8394 J. Am. Chem. Soc. **1994,** *116,* 8394–8395

Modeling Hydrolysis at Dinuclear Iron Centers

Elizabeth C. Wilkinson, Yanhong Dong, and
Lawrence Que, Jr.*

Department of Chemistry, University of Minnesota
Minneapolis, Minnesota 55455

Received March 16, 1994

Dinuclear metal centers have been found in a number of enzymes that catalyze hydrolytic reactions, such as the purple acid phosphatases[1] (Fe), alkaline phosphatase[2] and phospholipase C[3] (Zn), urease[4] (Ni), methionine aminopeptidase[5] (Co), and arginase[6] (Mn). Although the exact roles of the metal ions are not known, it is postulated that the dinuclear center facilitates hydrolysis by using one metal center to activate substrate and the other as a Lewis acid to increase the pK_a of bound water, thus efficiently delivering the hydroxide nucleophile to the substrate.[7] Dicobalt[8] and dicopper[9] complexes have been demonstrated to facilitate hydrolysis of amides, phosphate esters, and nitriles, but diiron complexes have not. We report here a (μ-oxo)diiron(III) complex with a terminal hydroxide that can hydrate acetonitrile to acetamide.

The reaction of $Fe(ClO_4)_3\cdot 10H_2O$ with $TPA\cdot 3HClO_4$[10] and 4 equiv of triethylamine affords the dinuclear complex $[Fe_2O(TPA)_2(H_2O)(ClO_4)](ClO_4)_3$ (**1**). The structure of **1**[11] (Figure 1) shows a nearly linear (μ-oxo)diiron(III) core, with an Fe–O–Fe angle of 174.1(4)° and an Fe–Fe distance of 3.570(9) Å. The core parameters are consistent with those found for other monobridged (μ-oxo)diiron(III) complexes.[12] Each iron is coordinated to a TPA ligand, with the amine nitrogen trans to the oxo ligand, as is found in $[Fe_2O(bpp)_2(H_2O)_2](ClO_4)_2$.[13] Fe2 has a perchlorate as the sixth ligand, with an Fe–O distance of 2.140(7) Å; Fe1 has a water as the sixth ligand, with an Fe–O distance of 2.094(7) Å. The Fe–N_{py} bonds are slightly shorter on Fe2 (av 2.106 Å) than on Fe1 (av 2.137 Å), reflecting the stronger Lewis acidity of Fe2, due in part to the poor electron-donating capability of the perchlorate ligand.

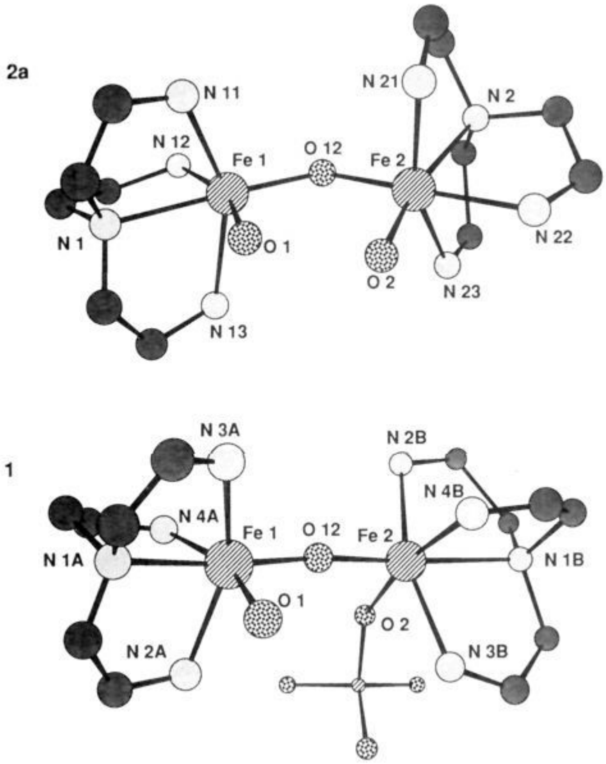


Figure 1. Core structure of **1** and **2a** showing a partial numbering scheme (carbon atoms are not labeled). The hydrogen atoms are omitted. Selected bond distances (Å) and angles (deg): **1**, Fe1–Fe2 3.570(9), Fe1–O12 1.791(7), Fe2–O12 1.783(7), Fe1–O1 2.094(7), Fe2–O2 2.140(7), Fe1–N1A 2.216(8), Fe1–N2A 2.153(9), Fe1–N3A 2.134(8), Fe1–N4A 2.124(8), Fe2–N1B 2.237(8), Fe2–N2B 2.118(8), Fe2–N3B 2.100(8), Fe2–N4B 2.100(8), Fe–O–Fe 174.1(4); **2a**, Fe1–Fe2 3.346(9), Fe1–O12 1.779(5), Fe2–O12 1.826(5), Fe1–O1 2.049(6), Fe2–O2 1.907(7), Fe1–N1 2.256(7), Fe1–N11 2.131(9), Fe1–N12 2.160(7), Fe1–N13 2.17(1), Fe2–N2 2.217(7), Fe2–N21 2.146(9), Fe2–N22 2.246(8), Fe1–N23 2.127(9), Fe–O–Fe 136.3(3).

Complex **1** shows no distinct absorption features, consistent with a nearly linear Fe–O–Fe angle.[14] Its ^1H NMR spectrum[15] shows that the six pyridine rings of the two TPA ligands are equivalent, suggesting that the aqua and perchlorate ligands are labile in solution. Treatment of **1** with 1 equiv of triethylamine affords a green complex, **2**, with distinct absorption features at 486 (ϵ = 360 $M^{-1}\ cm^{-1}$) and 608 nm (ϵ = 130 $M^{-1}\ cm^{-1}$) (Figure 2) that are diagnostic of a bent (μ-oxo)diiron(III) TPA complex.[16] Its ^1H NMR spectrum[17] shows that **2** retains its dinuclear structure in solution. X-ray crystallography shows the corresponding 5-ethyl-TPA complex **2a** (Figure 1) to be $[Fe_2O(H_3O_2)(5\text{-}Et\text{-}TPA)_2](ClO_4)_3$,[18] a ($\mu$-oxo)diiron(III) complex supported by a $H_3O_{2^-}$ bridge. The O1–O2 separation is 2.464(9) Å, indicative of a strong hydrogen bond between the oxygen atoms, a feature

---

(1) (a) Vincent, J. B.; Averill, B. A. *FASEB J.* **1990**, *4*, 3009–3014. (b) True, A. E.; Scarrow, R. C.; Randall, C. R.; Holz, R. C.; Que, L., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 4246–4255.

(2) Kim, E. E.; Wyckoff, H. W. *J. Mol. Biol.* **1991**, *218*, 449–464.

(3) (a) Hansen, S.; Hansen, L. K.; Hough, E. *J. Mol. Biol.* **1992**, *225*, 543–549. (b) Hough, E.; Hansen, L. K.; Birknes, B.; Jynge, K.; Hansen, S.; Hordvik, A.; Little, C.; Dodson, E.; Derewenda, Z. *Nature* **1989**, *338*, 357–360.

(4) (a) Clark, P. A.; Wilcox, D. E. *Inorg. Chem.* **1989**, *28*, 1326–1333. (b) Day, E. P.; Peterson, J.; Sendova, M. S.; Todd, M. J.; Hausinger, R. P. *Inorg. Chem.* **1993**, *32*, 634–638.

(5) Roderick, S. L.; Matthews, B. W. *Biochemistry* **1993**, *32*, 3907–3912.

(6) Reczkowski, R. S.; Ash, D. E. *J. Am. Chem. Soc.* **1992**, *114*, 10992–10994.

(7) (a) Karlin, K. D. *Science* **1993**, *261*, 701–708. (b) Aquino, M. A. S.; Lim, J.-S.; Sykes, A. G. *J. Chem. Soc., Dalton Trans.* **1994**, 429–436. (c) Mueller, E. G.; Crowder, M. W.; Averill, B. A.; Knowles, J. R. *J. Am. Chem. Soc.* **1993**, *115*, 2974–2975.

(8) (a) Hendry, P.; Sargeson, A. M. *Prog. Inorg. Chem.* **1990**, *38*, 201–258. (b) Chin, J. *Acc. Chem. Res.* **1991**, *24*, 145–152. (c) Vance, D. H.; Czarnik, A. W. *J. Am. Chem. Soc.* **1993**, *115*, 12165–12166.

(9) Murthy, N. N.; Mahroof-Tahir, M.; Karlin, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 10404–10405.

(10) Abbreviations: TPA, tris(2-pyridylmethyl)amine; bpp, 3-[bis(2-pyridylmethyl)amino]propionate.

(11) Crystal data: monoclinic, space group $P2_1/n$, a = 11.577(6) Å, b = 25.595(6) Å, c = 15.428(7) Å, β = 98.97(6)°, V = 4516(6) Å^3, D_{calcd} = 1.651 g cm^{-1}, Z = 4. Red crystals of **1** suitable for X-ray crystallographic analysis were grown from CH_3CN. The data crystal was mounted with oil on a glass fiber on an Enraf-Nonius CAD4 diffractometer with a graphite crystal monochromator (λ(Mo Kα) = 0.710 73 Å), $2\theta_{max}$ = 52.0°. Data were collected at −101 ± 1 °C and corrected for absorption, Lorentz, and polarization effects. The structure was solved by direct methods, and 4713 reflections were used in the refinement, R = 0.083 and R_w = 0.072.

(12) Kurtz, D. M., Jr. *Chem. Rev.* **1990**, *90*, 585–606.

(13) Hazell, A.; Jensen, K. B.; McKenzie, C. J.; Toftlund, H. *J. Chem. Soc., Dalton Trans.* **1993**, 3249–3257.

(14) Norman, R. E.; Holz, R. C.; Ménage, S.; O'Connor, C. J.; Zhang, J. H.; Que, L., Jr. *Inorg. Chem.* **1990**, *29*, 4629–4637.

(15) ^1H NMR (300 MHz, CD_3CN): δ 30.7 (α-pyr), 18.7 (β-pyr), 15.1 (CH_2 from ^2H NMR of **1** prepared from TPA-d_6) 6.0 (γ-pyr).

(16) (a) Norman, R. E.; Yan, S.; Que, L., Jr.; Backes, G.; Ling, J.; Sanders-Loehr, J.; Zhang, J. H.; O'Connor, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 1554–1562. (b) Holz, R. C.; Elgren, T. E.; Pearce, L. L.; Zhang, J. H.; O'Connor, C. J.; Que, L., Jr. *Inorg. Chem.* **1993**, *32*, 5844–5850.

(17) ^1H NMR (300 MHz, CD_3CN): δ 36.1, 28.9 (α-pyr or CH_2), 18.8 (β-pyr), 16–11 (multiple small features), 7.5, 6.5, 6.1 (γ-pyr).

(18) Crystal data: monoclinic, space group $P2_1/c$, a = 10.780(4) Å, b = 23.88(2) Å, c = 23.025(9) Å, β = 96.78(3)°, V = 5887(10) Å^3, D_{calcd} = 1.433 g cm^{-1}, Z = 4. Dark green crystals of **2a** suitable for X-ray crystallographic analysis were grown from CH_3OH/H_2O. Details of the crystallographic experiment are the same as in ref 11. The structure was solved by direct methods, and 5694 reflections were used in the refinement, R = 0.099 and R_w = 0.099.

0002-7863/94/1516-8394$04.50/0

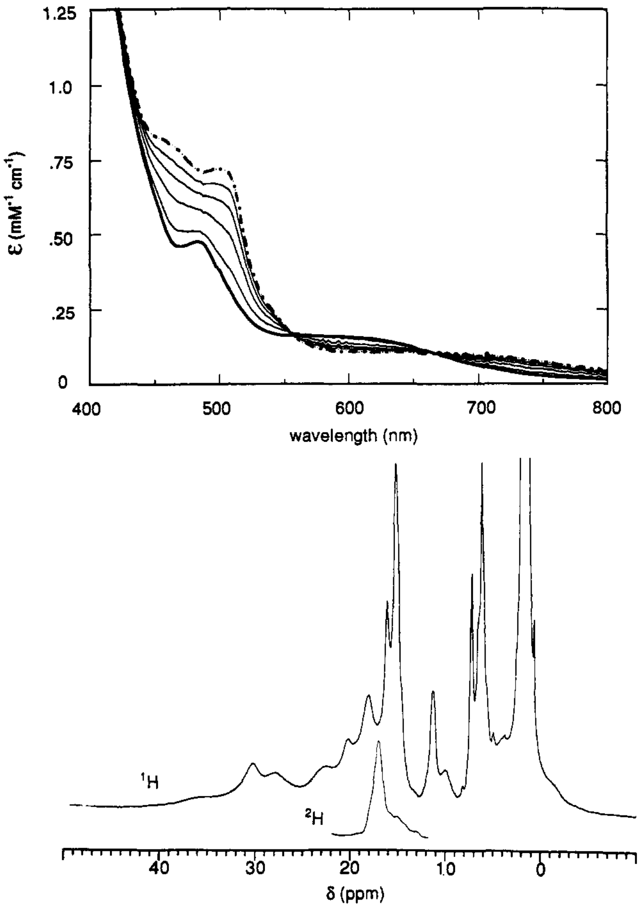
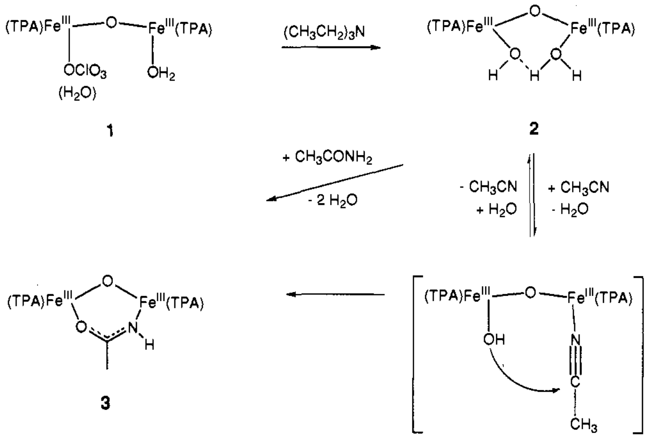


Figure 2. Upper panel: time course of the conversion of **2** (—) to **3** (– • –) in CH_3CN as followed by visible spectroscopy. Lower panel: NMR spectra of **3** in derived from the reaction of **2** with CD_3CN. See ref 19 for signal assignments.

also found in other metal complexes containing the $H_3O_2^-$ ligand.[19] The presence of the $H_3O_2^-$ bridge in **2a** engenders a smaller Fe–O–Fe angle (136.3(3)°) and a shorter Fe–Fe distance (3.346(9) Å) than those in the monobridged **1**. The bending of the Fe–O–Fe unit results in steric interactions between the TPA ligands which are alleviated by the coordination of the amine nitrogen on Fe2 cis to the oxo bridge; this unsymmetric arrangement of the TPA ligands is found in other dibridged diiron(III) TPA complexes.[16] The Fe2–O2 bond (1.907(7) Å) is shorter than the Fe1–O1 bond (2.049(6) Å), allowing us to assign O1 as a terminal water ligand and O2 as a terminal hydroxo ligand. Indeed, **2a** is the first iron(III) complex having a terminal hydroxo ligand to be characterized by X-ray crystallography.[20]

While **1** is stable even in refluxing acetonitrile, **2** converts to form a new brown species, **3**, when allowed to stand in acetonitrile. Complex **3** has visible features at 460 (ϵ = 780 M^{-1} cm^{-1}), 502 (ϵ = 700 M^{-1} cm^{-1}), and 696 nm (ϵ = 90 M^{-1} cm^{-1}) and a ^1H NMR spectrum indicative of inequivalent TPA ligands (Figure 2). The ^1H NMR and visible spectra of **3** are very similar to those of $[Fe_2O(TPA)_2(CH_3CO_2)](ClO_4)_3$;[16a] however, the expected ^1H NMR resonance of the methyl group of the bridging acetate at δ 13.7 is absent. When **2** is incubated in CD_3CN, ^2H NMR shows the appearance of a new paramagnetically shifted feature at δ 16.9 (Figure 2 inset). Thus CD_3CN has been converted to an iron ligand, affording a complex that is similar, but not identical, to $[Fe_2O(TPA)_2(CH_3CO_2)](ClO_4)_3$. This new complex, $[Fe_2O(TPA)_2(CH_3CONH)](ClO_4)_3$ (**3**) can be prepared independently by treatment of **2** with acetamide.[21] In **3**, the acetamide is bound as an anionic ligand, presumably bridging the two irons as in the corresponding acetate derivative.

Scheme 1. Proposed Mechanism for Hydration of Acetonitrile by **2**



The conversion of **2** to **3** in acetonitrile solvent displays pseudo-first-order kinetics, with a half-life at 40 °C of 7.4 h. The addition of water to the reaction mixture slows the rate of reaction, and when 400 equiv of water is added, the half-life increases to 19 h. This inhibitory effect of added water on the reaction rate suggests that water and acetonitrile compete for binding to the iron and that acetonitrile must displace the water ligand before the hydration can take place (Scheme 1). Once coordinated, the acetonitrile can then be attacked by the hydroxide on the other iron, resulting in the bridging acetamidato ligand. Kinetic studies to substantiate this mechanism are in progress.

In this paper we have reported the structure of a (μ-oxo)-diiron(III) complex with a terminal hydroxide and its hydration of acetonitrile. The observed reactivity supports the proposed mechanism for acetonitrile hydration by dicobalt complexes,[22] where coordinated hydroxide was implicated as the nucleophile but was not directly observed. These results provide insight into what roles the individual metal centers may play in the active site of a bimetallic hydrolase.

Note Added in Proof: The X-ray structure of **2**, $[Fe_2O(H_3O_2)TPA_2](ClO_4)_3$, was recently reported by Toftlund and co-workers.[23] They also observed the hydration of CH_3CN by **2**.

Acknowledgment. We are grateful to Professor J. D. Britton for his expertise and assistance in the X-ray diffraction experiments. This work was supported by the National Institutes of Health Grant GM-38767.

Supplementary Material Available: Tables of the atomic coordinates, thermal parameters, bond lengths, and bond angles for $[Fe_2O(TPA)_2(H_2O)(ClO_4)](ClO_4)_3$ and $[Fe_2O(H_3O_2)(5\text{-Et-}TPA)_2](ClO_4)_3$ (35 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

---

[19] (a) Ardon, M.; Bino, A. *Struct. Bonding (Berlin)* **1987**, *65*, 1–28. (b) Abu-Dari, K.; Freyberg, D. P.; Raymond, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 3688–3689.

[20] Due to the strong Lewis acidity of Fe(III) in TPA complexes, we have not been able to make mononuclear aqua or hydroxo complexes; instead the (μ-oxo)diiron(III) complexes reported in this paper are formed.

[21] ^1H NMR (300 MHz, CD_3CN): δ 31, 29, 23, 21, 18 (α pyr or CH_2), 16.9 (CH_3CONH), 16.8, 15.9, 11.9 (β pyr), 10.6 (α pyr or CH_2), 7.9, 6.8, 6.6, 2.3 (γ pyr). Anal. Calcd for $[Fe_2(TPA)_2O(CH_3CONH)](ClO_4)_3{\cdot}H_2O$, $C_{38}H_{42}Cl_3Fe_2N_9O_{15}$: C, 42.14; H, 3.91; N, 11.64. Found: C, 42.30; H, 4.39; N, 11.64.

[22] Alcock, N. W.; Creaser, I. I.; Curtis, N. J.; Roecker, L.; Sargeson, A. M.; Willis, A. C. *Aust. J. Chem.* **1990**, *43*, 643–654.

[23] Hazell, A.; Jensen, K. B.; McKenzie, C. J.; Toftlund, H. *Inorg. Chem.* **1994**, *33*, 3127–3134.