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### Benzo[h]quinoline based Macrocyclic Copper(II), Cobalt(II) Complexes: Synthesis, Characterization and Light induced DNA Cleavage Studies

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# Benzo[h]quinoline based Macrocyclic Copper(II), Cobalt(II) Complexes: Synthesis, Characterization and Light induced DNA Cleavage Studies

H. R. PRAKASH NAIK, H. S. BHOJYA NAIK\*, D. S. LAMANI, T. ARAVINDA, B. VIJAYA KUMAR, B. VINAY KUMAR, M. YOGESH, N. SHARATH and P. N. PRASHANTH KUMAR

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A new ligand dibenzo[h]quinolino[1,3,7,9] tetraazacyclododecine-7,15 (14H, 16H)-dibenzene (L) and its Co(II)/Cu(II) metal complexes of type [MLX<sub>2</sub>] (Where (M = Co(II) (5), Cu(II) (6) and X = Cl) were synthesized and are well characterized by FT-IR, <sup>1</sup>H-NMR, FAB mass elemental analysis, and electronic spectral data. The role of the cobalt/copper metals in photo-induced DNA cleavage reactions was explored by designing complex molecules having macrocyclic structure. Finally, we have shown that photocleavage of plasmid DNA is more efficiently enhanced when this macrocyclic ligand is irradiated in the presence of copper(II) than that of cobalt metal.

**Keywords:** Benzo[h]quinoline-macrocycles, Co(II)/Cu(II) complexes, photo-induced DNA cleavage

## 1 Introduction

In recent years, the discovery of cisplatin for cancer treatment, numerous transition metal complexes have been synthesized and screened for their anticancer properties. One strategy in such efforts is to synergize the beneficial effect of the ligand and the activity of the metal to produce a complex with enhanced activity (1).

Development of macromolecular architectures possessing defined structural motifs is a focus of intense research in the area of molecular or ion recognition (2), supramolecular chemistry (3), and drug design (4). A fundamental step to realize structure-based interactions should be an appropriate design and synthesis of structural modules, which can be assembled to build tailored molecular structures. Currently, there is considerable interest in complexes of polydentate macrocyclic ligands because of the variety of geometrical forms available and the possible encapsulation of the metal ion (5).

Deoxyribonucleic acid (DNA) is the primary target molecule for most anticancer and antiviral therapies ac-

ording to cell biology. Investigations of the interaction of DNA with small molecules are basic work in the design of new types of pharmaceutical molecules. Since the chemical nuclease activity of the copper and cobalt complexes were discovered in 1980s (6–8), studying the interaction model and the mechanism of transition metal complexes with DNA, and exploring the application of metal complexes in antineoplastic medication, molecular biology and bioengineering were hotspots in recent year. When some kinds of metal complexes interacted with DNA, they could induce the breakage of DNA strands by appropriate methods. Thus, after the double DNA strands are broken, the replication ability of cancer gene is destroyed. The interactions of metal complexes with DNA constitute a significant area of research which has attracted considerable attention from both inorganic chemists and biochemists because studies have shown that they are related to the development of new DNA reagents for biotechnology and medicine (9, 10). In recent years, binding studies of transition metal complexes have become very important in the development of DNA molecules probes and chemotherapeutics (11–13).

In view of above vast chemotherapeutic applications and in continuation of quest on quinoline based macrocycles (14). Here, we describe for the first time cobalt/copper-macrocyclic complexes of benzo[h]quinoline moiety and their DNA nuclease activity.

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## 2 Experimental

### 2.1 Chemicals

All chemicals used for the synthesis were of analytical grade and procured from Sigma Chemical Co., U.S.A., E. Merck, Germany, Sarabhai Merck Company, India and *o*-phenylenediamine was purchased from S. D. Fine Chemicals Pvt. Ltd. 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. <sup>1</sup>H-NMR spectra were recorded on a Jeol spectrometer (400 MHz), and chemical shifts ( $\delta$ ) 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 and Instrumentation Center, Kochi, Kerala, India. Conductivity measurements were determined in DMF ( $10^{-3}$  M) using an ELICO-CM82 Conductivity Bridge.

### 2.2 Preparation of N,N'-bis(Z)-(2-chlorobenzo[h]quinolin-3-yl)methylidene]ethane-1,2-dibenzene (3)

The ethanolic solution of 2-chloro-3-formyl-benzo[h]quinoline (9.64 g, 0.04 mol) and *o*-phenylenediamine (2.16 g, 0.02 mol) (25 ml each) in 2:1 molar ratio was refluxed for 3–4 h. A yellowish product separates out and was washed with cold ethanol, dried under vacuum, and recrystallized from an ethyl acetate/dichloromethane solvent system. Yield 94%, m.p. 156–158°C.

### 2.3 Preparation of Dibenzo[h]quinolino[1,3,7,9]tetraazacyclododecine-7, 15 (14H, 16H)-dibenzene (L)

The compound **3** (5.55 g, 0.01 mol) was dissolved in DMF (30 ml) and added to 25 ml *o*-phenylenediamine (1.08 g, 0.01 mol) in 1:1 molar ratio. The solution was refluxed in the presence of anhydrous potassium carbonate (2.76 g, 0.02 mol) as catalyst for 10–12 h. 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 81% m.p. 248–250°C, FT-IR  $\text{cm}^{-1}$  3462 (-NH-); 2938 (Ar-CH); 1626 (C=N); (other peaks) 1502, 1295, 1105, 958, 785, 675. <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$ : 8.96 (2s, 2H, NH); 8.87 (2d, 2H, CHN, D<sub>2</sub>O exchangeable proton); 7.0–7.9 (m, 22H, Ar-H, Quinoline and *o*-phenylenediamine).

### 2.4 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 h, at  $80 \pm 5^\circ\text{C}$ , the obtained residue was recrystallized from ethanol. Various attempts to develop the crystals suitable for X-ray diffraction studies such as slow diffusion, crystallization using mixtures of solvents and low temperature crystallization were unsuccessful.

### 2.5 [Co(L)Cl<sub>2</sub>]<sub>n</sub>H<sub>2</sub>O: Cobalt(II) Complex with ligand(L) dibenzo[h]quinolino[1,3,7,9]tetraazacyclododecine-7,15 (14H, 16H)-dibenzene

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 h (Scheme 1). 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 Table 1.

### 2.6 DNA Photocleavage Cleavage Experiments

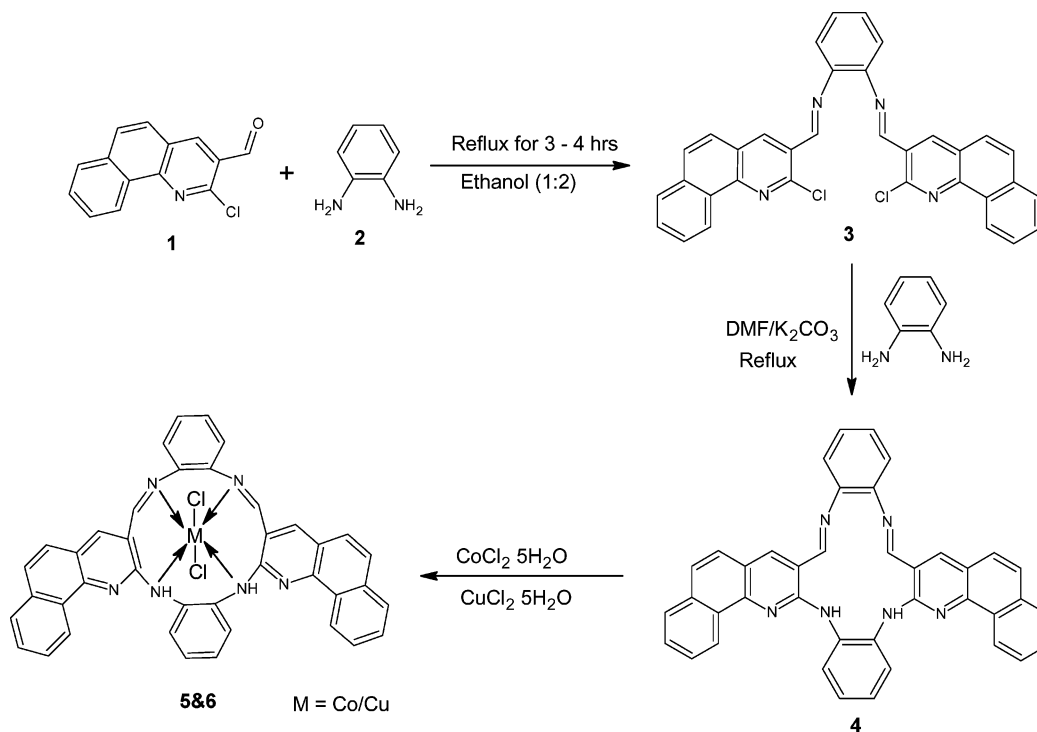
The experiments were performed in a volume of 2 ml containing pUC19 DNA in 5  $\mu\text{mol/L}$  phosphate buffer contained 10  $\mu\text{mol/L}$  NaCl, pH 7.4, in the presence of different concentrations (200–600  $\mu\text{mol/L}$ ) of complexes. Immediately prior to irradiating the samples with UV light, H<sub>2</sub>O<sub>2</sub> was added to a final concentration of 2.5  $\mu\text{mol/L}$ .

The reaction volumes were held in caps of polyethylene microcentrifuge tubes, which were placed directly on the surface of a trans-illuminator (8000 mW/cm) at 360 nm. The samples were irradiated for 5 min at room temperature. After irradiation, 0.5 ml of a mixture containing 0.25% bromophenol 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  $\mu\text{mol/L}$  Tris-borate, 1  $\mu\text{mol/L}$  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 h. Gel was stained in ethidium bromide (1 mg/ml) and photographed under UV light (15).

## 3 Results and Discussion

### 3.1 Chemistry

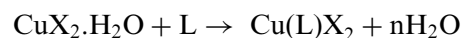
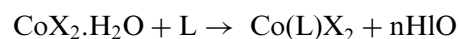
A novel dibenzo[h]quinolino[1, 3, 7, 9] tetraazacyclododecine-7,15 (14H, 16H)-dibenzene, macrocyclic ligand (L) has been synthesized in two steps as per Scheme 1. In the first step, the *o*-phenylenediamine (**2**) reacts with 2-chloro-3-formylbenzo[h]quinoline (**1**), in 1:2 molar ratio in ethanol, a brownish yellow colored product N-[-(2-chlorobenzo[h]quinolin-3-yl) methylene]-N-(2-chlorobenzo[h]quinolin-3-yl) methylene] benzene-1,2-diamine separated



**Sch. 1.** Synthetic pathway for the macrocyclic dibenzo[h]quinolineneno[1, 3, 7, 9] tetraazacyclododecine-7,15 (14H, 16H)-dibenzene ligand (L).

out. In a second step, it reacts with *o*-phenylenediamine in 1:1 molar ratio in DMF solvent, gave a greenish colored solid. The 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 was confirmed by the results of FT-IR and resonance peaks, <sup>1</sup>H-NMR and elemental analysis data's. Accordingly, these new macrocyclic complexes of the type [MLX<sub>2</sub>], were synthesized by the reaction

of the ligand (L) with the corresponding Co/Cu metal salts in 1:1 molar ratio in ethanol solution. The formation of the complex may be represented by the following reaction:



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<sub>2</sub>], [Cu(L)Cl<sub>2</sub>]. The magnetic moment

**Table 1.** Analytical and physical properties of the metal complexes dibenzo[h]quinolineneno[1, 3, 7, 9] tetraazacyclododecine-7,15 (14H, 16H)-dibenzene (L)

Complex	Color	Molecular Wt (Yield %)	m.p. °C	M <sub>eff</sub> (B.M)	(Δm Ω <sup>-1</sup> cm <sup>-1</sup> mol <sup>-1</sup> )	Elemental analysis Calcd. (Found %)
(4) C <sub>40</sub> H <sub>26</sub> N <sub>6</sub>	Greenish	590.67 (81)	248	—	—	C: 81.34 (80.95) H: 4.44 (4.32) N: 14.23 (14.01)
[Co(L)Cl <sub>2</sub> ] (5) C <sub>40</sub> H <sub>28</sub> N <sub>6</sub> Cl <sub>2</sub> CoN <sub>6</sub>	Dark blue	722.53 (78)	>255	2.56	72	C: 66.49 (66.39) H: 3.91 (3.84) N: 11.63 (11.55) Co: 8.16 (8.12)
[Cu(L)Cl <sub>2</sub> ] (6) C <sub>24</sub> H <sub>22</sub> N <sub>6</sub> Cl <sub>2</sub> Cu	Dark Red	727 (75)	>260	2.02	75	C: 66.07 (65.94) H: 3.88 (3.81) N: 18.35 (18.41) Cu: 8.74 (8.71)

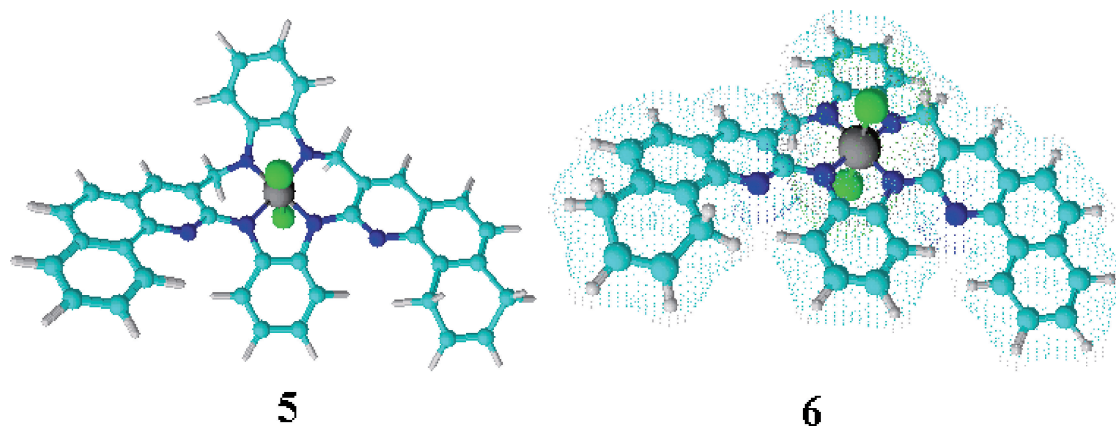


Fig. 1. Three Dimensional (3D) structure of Co(II) (5)/Cu(II)(6) Macrocylic complex.

value 2.56 for Co(II), and 2.02 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 (16). Hence, in the present studies, the experimental results suggest that the title complexes possess octahedral geometry. Molar conductivity was studied in DMF, the range of 72–75  $\Delta\text{m } \Omega^{-1} \text{ cm}^{-1} \text{ mol}^{-1}$  indicating that both the complexes are 1:1 electrolytes and may be formulated as  $[\text{MLX}_2]$ . In addition proposed three dimensional (3D) structures of both copper and cobalt macrocyclic complexes were shown in Figure 1.

### 3.2 FT-IR Spectra

IR spectra of complexes were recorded in the matrix of KBr pellets with a Perkin-Elmer 1430 spectrometer. 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 1626  $\text{cm}^{-1}$  and 3462  $\text{cm}^{-1}$  assignable to uncoordinated  $\nu(\text{C}=\text{N})$  and  $\nu(\text{N}-\text{H})$  of amine group, respectively confirms the proposed structure (17,18). In addition, the formation of macrocyclic structure was conformed by its  $^1\text{H-NMR}$  spectra. However, IR spectra of complexes derived from the ligand (L) shows a slight shift to the lower frequency in  $\nu(\text{C}=\text{N})$  and appeared in the region 1599–1621  $\text{cm}^{-1}$  suggesting its coordination with metal ion. In addition, a strong characteristic band of  $\nu(-\text{NH}-)$  appeared at

3176  $\text{cm}^{-1}$ , and bands at 1452–1421  $\text{cm}^{-1}$  for all the complexes correspond to C–H binding vibrations, respectively. The appearance of new medium-intensity bands in the region 762–769  $\text{cm}^{-1}$  in the macrocyclic complexes may be assigned to  $\nu(\text{M}-\text{N})$  vibrations. The bands at 451–478  $\text{cm}^{-1}$  were assigned to  $\nu(\text{M}-\text{Cl})$  vibrations, and the values are summarized in Table 2.

### 3.3 $^1\text{H-NMR}$ Spectra

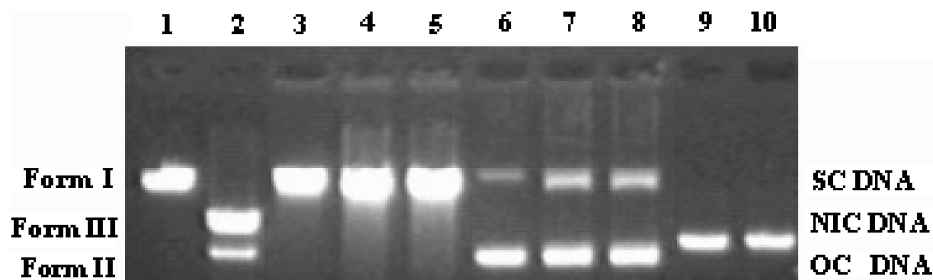
The  $^1\text{H-NMR}$  spectra were recorded on a Jeol spectrometer (400 MHz), and chemical shifts ( $\delta$ ) are given in ppm relative to the signal for TMS as the internal standard. The absence of proton resonance signals of free  $\text{NH}_2$  and aldehydic (CHO) groups indicates the condensation between amine and carbonyl group of aldehydic 2-chloro-3-formylquinoline. The  $^1\text{H-NMR}$  spectra of the ligand recorded in  $\text{CDCl}_3$  show a doublet at  $\delta$  : 8.87 ppm (d, 1H, CHN  $\text{D}_2\text{O}$  exchangeable), may be due to hydrogen bonding and anisotropy effect of the adjacent and other aromatic resonated protons, and signal exhibits singlate at  $\delta$  : 8.96 ppm (2s, 2H, NH) was ascribed. The multiplet signals attributed at 7.0–7.9 ppm are due to (m, 22H, Ar-H) aromatic quinoline moiety.

### 3.4 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  $\text{H}_2\text{O}_2$  or any reducing agents (Fig. 2) and a time/concentration dependent cleavage was observed. We

Table 2. Characterizations of IR  $\text{cm}^{-1}$  bands of ligands and their metal complexes

Compound	$\nu(\text{N}-\text{H})$	$\nu(\text{Ar}-\text{CH})$	$\nu(\text{C}=\text{N})$	$\nu(\text{C}-\text{C})$	$\nu(\text{C}-\text{H})$	$\nu(\text{M}-\text{N})$	$\nu(\text{M}-\text{Cl})$
(4) $\text{C}_{40}\text{H}_{26}\text{N}_6$	3462s	2938 m	1626s	1485 m	1454s	—	—
$[\text{Co}(\text{L})\text{Cl}_2]$ (5) $\text{C}_{40}\text{H}_{28}\text{N}_6\text{Cl}_2\text{CoN}_6$	3182s	2851 m	1611s	1457 m	1417s	762s	478 m
$[\text{Cu}(\text{L})\text{Cl}_2]$ (6) $\text{C}_{24}\text{H}_{22}\text{N}_6\text{Cl}_2\text{CuN}_6$	3179s	2854 m	1595s	1458 m	1416s	768s	451 m



**Fig. 2.** Effects of Co/Cu complexes (**5/6**) at various concentrations (200–600  $\mu\text{mol/L}$ ) on the pUC 19 supercoiled DNA against  $\cdot\text{OH}$  generated by photolysis at 360 nm in presence of  $\text{H}_2\text{O}_2$ . Lane 1, Untreated DNA (control); lane 2, DNA +  $\text{H}_2\text{O}_2$ ; lane 3, DNA + Complex **5** (200  $\mu\text{mol/L}$ ); lane 4, DNA + Complex **5** (400  $\mu\text{mol/L}$ ); lane 5, DNA + Complex **5** (600  $\mu\text{mol/L}$ ); lane 6, DNA + Complex **5** (800  $\mu\text{mol/L}$ ); lane 7, DNA + Complex **6** (200  $\mu\text{mol/L}$ ); lane 8, DNA + Complex **6** (400  $\mu\text{mol/L}$ ); lane 9, DNA + Complex **6** (600  $\mu\text{mol/L}$ ); lane 10, DNA + Complex **6** (800  $\mu\text{mol/L}$ ).

found that the supercoiled DNA (form I) was cleaved by **5** or **6** only after 1 and 2 h. The cleavage activity of **6** is considerably more than **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, and a concentration dependent cleavage was observed. Reaction that leads to formation of open circular DNA (form II) from the supercoiled from I over various concentrations of complexes **5/6** (100–600  $\mu\text{M/L}$ ) and constant DNA concentration was followed for different concentration at 37°C (Fig. 1).

It is now recognized that the extremely reactive  $\cdot\text{OH}$  radical derived from  $\text{O}_2^-$  and  $\text{H}_2\text{O}_2$  is a cause of DNA strand scission in cellular damage (19). Figure 1 shows the electrophoretic pattern of DNA after UV-photolysis of  $\text{H}_2\text{O}_2$  (2.5  $\mu\text{mol/L}$ ) in the absence or presence of the complex.

The faster-moving band corresponds 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  $\text{H}_2\text{O}_2$  (lane 2) caused the cleavage of scDNA to give open coiled DNA (ocDNA) and the linear form (linDNA), indicating that  $\cdot\text{OH}$  generated by UV-photolysis of  $\text{H}_2\text{O}_2$  produced DNA strand scission. The presence of the complexes under investigation increases the DNA damage which has been particularly implicated in carcinogenesis (20).

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 (21). Both complexes which are octahedral, may easily accommodate an electron in its co-planar  $d(x^2-y^2)$  orbital (22). Accordingly, which may likely to occur with a Fenton-type mechanism. 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

(23). 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 (24).

#### 4 Conclusions

In summary, we describe the preparation and photoreactivity of a novel benzo[h]quinoline based macrocyclic Co(II)/Cu(II) transition metal complexes. The overall strategy of metal complex activation *via* 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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