

INVESTIGATION OF TRIVALENT MACROCYCLIC COMPLEXES AS POTENT BIOLOGICAL ACTIVITY

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ABSTRACT

Two new Cr(III) macrocyclic complexes have been synthesized bearing the formula M(III)[DPTDH] (BF₄)₂, M(III)[DCTDH](BF₄), Where M=Cr(III), [DPTDH]=(2,6-diacetyl pyridine-N,N'-thiodiacetyl dihydrazone), [DCTDH] = (2,6-pyridine dicarbonyl dichloride-N,N'-thiodiacetyl dihydrazone), (BF₄) = Tetrafluoroborate. The synthesized complexes were investigated using different physical techniques such as elemental analyses, infra-red, electronic spectra and conductivity measurements. The IR and electronic spectral data in both complexes reveal that ligand is coordinated to the central metal ion. The result of analysis shows the complexes to be of octahedral geometry and of electronic nature. The new Macrocyclic complexes have been assessed for antifungal and antibacterial activities against certain microorganism. The complexes have been found to be manifold active biologically then the ligand.

KEYWORDS : Chromium(III) Macrocyclic Complexes, Elemental Analysis, Infra-red, Electronic Spectra, Antifungal and Antibacterial.

Transition metal complexes containing macrocycles are of considerable interest in terms of structural and coordination chemistry (Wang et. al., 2009). Macrocyclic compounds are synthetic or natural polydentate ligands, containing their donor atoms incorporated in a cyclic backbone or/and in substituents attached to it. They contain at least three donor atoms and the ring should have a minimum of nine atoms. The coordination chemistry of these compounds has now become a major subdivision of inorganic chemistry (Lindoy, 1989). Gokel and Korzeniowski report the synthesis of about 2100 macrocyclic compounds in their book published in 1982 (Gokel et. al., 1982). Now a days the future of this area still seems promising, as from the traditional co-ordination to the supramolecular chemistry; it has enlarged our vision and imagination on the co-ordination chemistry field. The research field dealing with macrocyclic metal complexes is very broad due in part to their potential interest for a number of interdisciplinary areas that include bioinorganic chemistry, catalysis, and magneto chemistry (Guerreiro et. al., 1995-Guerreiro et. al., 1993). A number of important macrocyclic molecules which show biological activities including antibacterial, antifungal (Kumar et. at., 2010 - Ramesh and Maheshwaran, 2003), antidiabetic (Vanco et. al., 2008), antitumor (Silveira et. at., 2008 - Zhong et al., 2006), antiproliferative (Chaviara et al., 2004- Illan-Cabeza et al., 2008), anticancer (Chaviara et al., 2004- Illan-Cabeza et al., 2008), herbicidal (Samadhiya and Halve 2001) and

anti-inflammatory activities (Baseer et al., 2000) have been reported. The chemistry of macrocyclic complexes is also important due to their use as dyes and pigments (Seto et al., 1996) as well as NMR shift reagents (Dong et al., 2001). Chromium(III) complexes of macrocyclic ligands are well known for their biological importance as well as their anticarcinogenic, antibacterial, and antifungal properties (Levana et al., 2002). The aim of the present work is to report synthesis, characterization and antimicrobial studies of a TDADH ligand and its transition metal complexes, which shows antifungal and antibacterial activities. In addition we have studied the elemental, infra-red spectroscopy and electronic data studies of these synthesized complexes.

MATERIALS AND METHODS

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

Synthesis of Ligand

The ligand, thiodiacetic acid dihydrazide was formed by mixing 1:2 stoichiometric quantities of transparent, thiodiacetic acid ester (1.62gm., 0.01M) solution and hydrazine hydrate (0.83cm³, 0.02M) were mixed in 20ml. 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 light-yellow crystal in bottom round flask was concentrated and cooled overnight

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and were filtered, washed with alcohol and ether then dried in vacuum over anhydrous CaCl_2 in a desiccator.

Synthesis of Metal Complexes I

1:1:1 stoichiometric quantities of ligand (1.78 gm., 0.01M), chromium acetate (2.42 gm., 0.01M) and 2,6-diacetyl pyridine (1.63 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 sodium tetrafluoroborate was added and the solution was cooled overnight, crystals separated out. These yellowish-brown crystals were filtered, washed with alcohol and then dried in vacuum over anhydrous CaCl_2 in a desiccator.

Synthesis of Metal Complexes II

1:1:1 stoichiometric quantities of ligand (1.78 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 sodium tetrafluoroborate was added and the solution was cooled overnight, crystals separated out. These greenish-blue crystals were filtered, washed with Alcohol and then dried in vacuum over anhydrous CaCl_2 in a desiccator.

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 (Mettler Toledo Model XP6). 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-Elmer- Model No.- C91158) in the range 4000-400 cm^{-1} . The electronic spectra of complexes in DMSO were recorded on a UV-VIS-NIR (Cary5E) spectrophotometer at room temperature.

INFRA-RED DATA

The band due to the $-\text{NH}_2$ group disappeared completely in the complexes. The band due to the $-\text{NH}$ group did not show any change in the spectra of complexes, confirming that the Nitrogen of $-\text{NH}$ group did not take part in reaction whereas a sharp band was seen in the range of 1350cm^{-1} proving that $-\text{NH}_2$ group is present in the ligand. Some entirely new absorption band appeared in the spectra of complexes viz. band around $560\text{--}550\text{cm}^{-1}$ due to M-N group, a band around $440\text{--}430\text{cm}^{-1}$ due to M-O group and a band around $340\text{--}320\text{cm}^{-1}$ due to presence of M-H group. These new band confirmed the coordination of nitrogen, oxygen and sulphur with the metal atom in the complexes.

ELECTRONIC DATA

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

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

COMPOUND	M.P. ($^{\circ}\text{C}$)	COLOR	YIELD (%)	ELEMENTAL ANALYSIS (%) (F/c)				MOLAR CONDUCTIVITY ($\text{ohm}^{-1}\text{cm}^2\text{mol}^{-1}$)
				C	H	N	M	
TDADH	176	Light-Yellow	2.35 gm.	26.91 (26.93)	5.60 (5.61)	31.32 (31.42)	-	-
$\text{Cr(III)[DPTDH](BF}_4)_2$	256	Yellowish-Brown	1.88 gm.	29.21 (29.26)	3.14 (3.18)	13.11 (13.13)	9.66 (9.75)	113.45
$\text{Cr(III)[DCTDH](BF}_4)_2$	260	Greenish-Blue	1.79 gm.	22.81 (23.00)	1.62 (1.91)	12.04 (12.19)	9.01 (9.06)	113.68

Table: 2 Infra-Red Spectral Data of Ligand and Newly Synthesized Cr(III) Macrocylic Complexes

S. NO.	FUNCTIONAL GROUPS	[TDADH]	Cr(III)[DPTDH](BF ₄) ₂	Cr(III)[DCTDH](BF ₄) ₂
1.	-CH ₂	2930	2870	2860
2.	-NH ₂	1350	-	-
3.	-NH	3400	3400	3400
4.	N-N	980	930	940
5.	C-H	820	780	770
6.	>C=N	-	1590	1580
7.	>C=O	1730	1690	1670
8.	M-N	-	560	550
9.	M-O	-	440	430
10.	M-S	-	340	320

Table: 3 Absorption Bands (in cm⁻¹) of Macrocylic Complexes in Electronic Spectra

S. NO.	COMPLEXES	TRANSITION (cm ⁻¹)	
		² E _g → ² T _{2g}	L→M
1.	Cr(III)[DPTDH](BF ₄) ₂	1900	24100
2.	Cr(III)[DCTDH](BF ₄) ₂	12450	24550

complexes in the range of 12,450-11,900 cm⁻¹ attributed to ²E_g→²T_{2g} transition and in the range of 24,550-24,100 cm⁻¹ attributed to L→M charge transfer transition. These transition confirmed the octahedral geometric of the complexes.

Determination of Antimicrobial Susceptibility By Agar Well Diffusion Method

Prepare Muller Hinton agar medium (38 gm. in 1000 ml of distilled water) according to the manufacturer's instructions, with supplementation for fastidious organisms. Medium should have a level depth of 4 mm ± 0.5 mm (25 ml. in a 90 mm petridish, 70 ml. in a 150 mm Petri dish). The surface of the agar should be dry before use. The dissolved medium was autoclaved at 15 lbs pressure at 121°C for 15 minutes. The autoclave medium was mixed well and poured onto petriplate while still molten. Petriplate containing 20 ml. Muller Hinton medium were seeded with 24 hr. culture of bacterial strains. Well were cut and 1 ml compound (0.1mg/ml) were added. The plates were then incubated at 37°C for 24 hours. The antibacterial activity was assayed by measuring the diameter of the inhibition zone formed around the well. Measure the diameters of zones of inhibition to the nearest millimeter with a ruler or an automated zone reader.

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., 50µg/ml. and 25µg/ml. respective concentrations of test compounds were inoculated with 100 µl of the bacterial suspension. The tubes were incubated at 37°C 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 macrocylic complexes derived from oxydiacetic acid ester and hydrazine hydrate and the ligand and complexes formulated as: TDADH and Cr(III)[DPTDH](BF₄)₂, Cr(III)[DCTDH](BF₄)₂. Ligand and all the macrocylic complexes are light-yellow, yellowish-brown, greenish-blue colored and soluble in dimethyl formamide (DMF) and dimethyl sulphoxide (DMSO). The higher values of molar conductance in dimethyl sulphoxide (DMSO) indicate them

Table 4 : Minimum Inhibitory Concentration (MIC) Value in Molar Concn. [X10⁻⁴] of Ligand and Newly Synthesized Cr(III) Macrocylic Complexes

COMPOUNDS	ACTIVITY AGAINST BACTERIAL STRAIN			ACTIVITY AGAINST FUNGAL STRAIN	
	<i>E. coli</i> (gram-negative)	<i>S. typhi</i> (gram-negative)	<i>S. aureus</i> (gram-positive)	<i>A. brasiliensis</i>	<i>C. albicans</i>
TDADH	0.625	0.617	0.610	0.602	0.615
Cr(III)[DPTDH](BF ₄) ₂	0.250	0.299	0.241	0.260	0.255
Cr(III)[DCTDH](BF ₄) ₂	0.215	0.271	0.214	0.210	0.210

to be electrolytic in nature. All compounds give satisfactory elemental analyses results as shown in the Table-1. in infra-red spectral data Table-2 nitrogen, oxygen and sulphur are suitably placed for coordination toward the metal ion, has been proposed for all the complexes, where as absent in ligand confirm a octahedral geometry of complex I and complex II. Electronic spectral data of ligand and Cr(III) Macrocylic complexes shown in Table-3. The Minimum inhibitory concentration (MIC) value in molar concn shown in Table-4 of ligand and complexes compared where as complexes showed good antimicrobial activity than ligand. All complexes were decomposed over 250°C indicating their thermal stability.

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