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Synthesis, crystal structure, electrochemical and bioactivities of pyridine-2-carboxylato bridged copper(II) complexes

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ABSTRACT

Two carboxylato bridged copper(II) complexes have been synthesized and characterized: $[Cu_4(2\text{-Pca})_4(NH)_2(bipy)_2](ClO_4)_2\cdot H_2O$ (**1**) and $[Cu(2\text{-Pca})_2]_n\cdot 3H_2O$ (**2**), (2-Pca = the pyridine-2-carboxylate ion, NH = nicotinic acid hydrazide and bipy = 2,2′-bipyridine). Two types of bridging are present in **1**; NH makes a bridge between the two copper atoms, along with 2-Pca. The crystal structure is stabilized by hydrogen bonds of the O–H...O type. Complex **1** belongs to triclinic system, having space group $P\bar{1}$. The copper–copper separation is 5.3220(5) Å for **1**. The coordination geometry of **1** is distorted square pyramidal and significant π...π stacking interactions are also present. The electrochemical and epr spectral studies at 77 K of complexes **1** and **2** have been investigated. Cleavage activities of both complexes have been investigated on double stranded pBR322 plasmid DNA by gel electrophoresis. Superoxide dismutase and antibacterial activity of both complexes have also been measured and discussed.

1. Introduction

Research on carboxylates has always been intriguing in that they play an important role in synthetic chemistry, with the essence of labile coordination modes [1,2], biological activities [3,4] and physiological effects [5]. Copper(II) carboxylates are structurally a very diverse group of coordination compounds due to the various coordination modes of the carboxylato ligands [6,7]. Reaction centers containing two or more transition metal ions are of particular interest to study the cooperative effects of redox active sites [8]. Different coordination modes of carboxylate groups lead to the formation of mono- and polynuclear complexes with transition metal ions. It is well known that the carboxylate group is able to create hydrogen bonds, leading to the formation of supramolecular networks which play an important role in the transmission of magnetic interactions. This particular interest has also recently been focused on the development of supramolecular structures created by hydrogen bonds. Non-covalent interactions, such as hydrogen bonding, hydrophobic, steric repulsion, aromatic ring stacking and electrostatic interactions play important roles in chemical reactions, molecular recognition and regulating biochemical processes [9–11]. Complexation with copper enhances the biological activity of a wide variety of organic ligands [12,13]. DNA cleavage is considered to be an important enzymatic reaction involved in a number of biological processes and in the biotechnological manipulation of genetic materials [14–21]. Application of metal complexes as chemical nucleases is the focus of current research [22,23]. DNA cleavage may take place via hydrolytic or oxidative pathways [24,25]. Hydrolytic cleavage of DNA causes hydrolysis of the phosphodiester bond, forming DNA fragments that could be rejoined. The oxidative cleavage of DNA results in the oxidation of the sugar moiety of the base. This process is suitable for foot printing and therapeutic studies.

Pyridine-2-carboxylic acid is an isomer of nicotinic acid and is one of the most important chelating agents in the human body. During digestion it is secreted to the intestine and is used as a complexing agent (bio-ligand) in the absorption of essential metals [26,27]. Nicotinic acid hydrazide is an isomer of isonicotinic acid hydrazide (INH) which is the most important drug of a series of compounds based on carboxylic acid hydrazide [28]. Recently some examples of structurally characterized copper(II) complexes containing 2-Pca have been reported in the literature [29–33]. In order to obtain mimicry of metalloprotein active sites, we decided to use bio-ligands. Using the bio-ligands pyridine-2-carboxylic acid (2-Pca) and nicotinic acid hydrazide (NH), we have synthesized and characterized two polynuclear copper(II) complexes using various physicochemical techniques. The different bioactivity properties, such as superoxide dismutase, antibacterial and DNA cleavage activity, of both complexes were also studied and discussed in detail.

2. Experimental

2.1. Materials and physical measurements

Copper perchlorate hexahydrate (Sigma Aldrich), nicotinic acid hydrazide (Acros Organics), copper carbonate (Acros Organics), 2-Pca (S.D. fine) and pBR322 plasmid DNA (Bangalore GeNei). All

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the solvents were purchased from commercial sources and were used without further purification.

The elemental analyses of the complexes were performed on an Elementar Vario ELIII Carlo Erba 1108 Elemental analyzer. Fast Atom Bombardment mass spectra of the complexes were recorded on a JEOL SX 102/DA 6000 mass spectrometer using xenon (6 kV, 10 mA) as the FAB gas. The accelerating voltage was 10 kV and spectra were recorded at room temperature (RT) with *m*-nitrobenzyl alcohol as the matrix. UV–Vis spectra were recorded at room temperature on a Shimadzu 1601 spectrophotometer. IR spectra were recorded in KBr medium on a Perkin-Elmer spectrophotometer. Cyclic voltammetry was carried out on a BAS-100 Epsilon electrochemical analyzer, using an electrochemical cell with a three-electrode system. Ag/AgCl was used as the reference electrode, glassy carbon as the working electrode and platinum wire as the auxiliary electrode. $NaClO_4$ (0.1 M) was used as supporting electrolyte and DMSO as the solvent. All measurements were carried out at 298 K under a nitrogen atmosphere. Electron paramagnetic resonance (epr) spectra were recorded with a Varian E-line Century Series epr spectrometer equipped with a dual cavity and operating at the X-band of the 100 kHz modulation frequency. Tetracyanoethylene was used as a field marker ($g = 2.00$, 277).

2.2. Synthesis of $[Cu_4(2\text{-}Pca)_4(NH)_2(bipy)_2](ClO_4)_2\cdot H_2O$ (**1**)

In the synthesis of complex **1**, $Cu(ClO_4)_2\cdot 6H_2O$ (1 mmol, 0.370 g) was dissolved in a 50 ml mixture of ethanol and water (1:1, V/V) then NH (1 mmol, 0.137 g), 2-Pca (1 mmol, 0.123 g) and bipy (1 mmol, 0.156 g) were added one by one with an interval of 10 min. The resulting mixture was stirred for 3 h at room temperature. After one week, light blue crystals suitable for single crystal X-ray diffraction were obtained. Yield: 65%. *Elemental analysis* calc. for $C_{56}H_{44}Cl_2Cu_4N_{14}O_{19}$ **1** ($M_r = 1542.12$): C, 43.62; H, 2.88; N, 12.72. Found: C, 43.05; H, 3.26; N, 12.45%. FAB mass (*m*/*z*) calc.: 664.61. Found: 664.

2.3. Synthesis of $[Cu(2\text{-}Pca)_2]_n\cdot 3H_2O$ (**2**)

Complex **2** was prepared from the reaction of $CuCO_3\cdot Cu(OH)_2$ with pyridine-2-carboxylic acid in a 50 ml mixture of ethanol and water (1:1, V/V). $CuCO_3\cdot Cu(OH)_2$ (0.5 mmol, 0.110 g) and 2-Pca (2 mmol, 0.246 g) were stirred for 4 h at 50 °C. Slow evaporation of the solvent led to the formation dark blue block shaped crystals suitable for single crystal X-ray studies. Yield: 71%. *Elemental analysis* calc. for $C_{12}H_{14}CuN_2O_7$ **2** ($M_r = 361.79$): C, 39.84; H, 3.90; N, 7.74. Found: C, 39.10; H, 3.50; N, 7.95%. FAB mass (*m*/*z*) calc.: 307.74. Found: 308.

2.4. Single crystal X-ray crystallography

Single crystal X-ray data were collected on a CCD detector based Oxford diffractometer using graphite monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å). The diffraction data were solved using SIR-92 [34] with GUI control and the structure was refined by SHELXL-97 [35] refinement of F^2 against all reflections. Non-hydrogen atoms were refined anisotropically and all hydrogen atoms were geometrically fixed and allowed to refine using a riding model. Molecular graphics were generated using different software, such as Diamond, ORTEP-3v2 for WINDOWS [36], PLATON and Mercury [37].

2.5. Biological activity measurements

The superoxide dismutase activity (SOD) of the present copper(II) complexes was evaluated using alkaline DMSO as the source of the superoxide radical (O_2^-) generating system, in association with nitro blue tetrazolium chloride (NBT) as a scavenger of superoxide [38,39]. With certain concentrations of the complex solution, 2.1 ml of 0.2 M potassium phosphate buffer (pH 8.6) and 1 ml of 56 μM NBT solutions were added. The mixtures were kept in ice for 15 min and then 1.5 ml of alkaline DMSO solution was added while stirring. The absorbance was monitored at 540 nm against a sample prepared under similar conditions, except NaOH was absent in DMSO. The *in vitro* antibacterial activities were tested against *Escherichia (E.) coli, Citrobacter (C.) gillenii* and *Vibrio (V.) cholera*, and comparisons were made with standard antibiotics. The agar disk diffusion method was adopted for determination of antibacterial activity [40–42]. Autoclaved Nutrient agar medium was poured into a sterile Petri-dish and allowed to solidify. Petri-dishes were seeded with bacterial species. A paper disc was placed on the dish after dipping the test compound (DMSO solution). The width of the growth inhibition zone around the disc was measured after 24 h incubation at 37 °C. The DNA cleavage experiment was performed by the agarose gel electrophoresis method [43–45]. The efficiency of DNA cleavage was measured by determining the ability of the complexes to form open circular (OC) and nicked circular (NC) DNA from its super coiled (SC) form. The DMSO solution (1×10^{-3} M) containing the metal complexes (5 μL, 250 μM) was taken in a clean Eppendroff tube and 30 μM of pBR 322 DNA was added. The content were incubated for 30 min at 37 °C and loaded on 0.8% agarose gel after mixing 3 μl of loading buffer (0.25% bromophenol blue + 0.25% xylene cynaol + 30% glycerol sterilized distilled water). The electrophoresis was performed at constant voltage (75 V) until the bromophenol blue reached up to ¾ length of the gel. The gel was stained for 10 min by immersing it in ethidium bromide solution (5 μg/ml of water) and then de-stained for 10 min by keeping it in sterile distilled water. The plasmid bands were visualized by photographing the gel under a UV transilluminator. The reactions were carried out under oxidative and/or hydrolytic conditions.

3. Results and discussions

3.1. Synthesis of the complexes

For the synthesis of polynuclear copper(II) coordination complexes, a conventional solution method was adopted and as a result single crystals of **1** suitable for X-ray diffraction analysis were obtained. The pyridine-2-carboxylic acid was used in both complexes, and is the main structural unit of the complexes in bridge formation. Both complexes **1** and **2** are deep blue in color, stable in air and soluble in DMF, DMSO and in a mixed CH_3OH:CH_3CN (1:1, V/V) solution, but they are only partially soluble in other organic solvents, such as $CHCl_3$ and CH_2Cl_2. Both complexes gave satisfactory elemental analysis and were further characterized by FAB^+ mass spectrometry.

3.2. Description of crystal structure

The crystalline structure of complex **1** belongs to the triclinic crystal system having space group $P\bar{1}$. An ORTEP view of complex **1** is shown in Fig. 1 and the crystal data and structure refinement parameters are listed in Table 1. Selected bond angles and bond distances are listed in Table 2. Complex **1** has three types of ligand, and of these, two ligands make a bridge between two copper atoms. The pyridine-2-carboxylate ion is the main structural unit of the complex. The $Cu–N_{Pyridine}$ bond distances (Cu1–N5, Cu1–N4, Cu2–N7, Cu2–N6) are similar in **1**, while the $Cu–N_{hydrazine}$ bond distance, Cu1–N1 = 2.006(2) Å, is quite a bit longer. The coordination sphere of complex **1** is shown in Fig. 2. The nature of NH in complex **1** is that of a mono negative ligand, due to keto–enol