

SHORT COMMUNICATION

Template synthesis of macrocyclic complexes and their spectroscopic and antibacterial studies

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Abstract

A new series of macrocyclic complexes of type $[M(\text{TML})\text{X}]_x$, where $M = \text{Cr(III)}, \text{Fe(III)}$, TML is tetradentate macrocyclic ligand, and $X = \text{Cl}^-, \text{NO}_3^-, \text{CH}_3\text{COO}^-$, have been synthesized by condensation of isatin and ethylenediamine in the presence of metal salt. The complexes were synthesized by both conventional and microwave methods. The complexes have been characterized with the help of elemental analysis, conductance measurement, magnetic measurement, and infrared, far infrared, and electronic spectral studies. Molar conductance values indicate them to be 1:2 electrolytes. Electronic spectra along with magnetic moments suggest five-coordinate square pyramidal geometry for these complexes. The complexes were also tested for their *in vitro* antibacterial activity. Some of the complexes showed satisfactory antibacterial activity.

Keywords: Macrocyclic complexes; antibacterial activity; minimum inhibitory concentration

Abbreviations: MIC, minimum inhibitory concentration; MTCC, microbial type culture collection; MHA, Müller Hinton agar; CFU, colony forming unit; B.M., Bohr magneton; DMF, N,N-dimethylformamide; DMSO, dimethylsulfoxide; BHI, brain heart infusion.

Introduction

The study of macrocyclic complexes is becoming a growing class of research. The chemistry of macrocyclic complexes has received much attention in recent years on account of its various applications in bioinorganic chemistry. The field of macrocyclic complexes has undergone enormous growth due to the synthesis of a variety of macrocycles which behave as coordinating agents for metal ions. Nitrogen containing macrocycles have a strong tendency to form stable complexes with transition metals. The condensation reaction between diketones and primary diamines in the presence of metal ions has played a vital role in the development of tetraazamacrocyclic complexes^{1–4}. Macrocyclic nickel complexes find use in DNA recognition and oxidation⁵, while macrocyclic copper complexes find use in DNA binding and cleavage⁶. Some macrocyclic complexes have been reported as showing antibacterial, antifungal, and anti-inflammatory activities^{7,8}. Macrocyclic metal chelating agents (e.g. DOTA) are useful to detect tumor lesions⁹. Isatin derivatives have been reported to exhibit antibacterial,

antifungal, and anti-human immunodeficiency virus (HIV) activities¹⁰. Prompted by these, in the present article, macrocyclic complexes of Cr(III) and Fe(III) derived from isatin and ethylenediamine synthesized by both the conventional method and microwave irradiation are discussed. The complexes have been characterized by various physicochemical techniques such as infrared (IR), far IR, electronic spectroscopy, magnetic susceptibility, elemental analysis, and molar conductance.

Experimental

Chemistry

All the reported macrocyclic complexes were prepared by both template and microwave methods.

Conventional method

To a hot, well stirred MeOH solution (~50 cm³) of ethylenediamine (10 mmol) was added trivalent chromium or iron salt (5 mmol) dissolved in a minimum quantity of MeOH (20 cm³). The resulting solution was refluxed for 0.5 h. After

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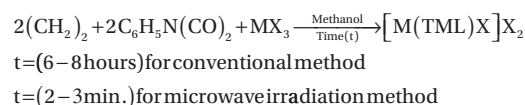
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that, isatin (10 mmol) dissolved in ~20 cm³ MeOH was added to the refluxing mixture, and refluxing continued for 6–8 h. The mixture was concentrated to half of its volume and kept in a desiccator for 2 days. The complexes were then filtered, washed with MeOH, Me₂CO, and Et₂O, and dried *in vacuo*. The complexes were soluble in DMF and DMSO, but were insoluble in common organic solvents and water. They were found to be thermally stable up to ~250°C and then decomposed.

Microwave irradiation method

A mixture of ethylenediamine (10 mmol) in 5 cm³ of MeOH and trivalent chromium and iron salt (5 mmol) dissolved in 5 cm³ of MeOH was subjected to microwave irradiation at an output of 300 W for a specified time of 0.5–1 min. After that, isatin (10 mmol) dissolved in 10 cm³ of MeOH was added to the reaction mixture. Irradiation of the reaction mixture was continued under the specified conditions for the next 1–2 min. The contents were cooled and kept in desiccators. The complexes thus obtained were washed with MeOH, Me₂CO, and Et₂O and then dried *in vacuo*.

Synthesis of the complexes by conventional and microwave irradiation methods may be shown by the following scheme:



where M = Cr(III) and Fe(III), X = Cl⁻, NO₃⁻, CH₃COO⁻, and TML is tetradentate macrocyclic ligand.

In vitro antibacterial activity (biological assay)

The synthesized macrocyclic complexes were tested for *in vitro* antibacterial activity against some bacterial strains using the method of spot-on-lawn on Müller Hinton agar¹¹.

Test pathogens

Four test pathogenic bacterial strains, viz *Bacillus cereus* (MTCC 1272), *Salmonella typhi* (MTCC 733), *Escherichia coli* (MTCC 739), and *Staphylococcus aureus* (MTCC 1144), were considered for determination of the MIC (minimum inhibitory concentration) of the 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 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 and centrifuged at 5000g for 10 min, and the pellet was suspended in 10 mL of phosphate buffered saline (PBS, pH 7.2). Optical density at 545 nm (OD-545) was adjusted to obtain 10⁸ CFU/mL, followed by plating of serial dilutions onto plate count agar (HiMedia, Mumbai, India).

Determination of minimum inhibitory concentration

The minimum inhibitory concentration (MIC) is the lowest concentration of antimicrobial agent that prevents the development of viable growth after overnight incubation. The antimicrobial activity of the compounds was evaluated using the spot-on-lawn method on Müller Hinton agar (MHA; HiMedia, Mumbai, India). Soft agar was prepared by adding 0.75% agar in Müller Hinton broth (HiMedia, Mumbai, India). Soft agar was inoculated with 1% of 10⁸ CFU/mL of the test pathogen and 10 mL was overlaid on MHA. From a ×1000 solution of compound (1 mg/mL of DMSO), ×1, ×2, ×4, ×8, ×16, ×32, ×64, and ×128 solutions were prepared. Dilutions of standard antibiotics (linezolid and cefaclor) were also prepared in the same manner. Five microliters of the appropriate dilution was spotted on the soft agar and incubated at 37°C for 24 h. Zones of inhibition of the compounds were considered after subtraction of the inhibition zone of DMSO. Negative control (with no compound) was also observed.

Analyses

The microanalysis of C, H, and N was recorded on an Elementar Vario EL III (Carlo Erba 1108) analyzer. These analyses were carried out at CDRI, Lucknow. Melting points were determined using capillaries in an electrical melting point apparatus. The metal contents were estimated using standard methods.

Physical measurements

Electronic spectra of the metal complexes were recorded in the region 1100–200 nm on a Hitachi U-2000 spectrophotometer. IR spectra were recorded on a Beckman IR-20 spectrophotometer in KBr/Nujol mull in the range 4000–200 cm⁻¹. Magnetic moment studies were carried out at SAIF, IIT, Roorkee, on a vibrating sample magnetometer (model PAR 155). The conductivity was measured on a digital conductivity meter (HPG System, G-3001).

Results and discussion

Chemistry

The analytical data suggest the formula of the macrocyclic complexes as: [M(C₂₀H₁₈N₆)X]₂X₂, where M = Cr(III), Fe(III) and X = Cl⁻, NO₃⁻, CH₃COO⁻. The test for anions was positive before and after decomposing the complexes with concentrated HNO₃, indicating their presence outside and inside the coordination sphere. Conductivity measurements in DMSO indicated them to be 1:2 electrolyte in nature (150–180 ohm⁻¹ cm² mol⁻¹)¹². All compounds gave satisfactory elemental analysis results as shown in Table 1.

Several attempts to grow crystals of complexes in different solvents or mixtures of solvents for the purpose of X-ray crystallography were unsuccessful.

Infrared spectra

A pair of bands at ~3230 cm⁻¹ and ~3260 cm⁻¹ was observed in the spectrum of ethylenediamine corresponding to

Table 1. Analytical data of trivalent chromium and iron complexes derived from isatin and ethylenediamine.

Sr. no.	Complex	M (%, found/calcd.)	C (%, found/calcd.)	H (%, found/calcd.)	N (%, found/calcd.)	Color	Mol. wt.
(1)	[Cr(C ₂₀ H ₁₈ N ₆)Cl]Cl ₂	10.39/10.52	48.25/48.33	3.60/3.93	16.78/16.98	Brown	500.5
(2)	[Cr(C ₂₀ H ₁₈ N ₆)(NO ₃)] (NO ₃) ₂	9.17/9.23	41.38/41.82	3.10/3.43	22.12/22.16	Yellowish brown	580
(3)	[Cr(C ₂₀ H ₁₈ N ₆)(OAc)] (OAc) ₂	9.19/9.63	54.64/54.96	5.13/5.12	14.98/15.11	Dark brown	571
(4)	[Fe(C ₂₀ H ₁₈ N ₆)Cl]Cl ₂	11.40/11.72	47.57/47.97	3.57/3.91	16.65/16.82	Reddish brown	504.5
(5)	[Fe(C ₂₀ H ₁₈ N ₆)(NO ₃)] (NO ₃) ₂	9.59/9.89	41.10/41.53	3.38/3.45	21.58/21.93	Orange red	584
(6)	[Fe(C ₂₀ H ₁₈ N ₆)(OAc)] (OAc) ₂	9.93/10.22	54.26/54.88	4.69/4.94	14.61/14.97	Dark brown	575

$\nu(\text{NH}_2)$, but was found to be absent from the spectra of all complexes. A strong peak was observed at $\sim 1700\text{ cm}^{-1}$ in the spectrum of isatin, which may be attributed to the $>\text{C}=\text{O}$ group. This peak was found to be absent from the spectra of all complexes, which indicates the absence of $>\text{C}=\text{O}$ groups of the isatin moiety in the complexes. This confirms the condensation of carbonyl groups of isatin and amino groups of ethylenediamine^{13,14}. This fact is also supported by the appearance of a new strong absorption band in the region $\sim 1590\text{--}1615\text{ cm}^{-1}$, which may be attributed to $\nu(\text{C}=\text{N})$ ^{15,16}. These results provide strong evidence for the formation of the macrocyclic frame¹⁷. The lower values of $\nu(\text{C}=\text{N})$ indicate coordination of azomethine nitrogens to metal¹⁸. The bands present at $\sim 1000\text{--}1350\text{ cm}^{-1}$ may be assigned to $\nu(\text{C}-\text{N})$ vibration. The bands presents at $\sim 2900\text{--}3130\text{ cm}^{-1}$ may be assigned to various $\nu(\text{C}-\text{H})$ vibrations.

Far infrared spectra

The far infrared spectra showed bands in the region $\sim 420\text{--}460\text{ cm}^{-1}$ corresponding to $\nu(\text{M}-\text{N})$ vibrations in all complexes^{19–21}. The presence of bands in all complexes in the region $\sim 420\text{--}460\text{ cm}^{-1}$ originates from the $\nu(\text{M}-\text{N})$ azomethine vibration modes and gives an idea about coordination of the azomethine nitrogen²². The bands present at $\sim 300\text{--}310\text{ cm}^{-1}$ may be assigned as being due to $\nu(\text{M}-\text{Cl})$ vibrations^{19,21}. The bands present at $\sim 210\text{--}250\text{ cm}^{-1}$ in all nitrate complexes are assignable to $\nu(\text{M}-\text{O})$ vibrations of the nitrate group¹⁹.

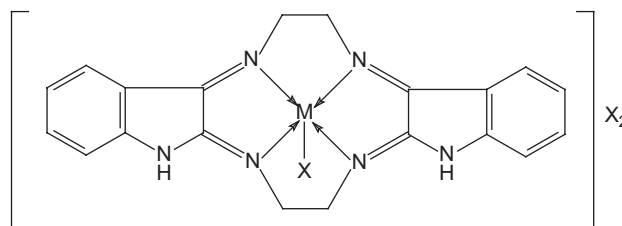
Magnetic measurements and electronic spectra

Chromium complexes Magnetic moments of chromium complexes were found in the range of 4.20–4.60 B.M. The electronic spectra of chromium complexes showed bands at $\sim 9100\text{--}9260$, $13,400\text{--}13,550$, $17,400\text{--}18,300$, $27,500\text{--}27,800$, and $34,850\text{ cm}^{-1}$. However, these spectral bands cannot be interpreted in terms of a four- or six-coordinated environment around the metal atom. In turn, the spectra are comparable to those of five-coordinated Cr(III) complexes, whose structure has been confirmed with the help of X-ray measurements²³. Thus, keeping in view the analytical data and electrolytic nature of these complexes, a five-coordinated square pyramidal geometry may be assigned to these complexes. Thus, assuming the symmetry C_{4v} for these complexes²⁴, the various spectral bands may be assigned as: ${}^4B_1 \rightarrow {}^4E_a$, ${}^4B_1 \rightarrow {}^4B_2$, ${}^4B_1 \rightarrow {}^4A_2$, and ${}^4B_1 \rightarrow {}^4E_b$.

Table 2. Minimum inhibitory concentration (MIC) shown by complexes against test bacteria using agar dilution assay.

Sr. no.	Complex	MIC ($\mu\text{g}/\text{mL}$)			
		Bc	Sa	Ec	St
(1)	[Cr(C ₂₀ H ₁₈ N ₆)Cl]Cl ₂	32	32	64	—
(2)	[Cr(C ₂₀ H ₁₈ N ₆)(NO ₃)](NO ₃) ₂	64	32	128	>128
(3)	[Cr(C ₂₀ H ₁₈ N ₆)(OAc)](OAc) ₂	—	64	>128	128
(4)	[Fe(C ₂₀ H ₁₈ N ₆)Cl]Cl ₂	64	64	128	>128
(5)	[Fe(C ₂₀ H ₁₈ N ₆)(NO ₃)](NO ₃) ₂	64	32	64	64
(6)	[Fe(C ₂₀ H ₁₈ N ₆)(OAc)](OAc) ₂	64	32	>128	64
	Linezolid	4	4	16	32
	Cefaclor	8	2	8	16

Note. Bc, *Bacillus cereus* (MTCC 1272); Sa, *Staphylococcus aureus* (MTCC 1144); Ec, *Escherichia coli* (MTCC 739); St, *Salmonella typhi* (MTCC 733). —, no activity. Cefaclor and linezolid are standard antibiotics.


Figure 1. Structure of complexes, where M = Cr(III), Fe(III) and X = Cl⁻, NO₃⁻, CH₃COO⁻.

Iron complexes The magnetic moments of iron complexes lay in the range 5.85–5.90 B.M. The electronic spectra of trivalent iron complexes showed various bands at 9850–9900, 15,300–15,500, and 27,500–27,600 cm^{-1} , and these bands do not suggest an octahedral or tetrahedral geometry around the metal atom. The spectral bands are consistent with the range of spectral bands reported for five-coordinated square pyramidal iron(III) complexes²⁵. 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 an 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.

Biological assay results

Six chemically synthesized macrocyclic complexes were tested for their *in vitro* antibacterial activity against four test bacteria, *Bacillus cereus* (MTCC 1272), *Salmonella*

Table 3. Comparative data of trivalent chromium and iron complexes for conventional and microwave methods.

Sr. no.	Complex	Conventional method			Microwave irradiation method		
		Yield (%)	Period (min)	Vol. of solvent (cm ³)	Yield (%)	Period (min)	Vol. of solvent (cm ³)
(1)	[Cr(C ₂₀ H ₁₈ N ₆)Cl] Cl ₂	45	430	90	71	2.38	20
(2)	[Cr(C ₂₀ H ₁₈ N ₆) (NO ₃)](NO ₃) ₂	40	450	90	63	2.50	20
(3)	[Cr(C ₂₀ H ₁₈ N ₆) (OAc)](OAc) ₂	49	435	90	73	2.42	20
(4)	[Fe(C ₂₀ H ₁₈ N ₆)Cl] Cl ₂	50	400	90	72	2.18	20
(5)	[Fe(C ₂₀ H ₁₈ N ₆) (NO ₃)](NO ₃) ₂	42	415	90	68	2.30	20
(6)	[Fe(C ₂₀ H ₁₈ N ₆) (OAc)](OAc) ₂	50	410	90	73	2.12	20

typhi (MTCC 733), *Escherichia coli* (MTCC 739), and *Staphylococcus aureus* (MTCC 1144). MIC values of standard antibiotics, i.e. linezolid and cefaclor, were also registered against these bacteria. Linezolid showed MICs of 4, 4, 16, and 32 µg/mL against *Bacillus cereus*, *Salmonella typhi*, *Escherichia coli*, and *Staphylococcus aureus*, respectively, while cefaclor showed MICs of 8, 2, 8, and 16 µg/mL against *Bacillus cereus*, *Salmonella typhi*, *Escherichia coli*, and *Staphylococcus aureus*, respectively. However, all the complexes showed MICs greater than those of the standard antibiotics. Some complexes showed poor or no antibacterial activity. The MIC values registered by the synthesized complexes are given in Table 2.

Conclusions

Chemistry

Based on elemental analysis, conductivity, magnetic, electronic, and IR spectral studies the structure as shown in Figure 1 may be proposed for the reported complexes. Further, it was found that microwave irradiation required a shorter reaction time and less solvent and gave higher product yield, as compared to the conventional method (Table 3).

Biological activity

It has been suggested that chelation/coordination reduces the polarity of the metal ion mainly because of partial sharing of its positive charge with the donor group within the whole chelate ring system. This process of chelation thus increases the lipophilic nature of the central metal atom, which in turn favors its permeation through the lipid layer of the membrane, thus causing the metal complex to cross the bacterial membrane more effectively and hence increasing the activity of the complexes. It has also been observed that some moieties such as an azomethine linkage or a 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, enhancing the biological utilization ratio and activity of the complexes^{26,27}.

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