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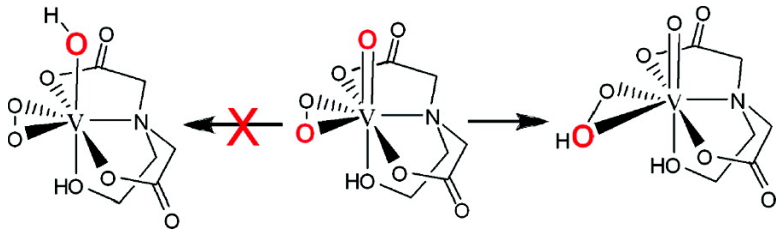

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Elucidating the Protonation Site of Vanadium Peroxide Complexes and the Implications for Biomimetic Catalysis

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Vanadium-dependent haloperoxidases (VHPOs) are a novel class of peroxidases that utilize a vanadate cofactor[1] to perform the two-electron oxidation of halides[2] and organic sulfides.[3] In contrast to heme peroxidases, which oxidize halides through a Compound I-type intermediate (Fe(4+)O species), there is no evidence that the vanadate cofactor (V(5+)O species) changes oxidation state during catalysis. Biochemical studies have shown that peroxide is necessary to oxidize halides with a catalytically relevant pK_a of 5.4.[4]

Coordination complexes of peroxo−oxovanadium(5+) played a key role in understanding the structure,[5] mechanism of peroxide coordination,[6] and substrate oxidation for VHPOs.[7] Our group has explored the reactivity of tripodal amine complexes of oxovanadium(5+) with peroxide to provide insight into the mechanism of this system and to develop biomimetic oxidation catalysts.[6,7b,c] To date, K[V(5+)O(O_2)Hheida][7e] has the highest reported rate with respect to bromide[7b] and thioether[7c] oxidation of any vanadium complex. Reactivity studies with tripodal amine compounds, including [V(5+)O(O_2)Hheida]$^-$, have shown that addition of 1.0 equiv of a strong acid is necessary for this activity. Protonation plays a two-fold role in the activation of the complex: (1) protonation labilizes an oxo bond, assisting the coordination of hydrogen peroxide,[6] and (2) protonation activates the peroxide complex[7c,8] for oxidation of a substrate molecule.

Under acidic conditions in nonaqueous solution, the peroxo−oxovanadium(5+) complex is capable of mimicking the bromide and thioether oxidation abilities of VHPOs, including the selective conversion of thioethers to sulfoxides without overoxidation to the sulfone. Experimental studies have shown that the proton interacts with the vanadium complex, causing a red shift of the charge-transfer band[7b] assigned to the peroxo moiety and the upfield shift of the ^{51}V NMR signal.[7c]

These studies led to the mechanistic proposal for substrate oxidation by V(5+)O(O_2) complexes depicted in Figure 1. Unfortunately, the data available do not allow a specific assignment of the site of protonation nor the transition-state geometry. To shed light on these issues, we and others have performed a variety of theoretical studies using DFT[9] and QM/MM[10] for both the enzyme and functional models. These studies showed that both the enzyme and our functional model proceed through an S_N2-type transition state, where the substrate is acting as the nucleophile attacking the coordinated peroxo moiety. The protonated peroxo moiety has an activation energy that is 9 kcal/mol lower than that of the corresponding unprotonated species. A similar change was observed for halide oxidation in both the enzyme and functional model systems. DFT studies on the functional model, [V(5+)O(O_2)Heida]$^-$, demonstrated that, of the three most basic sites (oxo, peroxo, or carboxylate), protonation of the peroxo moiety was energetically favored, with protonation of the oxo or the carboxylate oxygens being 2.9 and 11 kcal/mol higher in energy, respectively.[8] Transition

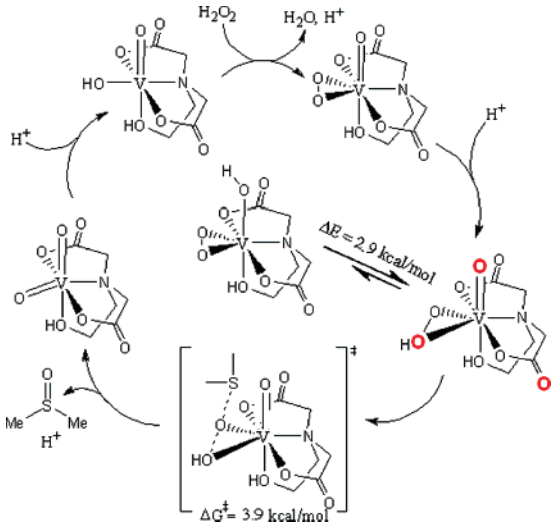

Figure 1. Derived mechanism for thioether oxidation based on DFT[8] and experimental studies[6,7c] of [V(5+)O(O_2)Hheida]$^-$. Highlighted oxygens (red, bold) indicate possible sites of protonation.

states for substrate oxidation could only be located for a hydroperoxo moiety. These results imply that protonation of the peroxo moiety is energetically favored and required for substrate oxidation, but without spectroscopic confirmation, we cannot definitively exclude the possibility that protonation of the oxo group plays a role in catalysis. Herein, we present X-ray absorption near-edge spectroscopy (XANES) data that provide spectroscopic evidence that protonation of the oxo atom in the intermediate does not occur under catalytic conditions.

XANES provides a sensitive probe of the electronic structure of transition metal complexes. The pre-edge feature, commonly assigned as a 1s→3d transition,[11] can be used as a direct probe of electronic structure. This orbitally forbidden transition increases in intensity with the degree of metal 4p character that is hybridized with the 3d molecular orbitals. Previous work has shown metal−oxo complexes to have an abnormally large pre-edge feature.[12] As the degree of d−p hybridization is dependent on the geometry and the donor set, we explored a well-defined set of vanadium coordination complexes to establish a trend in the pre-edge area relative to the number of vanadium−oxo bonds. This correlation allows us to examine if a peroxo−hydroxovanadium(5+) species, [V(5+)(OH)O_2(Hheida)], is the catalytically relevant form of our functional model.

X-ray absorption data were collected at SSRL BL9-3, the spectra were normalized,[13] and the pre-edge area was fit using a pseudo-Voigt method. A comparison of V(4+)O(SALEN) and V(4+)Cl_2-(SALEN)[14] shows a significant decrease in the pre-edge intensity for the dichloro species (Figure 2, inset). This is consistent with previous studies which demonstrated the pre-edge intensity scaled with oxo bonding within comparable complexes (consistent geom-

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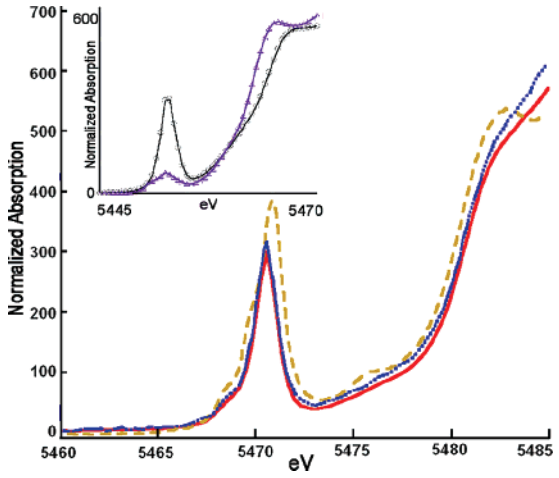

Figure 2. XANES pre-edge spectra of K[VO(O_2)Hheida] (red, solid), H[VO(O_2)Hheida] (blue, dotted), NH^4[VO_2(Hheida)] (orange, dashed), VO(SALEN) (black, inset), and VCl_2(SALEN) (purple, inset).

etry and donor set).[12] The contribution of the peroxo donor to the pre-edge intensity was examined using V(4+)O(Hheida), NH_4[V(5+)O_2(Hheida)], and K[V(5+)O(O_2)Hheida]. These complexes contain a mono-oxo, dioxo, and oxo−peroxo vanadium species, respectively. The dioxo complex, NH_4[V(5+)O_2(Hheida)], showed the largest pre-edge area. Replacement of an oxo by a peroxo reduced the pre-edge by 32%. This decrease is consistent with the loss of the π-bonding associated with a displaced oxo donor. The mono-oxo and oxo−peroxo complexes (V(4+)OHheida and [V(5+)O(O_2)Hheida)$^-$) have nearly identical pre-edge areas, indicating that addition of a peroxo donor does not significantly affect the π-bonding associated with oxo donor, nor does it form molecular orbitals with a significant 4p character.

Detailed comparison of the areas and energies of the pre-edge transitions shows complex behavior that is predominately dependent on strongly covalent donors, such as oxo/nitride, but is also influenced by coordination number, geometry, oxidation state, and donor set.[12,15] Recent studies on Mn(5+)═O species have estimated a 3-fold decrease in pre-edge area upon protonation of a Mn(5+)═O.[16] We believe that a similar change would be apparent in this closely related system. In order to determine if the oxo donor in the catalytically active species was protonated, we measured spectra for frozen solutions of K[V(5+)O(O_2)Hheida] and H[V(5+)O(O_2)-Hheida]. To ensure the integrity of the sample, both the red-shift in the charge-transfer band of the UV−visible spectrum and the catalytic oxidation of thioethers were tested prior to sample freezing. As is apparent from Figure 2, there is no appreciable change in the pre-edge area upon protonation of the complex. Given the sensitivity of the area on structure, we conclude that the degree of oxo bonding to the vanadium center has not decreased, and thus that the oxo donor has not been protonated. *This provides the first spectroscopic evidence that protonation of the oxo moiety does not occur under catalytic conditions.*

If protonation of the oxo moiety in peroxo−oxovanadium complexes has now been eliminated as a mechanistic possibility, what is the likely residue accepting the proton? The remaining two protonatable sites are the carboxylate oxygen atoms of the ligand set and the bound peroxo group. DFT has demonstrated that ligand protonation is 11 kcal/mol higher in energy than protonation of the peroxo, suggesting that the protonated carboxylate is not an energetically favored species.

Taking all of these observations together, these results provide strong support for the involvement of a hydroperoxo intermediate in our functional models. This conclusion may be broadly relevant to peroxo−oxovanadium complexes that can be used in a number of asymmetric oxidations,[17] with the asymmetric oxidation of thioethers[18] as a notable example. Chiral sulfoxides are synthetically useful, and pharmaceutically relevant functional groups[19] require careful control of the oxidation conditions to prevent over-oxidation to the sulfone. The results contained herein lend a deeper understanding to the mechanism of thioether oxidation and allows for rational design of catalysts capable of this important synthetic transformation.

DFT results have shown that VHPOs have a transition-state geometry nearly identical to that found for our models.[8,9d] On the basis of the similarities in reactivity (proton dependence on reactivity, transition-state geometry, and trends in the barrier to activation for substrate oxidation related to peroxo protonation), this work lends support to the role of a hydroperoxo intermediate in the catalytic cycle for VHPOs.

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Supporting Information Available: Cystallographic data of NH_4-VO_2(Hheida) and experimental preparations for all complexes; XANES spectra of all compounds; and tabulated pre-edge data. This material is available free of charge via the Internet at http://pubs.acs.org.

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