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Self-activated DNA cleavage and nitric oxide reactivity studies on mononuclear copper complexes derived from tetradentate ligands

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ABSTRACT

Two new tetradentate ligands Timpy (1,2-bis((E)-(2-phenyl-2-(pyridine-2-yl)hydrozono)methyl)benzene) and Gimpy ((1*Z*,2*Z*)-1,2-bis(2-phenyl-2-(pyridine-2-yl)hydrozono)ethane) were synthesized and characterized. Mononuclear complexes $[Cu(Timpy)(ClO_4)](ClO_4)$ (**1**) and $[Cu(Gimpy)](ClO_4)_2$ (**2**) were synthesized and characterized by IR, UV–visible and conductivity measurements. The molecular structure of $[Cu(Timpy)(ClO_4)](ClO_4)$ (**1**) was determined by single crystal X-ray diffraction and structural index parameter ($\tau = 0.4725$) supported distorted square planar geometry at the metal centre. Electrochemical studies for **1** and **2** were investigated. Two-fold applications of these complexes were examined. First, self-activated DNA cleavage activity of complexes **1** and **2** and mechanism of nuclease activity. Second, the complexes were utilized as fluorescence probe for the detection of nitric oxide in solution.

There has been considerable interest in the recent years for design and synthesis of DNA cleaving reagents for their applications in biotechnology and medicine [1,2]. Discovery of *cis*platin followed by platinum metal based anti-tumor drugs are important for their use as chemotherapeutic agents. However, platinum based drugs exhibit some serious side effects and toxicity [3,4]. Hence there are continuous quest for the metal based drug that could be used for cancer treatment and few ruthenium based anticancer drugs are in clinical trial [5]. Transition metal ions show diverse structural features, variable oxidation and spin states and redox properties in different complexes and these properties could be exploited to discover novel artificial nucleases. Among the first row transition elements, copper has got special interest in this regard since the discovery of first chemical nuclease by Sigman and coworkers [6]. Copper is one of the essential elements in biology and there are several metalloproteins which need copper for their activity [4]. Biologically relevant copper has high affinity for the nucleobases and copper complexes possess biologically accessible redox properties [7].

Investigation of literature revealed that oxidative DNA cleavage reaction by copper complexes are mediated by reactive oxygen species produced via oxidation of Cu^{II} to Cu^{III} by oxidizing agents and reduction of Cu^{II} to Cu^{I} by reducing agents [7–13]. Alternatively, a transient metal bound species formulated as $[CuOH]^{2+}$ $[CuOOH]^{+}$ and $[CuO]^{+}$ are also reported to be responsible for DNA strand scission [8,9,14]. However, addition of such oxidising or reducing agents is not useful for in vivo applications of such complexes in metallopharmaceutical research [15], hence it would be of interest to find a self-activated system that would not require any type of activation to generate reactive species for DNA cleavage activity. Reedijk and coworkers reported [15,16] copper complexes derived from ligand pbt and $[Cu^{II}(pyramol)(Cl)]$ which exhibited self-activated DNA cleavage. There are also few reports of such type of nuclease activity by Tonde et al. [17], Li et al. [18], Kellett et al. [19] and Sissi et al. [20]. Recently we have reported mononuclear copper(II) complex $[Cu(Pyimpy)(Cl)(ClO_4)]$ afforded cleavage of pBR322 plasmid DNA via self-activation and investigation of mechanism indicated the possible role of reactive oxygen species in DNA cleavage [21].

Herein we report two new copper complexes derived from ligands Timpy and Gimpy as shown in Scheme 1 and their self-activated nuclease activity. The new ligands were characterized by UV–visible, IR, NMR and fluorescence spectral studies. Copper complexes $[Cu(Timpy)(ClO_4)](ClO_4)$ (**1**) and $[Cu(Gimpy)](ClO_4)_2$ (**2**) were synthesized and characterized by spectroscopic studies. Molecular structure of complex $[Cu(Timpy)(ClO_4)](ClO_4)$ (**1**) was determined by single crystal X-ray diffraction. Stabilization of copper (II) centre was examined by electrochemical studies. Nuclease activity with plasmid pBR322 DNA was investigated and results of our mechanistic studies will be scrutinized in this report.

Interestingly, it has been found out during spectroscopic characterization that the new ligands reported in this communication exhibited fluorescence emission. During characterization of copper complexes we found out the quenching of fluorescence emission of the ligands. These data prompted us to study fluorescence based nitric oxide sensing by copper complexes. There has been considerable current interest in the fluorescence-based detection of nitric oxide (NO) [22,23], which is a diatomic radical species and is involved in variety of biological processes namely vasodilatation, immune response, neurotransmission,

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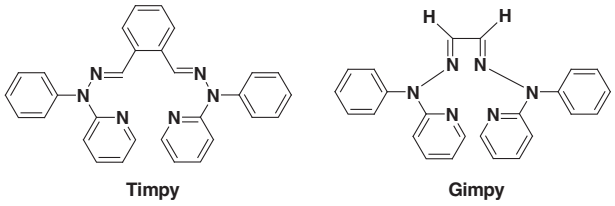

Scheme 1. Schematic drawing of ligands.

apoptosis etc. in different cells and tissues [24]. Reduction of Cu(II) to Cu (I) by NO is important for biological activity of several enzymes namely cytochrome c oxidase, laccase etc. [25]. Interestingly, this reduction generates a diamagnetic metal centre (Cu(I), d^{10}) [26] and helps the detection of NO in solution by fluorescence spectral studies [22]. Hence we report here two novel copper complexes which are not only important for self-activated DNA cleavage but also are useful for fluorescence-based detection of nitric oxide.

The tetradentate ligands Timpy and Gimpy were synthesized by reacting phthaladehyde and glyoxal with 2-(1-phenylhydrazinyl)pyridine respectively and characterized by elemental analysis, IR, UV–visible, and ^{1}H and ^{13}C NMR spectroscopic studies. Reaction of $Cu(ClO_4)_2\cdot 2H_2O$ with tetradentate ligands Timpy and Gimpy in dichloromethane solution afforded the complexes $[Cu(Timpy)(ClO_4)](ClO_4)$ (**1**) and $[Cu(Gimpy)](ClO_4)_2$ (**2**). Details of the synthesis of ligands, copper complexes and their spectra are shown in supporting information. In IR spectra of copper complexes, shifting of azomethine (−HC=N–) stretching frequency of the ligands indicated the ligation of azomethine nitrogen to metal centre [13, 21]. The splitting of the band near 1099 cm^{-1} and 1047 cm^{-1} in IR spectrum of complex **1** showed the coordinated perchlorate ion to the copper centre (Fig. S5) however, complex **2** has uncoordinated perchlorate ions (Fig. S6) [13]. In UV–visible spectra, the intense electronic bands observed between 361 and 445 nm for complexes **1** and **2** were due to ligand to metal charge transfer [27]. Both the complexes **1** and **2** showed absorption bands ~650 nm ($\varepsilon = 280\ M^{-1}\ cm^{-1}$) and ~660 nm ($\varepsilon = 150\ M^{-1}\ cm^{-1}$) due to d-d transitions [26]. Magnetic moment measurements at room temperature gave rise to one-electron paramagnetic metal centre for both the complexes [16]. The molar conductivity measurement of complexes **1** and **2** in DMF solution (*ca.* 10^{-3} M) were found to be 132 and 136 $\Omega^{-1}cm^2mol^{-1}$ respectively at 25 °C indicating bi-univalent electrolytic behaviors [28]. The ESI-MS spectra of complex **1** showed that $[Cu(Timpy)]^{2+}$ (100%) and $[Cu(Timpy)(ClO_4)]^{+}$ (15%) were present in the solution (Fig. S7). These data clearly expressed that coordinated perchlorate ion in **1** got detached from the metal centre and **1** and **2** possess similar behavior in solution although for complex **1** we found metal coordinated perchlorate ion in IR and in X-ray crystal structure (vide infra).

Molecular structure of mononuclear copper complex $[Cu(Timpy)(ClO_4)](ClO_4)$ (**1**) is depicted in Fig. 1 and the matrix parameters are described in Table S1. The stereochemistry around metal centre is described as distorted square pyramidal considering structural index parameters $\tau = 0.4725$ shown in supporting information (The percentage of trigonal distortion from square-pyramidal geometry is described by the parameter defined as $[(\alpha-\beta)/60]\times 100$, where α and β are the angles between the donor atoms forming the plane in a square pyramidal geometry) [29]. Two pyridine nitrogens and two imine nitrogens generated equatorial plane and the perchlorate oxygen occupied the axial positions. The Cu–N_{Py} and Cu–N_{im} distances were consistent with the reported values [13,30]. The axial Cu–$OClO_3$ distance 2.32 Å is consistent with the value reported by Palaniandavar and coworkers [10]. The copper centre is 0.245 Å above the plane generated by the N1, N3, N4 and N5 donors. Two pyridine rings and two imines are in the same plane whereas the phenyl ring is roughly perpendicular (78.47° and 87.57°) to the ligand binding plane. The two imine donors with copper form a seven membered ring which generated the distortion in the molecule. The angles N1 — Cu1 — N3 and N4 — Cu1 — N5 (79.91° and 82.36°) are

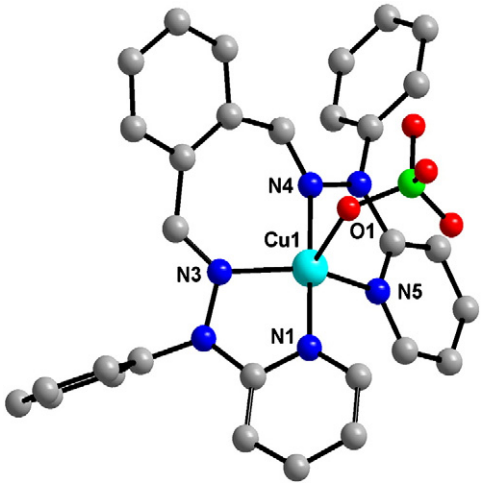

Fig. 1. Ball and stick representation of $[Cu(Timpy)(ClO_4)](ClO_4)$ (**1**) showing the atom numbering scheme. Perchlorate anion is omitted for clarity. Selected bond lengths (Å) and angles (°): Cu(1) — N(1) 1.944(3), Cu(1) — N(3) 1.987(3), Cu(1) — N(4) 1.964(3), Cu(1) — N(5) 1.975(3), Cu(1) — O(1) 2.321(3), N(1) — Cu(1) — N(3) 79.91(14), N(1) — Cu(1) — N(4) 177.23(14), N(1) — Cu(1) — N(5) 99.58(14), N(1) — Cu(1) — O(1) 90.05(14), N(3) — Cu(1) — N(4) 99.48(14), N(3) — Cu(1) — N(5) 148.91(13), N(4) — Cu(1) — N(5) 82.34(14), N(3) — Cu(1) — O(1) 99.96(13), N(4) — Cu(1) — O(1) 87.39(13), N(5) — Cu(1) — O(1) 111.13(15).

less than the angles N3 — Cu1 — N4 and N1 — Cu1 — N5 (99.47° and 99.57°). The distortion at the metal was also supported by the angles (N3 — Cu1 — N5) and (N1 — Cu1 — N4) which are found to be 148.89° and 177.24° respectively.

Non-covalent interactions in crystalline state are important in supramolecular chemistry and crystal engineering [31]. Crystal structure of **1** revealed that perchlorate ions in the crystal lattice were involved in several types of hydrogen bonding (distances of 2.302 Å–2.692 Å) interaction with aryl, imine, pyridine hydrogens (Fig. S8) [13,21]. The phenyl ring of phthalaldehyde moiety of one molecule exhibited π–π interaction with the same phenyl ring of the other molecule in the crystal lattice and the distance was calculated to be near 3.92 Å (Fig. S9) [15]. However distance between two closest carbon atoms of the phenyl rings involved in π–π interaction was found to be 3.38 Å.

The redox behavior of both Cu(II) complexes **1** and **2** was investigated by cyclic voltammetry at a glassy carbon electrode using Ag/AgCl reference electrode. The voltammograms for complexes **1** and **2** are shown in Fig. 2. Complexes **1** and **2** exhibited irreversible cathodic peaks near +0.075 V and +0.205 V vs Ag/AgCl respectively

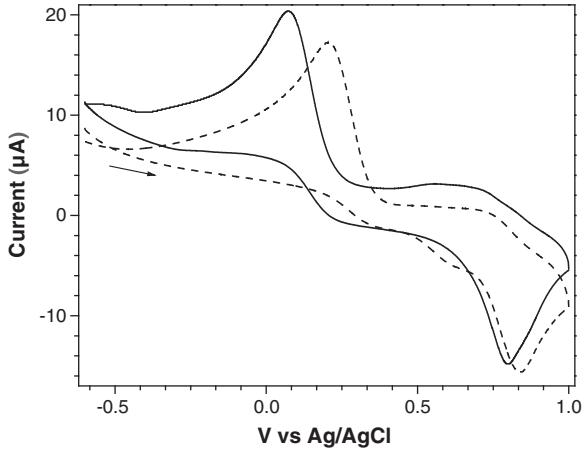

Fig. 2. Cyclic voltammograms of a 10^{-3} M solution of **1** (solid) and **2** (dotted) in dichloromethane in presence of 0.1 M TBAP as a supporting electrolyte, glassy-carbon as a working electrode; scan rate 0.1 V/s.

and are possibly due to Cu(II)/Cu(I) couple [13,21]. These complexes also exhibited an anodic peak at +0.798 V and +0.837 V for **1** and **2** respectively and these anodic peaks probably satisfy the condition for DNA cleavage via self-activation exhibited by complexes **1** and **2** [15,21] (vide infra).

We investigated the nuclease activity of the complexes **1** and **2**. The cleavage of supercoiled (SC) pBR322 DNA by **1** and **2** and formation of nicked (NC) and linear (LC) DNA were studied by several gel electrophoresis experiments in Tris-boric acid–EDTA buffer (TBE). The nuclease activity of **1** and **2** was observed in absence of any oxidizing or reducing agents and the amount of NC DNA was found to be increased with the concentration of **1** and **2** (10–100 μM) without the formation of LC form of DNA (Fig. 3). The enhancement of DNA cleavage activity was observed due to variation of incubation time. For complete conversion of SC form to NC and LC form, 6 h incubation was enough (Fig. S10).

In another experiment, we investigated the cleavage activity of ligands Timpy and Gimpy in presence of metal salts such as $Cu(ClO_4)_2\cdot 6H_2O$, $Mn(ClO_4)_2\cdot 6H_2O$, $Zn(ClO_4)_2\cdot 6H_2O$ and $CoCl_2$ (metal-ligand ratio 1:1) and we found out that $Cu(ClO_4)_2\cdot 6H_2O$ exhibited the nuclease activity in presence of both the ligands (Fig. S11). The ligand Timpy and Gimpy showed negligible nuclease activity (Fig. 3). DNA cleavages were also performed aerobically in the presence of oxidizing or reducing agent. Complexes **1** and **2** showed complete conversion of SC form into NC and LC form of pBR322 DNA in the presence of H_2O_2 and 2–mercaptoethanol (BME) (Fig. 4). In presence of H_2O_2 complex **1** and **2** afforded similar nuclease activity (Fig. 4, lanes 4,7) however, in the presence of 2-mercaptoethanol, complex **2** showed higher nuclease as compared to **1** (Fig. 4, lanes 5,8). Hence we found out the enhancement of DNA cleavage activity in presence of H_2O_2 and 2-mercaptoethanol (BME).

Investigation of the mechanism becomes very much important when copper complexes exhibited nuclease activity in absence of any external reagent. There are several reports in the literature where such type of activity was described; however, following reports [7–13] will be of our interest at this point. In few reports, authors explained such type of DNA cleavage activity via hydrolytic pathway because nuclease activity was not inhibited by radical scavengers. Later on religation experiment was examined to confirm hydrolytic cleavage. If nuclease activity was inhibited by the presence of radical scavengers we could speculate the possible role of reactive oxygen species (ROS) in nuclease activity. Involvement of reactive oxygen species (hydroxyl radical, superoxide ion, singlet oxygen and hydrogen peroxide) in nuclease activity could be diagnosed by monitoring the quenching of DNA cleavage in the presence of radical scavengers in solution [7–13]. The hydroxyl radical scavengers like DMSO, ethanol and urea did not show the inhibition of nuclease activity (Fig. 5, lanes 3–5 and lanes 10–12). These results suggested that hydroxyl radicals may not be involved in the cleavage process for both the complexes **1** and **2**. Addition of singlet oxygen scavengers like NaN_3 and L−histidine (Fig. 5, lanes 6,7 and lanes 13,14) showed inhibition of nuclease activity. So these results suggested that $^1O_2$ or any other singlet oxygen-like entity may participate in the DNA strand scission [13,21,32]. Probable participation of hydrogen peroxide was also included due to inhibition of nuclease activity upon addition of catalase (Fig. 5, lane 8,15). On the basis of

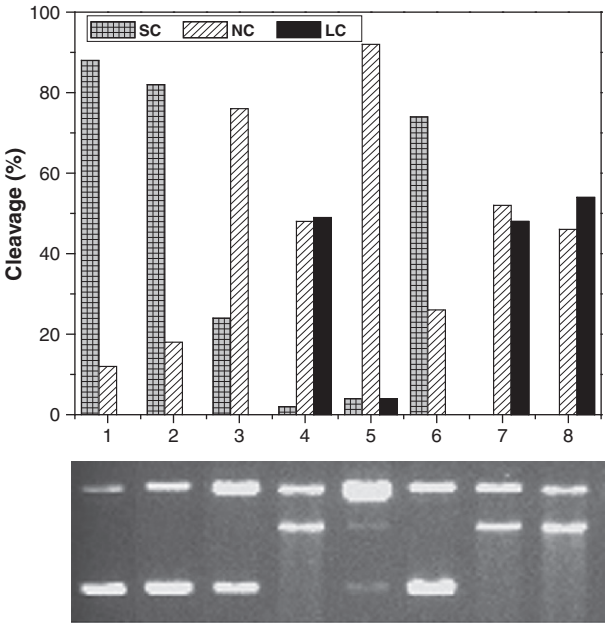

Fig. 4. Gel electrophoresis patterns and the proportions of DNA for different form of pBR322 DNA (40 ng) by complexes **1** and **2** (100 μM) in the presence of H_2O_2 (200 μM) and BME (200 μM) after 2 h incubation at 37 °C. Key: lane 1, DNA control; lane 2, DNA + $Cu(ClO_4)_2\cdot 2H_2O$ (100 μM); lane 3, DNA + **1**; lane 4, DNA + **1** + H_2O_2; lane 5, DNA + **1** + BME; lane 6, DNA + **2**; lane 7, DNA + **2** + H_2O_2; lane 8, DNA + **2** + BME.

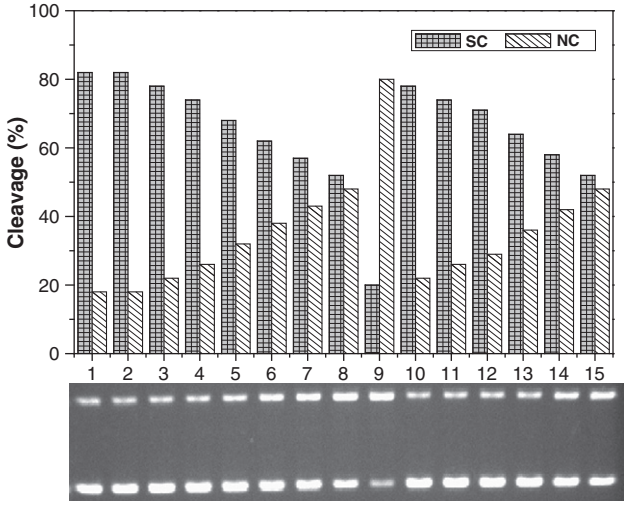

Fig. 3. Gel electrophoresis patterns and the proportions of DNA for different form of pBR322 DNA (40 ng) by complexes **1** and **2** after 2 h incubation at 37 °C. Key: lane 1, DNA control; lane 2, DNA + Gimpy; lane 3, DNA + Timpy; lanes 4–9, DNA + **1** = 10, 25, 40, 50, 75, 100 μM respectively; lanes 10–15, DNA + **2** = 10, 25, 40, 50, 75, 100 μM respectively.

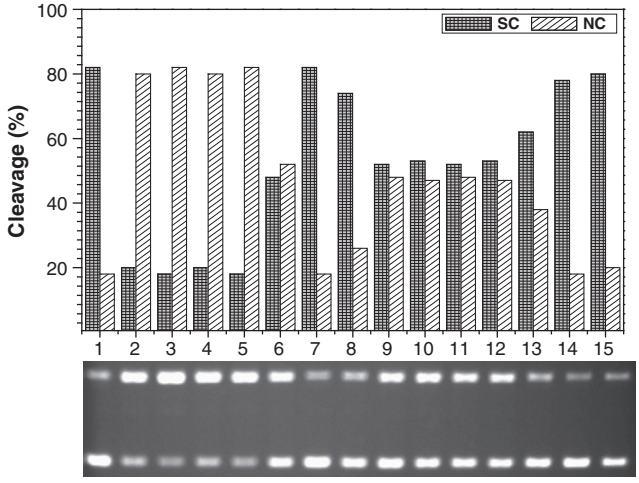

Fig. 5. Gel electrophoresis patterns and the proportions of DNA for different forms of pBR322 DNA (40 ng) by complexes **1** and **2** (100 μM) in the presence or absence of radical scavengers after 2 h of incubation at 37 °C. lane 1, DNA; lane 2, DNA + **1**; lanes 3–8, DNA + **1** + DMSO (20 mM), urea (20 mM), ethanol (20 mM), NaN_3 (20 mM), L-histidine (20 mM), catalase (10 U) respectively; lane 9, DNA + **2**; lanes 10–15, DNA + **2** + DMSO (20 mM), urea (20 mM), ethanol (20 mM), NaN_3 (20 mM), L-histidine (20 mM), catalase (10 U) respectively.

above observations we predict that complex **1** and **2** generated reactive oxygen species (ROS) (most probably singlet oxygen and hydrogen peroxide) which were responsible for nuclease activity. Hence we report that **1** and **2** are another novel examples by which nuclease activity happened via self-activation.

The ligands Timpy and Gimpy afforded fluorescence emission spectra near 440 nm upon excitation at 370 nm (i.e. $\lambda_{ex} = 370$ nm). Effect of solvent on the emission bands of Timpy and Gimpy was displayed in Fig. 6. Both the ligands showed the three humped emission curves near 415, 435 and 460 nm when methanol and ethanol were used as solvent. However, in more polar solvents like in acetonitrile and water, Timpy and Gimpy exhibited a broad band in the range 440–490 nm. A similar change was observed in the emission spectra of Timpy and Gimpy on going from toluene to dichloromethane. The fluorescence property of ligand is expected to be quenched on coordination to the paramagnetic center [33] hence the coordination of copper centre in these ligand frames completely quenched the fluorescence. As an alternative, the reduction of Cu(II) to Cu(I) by nitric oxide can offer a methodology for diamagnetic species formation and the recovery of the fluorescence property [22,23].

The reactivity of nitric oxide with both the copper complexes **1** and **2** was investigated in dichloromethane solution at room temperature. Nitric oxide was generated in situ by acid nitrite solution [34] which was layered on dichloromethane solution of **1** and **2** (details are described in the supporting information). NO molecules generated in situ reacted with copper complexes and afforded greenish-yellow and yellow colored solution respectively for **1** and **2**, which indicated the formation of new copper complexes. The d–d transitions for complexes **1** and **2** were found to appear at 650 nm and 660 nm respectively. On passing the nitric oxide by layering, these bands disappeared due to formation of some copper nitrosyl complexes (Fig. S12 and S13) [26]. The paramagnetic copper complexes **1** and **2** derived from ligands Timpy and Gimpy did not show any fluorescence; however, the in situ generated new nitrosyl copper complexes exhibited fluorescence in dichloromethane solution and spectra are shown in Fig. 7. The UV–visible and fluorescence data support the formation of copper complex containing $\{Cu\text{-}NO\}^{10}$[22] moiety according to Enemark and Feltham notation [35]. However we would like to mention that IR spectra of **1** and **2** afforded peaks at 1739 cm^{-1} and 1744 cm^{-1} respectively (shown in Fig. S14 and S15 respectively). These two peaks are consistent with the data reported by Fujisawa et al. [36] where copper complex, $[Cu(L3)(NO)](ClO_4)$, containing $\{Cu\text{-}NO\}^{11}$ moiety was derived from neutral ligand. Investigation of literature revealed that NO has the tendency to reduce the copper centre [25] during its reactivity with copper complexes. In fact in few cases we observed dissociation of the ligand from the metal complexes [26]. Hence coordination of NO to the metal centre could afford $\{Cu\text{-}NO\}^{10}$ species, on the other hand reduction of Cu(II) centre followed by NO coordination may lead to the formation of $\{Cu\text{-}NO\}^{11}$ species. At this point it is difficult to predict which particular species and/or both are formed in the solution however our data indicate the formation of copper nitrosyl complexes. Hence such metal complexes could be used for detection of NO in solution and insight into this work is under progress.

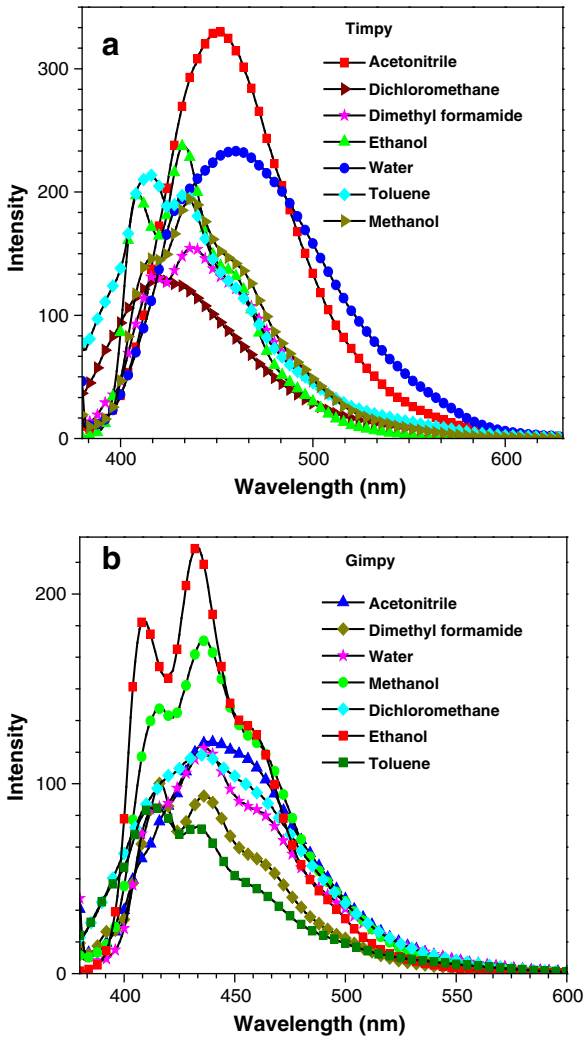

Fig. 6. Fluorescence emission spectra of ligands Timpy and Gimpy in different solvent ($\lambda_{ex} = 370$ nm).

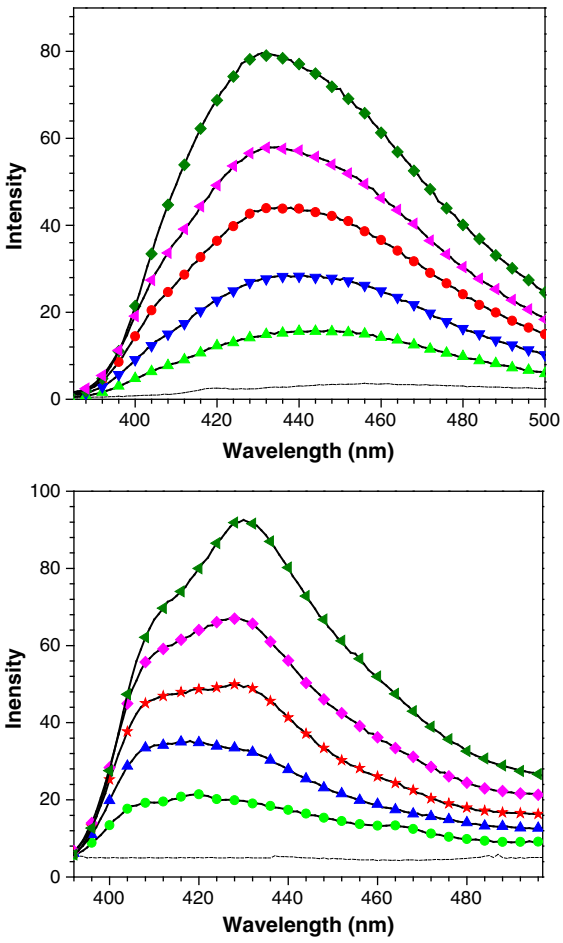

Fig. 7. Fluorescence spectra of complexes **1** and **2** (dotted lines ····) (100 μM) in dichloromethane. After passing NO five scans for each complex (solid lines ———) within 10 min at 298 K ($\lambda_{ex} = 370$ nm).

In conclusion, mononuclear copper(II) complex [Cu(Timpy)(ClO_4)](ClO_4) (**1**) and [Cu(Gimpy)](ClO_4)$_2$ (**2**) derived from tetradentate ligands Timpy and Gimpy respectively were synthesized and characterized. Molecular structure of complex **1** determined by X−ray crystallography showed the distorted square planar geometry around the metal centre and this was supported by structural index parameter. Redox property of **1** and **2** was investigated and both complexes exhibited two irreversible couples in the cyclic voltammograms.

We have found two-fold applications of complexes **1** and **2**. First, these complexes exhibited nuclease activity in absence of any oxidizing or reducing agent. Hence these complexes showed DNA cleavage activity via self-activation and enhancement of activity was found in presence of oxidizing and reducing agents. The self-activated DNA cleavage efficiency was dependent both on the complex concentration and on the time of incubation. Mechanistic investigation implicated possible role of singlet oxygen and hydrogen peroxide in DNA cleavage activity. Hence such types of complexes demand their applications in metallopharmaceutical research.

Second, these complexes exhibited fluorescence emission during their reactivity studies with nitric oxide, although complexes **1** and **2** did not show fluorescence emission. Hence these complexes could be used for the fluorescence-based detection of nitric oxide in solution. Details of mechanistic investigation on nuclease activity, biological activity studies, modification of the ligand frame and applications of these complexes are currently under progress.

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Appendix A. Supplementary material

The experimental and crystal structure details are in supporting information. The CCDC No. for [Cu(Timpy)(ClO_4)](ClO_4) is 825827. The data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html. Supplementary data to this article can be found online at doi:10.1016/j.inoche.2011.09.038.

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