behavior is due to the coordination of the oxygen atom of the ligand to the copper, as reported in the literature [41]. The absorptions at 524 and 483 cm⁻¹ are due respectively to the Cu–O and Cu–N vibration bands in the complex Cu(II)L [42].

3.3. Electronic spectra

The electronic spectra of the ligand and the copper (II) complex, were recorded, in DMF at room temperature, between 800-200 nm (Table 1). The electronic spectrum of H₂L shows two absorptions. The first at 275 nm is attributed to $\pi \rightarrow \pi^*$ transitions while the second one, very large, observed at 346 nm is ascribed to $n \rightarrow \pi^*$ transitions. Electronic spectrum of Cu(II)L complex exhibits three absorptions, the bands at the higher energy region 271 and 326 nm are assigned to the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions of the ligand as already reported [43]. The band appearing at 441 nm, less intense than the first, is associated to the ligand-metal charge-transfer (LMCT) transitions due to the transitions π (imine) \rightarrow metal [29].

Table.1. FT-IR and UV–Vis spectral data of the Schiff base ligand H_2L and the copper complex Cu(II)L.

Compounds		UV–Vis (in DMF)					
1	ΰ (О-Н)	ῡ (C=N)	ῡ (C=C)	ΰ(С-О)	ῡ (Cu—O)	ῡ (Cu—N)	$\lambda_{max} (nm)$
H_2L	3437	1622	1572	1274	/	/	275; 346
Cu(II)L	3446	1606	1560	1312	524	483	271 ; 326 ; 441

3.4.¹H-NMR

The proton NMR results (Figure 1) for the Schiff base ligand show two de-shielded signals for the protons of the hydroxyl groups at 12.80 and 13.38 ppm. The two singlets appearing at 8.57 ppm and 9.46 ppm, are attributed to the azomethine protons [44]. Aromatic protons appear as multiplets in the range of 6.5-8.5 ppm and are in good agreement with the integral areas [45].



Figure.1. ¹H-NMR spectrum of the ligand H₂L.

3.5. Mass spectra

The mass spectra of the Schiff base ligand and the copper complex were obtained using MALDI-TOF spectrometer in DMSO as solvent. The Mass spectra show that the molecular peaks observed at $[MH]^+$ = 473.938 and 534.825, are consistent with the molecular weight of ligand and complex respectively (Figure 2).

The molecular peak cluster, in the mass spectrum of the dibrominated complex, shows the expected relative abundance of the bromine isotopes [46].



Figure.2. The masse spectra of the H₂L ligand and the Copper complex Cu(II)L.

3.6. Single crystal X-ray diffraction

The single crystal X-ray diffraction reveals that the complex Cu(II)L has molecular formula $C_{19}H_{11}Br_2CuN_3O_2$. Table 2 shows crystal data, data collection and structure refinement parameters.

Table.2. Crystal data, data collection and structure refinement parameters.

Compound	Cu(II)L
Molecular formula	C ₁₉ H ₁₁ Br ₂ CuN ₃ O ₂
Molecular weight	536.67
Temperature (K)	173(2)
Radiation	Μο-Κα(0.71073)
Crystal system	Monoclinic
Space group	P21/c
a/Å	12.0712(7)
<i>b/</i> Å	8.0472(5)
<i>c/</i> Å	18.8974(9)
alpha°	90.00
Beta°	111.134(3)
gamma°	90.00
V/Å ³	1712.21 (17)
Z	4
D _{calc} (mg m ⁻³)	2.082
Crystal size (mm ³)	0.20 x 0.15 x 0.10
Crystal description	plate
Crystal colour	brown
Absorption coefficient	5.964
F(000)	1044
Reflections	9255/2607
Range/indices (h, k, l)	-150, 15; -10, 9; -24, 24
Teta _{limit}	1.81, -27.49
No. of observed data,	2607

No. of variables	244
Goodness of fit on F^2	1.013
$R_1, wR_2 [I > 2\sigma(I)]^a$	0.0519, 0.0968
R_1 , wR_2 (all data) ^a	0.0934, 0.1096

The asymmetric unit of Cu(II)L with atom numbering is shown in Figure 3.



Figure.3. Asymmetric unit of Cu(II)L, (a) opposite view, (b) side view.

The Figure 3(a) shows that the metal is coordinated to two oxygen atoms of two 5bromo-salicylaldehyde groups (O1 and O2) and two nitrogen atoms of 2,3-diaminopyridine (N1 and N2) of Schiff base ligand, the distances between the coordinated nitrogen and oxygen atoms and the metal Cu-O1, Cu-N2, Cu-O2 and Cu-N3 are 1.898(3), 1.941(3), 1.883(3) and 1.940(3) Å respectively. The chelating angles O2-Cu1-O1, O1-Cu1-N2, O2-Cu1-N3 and N2-Cu1-N3 have values 88.33(13), 93.89(14), 93.52(14) and 84.26(15) ° respectively. The bond distances and angles are in good agreement with those reported in similar Schiff bases complexes [47,48]. In addition, the Figure 3(b) shows that the atoms N2, N3, O1 and O2 are coplanar and define a basal plane, proving quadridentate symmetrical Schiff base ligand.

The Table 3 summarizes cited bonds lengths and angles values in comparison with theoretical calculated values, and proving a good arrangement, which confirm the structure conformation.

 Table. 3. Selected experimental and theoretical bond lengths (Å) and angles values (°)

 for Cu(II)L complex.

	Bond lenghts (Å	v)		Bond angles (°)	
	Experimental	calculated		Experimental	calculated
Cu1-O2	1.883(3)	1.887(6)	O2-Cu1-O1	88.33(13)	89.658(2)
Cu1-O1	1.898(3)	1.891(1)	O2-Cu1-N2	177.71(15)	177.176(3)
Cu1-N2	1.941(3)	1.961(3)	O1-Cu1-N2	93.89(14)	93.165(2)
Cu1-N3	1.940(4)	1.937(3)	O1-Cu1-N3	178.13(14)	177.474(1)
			N2-Cu1-N3	84.26(15)	84.309(2)
			O2-Cu1-N3	93.52(14)	92.868(3)

The packing of the Cu(II)L molecules is shown in Figure 4, it is observed that, four molecules (Z = 4) crystalize in a monoclinic unit cell with $P2_1/c$ space group, the unit cell is non centrosymmetric, characterized by an inversion point at the center O, 2-fold screw axis with direction [0, 1, 0] at 0, y, $\frac{1}{4}$ with screw component [0, $\frac{1}{2}$, 0] and glide plane perpendicular to the plan [0 1 0] with glide component [0, 0, $\frac{1}{2}$].



Figure.4. Packing in unit cell.

The 3D network is stabilized by intermolecular hydrogen bonds of the type C-H···Br, with the corresponding lengths, donor acceptor 3.303(3) Å, donor hydrogen 0.951(2) Å and hydrogen acceptor 3.127(2) Å, and with corresponding angle donor hydrogen acceptor about 92.17(5)°, this hydrogen bond builds helical chiral chains (Figure 5), however, in one formal unit cell, each molecule belongs to separate chiral helical chain, giving complicate wire rack 3D network.



Figure.5. Helical chiral chain constructed by C-H…Br, (1) Oab plan (2) Oca plan.

3.7. Quantum calculations results

A comparison of molecular electrostatic potential and frontier orbital molecular calculations, was effectuated between the ligand H_2L and the complex Cu(II)L.

3.7.1. Molecular Electrostatic Potential (MEP)

The total electron density surface mapped with electrostatic potential is very comparable for both molecules H₂L and Cu(II)L as shown in Figures 6 (a) and (b), which indicates the presence of high negative charge around oxygen atoms. The corresponding mapped electrostatic potential is indicated by red color, the most negative values are about $-5,786.10^{-2}$ V and $-6.333.10^{-2}$ V for H₂L and Cu(II)L respectively. The blue region indicates the mapped electrostatic potential generated by the partially positive charge. This last is centered around hydrogen and carbon atoms, the most positive values is about $+5,786.10^{-2}$ V and $+6.333.10^{-2}$ V for H₂L and Cu(II)L respectively. The yellow regions indicate the slightly rich electron and the green regions indicate neutral. The difference of charge density between the both molecules is attribute two different values of the dipolar moment: 3.707 and 4.767 Debeye for H₂L and Cu(II)L respectively.



Figure.6. The total electron density mapped with electrostatic potential of (a) H₂L (b) Cu(II)L.

3.7.2. Orbital frontiers (FMO_S)

Figure 7 shows the calculated electron acceptor distribution in lowest unoccupied molecular orbital and the calculated electron donor distribution in highest occupied molecular orbital. Figure 7 (a) shows the HOMO and LUMO orbitals for H₂L. The SOMO and SUMO orbitals, for Cu(II)L, are presented in Figure 7 (b) α -spin and (c) β -spin. The Table 4 summarizes the HOMO/SOMO and LUMO/SUMO energies and some related physicochemical parameters characteristic of both molecules H₂L and Cu(II)L.



Figure.7. Frontiers Molecular Orbitals plot (a) of H_2L (b) of $Cu(II)L \alpha$ -spin and (c) β -spin.

	H_2L	Cu(II)L
Electronic band energies (eV)		
E _{HOMO/SOMO}	-5.86	-5.64
E _{LUMO/SUMO}	-2.44	-2.33
Energy gap (Δ)	3.42	3.31
Electrochimical parameters		
Dipolar moment (Debye)	3.707	4.767
Ionization potentiel (I)	5.86	5.64
Electron affinity (A)	2.44	2.33
Global hardness (η)	1.71	1.65
Global softness (σ)	0.58	0.61
Electronegativity (χ)	4.04	3.98
Global electrophilicity (ω)	4.77	4.80
Chemical potentiel (μ)	4.14	4.14

Table.4.	Band	energies	chemical	reactivity	/ calculated	parameters
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I=-E_{HOMO}, A=-E_{LUMO}, χ =-[1/2(E_{LUMO}+ E_{HOMO})], η =1/2(E_{LUMO}- E_{HOMO}), ω = $\chi^2/2\eta$. σ =1/ η , μ =-1/2(A+I).

The frontier orbital calculations help to predict the chemical reactivity and kinetic stability of the molecule. For example, molecules with a small frontier orbital gap are more polarizable and are generally associated with a high chemical reactivity. In this work, we studied and compared biological activity of synthesized compounds.

3.8. Electrochemical study

Electrochemical properties of the H_2L and the Cu(II)L (Figure 8) were studied by cyclic voltammetry in the potential range +1600 to -2200 mV/SCE in DMF solvent containing 10^{-1} M LiClO₄ as supporting electrolyte, using 100 mVs⁻¹ under nitrogen atmosphere. The international standard Fc/Fc+ was used as reference.

The cyclic voltammogram of the copper (II) complex exhibits two quasi-reversible processes at $E_{1/2}^1=310$ and $E_{1/2}^2=-899$ mV/SCE. The first process is assigned to the oxidation of Cu^{II}/Cu^{III} redox couple ($E_{pa}=560$ and $E_{pc}=240$ mV) [49,50] and the second is attributed to the reduction of Cu^{II}/Cu^I redox system ($E_{pa}=-833$ and $E_{pc}=-965$ mV) [43,50].

On the other hand, two oxidation peaks observed at Epa1 = +1160 and Epa2 = +1400 mV/SCE, are attributed to the oxidation of the ligand [51], the reduction peak, reported at Epc = -1740 mV/SCE, is assigned to the reduction of the azomethine group [42], the latter accelerates the transfer of electrons on the metal [52].

Moreover, the DFT calculation can explain the electrochemical behavior, since a correlation can be established between CV waves and frontier orbitals energies, the HOMO and LUMO energies of the ligand H_2L can be calculated using the oxidation and reduction

waves respectively following the empirical relations $E_{HOMO} = -[E_{oxydation}-E_{1/2(ferrocene)}+4.8]$ eV and $E_{LUMO} = -[E_{reduction}-E_{1/2(ferrocene)}+4.8]$ eV. The corresponding gap value is found $\Delta = 4.1$ eV, which is close from the theoretical value.

For the complex Cu(II)L, the anodic peak observed at 560 mV removes an electron from the β -SOMO. Otherwise, the cathodic peak at -965 mV correspond to addition of an electron in β -SUMO, indicating that the first reduction and the first oxidation take place on the Cu(II) centers, finally, the peak observed at -1740 mV corresponds to the reduction of an electron from the conjugated π system of the ligand.



Figure.8. Cyclic voltammograms of H_2L (a), Cu(II)L (b), and Fc/Fc^+ (c) in 0.1 M LiClO₄/DMF at scan rate 100 mVs⁻¹.

An increase of the anodic current I_{pa} with the increase of the scanning speed, in the range -600 to -1400 mV/SCE (Figure 9), is observed and the square root of scan rate present a linear relationship with this current ($I_{pa} = f(v^{1/2})$) (inset of Figure 9). These facts mean that these electrochemical processes are mainly diffusion controlled [53].

The large peak-to-peak separation (ΔE_p), approximately equal to 132 mV, expressing an electrochemical oxidation of Cu(I), would be due to a quasi-reversible behavior of the couple Cu(II)L + e⁻ \rightarrow Cu(I)L. The results of cyclic voltammetry measurement are grouped in Table 5.



Figure.9. Cyclic voltammograms of Cu(II)L in 0.1 M LiClO₄/DMF at various scan rate of 25, 50, 75 and 100 mVs⁻¹. The inset shows the anodic peak current.

Table.5. Cyclic voltammetric parameters of the copper complex Cu(II)L at different scan rates

- 6									_
	V(mVs ⁻¹)	-E _{pa} (mV/SCE)	-E _{pc} (mV/SCE)	$-E_{1/2}(mV/SCE)$	$\Delta E_p(mV)$	$I_{pa}(\mu A)$	$I_{pc}(\mu A)$	$I_{pa}\!/\;I_{pc}$	
	25	806	922	864	116	2.4	3.5	0.68	
	50	812	934	873	122	2.6	3.7	0.70	
	75	821	944	882	123	2.8	3.9	0.71	
	100	833	965	899	132	3.1	4.1	0.75	

3.9. Antibacterial activity

The antibacterial activity of the ligand and the copper complex, against various strains of Gram negative bacteria (*Pseudomonas aeruginosa, Klebseilla pneumoniae, Escherichia coli and Proteus mirabilis*) and of Gram positive bacteria (*Staphylococcus aureus, Methicillin resistant S. aureus (MRSA), Streptococcus pyogones and Micrococcus luteus*), was tested by the disc diffusion method in Muller Hinton Agar medium (MHA).

Gentamicin, Amoxicillin and Ciprofloxacin were used as positive control and the DMSO solvent as negative control. The results are listed in Table 6 and they are represented graphically in Figure 10. It is observed that the Cu(II)L complex shows more inhibitory activity compared to the corresponding ligand. The antibacterial effect of these compounds on Gram (+) is higher than Gram (-) bacteria. This result can be explained by the difference in the complexity of structure of the cell walls of Gram (-) and Gam (+) bacteria which play a

role in the impermeability of the cell, or by the difference in ribosomes in microbial cell [54]. Furthermore, it is shown that the activity increases with increasing concentration of the test solution of the different compounds.

The reason for the increase in the antibacterial activity of Cu(II)L complex , can be demonstrated on the basis of Overtone's concept and Tweedy's chelation theory. Within the Overtone's concept of the cell permeability, the lipid membrane that surrounds the cell wall favors the passage of only the lipid soluble materials; this means that one of the most important factor to control this activity, is the liposolubility [55,39]. On chelation, the coordination reduces the polarity of the metal ion, principally because of the partial sharing of its cation with the donor groups. Moreover, the chelation increases the delocalization of π -electrons over the whole chelate ring; this consequently increases the lipophilic character of the chelates, favoring the permeation through lipid layers of the bacterial membrane [16, 28]. This process, in turn, may block the enzymatic activity of the cell which stopped the respiration process of the microorganisms [56].

M.P. Kumar and al. [25] have observed that the tetradentate copper complexes tested against the bacteria *E. coli, P. putida, K. pneumoniae, B. subtilisand S. aureus* exhibit a significant antimicrobial activity. Similarly, S.O. Bahaffi and al. [23] have studied and reported that copper complexes show a good inhibitory action against bacteria strains: *S. aureus, S. epidermidis, E. coli, and P. aeruginosai.* However, the results obtained for our complex are similar to those described.

Diameter of inhibition zone (mm)											
Compound m	Conc.	Gram negative				Gram positive					
	mg.mL ⁻¹	Klebseilla pneumoniae	Pseudomenas aeroginosa	E. coli	Proteus mirabilis	Staphylococcus aureus	MRSA	Streptococcus pyogones	Micrococcus luteus		
H_2L	10	15	11	11	/	13	16	17	18		
	5	11	9	10	/	13	15	15	17		
Cu(II)L	10	16	16	14	11	20	17	20	20		
	5	13	12	12	11	18	15	18	17		
Gentam	nicin	20	25	22	/	16	/	26	20		
Amoxic	illin	/	/	15	/	19	/	24	13		

Table.6. Antibacterial activity of Schiff base ligand and the copper (II) complex.

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Ciprofloxacin	40	34	38	/	35	22	40	35	
DMSO	/	/	/	/	/	/	/	/	



Figure.10. Zone of inhibitions (in mm) of reported compounds (10 mg/mL) and antibiotics against Gram (+) and Gram (-) bacteria strains.

3.10. Structure activity relationship

According to the chelation theory [57], the enhancement of antibacterial activity of the complex Cu(II)L compared to the ligand H2L can be explained by many major factors a nature of the coordinated groups, chelate effect, total charge of the complex and nuclearity of the central metal ion [58]. On the other side, the biological activity is correlated to the ground state properties, the higher reactivity of the complex Cu(II)L compared to the ligand can be explained by energy gap which having 3.42 eV and 3.31 eV for H2L and Cu(II)L respectively, the decrease of gap energy for the complex increases the reactivity, this decrease is accompanied by the increase of the amount of electronic charge transfer from the ligand to the central metal ion, and this last electronic factor influence considerably the biological activity [59]. This theoretical prediction is observed toward Gram (+) and Gram (-) bacteria.

It is well known that electron-transfer is involved in various Cu-catalyzed oxidative transformations in chemistry and biology and It is essential that the redox potential for the central Cu^{+2}/Cu^{+1} couple lies around -1-0 V, i.e. in a similar range as the potentials of the biologically important redox couples $O_2/O_2^-/O_2^{2-}$, $NO^+/NO^-/NO^-$. Hoshino et al. [60] state that recycling redox reactions between Cu^{2+} and Cu^{1+} are possible at the surface of E. coli cells, generating H₂O₂ and causing damage to the cytoplasmic membrane. So, we thought that electrochemical behavior of the electroactive metal is important to study to assess the redox characteristics of the complex, but it is not easy to make a direct correlation between the biological activity and the electrochemical parameters of the complex.

According to the recycling redox reactions between Cu^{2+} and Cu^{1+} , copper has the potential to disrupt cell function and destroy the bacterial cell wall; the cytoplasm is then degraded and disappears, leading finally to cell death, so the copper reduce ability of microorganisms to develop resistance against copper complex [60]. Furthermore, the complex may exhibit new set of bioactive properties which are not displayed by the free ligand. It is hoped that, in future, copper complex could replace some antibiotic medicines used to combat pathogenic bacteria.

4. Conclusion

A tetradentate copper complex (Cu(II)L) was prepared in good yield and well characterized by different spectroscopic techniques. The four coordinated complex, through both N and O donor sets, is revealed by the single crystal X-ray diffraction. DFT calculations were applied successfully to predict the structural geometry and a good agreement is shown between the theoretical and experimental results. Two quasi reversible processes, $E_{1/2}^1=310$ and $E_{1/2}^2=-899$ mV/SCE, are observed and a correlation is established between CV waves and frontier orbitals energies. The antimicrobial studies show that the complex has better inhibitory activity against the tested bacteria compared to the uncomplexed Schiff base and the inhibitory effect is correlated with the energy gap. These results are similar to those obtained from M.P. Kumar and al. [25] for Coppe (II) complexes containing heterocyclic bases. Furthermore, the novel complex exhibits good antibacterial effect upon the studies bacteria in comparison with the standard drugs gentamicin and amoxicillin. Taking a count of these results, the Copper(II) complex could replace some antibiotic medicines used to combat

pathogenic bacteria and could be also useful, in future work, to study the antifungal, anticancer, antioxidant and DNA cleavage activities.

Supplementary data

CCDC 730120 contains the supplementary crystallographic data for Cu(II)L. These data can be obtained free of charge via http:// www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

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Figure.7. Frontiers Molecular Orbitals plot (a) H_2L (b) $Cu(II)L \alpha$ -spin and (c) $Cu(II)L \beta$ -spin.

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Highlights

- A Schiff base ligand (H₂L) and the corresponding copper complex Cu(II)L are synthetized with good yields.
- Structural features are confirmed by different spectroscopic techniques.
- Structure of copper complex Cu(II)L was revealed by single crystal X-ray diffraction; the geometry was calculated and confirmed by DFT.
- Cyclic voltammetry study of the Cu(II)L complex indicated two quasi reversible processes.
- The antimicrobial activity of the copper complex Cu(II)L shows a better activity than the ligand (H₂L).

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