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Preparation, characterization and antibacterial activity of Mn(II), Cu(II) and Zn(II) complexes of methionine and 2,2-bipyridine co-ligands

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Abstract

Mn(II), Cu(II) and Zn(II) complexes of methionine with polypyridine co-ligand formulated as [Mn(MET)(bpy)2] ***(1)***, [Cu(MET)(bpy)2] ***(2)*** and [Zn(MET)(bpy)2] ***(3)*** (MET = methionine, bpy = 2,2-bipyridine) were prepared and characterized by elemental analysis and spectroscopic techniques(Infrared, Electronic and ESI-MS). Electronic absorption spectra data of the complexes are characteristic of octahedral structures. The infrared data revealed that the ligand (MET) behaved as a bidentate anionic ligand. It coordinated to the metal ions via oxygen and nitrogen atoms with exhibiting peaks for $\upsilon(NH_2)$ at 3365 cm^{-1}, $\upsilon_{as}(COO^-)$ and $\upsilon_{as}(COO^-)$ at 1410 and 1621 cm^{-1} respectively. The 2,2-bipyridine coordinated to the metal center characteristically via the polypyridyl nitrogen. The compounds showed moderate solubility in distilled water and in some common organic solvents. In vivo evaluation of the antimicrobial activities of the metal complexes and the ligands showed greater activity against some micro-organisms when compared to the parent compounds. For instance, MET has a highest growth inhibition zone diameter of 14 mm whereas ***(1), (2), (3)*** has a diameter of inhibition zones at 23, 28 and 28 mm against *C. albicans*, *A. niger* and *C. albicans* respectively.

Keywords: antibacterial, mixed ligands, methionine, polypyridyl

1. Introduction

The relationship between inorganic chemistry and biochemistry has grown into the recognized discipline of bioinorganic chemistry with tons of researches published in this hybrid area. There is good awareness that a little detail in a structure may have a major role in the function of a species, just as analytical methods and techniques for structure determination have become more sophisticated. It has become increasingly lucid that such small detail may be the presence of a metal ion. (Zhang *et al*., 2010). Metals, in particular, transition metals offer potential advantages over the more common organic-based drugs. For example, a wide range of coordination numbers and geometries, accessible redox states, 'tune-ability' of the thermodynamics and kinetics of ligand substitution. (Shimazaki, *et al*., 2009; Theophanides, *et al*., 2003). Metal-based drugs play an important role in medicine for the treatment of various diseases. The majority of chemical researches in this field is focused on the design of safe metallo-therapeutic drugs due to their ability to overcome the developed cell resistance, their biological activity, their side-effects, their low solubility and the advantages over the drugs themselves (Theophanides, *et al*., 2003; Thakkar and Thakkar, 2000; Shivankar and Thakkar, 2003).Various amino acid residues show several functions in biological systems. Their side chain groups are vital for formation of the metal center and in the catalytic action of proteins. They are also involved in other processes such as metal binding, enzyme catalysis, molecular recognition by weak interactions, and formation of the molecular environment (Howard-Lock and Lock, 1987). Amino acids and their derivatives are a wide and important family of ligands. The interactions of certain metal ions with amino acids side chains or with different organic complexes have vital significances in biological systems (Perin and Agarwal, 1973).

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Investigation of amino acids metal complexes has been the research focus of interest for many decades and quite a good number of complexes has been studied (Aurideia *et al*., 2020, Perin and Agarwal 1973).

Design of complexes containing mixed ligands are established to be biologically active against pathogenic microorganisms (Thakkar and Thakkar, 2000; Shivankar and Thakkar, 2003) and polypyridyl as co-ligands in complexes, has shown promising biological activities (Howard-Lock and Lock, 1987). Amino acids form coordination compounds that show significant enzymatic and biological activities ((Perin and Agarwal, 1973). Ternary complexes of amino acid as ancillary ligand are promising as they are interesting models for enzyme metal ion substrate complexes (Freeman, 1973). It is well-known that such coordination mode plays vital role in biological processes. Ternary complex formation occurs commonly in biological fluids, with several potential ligands, including certain amino acids, peptides, peptide derivatives or their analogues. Important transition metals such as Mn(II), Cu(II) and Zn(II) ions in the body are likely to be competed for by heterocyclic N-bases in vivo (Sigel and Sigel, 2005).

In continuation of our previous researches (Osunniran, *et al*., 2018; Rajee, *et al*., 2018 and Obaleye, *et al*., 2014), this paper reports the synthesis, structural characterization and antibacterial studies of mixed ligand metal (II) complexes of methionine amino acid as a primary ligand and 2,2-bpy, a polypyridine as co-ligands.

2. Methodology

2.1 Materials

Methionine was purchased from Loba Chemie Pvt Ltd, analytical grade purity, while manganese(II), copper(II) and zinc(II) chlorides, 2,2-bipyridine, DMSO, ethanol, and methanol, Muller Hinton agar, nutrient agar were purchased from Acros and Merck Laboratories, analytical grade purity.

2.2 Characterization

Elemental analyses were carried out using the CHNS-O EA1110 Analyzer. Electronic spectra were recorded on a Shimadzu UVPC-3001 spectrophotometer. Infrared spectra were recorded on a FTIR Spectrophotometer Spectrum 2000, Perkin Elmer; using KBr pellets.

2.3 Preparation of Complexes

The complexes were prepared according to the methods of Agwara and co-workers (Agwara et. al. 2010); $[Mn(MET)(bpy)_2]$ (**1**). 0.198 g (1 mmol) $MnCl_2{\cdot}4H_2O$ and 0.149 g (1 mmol) methionine were stirred at room temperature for 30 min in 15 mL water-methanol (1:3) after which 0.312 g (2 mmol) 2,2'-bipyridine was added. After additional 4 h of stirring, the resulting pink solution was allowed to evaporate slowly at room temperature. Yellow crystalline solid formed after one week was filtered and washed with water and dried in vacuum desiccator over calcium chloride. Yield: 0.305 g, 74%. FT-IR (KBr pellet, ν cm^{-1}): 3356 (H_2O), 3078 (ArH), 2889, 2775 (CH_2), 1608 (C=O), 1577, 1454 (C=C, C=N), 594, 520(Mn-N, Mn-O). Elem. Anal. Calc. (%) for $C_{25}H_{25}N_5O_2SMn$; C, 58.36; H, 4.90; N, 13.61. Found: C, 58.80; H, 4.88; N, 14.20. ESI-MS (*m/z* positive mode) Calc. 514.11, Found: 512.2.

$[Cu(MET)(bpy)_2]$ (**2**). The complex was prepared using a procedure similar to that for **1** by using $CuCl_2{\cdot}4H_2O$ instead of $MnCl_2{\cdot}4H_2O$. 0.206 g (1 mmol) $CuCl_2{\cdot}4H_2O$ and 0.149 g (1 mmol) methionine were stirred at room temperature for 30 min in 15 mL water-methanol (1:3) after which 0.312 g (2 mmol) 2,2'-bipyridine was added. Yield: 0.254 g, 65%. FT-IR (KBr pellet, ν cm-1): 3375(H_2O), 3059(ArH), 2823, 2752(CH_2), 1608(C=O), 1577, 1454(C=C, C=N), 513, 455(Cu-N, Cu-O). Elem. Anal. Calc. (%) for $C_{25}H_{25}N_5O_2SCu$; C, 57.40; H, 4.82; N, 12.15. Found: C, 57.80; H, 4.83; N, 12.10. ESI-MS (*m/z* positive mode) Calc. 522.10, Found: 522.4.

$[Zn(MET)(bpy)_2]$ (**3**).The complex was prepared using a procedure similar to that for **1** by using $Zn(CH_3COO)_2{\cdot}2H_2O$ instead of $MnCl_2{\cdot}4H_2O$. 0.219 g (1 mmol) $Zn(CH_3COO)_2{\cdot}2H_2O$ and 0.149 g (1 mmol) methionine were stirred at room temperature for 30 min in 15 mL water-methanol (1:3) after which 0.312 g (2 mmol) 2,2'-bipyridine was added. Yield: 0.420 g, 79%. FT-IR (KBr pellet, ν cm-1): 3375(H_2O), 3059(ArH), 2823, 2752(CH_2), 1608(C=O), 1577, 1454(C=C, C=N), 513, 455(Zn-N, Zn-O). Elem. Anal. Calc. (%) for $C_{25}H_{25}N_5O_2SZn$; C, 57.20; H, 4.80; N, 13.34. Found: C, 58.10; H, 4.63; N, 12.12. ESI-MS (*m/z* positive mode) Calc. 523.10, Found: 526.3.

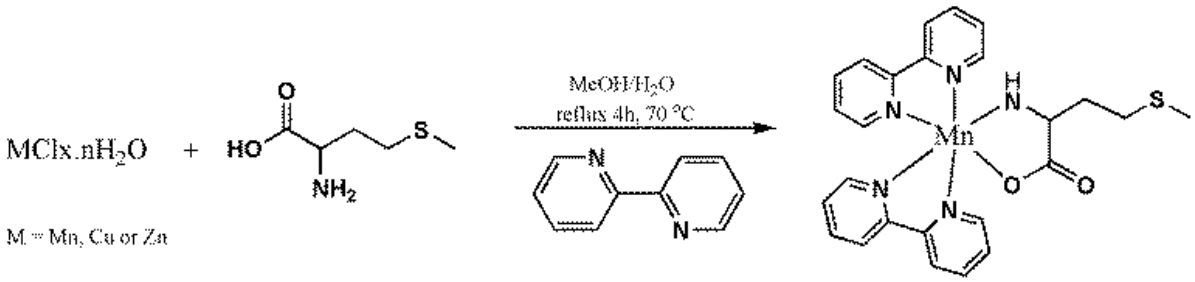
3. Results and Discussion

The mixed-ligand complexes have been prepared according to **scheme 1**. This involved the stirring of aqueous solution of the metal chloride with methionine, followed by the introduction of the 2,2-bipyridine and the entire mixture refluxed for 4 hours. The percent composition of carbon, hydrogen, nitrogen and metal were determined using the CHNS-O EA1110 Analyzer to establish the elemental composition of the coordination compounds. The results are listed in Table 1.

Infrared Studies

The infra-red (IR) spectra of the complexes are provided in the supporting information (SI - Figure 1). The IR spectra data of the complexes shows the characteristic bands of the ligands involved (Table 2). The amino acid, methionine exhibit $\upsilon(NH_2)$ at 3365 cm^{-1}, $\upsilon_s(COO\text{-})$ and $\upsilon_{as}(COO^-)$ at 1410 and 1621 cm^{-1}, respectively. The peak at 3365 and 3347 cm^{-1} which is due to asymmetric and symmetric stretching vibration of N–H in a primary amine group which shows that the group of zwitterions of free ligand is deprotonated to $–NH_2$ and participated in the coordination with metal ion.

For the complexes the stretching vibration of $\upsilon_s(COO^-)$ and $\upsilon_{as}(COO^-)$ appear in the range 1400–1405 cm^{-1} and 1570–1598 cm^{-1}, respectively. The $–COO^-$ asymmetric and symmetric absorption bands are at relatively lower frequencies compare to those of free ligand. The reduction of absorption frequencies may be due to the formation of coordination bond



Scheme 1. Synthetic scheme for the preparation of the complexes

Table 1: Empirical formula, molecular weight, elemental analysis data and molar conductance of complexes

Complex	Empirical formula	Molecular weight	Elemental analysis Found (Calculated)			Melting point (^oC)	Colour
			%C	%H	%N		
[Mn(MET)(bpy)$_2$]	$C_{25}H_{25}N_5O_2SMn$	514.11	58.36 (58.20)	4.90 (4.72)	13.61 (14.10)	242	Yellow
[Cu(MET)(bpy)$_2$]	$C_{25}H_{25}N_5O_2SCu$	522.10	57.40 (57.80)	4.82 (4.83)	12.15 (12.10)	216	Green
[Zn(MET)(bpy)$_2$]	$C_{25}H_{25}N_5O_2SZn$	523.10	57.20 (58.10)	4.80 (4.63)	13.34 (12.12)	208	White

Table 2: Infrared Spectral data of the complexes (cm^{-1})

	$\upsilon_s(COO^-)$	$\upsilon_{as}(COO^-)$	υ(N-H) str	υ(C=N)	υ(M-O)	υ(M-N)
[Mn(MET)(bpy)$_2$]	1400 m	1575 s,b	3350 m	1498	469 m	416 w
[Cu(MET)(bpy)$_2$]	1402 m	1662 s, sp	3232 m	1520	480 m	412 w
[Zn(MET)(bpy)$_2$]	1401 m	1604 s, b	3210 m	1520	482 m	418 w

KEY: s (strong), m (medium), w (weak)

through oxygen atom of –COO− group with metal ion (Gupta and Srivastava, 1985). No free carboxylic (COOH) groups could be detected from the IR spectral data, indicating coordination of all of the studied metal ions to the carboxylate anions. Since there is no significant absorption band at about $\nu > 3450$ cm^{-1} for ν(O–H) absorption in any of the complexes, we can conclude that there is no water molecule in the complexes as coordinated water or as water of crystallization.

Methionine (ν, cm^{-1}): 3414 , ν_{str} (NH_3^+) 2914 ν_{str} (C–H), 1630 ν_{as} (NH_3^+) , 1580 $\nu_{as}(COO^-)$, 1516 ν_{sb} (NH_3^+), 1413 $\nu_s(COO^-)$, 1220 ν_b(S–CH). From the foregoing band positions of $\upsilon(NH_2)$, $\upsilon(COO^-)$, υ(M-O) and υ(M-N) and comparison with similar compounds (Gupta and Srivastava, 1985), it may be concluded that the amino acid involved in the complexes are bidentate coordinating through the -NH_2 and COO^- groups.

Electronic Spectra

The electronic absorption spectra of the mixed metal complexes (SI - Figure 2) and their characteristics absorption bands with tentative assignments were recorded in dimethylformamide at various concentrations and are presented in Table 3. The assignments have been done on the basis of some standard references (Tweedy, 1964 and Singh *et al.*, 1995). The absorption bands between 200 and 400 nm were observed for the organic part of the complexes and that of >400 nm was due to the metal ion. The bonding pattern of the complexes were similar in most of the cases. The bands due to $\pi \rightarrow \pi^*$ transition in all the metal complexes at ~236–257 nm were broad. Whereas in DL–methionine it was found at about 236 nm.

Table 3: Electronic Spectra Data of the complexes

	λmax (nm)	**Assignment**
Methionine	236	π → π*
	294	n → σ*
	350, 338	n → π*
[Mn(MET)(bpy)$_2$]	253,	π → n*
	299,	n → σ*
	338, 365	n → π*
	413	d → d
[Cu(MET)(bpy)$_2$]	238	π → n*
	296	n → σ*
	349, 341	n → π*
	604	d→ d
[Zn(MET)(bpy)$_2$]	236	π → n*
	297	n → σ*
	346, 337	n → π*

The presence of the absorption band at ~295–299 nm in the complexes was due to $n \rightarrow \sigma^*$ transitions that was observed at 264 nm in ligand. The $n \rightarrow \pi^*$ transition bands were observed at 322–358 nm (at 330 and 344 nm in ligand) in all the metal complexes. The presence of $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ and $n \rightarrow \sigma^*$ bands in all the complexes indicate the presence of the functional groups of the parent ligands (e.g. –C═O, –NH_2 and C–S) intact in the complexes. A large shifting of the absorption bands in the complexes and appearing of a new band for d–d transitions also indicate the probability of forming M^+←L coordination bonds in the complexes. Transition metal complexes are generally colored and this color arises due to the absorption of light in visible region. Therefore, the broad bands centering around 421 and 632 nm in Mn(II) and Cu(II) complexes respectively are clearly due to the d–d electronic transitions, which causes color of the complexes. In case of Zn(II) complex, lack of absorption band for d–d transition in the visible region is due to the fact it is a d^{10} system. From the foregoing data, the structure of the complexes can be postulated as shown in Figure. 1:

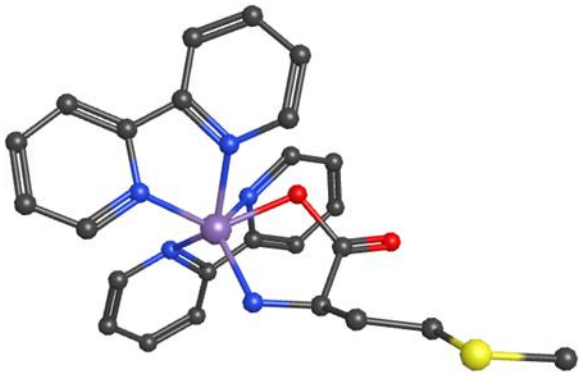


Fig 1: Proposed structure of metal complexes **(1-3)**
C= black; N= blue; O = red; S = yellow and M (Mn, Cu, Zn) = purple

Antimicrobial Activity

The mixed metal complexes were tested for their antimicrobial potential against strains of bacterial and fungi pathogens using the disc diffusion method viz-a-viz B. *subtilis* and S. *aureus* (gram-positive) and E. *coli* and P. *aeruginosa* (gram-negative) and A. *niger* and C. *albicans* (strains of fungi).

The results of the antibacterial screening of the prepared complexes are presented in Table 4. No growth inhibition was observed for solvent and metal salt used, suggesting that they do not mediate in the antimicrobial activity of the synthesized complexes.

Table 4: Results of antimicrobial screening of ligand and metal complexes

	Inhibition zone diameter (mm)					
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
Methionine	14	12	14	14	10	11
[Mn(MET)(bpy)$_2$]	22	21	22	20	23	21
[Cu(MET)(bpy)$_2$]	21	22	24	22	24	28
[Zn(MET)(bpy)$_2$]	24	22	24	26	28	24

The methionine has moderate activity with S. *aureus*, E. *coli*, P. *aeruginosa* and B. *subtilis*. The complexes exhibited significantly improved antibacterial activity against the tested microbial strains in comparison to the free ligand. The Cu(II) and Co(II) complexes displays higher inhibitory activity with Gram positive bacteria than negative ones. It is clearly observed that the complexes are also very active against the fungi *C. albicans* and *A. niger*. However, Zn(II) complexes show a higher antimicrobial activity than the Mn(II). The mixed complexes of Zu(II) and Cu(II) of methionine shows the highest antimicrobial inhibitory activities. Thus, the antimicrobial activity increases on going from ligand to complexation. Figure 2 shows the inhibition zones of methionine and complexes **(1-3)**.

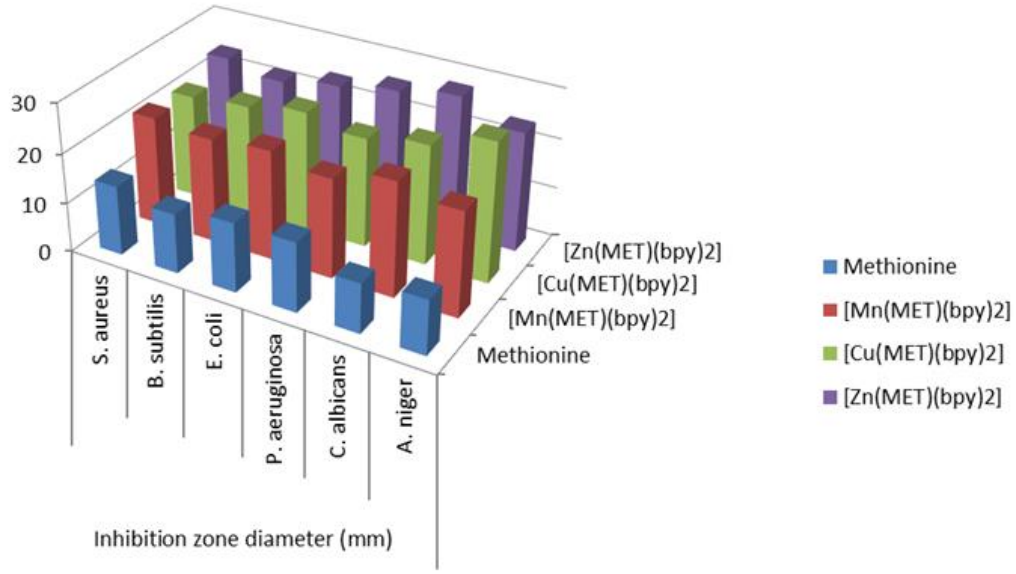


Fig 2: Chart showing the inhibition zones of methionine and complexes (**1-3**)

In the complexes, the part sharing of the positive charge on the central metal atom with the ligands reduces the polarity of the metal atom and there is an electron delocalization over the whole chelated ring (Tweedy, 1964 and Singh, *et al.,* 1995). Indeed, typical chelation tends to improve the lipophilic character of the central atom, which subsequently favours its permeation through the lipid layers of the cell membrane and obstructing the metal binding sites on enzymes of microorganism (Singh, *et al.,* 1995). Thus, we infer that complexation increases the antimicrobial activity.

Conclusion

Summarily, we have prepared and characterized six (6) mononuclear complexes of mixed Mn(II) Cu(II) and Zn(II) containing polypyridyl and methionine. Based on the results of physico-chemical and spectral techniques, the prepared complexes possess an octahedral geometry. The synthesized compounds have been screened for their antimicrobial activity. The results revealed that the mixed complexes have a better antimicrobial activity than the ligands. This is because of the chelation, which reduces the polarity of metal ion due to partial sharing of its positive charge with donor ligands and also due to the delocalization of π electrons over the chelate ring.

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