http://dx.doi.org/10.5012/bkcs.2012.33.7.2279

Template Synthesis of Polyaza Macrocyclic Copper(II) and Nickel(II) Complexes: Spectral Characterization and Antimicrobial Studies

P. Gurumoorthy, J. Ravichandran, N. Karthikeyan,† P. Palani,† and A. Kalilur Rahiman*

PG and Research Department of Chemistry, The New College (Autonomous), Chennai 600 014, India
**E-mail: akrahmanjkr@gmail.com*
†Centre for Advanced Studies in Botany, University of Madras, Guindy Maraimalai Campus, Chennai 600 025, India
Received February 8, 2012, Accepted April 9, 2012

The template synthesis of copper(II) and nickel(II) complexes derived from 2,6-diformyl-4-methylphenol with diethylenetriamine or 1,2-bis(3-aminopropylamino)ethane produce the 12-membered N_3O and 17-membered N_4O macrocyclic complexes, respectively. The geometry of the complexes has been determined with the help of electronic and EPR spectroscopic values and found to be five coordinated square pyramidal and, six coordinated distorted tetragonal for 12-membered and 17-membered macrocyclic complexes, respectively. Electrochemical studies of the mononuclear N_3O and N_4O copper(II) complexes show one irreversible one-electron reduction wave at E_{pc} = –1.35 and –1.15 V respectively, and the corresponding nickel(II) complexes show irreversible one-electron reduction wave at E_{pc} = –1.25 and –1.22 V, respectively. The nickel(II) complexes show irreversible one-electron oxidation wave at E_{pa} = +0.84 and +0.82 V, respectively. All the complexes were evaluated for *in vitro* antimicrobial activity against the human pathogenic bacteria and fungi.

Key Words : Template synthesis, Schiff base cyclocondensation, Macrocyclic complexes, Antimicrobial activity

Introduction

The term "template" has been widely used since early sixties. The routine use of metal template procedures for obtaining a wide range of macrocyclic systems was developed by Curtis.[1] 'Daryle Busch' also used the template notion in coordination chemistry in 1963.[2] Template Schiff base condensations between dicarbonyl compounds and diamines are among the successful and most popular methods for macrocycle synthesis.[3] Metal template condensation reactions are simple "one-pot reactions", cheap and high yielding. Macrocyclic complexes are best prepared with the aid of metal ions as templates to direct the condensation reaction which ultimately ends with ring closure.[4,5]

Studies on complexes of Schiff base macrocycles with different size and number of donor atoms for coordination with a variety of metal centers have been published.[6,7] These Schiff base complexes present suitable biometric properties that can mimic the structural features of the active sites, and they have been widely used in various fields such as illness treatment, biochemical reaction and biological regulator.[8,9] Furthermore, many Schiff bases exhibit antiviral, anticancer and antibacterial activity and can also be regarded as mimetic systems for enzyme models.

The coordination chemistry of Schiff base complexes involving oxygen and nitrogen donor ligands has attracted considerable attention from the biochemists due to their applications in catalysis and their relevance to bioinorganic systems.[10] Phenolic compounds are universal inhibitors of free-radical processes, retarding both oxidation and free-radical fragmentation reactions of important biomolecules (lipids, peptides, carbohydrates, vitamins, *etc*.) and many phenolic compounds have antibacterial activities.[11] In the presence of metal ions these phenolic compounds are believed to damage the cytoplasmic membrane, which is related to their bactericidal activity.[12] These data provide a good basis for attempts to use simple phenolic systems in the syntheses of new bioactive metal complexes.

Copper is a bioessential element in all living systems. It is a component of many metalloproteins and plays a vital role in electron transfer reactions of many cellular processes. However, excessive copper can be very toxic resulting in severe diseases.[13] Recently, numerous research groups have reported novel copper(II) complexes with organic ligands showing antifungal and antibacterial properties against several pathogenic fungi and bacteria.[14-16] Nickel is also an essential element involved in the life process can promote the absorption of iron element, the increase of red corpuscle and the synthesis of some amino-enzymes in body and its coordination compounds display interesting binding and cleavage reactivity with nucleic acids.[17,18] Nickel complexes have also drawn much attention due to their environmental toxicity, carcinogenic nature and chemotherapeutic property in the past years.[19]

This work focuses on the template synthesis of 12-membered N_3O and 17-membered N_4O-donor macrocyclic complexes of copper(II) and nickel(II) ions derived from 2,6-diformyl-4-methylphenol with diethylenetriamine or 1,2-bis(3-aminopropylamino)ethane. The formation of the complexes was confirmed by using spectral and electrochemical studies. The *in vitro* antibacterial activities against three bacterial stains as well as antifungal activities against

three fungal stains were also examined.

Experimental

Materials and Methods. 2,6-Diformyl-4-methylphenol was prepared according to the literature method.[20] TBAP used as supporting electrolyte in electrochemical measurement was purchased from Fluka and recrystallized from hot methanol. Diethylenetriamine, 1,2-bis(3-aminopropylamino)-ethane and the metal perchlorate salts were commercial products (from S.D. Fine, Merck and Fluka, respectively) and were used without further purification. Solvents were dried and purified before being used according to published procedure.[21] ***Safety note:*** Perchlorate salts are potentially explosive while we have not experienced any problems with the compounds described, they should be treated with caution and handled in small quantities.

All the melting points were uncorrected and determined using open capillary tube. Elemental analysis was carried out with a Heraeus CHN-Rapid Analyzer. IR spectra were recorded using KBr pellets in the range 4000-400 cm^{-1} on a JASCO FT IR-4100 spectrophotometer. ESI-mass spectra were recorded on a Q-Tof micromass spectrograph using CH_3CN as the mobile phase with an approximate concentration of 1.0 mmol dm^{-3}. This dilution was electrosprayed at a flow rate of 0.5 mL min^{-1} with a needle voltage of +4.5 kV. The temperature of the heated capillary in the interface was set at 200 ºC. UV-Vis spectra were recorded in HPLC grade CH_3CN at room temperature, on a Shimatzu UV-3100 spectrophotometer in the range of 200-1100 nm, with a quartz cells and ε are given M^{-1} cm^{-1}. Cyclic voltammograms were obtained on CHI 620D (CH Instruments Co., USA) electrochemical analyser using DMF. Platinum foils (1 cm^2) were used as the working and as well as counter electrodes, and Ag/AgCl as the reference electrode. The Ferrocene/ferrocenium (1+) couple was used as an internal standard. The potentials reported are relative to the Ag/AgCl electrode and $E_{1/2}$ of the Ferrocene/ferrocenium (Fc/Fc^+) couple, which under the experimental conditions is 470 mV in DMF and ΔE_p for Fc/Fc^+ is 70 mV. Electrochemical measurements were carried out under a nitrogen gas atmosphere. Tetra(*n*-butyl)ammonium perchlorate (TBAP) was used as the supporting electrolyte (0.1 M) and all the complex solutions were around 10^{-3} M concentration. X-band ESR spectra of the Cu(II) complexes were recorded using DMF as a solvent at room temperature on a Varian EPR-E 112 spectrometer. DPPH (2,2'-diphenyl-1-picrylhydrazyl) with *g* value 2.0023 was used as the standard *g* marker.

***In vitro* Antimicrobial Assays.** The agar diffusion method was followed for antibacterial and antifungal susceptibility tests. Petri plates were prepared by pouring 10 mL of Mueller Hinton Agar for bacteria, and allowed to solidify. These agar plates were inoculated with 0.1 mL of a standardized bacterial suspension (2×10^6 cells/mL) and uniformly spread. A 6 mm well was cut at the center of the agar plate and the well was filled with a solution of the complexes ($CuL^{1,2}$ and $NiL^{1,2}$, separately). The diameter of the inhibition zone observed around the well was measure for each bacterium after 24 h of incubation at 37 ºC. One well was filled with sterile distilled water to serve as a control.

For fungus, Sabouraud Dextrose Agar medium was amended with the complexes ($CuL^{1,2}$ and $NiL^{1,2}$, separately) when the medium was warm, and poured into Petri plates. After solidification of the medium, mycelial disks (6 mm diameter) of the test fungi were inoculated at the center of the plates. The diameter of the inhibition zone for each fungus was measured after 48 h of incubation at 28 ºC.

Template Synthesis of Polyaza Macrocyclic Complexes. To a mixture of the appropriate metal perchlorate hexahydrate (6.1 mmol) in absolute ethanol (10 mL) and 2,6-diformyl-4-methylphenol (1 g, 6.1 mmol) in absolute ethanol (10 mL), diethylenetriamine (0.66 mL, 6.1 mmol) or 1,2-bis(3-aminopropylamino)ethane (1.12 mL, 6.1 mmol) in absolute ethanol (10 mL) was added slowly with stirring. After the addition of amine, the reaction was carried out for 4-5 h under reflux. The solution volume was reduced to 10 mL by roto-evaporation and the precipitate formed on addition of a small amount of diethyl ether. This was filtered off, washed with ether and dried in vacuo.

CuL^1: Yield: 2.05 g (85.45%) (Green colour). mp: > 225 ºC (dec). Analytical data for $C_{13}H_{16}N_3O_5ClCu$ (FW = 393.28 g/mol): Calcd (%): C, 39.70; H, 4.10; N, 10.68. Found (%): C, 39.66; H, 4.06; N, 10.67. Selected IR data (KBr) (ν/cm^{-1}): 2927 (w) [ν(N-H)], 1635 (s) [ν(C=N)], 1555 (s) [ν(phenoxide)], 1114, 1088 (s) [coordinated ν(ClO_4^-)], 626 (s). ESI-mass spectrum: $[CuL^1+2H]^+$ *m/z* = 397 (25%), $[CuL^1+H]^+$ *m/z* = 395 (70%). $g_{\|} = 2.27$, $g_{\perp} = 2.03$.

CuL^2: Yield: 2.16 g (76.25%) (Green colour). mp: > 255 ºC (dec). Analytical data for $C_{17}H_{25}N_4O_5ClCu$ (FW = 464.41 g/mol): Calcd (%): C, 43.96; H, 5.42; N, 12.06. Found (%): C, 43.91; H, 5.45; N, 12.08. Selected IR data (KBr) (ν/cm^{-1}): 2928 (w) [ν(N-H)], 1659 (s) [ν(C=N)], 1547 (s) [ν(phenoxide)], 1114, 1088 (s) [coordinated ν(ClO_4^-)], 626 (s). ESI-mass spectrum: $[CuL^2+H]^+$ *m/z* = 466 (34%), $[CuL^2\text{-}ClO_4]^+$ *m/z* = 366 (42%). $g_{\|} = 2.14$, $g_{\perp} = 2.076$.

NiL^1: Yield: 1.84 g (77.8%) (Brownish red colour). mp: > 240 ºC (dec). Analytical data for $C_{13}H_{16}N_3O_5ClNi$ (FW = 388.43 g/mol): Calcd (%): C, 40.19; H, 4.11; N, 10.81. Found (%): C, 40.16; H, 4.11; N, 10.76. Selected IR data (KBr) (ν/cm^{-1}): 2926 (w) [ν(N-H)], 1658 (s) [ν(C=N)], 1538 (s) [ν(phenoxide)], 1109, 1086 (s) [coordinated ν(ClO_4^-)], 626 (s). ESI-mass spectrum: $[NiL^1+H]^+$ *m/z* = 390 (25%), $[NiL^1\text{-}ClO_4]^+$ *m/z* = 290 (22%).

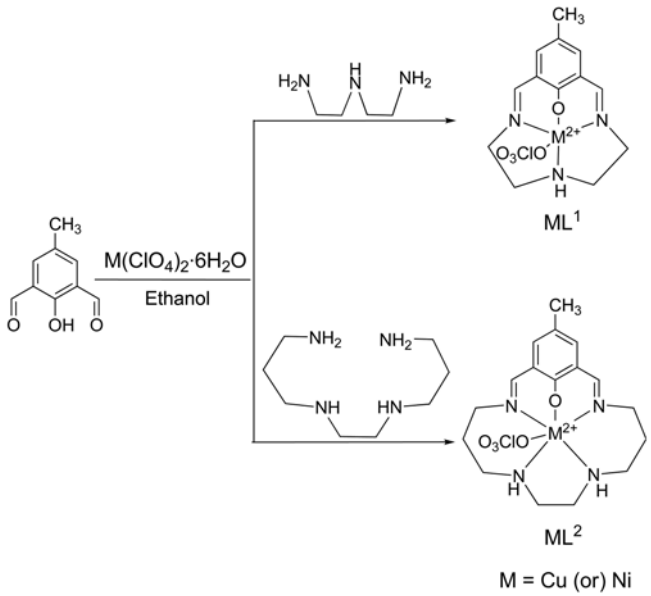
NiL^2: Yield: 2.10 g (74.91%) (Brown colour). mp: > 245 ºC (dec). Analytical data for $C_{17}H_{25}N_4O_5ClNi$ (FW = 459.55 g/mol): Calcd (%): C, 44.43; H, 5.48; N, 12.19. Found (%): C, 44.39; H, 5.52; N, 12.17. Selected IR data (KBr) (ν/cm^{-1}): 2926 (w) [ν(N-H)], 1653 (s) [ν(C=N)], 1542 (s) [ν(phenoxide)], 1114, 1089 (s) [coordinated ν(ClO_4^-)], 626 (s). ESI-mass spectrum: $[NiL^2+H]^+$ *m/z* = 461 (15%), $[NiL^2]$ *m/z* = 460 (35%), $[NiL^2\text{-}ClO_4]^+$ *m/z* = 360 (40%).

Results and Discussion

The attempt to synthesize the [1+1] condensation product of the Schiff base ligands using 2,6-diformyl-4-methylphenol and diamines under different experimental conditions did not yield the expected results. In all cases, the spectral data of the products exhibited the [2+2] dimeric product of Schiff base macrocycle. However, the use of metal perchlorate to template the above reaction was effective with the diamine precursors. Reactions between diamines and 2,6-diformyl-4-methylphenol in the presence of templating agent metal(II) perchlorate using absolute ethanol as solvent gave the expected mononuclear macrocyclic complexes. Infrared and ESI mass spectral data provide the evidence for the formation of mononuclear Schiff base complexes.[22]

The template reactions of 2,6-diformyl-4-methylphenol with diethylenetriamine or 1,2-bis(3-aminopropylamino)-ethane in the presence of templating agent, divalent copper or nickel perchlorate salt, in the 1:1:1 molar ratio, produce the 12-membered N_3O and 17-membered N_4O macrocyclic complexes, respectively. The proposed structure of the complexes, based on spectral analysis, is shown in Scheme 1. Reaction conditions (molar ratio and the method of adding starting materials, reaction time and range of temperatures) were employed to prevent the formation of acyclic products. The synthesized complexes were characterized by elemental analysis, FT IR, mass and electronic spectra. Cyclic voltammetry, ESR and antimicrobial studies were also carried out.

Spectral Studies. The ^{1}H NMR spectra of 2,6-diformyl-4-methylphenol was obtained in $CDCl_3$ at room temperature using TMS as an internal standard. The ^{1}H NMR spectrum of the compound shows the following signals: The aromatic region shows a sharp singlet at δ 7.76 ppm assigned to the phenyl protons, and a sharp singlet at δ 2.38 ppm, due to methyl protons. The spectra show the aldehydic resonance at δ 10.21 ppm, demonstrating the equivalence of the two aldehydic environments. The O-H proton of the phenolic group shows a sharp singlet at δ 11.45 ppm.



Scheme 1. Template cyclocondensation between 2,6-diformyl-4-methylphenol and diamines in the presence of M(II) perchlorate salt.

The IR spectra confirm the formation of the macrocyclic compounds by the absence of bands characteristic of carbonyl and amine groups of the starting materials. An important features is the occurrence of a strong band at 1659-1635 cm^{-1} attributable to C=N stretching modes indicating the Schiff base condensation. The bands at 2928-2926 cm^{-1}, in addition to the weak bands at 1493-1449 cm^{-1} suggest the coordination of the nitrogen atoms of the secondary amino groups. All the complexes showed two sharp peaks at 1100 cm^{-1} and 626 cm^{-1}, which are assigned to antisymmetric stretching and antisymmetric bending of perchlorate ions, respectively.[23] The peak around 1100 cm^{-1} is split, which clearly explains the presence of a coordinated perchlorate ion.[24] Further, the band observed around 1555-1538 cm^{-1} for all the complexes suggests phenoxide coordination with the metal atom.[25] The band observed around 1285-1275 cm^{-1} can be assigned to C-N stretching frequency.

The electron spray ionization mass spectra of all the mononuclear complexes were studied in positive mode. The ESI-MS data show the parent ion peak indicating the stability of the structure in a solution phase. The experimental results show that the metal ion in the complex present as a whole mononuclear entity in solution. The ESI mass spectral data of all the complexes confirm the proposed formula of the complexes. The different fragments of the complex give peaks with various intensities at different *m*/*z* values. Figure

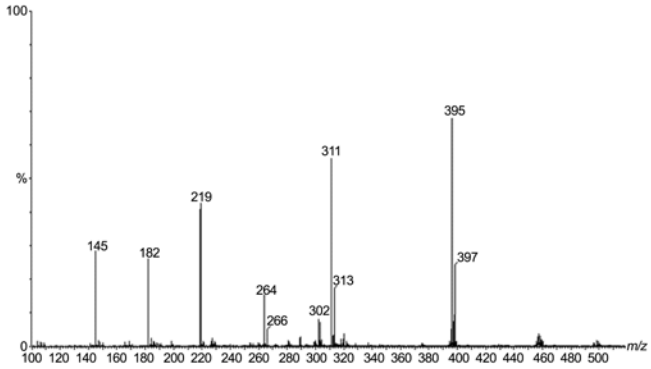


Figure 1. ESI mass spectrum of CuL^1 complex.

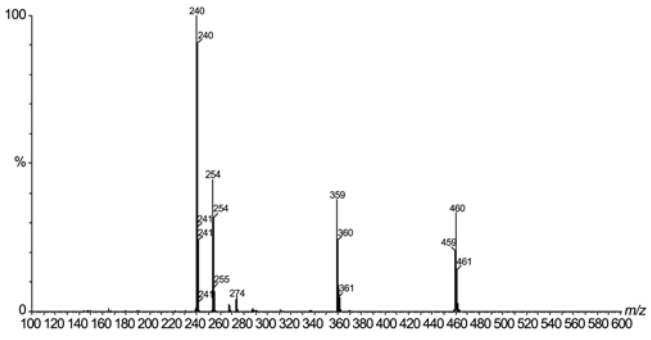
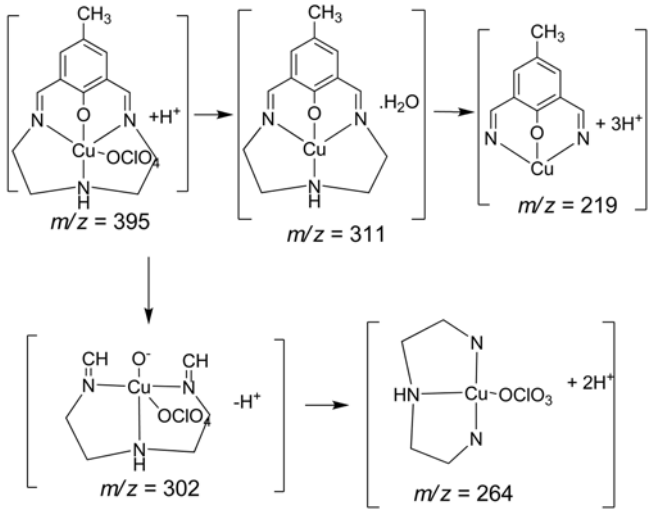
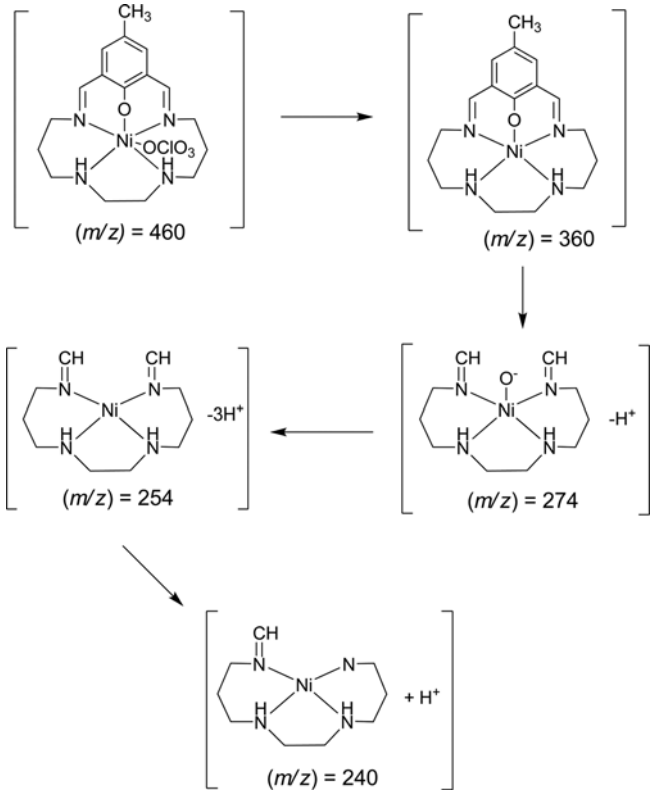


Figure 2. ESI mass spectrum of NiL^2 complex.



Scheme 1a. Fragmentation of the mass spectrum of CuL^1 complex.



Scheme 2a. Fragmentation of the mass spectrum of NiL^2 complex.

1 & 2 depicts the mass spectrum of CuL^1 and NiL^2 respectively. Their fragmentation patterns are depicted in Scheme 1(a) and 2(a) respectively.

Electronic spectra of all the complexes were obtained in CH_3CN medium. The electronic spectral data of the complexes are given in Table 1. The electronic spectra of all the complexes exhibit three main features.[26-29] (i) An intense peak in the range of 250-280 nm assigned to the intra-ligand charge transfer transition (π-π^*). (ii) A peak in the range 415-424 nm due to phenolate-to-metal charge transfer transitions, and (iii) the d-d transition for the copper(II) complexes shows one peak in the region 580-605 nm, which are characteristic of Cu^{2+} in a 5/6 coordination environment, where as the d-d transition for the nickel(II) complexes show three main bands in the range of 588-1028 nm, which is characteristic of Ni^{2+} in the 5/6 coordination environment.

The electronic spectrum of CuL^1 complex exhibit absorption maxima at 605 nm, and this strongly suggests that the coordination geometry around the metal ion might be distorted square pyramidal.[30] The absorption band observed at 580 nm for CuL^2 complex, corresponds to distorted tetragonal geometry around the metal ion.[31] The electronic spectrum of NiL^1 complex shows the d-d transition bands centered at 588, 736 and 1018 nm, which is corresponds to square pyramidal geometry,[32] whereas NiL^2 complex shows the d-d transition bands at 610, 835 and 1026 nm, characteristic of nickel(II) ion in an octahedral geometrical environment.[33] These geometry arrived from electronic spectra is also in agreement with the results obtained from ESI mass spectral analysis.

Electrochemical Properties of the Complexes. The electrochemical properties of all the mononuclear copper(II) and nickel(II) complexes were studied by cyclic voltammetry in dimethylformamide containing 10^{-1} M of tetra(*n*-butyl)-ammonium perchlorate as the supporting electrolyte.

Reduction Process at Negative Potential: The cyclic voltammogram of the copper(II) and nickel(II) complexes were obtained in the potential range of –0.5 V to –1.8 V. Reduction at negative potential is the usual trend observed for phenoxo copper and nickel complexes because of the electronegativity and hard nature of the phenoxide atoms in the ligand.[34,35] The cyclic voltammograms for the mononuclear copper(II) and nickel(II) complexes show an irreversible one-electron transfer reduction in the cathodic region. The cyclic voltammogram for mononuclear CuL^1 and NiL^1 complexes are show in Figure 3 & 4.

The copper(II) complexes $CuL^{1\&2}$ shows an irreversible

Table 1. Electronic spectral data of the complexes

No	Complexes	λ_{max}, nm (ε, M^{-1} cm^{-1}) in CH_3CN	
		d-d	Charge transfer
1	CuL^1	605 (125)	415 (13400) 260 (17500)
2	CuL^2	580 (140)	415 (12600) 280 (17100)
3	NiL^1	1018 (55) 736 (96) 588 (238)	424 (9800) 251 (18700)
4	NiL^2	1026 (62) 835 (108) 610 (260)	418 (10200) 280 (19350)

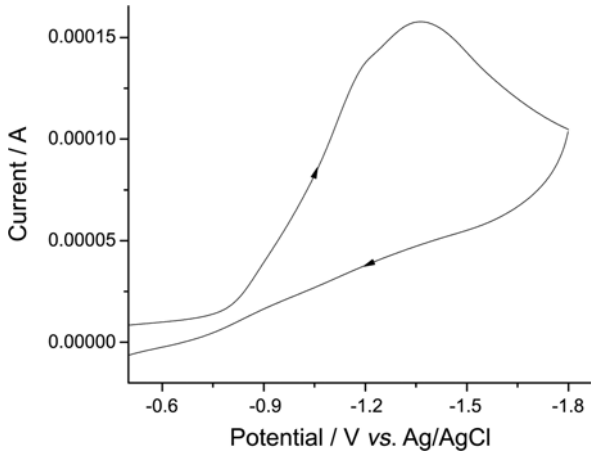


Figure 3. Cyclic voltammogram of CuL^1 complex (reduction process).

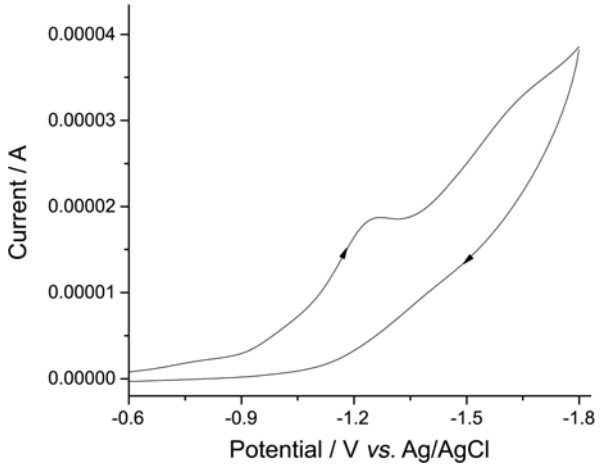


Figure 4. Cyclic voltammogram of NiL^1 complex (reduction process).

one-electron reduction wave at –1.35 V and –1.15 V, respectively, whereas nickel(II) complexes $NiL^{1\&2}$ shows irreversible one-electron reduction wave at –1.25 V and –1.22 V, respectively. Thus the one-electron reduction process occurring at the electrode surface was inferred to be

$$M^{II} \rightarrow M^{I}$$

Oxidation Process at Anodic Potential: The cyclic voltammogram for nickel(II) complexes were obtained at anodic potential in the range 0 V to +1.8 V. The cyclic voltammograms for mononuclear $NiL^{1\&2}$ complexes are shown in Figure 5 & 6. Each voltammogram of $NiL^{1\&2}$ complexes shows an irreversible one-electron oxidation wave at a positive potential of + 0.84 V and + 0.82 V, respectively. Thus the one-electron oxidation process occurring at the electrode surface was inferred to be

$$Ni^{II} \rightarrow Ni^{III}$$

ESR Spectral Analysis. The ESR spectra of $CuL^{1\&2}$ were recorded on X-Band at a frequency 9.4 GHz under the magnetic field strength of 3200 G scan rate 2000, recorded at room temperature. The ESR spectrum of CuL^2 is shown in Figure 7. The spectrum of the complexes at 298 K shows a well-resolved anisotropic signal.

The observed data of the copper(II) complexes show $g_{\|}$ =

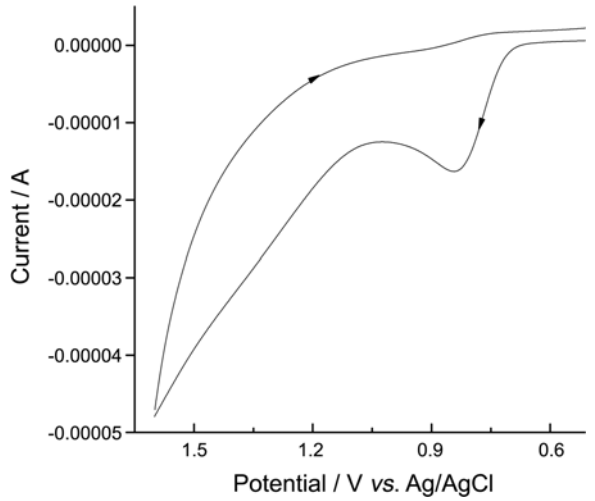


Figure 5. Cyclic voltammogram of NiL^1 complex (oxidation process).

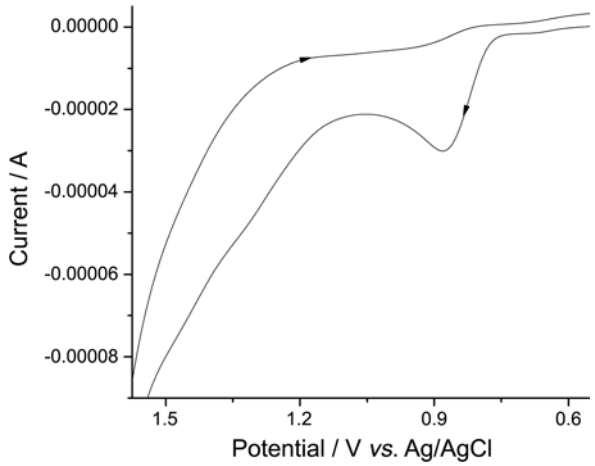


Figure 6. Cyclic voltammogram of NiL^2 complex (oxidation process).

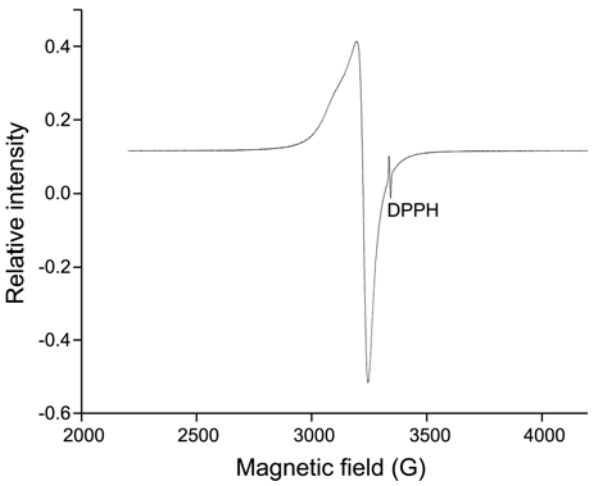


Figure 7. ESR spectrum of CuL^2 complex.

Table 2. ESR spectral data of Cu(II) complexes

Complexes	$g_{\parallel}$	$g_{\perp}$	G	$A_{\parallel} \times 10^{-4}$ (cm^{-1})	α^2
CuL^1	2.27	2.04	6.75	167	0.787
CuL^2	2.14	2.06	2.33	143	0.599

2.14-2.27, $g_{\perp}$ = 2.04-2.06 (Table 2). The trend $g_{\parallel} > g_{\perp} >$ 2.0023 observed for both the complexes indicate that the unpaired electron is localized in $d_{x^2}-d_{y^2}$ orbital of the Cu(II) ion. A five coordinate CuL^1 complex retain their square pyramidal geometry and give well-resolved axial ESR spectra with $g_{\parallel} > g_{\perp}$.[36] The $g_{\parallel}$ and $g_{\perp}$ values of six coordinated CuL^2 complex were closer to 2 and $g_{\parallel} > g_{\perp}$ it suggested major distortion from octahedral symmetry in the copper(II) complex.[37]

Kivelson and Neiman[38] have shown that $g_{\parallel}$ is a moderately sensitive function for indicating covalency. Relatively speaking, $g_{\parallel} > 2.3$ is characteristic of anionic environment and $g_{\parallel} <$ 2.3 of a covalent environment in metal-ligand bonding.[39] The observed $g_{\parallel}$ values of the complexes was less than 2.3 is an indication of significant covalent bonding in copper(II) complexes.

The relation $G = (g_{\parallel} - 2)/(g_{\perp} - 2)$, which measure the exchange interaction between the metal centers in a polycrystalline solid, has been calculated. According to Hathaway and Tomlinson,[40] if G > 4.0, the exchange interaction is negligible and for G < 4.0, indicates considerable exchange interaction in the solid complex. The calculated G values are 6.75 and 2.33 for CuL^1 and CuL^2, respectively. This suggests that there is no exchange interaction in CuL^1 complex and considerable interaction between the copper centres is possible in CuL^2 complex.

The fraction of unpaired electron density located on the copper ion *i.e.* the value in-plane sigma bonding parameter α^2 (molecular orbital coefficient) was estimated from the expression,[38]

$$\alpha^2 = (A_{\parallel}/0.036) + (g_{\parallel} - 2.0023) + 3/7\,(g_{\perp} - 2.0023) + 0.04,$$

where, $A_{\parallel}$ is the parallel coupling constant expressed in cm^{-1} and value of P = 0.036. The α^2 values for the present copper(II) complexes found in the range 0.599-0.787 supported the covalent nature of these complexes.[41,42]

***In vitro* Antimicrobial Activity.** Antimicrobial activities of the synthesized complexes were tested by the agar diffusion method using nutrient agar. The complexes were tested against the human pathogenic bacteria, Gram positive *Staphylococcus aureus* as well as Gram negative *Escherichia coli* and *Klebsiella pneumoniae*. Human pathogenic fungi *Aspergillus ochraceus*, *Paecilomyces variotii* and *Botrytis cinerea* were used for antifungal activity studies. The *In vitro* antimicrobial activities are expressed as diameter of inhibition zones and compared with that of the standard drugs. The radial growth of the colony was recorded on completion of the incubation, and the mean diameter for each complex at a concentration of 150 μg/mL was recorded. DMSO was used as a control and, the standards ciprofloxacin (antibacterial drug) and clotrimazole (antifungal drug) were taken at a concentration of 5 μg/mL and 100 μg/mL, respectively. The mean zone of inhibition values of the investigated compounds are summarized in Table 3.

Table 3. Antibacterial and antifungal screening data of the metal complexes

Compounds	Representation zone of inhibition (mm)					
	Antibacterial			Antifungal		
	E.c	*S.a*	*K.p*	*A.o*	*P.v*	*B.c*
Ciprofloxacin	24.0	25.0	25.0	-	-	-
Clotrimazole	-	-	-	26	29	25
CuL^1	13.0	11.1	12.3	11.7	14.5	12.8
CuL^2	15.5	15.2	12.9	14.6	18.2	16.6
NiL^1	15.9	19.3	15.6	14.8	18.0	17.8
NiL^2	18.2	19.6	18.3	16.8	18.5	18.2

*Standard: Ciprofloxacin 5 μg/mL; Clotrimazole 100 μg/mL; $CuL^{1,2}$ and $NiL^{1,2}$ each at a concentration of 150 μg/mL. *E.c – Escherichia coli; S.a – Staphylococcus aureus; K.p – Klebsiella pneumoniae; A.o – Aspergillus ochraceus; P.v – Paecilomyces variotii; B.c – Botrytis cinerea.*

The antimicrobial activity of mononuclear phenol-based macrocyclic complexes has been reported.[43,44] Metal ion plays a vital role in various biological processes through coenzyme system. The interaction of these ions with biologically active ligand is subject of great interest. The synthesized Schiff base macrocyclic complexes shows a profound antimicrobial activity. The order of increasing antibacterial and antifungal activities was $CuL^1 < CuL^2 < NiL^1 <$ NiL^2 (Figure 8 & 9). Among the four complexes, NiL^2 com-

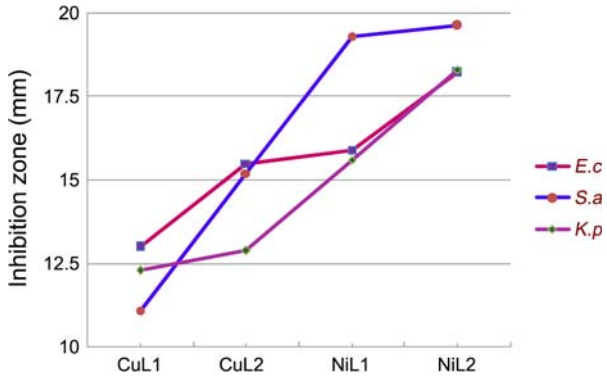


Figure 8. Antibacterial activity of metal complexes.

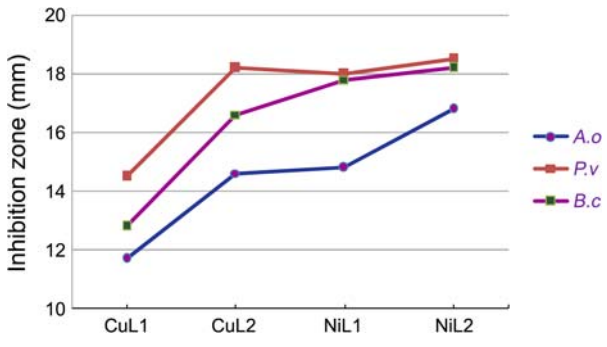


Figure 9. Antifungal activity of metal complexes.

plex shows good antimicrobial activity and CuL^1 complex shows lowest activity against the tested microorganisms, when compared with the standard drugs. The higher antimicrobial activity of the metal complexes may be due to the coordination and chelation, which tends to make metal complexes act as more powerful and potent bactereostatic agents, thus inhibiting the growth of the microorganisms.[45,46] Moreover, coordination reduces the polarity of the metal ion mainly because of the partial sharing of its positive charge with the donor groups within the chelate ring system formed during the coordination. This process, in turn, increases the lipophilic nature of the central metal atom, which favors its permeation more efficiently through the lipid layer of the microorganism, thus destroying them more aggressively. Bacteria are very resilient and have already developed resistance to many commonly used antibiotics.[47] This may open up new avenues for exploiting new drugs. The purpose of this work was to focus specifically on the scientific challenges of antimicrobial research.

Conclusion

The Cu(II) and Ni(II) ions are effective as a template for the Schiff base cyclocondensation of 2,6-diformyl-4-methylphenol with two different diamines. The electrochemistry of the complexes indicates an irreversible behavior. Based on the spectral data square pyramidal geometry around the metal ion has been assigned to the complexes containing N_3O set of donor atoms, whereas distorted tetragonal geometry has been assigned to the complexes having N_4O set of donor atoms. All the synthesized macrocyclic metal complexes show profound antimicrobial activities against the tested microorganisms. Ni(II) complexes shows higher antibacterial and antifungal activities compared to the Cu(II) complexes. These results also indicate a combination of metal and ligand environment plays a vital role in increasing a degree of inhibition.

Acknowledgments. The authors express their sincere thanks to the Management and the Principal, Prof. K. Altaff, The New College (Autonomous), Chennai 600 014, for providing research facilities.

References

1. House, D. A.; Curtis, N. F. *Chem. Ind*. **1961**, *42*, 1708-1709.
2. Busch, D. H. *Adv. Chem. Ser*. **1963**, *1*, 1-18.
3. Gerbeleu, N. V.; Arion, V. B.; Burgess, J. *Template Synthesis of Macrocyclic Compounds*; Wiley-VCH: New York, 1999.
4. Christensen, J. J.; Eatough, D. J.; Izatt, R. M. *Chem. Rev.* **1974**, *74*, 351-384.
5. Nelson, S. M. *Pure Appl. Chem*. **1980**, *52*, 2461-2476.
6. Bertolo, E.; Bastida, R.; Blas, A. D.; Fenton, D. E.; Loderio, C.; Macias, A.; Rodriguez, A.; Rodriguez-Blas, T. *J. Inclusion Phenom. Macrocyclic Chem.* **1999**, *5*, 191-198.
7. Chandra, S.; Gupta, K. *Trans. Met. Chem*. **2002**, *27*, 329-332.
8. Cozzi, P. G. *Chem. Soc. Rev.* **2004**, *33*, 410-421.
9. Bagihalli, G. B.; Patil, S. A.; Badami, P. S. *J. Enzyme Inhib. Med. Chem*. **2009**, *24*, 730-741.
10. Shankar, K.; Rohini, R.; Sharavankumar, K.; Muralidhar Reddy, P.; Ho, Y.-P.; Ravinder, V. *Spectrochim. Acta Part A* **2009**, *73*, 205-211.
11. Rajasekar, M.; Sreedaran, S.; Prabu, R.; Narayanan, V.; Jagadeesh, R.; Raman, N.; Rahiman, A. K. *J. Coord. Chem.* **2010**, *63*, 136-146.
12. Yamashita, N.; Tanemura, H.; Kawanishi, S. *Mutat. Res*. **1999**, *425*, 107-115.
13. Wang, T.; Guo, Z. *Curr. Med. Chem*. **2006**, *13*, 525-537.
14. Ruiz, M.; Perello, L.; Servercarrio, J.; Ortiz, R.; Garciagranda, S.; Diaz, M. R.; Canton, E. *J. Inorg. Biochem*. **1998**, *69*, 231-239.
15. Ibopishak Singh, O.; Damayanti, M.; Rajen Singh, N.; Hemakumar Singh, R. K.; Mohapatra, M.; Kadam, R. M. *Polyhedron* **2005**, *24*, 909-916.
16. Efthimiadou, E. K.; Katsarou, M. E.; Karaliota, A.; Psomas, G. *J. Inorg. Biochem*. **2008**, *102*, 910-920.
17. Yamanaka, T., Otsuka, S., Yamanaka, T., Eds.; *Metalloproteins*; Elsevier: Amsterdam, 1998; p 285-289.
18. Sudhamani, C. N.; Bhojya Naik, H. S.; Ravikumar Naik, T. R.; Prabhakaran, M. C. *Spectrochim. Acta Part A* **2009**, *72*, 643-647.
19. Kong, D. M.; Wang, J.; Zhu, L. N.; Jin, Y. W.; Li, X. Z.; Shen, H. X.; Mi, H. F. *J. Inorg. Biochem*. **2008**, *102*, 824-832.
20. Verani, C. N.; Rentschler, E.; Weyhermüller, T.; Bill, E.; Chaudhuri, P. *J. Chem. Soc., Dalton Trans*. **2000**, 251-258.
21. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: 1988.
22. (a) Esteban, D.; Banobre, D.; de Blas, A.; Rodriguez-Blas, T.; Bastida, R.; Macias, A.; Rodriguez, A.; Fenton, D. E.; Adams, H.; Mahia, J. *Eur. J. Inorg. Chem*. **2000**, 1445-1456. (b) Platas, C.; Avecilla, F.; de Blas, A.; Rodriguez-Blas, T.; Bastida, R.; Macias, A.; Rodriguez, A.; Adams, H. *J. Chem. Soc., Dalton Trans.* **2001**, 1699-1705. (c) Rodriguez-Infante, C.; Esteban, D.; Avecilla, F.; de Blas, A.; Rodriguez-Blas, T.; Mahia, J.; Macedo, A. L.; Geraldes, C. F. G. C. *Inorg. Chim. Acta* **2001**, *317*, 190-198.
23. (a) Radecka-Paryzek, W.; Litkowska, H. *J. Alloys. Comp*. **2000**, *300-301*, 435-438. (b) Lachkar, M.; Guilard, R.; Attamani, A.; Clan, A. D.; Fisher, J.; Weiss, R. *Inorg. Chem.* **1998**, *37*, 1575-1584.
24. Tandon, S. S.; Thompson, L. K.; Bridson, J. N.; Mekee, V.; Downard, A. J. *Inorg. Chem.* **1992**, *31*, 4635-4642.
25. Mandal, S. K.; Adhikary, B.; Naik, K. *J. Chem. Soc., Dalton Trans*. **1986**, 1175-1180.
26. Manonmani, J.; Kandaswamy, M.; Narayanan, V.; Thirumurugan, R.; Sundara Raj, S. S.; Shanmugam, G.; Ponnuswamy, M. N.; Fun, H. K. *Polyhedron* **2001**, *20*, 3039-3048.
27. Rybak-Akimova, E. V.; Busch, D. H.; Kahol, P. K.; Pinto, N.; Alcock, N. W.; Clase, H. J. *Inorg. Chem*. **1997**, *36*, 510-520.
28. Garber, Ty.; Wallendael, S. V.; Rillema, D. P.; Kirk, M.; Hatfield, W. E.; Welch, J. H.; Singh, P. *Inorg. Chem*. **1990**, *29*, 2863-2868.
29. Volkmer, D.; Hommerich, B.; Griesar, K.; Haase, W.; Krebs, B. *Inorg. Chem*. **1996**, *35*, 3792-3803.
30. García-Raso, A.; Fiol, J. J.; Adrover, B.; Caubet, A.; Espinosa, E.; Mata, I.; Molins, E. *Polyhedron* **2002**, *21*, 1197-1201.
31. Chandra, S.; Sharma, A. K. *Spectrochim. Acta Part A* **2009**, *72*, 851-857.
32. Téllez, F.; Peña-Hueso, A.; Barba-Behrens, N.; Contreras, R.; Flores-Parra, A. *Polyhedron* **2006**, *25*, 2363-2374.
33. Khandar, A. A.; Hosseini-Yazdi, S. A. *Polyhedron* **2003**, *22*, 1481-1487.
34. Thirumavalavan, M.; Akilan, P.; Kandaswamy, M. *Inorg. Chem.* **2003**, *42*, 3308-3317.
35. Benzekeri, A.; Dubourdeaux, P.; Latour, J. M.; Rey, P.; Laugier, J. J. *J. Chem. Soc., Dalton Trans*. **1991**, 3359-3365.
36. Hathaway, B. J. *Copper in Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1987; *5*, p 533.
37. Kumar, U.; Chandra, S. *Synth. React. Inorg. Met.-Org. Chem.* **2004**, *34*, 1417-1430.
38. Kivelson, D.; Neiman, R. *J. Chem. Phys.* **1961**, *35*, 149-155.

39. Guzar, S. H.; Qin-han, J. I. N. *J. Appl. Sci.* **2008**, *8*, 2480-2485.
40. Hathaway, B. J.; Tomlinson, A. A. G. *Coord. Chem. Rev.* **1970**, *5*, 1-43.
41. Ray, R. K.; Kauffman, G. B. *Inorg. Chim. Acta* **1990**, *173*, 207-214.
42. Singh, P. K.; Kumar, D. N. *Spectrochim. Acta Part A* **2006**, *64*, 853-858.
43. Mruthyunjayaswamy, B. H. M.; Ijare, O. B.; Jadegoud, Y. *J. Braz. Chem. Soc.* **2005**, *16*, 783-789.
44. Bharathi, K. S.; Sreedaran, S.; Priya, P. H.; Rahiman, A. K.; Rajesh, K.; Jagadish, L.; Kaviyarasan, V.; Narayanan, V. *J. Coord. Chem.* **2009**, *62*, 1356-1372.
45. Chohan, Z. H.; Scozzafova, A.; Supuran, C. T. *J. Enzyme Inhib. Med. Chem.* **2003**, *18*, 259-263.
46. Chohan, Z. H.; Arif, M.; Akhtar, M. A.; Supuran, C. T. *Bioinorg. Chem. Appl.* **2006**, 1-13.
47. Spigaglia, P.; Barbanti, F.; Mantrantonio, P. *Microb. Drug Resist.* **2007**, *13*, 90-95.