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Biomimetic nonheme iron catalysts for alkane hydroxylation

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Abstract

The catalytic functionalization of alkanes under mild conditions is a subject of great current interest. Nature has evolved a number of metalloenzymes such as the heme-contain

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ing cytochrome P450 and the nonheme methane monooxygenase, which are capable of effecting such transformations. There has thus been significant interest in modeling such enzyme active sites and developing biomimetic alkane hydroxylation catalysts. In this review, the efforts of the last 10 years in the development of nonheme iron catalysts are summarized and discussed. These catalysts typically act in concert with ROOH or H_2O_2. With ROOH as oxidant, it is clear from mechanistic studies that alkoxyl radicals are the principal agents that cleave the alkane C–H bond to generate long-lived alkyl radicals. This conclusion, for the most part, applies also for oxidations involving H_2O_2. In a few cases, however, stereospecific alkane hydroxylation is observed. For these instances, there is evidence from $H_2^{18}O$ exchange experiments that a high-valent iron-oxo species is involved.

Keywords: Biomimetic; Iron catalysts; Alkane hydroxylation; Nonheme iron enzymes; Peroxide

1. Introduction

Selective and catalytic oxidations of organic molecules are amongst the most important technological processes in the chemical industry [1]. However, despite great strides in organic synthesis in this century, most of the organic transformations still require some functionality in the starting materials to serve as the locus of the reaction. On the other hand, chemical raw materials are principally hydrocarbons, alkanes in particular, which come from natural gas and crude oil. Due to their intrinsic inert nature, the selective functionalization of alkanes is a key objective in the chemical industry [2]. Although alkane oxidation is a thermodynamically favored process, it is difficult to do so in a controlled and selective fashion. Traditional oxidants such as chromate or permanganate are rather inefficient and barely selective. Primarily, they have been discarded due to their economic and environmental costs in favor of cheap oxidants such as air or peroxides, but these latter processes are extremely inefficient and require constant recycling of substrates. For example, Nylon-6 and Nylon 6,6′ are manufactured on a scale of 10^6 tons per year using the DuPont process in which cyclohexane is initially oxidized to a mixture of cyclohexanol and cyclohexanone [3]. The conversion of the alkane into these products is kept under 5% to avoid their over-oxidation, so the unreacted cyclohexane needs to be extracted and recycled. Thus increasing the efficiency and selectivity of hydrocarbon transformations has been the goal of both academic and industrial research efforts.

Nature has developed an excellent solution for this problem, by utilizing metalloenzymes as catalysts in selective hydrocarbon oxidation [4–7]. Iron-containing biological molecules play important roles in these biologically essential transformations. For example, cytochrome P450 selectively oxidizes the long aliphatic side chain of cholesterol, in the biosynthesis of the female hormone progesterone [8]; methane monooxygenase converts methane to methanol as part of the metabolism of methanotrophs [5]; and the antitumor drug bleomycin cleaves DNA oxidatively by abstracting the 4′-hydrogens of the ribose rings on the DNA [9] (Fig. 1). In all

of these reactions, an aliphatic C–H bond on the substrate is oxidized to give an alcohol product that is susceptible to further transformation. The selectivity and the efficiency of these reactions and the mild reaction conditions indicate a methodology distinct from traditional industrial processes, which usually require higher temperatures and pressures. However, it is not straightforward to adapt the rather fragile biological catalyst to tolerate harsher industrial conditions. Thus the development of biomimetic inorganic catalysts has attracted the interest of the bioinorganic community. There is already a large body of work centered on the development of biomimetic heme catalysts paralleling our understanding of heme enzyme mechanisms [10]. With our improved understanding of nonheme iron biocatalysts, work on biomimetic analogs has also increased. In this review, we focus on these studies of biomimetic nonheme iron complexes and mechanistic insights derived therefrom.

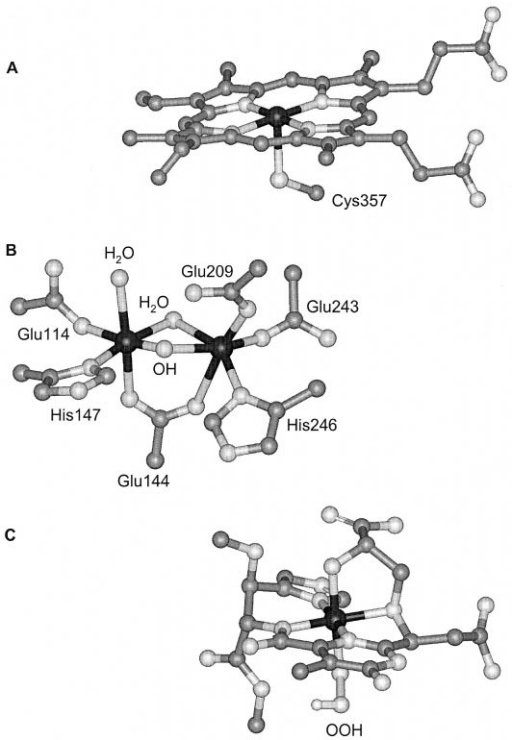

Fig. 1. The active sites of (A) cytochrome P450 (generated from PDB file 2CPP) [138]; (B) the oxidized form of methane monooxygenase (generated from PDB file 1MTY) [21]; and (C) the Co–OOH form of bleomycin (based on the coordinates provided by the authors of Ref. [139]). The amino acid side-chains and the non-coordinating moieties of bleomycin are omitted for clarity.

2. Biochemical precedents

Fig. 1 shows the active sites of three bioactive molecules that attack substrate aliphatic C–H bonds. Cytochrome P450 has a heme cofactor, which also serves as the active site for peroxidases [11,12], prostaglandin synthase [13,14], and NO synthase [15,16]. Methane monooxygenase has a carboxylate-bridged diiron site, found also in fatty acid desaturases to dehydrogenate saturated fatty acids and ribonucleotide reductase to generate its catalytically essential tyrosyl radical [5]. Bleomycin has a mononuclear nonheme iron center coordinated to five nitrogen ligands: an amidate, a pyrimidine, an imidazole, and two amines [9]. Much has been learned about the reactions performed by these catalysts.

2.1. Cytochrome P450

The extensive efforts to understand the catalytic mechanism of the heme-containing cytochrome P450 over the past 25 years have made it the paradigm for oxygen activation and hydrocarbon oxidation by an iron center [8]. As shown in Fig. 2, the first step entails the binding of the alkane substrate to the active site, which triggers the one-electron reduction of the Fe^{III}. The subsequent binding of O_2 to the Fe^{II} center forms an adduct analogous to oxyhemoglobin. The transfer of an electron and a proton to the active site generates an Fe^{III}–OOH species, strongly implicated by density functional calculations [17] and very recently observed with EPR and ENDOR techniques [18]. Decomposition of this putative intermediate by O–O bond heterolysis affords a formally Fe^{V}=O species that is responsible for substrate oxidation. This species is better described as $[(Por^{\bullet})Fe^{IV}=O]^{+}$, by analogy to the metastable but well characterized heme peroxidase compound I intermediate derived from the reaction of the Fe^{III} peroxidase with H_2O_2 [11,12]. In support of the correspondence between cytochrome P450 and heme peroxidase chemistry, the high-valent intermediate of cytochrome P450 can also be generated in the reaction of the Fe^{III} enzyme with peroxides through a 'peroxide shunt' or with single oxygen atom donors such as PhIO [19]. Substrate oxidation then occurs presumably by transfer of the terminal oxo atom.

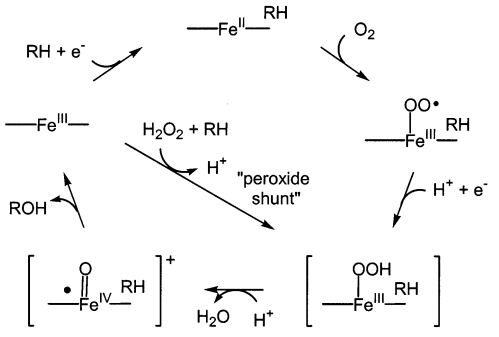

Fig. 2. The reaction mechanism of alkane hydroxylation proposed for cytochrome P450.

2.2. Methane monooxygenase

Methane monooxygenase (MMO) is an enzyme that exhibits a catalytic versatility similar to that of cytochrome P450 but has a carboxylate-rich nonheme diiron active site [20–22]. Oxygen binding to the diiron(II) enzyme generates two reactive intermediates that have been spectroscopically characterized: an intermediate called **P** or H_{peroxo}, whose properties suggest a (μ-1,2-peroxo)diiron(III) species [23,24], and an intermediate **Q**, which is best described as a diiron(IV) species [25,26] with an $Fe_2(\mu\text{-}O)_2$ core [27]. Strong support for these formulations is also provided by density functional theory calculations [28–31]. As shown in Fig. 3, MMO intermediate **P** is proposed to be analogous to the Fe^{III}–OOH intermediate of cytochrome P450, with the second iron replacing the proton, while MMO intermediate **Q** corresponds to the $[(Por^{\bullet})Fe^{IV}{=}O]^{+}$ species in cytochrome P450, with the second iron(IV) in place of the porphyrin radical. Intermediate **Q** has been shown to be kinetically competent to oxidize methane to methanol [26,32], and the mechanism of oxygen transfer to substrate has been the subject of intense discussion in the literature [33–37].

Related to MMO is a family of soluble fatty acid desaturases, one of which has been shown by X-ray crystallography to have a very similar carboxylate-rich nonheme diiron site [38]. This enzyme has also been shown to generate a **P**-like intermediate, which by Mössbauer and Raman spectroscopy is demonstrated to be a (μ-1,2-peroxo)diiron(III) species [39], but no high-valent intermediate analogous to MMO-**Q** has been observed to date. However, the structural and functional correspondence between the two nonheme diiron active sites suggests that such high-valent centers are useful for oxygen activation and consequent cleavage of unreactive C–H bonds.

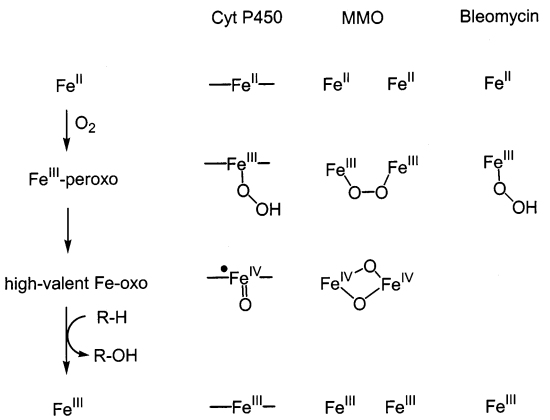

Fig. 3. Comparison of the reaction mechanisms of cytochrome P450, MMO, and bleomycin.

2.3. Bleomycin

The third component of Fig. 1 is bleomycin (BLM), a low molecular weight glycopeptide that in concert with Fe^{II} is effective as an antitumor drug [9,40]. Its antitumor activity is believed to derive from its ability to activate O_2 to cleave DNA oxidatively in a double strand fashion. From extensive studies, it is clear that the drug binds Fe^{II} and forms an O_2 adduct like oxyP450 [41]. Upon injection of an electron and a proton, an intermediate called 'activated BLM' is formed [42], which has been characterized to be a low-spin Fe^{III}–OOH species [43]. Subsequent O–O bond lysis results in the oxidative cleavage of the target DNA. The precise nature of the oxidant remains under discussion, but it is clear that there are both O_2-independent and O_2-dependent pathways by which the DNA is cleaved [9,40].

From a perusal of Fig. 3, one can glean the notion that there is much analogy among the reaction mechanisms of heme and nonheme iron-containing biological systems. Studies of metalloporphyrin-catalyzed hydrocarbon oxidations in the 1980s have played a significant role in enhancing our understanding of the mechanism of cytochrome P450 and other heme enzymes. With nonheme iron enzymes coming of age in the 1990s, there have been a number of studies of biomimetic nonheme iron oxidation catalysts. In this paper, we review those investigations that focus on alkane hydroxylation and place them within a common mechanistic framework.

3. Biomimetic nonheme iron catalysts

The reaction between iron(II) and H_2O_2 or 'Fenton's reagent' (Eqs. (1) and (2), R = H) [44], despite having been studied for over 80 years, still arouses intense disagreements with respect to the species generated in the reaction, as illustrated in several recent commentaries [45–48].

$$Fe^{III} + ROOH \rightarrow Fe^{II} + ROO^{\bullet} + H^{+} \quad (1)$$

$$Fe^{II} + ROOH \rightarrow Fe^{III} + RO^{\bullet} + HO^{-} \quad (2)$$

Tables 1 and 2 list the nonheme iron complexes that have been explored for their ability to catalyze alkane hydroxylation (Fig. 4). In almost all the studies, cyclohexane has been the substrate of choice due to the ease of product identification, and the systems discussed in this review consist of the iron complex in combination with a peroxide (ROOH or H_2O_2). The tables show that there are variations in the efficiency of converting the oxidizing equivalents stored in the peroxide into products and in the product distributions; only in few cases is stereospecific alkane hydroxylation observed. Therefore the mechanisms for alkane oxidation must vary.

Table 1
Oxidation of cyclohexane by ^{t}BuOOH with various nonheme iron catalysts[a]

Entry	Catalyst	Time	Eff. (%)[b]	A/K[c]	KIE[d]	3°/2°[e]	Ref.
1	$[Fe(OPPh_3)_4]^{2+}$	4–6 h	24	0.2	5.2		[119]
2	$[Fe(CH_3CN)_4]^{2+}$	4–6 h	22	0.1	5.6		[119]
3	$[Fe(bpy)_2]^{2+}$	4–6 h	20	0.1	4.8		[119]
4	$[Fe_2(OH)Mac16]^{3+}$	5 min					[120]
	100 equiv. ^{t}BuOOH		28	0.8			
	10 equiv. ^{t}BuOOH (sp)	60 min	34	14			
5	$FeCl_3$	4–6 h	34	0.6	4.3		[119]
6	$[Fe(PMA)]^{2+}$	30 min	40	1.0	6.5	6	[86]
7	$[Fe(PMC)]^{2+}$	30 min	22	1.1			[86]
8	$[FeCl_2(TPA)](ClO_4)$	2 h	23	1.3	5.4	7	[82,87]
9	$[FeCl_2(TPA)](BF_4)$	2 h	12	1.5			[90]
10	$[FeBr_2(TPA)](ClO_4)$	1 h	21	0.7		7	[82,87]
11	$[FeBr_2(NTB)](ClO_4)$	36 h	5	1			[82,87]
12	$[Fe_2O(bpy)_4(H_2O)_2](ClO_4)_4$	3–5 min	31	0.9	7.1[f]	10	[121,122]
13	$[Fe_2O(OAc)(bpy)_4](ClO_4)_3$	2 h	28	1.2	6.1[f]	11	[122]
14	$[Fe_2O(OAc)_2(bpy)_2(H_2O)_2](ClO_4)_2$	10 h	31	1.2			[122]
15	$[Fe_2O(OAc)_2Cl_2(bpy)_2]$	72 h	54	1.5			[123]
16	$[Fe_2O(tmima)_2(H_2O)_2](ClO_4)_4$ [g]		5%/h	1.0		10	[83]
17	$[Fe_2O(OAc)(tmima)_2](ClO_4)_3$ [g]	~24 h	26	0.9			[83,84]
18	$[Fe_2O(OAc)(bMimen)_2](ClO_4)_3$ [h]	1 h	6	0.8	4		[124]
19	$[Fe_2O(OAc)(bpmen)_2](ClO_4)_3$ [h]	1 h	21	0.9	3.7		[124]
20	$[Fe_2O(OAc)(bpia)_2(H_2O)](ClO_4)_3$ [h,i]	1 h	24	0.8			[125]
21	$[Fe_2O(OBz)_2(BPA)_2](ClO_4)_2$	16 h	25	1.2	6.1		[85]
22	$[Fe_2O(OAc)(NTB)_2](ClO_4)_3$	16 h	10	1.1	7.1		[85]
23	$[Fe_2O(OAc)(TPA)_2](ClO_4)_3$	15 min	24	0.8	4.6		[85]
24	$[Fe_2O(OBz)(TPA)_2](ClO_4)_3$	15 min	23	0.9	4.4		[85]
25	$[Fe_2O(CO_3)(TPA)_2](ClO_4)_2$	4 h	15	1.0	4.6		[85]
26	$[Fe_2O(TPA)_2(H_2O)_2](ClO_4)_4$	10 min					[88]
	150 equiv. ^{t}BuOOH		27	0.7	6[f]		
	150 equiv. ^{t}BuOOH (sp)		32	2.0			
	10 equiv. ^{t}BuOOH (sp)		40	>100	7–8		

[a] All reactions are performed at r.t. in acetonitrile under argon or N_2 unless noted.
[b] Eff. = Σ(oxidized products)/^{t}BuOOH × 100.
[c] A/K = cyclohexanol/cyclohexanone in the oxidation of cyclohexane.
[d] KIE = kinetic isotope effect for cyclohexanol formation in the oxidation of cyclohexane and cyclohexane-d_{12}.
[e] 3°/2° = 1-adamantanol/(2-adamantanol + 2-adamantanone) in the oxidation of adamantane multiplied by 3 (to correct for the threefold higher number of 2° C–H bonds).
[f] KIE value based on both alcohol and ketone.
[g] Under O_2.
[h] Under air.
[i] Carried out in aqueous micelles.

Table 2
Alkane oxidation by nonheme iron catalysts and H_2O_2[a]

Entry	Catalyst	Eff. (%)[b]	A/K[c]	KIE[d]	3°/2°[e]	RC(*cis*) (%)[f]	RC(*trans*) (%)[f]	Ref.
1	$HO^{\bullet}$		~1	1~2	2	9	8	[44,65,77,126]
2	(Por)Fe^{III} [g]		5~15	13	6~48	96	78	[69,76,127,128]
3	$Fe(ClO_4)_3$	37	1.9	1.5	3.3			[94]
4	$[Fe(OPPh_3)_4]^{2+}$	13	1.2	1.9				[119]
5	$[Fe(CH_3CN)_4]^{2+}$	10	1.0	1.8				[119]
6	$[Fe(bpy)_2]^{2+}$	9	0.8	1.4				[119]
7	$[Fe(PMA)]^{2+}$ [h]	10	0.9					[53]
8	$[FeCl_2(HDP)]^{+}$	3	1.2					[129]
9	$[Fe_2OCl_2(epy)_2]^{2+}$	2	1.4					[95]
10	$[Fe_2O(OAc)(bpmen)_2]^{3+}$	2.5	0.8					[130]
11	$[Fe_2O(OAc)_2Cl_2(bpy)_2]$	~8	~1	1.4	3.6			[94]
12	$[Fe_2O(OAc)(tmima)_2](ClO_4)_3$	~9	< 1	1.6	3.4			[94]
13	$[Fe_2OCl_2(tfpy)_2]^{2+}$	3	2.0					[95]
14	$[Fe(DPA)_2]^{2-}$	16	2.3					[96]
15	$[Fe_2O(5\text{-}NO_2Phen)_4(H_2O)_2]^{4+}$			2.0	3.5 (1.6[h])		72	[98]
16	$[Fe_2O(bpy)_4(H_2O)_2]^{4+}$ [h]	6~9	1.3		12			[99,122]
17	$[Fe_2O(bpy)_4(H_2O)_2]^{4+}$			2.4	4.5 (3.3[h])			[98]
18	$[Fe_2O(4,4'\text{-}Me_2bpy)_4(H_2O)_2]^{4+}$			3.1	6.2 (5.0[h])		48	[98]
19	$[Fe_2O(pb)_4(H_2O)_2]^{4+}$ [h]	30	2.0					[131]
20	$[Fe(N4Py)(CH_3CN)]^{2+}$ [h]	31	1.4	1.5	3.3	27 (31[i])	16 (30[i])	[102]
21	$[Fe(TPA)(CH_3CN)_2]^{2+}$	37	4.3	3.5	17	100	100	[58,132]
22	$[Fe(bpmen)(CH_3CN)_2]^{2+}$	63	8.0	3.2	15	100	100	[101,132]

[a] All reactions are performed at r.t. in acetonitrile in air unless noted.
[b] Eff. = (cyclohexanol + cyclohexanone)/$H_2O_2 \times 100$ in the oxidation of cyclohexane.
[c] A/K = cyclohexanol/cyclohexanone in the oxidation of cyclohexane.
[d] KIE = kinetic isotope effect of cyclohexanol formation in the oxidation of cyclohexane and cyclohexane-d_{12}.
[e] 3°/2° = 1-adamantanol/(2-adamantanol + 2-adamantanone) in the oxidation of adamantane taking into account of the correction for a number of C–H bonds in a group.
[f] RC = retention of configuration in the oxidation of the *tert*-C–H bonds of *cis*- or *trans*-1,2-dimethylcyclohexane, expressed as the ratio of the alcohols: (*cis* − *trans*)/(*cis* + *trans*) for RC(*cis*) and (*trans* − *cis*)/(*cis* + *trans*) for RC(*trans*).
[g] With single-oxygen donors such as PhIO or NaClO.
[h] Under inert atmosphere such as N_2 or Ar.
[i] In acetone.

3.1. General mechanistic considerations

The mechanism for alkane oxidation by an iron catalyst can be separated into two components: a C–H bond cleavage step and a C–O bond formation step, i.e.

$$\text{R–H} + \text{oxidant} \rightarrow \text{R}^{\bullet} + \text{Fe–OH} \rightarrow \text{R–OH} \quad (3)$$

The variation in the products observed for the catalysts in Tables 1 and 2 may be rationalized by the relative timing of these two steps. At one extreme the two steps may occur in a concerted fashion, so the oxygen atom is effectively inserted into the C–H bond. Alternatively, the C–H bond is cleaved to form an alkyl radical that is very quickly trapped to form the C–O bond. Thus the stereospecificity of alkane hydroxylation by cytochrome P450 [8] and the partial retention of configuration in the hydroxylation of chiral ethane and butane by methane monooxygenase [49,50] indicate a mechanism that approaches the concerted extreme. At the other extreme the two steps may be well separated in time, so that the long-lived alkyl radical can be trapped by other species such as O_2 in solution. For example, FeBLM affords distinct DNA oxidation products that depend on the presence or absence of O_2

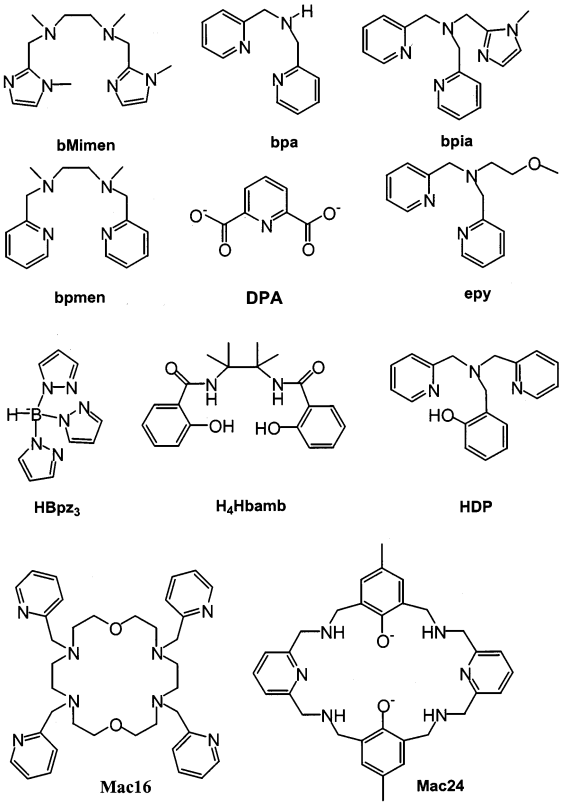

Fig. 4. Structures of the ligands reviewed in this work.

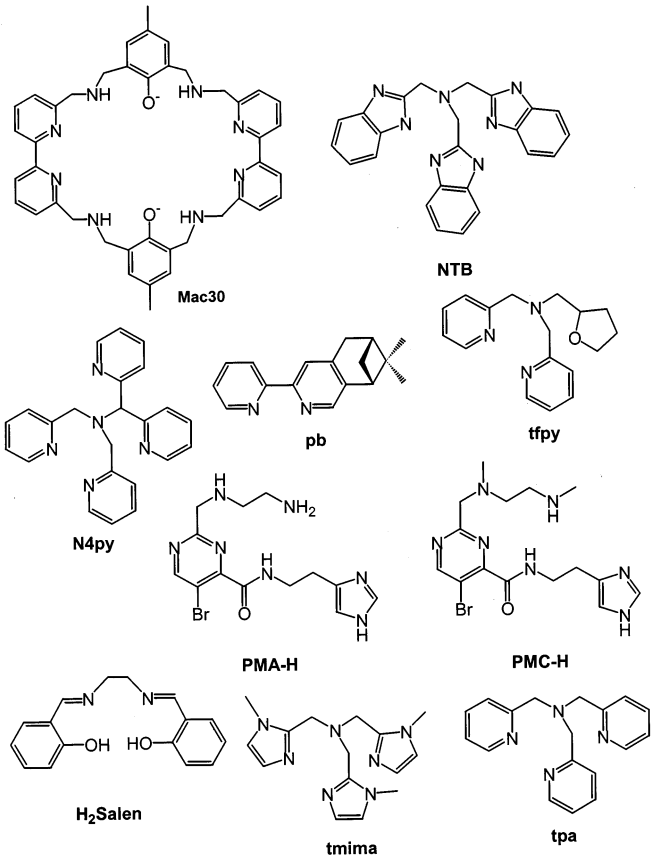

Fig. 4. (*Continued*).

[9,51,52]. Thus the lifetime of the nascent alkyl radical and its consequent reactions are symptomatic of the type of mechanism employed.

The biomimetic systems in Tables 1 and 2 all entail the formation of the oxidant by reaction of an iron complex with a peroxide, presumably via an Fe^{III}–OOR intermediate that has been observed spectroscopically in several cases [53–61]. Such an Fe^{III}–OOR intermediate can decompose in four distinct pathways and generate five different oxidants as shown in Fig. 5:

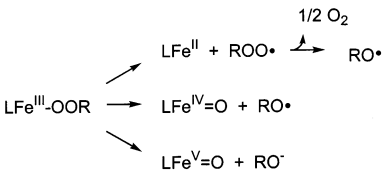

Fig. 5. Possible decomposition pathways of the Fe^{III}–OOR intermediate.

1. The Fe–O bond may homolyze to form Fe^{II} and an $ROO^{\bullet}$ radical. The $ROO^{\bullet}$ radical (ΔH_{DBE} ($^{t}BuOO$–H) = 89 kcal mol^{-1}, ΔH_{DBE} (HOO–H) = 88 kcal mol^{-1}) [62,63] can only attack alkane substrates with relatively weak C–H bonds (e.g. Ph(Me)CH–H, ΔH_{DBE} = 87 kcal mol^{-1}) [63]. However, bimolecular self-reaction of the $ROO^{\bullet}$ radical can generate a more powerful oxidant such as an $RO^{\bullet}$ radical (ΔH_{DBE} (^{t}BuO–H) = 105 kcal mol^{-1}, ΔH_{DBE} (HO–H) = 119 kcal mol^{-1}) [62], which in turn can attack the C–H bond of cyclohexane (ΔH_{DBE} = 95.5 kcal mol^{-1}) [63].
2. The Fe–OOR intermediate may attack the substrate directly by analogy to the reactivity of early transition metal peroxo complexes [64].
3. The Fe–OOR intermediate may undergo O–O bond homolysis to form Fe^{IV}=O and $RO^{\bullet}$, both of which can attack the substrate.
4. The Fe–OOR intermediate may undergo O–O bond heterolysis to form an Fe^{V}=O species analogous to the high-valent species in cytochrome P450 cycle.

Probing the lifetime of the nascent radical is the key to determining the mechanism of alkane oxidation, whether the oxidant is $HO^{\bullet}$ or $RO^{\bullet}$, or a metal-based oxidant such as Fe^{III}–OOH, Fe^{IV}=O, or Fe^{V}=O species. Based on the lifetime of the alkyl radical, the mechanisms of alkane oxidation can be divided into two different categories: those that produce short-lived alkyl radicals and those that produce long-lived alkyl radicals. The reactions catalyzed by cytochrome P450 and MMO involve the generation of metal-based oxidants in the catalytic mechanism and fall into the former category. Thus the alkyl radical that is formed remains near the metal center and is quickly trapped to give the alcohol product. On the other hand, long-lived alkyl radicals are generated by less selective oxidants such as hydroxyl radical or alkoxyl radical produced by Fenton or Haber–Weiss reactions (Eqs. (1) and (2), R = H or alkyl group) and can diffuse freely in solution. The presence of O_2 allows a radical chain oxidation to be initiated, which determines the product distribution. It is the goal of biomimetic studies to identify a catalyst that generates a selective metal-based oxidant analogous to those utilized by cytochrome P450 and methane monooxygenase, rather than $HO^{\bullet}$ or $RO^{\bullet}$ radicals that readily initiate radical chain autoxidations in the presence of O_2.

3.2. Mechanistic probes

Because it is often very difficult in catalytic oxidation systems to observe the actual reagent that carries out the key oxidative transformation, indirect probes have been useful to deduce the reaction mechanism. These probes provide insight into either the oxidative power of the species that produces the nascent alkyl radical or the lifetime of this radical.

3.2.1. Kinetic isotope effects (KIE)

The kinetic isotope effect is a competition reaction between protio- and deuteroalkanes based on the difference of C–H/D bond strength ($\sim$1.7 kcal·mol^{-1}). Both intermolecular KIE (such as cyclohexane/cyclohexane-d_{12}) and intramolecular KIE (such as CH_nD_{4-n}) experiments have been carried out. In a

radical-chain reaction initiated by hydroxyl radicals, KIE values between 1 and 2 have been reported [65], the low discrimination between C–H and C–D bonds consistent with the strong oxidative power of the oxidant. Similar reactions with $^tBuO^\bullet$ as the initiator give KIE around $4 \sim 5$ [66]. The higher KIE value of $^tBuO^\bullet$ than $HO^\bullet$ is consistent with the lower reactivity of an alkoxyl radical (ΔH_{DBE} (RO–H) = 105 kcal mol^{-1} vs. ΔH_{DBE} (HO–H) = 119 kcal mol^{-1}) [62,63]. Metal-based oxidants, on the other hand, may be more selective. In some enzymatic reactions, KIE values higher than the theoretical maximum of 7 [67] have been reported and explained by tunneling effects; for example, values of >11 for cytochrome P450 [12] and 50–100 for methane monooxygenase [32] have been found.

3.2.2. Regioselectivity

The nature of the oxidant can also be probed by an intramolecular competition reaction in the oxidation of adamantane, which contains both secondary and tertiary C–H bonds. The regioselectivity is parameterized as a 3°/2° ratio derived from the amount of 1-adamantanol divided by the amounts of 2-adamantanol and 2-adamantanone and multiplied by 3 to correct for the higher number of secondary C–H bonds. The indiscriminate $HO^\bullet$ typically affords values near 2, while $^tBuO^\bullet$-initiated reactions exhibit values around 10 [68]. For cytochrome P450 and heme catalysts, the adamantane regioselectivity can be as high as 48:1 [69].

3.2.3. Alcohol/ketone ratio (A/K)

The A/K ratio is the simplest test that reflects the lifetime of the alkyl radical. When long-lived alkyl radicals are generated in the oxidation of secondary alkanes such as cyclohexane, O_2 traps the radicals at a diffusion-controlled rate and gives alkylperoxyl radicals (Eq. (4)) [70]. Subsequent reaction of the alkylperoxyl radicals results in a Russell-type termination step leading to the formation of equimolar amounts of alcohol and ketone (Eq. (5)) [71]. When the reaction is performed in the absence of O_2, the product yield can decrease dramatically due to a lack of chain propagation.

$$R(R')CH^\bullet + O_2 \rightarrow R(R')CHOO^\bullet \quad (4)$$

$$R(R')CHOO^\bullet + R(R')CHOO^\bullet \rightarrow R(R')CHOH + R(R')C{=}O + O_2 \quad (5)$$

Alkyl radicals formed by some metal-based oxidants, on the other hand, react quickly with the metal center, to form the alcohol product (Eq. (3)). This so-called 'oxygen rebound' [72] has an estimated rate constant of $10^{10} \sim 10^{13}$ s^{-1} [73,74]. In this case, alcohol would be expected to be the sole oxidation product, although some ketone may also be formed presumably due to further oxidation of the product alcohol.

3.2.4. Substrate-based probes of radical lifetime

Two types of substrates have been commonly used to probe the lifetime of the nascent alkyl radical in the alkane hydroxylation reactions. The first type exem-

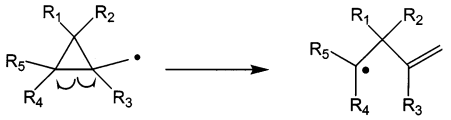

Fig. 6. Radical rearrangement of the cyclopropylcarbinyl radical clock.

plified by *cis* and *trans* isomers of 1,2-dimethylcyclohexane and decalin takes advantage of the competition between the epimerization of the putative tertiary alkyl radical intermediate and the formation of the product C–O bonds, which determines the ratio of *cis* and *trans* tertiary alcohol products. It is estimated that the tertiary carbon radical epimerizes with a first-order rate constant of 10^9 s^{-1} [75,76]. Reactions that give rise to long-lived free radicals should afford both *cis* and *trans* alcohols with a *cis*/*trans* ratio of approximately 1.2 [77]. On the other hand, short-lived alkyl radicals where the 'oxygen-rebound' or C–O bond formation step is extremely fast should afford a tertiary alcohol where the original configuration is retained. Since the oxygen-rebound step may be as fast as $10^{10} \sim 10^{13}$ s^{-1} in heme systems, stereospecific hydroxylation is observed with such catalysts [12,78].

The other commonly used substrate probe for radical lifetime is the cyclopropylcarbinyl radical clock [79]. This radical may rearrange to the ring-opened 3-buten-1-yl radical, before being trapped. Thus the relative amounts of unrearranged cyclopropylcarbinol and ring-opened but-3-en-1-ol allows us to estimate the lifetime of the nascent alkyl radical (Fig. 6). The lifetime of this radical can be modulated by the introduction of substituents on the cyclopropane ring and can range from picoseconds to nanoseconds [74,80]. Indeed, the fact that little or no rearrangement is observed in the hydroxylation of ultrafast radical clock substrates by cytochrome P450 and methane monooxygenase has led Newcomb and co-workers to question the likelihood of forming an alkyl radical in these reactions, no matter how short-lived, since the time scale for rearrangement (radical lifetime < 100 fps) is that of a molecular vibration [74].

3.2.5. Oxidation of alkenes

Alkene substrates serve as another useful probe for these alkane hydroxylation reactions. Olefins may be oxidized to either the epoxide or allylic oxidation products. The epoxide typically results from stereospecific oxygen atom transfer from the oxidant to the substrate, while the latter derives from the abstraction of the allylic hydrogen by the oxidant [81]. Oxidants such as hydroxyl or alkoxyl radicals cannot effect stereospecific epoxidation of olefins but instead abstract the allylic hydrogen and initiate radical chain autoxidation in the presence of O_2. Cyclohexene is particularly susceptible to radical chain autoxidation and, as a result, can give rise to yields of cyclohexenol and cyclohexenone that exceed the amount of peroxide used for the catalytic reaction.

Caution should be taken when the above tests are used to examine the mechanism of alkane oxidation. It is important to use a combination of different tests to ascertain the properties of the oxidant and the lifetime of the alkyl radicals before drawing a mechanistic conclusion.

3.3. Reactions with ROOH

A perusal of Table 1 shows that, despite the variety of iron complexes used, the catalytic reactions involving alkyl hydroperoxides share a number of common features (Fig. 7). First and foremost is the observation of an A/K ratio near 1 for most of the reactions listed. This result shows that alkane oxidations by ROOH essentially involve the formation of long-lived alkyl radicals. In the presence of O_2, these radicals participate in radical chain autoxidations that give rise to the observed A/K ratio. Even under Ar, some of these reactions afford comparable A/K ratios due to the formation of O_2 by Haber–Weiss decomposition of ROOH. The mixed peroxide ^{t}BuOOC$_6$H$_{11}$, presumably formed by reaction between cyclohexyl and *tert*-butylperoxyl radicals, is detected in significant amounts when reactions are carried out under Ar, but its formation is decreased or even suppressed in reactions performed under O_2. Secondly, kinetic isotope effects of ~ 5 and adamantane 3°/2° ratios near 10 point to an alkoxyl radical oxidant that is presumably formed from peroxide O–O bond homolysis. Thirdly the oxidation of cyclohexene affords principally allyllic products with epoxide at best a minor product [82]. Lastly, the oxidation of the radical clock *trans*-2-phenylmethylcyclopropane by $[Fe_2O(tmima)_2(H_2O)_2]^{4+}$ afforded only ring-opened products, 1-phenyl-but-3-en-1-ol and 1-phenyl-but-3-en-1-one (Fig. 8) [83]. So all the criteria discussed in the previous section point to the alkoxyl radical as the primary oxidant. We note that Fish and co-workers reached this conclusion early in their mechanistic analysis [84]. Indeed in their work, no alkane oxidation was observed unless some O_2 was present in their reaction.

Despite all the similarities, a perusal of Table 1 shows that the structure of the catalyst affects some of the characteristics of the reaction, principally the rate of the reaction. Three factors appear to enhance the rate at which the alkyl hydroperoxide is consumed.

1. Fewer anionic ligands: catalysts with a higher overall charge exhibit reactivities as much as two orders of magnitude higher (compare entries **12**–**15** and **19**–**26** in Table 1). This trend may be interpreted as an effect on the Lewis acidity of the iron center [85].
2. Pyridine versus other nitrogen heterocycles: catalysts with pyridine ligands exhibit better catalytic activity (compare entries **10** and **11**, **18** and **19**, **22** and **23**, and **16** and **26**).
3. The presence of a readily exchangeable ligand: catalysts with aqua ligands have the best catalytic activities (compare entries **12** and **13**, **14** and **15**, **16** and **17**, and **23** and **26** with 10 equivalents of ^{t}BuOOH). The labile ligand presumably allows ^{t}BuOOH to bind readily to the metal center and initiate the reaction. Indeed

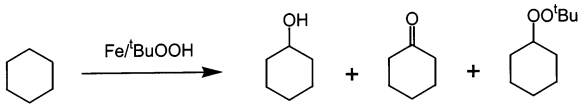

Fig. 7. Products obtained in the iron catalyzed ^{t}BuOOH oxidation of cyclohexane.

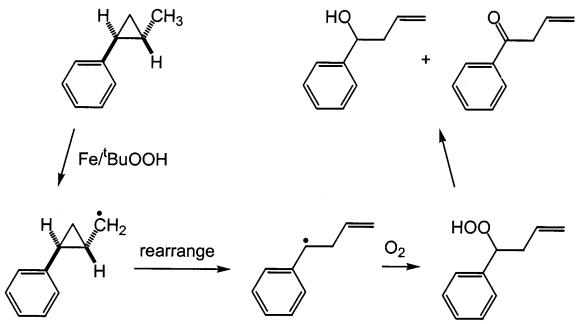

Fig. 8. Radical rearrangement on the $[Fe_2O(H_2O)_2(tmima)_2]^{4+}$ catalyzed ^{t}BuOOH oxidation of *trans*-2-phenylmethylcyclopropane.

several of the complexes containing aqua ligands are also the ones for which an Fe^{III}–OOR intermediate can be observed at low temperature [54,55,57,86].

3.3.1. The Fe(TPA) catalyst family

A particularly vigorous literature discussion has developed in the last few years regarding the mechanism of alkane oxidation by a family of iron(III) complexes coordinated to the tetradentate tris(2-pyridylmethyl)amine (TPA) ligand. This discussion between the Que and Ingold groups shed some interesting light on the mechanism by which Fe(TPA) complexes react with peroxides. In their initial reports, Que and co-workers found that these complexes could catalyze alkane oxidation quite efficiently under an argon atmosphere. The 150 equivalents of ^{t}BuOOH used in the reaction could be consumed in as little time as a few minutes to as long as hours depending on the nature of the ancillary ligands [85,87,88]. When the ancillary ligand was water, as in $[Fe_2O(TPA)_2(H_2O)_2]^{4+}$, a transient blue species could be detected upon mixing at room temperature (r.t.). Upon lowering the temperature to -40°C, the blue intermediate persisted and was characterized as the low spin Fe^{III} species $[Fe(TPA)(OO^tBu)(H_2O)]^{2+}$ by electrospray mass spectrometry, EPR, and resonance Raman spectroscopy (Fig. 9) [55,57]. The trapping of the alkylperoxoiron(III) intermediate, together with observed variations in reaction times, KIE values and adamantane 3°/2° ratios, led to the proposal that the active oxidant must be a metal-based species, either the Fe^{III}–OO^tBu intermediate observed spectroscopically at -40°C or a high-valent iron-oxo species derived therefrom [85].

Ingold and co-workers re-examined the published results and differed from the mechanistic conclusions drawn by Que and co-workers [89,90]. Key arguments for the re-interpretation were the near unity values of the A/K ratios and the fact that the introduction of O_2 substantially altered the yields of alcohol and ketone. As discussed earlier, both observations indicate the presence of long-lived alkyl radicals, which derive from the reaction of alkane and alkoxyl radicals generated from

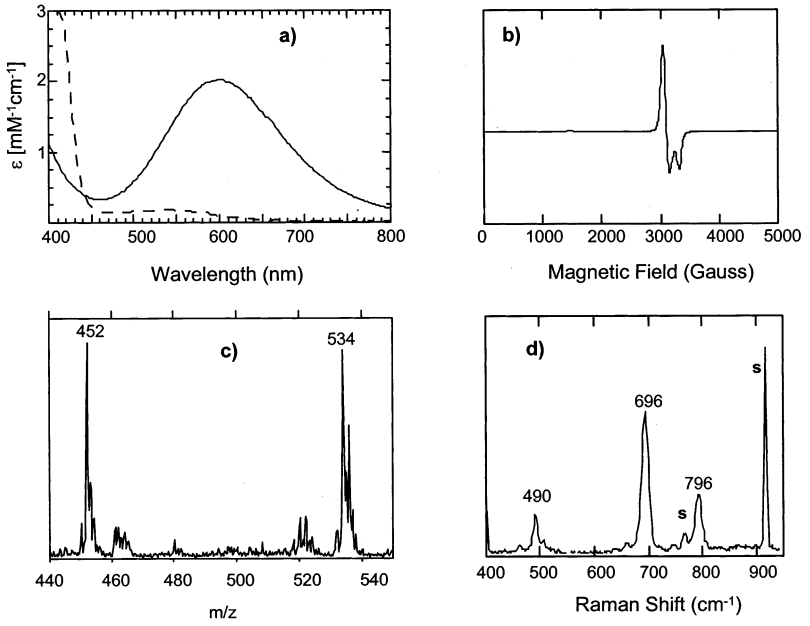

Fig. 9. Spectroscopic characterization of the $[Fe(TPA)(H_2O)(OO^tBu)]^{2+}$ intermediate: (a) absorption spectra of $[Fe(TPA)(CH_3CN)_2]^{2+}$ (dashed line) and $[Fe(TPA)(H_2O)(OO^tBu)]^{2+}$ (solid line) in CH_3CN at $-40°C$; (b) X-band EPR spectrum recorded at 2 K of $[Fe(TPA)(H_2O)(OO^tBu)]^{2+}$; (c) positive ion electrospray ionization mass spectrum of $[Fe(TPA)(H_2O)(OO^tBu)]^{2+}$; (d) resonance Raman spectrum of $[Fe(TPA)(H_2O)(OO^tBu)]^{2+}$ obtained with 599 nm excitation in frozen CH_3CN (solvent peaks are marked with s).

the metal-promoted homolysis of ^{t}BuOOH. The observed products thus result from a radical chain autoxidation process.

In support of the latter hypothesis, the same authors introduced the use of 2-methyl-1-phenyl-2-propyl-hydroperoxide (MPPH), an alkyl hydroperoxide like ^{t}BuOOH, as a probe for alkoxyl radical formation. This probe takes advantage of the fact that the alkoxyl radical derived from MPPH is quite unstable and undergoes a very fast ($k \sim 2.2 \times 10^8$ s^{-1}) β-scission to form benzyl radical and acetone (Fig. 10). The benzyl radical being resonance stabilized is much less energetic than the *tert*-butoxyl radical and would be incapable of abstracting

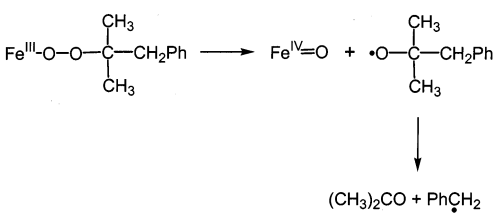

Fig. 10. Concerted fragmentation of Fe/MPPH to generate the benzyl radical.

hydrogen atoms from unactivated alkanes such as cyclohexane. Thus substitution of ^{t}BuOOH with MPPH should not affect the product yields if an iron-peroxo or a high-valent iron-oxo species were the key oxidant in the reaction. On the other hand, the yields of oxidized alkane should be significantly reduced if the alkoxyl radical were the key oxidant. Indeed when MPPH was used in place of ^{t}BuOOH, no cyclohexane oxidation was observed. The possibility that MPPH is a special peroxide that could undergo a concerted fragmentation to form the benzyl radical directly was refuted by the observation that MPPH could act as an even better oxidant than ^{t}BuOOH in 'genuine 2 e^- processes' such as Ti^{IV}-catalyzed alkene epoxidation [91].

In response to this criticism, Que and co-workers performed experiments using a syringe pump (sp) to deliver a more dilute solution of ^{t}BuOOH [88]. It was reasoned that the radical chain autoxidation pathway could be suppressed by minimizing the generation of O_2 from the decomposition of ^{t}BuO$^\bullet$ radicals if fewer molecules of ROOH were available. Indeed when the 150 equivalents of ^{t}BuOOH were delivered over a 10 min period by syringe pump to an CH_3CN solution of cyclohexane and $[Fe_2O(TPA)_2(H_2O)_2]^{4+}$, the A/K ratio observed increased from 0.5 to 2.0. Further reduction of the ^{t}BuOOH concentration resulted to increased A/K ratios; when only 10 equivalents ^{t}BuOOH was used, cyclohexanol was the only product observed and it was obtained in 40% yield. Thus the radical chain autoxidation pathway could be suppressed under these conditions, and a reaction more directly involving the metal center would become dominant.

Further studies, however, demonstrated that the alkoxyl radical remained the key oxidant under these conditions, albeit 'well disguised' [66]. Although alcohol was the only observed product when the reaction was carried out under Ar, equimolar amounts of alcohol and ketone were obtained when the reaction was carried out in air. Furthermore, both the KIE value for cyclohexanol formation and the selectivity in the competitive oxidation of cyclohexane/cyclooctane were virtually identical to those produced by ^{t}BuO$^\bullet$ generated from an organic source. Finally, the use of MPPH in place of ^{t}BuOOH under syringe pump conditions failed to elicit cyclohexane hydroxylation. The consensus mechanism that emerged from this discussion consisted of the following. The reaction of $[Fe_2O(TPA)_2(H_2O)_2]^{4+}$ and ROOH affords an $[Fe^{III}–OOR]^{2+}$ intermediate which undergoes O–O bond homolysis to form Fe^{IV}=O and RO$^\bullet$. The alkoxyl radical then reacts with the alkane to generate an alkyl radical. In the absence of O_2, this long-lived alkyl radical is trapped by the Fe^{IV}=O species to form the observed alcohol product. Evidence for this trapping step was obtained by the use of ^{t}BuO^{18}OH as oxidant in which the terminal oxygen atom was quantitatively transferred to the alkyl radical to give ^{18}O-labeled cyclohexanol product [66].

A very recent paper demonstrates that chemistry of the Fe(TPA)/^{t}BuOOH combination is not necessarily limited to that of the alkoxyl radical. Lange et al. took advantage of the homolytic cleavage of the Fe^{III}O–O^{t}Bu bond to show that an Fe^{IV}=O species can hydroxylate an arene moiety (Fig. 11) [92]. They designed the ligand 6-Ph-TPA, which introduces a pendant phenyl group on one of the pyridine rings of the TPA ligand, close enough to the nascent Fe^{IV}=O species so that phenyl

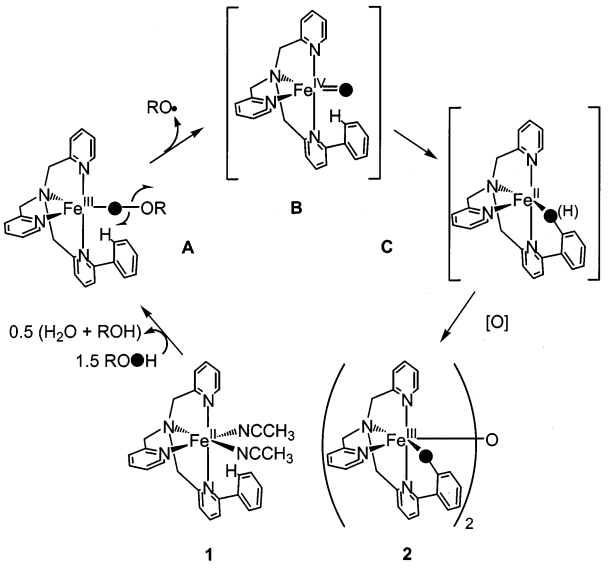

Fig. 11. Reaction mechanism proposed for the reaction of $[Fe(6\text{-Ph-TPA})(CH_3CN)_2](ClO_4)_2$ with ^tBuOOH.

ring hydroxylation at the 2-position could occur. Indeed, treatment of $[Fe(6\text{-Ph-TPA})(CH_3CN)_2](ClO_4)_2$ with ROOH resulted in the hydroxylation of the phenyl ring in the 2-position. Even MPPH was effective. Furthermore the use of $^tBu^{16}O^{18}OH$ unambiguously shows that the oxygen atom incorporated derives from the terminal oxygen atom of the peroxide. The proposed mechanism shown in Fig. 11 involves an Fe^{III}–OOR intermediate, observed at $-40°C$, which homolyzes to form the putative Fe^{IV}=O species. Proof for its involvement came from the demonstration that ^{18}O was incorporated into the phenolic oxygen when the reaction was run in the presence of $H_2^{18}O$. A high-valent metal-oxo complex is the only plausible oxidant capable of exchanging the oxygen atom with H_2O in this reaction [93]. Therefore, this work provides evidence that the Fe(TPA)/ROOH combination can generate a metal-centered oxidant that is capable of oxidizing some hydrocarbon substrates.

3.4. Reactions with H_2O_2

Table 2 shows that H_2O_2 has also been utilized as the oxygen donor in alkane oxidations by nonheme iron catalysts. In most reactions, the iron/H_2O_2 chemistry appears to be dominated by hydroxyl radicals, mainly produced by Haber–Weiss decomposition of H_2O_2 (Eqs. (1) and (2)) [44]. In the oxidation of cyclohexane, most catalytic systems give an A/K ratio of <2, and this ratio depends on the amount of O_2 present in the reaction mixture. Therefore, long-lived alkyl radicals are likely to be formed in the reaction. Fish and co-workers have in fact been able

to isolate cyclohexyl hydroperoxide from their reactions, which presumably derived from cyclohexylperoxyl radicals that form in the radical chain autoxidation [94]. With deuterated alkanes, KIE values of less than 2 for alcohol formation are obtained, which implicates a powerful and nonselective oxidant such as hydroxyl radical. Furthermore adamantane regioselectivies of about 3 are found, which are also consistent with the involvement of the hydroxyl radical. Taken together, these results suggest that most nonheme iron catalyst–H_2O_2 combinations for alkane oxidation in Table 2 generate hydroxyl radicals, which in turn produce long-lived alkyl radicals.

There are, however, a few catalytic systems in Table 2 with reactivity patterns that suggest the involvement of another oxidant besides hydroxyl radical. For example, $[Fe_2OCl_2(tfpy)_2]^{2+}$ [95] and $[Fe(DPA)_2]^{2-}$ [96] exhibit moderate A/K ratios in the oxidation of cyclohexane (~ 2) (Table 2, entries **13** and **14**), but further investigation is required to ascertain whether a metal-based oxidant may play a role in the oxidation. A more thoroughly investigated family of catalysts is the $[Fe_2O(L)_4(H_2O)_2]^{4+}$ series (L = bpy, phen, and their derivatives), which has been studied by a group in Russia [97,98] and a group in France [99] (Table 2, entries **15**–**19**). Although both groups report low A/K ratios that suggest the involvement of hydroxyl radicals, the Russian group finds relatively high KIE values ($2.0 \sim 3.1$) and moderate regioselectivity in the oxidation of adamantane ($3.5 \sim 6$), values that are higher than expected for oxidation solely by hydroxyl radical. More interestingly, the Russian group also reports partial retention of configuration in the oxidation of *trans*-1,4-dimethylcyclohexane and only partial cyclopropane ring opening in the oxidation of the fast radical-clock *trans*-1-methyl-2-phenyl-cyclopropane. These results suggest the involvement of two different oxidants in the reaction: hydroxyl radical and an iron-based oxidant. Therefore, both short-and long-lived alkyl radicals may be formed in these reactions [98,100].

The most interesting nonheme iron catalysts listed in Table 2 are two complexes with tetradentate pyridine containing ligands $[Fe(TPA)(CH_3CN)_2]^{2+}$ [58] and $[Fe(bpmen)(CH_3CN)_2]^{2+}$ [101] (Table 2, entries **21** and **22**). Firstly, both have high catalytic efficiency with 40–70% of H_2O_2 converted to product. Secondly, they exhibit high A/K ratios (4–8) which are independent of the presence of O_2, indicating that long-lived alkyl radicals are not formed. Thirdly, they afford KIE values of greater than 3 for cyclohexane oxidation and adamantane regioselectivities of 15–17, implicating a more selective oxidant than hydroxyl radical. Finally, the oxidation of either *cis*- or *trans*-1,2-dimethylcyclohexane by these catalysts results in the stereospecific hydroxylation of the tertiary C–H bonds. Taken together, these results strongly suggest the involvement of a metal-based oxidant to generate short-lived alkyl radicals.

3.5. The nature of the iron-based oxidant

The reactivity patterns exhibited by $[Fe(TPA)(CH_3CN)_2]^{2+}$ and $[Fe(bpmen)(CH_3CN)_2]^{2+}$ strongly implicate the participation of a metal-based oxidant in alkane hydroxylation; thus efforts have been made to obtain less indirect evidence

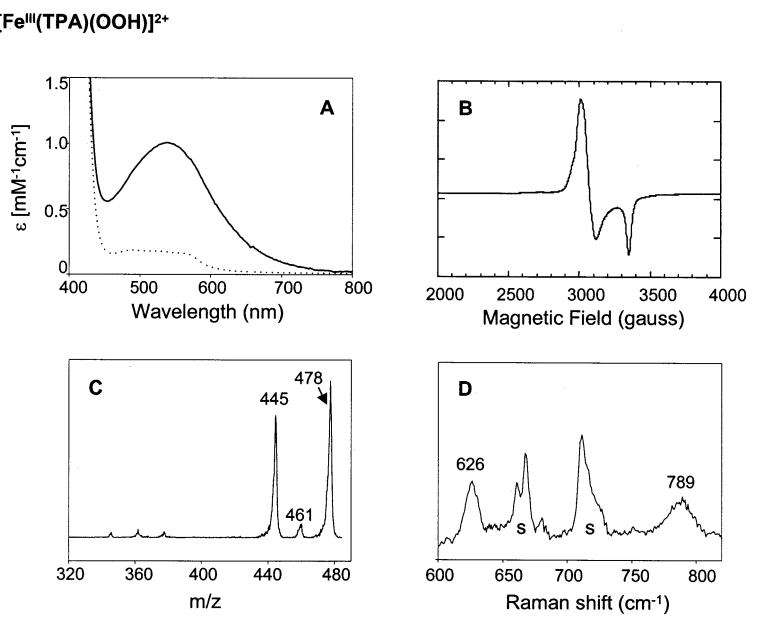

Fig. 12. Spectroscopic characterization of the $[Fe(TPA)(OOH)]^{2+}$ intermediate: (A) electron absorption spectra of the $[Fe(TPA)(OOH)]^{2+}$ intermediate (solid line) and $[Fe(TPA)(CH_3CN)_2]^{2+}$ (dashed line) in CH_3CN; (B) electron paramagnetic spectrum of $[Fe(TPA)(OOH)]^{2+}$; (C) electrospray ionization mass spectrum of $[Fe(TPA)(OOH)]^{2+}$; (D) resonance Raman spectrum of $[Fe(TPA)(OOH)]^{2+}$ (solvent peaks are marked with s).

for such species. The importance of having labile sites cannot be under-emphasized. We have noted in the Section 3.3 how the presence of easily displaceable ligands enhances the catalytic activity of the complex. Table 2 also shows examples of this feature. Compare, for example, the reactivity of $[Fe_2O(OAc)_2Cl_2(bpy)_2]$ versus that of $[Fe_2O(bpy)_4(H_2O)_2]^{4+}$ (entries **11** vs. **16**); the metal centers in the former are coordinatively saturated and exhibit a reactivity pattern associated with hydroxyl radicals, while the latter complex has labile solvent ligands and exhibits a reactivity pattern that shows some involvement of a metal-based oxidant. More striking is the comparison between $[Fe_2O(OAc)(bpmen)_2]^{3+}$ and $[Fe(bpmen)(CH_3CN)_2]^{2+}$ (entries **10** vs. **22**). The former, which is coordinatively saturated, exhibits reactivity associated with hydroxyl radicals, while the latter with two labile solvent ligands clearly oxidizes alkanes via a metal-based oxidant.

A transient intermediate has been observed in the reaction of $[Fe(TPA)(CH_3CN)_2]^{2+}$ and H_2O_2 by lowering the temperature to $-40°C$ [58,59], and its spectroscopic features (Fig. 12) strongly resemble those of the $[Fe(TPA)(OO^tBu)]^{2+}$ intermediate discussed earlier. This short-lived species has been formulated by electrospray ionization mass spectrometry as $[Fe(TPA)(OOH)]^{2+}$, by EPR spectroscopy to have a low-spin Fe^{III} center and by Raman spectroscopy to have a terminally bound hydroperoxo group. The O–O vibration observed for the

bound hydroperoxide (790 cm^{-1}) is significantly lower than those found for other iron-peroxo complexes [59]. The lower O–O stretching frequency suggests that the O–O bond in this species may be weakened and have an increased tendency to cleave for further reaction.

A similar low spin Fe^{III}–OOH intermediate has been found for the closely related $[Fe(N4Py)(CH_3CN)]^{2+}$ complex [56,60] with a comparably weak O–O bond [59]. However, $[Fe(N4Py)(CH_3CN)]^{2+}$ exhibits a different reactivity pattern in alkane oxidation (Table 2, entry **20**) [102] from that observed for $[Fe(TPA)(CH_3CN)_2]^{2+}$. The oxidation of cyclohexane has a KIE of 1.5 and a low A/K value (1.4) that varies with the presence of O_2. The 3°/2° ratio for adamantane oxidation is 3.3 and the oxidation of *cis*- and *trans*-dimethylcyclohexane to tertiary alcohols is not stereospecific. These observations suggest that hydroxyl radicals and long-lived alkyl radicals play important roles in the reactions. It is thus insufficient to be able to form an Fe^{III}–OOH intermediate to elicit the stereospecific alkane hydroxylation chemistry observed for $[Fe(TPA)(CH_3CN)_2]^{2+}$.

The principal difference between $[Fe(TPA)(CH_3CN)_2]^{2+}$ and $[Fe(N4Py)(CH_3CN)]^{2+}$ is ligand denticity; TPA is a tetradentate ligand, while N4Py is a pentadentate ligand. This ligand modification leaves only one labile site on the iron center of $[Fe(N4Py)(CH_3CN)]^{2+}$ for ancillary ligands, while $[Fe(TPA)(CH_3CN)_2]^{2+}$ has two *cis* labile sites (Fig. 13). From the reactivity pattern observed, the decomposition of $[Fe(N4Py)(OOH)]^{2+}$ appears to result in O–O bond homolysis, an outcome that clearly does not apply to the case of $[Fe(TPA)(OOH)]^{2+}$. It is thus tempting to suggest that the presence of the two labile sites on the metal center

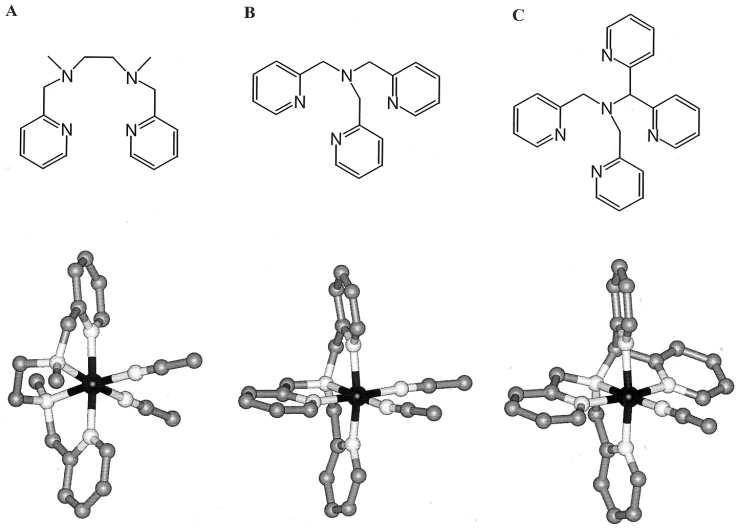

Fig. 13. The structures of the ligands (top) and the Fe^{II} complexes (bottom) of (A) $[Fe(bpmen)(CH_3CN)_2]^{2+}$ [101]; (B) $[Fe(TPA)(CH_3CN)_2]^{2+}$ [140]; and (C) $[Fe(N4Py)(CH_3CN)]^{2+}$ [56,60]. Atom code: Fe (black); N (white); and C (gray).

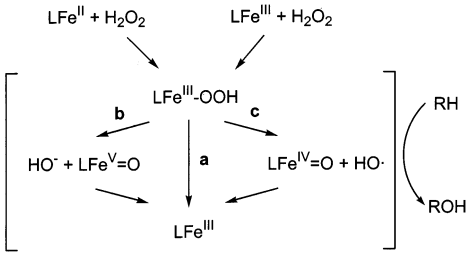

Fig. 14. Possible pathways for the $[Fe(bpmen)(CH_3CN)_2]^{2+}$ catalyzed H_2O_2 alkane hydroxylation.

is the key to the novel reactivity of $[Fe(TPA)(CH_3CN)_2]^{2+}$. Indeed $[Fe(bpmen)(CH_3CN)_2]^{2+}$, a related complex also with two *cis* labile sites, exhibits a very similar alkane oxidation reactivity pattern. Perhaps the key to eliciting stereospecific oxidation is the ability to form the Fe^{III}–OOH species rapidly, which is presumably the purpose of one labile site, and then to activate the bound peroxide and generate the metal-based oxidant, which may be the function of the second labile site. At this point however, how the second labile site promotes the metal-based oxidation pathway remains unclear and requires further investigation.

There are three ways for the Fe^{III}–OOH intermediate found for $[Fe(TPA)(CH_3CN)_2]^{2+}$ and $[Fe(N4Py)(CH_3CN)]^{2+}$ to decompose and elicit alkane oxidation, as shown in Fig. 14. Pathway a entails the reaction of the Fe^{III}–OOH intermediate directly with the substrate. Pathway b involves O–O bond homolysis to afford an Fe^{IV}=O species and a hydroxyl radical, and pathway c involves O–O bond heterolysis to afford an Fe^{V}=O species, analogous to that for cytochrome P450 but without a porphyrin ligand to help stabilize the high oxidation state. From the reactivity exhibited by $[Fe(N4Py)(CH_3CN)]^{2+}$, it seems clear that its Fe^{III}–OOH intermediate undergoes O–O bond homolysis. This pathway is excluded by the reactivity patterns of $[Fe(TPA)(CH_3CN)_2]^{2+}$ and $[Fe(bpmen)(CH_3CN)_2]^{2+}$. ^{18}O-labeling experiments have been helpful for distinguishing between pathways a and c for these latter catalysts, as described below.

^{18}O-labeled water is widely utilized as a probe to test the presence of an active species with an oxygen atom that exchanges with solvent water, such as Fe^{V}=O. This strategy has been used extensively in heme chemistry to ascertain whether a $[(Por^{\bullet})M^{IV}=O]^{+}$ (M = Fe or Mn) species is the oxidant in alkane hydroxylation [103–107], alkene epoxidation [106,108–111], and DNA cleavage [112]. In these reactions, solvent oxygen exchange has been proposed to go through a 'oxo-hydroxo tautomerism', as shown in Fig. 15 [93,113].

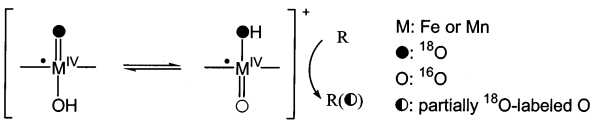

Fig. 15. Oxo-hydroxo tautomerism.

Evidence for the participation of a high-valent Fe^{V}=O species has been reported in alkane hydroxylations by the $[Fe(bpmen)(CH_3CN)_2]^{2+}/H_2O_2$ combination [101]. A significant amount of ^{18}O from $H_2^{18}O$ is incorporated into the alcohol product in the oxidation of cyclohexane. The balance of the oxygen atom inventory is provided by the oxidant H_2O_2, as demonstrated by the complementary experiment using $H_2^{18}O_2$. These observations indicate that oxygen exchange occurs during the reaction. ^{18}O from $H_2^{18}O$ is also incorporated into the product of stereospecific hydroxylation of *cis*-1,2-dimethylcyclohexane. Considering the fast rate of epimerization of tertiary carbon radicals (10^9 s^{-1}), it appears that oxygen exchange must occur prior to the interaction of the iron-based oxidant and the alkane C–H bond. Since the Fe^{III}–OOH intermediate can not exchange its oxygen atoms with solvent $H_2^{18}O$, an iron-based oxidant capable of oxygen-exchange with $H_2^{18}O$, i.e. an Fe^{V}=O species, must be involved in the mechanism of alkane hydroxylation by the $[Fe(bpmen)(CH_3CN)_2]^{2+}/H_2O_2$ system. Thus these results provide the first evidence strongly suggesting that even nonheme iron catalysts are capable of accessing the formally Fe^{V} oxidation state often associated with the active oxidant in cytochrome P450 and other heme enzymes (Fig. 2).

4. Perspectives

This review has summarized results stemming from efforts to develop nonheme iron catalysts for selective alkane oxidation using alkyl hydroperoxides or hydrogen peroxide as oxidants. In a few cases, stereospecific alkane hydroxylation has been observed, implying the participation of a metal-based oxidant, and these systems need a more thorough investigation. Excluded from this review were studies with PhIO as the oxidant. This reagent has been widely used in biomimetic heme catalysis to generate high-valent metal-oxo species capable of stereospecific hydrocarbon oxidation [10], and there seems little doubt that the oxygen atom from PhIO is transferred to the metal center prior to substrate oxidation. However in nonheme systems it is not established that this transfer occurs to form a discreet metal-oxo species, since Valentine and co-workers have reported studies that implicate the involvement of the catalyst:PhIO adduct in some oxidations [114]. Caradonna and co-workers recently reported the catalytic activity of a diiron(II) complex $[Fe_2(H_2Hbamb)_2(N\text{-MeIm})_2]$ with PhIO which oxidizes cyclohexane to give an A/K ratio of 57 and a KIE of 2.2 and adamantane to give 2-adamantanol exclusively; some evidence for a transient intermediate was observed [115,116]. This system clearly merits further attention.

The ultimate goal for biomimetic catalysis is to develop systems that use O_2 as the oxidant, which is the way nature carries out most oxidations. This has turned out to be quite a challenge, as the catalytic activation of O_2 requires reductants to bring the metal center to its original reduced state to begin the cycle again. However, reductants are, by definition, easily oxidized molecules and compete with the less easily oxidized hydrocarbon substrate for the oxidizing species. Nature has solved this problem by separating the substrate oxidation site from the site that

Table 3
Oxidation of alkanes by different iron complexes using O_2/reductant

Catalyst	Reductant	A/K[a]	3°/2°[b]	Ref.
$[Fe(OAc)_2(HBpz_3)_2]$	Zn/HOAc	1.2	7	[133]
$\{[Fe(HBpz_3)(hfacac)]_2O\}$	Zn/HOAc	23	82	[117]
$FeCl_2{\cdot}4H_2O$/Mac24	H_2S	1.9–2.0	3–4	[134]
$FeCl_2{\cdot}4H_2O$/Mac30	H_2S	1.1	3–4	[134]
$\{[Fe(salen)]_2O\}$	$HOCH_2CH_2SH$ or ascorbate		1–2	[135]
$FeCl_3$/PA/4-^{t}Bupy	H_2S	0.9–1.4		[136,137]
$FeCl_3$/PA-N-oxide/4-^{t}Bupy	H_2S	1.0–1.2		[136,137]

[a] A/K = cyclohexanol/cyclohexanone in the oxidation of cyclohexane.
[b] 3°/2° = 1-adamantanol/(2-adamantanol + 2-adamantanone) in the oxidation of adamantane, taking into account the correction for a number of C–H bonds in a group.

introduces electrons into the metal center(s). Unfortunately, as shown in Table 3, many of the biomimetic systems reported have A/K ratios for cyclohexane oxidation of around 1, suggesting mechanisms that produce long-lived alkyl radicals. For several systems, adamantane regioselectivity is low, comparable to that expected for hydroxyl radical. The most intriguing of the entries in Table 3 is that for $[Fe_2(O)(HBpz_3)_2(hfacac)_2]/O_2/Zn/HOAc$, (hfacac = hexafluoroacetylacetonate) which shows an A/K ratio of 23 and a high adamantane regioselectivity of 82 [117]. These values suggest that hydroxyl radicals are not involved in the reaction and may implicate an iron-based oxidant. However, this initial report needs substantiation and has thus far not been followed up. Lastly, the 'Gif' family of catalysts developed by Barton and co-workers should be mentioned here for their propensity to convert secondary CH_2 groups into carbonyls via cyclohexyl hydroperoxide [118]; the extensive work on these systems would fill a review of their own.

In summary, efforts in the last ten years to develop nonheme iron catalysts that catalyze alkane hydroxylations modeling the chemistry of methane monooxygenase have mostly given rise to complexes that generate alkoxyl or hydroxyl radicals. There are, however, a few exceptions that hint at the possibility that biomimetic alkane hydroxylation can actually be achieved. The further development of these promising systems and the design of other hydrocarbon oxidation catalysts that can carry out enantiospecific reactions are the challenges for the future.

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