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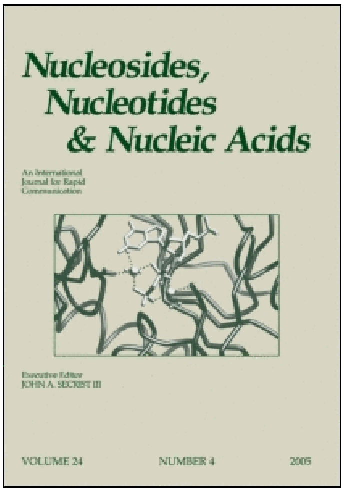

Nucleosides, Nucleotides and Nucleic Acids

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Synthesis, Characterization, and Photoactivated DNA Cleavage by Copper (II)/Cobalt (II) Mediated Macrocyclic Complexes

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SYNTHESIS, CHARACTERIZATION, AND PHOTOACTIVATED DNA CLEAVAGE BY COPPER (II)/COBALT (II) MEDIATED MACROCYCLIC COMPLEXES

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□ *We report the synthesis of new photonuclease consisting of two Co(II)/Cu(II) complexes of macrocyclic fused quinoline. Metal complexes are [MLX_2], type where M = Co(II) (**5**), Cu(II) (**6**), and X = Cl, and are well characterized by elemental analysis, Fourier transform infrared spectroscopy, ^{1}H-NMR and electronic spectra. We have shown that photocleavage of plasmid DNA is markedly enhanced when this ligand is irradiated in the presence of Cu(II), and more so than that of cobalt. The chemistry of ternary and binary Co(II) complexes showing efficient light induced (360 nm) DNA cleavage activity is summarized. The role of the metal in photoinduced DNA cleavage reactions is explored by designing complex molecules having macrocyclic structure. The mechanistic pathways are found to be concentration dependent on Co(II)/Cu(II) complexes and the photoexcitation energy photoredox chemistry. Highly effective DNA cleavage ability of* **6** *is attributed to the effective cooperation of the metal moiety.*

Keywords Macrocycles; Co(II)/Cu(II) complexes; photoinduced DNA cleavage

INTRODUCTION

Genetic engineering has brought new challenges and opportunities for medicine and biomedical research. DNA strands would be damaged in a cellular environment,[1–3] and the damage of DNA would cause mutations and genomic instabilities that could contribute to a variety of human genetic diseases. One of the most important achievements in our understanding

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of the biochemistry of DNA is our awareness that the DNA double helix has considerable conformational flexibility.[4] The discovery of left-handed DNA and other DNA conformations illustrates the concept of structural flexibility. The use of octahedral metal complexes to probe the structure of DNA is an active area of research at the interface of chemistry and biology.[5] Such metal complexes would permit the targeting of specific DNA sites by matching the shape, symmetry and functionality of the complexes to those of the DNA target.

Additionally, there is accumulating evidence that metal ions interfere with distinct steps of diverse DNA repair systems. First indications that metal ions may diminish DNA repair processes were obtained by pronounced co mutagenic effects of cobalt(II) and nickel(II) in bacteria as well as in mammalian cells. Based on these observations, detailed studies have been conducted to oxidative elucidate potential interactions with the removal of different types of DNA damage.[6] Due to the efficient hydrolysis rates and kinetic inertness cobalt(III)-chelator complexes have been used for mechanistic studies of phosphodiester cleavage. This dual property of metal chelator system has been exploited to produce an efficient artificial nuclease system for sequence specific disruption of gene function.[7]

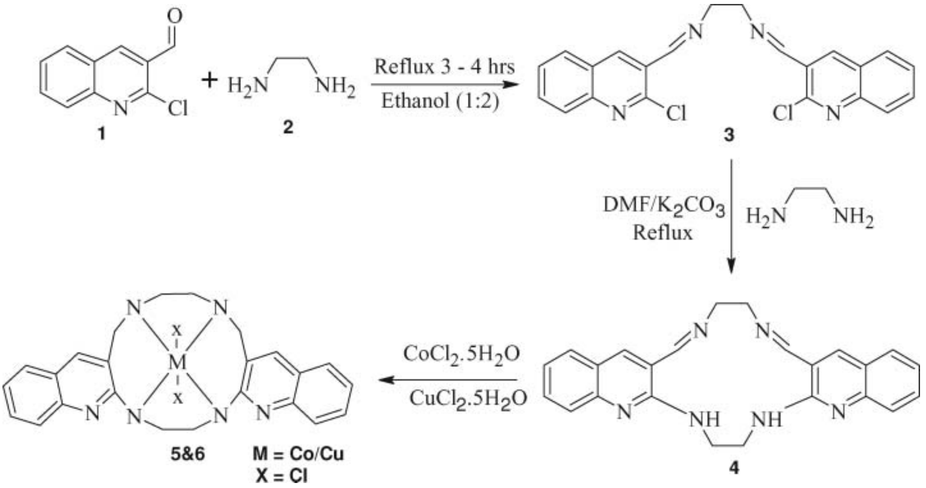
The increasing interest in using macrocycles and their coordination compounds as artificial restriction enzymes for cleaving DNA has prompted us to investigate the application of macrocyclic transition metal complexes in this area. Copper is a bio-essential element and copper complexes have been extensively utilized in metal-mediated DNA cleavage for the generation of activated oxygen species.[8] It has been reported that tetra-aza macrocyclic copper coordination compounds have anti-HIV activities.[8]

Much attention has been devoted to exploring the potential applications of metal complexes as non-radioactive probes of nucleic acid structure and as possible DNA cleaving agents in recent years.[9] In these complexes, the metals or ligands can be easily varied to facilitate the individual applications. Copper is a bio-essential element with relevant oxidation states. Among the complexes explored so far, attention has been primarily focused on the copper(II) complexes of 1,10-phenanthroline and its derivatives due to their high nucleolytic efficiency,[10–12] which are able to break the DNA chain in the presence of H_2O_2 and reducing agents. On the contrary, investigations of copper(II) complexes with acyclic ligands have received much less attention; their exact mode and extent of binding and cleavage mechanisms still remain unknown. Therefore, extensive studies, using different acyclic ligands to evaluate and understand the factors that determine the DNA-binding mode and cleavage mechanism, are necessary. In contrast to other ligands, acyclic ligands lack rigidity, and the first coordination sphere of the metal center of the acyclic complex has relatively little steric hindrance. This will be helpful for designing new useful DNA probes and effective inorganic quinoline based macrocyclic complex nucleases.

RESULTS AND DISCUSSION

A novel diquinolino[1,3,7,9] tetraazacyclotetradecine-7,15 (*14H, 16H*)-diethylenediamine, macrocyclic ligand (**L**) has been synthesized in two steps (see Scheme 1). In the first step, the ethylenediamine (**2**) reacts with 2-chloro-3-formylquinoline (**1**), in 1:2 molar ratio in ethanol, a yellowish colored product N-[-(2-chloroquinolin-3-yl) methylene]-*N*- (2-chloroquinolin-3-yl) methylene] ethylene-1,2-diamine separated out; in the second step, it reacts with ethylenediamine in 1:1 molar ratio in DMF solvent, gave a greenish white colored solid. The thin layer chromatography (TLC) has established the purity of the compound by dissolving the ligand in ethanol using petroleum ether and ethyl acetate (8:3) as eluent. One spot was observed in the TLC plate after developing in an iodine chamber indicating that the compounds were pure. The formation of this macrocyclic molecule frame work was confirmed based on the results of Fourier transform infrared spectroscopy (FTIR) and resonance peaks in the ^{1}H-NMR and elemental analyses. By using this, new macrocyclic complexes of the type [MLX_2], were synthesized by the reaction of the ligand (**L**) with the corresponding metal salts in 1:1 molar ratio in ethanol solution. The formation of the complex may be represented by the following reaction:

$$CoX_2 \cdot H_2O + L \rightarrow Co(L)X_2 + nH_2O$$
$$CuX_2 \cdot H_2O + L \rightarrow Cu(L)X_2 + nH_2O$$



SCHEME 1 Synthesis of diquinolino[1,3,7,9] tetraazacyclotetradecine-7,15 (*14H, 16H*)-diethylenediamine ligand and their Co/Cu complexes.

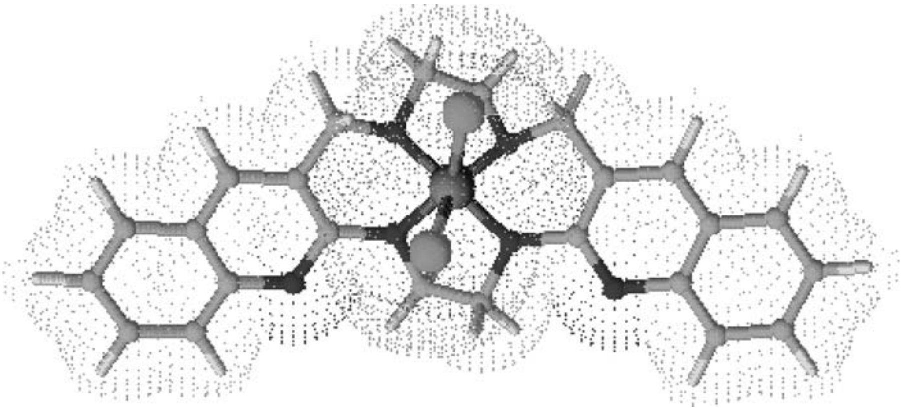


FIGURE 1 Three-dimensional structure of Co(II) macrocyclic complex.

The complexes are microcrystalline in nature and found to be soluble in most of the organic solvents. The elemental analysis data shows that the complexes have a composition of $[Co(L)Cl_2]$, $[Cu(L)Cl_2]$. The magnetic moment value 2.54 for Co(II), and 2.00 for Cu(II), which are greater than spin-only value 1.75 (B.M) and hence, paramagnetic in nature, exhibits high-spin octahedral geometry. The coordination spheres of complexes, similar to those of nickel(II)-type macrocyclic complexes, have been reported to be sixcoordinate octahedral geometry.[13] Hence, in the present studies, the experimental results suggest that the title complexes possess octahedral geometry (Figure 1). Molar conductivity was studied in DMF, the range of 73–76 $\Delta m\ \Omega^{-1}\ cm^{-1}\ mol^{-1}$ indicating that both the complexes are 1:1 electrolytes and may be formulated as $[MLX_2]$.

FTIR Spectra

Infrared (IR) spectra of complexes were recorded in the matrix of KBr pellets with a Perkin-Elmer 1430 spectrometer (Perkin-Elmer, Waltham, MA, USA). The absence of bands corresponding to the amino groups of ethylenediamine and carbonyl groups of aldehydic 2-chloro-3-formylquinoline, suggests the formation of the proposed macrocyclic ligand (**L**). Further, the two intensive bands at 1621 cm^{-1} and 3432 cm^{-1} assignable to uncoordinated v(C=N) and v(N−H) of amine group, respectively, confirms the proposed structure.[14,15] In addition, the formation of macrocyclic structure was conformed by its ^{1}H-NMR spectra. However, IR spectra of complexes derived from the ligand (**L**) shows a slight shift to the lower frequency in v(C=N) and appeared in the region 1596–1612 cm^{-1} suggesting its coordination with metal ion. In addition, a strong characteristic band of ν(-NH-) appeared at 3176 cm^{-1}, and bands at 1453–1417 cm^{-1} for all the complexes correspond to C−H binding vibrations, respectively. The

TABLE 1 Characterizations of IR cm^{-1} bands of ligands and their metal complexes

Compound	v(N—H)	v(Ar—CH)	v(C=N)	v(C=C)	ν(C—H)	v(M—N)	v(M—Cl)
(L) $C_{24}H_{22}N_6$	3432s	2924m	1621s	1488m	1453s	—	—
[Co(L)Cl_2] (5) $C_{24}H_{22}N_6Cl_2Co$	3186s	2854m	1612s	1458m	1416s	763s	479m
[Cu(L)Cl_2] (6) $C_{24}H_{22}N_6Cl_2Cu$	3177s	2851m	1596s	1459m	1417s	769s	450m

appearance of new medium-intensity bands in the region 763–769 cm^{-1} in the macrocyclic complexes may be assigned to v(M—N) vibrations. The bands at 450–479 cm^{-1} were assigned to v(M—Cl) vibrations, and the values are summarized in Table 1.

^{1}H-NMR Spectra

The ^{1}H-NMR spectra were recorded on a Jeol spectrometer (400 MHz; Tokyo, Japan), and chemical shifts (δ) are given in ppm relative to the signal for tetra methyl silane (TMS) as the internal standard. The absence of proton resonance signals of free NH_2 and aldehydic (CHO) groups indicates the condensation between amine and carbonyl group of aldehydic 2-chloro-3-formylquinoline. The ^{1}H-NMR spectra of the ligand recorded in $CDCl_3$ show a doublet at δ: 8.85 ppm (d, 1H, CHN D_2O exchangeable), may be due to hydrogen bonding and anisotropy effect of the adjacent and other aromatic resonated protons, and signal exhibits singlet at δ: 8.81 ppm (s, 1H, NH) and 8.96 (s, 1H, NH) ascribed. A multiplet signal at 3.9–4.5 ppm (s, 8H) corresponds to the ethylenediamine. The multiplet signals attributed at 7.1–7.9 ppm are due to (m, 10H, Ar-H) aromatic quinoline moiety.

The pUC 19 DNA Cleavage Studies

Supercoiled plasmid DNA cleavage by the Co(II)/Cu(II) complexes and their analogues was studied in the presence of H_2O_2 or any reducing agents (Figure 2) and a time/concentration dependent cleavage was observed. We found that the supercoiled DNA (form I) was cleaved by **5** or **6** only after 1 and 2 hours. The cleavage activity of **6** is much more than it is for **5**. In order to clarify the DNA cleavage mechanism, complexes **5** and **6** were investigated in the presence of chelating agent. Both the complexes were tested for DNA cleavage under hydrolytic conditions, a concentration dependent cleavage was observed. Reaction that leads to formation of open circular DNA (form II) from the supercoiled form I over various concentrations of complexes **5**/**6** (100–600 μM/L) and constant DNA concentration was followed for different concentration at 37°C (Figure 2).

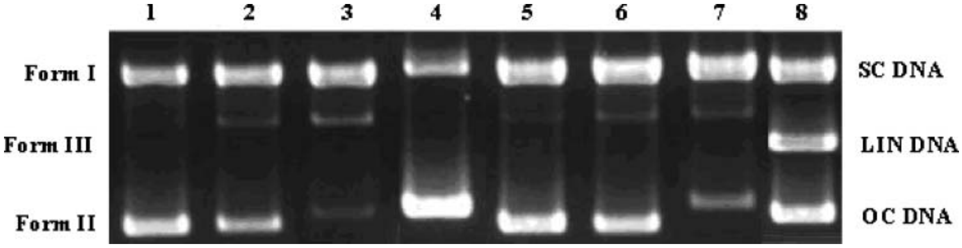


FIGURE 2 Effects of Co/Cu complexes (**5**/**6**) at various concentrations (200–600 μmol/L) on the pUC 19 supercoiled DNA against $^{\cdot}$OH generated by photolysis at 360 nm in presence of H_2O_2. Lane 1, untreated DNA (control); lane 2, DNA + H_2O_2; lane 3, DNA + Complex **5** (200 μmol/L) + H_2O_2 (2.5 μmol/L); lane 4, DNA + Complex **5** (400 μmol/L) + H_2O_2 (2.5 μmol/L); lane 5, DNA + Complex **5** (600 μmol/L) + H_2O_2 (2.5 μmol/L); lane 6, DNA + Complex **6** (200 μmol/L) + H_2O_2 (2.5 μmol/L); lane 7, DNA + Complex **6** (400 μmol/L) + H_2O_2 (2.5 μmol/L); lane 8, DNA + Complex **6** (600 μmol/L) + H_2O_2 (2.5 μmol/L).

It is now recognized that the extremely reactive $^{\cdot}$OH radical derived from $O_2{}^-$ and H_2O_2 is a cause of DNA strand scission in cellular damage.[16] Figure 2 shows the electrophoresis pattern of DNA after ultraviolet (UV)-photolysis of H_2O_2 (2.5 μmol/L) in the absence or presence of the complex.

The faster-moving band corresponding to the native form of supercoiled circular DNA (scDNA) and the slower-moving band being the open circular form (ocDNA). The UV irradiation of DNA in the presence of H_2O_2 (lane 2) caused the cleavage of scDNA to give open coiled DNA (ocDNA) and the linear form (linDNA), indicating that $^{\cdot}$OH generated by UV-photolysis of H_2O_2 produced DNA strand scission. The presence of the complexes under investigation increases the DNA damage which has been particularly implicated in carcinogenesis.[17]

It has been demonstrated that the cleavage of DNA in the absence of a reductant is possible with copper(II) complexes through an effective activation of molecular oxygen, generating reactive oxygen species.[18] The favorable Cu(II) to Cu(I) redox potential is then coupled with a self-hydrogen abstraction from the DNA molecule (most probably from the sugar moieties). The occurrence of this process instigates a single DNA cleavage event, through a Fenton mechanism. This DNA cleavage may become catalytic if the ligands coordinated to the Cu ion facilitate the Cu(II)/Cu(I) cycle.[19] In the present case, complex **6** is more effective than complex **5** to undergo a single cleavage event. So, the distinct cleavage efficiencies observed for the present complexes can be rationalized by their significantly different coordination geometries. Indeed, it has been shown that the coordination geometry plays an important role in Cu(II)/Cu(I) redox processes.[20] Both complexes, which are octahedral, may easily accommodate an electron in its co-planar d(x2−y2) orbital.[21] Accordingly, which may likely to occur with a Fenton-type mechanism.

There has been considerable interest in DNA endonucleolytic cleavage reactions that are activated by metal ions.[22,23] The delivery of high concentrations of metal ion to the helix, in locally generating oxygen or hydroxide radicals, leads to an efficient DNA cleavage reaction. DNA cleavage was monitored by relation of supercoiled circular pUC 19 (Form I) into open circular (form II) and linear (form III). When circular plasimd DNA is subjected to electrophoresis, relatively fast migration will be observed for the supercoiled form (form I). If scission occurs on one strand (nicking), the DNA supercoil will relax to generate a slower-moving open circular form (form II).[24] If both strands are cleaved, a linear form (form III) will be generated that migrates between forms I and II. Figure 2 shows the gel electrophoresis separations of plasmid pUC 19 DNA after incubation with Co/Cu complexes and irradiation at 360 nm. Figure reveals the conversion of Form I and II after 60 minutes irradiation in the presence of varying concentrations of complexes (**5**/**6**). It was observed that by increasing the concentration of 5 and 6, cleavage enhances. The same has been observed with increasing irradiation time.

EXPERIMENTAL

All chemicals used for the synthesis were of analytical grade and were procured from Sigma Chemical Co. (St. Louis, MO, USA), E. Merck (Darmstadt, Germany), and Sarabhai Merck Company (Baroda, India) and *o*-ethylinediamine was purchased from S.D. Fine Chemicals Pvt. Ltd. (Mumbai, India). The TLC was performed on Baker-Flex silica gel 1B-F (1.55) plates in the following solvent systems: ethyl acetate and petroleum ether (8:3). Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded in the matrix of KBr with a Perkin-Elmer 1430 spectrometer. ^{1}H NMR spectra were recorded on a Jeol spectrometer (400 MHz), and chemical shifts (δ) are given in ppm relative to the signal for TMS as internal standard. C, H, and N analyses were performed at Cochin University, Sophisticated Test & Instrumentation Center (Kochi, Kerala, India). Conductivity measurements were determined in DMF (10^{-3} M) using an ELICO-CM82 conductivity bridge.

Preparation of N,N′-bis[(Z)-(2-chloroquinolin-3-yl)methylidene] ethane-1,2-diamine (3)

The ethanolic solution of 2-chloro-3-formyl-quinoline (7.64 g, 0.04 mol) and ethelyenediamine (1.2 g, 0.02 mol) (25 ml each) in 2:1 molar ratio was refluxed for 3–4 hours. A yellowish product separates out and it was washed with cold ethanol, dried under vacuum, and recrystallized from ethyl acetate/dichloromethane solvent system. Yield 94%, m.p.132–134°C.

Preparation of Diquinolino[1,3,7,9] tetraazacyclotetradecine-7, 15 (*14H, 16H*)- diethylenediamine (L)

The compound **3** (4.07 g, 0.01 mol)was dissolved in (25 ml) DMF and added to the (25 ml) ethelyenediamine (0.60 g, 0.01 mol) in 1:1 molar ratio. The solution was refluxed in the presence of potassium carbonate (1.61 g, 0.01 mol) as catalyst for 10–12 hours. The reaction was monitored by TLC using petroleum ether and ethyl acetate (8:3) as eluent. A greenish-white precipitate was separated in ice-cold water. The resulting product was collected by filtration, washed with cold water, dried under vacuum, and recrystallized from ethanol. Yield 85% m.p.179–181°C, FT-IR cm^{-1} 3435 (-NH-); 2927 (Ar-CH); 1621 (C=N); (other peaks) 1452, 1274, 1036, 921, 652. ^{1}H-NMR($CDCl_3$) δ: 8.81 (s,1H,NH); 4.2–4.5 (2s, 4H, ethylenediamine); 3.9–4.1 (2s, 4H, ethylenediamine); 8.96 (s, 1H, NH); 8.85 (d, 1H, CHN, D_2O exchangeable proton); 7.1–7.9 (m, 10H, Ar-H, quinoline).

General Procedure for the Preparation of Complexes

A simple method has been adopted for the preparation of the complexes. The hot ethanol solution of ligand (**L**) and hydrated metal salt in 1:1 molar ratio were mixed. The mixture was refluxed for about 3–4 hours, at 80 ± 5°C, the obtained residue was recrystallized from ethanol. Various attempts to develop the crystals suitable for x-ray diffraction (XRD) studies such as slow diffusion, crystallization using mixtures of solvents and low temperature crystallization were unsuccessful.

$[Co(L)Cl_2]nH_2O$: Cobalt(II) Complex with Ligand(L) Diquinolino [1,3,7,9] tetraazacyclotetradecine-7, 15 (*14H, 16H*)- diethylyenediamine

Ligand (**L**) was dissolved in (25 ml) ethanol and added to the hot ethanolic solution of cobalt (II) chloride (25 ml) in 1:1 molar ratio under boiling conditions and refluxed for 3–4 hours. A blue colored precipitate formed was collected by filtration and dried. Similarly, the same procedure was followed for Cu(II) complex, and the experimental data were summarized in the Table 2.

DNA Photocleavege Cleavage Experiments

The experiments were performed in a volume of 2 ml containing pUC19 DNA in 5 μmol/L phosphate buffer contained 10 μmol/L NaCl, pH 7.4, in the presence of different concentrations (200–600 μmol/L) of complexes. Immediately prior to irradiating the samples with UV light, H_2O_2 was added to a final concentration of 2.5 μmol/L.

TABLE 2 Analytical and physical properties of the metal complexes diquinolino[1,3,7,9] tetraazacyclotetradecine-7,15 (*14H, 16H*)-diethylenediamine (L)

Complex	Color	Molecular wt (yield%)	m.p.°C	Meff (B.M)	(Δm Ω^{-1} cm^{-1}mol^{-1})	Elemental analysis calcd. (found%)
(4) $C_{24}H_{22}N_6$	Greenish white	394.47 (87)	192	—	—	C: 73.07 (73.05) H: 5.62 (5.65) N: 21.30 (21.34)
[Co(L)Cl_2] (5) $C_{24}H_{22}N_6Cl_2Co$	Blue	453.40 (82)	>230	2.54	73	C: 63.58 (63.61) H: 4.89 (4.85) N: 18.54 (18.59) Co: 13.00 (12.96)
[Cu(L)Cl_2] (6) $C_{24}H_{22}N_6Cl_2Cu$	Red	458 (79)	>250	2.00	76	C: 62.94 (62.98) H: 4.84 (4.81) N: 18.35 (18.39) Cu: 13.87 (12.78)

The reaction volumes were held in caps of polyethylene micro centrifuge tubes, which were placed directly on the surface of a transilluminator (8000 mW/cm) at 360 nm. The samples were irradiated for 5 minutes at room temperature. After irradiation, 0.5 ml of a mixture containing 0.25% bromo phenol blue, 0.25% xylene cyanol FF, and 30% glycerol was added to the irradiated solution. The samples were then analyzed by electrophoresis on a 1% agarose horizontal slab gel in tris-borate buffer (45 μmol/L Tris-borate, 1 μmol/L EDTA). Untreated pUC19 DNA was included as a control in each run of gel electrophoresis, which was carried out at 1.5 V/cm for 15 hours. Gel was stained in ethidium bromide (1 mg/ml) and photographed under UV light.[25]

CONCLUSION

In summary, we describe the preparation and photoreactivity of a novel Co(II)/Cu(II) transition metal complexes. The overall strategy of metal complex activation via ligand-to-metal charge transfer (LMCT) excitation in the visible spectral region is operative. This paper reports that the Cu(II) macrocyclic complex can effectively cleavage DNA in mild condition *via* a non-oxidative mechanism than that of Co(II) macrocyclic complex. Based on our experiment results, we may predict that the Cu(II)-L complex would be another potential DNA hydrolytic cleavage agent.

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