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Full Length Research Paper

Synthesis, physical properties, antimicrobial potentials of some mixed antibiotics complexed with transition metals and their effects on alkaline phosphatase activities of selected rat tissues

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Mixed ligand metal complexes of chloramphenicol and oxytetracycline were prepared by using Ni(II), Co(II) and Fe(III) metal chloride hexahydrate. They were characterized based on some physical technique and spectroscopic analysis such as AAS, UV, and IR spectroscopy. Based on the analytical and spectroscopic data, the complexes were proposed to have the formulae $[ML_1L_2](Cl)_n$ (where M = Ni(II), Co(II), Fe(III); L_1 = chloramphenicol, L_2 = oxytetracycline and n = 2 - 3). IR spectra suggested that both L_1 and L_2 coordinated to the metal ions in a terdentate manner with ν(O-H), ν(C=O) and ν(N-H) as donor sites in each of the ligands. The complexes were proposed to be of octahedral. The synthesized complexes, in compares to their ligands, were screened for their antibacterial activity against isolated strains of *Escherichia coli*, *Staphylococcus aureus* and *Klebsiella pneumonia* by using diffusion method. The activity data showed the metal complexes to be more potent antibacterial than the parent drugs against the three species. Toxicology tests against some tissues of albino rat (*Rattus novergicuss*) revealed toxicity of the complexes as compared to the parent drugs. Ni(II) complex was found to possess no significant difference ($P > 0.05$) in alkaline phosphatase from both homogenates of liver and kidney and rat serum. However, Co(II) and Fe(III) complexes were found to significantly increase ($P < 0.05$) alkaline phosphatase from homogenates of liver and kidney tissues of the tested doses but there was no significant difference ($P > 0.05$) in alkaline phosphatase from rat serum.

Key words: Metal complexes, complexation, antibiotics, antimicrobial properties, alkaline phosphatase.

INTRODUCTION

Metal metabolism is emerging as an exciting area of cell biology and a potential site for therapeutic intervention. The discovery of new metal based drugs has been largely based on cell and compounds that binds to DNA. Inorganic compounds have had an enormous important In medicine (Paul and Giann, 2006; Mohamed et al ., 2006). The development of metal based drugs that have more efficacy than the parent's drugs has been under investigation over the last thirty years (Jian et al., 2006; Mehmet et al., 2006). Literally, thousands of com-pounds have been prepared based on well conceived ideas to improve their efficacy and have been subsequently screened but few of them have successfully passed clinical tests (Paul and Giann, 2006). Oxytetracycline and chloramphenicol has gained recognition as anti-biotics used in the prevention of wide range of infections. They are active against gram-negative and gram-positive micro-organisms (Mayne, 1999). Due to increased in the development of resistance by micro-organisms to these

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antibiotics and unrealistically large doses of the drugs required for treatment of infections, more ideal drugs with enhanced activities with improved physical and bioavailability properties are urgently needed to replace these antibiotics. Efficacies of some therapeutics agents have been reported to have increased upon coordination to transition metals (Ogunniran et al., 2007; El-Ajaily et al., 2007). Some metal-based antibiotics such as bleo-mycin, streptonigrin, and bactracin have gained recogni-tion and are more effective than pure drugs (Li-june, 2003). Possible replacement of the present drugs is focused on metal-based drugs.

In continuation of our effort to find new chemotherapic agents in this class of compounds, we decided to prepare noble mixed ligands metal complexes of chloramphenicol and oxytetracycline. Our previous works (Ogunniran et al., 2007) confirmed the increased inhibitory activity single ligand metal complexes of these antibiotics against pathogenic micro-organisms used. However, the compounds were found to be toxic at the dosage level used. Thus, we report mixed ligands metal complexes of chloramphenicol and oxytetracycline. The study was aimed at isolation of transition metal complexes, structural elucidation using various physicochemical techniques and their biological screening against human pathogenic micro-organisms. The present work intends to incorporate two different ligands (chloramphenicol and oxytetracycline) into a metal complex with the aim of possible availability of more potent dual character antibiotic.

MATERIALS AND METHODS

Sources of materials

All the chemicals used were analytical grade reagents (Sigma). Oxytetracycline and chloramphenicol HCl were obtained from Rajrab pharmaceutical Company, Ilorin, Kwara state, Nigeria. They are product of Sigma Company, London. The metal salts used for complexation [iron (III) chloride hexahydrate, nickel (II) chloride hexahydrate, and cobalt (II) chloride hexahydrate] were obtained from British Drug House Chemical Limited Co. Poole, England. Alkaline phosphatase assay kit was obtained through Biochemistry Department, University of Ilorin, Nigeria from Randox Laboratories Limited Co. Antrim, United Kingdom, Isolates of *Escherichia coli*, *Klebsiella pneumonial* and *Staphylococcus aureus* were obtained from the Department of Microbiology, University of Ilorin, Nigeria, Albino rats (*Rattus novergicuss*) were obtained from the Department of Biochemistry, University of Ilorin, Nigeria.

Synthesis of the metal complexes

0.01 M (3.231 g) of chloramphenicol dissolved in 10 ml of distilled water was mixed with 0.01 M (4.604 g) of oxytetracycline hydrochloride in 10 ml of distilled water. The solution formed was mixed with the solution of each metal salts (0.01 M in 10 ml of distilled water) in a round bottom flask fitted with a condenser. The reaction mixture was refluxed for 4 h after which it was cooled using iced blocks. The crystalline precipitates that were separated after putting it on the bench for 48 h were filtered, washed thoroughly with distilled water and dried in a desiccator's.

Determination of physical properties of the complexes

The physical properties of the compounds were investigated. The melting points of the compounds were determined by using Gallenkamp melting point apparatus and were uncorrected. The electrical conductivity measurement (Λ_m, reported as $\Omega^{-1}cm^2mol^{-1}$) of metal complexes in methanol were taken with a Crimson CDTM 522 conductometer at room temperature. Molecular weight determi-nations (MW) were performed at 40°C with a Knaver KNA0280 vapour pressure osmometer calibrated with benzyl. The solvents were Baker analysed spectrophotometer grade chloroform or acetone. The results were reproducible to ± 2%.The metal content of the metal complexes were determined using an SP Pye Unicam Atomic Absorption Spectrophotometer. Infra-red spectra (KBr) were measured using Perkin-Elmer FT-IR instrument from 4000 to 600 cm^{-1}. UV spectra (MeOH) were obtained on a LKB 4053 spectrophotometer. Purity of the compounds was confirmed by using Thin Layer Chromatography (TLC).

Antibacterial screening

Antibacterial activities of the antibiotics and mixed ligands metal complexes were studied against three human pathogenic bacterial viz: *E. coli*, *K. pneumonia* and *S. aureus*. For the detection of the antibacterial activities, the filter paper disc diffusion method (Pal and Marika, 2004; Abd El and El-Sariag, 2004) was used. Both chloramphenicol and oxytetracycline were used separately as standard for antibacterial activities test. Nutrient agar (NA) was used as basal medium for the cultured bacterial. The agar media were innoculated with 0.5 ml of 24 h liquid cultures containing 10^7 micro-organisms/ml. Diffusion was down for 24 h at 5°C for all bacterial while incubation was done for 12 h at 37°C. Discs with only methanol were used as control. Inhibitory activity was measured (mm) as the diameter of the observed inhibition zone. The antibacterial activities were based on percentage inhibition calculated by using the average diameter of bacterial colony on the growth medium compared with their respective control.

Treatment of animals

A total of thirty albino rats of Wistar strain weighing between 160 – 180 g, housed in clean metabolic cages contained in well-ventilated house conditions (Temp. 28 - 31°C); photoperiod: 12 h natural light and 12 h dark; humidity:50 - 55%) were allowed free access to rat pellets (Bendel Feeds and Flour Mill, Ewu, Nigeria) and tap water. They were randomly categorised into six groups consisting of five animals each. Animals in group A serve as the control and received distilled water, whereas groups B and C were respectively administered with chloramphenicol and oxytetracycline only, while groups D, E, and F were administered accordingly with $Co(CHL)(OXY)Cl_2$, $Ni(CHL)(OXY)Cl_2$ and $Fe(CHL)(OXY)Cl_3$. The distilled water and solution of metal complexes (1 cm^3) were administered orally to the rats in the various groups three times daily for 5 days at the dose level of 3.33 mg kg^{-1} body weight. All the rats were sacrificed after five days of treatment and blood samples were collected in dry and clean tubes.

Preparation of serum and tissue homogenates

The method described by Yakubu et al. (2005) was modified and used to prepare the serum. The rats under ether anesthesia were made to bleed and blood collected into clean, dry centrifuge tube after which they were left for 10 min at room temperature. The tubes were then centrifuged for 15 min using Uniscope Laboratory Centrifuge (Model SM 800B, Surgifriend Medicals Essex, England).

Table 1. Some physical properties of the ligands/metal complexes.

Compounds	Colour (form)	Melting point (^oC)	Conductivity($\Omega^{-1}cm^{2m}mol^{-1}$) methanol (solvent)
Chloramphenicol (CHL)	White powder	151-152	9.9×10^{-7}
Oxytetracyclinel (OXY)	Yellow powder	199-201	4.3×10^{-7}
Ni(CHL)(OXY)Cl_2	Light green (crystal)	209 (Decomposed)	8.2×10^{-6}
Co(CHL)(OXY)Cl_2	Green (crystal)	198 (Decomposed)	11.5×10^{-5}
Fe(CHL)(OXY)Cl_3	Dark brown (shinning powder)	199 (Decomposed)	11.5×10^{-5}

Table 2. Yeild (%) of the metal complex of chloramphenicol (CHL) mixed with oxyetracycline (OXY) and their proposed structural formulae.

Ligands + metal salt	% Yield	Molecular mass [m.wt/g] theoretical (Exp.)	Metal content (%) theoretical (Exp)	Proposed Structural formulae
$NiCl_2$ + CHL + OXY	44.8	1050.59 (1049.70)	7.32 (7.40)	Ni(CHL)(OXY)Cl_2
$CoCl_2$ + CHL + OXY	46.5	776.19 (772.12)	7.34 (7.37)	Co(CHL)(OXY)Cl_2
$FeCl_3$ + CHL + OXY	51.1	1083-18 (1081.31)	6.69 (7.03)	Fe(CHL)(OXY)Cl_3

The sera were thereafter aspirated using pasteur pipettes into clean, dry sample bottles and kept at a temperature of -10^{o}C overnight. The rats were quickly dissected and the liver and kidneyorgans were removed. The kidneys were encapsulated after which the organs were blotted in tissue paper and weighed. The tissues were homogenized separately in 0.25 M sucrose solution (1:5 w/v). The homogenates were stored in a temperature of -10^{o}C for 24 h before being used for the estimation of alkaline phosphatase activities.

Estimation of enzyme activity

The activities of alkaline phosphatase concentration in the serum and homogenate of both liver and kidney were estimated using the method described by Wright et al. (1972).

Statistical analysis

Statistical significance was determined using Duncan Multiple Range Test and values were considered statistically significant at $P < 0.005$.

RESULTS AND DISCUSSION

Table 1 confirmed that the complexes are of various colours with varied state. The Ni(II) complex [Ni(CHL)-(OXY)Cl_2] appeared as light green crystal com-pound. Co(II) complex [Co (CHL)(OXY)Cl_2] is a greenish crystal compound while Fe(III) complex [Fe(CHL)(OXY)Cl_3] is a dark brown shinning powder. The yields (%) of the complexes are averagely commendable. [Fe(CHL)(OXY)Cl_3] has the highest % yield of 51.1 while Ni(II) complex has the lowest yield of 44.8%. The results obtained from micro analytical measurements and metal estimation data (Tables 1 and 2) confirm the stoichiometry of the complexes and suggest the formation of the complexes as per the equation below. Theoretical metal content (%) and molecular weight (g) obtained were found to compete favourably to experimental values obtained. The complexes are non-hygroscopic, air and photo stable crystalline powder with different melting point ranging from 199 - 209^{o}C. The melting points of the complexes are higher than their respective antibiotics. The results of the conductivity measurements (Table 1) in methanol re-vealed that the complexes are non-electrolyte. The solubility of the metal-complexes in various solvents (Table 3) confirmed the diversity of the complexes as the ligands. The complexes were found to be slightly soluble in distilled water and ethanol but were completely soluble in methanol and acetone. However, they were insoluble in benzene and petroleum ether.

The presence of chloride ion outside the coordination sphere was confirmed by the presence of white precipitate of AgCl with the use of $AgNO_3$ solution. Hence, the proposed synthetic equation for the synthesized complexes could be represented as:

$$M_1X_{2\cdot 6}H_2O + L_1 + L_2 \longrightarrow M_1L_1L_2X_2 + {}_6H_2O$$

$$M_2X_{3\cdot 6}H_2O + L_1 + L_2 \longrightarrow M_2L_1L_2X_3 + {}_6H_2O$$

Where M_1 = Co(II) & Ni(II), M_2 = Fe(III), X = Cl, L_2 = CHL, L_2 = OXY

The relevant infrared data of the ligands and metal complexes have been collected and assigned (Table 4). The two (weak and broad) absorption bands observed in the ranges of 3346.58 - 3557.3 cm^{-1} in the ligands spectra showed v(O - H) band at higher frequencies 3482.6 and 3346.58 cm^{-1} in CHL, 3557.3 and 3404.6 cm^{-1} in OXY) (Sayed, 2004). Similar bands were found in metal complexes at lower frequencies coupled with changes in their intensities. A broad medium band at (3793.8 cm^{-1} and a weak band at 3705.5 cm^{-1} in CHL spectrum was assigned to the v(N - H) vibration (El-

Table 3. Solubility of the ligands and metal complexes in some selected solvents.

Ligands/Complexes	Distilled water	Ethanol	Methanol	Acetone	Benzene	Petroleum ether
Chloramphenicol (CHL)	SS	SS	SS	SS	NS	NS
Oxytetracycline (OXY)	S	SS	SS	S	NS	NS
Ni (CHL)(OXY)Cl_2	SS	SS	S	S	NS	NS
Co(CHL)(OXY)Cl_2	SS	SS	S	S	NS	NS
Fe(CHL)(OXY)Cl_3	SS	SS	S	S	NS	NS

S = Soluble; SS = slightly soluble; NS = not soluble.

Table 4. Infrared spectroscopic and electronic spectra of the lagan and metal complexes.

Ligands/ complexes	Infrared frequencies						Methanol cm^{-1}(nm)
	v(*O-H*) cm^{-1}	v(*N-H*) cm^{-1} (amide)	v(*C=O*) cm^{-1}	v(*C-O*) cm^{-1}	v(*C-N*) cm^{-1}	v(*M-L*) cm^{-1}	
Chloramphenicol (CHL)	3482.6*w* 3346.5*b*	3793.8*m,b* 3705.5*w*	1692.2*v,s*	1078.9v,s	1241.5*s*	-	33333 (300) 40000 (250) 42553 (235) 45455 (205)
Oxytetracycline (OXY)	3557.3*w* 3404.6*m,b*	3801.5*w,b* 3732.8*w*	1690.8*m*	1150.8m	1257.6*m,b*	-	26316 (380) 33333 (300) 36364 (275) 37736 (265)
Ni(CHL)(OXY)Cl_2	3400.0*v,w* 3200.0*v,w*	3795.7*v,w* 3712.9*v,w*	1728.0*m*	1119.4*s*	1376.4*m*	684.1*w*	21277 (470) 25974 (385) 33898 (295) 37736 (265)
Co(CHL)(OXY)C_2	3456.4*v,w* 3355.1*m,b*	3755.1*m,b* 3674.4*w,b*	1726.8*m*	1064.8*v,s*	1245.6*m*	657.1*m*	23810 (420) 25974 (385) 33333 (300) 37736 (265)
Fe(CHL)(OXY)Cl_3	3471.4*v,w* 3343.6*w,b*	3788.6*w,b* 3708.6*w,b*	1733.6*m*	1079.5*s*	1278.6*w*	678.8*m,b*	33898 (295) 37736 (265) 39216 (255) 41667 (240)

Ajaily et al., 2006). These bands were also observed in the OXY spectrum at 3801.5 and 3732.8 cm^{-1}. The appearance of corresponding bands in the spectra of metal complexes with changes in vibrational frequencies coupled with lower changes in intensities support the involvement of NH_2 group in the complexation. The CHL spectrum displayed strong bands attributed to v(C = O) vibrational group at 1692.2 cm^{-1}. The band appeared in OXY spectrum at 1690.8 cm^{-1} as medium band. The band was found to have undergone hypsochromic changes in the metal complexes due to coordination with the metal ion. However, the bands observed in the range of 1078.7 - 1257.6 cm^{-1} were attributed to v(C - N) and v(C - O) vibrational band. They were observed in the metal complexes at higher frequencies due to effect of complexation. New bands observed (657.1 – 684.1 cm^{-1}) in the metal complexes were assigned to M - L bands.

The electronic data of the ligands and metal complexes were recorded in methanol and their assignments are as listed in Table 4. The ligands electronic spectra displayed several bands. The λmax band was found in CHL at 33,333 cm^{-1} (300 nm) and at 26,316 cm^{-1} (380 nm) in OXY. The complexes showed similar bands (sharp) at 21,277 cm^{-1} (470 nm), 23,810 cm^{-1} (420 nm) and 33,898 cm^{-1} (295nm) for Ni(CHL)(OXY)Cl_2, Co(CHL)(OXY)Cl_2 and Fe(CHL)(OXY)Cl_3 respectively. The complexes displayed similar bands as compared to other bands in the ligands at higher wavelength due to complexation.

Figures 1 - 3 exhibits the % inhibition of the ligands and the metal complexes synthesized against the tested bacteria. Both ligands displayed activity against the three bacteria tested. However, the metal complexes were found to be more active than their respective ligands at the concentration (1.0%) used. The percentage inhibition

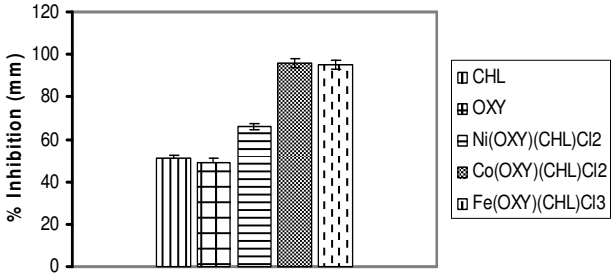

Figure 1. Zone of inhibition (%) of the ligands and metal complexes against *Escherichia coli*.

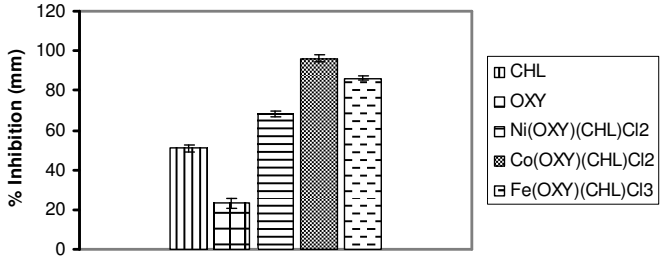

Figure 2. Zone of inhibition (%) of the ligands and metal complexes against *Staphylococcus aureus*.

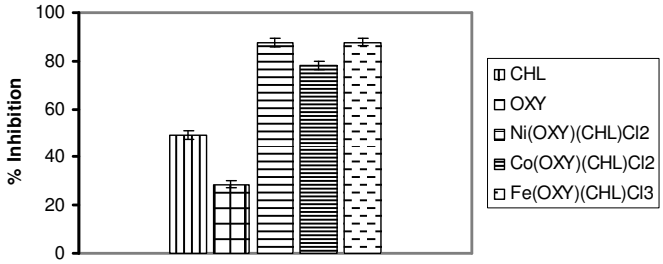

Figure 3. Zone of inhibition (%) of the ligands and metal complexes against *Klebsiella pneumonia*.

values obtained for the metal complexes against the three bacteria used were more significant than those of the parent drugs. They were almost double folds of those of the ligands. Also, they were more active than their respective single ligand metal complexes. The results show that the mixed ligands metal complexes are more active than their parent drugs.

The effect of oral administration of the ligands and the metal complexes on the serum and homogenates of liver and kidney of albino rats are as represented. (Figures 4 - 6). Compared with the control, administration of the ligands and metal complexes at the dose of 3.33 mg kg^{-1} body weight, Co(II) and Fe(III) complexes produced significant increase ($P < 0.05$) in the alkaline phosphatase activities of the serum, liver and kidney homogenates of albino rats. However, $Ni(CHL)(OXY)Cl_2$ produced no significant increase ($P > 0.05$) in the alkaline phosphatase activities of the serum, liver and kidney homogenates of albino rats. When compared to the control, $Ni(CHL)(OXY)Cl_2$ produced about 2.0 and 1.9 folds increase in kidney and liver activity respectively. $Co(CHL)(OXY)Cl_2$ produced about 2.5 and 2.1 folds increase of the enzyme activity in the kidney and liver, respectively, while $Fe(CHL)(OXY)Cl_3$ also produced about 2.5 and 2.5 folds increase in the activity of the kidney and liver respectively. However, administration of the ligands and the complexes at 3.33 mg kg^{-1} body weight did not produce any significant change ($P > 0.05$) in the serum alkaline phosphatase activities.

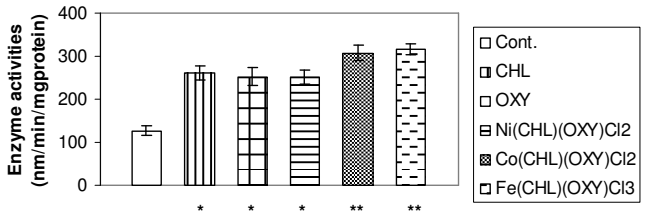

Figure 4. Result of toxicology test of the ligands and metal complexes against kidney homogenate (*$p > 0.05$, **$p < 0.05$).

Analytical, spectroscopic, antimicrobial, and toxicology data obtained confirmed new antibiotics with increased efficacy. The average percentage yield obtained indicates that complexes could be produced experimentally. The various colours observed by metal complexes could be attributed to d_{xz}, $d_{yz} \rightarrow d_{x2-y2}$ electronic transitions (Zeinab, 2006; Oladipo et al., 2005) which suggested octahedral geometry around metal ions in the complexes. The molar conductivity was applied to help in the investigation of the geometrical structures of the complexes. Higher conductivity observed in the complexes is an indication of higher degree of dissociation and solubility of the ions in solution as compared to the ligands. This further confirmed the presence of metal ions in the complexes. Increased melting points of the complexes were attributed to increase in the strength of C-O, C-N and perhaps M-L bonds in the metal complexes (Oladipo et al., 2005). The solubility of the complexes (> 60%) in the polar solvent is an indication that the compounds are practically useful in pharmacy. The similarity in the spectra is as expected due to the presence of the same ligands in the metal complexes. The metal complexes spectra indicated that v(O-H) stretching vibration band at 3346.58 - 3557.3 cm^{-1} in the ligands has shifted to lower frequencies, which indicated that the ligands coordinated to the metal ion through oxygen atom of the hydroxyl group. Weakening and broadening observed in the bands attributed to v(N-H) in the spectral of metal complexes as compared to the ligands spectral supported the coordination through v(N-H) vibrational group. Evidence of coordination through the carbonyl group was also suppor-

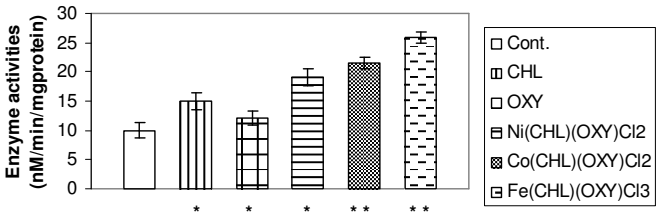

Figure 5. Result of toxicology test of the ligands and metal complexes against liver homogenate (*p > 0.05, **p < 0.05).

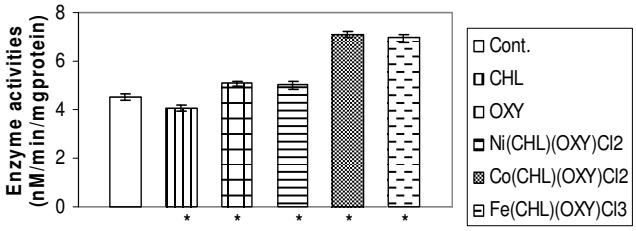

Figure 6. Result of toxicology test of the ligands and metal complexes against serum (*p > 0.05, **p < 0.05).

ted by hypsochromic changes observed in the intensities of these bands (1692.2 cm^{-1} in CHL, and 1690.8 cm^{-1} in OXY) in metal complexes. The other bands in the ligands spectral (1078.9 - 1257.6 cm^{-1}) assigned to the v(C-O) and v(C-N) vibrational stretching have shifted to a higher frequency due to effect of complexation with central metal ions.

Moreover, new bands found in the metal complexes at 657.1 - 684.1 attributed to M-L bands (Brian, 1999) are as a result of v(M-O) and v(M-N) vibrational stretching. This also confirmed the coordination of the central metal to the ligands.

The electronic spectral data of the metal complexes are compatible with an octahedral geometry (El-Ajaily et al., 2007). The electronic spectral bands of the $[Co(CHL)(OXY)Cl_2]$ complex shows bands at 23810, 2259.74 and 33333 cm^{-1} corresponding to $^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)$, $^4T_{1g}(F)\rightarrow{}^4A_{2g}(P)$ and $^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)$ transition, respectively. This result is in good agreement with an octahedral geometry around metal (II) ion. The extra band at 37736 cm^{-1} is due to transition of aromatic ring. The bands in $[Ni(CHL)(OXY)Cl_2]$ complex 21,227, 25974 and 33898 cm^{-1} were assigned to $^3T_{1g}(F)\rightarrow{}^3T_{2g}(F)$, $^3T_{1g}(F)\rightarrow{}^3A_{2g}(F)$ and $^3T_{1g}(F)\rightarrow{}^3T_{2g}(P)$, respectively. Also, the band at 33736 cm^{-1} was assigned to Л-Л* of carbonyl group which is the characteristic of an octahedral complex. The bands in $[Fe(CHL)(OXY)Cl_2]$ complex 33898, 37736, 39216 and 41667 were assigned to п-п* of *C=C* , n-п* of NO_2 and n-σ* of *–OH* and n-σ* of *C-N* respectively.

The increased percentage inhibition property (Figures 1 - 3) of the metal complexes as compared to the ligands confirmed increased in efficacy of the complexes. Mixed ligand complexes are about 30% higher in activity than the single ligand metal complexes (Ogunniran et al., 2007). Thus, mixed antibiotics complexes could be more toxic to pathogenic bacteria than pure antibiotics and therefore are better potential antibacterial drugs. Alkaline phosphatase is used as the marker for obstructive jaundice and intra-hepatic cholestasis. It is also a marker of kidney, placenta and bones (Mayne, 1999; Yakubu et al., 2005). The significant increase observed Co(II) and Fe(III) complexes in the alkaline phosphatase activity of rat kidney and liver (Figure 4 - 6) may be attributed to toxicity of the complexes to the enzymes of the organs and thereby increasing, indiscriminately, hydrolysis of phosphate ester of the organs and other cells requiring these essential molecules. This indicate that the complexes may likely cause damages to the external boundary of the cells of liver and kidney (Davern and Scharschmidt, 2002; Stanley, 2003). However, insignificant values obtained for Ni(II) complex is an indication that the complex is not toxic as compared to the control. All the complexes did not affect the serum enzymes in any way. This is an indication that, the complexes may not affect serum plasma (Yakubu, 2006). Therefore, they are non-toxic to the serum enzymes.

Conclusion

This study has shown the feasibility and a justification for the synthesis of mixed antibiotics metal complexes. The complexes possessed better physical properties and are much more effective as chemotherapy agents than their parent antibiotics. However, two of the complexes may be toxic at the dose level used to the liver and kidney but can be consider as potential antibiotics drugs after reduction in the level of metal ion which is responsible for the toxicity. However, Ni(II) complex, which was found to be non-toxic, could successfully be regarded to as possible potential metal-antibiotic.

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