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Synthesis and Characterization of Carboxylate-Rich Complexes Having the $\{Fe_2(\mu\text{-}OH)_2(\mu\text{-}O_2CR)\}^{3+}$ and $\{Fe_2(\mu\text{-}O)(\mu\text{-}O_2CR)\}^{3+}$ Cores of O_2-Dependent Diiron Enzymes

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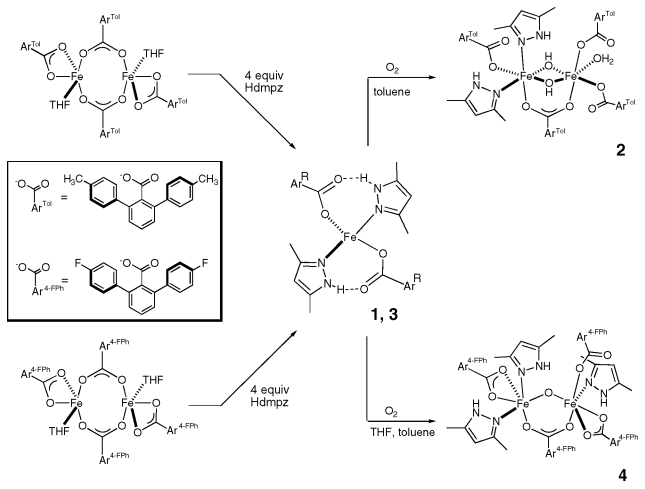
Carboxylate-bridged diiron centers activate dioxygen for radical generation and hydrocarbon oxidation at the active sites of enzymes such as class I ribonucleotide reductase (RNR-R2), soluble methane monooxygenase hydroxylase (sMMOH), and Δ^9 desaturase (Δ^9D).[1−3] The dimetallic cores in these enzymes are coordinated by four carboxylate and two imidazole ligands derived from amino acid residues housed in four-helix bundles.[4−7] This structural motif is effectively utilized to achieve diverse physiological functions in these and related proteins.[8] To understand the chemistry of these enzymes at the molecular level, much effort has been expended to reproduce their active-site architecture and reactivity in synthetic models. The $\{Fe_2(\mu\text{-}OH)_2(\mu\text{-}O_2CR)\}^{3+}$ and $\{Fe_2(\mu\text{-}O)(\mu\text{-}O_2CR)\}^{3+}$ cores at the active sites of many of these enzymes have been unexpectedly difficult to reproduce in a carboxylate-rich metal coordination environment, however, because of the propensity of iron(III) salts to form oligo- or polynuclear complexes.[9] As a consequence, our current understanding of the physical properties of these diiron units has had to rely upon comparisons with model complexes in N-rich metal coordination environments.[10] In this communication, we report that direct oxygenation of mononuclear iron(II) complexes generates carboxylate-rich compounds encapsulating the desired $\{Fe_2(\mu\text{-}OH)_2(\mu\text{-}O_2CR)\}^{3+}$ and $\{Fe_2(\mu\text{-}O)(\mu\text{-}O_2CR)\}^{3+}$ cores with geometries structurally similar to that of the diiron(III) sites in oxidized MMOH and RNR-R2, respectively. In addition to structural resemblance, these diiron(III) complexes share several key physical properties with the enzymes, including Mössbauer spectral and magnetic exchange coupling parameters.

Sterically hindered terphenyl-derived benzoate analogues provide a ligand framework that facilitates assembly of both mononuclear and dinuclear iron complexes.[11−13] Reaction of $[Fe_2(\mu\text{-}O_2CAr^{Tol})_2(O_2CAr^{Tol})_2(THF)_2]$, where $^-O_2CAr^{Tol}$ is 2,6-di(*p*-tolyl)benzoate, with 4 equiv of 3,5-dimethylpyrazole (Hdmpz) yielded the mononuclear iron(II) complex, $[Fe(O_2CAr^{Tol})_2(Hdmpz)_2]$ (**1**) (Scheme 1 and Supporting Information). Compound **1** has a pseudo-tetrahedral iron(II) center bound to two monodentate carboxylates and two Hdmpz ligands (Figure S1). Two hydrogen-bonding interactions occur between the $Ar^{Tol}CO_2^-$ and Hdmpz ligands, as revealed by O···H−N distances of 2.743(2) and 2.783(2) Å. The combined influence of these intramolecular hydrogenbonding interactions with sterically hindered carboxylate ligands stabilizes **1** with an uncommonly low coordination number of 4 for a $[M(O_2CR)_2L_2]$ complex.

Exposure of a colorless toluene solution of **1** to dioxygen at room temperature rapidly afforded the yellow diiron(III) complex, $[Fe_2(\mu\text{-}OH)_2(\mu\text{-}O_2CAr^{Tol})(O_2CAr^{Tol})_3(OH_2)(Hdmpz)_2]$ (**2**) (Figures 1 and S2), in 70% yield. The two iron atoms have pseudo-octahedral coordination and are bridged by one carboxylate and two hydroxo ligands. The Fe···Fe distance of 2.996(2) Å is similar to those previously reported for di(μ-hydroxo)(μ-carboxylato)diiron(III) cores: 2.99−3.14 and 2.9788(6) Å for resting state $sMMOH_{ox}$[5,14] and the $[Fe_2(\mu\text{-}OH)_2(\mu\text{-}O_2CAr^{Tol})(O_2CAr^{Tol})_3(Bn_2en)(Bnen)]$ complex,[15,16] respectively. The latter compound is the only other known synthetic analogue of oxidized MMOH having the $\{Fe_2(\mu\text{-}OH)_2(\mu\text{-}OCR)\}^{3+}$ core. In addition to bridging ligands, the coordination sphere of Fe1 includes one monodentate carboxylate and two Hdmpz ligands to complete an N_2O_4 donor atom set. For Fe2, an O_6 set of donor atoms arises by addition of two monodentate terminal carboxylates and a water molecule.

Scheme 1



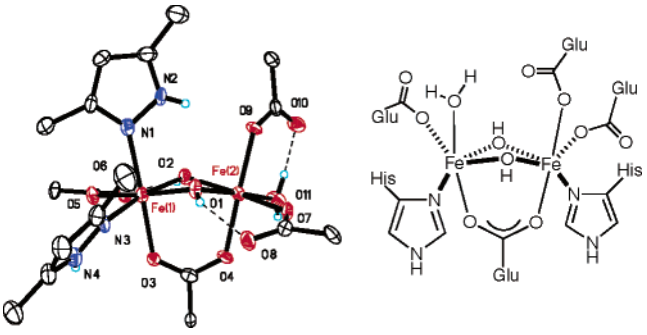


Figure 1. Left: ORTEP diagram with 50% probability thermal ellipsoids; $[Fe_2(\mu\text{-}OH)_2(\mu\text{-}O_2CAr^{Tol})(O_2CAr^{Tol})_3(OH_2)(Hdmpz)_2]$ (**2**). The phenyl rings of $Ar^{Tol}CO_2^-$ ligands are omitted for clarity. Selected interatomic distances (Å) and angles (deg): Fe1···Fe2, 2.996(2); Fe1−O1, 1.953(5); Fe1−O2, 1.958(5); Fe2−O1, 1.944(5); Fe2−O2, 2.012(5); O1···O8, 2.627(8); O2···O6, 2.801(7); O10···O11, 2.506(9); Fe1−O1−Fe2, 100.3(3); Fe1−O2−Fe2, 98.1(2). Right: The structure of the diiron core in the $MMOH_{ox}$ resting state.

The terminal carboxylates are each hydrogen-bonded to a bridging hydroxo or the water ligand. Interactions of this kind occur in $MMOH_{ox}$[5,14] and may be required for stability of the $\{Fe_2(\mu\text{-}OH)_2(\mu\text{-}O_2CR)\}^{3+}$ core. The two iron sites in **2** are asymmetric, and the molecule crystallizes as a racemate.

10.1021/ja031603o CCC: $27.50

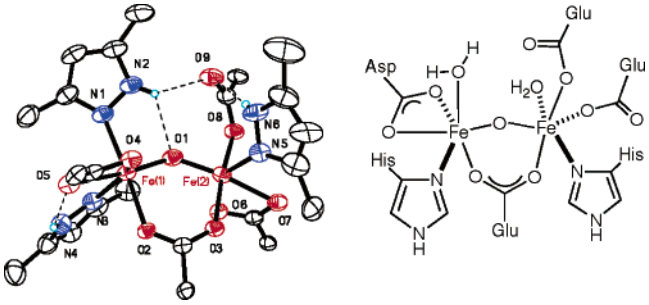


Figure 2. Left: ORTEP diagram with 50% probability thermal ellipsoids; $[Fe_2(\mu\text{-}O)(\mu\text{-}O_2CAr^{4-FPh})(O_2CAr^{4-FPh})_3(Hdmpz)_3]$ (**4**). The phenyl rings of $Ar^{Tol}CO_2^-$ ligands are omitted for clarity. Selected interatomic distances (Å) and angles (deg): Fe1···Fe2, 3.3429(9); Fe1−O1, 1.772(3); Fe2−O1, 1.786(3); O1···N2, 2.821(5); O5···N4, 2.780(5); N6···O9, 2.885(6); N2···O9, 2.857(6); Fe1−O1−Fe2, 139.94(14). The phenyl rings of $Ar^{4-FPh}CO_2^-$ ligands are omitted for clarity. Right: The structure of the diiron core in the RNR-$R2_{act}$ resting state.

The 4.2 K zero-field Mössbauer spectrum of solid **2** exhibits a quadrupole doublet with $\delta = 0.45$ (2) mm/s, $\Delta E_Q = 1.21$ (2) mm/s, and $\Gamma = 0.36$ (2) mm/s (Figure S3), indicating indistinguishable iron(III) atoms. The isomer shift (δ) falls in the range typical of the high-spin Fe(III) complexes.[10] The quadrupole splitting parameter (ΔE_Q) unexpectedly differs from that of the structurally related $[Fe_2(\mu\text{-}OH)_2(\mu\text{-}O_2CAr^{Tol})(O_2CAr^{Tol})_3(Bn_2en)(Bnen)]$ complex ($\Delta E_Q = 0.61$ (2) mm/s).[15,16] Considering that most of the reported hydroxo-bridged diiron(III) complexes have ΔE_Q values ~0.5 mm/s,[10] **2** is unique among synthetic models but more closely resembles the diiron core in $sMMOH_{ox}$ ($\Delta E_Q = 0.87$ and 1.16 mm/s).[17] This result most likely reflects the fact that **2** is the first complex to match the O-rich environment in the enzyme and is unique in having the terminally bound water molecule observed in all forms of sMMOH structurally characterized to date.[5,14] The similarities in the geometric and Mössbauer spectral properties of the diiron(III) centers in sMMOH and **2** led us to measure its temperature-dependent magnetic susceptibility (Figure S4). Analysis of the data revealed a spin exchange coupling constant J of −7.2 (2) cm^{-1} with g fixed as 2.0 ($H = -2JS_1 \cdot S_2$, where $S_1 = S_2 = 5/2$). This weak antiferromagnetic behavior is identical to that in $sMMOH_{ox}$, for which J is also −7 (3) cm^{-1},[17] consistent with the close similarities in their other physical properties.

The mononuclear complex $[Fe(O_2CAr^{4-FPh})_2(Hdmpz)_2]$ (**3**) (Figure S5), where $^-O_2CAr^{4-FPh}$ is 2,6-di(*p*-fluorophenyl)-benzoate, an analogue of **1**, was prepared in a similar manner from $[Fe_2(\mu\text{-}O_2CAr^{4-FPh})_2(O_2CAr^{4-FPh})_2(THF)_2]$. Oxygenation of a THF or toluene solution of **3** afforded the brown diiron(III) complex, $[Fe_2(\mu\text{-}O)(\mu\text{-}O_2CAr^{4-FPh})(O_2CAr^{4-FPh})_3(Hdmpz)_3]$ (**4**) (Figures 2 and S6) in 78% yield. The two asymmetric iron atoms have a distorted octahedral geometry and are linked by only one carboxylate and one oxo group. The Fe···Fe distance (3.3429(9) Å) of **4** is similar to the 3.3−3.4 Å found in the (μ-oxo)(μ-carboxylato)diiron(III) core of RNR-R2[4] and slightly longer than those of reported $\{Fe_2(\mu\text{-}O)(\mu\text{-}O_2CR)\}^{3+}$ complexes with N-rich coordination environments.[18−20] The remaining coordination sites of **4** are completed by three Hdmpz and three carboxylate ligands, again generating carboxylate-rich metal coordination environments for the two iron atoms. The 4.2 K Mössbauer spectrum of **2** exhibits a quadrupole doublet with $\delta = 0.51$ (2) mm/s, $\Delta E_Q = 1.26$ (2) mm/s, and $\Gamma = 0.30$ (2) mm/s (Figure S7). The small ΔE_Q value is at the lower end of the range (>1 mm/s) for most oxo-bridged diiron(III) complexes. The strong antiferromagnetic exchange coupling, $J = -117.2$ (1) cm^{-1}, in **4** (Figure S8) compares favorably with that of RNR-R2, where J is −110 cm^{-1}, and is typical for other reported (μ-oxo)(μ-carboxylato) diiron(III) complexes ($J = -90$ to −120 cm^{-1}).[10]

In summary, this work provides efficient syntheses, by direct oxygenation of the mononuclear iron(II) precursors, of diiron(III) complexes containing the biomimetic $\{Fe_2(\mu\text{-}OH)_2(\mu\text{-}O_2CR)\}^{3+}$ and $\{Fe_2(\mu\text{-}O)(\mu\text{-}O_2CR)\}^{3+}$ cores present in carboxylate-bridged diiron enzymes. Key physical properties of the enzyme active sites were successfully reproduced by these small molecules, which mimic both the bridging modes and the O-rich environments. Possible intermediate(s) and mechanistic details involved in the oxygenation pathway are currently under investigation.

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Supporting Information Available: Details of the synthetic procedures, physical characterization of **2** and **4**, and ORTEP diagrams including all non-hydrogen atoms of compounds **1**−**4** (PDF). X-ray crystallographic files for these compounds (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Solomon, E. I.; Brunold, T. C.; Davis, M. I.; Kemsley, J. N.; Lee, S.-K.; Lehnert, N.; Neese, F.; Skulan, A. J.; Yang, Y.-S.; Zhou, J. *Chem. Rev.* **2000**, *100*, 235−349.
(2) Wallar, B. J.; Lipscomb, J. D. *Chem. Rev.* **1996**, *96*, 2625−2657.
(3) Merkx, M.; Kopp, D. A.; Sazinsky, M. H.; Blazyk, J. L.; Müller, J.; Lippard, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2782−2807.
(4) Nordlund, P.; Eklund, H. *J. Mol. Biol.* **1993**, *232*, 123−164.
(5) Whittington, D. A.; Lippard, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 827−838.
(6) Rosenzweig, A. C.; Frederick, C. A.; Lippard, S. J.; Nordlund, P. *Nature* **1993**, *366*, 537−543.
(7) Lindqvist, Y.; Huang, W.; Schneider, G.; Shanklin, J. *EMBO J.* **1996**, *15*, 4081−4092.
(8) Du Bois, J.; Mizoguchi, T. J.; Lippard, S. J. *Coord. Chem. Rev.* **2000**, *200*−*202*, 443−485 and references cited therein.
(9) Lippard, S. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 344−361.
(10) Kurtz, D. M., Jr. *Chem. Rev.* **1990**, *90*, 585−606 and references cited therein.
(11) Lee, D.; Lippard, S. J. *Inorg. Chem.* **2002**, *41*, 2704−2719.
(12) Lee, D.; Lippard, S. J. *Inorg. Chim. Acta* **2002**, *341*, 1−11.
(13) Hagadorn, J. R.; Que, L., Jr.; Tolman, W. B. *Inorg. Chem.* **2000**, *39*, 6086−6090.
(14) Elango, N.; Radhakrishnan, R.; Froland, W. A.; Wallar, B. J.; Earhart, C. A.; Lipscomb, J. D.; Ohlendorf, D. H. *Protein Sci.* **1997**, *6*, 556−568.
(15) Lee, D.; Lippard, S. J. *Inorg. Chem.* **2002**, *41*, 827−837.
(16) Lee, D.; Lippard, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 4611−4612.
(17) Fox, B. G.; Hendrich, M. P.; Surerus, K. K.; Andersson, K. K.; Froland, W. A.; Lipscomb, J. D.; Münck, E. *J. Am. Chem. Soc.* **1993**, *115*, 3688−3701.
(18) Marlin, D. S.; Olmstead, M. M.; Mascharak, P. K. *Inorg. Chem.* **2003**, *42*, 1681−1687.
(19) Yan, S.; Que, L., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 5222−5224.
(20) Yan, S.; Cox, D. D.; Pearce, L. L.; Juarez-Garcia, C.; Que, L., Jr.; Zhang, J. H.; O'Connor, C. J. *Inorg. Chem.* **1989**, *28*, 2507−2509.

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