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SYNTHESIS, SPECTROSCOPIC CHARACTERIZATION AND ANTIOXIDANT PROPERTIES OF SOME METAL(II) COMPLEXES OF MIXED DRUGS- VITAMIN Bx AND PARACETAMOL

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ABSTRACT

Some metal(II) complexes of mixed drugs, Vitamin Bx (p-aminobenzoic acid) and Paracetamol(N-acetyl-p-aminophenol), were synthesized and characterized by solubility, percentage metal, melting points, room temperature magnetic moments, conductivity, infrared and electronic spectra measurements(M = Mn, Fe, Co, Ni, Cu and Zn). Infrared data showed that the Vitamin Bx coordinated to the metal through the un-deprotonated carboxylate oxygen atoms while the Paracetamol coordinated through its carbonyl oxygen and the un-deprotonated phenolic oxygen atoms respectively. The percentage metal analysis, electronic and infrared spectra corroborated octahedral geometry. Furthermore, the room temperature magnetic moments indicated that the Mn(II) and Co(II) complexes were dimeric, the Fe(II) complex exhibited spin-cross over and the remaining metal complexes were mononuclear. The antioxidant studies on the metal complexes showed that the Co(II) and Zn(II) complexes had the best antioxidant activity of about 98 % inhibition, which was higher than that of the standard, ascorbic acid (~88%), proving their potentials as an agents which can reduce the risk for lingering diseases such as cancer and heart disease.

Keywords: Metal complexes, mixed drugs, therapeutic agents, spin-crossover, octahedral .

INTRODUCTION

Vitamin B_x (p-aminobenzoic acid), is a chemical substance that is found in folic acid vitamin molecule (folate). Plants, fungi and many microorganisms synthesize folate but humans and other higher animals do not (Cossins, 2000). Vitamin B_x only supports folic acid production by the intestinal bacteria in mammals. It is used (along with biotin, panthothenic acid and folic acid) in the restoration of hair, to reduce aging of the skin, lessening wrinkles and vitiligo- a skin depigmenting condition. Therefore, there is a need for dietary supply of this from several food sources such as grains, brewer's yeast, molasses, liver, eggs, milk and kidney (Cossins, 2000; Green *et al.*, 1996; Scott *et al.*, 2000). Vitamin B_x has u*ltra violet* absorbing properties and is subsequently used in local anesthetic agents and sunscreen products to prevent the development of sunburn and skin cancer from excess ultraviolet light exposure (Levee *et al*., 1981; Ludwig, 1991; Zarafonetis *et al*., 1988). However, it is now seldom used as sunscreen products because it had been discovered from animal studies with Vitamin B_x in the early 1980s that there may be an increased risk of *ultra violet* cellular damage (Levee *et al*., 1981; Osgood *et al*., 1982).

Paracetamol is chosen as the second ligand due to its mild analgesic and weak anti-inflammatory activity(Larson *et al*., 2005). Furthermore being a phenolic molecule, it has good antioxidant properties which could be utilized in developing metallo-drugs for treatment of pain, essential metal and vitamin deficiencies (Osowole *et al*., 2014; Roberts and Morrow, 2001).

Thus, the objectives of this work are to design and characterize mixed drug metal complexes of Vitamin Bx and Paracetamol, with potential antioxidant properties. Secondly, assess the suitability of Vitamin Bx and Paracetamol as ligands in forming metal complexes with spin-crossover, antiferromagnetism and ferromagnetism by room temperature magnetic moment measurements; and predicting the geometry of the metal complexes based on IR and electronic spectroscopic analysis. These compounds are new, and a continuation of the research activities of our group on the design of potent metallo-drugs as chemotherapeutic agents in pain management and essential metal/vitamin deficiencies (Agbaje *et al*., 2015; Osowole *et al*., 2014; Osowole *et al*., 2015a; Osowole *et al*., 2015b)

MATERIALS AND METHODS

Materials and Reagents

Reagent grade para-aminobenzoic acid, DPPH (1,1-diphenyl-2-picryl-hydrazyl), ascorbic acid, manganese(II) sulphate monohydrate, iron(II) sulphate heptahydrate, cobalt(II) chloride hexahydrate, nickel(II) chloride hexahydrate, copper(II) sulphate pentahydrate and zinc(II) sulphate heptahydrate were obtained from Aldrich and BDH chemicals, while Paracetamol was freely collected from Bentos pharmaceutical products limited, new garage, Ibadan, Nigeria and were used as received. Solvents were purified by distillation.

SYNTHESIS

Preparation of $[Mn(HL)(HL^1)SO_4]$ and other metal complexes:

The metal (II) complexes were synthesized according to the procedure of Agbaje *et al*., (2015). 0.57 g (4.16×10^{-3} moles) of Vitamin Bx, (HL) and 0.63 g (4.16×10^{-3} moles) of Paracetamol, (HL^1) were dissolved in 20 mL of methanol. To the resulting homogenous solution, 0.70 g (4.16×10^{-3} moles) of the Mn(II) sulphate monohydrate was added while stirring at room temperature. After stirring for 30 minutes, the solution was buffered with 8-9 drops of concentrated ammonia up to pH of 9. The resulting homogenous solution was left on continuous stirring for 3 hours during which the product formed. The white precipitate obtained was filtered, washed with methanol and dried over silica gel. The same procedure was used for the preparation and isolation of Fe(II), Cu(II), Zn(II) complexes from their sulphate salts; and Co(II), Ni(II) complexes from their chloride salts respectively.

Physical measurements

The *UV*-visible spectra of the metal complexes were recorded using *UV*-1800/SHIMADZU *UV* spectrophotometer personal computer (PC) scanning and infrared spectra were recorded on a CARY 630 FTIR in the range 4000-650 cm^{-1}. The room temperature magnetic moment susceptibilities measurement were determined using a Sherwood susceptibility balance MSB Mark 1 at 299 K and diamagnetic corrections were calculated using Pascal's constant. The melting points and decomposition temperature were determined using Stuart SMP 10 machine while molar conductivity measurement of 1×10^{-3} M solutions of DCM (dichloromethane) were obtained using DDS-307A conductivity meter, and percentage metal was determined using EDTA by complexometric titration.

Antioxidant assay

The antioxidant activities of Vitamin Bx, Paracetamol and their metal complexes were studied spectrophotometrically by DPPH method. DPPH(1,1-diphenyl-2-picryl-hydrazyl) dissolves in DMSO to give a violet solution, which, upon reduction by an antioxidant, changes to yellow. A solution of 0.4 mM DPPH in DMSO was prepared and 1.0 mL of this solution was mixed with 1.0 mL DMSO solutions of the metal(II) complexes with a single concentration of 100 μg mL^{-1}. The reaction mixture was stirred thoroughly and left in the dark at room temperature for 30 min. The absorbance of the mixture was measured spectrophotometrically at 517 nm. Ascorbic acid (vitamin C) was used as the standard drug. The actual decrease in absorption was measured against that of the control. All tests and analyses were run in triplicate and the results obtained were averaged, and percentage scavenging inhibition of DDPH ability was expressed as:

% scavenging inhibition = {(Ac - As)/Ac} x 100.......................................(1)

where Ac is the absorbance of DPPH radical + dimethylsulphoxide, and As is the absorbance of DPPH radical + sample [test samples/standard].

RESULTS AND DISCUSSION

Analytical data

The reaction of Vitamin B_x (HL) and Paracetamol (HL^1) with the hydrated metal(II) sulphates (Mn, Fe, Cu, Zn) and chlorides (Co, Ni) respectively produced coloured complexes of low to good yields (10-70%) according to the generalized equations below:

$MSO_4.aH_2O + HL + HL^1 \rightarrow [M(HL)(HL^1)SO_4] + bH_2O$ ....(2)

where M = Mn, a = b = 1; M = Fe, a = b = 7; M = Cu, a = b = 5; M = Zn, a = b = 7)

$MCl_2.cH_2O + HL + HL^1 \rightarrow [M(HL)(HL^1)Cl_2] + dH_2O$ ....(3)

(where M = Co = Ni, c = d = 6)

All the metal complexes had expected colour due to d-d transition, and the Zn(II) complex was expectedly white due to its d^{10} configuration. The ligands, Vitamin Bx and Paracetamol melted at 188-190°C, while their metal(II) complexes decomposed in the range 212-252 °C, due to coordination.

The formation of the metal complexes was corroborated by formulated masses, since experimental values of the percentage metal analysis were very close to the theoretical values. In addition, the presence of metal-ligand bands in the IR and solid reflectance spectra of the metal complexes, and its absence in the spectra of both Vitamin Bx and Paracetamol, also confirmed coordination.

Table 1: Analytical data of the ligands and their metal(II) complexes

Complexes	Formula mass	Colour	M.Pt (^{o}C)	% yield	%Metal Theo.(Exp)	^m	µeff. (B.M)
HL	137.14	Off-white	188-190	-	-	-	D
HL^{1}	151.15	White	170-172	-	-	-	D
[Mn(HL)(HL^{1})SO$_4$]	439.25	White	218*	30.0	12.53(12.54)	21.0	0.7
[Fe(HL)(HL^{1})SO$_4$]	440.16	Brown	228*	30.0	12.73(12.77)	20.9	3.8
[Co(HL)(HL^{1})Cl$_2$]	418.22	Brown	212*	10.0	14.11(14.16)	21.1	5.95
[Ni(HL)(HL^{1})Cl$_2$]	418.00	Green	214*	40.0	14.06(14.09)	21.2	3.1
[Cu(HL)(HL^{1})SO$_4$]	447.85	Green	237*	70.0	14.59(14.29)	21.2	2.30
[Zn(HL)(HL^{1})SO$_4$]	449.68	White	252*	50.0	14.48(14.82)	21.2	D

HL = Vitamin Bx; HL^{1} = Paracetamol; M.pt = Melting point; * = decomposition temperature; Theo. = Theoretical; Exp = Experimental; ^m = Molar conductance (Ω^{-1}cm^{2}mol^{-1}); µeff = effective magnetic moment; B.M = Bohr Magneton; D = Diamagnetic

Solubility and molar conductance measurements

The complexes were insoluble in diethyl ether, slightly soluble in methanol and ethanol but showed good solubility in DMSO and water. The metal complexes had molar conductivities values in the range 20.9 - 21.2 ohm^{-1}cm^{2}mol^{-1} in dichloromethane(DCM) confirming their covalent nature, since values in the range 60 - 118 ohm^{-1}cm^{2}mol^{-1} is expected for 1:1 electrolyte (Ekennia *et al*.; 2015).

Electronic spectra and magnetic moments

The electronic spectra of the compounds were presented in Table 2. Their ultraviolet spectra were characterized by strong absorption bands 27,320 - 29,240 cm^{-1}, 32,360 - 39,400 cm^{-1} and 40,000 - 40,920 cm^{-1} assigned to $n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$ and charge transfer respectively. The Mn(II) complex exhibited a strong absorption band at 24,150 cm^{-1} (ε = 500) assigned to $^{2}T_{2g} \rightarrow {}^{2}A_{1g}$ transition, of a low spin octahedral geometry. An observed room temperature moment of 0.7 B.M, instead of an expected value of ~2.0 B.M was suggestive of a dimeric structure with strong antiferromagnetism operating through a Mn-Mn bond (Saha *et al*., 2000).

The Fe(II) complex on the contrary, had two absorption bands at 16,780 cm^{-1} (ε = 300) and 21,070 cm^{-1} (ε = 500) typical of high spin and low spin octahedral geometry and were assigned to $^{5}T_{2g} \rightarrow {}^{5}E_{g}$ and $^{1}A_{1g} \rightarrow {}^{1}T_{2g}$ transitions. High spin octahedral Fe(II) complexes should have moments within the range 5.0 - 5.5 B.M and low spin octahedral Fe(II) are expected to be diamagnetic. On the contrary, a moment of 3.8 B.M was observed for Fe(II) complex, which was indicative of spin-crossover, that is an equilibrium between the high spin and low spin octahedral geometry. This is a common feature within Fe(II) systems (Olguin and Brooker, 2011).

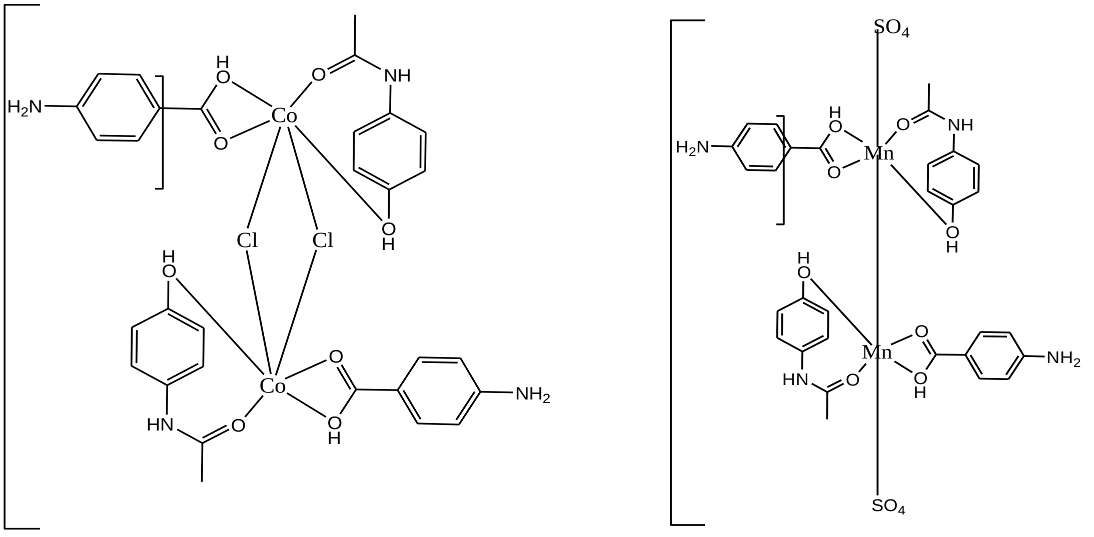
The Co(II) complex exhibited a lone band at 23,280 cm^{-1} (ε = 1.0 x 10^{3}), consistent with a low spin octahedral geometry and was assigned to $^{2}E_{g} \rightarrow {}^{2}T_{2g}$ transition. Low spin octahedral Co(II) complexes usually exhibit moments in the range 1.9-2.9 B.M., but in this study a moment of 5.95 B.M was observed, indicative of a dimeric octahedral cobalt (II) with bridging chloride such that each Co(II) atom had a moment of ~ 2.98 B.M (Barefield *et al.*, 1968; Goodwin, 2004).

Similarly, the Ni(II) complex had two absorption bands at 13,150 cm^{-1} (ε = 250) and 14,980 cm^{-1} (ε = 400) typical of six coordinate, high spin octahedral geometry. These bands were assigned as $^{3}A_{2g} \rightarrow {}^{3}T_{2g}$ and $^{3}A_{2g} \rightarrow {}^{3}T_{1g}$ transitions. Room temperature magnetic moments in the range 2.8-3.3 B.M are expected for high spin octahedral Ni(II) complexes. Thus, an observed moment of 3.10 B. M corroborated this geometry (Ohtsu and Tanaka, 2004).

The Cu(II) complex expectedly had a single band at 14,960 cm^{-1} (ε = 1000), typical of octahedral geometry, since octahedral Cu(II) complexes usually have lone band above 10,000 cm^{-1} whereas tetrahedral Cu(II) complexes had their lone band below 10,000 cm^{-1}. The transition was assigned as $^2E_g \rightarrow {}^2T_{2g}$ transition (Manonmani *et al.*, 2011). A complimentary moment of 2.30 B.M was observed since mononuclear copper(II) complexes, regardless of stereochemistry usually have moments in the range 1.9-2.20 B.M complex (Osanai et al., 2006).

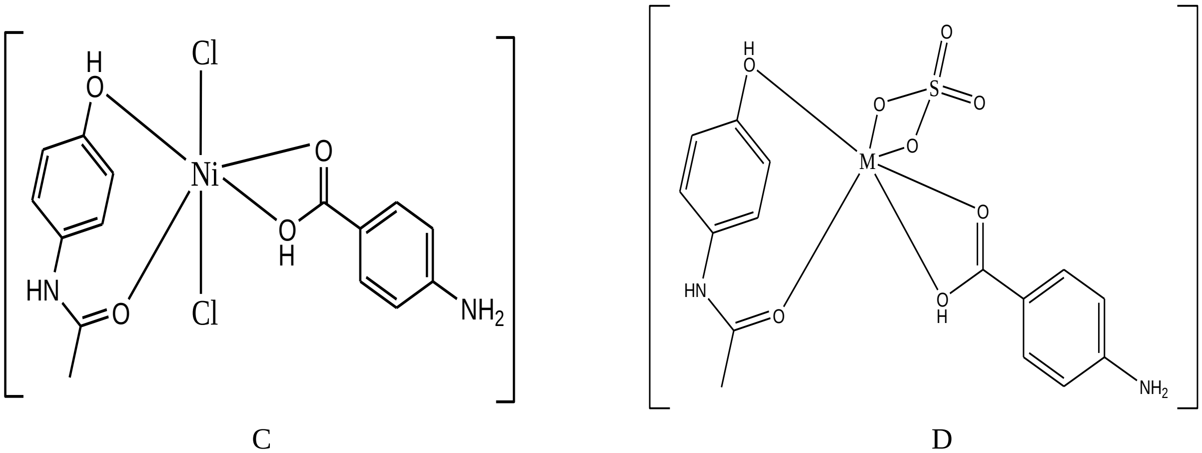
The Zn(II) complex had its M→L CT transition at 12,840 cm^{-1} (ε = 150) and 16,780 cm^{-1} (ε = 250) respectively since d-d transition was not possible. The complex was expectedly essentially diamagnetic with octahedral geometry (Raman *et al.*, 2004).

Conclusively, the ligands, Paracetamol and Vitamin Bx, were suitable designer ligands for formation of low spin complexes with strong magnetic interactions, that is, antiferro magnetism and spin crossover respectively.



A B

Figure1: Proposed structure for the Co(II) and Mn(II) complexes



C D

Figure 2: Proposed structure for Ni(II) and M(II) complexes: M= Fe, Cu and Zn

Infrared Spectra

The relevant bands are presented in Table 2. The bands at 3360 cm^{-1} and 3382 cm^{-1} in Vitamin Bx and Paracetamol were assigned as υ(OH) (Osowole et al., 2014; Osowole et al., 2015c), while the bands at 3319 cm^{-1}, 3457 cm^{-1} and 3377 cm^{-1} were assigned to υ(NH) of Paracetamol and Vitamin Bx respectively (Sangita *et al.*, 2012; Shipra *et al.*, 2015). The v(OH) bands of both ligands, were observed shifted in the metal complexes to the range 3368-3060 cm^{-1} due to coordination of the phenolic oxygen and carboxylate atoms of Paracetamol and Vitamin Bx to the metal ion respectively . In contrast, the υ(NH) bands were shifted in the metal complexes to 3556-3060 cm^{-1} due to hydrogen bonding and not coordination since M-N-bands were not observed (Sayyed *et al.*, 2014). The υ(C=O) bands of Vitamin Bx and Paracetamol were seen in the range 1657-1571 cm^{-1} and 1649-1560 cm^{-1}. These were bathochromic/hypochromic shifted in the metal complexes to the range 1707-1541 cm^{-1} due to coordination (Beyramabadi *et al.*, 2011). The observance of M-O bands in the metal complexes at 690-650 cm^{-1}, further confirmed coordination. However, υ(M-Cl) was not observed because it was outside the range of the equipment.

Table 2: Infra-red and electronic spectra data of the metal(II) complexes

Complex	v(OH)	v(NH$_2$)	v(C=O)	v(M-O)	Electronic spectra (cm^{-1})
HL	3360m	3457s 3377m	1657s 1597s 1571s	-------	27,320 29,240
HL^1	3382m	3319m	1649s 1610s 1560s	-------	32,890
[Mn(HL)(HL^1)SO$_4$]	3220m	3465m 3353m	1630s 1602s 1579s	669s	24,150 32,360 40,000
[Fe(HL)(HL^1)SO$_4$]	3214b	3524m	1597s 1541s	650s	16,780 21,070 28,410 40,130
[Co(HL)(HL^1)Cl$_2$]	3368b	3556b	1653s 1608s1560s	657s	23,280 33,850 37,710
[Ni(HL)(HL^1)Cl$_2$]	3289b	3360b 3319m	1649s 1602s 1560s	662s	13,150 14,980 39,400
[Cu(HL)(HL^1)SO$_4$]	3060b	3060b	1701s 1612s 1571s	690s	14,960 34,200 40,420
[Zn(HL)(HL^1)SO$_4$]	3256b	3314m 3256b	1707s 1679s 1573s	655s	12,840 16,780 40,920

HL = Vitamin Bx, HL^1 = Paracetamol, b = broad, m = medium, s = sharp

DPPH Free radical scavenging activity

Antioxidants when present in the body may offer protection against cancers, alzheimer's and Parkinson's diseases (Halliwell *et al.*, 1984). DPPH acts by accepting an electron from test compounds, and gets converted into a stable molecule. In this study, it was observed that Co(II) and Zn(II) complexes had highest percentage inhibition of ~98% which was higher than that of the positive standard, Vitamin C, with an activity of `~88%. The scavenging ability of the metal complexes decrease in the order; Zn ~Co> Ni> Mn>Fe> Cu. Thus, these compounds had potential as health protecting factor.

Table 3: Antioxidant properties of the metal complexes

Complex	**Average±SD**	% inhibition
$[Mn(HL)(HL^1)SO_4]$	0.040±0.0027	66.27
$[Fe(HL)(HL^1)SO_4]$	0.038±0.0012	63.53
$[Co(HL)(HL^1)Cl_2]$	0.059±0.0015	98.33
$[Ni(HL)(HL^1)Cl_2]$	0.044±0.0012	72.38
$[Cu(HL)(HL^1)SO_4]$	0.019±0.0015	32.03
$[Zn(HL)(HL^1)SO_4]$	0.059±0.0006	98.35
Standard (Ascorbic acid)	0.053±0.0026	87.66

HL =Vitamin Bx , HL^1 = Paracetamol, SD = Standard Deviation, % = percentage

CONCLUSION

Some Mn(II), Fe(II), Co(II), Ni(II) Cu(II) and Zn(II) complexes of mixed drugs, Vitamin Bx and Paracetamol, were synthesized and characterized by solubility, percentage metal, melting points, room temperature magnetic moments, conductivity, infrared and electronic spectra measurements. All the metal complexes adopted 6-coordinate octahedral geometry and the conductance measurements revealed that they are non electrolytes. Furthermore the metal complexes were magnetically dilute, with the exceptions of Fe(II), Mn(II) and Co(II) complexes which exhibited spin-cross over and antiferromagnetism respectively. The antioxidant studies on the metal complexes showed that all the metal complexes had very good percentage inhibition in the range 98.35-63.53, with the exception of Cu(II) complex with the lowest percentage inhibition of 32.03, suggesting them as potential agents for chronic ailments risk reduction.

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