Iron–Oxo Complexes

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Contrasting *cis* and *trans* Effects on the Reactivity of Nonheme Oxoiron(IV) Complexes**

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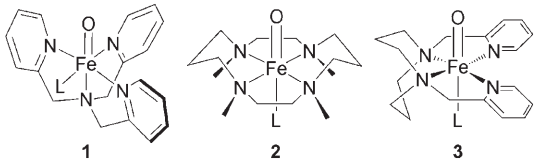
Oxoiron(IV) species are often implicated as the key oxidants in the catalytic cycles of oxygen-activating iron enzymes, both heme[1] and nonheme.[2] For heme enzymes, the only site available for significant ligand tuning is that *trans* to the oxo ligand because of the planar tetradentate nature of the common porphyrin cofactor. In contrast, the metal coordination environments in nonheme iron enzymes exhibit a greater variability, in that different ligands can occupy sites either *cis* or *trans* to the oxo group within this superfamily of enzymes. This flexibility may serve as an additional means for tuning the reactivity of the oxoiron(IV) unit.

Synthetic nonheme oxoiron(IV) complexes have recently been characterized, and the growing family of such complexes demonstrates that polydentate nitrogen ligands with different topologies can support the oxoiron(IV) center.[3] Herein, we compare the reactivities of two synthetic nonheme oxoiron(IV) complexes supported by closely related ligands. The tetradentate nature of these ligands leaves a sixth coordination site that is occupied by the solvent MeCN, which can easily be displaced by pyridine *N*-oxides (PyOs), and we find dramatic differences in reactivity trends depending on whether the ligand at the sixth site is *cis* or *trans* to the oxo group.

$[Fe^{IV}(O)(tpa)(NCMe)]^{2+}$ (**1**; tpa = tris(2-pyridylmethyl)-amine) and $[Fe^{IV}(O)(tmc)(NCMe)]^{2+}$ (**2**; tmc = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane) represent the first two well-characterized complexes of the nonheme



oxoiron(IV) family, and thus serve as prototypes.[4] They each have an easily displaceable MeCN ligand located *cis* and *trans*, respectively, to the oxo group, which has been shown to undergo ligand exchange reactions wherein the MeCN ligand can be replaced by anions such as halides and carboxylates.[5] For this study, the sixth ligand of choice is pyridine *N*-oxide (PyO), since several 4-substituted derivatives are available to allow a systematic investigation of substituent effects on reactivity. Indeed, addition of 5 equivalents of PyO to a solution of **1** in MeCN immediately broadens its signature near-IR band at 720 nm into two poorly resolved features at 675 and 745 nm (Figure 1a and Figure S1 in the Supporting Information), demonstrating that the d–d transitions of the $S = 1$ oxoiron(IV) center[5d] are perturbed by the binding of PyO. However, PyO addition to a solution of **2** in MeCN does

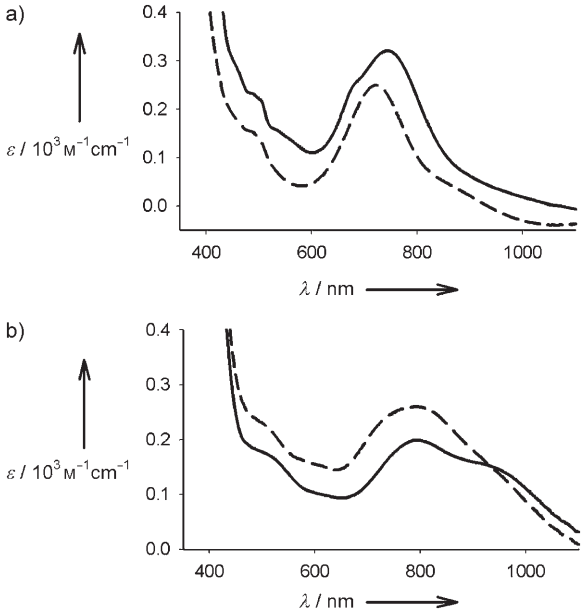


Figure 1. Visible spectra of a) **1** (– – –, *y* axis downshifted by 0.05 unit to provide a clearer view), **1**-(OPy) (——) and b) **3** (– – –), **3**-(OPy) (——) generated at −20 °C in CH_3CN.

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not affect its near-IR band at 820 nm, suggesting that PyO cannot bind to **2**. This observation can be rationalized by invoking steric effects of the four *N*-methyl groups of the tmc ligand, which are all oriented on one side of the macrocycle opposite to the oxo atom and define a pocket that limits the size of the sixth ligand.[4b]

Another nonheme ligand with four N donor groups constrained to be in a plane is L^8Py_2 (see **3**),[6] which has two pyridine rings in place of two of the tertiary amine donors in tmc to eliminate the steric constraints that prevented binding of PyO to **2**. The reaction of $[Fe^{II}(L^8py_2)(OTf)]^+$ (OTf = trifluoromethanesulfonate) with 1 equivalent of CH_3CO_3H in CH_3CN at −40 °C generates a pale green species **3** with a λ_{max} at 790 nm (Figure 1 b, dashed line). This chromophore resembles those associated with **1**, **2**, and other low-spin nonheme oxoiron(IV) complexes.[3,4] The formulation of **3** is established by its high-resolution electrospray ionization mass spectrum, in which the dominant ion cluster is observed at *m*/*z* 517.0818 with a mass and isotope distribution pattern corresponding to the $[Fe^{IV}(O)(L^8py_2)(OTf)]^+$ ion (calcd. *m*/*z* 517.0815) (Figure 2). The Mössbauer spectrum

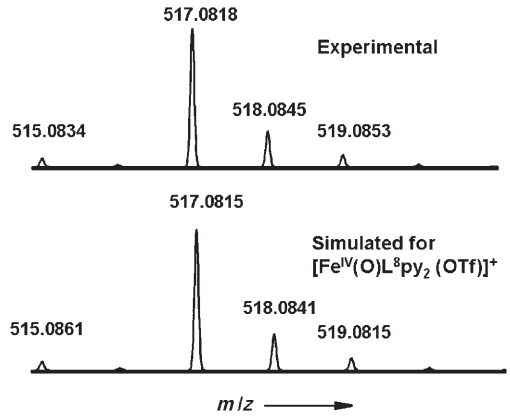

Figure 2. Dominant molecular ion cluster in the high-resolution electrospray mass spectrum of **3**.

of **3** exhibits a quadrupole doublet with $\delta = 0.08$ mm s^{-1} and $\Delta E_Q = 1.79$ mm s^{-1} (Figure S2 in the Supporting Information). Its isomer shift falls in the middle of the range established for other low-spin oxoiron(IV) complexes with neutral supporting ligands (−0.04 to 0.17 mm s)$^{-1}$, which is consistent with the two-amine, two-pyridine ligand combination.[3,4,7,8] Its quadrupole splitting, in contrast, is the largest found thus far for this family of complexes; it is larger by 0.55 mm s^{-1} than that of **2** ($\Delta E_Q = 1.24$ mm s^{-1}).[4b] Their large quadrupole splittings may reflect a large electric-field gradient resulting from an Fe=O unit that is perpendicular to a tetradentate N_4 donor set that occupies the *xy* plane, of which **2** and **3** represent the only examples thus far with neutral ligands. For comparison, oxoiron(IV) complexes of planar polyanionic macrocyclic ligands $[Fe^{IV}(O)(Cl_8tpp)(thf)]$ (Cl_8tpp = tetrakis(2,6-dichlorophenyl)porphinato; thf = tetrahydrofuran) and $[Fe^{IV}{}_2O(taml)_2]^{2-}$ (taml = tetraamido macrocyclic ligand) have ΔE_Q values of 2.08[9] and 3.3 mm s^{-1}.[10] Correlation of the Mössbauer data with the near-IR spectrum taken of the Mössbauer sample affords a molar extinction coefficient of 260 M^{-1} cm^{-1} for the 790-nm chromophore of **3**.

Addition of 5 equivalents of PyO to **3** in MeCN results in the splitting of the near-IR band into two components at 790 and 950 nm (Figure 1 b). These spectral changes are analogous to those observed for **2** upon complete displacement of the MeCN ligand by a carboxylate or a pseudohalide[5a,b] ligand and can be attributed to the dispersion of the three ligand-field bands found in this region.[5d] Titration of **3** with PyO shows that the spectral changes are complete with the addition of 2.5 equivalents, demonstrating that PyO competes well with the MeCN solvent for binding to the Fe=O moiety (Figures S3 and S4 in the Supporting Information). Furthermore, a Mössbauer spectrum of **3** with 5 equivalents of PyO shows a doublet with a smaller quadrupole splitting (1.59 mm s^{-1}), demonstrating complete formation of the PyO adduct under these conditions. Similar spectral shifts are observed upon addition of 4-Me-, 4-MeO-, or 4-Cl-substituted derivatives (Figure S5 and Table S1 in the Supporting Information), but not for 4-O_2N-PyO or 4-NC-PyO. However, addition of any PyO shortens the lifetime of **3** (see below). Thus our accumulated results show that pyridine *N*-oxides bind to **3**.

Both **1** and **3** have significant lifetimes at −20 °C. In the absence of added PyOs, the half-life of **1** is estimated to be longer than 30 hours, whereas that of **3** is about 7 hours. Addition of 5 equivalents of a particular pyridine *N*-oxide decreases these values, but the effects are different for **1** and **3**. The half-life of **1** is only slightly reduced by the addition of 4-MeO-PyO, but is cut by more than 20-fold with 4-O_2N-PyO. In contrast, the half-life of **3** decreases only threefold with added 4-O_2N-PyO but diminishes over 100-fold with 4-MeO-PyO. Thus *cis*- and *trans*-ligated PyOs affect the Fe=O unit in dissimilar ways.

These contrasting effects of *cis*- and *trans*-ligated PyOs are also manifested in the oxidations of benzyl alcohol and diphenyl sulfide by **1** and **3**, for which the organic products were identified to be benzaldehyde and diphenyl sulfoxide, respectively (Table S1 in the Supporting Information). No pyridine was observed as a by-product for the reaction, so PyO does not act as an oxo-atom donor in these reactions. The oxidation rates were measured in the presence of various PyOs (5 equiv) by monitoring the disappearance of the near-IR chromophores. These results (Table S1) show that the reactivity of **1** varies by at most a factor of 5 by the introduction of a 4-substituent, whereby electron-donating substituents decrease the oxidation rates relative to the parent MeCN complex. In contrast, the oxidative reactivity of **3** changes by a factor of about 25 over the entire range of substituents, and electron-donating groups accelerate the reactions.

The above points can be placed on a more quantitative basis by the Hammett plots shown in Figure 3. Good linear correlations are obtained with the standard Hammett substituent parameter σ_p[11] for the oxidations by **1**, affording small positive ρ values ($\rho = 0.42$ for $PhCH_2OH$ and $\rho = 0.56$ for Ph_2S). In contrast, the oxidations by **3** have ρ values that are larger and negative ($\rho = -1.4$ for $PhCH_2OH$ and $\rho = -1.3$ for Ph_2S). The point corresponding to Ph_2S oxidation by **3** in

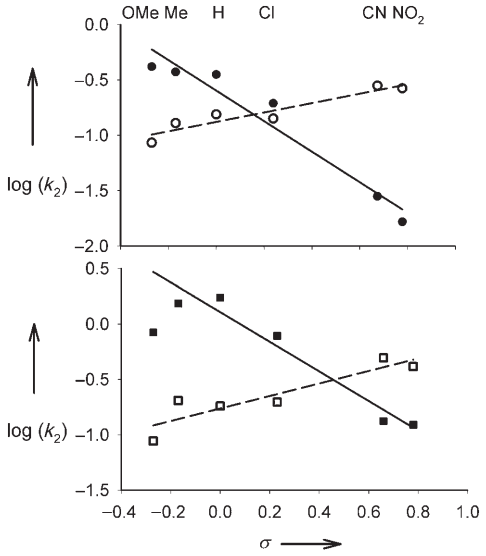

Figure 3. Hammett plots for the oxidations of benzyl alcohol (circles) and diphenyl sulfide (squares) by **1** (open) and **3** (filled) as a function of the 4-substituent of the added pyridine *N*-oxide. σ = standard Hammett substituent parameter.

the presence of 4-MeO-PyO deviates from the linear correlation in Figure 3 (bottom panel) and may indicate a change in oxidation mechanism. To probe the likelihood of a mechanistic change, we obtained kinetic isotope effect (KIE) data for benzyl alcohol oxidation by **1** and **3** in the presence of 4-MeO-PyO and 4-O_2N-PyO. The KIE was 15 for **1**, whereas it was 5 for **3**, independent of the PyO substituent. If there is a difference in mechanism with the methoxy substituent, the rate-determining H-atom abstraction step does not reveal it. We thus cannot explain why the rate of Ph_2S oxidation by **3** in the presence of 4-MeO-PyO is lower than expected. However, the accumulated data clearly demonstrate that PyOs exert opposite effects on the reactivity of the Fe=O unit depending on whether the PyO ligand is coordinated *cis* or *trans* to the Fe=O unit.

Literature precedents with which to compare our data are few. As found for **1**, a small and positive ρ value (0.31) was observed in the oxidation of benzyl alcohol by a series of $[Ru^{IV}(O)(bpy)_2(P(C_6H_4\text{-}p\text{-}X)_3)]^{2+}$ complexes (bpy = 2,2′-bipyridyl) in which the phosphine ligand is coordinated *cis* to the Ru=O unit.[12] Electron-withdrawing substituents make the Ru^{IV}=O moiety a better oxidant. Similarly, introduction of halogen substituents on the porphyrin periphery increases the reactivity of $[Fe^{IV}(O)(porphyrin)]$ complexes.[13] Thus, a *cis* ligand appears to exert its effect simply by modulating the Lewis acidity of the M=O center.

The effect of a *trans* ligand on an Fe=O center has attracted more attention because of its importance in tuning the oxidative reactivity of various heme enzymes.[1] In fact, many studies show that the reactivity of high-valent iron porphyrin complexes is affected by the axial ligand,[14–16] but there is only one systematic study that directly monitors the kinetics of substrate oxidation by oxoiron(IV) complexes.[16] In this study, the second-order rate constants for styrene epoxidation by $[Fe^{IV}(O)$(tetramesitylporphyrin radical)$(X)]$ complexes investigated as a function of the axial ligand span a 15-fold range and increase in the order of X = triflate, acetate, chloride, methanol, fluoride. Unfortunately, the observed order could not be correlated with any property of the axial ligand or of the corresponding Fe=O complex, leading the authors to suggest a multistep reaction mechanism with at least two steps that are partially rate-determining.

In contrast, for our study of **3**, it is clear that electron-donating substituents on the axial PyO ligand enhance the oxidative reactivity of the oxoiron(IV) complex. This behavior is in agreement with comparisons of reactivity among $[Fe^{IV}(O)(tmc)(X)]$ complexes, whereby the replacement of the neutral MeCN axial ligand in the parent complex with anions enhances the ability of the Fe=O unit to perform H-atom abstraction as the basicity of the anion increases (i.e., trifluoroacetate < azide < thiolate).[17] This notion is also consistent with the speculated role of the thiolate ligand in cytochrome P450.[1] We emphasize that this study of **3** represents the first for which a Hammett correlation has been established for an axial ligand effect on the reactivity of an Fe^{IV}=O unit.

The contrasting effects of *cis* and *trans* ligands on reactivity very likely derive from perturbations to the electronic structure of the highly covalent Fe=O moiety.[17–19] DFT calculations reported thus far describe the Fe=O bond as consisting of a σ bond, derived mainly from the overlap of the empty metal d_{z^2} orbital and the oxygen p_z orbital, and a π bond due to the interactions between the half-filled metal d_{xz} and d_{yz} orbitals and the oxygen p_π orbitals.[17–19] A ligand *trans* to the oxo group would exert a larger effect since it can interact strongly with both dσ and dπ orbitals and compete with the oxo group. In experimental support of this notion, we note a parallel behavior in the intensity of the 1s→3d pre-edge transition found in the X-ray absorption spectra of these complexes. The intensity of this transition is essentially unchanged for **1** at 25(1) units with variation of the sixth ligand,[5c,20] but it changes from 18–31 units in the case of **2** for axial ligands ranging from thiolate to trifluoroacetate.[21] Binding of thiolate results in a decrease of the pre-edge peak intensity and a lengthening of the Fe=O bond from 1.65 Å in the parent MeCN complex to 1.70 Å,[21a] suggesting a weakening of the Fe=O bond upon coordination of the more basic thiolate ligand. This change leads to a dramatic increase in the H-atom abstraction reactivity of the Fe=O unit. Similarly, electron-donating substituents make the $[Fe^{IV}(O)(L^8py_2)(OPy\text{-}4\text{-}R)]^{2+}$ complex 10–20-fold more reactive than with electron-withdrawing substituents.

In summary, we have demonstrated in this work that ligands *cis* and *trans* to the Fe=O unit modulate its reactivity in disparate ways, shedding light on the various strategies available for tuning the oxidative properties of nonheme iron oxygenases.

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