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Synthesis, Characterization and Electrochemical Studies of Acyclic End-Off Copper(II) and Nickel(II) Complexes: Nuclease Activity

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ABSTRACT

Novel acyclic binuclear copper(II) and nickel(II) complexes were synthesized and characterized by spectroscopic methods. Cyclic voltammogram of all the complexes **1-4** were recorded in the cathodic potential range 0 to -1.4 V. All the copper (II) and nickel(II) complexes exhibit two quasi-reversible steps at different potentials. In competitive binding experiments the K_{app} values for complexes were $3.1x10^5$ M^{-1}(**1**) $4.2x10^5$ M^{-1}(**2**), $3.78x10^5$ M^{-1}(**3**) and $4.93x10^5$ M^{-1} (**4**) respectively. DNA cleavage mechanism is an oxidative DNA pathway in the presence of activators, in which giving active oxygen species such as hydroxyl radical, probably a copper-peroxide, cleaves DNA.

1. Introduction

The war on cancer is still not won. Cancer is responsible for about 500,000 people deaths/year (20% to 50% of the total mortality) in the USA with about one million cases developing each year. The overall incidence and mortality rates in the USA between I973 and 1990 have increased by 18.3 and 6.7 % respectively. The three most common cancers in men are lung, prostate, and colorectal cancers. In women, breast, colorectal and lung cancer are the most common tumors [1]. Chemotherapy, no doubt, is the major cancer modality for patients having a tumor that has metastasized to distant sites of the body at the time of diagnosis or relapse at some time following primary surgery or radiation therapy. DNA has been used as a traditional target in chemotherapy for human cancer [2, 3]. Cisplatin is a widely used as an anticancer drug that is highly effective against testicular and ovarian cancers but the major limitations are severe toxicity to fast growing normal cells in the bone marrow, hair follicles and gastrointestinal tract because of the inability of the presently available anticancer drugs to distinguish cancer cells from the normal cells [4-6]. In spite of that the high therapeutic efficiency of anticancer drugs has inspired in the development of next generation agents that are effective against cancer cells with fewer side effects. With this connection copper(II) and nickel(II) complexes tend to be strongly mutagenic, and some have shown promising chemotherapeutic activity, which correlates well with DNA-binding affinity [7-9].

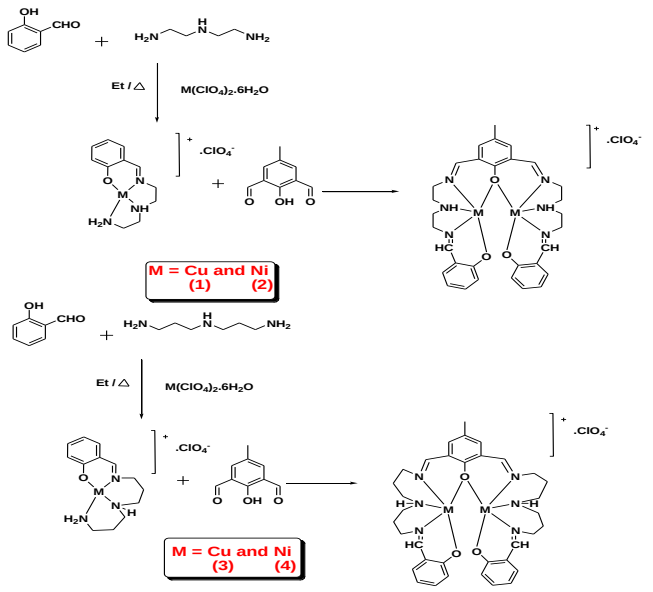
In this paper, we have described the synthesis and characterization of a series of acyclic end-off copper(II) and nickel(II) complexes. Binding affinity of copper(II) and nickel(II) complexes to calf thymus (CT-DNA) was monitored using spectroscopic titration, viscosity measurements. Nuclease activities of synthesized complexes were monitored and the mechanism of cleavage also studied.

2. Experimental Methods

2.1 Materials and Methods

The precursor compound, 2, 6-diformyl-4-methyl phenol was prepared by reported procedure [10]. Tetra(n-butyl)ammoniumperchlorate (TBAP) was purchased from Fluka and recrystallized from hot methanol and used as the supporting electrolyte in electrochemical measurement, (Caution! TBAP is potentially explosive and hence, care should be taken in handling the compound). All other chemicals and solvents were purified by reported procedures [11]. CT DNA and pBR322 DNA and Ethidium bromide (EtBr) were purchased from Bangalore Genie (India). Tris(hydroxymethyl)aminomethane-HCl (Tris-HCl) buffer was prepared using deionized water.

Elemental analysis was carried out in Carlo Erba model 1106 elemental analyzer. FT-IR spectra were recorded in (4000 – 400 cm^{-1}) Perkin Elmer FTIR spectrometer with samples prepared as KBr pellets. UV–visible spectra were recorded using a Perkin Elmer Lambda 35 spectrophotometer operating in the range of 200–900 nm. Emission intensity measurements were carried out using Perkin Elmer LS-45 fluorescence spectrometer. Electrochemical measurements were performed using electrochemical analyzer CHI 1008 using a three-electrode cell. Glassy carbon electrode is a working electrode with saturated Ag/AgCl electrode as the reference electrode and platinum wire act as auxiliary electrode. The concentration of all the complexes was made at 10^{-3} M. TBAP (10^{-1} M) was used as the supporting electrolyte in all electrochemical experiments.



Scheme 1 synthesis of new copper(II) and nickel(II) complexes (**1-4**)

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2.2 Synthesis of Binuclear Copper(II) Complexes

To ethanonlic solution of Salicylaldehyde (0.11 mL, 1 mmol) was added diethylene triamine (0.11 mL, 1 mmol) to prepare complex **1** and/or for complex **3** dipropalene triamine in the manner of dropwise under constant stirring (Scheme 1). To further ethanolic solution of $M(ClO_4)_2$. $6H_2O$ (1 mmol) was added and the solution was stirred well and refluxed for 1 h. The resulting hot solution was evaporated under room temperature for about one fourth of the solution, and then precipitated color solid was separated out and washed well with cold ethanol. For complex **1**; Yield: 0.24 g (60 %); Brown color solid; Anal.Cal for $C_{31}H_{35}Cu_2N_6O_3$: C, 55.84; H, 5.29; N, 12.6; Found: C55.77; H, 5.27; N, 12.62 and for complex **3**; Yield: 0.211 g (54 %); Green color solid; Anal.Cal for $C_{35}H_{43}Cu_2N_6O_3$; C, 58.16; H, 6.00; N, 11.63; Found: C, 58.11; H, 5.94; N, 11.66. The binuclear Cu (II) complex was prepared from a vigorously stirred suspension of 2,6-diformyl-4-methyl phenol (0.328 g, 2 mmol) in 50 mL ethanol/chloroform (9:1 mL), then ethanolic solution of complex **1** and complex **3** (4 mmol) was added slowly and the mixture was stirred for 15 min to obtain a clear solution. The reaction mixture was refluxed for 3 h, the hot solution was filtered and evaporated at room temperature, the dark red solid was separated out and dried well recrystallized in ethanol. For complex **2**; Red color solid; Yield: 0.449 g (61 %); Anal.Cal for $C_{31}H_{35}N_6Ni_2O_3$: C, 56.67; H, 5.37; N, 12.79; Found: C, 56.61; H, 5.31; N, 12.82 and for complex **4**; Green color solid; Yield: 0.450 g (57 %); Anal.Cal. $C_{35}H_{43}N_6Ni_2O_3$; C, 58.95; H, 6.08; N, 11.78; Found: C, 58.89; H, 5.98; N, 11.82.

2.3 DNA Binding Experiments

Fluorescence quenching experiment were carried out by addition of complexes to sample solution containing EtBr-DNA. The spectra were recorded at excitation wavelength 520 nm and emission wavelength between 610 nm. Using the fluorescence quenching spectra, the reduction emission intensity measures the binding propensity of complex to CT DNA. Stern-Volmer quenching constant (K_{sv}) and apparent binding constant (K_{app}) were calculated using $I_0/I=1+K_{sv}r$ and K_{EtBr} [EB]=K_{app}[Complex], where I_0 and I corresponds fluorescence intensities of EtBr-DNA in absence and presence of complex, r is the ratio of the total concentration of complex to that of DNA, and K_{EtBr} = 1 X 10^7, [EtBr] = 4 µM, [Complex] is the concentration of the complex at 50% reduction of emission intensity of EtBr respectively [12].

2.4 DNA Cleavage Studies

The DNA cleavage experiments were performed by agarose gel electrophoresis, by incubation at 37 °C as follows: pBR322 DNA (0.1 µg/µL) in 50 mM Tris–HCl buffer (pH=7.2) was treated with copper(II) complexes containing 1% DMF. The samples were incubated for 3 h, and then loading buffer (1 µL) was added. The sample was electrophoresis for 3 h at 50 V on 0.8% agarose gel using Tris–Acetic acid–EDTA buffer. After electrophoresis, bands were visualized by UV light and photographed. To identify the reactive oxygen species (ROS) involved in the cleavage reaction to introduce the scavengers like NaN_3, L-histidine (singlet oxygen), SOD (superoxide), and DMSO (hydroxyl). The extent of cleavage of the super coiled DNA (SC DNA) was determined by measuring the intensities of the bands using the UVITEC Gel Documentation System [13].

3. Results and Discussion

3.1 FTIR Spectral Characterization

All the complexes are stable in air and good solubility in DMF, DMSO, methanol, ethanol and 1% DMF/50 mM Tris-HCl buffer solution. The complexes are characterized by various spectroscopic and analytical methods. ESI-MS spectra of the copper(II) complexes (**1**-**4**) showed an essentially molecular ion peaks and their isotopic peak [M+1]. From IR spectra of acyclic copper(II) complexes shows the three important peaks (Table 1).

Table 1 FT-IR spectral data of all the complexes

Complexes	N-H (cm^{-1})	C=N (cm^{-1})	Aromatic (cm^{-1})	ClO^{-}_4 (cm^{-1})
1.	3176, 3264	1623	1558	1089
2.	3162, 3265	1623	1568	1089
3.	3205, 3293	1640	1582	1097
4.	3142, 3230	1640	1538	1093

One is sharp peak observed in the region of 1080-1100 cm^{-1} and sharp band in the region of 626 cm^{-1} which indicates that the perchlorate anion of antisymmetric stretching and antisymmetric bending respectively. Third a strong absorption band around 1600-1635 cm^{-1} is due to the azomethine (C=N) bond as a place of 1680 cm^{-1} as a result of this, the formation of Schiff base product is conformed. Absorption for the aromatic rings occurs around in the 1560 cm^{-1} region. Complexes (**1**-**4**) shows weak band around 3220 cm^{-1} and 3100 cm^{-1} indicates for the N-H stretching vibration of coordinated secondary amine groups. The non-ligand peaks at around 500-600 cm^{-1} were assigned to (Cu-N) and (Cu-O) stretching vibration respectively.

3.2 Electronic Spectroscopy

The electronic spectra were recorded in DMF solvent in the region 200-900 nm. The electronic spectra of the binuclear acyclic copper(II) complexes observed three main transitions (Table 2). One has less intense band in the range of 500-600 nm is due to d-d transition of the metal ion, a moderately intense band in range of 300-400 nm is due to ligand to metal charge transfer transition and a band observed at below 300 nm is assigned to an intraligand (π-π*) charge transfer transition. The electronic spectra of the copper(II) complexes **2** and **4** have higher wavelength compared to complexes **1** and **3**. As a result of red shift, the distortions of geometry with increase the aliphatic group of the complexes. The d-d band shows below 600 nm corresponding to $^2B_{1g} - {}^2B_{2g}$ [d_{x2-y2} to d_{yz}] transition which is in consistent with that of a square pyramidal geometry around the copper(II) complexes. Therefore, it appears that there is a distorted square-pyramidal geometry of the Cu(II) centers in the copper(II) complexes and Ni(II) centers in the nickel(II) complexes.

Table 2 UV-Vis spectral data of the complexes (**1**-**4**)

Complexes	λ_{max} (dm^{-3} cm^{-1})	
	d-d transition	C-T bands
1.	560(ε = 125)	362(ε=96,000), 312(ε=1,00,000), 260 (ε=1,20,000)
2.	630(ε=580)	358(ε=45,000), 308(ε=50,000), 270(ε=59,000)
3.	576 (ε=300)	375 (ε=70,000), 268(ε=1,30,000)
4.	620(ε=320)	346(ε=58,000), 260(ε=74,000)

3.3 Electrochemical Studies

Redox behavior of all the complexes reported in the present work were studied by suing cyclic voltammograme in the potential ranges 0 to 21.6 V and 0 to 1.6 V in dimethylformamide containing 0.1 M tetra(n-butyl)ammonium perchlorate (Caution! TBAP is potentially an explosive: hence care should be taken in handling the compound) as a supporting electrolyte. All the nickel(II) complexes undergo both reduction and oxidation in cathodic and anodic potentials, respectively. Systematic electrochemical studies on various metal complexes can distinguish three types of electrochemical behaviors, reversible, quasi-reversible and irreversible electron transfer processes.

(i) Reversible Systems

- The cathodic and anodic potential are independent of scan rate.
- ΔEp value is 59/n mv at 25 °C.
- The anodic to cathodic current ratio is unity.
- The wave shape doesn't change with change in scan rate.

(ii) Quasi-Reversible Systems

- The cathodic and anodic peak potential varies with respect to scan rates.
- ΔEp value is higher than 59/n mV and increases with this scan rate.
- The anodic to cathodic current ratio is greater than unity.
- The nature of the wave shape broadens as this scan rate increases.

(iii) Irreversible Systems

- Ep value shift cathodically by 30mV per tenfold increase in the scan rate.
- There is no current on the reverse scan.
- The wave shape in determined by the charge transfer co-efficient and it is independent of the scan rate.

Two different reduction and oxidation waves of all the copper(II) complexes maybe due to copper metal ions present in two different compartments during redox processes.

3.3.1 Reduction Process

The electrochemical property of all the complexes **1**-**4** were recorded by cyclic voltammetry. The electrochemical data of cathodic peak potential(E_{pc}), anodic peak potential(Epa), redox peak $E_{1/2}$, and peak

separation(ΔEp) are given in Table 3. In the cathodic potential range 0 to -1.4 V all the copper (II) and nickel(II) complexes exhibit two quasi-reversible steps at different potentials. In all the four complexes well defined peaks, observed in the potential range from -0.81 to -0.93 V were due to the reduction from $Cu^{2+}Cu^{2+}$ to $Cu^{2+}Cu^{1+}$ and $Ni^{2+}Ni^{2+}$ to $Ni^{2+}Ni^{1+}$. The second reduction waves observed the potential range from-1.04 to -1.17 V are due to reduction of $Cu^{2+}Cu^{1+}$ to $Cu^{1+}Cu^{1+}$ and $Ni^{2+}Ni^{1+}$ to $Ni^{1+}Ni^{1+}$ (Fig. 1). Based on the observations, it is reasonable to suggest that the reduction process may involve the following steps [14].

$$Cu^{II}Cu^{II} \rightleftharpoons Cu^{II}Cu^{I} \rightleftharpoons Cu^{I}Cu^{I}$$

$$Ni^{II}Ni^{II} \rightleftharpoons Ni^{II}Ni^{I} \rightleftharpoons Ni^{I}Ni^{I}$$

3.3.2 Oxidation Process

Fig. 2 shows the cyclic voltammogram of the binuclear Ni(II) complexes, which exhibit two quasireversible oxidation waves. The first oxidation potential ranges from 0.64 to 0.66 V and the second oxidation potential falls in the range from 1.08 to 1.10 V. The oxidation process can be described as below. The values are shown in Table 4.

$$Ni^{II}Ni^{II} \rightleftharpoons Ni^{II}Ni^{III} \rightleftharpoons Ni^{III}Ni^{III}$$

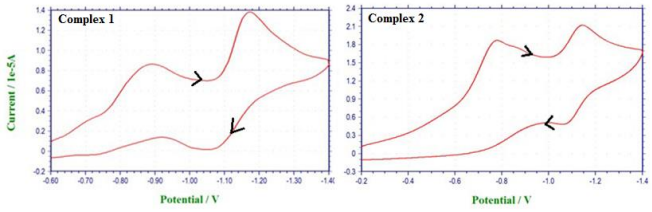

Fig . 1a-b Cyclic voltammogram of binuclear copper(II) complexes **1** and **2**

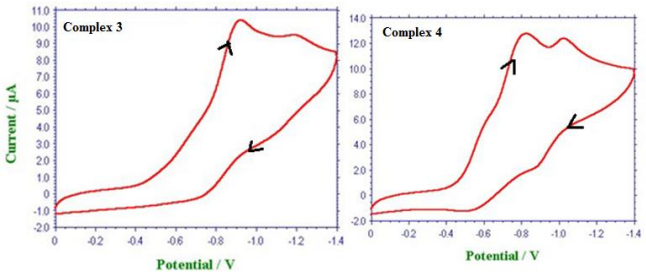

Fig . 1c-d, Cyclic voltammogram of binuclear nickel(II) complexes **3 and 4** in the reduction process

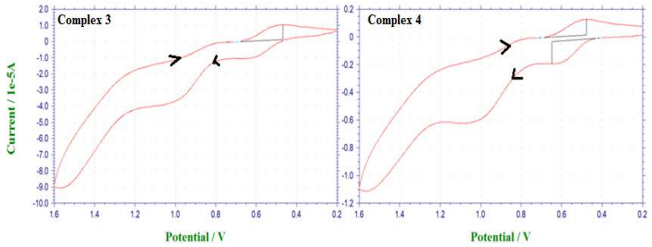

Fig . 2a-b, Cyclic voltammogram of binuclear nickel(II) complexes **3** and **4** in the oxidation process

Table 3 Electrochemical reduction data of copper(II) and Nickel(II) complexes

Comp.	E^1_{pc} (V)	E^1_{pa}(V)	$E^1_{1/2}$(V)	ΔE(mV)	E^2_{pc}(V)	E^2_{pa}(V)	$E^2_{1/2}$(V)	ΔE (mV)
1.	-0.88	-0.74	-0.81	140	-1.17	-1.10	-1.14	70
2.	-0.78	-0.65	-0.72	130	-1.15	-1.06	-1.11	90
3.	-0.93	0.73	-0.83	200	-1.2	-1.1	-1.15	100
4.	-0.81	-0.56	-0.69	250	-1.04	-0.90	-0.96	140

Table 4 Electrochemical oxidation data of Nickel(II) complexes

Comp.	E^1_{pa}(V)	E^1_{pc}(V)	$E^1_{1/2}$(V)	ΔE^1(mV)	E^2_{pa}(V)	E^2_{pc}(V)	$E^2_{1/2}$(V)	ΔE^2(mV)
1	0.64	0.46	0.55	180	1.08	0.88	0.98	200
2	0.66	0.48	0.72	180	1.10	0.82	0.96	280

3.4 DNA Binding and Cleavages Studies

3.4.1 Ethidium Bromide Displacement Assay

The competitive DNA binding of complexes has been studied by monitoring changes in emission intensity of ethidium bromide (EtBr) bound to CT-DNAas a function of added complex concentration. Though the emission intensity of EtBr in buffer medium (50 mM Tris-HCl) is quenched by the solvent molecules, it is enhanced by its stacking interaction between adjacent DNA base pairs. When complexes were added to DNA pretreated with EtBr ([DNA]/[EtBr]=1:1), the DNA-induced emission intensity of EtBr was decreased (Fig. 3) [15]. Addition of a second DNA binding molecule would quench the EtBr emission by either replacing the DNA-bound EtBr (if it binds to DNA more strongly than EtBr) or accepting an excited state electron from EtBr. Because the complexes have planar ligands, they efficiently compete with strong intercalators like EtBr for intercalative binding sites on DNA by replacing EtBr, which is reflected in quenching of emission intensity of DNA-bound EtBr. The apparent binding constant (K_{app}) has been calculated from the following equation

$$K_{EtBr}\,[EtBr] = K_{app}\,[complex]$$

where K_{EtBr} is 1 x 10^7 M^{-1} and the concentration of EtBr is 20 µL, [complex] is the concentration of the complex causing 50% reduction in the emission intensity of EtBr. The K_{app} values for complexes were 3.1x10^5 M^{-1}(**1**) 4.2x10^5 M^{-1}(**2**), 3.78x10^5 M^{-1}(**3**) and 4.93x10^5 M^{-1}(**4**) respectively. The higher values of Kapp indicate that these complexes bind to DNA by intercalation. The Stern-Volmer quenching constant Ksv of the complex **1** to DNA was calculated from the equation Io/I = 1+K_{sv} r, where Io and I are fluorescence intensity of EB-DNA in the absence and presence of complex respectively, Ksv is the Stern-Volmer quenching constant, r is the ratio of [Complex]/[DNA]. The calculated value of Ksv is 0.18(**1**), 0.41(**2**), 0.39(**3**) and 0.55(**4**).

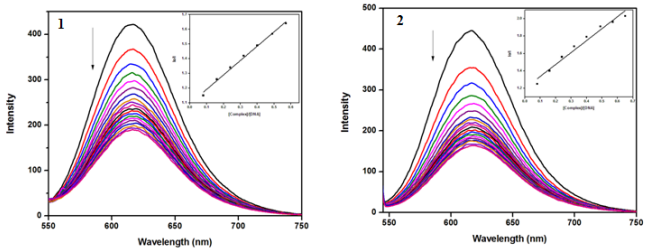

Fig. 3a-b Fluorescence emission spectra (λ_{ex} = 520 nm) of the EB-DNA system ([EB] = 4 µM, [DNA] = 4 µM) in the absence and presence of Complexes **1** and **2** ([Comp] = 60 µM). Inset: The plot shows the emission intensity I_0/I *Vs* [Comp]/[DNA]

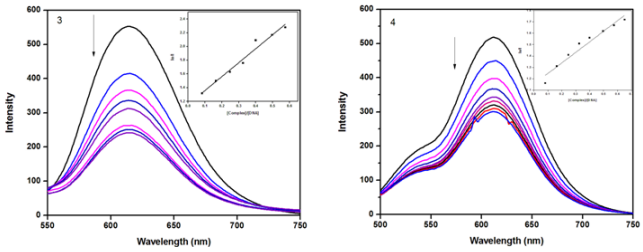

Fig. 3c-d Fluorescence emission spectra (λ_{ex} = 520 nm) of the EB-DNA system ([EB] = 4 µM, [DNA] = 4 µM) in the absence and presence of Complexes **3** and **4** ([Comp] = 60 µM). Inset: The plot shows the emission intensity I_0/I *Vs* [Comp]/[DNA]

3.4.2 DNA Cleavage of pBR322

In order to assess the chemical nuclease activities of the copper(II) complexes for DNA strand scission, pBR322 DNA was incubated with the copper(II) complexes under the reaction conditions. The cleavage reaction can be monitored by gel electrophoresis. When circular pBR322 DNA is subjected to electrophoresis, relatively fast migration will be observed for the intact supercoiled form (Form I). If scission occurs on one strand (nicking), the supercoiled form will relax to generate a slower-moving nicked form (Form II). If both strands are cleaved, a linear form (Form III) that migrates between Form I and Form II will be generated [16].

Firstly, the chemical nuclease activities of complex **2** has been studied using supercoiled pBR322 plasmid DNA as a substrate in the medium of 50 mM Tris-HCl/NaCl buffer (pH = 7.2) in the presence of hydrogen peroxide under physiological conditions. Complex **2** cleaves the supercoiled DNA(SC) to nicked circular DNA(NC) and linearised forms. In order to obtain information about the active oxygen species which was responsible for the DNA damage, we investigated the DNA cleavage in the presence of hydroxyl radical scavengers (DMSO), singlet oxygen quenchers (NaN_3, L-Histidine), superoxide scavenger (SOD), and chelating agent (EDTA) under our experimental conditions. From Fig. 4, we can see that no obvious inhibitions are observed for the complex **2** in the presence of SOD (lane 4), L-Histidine (lane 6) and NaN_3, as the results rule out the possibility of DNA cleavage by superoxide and singlet oxygen. The addition of EDTA (Lane 3) partly diminishes the nuclease activity of the complex which is indicative of the involvement of metal ion like entity in

the cleavage process. The inhibitory activity of DMSO (Lane 4) is more comparable to other inhibitors, so strongly suggests that the hydroxyl radical was involved in the cleavage mechanistic pathway. The copper(II) complex examined here may be capable of promoting DNA cleavage through an oxidative DNA damage pathway in the presence of activators, in which giving active oxygen species such as hydroxyl radical, probably a copper-peroxide, that cleaves DNA. As follows the same concentration of complex and scavenger used for the complexes **1**, **3** and **4** which have the same results collected for the gel electrophoresis picture (Fig. 5).

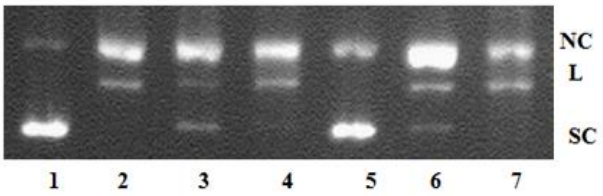

Fig. 4 Agarose gel showing the cleavage of pBR322 DNA(150 μg/mL) by copper(II) complex **2** (0.1 mM) in presence of hydrogen peroxide (500 μM) as reducing agent in (50 mM) Tris-HCl buffer at pH 7.2 and 37 °C with an incubation time of 3 h and different quenchers. Lane 1, DNA control; Lane 2, DNA + H_2O_2 +complex **2**; Lane 3, DNA + H_2O_2 + EDTA + complex **2** ; Lane 4, DNA + H_2O_2 + SOD (5 units) **+** complex **2** ; Lane 5, DNA + H_2O_2 + complex **2** + DMSO (2 μL); Lane 6, DNA + H_2O_2 + complex **2** L-Histidine +; Lane 7, DNA + H_2O_2 + complex **2** + NaN_3 (1 mM);

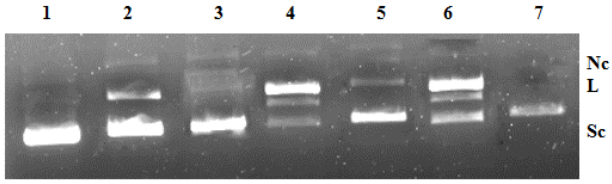

Fig. 5 Agarose gel showing the cleavage of pBR322 DNA(150 μg/mL) by copper(II) complexes **1, 3, 4** (0.1 mM) in presence of hydrogen peroxide (500 μM) as reducing agent in (50 mM) Tris-HCl buffer at pH 7.2 and 37 °C with an incubation time of 3h and DMSO is hydroxyl radical quencher. Lane 1, DNA control; Lane 2, DNA + H_2O_2 +complex **1**; Lane 3, DNA + H_2O_2 + DMSO (2 μL) + complex **1** ; Lane 4, DNA + H_2O_2 + complex **3** ; Lane 5, DNA + H_2O_2 + complex **3** + DMSO (2 μL); Lane 6, DNA + H_2O_2 + complex **4** + ; Lane 7, DNA + H_2O_2 + complex **4** + DMSO (2 μL);

4. Conclusion

The competitive DNA binding of complexes has been studied by monitored the changes in emission intensity of ethidium bromide (EtBr) bound to CT-DNAas a function of added complex concentration. The K_{app} values were calculated as $3.1x10^5$ M^{-1}(**1**) $4.2x10^5$ M^{-1}(**2**), $3.78x10^5$ M^{-1}(**3**) and $4.93x10^5$ M^{-1}(**4**) respectively. The higher values of Kapp indicate that synthesized complexes bind with DNA by intercalation mode. In cleavage studies, synthesized complexes cleave the DNA in presence of H_2O_2 as an activator and the reactive oxygen species were responsible for the DNA damage. In mechanistic investigation, the best inhibition activity as found in presence of DMSO, as result hydroxyl radical induces the DNA cleavage process.

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References

[1] T. Beardsley, A war not won, Sci. Amer. 270 (1994) 130-138.
[2] K.S. Park, C.Y. Lee, H.G. Park, Target DNA induced switches of DNA polymerase Activity, Chem. Commun. 51 (2015) 9942-9945.
[3] R. Palchaudhuri, P.J. Hergenrother, DNA as a target for anticancer compounds: methods to determine the mode of binding and the mechanism of action, Curr. Opin. Biotechnol. 18 (2007) 497-503.
[4] Y. Jung, S.J. Lippard, Direct cellular responses to platinum-induced DNA damage, Chem. Rev. 107 (2007) 1387-1407.
[5] K. Wang, J.F. Lu, R.C. Li, The events that occur when cisplatin encounters cells, Coord. Chem. Rev. 151 (1996) 53-88.
[6] Z.H. Siddik, D.R. Newell, F.E. Boxall, K.R. Harrap, The comparative pharmacokinetics of carboplatin and cisplatin in mice and rates, Biochem. Pharmacol. 36 (1987)1925-1932.
[7] A.I. Bush, Metal complexing agents as therapies for Alzheimer's disease, Neurobiol. Aging 23 (2002) 1031-1038.
[8] S.S. Bhat, A.A. Kumbhar, H. Heptullah, A.A. Khan, V.V. Gobre, S.P. Gejji, V.G. Puranik, Effect of N(4)-phenyl substitution in 2-Oxo-1,2-dihydroquinoline-3-carbaldehyde semicarbazones on the structure, DNA/protein interaction, and antioxidative and cytotoxic activity of Cu(II) complexes, Inorg. Chem. 50 (2011) 12852-12866.
[9] T. Miura, A. Hori, H. Mototani, H. Takeuchi, Raman spectroscopic study on the copper(ii) binding mode of prion octapeptide and its pH dependence, Biochem. 38 (1999) 11560-11569.
[10] N.V. Verani, E. Rentschler, T. Weyhermuller, E. Bill, P. Chaudhuri, Exchange coupling in a bis(heterodinuclear) $[Cu^{II}Ni^{II}]^2$ and a linear heterotrinuclear complex $Co^{III}Cu^{II}Ni^{II}$. Synthesis, structures and properties, J. Chem. Soc. Dalton Trans. (2000) 251-258.
[11] M. Thirumavalavan, P. Akilan, M. Kandaswamy, Synthesis of lateral macrobicyclic compartmental ligands: structural, magnetic, electrochemical, and catalytic studies of mono- and binuclear copper(II) complexes, Inorg. Chem. 42 (2003) 3308-3317.
[12] P.R. Reddy, A. Shilpa, N. Raju, P. Raghavaiah, Synthesis, structure, DNA binding and cleavage properties of ternary amino acid Schiff base-phen/bipy Cu(II) complexes, J. Inorg. Biochem. 105 (2011) 1603-1612.
[13] D.D. Li, J.L. Tian, W. Gu, X. Liu, H.H. Zeng, S.P. Yan, DNA binding, oxidative DNA cleavage, cytotoxicity, and apoptosis-inducing activity of copper(II) complexes with 1,4-tpbd (N,N,N′,N′-tetrakis(2-yridylmethyl)benzene-1,4-diamine) ligand, J. Inorg. Biochem. 105 (2011) 894-901.
[14] N.V. Verani, E. Rentschler, T. Weyhermuller, E. Bill, P. Chaudhuri, Exchange coupling in a bis(heterodinuclear) $[Cu^{II}Ni^{II}]$ and a linear heterotrinuclear complex $Co^{III}Cu^{II}Ni^{II}$, Synthesis, structures and properties, J. Chem. Soc. Dalton Trans. (3) (2000) 251-258.
[15] S. Anbu, M. Kandaswamy, P. Suthakaran, V. Murugan, B. Varghese, Structural, magnetic, electrochemical, catalytic, DNA binding and cleavage studies of new macrocyclic binuclear copper(II) complexes, J. Inorg. Biochem. 103 (2009) 401-410.
[16] P.G. Avaji, C.H.V. Kumar, S.A. Patil , K.N. Shivananda, C. Nagaraju, Synthesis, spectral characterization, in-vitro microbiological evaluation and cytotoxic activities of novel macrocyclic bis hydrazine, Eur. J. Med Chem. 44 (2008) 3552-3559.