Inorg. Chem. **2005**, *44*, 8656–8658

Inorganic Chemistry
Communication

Diiron(II) μ-Aqua-μ-hydroxo Model for Non-Heme Iron Sites in Proteins

Ivan V. Korendovych,[†] Sergey V. Kryatov,[†] William M. Reiff,*[,‡] and Elena V. Rybak-Akimova*[,†]

*Department of Chemistry, Tufts University, Medford, Massachusetts 02155, and Department of
Chemistry and Chemical Biology, Northeastern University, 360 Huntington Avenue,
Boston, Massachusetts 02115*

Received October 7, 2005

We have synthesized a diiron(II) complex with a novel aqua–hydroxo bridging motif, $[Fe_2(\mu\text{-}H_2O)(\mu\text{-}OH)(TPA)_2](OTf)_3$ (**1**). This is a new member of the diiron diamond core family. The complex is stable in solution in nonpolar solvents as well as in the solid state. Two high-spin iron(II) sites are antiferromagnetically coupled ($J = -9.6$ cm^{-1}). The drastic difference of ca. 1 V in the redox potential between complex **1** and its bis(hydroxo)-bridged analogue $Fe_2(OH)_2(TPA)^{3+}$ is accompanied by only a moderate difference in the dioxygen reactivity. This observation is consistent with the inner-sphere mechanism of iron(II)–dioxygen association rather than the outer-sphere electron transfer.

Diiron(II) centers participate in the binding or activation of dioxygen at a number of metalloprotein sites [e.g., hemerythrin, class I ribonucleotide reductase (RNR), stearoyl-ACP Δ^9-desaturase (Δ9D), soluble methane monooxygenase (sMMO), toluene monooxygenase, etc.].[1−3] Ligands derived from water (O^{2-}, HO^-, or H_2O) are essential for the specific functions of these proteins, although they may play opposite roles at individual reaction steps in the catalytic cycles. For example, recent computational studies of sMMO hydroxylase suggest that coordinated water facilitates the formation of the bis(oxo)-bridged high-valent ($Fe^{IV}{}_2O_2$) intermediate Q capable of oxidizing methane into methanol.[4] However, efficient oxygen binding to iron(II) sites in proteins, which must occur prior to substrate oxidation, often requires dissociation of precoordinated water.[2] The quantitative effects of coordinated water molecules on the rates of oxygenation are difficult to study in proteins dissolved in aqueous media.

Model complexes, which have provided synthetic precedents for the proposed structures of catalytic intermediates in non-heme diiron enzymes,[1,5−9] may also be beneficial in evaluating the role of water in various protonation states for dioxygen binding and activation.[10−12] The only example of this approach in oxygen-binding studies showed ca. 10-fold acceleration upon coordination of a terminal aqua ligand to carboxylate-rich diiron(II) centers.[12] Whether this effect is general remains unclear, and the answer requires the preparation of new types of model complexes.

We have succeeded in preparing a novel diiron(II) diamond core complex with bridging water and hydroxide, a motif often present in various protonation and oxidation state forms of sMMO.[1,13] Tris(picolylamine) (TPA) was used as a supporting multidentate ligand because TPA and its derivatives have provided a wealth of crucial data regarding Fe_2O_2 diamond-core species, such as intermediate Q in sMMO hydroxylase.[5,6,14] Previously synthesized diiron(II) complexes with a bis(μ-OH) core in these nitrogen-rich systems proved to be important precursors for high-valent iron species.[15,16] We report how changing the nature of one bridging ligand (from OH^- to H_2O) affects the properties and reactivity of the complex with O_2.

Reaction between iron(II) triflate and TPA in the presence of water and triethylamine results in the formation of a μ-hydroxo-μ-aquadiiron(II) complex, $[(TPA)Fe(\mu\text{-}OH)(\mu\text{-}$

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* To whom correspondence should be addressed. E-mail: wreiff@lynx.neu.edu (W.E.F.), elena.rybak-akimova@tufts.edu (E.V.R.-A.).

[†] Tufts University.

[‡] Northeastern University.

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10.1021/ic051739i CCC: $30.25

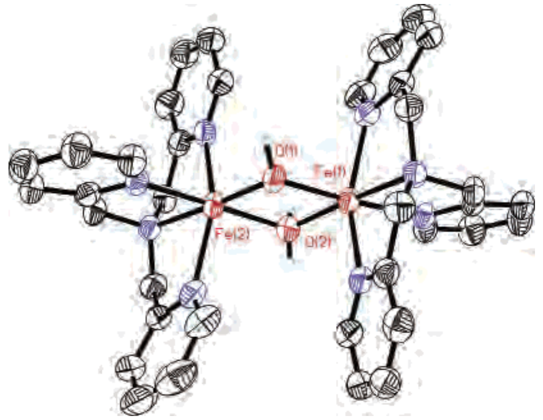
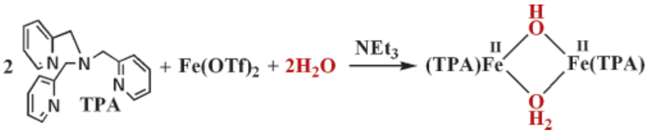


Figure 1. ORTEP diagram of $[Fe_2(\mu\text{-}H_2O)(\mu\text{-}OH)(TPA)_2](OTf)_3$ (**1**). Atoms are drawn at 50% probability thermal ellipsoids. The counterions and hydrogen atoms (except for those bound to bridging hydroxide and water molecule) are omitted for clarity. Selected interatomic distances (Å) and angles (deg): Fe(1)−O(1), 2.098(4); Fe(1)−O(2), 2.133(4); Fe(2)−O(1), 2.033(4); Fe(2)−O(2), 2.211(4); O(1)−Fe(1)−O(2), 81.34(16); Fe(2)−O(1)−Fe(1), 102.2(2); O(1)−Fe(2)−O(2), 80.91(16); Fe(1)−O(2)−Fe(2), 95.51(17).

$OH_2)Fe(TPA)](OTf)_3$ (**1**), which was isolated as yellow-green needles and characterized by X-ray crystallography.



To the extent of our knowledge, complex **1** is the first example of an aqua-bridged diiron(II) core that contains only bridging ligands derived from water. The assignment of bridging ligands as a hydroxy group and an aqua ligand is based on iron−oxygen distances and charge considerations; the formulation of **1** is also supported by Mössbauer and magnetic susceptibility data (see below).

The $Fe_2(\mu\text{-}OH)(\mu\text{-}H_2O)$ core is slightly asymmetric. The Fe−O distances to the bridging hydroxide [2.098(4) and 2.033(4) Å] are consistent with those in the previously reported bis(μ-OH)-bridged TPA complex [2.1344(18) and 1.9726(17) Å, respectively].[15] The somewhat longer Fe−O(μ-H_2O) distances [2.133(4) and 2.211(4) Å] are comparable to similar metric parameters in complexes with purely oxygen ligands[10,11] [from 2.152(2) to 2.3977(16) Å] and in carboxylate-rich complexes with several nitrogen donor atoms[11,17,18] [from 2.148(5) to 2.306(3) Å] and consistent with the general trend that introducing more nitrogen donors results in a shortening of the Fe−O bond. The distance between the iron atoms is 3.2156(8) Å, which is the longest reported distance among the $Fe_2(OH_x)_2$ complexes with nitrogen-rich ligands (Figure 1).[19,20]

Zero-field Mossbauer spectra of **1** at 293, 77.9 (Figure S1, in the Supporting Information), and 1.3 K correspond to the overlap of two quadrupole doublets. This is consistent with the two slightly inequivalent high-spin ferrous sites in the dimer, in agreement with the X-ray structure determination. Lorentzian fits to the doublets yield an isomer shift of 1.33 mm/s (relative to Fe) and quadrupole splittings of 2.42 and 2.65 mm/s.

The temperature dependence of the magnetic susceptibility of solid **1** (the moment is decreasing from 4.84 μ_B at 300 K to 0.38 μ_B at 1.8 K per Fe atom) indicates antiferromagnetic interaction between the two Fe centers with $T_\chi \sim 61$ K. A least-squares fit (Figure S2, in the Supporting Information) yielded the following parameters: $g = 2.06$; $J = -9.6$ cm^{-1}. It should be noted that the fit was done without incorporation of zero-field splitting parameter *D*, rhombicity *E*, or orbital contributions and therefore can only serve as an estimate of *J*. Attempts to fit the data assuming only a zero-field splitting contribution failed, confirming a nonzero value of *J*.

The obtained values for antiferromagnetic exchange are consistent with the literature data for other diiron(II) complexes with a bridging hydroxide.[2,21] Therefore, protonation of one of the two hydroxo bridges, which did not cause significant structural changes, has little effect on experimentally determined *J* values. In contrast, diiron complexes with two bridging aqua ligands are incapable of providing an efficient pathway for exchange interaction in the absence of additional anionic bridges.[10,17,18]

Electrospray ionization mass spectrometry (ESI-MS) and UV−vis data (Figures S3−S8, in the Supporting Information) suggest that complex **1** retains its identity in a dichloromethane (CH_2Cl_2) solution. The UV−vis spectrum of **1** in CH_2Cl_2 is dominated by a band with $\lambda_{max} = 400$ nm ($\epsilon = 3.1$ mM^{-1} cm^{-1}), which is assigned to the iron(II)-to-pyridine charge-transfer band. The absorbance maximum is blue-shifted compared to $[Fe_2(OH)_2(TPA)_2]^{2+}$ ($\lambda_{max} = 465$ nm).[15] These data are in agreement with the substitution of an OH^- ligand for the less donating H_2O ligand, resulting in stronger Lewis acidity of the iron(II) centers in **1** compared to that of $[Fe_2(OH)_2(TPA)_2]^{2+}$. The solid-state UV−vis spectrum of **1** ($\lambda_{max} = 416$ nm) is consistent with the spectrum of the CH_2Cl_2 solution of the compound, which suggests that the coordination sphere of iron is preserved. Nevertheless, the bridging ligands are sufficiently labile: **1** dissolved in CH_2Cl_2 undergoes rapid exchange with added $H_2{}^{18}O$ (Figure S9, in the Supporting Information), similarly to previously reported $Fe_2(OH_n)_2$ cores.[22] According to UV−vis and ESI-MS data, dissolution of **1** in coordinating solvents such as acetonitrile results in solvolysis, producing $[Fe_2(OH)_2(TPA)_2]^{2+}$ and $[Fe(TPA)(MeCN)_2]^{2+}$.

Cyclic voltammetry experiments showed that quasi-reversible oxidation of complex **1** in CH_2Cl_2 was observed at +0.487 V vs Fc^+/Fc (Figure S10, in the Supporting Information). The reported potential, attributed to the Fe^{III}-

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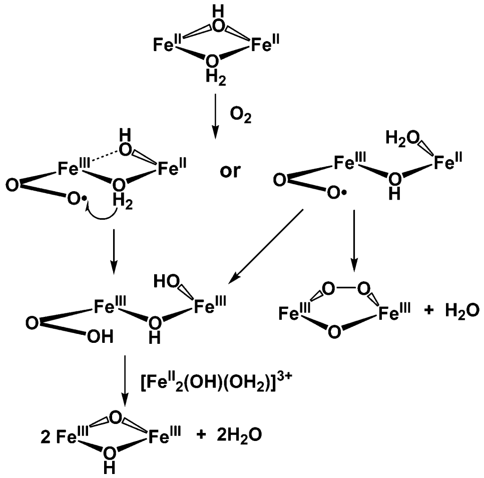
Scheme 1



$Fe^{II}/Fe^{II}Fe^{II}$ couple, is to our knowledge the highest for diiron(II) complexes. It is almost 1 V more positive than the potential of the corresponding bis(μ-hydroxo)-bridged TPA complex,[15] which can be explained by the poorer donating ability of the aqua ligands compared to the hydroxo ligands as well as by the increased overall charge on the complex.

Despite its relatively high redox potential, complex **1** reacts with dioxygen in CH_2Cl_2. ESI-MS and UV−vis data (Figures S3 and S11−S13, in the Supporting Information) indicate that a diiron(III) complex $[Fe^{III}_2(O)(OH)(TPA)_2]^{3+}$ is the product of the oxygenation reaction.[22] Stopped-flow UV−vis spectrophotometry (Figures S13−S15, in the Supporting Information) showed that the oxygenation reaction in CH_2Cl_2 within the temperature range from −30 to +20 °C proceeds in one kinetic step. Variation of the reagent concentration indicated that the reaction has mixed second order: $d[\mathbf{1}]/dt = -k[\mathbf{1}][O_2]$. Measuring the reaction rates at different temperatures (−30 to +20 °C) allowed for the calculation of the activation parameters: $\Delta H^{\ddagger} = 19(2)$ kJ mol^{-1} and $\Delta S^{\ddagger} = -170(10)$ J mol^{-1} K^{-1}. A small enthalpy of activation and a large negative entropy of activation are typical for the reactions of diiron(II) complexes with O_2 in organic solvents.[15,16] Entropic control of the reaction and the second order in both reagents suggest that, similarly to previously characterized reactions,[15,16] the rate-limiting step is the association of complex **1** and O_2.[23] The resulting adduct is apparently a short-lived steady-state intermediate that reacts quickly to eventually afford the diiron(III) product (Scheme 1). Oxidation of the second iron center may be facilitated by the exchange coupling through the bridge, as was proposed for hemerythrin.[2] We also observed at low temperature the formation of a new transient red intermediate (with strong absorbance between 500 and 600 nm; Figure S16, in the Supporting Information) from **1** and O_2 in the presence of a one-electron reducing agent ($CoCp_2$). The structure and reactivity of the new intermediate will be investigated in the future.

Complex **1** reacts with O_2 somewhat more slowly [k = 0.32(3) M^{-1} s^{-1} at 233 K] than the corresponding bis(hydroxo)-bridged complex $[Fe_2(OH)_2(TPA)_2]^{2+}$ [k = 12.1(6) M^{-1} s^{-1} at 233 K; $\Delta H^{\ddagger} = 30(4)$ kJ mol^{-1} and $\Delta S^{\ddagger} = -94(10)$ J mol^{-1} K^{-1}].[15] A lower activation enthalpy and a more negative activation entropy compared to $[Fe_2(\mu\text{-}OH)_2(TPA)_2]^{2+}$ are consistent with the increased asymmetry of the diamond core.

Although $Fe-OH_2$ bonds in **1** are longer than Fe−O(H) bonds in its bis(hydroxo)-bridged analogue, Fe−N bonds trans to the OH_2 ligand are shorter than analogous bonds trans to HO^-.[15] These changes in metric parameters together with the lower activation enthalpy of oxygenation of **1** indicate that O_2 binding to the first iron center in **1** likely involves breaking of the $Fe-OH_2$ bond rather than the Fe−N(py) bond. This is consistent with the unfavorable activation entropy. Access to the iron centers, shielded by bulky TPA ligands, is limited in the starting complex and is hardly improved by breaking the aqua bridge inside the core. The effective number of orientations of the O_2 molecule that may result in productive oxygenation is further limited by significant asymmetry of the core. Dissociation of one of the pyridine pendant arms in $[Fe_2(OH)_2(TPA)_2]^{2+}$ improved O_2 access to the diiron(II) core, as reflected in a less negative activation entropy, but resulted in a somewhat larger activation enthalpy.[15] Breaking an $Fe-O(H_2)-Fe$ bridge in **1** is a low-barrier process.

In summary, we have synthesized a diiron(II) complex with a novel aqua−hydroxo bridging motif, a new member of the diiron diamond core family. The complex is stable in solution in nonpolar solvents as well as in the solid state; two hydroxides are not required to keep the diiron core intact. Replacing one of the two hydroxy bridges with an H_2O bridge does not disrupt the electronic/magnetic communication between the two Fe(II) sites.

It is notable that the drastic difference of ca. 1 V in the redox potential between complex **1** and its bis(hydroxo)-bridged analogue $Fe_2(OH)_2(TPA)^{3+}$ is accompanied by only a moderate difference in the dioxygen reactivity. This observation is consistent with the inner-sphere mechanism of iron(II)−dioxygen association[14,15] rather than the outer-sphere electron transfer.[23] The presence of a labile aqua ligand allows for low-barrier reactions with dioxygen.

Acknowledgment. The authors thank Dr. Sungho Yoon for stimulating discussion. This research was supported by the NSF (Grant CHE 0111202). Instrumentation at Tufts University and Northeastern University was purchased through partial support of NSF and Air Force DURIP instrumentation grants.

Supporting Information Available: Details of the synthesis and characterization of **1**, kinetic studies of the reaction of **1** with dioxygen, X-ray crystallographic data in CIF format, IR spectrum of **1**, ESI-MS spectra for **1** and its oxygenation product in dichloromethane, and Mössbauer and magnetic susceptibility data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) For the outer-sphere mechanism, we estimate a 10^8-fold decrease in the rate of the reaction; see more discussion in the Supporting Information.