KEYNOTE
PERKIN 2

The selective functionalization of saturated hydrocarbons. Part 32.† Distinction between the Fe^{II}–Fe^{IV} and Fe^{III}–Fe^{V} manifolds in Gif chemistry. The importance of carboxylic acids for alkane activation. Evidence for a dimeric iron species involved in Gif-type chemistry

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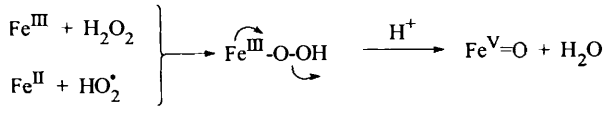
Gif chemistry permits the selective functionalization of saturated hydrocarbons under very mild conditions. The formation of alkyl chlorides is shown to derive from an Fe^{II}–Fe^{IV} manifold and is distinct from the usual ketonization process (Gif chemistry) produced by an Fe^{III}–Fe^{V} manifold. The importance of certain carboxylic acids such as picolinic acid 1 for hydrocarbon activation is highlighted. The ligand environment of the catalyst in solution is clarified using ^{13}C NMR spectroscopy. Evidence for a μ-peroxo-dimer species as a key intermediate in solution is provided.

Introduction

The use of Gif chemistry in the selective functionalization of saturated hydrocarbons [1] has been summarized.[2,3] Most of the work has involved the use of Fe^{II} + superoxide or Fe^{III} + hydrogen peroxide, as depicted in Scheme 1.



Scheme 1

The reactivity of the postulated oxenoid species is unusual as secondary positions are selectively substituted to afford, as isolated products, ketones. A careful study of intermediates showed that two (**A** and **B**) could be detected.[4] Intermediate **B** was firmly established in the Gif solvent pyridine–acetic acid to be a hydroperoxide which fragmented to ketone.[5] For several reasons intermediate **A** has been formulated as an iron–carbon bonded species.

The non-radical nature of the Fe^{III}–H_2O_2 system

In principle **A** could be a free carbon radical, but it does not respond to a number of tests for a free carbon radical. The formation of the oxygen-derived ($^{18}O_2$ experiments) hydroperoxide is, at first sight, compatible with a carbon radical reaction. However, experiments with PPh_3 and with $P(OMe)_3$ are not in agreement with hydroperoxyl radicals as intermediates.

Knight and Perkins[6] concluded that intermediate **A** must be a carbon radical formed from (say) a hydroxyl radical. In fact Fe^{III} + H_2O_2 in pyridine is an inefficient source of hydroxyl radicals. Pyridine is, of course, a good trap for carbon and hydroxyl radicals and genuine hydroxyl radicals do indeed afford 2- and 4-hydroxypyridines. However, in Gif chemistry the major products from pyridine are 2- and 3-hydroxypyridines in minor amount.[7]

When the oxidation of adamantane is carried out under reduced pressure (Fe^{II} + superoxide) a competition at the tertiary position between oxygen and pyridine is easily detected. Thus tertiary carbon radicals are present. The same process shows that secondary radicals are not present. The appropriate competition experiments for both secondary and tertiary positions were carried out using radicals generated from Barton PTOC esters and the genuine secondary radicals showed the same competition as tertiary radicals.[8] These critical experiments were not considered in the paper by Knight and Perkins.[6] The latter authors also report a *p*-hydroxylation of phenylalanine (no yield or mass balance) under Fe^{III}–H_2O_2 conditions. However we showed, with attention to mass balances, that diphenyl did not give any hydroxy-derivatives during Gif oxidation.[9] The report by the same authors that cyclohexyl radicals could be detected by nitroxide radical formation involved an experiment that was not reported to be carried out quantitatively.

Table 1 Comparison of adamantane selectivity (C^2/C^3) for *tert*-butoxyl radicals[a]

Entry	Conditions	Products	C^2/C^3
1	Argon	Pyr coupling only	0.28
2	Air	Pyr coupling and oxidation	0.28
3	Argon ($CBrCl_3$, 20 mmol)	Bromination only	0.34

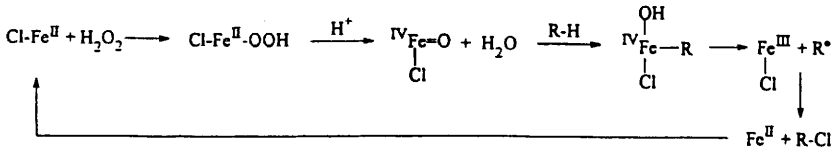
[a] See the Experimental section for more detailed conditions.

Fe^{III} + TBHP

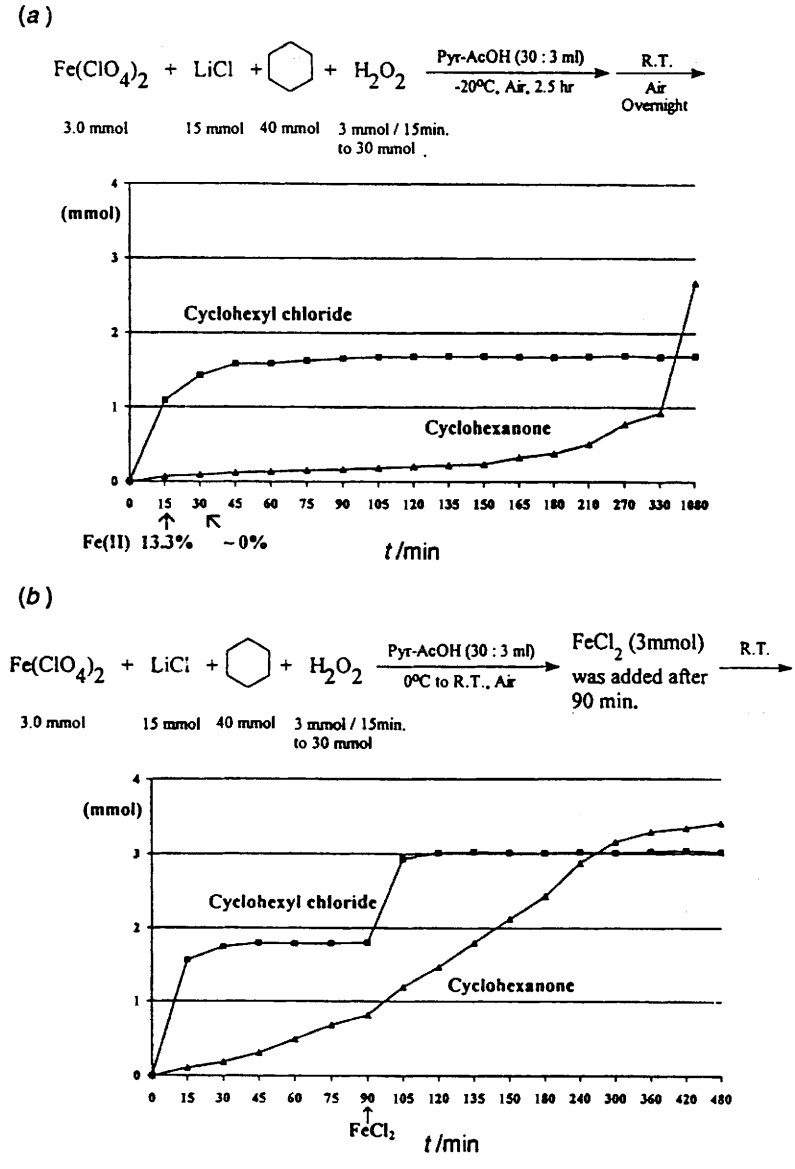
Another oxidation system is Fe^{III} + *tert*-butyl hydroperoxide (TBHP). This has a very different isotope effect (about 7) compared with the Fe^{II}–superoxide or the Fe^{III}–H_2O_2 systems both of which are identical (as they should be) at 2.1. The Fe^{III}–TBHP system has a C^2/C^3 selectivity for adamantane of less than 0.5. The Fe^{II}–superoxide and Fe^{III}–H_2O_2 systems have a value of 1.1.[2] The expression C^2/C^3 equals the total of secondary products divided by the total of tertiary products. For *tert*-butoxyl radicals in pyridine, the C^2/C^3 selectivity is 0.3–0.4 as shown in the data in Table 1.

However, the overall scheme for ketone formation in the Fe^{III}–TBHP system is also alkane ⟶ intermediate ⟶ hydroperoxide ⟶ ketone. In the course of our studies with TBHP we observed that, although the reaction at room temperature was sluggish, at 60 °C excellent yields of alkyl chlorides were formed from saturated hydrocarbons in the presence of chloride anion. This surprised us because we

† Part 31: D. H. R. Barton, A. H. Beck and D. K. Taylor, *Tetrahedron*, 1995, **51**, 5245.



Scheme 2



Scheme 3

had examined the effect of chloride and bromide anions in the Fe^{III}–H_2O_2 chemistry and had never seen even a trace of alkyl chloride or bromide, with one exception. When PPh_3 was added to Fe^{III} in pyridine–acetic acid in the presence of chloride anion the normal oxidation process changed to alkyl chloride formation.[10] This important observation can now be understood (*vide infra*). Although at 60 °C with TBHP carbon radicals could be detected by their habitual coupling to pyridine, as soon as chloride was added the mechanism changed. Although we at first considered this to be the transformation of a radical mechanism into a non-radical mechanism the incisive experiments of Minisci and his colleagues have shown that radical chemistry[11] is indeed involved.[12]

The contributions by Prof. Minisci and his colleagues[13] are welcome because they enable a clear demonstration to be drawn between non-radical Gif chemistry and the 60 °C–TBHP experiments which are indeed ordinary radical reactions involving *tert*-butoxyl radicals.[14] A consideration of the Minisci results at 60 °C suggested that Fe^{II} was the probable source of the radical chemistry. The Fe^{II} was being produced by a minor reduction process because the reaction was so slow.

The importance of ferrous iron

Fenton-type chemistry, which means the formation of hydroxyl radicals, exhibits a different kinetic isotope effect KIE (usually 1). As mentioned above, free $^•OH$ radicals can be ruled out as being responsible for hydrocarbon activation.[14,15] Therefore, an Fe^{II}–Fe^{IV} manifold was proposed to operate instead. If $FeCl_2$ is used in the presence of excess chloride ion in the H_2O_2–

pyridine–acetic acid–cyclohexane oxidation system (portion-wise addition of H_2O_2), cyclohexyl chloride (Scheme 2) is rapidly formed.[14] An important contribution to the sequel came from the ability to distinguish by titration[16] between Fe^{II} and Fe^{III}.

The distinction between the Fe^{II}–Fe^{IV} and Fe^{III}–Fe^{V} manifolds

As soon as all the Fe^{II} has been converted into Fe^{III} the mechanism changes from radical ($R^{\cdot}$ + Cl–Fe^{III} ⟶ R–Cl + Fe^{II}) to non-radical and the normal Gif mechanism takes over to make ketone according to the normal Fe^{III}–Fe^{V} manifold,[17] while the amount of alkyl chloride remains constant, even after an overnight reaction. These results for pyridine–acetic acid 10:1 are illustrated in Scheme 3(*a*).

Of course, during this second stage the Cl–Fe^{III} species is still present, because there is an excess of chloride ion. When adding a second portion of Fe^{II}, just at the time when the alkyl chloride formation becomes constant, of course the amount of alkyl chloride produced jumps again, *e.g.* from 1.8 mmol to 3 mmol R–Cl, while ketone formation is not affected. Indeed the chloride ion can be varied from 5 equiv. to 20 equiv. with respect to the Fe species without any change in the amount of alkyl chloride formed. Hence, only the amount of Fe^{II} is important. For a typical experiment in pyridine–acetic acid 10:1 see Scheme 3(*b*). A blank experiment with cyclohexyl chloride under the same oxidation conditions showed that the chloride was inert and that no ketone was formed.

Furthermore, running a Gif^{IV} reaction (Fe^{II} + Zn^0 + O_2)[2] in the presence of chloride anion with and without hydrogen peroxide clearly demonstrates the fundamental difference between the two manifolds: in the absence of H_2O_2, no alkyl chlorides are formed at all, and ketone is the only reaction product. In the presence of H_2O_2 however, alkyl chloride is by far the prevailing product besides the usual ketone formation. This is a clear proof, that in the Gif^{IV} system, the oxygen is reduced only to superoxide, but *not* to peroxide.

The fact that ferrous ion plus hydrogen peroxide produces alkyl chlorides and no ketone at all is a simple experimental fact, but, as will be seen below, of utmost important for the complete understanding of Gif chemistry.

Biochemical background

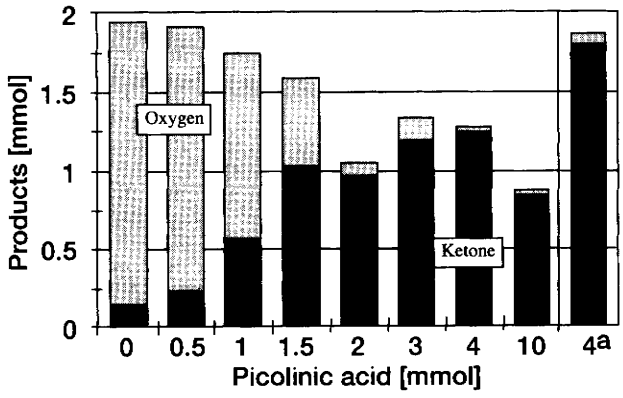
The structure and reactions of a number of metalloenzymes containing non-heme iron(II) and iron(III) centres has recently been highlighted.[18] Of these perhaps, the most intriguing is methane monooxygenase (MMO) which is capable of converting methane into methanol. The structure of this enzyme and others comprises a μ-oxo-diiron(III) core having a semi-bridging glutamate and an acetate bridge.[19] The latter is replaced during the catalytic cycle with a weakly co-ordinated monoatomic water bridge.[20] Considering that ferric ions in the presence of H_2O and acetic acid readily undergo 'self-assembly' forming bridged diiron cores,[21] we now provide chemical evidence for a dinuclear iron(III)-species as the key intermediate in Gif-type oxidation chemistry. This intermediate will be shown to enable us to rationalize *all* experimental facts accumulated so far in a simple way.

Results and discussion

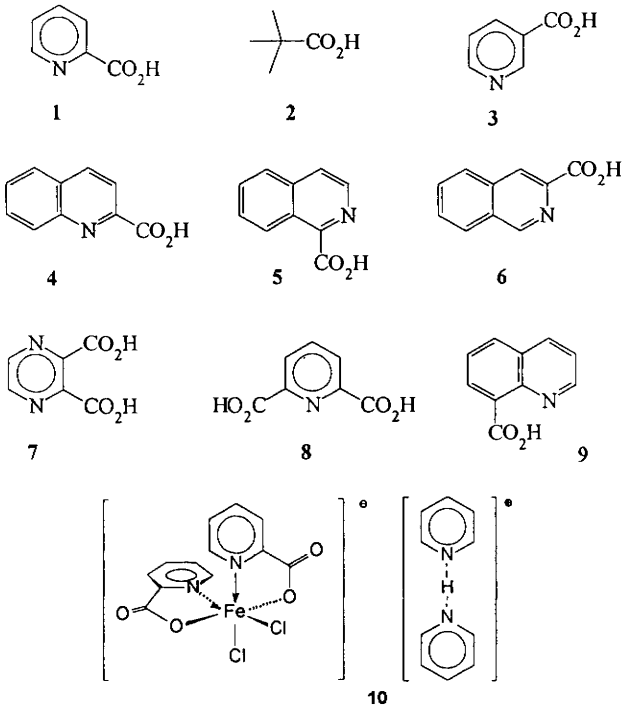
Distinction between oxygen formation (catalase reaction) and ketonization (Gif chemistry): the importance of carboxylic acids

In order to study the role of other carboxylic acids, the original Gif system had to be simplified by leaving out the acetic acid. First we carried out the catalase reaction (oxygen formation) in competition with Gif chemistry (ketonization) by using various amounts of picolinic acid (PA) **1**. The results are depicted in Scheme 4.

Three points deserve special attention. First, oxygen formation is almost completely suppressed by having 2 equiv.



Scheme 4 Ketone and oxygen formation with various amounts of picolinic acid: ferric chloride 1 mmol, cyclooctane 20 mmol, pyr 33 ml, hydrogen peroxide 4 mmol, Ar, 0 °C, overnight. [a] Same conditions except cyclooctane 40 mmol, pyr 16.5 ml.



Scheme 5

(with respect to the iron) of PA **1** in solution. Preliminary studies have shown that 4 equiv. of hydrogen peroxide were most efficient for ketonization, hence the large excess of oxidant used in the earlier studies is not necessary.[22] At 4 equiv. of PA, higher efficiencies for ketone formation are reached.[23] Finally, by doubling the amount of hydrocarbon and halving the amount of pyridine, efficiencies up to 93% with respect to the employed oxidant could be obtained (for details see the Experimental section).

Being able to suppress almost entirely the catalase reaction with a system Fe^{III}–PA–H_2O_2 1:4:4, we were able to study the influence of a variety of other carboxylic acids (Scheme 5). The results are shown in Table 2.

Here, the prerequisites for a successful ketonization reaction become clear immediately. Apparently, *N*-containing hetero-aromatics such as picolinic acid **1**, isoquinoline-3-carboxylic acid **6** or isoquinoline-1-carboxylic acid **5** produce ketone in a convenient way. Basically all other carboxylic acids fail. The reason becomes clear when looking at quinaldic acid **4**: in **1** or **5**, the aromatic N is free and used for chelation, in **4** it cannot contribute to the chelation due to the aromatic ring in the

Table 2 Effect of various carboxylic acids on oxygen and ketone formation from cyclooctane[a,g]

Entry	Carboxylic acid[b]	Oxygen (mmol)	Ketone (mmol)	Alkyl chloride (mmol)	Efficiency (%)[c]
1	Acetic acid	1.67	0.12	0.00	89
2	Pivalic acid **2**	1.41	0.14	0.00	77
3	Benzoic acid	1.43	0.15	0.00	79
4	Nicotinic acid **3**	1.36	0.21	0.00	79
5	Pyrazinecarboxylic acid	0.13	0.86	0.00	50
6	Pyrazine-2,3-dicarboxylic acid **7**	0.45	0.90	0.00	68
7	Pyridine-2,6-dicarboxylic acid **8**	0.04	0.35	0.00	20[d]
8	Picolinic acid **1**	0.06	1.28	0.00	67
9	Picolinic acid *N*-oxide	0.22	1.39	0.00	81
10	Quinaldic acid **4**	2.01	0.00	0.00	100
11	Quinoline-3-carboxylic acid	1.45	0.26	0.00	86
12	Isoquinoline-1-carboxylic acid **5**	0.05	1.57	0.00	81
13	Isoquinoline-3-carboxylic acid **6**	0.13	1.42	0.00	78
14	Quinoline-8-carboxylic acid **9**	1.68	0.21	0.00	95
15	Picolinic acid **1**–acetic acid[e]	0.07	1.14	0.00	61
16	$[(PA)_2FeCl_2]^-[pyr_2H]^+$ **10**	0.16	0.81	0.00	49
17	Picolinic acid **1**[f]	0.05	1.80	0.00	93

[a] To a stirred solution of $FeCl_3 \cdot 6H_2O$ in pyridine (1 mmol), cyclooctane (20 mmol) and the appropriate acid[b] were added. The reaction flask was made gas-tight and connected to a manometric burette filled with brine saturated with oxygen prior to use. Then, 30% aqueous H_2O_2 (4 mmol) were added dropwise within 10 s at 0 °C. [b] 4.0 mmol of acid were used in each experiment, unless otherwise indicated. [c] With respect to H_2O_2. Calculated considering 2.0 mmol H_2O_2 are consumed for each 1.0 mmol of ketone and oxygen formed. [d] 3.17 mmol residual oxidation power left after 24 h. [e] 2 mmol of each acid employed, respectively. [f] Carried out using 16.5 ml pyridine and 40 mmol cyclooctane. [g] For details see the Experimental section.

Table 3 Chemoselectivity study in the presence or absence of picolinic acid **1**[a,e]

Entry	Fe-salt (mmol)	Trapping reagent (mmol)	H_2O_2 (mmol)	Products [mmol] without **1**	Products [mmol] with **1**[b]	Efficiency[f] without/with **1**
1[c]	(1)[g]	$CBrCl_3$ (20)	(4)	R–Br [nd], CO_2 [nd], O_2 [1.65], R = O [nd]	R–Br [1.43], CO_2 [1.33], O_2 [nd], R = O [nd]	83/36
2[c]	(3)[g]	$CBrCl_3$ (20)	(1.5)	R–Br [0.08], CO_2 [nd], O_2 [0.67], R = O [nd]	R–Br [1.26], CO_2 [0.99], O_2 [nd], R = O [nd]	95/84
3[d]	(1)[g]	Ph_2S (10)	(4)	Ph_2SO [2.05], O_2 [0.71], R = O [0.10]	Ph_2SO [0.08], O_2 [0.05], R = O [1.57]	92/83
4[d]	(3)[g]	Ph_2S (10)	(1.5)	Ph_2SO [1.05], O_2 [0.23], R = O [nd]	Ph_2SO [nd], O_2 [0.11], R = O [0.21]	100/43
5[c]	(3)[h]	$CBrCl_3$ (20)	(3)	R–Br [0.21], CO_2 [0.03]	R–Br [2.03], Cl_3CCCl_3 [0.92], CO_2 [nd][j]	15/98

[a] General conditions: pyridine 33 ml, hydrocarbon 20 mmol, 0 °C→room temp., overnight. [b] 4 equiv. of **1** with respect to the ferric chloride used (4 or 12 mmol, respectively), except entry 5, were 3 equiv. (9 mmol) of **1** were used. [c] Cyclooctane used, experiment carried out under slow argon stream, CO_2 was trapped and quantified as $BaCO_3$. [d] Cyclohexane used. [e] Dioxygen was quantified manometrically. [f] [%], with respect to the amount of H_2O_2. Calculated considering 2.0 mmol H_2O_2 are consumed for each 1.0 mmol of R = O and O_2 formed, and only 1.0 mmol H_2O_2, is required for each 1.0 mmol R–Br and Ph_2SO formed. CO_2 is a side product from R–Br formation and need not be considered. [g] $Fe^{III}Cl_3 \cdot 6H_2O$ used. [h] $Fe^{II}(ClO_4)_2 \cdot 6H_2O$ used. [i] Fe^{II} [nd] after 0.5 h. [j] 10% Fe^{II} after 0.5 h.

α-position. Interestingly, picolinic acid *N*-oxide also produces ketone in similar amounts to picolinic acid (entry 9). Furthermore, pyridine-2,6-dicarboxylic acid **8** does not yield ketone efficiently. It slows down the reaction, and large amounts of residual oxidation power are left. Another structural prerequisite for ketonization is the carboxylic acid function α to the aromatic N-atom. With nicotinic acid **3**, where the acid function is in the β-position, the catalase reaction is by far predominant over Gif chemistry. Knowing these requirements, the results obtained for **7**, **2** or **9** are understandable and fit into the whole picture. Interestingly, the known complex **10**,[7] with an X-ray determined structure, does exhibit the same characteristics as the successful ketonization systems just described (entry 16).

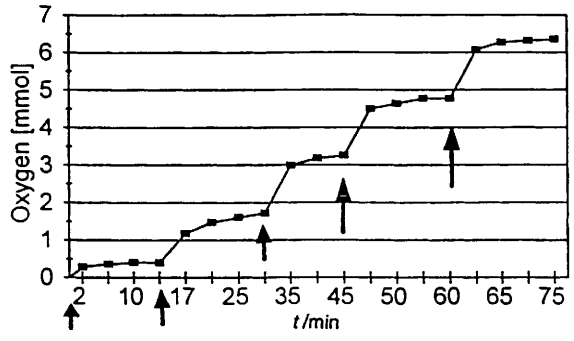
The importance of a carboxylic acid such as PA **1** becomes even more clear in the presence of $CBrCl_3$ or Ph_2S, and the results are shown in Table 3.

Using $CBrCl_3$, in the absence of picolinic acid, no alkyl bromides are formed at all. Instead only oxygen is produced. However, in the presence of PA, 1.43 mmol of R–Br is produced, accompanied by 1.33 mmol carbon dioxide (see entry 1). Entry 2 provides an understanding of the amounts of H_2O_2 needed to calculate the efficiencies. Using only half an equivalent of hydrogen peroxide (1.5 mmol) with respect to the iron (3 mmol)

Table 4 The effect of argon or oxygen on the Fe^{II}–Fe^{IV} and Fe^{III}–Fe^{V} manifolds[a]

Entry	Manifold	Ketone	Alcohol	Alkyl chloride	R-*o*-pyr	R-*p*-pyr
1[b]	Fe^{III}–Fe^{V}/ Argon	1.34	nd	0.08	nd	nd
2[b]	Fe^{III}–Fe^{V}/ O_2	1.38	nd	nd	nd	nd
3[c]	Fe^{II}–Fe^{IV}/ Argon	0.03	nd	nd	1.10	0.69
4[d]	Fe^{II}–Fe^{IV}/ O_2	0.45	nd	0.07	0.10	0.04

[a] General reaction conditions unless otherwise indicated: pyridine 33 ml, room temperature, cyclohexane 20 mmol. [b] $FeCl_3 \cdot 6H_2O$ 1 mmol, picolinic acid 4 mmol, H_2O_2 4 mmol, overnight. [c] $Fe(ClO_4)_2 \cdot 6H_2O$ 3 mmol, pyridine–acetic acid 33 ml, H_2O_2 3 mmol, 0 °C, 1 h then room temperature for 3 h. [d] $Fe(ClO_4)_2 \cdot 6H_2O$ 2 mmol, picolinic acid 6 mmol, H_2O_2 2 mmol (0.5 mmol/15 min), 0 °C, 30 min.



Scheme 6 Ferrous iron and hydrogen peroxide in the absence of a carboxylic acid: ferrous perchlorate 3 mmol, pyridine 30 ml, LiCl 15 mmol, cyclohexane 40 mmol, hydrogen peroxide 3 mmol/15 min up to 15 mmol (see arrows), 0 °C, air

still produces 1.26 mmol of alkyl bromide. Hence, one molecule of hydrogen peroxide is needed to generate one molecule of R–Br. As the carbon dioxide is a hydrolytic side product of the alkyl bromide formation, it is not taken into account in the efficiency calculations. Entries 3 and 4 show the behaviour of Ph_2S. In contrast with bromotrichloromethane, the absence of picolinic acid allows conventional formation of diphenyl sulfoxide, and the saturated hydrocarbon is not affected significantly (ratio of sulfoxide to ketone = 20:1). However, in the presence of picolinic acid, the chemoselectivity changes dramatically, and ketone is the product formed (ratio of sulfoxide to ketone 1:20). Entry 4 reveals that for the formation of one equivalent of diphenyl sulfoxide, one equivalent of hydrogen peroxide is necessary. Furthermore, here the presence of picolinic acid leads to a clear decrease in efficiency compared with the corresponding experiment in entry 2. No diphenyl sulfoxide, but only small amounts of O_2 and ketone are formed. Clearly, a second hydrogen peroxide per iron is needed for efficient ketonization.

As a conclusion, obviously a species is formed, which does not react with the hydrocarbon and also not with diphenyl sulfide. It does react, however, with $CBrCl_3$, and that very efficiently. What is this species? Evidence arose from further studies on the importance of ferrous ion in Gif chemistry and this is discussed in the section below.

The importance of ferrous iron—further studies

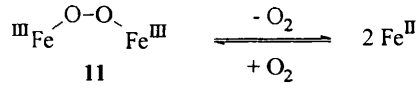
First, it is noteworthy, that as in ferric iron chemistry, in ferrous iron chemistry the presence of carboxylic acids is also a prerequisite for any alkane activation. Furthermore, carboxylic acid ligands are also necessary for the bromination reaction with the Fe^{II}–H_2O_2–$CBrCl_3$ system, and without such a ligand only Fe^{III} formation is observed (see Table 3, entry 5). Without an acid such as PA **1**, the Fe^{II} is first oxidized to Fe^{III} and then oxygen formation takes place, as can be seen in Scheme 6. As expected, the first equivalent of H_2O_2 produces only minor amounts of oxygen (0.40 mmol), compared with the equivalents following thereafter (typically between 1.3 and 1.6 mmol).

The impact of argon or oxygen on the Fe^{II}–Fe^{IV} manifold and on the Fe^{III}–Fe^{V} manifold in the presence of a carboxylic acid is given in Table 4.

For the Fe^{III}–Fe^{V} manifold, no change in product distribution was detected whether an experiment was run under argon or oxygen. Ketone was always found to be the only product in similar amounts. In contrast, the Fe^{II}–Fe^{V} manifold showed more sensitivity towards the reaction conditions. Under an O_2 stream, the ferrous iron was rapidly oxidized to ferric iron, which thereafter entered the Fe^{III}–Fe^{V} manifold and produced ketone. Under an argon stream however in the absence of chloride anion, the carbon radical once formed reacts with the solvent, pyridine, yielding the 2- and 4-pyridine coupled products, as is characteristic for a free carbon-centred radical.

In contrast, as already mentioned above, in the presence of chloride anion and a carboxylate ligand, Fe^{II} + H_2O_2 in pyridine affords alkyl chlorides exclusively and no ketone at all. Except in the presence of PPh_3 (see discussion above), the Fe^{III} + H_2O_2 system and acetic acid never produces alkyl chlorides, but ketone (major) and alcohol (minor). Even more of a surprise was when we treated the Fe^{III} + H_2O_2 system with an argon stream. The results are given in Table 5.

Suddenly alkyl chloride formation was observed, accompanied by ketonization and Fe^{II} formation (typically 15%).[16] The removed oxygen was quantified by Winkler's method[24,25] and shown to be always less than half of the amount of chloride formed (for details see the Experimental section). This fact plus the fact that both reactions are relatively slow ($t_{\frac{1}{2}} \approx 3$ h at 0 °C, respectively) shows that no dissolved oxygen is removed from the system. The loss of bound O_2 and the simultaneous formation of Fe^{II} is best rationalized as depicted in Scheme 7.



Scheme 7

It is important to mention that the oxygen loss of **11** is completely reversible,[26,27] as Table 5, entry 5 shows: if the reaction is flushed, after 2 h under an argon stream, with oxygen, alkyl chloride formation stops and the ketone formation carries on. Interestingly, complex **10** exhibits again the same characteristics as the $FeCl_3$–PA system (Table 5, entry 4), and in contrast, $Fe(PA)_3$ does not yield significant amounts of alkyl chloride (Table 5, entry 8), even though the reaction mixture was loaded with Cl^- (for details see the Experimental

Table 5 The effect of an argon stream, vacuum and PPh_3 on the Fe^{III}–PA–H_2O_2 system and **10**[a]

Entry	Carboxylic acid[b]	Oxygen (mmol)	Ketone (mmol)	Alkyl chloride (mmol)	Efficiency[c]
1	Picolinic acid **1**[d]	/	0.88	1.00	94
2	Picolinic acid **1**[e]	/	0.53	0.55	54
3	Picolinic acid **1**[f]	0.00	0.07	1.18	63
4	$[(PA)_2FeCl_2]^-$ $[pyr_2H]^+$ **10**[d]	/	0.51	0.65	58
5	Picolinic acid **1**[g]	/	(0.43)	(0.33)	(38)
		/	1.31	0.33	82
6	Picolinic acid **1**[h]	/	(0.22)	(0.14)	(18)
		/	0.87	0.31	59
7	Isoquinoline-1-carb. acid **5**/quinaldic acid **4**[i]	/	0.33	0.72	53
8	$Fe(PA)_3$[j]	/	0.65	0.06	40[j]
9	Quinaldic acid **4**	/	nd	nd	0

[a] For experimental conditions see Table 2, / = not determined. [b] 4 mmol employed. [c] With respect to H_2O_2. Calculated considering 2.0 mmol H_2O_2 are consumed for each 1.0 mmol of ketone and alkyl chloride formed. [d] Performed under constant argon stream. [e] Performed under vacuum (0.1 mmHg). [f] PPh_3 (4 mmol) added. [g] 2 h argon stream, then O_2 stream until completion (overnight). ( ) = Amounts of products formed after 2 h. [h] 1.5 h argon stream, then under static argon atmosphere. ( ) = Amounts of products formed after 1.5 h. [i] 2 mmol of each acid employed. [j] 0.09 mmol of R–OH are formed in this experiment and taken into account for the efficiency calculation.

Table 6 Iron/ligand combinations and their composition in pyridine solution[a,b,h,i]

Entry	Ferric salt[c]	Ligands	Acid on the iron[d,e]	Free acid[d,e]
1	$[(PA)_2FeCl_2]^-$ $[pyr_2H]^+$ **10**	(a) —	2	—
		(b) + oxalic acid[f]	—	2
2	$FeCl_3{\cdot}6H_2O$	(a) 4 equiv.[e] picolinic acid **1**	2	2
		(b) + oxalic acid[f]	—	4
3	$FeCl_3{\cdot}6H_2O$	(a) 4 equiv.[e] isoquin. carb. acid **5**	2	2
		(b) + oxalic acid[f]	—	4
4	$FeCl_3{\cdot}6H_2O$	(a) 2 equiv.[e] quinaldic acid **4**	2	—
		(b) + 1st equiv.[e] isoquin. carb. acid **5**	?	?
		(c) + 2nd equiv.[e] isoquin. carb. acid **5**	—	2
5	$FeCl_3{\cdot}6H_2O$	(a) 3 equiv.[e] picolinic acid **1**	2	1
		(b) + 3 equiv.[e] 2-hydroxypyridine[g]	2	1
6	$Fe(PA)_3$	(a) —	3	—
		(b) + oxalic acid[f]	—	3

[a] 1 ml pyridine + 0.5 ml [$^2H_5$]pyridine + 0.733 mmol cyclohexane were used. [b] All experiments were carried out at room temperature. [c] 0.055 mmol of each ferric salt was used. [d] Always refers to the carboxylic acid which was added first: entries 1, 2 and 5: picolinic acid **1**. Entry 3: isoquinoline-1-carboxylic acid **5**. Entry 4: quinaldic acid **4**. [e] Equivalents with respect to the iron salt. [f] Used in excess. [g] Three equivs. are quantified as being free in solution. [h] Instrumentation: a Varian Unity 500 equipped with a triple resonance probe (trp) or a broad band probe (bbp) was run using the following parameters: lock: [$^2H_5$]pyridine; frequency: 500 MHz; spectral window = 37 558.7 Hz;[38] number of transients = 100 000 (trp) or 50 000 (bbp); acquisition time = 0.601 s; pulse width = 6 (trp) or 5 (bbp), both are 30° pulses; decoupler mode = nny or yyy; delay = 0–3 s; decoupler power = 42 db (trp) or 46 db (bbp); decoupler mode frequency = 20 448 Hz (trp) or 9104 Hz (bbp); transmitter power = 54 db (trp) or 55 db (bbp). [i] Details of quantification technique: internal standard: Cl_3CCCl_3 (0.101 mmol) δ = 104.2; reference: cyclohexane δ = 27.03; for the integrations the aromatic peaks of the carboxylic acids which are not hidden or partially overlapped by the pyridine signals were used, in the case of **1**: C-5 (δ = 126.1) and C-4 (δ = 136.6), when an excess of oxalic acid was added, only C-5 was used for quantification purposes.

section). This result prompted us to examine the ligand environment of these systems.

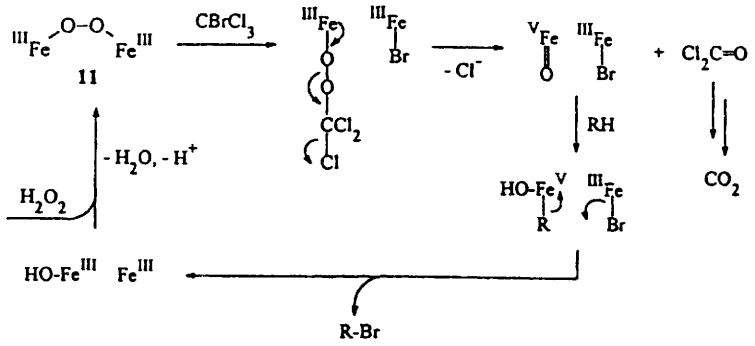
Determination of the ligand environment of the Gif catalyst using quantitative ^{13}C NMR spectroscopy

Quantitative ^{13}C NMR spectroscopy[28] has been widely used in polymer and protein chemistry.[29] However, the application of a metal centre as both hydrocarbon-activating catalyst and paramagnetic relaxation reagent is still an unexplored field.[30]

In a first approach, complex **10** was prepared and submitted to a ^{13}C NMR experiment. As predicted, no picolinic acid peaks were visible, even after 50 000 transients. From previous investigations it was known that upon addition of oxalic acid $[CO_2H]_2$, ketonization using iron(III) is suppressed completely. This reagent complexes with ferric iron very tightly and does not allow any peroxide reagents to reach the iron core. Based on these observations, we expected that addition of excess of oxalic acid would remove entirely all the ligands from the iron, including the picolinates, and that they should therefore become visible in the NMR. Indeed, we were not only able to see the free picolinic acids, but we were able to quantify them (Table 6, entry 1). The detection of two equivalents of picolinic acid is a demonstration of the effectiveness of this quantification technique as it correlates exactly with the X-ray structure of **10**.

Having confirmed the quantification results using a complex with known composition, we felt encouraged to use iron/ligand combinations with unknown compositions in solution. All results are summarized in Table 6.

Interestingly, having three or four equivalents of picolinic acid **1** or isoquinoline-1-carboxylic acid **5** in solution (Table 6, entries 2, 3 and 5) leads to only two equivalents of acid complexed to the iron, while the other two equivalents remain free in solution. It does not lead to the formation of the appropriate trisubstituted iron complexes FeL_3. With authentic samples of these compounds no free acids are observed when investigated by NMR spectroscopy. Therefore, the hydrocarbon oxidation mechanisms of, say, $Fe(PA)_3$ compared with $FeCl_3{\cdot}6H_2O$ + three picolinic acid could be different, as they differ in their starting materials. This conclusion is also confirmed by the result of entry 8 in Table 5, where an argon stream using $Fe(PA)_3$ did not show any effect on the product distribution, in contrast with the other iron salts. Upon addition of excess of oxalic acid, all previously co-ordinated



Scheme 8 Proposed mechanism for alkyl bromide formation using $CBrCl_3$

acids **1** or **5** were liberated and could be quantified as four equivalents of the free acids (Table 6, entries 2 and 3).

This quantification technique can be applied to aromatic, chelating, strongly co-ordinated ligands as described above. However, using quinaldic acid **4**, where the donating nitrogen is sterically hindered by the adjacent second aromatic ring in the α-position, the restriction applicable to this technique became clear (Table 6, entry 4): on addition of one equivalent of isoquinoline-1-carboxylic acid **5** to a solution already containing two equivalents of quinaldic acid **4**, some quinaldic acid was substituted and became visible in the NMR, but it could not be quantified. Addition of another equivalent of **5**, however, led again to accurate quantification results, namely two equivalents of **4** free in solution. Obviously, in the presence of only one equivalent of **5** the quinaldic acid **4** still has free co-ordination places at the catalyst to occupy. There exists therefore an equilibrium between co-ordinated and non-co-ordinated acid. The second equivalent of **5** occupies these free co-ordination places at the catalyst, and the quinaldic acid **4** is now completely replaced by **5** and cannot participate any more as a ligand in the first co-ordination sphere of the iron. Hence, the relaxation times of its nuclei are not affected by direct interaction with the paramagnetic iron, but are only influenced by the paramagnetic spin density through space in solution. As a consequence, quantification becomes possible again.

Another experiment has also demonstrated the usefulness of this quantification technique. Frequently, in the past we were concerned about side products such as hydroxypyridines interfering with the iron catalyst and hence changing its characteristics and, maybe, the oxidation mechanism. Therefore, we wanted to know if these hydroxypyridines were complexed to the iron or not in the presence of (say) three equivalents of picolinic acid **1**. We chose 2-hydroxypyridine (Table 6, entry 5), because it is expected that this isomer would have the strongest complexing capabilities. We found that it does not interfere with the iron in this system, and all employed three equivalents of the 2-hydroxypyridine were free and could be quantified.

Finally, while actually running a Gif reaction by adding four equivalents H_2O_2 at 0 °C to the systems in entries 1, 2 or 3 (Table 6), no liberation of ligands could be observed during any stage of the reaction.

Mechanistic conclusions

With regard to the proposed species **11** in Scheme 7, the results of Table 3 are best rationalized according to the mechanism outlined in Scheme 8.

The driving force for this reaction would be the formation of carbon dioxide. At this point, it has to be pointed out that $Fe^{II} + H_2O_2 + CBrCl_3$ with PA does not yield any CO_2, but only alkyl bromide and hexachloroethane (see Table 3, entry 5). Hence, in that case, an ordinary radical bromination occurs, in contrast with the analogous Fe^{III}–PA system.

All the results together can be put in a comprehensive mechanistic proposal which explains all data accumulated on Gif chemistry in pyridine to this day.

11 is proposed to be a key intermediate, which, under an argon stream or vacuum, loses O_2 and enters the Fe^{II}–Fe^{IV} manifold, producing alkyl chlorides. The effect of PPh_3 is rationalized in a similar way. PPh_3 reduces **11**, yielding Fe^{II} and Ph_3PO.[31] Under air, the normal Fe^{III}–Fe^{V} manifold prevails, yielding ketone *via* intermediates **A** and **B**.

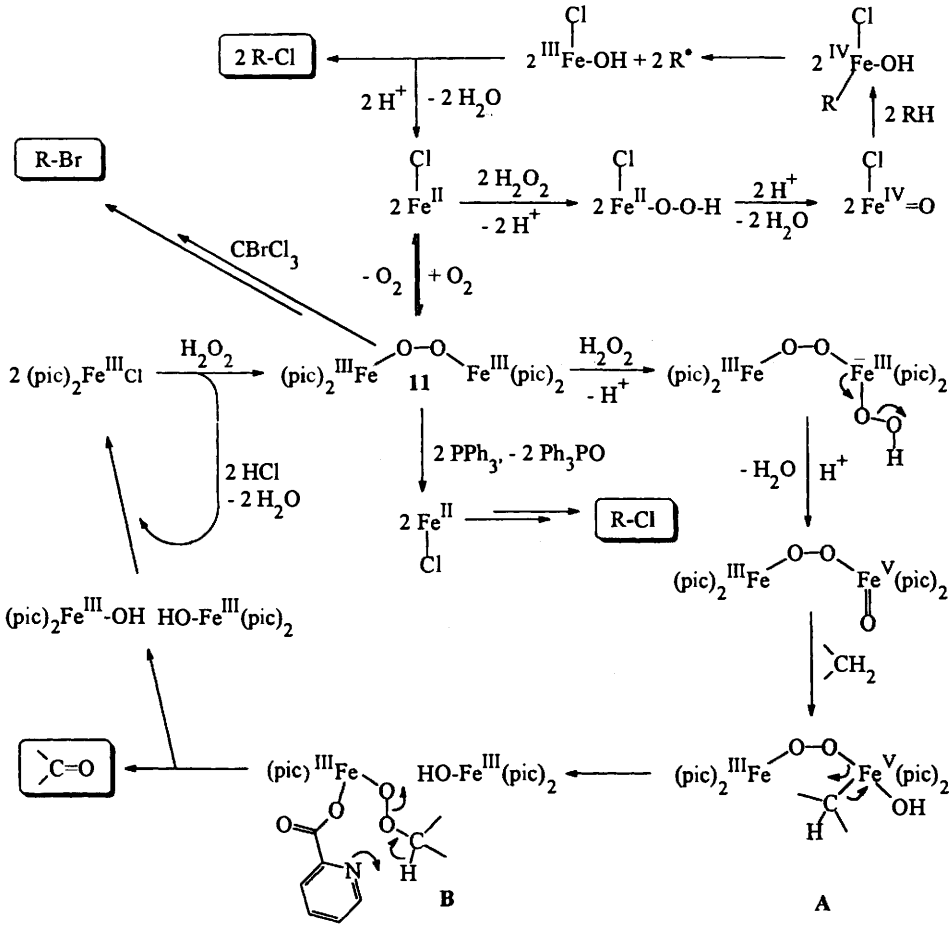
Due to the NMR results, for the first time we are able to assign the ligand at the iron. Note that the decomposition of **B** would occur *via* a nine-membered transition state, which is of course a disfavoured process. Hence, one can postulate decomposition with the aid of the second iron–picolinate, which would be evidence for carboxylate bridging. As this remains speculation at this time, this possibility is not considered in Scheme 9.

Conclusions

Recently, a μ-peroxo-dimer was found to be an intermediate in the catalytic cycle of MMO oxidations.[32] The current thinking regarding the mechanistic action of this enzyme is that an $^{III}FeOOFe^{III}$ species is the direct precursor for two Fe^{IV}=O species, which are believed to be able to activate the most inert of all saturated hydrocarbons, methane. In the past ten years, many so-called model systems for MMO have been designed, crystallized and most of them characterized by X-ray diffraction. However, none of these complexes can efficiently activate a saturated hydrocarbon![33]

This fact itself justifies some critical questions about the general strategy to approach this problem. For example in the case of MMO, what would be the driving force for the homolytic cleavage of a relatively stable $^{III}FeOOFe^{III}$ species to generate two highly unstable ferryl oxenoids? Is it really possible to draw meaningful conclusions from the structural characteristics of a compound in the solid state for the mechanistic action of the same compound in solution?

The answer can come, however, from model systems which actually *do* activate saturated hydrocarbons, like the various Gif systems. As certain carboxylic acids are necessary for ketonization, and an $^{III}FeOOFe^{III}$ unit is postulated to be the precursor of the Fe^{V} (the latter being formed by addition of a second H_2O_2), and as, furthermore, a heteroaromatic *N*-base like pyridine is prerequisite for the Gif mechanism to work, the claim of having an analogue of MMO at hand is not too far-fetched. MMO does have carboxylic acids (glutamates), the μ-peroxo-dimer intermediate and heteroaromatic *N*-bases (imidazoles) at the active site of the hydroxylase. It also has a water molecule, and it is known that water is present in the Gif systems, too. Furthermore, copper can serve as an alternative metal to iron for both MMO[34,35] and the Gif systems.



Scheme 9 Proposed mechanistic pathways for the functionalization of saturated hydrocarbons under Gif conditions

Experimental

1. General

All solvents and chemicals were, after verification, used as purchased. Unless otherwise stated H_2O_2 was used as a 30% solution in water. TBHP was 90% with Bu'OH (5%) and water (5%). The acetic acid used was glacial.

2. GC and GC–MS instruments and techniques

GC: all analyses were performed employing a Hewlett-Packard 5890 series II instrument, on a Chrompack Model 439 or 437S instrument with a flame ionization detector and Hewlett-Packard 3396A integrator. Prepurified N_2 was used as the carrier gas. The capillary columns used were DB-WAX (polyethylene glycol, 30 m × 0.32 mm, 0.25 μm) and/or DB-1 (chemically bonded methyl silicone, 15 m × 0.32 mm, 0.25 μm) from J&W Scientific. The routinely employed temperature program was: 50 °C, 5 min, 20 °C min^{-1}, 245 °C, 10 min (for cyclohexane and cyclooctane). Injector and detector temperatures were 245 °C and 300 °C, respectively. All products had identical retention times with authentic samples. GC–MS: all analyses were carried out on a Hewlett-Packard 5890A series II gas chromatograph using an HP-5971 series quadrupole mass-selective detector (40 eV, electron impact). The column in the GC was an HP-5MS (cross-linked 5% Ph Me Silicone, 30 m × 0.25 mm, 0.25 μm). The routinely employed temperature program was 50 °C, 5 min, 20 °C min^{-1}, 10 min.

3. Typical work-up procedures

Acidic work-up: an aliquot (usually 2 or 5 ml) was taken from the reaction mixture and added to 6 ml precooled (0 °C) 25% H_2SO_4 and extracted three times with 5 ml ether, respectively. The combined organic extracts were washed with a saturated solution of $NaHCO_3$ and 1 ml of a 0.08 M naphthalene solution (in ether) was added as an internal standard. After drying over $MgSO_4$, the mixture was analysed by gas chromatography.

Basic work-up: an aliquot (usually 2 or 5 ml) was taken from the reaction mixture and added to 6 ml of a 5% NaOH solution. After three extractions with ether, 1 ml of a 0.08 M naphthalene solution (in ether) was added as an internal standard. After drying over $MgSO_4$, the mixture was analysed by gas chromatography.

4. Functionalization of adamantane employing geniune *tert*-butoxyl radicals

To a solution of pyridine was added adamantane (0.681 g, 5.0 mmol) and TBHP (1.1 ml, 10 mmol). For Table 1, entry 3, $CBrCl_3$ (3.965 g, 20 mmol) was added. The mixture was then cooled to 0 °C and a solution of oxalyl chloride (0.635 g, 5 mmol) in CH_2Cl_2 was added in one portion. The reaction was initiated by warming to 40 °C. When the reactions were complete (5–15 h) the mixtures were submitted to the typical work-up procedures described above.

5. Quantification of hydroxypyridines in Gif-type systems

$FeCl_3 \cdot 6H_2O$ (0.270 g, 1 mmol) and picolinic acid (0.492 g, 4 mmol) were dissolved in 33 ml pyridine, and H_2O_2 (0.4 ml, 4 mmol) was added at 0 °C. The reaction was left overnight and allowed to come to room temperature. Then an excess of saturated aqueous sodium sulfide solution was added and the resulting mixture stirred overnight. Thereafter, the solution was passed through a layer of silica gel (flash filtration) using methanol as the eluent, and the solvent was evaporated from the resulting filtrate. The remaining solid was dissolved in $(CD_3)_2CO$ containing a few drops of water, and the products were quantified by ^1H NMR with $Cl_2CHCHCl_2$ as an internal standard. The products were identified by comparison of their ^1H NMR spectra with those of the appropriate authentic

specimen. Result: 2-hydroxypyridine: 1.04 mmol, 3-hydroxypyridine: 0.30 mmol, 4-hydroxypyridine: trace.

6. The distinction between the Fe^{II}–Fe^{IV} and Fe^{III}–Fe^{V} manifolds

With one portion of Fe^{II}. $Fe(ClO_4)_2 \cdot 6H_2O$ (1.089 g, 3 mmol), LiCl (0.630 g, 15 mmol) and cyclohexane (3.360 g, 40 mmol) were dissolved in a mixture of pyridine (30 ml) and acetic acid (3 ml). Then the mixture was cooled to −20 °C. The reaction was initiated by the addition of H_2O_2 (0.3 ml, 3 mmol, every 15 min, up to 30 mmol, total 10 portions). Every 15 min, a small portion (1 ml) was taken out and submitted to an acid work-up and the products were analysed by GC. During the first 2.5 h, the reaction was kept at −20 °C, and then allowed to come to room temperature.

With two portions of Fe^{II}. Same as above, but the reaction was started at 0 °C and then allowed to reach room temperature. 90 min after the initiation of the reaction, $FeCl_2 \cdot 4H_2O$ (0.597 g, 3 mmol) was added to the reaction mixture.

Stability of cyclohexyl chloride towards Fe^{III} and H_2O_2. Cyclohexyl chloride (1.186 g, 10 mmol) was added to a mixture of $FeCl_3 \cdot 6H_2O$ (0.270 g, 1 mmol) and picolinic acid (0.492 g, 4 mmol) in pyridine (33 ml). H_2O_2 (0.4 ml, 4 mmol) was added and the reaction left overnight. No ketone formation could be observed.

7. Gif^{IV} reaction in the presence of LiCl with and without hydrogen peroxide

Without H_2O_2: $FeCl_2 \cdot 4H_2O$ (0.198 g, 1 mmol), LiCl (0.424 g, 10 mmol) and cyclooctane (2.240 g, 20 mmol) were dissolved in 30 ml of pyridine, and Zn powder (1.308 g, 20 mmol) was added. The mixture was cooled to 0 °C and the reaction initiated by adding 3 ml acetic acid (to dissolve the Zn). The reaction was stirred vigorously and left open to air while it reached room temperature overnight. Then, an aliquot was submitted to a basic work-up. Typical result: 0.75 mmol cyclooctanone, no cyclooctyl chloride detected.

With H_2O_2: same as above, but adding H_2O_2, (1 ml, 10 mmol) one min after the acetic acid was added. Typical result: 1 mmol cyclooctanone, 2 mmol cyclooctyl chloride.

8. Typical catalase study

To a stirred solution of pyridine (33 ml), were added $FeCl_3 \cdot 6H_2O$ (0.270 g, 1 mmol), picolinic acid (0.492 g, 4 mmol) (or, unless otherwise indicated, 4 mmol of any other carboxylic acid used, see Table 2) and cyclooctane (2.240 g, 20 mmol) and the reaction flask was made gas-tight and connected to a manometric burette filled with brine, which had been saturated with oxygen prior to use. The mixture was then cooled to 0 °C and 15 min later the reaction was initiated by dropwise addition of H_2O_2 (0.4 ml, 4 mmol). During the readings, the pressure was always equilibrated using a separatory funnel by adjusting the brine levels to the same heights. Also, the appropriate temperature and atmospheric pressure were taken into account before each reading and considered in the calculations using the ideal gas law. The reported values were average values from three individual experiments.

9. Competition of catalase reaction with Gif chemistry

The same procedure as under section 8, but the amount of picolinic acid was varied from 0 to 10 mmol.

10. Chemoselectivity study in the presence or absence of PA

Experiments with Fe^{III} and $CBrCl_3$. To a solution of $FeCl_3 \cdot 6H_2O$ (0.270 g, 1 mmol or 0.810 g, 3 mmol) and cyclooctane (2.240 g, 20 mmol) in 33 ml pyridine was added picolinic acid (0.492 g, 4 mmol or 1.476 g, 12 mmol), and the mixture was cooled to 0 °C. Under a slow argon stream, H_2O_2 (0.4 ml, 4 mmol or 0.15 ml, 1.5 mmol) was added dropwise. The argon was bubbled through two consecutive traps filled with saturated $Ba(OH)_2$ and left overnight. While any precipitated $BaCO_3$ was filtered off, washed with distilled water, dried in a desiccator over KOH for 2 days and weighed, the reaction mixture was submitted to a basic work-up.

Experiments with Fe^{III} and Ph_2S. The same procedure was used, except that cyclohexane (1.680 g, 20 mmol) and Ph_2S (1.860 g, 10 mmol), $FeCl_3 \cdot 6H_2O$ (0.810 g, 3 mmol), picolinic acid (1.476 g, 12 mmol) and H_2O_2 (0.4 ml, 4 mmol or 0.15 ml, 1.5 mmol) were employed and the CO_2 analysis was omitted.

Experiments with Fe^{II} and $CBrCl_3$. $Fe^{II}(ClO_4)_2 \cdot 6H_2O$ (1.089 g, 3 mmol), cyclohexane (1.680 g, 20 mmol) and $CBrCl_3$ (1.983 g, 10 mmol) were dissolved in pyridine (33 ml) and the mixture was cooled to 0 °C. Then a slow argon stream was applied and the reaction was initiated by dropwise addition of H_2O_2 (0.3 ml, 3 mmol) and the reaction was allowed to warm to room temperature overnight. The analysis for CO_2 was carried out as described above, and the products were analysed by GC and GC–MS following an acidic work-up. All experiments were also performed as described in experiment 8 in order to quantify the amounts of liberated oxygen. Furthermore all experiments were also carried out without the picolinic acid.

11. Typical experiment using a constant argon stream

1 mmol of the appropriate iron salt (**10**: 0.530 g; $FeCl_3 \cdot 6H_2O$ 0.270 g; see also Table 5 and Table 2) was dissolved in 33 ml pyridine. Picolinic acid (0.492 g, 4 mmol) or isoquinoline-1-carboxylic acid (0.693 g, 4 mmol) or quinaldic acid (0.693 g, 4 mmol) were added to this solution (except in the case of **10**). After cyclooctane (2.240 g, 20 mmol) had been added, the mixture was cooled with an ice bath and left for 15 min at 0 °C. Then argon was flushed through the solution for 20 min. The reaction was initiated by dropwise addition of H_2O_2 (0.4 ml, 4 mmol) during the argon stream. The reaction was run overnight and kept at 0 °C and under the argon stream. It was submitted to basic work-up thereafter. The residual volume of the reaction mixture was measured and taken into account in the calculation for product quantification. For a kinetic study, aliquots were taken periodically over a timescale of 6 h.

12. Quantification of dioxygen removed by an argon stream according to Winkler's method

$FeCl_3 \cdot 6H_2O$ (0.270 g, 1 mmol), PA (0.492 g, 4 mmol) and cyclooctane (2.240 g, 20 mmol) were dissolved in 33 ml pyridine using a three-necked flask. This flask was connected to (in order) a cooling trap (CO_2–Et_2O), a 250 ml washbottle containing concentrated H_2SO_4 (oleum), a second cooling trap (CO_2–Et_2O) and three consecutive traps for dioxygen. Each of them contained $MnSO_4 \cdot H_2O$ (10.86 g, 64.38 mmol), KI (6 g, 36.15 mmol) and NaN_3 (0.15 g, 2.34 mmol) in 500 ml H_2O. The whole system was degassed with a slow argon stream overnight, while the reaction mixture itself was bubbled through with argon for 20 min and kept all the time at 0 °C. Then NaOH (12 g, 300 mmol) was added to each trap and the reaction was initiated by addition of H_2O_2 (0.4 ml, 4 mmol). The reaction was left overnight at 0 °C under a slow argon stream, while each trap was stirred vigorously. Then H_3PO_4 (85%) (40 ml) and three drops of starch were added to each trap. When the solutions had become homogeneous, all three traps were subsequently titrated *versus* $S_2O_3^{2-}$ (40 $mmol^{-1}$). The reaction mixture was analysed for the products as described under basic work-up. Typical result: 0.40 mmol of O_2 trapped, 0.64 mmol cyclooctyl chloride and 0.95 mmol cyclooctanone formed. Then a blank experiment, same as above, but without the addition of H_2O_2 was carried out. Typical amount of O_2 trapped: 0.24 mmol ⟹ 0.40 minus 0.24 = 0.16 mmol O_2 was removed by the argon stream during the reaction.

13. 500 MHz ^{13}C NMR quantifications

The appropriate ferric salt ($FeCl_3 \cdot 6H_2O$: 0.015 g, 0.055 mmol; $Fe(PA)_3$: 0.023 g, 0.055 mmol; **10**: 0.029 g, 0.055 mol) was dissolved in 1 ml pyridine and 0.5 ml ($FeCl_3 \cdot 6H_2O$, **10**) or 2 ml $[Fe(PA)_3]$ [$^2H_5$]pyridine was added. To this solution were added Cl_3CCCl_3 (0.024 g, 0.101 mmol) and cyclohexane (0.062 g, 0.733 mmol). Then the appropriate amounts of the carboxylic acid(s) (see Table 6) were added and the NMR tube was shaken until a completely homogeneous solution was obtained. For instrumental details see descriptive footnotes of Table 6. The addition of excess of oxalic acid sometimes required addition of 1 or 2 drops of H_2O in order to re-dissolve precipitated iron oxalate complexes. For running a reaction, H_2O_2 (0.022 ml, 0.220 mmol) was added slowly and the NMR tube was shaken two or three times thereafter.

14. Fe^{II} and H_2O_2 in the absence of a carboxylic acid

$Fe(ClO_4)_2 \cdot 6H_2O$ (1.089 g, 3 mmol), LiCl (0.630 g, 15 mmol) and cyclohexane (3.360 g, 40 mmol) were dissolved in pyridine (30 ml). The reaction mixture was cooled to 0 °C and the reaction was initiated by the addition of H_2O_2 (0.3 ml, 3 mmol, every 15 min, until 15 mmol, total 5 portions). The oxygen development was followed manometrically as described under experiment 8.

15. Fe^{II} + H_2O_2 under an argon stream in the absence of chloride anion

$Fe(ClO_4)_2 \cdot 6H_2O$ (1.089 g, 3 mmol) and cyclohexane (2.240 g, 20 mmol) were dissolved in a mixture of pyridine–acetic acid 10:1 (33 ml) and the solution was purged vigorously with argon for 10 min. The reaction was initiated by the addition of H_2O_2 (0.3 ml, 3 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 3 h and kept always under an argon stream. A basic work-up procedure was carried out and the products were quantified by gas chromatography.

16. Fe^{II} + H_2O_2 under an oxygen stream in the absence of chloride anion

$Fe(ClO_4)_2 \cdot 6H_2O$ (0.726 g, 2 mmol), PA (0.738 g, 6 mmol) and cyclohexane (1.680 g, 20 mmol) were dissolved in pyridine (33 ml). The reaction mixture was purged with oxygen for 10 min and the reaction was initiated by the addition of H_2O_2 (0.05 ml, 0.5 mmol, every 15 min, until 2 mmol, total 4 portions) at 0 °C. The reaction mixture was always kept under an oxygen flow and was stirred at 0 °C for 30 min after all the peroxide had been added. A basic work-up procedure was carried out and the products were quantified by gas chromatography.

17. Fe^{III} + H_2O_2 under argon (or oxygen)

$FeCl_3 \cdot 6H_2O$ (0.270 g, 1 mmol), PA (0.492 g, 4 mmol) and cyclohexane (1.680 g, 20 mmol) were dissolved in pyridine (33 ml). The reaction flask was purged with argon (or oxygen) and the reaction was initiated by addition of H_2O_2 (0.4 ml, 4 mmol) and left overnight at room temperature. Then an acid work-up was carried out and the products were analysed by gas chromatography.

Coda

A number of helpful referees have criticized our hypothesis of Fe^{IV} and Fe^{V} species. However, it is clear that in addition to the two well known oxidation states of Fe^{II} and Fe^{III} there are two other iron species which are completely different from Fe^{II} and Fe^{III} and from each other. It is these two states which both permit the functionalization of saturated hydrocarbons by a completely different mechanism.

Furthermore referees are unable to believe (Table 3, entry 3) that an Fe^{V} species could attack a saturated hydrocarbon twenty times more rapidly than diphenyl sulfide. In fact, we have already commented on the unusual capacity of the Gif systems to oxidize saturated hydrocarbons faster than substances that are normally regarded as more easily oxidized.[2,36] Our explanation has suggested that the contact between an iron species and the hydrocarbon created the Fe^{V} species that immediately inserts into the C–H bond (Sleeping Beauty effect[2]). Thus the reaction between Fe^{II} and Fe^{III} and hydrogen peroxide may furnish the species Fe^{II}–OOH and Fe^{III}–OOH. This kind of species, formed in the absence of the special carboxylate ligands needed for Gif chemistry, does show the expected selectivity of ease of oxidation of diphenyl sulfide (see, for example Table 3 above). With the right carboxylate ligands Fe^{II}–OOH and Fe^{III}–OOH are transformed by contact with the hydrocarbon into Fe^{IV} and Fe^{V}, respectively. There is evidence for complexes between σ-C–H bonds and various metal species.[2,37] If this is true then a saturated hydrocarbon should induce a reaction with (say) the Fe^{III}–OOH species which otherwise might be relatively stable. Investigations on this fascinating possibility continue.

Acknowledgements

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