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Synthesis, structure, redox properties and DNA interaction studies on mononuclear iron(III) complexes with amidate ligand

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ABSTRACT

A new family of mononuclear Fe(III) complexes [Fe(Pamp)(MeOH)Cl_2], **1** and [Fe(Pamp)$_2$](ClO_4), **2** were synthesized using designed tridentate ligand PampH having pyridine and amide nitrogen donors (PampH is N′-phenyl-N′-(pyridin-2-yl)picolinohydrazide) and H stands for dissociable proton). Both the complexes (**1** and **2**) were characterized by different spectroscopic studies and molecular structure of [Fe(Pamp)$_2$](ClO_4), **2** was determined by single crystal X-ray diffraction. Geometry around metal centre was described as distorted octahedral with two meridionally oriented $Pamp^-$ ligands. Electrochemical studies afforded $E_{1/2}$ values of Fe(III)/Fe(II) couple +0.065 V (for **1**) and −0.077 V (for **2**) versus Ag/AgCl electrode. DNA binding properties of these complexes were investigated and complex **1** exhibited nuclease activity. Mechanistic investigation revealed the possible participation of hydroxyl radical in nuclease activity which was supported by rhodamine B assay.

1. Introduction

There has been considerable current interest for the synthesis of metal based synthetic nuclease because of their applications in discovery of artificial DNA cleaving agents, DNA foot-printing and in medicinal chemistry [1–6]. Cis-platin and Fe-bleomycin are the established metal based anticancer drugs [7–9]. Cis-platin is having lot many side effects and researchers are interested to discover metal based anti cancer agents with biologically benign metal rather than toxic metal like platinum [10]. Among first row transition elements iron exhibit flexible range of coordination geometries, oxidation states, spin states and redox potential and hence, iron became one of the suitable metals for the synthesis of artificial nuclease [11–13]. Several iron complexes were reported as artificial nucleases, however, most of them are multinuclear [3,14–23] and very few of them are mononuclear [24–26]. Among mononuclear complexes most of them were reported with salen and salen related ligands [27–29]. On the other hand, Roelfes et al. and Mukherjee et al. reported synthetic DNA cleavage agent of mononuclear iron complex in which ligand was covalently attached to a DNA-binder arm or intercalator as imidazopyridine ring and 9-aminoacridine (also acts as photosensitizer) respectively [30–31]. Wong et al. also reported nuclease activity of mononuclear iron complexes with tripodal ligands [32]. It is now well known in the literature that the ligation of deprotonated amidate nitrogen(s) stabilizes the iron(III) centres due to their strong σ-donating abilities [33]. Coordination chemistry of iron-amidate group participate important role in biomolecules such as anti-tumor drug bleomycin [34] and enzyme nitrile hydratase [35–36]. Fe(III) complexes derived from such ligand(s) have been exploited now as DNA cleaving agents [37]. Mascharak and co-workers reported mononuclear iron complex mimicking the iron binding site of belomycine (by designing the ligand having amidate group) however DNA binding and nuclease activity of these complexes were not reported [38].

Recently, we have communicated the role of carboxamido nitrogen in superoxide scavenging activity and nuclease activity [39–40]. Herein, we report the synthesis and characterization of two mononuclear iron complexes [Fe(Pamp)(MeOH)Cl_2], **1** and [Fe(Pamp)$_2$](ClO_4), **2**, derived from the amidate ligand PampH (shown in Scheme 1). These complexes were characterized by spectroscopic and electrochemical studies. Molecular structure of complex **2** was determined by X-ray crystallography. DNA interaction and nuclease activity were examined. We also investigated the mechanism of nuclease activity.

2. Experimental

2.1. Materials

All the solvents used were reagent grade. Analytical grade reagents picolinic acid (Wilson Laboratories, Mumbai, India), dicyclohexylcarbodiimide (SRL, Mumbai, India), 1-hydroxybenzotriazol (Himedia Laboratories Pvt. Ltd., Mumbai, India), phenylhydrazine, (S. D. Fine, Mumbai, India) and 2-chloropyridine (Acros organics,

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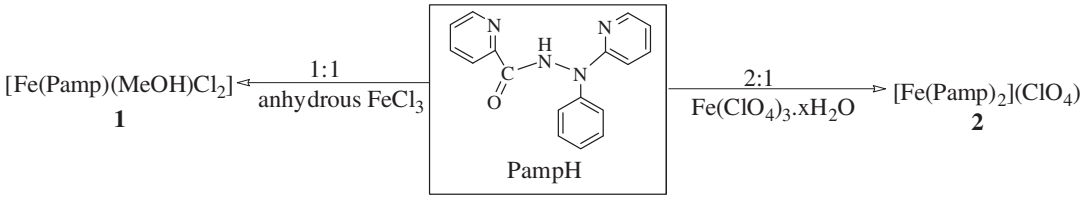

Scheme 1. Synthetic scheme of complex 1 and 2.

USA) were used as obtained. Anhydrous $FeCl_3$ was purchased from Rankem, Delhi, India and $Fe(ClO_4)_3{\cdot}xH_2O$, $Fe(ClO_4)_2{\cdot}xH_2O$, rhodamine B dye and 1,3-diphenylisobenzofuran (DPBF) were purchased from Sigma Aldrich, Steinheim, Germany. Solvent used for spectroscopic studies were HPLC grade and purified by standard procedure before use [41]. Supercoiled *pBR322* DNA and CT DNA were purchased from Bangalore Genei (India). Agarose was purchased from (Himedia Laboratories Pvt. Ltd., Mumbai, India). Tris(hydroxymethyl)aminomethane–HCl (Tris–HCl) buffer was prepared in deionised water.

Caution! Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amount of material should be prepared and handled with caution.

2.2. Synthesis of complexes

2.2.1. [Fe(Pamp)(MeOH)Cl_2], **1**

A batch of (34 mg, 0.27 mmol) anhydrous $FeCl_3$ in 5 mL of methanol was added dropwise to stirred solution of ligand PampH (79.7 mg, 0.27 mmol) in 15 mL of methanol. The colour of solution was changed to dark green. The green solution was filtered to remove dirty suspension. Filtrate was again stirred for 3 h and the solution was kept in freeze for slow evaporation. Green colour semi-crystalline precipitate was obtained which was filtered and washed with small amount of methanol and diethylether. Though, complex **1** is precipitated as nice crystalline solid but all attempts to get single crystals were unsuccessful. Yield: 52.2 mg, (42%). Selected IR data (KBr, ν_{max}/cm^{-1}): 1658, 1603 $\nu_{-C=O}$. UV–Vis [CH_2Cl_2, λ_{max}/nm ($\varepsilon/M^{-1}cm^{-1}$)]: 626 (1450), 321 (9750), 248 (15,000). μ_{eff} (296 K): 5.19 BM. Λ_M/Ω^{-1} cm^2 mol^{-1} (in DMF): 12. *Anal.* Calc. for $C_{18}H_{17}N_4O_2Cl_2Fe$: C, 48.25; H, 3.82; N, 12.50. Found: C, 49.01; H, 3.67; N, 12.53%.

2.2.2. [Fe(Pamp)$_2$](ClO_4)

2.2.2.1. Method A. A batch of (50 mg, 0.14 mmol) $Fe(ClO_4)_3{\cdot}xH_2O$ in 5 mL of methanol was added dropwise, to the stirred solution of (80.7 mg, 0.28 mmol) ligand (PampH) in 10 mL of methanol. The colour of solution changed to red and then to brown. After 5 min, it turns to brownish-green solution which was stirred for 4 h. Dark green solid was separated out which was filtered and washed with methanol and small amount of diethylether. Single crystals of the complex for X-ray crystallography were obtained within a week on slow diffusion of acetonitrile/ethylacetate-diethyl ether mixture in freezer. Yield: 75.0 mg, (73%). Selected IR data (KBr, ν_{max}/cm^{-1}): 1602, $\nu_{-C=O}$, 1090, 622 ν_{ClO4-}. UV–Vis [CH_3CN, λ_{max}/nm (ε/M^{-1} cm^{-1})]: 801 (2000), 437 (3100), 315 (14,300), 251 (23,150). μ_{eff} (296 K): 2.75 BM, Λ_M/Ω^{-1} cm^2 mol^{-1} (in DMF): 58. *Anal.* Calc. for $C_{34}H_{26}N_8O_6ClFe$: C, 55.64; H, 3.57; N, 15.27. Found: C, 55.60; H, 3.72; N, 15.23%.

2.2.2.2. Method B. A batch of (30 mg, 0.12 mmol) $Fe(ClO_4)_2{\cdot}xH_2O$ in 5 mL of methanol was added dropwise, to the stirred solution of (72.5 mg, 0.25 mmol) ligand (PampH) in 10 mL of methanol. The colour of solution was changed to purple and within 1 min brownish-green solid was separated out. This green solid was filtered and washed with methanol and diethylether. Yield: 45 mg, (51%).

2.3. Physical measurements

Elemental analyses were carried microanalytically at Elemenlar Vario EL III. IR spectra were obtained as KBr pellets with Thermo Nikolet Nexus FT-IR spectrometer, using 16 scans and were reported in cm^{-1}. Electronic absorption spectra were recorded with an Evolution 600, Thermo Scientific UV–Vis spectrophotometer. Emission quenching titrations were carried out on Varian fluorescence spectrophotometer. Circular dichroism (CD) spectra of complexes (**1** and **2**) were recorded on Chirascan circular dichroism spectrometer, Applied photophysics, UK. Magnetic susceptibilities were determined at 296 K with Vibrating Sample Magnetometer model 155, using nickel as a standard. Diamagnetic corrections were carried out with Pascal's increments [42]. Molar conductivities were determined in dimethylformamide (DMF) at 10^{-3} M at 25 °C with a Systronics 304 conductometer. Cyclic voltammetry measurements were carried out using a CH-600 electroanalyzer. A conventional three-electrode arrangement was using consisting a platinum wire as auxiliary electrode, glassy carbon as working electrode and the Ag(s)/AgCl as reference electrode. These measurements were performed in the presence of 0.1 M tetrabutylammonium perchlorate (TBAP) as the supporting electrolyte, using complex concentration 10^{-3} M in dichloromethane and acetonitrile. The ferrocene/ferrocenium couple occurs at $E_{1/2}$ = +0.40 (75) V versus Ag/AgCl under the same experimental conditions. All experiments were performed at room temperature and solutions were thoroughly degassed with nitrogen prior to beginning the experiments.

2.4. X-ray crystal structure determination of complex **2**

Crystal and refinement data is given in Table 1. The X-ray data collection and processing for complex **2** was performed on Bruker Kappa Apex-II CCD diffractometer by using graphite monochromated Mo Ka radiation (k = 0.71070 Å) at 296 K. Crystal structure was solved by direct methods. Structure solution, refinement and data output was carried out with the SHELXTL program [43–44]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in geometrically calculated positions and refined using a riding model. Images were created with the DIAMOND program [45].

2.5. DNA binding experiments

Fluorescence quenching experiments were carried out by the successive addition of complexes **1** and **2** to the DNA (25 μM) solutions containing 5 μM ethidium bromide (EB) in 100 mM phosphate buffer (pH 7.2). For better solubility of complex **1** and **2**, we use 5% DMF. These samples were excited at 250 nm and emissions were observed between 500 and 700 nm. Stern–Vol-