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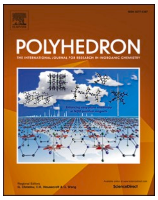

Histamine derived dimer of μ-Chlorido-μ-Phenoxido Dicopper(II) complex as a potential enzyme mimic with catecholase activity

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ABSTRACT

A new copper(II) complex, $[Cu_2(L^1)(\mu\text{-}Cl)_2]_2$ (**C1**), of the binucleating 2,6-bis((2-(4′-imidazolyl)ethyl)amino-methylidene)-4-methylphenol (**HL^1**) with N_4O binding sites, has been synthesized to investigate as potential structural and functional model for catecholase activity of the dicopper(II) site. It has been characterized by spectroscopic techniques and X-ray crystallography. The complex **C1** exists as chlorido bridged dimer of binuclear copper(II) units, each possessing one end-off compartmental ligand (**L^1**) with endogenous μ-phenoxido and exogenous μ-chlorido groups leading to intermetallic distance Cu1···Cu2 of 3.129 Å and Cu1-O1(phenoxo)-Cu2 angle of 107.67(10)°. Each copper(II) center has distorted octahedral geometry with bridging by chlorides in the tetranuclear dimer. The crystal system is monoclinc with space group $P2_1/c$. Magnetic measurements reveal that **C1** is strongly antiferromagnetically coupled with $J = -115.663 \pm 0.82547\ cm^{-1}$. The catecholase activity of the complex has been evaluated by oxidation of 3,5-di(*tert*-butyl)catechol and 4-methyl catechol to the corresponding quinones under aerobic conditions. A kinetic treatment on the basis of the Michaelis-Menten model has been applied for the kinetic study. The complex is found to be selective for the substrates with higher $V_{max} = 8.2726x10^{-8}\ M\ s^{-1}$ and $K_m = 0.0107$ M for 3,5-DTBC at 30 °C as compared to $V_{max} = 5.0371x10^{-8}\ M\ s^{-1}$ and $K_m = 0.027$ M for 4-methyl catechol at 50 °C while it is found to be practically inactive for dopamine, 2,3-dihydroxy naphthalene and pyrocatechol oxidation.

1. Introduction

The complexes of macrocyclic and compartmental ligands have invited lot of attention since last several years due to their ability to hold metal ions in close proximity and facilitate electron and spin delocalization. [1–4] The main focus of these studies has been to understand the spin exchange interactions which has led to the evolution of structure-magnetism correlations [5–12] and understanding the role of bridging moieties. [13–15] The capability of the bridging moieties to hold the metal ions in proximity can modulate their redox potentials. Hence, systematic structural variations in ligands in such complexes [16–23] are expected to help finely tune the redox behaviour of the metal centres. This fine tuning of redox potentials is expected to be the key factor in deciding the selectivity of active sites in redox enzymes, specially so in those having coupled binuclear active sites.

Attempts have been made to design dinuclear copper complexes using binucleating ligands, to accommodate two proximal copper ions which can have applications in modelling the active sites of many metalloenzymes [24–26] and hosting small molecules in catalysis. [27–31] Structural models of type-3 copper active sites in enzymes, like tyrosinase (hydroxylation of monophenols and oxidation of diphenols) and catechol oxidase (oxidation of catechols) with antiferromagnetically coupled binuclear copper centre have been developed. Some of them have been shown to possess catecholase activity. [32–41] The ability to oxidise diphenols is important in medical diagnosis for determination of hormonally active catecholamines, adrenaline, noradrenaline and dopa. [42,43] The direct use of these metalloproteins is difficult for their availability and stability in vitro while the synthetic mimics which function as highly efficient catalysts can be used to overcome this difficulty. [40,41,26] Thus, studies on the model compounds mimicking the catecholase activity are useful and promising for the development of new, more efficient bioinspired, environment friendly catalysts, for in vitro oxidation reactions. The development and design of relatively simple, synthetic models of active site structures of copper proteins are also of considerable interest for understanding their unusual spectroscopic characteristics and the catalytic mechanisms. [17,44,45]

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Supramolecular birefringent metallogels formed by trinuclear copper(II) complexes with myo-inositol and bipyridyl ligands†

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Birefringent metallohydrogels have been prepared *via* a supramolecular assembly resulting from the trinuclear copper(II) complex of myo-inositol (ins) and 2,2′-bipyridine (bipy), $[Cu_3(ins)(bipy)_3]X_3$, in which X has been varied as $HCOO^-$, CH_3COO^- and $CH_3CH_2COO^-$. The gel properties including T_{gel} are found to have a significant anion dependence. The metallogels have been characterized by thermal analysis and spectroscopic methods. The SEM analysis has indicated the presence of a fibrous supramolecular assembly. The metallogels were found to be highly birefringent and organize into quaternary structures that display unique patterns in the microscopic studies under polarized light.

Introduction

The discovery and design of specific hydrogels with small molecule gelators are envisaged for various applications such as super absorbent materials and sensors,[1] drug delivery systems,[2] tissue-engineering,[3] aerospace,[4] templated nonmaterial synthesis[5] and optoelectronic devices.[6] Their properties are mainly attributable in most cases to the presence of various metal ions and hence the research on metallogelators gained momentum initially with physical gels formed by adding metal ions to the gels. The metallogels involving coordination polymers were shown to exhibit unusual functional properties such as catalytic activity,[7] and redox responsive,[8] stimuli-responsive,[9,10] photoemissive,[9,11] and magneto-optical switching properties.[12] However, owing to their widespread applications extended over a broad spectrum, there has arisen an immense interest in developing new low molecular weight metallogelators[13] (LMWGs), which result in self-assembled supramolecular assemblies, held together by non-covalent interactions[14] like H-bonding and π–π stacking.[15] Such interactions have been found to be very important in sugar-based gelators.[16]

Among the non-covalent interactions, metal coordination often plays an important role, forming metallogels involving either discrete organometallic compounds or metal complexes, important candidates for relevant studies. When metal–ligand interactions extend along the backbone of aggregates, gel forming nano-fibrous materials are often formed.[17] Incorporation of metal ions into LMWGs and coordination-directed gels display novel properties useful in adsorption catalysis and as templates for porous materials,[18] which might find application in gas storage. These supramolecular self-assembled metallogels exhibit widespread and versatile applications right from the field of biomedicines as controlled drug delivery agents to the field of materials science for the synthesis of supramolecular nanostructured assemblies due to their ability to respond to an external stimulus like pH, temperature, solvent and radiation.

Among the stimuli-responsiveness of the LMWGs, shear responsiveness of bis(pyridyl)urea-based gelators in the presence of copper(II) bromide is somewhat unusual and was found to be anion dependent;[19] whereas, the supramolecular nitrilotriacetic acid-based hydrogelator formed a magneto-rheological gel in the presence of nickel particles and a metal ion absorbent hydrogel in the presence of holmium ions.[20] Recently, a redox assisted sol–gel transition was observed in a system where a ruthenium(II)-trisbipyridine moiety was integrated with a potential tripeptide gelator.[21] Light-driven assembly of a coordination polymeric gelator has been reported to result in interesting morphology,[22] while temperature driven host–guest assembly has been shown to work for controlled entrapment and release of a guest.[23]

Luminescence and chirality in metallogels appear to be of special interest from the point of view of developing optical/optoelectronic devices. The presence of metal ions in these types of gels can modify the gel formation and/or help in chirality control.[24] Copper(II) chloride with 4-(1*H*-pyrazol-3-yl)-pyridine and triethylamine formed a metallogel encapsulating a luminescent lanthanide cluster yielding a luminescent metallogel.[25] Luminescent metallogels made up of alkenyl rhenium complexes show rich thermotropic gelatinous behaviour upon Cu(I) or Ag(I) coordination.[26]

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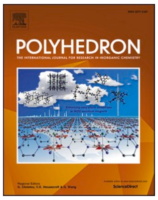

Design and synthesis of novel heterocyclic pivalamide ligands and their copper(II) complexes: Structure, BSA/DNA interactions and SOD *synzyme* activity

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ABSTRACT

Four new heterocyclic pivalamide based ligands (**L1-L4**) and their respective mononuclear copper(II) complexes (**C1** = [Cu(N-(thiazol-2-yl)pivalamide)$_2$], **C2** = [Cu(N-(5-methylthiazol-2-yl)pivalamide)$_2$], **C3** = [Cu(N-(benzothiazol-2-yl)pivalamide)$_2$], **C4** = [Cu(N-(benzoimidazol-2-yl)pivalamide)$_2$]) were synthesized to serve as low molecular weight SOD mimics. The complexes were characterized by single crystal XRD, Hirshfeld surface analysis, FT-IR, UV–vis, EPR and ESI-MS studies. **C1** crystallizes out in a triclinic system with P-1 space group, while **C2** and **C4** belong to $P2_1/c$ and $P2_1/n$ space groups respectively, from monoclinic system. The crystal structures indicate nearly square planar geometry where mononuclear copper(II) metal ions have coordinated with O and N donor atoms of the pivalamide ligands in *trans* fashion. All the complexes can scavenge superoxide concentration at low concentrations, in the order **C2** < **C3** < **C1** < **C4**. The interaction of all the complexes with BSA (bovine serum albumin) protein investigated using fluorescence titration method indicated a static quenching mechanism (K_{BSA} values of the order 10^5 M^{-1}). The ability of the complexes to bind with calf thymus DNA were also evaluated using absorption and fluorescence titration methods and an intercalative interaction mode of the complexes with DNA was established (K_b values of the order 10^4 M^{-1}). The complexes have a strong ability to cleave supercoiled plasmid DNA.

1. Introduction

Supramolecular chemistry is the study of non-covalent interactions in organic solids, metal complexes and organometallic compounds. In coordination chemistry, the binding of bioactive molecules to their bioactive targets occurs primarily through supramolecular interactions. With decades of dedicated work in the design and synthesis of novel supramolecular architectures, supramolecular synthesis of multi-functional systems has evolved and brought us closer to develop such systems for the betterment of mankind. The key is to gain control over supramolecular assemblies, which can contribute to development of host–guest assemblies, target selective drug delivery, biosensors, tissue engineering, etc. [1].

Thiazole containing compounds are widely known for their exclusive biological properties like anti-protozoal, anti-convulsant, anti-diabetic, anti-inflammatory, anti-tumor, antiviral, and many more because of the presence of –N═C–S– group. Thiazole based metal complexes have been widely studied in the past for their promising anti-fungal, anti-bacterial and cytotoxic behavior [2–5]. This inspired us to investigate the properties of synthesized complexes for their newer biological activities.

Redox-active transition metal ions in a coordination environment make good candidates for biological catalytic activity in redox reactions [6,7]. Specially, copper(II) containing coordination complexes possess redox potentials similar to those of reactive oxygen species, and hence, can be best utilized in catalyzing the dismutation of superoxide anion (a product of oxygen metabolism in the living systems). This superoxide ion can be a mediator of reperfusion diseases such as myocardial infarction (stroke), initiate inflammatory processes associated with diseases like arthritis, even cause oxidative injury to the tissues which can lead to various neurological disorders like Parkinson's and Alzheimer's [8]. Naturally occurring superoxide dismutases (SOD) in living

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