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Synthesis, characterization and biopotency of some mixed ligand metal(ii) complexes of 4-amino-6-hydroxy-2-mercaptopyrimidine and 2,2'-bipyridine.

Aderoju A. Osowole*, Reuben O. Yoade

Inorganic Chemistry unit, Department of Chemistry, University of Ibadan, Ibadan, Nigeria.
Corresponding author email : *aderoju30@gmail.com*

ABSTRACT: Mn(II), Co((II), Ni(II), Cu(II), Zn(II), and Pd(II) complexes of mixed ligands, 4-amino-6-hydroxy-2-mercaptopyrimidine (L) and 2,2'-bipyridine (L^1) were synthesized and characterized by infrared and electronic spectroscopies, room temperature magnetic moment, molar conductance and melting point measurements. The molar conductance measurements in DMSO indicated that that the Pd(II) complex was 1:1 electrolyte, and the Ni(II) and Zn(II) complexes were 1:2 electrolytes. Infrared spectra showed that the ligands coordinated using N_4 chromophores. The electronic spectra and room temperature magnetic moments indicated that the Mn(II) and Co(II) complexes were dimeric, and the Cu(II), Zn(II), Ni(II) and Pd(II) complexes were monomeric octahedral /tetrahedral /square-planar. The *in-vitro* antibacterial activities of these metal complexes against *Bacillus cereus, Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa, Klebsiella oxytoca* and *Staphylococcus aureus* were moderate to very good with inhibitory zones range of 11.0-38.0 mm

Keywords: 2,2'-bipyridine, chromophores, broad-spectrum, geometry, pyrimidine,

Introduction

Pyrimidines have been known to be one of the most important six membered heterocyclic compounds containing two nitrogen atoms. They occur in the living system in form of nucleic acids (RNA and DNA), in anti-malaria drugs and folic acid (Falco et al.,1951, Hadjikakou et al., 2000, Koetzle and Williams,1976, Ma et al., 2005, Ruggeri et al., 1999). The chemistry of Pyrimidines has been of interest to many researchers including us due to their various biological activities such as antimicrobial, anticancer and HIV inhibitors (Hafez and El-Gazza, 2009, Sriram et al., 2005, Then, 1993). Similarly, bipyridines are of great interest to inorganic chemist because of their structural flexibility and potentials as antibacterial agents (Fedchuk et al., 2001, Katsarou et al., 2008). Some mixed ligand complexes of mercaptopyrimidines and their derivatives have been reported to be potent antibacterial, anticancer and antifungal agents (Agwara, 2010, Crepaldi et al., 2009, Romero-Molina et al., 1984, Williams et al., 1949). However, no work has been reported on the metal(II) complexes of mixed ligands 4-amino-6-hydroxy-2-mercaptopyrimidine (L) and 2,2'-bipyridine (L^1) (Crepaldi et al., 2009, Falco et al., 1951, Fedchuk et al., 2001, Hadjikakou et al., 2000, Hafez and El-Gazza, 2009, Katsarou et al., 2008, Koetzle and Williams,1976, Ma et al., 2005, Romero-Molina et al.,1987, Ruggeri et al.,1999, Sriram et al., 2005, Then,1993, Williams et al., 1949). In addition, our group have worked on various pyrimidinyl Schiff base metal(II) complexes which had good potentials as broad spectrum anticancer and antibacterial agents (Osowole and Akpan, 2012, Osowole et al., 2010, Osowole et al., 2011, Osowole et al., 2012). This work is new and is similar to two other papers that proceeded from our laboratory(Osowole and Oni, 2013, Osowole and Oni, 2013), as a continuation of our research activities on various metal(II) mixed ligands complexes of various amino Pyrimidines and Lewis bases, 2,2'-bipyridine/1,10-phenanthroline with interesting structures and biological properties. Thus, our aims are to synthesise the above mixed ligand

complexes and investigate their magnetic, electronic and structural properties. Their antibacterial properties against some pathogenic bacteria will also be verified.

Experimental

Materials

$CuCl_2.2H_2O$, $NiCl_2.2H_2O$, $Mn(NO_3)_2.6H_2O$, $PdCl_2.3H_2O$, $Zn(NO_3)_2..6H_2O$, $Co(COOCH_3)_2.4H_2O$, 4-amino-6-hydroxy-2-mercaptopyrimidine monohydrate and 2,2'-bipyridine were of reagent grade and purchased from Aldrich and were used as received. Solvents were distilled and dried before use.

Physical measurement

The solid reflectance and infrared spectra for the complexes were recorded on a Perkin-Elmer λ25 and Perkin Elmer FT-IR BX spectrophotometers respectively. Electrolytic conductivities in DMSO and melting points were determined using electrochemical analyser and Mel-Temp electro thermal machine respectively, while the room temperature magnetic measurements at 303K were done by using Sherwood Susceptibility balance MSB Mark 1.

Preparation of Metal(II) complexes

The metal(II) complexes were prepared by stirring a solution of 0.2 g (1.24×10^{-3} moles) of 4-amino-6-hydroxy-2-mercaptopyrimidine and 0.19 g (1.24×10^{-3} moles) of 2,2'-bipyridine in 50 ml of 70 % ethanol at 50°C. To the resulting homogeneous solutions, 0.212 g – 0.369 g (1.24×10^{-3} moles) of the hydrated metal(II) chlorides, nitrates and acetates (M = Cu, Ni, Mn, Pd, Zn and Co) were added dry in bits while stirring. The resulting solutions were buffered with 6 drops triethylamine and were refluxed for 3 h. The precipitates formed were filtered, washed with 70 % ethanol and dried under vacuum.

Antimicrobial Studies

Anti-bacteria susceptibility tests were carried out on the ligands and its metal(II) complexes using agar diffusion technique. The surface of Muller Hinton's agar in a Petri dish was inoculated uniformly with 0.3 mL of 18 h old test bacteria cultures.10 mg/mL solution of each complex in DMSO was added to a 9mm well bore unto the agar. The plates were allowed to stand on the bench for 30 minutes followed by incubation at 37°C for 24 h inhibitory zones were then measured as a measure of antibacterial activities of the complexes. The experiments were conducted in duplicates and streptomycin was used as a reference drug.

Results And Discussion

The generalized equations for the formation of the mixed ligand complexes are shown below:

$MCl_2.nH_2O + L + L^1 \rightarrow [M(L)(L^1)]Cl_2.aH_2O + bH_2O$ ----------(1)

(When M= Cu, n = a = b = 2; M = Ni, n = 2, a = 0, b = 2)

$PdCl_2.3H_2O + L + L^1 \rightarrow [PdCl(L)(L^1)]Cl.\ 2.5H_2O + 0.5H_2O$ ----------(2)

$Zn(NO_3)_2.6H_2O + L + L^1 \rightarrow [Zn(L)(L^1)](NO_3)_2 + 6\ H_2O$ ----------(3)

$2M(X)_2.\ nH_2O + 2L + L^1 \rightarrow [M(L)(X)_2]_2L^1.aH_2O + bH_2O$ ----------(4)

(When M= Mn, $X = NO_3^-$, n = a = 6, b =0; M = Co, $X = CH_3CO_2^-$, n =4, a = 2, b =2)

The formation of the complexes was confirmed by %metal which was in close agreement with the theoretical values with the exceptions of the Mn(II) and Co(II) complexes. Furthermore, the ligands, 4-amino-6-hydroxy-2-mercaptopyrimidine (L) and 2,2'-bipyridine(L^1) decomposed at 312 °C and melted at 66°C respectively whereas all the complexes decomposed in the range 206-256 °C confirming coordination. The %metal, colours, molar mass, m.pt, conductance and room temperature magnetic moments are present in Table 1.

Molar conductance measurements

The conductivities of all the complexes were done in DMSO with the exception of the Cu(II) complex which was done in ethanol. The Mn(II), Co(II) and Cu(II) complexes have very low molar conductance values between 5.34-13.82 $\Omega^{-1}\ cm^2mol^{-1}$ which indicated that they were non-electrolyte. However, the Pd(II) complex had a value of 51.5 $\Omega^{-1}cm^2mol^{-1}$ which was indicative of 1:1 electrolyte while Ni(II) and Zn(II) complexes with

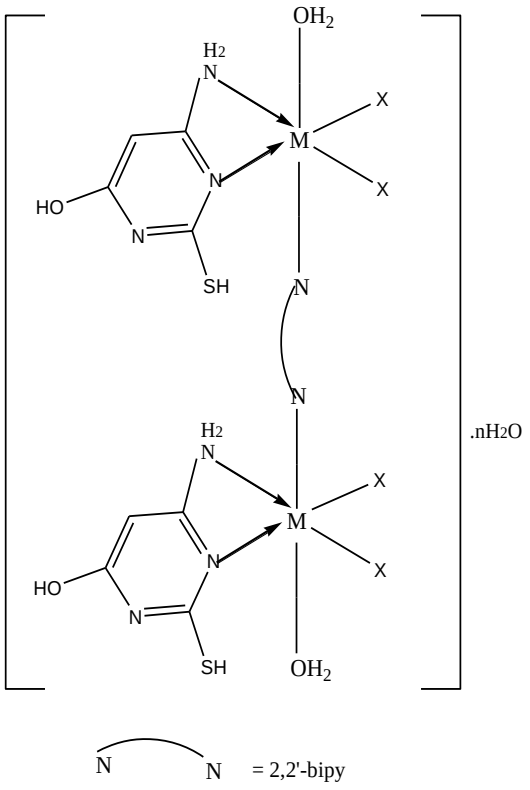
molar conductance values of 84.2 and 101.9 $\Omega^{-1}cm^2mol^{-1}$ were 1:2 electrolytes respectively. Literature had reported values in the range 51.5 - 59.2 $\Omega^{-1}cm^2mol^{-1}$ as 1:1 electrolytes while those within the range 84.2 – 101.9 $\Omega^{-1}cm^2mol^{-1}$ are 1:2 electrolytes (Geary, 1971).

Electronic spectra and magnetic moments

The electronic spectra data for the ligands and metal complexes are presented in Tables 2. The ultraviolet spectra of the compounds were characterized by two bands between 25.13 kK – 30.30 kK and 32.04 –39.22 kK assigned to n → π*, π → π*/charge transfer transitions respectively.

The spectra of the Mn(II) complex showed two absorption bands at 12.50 kK, and 15.78 kK typical of low spin octahedral geometry and were assigned to $^2T_{2g} \rightarrow {}^2A_{1g}$ and $^2T_{2g} \rightarrow {}^2B_{1g}$ transitions. An observed room temperature moment of 4.60 B. M was complimentary of low spin octahedral dimmer. A moment of about 2.0 B.M was reported for low spin Mn(II) (Figure 1, Sahar et al., 2000).

The Co(II) complex had two absorption bands at 17.86 kK and 25.52 kK assigned to $^2A_{1g} \rightarrow {}^2T_{1g}$ and $^2A_{1g} \rightarrow {}^2T_{2g}$ transitions respectively, typical of low spin octahedral geometry. An observed moment of 6.10 B.M was complimentary of a low spin octahedral dimmer, since a moment of about 3.0 B.M was reported for low spin octahedral Co(II) (Figure 1, Karipcin et al., 2010).



when M = Mn, X = NO_3^-, n = 2; M = Co, X = $CH_3CO_2^-$, n = 0

Figure 1. Proposed structure for the Mn(II) and Co(II) complexes

In this study, the Mn(II) and Co(II) complexes had moment's indicative of dimeric, low spin octahedral complexes (Figure 1). Thus, a dimeric structure was proposed in which the metal complexes were linked together by 2,2'-bipyridine, with each metal complex contributing to the overall magnetic moments. This we are unable to prove in the absence of viable crystals for single crystal X-ray structural investigation and facility for variable temperature magnetic moment measurement.

The Ni(II) complex had two bands at 17.97 kK and 24.51 kK assigned to $^3Ti\ (F) \rightarrow {}^3A_2(v_2)$ and $^3Ti\ (F) \rightarrow {}^3T_1(P)(v_3)$ transitions typical of tetrahedral geometry. This Ni(II) complex had a moment of 3.53 B.M

complimentary of tetrahedral geometry since moments in the range 3.4-4.2 B. M were documented for tetrahedral Ni(II) (Agwara, 2010, Saha et al., 2000).

The Cu(II) complex exhibited two transitions at 14.10 kK and 18.9 kK assigned to $^2E_g \rightarrow {}^2T_{2g}$ transition of a distorted octahedral geometry. An observed moment of 1.85 B.M was normal, indicative of mononuclear copper(II) complexes (Katsarou et al., 2008, Agwara, 2010).

The spectra of Zn(II) complex had only charge transfer transition from metal to ligand at 21.10 kK as no d – d transition is expected. The complex was expected to be diamagnetic because of its d^{10} configuration. However, a moment of 0.72 B.M was observed due to impurities/ polarization paramagnetism (Osowole et al., 2011).

The Pd(II) complex displayed two bands at 12.82 kK and 23.92 kK assigned to $^1A_{1g} \rightarrow {}^1B_{1g}$ and $^1A_{1g} \rightarrow {}^1E_{2g}$ transitions typical of four coordinate square planar geometry, and the complex was expectedly diamagnetic (Osowole and Akpan, 2012, Osowole et al., 2012).

Infrared spectroscopy

The relevant infrared bands of the complexes are presented in Table 2. The $\upsilon(NH_2)$/OH vibrations in the metal-free, 4-amino-6-hydroxy-2-mercaptopyrimidine (L) and 2, 2'-bipyridine(L^1) were observed at 3395 cm^{-1} and 3427 cm^{-1} respectively. These bands shifted in the metal complexes to 3367-3498 cm^{-1} indicating the coordination through the N donor atom of $\upsilon(NH_2)$ (Fedchuk et al., 2001, Katsarou et al., 2008). The υ(C=N) band in metal-free 4-amino-6-hydroxy-2-ligands (L) and 2, 2'-bipyridine (L^1) were observed at 1654 cm^{-1} and 1656 cm^{-1} respectively. These shifted to 1653-1657 cm^{-1} in the complexes indicating the involvement of N donor atom of υ(C=N) in coordination (Agwara, 2010). The υ(C=C) stretching frequency in the ligands was at 1423 cm^{-1} but it shifted to 1424-1425 cm^{-1} in the complexes due to coordination. In the metal(II) complexes, the bands due to υ(M-N) and υ(M-O) / ν(M-Cl) were observed in the range at 517-595 cm^{-1} and 356-381 cm^{-1} respectively. These bands were further evidence of coordination since they were not observed in the ligands (Romero-Molina et al., 1987).

Table 1. Analytical data for the metal complexes

Complex	Molar Mass	Colour	% Yield	% Metal		D.T (^oC)	^m ($\Omega^{-1}cm^2mol^{-1}$)	μeff (B.M)
				Exp	Theo			
L	161.18	Cream	-	-	-	312	-	-
L^1	156.18	White	-	-	-	*66	-	-
#$[Mn(NO_3)_2(L)]_2L^1.6H_2O$	944.41	Brown	30	9.67	11.63	256	9.68	4.60
$[Co(OAc)_2(L)]_2L^1.2H_2O$	868.61	Brown	30	11.05	13.57	227	5.34	6.12
$[Ni(L)(L^1)]Cl_2.2H_2O$	482.28	Green	40	11.92	12.02	250	84.2	3.53
$[PdCl(L)(L^1)]Cl.2.5\ H_2O$	539.74	Army Green	30	19.06	19.71	206	51.5	D
$[Cu(L)(L^1)Cl_2].2H_2O$	487.84	Army Green	50	13.06	13.02	240	+13.82	1.85
$[Zn\ L^1L^2](NO_3)_2$	506.73	White	40	12.53	12.83	252	101.9	0.72

Key: L = 4-amino-6-hydroxy-2-mercaptopyrimidine, L^1 = 2,2'-bipyridine, D.T= decomposition temperature, D = diamagnetic, * = melting point, Exp = Experimental, + = methanol, # = hygroscopic , ^m = molar conductance .

Antibacterial activities

The result of antimicrobial activities of the complexes against *B. cereus, E. coli, P. mirabilis, P. aeruginosa, K. oxytoca and S. aureus* are presented in Table 3. The metal(II) complexes were mostly more active than the metal-free pyrimidine ligand, whereas the metal complexes had varied antibacterial activity in comparison to 2,2'-bipyridine. Interestingly, the Mn(II) and Cu(II) complexes had better activities than both ligands being active against all the bacteria used with inhibitory zones range of 16.0-38.0 mm and 13.0-25.0 mm respectively. Thus, proving their potentials as broad-spectrum antibacterial agents. The better activities of some of the metal complexes against these bacteria was to chelation which reduces the polarity of the metal ion as a result of the partial sharing of its positive charge with the donor group and possible π – electron delocalization within the aromatic ring. This increases the lipophilic character of the complexes and

hence favouring its permeation through the lipid layers of the cell membrane (Agwara et al., 2010). The Co(II) complex was active against four organisms, that is, *E. coli, P. aeruginosa, K. oxytoca* and *S. aureus* with inhibitory zones range of 13.0-18.0 mm. Similarly, the Pd(II) complex was active against three organisms, *B. cereus, P. mirabilis* and *P. aeruginosa* with inhibitory zones range of 11.0-13.0 mm. The Ni(II) and Zn(II) complexes had activity against just two organisms *P. aeruginosa* and *S. aureus, B. cereus* and *S. aureus* with inhibitory zones range of 12.0 mm and 20.0-21.0 mm respectively. On ranking the antibacterial activities of the complexes against each organisms, an activity sequence was deduced in the order, Mn(II)~Cu(II) > Co(II) > Pd(II) > Zn(II) ~ Ni(II). Surprisingly, 2,2'-bipyridine showed higher activity than the standard drug (streptomycin) against the bacteria used with the exceptions of its activity against *P. aeruginosa* and *K. oxytoca* which were nil due to probable hydrogen bonding with the cellular content of the bacterial cell, thus causing their death(Osowole and Oni, 2013). In contrast, 4-amino-6-hydroxy-2-mercapto pyrimidine expectedly had lower activity than the standard drug, streptomycin, against the bacteria used with the exception of its activity against *S. aureus.*

Table 2. Electronic and Infrared Spectra of the metal complexes

Complex	υ(NH_2) /(OH)	υ(C=N)	υ(C=C)	υ(M-N)	υ(M-O) / ν(M-Cl)	Electronis spectra(kK)
L^1	3395b	1654s	1423m	-	-	30.30, 37.04
L^2	3427b	1656s	1423s	-	-	32.25, 38.46
$[Mn(NO_3)_2(L)]_2L^1.6H_2O$	3427b	1653s	1424s	573b	356m	12.5, 15.78, 32.26, 38.46
$[Co(OAc)_2(L)]_2L^1.2H_2O$	3498b	1656m	1425m	517b	365m	17.86, 25.52 33.56 39.22
$[Ni(L)(L^1)]Cl_2.2H_2O$	3367b	1652m	1424m	595b	374s	17.97,24.51,32.26, 38.48
$[Cu(L)(L^1)Cl_2].2H_2O$	3429b	1657m	1424s	593b	381m	12.82, 23.92 32.04, 38.46
$[Zn(L)(L^1)](NO_3)_2$	3436b	1653m	1424s	569b	356m	14.10, 18.90, 33.11, 38.46
$[[PdCl(L)(L^1)]Cl.2.5H_2O$	3428b	1657s	1424s	579b	377m	21.10, 32.68, 38.46

Key L =4-amino-2-mercaptopyrimidine, L^1 = 2,2'bipyridine s = strong, m = medium, b = Broad, 1kk = 1000 cm^{-1}

Table 3. Antibacterial of Mixed Ligand Complexes

Complexes	B. cereus	E. coli	P. mirabilis	P. aeruginosa	K. oxytoca	S. aureus
L	R	11.0±2.8	R	R	R	13.0±5.7
L^1	42.0±4.2	38.0±1.4	60.0±1.4	R	R	13.0±5.7
$[Mn(NO_3)_2(L)]_2L^1.6H_2O$	16.0±9.9	22.0±1.4	38.0±9.9	21.0±2.8	20.0±1.4	30.0±1.4
$[Co(OAc)_2(L)]_2L^1.2H_2O$	R	15.0±0.0	R	16.0±1.4	13.0±5.7	18.0±1.4
$[Ni(L)(L^1)]Cl_2.2H_2O$	R	R	R	12.0±4.2	R	12.0±4.2
$[Cu(L)(L^1)Cl_2].2H_2O$	20.0±7.1	16.0±1.4	22.0±4.2	13.0±5.7	17.0±2.8	25.0±2.8
$[Zn(L)(L^1)](NO_3)_2$	20.0±7.1	R	R	R	R	21.0±2.8
$[PdCl(L)(L^1)]Cl.2.5H_2O$	13.0±5.7	R	12.5±4.9	11.0±2.8	R	R
Streptomycin	40.0±1.4	35.0±0.0	37.0±0.0	36.0±1.4	22.0±1.4	R

Key: L =4-amino-2-mercaptopyrimidine , L^1 = 2, 2'- bipyridine, R = Resistance

Conclusion

Mn(II), Co((II), Ni(II), Cu(II), Zn(II), and Pd(II) mixed ligand complexes of 4-amino-6-hydroxy-2-mercaptopyrimidine (L) and 2,2'-bipyridine(L^1) had geometries in the range 4-coordinate, tetrahedral to 6-coordinate, octahedral geometry. The molar conductance measurements in DMSO indicated that that the Pd(II), Ni(II) and Zn(II) complexes were 1:1/1:2 electrolytes and the remaining complexes were covalent. The *in-vitro* antibacterial activities of these metal complexes against *Bacillus cereus, Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa, Klebsiella oxytoca* and *Staphylococcus aureus* were moderate to very good with inhibitory zones range of 11.0-38.0 mm.

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