Dioxygen binding and reactivity at copper centers

EMILY E. NORWINE
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iCID Meeting
Cu and O$_2$ in Nature

Tyrosinase

- An oxidase enzyme that hydroxylates phenols to catechols and quinones
- It is the rate-limiting enzyme for the production of melanin

Mini Review: electron counting and Cu

To start us off with chemistry discussion, let’s count some electrons!

For this Cu(TACN) complex, please provide the following:
1. The number of electrons in the system
2. The Cu oxidation state, and d-count
3. Whether the complex is diamagnetic or paramagnetic
4. Whether the complex is EPR active or inactive
To start us off with some chemistry discussion, let's count some electrons!

For both of these Cu(TACN) complexes, please provide the following:

1. The number of electrons in the system
2. The Cu oxidation state, and d-count
3. Whether the complex is diamagnetic or paramagnetic
4. Whether the complex is EPR active or inactive

Both dependent on unpaired e-

\[ \text{Cu} = 11 \times 1 = 11 \\
\text{N} = 2 \times 3 = 6 \\
\text{OTf} = 1 \times 1 = 1 \\
\text{total} = 18 \]

\[ 18 \text{ e}^- \quad \text{Cu(I)} \quad d^{10} \]

Diamagnetic

EPR inactive

\[ S = 0 \]
Electronic structure of peroxo-Cu(II) complexes

- Mononuclear vs. binuclear end-on binding

![Diagram of peroxo-Cu(II) complexes](image_url)
Electronic structure of peroxo-Cu(II) complexes

- Mononuclear vs. binuclear end-on binding

Cu centers now related by symmetry, and the HOMO-LUMO gap is large enough to result in a spin paired ground state.

Inorg. Chem. 2016, 55, 6364–6375
Faraday Discuss. 2011; 148: 11–108
Spectroscopy of peroxo-Cu(II) complexes

- Antiferromagnetic coupling observed in EPR spectrum of end-on Cu$_2$O$_2$

Inorg. Chem. 2016, 55, 6364−6375
Faraday Discuss. 2011 ; 148: 11–108
Spectroscopy of peroxo-Cu(II) complexes

• Resonance Raman reports on the relative O-O strength in the peroxo complexes

Inorg. Chem. 2016, 55, 6364−6375
Faraday Discuss. 2011; 148: 11–108
Structure of the dicopper $\mu$-$\eta^2$:\(\eta^2\)-peroxo complex

- Side-on binding also gives rise to antiferromagnetic coupling
Spectroscopy of the dicopper $\mu$-$\eta^2$:-$\eta^2$-peroxo complex is also EPR silent

Compared to end-on mononuclear Cu(II)-O$_2$ (light blue)

Inorg. Chem. 2016, 55, 6364–6375
Faraday Discuss. 2011; 148: 11–108
Discussion: Comparison of CuO$_2$ complexes

Quick discussion question:
Why does the LMCT observed between 350-500nm vary so much in molar absorptivity?
What is the cause of this trend?

Inorg. Chem. 2016, 55, 6364–6375
Reactivity of the $\mu$-$\eta^2:\eta^2$-peroxo

Proposed mechanism of Tyrosinase

Inorg. Chem. 2016, 55, 6364–6375
Reactivity of the $\mu$-$\eta^2$:$\eta^2$-peroxo

- The O-O bond is proposed to be in equilibrium in solution
  - First found in 1996 to be solvent dependent
  - More recently, a much more rapid equilibrium is thought to occur

Inorg. Chem. 1999, 38, 2161-2168
Science. 1996, 271, (5254) 1397-1400
Examples of synthetic Cu$_2$O$_2$ complexes

**Stack, 1999**

Various HAT and aerobic oxidation reactions found from bis-μ-oxo species

**Solomon, Stack, 2005**

Low temp hydroxylation and oxidation of phenols (parallel to tyrosinase)

Also have been observed

*Science.* 2005, 308, (5730) 1890-1892

*Science.* 1996, 271, (5254) 1397-1400
Specific case study: Room temp reactivity

- This robust $\mu$-$\eta^2: \eta^2$-peroxo is formed at room temp, via addition of air (rather than dry O$_2$)

$\text{Inorg. Chem. 2016, 55, 1102-1107}$
Specific case study: Room temp reactivity

- This robust $\mu$-$\eta^2: \eta^2$-peroxo is formed at room temp, via addition of air (rather than dry O$_2$)
- Employed for the aerobic oxidation of substituted phenols

![Reaction scheme]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Catalyst loading (mol%)</th>
<th>Temp. (°C)</th>
<th>Yield (time)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>21</td>
<td>r.t.</td>
<td>91%$^{[b]}$ (24h)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23</td>
<td>50</td>
<td>73%$^{[b]}$ (4h)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19</td>
<td>65</td>
<td>70%$^{[b]}$ (2h)</td>
</tr>
<tr>
<td></td>
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<td>20</td>
<td>r.t.</td>
<td>92% (4h)</td>
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<td></td>
<td></td>
<td>20</td>
<td>50</td>
<td>100% (1h)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>50</td>
<td>93% (29h)$^{[e]}$</td>
</tr>
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<td></td>
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<td>stoich.</td>
<td>r.t.</td>
<td>0%$^{[d]}$</td>
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<td></td>
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<td>stoich.</td>
<td>50</td>
<td>9% (76h)$^{[d]}$</td>
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<tr>
<td></td>
<td></td>
<td>stoich.</td>
<td>65</td>
<td>34% (76h)$^{[d]}$</td>
</tr>
</tbody>
</table>

Inorg. Chem. 2016, 55, 1102–1107
Discussion: RT decomposition and reactivity

• Breakout discussion (5 minutes, small group discussion)

For the following observations regarding this system, please provide a hypothesis for why each is observed (two separate hypotheses)

• This Cu$_2$O$_2$ complex is stable at RT while other known synthetic examples decompose above -40°C

\[
\text{Cu}^2+\ \text{Cu}^{2+}
\]

• This $\mu$-$\eta^2$:$\eta^2$-peroxo complex does not show parallel reactivity to the tyrosinase enzyme despite displaying the same O$_2$ binding mode

- This $\mu$-$\eta^2$:$\eta^2$-peroxo complex does not show parallel reactivity to the tyrosinase enzyme despite displaying the same O$_2$ binding mode

\[
\begin{align*}
\text{PhOH} & \quad \text{O}_2 \\
\text{Ph} & \quad \text{PhCO} + \text{H}_2\text{O}
\end{align*}
\]

(not observed)

Inorg. Chem. 2016, 55, 1102-1107
Room temperature decomposition

- Decomposition above cryogenic temperatures can often be attributed to intramolecular oxidation of activated C-H bonds

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- The tert-butyl groups do not have these reactive $\alpha$-CH bonds, so there is no pathway for this decomposition

*Chem. Rev. 2004*, 104, 1047−1076

*Inorg. Chem. 2016*, 55, 1102−1107
Lack of tyrosinase reactivity

Poor \( O_2 \) reactivity suggests that the Cu(I) is sterically inaccessible to associative substitution.

Which suggests that these higher coordinate intermediates are inaccessible as well.

*Inorg. Chem.* 2016, 55, 1102–1107

Conclusions

• To date, there are many examples of Cu$_x$O$_2$ adducts that are formed and stable at low temp
  • Only a single example (discussed today) has been shown to be an active catalyst at room temp
  • To date, no synthetic system has achieved what tyrosinase does: catalytic oxidation of phenols at room temp

• These Cu$_x$-O$_2$ adducts have characteristic UV-vis, resonance Raman, and EPR features