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Synthesis, characterization and antimicrobial activities of some metal(II) amino acids' complexes

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ABSTRACT

Metal(II) coordination compounds of glycine and phenylalanine were synthesized and characterized using infrared and electronic spectroscopic, and magnetic susceptibility measurements. The complexes were tested for antimicrobial activity against *Bacillus subtilis, Staphylococcus aureus,* Methicillin Resistant *Staphylococcus aureus* (MRSA), *Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris* and *Candida albicans*. The stoichiometric reaction between the metal (II) ions and ligands in molar ratio M:L (1:3) [where M = Mn, Co, Ni, Cu and Cd; L= glycine; phenylalanine] resulted in the formation of five-coordinate square pyramidal dinuclear geometry for both copper complexes and six-coordinate octahedral geometry for the other complexes. The spectroscopic and magnetic moment data suggested that the ligands coordinated via both their amino and carboxylate ion moieties. The complexes demonstrated better activities against one or more of the tested microbes than acriflavine, the standard drug used.

Keywords: Glycine; Phenylalanine; Coordination Compound; Antimicrobial; Chelation

1. INTRODUCTION

Antimicrobial resistance is fast becoming a global concern with rapid increase in multidrug-resistant bacteria and fungi [1,2]. This has mandated continued search for new antimicrobial compounds, including coordination complexes of biologically important molecules [3-5]. The increased lipophilic character of these coordinated compounds, with the resultant enhanced ability to permeate the cell membrane of the microbes, have been suggested as reasons for their improved activity over their parent ligands [6,7]. Chelation, which has been reported to reduce the polarity of the metal ion by partial sharing of its positive charge with the donor group of ligands, also supports this theory [8,9]. Promising antimicrobial activities of some amino acids chelates have been reported, including those of histidine [1,10], arginine and glutamic acid [11]. However, there is dearth of information on coordination compounds of phenylalanine. Coordination compounds of glycine (L_1) and phenylalanine (L_2) metal-ligand ratio 1:2 have been reported with marginal antimicrobial activities [12]. It was therefore suggested, based on the chelate theory [6,9], that increasing the number of chelate rings may improve the antimicrobial activities of these complexes. Hence the objective of this work was to synthesize, characterize and determine the antimicrobial activities of coordination compounds of L_1 and L_2 with metal-ligand ratio 1:3. This was with a view of identifying lead metal(II) compounds for further studies in drug development against multidrug resistant bacteria and fungi.

2. MATERIALS AND METHODS

2.1. General

All reagents and solvents used were of analytical grade. Melting points (M.P) or temperature of decomposition (d) were measured using open capillary tubes on a Gallenkamp (variable heater) melting point apparatus. The UV-Vis spectra were obtained using a Genesis 10 UV-Vis spectrophotometer, solid reflectance. The magnetic susceptibility measurement for some of the complexes was obtained at room temperature using a MSB- AUTO (Sherwood scientific) Gouy balance. The infrared spectra (KBr) were recorded on a Genesis II FT-IR spectrophotometer.

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2.2. Synthesis of Complexes

The coordination compounds were prepared according to a modification of previously reported method [13] by the addition of 0.01 M of appropriate metal salt (1.62, 2.17, 2.43, 2.51 and 2.69 g for copper, cadmium, nickel, cobalt and manganese, respectively) to a solution of the ligand L_1 0.03 M (2.29 g) and L_2 0.03 M (5.12 g) dissolved with stirring in distilled water with the addition of 0.005 M Na_2SO_4 (0.71 g). The mixture was then heated on a water bath for 2 h. An immediate precipitation was obtained for majority of the complexes, while some required further concentration and cooling. The products obtained were filtered, washed with methanol and dried *in vacuo* at 60˚C.

2.3. Antimicrobial Activity Using Disc Diffusion Assay

The antimicrobial properties of the complexes were obtained using an adaptation of the filter disc diffusion method [14]. The strains used were *Escherichia coli* NCTC 8196, *Pseudomonas aeruginosa* ATCC 19429, *Staphylococcus aureus* NCTC 6571, *Proteus vulgaris* NCIB, *Bacillus subtilis* NCIB 3610 and Methicillin resistant *S. aureus* (MRSA) clinical isolate for bacteria, and *Candida albicans* NCYC 6 for fungi while acriflavine was the standard drug.

3. RESULTS AND DISCUSSION

3.1. Physico-Chemical Properties

The colors, percentage yields and melting points (M.P) or temperature of decomposition (d) of the coordination compounds are presented in **Table 1**. The complexes showed a wide range of colors that were in agreement with those obtained for similar coordination compounds.

Some of the compounds decomposed before melting. All the complexes were sparingly soluble in general organic solvents and therefore efforts at growing their single crystals for X-ray structural studies were unsuccessful.

Table1. Some physical properties of the compounds.

Compound	% Yield	Colour	M.P./d. (˚C)
$Na[Co(L_1)_3]$	61.60	Pink	231 - 232
$[Cu(L_1)_2]_2$	67.40	Blue	191 - 193
$Na[Mn(L_1)_3]$	74.40	White	244 - 247
$Na[Ni(L_1)_3]$	60.20	Green	226(d)
$Na[Cd(L_1)_3]$	59.70	White	198(d)
$Na[Co(L_2)_3]$	84.30	Pink	223(dt)
$[Cu(L_2)_2]_2$	40.20	Lilac	198(d)
$Na[Mn(L_2)_3]$	69.60	White	229(d)
$Na[Ni(L_2)_3]$	72.80	Pale green	182(d)
$Na[Cd(L_2)_3]$	62.40	White	217(d)

Keys: L_1: glycine; L_2: *dl*-phenylalanine; M.P.: Melting point; d.: temperature of decomposition.

3.2. Electronic Spectra and Magnetic Moment

The absorption bands of the ligands (**Table 2**) corresponded to the $n \rightarrow \sigma^*$, $n \rightarrow \pi^*$ and $\pi^* \rightarrow \pi^*$ transitions of $-NH_2$ and $-COO^-$, the major chromophores, and $-C_6H_5$. Shifts in these bands and the observed *d-d* transitions of the compounds, as presented in **Table 2**, indicated coordination.

3.2.1. Glycinato Complexes

The visible spectrum for this Cu(II) complex displayed bands at 620 and 632 nm assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_{1g}$ transitions, ascribed to a square pyramidal geometry [15]. Its magnetic moment value of 1.53 B. M, indicative of an antiferromagnetic spin-spin interaction through molecular association with possible Cu-Cu interaction or dimerization, further confirmed this geometry [8,15,16]. Hence, these facts allowed the proposal of a dinuclear square pyramidal geometry for the complex. The spectrum for the Cd(II) complex exhibited bands at 772 and 829 nm, indicative of charge transfer transition (M→L) which is expected of Cd(II) with filled 4*d* orbital in the ground state [16]. An octahedral geometry is however proposed for the Cd(II) complexes [16]. Nickel(II) complexes are known to exhibit complicated equilibrium between coordination numbers six (octahedral) and four (square planar/tetrahedral) [17]. The absorption bands at 505, 523 and 544 nm (**Table 2**) were consistent with a six-coordinate octahedral geometry and were assigned to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$, $^3A_{2g}(F) \rightarrow {}^1T_g(F)$ and $^3A_{2g}(F) \rightarrow {}^1E_g$ transitions, respectively [16]. Its magnetic moment of 1.28 B.M was lower than the spin only value of 2.83 B.M and suggested interconversion of stereochemistries or dimerization [18,19]. The Co(II) complex gave two well resolved absorption bands at 520 and 667 nm, which were assigned to $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transitions, respectively consistent with a six coordinate octahedral

Table 2. Uv-Vis spectra bands (nm) of the compounds.

Compound	Band I	Band II	Band III	Band IV	*d-d*
L_1	199	211	244	-	-
L_2	-	217	232	268	-
$[Cu(L_1)_2]_2$	-	262	-	-	620, 632
$Na[Cd(L_1)_3]$	226	265	-	-	772, 829
$Na[Ni(L_1)_3]$	223	259	-	-	505, 523, 544
$Na[Co(L_1)_3]$	220	226	256	-	520, 667
$Na[Mn(L_1)_3]$	-	226	-	-	496, 526, 541
$[Cu(L_2)_2]_2$	196	226	247	265	499sh, 538
$Na[Cd(L_2)_3]$	205	-	238	265	-
$Na[Ni(L_2)_3]$	196	211	238	262	481sh, 496, 526
$Na[Co(L_2)_3]$	196	220	235	262	499, 526
$Na[Mn(L_2)_3]$	199	217	238	265	433,496, 523, 538

Keys: sh: shoulder; L_1: glycine; L_2: *dl*-phenylalanine.

geometry. Its magnetic moment of 5.20 B.M indicated a high spin d^7 system with three unpaired electrons, which corroborates the proposed octahedral geometry [16,20,21]. The Mn(II) complex exhibited low energy bands at 496, 526 and 541 nm that were consistent with a six coordinate octahedral geometry [16] and were assigned ${}^6A_{1g}\rightarrow{}^4E_g$, ${}^6A_{1g}\rightarrow{}^4T_{2g}(G)$ and ${}^6A_{1g}\rightarrow{}^4T_{1g}(G)$ transitions, respectively. These transitions are a consequence of forbidden transitions to excited states of spin multiplicity other than six [22,23].

3.2.2. Phenylalanito Complexes

For a perfect octahedral complex, transition spectrum for a Cu(II), d^9 complex is expected to show only a single band. However, the Cu(II) ion in an octahedral environment is subject to Jahn Teller distortion which lowers the symmetry of the molecule and reduces the degeneracy of the e_g orbitals [22,24]. The *d-d* transitions of the Cu(II) complex at 499sh and 538 nm (**Table 2**) were assigned to ${}^2B_{1g} \rightarrow {}^2A_{1g}$ and ${}^2B_{1g} \rightarrow {}^2E_{1g}$ transitions, respectively. Its magnetic moment value of 1.73 B. M suggested a dinuclear square pyramidal complex [16]. However, no distinct *d-d* transition band was observed with the cadmium-phenyalanito complex [22]. Bands at 496, 481sh and 526 nm, assignable 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, observed with the Ni(II) complex, suggested a distorted octahedral geometry. The Co(II) complex showed *d-d* transition bands at 499 and 526 nm and were assigned to ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ and ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ transitions, respectively typical of an octahedral geometry [24]. Weak transition bands were observed for the manganese complex at 433, 496, 523 and 538 nm and attributed to ${}^6A_{1g}\rightarrow{}^4A_{1g}(G)$, ${}^6A_{1g}\rightarrow{}^4E_g(G)$, ${}^6A_{1g}\rightarrow{}^4T_{2g}(G)$ and ${}^6A_{1g}\rightarrow{}^4T_{1g}(G)$ transitions, respectively for a distorted octahedral geometry [16].

3.3. Infrared Spectra

The IR spectral assignment of the metal complexes was achieved by comparing their vibration frequencies with those of the free ligands (**Table 3**) and literature reports of similar compounds [25,26].

3.3.1. Glycinato-Complexes

The N-H stretching vibration at 3119 cm^{-1} in glycine was shifted to higher frequencies with the complexes, suggesting that the coordination of the metal ions with the ligand was via the nitrogen atom [25-27]. This was corroborated by similar shifts in the weak C-N stretching frequency of the ligand at 1127 cm^{-1} to higher frequencies in the complexes [28].

Infrared studies on coordination compounds of amino acids have shown that the carboxylate ion is affected by coordination, making it a useful tool in structural studies [26]. Similarly, the asymmetric stretching vibration at 1615 cm^{-1} for the carboxylate ion was shifted to higher frequencies with the complexes, confirming coordination via this functional group. For the symmetric stretch, sharp extended bands were observed instead of distinct bands. This has been reported to be due to the zwitterionic nature of the ligand in the crystalline form [26]. Sharp extended bands at ~3480 - 3620 cm^{-1} in the complexes indicated intermolecular hydrogen bonding between the uncoordinated oxygen atom of the carboxyl group and the amino group of neighboring molecule. Broad bands at ~1340 cm^{-1} however confirmed the intramolecular hydrogen bonding [29]. New bands at 502 - 548 and 621 - 695 cm^{-1} were assigned to (M-N) and M-O bond stretching band frequencies, respectively and served as further evidence of coordination via the nitrogen and oxygen atoms of the ligand.

3.3.2. Phenylalanito-Complexes

Bathochromic shifts of the phenylalanine N-H stretching frequency at 3454 cm^{-1} was observed in all the complexes, with the exception of the hypsochromic shift given by the cobalt complex (**Table 3**). This ligand had weak bands at 1626 and 1566 cm^{-1} that were assigned to the asymmentric and symmentric stretching bands of the carboxylate ion. They were weak as a result of the zwitterionic nature of the ligand [26,30]. In the complexes, the asymmetric stretching band experienced hypsochromic shifts. However, cadmium and copper complexes gave bathochromic shifts. It has been reported that for aromatic compounds, their N-H bending vibration bands often overlapped the aromatic C=C absorption bands [30]. Consequently, a distinct C=C band was not obtained for most of the complexes.

Table 3. Infrared frequencies (cm^{-1}) of the ligands and compounds.

Compound	NH_2	${}_{as}COO^-$	${}_{sy.}COO^-$	C-N	M-N	M-O
L_1	3119br	1615s	1615s	1127w	-	-
L_2	3454br	1626m	1566w	1070s	-	-
$[Cu(L_1)_2]_2$	3333br	1632br	1416br	1210m	501sh	695sh
$Na[Cd(L_1)_3]$	3428br	1714m	1462m	1226m	503sh	668s
$Na[Ni(L_1)_3]$	3399br	1634m	1422w	1126m	501m	621m
$Na[Co(L_1)_3]$	3428br	1621s	1454s	1236m	509sh	672s
$Na[Mn(L_1)_3]$	3142br	1624m	1464m	1206m	548s	631w
$[Cu(L_2)_2]_2$	3289s	1608w	1454s	1214s	518s	695s
$Na[Cd(L_2)_3]$	3424br	1585s	1411s-	1208s	521s	699s
$Na[Ni(L_2)_3]$	3202br	1687s	-	1264m	598s	655s
$Na[Co(L_2)_3]$	3467br	1653w	-	1208m	524m	675s
$Na[Mn(L_2)_3]$	3261w	1656w	1456s	1209m	520s	679m

Keys: L_1: glycine; L_2: *dl*-phenylalanine; w: weak; m: medium; s: strong; vs: very strong; br: broad; sh: sharp.

Table 4. Zones of inhibition for the coordinated compounds (20 mg/ml).

Compounds	**Zone of inhibition (mm)**[*]						
	Gram (+)			*Gram* (–)			Fungus
	S. aureus	*B. subtilis*	*MRSA*	*E. coli*	*Ps. aeruginosa*	*P. vulgaris*	*C. albicans*
$Na[Cd(L_1)_3]$	13.0 ± 0.4	6.0	6.0	6.0	6.0	6.0	20.0 ± 0.4
$Na[Ni(L_1)_3]$	6.0	6.0	6.0	6.0	6.0	14.1 ± 0.3	6.0
$Na[Co(L_1)_3]$	13.0 ± 0.5	13.1 ± 1.0	12.0 ± 0.4	9.0 ± 0.3	20.2 ± 0.1	9.0 ± 0.2	6.0
$Na[Mn(L_1)_3]$	13.0 ± 0.5	6.0	6.0	13.1 ± 0.2	6.0	6.0	6.0
$Na[Cd(L_2)_3]$	22.0 ± 0.2	18.0 ± 0.2	20.2 ± 0.1	6.0	8.0 ± 0.3	13.0 ± 0.0	44.0 ± 0.4
$Na[Ni(L_2)_3]$	6.0	6.0	6.0	6.0	6.0	6.0	15.0 ± 0.7
$Na[Co(L_2)_3]$	6.0	15.0 ± 0.1	15.0 ± 0.0	6.0	21.0 ± 0.0	6.0	15.0 ± 0.0
$Na[Mn(L_2)_3]$	17.0 ± 0.4	8.0 ± 0.5	10.1 ± 0.5	8.1 ± 0.6	9.0 ± 0.3	8.0 ± 0.8	6.0
Acriflavine	20.0 ± 0.0	6.0	6.0	20.0 ± 0.0	6.0	15.0 ± 0.0	19.0 ± 6.0

[*] Zone size measured included the 6.0 mm size of the filter paper disc.

Broad bands at 3468 - 3823cm^{-1} in the complexes indicated N-H···O interaction [31]. In the low frequency region, the complexes had new bands at 598 - 518 and 699 - 655cm^{-1}, attributable to (M-N) and (M-O) stretching. This further supported that the coordination of the complexes was via the amino and carboxylate groups. Therefore, based on the above discussion of the results of the magnetic moment, electronic and infrared spectra, a dinuclear bipyramidal geometry is hereby proposed for the glycinato- and phenylalanito-Cu(II) complexes and octahedral geometry for the others. However, the octahedral geometry of the Mn(II) and Ni(II) complexes are suggested to be distorted.

3.4. Antimicrobial Activity

The antimicrobial activities of the compounds are presented in **Table 4**. The results obtained indicated that glycine, and both copper complexes were inactive to all the tested organisms while phenyalanine and $Na[Ni(L_2)_3]$ had marginal (zone of inhibition 14.0 mm) antifungal activity (**Table 4**). The activity of acriflavine against *E. coli* was significantly ($p < 0.05$) higher than all the coordinated compounds while the standard drug was inactive against some of the tested bacteria. The antimicrobial activities of some of the complexes against *B. subtilis*, MRSA, *Ps. aeruginosa* and *C. albicans* were significantly higher than the standard drug (**Table 4**), indicating their potentials as antimicrobial agents against these microbes. The compound with the highest antimicrobial spectrum was $Na[Cd(L_2)_3]$ followed by $Na[Co(L_1)_3]$ and $Na[Co(L_2)_3]$. Also, $Na[Cd(L_2)_3]$ had the greatest activity against *C. albicans* as well as against the Gram +ve bacteria tested. $Na[Co(L_1)_3]$ and $Na[Co(L_2)_3]$ demonstrated the highest activity against *Ps. aeruginosa*, the most susceptible Gram −ve bacterium tested. This may confirm the antimicrobial property of cobalt [6]. However, higher activities given by these cobalt complexes than those of copper, contrary to the antimicrobial potencies of their metals [4,32-35], may indicate the influence of the proposed dinuclear structure.

Similar to previous reports [4,36], the complexes showed better activity against the Gram +ve bacteria, with the exception of $Na[Cd(L_2)_3]$ and $Na[Ni(L_1)_3]$ against *P. vulgaris*, $Na[Co(L_1)_3]$, $Na[Mn(L_1)_3]$ against *E.coli* and $Na[Co(L_2)_3]$ against *Ps. aeruginosa* (**Table 4**). This indicates their usefulness as broad spectrum antibacterial agents. The four-coordinate $Cu(L_1)_2$ and $Cu(L_2)_2$ had better activities against *E. coli* and *S. aureus* [12] than the present dinuclear Cu(II) complexes. The activities of $Ni(L_1)_2$, $Co(L_1)_2$ and $Mn(L_1)_2$ against *C. albicans* [12] were also better than the current six-coordinate complexes while that of $Mn(L_1)_2$ against *B. subtilis* [12] was significantly higher. Apart from these exceptions, the six-coordinate complexes (**Table 4**) demonstrated better activities than their corresponding four-coordinate complexes [12]. This enhancement of activity suggests that chelation moderately increased the lipophilic character of the compounds and subsequently their permeation through the lipoid layer of the microbe's cell membrane [37-40].

4. CONCLUSION

The results of this study indicated that L_1 and L_2 coordinated in a bi-dentate manner using both nitrogen and oxygen atoms. This assignment is corroborated by spectral and magnetic moment data. The compounds exhibited a broad spectrum of activity against the tested microbes. Some of the compounds however exhibited increased antimicrobial activity with increased number of chelate rings. Hence, chelation may serve as a useful tool in the design of potential antimicrobial agents.

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