

Synthesis, Characterization and Biological Activity of Schiff Base Metal Complexes Derived from 2, 4-Dihydroxyactophenone

RAJU ASHOKAN¹, SARAVANAN SATHISHKUMAR¹,
EKAMPARAM AKILA² and RANGAPPAN RAJAVEL^{2*}

¹ Department of Chemistry, Periyar University, Salem-11, Tamilnadu, India

² Department of Chemistry, Sri Saradha College for Women, Salem-16, Tamilnadu, India
drrajavelpu@gmail.com

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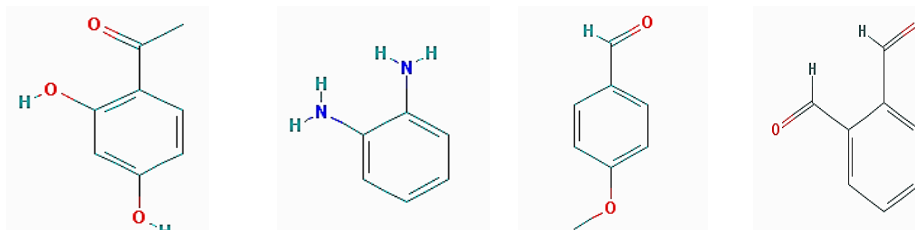
Abstract: A new series of Co(II), Cu(II), Mn(II) and Ni(II), complexes were prepared with ligand derived by condensation of 2,4-dihydroxyactophenone, *o*-phenylenediamine, anisaldehyde with *o*-phthalaldehyde. The Schiff base and its metal complexes were characterized on the basis of various spectroscopic investigation like IR, ¹H NMR, Photoluminescence and thermal analyses. The geometry of the complexes was confirmed by electronic spectra, magnetic moment measurements and ESR analysis. The Co(II), Cu(II), Mn(II) and Ni(II) complexes have also been studied for their plasmid (pUC18) DNA cleavage activity.

Keywords: Schiff base, 2,4-Dihydroxyactophenone, DNA cleavage, Anisaldehyde, *O*-phthalaldehyde

Introduction

Schiff base ligands have significant importance in chemistry; especially in the development of Schiff base complexes, because Schiff base ligands are potentially suitable of forming stable complexes with metal ions. Many Schiff base complexes show excellent catalytic activity in various reactions in the presence of moisture. Over the past few years, there has been much report on their applications in homogeneous and heterogeneous catalysis, hence the need for a review article highlighting the catalytic activity of Schiff base complexes¹. The development of the field of bioinorganic chemistry has increased the interest in Schiff base complexes, it has been recognized that many of these complexes may serve as models for biologically important species. Schiff base metal complexes have been studied extensively because of their attractive chemical and physical properties and their wide range of applications in numerous scientific areas. They play role in both synthetic and structural research, because of their preparative accessibility and structural diversity². Schiff bases of *o*-phenylenediamine and its complexes have a variety of applications including biological, clinical and analytical. Present investigation deals with the syntheses, spectral characterization,

thermal properties and DNA cleavage studies of series of Co(II), Cu(II), Mn(II) and Ni(II) metal complexes with four new Schiff base ligands derived from 2,4-dihydroxyacetophenone, *o*-phenylenediamine, anisaldehyde with *o*-phthalaldehyde³ (Figure 1).



2,4-Dihydroxyacetophenone *o*-Phenylenediamine Anisaldehyde *o*-Phthalaldehyde

Figure 1. Structure of compounds

Experimental

Schiff base ligand was prepared according to the literature procedures. Microbial studies were carried out according to reported procedures and DNA cleavage agarose gel electrophoresis by DNA binding studies by titration method.

Synthesis of Schiff base (H_2L_1)

The Schiff base ligands were synthesized according to the general procedure. To an ethanolic solution of 2,4-dihydroxyacetophenone (2 mmol), *o*-phenylenediamine (2 mmol) and anisaldehyde (1 mmol) with *o*-phthalaldehyde (2 mmol) was added in drop wise. The reaction mixture was kept on water bath for refluxion. It was stirred for 3 h. Pale yellow color solid was separated and were filtered off, washed with 5 mL of cold ethanol and then dried in air. Yield: 73%. M.p: 146-157 °C. Anal.Calc. For $C_{38}H_{30}NO_6Cl_2$: C, 67.21; H, 3.17; N, 8.26. Found: C, 69.91; H, 3.51; N, 7.35. (%). IR (KBr pellet, cm^{-1}): 3305 ν (-OH); 1691 ν (-CH=N) ; 1259 (-C-O). UV-Vis λ_{max} (nm), 280, 293 ($\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$). 1H NMR (DMSO, δ ppm): 6.1-7.3 ppm (m, Ar-H), 8.30 ppm (s, CH=N), 9.6 ppm (Ph-OH).

Synthesis of complexes

The ligand L_1 and L_2 was stirred with heating on water bath where upon a reddish brown solution was produced^{4,6}. The contents were cooled to room temperature and a solution of metal acetate (0.01 mol) in DMF was added drop wise. The resulting mixture was stirred for 3 h with heating on a water bath. The product was filtered by suction, washed with ethanol and dried *in vacuo*⁷.

Synthesis of metal complexes

An ethanolic solution (20 mL) containing L_1 (2,4 dihydroxyacetophenone(2 mmol), *o*-phenylenediamine (2 mmol), L_2 anisaldehyde (2 mM), *o*-phenylenediamine (2 mmol) were added to a solution of metal acetates of Co(II), Cu(II), Mn(II) and Ni(II) (1 mM) in 25 mL of ethanol. The solution was refluxed for 3 h and then allowed to stand at room temperature for 24 h. The product (Scheme 1) was filtered by suction and dried *in vacuum*⁸.

Physical data of Cu(II) ($C_{38}H_{30}NO_6Cl_2$)

Yield: 65%. M.p: 203-217 °C. Anal.Calc. For Cu(II)($C_{38}H_{30}NO_6Cl_2$): C, 67.71; H, 4.54; N, 7.81; Cu, 8.58. Found: C, 67.01; H, 4.73; N, 7.95; Cu, 8.94 (%). IR (KBr pellet, cm^{-1}): 1619

(-CH=N) ; 1216 (-C-O) ; 480 (-M-N) ; 579 (-M-O). UV-Vis λ_{\max} (nm), 290, 301 ($\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$, L \rightarrow MCT); 520, 575, 625 (d \rightarrow d). μ_{eff} (BM): 1.74.

Physical data of Mn(II) ($C_{38}H_{30}NO_6Cl_2$)

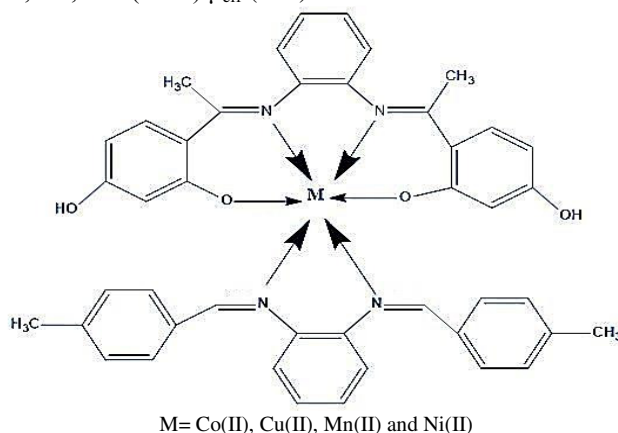
Yield: 64%. M.p: 218-225 °C. Anal.Calc. For Mn(II)($C_{38}H_{30}NO_6Cl_2$): C, 68.35; H, 4.38; N, 7.91; Mn, 7.69. Found: C, 67.59; H, 4.94; N, 7.79; Mn, 7.42 (%). IR (KBr pellet, cm^{-1}): 1782 (-CH=N) ; 1603 (-C-O) ; 463 (-M-N) ; 596 (-MO). UV-Vis λ_{\max} (nm), 281,317 ($\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$, L \rightarrow MCT); 647 (d \rightarrow d). μ_{eff} (BM): 5.73.

Physical data of Ni (II)($C_{38}H_{30}NO_6Cl_2$)

Yield: 74%. M.p: 241-259 °C. Anal.Calc. For Ni(II)($C_{38}H_{30}NO_6Cl_2$): C, 68.42; H, 4.71; N, 7.92; Ni, 7.57. Found: C, 69.71; H, 4.69; N, 7.31; Ni, 7.73 (%). IR (KBr pellet, cm^{-1}): 1623 (-CH=N); 1284 (-C-O); 459 (-M-N) ; 533 v(-M-O). UV-Vis λ_{\max} (nm), 280, 385, 465 ($\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$, L \rightarrow MCT); 513,555, 618 (d \rightarrow d). μ_{eff} (BM): 3.08.

Physical data of Co(II) ($C_{38}H_{30}NO_6Cl_2$)

Yield: 69%. M.p: 221-234 °C. Anal.Calc. For Co(II)($C_{38}H_{30}NO_6Cl_2$): C, 67.21; H, 4.73; N, 7.91; Co, 7.59. Found: C, 66.31; H, 4.53; N, 7.96; Co, 7.94 (%). IR (KBr pellet, cm^{-1}): 1729 (-CH=N); 1317 (-C-O); 497 (-M-N); 510 (-M-O). UV-Vis λ_{\max} (nm), 285, 320, ($\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$, L \rightarrow MCT); 510,563, 609 (d \rightarrow d). μ_{eff} (BM): 4.81.



Scheme 1. Structure of Schiff Base metal(II) complexes

Methodology for DNA cleavage study

Preparation of culture media DNA cleavage experiment was done according to the literature. Nutrient broth (10 g/L of peptone, 5 g/L of yeast extract, and 10 g/L of NaCl) was used for the culturing of Calf-thymus. After 50 mL of medium was prepared, it was autoclaved for 15 min at 121 °C under 15 lb of pressure⁹⁻¹¹. The autoclaved medium was inoculated with the seed culture and incubated at 37 °C for 24 h. DNA-Binding Experiments Electronic absorption spectroscopy has been widely employed to determine the binding characteristics of metal complexes with DNA¹².

Results and Discussion

The interaction of Co(II), Cu(II), Mn(II) and Ni(II) metal acetates with ligand L_1L_2 result in the formation of complexes have the general composition $[M(L_1L_2)]$. Where M = Co(II),

Cu(II), Mn(II) and Ni(II), L_1 = 2,4 dihydroxyactophenone, *o*-phenylenediamine, L_2 = *o*-phenylenediamine and anisaldehyde.

Thermogravimetric analysis

The TGA curve of the Cu(II) complex I_a is stable upto 120 °C. In the Cu(II) complex a weight loss of 12-14% was observed at a temperature range (Figure 2) of 244-249 °C corresponding to the removal of one acetate group. The complexes show a step weight loss of 27-29%. In the temperature range 343-372 °C corresponding to the elimination of part of the Schiff base ligand groups from the coordination sphere of the complex. The final residue corresponds to Cu(II) > 800 °C.

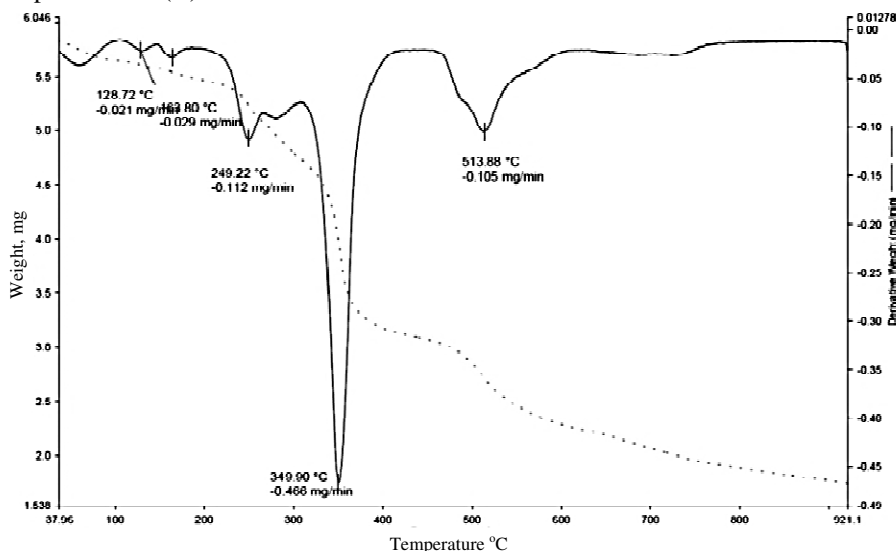


Figure 2. Thermogravimetric analysis of Cu(II) L_1L_2 complexes

Infrared spectra

The IR spectra provide valuable information regarding the nature of functional group attached to the metal atom. In order to study the bonding mode of Schiff base to the metal complexes, the IR spectrum of the free ligand is compared with the spectra values of the complexes. A band at 1660 cm^{-1} in free Schiff base is due to the stretching vibration of azomethine [$\nu\text{C}=\text{N}$]. The shifting of this group to lower frequency (1627-1688 cm^{-1}) in the metal complexes when compared to free ligand, suggests the coordination of metal ion through nitrogen of azomethine group¹³. New bands, which are not present in the (Figure 3) spectrum of ligand, appeared in the spectra of complexes in the range of 727-767 cm^{-1} corresponding to $\nu\text{M}-\text{N}$ and 623-662 cm^{-1} to $\nu\text{M}-\text{O}$ vibrations respectively. The appearance of vibrations $\nu(\text{M}-\text{N})$ and $\nu(\text{M}-\text{O})$ support the involvement of N and O atoms in complexation with metal ions. Therefore the IR spectral data indicate that the coordination sites of the metal ion are $-\text{C}=\text{N}$.

^1H -NMR spectra analysis

The ^1H NMR range of ligand (Cu(II) L_1L_2), (Figure 4) in DMSO solvent shows a particular signal at (δ = 10.93 ppm) correspondent to two protons assigned to (O-H) group¹⁴. Two protons of ($\text{C}_5\text{-OH}$, $\text{C}_{30}\text{-OH}$) group give the impression as a singlet signal at (δ = 13.1 ppm)¹⁵⁻¹⁶.

Two protons of ($\text{N}=\text{C}_7\text{-H}$, $\text{N}=\text{C}_{28}\text{-H}$) imine group appears as a singlet signal at ($\delta=8.36$ ppm). Two protons of ($\text{N}=\text{C}_{14}\text{-H}$, $\text{N}=\text{C}_{21}\text{-H}$) imine group appears as a single signal at ($\delta = 9.93$ ppm). The multiple signal at ($\delta = 6.33$ ppm), (7.23), (7.33), (7.46), (7.53), (7.63), (7.95) ppm are due to aromatic hydrogen of carbon^{17,18}.

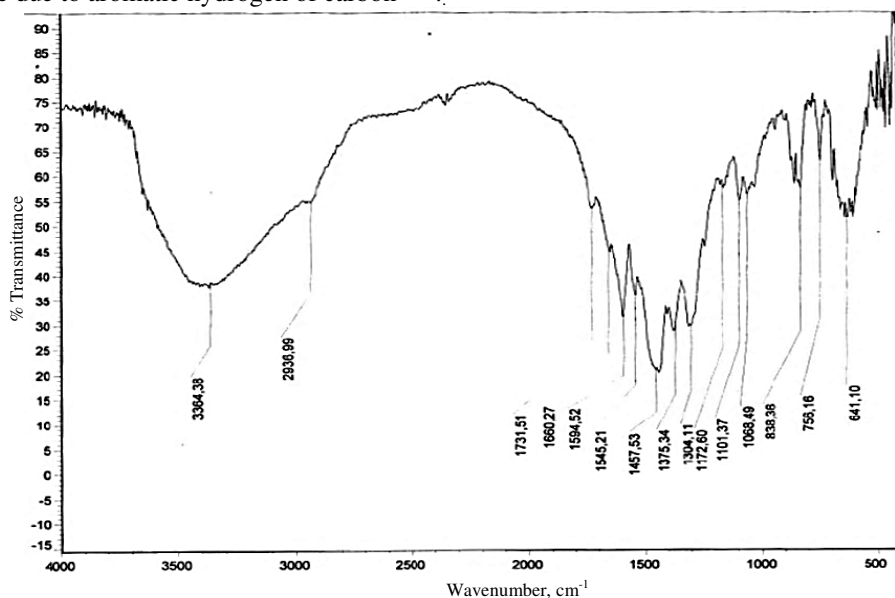


Figure 3. FTIR spectra for complex compounds of $\text{Cu(II)}\text{L}_1\text{L}_2$

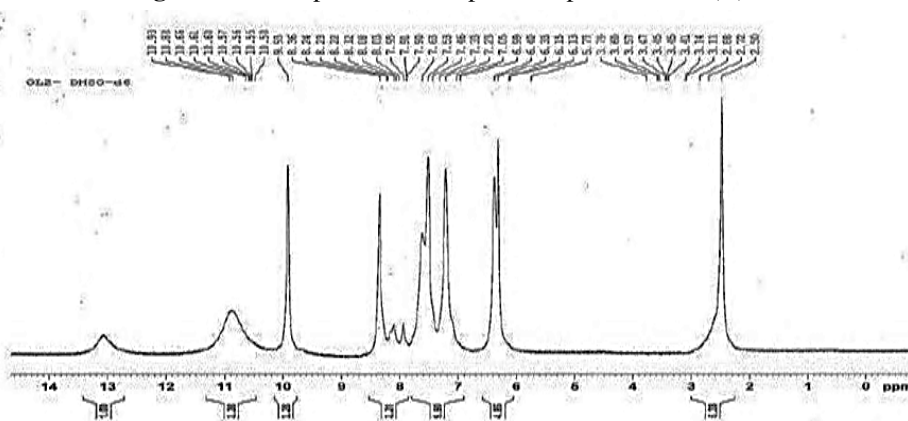


Figure 4. ^1H NMR spectrum of the ligand ($\text{Cu(II)}\text{L}_1\text{L}_2$)

Electronic spectra and magnetic moments

The electronic absorption spectral data of the ligand and its metal complexes were recorded. The UV-Vis spectra of complexes show a band at 610 nm, 600 nm and 620 nm respectively, corresponding to d-d transitions which are consistent with the octahedral geometry¹⁹. In the band at 445 nm for 1, 2 and 450 nm for 3 are due to $n \rightarrow \pi^*$ transitions of azomethine ($\text{C}=\text{N}$) function of Schiff base and remaining bands in the UV region at 300 nm for 1, 2 and 400 nm for 3 are due to $\pi \rightarrow \pi^*$ transitions of Schiff base respectively.

Photoluminescence spectra

The photoluminescence spectra of Schiff base and its Co(II), Cu(II), Mn(II) and Ni(II) complexes were recorded in DMSO with an excitation wavelength of 265 nm. The most enhancement in fluorescent intensity of metal complexes was observed in the case of Cu(II) complexes (Figure 5), with emission band observed at 497 nm as they are difficult to oxidize or reduce due to their stable d^{10} configuration. The emission bands for Co(II), Cu(II), Mn(II) and Ni(II) were observed at 471 nm, 406 nm and 403 nm, respectively²⁰. A weak fluorescent emission band at 370 nm was observed for Schiff base. The enhancement are in the order of Cu(II) > Co(II) > Mn(II) > Ni(II) > Schiff base. These enhancements in the fluorescent intensity of metal complexes show that Schiff base is one of the good chelating agents. Thus, Schiff base and metal complexes are fluorescent in nature and they open a way for the photochemical applications of the complexes²¹.

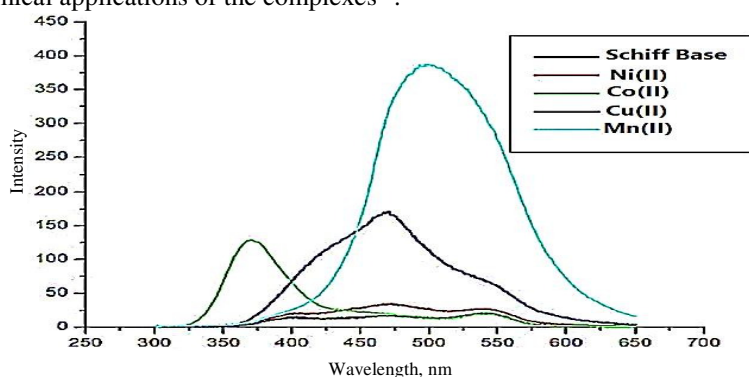


Figure 5. Photoluminescence spectra of Schiff base and its metal complexes

ESR Spectra

The X-band ESR spectra of complex Cu(II) was recorded in DMSO at room temperature. The spectra of copper complex exhibited anisotropic signals (Figure 6) with $g_{\parallel} = 2.17$ and $g_{\perp} = 2.04$, and $g_{\parallel} = 2.14$ and $g_{\perp} = 2.03$ respectively, which is a characteristic of the axial symmetry²². The observed g -tensor values were $g_{\parallel} (2.23) > g_{\perp} (2.17) > g_e (2.04)$ suggested the complex have octahedral geometry. An exchange coupling interaction between two Cu(II) ions was explained by Hathaway expression $G = (g_{\parallel} - 2)/(g_{\perp} - 2)$. If the value $G > 4.0$, the exchange interaction is negligible and if $G < 4.0$, a considerable exchange coupling is [Figure 5] present in the complex.

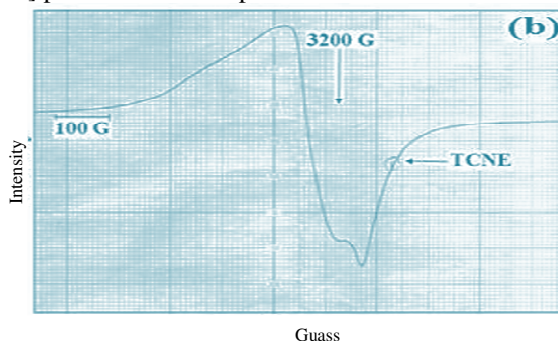


Figure 6. The ESR spectra of the [Cu(II)L₁L₂]

In the present complex, the 'G' value (4.25) is > 4 indicating that there is no interaction in the complex. In addition the absence of a half field signal at 1600 G corresponding to $DM = \pm 2$ transitions indicates the absence of any Cu–Cu interaction in the complex. Kivelson have shown that for an ionic environment g_{\parallel} is 2.3 or larger, but for a covalent environment g_{\parallel} is less than 2.3. The g_{\parallel} values for the present complex were 2.17, indicating a significant degree of covalency in the metal–ligand bond²³.

Cyclic voltammetry

The copper complex (0.001 M in DMF) was scanned in the potential range of -1.0 V to 1.0V in deareated condition with scan rate 0.1V/s. A cathodic peak observed in the voltammograms in the range $E_{pc} = 0.15$ to 0.07 V evidences the reduction of metallic species, Cu(II)L₁L₂. The reverse scan shows (Figure 7) two anodic peaks with potentials in the range $E_{pa1} = -0.1$ to -0.5V and $E_{pa2} = 0.35$ to 0.68V corresponding to the oxidation reactions Cu(II)L₁L₂. The Cu(II) complex display a quasireversible cyclic voltammetric response which can be assigned to the Cu(II)/Cu(I) couple near 0.45 V in DMF²⁴.

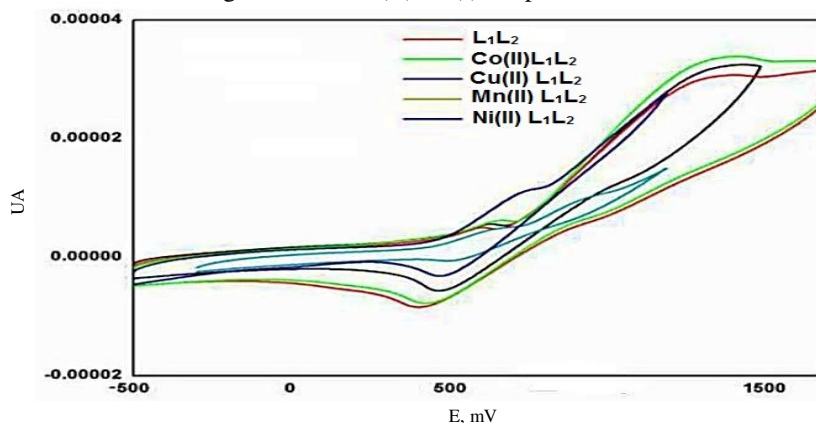


Figure 7. Cyclic voltammogram of synthesized complexes

DNA Binding studies

DNA Binding – Electronic absorption study

Electronic absorption spectroscopy transition metal complexes can bind to DNA through covalent bonding via replacement of a labile ligand of the complex by a nitrogen base of DNA such as guanine N₇ or non-covalent interactions such as intercalation, electrostatic, or groove binding²⁵. Electronic absorption spectroscopy is one of the most useful techniques in DNA binding studies since the observed changes in the spectra may give indication of the mode of interaction. The π - π^* intra ligand absorption bands with λ_{max} in the region 200-320 nm were used to monitor the interaction of compounds L₁–C₈ with double helical CT-DNA. The UV spectra have been recorded for a constant compound concentration in diverse [DNA]/[compound] ratios(r). The changes observed in the intra ligand transition of the compounds L₁–C₈ upon addition of CT-DNA solution in diverse r values may reveal the existence of interaction between each compound and DNA and may indicate the possible mode of binding²⁶.

Upon increasing the CT-DNA concentration, the UV spectra of compound-DNA solutions show a gradual decrease in the intensities of the absorption bands (hypochromism)

(Figure 8) for all compounds without any apparent red shift²⁷. The observed hypochromism may be attributed to stacking interaction between the aromatic chromophores of the free and bound ligands and DNA base pairs probably due to intercalation.

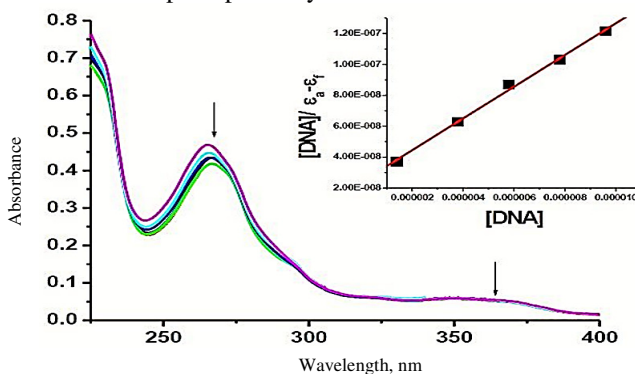


Figure 8. Electronic Absorption Spectroscopy complexes in Cu(II)L₁

DNA Cleavage studies

DNA cleavage is measured by relaxation of supercoiled pUC18 DNA to nicked circular conformation and linear conformation. During electrophoresis process supercoiled DNA will migrate faster when compared with DNA in nicked and linear confirmations. Figure 9 illustrates the gel electrophoresis experiments showing the cleavage of plasmid pUC18 DNA induced by the metal complexes interest of the study.

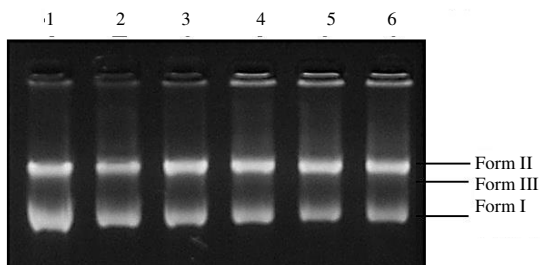


Figure 9. Changes in the Agarose gel electrophoresis pattern of pUC18, induced by H₂O₂ and metal complexes Lane 1 – pBR322 DNA - Control, Lane 2 – DNA + H₂O₂ (1 mM), Lane 3 – DNA + H₂O₂ (1 mM) + Cu, Lane 4 – DNA + H₂O₂ (1 mM) + Ni, Lane 5 – DNA + H₂O₂ (1 mM) + Mn, Lane 6 – DNA + H₂O₂ (1 mM) + Co respectively

DNA with newly synthesized its Cu(II), Co(II), Mn(II) and Ni(II) complexes was studied using agarose gel electrophoresis method. Gel electrophoresis experiments were performed with complexes in the presence of H₂O₂ as an oxidant. The nuclease activity was greatly enhanced by the incorporation of metal ion in the respective co-polymer, it is evident from Figure 8, which shows that the complexes L₁ and 2, 3, 4, 5 and 6 cleavage DNA more efficiently in the presence of oxidant, which may be due to the formation of hydroxyl free radicals. The production of hydroxyl free radical is due to the reaction between the metal complex and oxidant. These hydroxyl radicals participate in the oxidation of the deoxyribose moiety, followed by hydrolytic cleavage of the sugar phosphate backbone. The difference was observed in the bands of the complexes compared to that of the control DNA. This shows that the control DNA alone does not show any apparent cleavage whereas the

complexes show cleavage. However, the nature of reactive intermediates involved in the DNA cleavage by the complexes is not clear. These results indicate that the metal ions play an important role in the cleavage of isolated DNA. As the compound was observed to cleave the DNA, it can be concluded that the compound inhibits the growth of the pathogenic organism by cleaving the genome 51, 52. The studies reveal that complete cleavage of DNA was observed by Cu(II) and Mn(II) complexes and partial cleavage of DNA was observed by Co(II) and Ni(II) complexes²⁸.

Antibacterial study

In vitro antimicrobial activity of Schiff base and its metal chelates was examined against two gram-positive bacteria (*B. subtilis* and *S. aureus*), two gram-negative bacteria (*E. coli* and *K. Pneumoniae*) by using agar well-diffusion method. Inhibition zone for gram-positive bacteria was found in the range of 10-23 mm, for gram-negative bacteria 10-20 mm and for yeasts 10-21 mm. It has been observed that compounds Cu(II)L₁L₂ were very effective against²⁹ *B. subtilis* with zone of inhibition of 23 mm and 22 mm, *S. aureus* with zone of inhibition of 15 mm and 17 mm, *E. coli* with zone of inhibition of 20 mm and 19 mm, *K. Pneumoniae* with zone of inhibition of 16 mm and 15 mm, respectively (Figure 10). Thus metal complexes show enhanced biological activity as compared to ligand, and this can be better explained by the Overtone's concept of cell permeability and Tweedy's chelation theory.

According to Overtone's concept of cell permeability, the lipid membrane surrounding the cell favors the passage of only lipid-soluble material; therefore, lipid solubility is an important factor that controls the antimicrobial activity. On chelation, polarity of the metal ion is reduced to a greater extent due to the overlapping of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups³⁰.

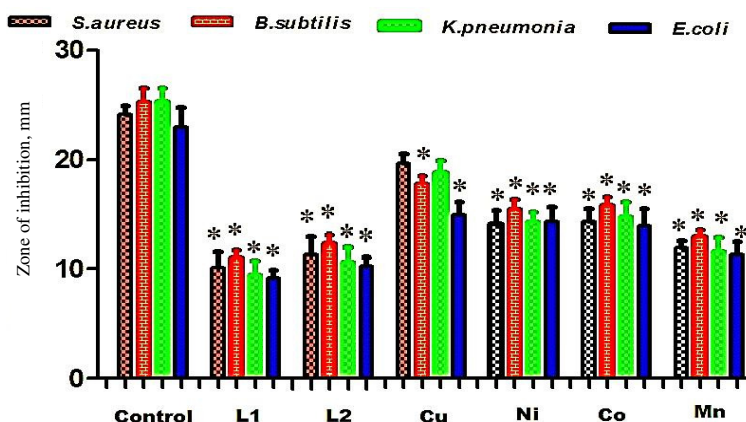


Figure 10. Biological evaluation of Schiff base and its metal complexes

Moreover, delocalization of the π -electrons over the whole chelate ring is increased and the lipophilicity of the complex is enhanced. The increased lipophilicity enhances the penetration of the complexes into the lipid membranes and blocks the metal binding sites in the enzymes of microorganisms.

Conclusion

Schiff base and metal complexes were synthesized and characterized by various physicochemical techniques like IR, ¹H NMR, ESR, electronic, magnetic moment, thermal,

photoluminescence and cyclic voltammetry. With the help of aforementioned techniques around the Co(II), Cu(II), Mn(II) and Ni(II) complexes octahedral geometry around the Cu(II) complexes have been proposed. The DNA cleavage studies revealed that the metal complexes showed good efficiency towards DNA cleavage. Based on the analytical and spectral studies, we propose octahedral geometry to all the synthesized complexes. For instance, Cu(II)L₁L₂ complexes show good activity.

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