

Hydrolysis of Unactivated Esters and Acetonitrile Hydration by a Hydroxo–Dicopper(II) Complex

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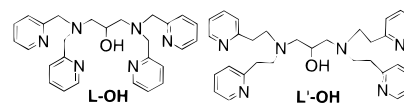
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The active sites of many enzymes that catalyze the hydrolysis of phosphate esters (DNA or RNA) or amides (peptides or urea) contain two metal ions (e.g., Mg, Zn, Fe, Ni, Co, Mn) in close proximity (2.9–4.3 Å) as demonstrated by a number of recent X-ray crystal structure determinations.¹ While the fundamental roles of the metal ions in hydrolases are understood,^{1–3} many details of the mechanism(s) of hydrolysis are yet uncertain, particularly in systems containing two metal ions.

We have begun to target discrete hydroxo-containing M₂ complexes for investigation, in order to elucidate structural and mechanistic aspects of hydrolases, in functional biomimetic systems.⁴ One goal is the design of binuclear copper(II) complexes which contain OH[−] (as a nucleophile) bound terminally to one copper while an open or solvent exchangeable (with substrate) coordination site remains on a second, adjacent copper;⁵ this may facilitate formation of a geometry favorable for hydrolysis, reminiscent of active site structures and proposed mechanisms for several M₂-containing hydrolases.¹ Herein we describe such a species. Tetranuclear complex [Cu₄(L–O[−])₂(OH[−])₂](ClO₄)₄·9CH₃CN·Et₂O (**1**(ClO₄)₄·9CH₃CN·Et₂O), which in CH₃CN solution contains a Cu₂–OH[−] moiety, is capable of

readily hydrolyzing unactivated esters such as methylacetate, and is also demonstrated to hydrate acetonitrile.



The ligand L–OH was chosen since it and other structurally related ligands are known to form alkoxide or phenoxide-bridged binuclear complexes with metal–metal distances greater than ~3.3 Å.⁶ This characteristically long metal separation results in complexes which forbid single atom, μ–1,1 bridging (e.g. OH[−]), but promote the formation of μ–1,3 bridging species (e.g. acetate or azide).⁶ Treatment of L–OH⁷ with 2 equiv of [Cu^I(CH₃CN)₄]ClO₄ in acetonitrile under argon, followed by exposure to O₂ results in an immediate color change from yellow to dark green. Concentration and addition of diethyl-ether affords dark green crystals of **1** in 55% yield.⁸ The X-ray crystal structure analysis⁹ reveals a tetranuclear complex **1**(ClO₄)₄·9CH₃CN·Et₂O, where the cationic portion [Cu₄(L–O[−])₂(OH[−])₂]⁴⁺ contains two Cu₂(L–O[−]) units bridged by a pair of OH[−] ions (Figure 1 and Scheme 1). Magnetic studies on **1**–(ClO₄)₄ indicate antiferromagnetic coupling between Cu(II) ions.¹⁰

The tetranuclear structure **1**(ClO₄)₄·9CH₃CN·Et₂O contrasts sharply with a complex that forms from L'–OH, a similar ligand containing ethylpyridyl instead of methylpyridyl groups. The anion of L'–OH forms a binuclear Cu(II) complex (Cu^{••}Cu = 2.995 Å) with a bridging μ–1,1 methoxide ion.¹¹ For the present case, we suggest that the long copper–copper separation (3.69 Å) induced by L–O[−] (the short methylpyridyl arms of L–O[−] “pull” the Cu^{II} ions back and apart) prevents the intramolecular-bridging coordination of OH[−]. Instead, intermolecular bridging of OH[−] results in the crystallization of **1**(ClO₄)₄·9CH₃CN·Et₂O from concentrated solutions. However,

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- (7) L–OH was synthesized by the reaction of 2-picolylchloride with 1,3-diamino-2-hydroxypropane in the presence of NaOH. ¹H NMR (CDCl₃, 300 MHz): δ 2.57–2.73 (m, 4H), 3.83–4.02 (m, 9H), 7.11 (t, 4H), (7.36 (d, 4H), 7.58 (t, 4H), 8.50 (d, 4H).
- (8) **1**(ClO₄)₄·9CH₃CN·Et₂O loses solvent upon standing. Drying in vacuo produces [Cu₄(L–O[−])₂(OH[−])₂](ClO₄)₄. Anal. Calcd for C₅₄H₆₀N₁₂O₂₀Cl₄Cu₄: C, 40.71; H, 3.80; N, 10.55. Found: C, 40.71; H, 3.93; N, 10.58. IR (Nujol) 3500 (OH, br, w), 1607 (C=C, s), 1572 (C=C, w) cm^{−1}. UV–vis (CH₃CN) 875 nm (ε = 233 M^{−1} cm^{−1}).
- (9) See Supporting Information for further details.

- (10) (a) Variable temperature data were fitted to an exchange expression based on $H = \sum_{ij} -J_{ij}S_i \cdot S_j$ for a rectangle of nominal D_2 symmetry, with two different J values, $J_1 = -244$ (10) cm^{−1}, across O1, O1'; $J_2 = -286$ (5) cm^{−1} across O2, O2').⁹
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- (15) Complex **4**(ClO₄)₂ is isolated as a turquoise crystalline solid. Anal. Calcd for C₂₉H₃₃N₇O₁₀Cl₂Cu₂: C, 41.58; H, 3.97; N, 11.71. Found: C, 41.20; H, 4.03; N, 11.30. UV–vis (acetonitrile) 892 nm (ε = 269 M^{−1} cm^{−1}). IR (Nujol) 1605 (C=C, w), 1564 (CONH[−], m), 1082 (ClO₄[−], br, s). ESMS (CH₃CN): m/z (M⁺): 738.0 corresponding to [(Cu₂(L–O[−])(CH₃CONH[−])](ClO₄)⁺.

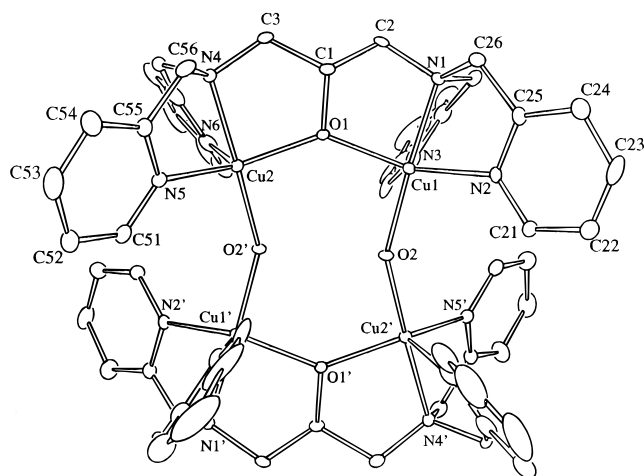
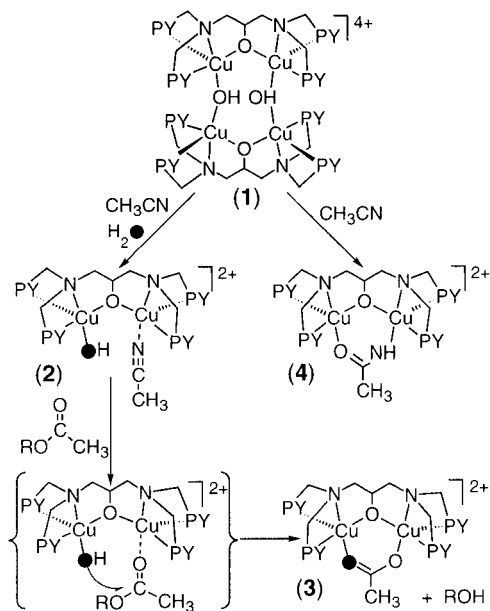


Figure 1. ORTEP diagram (20% ellipsoids) of the cationic portion of $[\text{Cu}_4(\text{L}-\text{O}^-)_2(\text{OH}^-)_2](\text{ClO}_4)_4 \cdot (\text{CH}_3\text{CN})_9 \cdot \text{Et}_2\text{O}$ ($\mathbf{1}$ - $(\text{ClO}_4)_4 \cdot 9\text{CH}_3\text{CN} \cdot \text{Et}_2\text{O}$) showing the atom labelling scheme. Selected interatomic distances (Å) and angles (deg): Cu1–Cu2, 3.685(2); Cu1–Cu1', 5.192(2); Cu2–Cu2', 5.227(2); Cu1–O1, 1.983(7); Cu1–O2, 1.931(7); Cu1–N1, 2.029(9); Cu1–N2, 2.045(9); Cu1–N3, 2.21(1); Cu2–O1, 1.960(7); Cu2–O2', 1.903(7); Cu2–N4, 2.006(9); Cu2–N5, 2.05(1); Cu2–N6, 2.19(1); Cu1–O1–Cu2, 138.3(4); Cu1–O2–Cu2', 147.7(4); N1–Cu1–O2, 176.9(4); O1–Cu1–N2, 142.1(4); N4–Cu2–O2', 177.4(4); O1–Cu2–N5, 137.1(4).

Scheme 1



solution electrical conductivity and electrospray mass spectrometric (ESMS) measurements⁹ indicate that a binuclear species, $[\text{Cu}_2(\text{L}-\text{O}^-)(\text{OH}^-)]^{2+}$ ($\mathbf{2}$), forms upon redissolving $\mathbf{1}(\text{ClO}_4)_4$ in CH_3CN solvent. We suggest that $\mathbf{2}$ contains OH^- bound terminally to one Cu^{II} ion and that CH_3CN coordinates to the second, as indicated in Scheme 1.

In acetonitrile or acetone, $[\text{Cu}_2(\text{L}-\text{O}^-)(\text{OH}^-)(\text{S})]^{2+}$ ($\mathbf{2}$) (S = solvent) reacts with methyl acetate, ethyl acetate or isopropyl acetate to produce the μ -1,3-acetato-bridged complex $[\text{Cu}_2(\text{L}-\text{O}^-)(\text{CH}_3\text{COO}^-)]^{2+}$ ($\mathbf{3}$).¹² The reaction proceeds quantitatively, also producing one equiv. of alcohol byproduct (Scheme 1). The identity of $\mathbf{3}$ has been verified by comparison of its physical properties to those obtained on a sample independently prepared.¹³ The ester hydrolysis reactions are easily monitored

Table 1. Second-Order Rate Constants, k ($\pm 6\%$; 25 °C), for the Reaction of $\mathbf{2}$ with Esters, and Literature Comparisons^a

complex	substrate	solvent	k ($\text{M}^{-1} \text{s}^{-1}$)
$\mathbf{2}$	methyl acetate	acetonitrile	1.7×10^{-3}
$\mathbf{2}$	ethyl acetate	acetonitrile	7.3×10^{-4}
$\mathbf{2}$	isopropyl acetate	acetonitrile	4.4×10^{-4}
$[(\text{dpa})\text{Cu}(\text{OH})_2]^{2+}$ ²³	methyl acetate	H_2O (pH 7.0)	7.2×10^{-4}
$[(\text{trpn})\text{Co}(\text{OH})(\text{OH}_2)]^{2+}$ ²³	methyl acetate	H_2O (pH 7.0)	5.5×10^{-3}

^a Abbreviations: dpa = 2,2'-dipyridylamine; trpn = tris(aminopropyl)amine.

by UV–vis spectroscopy; an isosbestic point at ~ 800 nm indicates a clean conversion from $\mathbf{1}$ to $\mathbf{3}$. Second-order rate constants for the formation of $\mathbf{3}$ from $\mathbf{1}$ and ester substrates are listed in Table 1.⁹ The rate constant for methylacetate is comparable to that reported previously for the hydrolysis of this substrate by other *mononuclear* copper or cobalt complexes.¹⁴

Further indication that the metal-bound OH^- in $\mathbf{2}$ is responsible for nucleophilic attack of the esters is provided by an ^{18}O incorporation experiment. Enrichment of the hydroxide moiety of $\mathbf{1}$ with ^{18}O , followed by reaction with methylacetate yields acetate complex $[\text{Cu}_2(\text{L}-\text{O}^-)(\text{CH}_3\text{COO}^-)]^{2+}$ ($\mathbf{3}$) which has $\sim 70\%$ incorporation of a single ^{18}O atom, as judged by ESMS.⁹ However, ESMS of ^{18}O enriched complex $\mathbf{1}(\text{ClO}_4)_4$ in CH_3CN (i.e., hydroxo-dicopper(II) species $\mathbf{2}(\text{ClO}_4)_2$, *vide supra*) used for this experiment, shows absolutely no ^{18}O incorporation, indicating the $\text{Cu}-\text{OH}^-$ moiety is extremely labile in solution (and/or under the ESMS conditions) and must easily exchange with adventitious H_2^{16}O . Therefore, an incorporation of 70% of the hydroxide oxygen from $\mathbf{2}$ into the acetate product $\mathbf{3}$ must be considered a lower limit.

Another interesting observation which affirms the hydrolase capability of the Cu_2-OH^- moiety in $\mathbf{2}$ is that the acetonitrile solvent, itself, is hydrated by the complex over a period of days to give an acetamide-containing product, $[\text{Cu}_2(\text{L}-\text{O}^-)(\text{CH}_3\text{CONH}^-)]^{2+}$ ($\mathbf{4}$) (Scheme 1).¹⁵ This product can be independently generated from reaction of $\mathbf{2}$ plus acetamide in acetone. Acetonitrile, which is very resistant toward hydration,² was shown previously to react with a diiron–hydroxide complex to give a similar bridging acetamide product.^{4h}

In conclusion, we have generated a binuclear metal complex much like those proposed in M_2 -containing hydrolases, which contains a critical $\text{M}-\text{hydroxide}$ moiety adjacent to a vacant (exchangeable) coordination site. The present complex is capable of facile hydrolysis of unactivated esters and hydration of acetonitrile. We plan to further probe mechanistic aspects of this chemistry and elaborate upon the design and generation of hydrolytically active hydroxo–dimetal compounds.

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Supporting Information Available: Text and figures of experimental notes, kinetic procedures, and plots, ESMS spectra of $\mathbf{1}(\text{ClO}_4)_4$ and $\mathbf{3}(\text{ClO}_4)_2$, with isotope labeling experiment and theoretical isotope distributions, text giving the variable-temperature magnetism procedure and plot, and tables giving full details of the X-ray structure of $\mathbf{1}(\text{ClO}_4)_4 \cdot 9\text{CH}_3\text{CN} \cdot \text{Et}_2\text{O}$ including atomic coordinates, bond lengths, and bond angles (31 pages). See any current masthead page for ordering information and Internet access instructions.