



SYNTHESIS, SPECTRAL CHARACTERIZATION AND DNA BINDING STUDIES OF DINUCLEAR COPPER (II) COMPLEXES WITH 1, 10-PHENANTHROLINE

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ABSTRACT

The mononuclear copper(II) complex, $\text{Cu}(\text{phen})(\text{H}_2\text{O})(\text{NO}_3)_2$ (1) has been obtained by the reaction of 1,10-phenanthroline with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ in methanol solution. The complex reacts with mono anionic ligands Cl^- , Br^- , I^- and CH_3O^- in methanolic solution to form the stable binuclear complexes $[\text{Cu}(\text{phen})(\mu\text{-X})(\text{H}_2\text{O})]_2 (\text{NO}_3)_2$. Where, $\text{X} = \text{Cl}^-$ (2), Br^- (3), I^- (4), and CH_3O^- (5). These complexes were characterized by electronic, IR, ESR, magnetic moments and conductivity measurements. The electrochemical behaviour of these complexes has been investigated by using cyclic voltammetry. The interactions of these complexes with calf thymus DNA were investigated using absorption spectrophotometry. Electronic absorption data suggest that the complexes bind DNA via intercalation.

KEY WORDS: Synthesis, dinuclear copper(II) complexes, 1,10-phenanthroline, spectral studies, DNA binding studies.



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INTRODUCTION

Copper(II) complexes have continued to attract attention of coordination chemists due to its various interesting structural features, its usefulness as models of the active centers of various metallo-enzymes, magnetic, electronic, catalytic and biological properties¹⁻⁴. Copper is a part of many redox-active metalloenzymes⁵. Copper(II) complexes containing heterocyclic bases have received considerable interest in nucleic acid chemistry due to their diverse applications following the discovery of the "chemical nuclease" activity of the $[\text{Cu}(\text{phen})_2]^{2+}$ (phen = 1,10-phenanthroline) complex by Sigman and coworkers⁶. Design and synthesis of molecules, mimicking natural enzyme, have important applications in the development of new therapeutics. DNA has become an interesting target for artificial enzymes, partly because of possible therapeutic applications. DNA is one of the most essential molecules in organisms, containing all the information necessary for organisms to live. It replicates and provides a mechanism for heredity and evolution. Various events cause the degradation of DNA into nucleotides. It has been shown that catalytic activity in several enzyme models is dependent on nuclearity; mononuclear complexes often appear to exhibit a decrease in, or absence of, catalytic activity in contrast to their dinuclear counterparts⁷. As a part of our ongoing research programme⁸⁻¹¹ concerning DNA-binding and cleavage activities of dinuclear transition metal complexes, herein we report the synthesis, characterization and nuclease activity of four di-copper phenanthroline complexes bridged by different anions.

MATERIALS AND METHODS

Analytical grade 1,10-phenanthroline (phen), $\text{CuNO}_3 \cdot 3\text{H}_2\text{O}$, NaCl, NaBr, NaI, and NaOMe were obtained from Merck. The solvents used for the synthesis of copper complexes were distilled before use. Calf thymus DNA (CT-DNA) was purchased from Genic Bio labs, Bangalore, India. Elemental analyses were

carried out on a Heraeus Vario-EL III Carlo Erba 1108 instruments. Molecular weights of the complexes were determined using Rast's method [12]. Magnetic measurements were taken at room temperature against variable field using a lakeshore VSM 7410 magnetometer and magnetic moments were calculated by the method described elsewhere. The conductivity measurements at $298 \pm 2\text{K}$ in dry and purified DMF were taken on a CM model 162 Conductivity cell (ELICO). Electronic spectra were recorded in DMF with a Perkin-Elmer UV lambda 50 spectrophotometer. IR spectra were recorded in the range $4000-400\text{ cm}^{-1}$ with a Perkin-Elmer spectrum 100 spectrometer as a KBr discs. ESR spectra were recorded with a Varian E-112 X-band spectrophotometer at room temperature and liquid nitrogen temperature (LNT) in both solution (DMF) and solid states. The g values are computed from the spectrum using tetracyanoethylene (TCNE) free radical as 'g' marker. Cyclic voltammetry was performed with a CH Instruments 660C electrochemical analyzer and a conventional type electrode, Ag/AgCl reference, glassy carbon working electrode and platinum counter electrode. Nitrogen was used as purge gas and all solutions were prepared in DMF containing 0.1M concentration in tetrabutylammonium hexafluorophosphate (TBAPF₆).

Preparation of complexes

Preparation of $\text{Cu}(\text{phen})(\text{H}_2\text{O})(\text{NO}_3)_2$ (1)

To a stirring solution of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (1.21 g, 5 mmol) in MeOH (10 mL), a solution of 1,10-phenanthroline (0.99 g, 5mmol) in methanol (10 ml) was added slowly. The stirring was continued for half an hour. The blue coloured complex was filtered off and washed with small quantity of methanol.

Synthesis of $[\text{Cu}(\text{phen})(\mu\text{-Cl})(\text{H}_2\text{O})_2]_2 (\text{NO}_3)_2$ (2).

To a stirring solution of complex (1) (0.77 g, 2mmol), in MeOH (20ml) excess NaCl was added and the stirring was continued for 1hour. The Bluish green coloured complex was filtered off, washed with small quantity of methanol.

(3) Synthesis of [Cu(phen)(μ-Br)(H₂O)]₂(NO₃)₂ (3).

To a stirring solution of complex (1) (0.77 g, 2 mmol), in MeOH (20ml) excess KBr was added and the stirring was continued for 1hour. The Brown coloured complex was filtered off, washed with small quantity of methanol.

Synthesis of [Cu(phen)(μ-I)(H₂O)]₂(NO₃)₂ (4).

To a small solution of complex (1) (0.77g, 2mmol) in MeOH (20ml) excess KI was added and the stirring was continued for 1hour. The Dark brown coloured complex was filtered off, washed with small quantity of methanol.

Synthesis of [Cu(phen)(μ-OMe)(H₂O)]₂(NO₃)₂ (5).

To a small solution of complex (1) (0.77g, 2mmol), excess NaOMe was added and the stirring was continued for 1hour. The Greenish blue colored complex was filtered off, washed with small quantity of methanol.

DNA binding experiments

Interaction of the complexes with CT-DNA was studied by electronic absorption spectroscopy. A solution of CT-DNA in 5 mM NaCl(pH 7.0) gave a ratio of UV absorbance at 260 and 280 nm (A_{260}/A_{280}) of 1.8-1.9, indicating that the DNA was sufficiently free of protein¹³. A concentrated stock solution of DNA was prepared in 5 mM Tris-HCl /50 mM NaCl in water at pH 7.0, and the concentration of CT-DNA was determined per nucleotide by taking the absorption coefficient ($6600 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$) at 260 nm¹⁴. Stock solutions were stored at 4 °C and used after no more than 4 days. Doubly distilled water was used to prepare buffer solutions. Solutions were prepared by mixing the complex and CT-DNA in DMF medium. After equilibration (ca. 5 min), the spectra were recorded against an analogous blank solution containing the same concentration of CT-DNA. UV spectral data were fitted into Eq. 1 to obtain the intrinsic binding constant (K_b);

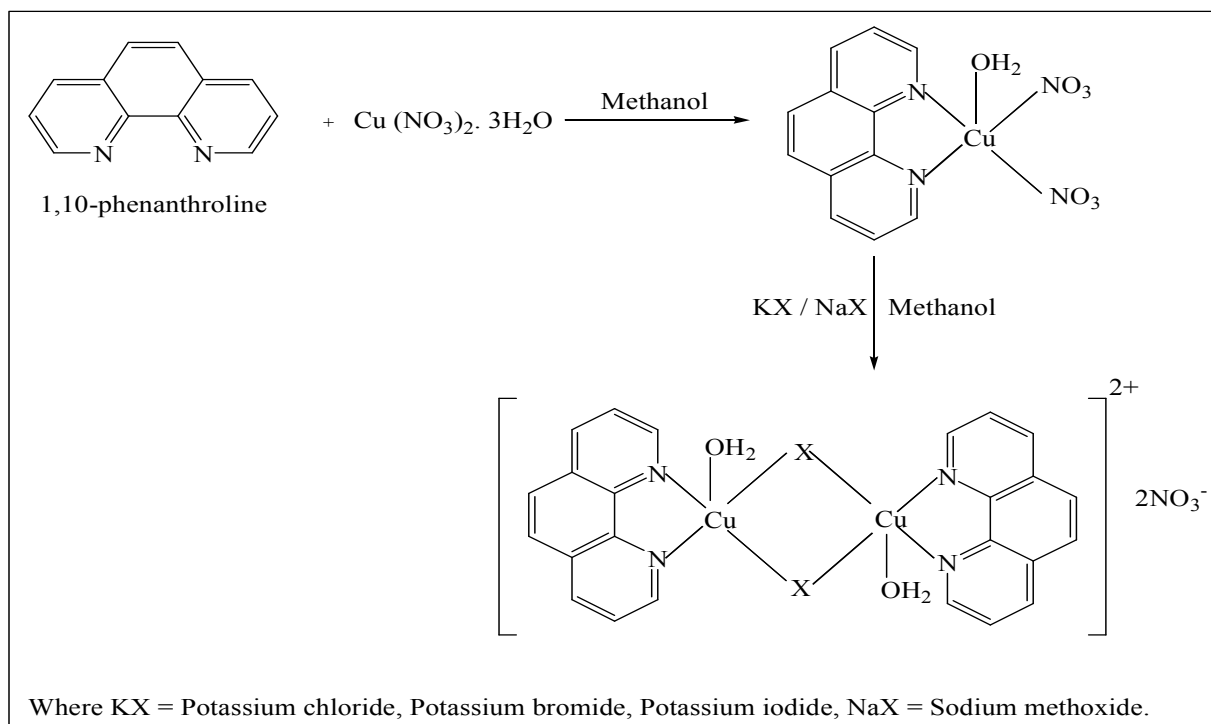
$$[\text{DNA}]/(\epsilon_a - \epsilon_f) = [\text{DNA}] / (\epsilon_b - \epsilon_f) + 1/ K_b(\epsilon_b - \epsilon_f) \quad \text{-----} \quad (1)$$

Where [DNA] is the concentration of DNA in the base pairs, ϵ_a , ϵ_b and ϵ_f are apparent extinction coefficient ($A_{\text{obs}}/[M]$), the extinction coefficient for the complex (M) in the fully bound form and the extinction coefficient for the free complex (M), respectively. A plot of $[\text{DNA}] / (\epsilon_a - \epsilon_f)$ versus [DNA] gave a slope of $1/(\epsilon_b - \epsilon_f)$, and vertical intercept equal to $1/ K_b(\epsilon_b - \epsilon_f)$; K_b was calculated from these values.

RESULTS AND DISCUSSION

The chemistry described here is summarized in Figure 1. The reaction of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ with an equimolar amount of 1,10-phenanthroline (phen) in methanol results in the formation of a blue complex (1). It reacts with mono anionic ligands, Cl^- , Br^- , I^- , and OCH_3^- in methanol to form the stable binuclear complexes, $[\text{Cu}(\text{phen})(\mu\text{-X})(\text{H}_2\text{O})]_2 (\text{NO}_3)_2$, where X= Cl^- (2), Br^- (3), I^- (4), and OCH_3^- (5).

Figure 1
Synthesis of Dinuclear copper (II) complex



The complexes are stable at room temperature, non-hygroscopic. Therefore, the complexes may be stored very easily. The complexes are partially soluble in water, ethanol, and readily soluble in acetonitrile (CH_3CN), DMF and DMSO. Our several attempts to obtain diffraction quality crystal for the complexes using different combination of solvents were not successful. Physicochemical and analytical data of complexes are given in Table 1. The magnetic moments

Table 1
Physico-chemical and analytical properties of copper(II) complexes

S. No	Formula of Complex	Colour (yield,%)	Decomposition Temp. °C	Magnetic moment μ_{eff} (B.M)	Molar conductivity ($\Omega^{-1}\text{cm}^2 \text{mol}^{-1}$)	Elemental analysis (calcd. %)			
						C	H	N	M
1	$\text{Cu(phen)(H}_2\text{O)(NO}_3)_2$	Blue (69%)	248-250 °C	1.47	6.0	37.65 (37.36)	2.59 (2.61)	14.79 (14.52)	19.10 (18.54)
2	$[\text{Cu(phen)(}\mu\text{-Cl)(H}_2\text{O)}]_2$ ($\text{NO}_3)_2$	Bluish green (58%)	296-298 °C	1.21	77.0	39.88 (40.10)	2.76 (2.80)	11.45 (11.70)	17.58 (17.69)
3	$[\text{Cu(phen)(}\mu\text{-Br)(H}_2\text{O)}]_2$ ($\text{NO}_3)_2$	Brown (81%)	282-286 °C	0.98	82.4	34.61 (35.68)	2.32 (2.49)	10.38 (10.41)	15.72 (15.74)
4	$[\text{Cu(phen)(}\mu\text{-I)(H}_2\text{O)}]_2$ ($\text{NO}_3)_2$	Dark brown (65%)	288-290 °C	0.67	82.5	30.78 (31.96)	2.19 (2.23)	9.28 (9.32)	14.08 (14.10)
5	$[\text{Cu(phen)(}\mu\text{-OMe)(H}_2\text{O)}]_2$ ($\text{NO}_3)_2$	Greenish blue (62%)	280-282 °C	1.02	79.4	43.28 (44.01)	3.48 (3.69)	11.91 (11.84)	17.59 (17.79)

Phen = 1.10-phenanthroline

of the dinuclear complexes (2-5) are less than the spin only value (1.73 B.M) suggesting the presence of magnetically coupled metal centers in these complexes¹⁵. The molar conductivity data suggest that complex 1 is a non electrolyte whilst complexes, 2-5 are 1:2 electrolytes¹⁶.

IR spectra

In the infrared spectrum of $[\text{Cu}(\text{H}_2\text{O})(\text{phen})(\text{NO}_3)_2](1)$ strong peaks are observed at 1384 and 1293 cm^{-1} which are assigned to $\nu(\text{NO})$ of mono coordinated nitrates¹⁷. It also exhibits strong bands at 3456 cm^{-1} assigned to -OH stretching of a water ligand. In the IR spectra of complexes 2, 3, 4, and 5 similar bands were observed at 3432, 3421, 3435, and 3429 cm^{-1} , respectively, also suggesting the presence of water ligands. A strong band is observed at 1422 cm^{-1} in the IR spectra of

complexes indicating the presence free nitrate ion. Molar conductivity data suggest that the complexes (2-5) are 1:2 electrolytes. Hence the complexes 2-5 have nitrate counter anions in analogy with our previous observation¹⁸.

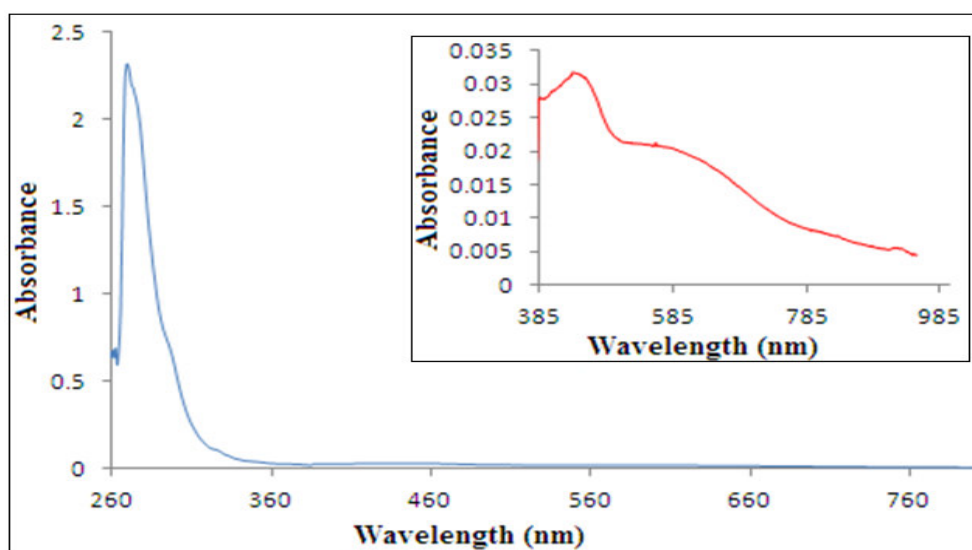
Electronic spectra

Typical electronic spectrum of complex (5) is shown in Figure 2. The copper (II) complexes exhibit two strong bands in the 36630- 38150 cm^{-1} region, assigned to the $\pi - \pi^*$ transition of the phenanthroline ring. The peak appeared in 25575-30487 cm^{-1} region is assigned to MLCT charge transfer transition. A weak band observed in 15060– 17241 cm^{-1} region (Table 2) is assigned to ${}^2\text{E}_g \rightarrow {}^2\text{T}_{2g}$ electronic (d-d) transition in favour of octahedral structure¹⁹ in DMF medium.

Table 2
Electronic spectral data (cm^{-1}) of copper (II) complexes

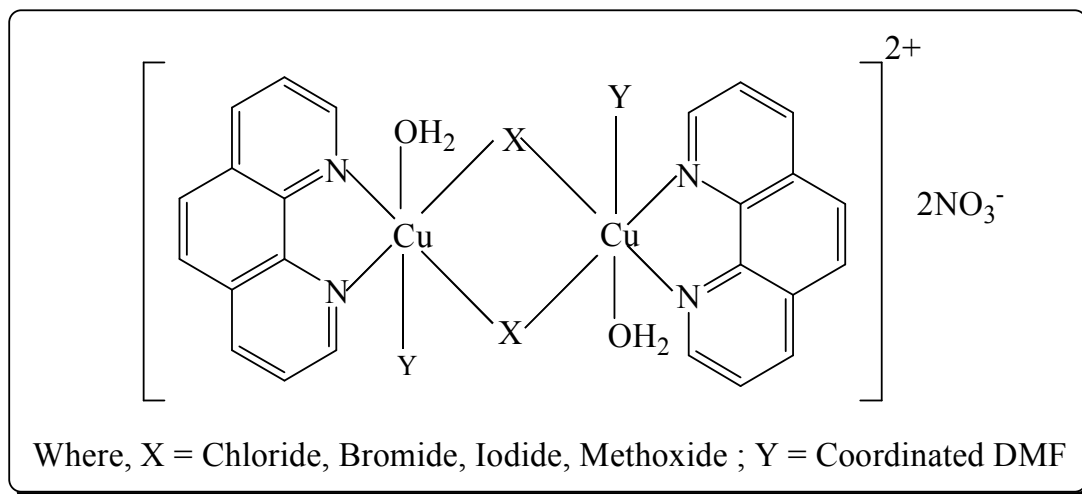
Complex	$\pi-\pi^*$ Transition	CT Transition	d-d Transition
1	36630	30487	15060
2	36496	26109	16528
3	38150	25706	17241
4	36764	25594	16722
5	37039	25575	16611

Figure 2
Electronic spectrum of $[\text{Cu}(\text{phen})(\mu\text{-OMe})(\text{H}_2\text{O})_2](\text{NO}_3)_2$



The sixth coordination site may be occupied by DMF solvent molecule to give edge-sharing bioctahedral structure as shown in Figure 3.

Figure 3
Suggested structure of dinuclear copper (II) complex in DMF medium

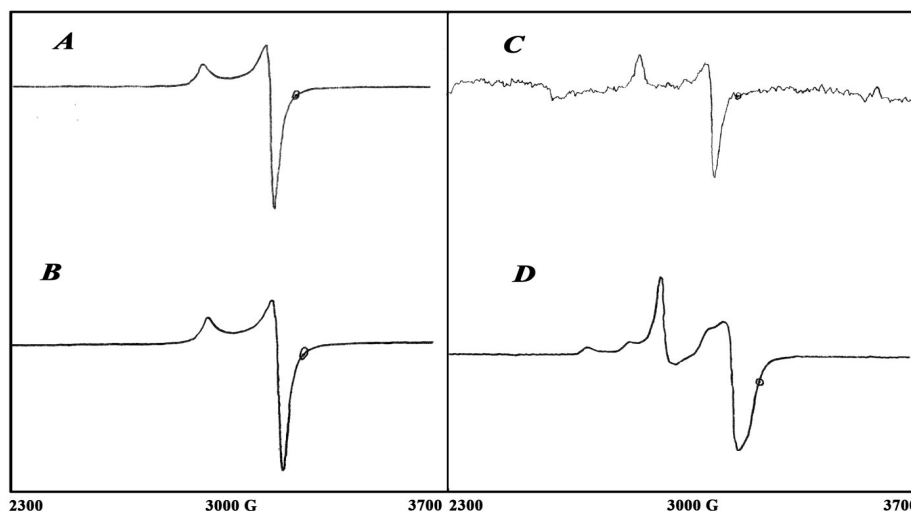


ESR spectra

ESR spectra of copper complexes were recorded at room temperature and at liquid nitrogen temperature (LNT) in both solution (DMF) and solid state. Typical ESR spectra of (2) in powder state at 300K, at liquid nitrogen temperature, in DMF solution at 300K and at liquid nitrogen temperature are shown in Fig 4. The spin Hamiltonian and orbital reduction parameters of copper complexes are given in Table 3. The g_{\parallel} and g_{\perp} values are computed

from the spectrum using tetracyanoethylene (TCNE) free radical as 'g' marker. It is significant from the data that the observed g_{\parallel} values for all these copper complexes are less than 2.3 suggesting covalent character of the metal-ligand bonding²⁰. In the solid state, similar spectra of these complexes at 77K and 300K indicates that the geometry around copper(II) ion is unaffected on cooling to liquid nitrogen temperature.

Figure 4
X-band ESR spectra of $[Cu(phen)(\mu-Cl)(H_2O)]_2(NO_3)_2$
(A) powder at 300K, (B) powder at LNT, (C) in DMF at 300 K and (D) in DMF at LNT.



In these conditions the axial symmetry parameter G , which measures the interaction between copper centers is calculated from the following equation²¹.

$$G = [g_{\parallel} - 2.0023 / g_{\perp} - 2.0023]$$

The calculated G values are found to be less than 4 for the copper complexes suggesting that there is considerable interaction between two copper ions in the solid complex²⁰. The broad ESR spectra clearly reveal that there is strong antiferromagnetic interaction between two metal ions in the complexes. This antiferromagnetic coupling occurs due to the quenching of the spin of electrons of one metal ion by the adjacent metal ion²⁰. ESR spectra were recorded in DMF at room temperature and liquid nitrogen temperature to obtain more accurate molecular values by giving four hyperfine signals for all the complexes.

Table 3

Spin Hamiltonian and orbital reduction parameters for copper (II) complexes at 300 and 77 K in solid state and in DMF solution

Complex	In solid state				In DMF solution									
	g_{\parallel}	g_{\perp}	g_{avg}	G	g_{\parallel}	g_{\perp}	g_{avg}	G	$A_{\parallel} \times 10^{-5}$	$A_{\perp} \times 10^{-5}$	K_{\parallel}	K_{\perp}	λ	α^2
1	2.218	2.063	2.114	3.547	2.138	2.049	2.078	2.905	0.0108	0.0031	1.802	0.571	295	0.61
2	2.151	2.072	2.072	2.089	2.192	2.066	2.129	2.978	0.0120	0.0018	2.050	0.457	579	1.55
3	2.107	2.091	2.102	1.083	2.257	2.071	2.133	3.676	0.0123	0.0016	1.914	0.524	573	0.66
4	2.111	2.092	2.098	1.202	2.268	2.077	2.140	3.558	0.0020	0.0023	1.889	0.531	594	0.67
5	2.190	2.082	2.118	2.359	2.143	2.059	2.104	3.318	0.0106	0.0034	1.830	0.559	432	0.77

The ESR parameters (g_{\parallel} , g_{\perp} , A_{\parallel} , A_{\perp}) of the complexes and the energies of d-d transitions are used to evaluate spin-orbit coupling constant (λ) and the orbital reduction parameters (K_{\parallel} , K_{\perp}). The trend $g_{\parallel} > g_{\perp} > g_e$ (2.0023) observed for these complexes suggests that the unpaired electron is localized in $d_{x^2-y^2}$ orbital of the copper(II) ion. For all the complexes the lowest g value greater than 2.0023 is also consistent with a $d_{x^2-y^2}$ ground state. The spin-orbit coupling constant (λ) value is calculated using the relation,

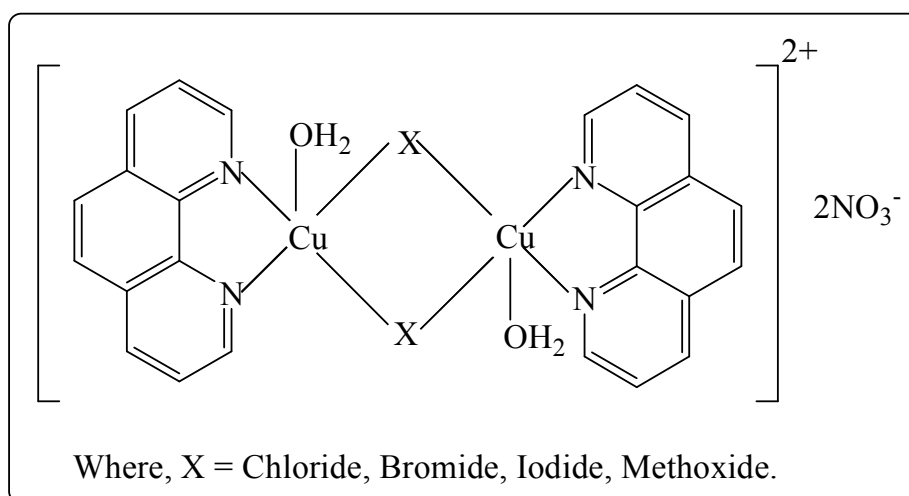
$$g_{ave} = (g_{\parallel} + 2 g_{\perp})^{1/3} \quad \text{and} \quad g_{ave} = 2(1 - 2\lambda/10Dq),$$

is less than the free copper(II) (832 cm^{-1}) which also supports covalent character of M-L bond. The observed $K_{\parallel} < K_{\perp}$ relation in all the complexes indicates the presence of in plane π -bonding. The factor α^2 is calculated using the following relation:

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

Based on molar conductance, magnetic moment, electronic, FT-IR and ESR spectral data a general structure (Figure 5) is assigned to copper(II) complexes having bridging monoanionic ligands.

Figure 5
Structure of Dinuclear complex in solid state



Electrochemical studies

The redox behaviour of the complexes has been investigated by cyclic voltammetry in DMF using 0.1 M tetrabutylammonium hexafluorophosphate as supporting electrolyte. A typical cyclic voltammogram of complex (3) at different scan rates (25, 50, 75 and 125 mVs^{-1}) is shown Figure 6. Table 4 gives the

electrochemical data obtained at the glassy carbon electrode in DMF. The cathodic peak current function values were found to be independent of the scan rate. The cyclic voltammograms obtained from repeated scans as well as various scan rates are very similar. The CV profiles suggest that dissociation of complex does not occur in DMF medium.

Figure 6
Cyclic voltammetric profile of $[\text{Cu}(\text{phen})(\mu\text{-Br})(\text{H}_2\text{O})_2](\text{NO}_3)_2$ at different scan rates

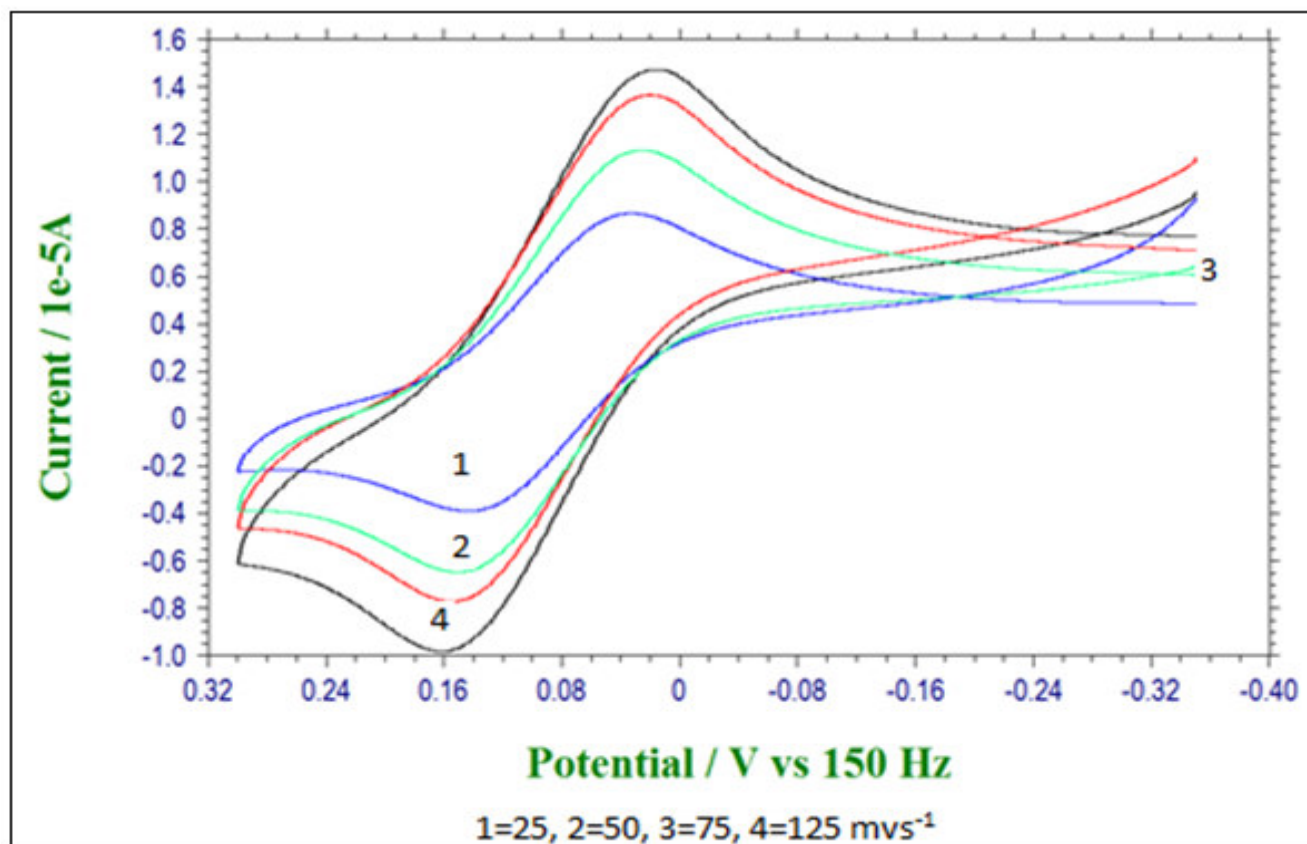


Table 4
Cyclic voltammetric data of copper(II) complexes

Complex	Redox couple	Peak Potentials (V)		ΔE_P (mV)	$E_{1/2}$	$-i_c/i_a$	$\log k_c^a$	ΔG^b
		E_{pc}	E_{pa}					
1	II/I	-0.016	0.246	262	0.118	1.061	0.1282	736
2	II/I	-0.044	0.531	575	0.243	0.827	0.0584	335
3	II/I	0.051	0.159	108	0.105	0.604	0.3111	1786
4	II/I	-0.226	0.652	878	0.213	0.426	0.0382	219
5	II/I	-0.047	0.382	429	0.032	0.772	0.0781	480

^a $\log K_c = 0.434 ZF/RT\Delta E_p$; ^b $\Delta G^0 = -2.303 RT \log K_c$

The difference between cathodic and anodic peaks (ΔE_p) increases with increasing scan rate. This observation suggests quasi-reversible behavior of complexes. Quasi-reversible nature reduction is evident from (i) non equivalent current intensity cathodic and anodic peaks and (ii) the difference (ΔE_p)

between the potentials of cathodic (E_{pc}) and anodic (E_{pa}) peaks. The ΔE_p in all these complexes exceeds the Nernstian requirement $59/n$ mV (n = number of electrons involved in the redox process) which suggests quasi-reversible character. All these complexes have large separation (108 - 878 mV) between the

anodic and cathodic peaks, indicating the quasi-reversible character. Log K values and ΔG values suggest that the complexes are stable in DMF medium.

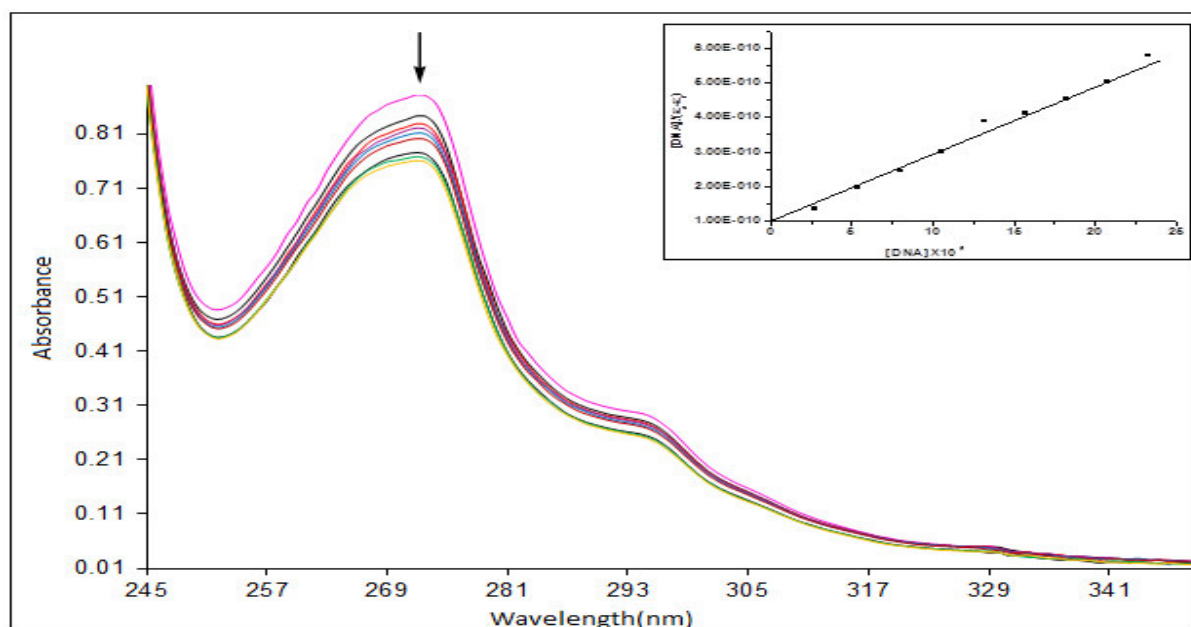
Electronic absorption titrations

The binding interactions of the complexes with CT-DNA were monitored by comparing their absorption spectra with and without CT-DNA.

In the presence of increasing amounts of DNA, the spectra of all complexes showed a strong decrease (Hypochromicity) in intensity with shift in absorption maxima towards higher (bathochromic shift) wavelengths in the case of complexes 1, 3 and 5. Figure 7 shows absorption spectra of complex (4) in the presence of increasing amounts of DNA.

Figure 7

Absorption spectra of $[Cu(phen)(\mu-I)(H_2O)]_2(NO_3)_2$ in the absence and in the presence of increasing concentration of CT-DNA; top most spectrum is recorded in the absence of DNA; A plot of $[DNA]/(\epsilon_a - \epsilon_f)$ versus $[DNA]$ is shown in the inset



The binding of an intercalative molecule to DNA is generally characterized by large hypochromism and significant red shift due to strong stacking interactions of aromatic chromophore between base pairs of DNA. The extent of hypochromism and red shift is commonly consistent with the strength of intercalative interaction²¹. However, in the present case, the magnitude of hypochromism

is as expected for typical classical intercalators²². The binding constants (Table 5) suggest that the complexes bind DNA very strongly. On addition of DNA the absorbance of the complexes decreases (hypochromism) and absorption maximum of all complexes is shifted to higher wavelength (bathochromism) in the case of complexes 1, 3 & 5.

Table 5
Electronic absorption data upon addition of CT-DNA to Cu (II) complexes

Complex	λ_{\max}		$\Delta\lambda/\text{nm}$	H%	$K_b^{-1} (\text{M}^{-1})$
	Free	Bound			
1	272	273	1	+ 5.6	2.76×10^5
2	272	271	1	+ 20.06	5.41×10^6
3	272	273	1	+ 9.36	6.68×10^5
4	272	271	1	+ 13.74	7.96×10^5
5	271	273	2	+ 23.33	4.86×10^5

These observations suggest that the complexes bind DNA through intercalation involving a strong π - stacking interaction of copper complex with planar polypyridyl ligand between the base pairs of DNA. From the Table 5, it is evident that the dinuclear complexes (2-5) binds DNA more strongly than the corresponding the parent mononuclear complex (1). Higher binding constants of dinuclear complexes are probably due to their more planar nature..

CONCLUSION

The dinuclear copper (II) complexes having bridging monoanionic ligands are characterized based on analytical and spectral data. In solid state the metal is 5- coordinate. In DMF medium the vacant sixth coordination site may be occupied by DMF(molecule), a well-known coordinating solvent. In DMF medium we predict the presence of 6-coordinate copper(II) in octahedral environment. The data (K_b) obtained in electronic absorption titrations

suggest that the complexes bind DNA strongly. The spectral changes of complexes upon addition of DNA suggest that the complexes bind DNA through intercalation between base pairs of DNA [23]. Electrostatic attraction between the cationic complex and the negatively charged phosphodiester backbone of DNA may also contribute to the binding constant²³

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