



Syntheses, Characterization and Biological Activity of Coordination Compounds of Propanedioic Acid and its Mixed Ligand Complexes with *N,N'*-Dihydroxy-2,3-butanediimine

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The coordination compounds of propanedioic acid with cobalt(II), nickel(II) and copper(II) ions were synthesized using metal:ligand 1:2. In addition to this, mixed ligand complexes using the same metal ions with propanedioic acid as the primary ligand and *N,N'*-dihydroxy-2,3-butanediimine as the secondary ligand were also synthesized using $M:L^1:L^2$ (1:1:1) where L^1 = propanedioic acid, L^2 = *N,N'*-dihydroxy-2,3-butanediimine and M = Cu(II), Ni(II) and Cu(II). The synthesized compounds were characterized using FTIR, UV-vis, magnetic susceptibility measurement and percentage metal composition. The ligand and its metal complexes were tested for their cytotoxic and antibacterial activities. Results indicated that a dimeric square planar geometry was assumed by the cobalt(II) and nickel(II) propanedioic acid complexes. Octahedral geometry was proposed for both cobalt(II) and copper(II) mixed ligand complexes. A dinuclear square pyramidal geometry was suggested for the copper(II) propanedioic acid complex and square planar/octahedral geometry for the nickel(II) mixed ligand complex. The copper(II) propanedioic acid complex elicited the best cytotoxic activity. On the other hand, the nickel(II) propanedioic acid complex showed the remarkable antimicrobial activity. The compounds exhibited good antimicrobial activity in most of the cases with the exception of the cobalt(II) propanedioic acid complex. It was concluded that coordination of the ligands to the metal ions lowered the toxicity of the ligands. It was further concluded that the antimicrobial activity of the compounds was partly dependent on the synergism/additive effect of the intrinsic therapeutic properties of the metal ion and the ligands within the coordination sphere of the complexes synthesized. And this is also in part a function of the geometry assumed by the complexes.

Keywords: Mixed ligands, Transition metal(II) complexes, Propanedioic acid, Antimicrobial activity.

INTRODUCTION

Coordination compounds have become an emerging tool in drug discovery, being widely used as therapeutic compounds in the treatment of several human diseases such as carcinomas, lymphomas, diabetes, inflammatory and neurological disorder [1-8]. This is partly due to the high diversity of these compounds, which enables them to exhibit wide range of coordination numbers, geometries, *in vivo* accessible metal oxidation states, reduction potentials and interesting thermodynamic and kinetic characteristics [1,4]. More importantly these properties can be fine-tuned to attain desirable target compounds. Additionally, they also offer the potential for synergism or additive effect of intrinsic therapeutic properties of the metal ion and the ligands included in the coordination sphere of the metal complexes [4,8,9]. This particular property has enhanced the

attention paid to mixed ligand complexes in recent years. Resulting in their wide application in various fields of chemical activity including biological systems [4].

One of the most challenging diseases to cure and a major cause of death worldwide is cancer. In 2015, about 90.5 million people had cancer [10,11]. As of 2019, about 18 million new cases occurred annually. It caused about 8.8 million deaths (15.7% of deaths) worldwide. Deaths from cancer worldwide are projected to continue rising, with an estimated 13.1 million deaths in 2030 (about a 70% increase) [10,11]. There are many approaches to the treatment of cancer, chemotherapy has been the most effective method since the discovery of cisplatin [12, 13]. Cisplatin however has the disadvantage of being ineffective against many common types of cancers. Drug resistance is also common with side effects, which include nerve damage, hair loss and nausea [4,5]. Therefore, alternative coordination

compounds are presently being evaluated for anticancer applications, which may overcome these limitations. Earlier reports have shown that propanedioic acid is a competitive inhibitor of enzyme succinate dehydrogenase in the respiratory electron transport chain. Inhibition of any step in this process will halt the rest of the process. There are several well-known drugs that their mechanism of activity partly involves the inhibition of oxidative phosphorylation process. This therefore, indicates the potential antimicrobial activity of propanedioic acid [14,15]. Previous study [4] reported that coordination of metals to organic ligands may significantly change their biological properties such as solubility, lipophilicity, stability and charge. A consequence of this is the modifications in bio-distribution, *in vivo* transformation and pharmacokinetics. Accordingly, coordination of organic compounds to metal ions may substantially modify their bioavailability and bioactivity, leading to desirable changes in their biological behaviour [4,16-18].

Coordination compounds of *N,N'*-dihydroxy-2,3-butanediimine have been extensively studied. This include divalent metal complexes namely: $[\text{Co}(\text{Hdmg})_2]$, $[\text{Ni}(\text{Hdm})_2]$ where $\text{Hdmg} = N,N'$ -dihydroxy-2,3-butanediimine, reported by Burger *et al.* [19]. Osunlaja *et al.* [20] also synthesized mixed ligand complexes of *N,N'*-dihydroxy-2,3-butanediimine and propanedioic acid, they also evaluated the complexes for antimicrobial activity. In this case *N,N'*-dihydroxy-2,3-butanediimine was the primary ligand and propanedioic acid the secondary ligand. In addition, the syntheses of their complexes were carried out using, primary ligand to secondary ligand ratio of 2:1. Although the coordination compounds of *N,N'*-dihydroxy-2,3-butanediimine and its mixed ligand complexes with propanedioic acid have been synthesized and their antimicrobial activity studied; however $\text{M:L}^1:\text{L}^2(1:1:1)$ where $\text{L}^1 =$ propanedioic acid and $\text{L}^2 = N,N'$ -dihydroxy-2,3-butanediimine have not been studied, as well as their cytotoxic properties. As a result of therapeutic effects that may arise as a result of the coordination of these compounds (L^1 and L^2) to metal ions: which may include bioavailability enhancement and toxicity decrease of metal ions; it was considered to synthesize coordination compounds propanedioic acid (L^1 , Fig. 1) of some first row transition metal ions M:L^1 1:2. Additionally mixed-ligand complexes using propanedioic acid as primary ligand and *N,N'*-dihydroxy-2,3-butanediimine (L^2 , Fig. 2) as secondary ligand $\text{M:L}^1:\text{L}^2(1:1:1)$, for the mixed ligand complexes. The ligands and the synthesized compounds were further studied as potential cytotoxic and antimicrobial agents.

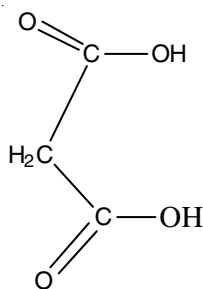


Fig. 1. Propanedioic acid (L^1)

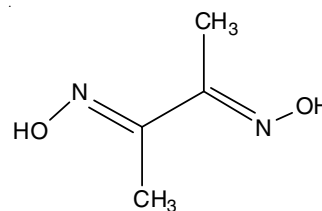
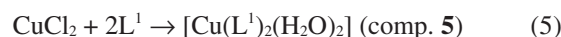
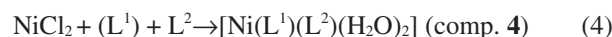
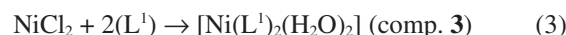
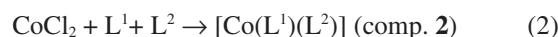
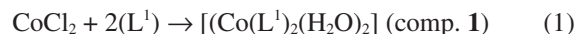


Fig. 2. *N,N'*-dihydroxy-2,3-butanediimine (L^2)

EXPERIMENTAL

All materials used are of high analytical grade. Melting points were determined in an open capillary tube on a Gallenkamp (variable heater) melting point apparatus. The infrared spectra of all the synthesized metal complexes and their ligands were obtained using Agilent Cary 630 FTIR. Magnetic susceptibility measurement of the metal complexes was obtained using a MSB Mk1 magnetic susceptibility balance, Sherwood Scientific with $[\text{HgCo}(\text{SCN})_4]$ as standard. The electronic spectra, of all the compounds, were obtained in solution, in the wavelength range 400-1000 nm using 1800 Shimadzu ultraviolet spectrophotometer. The metal analyses for all synthesized compounds were obtained using titrimetric method. The cytotoxic analysis of the compounds was carrying out using brine shrimp lethality assay. The antimicrobial activity was determined using disc diffusion method. The compounds were synthesized using an adaptation of previous method [21]. The equations of the reactions are given in eqns. 1-6:



where $\text{L}^1 =$ propanedioic acid; $\text{L}^2 = N,N'$ -dihydroxy-2,3-butanediimine.

Syntheses of compounds

Compound 1: An aqueous solution of cobalt(II) chloride hexahydrate (1.30 g, 0.01 M) was poured into a flat bottom flask and heated with stirring. To this was added, dropwise, an aqueous ethanolic solution of propanedioic acid (2.08 g, 0.02 M). The reaction mixture was heated for 2 h during, which a pink precipitate was obtained. This was filtered washed first with methanol then diethyl ether and dried in a desiccator. Similar procedure was used for the preparation of the under listed complexes. Yield: 2.07 g (69.58%), m.p.: 182-184 °C, Co (%): 18.64 (found); 19.53 (calcd.). The complex was soluble in water but sparingly soluble in ethanol and methanol.

Compound 2: Cobalt(II) chloride hexahydrate (0.65 g, 0.005 M) in a flat bottom flask to which was added propanedioic acid (0.58 g; 0.005 M) and *N,N'*-dihydroxy-2,3-butanediimine (0.52 g, 0.005 M) was heated with stirring. This gave a dark green precipitate. Yield: 1.11 g (81.08%), m.p./d.t.: 130-132 °C(d),

Co (%): 19.01 (found); 18.75 (calcd.). The complex was soluble in water but sparingly soluble in ethanol and methanol.

Compound 3: Nickel(II) chloride hexahydrate (1.24 g, 0.005 M) to which was added propanedioic acid (1.06 g; 0.01 M) and heated with stirring. This gave a light pink precipitate. Yield: 1.01 g (70.51%), m.p./d.t.: 245-246 °C(d), Ni (%): 17.02 (found); 16.61 (calcd.). The complex was soluble in water but sparingly soluble in ethanol and methanol.

Compound 4: Nickel(II) chloride (1.24 g, 0.005 M), propanedioic acid (0.52 g; 0.005 M) and *N,N'*-dihydroxy-2,3-butanediimine (0.60 g, 0.005 M) was heated and gave a pink precipitate. Yield: 0.91 g (62.35%), m.p./d.t.: 115-117 °C(d), Cu (%): 18.28 (found); 18.72 (calcd.). The complex was soluble in water but sparingly soluble in ethanol and methanol.

Compound 5: Copper(II) chloride (1.13 g, 0.005 M) to which was added propanedioic acid (1.05 g; 0.01 M) heated with stirring, gave a grey precipitate. Yield: 0.82 g (62.34%), m.p.: 201-203 °C, Cu (%): 19.81 (found); 20.78 (calcd.). The complex was soluble in water but sparingly soluble in ethanol and methanol.

Compound 6: Copper(II) chloride (1.10 g, 0.005 M), propanedioic acid (0.54 g; 0.005 M) and *N,N'*-dihydroxy-2,3-butanediimine (0.59 g, 0.005 M), gave a grey precipitate. Yield: 0.91 g (65.45%), m.p.: 193-194 °C, metal composition (%): 21.45 (found); 20.01 (calcd.). The complex was soluble in water but sparingly soluble in ethanol and methanol.

Cytotoxicity bioassay: The procedure used was modified from the assay described by Solis *et al.* [22]. 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 LC₅₀ values was estimated using probit[®] analysis on a USEPA computer program.

Antimicrobial activity: The organisms used were two Gram-positive and two Gram-negative bacteria. These were *Bacillus subtilis* 12 (NCIB 3610), *Bacillus subtilis* 82 (NCIB 6349), *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 25922), respectively. The agents were dissolved in water at room temperature to give concentrations of 10, 20 and 40 mg/mL. The resulting solutions were used to soak sterile Whatman No 2 discs (diameter = 6 mm) and allowed to dry in an oven at 50 °C. The discs were then used to determine antibacterial activities as described earlier [23]. Discs of streptomycin were used as positive controls. Zones of inhibition were used as indices of antimicrobial actions.

RESULTS AND DISCUSSION

FTIR of primary ligand L¹: The FTIR spectrum of L¹ displayed two medium bands at 3800 and 3340 cm⁻¹ (Table-1) ascribable to the -OH stretching frequency from the carboxylic acid moiety of L¹. This indicated both intermolecular and intramolecular hydrogen bonding in the molecule [24-26]. Therefore, it suggests the formation of dimers by the molecule. The spectrum further revealed two sharp bands at 1750 and 1490 cm⁻¹, which were assignable to ν(C=O) and ν(C=O) + δ(O-H), respectively. The spectrum also showed a band at 1250 cm⁻¹ and was attributed to ν(C-O) [24-26].

FTIR of secondary ligand L²: A broad band was observed at 3200 cm⁻¹ in the infrared spectrum of L², this may be attributed to the ν(O-H), observed at lower frequency than that expected as a result of intramolecular hydrogen bonding [24-26]. A sharp band at 1490 cm⁻¹ was assigned to the ν(C=N) imine portion of the oxime functionality of the molecule. Another medium band observed at 1150 cm⁻¹ was ascribed to the ν(N-O) + δ(O-H) of the oxime moiety [24-26].

FTIR of the complexes

Compound 1: The FTIR spectrum of the compound 1 exhibited a broad band at 3239 cm⁻¹, assigned to ν(O-H). This suggested intramolecular hydrogen bonding, with potential dimerization, in the molecule. Frequency bands observed at 1673, 1446, 1558 and 1360 cm⁻¹ were attributed to ν_{asy}(COO⁻) and ν_{sym}(COO⁻) [24-26]. The appearance of these bands suggested that the carboxylic acid end of ligand L¹ was deprotonated prior to coordination. Therefore, it serves as an indication that ligand L¹ coordinated to the metal ion *via* the carboxylate substituent. Corroborating this was the disappearance of the band

TABLE-1
KEY INFRARED SPECTRA BANDS (cm⁻¹) FOR THE LIGANDS AND ITS METAL(II) COMPLEXES

Band frequencies	L ¹	L ²	1	2	3	4	5	6
ν(O-H)	3800, 3340	3200	3239	3831, 3213	3242	3582	3334, 3213	3496
ν(C=O)	1750, 1490	-	-	-	-	-	-	-
ν(O-H)	-	-	-	1766	-	1774, 1772	-	1766
ν(COO) _{asy}	-	-	1673, 1446	-	1669, 1453	1423	1431	1647, 1416
ν(COO) _{sym}	-	-	1558, 1360	1524, 1364	1558, 1364	1509, 1364	1565, 1360	1569, 1353
ν(C=N)	-	1490	-	1438	-	-	-	-
ν(C-O)	1250	-	1222	-	1237	1237	1289	1220
ν(N-OH)	-	1150	-	1140	-	1095	-	1125
ν(M-O)	-	-	603, 535	550	585	551	648, 613	678
ν(M-N)	-	-	-	402	-	469	556	588

at 1750 cm^{-1} , ascribed to the $\nu(\text{C}=\text{O})$ stretching frequency, present in the free base ligand [24-26]. The observed energy difference between both asymmetric and symmetric stretching frequencies in this complex suggests the monodenticity of the carboxylate ion on coordination [24]. Further supporting the coordination of the oxygen atom of the carboxylate ion on, was the band observed at lower energy at 535 cm^{-1} which was due to the $\nu(\text{Co}-\text{O})$ stretching frequency [24].

Compound 2: The FTIR spectrum of this complex showed two broad bands at 3831 and 3213 cm^{-1} (Table-1) which were assigned to the (O-H) stretching frequency [24-26]. This suggested intermolecular hydrogen bonding, with probable dimerization. Bands observed at 1524 and 1364 cm^{-1} were attributed to $\nu_{\text{asy}}(\text{COO}^-)$ and $\nu_{\text{sym}}(\text{COO}^-)$, these also suggested coordination of ligand L^1 to the metal ion [24-26]. The $\nu(\text{Co}-\text{O})$ stretching frequency observed at 550 cm^{-1} supported this as well [24]. Evidence of the coordination of ligand L^2 to the metal ion and the formation of a mixed ligand complex, was given by the band frequency observed at 1438 cm^{-1} ascribable to the $\nu(\text{C}=\text{N})$ stretching frequency. The $\nu(\text{Co}-\text{N})$ stretching frequency observed at 402 cm^{-1} further supported this [24]. It should be noted that the $\nu(\text{M}-\text{N})$ was not present in the free ligand L^2 . Further attesting to coordination of L^2 to the central metal ion and as such the formation of a mixed ligand complex, was the band observed at 1766 cm^{-1} and assigned to $\delta(\text{O}-\text{H})$. Previously similar bands had been ascribed to the hydroxyl stretching frequency of ligand L^2 as a result of hydrogen bonding, however more recent studies, have shown that this is as a result of $\delta(\text{O}-\text{H})$ [24]. As a consequence, this suggests that the hydroxyl moiety of L^2 was not deprotonated and the probability of its not coordinated to the central metal ion. This is in agreement with previous reports [24,27].

Compound 3: The spectrum of compound 3 exhibited a band at 3242 cm^{-1} indicative of $\nu(\text{O}-\text{H})$, with H-bonding. Coordination of ligand L^1 as a carboxylate ion was suggested by the bands observed at 1669, 1453 cm^{-1} and 1558, 1364 cm^{-1} . These were assigned to the $\nu_{\text{asy}}(\text{COO}^-)$ and $\nu_{\text{sym}}(\text{COO}^-)$ respectively [24-26]. The difference in the energy between both bands suggested the monodentate nature of the coordination of the carboxylate substituent to the central metal ion [24]. Corroborating this further was the $\nu(\text{Ni}-\text{O})$ observed at 585 cm^{-1} [24].

Compound 4: The spectrum of compound 4 showed a band at 3582 cm^{-1} , suggestive of $\nu(\text{H}-\text{O})$ of the oxime moiety of ligand L^2 , observed at higher frequency as a result of hydrogen bonding [24-26]. Another evidence for the coordination of ligand L^2 to the central metal ion was given by the bands observed at 1774 and 1772 cm^{-1} , ascribable to $\delta(\text{O}-\text{H})$ [24-26]. Corroborating the coordination of ligand L^2 to the metal ion was also given by the $\nu(\text{C}=\text{N}) + \delta(\text{C}-\text{H})$ observed at 1423 cm^{-1} . Evidence for the coordination of ligand L^1 and as such formation of a mixed ligand complex was given by the bands at 1509 and 1364 cm^{-1} , attributable to $\nu_{\text{sym}}(\text{COO}^-)$ of the carboxylate substituent of ligand L^1 . Further supporting this are the $\nu(\text{C}-\text{O})$ and $\nu(\text{Ni}-\text{O})$ bands at 1237 and 551 cm^{-1} , respectively. Further support for the formation of a mixed ligand complex was also given by the bands observed at 1095 and 469 cm^{-1} . Both which were ascribed to the $\nu(\text{N}-\text{O})$ and $\nu(\text{Ni}-\text{N})$, respectively [24].

Compound 5: Two bands shaped as troughs were observed at the high energy end of the infrared spectrum of compound 5 at 3334 and 3213 cm^{-1} . These were attributed to $\nu(\text{O}-\text{H})$, suggestive of hydrogen bonding with plausible dimerization [24-26]. The deprotonation, formation and coordination of a carboxylate ion by ligand L^1 was suggested by the bands observed at 1431 and 1565, 1360 cm^{-1} , attributed to $\nu_{\text{asy}}(\text{COO}^-)$ and $\nu_{\text{sym}}(\text{COO}^-)$ [24-26]. The $\nu(\text{C}-\text{O})$ was observed at 1289 cm^{-1} . Bands observed at 648, 613 and 556 cm^{-1} , ascribable to $\nu(\text{Cu}-\text{O})$, suggest a tetragonally distorted octahedral geometry, with unequal axial bond lengths [24]. Therefore, we suggest that copper(II) ion coordinated with two molecules of L^1 , both occupying equatorial positions. In addition to this, it also coordinated to other oxygen atoms, in the axial position, to attain an octahedral geometry.

Compound 6: The spectrum of compound 6 indicated a broad band at 3496 cm^{-1} . Ascribable to $\nu(\text{O}-\text{H})$ of the NOH of ligand L^2 . This serves as evidence of the coordination of ligand L^2 to the copper(II) central metal ion. In support of this was the $\delta(\text{O}-\text{H})$ at 1766 cm^{-1} [24-26]. Additional support of coordination of L^2 was the bands at 1125 and 588 cm^{-1} attributable to $\nu(\text{N}-\text{O})$ and $\nu(\text{Cu}-\text{N})$ [24]. This suggested that L^2 coordinated using the nitrogen atom of the oxime. Bands observed at 1647, 1416 and 1569, 1353 cm^{-1} , suggests the carboxylate nature of L^1 and its monodenticity on coordination. Supporting this further were bands observed at 1220 and 678 cm^{-1} , corresponding to $\nu(\text{C}-\text{O})$ and $\nu(\text{Cu}-\text{O})$ [24-26]. Suggestive of the coordination of L^1 to the copper(II) ion, central metal ion. This also serves as evidence to validate the formation of a mixed ligand complex. With the more stable being one with the solvent molecules coordinating in the axial region, with distortion at the equatorial region as a consequence of mixed ligand formation.

Electronic spectra: The electronic spectra of the ligands exhibited bands in the ultraviolet region of the electromagnetic spectrum as a result of the major chromophores which exists on the ligands (Table-2). The spectrum of ligand L^1 elicited two intense bands at 220 and 342 nm and was assigned to $n \rightarrow \sigma^*$ and $\pi \rightarrow \pi^*$ transitions [25,26]. The spectrum of L^2 elicited two intense bands at 167, 366 nm, which corresponds to $n \rightarrow \sigma^*$ and $\pi \rightarrow \pi^*$ transitions [25,26]. Evidence of coordination of the metal ion with the corresponding ligands was provided by the $d-d$ transitions of the metal ion observed in the complexes, which were absent in the ligands. Further corroborating coordination of the ligands to the metal ions were shifts in the bands observed in the ultraviolet spectra of the coordination compounds in relation to that obtained for the free ligands.

Synthesized complexes

Compound 1: The spectrum for this compound showed three intense bands at 240, 310 and 350 nm and were assigned to $n \rightarrow \sigma^*$, $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ intra-ligand transitions [25,26]. It also exhibited two broad bands at 511 and 799 nm which were assigned to ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{A}_{2g}(\text{F})$ and ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{1g}(\text{P})$ transitions, respectively, this suggests a four coordinate square planar geometry [28,29]. A magnetic moment of 3.70 BM was obtained for compound 1, indicative of a dimeric square planar geometry [30-32].

TABLE-2
RELEVANT ELECTRONIC SPECTRA BANDS (nm),
FOR THE LIGANDS AND COMPLEXES (nm)

Compound	Intra-ligand bands	<i>d-d</i> Transition bands
L ¹	220, 342	–
L ²	167, 366	–
1	240, 310, 350	511, 799
2	215, 459	676, 760, 893
3	205, 396	542, 660, 717
4	220, 388	545, 657, 790
5	376	427 shld, 729
6	234	488, 652

Compound 2: The electronic spectrum of compound **2** exhibited five bands. Two intense bands were observed at 215 and 459 nm and were ascribed to $n \rightarrow \sigma^*$ and $\pi \rightarrow \pi^*$ intra-ligand transitions [25,26]. It also showed three broad frequency bands at 676, 760 and 893 nm attributable to ${}^4A_2(F) \rightarrow {}^4T_2(F)$ and ${}^4A_2(F) \rightarrow {}^4T_1(F)$ and ${}^4A_2(F) \rightarrow {}^4T_1(P)$ transitions, respectively [28, 29]. This is suggestive of an octahedral geometry for cobalt(II) ion. The magnetic moment of compound **2** is 5.34 BM, which is consistent with an octahedral geometry [29].

Compound 3: The spectrum of this compound showed five bands. Two intense bands were observed in the ultraviolet region of the spectrum at 205 and 396 nm. These were assigned to $n \rightarrow \sigma^*$ and $\pi \rightarrow \pi^*$ intra-ligand transitions [25,26]. Three broad bands were observed in the visible region of the spectrum at 542, 660 and 717 nm. These were attributed to ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$, ${}^3A_{2g}(F) \rightarrow {}^1T_g(F)$ and ${}^3A_{2g}(F) \rightarrow {}^1E_g$ transitions, respectively were consistent with a six-coordinated octahedral geometry [28,29]. The compound gave a magnetic moment 0.41, suggest a square planar geometry. Nickel(II) complexes are known to exhibit complicated equilibrium between coordination numbers six (octahedral) and four (square planar/tetrahedral). The results obtained may be interpreted as compound **3** having a square planar geometry in the solid state with possible inter-conversion of stereochemistries in solution [29].

Compound 4: The electronic spectrum of this compound exhibited two sets of bands: a strong band at 220 nm; one weak band at 338 nm, three broad bands at 545, 657 and 790 nm. The strong band in the ultraviolet region was ascribed to the $n \rightarrow \sigma^*$ and $\pi \rightarrow \pi^*$ transition of the ligand [25,26]. This therefore indicated a shift in this transition in comparison with the free ligand, L¹. On the other hand, the other three bands were attributed to the ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$, ${}^3A_{2g}(F) \rightarrow {}^1T_g(F)$ and ${}^3A_{2g}(F) \rightarrow {}^1E_g$ transitions respectively, characteristic of d^8 nickel(II) configuration, suggestive of an octahedral geometry [28,29]. This is in agreement with previous studies. A magnetic moment of 1.2 BM was observed for compound **4** lower than the spin only value of 2.83 B.M. This may be interpreted as an indication of a low-spin-high-spin equilibrium mixture [29].

Compound 5: The spectrum of this compound displayed three bands. An intense band was observed at 376 nm. This was ascribed to $\pi \rightarrow \pi^*$ intra-ligand transition of the ligands [25,26]. A shoulder and a broad band were observed in the visible region of the spectrum at 427 sh and 729 nm. These were assigned to ${}^2B_{1g} \rightarrow {}^2A_{1g}$ and ${}^2B_{1g} \rightarrow {}^2E_g$ transitions typical for a tetragonally distorted octahedral configuration [28,29].

However, its magnetic moment of 1.95 BM suggested a dinuclear square pyramidal complex [28,29,33]. This was supported by the results obtained from the infrared spectrum, with plausible three different environments for the Cu-O bond [24].

Compound 6: Similar to its counterpart compound **5**, three absorption frequency bands were observed. A high intensity band at 234 nm was assigned to $n \rightarrow \sigma^*$ [25,26]. In the visible region of the spectrum, two weak but broad bands were observed at 488 and 652 nm, attributed to ${}^2B_{1g} \rightarrow {}^2A_{1g}$ and ${}^2B_{1g} \rightarrow {}^2E_g$ transitions [28,29]. Its magnetic moment of 2.40 BM is consistent with an octahedral geometry and is in agreement with previous report [28,29,34,35].

Based on the results, it is suggested that ligand L¹ coordinated in a bidentate fashion *via* both carboxyate ions. Indicating that deprotonation of the carboxylic acid end of ligand L¹ occurred before coordination. This was suggested from the bands observed in their FTIR spectra. The FTIR spectrum of ligand L¹ exhibited $\nu(O-H)$ and $\nu(C=O)$, although it did not show $\nu_{asy}(COO)$ and $\nu_{sym}(COO)$. On the other hand, the spectra of the complexes exhibited $\nu_{asy}(COO)$ and $\nu_{sym}(COO)$, therefore this points to the deprotonation of the carboxylate group [24-26,36]. The result also suggested the monodentate nature of the carboxylate ion on coordination, for all the complexes. Therefore, the presence of the $\nu(O-H)$ in compounds **1**, **3** and **5** suggests the coordination of solvent molecule in addition to L¹. The results further suggested that the secondary ligand, L¹ coordinated in a bidentate fashion using both nitrogen atoms of the oxime moiety of the ligand for coordination. A dimeric square planar geometry is proposed for compound **1** [30-32]. The results obtained further indicated coordination of water molecules from the reaction medium, for compounds **2** and **6**. This in conjunction with the result obtained from the UV-vis spectra of the compounds, suggested that compounds **2** and **6** exhibited octahedral geometry (Fig. 3) [24,29,34,35]. This fact was further supported by the magnetic moment values and percentage metal analysis data. A square planar geometry is proposed for compound **3**, in solid state (Fig. 4) [29]. For compound **4**, an equilibrium of square planar and octahedral geometry is proposed. It has been suggested by previous reports that the oxygen atoms of the carbonyl groups which are not coordinated to the central metal ion are weakly bound to the metal ion of the neighbouring complex [54,29,35]. In case compound **5**, it is suggested that such carbonyl atoms are weakly bound to the metal of the neighbouring complex to give a dinuclear square pyramidal complex, compound **5** (Fig. 5).

Cytotoxicity activity: Brine shrimp lethality assay of the synthesized compounds and ligands was carried out. The result obtained indicated that both ligands exhibited similar cytotoxic ability towards brine shrimps with (LC₅₀ 14.46 and 14.42 $\mu\text{g}/\text{mL}$). The order of activity of the compounds is as follows: compound **5** > **4** > **1** > **3** > **6** > **2** with (LC₅₀ 18.124, 18.799, 22.8, 24.895, 25.864, 26.786 $\mu\text{g}/\text{mL}$), respectively. In general, the complexes showed lower activity when compared to the standard K₂Cr₂O₇ (LC₅₀ 5.56 FTIR of g/mL). The results indicated that the most active compound was **5** while compound **2** with the least activity. This suggests the effect of geometry assumed by a coordination compound on their activity. The

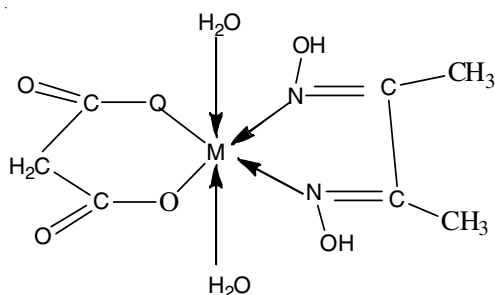


Fig 3. Proposed structural representation for compounds 2 and 6

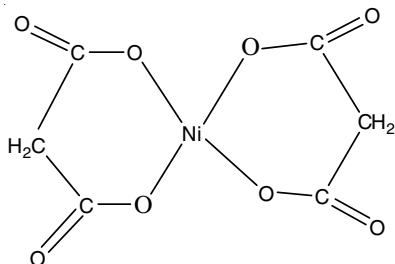


Fig. 4. Proposed structural representation for compound 3

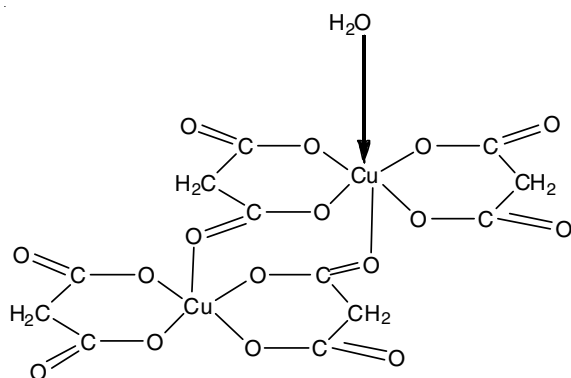


Fig 5. Proposed structural representation for compound 5

ternary complexes with L^1 generally had better activity in comparison with their mixed ligand counterpart with the exception of compound 4. The metal chloride salts gave an order of activity; cobalt(II) > nickel(II) > copper(II) with LC_{50} values of 111.486, 122.107 and 132.947 $\mu\text{g}/\text{mL}$, respectively. In this case the results obtained points to the fact that chelation of the ligands reduced the toxicity of the ligands [4,36,37]. This suggests the additive effect of intrinsic therapeutic properties of the metal ions to reduce the toxicity of the ligands [4,36,37]. As such the result validates the hypothesis of the reduction of toxicity of organic compounds as a consequence of chelation [4,36,37]. Additionally, as a result of the varied activity of the individual compound, it also attests to the ability of the biological properties of coordination compounds to be tuned by the variation the metal ion used [4,16-18,21].

Antimicrobial activity: The antimicrobial studies of the synthesized compounds and ligands were carried out against two Gram-positive and two Gram-negative bacteria namely: *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa*. The activity was assessed by monitoring the presence or absence of inhibition zones and zone

diameters. Streptomycin at 1 mg/mL concentration served as the positive control. For the synthesized compounds 1-6 and the two ligands concentrations of 40, 20 and 10 mg/mL was employed. Results from the antimicrobial disc diffusion assays are shown in Table-3. The result obtained indicated that at 10 mg/mL concentration only compound 3 exhibited comparable activity to the standard against *Pseudomonas aeruginosa*. Ligand L^2 and compound 1 were both devoid of any antibacterial activity at all concentrations employed. L^1 on the hand was endowed with appreciable antibacterial activity. At 10 mg/mL compound 3 exhibited moderate significant activity ($p < 0.05$) against all tested microbes. In fact, it showed similar activity to the standard against *Pseudomonas aeruginosa* at

TABLE-3
RESULT OF ZONE OF ANTIMICROBIAL INHIBITION
(mm) FOR THE LIGANDS AND COMPLEXES

Sample number/ organisms	Zones of inhibition (mm) against concentration (mg/mL)			Streptomycin (mg/mL)
	40	20	10	
Compound 1				
<i>Escherichia coli</i>	-	-	-	20
<i>Staphylococcus aureus</i>	-	-	-	25
<i>Pseudomonas aeruginosa</i>	-	-	-	22
<i>Bacillus subtilis</i>	-	-	-	35
Compound 2				
<i>Escherichia coli</i>	-	-	-	15
<i>Staphylococcus aureus</i>	22	15	-	25
<i>Pseudomonas aeruginosa</i>	-	-	-	22
<i>Bacillus subtilis</i>	25	20	15	35
Compound 3				
<i>Escherichia coli</i>	22	18	16	20
<i>Staphylococcus aureus</i>	25	22	18	25
<i>Pseudomonas aeruginosa</i>	25	20	20	20
<i>Bacillus subtilis</i>	30	25	22	40
Compound 4				
<i>Escherichia coli</i>	18	15	-	17
<i>Staphylococcus aureus</i>	20	15	-	25
<i>Pseudomonas aeruginosa</i>	20	15	12	22
<i>Bacillus subtilis</i>	22	20	17	32
Compound 5				
<i>Escherichia coli</i>	-	-	-	17
<i>Staphylococcus aureus</i>	-	-	-	20
<i>Pseudomonas aeruginosa</i>	-	-	-	22
<i>Bacillus subtilis</i>	12	-	-	40
Compound 6				
<i>Escherichia coli</i>	20	16	12	18
<i>Staphylococcus aureus</i>	20	16	11	20
<i>Pseudomonas aeruginosa</i>	10	10	7	30
<i>Bacillus subtilis</i>	12	12	11	30
L^2				
<i>Escherichia coli</i>	-	-	-	16
<i>Staphylococcus aureus</i>	-	-	-	25
<i>Pseudomonas aeruginosa</i>	-	-	-	20
<i>Bacillus subtilis</i>	-	-	-	35
L^1				
<i>Escherichia coli</i>	16	12	-	16
<i>Staphylococcus aureus</i>	16	12	-	22
<i>Pseudomonas aeruginosa</i>	15	12	10	20
<i>Bacillus subtilis</i>	20	16	11	35

this concentration. At 40 mg/mL concentration compound **5** exhibited moderate activity against *Bacillus subtilis* alone. Compound **3** elicited better activity than streptomycin, the standard, against both Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) at 40 mg/mL. Similarly, compounds **4** and **6** elicited significantly better activity ($p < 0.05$) than the standard against *Escherichia coli* at this concentration as well. Also at 40 mg/mL equable activity to the standard was exhibited by compounds **3** and **6** against *Staphylococcus aureus*.

Traditionally compounds with good or comparable activity with the standard at 40 mg/mL are considered to be active with potential antimicrobial activity. All the compounds exhibited good to moderate activity with the exception of compound **5**. Generally, the active compounds exhibited better activity with the Gram-negative bacteria. This observed activity of this compound is in accord with previously reported sensitivity of *Escherichia coli* and *Pseudomonas aeruginosa* to coordination compounds [38,39]. Additionally, the compounds also exhibited good activity against the gram positive bacteria in most cases. The activity of the compounds towards both Gram-positive and Gram-negative bacteria indicated their broad spectrum of activity [40-42]. As a consequence, this suggest their potential as good antimicrobial agents. Comparison of sensitivity of the tested microbes to the ligands with that of the synthesized compounds corroborated the hypothesis that chelation may substantially modify their bioavailability and bioactivity, leading to desirable changes in their biological behaviour [43-45]. The results further indicated the synergetic or additive effect of the intrinsic therapeutic properties of the metal ion and ligands upon chelation. Evidently, this is also partly dependent on the geometry assumed by the complexes.

Conclusion

It was demonstrated that coordination compounds of propanedioic acid and its mixed ligand complexes with *N,N'*-dihydroxy-2,3-butanediimine, yielded complexes with different spatial structure and compositions. It was concluded that coordination of metal(II) ion with ligands may induce an additive effect on the biological activity of coordination compounds in comparison with the ligand. As such coordination may act as a tool to fine-tune complexes to attain desirable biological activity.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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