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Regioselective hydroxylation of the xylyl linker in a diiron(III) complex having a carboxylate-rich ligand with H_2O_2†

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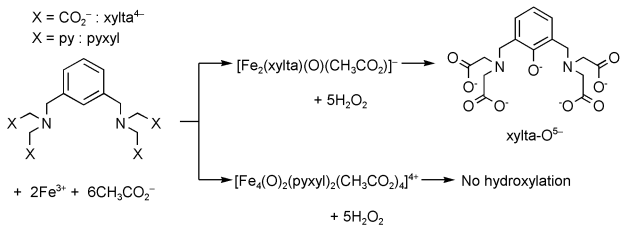
Reaction of a diiron(III) complex having a xylta^{4-} ligand (*N*,*N*,*N*′,*N*′-*m*-xylylenediamine tetraacetate) with H_2O_2 resulted in regioselective hydroxylation of the *m*-xylyl linker. The reaction mimics the self-hydroxylation of a phenylalanine side chain found for ribonucleotide reductase (R2-W48F/D84E).

Hydroxylation of alkanes and arenes catalyzed by iron complexes is of current interest for understanding the dioxygen activation mechanisms of non-heme diiron proteins such as methane monooxygenase, ribonucleotide reductase, and fatty acid desaturase.[1,2] Recently, self-hydroxylation of a phenylalanine side chain, which is located in close proximity to the diiron center, has been reported for ribonucleotide reductase (R2-W48F/D84E).[3] Many model compounds have been developed and their reactivity toward various substrates has been investigated.[2,4] Even though excellent systems for hydroxylation of arenes have been developed for the copper complexes,[2,5] only a limited number of examples for efficient hydroxylation of arene groups by iron complexes have been known.[6] The hydroxylation of a phenyl group in the ligand was reported for some diiron complexes having a carboxylate-rich coordination environment such as edtp in their reactions with either H_2O_2 or O_2.[6a] It was also found that the reaction of a mononuclear iron(II) complex of 6Ph-tpa (N_4-donor set) with ^{t}BuOOH hydroxylates a phenyl pendant of the supporting ligand.[6b] Since the diiron centers of the above enzymes share carboxylate-rich coordination environment, it is of particular interest to investigate the oxidation reactions of diiron complexes having carboxylate-rich ligands. Herein, we report a regioselective hydroxylation of a xylyl linker by the reaction of a diiron(III) complex bearing carboxylate-rich coordination environment (*N*,*N*,*N*′,*N*′-*m*-xylylenediamine tetraacetate: xylta^{4-}) with H_2O_2, where two iron(III) ions are linked by a xylyl group. The reaction mimics the self-hydroxylation of a phenylalanine side chain found for R2-W48F/D84E.[3]

To an aqueous suspension containing 1 equiv. of H_4xylta, 4 equiv. of Et_3N, and 2 equiv. of $FeCl_3$ was added 6 equiv. of sodium acetate to generate a dark yellowish green solution (Scheme 1). The negative ion ESI-TOF/MS spectrum of the solution diluted by acetonitrile (1 : 1) in the range of m/z = 20 to 1000 showed a signal at m/z (%): 550.9614 (100) with a characteristic distribution of isotopomers attributable to a diiron(III) species $\{[Fe_2(xylta)(O)(CH_3CO_2)]\}^-$ (accurate mass : m/z = 550.9688) (Fig. S1).† All attempts to crystallize this species were in vain so far. Addition of 5 equiv. of H_2O_2 to the solution at 0 °C resulted in a rapid color change to red. The electronic spectral change showed that the reaction quickly proceeds within several seconds at 0 °C and no detectable intermediate was observed at present stage (Fig. S2).†[7] The ESI-TOF/MS spectrum of the solution diluted by acetonitrile (1 : 1) showed two signals at m/z (%): 608.9652 (100) and 506.9423 (29) attributable to the hydroxylated species having a (μ-phenoxo)diiron(III) core $\{[Fe_2(xylta\text{-}O)(CH_3CO_2)_2]\}^-$ (**1**, accurate mass : m/z = 608.9743) and a $\{[Fe_2(xylta\text{-}O)(O)]\}^-$ (accurate mass : m/z = 506.9426), respectively, together with a signal of $\{[Fe_2(xylta)(O)(CH_3CO_2)]\}^-$ (I = 27%) (Fig. S1).† Addition of a methanol solution of $(n\text{-}Bu)_4NBr$ into the red aqueous solution afforded red crystals $(n\text{-}Bu)_4N[Fe_2(xylta\text{-}O)(CH_3CO_2)_2]\cdot 3H_2O$ (**1·Bu$_4$N**) (yield = 62%) suitable for X-ray crystallography (Fig. 1).‡ The crystal structure of **1** clearly shows that the xylyl linker of xylta^{4-} is hydroxylated and the resulting phenolate oxygen bridges the two iron atoms. Each iron atom has a distorted octahedral geometry with the N_1O_5 donor set and is triply bridged by the phenolate oxygen and two acetate groups providing a bis(μ-acetato)(μ-phenoxo)diiron(III) core as found for a closely related complex $Me_4N[Fe_2(5Me\text{-}HXTA)(CH_3CO_2)_2]$.[8]

Isotope labeling experiments using $H_2{}^{18}O_2$ (in $H_2{}^{16}O$) showed that the phenolate oxygen of **1** comes from the hydrogen peroxide ($\{[Fe_2(xylta\text{-}{}^{18}O)(CH_3CO_2)_2]\}^-$ (m/z (%): 610.9687 (100)) (Fig. S3).† The yield and regioselectivity for hydroxylation of the xylyl linker were assessed by the ^{1}H NMR spectrum after the reaction mixture was treated by sodium dithionite and potassium cyanide. The ^{1}H NMR spectrum of the reaction mixture clearly showed only two sets of signals arising from xylta^{4-} and the oxidized ligand (xylta-O^{5-}), and there was no signal due to other modified ligand (Fig. S4).† About 74 (±2)% of xylta^{4-} was converted into xylta-O^{5-} (H_2O_2 = 5 equiv./[Fe_2]). Thus, the reaction demonstrates the regioselective hydroxylation of the xylyl linker as observed for the reaction of $[Cu_2(XYL\text{–}H)]^{2+}$ with dioxygen.[5a] The oxygenation yield of xyta-O^{5-} was almost the same even when excess H_2O_2 was used. Unlike the diiron complexes reported by Fontecave *et al.*,[6a] no hydroxylation occurred when H_2O_2 was replaced with dioxygen in the presence of ascorbic acid as a reductant.

Replacement of the carboxylate groups in xylta^{4-} by pyridyl groups (pyxyl) afforded a very different tetranuclear iron(III)



Scheme 1 Reaction scheme for iron(III) complexes with H_2O_2.

† Electronic supplementary information (ESI) available: experimental details, ESI-mass, UV–vis, and ^{1}H NMR spectra. See http://www.rsc.org/suppdata/cc/b3/b304171a/

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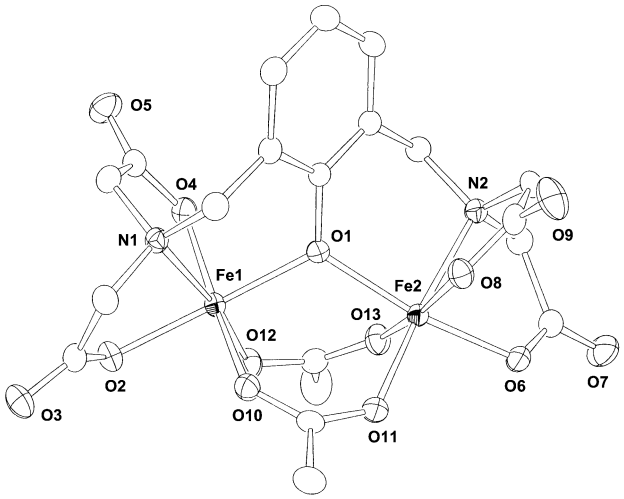

Fig. 1 ORTEP view (40% probability) of a complex anion of **1**·Bu_4N. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angle (°): Fe1···Fe2 3.458(1), Fe1–O1 2.017(1), Fe1–O2 1.982(2), Fe1–O4 1.958(2), Fe1–O10 2.045(2), Fe1–O12 1.975(1), Fe1–N1 2.168(2), Fe2–O1 2.029(1), Fe2–O6 1.981(1), Fe2–O8 1.955(2), Fe2–O11 1.970(2), Fe2–O13 2.035(2), Fe2–N2 2.174(2); Fe1–O1–Fe2 117.43(6).

complex, $[Fe_4(O)_2(pyxyl)_2(CH_3CO_2)_4]^{4+}$ (**2**), whose crystal structure was determined by X-ray crystallography (Fig. 2).‡ Complex **2** has a dimer of dimer structure where two (μ-oxo)bis(μ-acetato)diiron(III) cores are linked by a xylyl linker as found for closely related complexes.[9] The reaction of **2** with H_2O_2 in CH_3CN/H_2O (1 : 1) resulted in no hydroxylation of the xylyl linker of the pyxyl ligand and only original ligand was recovered, which was confirmed by the ligand recovery experiment. The results show a sharp contrast with those of the xylta^{4-} system. The reactivity of xylyl linkers in the xylta^{4-} and pyxyl ligand seems to be regulated by their structures in solution; ESI-TOF/MS spectroscopy of **2** in CH_3CN revealed that the tetranuclear unit remains intact (Fig. S5).† The crystal structure of **2** indicates that the closest carbon atom of the xylyl linker is apart from the diiron core by ~5 Å, which is too far for the hydroxylation. In contrast, the hydroxylated carbon atom of the xylyl linker in xylta^{4-} is expected to be close to the diiron core as postulated for the hydroxylation of $[Cu_2(XYL–H)]^{2+}$ with dioxygen.[5a] Thus the regioselective hydroxylation occurred at the 2-position of the xylyl linker in xylta^{4-} appears to be mostly due to the proximity effect of the metal center depending upon their core structures in solution.

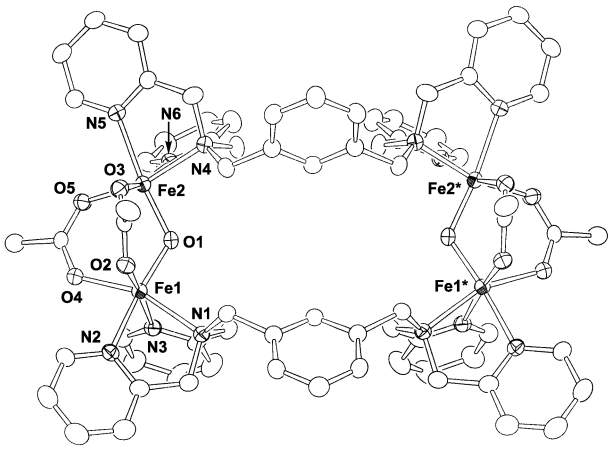

Fig. 2 ORTEP view (40% probability) of a complex cation of **2**. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angle (°): Fe1···Fe2 3.117(1), Fe1···Fe1* 9.336(1), Fe1···Fe2* 10.259(1), Fe2···Fe2* 9.614(1), Fe1–O1 1.791(3), Fe1–O2 2.073(3), Fe1–O4 2.038(3), Fe1–N1 2.246(3), Fe1–N2 2.173(3), Fe1–N3 2.177(4), Fe2–O1 1.800(3), Fe2–O3 2.022(3), Fe2–O5 2.030(3), Fe2–N4 2.211(3), Fe2–N5 2.200(3), Fe2–N6 2.141(3); Fe1–O1–Fe2 120.4(1). The atoms asterisked are those of the counter part of the dimer and generated by the symmetry transformations: *x*, 1/2 − *y*, *z*.

In summary, we have succeeded for the first time in the regioselective hydroxylation of the xylyl linker of the carboxylate-rich ligand (xylta^{4-}) by a $Fe^{3+}/CH_3CO_2^-/H_2O_2/H_2O$ system. The reaction mimics the self-hydroxylation of a phenylalanine side chain found for R2-W48F/D84E. Unfortunately, no intermediate was observed for the present system due to the rapid hydroxylation of xylta^{4-}, although a peroxo intermediate has been detected for R2-W48F/D84E system. The present ligands xylta^{4-} and pyxyl afford two types of the intramolecular diiron and intermolecular tetrairon complexes, depending upon the side arms of the xylyl linker, whose core structures seem to be responsible for hydroxylation of the xylyl linker in this system.

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Notes and references

‡ Crystal data for **1·Bu$_4$N** at −120 °C; $C_{36}H_{63}N_3Fe_2O_{16}$, monoclinic, space group $P2_1/a$ with Z = 4, a = 15.986(5), b = 17.475(3), c = 15.193(3) Å, β = 91.69(2)°, V = 4243(1) Å^3, ρ_{calcd} = 1.418 g cm^{-3}, R = 0.040, R_w = 0.061 for 6979 data with $I > 3\sigma(I)$. Crystal data for **2** at −120 °C; $C_{75}H_{83}N_{13}Cl_4Fe_4O_{27}$, orthorhombic, space group *Pnma* with Z = 4, a = 24.961(2), b = 28.608(3), c = 12.617(4) Å, V = 9009(2) Å^3, ρ_{calcd} = 1.448 g cm^{-3}, R = 0.064, R_w = 0.106 for 6628 data with $I > 3\sigma(I)$. CCDC 200159 and 200160. See http://www.rsc.org/suppdata/cc/b3/b304171a/ for crystallographic data in .cif format.

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