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Research Letter

Synthesis and Characterization of Biologically Active 10-Membered Tetraazamacrocyclic Complexes of Cr(III), Mn(III), and Fe(III)

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A new series of macrocyclic complexes of type $[M(TML)X]X_2$; where M = Cr(III), Mn(III), or Fe(III); TML is tetradentate macrocyclic ligand and X = Cl^{-1}, $NO_3{}^{-1}$, CH_3COO^{-1} for Cr(III), Fe(III), and X = CH_3COO^{-1} for Mn(III) has been synthesized by template condensation of succinyldihydrazide and glyoxal. The complexes have been formulated as $[M(TML)X]X_2$ due to 1:2 electrolytic natures of these complexes as shown by conductivity measurements. The complexes have been characterized with the help of elemental analyses, molar conductance, electronic, infrared, far infrared spectral studies and magnetic susceptibilities. On the basis of these studies, a five-coordinate distorted square-pyramidal geometry, in which two nitrogens and two carbonyl oxygen atoms are suitably placed for coordination toward the metal ion, has been proposed for all the complexes. The complexes were tested for their in vitro antibacterial activity. Some of the complexes showed remarkable antibacterial activities against some selected bacterial strains. The minimum inhibitory concentration shown by these complexes was compared with minimum inhibitory concentration shown by some standard antibiotics like linezolid and cefaclor.

1. Introduction

During the past few decades macrocyclic chemistry has attracted the attention of both inorganic and bioinorganic chemists. The synthesis of macrocyclic complexes has been a fascinating area of research and growing at a very fast pace owing to their resemblance with naturally occurring macrocycles and analytical, industrial, and medical applications [1–3]. In the present paper a new series of macrocyclic complexes of Cr(III), Mn(III), and Fe(III) obtained by template condensation reaction of succinyldihydrazide and glyoxal has been reported. These complexes were also tested for their in vitro antibacterial activities. Some complexes showed remarkable antibacterial activities.

2. Experimental

All the complexes were prepared by template method. To a stirring methanolic solution (~50 cm^3) of succinyldihydrazide (10 mmol) was added trivalent chromium, manganese, and iron salt (10 mmol) dissolved in a minimum quantity of methanol (20 cm^3). The resulting solution was refluxed for 0.5 hour. After that glyoxal (10 mmol) dissolved in ~20 mL of methanol was added to the refluxing mixture and refluxed again for 6–8 hours. On overnight cooling, a dark colored precipitate formed which was filtered, washed with methanol, acetone, and diethyl ether and dried in vacuo (Yield 45%). The complexes were found soluble in DMF and DMSO, but were insoluble in common organic solvents and water. They were found thermally stable up to ~240°C and then decomposed.

3. Pharmacology

3.1. In Vitro Antibacterial Activity. Some of the synthesized macrocyclic complexes were tested for their in vitro antibacterial activity against some bacterial strains using spot-on-lawn on Muller Hinton Agar by following the reported method [4]. Four test pathogenic bacterial strains viz *Bacillus cereus* (MTCC 1272), *Salmonella typhi* (MTCC 733),

Table 1: Analytical data of trivalent chromium, manganese, and iron complexes derived from succinyldihydrazide and glyoxal. Found (Calcd.) %.

Serial no.	Complexes	M	C	H	N	Colour	Mol. Wt.
1	$[Cr(C_6H_8N_4O_2)Cl]Cl_2$	15.12(15.95)	22.39 (22.08)	2.43 (2.45)	17.19 (17.17)	Light green	326
2	$[Cr(C_6H_8N_4O_2)(NO_3)](NO_3)_2$	12.78(12.80)	17.49 (17.73)	1.79 (1.97)	24.31 (24.13)	Light mustered	406
3	$[Cr(C_6H_8N_4O_2)(OAc)](OAc)_2$	13.15(13.09)	36.31 (36.27)	4.29 (4.28)	14.12 (14.10)	Yellowish white	397
4	$[Mn(C_6H_8N_4O_2)(OAc)](OAc)_2$	13.81(13.75)	36.10 (36.00)	4.19 (4.25)	14.01 (14.00)	Creamy	400
5	$[Fe(C_6H_8N_4O_2)Cl]Cl_2$	16.84(16.96)	21.89 (21.81)	2.39 (2.42)	16.94 (16.96)	Light yellow	330.5
6	$[Fe(C_6H_8N_4O_2)(NO_3)](NO_3)_2$	13.89 (13.65)	17.58 (17.56)	1.92 (1.95)	23.87 (23.90)	Creamy	410
7	$[Fe(C_6H_8N_4O_2)(OAc)](OAc)_2$	13.87 (13.96)	35.88 (35.91)	4.27 (4.23)	13.82 (13.95)	Light brown	401

Escherichia coli (MTCC 739), and *Staphylococcus aureus* (MTCC 1144) were considered for determination of Minimum Inhibitory Concentration (MIC) of selected complexes.

3.2. Culture Conditions. The test pathogens were subcultured aerobically using Brain Heart Infusion Agar (HiMedia, Mumbai, India) at 37°C/24 hours. Working cultures were stored at 4°C in Brain Heart Infusion (BHI) broth (HiMedia, Mumbai, India), while stock cultures were maintained at −70°C in BHI broth containing 15% (v/v) glycerol (Qualigens, Mumbai, India). Organisms were grown overnight in 10 mL BHI broth, centrifuged at 5000 g for 10 minutes, and the pellet was suspended in 10 mL of phosphate buffer saline (PBS, pH 7.2). Optical density at 545 nm (OD-545) was adjusted to obtain 10^8 cfu/mL followed by plating serial dilution onto plate count agar (HiMedia, Mumbai, India).

3.3. Determination of Minimum Inhibitory Concentration. The minimum inhibitory concentration (MIC) is the lowest concentration of the antimicrobial agent that prevents the development of viable growth after overnight incubation. Antimicrobial activity of the compounds was evaluated using spot-on-lawn on Muller Hinton Agar (MHA, HiMedia, Mumbai, India). Soft agar was prepared by adding 0.75% agar in Muller Hinton Broth (HiMedia, Mumbai, India). Soft agar was inoculated with 1% of 10^8 Cfu/mL of the test pathogen and 10 mL was overlaid on MHA. From 1000X solution of compound (1 mg/mL of DMSO) 1, 2, 4, 8, 16, 32, 64, and 128X solutions were prepared. Dilutions of standard antibiotics (Linezolid and Cefaclor) were also prepared in the same manner. 5 μL of the appropriate dilution was spotted on the soft agar and incubated at 37°C for 24 hours. Zone of inhibition of compounds was considered after subtraction of inhibition zone of DMSO. Negative control (with no compound) was also observed.

4. Results and Discussion

The analytical data show the formula of macrocyclic complexes as $[M(C_6H_8O_2N_4)X]X_2$. The test for anions was positive before and after decomposing the complexes with concentration of HNO_3, indicating their presence inside as well as outside the coordination sphere. Conductivity measurements in DMSO indicated them to be electrolytic in nature (140–150 ohm^{-1} cm^2 mol^{-1}) [5]. All compounds gave satisfactory elemental analyses results as shown in Table 1.

4.1. IR Spectra. In the infrared spectrum of succinyldihydrazide a pair of band corresponding to $\nu(NH_2)$ is present at ~3200 cm^{-1} and ~3250 cm^{-1}, but is absent in the IR spectra of all the complexes. However, a single broad medium band at ~3350–3400 cm^{-1} was observed in the spectra of all the complexes which may be assigned due to ν(NH). Further no strong absorption band was observed near 1710 cm^{-1} as observed in spectrum of glyoxal indicating the absence of >C=O groups of glyoxal molecule. This confirms the condensation of carbonyl groups of glyoxal and amino groups of succinyldihydrazide [6]. This fact is further supported by appearance of a new strong absorption band in the region ~1590–1610 cm^{-1} in the IR spectra of all complexes which may be attributed due to ν(C=N) [7]. These results provide strong evidence for the formation of macrocyclic frame [8]. The lower value of ν(C=N) indicates coordination of nitrogens of azomethine to metal [9]. A strong peak at ~1665 cm^{-1} in the IR spectrum of succinyldihydrazide is assigned due to >C=O group of the CONH moiety. This peak gets shifted to lower frequency (~1625–1640 cm^{-1}) in the spectra of all the complexes [10] suggesting the coordination of oxygen of amide group with metal.

4.2. Far Infrared Spectra. The far infrared spectra show bands in the region ~425–445 cm^{-1} corresponding to ν(M–N) vibrations in all the complexes. The bands present at ~300–315 cm^{-1} are assigned to ν(M–Cl) vibrations. The bands present at ~220–250 cm^{-1} in all nitrato complexes to ν(M–O) vibrations of nitrato group [11].

4.3. Magnetic Measurements and Electronic Spectra

4.3.1. Chromium Complexes. Magnetic moment of chromium complexes were found in the range of 4.20–4.50 B.M. These values of magnetic moment support the predicted geometry of the complexes [12]. The electronic spectra of chromium complexes show bands at ~9030–9250, 13020–13350, 17450–18320, 27435–27840, and 34820 cm^{-1}. However, these spectral bands cannot be interpreted in terms of four or six coordinated environment around the metal atom.

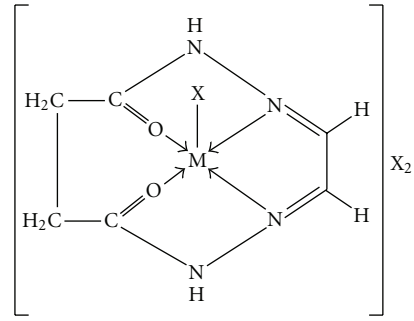
Table 2: Minimum Inhibitory Concentration (MIC) shown by complexes against test bacteria by using agar dilution assay. (—) No activity, a: *Bacillus cereus* (MTCC 1272); b: *Staphylococcus aureus* (MTCC 1144); c: *Escherichia coli* (MTCC 739); d: *Salmonella typhi* (MTCC 733); Cefaclor and Linezolid are standard antibiotics.

Serial no.	Complexes	MIC (μg/mL)			
		a	b	c	d
(1)	$[Cr(C_6H_8N_4O_2)Cl]Cl_2$	32	32	8	64
(2)	$[Cr(C_6H_8N_4O_2)(NO_3)](NO_3)_2$	—	—	64	>128
(3)	$[Cr(C_6H_8N_4O_2)(OAc)](OAc)_2$	8	64	64	32
(4)	$[Mn(C_6H_8N_4O_2)(OAc)](OAc)_2$	64	>128	16	64
(5)	$[Fe(C_6H_8N_4O_2)Cl]Cl_2$	>128	64	64	>128
(6)	$[Fe(C_6H_8N_4O_2)(NO_3)](NO_3)_2$	32	4	64	>128
(7)	$[Fe(C_6H_8N_4O_2)(OAc)](OAc)_2$	>128	64	>128	32
	Cefaclor	8	2	8	16
	Linezolid	4	4	16	32

In turn, the spectra are comparable to that of five coordinated Cr(III) complexes, whose structure has been confirmed with the help of X-ray measurements [13]. Thus keeping in view, the analytical data and 1 : 2 ionic nature of these complexes, a five-coordinated square-pyramidal geometry may be assigned for these complexes. Thus, assuming the symmetry C_{4V} for these complexes [14], the various spectral bands may be assigned as $^4B_1 \rightarrow {}^4E^a$, $^4B_1 \rightarrow {}^4B_2$, $^4B_1 \rightarrow {}^4A_2$, and $^4B_1 \rightarrow {}^4E^b$. The complexes do not have idealized C_{4V} symmetry but it is being used as approximation in order to try and assign the electronic absorption bands.

4.3.2. Manganese Complex. The magnetic moment of manganese complex was found to be 4.85 B.M. The electronic spectrum of manganese complex show three d-d bands at approximately 12.250, 16.045, and 35.435 cm^{-1}. The higher energy band at 35465 cm^{-1} may be assigned due to charge transfer transitions. The spectrum resembles those reported for five-coordinate square-pyramidal manganese porphyrins [14]. This idea is further supported by the presence of the broad ligand field band at 20410 cm^{-1} diagnostic of C_{4V} symmetry and thus the various bands may be assigned as follows: $^5B_1 \rightarrow {}^5A_1$, $^5B_1 \rightarrow {}^5B_2$, and $^5B_1 \rightarrow {}^5E$, respectively. The band assignment in single electron transition may be made as $d_{z^2} \rightarrow d_{x^2-y^2}$, $d_{xy} \rightarrow d_{x^2-y^2}$ and d_{xy}, $d_{yz} \rightarrow d_{x^2-y^2}$, respectively, in order of increasing energy. However, the complexes do not have idealized C_{4V} symmetry.

4.3.3. Iron Complexes. The magnetic moments of iron complexes lay in the range 5.82–5.90 B.M. and are in accordance with proposed geometry of the complexes. The electronic spectra of trivalent iron complexes show various bands 9825–9975, 15525–15570, 27635–27710 cm^{-1}, and these bands do not suggest the octahedral or tetrahedral geometry around the metal atom. The spectral bands are consistent with the range of spectral bands reported for five coordinate square pyramidal iron (III) complexes [15]. Assuming C_{4V} symmetry for these complexes, the various bands can be assigned as $d_{xy} \rightarrow d_{xz}$, d_{yz} and $d_{xy} \rightarrow d_{z^2}$. Any attempt to make accurate assignment is difficult due to interactions of the metal-ligand pi-bond systems lifting the degeneracy of the d_{xz} and d_{yz} pair.



Where M = Cr(III), Mn(III), Fe(III)
X = Cl^{-1}, $NO_3{}^{-1}$, CH_3COO^{-1} for Cr(III) and Fe(III) and X = CH_3COO^{-1} for Mn(III)

Figure 1

5. Biological Assay

The minimum inhibitory concentration (MIC) shown by the complexes against these bacterial strains was compared with MIC shown by standard antibiotics *Linezolid* and *Cefaclor* (Table 2). Complex 1 showed an MIC of 8 μg/mL against bacterial strain *Escherichia coli* (MTCC 739), which is equal to MIC shown by standard antibiotic *Cefaclor* against the same bacterial strain. Complex 3 registered an MIC of 8 μg/mL, against bacterial strain *Bacillus cereus* (MTCC 1272), which is equal to MIC shown by standard antibiotic *Cefaclor* against the same bacterial strain. Further complexes 3 and 7 showed a minimum inhibitory concentration of 32 μg/mL against bacterial strain *Salmonella typhi* (MTCC 733), which is equal to MIC shown by standard antibiotic *Linezolid* against the same bacterial strain. The MIC of complex 4 against *Escherichia coli* (MTCC 739) was found to be 16 μg/ml, which is equal to the MIC shown by standard antibiotic *Linezolid* against the same bacterial strain. Complex 6 registered an MIC of 4 μg/mL against bacterial strain *Staphylococcus aureus* (MTCC 1144) which is equal to MIC shown by standard antibiotic *Linezolid* against the same bacterial strain. Among the series under test for determination of MIC, complexes 1 and 3 were found most potent as compared to other complexes. However, complexes 2 and 5 showed poor antibacterial activity or no activity against all bacterial strains among the whole series. (Table 2).

6. Conclusions

6.1. Chemistry. Based on elemental analyses, conductivity and magnetic measurements, electronic IR, and far IR spectral studies, the structure as shown in Figure 1 may be proposed for these complexes.

6.2. Biological Assay. It has been suggested that chelation/coordination reduces the polarity of the metal ion mainly because of partial sharing of its positive charge with donor group within the whole chelate ring system [16]. This process of chelation thus increases the lipophilic nature of the central metal atom, which in turn, favors its permeation through the lipoid layer of the membrane thus causing the metal complex to cross the bacterial membrane more effectively thus increasing the activity of the complexes.

Abbreviations

MIC: Minimum inhibitory concentration
MTCC: Microbial type culture collection
MHA: Muller Hinton Agar
CFU: Colony forming unit
B.M.: Bohr Magneton
DMF: N,N-dimethylformamide
DMSO: Dimethylsulphoxide
BHI: Brain heart infusion

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