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Biomimetic Model

Oxidative Carbon–Carbon Bond Cleavage of a α-Hydroxy Ketone by a Functional Model of 2,4′-Dihydroxyacetophenone Dioxygenase**

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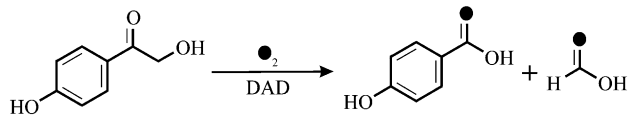
2,4′-Dihydroxyacetophenone dioxygenase (DAD), an enzyme from aerobic soil bacterium *Alcaligenes* sp., is involved in the catabolism of 4-hydroxyacetophenone.[1–3] DAD catalyzes the cleavage of 2,4′-dihydroxyacetophenone into 4-hydroxy benzoate (HB) and formate in the presence of dioxygen.[3] In the C–C bond cleavage reaction, an oxygen atom from dioxygen is incorporated into each product (Scheme 1).[3] DAD was first purified and sequenced by



Scheme 1. Reaction carried out by DAD.

Hopper and Kaderbhai revealing that the enzyme has little sequence homology to other dioxygenases.[3] This enzyme has been proposed to be a member of the "cupin" superfamily.[4] DAD, not yet structurally characterized, is a homotetramer and contains one atom of iron per molecule of enzyme.[3] However, little is known about the oxidation state of iron and its role in the C–C bond cleavage mechanism.[3,4] In biomimetic studies, small-molecule transition-metal model complexes play an important role in understanding the mechanism of enzymatic reactions.[5–13] Thus to develop a mechanistic understanding of the reaction carried out by DAD, we have studied the dioxygen reactivity of biomimetic iron(II)–α-hydroxy ketone complexes. Here we report the synthesis, characterization, and dioxyen reactivity of an iron(II)–α-hydroxy ketone complex, [(Tp^{Ph2})Fe^{II}(HAP)] (**1**), where Tp^{Ph2} is hydrotris(3,5-diphenylpyrazolyl)borate and HAP-H is 2-hydroxyacetophenone.

The model iron(II) complex (**1**) was prepared by reacting equivalent amounts of KTp^{Ph2}, iron(II) perchlorate, 2-hydroxy acetophenone, and triethylamine in methanol. The complex was isolated as pink solid. Complex **1** exhibits weak charge transfer bands at 505 ($460\,M^{-1}cm^{-1}$) and 560 nm ($325\,M^{-1}cm^{-1}$) in benzene. Similar charge-transfer (CT) bands in the region between 500–600 nm have been reported for [(Tp^{Ph2})Fe^{II}(benzoylformate)],[8,9] [(Tp^{Ph2})Fe^{II}-(pyruvate)],[9] [(Tp^{Me2})Fe^{II}(benzoylformate)],[14] and [(6-Me_3-TPA)Fe^{II}(benzoylformate)][15] complexes (Tp^{Me2} = hydrotris(3,5-dimethylpyrazolyl)borate, 6-Me_3-TPA = tris(6-methyl-2-pyridylmethyl)amine. The peaks have been attributed to the charge-transfer transition from the filled d orbital of the iron(II) to the empty π* orbital of the keto group of α-keto acid.[9,15] The CT bands of **1**, by analogy to the reported ion(II)-benzoylformate complexes, may be attributed to the iron(II)-to-keto charge-transfer transitions. The optical spectral features suggest that the α-hydroxy ketone binds to the metal center in the keto form. The ^1H NMR spectrum of the complex in [D_6]benzene displays paramagnetically shifted proton resonances, typical for a high-spin iron(II) complex (Figure S1 in the Supporting Information).

X-ray quality single-crystals of **1** were isolated from a solvent mixture of dichloromethane and methanol. The crystal structure of **1** shows a five-coordinate iron center ligated by three nitrogen donors from the facial tridentate ligand and two oxygen donors from a bidentate HAP anion (Figure 1). The average Fe–N bond distance of 2.13 Å is similar to that reported for other high-spin iron(II) complexes, [(Tp^{Ph2})Fe^{II}(benzoylformate)],[8,9] [(Tp^{Ph2})Fe^{II}-

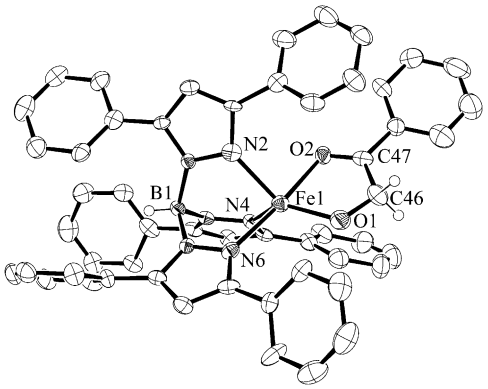


Figure 1. ORTEP plot of [(Tp^{Ph2})Fe^{II}(HAP)] (**1**) with 50% thermal ellipsoids. All hydrogen atoms except those attached to C46 and B1 have been omitted for clarity. Selected bond lengths [Å] and angles [deg] for **1**: Fe1–O1 1.915(6), Fe1–O2 2.230(5), Fe1–N2 2.096(7), Fe1–N4 2.116(6), Fe1–N6 2.199(6), C46–O1 1.386(10), C47–O2 1.236(10), C46–C47 1.500(12); O1-Fe1-N4 128.8(2), O1-Fe1-N6 106.6(2), O1-Fe1-N2 137.3(3), O2-Fe1-N2 90.1(2), O2-Fe1-N6 174.4(2), O2-Fe1-N4 89.6(2), O1-Fe1-O2 78.9(2), N2-Fe1-N4 91.8(2), N2-Fe1-N6 85.8(2), N4-Fe1-N6 86.8(2).

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(benzilate)],[6] and [(Tp^{Ph2})Fe^{II}(catecholate)].[16] HAP binds to the metal center through a keto oxygen (O2) and an alcoholate oxygen (O1) with the Fe1–O1 and Fe1–O2 distances of 1.915(6) and 2.230(5) Å, respectively (see Table S1 in the Supporting Information). The asymmetric Fe–O bond distances clearly establish that HAP does not enolize upon binding with iron(II) center. The Fe1–O2 distance in **1** is comparable to the Fe^{II}–O$_{keto}$ distance in [(Tp^{Ph2})Fe^{II}(benzoylformate)].[8] The oxygen atom (O2) and a nitrogen atom (N6) occupy the axial positions with the O2-Fe1-N6 angle of 174.4(2)°. The alcoholate oxygen (O1) and two other nitrogens (N2 and N4) form the equatorial plane giving rise to a distorted trigonal bipyramidal ($\tau = 0.62$)[17] coordination geometry at the iron(II) center. The crystal structure of **1** represents the first example of a biomimetic iron(II) complex coordinated by a bidentate α-hydroxy ketone.

The model iron(II)–α-hydroxy ketone complex (**1**) reacts rapidly with dioxygen in benzene at 10 °C. During the reaction, metal-to-ligand charge-transfer bands of the complex disappear with time and the pink solution turns to colorless within 5 min (Figure 2). ESI-MS of the colorless

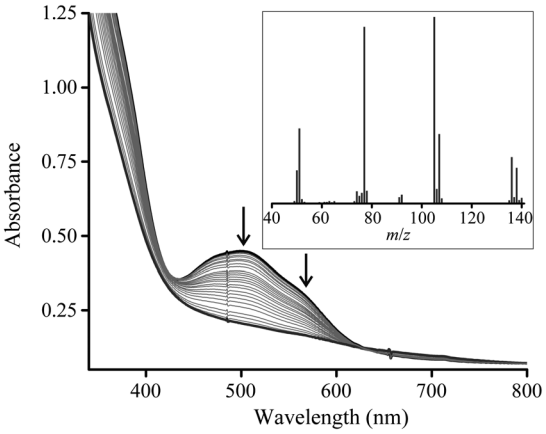
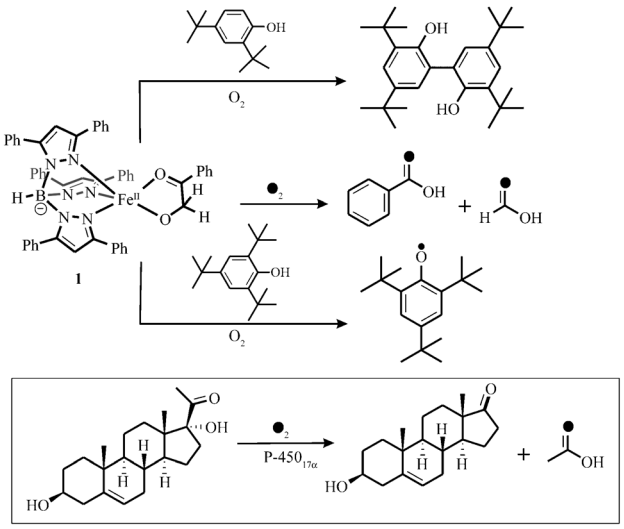


Figure 2. Optical spectral changes during the reaction of **1** (0.98 mM solution in benzene) with dioxygen at 10 °C. Inset: GC mass spectrum of the methyl ester of benzoic acid with $^{18}O_2$.

solution displays a predominant peak at $m/z = 725.15$ with isotope distribution pattern calculated for [(Tp^{Ph2})Fe]$^+$ (see Figure S2 in the Supporting Information). The ^{1}H NMR spectrum of the final reaction solution supports the formation of a high-spin iron(II) complex after oxidative cleavage of HAP (see Figure S3 in the Supporting Information). The organic products, after separation of iron from the reaction solution, were analyzed by GC-MS and ^{1}H NMR spectroscopy. The ^{1}H NMR spectral data of the organic products after oxidation of **1** reveal that HAP is quantitatively converted to benzoic acid and formic acid (see the Experimental Section and Figures S4 and S5 in the Supporting Information). The formation of formic acid was further confirmed spectrophotometrically in the presence of mercuric acetate according to the procedure described by Khabarov et al. (see Figure S6).[18] The incorporation of atomic constituents of dioxygen into benzoate was tested by ^{18}O labeling experiments. The GC mass spectrum of the methyl benzoate derived from benzoic acid, formed in the reaction of **1** with $^{18}O_2$, shows around 40 % incorporation of one ^{18}O into benzoate; the peak at $m/z =$ 136.2 is shifted to 138.2 upon incorporation of one ^{18}O atom (Figure 2 (inset) and Figure S7 in the Supporting Information). A lower percentage of ^{18}O incorporation into benzoic acid arises most likely because of the exchange of ^{18}O with H_2O during the acidic workup of benzoate as previously observed.[19] The other oxygen atom is presumably incorporated into formic acid. The results unambiguously establish that the C–C bond of α-hydroxy ketone cleaves when **1** reacts with dioxygen and functionally mimics the reaction catalyzed by 2,4′-dihydroxyacetophenone dioxygenase.

It is important to mention here that the ligand (Tp^{Ph2}) remains unchanged after the C–C bond cleavage of 2-hydroxyacetophenone. This is strikingly different from the reactivity patterns of [(Tp^{Ph2})Fe^{II}(benzoylformate)],[8,9] [(Tp^{Ph2})Fe^{II}(benzilate)],[6] or [(Tp^{Ph2})Fe^{II}(phenylpyruvate)][13] complexes, where a simultaneous C–C bond cleavage of coordinated substrate and hydroxylation of one of the phenyl rings of Tp^{Ph2} take place. In all these cases, an Fe^{IV}=O species has been proposed to hydroxylate the ligand.[10] Thus, the high-valent iron–oxo intermediate may not be involved during the C–C bond cleavage of the α-hydroxy ketone. Namely, a different dioxygen activation mechanism may be operating in the present reaction. However, the final colorless solution slowly turns to green over a period of days as a result of further dioxygen activation by the resulting [(Tp^{Ph2})Fe^{II}-(benzoate)] complex (Figures S8 and S9 in the Supporting Information). Que and co-workers have previously reported that [(Tp^{Ph2})Fe^{II}(benzoate)] reacts with dioxygen for 2–3 days and during the reaction the intramolecular ligand hydroxylation takes place to the extent of 55(5) %.[9] An iron(IV)–oxo species, formed by O–O bond homolysis of a peroxo-bridged diiron(III) intermediate, was proposed as the active oxidant responsible for the hydroxylation of the phenyl ring.[9] The latter intermediate was spectroscopically characterized with the [(Tp^{iPr2})Fe^{II}(benzoate)] complex by Kitajima et al. (Tp^{iPr2} = hydrotris(3,5-diisopropylpyrazolyl)borate).[20] By analogy, it is proposed that further oxygen activation by the iron(II) benzoate complex derived from **1** follows a similar mechanism (Figure S10 in the Supporting Information).

To understand the mechanism of oxidative C–C bond cleavage of the α-hydroxy ketone, **1** was allowed to react with O_2 in the presence of excess radical scavengers like dimethyl sulfoxide (DMSO) or D-mannitol.[21,22] The C–C bond cleavage reaction is not inhibited by the radical scavengers and rules out the possibility of involvement of any free radical species. In a related cytochrome P-450 enzyme 17α-hydroxylase-17,20-lyase (P-450$_{17\alpha}$), which catalyzes the conversion of 17α-hydroxypregnenolone (an α-hydroxy ketone) to dehydroisoandrosterone and acetic acid (Scheme 2), an iron(III)–peroxide intermediate has been proposed to initiate the transformation reaction.[23–25] According to the proposed mechanism, an iron(III)–superoxide intermediate is formed initially which is reduced by one electron to an iron(III)–peroxide. The reduction by an external electron is a common feature for cytochrome P450 related enzymes.[26] The peroxide then attacks the keto group of the α-hydroxy ketone



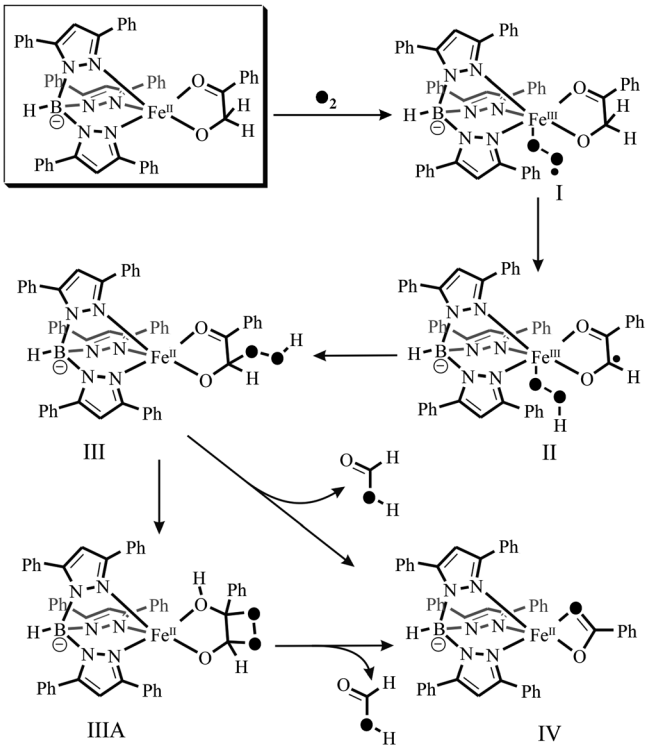
Scheme 2. Reaction of **1** with dioxygen in the presence of different intercepting reagents. Bottom: Reaction catalyzed by a cytochrome P-450 enzyme, 17α-hydroxylase-17,20-lyase (P-450$_{17\alpha}$).

resulting in an iron(III)–alkylperoxo species, which subsequently decays to the products.[25] However, for the model complex (**1**), no such external electron source is available for the formation of a peroxide intermediate and importantly, benzoic acid and formic acid (no aldehyde) are formed in the oxidative cleavage of 2-hydroxyacetophenone. Thus, the involvement of a possible peroxide intermediate during the oxidative C–C cleavage in **1** may be ruled out. Moreover, the reaction of equimolar amounts of the ligand, iron(II) perchlorate, 2-hydroxy-1,2-diphenyl-propan-1-one (HDPO), and triethyamine with dioxygen in a benzene–methanol (9:1) solvent mixture does not produce any C–C cleavage products from HDPO (see Figure S11 in the Supporting Information). The presence of a C–H bond in the α-hydroxy ketone is, therefore, important for the oxygen-dependent C–C bond cleavage reaction.

To get an idea about the iron–oxygen intermediates, reaction of **1** with dioxygen was separately carried out in acetone and toluene at −80 °C. Unfortunately, no intermediate species could be observed at low temperature in both the solvents for characterization by IR or resonance Raman studies. While no direct evidence is obtained about the intermediate species, use of intercepting reagents provides indirect evidence about the intermediate species involved in the reaction pathway. When the reaction of **1** with dioxygen is carried out in the presence of 10 equivalents of 2,4-di-*tert*-butylphenol (DTBP) at 10 °C an intense green solution is formed. The ^{1}H NMR spectrum of the organic products derived from DTBP, after separation of the metal ion, confirms a quantitative transformation of DTBP to 3,3′,5,5′-tetra-*tert*-butyl-2,2′-biphenol (see Figure S12 in the Supporting Information).

Additionally, in the reaction of **1** with dioxygen in the presence of 2,4,6-tri-*tert*-butylphenol (TTBP) at 10 °C, formation of the 2,4,6-tri-*tert*-butyl phenoxyl radical is confirmed from the charge-transfer bands at 383, 403, 427, and 630 nm in the optical spectrum (Figure S13 in the Supporting Information). The X-band EPR spectrum of the reaction solution shows resonances at $g = 1.99$ and supports the formation of a radical species in the reaction pathway. In addition, the EPR spectrum shows another signal at $g = 4.25$ corresponding to a high-spin iron(III) species (Figure S13). The unstable 2,4,6-tri-*tert*-butyl phenoxyl radical slowly decomposes to give 2,6-di-*tert*-butyl benzoquinone with 60 % yield as identified by ^{1}H NMR spectroscopy (Figure S14).

Iron(III)–superoxide and copper(II)–superoxide radical species have been shown to abstract hydrogen atom from the O–H groups of phenols.[27–29] We have recently shown that the oxidative C–C bond cleavage of α-hydroxy acid was initiated via hydrogen-atom abstraction from O–H or C–H bonds by an iron(III)–superoxide species.[6,7] On the basis of the experimental results described above, a mechanistic proposal may be envisaged (Scheme 3). Complex **1** activates dioxygen



Scheme 3. Proposed mechanism for the oxidative C–C bond cleavage reaction of 2-hydroxyacetophenone.

to form an iron(III)–superoxide radical species (**I**) initially, which abstracts an hydrogen atom from the α carbon of the hydroxy ketone to form an iron(III)–hydroperoxide intermediate (**II**). This bears resemblance to an iron(III)–hydroperoxide species proposed in the reaction mechanism for 2-hydroxyethylphsphonate dioxygenase (HEPD),[30] *myo*-inositol oxygenase (MIOX),[31] CloR,[32] and isopenicilin N synthase (IPNS).[5] The resulting iron(III)–hydroperoxide species then undergoes a hydroperoxylation reaction through a hydroperoxide-rebound pathway to form intermediate **III**. The rebound of the hydroperoxo radical has been proposed in the reaction pathway of HEPD and *myo*-inositol oxygenase.[33] Intermediate **III** may convert to a dioxetane ring

(**IIIA**). The formation of such a ring has recently been proposed by Siewert and Limberg for the C–C bond cleavage of acetylacetone by a model complex of Dke1.[11] The heterolytic O–O bond cleavage of intermediate **III** or **IIIA** results in the formation of two equivalents of carboxylic acids. This pathway accounts a quantitative formation of benzoic acid in the reaction of **1** with O_2. The mechanism outlined above provides an explanation for the requirement of iron in the +II oxidation state to activate dioxygen. Furthermore, the ligand (Tp^{Ph2}) controls the metal environment during the selective C–C bond cleavage reaction of the α-hydroxy ketone. A control reaction without the ligand yields a complex mixture of products from 2-hydroxyacetophenone. The iron(II) center coordinated by a facial three nitogen ligand has similarity with the active site of several enzymes in the cupin family.

In conclusion, we have isolated and structurally characterized a biomimetic iron(II)–α-hydroxy ketone complex supported by a tridentate facial three nitrogen ligand. This iron(II) complex has been shown to react with O_2 to oxidatively cleave the C–C bond of 2-hydroxyacetophenone to benzoic acid and formic acid. In the C–C bond cleavage reaction, an oxygen atom from dioxygen is incorporated into each product. An iron(III)–superoxo intermediate is proposed to initiate the oxidative transformation reaction. To the best of our knowledge, this is the first functional model of 2,4′-dihydroxyacetophenone dioxygenase. The C–C bond cleavage of 2-hydroxyacetophenone reported in this work highlights the importance of model complexes in understanding the mechanism of the oxygen-dependent transformation reaction carried out by DAD. Detailed mechanistic studies on oxidative C–C bond cleavage of α-hydroxy ketones by model iron(II) complexes are in progress in our laboratory.

Experimental Section

$[Fe^{II}(Tp^{Ph2})(HAP)]$ (**1**): A mixture of KTp^{Ph2} (0.177 g, 0.25 mmol) and iron(II) perchlorate hydrate (0.063 g, 0.25 mmol) in methanol (3 mL) was stirred for 2 min. To the white slurry, a mixture of 2-hydroxyacetophenone (0.034 g, 0.25 mmol) and triethylamine (35 μL, 0.25 mmol) dissolved in methanol (2 mL) was added slowly. The solution turned to pink immediately. The reaction mixture was then stirred for 2 h to precipitate a pink solid. The solid was isolated by filtration and dried under vacuum. Single crystals of **1** were grown from a solvent mixture of dichloromethane and methanol. Yield: 0.19 g (76%). Elemental analysis calcd (%) for $C_{53}H_{41}BFeN_6O_2{\cdot}CH_3OH{\cdot}CH_2Cl_2{\cdot}H_2O$ (995.57 g mol^{-1}): C 66.35, H 4.96, N 8.44; Found: C 66.52, H 4.59, N 8.36. IR (KBr): $\tilde{\nu}$ = 3437(br), 3063(m), 2926(m), 2854(m), 2621(m), 1736(m), 1663(m), 1597(m), 1547(s), 1477(s), 1412(m), 1358(m), 1302(m), 1238(m), 1171(s), 1068(m), 1009(m), 918(m), 816(m), 764(vs), 696(vs), 673(m), 569(m) cm^{-1}. The presence of solvent molecules in the microcrystalline solid of **1** was confirmed by thermogravimetric analysis. Nearly 15% weight loss took place within 150 °C, which corresponds to the loss of one molecule of CH_2Cl_2, one molecule of CH_3OH, and one molecule of H_2O (Figure S15, SI).

Crystal data of **1**: MF = $C_{53}H_{41}BFeN_6O_2$, M_r = 860.58, monoclinic, space group $P21/c$, a = 10.0081(9), b = 38.476(3), c = 16.670(1), α = 90.00, β = 126.454(4), γ = 90.00, V = 5163.0(7) Å^3, Z = 4, ρ = 1.107 mg m^{-3}, $\mu_{Mo\text{-}K\alpha}$ = 0.334 mm^{-1}, $F(000)$ = 1792, GOF = 1.084. A total of 52012 reflections were collected in the range $1.61 \le \theta \le 23.52$, 7616 of which were unique (R_{int} = 0.0996). $R_1(wR_2)$ = 0.1179 (0.2952) for 573 parameters and 6027 reflections ($I > 2\sigma(I)$). CCDC 870252 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.

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