Synthetic Approach to the Mononuclear Active Sites of Molybdoenzymes: Catalytic Oxygen Atom Transfer Reactions by Oxomolybdenum(IV,VI) Complexes with Saturation Kinetics and without Molybdenum(V) Dimer Formation

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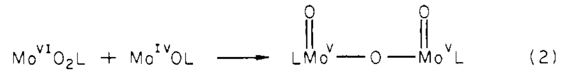
The mononuclear active sites of certain molybdoenzymes[2,3] that catalyze oxygen atom transfer reactions are becoming increasingly defined structurally from chemical, EPR,[4] and Mo EXAFS[5,6] results. Sulfite oxidase, for example, appears to have the (minimal) coordination units $Mo^{VI}O_2S_{2,3}(N/O)$ and $Mo^{IV}OS_3$ in its oxidized and fully reduced forms,[6] respectively. Credible synthetic representations of such sites must, inter alia, (i) approach the native ligand set, (ii) execute the forward or reverse reaction 1 with substrate X/XO, and (iii) not exhibit the dimerization reaction 2. The latter, prevented by enzyme structural constraints, is

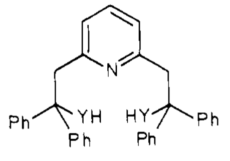
$$Mo^{VI}O_2L + X \rightleftarrows Mo^{IV}OL + XO \qquad (1)$$



$$Mo^{VI}O_2L + Mo^{IV}OL \longrightarrow L\overset{\overset{O}{\|}}{Mo^{V}}-O-\overset{\overset{O}{\|}}{Mo^{V}}L \qquad (2)$$

pervasive and frequently irreversible in synthetic molybdenum chemistry.[7-9] When irreversible, its occurrence forecloses catalytic or even stoichiometric substrate conversion on the basis of reaction 1. While attractive structural models of oxidized enzyme sites have been prepared,[7,10-12] none has been shown to satisfy (i)-(iii) simultaneously. We disclose here our initial approach to this problem.

Starting with 2,6-lutidine, two sequential steps of lithiation (*n*-BuLi, ether) and reaction with benzophenone gave the diol **1**-N(OH)$_2$[13] (36%, mp 130-131 °C). Reaction of diphenylmethanethiol[14] with 2,3-dihydropyran (dichloromethane, pyridinium tosylate catalyst[15]) afforded $Ph_2CHS(THP)$ (87%). Lithiation (*n*-BuLi, ether) followed by reaction with 2,6-bis(bromomethyl)pyridine[16] produced the diprotected dithiol **2** (82%, mp 155-158 °C), a useful storage form of the sensitive dithiol **3**-N(SH)$_2$. Equimolar amounts of **1**-N(OH)$_2$ and $MoO_2(acac)_2$[17] in methanol gave MoO_2(**1**-NO_2)(MeOH) (90%, ν_{MoO} 922, 877 cm^{-1}) as a white microcrystalline product. Crystallization of this compound from ~10:1 v/v EtOAc/Me_2SO gave highly crystalline MoO_2(**1**-NO_2)(Me_2SO) (ν_{MoO} 922, 899 cm^{-1}). Deprotection of **2** ((1) $AgNO_3$/pyridine, (2) H_2S, (3) pH 7 buffer) yielded **3**-N(SH)$_2$. Addition of the dithiol in dichloromethane to $MoO_2(acac)_2$ in methanol afforded orange MoO_2(**3**-NS_2) (85%, ν_{MoO} 950, 915 cm^{-1}; λ_{max} (ϵ_M) 449 (3900), 385 (4400) nm, DMF). Anaerobic treatment of MoO_2(**3**-NS_2) in DMF with 1.5 equiv of PPh_3 (12 h) and precipitation with ether yielded microcrystalline purple MoO(**3**-NS_2)(DMF) (ν_{MoO} 945 cm^{-1}; λ_{max} (ϵ_M) 734 (1200), 528 (6300), 365 (5900) nm, DMF).



1-N(OH)$_2$, Y = O
3-N(SH)$_2$, Y = S

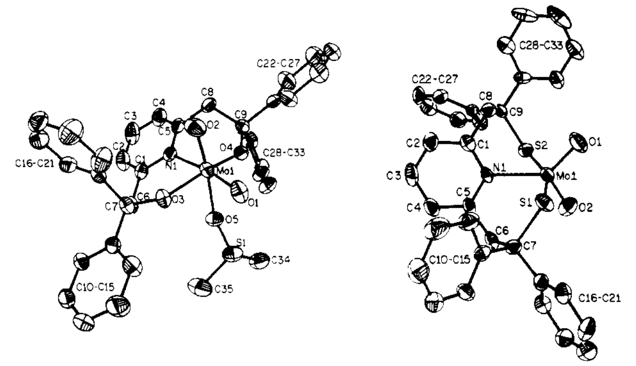


Figure 1. (Left) Structure of MoO_2(**1**-NO_2)(Me_2SO). Bond distances (Å): Mo-O1, 1.702 (4); Mo-O2, 1.708 (4); Mo-O3, 1.899 (3); Mo-O4, 1.904 (3); Mo-N1, 2.417 (4); Mo-O5, 2.382 (3). Bond angles (deg): O1-Mo-O2, 105.4 (2); O1-Mo-O3, 96.8 (2); O3-Mo-N1, 81.7 (2); O3-Mo-O4, 153.2 (1); O1-Mo-N1, 166.3 (2); O2-Mo-O5, 167.6 (2). (Right) Structure of MoO_2(**3**-NS_2). Bond distances (Å): Mo-O1, 1.691 (6); Mo-O2, 1.696 (6); Mo-S1, 2.412 (2); Mo-S2, 2.419 (2); Mo-N1, 2.244 (7). Bond angles (deg): O1-Mo-O2, 110.5 (2); O1-Mo-N1, 126.4 (2); S1-Mo-O1, 95.2 (2); S1-Mo-N1, 78.4 (2); S1-Mo-S2, 156.4 (1). 50% probability ellipsoids are shown.

Compounds MoO_2(**1**-NO_2)(Me_2SO) and MoO_2(**3**-NS_2) crystallize as discrete molecules whose structures[18] are provided in Figure 1. MoO_2(**1**-NO_2)(Me_2SO)[18a] has distorted octahedral stereochemistry with cis oxo and trans alkoxide ligands; Me_2SO is oxygen bound and trans to an oxo group. The stereochemistry is rather similar to those of other six-coordinate MoO_2 complexes.[10-12] On the other hand, MoO_2(**3**-NS_2) provides a new MoO_2 structural type. The Mo(VI) atom is five-coordinate, and the MoO_2NS_2 unit is distorted trigonal bipyramidal with trans sulfur atoms and a pseudo-C_2 axis coincident with the Mo-N bond. The mean Mo-O (1.694 Å) and Mo-S (2.416 Å) distances are in good agreement with those (1.68, 2.41 Å) derived from EXAFS analysis of oxidized sulfite oxidase,[6] which also suggests one N/O atom at ~2.19 Å. The Mo-N distance of 2.244 (7) Å is consistent with that possibility. The LMCT bands at 449 and 385 nm find possible counterparts in the ~475- and 350-nm features in the spectrum of the isolated Mo domain of sulfite oxidase.[19,20]

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(18) X-ray diffraction experiments were performed on a Nicolet R3m diffractometer using graphite-monochromatized Mo Kα radiation. All calculations were performed with use of the SHELXTL program package. (a) MoO_2(**1**-NO_2)(Me_2SO): a = 8.738 (2) Å, b = 17.799 (4) Å, c = 19.927 (3) Å, β = 93.77 (1)°, space group $P2_1/c$, Z = 4, 2742 unique data ($F^2 > 3\sigma(F^2)$), R (R_w) = 3.7 (3.7)%. (b) MoO_2(**3**-NS_2): a = 8.910 (2) Å, b = 16.350 (4) Å, c = 19.193 (4) Å, space group $P2_12_12_1$, Z = 4, 1877 unique data ($F^2 > 3\sigma(F^2)$), R (R_w) = 3.6 (3.4)%.

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A significant feature of both MoO$_2$(**1**-NO$_2$)(Me$_2$SO) and MoO$_2$(**3**-NS$_2$) is the projection of structure of the *gem*-diphenyl groups on the Mo=O bonds. This steric protruberance in the direction of potential Mo-O-Mo bond formation is sufficient to eliminate reaction 2. Reaction of ~0.1 mM MoO$_2$(**3**-NS$_2$) and 3.0 equiv of Ph$_3$P in DMF gave clean isosbestic points at 473 and 386 nm and a final spectrum consistent with the MoO(**3**-NS$_2$)(ligand) chromophore. ^{31}P NMR signals at 43.5 (1.0, MoO(**3**-NS$_2$)(OPPh$_3$)), 25.9 (6.8, Ph$_3$PO), and -4.6 (7.1, Ph$_3$P) ppm[21] were observed after completion of reaction (20 h) in a system initially containing 10 mM MoO$_2$(**3**-NS$_2$)/1.88 equiv Ph$_3$P. The observed intensity ratio $(6.8 + 1.0)/7.1 = 1.10$ agrees closely with the expected value of 1.14 for reaction 1 and is completely inconsistent with the ratio $0.5/1.38 = 0.36$ for formation of a Mo$_2$O$_3$ species. Thus, MoO$_2$(**3**-NS$_2$) is cleanly converted to MoO(**3**-NS$_2$)L (L = DMF, Ph$_3$PO) without interference from reaction 2. The reaction is second order with $k = 7\ (1) \times 10^{-3}$ M^{-1} s^{-1} (23 °C). In contrast, MoO$_2$(**1**-NO$_2$)(DMF) does *not* react with Ph$_3$P, a result ascribed to the large negative shift in $E_{\mathrm{p,c}}$ values (-0.89 to -1.82 V vs. SCE) upon oxygen-for-sulfur atom substitution.

The system MoO(**3**-NS$_2$)(DMF)/Me$_2$SO affords MoO$_2$(**3**-NS$_2$) and Me$_2$S, with no intervention by reaction 2, and exhibits substrate saturation kinetics at sufficient Me$_2$SO concentrations. These observations, the last of which parallels frequent enzymatic behavior, are interpreted in terms of reactions 3 and 4. A

$$\mathrm{MoO(\mathbf{3}\text{-}NS_2)(DMF)} + \mathrm{Me_2SO} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{MoO(\mathbf{3}\text{-}NS_2)(Me_2SO)} + \mathrm{DMF} \tag{3}$$

$$\mathrm{MoO(\mathbf{3}\text{-}NS_2)(Me_2SO)} \xrightarrow{k_2} \mathrm{MoO_2(\mathbf{3}\text{-}NS_2)} + \mathrm{Me_2S} \tag{4}$$

double-reciprocal plot[22] gives $V_{\max}$ $(=k_2) = 1.5\ (1) \times 10^{-3}$ s^{-1} and an apparent K_{m} $(\approx k_{-1}[\mathrm{DMF}]/k_1) = 3\ (1) \times 10^{-3}$ M at 23 °C in DMF. Coupling of reactions 1 (X = Ph$_3$P) and 3 + 4 yields a catalytic cycle capable of reducing Me$_2$SO with concomitant Ph$_3$P oxidation. The ^{31}P NMR spectrum of the system MoO$_2$(**3**-NS$_2$)/25 equiv Ph$_3$P in neat Me$_2$SO after 18 h revealed formation of $\gtrsim 20$ equiv of Ph$_3$PO. In a parallel experiment, the Me$_2$S product was isolated as (Me$_2$S)$_2$(HgCl$_2$)$_3$[23] in 97% yield based on phosphine. No reaction occurs between Ph$_3$P and Me$_2$SO at 189 °C for at least 1 h.[23]

Reduction of sulfoxides by an oxomolybdenum complex is especially noteworthy in light of the finding that *d*-biotin-*d*-sulfoxide reductase is a Mo cofactor-dependent enzyme.[24] Significantly, *d*-biotin *d*-sulfoxide[25] is reduced to *d*-biotin by MoO(**3**-NS$_2$)(DMF); saturation kinetics are observed and kinetic parameters are comparable to those with Me$_2$SO. Saturation behavior will permit a direct comparison of synthetic system and enzymatic reaction rates. MoO$_2$(**3**-NS$_2$) and MoO(**3**-NS$_2$)(ligand) satisfy requirements ii and iii, including catalytic transformation of a biological substrate. Although the structure of MoO$_2$(**3**-NS$_2$) is related to the Mo site of one Mo cofactor-dependent enzyme, requirement i for the sulfoxide reductase cannot be examined without further enzyme characterization. No reaction in the system MoO$_2$(**3**-NO$_2$)(DMF)/Ph$_3$P implies a ncessity for thiolate ligation in, at least, oxygen atom transfer from catalyst to substrate. Work directed toward the development of reaction systems based on biologically relevant reductants and on the characterization of intermediate oxidation level Mo(V) species is in progress.

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Supplementary Material Available: Atom coordinates and anisotropic temperature factors for MoO$_2$(**1**-NO$_2$)(Me$_2$SO) and MoO$_2$(**3**-NS$_2$) (8 pages). Ordering information is given on any current masthead page.

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Free Radical Route to Formation of the Metal Hydride Complex Hydridoaquobis(2,2′-bipyridine)cobalt(III)[1]

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In recent years the thermodynamics and kinetics of formation of d^6 metal hydrides via proton addition to the d^8 conjugate base have been characterized in a number of systems.[2-6] As a result it is now recognized that "metal acids" (hydride complexes) generally undergo proton-transfer reactions much more slowly than nitrogen or oxygen acids of comparable strength owing to the substantial changes in metal coordination that accompany the reaction.[4,5] Here we report our observations on the formation of Co(bpy)$_2$(H$_2$O)H^{2+} (bpy = 2,2′-bipyridine) from high-spin d^8 Co(I) bipyridine complexes in aqueous solutions: in this system no pathway attributable to a proton transfer is detected. The hydride is formed entirely through reactions of Co(II) complexes and (bpy)H· radicals.

The Co(I) species were produced[7-9] by pulse radiolysis of aqueous CoSO$_4$-2,2′-bipyridine mixtures (2-MeV electrons produced by a Van de Graaff accelerator;[10] formate, 2-propanol, or ethanol as OH scavenger). The cobalt(I) complexes initially present are determined by the distribution of Co(bpy)$_n$$^{2+}$ species as all are reduced rapidly by e_{aq}^-,[7] but equilibrium is rapidly attained through sequences of electron-transfer reactions between the Co(I) ($\sim 10^{-6}$ M) and Co(II) ($>10^{-4}$ M) species, e.g.,

$$\mathrm{Co(bpy)_2^+ + Co(bpy)_3^{2+} \rightleftharpoons Co(bpy)_2^{2+} + Co(bpy)_3^+} \tag{1}$$

$K_1 = 200$, $k_1 = 2 \times 10^9$ M^{-1} s^{-1}.[8] (Coordinated water molecules are omitted.) In the experiments considered here Co(bpy)$_3$$^+$ is the dominant form (>75%) of Co(I) present after the equilibration (<0.1 ms).

The equilibration of Co(bpy)$_3$$^+$ with acid to form the hydride complex occurs on the 0.1-0.001-s time scale and was followed by monitoring the bleaching of the 610-nm Co(bpy)$_3$$^+$ absorption. The net equilibration reaction is given by eq 2 and analysis of the

$$\mathrm{Co(bpy)_3^+ + H_3O^+ \rightleftharpoons Co(bpy)_2(H_2O)H^{2+} + bpy} \tag{2}$$

equilibrium absorbance values that are presented in Figure 1 gives $K_2 = 1.0$.[11] The rate of approach to equilibrium is first order in [Co(I)] and increases with [H$^+$]. Plots of k_{obsd} vs [H$^+$] at different [bpy] levels are also presented in Figure 1. Consistent with the stoichiometry (eq 2), intercepts increase with the con-

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$$\mathrm{Co(bpy)_2^+ + H_3O^+ \rightleftharpoons Co(bpy)_2(H_2O)H^{2+}}$$