A Bulky Benzoate Ligand for Modeling the Carboxylate-Rich Active Sites of Non-Heme Diiron Enzymes

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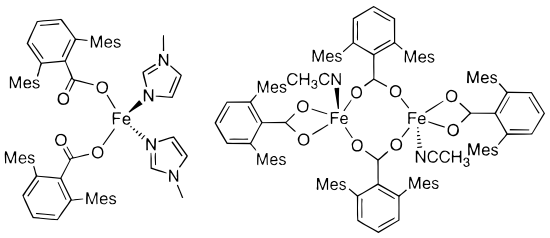
Received September 18, 1998

A growing class of biologically important catalysts are the dioxygen-activating non-heme diiron enzymes, noteworthy members of which include methane monooxygenase (MMO), ribonucleotide reductase (RNR), and stearoyl-ACP Δ^9-desaturase (Δ9D).[1] Carboxylate ligation to the diiron active site of these enzymes is a common feature that allows for tremendous structural flexibility during catalysis (via carboxylate shifts)[2] and helps stabilize the high oxidation states proposed for the intermediates involved in the various reaction cycles. Previous synthetic routes to diiron models of the biological centers have used polydentate N-donors with simple unhindered carboxylates[1b,f] or semirigid linked derivatives (cf. the xylyl-bridged ligand derived from Kemp's triacid).[3] We have begun to pursue an alternative strategy (albeit one with precedence in the organometallic chemistry literature)[4] involving the use of extreme steric hindrance about the carboxylate ligand in order to control metal complex nuclearity, to stabilize biorelevant dioxygen adducts and derived intermediates, and to mimic the protein scaffold that encapsulates the metalloprotein active site. Here we report a new, very bulky benzoate ligand[5] that has enabled the preparation of coordinatively unsaturated mono- and dinuclear iron(II) complexes, the latter of which accurately mimics the structural characteristics of the reduced forms of Δ9D[6] and RNR.[7] Additionally, studies of the reactivity of this complex with dioxygen have revealed the generation of a room-temperature stable purple species which spectroscopic data suggest is a (μ-peroxo)diiron(III) complex.

Scheme 1



The bulky carboxylate 2,6-dimesitylbenzoate ($Mes_2ArCO_2^-$, Scheme 1) was prepared from 2,6-$Mes_2C_6H_3I$[8] (Mes = 2,4,6-trimethylphenyl) by lithiation[9] with BuLi followed by reaction with dry CO_2 in Et_2O. The product was isolated in 82% yield as the Et_2O adduct $[(Mes_2ArCO_2)Li(Et_2O)]_2$ and characterized fully, including by X-ray crystallography (Figure S1 and S2).[10,11] The extreme steric bulk of the ligand derived from the enforcement of an orthogonal relationship between the Mes rings and the benzoate aryl unit results in a dimeric structure distinct from the polymeric topologies typically adopted by smaller carboxylates.[12] The reaction of 1 equiv of $[(Mes_2ArCO_2)Li(Et_2O)]_2$ with $FeCl_2$ or $Fe(OTf)_2$ in CH_2Cl_2 in the presence of 1-methylimidazole (MeIm) gave $[(Mes_2ArCO_2)_2Fe(MeIm)_2]$ as colorless crystals (Scheme 1); the same product was formed irrespective of the amount of MeIm used (1 equiv or an excess).[10] X-ray structural characterization (Figure 1a) revealed a pseudo-tetrahedral iron center coordinated to two carboxylates, each in monodentate fashion with one short Fe−O distance (av 2.01 Å) and one much longer [2.544(2) Å and 3.263(2) Å]. The influence of the large carboxylate is manifested by a bowl-like cavity lined by the Mes rings which only allows for the binding of two MeIm ligands. The resulting low coordination number (CN) of 4 for the complex contrasts with the higher CNs for related structurally characterized complexes such as $[Fe(O_2CCH_3)_2(py)_4]$ and $[Fe_2(O_2CR)_4(py)_2]$ (R = CMe_3, Ph; py = pyridine).[13]

When the smaller N-donor CH_3CN (as a 5:1 toluene/CH_3CN mixture) was used in the synthesis instead of MeIm, the diiron(II) complex $[(Mes_2ArCO_2)_4Fe_2(CH_3CN)_2]$ was isolated (Scheme 1).[10] Its X-ray crystal structure (Figures 1b and 2) shows identical iron sites related by a crystallographic inversion center, each having a square pyramidal geometry ($\tau = 0.04$) with the CH_3CN ligand occupying the apical position and the remaining sites occupied by the O atoms of the bidentate bridging or chelating carboxylates. The space-filling model (Figure 2) dramatically displays the steric "wall" imposed by the mesityl groups, forming a hindered interior pocket just large enough to fit the rod-shaped CH_3CN ligands (revealed by removal of a Mes group in Figure 2b) that are forced to adopt bent geometries [cf. Fe(1)−N(1)−C(51) = 125.6(2)°]. The most remarkable aspect of the structure is the similarity it possesses to the reduced forms of the active sites of Δ9D and RNR−R2 (Figure S5).[6,7] In addition to similar ligand environments (one N-donor and a chelating carboxylate per Fe, with two bidentate carboxylate bridges), the Fe−Fe distances are all approximately 4 Å [$(Mes_2ArCO_2)_4Fe_2(CH_3CN)_2$, 4.122(1) Å; Δ9D, 4.2 Å; RNR−R2, 3.9 Å] due to their closely analogous carboxylate bridging geometries. ^{1}H NMR spectroscopy shows a downfield signal at 50 ppm which disappears upon the addition of CD_3CN (in $CDCl_3$ solution), demonstrating that the nitrile remains coordinated in solution but is susceptible to exchange despite its encapsulation by the steric wall of mesityl goups.[14]

Like the diiron(II) sites in the enzymes, $[(Mes_2ArCO_2)_4Fe_2(CH_3CN)_2]$ reacts rapidly with O_2.[15] Oxygenation (1 atm) of a solution

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10.1021/ja983333t CCC: $15.00
Published on Web 12/11/1998

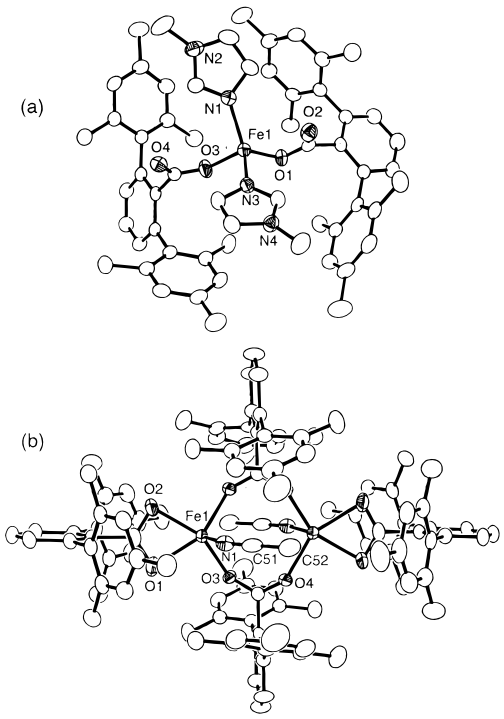

Figure 1. Representations of the X-ray crystal structures of (a) $(Mes_2ArCO_2)_2Fe(MeIm)_2 \cdot 0.5C_5H_{12}$ and (b) $(Mes_2ArCO_2)_4Fe_2(CH_3CN)_2 \cdot C_7H_8$ (50% ellipsoids, hydrogen atoms, and solvate molecules not shown for clarity). Selected bond distances (Å) for $[(Mes_2ArCO_2)_2Fe(MeIm)_2]$: Fe(1)−O(1), 2.028(2); Fe(1)−O(2), 2.544(2); Fe(1)−O(3), 1.989(2); Fe(1)−O(4), 3.263(2); Fe(1)−N(1), 2.066(2); Fe(1)−N(3), 2.057(2) Å. Selected bond distances for $[(Mes_2ArCO_2)_4Fe_2(CH_3CN)_2]$: Fe(1)−Fe(1A), 4.122(1); Fe(1)−O(1), 2.121(2); Fe(1)−O(2), 2.153(2); Fe(1)−O(3), 2.035(2); Fe(1)−O(4A), 2.026(2); Fe(1)−N(1), 2.093(3).

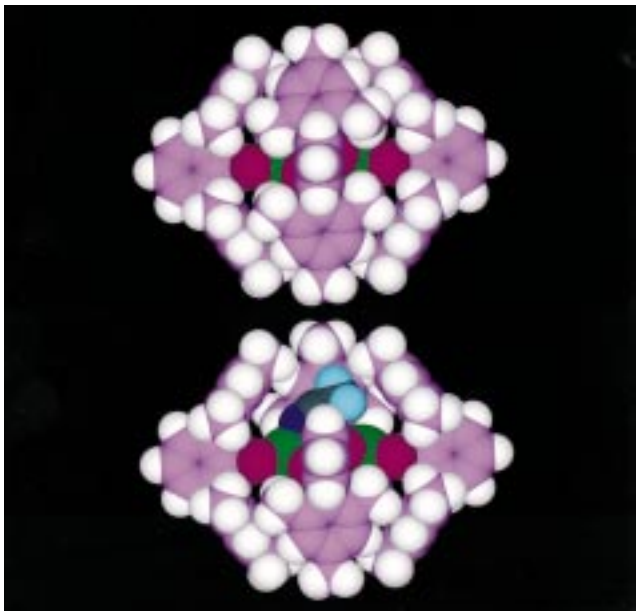

Figure 2. Top: space-filling representation of $[(Mes_2ArCO_2)_4Fe_2(CH_3CN)_2]$ drawn as in Figure 1b, except rotated 90° about the Fe−Fe vector. Bottom: same view, except one Mes group is omitted to reveal a CH_3CN ligand (shown with N = blue, C = gray, H = pale blue).

of the complex in CH_2Cl_2 at −50 °C resulted in the immediate and irreversible formation of an EPR silent purple species with $\lambda_{max} = 540$ nm ($\epsilon = 2300\ M^{-1}\ cm^{-1}$, Figure 3), properties similar to those associated with a number of well-characterized (μ-peroxo)diiron(III) complexes.[16] Characterization by resonance Raman spectroscopy (Figure 3 insert) reveals an isotope-sensitive

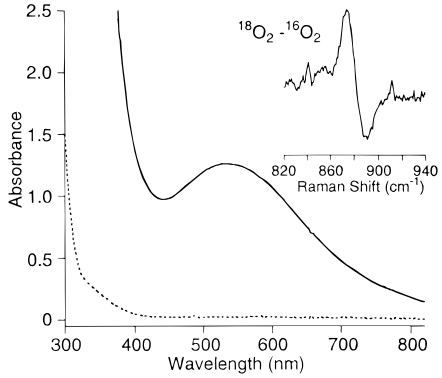

Figure 3. UV−vis spectra of $(Mes_2ArCO_2)_4Fe_2(CH_3CN)_2$ (dashed line) and the product of its oxygenation (solid line) in CH_2Cl_2 (0.55 mM) at −50 °C. Inset: difference resonance Raman spectrum of the product of oxygenation ($^{18}O_2 - {}^{16}O_2$, frozen chlorobenzene, $\lambda_{ex} = 514.5$ nm).

vibration at 885 cm^{-1} which shifts by 14 cm^{-1} upon the use of $^{18}O_2$. No other isotope-sensitive vibrations were observed. Although energetically consistent with O−O vibrations reported for known $Fe_2(\mu$-1,2-peroxo) complexes[16] and recently characterized diiron enzyme intermediates,[17] the isotope shift is much smaller than expected for a pure O−O stretch.[18] There was no evidence of decay of the purple species after 12 h at −50 °C. Even upon warming to ambient temperature, the species was quite stable, decomposing only slowly ($t_{1/2} \approx 30$ h) to a brown solution at 25 °C. The stability of the intermediate undoubtedly stems from the steric hindrance of the carboxylate ligands that shields the dioxygen adduct from exogenous agents that would promote its decay.

In conclusion, we have shown the utility of bulky benzoate ligands for the preparation of unsaturated, carboxylate-rich, iron(II) complexes which were previously inaccessible. The diiron(II) derivative readily reacts with molecular oxygen to form a stable purple species which we tentatively assign as a (μ-peroxo)diiron(III) species. Further characterization of this and other species are in progress.

Acknowledgment. We thank the NIH (GM47365 to W.B.T., GM38767 to L.Q., and F32-GM19374 to J.R.H.) and the NSF (NYI Award to W.B.T.) for financial support. We also are grateful for the assistance of Dr. R. Y. N. Ho for obtaining resonance Raman spectral data.

Note Added Proof. A related approach was reported recently: Lee, D.; Lippard, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 12153−12154.

Supporting Information Available: Synthetic procedures and characterization and crystallographic data for all new compounds (28 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA983333T

(14) In further support of the substitution lability of the CH_3CN ligand, addition of MeIm (1−2 equiv per Fe) converts $[(Mes_2ArCO_2)_4Fe_2(CH_3CN)_2]$ to $[(Mes_2ArCO_2)_2Fe(MeIm)_2]$ (by NMR spectroscopy in $CDCl_3$).

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