Pergamon

Tetrahedron Vol. 51, No. 18, pp. 5245-5254, 1995
Copyright © 1995 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4020/95 $9.50+0.00

0040-4020(95)00204-9

THE FUNCTIONALIZATION OF SATURATED HYDROCARBONS. PART 31.+ THE Fe(PA)$_3$ - AND [Fe(TPA)Cl$_2$]ClO$_4$ - CATALYZED OXIDATIONS OF SATURATED HYDROCARBONS BY HYDROGEN PEROXIDE: A COMPARATIVE MECHANISTIC STUDY.

Derek H. R. Barton*, Albert H. Beck and Dennis K. Taylor.

Department of Chemistry, Texas A&M University. College Station, Texas 77843-3255.

Key Words: Gif-systems; Saturated Hydrocarbons, Selective Functionalization; Hydrogen Peroxide; Iron(III) Catalysts; Reaction Mechanism.

Abstract: The Fe(pa)$_3$ and [Fe(tpa)Cl$_2$]ClO$_4$ catalyzed *(pa* = picolinic acid, *tpa* = *tris*(2-pyridylmethyl)amine) functionalization of saturated hydrocarbons by H_2O_2 in pyridine / acetic acid follows a common reaction pathway. Regioselectivity studies indicate, that a high valent iron species is responsible for the activation of the alkane. Alkyl hydroperoxides are the precursors for ketone and alcohol formation. Dioxygen provides the oxygen atoms in the alkyl hydroperoxide.

Introduction.

The C-H bonds in saturated hydrocarbons are chemically transformed with difficulty due to their large dissociation bond energies[1] around 95 kcal mol^{-1}. Therefore the functionalization of alkanes requires either severe conditions as realized for industrial autoxidation processes[2] or extremely reactive reagents.[3] However, formation of reactive species in a catalytic cycle circumvents any inconvenience and remains a challenging subject attracting continued current interest.[4]

Major current objectives are the elucidation of the mechanisms for the catalytic oxygen activation by different oxygenase enzymes and structure related model systems as well as designing new highly efficient and selective oxidation catalysts. Catalysts utilizing oxygen under mild conditions are naturally of economical importance because radical autoxidation reactions are unselective and give low conversions.[2]

Extensively studied biological catalysts for the insertion of oxygen atoms into C-H bonds of aliphatic hydrocarbons are the enzymes *cytochrome P-450*[5] and *methane monooxygenase (MMO)*. The *P-450* enzymes are based on heme complexed with one iron.[5] Methane monooxygenase on the other hand is devoid of heme and has two iron atoms bridged together at the active site[6]. The presence of an Fe(V) oxenoid in the *P-450* mechanism is well established.[7] By electron transfer from the heme this becomes an Fe(IV) oxenoid

---

+ Part 30 : Barton, D. H. R.; Bardin, C. O.; Doller, D. *Bioorg. and Med. Chem.*, **1994**, 2, 259-266.

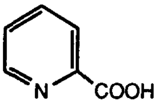
which can also be written as ^{III}Fe-O·. The latter explains that it behaves like an alkoxy radical. For methane monooxygenase (MMO) one of the possibilities is an Fe(IV)-Fe(IV) dimer.[8] Indeed spectroscopic evidence has been found for Fe(IV) and Fe(V) valence states[9] and some Fe(IV) complexes have been thoroughly characterised[10].

We have developed a number of systems for the selective activation of hydrocarbons known as the *Gif*-family.[11] Homogeneous modifications are systems that employ a catalytic amount of ferric chloride or ferric picolinate and hydrogen peroxide as oxidant in pyridine / acetic acid solution. These iron based models activate saturated hydrocarbons in high yields, on a limited conversion, to give ketones as major products.[12] However, when *MMO* and *P-450* enzymes utilize hydrogen peroxide as oxidant exclusively alcohols are produced.[13] In *Gif*-systems an iron(V) oxenoid species is postulated to be the first reaction intermediate.[11]

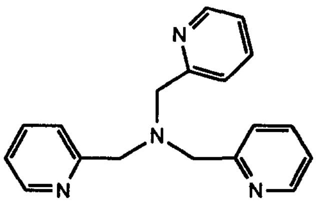
Addition of the picolinic acid ligand (pa) to the $FeCl_3$ / H_2O_2 system affects the efficiency insignificantly but increases markedly the rate of the oxidation reaction by a factor of thirty.[14] Other acids with pyridine or pyrazine moieties also accelerate the oxidation process, while pyridine-2-phosphonic acid and excess oxalic acid inhibits it completely. This shows clearly the importance of the Fe-ligand bond strength for the hydrogen peroxide activation.

Recently an important series of iron(III) complexes containing a tetradentate tripodal ligand, *tris*(2-pyridylmethyl)amine (tpa), have been described by Que and coworkers.[15] These complexes catalyzed the oxidation of cyclohexane by *tert*-butyl hydroperoxide (TBHP) using acetonitrile as solvent.[16]

Their particular structural feature is a defined coordination sphere of pyridyl ligands. We have been always aware of the fact that pyridine as solvent, is most likely coordinated to the iron catalysts in *Gif*-systems. This apparent structural relationship prompted us, with the approval of Prof. Que, to make a comparative study of the $Fe(pa)_3$ **1** and $[Fe(tpa)Cl_2]ClO_4$ **2** catalyzed activation of alkanes by hydrogen peroxide.



(pa)



(tpa)

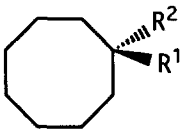
Results and Discussion.

Cyclooctane **3** was employed for the quantitative studies as this proved to be the most reactive hydrocarbon in the Fe(III) / H_2O_2 systems and therefore may reveal any differences in reactivity best. Several experiments with and without trapping reagents were carried out and the results are summarized in Table 1. In the oxidation of cyclooctane double the amount of ketone and alcohol are formed in the presence of the $Fe(pa)_3$ catalyst **1** compared to the $[Fe(tpa)Cl_2]ClO_4$ catalyzed reaction. The half-lifes for these oxidations at 0°C are 35 min (for **1**) and 60 min (for **2**) respectively. Thus, the picolinic acid complex **1** catalyzes the oxidation of saturated hydrocarbons more efficiently at a higher rate.

Table 1. $Fe(pa)_3$ and $[Fe(tpa)Cl_2]ClO_4$ catalyzed functionalization of cyclooctane **3** by hydrogen peroxide.[a]

Catalyst	Halogenating Reagent	Products (mmol)				Total Products (mmol)	Reaction Efficiency (%)[17]
		$R_2C=O$ **4**	$R_2CH\text{-}OH$ **5**	$R_2CH\text{-}Br$ **6**	$R_2CH\text{-}Cl$ **7**		
	----	1.66	0.33			1.99	39.8
$Fe(pa)_3$	CCl_4	1.44	0.22		0.31	1.97	39.4
1	CCl_4[b]	0.67	0.14		0.56	1.37	27.4
	$BrCCl_3$	0.13	nd[c)]	1.89		2.02	40.4
$[Fe(tpa)Cl_2]$	----	0.80	0.11			0.91	18.2
ClO_4	CCl_4	0.81	0.11		nd[c)]	0.90	18.0
2	CCl_4[b]	0.31	0.04		0.02	0.36	7.2
	$BrCCl_3$	0.35	trace	1.35	trace	1.70	34.0

[a] Reaction conditions: Cyclooctane (20 mmol), catalyst (0.2 mmol), H_2O_2 (30%, 10 mmol), trapping reagent (20 mmol), pyridine (30 mL) and acetic acid (3 mL), 0°C, 18 h. [b] Reaction carried out under vacuum (7 mmHg), - 40°C, after 12 h quenched by addition of oxalic acid (2 mmol). [c] Not detected.

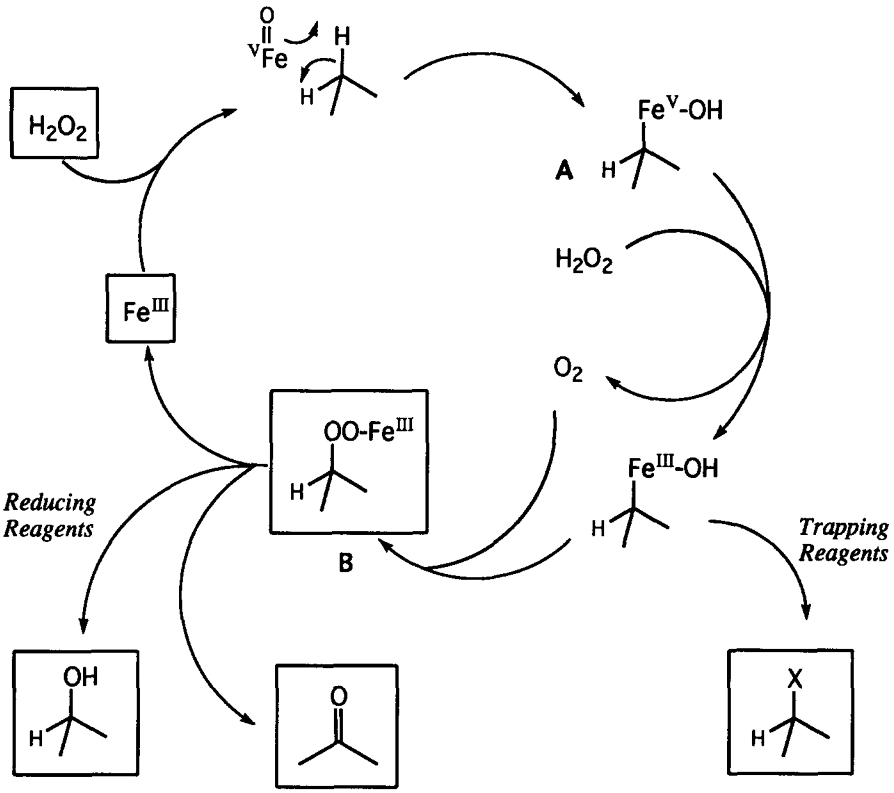


3 $R^1 = R^2 = H$
4 $R^1 = R^2 = O$
5 $R^1 = H, R^2 = OH$
6 $R^1 = H, R^2 = Br$
7 $R^1 = H, R^2 = Cl$
14 $R^1 = H, R^2 =$ *o*-Pyr
15 $R^1 = H, R^2 =$ *p*-Pyr

The efficiency[17] is mainly determined by the relative rates of hydrogen peroxide disproportionation, producing dioxygen and water, and hydrocarbon activation. The Fe(III) catalyzed decomposition of the thermodynamically unstable H_2O_2 is a well documented[18] reaction and, of course, occurs also in the presence of hydrocarbon. The *Kremer-Stein*-mechanism[19] suggests a Fe(III)-Fe(V) redox couple performing the catalytic cycle. First a Fe(V)=O intermediate is formed that turns back into Fe(III) by oxidizing hydrogen peroxide to oxygen (Equation 1). Our proposed mechanism for the activation of hydrocarbons by H_2O_2 (Scheme 1) is based on the same redox chemistry, but here the hydrocarbon intercepts the Fe(V) stage.[11,20] According to this model there must be a competition between the hydrogen peroxide and the hydrocarbon for the Fe(V) species. In case of the $[Fe(tpa)Cl_2]ClO_4$ catalyst (**2**) the rate of decomposition is apparently high, thus less hydrocarbon activation takes place.

$$\begin{gathered} \mathrm{Fe(III)} + {}^{-}\mathrm{O\text{-}OH} \longrightarrow \mathrm{Fe(III)\text{-}O\text{-}OH} \xrightarrow{+\ H^+} \mathrm{Fe(V){=}O} + \mathrm{H_2O} \\ \mathrm{Fe(V){=}O} + {}^{-}\mathrm{O\text{-}OH} \xrightarrow{+\ H^+} \mathrm{Fe(III)} + \mathrm{O_2} + \mathrm{H_2O} \end{gathered} \qquad (1)$$

Scheme 1. Proposed catalytic cycle for Fe(III)-H_2O_2-systems.



The reactions conducted in the presence of carbon tetrachloride also reflect a high catalytic reactivity of 2 for hydrogen peroxide decomposition. These trapping reactions are rationalized in terms of a competition between O_2 and CCl_4 for a reactive Fe(III) intermediate. Based on all our experimental evidence, we have postulated that this intermediate has an Fe(V) or Fe(III)-carbon bond.[20] For 2 no cyclooctyl chloride 7 could be detected under an air atmosphere most likely due to high oxygen concentrations in the reaction mixture (see Table 1). Running the same reaction under vacuum in order to remove formed oxygen and at low temperatures (-40°C) to avoid the loss of the volatile carbon tetrachloride produced only traces of the alkyl chloride. On the other hand, removal of oxygen is more effective in the $Fe(pa)_3$ / H_2O_2 system and increases the ratio of halogenated to oxygenated products by a factor of 4 to a value of 1:1.4 (1:18 for 2).

The addition of bromotrichloromethane to the Fe(III) / H_2O_2 system diverts the formation of oxygenated products in favor of cyclooctyl bromide 6 (Table 1). Again, the ratio of halogenated to oxygenated products is smaller for the $[Fe(tpa)Cl_2]ClO_4$ catalyst (2), 4:1 for 2 versus 15:1 for 1, indicating a greater reactivity of dissolved oxygen. But the presence of $BrCCl_3$ decreases the rate of oxidation for both catalytic systems. The half-lifes at 0°C are 150 min for 1 and 90 min for 2 respectively. Therefore we suspect a reaction of $BrCCl_3$ with the ^{III}Fe-carbon bond after the hydrocarbon activation being responsible for a change of the reaction pathway. In the absence of hydrocarbon this new intermediate produces a considerable amount of 2-bromopyridine (0.7 mmol, standard conditions). However, in the presence of hydrocarbon this is a side reaction and less halogenated pyridine (0.2 mmol) was found for the Fe(pa)$_3$-catalyzed as well as for the [Fe(tpa)Cl$_2$]ClO$_4$ catalyzed bromination.

We have gained valuable mechanistic information about the process of C-H bond activation by the use of adamantane.[21] This highly symmetrical caged hydrocarbon has 12 equivalent secondary C-H bonds and 4 equivalent tertiary C-H bonds. If all adamantane hydrogens would have the same reactivity a normalized C^2/C^3 ratio of 3 would be obtained in a purely statistical activation step.

Table 2. Fe(pa)$_3$ and [Fe(tpa)Cl$_2$]ClO$_4$ catalyzed functionalization of adamantane **8** by hydrogen peroxide. [a]

Catalyst	Products (%) [b]					Total Products (%)	C^2/C^3 [c]
	2=O **9**	2-OH **10**	1-OH **11**	1-o-Pyr **12**	1-p-Pyr **13**		
Fe(pa)$_3$	7.0	3.4	3.2	5.0	3.0	21.6	0.93
[Fe(tpa)Cl$_2$] ClO$_4$	4.8	1.4	3.8	1.4	1.4	12.8	0.94
no catalyst[d]	12.8	nd [e]	7.0	23.8	14.0	57.6	0.29

[a] Reaction conditions: Adamantane (5 mmol), catalyst (0.2 mmol), H_2O_2 (30%, 10 mmol), pyridine (30 mL) and acetic acid (3 mL), 25°C, 18 h. [b] Yield based on adamantane as limiting reagent. [c] The C^2/C^3 ratio is defined as C^2 being the total of products oxidized at the secondary position and C^3 similarily for the tertiary position. [d] *tert*-Butoxy radicals generated by decomposition of di-*tert*-butyl peroxalate. Reaction conditions: Adamantane (5 mmol), *tert*-butyl hydroperoxide (10 mmol), dry pyridine (30 mL), addition of oxalyl chloride (5 mmol) at 0°C, temperature raised to 40°C, 1 h under oxygen. We thank Dr C. O. Bardin for performing this experiment. [e] Not detected.

A C^2/C^3 value of 0.15 has been recently reported for an alkoxy radical attack on adamantane[22]. Futhermore the C^2/C^3 ratios obtained for hydrogen abstraction by a oxoferryl porphyrin species[23] and by the cobalt catalyzed autoxidation[24] are 0.21 and 0.53 respectively, indicating a preference for tertiary C-H bonds. It is also noteworthy that *P-450* enzymes hydroxylate adamantane almost exclusively at the tertiary position with a C^2/C^3 ratio of approximately 0.10.[25]

In addition we studied the selectivity of *tert*-butoxy radicals in pyridine. The radicals are readily formed by thermal decomposition of di-*tert*-butyl peroxalate, which in turn was prepared *in situ* from oxalyl chloride and TBHP as reported.[26] The obtained C^2/C^3 ratio is 0.29 (Table 2). In contrast to this, a common and unusually high C^2/C^3 value around 1 has been established for *Gif*-systems (Fe(II) / O_2 / Zn[27], Fe(II) / KO_2, $FeCl_3$ / H_2O_2[28] and Fe(pa)$_3$ / H_2O_2[29]). Remarkably *MMO* shows a similar regioselectivity of 1.0.[30] The absence of hydroxyl radicals was previously highlighted since the formation of 3-hydroxypyridine in these systems reflects the weak electrophilic character of the oxidizing species and not the formation of hydroxyl radicals. [11]

Also the[Fe(tpa)Cl$_2$]ClO$_4$ / H_2O_2 system gives a *Gif*-type C^2/C^3 selectivity of 0.94 which is identical to the Fe(pa)$_3$ catalysis within experimental error (Table 2). Furthermore, the same reaction products are formed, although in lower yield, without any pyridine coupling to the secondary position of adamantane.

Since adamantane has a rigid molecular framework hydrogen abstraction from a tertiary position generates necessarily a pyramidalized and destabilized bridgehead radical.[31] Photoelectron spectroscopy data and the ability of 1-adamantyl radicals to abstract readily hydrogen from saturated hydrocarbons like cyclohexane constitute strong evidence that the tertiary C-H bonds of adamantane are stronger than the secondary C-H bonds.[32] Consequently, the observed C^2/C^3 selectivities for adamantane are contrary to the order of decreasing bond energies and the regioselectivity of highly reactive alkoxy radicals is probably controlled by steric factors. Only the tertiary hydrogens are easily accessible in a co-linear fashion. The high C^2/C^3 value observed for the Fe(III) catalysis is clearly distinct from alkoxy radical-like chemistry and can consequently be attributed to the presence of a less reactive, more selective Fe(V)=O oxenoid species. The bulkiness of such a species should create a reasonable steric hindrance preventing even a higher selectivity pattern.

Since trapping reagents like CCl_4, $BrCCl_3$ as well as dioxygen scavenge radicals, it seems a likely supposition that carbon centred radicals might be formed by a hydrogen abstraction step and be responsible for the observed chemistry. But also hydrogen sulfide or phenylselenol would readily trap genuine carbon radicals and reduce them back to the starting hydrocarbon. However, the presence of these compounds does not suppress the oxidation reaction and gives rise to dialkyl disulfides[33] and alkylphenyl selenides[34] respectively.

Furthermore, free carbon radicals are also trapped by protonated pyridine, affording *ortho* and *para*-coupled alkyl pyridines.[35] Indeed, in the Fenton system, Fe(II) / H_2O_2 (1:1), alkyl pyridines are the major reaction products, while ketone and dialkyl are formed to less extent.[36a] When adamantyl and cyclohexyl radicals were generated by photolysis of acyl derivatives of *N*-hydroxy-2-thiopyridone, alkyl pyridines could also be detected in the presence of oxygen.[28] The experiments showed, that the large excess of the solvent pyridine competes successfully with dioxygen for alkyl radicals. Additionally, we have recently shown that the Fenton system, Fe(II) / H_2O_2 (1:1) produces chloride via a radical pathway even though the activation of the hydrocarbon occurs via a Fe(IV) oxenoid species.[36b]

Again we studied the fate of cyclooctyl radicals in pyridine, generated by the decomposition of di-*tert*-butyl peroxalate, under an atmosphere of argon and dioxygen. The results are presented in Table 3. Oxygen captures free radicals efficiently, but even with a maximum concentration of oxygen, realized by bubbling the oxidant through the reaction mixture, some pyridine coupling was found (Entry 2). Therefore, if free alkyl radicals were involved in the Fe(III) catalyzed activation of saturated hydrocarbons by H_2O_2, coupling to pyridine would inevitably occur and be detected.

However, none of the experiments conducted with the $Fe(pa)_3$ or $[Fe(tpa)Cl_2]ClO_4$ catalyst showed any trace of pyridine coupled products *at secondary positions.* It has been reported earlier, that also under reduced pressure no alkyl pyridines have been observed.[12] These and other[37] experimental data strengthen the hypothesis, that the intermediate derived from the reaction of a Fe(V)=O species with the hydrocarbon has non-radical behavior. We therefore suggest a high valent iron-carbon sigma bonded intermediate (Scheme 1).

An intermediate being definitely identified by chemical and spectroscopical means is the alkyl hydroperoxide of the corresponding hydrocarbon. The accumulation and decay of the alkyl hydroperoxide could be demonstrated for different Fe(III) catalyzed oxidation reactions by employing a ^{13}C labeled hydrocarbon and by monitoring the time courses of the reactions with the ^{13}C NMR. technique.[38] Addition of the reducing reagent triphenylphosphine to the Fe(II) / O_2 / Zn system altered the ketone to alcohol ratio but did not affect the total amount of hydrocarbon activation. A pure sample of cyclohexyl hydroperoxide yielded, when subjected to the pyridine / acetic acid solvent mixture containing the Fe(III) catalyst, ketone and alcohol in the same ratio as was observed for the original oxidation reaction (10:1). Hence the alkyl hydroperoxide is the common precursor for ketone and alcohol.

Table 3. Competition between dioxygen and pyridine for free cyclooctyl radicals .[a]

Entry	Reaction Conditions	*Products (mmol)*			
		$R_2C{=}O$ **4**	R_2CH-OH **5**	R_2CH-*o*-Pyr **14**	R_2CH-*p*-Pyr **15**
1	under Ar	0.41	nd[b]	2.47	0.97
2	under O_2[c]	0.84	0.13	1.22	0.68

[a] Reaction conditions: Cyclooctane (50 mmol), *tert*-butyl hydroperoxide (10 mmol), dry pyridine (30 mL) addition of oxalyl chloride (5 mmol) at 0°C, temperature raised to 40°C, 1 h. [b] Not detected. [c] steady stream of oxygen through reaction mixture.

We also used ^{13}C-NMR spectroscopy to follow the oxidation of cyclohexane by the $[Fe(tpa)Cl_2]ClO_4$ / H_2O_2 system at - 20°C and detected cyclohexyl hydroperoxide as a reaction intermediate. This important piece of evidence confirms a general reaction pathway for the Fe(III) catalyzed activation of saturated hydrocarbons, regardless of the ligand coordinated to the iron.

From experiments conducted under an atmosphere of $^{18}O_2$ or in the presence of $H_2{}^{18}O$ we learned that the oxygen atoms incorporated into the ketone or alcohol originate from dioxygen and not from hydrogen peroxide or H_2O. This rules out any ligand coupling mechanism. Hence we proposed the insertion of oxygen into an iron-carbon bond (Scheme 1).

The mechanistic studies on the activation of saturated hydrocarbons by the $Fe(pa)_3$ / H_2O_2 and $[Fe(tpa)Cl_2]ClO_4$ / H_2O_2 systems show clearly, that a general reaction mechanism operates. The reaction proceeds via a pathway alkane to alkyl hydroperoxide to ketone and alcohol. All experimental findings support the hypothesis, that a high valent iron species achieves the activation of unactivated C-H bonds. Subsequently a first intermediate is formed. This intermediate **A** is proposed to have a Fe(V)-carbon bond and to be trapped (probably after reduction to the Fe(III) species) by reagents like carbon tetrachloride (Fe(III) / H_2O_2 system) affording monosubstituted alkyl derivatives. In the absence of a trapping reagent, intermediate A is transformed to a second intermediate by reduction and oxygen insertion. Intermediate **B** is the fully characterized alkyl hydroperoxide and the sole precursor for ketone and alcohol.

Conclusions.

The $Fe(pa)_3$ and $[Fe(tpa)Cl_2]ClO_4$ catalyzed (*pa* = picolinic acid, *tpa* = *tris*(2-pyridylmethyl)amine) functionalization of saturated hydrocarbons by H_2O_2 in pyridine / acetic acid follows a common reaction pathway. Regioselectivity studies provide evidence that a high valent iron species is responsible for the activation of the alkane. Alkyl hydroperoxides are the precursors for ketone and alcohol formation while dioxygen provides the oxygen atoms in the alkyl hydroperoxide. It should, however, be noted that the results reported here cannot be compared directly with the prior work[15] of Que et al. All the earlier work was carried out in acetonitrile, a solvent which is more likely than pyridine to encourage radical chemistry. Indeed the selectivity for the various reactions of adamantane that were investigated[15] correspond well to radical reaction selectivity and not to the normal Gif selectivity seen in pyridine.

Experimental Section.

General Methods. Mass spectrometric analyses were performed on a Hewlett-Packard 5790A Series II gas chromatograph equipped with a flame ionisation detector. The columns used for chromatography were DB-WAX (30 m) or DB-5 (15 or 30 m) capillary columns from J&W Scientific. Gas chromatography-mass spectrometry (GC-MS) was conducted on a Hewlettt-Packard 5970A gas chromatograph coupled to a mass selective detector (40 eV). ^{1}H and ^{13}C N.M.R experiments were carried out at room temperature on a Varian Gemini 200, Varian XL 200E instrument or a Unity 500. Silica gel (Kieselgel 60; EM Science, 70-230 mesh or Merck, 230-400 mesh) was used for column chromatography.

Materials. Unless otherwise stated, chemicals were purchased from commercial sources and used without further purification. Tris(2-pyridylmethyl)amine (tpa) was synthesized following the protocol of *Anderegg* and *Wenk*.[39] The work-up procedure was modified by extracting the dark reaction mixture twice with toluene. After drying (Na_2SO_4) and evaporation of the solvent, a dark brown oil was obtained. Separation of the colorless amine was accomplished by several extraction steps with boiling hexanes. Yield 29%. The corresponding perchlorate salt $(H_3tpa)(ClO_4)_3$ was obtained by dissolving tpa in ethanol and addition of the stoichiometric amount of 70% perchloric acid. A colorless precipitate was formed instantaneously and recrystallized by the addition of a some water. Colorless needles were isolated in quantitative yield. $[Fe(tpa)Cl_2]ClO_4$ was synthesized as reported previously by *Que* and co-workers.[15]

Authentic samples of *ortho-* and *para-*cycloalkyl pyridines were prepared by photolysis of the N-hydroxy-pyridine-2-thione derivatives of the corresponding carboxylic acids in pyridine-trifluoroacetic acid as reported elsewhere. *Tert*-adamantyl pyridines were obtained by oxidizing 1-adamantanecarboxylic acid with lead tetraacetate in pyridine.[40]

General procedure for oxidation reactions. The iron catalyst (0.2 or 1.0 mmol) was dissolved at room temperature in a solution of 30 ml pyridine, 3 ml acetic acid and the appropriate saturated hydrocarbon (5 or 20 mmol). This solution was cooled to 0°C by a ice-water bath, the reaction started by addition of 1 ml H_2O_2 (30% in water, 10 mmol) and kept over night at 0°C. Reactions were carried out in a 125 ml Erlenmeyer flask, loosely closed by a rubber stopper.

General work-up procedure. An 10 ml aliquot was taken from the reaction mixture and added to 20 ml ether containing 0.16 mmol naphthalene (internal standard). This ethereal solution was washed with 30 ml 5n KOH and 30 ml saturated $NaHCO_3$ solution, dried over Na_2SO_4 and analyzed by gas chromatography. For quantification of carboxylic acids the chilled ethereal solution was washed with 30 ml ice-cold 25% H_2SO_4, dried and analyzed.

Modified work-up procedure in order to determine oxidation rates. At appropriate times a 2 mL aliquot was taken from the reaction mixture, poured into a chilled mixture of 10 mL ether, 0.08 mmol naphthalene (internal standard), 5 mL 25% H_2SO_4 and 1 mmol oxalic acid and shaken vigorously. The ether fraction was analyzed by means of gas chromatography.

^{13}C NMR Studies. The ^{13}C spectra of the reactions (prepared according to the general procedure described above) were measured on a Unity 500 approximately every 4-8 hours over the time course of several days. Parameters used: Referenced to cyclohexane, $\delta = 27.03$ ppm; Lock (pyridine-d5); sfrq = 125.697 Hz, at = 1.277s, sw = 50125 Hz, tpwr = 54 dB, pw = 6.0 dB, dmf = 20448 Hz, dpwr = 42 dB, d1=0.0 s, nt =

20-60,000, lb = 2.0 Hz. The ^{13}C resonances of the cyclohexyl hydroperoxide were 82.63, 30.97, 24.08, 26.22 ppm and were identical to those previously reported.[38]

Acknowledgements. We thank the Welch Foundation for financial assistance as well as Quest International. We thank Professor L. Que for a helpful exchange of information.

References and Notes

1. Lide, D. R. (ed.) *CRC Handbook of Chemistry and Physics;* CNC (71st ed.): Boca Raton, FL. 1990; pp. **9**, 86-98.
2. Ingold, K. U. *Aldrichimica Acta.*, **1989**,*22*, 69-73.
3. The traditional oxidant, a powerful electrophile, was CrO_3. For example: Fieser, L. F.; Fieser, M. in Natural Products Related to Phenanthrene, Reinhold Pub. Corpn. New York, 1949, pp. 364-368.
4. a) Drago, R. S. *Coord. Chem. Rev.* **1992**, *117*, 185-213. b) Hill, C. L. (ed.) *Activation and Functionalization of Alkanes*, J. Wiley & Sons, Inc.: New York, 1989. c) Sawyer, D. T. *Oxygen Chemistry* , Oxford University Press: New York, 1991. d) Sheldon, R. A. ; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press: New York, 1981. e) Simandi, L. I. *Catalytic Activation of Dioxygen by Metal Complexes*, Kluwer Academic Publishers: Dordrecht, 1992. f) Martell, A. E.; Sawyer D. T. *Oxygen Complexes and Oxygen Activation by Transition Metals*, Plenum Press: New York, 1988. g) Schuchardt, U.; Carvalho, W. A.; Spinace, E. V. *Synlett*, **1993**, 713-718. h) Barton, D. H. R.; Martell, A. E.; Sawyer, D. T. (ed.) *The Activation of Dioxygen and Homogenious Catalytic Oxidation*, Plenum Press, New York, 1993, 225-242.
5. Porter, T. D.; Coon, M.J. *J. Biol. Chem..*, **1991**, *266*, 13469-13472.
6. a) Raag, R.; Poulos, T. L. *Biochemistry*, **1989**, *28*, 917-922. b) Rosenzweig, A. C.; Frederick, C. A.; Lippard, S. J.; Nordlund P. *Nature*, **1993**, *366*, 537-543.
7. Ortiz de Montellano, P. R. (ed.) *Cytochrome P-450: Structure, Mechanism and Biochemistry;* Plenum Press: New York, 1985.
8. Fox, B. G.; Borneman, J. G.; Wackett, L. P., Lipscomb, J. D. *Biochemistry*, **1990**, *29*, 6419- 6427.
9. a) Ochsenbein, P.; Mandon, D.; Fischer, J.; Weiss, R.; Austin, R.; Jayaraj, K.; Gold, A.; Terner, J.; Bill, E.; Müther, M.; Trautwein, A. X. *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 1437-1439. b) Leising, R. A.; Brennan, B. A.; Que, L., Jr.; Fox, B. G.; Münck, E. *J. Am. Chem. Soc.*, **1991**, *113*, 3988-3990. c) Bielski, B. H. J.; Thomas, M. J. *J. Am. Chem. Soc.*, **1987**, *109*, 7761-7764.
10. a) Sellmann, D.; Geck, M.; Knoch, F.; Ritter, G.; Dengler, J. *J. Am. Chem. Soc.*, **1991**, *113*, 3819-3828.b) Kostka, K. L.; Fox, B. G.; Hendrich, M. P.; Collins, T. J.; Rickard, C. E. F.; Wright, L. J.; Münck, E.*J. Am. Chem. Soc.*, **1993**, *115*, 6746- 6757. c) Hiller, W.; Strähle, J.; Datz, A.; Hanack, M.; Hatfield, W. E.; ter Haar, L. W.; Gütlich, P. *J. Am. Chem. Soc.*, **1984**, *106*, 329 - 335.
11. Barton, D. H. R.; Doller, D. *Acc. Chem. Res.*, **1992**, *25*, 504-512.
12. Barton, D. H. R.; Bévière, S. D.; Chavasiri, W.; Csuhai, E.; Doller D. *Tetrahedron*, **1992**, *48*, 2895-2910.
13. Andersson, K. K.; Froland, W. A.; Lee, S.-K.; Lipscomb J. D. *New J. Chem.*, **1991**, *15*, 411-415.
14. About-Jaudet, E.; Barton, D. H. R.; Csuhai, E.; Ozbalik, N. *Tetrahedron Lett.*, **1990**, *31*,1657-1660.
15. a) Norman, R. E.; Yan, S.; Que, L., Jr.: Backes, G.; Ling, J.; Sanders-Loehr, J.; Zhang, J. H. *J. Am.. Chem. Soc.*, **1990**, *112*, 1554-1562. b) Kojima, T.; Leising, R. A.; Yan, S.; Que, L., Jr. *J. Am. Chem. Soc.*, **1993**, *115*, 11328-11335.
16. Leising, R. A.; Zang, Y.; Que, L.,Jr. *J. Am. Chem. Soc.*, **1991**, *113*, 8555-8557.
17. The efficiency is based on the amount of oxidant used. The calculations consider, that 2 equivalents of H_2O_2 is required for the formation of ketone, alcohol and alkyl halogenides.
18. Brown, S. B.; Jones, P.; Suggett, A. *Prog. Inorg. Chem.*, **1970**, *13*, 159-204.
19. Kremer, M. L. *Int. J. Chem. Kinet.*, **1985**, *17*, 1299-1314.
20. Barton, D. H. R.; Bévière, S. D.; Chavasiri, W.; Csuhai, E.; Doller, D.; Liu, W.-G. *J. Am. Chem. Soc.*, **1992**, *114*, 2147-2156.
21. Barton, D. H. R.; Csuhai, E.; Doller, D.; Ozbalik, N.; Balavoine, G. *Proc. Natl. Acad. Sci. USA* ,**1990**, *87*, 3401-3404.
22. Fossey, J.; Lefort, D.; Massoudi, M.; Nedelec, J.-Y.; Sorba, *Can. J. Chem.*, **1985**, *63*, 678-680.
23. Brown, R. B., Jr.; Hill, C. L. *J. Org. Chem.*, **1988**, *53*, 5762-5768.
24. Goldstein, A. S.; Drago, R. S. *Inorg. Chem.*, **1991**, *30*, 4506-4510.
25. Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.*, **1979**, *101*, 1032-1033.
26. a) Bartlett, P. D.; Benzing, E. P.; Pincock, R. E. *J. Am. Chem. Soc.*, **1960**, *82*, 1762-1768.
    b) Lüning, U.; Seshadri, S.; Skell, P. S. *J. Org. Chem.*, **1986**, *51*, 2071-2077.

27. Barton, D. H. R.; Ozbalik, N. in *Activation and Functionalization of Alkanes*, Hill, C. L. (ed.), J. Wiley &Sons, Inc.: New York, **1989**, pp 281-301.
28. Barton, D. H. R.; Halley, F.; Ozbalik, N.; Schmitt, M.; Young, E.; Balavoine, G. *J. Am. Chem. Soc.*, **1989**, *111*, 7144-7149.
29. Barton, D. H. R.; Csuhai, E.; Doller, D.; Geletii, Y. V. *Tetrahedron.*, **1991**, *47*, 6561-6570.
30. Green, J.; Dalton, H. *J. Biol. Chem.*, **1989**, *264*, 17698-17703.
31. Walton, J. C. *Chem. Soc. Rev.*, **1992**, 105-112.
32. a) Engel, P. S.; Chae, W.-K.; Baughman, S. A.; Marschke, G. E.; Lewis, E. S.; Timberlake, J. W.; Luedtke, A. E. *J. Am. Chem. Soc.*, **1983**, *105*, 5030-5034.
    b) Kruppa, G. H.; Beauchamp, J. L. *J. Am. Chem. Soc.*, **1986**, *108*, 2162-2169.
33. Balavoine, G.; Barton, D. H. R.; Gref, A.; Lellouche, I. *Tetrahedron.*, **1992**, *48*, 1883-1894.
34. Barton, D. H. R.; Boivin, J.; Le Coupanec, P. *J. Chem. Soc. Chem. Commun.*, **1987**, 1379-1381.
35. Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489-519.
36. (a) Sheu, C.; Sobkowiak, A.; Zhang, L.; Ozbalik, N.; Barton, D. H. R.; Sawyer, D. T. *J. Am. Chem. Soc.*, **1989**, *111*, 8030-8032. (b) Bardin, C.; Barton, D. H. R.; Hu, B.; Rojas-Wahl, R.; Taylor, D. K. *Tetrahedron Lett.*, **1994**, *35*, 5805-5808.
37. Barton, D. H. R.; Bévière, S. D.; Doller, D. *Tetrahedron Lett.*, **1991**, *32*, 4671-4674.
38. Barton, D. H. R.; Csuhai, E.; Doller, D.; Balavoine, G.; *J. Chem. Soc. Chem. Commun.*, **1990**, 1787-1789.
39. Anderegg, G.; Wenk, F. *Helv. Chim. Acta.*, **1967**, *50*, 2330-2332.
40. Barton, D. H. R.; Boivin, J.; Motherwell, W. B.; Ozbalik, N.; Schwartzentruber, K. M.; Jankowski, K. *New. J. Chem.*, **1986**, 387-398.

(*Received in USA* 5 *December* 1994; *accepted* 3 *March* 1995)