

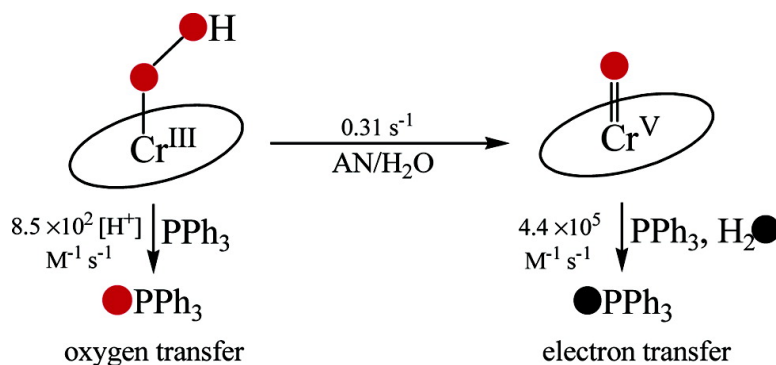
Communication

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## Direct Kinetic Studies of Atom Transfer and Electron Transfer Reactions of Hydroperoxo and High-Valent Oxo Complexes of Chromium

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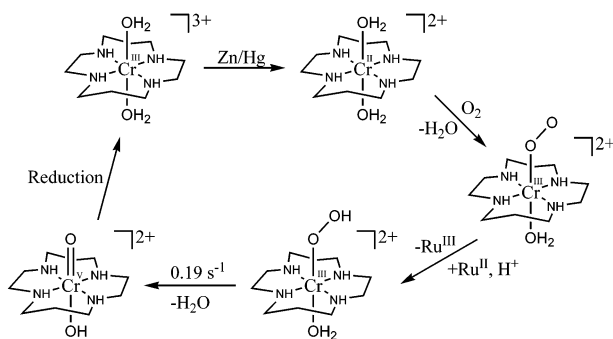
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Direct involvement of hydroperoxoiron species in catalytic oxidations by cytochrome P450 enzymes is a subject of continuing debate. Until recently, only the high-valent iron oxo intermediates were believed responsible for electrophilic oxidations.<sup>1</sup>

The products and kinetic isotope effects observed by several groups in wild-type enzymes pointed, however, to the involvement of more than one reactive intermediate.<sup>2–5</sup> Several reports<sup>6–9</sup> proposed metal hydroperoxo species as oxidants in mutant systems where high-valent oxo species were presumably unavailable. Arguing against this proposal is the reported lack of reactivity of a cryo-generated hydroperoxoiron species.<sup>10</sup> Some DFT calculations suggested the existence of two spin isomers of iron oxo species, which could account for the observation of two reactive intermediates.<sup>11</sup> A possibility that the disruption of hydrogen bonding in mutants might lead to different reactivity patterns for the oxo intermediates has also been recognized.<sup>12</sup>

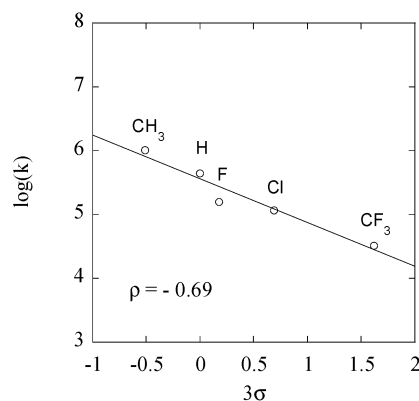
Several years ago, we discovered<sup>13,14</sup> a macrocyclic chromium-based system that exhibited transformations similar to those proposed for catalytic oxidations by cytochrome P450 enzymes, Scheme 1. The hydroperoxo complex, generated by one-electron reduction of the superoxo precursor, yields a strongly oxidizing Cr(V),  $E(\text{Cr}^{\text{V}}/\text{Cr}^{\text{IV}}) \geq 1.1 \text{ V}$ .<sup>14</sup> In the absence of added reductants, Cr(V) decomposes with a rate constant of  $0.43 \text{ s}^{-1}$ , presumably by intramolecular oxidation of the macrocycle.

### Scheme 1



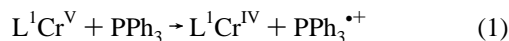
Direct studies of the reactivities of  $\text{L}^1(\text{H}_2\text{O})\text{CrOOH}^{2+}$  and  $\text{L}^1\text{Cr}(\text{V})$  ( $\text{L}^1 = \text{trans-[14]janeN}_4$ ) proved challenging, but we have now observed the oxidation of triarylphosphines with each form separately. To the best of our knowledge, this is the first case of a dynamic hydroperoxo/high-valent oxo system where kinetic measurements on the individual forms have been reported.

The reaction between  $\text{L}^1\text{Cr}^{\text{V}}$ <sup>15</sup> and triarylphosphines  $\text{P}(\text{C}_6\text{H}_4\text{-R})_3$ <sup>16</sup> exhibited a 1:1 stoichiometry and mixed second-order kinetics independent of  $[\text{H}^+]$  (0.013–0.027 M). Figure 1 shows a Hammett plot for the reaction with five different phosphines, giving  $\rho = -0.69$ , consistent with the electrophilic character of Cr(V) in these reactions.



**Figure 1.** Hammett plot for the reaction between  $\text{L}^1\text{Cr}(\text{O})_2^+$  and  $\text{P}(p\text{-C}_6\text{H}_4\text{-R})_3$  in 67% aqueous acetonitrile, 0.013 M  $\text{HClO}_4$ , 25 °C,  $k$  in units  $\text{M}^{-1} \text{s}^{-1}$ .

When  $\text{L}^1\text{Cr}^{\text{V}}$  was generated from  $\text{L}^1\text{Cr}^{18}\text{O}^{18}\text{OH}^{2+}$  in  $\text{H}_2^{16}\text{O}$ , in a solution containing either  $^{16}\text{O}_2$  or  $^{18}\text{O}_2$ , the product  $\text{OPPh}_3$  contained no labeled oxygen.<sup>17</sup> As described below, the most reasonable formula for Cr(V) under these conditions is  $\text{L}^1\text{Cr}^{(16}\text{O})(^{18}\text{O})^+$ . Thus, the source of O in  $\text{OPPh}_3$  is solvent  $\text{H}_2\text{O}$ . None of the chromium species should exchange oxygen with  $\text{H}_2\text{O}$  on the time scale of these reactions,<sup>18</sup> which suggests electron transfer, eqs 1–3, as the most likely mechanism.



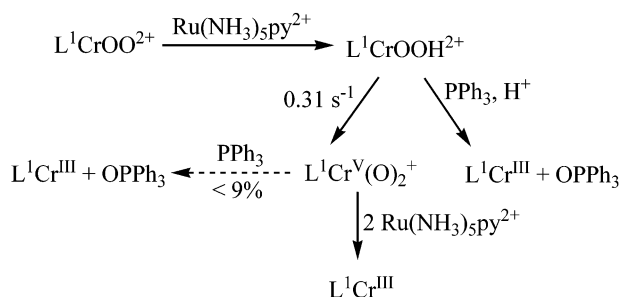
The reaction of eq 2 is fast<sup>19,20</sup> and provides a mechanism for the incorporation of water oxygen into  $\text{OPPh}_3$ . Reaction 3 is similar to the radical/oxoiron recombination in the “rebound” mechanism of cytochrome P450 and should be very fast.<sup>21</sup>

The study of the  $\text{L}^1(\text{H}_2\text{O})\text{CrOOH}^{2+}/\text{PPh}_3$  reaction employed competition kinetics and took advantage of the catalysis by  $\text{H}^+$ . The absorbance change was provided by  $\text{Ru}(\text{NH}_3)_5\text{py}^{2+}$ , which also has the necessary reactivity toward  $\text{L}^1\text{Cr}^{\text{V}}$ ,  $k_{\text{Rupy}} = (6.5 \pm 0.6) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$  at 0.013 M  $\text{HClO}_4$  and 0.017 M ionic strength.<sup>22,23</sup>

A solution of  $\text{L}^1(\text{H}_2\text{O})\text{CrOO}^{2+}$  was allowed to react with an excess of  $\text{Ru}(\text{NH}_3)_5\text{py}^{2+}$  (1 mM) in the presence of  $\text{PPh}_3$ . The chemistry is shown in Scheme 2, and the kinetic treatment is shown in the Supporting Information.

At low acid concentrations (3.7–20 mM) and an ionic strength of 0.83 M,<sup>23</sup> 3 equiv of  $\text{Ru}(\text{NH}_3)_5\text{py}^{2+}$  was consumed for each equivalent of  $\text{L}^1(\text{H}_2\text{O})\text{CrOO}^{2+}$ . One equivalent generates  $\text{L}^1(\text{H}_2\text{O})\text{-CrOOH}^{2+}$ , and the rest scavenges  $\text{L}^1\text{Cr}(\text{O})_2^+$ . At higher  $[\text{H}^+]$ , up to 0.83 M, the amount of consumed  $\text{Ru}(\text{NH}_3)_5\text{py}^{2+}$  was lower, and

Scheme 2



the absorbance changes exhibited saturation behavior. In the limit of high  $[\text{H}^+]$ , only 1 equiv of  $\text{Ru}(\text{NH}_3)_5\text{py}^{2+}$  was consumed per mole of  $\text{L}^1(\text{H}_2\text{O})\text{CrOO}^{2+}$ . The data were treated according to Scheme 2, showing a competition between the  $\text{L}^1(\text{H}_2\text{O})\text{CrOOH}^{2+}/\text{PPh}_3$  reaction and the conversion of  $\text{L}^1(\text{H}_2\text{O})\text{CrOOH}^{2+}$  to  $\text{L}^1\text{Cr}(\text{O})_2^+$ . The calculated pseudo-first-order rate constant for the  $\text{L}^1(\text{H}_2\text{O})\text{CrOOH}^{2+}/\text{PPh}_3$  reaction varied linearly with  $[\text{H}^+]$  (0.004–0.83 M) and  $[\text{PPh}_3]$  (0.31–0.62 mM), yielding a third-order rate constant of  $850 \text{ M}^{-2} \text{ s}^{-1}$ .<sup>24</sup> The  $^{18}\text{O}$ -labeled material,  $\text{L}^1(\text{H}_2\text{O})\text{Cr}^{18}\text{O}^{18}\text{OH}^{2+}$ , produced  $^{18}\text{OPPh}_3$  (71% by EI-MS), in the presence of either  $^{16}\text{O}_2$  or  $^{18}\text{O}_2$ , clearly demonstrating O-atom transfer.

The clear kinetic and mechanistic differences observed under the two limiting sets of conditions in this work confirm that two distinct forms of the oxidant –  $\text{L}^1\text{Cr}(\text{O})_2^+$  and  $\text{L}^1(\text{H}_2\text{O})\text{CrOOH}^{2+}$  – exist and react.  $\text{L}^1\text{Cr}(\text{O})_2^+$  reacts by electron transfer in an  $\text{H}^+$ -independent process.  $\text{L}^1(\text{H}_2\text{O})\text{CrOOH}^{2+}$  transfers oxygen to the phosphine in an acid-catalyzed reaction. Reactions of  $\text{PPh}_3$  with other, well-characterized hydroperoxo metal complexes<sup>25,26</sup> are also strictly first-order in  $\text{H}^+$ , a finding that adds further support to the mechanistic assignments in the present work.

Interestingly, the rate constant for  $\text{PPh}_3$  oxidation by  $\text{L}^1(\text{H}_2\text{O})\text{CrOOH}^{2+}$  is nearly identical to that for the oxidation by  $\text{Cr}_{\text{aq}}\text{OOH}^{2+}$ .<sup>26</sup> Thus,  $\text{L}^1(\text{H}_2\text{O})\text{CrOOH}^{2+}$  is exceptional in that it converts to a high-valent oxo form, but its reactivity in O-atom transfer reactions appears quite ordinary. The investigations of  $\text{L}^1(\text{H}_2\text{O})\text{CrOOH}^{2+}$  in other types of reactions, currently underway in our laboratory, should provide some clues as to the reactivity of hydroperoxo intermediates in P 450-catalyzed reactions.

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**Supporting Information Available:** Kinetic treatment for triphenylphosphine/hydroperoxo reaction, data for hydroperoxo/oxo conversion (Table S1), and determination of electrostatic charges for Cr(V) (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (15) All of the experiments were performed in a 67% acetonitrile–water mixture, unless stated otherwise.  $\text{L}^1\text{Cr}^{\text{V}}$  was generated by rapid mixing of  $\text{L}^1(\text{H}_2\text{O})\text{CrOO}^{2+}$  and a stoichiometric amount of  $\text{Ru}(\text{NH}_3)_6^{2+}$  in the first stage of the sequential stopped flow, followed by the aging step during which a portion of the initially formed  $\text{L}^1(\text{H}_2\text{O})\text{CrOOH}^{2+}$  was converted to  $\text{L}^1\text{Cr}^{\text{V}}$ . When the concentration of  $\text{L}^1\text{Cr}^{\text{V}}$  reached a maximum (~20% of total chromium), the solution was mixed with  $\text{P}(\text{C}_6\text{H}_4\text{-R})_3$ , and the reaction was monitored at 470 nm. The reaction of interest was much faster than the background conversion of the remaining  $\text{L}^1(\text{H}_2\text{O})\text{CrOOH}^{2+}$  to  $\text{L}^1\text{Cr}^{\text{V}}$ .
- (16) The stopped-flow determinations yielded the rate constants  $k_1 = 0.31 \text{ s}^{-1}$  for the formation of Cr(V) from the hydroperoxide, and  $k_2 = 0.51 \text{ s}^{-1}$  for the decay of Cr(V). In 40% aqueous acetonitrile,  $\text{L}^1\text{Cr}^{\text{V}}$  exhibits a single broad maximum at 470 nm,  $\epsilon = 1200 \text{ M}^{-1} \text{ cm}^{-1}$ .
- (17) By electron impact mass spectroscopy (EI MS).
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- (21) The data are also consistent with a chain mechanism of eqs 1–3 and the two propagating steps shown below. Under the long-chain approximation, the kinetics remain mixed second-order.  $\text{L}^1\text{Cr}^{\text{IV}} + \text{PPh}_3 \rightarrow \text{L}^1\text{Cr}^{\text{III}} + \text{PPh}_3^+$  and  $\text{HO}^-\text{PPh}_3 + \text{L}^1\text{Cr}^{\text{V}} \rightarrow \text{OPPh}_3 + \text{L}^1\text{Cr}^{\text{IV}} + \text{H}^+$ .
- (22) Conditions and considerations as in ref 15, except  $\lambda = 460 \text{ nm}$ .
- (23)  $k_{\text{RUP}}$  increases with the ionic strength. The Debye–Huckel treatment yielded a charge of +0.96 for  $\text{L}^1\text{Cr}^{\text{V}}$ , see Supporting Information. (Under the same conditions, the  $\text{Ru}(\text{NH}_3)_5\text{py}^{2+}/\text{Co}(\text{NH}_3)_5\text{Br}^{2+}$  reaction yielded an average charge of +1.84 per reactant.) The charge of approximately 1+ for Cr(V) strongly suggests that it is a dioxo cation,  $\text{L}^1\text{Cr}(\text{O})_2^+$ , with one O derived from peroxo group and the other from solvent water. The geometry is probably trans, because the folding of the macrocycle to the cis form should not be fast or thermodynamically favored. Notice that, in pure water, one of the oxo ligands is protonated at similar acid concentrations.
- (24) Triphenylphosphines substituted in the *para* position with electron-withdrawing substituents (such as those in Figure 1) also react with  $\text{L}^1(\text{H}_2\text{O})\text{CrOOH}^{2+}$ , but these reactions are complicated by what appears to be the formation of mixed hydroperoxo/phosphine complexes,  $\text{L}^1(\text{P}(\text{p}-\text{C}_6\text{H}_4\text{-R})_3)\text{CrOOH}^{2+}$ . In support of this idea, the rate of  $\text{L}^1\text{Cr}(\text{O})_2^+$  formation is different in the presence of different phosphines, Table S1 (Supporting Information). These experiments were done at low  $[\text{H}^+]$  to prevent the oxidation of triaryl phosphines by the hydroperoxo complex. The reaction of  $\text{PPh}_3$  itself is free of complications because the reaction with  $\text{L}^1(\text{H}_2\text{O})\text{CrOOH}^{2+}$  is sufficiently fast, and concentrations of  $\text{PPh}_3$  required are sufficiently low so that measurable amounts of the mixed complexes are not produced.
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