Nonheme Iron Complexes

Direct Evidence for Oxygen-Atom Exchange between Nonheme Oxoiron(IV) Complexes and Isotopically Labeled Water[**]

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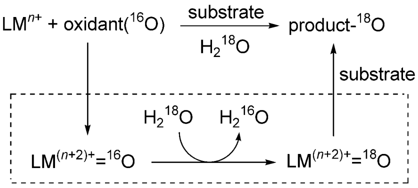
The establishment of the involvement of high-valent iron-oxo intermediates in the catalytic cycles of heme and nonheme iron monooxygenases and their model compounds has been an important goal in mechanistic enzymology and bioinorganic chemistry.[1,2] These highly reactive and unstable intermediates are often difficult to characterize directly; therefore, ^{18}O-labeled water experiments have frequently been carried out to obtain indirect insight into the nature of the reactive intermediates involved in the catalytic oxygenation reactions.[3–5] Since metal-oxo species can in principle exchange their oxygen with labeled water prior to oxo transfer to organic substrates (Scheme 1),[3] the incorporation of labeled ^{18}O from $H_2{}^{18}O$ into oxidation products has been



Scheme 1. Proposed mechanism for ^{18}O-incorporation from $H_2{}^{18}O$ into products in metal-catalyzed oxygenation reactions.

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considered as evidence for the participation of high-valent metal-oxo intermediates in oxygen-atom transfer reactions. However, the mechanisms of oxygen exchange between high-valent metal-oxo species and $H_2{}^{18}O$ are not well understood. For example, the rate of oxygen exchange has not yet been directly measured in enzymes and biomimetic systems.[6] A mechanism involving oxo-hydroxo tautomerism has been proposed by Meunier and co-workers for heme models[3,4f] but may not be generally applicable to nonheme models. The recent isolation and unexpected stability of nonheme oxoiron(IV) complexes[7] provide us with an unprecedented opportunity to investigate mechanisms of oxygen exchange in nonheme iron models. Herein, we report the first direct evidence of ^{18}O exchange between nonheme oxoiron(IV) complexes and $H_2{}^{18}O$, and the determination of activation parameters for the ^{18}O exchange reactions.

The addition of H_2O_2 to a reaction solution containing $[Fe(TMC)(OTf)_2]$ (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane, $OTf = CF_3SO_3$), thioanisole, and a small amount of $H_2{}^{18}O$ in CH_3CN at 10 °C produced a green-colored solution with an absorption maximum wavelength λ_{max} at 820 nm, thus indicating that $[(TMC)Fe^{IV}{=}O]^{2+}$ (**1**) is generated in this reaction.[7a] After the intermediate reverted back to the starting $[Fe(TMC)]^{2+}$ complex ($t_{1/2} \approx 70$ s),[8] analysis of the reaction solution with GC and GC/MS revealed that methyl phenyl sulfoxide[9] was obtained as a major product (≈80% yield based on the amount of H_2O_2 used) and 54% of the oxygen in the sulfoxide product derived from the labeled water. The ^{18}O-incorporation from $H_2{}^{18}O$ into the sulfoxide product was found to increase linearly with the increase of ^{18}O% in the water (Figure 1).[4f] Since the oxygen atom of methyl phenyl sulfoxide does not exchange with $H_2{}^{18}O$ under the reaction conditions, the observed ^{18}O-incorporation from $H_2{}^{18}O$ demonstrates that **1** is generated as a reactive species in the reaction of $[Fe(TMC)]^{2+}$ and H_2O_2, and that **1** exchanges its oxygen atom with $H_2{}^{18}O$ before the oxo group of **1** is transferred to thioanisole (see Scheme 1).[3–5]

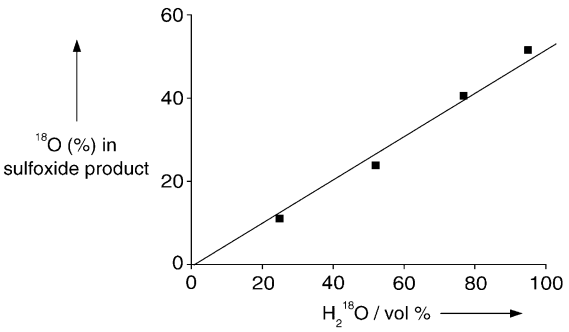


Figure 1. Plot of ^{18}O (%) in methyl phenyl sulfoxide against $H_2{}^{18}O$ (vol%) in water. See Experimental Section for detailed reaction procedures.

This observation led us to monitor oxygen-atom exchange between **1** and $H_2{}^{18}O$ directly with electrospray ionization mass spectrometry (ESI-MS).[7,10,11] Figure 2 shows that upon the addition of $H_2{}^{18}O$ to a reaction solution of **1**, the mass peak corresponding to $[Fe^{IV}(^{16}O)(TMC)(OTf)]^+$ (m/z = 477.3) decreased, whereas the mass peak corresponding to $[Fe^{IV}(^{18}O)(TMC)(OTf)]^+$ (m/z = 479.2) increased. By plotting the percentages of ^{18}O in **1** against the incubation time, we were able to determine a pseudo-first-order rate constant $k_{obs} = 1.5(3) \times 10^{-3}\ s^{-1}$ at 10 °C (Figure 3a). The rate of oxygen exchange increased concomitantly with the amount of $H_2{}^{18}O$ in the reaction mixture, affording a second rate constant k_2 of $5.4(6)\ M^{-1}s^{-1}$ (Figure 3b). We also found that the rate of oxygen exchange was retarded as the reaction temperature lowered. By determining the rates from 283 to 308 K, we obtained activation parameters of $\Delta H^{\neq} = 4.1(6)$ kcal mol^{-1} and $\Delta S^{\neq} = -57(8)$ cal mol^{-1}K^{-1} (Figure 3c).

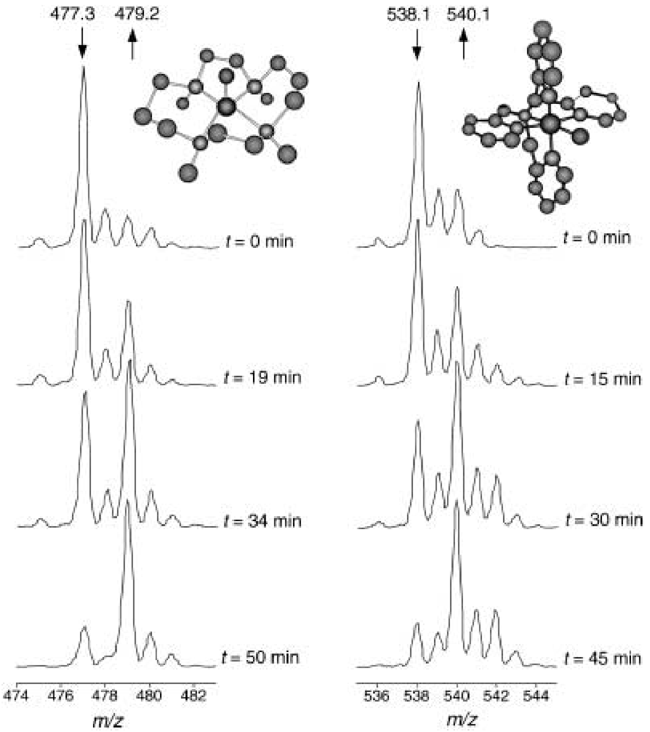


Figure 2. ESI-MS spectral changes of **1** (left) and of **2** (right) upon the addition of $H_2{}^{18}O$ (20 µL) to reaction solutions containing in situ-generated **1** and **2** (2 mM) at 10 °C.

Much to our surprise, we also observed ^{18}O exchange with $[(N4Py)Fe^{IV}{=}O]^{2+}$ (**2**) (N4Py = *N*,*N*-bis(2-pyridylmethyl)-bis(2-pyridyl)methylamine), a complex with a pentadentate ligand.[7c] As with **1**, this exchange could easily be monitored by the decrease of the mass peak corresponding to $[Fe^{IV}(^{16}O)(N4Py)(ClO_4)]^+$ (m/z = 538.1) and the increase of the mass peak corresponding to $[Fe^{IV}(^{18}O)(N4Py)(ClO_4)]^+$ (m/z = 540.1) upon the addition of $H_2{}^{18}O$ to a reaction solution of **2** (Figure 2). The pseudo-first-order rate constant was determined to be $k_{obs} = 1.7(3) \times 10^{-3}\ s^{-1}$ at 10 °C (Supporting Information). As observed in the reactions of **1**, the rate of oxygen-atom exchange between **2** and $H_2{}^{18}O$ increased concomitantly with the amount of $H_2{}^{18}O$ in the reaction mixture, affording a second rate constant k_2 of $4.8(5)\ M^{-1}s^{-1}$ (Supporting Information). The rate of oxygen-atom exchange was faster at higher temperature, and analysis of the rates of oxygen-atom exchange from 283 to 308 K afforded activation parameters of $\Delta H^{\neq} = 4.0(6)$ kcal mol^{-1} and $\Delta S^{\neq} =$

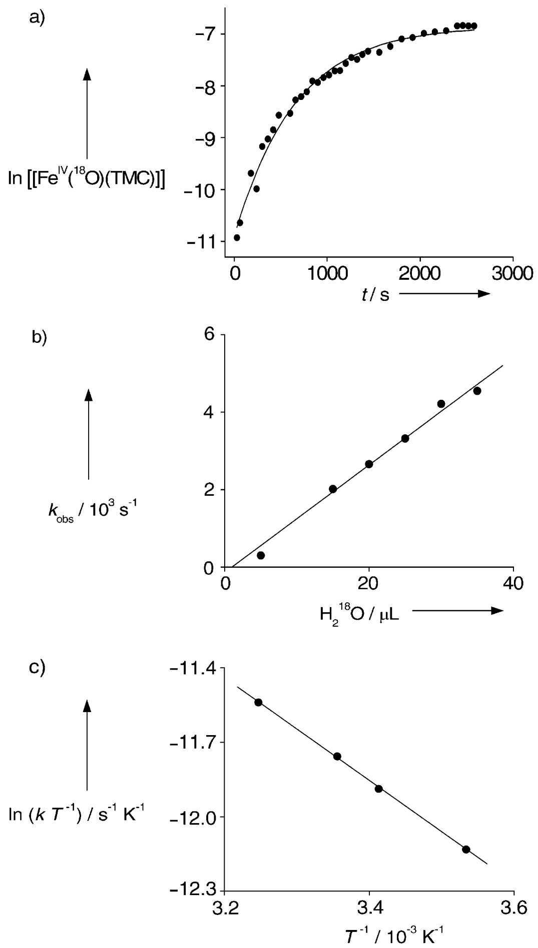
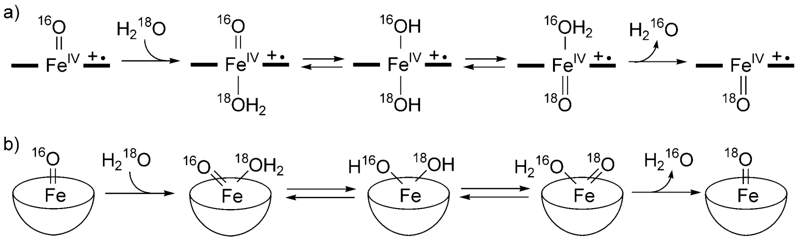


Figure 3. a) Plot of ln [[Fe^{IV}(^{18}O)(TMC)]] against incubation time for the oxygen-atom exchange between **1** and $H_2{}^{18}O$ (20 µL) at 10 °C. b) Plot of k_{obs} against the amounts of $H_2{}^{18}O$ for the oxygen-atom exchange between **1** and $H_2{}^{18}O$ at 25 °C. c) Determination of activation parameters for the oxygen exchange of **1** with $H_2{}^{18}O$ (20 µL). See Experimental Section for detailed reaction procedures.



Scheme 2. Proposed oxo–hydroxo tautomerism mechanisms for ^{18}O exchange in a) heme and b) nonheme iron models.

$-57(8)\,cal\,mol^{-1}\,K^{-1}$, which are quite similar to those obtained for **1** (Supporting Information).

How do nonheme oxoiron(IV) complexes exchange their oxygen atoms with labeled water? For high-valent metal-oxo porphyrin species, the prevailing exchange pathway is through the oxo–hydroxo tautomerism mechanism proposed by Meunier and co-workers,[3,4f] which entails the binding of labeled water trans to the oxo group and then tautomerization of this species to a symmetric *trans*-dihydroxoiron(IV) intermediate that scrambles the label (Scheme 2a). This pathway clearly cannot be operative for **1** and **2**, since such a symmetric *trans*-dihydroxoiron(IV) species cannot be attained for these nonheme complexes. The crystal structure of **1** shows that the top and bottom of the TMC ligand, unlike for the planar porphyrin ligands, are not equivalent; in fact all four *N*-methyl groups point away from the oxo group.[7a] Thus, although it is conceivable for labeled water to bind *trans* to the oxo group by displacement of the bound acetonitrile ligand, a symmetric *trans*-dihydroxoiron(IV) transition state cannot be obtained. In the case of **2**, the pentadentate nature of the N4Py ligand and the way it wraps around the iron center does not permit binding of a water molecule *trans* to the oxo atom (see the proposed structure of **2** in Figure 2). Despite these constraints, $H_2{}^{18}O$ exchanges readily with the iron-oxo units of **1** and **2**, with very similar activation barriers (see above). We are thus compelled to propose an alternative to the oxo–hydroxo tautomerism mechanism, in which oxygen exchange occurs via a twofold symmetric *cis*-dihydroxoiron(IV) transition state that is formed by coordination of a water molecule to the iron center adjacent to the oxo group (Scheme 2b). The unusual geometry of the proposed intermediate is similar to that associated with η^2-peroxoiron complexes.[11,12] Indeed the fact that such a side-on peroxo complex has been characterized for [Fe^{III}(N4Py)] complex[12a] is a strong argument for this proposed transition state.

In summary, we report the first direct evidence for oxygen-atom exchange between nonheme oxoiron(IV) complexes and $H_2{}^{18}O$, and the first direct measurement for the rates and activation parameters for the ^{18}O-exchange reactions. Oxygen-atom exchange in nonheme oxoiron(IV) models is proposed to occur not through the *trans* oxo-hydroxo tautomerism pathway proposed in high-valent metal-oxo porphyrins but by a variant that involves a *cis*-dihydroxoiron(IV) transition state.

Experimental Section

General: $H_2{}^{18}O$ (95 % ^{18}O-enriched) was purchased from ICON Services Inc. (Summit, NJ, USA). UV/Vis spectra were recorded on a Hewlett Packard 8453 spectrophotometer equipped with an Optostat variable-temperature liquid-nitrogen cryostat (Oxford instruments) or a circulating water bath. Electrospray ionization mass spectra were collected on a Thermo Finnigan (San Jose, CA, USA) LCQ Deca XP Plus and Advantage quadrupole ion trap instrument. Product analyses were performed on a Hewlett-Packard 5890 II Plus gas chromatograph interfaced with Hewlett-Packard model 5989B mass spectrometer.

Oxidation of thioanisole by Fe(TMC)$(OTf)_2$ and H_2O_2: This reaction was run at least in duplicate under air, by monitoring the UV/Vis spectral changes of reaction solutions. The addition of H_2O_2 (6 mM, diluted in 20 µL CH_3CN) into a 1 cm UV cuvette containing [Fe(TMC)$(OTf)_2$] (6 mM), thioanisole (0.12 M), and $H_2{}^{18}O$ (0.12 mL, 95 % ^{18}O) in CH_3CN (3 mL) at 10 °C resulted in the formation of a green species, $[(TMC)Fe^{IV}{=}O]^{2+}$. After the green intermediate reverted back to the starting $[Fe(TMC)]^{2+}$ complex, the reaction solution was directly analyzed by GC and GC/MS. The ^{16}O and ^{18}O compositions in thioanisole oxide were analyzed by the relative abundances of $m/z = 125$ and 140 for ^{16}O and $m/z = 127$ and 142 for ^{18}O.

Isotope labeling studies with oxoiron(IV) complexes and $H_2{}^{18}O$: Complexes **1** and **2** were prepared by treating $[Fe(TMC)(OTf)_2]$ (2 mM) and $[Fe(N4Py)(ClO_4)_2]$ (2 mM), respectively, with 1 equivalent of peracid (peracetic acid for **1** and *m*-chloroperbenzoic acid for **2**) in CH_3CN (3 mL) at 10 °C.[7] After appropriate amounts of $H_2{}^{18}O$ were added to the reaction solution at the given temperature controlled by a circulating water bath, samples were infused directly into the source at 20 $\mu L\,min^{-1}$ by using a syringe pump. The spray voltage was set at 4 kV and the capillary temperature at 70 °C. The percentages of ^{18}O in the mass spectra of **1** and **2** were calculated by fitting the characteristic isotope distribution patterns. Two traces of observed isotopic distribution patterns of **1** before and after addition of labeled water were provided with the bars representing the calculated isotope distributions (Supporting Information).

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