Catalytic hydroxylation of alkanes by immobilized mononuclear iron carboxylate

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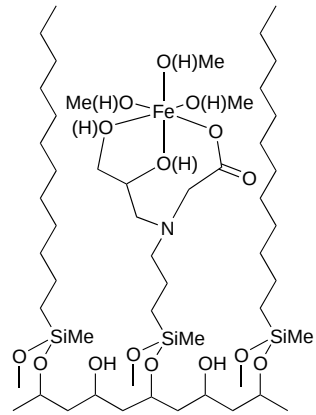
Mononuclear iron carboxylate complex immobilized and isolated on a modified silica surface (1) catalyzes oxidation of hexane to a mixture of hexan-1-ol, -2-ol and -3-ol without ketone formation in the presence of mercaptan, acetic acid, triphenylphosphine and O_2 at ambient conditions.

Biomimetic oxidation studies on non-heme iron enzymes have been extensively reported for the direct hydroxylation of saturated hydrocarbons at ambient conditions.[1,2] Most of the efforts have been focused on the modeling of dinuclear iron complexes, because of the structural correspondence to the active site of methane monooxygenase (MMO). In this report we describe a novel catalytic oxidation yielding only alcohols from alkanes by mononuclear iron carboxylate complex immobilized and isolated on a modified silica surface (**1**) in the presence of mercaptan (propane-1,3-dithiol, PDT), acetic acid (AcOH), triphenylphosphine (PPh_3) and O_2.

For the effective catalytic turnover, it was necessary to protect the complex against decomposition. Immobilization and isolation on an amorphous silica powder (Aerosil 200, specific surface area = 200 $m^2\ g^{-1}$) was employed for this purpose. A dilute solution of masked ligand, isopropylidene ketal and *tert*-butyl ester of 3-[*N*-(2,3-dihydroxypropyl)-*N*-carboxymethyl]-aminopropylmethylsilyl group,† was first anchored on the surface and the remnant silanols were subsequently blocked by diethoxydodecylmethylsilane. Removal of the protecting groups resulted in the attachment of highly dispersed ligands at a concentration of 4.8×10^{-2} mmol g^{-1} (3.2% of total silanols) as quantified by the measurement of nitrogen content. Loaded dodecylmethylsilyl groups, 3.75×10^{-1} mmol g^{-1} based on carbon content, were estimated to cover 25.3% of total silanols. The high coverage implies that long alkylsilyl groups are tightly packed in the cylindroid arrangement on the surface.[3]

Complexation in 2.5 mM $Fe(NO_3)_3$–methanol, followed by thorough washing with methanol yielded immobilization of 4.3×10^{-2} mmol g^{-1} iron (determined colorimetrically) which occupied 90% of the ligands previously anchored. The formation of complex was confirmed by the appearance of asymmetric CO vibration at 1570 cm^{-1} and a decrease in the signal representing free carboxyl groups at 1715 cm^{-1} with FTIR. Taking into account the remainder of a trace amount of ester (1740 cm^{-1}), the complexation seemed to be accomplished in almost quantitative yield. In addition treatment of the white powder in 200 mM HCl–dioxane gave three methanol molecules per iron, while the elemental analysis did not show the presence of nitrogen derived from NO_3. The EPR spectrum revealed a broad signal at $g = 4.2$ which was assigned to a high spin mononuclear iron(III). We thus propose the structure shown in Scheme 1 for synthesized complex **1**.

Oxidation of alkanes was carried out in an acetonitrile solution as described in Table 1. No oxidation took place if either O_2 or PDT was omitted. In the presence of PDT alone or AcOH/PDT without PPh_3, hexane was not oxidized, but cyclohexane yielded a trace of cyclohexanol. By contrast, assay containing PPh_3 remarkably improved the reaction. Without AcOH, conversion was low, but in the complete system, hexane was selectively oxidized to hexanols with a total turnover number of 59 in the ratio of 1-ol (14%), 2-ol (44%) and 3-ol (42%). Similarly cyclohexane was converted to cyclohexanol alone with a turnover of 109. Catalyst recovered by acetonitrile washing after the assay showed a slight decrease in iron content,‡ but there was no change in the hydroxylation activity. The catalytic turnover is evidently due to the immobilized mononuclear iron carboxylate. Recovered catalyst, however, showed an iron : methanol molar ratio of 1 : 1 which differed from the original 1 : 3. Since this phenomenon was not observed in the catalyst recovered from an anaerobic assay, the change in the iron environment can be accounted for through the



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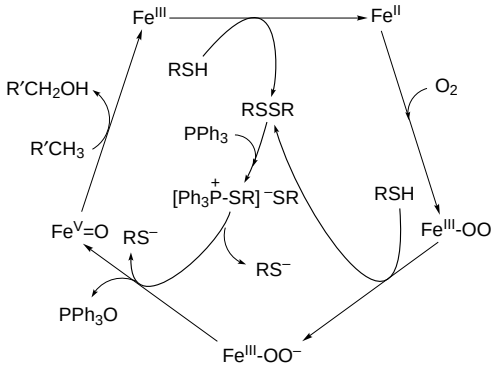
Scheme 1 Proposed structure for immobilized iron carboxylate

Table 1 Hydroxylation of alkanes by immobilized mononuclear iron carboxylate (**1**)[a]

Run	Substrate	Additives	Products (yield)[b]	Total yield
1	Hexane	PDT, PPh_3	1-ol (1.0), 2-ol (1.7), 3-ol (1.4)	4.1
2	Hexane	AcOH, PDT, PPh_3	1-ol (8.1), 2-ol (26.0), 3-ol (25.3)	59.4
3[c]	Hexane	AcOH, PDT, PPh_3	1-ol (8.3), 2-ol (25.5), 3-ol (24.8)	58.6
4	Cyclohexane	PDT, PPh_3	Cyclohexanol (10.0)	10.0
5	Cyclohexane	AcOH, PDT, PPh_3	Cyclohexanol (109.2)	109.2

[a] Catalyst (0.5 μmol iron), substrate (3.5 mmol), AcOH (0.25 mmol), PDT (0.25 mmol), PPh_3 (0.25 mmol) were placed into a 20 ml vial containing acetonitrile (2.6 ml) and sealed with a Teflon septum. After replacing the gas phase by O_2, the vial was shaken at 180 strokes min^{-1} and 25 °C for 4 h using a Bioshaker. [b] Moles of product per mole of iron. [c] Catalyst recovered from the assay scaled up tenfold was used.



Scheme 2 Hypothetical catalytic cycle of immobilized mononuclear iron carboxylate (**1**) for alkane hydroxylation

participation of oxygen during the catalytic cycle. After release of oxygen, acetonitrile may serve as alternative ligands.

When oxidation was carried out without substrate, PPh_3 was converted to PPh_3O with a turnover number of 136. Also we can not rule out unavoidable oxidation of the alkane chains adjacent to the active center in **1**, considering the strong oxidative capability toward primary C–H. Such competitive oxidation explains the rapid consumption of PPh_3 causing unexpected termination of the catalytic turnover as well as the requirement of high concentration of substrate for effective hydroxylation in our system.

A hypothetical mechanism for this notable catalytic hydroxylation is illustrated in Scheme 2. The reduction of Fe^{III} to Fe^{II} by mercaptan initiates the reaction. Mercaptan consumed at this stage is converted to alkyl disulfide which is subsequently attacked by the PPh_3 nucleophile to form thioalkoxyphosphonium cation intermediate.[4] Since the intermediate is known to be readily trapped by a carboxylic acid in refluxing acetonitrile to yield mercaptan, thioester and PPh_3O,[5] a similar reaction could be possible in the presence of AcOH. On the other hand, the assay using $^{18}O_2$ demonstrated almost quantitative ^{18}O incorporation into both PPh_3O and hexanols regardless of the AcOH addition. Accordingly the intermediate is directly attacked by a dioxygen– metal adduct, presumably a peroxoiron species, to release PPh_3O. The resulting O–O bond scission is thought to allow the generation of an iron–oxo species from which oxygen is transferred to the substrate. The role of AcOH is therefore assumed to protonate the thiolate anion and promote its dissociation from the intermediate ion pair.

The participation of PPh_3 in the O–O bond cleavage is similar to that of acylating reagents in cytochrome P450 model studies.[6] In fact we could detect the same hexanols in the hydroxylation of hexane using **1**, KO_2–18-crown-6 and acetic anhydride in benzene although the yield was low (total turnover number = 0.12). Furthermore [tetrakis(pentafluorophenyl)porphyrinate] iron(III) hydroxide instead of **1** oxidized hexane to only hexanols in comparable product yield and distribution in our system. The results again support the formation of a high-valent iron–oxo species being responsible for the hydroxylation of alkanes by **1**.

Interestingly a hydroperoxoiron(III) species was identified by EPR spectroscopy at 77 K (g = 2.27, 2.20, 1.97)[7] when the porphyrin iron complex was reduced with an equivalent of PDT and then exposed to O_2. Addition of H_2O_2 gave an identical EPR signal. The same intermediate has been reported in the model studies of bleomycin with mononuclear iron coordinating nitrogen ligands.[8] By contrast this phenomenon was not found in the investigation using **1**, and there was no effect of the intermediate on the hydroxylation of alkanes even with the addition of PPh_3 or AcOH–PPh_3. The fact may reflect a characteristic nature of the iron complex with oxygen-rich ligands involving carboxylate different from those bearing a porphyrin or nitrogen ligands.

It now appears that mononuclear iron carboxylate can catalyze highly selective hydroxylation of alkanes by reductive dioxygen activation. The key reaction is assumed to be the efficient heterolytic scission of the O–O bond by the PPh_3 participated deoxygenation. However, regarding the generation of putatively unstable Fe^{V}=O species in a mononuclear iron core, there is an argument against delocalization of the oxidizing equivalents.[2] This point contrasts to a Fe^{IV}=O dinuclear cluster which has been reported recently as the critical intermediate of MMO.[9] The results obtained in this work could be attributed to unique properties of the complex with predominantly oxygen ligation in a hydrophobic microenvironment analogous to the active site of an enzyme buried in a protein matrix.

Footnotes and References

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† Ligand was prepared from 3-aminopropyldiethoxymethylsilane *via* 2 steps: (a) condensation with 2,2-dimethyl-4-chloromethyl-1,3-dioxolan at 220 °C; (b) treatment with chloroacetic acid *tert*-butyl ester in acetonitrile at 50 °C in the presence of triethylamine, followed by extraction with hexane and purification using an activated carbon column. Purity was checked by GC, GCMS and NMR spectroscopy.

‡ Iron content of the recovered catalyst after hexane oxidation was 3.7×10^{-2} mmol g^{-1} (86% of the initial catalyst).

1 J. B. Vincent, J. C. Huffman, G. Christou, Q. Li, M. A. Nancy, D. N. Hendrickson, R. H. Fong and R. H. Fish, *J. Am. Chem. Soc.*, 1988, **110**, 6898; R. M. Buchanan, S. Chen, J. F. Richardson, M. Bressan, L. Forti, A. Morvillo and R. H. Fish, *Inorg. Chem.*, 1994, **33**, 3208; A. L. Feig and S. J. Lippard, *Chem. Rev.*, 1994, **94**, 759; A. L. Nivorozhkin and J.-J. Girerd, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 609; B. J. Wallar and J. D. Lipscomb, *Chem. Rev.*, 1996, **96**, 2625.
2 L. Que, Jr. and R. Y. N. Ho, *Chem. Rev.*, 1996, **96**, 2607.
3 D. W. Sindorf and G. E. Maciel, *J. Phys. Chem.*, 1982, **86**, 5208; K. Miki and Y. Sato, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 2385.
4 L. E. Overman and E. M. O'Connor, *J. Am. Chem. Soc.*, 1976, **98**, 771.
5 T. Mukaiyama, *Angew. Chem.*, 1976, **88**, 111.
6 J. T. Groves, Y. Watanabe and T. J. McMurry, *J. Am. Chem. Soc.*, 1983, **105**, 4489; A. M. Khenkin and A. A. Shteinman, *J. Chem. Soc., Chem. Commun.*, 1984, 1219.
7 K. Tajima, M. Shigematsu, J. Jinno, K. Ishizu and H. Ohya-Nishiguchi, *J. Chem. Soc., Chem. Commun.*, 1990, 144.
8 R. J. Guajardo and P. K. Mascharak, *Inorg. Chem.*, 1995, **34**, 802; M. Lubben, A. Meetsma, E. C. Wilkinson, B. Feringa and L. Que, Jr., *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1512.
9 L. Shu, J. C. Nesheim, K. Kauffmann, E. Münck, J. D. Lipscomb and L. Que, Jr., *Science*, 1997, **275**, 515.

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