



SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL PROPERTIES OF MIXED-LIGAND TRANSITION METAL (II) COMPLEXES OF CEFTRIAXONE AND METHIONINE

A. M. Bulama¹; N. P. Ndahi²; M. B. Fugu³; A. M. Ngubdo⁴ and A. A. Mindia⁵

^{1&4}Department of Remedial Science, Ramat Polytechnic Maiduguri, Borno state, Nigeria

^{2,3 & 5}Department of Pure and Applied Chemistry, University of Maiduguri, Borno state, Nigeria

Abstract: This study exploited the potentials of synthesized mixed-ligand transition metal(II) complexes of ceftriaxone and methionine. The complexes were characterized using melting point, conductivity, solubility, UV-Visible, and FT-IR spectroscopy. The antimicrobial activities of the ligands and the synthesized complexes were also evaluated. The ratio of metal to ligand in the complexes is 1:1:1. The complexes are bright green, light yellow and pink in colour and appreciable in percentage yield (45-91) %. The complexes are solid with high melting point (93-289) °C. All the complexes are air stable and generally soluble in dimethyl sulfoxide (DMSO) and insoluble in n-hexane which indicates that the complexes are polar. Result from conductivity measurement for all the complexes gives low values (6.8-7.3) $\text{Scm}^2\text{mol}^{-1}$ which indicates poor electrolytic nature of the complexes. It has been observed from the results of infrared study, that the ligands coordinate to the metal through oxygen and nitrogen atom of the ligands and the UV-Visible spectra suggest an octahedral geometry for all the complexes formed. The antimicrobial screening of the complexes revealed that some of the complexes show considerable antibacterial activities against the micro-organisms tested within 10-30 $\mu\text{g}/\text{mL}$.

Keywords: Mixed-ligand, transition metal complexes, ceftriaxone, methionine, antimicrobial.

1.0 Introduction

Recent data revealed the crucial role of transition metal ions in numerous critical biological processes (Hany, *et al.*, 2024), and research in bio-inorganic chemistry strongly supports studying transition metal complexes with mixed ligands, Binesh *et al.*, (2023). Mixed ligand complexes are compound containing two distinct ligand types attached to the same metal ion, often display unique properties compared to simpler complexes. Consequently, there is significant interest in designing mixed ligand systems with diverse attributes (Abd El-Lateef *et al.*, 2023(a); Abd El-Lateef *et al.*, 2023(b)). The efficacy of many pharmaceuticals depends on their ability to coordinate with metal ions or inhibit metalloenzyme activity (Khan *et al.*, 2022). Coordination compounds, characterized by their diverse coordination numbers, geometries, oxidation states, and ability to bind a range of organic and mixed ligands, exhibit unique properties (Dar *et al.*, 2019). Many antibiotics have been found to include metal-binding sites, and extensive research has been conducted on the role of metal complexes in biological functions (Gull *et al.*, 2016). The presence of transition metal ions in stable coordination complexes often enhances the effectiveness of antibiotics, making them more potent than

their uncomplexed forms (Malik *et al.*, 2019). The function of certain antibiotics is contingent upon metal ion cofactors, highlighting the importance of coordination chemistry involving mixed ligands with both transition and non-transition metals (Ayipo *et al.*, 2022). Generally, metal complexes exhibit higher bioactivity compared to free ligands as revealed by Li *et al.*, (2021). One of the most critical issues facing the growing populace is antimicrobial resistance and is escalating rapidly worldwide, driven by the swift rise of multidrug-resistant pathogens, making once-treatable infections increasingly difficult to cure. In the quest to develop new metalloantibiotic drugs with enhanced antibacterial efficacy, several mixed-ligand complexes have been found to demonstrate stronger activity than the original antibiotic ligands. Therefore this study aimed at synthesized some mixed-ligands transition metal(II) complexes with ceftriaxone and methionine ligands, characterize the complexes using melting point, conductivity, solubility, UV-Visible, and FT-IR spectroscopy and evaluate the antimicrobial activities of the ligands and the synthesized complexes

1.1 Importance of Mixed-ligand Complexes

Mixed-ligand complexes play an essential role in various chemical and biological processes, such as photosynthesis in plants, the removal of harmful metals from organisms, electroplating, dyeing, and water softening through ion exchange resins, among others. Many of these complexes are suitable for studying the toxic effects of metal ions, detoxification mechanisms, and therapeutic designs, as they can effectively simulate the function of metal ions in the active sites of metal enzymes. Additionally, understanding the formation of mixed-ligand complexes is vital for grasping how contaminants behave in natural water environments (Swami & Akuskar, 2008).

Moreover, it has been found that these complexes serve as effective catalysts for significant industrial reactions, including the carboxylation of methanol and the oxidative hydrolysis, hydro formation, and hydrogenation of olefins. Additionally, they have shown catalytic activity in various biologically and environmentally important oxidation processes. Mixed-ligand complexes that incorporate amino acids as secondary ligands are particularly valuable, as they can serve as models for enzyme-metal ion substrate complexes (Patil *et al.*, 2012). It is also vital for the processes of dissociation and ligand exchange (Thompson & Loraas, 1963).

2.0 Methodology

2.1 Materials

2.1.1 Chemicals and Reagents

Analytical-grade chemicals and reagents were used without further purification. All solvents, reagents, and ligands were sourced from Sigma Aldrich, BDH, or Kermel, while the metal(II) salts ($\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, and $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$) were procured from AR Company.

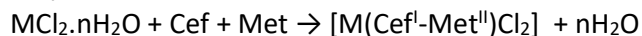
2.2 Methods

2.2.1 Synthesis of the Metal Complexes

The synthesis of the complexes was performed following a modified procedure from the literature (Anacona *et al.*, 2008). A mixture of 0.01 mole (4.085 g) of ceftriaxone was dissolved in 10 mL of distilled water, while 0.01 mole (3.231 g) of the methionine was also dissolved in 10 mL of distilled water and heated on a steam bath until a homogeneous solution was achieved. The resulting solution was combined with a solution of each metal salt (0.01 mole)

in 10 mL of distilled water within a round-bottom flask fitted with a condenser. The reaction mixture was refluxed for 3 hours, then cooled using ice water. The crystalline precipitates formed were separated using simple filtration. The products were thoroughly washed with distilled water and dried in a desiccator for one week.

Equation for the reaction;



Where M = Metal (Ni, Co or Mn), Cef = Ceftriaxone, Met = Methionine.

2.3 Physicochemical Properties of the Metal Complexes

The melting points of the complexes were recorded using a Griffin melting point apparatus. The metal content of the complexes was determined using an Atomic Absorption Spectrophotometer of MODEL AA6800, while conductivity measurements at 25°C were conducted using a conductometer (Mettler P163). FT-IR spectra of the ligand and the complexes were obtained in KBr pellets over the range of 4000–400 cm⁻¹ using a FTIR spectrophotometer. Electronic spectra were measured with a 721 UV-Vis Spectrophotometer across a wavelength range of 200 nm to 800 nm, and antibacterial activity was assessed using the disc diffusion method.

2.3.1 Solubility

The solubility of the ligand and the complexes were determined at room temperature (35°), in polar and non-polar solvents such as methanol, ethanol, chloroform, n-hexane, acetone and DMSO. A small quantity of the powdered sample was placed on a spatula and transferred into separate test tubes for each determination. For instance, 3 mL of cold distilled water was added to 0.1 g of the sample in a test tube and shaken. If the sample did not completely dissolve at room temperature, it was warmed over a water bath and the results were recorded.

2.3.2 Determination of Melting Point

The melting points of all the compounds were determined using a Griffin melting point apparatus. Each synthesized complex was placed into a sealed capillary tube. The capillary tube containing the sample was positioned in one hole of the apparatus, while a thermometer was inserted into the adjacent hole. The temperature each sample melted was recorded as its melting point.

2.3.3 Conductivity

Molar conductivity was measured using a Mettler P163 conductivity meter in dimethyl sulfoxide (DMSO) solutions at a concentration of 10⁻³ M and at 25°C. The measurements were conducted at the Water and Soil Laboratory, Department of Soil Science, University of Maiduguri. The solution was prepared by dissolving the solute in DMSO, and the conductivity was determined at room temperature.

2.3.4 Metal analysis

The metal analysis was determined using atomic absorption spectrophotometer of MODEL AA6800 SHIMADZU at the National Research Institute for Chemical Technology (NARICT) Zaria, Kaduna State, Nigeria. Each complex (0.0004g) was digested in 2.0 cm³ of 50 % of water/nitric

acid. The digest was rinsed quantitatively into a 100 ml standard flask and made up to the mark with distilled water.

2.3.5 Infrared Spectra

The infrared (IR) spectra were recorded as KBr discs using FTIR 8400S Fourier transform spectrophotometer at the National Research Institute for Chemical Technology, Zaria, in the range of 250 to 4000 cm^{-1} for both the ligand and its metal complexes.

2.3.6 Electronic Spectra

The electronic spectra of the ligand and the complexes were recorded in DMSO at a concentration of 10^{-3} M at 25°C using a UV-2500PC series Shimadzu Spectrophotometer, over the range of 250 to 800 nm at the National Research Institute for Chemical Technology (NARICT), Federal Ministry of Science and Technology, Zaria, Nigeria.

2.4 Antimicrobial Activities

Antimicrobial efficacy of the antibiotics and their corresponding metal complexes was assessed against five pathogenic bacterial strains: *Escherichia coli*, *Bacillus subtilis*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Candida albicans*. The agar diffusion technique utilizing filter paper discs was employed to evaluate antibacterial activities. Pure ceftriaxone served as standards for the antibacterial assays. Nutrient agar (NA) was utilized as the growth medium for the bacterial cultures. A volume of 0.1 mL of each compound was deposited onto agar plates, where wells measuring 1.0 cm in diameter were previously created, followed by incubation at 37°C for one to three days. A 1.0% w/v solution of the sterile-filtered ligands and metal complexes was prepared using methanol, while methanol-only discs served as controls. The inhibitory effects were quantified by measuring the diameter (in mm) of the inhibition zones surrounding the wells on the seeded agar plates. Antibacterial activity was determined based on percentage inhibition, calculated by comparing the average diameter of bacterial colonies on the growth medium to that of the respective controls, as follows:

$$\text{Percentage (\%)} \text{ inhibition} = \frac{(A-B \times 100)}{A}$$

Where; A = Average diameter of growth of organisms in the control

B = Average diameter of growth of organisms in the test plates

2.5 Statistical analysis

The collected data were analyzed statistically using Graph Pad prism 9.5 and the results were presented as mean \pm SD.

3.0 Results

Table 1: Physical Properties of the Ligands and their Metal Complexes

Compound	Molecular Formula (Molar Mass)	Colour	Yield(g) (%)	Melting point (d)(°C)	Conductivity (Scm ² mol ⁻¹) Found	Percentage of Metal found (Cald)
Ceftriazone	[C ₁₈ H ₁₈ N ₈ O ₇ S ₃] (554.58)	White	-----	360	-----	-----
Methionine	[C ₅ H ₁₁ NO ₂ S] (149.21)	White	-----	280	-----	-----
[Ni(Cef)(Met)Cl]	[Ni(C ₂₃ H ₂₉ N ₉ O ₉ S ₄)] (762.48)	Bright Green	6.53 (91.0)	93-94 ^d	7.2	8.14 (7.69)
[Mn(Cef)(Met)Cl]	[Mn(C ₂₃ H ₂₉ N ₉ O ₉ S ₄)] (758.72)	Light yellow	3.40 (68.0)	107	6.8	10.50 (7.76)
[Co(Cef)(Met)Cl]	[Co(C ₂₃ H ₂₉ N ₉ O ₉ S ₄)] (762.72)	Pink	2.25 (45.0)	287- 289	7.3	9.16 (7.72)

M=Mn(II), Ni(II), Co(II) CEF=Ceftriazone, MET=methionine, d= decomposition temperature.

Table 2: Solubility of the Ligands and their Metal (II) Complexes

Compound	Distilled Water		Methanol		Ethanol		Acetone		N-hexane		Chloroform		DMSO	
	C	H	C	H	C	H	C	H	C	H	C	H	C	H
Ceftriazone	S	S	S	S	S	S	SS	SS	SS	S	S	S	S	S
Methionine	S	S	SS	SS	SS	SS	SS	SS	IS	SS	SS	SS	S	S
[Ni(Cef)(Met)Cl]	SS	SS	SS	SS	SS	SS	IS	SS	IS	SS	SS	SS	SS	SS
[CO(Cef)(Met)Cl]	SS	SS	SS	SS	SS	SS	IS	SS	SS	SS	SS	SS	SS	SS
[Mn(Cef)(Met)Cl]	IS	SS	SS	SS	SS	SS	SS	SS	IS	IS	IS	SS	S	S

C=Cold, H=Hot, S=Soluble, IS=Insoluble, SS=Springly Soluble

Table 3: Infrared Spectra Data for the Ligands and Drug-Metal Complexes

Compounds	$\nu(\text{OH})$	$\nu(\text{C=O})$	$\nu(\text{C-N})$	$\nu(\text{C-O})$	$\nu(\text{M-O})$	$\nu(\text{M-N})$
CEF	3398	1687	1352	-	-	-
MET	3404	1751	-	-	-	-
[Ni(Cef)(Met)Cl]E	3410b	1643s	-	1141s	671w	-
[Co(Cef)(Met)Cl]I	3417b	1643s	-	1149s	671m	609w
[Mn(Cef)(Met)Cl]J	3379b	1627s	-	1126w	671w	532w

s= strong, w= weak, m= medium, b= broad

Table 4: UV- Visible Spectral data of the Ligands and the Mixed-Metal Complexes

Compounds	Wavelength (nm)	Energies (cm ⁻¹)	Assignments
CEF	270	37037	$\pi \rightarrow \pi^*$
MET	280	35714	$n \rightarrow \pi^*$
[Ni(Cef)(Met)Cl]	305	32786	$n \rightarrow \pi^*$
[Mn(Cef)(Met)Cl]	410	24390	${}^6A_{1g} \rightarrow {}^4T_{1g}$
[Co(Cef)(Met)Cl]	248	40233	$\pi \rightarrow \pi^*$

Table 5: Antimicrobial Activities of the Ligands and their Metal(II) Complexes

Compound	Conc mg/MI	S. Aureus	B. Subtilis	E. Coli	K. Pneumoniae	C. Albicans
CEF	30	29.3±0.5	23.3±0.4	23.0±0.0	30.0±0.0	0.00±0.0
	20	23.3±0.5	17.7±0.5	16.3±0.5	23.3±0.5	0.00±0.0
	10	16.0±0.0	11.0±0.0	10.7±0.5	16.7±0.5	0.00±0.0
[Ni(Cef)(Met)Cl]	30	13.0±0.0	17.0±0.0	23.0±0.0	15.0±0.0	11.0±0.0
	20	9.00±0.0	11.5±0.5	17.7±0.5	9.67±0.5	7.00±0.0
	10	0.00±0.0	7.00±0.0	11.7±0.5	0.00±0.0	0.00±0.0
[Co(Cef)(Met)Cl]	30	16.0±0.0	20.7±0.0	23.0±0.0	20.0±0.0	13.0±0.0
	20	11.0±0.0	15.0±0.0	17.7±0.0	15.0±0.0	8.33±0.5
	10	0.00±0.0	9.33±0.5	9.67±0.5	9.67±0.5	0.00±0.0
[Mn(Cef)(Met)Cl]	30	15.0±0.0	21.7±0.5	28.0±0.0	19.0±0.0	15.0±0.0
	20	10.3±0.5	17.0±0.0	21.7±0.5	13.0±0.0	10.0±0.0
	10	0.00±0.0	12.0±0.0	15.3±0.5	7.00±0.0	0.00±0.0

S. aureus = staphylococcus aureus, *B. subtilis* = Bacillus subtilis, *E. coli* = Escherichia coli, *K. pneumoniae* = Klebsiella pneumoniae, and *C. albicans*=Candida albicans

4.0 Discussion and Conclusion

4.1 Discussion

4.1.1 Physical Properties of the Synthesized Complexes

The synthesized metal(II) complexes exhibit diverse physical properties, including colors, yields, thermal stability, conductivity, metal content, and solubility. The complexes display distinct colors such as light yellow, bright green, and pink, attributed to d-d electronic transitions or ligand-to-metal charge transfer, consistent with literature (Anacona & Rodrigues, 2005; Nair & Joseyphus, 2008). Their percentage yields range from 45% to 91%, influenced by ligand denticity (Osunlaja, 2008). Decomposition temperatures, generally above 100°C, confirm the formation of coordination compounds distinct from the precursor ligands (Al-Bayati *et al.*, 2011). Molar conductivity values (6.8–7.3 Scm² mol⁻¹) indicate non-electrolytic behavior (Ashoor *et al.*, 2020). Experimentally determined metal percentages align with theoretical values, validating the proposed structures. Solubility tests reveal slight.

4.1.2 Infrared Spectra

The significant IR bands for free ceftriaxone and methionine ligands, along with those of their metal (II) complexes, were recorded, and the results are summarized in Table .3 and also presented in Figures 2-7. The infrared spectra of the free ligands were analyzed in comparison to those of the metal (II) complexes to identify any band shifts. Such shifts can provide valuable insights and evidence regarding the coordination of the ligands to the metal ion. (Ajayeoba, *et al.*, 2017).

v(O-H) Stretching

The band assignment in the range of 3398–3417 cm⁻¹ was observed in both the free ligands and the synthesized metal(II) complexes. These bands are indicative of O-H stretching vibrations, aligning with the O-H stretching reported by (Rotimi, *et al.*, 2017), (Sheal, 2015; Jassim, *et al.*, 2015). The v(O-H) band was detected at 3404 cm⁻¹ for the free ligand methionine and at 3398 cm⁻¹ for ceftriaxone. In the metal complexes, this band exhibited various shifts: 3410 cm⁻¹ for [Ni(Cef)(Met)Cl], 3417 cm⁻¹ for [Co(Cef)(Met)Cl] and 3397cm⁻¹ for [Mn(Cef)(Met)Cl] respectively. The complexation involved the O-H group of the amino acids, not of the ceftriaxone, a finding consistent with the results reported by Sankaranayana and Pushpa (2012).

v(C=O) Stretching

The bands at 1687 cm⁻¹ and 1751 cm⁻¹ in the free ligands ceftriaxone and methionine respectively, shifted to 1643 cm⁻¹ in the [Ni(Cef)(Met)Cl] and [Co(Cef)(Met)Cl] complexes, and to 1627 cm⁻¹ in the [Mn(Cef)(Met)Cl] complex. The stretching modes observed in the range of 1627-1766 cm⁻¹ are attributed to the v(COO) stretching vibration. The shift to lower wavenumbers in the complexes suggests that the carbonyl group coordinated with the metal center, aligning with similar findings reported by Waziri *et al.*,(2014)

v(C-O) Stretching

The v(C-O) band was absent in the free ligand ceftriaxone and methionine (Table 3), but appeared in their respective complexes. The emergence of these bands in the complexes indicates that the O atom of the hydroxyl group coordinated with the metal ion.

v(M–O) Stretching

The IR spectra of the Ni(II) complex revealed bands at 671 and 678 cm^{-1} , is indicative of M–O stretching, characteristic of mixed-ligand complexes, as noted by Lever (1984). In the case of the Mn(II) complexes, bands at 586, 570, 609, 625, 578, 544, and 502 cm^{-1} were observed, which were not present in the spectra of the parent ligands. The emergence of new bands in the lower frequency region (536-650 cm^{-1}) is attributed to the M–O interactions, confirming the coordination of the metal to oxygen atoms within the complexes (Abdul-Aziz *et al.*, 2009). Similarly, metal-oxygen (M–O) stretching vibrations were detected in the range of 540-609 cm^{-1} , further corroborated by additional bands observed around 650-450 cm^{-1} and 570-400 cm^{-1} . These bands are indicative of strong M–O coordination, supporting the formation of metal-ligand complexes (Fayad *et al.*, 2012).

v(M–N) Stretching

Waziri *et al.*, (2017) reported similar observations, noting the emergence of new bands corresponding to M–N and M–O stretching vibrations, found in the ranges of 494-524 cm^{-1} and 665-681 cm^{-1} , respectively, in the spectra of the synthesized complexes. Additionally, bands appearing at 432-540 cm^{-1} , likely indicate the coordination of the metal ion through the nitrogen atoms of methionine and ceftriaxone.

4.1.2.1 Infrared Spectra of the Ligands and the metal complexes

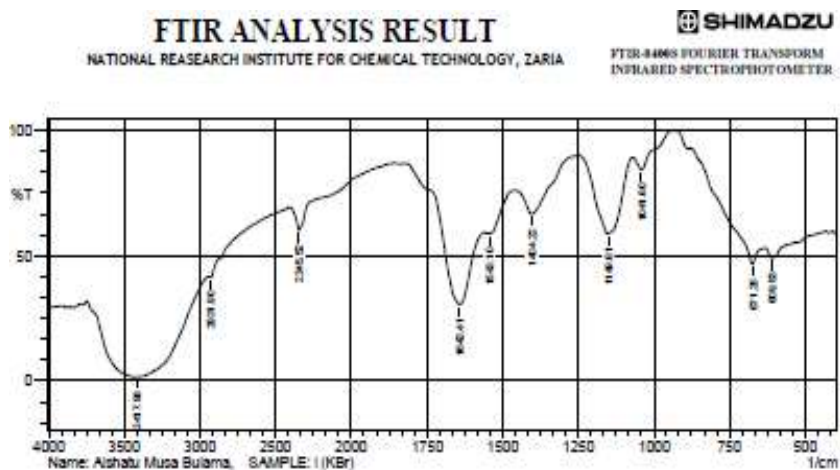


Figure 2: infrared spectrum of ceftriaxone

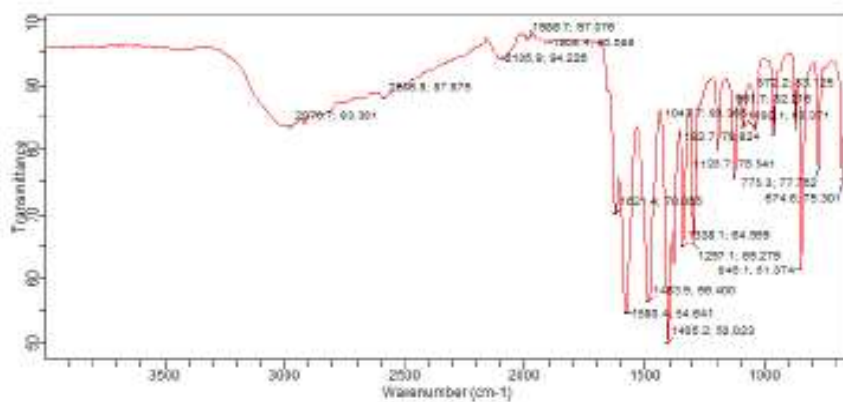


Figure 3: Infrared spectrum of methionine

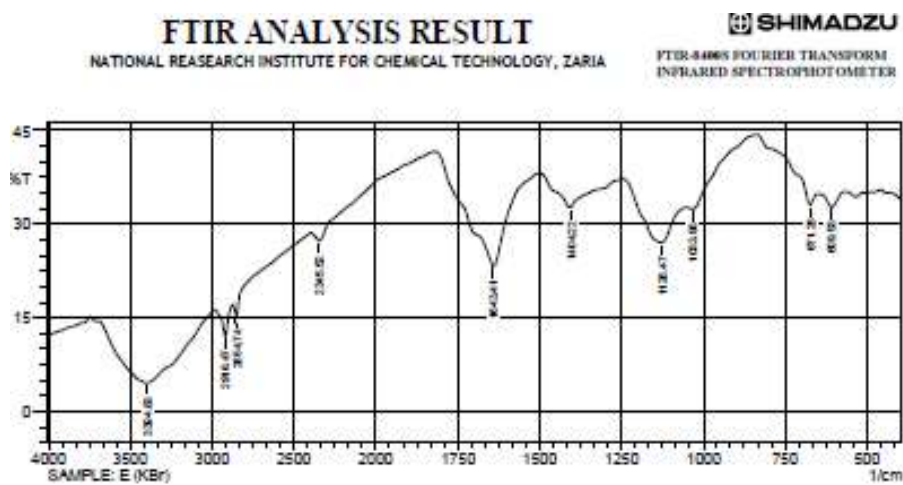


Figure 4: Infrared spectrum of [Ni(Cef)(Met)Cl₂]

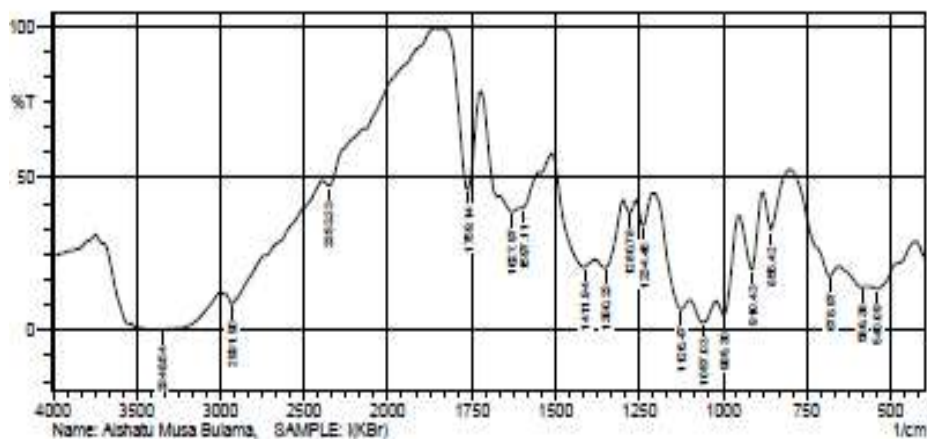


Figure 5: Infrared spectrum of $[Co(Cef)(Met)Cl_2]$

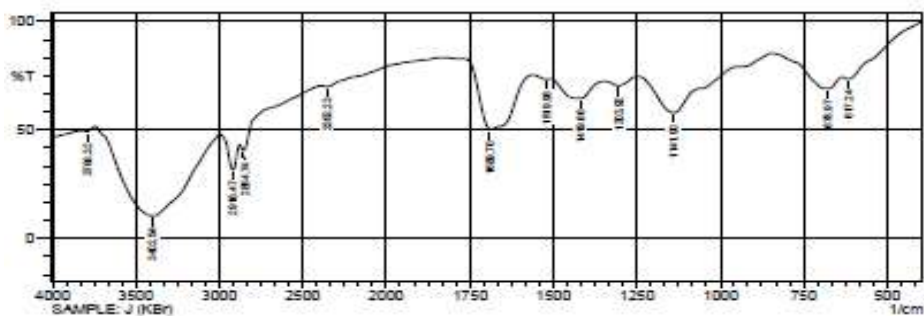


Figure 6: Infrared spectrum of $[Mn(Cef)(Met)Cl_2]$

Figure 7: Infrared spectrum of $[Mn(Cef)(Met)Cl_2]$

4.1.3 Electronic Spectra

The UV-Visible absorption spectra of the free ligands, ceftriaxone and methionine exhibited prominent absorption bands at 270 nm and 280 nm, respectively. In contrast, the electronic spectra of the metal complexes displayed absorption bands in the range of 305-410 nm as presented in Table 4 and also were presented in Figure 8-12. These bands differ from those observed for the ligands and are likely indicative of intra-ligand transitions, specifically $\pi \rightarrow \pi^*$ excitations (Ajayeoba *et al.*, 2017; Babahan *et al.*, 2013). This aligns with previous findings that absorption bands in the range of 200-300 nm are primarily attributed to $n \rightarrow \pi^*$ transitions (Padilha *et al.*, 2008). Conversely, absorption bands below 300 nm can be attributed to $\pi \rightarrow \pi^*$ transitions as reported by Omar & Abdulhady (2012).

The complex, $[Ni(Cef)(Met)Cl]$ exhibit bathochromic shifts at wavelengths of 305 nm indicating a transition to longer wavelengths compared to the free ligands. In contrast, the Co(II) complex

display both hypsochromic and bathochromic shifts. These changes in λ_{max} are likely attributed to d-d transitions within the metal centers (Al-Adilee *et al.*, 2021).

Conversely, the Mn(II) complex formed with ceftriaxone-methionine exhibit absorption band at 410 nm. This band is much longer than that of the free ligand, assignable to the transition $^3A_{2g} \rightarrow ^3T_{1g}$. These transitions occur at higher energy levels, resulting in absorption bands in the UV region that can be attributed to ligand-to-metal charge transfer (LMCT) processes (Nogheua *et al.*, 2017).

4.3.1 UV/Visible Spectra of the Ligands and the Metal Complexes

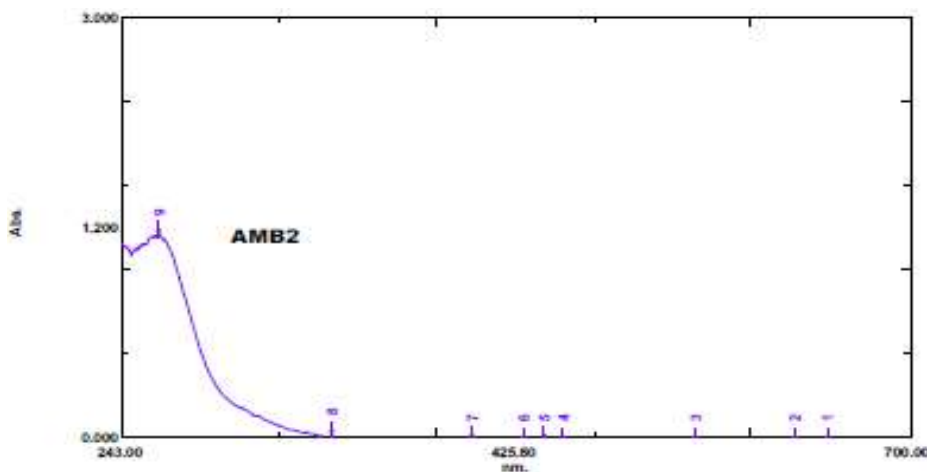


Figure 8: UV/Visible spectrum of ceftriaxone (CEF)

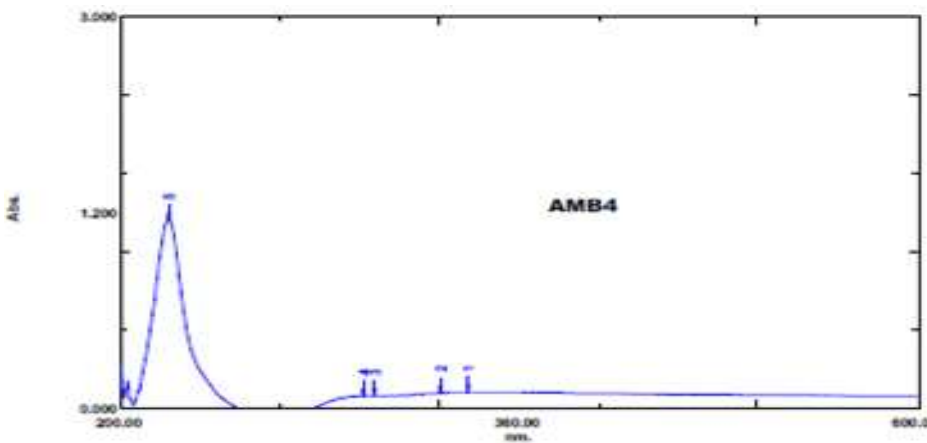


Figure 9: UV/Visible spectrum of methionine (MET)

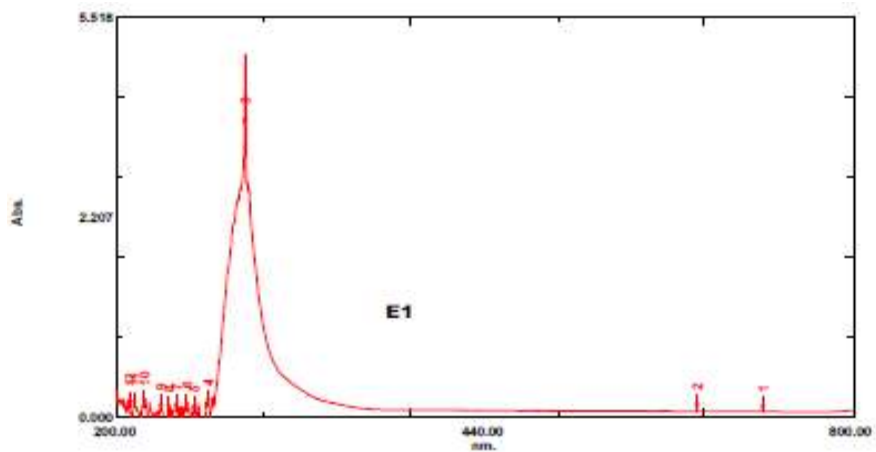


Figure 10: UV/Visible spectrum of $\{Ni(Cef)(Met)Cl_2\}$

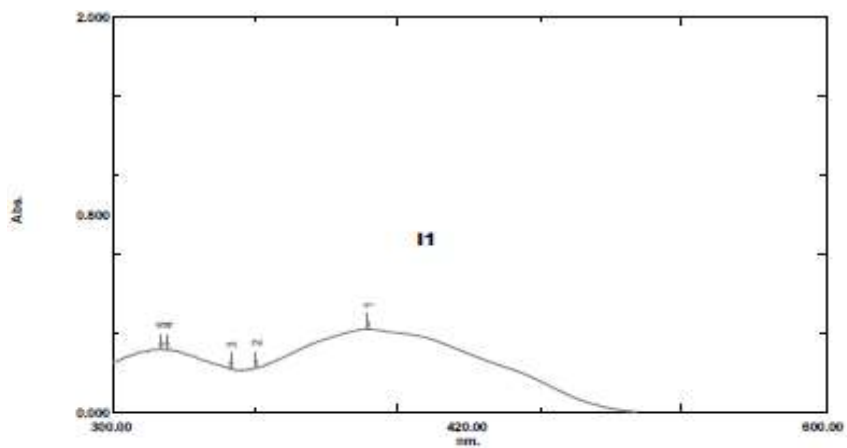


Figure 11: UV/Visible spectrum of $\{Co(Cef)(Met)Cl_2\}$

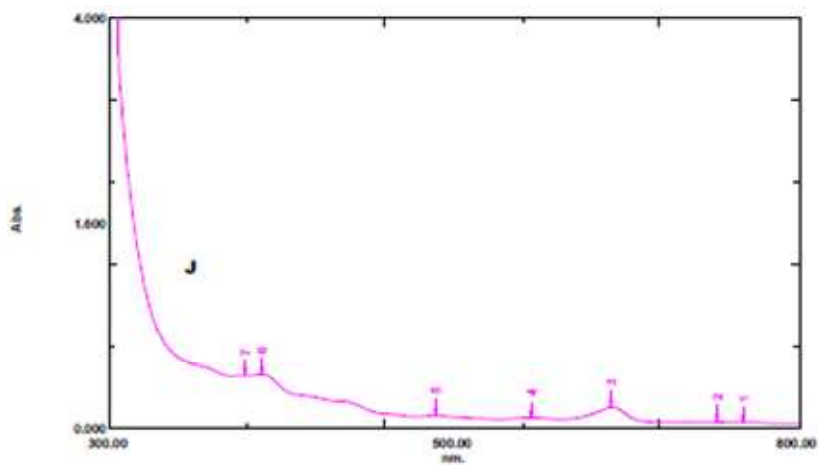
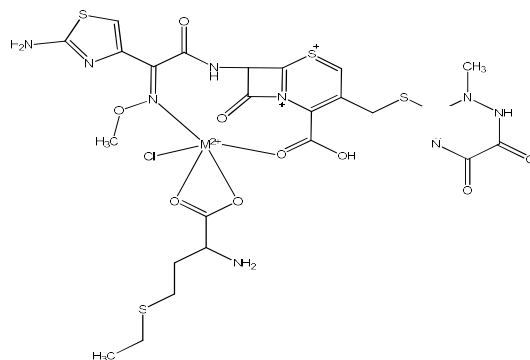


Figure 12: UV/Visible spectrum of $\{Mn(Cef)(Met)Cl_2\}$

Based on the results obtained, the following structure is proposed for the complexes (Figure 1).



Where; $M^{2+} = \text{Mn(II)}, \text{Ni(II)} \text{ or } \text{Co(II)}$

Figure 13: Proposed Structure for Cef-Met M(II) Complexes

4.2 Conclusion

Mixed-ligand complexes of ceftriaxone and methionine were synthesized with Mn(II), Co(II) and Ni(II) through solution based method. The complexes were characterized by solubility, conductivity, melting point, UV-Visible and FTIR spectroscopy. The complexes were observed to display various range of colours such as light yellow, bright green and pink and were characterized by relatively high melting point/decomposition temperatures. The ratio of metal to ligand in the complexes is 1:1:1, and the complexes are all air stable and almost soluble in DMSO and insoluble in n-hexane indicates the complexes are probably polar. Results from conductivity measurement for all the complexes gives low values which indicates that the complexes are non-electrolytes. The infrared study suggests the coordination occur through oxygen of O-H or C=O and also through nitrogen of NH_2 .

The antimicrobial screening of the complexes revealed that some of the complexes show considerable antibacterial activities against the micro-organisms tested within 10-30 $\mu\text{g}/\text{mL}$. However, microanalysis and magnetic moment measurement was not carried out on the complexes due to limitation of instrument in order to further confirm the geometry of the complexes.

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