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Synthesis Characterization and Biological Activities of an Enamine Derivative and Its Coordination Compounds

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Abstract

The medicinal uses and applications of metal complexes are of increasing clinical and commercial importance; this is as a result of some level of success achieved so far. In this regard, novel enamine free-base ligands were synthesized by the condensation of terephthalaldehyde and 2-(methylamino)ethanol. This afforded a dinegative *ONNO* donor enamine, free base, characterized using ^{1}H and ^{13}C NMR, Fourier-transformed infrared and UV-vis spectroscopy. Coordination compounds of the enamine were also synthesized using Cu(II), Ni(II), Co(II) and VO(IV) ions. These complexes were characterized by electronic, IR spectrophotometry, mass spectrometry, magnetic susceptibility and EDX. The compounds were thereafter evaluated for their antimicrobial and cytotoxic activities. The data obtained were supportive of an octahedral geometry for the Cu(II) complex, a square-pyramidal geometry for the vanadium complex and a 4-coordinate square-planar geometry for both the cobalt and nickel complexes. The magnetic susceptibility data revealed that the complexes are magnetically dilute and mononuclear with exception of the cobalt complex. The ligands and the complexes did not exhibit significant antimicrobial and cytotoxic assays, indicative of the nontoxicity of the ligand and complexes.

Keywords

Enamine, Nuclear Magnetic Resonance, Antimicrobial Activity, Cytotoxicity, EDX, Therapeutic Coordination Compound, Brine Shrimp Lethality Bioassay

1. Introduction

A fundamental principle in coordination chemistry is the tuning of the properties of metal ions using different ligands [1]-[7]. As a result, syntheses of different compounds with desired properties by ligand tailoring have become a fascinating research field. Of great interest, and in high demand, are new coordination compounds with therapeutic properties [8] [9] [10] [11] [12]. This may be attributed to the success achieved with some inorganic compounds such as cisplatin against cancer, trisenox for acute promyelocytic leukemia and flamazine as an antibacterial in the treatment of burn wounds [13] [14] [15] [16]. From this perspective, there has been a growing interest in the chemistry community to examine the biological activities of compounds such as enamines and their coordination compounds [17]-[29].

Enamines are species that have an amino moiety bound to a doubly bonded carbon atom (**Figure 1**). This group of compounds and their derivatives represent an important class of compounds with diverse biological activities, which include anti-convulsant, -microbial, -cancer, -inflammatory and -tumor properties [17]-[24]. Enamines have three potential sites of interaction with metal ions viz: the nucleophilic carbon, nitrogen atom and the π-system of the carbon-carbon double bond. Previous studies have however shown that enamines generally coordinate to metal ions via either the nitrogen atom or the π-system of the carbon-carbon double bond [17]-[24]. Compounds bearing the enamine moiety may be designed with strategically placed donor atoms such that chelation may be achieved. Hence, enhanced stability of the resultant coordination compound occurs [24]-[29].

It has been shown from previous reports, that coordination of metal ions to biologically active agents may not only tune the metal ion properties, but also the properties of the ligands themselves. Therefore, it may lead to altered activity of such compounds [25]-[42]. There is however, a dearth of information regarding the antimicrobial and cytotoxic activities of thesecompounds and their coordination compounds.

An important consideration for any drug synthesis is the balance between its activity and toxicity [13]. As a result of resistance and toxicity to normal cells, the clinical usage of some anti-cancer and -microbial drugs is being limited [13]. There is therefore, a growing need for obtaining potential anti-microbial and -cancer agents, more importantly, lead compounds with minimal side effects [13].

Consequently, this resulted in the synthesis of a novel enamine derivative, ligand **L**, obtained by the reaction of terephthalaldehyde and 2-(methylamino)ethanol (**Figure 1**). This was characterized by ^{1}H and ^{13}C nuclear magnetic resonance, Fourier-transformed infrared (FTIR) and UV-vis spectrometry. Coordination compounds of the enamine were also synthesized using copper(II), nickel(II), cobalt(II) and vanadium(IV) ions. These were characterized using Fourier-transformed infrared and UV-vis spectroscopy, magnetic susceptibility, mass

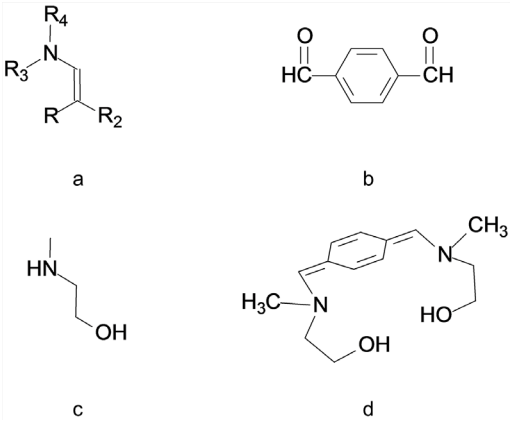

Figure 1. (a) Enamine, (b) Terephthalaldehyde, (c) 2-(methylamino)ethanol and (d) Ligand L.

spectrometry and energy-dispersion X-ray spectroscopy (EDX). The antimicrobial activity and brine shrimp lethality bioassay for these compounds were determined. The metal complexes and the ligand are new and the biological activities evaluated are being reported here for the first time.

2. Materials and Methods

All starting materials and solvents used were purchased from Aldrich and Fluka and were used without further purification. The melting points were determined on a Gallenhamp melting point apparatus and are uncorrected. The infrared spectra were recorded in the region 4000 - 400 cm^{-1} on a Nicolet 410 impact Fourier-Transform infrared spectrophotometer at North West University, Mafikeng Campus. Electronic transitions were measured on a Varian Cary 50 UV-visible spectrophotometer also at the North West University; measurements were made from 200 to 800 nm. Magnetic susceptibility measurements were carried out at room temperature in the Department of Chemistry, Kwara State University, Ilorin, using a Sherwood scientific balance with $[HgCo(SCN)_4]$ as standard. EDX analyses were obtained using Shimadzu Ray ny EDX 720 at the Department of Chemistry North West University, Mafikeng Campus. The mass spectrum was obtained at the Laboratory for Analytical Services, North West University, Potchefstroom, on a Bruker Ser# 10390 micrOTOF-Q II mass spectrometer, using atmospheric pressure and chemical ionization APCI. NMR spectra were recordedon a Bruker spectrophotometer topspin2.1PL6 model ultra shield plus at 600 MHz for ^{1}H NMR spectrum and 150 MHz for ^{13}C spectrumin DMSO-d_6 with TMS as internal standard. Screening of the compounds for antimicrobial activity was done at the Pharmaceutics Laboratory, Obafemi Awolowo University, Ile-Ife. Brine shrimp lethality assay was carried out at the Department of Biochemistry and Molecular Biology, Obafemi Awolowo University, Ile-Ife.

The complexes were synthesized *in situ* by refluxing the reaction mixture of ethanolic solution of terephthalaldehyde, the secondary amine, 2-(methylamino)ethanol

and a solution of the corresponding metal ion salt. The compounds were synthesized using adaptation of previous reports [43] [44].

2.1. Syntheses of Ligand and Coordination Compounds

2.1.1. Synthesis of Ligand L

A solution of 2-(methylamino)ethanol (1.61 mL, 0.02 M) in absolute ethanol was added to a stirring solution of terephthalaldehyde (1.34 g, 0.01 M) in 30 mL absolute ethanol. Four drops of glacial acetic acid was added to this and the resultant solution refluxed for 4 h. A yellow precipitate was obtained, which was recrystallized using ethanol-water mixture (70/30, v/v), washed, filtered and dried in a vacuum oven at 60˚C to givel **L**. 1.61 g (64%), M.p: 120˚C - 122˚C. The compound was soluble in chloroform, ethanol and methanol.

^{1}H NMR (600 MHz): DMSO-d_6 δ (ppm): 10.12 (d, 2H, OH), 8.06 (m, 4H, Ar-H), 3.34 (s, 2H, N-CH=), 2.49(t, 4H, J = 1.8 Hz, CH_2), 2.02 (s, 4H, CH_2), 1.89 (s, 6H, CH_3).^{13}C NMR (150 MHz): DMSO-d_6 δ (ppm): 193.66, 133.17 and 40.04.

2.1.2. Cu Complex

An ethanolic solution of terephthalaldehyde (1.34 g, 0.01 M) was heated whilst stirring. A solution of 2-(methylamino)ethanol (1.61 mL, 0.02 M) and a solution of copper(II) chloride (1.36 g, 0.01 M) in absolute ethanol, were added dropwise. The reaction solution was then refluxed for 4 h after the addition of 4 drops of glacial acetic acid. A pale blue precipitate was obtained, which was recrystallized using ethanol-water mixture (70/30, v/v), washed, filtered and dried in a vacuum oven at 60˚C to give a green precipitate as the Copper(II) complex of **L**. Yield: 2.17 g (69%). M.p: 298˚C - 300˚C (d), metal composition (%): anal: 21.04; cal.: 20.71. The complex was sparingly soluble in ethanol, methanol and water. A similar method was used to synthesize the coordination compounds.

2.1.3. Ni Complex

An ethanolic solution of terephthalaldehyde (1.35 g, 0.01 M) was poured into a round bottom flask and was subsequently heated and stirred. To this was added 2-(methylamino)ethanol (1.66 mL, 0.02 M) and a solution of nickel(II) chloride (1.76 g, 0.01 M) in absolute ethanol, which were added dropwise. Further addition of four drops of glacial acetic acid and catalytic amount of titanium tetrachloride (0.19 g, 0.001 M) in 5 mL of trimethylamine was made. The mixture was then refluxed for 4 hto afford a pale green precipitate, which was recrystallized using water-ethanol mixture (80/20, v/v), washed, filtered and dried in a vacuum oven at 60˚C to give Ni(II) complex. Yield: 1.60 g (52%), M.p: 290˚C - 292˚C (d); metal composition (%): anal.: 20.13; cal.: 19.86, $[M + 1]^+$. (m/z): 310. The complex was sparingly soluble in ethanol, methanol but soluble in water.

2.1.4. Co Complex

An ethanolic solution of terephthalaldehyde (1.34 g, 0.01 M) was prepared by heating in absolute ethanol. Subsequently, a solution of 2-(methylamino)ethanol (1.61 mL, 0.02 M) and a solution of cobalt(II) chloride (2.05 g, 0.015 M) in ab-

solute ethanol were added. Four drops of glacial acetic acid and catalytic amount of titanium tetrachloride (0.19 g, 0.001 M) in 5 mL of triethylamine were thereafter added. The resultant mixture was refluxed for 4 h. A pink precipitate was obtained, which was recrystallized using ethanol mixture (80/20, v/v), washed and filtered and dried in a vacuum oven at 60˚C to give the Co(II) complex. Yield: 1.88 g (61%), M.p: 132˚C - 134˚C (d), metal composition (%): anal.: 20.23; cal.: 19.58. The complex was sparingly soluble in ethanol, methanol but soluble in water.

2.1.5. VO Complex

An ethanolic solution of terephthalaldehyde (1.34 g, 0.01 M), was prepared and heated. To this solution was added a solution of 2-(methylamino)ethanol (1.61 mL, 0.02 M) and a solution of vanadyl sulphate (1.72 g, 0.01 M) in absolute ethanol. Furthermore catalytic amount of titanium tetrachloride (0.19 g, 0.001 M) in 5 mL of triethylamine and four drops of glacial acetic acidwas added. The resultant reaction mixture was subsequently refluxed for 4 h. A bluish green precipitate was obtained, which was recrystallized using ethanol-water mixture (70/30 v/v), washed, filtered and dried in a vacuum oven at 60˚C to give the vanadyl complex. Yield: 1.87 g (59%), M.p: 168˚C - 180˚C, metal composition (%): anal.: 23.52; cal.: 22.24. The complex was sparingly soluble in ethanol, methanol and water.

2.2. Antimicrobial Activity

The organisms used were five Gram-positive and three Gram-negative bacteria and two fungi. These were *Staphylococcus aureus* (ATCC 29213), *Staphylococcus epidermidis* (clinical strain), *Bacillus subtilis* 12 (NCIB 3610), *Bacillus subtilis* 82 (NCIB 6349), *Clostridium sp*. (NCIB 532), *Klebsiella pneumonia* (clinical strain), *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 25922), *Candida albicans* (ATCC 24433) and *Candida pseudotropicalis* (NCYC 6), respectively. The agents were dissolved in water at room temperature or hot water as appropriate to give a concentration of 40 mg/mL.

The resulting solutions were used to soak sterile Whatman No 2 discs (diameter of 6 mm) and allowed to dry in an oven at 50˚C). The discs were then utilized to determine antibacterial and antifungal activities as previously described by Aiyelabola *et al.* [45]. Discs that were impregnated with imipenem and chlorhexidine were used as positive controls for bacteria and fungi, respectively. Zones of inhibition were used as indices of antimicrobial actions.

2.3. Cytotoxicity Bioassay

The procedure used was modified from the assay described by Solis *et al.* [46]. Brine shrimp (*Artemia salina*) were hatched from shrimp eggs in a conical shaped vessel (1 L). Subsequently the vessel was filled with sterile, artificial seawater under continuous aeration for 48 h. After hatching, active nauplii free from eggshells were collected from brighter portion of the hatching chamber.

These were employed for the assay.

Ten nauplii were drawn through a Pasteur pipette and placed in each vial containing 4.5 mg/L of brine solution. In each experiment, different volumes of the sample chelates were added to 4.5 mL of brine solution. This produced different concentrations of 20, 40, 60, 80 and 100 μg/mL. Solutions were maintained at room temperature for 24 h under light. The surviving larvae were counted.

Experiments were conducted along with the control (vehicle treated), of the test substances in a set of three tubes per dose. Estimation of the LC_{50} values was estimated using probit® analysis on a USEPA computer program.

3. Results

3.1. Ligand

3.1.1. NMR

Evidence for the formation of an enamine was obtained from the ^{1}H NMR data of ligand **L** as evidenced by the singlet observed at δ 3.34 ppm. This is ascribed to enamine protons (-C=C**H**-N), and thus suggestive of the formation of a double bond [47] [48] [49]. This was supported by the disappearance of the signal for the aldehylic proton present in the spectrum of the terephathaldehyde, one of the starting reagents, and the proton of the tertiary amine, which was also a starting reagent.

The spectrum of compound **L** further exhibited a triplet with δ at 8.06 ppm, characteristic of aromatic protons [47] [48] [49] [50]. A triplet was observed at δ 2.49 ppm, and was ascribed to the methylene protons (-N-C$\mathbf{H_2}$-CH_2) attached to the tertiary amine. The methylene protons attached to the alcohol (-HO-C$\mathbf{H_2}$-CH_2), however, resonated as a singlet at δ 2.02 ppm. A signal at δ 1.89 ppm was assigned to the methyl protons attached to the tertiary amine (N-C$\mathbf{H_3}$) [47] [48]. Evidence that the hydroxyl substituent was not deprotonated was given by the doublet observed at δ 10.12 ppm. This multiplicity suggests the non-planarity of this molecule.

The ^{13}C NMR confirmed the formation of an enamine by the observed signal attributable to the allyllic carbon (C=**C**-N) [47] [48], which resonated at δ 139.73 ppm as a singlet. A quadriplet was observed downfield at δ 193.66 ppm, attributed to the carbon attached to the hydroxyl substituent (**C**H_2-OH) [47] [48]. This however, corroborated the non-planarity of the molecule and probable hydrogen bonding and therefore, of the splitting of this signal to produce the quadruplet [47] [48] [51]. A multiplet observed at δ 133.17 ppm was assigned to aromatic carbon. Another multiplet observed at δ 40.04 ppm was ascribed to the methylene carbon (**C**H_2-N) attached to the tertiary amine. This observed multiplicity; further confirmed the non-planarity of the molecule [47] [48] [51].

3.1.2. Fourier-Transformed Infrared Spectrum

The FTIR spectrum of **L** exhibited a weak broad band at 3699 cm^{-1} assignable to the (O-H) stretching frequency of an alcohol [47] [48] [52]. Sharp, extended

bands were observed at 3788 cm^{-1} and these suggested hydrogen bonding [47] [48] [52]. This was further corroborated by a weak and broad band at 2865 cm^{-1} and the ν(C-OH) observed at 1010 cm^{-1} [47] [48] [52].

A sharp band at 1687 cm^{-1} was attributed to the ν(C=C) + ν(C-N) [47]. Previous studies have suggested that this is indicative of the formation of a carbon-nitrogen bond [52]. A broad weak band at 1587 cm^{-1} according to Nakamoto 2009, may be ascribed to the ν(C=N) + ν(C=C), thus validating the formati, on the enamine [52]. Further attesting to this was the absence of N-H stretching frequency, present in the starting reagent [47] [48] [52]. This was supported by the presence of the bands at 1497, 1384 and 1300 cm^{-1} ascribable to the following vibrational frequencies ν(C=N) + δ(C-H), δ(C-H) + ν(C-N) and δ(C-H) + ν(C-N), respectively [47] [48] [52]. A medium band observed at 1193 cm^{-1}, typical of the ν(C-N), further confirmed the formation of the carbon-nitrogen bond and therefore supported the formation of an enamine. A band observed at 1428 cm^{-1} was assigned to the $\delta(CH_3)$ of the methyl group attached to the tertiary amine [47] [48] [52].

3.1.3. Electronic Spectrum

The spectrum of ligand **L** exhibited a band at 202, 220 and 345 nm these are attributed as $n \rightarrow \sigma^*$, $n \rightarrow \pi^*$ and $\pi^* \rightarrow \pi^*$ transitions for the major chromophores in **L**, hydroxyl, tertiary amine and sp^2 hybridized carbon. These results confirmed the expectation that the ligand was produced successfully [47] [48] [53].

3.2. Complexes of Ligand L

3.2.1. Copper(II) Complex

The infrared spectrum of the copper(II) complex provided evidence for the formation of the ligand and coordination of the copper(II) ion with the ligand. This was evidenced by the shift in some of the observed frequency bands in comparison with that of the ligand. The spectrum showed two bands at 3462 and 3367 cm^{-1} which were assignable to the (O-H) stretching frequency [47] [48] [52] [54] [55]. Thus, indicative of a bathochromic shift of about 237 cm^{-1} in comparison with that obtained for the ligand. Supporting the ν(O-H) frequency was the band at 1035 cm^{-1} and ascribed to the ν(C-OH) indicative of a hypsochromic shift in comparison with the ligand [47] [48] [52].

Both batochromic and hypsochromic shifts suggest coordination of the oxygen atom of the hydroxyl substituent to the central metal ion [47] [48] [52]. Further supporting evidence was the ν(Cu-O) observed at 688 and 628 cm^{-1} [52] [56] [57]. Additionally another band observed in the spectrum of the complex at 1597 cm^{-1} which was attributable to ν(C=N) + ν(C=C) stretching frequency further alluded to the formation of an enamine [47]. Supporting this was the ν(C=N) + δ(C-H) observed at 1440 cm^{-1}. Coordination of the metal ion with the nitrogen atom of the enamine was suggested by the ν(Cu-N) observed at 568 cm^{-1} [52] [56] [58] [59] [60].

The electronic spectrum of the Cu(II) complex exhibited two bands in the ul-

traviolet region at 234 and 309 nm. These bands correspond to shifts in the n → σ* and n → π* transitions in relation with the ligand and thus, is indicative of the coordination of the ligand with the copper(II) ion.

Conversely, the visible region elucidated a band at 634 nm and a shoulder at 506 nm typical for a tetragonally distorted octahedral configuration and may be assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_g$ transition. The magnetic moment of 2.54 BM, further corroborates an octahedral geometry [5] [6] [61] [62].

3.2.2. Nickel(II) Complex

The FTIR spectrum for the nickel(II) complex of **L** elucidated a band at 3446 cm^{-1} attributable ν(O-H) and is indicative of a bathochromic shift in relation with that obtained for the free base [47] [48] [52] [54] [55]. Supporting this was the band at 1035 cm^{-1} ascribed to the ν(C-OH) (**Table 1**) [47] [48]. Evidence for the coordination of the metal ion with the oxygen atom of the hydroxyl moiety was suggested by the ν(Ni-O) observed at 624 cm^{-1}. Two sharp bands at 1676 cm^{-1} ascribed to the ν(C=C) + ν(C-N) and 1583 cm^{-1} ν(C=N) + ν(C=C) corroborated the formation of an enamine. A band obtained at 1172 cm^{-1} was attributed to the ν(C-N), thus suggestive of the formation of carbon–nitrogen bond. Further evidence for the support of the coordination of the metal ion was given by the ν(Ni-N) at 545 cm^{-1} [52] [56] [59].

The UV spectrum for this complex displayed a band at 324 nm, indicative of a shift in the n → π* compared with the ligand and thus serves as evidence of the coordination of the ligand with the metal ion. The spectrum for the Ni(II) complex showed *d-d* bands at 525 and 714 nm, which were assigned to spin-allowed transitions of $^3A_{2g}(F) \rightarrow {}^5T_{1g}(F)$ and $^3A_{2g}(F) \rightarrow {}^5T_{1g}(P)$ suggestive of a four-coordinate square-planar geometry [63]. The magnetic moment of 0.00 BM validated a square planar geometry for the complex [33].

3.2.3. Cobalt(II) Complex

Although the infrared spectrum of the cobalt(II) complex did not exhibit a distinctive ν(O-H), weak, sharp extended bands were observed at about 3462 cm^{-1} (**Table 1**). These bands were suggestive of hydrogen bonding. Corroborating the presence of hydrogen bonding was the band observed at 1027 cm^{-1} assignable to ν(C-OH). Similar to what obtained for compounds **1** and **2**, the shifts in these vibrational frequencies in relation to the ligand suggested the involvement of the oxygen atom of the hydroxyl moiety of the ligand in coordination with the metal ion. Corroborating this was the band at 623 cm^{-1} and was ascribed to the (Co-O) stretching frequency.

Confirming the formation of the enamine was the absence of the carbonyl stretching frequency of terephthalaldehyde in conjunction with the band observed at 1575 cm^{-1} and ascribed to the (C=N) + (C=C) stretching vibrational frequencies. The band observed at 546 cm^{-1}, which was absent in the ligand, was assigned to the ν(Cu-N) may serve as further evidence for coordination of the nitrogen atom of the ligand to the metal ion.

Table 1. Relevant infrared spectra bands for the ligand and complexes (cm^{-1}).

Compound	ν(O-H)	ν(C=C) + ν(C-N)	ν(C=N) + ν(C=C)	ν(C=N) + δ(C-H)	δ(C-H) + ν(C=N	ν(C-N)	ν(C-OH)	ν(M-N)	ν(M-O)
Ligand	3699	1687	1587	1440	1384, 1300	1193	1010	-	-
Cu(II)	3462	-	1597	-	-	-	1035	688, 628	568
Ni(II)	3367	1676	1583	-	1334	1172	1040	624	545
Co(II)	3446	-	1575	-	-	-	1027	623	546
VO(IV)	3462	-	-	1432	-	-	-	664	525

The electronic spectrum of compound exhibited two bands in the UV region at 224 and 325 assignable to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions of the ligand. It also exhibited two bands in the visible region at 765 nm and 536 nm corresponding to $^4A_2(F) \rightarrow {}^4T_2(F)$ and $^4A_2(F) \rightarrow {}^4T_1(P)$, respectively [47] [48].

The effective magnetic moment for the complex was 1.96 BM. This observed magnetic moment was much lower than that expected for high spin cobalt(II) complex with d^7 configuration. This may be interpreted according to previous reports to be attributable to four-coordinate, square planar geometry for cobalt(II) with antiferromagnetism. This feature was studied previously by other workers and they suggested that the subnormality in the magnetic moments may be ascribed to antiferromagnetism which is due to the interaction between electron spins on neighbouring metal ions [64] [65] [66] [67]. It is generally accepted that the mechanism of the exchange interactions involves the mutual pairing of electron spins via orbital overlap. Antiferromagnetic exchange may be metal–metal interaction or super-exchange. Metal-metal interactions involve direct overlap of orbitals containing the unpaired electrons, which influences the magnetic behaviour whereas super exchange involves the interaction of electrons with opposite spins on the two interacting ions via an intermediate diamagnetic anion(s), which results in effective pairing leading to a minimum number of unpaired spins in the ground state of the system. Both mechanisms seem to be active, thereby leading to the observed magnetic moment [64] [65] [66].

3.2.4. Vanadyl(IV) Complex

The FTIR spectrum of the complex elucidated a band at 3462 cm^{-1} which was assignable to the ν(O-H) [52]. This indicated a bathochromic shift as coordination of the oxygen atom of the hydroxyl substituent to the central metal ion. The ν(V-O) 664 cm^{-1} further supports this. Supporting this was the ν(C=N) + δ(C-H) observed at 1432 cm^{-1} (**Table 1**). The spectrum of the complex also exhibited a new medium intensity band in the region 525 cm^{-1} which was ascribed to the (V-N), thus suggestive of the coordination of the metal ion with the nitrogen atom of the enamine. Corroborating this was the absence of the carbonyl and amine stretching frequencies. The spectrum exhibited a signal at 980 cm^{-1} attributable to the ν(V=O) [67].

The electronic spectrum of compound **4** revealed two bands in the 236 and 379 nm UV region that were ascribed to n → π* and π* → π* transitions, Table 2. The visible region of the spectrum exhibited two bands at 450, and 847 nm typical for a square pyramidal geometry and assigned to $^2B_2 \rightarrow {}^2E_1$ and $^2B_2 \rightarrow {}^2A_1$ transitions respectively. The magnetic moment obtained for the complex further supports the square pyramidal geometry.

3.3. Antimicrobial Properties

The ligand **L** and the synthesized complexes were evaluated for their antimicrobial activity against five Gram-positive bacteria, three Gram-negative bacteria and two fungi. The results obtained are presented in Table 3. The result indicated that **L** was inactive against all the tested organisms. The only compound that exhibited any form of antimicrobial activity was vanadyl(IV) complex.

Table 2. Electronic spectra bands (nm) for the ligand and complexes.

Compound	1	2 Bands	3 (nm)	d-d	μ_{eff} BM
Ligand	202	220	345	-	
Cu(II)		234	309	499, 614	2.54
Ni(II)			324	525, 880	0.00
Co(II)		224	325	765, 536	1.96
VO(IV)		236	376	450, 628 and 847	1.75

Table 3. Zone of antimicrobial inhibition (mm) for the ligand and complexes.

Microbes	L	Cu(II)	Ni(II)	Co(II)	VO(IV)	C
S. aureus	–	–	–	–	–	44
S. epidermidis	–	–	–	–	–	34
B. subtilis 12	–	–	–	–	–	34
B. subtilis 82	–	–	–	–	–	29
Clostridium	–	–	–	–	–	34
K. pneumonia	–	–	–	–	–	34
P. aeruginosa	–	–	–	–	–	39
E. coli	–	–	–	–	–	33
C. albicans	–	–	–	–	–	36
C. pseudotropicalis.	–	–	–	–	9	36

Where C = imipenem and chlorhexidine for bacteria and fungi respectively.

3.4. Cytotoxicity

Chemotherapy with cytotoxic drugs is the main treatment modality for certain types of cancer. Cytotoxicity is the quality of an agent to being toxic to cells. The brine shrimp lethality assay serves as a preliminary assay for the cytotoxicity for probable potent compounds [68] [69] [70]. Brine shrimp lethality assays of the synthesized compounds, metal ions and the ligand were conducted.

The result obtained, indicated that the ligand **L** (LC_{50} 153.139 μg/mL) was the least active of the compounds. The order of activity for the synthesized compounds is as follows cobalt(II) complex > nickel(II) complex > copper(II) complex > vanadyl(IV) with LC_{50} values of 111.486, 122.107, 132.947, 133.019 μg/mL, respectively.

The standard control substance $K_2Cr_2O_7$ (LC_{50} 5.56 μg/mL), however, exhibited significantly higher cytotoxic activity ($P < 0.05$) compared with that of the ligands and synthesized compounds. The metal salts exhibited superior activity relative to synthesized compounds. The metal salt cytotoxicity, viz: cobalt(II) chloride, vanadyl suphate, nickel(II) and copper(II) chloride, was ranked in the order of Co > VO > Ni > Cu, (LC_{50} 30.512, 39.466, 63.533, 91.208 μg/mL).

4. Discussion

In the preparation of the ligand, Cu(II) and Co(II) complexes direct combination of the reactants in absolute ethanol with catalytic amount of glacial acetic acid and refluxing gave products which were then isolated and recrystallized. However, in the case of the Co(II) complexa yield of 33% was obtained. Synthesesof Ni(II) and VO(IV) complexes via this method afforded a gelatinous precipitate. However, on further additionof catalytic amount of titanium tetrachloride, according to White and William, 1967, products were obtained which were recrystallized and dried. It is suggested therefore, that to obtain compounds Ni(II) andVO(IV) complexes in high yields, a drying agent was required. We do not have any reason for this observed variation.

Based on the results obtained, for the structural analyses of the compounds, it was therefore suggested that the reaction of terephthalaldehyde and the secondary amine; 2-(methylamino)ethanol afforded an enamine. This acted as a teradentate ligand with the use of the enamine nitrogen and the oxygen atom of the hydroxyl moiety, *N*,*N*,*O*,*O* indicating that both the nucleophilic carbon and the π-system of the carbon-carbon double bond does not participate in coordination, this is in agreement with previous reports [17]-[24]. On coordination with the cobalt ion, an octahedral complex was obtained. The result obtained for the magnetic moment, the ν(O-H) and ν(Cu-O) suggest the coordination by two molecules of ethanol in addition to the enamine free base, affording a complex of composition $[Cu(L)(et)_2]$, indicative of an octahedral geometry (**Figure 2**) [5] [6] [60] [61] [62]. For the Ni(II) and Co(II) complexes however square planar complex were obtained (**Figure 2**). On the other hand, in the case of the vanadium complex a tetragonal-pyramidal complex was suggested (**Figure 2**). Further

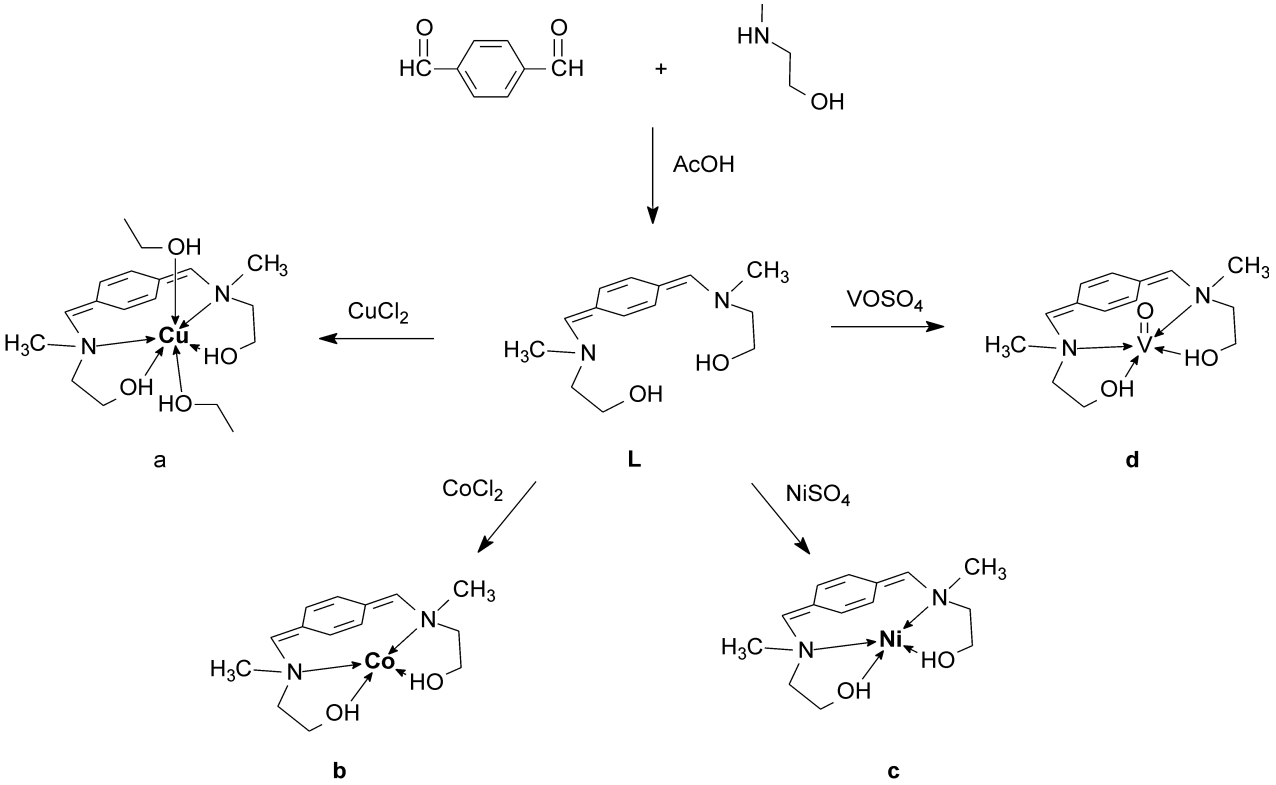

Figure 2. Schematic diagram for the syntheses of ligand **L** (a) Cu(II) (b) Co(II) (c) Ni(II) (d) VO(IV) complex.

evidence for the proposed geometry for compound **2** was obtained via APCI-MS where the relevant molecular peak at $[M + 1]^+$ (m/z): 310 was observed. This finding was supported by the results obtained from the EDX analysis. For all the complexes the percentage metal composition obtained using EDX was in good agreement with that of the proposed structures of the complexes.

Results obtained from the antimicrobial studies for the ligand and complexes, indicated activity for VO(IV) complex only. Previous reports indicated that chelation may increase the lipophilicity of the chelates, resulting in possible enhancement of penetration of the complexes through the lipid membrane of the microbes. Subsequently, the complexes interfere with the normal activities of the microbe, however in this case it was not so [71]-[77]. Chelation did not enhance the antimicrobial activity of the complexes in comparison with the ligand. The clear exception was that of the VO(IV) complex. The reason for the inactivity of the compounds is not readily evident. However, the results obtained, therefore reiterates the fact that increased lipophilicity due to chelation, is effectively a factor that enhances the inherent potential antimicrobial properties of a particular compound. As such it demonstrated the fact that both the former and latter factors are mutually exclusive [74]-[80].

The results obtained from the brine shrimp lethality bioassay of the ligand in comparison with what obtained for the synthesized complexes indicated that coordination enhanced the cytotoxic activity of the complexes relative to the ligand. This is in agreement with previous reports. The results obtained further

suggest the non-toxic nature of the ligand and hence that of the complexes as well [79] [80].

5. Conclusion

The results obtained from this study indicated the formation of an enamine from the reaction of terephthalaldehyde and 2-(methylamino)ethanol. This however coordinated with metal ions via the enamine nitrogen and the oxygen atom of the hydroxyl moiety, *N*,*N*,*O*,*O* in a tetradentate fashion. The results obtained demonstrated that increased lipophilicity due to chelation is effectively a factor that enhances the inherent potential antimicrobial properties of a compound. On the other chelation increased the cytotoxic activity of the complexes relative to the ligand.

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Author's Contributions

All the authors contributed to the conceptualization and critical revisions of the work and T.O. compiled the original draft.

Conflicts of Interest

The authors declare no conflict of interest.

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