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Molybdenum(VI)- and Tungsten(VI)-Mediated Biomimetic Chemistry of Vanadium Bromoperoxidase

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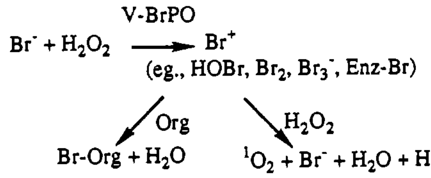
Molybdenum(VI) and tungsten(VI) catalyze the oxidation of bromide by hydrogen peroxide and thus are functional mimics of vanadium bromoperoxidase. Relatively few functional mimics are known. The oxidation of bromide by the oxodiperoxo complexes of molybdenum(VI) and tungsten(VI) has been investigated as a function of hydrogen peroxide, acid, bromide, and molybdenum(VI) or tungsten(VI) concentration. The oxidized bromine species were trapped by bromination of trimethoxybenzene (TMB) or followed by the formation of tribromide. The rate of bromide oxidation by the oxodiperoxometalate(VI) species is first order in bromide and Mo(VI) or W(VI). The rate constant for bromide oxidation by $MoO(O_2)_2(H_2O)_2$ is 1.51×10^{-2} M^{-1} s^{-1} and by $MoO(O_2)_2(H_2O)(OH)^-$ is 2.39×10^{-3} M^{-1} s^{-1}; the K_a of $MoO(O_2)_2(H_2O)_2$, determined spectrophotometrically, is 5.0×10^{-3} under the conditions employed (i.e., 10^{-4}–0.1 M $HClO_4$ in 25% MeOH). Under conditions of excess hydrogen peroxide the oxidation of bromide is fully catalytic in molybdenum(VI) or tungsten(VI); coordination of H_2O_2 is fast compared to bromide oxidation. A catalytic cycle is proposed. Chloride was found to inhibit bromide oxidation by $MoO(O_2)_2(H_2O)_2$ but not by the oxalato complex, $MoO(O_2)_2(ox)^{2-}$ or $WO(O_2)_2(H_2O)_2$. The shift in λ_{max} from 324 to 329 nm upon chloride addition to $MoO(O_2)_2(H_2O)_2$ indicates that chloride coordinates to the $MoO(O_2)_2$ moiety. Spectral changes on chloride addition to $MoO(O_2)_2(ox)^{2-}$ and $WO(O_2)_2(H_2O)_2$ were not observed. The Mo(VI)- and W(VI)-catalyzed peroxidation bromination reactions are compared to the halogenation reactivity of VO_2^+ and vanadium(V) bromoperoxidase and to the oxygen atom transfer reactivity of oxoperoxomolybdenum(VI) and –tungsten(VI) complexes.

Introduction

Haloperoxidase enzymes catalyze the oxidation of halides by hydrogen peroxide. Most of these enzymes are metalloproteins containing either the FeHeme moiety[1,2] or a vanadium(V) cofactor,[3–5] although the identity of the metal cofactor, if any, in some haloperoxidases has not been determined.[6,7] Vanadium bromoperoxidase (V-BrPO), an enzyme isolated primarily from marine organisms, is thought to function in the biosynthesis of the numerous halogenated marine natural products. Many of these compounds have potent biological activities (e.g., antifungal, antibacterial, antiviral, antineoplastic, feeding deterrent, etc.) and thus may serve chemical defense functions for the marine organism.[8]

V-BrPO functions by coordinating hydrogen peroxide[9,10] and then oxidizing a halide (i.e., Cl^-[11] Br^-, and I^-). The oxidized halide species subsequently halogenates an organic substrate or is reduced by hydrogen peroxide producing dioxygen.[12] Dioxygen has been shown to be produced in the singlet excited state in the case of bromide oxidation (Scheme 1).[13] Kinetic analyses of halogenation (i.e., bromination[14,15] and chlorination[11]) and dioxygen formation show that both reaction pathways occur via the formation of a common intermediate, the production of which is rate-limiting.[11,14] While the exact halogenating species under physiological turnover conditions is still in question, it is formally the equivalent of a bromonium ion (Br^+) as opposed to a bromine radical species ($Br^•$).[16]

Scheme 1



Protein-bound vanadium(V) is essential for catalytic activity, since removal of vanadium(V) leads to the formation of the inactive apoprotein derivative.[3,9,10] The haloperoxidase activity can be fully restored by the incorporation of one equivalent vanadium(V) per subunit (MW 65 000).[10] Other metals have not been found to reactivate apo-V-BrPO.[3,17] The vanadium(V) coordination environment is thought to be best characterized by a distorted octahedral site coordinated by one oxo ligand, one or two histidine ligands, and three or four other light-atom ligands.[18]

Conventional spectroscopic techniques have not proved useful to monitor vanadium in V-BrPO during turnover, but the

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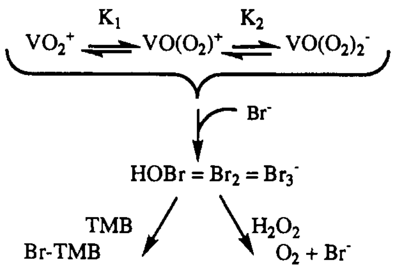
Scheme 2



vanadium can be observed in functional model complexes.[19,20] Cis-dioxovanadium(V), VO_2^+, functions in acid as a biomimic of V-BrPO by catalyzing the bromination of organic substrates and the bromide-assisted disproportionation of hydrogen peroxide forming dioxygen (Scheme 2).[19] VO_2^+ coordinates 1 or 2 equiv of hydrogen peroxide, forming $VO(O_2)^+$ or $VO(O_2)_2^-$, respectively, depending on the concentrations of acid and H_2O_2. The first formation constant, K_1, is 3.5×10^4 and the second formation constant, K_2, is about 1, depending on ionic strength.[21,22] Thus in acid even in the presence of excess H_2O_2 both the monoperoxo and diperoxo species are present. In contrast to V-BrPO, which functions optimally at approximately neutral pH, VO_2^+ functions only in acidic medium and at a rate *ca.* 10^4 slower than V-BrPO: the turnover rate for V-BrPO under optimum bromide and hydrogen peroxide concentrations at pH 6.5 is 4.7×10^5 mol of Br product/(mol enzyme) h^{-1} whereas the turnover rate for VO_2^+ is 15 mol of Br product/(mol V) h^{-1} in 0.05 M $HClO_4$.[19] Thus clearly the protein mediates the rapid peroxidative halogenation reaction at near-neutral pH.

(HPS)VO(OH), where H_2HPS is hydroxyphenylsalicylideneimine, is also a catalyst of bromide oxidation by hydrogen peroxide in aqueous DMF solution.[23] ^{51}V NMR results establish that (HPS)VO(OH) coordinates 1 equiv of H_2O_2 forming the monoperoxo, $(HPS)VO(O_2)^-$ species and releasing 1 equiv of H_3O^+. The monoperoxo complex $(HPS)VO(O_2)^-$ then oxidizes bromide forming the dioxo species $(HPS)VO_2^-$, which can then coordinate another equivalent of H_2O_2 and start through the cycle again. In the absence of added acid only one turnover is observed, however, upon the addition of stoichiometric acid with respect to H_2O_2 consumed, the reaction becomes catalytic. Thus the model system requires relatively mild acidic conditions for catalytic bromination compared to cis-dioxovanadium(V).

Surprisingly little is known about transition metal catalyzed peroxidative halogenation reactions. Aside from the VO_2^+- and (HPS)VO(OH)-catalyzed oxidation of bromide by hydrogen peroxide described above, vanadium(V)[21] and molybdenum(VI)[24,25] have been reported to catalyze iodide oxidation by hydrogen peroxide in acidic solution. Titanium(IV), in contrast, has been reported to stabilize hydrogen peroxide against oxidation of iodide.[26] Vanadium(IV) (VO^{2+}) has also been reported to be a catalyst of the peroxidation of bromide;[27] however, the mechanism of this reaction seems to differ from iodide peroxidation by V(V) and Mo(VI) and bromide peroxidation by V(V). Vanadium(IV) is thought to reduce hydrogen peroxide, forming an hydroxyl radical which can oxidize bromide to bromine radical ($Br^\bullet$). V(V)-, Mo(VI)-, and Ti(IV)-mediated reactions are thought to proceed by two-electron oxidation of iodide, although this hypothesis has not been tested. The $(HPS)VO_2^-$-mediated reaction described above has been shown to occur by an electrophilic bromination process.[23]

As part of our interest in the reactivity of vanadium bromoperoxidases and functional model complexes, we are investigating the factors which govern transition metal catalyzed peroxidative halogenation reactions. We report herein that molybdenum(VI) and tungsten(VI) are very efficient catalysts of bromide oxidation by hydrogen peroxide.

Experimental Section

Bromination Reactions. The peroxidative oxidation of bromide mediated by molybdenum(VI) was studied using $Na_2MoO_4 \cdot 2H_2O$ at concentrations less than 0.5 mM to limit oligomerization.[28] Typically 0.15 mM $Na_2MoO_4 \cdot H_2O$ was used, except where noted. The ratio of Mo(VI) to H_2O_2 concentration ranged from 1:1 to 1:12. Acidity was controlled with $HClO_4$ in strongly acidic solutions (i.e. 0.1 M $HClO_4$) and 10–50 mM sodium acetate buffer at pH > 3; acetate does not coordinate to MoO_3 in acid.[29] The concentrations of acid (i.e., $HClO_4$) and buffer were always at least 10-fold larger than the concentration of H_2O_2. 1,3,5-Trimethoxybenzene (TMB) was used as the primary substrate to monitor bromination reactions. The concentration of TMB was kept in slight excess of the H_2O_2 concentration to prevent formation of Br_2-TMB. All reaction solutions contained 20–25% methanol to solubilize TMB (2.0 mM) and to prevent precipitation of Br-TMB. The ionic strength was controlled with $NaClO_4$ in the bromide dependence and acid dependence experiments.

In the tungsten-mediated reactions, $Na_2WO_4 \cdot 2H_2O$ was used at concentrations less than 0.1 mM and typically less than 25 μM. Hydrogen peroxide was present in at least a 50-fold excess over tungsten(VI) to prevent formation of polyoxotungstates. Otherwise the reaction conditions were the same as described above.

UV/Visible and Kinetic Experiments. The molybdenum(VI)-mediated reactions were monitored primarily by following the disappearance of the oxodiperoxomolybdenum(VI) species at 328 and 310 nm (see Results).[28] Spectrophotometric data were recorded at 25.0 °C on a Hewlett-Packard HP8452A diode array spectrophotometer or a Uvikon 860 spectrophotometer. The tungsten-mediated reactions were best followed by formation of Br-TMB at 266 nm as opposed to the absorbance of oxodiperoxotungsten(VI) species (sh 250 nm) because the low concentrations of $WO(O_2)_2$ required to limit polymerization (i.e., μM) do not absorb significantly. For both metal systems the dependence of the rate of bromide oxidation on metal complex concentration was monitored by the formation of tribromide (Br_3^-): 266 nm, $\epsilon = 31\ 100\ M^{-1}\ cm^{-1}$.

GC Experiments. GC data were recorded using an Hewlett-Packard HP5890 Series II gas chromatograph with a flame ionization detector using a glass capillary HP Ultra 2 column. The concentrations of TMB and Br-TMB were determined from standard curves.

General Reagents and Procedures. H_2O_2 stock solution concentrations were determined from triiodide formation according to the method of Cotton and Dunford.[30] All chemicals were analytical reagent grade. Puratronic grade $Na_2WO_4 \cdot 2H_2O$ was purchased from Aesar.

Results and Interpretation

Molybdenum(VI)-Mediated Peroxidative Bromination Reactions. In acidic solution (0.1 M $HClO_4$), diaquooxodiperoxomolybdenum(VI), $MoO(O_2)_2(H_2O)_2$ (0.15 mM), oxidizes bromide (0.5 M) to produce tribromide (Br_3^-) and molybdenum(VI), formulated as MoO_3 and omitting waters of coordination.[31] Because tribromide is somewhat unstable under these reaction conditions, particularly at long reaction times, the stoichiometry of the reaction was monitored by the bromination of 1,3,5-

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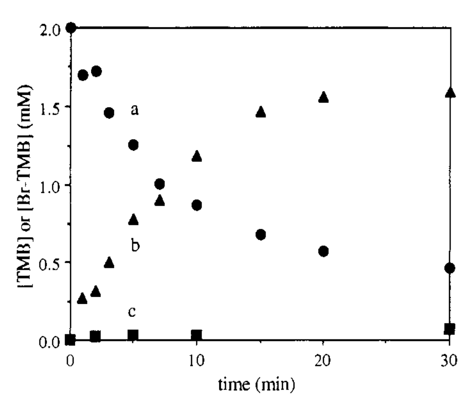

Figure 1. Gas chromatographic analysis of the peroxidative brominations of TMB in acid solution catalyzed by MoO_3: (a and c) [TMB]; (b) [Br-TMB]. Conditions for parts a and b: 0.15 mM Na_2MoO_4, 1.5 mM H_2O_2, 0.5 M NH_4Br, and 2.0 mM TMB in 0.1 M $HClO_4$/25% MeOH; Conditions for part c: same as parts a and b but without Na_2MoO_4.

trimethoxybenzene (TMB) under conditions which favor the production of the monobromotrimethoxybenzene (Br-TMB), i.e., excess of TMB over H_2O_2. Gas chromatographic analyses of TMB consumed and Br-TMB produced (Figure 1) show that 1 equiv of Br-TMB is produced per equivalent of hydrogen peroxide consumed (eq 1). In the absence of MoO_3, Br-TMB is not formed

$$H^+ + H_2O_2 + Br^- + TMB \rightarrow Br\text{-}TMB + 2H_2O \qquad (1)$$

in the same time frame (Figure 1), establishing that MoO_3[31] is a catalyst of Br^- oxidation by H_2O_2. The turnover rate of MoO_3 is *ca.* 180 mol of Br-TMB/(mol Mo) h^{-1} which is *ca.* 45 times faster than VO_2^+ under the same conditions (i.e., 0.15 mM metalate, 1.5 mM H_2O_2, 2.0 mM TMB, and 0.5 M NH_4Br in 0.1 M $HClO_4$/25% MeOH; see below).

The oxidation of bromide by $MoO(O_2)_2(H_2O)_2$ and $MoO(O_2)_2(H_2O)(OH)^-$, the primary peroxo complexes of molybdenum(VI) in acidic aqueous solution,[28] was also monitored spectrophotometrically at 328 nm and 310 nm, which are the absorption maxima of the diaquo- and aquohydroxo- oxodiperoxomolybdenum(VI) species, respectively. Figure 2 shows the time course of bromide oxidation by $MoO(O_2)_2(H_2O)_2$ as a function of the ratio of hydrogen peroxide to molybdenum(VI). Under conditions of 0.15 mM Na_2MoO_4, 0.3 mM H_2O_2, 0.5 M NH_4Br, and 2.0 mM TMB in 0.1 M $HClO_4$/25% MeOH, in which the molybdenum(VI) is present predominantly as $MoO(O_2)_2(H_2O)_2$,[28] the kinetic data fit well to a first-order decay (Figure 2a) for more than 90% of the reaction. When the hydrogen peroxide concentration is increased, but under otherwise identical conditions, a lag phase in the absorbance profile occurs before the exponential decay of $MoO(O_2)_2(H_2O)_2$ is observed (Figure 2b–d). The duration of the lag phase in the absorbance profile is proportional to the concentration of excess H_2O_2.

MoO_3-mediated peroxidative bromination of TMB occurs during the time-frame of the lag phase in Figure 2, which is seen by comparison of Figure 1 with Figure 2c. GC results of Br-TMB formation in Figure 1 performed under identical reaction conditions as Figure 2c show that approximately 1.2 mM Br-TMB is formed in the first 10 min which roughly corresponds to the approximate time of the lag phase in Figure 2c. Thus the exponential absorbance decay in Figure 2 is the oxidation of bromide by $MoO(O_2)_2(H_2O)_2$, since approximately 2 equiv of H_2O_2 per equivalent of Mo(VI) are present at the end of the apparent lag phase in Figure 2. The constant absorbance value of approximately 0.175 corresponds to a total $MoO(O_2)_2(H_2O)_2$ concentration of 0.15 mM (ϵ = 1170 M^{-1} cm^{-1}), which is the initial concentration of $MoO(O_2)_2(H_2O)_2$. Thus in the presence of excess hydrogen peroxide, a constant concentration of $MoO(O_2)_2(H_2O)_2$ is maintained by rapid recoordination of H_2O_2 to $MoO(O_2)$ or MoO_3 (see below).

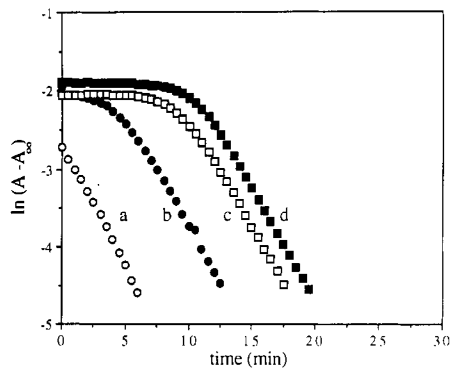

Figure 2. Time course for the disappearance of $MoO(O_2)_2(H_2O)_2$ in the presence of Br^- and TMB as a function of H_2O_2 concentration at 25.0 °C. Conditions: 0.15 mM Na_2MoO_4, 0.5 M NH_4Br, 2.0 mM TMB in 0.1 M $HClO_4$/25% MeOH at (a) 0.3 mM H_2O_2, (b) 0.9 mM H_2O_2, (c) 1.5 mM H_2O_2, and (d) 1.8 mM H_2O_2. The reaction was monitored at 328 nm.

As established above, the oxidation of bromide by $MoO(O_2)_2(H_2O)_2$ in the presence of TMB produces 2 equiv of Br-TMB per equivalent of $MoO(O_2)_2(H_2O)_2$ consumed; thus both equivalents of H_2O_2 are used to oxidize Br^-. The disappearance of $MoO(O_2)_2(H_2O)_2$, which was followed at 328 nm, proceeds in a single exponential decay (>90% reaction). Oxidation of the first equivalent of Br^- likely produces HOBr and $MoO_2(O_2)$ (eq 2). This monoperoxo species can either oxidize a second equivalent of Br^- in a faster reaction, coordinate another equivalent of H_2O_2 to reform the diperoxo species, or disproportionate producing MoO_3 and $MoO(O_2)_2(H_2O)_2$ (eqs 3–5). Recoordination of H_2O_2 to MoO_3 could also occur rapidly if MoO_3 is formed (eq 6). The rate of bromination of TMB is very fast with respect to the rate of oxidation of Br^- by $MoO(O_2)_2$ (see below).

$$MoO(O_2)_2 + Br^- + H^+ \rightarrow MoO_2(O_2) + HOBr \qquad (2)$$

$$MoO_2(O_2) + Br^- + H^+ \rightarrow MoO_3 + HOBr \quad k_{fast} \qquad (3)$$

$$MoO_2(O_2) + H_2O_2 \rightarrow MoO(O_2)_2 + H_2O \quad k_{fast} \qquad (4)$$

$$2MoO_2(O_2) \rightarrow MoO(O_2)_2 + MoO_3 \quad k_{fast} \qquad (5)$$

$$MoO_3 + 2\,H_2O_2 \rightarrow MoO(O_2)_2 \quad k_{fast} \qquad (6)$$

The rate of bromide oxidation by oxodiperoxomolybdenum(VI) was found to depend on acid concentration. A plot of k_{obs} versus $-\log[H^+]$ is sigmoidal with an inflection point at *ca.* pH 2.3 (Figure 3) which is in agreement with the pK_a of $MoO(O_2)_2(H_2O)_2$, determined spectrophotometrically under the reaction conditions of the kinetics experiments, i.e., pK_a 2.2.[32] The observed rate constant for the disappearance of the oxodiper-

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[31] The exact speciation of molybdenum(VI) in 0.1 M $HClO_4$/25% MeOH is not known due to the possible coordination of MeOH. The reactions were carried out in 25% MeOH to solubilize TMB and Br-TMB. In 0.1 M $HClO_4$, a roughly equal mixture of MoO_3 (i.e., considered to be $MoO_3(H_2O)_3$[41] and $HMoO_3^+$ is present because the pK_a is *ca.* 1, although the possible effect of MeOH on the pK_a is not known. We have continued to refer to Mo(VI) in solution as MoO_3, omitting water and methanol of coordination. The speciation of $MoO(O_2)_2$ in 0.1 M $HClO_4$/25% MeOH is also not known, however, the λ_{max} of the diperoxo species in $HClO_4$/MeOH is the same as for $MoO(O_2)_2(H_2O)_2$ and $MoO(O_2)_2(H_2O)(OH)^-$ in aqueous solution,[28,32] indicating the species is not changed dramatically. In experiments in which TMB and MeOH were omitted the reactivity was not changed, except that Br_3^- was produced instead of Br-TMB.

[32] The pK_a of $MoO(O_2)_2(H_2O)_2$ in 25% MeOH was determined spectrophotometrically at 370 nm as published by Thompson.[28] The small difference between Thompson's value for the pK_a of 1.85 and our value of 2.2 may be due to the presence of MeOH, however the λ_{max} of the diperoxo species is the same in the presence and absence of MeOH.

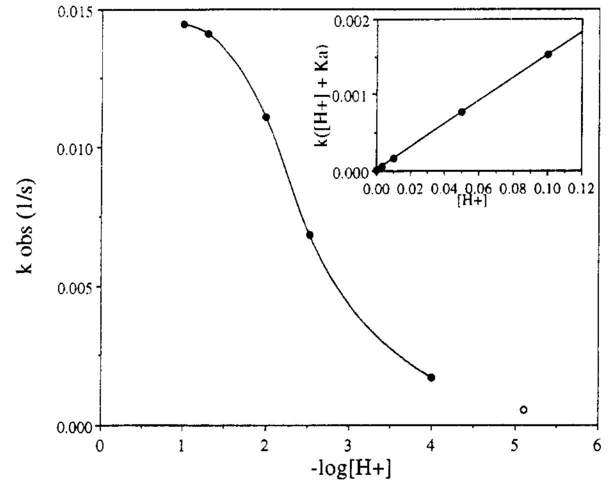

Figure 3. Plot of the observed rate constant for the disappearance of $MoO(O_2)_2(H_2O)_2$ and $MoO(O_2)_2(H_2O)(OH)^-$ monitored at 328 nm during the peroxidative bromination of TMB vs acid concentration. Conditions: 0.15 mM Na_2MoO_4, 0.3 mM H_2O_2, 1.0 M NH_4Br, 2 mM TMB in 25% MeOH with varying H^+ concentration. The acid concentration was adjusted with $HClO_4$ below pH 3 and with 10 mM acetate buffer above pH 3. $I = 2.1$ M $NaClO_4$; Temperature = 25.0 °C. The open circle, ○, is at 20 mM acetate buffer, pH 5.1 with 0.4 mM TMB. Inset: Plot of $k_{obs}(K_a + [H^+])$ vs $[H^+]$ to determine k_{A^-} and k_{AH}.

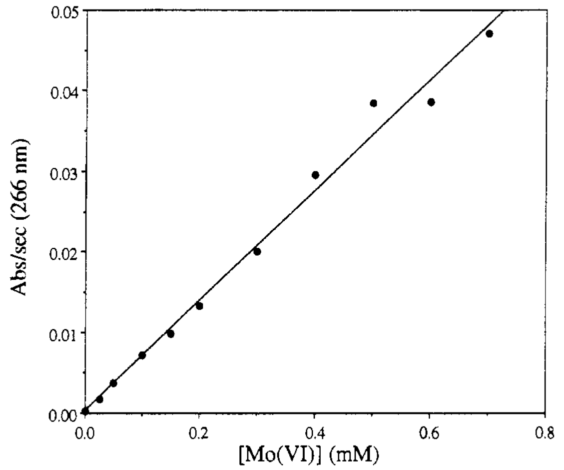

Figure 4. Plot of the initial rate of tribrimide formation mediated by $MoO(O_2)_2(H_2O)_2$ oxidation of bromide vs molybdenum(VI) concentration. Conditions: 0.1 M NH_4Br, 2 mM H_2O_2, and varying Na_2MoO_4 concentrations in 0.1 M $HClO_4$/25% MeOH. Temperature = 25.0 °C.

oxomolybdenum(VI) species is given by $k_{obs} = (k_{AH}[H^+] + k_{(A^-)K_a})/([H^+] + K_a)[Br^-]$. The values of k_{AH} (for $MoO(O_2)_2(H_2O)_2$) and k_{A^-} (for $MoO(O_2)_2(H_2O)(OH)^-$) were found to be 1.51×10^{-2} M^{-1} s^{-1} and 2.38×10^{-3} M^{-1} s^{-1} using 5.0×10^{-3} as the value for K_a (Figure 3 inset). Thus $MoO(O_2)_2(H_2O)_2$ oxidizes bromide faster than $MoO(O_2)_2(H_2O)(OH)^-$.

The rate of oxidation of Br^- by $MoO(O_2)_2(H_2O)_2$ was also found to be first-order in $MoO(O_2)_2(H_2O)_2$ concentration (Figure 4). These experiments were performed under turnover conditions (i.e., 0–0.8 mM $Na_2MoO_4 \cdot H_2O$, 2 mM H_2O_2, and 0.1 M NH_4Br in 0.1 M $HClO_4$/25% MeOH) by following the initial rate of Br_3^- formation spectrophotometrically. Under these conditions, the oxodiperoxomolybdenum(VI) species is known to be present as the monomeric oxidiperoxo species.[33,34] The second-order rate constant calculated from this experiment is 1.88×10^{-2} M^{-1} s^{-1}, which is in agreement with the rate constant determined from the acid dependence experiments, 1.51×10^{-2} M^{-1} s^{-1}. The rate of oxidation of Br^- by $MoO(O_2)_2(H_2O)_2$ was also found to be first-order in bromide concentration (Figure 5). These experiments were performed under conditions of 0–2 M NH_4Br, 0.15 mM $Na_2MoO_4 \cdot H_2O$, 1.5 mM H_2O_2, and 2 mM TMB in 0.1 M $HClO_4$/25% MeOH by monitoring the disappearance of $MoO(O_2)_2(H_2O)_2$ at 328 nm. Thus the molybdenum(VI)-catalyzed peroxidation of bromide is, like the vanadium(V) reaction,[20,23] first order in bromide concentration and does not show saturation behavior up to 2 M bromide. The rate constant for Br^- oxidation by $MoO(O_2)_2(H_2O)_2$ was also found to be independent of TMB concentration (i.e., 0.4–2.0 mM TMB; data not shown), which is consistent with rapid TMB bromination after the rate limiting step of Br^- oxidation. These reactions were followed spectrophotometrically at 266 nm to monitor the appearance of Br-TMB. Accordingly, from the results of the acid, bromide, molybdenum complex, and TMB concentration dependence experiments, the overall rate expression for the oxidation of bromide by the oxodiperoxomolybdenum(VI) species can be expressed as

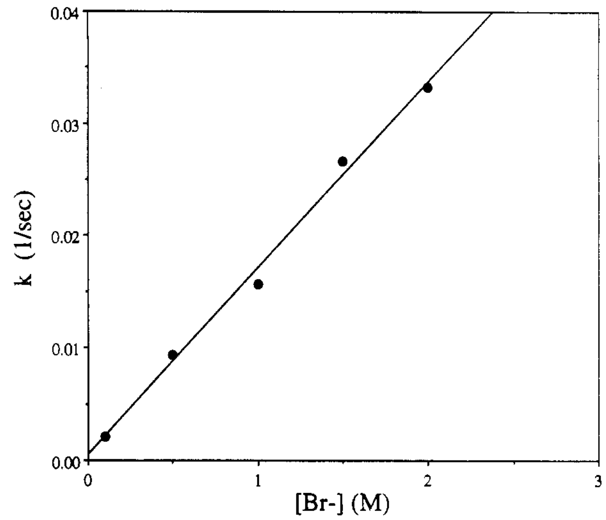

Figure 5. Plot of the observed rate constant for the disappearance of $MoO(O_2)_2(H_2O)_2$ monitored at 328 nm during the peroxidative bromination of TMB vs bromide concentration. Conditions: 0.15 mM $Na_2MoO_4 \cdot 2H_2O$, 1.5 mM H_2O_2, 2.0 mM TMB, and varying NH_4Br in 0.1 M $HClO_4$/25% MeOH. $I = 2.1$ M ($NaClO_4$). Temperature = 25.0 °C.

$$-d[MoO(O_2)_2(H_2O)_2 + MoO(O_2)_2(H_2O)(OH)^-]/dt = ((k_{AH}[H^+] + k_A K_a)/([H^+] + K_a))[Br^-] \times ([MoO(O_2)_2(H_2O)_2] + [MoO(O_2)_2(H_2O)(OH)^-]) \quad (7)$$

Oxygen Formation. As stated above, in the absence of an organic halogen acceptor, MoO_3 catalyzes the formation of tribromide. On the basis of the reactivity of oxidized bromine species with hydrogen peroxide,[35] one might expect that dioxygen would be formed when MoO_3 catalyzes the oxidation of Br^- by H_2O_2. Under the acidic conditions of these kinetic experiments (i.e., 0.05–0.1 M $HClO_4$), the reduction of tribromide by hydrogen peroxide to form dioxygen is very slow. In fact experiments to monitor the possible MoO_3-catalyzed halide-assisted disproportionation of hydrogen peroxide forming dioxygen under conditions of 0.15 mM MoO_3, 1.5 mM H_2O_2, and 0.5 M NH_4Br in 0.05 M $HClO_4$ showed that the response on the oxygen probe was indistinguishable from the base line, although tribromide was formed as detected spectrophotometrically. Thus under these conditions, the halide-assisted disproportionation of hydrogen

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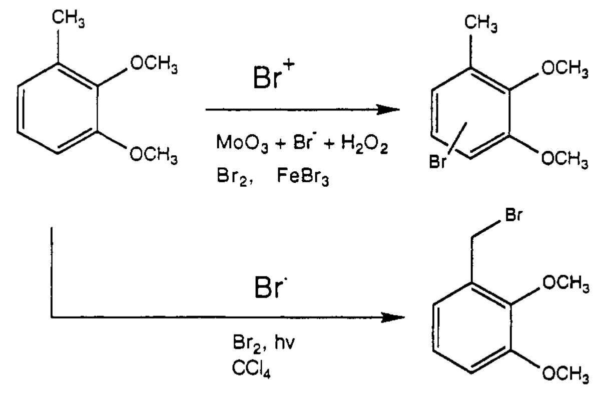
(33) Schwane, L. M.; Thompson, R. C. *Inorg. Chem.* **1989**, *28*, 3938–3946.

(34) If instead of using Br_3^- formation to investigate the dependence of the rate or molybdenum concentration, the disappearance of oxodiperoxomolybdenum(VI) complex is followed spectrophotometrically (i.e., at 328 nm and at 0.1–0.6 mM MoO_3, 1.8 mM H_2O_2, 1.0 M NH_4Br, and 2 mM TMB in 0.1 M $HClO_4$/25% methanol), the rate constant varies approximately 1.6-fold. The increase in rate constant with increase in molybdenum concentration is accompanied by an increase in the scatter of the value of the rate constant, for which the origin is under investigation.

(35) Kanofsky, J. R. *Arch. Biochem. Biophys.* **1989**, *274*, 229–23.

Scheme 3



peroxide is not observed. By contrast both VO_2^+ in acidic aqueous solution and V-BrPO at neutral pH catalyze dioxygen formation in the absence of an organic halogen acceptor.[19] In the case of VO_2^+, even though the acid concentration is 0.05 M, the concentration of hydrogen peroxide is sufficiently higher (5 mM) than in the MoO_3 (1.5 mM) experiments that the rate of H_2O_2 reduction of Br_3^- is observable, although this rate is still much less than the rate of VO_2^+-catalyzed bromination of TMB. At 5 mM H_2O_2, O_2 was formed slowly in the MoO_3-catalyzed reaction. In the case of V-BrPO, the rate-limiting step for dioxygen formation is the oxidation of bromide because at the higher pH used in these reactions the reduction of the oxidized bromine species is fast.[12,14,35] On the other hand, the rate of Br^- oxidation by $MoO(O_2)_2(H_2O)_2$ forming Br_3^- is much faster than the reduction of Br_3^- by H_2O_2.

Radical versus Electrophilic Bromination. Experiments performed using the substrate 2,3-dimethoxytoluene (DMT) under conditions of 0.25 mM MoO_3, 2.5 mM H_2O_2, 1.0 M NH_4Br, and 3 mM DMT in 0.1 M $HClO_4$ resulted in the exclusive formation of ring-substituted Br-DMT (Scheme 3), establishing an electrophilic bromination mechanism. Br-DMT was identified by comparison of the GC retention time to that of standards of Br-DMT.[23] Thus, the absence of the methyl-substituted product, 2,3-dimethoxybenzylbromide, shows that the oxidation of bromide by $Mo(O_2)_2(H_2O)_2$ proceeds via a two-electron oxidation to form Br^+ and not $Br^•$.

Effect of Chloride on Peroxidative Bromide Oxidation Catalyzed by Molybdenum(VI). The influence of chloride on the peroxidation of bromide catalyzed by molybdenum(VI) was also examined. MoO_3 is capable of catalyzing the oxidation of this more electronegative halide by hydrogen peroxide; however, this reaction is much slower than the peroxidation of bromide and does not go to completion over several days. Under conditions of 0.4 mM MoO_3, 4 mM H_2O_2, 2 M NaCl, and 5 mM TMB in 0.1M $HClO_4$/25% MeOH, 59% of the TMB was converted to Cl-TMB in 15 h.

Despite the slow rate of chloride peroxidation, the presence of chloride does affect the rate of bromide oxidation. The time period of the lag phase was found to increase and the rate of oxidation of bromide by $MoO(O_2)_2(H_2O)_2$ was found to decrease as a function of increasing chloride concentration (Figure 6). Moreover, saturation was observed above *ca.* 1 M chloride. GC analyses showed that Cl-TMB was not formed under these conditions. The rate constant for bromide oxidation by the $MoO(O_2)_2$ species in the presence of 1 M NaCl is 7.57×10^{-3} M^{-1} s^{-1}, which is significantly reduced from the rate constant of 1.51×10^{-2} M^{-1} s^{-1} in the absence of chloride. In contrast, chloride did not have an effect on the rate of bromide oxidation by the oxodiperoxooxalato complex of molybdenum(VI), $MoO(O_2)_2(ox)^{2-}$, a complex that does not have a dissociable ligand.[36] The rate constants for the oxidation of bromide by $MoO(O_2)_2(ox)^{2-}$ in the absence and presence of 0.75 M NaCl (under conditions of 0.5 mM $MoO(O_2)_2(ox)^{2-}$, 0.75 M NH_4Br, and 1.5 mM TMB in 10 mM oxalate buffer, pH 5.1, with 20% MeOH) are 9.21×10^{-3} M^{-1} s^{-1} and 9.67×10^{-3} M^{-1} s^{-1}, respectively, showing that chloride does not inhibit bromide oxidation.

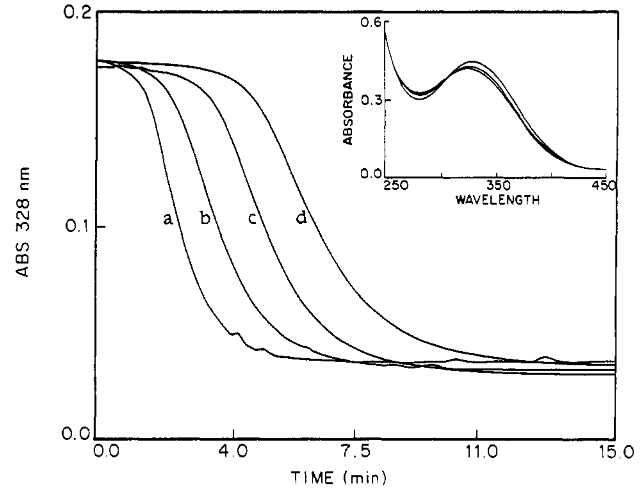


Figure 6. Effect of chloride on the time course of the disappearance of $MoO(O_2)_2(H_2O)_2$ monitored at 328 nm during the peroxidative bromination of TMB. Conditions: 0.15 mM $Na_2MoO_4 \cdot 2H_2O$, 1.5 mM H_2O_2, 2.0 mM TMB, 1.0 M NH_4Br in 0.1 M $HClO_4$/25% MeOH with (a) no NaCl, (b) 0.25 M NaCl, (c) 0.5 M NaCl, and (d) 1.0 M NaCl. $I = 2.1$ M ($NaClO_4$). Temperature = 25.0 °C. Inset: Effect of chloride on the UV-vis spectrum of $MoO(O_2)_2(H_2O)_2$ in 0.1 M $HClO_4$/2.1 M ionic strength.

Changes in the UV-vis spectrum of $MoO(O_2)_2(H_2O)_2$ upon chloride addition are suggestive of Cl^- coordination to $MoO(O_2)_2(H_2O)_2$; the λ_{max} of 324 nm for $MoO(O_2)_2(H_2O)_2$ shifts to 329 nm upon addition of 0.5 M NaCl (Figure 6 inset). A similar shift on addition of bromide to $MoO(O_2)_2(H_2O)_2$ was not observed, however the oxidation of bromide by $MoO(O_2)_2(H_2O)_2$ is sufficiently fast such that its observation may be precluded. As might be expected, the addition of chloride to $MoO(O_2)_2(ox)^{2-}$ does not induce an absorption maximum shift. It could be argued that for a d^0 metal ion complex with no ligand field stabilization energy, the oxalate ligand can be expected to exchange rapidly. However, the fact that neither a shift in the λ_{max} of the $MoO(O_2)_2(ox)^{2-}$ complex in the presence of Cl^- nor a change in the rate of Br^- oxidation in the presence of Cl^- occurs suggests that the $MoO(O_2)_2(ox)^{2-}$ complex remains intact.

Several explanations are plausible to account for the chloride effect. The decreased rate of bromide oxidation could indicate that Br^- competes with Cl^- coordination to the $MoO(O_2)_2$ moiety and that Br^- oxidation occurs after coordination to Mo(VI). The decreased rate of Br^- oxidation could also arise from changes in the oxidation potential or the charge on the $MoO(O_2)_2(H_2O)Cl^-$ complex. While the chloride competition experiments do not allow us to determine whether halide oxidation occurs by X^- coordination to $MoO(O_2)_2$ before oxidation or whether X^- oxidation occurs by direct attack on Mo-bound peroxide, it is clear that Cl^- does coordinate to the $MoO(O_2)_2$ moiety in acidic aqueous solution. Other examples of oxoperoxochloro complexes of molybdenum(VI) are known[37] (see below).

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(36) (a) $K_2MoO(O_2)_2(ox)$ was prepared according to: Dengal, A. C.; Griffith, W. P.; Powell, R. D.; Skapski, A. C. *J. Chem. Soc. Dalton Trans.* **1987**, 991–995. (b) Bromide oxidation was followed gas chromatographically by the formation of Br-TMB and spectrophotometrically by monitoring the decrease of $MoO(O_2)_2(ox)^{2-}$. Under conditions of 0.77 mM $MoO(O_2)_2(ox)^{2-}$, 1.0 M NH_4Br, and 2.0 mM TMB in 20 mM oxalate buffer, pH 5.14 with 25% MeOH, 0.65 mM Br-TMB was formed in 30 min. Br-TMB production appears to be biphasic which is consistent with 70% Br-TMB production occurring in the first 5 min of reaction which is consistent with the spectrophotometric results which show good first-order fits for 70% of the reaction. (c) Bromide oxidation by $MoO(O_2)_2(ox)^{2-}$ has been investigated: Reynolds, M. S. Manuscript submitted for publication.

(37) Chaumette, P.; Mimoun, H.; Saussine, L. *J. Organomet. Chem.* **1983**, *250*, 291–310.

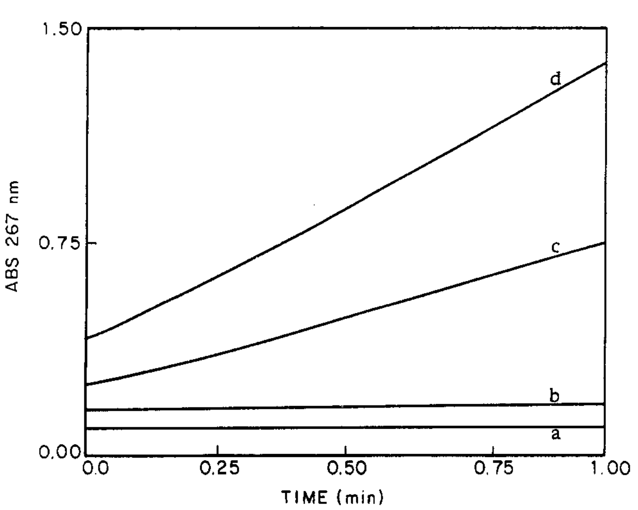

Figure 7. Comparison of the rates of molybdenum(VI)-, tungsten(VI)- and vanadium(V)-catalyzed formation of tribromide. Conditions: 1 mM H_2O_2, 0.1 M NH_4Br in 0.5 M $HClO_4$ with (a) no added metal, (b) 0.1 mM NH_4VO_3, (c) 0.1 mM $Na_2MoO_4 \cdot 2H_2O$, and (d) 0.1 mM Na_2WO_4.

Tungsten(VI)-Mediated Peroxidative Bromination Reactions. Tungsten(VI) was also found to catalyze bromide oxidation by hydrogen peroxide, similar to the molybdenum(VI)-mediated system. The tungsten(VI)-catalyzed peroxidation of bromide forming tribromide is faster than catalysis by molybdenum(VI) and vanadium(VI) and much faster than the uncatalyzed oxidation of bromide by hydrogen peroxide (Figure 7). Analysis by GC using TMB as trap for the oxidized bromine species shows that 1 equiv of bromide is oxidized per equivalent of hydrogen peroxide added (eq 1) under conditions of 40 μM tungstate, 4 mM H_2O_2, 2M NH_4Br, and 5 mM TMB in 0.1 M $HClO_4$/25% MeOH (data not shown).

The kinetics of the tungstate-mediated reactions were best analyzed by following the bromination of TMB at 266 nm. At the low concentrations of tungsten(VI) required to limit oligomerization,[38] the disappearance of the peroxotungsten species could not be monitored spectrophotometrically. The absorbance data recorded at 266 nm exhibited first-order behavior for at least 70% of the reaction provided that H_2O_2 was initially present in at least 50-fold excess over tungsten. At smaller ratios of H_2O_2 to W(VI), dimerization of W(VI) interferes.[38] In addition, k_{obs} values were independent of H_2O_2 concentration (i.e., 0.25–1.8 mM) under conditions of 5 μM Na_2WO_4, 2.0 M NH_4Br, and 2.0 mM TMB in 0.1 M $HClO_4$/25% MeOH (data not shown).

The acid dependence on the rate of tungsten-mediated Br-TMB formation followed spectrophotometrically at 266 nm shows that bromide oxidation is faster at lower pH (Figure 8), similar to the molybdenum(VI)-mediated reactions. The pK_a of $WO(O_2)_2(H_2O)_2$ is 0.12;[39] it was not possible to obtain kinetic data above 0.1 M H^+ due to complications from the increased rate of the uncatalyzed rate of oxidation of bromide by hydrogen peroxide. The rate of the tungsten-catalyzed oxidation of bromide forming tribromide was found to increase linearly with tungsten concentration between 2.5–25 μM $Na_2WO_4 \cdot 2H_2O$ under conditions of 2 mM H_2O_2 and 0.1 M NH_4Br in 0.1 M $HClO_4$/25% MeOH (data not shown), establishing a first-order dependence. The rate of the tungsten(VI)-catalyzed Br-TMB formation was also found to increase linearly with bromide concentration (i.e., 0–2.0 M NH_4Br) as determined under conditions of 15 μM $Na_2WO_4 \cdot 2H_2O$, 1.8 mM H_2O_2, and 2.0 mM TMB in 0.1 M $HClO_4$/25% MeOH (data not shown). Finally, the tungsten-mediated peroxidative bromination reactions were found to occur by electrophilic bromination and not a radical process from the product analysis of DMT bromination, like the molybdenum(VI)-mediated reactions.

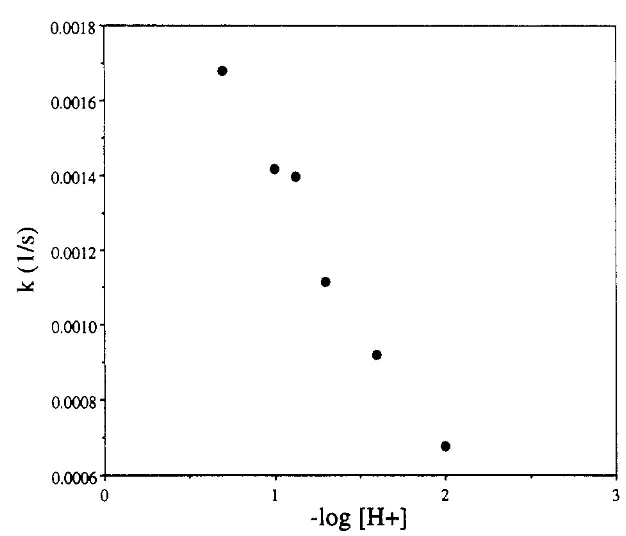

Figure 8. Plot of the observed rate constant for the appearance of Br-TMB during the peroxidative bromination of TMB catalyzed by tungsten(VI) vs acid concentration. Conditions: 5 μM Na_2WO_4, 1.0 mM H_2O_2, 2.0 M NH_4Br, 1.5 mM TMB in 25% MeOH with varying H^+ concentration (0.01 M to 0.1 M $HClO_4$) at 25.0 °C. The ionic strength was 2.01–2.10 M. The reaction was monitored at 266 nm.

The effect of chloride on the peroxidation of bromide catalyzed by tungsten(VI) was also examined. Like molybdenum(VI), tungsten(VI) catalyzes the oxidation of chloride by hydrogen peroxide in acidic solution at a much slower rate than the oxidation of bromide. For example, less than 1% Cl-TMB was formed in 30 min (based on TMB consumed), under conditions of 40 μM Na_2WO_4, 4 mM H_2O_2 2 M NaCl, and 5 mM TMB in 0.1M $HClO_4$/25% MeOH, whereas under similar conditions with bromide 100% Br-TMB is formed based on the initial concentration of H_2O_2. Cl-TMB formation increases to 25% in 48 h. However, unlike Mo(VI), up to 1.5 M NaCl did not affect the rate of bromide oxidation (15 μM W(VI), 1.8 mM H_2O, 2.0 mM TMB, and 1.0 M Br^- in 0.1 M $HClO_4$/25% MeOH and 2.5 M ionic strength ($NaClO_4$) with replacement of $NaClO_4$ by NaCl [i.e., 0–1.5 M Cl^-] and maintaining ionic strength). The absence of a chloride effect in the tungsten(VI) may be due to the "softer" nature of this complex.

Discussion

We have shown that both Mo(VI) and W(VI) catalyze the oxidation of bromide by hydrogen peroxide in acidic solution. The metal-mediated reactions are fully stoichiometric, with the production of 1 equiv of oxidized bromine species per equivalent of hydrogen peroxide consumed. The oxidized bromine species then brominates an appropriate substrate, which in the case of TMB is a very rapid reaction compared to the rate of oxidation of the halide. The oxodiperoxo species of Mo(VI), i.e., $MoO(O_2)_2(H_2O)_2$ and $MoO(O_2)_2(H_2O)(OH)^-$ are in acid dependent equilibrium (pK_a 2.3) and have somewhat different reactivities toward bromide oxidation. A consistent catalytic mechanism is shown in Scheme 4. The rate limiting step is the oxidation of bromide, although the detailed mechanism, such as whether nucleophilic attack occurs on Mo(VI) or bound peroxide is still speculative. The fate of the monoperoxo species, $MoO_2(O_2)$, is not known because it cannot be observed under our experimental conditions. As shown in Scheme 4, it could recoordinate hydrogen peroxide. Thompson's investigations show that in 0.1–1.0 M acid the rate of coordination of hydrogen peroxide to $MoO_2(O_2)$ is slow with respect to formation of $MoO_2(O_2)$ from MoO_3, showing that addition of the second peroxide is rate limiting in $\geq$0.1 M H^+;[28] nevertheless, the overall rate of bromide oxidation is still

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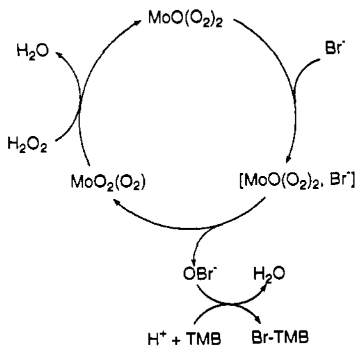
[38] Islam, M.; Thompson, R. C. *Inorg. Chem.* **1989**, *28*, 4419–4422.

[39] Ghiron, A.; Thompson, R. C. *Inorg. Chem.* **1988**, *27*, 4766–4771.

Scheme 4



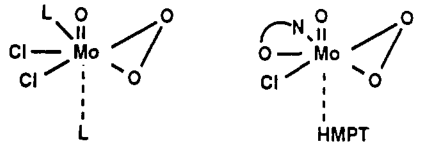
slower than the rate of formation of $MoO(O_2)_2$. $MoO_2(O_2)$ could also oxidize a second equivalent of bromide, although Thompson argues that the oxomonoperoxo species is not reactive.[28] A third possibility is that $MoO_2(O_2)$ could disproportionate to $MoO(O_2)_2$ and MoO_3; MoO_3 could then recoordinate 2 equiv of hydrogen peroxide, re-forming $MoO(O_2)_2$. All of these possibilities are consistent with the experimental results since bromide oxidation is the rate-limiting step.

Previous examination of the activation of peroxide by molybdenum(VI) to oxidize iodide in acidic aqueous solution (i.e., 0.05 M H^+ [24] and 0.005 M H^+ [25]) gave results similar to those obtained in the current work. The significant differences between the iodide oxidation reaction and the current bromide oxidation reactions are (1) the dependence of the rate of the former on hydrogen peroxide concentration due to the more comparable rates of hydrogen peroxide coordination and iodide oxidation and (2) the interference from the significant rate of the uncatalyzed oxidation of iodide by hydrogen peroxide. Smith and Kilford also observed iodide saturation,[24] whereas bromide saturation kinetics were not observed in the present study up to 2 M bromide.

While Mo(VI) and W(VI) function similarly to V(V) in acidic aqueous solution, the group VI metals are in fact much more reactive. One reason for the enhanced reactivity is the higher oxidation state of Mo(VI) and W(VI) versus V(V), which would tend to increase the oxidation potential of the bound peroxide. Another reason is the speciation of the peroxide complexes of W(VI), Mo(VI), and V(V) in acid. It was shown previously by Ghiron and Thompson that the oxodiperoxo configuration is a much better activator of peroxide for oxygen atom transfer reactions in aqueous solution.[40] This enhanced reactivity may be due to a longer peroxo O–O bond and one longer $M\text{-}O_{peroxide}$ bond in the diperoxo form versus the monoperoxo form.[40] Ti(IV) forms only a monoperoxo complex, and it actually stabilizes peroxide against attack in these reactions.[26] Under the conditions which were used to study the VO_2^+-mediated reactions (i.e., 0.1 M H^+, 10:1 H_2O_2/VO_2^+), the monoperoxo species ($VO(O_2)^+$) is favored over the diperoxo species, and the overall rate of bromide oxidation is much less than in the Mo(VI)- and W(VI)-mediated reactions.[19] Thus the large formation constants for formation of the oxodiperoxo Mo(VI) and W(VI) in relativley concentrated acid,[28] in contrast to oxodiperoxovanadium(V) formation,[21,22] are consistent with the greater reactivity of the Mo(VI)- and W(VI)-catalyzed oxidation halides by hydrogen peroxide.

While the speciation of the peroxide complexes in acid solution may be an issue, evidence from numerous studies on the activation of peroxide for oxygen atom transfer reactions and inner sphere one electron oxidation reactions show that the identity of the metal center is key to the reactivity of the complex. Ghiron and Thompson, for example, showed that under conditions where V(V), Mo(VI), and W(VI) all form oxodiperoxo complexes, the relative reactivities were $10:10^4:10^5$ for oxygen atom transfer reactions in acidic aqueous solution.[40] While the behavior is not well understood, a simple correlation can be drawn between the acidity of a complex and its reactivity. The stabilization given peroxide by Ti(IV), which can be expected to have less Lewis acid character, further extends this argument.

The inhibition of the peroxidation of bromide by chloride in the molybdenum(VI) system in the absence of significant Cl-TMB production suggests that chloride coordinates to the peroxomolybdenum(VI) complex, although the reason for the inhibition could not be determined from these studies. Several examples of chloride coordinated to the oxoperoxoMo(VI) moiety in organic solvents are well known, such as **1**–**4**, of which **1** and **2** are active epoxidation catalysts and **3** has been characterized by X-ray crystallography.[36] Chloride oxidation by **1**–**4** was not reported, and it may not occur if the monoperoxo moiety does not have the driving force to oxidize chloride. Moreover, these reactions were carried out in the absence of acid, which would prevent chloride oxidation;[20] thus it is not known whether **1**–**4** could also effect chlorination, whether the monoperoxo species cannot oxidize chloride, or whether halide coordination stabilizes it against oxidation by peroxide. In any case, halide coordination to the metal center is not a prerequisite for halide oxidation because $MoO(O_2)_2(ox)^{2-}$, which does not have a dissociable ligand, oxidizes bromide.



1. L = DMF
2. L = $OP\text{-}(N(CH_3)_2)_3$
3. O-N = picolinate
4. O-N = quinolinate

The unmatched reactivity of vanadium bromoperoxidase shows that peroxide activation could be dependent on ligation and surrounding environment in addition to or perhaps in spite of the identity of the metal center. The vanadium center in the enzyme may form a monoperoxo complex which is unusually capable of peroxide activation. The influence of ligation on the reactivity of peroxide complexes of V(V), Mo(VI), W(VI), and other transition metal ions is a topic of much current interest. One key question which remains to be answered is whether halide oxidation can occur by coordination to the metal or whether it proceeds via attack directly on the peroxo ligand. We are continuing our investigations into the mechanism of chloride inhibition of bromide peroxidation.

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(40) Ghiron, A. F.; Thompson, R. C. *Inorg. Chem.* **1990**, *29*, 4457.

(41) Cruywagen, J. J.; Heyns, J. B. B.; Rohwer, E. F. C. H. *J. Inorg. Nucl. Chem.* **1976**, *38*, 2033.