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Mn(II), Fe(III) and Ni (II) Complexes of Mixed Citric acid - Sulphamethoxazole: Synthesis, Characterization and Antibacterial activity

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Abstract

Three mixed ligand complexes of sulphamethoxazole and citric acid have been synthesized using Mn(II), Fe(III) and Ni(II) chlorides. The complexes were characterized by elemental analysis, melting point, conductivity test, magnetic measurement, UV-Visible and infrared spectroscopy. The infrared spectra data revealed that the ligands act as bidentate, in which citric acid coordinate through C=O of the carboxyl and oxygen of the hydroxyl groups, while sulphamethoxazole coordinates through nitrogen atom of the primary amine group and O=S=O of the sulphonyl group. The result of the elemental analysis was consistent with the proposed pattern for the complexes, while the melting point determination confirmed that the synthesized compounds were pure. Antibacterial activity of metal complexes were screening against five strain bacteria microorganism of g(+) *Pseudomonas aeruginosa*, *Eschericia coli*, g(+) *Klebsiella pneumonia*, g(+) *Staphylococcus aureus* and g(+) *Candida* using Muller Hinton diffusion method. The result showed that the overall zone of inhibition against bacterial isolate follows an increasing order of priority Fe(III) > Ni(II) > Mn(II) complexes.

Keywords: Sulphamethoxazole, Citric acid, Metal complexes, Antibacterial activity.



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1.0 Introduction

The spread of infectious diseases is not just associated with poverty but also serve as major hindrance to economic development (Leonard, 1986; Ajibade, 2008). The current challenge faced by synthetic inorganic chemists is how to combat the resistance posed by pathogens to all classes of antimalarial drugs (Peter and Zijian, 1998; Obaleye et al., 2007; Rajee et al., 2018; Chu et al., 1996). Malaria is a major threat to health especially in Africa (Kannan et al., 2005). Sulphamethoxazole is most often used as part of a synergistic combination with trimethoprim in a 5:1 ratio in co-trimoxazole, it is commonly used to treat urinary tract infections. In addition, it can be used as an alternative to amoxicillin-based antibiotics to treat sinusitis (Elzahany et al., 2008; Garg et al., 1986). Since some of this antimalarial drug is lost as a result of either vomiting or individual abnormalities in metabolism, disposition and elimination of drug action. Most researches carried out on drug metal complexes showed they have higher inhibitory activity and the needs to search for better ones continue to received attention of inorganic chemists. Therefore, this study report the synthesis and characterize some mixed Sulphamethoxazole- Citric acid metal complexes of Mn(II), Fe(III), and Ni(II) ions, with focus on their antibacterial activity.

2.0 Materials and methods

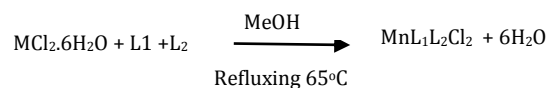
Sulphamethoxazole were obtained from Emzor pharmaceutical company, Lagos, Nigeria. Citric acid was purchased from Sigma chemical company, USA. All the solvents and other reagents were of high purity (Sigma-Aldrich) and were used as supplied without further purification. The metal salts used were Mn(II), Fe(III) and Ni(II) hexahydrate salts. Five isolate of g(+) *Pseudomonas aeruginosa*, g(+) *E. coli*, g(+) *Klebsiella pneumonia*, g(+) *Staphylococcus aureus* and g(+) *Candida* were obtained from Department of Microbiology, University of Ilorin, Ilorin, Nigeria.

Characterization methods

Infrared spectra of the compound in KBr pellets were measured in the range of 4000 -500 cm⁻¹ on a Thermo Nicolet FTIR spectrophotometer. Micro-elemental analysis of carbon, hydrogen, nitrogen, and sulphur were carried out on Perkin-Elmer 204C micro analyzer, UV-Vis spectra were obtained on Beckman Coulter Du(R) 730 Scanning UV-Vis spectrophotometer. Magnetic moment was carried out on a Faraday balance. The melting point determination was carried out using Gallenkamp melting point apparatus. Conductivity measurement was carried out using Hanna EC 214 Conductivity meter with DMSO as control. All other physical measurements and analytical procedures were similar to those described previously (Obaleye, 1996).

Synthesis of metal complexes

0.192 g (1mmol) of citric acid and 0.253 g (1mmol) of sulphamethoxazole were both dissolved in 10 ml of methanol. The solution were mixed thoroughly together in round bottom flask, and introduced ia solution of 0.134 g (1mmol) of the hydrated chloride salts of the metals. The resulting solution was stirred under reflux for 2 hours at 65 °C and left to stand for 15 days. After, which the precipitate was filtered, washed with the solvents, dried at room temperature and finally characterized.



Where M= Mn(II), Fe(III) and Ni(II), L₁= Citric acid, L₂= Sulphamethoxazole

Antimicrobial activity

The antibacterial activity of the new synthesized complexes and their free ligands were screened by agar well diffusion method in DMSO (Collin et al., 1995; Rajee et al., 2022). The test organisms were reconstituted from the stocks on Muller Hinton agar. Broth cultures of the organisms were used in seeding the agar each time the susceptibility test was done. After seeding, the binocular was uniformly spread with sterile swab sticks on the agar surface. The agar wells were then made with a cork borer, which is sterilized by dipping in 70% ethanol and flaming each time. Aliquots (200-300 µl) of the compounds were introduced aseptically into the wells in each plate using the micropipette with sterile tips. Sulphamethoxazole were used as positive control whereas the medium of DMSO was used as negative control. The compounds were then allowed to diffuse slowly and the plates were incubated at 24 hours for 37 °C. The incubated plates were observed after the incubation periods for inhibition zones around the agar well and the zones were measured with a metre rule in cm.

3.0 Results and Discussions

The results of the elemental analyses with the proposed molecular formulae are presented in Table 1. The results obtained are in good agreement with the composition pattern suggested for formulae 1:2 (M: L) solid chelates and found to have the general formulae [(ML₁L₂)]X₂; M=Mn(II), Ni(II) and Fe(III) (X=Cl). L₁ = Citric acid, L₂ = Sulphamethoxazole

The colour of the complexes varied ranging from pinkish to greenish and to brownish. The complexes also showed variable solubility in different solvents used, but they were readily soluble in non-polar solvent dimethylsulfoxide (DMSO) and dimethylformamide (DMF). The complexes showed molar conductance values ranging from 17-28µs cm⁻¹ indicating their non-electrolytic nature (Vogel, 1989). The melting points of the mixed complexes were found to be high when compared to the free ligands. The complexes are of average percentage yield range from 58-68%.

The IR spectra of the ligands and their metal complexes were compared. The assignments have been carried out based on literature values obtained for structurally similar compounds [Obaleye et al., 1999]. The specific IR frequencies of the ligand L and their metal complexes (in KBr) with their tentative assignments are given in Table 2. They showed similar bands as expected. The spectra of the three complexes have bands at around the same value. The broad band at 3463.13 cm⁻¹ due to hydroxyl group present in citric acid was shifted in the complexes of Fe(III), Ni(II) and Mn(II) respectively. This is indicative of the deprotonation and coordination through the O-H group (Deacon and Phillips, 1980). The absorption bands of the ν(C=O) that normally appear around 1726 cm⁻¹ was observed to have shifted to 1639 cm⁻¹, 1622 cm⁻¹ and 1627 cm⁻¹ for three complexes.

Table 1: Analytical and Physical data of ligands L₁ and L₂ and their mixed ligands metal complexes.

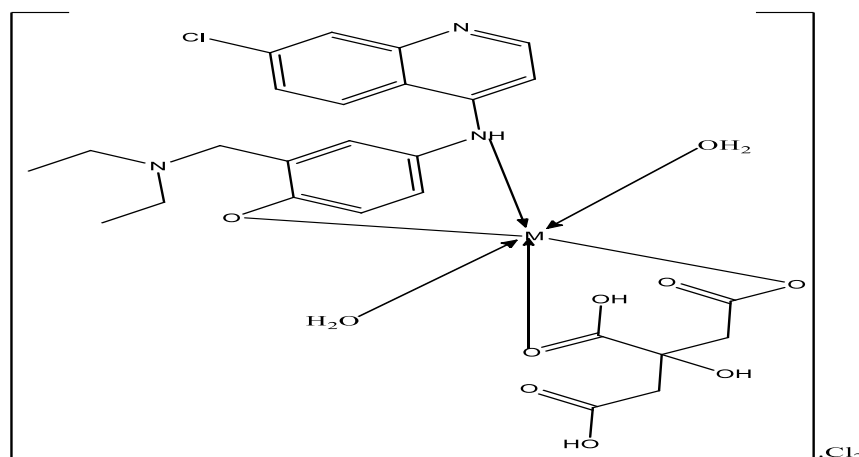
Compounds	C (%)	H (%)	N (%)	S (%)	O (%)	M.Pt.	Colour	Conductivity	Yield (%)
	Found	Found	Found	Found	Found	(°C)		(μs/cm)	
	(Calc)	(Calc)	(Calc)	(Calc)	(Calc)				
L ₁	37.50 (37.35)	4.17 (4.06)	- -	- -	58.33 (58.30)	152	White	18.23	-
L ₂	47.43 (47.42)	4.35 (4.34)	16.60 (16.57)	12.65 (12.63)	18.97 (18.95)	213	White	15.34	-
Mn(L ₁)(L ₂)Cl ₂	31.72 (31.76)	3.59 (3.47)	7.01 (6.95)	5.33 (5.29)	31.80 (31.76)	276	Pink	23.03	58
Ni(L ₁)(L ₂)Cl ₂	31.33 (31.33)	3.62 (3.44)	7.01 (6.90)	5.37 (5.24)	31.11 (31.48)	342	Green	28.41	68
Fe(L ₁)(L ₂)Cl ₃	31.78 (31.76)	3.65 (3.47)	7.03 (6.95)	5.34 (5.29)	31.78 (31.76)	321	Brown	17.32	62

Table 2: FTIR Spectra data of the ligands L₁ and L₂ and their mixed metal complexes.

Compound	$\bar{\nu}(\text{OH})$	$\bar{\nu}(\text{NH}_2)$	$\bar{\nu}(\text{C=O})$	$\bar{\nu}(\text{NH})$	$\bar{\nu}(\text{SO}_2)$	$\bar{\nu}(\text{M-L})$	$\bar{\nu}(\text{M-OH})_2$
L ₁	3463.13(br)	-	1726.35(s)	-	-	-	-
L ₂	-	3379.40m	-	3301.28m	1383.97m	-	-
[Fe(L ₁)(L ₂)Cl ₃]	3441.01s	3240.41s	1639.49s	-	1303.88m	536.21s	684.73m
[Ni(L ₁)(L ₂)Cl ₂]	3468.01s	3298.28s	1622.13br	3143.97s	1309.67s	549.71w	684.73m
[Mn(L ₁)(L ₂)Cl ₂]	3419.79br	-	1627.92sh	-	1365.50	597.93s	684.73m

Table 3: Ultraviolet /visible spectral data and magnetic studies of the ligands and the complexes

compounds	Electronic configuration	Ground state	Wavelength(nm)	Energy (cm ⁻¹)	Assignment	Magnetic moment (BM)
L ₁	-		285	35088	-	-
L ₂	-		302	33113	-	-
Fe(III)	d ⁵	⁶ S	313	31949	n→π*	4.01
Ni(II)	d ⁸	³ F	324	30864	³ A _{1g} (F)- ³ T _{1g} (P)	3.28
Mn(II)	d ⁵	⁶ S	313	31949	n→π*	5.24



Where M= Fe (III) , Ni(II) and Mn(II).

Figure 1: Proposed structure of synthesized complexes $[M(L_1)(L_2)]Cl_n$

This clearly indicates the coordination of the metal to citric acid through the carbonyl group (C=O). The absorption bands of the $\nu(\text{NH}_2)$ shifted from 3379 cm^{-1} to 3240, 3298 cm^{-1} for the $[\text{Fe}(\text{L}_1)(\text{L}_2)\text{Cl}_3]$ and the $[\text{Ni}(\text{L}_1)(\text{L}_2)\text{Cl}_2]$ complexes respectively. These could be attributed to the overlap of $\nu(\text{N-H})$ and $\nu(\text{O-H})$ of methanol or inter and intra molecular hydrogen bonding (Vogel, 1989). This observation however, was confirmed by the presence of C-N bending vibration, which appeared in the medium intensity in the complexes, which further supports the involvement of nitrogen in the complexation. Also, the M→L bands, which were found in the range of 500 - 780 cm^{-1} in the spectra of metal complexes, were conspicuously absent in the spectra of the ligands. [Ajibade, 2008; Rajee et al., 2020; Obaleye et al., 2001]

The UV-Visible spectra of citric acid, sulphamethoxazole and their metal complexes in DMSO showed absorption band ranging from 313-324 nm which was assigned to $n \rightarrow \pi^*$ respectively. The intense green colour of Ni(II) complex showed one weak absorption bands at 30864 cm^{-1} due to the splitting of ground state term $3F$ term and the presence of the $3P$ term. The bands were attributed to ${}^3A_{1g}(\text{F}) \rightarrow {}^3T_{1g}(\text{P})$. However, the magnetic moment value of 3.28 gotten for the complex is within the octahedral geometry range of 2.8-3.5 BM from the literature, and thus, the complex could be distorted octahedral [Cotton and Wilkinson, 1985]. Fe (III) complex band have been assigned to be due charge transfer or intra-ligand transition because Fe (III) is expected not to have d-d transition. Also, magnetic Bohr for Fe(III) complex which is 4.01BM is consistent with the table value for octahedral shape. A moderately intense peak observed in the range of 31949 cm^{-1} for Mn (II) with no splitting pattern expected and magnetic moment value of 5.24 was proposed for an octahedral geometry. Hence the value of magnetic moment of a complex would give valuable insights into its constitution and stereochemistry.

The antibacterial screening against five different isolates of (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella spp.* and *Candida spp.*), of the ligands and the mixed complexes were carried out by Muller Hinton agar diffusion method and the resulted is presented in Table 4. The diameters of zone of

inhibition (ppm) for the ligands (sulphamethoxazole + citric acid) were in the range of 0.3-1.67 for the five bacteria used. The results showed that the overall zone of inhibition against bacterial isolate is highest Fe(III) complex followed by Ni(II) and while Mn(II) complex appeared to have least zone of inhibition, with reference to all tested organisms. It is also evident to say that nearly all the metal complexes possess mild zone of inhibition against bacterial species compared with the free ligands, .

4.0 Conclusion

Mn(II), Fe(III) and Ni(II) complexes of citric acid and sulphamethoxazole have been synthesized and characterized by some physiochemical analysis and spectroscopic techniques by elemental analysis, melting point, conductivity test, magnetic Bohr moment, uv-visible and Fourier transform infrared spectroscopy. The three novel compounds prepared were generally soluble in non-polar solvent of DMF and DMSO.

Based on the result obtained, distorted octahedral shapes were proposed for all the complexes under investigation. In the complexes, The Ligands were bidentate in their mode of coordination with the metal ions. However, the analytical data and physical properties as compared to the free ligands. The antimicrobial activity indicate that the complexes showed higher inhibition activity against all the tested organisms.

5.0 Acknowledgement

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Declaration of Conflict of Interests

No conflict of interests to declare

Authors' Contribution

Supply of ligands : SO and HOS

Synthesis: AL and SO

Characterization: AOR, HFB and SEE
Antimicrobial: SO,MOB and AM
Writing of Manuscript : AL, SAA,MTY

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