

Template Synthesis and Characterization of Macrocyclic Complexes of Trivalent Metal Ions Derived from Oxalyldihydrazide and Isatin

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A new series of complexes of the type $M(C_{20}H_{14}N_{10}O_4)X_2$; where $M = Cr(III), Fe(III)$ and $X = Cl^-, NO_3^-, CH_3COO^-$ have been synthesised by template condensation reaction of oxalyldihydrazide and isatin resulting into the formation of the macrocyclic complexes. The complexes has been characterized with the help of elemental analyses and conductance measurements, electronic, IR, Far IR, mass spectral studies and these metal complexes were also tested for their *in vitro* antimicrobial activities to assess their inhibiting potential.

Keywords: Macrocyclic complexes, Infrared, Mass spectra, EPR spectra.

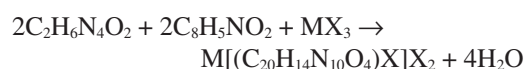
INTRODUCTION

The field of macrocyclic chemistry of metals is developing very rapidly due to its importance in the area of coordination chemistry¹. A large number of nitrogen donor macrocyclic derivatives have long been used in analytical, industrial and medicinal applications². The possibility of using synthetic macrocyclic complexes as model for biologically important system has initiated a broad spectrum of research activities ranging from synthesis of new ring systems and studies on the properties and function of macrocyclic complexes to their application in industry, medicine and other fields³. Macrocyclic Schiff base of Cu(II) complexes with isatin ligands are potential antitumour agents⁴. Prompted by these, in present paper, the synthesis and characterization of chromium(III) and iron(III) macrocyclic complexes derived from ligands oxalyldihydrazide and isatin have been reported.

EXPERIMENTAL

Isolation of complexes: All the complexes were synthesized by template method *i.e.*, by the condensation of oxalyldihydrazide and isatin in the presence of respective trivalent metal salts. To a hot stirring methanol solution (50 cm³) of oxalyldihydrazide (5 mmol, 0.63 g) was added trivalent chromium, iron (2.5 mmol) in the minimum quantity of MeOH (20 cm³). The resulting solution was refluxed for 0.5 h. After that isatin (5 mmol, 0.665 g) was added in the refluxing mixture and refluxing was continued for 8-10 h. On overnight cooling dark brown and yellow coloured precipitates formed which were filtered, washed with methanol, acetone and diethyl ether

and dried in vacuum. Yield was 55-60 %. The complexes are soluble in DMSO and DMF, but are insoluble in common organic solvents and water. They are thermally stable up to 250-300 °C and then decomposed. The template condensation of oxalyldihydrazide and isatin in the presence of trivalent metal salts in the molar ratio 2:2:1 is represented by the following scheme



where $M = Cr(III), Fe(III)$ and $X = Cl^-, NO_3^-, CH_3COO^-$.

Biological assay: Four bacterial strains were selected on the basis of their clinical importance in causing diseases in humans. Two gram-positive bacteria (*Staphylococcus aureus* MTCC 96 and *Bacillus subtilis* MTCC 121); two Gram-negative bacteria (*Escherichia coli* MTCC 1652 and *Pseudomonas aeruginosa* MTCC 741) and two fungi, *A. niger* and *A. flavus* were screened for antibacterial and Antifungal activity of the compounds, respectively. The antibacterial and antifungal activities were determined by literature method⁵.

RESULTS AND DISCUSSION

The analytical data represents the formula for macrocyclic complexes as $M[(C_{20}H_{14}N_{10}O_4)X]X_2$; where $M = Cr(III), Fe(III)$ and $X = Cl^-, NO_3^-, CH_3COO^-$. The measurements of molar conductance in DMSO show that these chelates are 1:2 electrolytes having conductance⁶ in range 115-165 ohm⁻¹ cm² mol⁻¹. The tests for anions are positive before as well as after decomposing the chelates with concentrated HNO₃ showing their presence outside as well as inside of coordination sphere. All

complexes gave satisfactory elemental analyses results as shown in the Table-1.

Infrared spectra: All the macrocyclic complexes show a single medium band in the region 3300 cm^{-1} in the infrared spectra which may be assigned due to N-H stretch⁷ and a pair of bands corresponding to $\nu(\text{NH}_2)$ at 3400 and 3250 cm^{-1} disappeared in the spectra of complexes. Further no strong absorption band was observed near 1700 cm^{-1} indicating the absence of $>\text{C}=\text{O}$ group of isatin moiety. All the macrocyclic metal complexes exhibit strong absorption band near $1628\text{--}1605\text{ cm}^{-1}$ confirms the condensation of carbonyl group of isatin and amino group of oxalyldihydrazide and formation of macrocyclic Schiff base⁸ as these band may be assigned due to $\nu(\text{C}=\text{N})$ ⁹ azomethine nitrogen. The lowering of this band in the complexes indicates the coordination of nitrogen atoms of azomethine groups to metal atom¹⁰. The band present in the range $1705\text{--}1674\text{ cm}^{-1}$ may be assigned due to $>\text{C}=\text{O}$ group of CONH moiety¹¹ in all the complexes. This indicates that coordination to metal atom through oxygen of carbonyl group of oxalyldihydrazide is ruled out. The various bands present in the range $1300\text{--}1000\text{ cm}^{-1}$ in all the complexes may be assigned to $\nu(\text{C}-\text{N})$ stretch. The presence of absorption bands at $1440\text{--}1408$, $1325\text{--}1290$ and $1040\text{--}1010\text{ cm}^{-1}$ in the IR spectra of all the nitrate complexes suggests the both the nitrate group was coordinated to central metal ion in a unidentate manner¹². The IR spectra of all the acetate complexes show absorption bands in the region $1685\text{--}1650\text{ cm}^{-1}$ which were assigned to the $\nu(\text{COO}^-)$ asymmetric stretching of acetate ion another in the region $1295\text{--}1258\text{ cm}^{-1}$, which were assigned to $\nu(\text{COO}^-)$ symmetric stretching vibration of acetate ion. A difference between $(\nu_{\text{as}}-\nu_{\text{s}})$ was around $392\text{--}370\text{ cm}^{-1}$ which was greater than 144 cm^{-1} indicates the unidentate coordination of the acetate ion with the central metal ion¹². The far infrared spectra show bands in the region $450\text{--}420\text{ cm}^{-1}$ corresponding to $\nu(\text{M}-\text{N})$ vibration¹³. The presence of bands in all the complexes in the region $420\text{--}450\text{ cm}^{-1}$ originate from (M-N) azomethine vibration modes and indicate the coordination of azomethine nitrogen¹⁴. The bands present in the region $240\text{--}220\text{ cm}^{-1}$ in all the nitrate complexes are assignable to $\nu(\text{M}-\text{O})$ ¹⁵. The bands present at $300\text{--}250\text{ cm}^{-1}$ may be assigned due to $\nu(\text{M}-\text{Cl})$ vibration¹⁶.

Mass spectra: The ESI mass spectra of chromium(III) and iron(III) macrocyclic metal complexes have been recorded. All the spectra exhibit parent's peaks due to molecular ion (M^+). The proposed molecular formulae of these complexes were confirmed by comparing their molecular formula weights with m/z values. The molecular ion (M^+) peaks obtained for various complexes are as follows (1) $m/z = 623$ (2) $m/z = 694$

(3) $m/z = 695$ chromium complexes (4) $m/z = 620$ (5) $m/z = 700$ (6) $m/z = 691$. This data is in good agreement with the proposed molecular formula for their complexes *i.e.*, $[\text{M}[(\text{C}_{20}\text{H}_{14}\text{N}_{10}\text{O}_4)\text{X}]\text{X}_2]$; where $\text{M}=\text{Cr}$ (III), Fe (III) and $\text{X}=\text{Cl}^-$, NO_3^- , CH_3COO^- this confirms the formation of the macrocyclic frame.

Magnetic measurements and electronic spectra: Magnetic moments of chromium(III) complexes were found in the range of $4.15\text{--}4.52\text{ B.M.}$ at the room temperature which was close to the predicted values for the three unpaired electrons in the metal ion¹⁷. The electronic spectra of chromium complexes recorded in DMSO show bands at $9010\text{--}9320$, $13030\text{--}13550$, $17460\text{--}18350$, $27320\text{--}27880$, 33333 and 34820 cm^{-1} . These spectral bands were consistent with that of five coordinated square-pyramidal chromium(III) complexes¹⁸. So, on the basis of analytical data, spectral studies and electrolytic nature of these complexes, a five coordinated square-pyramidal geometry may be assigned for these complexes¹⁹ thus assuming the symmetry C_{4v} for these complexes, the various spectral bands may be assigned as: ${}^4\text{B}_1 \rightarrow {}^4\text{E}_a$, ${}^4\text{B}_1 \rightarrow {}^4\text{B}_2$, ${}^4\text{B}_1 \rightarrow {}^4\text{A}_2$ and ${}^4\text{B}_1 \rightarrow {}^4\text{E}^b$. The chromium complexes exhibit an isotropic ESR spectra having a $g^{\text{iso}} = 2.043$ which is characteristic of square pyramidal geometry.

Magnetic moments of iron(III) complexes was found in the range of $5.80\text{--}5.90\text{ B.M.}$, corresponding to the five unpaired electrons and was close to the predicted high spin values for these metal ions¹⁷. The electronic spectra of iron complexes recorded in DMSO show various bands $9820\text{--}9978$, $15520\text{--}15575$ and $27550\text{--}27750\text{ cm}^{-1}$ and these spectral bands were consistent with the range of spectral bands reported for five coordinate square pyramidal iron(III) complexes^{18,19} 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 was difficult due to interaction of the metal-ligand pi-bond system lifting the degeneracy of the d_{xz} and d_{yz} pair.

Biological results and discussion: All the synthesized macrocyclic complexes were screened for their antibacterial and antifungal activity. Tested chemical compounds possessed variable antibacterial activity against gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*). All tested compounds displayed variable antifungal activity against *A. niger* and *A. flavus*. However, compounds did not exhibit any activity against gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria. Positive controls produced significantly sized inhibition zones against the tested bacteria and fungi; however, negative control produced no observable inhibitory effect against any of the test organism as shown in Table-2.

TABLE-1
ANALYTICAL DATA OF THE SYNTHESIZED Cr(III) AND Fe(III)
COMPLEXES DERIVED FROM OXALYLDIHYDRAZIDE AND ISATIN

Complexes	Colour	*M	Elemental analysis (%) found (calcd.)				$\mu_{\text{eff.}}$ (BM)
			M	C	H	N	
$[\text{Cr}(\text{C}_{20}\text{H}_{14}\text{N}_{10}\text{O}_4)\text{Cl}]\text{Cl}_2$ 1	Light brown	150	9.28 (9.45)	38.24 (38.4)	2.16 (2.24)	22.35 (22.4)	4.15
$[\text{Cr}(\text{C}_{20}\text{H}_{14}\text{N}_{10}\text{O}_4)(\text{NO}_3)](\text{NO}_3)_2$ 2	Brown	154	8.01 (8.30)	34.37 (34.5)	1.79 (2.01)	25.37 (25.81)	4.21
$[\text{Cr}(\text{C}_{20}\text{H}_{14}\text{N}_{10}\text{O}_4)(\text{OAc})](\text{OAc})_2$ 3	brown	135	8.10 (8.50)	34.25 (34.6)	1.56 (1.90)	20.13 (20.10)	4.52
$[\text{Fe}(\text{C}_{20}\text{H}_{14}\text{N}_{10}\text{O}_4)\text{Cl}]\text{Cl}_2$ 4	Yellow	155	8.48 (8.95)	38.10 (38.6)	2.12 (2.25)	21.09 (22.5)	5.80
$[\text{Fe}(\text{C}_{20}\text{H}_{14}\text{N}_{10}\text{O}_4)(\text{NO}_3)](\text{NO}_3)_2$ 5	Yellow	176	7.2 (8.07)	34.46 (34.7)	2.0 (2.03)	20.10 (20.2)	5.90
$[\text{Fe}(\text{C}_{20}\text{H}_{14}\text{N}_{10}\text{O}_4)(\text{OAc})](\text{OAc})_2$ 6	Yellow	165	7.80 (8.00)	33.9 (34.0)	1.87 (2.07)	19.9 (20.0)	5.85

TABLE-2
in vitro ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF CHEMICAL
 COMPOUNDS THROUGH AGAR WELL DIFFUSION METHOD

Compound	Diameter of growth of inhibition zone (mm) ^a		Mycelial growth inhibition (%)		Minimum inhibitory concentration (MIC) (in µg/mL)	
	<i>Staphylococcus aureus</i>	<i>Bacillus Subtilis</i>	<i>Aspergillus niger</i>	<i>Aspergillus flavus</i>	<i>Staphylococcus aureus</i>	<i>Bacillus Subtilis</i>
1	14.3	15.3	47.7	53.3	256	128
2	14.6	16.3	45.5	51.1	256	128
3	16.3	18.6	56.6	61.1	128	64
4	15.6	16.3	51.1	55.5	128	128
5	17.6	19.6	58.8	63.3	64	64
6	13.6	15.3	45.5	48.8	256	128
Ciprofloxacin	26.6	24.0	Nt	Nt	6.25	6.25
Fluconazole	Nt	Nt	81.1	77.7	Nt	Nt

No activity, ^aValues, including diameter of the well (8 mm), are means of three replicates.

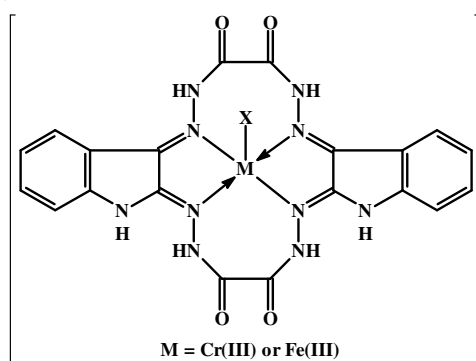


Fig. 1. Proposed structure of complexes

Tested chemical compounds showed zone of inhibition ranging between 14.3 and 19.6 mm against the gram positive bacteria. On the basis of zone of inhibition produced against the test bacterium, compound number 5 was found to be most effective against *B. subtilis* and *S. aureus*, with zone of inhibition of 19.6 and 17.6 mm, respectively. However, other tested compounds showed moderate antibacterial activity. In the whole series, the MIC of chemical compounds ranged between 64 and 256 µg/mL against gram positive bacteria. Compound No. 5 was found to be best as they exhibit the lowest MIC of 64 µg/mL against *B. subtilis* and *S. aureus*.

All the complexes screened for their antifungal activity, two compounds **3** and **5** showed more than 55 % inhibition of mycelial growth against *A. flavus* and *A. niger* (Table-2). Among all the tested chemical compounds, compound no **5** showed good antibacterial and antifungal activity. Therefore this compound can be further explored in the pharmaceutical industry, after testing its cytotoxicity to human beings.

Conclusion

Based on various studies, 5-coordinated, square pyramidal geometry as shown in Fig. 1 may be proposed for all the synthesized complexes. It has been observed that the process of chelation increases the lipophilic nature of the central metal

atom, which in turn, favours its permeation through the lipid layer of the membrane thus causing the metal complex to cross the bacterial membrane more effectively hence enhanced the biological activity of the complexes²⁰.

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