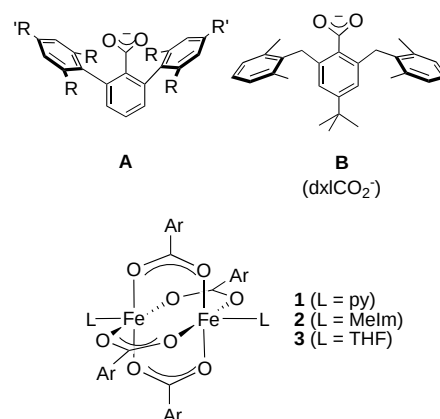


Unusual Peroxo Intermediates in the Reaction of Dioxygen with Carboxylate-Bridged Diiron(II,II) Paddlewheel Complexes**

Ferman A. Chavez, Raymond Y. N. Ho, Maren Pink, Victor G. Young, Jr., Sergei V. Kryatov, Elena V. Rybak-Akimova,* Hanspeter Andres, Eckard Münck,* Lawrence Que, Jr.,* and William B. Tolman*

The class of nonheme diiron enzymes comprising methane monooxygenase (MMOH), ribonucleotide reductase (RNR), Δ^9 stearoyl-acyl carrier protein desaturase (Δ^9 D), and others^[1,2] performs a diverse array of important biological reactions that involve the binding and activation of dioxygen at a diferrous site ligated by four carboxylate and two histidine imidazole groups. Several intermediates in these systems have been identified, including (peroxo)diiron(II,II) species^[3] that evolve into substrate-oxidizing diiron(II,IV) ("X" in RNR)^[4] or diiron(IV,IV) ("Q" in MMO) units.^[5] Investigations of synthetic models of these intermediates have provided key chemical insights.^[2,6] Notwithstanding these successes, further efforts with models that incorporate the biological 4-carboxylate/2-N-donor ligand set are required to address key unresolved mechanistic issues, such as the factors responsible for the divergent reactivity of the structurally similar active sites in the various enzymes. We^[7] and others^[8] have begun to apply a new strategy toward this end involving the use of sterically hindered carboxylate ligands such as **A** (Scheme 1) to control structure and coordination number and to mimic the hydrophobic protein environment in diiron complexes. Herein we report a new member of this ligand class (dxlCO_2^- , **B**) that has less bulky *ortho*-dibenzyl substituents for the synthesis of a series of diiron(II,II) complexes with the common "paddlewheel" motif. Although structurally similar to other reported diiron(II,II) compounds of this type,^[8b,c,9] the complexes supported by **B** react differ-



Scheme 1. Hindered carboxylate ligands (**A** and **B**) and diiron(II,II) paddlewheel complexes (**1–3**).

ently with dioxygen at low temperature to cleanly generate stable O_2 adducts with unusual characteristics.

Reaction of the aryl bromide dxlBr ^[10] with 2.1 equivalents of *t*BuLi in Et_2O at -80°C followed by addition of $\text{CO}_2(\text{g})$ and acidification yielded the carboxylic acid dxlCO_2H in excellent yield (96 %; see Supporting Information for details). Admixture of $(\text{Et}_3\text{NH})(\text{dxlCO}_2^-)$ (2 equiv), $\text{Fe}(\text{OTf})_2 \cdot 2\text{MeCN}$ (1 equiv), and ligand **L** (1 equiv, **L** = pyridine (py) or 1-methylimidazole (MeIm)) in CH_2Cl_2 yielded the respective complexes **1** (**L** = py) and **2** (**L** = MeIm) that were recrystallized from CH_2Cl_2 /pentane (Scheme 1). In the absence of added **L**, recrystallization of the reaction product from THF/pentane yielded **3** (**L** = THF), which could be converted to **1** or **2** by adding the appropriate N-donor ligand. The formulations of **1–3** as paddlewheel complexes were confirmed by X-ray crystallography.^[11]

Exposure of colorless or pale yellow solutions of **1–3** in scrupulously^[12] dry CH_2Cl_2 or toluene at -80°C to O_2 yielded deep red-brown intermediates, which are characterized by a broad absorption feature with λ_{max} 500–550 nm and $\epsilon \sim 1000\text{--}1200\text{ M}^{-1}\text{cm}^{-1}$. Although stable at -80°C for days, warming induced decomposition as indicated by conversion to light green solutions. Stopped-flow kinetics studies of the oxygenation reactions (CH_2Cl_2 , -80°C to -20°C)^[13] showed that the rate of intermediate formation is described by $d[\text{intermediate}]/dt = k[\text{diiron(II,II) complex}][\text{O}_2]$, with second-order rate constants $k(-40^\circ\text{C}) = 210\text{--}320\text{ M}^{-1}\text{s}^{-1}$. Small $\Delta H^\ddagger$ and large negative $\Delta S^\ddagger$ values typical of associative processes were observed (Table 1) that are similar to those previously reported for other associative oxygen-binding reactions of diiron(II,II) complexes.^[14] The activation parameters are closely correlated, and the Arrhenius plots cross at an isokinetic temperature of -57°C , indicating similar rate-limiting steps for the series of complexes.

Table 1. Activation parameters for the oxygenations of complexes **1–3**.

Complex	$\Delta H^\ddagger$ [kJ mol ⁻¹]	$\Delta S^\ddagger$ [J K ⁻¹ mol ⁻¹]
1	7 ± 2	-178 ± 20
2	10 ± 2	-153 ± 20
3	14 ± 2	-135 ± 20

[*] Prof. Dr. E. V. Rybak-Akimova, Dr. S. V. Kryatov

Department of Chemistry

Tufts University

Medford, MA 02155 (USA)

Fax: (+1) 617-627-3443

E-mail: erybakak@emerald.tufts.edu

Prof. Dr. E. Münck, Dr. H. Andres

Department of Chemistry

Carnegie Mellon University

Pittsburgh, PA 15213 (USA)

Fax: (+1) 412-268-1061

E-mail: em40@andrew.cmu.edu

Prof. Dr. L. Que, Jr., Prof. Dr. W. B. Tolman, Dr. F. A. Chavez,

Dr. R. Y. N. Ho, Dr. M. Pink, Dr. V. G. Young, Jr.

Department of Chemistry and Center for Metals in Biocatalysis

207 Pleasant Street SE

University of Minnesota

Minneapolis, MN 55455 (USA)

Fax: (+1) 612-624-7029

E-mail: que@chem.umn.edu, tolman@chem.umn.edu

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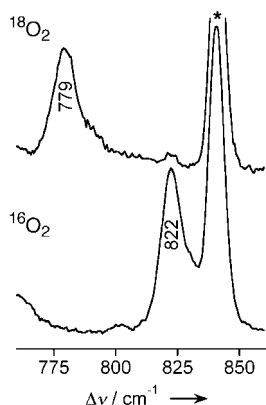


Figure 1. Resonance Raman spectra of the intermediates derived from the oxygenation of **1** with $^{16}\text{O}_2$ and $^{18}\text{O}_2$ ($\lambda_{\text{ex}} = 615$ nm, $[\text{D}_8]\text{toluene}$ solutions, 77 K). The asterisk indicates a solvent band.

Spectroscopic studies of the intermediate derived from **1** ($\text{L} = \text{py}$) have provided key insights into its nature. Resonance Raman spectra were acquired on frozen $[\text{D}_8]\text{toluene}$ solutions at 77 K using $\lambda_{\text{ex}} = 615$ nm with $^{16}\text{O}_2$ and $^{18}\text{O}_2$ (Figure 1). We attribute the feature centered at 822 cm^{-1} that shifts by 43 cm^{-1} upon use of $^{18}\text{O}_2$ to a peroxo O–O stretch.^[15] The $\nu(\text{O}–\text{O})$ value is notably lower than those associated with most^[16] diiron complexes with μ -1,2-peroxo ligation (848 – 910 cm^{-1}),^[17, 18] but compares more favorably to those identified in nonheme monoiron compounds with $\eta^2\text{-O}_2$ coordination (range 816 – 827 cm^{-1}).^[17a, 19, 20]

The Mössbauer spectrum at 4.2 K of diferrous **1** (not shown) consists of one quadrupole doublet with $\Delta E_Q = 3.23(3)$ and $\delta = 1.14(2)\text{ mms}^{-1}$. The spectrum of the intermediate derived from **1** in frozen toluene solution at 4.2 K (Figure 2a) exhibits two doublets in a 1:1 ratio, with $\Delta E_Q(1) = 1.27(3)$, $\delta(1) = 0.65(2)\text{ mms}^{-1}$ and $\Delta E_Q(2) = 0.71(2)$, $\delta(2) = 0.52(2)\text{ mms}^{-1}$. While the value of $\delta(2)$ is characteristic of

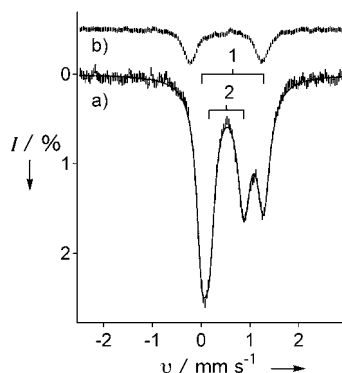
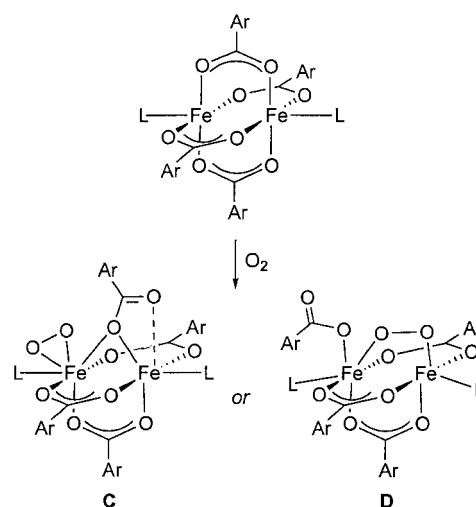


Figure 2. Mössbauer spectra recorded at 4.2 K of toluene solutions of (a) the intermediate derived from the oxygenation of **1** minus the spectrum of its decay product (b), comprising $\sim 10\%$ of the sample. See text for the parameters associated with the doublets labeled 1 and 2.

high-spin ferric complexes with N/O coordination,^[21] the value for $\delta(1)$ is atypical. Such an isomer shift has been associated with the iron centers of peroxo intermediates of nonheme diiron enzymes,^[3a, 22] some (μ ,-1,2-peroxo)diferric complexes,^[23] and (η^2 -peroxo)monoiron(III) complexes.^[24] The observation of two doublets allows two interpretations: 1) Doublet 1 reflects a symmetric peroxo complex with equivalent iron sites and doublet 2 represents a symmetric diferric complex, or 2) the spectrum is derived from one complex with distinct ferric sites. We favor the latter interpretation because the two doublets occur in a 1:1 ratio (in multiple samples comprising different mixtures of the intermediate and its decay product) and their parameters differ from those of a

diferric product of the intermediate's decay (Figure 2b). A diiron(III,III)–peroxo intermediate with similarly distinct iron sites ($\delta(1)\ 0.63\text{ mms}^{-1}$; $\delta(2)\ 0.48\text{ mms}^{-1}$) also has been reported, but other properties of this species differ from those of the intermediate derived from **1**.^[23c] Finally, Mössbauer spectra recorded at 4.2 K in strong applied magnetic fields (8.0 T) showed that both doublets belong to a diamagnetic site, and data obtained at 20, 40 and 80 K showed that $J \approx 30(5)\text{ cm}^{-1}$ ($J\text{S}_1 \cdot \text{S}_2$). This value is lower than those reported previously for $\text{Fe}_2(\mu\text{-}1,2\text{-O}_2)$ compounds (66 – 200 cm^{-1}).^[16, 25] Consistent with the finding of a diamagnetic ground state, solutions of the intermediates derived from **1** and **2** are EPR silent (X-band, 4 K).

Several novel structures for the intermediate are consistent with the combined spectroscopic data (Scheme 2). The low $\nu(\text{O}–\text{O})$ value (822 cm^{-1}) and the relatively weak antiferromagnetic coupling between the ferric centers ($J \approx 30\text{ cm}^{-1}$) diverge from values for all $\text{Fe}_2(\mu\text{-}1,2\text{-O}_2)$ complexes reported



Scheme 2. Postulated structures for the intermediate derived from the oxygenation of the paddlewheel complexes.

to date.^[17, 18, 25] To explain these data, as well as the inequivalent Fe^{III} sites indicated by Mössbauer spectroscopy, we suggest a $\text{Fe}^{\text{III}}\text{-X-Fe}^{\text{III}}(\eta^2\text{-O}_2)$ unit as one possible formulation (**C**), with the peroxo group bound to the Fe^{III} center with $\delta = 0.65\text{ mms}^{-1}$ (ligand L may or may not be bound). The observed $J \approx 30(5)\text{ cm}^{-1}$ is consistent with magnetic superexchange via a monodentate carboxylate O-atom bridge, as similar values are well-established for diiron sites bridged by $-\text{OR}$ ($\text{R} = \text{H}$, alkyl, aryl) groups.^[26] The indicated carboxylate coordination is that derived from a “least motion pathway” from the paddlewheel starting material that would provide a single O-atom bridge through one carboxylate shift,^[27] but other related carboxylate dispositions may be envisaged that also would be consistent with the experimental data. A peroxo-bridged formulation (e.g. **D**) like those proposed previously for another system^[23c] cannot be excluded. However, such a structure must be sufficiently asymmetric to rationalize the two doublets in the Mössbauer spectrum and, furthermore, would have to give rise to unusually low $\nu(\text{O}–\text{O})$ and low J values.

Whatever the detailed structure of the intermediate, it is important to note that the generation of an unsymmetric diiron–peroxo species in the oxygenations of diiron(II,II) complexes supported by dxlCO_2^- contrasts with the reactivity of diiron(II,II) complexes supported by more sterically hindered carboxylates **A** (Scheme 1). For $\text{R}=\text{R}'=\text{Me}$, a symmetric diiron–peroxo species is formed,^[7a] while for $\text{R}'=\text{Me}$ and $\text{R}=\text{H}$, a mixture of $\text{Fe}^{\text{II}}\text{Fe}^{\text{III}}$ and $\text{Fe}^{\text{III}}\text{Fe}^{\text{IV}}$ species is generated,^[8b,c] presumably via an as yet unobserved peroxo intermediate. The entirely different O_2 reactivity of diiron(II,II) complexes that have closely similar paddlewheel core topologies yet different carboxylate substituents underscores the importance of slight variations in steric bulk and flexibility of supporting ligands in diiron complex chemistry. Moreover, the findings suggest that similar perturbations beyond the primary metal coordination sphere should be considered in efforts to rationalize the divergent dioxygen activation pathways followed by the structurally similar active sites in the class of nonheme diiron enzymes.

Experimental Section

$(\text{py})_2\text{Fe}_2(\mu\text{-dxlCO}_2)_4$ (**1**): A solution of dxlCO_2H (1.00 g, 2.4 mmol) and Et_3N (336 μL , 2.41 mmol) in CH_2Cl_2 (6 mL) was added to a solution of $\text{Fe}(\text{OTf})_2 \cdot 2\text{MeCN}$ (0.53 g, 1.2 mmol) in CH_2Cl_2 (2 mL), all under an N_2 atmosphere. Pyridine (py, 98 μL) was added to this mixture and the solution was allowed to stir for 14 h. The solution was then allowed to stand at room temperature for 24 h and crystals formed (note: seeding hastens this process). The crystallization mixture was then cooled to -20°C for 14 h to afford more crystals. The crystals were harvested and pentane (15 mL) was added to the mother liquor followed by cooling at -20°C to afford a second crop (total yield 0.89 g, 77%). UV/Vis (CH_2Cl_2 , λ_{max} , nm (ϵ , $\text{M}^{-1}\text{cm}^{-1}$): 367 (1430); FTIR (KBr pellet, cm^{-1}): $\tilde{\nu}=3068$ (m), 3022 (m), 2965 (s), 2868 (m), 1603 (vs), 1470 (s), 1449 (s), 1398 (s), 1280 (w), 1224 (w), 1173 (m), 1101 (m), 1039 (m), 963 (w), 886 (w), 768 (s), 701 (m), 584 (m); elemental analysis calcd for $\text{C}_{126}\text{H}_{142}\text{N}_2\text{O}_8\text{Fe}_2$: C 78.65, H 7.44; found: C 78.07, H 7.22. Data for compounds **2** and **3** are listed in the Supporting Information.

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- [11] Crystal data for **1**: $\text{C}_{126}\text{H}_{142}\text{Fe}_2\text{N}_2\text{O}_8$, $M_r=1924.12$, yellow blocks of dimensions $0.22 \times 0.08 \times 0.07$ mm, monoclinic, space group $P2_1/c$, $a=11.1180(8)$, $b=26.635$ (2), $c=19.277(2)$ Å, $\beta=92.819(1)^\circ$, $V=5701.4(7)$ Å³, $Z=2$, $\rho_{\text{calcd}}=1.121$ mgm⁻³. The data were collected at 173(2) K on a Bruker SMART diffractometer equipped with a CCD detector ($2\theta=55^\circ$) using MoK_α radiation ($\lambda=0.71073$). A total of 40177 reflections were measured, of which 12926 were unique. The structure was solved by the direct methods program SHELXS and refined by full-matrix least-squares on F^2 and Fourier techniques using SHELXTL-97 (Bruker-AXS, Inc., Madison, WI). Absorption corrections were applied with the program SADABS. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned idealized positions and refined as riding atoms with individual (or group if appropriate) isotropic displacement parameters. Final residuals were $R1=0.0544$ and $wR2=0.1459$ for 6637 observed reflections having $I>2(I)$ and 634 variable parameters. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-169142–169144 (**1–3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [12] The presence of trace water in the solutions of **1–3** prior to oxygenation inhibits formation of the intermediates.
- [13] Reactions were studied under conditions of excess O_2 (pseudo-first order, [diiron complex]=0.15–0.3 mM, $[\text{O}_2]=1.2\text{–}3$ mM) and equal O_2 (second-order, [diiron complex]=[O_2]=1.5 mM), with monitoring at 550 nm. The kinetic measurements were performed by using a cryogenic stopped-flow instrument (Hi-Tech Scientific SF-43, Salisbury, Wiltshire, UK) equipped with stainless steel plumbing, a 1.00 cm stainless steel mixing cell with sapphire windows, and an anaerobic gas-flushing kit. The mixing cell was maintained to ± 0.1 K, and the mixing time was 2–3 ms. Representative kinetic traces and Eyring plots are provided in the Supporting Information.
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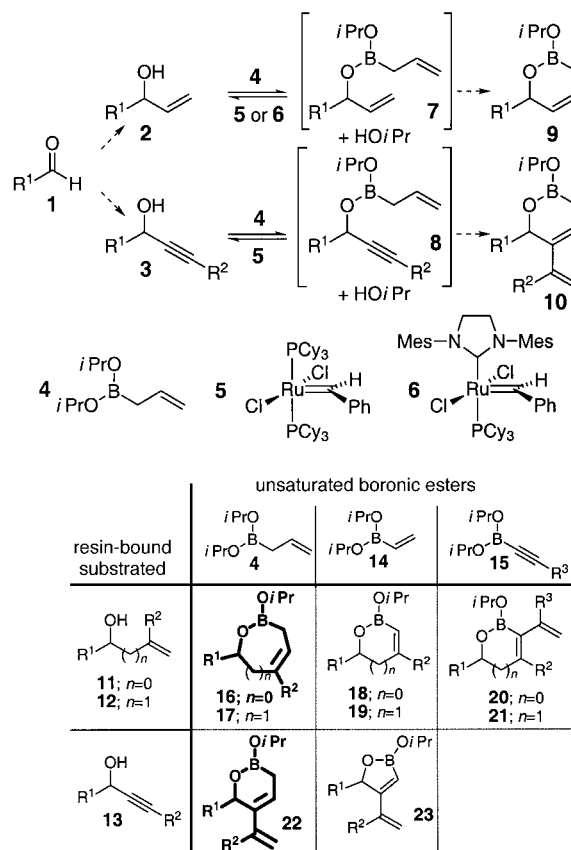
A Boronic Ester Annulation Strategy for Diversity-Oriented Organic Synthesis**

Glenn C. Micalizio and Stuart L. Schreiber*

Diversity-oriented organic synthesis^[1] can be used to prepare complex and diverse small molecules efficiently. By coupling this approach to phenotypic and proteomic screening, a systematic means to explore biology may be realized.^[2, 3] Although efficient pathways leading to families of structurally complex small molecules are being reported with increasing frequency,^[4] pathways leading to structurally diverse products, with many different skeletal arrays, are rare. The primary reason for this gap in our planning capabilities is that efficient and effective “branching” pathways remain elusive. Such pathways require the identification of a substrate or class of substrates that can be differentially manipulated, in single transformations, to afford products containing distinct skeletal arrays of connecting atoms. Here we report new annulation reactions of unsaturated boronic esters with allylic and propargylic alcohols, as well as oxidation and cycloaddition reactions of the resulting cyclic organoboronic esters,

which are well-suited for diversity-generating, branching pathways.^[5, 6]

We anticipated that the transesterification of unsaturated boronic esters (**4**) with allylic (**2**) or propargylic alcohols (**3**) would transiently provide mixed organoboronic esters (**7** or **8**) (Scheme 1),^[7] which could be trapped using ring-closing metathesis^[8] to afford cyclic boronic esters (**9** and **10**).^[9] The pairing of unsaturated carbinols (**11**, **12**, or **13**) and unsaturated boronic esters (**4**, **14**, or **15**) was envisioned to provide a diverse family of boron-containing heterocycles (**16–23**) whose unsaturation would facilitate subsequent functionalization reactions.



Scheme 1. Boronic ester annulation and conceptual matrix of resulting boron-containing heterocycles; bolded structures illustrate the skeletal types realized in this study. Mes = mesityl = 2,4,6-trimethylphenyl.

[*] Prof. S. L. Schreiber, Dr. G. C. Micalizio
Howard Hughes Medical Institute
Department of Chemistry and Chemical Biology, and
Harvard Institute of Chemistry and Cell Biology (ICCB)
Harvard University, 12 Oxford St.
Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-0751
E-mail: sls@slsiris.harvard.edu

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The annulation was tested with the triisopropylsilyl ether containing propargylic (**24**) and allylic alcohols (**25** and **26**) as a model for the alkylsilyl-tethered, high-capacity solid support^[10] used in a one-bead, one-stock solution technology platform.^[11] Treatment of propargylic alcohol **24** with allylboronic ester **4**^[12] and Grubbs' catalyst (**5**) in CH_2Cl_2 at reflux afforded the cyclic dienyl boronic acid **31** in 91% yield (Table 1, entry 1). The allylic alcohol **25** was transformed under similar reaction conditions to the cyclic allylboronic acid **32** (84% yield), whereas the substituted allylic alcohol **26** afforded **33**, which, after oxidation, gave the stereodefined trisubstituted olefin **38** in 56% overall yield (Table 1, entries 2 and 3). The annulation-oxidation sequence was similarly