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Fe^{2+}-Catalyzed Heterolytic RO−OH Bond Cleavage and Substrate Oxidation: A Functional Synthetic Non-Heme Iron Monooxygenase System

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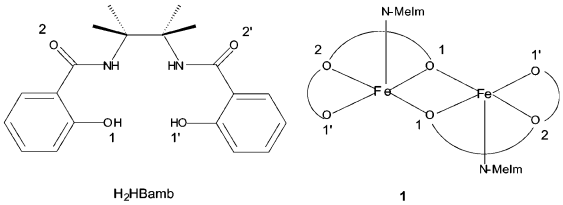
Nature has evolved a variety of strategies to utilize O_2 for the controlled oxidation of organic molecules.[1,2] The formal incorporation of an oxygen atom into unactivated C−H bonds typically requires the use of transition metal centers in either the reduction of dioxygen to peroxide and/or in the formation of the reactive intermediate responsible for the oxidation reaction.[1,3,4] Two fundamental mechanistic features observed in both mono- and binuclear non-heme iron-dependent monooxygenase pathways are (i) the heterolytic O−O bond cleavage of an iron coordinated peroxide ligand and (ii) the subsequent tightly coupled transfer of one oxygen atom to substrate for each equivalent of dioxygen/peroxide consumed.[3,5] Despite significant advances in our understanding of the structural, spectroscopic, and mechanistic issues of iron-based enzymatic alkane oxidation processes, the development of synthetic analogue systems that parallel key steps in the biological oxidation of hydrocarbons is still a major challenge.[6] Although synthetic ferric mono- and binuclear model systems are reported to hydroxylate organic substrates in the presence of dioxygen or peroxides, studies implicate the significant involvement of oxygen-based free radical chemistry initiated by the homolytic cleavage of the peroxy O−O bond. We have previously reported the ability of a synthetic binuclear ferrous compound, $[Fe_2{}^{2+}(H_2Hbamb)_2(N\text{-MeIm})_2]$, **1**[7] (Figure 1), to catalyze the hydroxylation of alkanes, arenes, and sulfides in the presence of oxygen atom donor (OAD) molecules.[8] Herein, we report (i) the ability of **1** to induce heterolytic cleavage of the alkyl hydroperoxide 2-methyl-1-phenylprop-2-yl hydroperoxide (MPPH) and (ii) the ability of **1** to efficiently catalyze the oxidation of phenyl methyl sulfide and cyclohexane using MPPH as the source of oxygen atom.



H_2HBamb **1**

Figure 1. Structures of ligand and iron complexes.

The use of MPPH as a mechanistic probe to distinguish homolytic versus heterolytic cleavage of alkyl hydroperoxide O−O bonds is well established.[6] The rapid β-scission process ($k_\beta = 2 \times 10^8$ s^{-1}) resulting in formation of the benzyl radical following homolytic cleavage of the peroxy O−O bond allows the clear differentiation between modes of metal-mediated peroxide cleavage (Scheme 1).

The reactions of excess MPPH[9] (5.21 mM) in the presence of either $[Fe^{2+},Fe^{2+}]$, **1**, $[Fe^{3+},Fe^{3+}]$, **2**, or μ-oxo-$[Fe^{3+},Fe^{3+}]$, **3** ([complex] = 0.10 mM), were investigated under strict anaerobic conditions using MeOH as solvent. All iron complexes were stable under the reaction conditions in the absence of MPPH for over 12 hours. MPPH showed equivalent stability in the absence of metal complexes; GC analyses and iodometric titration[10] showed the absence of either homolytic or heterolytic cleavage for a period of 15 h. Parallel control reactions (absence of catalysts) were used to correct for nonmetal-mediated peroxide cleavage. Total mass balance of the parent peroxide and the various cleavage products at the end of 6 h was obtained by GC analyses and iodiometric titrations. The effect of iron core oxidation state on MPPH cleavage pathway is dramatically shown in Table 1. After 6 h (room temperature), approximately 90% of the initial [MPPH] (45 turnovers) reacted with **1** by the heterolytic pathway to yield 2-methyl-1-phenyl-propan-2-ol; any iron-induced homolytic cleavage products formed were below our limits of detection. These data directly contrast the results obtained with the $[Fe^{3+},Fe^{3+}]$ complex **2** (19 turnovers) and with the μ-oxo-$[Fe^{3+},Fe^{3+}]$ complex **3** (17 turnovers), where only homolytic cleavage products (phenyl methyl ether, bibenzyl, benzyl alcohol) of MPPH were observed. Peroxide activity assays performed at the end of each reaction showed the appropriate concentration of unreacted MPPH.[10] Free Fe^{2+} and Fe^{3+} ions supported only homolytic cleavage (22 and 31 turnovers, respectively) under equivalent conditions, suggesting that the electronic environment generated by the H_2Hbamb^{2-} ligand is important for heterolytic cleavage chemistry to occur. Neither free H_4Hbamb nor

Scheme 1

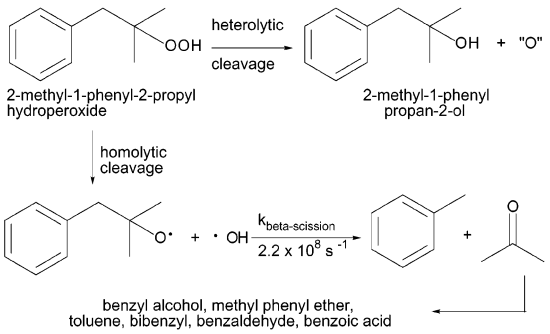


Table 1. Product Distributions for the Cleavage of MPPH by Iron Complexes

species	products heterolytic cleavage[a,b] %	products heterolytic cleavage[a,b] T. N.	products homolytic cleavage[a,c] %.	products homolytic cleavage[a,c] T. N.	mass balance[d]
$[Fe^{2+},Fe^{2+}]$, **1**	85 ± 1	44 ± 1	0 ± 0	0	101 ± 2
$[Fe^{3+},Fe^{3+}]$, **2**	0 ± 0	0	37 ± 1	19 ± 1	99 ± 1
μ-oxo-$[Fe^{3+},Fe^{3+}]$, **3**	0 ± 0	0	34 ± 2	17 ± 1	101 ± 2

[a] All reactions were performed with an excess of peroxide (52:1 MPPH(5.21 mM):iron complex(0.10 mM)) under strict anaerobic conditions in MeOH for 6 h. Turnover numbers are corrected for nonmetal-catalyzed products. [b] 1-Methyl-2-phenyl-propan-2-ol. [c] Phenyl methyl ether, bibenzyl, benzyl alcohol and benzaldehyde were observed in a 50:10:7:1 ratio. Other possible products, including toluene and benzoic acid, were below levels of detection. [d] Quantitative analyses were performed by gas chromatographic methods using chlorobenzene as internal standard.

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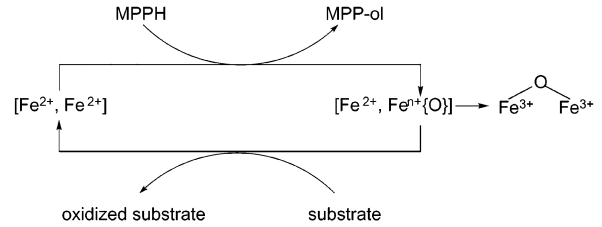
Scheme 2



$Li_2(H_2Hbamb)$ ligand catalyzed MPPH cleavage. The catalytic reaction of **1** with MPPH was facilitated by MeOH, which reacted quantitatively with the iron-based intermediate to form formaldehyde during peroxide turnover.[11] The absence of a suitable substrate (solvent) led to formation of diamagnetic μ-oxo-[Fe^{3+},Fe^{3+}], **3** (EPR silent, $\nu_{as\ Fe-O-Fe} = 840\ cm^{-1}$), resulting from collapse of the reactive intermediate formed by the 1:1 interaction of MPPH and the diferrous core of **1**.

The above data can be explained by the formal transfer of an oxygen atom obtained from the heterolytic cleavage of MPPH to a ferrous center in **1**, resulting in a two-electron oxidation of the electronic structure of **1** (Scheme 2). The subsequent intermediate can be viewed as an [Fe^{2+},Fe^{4+}═O] ↔ [Fe^{2+},Fe^{n+}{O}•] species where the latter electronic description is meant to convey the potential for unpaired electron density on either the diamide or terminal oxo ligands. This intermediate may also collapse to a μ-oxo-[Fe^{3+},Fe^{3+}] dimer which in itself is inert as an oxygen atom transfer catalyst. The data also suggest that while the ligand system is capable of stabilizing an Fe^{4+} intermediate species generated from heterolysis of the Fe^{2+}-OOR species, it is unable to afford the Fe^{5+} species that would result from heterolysis at an Fe^{3+}-OOR center.

Catalytic oxygen atom transfer reactions utilizing PhSMe and cyclohexane (C−H bond strength ∼ 95 kcal/mol)[12] as substrates are summarized in Table 2. In each case, phenyl methyl sulfoxide (500 turnovers) and cyclohexanol (230 turnovers) were initially formed prior to the production of phenyl methyl sulfone (11 turnovers) and cyclohexanone (5 turnovers). Parallel control reactions showed negligible product formation (≤10 turnovers) in the absence of catalyst, suggesting the primary role of an iron-based oxidant. Tight coupling between MPPH O−O bond cleavage and the oxygen atom transfer process is demonstrated by quantitatively comparing the levels of 2-methyl-1-phenylpropan-2-ol with equivalents of product (sulfoxide or alcohol). The results indicate the high efficiency of MPPH utilization (99 ± 1%) and that only heterolytic cleavage of MPPH occurs during catalysis. The data in Table 2 also establish that the ferrous centers in **1** return to their reduced states at the end of each cycle (Scheme 2). Adventitious oxidation of **1** or collapse of the intermediate to the μ-oxo-[Fe^{3+},Fe^{3+}] dimer would result in an iron complex population that would facilitate homolytic cleavage of the alkyl peroxide O−O bond, leading to detection of MPPH products based on the reactivity of the benzyl radical. The observed absence of these species only allows for a lower bound for the partitioning of productive versus nonproductive processes (≥500:1) during catalysis.

These data demonstrate the ability of reduced binuclear **1** to act as an efficient catalyst for the heterolytic cleavage of MPPH and for subsequent oxygen atom transfer to substrate. Heterolytic cleavage of the peroxide argues against the possibility of freely diffusing radicals being responsible for the oxidative chemistry that is observed. This fulfills an essential requirement for modeling oxygenases, which proceed exclusively via a heterolytic pathway in order to avoid the formation of biologically damaging hydroxy radicals. Furthermore, the observed tight coupling between heterolytic cleavage of the alkyl peroxide and the transfer of an oxygen atom to an organic substrate (reaction efficiency >99%) models the chemistry exhibited at the active site of iron-based monooxygenases where one oxidized substrate is generated per equivalent of O_2 consumed. Studies designed to define both the scope and mechanism of the substrate oxidation reactions are underway.

Table 2. Product Distributions of Catalytic Atom Transfer Reactions

substrate[a]	equivalents MPPH used	equivalents products		mass balance (%)
		sulfoxide/alcohol	sulfone/aketone	
thioanisole	524	500 ± 13	11 ± 2	98 ± 2
cyclohexane	239	230 ± 30	5 ± 1	97 ± 3

[a] All reactions were run in DMF/CH_2Cl_2 (30/70) which were freshly distilled and degassed several times prior to use (Fe:MPPH:Ph-S-Me − 1:596:6011, Fe:MPPH:C6H12−1:600:2500); reaction time = 6 h).

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(7) Abbreviations: H_4Hbamb, 2,3-bis(2-hydroxybenzamido)2,3-dimethylbutane; [Fe^{2+},Fe^{2+}], $Fe_2^{2+}(H_2Hbamb)_2(N\text{-MeIm})_2$; [$Fe^{3+}$,$Fe^{3+}$], [$Fe^{2+3+}(H_2Hbamb)_2(N\text{-MeIm})_2$]($I^-$); μ-oxo-[Fe^{3+},Fe^{3+}], μ-oxo-[$Fe_2^{3+}(H_2Hbamb)_2(N\text{-MeIm})_2$].
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