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Research Article

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Synthesis, Characterization, DNA Binding studies and Biological activities of Copper (II) Complexes containing 1, 10 Phenanthroline, L - Ornithine and Urea & Thiourea

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Abstract

Ternary copper(II) complexes [Cu(phen)(L-Orn) U] ClO_4 **1** & [Cu(phen)(L-Orn)TU] ClO_4 **2** (phen = 1,10-phenanthroline, L-Ornithine, U= Urea and TU = Thiourea), have been synthesized and characterized by CHN analysis, molar conductance, electronic absorption, IR and EPR spectral studies. They have been tested for their in vitro DNA binding activities by the spectroscopic methods such as UV-Visible, Cyclic volumetric and viscosity measurement. Further complexes 1 & 2 were tested for their antimicrobial activities and it was found to have good antimicrobial activities.

Keywords: Copper (II) Complexes, L-Ornithine, U= Urea and TU = Thiourea, DNA Binding & antimicrobial activity.

1.1 Introduction

Copper complexes of 1,10-phenanthroline and its derivatives are of great interests since they exhibit numerous biological activities such as antitumor[1], anti-Candida[2], antimycobacterial[3], and antimicrobial[4] activity etc. Numerous biological experiments have also demonstrated that DNA is the primary intracellular target of anticancer drugs due to the interaction between small molecules and DNA, which can cause DNA damage in cancer cells, blocking the division of cancer cells and resulting in cell death[5].

Amino acids are the basic structural units of proteins, and some copper complexes of amino acids were reported to exhibit potent antitumor and artificial nuclease activity.[6, 7]. In this context, we focused our interests on the development of copper(II) complexes of 1,10 phenanthroline with amino acids, and investigated their DNA cleavage activity and in vitro cytotoxicity. The selection of L-Ornithine as a second ligand in the copper(II) complexes may enhance the affinity of the complex towards DNA.[8-11]

In this chapter, we synthesized and characterization of copper(II) complexes by IR, EPR spectra and elemental analysis. The binding properties of the title complexes of CT-DNA were carried out using UV–Visible absorption, fluorescence spectroscopic, cyclic voltametric and viscosity techniques . The binding mode of the copper complexes to DNA is accessed to be intercalation from the experimental results, which implicated that the copper(II) complexes can be a candidate for DNA-binding reagents, as well as laying the foundation for the rational design of new useful DNA probes.

1.2 Experimental

1.2.1 Materials

All the reagents were of analytical grade (Sigma-Aldrich and Merck). Calf thymus DNA obtained from Sigma-Aldrich, Germany, was used as such. The spectroscopic titration was carried out in the buffer (50 mM NaCl–5 mM Tris–HCl, pH 7.1) at room temperature. A solution of calf thymus DNA in the buffer gave a ratio of UV absorbance 1.8–1.9:1 at 260 and 280 nm, indicating that the DNA was sufficiently free of protein.[12] Milli-Q water was used to prepare the solutions. Absorption spectra were recorded on a UV–VIS–NIR Cary 5E Spectrophotometer using cuvettes of 1 cm path length, and emission spectra were recorded on a flurolog.

1.2.2 Synthesis of [Cu(phen)(L-Orn)(H_2O)]ClO_4[13]

To the mixture of L-Ornithine (1 mmol) and NaOH (1mmol) in water, an aqueous solution of $Cu(NO_3)_2.3H_2O$ (1 mmol) was added with stirring. Several minutes later, the ethanolic solution of phen (1 mmol) was added and the solution was stirred for about 3 hrs at 60^0C. Then the cooled solution was filtered and the filtrate was placed at room temperature on slow evaporation. After two weeks some blue crystals were obtained. Yield 72%

1.2.3 Synthesis of [Cu (Phen)(L-Orn) U] ClO_4 (1)

About (3 mmol) of [Cu(phen)(L-Orn)(H_2O)] ClO_4 complex dissolved in 50 ml of water. To this (3 mM) of Urea in 15 ml of distilled water was added slowly with constant stirring for 40 min. A bluish substance was separated out, which was filtered and dried. Yield 64%

1.2.4 Synthesis of [Cu(phen)(L-Orn) TU] ClO_4 (2)

About (3 mmol) of [Cu(phen)(L-Orn) TU] ClO_4 complex dissolved in 50 ml of water. To this (3 mmol) of thiourea in 15 ml of distilled water was added slowly with constant stirring for 35 min. A bluish substance was separated out, which was filtered and dried. Yield 51%

1.3 Results and discussion

1.3.1 Elemental Analysis

The elemental analysis data were found to be in good agreement, with those of the calculated values, the molar conductance value of the complexes indicated that the complexes is 1:1 electrolytes[14], the values given in the table 1.1. Synthetic route of the complexes is given scheme 1 and 2.

1.3.2 Electronic Spectra

The complexes are one electron paramagnetic at room temperature, corresponding to d^9 electronic configuration for the copper (II) center. The complexes display a copper (II) centered d-d bands 684 nm and 640 nm in addition to the ligands centered bands in the UV region of the electromagnetic spectra (Table 1.2). The electronic spectra of the complexes are in good agreement with the previously reported square pyramidal geometry of the complexes.[15-17]

In the UV–Vis region, the intense absorption bands appeared from 240 to 300 nm is attributed to intraligand transitions. Another band which appeared around 270 nm is assigned to ligand field transitions[18]. The UV-Visible spectral data of complexes are given in table 1.2

1.3.3 Infrared spectra

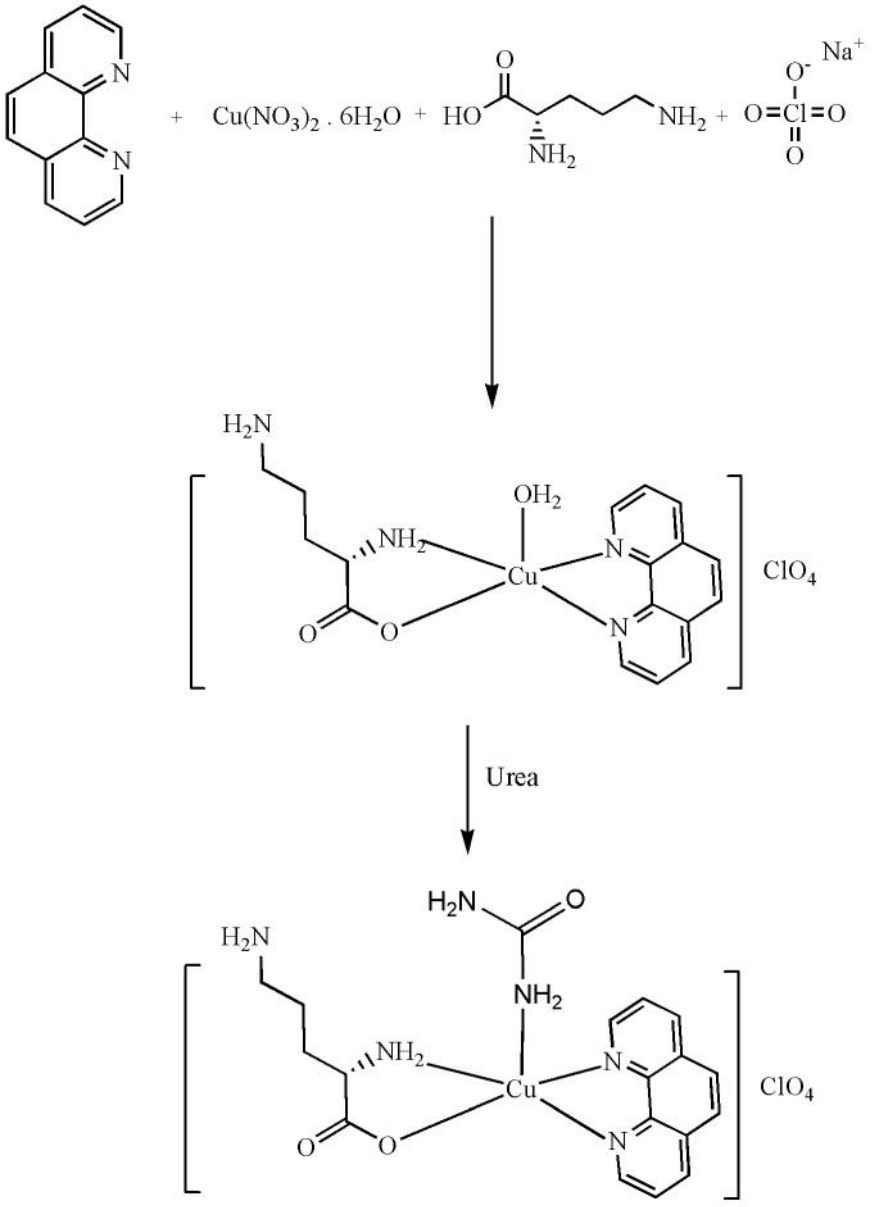
In the IR spectra, the N-H stretching vibrations were observed at 3390 cm^{-1} for complex **1**, and 3441 cm^{-1} for complex **2**. In complex 1, the peaks obtained corresponding to the ring stretching frequencies (ν (C=C) and ν (C=N)) at 1581 & 1515 cm^{-1}, in phen at 1599 & 1514 cm^{-1}. The strong bands at 1086 cm^{-1} for complex 1 and 1098 cm^{-1} for complex 2 were assigned to ν (Cl-O) of ClO_4. The non ligand peaks at 721 and 616 cm^{-1} were assigned to ν (Cu-O) and ν (Cu-N) for complex 1 (for complex 2, 722 & 645 cm^{-1}) (Fig 6.3 and 6.4)[19].

Table 1.1: Elemental analysis and molar conductance values of the complexes

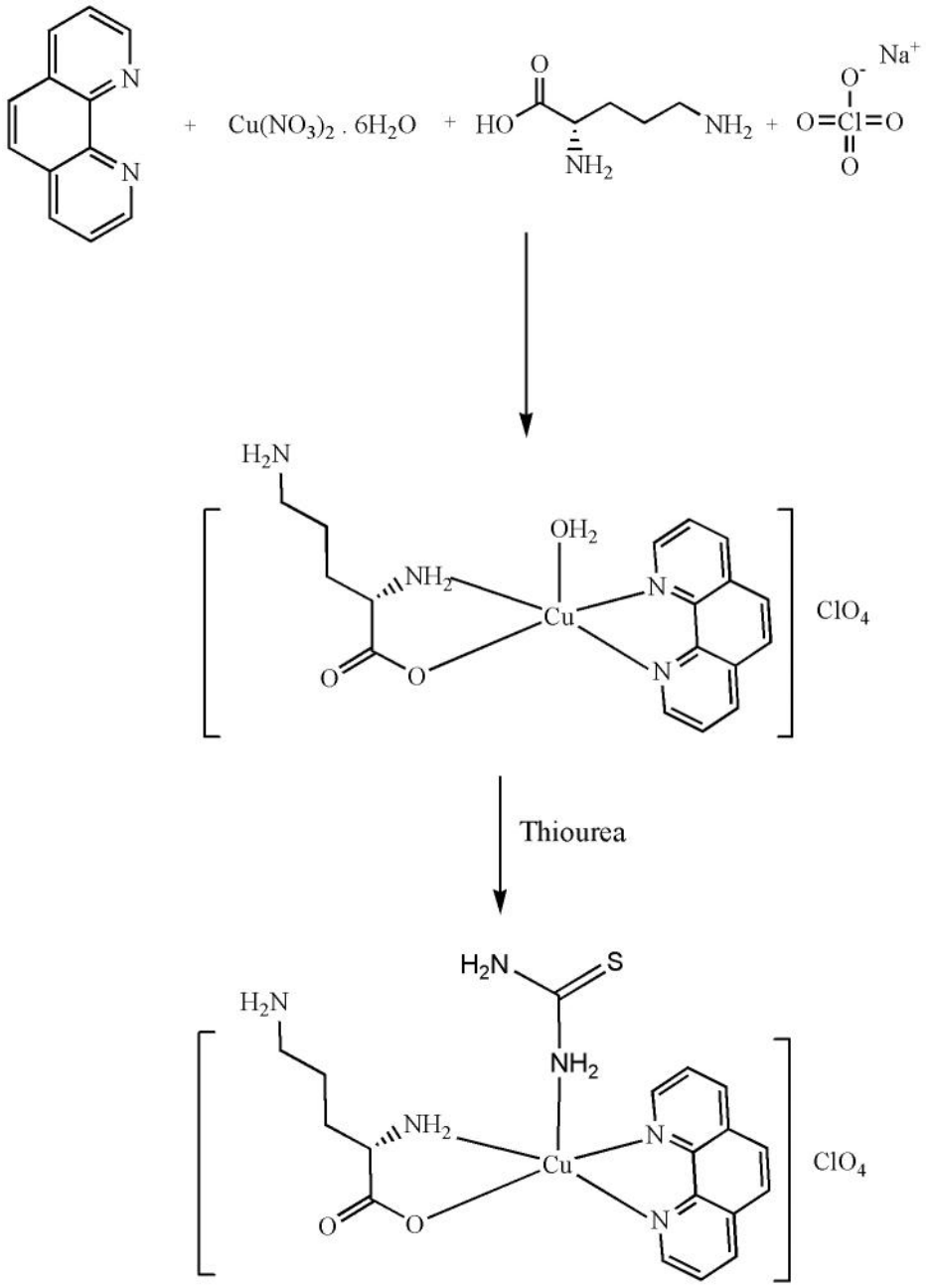
Complexes	Calcd (Found)			Molar Conductance (Sm^2mol^{-1})
	Carbon	Hydrogen	Nitrogen	
Complex 1	43.52(43.26)	14.50(14.46)	5.51(5.42)	91
Complex 2	42.35(42.35)	14.11(14.04)	5.42(5.31)	93

Table: 1.2: UV-Visible spectral of the complexes

Complex Name	λ_{max} (nm)	ε_{max} ($mol^{-1} cm^{-1}$)
[Cu(Phen)(L-Orn) U] ClO_4	213 274	862800 126600
[Cu(phen)(L-Orn) TU] ClO_4	221 266	174230 94120



Scheme 1: Synthesis of complex [Cu (Phen)(L-Orn) U] ClO_4 (1)



Scheme 2: Synthesis of complex [Cu (Phen)(L-Orn) TU] ClO_4 (2)

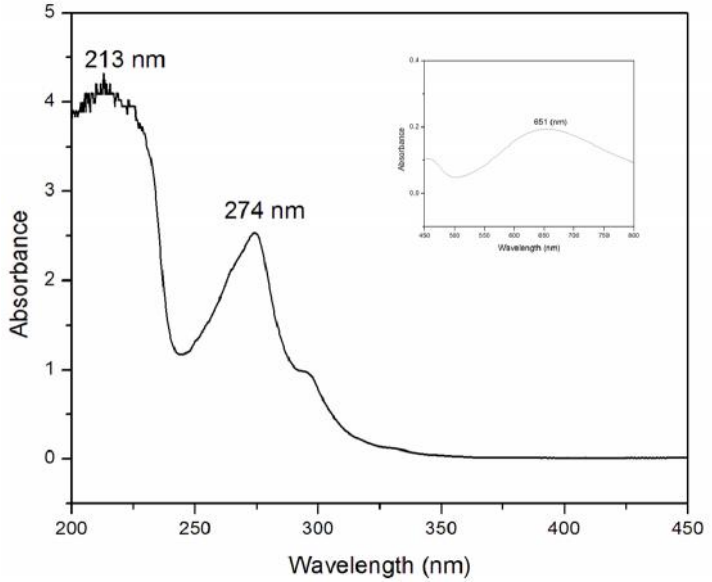


Fig 1.1: UV-Visible spectrum of complex **1**

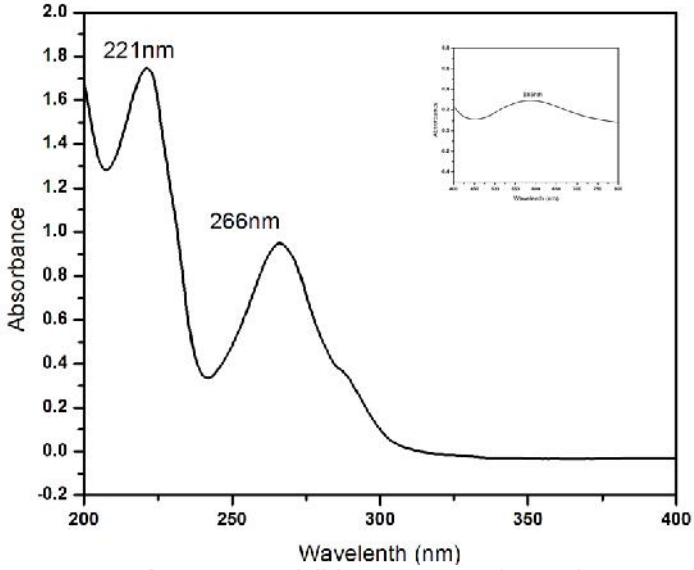


Fig 1.2: UV-Visible spectrum of complex 2

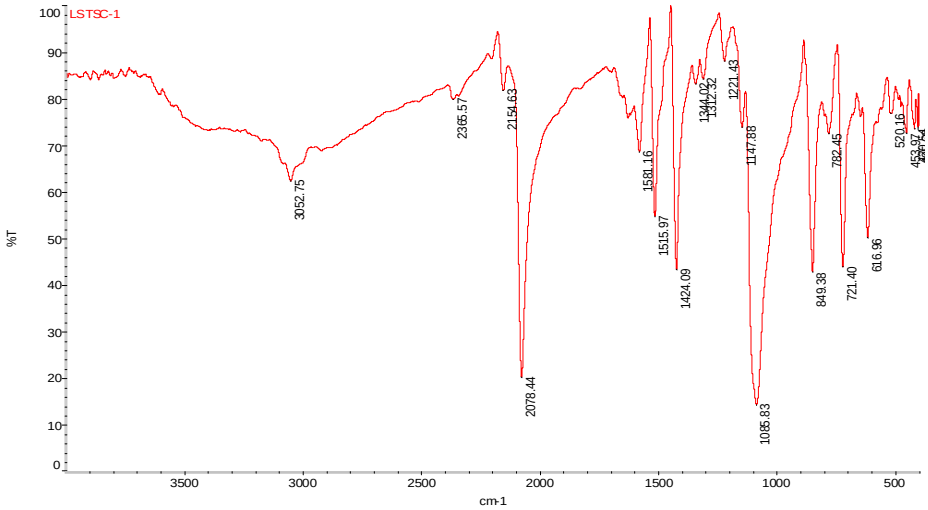


Fig 1.3: Infrared spectrum of complex **1**

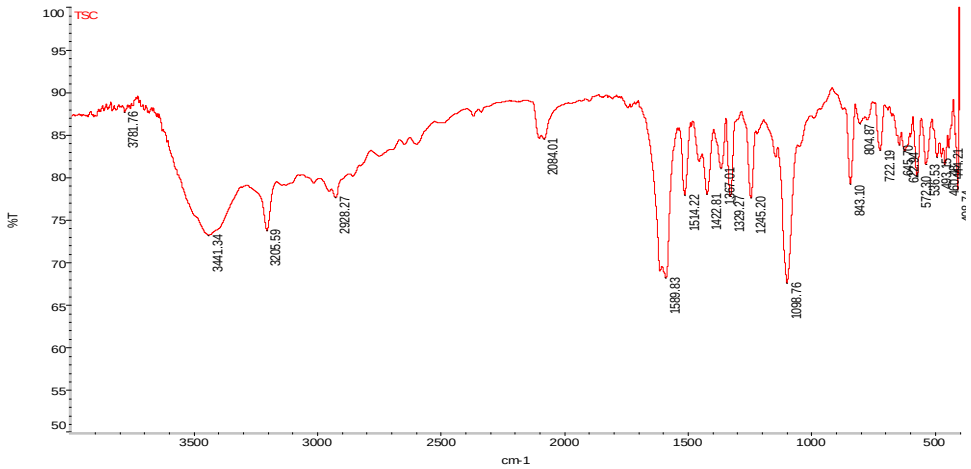


Fig 1.4: Infrared spectrum of complex **2**

1.3.4 Electron Paramagnetic Resonance

The solid state EPR spectra of the copper (II) complexes were recorded in X-band frequencies (Fig 1.5 and 1.6). At liquid nitrogen temperature, complex 1 and 2 exhibits well defined single isotropic feature near g = 2.16 and 2.19 respectively. Such isotropic lines are usually the results of intermolecular spin exchange, which broaden the lines. This intermolecular type of spin exchange is caused by the strong spin coupling which occurs during a coupling of two paramagnetic species[20].

1.4 DNA binding studies

1.4.1 Electronic spectral studies

Electronic absorption spectroscopy was an effective method to examine the binding mode of DNA with metal complexes[21]. In general, hyperchromism and blue-shift associate with the binding of the complexes to the helix by an intercalative mode, involving strong stacking interaction of the aromatic chromophore of the complex between the DNA base pairs.

Figure 1.7 and 1.8 show the UV absorption spectral study of complexes (**1** and **2**) in the absence and presence of DNA. In the ultraviolet region from 240 to 300 nm, the complex 1 had a strong absorption peak at 274 nm, for complex **2** the absorption peak at 266 nm. The absorption intensity of complex **1** increased and complex 2 increased evidently after the addition of DNA, which indicated the interactions between DNA and the complex. We have observed a minor bathochromic shift along with significant hyperchromicity for complexes. The intrinsic binding constant, Kb, was determined by using the following equation.[22]

$$[DNA] / (\varepsilon_a-\varepsilon_f) = [DNA] / (\varepsilon_o-\varepsilon_f) +1/K_b(\varepsilon_o-\varepsilon_f)$$

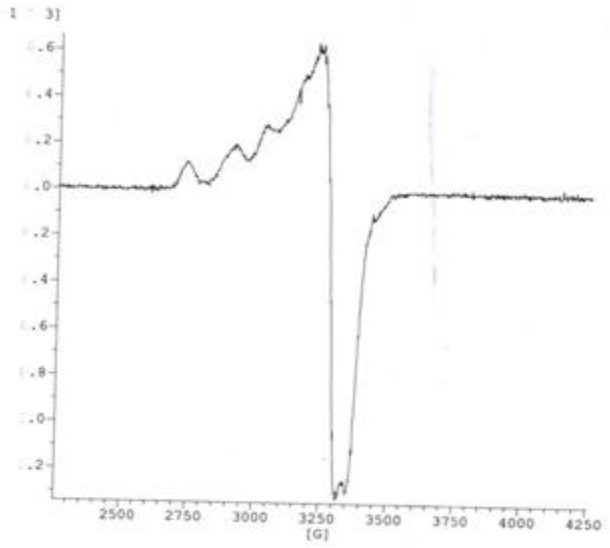


Fig 1.5: EPR spectrum of complex **1** DMSO at liquid nitrogen temperature.

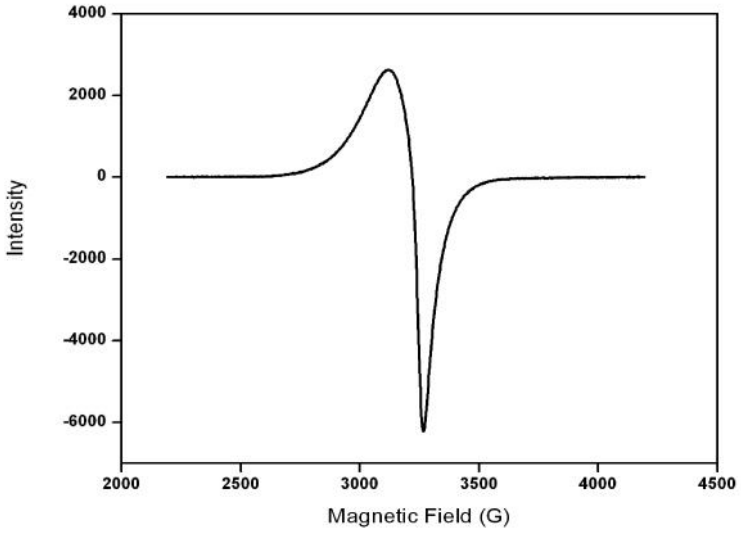


Fig 1.6: EPR spectrum of complex 2 (DMSO at liquid nitrogen temperature)

Where [DNA] is the concentration of DNA in base pairs, ε_a, ε_f and ε_o correspond to A_{obsd} / [Cu], the extinction coefficient of the free copper complexes and the extinction coefficient of the complexes in the fully bound form, respectively, and Kb is the intrinsic binding constant. The ratio of the slope to intercept in the plot of [DNA] / (ε_a-ε_f) versus [DNA] gives the value of K_b and for complex 1 is 2.458 x 10^{-5} (for Complex 2 K_b = 2.292 x 10^{-5} M). The binding propensity of the complex **1** is more than complex 2 due to the presence of the extended planar aromatic ring. Earlier studies on bis-phen copper complex have shown that this complex binds to DNA either by partial intercalation or binding of one phen ligand to the minor groove while the other phen making favourable contacts within the groove[23-25]. The nature of binding of the phen complex is proposed to be similar as observed for the bis-phen species.

1.4.2 Fluorescence spectral studies

As the copper (II) complexes are non-emissive, competitive binding studies with EtBr (Ethidium Bromide) were carried out to gain support for the mode of binding of the complexes with DNA. The study involves addition of the complexes to DNA pretreated with EtBr ([DNA]/[EthBr] = 1) and then measurement of intensity of emission. The observed enhancement in the emission intensity of EtBr bound to DNA is due to intercalation of the fluorophore in between the base pairs of DNA and stabilization of its excited state (Fig 1.9 and 1.10)[26]. The addition of the complexes to DNA pretreated with EB causes appreciable reduction in the emission intensity. This behaviour can be analyzed through the Stern–Volmer equation[27], $I_o/I = 1 + K_{sv}r$, where I_o and I are the fluorescence intensities in the absence and the presence of complexes, respectively. K_{sv} is a linear Stern–Volmer quenching constant, r is the ratio of the total concentration of complexes to that of DNA.

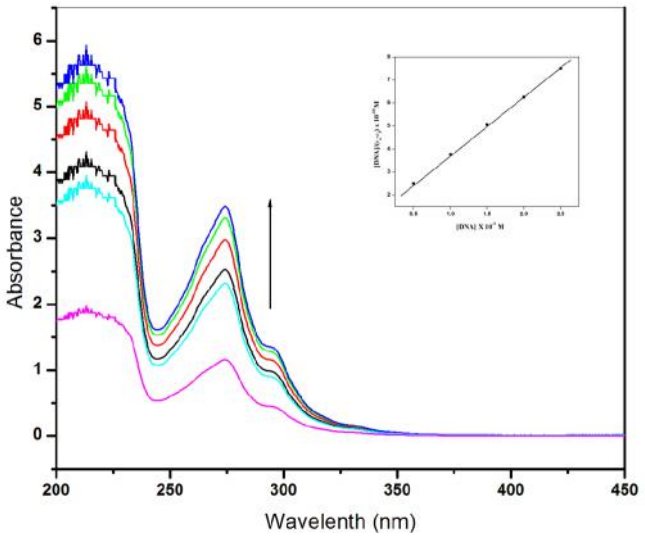


Fig 1.7: Absorption spectra of Complex **1**. In the absence and in the presence of increasing amounts of DNA. (Complex) = 15 µM. (DNA) = (5, 10, 15, 20, 25) µM. Inset: plot of (DNA) / (ε_a -ε_f) vs. (DNA). Spectra shows the absorbance changes upon increasing DNA concentrations.

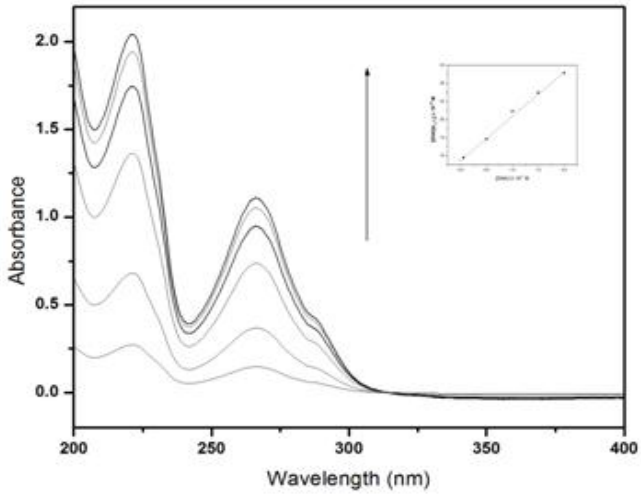


Fig 1.8: Absorption spectra of Complex 2. In the absence and in the presence of increasing amounts of DNA. (Complex) = 15 µM. (DNA) = (5, 10, 15, 20, 25) µM. Inset: plot of (DNA) / (ε_a -ε_f) vs. (DNA). Spectra shows the absorbance changes upon increasing DNA concentrations.

The quenching plot (Fig 1.9 and 1.10) illustrates that the quenching of EB bound to DNA by the copper(II) complexes is in good agreement with the linear Stern–Volmer equation, which also indicates that the complex binds to DNA. In the plot of I_o/I versus [Complex]/ [DNA], K_{sv} is given by the ratio of the slope to intercept. The K_{sv} value for complexes (**1** and 2) is 0.614 and 0.51, which is higher than that for ordinary transition metal copper complex[28]. This suggests that copper(II) complexes bind strongly with DNA, which is also consistent with our absorption spectral results.

1.4.3 Viscosity studies

To explore further the interaction between the copper (II) complexes and DNA, viscosity measurements were carried out on CT DNA by varying the concentration of the complexes. Spectroscopic data are necessary, but insufficient to support an intercalative binding mode. Hydrodynamic measurements which are sensitive to length increases (i.e. Viscosity, sedimentation et. al) are regarded as the least ambiguous and the most critical tests of binding on a solution in the absence of crystallographic structure data[29]. A classical intercalation mode causes a significant increase in the viscosity of DNA solution due to the increase in separation of the base pairs at intercalations sites and hence to an increase in overall DNA contours length. A partial and/or nonclassical intercalation of ligand would reduce the DNA viscosity[30]. The effects of the complexes (**1** and **2**) on the viscosity of the CT DNA solution are given in Fig 1.11 and 1.12.

The plot shows that the complex had a reverse effect on the relative viscosity of the CT DNA. With the addition of the complex, the relative viscosity of DNA increased. Since the increase is far less than that observed for an intercalator such as EB. This observation leads us to support the above spectral studies which suggest that the complex **1** interaction with DNA via partial intercalation between DNA base pairs, which is similar to the interaction of $[Cu(phen)_2]^{2+}$ with DNA[31,32]. Similarly, the same results were obtained from complex **2** (Fig 1.11 and 1.12).

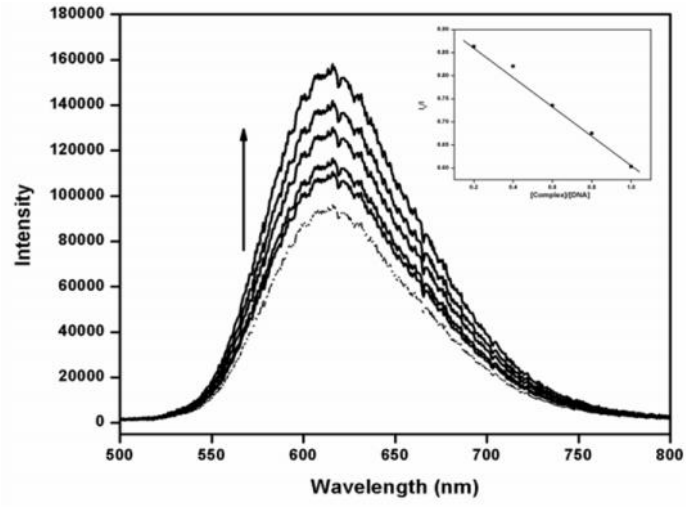


Fig 1.9: Emission spectra of EB bound to DNA in the absence (a) and in the presence of Complex **1** (Complex) = 8 - 32 x 10^{-6} M. (DNA) = 3 x 10^{-5} M, (EB) = 3 x 10^{-5} M. The arrow shows the intensity changing upon the increasing complex. Inset: plot of I_o/I vs. (Complex) /(DNA). Emission spectrum of EB alone (a) concentrations.

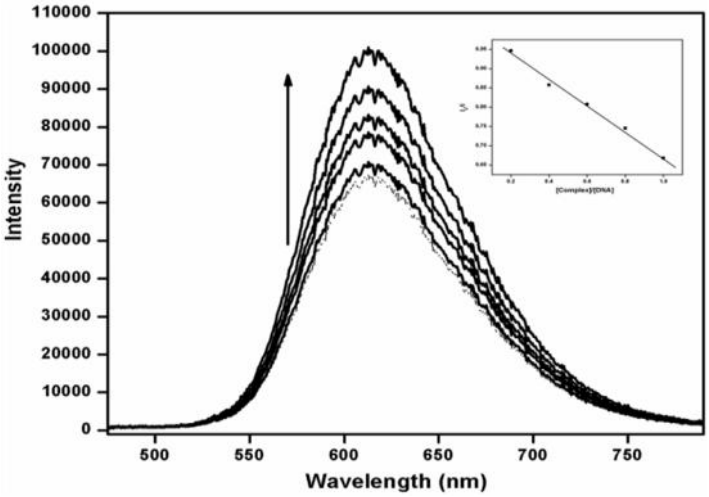


Fig 1.10: Emission spectra of EB bound to DNA in the absence (a) and in the presence of Complex **2** (Complex) = 8.32 x 10^{-6} M. (DNA) = 3 x 10^{-5} M, (EB) = 3 x 10^{-5} M. The arrow shows the intensity changing upon the increasing complex. Inset: plot of I_o/I vs. (Complex) /(DNA). Emission spectrum of EB alone (in dotted alone).

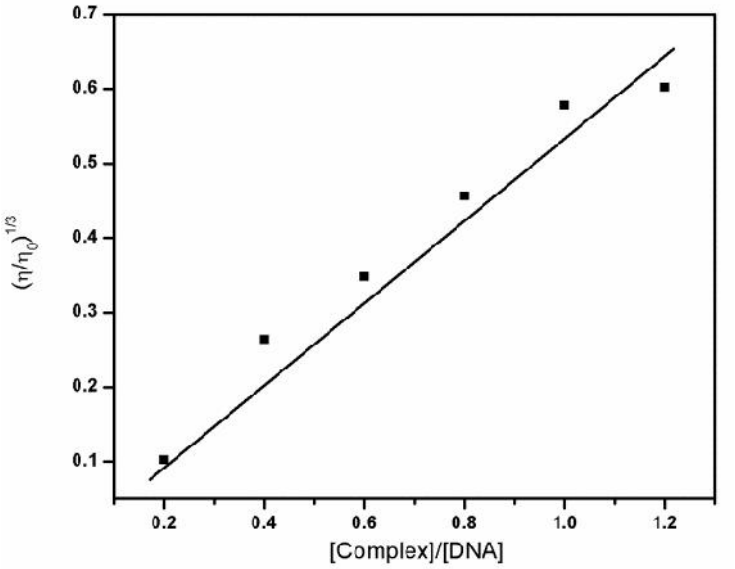


Fig 1.11: Effect of increasing amount of complex **1** [Cu(Phen)(L-Orn)(U)]ClO_4 (1,15,20,25,30,35,40,45,50 µM) on the relative viscosity of calf thymus DNA (15 µM) in 5mM Tris-HCl/50mM NaCl buffer.

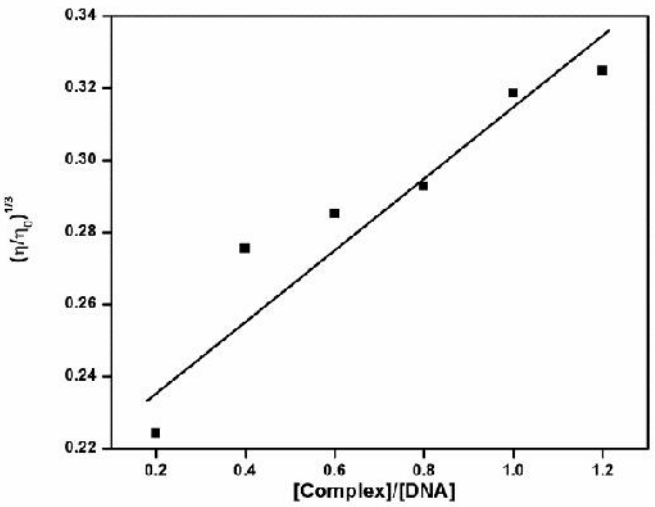


Fig 1.12: Effect of increasing amount of complex **2** [Cu (Phen)(L-Orn)(TU)]ClO_4 (1, 15, 20, 25, 30, 35, 40, 45, 50 µM) on the relative viscosity of calf thymus DNA (15 µM) in 5mM Tris-HCl/50mM NaCl buffer.

1.4.4 Cyclic voltammetric study

Cyclic voltammetric techniques were employed to study the interaction of the present redox active metal complex with DNA with a view to further explore the DNA binding modes assessed from the above spectral and viscometric studies. Typical cyclic Voltammetry (CV) behaviors of complexes 1 and 2 in the absence and presence of CT-DNA are shown in (Fig 1.13 and 1.14). The cyclic voltammogram of copper(II) in the absence of DNA featured reduction of Cu(II) to the Cu(I) form at a cathodic peak potential,[33] E_{pc} of -0.7 V and anodic peak potential, E_{pa} of -0.65 V for complex 1 and cathodic potential E_{pc} of -0.65 V and anodic peak potential E_{pa} of -0.6 V for complex **2** respectively. The separation of the anodic and cathodic peak potentials, Ep = -0.05 V for Complex 1 and E_p = -0.05V for complex 2 respectively. The formal potential $E_{1/2}$, was taken as the average of Epc and Epa, is -0.067 V in the absence of DNA for complex 1 and -0.14 V in the absence of DNA for complex 2 respectively.

The presence of DNA in the solution at the same concentration of Copper (II) causes a considerable decrease in the voltammetric current coupled with a slight shift in the $E_{1/2}$ ($E_{1/2}$ = -0.067 V for complex **1** and $E_{1/2}$ = -0.065 V for complex **2**). The drop of the voltammetric currents in the presence of CT-DNA can be attributed to diffusion of the metal complex bound to the large, slowly diffusing DNA molecule. Obviously, $E_{1/2}$ undergoes a positive shift (25 mV) after forming an aggregation with DNA, suggesting that the copper complex bind to DNA mainly by intercalation binding mode,[34] and this result also proves the results obtained from viscosity and absorption spectrum studies again.

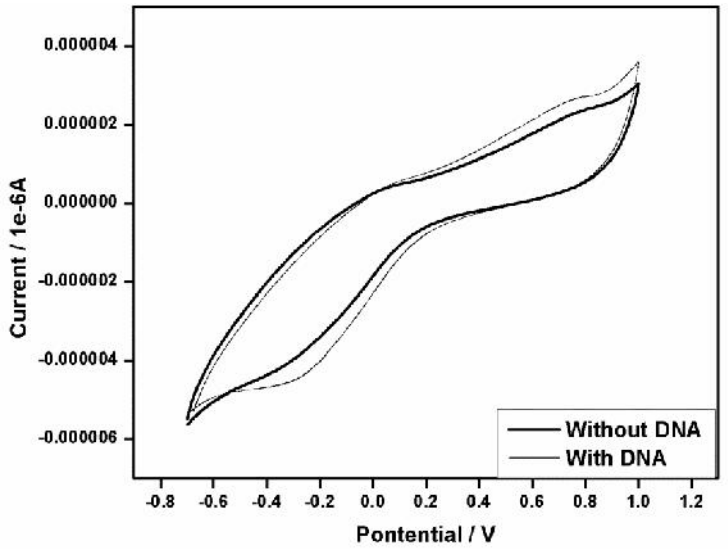


Fig 1.13: Cyclic voltammogram of Complex 1(1 mM) in the absence (—) and in the presence (---) of CT-DNA (1.5 x 10^{-5} M). 5 mM in buffer containing 50 mM NaCl–5 mM Tris–HCl, pH 7.2. Scan.

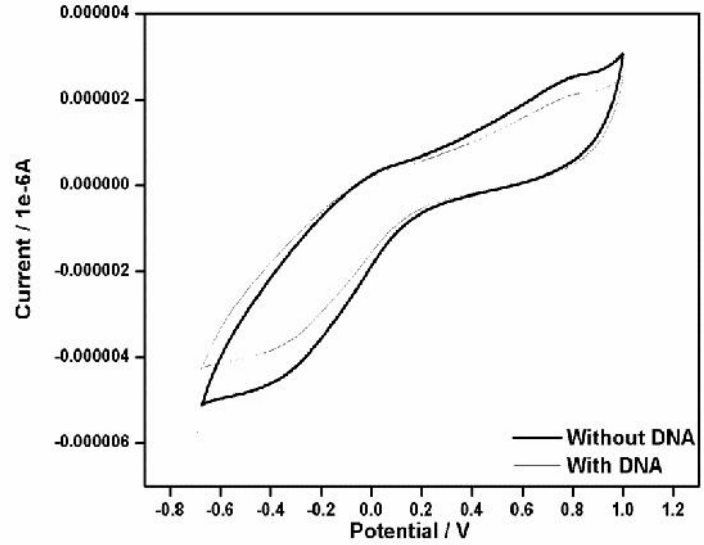


Fig 1.14: Cyclic voltammogram of Complex 2(1 mM) in the absence (—) and in the presence (---) of CT-DNA (1.5 x 10^{-5} M). 5 mM in buffer containing 50 mM NaCl–5 mM Tris–HCl, pH 7.2. Scan.

1.5 Antibacterial and Antifungal screening

The copper(II) complex was screened in vitro for its microbial activity against certain pathogenic bacterial and fungal species using disc diffusion method (Fig 1.15 and 1.16). The complex was found to exhibit considerable activity against Gram positive and Gram negative bacteria and the fungus *C. albicans*. The test solutions were prepared in dimethyl sulphoxide and the results of the antimicrobial activities are summarized in table 1.3. Zoroddu et al[35] have reported that copper complex show any significant activity against the Gram positive and Gram negative bacteria. Recently Patel et al. Have indicated that the copper(II) complexes with L-phenylalanine have exhibited considerable activity against some human pathogens.[36,37] In our biological experiments, using copper(II) complexes (**1** and **2**), we have observed antibacterial activity against Gram positive bacteria *Staphylococcus aureus* and *B. Cereus* and Gram negative bacteria *E. Coli* and *Pseudomonas Aeruginosa*. The copper(II) complexes have shown high activity against Gram positive than Gram negative bacteria. The copper(II) complexes are also very active against the fungus *C. Albicans* than the standard antifungal drug, clotrimazole. It may be concluded that our copper(II) complexes inhibit the growth of bacteria and fungi to a greater extent.

Fig 1. 15: Antimicrobial activity of complex **1**

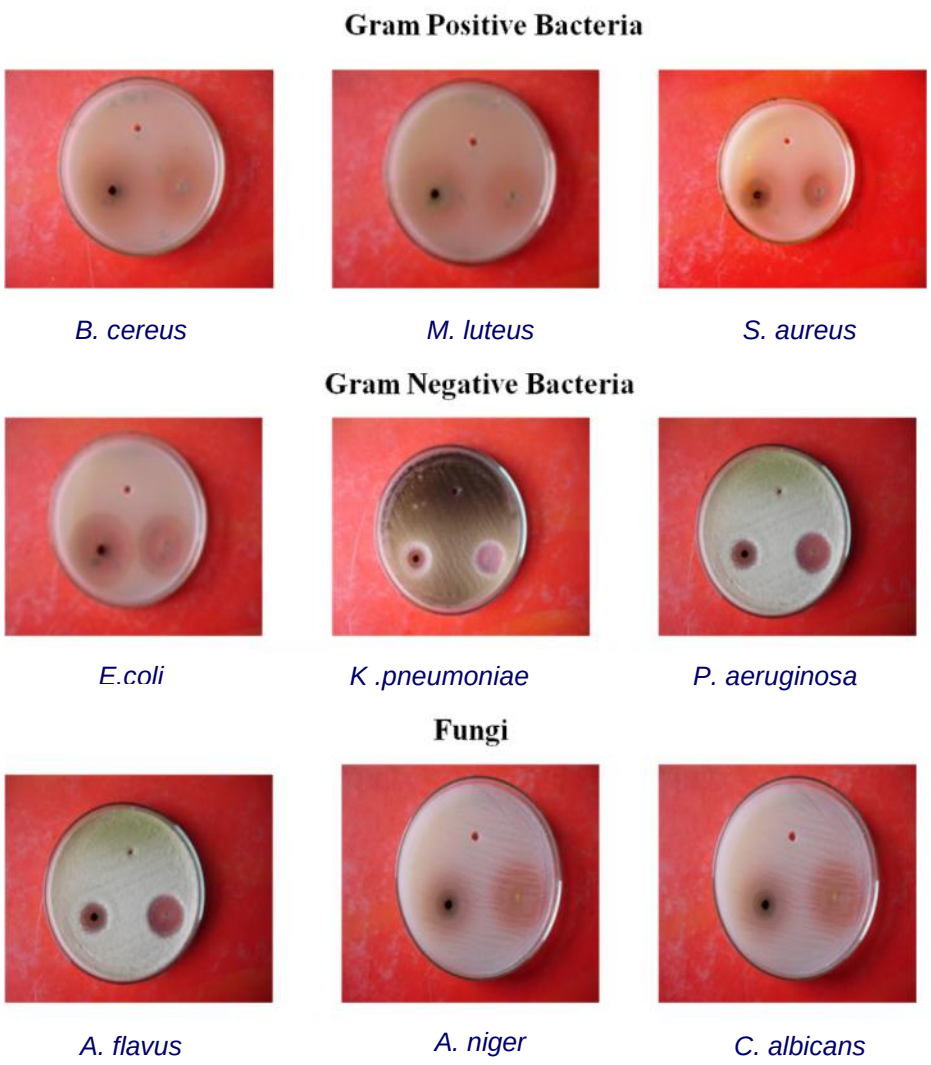


Fig 1. 16: Antimicrobial activity of complex 2

Table 1.3: Biological activity of complexes **1** and **2**

Name of the Organism	Diameter Zone of Inhibition (mm)	
	Complex 1	**Complex 2**
B. cereus	20	12
M. luteus	19	18
S. aureus	16	22
E. coli	12	14
K. pheumoniae	18	19
P. aeruginosa	10	22
A. flavus	16	25
A. niger	12	10
C. albicans	9	8

1.6 Conclusion

In this chapter, we have described new copper(II) complexes. Further characterization of the complexes was achieved through physio-chemical and spectroscopic methods. The effectiveness of the binding of the complexes is being confirmed by means of hypochromism in the electronic spectral studies and change in intensity of emission in the case of emission spectral studies. Besides, the effect of binding is also confirmed by the viscometric and cyclic voltammetric studies. This shows that the complexes interact with DNA base pairs effectively. The copper(II) complexes exhibit good antimicrobial activity.

1.7 References

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