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Synthesis, Characterization and Kinetics of N,N'-Ethane Bridged Copper(II) Complex with ct-DNA

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Novel N,N′-ethane bridged complexes of copper(II) were prepared, which can act as potential drug. Structural elucidation of the complexes was performed on the basis of elemental analysis, IR, UV-vis, EPR, conductance measurements and NMR spectroscopy. All the spectroscopic data indicate ionic nature and square planar geometry for the metal ion. Kinetic studies were carried out with ct-DNA to ascertain the metal DNA interaction by spectrophotometric method at λ_{max} (446 nm) of Cu(II) complex at 30 ± 1 ºC. On interaction with ct-DNA, the absorption spectra exhibits a shift in wavelength and steep decrease in the absorbance, indicates the binding of ct-DNA with Cu(II) complex. The rate constants were calculated under pseudo-first order conditions and the plot of K_{obs} *versus* [DNA] give a straight line. The electrochemistry of ct-DNA-metal binding was carried out in H_2O/DMSO (95:5). The shift in formal potential after interaction with ct-DNA evidences the binding of Cu(II) complex to the ct-DNA. The ratio of anodic to cathodic peak currents I_{pa}/I_{pc} for free Cu(II) complex is 0.8 while for the DNA bound metal complex the ratio decrease to 0.5, suggesting that ct-DNA is bound strongly to the complex.

Key Words: Intercalation, Hypochromicity, Peak potential, Half wave potential, Rate constant, Pseudo-first order.

INTRODUCTION

DNA-metal interaction has become a subject of intense research[1-7]. This interaction is essentially noncovalent[8,9] either by intercalation, groove binding or external electrostatic binding. The binding of DNA to metal complexes is closely related to the structure of the complex and the macrocyclic frame work forms the suitable platform for holding the metal ions through nitrogen, sulphur and oxygen donor atoms. The cancer is derived from numerous tissues with multiple etiologies, thus therapy for curing cancer must be diverse, as the disease itself. The chemotherapy is widely used for treating cancer[10-12]. Majority of chemotherapeutic drugs are DNA targeted *e.g.*, cisplatin and its analogue intercalate into the DNA helix[13]. Much emphasis must be laid on molecular design of chemotherapeutic drugs[14,15], so that they work on the specific target on particular tumour type. In this regard, Chiral complexes can prove as more efficient and are regiospecific promising drugs.

In this work complexes of Cu(II) and Ni(II) were synthesized and the interaction of Cu(II) complex with ct-DNA was studied by UV-vis spectroscopy and cyclic voltammetry, as the changes in absorbance and redox values are directly related to the structure of the complex.

EXPERIMENTAL

All experiments involving interaction of the Cu(II) complex with ct-DNA were carried out in aqueous solution with varying concentration of ct-DNA (10×10^{-5}, 12×10^{-5}, 14×10^{-5}, 16×10^{-5}, 18×10^{-5} and 20×10^{-5} mol dm^{-3}). The ct-DNA concentration was determined by absorption spectrophotometry. Doubly distilled water was used through out the experiment. The stock solution of ct-DNA was prepared by dissolving it in 10 mL tris HCl buffer at pH 7 and dialyzing against the same buffer for 48 h. The solution gave a ratio of >> 1.8 at A260/280, indicating that ct-DNA was free from protein[16]. The concentration of ct-DNA was determined by monitoring the UV absorbance at 260 nm using Σ260 = 6600 cm^{-1}. The stock solution was stored at -20 ºC. $NiCl_2$, $CuCl_2$, (hydrated) (BDH), benzaldehyde (BDH) and *o*-phenylenediamine (Fluka) were used as received. ct-DNA was obtained from Sigma. IR spectra (4000-200) cm^{-1} were recorded on Carl Zeiss Specord M-80 spectrophotometer in nujol mulls. The electronic spectra were recorded on Systronic119 spectrophotometer (ESP-300) and the NMR spectra on amx-500 instrument. Cyclic voltammetry measurements were recorded on a CH instrument electrochemical analyzer. High purity H_2O/DMSO (95:5) was employed for the cyclic voltammetric studies with 0.4 M KNO_3 as supporting electrolyte. A three electrode configuration was used, comprised a Pt disc as working electrode, Pt wire as auxillary electrode and Ag/AgCl as the reference electrode. Experiments were carried out at 30 ± 1 ºC.

Synthesis of the ligand L ($C_{15}H_{12}N_2S_4$): Carbon disulfide (6.1 cm^3, 0.1 mol) was added dropwise with constant stirring

TABLE-1
COLOUR, m.p. YIELD AND ELEMENTAL ANALYSIS OF THE LIGANDS AND Cu(II)/Ni(II) COMPLEXES

Compound	Colour	m.p. (%)	Yield (%)	Elemental analysis (%) Found/(calcd.)		
$C_8H_8N_2S_4$	Brown	80-83	80	36.9 (36.7)	3.1 (2.9)	10.7 (10.8)
$C_{15}H_{12}N_2S_4$	Red	260-265	72	41.9 (41.9)	3.9 (3.9)	9.8 (9.8)
$C_{32}H_{26}N_4S_8$	Black	245 (d)	59	53.5 (53.2)	3.8 (3.6)	8.0 (7.8)
$C_{32}H_{26}N_4S_8CuCl_2$	Brown	260 (d)	54	39.2 (38.9)	2.7 (2.60	5.8 (5.7)
$C_{32}H_{26}N_4S_8NiCl_2$	Red	250 (d)	51	39.2 (38.9)	2.7 (2.6)	5.8 (5.7)

d = Decomposes.

to a solution of *o*-phenylenediamine (10.8 g, 0.05 mol) in absolute EtOH (50 cm^3) maintained at 0-4 ºC . The reaction mixture was stirred constantly for 1 h till a brown precipitate was obtained, filtered, washed thoroughly with hexane and dried *in vacuo*. The solid brown product (5.2 g, 0.02 mol) was dissolved in MeOH (25 cm^3) and benzaldehyde (2.12 cm^3, 0.02 mol) was added. The reaction was boiled to reflux for 5 h. A dark red precipitate was obtained. It was filtered, washed with ether and dried *in vacuo*.

Synthesis of ligand L'($C_{32}H_{26}N_4S_8$): To a solution of ligand $C_{15}H_{12}N_2S_4$ (3.48 g, 10 mmol) was added 1,2-dibromoethane (0.43 cm^3, 5 mmol) in 2:1 ratio. The reaction mixture was boiled to reflux for 6 h. A black precipitate was obtained, which was filtered, washed thoroughly with ether and dried *in vacuo*.

Synthesis of metal complexes: To a solution of ligand L' ($C_{32}H_{26}N_4S_8$) (0.723 g, 1 mmol) in MeOH was added metal chloride hydrated (0.342 g, 2 mmol) in 1:1 molar ratio. The reaction mixture was boiled to reflux for *ca.* 5 h and a brown precipitate was obtained, washed thoroughly and then dried *in vacuo*. The physico-chemical data of the ligands and Cu(II)/ Ni(II) complexes are given in Table-1.

RESULTS AND DISCUSSION

IR Spectra: The characteristic frequencies observed in the IR spectra of the ligand and the complexes are given in Table-2. The ligand exhibits thione-thiol tautomerism, since they contain a thioamide (-HN-C=S) functional group[17,18].

TABLE-2
KEY IR BANDS (cm^{-1})

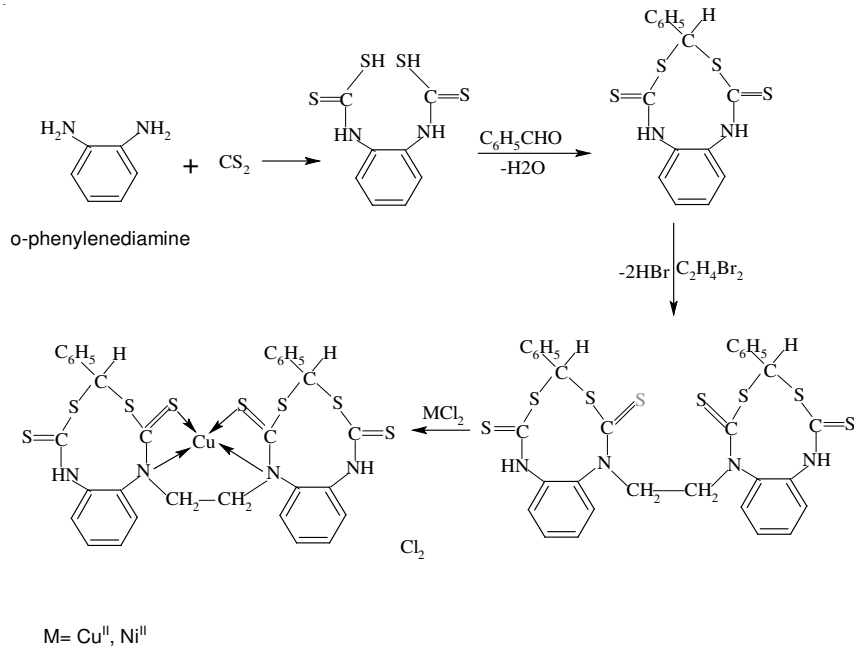
Compound	ν(NH)	ν(C-N)	ν(C-S)	ν(M-S)	ν(M-N)
$C_{15}H_{12}N_2S_4$	3375	1365	739	–	–
$C_{32}H_{26}N_4S_8$	3400	1399	741	–	–
$C_{32}H_{26}N_4S_8CuCl_2$	3423	1382	757	355	430
$C_{32}H_{26}N_4S_8NiCl_2$	3421	1379	755	353	422

However absence of SH bond and presence of (NH) indicates that the ligand in the solid state remains in the thione form. This contention is further supported by ^1H NMR which does not show any signal due to presence of SH protons. The ν(C-S) and ν(C=S) bands appear at 755-739 and 1084-1067 cm^{-1}, respectively. The appearance of new band at 2840 cm^{-1} due to CH_2 group supports the formation of ligand. The far IR spectra reveal ν(M-N) and ν(M-S) bands at 430-422 and 355-353 cm^{-1} region, respectively[19,20].

Electonic absorption spectra: The absorption spectrum of the [L'] recorded in MeOH exhibits bands at 224, 244 and 304 nm. These bands are attributed to π-π* and n-π* transitions, respectively.

The absorption spectra of Cu(II) complex in DMSO reveals characteristic bands of MLCT transition at 378 and 392 nm. A strong band and weak shoulder appears at 446 and 464 nm, respectively assigned to $^2B_{1g} \rightarrow {}^2E_g$ transitions characteristic of square planar geometry[21].

The nickel(II) complex exhibits a broad band at 452 nm assigned to $^1A_{1g} \rightarrow {}^1B_{1g}$ transitions typical of square planar geometry[22].



EPR spectra: The room temperature EPR spectrum recorded for the Cu(II) complex reveals $g_{\|}$ and $g_{\perp}$ at 2.20 and 2.07, respectively for square planar geometry[23]. The presence of $g_{\|} > g_{\perp}$ in the EPR spectrum of Cu(II) complex supports square planar geometry[24].

NMR studies: The ^{1}H NMR spectra of ligand shows peaks at 7.2-8.2 ppm assigned to phenyl protons. The signal due to CH_2 protons was observed at 3.6 ppm[25]. The NH and CH signal was observed 4.6 and 5.2 ppm, respectively.

Cyclic voltammetry: The cyclic voltammetry is an important tool to measure the formal electrode potential of electron transfer reactions. Recently, its application to study metallintercalation and coordination of metal into ct-DNA has given insight to this subject. Cyclic voltametry also complements the other spectroscopic techniques to understand the nature of DNA binding[26,27]. To study the redox properties of Cu(II) complex intercalation with ct-DNA, we have investigated the cyclic voltammogram of free Cu(II) complex and the DNA bound Cu(II) complex in H_2O/DMSO (95:5). The cyclic voltammogram of Cu(II) complex at scan rate of 0.1 V/s reveals a quasireversible well separated redox wave due to one electron transfer reaction attributed to the Cu(II)/Cu(I) couple with $E_{1/2}$ values 0.498V and -0.532 V, respectively (Fig. 1).

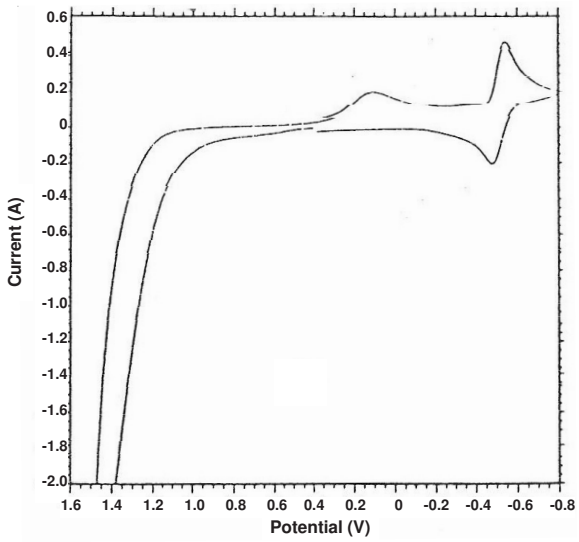
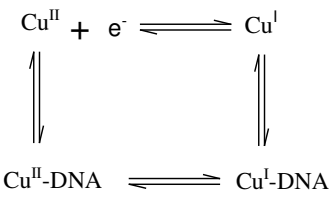


Fig. 1. Cyclic voltammogram of copper(II) complex

The profile of voltammogram obtained at variable scan rates is almost similar (Fig. 2). For a reversible wave, E_p is independent of the scan rate and i_p (as well as current at any point of the wave) is propotionl to the $\Delta_{1/2}$[28]. The limiting peak separation ΔE_p is equal to 63 mV which is in good agreement with Nernstian value for one electron transfer couple (59 mV). On addition of ct-DNA, the complex experiences shift in $E_{1/2}$ and E_p values of 9 and 13 mV at the scan rate of 0.1 V/s (Fig. 3). The ratio of anodic to the cathodic peak currents I_{pa}/I_{pc} is 0.8 in the free Cu(II) complex while on addition of ct-DNA, the ratio of I_{pa}/I_{pc} decreases to 0.5 suggesting that ct-DNA is bound strongly to the complex. Moreover there is decrease in voltametric peak currents upon addition of ct-DNA due to diffusion of equilibrium mixture ofthe free and DNA bound metal complex to the electrode surface[29]. The change in formal electrode potential of free Cu(II) complex and ct-DNA bound complex reveals strong intercalation of the complex with DNA helix and also suggests the stabilization of Cu(II) over Cu(I) as depicted in the square redox scheme shown below:



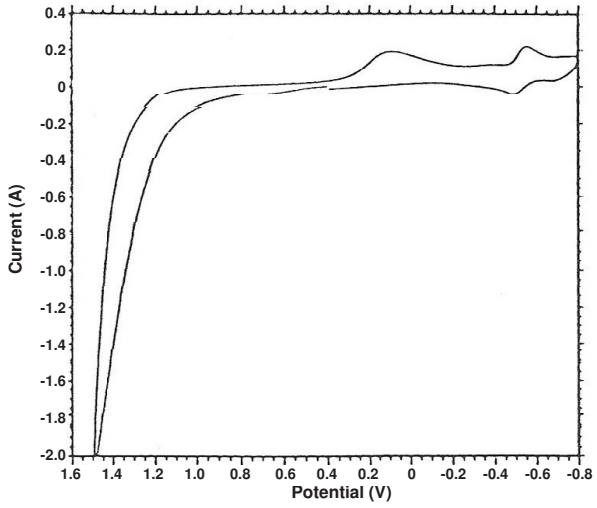


Fig. 2. Cyclic voltammogram of copper(II) complex at different scan rates

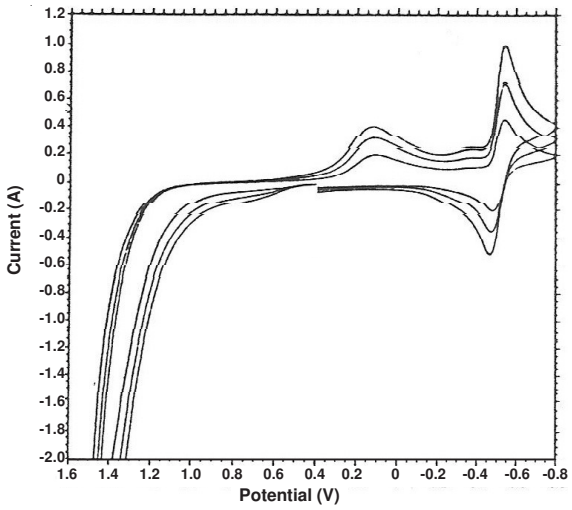


Fig. 3. Cyclic voltammogram of copper(II) complex after addition of ct-DNA

Kinetic studies: The binding of Cu(II) complex to ct-DNA has been characterized through absorption changes spectrophotometrically. The absorption spectrum of the Cu(II) complex in H_2O/DMSO (95:5) at 30 ± 1 ºC. Kinetic experiments were carried out at λ_{max} of Cu(II) complex at a fixed concentration (10^{-3} mol dm^{-3}) with varying concentration of ct-DNA (10×10^{-3}-18×10^{-3} mol dm^{-3}). On addition of ct-DNA to the Cu(II) complex, there is a decrease in absorption intensity and significant shift in λ_{max} (40 nm). The rate constants k_{obs} values were obtained by plotting log A *versus* time and are shown graphically (Fig. 4) which clearly indicates pseudo-first order kinetics with respect to concentration of ct-DNA. The following mechanistic pathway has been proposed (**Scheme-I**).

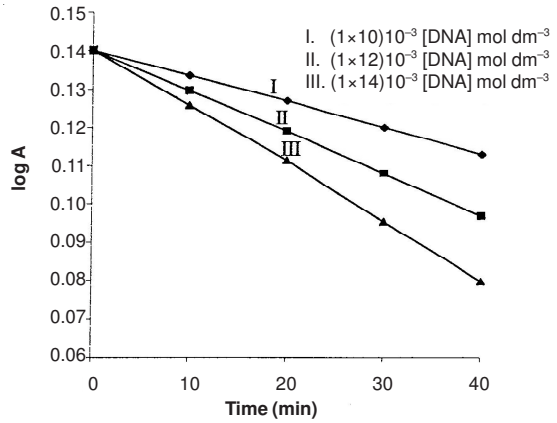
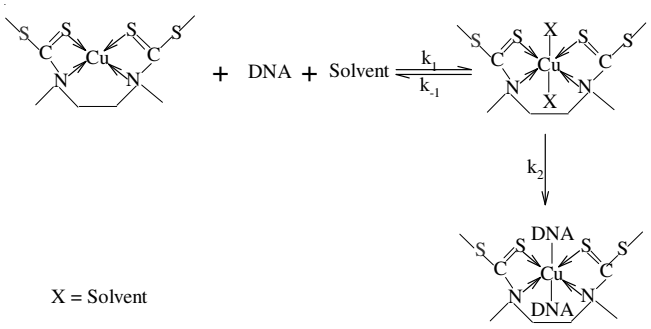


Fig. 4. Plot of log A *versus* time for copper(II) complex at varying concentration of ct-DNA(10-18 × 10^{-3} mol dm^{-3})



Scheme-I

If the proposed mechanism is correct, then this rate law holds good

$$k_{obs} = k_1k_2[DNA]/k_{-1} + k_2 \quad (1)$$

The rate law according to the eqn. 1 should give a straight line for k_{obs} *versus* [DNA] (Fig. 5). Present results are consistent with eqn. 1 which give linear plot with slope equal to $\frac{k_1k_2}{k_{-1}+k_2}$ showing pseudo-first order dependence for interaction of Cu(II) complex with ct-DNA.

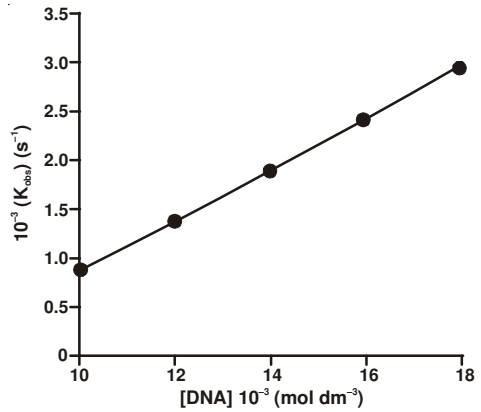


Fig. 5. Plot of K_{obs} *versus* concentration of ct-DNA for copper(II) complex [fixed concentration of complex = 1 × 10^{-3} mol dm^{-3}]

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