Biomimics of Vanadium Bromoperoxidase: Vanadium(V)–Schiff Base Catalyzed Oxidation of Bromide by Hydrogen Peroxide

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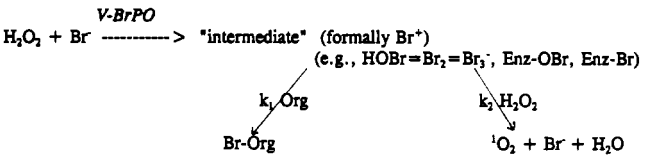
A six-coordinate vanadium(V) complex, LVO(OEt)(EtOH), where H_2L = *N*-(2-hydroxyphenyl)salicylideneamine, is shown to be a catalyst precursor in the oxidation of bromide by hydrogen peroxide in DMF solution. The oxidized bromine species is trapped by organic substrates and, by product analysis, is shown to be a two-electron-oxidized species, rather than a bromine radical. The bromination reaction is quantitative with respect to hydrogen peroxide. The acid dependence of the stoichiometry of the bromination reaction is established. Using UV/vis spectrophotometry, ^{51}V NMR spectroscopy, and kinetic data, a mechanism is proposed: the active catalyst is LVO(OH), which, upon binding peroxide and releasing H_3O^+, oxidizes bromide and binds another equivalent of peroxide, generating the observed $LVO(O_2)^-$. L*VO(OEt)(EtOH), where H_2L^* is *N*-(2-carboxyphenyl)salicylideneamine, also supports catalytic bromination reactions. ^{51}V NMR data indicate that L^{*2-} dissociates upon the complexation of peroxide. The structures of LVO(OEt)(EtOH) and L*VO(OEt)(EtOH) have been determined by X-ray crystallography. LVO(OEt)(EtOH), $VC_{17}H_{20}NO_5$, crystallizes in the orthorhombic system, space group *Pbca*, with a = 20.218(5) Å, b = 20.955(4) Å, c = 16.196(3) Å, and Z = 16. The refinement converged to R = 0.066 and R_w = 0.073. L*VO(OEt)(EtOH), $VC_{18}H_{20}NO_6$, crystallizes in the orthorhombic system, space group *Fdd*2, with a = 17.7951(7) Å, b = 33.118(3) Å, c = 12.8834(5) Å, and Z = 16. The refinement converged to R = 0.040 and R_w = 0.048.

Introduction

Vanadium bromoperoxidase (V-BrPO), which is isolated from marine algae, is thought to play a role in the biosynthesis of the numerous halogenated marine natural products.[1] V-BrPO catalyzes the oxidation of halides (i.e., iodide,[1] bromide,[1] and chloride[2]) by hydrogen peroxide, forming either a halogenated organic substrate or dioxygen by reaction with a second equivalent of hydrogen peroxide (Scheme I).[1] In the case of bromide oxidation, dioxygen has been shown to be in the singlet excited state ($^1O_2$).[3] V-BrPO contains one vanadium(V) ion per subunit (MW 65 000). Removal of vanadium from V-BrPO produces the inactive apoprotein; subsequent addition of vanadate to the apo derivative fully restores the activity. In the resting state of the enzyme, vanadium is present as vanadium(V).

While vanadium is the essential cofactor in V-BrPO, it has only been recently that the role of vanadium was shown to be in coordination of hydrogen peroxide and thus activation of hydrogen peroxide toward bromide oxidation.[4] *cis*-Dioxovanadium(V) in acidic solution coordinates 1 or 2 equiv of hydrogen peroxide, forming the monoperoxo, $VO(O_2)^+$, or diperoxo, $VO(O_2)_2^-$, species, both of which oxidize bromide. The oxidized bromine equivalent (*i.e.*, $HOBr{=}Br_2{=}Br_3^-$) can then brominate an organic substrate or oxidize a second equivalent of H_2O_2, forming O_2. Thus VO_2^+ is a functional mimic of V-BrPO although, unlike V-BrPO, it functions in acid and at much lower turnover rates.[4] VO_2^+ has also been reported to catalyze iodide oxidation by hydrogen peroxide in acidic solution[5] although this system breaks down because VO_2^+ oxidizes iodide directly at low pH, a reaction that does not occur with bromide. In comparison to the chemistry

Scheme I



of VO_2^+ and peroxide, the vanadium(V)-mediated chemistry of halide and peroxide has been largely unexplored. We report here two homogeneous vanadium(V) complexes which catalyze the oxidation of bromide by hydrogen peroxide in organic medium.

Vanadium(V) has been used in homogeneous catalysis of oxygen-transfer and oxidation reactions involving organic substrates and various peroxides. Peroxo- and diperoxovanadium(V) species have been used to convert sulfides to sulfoxides.[6-8] Other vanadium peroxo species hydroxylate benzene[9,10] and oxygenate olefins and acetylenes.[11] Vanadium complexes of alkyl hydroperoxides and the ligands described below epoxidize olefins.[12] Despite the wide variety of oxygen-based transformations which are mediated by vanadium(V) complexes, investigations of halide oxidation are limited to the oxidation of iodide,[5] bromide,[4] and chloride[4] by hydrogen peroxide in the presence of dioxovanadium(V) and aerobic oxidation of HBr catalyzed by the tetraethylene glycol complex of vanadium(V).[13]

In order to explore the relationship between vanadium-mediated oxygenation and oxidation reactions, on the one hand, and biomimetic halogenation reactions, on the other, we chose to investigate the halide-oxidizing properties of the peroxo adducts

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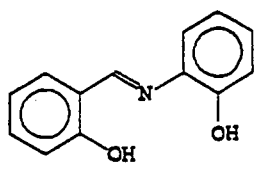
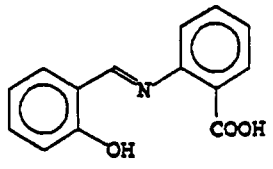
of two complexes, *i.e.*, the $V^{V}O^{3+}$ complexes of *N*-(2-hydroxyphenyl)salicylidenamine (H_2L) and *N*-(2-carboxyphenyl)salicylidenamine (H_2L^*). Bromide is oxidized by hydrogen peroxide in reactions mediated by these complexes. The reactions become catalytic with the addition of stoichiometric amounts of acid. These two systems are the first models of vanadium bromoperoxidase which require only mildly acidic conditions for catalytic bromide oxidation.



H_2L



H_2L^*

Materials and Methods

General Procedures. All chemicals were reagent grade or better and were used without further purification, except *N*,*N*-dimethylformamide (DMF), which was stirred over CaO, distilled from CaH_2 under reduced pressure, and stored over molecular sieves.

Synthesis of LVO(OEt)(EtOH). H_2L was synthesized by the condensation of salicylaldehyde and *o*-aminophenol as previously reported,[14] except that the solvent was absolute ethanol instead of ethanol/toluene. A 0.73-g sample (3.4 mmol) of the red-orange ligand recrystallized from methanol was dissolved in 40 mL of absolute ethanol, 0.84 g (3.4 mmol) of $VO(O^iPr)_3$ (Johnson Matthey Electronics) was added, and the flask was sealed and stored at ambient temperature. The solution immediately turned from orange to brown. Dark green flat needles were isolated 2 weeks later. Elemental analysis was consistent with this formulation. Anal. Found (calcd): C, 55.15 (55.28); H, 5.30 (5.42); N, 3.94 (3.97). Characteristic features of LVO(OEt)(EtOH): ^{51}V NMR (DMF) −530, −542, −563, −568 ppm; ^1H NMR (CD_3OD) δ 9.21 ppm (imine); UV/visible (DMF) shoulders at ~300 and ~370 nm (ϵ = 18 800 and 11 200 M^{-1} cm^{-1}, respectively). LVO_2^-, formed by addition of equimolar NaOH, has absorption maxima at 280 nm (ϵ = 17 200 M^{-1} cm^{-1}) and 426 nm (ϵ = 10 100 M^{-1} cm^{-1}).

Synthesis of a derivative without ethanol was accomplished as follows. Approximately 50 mg of LVO(OEt)(EtOH) was dissolved in a minimum of acetonitrile. Addition of a few drops of water resulted in immediate precipitation of a dark crystalline solid. Elemental analysis was consistent with a formulation of $(LVO)_2O{\cdot}CH_3CN$. Anal. Found (calcd): C, 54.32 (54.81); H, 3.38 (3.43); N, 6.82 (6.85). $(LVO)_2O{\cdot}CH_3CN$ in DMF shows ^{51}V NMR resonances at −542, −563, and −568 ppm.

Synthesis of L*VO(OEt)(EtOH). The ligand H_2L^* was synthesized from salicylaldehyde and anthranilic acid (2-aminobenzoic acid) in the same manner as H_2L.[14] Recrystallization from methanol afforded orange needles. The synthesis of the vanadium complex was analogous to that of LVO(OEt)(EtOH). Red-brown crystals suitable for X-ray diffraction studies were isolated 1 month later. A subsequent synthesis gave crystalline material in minutes upon the addition of several milligrams of seed crystals. Elemental analysis was consistent with this formulation. Anal. Found (calcd): C, 54.24 (54.37); H, 4.93 (5.03); N, 3.64 (3.52). ^{51}V NMR (DMF): −550 ppm. UV/visible (DMF): shoulders ~320 and ~390 nm.

^{51}V NMR. NMR spectra were recorded in 10-mm tubes on a General Electric GN300 at 79 MHz and 25 °C, using a 20-μs 90° pulse length and 100-ms delay time; 2000 and 5000 scans (8K points) were used for 1.0 mM vanadium solutions, and line broadening was 20 Hz. Spectra were referenced to $VOCl_3$ (0 ppm) as an external reference. Curve deconvolution was done using GEMCAP, an interactive curve-fitting program supplied in the GE software.

UV/Vis Spectroscopy. UV/visible spectra were recorded on an HP8452a diode array spectrophotometer in 1 mm path length quartz cuvettes.

Bromination Reactions. A 30% aqueous H_2O_2 solution (Fisher) was standardized spectrophotometrically by measuring the chloroperoxidase-catalyzed formation of I_3^- (λ_{max} 353 nm, ϵ = 26 400 M^{-1} cm^{-1}), as described.[15] Hydrogen peroxide was diluted to 0.2 M with DMF, and the solution was stored at 4 °C. A stock solution of 0.2 M $NaVO_3$ was prepared as described.[16] Halogenation was followed by the bromination of 1,3,5-trimethoxybenzene (TMB) under conditions where only 2-bromo-1,3,5-trimethoxybenzene (BrTMB) was formed. Reactions were performed on a 1-mL scale and initiated with freshly made DMF solutions of the vanadium complexes. The order of addition of reagents was critical to obtaining reproducible results in the bromination reactions. The vanadium complex was added to a solution containing DMF, TMB, hydrogen peroxide, and bromide. Acid (if needed) was added immediately before or after the vanadium complex. This order of addition avoids two complications: the vanadium complex catalyzes the degradation of hydrogen peroxide; V^V is unstable in acidic DMF solution and undergoes reduction to V^{IV}, as identified by loss of the NMR signal and appearance of the typical eight-line EPR signal. No special efforts were made to exclude air or water from these reactions. Aliquots of the reaction solution (0.1–0.25 mL) were added to 3 mL of H_2O and extracted with 1 mL of ethyl acetate. The reaction mixtures in which less than 5 mM BrTMB was synthesized were extracted after 45-min reaction time, while the reaction mixtures in which 5–10 mM BrTMB was synthesized were extracted after 1.5 h. The organic phase was analyzed by an HP5890 Series II gas chromatograph equipped with a fused-silica capillary column (25 m) of cross-linked 5% phenyl methyl silicone. The concentrations of BrTMB have an average standard deviation of 6%.

The reactions in which the vanadium complexes were incubated with NaOH were initiated with H_2O_2.

Characterization of Brominated Products. BrTMB was also prepared by addition of aqueous HOBr to a solution of TMB in methanol and characterized by mass spectrometry and ^1H NMR. Ring-substituted bromo-2,3-dimethoxytoluene (BrDMT) was made by addition of bromine vapors to a methylene chloride solution of 2,3-dimethoxytoluene (DMT) and $FeBr_3$. The sole product was characterized by mass spectrometry and ^1H NMR. 2,3-Dimethoxybenzyl bromide was made by addition of bromine vapors to a CCl_4 solution of DMT in a quartz cuvette followed by immediate irradiation with a Hg UV pen lamp (Oriel Corp., Model 6047). When the orange color of bromine bleached, usually in 2–3 min, the cycle of addition of bromine vapors and irradiation was repeated until the starting material was consumed. The methyl-substituted and ring-substituted brominated products were observed simultaneously by GC. Only the ring-substituted product was observed under these conditions in the absence of light.

X-ray Crystallography. LVO(OEt)(EtOH). A yellow-green flat needle of approximate dimensions 0.05 × 0.4 × 0.25 mm was attached to a glass fiber with epoxy. Data were collected at ambient temperature on a Huber four-circle diffractometer automated by Crystal Logic, Inc., utilizing graphite-monochromatized Mo Kα radiation (λ = 0.710 73 Å). A total of 4999 reflections (positive octant) were collected in the $\theta/2\theta$ scan mode to a maximum 2θ of 45° at a scan speed of 3.0°/min. Three standard reflections were measured after every 47 reflections. Their intensities decreased an average of 5.2% over the course of the data collection; this decrease was not linear; thus no correction was applied. The data were corrected for Lorentz and polarization effects. Due to the small size of the absorption coefficient (5.83 cm^{-1}), no absorption correction was applied. A total of 1747 reflections with $I > 3\sigma(I)$ were used in the structural analysis. Inspection of the intensity data revealed reflection conditions consistent with space group *Pbca* (No. 61). Sixteen LVO(OEt)(EtOH) molecules can be accommodated within the unit cell. The asymmetric unit contains two such molecules which are nearly related by a C_2 axis; the difference in the positions of the ethanol and ethoxide moieties breaks the symmetry. The vanadium atoms were located by utilizing the direct methods program SHELXS-86.[17] The remaining atoms were located by successive cycles of full-matrix, least-squares refinement[18] and difference Fourier syntheses using the Oxford CRYSTALS system.[19,20] The positions of all non-hydrogen atoms were refined. The V, O, N, and C(imine and ethyl) atoms were refined with anisotropic thermal parameters. The phenyl ring carbons were refined with isotropic thermal parameters. The initial refinement led to chemically unreasonable bond lengths for the imine bonds (N(13)–C(27) = 1.14 Å; N(23)–C(47) = 1.05 Å); consequently, these bond lengths were restrained to 1.3 Å. These restraints led, in turn, to some changes in the N(imine)–C(phenyl)

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and N(imine)–V bonds. In the final refinement, the N(imine)–C(phenyl) and the N(imine)–V bonds were also restrained (1.45 and 2.10 Å, respectively). All hydrogen atoms were constrained to ride on their respective carbons (C–H bond length 1.0 Å), except the ethanol protons, whose positions were fixed at locations from the difference map. The hydrogen thermal parameters were fixed at 3.95 Å^2.

L'VO(OEt)(EtOH). A red-brown rhombohedral bipyramid of approximate dimensions 0.35 × 0.35 × 0.3 mm was attached to a glass fiber with epoxy. Data were collected and reduced as described above with the following exceptions: 3341 reflections (positive octant) collected, maximum 2θ of 55°, scan speed 4.5°/min. Three standard reflections were collected after every 47 reflections and showed no significant change during the data collection. Due to the small size of the absorption coefficient (5.35 cm^{-1}), no absorption correction was applied. A total of 1808 reflections with $I > 3\sigma(I)$ were used in the structural analysis. Inspection of the intensity data revealed reflection conditions consistent with space group *Fdd*2 (No. 43). This space group is polar: inversion of the refined structural coordinates through $^1/_8, ^1/_8, ^1/_8$ and re-refinement led to a higher R factor, indicating that the original choice of polarity is correct. Sixteen L'VO(OEt)(EtOH) molecules can be accommodated within the unit cell. The asymmetric unit contains one such molecule. The vanadium atom was located by utilizing the direct methods program SHELXS-86.[17] The remaining atoms were located by successive cycles of full-matrix, least-squares refinement[18] and difference Fourier syntheses using the UCLA Crystallographic Computing Package.[20,21] The positions and anisotropic thermal parameters of all non-hydrogen atoms were refined, except that the z coordinate of V(1) was fixed to define the origin, and C(35A) and C(35B) were refined isotropically (see below). Hydrogen atom positions were calculated (C–H bond length 1.0Å) and included as fixed contributors with isotropic thermal parameters fixed to 4.0 Å^2. However, the ethanol proton was fixed at the position located in the difference map. Due to static disorder in the methyl group of the ethoxide, the methyl carbon was refined in two positions (C(35A) and C(35B)), the sum of whose occupancies was constrained to be 1.0. Their thermal parameters were refined isotropically to prevent chemically unreasonable merging of the two positions.

Results and Interpretation

Reactivity of LVO(OEt)(EtOH). ^{51}V NMR. The ^{51}V NMR spectrum of LVO(OEt)(EtOH)[22] dissolved in DMF has four resonances at –530, –542, –563, and –568 ppm, relative to external $VOCl_3$ (Figure 1a). The assignment of these resonances was facilitated by the following experiments. Precipitation with water of an acetonitrile solution of LVO(OEt)(EtOH) results in a crystalline solid, whose elemental analysis is consistent with $(LVO)_2O$·MeCN and whose NMR spectrum in DMF contains only the three upfield resonances (–542, –563, and –568 ppm) (Figure 1b). Addition of 0.5 M ethanol to a 1 mM DMF solution of LVO(OEt)(EtOH) converts all the vanadium species to the single species with the low-field resonance at –530 ppm (Figure 1c). Moreover, addition of ethanol to a DMF solution of $(LVO)_2O$·MeCN (Figure 1b) also results in complete conversion to the –530 ppm form. Thus, the resonance at –530 ppm is assigned to LVO(OEt).

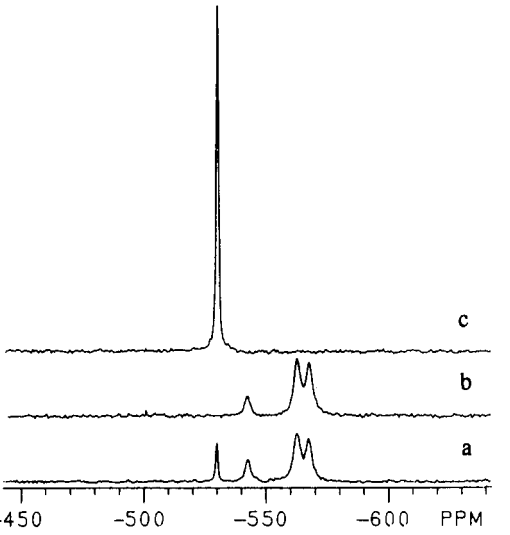

Figure 1. ^{51}V NMR spectra of (a) 1 mM LVO(OEt)(EtOH) in DMF, (b) 1 mM LVO(OEt)(MeCN) in DMF, and (c) 1 mM LVO(OEt)-(EtOH) + 1 M EtOH in DMF; (the same spectrum is also obtained for solution b + 1 M EtOH). The integrated signal areas are constant within 10%. In the solid state, LVO(OEt)(EtOH) slowly loses ethanol, as judged from the decreasing magnitude of the resonance at –530 ppm; see asignment of the –530 ppm resonance in text.

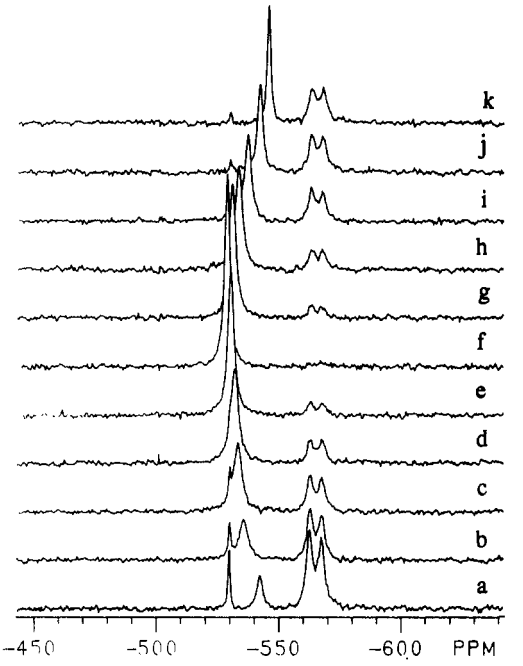

Figure 2. ^{51}V NMR spectra of the titration of 1 mM LVO(OEt)(EtOH) with NaOH and HCl in DMF: (a) 1 mM LVO(OEt)(EtOH) in DMF; (b–f) addition of 0.2 mM aliquots of NaOH (a total of 1 mM NaOH added at f); (g–k) addition of 0.2 mM aliquots of HCl (a total of 1 mM HCl added at k). The resonance at –542 ppm moves to –529 ppm with addition of base and back to –542 ppm on neutralization. Spectrum k differs from spectrum a in that the –542 ppm resonance is larger at the expense of the other resonances as a result of the increased water content.

The resonance at –542 ppm shifts upfield to –547 ppm upon addition of acid (data not shown) and downfield to –529 ppm upon addition of base. These are the extremes of the upfield and downfield resonances upon the addition of acid or base. The titration of LVO(OEt)(EtOH) with NaOH followed by HCl is shown in Figure 2. These results in combination with UV/vis results (see below) led to the assignment of the acid-dependent resonance (–529 to –547 ppm) to LVO_2^-/LVO(OH). Upon the addition of 20% water to a DMF solution of LVO(OEt)(EtOH), the four species convert to a single species with a resonance at –545 ppm, consistent with the LVO(OH) assignment. As presented above, addition of ethanol to a 1 mM solution of LVO-

(18) The function minimized in the least squares refinement is $\sum w||F_o| - |F_c||^2$. All least-squares refinements computed the agreement factors according to:

$$R = \sum||F_o| - |F_c||/\sum|F_o|$$

$$R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$$

$$\mathrm{EOF} = [\sum w(|F_o| - |F_c|)^2/(m-n)]^{1/2}$$

where F_o is the observed structure factor, F_c is the calculated structure factor, $w = 1/\sigma^2(F_o)$, m is the number of refelctions used in the refinement, and n is the number of parameters refined.

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(20) Neutral-atom scattering factors and corrections for anomalous dispersion were taken from: *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, U.K., 1974; Vol. IV.

(21) A locally modified version of the UCLA crystallographic computing package: C. E. Strouse, Department of Chemistry, UCLA, Los Angeles, CA, 1985.

(22) LVO(OEt)(EtOH) denotes the solid complex, rather than a particular form in solution.

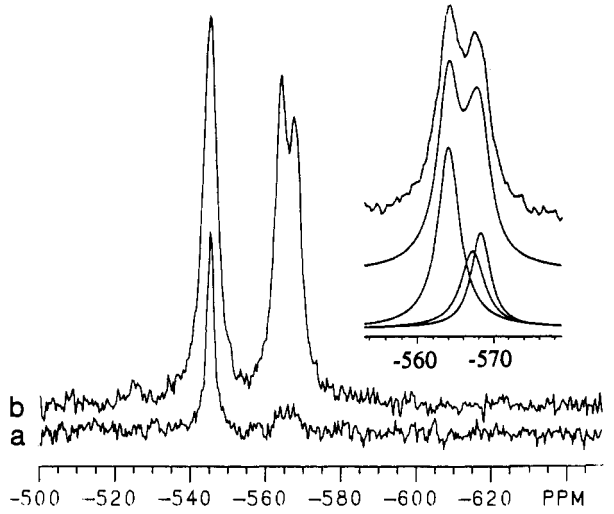


Figure 3. ^{51}V NMR spectra of equimolar $NaVO_3$, H_2L, and HCl in 3% H_2O/DMF: (a) 0.5 mM; (b) 5.0 mM. Inset: curve fitting using GEMCAP. The three curves are at −564, −567, and −568 ppm, with line widths of 273, 299, and 238 Hz.

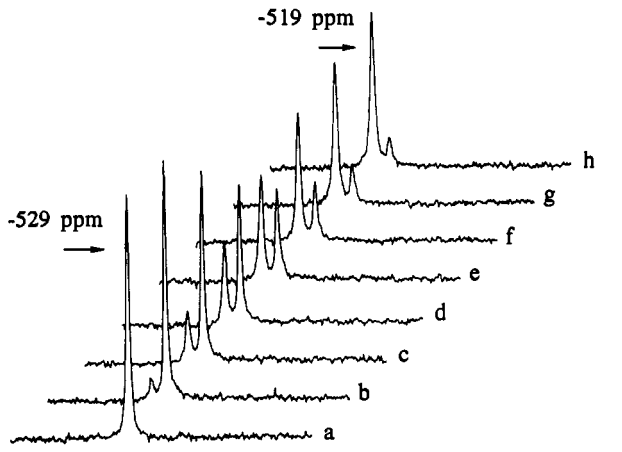


Figure 4. ^{51}V NMR spectra of the conversion of LVO_2^- to $LVO(O_2)^-$: (a) 1 mM LVO(OEt)(EtOH) + 1 mM NaOH in DMF; (b) solution in a + 4 mM H_2O_2. The spectrum was recorded immediately. The remaining spectra were collected at (c) t = 10 min, (d) t = 15 min, (e) t = 20 min, (f) t = 25 min, (g) t = 50 min, and (h) t = 1 h. No changes were observed after 1 h.

(OEt)(EtOH) dissolved in DMF (*i.e.*, the solution with four resonances, Figure 1a) results in an increase in the −530 ppm resonance. However, if only 1 mM ethanol is added, this increase is small and is accompanied by a shift in the resonance at −542 ppm to −547 ppm, suggesting that ethoxide binds to vanadium and the hydroxyl H^+ protonates the LVO_2^- moiety (data not shown).

The formation of LVO_2^- *in situ* by addition of aqueous $NaVO_3$ to a DMF solution of equimolar H_2L also produces the species with an NMR signal at −529 ppm. Addition of equimolar HCl results in loss of the resonance at −529 ppm and new resonances at −545, −563, and −568 ppm, as shown in Figure 3 for two different concentrations of the vanadium complexes. The shift from −529 to −545 ppm is consistent with the protonation of LVO_2^- (eq 1).

$$H^+ + LVO_2^- \rightleftharpoons LVO(OH) \qquad (1)$$

The absence of ethanol further restricts the nature of the species which give(s) rise to these resonances. Clearly, the formation of the species with the high-field resonances is concentration dependent, with only slight formation at 0.5 mM and significant formation at 5 mM. LVO(OEt)(EtOH) is a chiral molecule; both enantiomers are present in the crystal (see below). Dimers formed from these monomeric precursors would be d,l and meso, resulting in three distinct vanadium sites. The resonances at −563 and −568 ppm can be fit by the superposition of three curves, comprising 52, 24 and 24% of the signal intensity (Figure 4, inset); this fit is consistent with a dimeric formulation.

Addition of hydrogen peroxide to a DMF solution of LVO(OEt)(EtOH) results in an additional resonance at −519 ppm. Nearly complete conversion to this peroxo species can be achieved under the following conditions: a 1 mM solution of LVO(OEt)(EtOH) with equimolar NaOH in DMF gives rise to a single resonance at −529 ppm, from LVO_2^- (Figure 4a); then addition of excess hydrogen peroxide (4 mM) results in the conversion to the peroxo species over the course of 1 h (Figure 4b–k). Clearly, peroxide competes effectively with hydroxide for vanadium coordination. Proton release on peroxide binding is demonstrated by the reaction of 1 mM LVO(OEt)(EtOH), excess hydrogen peroxide (4 mM), and only 0.5 equiv of NaOH (0.5 mM). The NMR spectrum (not shown) exhibits a resonance at −519 ppm (which comprises *ca.* half the total signal area) and resonances at -542, −563, and −568 ppm (which together comprise *ca.* half the total signal area). The position of the acid-dependent resonance is critical here: its position at −542 ppm indicates that the acid concentration is the same as that in a solution consisting of only LVO(OEt)(EtOH) in DMF. Since the 0.5 equiv of hydroxide can be thought of as formally giving 0.5 equiv of LVO_2^-, the binding of hydrogen peroxide requires the release of two protons, in order for the overall reaction involving peroxide to be proton-neutral:

$$LVO_2^- + H_2O_2 \rightarrow LVO(O_2)^- + H_2O$$

The −519 ppm resonance is assigned to the peroxo species, $LVO(O_2)^-$, which, by analogy to known peroxo species,[23] is likely to be coordinated in an η^2 manner.

UV/Vis. The ^{51}V NMR assignments are also supported by UV/vis spectra. H_2L in DMF has a λ_{max} of 354 nm (ϵ = 13 900 M^{-1} cm^{-1}) and L^{2-} (formed by addition of 2 equiv NaOH to H_2L) has a λ_{max} of 434 nm (ϵ = 13 800 M^{-1} cm^{-1}). LVO(OEt)(EtOH) in DMF has shoulders at ~300 and ~370 nm (ϵ = 18 800 and 11 200 M^{-1} cm^{-1}, respectively). Addition of equimolar NaOH to the solution of LVO(OEt)(EtOH), to form LVO_2^-, results in a blue shift in the high-energy transition to 280 nm (ϵ = 17 200 M^{-1} cm^{-1}) and a red shift in the visible transition from a shoulder ~370 nm to a maximum at 426 nm (ϵ = 10 100 M^{-1} cm^{-1}). The π–π^* transition of L^{2-} is shifted ~10 nm to higher energy upon coordination to vanadium(V). Addition of acid causes little change in the spectrum of LVO(OEt)(EtOH), aside from a slow loss of absorption attributed to reduction of vanadium(V) by the loss of ^{51}V NMR signal intensity (see Materials and Methods) and confirmed by EPR measurements (data not shown). The fact that the spectrum of H_2L is not restored by addition of acid is further evidence that L^{2-} remains bound to vanadium(V).

Addition of 4 mM hydrogen peroxide to the DMF solution of 1 mM LVO(OEt)(EtOH) and equimolar NaOH leads over a 30-min period to a new absorption band at 366 nm (ϵ = 20 300 M^{-1} cm^{-1}) (Figure 5). By constrast, the DMF solution of 1 mM sodium vanadate and 2 mM hydrogen peroxide has only a weak absorbance (ϵ = 730 M^{-1} cm^{-1}) at 350 nm and no absorbances in the UV.

Bromination Reactions. The addition of LVO(OEt)(EtOH) to a solution of hydrogen peroxide and bromide results in an oxidized bromine species capable of brominating organic substrates. 1,3,5-Trimethoxybenzene (TMB) traps this oxidized species to yield 2-bromo-1,3,5-trimethoxybenzene (BrTMB) in concentrations nearly equal to the vanadium complex concentration. For example, the reaction of 1 mM LVO(OEt)(EtOH) with 4 mM H_2O_2, 0.1 M $(Bu^t)_4NBr$, and 20 mM TMB in DMF

(23) Butler, A. The Coordination and Redox Chemistry of Vanadium in Aqueous Solution. In *Vanadium in Biological Systems*; Chasteen, N. D., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1990; pp 25–49.

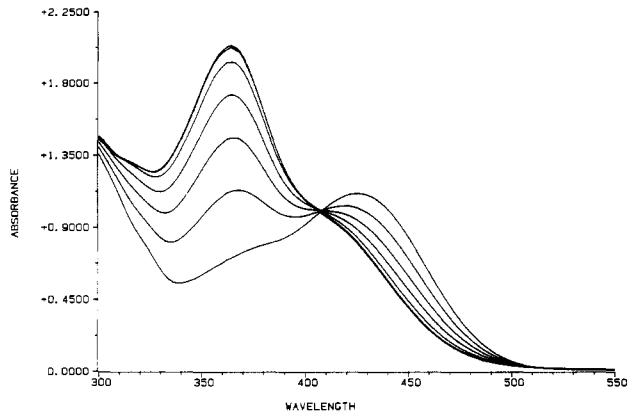


Figure 5. UV/vis spectra of the conversion of LVO_2^- to $LVO(O_2)^-$. Conditions: 1 mM LVO(OEt)(EtOH), equimolar NaOH, and 4 mM H_2O_2 in DMF. Spectra were collected every 5 min. Path length is 1 mm.

Table I. BrTMB Formation as a Function of $[H^+]$, $[H_2O_2]$, and [V][a]

	[LV(OEt)(EtOH)]	$[H_2O_2]$	$[H^+]$	[BrTMB]
a	1.0	4	0	0.98
b	1.0	4	1	2.10
c	1.0	8	2	3.10
d	1.0	8	3	4.10
e	1.0	8	4	5.06
f	1.0	16	5	5.96
g	0.1	4	0	0.21
h	0.1	4	1	1.21
i	0.1	4	2	2.29
j	0.1	6	3	3.47
k	0.1	6	4	4.32
l	0.1	6	5	5.46
m	0.1	0	6	0.02
n	0.1	1	6	0.93
o	0.1	2	6	1.93
p	0.1	4	6	3.88
q	0.1	8	12	8.06
r	0.1	4	0	0.21
s	0.3	4	0	0.30
t	0.5	4	0	0.48
u	1.0	4	0	0.98
v	2.0	4	0	1.08
w	3.0	6	0	1.05
x	4.0	6	0	1.03
y	0.0	4	0	0.03
z	0.0	4	5	0.60

[a] Reactions were run at ambient temperature for 45 min–1.5 h, until no further bromination was observed by GC. The reactions were initiated by the addition of the vanadium complex. The order of addition of reagents is important, as described under Materials and Methods. All reactions were run in DMF with 0.1 M Bu^t_4NBr. In entries a–f, g–l, and r–x, acid is the limiting reagent, while hydrogen peroxide is limiting in entries m–q. Entries y and z are controls, without vanadium complex. Entries r and u repeat entries g and a, respectively. They are included for clarity.

yields 0.98 mM BrTMB (Table Ia). In the absence of the vanadium complex, by contrast, only 0.03 mM BrTMB is produced (Table Iy).

The oxidation of bromide can be made to be catalytic with respect to the vanadium complex in the presence of added acid (*e.g.*, HCl or $HClO_4$).[24] For example, the reaction of 1 mM LVO(OEt)(EtOH), 0.1 M Br^-, 20 mM TMB, 4 mM H_2O_2, and 1 mM $HClO_4$ results in the formation of 2.10 mM BrTMB (Table Ib). Table I shows the results of experiments at 1.0 and 0.1 mM vanadium complex and various acid concentrations (Table Ia–l); in all these cases, the concentration of H_2O_2 is in excess of the sum of the concentrations of the vanadium complex and the acid.

(24) Despite the potential for chlorination, where the choice of acid was HCl, chlorinated products were not observed. Even in experiments where $[Cl^-]$ exceeds $[Br^-]$ by a factor of 6, only BrTMB is observed.

Even in the presence of acid, but without LVO(OEt)(EtOH), very little BrTMB is formed (Table Iz *vs.* If,l).

Higher initial concentrations of acid yield more BrTMB; each additional equivalent of acid allows another turnover and the formation of an additional equivalent of BrTMB. The acid requirement is explicable in light of the overall reaction stoichiometry:

$$H_2O_2 + Br^- + TMB \rightarrow BrTMB + H_2O + OH^-$$

Hydrogen peroxide can only oxidize bromide under approximately neutral or acidic conditions in aqueous medium. The accumulation of base, it may be inferred, leads to the cessation of bromide oxidation in DMF as well. This putative hydroxide effect was investigated directly by reacting sodium hydroxide with the vanadium complex prior to initiation of the bromination reaction with hydrogen peroxide. The addition of 0.1 mM sodium hydroxide to the mixture of 0.1 mM LVO(OEt), 0.1 M bromide, and 5 mM TMB before initiation of the reaction with 4 mM hydrogen peroxide prevents any formation of BrTMB. The subsequent addition of 6 mM HCl results in the formation of 3.9 mM BrTMB. Only 3.9 mM BrTMB is produced because the reaction is limited by $[H_2O_2]$ (*i.e.*, 4 mM; see below). The acid neutralizes the hydroxide and permits catalytic turnover. From ^{51}V NMR studies, it appears that the hydroxide effect is an indirect one, rather than a consequence of OH^- binding to the vanadium(V) center (see above).

The consumption of H_2O_2 is quantitative with respect to BrTMB production at 0.1 mM LVO(OEt)(EtOH), provided the acid concentration is at least equal to the difference between $[H_2O_2]$ and [V] (Table Im–q), so that the reaction does not become limited in acid. For example, the reaction of 0.1 mM LVO(OEt)(EtOH), 0.1 M Br^-, 1 mM H_2O_2, 1 mM HCl, and 5 mM TMB results in 0.93 mM BrTMB (Table In). At 1.0 mM LVO(OEt)(EtOH), however, hydrogen peroxide is decomposed, as demonstrated by ^{51}V NMR experiments (data not shown). The decomposition of hydrogen peroxide results in substoichiometric bromination with respect to hydrogen peroxide consumption. The bromination of TMB was found to be slow with respect to the oxidation of bromide, since the formation and disappearance of tribromide (Br_3^-) is observed spectrophotometrically (λ_{max} 272 nm in DMF).[25]

After completion of bromination reactions catalyzed by LVO(OEt)(EtOH) in which acid is the limiting reagent (*e.g.*, 1 mM LVO(OEt)(EtOH), 4 mM H_2O_2, 0.1 M Br^-, 5 mM TMB, and 2 mM HCl), spectroscopic data are consistent with $LVO(O_2)^-$ as the final species in solution. ^{51}V NMR shows a single resonance at –519 ppm. An absorbance maximum is observed at 366 nm.

Comparisons of LVO(OEt)(EtOH)- and VO_3^--Mediated Bromination. As discussed above, LVO(OEt)(EtOH) is capable of mediating one turnover of bromide oxidation by hydrogen peroxide without added acid. The analogous reaction using $NaVO_3$ instead of LVO(OEt)(EtOH) (1 mM $NaVO_3$, 2 mM H_2O_2, 0.1 M $(Bu^t)_4NBr$, and 20 mM TMB in DMF) does not yield any BrTMB. However, the addition of equimolar $HClO_4$ to the reaction of 1 mM VO_3^- under the conditions described above yields 0.95 mM BrTMB. This requirement of VO_3^- for an additional equivalent of acid compared with LVO(OEt)(EtOH) may be understood by considering the availibility of protons in each case. VO_3^- hydrolyzes, forming $H_2VO_4^-/HVO_4^{2-} + H^+$, which upon binding hydrogen peroxide releases water. By contrast, LVO(OEt)(EtOH) hydrolyzes to 2EtOH + LVO(OH), which upon binding hydrogen peroxide as O_2^{2-} (see NMR section above) releases H_3O^+ (see Scheme III below).

(25) A complete kinetic analysis was not undertaken at this time because two factors complicate these reactions and the interpretation of them: (1) Bromination of L^{2-} depletes the Br_3^- we are observing. $H_2(BrL)$ detected by mass spectral analysis: M – 1 of $H_2(BrL)$ at *m/e* 290, 292. (2) reduction of Br_3^- by hydrogen peroxide is another side reaction with the same consequences.

Effect of Ethanol on Bromination. The addition of 1 M ethanol to 1 mM LVO(OEt)(EtOH), 0.1 M Br^-, 20 mM TMB, and 2 mM H_2O_2 slows bromination: no bromination is observed in the time in which the reaction without ethanol is complete although, over several hours, bromination is observed. This result suggests that ethanol competes with hydrogen peroxide for the coordination of the vanadium complex. ^{51}V NMR results under these reaction conditions confirm this interpretation, since in addition to a (now small) −519 ppm resonance, a −530 ppm resonance becomes prominent (data not shown). By contrast, the effect of ethanol on rate of formation of Br_3^-, followed spectrophometrically, in the unligated vanadium(V) reaction (1 mM $NaVO_3$/1 mM HCl instead of LVO(OEt)(EtOH) under the same conditions as above) is negligible.

Since the bromination of TMB is slow compared to the oxidation of bromide, the catalytic reactions do not show an ethanol effect on the rate of the bromination reaction. However, when bromide oxidation is observed directly (by following the formation of Br_3^- at 272 nm), the presence of ethanol substantially inhibits the reaction. Under conditions of 0.1 mM LVO(OEt)(EtOH), 0.1 M Br^-, 1 mM H_2O_2, and 0.2 mM HCl, the absorbance at 272 nm increases rapidly: at a maximal rate of 0.135 AU/min after an initial lag phase of ~2 min. In the presence of 1 M ethanol under the otherwise identical conditions, the increase at 272 nm increases with a rate of 0.003 AU/min, a decrease of nearly 50-fold.

Bromination Reactions as a Function of Vanadium Complex Concentration. The production of BrTMB from H_2O_2, Br^-, TMB, and LVO(OEt)(EtOH) is approximately stoichiometric with respect to the vanadium complex at vanadium concentrations under 1 mM (Table Ir–u). As the vanadium concentration increases above 1 mM, the concentration of BrTMB synthesized levels off at *ca.* 1 mM (Table Iu–x). This behavior appears to be a result of two effects. First, at low vanadium complex concentrations, the accumulation of hydroxide leads to competition with peroxide for binding to the vanadium complex. Such a competition may explain why, at 0.1 mM vanadium complex, BrTMB production is greater than stoichiometric. Second, at higher complex concentrations, bromide oxidation ceases as a result of a change in redox potential due to the change in acid concentration as the reaction proceeds. Thus, the extent of bromide oxidation does not increase linearly with vanadium complex concentration.

Electrophilic Bromination. The brominating species was shown to be Br^+ rather than $Br^\cdot$ by investigating the products of bromination of 2,3-dimethoxytoluene (DMT): 0.1 M bromide, 4 mM hydrogen peroxide, 4 mM HCl, and 5 mM DMT react with 1 mM LVO(OEt)(EtOH) in DMF to produce only the ring-substituted bromo-2,3-dimethoxytoluene derivative,[26] demonstrating that the reaction occurs by a nonradical, or polar, process (Scheme II). The reaction of DMF with Br_2 and a catalytic amount of $FeBr_3$ in dichloromethane gave the same product, while the reaction of DMT and Br_2 in CCl_4 under UV irradiation gave the expected product from a radical reaction, 2,3-dimethoxybenzyl bromide. This chemistry is well-established for the bromination of toluene.[27] The change in the splitting pattern of the aromatic proton resonances from a triplet (δ 6.95 ppm) and two doublets (δ 6.77 and 6.76 ppm) to a pair of doublets (centered at δ 6.66 and 7.24 ppm) indicates that bromination occurred in either the 4- or the 6-position. The methyl ^1H resonance shifts slightly, from 2.27 to 2.34 ppm, upon bromination.

These DMT reactions are not quantitative with peroxide: *ca.* 0.2 mM BrDMT is synthesized in 30 min. All the organic substrate is recovered as product or starting material, showing that the organic substrate is not destroyed during the reaction.

(26) In the absence of acid, no BrDMT is observed: only one turnover is expected and L^{2-} is presumably brominated in preference to the less activated DMT.

(27) Volhardt, K. P. C. *Organic Chemistry*; W. H. Freeman & Co.: New York, 1987; pp 1090–1092.

Scheme II

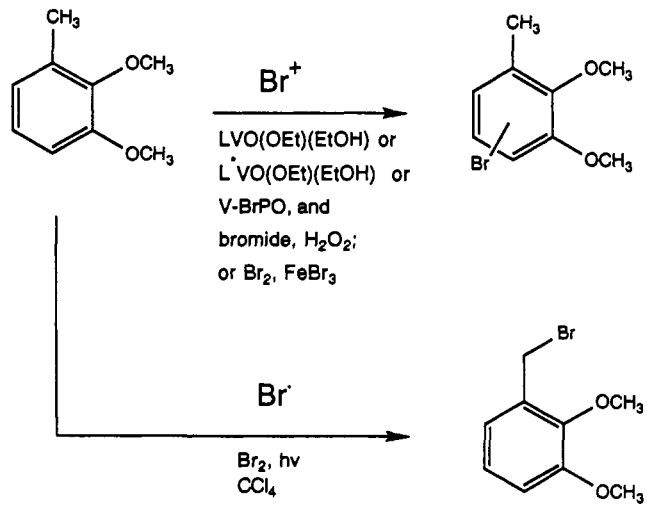


Table II. BrTMB Formation as a Function of $[H^+]$ and $[H_2O_2]$[a]

	[L*VO(OEt)(EtOH)]	$[H_2O_2]$	$[H^+]$	[BrTMB]
a	1.0	4	0	0.95
b	1.0	8	5	5.9
c	1.0	0	4	0.56
d	1.0	1	5	1.3
e	1.0	2	5	2.2
f	1.0	4	5	4.0
g	1.0	5	10	5.1
h	1.0	8	10	7.7

[a] Conditions were identical to those in Table I. Entries a and b are limited in acid, while entries c–h are limited in hydrogen peroxide.

In the absence of LVO(OEt)(EtOH), no BrDMT is produced under the conditions described above. Hydrogen peroxide is required for any bromination to occur.

Reactivity of L*VO(OEt)(EtOH). L*VO(OEt)(EtOH), where H_2L^* = *N*-(2-carboxyphenyl)salicylideneamine, shows bromination reactivity quite similar to that of LVO(OEt)(EtOH). As summarized in Table II: (1) BrTMB, stoichiometric with respect to vanadium is produced in the absence of acid; (2) equivalents of acid yield additional equivalents of BrTMB, provided the concentration of hydrogen peroxide is in excess of the sum of the vanadium and acid concentrations; (3) when the concentration of acid exceeds the concentration of hydrogen peroxide, BrTMB formation is stoichiometric with hydrogen peroxide. L*VO(OEt)-(EtOH) dissolved in DMF has a single ^{51}V NMR resonance at −550 ppm, which is unchanged by the addition of ethanol. The titration of 1 mM L*VO(OEt)(EtOH) with H_2O_2 results in the gradual replacement of the resonance at −550 ppm by two resonances at −502 and −585 ppm. The resonance at −502 ppm becomes the prominent one at H_2O_2:V = 3:1. The identity of the species giving rise to the resonance at −502 ppm is not known, but it is not observed in more dilute solution: addition of excess hydrogen peroxide (4 mM) to 0.1 mM L*VO(OEt)(EtOH) yields a single resonance at −585 ppm. This resonance is also the one observed upon the addition of 2 equiv of hydrogen peroxide to sodium vanadate in DMF. Like LVO(OEt)(EtOH), the L*VO-(OEt)(EtOH)-mediated DMT reaction yields only the ring-substituted product. Moreover, as for LVO(OEt)(EtOH), the addition of 1 mM sodium hydroxide to the mixture of 1 mM L*VO(OEt)(EtOH), 0.1 M bromide, and 5 mM TMB before initiation of the reaction with 4 mM peroxide prevents the formation of BrTMB.

Crystal Structures. The molecular structures of the two Schiff base ligand complexes of V(V) were determined by X-ray crystallography. Crystallographic data and atomic positions are given in Tables III and IV. The vanadium(V) complexes of these ligands crystallize from ethanolic solution with one coordinated ethoxide and one ethanol. The coordination environment of the

Table III. Crystallographic Data for LVO(OEt)(EtOH) and L*VO(OEt)(EtOH)

	LVO(OEt)(EtOH)	L*VO(OEt)(EtOH)
chem formula	$VC_{17}H_{20}NO_5$	$VC_{18}H_{20}NO_6$
fw	369.3	397.3
space group (No.)	*Pbca* (61)	*Fdd*2 (43)
a, Å	20.218(5)	17.7951(7)
b, Å	20.955(4)	33.118(3)
c, Å	16.196(3)	12.8834(5)
α, deg	90	90
β, deg	90	90
γ, deg	90	90
V, Å^3	6861.5	7592.6
Z	16	16
T, °C	23	23
λ, Å	0.71073	0.71073
ρ_{calc} g cm^{-3}	1.43	1.39
μ, cm^{-1}	5.83	5.35
$R(F_o)$, %	6.58	3.97
$R_w(F_o)$, %	7.27	4.78

Table IV. Selected Atomic Positions for LVO(OEt)(EtOH) and L*VO(OEt)(EtOH)[a]

LVO(OEt)(EtOH)

atom	*x/a*	*y/b*	*z/c*
V(1)	0.1099(1)	0.5550(1)	0.3008(1)
O(11)	0.1375(4)	0.5195(4)	0.3801(6)
O(12)	0.1478(4)	0.6362(4)	0.3183(6)
N(13)	0.1954(4)	0.5383(5)	0.2289(6)
O(14)	0.0859(4)	0.4857(4)	0.2317(6)
O(15)	0.0276(4)	0.5717(4)	0.3298(6)
O(16)	0.0798(4)	0.6090(4)	0.1806(5)
V(2)	0.0970(1)	0.8030(1)	0.1565(1)
O(21)	0.1164(4)	0.8444(4)	0.0783(6)
O(22)	0.1375(4)	0.7247(4)	0.1288(6)
N(23)	0.1846(5)	0.8253(6)	0.2220(8)
O(24)	0.0751(5)	0.8701(4)	0.2315(6)
O(25)	0.0129(4)	0.7846(4)	0.1358(5)
O(26)	0.0764(4)	0.7432(4)	0.2753(6)

L*VO(OEt)(EtOH)

atom	*x*	*y*	*z*
V(1)	0.14670(4)	−0.17950(2)	−0.48335
N(13)	0.0956(2)	−0.1869(1)	−0.3311(3)
O(12)	0.0463(2)	−0.1805(1)	−0.5283(3)
O(14)	0.2351(2)	−0.1964(1)	−0.4082(3)
O(15)	0.1883(2)	−0.1880(1)	−0.6068(3)
O(16)	0.1310(2)	−0.2464(1)	−0.4755(3)
O(11)	0.1572(2)	−0.1320(1)	−0.4735(3)

[a] The distances of the bonds involving N(13) and N(23) in LVO(OEt)(EtOH) were restrained as described under Materials and Methods.

vanadium consists of an oxo group and a weakly coordinated ethanol (bond length ~2.2 Å) in the axial positions; in the equatorial plane are an ethoxide and the Schiff base ligand, which is bonded through two oxygen atoms and one nitrogen atom. These complexes are structurally similar to another Schiff base complex of vanadium(V), L'VO(OMe)(MeOH), where H_2L' is *N*-(carboxymethyl)salicylideneamine.[7] Important bond lengths and angles are given in Table V. The vanadium sits in a distorted octahedral environment, with a typically short vanadium(V)–oxo distance and a very long vanadium–ethanol contact. The rings of the coordinated ligands are twisted, with dihedral angles of 19 and 13.6° for the two distinct L^{2-}ligands and 57° for L^{*2-}. The vanadium atoms lie above the least-squares planes defined by the equatorial ligands by 0.319 and 0.305 Å in LVO(OEt)(EtOH) and by 0.279 Å in L*VO(OEt)(EtOH). The structures are shown in Figures 6 and 7.

Discussion and Conclusions

A catalytic mechanism is proposed in Scheme III. The dissolution of LVO(OEt)(EtOH) gives rise to five species in solution (LVO(OEt), the active catalyst LVO(OH), and three stereoisomers of the dimer $(LVO)_2O$), as identified by ^{51}V NMR.

Table V. Selected Bond Distances and Angles in LVO(OEt)(EtOH) and L*VO(OEt)(EtOH)[a]

LVO(OEt)(EtOH)

Bond Distances, Å

V(1)–O(11)	1.586(9)	V(2)–O(21)	1.585(9)
V(1)–O(12)	1.886(9)	V(2)–O(22)	1.888(8)
V(1)–N(13)	2.114(5)	V(2)–N(23)	2.117(6)
V(1)–O(14)	1.897(9)	V(2)–O(24)	1.91(1)
V(1)–O(15)	1.764(8)	V(2)–O(25)	1.775(8)
V(1)–O(16)	2.332(8)	V(2)–O(26)	2.333(9)

Bond Angles, deg

O(12)–V(1)–O(11)	99.1(4)	O(22)–V(2)–O(21)	100.2(4)
N(13)–V(1)–O(11)	94.6(5)	N(23)–V(2)–O(21)	94.2(5)
N(13)–V(1)–O(12)	84.3(4)	N(23)–V(2)–O(22)	87.0(5)
O(14)–V(1)–O(11)	102.0(4)	O(24)–V(2)–O(21)	99.4(5)
O(14)–V(1)–O(12)	152.0(4)	O(24)–V(2)–O(22)	153.1(4)
O(14)–V(1)–N(13)	76.0(4)	O(24)–V(2)–N(23)	73.3(5)
O(15)–V(1)–O(11)	102.0(5)	O(25)–V(2)–O(21)	101.8(5)
O(15)–V(1)–O(12)	99.5(4)	O(25)–V(2)–O(22)	100.4(4)
O(15)–V(1)–N(13)	162.0(5)	O(25)–V(2)–N(23)	160.8(5)
O(15)–V(1)–O(14)	93.8(4)	O(25)–V(2)–O(24)	93.4(4)
O(16)–V(1)–O(11)	174.6(4)	O(26)–V(2)–O(21)	175.7(4)
O(16)–V(1)–O(12)	78.1(3)	O(26)–V(2)–O(22)	78.9(4)
O(16)–V(1)–N(13)	80.5(4)	O(26)–V(2)–N(23)	81.7(4)
O(16)–V(1)–O(14)	79.2(3)	O(26)–V(2)–O(24)	80.2(4)
O(16)–V(1)–O(15)	83.1(4)	O(26)–V(2)–O(25)	82.4(4)

L*VO(OEt)(EtOH)

Bond Distances, Å

V(1)–O(11)	1.589(3)	V(1)–O(14)	1.930(3)
V(1)–O(15)	1.777(3)	V(1)–N(13)	2.176(4)
V(1)–O(12)	1.879(3)	V(1)–O(16)	2.237(3)

Bond Angles, deg

O(11)–V(1)–O(15)	100.3(2)	O(15)–V(1)–O(16)	86.3(2)
O(11)–V(1)–O(12)	98.8(2)	O(12)–V(1)–O(14)	157.7(1)
O(11)–V(1)–O(14)	98.7(2)	O(12)–V(1)–N(13)	83.0(1)
O(11)–V(1)–N(13)	95.0(2)	O(12)–V(1)–O(16)	83.0(1)
O(11)–V(1)–O(16)	172.8(2)	O(14)–V(1)–N(13)	81.7(1)
O(15)–V(1)–O(12)	96.7(2)	O(14)–V(1)–O(16)	78.0(1)
O(15)–V(1)–O(14)	93.6(1)	N(13)–V(1)–O(16)	78.2(1)
O(15)–V(1)–N(13)	164.5(2)		

[a] The distances of the bonds involving N(13) and N(23) in LVO(OEt)(EtOH) were restrained as described under Materials and Methods.

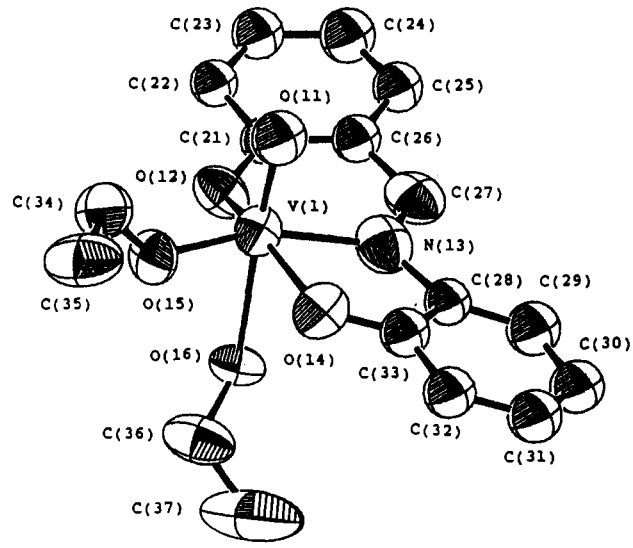


Figure 6. Molecular structure of LVO(OEt)(EtOH), showing the one of the two molecules in the asymmetric unit and the numbering scheme. The ORTEP[30] drawing shows the atoms at the 50% probability level. Hydrogen atoms were omitted for clarity.

Coordination of hydrogen peroxide produces a peroxo species, $LVO(O_2)^-$, with an NMR resonance at −519 ppm and an LMCT band at 366 nm. If the solution is suffiently acidic, bromide is oxidized, resulting in a two-electron-oxidized form (*e.g.*, HOBr, Br_2, Br_3^-, or V-OBr). One could envision binding of Br^- to

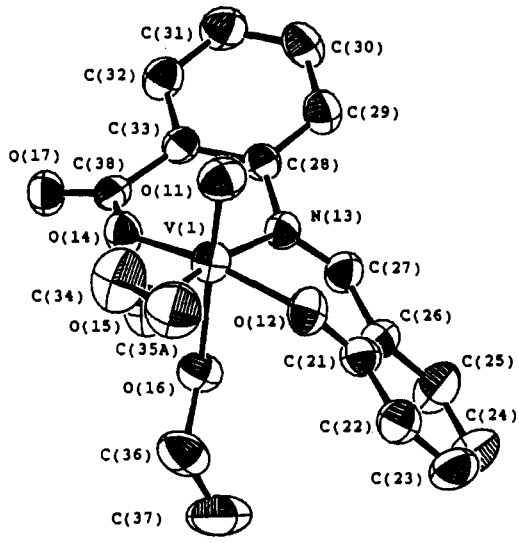
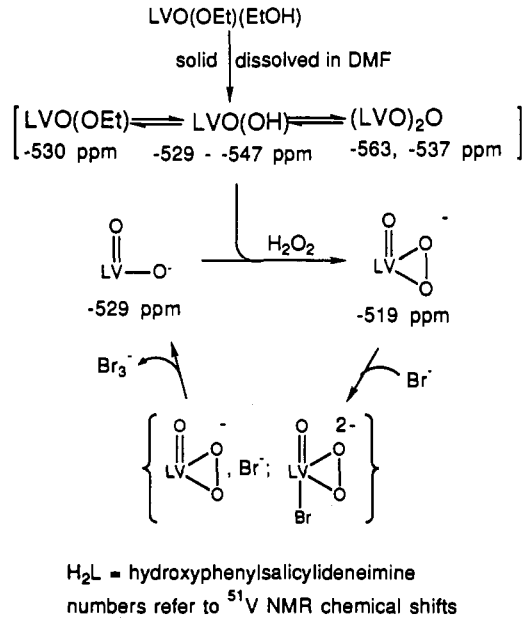


Figure 7. Molecular structure of L*VO(OEt)(EtOH), drawn as in Figure 6. Hydrogen atoms were omitted for clarity. The methyl group of the coordinated ethoxide in L*VO(OEt)(EtOH) is shown in only one of the two positions in which it was refined; its occupancy in this position is 67%.

Scheme III



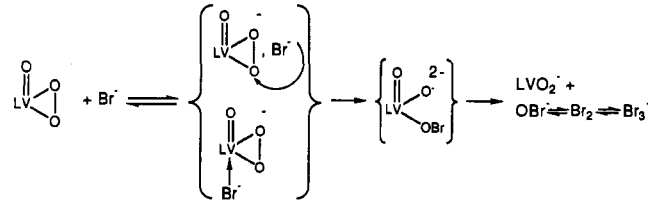
H_2L = hydroxyphenylsalicylideneimine
numbers refer to ^{51}V NMR chemical shifts

vanadium, followed by oxidation by the vanadium peroxo species, or direct nucleophilic attack by Br^- on the coordinated peroxide, giving rise to bound OBr^- (Scheme IV). Such an intermediate would be subject to rapid equilibration with HOBr, Br_2, and Br_3^-. Under our conditions (0.1 M Br^-), the only observable form of the oxidized species is Br_3^-, which accumulates in solution and brominates TMB. The identity of the initial product of bromination is obscured by this equilibrium.

The only spectroscopically observable vanadium species in solution is ligated by L^{2-}. The catalytically active species LVO(OH) binds peroxide and releases H_3O^+, generating the oxidatively competent $LVO(O_2)^-$. Ethoxide competes with peroxide for binding to vanadium, so the addition of ethanol lowers the rate of bromide oxidation in both stoichiometric and catalytic reactions. This reduction of the rate in reactions of LVO(OEt)(EtOH) is distinct from that of unligated V^V, where the effect of ethanol is negligible. The nature of the intermediate is not known; several possibilities are suggested.

The reactivity of LVO(OEt)(EtOH) and L*VO(OEt)(EtOH) is well-defined: these vanadium complexes catalyze the oxidation

Scheme IV



of bromide by hydrogen peroxide in DMF solution, analogous to the aqueous reaction of vanadium bromoperoxidase. The oxidized bromine species can be trapped by TMB to give BrTMB. The production of BrTMB is quantitative with consumption of hydrogen peroxide and catalytic in the vanadium species. The catalytic bromination reaction requires 1 equiv of acid per turnover after the first turnover. The oxidized bromine species is shown to be a Br^+ equivalent through the formation of bromo-2,3-dimethoxytoluene, not 2,3-dimethoxybenzyl bromide.[27] Vanadium bromoperoxidase also catalyzes the bromination of DMT only at the ring position,[28] indicating that the enzymatic reaction is not a radical process.[27]

In aqueous solution, bromide oxidation by hydrogen peroxide is only thermodynamically feasible under approximately neutral or acidic conditions.[29] Because the reduction potentials in DMF are not known, these thermodynamic considerations cannot be directly assessed. Inclusion of sodium hydroxide in the bromination reactions results in the cessation of bromide oxidation. Nevertheless, hydroxide binding to the vanadium complex is not the reason bromide oxidation ceases under conditions where either hydroxide is added or added acid is consumed. Both ^{51}V NMR and UV/vis data reveal that peroxide displaces hydroxide from the vanadium(V) center and that *after* bromination ceases, the $LVO(O_2)^-$ species remains spectroscopically observable. The function of the acid is to neutralize the base produced, in order for catalysis to occur. This acid dependence, and the ability to turn over once without any added acid, is distinct from the requirement of dioxovanadium(V) in aqueous solution, where a minimum of millimolar acid is necessary for the catalytic oxidation of bromide. In their acid requirement, LVO(OEt)(EtOH) and L*VO(OEt)(EtOH) more closely resemble vanadium bromoperoxidase, which functions optimally in buffered solutions at pH 5–7.[1]

LVO(OH) in aqueous DMF solution, as well as dioxovanadium(V) in acidic aqueous solution,[4] catalyze the peroxidative bromination of organic substrates. These functional mimics of vanadium bromoperoxidase suggest that the V^V-catalyzed oxidation of halides by hydrogen peroxide may be a fairly general property of the oxovanadium(V) moiety. Further investigations of bromide oxidation by $VO(O_2)^+$ in various ligand environments are underway.

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Supplementary Material Available: Tables VI–X and XI–XV, giving crystallographic details, positional and thermal parameters, bond distances, and bond angles for LVO(OEt)(EtOH) and L*VO(OEt)(EtOH), respectively (29 pages). Ordering information is given on any current masthead page.

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