Oxidation of a Vanadium(V)−Dithiolate Complex to a Vanadium(V)−η^2,η^2-Disulfenate Complex

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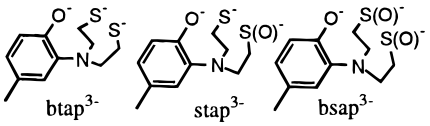
Vanadium-associated inhibition of protein tyrosine phosphatase (PTP) may be responsible for the insulin-mimetic effect observed for vanadium.[1] It has recently been shown that vanadium(V) can inhibit PTP either by coordinating to the active site thiolate (cysteine)[2] or by oxidation of the thiolate, *via* peroxovanadium complexes, to form an inactive sulfonate derivative of the enzyme.[3] Peroxovanadium(V) complexes have been shown to oxidize thiols[4] and dialkylsulfides;[5] however, the coordination and reaction chemistry of the V^V−SR unit, which is involved in PTP inhibition, is poorly understood due to the tendency of vanadium(V) to oxidize coordinated thiolate ligands.[6,7] Herein we report the synthesis and structure of V^VO(btap) (**1**), a trigonal bipyramidal (tbp) complex that has mixed oxygen/sulfur/nitrogen ligation.[8] Oxidation of **1** with peroxides or *m*-CPBA yields the corresponding monosulfenate complex, V^VO(stap) (**2**), and an unprecedented η^2,η^2-disulfenate complex, V^VO(bsap) (**3**).



The ligand H_3btap was prepared from ethylene sulfide and 2-amino-4-methylphenol. Addition of 1 equiv of H_3btap to V^VO(O-*i*-Pr)$_3$ yields **1** in 60% yield. Figure 1 presents the molecular structure of **1** as determined by X-ray crystallography.[9] Similar to the only other structurally characterized V^V−thiolate complex[6] and to five-coordinate V^V−alkoxide complexes,[10] this tbp complex has an oxo ligand as one of the axial ligands of the molecule. The phenolate oxygen and two thiolate sulfur ligands comprise the equatorial plane of the molecule and the amine nitrogen is coordinated *trans* to the oxo group. The vanadium−heteroatom distances and angles

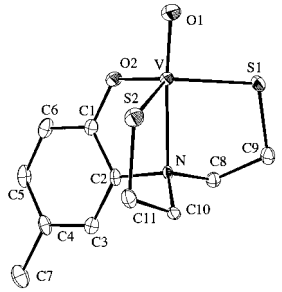


Figure 1. ORTEP drawing (50% probability) of **1**. Important bond distances (Å) and angles (deg): V−O1 1.596(2), V−S1 2.2558(11), V−S2 2.2386(12), V−O2 1.855(2), V−N 2.313(3); O1−V−N 175.52(10), O1−V−O2 104.90(11), O1−V−S1 94.13(10), O1−V−S2 96.84(10), S1−V−S2 121.00(4), S1−V−O2 118.50(8), S2−V−O2 114.01(8).

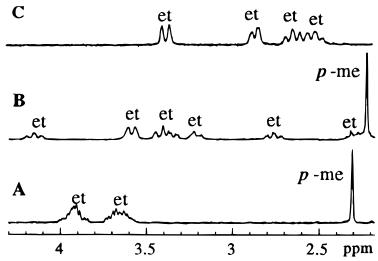


Figure 2. ^{1}H NMR monitoring of the *m*-CPBA oxidation of **1** at −70 °C (only the ethyl region is shown): (A) **1** in CD_2Cl_2, (B) after addition of approximately 1.2 equiv of *m*-CPBA, and (C) after addition of approximately 3 equiv of *m*-CPBA.

are within the ranges expected for these bond types.[11] The average V−S distance of 2.247 Å is identical (within error) to that previously reported (V−S_{av} = 2.248 Å).[5]

Complex **1** is readily soluble in many organic solvents to yield a red solution that is stable for days. Addition of aqueous H_2O_2 (30%) or *m*-CPBA (dilute in CH_2Cl_2) to a CH_2Cl_2 solution of **1** yields first a purple solution and then, with excess peroxide, a pale yellow−green/brown solution. These changes were monitored by ^{51}V NMR at −70 °C.[12] Complex **1** has a chemical shift at δ = +338 ppm (vs $VOCl_3$). This chemical shift is entirely consistent with the coordination of two, relatively soft, thiolate ligands.[13] Addition of ∼1.2 equiv of *m*-CPBA yields complex **2**, which has a chemical shift at δ = −186 ppm. Addition of another 2 equiv of *m*-CPBA provides a solution of complex **3**, which resonates at δ = −666 ppm. The similar upfield shifts on converting from **1** to **2** and then to **3** (502 ± 22 ppm) suggest that similar electronic/structural changes are occurring at each step.

The symmetry of complexes **1**−**3** can be determined by ^{1}H NMR (CD_2Cl_2, −70 °C) as shown in Figure 2. Complex **1** has nearly C_s symmetry in the solid state, and this is also the case in solution. As shown in Figure 2A, the ethyl groups of **1** have a pattern consistent with four inequivalent methylene proton magnetic environments, the maximum allowed for C_s symmetry. Oxidation of **1** to **2** yields a solution with six methylene proton resonances (Figure 2B), indicating that the symmetry of the complex has been decreased from C_s to C_1. Oxidation of **2** to **3** yields a solution with four methylene resonances, again consistent with C_s symmetry.

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(8) Abbreviations used: PTP, protein tyrosine phosphatase; H_3btap, 2-(bis(ethylthiolato)amino)-4-methylphenol; *m*-CPBA, *m*-chloroperoxybenzoic acid; H_3stap, 2-(((ethylsulfenato)ethylthiolato)amino)-4-methylphenol; H_3bsap, 2-(bis(ethylsulfenato)amino)-4-methylphenol; et and *p*-me, ethyl and *p*-methyl resonances, respectively.

(9) X-ray quality crystals of **1** were obtained by slow diffusion of hexane into an acetone solution of **1**. Crystal data for **1**: triclinic, space group *P*1, crystal color = red, a = 6.798(2) Å, b = 7.137(2) Å, c = 14.730(4) Å, α = 90.85(3)°, β = 100.93(2)°, γ = 115.05(3)°, V = 632.0(3) Å^3, Z = 2, R_F = 0.035, R_w = 0.044 for 1827 reflections with $I_{net} > 1.0\sigma(I_{net})$, GOF = 1.23.

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(11) Elongation of the V−N bond due to the *trans* influence (or structural *trans* effect) is observed: Scheidt, W. R. *Inorg. Chem.* **1973**, *8*, 1758−1761.

(12) At room temperature, this reaction gives mixtures of **1**−**3** with substoichiometric amounts of peracid.

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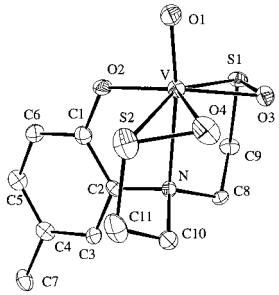

Figure 3. ORTEP drawing (50% probability) of **3**. Important bond distances (Å) and angles (deg): V−O1 1.900(3), V−S1 2.3575(14), V−S2 2.3720(16), V−O2 1.9543(3), V−O3 1.960(3), V−O4 1.966(3), V−N 2.369(4); O1−V−N 175.52(10), O1−V−O2 104.90(11), O1−V−S1 94.13(10), O1−V−S2 96.84(10), S1−V−S2 121.00(4), S1−V−O2 118.50(8), S2−V−O2 114.01(8).

The changes in chemical shift and symmetry on going from **1** to **2** and then to **3** suggest that the soft thiolate ligands are being sequentially replaced by (or converted to) harder donors.[12] By analogy to the peroxide-based oxidation chemistry of nickel(II)- and palladium(II)−thiolate complexes, it is likely that the thiolate ligands in **1** are being sequentially oxidized to sulfenate ligands.[14] The first oxidation takes the C_s-symmetric complex **1** to the C_1-symmetric, monosulfenate complex **2**, and the second oxidation yields the C_s-symmetric disulfenate **3**. This oxidation chemistry has been confirmed by X-ray crystallography of **3**.

Hexane precipitation of a dilute solution of **1** and *m*-CPBA (CH_2Cl_2) yields a dark solid that contains a mixture of **2** and **3**, as evidenced by ^{51}V and ^{1}H NMR. Recystallization of this solid by slow diffusion of hexane into a CH_2Cl_2 solution of this mixture yields X-ray quality crystals of the disulfenate complex **3**. The molecular structure of **3**, presented in Figure 3, is best described as a pentagonal bipyramid.[15] Both thiolate ligands of **1** have been converted to sulfenate ligands in **3**. Remarkably, these sulfenate ligands are bound to the vanadium(V) center in an unprecedented η^2-coordination mode.[16] The average V−S distance in **3**, 2.365 Å, is 0.116 Å longer than in the corresponding thiol complex (**1**) and is considerably longer than the Ni−S distance in nickel-sulfenates (2.157 Å).[13] The average S−O distance in **3** (1.598 Å) is also longer than the corresponding distance in nickel sulfenate complexes (1.545 Å). The average bite-angle for the η^2-sulfenate (S−V−O) is 42.05°. For comparison, the bite-angle in an alkylperoxo complex, $LV^VO(\eta^2\text{-OOR})$, is 43.4°,[17] and the bite-angles in peroxovanadium complexes, $LV^VO(\eta^2\text{-}O_2)$, are around 45°.[18] The average distance between the vanadium and the sulfenate oxygen in **3** (1.963 Å) is considerably longer than the $V-O_{peroxo}$ distance (terminal, 1.872 Å) in the alkylperoxo complex mentioned above. This may be a result of the long V−S distance in **3** (2.365 Å) relative to the internal $V-O_{peroxo\ distance}$ (1.992 Å). The balance of the coordination sphere in **3** is slightly expanded compared to **1**: the V−O2 (phenolate oxygen) distance is 0.099 Å longer, while the V−N distance is 0.056 Å longer. The V−O1 (oxo) distance is unchanged. On the basis of the NMR data, we believe that the structure of **2** is analogous to **3** except that it has a *single* η^2-sulfenate ligand. The IR spectra of **2** and **3** (Figure S4, Supporting Information) do not show any peaks that can be assigned to an S−O vibration. For η^1-sulfenates, ν(S−O) is usually between 900 and 1000 cm^{-1}.[14] Vibrational spectroscopic studies with ^{18}O-substituted complexes are in progress.

In summary, we have prepared and structurally characterized a rare vanadium(V)−dithiolate complex that has O, S, and N coordination. This complex is a structural analog of the interaction of vanadium with the active site thiol of PTPs. Oxidation of this dithiolate complex yields a unique η^2,η^2-disulfenate complex that has also been structurally characterized. We are currently examining the spectroscopy and reactivity of these and related compounds to better understand the biochemistry of vanadium.

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Supporting Information Available: Synthesis of **1**, Figure S1 showing the ^{51}V NMR spectra of **1**−**3**, Figure S4 showing IR spectra for **1**−**3**, Figures S2 and S3 showing full numbering schemes for **1** and **3**, and tables of crystal data, positional parameters, bond distances and angles, anisotropic displacement parameters, and hydrogen atom coordinates (16 pages). See any current masthead page for ordering and Internet access instructions.

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(15) Crystal data for **3**: orthorhombic, space group *Pbca*, crystal color = brown/dark yellow, a = 7.6495(14) Å, b = 12.384(6) Å, c = 27.867(12) Å, V = 2639.9(18) Å^3, Z = 8, R_F = 0.046, R_w = 0.047 for 1627 reflections with $I_{net} > 1.0\sigma(I_{net})$, GOF = 1.15.

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