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SYNTHESIS AND CHARACTERIZATION OF BIOLOGICALLY ACTIVE CR(III) TRANSITION METAL MACROCYCLIC COMPLEXES

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ABSTRACT

A noval series of new macrocyclic ligand was synthesized by refluxing 1: 2 stoichiometric quantities oxydiacetic acid ester and hydrazine hydrate in ethanolic medium and formulated as: ODADH and further new macrocyclic complexes I were synthesized by template condensation of 1:1:1stoichiometric quantities of ligand, and 2, 6-diacetyl pyridine and in complex II were synthesized by ligand and 2,6-pyridine dicarbonyl dichloride, were mixed in ethanolic medium individually in the presence of trivalent chromium, represented by formula: Cr(III)[DPODH] (BF4)2,Cr(III)[DCODH](BF4)2. The ligand and complexes were characterized with the help of various physico-chemical techniques like IR, elemental analyses, electronic spectra, and conductance. On the basis of these studies, a octahedral geometry, in which three nitrogen ,one oxygen and carbonyl oxygen atoms are suitably placed for coordination toward the metal ion, has been proposed for complexes. Ligand and complexes were also screened for their in-vitro antimicrobial activities against gram negative, gram positive bacterial strains and fungal activity by *A. brasiliensis* (ATCC 6404) & *C. albicans* (ATCC 10231). Minimum inhibitory concentration of ligand and complexes was compared whereas complexes showed good antimicrobial activity than ligand. All the newly synthesized complexes show antibacterial activity as well as antifungal activity.

KEYWORDS : Macrocyclic ligand , Macrocyclic Complexes , Infra-red, Minimum Inhibitory Concentration (MIC), *Escherichia coli* (ATCC 8739), *Salmonella typhi* (ATCC 9150), *Staphylococcus aureus* (ATCC 6538), *Aspergillus brasiliensis* (ATCC 6404), *Candida albicans* (ATCC 10231).

Macrocycles and macrocyclic metal compounds design and synthesis is one of the fascinating areas of current research to the inorganic chemists all over the world because of their biological, analytical and catalytical applications (Reddy et al., 2009, 2008, 2007; Halma et al., 2006; Wolkert and Hoffman, 1999). Macrocyclic complexes are considered to mimic the synthetic models of metalloporphyrins and metallocorrins due to their intrinsic structural properties (Mruthyunjayaswamy et al., 2005; Shankar et al., 2009).

The uses of metal complexes as therapeutic agents for the treatment of different diseases have been extensively studied. As they generally have different mechanism of activity from the organic compounds, the development of metal complexes provides an alternative route of novel drug. Presently, there is a growing interest in the design and syntheses of macrocyclic compound are increasing, due to their resemblance with many natural macrocycles like metalloproteins, porphyrins and cobalaminess (Gloe, 2005; Lindoy, 1989; Constable, 1999; Singh, 2007). Transition metal macrocyclic complexes have received a great attention because of their biological activities, including antiviral, anticarcinogenic, antifertile, antibacterial and antifungal. Macrocyclic metal complexes of lanthanide e.g., Gd^{3+} are used as magnetic resonance imaging (MRI) contrast agents (Shakir et al., 2007; Chandra and Sharma, 2006; Prasad and Upadhyay, 2006; Fox et al., 2000; Chandra et al., 2006, 2007).

In the present paper, we report the synthesis and characterization of macrocyclic ligand prepared from oxydiacetic acid and its complexes derived with trivalent chromium. The synthesised complexes have been characterized by Infra-red, elemental analysis, electronic spectra and conductance. The five microbial strains were selected on the basis of their clinical importance in causing diseases in humans. Two gram negative bacteria [*Escherichia coli* (ATCC 8739), *Salmonella typhi* (ATCC 9150)], one gram positive bacteria [*Staphylococcus aureus* (ATCC 6538)] and two fungus [*Aspergillus brasiliensis* (ATCC 6404) and *Candida albicans* (ATCC 10231)] were screened for evolution of antibacterial and antifungal activity of chemical complexes. Minimum inhibitory concentration (MIC) of ligand and its complexes were compared whereas complexes showed good antimicrobial activity than ligand.

MATERIALS

All the chemicals and solvents used of A.R. grade, purchased from Aldrich, Himedia, Merck and CDH and were used as received.

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Table 1 : Elemental Analysis and Molar Conductivity Data of the Ligand and Newly Synthesized Cr (iii) Macrocyclic Complexes

Compound	M.P. (^{0}C)	Color	Yield (%)	Elemental Analysis (%) (F/c)				Molar Conductivity (ohm^{-1} cm^2 mol^{-1})
				C	H	N	M	
ODADH	162	White	1.42 gm	29.35 (29.60)	6.11 (6.16)	34.20 (34.53)	-	-
Cr(III)[DPODH] (BF4) 2	255	Greenish-Yellow	1.88 gm.	30.02 (30.17)	3.23 (3.28)	13.21 (13.54)	10.01 (10.05)	113.25
Cr(III)[DCODH](BF4)2	262	Dusk-Green	1.79 gm.	23.35 (23.67)	1.96 (1.97)	12.51 (12.55)	9.29 (9.32)	113.18

Synthesis of Ligand

The ligand, oxydiacetic acid dihydrazide was formed by mixing 1: 2 stoichiometric quantities of transparent oxydiacetic acid ester (1.62gm., 0.01M) solution and hydrazine hydrate (0.83cm^3, 0.02M) were mixed in 20 ml. ethyl alcohol with continuous stirring. The obtained solution was refluxed over a water-bath at 40-50°C for around 5-6 hours. The obtained white crystal in bottom round flask was concentrated and cooled overnight and were filtered, washed with alcohol and ether then dried in vacuum over anhydrous $CaCl_2$ in desicator.

Synthesis of Metal Complexe I

1:1:1 stoichiometric quantities of ligand (1.60 gm., 0.01M), chromium acetate (2.42 gm., 0.01M) and 2,6-diacetyl pyridine (1.63gm., 0.01M) were mixed in 20 ml. ethanol with continuous stirring. The obtained solution was refluxed over a water-bath for around 6-7 hours and concentrated. Then a little of sodiumtetrafluoroborate was added and the solution was cooled overnight, crystals separated out. These greenish-yellow crystals were filtered, washed with alcohol and then dried in vacuum over anhydrous $CaCl_2$ in desicator.

Synthesis of Metal Complexe II

1:1:1stoichiometric quantities of ligands (1.60 gm., 0.01M), chromium acetate (2.42 gm., 0.01M) and 2,6-pyridine dicarbonyl dichloride (1.90 gm., 0.01M) were mixed in 20 ml. ethanol with continuous stirring. The obtained solution was refluxed over a water-bath for around 6-7 hours and concentrated. Then a little of sodiumtetrafluoroborate was added and the solution was cooled overnight, crystals separated out. These dusk-green crystals were filtered, washed with alcohol and then dried in vacuum over anhydrous $CaCl_2$ in desicator.

Analytical and Physical Measurements

The elemental analysis helps in fixing the stoichiometric composition of the ligand and metal complexes. The carbon, hydrogen, nitrogen, oxygen analyzed by sophisticated analytical instrument facility such as Elemental Analyzer (Thermo Scientific 338 35210) and for weighing by Micro Balance (Make-Mettler, Model-XP6). For Melting Point Determine by (Make-VEEGO, Model-VMP-PM). For metal estimation, using gravimetric method of analysis Vogel's Quantitative Inorganic Analysis (seventh edition) revised by G.SVEHLA. Infra-red spectra of synthesized compounds were recorded on (Perkin-Elemer"- Model - C91158, in the range 4000-400 cm^{-1}. The electronic spectra of complexes in DMSO were recorded on a UV-VIS-NIR (Cary 5 E) spectrophotometer at room temperature.

Infra-red Data

The band due to the NH_2 group disappeared completely in the complexes. The band due to the NH group did not show any change in the spectra of complexes, confirming that the Nitrogen of NH group did not take part in reaction whereas a sharp band was seen in the range of 1320cm-1 proving that -NH_2 group is present in the ligand. Some entirely new absorption band appeared in the spectra of complexes viz. band around 520-510cm^{-1} due to M-N group, a band around 430-410 cm^{-1} due to M-O group.

Electronic Data

The synthesized macrocyclic complexes are stable in air, completely insoluble in water and common organic

Table 2

S. NO.	FUNCTIONAL GROUPS	[ODADH]	Cr(III)[DPODH]$(BF_4)_2$	Cr(III)[DCODH]$(BF_4)_2$
1.	$-CH_2$	2820	2790	2780
2.	$-NH_2$	1320	-	-
3.	-NH	3360	3360	3360
4.	N-N	910	890	880
5.	C-H	800	770	760
6.	>C=N	-	1540	1530
7.	>C=O	1670	1640	1630
8.	M-N	-	510	520
9.	M-O	-	430	410

Table 3 : Absorption Bands (in cm^{-1}) of Macrocyclic Complexes in Electronic Spectra

S. No.	COMPLEXES	TRANSITION (cm^{-1})	
		$^2E_g \rightarrow {}^2T_{2g}$	L→M
1.	Cr(III)[DPODH]$(BF_4)_2$	11800	23400
2.	Cr(III)[DCODH]$(BF_4)_2$	11750	23450

Table 4 : Minimum Inhibitory Concentration (MIC) Value in Molar Conc^n.

Compounds	Activity against Bacterial Strain			Activity against Fungal Strain	
	E. coli (gram-negative)	*S. typhi* (gram-negative)	*S. aureus* (gram-positive)	*A. brasiliensis*	*C. albicans*
ODADH	0.595	0.595	0.625	0.585	0.590
Cr(III)[DPODH]$(BF_4)_2$	0.260	0.246	0.235	0.225	0.235
Cr(III)[DCODH]$(BF_4)_2$	0.230	0.230	0.221	0.223	0.215

solvents, but they are soluble in DMSO. The electronic spectra of the complexes recorded in DMSO (HPLC grade). All the absorption bands in electronic spectra were found for complexes in the range of 11,800 - 11,750 cm^{-1} attributed to $^2Eg \rightarrow {}^2T_2g$ transition and in the range of 24,450 - 23,400cm^{-1} attributed to L→M charge transfer transition. These transition confirmed the octahedral geometric of the complexes.

Minimum Inhibitory Concentration (MIC)

The antibacterial activity of ligand and its newly synthesized complexes determined by following methods, successive ten sterilized tubes filled with 2 ml nutrient broth (8 gm. in 1000 ml distilled water) containing 500µg/ml, 250µg/ml, and 100µg/ml, 50 µg/ml and 25µg/ml respective concentrations of test compounds were inoculated with 100 µl of the bacterial suspension. The tubes were incubated at 37^0C in a BOD incubator and observed for change in turbidity after 24 hours. A tube containing nutrient broth without sample was taken as control. The least sample concentration which inhibited the growth of the test organisms was taken as MIC.

RESULTS AND DISCUSSION

The analytical data of ligand and trivalent macrocyclic complexes derived from oxydiacetic acid ester and hydrazine hydrate, formulated as: ODADH and Cr(III)[DPODH](BF4)2, Cr(III)[DCODH](BF4)2. Ligand and both the macrocyclic complexes are white, greenish-yellow, and dusk-green in color and are soluble in dimethylformamide (DMF) and dimethylsulphoxide DMSO). The anions test for trivalent metal ion complexes is positive before and after decomposing the complexes, indicating their presence inside as well as outside the coordination sphere. The higher values of molar conductance in dimethylsulphoxide (DMSO) indicate them to be electrolytic in nature (Kumar and Singh, 2006). Both complexes were decomposed over 250ºC, indicating their thermal stability. All compounds give satisfactory elemental analyses results as shown in the Table-1. In Infrared spectral data Table-2, nitrogen and oxygen are suitably placed for coordination toward the metal ion, has been proposed for both complexes, whereas absent in ligand confirm an octahedral geometry of complex I and complex II. Electronic Spectral Data of ligand and Cr(III) macrocyclic complexes shown in Table-3, spectral studies confirmed the permission of macrocyclic structure and its binding with metal ion. The complexes were proved to be coordinated with donor atoms and showed coordination with transition metal specially Chromium. Based on all these studies an octahedral geometry may be proposed for both complexes. Both the complexes were found to be potentially active towards microbial strains. The minimum inhibitory concentration (MIC) value in molar concn. shown in Table-4 of ligand and complexes compared whereas complexes showed good antimicrobial activity than ligand. It has been suggested that cheleation/coordination reduces the polarity of the metal ion mainly because of partial sharing of it positive charge with donor group within the whole chelate ring system (Chohan et al., 2004). This process of cheleation thus increases the lipophillic 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, conductivity influenced by metal ion may be possible reasons for remarkable antibacterial activities of these complexes (Chohan et al., 2006).

Abbreviations

MIC : Minimum Inhibitory Concentration
ATCC : American Type Culture Collection
DMF : N, N-dimethylformamide
DMSO : Dimethylsulphoxide

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