Thermodynamic Fitness of Molybdenum(IV,VI) Complexes for Oxygen Atom Transfer Reactions, Including Those with Enzymatic Substrates

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Abstract: The oxygen (oxo) atom transfer hypothesis for the enzymatic oxidation/reduction of generalized substrate X/XO by the molybdenum oxotransferases (hydroxylases) has been further pursued by an investigation of the reactions of the Mo(VI) and Mo(IV) complexes MoO_2(L-NS_2) and MoO(L-NS_2)(DMF) (L-NS_2 = 2,6-bis(2,2-diphenyl-2-thioethyl)pyridinate(2-)), respectively, in DMF solution. Because of steric hindrance, these molecules execute oxo transfer without formation of a binuclear μ-oxo Mo(V) species. MoO(L-NS_2)(DMF) was previously found to reduce quantitatively a variety of sulfoxides, including at least one enzyme substrate. Here this complex is shown to reduce, with formation of MoO_2(L-NS_2), a series of *N*-oxides including those of pyridine, nicotinamide, adenine, and tribenzylamine, which are enzyme substrates or pseudosubstrates. Ph_3AsO is also reduced by this complex. A previous demonstration of the catalytic partial transfer of ^{18}O in nicotinamide *N*-oxide to uric acid by xanthine oxidase is interpreted as supporting the oxo transfer hypothesis. MoO_2(L-NS_2) is reduced by PhSH to MoO(L-NS_2)(DMF), further indicating the feasibility of thiols as physiological electron donors. A thermodynamic criterion for the ability of a $Mo^{IV}O$ or $Mo^{VI}O_2$ complex to reduce or oxidize substrate has been developed on the basis of ΔH values for the reaction $X + {}^1/_2O_2 \rightarrow XO$. MoO(L-$NS_2$)(DMF) (**21**)/$MoO_2$(L-$NS_2$) (**22**) and $MoO(S_2CNEt_2)_2$ (**20**)/$MoO_2(S_2CNEt_2)_2$ (**19**) are positioned in the reaction series so as to oxidize or reduce (as appropriate) all enzymatic substrates for which thermodynamic data are available. Intermetal oxo transfer reactions of the type $MoOL_n + MoO_2L'_n \rightarrow MoO_2L_n + MoOL'_n$ were investigated with **19**-**22** and the Schiff base complexes MoO(ssp)(DMF) (**18**), MoO_2(ssp)(DMF) (**15**), MoO(sap)(DMF) (**17**), and MoO_2(sap)(DMF) (**13**). These demonstrate the thermodynamic oxo donor order to be S_4 (**19**) > NS_2 (**22**) > ONS (**15**) > O_2N (**13**); the oxo acceptor order is the reverse. All $Mo^{IV}O$ complexes in the set are able to reduce Me_2SO to Me_2S. This is a necessary but not sufficient thermodynamic criterion for a functional oxo transferase site model. Under the oxo transfer hypothesis, a sufficient model requires access to both the $Mo^{IV}O$ and $Mo^{VI}O_2$ states at real or effective potentials that can be reached with physiological reductants such that catalysis can be sustained. Evidence is presented that anionic sulfur ligands significantly modulate potentials to values appropriate for catalysis, and that tungsten, having more negative potentials than molybdenum in analogous complexes, is unsuitable for this purpose.

Recent research in this laboratory[2-6] has been directed toward the development of analogue reaction systems for the molybdenum hydroxylases.[7-9] Without mechanistic implication we have termed this class of enzymes, which includes inter alia xanthine oxidase/dehydrogenase, aldehyde oxidase, sulfite oxidase, and nitrate reductase, "oxo-transferases". We have adopted as a working hypothesis that oxygen atom transfer reaction 1 for oxidation/reduction of generalized substrate X/XO applies to enzymatic processes, some of which require no exogeneous reactant other than the substrate. This reaction, which is a two-electron process formally equivalent to $X + H_2O \rightleftharpoons XO + 2H^+ + 2e^-$, has been executed in DMF solution in the form of reaction 2, which is illustrated in Figure 1.

$$Mo^{VI}O_2L_n + X \rightleftharpoons MoO^{IV}L_n + XO \quad (1)$$

$$MoO_2(L\text{-}NS_2) + X \rightleftharpoons MoO(L\text{-}NS_2)(DMF) + XO \quad (2)$$

The *gem*-diphenyl groups of the L-NS_2 ligand provide steric encumbrance sufficient to prevent the formation of a μ-oxo Mo(V) "dimer", a common reaction of Mo(VI,IV) species. On the assumption of competitive rates, dimer formation would prevent even stoichiometric conversion of substrate to product. The ligand atom sets MoO_2S_2N and $MoOS_2N$ are consistent with the minimal coordination units of several oxo-transferases as deduced from their Mo EXAFS.[10,11] As will be seen, the presence of thiolate sulfur atoms is significant in facilitating oxo-transfer reactions. Prior to this work, reaction 2 had been accomplished only with tertiary phosphines as reductants and sulfoxides as oxidants.[5] The latter include *d*-biotin *d*-(*S*-oxide), the natural substrate of *d*-biotin *d*-(*S*-oxide) reductase,[12] and Me_2SO and methionine *S*-oxides (N-substituted), all of which are reduced to the corresponding sulfides by crude extracts containing enzymes[13] requiring the molybdenum cofactor.[14,15] Consequently, reaction system 2 has the attractive property of executing stoichiometric conversions of actual enzyme substrates by using Mo complexes that, at least at this stage, are reasonable structural representations of catalytic sites. It has further been shown that Me_2SO can be catalytically reduced in system 2 containing excess Ph_3P.[5]

In this investigation, the reactivity of system 2 has been extended to other enzymatic substrates and pseudosubstrates XO. It is demonstrated that thiols can reduce Mo(VI) to Mo(IV), providing a plausible electron donor in enzymatic reductions of XO. Additionally, it is shown that Mo(IV) complexes of system 2 are inherently thermodynamically fit to reduce by oxo-transfer reactions certain oxidized substrates of oxo-transferases.

Experimental Section

Preparation of Compounds. Bis(*p*-fluorophenyl)sulfide and -sulfoxide,[16] tribenzylamine *N*-oxide,[17] *N*,*N*-dimethylaniline *N*-oxide,[17] ade-

(1) (a) Harvard University. (b) Present address: Department of Chemistry, Johns Hopkins University, Baltimore, MD 21218.
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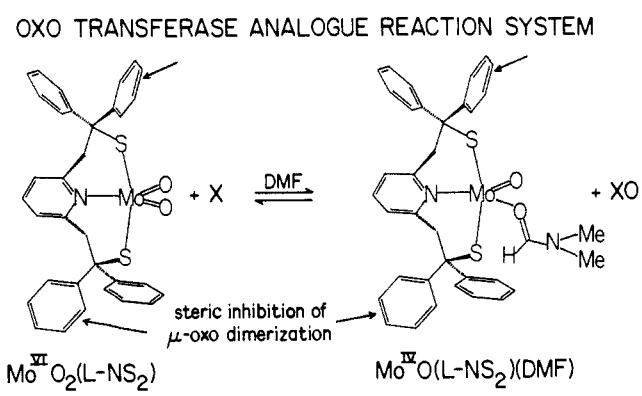
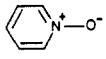
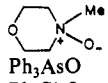
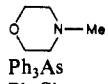
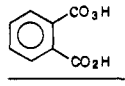
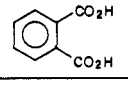


Figure 1. Schematic depiction of generalized substrate oxidation and reduction in oxo transferase analogue reaction systems utilizing sterically hindered Mo(VI,IV) complexes in DMF solution. L-NS_2 = 2,6-bis-(2,2-diphenyl-2-thioethyl)pyridinate(2−).

Table I. Oxo Transfer Reactions of $MoO_2(S_2CNR_2)_2$ + X and $MoO(S_2CNR_2)_2$ + XO

substrate (X/XO)	product (XO/X)	ref
R_3P (R = Ph)	R_3PO	24–30
($R_3 = Ph_{3-n}Et_n$, n = 1–3)	R_3PO	26, 30
PhCHO (+$h\nu$)	$PhCO_2H$	31
Me_2SO	Me_2S	30, 32–34
		32, 34
		30
Ph_3AsO	Ph_3As	34
Ph_3SbO	Ph_3Sb	34
t-$BuONO_2$	t-BuONO	32
PhN(O)=NPh	PhN=NPh	32
		28

nine-1-oxide,[18] triphenylarsine oxide,[19] monoperphthalic acid,[20] MoO(ssp)(DMF),[21] MoO(sap)(DMF),[21] MoO_2(ssp),[22,23] MoO_2(sap),[22,23] MoO(L-NS_2)(DMF),[4] and MoO_2(L-NS_2)[4] were prepared by literature procedures.

Reactions. All reactions were carried out in DMF (Burdick and Jackson) which had been stored over 4 Å molecular sieves and degassed prior to use. Solutions were prepared under a pure dinitrogen atmosphere. Reactions were monitored spectrophotometrically with Cary 219 or 2390 instrument, by ^{19}F NMR spectroscopy at 253 MHz, or by ^1H NMR spectroscopy at 500 MHz. Chemical shifts refer to external CCl_3F or internal Me_4Si references. A number of reaction products were identified by TLC with use of an ethyl acetate or ethyl acetate/hexane mobile phase. In all cases product was readily distinguished from reactant.

Results and Discussion

Prior to this work, nearly all of the relatively small number of oxo-transfer reactions 1 of Mo species had been accomplished with the dithiocarbamate complexes $MoO_2(S_2CNR_2)_2$ and MoO-$(S_2CNR_2)_2$.[24–34] The substrates and products in these reactions,

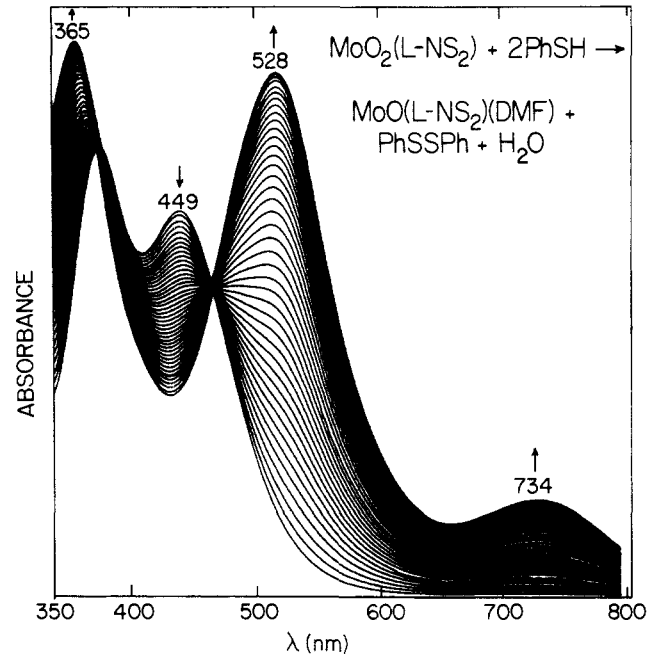


Figure 2. The reduction of MoO_2(L-NS_2) (17.5 mM) by PhSH (42 mM) in DMF at ~25 °C. In this and subsequent spectra λ_{max} values are given; arrows indicate increase (↑) or decrease (↓) of absorbance with time. These spectra were recorded over a period of 57 h.

most of which are relevant to the present study, are listed in Table I. In these cases, oxo transfer is accompanied by the structural change square pyramidal (Mo(IV)) ⇌ distorted cis-octahedral (Mo(VI)).[35] These complexes exist in labile equilibrium with the Mo(V) μ-oxo dimer $Mo_2O_3(S_2CNR_2)_4$[26,36] until substrate consumes the initial Mo reactant. The first example of a Mo-mediated oxo-transfer process was the oxidation of Ph_3P to Ph_3PO with $MoO_2(S_2CNR_2)_2$ reported by Barral et al.[24] A catalytic cycle was achieved in the presence of dioxygen, which oxidized MoO-$(S_2CNR_2)_2$ to the reactive Mo(VI) complex. Thereafter, Mitchell and Scarle[32] demonstrated oxidation with other reactants, including Me_2SO and pyridine N-oxide.[37] More recently, other catalytic cycles based on sulfur-ligated Mo(VI,IV) complexes have been developed which include at least one oxo-transfer reaction as part of the cycle.[38]

Oxo-Transfer Reactions of MoO_2(L-NS_2) and MoO(L-

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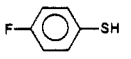
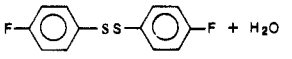
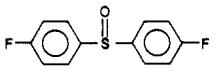
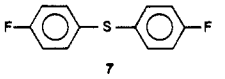
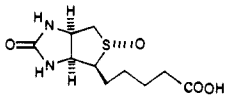
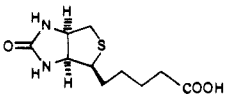
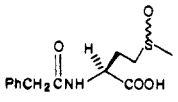
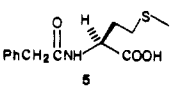
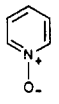
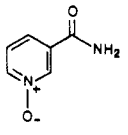
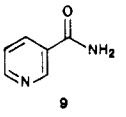
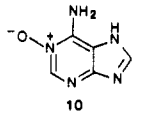
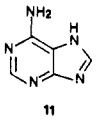
Table II. Oxo Transfer Reactions of $MoO_2(L\text{-}NS_2)$ + X and $MoO(L\text{-}NS_2)(DMF)$ + XO in DMF Solution at ~25 °C

substrate (X,XO)	$[X,XO]/[Mo^{VI,IV}]^a$	product (^{XO},X)	ident.	abs ratio[f]
Ph_3P^b	1.0–10	Ph_3PO	^{31}P NMR	0.94
PhSH	2.0–2.4	PhSSPh + H_2O	*d*	1.06
	5.3	 1	^{19}F NMR[e]	
R_2SO (R = Me, Ph)[b]	1.0–200	R_2S	chemical[g]	1.18
 6	2.7	 7	^{19}F NMR[e]	1.18
 2	45	 3	TLC	1.17
 4	~40	 5	TLC	1.16
	1.3		TLC	1.22
 8	1.0	 9	TLC	1.16
 10	1.0	 11	TLC	1.18
$(PhCH_2)_3{}^+N\text{-}O^-$ (0 °C)	1.4	$(PhCH_2)_3N$	TLC	1.28
Ph_3AsO	1.1	Ph_3As	TLC	1.14

[a] Typically, [Mo] = 1–40 mM. [b] Reference 5. [c] Two diastereomers. [d] Analogy assumed with *p*-FC_6H_4SH reaction. [e] ^{19}F chemical shifts (ppm vs. CCl_3F): *p*-FC_6H_4SH, −114.6; $(p\text{-}FC_6H_4S)_2$, −110.2; $(p\text{-}FC_6H_4)_2SO$, −105.7; $(p\text{-}FC_6H_4)_2S$, −110.9. [f] Substrate reduction: A_{385}/A_{449} = 1.13 for $MoO_2(L\text{-}NS_2)$. Substrate oxidation: A_{365}/A_{528} = 0.94 for $MoO(L\text{-}NS_2)(DMF)$. [g] Reference 5 and: Szmant, H. E.; Cox, O. *J. Org. Chem.* **1966**, *31*, 1595.

$NS_2)(DMF)$. Reactants and products in reactions 2 conducted in DMF are collected in Table II, which includes all systems affording well-defined reactions in this and our prior[2,3,5] investigations. Substrate products were identified by the indicated methods. The integrity of the product Mo complex was established from absorbance ratios compared to those of the pure complexes. Spectrophotometric quantitation of the Mo product showed conversions of ≥90%, unless noted otherwise. In some cases rather large sulfoxide:$MoO(L\text{-}NS_2)(DMF)$ ratios were used for the purpose of kinetics measurements.[5] However, from Mo product yields with other sulfoxides at a ~1:1 mol ratio, it is clear that the reactions are essentially quantitative. The reaction systems of Table II differ from those of Table I in that there is no indication of the formation of a μ-oxo Mo(V) dimer, and the structural change is presumably that in Figure 1. Here the distorted trigonal-bipyramidal stereochemistry established in $MoO_2(L\text{-}NS_2)$[4] is assumed to be retained in the Mo(IV) complex, which binds the oxo donor in the initial event leading to substrate reduction. Substrate reactions and their biological relevance are next considered. As will be seen, certain reactants in Table II were chosen because they are substrates of oxo-transferases.

(a) Mo(VI) → Mo(IV) Reductions. The quantitative reaction 3 has previously been demonstrated.[5] It has now been established that arenethiols will slowly reduce Mo(VI) to Mo(IV) in reaction 4, whose stoichiometry follows from several observations. The

$$MoO_2(L\text{-}NS_2) + Ph_3P \rightarrow MoO(L\text{-}NS_2)(DMF) + Ph_3PO \quad (3)$$

$$MoO_2(L\text{-}NS_2) + 2RSH \rightarrow MoO(L\text{-}NS_2)(DMF) + RSSR + H_2O \quad (4)$$

disulfide $(p\text{-}FC_6H_4S)_2$ (**1**) was detected in the ^{19}F NMR spectrum of a reaction system with the reactant mole ratio *p*-FC_6H_4SH:$MoO_2(L\text{-}NS_2)$ = 5.3:1. The time course of the system PhSH:$MoO_2(L\text{-}NS_2)$ = 2.4:1 as monitored spectrophotometrically in Figure 2 clearly shows decay of the reactant bands at 385 and 449 nm and buildup of the characteristic spectrum of $MoO(L\text{-}NS_2)(DMF)$ with λ_{max} = 365, 528, and 734 nm. The final absorption ratio A_{365}/A_{528} = 1.06 differs somewhat from the value of pure $MoO(L\text{-}NS_2)(DMF)$ due to slight precipitation of the latter over the relatively long course (57 h) of the reaction. The apparent spectrophotometric yield is 84%. Previously, $MoO_2(S_2CNEt_2)_2$ had been reduced to $MoO(S_2CNEt_2)_2$ with PhSH in good yield on a preparative scale.[39]

(b) Oxo Transfer from Substrate. This reaction type was accomplished primarily with two types of oxo donors: sulfoxides and *N*-oxides. The reductions of simple sulfoxides to sulfides, *d*-biotin *d*-(*S*-oxide) (**2**) to *d*-biotin (**3**), and the diastereomeric N-substituted methionine *S*-oxides **4** to the sulfides **5** in reaction 5 have been demonstrated.[5] The stoichiometric reduction of the fluorinated sulfoxide **6** to the sulfide **7** has been shown in this work by ^{19}F NMR.

$$MoO(L\text{-}NS_2)(DMF) + R_2SO \rightarrow MoO_2(L\text{-}NS_2) + R_2S \quad (5)$$

The oxo-transfer propensities of a variety of *N*-oxides, collectively designated as R′NO in reaction 6, have been examined. The

(39) (a) McDonald, J. W.; Corbin, J. L.; Newton, W. E. *Inorg. Chem.* **1976**, *15*, 2056. (b) For related reductions by thiols cf.: Jowitt, R. N.; Mitchell, P. C. H. *J. Chem. Soc. A* **1969**, 2632; Pickett, C.; Kumar, S.; Vella, P. A.; Zubieta, J. *Inorg. Chem.* **1982**, *21*, 908.

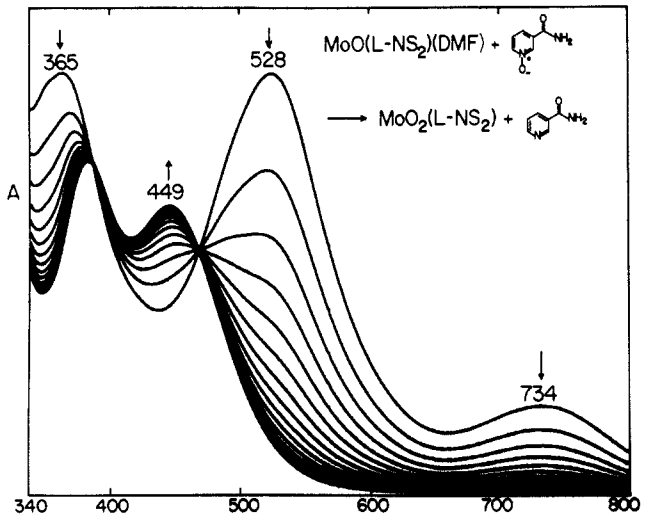


Figure 3. The oxidation of $MoO(L\text{-}NS_2)(DMF)$ (1.4 mM) by 1.0 equiv of nicotinamide *N*-oxide in DMF at ~25 °C; spectra were recorded over a period of 50 min.

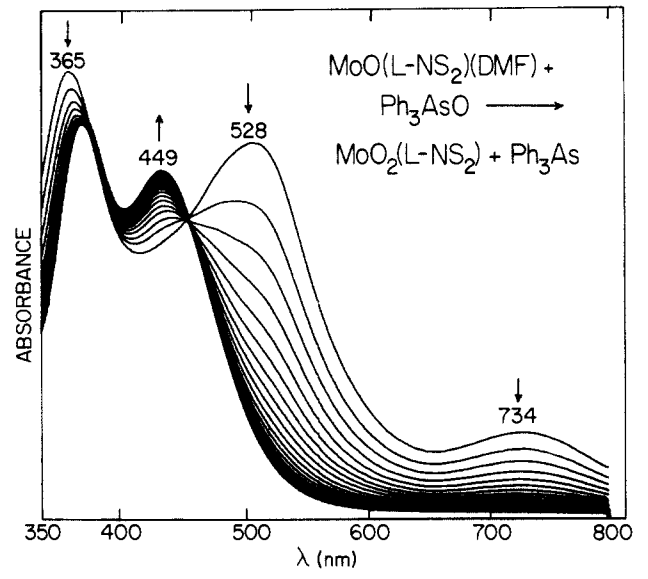


Figure 4. The oxidation of $MoO(L\text{-}NS_2)(DMF)$ (0.85 mM) by 1.1 equiv of Ph_3AsO in DMF at ~25 °C; spectra were recorded over a period of 45 min.

transformations pyridine *N*-oxide/pyridine, nicotinamide *N*-oxide (**8**)/nicotinamide (**9**), adenine 1-oxide (**10**)/adenine (**11**), and tribenzylamine *N*-oxide/tribenzylamine proceeded rapidly and in high yield. The reduction **8** → **9** is typical and is spectrophotometrically depicted in Figure 3. The tight isosbestic points at 386 and 473 nm indicate only two absorbing species. The final spectrum, with bands at 385 and 449 nm, is identical with that of $MoO_2(L\text{-}NS_2)$. The reduction of Ph_3AsO to Ph_3As in reaction 7, whose time course is shown in Figure 4, proceeds in a similarly clean fashion.

$$MoO(L\text{-}NS_2)(DMF) + R'NO \rightarrow MoO_2(L\text{-}NS_2) + R'N \quad (6)$$

$$MoO(L\text{-}NS_2)(DMF) + Ph_3AsO \rightarrow MoO_2(L\text{-}NS_2) + Ph_3As \quad (7)$$

Certain compounds, which are effective oxo-transfer reagents in other systems, did not afford clean reactions here. Treatment of $MoO(L\text{-}NS_2)(DMF)$ with 1 equiv of Me_3NO, *N,N'*-dimethylaniline *N*-oxide, *m*-chloroperbenzoic acid, and monoperphthalic acid in DMF solution at ambient temperature resulted in rapid bleaching. A similar but slower reaction of PhIO with $MoO(L\text{-}NS_2)(DMF)$ was observed. The latter reagent has proven generally useful for the production of M=O groups in a variety of M = Cr, Mn, and Fe systems,[40] and *p*-$NCC_6H_4NMe_2O$ has been employed similarly with Mn and Fe porphyrins.[41] Monoperphthalic acid has been reported to oxidize $MoO(S_2CNEt_2)_2$ to $MoO_2(S_2CNEt_2)_2$ in 1,2-dichloroethane solution (Table I). These observations indicate one deficiency of $MoO(L\text{-}NS_2)(DMF)$ as an enzyme site model, viz., a lack of robustness in reactions with the stronger oxidants. Note the existence of trimethylamine *N*-oxide reductase.[42,43] While its substrate decomposes $MoO(L\text{-}NS_2)(DMF)$, the ability of this complex to reduce a tertiary amine *N*-oxide is satisfactorily demonstrated by use of the less reactive $(PhCH_2)_3NO$ at 0 °C. In this case the final absorbance ratio $A_{385}/A_{449} = 1.28$ is slightly higher than that of the pure Mo(VI) complex (1.13), and the apparent spectrophotometric yield is 90%.

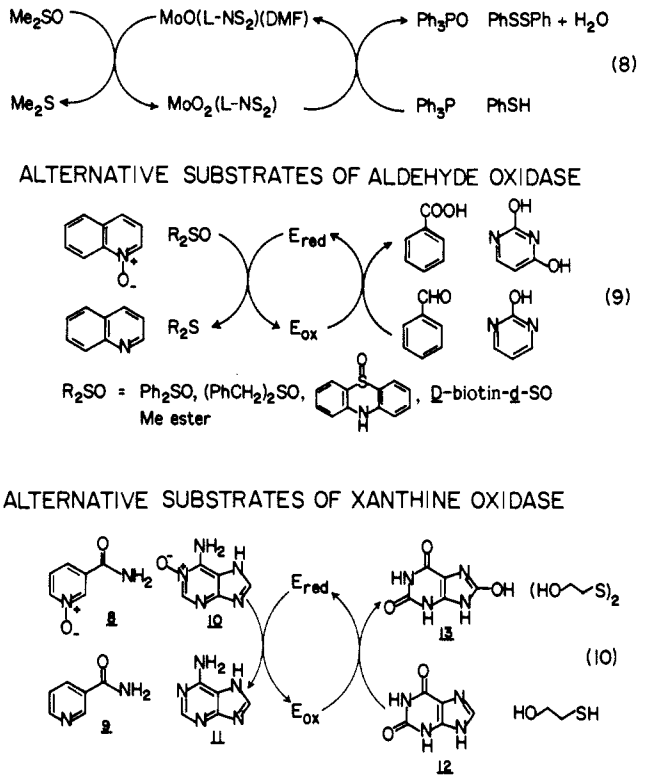


Figure 5. Catalytic cycles for the reduction of sulfoxides and *N*-oxides. Top: reduction of Me_2SO to Me_2S in an analogue system utilizing Ph_3P or PhSH as the reductant. Middle: reduction of sulfoxides and quinoline *N*-oxide by liver aldehyde oxidase with benzaldehyde or 2-hydroxypyrimidine as the electron donor. Bottom: reduction of adenine 1-oxide and nicotinamide *N*-oxide by xanthine oxidase with xanthine or 2-hydroxyethanethiol as the electron donor. E = enzyme.

Biological Relevance of Oxo-Transfer Reactions. The significance of generalized reactions 5 and 6 in the biological context is that they describe processes now known to be catalyzed by Mo-containing (equivalently, Mo cofactor-dependent) enzymes. As will be illustrated, certain of these enzymes enjoy rather broad substrate selectivity, which includes several molecules XO in Table II.

(a) With Sulfoxides. In our initial reports of reaction 5,[2,3,5] we emphasized the significance of the reduction of **2** because it is the substrate of *d*-biotin *d*-(*S*-oxide) reductase.[12] By coupling reactions 3 and 5, the catalytic cycle 8 in Figure 5 was developed and provided the basis of a proposed cycle for enzymatic sulfoxide

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reduction.[5] At that time, however, $MoO_2(L\text{-}NS_2)$ had been reduced cleanly only with tertiary phosphines. Given the demonstrations of sulfoxide reduction by rat liver cytosolic enzymes[44] and yeast methionine *S*-oxide reductase[45] in the presence of thioredoxin,[46] which provides electrons by the reaction 2Cys·SH $\rightleftharpoons$ Cys·SS·Cys + $2H^+$ + $2e^-$, thiols are suitable physiological electron donors. The occurrence of reaction 4, in which Mo(VI) is reduced to Mo(IV) by a thiol, is an appropriate simulation of biological reduction. Further, with use of *p*-FC_6H_4SH as the reductant and **6** as the substrate in the presence of $MoO(L\text{-}NS_2)(DMF)$, formation of the sulfide **7** and disulfide **1** in equal amounts has been established by ^{19}F NMR. There is no reaction between the thiol and **6** in the absence of the Mo(IV) complex. These results will be described in full elsewhere.[6]

Recent work has shown that guinea pig liver aldehyde oxidase is a broad spectrum enzyme whose substrates include a number of sulfoxides.[47] This oxidase has been proven to be a molybdoenzyme with a Mo and Fe content[47a] the same as that of rabbit liver aldehyde oxidase. Because of its broad substrate specificity and lack of knowledge of true physiological function, aldehyde oxidase is considered to have been misnamed.[48] In one interesting manipulation of alternative substrates (Figure 5), benzaldehyde (or 2-hydroxypyrimidine) acts as an electron donor in cycle 9 for the catalytic reduction of certain sulfoxides to sulfides. Oxidation of the electron donor results in reduction of the enzyme such that it adopts the function of a sulfoxide reductase. A modicum of selectivity is apparent since the enzyme system does not reduce Me_2SO, neither of the two diastereomeric *d*-biotin *S*-oxides, and one of the two methyl esters of these *S*-oxides.[47b] On the basis of these results for the guinea pig enzyme, it is probable that the sulfoxide reductase activity in rat liver cytosol[44] arises from aldehyde or xanthine oxidase.

(b) With *N*-Oxides. These compounds are alternative substrates for enzymes originally recognized for another activity. Thus in 1966 it was first shown that liver xanthine oxidase in the presence of the natural substrate xanthine (**12**), which was oxidized to uric acid (**13**), or a thiol as an electron donor, developed nicotinamide *N*-oxide (**8**) reductase activity.[49] Subsequently, the reduction of purine *N*-oxides to purines was demonstrated with milk xanthine oxidase by using as electron donors a thiol or xanthine, among others.[50] Adenine 1-oxide (**10**) was an active substrate, being reduced to adenine. The reductions of **8** and **10** are depicted in the catalytic cycles 10 in Figure 5. Thereafter, reductions of the same and other heterocyclic *N*-oxides[43,47b,51] and of tertiary amine *N*-oxides[52] by liver aldehyde oxidase have been reported. One reduction system for quinoline *N*-oxide,[47b] with 2-hydroxypyrimidine as the electron donor, is represented in cycle 9. The demonstrated catalytic partial transfer of ^{18}O from **8** to **13** via **12** by xanthine oxidase[49] provides one instance of a direct oxo transfer enzymatic pathway.

The results in Table II further establish that the complexes in Figure 1 do in fact constitute an oxo-transferase analogue reaction system, at least in respect of the reduction of sulfoxides and *N*-oxides. It is likely that these reactions can be extended to a large number of other compounds of these substrate types. Some of those examined here (Me_2SO, Ph_2SO, **2**, **8**, **10**) are actual enzyme substrates while others (**4**, C_5H_4NO, $(PhCH_2)_3NO$) are "pseudosubstrates". Reactions of $MoO(L\text{-}NS_2)(DMF)$ with these species provide presumptive evidence that enzymatic reactions proceed in the same fashion, viz., by simple oxo atom transfer between Mo(IV) and substrate, without the intervention of another reactant. The turnover of alternative substrates by the enzymes in Figure 5 is readily interpreted in these terms. The natural substrate or another electron donor reduces the enzyme to the Mo(IV) state, which then reduces the alternative substrate by oxo transfer and becomes oxidized to Mo(VI). In this picture any EPR-active enzyme state would appear only in the enzyme reduction step. Substrate transformation itself proceeds by the two-electron event that is reaction 1.

Having demonstrated biologically relevant examples of reaction 2, we next turn to considerations of the thermodynamic fitness of $MoO_2(L\text{-}NS_2)$ and $MoO(L\text{-}NS_2)(DMF)$ in real and potential oxo-transfer reactions.

Thermodynamic Fitness. (a) Enthalpy Criteria. In seeking a thermodynamic basis for the occurrence of reaction 2, we utilize an enthalpy reaction series composed of measured and computed ΔH values for the generalized oxidation reactions 11, 12, and 13. This reduces oxo-transfer reaction enthalpies to a common scale. Under the condition $\Delta H_{11} > \Delta H_{Mo} > \Delta H_{13}$, reactions 14 and 15 are spontaneous by the criterion of negative ΔH. Values of ΔH for the oxidation of a variety of species, including all enzyme substrates for which data are available, are collected in Table III.[28,53-55] The results clearly do not constitute a precisely com-

$$X + {}^1/_2O_2(g) \rightarrow XO \qquad \Delta H_{11} \tag{11}$$

$$Mo^{IV}OL_n + {}^1/_2O_2(g) \rightarrow Mo^{VI}O_2L_n \qquad \Delta H_{Mo} \tag{12}$$

$$X' + {}^1/_2O_2(g) \rightarrow X'O \qquad \Delta H_{13} \tag{13}$$

$$MoOL_n + XO \rightarrow MoO_2L_n + X \qquad \Delta H_{14} = \Delta H_{Mo} - \Delta H_{11} \tag{14}$$

$$MoO_2L_n + X' \rightarrow MoOL_n + X'O \qquad \Delta H_{15} = \Delta H_{13} - \Delta H_{Mo} \tag{15}$$

Table III. Thermodynamic Data[a] for the Reactions $X + {}^1/_2O_2(g) \rightarrow XO$

X[b]	XO[b]	ΔH (kcal/mol)	ΔG^i (kcal/mol)
o-$C_6H_4(CO_2H)_2$	*o*-$C_6H_4(CO_2H)(CO_3H)$	+28[c]	
$N_2(g)$	$N_2O(g)$	+20	
t-BuOH	*t*-BuOOH	+15[e,h]	
$S_2O_3^{2-}(aq)$	$S_2O_4^{2-}(aq)$	+12	
$ClO_2^-(aq)$	$ClO_3^-(aq)$	−8	−5
$NO_2^-(aq)$	$NO_3^-(aq)$	−25 (−32[c])	−18
$C_2H_4(g)$	$C_2H_4O(g)$	−25	−19
$Me_2S(g)$	$Me_2SO(g)$	−27	−21
$CH_4(g)$	$CH_3OH(g)$	−30	−27
Ph_3As	Ph_3AsO	>−35[d] (−44[d,e,h])	
$MoO(S_2CNEt_2)_2$	$MoO_2(S_2CNEt_2)_2$	−35[c]	
$MoO(L\text{-}NS_2)(DMF)$	$MoO_2(L\text{-}NS_2)$	d	
MeNC(g)	MeNCO(g)	−50	
$Me_2SO(g)$	$Me_2SO_2(g)$	−52	−46
2MeSH(g)	MeSSMe(g) + $H_2O(g)$	−53	−47
2PhSH(g)	PhSSPh(g) + $H_2O(g)$	−54[f] (−50[g])	
$H_2(g)$	$H_2O(g)$	−58	−55
MeCHO(g)	$MeCO_2H(g)$	−64	−59
$HCO_2^-(aq)$	$HCO_3^-(aq)$	−64	−56
$SO_3^{2-}(aq)$	$SO_4^{2-}(aq)$	−65 (−64[c])	−62
$Ph_3P(g)$	$Ph_3PO(g)$	−67 (−67[c])	
CO(g)	$CO_2(g)$	−68	−62
n-$Bu_3P(g)$	*n*-$Bu_3PO(g)$	−80[f]	

[a] Data from ref 53 unless otherwise noted. [b] Enzyme substrates in boldface. [c] Reference 28; 1,2-dichloroethane solution. [d] See text. [e] Reference 55. [f] Reference 54. [g] 1,2-Dichloroethane solution: Watt, G. D., private communication. [h] Benzene solution. [i] $G_f(XO) - G_f(X)$ at 298 K.

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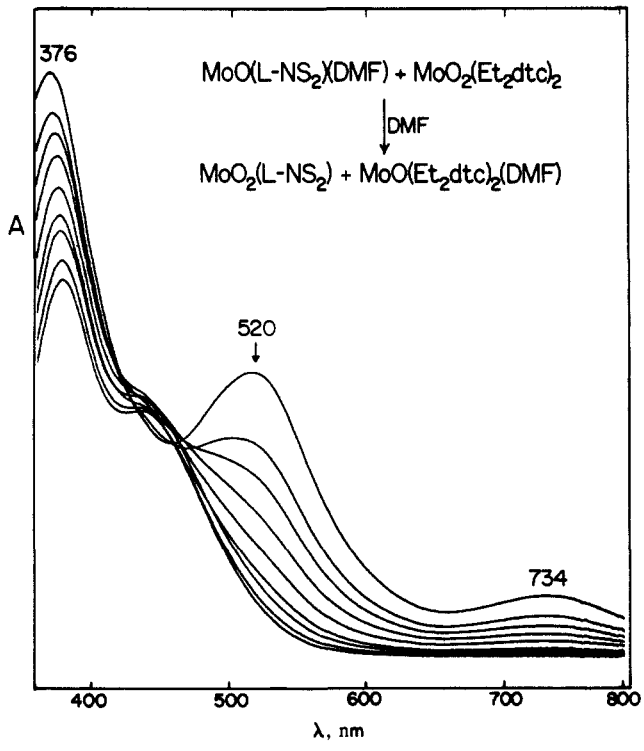

Figure 6. The reaction of $MoO(L\text{-}NS_2)(DMF)$ (0.11 mM) with 1.5 equiv of $MoO_2(S_2CNEt_2)_2$ in DMF at ~25 °C; spectra were recorded over a period of 45 min. The trace with the lowest absorbance near 400 nm and after 500 nm is the final spectrum.

parable data set owing to differences in physical state and in solvent. Also, no account is taken of the (sometimes substantial) estimated uncertainties in the values. It would of course be more accurate to employ ΔG values to decide the spontaneity of reactions 14 and 15. To the extent that ΔG data are available for reactions 11 and 13, their order parallels that of ΔH. Further, the data show that $|\Delta H| > |T\Delta S|$, with the last term amounting to only 3–8 kcal/mol. With these points noted, Table III provides a thermochemical series with a utility analogous to that of a series of half-reactions and their standard potentials. Reactions 14 and 15 may be restated as follows: Mo(IV) can reduce to X any species XO which occurs in a reaction with a more positive ΔH, and Mo(VI) can oxidize to XO any species X which occurs in a reaction with a less positive ΔH. In an important contribution, Watt et al.[28] have provided a number of ΔH values, including that for reaction 16 in 1,2-dichloroethane solution.

$$MoO(S_2CNEt_2)_2 + \tfrac{1}{2}O_2(g) \rightarrow MoO_2(S_2CNEt_2)_2 \qquad \Delta H = -35.0 \pm 3.2 \text{ kcal/mol} \qquad (16)$$

The enthalpy change for the oxidation of $MoO(L\text{-}NS_2)(DMF)$, reaction 17, is not available. However, this species may still be interleaved in the series of Table III on the basis of several observations. The spectrophotometric results in Figure 6 establish that reaction 18 proceeds essentially completely to the right. The final spectrum lacks the intense visible bands of $MoO(L\text{-}NS_2)(DMF)$ and is completely consistent with a mixture of $MoO_2(S_2CNEt_2)_2$, $MoO_2(L\text{-}NS_2)$, and $MoO(S_2CNEt_2)_2$. At these concentrations very little of the μ-oxo species $Mo_2O_3(S_2CNEt_2)_4$ is expected to form,[26,36] and the weak absorption of $MoO(S_2CNEt_2)_2$ (λ_{max} (ϵ_M) 508 (670) nm[56]) contributes little to the final spectrum. Reaction 18 and others that follow are among the few examples of nondegenerate intermetal oxo transfer.[57] The occurrence of this reaction shows that ΔG, and presumably ΔH, for the oxidation of $MoO(L\text{-}NS_2)(DMF)$ is less positive than that of $MoO(S_2CNEt_2)_2$. Because $MoO_2(L\text{-}NS_2)$ is reduced by PhSH, ΔH of reaction 17 is in the approximate interval of ca. −35 to −55 kcal/mol. An attempt to narrow this range by demonstration of the oxidation of Ph_3As with $MoO_2(L\text{-}NS_2)$ failed because, as already observed, the reverse reaction 7 occurs instead. Further, Ph_3AsO is also reduced by $MoO(S_2CNEt_2)_2$ (Table I). The enthalpy of oxidation of Ph_3As in Table III was obtained indirectly by utilizing thermochemical data for its oxidation with *t*-BuOOH.[55] Either ΔH = −44 kcal/mol (benzene solution) is grossly incorrect, which seems unlikely, or it is not known with sufficient accuracy to make it of predictive value in the present context. The opposite directions of reactions 3 and 7 appear to be enthalpic in origin, given that the P–O bond strength in Ph_3PO(g) exceeds the As–O bond strength in Ph_3AsO(g) by ca. 27 kcal/mol.[55]

$$MoO(L\text{-}NS_2)(DMF) + \tfrac{1}{2}O_2(g) \rightarrow MoO_2(L\text{-}NS_2) \qquad (17)$$

$$MoO(L\text{-}NS_2)(DMF) + MoO_2(S_2CNEt_2)_2 \rightleftharpoons MoO_2(L\text{-}NS_2) + MoO(S_2CNEt_2)_2 \qquad (18)$$

The significant aspect of the enthalpy series in Table III is that *the Mo(IV,VI) complexes of reactions 16 and 17 are positioned so as to oxidize or reduce spontaneously all enzymatic substrates for which thermochemical data are available.* The earlier thermochemical studies of Watt et al.[28] lead to an analogous conclusion for dithiocarbamate complexes and a smaller group of substrates (NO_3^-, SO_3^{2-}, MeCHO), all in the same solvent (1,2-dichloroethane). This is a thermodynamically permissive situation (with the preceding qualifications) and does not take account of kinetics or alternative reactions. For example, $MoO_2(L\text{-}NS_2)$ does not oxidize MeNC, Me_2SO, and CO at any appreciable rate. $MoO(L\text{-}NS_2)(DMF)$ is oxidized to $MoO_2(L\text{-}NS_2)$ by nitrate but the reaction is accompanied by bleaching,[5] indicating destruction of the Mo chromophores. While further studies of reaction 2 with various substrates X/XO remain, it is evident that the complexes in Figure 1 possess an extent of thermodynamic fitness, or competence, for the oxidation or reduction of biological substrates by an oxo-transfer pathway. Next we consider certain factors which render these molecules "fit" in this respect. A rather complete list of oxo-transferases and their substrates is available elsewhere.[58]

(b) Donor Atom Effects. Collected in Table IV are differences in redox potentials for pairs of Mo complexes which are identical except for the substitution of a negative oxygen donor ligand for sulfide or thiolate.[4,22,23,59–61] The potentials derive from cyclic voltammetry in nonaqueous solvents and include both peak potentials for irreversible reductions and $E_{1/2}$ values for reversible reactions. When it occurs, irreversibility is found with both members of a given pair and is a usual feature of the reduction of $Mo^{VI}O_2$ complexes. The reactions involved are not necessarily related to redox processes of oxo-transferases.[62] Only potential

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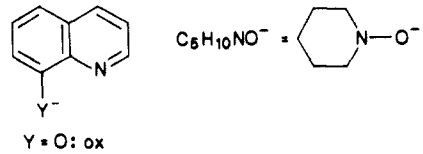
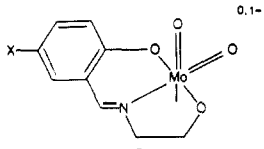
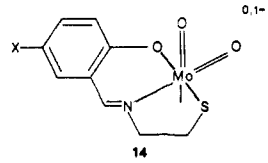
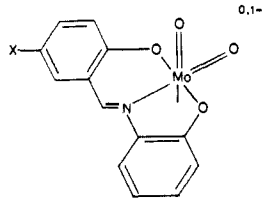
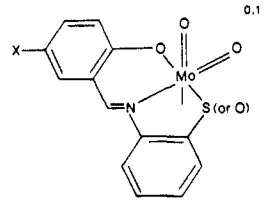
(58) Garner, C. D.; Bristow, S., in ref 9, Chapter 7.
(59) Taylor, R. D.; Street, J. P.; Minelli, M.; Spence, J. T. *Inorg. Chem.* **1978**, *17*, 3207.
(60) Bristow, S.; Garner, C. D.; Pickett, C. J. *J. Chem. Soc., Dalton Trans.* **1984**, 1617.
(61) (a) Schultz, F. A.; Ott, V. R.; Rolison, D. S.; Bravard, D. C.; McDonald, J. W.; Newton, W. E. *Inorg. Chem.* **1978**, *17*, 1758. (b) A similar trend applies to EDTA and cysteinate complexes: Ott, V. R.; Swieter, D. S.; Schultz, F. A. *Inorg. Chem.* **1977**, *16*, 2538.
(62) The reduction $MoO_2L_n + e^- \rightarrow [MoO_2L_n]^{1-}$ has no precedent in protic media, presumably because the Mo^VO_2 group is strongly basic and would be protonated to MoO(OH).[63] Reactions of the type $Mo^VOL_n + e^- \rightleftharpoons [Mo^{IV}OL_n]^{1-}$ are not objectionable in this respect.
(63) Paffett, M. T.; Anson, F. C. *Inorg. Chem.* **1981**, *20*, 3967.

Table IV. Effect of Thiolate Ligands on Molybdenum Redox Potentials



Y = O: ox
Y = S: tox

species			
O-bonded	S-bonded	$E_S - E_O$, V	ref
$[MoO_2(C_5H_{10}NO)_2]^{0,1-}$	$[MoOS(C_5H_{10}NO)_2]^{0,1-}$	0.56	60
$[MoOS(C_5H_{10}NO)_2]^{0,1-}$	$[MoS_2(C_5H_{10}NO)_2]^{0,1-}$	0.35	60
$[MoO_2(L\text{-}NO_2)(DMF)]^{0,1-}$	$[MoO_2(L\text{-}NS_2)]^{0,1-}$	0.94	4
 12	 14	0.24	22
 13	 15	0.10	23
$[MoOCl(ox)]^{0,1-}$	$[MoOCl(tox)]^{0,1-}$	0.11	59
$[MoOCl(ox)]^{0,1+}$	$[MoOCl(tox)]^{0,1+}$	0.69	59
$[Mo_2O_{4-n}S_n(S_2CNEt_2)_2]^{0,1-}$			61
$n = 1$	$n = 2$	0.11	
$n = 2$	$n = 3$	0.33	
$n = 3$	$n = 4$	0.13	

differences are employed, and these are taken as approximate measures of relative reducibilities in the absence of proper thermodynamic values of individual potentials. Data are available for only O/S substitution.

Without exception, the S-ligated complexes are more easily reduced than are their O-ligated counterparts. The largest difference, 0.94 V, occurs in the reductions of $MoO_2(L\text{-}NS_2)$ and $MoO_2(L\text{-}NO_2)$ in DMF ($L\text{-}NO_2$ = 2,6-bis(2,2-biphenyl-2-oxyethyl)pyridinate(2−)). A manifestation in reaction kinetics of this general effect is found in the reactions of the Schiff base complexes **12–15** in Table IV with Ph_2PEt.[64] The O-ligated species **12** and MoO_2(sap)(DMF) (**13**) do not react at any appreciable rate with the phosphine at temperatures up to 60 °C in DMF. In contrast, the S-ligated complexes **14** and MoO_2(ssp)(DMF) (**15**) react readily and cleanly to produce the corresponding $Mo^{IV}O$ products. By comparing activation enthalpies, Topich and Lyon[64] formulated the donor atom reactivity series 19 for the reduction of MoO_2

$$S_4 > N_2S_2 > ONS \gg O_2N \qquad (19)$$

complexes (including $MoO_2(S_2CNEt_2)_2$) by phosphines. Inasmuch as rates of reduction of sets of complexes **14** and **15** with variant X substituent decrease linearly with decreasing potential,[64] the conclusion is inescapable that the activation energy for oxo transfer *to* substrate increases as the potential for reduction of Mo(VI) decreases. The opposite is true for oxo transfer *from* substrate, but both steps must be feasible if catalysis, as in reaction cycle 8 or in an enzyme system, is to occur. If the hypothesis of reaction 1 is entertained, the function of thiolate ligands in oxo-transferases could be to place the effective Mo(VI/IV) potentials for atom transfer and Mo(VI/V/IV) potentials for regeneration of the catalytic form at values compatible with physiological reactants. The Mo EXAFS data support the presence of two or three negative sulfur ligands in enzymes such as sulfite oxidase and *Chlorella* nitrate reductase,[10,11] and two such ligands are proposed in the minimal model of the Mo cofactor.[14a] These results also allow the presence of one or more low Z donors, here simulated by the pyridine nitrogen atom of the $L\text{-}NS_2$ ligand.

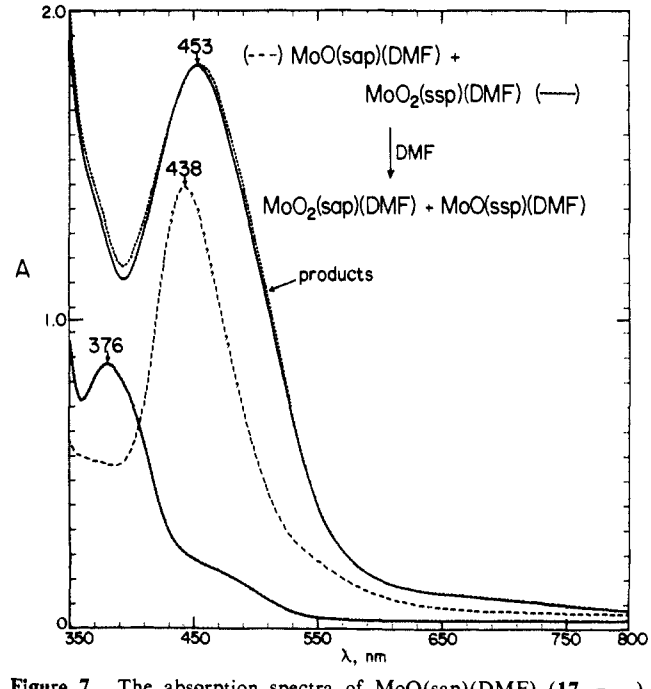


Figure 7. The absorption spectra of MoO(sap)(DMF) (**17**, ---), MoO_2(ssp)(DMF) (**15**, —), and the reaction products of these complexes (—), both initially present at 1.40 mM; (···) calculated spectrum assuming formation of MoO_2(sap)(DMF) (**13**) and MoO(ssp)(DMF) (**18**), both at 1.40 mM. All spectra were recorded in DMF solutions.

(64) Topich, J.; Lyon, J. T., III *Inorg. Chem.* **1984**, *23*, 3202; *Polyhedron* **1984**, *3*, 61.

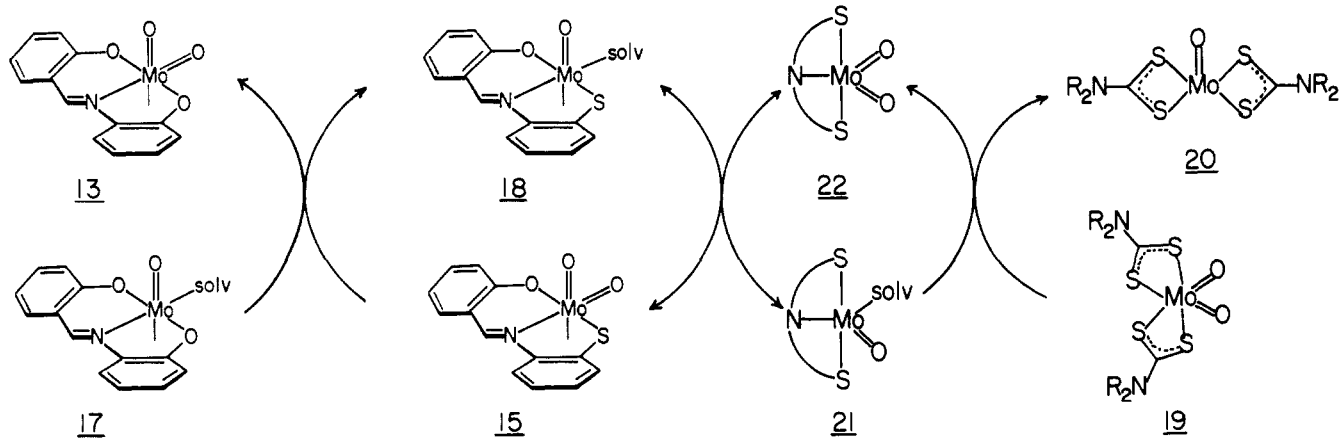


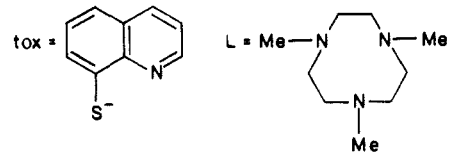
Figure 8. Schematic representation of spontaneous intermetal oxo-transfer reactions in DMF solution. The orders of oxo atom donor and acceptor tendencies are **19** > **22** > **15** > **13** and **17** > **18** > **21** > **20**, respectively.

(c) Mo/W Substitution. The lack of fitness of tungsten for oxo-transferase activity has been most clearly demonstrated in the case of rat liver sulfite oxidase.[65] The W-containing enzyme is inactive. The generally accepted idea is that W is harder to reduce than Mo. Indeed, this enzyme does not appear to have been reduced below the W(V) level.[65b] Experimental substantiation of the reducibility order Mo > W requires strictly analogous pairs of complexes, few of which exist and have known potentials. Available potential differences, listed in Table V,[59,66-71] show that, without exception, tungsten complexes are the more difficult to reduce. Although the sample is small, the differences appear to be largest when the ligands have minimal charge delocalization capability. Thus there is a difference of ca. −0.6 V in the reversible V,IV reactions of $[MCl_6]^{1-,2-}$ and $[MOLCl_2]^{1+,0}$, which contains the saturated triamine **16**. These data confirm the preceding reducibility order and suggest that W(VI/V/IV) potentials in enzymes could be substantially displaced cathodically compared to those of the native molybdo forms.

Another contributing factor is the bond energy order W=O > Mo=O, which in compounds such as $MOCl_4$ and MO_2Cl_2 has been estimated to amount to a difference of 10–20 kcal/mol.[72] These results predict that in oxo transfer a $W^{VI}O_2$ complex would be a poorer oxidant than its Mo(VI) analogue. It also follows that a $W^{IV}O$ complex would be a better reductant than its $Mo^{IV}O$ analogue. These predictions have not been clearly demonstrated experimentally.

At present it is difficult to interpret the activity of the W-containing formate dehydrogenase of *C. thermoaceticum*[73] in terms of the properties of the tungsten site. The EXAFS of the dithionite-reduced enzyme indicated the absence of W=O groups.[74] It is of course possible that the activity (formate → CO_2) of this, the only purified tungsten enzyme, does not derive from a pure oxo-transfer reaction.

Table V. Comparative Molybdenum/Tungsten Redox Potentials



16

species	$E_W - E_{Mo}$, V	ox. states	ref
$[MO_2(tox)_2]^{0,1-}$	−0.31	VI, V	59, 66
$[MCl_6]^{0,1-}$	−0.61	VI, V	69
$[MCl_6]^{1-,2-}$	−0.65	V, IV	69
$[MOLCl_2]^{1+,0}$	−0.62	V, IV	67
$[MO(SR)_4]^{1-,2-}$	−0.28	V, IV	68
$[M(PhP(CH_2CH_2S)_2)_2]^{1+,0}$	−0.09	V, IV	71
$[M(PhP(CH_2CH_2S)_2)_2]^{0,1-}$	−0.05	IV, III	71
$[MCl_3(HB(Me_2pz)_3]^{0,1-a}$	−0.82	IV, III	70
$[MCl_6]^{2-,3-}$	−0.87	IV, III	69
$[ML_3Cl_3]^{1+,0}$	−0.84	IV, III	67
$[ML_3(CO)_3]^{1+,0}$	−0.09	I, 0	67

[a] $HB(Me_2pz)_3$ = tris(3,5-dimethylpyrazolyl)hydroborate(1−).

Intermetal Oxo Transfer. The donor atom kinetics series 19 is an important reflection of ligand structure on oxo-transfer reactivity. The corresponding thermodynamic reactivity series can be arrived at in a direct manner, by the simple means of intermetal oxo-transfer reactions. Reaction 18, which shows the MoO(L-NS_2)(DMF) is a stronger reductant than MoO-$(S_2CNEt_2)_2$, has already been introduced. While numerous complexes could be examined in this context, we illustrate the procedure with a set which includes Mo(IV,VI) species derived from the dithiocarbamate (**19**, **20**), L-NS_2 (**21**, **22**), ssp (**15**, **18**), and sap (**13**, **17**) ligand systems. All of these are involved in series 19. The spectral results in Figure 7 clearly show that MoO-(sap)(DMF) (**17**, λ_{max} 438 nm) quantitatively reduces MoO_2-(ssp)(DMF) (**15**, λ_{max} 376 nm). The final spectrum (λ_{max} 453 nm) can be accurately simulated assuming the equimolar formation of MoO_2(sap)(DMF) (**13**) and MoO(ssp)(DMF) (**18**) at the same concentration as that of the reactants. To relate the reducing ability of **18** to MoO(L-NS_2)(DMF), the reaction of the latter with MoO_2(ssp)(DMF) was examined by ^1H NMR in DMF-d_7 solutions. MoO(L-NS_2)(DMF) was generated in situ by reaction 3, and varying amounts of MoO_2(ssp)(DMF) were added. These systems display the equilibrium 20, in which the relative concentrations of **15** (9.03 ppm) and **18** (9.12 ppm) can

$$MoO_2(L\text{-}NS_2) + MoO(ssp)(DMF) \rightleftharpoons MoO(L\text{-}NS_2)(DMF) + MoO_2(ssp)(DMF) \quad (20)$$

be obtained from the integrated intensities of the azomethine protons having the indicated chemical shifts. A series of experiments with different ratios of reactant concentrations clearly showed that the equilibrium position lies to the right with $K_{eq} \approx$

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30. Spectrophotometry indicated that Ph_3PO had no effect on the reaction. The results thus far require that MoO(sap)(DMF) quantitatively reduce $MoO_2(L\text{-}NS_2)$. This point was spectrophotometrically established with use of an equimolar DMF reaction system at ambient temperature.

The foregoing results are summarized in Figure 8, which depicts spontaneous intermetal oxo-transfer reactions. In the set of complexes, MoO(sap)(DMF) (**17**) is the strongest reductant and $MoO_2(S_2CNEt_2)_2$ (**19**) is the strongest oxidant. This thermodynamic series is the same as kinetic series 19, thereby showing that the activation barrier to oxo transfer is largely set by those factors which stabilize/destabilize Mo(IV) and Mo(VI). This in turn reemphasizes the beneficial effect of anionic sulfur ligands in stabilizing Mo(IV). Lastly, the reactions **17** + $^1/_2O_2$ → **13** and **18** + $^1/_2O_2$ → **15** cannot be placed precisely in the oxidative enthalpy series of Table III. However, it is clear that the first of these reactions lies below the second and that the ΔH values of both are more negative than that for the oxidation of MoO(L-NS_2)(DMF). The lack of reaction between **17** and 10 equiv of Ph_3PO in DMF for 6 h at ambient temperature suggests that $\Delta H \gtrsim -67$ kcal/mol, but slow reaction kinetics cannot be ruled out. In any case, **17** and **18**, as MoO(L-NS_2)(DMF) and MoO(S_2CNEt_2)$_2$, should reduce Me_2SO to Me_2S. This has been confirmed for the stronger reductant **17**, which is quantitatively oxidized to **13** in a system initially containing 2 equiv of Me_2SO.

All $Mo^{IV}O$ complexes in Figure 8 are now recognized to be thermodynamically competent to reduce Me_2SO,[75] the most reductively resistant enzyme substrate for which thermodynamic data are available. The stoichiometric reduction of substrate XO by a $Mo^{IV}O$ complex is, therefore, a highly necessary but not a sufficient thermodynamic criterion for a functional oxo-transferase site model. What is required for sufficiency under the oxo atom transfer hypothesis are those factors which permit at least one such atom transfer to or from substrate followed by regeneration of the original $Mo^{IV}O$ or $Mo^{VI}O_2$ species either by electron or oxo transfer, such that catalysis is sustained. The results presented here show that anionic sulfur ligation is a critical modulator of these factors and, as already mentioned, appears to place real or effective Mo redox potentials in a range accessible to physiological reactants.

Ongoing research on biologically related oxo-transfer reactions includes development of catalytic systems for substrate oxidation and reduction, examination of reactions in aqueous solution, and the possible role of pterins in enzymic electron transfer.

Acknowledgment. This research was supported by National Science Foundation Grant CHE 81-06017. Useful discussions with Dr. John Caradonna are acknowledged. We thank Dr. G. D. Watt for provision of unpublished thermodynamic data.

(75) In the only other related case that has been reported, $[MoO(dttd)Cl]^{1-}$ reduces Me_2SO: Kaul, B. B.; Enemark, J. H.; Merbs, S. L.; Spence, J. T. *J. Am. Chem. Soc.* **1985**, *107*, 2885. dttd = 2,3:8,9-dibenzo-1,4,7,10-tetrathiadecane(2-).

Molecular Hydrogen Complexes of the Transition Metals. 4. Preparation and Characterization of $M(CO)_3(PR_3)_2(\eta^2\text{-}H_2)$ (M = Mo, W) and Evidence for Equilibrium Dissociation of the H-H Bond To Give $MH_2(CO)_3(PR_3)_2$

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Abstract: The syntheses, properties, and spectral characterization of the first examples of molecular hydrogen complexes, $M(CO)_3(PR_3)_2(H_2)$ (M = Mo, W; R_3 = Cy_3, *i*-Pr_3, Cy_2-*i*-Pr), are reported in full. All six of the expected fundamental vibrational modes for η^2-H_2 binding, including ν(HH) at 2690 cm^{-1}, have been located. The hydrogen atoms of the H_2 ligand, but not of the phosphines, undergo exchange with D_2 to give HD, even in the solid state. Solid-state ^2H NMR of $W(CO)_3(P\text{-}i\text{-}Pr_3)_2(D_2)$ shows rapid rotation of the D_2 about the metal-D_2 axis. IR and variable-temperature ^1H and ^{31}P NMR of solutions of the H_2 complexes reveal the presence of equilibrium amounts (10–30%) of a species that the data indicate is a 7-coordinate *dihydride*, $MH_2(CO)_3(PR_3)_2$. The latter is presumably formed by dissociation of the H-H bond, thus completing oxidative addition of H_2 to the metal. The dihydride is fluctional, but low-temperature NMR spectroscopy shows that both the hydride and phosphorus ligands are inequivalent. At −80 °C the T_1 value for the ^1H NMR signal of the H_2 ligand is 0.004 s, almost three orders of magnitude less than that of the hydride protons (1.7 s) in $WH_2(CO)_3(P\text{-}i\text{-}Pr_3)_2$.

The activation of hydrogen by transition-metal complexes, e.g., oxidative addition to form hydride complexes, has been extensively studied because of its critical importance in catalytic hydrogenation.[1] The nature of the initial interaction of H_2 with a metal center and the geometry of approach of the H_2 molecule ("end-on" or "side-on") has long been the subject of discussion. Halpern[1a] had suggested that the bonding electrons of hydrogen could attack a vacant metal orbital, and coordination of molecular hydrogen to a metal has often been proposed and studied theoretically.[1g,2,3]

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