

Catalytic Oxidation with a Non-Heme Iron Complex That Generates a Low-Spin Fe^{III}OOH Intermediate

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Abstract: The antitumor drug bleomycin (BLM) is proposed to act via a low-spin iron(III) hydroperoxide intermediate called “activated bleomycin”. To gain more insight into the mechanistic aspects of catalytic oxidation by these intermediates we have studied the reactivity of [(N4Py)Fe(CH₃CN)](ClO₄)₂ (**1**) (N4Py = *N,N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine) with excess H₂O₂. Under these conditions a transient purple species is generated, [(N4Py)FeOOH]²⁺ (**2**), which has spectroscopic features and reactivity strongly reminiscent of activated bleomycin. The catalytic oxidation of alkanes such as cyclohexane, cyclooctane, and adamantane by **1** with H₂O₂ gave the corresponding alcohols and ketones in up to

31 % yield. It was concluded, from the O₂ sensitivity of the oxidation reactions, the formation of brominated products in the presence of methylene bromide, and the nonstereospecificity of the oxidation of *cis*- or *trans*-dimethylcyclohexane, that long-lived alkyl radicals were formed during the oxidations. Oxidation of alkenes did not afford the corresponding epoxides in good yields but resulted instead in allylic oxidation products in the case of cyclohexene, and cleavage of the double bond in the case of styrene. Addition of hydroxyl

radical traps, such as benzene and acetone, led to only partial quenching of the reactivity. The kinetic isotope effects for cyclohexanol formation, ranging from 1.5 in acetonitrile to 2.7 in acetone with slow addition of H₂O₂, suggested the involvement of a more selective oxidizing species in addition to hydroxyl radicals. Monitoring the UV/Vis absorption of **2** during the catalytic reaction showed that **2** was the precursor for the active species. On the basis of these results it is proposed that **2** reacts through homolysis of the O–O bond to afford two reactive radical species: [(N4Py)Fe^{IV}O]²⁺ and •OH. The comparable reactivity of **1** and Fe–BLM raises the possibility that they react through similar mechanistic pathways.

Keywords: homogeneous catalysis • iron • N ligands • O–O activation • oxidations

Introduction

Iron–peroxo species are invoked in the mechanisms of several iron-requiring biological oxidation catalysts.^[1] Such intermediates have been observed for non-heme diiron enzymes such as methane monooxygenase,^[2] ribonucleotide reductase,^[3] and stearyl acyl carrier protein Δ⁹-desaturase.^[4] These peroxo intermediates serve as precursors for high-

valent iron–oxo species that effect substrate oxidation.^[5] In the case of cytochrome P450, an iron(III)–peroxo species is assumed to be formed when the key second electron is injected into oxy-P450 (Fe^{III}–O₂[–]). Due to the apparently low oxidative reactivity of Fe^{III}–η²-O₂[–] species, it is proposed that this moiety, if formed in the P450 active site, must be protonated to form an Fe^{III}OOH species before its conversion to a high-valent iron–oxo species.^[6]

A low-spin Fe^{III}OOH species has been characterized for “activated BLM”,^[7] the active form of the antitumor drug bleomycin (BLM), which is a metalloglycopeptide.^[8] Activated BLM is formed by the reaction of the Fe^{II} form, O₂, and a one-electron reductant to form a metastable Fe^{III}OOH species, of which the formulation has been established by electrospray ionization mass spectrometry.^[7b] The decomposition of this intermediate is thought to be responsible for the drug’s ability to cleave DNA by an oxidative mechanism.^[9] The accepted mechanism for bleomycin action^[8, 9] involves hydrogen abstraction by activated BLM at the deoxyribose unit of a nucleotide to form a C4′ carbon radical whose fate is

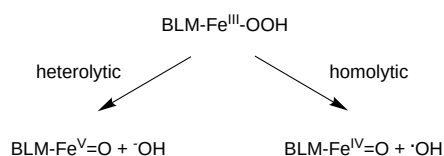
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determined by two subsequent pathways, one that requires additional O_2 and another that does not. Besides DNA cleavage, activated BLM is also capable of the epoxidation of styrene,^[10] the oxidation of stilbene to give the corresponding epoxide and other oxidation products such as benzoin and benzaldehyde,^[11] the hydroxylation of naphthalene and anisole,^[12] and the demethylation of *N,N*-dimethylaniline (DMA).^[12]

How the low-spin $Fe^{III}OOH$ moiety of activated BLM is involved in its oxidative reactions has been the subject of considerable debate. Three pathways can be considered. First, following the heme enzyme precedent, the iron hydroperoxide intermediate may undergo O–O bond heterolysis to give rise to a (formally) $Fe^V=O$ species,^[8] analogous to heme peroxidase (Scheme 1).^[6, 13] This is supported by the observa-



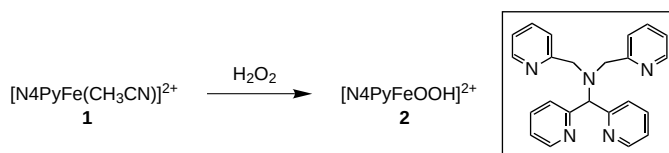
Scheme 1. Possible O–O bond cleavage pathways for activated bleomycin.

tion of olefin epoxidation activity of Fe^{III} –BLM with oxygen atom donors such as iodosylbenzene,^[12, 14] but it is weakened by the fact that iodosylbenzene can also be activated by redox-inactive Lewis-acidic metal centers.^[15] A second pathway is the homolytic scission of the O–O bond to give an $Fe^{IV}=O$ species and $\cdot OH$, which would generate a highly reactive oxidant with low discrimination. Thirdly, the $Fe^{III}OOH$ intermediate itself could be involved in substrate oxidation. This option has the advantage of invoking an oxidant with more moderate reactivity and thus greater selectivity, and is considered to rationalize the reactivity of certain heme enzymes.^[16]

There has been much effort to improve understanding of the chemistry of Fe –BLM through the use of model complexes. To date, the 2-(2',5'-diazapentyl)-5-bromopyrimidine-6-carboxylic acid *N*-[2-(4'-imidazolyl)ethyl]amide anion (pma) ligand designed by Mascharak and co-workers and the *N*-[6-([(S)-2-amino-2-carbamoyl-ethyl]amino)methyl]pyridine-2-carbonyl]-L-histidine (pyml) ligand most closely reproduce the iron coordination environment of BLM. Indeed, like Fe^{II} –BLM, Fe^{II} –pma and Fe^{II} –pyml react with O_2 to give rise to intermediates with EPR parameters similar to those of activated BLM.^[17] However, the $Fe^{III}OOH$ formulation has not been established in these cases. More recently, a number of synthetic iron complexes have been found to react with H_2O_2 or alkyl hydroperoxides to give low-spin $Fe^{III}OOH$ ^[18] and $Fe^{III}OOR$ intermediates^[19] analogous to activated BLM. Several of these complexes have been found to be good catalysts for hydrocarbon oxidation. From a detailed mechanistic study, it has been established that the $[Fe(tpa)(H_2O)_2O](ClO_4)_4/tBuOOH$ system (*tpa* = tris(2-pyridylmethyl)amine) generates a low-spin $Fe^{III}OOR$ intermediate which reacts by O–O bond homolysis giving $Fe^{IV}=O$ and $\cdot O^tBu$.^[20] The $\cdot O^tBu$ radical reacts with the substrate to give a substrate radical which can then be trapped by the $Fe^{IV}=O$

moiety to give alcohol or undergo a radical chain autoxidation reaction with O_2 to generate equimolar amounts of alcohol and ketone. On the other hand, $[Fe(tpa)(CH_3CN)_2](ClO_4)_2$ and $[Fe(bpmen)(CH_3CN)_2](ClO_4)_2$ (*bpmen* = *N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)ethylene-1,2-diamine) are capable of stereospecific oxidation of alkanes and alkenes with H_2O_2 , results that are inconsistent with free radical chemistry.^[18d, 21]

We previously reported the synthesis and characterization of iron complexes of the ligand *N,N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine (N4Py).^[18a, 22] Like BLM, N4Py can act as a pentadentate ligand, leaving one available coordination site in the corresponding iron complex. We have demonstrated by X-ray crystallography that this site can be occupied by CH_3CN or Cl^- in Fe^{II} complexes and by CH_3O^- or O^{2-} in Fe^{III} complexes. Reaction of $[Fe(N4Py)(CH_3CN)](ClO_4)_2$ (**1**) with H_2O_2 resulted in the formation of a transient purple species which has been characterized spectroscopically (UV/Vis, EPR, resonance Raman^[23] and ESI-MS) as $[Fe^{III}(N4Py)OOH]^{2+}$ (**2**) (Scheme 2).^[18a]



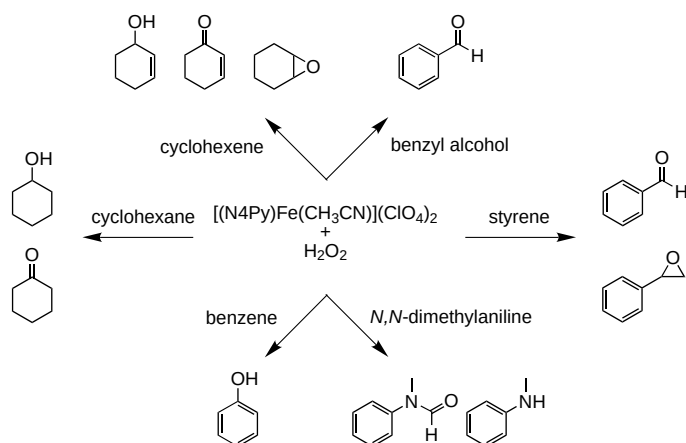
Scheme 2. Reaction of the N4Py–iron(II) complex **1** with H_2O_2 to generate the $Fe^{III}OOH$ intermediate **2** and (inset) the ligand N4Py.

Here we report on a detailed study of the reactivity of the $[Fe(N4Py)(CH_3CN)](ClO_4)_2/H_2O_2$ system in catalytic oxidations, giving a mechanistic interpretation of the results and discussing the relevance of these results to an understanding of the chemistry of Fe –BLM.

Results and Discussion

Catalytic oxidations with **1** were examined, focusing on: i) parameters that affect the oxidation pathway; and ii) the reactivity of the key peroxide complex **2**. To determine whether **2** reacts by homolysis or heterolysis, catalytic oxidations in acetonitrile were investigated. Studies with hydroxyl radical traps such as acetone and benzene and mechanistic probes such as kinetic isotope effects, tertiary/secondary ($3^\circ/2^\circ$) ratios in adamantane oxidation, and stereoselectivity in the oxidation of *cis*- and *trans*-1,2-dimethylcyclohexane led to a proposed mechanism entailing homolysis of the O–O bond of **2**, affording two active oxidizing species: $[N4PyFe^{IV}O]^{2+}$ and $\cdot OH$.

Scheme 3 summarizes the reactions catalyzed by **1**. They include oxidation of alkanes, alkenes, alcohols, benzene, and *N,N*-dimethylaniline (DMA). All reactions were carried out under an argon atmosphere, unless noted otherwise, at 25 °C. The reaction was started by adding 100 equivalents of H_2O_2 to a solution containing the catalyst and 1000 equivalents of substrate. Acetonitrile and acetone were each used as solvent for the catalytic oxidation reactions; samples for GC analysis were taken after 30 min (acetone) or 90 min (acetonitrile). We

Scheme 3. Overview of reactions catalyzed by **1** and H₂O₂.

have shown previously that **2** is formed in either acetone or acetonitrile, although the intermediate is formed quantitatively only in acetone.^[22]

Oxidations in acetonitrile: Under the conditions mentioned above, the oxidation of alkanes gave considerable yields of the corresponding alcohols and ketones. In the case of cyclohexane, cyclohexanol and cyclohexanone were formed in 31% combined yield (based on hydrogen peroxide) in acetonitrile (Table 1, entry 1). The large yields observed make **1** among the most reactive and efficient non-heme iron oxidation catalysts. Cyclohexanol was the main product, with an alcohol/ketone (A/K) ratio of 1.4, when the reaction was carried out under Ar (Table 1, entry 1). A/K decreased to nearly 1 when the reaction was in air (Table 1, entry 2) and

Table 1. Catalytic oxidation of cyclohexane to cyclohexanol and cyclohexanone.

Entry	Additive	Alcohol ^[a]	Ketone ^[a]	A/K	<i>k_H</i> / <i>k_D</i>
acetonitrile					
1		18.5	12.9	1.4	1.5
2	air	14.9	15.6	0.96	–
3	syringe pump (200 min)	17.5	9.1	1.9	–
4	CH ₂ Br ₂ (2500 equiv)	13.4	9.3	–	–
		4.0 (RBr)			
5	benzene (10% v/v)	16.7	8.4	2.0	–
6	benzene (50% v/v)	10.5	4.0	2.6	1.7
acetone					
7		16.9	6.6	2.6	2.3
8	air	13.4	14.9	0.9	–
9	syringe pump (70 min)	17.7	4.8	3.7	–
10	syringe pump (200 min)	12.4	2.4	5.2	2.7
11	CH ₂ Br ₂ (2500 equiv)	11.4	5.3	–	–
		7.9 (RBr)			
[D ₆]acetone					
12		20.0	9.4	2.1	1.9

[a] Turnover number (TON) = mol product per mol catalyst.

increased to 1.9 upon syringe-pump addition of H₂O₂ under argon (entry 3), suggesting the involvement of O₂ that propagates a radical chain autoxidation process.^[20]

Experiments were performed under a vigorous argon purge in an attempt to remove all traces of dioxygen and block the radical chain reaction. Since cyclohexane is too volatile for this purpose, cyclooctane was used as substrate. Under the standard reaction conditions in acetonitrile both cyclooctanol and cyclooctanone were produced (Table 2, entry 1), but in this case the ketone proved to be the main product (A/K = 0.3). A similar shift in alcohol/ketone selectivity on going from cyclohexane to cyclooctane as substrate was observed

Table 2. Catalytic oxidation of other substrates.

Entry	Substrate	Products	TON in CH ₃ CN	TON in acetone	Remarks
1 ^[a]	cyclooctane	cyclooctanol	2.7	–	A/K = 0.3
		cyclooctanone	9.0		
2 ^{[a],[b]}	cyclooctane	cyclooctanol	1.1	–	A/K = 0.4
		cyclooctanone	3.0		
3	<i>cis</i> -1,2-dimethylcyclohexane	<i>cis</i> -1,2-dimethylcyclohexanol	1.4	2.3	<i>cis/trans</i> 1.8 (CH ₃ CN)
		<i>trans</i> -1,2-dimethylcyclohexanol	0.8	1.2	1.9 (acetone)
4	<i>trans</i> -1,2-dimethylcyclohexane	<i>cis</i> -1,2-dimethylcyclohexanol	1.1	1.7	<i>cis/trans</i> 1.4 (CH ₃ CN)
		<i>trans</i> -1,2-dimethylcyclohexanol	0.8	0.9	1.9 (acetone)
5	adamantane ^[c]	1-adamantanol	8.3	–	3°/2° = 3.1
		2-adamantanol	4.9		
		2-adamantanone	3.1		
6 ^[d]	adamantane ^[c]	1-adamantanol	8.9	–	3°/2° = 3.3
		2-adamantanol	4.6		
		2-adamantanone	3.4		
7	cyclohexene	cyclohexenol	27.8	23.1	–
		cyclohexenone	7.0	5.4	
		cyclohexene oxide	1.3	0.9	
8	cyclooctene	many products	–	–	–
9	styrene	benzaldehyde	21.3	25.6	–
		styrene oxide	6.7	1.6	
10	benzene	phenol	16.6	2.4(3.4) ^[e]	–
11	cyclohexanol	cyclohexanone	13.6	10.6	–
12	benzyl alcohol	benzaldehyde	54.9	64.4	–
13	<i>N,N</i> -dimethylaniline	<i>N</i> -methyl aniline	–	15.3	–
		<i>N</i> -methylformanilide	–	16.7	

[a] 50 equivalents of H₂O₂ used. [b] Ar purge. [c] 100 equivalents of substrate were suspended in the solvent. [d] Under air. [e] In [D₆]acetone.

with the $[\text{Fe}_2\text{O}(\text{bpy})_4(\text{H}_2\text{O})_2](\text{ClO}_4)_4/\text{H}_2\text{O}_2$ system ($\text{bpy} = 2,2'$ -bipyridine).^[24] Under argon purge, the yields of both alcohol and ketone were strongly decreased (Table 2, entry 2), proving that trace amounts of O_2 play an important role during the reaction.

The behavior of $1/\text{H}_2\text{O}_2$ towards alkane substrates can be compared with several groups of non-heme iron catalysts: a) the Gif family of catalysts, which afford mainly ketone products;^[25] b) catalysts with $A/K \approx 1$ such as $[\text{Fe}_2\text{O}(\text{OAc})_2(\text{bpy})_2]\text{Cl}_2$, $[\text{Fe}_2\text{O}(\text{OAc})(\text{tmima})_2](\text{ClO}_4)_3$ ($\text{tmima} = \text{tris}[(1\text{-methylimidazol-2-yl)methyl}]\text{amine}$),^[26] $[\text{Fe}(\text{pma})](\text{ClO}_4)_2$,^[27] and $[\text{Fe}_2\text{O}(\text{bpy})_4(\text{H}_2\text{O})_2](\text{ClO}_4)_4$,^[24] and c) catalysts with large A/K ratios such as $[\text{Fe}(\text{bpmen})(\text{CH}_3\text{CN})_2](\text{ClO}_4)_2$ ($A/K = 6.3$)^[21] and $[\text{Fe}(\text{tpa})(\text{CH}_3\text{CN})_2](\text{ClO}_4)_2$ ($A/K = 4.3$).^[18d] Thus the A/K ratio found for $1/\text{H}_2\text{O}_2$ corresponds most closely to those associated with the catalysts in group b. An A/K ratio of approximately 1 is symptomatic of the presence of free alkyl radical intermediates, which react rapidly with O_2 to initiate a radical chain autoxidation.^[20c] In support, significant amounts of cyclohexyl bromide were formed in the presence of excess methylene bromide (Table 1, entries 4 and 11), which serves as an excellent trap for free alkyl radicals.^[28] These radicals can then be trapped by dioxygen to form alkylperoxy radicals that afford equimolar amounts of ketone and alcohol in a Russell termination reaction^[20] or by $\text{Fe}^{\text{IV}}\text{O}$ species to give alcohols.^[20a]

The behavior of $1/\text{H}_2\text{O}_2$ with olefins supports mechanistic conclusions derived from the alkane oxidation experiments. Styrene was converted to styrene oxide and benzaldehyde (Table 2, entry 9), whereas cyclohexene oxidation afforded the corresponding allylic alcohol and ketone, and very little epoxide (Table 2, entry 7). With cyclooctene, which is less susceptible to allylic oxidation,^[29] many different oxidation products were found, each accounting for less than one turnover (Table 2, entry 8). These observations contrast with those for $[\text{Fe}(\text{tpa})(\text{CH}_3\text{CN})_2](\text{ClO}_4)_2$ ^[18d] and $[\text{Fe}(\text{cyclam})](\text{CF}_3\text{SO}_3)_2$ ($\text{cyclam} = 1,4,8,11\text{-tetraazacyclotetradecane}$),^[30] non-heme iron complexes which catalyze the stereospecific epoxidation of olefins with H_2O_2 as oxidant. The observations that the $[\text{Fe}(\text{N4Py})(\text{CH}_3\text{CN})](\text{ClO}_4)_2/\text{H}_2\text{O}_2$ oxidation of cyclohexene gives mainly allylic oxidation products and that the oxidation of styrene gives benzaldehyde as the major product point to the involvement of a radical oxidant. The formation of small amounts of styrene oxide might implicate a two-electron oxidant, but the absence of significant amounts of epoxide in the oxidation of cyclohexene and cyclooctene suggests that the styrene oxide observed is more likely to be the result of a radical addition to the double bond followed by ring closure, as proposed for the epoxidation of styrene by $[(\text{tmp})\text{Fe}^{\text{IV}}\text{O}](\text{tmp} = \text{tetramesitylporphyrin dianion})$.^[31]

The $1/\text{H}_2\text{O}_2$ system also catalyzed efficient oxidation of cyclohexanol to cyclohexanone and benzyl alcohol to benzaldehyde (Table 2, entries 11 and 12) as well as the *N*-demethylation of *N,N*-dimethylaniline (Table 2, entry 13). However, since such oxidations are not unique for a particular oxidizing agent, little mechanistic insight can be drawn from these results.

Effect of hydroxyl radical traps on alkane oxidation: The alkane hydroxylation mechanism was further elucidated with

benzene and acetone as hydroxyl radical traps. The use of benzene as a substrate under standard conditions resulted in the formation of phenol (Table 2, entry 10), and no diphenyl was detected. Although this oxidation may occur with a metal-based oxidant, the pronounced effect of the solvent strongly suggests the attack of $\cdot\text{OH}$ radicals.^[32] In acetonitrile 17 turnovers of benzene to phenol were found, but in acetone only 2.6 turnovers were obtained, a decrease in activity of more than sixfold. These observations may be rationalized by the fact that acetone is a good trap for $\cdot\text{OH}$ radicals as well,^[33] thus reducing the turnover number (TON) of benzene to phenol in that solvent. Since a $k_{\text{H}}/k_{\text{D}}$ ratio of approximately 2 has been reported for hydrogen abstraction from acetone by $\cdot\text{OH}$,^[33] the use of $[\text{D}_6]\text{acetone}$ as solvent should lead to increased yields of oxidized products; indeed the turnover number for phenol increased to 3.4. The presence of benzene during cyclohexane oxidation decreased the yields of the oxidation products. With 10% (v/v) benzene, the turnover numbers for cyclohexanol and cyclohexanone were 16.7 and 8.4, respectively (Table 1, entry 5); they decreased further, to 10.5 and 4.0, respectively, in 50% v/v benzene (Table 1, entry 6), presumably because of the trapping of hydroxyl radicals. Furthermore, the A/K ratios observed increased steadily from 1.4 in pure acetonitrile to 2.0 in 10% (v/v) benzene and 2.6 in 50% (v/v) benzene. These results strongly suggest the involvement of other oxidation mechanisms.

Alkane hydroxylation experiments in acetone as solvent support the possible participation of other mechanisms of cyclohexane oxidation. The oxidation of cyclohexane in acetone afforded 16 turnovers of alcohol and 6 of ketone (Table 1, entry 7), a 35% decrease in turnover number relative to that in acetonitrile, consistent with the trapping of hydroxyl radicals. In support, the turnover numbers in $[\text{D}_6]\text{acetone}$ increased to 20.0 and 9.4 for cyclohexanol and cyclohexanone (Table 1, entry 12), respectively; these are comparable with those found in acetonitrile. As in the case of benzene, the A/K ratio increased from 1.4 in acetonitrile to 2.1 in $[\text{D}_6]\text{acetone}$ and 2.6 in acetone, but the latter value decreased to 0.9 for the reaction in air (Table 1, entry 8), demonstrating that free alkyl radicals were formed in the reaction and trapped by O_2 . However the A/K ratios increased to 3.7 and 5.2 when the H_2O_2 was introduced by syringe pump over 70 and 200 min periods, respectively (Table 1, entries 9 and 10). These results strongly suggest that $\cdot\text{OH}$ radicals do play a role in the oxidation reaction catalyzed by **1**, particularly in acetonitrile. However, trapping of $\cdot\text{OH}$ radicals by acetone or benzene leads to only partial quenching of cyclohexane oxidation. In the presence of these traps, the A/K ratio can jump from 1.3 to as much as 5.2, suggesting that the radical chain autoxidation pathway can be suppressed. These observations raise the possibility that a second oxidizing species may be involved.

Mechanistic probes of alkane hydroxylation: The $k_{\text{H}}/k_{\text{D}}$ ratios for the formation of cyclohexanol were determined in competition experiments between cyclohexane and $[\text{D}_{12}]\text{cyclohexane}$. In acetonitrile the value of 1.5 (Table 1, entry 1) approached that associated with hydroxyl radicals.^[34] As the reaction conditions were modified to trap hydroxyl radicals,

the k_H/k_D ratio rose (Table 1, entries 6, 7, and 12), and it could be further increased to 2.7 by syringe-pump addition of H_2O_2 in acetone over a 200 min period (Table 1, entry 10). Values of 1–2, generally associated with radical chain autoxidations,^[35] have been reported for many systems, for example, $Fe(ClO_4)_3 \cdot 6H_2O$ (1.5),^[26] $[Fe_2O(OAc)_2(bpy)_2]Cl_2$ (1.4),^[26] and $[Fe_2O(bpy)_4(H_2O)_2](ClO_4)_4$ (2.1).^[24] Larger k_H/k_D ratios have been found for hydrogen abstraction by stereospecific alkane hydroxylation catalysts such as $[Fe(tpa)(CH_3CN)_2](ClO_4)_2$ (3.5)^[18d] and iron porphyrins (10–24).^{[13], [36]} The increase in k_H/k_D under conditions that diminish the effect of hydroxyl radicals supports the deduction from the radical trap experiments that an oxidant more selective than the hydroxyl radical is also involved in the oxidation.

With adamantane as substrate, oxidation occurred at both secondary and tertiary carbon centers (Table 2, entries 5 and 6), but there was selectivity for oxidation at the tertiary position ($3^\circ/2^\circ$ 3.1–3.3, normalized on a per-hydrogen basis). For comparison: $3^\circ/2^\circ$ ratios of 2.7, on average, have been found for Gif-type oxidations,^[37] about 2 for the oxidation of alkanes by $\cdot OH$,^[37b] 3.5 for oxidations with $[Fe_2O(OAc)_2(bpy)_2]Cl_2/H_2O_2$,^[26] 9.5–10 for oxidations with $[Fe_2O(bpy)_4(H_2O)_2](ClO_4)_4/tBuOOH$ or $[FeCl_2(tpa)](ClO_4)_4/tBuOOH$,^[38] and 11–48 for oxidations with PhIO catalyzed by P450 mimics.^[39] Thus the oxidant involved in $[Fe(N4Py)(CH_3CN)](ClO_4)_2/H_2O_2$ is not as reactive as hydroxyl radicals, but only slightly less so.

The stereoselectivity of the alkane hydroxylation reaction was examined with *cis*- and *trans*-1,2-dimethylcyclohexane as substrates (Table 2, entries 3 and 4). Both isomeric 1,2-dimethylcyclohexanols were formed, with *cis/trans* ratios of 1.4–1.9. These ratios were in sharp contrast with the stereospecificity found for $[Fe(tpa)(CH_3CN)_2](ClO_4)_2/H_2O_2$,^[18d] $[Fe(bpmen)(CH_3CN)_2](ClO_4)_2/H_2O_2$,^[21] and cytochrome P450 models,^[40] but were more in the range of the *cis/trans* ratios found for catalytic autoxidation reactions (1.1–1.3).^[41] Again, this indicates the formation of alkyl radicals with a lifetime sufficient to allow epimerization at the radical site.

Nature of the key oxidizing species: The fact that **1** reacts with H_2O_2 to form the $Fe^{III}OOH$ intermediate **2** raises the question of its involvement in the oxidation reaction, either as the oxidant or as its precursor by cleavage of the O–O bond. The 530 nm absorption of **2** in acetone was monitored concomitantly with the oxidation of cyclohexane to cyclohexanol and cyclohexanone. Figure 1 shows that the reaction is essentially complete after 15 min, coincident with the disappearance of the characteristic visible absorption of the intermediate, and demonstrates that the intermediate is indeed involved in the catalytic oxidation. However, the lifetime of the intermediate was not affected when $[D_{12}]$ cyclohexane was used as substrate, despite a kinetic isotope effect (KIE) of 2.3 for cyclohexane oxidation. It thus appears likely that the $Fe^{III}OOH$ intermediate itself is not the active oxidant, but serves as the precursor for the active species.

Decay of the $Fe^{III}OOH$ intermediate to form the active oxidant can occur through O–O bond homolysis or heterolysis. From the results described above it is clear that the

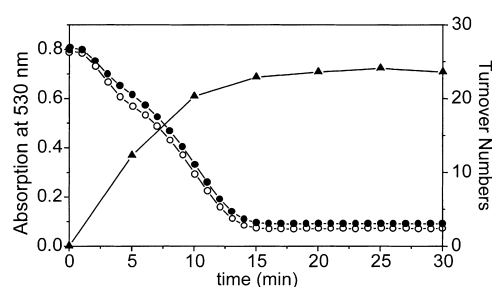


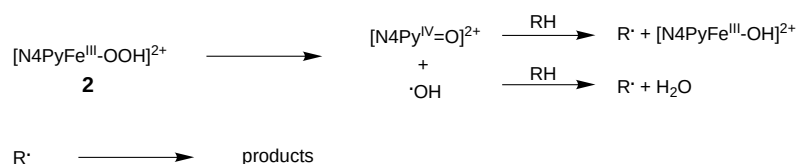
Figure 1. Catalytic oxidation, in acetone at 25 °C, of cyclohexane and $[D_{12}]$ cyclohexane and UV/Vis absorption monitored over time: ▲ total TON; ● absorption at 530 nm with cyclohexane as substrate; ○ absorption at 530 nm with $[D_{12}]$ cyclohexane as substrate.

reactivity of the **1**/ H_2O_2 system can be explained only in terms of one-electron oxidation and not by the involvement of a two-electron oxidant such as the (formally) Fe^VO species proposed for cytochrome P450. The arguments for a radical-type oxidation are:

- The oxygen sensitivity of the oxidation of cyclohexane and cyclooctane and the formation of cyclohexyl bromide in the presence of methylene bromide reveals the involvement of free alkyl radicals, which is further supported by the lack of stereoselectivity in the oxidation of dimethylcyclohexane. This indicates hydrogen abstraction by a radical species and not by an Fe^VO species followed by oxygen rebound as proposed for cytochrome P450 and P450 model compounds.^[6, 13] Furthermore, addition of radical scavengers resulted in partial quenching of the reactivity towards cyclohexane.
- The KIE values of approximately 2 are in the range for radical-type oxidations. Oxidation by two-electron oxidants typically results in much higher KIE values.
- The observed C3/C2 ratio of approximately 3 in adamantane oxidation is comparable with that found for radical-type oxidations, whereas cytochrome P450 mimics give higher selectivity for tertiary positions.
- Complex **1** is unable to catalyze epoxidation, a typical two-electron oxidation process. Although the oxidation of styrene yielded the oxide in significant amounts, this result can also be explained in terms of radical addition to the double bond followed by ring closure. Furthermore, the formation of large amounts of benzaldehyde during styrene oxidation indicates a radical-type oxidation.

Hence it can be concluded that the $Fe^{III}OOH$ intermediate does not react through heterolysis of the O–O bond to give a (formally) Fe^VO species, which would be a two-electron oxidant. All the evidence points to one-electron oxidants and strongly suggests that **2** reacts by homolysis to give two radical species: $[(N4Py)Fe^{IV}O]^{2+}$ and $\cdot OH$ (Scheme 4).

The involvement of $\cdot OH$ radicals is evident from the results with acetonitrile as solvent: a low A/K ratio in the oxidation of cyclohexane, a low KIE for cyclohexanol formation and significant hydroxylation of benzene to phenol. Furthermore, the turnover numbers for the last of these reactions decreases drastically in the presence of a radical trap such as acetone. These observations lead to the conclusion that at least part of the observed reactivity results from free radical chemistry initiated by hydroxyl radicals.

Scheme 4. Possible mechanism for oxidation by **2**.

Whether the $[(\text{N4Py})\text{Fe}^{\text{IV}}\text{O}]^{2+}$ species itself is (re)active is more difficult to solve. In heme chemistry oxidative transformations by the $\text{Fe}^{\text{IV}}\text{O}$ moiety, such as the oxygenation of triphenylphosphine to triphenylphosphine oxide^[42] and the nonstereospecific epoxidation of olefins,^[31, 43] have been reported. Recently, the intramolecular hydroxylation of an aromatic ring has been observed for a non-heme $\text{Fe}^{\text{IV}}\text{O}$ moiety also.^[44] No examples of hydrogen abstraction from saturated alkanes by $\text{Fe}^{\text{IV}}\text{O}$ moieties have been reported, to our knowledge. However, an important difference between heme systems and **1** is that the porphyrin ligands have a double negative charge and N4Py is a neutral ligand. Therefore a more electronegative $\text{Fe}^{\text{IV}}\text{O}$ species will be formed in the homolysis of **2**, making hydrogen abstraction from saturated alkanes more likely. Several observations support the idea that $[(\text{N4Py})\text{Fe}^{\text{IV}}\text{O}]^{2+}$ may be involved in oxidations catalyzed by **1**. First, trapping of $\cdot\text{OH}$ radicals by added radical traps such as acetone leads to only a minor reduction in turnover numbers, strongly suggesting that the $\cdot\text{OH}$ radical is not the sole species responsible for oxidation. Indeed, the only catalytic reaction that is significantly affected by the use of acetone as solvent is the hydroxylation of benzene, which is typically carried out by $\cdot\text{OH}$ radicals. Furthermore, the use of $\cdot\text{OH}$ radical traps leads to an increase in the A/K ratio in cyclohexane oxidation, a result inconsistent with radical chain autoxidation chemistry. Most convincing, however, are the KIE values obtained for cyclohexane oxidation. The low value in acetonitrile indicates large contribution of $\cdot\text{OH}$ radicals. Trapping of $\cdot\text{OH}$ radicals by benzene or acetone leads to an increase in $k_{\text{H}}/k_{\text{D}}$ to 2.3. With slow addition of H_2O_2 , to decrease the effect of radical chain autoxidations, $k_{\text{H}}/k_{\text{D}}$ increases further to 2.7, which is significantly beyond the range normally observed for $\cdot\text{OH}$ oxidations. This strongly suggests the involvement of a more selective oxidizing species, for example metal-based. On the basis of these observations we propose that the iron hydroperoxide intermediate **2** reacts through homolysis of the O–O bond and that the resulting species, $[(\text{N4Py})\text{Fe}^{\text{IV}}\text{O}]^{2+}$ and $\cdot\text{OH}$, are both capable of effecting hydrogen bond abstraction of organic substrates.

Comparison with other systems: Comparison of the chemistry of the low-spin $\text{Fe}^{\text{III}}\text{OOH}$ intermediates involved in the present system with that of those in oxidations catalyzed by $[\text{Fe}(\text{tpa})(\text{CH}_3\text{CN})_2](\text{ClO}_4)_2$ and Fe–BLM reveals marked differences, which appear to be related to the number of coordinating N atoms in the ligand. The systems (**1** and Fe–BLM) with pentadentate ligands show similar reactivity to a number of substrates. In both systems epoxidation of styrene is accompanied by formation of benzaldehyde, hydroxylation of aromatic compounds, and demethylation of DMA. Furthermore, the observation that **1**/ H_2O_2 reacts with alkanes to

form long-lived alkyl radicals which react mainly with O_2 to give the products corresponds with the proposed mechanism for DNA degradation by Fe–BLM,^[8] according to which hydrogen abstraction occurs at the C4' position of the deoxyribose

ring to generate a long-lived alkyl radical that can trap dioxygen to form a peroxy radical intermediate that degrades further to cause DNA strand cleavage (the oxygen-dependent route). These observations suggest that Fe–BLM and **1** react through similar mechanistic pathways, through homolysis of the O–O bond of the $\text{Fe}^{\text{III}}\text{OOH}$ intermediate. The alternative mechanism, which involves a (formally) Fe^{VO} species derived from O–O bond heterolysis, has been considered for Fe–BLM, mainly on the basis of the observed reactivity of Fe–BLM with iodosylbenzene. As discussed in the literature,^[15] the interpretation of these results is complicated by the fact that iodosylbenzene can also be activated by redox-inactive Lewis acids, so the involvement of an Fe^{VO} moiety is not established. Therefore our analysis of the cumulative data presented here on the reactivity of **2**, an intermediate strongly reminiscent of activated bleomycin, provides strong support for a mechanism for Fe–BLM involving homolytic scission of the O–O bond in activated bleomycin, giving $[\text{BLM}-\text{Fe}^{\text{IV}}\text{O}]$ and $\cdot\text{OH}$.

The oxidation chemistry of the $[\text{Fe}(\text{tpa})(\text{CH}_3\text{CN})_2](\text{ClO}_4)_2$ system^[18d] differs from those observed for **1** and Fe–BLM, even though an $\text{Fe}^{\text{III}}\text{OOH}$ intermediate very similar to **2** and activated BLM is observed.^[7] The tpa-based catalysts are capable of stereospecific epoxidation of olefins and hydroxylation of alkanes with H_2O_2 . This could suggest heterolysis of the O–O bond of the $[\text{Fe}(\text{tpa})\text{OOH}]^{2+}$ (**3**) intermediate to give (formally) $[(\text{tpa})\text{Fe}^{\text{VO}}]^{3+}$. Evidence in support of this hypothesis was provided recently for the $\text{Fe}[(\text{bpmen})(\text{CH}_3\text{CN})_2](\text{ClO}_4)_2$ system.^[21] Incorporation of ^{18}O in the product in the presence of H_2^{18}O suggested the involvement of an oxidant that could undergo solvent exchange.

Since resonance Raman spectroscopy showed that the O–O bonds in **2** and **3** were of comparable strength ($\nu(\text{O}-\text{O})$ 790 and 789 cm^{-1} , respectively)^[23] it is difficult to imagine why **2** would react through homolysis of the O–O bond and **3** through heterolysis. Therefore there appears to be a more important factor controlling the decomposition pathway of the $\text{Fe}^{\text{III}}\text{OOH}$ intermediate.

The explanation may be that tpa is a tetradentate ligand, leaving two “open” coordination sites in the iron complex, in contrast to the pentadentate N4Py (and BLM). Whereas **2** reacts through homolysis of the O–O bond of the η^1 -coordinated hydroperoxide as described above, $[\text{Fe}(\text{tpa})(\eta^1\text{-OOH})]^{2+}$ (**3**) may react through a transition state in which the hydroperoxide is bound in an η^2 fashion (Figure 2), analogously to proposed mechanisms for other peroxide-utilizing transition metal catalysts such as the Sharpless epoxidation catalyst^[45] and MeReO_3 .^[46] The $\text{Fe}^{\text{III}}-(\eta^2\text{-OOH})$ complex could then react through heterolysis of the O–O bond to give a (formally) Fe^{VO} species that elicits stereospecific oxidation of a substrate. Whether this difference in peroxide coordina-

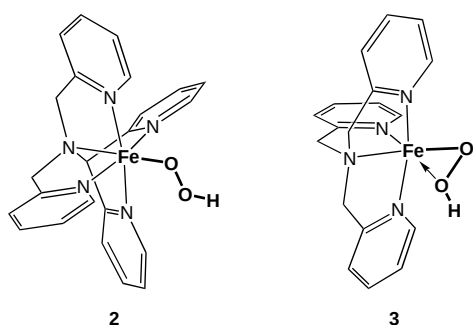


Figure 2. Coordination modes for the hydroperoxide ligand in intermediates **2** and **3**.

tion mode is the reason for the difference in reactivity remains to be elucidated.

Conclusion

We have shown that the N4Py–Fe system is one of the most reactive non-heme iron catalysts known to date, capable of oxidizing a wide range of organic substrates including alkanes, alkenes, alcohols, benzene, and DMA. Complex **1** reacts with H_2O_2 to give the well characterized $[(\text{N4Py})\text{Fe}^{\text{III}}\text{OOH}]^{2+}$ intermediate **2**, with properties strongly reminiscent of activated BLM. Intermediate **2** reacts through homolysis of the O–O bond, affording two species: $[(\text{N4Py})\text{Fe}^{\text{IV}}\text{O}]^{2+}$ and $\cdot\text{OH}$. Although $\cdot\text{OH}$ radicals are involved in substrate oxidation, the results obtained cannot be explained solely by the action of $\cdot\text{OH}$ radicals. Therefore we propose that the $\text{Fe}^{\text{IV}}\text{O}$ species also plays a prominent role in oxidation of the substrate. The involvement of this species and the nature of the oxidizing complex need to be elucidated further. The formation of a low-spin iron(III) intermediate by both **1** and Fe–BLM, and their similar oxidation chemistry, lead to the attractive hypothesis that **1** and Fe–BLM react through the same mechanistic pathways. In view of the results described above, the chemistry of Fe–BLM should be considered in terms of homolysis of the O–O bond in activated bleomycin.

Experimental Section

Instrumentation and materials: UV/Vis spectra were recorded on a Hewlett Packard 8453 UV–Visible Spectrophotometer. GC analyses were performed on a Hewlett Packard 6890 Gas Chromatograph using an HP-1 dimethyl polysiloxane column, an HP-5 5% phenyl methyl siloxane column, or a CP-wax 52 CB column. Retention times of oxidation products were compared with commercial or independently prepared samples. Complex **1** was prepared according to published procedures.^[18a, 47] **Caution:** Perchlorate salts are potentially explosive and should be handled with care.

Catalytic oxidations: All experiments were carried out under argon, unless noted otherwise, in a water bath thermostatted at 25 °C.

In a typical procedure, cyclohexane (0.38 mL, 1000 equiv) was added to a solution of **1** (8.75×10^{-4} M, 4 mL) and a known amount of bromobenzene (internal standard) in acetone. The reaction was started by addition of 30% H_2O_2 (35 μL). After 30 min an aliquot (1 mL) was taken from the reaction and filtered over a small silica column. The silica was washed thoroughly with diethyl ether or diethyl ether/10% methanol. The sample was concentrated to 2 mL by passing an argon stream over the solution, then analyzed by GC.

Kinetic isotope effect determination: In essentially the procedure described above, a cyclohexane/ $[\text{D}_{12}]$ cyclohexane (1:1) mixture was used. The KIE was determined by comparing the turnover numbers for cyclohexanol and $[\text{D}_{11}]$ cyclohexanol (determined by GC with the CP-wax 52 CB column) and corrected for the relative concentrations of cyclohexane and $[\text{D}_{12}]$ cyclohexane.

Acknowledgement

This work was supported by the Unilever Research Laboratory, Vlaardingen (The Netherlands), and the National Institutes of Health, Washington DC (GM-33162).

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Received: October 12, 1999 [F2083]