

Synthesis, Characterization and Antimicrobial Activities of mixed Ligand Metals Complexes with Trimethoprim and Potassium Thiocyanate

Olagboye S. A.

Department of Chemistry, Faculty of Science
Ekiti State University, Ado-Ekiti, Nigeria

ABSTRACT

A new series of Mn (II) and Ni (II) mixed ligands-metal complexes derived from trimethoprim (TMP) and thiocyanate (TC) have been synthesized in aqueous medium and characterized by spectroscopic studies using IR. The coordination of the two ligands towards central metal ions has been proposed in the light of elemental analysis using barium chloride gravimetric method, various colours of metal complexes were obtained ranging from green to light green and found to be soluble in ethanol, butanol, and insoluble in n-hexane, propan-2-ol, and benzene. The following physical parameters were also observed; solubility, melting point and conductivity. The results of the physical and spectroscopic data confirmed that the ligands are chelating agents. The results of spectroscopic studies revealed that TMP acts as a mono-dentate ligand coordinating through the nitrogen of the pyrimidine group and coordination through the nitrogen of the amine group, while in the TC coordination occurred through the sulphur and nitrogen groups because thiocyanate shares its negative charge approximately equally between sulfur and nitrogen. As a consequence, thiocyanate can act as a nucleophile at either sulfur or nitrogen, it is an ambidentate ligand. Antimicrobial activity of the mixed ligands metal complexes and the free ligands were carried out against the bacterial *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and the fungi; *Sclerotinia trifoliorum*, *Fusarium oxysporum*, *Stemania paradoxa*, *Botrytis cinerea*. The mixed ligands metal complexes showed higher activities when compared to the free ligands of TMP but were less active than the free TC ligand. The complexes of Mn (II) showed the highest antimicrobial activity while the Ni (II) complex showed the least activity against the bacterial and fungi organisms. Structure activity relationship showed that Ni (II) complexes containing sulphate ions are more active, while for Mn (II) complexes containing thiocyanate ions showed more enhanced activity than those containing sulphate ions.

Keyword: Trimethoprim; Thiocyanate; *Staphylococcus aureus*; *Stemania paradoxa*

INTRODUCTION

Trimethoprim is an antibiotic used to treat bacterial infections such as prophylaxis and treatment for urinary tract infections [1, 2]. It works by stopping the growth of bacteria. This antibiotic treats only bacterial infections. It will not work for viral infections (such as common cold, flu). Using any antibiotic when it is not needed can cause it to not work for future infections. Thiocyanate blocks active ingestion of inorganic iodide by the thyroid. It prevents

the enzyme thyroperoxidase, thereby inhibiting the incorporation of iodine into thyroglobulin thereby contributing to the hyperthyroid effect of vegetables. Thiocyanate is a competitive inhibitor of the sodium iodide symporter (NIS) at thiocyanate levels normally found in blood. Thereby, it worsens iodine deficiency by inhibition of thyroidal iodide accumulation and by inhibition of iodide transport into breast milk for infant nutrition. Thiocyanates are a group of compounds formed from a combination of sulfur, carbon, and nitrogen. Thiocyanates are found in various foods and plants.

They are produced primarily from the reaction of free cyanide with sulfur. It is also a break down product of Gls. Although thiocyanates are less harmful than cyanide in humans, they are known to affect the thyroid glands, reducing the ability of the gland to produce hormones that are necessary for the normal function of the body [3]. Dietary or nutritional thiocyanate is a very important substance necessary for optimal health and well-being. Thiocyanate is found in specific foods, common to the indigenous African diet as well as some Middle Eastern and Mediterranean diets. When thiocyanate is present in the diet, it acts as an oxygen carrier and increases the capacity of the blood to transport the life-giving oxygen to every single cell of the body. Because of its oxygen – enhancing properties, a diet rich in thiocyanate is effective in helping mitigate sickling of the red blood cells [4]. Exposure to thiocyanate corresponds to a decrease in iodine intake. Cessation of smoking, reduction of industrial pollution and improved diet will reduce the role of thiocyanate in thyroid disease. Large amounts of thiocyanate are generated in people with a high intake of cyanide from tobacco smoking, from cyanide in food, or from industrial pollution of the environment with cyanide. In individuals exposed to high levels of thiocyanate, adverse effects may be prevented by an increase in iodine intake. In areas of low iodine intake, thiocyanate exposure increases the risk of developmental and other iodine deficiency disorders. As the overall effect of thiocyanate is to hamper utilization of iodide, the main effect of thiocyanate is to worsen iodine deficiency. By this mechanism thiocyanate is one of the most important environmental compounds influencing the occurrence of thyroid disease. Thiocyanate shares its negative charge approximately equally between sulfur and nitrogen. As a consequence, thiocyanate can act as a nucleophile at either sulfur or nitrogen, it is an ambidentate ligand. $[\text{SCN}]^-$ can also bridge two ($\text{M}-\text{SCN}-\text{M}$) or even three metals ($>\text{SCN}-$ or $-\text{SCN}<$). Experimental evidence leads to the general conclusion that class A metals (hard acids) tend to form *N*-bonded thiocyanate complexes, whereas class B metals (soft acids) tend to form *S*-bonded thiocyanate complexes. Other factors, e.g. kinetics and solubility, are sometimes involved, and linkage isomerism can occur, for example $[\text{Co}(\text{NH}_3)_5(\text{NCS})]\text{Cl}_2$ and $[\text{Co}(\text{NH}_3)_5(\text{SCN})]\text{Cl}_2$.

The realization of metal chelates increases the lipophilicity of the bioactive compounds and effective permeability of the compounds into the site of action [5]. Antibiotics have modernized medicine but the rapid appearance of resistant strains remains a challenge [6]. This has prompted the search for novel drugs for bacterial chemotherapy. Metal-ligand (drug) complexation is one of the chemotherapeutic routes to inducing biological activity of medicinal agents. The biochemical activity of bioactive species can be boosted by chelation also, chelation reduces the polarity of the metal ion due to overlapping of the ligand orbital and partial sharing of the positive charge of the metal ion [7]. Additionally, such complexes intensify the respiration of the cell and as a result, the growth of the organism is limited by upsetting the protein synthesis.

Transition metal complexes are cationic, neutral or anionic species in which a transition metal is coordinated by ligands [8, 9]. Transition metal ions are known to play very important roles in biological processes in the human body. For example, Zn (II) and Cu (II) ions are the second and third most abundant transition metals in humans [10, 11]. They are found either at the active sites or as structural components of a good number of enzymes. Cobalt is present in vitamin B₁₂, a co-enzyme that plays significant roles in some biochemical processes. There are numerous lists of transition metals which are effective therapeutic agents especially when coordinated to a ligand to form metal complexes [12]. A list of metal containing compounds used in chemotherapy for treatment of diseases include platinum (anticancer), silver (antimicrobial), gold (antiarthritic), bismuth (antiulcer), antimony (antiprotozoal), vanadium (antidiabetic) and iron (antimalaria) [13]. Nitrogen containing chiral ligands have found wide applications in chemotherapy and asymmetric catalysis. Among them 1, 10 – phenanthroline is particularly attractive for its ability to coordinate several metal ions, and thus to generate different catalytic species involved in a great variety of reactions [14]. The ligand (1, 10 – phenanthroline) is a strong field bidentate ligand that forms very stable chelates with many first row transition metals [15]. Salicylic acid is biosynthesized from the amino acid phenylalanine and can be produced by sodium salicylate Diarmiud, [16] and Philip, [17]. In modern medicine, salicylic acid and its derivatives are used as constituents of some rubefacient products, for example, methyl salicylate is used as a liniment to soothe joint and muscle pain, choline salicylate is used typically to relieve the pain of aphthous ulcers [18]. This study was undertaken to give an account on the synthesis, characterization and antimicrobial activity studies of mixed ligands metal complexes of trimethoprim and thiocyanate.

MATERIALS AND METHODS

Reagents and Instruments

All the chemicals were obtained commercially and used as received. Pure sample of Trimethoprim salt, molecular formula C₁₄H₁₈N₄O₃, and potassium thiocyanate (KSCN) salt were obtained from Sigma – Aldrich. Metal salts MnSO₄.6H₂O and NiSO₄.6H₂O were obtained British Drug Chemical House Limited Co, Poole, England. Analytical Reagent grade hydrated metal sulphides from British Scientific Chemicals were used for the preparation of the complexes. Elemental analysis (C, H, N and O) were carried out using micro analytical technique on C, H, N, S, O Elemental analyzer at Universiti Teknologi Petronas (UTP) Malaysia. Other reagents includes ethanol C₂H₅OH, chloroform (CCl₄), propan-2-ol (CH₃CHOHCH₃), benzene, butanol, n-hexane, toluene, acetone, hydrochloric acid, hydrogen peroxide, and nitric acid. The melting points were carried out on a Gallenkamp melting point apparatus. Infra-red spectral analyses were recorded using Shimadzu FTIR-8400S (Fourier Transform Infrared Spectrophotometer) in the range 4500 – 300 cm⁻¹. The solid reflectance studies were also determined using a double beam machine scan in the range 200 – 800 nm.

Synthesis

The complexes were synthesized by the procedure described by Idemudia *et al.* [19] with minor variation. A methanolic solution of the metal salt and the ligands were mixed in a mole ratio of 1:1; 1:2; 1:1:1; 1:2:1 and refluxed at a constant temperature of 100°C for 3 hours 30 minutes. The complexes were recovered after two days, washed and dried in a desiccator. Digestion was carried out by weighing 0.05g of the complex into a beaker, then add about 10ml of 2% NaOH solution to it. Heat until all the H₂O₂ escaped. Allow to cool down and transferring the content into a 50ml standard flask and add distilled water to the mark.

After digestion the sample was acidified with HCl to obtained pH of 1 and heated to 95°C - 100°C. 10ml of 5% BaCl₂, barium chloride solution was added and stirred continuously for 2-3 minutes and leaves the emerging precipitate overnight. The precipitate was filtered using sintered glass and the precipitate was washed with boiling water. The residue was kept inside desiccator and sulphur in form of sulphate was calculated as stated below:

% of sulphur determination in the complexes

$$\text{Percentage sulphur} = \frac{\text{Quantity Sulphur}}{\text{Weight of sample}} \times 100$$

$$1\text{g of BaSO}_4 = \frac{32}{\text{Weight of sample}} \times 100$$

$$\% \text{ of sulphur} = \frac{\text{Total vol.Weight} \times \text{weight of BaSO}_4 \times 0.1373}{\text{Vol.of aliquot} \times \text{weight of sample}} \times 100$$

Weight of BaSO₄ = Difference of final and initial weight

Antibacterial Activities

The test microorganisms used for screening antimicrobial activities were standard pathogenic stains obtained from the culture collection unit of the Department of Microbiology, Ondo state University Teaching Hospital, Akure, Nigeria. The laboratory tests were carried out at the Pest and Control Section of the Department of Crops and protection, Federal University of Technology, Akure, Nigeria. The antimicrobial activities of newly generated complexes were screened against the following fungi: *Sclerotium roofil*, *Mansourian phomoides*, *Collectotrichum lindimuchianum*. Using poisoned food techniques at 0.025g/ml concentration, under sterile culture molten potato dextrose (PDA) and solvent used was dimethylsulphuroxide at 0.025g/ml concentration. A negative control plate (NTR) without any treatment was also set up. The mycelia growth inhibition was calculated in percentage [20]. All newly synthesized complexes were tested for their antibacterial activities against *Streptococcus fecalis*, *Xantomonas axinopolis*, *Salmonella entrica*, *Clavibacter michiganense*, *Xanthomonas phaseoli alongside* with the control (amoxillin), and using Broth Dilution method. At 0.035g/ml concentrations. The MIC (minimal inhibitory concentration) of the control organism is used and read to check the accuracy of the complexes [21]. The lowest concentration inhibiting growth of the organism is recorded as the MIC. This result is compared with the control amoxillin. Mycelia growth were measured with the aid of Vernier calipers, mycelia growth inhibition were calculated in percentage using the formula:

$$\% \text{ ZONE OF INHIBITION} = \frac{\text{NTR} - \text{TR}}{\text{TR}} \times 100$$

Where NTR= Average diameter of fungal colony in negative control sets (plates without any treatment) and TR= Average diameter of fungal colony in treated sets.

RESULTS AND DISCUSSION

Results

The physical properties of nickel and manganese (II) were shown in Tables (1a and b). Tables (2a and b) shows the ratio of different solvent used for the solubility tests of nickel and manganese complexes. Tables (3a and b) shown the elemental analysis of sulfur using gravimetric method and Table (4a and b) redeemed the prominent regions of FTIR spectra of mixed ligand complexes with nickel and manganese (II) while the evaluation of antifungal

activities of Ni^{2+} and Mn^{2+} complexes are shown in Tables 5 and 6 respectively. And finally, evaluation of antibacterial screening of Ni^{2+} and Mn^{2+} complexes are shown in Table 7 and 8.

Table1a: physical properties of Nickel (II) complex

COMPLEX	RATIO	COLOUR	%YIELD	MELTING POINT
$\text{NiLSO}_4(\text{H}_2\text{O}_2)_2$	1:1	Light green	40%	140-250°C
$\text{NiL2SO}_4(\text{H}_2\text{O}_2)_2$	1:2	Light green	40%	90-180°C
$\text{NiLSCNSO}_4(\text{H}_2\text{O}_2)_2$	1:1:1	Green	40%	100-210°C
$\text{NiL2SCNSO}_4(\text{H}_2\text{O}_2)_2$	1:2:1	Green	40%	70-195°C

Table1b: physical properties of manganese complex

COMPLEX	RATIO	COLOUR	%YIELD	MELTING POINT
$\text{MnLSO}_4(\text{H}_2\text{O}_2)_2$	1:1	Light brown	40%	140-250°C
$\text{MnL2SO}_4(\text{H}_2\text{O}_2)_2$	1:2	Light brown	40%	100-200°C
$\text{MnLSCNSO}_4(\text{H}_2\text{O}_2)_2$	1:1:1	Brown	40%	90-190°C
$\text{MnL2SCNSO}_4(\text{H}_2\text{O}_2)_2$	1:2:1	Brown	40%	50-140°C

Table2a: Solubility of the Nickel (II) complex

Complex	Ratio	Toluene	Benzene	Ethanol	Hexane	Acetone
$\text{NiLSO}_4(\text{H}_2\text{O}_2)_2$	1:1	Insoluble	Soluble	Solution	Insoluble	Slightly soluble
$\text{NiL2SO}_4(\text{H}_2\text{O}_2)_2$	1:2	Insoluble	Soluble	Soluble	Insoluble	Slightly soluble
$\text{NiLSCNSO}_4(\text{H}_2\text{O}_2)_2$	1:1:1	Insoluble	Soluble	Soluble	Insoluble	Slightly soluble
$\text{NiL2SCNSO}_4(\text{H}_2\text{O}_2)_2$	1:2:1	Insoluble	Soluble	Soluble	Insoluble	Slightly soluble
$\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_3$						

Table2b: Solubility of the manganese (II) complex

Complex	Ratio	Acetone	Butanol	Ethanol	Carbontetrachloride	Benzene
$\text{MnLSO}_4(\text{H}_2\text{O}_2)_2$	1:1	Soluble	Insoluble	Soluble	Soluble	Soluble
$\text{MnL2SO}_4(\text{H}_2\text{O}_2)_2$	1:2	Soluble	Insoluble	Soluble	Soluble	Soluble
$\text{MnLSCNSO}_4(\text{H}_2\text{O}_2)_2$	1:1:1	Soluble	Insoluble	Soluble	Soluble	Soluble
$\text{MnL2SCNSO}_4(\text{H}_2\text{O}_2)_2$	1:2:1	Soluble	Insoluble	Soluble	Soluble	Soluble
$\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_3$						

Table 3a: Elemental analysis of sulphur using gravimetric

Complex	Ratio	Initial	Final	Amt. of S found	Amt. of S in the complex
$\text{NiLSO}_4(\text{H}_2\text{O}_2)_2$	1:1	29.26	29.3	0.4g	10.9
$\text{NiL2SO}_4(\text{H}_2\text{O}_2)_2$	1:2	29.53	29.59	0.6g	16.4
$\text{NiLSCNSO}_4(\text{H}_2\text{O}_2)_2$	1:1:1	29.26	29.34	0.8g	21.9
$\text{NiL2SCNSO}_4(\text{H}_2\text{O}_2)_2$	1:2:1	29.26	29.33	0.5g	13.7

Table 3b: Elemental analysis of sulphur using gravimetric

Complex	Ratio	Initial	Final	Amt. of S found	Amt. of S in the complex
MnLSO ₄ (H ₂ O) ₂	1:1	29.26	29.31	0.5g	13.7
MnL2SO ₄ (H ₂ O) ₂	1:2	29.26	29.62	0.9g	24.6
MnLSCNSO ₄ (H ₂ O) ₂	1:1:1	29.53	29.6	0.7g	19.2
MnL2SCNSO ₄ (H ₂ O) ₂	1:2:1	29.26	29.32	0.6g	16.4

Where S= Sulphur

Table 4a: PROMINENT IR SPECTRA BANDS (cm⁻¹) OF NICKEL

Ligand	MnLSO ₄ (H ₂ O) ₂	MnL2SO ₄ (H ₂ O) ₂	MnLSO ₄ (H ₂ O) ₂
400-600	504.4	406.99,509.22	389.31,509.22
600-800	609.53,786.98(H ₂ O)	786.98(H ₂ O)	789.98(H ₂ O)
800-1000	830,860,903,993	994.34(SO ₄) ²⁻	1123.57(SO ₄) ²⁻
1000-1200	1,005,103,911,351,150	1125.5(SO ₄) ²⁻	1123.54(SO ₄) ²⁻
1200-1400	1290,1337 (CN)	1238.34(CN)1336.71	1238.34(CN)1337.68
1400-1600	14,501,455	1451.48	1452.5
1600-1800	1650(C=O)	1627.97(C=O)	1624.12(C=O)
1800-2000		1854.62,1979.03(C=H)	1981.92(C=N)
2000-2200		SCN	2195.07-S-(C=N)
2200-2400			
2400-2600	2571		
2600-2800	2798	2720.7	2712
2800-3000	2879-(C-H)	2930.93(C-H)	2937.68(C-H)

3000				
-		3140.22(-C=H)	3138.3	3136.36
3200				
3200				
-	3320-(NH ₂)	3310.92-(NH ₂)	3310.92(NH ₂)	3311.89(NH ₂)
3400				
3400				
-	34789(NH)	3465.23(NH)	3466.2(N-H)	3468.1(N-H)
3600				
3600				
-		3768.07		
3800				
3800				
-		3886.69,3979.28	3879.94(OH)	3895.37(OH),3909.84
4000				
4000				
-				
4200				
4200				
-		4230.03,4391.1		
4400				
4400				
-		4457.64(-OH)		4466.32,4481.75
4600				

Table 4b: PROMINENT IR SPECTRA BANDS (cm⁻¹) OF MANGANESE

	Ligand	NiLSO ₄ (H ₂ O) ₂	NiL2SO ₄ (H ₂ O) ₂	NiL2SO ₄ (H ₂ O) ₂
400-600		406.99,481.26	398.31,509.22	404.1,471.61
600-800		606.63(H ₂ O)	786.98(H ₂ O)	606.63(H ₂ O)
800-1000	830,860,903,993	(Ni-L)	991.44(Ni-L)	(Ni-L)
1000-1200	1,005,103,911,351,150	1010.73,1124.5 (SO ₄) ²⁻	1125.50(SO ₄) ²⁻	1011.7(SO ₄) ²⁻ 1125.5
1200-1400	1290,1337 (CN)	1242.2	1238.34(CN)1335.75	1238.34(C-N)1335.75
1400-1600	14,501,455	1460.16	1457.27	1458.23
1600-1800	1650	1624.12(C=O)	1629.27(C=O)	1626.05, (C=O)
1800-2000			1978.07(C=N)	1851.72, (C=N)
2000-2200		2020.5	2195.07	2019.54, (C=N)
2200-2400				2279.94,-S-(C=N)
2400-2600	2571			2407.24

2600-2800	2798	2712.97	
2800-3000	2879-(C-H)	2838.35,2932.86	2927.08(C-H)
3000-3200		3136.36(N-H)	3144.08(N-H)
3200-3400	3320(NH ₂)	3311.86(NH)	3324.42(-NH)
3400-3600	3478(-NH)	3468.13,3560.71	3468.1(-COOH)
3600-3800			3600.25,3747.81
3800-4000		3879.94(OH)	3865.45
4000-4200			FREE (OH)
4200-4400			
4400-4600		4466.32	4473.07
4600-4800		FREE (OH)	FREE (OH)

Table 5: Antibacterial Activity of Mn (Ii) Complex

Complex	X.unto	B.sub	B.curve	E.coli	P.aur	P.sign	E.coli	S.aures
MnLSO ₄ (H ₂ O ₂) ₂	16	20	-	-	-	-	-	6
MnL2SO ₄ (H ₂ O ₂) ₂	15	5	23	6	-	-	-	14
MnLSCNSO ₄ (H ₂ O ₂) ₂	-	-	-	-	32	6	21	-
CIPRO	24	40	41	27	31	34	35	40
STRED	24	42	36	36	20	22	26	33
METRO	22	27	21	22	23	26	33	32

Table 6: Antibacterial Activity of Ni (Ii) Complex

Complex	X.unto	B.sub	B.curve	E.coli	P.aur	P.sign	E.coli	S.aures
NiLSO ₄ (H ₂ O ₂) ₂	-	-	20	32	32	18	27	31
NiL2SO ₄ (H ₂ O ₂) ₂	-	-	24	15	28	18	26	25
NiLSCNSO ₄ (H ₂ O ₂) ₂	-	-	10	-	36	6	24	21
NiL2SCNSO ₄ (H ₂ O ₂) ₂	-	-	24	15	28	18	26	25
CIPRO	24	40	41	27	31	34	35	40
STRED	24	42	36	36	20	22	26	33
METRO	22	27	21	22	23	26	33	32

Table 7: The Antifungi Result of Ni (II) Complex

Complex	Sclerotium rolfsii	Collectotricium capsicia	Collectotricium capsicia
NiLSO ₄ (H ₂ O) ₂	81(27.68)%	60(36.17)%	41(10.86)%
NiL2SO ₄ (H ₂ O) ₂	82(26.79)%	22.5(76.06)%	(No inhibition)
NiLSCNSO ₄ (H ₂ O) ₂	16.5(85.36)%	28(67.82)%	13(52.42)%
NTR	112	NTR=94	NTR=46

Table 8: The Antifungi Result of Mn (II) Complex

Complex	Sclerotium rolfsii	Collectotricium lindi	Collectotricium capsicia
NiLSO ₄ (H ₂ O) ₂	87.5(21.88)%	56(40.43)%	(No inhibition)
NiL2SO ₄ (H ₂ O) ₂	31(72.32)%	17(81.92)%	18(60.87)%
NiLSCNSO ₄ (H ₂ O) ₂	90(19.64)%	68(27.66)%	33(4.35)%
NTR	112	NTR=94	NTR=46

DISCUSSION

All the complexes formed were colored, pale green being the most predominant color, showing that ligand dominates the metal ions. The percentage yields of the complexes were below 100% increased as the concentration increased, the melting point of complexes Ni and Mn (II) ions ranges from 50-250°C according to results in Table 1a and b. Table 2a and b showed the solubility of the metal Ni and Mn (II) ions complexes, and the results indicated that they were most soluble in ethanol and benzene, Mn ion complexes also soluble in acetone. The gravimetric analysis advocated for the presence of sulfur in the metal-ligand complexes and the amount of sulfur present in each sample, following analytical procedure was higher in Mn than Ni ion, Table 3a, and b.

The infra-red spectroscopic studies of nickel and manganese (II) ion complexes demonstrated different bands between the ligands and metal complexes as shown in Table 4a and b, the bands found around 4500-500cm⁻¹. The prominent bands in the free ligand were 432.15, 521.51 with some pronounced bands at 620.52, 607.42, and 625.89 cm⁻¹ this validates the coordination of metal to the ligand through the nitrogen atom [7]. The absorption bands at 3748-3760 in cm⁻¹ found in the metal complexes revealed the presence of the -OH group from the water of crystallization of Ni (II) salt.

The strong peak at 1625 cm⁻¹ in the mixed ligand complexes of the nickel showed the presence of the C=N group in the other complex and the free ligand [22]. The prominent bands at 1554 cm⁻¹ and 1677 cm⁻¹ in the free ligand complexes whose shifted from 1382 to 1765 cm⁻¹ in the metal complexes, have shown the presence of C=O bonds. Also, the characteristics peak of -S-C=N found around 2195 cm⁻¹ was as a result of thiocyanate present in the mixed ligand of trimethoprim and metals ion [23]. All the complexes formed in the region of 3550-3450 cm⁻¹ have weak and broad bands responsible for the vibrational peaks at this region O-H stretch vibration (intermolecular hydrogen bonding). Olagboye [24] stated that the -OH band could be attached to the activities of water present in the complexes and synthesis. All the complexes of Trimethoprim and the mixed ligand (thiocyanate) showed bands at 406, 404 cm⁻¹ and 504, 509 cm⁻¹ at lower frequency regions indicating the coordination of metal ions to the ligand, and this

fact had been demonstrated and supported by the results of elemental analysis (Mn-L). The sharp band present at 1290 cm^{-1} in the ligand corresponding to $\text{VC}=\text{N}$ disappeared in IR Spectra of all the complexes while a new band at 1238, 1326, 1337, and 1335 cm^{-1} seen in the Mn (II) complexes in attributed $\text{C}=\text{N}$ [23]. The sharp peak found in the ligand 1650 cm^{-1} shows the presence of $\text{C}=\text{O}$ carbonyl in the ligand but with a pronounced shift in all-metal complexes to 1627, 1624, and 1629 cm^{-1} respectively, indicating coordination of metal ions (Mn) to the ligand.

The infra-red spectroscopic studies of cobalt (II) ion complexes demonstrated different bands between the ligands and metal complexes as shown in Table (4a and b), the bands found around (3320) to 3478 cm^{-1} in the spectra of the ligand was assigned to $\text{V}(\text{NH})$ group. The coordination of metal to the ligand through the nitrogen atom has shown in the complexes. The introduction of thiocyanate ion into the complexes was evident regardless of a sharp peak appearing at 2279.94 cm^{-1} for the Mn mixed ligand complex as characterization peak for $\text{S}-\text{C}=\text{N}$ ion from the mixed ligand. The prominent peaks between 1011.7 to 1125 cm^{-1} found in the Ni (II) and Mn (II) complexes were due to the participation of sulfate ions in the complexation confirmed by the gravimetric analysis.

The bioactive activities were carried out against bacteria and fungi using metal-ligand complexes; the results in this prospective showed no or little antimicrobial potency. All the metal complexes are toxic and more or less to fungi species. According to Rahimzadeh *et al.* [25], most complex metals inhibit the growth of organisms directly or indirectly. The results obtained in Tables 5 to 8 give a correct account of the effectiveness of the drug-coated with Ni assay against fungal disease than that of Mn supplements.

CONCLUSION

Having studied the synthesis, characterization, and antimicrobial activities of nickel (II) ion complexes and manganese (II) ion complexes with Trimethoprim and thiocyanate mixed ligand at different ratio concentrations. The solubility tests of the metal complexes in some organic solvents confirmed that they are non-polar and non-electrolyte in nature. The IR spectroscopic characterization revealed the position of attachment of the manganese (II) ion and nickel (II) ion to the ligands manganese was through the oxygen atom of the carbonyl group ($\text{C}=\text{O}$) and the nitrogen atom of $\text{N}-\text{H}$. The antimicrobial activities of manganese (II) ion and nickel (II) ion revealed the bioactivity of the complexes, and they were better inhibitors of fungi and bacteria. Coordination of metal-ligand reduces the polarity of the metal ion mainly because of the partial sharing of its positive charge with donor groups within the chelate ring system. The increase in the antibacterial activities of the complexes compared to the free ligands may be due to the electropositive nature of metals, ultimately enhancing their antibacterial.

References

- [1]. Bergh J. J., Breytenbach, J. C. and Wessels, P. L. (1989). "Degradation of trimethoprim," *Journal of Pharmaceutical Sciences*, vol. 78, no. 4, pp. 348–350.
- [2]. Muthiah, P. T. and Robert, J. J. (1999). Metal-pyrimidine interaction: synthesis and crystal structure of a cadmium complex of trimethoprim $[\text{CdBr}_2(\text{TMP})_2(\text{H}_2\text{O})_2] \cdot \text{H}_2\text{O}$, TMP 5 trimethoprim). *Journal of Chemical Crystallography*. 29(2): 223- 226.
- [3]. ATSDR (2006). A toxicological profile for Cyanide. 74:90-98
- [4]. Medani, A. A., Abel, M. H., Elnour, A. and Amal, M. S. (2010). Endemic goiter in the Sudan despite longstanding programmes for the control of iodine deficiency. *Bulletin of the World Health Organization*, 89:121-126.
- [5]. Zarranz, B., Jaso, A., Aldana, I., and Monge, A. (2003). Synthesis and antimycobacterial activity of new quinoxaline-2-carboxamide-1,4-di-N-oxide derivatives. *Bioorg. Med. Chem.*, 11: 2149–2156.
- [6]. Ekpoudo, U., Lawal, A. and Johnson, A. (2018). Synthesis, Characterization and Antimicrobial Activity of Mixed Trimethoprim-Aspirin Metal Complexes. *World Journal of Applied Science and Technology*, 10(1): 50 – 53.
- [7]. Olagboye, S. A. and Adebawore, A. A. (2021). Synthesis, Characterization, and Antimicrobial Studies of Mixed Ligand Complexes of Acetanilide and Ampicillin with Cobalt (II) and Nickel (II) Ions. *Global Scientific Journal*, 9(11): 1327-1338.
- [8]. Cox, P.A. (2005) "Instant Notes Inorganic Chemistry". (2nded.) BIOS Scientific Publishers New York, NY 10001–2299, USA. p237
- [9]. Warra, A. A. (2011). Transition metal complexes and their application in drugs and cosmetics – "A Review" *J. Chem. Pharm. Res.*, 2011, 3(4):951-958.
- [10]. Kaim, W. and Schwederski, B. (1996). *Bioinorganic Chemistry: Inorganic Elements of Life*, John Wiley and Sons: London, pp 39-262.
- [11]. Xiao-Ming, C., Bao-Hui, Y., Xiao, C.H. and Zhi-Tao, X. J. (1996). *Chem. Soc., Dalton Trans.* 3465.
- [12]. Bhowmick, A. C. and Bikash, D. N. (2019). Coordination complexes of transition metals and schiff base with potent medicinal activity. *American Journal of Chemistry*, 9:109–114.
- [13]. Huang, R., Wallqvist, A. and Covell, G. (2005). Anticancer metal compounds in NCI's tumor – screening database: putative mode of action. *Biochemical Pharmacology*, 69, 1009-1039.
- [14]. Puglisi, A., Benaglia, M., Annunziata, R. and Bologna, A. (2003). Enantiomerically pure phenanthroline or bipyridine containing macrocycles: a new class of ligands for asymmetric catalysis. *Tetrahedron Letters*, 44, 2947–2951.
- [15]. Lee, J. D. (1991). *Concise Inorganic chemistry*. 4th ed, Chapman and Hall: London, pp 607- 1074.
- [16]. Diarmiud J. (2005), "Aspirin the remarkable story of a wonder drug", By: Bloomsbury, pp.38- 40.
- [17]. Philip A. M. (2000) "Brief History of Antipyretic Therapy Clinical infection Diseases", London, pp154-156.
- [18]. Wecker, H. and Laubert, A. (2000) "Reversible hearing loss in acute salicylate", New York, pp.52-65.
- [19]. Idemudia, O. G., Ajibade, P. A. and Okoh, A. I. (2012). Synthesis, characterization and antibacterial screening of 2,4-diaminopyrimidine pyrimethamine and trimethoprim silver complexes. *African Journal of Biotechnology*, 11(39): 9323-9329.
- [20]. Singh, P. and Srivastava, D. (2013). Phytochemical screening and in vitro antifungal investigation of Parthenium hysterophorus extracts against *A. alternata*. *International Research Journal of Pharmacy*. 4:190-193.
- [21]. Konaté, K., Mavoungou, J. F. and Lepengué, A. N. (2012). Antibacterial activity against β -lactamase producing Methicillin and Ampicillin-resistants *Staphylococcus aureus*: Fractional Inhibitory Concentration Index (FICI) determination. *Ann. Clin. Microbiol. Antimicrob.* 11:18.

- [22]. Fetoh, A., Mohammaed, M. A., Youssef, M. M. and El-rash, G. M. A. (2019). Characterization, cyclic voltammetry and biological studies of divalent Co, Ni and Cu complexes of water-soluble, bioactive and photoactive thiosemicarbazone salt. *Journal of Molecular Liquids*, 287:110958–110958.
- [23]. Jacob, J. M., Prathapachandra-Kurup, M. R., Nisha, K., Serdaroğlu, G. and Kaya, S. (2020). Mixed ligand copper (II) chelates derived from an O, N, S- donortridentate thiosemicarbazone: Synthesis, spectral aspects, FMO, and NBO analysis. *Polyhedron*. 189:114736–114736.
- [24]. Olagboye, S. A. (2015). Mixed Ligand Complexes of Cobalt (II) Barbitone in Aqueous Medium and their Biological Activities. *Chemistry and Materials. Research* www.iiste.org. ISSN 2224-3224 (Print) ISSN 2225-0956 (Online). Vol.7, Pg. 129-133.
- [25]. Rahimzadeh, M. R., Rahimzadeh, M. R., Kazemi, S. and Moghadamnia, A. (2017). Cadmium toxicity and treatment: An update. *Caspian Journal of Internal Medicine*. 8(3):135-145.