

Biologically relevant macrocyclic complexes of copper spectral, magnetic, thermal and antibacterial approach

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Abstract

Copper(II) macrocyclic complexes have been synthesized with five novel ligands: L¹-1,7,10,16-tetraaza-2,6,11,15-tetraone-4,13-dithiacycloocta-decane, L²-1,7,11,17-tetraaza-2,6,12,16-tetraone-4,14-dithia-cyclooctane, L³-1,7,10,13,19,22-hexaaza-2,6,14,18-tetraone-4,16-dithiacyclo-tetracosane, L⁴-1,7,14,20,tetraaza-2,6,15,19-tetraone-4,17,dithiatricyclo [22, 4, O^{21,26}, O^{8,13}] hexacosane-8,10,12,21,23,25-hexene, L⁵-1,7,13,19,25,26-hexaaza-2,6,14,18 tetraone-4,16 dithia tricyclo [23, 3, 1, I^{8,12}] hexacosane [8(26), 10, 12, 20(25), 22, 24] hexane and characterized by elemental analysis, molar conductance, magnetic susceptibility, i.r, u.v.–vis, EPR spectral studies, thermal studies and electrochemical properties. The molar conductance measurements of the complexes in DMSO correspond to 1:2 electrolytes. *g*-Values are calculated for all of the complexes in the polycrystalline form as well as in DMSO solution. On the basis of i.r, electronic and EPR spectral studies a square planar geometry has been assigned to these complexes. Cyclic voltammograms for all the complexes are similar to quasi-reversible redox processes Cu^{II}Cu^{II} ⇌ Cu^{II}Cu^I ⇌ Cu^ICu^I. The complexes were also evaluated against the growth of bacteria (*S. fecalis* and *E.coli*) *in vitro*.

Introduction

Macrocyclic complexes are thermodynamically more stable and more selective metal ion chelates than open chain analogues. So the study of macrocyclic complexes is a growing class of research [1–4]. Transition metal complexes of synthetic macrocyclic ligands are of significance because porphyrins and cobalamines play vital roles in biological systems, such chelating molecules are important since they are capable of furnishing an environment of controlled geometry and ligand field strength. Macrocyclic Schiff base nitrogen donor ligands have received special attention because of their mixed hard-soft donor character and versatile coordination behaviour [5–6]. Azatype ligands appear as very promising to be used as antifertile, antibacterial, antifungal and for other biological properties [7–11]. Transition metal complexes have received much attention as catalyst in oxidation and epoxidation processes [12, 13]. Macrocyclic complexes containing manganese and copper centre have been prepared to study cyclic voltammetry and biological activity [14, 15].

In order to synthesise the requisite type of superstructured macrocycles, the obvious approach is to first prepare the more basic macrocyclic ligand and then add a suitable metal ion to the ligand. However if the ligand

yield is low, it can be characterized by various studies and then the complexes can be prepared by the template method. As in the present case, we intend to explore the synthesis of new polyaza macrocyclic complexes. Along this route some hexaaza macrocyclic ligands and complexes have been isolated and their spectral, magnetic, electrochemical and biological properties are explored.

Physical measurements

IR spectra were recorded on a Perkin-Elmer 137 instrument in KBr pellets. Microanalyses (C, H and N) of these complexes were carried out on a Carlo-Erba 1106 elemental analyzer. Electronic spectra were recorded in DMSO solution on a Shimadzu UV mini – 1240 spectrophotometer. The molar conductance was measured on an Elico conductivity bridge (type CM82T). Magnetic moment measurements (Gouy balance) were made at room temperature using CuSO₄ · 5H₂O as calibrant. EPR spectra of the complexes were recorded as polycrystalline samples and in the DMSO solution, at room temperature on an E₄-EPR spectrometer using DPPH as the *g*-marker. Electrochemical procedures were carried out on a PAR 173 potentiostat/galvanostat instrument with a PAR 175 model universal programmer coupled to a PAR 179 digital coulometer. The voltammograms and the simultaneous current intensity-time plots for electrolysis were registered in a X–Y Houston-

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Ommigraphic 2000 recorder. Cyclic voltammetry and controlled potential electrolysis coulometry at room temperature (r.t.) (approximately 25 °C) under either an inert (N₂) or a saturated CO₂ atmosphere were performed in a specially designed air-tight electrochemical cell with a double three-electrode system, to obtain cyclic voltammograms “*in situ*” for the electrolytically generated products. All electrodes were introduced into the cell body by means of an ST glass joint and caps with Teflon-faced-silicon septa were used for the needles that bubble and exit gases. CV measurements were performed using a reticulated vitreous carbon (ERG) and GC as working and Ag/AgCl reference electrodes, respectively. The last one was supplied by a vycor tip glass end. The platinum spiral wire counter electrode was separated by means of a salting bridge through sinterized glass ends. *In vitro* antibacterial activities of these complexes were tested using the paper disc diffusion method. The chosen strains were *Streptococcus fecalis* (Gram positive) and *Escherichia coli* (Gram negative). The liquid medium containing the bacterial sub-cultures was autoclaved for 20 min at 121 °C and at 15 lb pressure before inoculation. The bacteria were then cultured for 24 h at 36 °C in an incubator. Nutrient agar was poured onto a plate and allowed to solidify. The test compounds (DMSO solutions) were added dropwise to a 10 mm diameter filter paper disc placed at the centre of each agar plate. The plates were then kept at 5 °C for 1h, then transferred to an incubator maintained at 36 °C. The width of the growth inhibition zone around the disc was measured after 24 h incubation. Four replicas were made for each treatment. Thermogravimetric analysis measurements were carried out using a Mettler Toledo thermal analysis system. The experiments were done in nitrogen atmosphere using alumina powder as reference material. The weight of sample taken was 8–10 mg and heating rate was 10 °C/min.

Experimental

Synthesis of complexes

To a hot EtOH solution of L¹; ethylenediamine (2 mmol; 0.158 gm), L²; 1,3-diaminopropane (2 mmol; 0.17 gm), L³; Diethylenetriamine (2 mmol; 0.18 gm), L⁴; o-phenylenediamine (2 mmol; 0.21 gm), L⁵; 2,6-diaminopyridine

(2 mmol; 0.22 gm), an EtOH solution (2 mmol) of metal salt were added. The precipitate which formed readily dissolved and then to it an EtOH solution (2 mmol; 0.376 gm) of thiodiglycolic acid was added. The resulting solution was refluxed for 6–9 h at 79–80 °C. On cooling, to room temperature a colored complex precipitated. It was filtered, washed with cold EtOH and dried under vacuum over P₄O₁₀.

Results and discussions

A new series of binuclear Cu(II) complexes [M₂LX₂]₂X₂ [M = Cu and X = NO₃] have been prepared. The complexes were stable in the atmosphere and were polycrystalline. On the basis of elemental analysis data (Table 1) all the complexes have the general composition Cu₂LX₄. The molar conductance measurements in DMSO shows that the complexes are 1:2 electrolytes, so the complexes may be formulated as [Cu₂LX₂]₂X₂ and X = NO₃⁻. The effective magnetic moments of all complexes at room temperature lie in the range 1.54–1.62 B.M., corresponding to one unpaired electron in a square planar environment [16] (Table 2). The magnetic moment was found to be 1.54–1.62 and 1.25–1.5 at 300 K and 77 K; this decrease of magnetic moment with the decrease of temperature indicates some anti-ferromagnetic interaction in these complexes [17]. The i.r spectra of the complexes show four new bands corresponding to amide groups in the regions 1638–1647, 1553–1582, 1380–1385 and 698–779 cm⁻¹. These bands may be assigned to amide I [ν(C=O)], amide II [ν(C–N) + δ(N–H)], amide III [δ(N–H)] and amide IV [δ(C=O)], respectively, supporting the macrocyclic structure. The complexes exhibits three NO stretching bands at 1430–1435 cm⁻¹ (ν₁), 1374–1377 cm⁻¹ (ν₃), 1209–1203 cm⁻¹ (ν₅), 1010–1013 cm⁻¹ (ν₂) and 839–835 cm⁻¹ (ν₆). The absence of a broad band at 1390 cm⁻¹ and separation between ν₁ and ν₅ of ~125 indicates the coordination of both nitrate groups as unidentate [18] in these complexes.

Electronic spectra show bands near 15,382–15,780 and 21,752–22,980 cm⁻¹ and charge transfer bands above 30,000 cm⁻¹ (Table 2) which suggests the square planar geometry for the bimetallic complexes. The two bands may be assigned as probable the transitions

Table 1. Molar conductance and elemental analysis data of binuclear Cu(II) complexes

Complexes	M.W. Calcd. (Found)	Molar cond. Ω ⁻¹ cm ² mol ⁻¹	Colour	Yield (%)	M.Pt. (°C)	Element analysis (Calcd. Found)			
						Cu	C	H	N
[Cu ₂ L ₁ (NO ₃) ₂](NO ₃) ₂ Cu ₂ C ₁₂ H ₂₀ N ₈ S ₂ O ₁₆	724 (723.17)	237	Green	69	175	17.95 (8.0)	19.9 (19.9)	2.8 (2.85)	15.5 (15.53)
[Cu ₂ L ₂ (NO ₃) ₂](NO ₃) ₂ Cu ₂ C ₁₄ H ₂₄ N ₈ S ₂ O ₁₆ N ₄	752 (751.29)	262	Bluish green	64	172	17.3 (17.3)	22.3 (22.4)	3.2 (3.2)	7.4 (7.5)
[Cu ₂ L ₃ (NO ₃) ₂](NO ₃) ₂ Cu ₂ C ₁₆ H ₃₀ N ₁₀ S ₂ O ₁₆	810 (809.47)	233	Green	67	192	16.0 (16.1)	23.7 (23.8)	3.7 (3.8)	17.3 (17.3)
[Cu ₂ L ₄ (NO ₃) ₂](NO ₃) ₂ Cu ₂ C ₂₀ H ₂₀ N ₈ S ₂ O ₁₆	820 (819.89)	217	Green	52	183	15.85 (15.9)	29.3 (29.3)	2.4 (2.5)	13.65 (13.7)
[Cu ₂ L ₅ (NO ₃) ₂](NO ₃) ₂ Cu ₂ C ₁₈ H ₁₈ N ₁₀ S ₂ O ₁₆	822 (821.29)	232	Bluish green	62	175	15.8 (15.9)	26.3 (26.3)	2.2 (2.2)	17.0 (17.1)

Table 2. Electronic and ESR spectral bands of binuclear Cu(II) complexes

Complexes	Spectral bands (cm ⁻¹)	μ_{eff} (B.M.)	g_{\parallel}	g_{\perp}	g_{iso}	A_{iso}	A_{\parallel}
[Cu ₂ L ₁ (NO ₃) ₂](NO ₃) ₂ ^a	15382, 21752	1.57	2.17	2.062	2.085	–	–
[Cu ₂ L ₂ (NO ₃) ₂](NO ₃) ₂ ^b	15501, 22269	1.54	2.20	2.061	2.114	81.6	182
[Cu ₂ L ₃ (NO ₃) ₂](NO ₃) ₂ ^a	15780, 22742	1.60	2.18	2.027	2.091	–	–
[Cu ₂ L ₄ (NO ₃) ₂](NO ₃) ₂ ^b	15479, 21777	1.60	2.24	2.060	2.117	78.7	182
[Cu ₂ L ₅ (NO ₃) ₂](NO ₃) ₂ ^b	15672, 22980	1.57	2.27	2.064	–	–	–

^aas polycrystalline sample at room temperature.

^bas Polycrystalline sample at LNT.

$$g_{\perp} = (3g_{\text{iso}} - g_{\parallel})/2.$$

$$A_{\perp} = (3A_{\text{iso}} - A_{\parallel})/2.$$

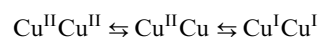
$${}^2A_{1g} \leftarrow {}^2B_{1g} (a_1g^2 \cdot b_1g^2 \cdot b_1g^1 \rightarrow a_1g^1 \cdot b_1g^2), {}^2E_g \leftarrow {}^2B_{1g} (eg^4 \cdot a_1g^2 \cdot b_1g^1 \rightarrow eg^3 \cdot a_1g^2 \cdot b_1g^2)$$

The X-band room temperature EPR spectra of polycrystalline samples of the complexes were recorded. The parameters g and G obtained from the spectra are listed in (Table 2). The g_{\parallel} , A_{\parallel} and A_i values for four-coordinate copper(II) complexes with different ligands confirms the square planar geometry around the metal ion [19, 20]. Results of antibacterial screening are as shown in Figure 1.

The thermal stabilities of the complexes were investigated using TGA. The TGA curves were obtained at a heating rate of 10 °C/min in N₂ atmosphere over the temperature range of 25–650.0 °C and their decompositions started in this temperature range and were completed at 530.0 °C. No weight loss up to 100 °C indicates the absence of lattice water molecules in all complexes. The complexes decomposed and procured 2CuO as a residue in three steps in the temperature ranges 185.0–268.0, 265.0–310.0 and 310.0–530.0 °C. The three stages of the decomposition of the Cu(II) complexes are irreversible. (Table 3)

The cyclic voltammograms for the copper(II) complexes at negative potential were recorded in the potential range 0 to –1.5 V; the data are summarised

in (Table 4). The cyclic voltammograms were obtained for the complexes [Cu₂L¹] and [Cu₂L⁵] in the cathodic region. All the binuclear Cu(II) complexes shows two step, one-electron, quasi-reversible reduction waves. Controlled potential electrolysis performed at a potential of 100 mV more negative than the reduction wave indicates the consumption of one electron per molecule for both the first and second reduction wave. Cyclic voltammograms for all the complexes are similar and involve two quasi-reversible redox processes. Even though all the complexes both the metal ions have the same geometry and same environment, two reduction waves are obtained in the cathodic region corresponding to stepwise one-electron reductions through a Cu^ICu^{II} intermediate to give a binuclear Cu^I species. In spite of the ligands being symmetrical, their bicopper(II) complexes show two quasi-reversible reduction waves [21]. The two redox processes are represented as follows:



The reason for the observation of two reduction waves may be due to electronic exchange between the metal ions: after the first one-electron reduction some of the electron density is transferred from the reduced metal

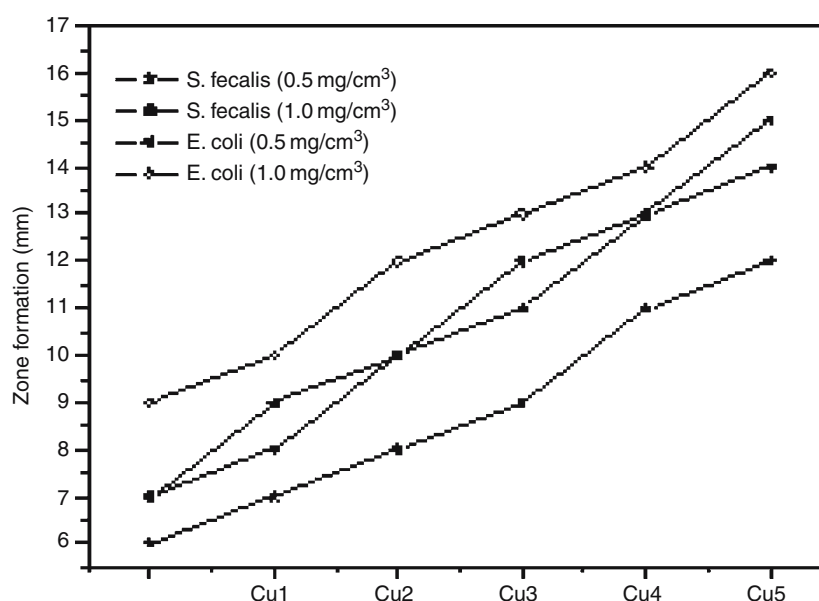


Fig. 1. Antibacterial activity shown by the complexes.

Table 3. TGA data of the complexes [weight loss %, found (calculated)]

Complexes	First step (°C)	Second step (°C)	Third step (°C)	Residue (%) Found (Calcd.)
[Cu ₂ L ₁ (NO ₃) ₂](NO ₃) ₂	185.0–268.0 33.0(33.15)	268.0–305.0 14.55(14.86)	305.0–530.0 29.94(31.02)	22.51(20.97) 77.64(79.03) ^a
[Cu ₂ L ₂ (NO ₃) ₂](NO ₃) ₂	185.0–267.0 30.89(31.91)	267.0–300.0 18.03(18.12)	300.0–525.0 29.55(29.82)	21.53(20.15) 78.47(79.85) ^a
[Cu ₂ L ₃ (NO ₃) ₂](NO ₃) ₂	180.0–250.0 29.50(29.80)	250.0–300.0 22.88(23.11)	300.0–528.0 27.32(27.54)	20.30(19.55) 79.70(80.45) ^a
[Cu ₂ L ₄ (NO ₃) ₂](NO ₃) ₂	185.0–255.0 29.50(29.14)	255.0–310.0 24.06(24.17)	310.0–530.0 27.34(27.29)	19.1(19.40) 80.90(80.60) ^a
[Cu ₂ L ₅ (NO ₃) ₂](NO ₃) ₂	180.0–265.0 28.84(29.13)	265.0–300.0 25.15(25.30)	300.0–530.0 27.94(28.22)	18.07(19.35) 81.93(80.65) ^a

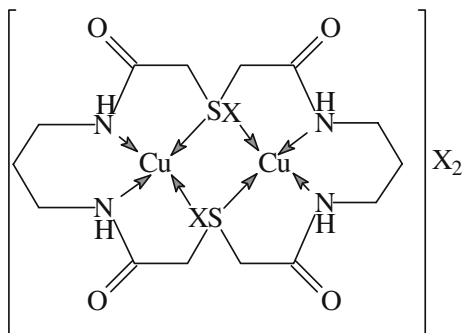
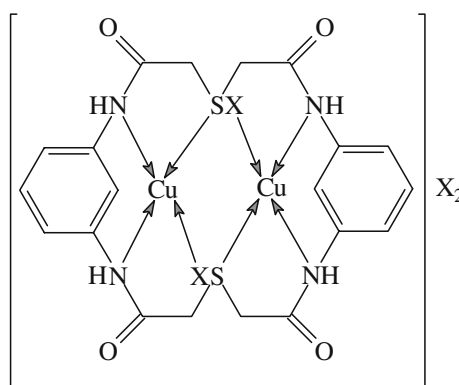
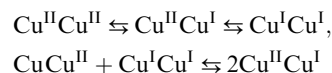
a = Total weight loss.

Table 4. Electrochemical data of copper(II) complexes

Complexes	E_{pc}^1	E_{pa}^1	$E_{1/2}^1$	ΔE	E_{pc}^2	E_{pa}^2	$E_{1/2}^2$	ΔE	K_{con}
[Cu ₂ L ₁ (NO ₃) ₂](NO ₃) ₂	-0.83	-0.69	-0.74	140	-1.09	-0.95	-1.02	110	3.6×10^4
[Cu ₂ L ₂ (NO ₃) ₂](NO ₃) ₂	-1.03	-0.91	-0.95	110	-1.35	-1.25	-1.29	100	3.7×10^5
[Cu ₂ L ₃ (NO ₃) ₂](NO ₃) ₂	-0.54	-0.44	-0.46	100	-0.88	-0.80	-0.85	90	2.6×10^6
[Cu ₂ L ₄ (NO ₃) ₂](NO ₃) ₂	-0.49	-0.38	-0.45	90	-0.66	-0.63	-0.65	60	3.4×10^3
[Cu ₂ L ₅ (NO ₃) ₂](NO ₃) ₂	-0.56	-0.32	-0.42	250	-0.89	-0.77	-0.83	110	5.6×10^6

Measured by CV at 50 mV/s. E versus Ag/AgCl. Conditions. Complex Conc. = 1×10^{-3} M.

ion to the other metal ion and hence the second reduction appears at a high negative potential. The reduction waves are somewhat broad. This may be due to the equilibrium binding of the solvent to the Cu^{II} centre. The peak broadening diminishes as the scan rate increases [22]. The first reduction wave appears in the potential range -0.48 to -1.02 V. The second reduction wave occurs in the potential range -0.68 to -1.34 V. The potentials at the first reduction waves of the [Cu₂L³⁻⁵] are lower than for [Cu₂L^{1,2}]. This indicates that [Cu₂L^{4,5}], with a ring environment (benzene and pyridine) are reduced more easily. The conproportionation constant for the equilibrium was calculated using the relationship $\log K_{con} = \Delta E / 0.0591$. A greater K_{con} value indicates greater stability for the mixed valence species or that the exchange interaction is greater with respect to the isoivalent species [23]. The conproportionation constant was calculated from the following equilibrium:

Fig. 2. Complexes with ligand L₂ (1,7,11,17-tetraaza-2,6,12,16-tetraone-4,14-dithia-cyclocosane) X = N₃⁻.Fig. 3. Complexes with ligand L₄ (1,7,14, 20-tetraaza-2,6,15,19-tetraone-4,17, dithiatricyclo [22, 4, O^{21,26}, O^{8,13}] hexacosia 8,10,12,21,23,25 hexene) X = N₃⁻.

Single crystals of the complexes could not be isolated from any solutions, thus no definitive structure may be described. However, the analytical, spectroscopic, magnetic data and thermal investigation enable us to predict the possible structures as shown in Figures 2 and 3.

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