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Synthesis, characterization, DNA-binding and cleavage studies of polypyridyl copper(II) complexes

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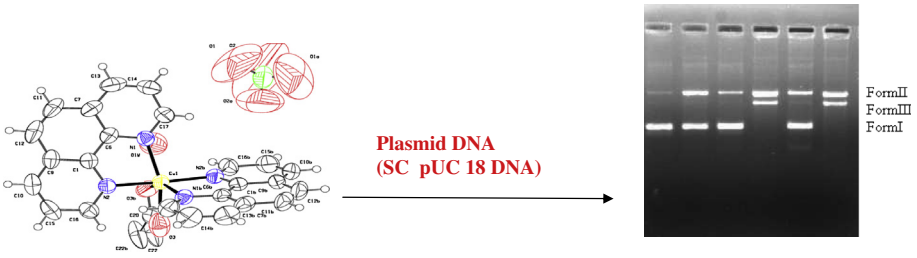
HIGHLIGHTS

- Single crystal X-ray studies of the complex **1** shows Cu(II) ions are located in a highly distorted octahedral environment.
- Binding constant values (UV & CV) indicate that complexes **1**, **2** & **3** bind strongly with DNA possibly by an intercalative mode.
- The shift in the $E_{1/2}$ and CD spectral studies suggest groove or electrostatic binding mode for the complexes **4–6**.
- Complex **1** can cleave (SC) pUC18 DNA into form II & form III in the presence of H_2O_2, while the complex **2** does not cleave DNA.

GRAPHICAL ABSTRACT



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ABSTRACT

Six new mixed-ligand copper(II) complexes were synthesized namely $[Cu(phen)_2OAc]ClO_4{\cdot}H_2O$**(1)**, $[Cu(bpy)_2OAc]ClO_4{\cdot}H_2O$**(2)**, [Cu(*o*-ampacac)(phen)]ClO_4**(3)**, [Cu(*o*-ampbzac)(phen)]ClO_4**(4)**, [Cu(*o*-ampacac)(bpy)]ClO_4**(5)**, and [Cu(*o*-ampbzac)(bpy)]ClO_4 **(6)** (phen = 1,10-phenanthroline, bpy = 2, 2′-bipyridine, *o*-ampacac = (Z)-4-(2-hydroxylamino)pent-3-ene-2-one,*o*-ampbzac = (Z)-4-(2-hydroxylamino)-4-phenylbut-3-ene-2-one)and characterized by UV–Vis, IR, EPR and cyclic voltammetry. Ligands were characterized by NMR spectra. Single crystal X-ray studies of the complex **1** shows Cu(II) ions are located in a highly distorted octahedral environment. Absorption spectral studies reveal that the complexes **1–6** exhibit hypochromicity during the interaction with DNA and binding constant values derived from spectral and electrochemical studies indicate that complexes **1**, **2** and **3** bind strongly with DNA possibly by an intercalative mode. Electrochemical studies reveal that the complexes **1–4** prefer to bind with DNA in Cu(I) rather than Cu(II) form. The shift in the formal potentials $E_{1/2}$ and CD spectral studies suggest groove or electrostatic binding mode for the complexes **4–6**. Complex **1** can cleave supercoiled (SC) pUC18 DNA efficiently into nicked form II under photolytic conditions and into an open circular form (form II) and linear form (form III) in the presence of H_2O_2 at pH 8.0 and 37 °C, while the complex **2** does not cleave DNA under similar conditions.

Abbreviations: bpy, 2,2′-bipyridine; Phen, 1,10-phenanthroline; CD, circular dichroism; DMSO, dimethyl sulfoxide; EDTA, ethylenediamine tetra acetate; EPR, electron paramagnetic resonance; SC, supercoiled; Tris, tris(hydroxymethyl)aminomethane; TAE, tris-acetate EDTA.

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Introduction

The interaction of transition metal complexes with DNA has gained much attention due to their possible applications as new therapeutic agents. Since copper is importance bioessential element in biological processes, the synthesis of copper(II) complexes and the studies on the bio-activity have been the focus from different perspectives. Among copper complexes explored so far, the copper(II) complexes of 1,10-phenanthroline and its derivatives attract great attentions due to their high nucleolytic efficiency [1,2], which are able to break the DNA chain in the presence of H_2O_2 and other reducing agents. These complexes have also been widely used as foot printing agents of both proteins and DNA, probes of the dimensions of the minor groove of duplex structures and identifiers of transcription starting sites [3–5]. Owing to the fact that these complexes show their own selectivity for a cleavage mechanism or for DNA interaction, the design of new DNA cleavage agents is of great interest. In order for mixed-ligand coordination compounds to intercalate more efficiently in DNA, the intercalating ligand needs a flat, large surface area and a spatial geometry that permit overlapping between the aromatic ring of the intercalating ligand and the base pairs in DNA [6]. By changing both the metal ions and ligands, it is also possible to modify the mode of interaction of the complex with nucleic acids [7–9]. Palaniandavar et al. have reported the novel conversion of right-handed B-DNA to left-handed Z conformation on interaction of calf thymus (CT) DNA with methyl substituted *bis*(phen)copper(II) complexes [10,11]. In recent years, large number of papers involving copper(II) complexes have been reported [12].

Our group has reasonable expertise on the synthesis of metal complexes bearing bioactive ligands (e.g. curcumin), tetradentates (N_4) and different mixed ligand metal complexes have also been synthesized and all these new complexes have been characterized by various spectroscopic techniques. Their possible interactions with DNA have also been investigated [13–17]. The present work stems from our interest to explore the DNA cleavage activity of N,N-donor heterocyclic bases like bpy, phen and of ternary copper(II) complexes comprising NNO Schiff base ligands and bpy or phen. Thus, we studied the interaction of DNA and ternarycopper(II)complexes **1**–**6** in Tris–HCl buffer at pH 7.2. The interaction of these complexes with DNA has been investigated using electronic absorption spectroscopy, circular dichroic spectral methods and cyclicvoltammetric techniques. The results were analyzed to find out the suitability of these complexes for understanding the mode of binding with DNA as well as laying a foundation for the rational design of novel, powerful agents for probing and targeting nucleic acids.

Experimental

Materials and instrumentation

1,10-Phenanthrolinemonohydrate (MERCK), 2,2′-Bipyridyl (MERCK), 2-Aminophenol (MERCK), Benzoylacetone (MERCK), Acetylacetone (MERCK), Sodium perchlorate (MERCK), Sodium chloride (MERCK), Herring sperm DNA (SRL), Tris-hydrochloride (SRL) and Sodium chloride (SRL) were used as received. Supercoiled pUC18 DNA was purchased from Genei, Bengaluru, India. Double Distilled water was used for all the experiments. All reagents and solvents were analytical, spectroscopic grade and they were used without further purification and then used for the preparation of ligands and complexes. The ligand and its Cu(II) complexes were prepared by reported literature methods [18].

UV–Vis spectral measurements were made on DMSO solution of the Cu(II) complexes using JASCO double beam recording spectrophotometer in the range 200–1100 nm. The infrared spectra of all complexes as well as the free ligand were recorded using KBr pellet on a JASCO FT-IR 410 double beam infrared spectrophotometer in the range of 400–4000 cm^{-1}. Electron paramagnetic resonance spectra of the complexes **1**–**6** were obtained on a Varian-E-112 EPR spectrometer. The spectra were recorded for solutions of the complexes in DMSO solvent at room temperature (RT) as well as at liquid nitrogen temperature (77 K). DPPH (2,2-Diphenyl-1-Picrylhydrazyl) was used as the field marker. Cyclic voltammetric measurements were carried out on a Bio-Analytical System (BAS) model CV-50W electrochemical analyzer. The three electrode cell comprising of a reference Ag/AgCl, counter electrode as platinum wire and working glassy carbon (GC) electrodes with surface area of 0.07 cm^2. The GC was polished with 0.3 and 0.005 mm alumina before each experiment and if necessary the electrode was sonicated in distilled water for 10 min. Dissolved oxygen was removed by purging pure nitrogen gas into the solution for about 15 min before each experiment. Scanning the cyclic voltammogram for a blank solution checked the purity of the supporting electrolyte and the solvent.

Crystal structure determination

Single-crystal X-ray diffraction measurement for the complex $[Cu(phen)_2(OAc)](ClO_4)\cdot H_2O$ was carried out on a Nonius MACH3 diffractometer with graphite monochromated Mo Kα (λ = 0.71069 nm) radiation at the temperature of 293(2) K. Intensities were corrected for Lorentz and polarization effects and empirical absorption, and the data reduction using XCAD4 program [19]. The structure was solved by direct methods using SHELXS-97 program [20]. All the non-hydrogen atoms were refined on F^2 anisotropically by full-matrix least-squares method. All hydrogen atoms were placed in calculated positions with assigned fixed isotropic thermal parameters and allowed to ride on their respective parent atoms. The contributions of these hydrogen atoms were included in structure-factor calculations. Atomic scattering factors and anomalous dispersion corrections were taken from International Table for X-ray Crystallography [21].

Spectroscopic studies on DNA interaction

Electronic absorption spectra

All the experiments involving the interaction of the complexes 1–6 with CT-DNA were carried out in Tris buffer (5 mM, pH 7.2). A solution of CT-DNA in the buffer gave a ratio of UV absorbance at 260 and 280 nm of about 1.8–1.9:1, indicating that the DNA was sufficiently free from protein [22]. The DNA concentration per nucleotide and polynucleotide concentration were determined by absorption spectroscopy using the molar extinction coefficient (6600 M^{-1} cm^{-1}) at 260 nm [23]. The intrinsic binding constant K_b for the interaction of these Cu(II) complexes with DNA has been calculated from the absorption spectral titration data. The intrinsic binding constant K_b was determined from Eq. (1) [24],

$$[DNA]/(\varepsilon_a - \varepsilon_f) = [DNA]/(\varepsilon_b - \varepsilon_f) + 1/K_b(\varepsilon_b - \varepsilon_f) \quad (1)$$

where [DNA] is the concentration of DNA in base pairs, the apparent absorption coefficient ε_a, ε_f and ε_b correspond to A_{obs}/[M], the extinction coefficient of the free compound and the extinction coefficient of the compound when fully bound to DNA, respectively. Plot of $[DNA]/(\varepsilon_a - \varepsilon_f)$ *vs.* [DNA] gave a straight line with a slope of $1/(\varepsilon_b - \varepsilon_f)$ and an intercept of $1/K_b$ $(\varepsilon_b - \varepsilon_f)$ and K_b was determined from the ratio of the slope to intercept.