Iron catalyzed oxidation chemistry
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Chapter 6

Catalytic oxidation of alkanes with Fe(N4Py) and peracids

In addition to the ability to catalyze the oxidation of DNA, Fe(N4Py) can be used to catalyze the oxidation of a broad range of (organic) substrates. Previous studies in our group focused on the use of hydrogen peroxide as terminal oxidant. It was found that the use of peracids enabled more selective oxidation of the target substrates. Moreover, a detailed study of Fe(N4Py) as catalyst in the oxidation of alkanes was performed. It was found that a high-valent Fe^{IV}=O species acts as the terminal hydrogen abstracting species during catalysis, when peracids were employed as oxidants. Crucial for catalytic activity is the exclusion of molecular oxygen, which was found to have a detrimental effect on the overall oxidation activity and the product selectivity.*

* Parts of this chapter have been published: T.A. van den Berg, J.W. de Boer, W.R. Browne, G. Roelfes, B. L. Feringa, Chem. Commun. 2004, 2550-2551.
6.1 Introduction

The previous chapters focused on the use of \([\text{Fe}^{II}(\text{N4Py})(\text{CH}_3\text{CN})]^2+\) (1) and closely related complexes as catalyst in the aerobic oxidation of DNA. However, this class of catalysts is not limited to the oxidation of DNA. Previous studies in our group have demonstrated the application of 1 as catalyst in the oxidation of a broad range of substrates in organic solvents using hydrogen peroxide as terminal oxidant. Moreover, under catalytic conditions important intermediates have been characterized and studied, including a transient low spin iron(III) hydroperoxy intermediate. This ‘purple intermediate’ \(\left[[\text{N4Py}]\text{Fe}^{\text{III}}-\eta^1\text{-OOH}\right]^2+\) (2) was found to be an excellent spectroscopic model for ‘activated bleomycin’, the last detectable intermediate prior to iron bleomycin mediated DNA cleavage. This chapter focuses on the use of \([\text{Fe}^{II}(\text{N4Py})(\text{CH}_3\text{CN})]^2+\) (1) as a catalyst in the oxidation of various alkanes in organic solvents with peracids as oxidant. First, the oxidation chemistry of 1 with hydrogen peroxide towards C-H bond activation will be discussed. It was found that a change from hydrogen peroxide to peracids, such as \(m\text{CPBA}\) and peracetic acid, resulted in a cleaner substrate oxidation, whilst retaining a comparable efficiency. These results with 1/peracid are discussed in section 6.2. The use of peracids as oxidants also allowed a spectroscopic and spectrometric study of new transient intermediates, which are formed during catalytic activity. These studies, described in section 6.3 of this chapter, provide clear evidence for a high-valent \([\text{N4Py}]\text{Fe}^{\text{IV}}\text{-=O}\]^2+ (3) as the hydrogen abstracting species in the catalytic cycle. Crucial for efficient activity is the exclusion of molecular oxygen. Section 6.4 provides an overview of the research towards the fate of the catalyst 1 after reaction.

6.1.1 The chemistry of \text{Fe}^{II}(\text{N4Py})

In nature, many (non-heme) iron based enzymes are known, which are capable of oxidizing a broad range of substrates. The natural glycopeptide bleomycin (BLM), introduced in Chapter 1, can be placed in this class also. BLM is capable of inducing strand breaks in DNA using a metal in a low oxidation state (preferably iron(II)) and molecular oxygen as co-factors. These DNA strand breaks are the result of hydrogen abstraction from the DNA sugar backbone, after which oxidation at these positions result in the actual DNA breaks. A key role in the catalytic cycle of DNA oxidation by Fe(BLM) is the formation of a low spin iron(III) hydroperoxy intermediate (BLM)Fe^{III}OOH) prior to DNA oxidation. The exact role of this intermediate, called ‘activated bleomycin’, is still a subject of discussion amongst researchers. To date, it is still not established whether this intermediate is involved directly in a hydrogen abstraction process or is it a precursor to another (still not observed and characterized) intermediate (such as high-valent iron intermediates). Recent insights suggest the possibility of direct involvement of the ‘activated bleomycin’ in the hydrogen abstraction. However, this hypothesis does also not exclude involvement of high-valent intermediates. It has been proposed that the (BLM)Fe^{III}OOH intermediate is responsible for a hydrogen abstraction to form \(\text{H}_2\text{O}\) and a high-valent (BLM)Fe^{IV}O intermediate, but no physical evidence has been presented to date.

An established method to mimic, and in this way investigate, the activity of complex (natural) molecules is by studying synthetic molecules, which have spectroscopic and functional aspects comparable to those of the original (bio)molecules. Many (iron) complexes have been synthesized and studied as models for iron bleomycin.
many of these synthetic complexes, transient intermediates have been observed, which have spectroscopic features similar to those of (BLM)Fe$^{III}$OOH. The first successful independent generation and characterization of a low spin Fe$^{III}$OOH intermediate was published in 1995. Treatment of [Fe$^{II}$N4Py(CH$_3$CN)]$^{2+}$ (1) with excess hydrogen peroxide in methanol or acetone resulted in the formation of [(N4Py)Fe$^{III}$-η$_1$-OOH]$^{2+}$ (2). This species, which is referred to as the ‘purple intermediate’ (Scheme 6.1) due to its intrinsic purple color, was found to have spectroscopic features nearly identical to those of ‘activated bleomycin’, including X-band ESR, UV/Vis, resonance raman and Mössbauer data. The exact formulation of this ‘purple intermediate’ as 2 was established by electrospray mass spectral analysis.

Scheme 6.1 Generation of the ‘purple intermediate’ (2) from 1. Treatment of 2 with a base results in the formation of 4.

Treatment of 2 with an appropriate base resulted in the formation of another intermediate, referred to as the ‘blue intermediate’. This ‘blue intermediate’ was found to be [(N4Py)Fe$^{III}$-η$_2$-OO]$^{3+}$ (4) (Scheme 6.1). Importantly, this intermediate was not capable of initiating hydrogen abstraction events from target substrates. In contrast, the ‘purple intermediate’ 2 has been proposed to function as a precursor in the catalytic cycle for the generation of a high-valent intermediate, which is capable of abstracting hydrogen atoms from target substrates.

When [Fe$^{III}$N4Py(CH$_3$CN)]$^{2+}$ (1) was employed as catalyst together with hydrogen peroxide as oxidant in the oxidation of alkanes in acetone as solvent, the iron(III) hydroperoxy species 2 was present during the whole course of the catalysis. This observation was a first indication that this intermediate was involved in the catalysis (vide infra). The use of certain catalytic probes and various observations, including benzene oxidation, low kinetic isotope effects (KIE) and low regiospecificity suggested the formation of hydroxyl radicals during catalysis. This was further supported by a clear reduction of catalytic activity when hydroxyl scavengers were employed in the reaction. The formation of these hydroxyl radicals during catalysis can be rationalized by a homolysis of the O-O bond of the [(N4Py)Fe$^{III}$-η$_1$-OOH]$^{2+}$ (2) species into these hydroxyl radicals and a high-valent [(N4Py)Fe$^{IV}$=O]$^{2+}$ (3) intermediate (Scheme 6.2). Further support for this hypothesis came from spectroscopic studies, such as resonance raman studies, which indicated a weakened O-O bond in the [(N4Py)Fe$^{III}$-η$_1$-OOH]$^{2+}$ (2) complex.

Scheme 6.2 Homolysis of the O-O bond of [(N4Py)Fe$^{III}$-η$_1$-OOH]$^{2+}$ (2) to form [(N4Py)Fe$^{IV}$=O]$^{2+}$ (3) and a hydroxyl radical.
No direct evidence has been found for the presence of \((N4Py)Fe^{IV}=O\) (3) in the catalytic oxidation of alkanes with hydrogen peroxide. Recently, Que and co-workers have independently generated and characterized high-valent \(Fe^{IV}=O\) intermediates of iron \(N4Py\) and related complexes.\(^{37-39}\) Treatment of the iron(II) complexes with oxidants such as iodosyl benzene or peracids resulted in the formation of intermediates, which are characterized by weak absorption bands in the near infrared region in the UV/Vis spectrum. Since these initial results, many other synthetic high-valent non-heme iron complexes have been identified and characterized.\(^{40-48}\)

The independently isolated \([N4Py]Fe^{IV}=O\)^{2+} species (3) was found to be capable of inducing hydrogen abstraction.\(^{39}\) When ethylbenzene was employed as substrate, under single turnover conditions, an exceptionally high KIE (as high as 30) was found, pointing towards the involvement of a selective hydrogen abstracting species.\(^{49}\) Indeed, these high KIE values are in strong contrast to the low KIE values that are normally found when highly reactive hydroxyl radicals are present.\(^4\) The high oxidative power of the \((N4Py)Fe^{IV}=O\) was further suggested by theoretical studies,\(^{50}\) which predict a higher reactivity of this species than Cytochrome P450 P Cpd I.\(^{51}\)

As mentioned, \([Fe^{II}(N4Py)(CH_{3}CN)]^{2+}\) (1) together with hydrogen peroxide is a powerful catalyst and oxidant for the oxidations of many substrates. The scope of this system includes the oxidation of various alkanes, alkenes, alcohols, benzene, \(N,N\)-dimethyl aniline and more recently small peptides.\(^{2-4,52}\)

Much research has been devoted in unraveling the catalytic cycle of C-H bond activation with 1/H\(_2\)O\(_2\). Careful examination has shown that the formation of the hydroperoxy species \((N4Py)Fe^{III}-OOH\) (2) is a two-step process. Firstly, 1 is oxidized to a mixture of iron(III) species, which undergo a rapid ligand exchange with hydrogen peroxide. Homolysis of the O-O bond (Scheme 6.2) results in the formation of \((N4Py)Fe^{IV}=O\) (3) and a hydroxyl radical (whose presence has been demonstrated unequivocally, \textit{vide supra}). These species are both capable of abstracting a hydrogen from the target substrate, which is then oxidized with either molecular oxygen or a metal bound oxygen species. The resulting iron(III) complex can undergo another ligand exchange with hydrogen peroxide, thus completing the catalytic cycle (Scheme 6.3).

### 6.1.2 Focus of this chapter

The previous paragraph shows that \(Fe^{II}(N4Py)\) (1) together with hydrogen peroxide can be employed as an efficient catalyst for the oxidation of various substrate. The formation of the iron(III) hydroperoxy species (‘purple intermediate’, 2) was found to be a key step in the catalytic cycle. However, the formation of highly reactive hydroxyl radicals, besides the formation of \((N4Py)Fe^{IV}=O\) (3), after a homolysis step (Scheme 6.2) complicates a study of the latter. It was envisioned that a change of oxidant from hydrogen peroxide to other oxidants (e.g. peracids) might reduce the influence of these highly reactive hydroxyl radicals in the oxidation process. This would open up the possibility of examining \((N4Py)Fe^{IV}=O\) in more detail.

The major focus is on the catalytic oxidation of cyclohexane, as this would allow facile comparison with results obtained earlier with H\(_2\)O\(_2\). Several catalytic probes together with spectroscopic techniques have been employed to gain insight at the catalytic cycle of 1/peracid oxidation system.
Catalytic oxidation of alkanes with Fe(N4Py) and peracids

6.2 Catalytic oxidation with peracids as oxidants

Catalytic oxidations with iron N4Py complexes were performed focusing on two major aspects: i) parameters that affect the oxidation pathway and ii) the reactivity of intermediates formed during the reaction.

The catalytic activity of the iron N4Py complex 1 in the oxidation of cyclohexane to cyclohexanol and cyclohexanone was examined using either meta-chloroperbenzoic acid (mCPBA) or peracetic acid (PAA) as oxidant (Scheme 6.4).

Scheme 6.4 Catalytic oxidation of cyclohexane to cyclohexanol and cyclohexanone with [Fe\textsuperscript{II}(N4Py)(CH\textsubscript{3}CN)][BF\textsubscript{4}]	extsuperscript{2-} (1).

The conditions for both screening and mechanistic studies (vide infra) was a ratio of 1: 100: 1000 of catalyst: oxidant: substrate (catalyst concentration ~ 0.7 mM), identical to conditions used in previous studies, facilitating direct comparison with results obtained earlier with hydrogen peroxide as oxidant. The excess of cyclohexane as substrate with
respect to the catalyst (10-fold excess with respect to the oxidant) reduces unwanted side reactions, such as overoxidation of the products. The oxidation reactions were performed under an inert atmosphere (N₂ or Ar) to avoid auto-oxidation reactions with dioxygen (vide infra).

The oxidation of cyclohexane to cyclohexanol and cyclohexanone in acetonitrile with I as catalyst was followed in time. (Figure 6.1). When the overall yield of products (i.e. the sum of both alcohol and ketone) is plotted against time, it is apparent that product formation has ceased after 45 min for both oxidants. Product formation is significantly higher when mCPBA is used as oxidant (33 TON overall) compared to PAA (8.5 TON overall).

![Figure 6.1](image)

**Figure 6.1** Oxidation of cyclohexane to cyclohexanol and cyclohexanone followed in time with either mCPBA (■) or PAA (●) as oxidant employing I as catalyst.

This reaction was examined in more detail (Table 6.1). When I was employed as catalyst and mCPBA as oxidant, a conversion to cyclohexanol and cyclohexanone of 28 and 5 TON, respectively, was observed (entry 1). When PAA was employed as oxidant significantly lower activity was observed (6.4 and 1.4 for alcohol and ketone, respectively, entry 2), whilst a similar alcohol to ketone ratio (A/K = 4.6 vs. 5.6 for mCPBA) was observed. With hydrogen peroxide as oxidant, a similar overall yield of products was obtained compared to mCPBA (31.4 vs. 33 for mCPBA), albeit with an A/K ratio that is significantly lower than for both peracids (entry 3).

Under aerobic conditions, a dramatic drop in activity was observed in the case of mCPBA as oxidant (Table 6.1, entry 4), which can presumably be attributed to catalyst deactivation (vide infra). Moreover, the A/K ratio drops to 1.3, which is characteristic for a Russell type termination mechanism (vide infra). In contrast, the oxidation activity in acetonitrile with H₂O₂ is hardly affected, both in terms of overall oxidation and product ratio (entry 5). Slow addition of mCPBA to the reaction did not have a significant influence on the outcome of the reaction (entry 6), indicating that the oxidation reaction is not hampered by degradation of the mCPBA.
Table 6.1 Catalytic oxidation of cyclohexane to cyclohexanol and cyclohexanone in acetonitrile.\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>TON alcohol</th>
<th>TON ketone</th>
<th>A/K</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>mCPBA</td>
<td>28</td>
<td>5.0</td>
<td>5.6</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>PAA</td>
<td>6.4</td>
<td>1.4</td>
<td>4.6</td>
<td>-</td>
</tr>
<tr>
<td>3\textsuperscript{c}</td>
<td>H$_2$O$_2$</td>
<td>18.5</td>
<td>12.9</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>mCPBA</td>
<td>5.5</td>
<td>4.1</td>
<td>1.3</td>
<td>Under air</td>
</tr>
<tr>
<td>5\textsuperscript{c}</td>
<td>H$_2$O$_2$</td>
<td>14.9</td>
<td>15.6</td>
<td>0.9</td>
<td>Under air</td>
</tr>
<tr>
<td>6\textsuperscript{d}</td>
<td>mCPBA</td>
<td>27</td>
<td>3.7</td>
<td>7.2</td>
<td>Slow addition oxidant</td>
</tr>
<tr>
<td>7\textsuperscript{e}</td>
<td>mCPBA</td>
<td>11</td>
<td>3.0</td>
<td>-</td>
<td>2500 eq. CH$_2$Br$_2$ added</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Results after 60 min of reaction time under an inert atmosphere with [Fe$^{II}$(N$_4$Py)(CH$_3$CN)]$^+$(BF$_4$)$_2$ (1) as catalyst unless stated otherwise. \textsuperscript{b} Non-catalyzed reaction equivalent to < 0.5 TON based on normal catalyst concentrations, Fe$^{II}$(BF$_4$)$_2$ 1 TON and Fe$^{III}$(NO$_3$)$_3$ 1.5 TON for alcohol and ketone. \textsuperscript{c} [Fe$^{II}$(N$_4$Py)(CH$_3$CN)](ClO$_4$)$_2$ as catalyst, data from reference 4. \textsuperscript{d} Addition of oxidant over 2 h, TON after 3 h. \textsuperscript{e} TON for bromocyclohexane.

Addition of excess methylene bromide led to the formation of significant amounts of bromocyclohexane (12 TON, entry 7), which is indicative for the presence of relatively long lived cyclohexyl radicals. This is in agreement with the results obtained under aerobic conditions (entry 4), where the low A/K ratio indicates an auto-oxidation process involving reaction of the cyclohexyl radicals with molecular oxygen to form equimolar amount of alcohol and ketone (Scheme 6.5). Similar observations have been made with analogous iron complexes. Addition of excess methylene bromide led to the formation of significant amounts of bromocyclohexane (12 TON, entry 7), which is indicative for the presence of relatively long lived cyclohexyl radicals. This is in agreement with the results obtained under aerobic conditions (entry 4), where the low A/K ratio indicates an auto-oxidation process involving reaction of the cyclohexyl radicals with molecular oxygen to form equimolar amount of alcohol and ketone (Scheme 6.5). Similar observations have been made with analogous iron complexes.\textsuperscript{55,56-58}

\[ R^1R^2CH\bullet + O_2 \rightarrow R^1R^2CHOO\bullet \]

\[ 2 R^1R^2CHOO\bullet \rightarrow R^1R^2CHOH + R^1R^2CHO = O + O_2 \]

Scheme 6.5 Auto-oxidation of alkyl radicals with molecular oxygen to form equivalent numbers of alcohol, ketone and molecular oxygen.

The reaction using PAA as terminal oxidant yields significantly lower amounts of products compared to mCPBA (Table 6.1, entries 1 and 2). Commercially available PAA contains significant amounts of acetic acid, which could alter the outcome of the reaction. However, no change in the oxidation rate was observed when 100 equivalents of acetic acid were added to the reaction mixture.

Besides cyclohexane, other substrates are prone to undergo oxidation as well (Table 6.2). Ethylbenzene was oxidized by 1/mCPBA to phenylethyl alcohol and acetophenone with a high A/K ratio (entry 1). Both secondary and primary alcohols undergo oxidation to the corresponding ketones and aldehydes, respectively, in high turnover numbers. Benzyl alcohol was oxidized to benzaldehyde in 55 TON (entry 2). This overall activity is identical to that of 1/H$_2$O$_2$ and with an analogous μ-oxo bridged diiron complex with H$_2$O$_2$. Comparable turnover numbers are obtained for the formation of cyclooctanone from...
cyclooctanol (50 TON, entry 3). However, in this case, the aforementioned μ-oxo bridged diiron complex only yields up to 11 TON of cyclooctanone with H₂O₂.

Table 6.2 Oxidation of selected substrates with mCPBA as oxidant.⁶⁰

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>TON alcohol</th>
<th>TON ketone</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethylbenzene</td>
<td>11</td>
<td>1.4</td>
<td>A/K = 7.9</td>
</tr>
<tr>
<td>2</td>
<td>Benzyl alcohol</td>
<td>55</td>
<td></td>
<td>Benzaldehyde</td>
</tr>
<tr>
<td>3</td>
<td>Cyclooctanol</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Benzene</td>
<td>&lt; 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5ᵇ</td>
<td>Benzene</td>
<td>17</td>
<td></td>
<td>H₂O₂ as oxidant</td>
</tr>
</tbody>
</table>

ᵇ Results after 60 min of reaction time in acetonitrile under inert atmosphere with [Fe(N₄Py)(CH₃CN)](BF₄)₂ (1) as catalyst. ᵇ [Fe(N₄Py)(CH₃CN)](ClO₄)₂ as catalyst, data from reference 4.

No benzene oxidation is observed with I and mCPBA in acetonitrile (Table 6.2, entry 4). In contrast, significant numbers of phenol are produced when H₂O₂ is employed as oxidant (entry 5).⁴ The absence of benzene oxidation excludes the presence of hydroxyl radicals.⁶¹ Indeed, the role of hydroxyl radicals is well established when H₂O₂ is employed as oxidant.⁴

The oxidation catalysis was examined in EtOAc also (Table 6.3). For solubility reasons [Fe(N₄Py)(CH₃CN)](BArF)₂ was used as the catalyst (BArF = [B{3,5-(CF₃)₂C₆H₃}₄]). Oxidation of cyclohexane and adamantane resulted in similar TON for alcohol and ketone compared to the reaction in acetonitrile (cf. results from Table 6.1 and Table 6.4). Moreover, the values of the catalytic probes (kinetic isotope effect (KIE, kH/kD) and regioselectivity between secondary (2°) and tertiary C-H bonds (3°) in adamantane oxidation (3°/2°)) are similar to the values obtained in acetonitrile (Table 6.4 and Table 6.5). From these observations, it may be concluded that the oxidation chemistry is similar in EtOAc and acetonitrile.

Table 6.3 Catalytic oxidation of alkanes in EtOAc with 1 catalyst.⁶²

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Oxidant</th>
<th>TON alcohol</th>
<th>TON ketone</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cyclohexane</td>
<td>mCPBA</td>
<td>20</td>
<td>4.9</td>
<td>A/K = 4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>kH/kD = 4.6</td>
</tr>
<tr>
<td>2</td>
<td>Cyclohexane</td>
<td>PAA</td>
<td>3.2</td>
<td>0.8</td>
<td>A/K = 4.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>kH/kD = 6.0</td>
</tr>
<tr>
<td>3</td>
<td>Adamantaneᵇ</td>
<td>mCPBA</td>
<td>11 (1-ol)</td>
<td>1.3</td>
<td>3°/2° = 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.5 (2-ol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Adamantaneᵇ</td>
<td>PAA</td>
<td>2.6 (1-ol)</td>
<td>0.2</td>
<td>3°/2° = 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.3 (2-ol)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ᵇ Results after 60 min of reaction time in acetonitrile under inert atmosphere with [Fe(N₄Py)(CH₃CN)](BArF)₂ (1) as catalyst.ᵇ 100 equivalents suspended in solvent.
6.3 Nature of the hydrogen abstracting species

6.3.1 Catalytic probes

A wide variety of mechanistic probes is available and can provide valuable insight into the nature of the hydrogen abstracting species in the C-H bond activation of alkanes. The absence of benzene oxidation already points to a more selective hydrogen abstracting species than highly reactive hydroxyl radicals (Table 6.2, entry 4). The oxidation of adamantane is an useful probe to test the regioselectivity between secondary (2°) and tertiary C-H bonds (3°). The indiscriminate hydroxyl radical affords values of ~ 1, whereas with more selective hydrogen abstracting species (e.g. high-valent iron(V)oxo intermediates in heme systems) much higher values can be attained. Results obtained for the catalytic oxidation of adamantane using 1 are presented in Table 6.4.

Oxidation of adamantane in acetonitrile with 1 as catalyst and peracids as oxidant resulted in high 3°/2° ratios (Table 6.4, entries 1 and 2), whereas hydrogen peroxide as oxidant provided a low 3°/2° ratio (entry 3). Low 3°/2° ratios are indicative for the presence of non-selective oxidizing species. The high 3°/2° ratios obtained with peracids are not consistent with the involvement of hydroxyl radicals.

Table 6.4 Oxidation of adamantane in acetonitrile.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>1-ol</th>
<th>2-ol</th>
<th>Ketone</th>
<th>3°/2°</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>mCPBA</td>
<td>6.4</td>
<td>0.4</td>
<td>0.7</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>PAA</td>
<td>2.2</td>
<td>0.4</td>
<td>0.3</td>
<td>9.4</td>
</tr>
<tr>
<td>3b</td>
<td>H2O2</td>
<td>8.3</td>
<td>4.9</td>
<td>3.1</td>
<td>3.1</td>
</tr>
</tbody>
</table>

* 100 equivalents adamantane suspended in acetonitrile. Samples taken after 60 min reaction time under an inert atmosphere with [Fe(II)(N4Py)(CH3CN)](BF4)2 (1) as catalyst unless stated otherwise. b [Fe(II)(N4Py)(CH3CN)](ClO4)2 as catalyst, data from reference 4.

Another useful probe is the kinetic isotope effect (KIE) in the oxidation of cyclohexane to cyclohexanol. A high KIE points to a selective hydrogen abstracting species, whereas a low KIE would further support the involvement of highly reactive intermediates, such as hydroxyl radicals. The results of a competition reaction between cyclohexane and cyclohexane-d12, are presented in Table 6.5.

Table 6.5 Kinetic isotope effect (KIE) of the oxidation of cyclohexane-d12.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>KIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>mCPBA</td>
<td>4.5</td>
</tr>
<tr>
<td>2</td>
<td>PAA</td>
<td>4.9</td>
</tr>
<tr>
<td>3b</td>
<td>H2O2</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* Results after 60 min of reaction time in acetonitrile under inert atmosphere with [Fe(II)(N4Py)(CH3CN)](BF4)2 (1) as catalyst unless stated otherwise. b [Fe(II)(N4Py)(CH3CN)](ClO4)2 as catalyst, data from reference 4.

High KIE values (4.5-4.9) were obtained for the oxidation of cyclohexane using peracids as terminal oxidants (Table 6.5, entries 1 and 2). In contrast, the use of hydrogen peroxide as oxidant yielded a significantly lower KIE value of 1.5 (entry 3). This latter value is to be expected due to the involvement of non-selective hydroxyl radicals in the hydrogen
abstracting step in the catalytic cycle. Que and co-workers found a high KIE value of about 30 for the hydrogen abstraction and subsequent oxidation of ethylbenzene using the independently prepared high-valent (N4Py)Fe IV=O species (3). It should be mentioned that this high KIE value was obtained under single turnover conditions, whereas the KIE reported in Table 6.5 are obtained under catalytic conditions and thus competing processes cannot be excluded.

Oxidation experiments with 1, as catalyst, and peracids as oxidants in C-H bond activation demonstrate that a more selective oxidation is achieved when compared to experiments where H2O2 is employed as the terminal oxidant. The main reason for a more selective reaction with peracids than with H2O2 is due to the exclusion of highly reactive hydroxyl radicals as hydrogen abstracting species. Thus, another (selective) species is responsible for the hydrogen abstraction process when peracids are employed as oxidant, as indicated by: i) the absence of benzene oxidation (Table 6.2, entry 4), ii) a high 3°/2° ratio in adamantane oxidation (Table 6.4), and iii) high KIE values (Table 6.5).

6.3.2 Spectroscopy and spectrometry

What is the exact nature of this selective hydrogen abstracting species in the oxidation of alkanes with 1/mCPBA? Earlier studies in our group with hydrogen peroxide as oxidant have demonstrated a possible involvement of a high-valent Fe IV=O species in this process. This intermediate, (N4Py)Fe IV=O (3), was generated independently by reaction of 1 with excess iodosyl benzene followed by characterization by high resolution electrospray mass spectrometry, Mössbauer and UV/Vis spectroscopy. Therefore, its spectroscopic signature is well-known. A distinct green color is characteristic for 3, which corresponds to a near IR absorption at 695 nm (ε ~ 400 M⁻¹cm⁻¹). Furthermore, 3 was capable of effecting abstraction of hydrogens from target alkanes under single turnover conditions.

The oxidation of cyclohexane to cyclohexanol and cyclohexanone was monitored by UV/Vis spectroscopy (Figure 6.2). The initial complex 1 is characterized by a distinct absorption around 455 nm. When mCPBA is added to the reaction mixture, an immediate formation of a new ‘green species’ is observed with an absorption around 700 nm (ε > 170 M⁻¹cm⁻¹), accompanied by a complete loss of the absorption of 1 at 455 nm. This new feature persists for ~ 1 h, followed by a slow recovery of 1 over a period of 24 h.

Figure 6.2. Oxidation of cyclohexane with [FeIV(N4Py)(CH3CN)](BF4)2 (1) and mCPBA monitored by UV/Vis spectroscopy under N2 with the initial spectrum of 1 prior to addition of mCPBA (solid line), after addition of mCPBA (dashed line) and after 1 h reaction time (dotted line). Inset: Absorbance at λ 455 nm followed in time.
In contrast to mCPBA under N$_2$, the recovery of 1 does not take place when the reaction is performed under air or with PAA as oxidant. Molecular oxygen cannot be excluded from PAA due to a 6% H$_2$O$_2$ content. Therefore, it is plausible that another complex is formed after reaction in the presence of dioxygen.

The reaction mixture was examined with electrospray mass spectrometry, employing [Fe$^{III}$(N4Py(CH$_3$CN))(OT)$_2$ (OT$^-$ = [OSO$_2$CF$_3$]$^-$) as catalyst. The ‘green species’ was identified as 3; the mass peak at $m/z$ 219.2 corresponds to [(N4Py)Fe$^{IV}=O$]$^2+$ and 587.9 to [(N4Py)Fe$^{IV}=O$(OT)]$^+$ (Figure 6.3). These data are in agreement with the mass spectra published by Que et al. for independently isolated 3.$^{39}$

Figure 6.3 Electrospray mass spectral analysis of the reaction mixture of [Fe$^{III}$(N4Py)(CH$_3$CN))(OT)$_2$ (1) with mCPBA as oxidant.

The hydroperoxy species (N4Py)Fe$^{II}$OOH (2) is present during the whole course of the oxidation activity when H$_2$O$_2$ was used as oxidant.$^{3,4}$ However, no direct evidence was provided for the presence of a (N4Py)Fe$^{IV}=O$ (3) intermediate. In contrast, this intermediate 3 is present when catalysis with mCPBA as oxidant was carried out in air (cf Figure 6.1 and Figure 6.2). A key step in the proposed catalytic cycle of alkane oxidation with 1/H$_2$O$_2$ is the homolysis of 2 into 3 and a hydroxyl radical (Scheme 6.2).$^{3,30,31}$ This homolysis step has been proposed also in the catalytic cycles of non-heme iron complexes related to Fe(N4Py), when tBuOOH was employed as oxidant.$^{57}$ Therefore, it is conceivable that the formation of (N4Py)Fe$^{IV}=O$ (3) is the result of a similar homolysis reaction, e.g. an iron(III) peroxybenzoate intermediate, when peracids are employed as oxidants (Scheme 6.6).

Scheme 6.6 Formation of [(N4Py)Fe$^{IV}=O$]$^2+$ (3) via a homolysis step of a proposed iron(III) peroxybenzoate intermediate.

A homolysis of the O-O bond in this putative iron(III) peroxybenzoate intermediate would result in 3 and a carboxyl radical (Scheme 6.6). A significant amount of 3-chlorobenzene (up to 40 TON) was observed after catalysis, which could be the result of a decarboxylation of this carboxyl radical. Recently, Ray et al. have demonstrated that the interaction between a (N4Py)Fe$^{II}$OH complex and mCPBA at -30°C in CH$_2$Cl$_2$ favors a homolysis of the O-O bond, resulting in 3 and chlorobenzene.$^{66}$ These results correspond quite well to these
results found under catalytic conditions. However, no further (spectroscopic) evidence is available as yet to further substantiate this homolysis step.

### 6.3.3 Nature of the oxidative species

The spectroscopic and catalytic data point towards 3 as the hydrogen abstracting species in catalysis (vide supra). The nature of the species responsible for the actual oxidation of the alkyl radical, which is formed as a result of this step, is still unknown. Although the reactions have been performed under anaerobic conditions, it is conceivable that trace amounts of dioxygen are responsible for some of the oxidation via auto-oxidation pathways (vide supra). However, the majority of the oxidation has to proceed via another pathway, as auto-oxidation results in the formation of equimolar amounts of alcohol and ketone (Scheme 6.5).

It was examined whether water has an interaction with the formed alkyl radicals. Residual water is present in the reaction mixture, as commercially available mCPBA is ~70-75% pure, the rest being both water and 3-chlorobenzoic acid. To the reaction mixture was added 10% v/v H$_2$O$_{18}$O (H$_2$O has no profound effect on the reaction outcome) and the reaction was examined with GC-MS (CI +). However, no $^{18}$O labeled atoms were incorporated in the cyclohexanol.53 These results also exclude an interaction between [(N$_4$Py)Fe$^{III}$O$^-$]$_2^+$ and the alkyl radicals, as a rapid equilibrium between this species and its dimer [(N$_4$Py)Fe$^{III}_2$]$_2^+$ is established in the presence of water.3

The large A/K ratios for cyclohexane oxidation (Table 6.1) point towards a more selective species for the oxidation step of the formed alkyl radicals. A related study shows that a metal bound oxidant is plausible. Oxidation of cyclohexane with tBuOOH catalyzed by the non-heme complex [Fe$^{III}_{2}$O(TPA)$_2$(H$_2$O)$_2$]$^{4+}$ resulted only in the formation of cyclohexanol.57 Crucial for the conclusion that a metal bound intermediate is responsible for the actual oxidation of the formed alkyl radicals, is the exclusion of oxidant radicals and dioxygen in the reaction.

From this point of view an interaction between [(N$_4$Py)Fe$^{IV}=O$]$_2^+$ (3) (or perhaps [(N$_4$Py)Fe$^{IV}$OH$^-$]$_3^+$) and the alkyl radical would be plausible. In a rebound type reaction,51 this would result in the formation of (N$_4$Py)Fe$^{II}$-OR and cyclohexanol. This (N$_4$Py)Fe$^{II}$-OR species could undergo a ligand exchange with mCPBA and re-enter the catalytic cycle. Ray et al. have provided evidence in a recent report that Fe$^{III}$(N$_4$Py) is oxidized to Fe$^{IV}$(N$_4$Py) with 0.5 equivalents of mCPBA.66 This Fe$^{III}$(N$_4$Py) complex can undergo a ligand exchange with mCPBA to form 3 after subsequent homolysis. This cascade of reactions is identical as was found for 1 with H$_2$O$_2$ (vide supra).3

An indirect indication for a possible interaction between a metal bound oxidant and the formed alkyl radicals might lie the observation that high A/K numbers are achieved with peracetic acid as oxidant (Table 6.1, entry 2). Molecular oxygen cannot be excluded from the reaction mixture due to a 6% H$_2$O$_2$ content. Molecular oxygen was found to cause a drop in the A/K ratio due to auto-oxidation reactions.53,54 This is in contrast to the experimentally found data and could imply an oxidation mechanism, which is faster than reaction with dioxygen, e.g. 3 or mCPBA. The presence of a significant concentration of dioxygen was established due to catalyst inactivation during reaction (vide infra).

Another option, which cannot be excluded, is a direct interaction between the alkyl radicals and mCPBA. This would result in the formation of cyclohexanol and a carboxyl radical as discussed earlier (vide supra). In turn, this carboxyl radical would lead also to the formation of chlorobenzene. It is known in organic synthesis that peracids can be used in the hydroxylation of hydrocarbons, using UV-light as an initiator of a free radical process.68-73
In this case the hydrogen abstraction by 3 is the initiative process and interaction between the formed alkyl radical and the peracid can be viewed as the propagative step in the cycle. If, for the sake of argument, all ketone is produced via auto-oxidation pathways with residual dioxygen,\textsuperscript{53,54} about 20 TON of alcohol has to be formed via other pathways. Since 40 TON of chlorobenzene is formed during the course of the reaction it is conceivable that two equivalents of \textit{m}CPBA per equivalent of cyclohexanol is consumed. In theory, both of the aforementioned oxidation pathways require this double amount of \textit{m}CPBA, which is in agreement with the experimentally found values. In other words, the maximum turnover which can be achieved is only 50 instead of 100.

Mass spectrometry in acetonitrile did not provide any evidence for an iron(III) peroxybenzoate intermediate, nor for any other intermediate. However, when the reaction with \textit{m}CPBA was examined in EtOAc as solvent (for solubility reasons \([\text{Fe}^{III}(N4Py)(CH\text{\textsubscript{3}}CN)](\text{BArF})_2\) was used as the catalyst (\textit{vide supra}), other species were observed. Initially, peaks at \(m/z\ 219.6\) \(([(\text{N4Py})(\text{CH\text{\textsubscript{3}}CN})\text{Fe}^{IV}=\text{O}]^{2+}\) and 1302.5 \(([(\text{N4Py})\text{Fe}^{IV}=\text{O})(\text{BarF})]^{+}\) were observed (Figure 6.4a), which is in agreement with earlier observations (Figure 6.3). The intensity of these peaks decreases with time together with an increase of a peak at \(m/z\ 593.4\) (Figure 6.4b).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6_4.png}
\caption{Electrospray mass spectral analysis of the reaction mixture with \([\text{Fe}^{III}(N4Py)(\text{CH\text{\textsubscript{3}}CN})](\text{BArF})_2\) and \textit{m}CPBA in EtOAc (10 x concentrated). a) Spectrum at \(t = 1.5 – 2.0\) min. b) Spectrum at \(t = 7.0 – 7.5\) min.}
\end{figure}

From the isotope pattern it is clear that this peak has one chlorine atom in its molecular structure and is overall singly charged. This could correspond to the possible complexes in Figure 6.5, but more (spectroscopic) evidence is required for a clear identification of this species. Complex A could be an intermediate in the formation of 3 via a heterolysis step.\textsuperscript{66} Oh \textit{et al.} found that iron(III) salicylate complexes could be formed after treatment of non-heme iron(II) complexes with perbenzoic acids.\textsuperscript{74} The mechanism proceeds via auto-hydroxylation of the aromatic ring through an intramolecular oxotransfer process and requires two available \textit{cis}-labile sites in the iron(II) complex. The formation of such an intermediate (complex B) is possible if one of the pyridines in the \textit{Fe}^{III}(N4Py) is rather labile.
When the reaction is monitored by UV/Vis, the formation of the ‘green species’ is observed as is apparent from the appearance of the distinctive absorption at 700 nm (Figure 6.6). However, after several minutes the absorption band belonging to this Fe$^{IV}=O$ species had disappeared. This disappearance is accompanied by the formation of a new weak broad absorption band around 540 nm ($\varepsilon > 200$ M$^{-1}$ cm$^{-1}$).

**Figure 6.5** Possible complexes, which might be formed in the cyclohexane oxidation catalyzed by [Fe$^{III}$(N4Py)(CH$_3$CN)](BarF)$_2$ (1) in EtOAc.

**Figure 6.6** Oxidation of cyclohexane with [Fe$^{III}$(N4Py)(CH$_3$CN)](BarF)$_2$ (1) and mCPBA under N$_2$ in EtOAc followed in time. Solid line: prior to addition of mCPBA, dashed line: 30 s after addition mCPBA and dotted line: 5 min after addition of mCPBA.

### 6.4 Fate of the catalyst

The reactivity of the Fe(N4Py) catalyst after ceasing of the reaction was examined. When another aliquot of mCPBA (100 equivalents) was added to the reaction mixture after 3 h under N$_2$, no decrease in activity was observed as 47 and 11 TON were found for alcohol and ketone, respectively (Table 6.6, entry 1). This means that depletion of the oxidant causes the reaction to stop and does not lead to degradation of the catalyst. An independent synthesized iron(III) N4Py complex ([Fe$^{III}$(N4Py)(OMe)]$^2+$[ClO$_4$])$_2$ (5)) was used as catalyst also. Similar activity was observed for 5 as for 1 (Table 6.6, entry 2). This excludes the notion that this iron(III) complex is a catalytically dead species.

An important question is what happens to the catalyst when molecular oxygen is present in the reaction mixture. UV/Vis data presented in Figure 6.2, shows that 1 reforms slowly from the iron(III) complex when the reaction is kept under N$_2$. This matter has been studied, but the exact details of this step remain unclear.
When the same reaction was carried out under air, not only a diminished activity (Table 6.1, entry 4) was observed, but also this spontaneous reduction to the initial complex I is not observed. This reaction was examined in more detail with electrochemistry (Figure 6.7). The initial iron(II) complex I (Figure 6.7a) was fully oxidized to an iron(III) complex (Figure 6.7b). When this complex was reduced by means of bulk electrolysis at -0.2 V, a recovery of the initial complex I was observed (Figure 6.7c). This was confirmed by UV/Vis spectroscopy also. When placed under nitrogen followed by the addition of mCPBA, normal activity was observed (Table 6.6, entries 4 and 5). This indicates that the catalyst can be regenerated completely.

![Figure 6.7](image-url)

**Figure 6.7** Electrochemical analysis of the oxidation reaction of cyclohexane with [FeII(N4Py)(CH3CN)](BF4)2 (I) / mCPBA under air (100 mVs⁻¹, initial scan direction indicated by the arrows). a) Before reaction. b) After one hour of reaction time under air. c) After bulk electrolysis under air.

The reactivity of iron N4Py complexes was further investigated by bulk electrolysis (Table 6.6). When a first catalytic run under N2 was followed by the addition of a second aliquot of mCPBA, additional catalytic activity was observed (Table 6.6, entry 1). The oxidation of cyclohexane showed a dramatic decrease when the reaction was performed under air (Table 6.1, entry 4). Indeed, when a reaction under N2 was followed by the addition of another batch of oxidant and this reaction was performed under air, no additional activity was observed (Table 6.6, entry 3). In contrast, if the reaction was performed in first instance under air, and the resulting reaction mixture was reduced back to I by bulk electrolysis, either under air or under N2, activity was observed when the 2nd reaction was performed under inert atmosphere (Table 6.6, entries 4 and 5, *vide supra*).

When the initial complex I was oxidized to iron(III) prior to the actual reaction, either under N2 or air, normal activity was observed (Table 6.6, entries 6 and 7). However, when the reaction was performed under air after the bulk oxidation, no activity was observed in the oxidation reaction (Table 6.6, entry 8).
Table 6.6 Catalytic oxidation of cyclohexane and mCPBA with $[\text{Fe}^\text{II}(\text{N4Py})(\text{CH}_3\text{CN})]_2^\text{2+}(\text{BarF})_2$ (1) under various conditions.$^a$

<table>
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<tr>
<th>Entry</th>
<th>Bulk oxidation</th>
<th>1st Reaction$^b$</th>
<th>TON$^b$</th>
<th>Bulk reduction</th>
<th>2nd Reaction$^c$</th>
<th>TON</th>
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<td>-</td>
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<tr>
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<td>-</td>
<td>N$_2$</td>
<td>yes</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
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<td>-</td>
<td>air</td>
<td>no</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>air</td>
<td>no</td>
<td>air</td>
<td>N$_2$</td>
<td>yes</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>air</td>
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</tr>
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<tr>
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<td>N$_2$</td>
<td>air</td>
<td>no</td>
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</tr>
</tbody>
</table>

$^a$ Reaction conditions as were used for Table 6.1, either under N$_2$ or air. $^b$ TON cyclohexanol $>$ 20. $^c$ 2nd reaction denotes the addition of a second aliquot of mCPBA (100 eq) to the reaction mixture. Activity measured after 1 h after addition. $^d$ $[\text{Fe}^\text{II}(\text{N4Py})(\text{OMe})]_2^\text{2+}(\text{ClO}_4)_2$ (5) as catalyst.

These experiments demonstrate the crucial role for molecular oxygen in the reaction. When dioxygen is excluded from the reaction, the catalyst is active starting from either the iron(II) or iron(III) state. However, reaction with any of these complexes in the presence of molecular oxygen results in the formation of another iron(III) complex, which is catalytically dead. Reduction to an iron(II) complex restores the original catalytic activity (Scheme 6.7).

Scheme 6.7 Fate of the catalyst after catalysis under different conditions.

Despite several attempts to characterize this inactive iron(III) complex formed under aerobic conditions, the exact nature of this species is still unknown. It is unlikely that a direct interaction between a high-valent iron intermediate such as 3 and dioxygen results in the formation of an iron(III) species. Therefore, it is more likely that dioxygen reacts with another (perhaps still not characterized) iron intermediate. Another option is that molecular oxygen reacts with formed alkyl- or aryl radicals. In turn, these products might undergo interaction with an iron intermediate.

6.5 Summary and conclusions

The catalytic oxidation of several (unactivated) alkanes in organic solvents is examined in this chapter. The oxidation of cyclohexane into cyclohexanol and cyclohexanone proceeded with high efficiency when mCPBA is employed as terminal oxidant. Remarkably, the overall turnover numbers of the products are comparable to those obtained with hydrogen peroxide as oxidant, but the selectivity is significant higher with the former. Indeed, the
high A/K ratio points towards a more selective oxidation than Russell type oxidation processes, which have been established as a major oxidation pathway with hydrogen peroxide. Other catalytic probes (such as adamantane oxidation, high kinetic isotope effects (KIE) and the absence of benzene oxidation) confirm the hypothesis that a more selective process is responsible for the oxidation of cyclohexane.

With various analytical methods such as UV/Vis, electrospray mass spectral analysis and electrochemistry the involvement of the high-valent complex \((\text{N4Py})\text{Fe}^{\text{IV}}=\text{O}\) (3) was confirmed. This complex is capable of inducing hydrogen abstraction processes from target substrates as was demonstrated by various other studies. Most likely, this species is the actual terminal hydrogen abstracting species in the catalytic cycle resulting in an alkane radical, which undergoes subsequent oxidation.

Molecular oxygen can be excluded when \(m\)CPBA is employed, which leads to high A/K ratios. When the same reaction is performed under air, low TON are obtained, together with a low A/K, which points towards a termination step with molecular oxygen of the formed radicals. Moreover, the catalyst reacts with dioxygen to form a catalytically dead species. However, reduction of this species by bulk electrolysis results in the formation of an active catalyst. This indicates that destructive processes, such as ligand oxidation, do not take place.

The nature of the species responsible for the actual oxidation step of the formed alkyl radicals is still unknown. It is likely that residual dioxygen in the reaction mixture is responsible for (a minor) part of the observed oxidation products. The major part of the products (mainly alcohol) has to be formed via another route. It can be speculated, based on literature precedents, that the \(\text{Fe}^{\text{IV}}=\text{O}\) intermediate 3 might involved in this step. On the other hand, a direct interaction between \(m\)CPBA and alkyl radicals cannot be excluded as well.

Based on the data available, a catalytic cycle can be proposed (Scheme 6.8). Firstly, interaction between \(m\)CPBA and the iron(II) complex 1 results in the formation of the \(\text{Fe}^{\text{IV}}=\text{O}\) intermediate 3. This high-valent oxo intermediate is capable of inducing hydrogen abstractions from target substrates. The resulting iron(III) complex can then undergo a ligand exchange with the \(m\)CPBA to form a iron(III) \(m\)CPBA intermediate. When an iron(III) complex is employed as catalyst, this complex can undergo a direct ligand exchange with \(m\)CPBA to enter the catalytic cycle. Homolysis of the O-O bond, analogous to the O-O bond homolysis in \((\text{N4Py})\text{Fe}^{\text{II}}\text{OOH}\) (2), results in the formation of the iron(IV) oxo intermediate. Thus, the \((\text{N4Py})\text{Fe}^{\text{IV}}=\text{O}\) intermediate 3 can be accessed via two independent initial routes.

A discrepancy in this proposal is that the overall catalysis rate is significantly higher than would be expected from the reported rate constant for the hydrogen abstraction from cyclohexane by 3 \((k_{\text{obs}} = 0.00039 \text{ s}^{-1})\). These kinetic data were determined under conditions other than in the present study, but nevertheless the discrepancy highlights the point that not all aspects are understood at the present time.

Under aerobic conditions, an inactive catalyst is formed. This inactive catalyst can be reduced back to the initial complex 1 by means of bulk electrolysis without loss of activity. To date, the exact nature of this inactive catalyst is still unknown.
Scheme 6.8 Proposed catalytic cycle for the oxidation of alkanes with 1 as catalyst and mCPBA as oxidant.

In conclusion, a high selectivity has obtained in the catalytic oxidation of alkanes employing 1 as catalyst and mCPBA as oxidant. A clear role in the catalytic cycle for the high-valent Fe$^{IV}$=O intermediate 3 has been proposed as the terminal hydrogen abstracting species in the catalytic cycle. Since this intermediate 3 might be involved in the oxidation of the resulting alkyl radical also, this would imply that two equivalents of oxidant would be required for the oxidation of one equivalent of substrate. This makes the 1/mCPBA-system one of the most efficient catalytic systems in the field of catalytic oxidation of alkanes.

6.6 Experimental Section

General

For general remarks, see Chapters 3, 4 and 5. Electrochemical measurements were carried out on a CH Instruments workstation CHI630B. A Teflon® shrouded glassy carbon working electrode, a Pt-wire counter electrode and a SCE reference electrode were employed. Prior to analysis, KPF$_6$ was added to the solution until a final solution of 100 mM. Bulk electrolysis of reaction solutions were performed with a Pt Gauze working electrode and a Pt-wire counter electrode. Recently, an excellent overview on this technique was published, which describes typical electrochemical experiments in close detail, even though these experiments were based on the somewhat inferior metal manganese.$^{76}$

GC analyses were performed on an Agilent 6890 instrument or a Shimadzu GC-17A, both equipped with HP-1 dimethylpolysiloxane column.$^{77}$ For the determination of kinetic isotope effects a CPWax52 column was used. Products were quantified with respect to the internal standard (bromobenzene). Methods: i) Cyclohexane and cyclohexane-$d_{12}$: Initial temperature (35°C) maintained for 7.5 min. The temperature was increased to 70°C (25°C/min), which was maintained for 2 min. Then 100°C (10°C/min), followed by an increase to 250°C (25°C/min). ii) Adamantane: Initial temperature (150°C) maintained for 1 min. The temperature was increased to 300°C (10°C/min), which was maintained for 10 min. iii) Benzene: Initial temperature (35°C) maintained for 15 min. The temperature was increased to 250°C (25°C/min), which was maintained for 1 min. iv) Ethylbenzene,
Catalytic oxidation of alkanes with Fe(N4Py) and peracids

benzylalcohol and cyclooctanol: Initial temperature (50°C) maintained for 5 min. The temperature was increased to 100°C (5°C/min), then to 250°C (20°C/min), which was maintained for 2 additional min.

Complex synthesis
Complexes of \( \text{I} \) used in this chapter, namely \([\text{Fe}^\text{II}(\text{N4Py})(\text{CH}_3\text{CN})](\text{BF}_4)_2\), \([\text{Fe}^\text{II}(\text{N4Py})(\text{CH}_3\text{CN})](\text{BarF})_2\) and \([\text{Fe}^\text{II}(\text{N4Py})(\text{CH}_3\text{CN})](\text{OTf})_2\) were prepared analogous to literature procedures. Spectroscopic data are consistent with the structures.

Anal. calcd. for \([\text{Fe}^\text{II}(\text{N4Py})(\text{CH}_3\text{CN})](\text{BF}_4)_2\) \(\text{C}_{23}\text{H}_{30}\text{B}_2\text{F}_8\text{FeN}_5\cdot\text{H}_2\text{O}\): C 45.73, H 3.99, N 12.81; found: C 45.95, H 3.88, N 12.57.

Anal. calcd. for \([\text{Fe}^\text{II}(\text{N4Py})(\text{CH}_3\text{CN})](\text{BarF})_2\) \(\text{C}_{57}\text{H}_{45}\text{B}_2\text{F}_{48}\text{FeN}_6\cdot\text{H}_2\text{O}\): C 47.86, H 2.17, N 3.85; found: C 47.80, H 2.29, N 3.56.

Anal. calcd. for \([\text{Fe}^\text{II}(\text{N4Py})(\text{CH}_3\text{CN})](\text{OTf})_2\) \(\text{C}_{27}\text{H}_{24}\text{F}_6\text{FeN}_6\text{O}_6\text{S}_2\): C 42.53, H 3.17, N 11.02; found: C 42.45, H 3.17, N 10.95.

Catalytic oxidations
Typical reaction conditions: to a solution of substrate (3.48 mmol; 0.348 mmol in the case of adamantane), bromobenzene (87 μmol, internal standard) and \( \text{I} \) (3.48 μmol) in 4 mL of solvent was added either \( m\text{CPBA} \) or \( \text{PAA} \) (0.347 mmol) in 400 mL solvent. Samples were filtered over a short silica plug and analyzed by GC.

Kinetic isotope effect determination
Similar to normal catalytic oxidation, however using a mixture of cyclohexane and cyclohexane-\(d_{12} \) (1:1) as substrate. The TON’s were determined on a CPWax52 column. The KIE was determined by comparing the TON for cyclohexanol and cyclohexanol-\(d_{12} \) (corrected for the initial relative concentration of cyclohexane and cyclohexane-\(d_{12} \)).

6.7 References and notes

1. See Appendix for abbreviations used.
Catalytic oxidation of alkanes with Fe(N4Py) and peracids

67 Incorporation of 18O was found for cyclohexanone, but this is the result of a reversible hydration, via a geminal diol.
75 H. Logtenberg, Ligand on/off Studies of a Bleomycine Analogue, Undergraduate report, University of Groningen 2006.
Alternatively, a HP-5 column (5%-phenyl)-methylpolysiloxane) could be used for this purpose.