



Synthesis, Characterization and Biochemical Activity of Dinuclear Cu(II)/Ni(II)/Co(II) and Tetranuclear Cu(II) Complexes of Schiff Base

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A new Schiff base *bis*-[2,2'-(1,2-phenylenebis[nitrilo(E)methylidene])diphenol] (**3**) was prepared by reacting biphenyl-3,3',4,4'-tetramine (**1**) and salicylaldehyde (**2**) in EtOH. The new ligand was characterized by elemental analyses, ¹H and ¹³C-NMR, IR and mass spectral studies. Dinuclear copper(II), nickel(II), cobalt(II) and tetranuclear copper(II) complexes of ligand were prepared and characterized by elemental analyses, magnetic moments, IR, UV-VIS and mass spectral studies. Metal:ligand ratio was found as 2:1 in the dinuclear metal complexes. Elemental analyses, stoichiometric and spectroscopic data of the metal complexes indicated that the metal ions were coordinated to the nitrogen atoms and oxygen atoms of Schiff base ligand. Testing the bacteriostatic diameter can test the susceptibility of a bacterium towards a drug. The ligand and its metal complexes had no inhibitor activity against G(-) *E. coli*. But the content was used 0.2 % ligand and its metal complexes had inhibitory activity against G(-) *S. aureus* and *P. aeruginosa*.

Key Words: Schiff base, Nickel(II) complex, Tetranuclear Cu(II) complex.

INTRODUCTION

In coordination chemistry, Schiff bases have been used for over 150 years^{1,2}. These ligands have played an important role in the development of coordination chemistry as they readily form stable complexes with most of the transition metals. Particularly, compound with tetradentate Schiff base and related liganda are potential models of protein active sites, showing different structures and properties^{3,4}. Various mononuclear metal complexes have been shown to possess enzyme-like activities⁵. Schiff base ligands with additional donor atoms appended to ring have attracted considerable interest because of their capacity to bind and transport metals ions, for the potential to prepare and study their mixed-valence forms and as models for metalloproteins⁶. Cobalt Schiff base complexes are also used as potent antiviral, antibacterial and antitumor agents⁷. The chemistry of dinuclear copper complexes with ligands of biological relevance and with metal centers at close proximity is one of the central themes of current research⁸ due to their interesting structural, electrochemical and magnetic properties and also because of their relevance to the active sites of several metalloenzymes⁹ as synthetic models¹⁰⁻¹⁴.

In the present work, we have synthesized a new Schiff base by reaction of salicylaldehyde and biphenyl-3,3',4,4'-tetramine. Then, its dinuclear copper(II), nickel(II), cobalt (II) and tetranuclear copper(II) complexes were prepared and characterized by elemental analyses, magnetic moments, IR, ¹H

NMR, ¹³C NMR, mass spectral studies. The dinuclear metal complexes were found to have a 2:1 metal:ligand ratio. Testing the bacteriostatic diameter can test the susceptibility of a bacterium towards a drug. The ligand and its metal complexes had no inhibitor activity against G(-) *E. coli*. But the content was used 0.2 % ligand and its metal complexes had inhibitory activity against G(-) *S. aureus* and *P. aeruginosa*.

EXPERIMENTAL

¹H, ¹³C NMR spectra were recorded on a Varian Gemini 200 spectrometer using DMSO-d₆ as solvent. Chemical shifts (δ) were reported in ppm relative to Me₄Si, using the solvent signal as internal reference. C, H and N contents were determined microanalytically on a CHNS Costech 4010 analyzer and metal contents were estimated spectrophotometrically. IR spectra were recorded on an ATI Unicam Matson 1000 Model FTIR spectrophotometer and UV-VIS spectra on an ATI Unicam UV2 Model UV/VIS spectrophotometer. Mass spectra (ESI) were recorded on a micromass quattro LC-MS/MS spectrophotometer. Room temperature magnetic susceptibility measurements were done on a PAR model 155 vibrating sample magnetometer.

Preparation of the ligand (3): To a solution of biphenyl 3,3',4,4'-tetramine (230 mg, 1.07 mmol) in 25 mL absolute EtOH, salicylaldehyde (520 mg, 4.26 mmol) dissolved in 20 mL absolute EtOH were mixed together. Then this mixture

was refluxed with stirring for 4 h. The resulting dark yellow solution was filtered while hot and concentrated slowly. As this solution cooled, dark yellow crystalline product precipitated. This product was isolated by vacuum filtration, washed with EtOH, Et₂O respectively, then dried in air to give dark yellow solid product 600 mg (88 %). m.p. 244 °C. MS: (ESI) m/z 630 [M]⁺, Anal. calcd % (found) for C₄₀H₃₀N₄O₄: C, 76.2 (76.3); H, 4.76 (4.8); N, 8.9 (8.8); O, 10.2 (10.1). ¹H NMR (in DMSO-d₆, δ, ppm): 10.25 (s, 4H, HC=N); 6.75-8.10 (m, 22H, Ar-H); 10.80 (s, 4H, -OH). ¹³C NMR: 117.18; 119.21; 119.90; 124.40; 125.50; 128.60; 130.95; 134.10; 140.55; 144.15; 145.20; 159.40; 180.40.

[Ni₂(H₂L)(ClO₄)₄], (4): A solution of Ni(ClO₄)₂·6H₂O (232 mg, 0.634 mmol) in dried EtOH (10 mL) was added to the ligand solution (200 mg, 0.32 mmol) in 25 mL of EtOH and this mixture was refluxed with stirring for 3 h. The red-brown solid product was filtered-off and then washed with EtOH and Et₂O respectively. Then the red-brown solid product (yield: 215 mg, 59 %) was dried *in vacuo*. MS: (ESI) m/z 1145 [M]⁺ Anal. calcd % (found) for C₄₀H₃₀N₄O₂₀Cl₄Ni₂: C, 41.9 (41.8); H, 2.6 (2.5); N, 4.9 (4.8); Ni, 10.2 (10.1). ¹³C NMR (in DMSO-d₆, δ, ppm): 119.10; 121.20; 122.80; 126.30; 128.40; 130.40; 134.90; 137.20; 144.45; 148.10; 149.70; 161.50; 186.40.

[Cu₂(H₂L)(ClO₄)₄], (5): In EtOH (10 mL), a solution of Cu(ClO₄)₂·6H₂O (144 mg, 0.390 mmol) was added to the ligand solution (122 mg, 0.194 mmol) in 25 mL of EtOH and this mixture was refluxed with stirring for 3 h. The resulting pale brown solution was filtered while hot and concentrated slowly. As the solution cooled a pale brown crystalline product precipitated. The brown product was filtered off, then washed with EtOH and Et₂O, the brown solid product (yield 0.132 g, 59 %) was dried *in vacuo*. MS: (ESI) m/z 1165 (1151) [M + H₂O - 4H]⁺, Anal. calcd % (found) for C₄₀H₃₀N₄O₂₀Cl₄Cu₂: C, 41.6 (41.5); H, 2.6 (2.7); N, 4.8 (4.7); Cu, 11.0 (11.1).

[Co₂(H₂L)(ClO₄)₄], (6): A solution of Co(ClO₄)₂·6H₂O (232 mg, 0.634 mmol) in dried EtOH (10 mL) was added to the ligand solution (200 mg, 0.32 mmol) in 25 mL of EtOH and this mixture was refluxed with stirring for 3 h. The brown solid product was filtered-off and then washed with EtOH and Et₂O respectively. Then the brown solid product (yield: 240

mg, 66 %) was dried *in vacuo*. MS: (ESI) m/z 1146 [M+1]⁺ Anal. calcd % (found) for C₄₀H₃₀N₄O₂₀Cl₄Co₂: C, 41.9 (41.75); H, 2.64 (2.70); N, 4.90 (4.78); Co, 10.28 (10.35).

[Cu₄(L)(phen)₂(ClO₄)₄(H₂O)], (7): In EtOH (10 mL), a solution of Cu(ClO₄)₂·6H₂O (104 mg, 0.281 mmol) was added to the dinuclear copper (II) complex (5) (162 mg, 0.140 mmol) in 25 mL of EtOH and this mixture was refluxed with stirring for 2 h. Then the separated solution of 1,10-phenanthroline monohydrate (56 mg, 0.283 mmol) in EtOH was successively added to the resulting mixture, which was boiled under reflux for 5 h. The dark brown product 0.144 g, (64 %) was filtered-off, washed with EtOH and dried *in vacuo*. MS: (ESI) m/z 1653 [M+1]⁺, Anal. calcd % (found) for C₆₄H₄₄N₈O₂₁Cl₄Cu₄: C, 46.39 (46.50); H, 2.68 (2.58); N, 6.76 (2.70); Cu, 15.34 (15.4).

Antibacterial activity test: The antibacterial activities *in vitro* of the ligand and the Cu(II), Ni(II) and Co(II) complexes have been tested by the paper disc diffusion method¹⁵. The chosen strains were G(+) *Staphylococcus aureus*, G(-) *Escherichia coli* and G(-) *Pseudomonas aeruginosa*. The solutions of ligand and metal complexes were prepared in DMSO. Nutrient agar was poured onto a plate and allowed to solidify. The liquid medium containing the bacterial subcultures was autoclaved before inoculation. The bacteria were then cultured for 24 h at 37 °C in an incubator. Bacterial strains were inoculated onto the medium plates with absorbent cotton and 10 mm³ of the test compounds (DMSO solutions) were added drop wise to a 6 diameter filter paper disc placed at the centre of each agar plate. The plate were kept at 5 °C for 1 h and then transferred to an incubator maintained at 37 °C. The width of the growth inhibition zone around the disc was measured after 24 h incubation. Four replicas were made for each test.

RESULTS AND DISCUSSION

Bis-[2,2'-{1,2-phenylenebis[nitrilo(E)methylidene]}diphenol] (3) were prepared in EtOH by reacting biphenyl-3,3',4,4'-tetraamine (1) and salicylaldehyde (2) (Fig. 1). The structures of the ligand and the complexes were established from their ¹H and ¹³C NMR, IR, UV-VIS spectra data, elemental analyses. In the proposed structure of (3), N₂O₂ units were

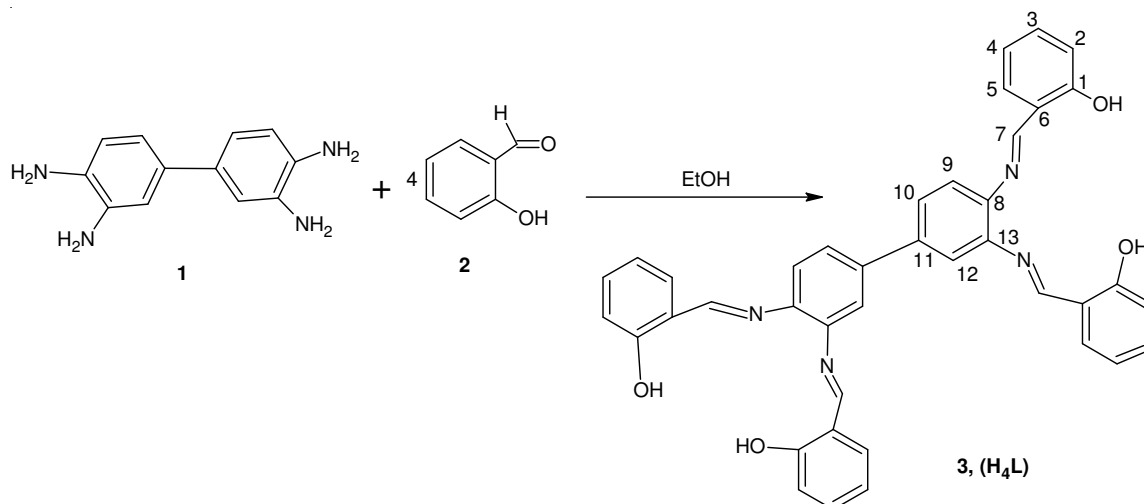


Fig. 1. The synthesis route of the H₄L

TABLE-1
 CHARACTERISTIC IR BANDS (cm⁻¹) OF THE H₄L AND ITS METAL COMPLEXES

Compounds	v(O-H)	v(C-N)	v(C=N)	v(ClO ₄ ⁻)	v(C-O)
H ₄ L, (3)	3436-3395	1403	1614	-	1192
[Ni ₂ (H ₂ L)(ClO ₄) ₂] (4)	3401	1374	1600	1078-1020-624	1186
[Cu ₂ (H ₂ L)(ClO ₄) ₂] (5)	3412	1376	1595	1090-1050-624	1188
[Co ₂ (H ₂ L)(ClO ₄) ₂] (6)	3410	1375	1605	1080-1050-625	1165
[Cu ₄ L(ClO ₄) ₂ (phen) ₂] (7)	-	1376	1590	1075-1020-624	1180

 TABLE-2
 LIGAND FIELD PARAMETER OF THE COMPLEXES

Complex	Ligand field splitting energy (Dq cm ⁻¹)	Racah interelectronic repulsion parameter (B cm ⁻¹)	Covalent factor (β)	β (%)	v ₂ /v ₁	LFSE (kcal mol ⁻¹)
Cu ₂ (H ₂ L) (5)	13500	96.06	-	-	-	38.57
Ni ₂ (H ₂ L), (4)	12645	843.6	0.8115	23.45	1.59	36.12
Co ₂ (H ₂ L) (6)	10270	914.0	0.9425	6.25	1.85	29.34
Cu ₄ (L)(phen) ₂ (7)	13420	96.2	-	-	-	38.34

available for the complexation of metal ions in tetradentate coordination. In the Ni(II), Cu(II) and Co(II) (**4-6**) complexes were obtained through the reaction of the ligand and the Ni(ClO₄)₂·6H₂O, Cu(ClO₄)₂·6H₂O and Co(ClO₄)₂·6H₂O solution in the EtOH (1:2) ligand:metal ratio. The ¹H NMR spectra of a DMSO-d₆ solution of Schiff base ligand (**3**) showed well resolved signals. The spectrum of compound (**3**) showed singlets at 10.25 (4H), multiplet at 6.75-8.10 (22H) and singlet at 10.80 (4H) ppm, corresponding to the HC=N (C-7), Ar-H, -OH resonances, respectively. The signal at 10.80 ppm was disappeared upon addition of D₂O to the solution. The thirteen resonances observed in the ¹³C NMR spectra of (**3**), were also consistent with the proposed formula. The ¹H and ¹³C NMR spectral data supported the proposed structures and indicated the formation of the ligand (**3**). The ¹H NMR integral intensities have supported the proposed structure¹⁶⁻¹⁹.

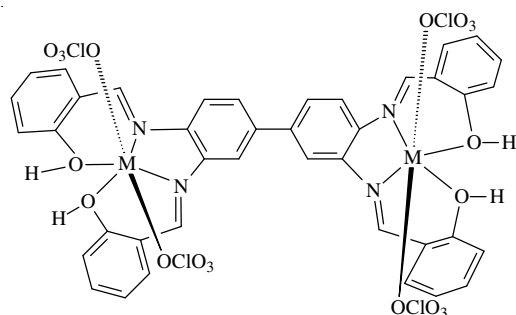
The main IR bands of ligand and metal complexes were given in the Table-1. In general, the complexes exhibited very comparable IR features suggesting that they are similar of structure. In the IR spectrum of ligand (**3**), the v(O-H), v(C=N), v(C-O) stretching vibrations were observed at 3436, 1614 and 1192 cm⁻¹ respectively. The complexes (**4-6**) had the v(O-H), v(C=N), v(C-O) stretching vibrations *ca.* at 3410, 1600 and 1180 cm⁻¹ respectively. The C-O vibration of the ligand at 1192 cm⁻¹ was shifted to lower frequencies after complexation, at 1186, 1188, 1165 and 1180 cm⁻¹ for complexes (**4-7**) respectively. The band assigned to v(O-H) is shifted to higher frequency by 20-30 cm⁻¹ in the complexes¹⁹. The band assigned to v(C-N) shows a shift of 25 cm⁻¹ towards a lower frequency. A strong band at 1614 cm⁻¹, which shifts by 15-25 cm⁻¹ towards lower frequency upon coordination, is assigned to v(C=N). The significant shifts in v(O-H), v(C=N), v(C-N) and v(C-O) upon complexation support the concept of coordination of the ligand through the azomethyn nitrogen and phenolic oxygen. The metal complexes shows a doublet at *ca.* 1080-1020 cm⁻¹, due to splitting of the [v(T₂)] vibration into [v₃(A)] and [v₃(E)]²⁰. The presence of these bands shows that the perchlorate is coordinated in the complexes. The complex (**7**) showed strong band at 805 cm⁻¹ and weak band at 755 cm⁻¹, attributable to 1,10-phenanthroline units. This clearly indicated coordination of the Schiff base ligand through the oxygen and azomethine nitrogen^{16-19, 21}.

The mass (ESI) of Schiff base ligand exhibited the molecular ion at m/z 630 [M]⁺, which indicated the formation of the ligand. The molecular ion peak appeared at (m/z, ESI) 1145 [M]⁺, 1165 [M + H₂O - 4H]⁺, 1146 [M]⁺ and 1653 [M+1]⁺ (**4-7**) respectively. The copper(II) complex containing an additional one mole of water was observed. Furthermore, the metal to ligand ratio of the dinuclear nickel(II), copper(II) and cobalt(II) complexes were found to be 2:1 metal:ligand ratio according spectroscopic studies. The elemental analysis data for the ligand (**3**) and its metal complexes (**4-7**) were consistent with the general formula.

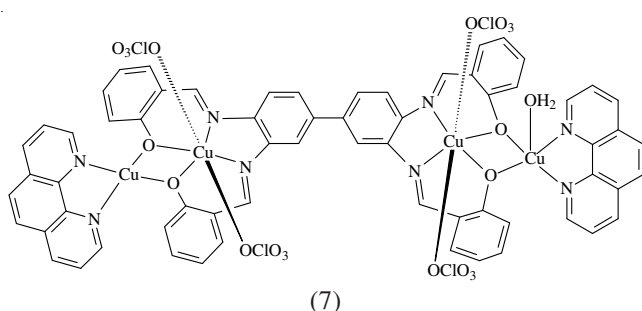
Electronic spectra of the complexes were recorded in DMSO (ε in L mol⁻¹ cm⁻¹). Electronic spectra of Cu(II) complex (**5**) show bands at 13,500 (755), 16,650(605) and 26,250(340) cm⁻¹; Cu(II) complex(**7**) show bands at 13,420 (774), 15,950 (580) and 25,650 (360) cm⁻¹ assignable to a ²E_g→²T_{2g} transition and charge transfer. Electronic spectral data coupled with detected magnetic moment of Cu(II) complexes(**5** and **7**) as 1.75 and 1.85 BM respectively suggests octahedral geometry²² Ni(II) complex displays bands at 12,645 (1045), 18,150 (660) and 24,850 (385) cm⁻¹ assignable to ³A_{2g}→³T_{2g}(F), ³A_{2g}→³T_{1g}(F) and ³A_{2g}→³T_{1g}(P), respectively. These electronic transitions along with magnetic moment 2.95 BM suggest octahedral geometry for Ni(II) complex^{23,24}. The Co(II) complex shows three bands at 10,270 (966), 18,410 (535) and 25,675 (410) cm⁻¹ assignable to ⁴T_{1g}(F)→⁴T_{1g}(P), ⁴T_{1g}(F)→⁴A_{2g} and ⁴T_{1g}(F)→⁴T_{1g}(P) transitions, respectively. These transitions and observed magnetic moment of 4.70 BM indicate high spin octahedral complex^{25,26}. The calculated values of ligand field splitting energy (10 Dq), Racah interelectronic repulsion parameter (β), covalent factor (β), ratio v₂/v₁ and ligand field stabilization energy (LFSE), given in Table-2, support the proposed geometry for all the complexes (Fig. 2).

Testing the bacteriostatic diameter can test the susceptibility of a bacterium towards a drug. The results of antibacterial activities *in vitro* are shown in Table-3. The content of ligand and metal complexes was used 0.1 and 0.2 %. They had no inhibitor activity against G(-) *E. coli*. When the content was used 0.1 % ligand and its metal complexes showed no inhibitory activity against G(-) *S. aureus* and *P. aeruginosa*. But when the content was used 0.2 % ligand and its metal complexes had inhibitory activity against G(-) *S. aureus* and *P. aeruginosa*.

As the content was changed to 0.2 %, the biological activity of the metal complexes against G(-) *P. aeruginosa* was decreased. The inhibitor activities of the metal complexes against other strains are currently being tested.



M = Ni(II) (4); Cu(II) (5); Co(II) (6)



(7)

Fig. 3. Proposed structure for the metal complexes

TABLE-3
ANTIBACTERIAL ACTIVITY DATA FOR H₄L
LIGAND AND ITS METAL COMPLEXES

Comp.	% Content	Average value of bacteriostatic diameter*/mm		
		<i>E. coli</i>	<i>S. Aureus</i>	<i>P. aeruginosa</i>
H ₄ L (3)	0.1	6.0	6.0	6.0
	0.2	6.0	8.0	8.0
Ni ₂ (H ₂ L) (4)	0.1	6.0	6.0	9.0
	0.2	6.0	9.0	7.0
Cu ₂ (H ₂ L) (5)	0.1	6.0	6.0	10.0
	0.2	6.0	10.0	8.0
Co ₂ (H ₂ L) (6)	0.1	6.0	6.0	8.0
	0.2	6.0	8.0	7.0
Cu ₄ (L)(phen) ₂ (7)	0.1	6.0	6.0	10.0
	0.2	6.0	10.0	9.0

*Average values from four experiments

Conclusion

In the present study, we demonstrated the preparation of a new Schiff base ligand providing binucleation N₂O₂ donor array moiety and its dinuclear-nickel(II), cobalt(II) or copper(II) and homo tetranuclear copper(II) complexes. The Ni(II), Co(II) or Cu(II) metal ions were complexed with nitrogen atoms of the Schiff base oxygen atoms in square-planar geometry. All the spectral data and elemental analyses

supported the formation of the Schiff base ligand and its copper(II), cobalt(II) and nickel(II) complexes. The calculated values of ligand field splitting energy (10 Dq), Racah inter-electronic repulsion parameter (β), covalent factor (β), ratio ν_2/ν_1 and ligand field stabilization energy (LFSE), given in Table-3, support the proposed geometry for all the complexes. The ligand and its metal complexes had no inhibitor activity against G(-) *E. coli*. But the content was used 0.2 % ligand and its metal complexes had inhibitory activity against G(-) *S. aureus* and *P. aeruginosa*.

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