Protonation of a Bridging Oxo Ligand Is Slow

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Oxo-bridged polynuclear complexes are common in metalloproteins, as numerous reviews attest.[1] Examples include hemerythrin, ribonucleotide reductase, purple acid phosphatases, methane monooxygenase, and the oxygen-evolving center from photosystem II. In the isolated and structurally characterized forms of some metalloproteins (e.g., purple acid phosphatases,[2] the hydroxylase subunit of methane monooxygenase[3]) the oxo bridges are believed to be protonated. In other cases the oxo bridges undergo protonation and deprotonation as the metalloproteins perform their physiological function. For example, the deoxy form of hemerythrin has a hydroxo bridge; during O_2 uptake a proton is transferred from that μ-OH to the incoming O_2, although the proton remains connected by a hydrogen bond to the resulting μ-O.[1] Another example is O_2 evolution from photosystem II, which requires that water be deprotonated to μ-OH and eventually to μ-O.[4]

Que and True[1c] have suggested that the proton transfer during O_2 uptake by hemerythrin is "facile". However, the *rates* of such proton-transfer reactions have never been measured in model compounds. Typically proton transfer to or from oxygen in an organic compound is fast;[5] there is little barrier to transferring a proton to, or removing a proton from, an oxygen lone pair as long as the hybridization remains sp^3. Oxo ligands are not, however, ordinary oxygens. There is significant π bonding between them and the d orbitals of the metal to which they are attached, so their hybridization is not sp^3. Protonation should change this hybridization[6] and is known to change M–O distances[7] by about 0.1 Å. Protonation of an oxo bridge thus requires extensive geometric and electronic rearrangement like that responsible for the large kinetic barriers attending protonation and deprotonation at carbon[5] and at transition metals.[8]

Table I. Equilibrium and Rate Constants for the Protonation of Bridging Oxo Ligands

compd	pK_a of compd H^+ (in CH_3CN)	acid[a]	$\log_{10} K_{eq}$[b]	k_{H^+} (M^{-1} s^{-1})	T (°C)
2	≈14[c]	pyH^+	>1	**1920**	−20
3	16.2	H^+	16.2	**5440**	25
4	≈13[d]	H^+	≈13	**11200**	−10

[a] As $HClO_4$ is a strong acid in CH_3CN (ref 17), the acid is given as "H^+" when $HClO_4$ is used. [b] For the protonation equilibrium. [c] Completely protonated by pyH^+ and negligibly protonated by NH_4^+. As pyH^+ has a CH_3CN pK_a of 12.3 and NH_4^+ has a CH_3CN pK_a of 16.46 (Coetzee, J. R.; Padmanbhan, G. *J. Am. Chem. Soc.* **1965**, *87*, 5005) the pK_a of **4H**$^+$ must be ≈14. [d] Reported as 6.5 in H_2O in ref 7b; can therefore be estimated as about 13 in CH_3CN by the procedure of ref 8d.

As a result *proton transfers involving oxo bridges should be considerably slower than those with comparable equilibrium constants involving oxygen in an organic compound.* Qualitative evidence that this prediction is correct has been offered by observations of Finke and co-workers[9] on $HSiW_9V_3O_{40}^{6-}$ and by the work of Thorp and Brudvig[10] on the proton-coupled electrochemical reduction of [(bispicen)$Mn^{(IV)}(\mu\text{-O})_2Mn^{(III)}$(bispicen)]$[ClO_4]_3$ (**1**)[11,12] and by the work of Pecoraro, Penner-Hahn, and co-workers on [(Salpn)$Mn^{(IV)}(\mu\text{-O})(\mu\text{-OH})Mn^{(IV)}$(Salpn)]$[ClO_4]$ (**2H**$^+$).[13] We present here the first measurement of the rate of an oxo bridge protonation reaction that is slow despite a large thermodynamic driving force.

When a solution of [(6-methylbispicen)$Mn^{(III)}(\mu\text{-O})]_2[ClO_4]_2$ (**3**)[14] in CH_3CN was mixed with excess $HClO_4$ in a stopped-flow apparatus, the growth and decay of an intermediate were observed. When only 1 equiv of $HClO_4$ was added to a CH_3CN solution of **3**, the intermediate persisted and could be isolated and identified[15] as [(6-methylbispicen)$Mn^{(III)}(\mu\text{-O})(\mu\text{-OH})Mn^{(III)}$(6-methylbispicen)]$[ClO_4]_3$ (**3H**$^+$); its UV–vis spectrum in CH_3CN showed λ_{max} at 490 (ϵ = 235) and 684 (ϵ = 130) nm. The protonation was reversible: addition of an equiv of Et_3N to a solution of **3H**$^+$ regenerated the UV–vis spectrum of **3**. Other acids (e.g., triflic and sulfuric) with conjugate bases that are weakly nucleophilic in CH_3CN also produced **3H**$^+$ from **3**; however, **3H**$^+$ proved unstable in the presence of any reasonably good nucleophile (e.g., Cl^-, $PhCO_2^-$, NO_3^-) or of excess acid.

We could now explain the growth and decay of the intermediate in the stopped-flow reaction of **3** with excess $HClO_4$. Rapid scan data, obtained from 300 to 600 nm, showed that the intermediate had the characteristic peak of **3H**$^+$ at 490 nm; the decay of **3H**$^+$ was then due to its instability in excess acid. The pseudo-first-order rate constant for the formation of **3H**$^+$ from **3** was obtained by fitting the absorbance at 340 nm to the standard equation[16] for

(1) (a) Oxo-bridged polyiron centers: Lippard, S. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 344. (b) See: Chapters 4, 8, 9, 10, 11, and 12 In *Metal Clusters in Proteins*; Que, L., Jr., Ed.; ACS Symposium Series 372; American Chemical Society: Washington, DC, 1988. (c) Oxo-bridged diiron and dimanganese proteins: Que, L., Jr.; True, A. E. *Prog. Inorg. Chem.* **1990**, *38*, 98–200. (d) Oxo- and hydroxo-bridged diiron complexes: Kurtz, D. M., Jr. *Chem. Rev.* **1990**, *90*, 585–606. (e) Oxo-bridged diiron centers: Vincent, J. B.; Olivier-Lilley, G. L.; Averill, B. A. *Chem. Rev.* **1990**, *90*, 1447.

(2) There is reason to believe that the oxo bridge between the Fe(II) and Fe(III) in purple acid phosphatases bears a proton,[1a,c] although some disagree.[1d]

(3) The bridge between the irons in the hydroxylase subunit of methane monooxygenase may be a hydroxo ligand: DeWitt, J. G.; Bentsen, J. G.; Rosenzweig, A. C.; Hedman, B.; Green, J.; Pilkington, S.; Papaefthymiou, G. C.; Dalton, H.; Hodgson, K. O.; Lippard, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 9219.

(4) Thorp, H. H.; Brudvig, G. W. *New J. Chem.* **1991**, *15*, 479. See, also: Chapters 11 and 12 in ref 1b.

(5) (a) Bell, R. P. *The Proton in Chemistry*; Cornell University Press: Ithaca, NY, 1973; p 130. (b) Stewart, R. *The Proton: Applications to Organic Chemistry*; Academic: New York, 1985; pp 280–281. (c) Connors, K. A. *Chemical Kinetics: The Study of Reaction Rates in Solution*; VCH: New York, 1990; p 149.

(6) Particularly good evidence of this is offered by the change in sign of J when $[(TACN)_2V^{III}_2(\mu\text{-OH})(\mu\text{-}O_2CR)_2]^{2+}$ is protonated: Knopp, P.; Wieghardt, K. *Inorg. Chem.* **1991**, *30*, 4061.

(7) (a) Wieghardt, K.; Bossek, U.; Nuber, B.; Weiss, J.; Bonvoisin, J.; Corbella, M.; Vitols, S. E.; Girerd, J. J. *J. Am. Chem. Soc.* **1988**, *110*, 7398. (b) Hagen, K. S.; Westmoreland, T. D.; Scott, M. J.; Armstrong, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 1907. (c) Hagen, K. S.; Westmoreland, T. D.; Scott, M. J.; Armstrong, W. H.; Pal, S. Manuscript in preparation. (d) Armstrong, W. H.; Lippard, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 4632.

(8) (a) Jordan, R. F.; Norton, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 1255. (b) Edidin, R. T.; Sullivan, J. M.; Norton, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 3945. (c) Kristjánsdóttir, S. S.; Norton, J. R.; Moroz, A.; Sweany, R. L.; Whittenburg, S. L. *Organometallics* **1991**, *10*, 2357. (d) Kristjánsdóttir, S. S.; Norton, J. R. *Transition Metal Hydrides: Recent Advances in Theory and Experiment*; Dedieu, A., Ed.; VCH Publishers: in press.

(9) The proton in $HSiW_9V_3O_{40}^{6-}$, bound to an oxygen bridging two vanadiums, shows little mobility in the absence of added acid or base: Finke, R. G.; Rapko, B.; Saxton, R. J.; Domaille, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 2947. It is also worth noting that the tautomerization between the *terminal* hydroxo and oxo ligands in $(2\text{-butyne})_2Re(O)(OH)$ is extremely slow (half-life ≈ 11 h): Erikson, T. K. G.; Mayer, J. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1527.

(10) Kalsbeck, W. A.; Thorp, H. H.; Brudvig, W. G. *J. Electroanal. Chem.* **1991**, *314*, 335; Thorp, H. H., North Carolina State University, personal communication.

(11) Collins, M. A.; Hodgson, D. J.; Michelsen, K.; Pedersen, E. *J. Chem. Soc., Chem. Commun.* **1987**, 1659.

(12) Abbreviations: $HBPz_3$ = hydrotris(1-pyrazoyl)borate, bispicen = *N,N'*-bis(2-pyridylmethyl)ethane-1,2-diamine), 6-methylbispicen = *N,N'*-bis((6-methylpyrid-2-yl)methyl)ethane-1,2-diamine, H_2Salpn = 1,3-bis(salicylideneiminato)propane, TACN = 1,4,7-triazacyclononane.

(13) Larson, E. J.; Riggs, P.; Penner-Hahn, J. E.; Pecoraro, V. L. *J. Chem. Soc., Chem. Commun.* **1992**, 102.

(14) Goodson, P. A.; Oki, S.; Glerup, J.; Hodgson, D. J. *J. Am. Chem. Soc.* **1990**, *112*, 6248.

(15) Anal. Calcd for $C_{32}H_{45}N_8O_2Mn_2$: C, 39.14; H, 4.62; N, 11.41. Found: C, 38.75; H, 4.53; N, 11.19; IR (KBr) ν_{OH} 3407 cm^{-1}. Conductivity (CH_3CN) Λ_e 370 cm^2 Ω^{-1} mol^{-1}. The "fingerprint" IR bands (1700–700 cm^{-1}) associated with the 6-methylbispicen ligand are virtually identical in **3** and **3H**$^+$ as solids in KBr, implying that that ligand is not protonated in **3H**$^+$ and that an oxo bridge must be; the agreement between the diffuse reflectance spectrum of solid **3H**$^+$ and its UV–vis spectrum in CH_3CN implies that the μ-OH structure of **3H**$^+$ persists in solution.

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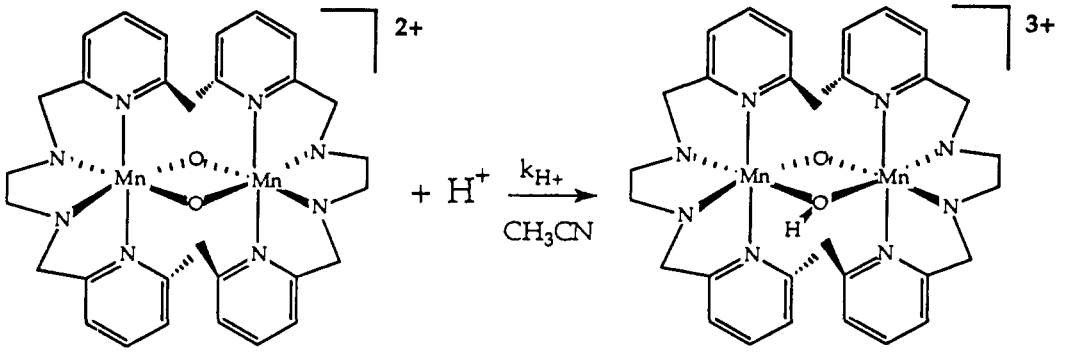
Scheme I



[3] [3H]+

two consecutive first-order reactions. We thus, after taking into account the fact that $HClO_4$ is a strong acid in CH_3CN,[17] obtained a value of 5440 M^{-1} s^{-1} at 25 °C for k_{H+}, the second-order rate constant in Scheme I. The temperature dependence of k_{H+} showed that the slowness of this protonation reaction is due to the activation enthalpy ($\Delta H^{\ddagger}$ = 16 kcal/mol, $\Delta S^{\ddagger} \approx 0$ eu).

Spectrophotometric titration[18] of $3H^+$ with the triflate salt of 2,6-lutidinium[19] showed its CH_3CN pK_a to be 16.2 (5), implying[8d] a pK_a of approximately 8.7 in water. The protonation in Scheme I is thus thermodynamically downhill by over 16 pK_a units. With ordinary oxygens diffusion-controlled rates are observed when ΔpK_a is downhill by more than four pK_a units,[5a] so k_{H+} is more than 10^6 slower than the rate constant expected for such an oxygen.

We have obtained measurable rate constants at reduced temperatures (see Table I) for two other oxo-bridged manganese complexes, $[(TACN)_4Mn^{(IV)}{}_4(\mu\text{-}O)_6][Br]_4$ (**4**)[7a] and $[(Salpn)Mn^{(IV)}(\mu\text{-}O)]_2$ (**2**).[20] As before, rapid scan data on the protonation of **4** in excess $HClO_4$ showed the formation and decay of the known[7b,c,21] $4H^+$. The protonation of **2** with pyH^+ gave a stable product identified by its UV-vis spectrum[22] as $2H^+$. In all three cases the rate constants are *substantially slower* than those for the protonation of organic oxygens with comparable equilibrium constants.

We have been unable to measure rate constants for the protonation of $[(bispicen)Mn^{(III)}(\mu\text{-}O)_2Mn^{(III)}(bispicen)][ClO_4]_3$ (**1**)[11] (the III,III) compound could not be generated from the reduction of the III,IV) precursor fast enough to allow measurement of k_{H^+}), $[(HB(Pz)_3)Fe^{(III)}(\mu\text{-}O)(\mu\text{-}O_2CCH_3)_2Fe^{(III)}(HB(Pz)_3)]$ (**5**)[23] (even at −30 °C the formation of $5H^+$ [7d] was too fast to observe), and $[(bipy)_2Mn^{(III)}(\mu\text{-}O)_2Mn^{(IV)}(bipy)_2][ClO_4]_3$ (**6**)[24] ($6H^+$ decayed to a known trimer[4] faster than the mixing time of our stopped-flow; k_{obs} = 25.2 s^{-1} at 25 °C, pH 2.3).

The slow protonation rates we have observed suggest that proton transfers could be rate-determining in the action of oxo-bridged metalloproteins. We are now investigating the effects of various structural features of oxo-bridged complexes on the rates at which they accept protons.

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(16) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*; McGraw-Hill: New York, NY, 1981; p 67.
(17) Kolthoff, I. M.; Bruckenstein, S.; Chantooni, M. K. *J. Am. Chem. Soc.* **1961**, *83*, 3927.
(18) The pK_a is calculated from the spectrophotometrically measured equilibrium constant for **3** + lutidinium ⇌ $3H^+$ + lutidine as in ref 8b.
(19) pK_a = 15.4: Cauquis, G.; Deronzier, A.; Serve, D.; Vieil, E. *J. Electroanal. Chem. Interfacial Electrochem.* **1975**, *60*, 205.
(20) Larson, E. J.; Lah, M. S.; Li, X.; Bonadies, J. A.; Pecoraro, V. L. *Inorg. Chem.* **1992**, *31*, 373.
(21) The fact that the relatively featureless UV-vis spectrum of $4H^+$ in CH_3CN is reproduced in the diffuse reflectance spectrum of solid $4H^+$ implies that the μ-OH structure established for $4H^+$ by X-ray crystallography (refs 7b,c) persists in solution. UV-vis observation of the reaction of **4** with $HClO_4$ gives the same two isosbestic points (530 and 620 nm) observed by Armstrong[7c] during the spectrophotometric titration of **3** with triflic acid.
(22) A μ-OH structure has been proposed for $2H^+$ on the basis of the increase (≈0.1 Å) in the Mn-Mn distance (EXAFS) of $2H^+$ over that of **2**. The UV-vis spectrum of $2H^+$ in CH_3CN agrees with that reported in ref 13.
(23) Armstrong, W. H.; Spool, A.; Papaefthymiou, G. C.; Frankel, R. B.; Lippard, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 3653.
(24) Calvin, M.; Cooper, S. R. *J. Am. Chem. Soc.* **1977**, *99*, 6623.

A Novel Pd-Catalyzed Cycloalkylation to Isoxazoline 2-Oxides. Application for the Asymmetric Synthesis of Carbanucleosides

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2-Ene-1,4-diols constitute useful building blocks for synthesis via Pd-catalyzed reactions because of their potential for sequential replacement of each oxygen leaving group and for enantioselective synthesis via dissymmetrization with chiral ligands.[1-4] The ambident nature of nitro-stabilized anions permits both C and O alkylation.[5,6] We wish to record an unusual Pd-catalyzed cy-

(1) Trost, B. M.; Van Vranken, D. L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 228. Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 6317; **1990**, *112*, 1261. Mori, M.; Nukui, S.; Shibasaki, M. *Chem. Lett.* **1991**, 1797.
(2) Deardorff, D. R.; Linde, R. G., II; Martin, A. M.; Shulman, M. J. *J. Org. Chem.* **1989**, *54*, 2759.
(3) Montforts, F. B.; Gesing-Zibulak, I.; Grammenos, W.; Schneider, M.; Laumen, K. *Helv. Chim. Acta* **1989**, *72*, 1852.
(4) Cf. Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480. Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847.
(5) For reviews, see: Barrett, A. G. M. *Chem. Soc. Rev.* **1991**, *20*, 95. Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423. Rosini, G.; Ballini, R.; Petrini, M.; Marotta, E.; Righi, P. *Org. Prep. Proc. Int.* **1990**, *22*, 707. Ono, N. In *Nitro Compounds; Recent Advances in Synthesis and Chemistry*; Feuer, H., Nielsen, A. T., Eds.; VCH Publishers: New York, 1990. Rosini, G.; Ballini, R. *Synthesis* **1988**, 833. Kabalka, G. W.; Varma, R. S. *Org. Prep. Proc. Int.* **1987**, *19*, 283. Varma, R. S.; Kabalka, G. W. *Heterocycles* **1986**, *24*, 2645. Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751. Ono, N.; Kaji, A. *Synthesis* **1986**, 693. Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* **1985**, *18*, 284.
(6) Cf. Rosini, G.; Marotta, E.; Righi, P.; Seerden, J. P. *J. Org. Chem.* **1991**, *56*, 6258. Bäckvall, J. E.; Karlsson, U.; Chinchilla, R. *Tetrahedron Lett.* **1991**, *32*, 5607. Melot, J. M.; Texier-Boullet, F.; Foucaud, A. *Synthesis* **1988**, 558. Seebach, D.; Brook, M. A. *Can. J. Chem.* **1987**, *65*, 836. Denmark, S. E.; Cramer, C. J.; Sternberg, J. A. *Helv. Chim. Acta* **1986**, *69*, 1971. Denmark, S. E.; Dappen, M. S.; Cramer, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 1306. Magdesieva, N. N.; Sergeeva, T. A.; Kyandzhetsian, R. A. *Zh. Org. Khim.* **1985**, *21*, 1980; *Chem. Abstr.* **1985**, *103*, 215232. Kaji, E.; Zen, S. *Chem. Pharm. Bull.* **1980**, *28*, 479. Nielsen, T. A.; Archibald, T. G. *Tetrahedron* **1979**, *26*, 3475.

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