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Selective oxidation of cyclohexane to cyclohexanol catalyzed by a μ-hydroxo diiron(II) complex and *tert*-butylhydroperoxide

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Received 22nd March 1999, Accepted 13th May 1999

A new μ-hydroxo diiron(II) complex $[Fe_2L(OH)]^{3+}$ obtained with a dinucleating macrocyclic ligand catalyzes the selective oxidation of cyclohexane into cyclohexanol (≈85%) using the controlled addition of *tert*-butylhydroperoxide.

Functional modeling of the soluble methane monooxygenase (MMO) enzyme,[1] which contains a dinuclear non-heme iron center, has provided new catalysts for the oxidation of alkanes using hydroperoxide oxidants. The most efficient models are μ-oxo dinuclear iron(III) complexes with bidentate (bipyridine, bpy) or tetradentate [tris(2-pyridylmethyl)amine, TPA] pyridine-type and exchangeable μ-acetato or terminal aqua ligands.[2] *tert*-Butylhydroperoxide (TBHP), widely used in oxidation reactions, has proved to be the most useful oxidant in association with these catalysts. Mixtures of alcohol, ketone and dialkyl peroxide are obtained in agreement with autoxidation reactions involving alkoxyl- or alkyl-radicals and O_2. Here, we report that a μ-hydroxo diiron(II) complex of a dinucleating macrocyclic ligand, a good MMO model, is an efficient catalyst for cyclohexane oxidation with TBHP as oxidant. Moreover, selective oxidation of cyclohexane to cyclohexanol was achieved using a controlled addition of TBHP *via* a syringe-pump as shown recently by Que and co-workers.[3]

The macrocyclic ligand 1,4,10,13-tetrakis(2-pyridyl)methyl-1,4,10,13-tetraaza-7,16-dioxacyclooctadecane L (Fig. 1), with four pendant 2-pyridylmethyl arms, was synthesized according to a previously reported procedure.[4]

The iron complex $[Fe_2L(OH)][BF_4]_3$ **1** was prepared by adding a deoxygenated methanolic solution (10 ml) of the ligand L (1.6 mmol) to a degassed methanolic solution of $Fe(BF_4)_2{\cdot}6H_2O$ (3.2 mmol). Dropwise addition of deoxygenated diethyl ether allows the precipitation of the complex as a pale yellow powder in 80% yield. Complex **1** can be further recrystallized by slow diffusion of diethyl ether into an acetonitrile solution of the complex.

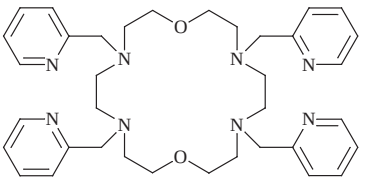

Fig. 1 Schematic representation of the dinucleating ligand L.

Elemental analysis† and electrospray mass spectroscopy support the proposed structure with a hydroxo bridged diiron core. Electrospray ionization mass spectra shown an ion cluster at *m*/*z* 927.2, the mass and isotope patterns of which are consistent with the $[\{Fe_2L(OH)\}(BF_4)_2]^+$ ion. The UV-visible spectrum of **1** is in agreement with the presence of an iron(II) complex.[5] We speculate that the structure of **1** is related to that previously reported for the Mn(II) analogue $[Mn_2L(OH)][ClO_4]_3$ in which the manganese atoms are hexa-coordinated with the ether function completing the coordination sphere.[4] Interestingly, the complex is poorly oxygen sensitive even in acetonitrile solution, as checked by UV-visible spectroscopy. This is also in agreement with hexa-coordinated iron(II) lacking binding sites for O_2 coordination.

We tested the ability of this novel iron(II) complex to catalyze the oxidation of cyclohexane with TBHP as oxidant. Oxidation reactions were carried out in acetonitrile at 25 °C using conventional Schlenk techniques to ensure very efficient deoxygenation when required. Cyclohexane oxidation results are reported in Table 1.

In a typical reaction 0.5 μmol of catalyst was reacted with 0.5 mmol TBHP and 5 mmol cyclohexane in 5 ml acetonitrile. A nearly equimolar mixture of cyclohexanol and cyclohexanone was obtained in 16% yield, corresponding to 160 turnovers in less than 20 minutes. It has to be noted that 85% of the TBHP was consumed (checked by GC titration) revealing the high 'catalase-like' activity of **1** leading to the production of O_2 in the reaction mixture. Increasing the catalyst concentration (5 μmol) led to a 46% yield of oxidation products in 2 minutes. These results are similar to those obtained with the best systems reported so far.[2] Dialkylperoxide is also formed but in smaller amounts than was observed by Que *et al*. with the iron(III) TPA complexes.[2] Addition of another aliquot of TBHP at the end of the reaction did not increase the amount of product suggesting inactivation of the catalyst.

When 10 equiv. of dilute TBHP (50 μmol in 2 ml MeCN)

Table 1 Product distribution in the oxidation of cyclohexane catalyzed by **1** and TBHP

		Products[c]					
Cat[a]	Ox[b]	CyO	CyOH	CyOOtBu	CyBr	Reaction time/min	Yields[d] (%)
0.5	500	26	25	4	—	20	16
5	500	64	54	24	—	5	46
5	50 (sp)	1	14	2	—	60	36
5	50 (sp)[e]	4	4	0	—	60	24
5	50 (sp)[f]	0.4	0.5	0	18.2	60	39

[a] μmol of catalyst. [b] μmol of TBHP, (sp) when added with a syringe-pump. [c] μmol of product. [d] Total yield based on oxidant. The ketone yields are molar yields multiplied by 2 since 2 equivalents of TBHP are required to make one equivalent of ketone. [e] Solutions not degassed. [f] 250 μmol of CCl_3 were added.

were added to a solution of **1** with a syringe-pump over a 1 hour period, selective oxidation (≈85%) of cyclohexane into cyclohexanol occurred in 37% yield. Under the same conditions but in non-degassed solution no selectivity was observed. A selective oxidation of alkane to alcohol could be assigned to a metal centered oxidation reaction expected from a genuine monooxygenase mimic. However, MacFaul and co-workers have clearly shown by using the 2-methyl-1-phenylprop-2-yl hydroperoxide (MPPH) that alcohol oxidation selectivity can be due to freely diffusing alkoxyl radicals.[6] The *tert*-alkoxyl radical formed after homolysis of the MPPH O–O bond undergoes β-scission ($k_\beta \approx 2 \times 10^8$ s^{-1}) too quickly for it to abstract a hydrogen atom from a saturated hydrocarbon. When MPPH (10 equiv. added with a syringe-pump and diluted in 2 ml Me_3CN) is used, no oxidation products are detected, showing that the hydrogen abstracting species with TBHP [eqn. (2)] is the *tert*-butoxyl radical produced from the homolysis of the FeO–OBu^t bond [eqn. (1)].

$$FeOOBu^t \longrightarrow FeO^\bullet + Bu^tO^\bullet \quad (1)$$

$$Bu^tO^\bullet + CyH \longrightarrow Bu^tOH + Cy^\bullet \quad (2)$$

$$Cy^\bullet + O_2 \longrightarrow CyOO^\bullet \longrightarrow \text{alcohol and ketone} \quad (3)$$

$$Cy^\bullet + FeO^\bullet \longrightarrow FeOCy \longrightarrow \text{alcohol} \quad (4)$$

Cy = cyclohexyl

Preliminary, low temperature UV-visible and ESR studies have shown that a transient iron(III) alkylperoxo species is formed in the early stages of the reaction. A blue intermediate, stabilized at −40 °C and generated by the addition of 50 equiv. TBHP in an acetonitrile solution of **1**, displays a broad and intense absorption band at 600 nm. This species has a rhombic ESR signal centered at $g = 2$ (2.15, 1.94), characteristic of low spin iron(III) complexes. This strongly suggests the participation of an iron(III) alkylperoxo intermediate as previously found with the iron–bpy and iron–TPA catalysts.[7]

Addition of a small amount of CCl_3Br (50 equiv., 250 μmol) to a cyclohexane oxidation reaction gave mainly cyclohexyl bromide demonstrating that freely diffusing cycloalkyl radicals are formed during the reaction. These radicals can either: (i) be trapped by O_2 when a large excess of TBHP is used, to produce cyclohexyl peroxy radicals [eqn. (3)] leading to mixtures of alcohol and ketone or (ii) react with FeO$^\bullet$ when the TBHP concentration is very low to produce an iron alkoxy species. The latter pathway leads to alcohol selectively [eqn. (4)].

Complex **1** represents one of the few examples of a MMO mimic able to selectively oxidize cyclohexane to cyclohexanol *via* the well-disguised free radical chemistry recently evidenced by MacFaul *et al.*[6] for the iron–TPA catalysts developed by Que and co-workers.[3] We are currently testing the ability of the diiron(II) complex to perform hydrocarbon oxidations in the presence of other oxidants such as hydrogen peroxide.

Acknowledgements

We are indebted to the CNRS and the Bordeaux 1 University for financial support. We thank Dr. J.-M. Bassat for providing the ESR spectrum of the peroxo intermediate.

Notes and references

† Analytical and spectroscopic data for complex **1**: Found: C, 41.73; H, 5.21; N, 10.60; Fe, 9.51; B, 3.22. Calc. for $C_{38}H_{59}N_8F_{12}Fe_2O_6B_3 \cdot 2CH_3OH \cdot H_2O$: C, 41.65; H, 5.38; N, 10.22; Fe, 10.19; B, 2.96%. λ_{max}/nm (Me_3CN) 365 (ε/dm^3 mol^{-1} cm^{-1} 1230). ^{1}H NMR (250 MHz in CD_3CN) : the spectrum of complex **1** displays broad resonances ranging from δ −40 to 150 in agreement with high spin iron(II) atoms. By comparison with the diiron(II)–TPA complex described by Que *et al.*,[5] the resonances observed at δ 41 and 43 are tentatively attributed to the β-protons of the pyridine ring. A minor species (<10%) is also detected in solution and is assigned to OH ligand exchange by residual water molecules.

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Communication 9/02225B