Dioxygen Activation

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Oxidative Decarboxylation of Benzilic Acid by a Biomimetic Iron(II) Complex: Evidence for an Iron(IV)–Oxo–Hydroxo Oxidant from O_2**

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The existence of dioxygen-activating nonheme iron enzymes that carry out four-electron substrate oxidations requires a mechanism where the initially formed iron(III)–superoxide species must be involved as an oxidant to initiate the reaction.[1–4] Such a step has been proposed for many aromatic and aliphatic C–C bond cleaving dioxygenases.[1,5] Recently discovered examples include 2-hydroxyethylphosphonate (HEP) dioxygenase (HEPD) which catalyzes the cleavage of the HEP C1–C2 bond to form hydroxymethylphosphonate and formate,[3] and CloR, which is involved in the conversion of a mandelate moiety to benzoate in the biosynthesis of chlorobiocin, an aminocoumarin antibiotic.[6] For the above examples, the substrate provides all four electrons needed for the reduction of O_2 to water. In contrast, the Rieske dioxygenases require two electrons from NADH to carry out the *cis*-dihydroxylation of aromatic C=C bonds.[1,7] A high-valent iron–oxo–hydroxo intermediate has been proposed to carry out this transformation.

Recently, a synthetic iron(II)–mandelate complex supported by a tripodal N_4 donor ligand was reported by us[8] to undergo nearly quantitative oxidative decarboxylation in the presence of dioxygen, thereby mimicking the C–C bond cleavage reaction of CloR. An iron(III)–superoxo species has been implicated in the reaction pathway. In exploring the O_2 reactivity of related iron(II)–α-hydroxy acid complexes, specifically those of benzilic acid (2,2-diphenyl-2-hydroxyacetic acid), we discovered a new mode of O_2 activation that leads to the formation of an iron(IV)–oxo–hydroxo oxidant. These intriguing results are reported here.

The iron(II) model complex $[(Tp^{Ph_2})Fe^{II}(benzilate)]$ (**1**), where Tp^{Ph_2} = hydrotris(3,5-diphenylpyrazolyl)borate, was synthesized by reacting equimolar amounts of the polydentate ligand, iron(II) perchlorate, benzilic acid, and triethylamine in methanol. The ^1H NMR spectrum of **1** shows broad and paramagnetically shifted peaks indicative of the high-spin nature of the iron(II) complex (Figure S1 in the Supporting Information). The X-ray crystal structure of **1** shows a distorted square-pyramidal iron(II) center ($\tau = 0.46$[9]) that is coordinated by the facial tridentate Tp^{Ph_2} ligand and the carboxylate of the benzilate monoanion (Figure 1). The

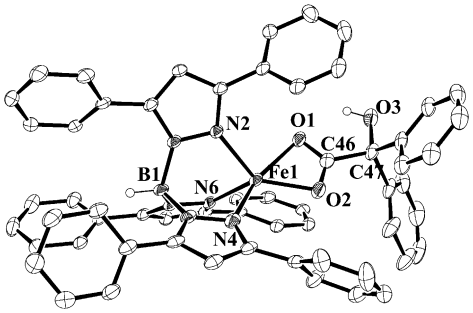

Figure 1. Molecular structure of $[(Tp^{Ph_2})Fe^{II}(benzilate)]$ (**1**). All hydrogen atoms except that attached to O3 and B1 have been omitted for clarity. Selected bond lengths [Å] and angles [deg] for **1**: Fe1–O1 2.346(3), Fe1–O2 2.008(3), Fe1–N2 2.075(3), Fe1–N4 2.120(3), Fe1–N6 2.082(3), C46–O1 1.248(4), C46–O2 1.273(5); O1-Fe1-N4 162.16(11), O1-Fe1-N6 107.88(10), O1-Fe1-N2 98.23(10), O2-Fe1-N2 134.82(11), O2-Fe1-N6 131.04(11), O2-Fe1-N4 103.85(12), O1-Fe1-O2 59.83(10), N2-Fe1-N4 88.75(11).

average Fe–N bond length of 2.092 Å is comparable to those of other $Fe^{II}(Tp^{Ph_2})$ complexes,[10] while the iron–carboxylate distances indicate an unsymmetric bidentate binding mode (r(Fe1–O1), 2.346(3) and r(Fe1–O2), 2.008(3) Å) (Table S1). The hydroxy group of the benzilate does not coordinate with the iron center, possibly due to the steric crowding from the phenyl rings on the Tp^{Ph_2} ligand. Structural parameters are quite similar to those obtained previously for $[Fe^{II}(Tp^{Ph_2})(benzoate)]$ and $[Fe^{II}(Tp^{Ph_2})$-(benzoylformate)] (**2**).[10]

The colorless solution of **1** in benzene reacts with pure O_2 at ambient temperature over a period of 10–15 min to generate a green solution with a broad charge transfer band at 600 nm (Figure S2). The green solution corresponds to the formation of an iron(III)–phenolate complex of the Tp^{Ph_2*} ligand in which an *ortho* carbon of one 3-phenyl ring on the ligand becomes hydroxylated. The ESI-MS spectrum of the green solution shows ion peak at m/z 740.2 with the expected isotope distribution pattern calculated for $[(Tp^{Ph_2*})Fe]^+$ ion (Figure 2a and Figure S3). Upon acidic work-up of the oxidized solution, ^1H NMR analysis clearly establishes the

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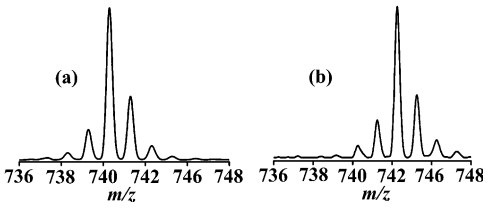
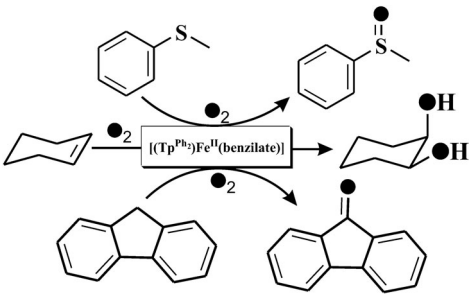


Figure 2. ESI-MS of the reaction solution after oxidation of **1** with a) $^{16}O_2$ and b) $^{18}O_2$.

quantitative decarboxylation of benzilate to benzophenone (Figure S4), a result supported by GC analysis of the reaction mixture after the removal of metal components. The reaction also affords about 90% of the ring-hydroxylated product $[(Tp^{Ph_2*})Fe^{III}]^+$ (**3**), as estimated from its extinction coefficient.[10]

The fate of the atomic constituents of dioxygen was determined by ^{18}O labeling experiments. ESI-MS analysis of the reaction solution after reaction of **1** with $^{18}O_2$ in benzene shows a peak at *m*/*z* 742.2 (Figure 2b) with expected isotope distribution pattern attributable to $[(Tp^{Ph_2*})Fe]^+$. This indicates that one oxygen atom from $^{18}O_2$ is incorporated into the ligand backbone. However, the decarboxylated product from benzilate (i.e. benzophenone) does not contain any labeled oxygen. It can thus be assumed that the second atom from O_2 is converted to water.

The ring hydroxylation of Tp^{Ph_2} ligand along with the formation of benzoic acid has previously been reported in the reaction of $[Fe^{II}(Tp^{Ph_2})(benzoylformate)]$ with O_2.[10,11] This hydroxylation reaction can be inhibited by the presence of different reagents that can intercept the putative high-spin Fe^{IV}=O oxidant formed in the oxidative decarboxylation of the iron(II)–benzoylformate complex **2**.[11] As aromatic ring hydroxylation also takes place in the reaction of **1** with dioxygen, we have studied the reaction in the presence of different intercepting reagents to gain insight into the nature of the active oxidant (Scheme 1). Figure 3 shows the effects of



Scheme 1. Oxidation of different substrates during the reaction of **1** with dioxygen.

adding fluorene, cyclohexene, or thioanisole to the amount of $[Fe(Tp^{Ph_2*})]^+$ formed. Thioanisole is most effective with 10 equiv resulting in a 92% interception of the oxidant (Figure S5). GC-MS analysis of the reaction mixture after separation of the metal shows ions at *m*/*z* 140.03 and 156.03

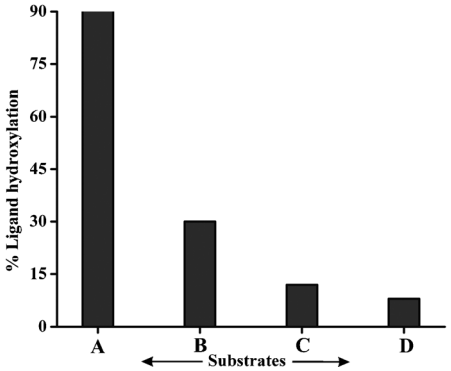


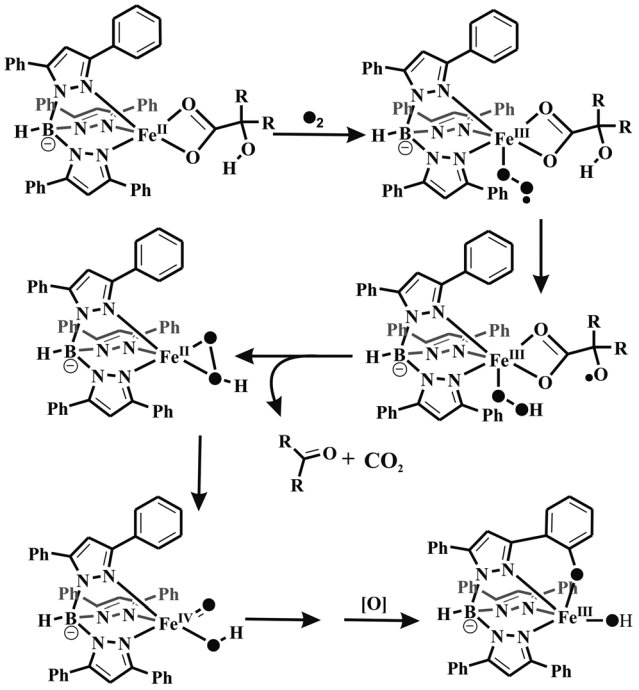
Figure 3. Percentage of ligand hydroxylation during the reaction of **1** with dioxygen in the presence of different substrates: **A**: no substrate; **B**: 100 equiv fluorene; **C**: 100 equiv cyclohexene; **D**: 10 equiv thioanisole.

corresponding to $[PhS(O)CH_3)]^{\bullet+}$ and $[PhSO(O)CH_3)]^{\bullet+}$, respectively (Figure S6). ^1H NMR analysis of the organic products supports the formation of about 85% methyl phenyl sulfoxide (relative to Fe) and only a very small amount (6–8%) of methyl phenyl sulfone (Figure S7). In addition, benzilate is converted quantitatively to benzophenone. The oxidant that is generated by this reaction is thus capable of intermolecular oxo transfer.

The reaction of **1** with dioxygen in the presence of 100 equiv of fluorene inhibits the intramolecular ring hydroxylation by 70% (Figure S5). GC analysis shows that benzilate is converted to benzophenone in 80% yield, while fluorene is oxidized to fluorenone in 50% yield (relative to Fe). This result shows that the oxidant formed is also capable of intermolecular hydrogen-atom abstraction. Therefore it is reasonable to postulate the formation of a high-valent iron–oxo species upon oxidative decarboxylation of the bound benzilate, similar to that proposed in the reaction of the corresponding benzoylformate complex **2** with O_2.

The results of cyclohexene interception reveal, however, that the oxidant formed in this reaction is not identical to that formed in the reaction of the benzoylformate complex. Cyclohexene is also quite an effective interception agent, with 100 equiv inhibiting the ring hydroxylation to the extent of 85–90% (Figure S5), while the decarboxylation of benzilate to benzophenone is quantitative. Most interestingly, the ^1H NMR spectrum of the reaction solution shows the formation of approximately 60% of *cis*-cyclohexane-1,2-diol ($C_6H_{12}O_2$) as the only product derived from cyclohexene (Figure S8). GC-MS analysis of the oxidized product exhibits a predominant peak at *m*/*z* 116.02 attributable to $[C_6H_{12}O_2]^{\bullet+}$. This *m*/*z* value increases by four units when $^{18}O_2$ is used in place of $^{16}O_2$, clearly demonstrating O_2 to be the source of both oxygen atoms of the diol (Figure S9). Furthermore a mixed $^{16}O_2/^{18}O_2$ labeling experiment showed that both oxygen atoms on the diol product derived from one O_2. The results implicate that **1** can activate O_2 to form an oxidant capable of transferring both oxygen atoms to cyclohexene. It is important to note here that addition of $H_2{}^{16}O$ in the labeling experiment with $^{18}O_2$ does not show incorporation of any ^{16}O into the diol formed.

On the basis of the above experimental results, we propose the mechanism shown in Scheme 2. O_2 binding to **1** forms an adduct that is best described as an iron(III)–superoxide complex. As we have previously shown that iron(III)–superoxide species derived from related biomimetic nonheme iron complexes are capable of hydrogen-atom abstraction from C–H or O–H groups,[8,12] we propose that



Scheme 2. Proposed mechanism for the oxidation of **1** in the presence of dioxygen.

the bound superoxide radical of the **1**·O_2 adduct abstracts the hydrogen atom from the OH group of benzilate to form an iron(III)–hydroperoxide species and a bound benzilate oxyl radical. The latter spontaneously decomposes, resulting in C–C bond cleavage to form benzophenone and CO_2 with concomitant reduction of iron(III) to iron(II). The thus formed iron(II)–hydroperoxide intermediate then undergoes O–O bond cleavage to generate an iron(IV)–oxo–hydroxo oxidant that carries out the various observed oxidations.

In the absence of any external substrate, the oxoiron(IV) species hydroxylates one of the 3-phenyl rings of the Tp^{Ph_2} supporting ligand, as previously observed for the corresponding benzoylformate complex. The resulting iron(II)–phenolate complex readily reacts with the residual O_2 present and is oxidized to an iron(III)–phenolate species with a charge-transfer (CT) band at 600 nm. This result is somewhat distinct from that reported for the reaction of O_2 with the corresponding benzoylformate complex, which forms a green chromophore with λ_{max} at 650 nm.[10,11,13] When the oxidized solution of **1** is treated with 10 equiv of pyridinium- or lutidinium perchlorate, the CT band immediately shifts from 600 to 650 nm and subsequent treatment with tetrabutylammonium hydroxide returns the CT band back to 600 nm (Figure S10). These observations are consistent with a hydroxide ion coordinated to the $Fe^{III}(Tp^{Ph_2*})$ center after the oxidation of **1**. The basic hydroxide ligand would decrease the Lewis acidity of the iron(III) center, resulting in the observed higher-energy CT band relative to those of corresponding $Fe^{III}(Tp^{Ph_2*})$ complexes with bound water (from protonation of the hydroxide) or benzoate (from oxidative decarboxylation of **2**). It is important to mention here that the peak at 600 nm slowly shifts to 650 nm upon standing the reaction solution for 2 days.

As previously documented for the corresponding benzoylformate complex **2**, intermolecular oxidation of added substrates competes with intramolecular ligand hydroxylation. Thioanisole and cyclohexene are both good substrates for **1**, inhibiting ligand hydroxylation by 92% and 85%, respectively. Oxo transfer occurs for thioanisole, affording the corresponding sulfoxide as expected. Interestingly however, cyclohexene is converted to *cis*-cyclohexane-1,2-diol, an outcome completely different from that observed for **2**, where 1,3-cyclohexadiene was identified as the product. This difference presumably arises from the nature of the anionic ligand bound to the nascent oxoiron(IV) center, hydroxide in the case of **1** and benzoate in the case of **2**. The data presented herein strongly suggest the formation of an iron(IV)–oxo–hydroxo oxidant in the oxygenation of **1** that is capable of the *cis*-dihydroxylation of an alkene.

There is ample supporting evidence from the biochemical and biomimetic literature. A similar high-valent iron–oxo–hydroxo oxidant has been postulated for the *cis*-dihydroxylation of arenes that occurs at the mononuclear nonheme iron active site of Rieske dioxygenases.[14–17] For the enzymes, the accumulated mechanistic evidence favors an iron(V)–oxo–hydroxo oxidant,[14–16] although the corresponding iron(IV)–oxo–hydroxo species has also been suggested.[17] Indirect evidence for a high-valent iron–oxo–hydroxo oxidant has also been obtained from studies of biomimetic nonheme iron complexes that catalyze alkene *cis*-dihydroxylation using hydrogen peroxide as oxidant;[18–21] an iron(V)–oxo–hydroxo oxidant is proposed for iron catalysts with tetradentate N_4 ligands,[19–21] while a dihydroxoiron(IV) oxidant is postulated for iron catalysts with facial N,N,O ligands.[18]

In summary, we have reported a biomimetic iron(II) complex (**1**) which reacts with O_2 to oxidatively cleave benzilic acid to benzophenone. The oxidant formed is capable of converting cyclohexene to *cis*-cyclohexane-1,2-diol with both oxygen atoms derived from O_2. An iron(IV)–oxo–hydroxo intermediate has been proposed as the active oxidant in the reaction pathway. Thus **1** serves as a functional model of Rieske dioxygenases where the monoanionic benzilate ligand serves as the sacrificial co-substrate to provide two electrons and one proton to carry the *cis*-dihydroxylation of cyclohexene. The results discussed here show the importance of model complexes in developing bioinspired oxidation catalysts. With small-molecule models, the presence of a reductant is necessary to carry out catalytic oxygen-dependent transformation reactions. Detailed studies in this direction are in progress in our laboratories.

Experimental Section

$[Fe^{II}(Tp^{Ph_2})(benzilate)]$ (**1**). To a suspension of KTp^{Ph_2} (0.35 g, 0.5 mmol) and $Fe(ClO_4)_2{\cdot}6H_2O$ (0.12 g, 0.5 mmol) in methanol (5 mL) was added a methanolic solution (5 mL) of benzilic acid (0.114 g, 0.5 mmol) and triethylamine (70 μL). The resulting white suspension was stirred at room temperature for 2 h to isolate a white solid. Single crystals suitable for X-ray diffraction were grown by diffusing diethylether into a solution of **1** in dichloromethane. Yield: 0.41 g (86%). Elemental analysis calcd (%) for $C_{59}H_{45}BFeN_6O_3$ (952.68 g mol^{-1}): C 74.38, H 4.76, N 8.82; found: C 73.8, H 4.7, N 8.5. IR (KBr): $\tilde{\nu}$ = 3466(br), 2924(vs), 2856(s), 1741(m), 1639(br), 1553(m), 1468(m), 1354(m), 1169(s), 1068(s), 764(vs), 694(vs), 403(vs) cm^{-1}.

Crystal data of **1**: $MF = C_{63}H_{55}BFeN_6O_4$, $M_r = 1026.79$, triclinic, space group $P\bar{1}$, $a = 11.861(4)$, $b = 14.817(5)$, $c = 15.909(6)$ Å, $\alpha = 100.616(8)°$, $\beta = 100.626(8)°$, $\gamma = 101.458(7)°$, $V = 2621.4(15)$ Å^3, $Z = 2$, $\rho = 1.301$ mg m^{-3}, $\mu(Mo_{K\alpha}) = 0.344$ mm^{-1}, $F(000) = 1076$, GOF = 1.061. A total of 25593 reflections were collected in the range $1.34 \le \theta \le 26.00$, 10250 of which were unique ($R_{int} = 0.0717$). R_1-(wR_2) = 0.0532(0.1327) for 672 parameters and 10250 reflections ($I > 2\sigma(I)$). CCDC 826082 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Analysis of organic products after reaction with oxygen: The iron(II) complex (0.020 mmol) was dissolved in 10 mL of dioxygen-saturated benzene. The solution was stirred at room temperature, and after the reaction the solvent was removed under vacuum and the residue treated with 10 mL of 2 M hydrochloric acid solution. The organic products were extracted with diethyl ether (3 × 15 mL), and the organic layer was dried over anhydrous sodium sulfate. After removal of solvent, the colorless residue was analyzed by GC-MS and ^{1}H NMR spectroscopy. Quantification of benzophenone was done by comparing the peak area of four aromatic *ortho* protons (δ = 7.81 ppm) with one CH proton (δ = 6.23 ppm) of 3,5-di-*tert*-butylbenzoquinone (internal standard).

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