Facile Amide Hydrolysis Effected by Dinuclear Copper Complexes

Narasimha N. Murthy, Mohammad Mahroof-Tahir, and Kenneth D. Karlin*

Department of Chemistry
The Johns Hopkins University
Baltimore, Maryland 21218

Received April 28, 1993

Our recent efforts in bioinorganic copper chemistry have included studies on reversible O_2-binding and/or ligand hydroxylation reactions.[1,2] Here, we describe two instances in which dinuclear copper complexes effect the stoichiometric hydrolysis of an unactivated secondary amide under mild conditions. In one situation dicopper(I) complex $[Cu_2(PD)]^{2+}$ (**1**) reacts with O_2 effecting the hydrolysis of *N,N*-dimethylformamide (DMF) solvent. The other involves the phenoxo-bridged complex $[Cu^{II}_2(PD\text{–}O^-)(OMe^-)_2]^+$ (**2**), which serves as a precursor for the same hydrolysis reaction. In both cases, the product of reaction is the phenoxo- and formato-bridged dicopper(II) compound $[Cu_2(PD\text{–}O^-)(HCO_2^-)]^{2+}$ (**4**) (Scheme I, PY = 2-pyridyl).

Oxygenation of **1**[3] in acetonitrile at room temperature generates a dark purple species, λ_{max} = 558 nm (ϵ = 3300 M^{-1} cm^{-1}). A corresponding purple solid isolated by precipitation using Et_2O is formulated as $[Cu_2(PD)(O_2)]^{2+}$ (**3**) based on its physical properties[3] and the observed Cu/O_2 = 2:1 (manometry) stoichiometry. While the spectroscopic properties and reactivity (e.g., with H^+ or PPh_3) of **3** are different from those Cu_2O_2 species previously characterized,[2,4] this remarkably stable material possesses an O_2-oxidizing equivalent, as seen from its reaction chemistry (*vide infra*); the PD ligand remains intact in **3**, based on the ability to recover it (81%) by extraction using NH_4OH_{aq}.

Either by reaction of **3** with DMF under argon or by direct addition of O_2 to a DMF solution of **1**, an immediate change to green occurs, producing **4** in >70% yield.[3] The acetate complex $[Cu_2(PD\text{–}O^-)(CH_3CO_2^-)]^{2+}$ was produced in a corresponding reaction carried out in *N,N*-dimethylacetamide. The identities of these products have been confirmed in an X-ray diffraction study on **4**, Figure 1.[5] Thus, this reaction has resulted in both the hydrolysis of DMF to give formate,[6] as well as the hydroxylation of the PD ligand, to give the resulting phenolate. This reaction resembles monooxygenase model systems we have previously described, in which O_2-addition (Cu/O_2 = 2:1, manometry) with dicopper(I) complexes similar to **1** led to Cu_2O_2 intermediates which effected an arene hydroxylation reaction giving phenoxo- and hydroxo-bridged products $[Cu_2(L\text{–}O^-)(OH)]^{2+}$ (L–OH = phenol dinucleating ligand).[1b,2] However, in the present case, *no* corresponding μ-hydroxo complex (OH^- derived from O_2)[1b,2] is produced, since an additional DMF hydrolysis has occurred. Electrospray ionization and FAB mass spectrometric analysis of product **4** isolated from reaction of **1** with $^{18}O_2$ indicate that one O-atom derived from dioxygen inserts into the arene C–H bond, while the other resides in the formate product,[7] eq 1. Corroborating evidence is that the 18-O label is retained in the PD–OH organic product, which was isolated by NH_4OH_{aq} extraction of copper ion from **4**:

$$[Cu_2(PD)]^{2+}\ (\mathbf{1}) + {}^{18}O_2 \rightarrow [Cu_2(PD\text{–}{}^{18}O^-)(HC{}^{18}O{}^{18}O^-)]^{2+}\ (\mathbf{4})\quad (1)$$

The structure of **4** suggests that dicopper complexes with PD–O^- may *not* be suitable for ligand (e.g., OH^-) μ-1,1-bridging, but stabilize 1,3-bridging interactions (e.g., O,O′-carboxylato).[8] Hence, the $[Cu_2(PD\text{–}O^-)]^{n+}$ framework could facilitate adjacent coordination of two monodentate ligands, perhaps a terminal hydroxide (nucleophile) and DMF (substrate) (*vide infra*). This notion is supported by a structural analysis of **2**,[5] which was produced by diphenylhydrazine reduction of **4** followed by O_2 reoxidation in methanol.[3] In **2** (Figure 2), two adjacent terminal methoxide ligands are coordinated to the copper(II) ions of the dinuclear unit. When **2** is reacted with DMF (23 °C) in the presence of 1 equiv of $HClO_{4aq}$ (so as to optimize the likely formation of a (OH^-)—Cu···Cu—(L) {L = H_2O or DMF} species), facile stoichiometric amide hydrolysis again occurs generating **4** (>60% isolated, Scheme I); preliminary kinetic measurements indicate a pseudo-first-order process with k_{obs} = 0.3 h^{-1}.

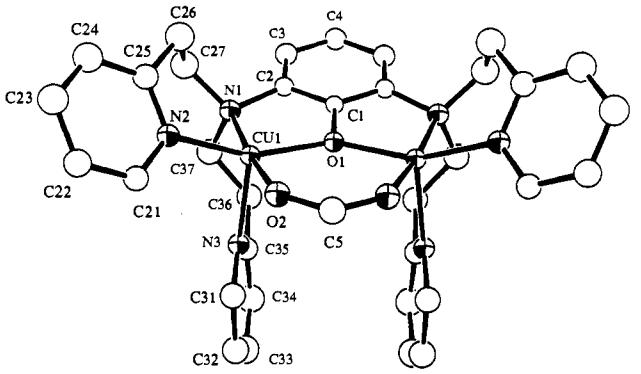
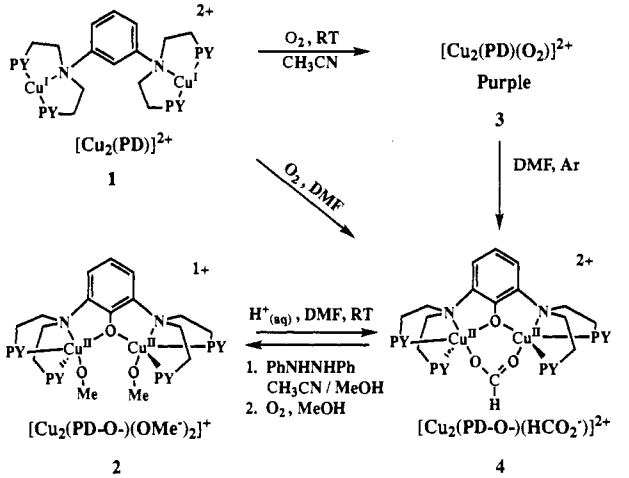


Figure 1. ORTEP view of the cationic portion of $[Cu_2(PD\text{–}O^-)(HCO_2^-)](PF_6)_2{\cdot}CH_3CN$ [**4**-$(PF_6)_2$]·CH_3CN. Selected bond distances (Å): Cu1–O1, 1.974(2); Cu1–O2, 1.976(4); Cu1–N1, 2.056(4); Cu1–N2, 2.010(4); Cu1–N3, 2.232(4); Cu1···Cu1′, 3.6517(7).

Scheme I



(1) (a) Tyeklár, Z.; Jacobson, R. R.; Wei, N.; Murthy, N. N.; Zubieta, J.; Karlin, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 2677–2689. (b) M. S. Nasir, M. S.; Cohen, B. I.; Karlin, K. D. *J. Am. Chem. Soc.* **1992**, *114*, 2482–2494.

(2) Karlin, K. D.; Tyeklár, Z.; Zuberbühler, A. D. In *Bioinorganic Catalysis*; Reedijk, J., Ed.; Marcel Dekker: New York, 1993; Chapter 9, pp 261–315. (b) Karlin, K. D.; Tyeklár, Z. *Adv. Inorg. Biochem.* **1993**, *9*, 123–172. (c) Tyeklár, Z.; Karlin, K. D. In *Bioinorganic Chemistry of Copper*; Karlin, K. D., Tyeklár, Z., Eds., Chapman & Hall: New York, 1993; pp 277–291.

(3) See Supplementary Material for analyses and physical data.

(4) Paul, P. P.; Tyeklár, Z.; Jacobson, R. R.; Karlin, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 5322–5332.

(5) Crystal data (3.5 ≤ 2θ ≤ 50°), Rigaku AFC6S diffractometer. **4**-$(PF_6)_2{\cdot}CH_3CN$ (−120 °C): orthorhombic, *Pnma*, a = 15.889(3), b = 22.379(2), and c = 11.466(3) Å; V = 4077(1) Å^3, Z = 4. 2172 reflections ($I \geq 3\sigma(I)$); R = 0.039, R_w = 0.042. **2**-ClO_4 (−85 °C): monoclinic, $C2/c$, a = 11.251(2), b = 17.781(3), and c = 20.165(3) Å, β = 102.31(1)°; V = 3941(1) Å^3, Z = 4. 2402 reflections ($I \geq 3\sigma(I)$); R = 0.049, R_w = 0.063.

(6) The qualitative production of diethylamine was confirmed for a reaction carried out in *N,N*-diethylformamide, studied with GC-MS analysis.

(7) Electrospray ionization mass spectra were supplied to the reviewers.

(8) Sorrell observed that acetate and N_3^- coordinate only in a μ-1,3-bridging mode in a complex similar to **4**: Sorrell, T. N.; O'Connor, C. J.; Anderson, O. P.; Reibenspies, J. H., *J. Am. Chem. Soc.* **1985**, *107*, 4199–4206.

0002-7863/93/1515-10404$04.00/0

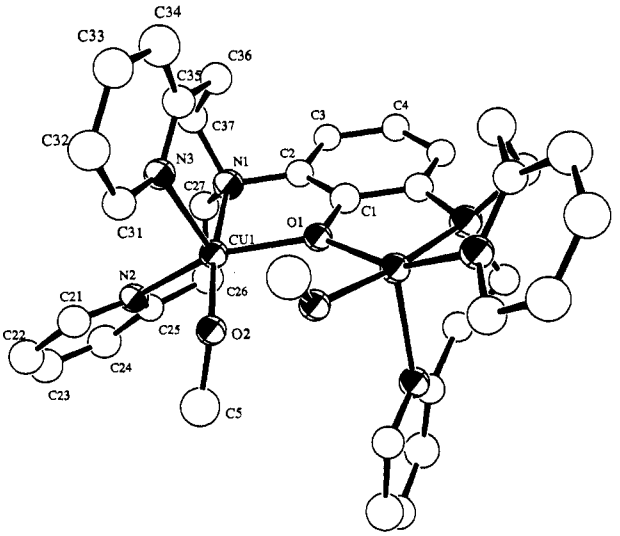
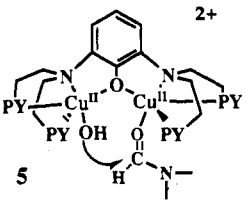
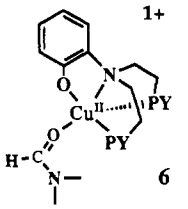


Figure 2. ORTEP view of the cationic portion of $[Cu_2(PD\text{-}O^-)(OMe^-)_2](ClO_4)$ (**2**-ClO_4). Selected bond distances (Å): Cu1–O1, 2.008(2); Cu1–O2, 1.943(4); Cu1–N1, 2.063(4); Cu1–N2, 2.001(4); Cu1–N3, 2.214(4); Cu1···Cu1′, 3.7413(9).

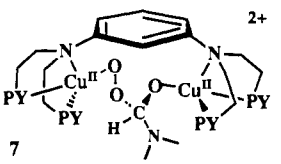
There is considerable interest in the hydrolysis of amides by metal complexes.[9-12] In biological systems, many metalloproteins involved in hydrolytic processes contain mononuclear zinc active sites.[13] However, recent studies have revealed that di- or trinuclear enzyme metal ion centers (i.e., with Zn, Mg, Mn, Fe, or Ni) effect peptidase or phosphatase reactions.[14] Thus, the present results may be relevant to the mode of action of this latter group of enzymes.[15,16] The importance of adjacent *cis* metal–hydroxide (nucleophile) and Lewis acid-activated substrate, i.e., M–(OH^-)(substrate), has been extensively discussed with regard to mononuclear metal complex promoted hydrolysis reactions.[10-12]

Based on the observed structure of **2**, the key feature relevant to the hydrolysis reaction **2** + DMF → **4** would appear to be the presence of a *di*copper(II) complex capable of coordinating a terminal Cu–OH^- nucleophilic species adjacent to Cu′–DMF, i.e., ligated substrate species **5**.[12,17] The possibility of amide hydrolysis catalyzed by only *one* of the two copper ions in **2** (or **5**) is unlikely, since the four donor atoms (per Cu) provided by PD–O^- (in **2** and **4**) leave only one site vacant for exogenous ligand coordination. Thus, simultaneous ligation by OH^- and DMF on *one* Cu(II) ion is unfavorable.[18] Support for this argument comes from studies on a mononuclear analog **6**;[19] reaction with 1 equiv $NaOH_{aq}$ in DMF solution produced *no* detectable formate, even after 6 h.





While the rate of the stoichiometric amide hydrolysis reaction mediated by **2** is comparable to those of many other synthetic metal-complex-promoted processes,[11,12] the reaction occuring via oxygenation of **1** or DMF reaction with **3** is very rapid, proceeding in an immediate fashion. We speculate that this difference in reactivity may be due to (i) production of a "dry" (e.g., without competition from aquo ligands) dinuclear species **5** following PD hydroxylation or, alternatively, (ii) attack by a Cu–peroxo species (as a strong α-nucleophile analogous to OOH^-) in **3** upon DMF,[20] producing a peroxo amidate intermediate **7** capable of effecting subsequent hydroxylation of the proximate PD arene.



Further mechanistic studies and the development of multimetal hydrolysis reagents is being pursued.

Acknowledgment. We thank the NIH (GM 28962) for partial support of this research and the NSF (CHE-9000471) for the purchase of the X-ray diffractometer. We are also grateful to Professor Sue Weintraub, University of Texas Health Science Center, San Antonio, for electrospray ionization mass spectra and to Dr. Joseph Kachinski, Johns Hopkins University, for FAB mass spectral and GC-MS measurements.

Supplementary Material Available: Positional and isotropic thermal parameters for complexes **2**-ClO_4 and **4**-$(PF_6)_2$·CH_3CN and analyses and physical data for **1**–**4** (4 pages). Ordering information is given on any current masthead page.

(9) The half-life of a typical peptide amide bond is ~7 years at pH 7 and 25 °C; Kahne, D.; Still, W. C. *J. Am. Chem. Soc.* **1988**, *110*, 7529–7534.

(10) General articles: (a) Fife, T. H. *Persp. Bioinorg. Chem.* **1991**, *1*, 43–93. (b) Chin, J. *Acc. Chem. Res.* **1991**, *24*, 145–152. (c) Sayre, L. M. *J. Am. Chem. Soc.* **1986**, *108*, 1632–1635.

(11) Specific examples include (a) Suh, J. *Acc. Chem. Res.* **1992**, *25*, 273–279. (b) Burgeson, I. E.; Kostić, N. M. *Inorg. Chem.* **1991**, *30*, 4299–4305. (c) Reddy, K. V.; Jacobson, A. R.; Kung, J. I.; Sayre, L. M. *Inorg. Chem.* **1991**, *30*, 3520–3525. (d) Chin, J.; Jubian, V.; Mrejen, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1326–1328. (e) Duerr, B. F.; Czarnik, A. W. *J. Chem. Soc., Chem. Commun.* **1990**, 1707–1709. (f) Groves, J. T.; Baron, L. A. *J. Am. Chem. Soc.* **1989**, *111*, 5442–5448. (g) Iverson, B. L.; Lerner, R. A. *Science* **1989**, *243*, 1184–1188. (h) Schepartz, A.; Breslow, R. *J. Am. Chem. Soc.* **1987**, *109*, 1814–1826.

(12) For the equilibrium metal-binding constant for an amide carbonyl to a cobalt complex, see: Takasaki, B. K.; Kim, J. H.; Rubin, E.; Chin, J. *J. Am. Chem. Soc.* **1993**, *115*, 1157–1159.

(13) (a) Coleman, J. E. *Annu. Rev. Biochem.* **1992**, *61*, 897–946, (b) Vallee, B. L.; Auld, D. S. *Biochemistry* **1990**, *29*, 5647–5659.

(14) (a) Karlin, K. D. *Science* **1993**, *261*, 701–708 and references cited therein. (b) Vallee, B. L.; Auld, D. S. *Biochemistry* **1993**, *32*, 6493–6500.

(15) Recent examples of structural models for hydrolytic proteins with di- or trinuclear metal centers are (a) Chaudhuri, P.; Stockheim, C.; Wieghardt, K.; Deck, W.; Gregorzik, R.; Vahrenkamp, H.; Nuber, B.; Weiss, J. *Inorg. Chem.* **1992**, *31*, 1451–1457. (b) Uhlenbrock, S.; Krebs, B. *Angew. Chem., Int. Engl.* **1992**, *31*, 1647–1648.

(16) For examples of ester hydrolysis reactions involving dinuclear metal complexes, see: ref 11a and (a) Hikichi, S.; Tanaka, M.; Moro-oka, Y.; Kitajima, N. *J. Chem. Soc., Chem. Commun.* **1992**, 814–815. (b) Chung, Y.; Akkaya, E. U.; Venkatachalam, T. K.; Czarnik, A. W. *Tetrahedron Lett.* **1990**, *31*, 5413–5416. (c) Hendry, P.: Sargeson, A. M. *Prog. Inorg. Chem.* **1990**, *38*, 201–258. (d) Clewley, R. G.; Slebocka-Tilk, H.; Brown, R. S. *Inorg. Chim. Acta*, **1989**, *157*, 233–238.

(17) Related concepts have been discussed for diizinc enzymes.[14]

(18) Pentacoordinate Cu(II) is very common, while hexacoordination is not, in part due to the Jahn–Teller effect.

(19) The structure indicated has been confirmed by X-ray diffraction.

(20) For reactions thought to involve nucleophilic attack by iron–peroxo species, see: (a) Cole, P. A.; Bean, J. M.; Robinson, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 2999–3003 and references cited therein. (b) Vaz, A. D. N.; Roberts, E. S.; Coon, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 5886–5887. (c) Rana, T. M.; Meares, C. F. *J. Am. Chem. Soc.* **1991**, *113*, 1859–1861.