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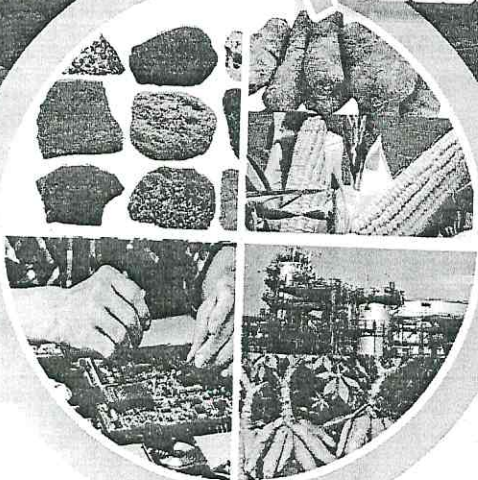
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MIXED LIGANDS COMPLEXES OF METRONIDAZOLE: SYNTHESIS AND ANTIBACTERIAL STUDIES

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ABSTRACT

The synthesis of some transition metal mixed complexes of metronidazole with oxalic acid have been reported and characterized using conductivity measurement, melting point determination, elemental analysis, infrared and ultraviolet/ visible spectroscopic methods. Both ligands were bidentate in their mode of coordination with the metal ions. The antibacterial studies were investigated against *Escherichia Coli*, *Bacillus Subtilis*, *Staphylococcus aureus* and *Klebsiella Pneumonia*. Mn(MET)(OXA)Cl₂ has the highest inhibition against *Klebsiella Pneumonia*, while Cu(MET)(OXA)Cl₂ has the lowest inhibition against *Bacillus Subtilis*.

Keywords: Mixed complexes, Metronidazole, Oxalic acid, Antibacterial.

1.0 Introduction

The main target present-day day coordination chemists is the discovery and development of better drugs to combat diseases[I]. It has reported that many drugs possess modified pharmacological properties when administered as metal complexes. The synthesis of mixed drug metal complexes had received much attention because of its effective as chemotherapeutic agents for prevention and cure of bacterial infections [2]. The pharmacological activity of these types of molecules is often enhanced upon coordination with transition metal ions [3].

In continuation to our work on metronidazole-metal based complexes [4,5], this article involves the synthesis and antibacterial studies of mixed ligands complexes of metronidazole with oxalic acid.

2.0 Materials and Methods

The under listed materials and equipments were used for the research work;

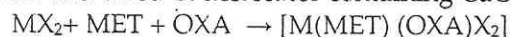
The metal salts, reagents and chemicals are of analytical grade and used as supplied, without further purification. Metronidazole were obtained from Sam Pharmaceutical Company Limited, Ilorin, Kwara state, Nigeria. Metal salts used include Copper chloride dihydrate, Cobalt (II) Chloride hexahydrate and Zinc (II) nitrate were products of sigma and Aldrich, UK. Cultures of the micro-organisms used were obtained from University Teaching Hospital and Department of Microbiology, University of Ilorin, Ilorin, Nigeria.

Infrared spectra of the compounds were recorded on SHIMADZU Scientific model FT-IR Spectrophotometer at Department of Chemistry, University of Ilorin, Ilorin, Nigeria. The Ultraviolet/visible spectra were obtained from SHIMADZU -1650 UV/VIS Spectrophotometer Department of Chemistry, University of Ilorin, Ilorin, Nigeria

2.1 Synthesis

The procedure described by Abd El-Wahab and El-Sarrag(6) , with slight modification was adopted in the preparation of the complexes.

0.3423g (2 mmol) of Metronidazole and 0.3782g (3 mmol) Oxalic acid were dissolved separately in 20 ml of methanol. The solutions was mixed thoroughly together in round bottom flask. The resulting mixture was stirred under reflux for one hour at 60 °C after which 2 mmol) of metal salts in 20 ml methanol was added .The reaction mixture was refluxed for 3 hours, after which the solution was allowed to cool at room temperature and left for 2 weeks to formed crystals. The crystals formed were filtered under vacuum, washed twice with an appropriate solvent and dried in desiccator containing CaCl₂ as drying agent.



M= Cu(II), Mn(II), Zn(II)

3.0 Results and Discussion

Table 1: Physical properties of the compounds

Compounds	State	Colour	M.Pt(°C)	Conductivity S _{cm} ² mol ⁻¹	% Yield
Metronidazole	Crystalline	yellow	163	1.40 x10 ⁻⁶	-
Oxalic acid	Crystalline	White	101.5	1.33 x10 ⁻⁶	-
Cu(MET)(OXA)Cl ₂	Powder	Blue	183.2	1.98 x10 ⁻³	45.67
Mn(MET)(OXA)Cl ₂	Powder	White	190.1	3.40 x10 ⁻³	39.76
Zn(MET)(OXA)NO ₃	Powder	White	212.7	5.670 x10 ⁻³	76.76

The result of the physical properties are presented in Table 1. All the mixed ligands complexes decomposed between 183°C and 212°C. The Mn(II) and Zn(II) mixed complexes were whitish in colour, which may be due to half filled and completely filled d-orbitals, attributed to these transition metals. The result of conductivity data in DMSO showed that all the three complexes are non-electrolytes. This result is similar to that reported by Adediji *et al* [7].

Table 2: Result of UV/Visible Spectra for Metronidazole-Oxalic Acid metal complexes.

COMPOUNDS	Wave length(nm)	Energies(cm ⁻¹)	Assignment
Metronidazole(MET)	360	27777.78	n→π*
Oxalic acid (OXA)	270	37037.04	π→π*
Cu(MET)(OXA)Cl ₂	380	26315.79	n→π*
Mn(MET)(OXA)Cl ₂	330	30303.03	n→π*
Zn(MET)(OXA)NO ₃	360	27777.78	n→π*

The result of ultraviolet/ visible spectra are presented in Table 2

The UV/Visible spectra of both metronidazole (MET) and oxalic acid (OXA) showed absorption bands each at 360 nm and 270 nm respectively. These bands have been shifted to 330 nm, 360 nm and 380 nm in the three complexes, due to coordination [8].

Table 3: SELECTED IR DATA (cm⁻¹) OF THE LIGANDS AND MIXED-METAL COMPLEXES

Ligands/Complexes	ν(C=C) (cm ⁻¹)	ν(C-N) (cm ⁻¹)	ν(C=N) (cm ⁻¹)	ν(C=O) (cm ⁻¹)	ν(O-H) (cm ⁻¹)	ν(M-N) (cm ⁻¹)	ν(M-H ₂ O) (cm ⁻¹)
Metronidazole	-	-	1537m	-	3240br	-	-
Oxalic Acid	-	-	-	1654m	3417br	-	-
Cu(MET)(OXA)Cl ₂	1492s	1369m	1562s	1654m	3386s	504w	739w
Mn(MET)(OXA)Cl ₂	1479s	1365s	1539s	1539s	3218s	504m	824m
Zn(MET)(OXA)NO ₃	1482s	1368s	1536s	1644m	3230br	504m	824s

S= strong, m= medium, w=weak, br= broad

The important IR frequencies of the ligands and the mixed complexes with their tentative assignments are given in Table 3. Comparing the IR of the ligands and the mixed-metal complexes, a shift of some characteristic frequencies were observed as well as appearance of some new frequencies. C=N absorption was observed at 1537cm⁻¹ in the ligand metronidazole while a shift to a new value was observed in the complexes such as in the Cu(MET)(OXA)Cl₂ where the absorption is 1369cm⁻¹. Also, there was a decrease in the C=O absorption. In Oxalic acid the absorption occurs at 1654cm⁻¹ while in the corresponding complexes such as in Fe(MET)(OXA)Cl₂, the absorption occurs at 1644cm⁻¹. Some other new frequencies were observed showing metal-ligands coordination. Of such absorptions is M-N with the value 504cm⁻¹ and 498cm⁻¹ in Cu(MET)(OXA)Cl₂ and Fe(MET)(OXA)Cl₂ respectively. Coordination due to M-H₂O also appeared such as in Cu(MET)(OXA)Cl₂ and Mn(MET)(OXA)Cl₂.

which occurred at 739cm^{-1} and 824cm^{-1} respectively. Thus, Metronidazole coordinated through one of its nitrogen groups while Oxalic acid coordinated through its carbonyl and oxygen groups.

3.1 Results of the Antibacterial activities of the ligands and the complexes

The culture of each bacterial species ; *Escherichia coli*, *Bacillus Subtilis*, *Staphylococcus aureus* and *Klebsiella Pneumonia*) was carried out using Sterile Nutrient agar (NA) and Sterile Nutrient broth (NB). The bacterial plates were observed after 24hrs of incubation, it was observed that there were clear zones of inhibition on the plates at higher concentrations and variable zones of inhibition at the lower concentration.

Table 4: The result of the Antibacterial activities of the ligands and the mixed complexes.

	<i>Bacillus subtilis</i>		<i>Escherichia Coli</i>		<i>Staphylococcus aureus</i>		<i>Klebsiella pneumonia</i>	
	Zone of inhibition							
	100 ppm	200 ppm	100 ppm	200 ppm	100 ppm	200 ppm	100 ppm	200 ppm
Oxalic acid(OXA)	7.34	10.30	9.25	11.41	8.30	12.25	9.40	11.20
Metronidazole (MET)	9.53	11.12	8.20	11.43	10.40	13.21	9.00	13.34
Mn(MET)(OXA)Cl ₂	15.24		20.33	17.23	19.30	24.51	28.42	28.30
Cu(MET)(OXA)Cl ₂	13.00		17.20	17.00	21.33	22.40	27.32	20.25
								23.10

4.0 Conclusion

The combined results of physical and spectroscopic data of the compounds confirmed the formation of mixed metal complexes. The ligands were bidentates in their mode of coordination with the transition metal ions. The result of antibacterial activities of the metal complexes showed that some of the complexes were more active than the free ligands especially at higher concentrations.

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