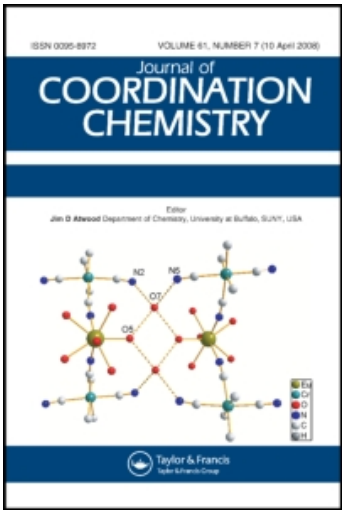

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Tetraaza macrocyclic complexes: synthesis, spectral and antimicrobial studies

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Tetraaza macrocyclic complexes: synthesis, spectral and antimicrobial studies

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A tetradentate nitrogen donor [N_4] macrocyclic ligand, 1,3,7,9-tetraaza-2,8-dithia-4, 10-dimethyl-6,12-diphenylcyclododeca-4,6,10,12-tetraene has been synthesized by using thiourea and benzoylacetone. Complexes of Mn(II), Co(II), Ni(II), and Cu(II) have been synthesized with this ligand and characterized by element chemical analysis, molar conductance, magnetic susceptibility, mass, ^{1}H nuclear magnetic resonance, Fourier transform–infrared, electronic, and electron paramagnetic resonance spectral studies. The molar conductance measurements of Mn(II), Co(II), and Cu(II) complexes in dimethyformamide correspond to nonelectrolytes, whereas Ni(II) complex is a 1: 2 electrolyte. The complexes are high-spin except for Ni(II) which is diamagnetic. Octahedral geometry has been assigned for Mn(II) and Co(II) complexes, square planar for Ni(II) and tetragonal geometry for Cu(II). The ligand and its complexes were screened *in vitro* against two pathogenic fungi (*Fusarium moniliformae* and *Rhizoctonia solani*) and bacteria (*Staphylococcus aureus* and *Pseudomonas aeruginosa*) to assess their growth inhibiting potential.

Keywords: Macrocyclic; Transition metals; Antifungal; Antibacterial screening

1. Introduction

Macrocyclic complexes are thermodynamically more stable and selective toward metal ion chelate complexes as compared to open chain analogs [1, 2]. Tetraaza macrocyclic ligands and their metal complexes have attracted growing interest as models for intricate biological systems such as metalloporphyrins (hemoglobin, myoglobin, cytochromes, chlorophylls), corrins (vitamin B_{12}), and antibiotics (valinomycin, nonactin). Such chelating molecules are capable of furnishing an environment of controlled geometry and ligand field strength. Macrocyclic Schiff-base nitrogen donors have received special attention because of their mixed hard-soft donor character and versatile coordination behavior [3, 4]. Interest has been stimulated by the diagnostic and therapeutic medical applications of transition metal complexes

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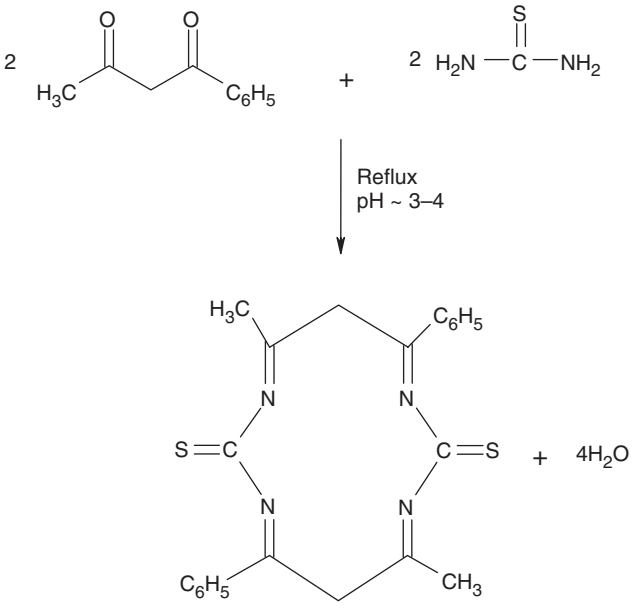


Figure 1. Preparation and structure of the ligand (L).

of macrocyclic ligands [5–8]. Aza-type macrocyclic ligands can be used as antibacterial, antifungal, or for other biological applications [9–12]. Transition metal complexes of such ligands have been used as catalysts in oxidation and epoxidation processes [13–16].

In this article, we report the synthesis, spectroscopic characterization, and biological screening of Mn(II), Co(II), Ni(II), and Cu(II) complexes with a 12-membered macrocyclic ligand (L) (figure 1), 1,3,7,9-tetraaza-2,8-dithia-4,10-dimethyl-6,12-diphenyl cyclododeca-4,6,10,12-tetraene.

2. Experimental

All chemicals used were of analytical grade and used as received. Solvents were of standard/spectroscopic grade.

2.1. *Synthesis of ligand*

A hot ethanolic solution (20 mL) of benzoyl acetone (3.24 g, 0.02 mol) and a hot ethanolic solution (20 mL) of thiourea (1.52 g, 0.02 mol) were mixed slowly with constant stirring. The mixture was refluxed at 85°C (±5) for 10 h in the presence of a few drops of concentrated HCl (pH ≅ 3–4). On cooling the mixture, a solid yellow precipitate formed, was filtered, washed with cold EtOH, and dried under vacuum over P_4O_{10}: yield ~75%, m.p.: 196°C. Elemental analysis calculated for $C_{22}H_{20}N_4S_2$ (%): C, 65.3; H, 4.9; N, 15.8. Found: C, 65.3; H, 5.0; N, 15.8.

2.2. *Synthesis of complexes*

A hot ethanolic solution of ligand (0.40 g, 0.001 mol) and hot ethanolic solution (20 mL) of corresponding metal salt (0.001 mol) were mixed with constant stirring. The mixture was refluxed for 4 h at 80–85°C. On cooling the mixture, a colored complex was formed, filtered, washed with cold EtOH and dried under vacuum over P_4O_{10}.

2.3. *Physical measurements*

The C, H, and N were analyzed by using a Carlo-Erba 1106 elemental analyzer. Molar conductance was measured on a ELICO(CM82T) conductivity bridge. Magnetic susceptibility was measured at room temperature on a Gouy balance using $CuSO_4 \cdot 5H_2O$ as a calibrant. Electron impact mass spectra were recorded on a JEOL, JMS, DX-303 mass spectrometer. ^{1}H NMR (Nuclear Magnetic Resonance) spectra were recorded on a Hitachi FT–NMR, model R-600 spectrometer using $CDCl_3$ as solvent. Chemical shifts are given in parts per million relative to tetramethylsilane. Infrared (IR) spectra (KBr) were recorded in the range 4000–200 cm^{-1} on a FT–IR BX-II spectrophotometer. Electronic spectra were recorded in Dimethyl Sulfoxide (DMSO) on a Shimadzu UV mini-1240 spectrophotometer. Electron Paramagnetic Resonance (EPR) spectra of the complexes were recorded as polycrystalline samples and in DMSO solution, at liquid nitrogen temperature for Co(II) and at room temperature for the Mn(II) and Cu(II) complexes on an E_4-EPR spectrometer using 2,2,-diphenyl-1-picrylhydrazyl as a g-marker.

2.4. *Antifungal screening*

In vitro antifungal activities of the ligand and its complexes were tested using food poison technique [17]. *Fusarium moniliformae* and *Rhizoctonia solani* were used as test fungi. Compounds were mixed with Potato Dextrose Agar (PDA) and the solution in distilled water was prepared of 1000, 750, 500, and 250 ppm concentrations. These were autoclaved at 100°C and then cooled adequately. The medium was dispensed into sterilized Petri plates. A mycelial disc of 5 mm diameter of the test fungi were taken from 10-day-old culture with the help of sterilized cork borer and placed at the center of the medium in the Petri plate. The mycelial discs on PDA without any test chemical served as control and the plates with 500 ppm mancozeb served as the fungicide reference. Three replicates were kept for each treatment. Plates were then incubated for 8 days at 30°C. On the eighth day, radial growth of colonies was measured at two points along the diameter of the plate. The average of these two readings was taken as the diameter of the fungal colony. The percent inhibition was measured according to the formula C-T $\times$ 100/C, where C and T are the radial diameters of the control and treatment colony, respectively.

2.5. *Antibacterial activity*

In vitro antibacterial activities of the ligand and complexes were tested using the paper disc diffusion method. *Staphylococcus aureus* and *Pseudomonas aeruginosa* bacteria were used. The liquid medium containing the bacterial subcultures was autoclaved for

Table 1. Antibacterial screening data of compounds showing growth inhibition (mm) at 500 and 1000 ppm concentrations after 24 h at 30 ± 6°C.

	P. aeruginosa		*S. aureus*	
Compounds	500	1000	500	1000
Benzoyl acetone	2	3	2	3
Thiourea	2	4	2	4
L	3	4	3	5
$[Mn(L)Cl_2]$	5	9	7	10
$[Co(L)Cl_2]$	8	11	11	14
$[Ni(L)]Cl_2$	4	6	4	7
$[Cu(L)Cl_2]$	5	8	7	9
Standard (Streptomycin)	9	12	16	20

20 min at 36°C in an incubator. Nutrient agar was poured in a sterilized plate and allowed to solidify. The test compounds (distilled water solutions) were added dropwise to a 10 mm diameter filter paper disc placed at the center of each agar plate. Three replicas were made for each treatment. The plates were then kept at 5°C for 1 h and transferred to an incubator maintained at 36°C. The growth inhibition was calculated after 24 h incubation. The results are presented in table 1.

3. Results and discussion

The complexes were synthesized by reaction of ligand with the metal ion in 1 : 1 molar ratio in an ethanolic medium. The molar conductance measurements of complexes in dimethyformamide solution correspond to nonelectrolytes for Mn(II), Co(II), and Cu(II) and 1 : 2 electrolyte for Ni(II). Thus, these complexes may be formulated as $[M(L)Cl_2]$ and $[Ni(L)]Cl_2$, respectively [where M = Mn(II), Co(II), Cu(II)].

3.1. *Mass spectrum*

The mass spectrum of free ligand (L) (Supplementary Material) shows the molecular ion peak at m/z 404 $[M^+]$ corresponding to $[C_{22}H_{20}N_4S_2]^+$ macrocyclic moiety.

3.2. *^{1}H NMR spectrum*

^{1}H NMR spectrum of L in $CDCl_3$ shows signals at δ 2.12–2.74 ppm (m, 6H, CH_3–C=N, and 4H, N=C–CH_2–C=N) and δ 7.24–7.32 ppm (m, Ph) [18, 19]. ^{1}H NMR spectrum of the Ni(II) complex in $CDCl_3$ exhibits signals at δ 2.26–2.98 ppm (m, 6H, CH_3–C=N, and 4H, N=C–CH_2–C=N) and δ 7.28–7.44 ppm (m, Ph). The red shift of these signals indicates coordination takes place through azomethine nitrogen [20, 21].

3.3. *IR spectra*

The IR spectrum of the ligand does not show a band corresponding to either free primary diamine or free keto [22], suggesting that the amino groups and keto groups

Table 2. Electronic spectral and magnetic data of the complexes.

Complexes	Electronic spectra (nm)	μ_{eff} (B.M.)
$[Mn(L)Cl_2]$	535, 429, 355, 257	5.88
$[Co(L)Cl_2]$	829, 679, 535, 309	4.86
$[Ni(L)]\ Cl_2$	738, 476, 408	Diamagnetic
$[Cu(L)Cl_2]$	881, 536, 365	1.99

combined [23]. Bands due to ν(C=N) of phenyl, methyl, and ν(C=S) groups are at 1599, 1561, and 1236 cm^{-1}, respectively. Strong bands in the region 2800–3049 and 1402–1466 cm^{-1} in all the complexes may be due to C–H stretching and bending vibrations, respectively [24–26]. On complexation the ν(C=N) bands shift to lower energy by 18–34 cm^{-1}, indicating coordination through nitrogen of the imines. On complex formation some new bands appear in the region 372–556 and 225–285 cm^{-1}, corresponding to ν(M–N) and ν(M–Cl) vibrations, respectively.

3.4. *Electronic spectra*

Electronic spectrum of Mn(II) complex (table 2) displays weak absorption bands at 535, 429, 355, and 257 nm, assigned to $^6A_{1g} \rightarrow {}^4T_{1g}$ (^4G), $^6A_{1g} \rightarrow {}^4E_{2g}$, $^4A_{1g}$ (^4G), $^6A_{1g} \rightarrow {}^4E_{2g}$ (^4D) and charge transfer, respectively [27–29]. Electronic spectrum of Co(II) complex displays absorptions at 829, 679, 535, and 309 nm, assigned to $^4T_{1g}$ (F) $\rightarrow {}^4T_{2g}$ (F) (ν_1), $^4T_{1g} \rightarrow {}^4A_{2g}$ (ν_2), and $^4T_{1g}$ (F) $\rightarrow {}^4T_{2g}$ (P) (ν_3) and charge transfer, respectively [30–32]. Electronic spectrum of Ni(II) complex displays absorption bands at 738, 476, and 408 nm, assigned to $^1A_{1g} \rightarrow {}^1A_{2g}$ (G) (ν_1), $^1A_{1g}$ (D) $\rightarrow {}^1B_{2g}$ (G) (ν_2), and $^1A_{1g}$ (D) $\rightarrow {}^1E_g$ (G) (ν_3), respectively [33, 34]. Cu(II) complex displays bands at 881, 536, and 365 nm; the first band may be assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$ ($d_{x^2-y^2} \rightarrow d_z^2$) ($\nu_1$), however, the assignment of second and third bands is quite difficult due to involvement of metal ligand charge transfer in this region [35–37].

3.5. *Magnetic susceptibility measurements*

At room temperature (table 2), complexes of Mn(II), Co(II), and Cu(II) are high spin with magnetic moments corresponding to five, three, and one unpaired electrons, respectively [38, 39]. Ni(II) complex is diamagnetic as expected for low-spin, square-planar geometry [40].

3.6. *EPR spectral studies*

Electron paramagnetic resonance spectrum of the Mn(II) complex was recorded as polycrystalline sample and in DMSO solution. The polycrystalline sample gives one broad isotropic signal centered at the free electron g-value ($g_o = 2.0023$). The broadening of the spectrum is probably due to spin relaxation [41]. In DMSO, the Mn(II) complex gives an EPR spectrum containing six lines from hyperfine interaction between unpaired electrons with the ^{55}Mn nucleus ($I = 5/2$). The nuclear magnetic

Table 3. EPR spectral data of the complexes.

Complexes	Temperature (K)	Data as polycrystalline				Data in DMSO solution			
		$g_{\|\|}$	$g_{\perp}$	g_{iso}	G	$g_{\|\|}$	$g_{\perp}$	g_{iso}	G
$[Mn(L)Cl_2]$	300	–	–	2.0054	–	–	–	2.0016	–
$[Co(L)Cl_2]$	77	2.3387	2.0174	2.1245	–	2.3294	2.0052	2.1134	–
$[Cu(L)Cl_2]$	300	2.1182	2.0669	2.0842	1.7668	2.0834	2.0690	2.0737	–

quantum number, M_I, corresponding to these lines is $-5/2$, $-3/2$, $-1/2$, $+1/2$, $+3/2$, and $+5/2$ from low to high field [42].

Electron paramagnetic resonance spectrum of Co(II) complex (table 3) was recorded as polycrystalline sample and in the DMSO solution at liquid nitrogen temperature (77 K). In both cases, the g-values were almost the same. The large deviation in g-values from the free electron value ($g - 2.0023$) is due to large angular momentum contribution [43].

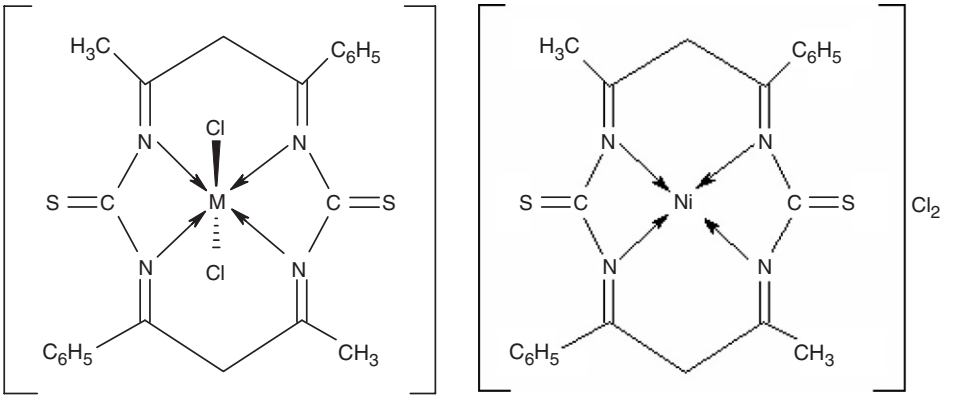
Electron paramagnetic resonance spectra of Cu(II) complex were recorded at 300 K as polycrystalline sample and in DMSO solution on the X-band at frequency 9.3 GHz under the magnetic field strength 3400G. Polycrystalline spectrum shows a well-resolved anisotropic broad signal with $g_{||} = 2.08$–2.33 and $g_{\perp} = 2.01$–2.06 (table 3). The trend $g_{||} > g_{\perp} > 2.0023$, observed for the complex, indicates that the unpaired electron is localized in the $d_{x^2-y^2}$ orbital of the Cu(II) ion [44]. In addition, $G = (g_{||} - 2)/(g_{\perp} - 2)$, which measures the exchange interaction between the metal centers in a polycrystalline solid has been calculated. According to Hathaway [45], if $G > 4$, the exchange interaction is negligible, but $G < 4$ indicates considerable exchange interaction in the solid complex. In the complex reported in this article (table 3), the G value is <4 indicating exchange interaction in solid complex. EPR spectra are shown in Supplementary Material.

On the basis of spectral studies, octahedral geometry has been assigned for Mn(II) and Co(II) complexes, square planar for Ni(II), and tetragonal for Cu(II) (figure 2) [46].

4. Antimicrobial studies

The complexes exhibit better activities than the ligand toward the inhibition of test fungi. Minimum inhibitory concentration of test compounds against both fungi was 750 ppm, at which 100% inhibition was observed. The compounds show fungal inhibition (table 4) in the following order: benzoyl acetone < thiourea < L < Ni(II) < Cu(II) < Mn(II) < Co(II).

For the test bacteria studied, antibacterial activity increased with increasing concentration of the test compounds; activity of the compounds for the test bacteria (table 1) was in the following order: benzoylacetone < thiourea < L < Ni(II) < Mn(II) < Cu(II) < Co(II). The data reveal that the antimicrobial activity of the complexes is better than the ligand. The results (figure 3) also indicate that the complexes were more active on *S. aureus* than *P. aeruginosa*.



[where M=Mn(II), Co(II), Cu(II)]

Figure 2. Suggested structure of the complexes.

Table 4. Fungicidal screening data of compounds showing percentage growth inhibition at 250 and 500 ppm concentrations after 8 days at 30 ± 2°C.

	F. moniliformae		*R. solani*	
Compounds	250	500	250	500
Benzoyl acetone	32	50	36	52
Thiourea	48	64	52	66
L	56	67	59	70
$[Mn(L)Cl_2]$	68	85	70	84
$[Co(L)Cl_2]$	73	86	75	88
$[Ni(L)]Cl_2$	60	75	62	76
$[Cu(L)Cl_2]$	64	79	67	80
Standard (Mancozeb)	82	94	85	96

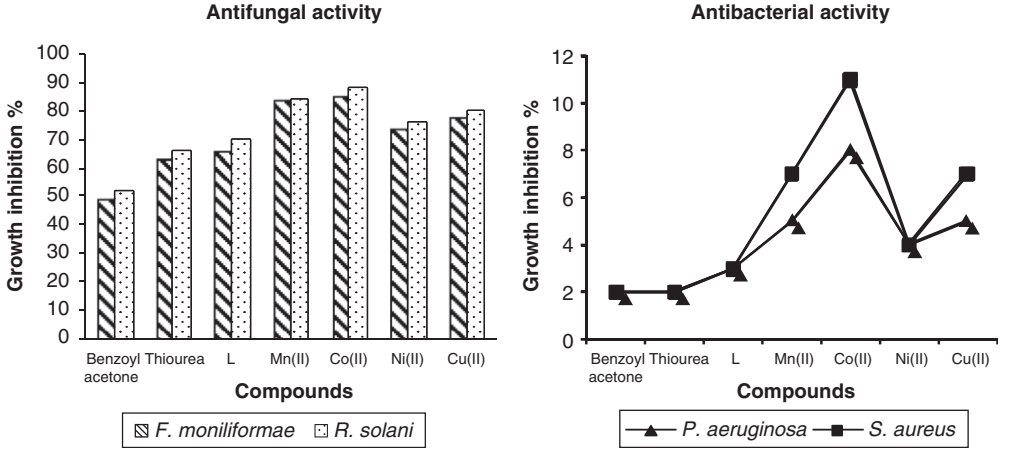


Figure 3. Biological screening data of the ligand and complexes.

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