



Dinuclear Cu(II), Co(II), Ni(II) and Mn(II) complexes Framework Based on 1-(2-hydroxyphenyl) ethanone ligand: Synthesis, Structural Investigation and Biological properties

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ABSTRACT

Reaction of Benzene-1,4-dicarbaldehyde, 1-(2-hydroxyphenyl)ethanone and 2,6 diaminopyridine with 2,2'-bipyridyl and M(II) salts in ethanol solution afforded homo binuclear Schiff base complexes, which was characterized by various spectroscopic methods. Upon complex formation, the ligand behaves as a dibasic tetradentate species with the involvement of the nitrogen atoms of the pyridine groups, azomethine and phenolic oxygen in coordination for all complexes. These studies revealed octahedral geometries for Mn(II), Co(II), Ni(II), and Cu(II) complexes of general formulae $[M_2LY_2]Z_2$ where Y=2,2'-bipyridyl and Z = acetate ion. The DNA binding properties and cleavage efficiencies of the complexes have been investigated by spectroscopic method, viscosity measurements and agarose gel electrophoresis. The results suggest that binuclear Schiff base complexes can bind to CTDNA in an intercalative mode and can also cleave pUC18DNA. In order to evaluate the biological activity of Schiff bases and their metal complexes, the Schiff-bases and their new metal complexes have been screened for their antibacterial and antifungal activity against bacterial species like- *Bacillus subtilis*, *Staphylococcus aureus* (as Gram-positive bacteria) and *Klebsilla pneumonia* and *Escherichia coli* (as Gram-negative bacteria).

Keywords: Antibacterial activity, Binuclear metal complexes, DNA interaction, Symmetric Schiff base.

INTRODUCTION

The development of new biologically active binuclear Schiff base metal complexes with identical ligating environments has undergone an inspiring growth and significant attention in recent years to study the inorganic perspectives of these metal centers for small molecule activation in biological process. The relative nature of the metal centers and the ligands environment are key issues that determine their physical and chemical behavior of the complexes. Schiff base complexes derived from heterocyclic compounds have found to be augmented interest in the context of bioinorganic chemistry.¹⁻³ Not only they have played a seminal role in the development of modern coordination chemistry, but they can also a key point in the development of inorganic biochemistry.⁴ Heterocyclic compounds such as pyridine, 2, 2'-bipyridine and related molecules are good ligands due to the presence of one or more ring nitrogen atoms with a localized pair of electrons. The application potential has led to the formation of series of novel Schiff base compounds with a wide range of reactivity and stability, physical, chemical and biological properties.⁵⁻⁸ Though anionic Schiff base ligands have been exploited for complexation, those with neutral Schiff base ligands have not been adequately studied. Several Schiff base ligands derived from pyridine derivatives and their copper(II) complexes have also been found to inhibit the growth of tumor cells.⁹

The synthesis and spectral characterizations of dinuclear transition-metal complexes propagated by bridging atoms are of recent interest. The present work deals with the synthesis and characterization of two Schiff-base ligands

derived from Benzene-1,4-dicarbaldehyde and their binuclear Cu^{2+} , Co^{2+} , Ni^{2+} and Mn^{2+} complexes.

Analytical and physical measurements

Elemental analyses for C, H and N were carried out using a Perkin-Elmer 2400-II elemental analyzer. FT-IR data were recorded as KBr disc using Thermo Nicolet, Avatar 370 model spectrometer in the range 4000-400 cm^{-1} . UV-Vis. spectra were obtained in DMF on a Perkin-Elmer Lambda 40(UV-Vis) spectrometer in the range 200-800 nm. Molar conductance of the complexes in DMF was measured using an Elico model conductivity meter. Magnetic susceptibility measurements were carried out by employing the Gouy method at room temperature. NMR signals were obtained from Bruker Avance III, 400MHz model spectrometer. EPR spectra of compounds were recorded on an E-112 ESR Spectrometer with X-band microwave frequency (9.5 GHz). TG studies were carried out in the range between 0-500°C using a NETZSCH model thermal analyzer.

Syntheses of Binucleating Schiff base ligand

To the solution of Benzene-1,4-dicarbaldehyde (1mmol), ethanolic solution of solid 2,6 diaminopyridine (2 mmol) was added and the mixture was stirred until complete dissolution. After the addition of the equimolar amount of 1-(2-hydroxyphenyl)ethanone (2 mmol) the mixture was stirred for 3 hrs at room temperature and a dark solution was formed. After evaporation of this solution, a dark yellow product was formed.

Synthesize of Binuclear Schiff base metal Complexes

A mixture of synthesized Schiff base ligand (1 mmol) and 2,2'-bipyridyl (2 mmol) was added to an ethanolic solution

of solid Metal acetate salt (2 mmol). The reaction mixture was stirred for 3hrs at room temperature. The precipitate was filtered washed with diethyl ether and the collected solid was air dried overnight and then dried in a

desiccator, whereupon dark color precipitate was formed. The structure of complexes was confirmed by spectroscopic techniques.

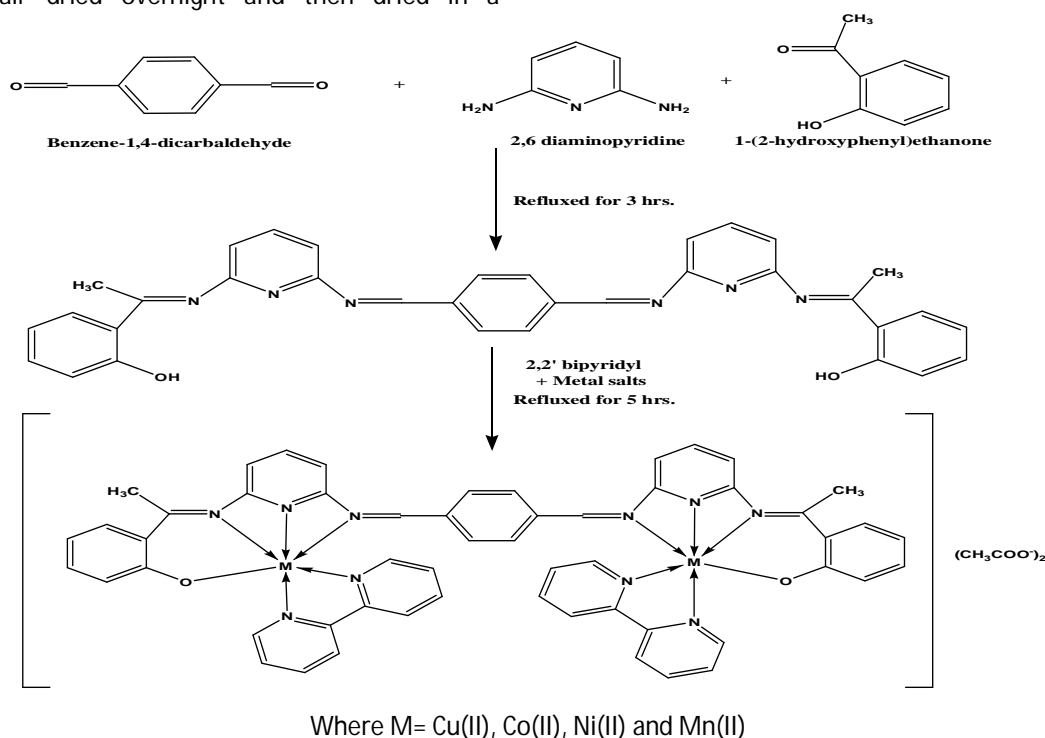


Figure 1: Synthesis pathway for Schiff Base ligand and its Binuclear Schiff base Metal Complexes

Antibacterial assay

The standard disc diffusion method was followed to determine the activity of the synthesized compounds against the sensitive organism *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis* and *Klebsilla pneumonia*. The tested compounds were dissolved in DMF (Which have no inhibition activity). The disc of Whatmann no.4 filter paper having the diameter 8.00 mm were soaked in the solution of compounds in DMF. Uniform size filter paper disks were impregnated by equal volume from the specific concentration of dissolved tested compounds and carefully placed on incubated agar surface. After incubation for 36 hrs at 27°C in the case of *bacteria*, inhibition of the organism which evidenced by clear zone surround each disk was measured and used to calculate mean of inhibition zones.

DNA-binding experiments

Electronic absorption spectroscopy has been widely employed to determine the binding characteristics of metal complexes with DNA. The DNA binding experiments were performed in Tris-HCl/ NaCl buffer (50 mM Tris-HCl/ 1 mM NaCl buffer, pH 7.5) using DMF (dimethylformamide) solution (10%) of the metal complexes. The concentration of calf-thymus (CT) DNA was determined from the absorption intensity at 265 nm. Absorption titration experiments were made using different concentrations of CTDNA [40, 60, 80 μM], keeping the concentration of the complexes constant, with due correction for the absorbance of the CT-DNA

itself. The absorbance (A) was recorded after successive additions of CT-DNA. While measuring the absorption spectra an equal amount of CT-DNA was added to both the compound solution and the reference solution to eliminate the absorbance of the CT-DNA itself. Samples were equilibrated before recording each spectrum.¹⁰

Viscosity measurements were conducted on Ostwald's viscometer at 30 ± 0.01°C using fixed concentration of DNA solution (50 μM) with increasing concentration of chiral Schiff base metal complexes (0–60 μM) in phosphate buffer (10 mM, pH 7.0) for flow time measurements. Each sample was measured in triplicate and the average flow time was calculated with a digital stopwatch. Data were presented as $(\eta/\eta^0)^{1/3}$ versus the ratio of the concentration of the compound and DNA, where η is the viscosity of DNA in the presence of the complex, and η^0 is the viscosity of DNA alone.¹¹

DNA cleavage experiments

For the gel electrophoresis experiments, supercoiled pUC18 DNA was treated with synthesized complexes in Tris buffer (50 μM H₂O₂ in Tris-HCl buffer pH 7.2), and the solution was irradiated at room temperature with a UV lamp (365 nm, 10 W). After being incubated at 37 °C for 2 hrs, electrophoresis was carried out at 50 V for 2 h in Tris-acetic acid- EDTA buffer. Electrophoresis was carried out and bands were visualised by UV light and photographed to determine the extent of DNA cleavage from the intensities of the bands.¹²

RESULTS AND DISCUSSION

The binucleating Schiff base ligand and its corresponding dinuclear complexes were obtained as solid, air stable, sparingly soluble in common organic solvents but soluble in DMSO, DMF and acetonitrile. The stoichiometry of the complexes was established on the basis of their elemental analysis. The results of elemental analysis are presented in Table 1. The structure pattern and geometry (Figure 1)

of the complexes were assigned on the basis of the physico-chemical parameters. The conductance of the acetate complexes were carried out in DMF and the values were found to be in the range 143-152 $\text{ohm}^{-1}\text{cm}^2\text{mol}^{-1}$ suggesting that the complexes belong to 1:2 electrolytes. This indicates that the acetate is not coordinated to the metal in solution.

Table 1: Analytical data of the Schiff base ligand and its binuclear metal complexes

Compound	Molecular Formula	color	M. Wt	Melting Point (°)	% of Nitrogen		% of Metal		Molar conductance $\text{scm}^2\text{mol}^{-1}$
					Cal	Exp	Cal	Exp	
L ₁	C ₃₄ H ₂₈ N ₆ O ₂	Yellow	552.625	165	15.20	15.18	-	-	-
[Cu ₂ L ₁ X ₂]Y ₂	C ₅₈ H ₄₈ Cu ₂ N ₁₀ O ₆	Dark green	1108.16	>200	12.63	12.62	11.49	11.47	143
[Co ₂ L ₁ X ₂]Y ₂	C ₅₈ H ₄₈ Co ₂ N ₁₀ O ₆	Brown	1098.93	>200	12.74	12.70	10.72	10.69	150
[Ni ₂ L ₁ X ₂]Y ₂	C ₅₈ H ₄₈ Ni ₂ N ₁₀ O ₆	Brown	1098.45	>200	12.75	12.71	10.68	10.66	147
[Mn ₂ L ₁ X ₂]Y ₂	C ₅₈ H ₄₈ Mn ₂ N ₁₀ O ₆	Black	1090.94	>200	12.83	12.79	10.07	10.05	152

Table 2: Infrared spectroscopic data of the Schiff base ligand and its binuclear metal complexes

Compound	Free-OH	ν (C=N)	Pyridine ring deformations	ν (C-O)	ν (M-O)	ν (M-N)	μ_{eff} (B.M)
L ₁	3436	1621	565, 406	1280	-	-	
[Cu ₂ L ₁ X ₂]Y ₂	-	1605	618, 426	1297	557	452	1.67
[Co ₂ L ₁ X ₂]Y ₂	-	1602	645, 441	1303	580	458	4.84
[Ni ₂ L ₁ X ₂]Y ₂	-	1607	655, 422	1299	579	445	2.90
[Mn ₂ L ₁ X ₂]Y ₂	-	1609	632, 435	1304	577	456	5.91

Table 3: Antimicrobial activity of Schiff base ligand and its binuclear metal complexes

Compound	Diameter of inhibition zone (mm)															
	Bacillus subtilis				Staphylococcus aureus				E-Coli				Klebsilla pneumonia			
	Concentrations ($\mu\text{g}/\text{mL}$)															
	25	50	75	100	25	50	75	100	25	50	75	100	25	50	75	100
L	+	++	++	++	+	++	++	++	+	++	++	++	+	+	+	++
[Cu ₂ L ₁ X ₂]Y ₂	++	++	++	+++	++	++	++	++	++	++	+++	+++	++	++	++	++
[Co ₂ L ₁ X ₂]Y ₂	++	++	++	+++	++	++	++	+++	++	++	+++	++++	++	++	++	+++
[Ni ₂ L ₁ X ₂]Y ₂	++	++	++	++	+	++	++	++	++	++	++	++	+	++	++	++
[Mn ₂ L ₁ X ₂]Y ₂	+	++	++	++	+	++	++	++	+	++	++	++	+	++	++	++
Streptomycin	++	++	++	+++	++	++	++	+++	++	++	+++	++++	++	++	++	++++

-No inhibition zone=inactive; 1-10 mm(+) = less active; 11-20 mm(++) = moderately active; 21-30 mm(+++) = highly active

IR spectra

The IR spectrum of the ligand (L) shows a ν (C=N) peak at 1621 cm^{-1} , and the absence of a ν (C=O) peak at around 1700 cm^{-1} . These observations confirm the condensation of Benzene-1,4-dicarbaldehyde, 2,6 diaminopyridine and 1-(2-hydroxyphenyl)ethanone. The IR spectra of all complexes show ν (C=N) bands at 1602– 1610 cm^{-1} and it is found that the ν (C=N) bands in the complexes are shifted to lower energy regions compared to that in the free ligand (L). This phenomenon appears to be due to the coordination of azomethine nitrogen to the metal ion¹³. The ν OH band of the ligand is seen at 3436 cm^{-1} and its absence in the complexes is due to the involvement of

the phenol O in bonding to the metal ions. The IR spectrum showed a medium intensity band at 1116 cm^{-1} , which is characterized of the coordinated pyridine nitrogen base. The shift in the bands due to in plane and out of plane deformation of pyridine of the ligand from 565 and 406 cm^{-1} to 655-618 and 441-422 cm^{-1} (Table 2) respectively in case of metal complexes indicate the coordination of pyridine nitrogens.

Further support for this coordination were indicated by the appearance of new bands 557-580 and 445-458 cm^{-1} in the infrared of the complexes are assigned to M-O and M-N stretching vibration, respectively.¹⁴ The band at 1442 cm^{-1} and 1519 cm^{-1} were due to symmetric stretching

frequency and asymmetric frequency of acetate ion. This result predicts that the acetate ions were coordinated outside the coordination sphere. The above discussion reveals that the metal ions form coordination complexes through carbonyl oxygen, azomethine nitrogen and hetero-atoms.

Electronic spectra and Magnetic Moment

The electronic spectra of the complexes in DMF solution and the spectrum of Schiff base ligand, L exhibits band at 250 nm, 285 nm, 340 nm attributable to $\pi-\pi^*$ transitions of aromatic benzene ring and imino group and $n-\pi^*$ transitions of imino group.¹⁵ In the complexes these bands are shifted to longer wavelengths as an outcome of coordination when binding with metal, thus confirming the formation of Schiff base metal complexes. $[\text{Cu}_2\text{L}_1\text{X}_2]\text{Y}_2$ complex gave only one band due to ${}^2\text{E}_g \rightarrow {}^2\text{T}_{2g}$ transition at 695 cm^{-1} and charge Transfer Transition was observed in the range of 445 nm. This electronic spectral data conclude the suggested octahedral geometry for the synthesized $[\text{Cu}_2\text{L}_1\text{X}_2]\text{Y}_2$ complex. The magnetic moment for Cu(II) complex is 1.67 B.M. this clearly shows that there is no major spin interactions.¹⁶ These bands are shifted when compared to the ligand, indicating the involvement of imine and pyridyl nitrogen in coordination with copper atom. The octahedral geometry for the dark coloured complex of $[\text{Co}_2\text{L}_1\text{X}_2]\text{Y}_2$ as confirmed by magnetic moment 4.84 B.M the observation of two bands in the visible region. The assignment of the two most intense bands ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{2g}(\text{F})$, ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}(\text{P})$ to the spin allowed transitions from the ${}^3\text{A}_{2g}$ ground shows octahedral arrangement around nickel(II) ions^{17,18}. The Mn(II) binuclear complex shows bands at 550, 685 nm respectively corresponds to ${}^6\text{A}_{1g} \rightarrow {}^4\text{E}_g(4\text{D})$, ${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{2g}(4\text{G})$ transitions which are compatible to an octahedral geometry around manganese(II) ion.^{19,20}

ESR spectra

The ESR spectra of the binuclear Cu(II) complexes were recorded at room temperature. The observed $g_{\parallel} = 2.257$ and $g_{\perp} = 2.059$ values of the Cu(II) complex under present study followed the same trend $g_{\parallel} > g_{\perp} > g_e$ ($g_e = 2.0036$ free ion value) which suggest that the presence of unpaired electron with ${}^2\text{B}_{1g}$ as ground state lies in dx^2-y^2 orbital giving octahedral geometry.²¹ $G = (g_{\parallel} - 2) / (g_{\perp} - 2)$ which measures the exchange interaction between Cu(II) centres. The observed $G = 4.92$ for the complex under present study evidenced the monomeric nature of the binuclear Schiff base Cu(II) complex and indicates that there is no spin exchange interaction in the copper complexes and hence distorted octahedral geometry proposed for the Cu(II) complex.

¹H NMR spectrum

The ¹H NMR spectra of the H₂L, ligand dissolved in dimethyl-sulphoxide, DMSO-*d*₆. The signals at 10.7 ppm were assigned to the protons of the phenolic OH group due to the effect of the hydrogen bonds with the azomethine group. The presence of the azomethine

group is also characterized as a singlet at 8.86 ppm.²² The aromatic protons of the ligands showed multiplets at $\delta = 7.96-6.71$ assigned to both phenyl and bipyridyl protons of H₂L. These protons, in each case, could not be distinguished from each other. These chemical shifts may be compared with those of literature.^{23,24}

Antibacterial studies

The synthesized ligand and its binuclear metal complexes were tested for their in vitro antibacterial activity. Significant inhibitory data was observed in the screening Table 3. The susceptibilities of certain strains of bacteria cultures to Schiff base and their complexes were evaluated by measuring the size of the bacteriostatic diameter. This enhancement in the activity may be to the structures of Schiff base ligand by possessing an azomethine (C=N) linkage.

The toxic activity of the complexes with the ligand can be ascribed to the increase in the lipophilic nature of the complexes arising from chelation. The mode of action of complexes involves the formation of hydrogen bonds with the imino group by the active sites leading to interference with the cell wall synthesis. This hydrogen bond formation damages the cytoplasmic membrane and the cell permeability may also be altered leading to cell death. The higher activity of Cu(II) complexes can be explained as, on chelation the polarity of Cu(II) ion is found to be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the copper ion with donor groups. Therefore, Cu(II) ions are adsorbed on the surface of the cell wall of microorganisms. The adsorbed Cu(II) ions disturb the respiratory process of the cells, thus blocking the synthesis of proteins and this, in turn, restricts further growth of the organisms.²⁵

Hence the Schiff base complexes have more antibacterial, and this effect may be due to the presence of -ph, -OH and -N=C- groups which are electron releasing. The antibacterial results evidently showed that the activity of the ligand became more pronounced when coordination to the metal ions.

Absorption spectral characteristics of DNA binding

The interactions of metal complexes with DNA have been the focus of interest for the progress of effective chemotherapeutic agents. Transition metal centres with their well-defined coordination geometries and distinctive electrochemical or photophysical properties, enhances the functionality of the binding agent. Currently, spectrophotometric DNA titration appears to be the most commonly used method to determine DNA binding modes with metal complexes. The complexes binding to DNA through intercalation usually results in hypochromism with or without a small red or blue shift, due to the intercalation mode involving a strong stacking interaction between the planar aromatic chromophore and the base pairs of DNA.²⁶ The absorption spectrum of Cu(II) complex in the absence and presence of CT-DNA are

shown in Figure 2. Whereas, the absorption band of the Cu(II) complex at 378 nm exhibits the same phenomenon of hypochromism with a blue shift of about 5 nm. These spectral characteristics reveal that the complexes interact with CT-DNA most likely through an interaction mode that involves π - π stacking interaction between the aromatic chromophore and the base pairs of DNA. The extent of hypochromism depends on the strength of the intercalative DNA binding interaction of metal complexes and these outcome shows that the absorbance decreases with increase in addition of DNA to the metal complexes.²⁷

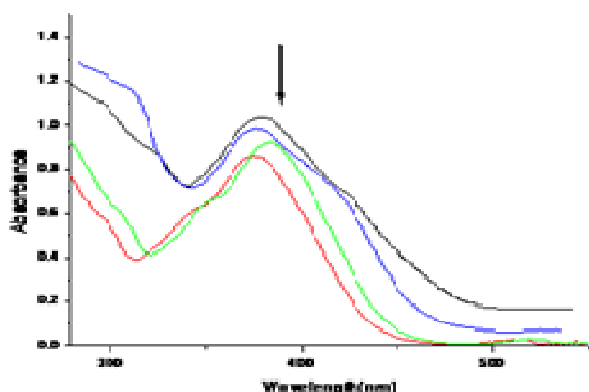


Figure 2: Electronic spectra of complexes $[Cu_2L_1X_2]Y_2$ in DMF in the absence and presence of plasmid DNA. Arrow shows the absorbance changes upon increasing DNA concentrations.

Table 4: Absorption properties of Binuclear Schiff Cu(II) complexes-DNA Binding Activity

Complexes	λ_{max} (nm)		$\Delta\lambda$ (nm)
	Free	Bound	
$[Cu_2L_1X_2]Y_2$	378	383	5.0
$[Co_2L_1X_2]Y_2$	382	385	3.0
$[Ni_2L_1X_2]Y_2$	393	398	5.0
$[Mn_2L_1X_2]Y_2$	396	400	4.0

Viscosity measurements

The viscosity measurements of CT-DNA are regarded as the most essential tests for binding model in solution. A classical intercalation model demands that as the base pairs separates, DNA helix lengthens to accommodate the bound complexes, leading to the increase of DNA viscosity. In contrast, complexes that binds exclusively in the DNA by partial and/or non classical intercalation, under the same conditions, typically cause less pronounced (positive or negative) or no change in viscosity.²⁸ The values of the relative specific viscosities for complex $(\eta/\eta_0)^{1/3}$, were plotted against $[Complex]/[DNA]$ (Figure 3). Hence the observed increase in viscosity indicates intercalative mode of the complexes.²⁹

DNA Cleavage Studies

Agarose gel electrophoresis assay is an effective method to investigate various binding modes of synthesized

complexes to supercoiled DNA. Natural-derived plasmid DNA mainly has a closed-circle supercoiled form (Form I), as well as nicked form (Form II) and linear form (Form III) as small fractions. Intercalation of synthesized complexes to plasmid DNA can loosen or cleave the supercoiled form DNA, which decreases its mobility rate and can be separately visualized by agarose gel electrophoresis method. To assess the DNA cleavage ability of the free ligand and copper(I) complex, supercoiled (SC) pUC18 DNA was incubated in 5 mM Tris-HCl/50 mM NaCl buffer at pH 7.2 for 2 h. The relatively fast migration is the intact supercoil form (Form I) and the slower moving migration is the open circular form (Form II), which was generated from supercoiled. The binuclear Schiff base metal complexes is able to perform cleavage of pUC18 DNA (lane 3, 4, 5, and 6; Figure 4). The supercoiled SC (Form I) gradually converted to nicked form NC (Form II). The production of a hydroxyl radical due to the reaction between the metal complex and oxidant may be explained as shown below

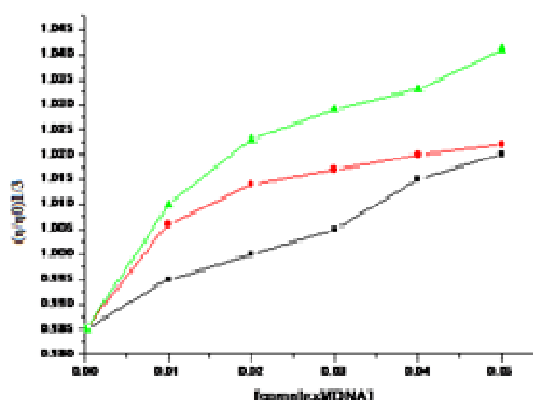
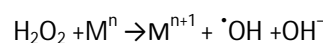


Figure 3: Effect of increasing amounts 1) $[Cu_2L_1X_2]Y_2$ complex 2) $[Co_2L_1X_2]Y_2$ complex and 3) $[Ni_2L_1X_2]Y_2$ complex on the relative viscosities of DNA at 30.0 ± 0.1 °C. $[DNA] = 1$ mM, $[Complex]/[DNA] = 0, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06$, respectively.

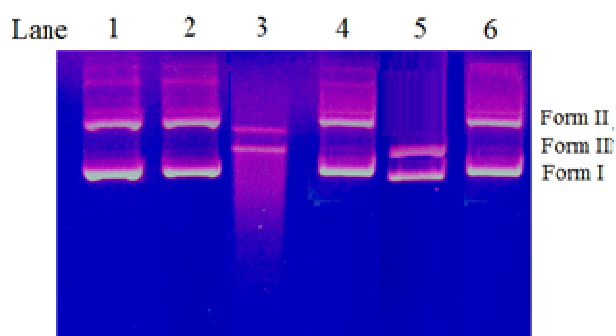


Figure 4: Changes in the agarose gel electrophoretic pattern of pUC18DNA induced by H_2O_2 and metal complexes. From left to right: Lane 1-DNA alone; Lane 2-DNA alone + H_2O_2 ; Lane 3-DNA + $[Cu_2L_1X_2]Y_2$ + H_2O_2 ; Lane 4-DNA + $[Co_2L_1X_2]Y_2$ + H_2O_2 ; Lane 5-DNA + $[Ni_2L_1X_2]Y_2$ + H_2O_2 ; Lane 6-DNA + $[Mn_2L_1X_2]Y_2$ + H_2O_2 .

The OH• free radicals participate in the oxidation of the deoxyribose moiety, followed by hydrolytic cleavage of a sugar phosphate back bone. The increase in hydroxyl radical leads to the pronounced nuclease activity in the presence of oxidant H₂O₂. Control experiments using DNA alone do not show any significant cleavage of pUC18 DNA even on longer exposure time. From the observed results, it is concluded that all the complexes effectively cleave the DNA as compared to control DNA.³⁰

CONCLUSION

In conclusion, the synthesis, structural elucidation and DNA interaction properties of new binuclear Schiff base metal complexes have been reported in this paper. The DNA-binding results revealed that the complexes can bind CT-DNA moderately in an intercalation mode. The synthesized complexes show DNA cleavage activity via hydroxyl radical pathway. The anti-bacterial activity screening results of the tested compounds proved that both the ligands and the complex combinations have specific anti-microbial activity, depending on the microbial species tested.

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