Supporting Information

Mechanistic Study of Alcohol Oxidation by the Pd(OAc)$_2$/O$_2$/DMSO Catalyst System and Implications for the Development of Improved Aerobic Oxidation Catalysts

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Tests for Hydrogen Peroxide as a Stoichiometric Oxidant in the Pd(OAc)$_2$/O$_2$/DMSO Catalytic Oxidation System.

Hydrogen peroxide is proposed as an intermediate in Pd(OAc)$_2$/O$_2$/DMSO catalytic oxidation reactions based on precedent in related palladium-catalyzed oxidation reactions.$^1$ The following experiments were performed to investigate the fate of hydrogen peroxide under the catalytic reaction conditions.

When one equivalent of hydrogen peroxide is added in a single aliquot to a Pd(OAc)$_2$/DMSO solution or to the catalytic reaction mixture at 80 °C, it undergoes rapid disproportionation to molecular oxygen and water.

Certain palladium-catalyzed oxidation reactions use hydrogen peroxide as a stoichiometric oxidant,$^2$ and this precedent raised the possibility that hydrogen-peroxide-mediated substrate oxidation might compete with disproportionation at the low hydrogen peroxide concentration expected during catalysis.$^3$ This possibility was tested by adding hydrogen peroxide slowly to the catalytic reaction mixture and determining the pressure change and product yield arising from the reaction (Figure S1). If hydrogen peroxide serves as a stoichiometric oxidant (Pathway A, eq S1), the aldehyde product yield should increase based on the amount of hydrogen peroxide added. Alternatively, hydrogen peroxide disproportionation (Pathway B, eq S2) will not affect the product yield but will increase the oxygen gas pressure within the sealed reaction vessel.
Figure S1: Experimental set-up to allow slow addition of hydrogen peroxide during the catalytic reaction. Pressure changes were monitored with the attached manometer.

Pathway A: \( \text{H}_2\text{O}_2 + \text{RCH}_2\text{OH} \rightarrow \text{RCHO} + 2 \text{H}_2\text{O} \)  
(S1)

Pathway B: \( \text{H}_2\text{O}_2 \rightarrow \text{H}_2\text{O} + 0.5 \text{O}_2 \)  
(S2)

The catalytic reaction was carried out for two hours in order to achieve approximately 25-35% conversion of the alcohol to aldehyde. Incomplete conversion ensured adequate substrate concentration for oxidation by hydrogen peroxide if Pathway A operates. Slow addition of hydrogen peroxide over the two-hour reaction time was achieved by using a syringe pump. The
molar ratio of dioxygen consumed to aldehyde produced \([n(O_2)/n(RCHO)]\) was monitored as a function of hydrogen peroxide addition. If no hydrogen peroxide is added, the \([n(O_2)/n(RCHO)]\) ratio is 0.50(3) (see main text). Addition of hydrogen peroxide will alter this ratio depending of the fate of hydrogen peroxide under the reaction conditions. In Pathway A, one equivalent of aldehyde will be produced for each equivalent of added hydrogen peroxide, and in Pathway B, 0.5 equivalents of dioxygen will be produced for each equivalent of hydrogen peroxide.

Mathematical expressions that relate the \([n(O_2)/n(RCHO)]\) ratio to the equivalents of hydrogen peroxide for the two pathways are provided in eqs S3 and S4.\(^4\) Theoretical curves from these expressions are plotted in Figure S2 together with the experimental data. The data corresponds well to the curve predicted for disproportionation of hydrogen peroxide (Pathway B). Evidence for disproportionation under these "slow-addition" conditions strongly supports the mechanism proposed and discussed further in the main text (Scheme 1).

Pathway A: \[
\frac{n(O_2)}{n(RCHO)} = \frac{1}{2 + [\text{eq. } H_2O_2]} \tag{S3}
\]

Pathway B: \[
\frac{n(O_2)}{n(RCHO)} = 0.5 - 0.5 \cdot [\text{eq. } H_2O_2] \tag{S4}
\]
**Experimental**

**General Considerations.** Anhydrous dimethylsulfoxide (Aldrich), oxygen gas (BOC), and 2,5-dimethoxybenzyl alcohol (Aldrich) were used as received. Palladium acetate (DuPont) was recrystallized prior to use from benzene/acetic acid. Hydrogen peroxide (30%, Aldrich) was titrated against a standardized KMnO$_4$ (aq) solution ($Na_2C_2O_4$ primary standard). All reactions were performed in a 3-necked round-bottom flask, with known volume, attached to a mercury monometer with a calibrated volume. A glass tube (sidearm) with a 90° bend and known volume was attached to one of the
necks of the round-bottom flask and the remaining neck was sealed with either a glass stopper or a rubber septum (Figure S1). A stirbar was included.

**Rapid addition of hydrogen peroxide to Pd(OAc)$_2$ under anaerobic conditions.** In the round-bottom flask (Figure S1), a freshly prepared Pd(OAc)$_2$ solution (0.10 M in DMSO, 1.00 mL) was heated to 80 °C under nitrogen with stirring. The sidearm contained a freshly prepared H$_2$O$_2$ solution (1.83 M in DMSO, 1.00 mL). A partial vacuum was placed on the system and the pressure was recorded. The sidearm was rotated to add the H$_2$O$_2$ solution to the Pd(OAc)$_2$ solution. Immediate bubbling ensued and the pressure increased, corresponding to the generation of 0.94(7) mmol O$_2$ (0.51(4) eq. with respect to H$_2$O$_2$).

**Rapid addition of hydrogen peroxide to the catalytic reaction mixture under aerobic conditions.** In the round-bottom flask (Figure S1), 2,5-dimethoxybenzyl alcohol solution (2.00 M in DMSO, 1.00 mL) was heated to 80 °C under nitrogen with stirring. The sidearm contained a freshly prepared H$_2$O$_2$ solution (1.83 M in DMSO, 1.00 mL). The system was evacuated and refilled with oxygen to 525 torr. Through a septum, a freshly prepared Pd(OAc)$_2$ solution (0.10 M in DMSO, 1.00 mL) was added and the pressure was recorded. After 5.5 hours, a partial vacuum was placed on the system to lower the pressure. The pressure was recorded and the sidearm was rotated to add the H$_2$O$_2$ solution to the Pd(OAc)$_2$ solution. Immediate bubbling ensued and
the pressure increased, corresponding to the generation of 0.97(8) mmol $O_2$
(0.53(4) eq. with respect to $H_2O_2$).

Slow addition of hydrogen peroxide to the catalytic reaction mixture under aerobic conditions. In the round-bottom flask (Figure S1), 2,5-dimethoxybenzyl alcohol solution (2.00 M in DMSO, 2.00 mL) was heated to 80 °C under nitrogen with stirring. The sidearm contained a freshly prepared Pd(OAc)$_2$ solution (0.10 M in DMSO, 2.00 mL). The system was evacuated and refilled with oxygen gas to 550 torr. A syringe was filled with a freshly prepared stock solution of $H_2O_2$ (0.21 – 0.89 M in DMSO, 2.00 mL). The needle of the syringe was inserted through the septum and the entry point was greased thoroughly to prevent a leak. The pressure was recorded and the sidearm was rotated to add the Pd(OAc)$_2$ solution to the alcohol solution. A syringe pump was started to add the $H_2O_2$ solution over two hours. After that time, the pressure was recorded. The pressure changes corresponded to the generation of 0.20 – 0.90 mmol $O_2$, respectively (0.50(3) eq. with respect to $H_2O_2$). The system was evacuated and refilled with nitrogen to prevent further oxidation by oxygen while the system was cooled. When the solution reached room temperature, an aliquot was analyzed by GC to determine the yield of aldehyde. Complete results of these experiments are summarized in Table S1 and Figure S2.
Table S1: The effect of added hydrogen peroxide on the oxygen pressure and aldehyde yield in the catalytic reaction.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>$n$(H$_2$O$_2$) added (mmol)</th>
<th>$n$(RCHO) produced\textsuperscript{b} (mmol)</th>
<th>$n$(O$_2$) consumed (mmol)$^c$</th>
<th>$n$(H$_2$O$_2$)$^d$</th>
<th>$n$(O$_2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.420</td>
<td>1.432</td>
<td>0.5173</td>
<td>0.29</td>
<td>0.36</td>
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<td>2</td>
<td>1.152</td>
<td>1.624</td>
<td>0.2906</td>
<td>0.71</td>
<td>0.18</td>
</tr>
<tr>
<td>3</td>
<td>1.281</td>
<td>1.453</td>
<td>0.06531</td>
<td>0.88</td>
<td>0.04</td>
</tr>
<tr>
<td>4</td>
<td>1.314</td>
<td>1.143</td>
<td>-0.1444</td>
<td>1.15</td>
<td>-0.13</td>
</tr>
<tr>
<td>5</td>
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<td>1.415</td>
<td>-0.1924</td>
<td>1.26</td>
<td>-0.14</td>
</tr>
<tr>
<td>6</td>
<td>1.677</td>
<td>0.9135</td>
<td>-0.4156</td>
<td>1.84</td>
<td>-0.45</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: 80 °C, 4.00 mmol 2,5-dimethoxybenzyl alcohol, 0.200 mmol Pd(OAc)$_2$, 4.00 mL DMSO, 72.56 mL sealed vessel volume. H$_2$O$_2$ added over 2 hour time period. RCHO = 2,5-dimethoxybenzaldehyde. \textsuperscript{b}Determined by gas chromatography. \textsuperscript{c}Determined by manometry; a negative value reflects the generation of O$_2$. \textsuperscript{d}Stoichiometry of H$_2$O$_2$ added relative to the product yield, $n$(RCHO).

3 Hydrogen peroxide disproportionation is expected to have a bimolecular concentration dependence, whereas substrate oxidation will have a unimolecular dependence. These kinetic features favor substrate oxidation at low hydrogen peroxide concentrations. We thank a reviewer for alerting us to this possibility and suggesting the syringe pump experiments described herein.
4 With no added hydrogen peroxide, both pathways converge at $n$(O$_2$)/$n$(RCHO) = 0.50, the experimentally observed value. In Pathway A, dioxygen pressure will be unaffected by addition of hydrogen peroxide, but the yield of aldehyde will increase. The $n$(O$_2$)/$n$(RCHO) ratio will approach zero asymptotically. Pathway B predicts that the pressure in the reaction vessel will actually rise if the molar ratio of added hydrogen peroxide to aldehyde produced, i.e., "Equiv. H$_2$O$_2$" (Figure S2) (also column "$n$(H$_2$O$_2$)/$n$(RCHO)”, Table S1), is greater than one.