



Alkane hydroxylation catalyzed by a series of mononuclear nonheme iron complexes containing 4-nitropyridine ligands

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ABSTRACT

We have prepared a series of mononuclear nonheme iron(II) complexes supported by TPA (TPA = tris(2-pyridylmethyl)amine) and its derivatives that have one to three nitro-groups at 4-position of the pyridine ligand, and evaluated the effect of the nitro-groups on the catalytic oxidation activity of these complexes. The introduction of nitro-group to the TPA ligand proved to decrease the product yield of cyclohexane oxidation with hydrogen peroxide as well as the product ratio of alcohol to ketone. During the catalytic reaction, a significant amount of Fe(II) species exists in cases of nitro-substituted complexes, while the parent Fe-TPA complex was rapidly oxidized to Fe(III) state. These results suggest that the introduction of nitro-groups prevents from the generation of *cis*-oxo-hydroxo-iron(V) species, but induces homolysis of the Fe–O bond of Fe(III)OOH species to initiate radical oxidation of cyclohexane.

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1. Introduction

Mononuclear nonheme iron enzymes catalyze the selective oxidation of unactivated organic substrate under ambient conditions [1], most of which are still rather difficult tasks for man-made catalysts. For example, naphthalene dioxygenase is able to perform *cis*-dihydroxylation of the aromatic ring of naphthalene [2], but such a type of oxidation reactions has never been archived by any catalysts and oxidants. To mimic the oxidation ability of these enzymes, a number of nonheme iron complexes have been synthesized and examined as catalysts for oxidation reactions [3–5]. One of intriguing successes is *cis*-dihydroxylation of alkenes catalyzed by Fe-TPA complex (TPA = tris(2-pyridylmethyl)amine), which was discovered by Que and co-workers in 1999 [6]. Their mechanistic and theoretical studies indicated the involvement of *cis*-oxo-hydroxo-iron(V) species as an oxidant for *cis*-dihydroxylation [7–11]. The same system, i.e., the reaction with hydrogen peroxide catalyzed by Fe-TPA complex, was also applied for alkane hydroxylation [12–14]. Although the turnover number was moderate, the reaction took place through hydrogen atom abstraction by a metal-based oxidant, *cis*-oxo-hydroxo-iron(V) species. In this study, we focused on the effect of substituent groups on the TPA ligand on the catalytic alkane hydroxylation, since modification of the electronic structure of *cis*-oxo-hydroxo-iron(V) species should make a great impact on the catalytic activity in alkane hydroxylation. Very

recently, a theoretical study, that supports our idea, was reported by Ma and Balubuena [15]. In this report, they have proposed that the reactivity of *cis*-oxo-hydroxo-iron(V) species for the hydrogen atom abstraction could be enhanced by introducing electron-withdrawing groups to the aromatic rings of TPA. Enhancement of oxidation power of the active species might enable us to oxidize substrates otherwise difficult to be oxidized, such as methane.

Herein, we have synthesized a series of iron(II) complexes (Fig. 1, 1–4) supported by TPA and nitro-substituted TPA ligands, and evaluated how the introduction of nitro-groups to TPA ligand affects the catalytic activity of 1–4 in cyclohexane oxidation with hydrogen peroxide. The introduction of nitro-groups at 4-position of the pyridine ligand of TPA has an advantage in being able to modulate only electronic, but not steric factors that should control the reactivity of metal complexes [16–21].

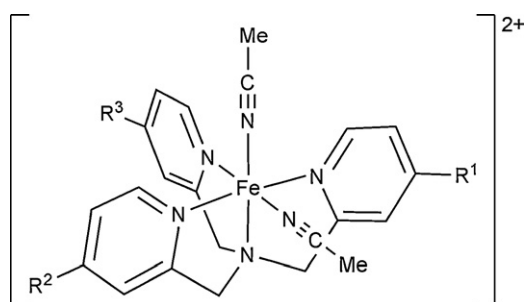
2. Characterization of a series of iron(II) complexes

TPA and TPA derivatives with one and two nitro-groups were synthesized according to published procedures [17]. Tris(4-nitro-pyridin-2-ylmethyl)amine was readily obtained by coupling 2-(chloromethyl)-4-nitropyridine and 2-(aminomethyl)-4-nitropyridine.

Complexation of the ligand with Fe(ClO₄)₂ in MeCN gave the corresponding complexes 1–4 as a crystalline solid in high yield. These complexes can be formulated as [Fe^{II}(L)(CH₃CN)₂](ClO₄)₂. The NMR spectra of 1–4 in MeCN-*d*₃ at 298 K show proton signals at a range of 4–12, indicating that these complexes predominantly have a diamagnetic low spin ferrous ion [18,23] (Fig. S1).

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- 1:** $R^1 = \text{H}$, $R^2 = \text{H}$, $R^3 = \text{H}$
2: $R^1 = \text{NO}_2$, $R^2 = \text{H}$, $R^3 = \text{H}$
3: $R^1 = \text{NO}_2$, $R^2 = \text{NO}_2$, $R^3 = \text{H}$
4: $R^1 = \text{NO}_2$, $R^2 = \text{NO}_2$, $R^3 = \text{NO}_2$

Fig. 1. Structure of the cations of 1–4.

UV–vis spectra of **2** and **3** in MeCN show two intense broad bands, while one intense broad band was observed for **1** and **4** (Fig. S2). As listed in Table 1, the broad bands could be categorized into two classes; lower energy band at around 490 nm and higher energy at around 350 nm. The former is due to charge transfer from iron(II) to a low-lying π^* orbital of 4-nitropyridine ligand, and the latter is assignable to the charge transfer from iron(II) to a low-lying π^* orbital of pyridine ligand, which has been observed for other iron(II) complexes supported by pyridine-based ligands [22–27].

Cyclic voltammetry shows a reversible oxidation corresponding to the $\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$ couple for complexes 1–4. The oxidation potentials successively increased on going from **1** to **4** (**1**: 1.00 V; **2**: 1.12 V; **3**: 1.22 V; **4**: 1.32 V vs. NHE in MeCN).

3. Catalytic oxidation

The catalytic activities of 1–4 in cyclohexane oxidation was evaluated by the following procedure: to a vigorously stirred solution containing the ferrous complex and 1000 equiv. of cyclohexane in MeCN was slowly supplied 30 equiv. of hydrogen peroxide by using a syringe pump over 90 min at room temperature. Samples for GC analysis were taken periodically to determine the time course of the oxidation of cyclohexane. In all the cases, an induction period was observed up to 10 min, and the oxidized products then increased almost linearly until 90 min, at which time the supply of hydrogen peroxide was ended (Fig. 2). The reaction mixture contained considerable amounts of the corresponding alcohol and ketone, but the total yields were decreased on going from **1** to **4**. Table 2 shows the yields of cyclohexanol and cyclohexanone with respect to hydrogen peroxide at 90 min. Interestingly, the alcohol/ketone (A/K) ratios shows the highest value of 11 for **2**, which is rather higher even compared with ever reported mononuclear nonheme iron catalysts

Table 1
MLCT bands of 1–4 in MeCN at 298 K^a

Complex	Higher energy MLCT band (nm)	Lower energy MLCT band (nm)
1	398 (7040), 370 sh (6350)	–
2	359 (4431)	493 (3972)
3	336 (2828)	489 (7389)
4	–	486 (9656)

^a In parentheses, molar absorption coefficient is expressed in $\text{M}^{-1} \text{cm}^{-1}$.

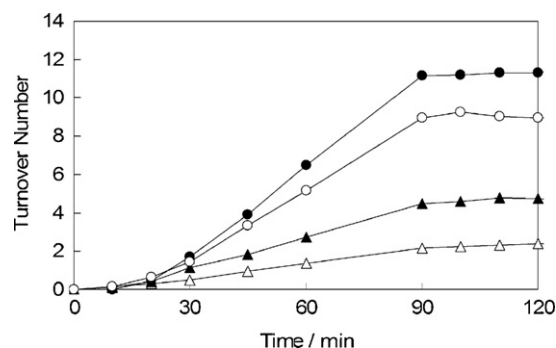


Fig. 2. Time course of the product formation in cyclohexane oxidation catalyzed by 1–4. The supply of hydrogen peroxide was stopped at 90 min (filled circle: **1**, open circle: **2**, filled triangle: **3**, open triangle: **4**).

[4], while **3** and **4** show the A/K values close to 1. The results indicate the involvement of radical oxidants for the cyclohexane oxidation in the presence of **3** and **4**.

To gain more insights into the catalytic oxidation, we monitored the UV–vis spectral changes of 1–4 under the aforementioned catalytic conditions. Fig. 3a shows the UV–vis spectral changes of **1**. The $\text{Fe}(\text{II})$ -to-pyridine MLCT band at 398 nm rapidly disappeared, and the spectrum of **1** was converted to that of $\text{Fe}(\text{III})$ -TPA species [28]. The spectral change clearly demonstrated that an oxidation from $\text{Fe}(\text{II})$ to $\text{Fe}(\text{III})$ took place within 3 min, which corresponds to the observed induction period of product formation.

In contrast to complex **1**, complexes **2–4** showed only a slight to moderate decrease of the corresponding MLCT bands (Fig. 3b–d), whose extent became larger as the number of nitro-groups increased. Thus, **2–4** retained the $\text{Fe}(\text{II})$ state even during the catalytic reaction. Since the iron(III) species is prerequisite to the formation of *cis*-oxo-hydroxo-iron(V) oxidizing species [29], it is conclusive that the decrease in the product yields on going from **1** to **4** should be caused mainly by the ineffective conversion to the iron(III) species. The preference of the iron(II) state of nitro-substituted complexes is in agreement with their high oxidation potentials.

4. Proposed reaction cycle

There are two possible mechanisms that can account for the ineffective formation of iron(III) species during the oxidation reaction catalyzed by **2–4**: one is slow-down of the reaction rate of $\text{Fe}(\text{II})$ complex with hydrogen peroxide due to the high oxidation potentials of **2–4**. As shown in Fig. 2, however, the oxidation reaction was ceased as the supply of hydrogen peroxide was stopped in all the cases. This result suggests that complexes **2–4** have a considerable reactivity with hydrogen peroxide, like complex **1**. The other possible mechanism is regeneration of $\text{Fe}(\text{II})$ species by hydrogen peroxide. To explore this possibility, we added hydrogen peroxide to the solution of **4** after the catalytic reaction, and observed a growth of the MLCT band at around 490 nm, indicating regeneration of ferrous complex **4** (Fig. 4). ESI–mass measurements verified the for-

Table 2
Product yields and A/K ratios in cyclohexane oxidation catalyzed by 1–4

Complex	Cyclohexane (%) ^a	Cyclohexanol (%) ^a	A/K ratio
1	32	5.3	6.0
2	27	2.6	11
3	12	2.5	4.9
4	4.6	2.6	1.8

^a Yield at 90 min, with respect to the total hydrogen peroxide.

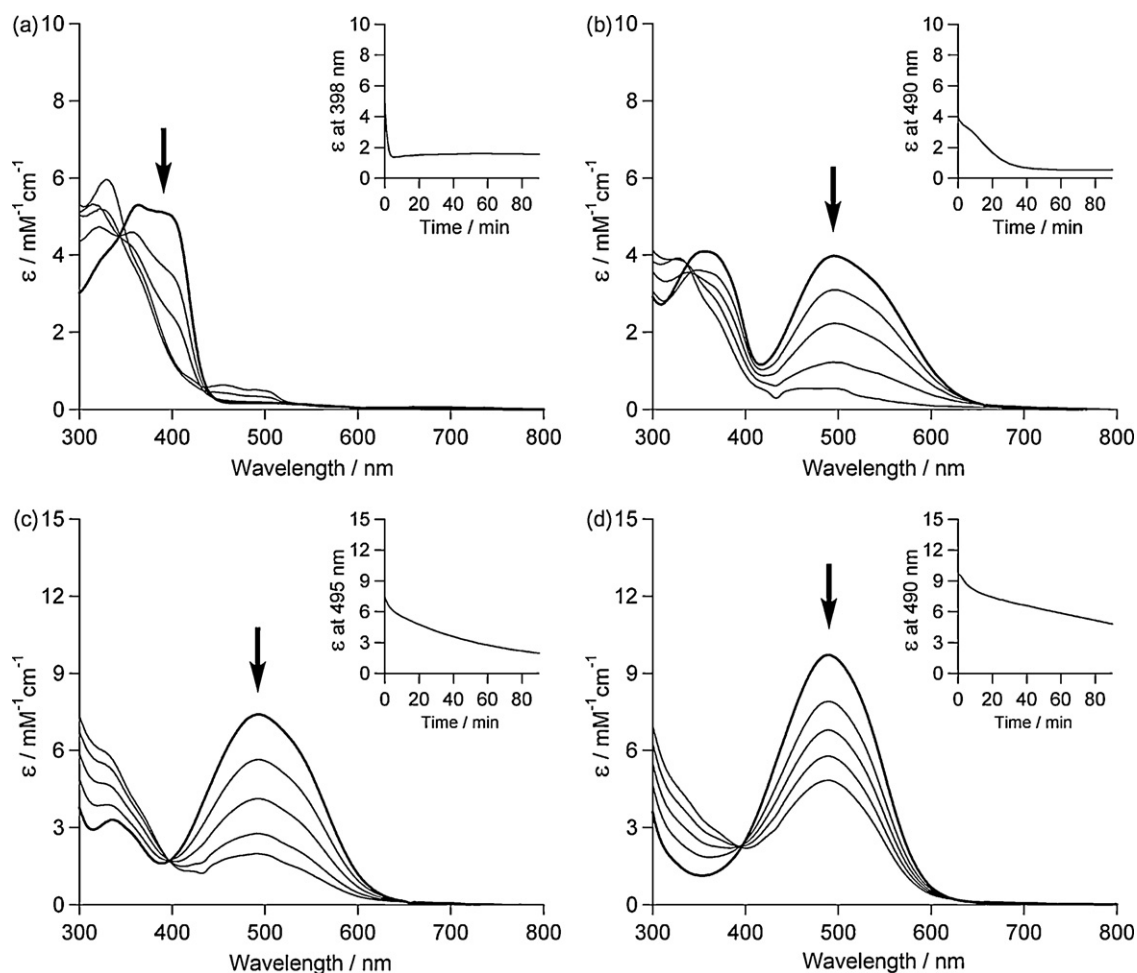


Fig. 3. UV-vis spectral changes of **1–4** during the catalytic reaction: (a) **1**, (b) **2**, (c) **3** and (d) **4**.

mation of ferrous complex **4** as major species, together with a small amount of Fe(III)OOH species (Fig. S3). The formation of ferrous complex **4** might be through homolytic dissociation of the Fe–O bond of Fe(III)OOH species, which should also produce hydroperoxo radical. Such reduction of metal center by hydrogen peroxide was observed for Cu(II) complexes, especially when the metal center is supported by ligands that stabilize Cu(I) state [30,31]. Scheme 1

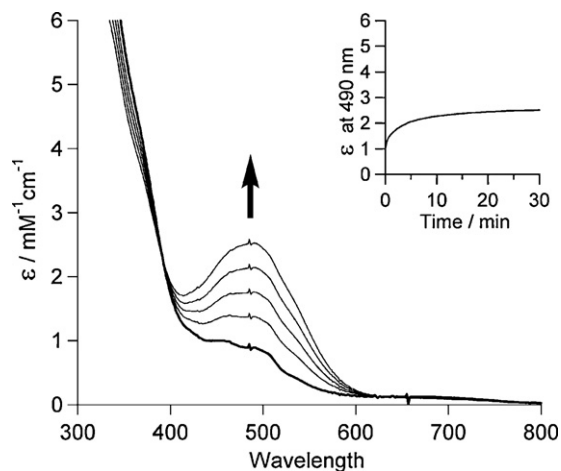
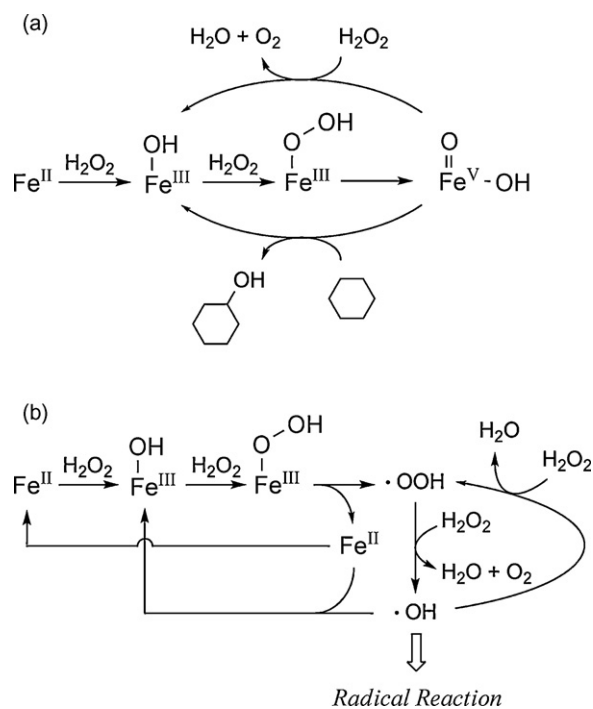


Fig. 4. UV-vis spectral changes upon addition of 10 equiv. of hydrogen peroxide to the solution of **4** after the catalytic reaction.



Scheme 1. Proposed catalytic cycles of cyclohexane oxidation catalyzed by **1** (a) and **4** (b).

depicted a possible catalytic reaction cycle of complex **4**, together with that for **1** [29,32,33]. The OH radical in the cycle for **4** would give an explanation for the observed A/K ratio close to 1.

5. Conclusions

A number of mononuclear nonheme iron complexes have been prepared and examined as catalysts for alkane hydroxylation with hydrogen peroxide [4,5,22,31], but there is no systematic exploration on the effects of the electronic structures of these catalysts on their catalytic oxidation activity. In this study, we have prepared a series of mononuclear nonheme iron(II) complexes supported by TPA and its nitro-derivatives, and evaluated the effect of the nitro-groups on the catalytic oxidation activity. The introduction of nitro-group to the TPA ligand proved to lower the product yields as well as A/K ratio. During the catalytic oxidation, a significant amount of Fe(II) species is present in the cases of nitro-substituted complexes, while the unsubstituted Fe-TPA complex was rapidly oxidized to Fe(III) state. Theoretical calculations predicted that introducing nitro-groups should facilitate H-atom abstraction from alkane by *cis*-oxo-hydroxo-iron(V) species [15], but our experimental study demonstrated that such energetically unfavorable species cannot be obtained by the reaction with hydrogen peroxide. In fact, it induces homolysis of the Fe–O bond of Fe(III)OOH to afford Fe(II) and hydroperoxide radical. The A/K ratio of **3** and **4** decreases dramatically to reach 1, which should be caused by the radical [32,33].

6. Experimental

6.1. Synthesis of tris(4-nitro-pyridin-2-ylmethyl)amine

To a stirred mixture of 2-chloromethyl-4-nitropyridine (0.66 g, 3.8 mmol) and 2-aminomethyl-4-nitropyridine dihydrochloride (0.54 g, 1.9 mmol) in water (1 mL) was slowly added 5.0 N NaOH (2.0 mL, 10 mmol). The reaction mixture was stirred at 0 °C for 4 days. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ several times. The combined organic layers were dried over Na₂SO₄, and volatile components were removed. Purification of the product on an alumina column (8:1 CH₂Cl₂/AcOEt) gave a yellow solid of tris(4-nitro-pyridin-2-ylmethyl)amine (0.26 g, yield 32%); ¹H NMR(400 MHz, CDCl₃): 8.78 (3H, d, *J* = 5.5 Hz), 8.22 (3H, d, *J* = 1.8 Hz), 7.85 (3H, dd, *J* = 5.4 Hz, *J*' = 2.3 Hz), 4.11 (6H, s); ¹³C NMR (CDCl₃, 99.5 MHz): 163.7, 155.5, 152.4, 116.6, 115.7 and 60.9.

6.2. Synthesis of Fe-TPA and nitro-derivatives

Typical procedure: to a stirred solution of Fe(ClO₄)₂·nH₂O (0.109 g, 0.30 mmol) in MeCN was added a solution of TPA or TPA derivatives (0.3 mmol) in MeCN under N₂. The reaction mixture was stirred for 30 min. The solid was obtained by diffusion of diethyl ether into the MeCN solution.

[Fe(TPA)(MeCN)₂](ClO₄)₂ (**1**): ¹H NMR(400 MHz, CD₃CN): 11.19 (3H, s, H_α(Py)), 8.66 (3H, s, H_β'/β(Py)), 8.57 (3H, s, H_β''/β''(Py)), 7.26 (3H, t, *J* = 7.7 Hz, H_γ(Py)), 6.57 (6H, s, H_{Me}). ESI-MS: *m/z* 193.5 ([Fe^{II}(TPA)(CH₃CN)]²⁺).

[Fe(monoNO₂-TPA)(MeCN)₂](ClO₄)₂ (**2**): ¹H NMR(400 MHz, CD₃CN): 10.41 (1H, br s, H_α(NO₂-Py)), 10.02 (2H, br s, H_α(Py)), 8.63 (1H, s, H_β'/β(NO₂-Py)), 8.55 (1H, br s, H_β''/β''(NO₂-Py)), 8.02–8.00 (4H, br m, H_β+β'(Py)), 7.54 (2H, t, *J* = 7.7 Hz, H_γ(Py)), 5.76 (2H, s, H_{NO₂-Me}), 5.70 (2H, d, *J* = 16.6 Hz, H_{Me}), 5.40 (2H, d, *J* = 16.6 Hz, H_{Me}). ESI-MS: *m/z* 216.6 ([Fe(monoNO₂-TPA)(CH₃CN)]²⁺).

[Fe(diNO₂-TPA)(MeCN)₂](ClO₄)₂ (**3**): ¹H NMR(400 MHz, CD₃CN): 9.93 (2H, br d, *J* = 4.0 Hz, H_α(NO₂-Py)), 9.95 (1H, br s, H_α(Py)),

8.40 (2H, s, H_β'/β(NO₂-Py)), 8.35 (2H, br d, *J* = 4.0 Hz, H_β''/β''(NO₂-Py)), 7.77–7.78 (2H, br m, H_β+β'(Py)), 7.68 (1H, t, *J* = 7.7 Hz, H_γ(Py)), 5.43 (2H, d, *J* = 17.4 Hz, H_{Me}), 5.20 (2H, d, *J* = 17.4 Hz, H_{Me}), 5.18 (2H, s, H_{NO₂-Me}). ESI-MS: *m/z* 259.2 ([Fe(diNO₂-TPA)(MeCN)₂]²⁺).

[Fe(triNO₂-TPA)(MeCN)₂](ClO₄)₂ (**4**): ¹H NMR(400 MHz, CD₃CN): 9.68 (3H, br d, *J* = 5.1 Hz, H_α(NO₂-Py)), 9.95 (3H, br s, H_α(Py)), 8.30 (3H, s, H_β'/β(NO₂-Py)), 8.26 (3H, br d, *J* = 4.0 Hz, H_β''/β''(NO₂-Py)), 5.20 (3H, d, *J* = 17.4 Hz, H_{Me}). ESI-MS: *m/z* 281.9 ([Fe(triNO₂-TPA)(MeCN)₂]²⁺).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2008.03.021.

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