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Synthesis, physicochemical and biological activities of some metal(II) complexes of (methylsulfanyl)-2,4-benzenediol Schiff base

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ABSTRACT

Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) ions form complexes of the type $[ML_2]xH_2O$ with the Schiff base, [{4-(methylsulfanyl)phenyl]imino}methyl]benzene-2,4-diol, using the phenolic *O* and imine *N* atoms. These compounds are characterized by microanalysis, conductance, ^{1}H NMR, infrared and electronic spectral measurements. The IR measurements reveal that the Zn(II) complex is in the trans-isomeric form while electronic measurements are corroborative of a four coordinate, tetrahedral/square-planar geometry for the metal complexes. None is an electrolyte in nitromethane, and all the complexes are air stable but decomposed on heating in the temperature range 210-330^{o}C. The antibacterial studies show that the ligand, the Mn(II), Co(II), and Zn(II) complexes are active against *Staphylococcus aureus* with inhibitory zones range of 9.0-17.0 mm. The cytotoxic study shows that the Cu(II) complex has the best in-vitro anticancer activity against HT-29 (colon carcinoma) cells with an IC_{50} value of 30.17 µM, which is about a quarter as active as Cis-platin.

Introduction

Schiff bases derived from dihydroxybenzaldehydes and various thio amines are of interest to us because of their interesting biological activities. e.g. those prepared from 2-amino-pyridin-3-ol and 3,4-dihydroxy benzaldehyde have good antimicrobial activities against *Escherichia coli*, *Agrobacterium sp*., *Staphylococcus aureus*, *Bacillus spp*., *Candida albicans*, and *Aspergillus niger* [1]. Similarly, the crown ether Schiff base,{2,3,5,6-di[4-N-(salicylidene) benzo]-1,7,10,13-tetraoxacyclopentadeca-2,5-diene}, and its Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes have very good antibacterial activities against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus cereus*, *Proteus vulgaris*, *Salmonella typhimurium* and *Corynebacterium xerosis* [2]; while 7-bromo-5-cyclopropyl-8-[3-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl] sulfinyl]propoxy]-N-[4-(trifluoromethoxy)phenyl]-5H-pyridazino[4,5-b]indole has potent anticancer activity against cancer cell lines Bel-7402 (human liver cancer, hepatoma) and HT-1080 (human fibrosarcoma [3]; while Additionally, Schiff bases derived from the condensation of o-aminophenol with benzaldehydes are precursors in the synthesis of arylbenzoxazoles [3], and Ru(III) complex of the polymeric Schiff base ligand synthesized from 5,6-diamino-1,10-phenanthroline and 4',5-dihydroxy-7-methoxy isoflavone is a good catalyst for the oxidation of benzyl alcohol and cyclohexanol to benzaldehyde and cyclohexanone respectively; in the presence of cooxidant N-methylmorpholine-N-oxide (NMO) [4].

Furthermore, the Schiff base, 3-(anilino-methyl)-benzothiazole-2-thione is an efficiently inhibitor of corrosion in N80 steel in simulated corrosive medium of saturated CO_2 environment [5]. In-depth literature search revealed that no information is available on the Schiff base, [{4-(methylsulfanyl) phenyl]imino}methyl]benzene-2,4-diol, (derived from condensation of 2,4-dihydroxy benzaldehyde and 4-methylthio aniline) and its Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes [6-10].

Thus, our aims are to synthesize, characterize and investigate the in-vitro antibacterial properties of the ligand and all the metal complexes; as well as the anticancer properties of the ligand and it's Cu(II) and Zn(II) complexes.

Copper is chosen for its antioxidant property and prevention of lipid deposition in the mammalian myocardium [11], while Zn is chosen for being an essential trace element to both humans and microorganisms required for vital cell growth, division and function [12].

The ligand and its metal(II) complexes are new and are now reported by us as a continuation of our studies on the Synthesis, characterization and bioactivities of various metal(II) Schiff base complexes [13-15].

Experimental

Materials

All chemicals, 2,4-dihydroxybenzaldehyde, 4-methylthio aniline, hydrated cobalt(II) nitrate, nickel(II) nitrate, copper(II) nitrate, zinc(II) nitrate and manganese(II)nitrate, are of reagent grade from Aldrich and BDH chemicals and are used as received.

Syntheses

The ligand, HL, is prepared by adding 0.02mmol (2.0 g) of 4-methylthioaniline in 20 mL of absolute ethanol drop wise to a stirring hot 30 mL ethanolic solution of 0.02 mmol (2 g) of 2,4-dihydroxybenzaldehyde at 60^{0}C.

The resulting homogeneous yellow solution is then refluxed for 4 h after the addition of 6 drops of acetic acid. The yellow product, formed on cooling in ice, is filtered and recrystallized from ethanol and dried *in vacuo* over anhydrous calcium chloride.

The yield of the resulting Schiff base (Figure 1) is 3.0g (60%). ^{1}H nmr (ppm) δ 11.5(s, 1H, $C^{2'}$ OH), 9.8(s, 1H, $C^{4'}$ OH), 7.17-7.32 (m, 3H, $C^{3'}$, $C^{5'}$, $C^{6'}$), 8.52(s, 1H, $C^{7'}$), 6.38-6.49 (m, 4H, C^2, C^3, C^5, C^6), 2.51 (s, 3H, CH_3S).

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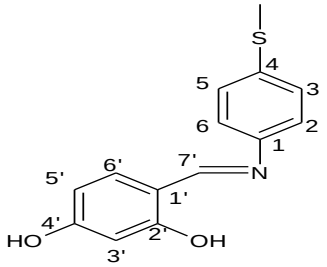

Figure 1: Proposed structure for the ligand

Preparation of the Metal(II) Complexes

The various complexes are prepared by adding 0.30 mmol (0.053-0.089 g) of hydrated M(II) nitrates (M = Co, Ni, Cu, Zn) in bits to a stirring 0.60 mmol (0.16 g) of the ligand in 30 mL of methanol. The resulting homogeneous solution is then buffered with 0.06 mmol (0.06 g) of triethylamine and is further stirred at 15^{o}C for 6 h. The products formed are filtered, washed with methanol, and dried *in vacuo* over anhydrous calcium chloride. Similar procedure was used to isolate the Pd(II) complex from its chloride.

Biological Studies

The antibacterial tests are done at the Department of Microbiology, University of Ibadan, Ibadan, Nigeria while the anticancer tests are carried out at the Institute of Medicinal and Pharmaceutical Chemistry, Technical University Braunschweig, Beethovenstrasse, 55, 38106 Braunschweig, Germany.

Antimicrobial assay

The assay is carried out on the ligand and its metal(II) complexes using the Agar diffusion technique. The surface of the Muller Hinton's agar in a Petri dish is uniformly inoculated with 0.3 mL of 18 hour old *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae* and *Proteus mirabilis* cultures. Using a sterile cork borer, 7 mm wells are bored into agar. Thereafter 10 mg/mL concentration of each metal complex in DMSO is then introduced into the wells and the plates are allowed to stand on bench for 30 min before incubation at 37^{0}C for 24 h, after which inhibitory zones (in mm) are taken as a measure of antimicrobial activity. The experiments are conducted in duplicates with Sulfamethoxazole as the reference drug.

Cytotoxicity assay

The antiproliferative effects in MCF-7 and HT-29 cells after 72 h (HT-29) or 96 h (MCF-7) exposure to the complexes are evaluated according to an established literature method [16]. Briefly, In 96 well plates, 100 mL of a cell suspension in culture medium at 7500 cells/mL (MCF-7) and 2500 cells/ml (HT-29) are plated into each well and incubated for three days under culture conditions. After the addition of various concentrations of the test compounds, cells are incubated for another 96 h and 72 h respectively. The medium is then removed and the cells are fixed with 1% glutardialdehyde solution and stored under phosphate buffered saline (PBS) at 4^{O}C. Cell biomass is determined by a crystal violet staining, followed by extracting of the bound dye with ethanol, and a photometric measurement at 590 nm. The test compounds are prepared fresh as stock solutions in DMF and diluted with the cell culture medium to the final assay concentrations (0.1% V/V DMF) and Cis-platin is used as the reference drug. The IC_{50} value is determined as the concentration causing 50% inhibition of cell proliferation and calculated as mean of at least two independent experiments [17].

Physical Measurements

The solid reflectance spectra are recorded on a Perkin-Elmer λ25 spectrophotometers while infrared spectra are done with Thermo Nicolet FTIR 200 spectrophotometer in the range 4000-400 cm^{-1} as KBr discs. The ^{1}H nmr spectrum is recorded on a 300 MHz Brucker DRX-400 NMR instrument in $CDCl_3$ at 295K, and ^{1}H chemical shifts are referenced to the residual signals of the protons of $CDCl_3$ and are quoted in ppm. The elemental analyses for C, H and N are recorded on Thermo Quest CE Instruments flash EA1112 analyser, while manganese, cobalt, nickel, copper and zinc are determined titrimetrically [18]. Electrolytic conductivities in nitromethane are determined using a HANNA HI 991300 conductivity meter and melting points (uncorrected) are done with Mel-Temp electro thermal machine.

Results and discussion

The formation of ligand is confirmed by microanalyses and ^{1}H nmr measurements. All the complexes adopt $[ML_2]xH_2O$ stoichiometry. The generalized equation for the formation of the complexes is:

$M(NO_3)_2 \cdot 6H_2O + 2HL \rightarrow [ML_2]aH_2O + 2HNO_3 + bH_2O$

(When M(II) = Mn{a = 1.5, b = 4.5}; Zn{a = 2, b = 4}; Cu{a = 3, b = 3}; Co/Ni{a = 6, b = 0})

The analytical data, colors, percentage yields, melting points, molar conductivities, and room temperature magnetic moments of the complexes are presented in Table 1. The ligand melted at 138-140^{o}C while the complexes decomposed in the temperature range 210-330^{o}C, an evidence of coordination. Single X-ray diffraction measurements could not be done due to formation of non-suitable crystal.

Conductance Measurements

The molar conductivities of the complexes in nitromethane are in the range 32.0- 47.0 ohm^{-1} cm^{2} mol^{-1}, showing that they are non-electrolytes in the solvent. A value of 94.0-105.0 ohm^{-1} cm^{2} mol^{-1} is expected for a 1:1 electrolyte [19].

Infrared and Electronic Spectra

The relevant infrared data are presented in Table 2. The band at 3404 cm^{-1} in the ligand is assigned as νOH and its broadness is attributed to intramolecular hydrogen bonding between the two hydroxyl groups [15]. The absence of the band at 3404 cm^{-1} indicates coordination through one of the phenolic oxygen atoms, and the presence of a broad band in the complexes in the range 3500-3412 cm^{-1} indicates *ν*OH of non-bonding phenol, and that of crystallization water. The uncoordinated C=N vibrations in the ligand are observed as three bands in the range 1625-1543 cm^{-1}. These bands are still observed as three in the complexes, with the exception of the Zn(II) complex which has two bands, and are bathochromic shifted to 1616-1539 cm^{-1}, confirming the involvement of the imine *N* atom in coordination to metal(II) ion. The two *ν*C=N bands observed in the Zn(II) complex is indicative of its existence in the trans-isomeric form (Figure 2) [20]. The δC—H vibration of the ligand is observed at 968 cm^{-1} and it suffers a bathochromic shift to 828-755 cm^{-1} in the complexes due to the pseudo-aromatic nature of the chelates [21]. Further evidence of coordination is the appearance of the bands due to ν(M—O) and ν(M—N) in the complexes at 499-421 and 566-514 cm^{-1} respectively.

The electronic spectra are presented in Table 2. The ligand bands are observed at 28.25, 34.97 and 40.32 kK, and are assigned to n→π*, π→π* and CT transitions. These bands are bathochromic shifted in the complexes to 26.18-28.24, 30.30-34.84 and 35.84-39.84. kK due to coordination [14]. The Mn(II) complex, shows an absorption bands at 15.39 and 22.37 kK consistent with a four-coordinate, tetrahedral geometry and are

assigned to $^6A_1 \rightarrow {}^4E_1$ (ν_1) and $^6A_1 \rightarrow {}^4A_1$ (ν_2) transitions [15]. The Co(II) complex shows two absorption bands at 20.83 and 22.37 kK typical of a 4-coordinate, square-planar geometry [20]. The Ni(II) complex has two absorption bands typical of a tetrahedral geometry at 14.47 and 20.66 kK assigned to $^3T_1(F) \rightarrow {}^3T_2$, ($\nu_2$) and $^3T_1(F) \rightarrow {}^3A_2$, ($\nu_3$) transitions [22]. The observance of two bands at 14.71 and 19.60 kK in the Cu(II) complex is indicative of square planar geometry with the assignment $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_{1g}$, since tetrahedral and octahedral complexes both have a single absorption band below and above 10.0 kK respectively [23]. The Zn(II) complex is expectedly tetrahedral, with no d-d absorption band [24].

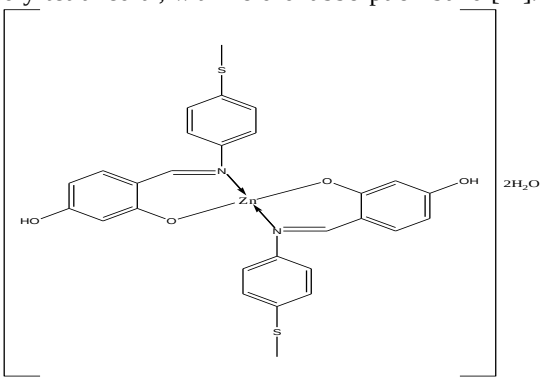

Figure 2: Proposed Structure for the Zn(II) complex

Antibacterial activity

The results of antibacterial activities are presented in Table 3. The ligand and all the complexes are inactive against *Klebsiella pneumoniae*, *E. coli* and *Proteus mirabilis* but are active against *Staphyloccous aureus* with inhibitory zones range of 9.0-17.0 mm respectively; with exceptions of the Ni(II) and Cu(II) complexes whose activities are nil. The inactivity of the metal complexes against the gram negative bacteria is contrary to expectation, since gram negative bacteria have a thin peptidoglycan layer which makes them more permeable to chemicals, and may be attributed to their low lipophilic nature and consequently they could not permeate the bacteria membrane [25]. Furthermore, the resistance of the *Klebsiella pneumoniae* to the ligand, the metal complexes and the antibiotic, Sulfamethoxazole, is attributed to its ability to produce extended-spectrum beta-lactamases (ESBL) which inactivates the compounds [26]. The activity of the ligand against *S.aureus* is 15.0 mm, which is expectedly lower than that of the Zn(II) complex 17.0 mm due to chelation and π-electron delocalisation which increase the lipophilic character, favouring its permeation into the bacterial membrane, thus causing the death of the organism [27]. The reduced activity of the Co(II) [9.0 mm] and Mn(II) [11.0 mm] complexes respectively relative to the ligands activity of 15.0 mm against *S.aureus* may be attributed to the degree of permeability of the bacteria cell [25]. In all cases, the antibiotic has higher activity than the ligand and the complexes against *S. aureus, E. coli* and *P. mirabilis* with inhibitory zones range of 27.0-37.0 mm.

Anticancer activity

The results of the anticancer activities are presented in Table 4. The HT-29 (colon carcinoma) and MCF-7 (human breast adenocarcinoma) cells are not sensitive to the ligand but are sensitive to the Cu(II) and Zn(II) complexes with IC_{50} values of 30.17 µM and 89.99 µM, and 38. 36 µm and 57.82 µm respectively. The Cu(II) complex activity against HT-29 cells is the best, being about a quarter, that of Cis-platin. On the contrary, the Cu(II) complex activity against MCF-7 cells is not within the same order as Cis-platin but it is still better than that of the Zn(II) complex against the same cells .i.e. the activity of the Zn(II) complex is about 2/3rd that of the Cu(II) complex. Thus, chelation enhances the cytotoxic activities of the compounds. The best and good activity of the Cu(II) complex against both HT29 and MCF-7 cells is attributed to its planar geometry which avoids possible steric hindrance during physiological actions [28].

Conclusion

The ligand coordinates to the Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) ions using the azomethine *N* and phenolic *O* atoms, and the Zn(II) complexes is in the trans-isomeric form as shown by the IR measurements. The assignment of a 4-coordinate, tetrahedral geometry to Mn(II), Ni(II) and Zn(II) complexes, and square-planar geometry to the Cu(II) and Co(II) complexes is corroborated by electronic spectral measurements. The ligand, the Mn(II), Co(II), and Zn(II) complexes are active against *Staphylococcus aureus* with inhibitory zones range of 9.0-17.0 mm. The cytotoxic study shows that the Cu(II) complex has the best in-vitro anticancer activity against HT-29 (colon carcinoma) cells with an IC_{50} value of 30.17 µM, which is about a quarter as active as Cis-platin.

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Table 1 Analytical data for the compounds

Compound (Empirical formula)	Formula mass	Color	% Yield	Λ_m^*	M.pt (^oC)	Analysis (Calculated) %C	%H	%N	%M
HL ($C_{14}H_{13}NSO_2$)	259.39	Yellow	60	-	138-140	64.74 (64.84)	4.90 (5.05)	5.56 (5.40)	-
$[ML_2]1.5H_2O$ ($MnC_{28}H_{27}N_2S_2O_{5.5}$)	598.75	Brown	60	32.0	330+	55.75 (56.17)	4.01 (4.55)	4.73 (4.68)	9.20 (9.00)
$[CoL_2]6H_2O$ ($CoC_{28}H_{36}N_2S_2O_{10}$)	683.85	Orange	60	35.0	220+	49.18 (49.18)	4.13 (5.31)	4.25 (4.10)	8.68 (8.62)
$[NiL_2]6H_2O$ ($NiC_{28}H_{36}N_2S_2O_{10}$)	683.63	Brown	60	44.0	310+	49.40 (49.19)	4.67 (5.31)	4.18 (4.10)	8.55 (8.59)
$[CuL_2]3H_2O$ ($CuC_{28}H_{30}N_2S_2O_7$)	633.40	Green	60	42.0	210+	48.91 (49.30)	3.97 (4.77)	4.47 (4.42)	10.02 (10.03)
$[ZnL_2]2H_2O$ ($ZnC_{28}H_{28}N_2S_2O_{8.}$)	617.84	Yellow	60	47.0	280+	53.78 (54.43)	4.49 (4.57)	4.98 (4.53)	10.49 (10.52)

+ = decomposition temperature; $*\Omega^{-1}\ cm^2\ mol^{-1}$

Table 2 Relevant infrared and electronic spectral data of the complexes

Compound	νOH	ν(C=N)	δC—H	ν(M—N)	ν(M—O)	Electronic transitions (kK)
HL	3404b	1625s 1587s 1543s	968m	-	-	28.25, 34.97, 40.32
$[ML_2]1.5H_2O$	3414b	1592s 1565s 1541s	769s	566s 528s	485s 421m	15.39, 22.37, 28.24, 34.84, 39.84
$[CoL_2]6H_2O$	3421b	1616s 1595s 1539s	783s	556s 528s	426m 414m	20.83, 22.37, 27.47, 39.84.
$[NiL_2]6H_2O$	3412b	1605s 1579s 1547s	755s	556s528s	471s 421m	14.47, 20.66, 28.09, 35.84, 38.61
$[CuL_2]3H_2O$	3500b	1598s 1571s 1541s	828s	552s526s	472m 428m	14.71, 19.60, 26.25, 31.55, 38.61
$[ZnL_2]2H_2O$	3418b	1597s 1568s	827m	556m 514m	494m 428s	26.18, 30.30, 39.37

Key: s = strong, m = medium, b = broad, s = strong; 1 kK = 1000 cm-1

Table 3 Zones of inhibition (mm) of the compounds against various bacteria isolates

Compounds	*S.aureus*	*E. coli*	*P. mirabilis*	*K.pneumoniae*
HL	15.0±0.1	R	R	R
$[ML_2]1.5H_2O$	11.0±0.0	R	R	R
$[CoL_2]6H_2O$	9.0±0.6	R	R	R
$[NiL_2]6H_2O$	R	R	R	R
$[CuL_2]3H_2O$	R	R	R	R
$[ZnL_2]2H_2O$	17.0±0.0	R	R	R
Sulfamethoxazole+	27.0±0.2	39.0±0.1	36.0±2.2	R

Results are expressed as means (± error) of two independent experiments; R = Resistance; + = positive standard.

Table 4 IC_{50} values of the ligand and its Cu(II), Zn(II) complexes against MCF-7 and HT-29 cells

Compounds	MCF-7(human breast adenocarcinoma) [μM]	HT-29(colon carcinoma cells) [μM]
CDDP(Cis-platin)	2.0	7.0
HL	>100	>100
$[CuL_2]3H_2O$	38.36±0.0	30.17±0.1
$[ZnL_2]3H_2O$	57.82 ± 0.2	89.99 ±0.0

Results are expressed as means (± error) of at least two independent experiments