

Aerobic oxidation of methanol by a Ni(II)-O<sub>2</sub> reaction†Sara E. Edison,<sup>a</sup> Richard P. Hotz<sup>b</sup> and Michael J. Baldwin<sup>\*a</sup><sup>a</sup> Department of Chemistry, University of Cincinnati, Cincinnati OH 45221, USA.

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**An unusual oxygen-activating Ni(II)-oximate complex oxidizes two-hydrogen atom donating substrates, including the traditionally inert alcohol, methanol, as well as ethanol, benzyl alcohol, benzylamine, and *N*-methylbenzylamine.**

The chemistry of transition metals with dioxygen is important both biologically and commercially. Many biological oxidations using O<sub>2</sub> are catalyzed by enzymes that contain transition metals in their active sites.<sup>1</sup> These processes inspire development of new transition metal catalysts for industrial substrate oxidations by dioxygen, an inexpensive and environmentally friendly oxidant.<sup>2</sup> Understanding the mechanism of atypical M–O<sub>2</sub> reactions may lead to the rational design of oxygen activation catalysts that are capable of unusual substrate oxidations.

Reactions of Ni(II) complexes with O<sub>2</sub> are uncommon, but not unprecedented. However, they generally require irreversible ligand oxidation. Some Ni(II)-amidate complexes (including complexes of peptides) react with O<sub>2</sub>, inevitably undergoing ligand oxidation by hydrogen atom transfer,<sup>3</sup> rendering the complex unsuitable for catalysis. Ni(II) thiolates react with O<sub>2</sub> at the sulfur rather than the nickel, resulting in various sulfur oxygenates.<sup>4</sup> The recently reported reaction of a Ni(II)–carbene complex with O<sub>2</sub> appears to be driven by hydrogen atom abstraction from a  $\pi$ -allyl co-ligand.<sup>5</sup> Reactions of Ni(I) with O<sub>2</sub><sup>6</sup> and Ni(II) with H<sub>2</sub>O<sub>2</sub>,<sup>7</sup> (systems containing either a reduced metal or oxygen species relative to Ni(II) or O<sub>2</sub>), form [LNi(III)( $\mu$ -O)]<sub>2</sub> products without requiring ligand oxidation.

We previously reported that deprotonation of a single oxime in Ni(II)(TRISOXH<sub>3</sub>)(NO<sub>3</sub>)<sub>2</sub> ([TRISOXH<sub>3</sub> = tris(2-hydroxyimino-propyl)amine]), (**1**), results in formation of a structurally characterized oximate-bridged dimer, [Ni(II)(TRISOXH<sub>2</sub>)(CH<sub>3</sub>CN)]<sub>2</sub><sup>2+</sup> (**2**). Further deprotonation of the complex forms another putative oximate-bridged dimer, (**3**), Fig. 1. **3** undergoes multiple turnovers during reaction with O<sub>2</sub> without significant ligand decomposition, making this the first homogeneous Ni(II) + O<sub>2</sub> reaction that is not driven by ligand oxidation.<sup>8</sup> Here we report this reaction with several oxidation substrates (including relatively inert methanol<sup>9</sup>).

Adding three equivalents of hydroxide to a methanolic solution of **1** to form **3** under air or O<sub>2</sub> results in a rapid color change from purple to brown that is not observed under anaerobic conditions. This color change is accompanied by consumption of O<sub>2</sub> as determined by manometry. In contrast, no color change or O<sub>2</sub>

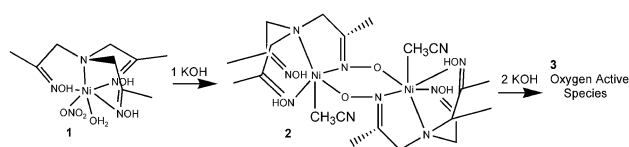


Fig. 1 Formation of the oxygen active species, **3**.

† Electronic supplementary information (ESI) available: experimental details and data for the O<sub>2</sub> reaction with **3** and its oxidation substrates, manometry data for the disproportionation of H<sub>2</sub>O<sub>2</sub>, and calibration curves for chemical detection of products. See <http://www.rsc.org/suppdata/cc/b4/b403668a/>

uptake is observed when an acetonitrile solution of **3** is exposed to air. Formaldehyde is formed in the methanol reaction, and was monitored colorimetrically using the Hantzsch reaction.<sup>10</sup> Fig. 2 shows that the amount of dioxygen consumed is approximately half the amount of formaldehyde produced. It is proposed that hydrogen peroxide is a product of this reaction in a 1:1 ratio with formaldehyde; however, the efficient catalase-like activity of **3** prevents its detection. One equivalent of O<sub>2</sub> is produced for every two equivalents of H<sub>2</sub>O<sub>2</sub> disproportionated, resulting in the observed ~2:1 ratio of formaldehyde production to net dioxygen consumption.

The catalase efficiency of **3** was confirmed in separate manometry and colorimetry experiments. During the colorimetry experiment, 400 equivalents of H<sub>2</sub>O<sub>2</sub> were added to a methanolic solution of **1**. Addition of hydroxide to form **3** resulted in the expected color change from purple to brown and was accompanied by a vigorous bubbling of the solution as the H<sub>2</sub>O<sub>2</sub> was disproportionated. After approximately fifteen minutes the bubbling ceased and an aliquot of the solution was added to a Ti(SO<sub>4</sub>)<sub>2</sub> reagent to test for H<sub>2</sub>O<sub>2</sub>.<sup>11</sup> No H<sub>2</sub>O<sub>2</sub> remained. As a control, Zn(TRISOXH<sub>3</sub>)Cl<sub>2</sub> was treated in an identical fashion to **1** and the H<sub>2</sub>O<sub>2</sub> remained after the same time period. For the manometry experiment, 200 equivalents of H<sub>2</sub>O<sub>2</sub> were added to a solution of **1**. Three equivalents of hydroxide were added to form **3** and the amount of O<sub>2</sub> generated from the disproportionation of H<sub>2</sub>O<sub>2</sub> was monitored. All of the H<sub>2</sub>O<sub>2</sub> was disproportionated within 15 minutes, much faster than its formation during the methanol oxidation reaction.

The observation of methanol oxidation led us to investigate other possible substrates. A 2 mM solution of **3** was reacted with O<sub>2</sub> using either the substrate as the solvent (methanol, ethanol, benzyl

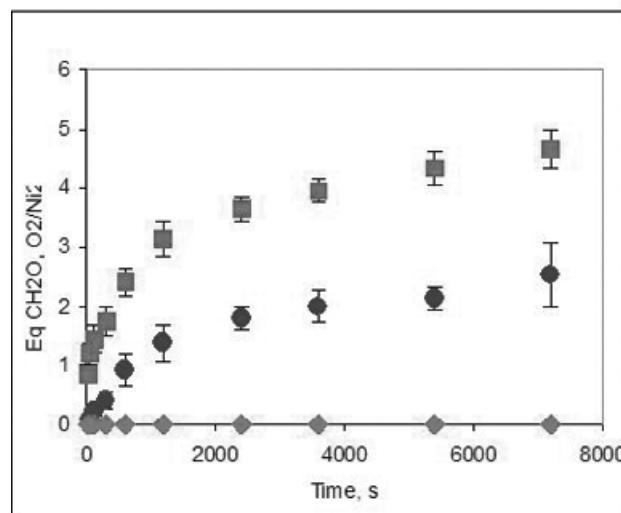


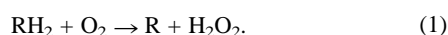
Fig. 2 Production of formaldehyde and consumption of dioxygen from the reaction of 1 mM **3** in methanol and acetonitrile (CH<sub>2</sub>O formation in MeOH = squares, O<sub>2</sub> uptake in MeOH = circles, O<sub>2</sub> uptake in MeCN = diamonds). Each data point is the average of three trials and the error bars are the standard deviations.

**Table 1** Bond dissociation energies (kcal mol<sup>-1</sup>) for hydrogen atom donors and hydrogen peroxide.<sup>12</sup> Product quantities are the average of three experiments. (NA = not available, NR = no reaction)

| Substrate                     | 1 <sup>st</sup> H· | 2 <sup>nd</sup> H· | Total | Eq. of Product after 1 hour | Eq. of Product after 24 hours |
|-------------------------------|--------------------|--------------------|-------|-----------------------------|-------------------------------|
| Methanol                      | 93                 | 31                 | 124   | 3.95 ± 0.19                 | 10.37 ± 0.45                  |
| Ethanol                       | 90                 | 26                 | 116   | 2.90 ± 1.23                 | 8.54 ± 3.14                   |
| Benzyl alcohol                | 87.5               | 18                 | 105.5 | 0.85 ± 0.02                 | 3.02 ± 0.57                   |
| 2-Propanol                    | 91                 | 26                 | 117   | NR                          | NR                            |
| D,L-1-Phenylethanol           | 88                 | 14                 | 102   | NR                          | NR                            |
| N-Methylbenzyl amine          | NA                 | NA                 | NA    | 0.24 ± 0.04                 | 0.64 ± 0.10                   |
| Benzyl amine                  | 100                | 23                 | 123   | 0.93 ± 0.30                 | 4.95 ± 0.95                   |
| α-Methylbenzyl amine          | NA                 | NA                 | NA    | NR                          | NR                            |
| H <sub>2</sub> O <sub>2</sub> | 88.5               | 46                 | 134.5 |                             |                               |

alcohol), or by using acetonitrile as the solvent and adding 200 equivalents of substrate (benzylamine, *N*-methylbenzylamine). Both protocols resulted in the expected color change and produced multiple equivalents of most oxidized products (Table 1). The primary alcohols produced aldehydes, and the amines produced *N*-benzylidene benzylamine. The oxidation of benzylamine may follow one of two pathways. It may undergo oxidative deamination to form benzaldehyde and ammonia (ammonia was detected as one of the products of this reaction) with the benzaldehyde further reacting with excess amine to form the Schiff base product, *N*-benzylidene benzylamine. Alternatively, two hydrogen atoms may be abstracted to form the imine, which then reacts with excess amine to form ammonia and the same Schiff base product. *N*-Methylbenzylamine likely undergoes reversible addition–elimination through an amination intermediate, also forming *N*-benzylidene benzylamine, as previously reported by Murahashi, *et al.*<sup>13</sup>

All of the substrates studied were oxidized by the abstraction of two hydrogen atoms according to reaction (1):



The bond dissociation energies in Table 1 show that transfer of the first hydrogen to O<sub>2</sub> is unfavorable. Transfer of the second H-atom to form H<sub>2</sub>O<sub>2</sub> makes the overall reaction exothermic. Thus, there is a thermodynamic requirement for a two H-atom reaction. However, several potential substrates whose oxidations are thermodynamically favorable (2-propanol, D,L-1-phenylethanol, α-methylbenzylamine) produce no color change with **3**, and no ketones were formed from the alcohols. These unreactive substrates share the common feature that they are branched at the α-carbon.

The reactivity of **3** is reminiscent of several enzymatic processes. Galactose oxidase catalyzes the aerobic oxidation of a primary alcohol to an aldehyde with concurrent H<sub>2</sub>O<sub>2</sub> formation,<sup>14</sup> similar to the oxidation of methanol, ethanol, and benzyl alcohol by **3**. Copper amine oxidases catalyze the aerobic oxidation of a primary amine to form an aldehyde, NH<sub>3</sub>, and H<sub>2</sub>O<sub>2</sub>,<sup>15</sup> related to the reaction of **3** with benzylamine to form *N*-benzylidene benzylamine and ammonia. Both heme and dinuclear Mn catalase enzymes catalyze H<sub>2</sub>O<sub>2</sub> disproportionation.<sup>16</sup>

The oxidation of methanol or benzylamine was also investigated in aqueous solution. The aqueous environment inhibited formaldehyde production (1.88 ± 0.03 equiv. after 24 h, *versus* 5.07 ± 0.31 in acetonitrile, both experiments containing 50% methanol) but does not significantly affect benzylamine oxidation (5.44 ± 0.54 equiv. after 24 h).

In summary, we have reported substrate oxidation by the first Ni(II) + O<sub>2</sub> reaction that does not proceed *via* irreversible ligand oxidation. It instead requires an exogenous source of hydrogen atoms. This can come from a relatively inert substrate such as methanol, provided a second low energy H-atom dissociation is available. The aerobic oxidation of methanol by discrete transition metal complexes has been reported in only a few instances, most notably in Wieghardt and coworkers' Zn complex with a redox active ligand that displayed catalytic oxidation, and Karlin and

coworkers' Cu complex that oxidized less than one equivalent of methanol.<sup>9</sup>

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