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Synthesis, spectroscopic and biological studies of Cobalt(II), Nickel(II) and Iron(III) mixed antibiotic metal complexes

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ABSTRACT

Complexes of Co(II), Ni(II) and Fe(III) with ampicillin and amoxicillin as ligands have been synthesized in aqueous solution and characterized by physical, IR and electronic spectra. The elemental data obtained agreed with the general formula [M(A)(C)].3H_2O, where A= amoxicillin, C= ampicillin and M= metal ion. The IR spectra shows that the ligands coordinated to the metal ions through v(C=O), v(COO) and v(N-H) respectively due to their structural similarities. Electronic spectral data further revealed the probable geometry of Co(II) and Fe(III) complexes to be octahedral, while that of Zn(II) complex is tetrahedral. All the complexes and the ligands were screened for their biological activity on some selected bacterial species which includes:- Staphylococcus aurous, Streptococcus pyogene, Bacillus subtilis, Escherichia coli, Salmonella shigela, Klebsiella pneumoniae and Pseudomonas aeuroginosa. The results of biological activity indicated that the Co(II) and Ni(II) complexes have increased activity while Fe(III) had decreased activity. The complexes are also soluble in polar solvents.

Key words: Metals, transition metals, complexes, Antibacterial resistance, spectroscopic.

INTRODUCTION

Metals have been used in the treatment of diseases since ancient times. The Elbers Papyrust from 1500BC is the first written account of the use of metals for treatment and describes the use of copper to reduce inflammation and use of iron to treat anaemia. Sodium vanadate has been used since early 20th century to treat rheumatoid arthritis. Recently metals have been used to treat cancer, by specifically attacking cancer cells and interacting directly with DNA [1]. While many metals, such as Cu, Zn and Fe are essential for human health and protect us against many disease, they are also implicated as being involved in many degenerative disease, including atherosclerosis(heart disease and stroke). Metals are essential to all forms of life, but metal metabolism is different in different organism and in disease and non-disease tissues in the same organs [2]. Metals have an esteemed place in medicinal chemistry. Transition metals represent the d- block element which includes groups 3-12 on the periodic table. Their d-shells are in process of filling. This property of transition metals resulted in the foundation of coordination compounds or complex compounds [3]. Metal complexes or coordination compounds consist of central atom (metal ion) surrounded by array of oppositely charge ions or neutral molecules. The problem of bacteria resistance to antibiotics or antimicrobial agents is increasing at an alarming rate globally. This problem is attributed to wider use of antibiotics in human and animals and in areas other than treatment and prophylaxis of disease [4]. In view of this, different approaches and strategies have been adopted in order to find alternative to the problem of bacteria resistance to antibiotic [5]. These strategies include, enhancing the activities or broaden the spectrum of the antibiotics to be active against both Gram positive and Gram negative bacteria. Preparation of different synthetic derivatives of antibiotics based on structural activity relationship has been one of the best approaches [6]. Mixed ligand antibiotics metal complexes of transition metals are gaining recognition due to their efficacy against the parent drug used [7-8]. Many metal complexes have powerful anti-microbial activities and are already in common day to day use in medicine, in areas such as silver bandages for treatment of burns, zinc antiseptics creams, bismuth drugs for the treatment of ulcer and metal cluster as anti-HIV drugs [2]. The potential for further development of

metal-based drugs and treatments as anti-microbial agent are enormous and also of great importance with the evolution of drug-resistance bacteria. In continuation of our earlier report, on mixed antibiotic metal complexes [4], we here by present another model of mixed antibiotic metal complexes with a view of finding alternative to bacteria resistance to antibiotic.

MATERIALS AND METHODS

All the reagents and solvents used were of analytical grade and were used without further purification. The melting points of the complexes were determined using Griffin melting point apparatus. Molar conductivity measurement (10^{-3} M solution in methanol) was obtained on the metler P163, while elemental analysis were carried out on a Perkin-Elmer model 2400 series 11CHNS/O elemental analyser. The metal content of the complexes was determined using AA240FS, Fast Sequential Atomic Absorption Spectrometer. The electronic absorption spectra of the complexes were obtained using UV-2550 Shimadu Spectrophotometer in the wavelength range of 250-800nm. The infrared (IR) spectra were recorded as NaBr disc on Perking Elmer 1310(IR) in the range of 4000-400cm^{-1}. The antibacterial activity was determined using disc diffusion method.

Synthesis of the complexes

The complexes were prepared using a literature procedure [9]. The antibiotics were labelled as A and C for Amoxicillin trihydrate and Ampicillin trihydrate respectively. Aqueous (20mL) solutions of the antibiotics, [10mmol, 4.196g of A and 10mmol, 3.494g of C] were mixed as AC in 1:1 mole ratio. The solution of mixed antibiotics was further mixed with the aqueous (20mL) solution of the metal(II) salts [10mmol, 2.376g of $NiCl_2.6H_2O$, 10mmol, 2.235g of $FeCl_3.6H_2O$ and10mmol, 2.380g of $CoCl_2.6H_2O$] respectively in 1:1:1 mole ratio. The reaction mixture was refluxed for 4hrs on a hot plate magnetic stirrer. The volume of the solution was concentrated to half of the initial volume. The product obtained was allowed to cool, washed with water, diethyl ether and then dried in a vacuum over $CaCl_2$.

Antimicrobial screening

The in vitro antimicrobial properties of the antibiotics and their metal complexes were assayed using the following bacterial species: *Staphlylococcus aureus, Streptococcus Pyogenes, Bacillus Subtilis, Salmonella Typhi, Escherichia Coli, Klebsiella Pnuemoniae,*and *Psuedomonas aeruginosa,* by the disc diffusion method. The suspension of each micro-organism was added to a sterile agar medium, then poured in to a sterile petri plates and left to solidification. Different concentrations (30,20 and 10µg/ml) of antibiotics and their metal complexes in methanol were placed on the culture media and incubated for 24hrs at 37°C. Activities were determined by measuring the diameter of the zone showing complete inhibition (mm).

RESULTS AND DISCUSSION

All the complexes are non-hygroscopic, air and photo stable at room temperature. The Co(II), Ni(II), and Fe(III) complexes are either soluble or slightly soluble in solvents like; distilled water, methanol, ethanol and chloroform. The complexes exhibit various shades of colours ranging from yellow to green and brown. This is typical of transition metal complexes due to d-d transitions. The complexes showed higher melting points when compared with their parent drugs (Table1). Similar observation was reported by some workers [9]. . The molar conductivity of the complexes fall within the range of 9.5 x 10^{-3} – 20 x 10^{-3} Scm^2/mol, indicating that, they are non-electrolytes. [10].The ligands (A and C) on interaction with Co^{II}, Ni^{II} and Fe^{III}, formed complexes with moderate yields ranging from 23- 67% (Table 1).

Table 1: Physical characteristics of the ligands and their metal (II) complexes

Compounds	Colour	M.pt/d(°C)	Yield (g) (%)	Molar conductivity Scm^2/mol
A	White	197	_	$3.9x10^{-3}$
C	White	195	_	$7.5x10^{-3}$
$[Co(A)(C)]\cdot 3H_2O$	Yellow	230-250	3.0 (67)	$10.5x10^{-3}$
$[Ni(A)(C)]\cdot 3H_2O$	Green	230-250	4.0 (47)	$20x10^{-3}$
$[Fe(A)(C)]\cdot 3H_2O$	Brown	195	2.0 (23)	9.5 x 10^{-3}

Table 2: The microanalysis and metal estimation data of the complexes

Compounds	Molecular formula (molar mass)	Microanalysis: Found(calculated) %			
		C	H	N	M
$[Co(A)(C)]\cdot 3H_2O$	$Co(C_{32}H_{42}N_6O_{12}S_2)$ (824.93)	46.47 (46.55)	5.06 (5.10)	10.20 (10.18)	7.85 (7.81)
$[Ni(A)(C)]\cdot 3H_2O$	$Ni(C_{32}H_{42}N_6O_{12}S_2)$ (824.71)	46.50 (46.56)	5.05 (5.09)	10.17 (10.19)	7.84 (7.80)
$[Fe(A)(C)]\cdot 3H_2O$	$Fe(C_{32}H_{42}N_6O_{12}S_2)$ (821.86)	46.70 (46.72)	5.10 (5.11)	10.21 (10.22)	7.42 (7.43)

Microanalysis

The microanalysis of the metal (II) complexes is presented in Table 2. The results revealed that the %C, H and N are in good agreement with the proposed structures. From the data obtained, it appears that the compounds analysed as $[M(A)(C)].3H_2O$ where M = Co^{II}, Ni^{II}, Fe^{III}. While, A and C are amoxicillin and ampicillin. Metal ion % also agrees with proposed structures (Table 2.)

Infrared spectra

The band assignment is based on comparison with similar studies on mixed ligand complexes and some drug based metal complexes [11-14]. The spectra that appear in the free ligands were found to be present in the complexes because of the similarity in their structures.

Table 3: The relevant vibrational bands for the antibiotics and their metal complexes

Compounds	V(N-H)	V(O-H)	V(C=O)	V(COO)	V(C-N)	V(NH_2)	M-N	M-O
A	3020s	3500w	1760s	1480m	1400m	2900s	-	-
C	3020s	3560m	1750s	1540m	1450m	2940w	-	-
$[Co(A)(C)]\cdot 3H_2O$	3280s	3500w	1780s	1590m	1420w	-	-	730w
$[Ni(A)(C)]\cdot 3H_2O$	3000s	3280b	1660m	1590m	1430w	3000s	-	600b
$[Fe(A)(C)]\cdot 3H_2O$	3000s	3100s	1640m	1430m	-	-	-	660w

Table 4: Electronic absorption spectral data for the antibiotics and their metal (II) complexes

Compounds	Absorption(cm^{-1})	Band assignment	ε_{max} ($mol^{-1}cm^{-1}$)	Geometry
A	30461, 42633	$n \rightarrow \pi^*$	-	
C	30749, 42915	$n \rightarrow \pi^*$	-	
$[Co(A)(C)]\cdot 3H_2O$	18182 16529 15385	$^4T_{1g}$ (F) → $^4T_{1g}$ (P) $^4T_{1g}$ (F) → $^4A_{2g}$ (P) $^4T_{2g}$ (F) → $^4A_{2g}$	164810	Octahedral
$[Ni(A)(C)]\cdot 3H_2O$	20000 15873 13793	$^3A_{2g}$ (F) → $^3T_{2g}$ (F) $^3A_{2g}$ (F) → $^3T_{1g}$ (P) $^3A_{2g}$ (F) → $^3T_{1g}$ (P)	157540	Octashedral
$[Fe(A)(C)]\cdot 3H_2O$	18182 16667	$^5T_{2g}$(F) → ^5E_g $^5T_{2g}$(F) → ^5E_g	2274900	Octahedral

The appearance of strong bands at 3020cm^{-1} in the ligands, which shifted to 3000 – 3280cm^{-1} in the complexes is assigned to v(NH) stretching frequency. The v(COO) mode absorb as medium in the region of 1480 – 1540cm^{-1} in the free ligands and shifted to 1430 – 1590cm^{-1} in the complexes. The band at region of 1750 – 1760cm^{-1} in the free ligands was assigned to v(C=O) stretching mode. This was shifted to 1640 – 1780 cm^{-1} in the complexes which suggest coordination through the carbonyl functional group to the metal ion in complex.

Electronic spectra

The electronic spectral data of the ligands and their metal complexes are presented in Table 4. The ligands A and C respectively showed two distinct bands at the region of 30461- 42915cm^{-1} which could be assigned to the $n \rightarrow \pi^*$ transition in the free ligand [15]. Co(II) complex showed three bands at 18182,16529 and 15385cm^{-1} which could be assigned to the $^4T_{1g}$ (F) → $^4T_{1g}$ (P), $^4T_{1g}$ (F) → $^4A_{2g}$ (P) and $^4T_{2g}$ (F) → $^4A_{2g}$ transition in octahedral environment respectively [16]. The Ni(II) complex gave three bands at 20000, 15873 and 13793 cm^{-1} assignable to $^3A_{2g}$ (F) → $^3T_{2g}$ (F), $^3A_{2g}$ (F) → $^3T_{1g}$ (P) and $^3A_{2g}$ (F) → $^3T_{1g}$ (P) transition in octahedral environment [16]. Fe(III) complex showed two bands at 18182 and 16667 cm^{-1} assignable to $^5T_{2g}$(F) → ^5E_g and $^5T_{2g}$(F) → ^5E_g transition respectively. These transitions are typical of octahedral geometry [16].

Antibacterial activity

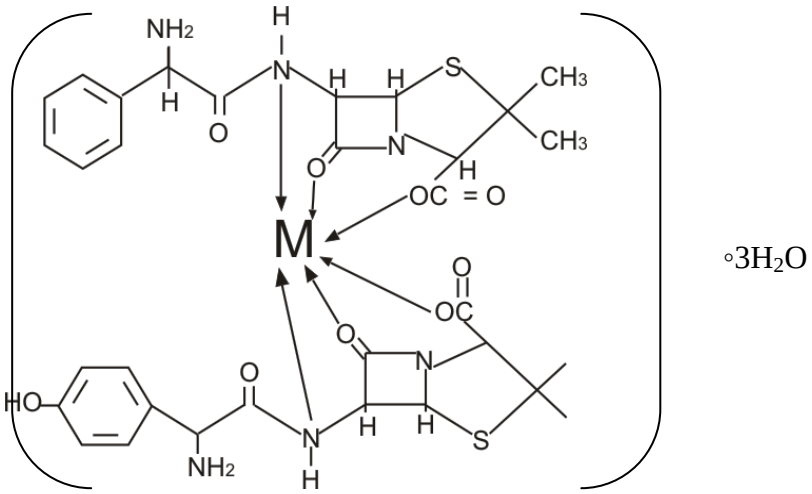
In vitro antibacterial activity of the newly synthesised complexes and their parent drugs were investigated against three Gram positive bacteria species includes: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Bacillus subtilis* and four Gram negative; *Salmonella typhi*,*Escherichia coli*, *Klebsiella pnuemonie* and *Psuedomonas aeruginosa* using disc diffusion method [17]. The concentrations of (10, 20 and 30µg/mL) for both the ligands and their complexes

were used. The result shows that, the complexes Co(II) and Ni(II) showed increased activity on some of the organism when compared with the ligands. The Fe(III) complex showed increased activity on staphylococcus aureus only (Table 5).

Table 5: Antimicrobial activities of antibiotics and their metal complexes

Compound	Conc. µg/g	*S.aureus*	*S.pyogenes*	*B.subtilis*	*E.coli*	*S.typhi*	*K.pneumoniae*	*P.aeruginosa*
A	10	+	+	+	-	-	+	-
	20	++	++	+	+	-	+	-
	30	++	++	++	+	-	+	-
C	10	+	-	+	+	-	+	-
	20	++	-	+	+	-	+	-
	30	++	-	+	++	-	+	-
[Co(A)(C)]·3H_2O	10	+	-	+	++	-	-	++
	20	++	-	++	+++	-	-	++
	30	+++	-	+++	+++	-	-	++
[Ni(A)(C)]·3H_2O	10	+	++	+	++	-	++	+
	20	+	++	+	++	-	+++	++
	30	+	++	+	++++	-	+++	++
[Fe(A)(C)]·3H_2O	10	-	-	-	-	+	+	-
	20	-	-	-	-	+	+	-
	30	-	-	-	-	+	+	-

(-) = 0 – 5 ±0.15mm = resistant, (+) = 5 – 10 ±0. 07mm = slightly susceptible, (++) = 10 – 15 ±0.33mm = susceptible and (+++) = > 15 ± 1.2mm = highly susceptible



◦3H_2O

Fig : Proposed structure of the metal Complexes, where M = Co(II), Ni(II) and Fe(III)

CONCLUSION

Based on the data obtained, the ligands coordinated the metal ion through v(NH), v(C=O) and v(COO) respectively due to their structural similarities. The proposed geometry of the complexes is octahedral. The elemental percentages are in good agreement with those of proposed structure. The complexes of Co(II) and Ni(II) showed increased antimicrobial activity compared to the parent drugs while Fe(III) showed decreased activity.

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