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C_3 Vanadium(V) Amine Triphenolate Complexes: Vanadium Haloperoxidase Structural and Functional Models

Miriam Mba,[†] Marta Pontini,[†] Silvia Lovat,[†] Cristiano Zonta,[†] Gerald Bernardinelli,[‡] Peter E. Kündig,[§] and Giulia Licini*,[†]

Dipartimento di Scienze Chimiche, Università di Padova, via Marzolo 1, 35131 Padova, Italy, Laboratorie de Cristallographie, Université de Genève, 24 Quai Ernest Anserment 1211, Genève 4, Switzerland, and Department of Organic Chemistry, Université de Genève, 30 Quai Ernest Anserment 1211 Genève 4, Switzerland

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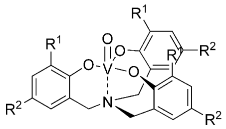
The C_3 vanadium(V) amine triphenolate complex **1f** has been characterized as a structural and functional model of vanadium haloperoxidases. The complex catalyzes efficiently sulfoxidations at room temperature using hydrogen peroxide as the terminal oxidant, yielding the corresponding sulfoxides in quantitative yields and high selectivities (catalyst loading down to 0.01%, TONs up to 9900, and TOFs up to 8000 h^{-1}) as well as bromination of 1,3,5-trimethoxybenzene (catalyst loading down to 0.05%, TONs up to 1260, and TOFs up to 220 h^{-1}).

Vanadium haloperoxidases (VHPOs), first discovered in 1984,[1] are vanadium-dependent enzymes able to oxidize halides to the corresponding X^+ species in the presence of hydrogen peroxide (H_2O_2), leading to halogenation of suitable substrates.[2] It has been shown that VHPOs catalyze also the oxidation of different organic substrates, i.e., sulfides to sulfoxides.[3]

In the native state, VHPOs show a five-coordinated V^V center with trigonal-bipyramidal geometry, where three oxygens are in the equatorial plane and one nitrogen (N_ϵ from His) and one oxygen in the axial positions.[4]

Several V^V complexes emulating the coordination sphere of the metal in these enzymes have appeared in the literature as structural and functional models for VHPOs.[5] Recently, vanadium(V) oxoamine triphenolate complexes **1a**−**1c** have been reported as structural models for VHPOs (Figure 1).[6]

The complexes exhibit a trigonal-bipyramidal geometry with the three phenolate oxygens in the equatorial plane and the oxo moiety and the nitrogen atom occupying the two axial positions.



1a $R^1 = R^2 = Cl$
1b $R^1 = R^2 = Me$
1c $R^1 = R^2 = t\text{-}Bu$
1d $R^1 = R^2 = H$
1e $R^1 = Me$, $R^2 = H$
1f $R^1 = t\text{-}Bu$, $R^2 = H$

Figure 1. C_3-symmetric vanadium(V) amine triphenolate complexes **1a**−**1f** as structural models for VHPOs.

Recently, we have been involved in the study of coordination chemistry and catalytic activity of C_3-symmetric amine triphenolate complexes.[7,8] In a recent study, we have shown that in situ prepared titanium(IV) amine triphenolate complexes are able to activate H_2O_2 and catalyze the oxidation of sulfides, with catalyst loadings down to 0.01%, TONs up to 8000, and TOFs up to 1700 h^{-1}.[7b] These results prompted us to synthesize the novel V^V complexes **1d**−**1f** and study their ability to catalyze the oxidation of sulfides and halides with H_2O_2. The reaction of triphenolamines[9] with VO(O*i*-Pr)$_3$ in dry tetrahydrofuran under nitrogen yielded complexes **1d**−**1f** as deep-red crystalline solids in high yields (92−94%). The observed complexation behavior is in complete accordance with the

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* To whom correspondence should be addressed. E-mail: giulia.licini@unipd.it.

[†] Università di Padova.

[‡] Laboratorie de Cristallographie, Université de Genève.

[§] Department of Organic Chemistry, Université de Genève.

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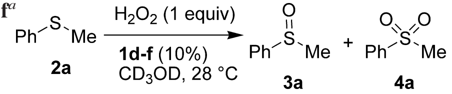
Table 1. Oxidation of **2a** by Aqueous H_2O_2 (35%) Catalyzed by **1d**−**1f**[a]



entry	catalyst	time (min)[b]	yield (%)[c]	**3a**:**4a**[c]
1	**1d**	720	7	>99:1
2	**1e**	10	89	99:1
3	**1f**	10	99	99:1
4		720	3	>99:1

[a] Reaction conditions: $[\mathbf{2a}]_0 = [H_2O_2]_0 = 0.09$ M, 10% catalyst, CD_3OD, 28 °C. [b] Time required for complete oxidant consumption. [c] Determined on the oxidant by ^{1}H NMR (CD_3OD, 300 MHz), with dichloroethane as the internal standard, and quantitative gas chromatography analysis on the crude reaction mixture after complete oxidant consumption (iodometric test).

structurally similar complexes described in the literature, which contain additional *para* substituents on the phenolic moiety.[6−8] Complexes **1e** and **1f** (R^1 = Me and *t*-Bu, respectively) show highly symmetric ^{1}H NMR spectra, in agreement with the formation of single C_3-symmetric, mononuclear species with a single ^{51}V NMR signal (in $CDCl_3$, −381.9 and −389.1 ppm, respectively), whereas complex **1d** shows complicated, nonsymmetric ^{1}H NMR spectra and two different signals in ^{51}V NMR (in $CDCl_3$, −396.8 and −428.8 ppm), indicative of the presence of aggregates or a mixture of species.

The X-ray structure of complex **1f**,[10] crystallized from dichloromethane/hexane, turned to be structurally analogous to the reported X-ray structures of complexes **1a**−**1c**.[6]

The reactivity of complexes **1d**−**1f** as functional models of VHPOs was examined in the sulfide and halide oxidations using H_2O_2 as the terminal oxidant.

Sulfide oxidations were performed under homogeneous conditions following the reaction course via ^{1}H NMR [CD_3OD, 10% catalyst, and a 1:1 ratio of thioanisole **2a** and H_2O_2 (35% in water); Table 1]. We were pleased to find that, in the presence of the mononuclear complexes **1e** and **1f**, sulfide **2a** was oxidized to the corresponding sulfoxide **3a** in high yields, with almost complete sulfoxide/sulfone selectivity and in very short reaction times (10 min; Table 1, entries 2 and 3).

In contrast, complex **1d** (R^1 = H) gave very low conversions and only after extended reaction times (7%, 12 h) while the reaction performed without V^V catalyst afforded even lower conversions. With complex **1f** being the most active and efficient catalyst and, in addition, not requiring handling under an inert atmosphere, our studies were continued by testing only **1f** catalytic performances.

The effects of the substrate concentration and catalyst loading on the oxidation of **2a** are reported in Table 2.

Substrate concentrations were varied from 0.1 to 1 M (Table 2, entries 1 and 2; catalyst loading 1% and 0.1%, respectively). Fast reactions with high yields were obtained in all cases. In particular, using 0.1% catalyst and 70% aqueous H_2O_2, yields and reaction times comparable to those of the reaction performed with 1% catalyst could be achieved with a remarkable TOF (8000 h^{-1}; Table 2, entry 3).

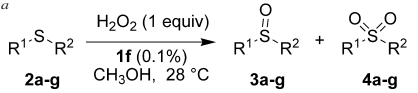
The catalyst loading was then further decreased to 0.01% without affecting the efficiency of the system but simply slowing down the reactions (Table 2, entries 4 and 5). Also in this case, the use of more concentrated H_2O_2 increases the system performances: the reaction is complete in less than 5 h, with 9900 TONs and still significative TOFs (2667 h^{-1}). The system reported here is more efficient than the vanadium-dependent bromoperoxidases, which present TONs of 450−520 in 20 h.[3] Moreover, to the best of our knowledge, the **1f**/H_2O_2 system seems to be the most active VHPO model so far reported, as far as TONs (9900 in 4 h) and TOFs (up to 8000) are concerned.[5e]

Table 2. Oxidation of **2a** by Aqueous H_2O_2 (35%) Catalyzed by **1f**: Effects of the Concentration and Catalyst Loading[a]

	$[\mathbf{2a}]_0$ (M)	**1f** (%)	$t_{1/2}$ (min)[b]	yield (%)[c]	**3a**:**4a**[c]	time (min)[d]	TON	TOF (h^{-1})[e]
1	0.1	1	6	97	96:4	25	97	240
2	1.0	0.1	24	98	98:2	80	980	1330
3	1.0[f]	0.1	6	98	97:3	20	980	8000
4	1.0	0.01	265	97	97:3	850	9700	1790
5	1.0[f]	0.01	110	99	98:2	255	9900	2667

[a] Reactions conditions: **2a**:H_2O_2 = 1:1, 28 °C, CD_3OD. [b] Time for a 50% decrease of $[H_2O_2]_0$. [c] Determined on the oxidant by ^{1}H NMR (CD_3OD, 300 MHz) in the presence of dichloroethane as the internal standard and quantitative gas chromatography analysis on the crude reaction mixture after total oxidant consumption (iodometric test). [d] Time required for total oxidant consumption. [e] Determined at 20% conversion. [f] Reactions performed with H_2O_2 (70%).

Table 3. Oxidation of Sulfides **2a**−**2g** by Aqueous H_2O_2 (35%) Catalyzed by **1f** (0.1%)[a]



no.	sub	R^1	R^2	yield (%)[b]	**3**: **4**[b]	time (min)[c]
1	**2a**	Ph	Me	98 (98)	99:1	120
2	**2b**	*p*-Tol	Me	>99 (99)	99:1	120
3	**2c**	*p*-Tol	*n*-Bu	96 (94)	>99:1	120
4	**2d**	Ph	Bn	>99 (99)	>99:1	90
5	**2e**	*n*-Bu	*n*-Bu	99 (91)	>99:1	60
6	**2f**	*p*-MeO−C_6H_4	Me	98 (94)	>99:1	100
7	**2g**	*p*-NO_2−C_6H_4	Me	98 (70)	97:3	240

[a] Reaction conditions: $[\mathbf{2a}-\mathbf{2g}]_0 = [H_2O_2]_0 = 0.5$ M, **1f** 0.1%, 28 °C, MeOH. [b] Determined by quantitative gas chromatography analysis on the crude reaction mixture after total oxidant consumption (iodometric test). Isolated yields are given in parentheses. [c] Time required for total oxidant consumption.

The scope of the reaction was explored under optimized conditions (Table 3).

A series of alkyl aryl and dialkyl sulfides were oxidized using $[\mathbf{2a}-\mathbf{2g}]_0 = [H_2O_2]_0 = 0.5$ M, 0.1% of catalyst, working on a preparative scale (8 mmol). In analogy with what was observed previously for **2a**, in all cases the oxidation with H_2O_2 afforded the corresponding sulfoxides in short reaction times (1−4 h), quantitative yields, and very high selectivity for the sulfoxide formation. Dialkyl sulfides were oxidized faster than the corresponding aryl alkyl ones (Table 3, entry 5), with methyl-*p*-nitrophenyl sulfide **2g** being the less reactive substrate (Table 3, entry 7). All of these results are consistent with the occurrence of an electrophilic oxygen transfer process and prove the generality and applicability of the method also on the preparative scale.

The solution behavior of **1f** under turnover conditions has been explored via ^{51}V and ^{1}H NMR spectroscopy.[11] A CD_3OD solution of **1f** (Figure 2, spectrum 1) showed a singlet at −396.2 ppm. The stepwise addition of up to 3 equiv of H_2O_2 afforded a new species (−649.3 ppm; Figure 2, spectra 2−5) in the range

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(10) For **1f** crystallographic data, see the Supporting Information.

(11) See the Supporting Information.

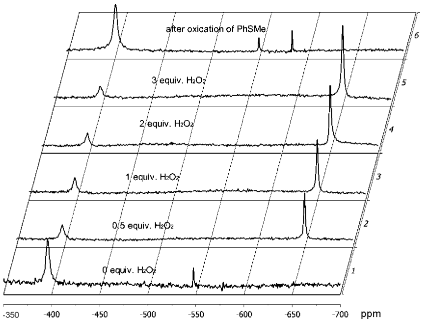


Figure 2. ^{51}V NMR (CD_3OD, 300 MHz) spectra of complex **1f**. Effect of the addition of 35% H_2O_2 (spectra 1−5). Spectrum after the addition of thioanisole and consumption of the oxidant (iodometric test; spectrum 6).

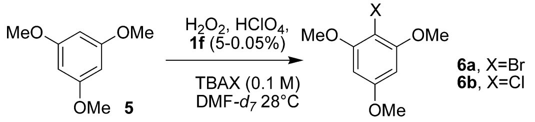
expected for diperoxovanadium complexes[5e,12] associated with color change from red to light yellow. The addition of an excess of sulfide **2a** gave complete oxidation to the sulfoxide **3a**, restoring catalyst **1f** (−400.6 ppm; Figure 2, spectrum 6) and a blue solution.[13] A similar behavior could be detected in the ^1H NMR spectra: *t*-Bu proton signal moved from 1.52 to 1.31 ppm to go back to 1.52 ppm after **2a** oxidation.[11]

The activity of complex **1f** was tested also in halide oxidation. Reactions were performed with tetrabutylammonium bromide (TBAB) and tetrabutylammonium chloride as halogen sources in the presence of 1,3,5-trimethoxybenzene **5** as the substrate for halogenation.[5a,b] Under the reaction conditions described by Butler et al.[5a,b] ($[\mathbf{1f}]_0 = 1$ mM, $[H_2O_2]_0 = 8$ mM, $[\text{TBAB}]_0 = 100$ mM, $[\mathbf{5}]_0 = 20$ mM, $[HClO_4]_0 = 3$ mM in *N*,*N*-dimethylformamide, DMF), the bromination proceeds almost instantaneously to the monobrominated product **6a**. Yields slightly exceed 100%, based on the limiting reagent that, in this case, is the acid (Table 4, entry 1). Working in the absence of acid afforded only 2.5% of **6a**, consistently with the expected stoichiometry of the reaction that requires also 1 equiv of acid (Table 4, entry 2).[5a,b] Increasing both H_2O_2 and acid up to a **5**:H_2O_2:$HClO_4$ = 1:1:1 ratio gave **6a** in 87% yield, which could be further increased up to 92% working in the presence of a 2-fold excess of H_2O_2 (Table 3, entries 3 and 4). Decreasing the catalyst amount (0.1 mM, 0.5% loading), in order to test the catalysis of the system, allowed one to obtain **6a** in high yields (87%) with TON = 173 (Table 4, entry 6).

The catalyst amount could be further decreased down to 0.05%: **6a** was recovered in 63% yield with a TON up to 1260. In order to prove catalyst **1f** stability under turnover conditions, analogous reactions were performed with $VO(acac)_2$ (5% and 0.05%): in both cases, slower reaction and lower conversions into products were obtained (54% vs 92% using 5% of the catalyst and 30% vs 63% using 0.05%; Table 3, entries 4, 5, 8, and 9).

The reaction performed without catalyst afforded **6a** in low yields (11%) after much longer reaction times (Table 4, entry 6). Reactions were also carried out in the presence of Cl^- ions. Slow chlorination of **5** could be achieved (**1f** = 5%) obtaining **6b** in 40% yields after 2 days (Table 4, entry 10). Increasing the acid and oxidant to a **5**:H_2O_2:$HClO_4$ = 1:2:1 ratio (Table 4, entry 11) did not increase the system performances: similar substrate conversions were obtained (1.1 mM), indicating that the system cannot perform more than one catalytic cycle.[14]

Table 4. **6a** or **6b** Formation as a Function of $[H^+]$, $[H_2O_2]$, and Vanadium Catalysts [**1f** or $VO(acac)_2$][a]



no.	X	**1f** (%)	$[H_2O_2]_0$ (mM)	$[H^+]_0$ (mM)	[**6a**] and [**6b**] (mM)	$t_{1/2}$ (min)[b]	yield (%)[c]	TON
1	Br	5	8	3	3.3	<5	110	3.3
2	Br	5	40		0.5			0.5
3	Br	5	20	20	17.3	17	87	17
4	Br	5	40	20	18.4	6	92	18
5	Br[d]	5	40	20	10.7	250	54	11
6	Br		20	20	2.2		11[e]	
7	Br	0.5	20	20	17.3	33	87	173
8	Br	0.05	20	20	12.6	1440	63	1260
9	Br[d]	0.05	20	20	6.0	>5000	30	600
10	Cl	5	8	3	1.2		40[e]	1.2
11	Cl	5	40	20	1.1		5[e]	1.1

[a] Reaction conditions: DMF-d_7, 28 °C using $[\mathbf{5}]_0 = 20$ mM, $[\text{TBAX}]_0 = 0.1$ M, where X = Br or Cl. [b] Time for a 50% decrease of $[H_2O_2]_0$. [c] Based on the limiting agent $HClO_4$ and determined by ^1H NMR (dichloroethane as the internal standard) on the crude reaction mixture after total oxidant consumption (iodometric test). [d] $VO(acac)_2$ has been used as the catalyst. [e] After 2 days.

In summary, here we have shown that mononuclear C_3 vanadium(V) amine triphenolate complex **1f** is both a structural and a functional model of VHPOs, effectively catalyzing the oxidation of sulfides and bromide ions.

Sulfoxidations proceed in high yields, without oxidant decomposition, with catalyst loadings down to 0.01%, TONs up to 9900, and TOFs up to 8000 h^{-1}. Moreover, bromide oxidation can be performed efficiently, leading to the halogenation of **5** and confirming that this complex can emulate the reactivity of VHPOs. More detailed studies on the use of different oxidants and substrates, together with the mechanism of the reaction and the characterization of the species involved in the process, are currently under investigation and will be reported elsewhere.

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Supporting Information Available: Experimental details and spectroscopic characterization for **1d**−**1f**, together with **1f** crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The upfield chemical shift and the change of color originate by the presence of **3a** in solution, as proven by the independent addition of **3a** to the original catalyst solution.

(14) Cl^- oxidation can be observed under the present reaction conditions probably because of the partial protonation of the active vanadium peroxo complex even in the presence of a large excess of chloride ions. Schneider, C. J.; Zampella, G.; Greco, C.; Pecoraro, V. L.; De Gioia, L. *Eur. J. Inorg. Chem.* **2007**, 515.