

Preparation and structural characterization of a novel dicopper(II) complex with a terminal hydroxide: a structural model of an active site in phosphohydrolases †

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As an intermediate model for active dinuclear metal sites in phosphohydrolases, a novel dicopper(II) complex with a terminal hydroxide has been prepared using a new dinucleating ligand with intramolecular hydrogen-bonding N–H sites and sterically hindered *tert*-butyl groups. It has been characterized by X-ray structure analysis, magnetic susceptibility, and ESR and electronic absorption spectroscopies.

Phosphohydrolases, metalloproteins that hydrolyze phosphate ester to phosphate, contain di- or trinuclear centers consisting of various metal ions in the active site, for example, the dinuclear units for purple acid phosphatases (PAP) have $\text{Fe}^{\text{II}}\text{Fe}^{\text{III}}$, $\text{Zn}^{\text{II}}\text{Fe}^{\text{III}}$, and $\text{Mn}^{\text{II}}\text{Fe}^{\text{III}}$,¹ and the trinuclear ones for alkaline phosphatases (AP) possess $\text{Zn}^{\text{II}}_2\text{Mg}^{\text{II}}$ cores.² The hydrolysis of phosphate ester by these proteins functions in different pH ranges according to the acidity of metal ions: pH 4.9–6.0 for PAP, >7.5 for AP, and ~9.8 for DNA polymerase I.^{2b} Though phosphohydrolases have some different active centers, the following two kinds of metal-hydroxo species are mainly proposed as the active reaction centers: one is $\text{M}_2(\mu\text{-OH})$ with a μ -hydroxide anion bridged to two metals³ and the other one is $\text{M}(\text{M}-\text{OH})$ species with a hydroxide coordinated to one metal site of dinuclear centers in a terminal fashion.⁴ The hydrogen-bonding interaction of an amino acid residue with a hydroxide ion and/or water molecule coordinated to metal ion has been observed at the active site in DNA polymerase I of the phosphohydrolase families, which affects the pK_a value of metal-hydroxo species to some extent.^{2b} The activity of phosphate esters in dinuclear model complex systems containing metal ions such as cobalt,⁵ nickel,⁶ copper,⁷ and zinc⁸ has been investigated. However, most of the isolated complexes reported hitherto have possessed a bridged μ -hydroxo species. Not only have dinuclear metal complexes with terminal metal-hydroxide rarely been reported,⁹ but also there are no reports for model metal complexes with a hydrogen-bond with hydroxide. This is because, once formed, the terminal metal-hydroxide proceeds immediately to the dimerization of metal complex or formation of bridging μ -hydroxo due to its higher donor ability. We designed and prepared a new polypyridine ligand of *N,N,N',N'*-tetrakis(6-neopentylamino-2-pyridylmethyl)-1,3-diaminopropan-2-ol (HTNPDO), in which the bulky neopentylamino groups at the 6-position of pyridine will protect the terminal hydroxide from attack by the other metal complexes and the N–H groups will interact with the hydroxide by intramolecular hydrogen-bonding.

Reaction of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, HTNPDO,¹⁰ Et_4NF and triethylamine in a 2 : 1 : 1 : 2 molar ratio in a methanol solution gave $[\text{Cu}^{\text{II}}_2(\text{TNPDO})(\text{OH})(\text{F})\text{ClO}_4]$ (**1**). ‡ A green crystal suitable for X-ray diffraction measurement was obtained from the

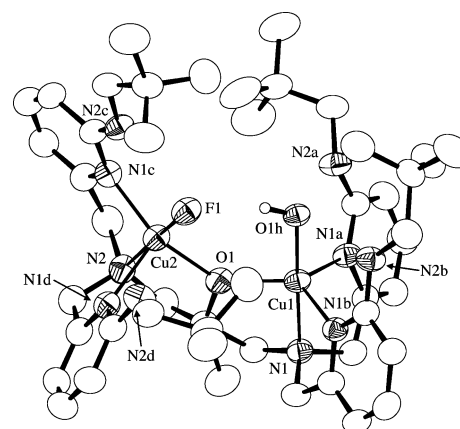


Fig. 1 ORTEP view of **1** showing 30% probability thermal ellipsoids. The counter anions and hydrogen atoms, except for the hydroxide hydrogen, are omitted for clarity. Selected bond lengths (Å) and angles (°): Cu(1)–O(1) 1.989(4), Cu(1)–O(1h) 1.882(4), Cu(1)–N(1) 2.027(5), Cu(1)–N(1a) 2.125(5), Cu(1)–N(1b) 2.073(5), Cu(2)–O(1) 1.956(4), Cu(2)–F(1) 1.881(4), Cu(2)–N(2) 2.045(6), Cu(2)–N(1c) 2.032(6), Cu(2)–N(1d) 2.244(6); O(1h)–Cu(1)–N(1) 178.3(2), O(1)–Cu(1)–N(1b) 127.8(2), F(1)–Cu(2)–N(2) 177.8(2), O(1)–Cu(2)–N(1c) 147.5(2), Cu(1)–O(1)–Cu(2) 134.8(2).

methanol solution. The structure of **1** (Fig. 1) revealed that the two $\text{Cu}(\text{II})$ ions, with slightly different geometries, are bridged by alkoxide of TNPDO and that the Cu(1) and Cu(2) atoms are coordinated by hydroxide ($\text{Cu}(1)\text{--O}(1\text{h}) = 1.882(4)$ Å) and fluoride anions ($\text{Cu}(2)\text{--F}(1) = 1.881(4)$ Å), respectively. The Cu(1) has a trigonal bipyramidal structure with a donor set of three nitrogen and two oxygen atoms, and another Cu(2) has a distorted trigonal bipyramidal structure with a donor set of one fluoride, three nitrogen and one oxygen atoms, which are well understandable from the τ values of 0.84 and 0.51 for Cu(1) and Cu(2) sites, respectively.¹¹ The separation distance of two Cu atoms is 3.642(1) Å, which is longer than those of dicopper(II) complexes with alkoxide bridge reported hitherto (3.4–3.5 Å).¹² It is attributed to the steric repulsion of bulky neopentylamino groups attached on the 6-position of the pyridines. It is clear that the labile terminal hydroxide is stabilized by intramolecular hydrogen bonds with N(2a) and N(2b) of neopentylamino groups ($\text{O}(1\text{h}) \cdots \text{N}(2\text{a}) = 2.748(9)$, $\text{O}(1\text{h}) \cdots \text{N}(2\text{b}) = 2.722(9)$ Å) and by the sterically hindered hydrophobic *tert*-butyl groups. The distance of the hydrogen atom on O(1h) to F(1) was 1.97 Å, in which the hydroxide hydrogen atom has been located on O(1h). To our knowledge, this is the first confirmation of the terminal coordination of an M–OH species assisted with hydrogen-bonding interaction, although some terminal metal-hydroxo species in monomeric metal complexes have been reported.¹³ The fluoride atom attached at the Cu(2) atom was confirmed from the absence of hydrogen atom around the atom, F^- , in the crystal structure and ESI-mass spectra showing the mass number ($m/z = 955.3$) and isotopic simulated pattern corresponding to the complex $[\text{Cu}^{\text{II}}_2(\text{TNPDO})(\text{OH})(\text{F})]^+$ (calculated $m/z = 955.5$).

† Electronic supplementary information (ESI) available: the effective magnetic moments and the molar magnetic susceptibilities of **1**, the positive ion electrospray ionization mass spectrum of $[\text{Cu}^{\text{II}}_2(\text{TNPDO})(\text{OH})(\text{F})]^+$ and the structure of HTNPDO. See <http://www.rsc.org/suppdata/dt/b3/b303787h/>

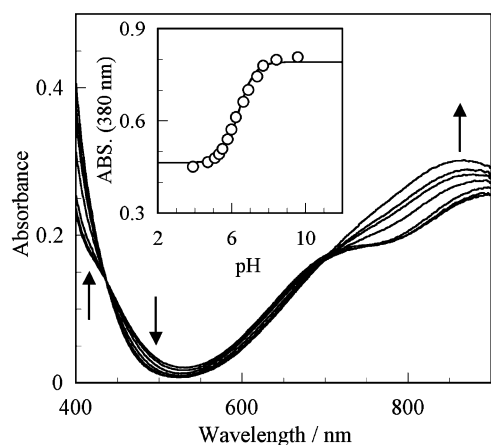


Fig. 2 Spectral change of **1** (0.50 mM) from pH 3.9 to 9.6 in MeCN/H₂O (with a 1 : 1 ratio) solution containing NaClO₄ (100 mM) as electrolyte (See Fig. S4 for the spectral change at the range of 300–600 nm). Inset: plots of absorbance at 380 nm vs. pH.

The long separation between the two Cu(II) ions is supported from the magnetic susceptibility measurement. The effective magnetic moment per complex decreased from 2.36 μ_B at 300 K to 0.27 μ_B at 20 K. The molar susceptibility of **1** fitted by the modified Bleaney–Bowers equation¹⁴ gave the following magnetic parameters $-2J = 111 \text{ cm}^{-1}$, $g = 2.01$, and $p = 0.008$. The magnetic behavior obtained is typical of antiferromagnetic coupling between a pair of cupric ions, and the $-2J$ value is similar to those of the complexes with a bridged hydroxo reported previously as is attributed to the metal-to-metal distance and the angle of Cu(1)–O(1)–Cu(2).¹⁵ The low g value describes well the two Cu(II) atoms with the trigonal bipyramidal geometry. The solid state ESR spectra of **1** were featureless at room temperature and 77 K.

The electronic absorption spectrum at pH 3.5 showed a broad d–d band at ~900 nm (Fig. 2), which is typical of the Cu(II) complex with the geometry of trigonal bipyramidal structure. According to the increase of pH, the spectrum changed with two isosbestic points at 436 and 698 nm and the new bands were observed at ~400 nm. The blue shift in the d–d band to 867 nm indicates the increase in the donor ability of coordination atoms to Cu(II) ion, although both Cu(II) ions keep the trigonal bipyramidal structure. The proton dissociation constant of the water molecule coordinated to **1** was estimated using the absorbance change of the peaks at 380 nm and gave a pK_a of 6.4, which was a smaller value in comparison with those of monomeric Cu–OH complexes reported hitherto (7.3–8.1).¹⁶ The most essential cause of this lower pK_a value is considered to be the intramolecular hydrogen-bonds of the terminal hydroxide oxygen with the N–H groups of the neopentylamino groups of the ligand, although the solvent used, a 1 : 1 mixture of MeCN/H₂O because of the lower solubility of the complex in water, may also be one of the causes.

In conclusion, we succeeded in the preparation and structural and magnetic characterizations of a dinuclear Cu(II) complex with a terminal Cu–OH species (**1**), which shows the stabilization of a terminal hydroxo species by the intramolecular hydrogen-bonding interaction and the protection of the hydroxide by sterically hindered substituents of neopentylamino groups. On the basis of these findings, we can suggest that the hydrogen-bond causes a decrease in the pK_a value of the water molecule coordinated to metal ions.

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‡ Crystal data for compound **1**·2.5H₂O: C₄₇H₇₉ClCu₂FN₁₀O_{8.5}, $M = 1101.75$, monoclinic, space group $C2/c$ (no. 15), $a = 43.533(9)$, $b = 11.057(1)$, $c = 29.90(1) \text{ \AA}$, $\beta = 127.08(1)^\circ$, $V = 11482(5) \text{ \AA}^3$, $Z = 8$, $\rho_{\text{calcd}} = 1.275 \text{ g cm}^{-3}$, $\mu = 8.47 \text{ cm}^{-1}$, $2\theta_{\text{max}} = 51.5^\circ$, Mo $K\alpha$ radiation ($\lambda = 0.71070 \text{ \AA}$), $T = 288 \text{ K}$, $R_1 = 0.080$, $R_w = 0.122$, and $\text{GOF} = 1.49$ for 6521 independent reflections with $I > 3.0\sigma(I)$ and 650 variables. CCDC reference number 196485. See <http://www.rsc.org/suppdata/dt/b3/b303787h/> for crystallographic data in CIF format. Found: C, 51.35; H, 7.45; N, 12.48%. C₄₇H₇₉ClCu₂FN₁₀O_{8.5} requires C, 51.24; H, 7.23; N, 12.71%. The ratio of **1** to fluoride was determined to be 1 : 0.95 by a fluoride ion-selective electrode.¹⁷ **Caution:** perchlorate salts are potentially explosive and should be carefully treated.

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