Synthesis, Structural Characterization, and Antibacterial Studies of a Tetradentate Macrocyclic Ligand and Its Co(II), Ni(II), and Cu(II) Complexes¹

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Abstract—A novel macrocyclic tetradentate ligand 1,5,8,12-tetraaza-2,4,9,11-tetraphenyl-6,7:13,14-dibenzocyclohexadeca-1,4,8,11-tetraene (L) has been synthesized. Cobalt(II), nickel(II), and copper(II) complexes of this ligand have been prepared and characterized by elemental analysis, molar conductance measurements, magnetic susceptibitity measurements, and mass, IR, electronic, and ESR spectral studies. The molar conductance measurements correspond to a nonelectrolytic nature for all the complexes, which can be formulated as $[M(L)X_2]$ (where M = Co(II), Ni(II), and Cu(II); X = Cl⁻ and NO₃). On the basis of IR, electronic, and ESR spectral studies, an octahedral geometry has been assigned to the Co(II) and Ni(II) complexes, whereas a tetragonal geometry was found for the Cu(II) complexes. The investigated compounds and uncomplexed metal salts and the ligands were tested against bacterial species like *Sarcina lutea, Escherchia coli*, and *Staphylococcus aureus*. The metal complexes have higher activity than the free ligand and metal salts.

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INTRODUCTION

The synthesis of macrocyclic ligands and their metal complexes is a growing area of research in inorganic and bioinorganic chemistry in view of their presence in many biologically significant systems [1-3]. The synthesis and study of macrocycles underwent tremendous growth in recent years, and their complexation chemistry with a wide variety of metal ions has been extensively studied. Macrocyclic metal complexes are considered to be the model of metalloporphyrins [4] owing to their intrinsic structural properties. Macrocyclic ligands have been used successfully for diverse processes, such as separation of ions by transport through artificial and natural membranes, liquidliquid or solid-solid phase transfer reactions, preparation of ion-selective electrodes, and isotope separation, and in the understanding of some natural processes, through mimicry of metalloenzymes [5]. Macrocyclic ligands and their metal complexes have a wide range of biological properties. A lot of work has been done on transition metal complexes with macrocyclic ligands, such as antifungal, antibacterial, anticancer, antiviral, and anti-HIV activity [6–13].

The present paper describes the synthesis, characterization, and antimicrobial activities of a novel macrocyclic tetradentate ligand, 1,5,8,12-tetraaza-2,4,9,11tetraphenyl-6,7:13,14-dibenzocyclohexadeca-1,4,8,11tetraene (L) and its Co(II), Ni(II), and Cu(II) complexes.

EXPERIMENTAL

All the chemicals used were of AnalaR grade and procured from Sigma-Aldrich. Metal salts were purchased from E. Merck and were used as received. All solvents used were of standard (spectroscopic) grade.

Synthesis of the ligand. A hot ethanolic solution (20 ml) of dibenzoylmethane (4.48 g, 0.02 mol) and a hot ethanolic solution (20 ml) of *o*-phenylenediamine (2.16 g, 0.02 mol) were mixed slowly with constant stirring. This mixture was refluxed at 80°C for 8 h in the presence of few drops of concentrated hydrochloric acid. On cooling, a solid light brown precipitate formed, which was filtered off, washed with cold EtOH, and dried under vacuum over P_4O_{10} . The yield was 68%, mp = 180°C.

For $C_{42}H_{32}N_4$			
anal. calcd, %:	C, 85.13;	Н, 5.40;	N, 9.45.
Found, %:	C, 85.20;	Н, 5.35;	N, 9.38.

The preparation and structure of the ligand L are shown below:

¹ The text was submitted by the authors in English.



Synthesis of the complexes. A hot ethanolic (20 ml) solution of the ligand (0.592 g, 0.001 mol) and a hot ethanolic (20 ml) solution of the corresponding metal salt (0.001 mol) were mixed together with constant stirring. The mixture was refluxed for 5–7 h at 75–80°C. On cooling, a colored complex was formed, which was filtered off, washed with cold EtOH, and dried under vacuum over P_4O_{10} .

Physical measurements. Analytical data were obtained with a Carlo-Erba 1106 elemental analyzer. Molar conductance was measured on an ELICO (CM82T) conductivity bridge. Magnetic susceptibility was measured at room temperature on a Gouy balance using $CuSO_4 \cdot 5H_2O$ as a callibrant. Electron impact mass spectra were recorded on TOF MS ES + mass spectrometer. ¹H NMR spectra was recorded on a Hitachi FT-NMR (model R-600) spectrometer using CDCl₃ as a solvent. Chemical shifts are given in ppm relative to tetramethylsilane. IR spectra (KBr pellets) were recorded on a FT-IR Spectrum BX-II spectrophotometer. The electronic spectra were recorded in DMF on a Shimadzu UV mini-1240 spectrophotometer. ESR spectra of the complexes were recorded as polycrystalline samples and in a DMSO solution at liquid nitrogen temperature (LNT) for the Co(II) complex and at room temperature (**RT**) for the Cu(II) complex on an E_4 -EPR spectrometer using DPPH as the g-marker. Cyclic voltammetry of the complexes was recorded in DMF at a scan rate of 100 mV s⁻¹. The redox potential was recorded with Ag/AgCl as the reference electrode and platinum as the working electrode, tetrabutylammonium phosphate was the supporting electrolyte, and the concentration of the complex was 1×10^{-3} mol/l.

RESULTS AND DISCUSSION

The electron impact mass spectrum of the metalfree ligand confirms the proposed formula by showing a peak at 616 amu (i.e., atomic mass 592 corresponding to the macrocyclic moiety $[C_{42}H_{32}N_4]$ + atomic mass 23 of Na⁺ ion). The spectrum shows a series of peaks, i.e., 300, 326, 367, 466, 480, 524, 582, etc., corresponding to various fragments. The ¹H NMR spectrum of the ligand L in CDCl₃ does not give any signal corresponding to primary diamine or alcoholic protons. The presence of a sharp multiplet in the region δ 7.27 ppm can be assigned to the benzoid hydrogen (6H), having the same chemical shift and thus behaving as equivalent [14]. A signal at δ 1.82–2.23 ppm can be assigned to (C–CH₂–C, 4H), and a strong triplet appeared for (C–C₆H₅, 20H) at δ 7.93–8.30 ppm.

In the IR spectrum of the ligand, the absence of a band in a region of ~3400 cm⁻¹ corresponding to a free primary diamine and keto group suggests the complete condensation of the amino group with the keto group. The appearance of a new strong absorption band at 1592 cm⁻¹ attributable to the characteristic stretching frequencies of the imino linkage v(C=N) provides strong evidence for the presence of a cyclic product [15, 16]. The bands at 755 and 1458 cm⁻¹ are due to the presence of the phenyl ring in the macrocycle. The shifting of the v(C=N) band toward the lower side in the complexes indicates that coordination takes place through the nitrogen of the C=N group, thus implying that the ligand acts in a tetradentate manner.

On the basis of elemental analysis data, the complexes were found to have the composition as shown in Table 1. The molar conductance measurements of the complexes in DMSO correspond to a nonelectrolyte nature. Thus, these complexes may be formulated as $[M(L)X_2]$ (where M = Co(II), Ni(II), and Cu(II); X = Cl^- and NO_3^-). The IR spectra of the complexes show bands toward the lower side, indicating coordination through the nitrogen atom of the C=N groups. The presence of the absorption bands at 1473–1480, 1309– 1315, and 1000–1014 cm⁻¹ in the IR spectra of the Co(II), Ni(II), and Cu(II) of the nitrato complexes suggests that both nitrate groups are coordinated to the central metal ion in a unidentate manner [17].

Cobalt(II) complexes. At room temperature, the magnetic moment of the Co(II) complexes lies in the range 4.91–5.04 $\mu_{\rm B}$ corresponding to three unpaired electrons (Table 2). The electronic spectra of the Co(II) complexes give three peaks in the range 9619–9950 ($\epsilon = 68.5 \text{ l}$), 14862–15503 ($\epsilon = 75$), and 18621–19493 cm⁻¹ ($\epsilon = 92 \text{ l} \text{ mol}^{-1} \text{ cm}^{-1}$). These bands may be assigned to the transitions ${}^{4}T_{1g}(F) \longrightarrow {}^{4}T_{2g}(F)$ (v₁), ${}^{4}T_{1g} \longrightarrow {}^{4}A_{2g}$ (v₂), and ${}^{4}T_{1g}(F) \longrightarrow {}^{4}T_{1g}(P)$ (v₃), respectively. The

Complex	Molarconduc-	Color	Melting-	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Contents (found/calcd), %			
Complex	$\Omega^{-1} \mathrm{cm}^2 \mathrm{mol}^{-1}$	COIOI	point,°C		М			
$[\text{Co}(\text{L})\text{Cl}_2], \text{Co}\text{C}_{42}\text{H}_{32}\text{N}_4\text{Cl}_2$	12	Pink	275	60	69.87/69.80	4.51/4.43	7.84/7.75	8.23/8.15
$[Co(L)(NO_3)_2], CoC_{42}H_{32}N_6O_6$	08	Pink	282	58	65.12/65.03	4.21/4.12	10.76/10.83	7.67/7.60
[Ni(L)Cl ₂], NiC ₄₂ H ₃₂ N ₄ Cl ₂	15	Light green	290	65	69.74/69.80	4.38/4.43	7.68/7.75	8.22/8.13
$[Ni(L)(NO_3)_2], NiC_42H_{32}N_6O_6$	10	Light green	284	60	65.12/65.03	4.19/4.12	10.90/10.83	7.49/7.57
$[Cu(L)Cl_2], CuC_{42}H_{32}N_4Cl_2$	09	Green	287	65	69.41/69.32	4.32/4.40	7.63/7.70	8.81/8.73
[Cu(L)(NO ₃) ₂], CuC ₄₂ H ₃₂ N ₆ O ₆	13	Green	278	62	64.55/64.61	4.14/4.10	10.66/10.76	8.22/8.14

Table 1. Elemental analysis data and some physical properties of the complexes

positions of these bands suggest an octahedral environment around the Co^{2+} ions [18].

The ESR spectra of the Co(II) complexes were recorded as polycrystalline samples and in a DMSO solution at LNT. The *g* values were found to be almost the same in both cases in polycrystalline samples, as well as in the solution (Table 3). The large deviation in the *g* values in the ESR spectra from the spin only value (g = 2.0023) is due to a large angular momentum contribution [19]. This indicates that the complexes have the same geometry in the solid, as well as in solution.

Nickel(II) complexes. The magnetic moment of the Ni(II) complexes at room temperature lies in the range 2.98–3.14 μ_B (Table 2). These values are in tune with a high spin configuration and show the presence of an octahedral environment around the Ni²⁺ ion in the complexes. The electronic spectra of the Ni(II) complexes show bands in the range 9898–10449 ($\varepsilon = 42.5$), 15037–17600 ($\varepsilon = 67$), and 22 675–24 189 cm⁻¹ ($\varepsilon = 96.5 \ 1 \ mol^{-1} \ cm^{-1}$) characteristic of an octahedral geometry [20] and presumably possessing D_{4h} symmetry. Thus, these bands can be assigned to the three spinallowed transitions ${}^{3}A_{2g}(F) \longrightarrow {}^{3}T_{2g}(F)$ (ν_1), ${}^{3}A_{2g}(F) \longrightarrow {}^{3}T_{1g}(F)$ (ν_2), and ${}^{3}A_{2g}(F) \longrightarrow {}^{3}T_{1g}(P)$ (ν_3), respectively.

Copper(II) complexes. The magnetic moment values for the Cu(II) complexes lie in the range 1.95–2.11 $\mu_{\rm B}$ corresponding to one unpaired electron. The complexes may be considered to possess a tetragonal geometry. The electronic spectra of the Cu(II) complexes reported here display bands in the range 10427–10438 ($\varepsilon =$ 57.5), 18621 ($\varepsilon =$ 65), and 25773–28169 cm⁻¹ ($\varepsilon =$ 154.5 l mol⁻¹ cm⁻¹). The first two bands can be assigned to the transitions ${}^{2}B_{1g} \longrightarrow {}^{2}A_{1g}(d_{x^{2}-y^{2}} \longrightarrow d_{z^{2}})(v_{1})$ and ${}^{2}B_{1g} \longrightarrow {}^{2}B_{2g}(d_{x^{2}-y^{2}} \longrightarrow d_{zy})(v_{2})$, respectively, and the third band is due to charge-transfer spectra [21]. The complexes can be considered to possess a tetragonal geometry.

The ESR spectra of the Cu(II) complexes were recorded at room temperature as polycrystalline samples and in a DMSO solution at LNT. The polycrystalline spectra show a well-resolved anisotropic broad signal [22]. The analysis of the spectra give $g_{\parallel} = 2.22-2.28$ and $g_{\perp} = 2.05-2.10$ (Table 3). The trend $g_{\parallel} > g_{\perp} > 2.0023$ observed for the complexes indicates that the unpaired electron is localized in the $d_{x^2-y^2}$ orbital of the copper(II) ion, and the spectral figures are characteristic of the axial symmetry. The tetragonal elongated structure is thus confirmed for the aforesaid complexes [23].

Various ligand field parameters were calculated for the complexes and are listed in Table 4. The Nephelauxetic parameter β was readily obtained by using the rela-

Table 2. Magnetic moment and electronic spectral data of the complexes

Complex	μ_{eff}, μ_B	Electronic spectral bands, cm ⁻¹
[Co(L)Cl ₂]	5.04	9950, 15503, 18621
[Co(L)(NO ₃) ₂]	4.91	9619, 14862, 19493
[Ni(L)Cl ₂]	2.98	10449, 15037, 22675
[Ni(L)(NO ₃) ₂]	3.14	9898, 17600, 24189
[Cu(L)Cl ₂]	2.11	10427, 18621, 25773
[Cu(L)(NO ₃) ₂]	1.95	10438, 18621, 28169

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Complex	Tem- pera-	poly	Data as verystal	lline	Data in DMSO solution			
	Temperaturepc g_{\parallel} g_{\parallel} LNT 3.79 LNT 3.52 RT 2.28		g_{\perp}	g _{iso}	g∥	g_{\perp}	g _{iso}	
[Co(L)Cl ₂]	LNT	3.79	3.35	3.49	3.95	3.55	3.68	
[Co(L)(NO ₃) ₂]	LNT	3.52	3.20	3.31	3.70	3.49	3.56	
$[Cu(L)Cl_2]$	RT	2.28	2.10	2.16	2.25	2.07	2.13	
[Cu(L)(NO ₃) ₂]	RT	2.26	2.06	2.12	2.22	2.05	2.11	

Table 3. ESR spectral data of the complexes

tion $\beta = B(\text{complex})/B(\text{free ion})$, where $B(\text{free ion})$ for
Co(II) is 1120 cm ⁻¹ and for Ni(II) is 1041 cm ⁻¹ [24]. The
values of β lie in a range of 0.58–0.98. These values
indicate the appreciable covalent character of the metal
ligand σ bond. On the basis of the above spectral stud-
ies, the following structure can be suggested for the
complexes. The structure of the complexes is shown
below:



M = Co(II), Ni(II), and Cu(II); $X = Cl^{-}$ and NO_{3}^{-}

The cyclic voltammogram of the copper(II) complexes shows a quasi-reversible peak. The chloro complex gives a peak at 0.70 V, which corresponds to Cu(II) \longrightarrow Cu(III), and a cathodic peak at $E_{pc} = 0.37$ V, which corresponds to Cu(III) \longrightarrow Cu(II), while the nitrato complex gives peaks at $E_{pc} = 0.68$ and 0.40 V. The complexes exhibit irreversible peaks characteristic for the Cu(II) \longrightarrow Cu(I) ($E_{pc} = -0.54$ and -0.69 V) and Cu(I) \longrightarrow Cu(0) ($E_{pc} = -0.90$ and -0.93 V). The peaks suggest single-electron reduction processes. On the anodic side, two peaks are also observed, which correspond to the oxidation Cu(0) \longrightarrow Cu(II). This quasi-reversible behavior of the Cu(II)/Cu(III) couple was observed by varying the scan rates with peak potentials. It has also been observed that E_{pc} increases with increasing scan rate. I_{pc}/I_{pa} (where I_{pc} = cathodic peak current and I_{pa} = anodic peak current) being equal to unity indicates the chemical reversibility of the redox process.

Table 4. Ligand field parameters of the complexes

Complex	Dq, cm ⁻¹	B, cm^{-1}	β	LFSE, kJ mol ⁻¹ *	
[Co(L)Cl ₂]	1243	672	0.60	118.94	
[Co(L)(NO ₃) ₂]	1203	650	0.58	115.11	
[Ni[(L)Cl ₂]	1044	1023	0.98	149.85	
[Ni(L)(NO ₃) ₂]	989	970	0.93	141.96	

* LFSE is ligand field stabilization energy.

The antibacterial activities of the ligand, metal salts, and the complexes have been tested for their effects on the growth of microbial cultures and were studied for their interaction with Sarcina lutea, Escherchia coli, and Staphylococcus aureus using the disc diffusion method [25, 26]. The test compounds in measured quantities were dissolved in DMF to get concentrations of 125, 250, and 500 ppm of the compounds. Twenty-five milliliters of nutrient agar media were poured in each Petri plate. After solidification, 0.1 ml of test bacteria was spread over the medium using a spreader. The discs of Whatmann no. 1 filter paper were placed at four equidistant places at a distance of 2 cm from the center in the inoculated Petri plates. Filter paper discs treated with DMF served as a control and Streptomycin was used as a standard drug. All determinations were made in duplicate for each of the compounds. Finally, the Petri plates were incubated for 26-30 h at 28 ± 2 °C. The zone of inhibition was calculated in millimeters carefully.

The antimicrobial screening data (Table 5) show that metal chelates exhibit higher inhibitory effects than the parents ligand and metal salts. The increased activity of the metal chelates can be explained on the basis of chelation theory [27]. It is known that chelation tends to make the ligand act as a more powerful and potent bactericidal agent, thus killing more of the bacteria than the ligand. It is observed that, in the complex, the positive charge of the metal is partially shared with the donor atoms present in the ligands and there is may be π -electron delocalization over the whole chelating. This increases the lipophilic character of the metal chelate and favors its permeation through the lipoid layer of the bacterial membranes. The bacterial growth inhibitory capacity of the ligands, metal salts, and metal complexes shows the following order: Cu(II) > Ni(II) > Co(II) > metal salts > ligand.

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	Diameter of Inhibition Zone, mm (c , µg ml ⁻¹)									
Compound	Sarcina lutea			E	Echerchia coli			Staphylococcus aureus		
	125	250	500	125	250	500	125	250	500	
L	09	14	19	10	15	21	00	12	17	
$CoCl_2 \cdot 6H_2O$	14	17	22	12	19	23	08	16	20	
$Co(NO_3)_2 \cdot 3H_2O$	13	15	21	12	18	23	09	14	21	
$NiCl_2 \cdot 6H_2O$	12	16	25	11	17	22	08	13	19	
$Ni(NO_3)_2 \cdot 5H_2O$	11	16	24	11	17	23	08	12	18	
$CuCl_2 \cdot 5H_2O$	14	19	26	12	18	24	10	16	22	
$Cu(NO_3)_2 \cdot 3H_2O$	14	18	25	12	17	24	09	16	22	
$[Co(L)Cl_2]$	15	20	28	14	20	25	19	22	31	
$[Co(L)(NO_3)_2]$	14	20	27	16	19	27	20	22	29	
[Ni[(L)Cl ₂]	17	22	29	16	22	31	21	25	35	
$[Ni(L)(NO_3)_2]$	17	24	30	14	24	31	22	29	34	
$[Cu(L)Cl_2]$	20	25	31	19	29	32	25	32	37	
$[Cu(L)(NO_3)_2]$	22	27	32	18	27	34	24	31	29	
Streptomycin	24	28	34	20	30	36	26	32	40	

 Table 5. Antibacterial screening data of the ligand and its complexes

spectra; and ACBR (New Delhi) for recording IR spectra.

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