Reaction Mechanisms

Mechanistic Insight into Alcohol Oxidation by High-Valent Iron–Oxo Complexes of Heme and Nonheme Ligands**

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High-valent iron–oxo species are frequently invoked as the key intermediates in the catalytic oxidation of organic substrates by heme and nonheme iron mono-oxygenases.[1,2] In the case of heme-containing enzymes such as cytochromes P450, oxoiron(IV) porphyrin π-cation radicals have been proposed as active oxidants that effect a number of oxidation reactions, which include alkane hydroxylation, olefin epoxidation, and alcohol oxidation.[1] Indeed, a number of synthetic oxoiron(IV) porphyrin π-cation radicals have been prepared and used in mechanistic studies of alkane hydroxylation and olefin epoxidation.[3] In mononuclear nonheme iron enzymes, oxoiron(IV) intermediates have been unveiled very recently in enzymatic and biomimetic reactions.[4–6] The mononuclear nonheme oxoiron(IV) species have been well-characterized with various spectroscopic techniques and with X-ray crystallography and were shown to be active in a variety of oxidation reactions such as alkane hydroxylation, olefin epoxidation, and the oxidation of sulfides and PPh_3.[4–6]

The oxidation of alcohols to the corresponding carbonyl compounds is an important chemical process in industrial and

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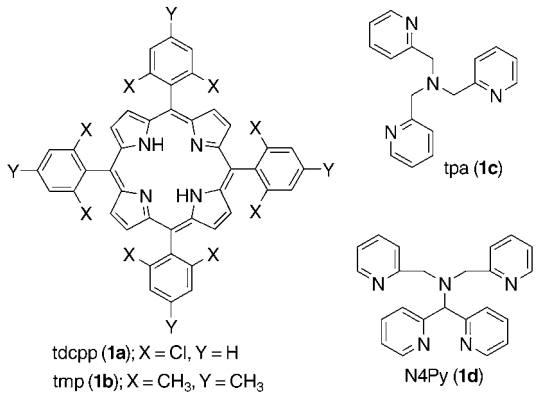
biological reactions.[7,8] Thus, tremendous effort has been devoted to developing environmentally benign catalysis and bioinspired oxidation reactions. In the latter case, the oxidation of alcohols by synthetic copper complexes has been intensively investigated as chemical models of galactose oxidase (GOase).[9,10] It has been also shown that cytochromes P450 and their model compounds are able to catalyze the oxidation of alcohols,[11,12] although mechanistic details of iron-complex-mediated alcohol oxidation have never been investigated with in situ generated intermediates of oxoiron(IV) porphyrin π-cation radicals. In the present work, we carried out alcohol oxidation reactions with spectroscopically well characterized oxoiron(IV) porphyrin π-cation radicals, $[(tdcpp)^{\bullet+}Fe^{IV}{=}O]^{+}$ (**1a**) and $[(tmp)^{\bullet+}Fe^{IV}{=}O]^{+}$ (**1b**),[13] and mononuclear nonheme oxoiron(IV) complexes, $[(tpa)Fe^{IV}{=}O]^{2+}$ (**1c**)[5b] and $[(N4Py)Fe^{IV}{=}O]^{2+}$ (**1d**)[5c] (see Scheme 1 for structures of heme and nonheme ligands).[14] To the best of our knowledge, this study provides the first mechanistic details of alcohol oxidation with oxoiron(IV) complexes generated in situ, which bear heme and nonheme ligands.

The high-valent iron–oxo complexes were prepared by using reported methods (see Supporting Information), and kinetic studies with benzyl alcohol were performed at different temperatures due to the different reactivity of the oxoiron(IV) complexes in the oxidation reactions; reaction temperatures were −100 °C for **1a**, −60 °C for **1b**, −40 °C for **1c**, and 0 °C for **1d**. Upon adding 25 equivalents of benzyl alcohol to the solutions of **1**, the intermediates reverted back to the starting iron complexes and showed pseudo-first-order decay as monitored by a UV/Vis spectrophotometer (see Figure 1a for **1d** and Supporting Information for **1a–c**). Pseudo-first-order fitting of the kinetic data allowed us to determine k_{obs} values for the reactions of **1a–d** (Table 1; k_{obs} is the observed rate constant), and product analysis of the resulting solutions with HPLC and GC revealed that benzaldehyde was produced with high yields in all of the reactions (> 70 % based on the intermediates generated; Scheme 2).



Scheme 1. Structures of heme and nonheme ligands of the iron complexes **1a–d** used in this study.

The pseudo-first-order rate constants increased proportionally with benzyl alcohol concentration, thus leading us to determine second-order rate constants (see Table 1, Figure 1b, and Supporting Information). We then determined activation enthalpy, entropy, and Gibbs energy ($\Delta H^{\neq}$, $\Delta S^{\neq}$,

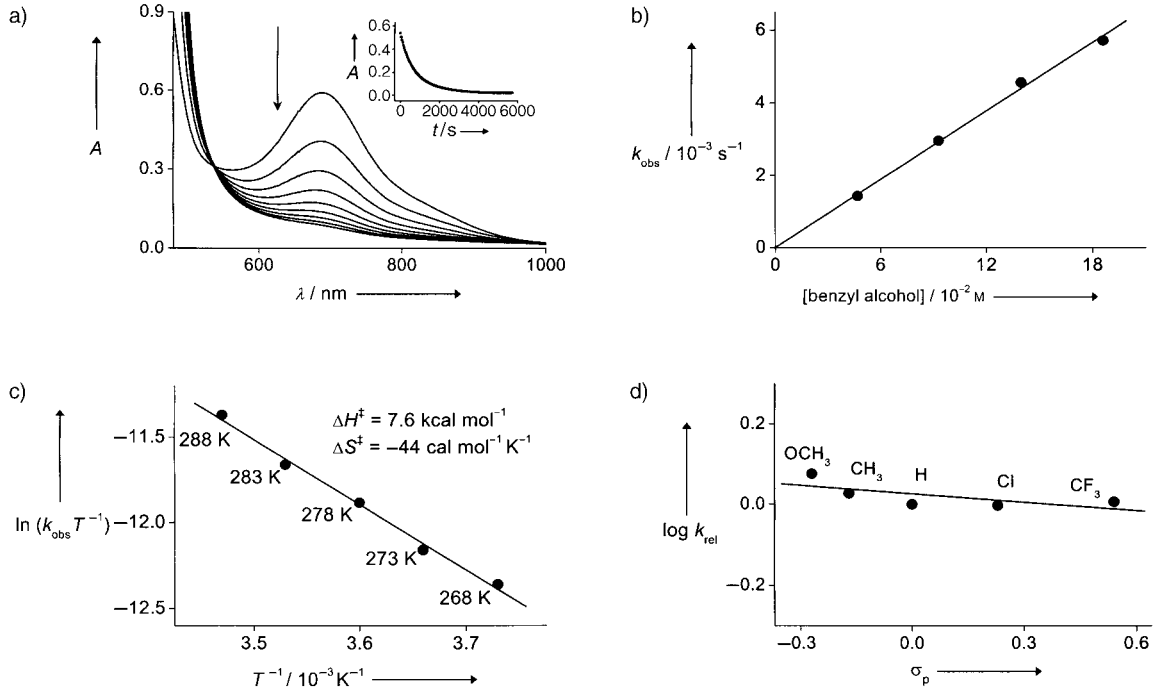
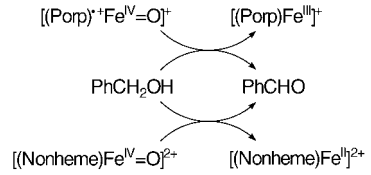


Figure 1. Reactions of **1d** with benzyl alcohols at 0 °C. a) UV/Vis spectral changes of **1d** (2 mM) upon addition of 25 equivalents of benzyl alcohol (50 mM, interval 300 s, A = absorbance). Inset shows absorbance traces monitored at 695 nm. b) Plot of k_{obs} against the concentration of benzyl alcohol to determine a second-order rate constant. c) Plot of first-order rate constants against $1/T$ to determine activation parameters. d) Hammett plot of $\log k_{rel}$ against substituent constants σ_p of benzyl alcohols. The k_{rel} values were calculated by dividing k_{obs} of *para*-X-benzyl alcohol by k_{obs} of benzyl alcohol.

Table 1: Kinetic parameters determined in the oxidation of benzyl alcohol by oxoiron(IV) complexes of heme and nonheme ligands.[a]

Intermediate[b]	T [°C]	k_{obs} [10^{-3} s^{-1}]	k_2 [10^{-1} M^{-1} s^{-1}][c]	$\Delta G^{\neq}$ [kcal mol^{-1}][d]	k_H/k_D[e]	ρ[f]
1a	−100	6.9 ± 0.3	1.7 ± 0.2	11 ± 1	21 ± 3	−0.39
1b	−60	3.5 ± 0.2	0.84 ± 0.03	16 ± 2	> 20 [g]	−0.43
1c	−40	5.5 ± 0.3	1.2 ± 0.1	16 ± 2	58 ± 5	−0.06
1d	0	1.4 ± 0.1	0.31 ± 0.02	20 ± 2	48 ± 4	−0.07

[a] See Supporting Information for detailed reaction procedures. [b] Intermediates were prepared as described in the Supporting Information. [c] k_2 is the second-order rate constant, see Figure 1b and Supporting Information. [d] Data of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are reported in Figure 1c and Supporting Information. [e] Data of k_H and k_D are listed in Supporting Information; k_H is the rate constant obtained with $C_6H_5CH_2OH$, k_D is the rate constant obtained with $C_6D_5CD_2OH$. [f] See Figure 1d and Supporting Information. ρ = Hammett reaction constant. [g] The k_D value was similar to the natural decay of **1b**, which indicates that the k_H/k_D value should be greater than that reported. See the k_D value and the rate of natural decay of **1b** in Supporting Information.

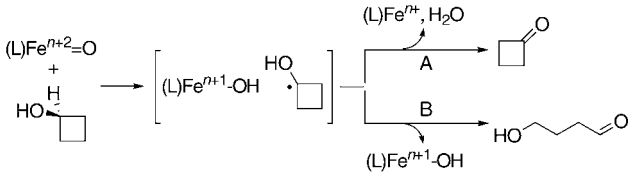


Scheme 2. Oxidation of benzyl alcohol by high-valent iron–oxo complexes of heme and nonheme ligands.

and $\Delta G^{\neq}$) for the benzyl alcohol oxidation with **1** by plotting first-order-rate constants determined at different temperatures against $1/T$ (see Table 1, Figure 1c, and Supporting Information). Taking into consideration that the reactions were performed at different temperatures, we find the kinetic and activation parameters indicate that the relative reactivities of oxoiron(IV) complexes are in the order of **1a** > **1b** > **1c** > **1d**. The greater reactivity of oxoiron(IV) porphyrin π-cation radicals compared to nonheme oxoiron(IV) complexes is rationalized with the higher oxidation state of the iron center in oxoiron(IV) porphyrin π-cation radicals (i.e., the formal oxidation states of Fe^{V} and Fe^{IV} in oxoiron(IV) porphyrin π-cation radical and nonheme oxoiron(IV) species, respectively).[15] In the case of oxoiron(IV) porphyrin π-cation radicals, it has been well documented that the reactivity of electron-deficient iron porphyrins is greater than that of electron-rich iron porphyrins.[16] It has been also shown that the reactivity of nonheme oxoiron(IV) species is dependent on the ligand architecture,[5a–c] and the results presented herein demonstrate that **1c** is more reactive than **1d** in alcohol oxidation.

The kinetics of benzyl alcohol oxidation have also been measured with [D_7]-deuterated benzyl alcohol ($C_6D_5CD_2OH$) to investigate the C–H kinetic isotope effect (KIE). The KIE values determined were large in all of the reactions (see Table 1 and Supporting Information), and such large KIE values have also been observed in GOase[17] and its models[10a,c,18] as well as in the oxidation of benzyl alcohol by high-valent ruthenium-oxo complexes[19] and hydrogen atom abstraction reactions by the iron(IV) intermediates of mono-iron Taurine/α-Ketoglutarate Dioxygenase (TauD)[4b] and diiron methane monooxygenase enzymes.[20] The large, non-classical KIE values indicate that heme and nonheme oxoiron intermediates activate alcohols exclusively by hydrogen atom abstraction from the α-CH of benzyl alcohol and that C–H bond cleavage is the rate-determining step in the alcohol oxidation.[10a,c,17–19] Consistent with this mechanism, studies with *para*-substituted benzyl alcohols reveal that the reaction rates are not greatly influenced by the electron-withdrawing and electron-donating ability of the *para* substituents and that plotting the rates as a function of σ_p of the substituents affords small Hammett ρ values (see Table 1, Figure 1d, and Supporting Information). It is of interest to note that Hammett ρ values obtained in the reactions of GOase and its model compounds are small (e.g., ≈ −0.1)[17,18] and that the Hammett ρ values of synthetic oxoiron(IV) porphyrin π-cation radicals, **1a** and **1b**, are similar to those reported in cytochrome P450 enzymes (e.g., ≈ −0.4).[11]

We then studied cyclobutanol oxidation with the oxoiron(IV) species, as the substrate has been often used as a mechanistic probe to distinguish a one-electron versus a two-electron process in alcohol oxidation by high-valent transition-metal oxidants.[21] For example, if cyclobutanone is produced predominantly, then the reaction occurs by hydrogen atom abstraction followed by an electron transfer (i.e., a two-electron process, see Scheme 3, pathway A). If a carbon

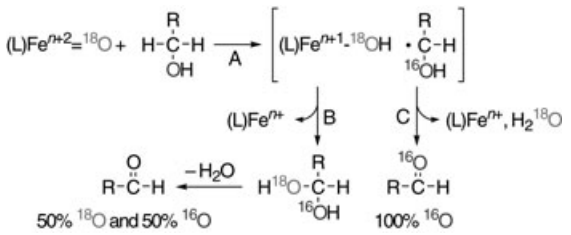


Scheme 3. Oxidation of cyclobutanol by heme and nonheme oxoiron(IV) complexes.

radical formed by hydrogen atom abstraction of cyclobutanol escapes from the solvent cage, a ring-opened product, 4-hydroxybutyraldehyde, is formed (Scheme 3, pathway B).[21a] In the present study, when the oxidation of cyclobutanol was carried out with two oxoiron(IV) complexes, **1a** and **1c**, we found that cyclobutanone was formed exclusively (80–90% yields; see Supporting Information), thus demonstrating that the alcohol oxidation by heme and nonheme oxoiron(IV) complexes proceeds by a two-electron process (Scheme 3, pathway A). A similar observation was reported in the oxidation of cyclobutanol by $Fe^{IV}O^{2+}$ in aqueous solution.[21a]

Finally, the oxidation of benzyl alcohol was carried out with an ^{18}O-labeled oxoiron(IV) complex, [(N4Py)Fe^{IV}=^{18}O]$^{2+}$ ([^{18}O]**1d**), to understand whether the final step of the alcohol oxidation is the dehydration of a *gem*-diol intermediate or hydride transfer in the solvent cage to yield a carbonyl

product (Scheme 4). We therefore prepared [^{18}O]**1d** by treating [(N4Py)Fe^{IV}=O]$^{2+}$ with $H_2{}^{18}O$ and checked the percentage of the ^{18}O isotope in [^{18}O]**1d** with electrospray ionization mass spectrometry (80% ^{18}O in [^{18}O]**1d**, see



Scheme 4. Proposed mechanism for the oxidation of alcohol by heme and nonheme oxoiron(IV) complexes.

Supporting Information).[22] Upon addition of 25 equivalents of benzyl alcohol to the solution of [^{18}O]**1d**, the intermediate reverted back to the starting [Fe^{II}(N4Py)]$^{2+}$, and product analysis with GC–MS revealed that ca. 5% of the oxygen in the benzaldehyde product derived from the oxoiron(IV) species. A control experiment, carried out by incubating benzaldehyde in $H_2{}^{18}O$ under the identical conditions, showed ca. 6% incorporation of the ^{18}O isotope from $H_2{}^{18}O$ in benzaldehyde due to solvent exchange. Based on the observation that the oxygen atom in the aldehyde product does not derive from the oxoiron(IV) complex, we conclude that the benzaldehyde product is formed by hydride transfer (Scheme 4, pathway C), not by a *gem*-diol dehydration (Scheme 4, pathway B).[21a,23]

In summary, we have reported the first example of alcohol oxidation by mononuclear nonheme oxoiron(IV) complexes. We have also reported mechanistic details of alcohol oxidation that have been investigated with in situ generated high-valent iron–oxo complexes of heme and nonheme ligands. The reactivity of heme and nonheme oxoiron(IV) complexes has been briefly compared as well. Finally, we have proposed a plausible mechanism for alcohol oxidation by heme and nonheme oxoiron(IV) intermediates, in which the oxidation of alcohols occurs by an α-CH hydrogen atom abstraction followed by electron transfer (Scheme 4, pathways A and C).

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[14] Abbreviations used: tdcpp = *meso*-tetrakis(2,6-dichlorophenyl)-porphinato dianion, tmp = *meso*-tetramesitylporphinato dianion, N4Py = *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine, tpa = tris(2-pyridylmethyl)amine.

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