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Structural and Antimicrobial Studies of Some Macrocyclic Complexes of Copper(II) of Bioinorganic Relevance

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Two new macrocyclic complexes have been synthesized by condensing thiodiacetic acid dihydrazide with 2,6-diacetylpyridine2,6-pyridinedicarbonyldichloride in presence of copper(II) ions. The complexes have the formulae $Cu[DPTDH](BF_4)_2$ and $Cu[DCTDH](BF_4)_2$ (where DPTDH = 2,6-diacetylpyridine-N-thiodiacetoylhydrazone and DCTDH = 2,6-pyridinedicarbonyl-dichloride-N-thiodiacetoylhydrazone). The synthesized complexes have been characterized by elemental studies, conductivity measurements, and spectral (IR and electronic) studies. All these complexes have been tested *in vitro* for their antimicrobial activity against bacteria *Staphylococcus arueus* (gram positive) and *Escherichia coli* (gram negative) and fungi *Candida albicans* and *Aspergillus niger.*

INTRODUCTION

There has been tremendous research work on macrocyclic chemistry during the last two to three decades. Such an activity has gained momentum due to the realisation that metal ions play an important role in biological systems. Many complexes containing synthetic macrocyclic ligands may serve as models for biologically important species.[1] The biological system contains the naturally occurring chelates[2] of metals such as cobalt, copper and zinc with amines and related compounds.

Macrocyclic compounds are ideally applicable as complexing agents and ion-chelating resins, for example, synthetic cyclic polyethers, cyclic polythiaethers, cyclic polyazaethers and bicyclic amines. The selectivity of cyclic antibiotics toward cations has commercial application, *e.g.* valinomycin in ion-selective electrodes.[3] Kimura *et al.*[4] recently synthesized 6-hexadecyl-1,4,8,11-tetraazacyclotetradecane-5,7-dione and found that it selectively encloses copper(II) and is potentially useful for the separation of copper(II) by solvent extraction. Recently copper(II) complexes of the macrocyclic ligand 1,4,7,10,13,16-hexaazaoctadecane (hexacyclen) have been isolated.[5] This N-containing analogue of 18-Crown-6 has been explored with reference to its metal complexes.[6–9] It was also used as an extracting agent for different metal ions.[10,11]

In the series of macrocyclic compounds, research investigations have been done with the complexes of porphyrins, corrins and phthalocyanins and their relation with prominent species containing macrocycles occurring in nature such as cytochrome, haemoglobin, haemocyanin and chlorophyll. The natural product, coenzyme B_{12}, is a Co(III) corrinoid complex containing a σ-bonded alkyl ligand.[12] This discovery has prompted the preparation and study of synthetic analogues of vitamin B_{12} and its coenzymes. The phthalocyanines, an important commercial class of pigments, were one of the earliest synthetic macrocyclic tetraamines to be discovered. Similar nitrogen-containing macrocylics[13] could be prepared by the Schiff base condensation reaction, often with a metal ion as a template.

With a view to correlating the widely applicable synthetic macrocyclic ligands and their copper(II) complexes with the naturally occurring systems containing macrocycles, some new macrocyclic chelates of copper(II) were previously synthesized by the condensation of the dihydrazides of iminodiacetic acid/pyridine-2,6-dicarboxylic acid with 2,6-diacetylpyridine and 2,6-pyridinedicarbonyldichloride. These complexes were found to have octahedral geometry and exhibited antimicrobial activity against bacterial and fungal species.[14]

Continuing the work carried out earlier, here the author present the synthesis of two new macrocyclic complexes by condensing thiodiacetic acid dihydrazide with 2,6-diacetylpyridine/2,6-pyridinedicarbonyldichloride in presence of copper(II) ions.

EXPERIMENTAL

Chemicals of AR grade were used for synthesizing the compounds.Thiodiacetic acid dihydrazide was synthesized from their corresponding dimethyl ester of the acid and hydrazine hydrate by the reported procedure.[15] Its purity was ascertained by preliminary investigations, *viz.* melting point determination and TLC method for single spot.

Synthesis of metal complexes

1. *Cu[DPTDH]*$(BF_4)_2$: Equimolar amounts of thiodiacetic acid dihydrazide (0.01 M), copper acetate (0.01 M) and 2,6-diacetylpyridine (0.01 M) were mixed in ethanol with continuous stirring. The solution thus obtained was refluxed over a water-bath for around six hours. Subsequently, it was concentrated to one-third of its original volume. Then, a little of sodiumtetrafluoroborate was added and the solution was cooled overnight, when black crystals separated out. The crystals were filtered, washed with alcohol, ether and then dried in vacuum over anhydrous $CaCl_2$ in a desiccator.

2. *Cu[DCTDH]*$(BF_4)_2$: Equimolecular quantities of thiodiacetic acid dihydrazide (0.01 M), copper acetate (0.01 M) and 2,6-pyridinedicarbonyldichloride (0.01 M) were mixed in ethanol with constant stirring. The solution obtained was refluxed over a water-bath for around five to six hours. Thereafter, it was concentrated, some sodiumtetrafluoroborate was added and the solution was cooled overnight, when blue crystals separated out. The crystals were filtered, washed with alcohol, ether and dried in vacuum over anhydrous $CaCl_2$ in a desiccator.

The synthesized complexes were tested for their purity by melting point and

TLC methods and their CHN analysis. Metal contents were estimated by standard procedures.[16] IR spectra were recorded on a Perkin-Elmer Model 577 Spectrophotometer in the range of 4000–200 cm^{-1} in CsI matrix. Electronic spectra were carried out in pure DMSO on a UV-Visible Digital Spectrophotometer CL10A4 Model. The molar conductance values of the complexes were measured in dry DMSO using a Toshniwal conductivity Meter CL 01–10A Model at room temperature (27 ± 2°C).

RESULTS AND DISCUSSION

Both the synthesized complexes were coloured solids and stable at room temperature. They were found to be soluble in DMSO, DMF and propylene glycol, but insoluble in rest of the common organic solvents. The analytical data of the metal complexes suggest their 1 : 1 : 1 stoichiometry. The ligand fragment, *i.e.* thiodiacetic acid dihydrazide, exhibits 1 : 2 stoichiometry. The molar conductance values of both the complexes were in the range of 105.7–106.9 ohm^{-1} cm^{-1} $mole^{-1}$ which confirmed the strongly electrolytic nature of both the complexes. The analytical data of the ligand fragment and metal complexes are presented in Table-1.

TABLE -1
ANALYTICAL DATA OF LIGAND FRAGMENT AND Cu(II) MACROCYLIC COMPLEXES

S.No.	Compound	Colour	m.p. (°C)	m.w. Found (Calcd.)	Mol. formula
1.	TDADH	Yellowish White	108	177.4 (178.0)	$C_4H_{10}O_2N_4S$
2.	Cu [DPTDH] $(BF_4)_2$	Black	179	541.6 (542.1)	$Cu[C_{13}H_{15}O_2N_5S]$ $(BF_4)_2$
3.	Cu [DCTDH] $(BF_4)_2$	Blue	185	582.5 (583.1)	$Cu[C_{11}H_9O_2N_5SCl_2]$ $(BF_4)_2$

In the IR spectrum of thiodiacetic acid dihydrazide, sharp and prominent bands were observed at 3150, 1710 and 1600 cm^{-1}. These were assigned to the presence of ν(NH), ν(C=O) and $\nu(NH_2)$ groups, respectively. ν(N—N) transitions were observed around 1050 cm^{-1}. Another distinct band was observed in the spectrum of ligand fragment at 1190 cm^{-1} which was characteristic of the ν(C—S) bond.

In the IR spectra of metal complexes, the peak due to ν(NH) did not show any shift (3150 cm^{-1}), ruling out the coordination of nitrogen of (NH) with the central metal atom. However, the band due to ν(C=O) experienced a negative shift by 50–40 cm^{-1}, appearing at 1650 cm^{-1}, while the position of ν(N—N) band shifted to higher wave numbers (1080 cm^{-1}). These observations led to the conclusion that the amide oxygen of ν(C=O) and the nitrogen of N—N bond have involved in complexation. The peak due to ν(C—S) bond underwent a lowering. It appeared at 1120 cm^{-1} in the spectra of complexes, indicating the coordination of sulphur of C—S with central metal atom.

The spectra of complexes exhibited certain additional bands. An intense band appeared at 1590 cm^{-1} which was due to the formation of C═N bond *in the* complexes. This bond was formed due to the condensation of acetyl group with the dihydrazide. A band was also seen around 2900 cm^{-1} due to $\nu(CH_2)$ group in the spectra of complexes, which is unaltered as compared to the peak shown by the ligand fragment.

The IR spectra of metal complexes showed certain new bands which did not exist in the spectrum of ligand fragment. In both the complexes, intense peaks appeared at 460–450 cm^{-1}, 375 cm^{-1} and 310 cm^{-1}. These peaks could be attributed to the coordination of azomethine and pyridinyl nitrogen on one hand and amide and carbonyl oxygen on the other, thus supporting the formation of M—N and M—O bonds in the complexes. The third band confirmed the presence M—S bond in the complexes.

Electronic spectra

Both the Cu(II) complexes exhibited two broad bands, one in the region of 15,960–15,800 cm^{-1} and another in the range of 29,160–28,850 cm^{-1}. The former band may be assigned to $^2E_g \rightarrow {}^2T_{2g}$ transitions, suggesting an octahedral geometry for these complexes.[15] The latter band can be attributed to L → M charge transfer band.

The values for various characteristic bands displayed in the IR Spectra and electronic spectra of Cu(II) complexes are presented in Table-2.

TABLE-2
ELEMENTAL ANALYSIS AND MOLAR CONDUCTANCE DATA OF THE COMPOUNDS

S.No.	Compound	% Analysis, found (calcd.)				Molar conductivity (ohm^{-1} cm^{-1} mol^{-1})
		C	H	N	Cu	
1.	TDADH	26.29 (26.96)	5.23 (5.61)	30.74 (31.46)	—	—
2.	Cu[DPTDH] $(BF_4)_2$	27.93 (28.77)	2.69 (2.76)	12.09 (12.91)	11.31 (11.71)	105.70
3.	Cu[DCTDH] $(BF_4)_2$	22.19 (22.63)	1.47 (1.54)	11.78 (12.00)	10.51 (10.89)	106.90

Antimicrobial study

The ligand fragment and the two Cu(II) macrocyclic complexes were screened *in vitro* for their antimicrobial activity using serial dilution method against two bacteria, viz., *Escherichia coli* (gram negative) and *Staphylococcus aureus* (gram positive) [incubation period 24 h at 37°C] and two fungi, *viz.*, *Aspergillus niger* and *Candida albicans* [incubation period 96 h at 28°C].

TABLE-3

IR SPECTRAL DATA (cm^{-1}) OF THE COMPOUNDS

S. No.	Functional group	TDADH	Cu [DPTDH] (BF$_4$)$_2$	Cu [DCTDH] (BF$_4$)$_2$
1.	—CH$_2$	2880	2880	2880
2.	—NH	3150	3150	3150
3.	$>$C=O—	1710	1670	1670
4.	—NH$_2$	1610	—	—
5.	N—N	1050	1075	1075
6.	$>$C=N—	—	1590	1590
7.	$>$C=S—	1190	1120	1120
8.	M—O	—	445	460
9.	M—N	—	375	375
10.	M—S	—	305	310

TABLE-4

ELECTRONIC SPECTRAL DATA (cm^{-1}) OF THE COMPLEXES

S.No.	Compounds	Transitions (cm^{-1})	
		$^2E_g \rightarrow {}^2T_{2g}$	L → M
1.	Cu[DPTDH] (BF$_4$)$_2$	15,800	28,850
2.	Cu[DCTDH] (BF$_4$)$_2$	15,960	29,160

The minimum inhibitory concentration values of the ligand fragment and the two metal complexes were measured by preparing graded dilutions of the test compounds in 2.5% DMSO for the complexes and propylene glycol for the ligand fragment (dihydrazide). The minimum concentration of the test compound showing no visible trubidity was termed the 'MIC' value for that compound, *i.e.* the minimum concentration which is able to prevent any detectable growth of the micro-organism.

TABLE-5

MIC VALUES OF THE COMPOUNDS IN MOLAR CONCENTRATION (×10^{-4})

S.No.	Compounds	Bacteria		Fungi	
		E. coli	*S.aureus*	*A. niger*	*C. albicans*
1.	TDADH	1.40	1.40	2.80	1.40
2.	Cu [DPTDH] (BF$_4$)$_2$	0.23	0.23	0.11	0.11
3.	Cu [DCTDH] (BF$_4$)$_2$	0.11	0.23	0.11	0.11

The 'MIC' values for the compounds have been represented in Table 5. The results follow the order given below:

Against Bacteria

$$Cu[DCTDH](BF_4)_2 > Cu[DPTDH](BF_4)_2 > TDADH.$$

Against Fungi

$$Cu[DPTDH](BF_4)_2 = Cu[DCTDH](BF_4)_2 > TDADH.$$

The results show that the ligand fragment is antimicrobially active at a definite concentration against both, bacterial as well as fungal species. However, the two metal complexes are much more active than the ligand fragment against the microbes.

The reasons for the observed trend of activity may be:

(1) More liposolubility of the macrocyclic complexes.

(2) The foreign metal ion of the macrocyclic complex may have been replaced by the metal ion of the biological enzymic system, thus causing rupturing of the biological enzymic system.

(3) The combined activity effect of the ligand fragment and the metal ion may have enhanced the antimicrobial activity.

(4) More rapid penetration of the complex as a whole through the cell-walls of the micro-organism, causing damage to the synthesis of proteins and nucleic acids of the microbe.

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