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Synthesis, characterization and antibacterial activities of some metal(II) complexes of 4-amino-2,6-dichloropyrimidine.

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ABSTRACT: The metal(II) complexes of 4-amino-2,6-dichloropyrimidine (L) have been synthesized and characterized by IR and electronic spectroscopies, percentage metal, magnetic moments, conductance and melting point measurement{where M = Mn, Fe, Co, Ni, Cu and Zn}. The ligand coordinates to the metal ions in the ratio 2L: 1M, through the nitrogen atoms of the pyrimidine ring and the amino group. The electronic spectra and room temperature magnetic measurements were consistent with the adoption of a 6-coordinate octahedral geometry for Fe(II) and Ni(II) complexes while Mn(II), Cu(II),Co(II) and Zn(II) complexesassume a 4-coordinate square-planar/ tetrahedral geometry.The conductance measurements in DMSO showed that the Fe(II) complex was covalent, the Ni(II) complex wasa 1:1 electrolyte and the remaining metal complexes were 1:2 electrolytes respectively. The in-vitro antibacterial studies revealed that the Co(II) complex had a broad-spectrum antibacterial activity against Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus with inhibitory zones range of 11.0-25.0 mm proving its potential usefulness as a broad-spectrum antibacterial agent.

Keywords: antibacterial, broad-spectrum, covalent, geometry.

Introduction

Pyrimidine is the parent heterocyclic of a very important group of compounds that occurs in living system. They are considered simple as far as their interactions with metal ion are concerned since they possess fewer coordination sites (Reddy and Reddy, 2000). Pyrimidine derived metal ion complexes have been studied in recent years (Ahmed et al., 2011, Ajibade and Idemudia, 2011; Beyramabadi etal., 2011, Gulcan et al., 2012, Hitchings and Smith, 1980, Jin et al., 2011, Khan and Asnani, 2011, Masoud et al., 2003, Masoud et al., 2008, Mostafa and badria, 2008, Onal et al., 2011), owning to their numerous biological activities ranging from antimalaria, antiviral, antibacterial, antitumor and antifungal(Reddy and Reddy, 2000, Roy et al., 2007, Sakthilatha and Rajavel, 2013) which often have been related to their chelating ability with trace metal ions. There are some literatures on metal (II) complexes of trimethoprim, pyrimethamine, various pyrimidineand pyrimidinyl Schiff base chelates (Onal et al., 2011, Osowole and Akpan, 2012, Osowole et al., 2010, Osowole et al., 2011, Osowole et al., 2012, Osowole and Ott, 2012, Reddy and Reddy, 2000, Roy et al., 2007, Sakthilatha and Rajavel, 2013). However, no work has been reported on of metal(II) complexes of 4-amino-2,6-dichloropyrimidine. Thus, our aim is to synthesize, characterize and investigate the magnetic properties of these novel metal(II) complexes for possible magnetic interactions such as antiferromagnetism, and their antibacterial properties will also be investigated for potentials as broad-spectrum antibacterial agents in-vitroas a continuation of the research activities of our group on metal-based therapeutics agents(Osowole and Akpan, 2012, Osowole et al., 2010, Osowole et al., 2011, Osowole et al., 2012, Osowole and Ott, 2012).

Experimental

Materials And Physical Measurement

Reagent grade 4-amino-2,6-dichloropyrimidine, Manganese(II)chloride tetrahydrate, Iron(II) sulphate heptahydrate, Cobalt(II)chloride hexahydrate, Nickel(II) chloride hexahydrate, Copper(II)chloride dihydrate, and Zinc(II)nitrate hexahydrate were obtained from Aldrich and BDH chemicals, and were used as received. Solvents were purified by distillation.

Melting pointswere obtained with Mel-Temp electrothermal machine and molar conductivity measurement (10^{-3} M solutions in DMSO) was obtained using electrochemical analyzer. Solid reflectance spectra of the complexes were recorded on a Perkin-Elmer λ20 UV-VIS spectrophotometer and infrared spectra were recorded as KBr disc on a Perkin-Elmer FT-IRspectrum BX spectrometer in the range 4000-400 cm^{-1}. The room temperature magnetic susceptibilities were measured on a Sherwood Susceptibility balance MSB Mark1 at 303K.

Preparation of Metal(II) complexes

The various complexes were prepared by refluxing homogeneous coloured solutions of 2.44×10^{-3}mole (0.40 g) 4-amino-2,6-dichloropyrimidine and 1.22×10^{-3} moles (0.21-0.29 g) of hydrated metal(II) chloride, to which 3 drops of triethylamine were added in 30 mL of ethanol for 3 hours. The precipitated solids were filtered under suction, washed with ethanol and dried over silica gel [M = Cu(II), Mn(II), Ni(II) and Co(II)]. Similar procedure was used to isolate the Zn(II) and Fe(II) complexes from their nitrate and sulphate salts.

Antibacterial assay

The assay was carried out on the ligand and its metal(II) complexes using the agar diffusion technique. The surface of the agar in a petri dish was uniformly inoculated with 0.2 mL of 18 hour old test bacterial culture of Bacillus cereus, Escherichia coli, Proteus mirabilis, Pseudomonia aureginosa, Klebsiella oxytoca and Staphylococus aureus. Using a sterile cork borer, 9 mm wells were bored into the agar. Then 0.06 mL of 10 mg/mL concentration of each metal complex in DMSO was introduced into the wells and the plates were allowed to stand on the bench for 30 minutes before incubation at 37^{0}C for 24 hours after which inhibitory zones (in mm) were taken as a measure of antibacterial activity. The experiments were conducted in duplicates and Streptomycin was used as the reference drug.

Results And Discussion

The reaction of the 4-amino-2,6-dichloropyrimidine (L) with the metal(II) chlorides (Mn, Co, Ni and Cu) , $FeSO_4.7H_2O$ and $Zn(NO_3)_2.6H_2O$ gave coloured complexes in moderate good yields (30-50%) according to equations 1- 4.

$MCl_2.6H_2O + 2L \rightarrow [M(L)_2]Cl_2.xH_2O + bH_2O$ -------------------------------- (1)

(when M = Mn{x = 1, b = 5}, Co, { x = 6, b = 0}; Cu{x = 0, b =6})

$NiCl_2.6H_2O + 2L \rightarrow [Ni(L)_2Cl(H_2O)]Cl + 5H_2O$ -------------------------------- (2)

$FeSO_4 \cdot 6H_2O + 2L \rightarrow [Fe(L)_2SO_4] + 6H_2O$ --------------------------------- (3)

$Zn(NO_3)_2. 6H_2O + 2L \rightarrow [Zn(L)_2](NO_3)_2 + 6H_2O$ --------------------------------- (4)

The ligand had a decomposition temperature of 230^{0}C, whereas its metal complexes decomposed in the range154-196^{0}C, confirming coordination. The complexes were all slightly soluble in water, methanol, ethanol, nitromethane and methylene chloride but are soluble in DMSO. The analytical data, colours, % metal, %yields, melting points, molar conductivity and room temperature magnetic moments for the complexes are presented in Table 1.

Conductance Measurements

The molar conductance value of 65.0 $\Omega^{-1}cm^2mol^{-1}$ for the Ni(II) complex and values in the range of 89.6- 111.9 $\Omega^{-1}cm^2mol^{-1}$ for the remaining complexes with the exception of the Fe(II) complex were indicative of 1:1 and 1:2 electrolytes respectively, since values in the range 50.0-80.0 and 85.0-120.0 $\Omega^{-1}cm^2mol^{-1}$ have been reported for 1:1 and 1:2 electrolytes (Figure 1, Reddy and Reddy, 2000).

Electronic Spectra and Room Temperature Magnetic Moments

The relevant UV/visible data are presented in Table 2. The ultraviolet spectra of the compounds were characterized by two peaks between 33.11 - 35.71 kK and 40.0 kK respectively, assigned to $\pi \rightarrow \pi^*$ and charge transfer respectively. The Mn(II) complex showed two absorption bands at 19.23 kK and 23.92 kK assigned to ${}^4A_{1g} \rightarrow {}^4E_g$ and ${}^4A_{1g} \rightarrow {}^4B_{1g}$ transitions of 4-coordinate square-planar geometry(Masoudet al., 2003, Onal et al., 2011). A moment of 3.70 B.M was complimentary of this geometry since spin = 3/2.

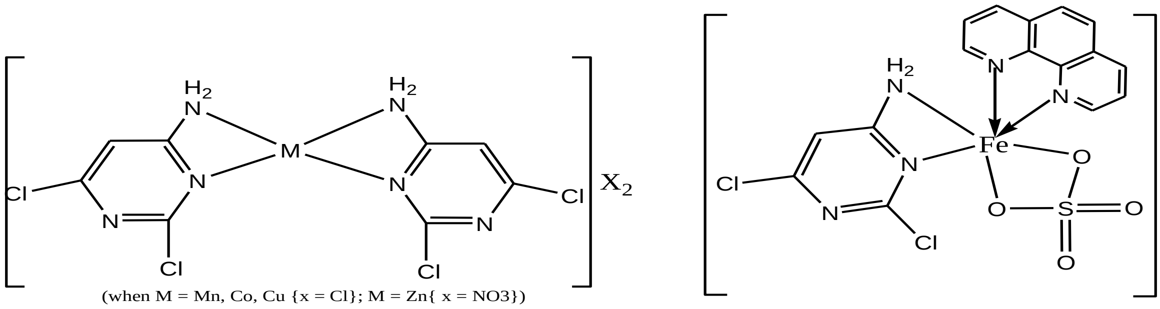
The Fe(II) complex had a lone band 24.88 kK typical of a 6-coordinate octahedral geometry, with the band assignment ${}^5T_{2g} \rightarrow {}^5E_g$ transitions. A moment of 5.0-5.5 B. M is usually observed for Fe(II) complexes due to orbital contribution and spin-orbit coupling. In this study, the Fe(II) complex moment was 4.71 B. M. indicative of spin cross over from a high spin octahedral to low spin octahedral forms(Salmon et al., 2009). However, we could not probe this further due to lack of facilities for variable temperature magnetic susceptibility measurements.

The electronic spectrum of the Co(II) complex displayed two absorption bands at 13.16 kK and 18.80 kK assigned to $^4A_2 \rightarrow ^4T_1(F)$ and $^4A_2 \rightarrow ^4T_1(P)$ transitions respectively, typical of a 4-coordinate tetrahedral geometry. An observed moment of 4.50 B.M was complementary of tetrahedral geometry since moments in the range 4.2-4.6 B.M is usually observed for tetrahedral Co(II) compounds(Jin et al., 2011, Osowole et al., 2010).

The Ni(II) complex displayed two absorption bands at 12.50 kK and 23.26 kK typical of an octahedral geometry and were assigned to $^3A_{2g} \rightarrow ^3T_{2g}$ (v_1)and $^3A_{2g} \rightarrow ^3T_{1g}$ (v_2) transitions. Generally, square planar Ni(II) complexes are diamagnetic while octahedral and tetrahedral complexes are paramagnetic with moments in the range 2.90-3.40 B.M and 3.50- 4.10 B.M respectively. The Ni(II) complex in this study had a moment of 3.40 B.M. and hence it was octahedral(Khan and Asnani, 2011, Masoud et al., 2008).

The Cu(II) complex exhibited a band at 23.92 kK which was suggestive of a 4-coordinate square-planar geometry with the band assignment $^2B_{1g} \rightarrow ^2E_{1g}$ transition, because tetrahedral Cu(II) complexes usually have a single absorption band below 10.0 kK. A moment of 1.9-2.2 B.M. is usually observed for mononuclear copper(II) complexes, regardless of stereochemistry, expectedly higher than the spin only moment due to orbital contribution and spin-orbit coupling(Mostafa and Badria, 2008, Osowole et al., 2012) . Thus, a moment of 1.89 B.M indicated that the Cu(II) complex was mononuclear.

The Zn(II) complex had no d-d band expectedly due to its d^{10} configuration, and was expectedly diamagnetic with a tetrahedral geometry (Osowole et al., 2012).



(a) (b)

Figure 1. Proposed structures for of the metal(II) complexes

Infrared Spectra

The relevant infrared data are presented in Table 2. The ligand, 4-amino-2,6-dichloropyrimidine (L), showed characteristic bands at 3487 and 3309 cm^{-1} due to $\upsilon_{as}(NH_2)$ and $\upsilon_s(NH_2)$(Hitchings and Smith, 1980, Khan and Asnani, 2011). The bands at 1653 and 1580 cm^{-1} were attributed to $\upsilon(C=N)$ vibrations (Ahmed et al., 2011). The spectra of the complexes were compared with that of the free ligand to confirm coordination. The $\upsilon(NH_2)$ bands shifted to 3519 - 3364 cm^{-1} in the spectra of the complexes indicating the coordination of the amino group's nitrogen to the metal(II) ions (Beyramabadi et al., 2011). The azomethine vibration of the ligand at 1653 cm^{-1} and 1580 cm^{-1} shifted to 1657 - 1654 cm^{-1} and 1587 - 1582 cm^{-1}(Gulcan et al., 2012) in the metal complexes, confirmed the coordination of the imine nitrogen to the metal(II) ions. The bands observed in the range 373 - 388 cm^{-1} and 535 - 580 cm^{-1}, were assigned as υ(M-O)/ υ(M-Cl) and υ(M-N) respectively, a further evidence of coordination. These bands were absence in the spectrum of 4-amino-2,6-dichloropyrimidine (Gulcan et al., 2012, Reddy and Reddy, 2000).

Antibacterial activities of the ligand and its metal(II) complexes

The antibacterial activities of the ligand and its complexes against Bacillus cereus, Escherichia coli, Proteus mirabilis, Pseudomonas aureginosa, Klebsiella oxytoca and Staphylococcus aureus are presented in Figure 2 and Table 3. The ligand, 4-amino-2,6-dichloropyrimidine and its Fe(II) complex had no activity against all the bacteria used.Generally, the remaining metal complexes were more active(moderately/weakly) than the ligand expectedly due to chelation, which reduced the polarity of the metal atom, mainly because of partial sharing of its positive charge with donor groups of the ligand and possible π-electron delocalisation on the aromatic rings. This increased the lipophilic character, favouring its permeation into the bacterial membrane, causing the death of the organisms (Willy et al., 2008).

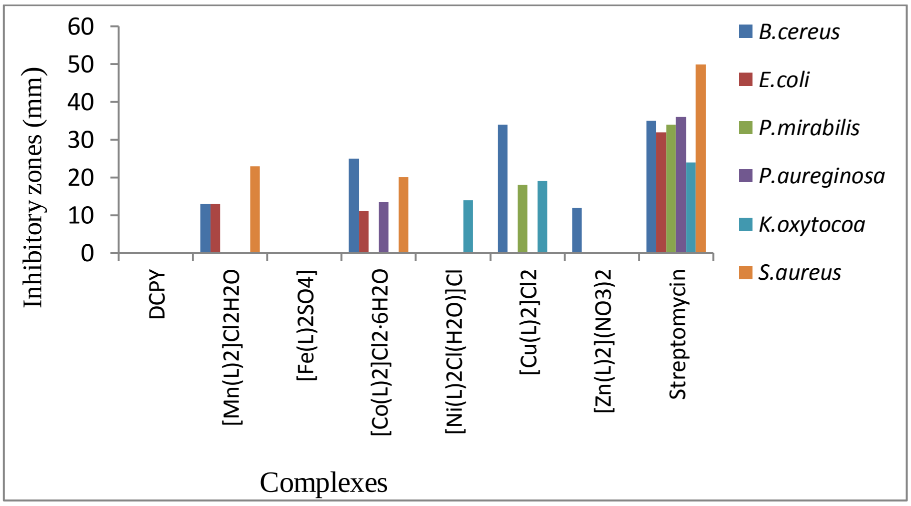


Figure 2. Histogram of the antibacterial activities of the ligand and its complexes

All the metal(II) complexes were inactive against Proteus mirabilis and Pseudomonasaeruginosa with the exceptions of Cu(II) and Co(II) complexes with inhibitory zones of 18.0 and 13.5 mm respectively. Similarly, all the complexes were inactive against Escherichia coli with the exceptions of Mn(II) and Co(II) complexes with inhibitory zones of 13.0 and 11.0 mm respectively. The inactivity of the ligand and some its metal complexes was attributed to their probable lipophobic nature. The resistance of Klebsiella oxytocoa to Mn(II), Fe(II), Co(II) and Zn(II) complexes was attributed to its ability to produce extended-spectrum beta-lactamase (ESBL) which inactivate the metal complexes(Willy et al., 2008). In addition, the Mn(II) and Co(II) complexes were active against Staphylococus aureus with inhibitory zones of 23.0 and 20.0 mm respectively.

Furthermore, Cu(II), Mn(II), Co(II) and Zn(II) complexes had activity against Bacillus cereus with inhibitory zones range of 12.0 - 34.0 mm.In all cases, the antiobiotic, streptomycin, was more active expectedly than the metal complexes with the exception of the Cu(II) complex (34.0 mm) which had almost the same activity activity to the antibiotic (35.0 mm) against B. cereus. Its interesting to note that the Co(II) complex had a broad-spectrum antibacterial activity against Bacillus cereus, Escherichia coli, Pseudomonas aureginosa and Staphylococcus aureuswith inhibitory zones range of 11.0-25.0 mm proving its potential usefulness as a broad-spectrum antibacterial agent.

Table 1 . Analytical data of the Ligands and their metal(II) complexes.

Complexes	Formula Mass	Colour	D. T (^{o}C)	%Metal (Exp)	$^\wedge_m$ ($\Omega^{-1}cm^2mol^{-1}$)	%Yield	μ_{eff} (B.M)
L	163.99	White	230	-	-		
$[Mn(L)_2]Cl_2. H_2O$	471.83	Brown	196	11.73 (11.64)	95.4	30	3.70
$[FeSO_4(L)_2]$	479.85	Brown	188	11.45 (11.64)	6.92	50	4.71
*$[Co(L)_2]Cl_2 \cdot 6H_2O$	565.91	Light pink	154	10.03 (10.41)	103.8	40	4.50
$[Ni(L)_2Cl(H_2O)]Cl$	475.57	Green	190	12.47 (12.34)	65.0	50	3.40
$[Cu(L)_2]Cl_2$	462.42	Green	160	13.30 (13.73)	89.6	50	1.89
$[Zn(L)_2](NO_3)_2$	517.35	White	170	12.30 (12.57)	111.9	45	D

Key: L = 4-amino-2,6-dichloropyrimidine, Exp = experimental, D.T = Decomposition temperature, * = hygroscopic.

Table 2. Infrared and electronic spectra data of the complexes

Compound	$\upsilon(NH_2)$/ $v(OH)$	$\upsilon(C=N)$	$\upsilon(M\text{-}N)$	$\upsilon(M\text{-}O)$/ $\upsilon(M\text{-}Cl)$	Electronic spectra (kK)
L	3487m 3309s	1653s 1580s	-	-	33.11, 35.71
$[Mn(L)_2]Cl_2.\ H_2O$	3437m 3500b	1657s 1587	549m	373s	19.23 , 23.92, 35.71, 40.0
$[FeSO_4(L)_2]$	3447m	1656s 1582s	549m	376s	24.88, 35.71
$[Co(L)_2]Cl_2 \cdot 6H_2O$	3424b 3500b	1654s	550m	380m	13.16, 18.80, 35.71
$[Ni(L)_2Cl(H_2O)]Cl$	3456m	1656s 1584s	572m	377s	12.50, 23.26, 35.71
$[Cu(L)_2]Cl_2$	3446m	1657s 1584s	535m	-	23.92 , 35.71
$[Zn(L)_2](NO_3)_2$	3519m 3365m	1656s 1584m	580b	388s	34.72

Key: 1kK = 1000 cm^{-1}, m = medium, s = strong, b = broad, w = weak.

Table 3 . Zones of Inhibition (mm) of the compounds against various microbes

Complexes	B. cereus	E. coli	P. mirabilis	P.aureginosa	K. oxytocoa	S. aureus
L	R	R	R	R	R	R
$[Mn(L)_2]Cl_2.\ H_2O$	13.0±0	13.0±0	R	R	R	23.0±0
$[Fe(L)_2SO_4]$	R	R	R	R	R	R
$[Co(L)_2]Cl_2 \cdot 6H_2O$	25.0±2.8	11.0±0	R	13.5±2.1	R	20.0±1.4
$[Ni(L)_2Cl(H_2O)]Cl$	R	R	R	R	14.0±1.4	R
$[Cu(L)_2]Cl_2$	34.0±1.4	R	18.0±1.4	R	19.0±0	R
$[Zn(L)_2](NO_3)_2$	12.0±4.2	R	R	R	R	R
Streptomycin	35.0±0	32.0±4.2	34.0±1.4	36.0±1.4	24.0±1.4	50.0±1.4

R = resistance

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Conclusion

The metal(II) complexes of 4-amino-2,6-dichloropyrimidine (L) {where M = Mn, Fe, Co, Ni, Cu and Zn} were found to be either square-planar/tetrahedral/ octahedral in geometry as corroborated by electronic and IR spectra measurements. Furthermore, the conductance measurements in DMSO showed all were 1:1 /1:2 electrolytes with the exception of the Fe(II) complex, which was covalent. The in-vitro antibacterial studies revealed that the metal complexes mostly had moderate to weak antibacterial activities.

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