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New mechanistic insight into intramolecular arene hydroxylation initiated by (μ-1,2-peroxo)diiron(III) complexes with dinucleating ligands

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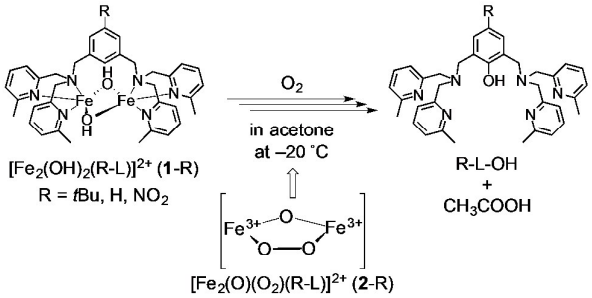
(μ-1,2-Peroxo)diiron(III) complexes (2-R) with dinucleating ligands (R-L) generated from the reaction of bis(μ-hydroxo)diiron(II) complexes $[Fe_2(R\text{-}L)(OH)_2]^{2+}$ (1-R) with dioxygen in acetone at –20˚C, provides a diiron-centred electrophilic oxidant, presumably diiron(IV)-oxo species, which is involved in the aromatic ligand hydroxylation.

The Fe/O_2- and Fe_2/O_2-mediated arene hydroxylation is of current interest for understanding the reaction mechanism of dioxygen activating none-heme mononuclear and dinuclear iron enzymes such as tetrahydropterin-dependent aromatic amino acid hydroxylase[1] and toluene/o-xylene monooxygenase (ToMO).[2] In these enzymes, an iron(IV)-oxo and a (μ-peroxo)diiron(III) species have been spectroscopically identified,[1,2] which are responsible for arene hydroxylation. To date, intramolecular aromatic ligand hydroxylation[3-6] and intermolecular hydroxylation of aromatic compounds such as benzoic acid,[7] benzene,[8] and anthracene[9] by synthetic mononuclear iron model complexes with various oxidants such as O_2, H_2O_2, *m*-CPBA, *t*-BuOOH, and PhIO have been extensively studied. In some of these, the iron(IV)-oxo species have been identified as the active oxidant in the intramolecular aromatic ligand hydroxylation.[5b,6b,9] Some synthetic ToMO model complexes have also been reported so far;[10] yet only for one, a (μ-peroxo)diiron(III) complex $[Fe_2(L^{Ph4})(O_2)(Ph_3CCO_2)]^{2+}$ with a dinucleating ligand (L^{Ph4} = *N*,*N*,*N*′,*N*′-tetrakis(1-methyl-2-phenyl-4imidazolyl)methyl-1,3-amino-2-propanolate), has been shown to be directly involved in the intramolecular aromatic ligand hydroxylation,[10d] although an electronic effect of substituent on the aromatic ligand hydroxylation was not investigated. To obtain further insights into the arene hydroxylation perfomed by (μ-peroxo)diiron(III) species, further (μ-peroxo)diiron(III) model complexes are demanded, which exhibit the monooxygenase activity like ToMO.



Scheme 1 Intramolecular arene hydroxylation and intermolecular acetone oxidation initiated by (μ-1,2-peroxo)diiron(III) complexes (**2**-R) with dinucleating ligands (R-L).

In this study, we have applied the dinucleating ligands (R-L = 1,3-bis[bis(6-methyl-2-pyridylmethyl)aminomethyl]-5-R-benzene; R = *t*Bu, H, and NO_2) to the diiron complex system in order to examine the Fe_2/O_2-mediated arene hydroxylation (Scheme 1), since R-L provides crucial active oxygen species that are capable of hydroxylating the xylyl linker of R-L via an electrophilic aromatic substitution mechanism, as found for dicopper[11] and dinickel[12] complexes with R-L. Herein, we report intramolecular arene hydroxylation together with intermolecular acetone oxidation initiated by (μ-1,2-peroxo)diiron(III) complexes (**2**-R) with dinucleating ligands R-L (Scheme 1), generated from the reaction of bis(μ-hydroxo)diiron(II) complexes $[Fe_2(R\text{-}L)(OH)_2]^{2+}$ (**1**-R) with dioxygen in acetone at –20˚C. We found a decisive mechanistic evidence that a diiron-centred electrophilic oxidant, presumably diiron(IV)-oxo species, is involved in the aromatic ligand hydroxylation, whose species is capable of exchanging with exogenous water.

The diiron(II) complex $[Fe_2(H\text{-}L)(OH)_2]^{2+}$ (**1**-H) was obtained by treatment of $[Fe(CH_3CN)_4(OTf)_2]$ with H-L in the presence of triethylamine and H_2O in dry-THF under N_2 atmosphere. **1**-H has a

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† Electronic Supplementary Information (ESI) available: Experimental details of synthesis and structural (CCDC 1430633 and 1430634), spectroscopic, kinetic data. See DOI: 10.1039/x0xx00000x

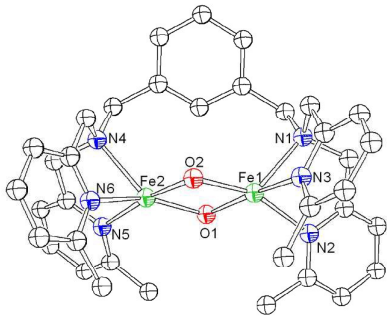


Fig. 1 An ORTEP view of $[Fe_2(OH)_2(H\text{-}L)]^{2+}$ (**1**-H). Hydrogen atoms are omitted for clarity.

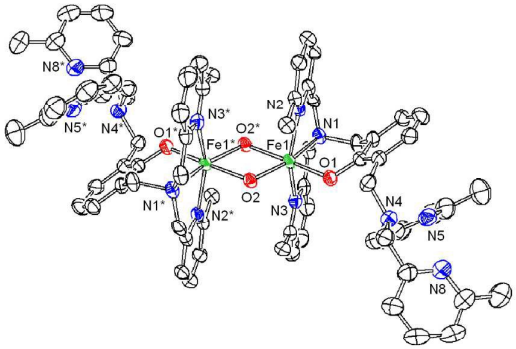


Fig. 3 An ORTEP view of $[Fe_2(OH)_2\{H(H\text{-}L\text{-}O)\}_2]^{4+}$ (**3**-H). Hydrogen atoms are omitted for clarity.

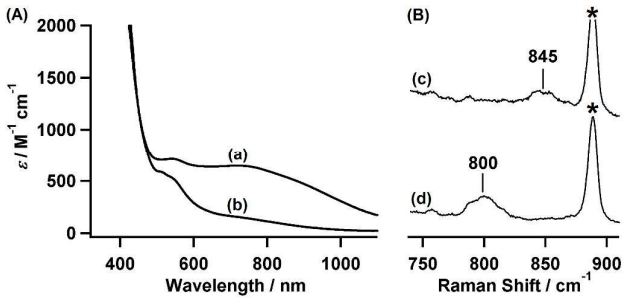


Fig. 2 (A) Electronic spectra of **2**-H (a) and its decomposition species (b) in acetone at –20˚C. (B) Resonance Raman spectra of **2**-H generated from the reaction of **1**-H with $^{16}O_2$ (c) and $^{18}O_2$ (d) in d_6-acetone at –40˚C with a 647.1 nm laser excitation. The asterisk denotes solvent band.

bis(μ-hydroxo)diiron(II) core bridged by exogenous hydroxo groups (Figs. 1 and S1) as found for a closely related dicopper(II) complex $[Cu_2(H\text{-}L)(OH)_2]^{2+}$.[11]

Reaction of a pale green acetone solution of **1**-H with O_2 at −20 °C generated a dark green peroxo species, **2**-H, that exhibits a broad absorption band at the 500-800 nm (Fig. 2(A), (a): 530 nm, ε = ~710 M^{-1} cm^{-1} ; 700 nm, ε = ~645 M^{-1} cm^{-1}) that can be assigned to the CT transition from O_2^{2-} to Fe(III) center, as found in related (μ-peroxo)diiron(III) complexes.[13,14] Similar UV-vis spectral features were also observed for **2**-*t*Bu and **2**-NO_2 (Fig. S3). Unlike in acetone, no peroxo complexes **2**-R were generated in acetonitrile and dichloromethane. The resonance Raman (rR) spectrum of **2**-H prepared by $^{16}O_2$ showed a band at 845 cm^{-1}, which shifted to 800 cm^{-1} when $^{18}O_2$ was used (Figs. 2(B) and S4). The band at 845 cm^{-1} can be assigned to ν(O-O) vibration and is similar to those of well characterized (μ-oxo)(μ-peroxo)diiron(III) complexes (835-874 cm^{-1}),[14] suggesting that **2**-H has a similar (μ-oxo)(μ-peroxo)diiron(III) core. In contrast to ν(O-O) vibration, ν(Fe-O) and ν(Fe-O-Fe) vibrations of **2**-H were not observed (Fig. S4), which might be due to their poor signal-to-noise ratios.

2-H is unstable at −20 °C and decomposes to give a red solution that showed an absorption band at 550 nm (Fig. 2(A), (b)). The red solution slowly converted into a purple solution at ambient temperature that afforded purple crystals of $[Fe_2(OH)_2\{H(H\text{-}L\text{-}O)\}_2](OTf)_4$ (**3**-H) suitable for X-ray crystallography. The crystal structure of **3**-H clearly shows that the xylyl linker is hydroxylated and the resulting phenolates coordinate to the iron(III) centers (Figs. 3 and S2). Decomposition of **2**-*t*Bu and **2**-NO_2 also afforded the corresponding hydroxylated ligands *t*Bu-L-OH and NO_2-L-OH (Fig. S5). Unlike O_2, no hydroxylation occurred when H_2O_2 was used as an oxidant. The yields of hydroxylated ligands (R-L-OH) were determined by ^{1}H NMR spectroscopy (Figs. S6-8, details in the ESI). The hydroxylation yields of the xylyl linker depend on the electron-donor ability of the substituent (R-) of R-L and decreased as the following: *t*Bu-L-OH (~32%) > H-L-OH (~26%) > NO_2-L-OH (~8%) (Fig. S9(a)). A similar observation was also made for a series of (μ-η^2;η^2-peroxo)dicopper(II) complex $[Cu_2(R\text{-}L)(O_2)]^{2+}$ (**Cu**-R)[11] and bis(μ-oxo)dinickel(III) complex $[Ni_2(R\text{-}L)(O)_2]^{2+}$ (**Ni**-R),[12] suggesting that aromatic hydroxylation of R-L in the present diiron system also proceeds via an electrophilic aromatic substitution mechanism. Thus, the substituent-dependent intramolecular arene hydroxylation observed upon decay of (μ-peroxo)diiron(III) species **2**-R is closely relevant to arene hydroxylation catalyzed by ToMO, where a (μ-peroxo)diiron(III) intermediate is directly involved in the arene hydroxylation.[2] However, the hydroxylation yield of **2**-R is lower than those of **Cu**-R (98~72%), **Ni**-R (88~30%), and $[Fe_2(L^{Ph4})(O_2)(Ph_3CCO_2)]^{2+}$ (~90%), suggesting that some other side reaction(s) takes place simultaneously in the present diiron system.

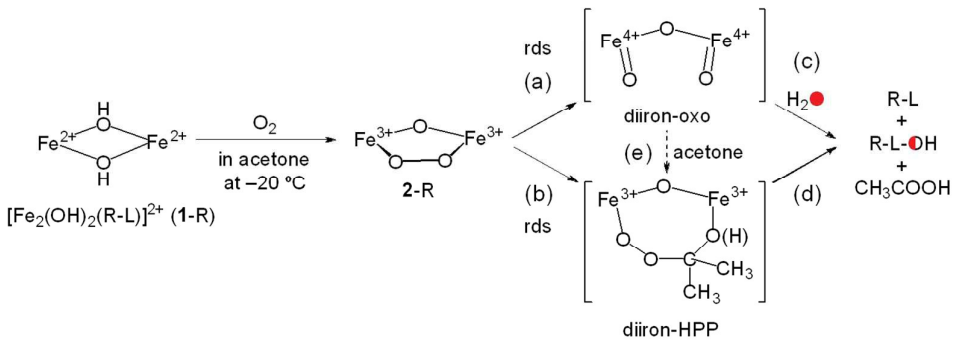
The ESI-TOF/MS of a red solution (Fig. 2(A), (b)) obtained by decomposition of **2**-H at −20 °C showed a signal at *m/z* 379.1 (Fig. S10(a)), which can be assigned as $[Fe_2(H\text{-}L\text{-}O)(O)(CH_3CO_2)]^{2+}$ having a hydroxylated ligand (H-L-O^-) and an acetate. The signal at *m/z* 379.1 in acetone shifted to *m/z* 380.6 when **2**-H decomposed in d_6-acetone (Fig. S10(b)), indicating that acetone solvent is indeed the source of the acetate in this species. The acetic acid was also identified by GC-MS analysis (Fig. S11). Thus, these results clearly demonstrate intramolecular arene hydroxylation and intermolecular acetone oxidation initiated by **2**-H. Unlike the hydroxylation yields of R-L-H, the electron-donor ability of the substituent (R-) of R-L has only a small influence on the oxidation yields of acetone, where ~40 % yield of acetic acid was obtained in each ligand system (Fig. S9(b), details in the ESI). Moreover, the yields of R-L-OH and acetic acid observed upon decay of **2**-R are not influenced by the reaction conditions under both O_2 and N_2, indicating that there is no participation of radical species in the

present reaction system. It has been reported that acetic acid is formed by decomposition of Fe- and Cu-HPP (HPP = 2-hydroxy-2-peroxy-propane) species generated by the reaction of mononuclear Fe and Cu complexes with H_2O_2 in acetone solvent.[15,16] Recently, an electrophilic aromatic ligand hydroxylation by a mononuclear Cu-HPP complex has also been reported by Itoh et al., where an acetate species was not formed and only acetone is regenerated during the course of reaction.[15] Thus, a diiron-HPP species, probably produced by a nucleophilic attack of **2**-R to acetone, seems to be a candidate of the precursor to give acetic acid, but not to give rise to ligand hydroxylation in the present system (Scheme 2).

To gain further insight into the oxidation mechanism, kinetic studies of **2**-R were carried out by monitoring the absorbance change at 700 nm in acetone at –20˚C. Decomposition of **2**-R under the conditions obeys first-order kinetics (Fig. S12). It should be noted that the decomposition rates of **2**-R is independent of the electron-donor ability of the substituent (R-) of R-L (Fig. S12(d)). In contrast to those of substituent-dependent decay observed for (μ-η^2:η^2-peroxo)dicopper(II) complex $[Cu_2(R\text{-}L)(O_2)]^{2+}$ (**Cu**-R)[11] and bis(μ-oxo)dinickel(III) complex $[Ni_2(R\text{-}L)(O)_2]^{2+}$ (**Ni**-R),[12] this observation indicates that the rate determining step in the decay of **2**-R does not involve an electrophilic attack by the peroxo species **2**-R to the xylyl linker, but involves unimolecular reaction such as conversion of **2**-R into a diiron(IV)-oxo species. Activation parameters obtained from the temperature dependence of decay of **2**-R are $\Delta H^{\ddagger}$ = 76~80 kJ mol^{-1} and $\Delta S^{\ddagger}$ = –8~–26 J K^{-1} mol^{-1} (Fig. S13, Tables S3 and S4). The observed small negative activation entropy implies that a bimolecular reaction such as a nucleophilic attack of **2**-R to acetone affording a diiron-HPP species (Scheme 2, step b) is also partially involved in the rate determining step of the decay of **2**-R as well as O–O bond cleavage of **2**-R (Scheme 2, step a), since a large negative activation entropy has been observed for the reaction system in which bimolecular reaction is dominantly included in the rate-limiting step.[17]

It should be noted that isotope labeling experiments by using $^{18}O_2$ and $H_2{}^{18}O$ strongly support involvement of the diiron(IV)-oxo species in the aromatic ligand hydroxylation. Surprisingly, decomposition of **2**-H generated by $^{18}O_2$ in acetone resulted in only ~33% incorporation of ^{18}O into H-L-OH, which is confirmed by ESI-TOF/MS (Fig. S14(b)). This observation is in contrast to that of $[Fe_2(L^{Ph4})(O_2)(Ph_3CCO_2)]^{2+}$,[10d] where incorporation of the ^{18}O label mainly originates from $^{18}O_2$. The complementary experiment with **2**-H generated by $^{16}O_2$ in the presence of $H_2{}^{18}O$ (1000 equiv) corroborates this result (Fig. S14(c)). Thus, incorporation of ^{18}O label from $H_2{}^{18}O$ into H-L-OH requires the participation of an oxidant capable of exchanging with exogenous water, such as a diiron(IV)-oxo species, that carries out the ligand hydroxylation (Scheme 2, step c). A similar labeling result has been reported for the formation of the DOPA208 residue from the F208Y mutant of ribonucleotide reductase (RNR) R2 protein[18] as well as a few synthetic iron model complexes.[3a,4c,10c] An electrophilic character of this species is supported by the observed substituent-dependent hydroxylation yields of the xylyl linker. Thus, observation of ^{18}O incorporation from $H_2{}^{18}O$ as well as substituent-dependent hydroxylation yields of the xylyl linker in this system are indirect but compelling evidence for high-valent diiron(IV)-oxo species bearing an electrophilic character, which is well-known for synthetic mononuclear iron(IV)-oxo model complexes.[3-9]

Based on the kinetics data together with the experimental results mentioned above, we thus propose a plausible mechanism for intramolecular arene hydroxylation and intermolecular acetone oxidation initiated by **2**-R (Scheme 2), which involves rate determining O–O bond cleavage of **2**-R into diiron(IV)-oxo species (step a) and nucleophilic attack of **2**-R to acetone into diiron-HPP species (step b) prior to rapid decay. Conversion of (μ-peroxo)diiron(III) species to high-valent diiron(IV)-oxo species has also been reported for a few synthetic diiron model complexes.[14a,d,f,19] The generated diiron(IV)-oxo spesies is the electrophilic active oxidant capable of exchanging with exogenous water prior to an electrophilic attack on the aromatic ring, to provide the partially ^{18}O labeled phenol (R-L-OH), whose hydroxylation yields are substituent-dependent (step c). It has been reported that a well-defined mononuclear non-heme iron(IV)-oxo complex shows a poor nucleophilic oxidative reaction toward 2-phenylpropionaldehyde compared with (hydro)peroxo-iron(III) complexes.[17a,20] Thus, the diiron(IV)-oxo species derived from **2**-H seems not to give rise to acetone oxidation via the formation of diiron-HPP species (step e), although the formation of diiron-HPP species derived from the diiron(IV)-oxo species may not be ruled out. Decay of diiron-HPP species is independent of the electron-donor ability of the substituent (R-) of R-L to give acetic acid and the yield of acetic acid is expected to be nearly constant in each ligand



Scheme 2 Proposed mechanism for intramolecular arene hydroxylation and intermolecular acetone oxidation initiated by **2**-R.

system (step d), which is consistent with the observed yield of acetic acid (~40 %).

In summary, we have succeeded in intramolecular arene hydroxylation and intermolecular acetone oxidation initiated by the (μ-1,2-peroxo)diiron(III) complexes (**2**-R) with the dinucleating ligands (R-L) for the first time. The former reaction mimics the function of ToMO[2] and involves the diiron(IV)-oxo species as the electrophilic active oxidant capable of exchanging with exogenous water, whereas the latter one is closely relevant to a nucleophilic attack of peroxo species to C=O group proposed for ADO.[17a,21] The observed oxidation reactions initiated by **2**-R provide a chemical insight into the nature of (μ-1,2-peroxo)diiron(III) species for oxidation reactivity and O-O bond activation, which are found for dioxygen-activating non-heme diiron proteins, although further comprehensive functional model studies are needed.

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