Journal of Enzyme Inhibition and Medicinal Chemistry, June 2009; 24(3): 883–889

Antibacterial activity and spectral studies of trivalent chromium, manganese, iron macrocyclic complexes derived from oxalyldihydrazide and glyoxal

D. P. SINGH[1], RAMESH KUMAR[1], & JITENDER SINGH[2]

[1]*Department of Chemistry, National Institute of Technology, Kurukshetra, Haryana 136 119, India, and* [2]*Department of Microbiology, Kurukshetra University, Kurukshetra, Haryana 136 119, India*

(*Received 11 July 2007; revised 5 October 2007; accepted 22 August 2008*)

Abstract

A new series of complexes is synthesized by template condensation of oxalyldihydrazide and glyoxal in methanolic medium in the presence of trivalent chromium, manganese and iron salts forming complexes of the type: $[M(C_8H_8N_8O_4)X]X_2$ where M = Cr(III), Mn(III), Fe(III) and X = Cl^{-1}, NO_3^{-1}, CH_3COO^{-1}. The complexes have been characterized with the help of elemental analyses, conductance measurements, magnetic susceptibility measurements, electronic, NMR, infrared and far infrared spectral studies. On the basis of these studies, a five coordinate square pyramidal geometry for these complexes has been proposed. The biological activities of the metal complexes were tested *in vitro* against a number of pathogenic bacteria and some of the complexes exhibited remarkable antibacterial activities.

Keywords: *Antibacterial activity, macrocyclic complexes, infrared spectra, magnetic measurements, metal complexes*

Abbreviations: *MRI, Magnetic Resonance Imaging; BHI, Brain Heart Infusion; MTCC, Microbial Type Culture Collection; MHA, Muller Hinton Agar; MIC, Minimum Inhibitory Concentration; CFU, Colony Forming Unit; B.M., Bohr Magneton*

Introduction

The chemistry of macrocyclics has received much attention and such compounds have been studied extensively in recent years and have attracted growing interest among coordination chemists [1,2]. Template reactions lie at the heart of macrocyclic chemistry and are best aid for the preparation of macrocyclic complexes [3,4]. Generally transition metal ions have been used as templates [5]. The importance of macrocyclic complexes in coordination chemistry is because of its various applications in biological processes such as photosynthesis and dioxygen transport; catalytic properties, potential applications as metal extractants and radio therapeutic agents [6]. The importance of macrocyclic complexes is due to their resemblance with many natural systems like porphyrins and cobalamines [7]. Macrocyclic complexes have attracted attention because of their pharmacological properties i.e. toxicity against bacterial and fungal growth [8,9]. Some macrocyclic complexes have been reported to have anti-inflammatory approach [10]. Several macrocyclic complexes with tetraazamacrocyclic ligands, such as cyclen, cyclam or bicyclam were reported to exhibit antitumour activity [11]. Macrocyclic metal complexes of lanthanides *e.g.* Gd^{+3} are used as MRI contrast agents [12]. The chemistry of macrocyclic complexes is also important due to their use as dyes and pigments [13] as well as NMR shift reagents [14]. The amide macrocyclic complexes are of special interest since they can function as catalyst in many oxidation reactions [15]. Several macrocyclic complexes containing amide groups have been reported [16,17]. In our previous paper we have reported template synthesis of biological active amide macrocyclic complexes of Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) derived from

Correspondence: D. P. Singh, Department of Chemistry, National Institute of Technology, Kurukshetra, Haryana 136 119, India. Tel: 91 174 423 35 12. Fax: 91 174 423 80 50. E-mail: dpsinghchem@yahoo.co.in

ISSN 1475-6366 print/ISSN 1475-6374 online © 2009 Informa UK Ltd.
DOI: 10.1080/14756360802456397

oxalyldihydrazide and glyoxal [18]. Prompted by these applications, in the present paper template synthesis of amide macrocyclic complexes of Cr(III), Mn(III) and Fe(III) is reported. These complexes were characterized with the help of various physicochemical techniques like IR, NMR, magnetic susceptibilities, elemental analyses, and conductance measurements. Further these complexes were also tested for their biological activities against some pathogenic bacterial strains viz *Bacillus cereus, Salmonella typhi, Escherichia coli, Staphylococcus aureus* and results so obtained were compared with antibacterial activities shown by standard antibiotics such as cefaclor and linezolid.

Experimental

Chemistry

The complexes were synthesized by template method by condensing oxalyldihydrazide and glyoxal in the presence of the respective trivalent metal salt. To a hot stirring methanolic solution (~50 mL) of oxalyldihydrazide (10 mmol) was added trivalent chromium, manganese or iron salt (5 mmol) dissolved in the minimum quantity of methanol (~20 mL). The resulting solution was boiled under reflux for 0.5 h. After that, glyoxal (10 mmol) was added in the refluxing mixture and refluxing was continued for 6-8 h. The mixture was concentrated to half of its volume and kept in a desiccator overnight. The complexes were then filtered, washed with methanol, acetone and ether, dried *in vacuo*; Yield obtained ~45-50%. The complexes are soluble in DMF and DMSO, but are insoluble in common organic solvents and water. The complexes were found thermally stable up to ~240-260°C and then decomposed.

The template syntheses of complexes derived from oxalyldihydrazide and glyoxal may be represented by the following scheme:

Analyses. The microanalysis of C, H, and N were recorded on a Elementar Vario EL III (Carlo Erba 1108) at CDRI, Lucknow. Melting points were determined using capillaries in electrical melting point apparatus. The metal contents were estimated using standard methods [19].

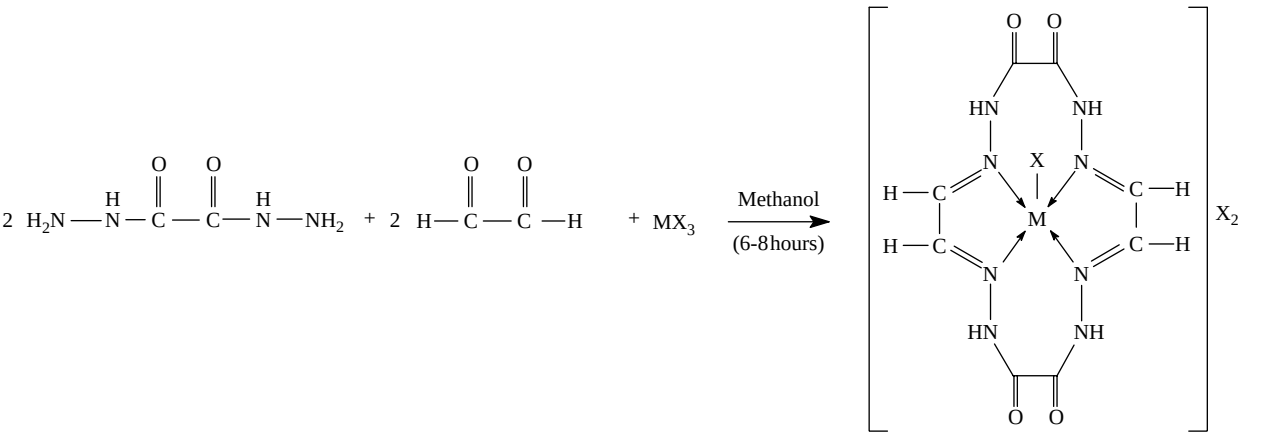
Physical measurements. Electronic spectra of metal complexes were recorded in the region 1100-200 nm on a Hitachi U-2000 spectrophotometer. IR spectra were recorded on Beckman IR-20 spectrophotometer in KBr/Nujol mull in the range 4000-200 cm^{-1}. Proton NMR spectra was recorded in DMSO (d6) on Brucker ACF 300 spectrometer at 300 MHz reference to Me_4Si (0.0 ppm). Magnetic moments studies were carried out at SAIF, IIT, Roorkee, on Vibrating Sample Magnetometer (Model PAR 155). The conductivity was measured on digital conductivity meter (HPG System, G-3001).

In vitro *antibacterial activity*

Some of the synthesized macrocyclic complexes were tested for *in vitro* antibacterial activity against some bacterial strains using spot-on-lawn on Muller Hinton Agar.

Test pathogens. Four test pathogenic bacterial strains viz *B. cereus* (MTCC 1272), *S. typhi* (MTCC 733), *E. coli* (MTCC 739) and *S. aureus* (MTCC 1144) were considered for determination of MIC (Minimum Inhibitory Concentration) of selected complexes.

Culture conditions. The test pathogens were subcultured aerobically using Brain Heart Infusion Agar (HiMedia, Mumbai, India) at 37°C/24 h. Working cultures were stored at 4°C in Brain Heart



Where M = Cr(III), Mn(III), Fe(III)
X = Cl^-, NO_3^-, CH_3COO^-

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). Organism was grown overnight in 10 mL BHI broth, centrifuged at 5,000 × g for 10 min and the pellet was suspended in 10 mL of phosphate buffer saline (PBS, pH 7.2). Absorbance 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).

Determination of minimum inhibitory concentration. 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 h. Zone of inhibition of compounds were considered after subtraction of inhibition zone of DMSO. Negative control (with no compound) was also observed.

Results and discussion

The analytical data of the metal chelates are given in Table I, which shows that metal chelates derived from oxalyldihydrazide and glyoxal may be represented by the formula: $[M(C_8H_8N_8O_4)X]X_2$; where M = Cr(III), Mn(III), Fe(III) and X = Cl^{-1}, NO_3^{-1}, CH_3COO^{-1}. The measurements of molar conductance in DMSO show that these chelates are 1:2 electrolytes [20] (conductance 150-185 $ohm^{-1}\,cm^2\,mol^{-1}$). The tests for anions are positive before decomposing and after decomposing the chelates showing their presence outside as well as inside the coordination sphere. All macrocyclic complexes are dark colored solids and are freely soluble in DMF or DMSO. All complexes give satisfactory elemental analyses results as shown in the Table I.

Table I. Analytical data of trivalent chromium, manganese and iron complexes derived from oxalyldihydrazide and glyoxal.

Sr. No.	Complexes	Found (calcd.) %				Colour	Mol. Wt.
		M	C	H	N		
1	$[Cr(C_8H_8O_4N_8)Cl]Cl_2$	11.65 (11.84)	21.67 (21.86)	1.80 (1.82)	25.47 (25.51)	Yellowish Green	439
2	$[Cr(C_8H_8O_4N_8)(NO_3)](NO_3)_2$	9.89 (10.03)	18.44 (18.53)	1.32 (1.54)	29.51 (29.72)	Yellowish Brown	518
3	$[Cr(C_8H_8O_4N_8)(OAc)](OAc)_2$	10.13 (10.21)	32.87 (33.00)	3.14 (3.33)	21.92 (22.00)	Yellowish Brown	509
4	$[Mn(C_8H_8O_4N_8)Cl]Cl_2$	12.32 (12.44)	21.56 (21.71)	1.69 (1.80)	25.21 (25.33)	Brown	442
5	$[Mn(C_8H_8O_4N_8)(OAc)](OAc)_2$	10.59 (10.74)	32.37 (32.81)	3.08 (3.32)	21.82 (21.87)	Brown	512
6	$[Fe(C_8H_8O_4N_8)Cl]Cl_2$	12.50 (12.64)	21.62 (21.67)	1.71 (1.80)	25.14 (25.28)	Yellowish brown	443
7	$[Fe(C_8H_8O_4N_8)(NO_3)](NO_3)_2$	10.67 (10.72)	18.22 (18.39)	1.43 (1.53)	29.41 (29.50)	Light Brown	522
8	$[Fe(C_8H_8O_4N_8)(OAc)](OAc)_2$	10.78 (10.91)	32.56 (32.74)	3.17 (3.31)	21.59 (21.83)	Light Brown	513

IR spectra

The presence of a single medium band in the region ~3200-3290 cm^{-1} in the spectra of all complexes may be assigned due to N-H stretch [16,21,22]. It was noted that a pair of bands corresponding to $\nu(NH_2)$ at ~3300 cm^{-1} and 3310 cm^{-1} were present in the spectrum of oxalyldihydrazide but were absent in the infrared spectra of all the complexes. The disappearance of these bands and appearance of absorption band near

$\sim$1600-1615 cm^{-1} indicates the formation of macrocyclic Schiff's base [23,24] as these bands may be assigned due to ν(C=N) [25,26]. The value of ν(C=N) is lower than that usually found for azomethine linkage, may be explained on the basis of a drift of lone pair density of azomethine nitrogen towards the metal atom [27,28] indicating the involvement of the pi electrons throughout the macrocyclic framework [16] and confirm that coordination takes place through nitrogen of C=N groups. The bands present $\sim$2950-3070 cm^{-1} may be assigned due to ν(C-H) stretch [17] of glyoxal moiety. The band present in the range 1650-1690 cm^{-1} may be assigned due to the C=O group of the CONH moiety [16,29] in all complexes. This indicates that coordination through oxygen of carbonyl group to metal atom is ruled out. The bands present in the range $\sim$1350-1000 cm^{-1} in all complexes are assigned due to ν(C-N) stretch.

NMR spectra

The ^{1}H NMR spectrum of Zn complex show broad signal at 8.05-8.10 ppm due to amide protons [18]. The singlet in the region 4.50-5.20 may be assigned due to protons of glyoxal moiety [30].

Far IR spectra

The far IR spectra show bands in the region $\sim$415-465 cm^{-1} corresponding to ν(M-N) vibrations [31–33]. The presence of bands in all complexes in the region 415-465 cm^{-1} originate from (M-N) azomethine vibrational modes and gives idea about coordination of azomethine nitrogens [34]. The bands present at 305-325 cm^{-1} may be assigned due to ν(M-Cl) vibrations [31,33]. The bands present at 210-250 cm^{-1} in all nitrato complexes are assignable to ν(M-O) [31].

Magnetic measurements and electronic spectra

Chromium complexes. Magnetic moment of chromium complexes were found in the range of 4.15-4.52 B.M. The electronic spectra of chromium complexes show bands at $\sim$9010-9320 cm^{-1}, 13030-13340 cm^{-1}, 17460-18320 cm^{-1}, 27420-27850 cm^{-1} and 34810 cm^{-1}. However, these spectral bands cannot be interpreted in terms of four or six coordinated environment around the metal atom. In turn, the spectra are consistent with that of five coordinated Cr(III) complexes, whose structure have been confirmed with the help of X-ray measurements [35]. Thus keeping in view, the analytical data and electrolytic 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,[36] the various spectral bands may be assigned as: $^4B_1 \rightarrow {}^4E^a$, $^4B_1 \rightarrow {}^4B_2$, $^4B_1 \rightarrow {}^4A_2$ and $^4B_1 \rightarrow {}^4E^b$.

Manganese complexes. The magnetic moment of manganese complexes lay in the range 4.80-4.90 B.M. The electronic spectra of manganese complexes show three d-d bands which lay in the range 12250-12590, 16050-18920 and 35420-35750 cm^{-1}. The higher energy band at 35440-35750 cm^{-1} may be assigned due to charge transfer transitions. The spectra resemble to those reported for five coordinate square pyramidal manganese porphyrins [34,36]. This idea is further supported by the presence of the broad ligand field band at 20400 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 $d_{xz}, d_{yz} \rightarrow d_{x^2-y^2}$, respectively in order of increasing energy. However, the complexes do not have idealized C_{4V} symmetry.

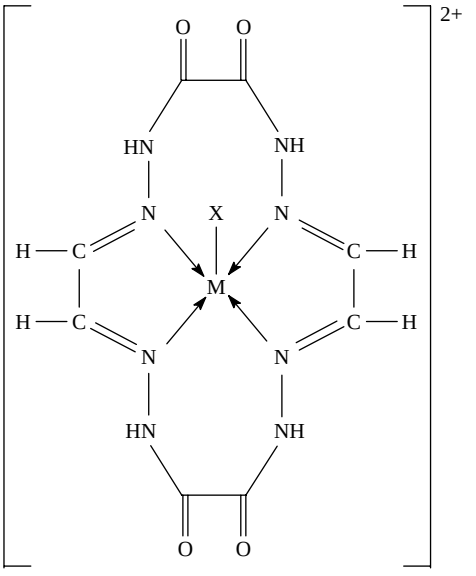
Iron complexes. The magnetic moment of iron complexes lay in the range 5.81-5.91 B.M. The electronic spectra of iron (III) complexes show various bands 9820-9970, 15510-15575, 27600-27730 cm^{-1} and these bands do not suggest the octahedral or tetrahedral geometry around the metal atom. The spectral bands are consistent with the range of spectral bands reported for five coordinate square pyramidal iron (III) complexes [37]. 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 π-bond systems lifting the degeneracy of the d_{xz} and d_{yz} pair.

Proposed structure

Therefore based on elemental analyses, conductivity, magnetic, electronic, NMR and IR spectral studies the following structure (Figure 1) may be proposed for these complexes.

Biological results

Six chemically synthesized macrocyclic complexes were tested for their *in vitro* antibacterial activity against four test bacteria *B. cereus* (MTCC 1272), *S. typhi* (MTCC 733), *E. coli* (MTCC 739) and *S. aureus* (MTCC 1144). Complex **2** showed a minimum inhibitory concentration of 32 μg/mL against bacterial strain *S. typhi* (MTCC 733), which is equal to the MIC shown by standard antibiotic linezolid against the same bacterial strain (Table II and Figure 2). Complex **6** showed minimum inhibitory concentration of 8 μg/mL against bacterial strain *B. cereus* (MTCC 1272), which is equal to the MIC shown by standard antibiotic cefaclor against the same bacterial strain. Complex **6** registered minimum inhibitory



Where M = Cr(III), Mn(III), Fe(III)

X = Cl^{-1}, NO_3^{-1}, CH_3COO^{-1}

Figure 1. Structure of the metal complexes.

concentration of 32 μg/mL against bacterial strain *S. typhi* (MTCC 733), which is equal to the MIC shown by standard antibiotic linezolid against the same bacterial strain (Table II and Figure 2). Complex **3** was found to have minimum inhibitory concentration of 32 μg/mL against bacterial strain *S. typhi* (MTCC 733), which is equal to that shown by standard antibiotic linezolid against the same bacterial strain. Further MIC of complex **3** against *E. coli* (MTCC 739) was 16 μg/mL, which is again equal to the minimum inhibitory concentration shown by standard antibiotic linezolid against the same bacterial strain. Complex **5** showed a minimum inhibitory concentration of 16 μg/mL against bacterial strain *E. coli* (MTCC 739) which is equal to that of shown by standard antibiotic linezolid against the same bacterial strain. Complexes **1** and **4** showed poor antibacterial activity against all bacterial strains among the whole series under test. Complex **3** was the most potent out of all the complexes with MIC ranging from 16-64 μg/mL. Complex **6** also showed satisfactory antibacterial activity (Table II and Figure 2).

Table II. Minimum inhibitory concentration (MIC) shown by trivalent chromium and iron complexes derived from oxalyldihydrazide and glyoxal against test bacteria.

Sr. No.	Complexes	MIC (μg/mL)			
		Bc	Sa	Ec	St
(1)	$[Cr(C_8H_8O_4N_8)Cl]Cl_2$	64	128	64	128
(2)	$[Cr(C_8H_8O_4N_8)NO_3](NO_3)_2$	128	>128	64	32
(3)	$[Cr(C_8H_8O_4N_8)(OAc)](OAc)_2$	32	64	16	32
(4)	$[Fe(C_8H_8O_4N_8)Cl]Cl_2$	64	32	>128	128
(5)	$[Fe(C_8H_8O_4N_8)(NO_3)](NO_3)_2$	>128	64	16	64
(6)	$[Fe(C_8H_8O_4N_8)(OAc)](OAc)_2$	8	128	>128	32
	Linezolid	4	4	16	32
	Cefaclor	8	2	8	16

Bc - *Bacillus cereus* (MTCC 1272); Sa - *Staphylococcus aureus* (MTCC 1144); Ec - *Escherichia coli* (MTCC 739); St - *Salmonella typhi* (MTCC 733). Cefaclor and linezolid are standard antibiotics.

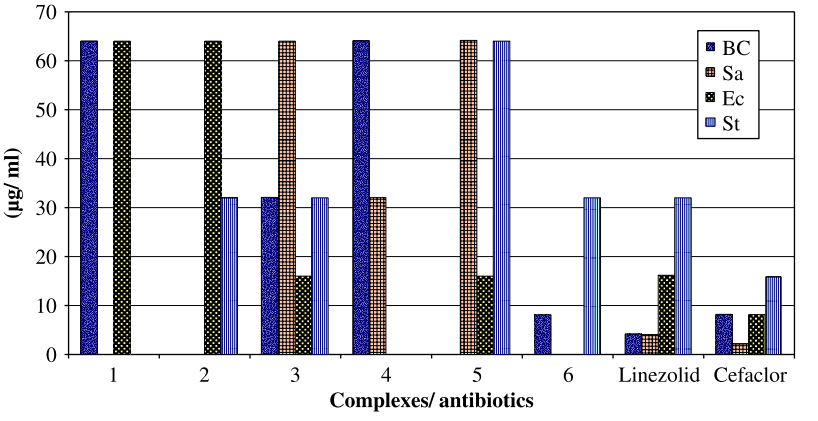


Figure 2. Comparison of MIC of complexes with standard antibiotics up to a concentration of 64 μg/mL.

Conclusions

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 [38–40]. This process of chelation thus increases the lipophilic nature of the central metal atom, which in turn, favours 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. Besides from this many other factors such as solubility, dipole moment, conductivity influenced by metal ion may be possible reasons for remarkable antibacterial activities of these complexes [41–43]. It also has been observed that some moieties such as azomethine linkage or heteroaromatic nucleus introduced into such compounds exhibit extensive biological activities that may be responsible for the increase in hydrophobic character and liposolubility of the molecules in crossing the cell membrane of the microorganism and enhance biological utilization ratio and activity of complexes [44, 45].

Acknowledgements

D.P. Singh thanks the *University Grants Commission*, *New Delhi* for financial support in the form of *Major Research Project (MRP-F.12-62/2003)* and Ramesh Kumar for the award of Project Fellowship under the above project. Thanks are also due to authorities of N.I.T., Kurukshetra for providing necessary research facilities.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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