Inorganic Chemistry

Article

Oxidation of Organic Sulfides by Vanadium Haloperoxidase Model Complexes

Thomas S. Smith, II and Vincent L. Pecoraro*

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109-1055

In addition to halide oxidation, the vanadium haloperoxidases are capable of oxidizing sulfides to sulfoxides. Four vanadium complexes with tripodal amine ligands, $K[VO(O_2)(heida)]$ (**1**), $VO_2(bpg)$ (**2**), $K[VO_2(ada)]$ (**3**), and $K_2[VO(O_2)(nta)]$ (**4**), previously shown to perform bromide oxidation (Colpas, G. J.; Hamstra, B. J.; Kampf, J. W.; Pecoraro, V. L. *J. Am. Chem. Soc.* **1996**, *118*, 3469–3477), have now been shown to oxidize aryl alkyl sulfides to the corresponding sulfoxides. The oxidation was observed by the disappearance of thioanisole's ultraviolet absorption at 290 nm, by the change in the aromatic region of the ^{1}H NMR spectrum of the sulfides, and by changes in the complexes' ^{51}V NMR spectra. The amount of methyl phenyl sulfide oxidized in 3 h was 1000 equiv (per metal complex). The oxidation product is almost exclusively sulfoxide, with very little sulfone (less than 3% over a 3 h experiment) formed. This is consistent with an electrophilic oxidation mechanism, as had been proposed for oxidation of bromide by **1**–**4**. The rate was found to be first order in substrate concentration, similar to the rate law observed for bromide oxidation. Unlike the bromide oxidation, the equivalent of acid required for peroxovanadium complex activation is not consumed. The complexes **1**–**4** are not reactive with styrene or cyclooctene. The relevance of these reactions to the mechanism of the vanadium haloperoxidases and, more generally, peroxovanadium oxygenation of sulfides will be discussed.

Introduction

The study of vanadium has been promoted by its presence in biological systems and its ability to serve as an oxidation catalyst. Vanadium is found naturally in ascidians, algae, and fungi.[1,2] It is also an essential cofactor in vanadium nitrogenase and the vanadium haloperoxidases (VHPOs).[3−9] Industrially, vanadium has been used in the Stretford process to aid in the removal of hydrogen sulfide from natural gas and petroleum fractions.[10−14]

Although the oxidation of sulfides by vanadium complexes is not new,[15−25] the exact mechanism by which it is accomplished is still a subject of study. Consistently, the

* Author to whom correspondence should be addressed. E-mail: vlpec@umich.edu.

(1) Henze, M. *Hoppe-Seyler's Z. Physiol. Chem.* **1911**, *72*, 494.
(2) ter Meulen, H. *Recl. Trav. Chim. Pays-Bas* **1931**, *50*, 491.
(3) Robson, R. L.; Eady, R. R.; Richardson, T. H.; Miller, R. W.; Hawkins, M.; Postgate, J. R. *Nature* **1986**, *322*, 388−390.
(4) Hales, B. J.; Langosch, D. J.; Case, E. E. *J. Biol. Chem.* **1986**, *261*, 15301−15306.
(5) Hales, B. J.; Case, E. E.; Morningstar, J. E.; Dzeda, M. F.; Mauterer, L. A. *Biochemistry* **1986**, *25*, 7251−7255.
(6) Blanchard, C. Z.; Hales, B. J. *Biochemistry* **1996**, *35*, 472−478.
(7) Eady, R. R.; Robson, R. L.; Richardson, T. H.; Miller, R. W.; Hawkins, M. *Biochem. J.* **1987**, *244*, 197−207.
(8) Ruttimann-Johnson, C.; Chatterjee, R.; Shah, V. K.; Ludden, P. W. In *Vanadium Compounds: Chemistry, Biochemistry, and Therapeutic Applications*; Tracey, A. S., Crans, D. C., Eds.; American Chemistry Society: Washington, DC, 1998; pp 228−240.
(9) Vilter, H. In *Metal Ions in Biological Systems*; Sigel, H., Sigel, A., Eds.; Marcel Dekker: New York, 1995; Vol. 31; pp 325−362.

(10) Nicklin, T.; Bruning, E. *Inst. Gas Eng. J.* **1961**, *8*, 523.
(11) Moyes, A. J.; Wilkinson. *Chem. Eng.* **1974**, 84.
(12) Ryder, C.; Smith, A. V. *Inst. Gas Eng. J.* **1963**, *10*, 283.
(13) Nicklin, T.; Holland, B. H. *Gas World* **1963**, *4123*, 273.
(14) Jhanji, A. K.; Carrano, C. J. *Inorg. Chim. Acta* **1993**, *214*, 141−144.
(15) Nakajima, K.; Kojima, K.; Kojima, M.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2620−2630.
(16) Vetter, A. H.; Berkessel, A. *Tetrahedron Lett.* **1998**, *39*, 1741−1744.
(17) Ghiron, A. F.; Thompson, R. C. *Inorg. Chem.* **1990**, *29*, 4457−4461.
(18) Bortolini, O.; Di Furia, F.; Modena, G. *J. Mol. Catal.* **1982**, *16*, 61−68.
(19) Cenci, S.; Di Furia, F.; Modena, G.; Curci, R.; Edwards, J. O. *J. Chem. Soc., Perkin Trans.* **1978**, 979−984.
(20) Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325−326.
(21) Nakajima, K.; Kojima, M.; Fujita, J. *Chem. Lett.* **1986**, 1483−1486.
(22) Nakajima, K.; Kojima, M.; Toriumi, K.; Saito, K.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 760−767.
(23) Bolm, C.; Bienewald, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2640−2642.
(24) Bryliakov, K. P.; Karpyshev, N. N.; Fominsky, S. A.; Tolstikov, A. G.; Talsi, E. P. *J. Mol. Catal. A* **2001**, *171*, 73−80.
(25) Ballistreri, F. P.; Tomaselli, G. A.; Toscano, R. M.; Conte, V.; Di Furia, F. *J. Am. Chem. Soc.* **1991**, *113*, 6209−6212.

active species is a vanadium(V) complex associated with and/ or generated by hydrogen peroxide or an organic peroxide.[15−25] As steric bulk has no effect on the rate of sulfide oxidation, direct coordination of sulfide to vanadium is unlikely.[26] There are apparently two mechanisms for sulfide oxidation, an electrophilic route[18] and a radical one.[25] The radical mechanism is more prevalent with diperoxovanadium complexes.[25] The electrophilic mechanism proceeds via nucleophilic attack by sulfide on a coordinated peroxide.[26]

It has recently been observed that VHPOs from several different species are capable of oxidizing organic sulfides.[27−31] The mechanism of this reactivity may be the same as that for the enzymes' haloperoxidase activity, as it is observed under identical conditions and there is no redox cycling of the vanadium. It is also similar to the electrophilic mechanism reported for monomeric vanadium complexes[18] as there is little observed further oxidation of the sulfoxide product. Sulfoxidation activity has also been observed in a vanadate-substituted phytase from *Aspergillus ficuum*.[32] The residues at the metal binding site of the phytase are remarkably similar to those near vanadium in the chloroperoxidase from *Curvularia inaequalis*.

The previous work with model complexes for the VHPOs has focused on halide oxidation. The Butler group has studied several successful reactivity models[33−35] and has recently detailed a compound with an intramolecular hydrogen bond to a vanadium-bound peroxide.[36] Colpas et al. reported an excellent set of model complexes with tripodal amine ligands.[37] While proficient at bromide oxidation, these compounds have not been tested yet for sulfide oxidation. In order to test whether the mechanisms of halide and sulfide oxidation are linked, as well as establish the tripodal amine complexes as complete models of VHPO activity, the following study into their sulfide oxidation activity was undertaken. As we will show, the halide and sulfide oxidation mechanisms are indeed the same. Therefore, the importance of an equivalent of acid (which is required for halide oxidation) for sulfide oxidation was examined. Despite the fact that little work into this particular aspect of catalytic initiation of vanadium complexes has been reported, we show
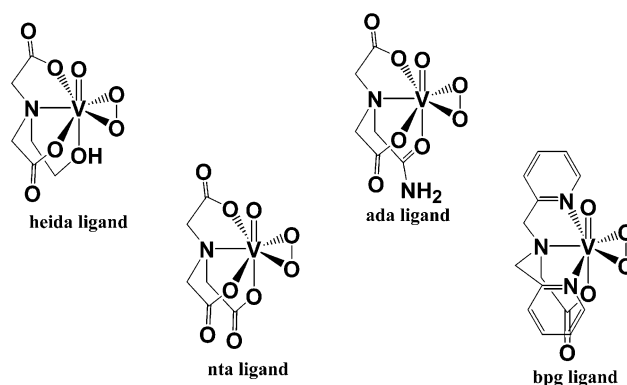

Figure 1. Vanadium haloperoxidase halide oxidation models by Colpas et. al examined in this study for sulfide oxidation.[37]

that in this system protonation of the peroxo compound is essential.

Materials and Methods

The following abbreviations are used throughout this manuscript: H_2heida = N-(2-hydroxyethyl)iminodiacetic acid; Hbpg = N,N-bis(2-pyridylmethyl)glycine; H_2ada = N-(2-amidomethyl)-iminodiacetic acid; H_3nta = nitrilotriacetic acid.

$K[VO(O_2)(heida)]$ (**1**), $K_2[VO(O_2)(nta)]$ (**2**), $K[VO_2(ada)]$ (**3**), and $VO_2(bpg)$ (**4**) (shown in Figure 1) were all synthesized according to previously reported procedures.[37] **CAUTION**: Metal−peroxo complexes have the potential to be explosive. Although this group has had no incidences of peroxovanadium complexes detonating, they should always be treated with the utmost caution, including working with as small amounts as possible and preventing exposure to elevated temperatures. In order to ensure that no appreciable decomposition of isolated peroxovanadium complexes or their solutions were affecting experiments, no solid samples older than 1 week were used, and no solution samples older than 6 h were used.

UV−visible spectra were measured with a Perkin-Elmer Lambda-9 spectrometer controlled by a Dell Optiplex PC. ^{1}H NMR spectra were performed on a Varian 300 MHz NMR. [51]V NMR spectra were obtained with 5000 scans on a Bruker 360 MHz instrument with a broadband probe and using $VOCl_3$ as an external standard.

All reactions were performed in CH_3CN, or CD_3CN for ^{1}H NMR studies. Solvents were purchased from Fisher (or Isotec for CD_3CN) and were pretreated with $CuSO_4/MgSO_4$ to remove basic impurities as in previous studies.[37] All other reagents were purchased from Aldrich Chemical. Vanadium complexes were dissolved by the addition of between 2 and 3 equiv of 18-crown-6 per potassium ion present, as needed. Unless otherwise specified, the vanadium complex concentration of all solutions was 250 μM. Et_4NPF_6 (100 equiv) was added to each solution to maintain constant ionic strength relative to vanadium concentration. Experiments with and without tetraethylammonium hexafluorophosphate showed no difference in reactivity. Reagents in aqueous solution (H_2O_2 and HPF_6) were used as concentrated as possible. While HPF_6 was the acid used in these experiments, both perchloric and triflic acids are also sufficient for sulfide oxidation to take place. The substrate used was thioanisole (methyl phenyl sulfide) unless otherwise stated. Unless otherwise specified in the text, the UV−visible experiments were 1:100:2:1 in vanadium complex:H_2O_2:substrate:acid, and reactants were added to solution in that order. Order of addition affected the reaction only if acid were added before hydrogen peroxide, resulting in degradation of the vanadium complex. Ratios

(26) Butler, A.; Clague, M. J.; Meister, G. E. *Chem. Rev.* **1994**, *94*, 625−638.
(27) ten Brink, H. B.; Tuynman, A.; Dekker, H. L.; Hemrika, W.; Izumi, Y.; Oshiro, T.; Schoemaker, H. E.; Wever, R. *Inorg. Chem.* **1998**, *37*, 6780−6784.
(28) Andersson, M. A.; Willetts, A.; Allenmark, S. G. *J. Org. Chem.* **1997**, *62*, 8455−8458.
(29) Andersson, M. A.; Allenmark, S. G. *Tetrahedron* **1998**, *54*, 15293−15304.
(30) ten Brink, H. B.; Holland, H. L.; Schoemaker, H. E.; van Lingen, H.; Wever, R. *Tetrahedron: Asymmetry* **1999**, *10*, 4563−4572.
(31) ten Brink, H. B.; Schoemaker, H. E.; Wever, R. *Eur. J. Biochem.* **2001**, *268*, 132−138.
(32) van de Velde, F.; Arends, I. W. C. E.; Sheldon, R. A. *J. Inorg. Biochem.* **2000**, *80*, 81−89.
(33) de la Rosa, R. I.; Clague, M. J.; Butler, A. *J. Am. Chem. Soc.* **1992**, *114*, 760−761.
(34) Clague, M. J.; Butler, A. *J. Am. Chem. Soc.* **1995**, *117*, 3475−3484.
(35) Clague, M. J.; Keder, N. L.; Butler, A. *Inorg. Chem.* **1993**, *32*, 4754−4761.
(36) Kimblin, C.; Bu, X.; Butler, A. *Inorg. Chem.* **2002**, *41*, 161−163.
(37) Colpas, G. J.; Hamstra, B. J.; Kampf, J. W.; Pecoraro, V. L. *J. Am. Chem. Soc.* **1996**, *118*, 3469−3477.
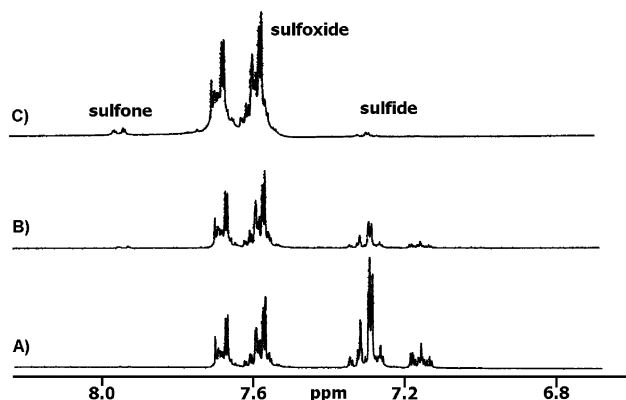
Figure 2. ^{1}H NMR spectra following the oxidation of 1000 equiv of thioanisole by K[VO(O$_2$)(heida)]. Spectra after (A) 1 h, (B) 2 h, and (C) 3 h.

for ^{1}H NMR experiments were 1:2000:1000:1 unless otherwise stated, and ^{1}H NMR experiments used the same order of reagent addition to solution. Addition of 2000 equiv of nitrosobenzene (radical trap) to the reaction solutions yielded no discernible effect on product amounts or distribution as observed by ^{1}H NMR.

Results

Identity of Oxidation Products. Sulfide oxidation by the vanadium complexes was monitored via ^{1}H NMR to determine the identity of the products. With thioanisole, the aromatic region is particularly informative, as no other species in the experiment contains aromatic protons. The aromatic protons in thioanisole show up as multiplets centered at 7.16 and 7.30 ppm. For comparison, the aromatic protons from an authentic sample of phenyl methyl sulfoxide appear as multiplets centered at 7.58 and 7.68 ppm.

With 1000 equiv of substrate per equivalent of K[VO(O$_2$)-(heida)], spectra were recorded every hour. These spectra are shown in Figure 2. After 1 h, just over half of the sulfide appears to have been oxidized to the sulfoxide. At 2 h, about 80% of the sulfide had reacted. After 3 h, nearly all of the sulfide had been consumed, and only a minimal amount (<3%) of overoxidation to the sulfone was observed. This product distribution is observed with 10 and 100 equiv of substrate as well.

The oxidation of phenyl ethyl sulfide can also be observed under these conditions. Its oxidation was somewhat slower, taking 3.5 h to reach completion, with a half-life of just over 1 h. Alkenes were also used as substrates to attempt to generate the corresponding epoxide. Neither styrene nor *cis*-cyclooctene was oxygenated in 24 h, as observed by ^{1}H NMR.

Solution Behavior of Vanadium Complexes under Catalytic Conditions. [51]V NMR spectroscopy was employed to observe the behavior of K[VO(O$_2$)(heida)] under different experimental conditions (Figure 3). The complex's lone observed NMR signal at $\delta = -523$ ppm, within the range expected for monoperoxovanadium complexes in acetonitrile, did not change upon addition of excess hydrogen peroxide. Addition of a single equivalent of HPF$_6$ broadened this signal and shifted it downfield by 5 ppm. This effect was not seen with addition of an equal volume of water. Two equivalents
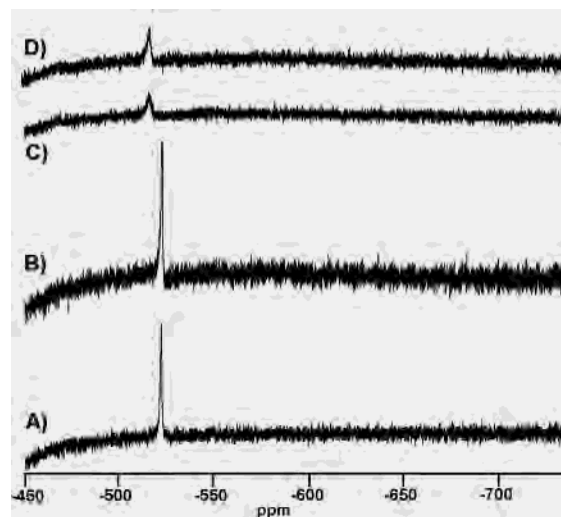

Figure 3. [51]V NMR spectra of K[VO(O$_2$)(heida)], showing changes with sequential addition of (A) complex only, (B) peroxide, (C) peroxide, then substrate, and (D) peroxide, then substrate, then acid. The added dotted line for ease of comparison is at $\delta = -520$ ppm.

of thioanisole did not yield any observable change to the shifted peak. Conditions which caused significant changes to the spectrum were those expected to cause degradation of the complex: addition of 2 equiv of acid rather than 1 equiv, and no hydrogen peroxide added such that the only peroxide present is the one already bound. The degradation products show two peaks at $\delta = -500$ to -510 and -470 to -475 ppm. These peaks are close to those assigned to decavanadate in previous work from our group on the [51]V NMR of vanadate species.[38] They are shifted downfield somewhat from the major peaks normally attributed to decavanadate species due to a decrease in water concentration.

Effects of Concentration Variations on Sulfide Oxidation Chemistry. The disappearance of the UV absorption at 290 nm can be used to monitor the consumption of thioanisole. This is then a convenient way to monitor catalytic oxidations of a small amount of substrate. The extinction coefficient difference at 290 nm between sulfide and sulfoxide is $\Delta\epsilon = -0.44$ mM^{-1} cm^{-1}, or an absorbance difference under these experimental conditions of about 0.12 absorbance units per equivalent of sulfide consumed.[27] The effect of changing the number of equivalents of thioanisole used in the reaction (from 1 to 4) was then followed as shown in Figure 4A. Regardless of the initial concentration, all sulfide was consumed in about 20 min. The initial delay in absorbance drop is actually a result of the increase in vanadium complex absorption at 290 nm due to formation of the active species, as seen in a spectrum taken upon addition of acid to the peroxovanadium complex without substrate present (Figure S2, Supporting Information). The spectrum of vanadium complex plus acid was subtracted from the peroxovanadium complex plus acid and substrate spectra to give the spectra shown in Figure 4B, from which initial rates were calculated.

(38) Slebodnick, C.; Pecoraro, V. L. *Inorg. Chim. Acta* **1998**, *283*, 37−43.
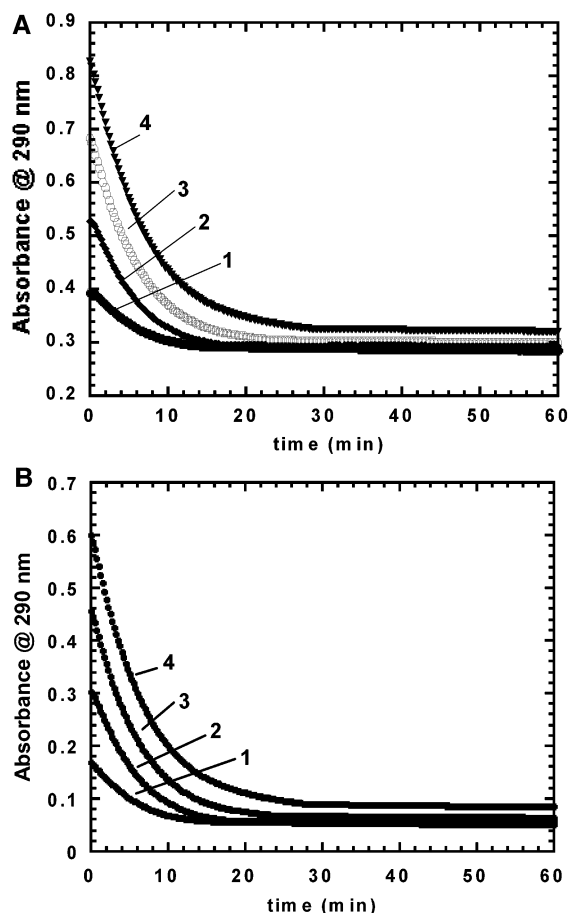
Figure 4. (A) Oxidation of thioanisole by K[VO(O₂)(heida)], monitored at 290 nm when substrate concentration is varied. Equivalents of PhSMe are indicated by numbers in the figure. (B) Oxidation of thioanisole by K[VO(O₂)(heida)], monitored at 290 nm when substrate concentration is varied. These spectra are the result of subtracting the absorbance increase due to active species formation from the spectra in Figure 4A. Equivalents of PhSMe are indicated by numbers in the figure.

As increasing the equivalents of acid used above 1 would result in the decomposition of the vanadium complex, only substoichiometric amounts of acid were studied. The number of equivalents of acid used was reduced at 0.2 equiv intervals. The decrease in reaction rate with decrease in amount of acid added can be seen in Figure 5. Observations were made at smaller amounts of hydrogen peroxide, down to 2.5 equiv per vanadium complex. A larger excess of hydrogen peroxide than 100 equiv gave no increase in rate. The effects of changes in peroxide concentration are provided in Figure 6. Four tripodal amine complexes were examined for sulfide oxidation activity. The oxoperoxovanadium complexes with heida and nta ligands displayed appreciable activity. [VO(O₂)(ada)]⁻ resulted in slight sulfoxidation activity, while **4** displayed no activity. The relative activity of these complexes can be seen in the spectra in Figure 7.

Discussion

Kinetics and Concentration Effects. The change in sulfide consumption has been monitored by UV−visible spectroscopy upon variations in acid, peroxide, and substrate concentrations relative to catalyst concentration. These
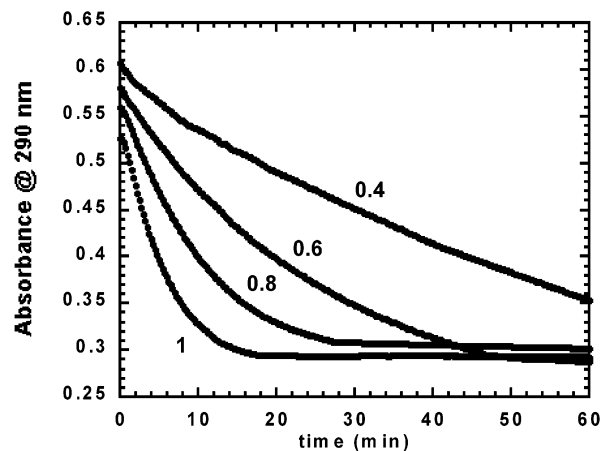

Figure 5. Oxidation of thioanisole by K[VO(O₂)(heida)], monitored at 290 nm when acid concentration is varied. Equivalents of HPF₆ are indicated next to each curve.
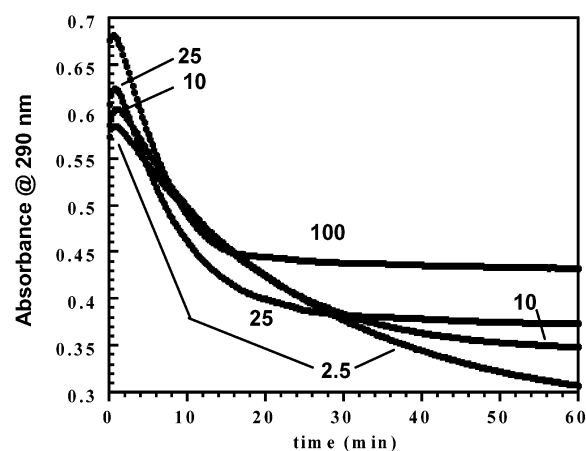

Figure 6. Oxidation of thioanisole by K[VO(O₂)(heida)], monitored at 290 nm when hydrogen peroxide concentration is varied. Equivalents of H₂O₂ are indicated directly in the figure.
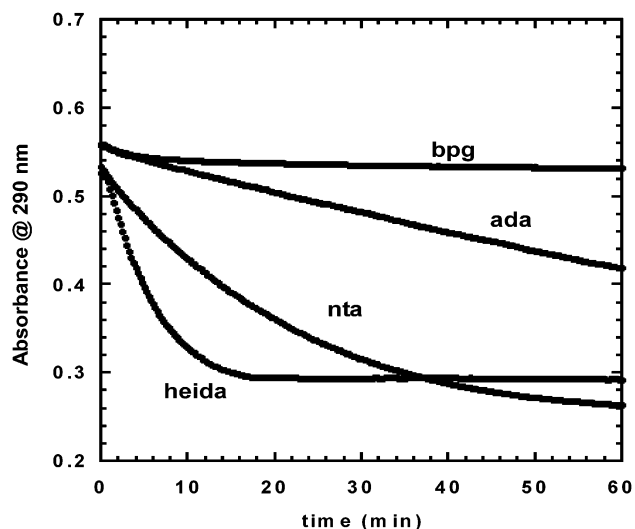

Figure 7. Oxidation of thioanisole by peroxovanadium complexes with differing ligands, monitored at 290 nm.

variations provide differing insights into the mechanism of sulfide oxidation.

Varying sulfide concentration from 1 to 4 equiv per vanadium results in an increase in the rate of sulfide
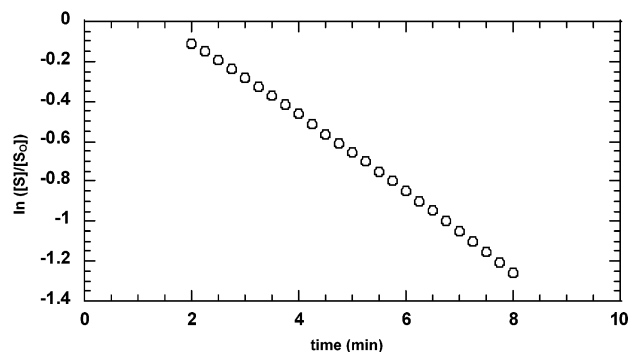
Figure 8. Application of the integrated first-order rate law for sulfide oxidation by $K[VO(O_2)(heida)]$ when substrate concentration is varied.

Table 1. Pseudo-First-Order Rate Constant Calculated by Varying Acid Amounts

		k	
substrate equiv.	$t_{1/2}$ (min)	from half-life	from rate law
1	4.226	0.00273	0.00171
2	4.215	0.00274	0.00215
3	4.349	0.00266	0.00217
4	4.857	0.00238	0.00195

consumption. This increase in rate is regular with the observed half-life at all four concentrations being approximately 5 min. The constant half-life with increase in concentration points toward the sulfoxidation being first order in substrate concentration. The UV−visible data from the initial 10 min of the reaction was fit to the integrated first-order rate law,

$$\ln([S]/[S_0]) = -kt$$

which gives straight lines with a slope equal to a pseudo-first-order rate constant. An example of this is found in Figure 8. A summary of all rate constants can be found in Table 2. The observed pseudo-first-order rate constant averaged from the integrated rate law calculations is $(2.00 \pm 0.29) \times 10^{-3}$ s^{-1}.

The rate law previously determined for halide oxidation was[37]

$$\text{rate} = k[\text{oxidizing species}][\text{substrate}]$$

or

$$\text{rate} = k_{\text{pseudo}}[\text{substrate}], \quad k_{\text{pseudo}} = k[\text{oxidizing species}]$$

This rate law is consistent with the sulfide oxidation reaction since it is also first order in substrate concentration. Therefore, we next assessed the rate dependence on the vanadium peroxo complex which is the oxidizing species and which is predicted to be first order. However, the dependence on vanadium complex concentration, acid, and peroxide is not as simple as the substrate dependence described above.

Decreasing the amount of acid present to substoichiometric levels does decrease the speed of sulfide oxidation, but the relationship is not merely first or second order. The order of the reaction in acid calculates to less than 1. Similarly, the peroxide dependence is not simple. As the number of

equivalents of hydrogen peroxide is increased, the reaction rate increases until approximately 25 equiv, and then the rate levels out. These observations can be explained by considering how peroxide binds to vanadium.

Previous study into peroxide binding has shown that the rate of peroxovanadium complex creation is dependent upon the amount of acid present.[39] Peroxovanadium complex formation proceeds by an associative mechanism with the rate-determining step as the dissociation of water or hydroxide[40] (Figure 9). In the presence of up to 1 equiv of acid, peroxo-complex formation is first order in acid concentration. At more than 1 equiv, no increase in reaction rate is observed. Peroxovanadium complex formation shows saturation behavior with regard to hydrogen peroxide concentration in the absence of acid.[39] In the presence of acid, the peroxovanadium complex formation is first order in hydrogen peroxide.[39] This leads to the conclusion that at substoichiometric acid concentrations or at less than 25 equiv of hydrogen peroxide, the rate of peroxovanadium complex formation is slower than the rate of sulfide oxidation. At stoichiometric acid concentrations and greater than 25 equiv of hydrogen peroxide, the rate of sulfide oxidation is then rate-determining.

The four complexes studied show the same trend in rate of sulfide oxidation as they do for halide oxidation.[37] The $VO(HO_2)(bpg)$ complex is inactive as far as sulfide oxidation is concerned. This same complex is worse by an order of magnitude than the other three vanadium tripodal amine complexes at halide oxidation. The rate of sulfide oxidation also follows the same trend in the pK_a of the protonated peroxovanadium complex. The lower the pK_a of the complex, the worse the complex is at sulfide oxidation, reinforcing the notion that the protonated peroxo complex is needed for oxidation. As the pK_a of hydrogen peroxide is similar to that of the peroxo complexes,[37] the increasing competition for the proton will decrease the sulfide oxidation activity of the complex.

Mechanism. The sulfide oxidation mechanism has proven to be highly similar to halide oxidation by these complexes. A simple form of the halide oxidation mechanism is shown in Figure 10. Once the initial oxoperoxovanadium complex is protonated, the substrate then engages in a nucleophilic attack on the protonated peroxide ligand. The product distribution of almost exclusively sulfoxide products with little further oxidation points to an electrophilic rather than radical mechanism. Figure 11 highlights the only difference between the halide and sulfide oxidation mechanisms: the fate of the acid equivalent required for reactivity. In halide oxidation, the acid is consumed in each cycle, necessitating the addition of an equivalent of acid for each turnover. In sulfide oxidation, the acid is not consumed, and approximately a thousand turnovers have been observed with only the single initial equivalent of acid added to the reaction. ^{51}V NMR reveals that amounts of acid above 1 equiv per vanadium lead to decomposition of the complex. In order to

(39) Hamstra, B. J.; Colpas, G. J.; Pecoraro, V. L. *Inorg. Chem.* **1998**, *37*, 949−955.
(40) Yamada, S.; Ukei, Y.; Tanaka, M. *Inorg. Chem.* **1976**, *15*, 964−967.

Table 2. Sulfide Oxidation Parameters for Selected Systems[a]

system	max. reported turnovers (time, h)	pseudo-first-order k, s^{-1}	corrected or second-order k, M^{-1} s^{-1}	ref
K[VO(O$_2$)(heida)] + H$_2$O$_2$	~950 (3)	2.00×10^{-3}	8.1[b]	this work
K[VO(O$_2$)(heida)] + H$_2$O$_2$ (PhSEt)	~950 (3.5)			this work
VBrPO (*A. nodosum*) + H$_2$O$_2$	520 (20)			29
VBrPO (*C. pilulifera*) + H$_2$O$_2$	450 (20)			28
VClPO (recomb) + H$_2$O$_2$	560 (20)			27
Kagan-modified Sharpless reagent (Ti/diethyltartrate) + *t*-BuOOH	20 (3)			41
(VO(acac)$_2$ + H$_2$O$_2$)			2.9[c]	18
(VO(OEt)$_3$ + *t*-BuOOH) (Bu$_2$S)			6.1×10^{-3}	19
(VO(O-*i*-Pr)$_3$ + diethyltartrate + *t*-BuOOH) (*p*-tolyl methyl sulfide)	1 (6)			20
(VO(3-MeOSal-RR-chxn) + cumene-OOH)	10 (37)			21
VO(sal-L-ala)(OMe)(MeOH) + *t*-BuOOH	10 (5.5)			22
(VO(acac)$_2$ + chiral shed L) + H$_2$O$_2$	100 (16)			23
VO(O-*i*-Pr)$_3$ + chiral shed L + H$_2$O$_2$	73 (13)			24
VO$_4^{3-}$ substituted phytase (*A. ficuum*) + H$_2$O$_2$			0.130	32
K[VO(O$_2$)(dipic)] + H$_2$O$_2$ ([(en)$_2$Co(SCH$_2$CH$_2$NH$_2$)]$^{2+}$)	~0.1	4.0×10^{-9}	8×10^{-4} [b]	17

[a] Substrate is PhSMe unless stated otherwise. [b] Calculated from pseudo-first-order constant correcting for V complex concentration. [c] Calculated from pseudo-zero-order constant.
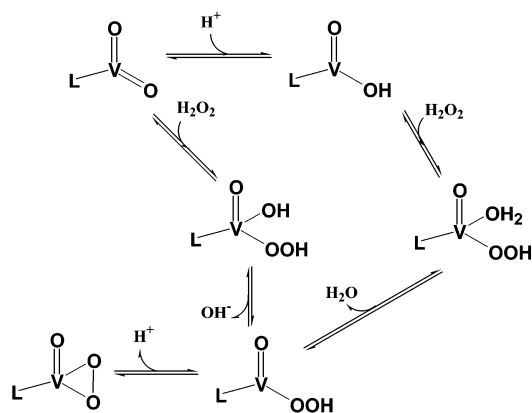

Figure 9. Scheme for the binding of peroxide to vanadium. Adapted from Hamstra, B. J.; Colpas, G. J.; Pecoraro, V. L. *Inorg. Chem.* **1998**, *37*, 949−955. Copyright 1998 American Chemical Society.
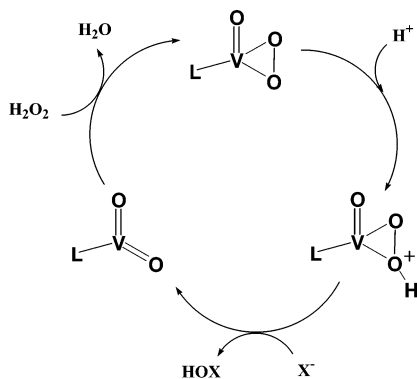

Figure 10. Simplistic halide oxidation mechanism, abbreviating steps regarding peroxide coordination to vanadium.

complete the catalytic cycle, the active protonated peroxovanadium species must be regenerated. In the presence of sufficiently strong acid, the dioxovanadium complex is first protonated. Then hydrogen peroxide binds, losing a proton to the coordinated hydroxide. This bound water molecule is then lost in the rate-determining step.[39] Without excess hydrogen peroxide, the equivalent of acid leads to decomposition of the complex after turnover. At stoichiometric acid
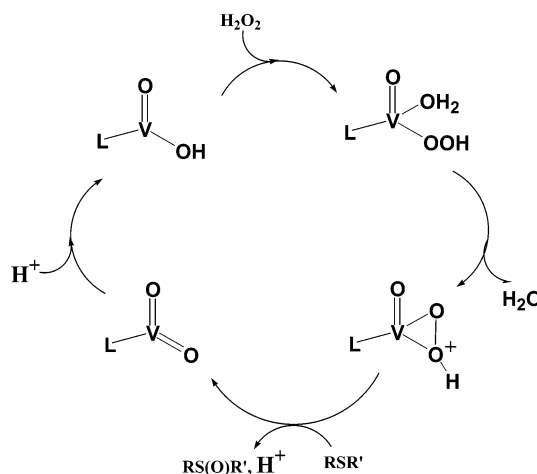

Figure 11. Complete scheme for the catalytic cycle of sulfide oxidation by monoperoxovanadium(V) tripodal amine complexes.

concentration and greater than 25 excess equiv of hydrogen peroxide, this regeneration step is not the rate-determining step.

Comparison to Existing Systems. Most studies into sulfide oxidation by vanadium complexes use VO(acac)$_2$ as a precursor, and generate the active catalyst in situ by adding a ligand and hydrogen peroxide or an organic hydroperoxide.[18,21−23] In almost all cases, the active species formed is not isolated. These complexes are generally capable of ~100 turnovers in 16 h (Table 2). K[VO(O$_2$)(heida)] is superior to these systems and any other electrophilic vanadium sulfide oxidation catalyst in terms of number of turnovers, turnovers per unit time, and rate.[17−24,27−29,32,41]

One procedural difference in the use of these tripodal amine complexes is the added equivalent of acid. Most other compounds are used with no added acid, or substoichiometric amounts of acid to prevent the formation of diperoxovanadate.[17] As the tripodal amine complexes show no

(41) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188−8193.

oxidation capability in the absence of acid, it is reasonable to believe that the sulfoxidation activity could, in at least some of the other systems, have their oxidation activity enhanced by addition of stoichiometric amounts of strong acid. These other systems could react via the same mechanism, using instead the slower route with hydrogen peroxide filling the role of acid from Figure 10.

Comparison to the Vanadium Haloperoxidases. The oxidation of sulfides by these model complexes follows a mechanism related to that of the sulfide oxidation by the vanadium bromoperoxidases. It is of interest that vanadium chloroperoxidase does not exhibit sulfoxidation chemistry. Isotopic labeling experiments have determined that the sulfoxide oxygen in the products of VBrPO oxidation is exclusively from hydrogen peroxide.[31] Optimization of this catalysis has determined that the reaction is pH-dependent, with an abrupt change at a pH of about 6, or approximately the pK_a of a histidine side chain.[29] The model proposed by Wever et al. includes nucleophilic attack of the substrate sulfur atom onto a peroxide coordinated to the V(V), but does not explicitly feature a proton on this bound peroxide. As was the case with halide oxidation, it is our contention that protonation of the bound peroxide is an essential feature of peroxide activation. Therefore, we prefer the modified mechanism shown in Figure 11. We have previously suggested that a nearby histidine, or other basic residue, could serve a proton carrier role to the VHPO active site.[42] The oxidation of sulfides by the VHPOs should therefore proceed as shown in Figure 11.

(42) de Boer, E.; Wever, R. *J. Biol. Chem.* **1988**, *263*, 12326−12332.

Conclusion

Dioxovanadium(V) tripodal amine complexes that have previously been shown to be superior models for the halide oxidation activity of the vanadium haloperoxidases have now demonstrated significant sulfide oxidation activity as well. K[VO(O$_2$)(heida)], the fastest halide oxidation catalyst, is the best (in terms of number of turnovers as well as rate) at oxidizing organic sulfides to sulfoxides. This complex is capable of 1000 turnovers with thioanisole as substrate in 3 h, with little overoxidation to the sulfone. The sulfide oxidation reaction is first order in substrate concentration, just as the halide oxidation is. This electrophilic oxidation is proposed to proceed via the same mechanism as the halide oxidation does, with a protonated monoperoxovanadium complex as the active species. The only difference between the two involves the equivalent of acid necessary for activity. Whereas in halide oxidation 1 equiv of acid is needed per turnover, for sulfide oxidation the equivalent of acid is not consumed. One equivalent of acid is sufficient for 1000 turnovers of activity.

Supporting Information Available: Complete numerical data detailing the changes in oxidation rate with changing conditions, [51]V NMR spectra of **1** under control and decomposition conditions, and a UV spectrum of the absorbance increase of **1** upon activation by acid. This material is available free of charge via the Internet at http://pubs.acs.org.

IC025650D