Bioinorganic Enzyme Models

Electron-Transfer Properties of an Efficient Nonheme Iron Oxidation Catalyst with a Tetradentate Bispidine Ligand**

Peter Comba,* Shunichi Fukuzumi,* Hiroaki Kotani, and Steffen Wunderlich

The interest in nonheme iron systems has lead to an increasingly detailed knowledge of the coordination geometries, electronic structures, and reaction mechanisms of oxygenases and halogenases (for example TauD and SyrB2), and this is due to numerous studies involving the biological processes, small molecule model systems, and quantum-chemical model studies.^[1-7] The thorough analysis of a variety of model systems has yielded a detailed understanding of the nature of the catalytically active high-valent iron oxo intermediates.^[2,4-8] Current focal points in experimental and theoretical modeling of the enzyme reactions are ambiguities in the degree of protonation, the oxidation and spin states of the catalytically active high-valent iron complex, and their relation to the reactivities (Fe^{IV} vs. Fe^V; S = 1 versus S = 2; O versus OH versus OH₂).

Important parameters for the characterization of the highvalent iron oxo complex and for the interpretation of its reactivity are 1) the reduction potential $E_{\rm red}$ of the ferryl complex,^[9-11] 2) the kinetic barrier for the electron-transfer process, 3) the basicity of the oxidized and reduced iron oxo species,^[12] and 4) the energy gap between the various spin states, because computational studies indicate that the potential energy for oxidation reactions on the high-spin surface has lower barriers, whereas most low-molecularweight biomimetic Fe^{IV}=O systems, in contrast to the enzymes, have an intermediate spin (S=1) ground state.^[6,13-15]

Herein, we report the electron-transfer properties of an Fe^{IV}=O complex with the tetradentate bispidine ligand L (Scheme 1).^[16] The coordination chemistry of ligand L has

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Scheme 1. Structure and proposed geometry of the ligand L (left) and of complex 1 (right).

been thoroughly studied by computational (molecular mechanics, DFT) and experimental methods, and it was shown to be enforced by the rigid adamantane-type ligand backbone. A variety of X-ray crystal structures have been used to show that tetra- and pentadentate derivatives of L with different donor sets have an elastic coordination sphere as a consequence of the flat potential energy surface with various close-to-degenerate minima. The rigid and relatively large cavity of the bispidines is one reason for their high metal ion selectivity, and these ligands exhibit uncommon dependencies of the stability constants.^[17,18] Their iron chemistry has been developed in the fields of alkane and alkene oxidation and biomimetic nonheme-halogenase reactivity.[19-23] Computational studies related to the bispidine-Fe^{IV}=O species reveal a very small energy gap between the intermediate-spin (S=1) and high-spin (S=2) electronic configurations.^[21-23] Furthermore, the reorganization energy of the electron transfer between the oxo Fe^{IV} and the oxo Fe^{III} species is expected to be small owing to the rigid ligand backbone, which is a possible reason for the exceptionally high reactivity. Therefore, we report herein the fundamental electron-transfer properties of $[Fe^{IV}=O(L)(NCMe)]^{2+}$ (1).

The high-valent complex **1** is generated quantitatively with 1.2 equivalents of iodosylbenzene diacetate (PhI(OAc)₂) and stabilized at 238 K in concentrations of up to 5×10^{-4} M. The absorption maximum of **1** (760 nm; $\varepsilon = 130$ L mol⁻¹ cm⁻¹) is typical for an S = 1 Fe^{IV}=O system and consistent with the solution magnetic moment of 3.01 B.M. that was determined by the Evans method (this value is close to the spin-only value of 2.83 for two unpaired electrons).^[24-26] At higher temperatures **1** is unstable, and at higher concentrations an inactive Fe^{III}–O–Fe^{III} dimer forms.^[27] A series of ferrocene derivates (ferrocene ($E_{ox} = 0.38$ V vs. SCE), bromoferrocene (0.54 V), acetylferrocene (0.62 V), and dibromoferrocene ($E_{ox} =$ 0.69 V))^[10] were used as one-electron reductants to reduce the ferryl complex **1** in dry acetonitrile to the corresponding Fe^{III}–O compound [Eq. (1)].^[28] A series of organic substrates



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$$Br_{2}Fc + [Fe^{IV}(O)(L)(NCMe)]^{2+} \stackrel{K_{ef}}{\longleftrightarrow} Br_{2}Fc^{+} + [Fe^{III}(O)(L)(NCMe)]^{+}$$
(1)

(10-methyl-9,10-dihydroacridine, xanthene, dihydroanthracene, and fluorene) was used to promote the proton-coupled electron transfer (PCET) to $Fe^{III/II}$ –OH.

The electron transfer from dibromoferrocene (Br₂Fc) to **1** is confirmed by the UV/Vis spectral changes, with an increase of the absorption observed at 690 nm for the Br₂Fc⁺ cation and the concomitant decrease of the absorption of **1** at 760 nm. The electron-transfer equilibrium of the reaction was studied at various Br₂Fc concentrations (0.1–2.0 mM, [**1**] = 0.2 mM). The plot in Figure 1 indicates that Br₂Fc⁺ is



Figure 1. a) Observed spectral changes in the electron-transfer reaction of Br₂Fc with 1 (2×10⁻⁴ m) in oxygen-free MeCN at 238 K. b) Concentration of Br₂Fc⁺ observed in the electron-transfer reaction of Br₂Fc with 1 (2×10⁻⁴ m) as a function of the initial concentration of Br₂Fc.

generated quantitatively under the conditions used, and was used to determine the equilibrium constant $K_{\rm et}$ of the electron-transfer reaction to be 5.9 (see the Supporting Information for details). This value and the known potential of Br₂Fc were used to determine the one-electron reduction potential of **1**, namely $E_{\rm red} = 0.73$ V vs. SCE [Eq. (2)].

$$E_{\rm red} = E_{\rm ox} + (RT/F) \ln K_{\rm et} \tag{2}$$

This one-electron reduction potential is the highest reported to date for Fe^{IV}=O compounds. A previous similar study on Fe^{IV}=O compounds with other tetra- and pentadentate ligands reported $E_{\rm red}$ values of 0.39 V vs. SCE for the complex of tmc (1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane), 0.49 V for bn-tpen (*N*-benzyl-*N*,*N'*,*N'*-tris(2-pyridylmethyl)ethane-1,2-diamine) and 0.51 V for N4py (*N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridylmethyl)methylamine), and these values are significantly lower than $E_{\rm red} = 0.73$ V vs. SCE obtained herein for **1**.^[10]

The kinetics of the one-electron transfer between the intermediate-spin (S=1) ferryl complex **1** and a variety of ferrocene derivates were analyzed by pseudo first-order kinetics using an excess of the corresponding ferrocene derivative. The observed rate constants k_{obs} increase linearly with the ferrocene concentrations, and the second order rate constants k_{et} were determined from the slopes of the curves. All spectrophotometric experiments show an isosbestic point between the absorption of the corresponding ferrocenium cation derivative (615–690 nm) and **1** (760 nm). For acetyl-ferrocene (AcFc), where the two absorptions are well-separated (640 and 760 nm, respectively), the decrease of the absorption for **1** and the increase of the absorption of

AcFc⁺ lead to identical second-order rate constants (see the Supporting Information). This result supports our interpretation and analysis that **1**, with an absorption at 760 nm, is indeed the reactive species and is reduced to Fe^{III}–O. A plot of the driving force versus the rate constants of the electron-transfer processes involving Fe^{IV}=O and the ferrocene derivatives in acetonitrile at 238 K is shown in Figure 2, where the log $k_{\rm et}$ values are plotted against the $-\Delta G_{\rm et}$ values $(-\Delta G_{\rm et} = \exp(E_{\rm red} - E_{\rm ox})$ in eV). The data is well-fitted by the



Figure 2. Driving force dependence of the rate constants ($\log k_{el}$) for the electron transfer from different ferrocene derivates to 1 in oxygenfree MeCN at 238 K.

solid line in light of the Marcus theory of adiabatic outersphere electron transfer [Eq. (3)], where Z is the collision

$$k_{\rm et} = Z \exp[-(\lambda/4)(1 + \Delta G_{\rm et}/\lambda)^2/k_{\rm B}T]$$
(3)

frequency taken as $1 \times 10^{11} \text{ Lmol}^{-1} \text{ s}^{-1}$, λ is the reorganization energy of the electron-transfer process, k_{B} is the Boltzmann constant, and *T* is the absolute temperature (see references [30,31] for the Marcus analysis of electron-transfer reactions with large λ values).^[32]

From the plot of $\Delta G_{\rm et}$ versus $k_{\rm et}$ in Figure 2, the reorganization energy λ was calculated to be 2.05 eV (197.8 kJ mol⁻¹); this value is significantly lower than values for other Fe^{IV}=O complexes studied previously (2.37–2.74 eV).^[10] This result is not unexpected because of the rigid bispidine backbone. The one-electron reduction of **1** (S = 1) to Fe^{III}–O (S = 3/2) is a spin-allowed process, and the spin-state change is not believed to make a large contribution to λ .

The product of the one-electron transfer, $[Fe^{III}(O)(L)]^+$, has a high basicity and will immediately be protonated in oxidation reactions of organic substrates.^[11,12] This protonation will lead to the thermodynamically more stable hydroxo complex $[Fe^{III}(OH)(L)]^{2+}$ and will, as a consequence of a larger equilibrium constant, lead to a higher value of E_{red} (proton-coupled electron transfer, PCET). Such a PCET reaction is observed between 4-*tert*-butylphenol ($E_{ox} = 1.66$ V vs. SCE) and **1**, but no reaction occurs with 4-nitrophenol ($E_{ox} = 2.24$ V vs. SCE).^[33] In the course of the reaction, the formation of an absorption at 685 nm occurs, which is proposed to be an Fe^{III} phenoxyl radical complex (see Supplementary Information).^[34] The second-order rate con-

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stants $k'_{\rm H}$ with the organic substrates 10-methyl-9,10-dihydroacridine (AcrH₂), xanthene, dihydroanthracene (DHA), and fluorene with different bond-dissociation energies were determined.^[35,36] The reaction between the NADH analogue $AcrH_2$ and 1 leads to formation of the acridinium ion ($AcrH^+$) with an absorption maximum at 357 nm. This reaction is a consequence of hydride transfer, and the corresponding mechanism has been thoroughly studied.^[37] It is interesting to note that E_{ox} of AcrH₂ is higher than that of Br₂Fc (0.81 V and 0.69 V vs. SCE, respectively),^[38] but k_{et} increases from 10.5 to $475.9 \,\text{Lmol}^{-1}\text{s}^{-1}$ in the case of the PCET process. A kinetic isotope effect (KIE) of 2.3 was observed when AcrH₂ was replaced by the doubly deuterated substrate (AcrD₂), and this effect is much smaller than that observed in the N4pybased system.^[37] The hydrogen abstraction is thus the ratedetermining step, but in the present case, the barrier for the ET process is very similar in energy. The dependence of the $\log k'_{\rm H}$ values and the BDE of the organic substrates is shown in Figure 3.[35,39]



Figure 3. Rate constants (log k'_{H}) of the hydrogen abstraction reaction of the ferryl oxidant 1 with different organic substrates as a function of their bond dissociation energy (BDE).^[39]

We have analyzed the electron-transfer properties of the ferryl complex $\mathbf{1}$, which has the highest reduction potential reported to date and a comparably low reorganization energy. Further experiments of oxo Fe^{IV} complexes with other tetraand pentadentate bispidine ligands are currently being performed in our laboratories and will be supported by DFT calculations.

Experimental Section

Commercially available reagents, such as ferrocene (Tokyo Chemical Industry Co., Ltd.) were of the highest available grade and used without further purification unless otherwise noted. Acetonitrile was dried according to the literature procedures and distilled under argon prior to use.^[40] Preparation and handling of air-sensitive materials was done under an inert atmosphere. NMR Spectra were recorded on a 400 MHz (1 H), BRUKER AVANCE II 400 instrument with TMS as internal reference; δ in ppm, *J* in Hz. The oxo Fe^{IV} complex **1** was prepared by the reaction of [Fe^{II}(L)(OTf)₂] (0.1–0.5 mM) with 1.2 equiv of PhI(OAc)₂ in deaerated MeCN at 238 K. [Fe^{II}(L)(OTf)₂] was synthesized as reported.^[41]

Spectrophotometric redox titration: Electron transfer from dibromoferrocene to $\mathbf{1}$ (2×10⁻⁴ M) was examined from the spectral

change in the presence of various concentrations of dibromoferrocene at 238 K using a Hewlett Packard 8453 spectrophotometer with a quartz cuvette (path length = 10 mm). Typically, a deaerated MeCN solution of Br₂Fc was added by means of a microsyringe to a deaerated MeCN solution containing **1**. The concentration of Br₂Fc⁺ was determined from the absorption band at $\lambda_{max} = 690$ nm ($\varepsilon = 3.9 \times 10^2$ Lmol⁻¹ cm⁻¹). The ε value of Br₂Fc⁺ was confirmed by the electron-transfer oxidation of Br₂Fc with an excess of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

Kinetic measurements were performed on a UNISOKU RSP-601 stopped-flow spectrometer equipped with a MOS-type highly sensitive photodiode array or a Hewlett Packard 8453 spectrophotometer. Rates of electron transfer from ferrocene derivatives and different organic substrates to 1 at 238 K were monitored by the rise of the absorption band owing to product formation (e.g. for AcrH₂ to AcrH⁺ at 357 nm or for DHA to anthracene at 377 nm) or the decay of 1, respectively. All kinetic measurements were carried out under pseudo first-order conditions in which concentrations of substrates were maintained to be more than ten-fold in excess of 1.

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