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Synthesis, Characterization and Antimicrobial Studies of Some Macrocyclic Ligands and Their Nickel(II) Complexes

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18-Membered macrocyclic ligand 4,5;10,11;16,17-B_zO_3-12,15-dioxo-1,2,7,8-tetraaza-3,6-dione cyclooctadeca-8,18-diene. {(18) diene N_4O_4} and 19-membered 4,5;10,11;17,18-B_zO_3-12,16-dioxo-1,2,7,8-tetraaza-3,6-dione cyclonona-odeca-8,19-diene, {(19) diene N_4O_4} macrocyclic ligand having nitrogen and oxygen atoms as donor sites, have been used to synthesize Ni(II) complexes by template condensation reaction. *In-vitro* biocidal studies of the complexes and their constituting fragments against two bacteria *Staphylococcus aureus* and *Escherichia coli* and two fungi *Asperigillus niger* and *Candida albicans* reveal that the macrocyclic complexes show greater antimicrobial activity in comparison to other constituting elements.

INTRODUCTION

The field of macrocyclic chemistry of metals is developing very fast because of its variety of applications[1] and importance in the area of coordination chemistry.[2] Many macrocyclic complexes of transition metals have vital importance in biological systems. It is a well known fact that iron in haemoglobin, cobalt in vitamin B_{12}, magnesium in chlorophyll, copper in copper blue proteins and nickel in enzyme hydrogenase are present in a macrocyclic moiety. These metal containing macrocyclic compounds play an important role in many redox reactions[3] of vital importance for the living kingdom. In the present work, we report the synthesis, characterization and biocidal studies of two macrocyclic ligands: {(18) diene N_4O_4} and {(19) diene N_4O_4} and their Ni(II) macrocyclic complexes of bioinorganic relevance.

EXPERIMENTAL

All the chemicals used were of AR grade and were used without further purification. Authenticity of the purity of all the compounds was checked by running their T.L.C. for single spot on silica gel plate and by their repeated melting point determination taken in open capillary tubes and thus uncorrected.

Synthesis of Dialdehydes: To 10 mL ethanolic solution of (0.01 M) salicyaldehyde, an aqueous solution of sodium bicarbonate (0.01 M) in minimum volume of distilled water was added slowly with constant stirring. The mixture thus obtained was refluxed under nitrogen for 1/2 h and cooled. 10 mL ethanolic solution of (0.005 M) 1,2-ethylene dibromide/1,3-propylene dibromide was added slowly in drops. The contents were again refluxed for about 3 h over a water bath using water condenser and then concentrated to half of its original volume. On cooling the solution thus produced, yellowish white crystalline product was obtained. It was filtered under reduced pressure, first washed with water, then alcohol followed by ether and dried under reduced pressure over anhydrous $CaCl_2$.

Synthesis of Macrocyclic Ligands: To 15 mL methanolic solution of synthesized dialdehyde (0.1 M), phthalic acid dihydrazide (0.1 M) was added and stirred well. The contents were refluxed for about 2 h, then concentrated and cooled. The resulting yellowish crystals were filtered, washed with ethanol followed by ether and dried under reduced pressure over anhydrous $CaCl_2$.

Synthesis of Metal Complexes: 0.195 g (0.001 M) phthalic acid dihydrazide and 0.29 g (0.001 M) nickel nitrate ($6H_2O$) were taken in a round bottom flask and heated to dissolve. To the above hot solution, the synthesized 2,2′-ethylenedioxobenzaldehyde/(EDB) 2,2′-propylenedioxobenzaldehyde (PDB) (0.001 M) dissoloved in 10 mL methanol was added. The contents thus obtained were again refluxed for 2 h using water condenser. The resulting solid product was cooled at room temperature, filtered, washed with ethanol followed by ether and dried under reduced pressure over anhydrous $CaCl_2$.

Antimicrobial Studies: The ligands and their respective metal chelates were screened for their antimicrobial activity using Serial Dilution method[4] against the two bacteria *viz. Staphylococcus aureus* (*S.a.*) gram-positive and *Escherichia coli* (*E.c.*) gram-negative keeping the incubation period 24 h at 37°C and the two fungi *viz. Aspergillus niger (A.n.)* and *Candida albicans* (*C.a.*) in suitable culture medium keeping the incubation period 96 h at 28°C.

Carbon, hydrogen and nitrogen analyses were done in the Microanalytical Laboratory, CDRI Lucknow. Ni(II) metal was estimated by its established method.[5] IR spectra were recorded in the 4000–400 cm^{-1} range as KBr disc using a Perkin-Elmer-577 Spectrophotometer. Electronic spectra in DMSO were taken in DMSO-D_6 using Jeol Model Fx-90 Q (60 MHz). Nuclear Magnetic Resonance Spectrometer at the Regional Research Laboratory, Jammu using Me_4Si as an internal standard. Conductivity measurements were done on Toshniwal Digital Conductivity Meter in commercially available AR-DMSO.

RESULTS AND DISCUSSION

The analytical data of the two ligands and their 1 : 1, Ni(II) : ligand complexes having the composition {NiL} $(NO_3)_2$ are shown (Table-1). Both the complexes were found coloured, stable at room temperature and insoluble in common organic solvents but soluble in DMF and DMSO. The higher molar conductance values {120–140 Ω^{-1} cm^2 mol^{-1}} indicated their electrolytic nature. A comparative study of the IR spectra of the ligands and their metal complexes indicates that the strong band at 1700 cm^{-1} due to stretching vibration of (C═O) group of the ligand undergoes a negative shift by 20–30 cm^{-1} in the IR spectra of the metal complexes, which infers the participation of carbonyl group. A band around 1025 cm^{-1} due to (N—N) vibration in the ligand experiences a positive shift by 10–20 cm^{-1} in metal complexes showing the involvement of their moiety in complexation[6] through N—N atom. A strong band at 1610 cm^{-1} due to ν(C═N) in the ligand spectra is shifted to lower frequency by 10–15 cm^{-1} in their metal complexes. This indicates the coordination of azomethine nitrogen (C═N) with the metal ion.[7, 8] The stretching vibrations of (NH) around 3220 cm^{-1} remain unchanged in the IR spectra of metal complexes which reveals the non-participation of NH group of the ligands in complexation. A strong band at 1225 cm^{-1} is due to ν(C—O) present in the ligand has shifted to lower frequency. This observation indicates the involvement of oxo-group in coordination. The appearance of some new bands of medium intensity in the IR spectra of macrocyclic complexes in the region of 600–400 cm^{-1} could be assigned to M—O and M—N vibrations[9, 10] respectively, which have developed on complexation and were absent in the IR spectra of the ligands.

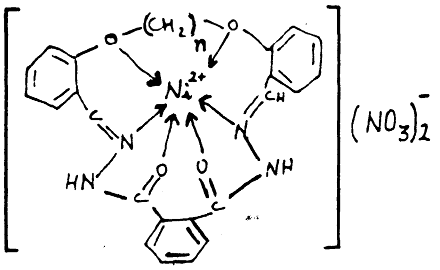
TABLE-1
ANALYTICAL AND PHYSICAL DATA OF THE LIGANDS AND THEIR Ni(II) COMPLEXES

S. No.	Compounds (Colour, m.pt./decomposition temp (°C))	Molecular Formula	Analysis % (Found/Caled.) C	H	N
1.	EDB (Yellowish white)(112)	$C_{16}H_{14}O_4$	70.40 (71.10)	5.22 (5.40)	—
2.	PDB (Yellowish white)(88)	$C_{17}H_{16}O_4$	70.60 (71.82)	5.87 (5.67)	—
3.	{(18) diene N_4O_4} (Light yellow)(222)	$C_{24}H_{20}N_4O_4$	66.70 (67.28)	4.40 (4.70)	12.80 (13.07)
4.	{(19) diene N_4O_4} (Yellow)(210)	$C_{25}H_{22}N_4O_4$	67.40 (67.86)	4.40 (4.99)	11.80 (12.66)
5.	{Ni (18) diene N_4O_4}$(NO_3)_2$ (Light brown)(322)	$[Ni(C_{24}H_{20}N_4O_4)](NO_3)_2$	58.00 (59.17)	4.00 (4.10)	10.30 (11.50)
6.	{Ni (19) diene N_4O_4}$(NO_3)_2$ (Grey)(352)	$[Ni(C_{25}H_{22}N_4O_4)](NO_3)_2$	59.10 (58.69)	4.05 (4.39)	10.70 (11.18)

Electronic spectra of Ni(II) complexes exhibit bands in the region 10800–10300 cm^{-1}, 11800–11500 cm^{-1} and 18250–18100 cm^{-1} along with a shoulder at 9100–8200 cm^{-1} which may reasonably be assigned to ${}^3A_{2g} \rightarrow {}^3T_{2g}(F)$, ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$, ${}^3A_{2g} \rightarrow {}^3T_{2g}(F)$ and ${}^3A_{2g} \rightarrow {}^3T_{g}(F)$ transitions respectively and are inconsistent with the reported observations for the distorted octahedral geometry[11] around the Ni^{2+} ion.

The nuclear magnetic resonance spectrum of the complex obtained in DMSO-D_6 solution, with TMS as an internal standard, shows the signals of phenyl protons in the range of δ 7.2 – 8.2 ppm, —CH_2 (methylene) protons at δ 2.8 ppm, the —NH protons at δ 4.5 ppm and —CH protons at δ 0.6 ppm. Integrated intensities of the above signals are in the ratio of 6 : 2 : 1 : 1 respectively.[12] This is consistent with the proposed formulatio in of the complex.

On the basis of spectral (IR, UV and NMR) and analytical data it seems reasonable to assume that the Ni(II) complex has octahedral structure with two nitrogen and four oxygen donor atoms of the 18 and 19 membered macrocyclic ligands.



where $n = 2, 3$.

The biological activity data (Table-2) shows that antimicrobial activity of ligand fragments is enhanced several-folds on complexation with the metal ion. This increase in antimicrobial activity is probably either due to faster diffusion of metal complexes as a whole through the cell membrane or due to the combined activity effect of the metal and ligand.[13]

TABLE-2
MINIMUM INHIBITORY CONCENTRATION (MIC IN MOLAR CONCENTRATION $\times 10^{-4}$) OF SYNTHESIZED LIGANDS AND THEIR Ni (II) COMPLEXES

S. No.	Compounds	Bacteria		Fungi	
		S.a. (Gram-positive)	*E.c.* (Gram-negative)	*A.n.*	*C.a.*
1.	EDB	1.85	1.85	2.78	2.78
2.	PDB	2.64	2.64	1.76	2.64
3.	PADH	2.57	2.57	2.57	2.57
4.	{(18) diene N_4O_4}	0.58	1.17	1.17	1.17
5.	{(19) diene N_4O_4}	0.56	0.56	1.13	0.56
6.	{Ni(18) diene N_4O_4}$(NO_3)_2$	0.13	0.13	0.13	0.13
7.	{Ni(19) diene N_4O_4}$(NO_3)_2$	0.25	0.12	0.25	0.12

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