

## Enhanced selectivity in non-heme iron catalysed oxidation of alkanes with peracids: evidence for involvement of Fe(IV)=O species†

Tieme A. van den Berg, Johannes W. de Boer, Wesley R. Browne, Gerard Roelfes and Ben L. Feringa\*  
Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4,  
9747 AG Groningen, The Netherlands. E-mail: Feringa@chem.rug.nl; Fax: +31 50 3634296;  
Tel: +31 50 3634235

Received (in Cambridge, UK) 5th August 2004, Accepted 14th September 2004  
First published as an Advance Article on the web 14th October 2004

Catalytic alkane oxidation with high selectivity using peracids and an (N4Py)Fe complex is presented and the role of [(N4Py)Fe(IV)=O]<sup>2+</sup> species, molecular oxygen and hydroxyl radicals in the catalysis is discussed.

Achieving both the selectivity and efficiency of non-heme iron systems (e.g., methane monooxygenase (MMO) and bleomycin (BLM)) in the C–H activation of alkanes and alkyl aromatics is an important and challenging goal in transition metal based oxidation catalysis. In an effort to achieve comparable levels of efficiency, ligand design has drawn inspiration from the enzymes both in terms of ligand environment and redox chemistry.<sup>1</sup> In recent years, Fe(II) complexes (e.g., **1a/1b**, see Scheme 1) of pentadentate ligands, e.g. *N,N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine (N4Py),<sup>2</sup> designed as functional mimics of FeBLM, have proven to be excellent catalysts in the oxidation of organic substrates with H<sub>2</sub>O<sub>2</sub>.<sup>3</sup> The mode of action of these catalysts is, however, unclear and in earlier studies we proposed that homolytic cleavage of the iron(III) hydroperoxo complex, leads to formation of the active oxidising species (i.e., a high valent LFe(IV)=O species and a hydroxyl radical, Scheme 1).<sup>3</sup> The dominant role of hydroxyl radicals (and possible involvement of O<sub>2</sub>) in these systems was demonstrated by the low kinetic isotope effects (KIE), alcohol/ketone (A/K) and 3°/2° ratios (adamantane, *vide infra*) obtained and the observation of benzene oxidation to phenol, however no direct evidence for high valent iron oxo species was obtained.<sup>3</sup> Recently, the preparation and isolation of [(N4Py)Fe(IV)O]<sup>2+</sup> by Que and coworkers [who demonstrated the ability of this complex to effect single turnover C–H abstraction from alkanes],<sup>4</sup> has raised the possibility that such a high valent species is formed under catalytic conditions.

We report here the use of peracids (i.e., peracetic acid (PAA) and *m*-chloroperbenzoic acid (*m*CPBA))<sup>5</sup> instead of H<sub>2</sub>O<sub>2</sub> leading to a strong enhancement of both the chemoselectivity (towards oxidation of alkanes to alcohols) and the regioselectivity of the catalytic system, without concomitant loss in overall efficiency. The role of hydroxyl radicals, molecular oxygen and high valent Fe(IV)=O species in this improved catalytic oxidation is explored. The use of peracids enables the exclusion of both molecular oxygen and hydroxyl radicals and provides evidence for the direct involvement

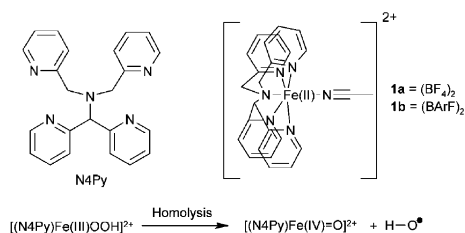
of the Fe(IV)=O species in the catalytic event as well as factors, which determine selectivity and efficiency.

The results of the catalytic oxidation of alkanes, and alcohols by peracids using 1 mol% of catalyst **1a** or **1b** are summarised in Table 1.† The time dependence of the catalysed oxidation of cyclohexane (Fig. 1) shows the reaction to be complete within 60 min for both *m*CPBA and PAA. In general, higher yields were achieved with *m*CPBA than with PAA (38% and 8.2% yield, respectively, for cyclohexane based on oxidant, Table 1) and, in the absence of **1a**, negligible reactivity was observed.<sup>6</sup> Although, a similar overall efficiency with *m*CPBA, compared to H<sub>2</sub>O<sub>2</sub>, is reached (38% vs. 43.3% yield, entries 1 and 3), a much higher selectivity towards alcohol formation is observed with the peracids (A/K = 5.6, *m*CPBA; 4.6, PAA and 1.4, H<sub>2</sub>O<sub>2</sub>). For *m*CPBA

Table 1 Oxidation of alkanes, alcohols catalysed by **1a** and **1b**

Entry	Substrate	Oxidant	T.o.n. <sup>a</sup>	Alcohol	Ketone	A/K	Remarks
<i>Acetonitrile</i> <sup>b</sup>							
1	Cyclohexane	<i>m</i> CPBA	28	5.0	5.6	5.6	<i>k</i> <sub>H</sub> / <i>k</i> <sub>D</sub> = 4.5
2	Cyclohexane	PAA	6.4	1.4	4.6	4.6	<i>k</i> <sub>H</sub> / <i>k</i> <sub>D</sub> = 4.9
3	Cyclohexane <sup>c</sup>	H <sub>2</sub> O <sub>2</sub>	18.5	12.9	1.4	1.4	<i>k</i> <sub>H</sub> / <i>k</i> <sub>D</sub> = 1.5
4	Cyclohexane <sup>d</sup>	<i>m</i> CPBA	47	11	4.3		
5	Cyclohexane <sup>e</sup>	<i>m</i> CPBA	27	3.7	7.2		
6	Cyclohexane <sup>f</sup>	<i>m</i> CPBA	11 [12 <sup>g</sup> ]	3			CH <sub>2</sub> Br <sub>2</sub> under air
7	Cyclohexane	<i>m</i> CPBA	5.5	4.1	1.3		
8	Ethylbenzene	<i>m</i> CPBA	11	1.4	7.9		
9	Benzyl alcohol	<i>m</i> CPBA	–	55			benzaldehyde
10	Cyclooctanol	<i>m</i> CPBA	–	50			cyclooctanone
<i>Ethyl acetate</i> <sup>h</sup>							
11	Cyclohexane	<i>m</i> CPBA	20	4.9	4.1	4.6	<i>k</i> <sub>H</sub> / <i>k</i> <sub>D</sub> = 4.6
12	Cyclohexane	PAA	3.2	0.8	4.0	6.0	<i>k</i> <sub>H</sub> / <i>k</i> <sub>D</sub> = 6.0
<i>Acetone</i> <sup>b</sup>							
13	Cyclohexane	<i>m</i> CPBA	20	4.7	4.3		

<sup>a</sup> T.o.n. = mol product per mol catalyst (average of 2 runs) at *t* = 60 min. <sup>b</sup> **1a** catalyst. <sup>c</sup> From ref. 3. <sup>d</sup> 2nd addition of oxidant after 3 h., t.o.n. determined after 6 h. <sup>e</sup> Addition of *m*CPBA over 2 h., t.o.n. after 3 h. <sup>f</sup> 2500 mol eq. CH<sub>2</sub>Br<sub>2</sub> added. <sup>g</sup> T.o.n. for cyclohexyl-bromide. <sup>h</sup> **1b** catalyst.



Scheme 1

† Electronic supplementary information (ESI) available: Electronic and redox data. See <http://www.rsc.org/suppdata/cc/b4/b412016g/>

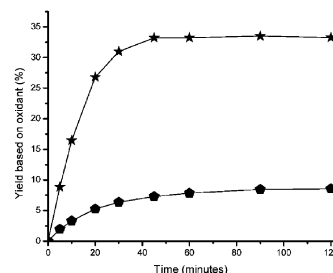


Fig. 1 Time dependence of conversion of cyclohexane (to cyclohexanol and -one) after addition of 100 mol. eq. of oxidant {*m*CPBA (–★–), PAA (–)} to 1000 mol. eq. cyclohexane, 1 mol. eq. **1a** in CH<sub>3</sub>CN under N<sub>2</sub> at 298 K.

**Table 2** Oxidation of adamantane<sup>a</sup> in CH<sub>3</sub>CN catalysed by **1a**

Entry	Oxidant	T.o.n. <sup>b</sup>			
		1-ol	2-ol	Ketone	3 <sup>o</sup> /2 <sup>o</sup>
14	<i>m</i> CPBA	6.4	0.4	0.7	18
15	PAA	2.2	0.4	0.3	9
16 <sup>c</sup>	H <sub>2</sub> O <sub>2</sub>	8.9	4.9	3.1	3.1
17 <sup>d</sup>	<i>m</i> CPBA	11	1.5	1.3	12
18 <sup>d</sup>	PAA	2.6	0.3	0.2	16

<sup>a</sup> 100 eq. of substrate suspended in solvent. <sup>b</sup> T.o.n. = mol product per mol catalyst (average of two runs) at *t* = 60 min. <sup>c</sup> from ref. 3. <sup>d</sup> **1b** in EtOAc

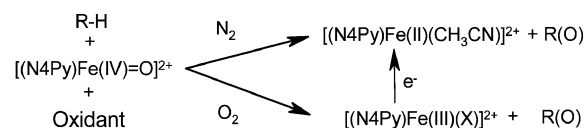
(under N<sub>2</sub>), the catalyst shows only a moderate decrease in activity (after the initial addition of oxidant), as addition of a second 100 eq. of *m*CPBA after 180 min results in a total of 47 and 11 turnovers for alcohol and ketone, respectively. Surprisingly, slow addition of oxidant to the reaction had only a relatively modest effect on the selectivity with the A/K ratio remaining unchanged. The exclusion of oxygen was found to be crucial in this reaction as a dramatic drop in overall efficiency (by 64%) and selectivity (A/K = 1.3) was observed when the reaction was performed under air. The decrease in selectivity can be attributed to the involvement of a Russell type mechanism, whilst the decrease in activity may be attributed, at least in part, to formation of an inactive catalyst (*vide infra*).<sup>7</sup>

The solvent dependence of the reaction was examined, and a similar reactivity to CH<sub>3</sub>CN was observed in both acetone as well as EtOAc; in the latter case the BARF (tetrakis(3,5-di(trifluoromethyl)phenyl)borate) complex was used *i.e.*, **1b**. In contrast, no catalytic activity was observed in DCM. The poor solubility of both **1a** and **1b** in dioxane and diethyl ether resulted in only low levels of oxidation being achieved in these solvents.

The catalytic oxidation of adamantane (a useful mechanistic probe) is described in Table 2. In contrast to cyclohexane, a moderately higher overall activity was observed with H<sub>2</sub>O<sub>2</sub> compared to *m*CPBA. However, the selectivity in terms of tertiary to secondary C–H activation (3<sup>o</sup>/2<sup>o</sup> ratio) was drastically improved with *m*CPBA and PAA, indicating that a more selective oxidising species is present than with H<sub>2</sub>O<sub>2</sub>. Similarly, ethylbenzene is oxidised to phenyl ethyl alcohol and acetophenone with 11 and 1.4 t.o.n., respectively, and alcohols (*i.e.*, benzyl alcohol and cyclooctanol) are converted efficiently into the corresponding aldehyde and ketone (Table 1).

To gain further insight into the nature of the oxidising species, the KIE for cyclohexanol formation (based on a competition experiment between H<sub>12</sub>- and D<sub>12</sub>-cyclohexane) was determined (Table 1).<sup>3</sup> In all cases a high KIE (4.5 to 6.0) is observed, which is significantly higher than with H<sub>2</sub>O<sub>2</sub> (KIE = 1.5). The high KIE in cyclohexanol formation and the high regioselectivity (3<sup>o</sup>/2<sup>o</sup>-ratios) in adamantane oxidation (*vide supra*) indicate that significant participation of hydroxyl radicals in the peracid based oxidation systems can be excluded. This is further supported by the absence of benzene oxidation and the minor effect of acetone on the yield of the reaction (with H<sub>2</sub>O<sub>2</sub> as oxidant acetone reduces the contribution of hydroxyl radicals to the overall reaction).<sup>3</sup> In the presence of CH<sub>2</sub>Br<sub>2</sub>, a significant amount of alkyl bromide was formed, without concomitant loss in overall t.o.n. of the catalyst (Table 1, entry 6). This points to the formation of alkyl radicals and indicates that the reaction involves a single electron type oxidant capable of hydrogen abstraction from C–H bonds (*e.g.*, an Fe(IV)=O species). The similar KIE's, 3<sup>o</sup>/2<sup>o</sup>- and A/K-ratios observed for *m*CPBA and PAA suggests that in both systems oxidation occurs through a similar mechanism and points to the involvement of the [(N4Py)Fe(IV)=O]<sup>2+</sup> species as suggested earlier.<sup>3</sup>

The catalysed *m*CPBA oxidation of cyclohexane was monitored by UV-Vis spectroscopy and electrochemistry (see supplementary material).<sup>†</sup> Addition of oxidant results in an immediate loss in absorption bands of **1a** at λ<sub>max</sub> 355 and 455 nm and a concomitant formation of a weak band at λ<sub>max</sub> 695 nm (ε > 170 M<sup>-1</sup> cm<sup>-1</sup>) consistent with the spectrum reported for [(N4Py)Fe(IV)=O]<sup>2+</sup>.<sup>4</sup>

**Scheme 2**

The feature persists for ~1 h followed by a slow recovery of the original spectrum (over 24 h), indicating reformation of **1a**. In contrast, both in the presence of O<sub>2</sub> and with PAA (O<sub>2</sub> cannot be excluded from PAA due to 6% H<sub>2</sub>O<sub>2</sub> content) as oxidant, the original spectrum does not recover. Electrochemical analysis of the reaction mixtures indicates that the *m*CPBA/N<sub>2</sub> system contains the catalyst in the Fe(II) oxidation state whilst for the PAA and *m*CPBA/O<sub>2</sub> reactions the catalyst forms an inactive Fe(III) complex. Electrochemical reduction of the solutions of the latter complexes results in reformation of the active catalyst in the Fe(II) state (Scheme 2).

In summary, we have examined the role played by hydroxyl radicals and oxygen in the (N4Py)Fe catalysed oxidation of alkanes. It is clear that the exclusion of hydroxyl radicals leads to a dramatic improvement in the regioselectivity of the reaction and the exclusion of O<sub>2</sub> dramatically improves the A/K ratios obtained. An unexpected benefit of O<sub>2</sub> exclusion is the improved cycling of the catalyst once the reaction has reached completion (in terms of oxidant consumption). Furthermore, we have confirmed that the high valent [(N4Py)Fe(IV)=O]<sup>2+</sup> complex is in fact formed during the oxidation reaction as proposed in earlier studies<sup>3</sup> and have demonstrated that this species is present during the entire period during which catalysis takes place, suggesting its intimate involvement in the catalytic cycle.

The use of peracids and thus the exclusion of hydroxyl radicals and molecular oxygen leads to a significant enhancement in the effectiveness of this non-heme iron catalyst in alkane oxidation, enabling high selectivity (compared with H<sub>2</sub>O<sub>2</sub>) to be achieved without concomitant loss in overall oxidation efficiency. (For analytical data for **1a** and **1b** see supporting information.†)

The authors thank NRSC-Catalysis (T. A. B.) and, the Dutch Economy, Ecology, Technology (EET) programme, a joint programme of the Ministry of Economic Affairs, the Ministry of Education, Culture and Science, and the Ministry of Housing, Spatial Planning and the Environment (J. W. B., W. R. B.) for financial support.

## Notes and references

† Typical reaction conditions: to a solution of substrate (3.48 mmol), bromobenzene (87 μmol, internal standard) and **1a** (or **1b**) (3.48 μmol) in 4 ml of solvent was added either *m*CPBA or PAA (0.347 mmol) in 400 μl solvent. Samples were filtered over a short silica plug and analysed by GC on an Agilent 6890 instrument equipped with a HP-1 dimethylpolysiloxane column (for KIE determination a CPWax52 column). Products were quantified with respect to the internal standard. KIE experiments were carried out as described in ref. 3.

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