The selective functionalization of saturated hydrocarbons: recent developments in Gif chemistry
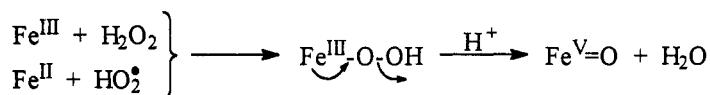
Derek H. R. Barton* and Bin Hu*

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

Abstract: The Gif systems permit the selective functionalization of saturated hydrocarbons under mild conditions and with high efficiencies. A newly discovered Fe^{II}-Fe^{IV} manifold is shown to form alkyl chlorides by a process involving carbon-centered radicals as intermediates. This 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 for hydrocarbon activation has been demonstrated. The ligand environment of the catalyst in solution is clarified using quantitative ^{13}C-NMR spectroscopy. Evidence for a μ-peroxo dimer species as a key intermediate in solution is provided and recent mechanistic studies are reported.

INTRODUCTION

The selective functionalization of saturated hydrocarbons under mild conditions is an important biochemical and industrial task.[1] Enzymes which are capable of catalyzing these reactions include the iron heme-based Cytochromes P-450 [2] and non-heme-based enzymes like methane monooxygenase (MMO). Studies on MMO showed that the active site of this enzyme contains a μ-oxo diiron center with a semi-bridging glutamate and an acetate bridge.[3] The latter is replaced during the catalytic cycle with a weakly coordinated monoatomic bridge. On the other hand, several other non-heme iron-based biological systems contain a single iron core. This group includes γ-butyrobetaine hydroxylase, proline hydroxylase, isopenicillin N-synthase and bleomycin. The case of MMO, which is capable of converting methane, one of the most inert hydrocarbons, to methanol, deserves special attention. However, despite the fact that enzymes that catalyze reactions involving dioxygen are so largely distributed in nature, the molecular mechanisms of their reactions are known in considerably less detail than those for most other biological reactions.[4] This is also true for MMO. Although several mechanisms have been proposed for MMO, a universal mechanism which can explain all the observations still can not be reached at the present time.[5] One very important approach to gaining a deeper understanding of these biological processes consists of using model systems to emulate the enzymatic activity. We have developed a family of chemical systems which permits the functionalization of saturated hydrocarbons under mild and neutral conditions.[6,7] These systems are grouped under the name of Gif systems.

The use of Gif Chemistry in the selective functionalization of saturated hydrocarbons has been summarized.[8] Most of the work has involved the use of Fe^{II} + superoxide or Fe^{III} + hydrogen peroxide, as depicted in Scheme 1.

$$\left.\begin{array}{c} Fe^{III} + H_2O_2 \\ Fe^{II} + HO_2^{\bullet} \end{array}\right\} \longrightarrow Fe^{III}\text{-}O\text{-}OH \xrightarrow{\ H^+\ } Fe^{V}{=}O + H_2O$$

Scheme 1

The reactivity of the postulated oxenoid species is unusual as secondary positions are selectively substituted to afford, as isolated products, ketones and alcohols (minor). A careful study of intermediates showed that two (**A** and **B**) could be detected.[9] Intermediate **B** was firmly established in the solvent pyridine-

acetic acid to be a hydroperoxide which fragmented to ketone and alcohol.[10] Intermediate A has been proved not to be the carbon radical therefore it is formulated as an iron-carbon bonded species.

THE NON-RADICAL NATURE OF INTERMEDIATE A

In principle intermediate 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 alkyl peroxyl radicals (R-O-O•) as intermediates.[11,12]

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-hydroxypyridine. However, in Gif chemistry the major products from pyridine are 2- and 3-hydroxypyridine in minor amounts.[13]

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.[14,15]

THE IMPORTANCE OF FERROUS IRON

The discovery of the formation of alkyl chloride in the presence of PPh_3 under Fe^{III}-H_2O_2 conditions was an important observation. By ^{31}P-NMR, we determined that the rates for the oxidation of PPh_3 by H_2O_2 are very fast. The presence of Fe^{III} decreases the half-life of this oxidation reaction to only several seconds even at -20 °C. It is remarkable that the hard to oxidize saturated hydrocarbons are being oxidized at the same time as easy to oxidize PPh_3. Since alkyl chloride is never detected under normal Gif oxidation conditions (Fe^{III} + H_2O_2 or Fe^{II} + superoxide), the presence of PPh_3 must change the whole chemistry. Considering that PPh_3 is also an mild reducing agent, it should be able to reduce Fe^{III} to Fe^{II}. In fact, by Fe^{II} titration,[16] we do detect Fe^{II} (typically 10 % of the total iron), but only when PPh_3 and H_2O_2 are used together. Therefore, we decided to investigate the Fe^{II}-H_2O_2 system in pyridine or pyridine-acetic acid.

In a typical Gif Fe^{II}-H_2O_2 system, we use a 1 to 1 ratio of Fe^{II} and H_2O_2, since with excess amounts of H_2O_2, Fe^{II} will finally be oxidized to Fe^{III}. As in the Fe^{III}-H_2O_2-PPh_3 system, alkyl chloride is produced when LiCl is used in the Fe^{II}-H_2O_2 system.[17] Some other salts, such as NaN_3, NaSCN and $NaNO_2$, are also successfully used in this system to form the corresponding mono-substituted alkyl derivatives (R-N_3, R-SCN and R-NO_2 respectively).[18] The rates of these reactions are extremely fast. Half-life times are much less than 30 s even at -20 °C. These same results obtained by the Fe^{II}-H_2O_2 system and the Fe^{III}-H_2O_2-PPh_3 system prove that similar chemistry should be involved in these two systems.

To understand the mechanistic pathway of the Fe^{II}-H_2O_2 based system, the first question we asked was " Does the reaction pathway still involve the Fe-C σ-bonded species or some other intermediate such as a carbon-centered radical? ". Thus, the reaction was conducted in the presence of some radical traps.

First we carried out the reaction in the absence of certain ionic trapping reagents. Since the solvent, pyridine, is also a good radical trap, if carbon radicals are formed in the reaction they should be trapped by solvent molecules when other radical traps are not present. In fact, alkyl pyridine coupling products were observed under these conditions. When the reactions were carried out under either argon or air (with cyclohexane), two cyclohexyl pyridine coupling compounds, at the 2- and 4-positions of the pyridine ring, were formed. The formation of these two compounds is characteristic of cyclohexyl radicals attacking pyridine. These secondary alkyl pyridine coupling products are never observed in the normal Fe^{III}-H_2O_2 system. Clearly, these two systems involve different intermediates. Furthermore, when the Fe^{II}-H_2O_2 reaction was carried out under a stream of O_2, a competition between O_2 trapping (forming alkyl hydroperoxide then decomposing to ketone) and pyridine trapping (minor) was observed. These results suggest that, unlike in the Fe^{III}-H_2O_2 system, a carbon-centered radical is one of the intermediates involved in the reaction pathway of the Fe^{II}-H_2O_2 system.

The carbon-centered radical intermediate in the Fe^{II}-H_2O_2 system is further proven by trapping the intermediate with other common carbon radical traps. For instance, when using 2-methyl-1,4-naphthoquinone, the formation of cyclohexyl chloride was completely avoided.[19] The cyclohexyl radical formed in the reaction was trapped by the quinone to give the adduct, 2-cyclohexyl-3-methyl-1,4-

naphthoquinone, in approximately the same yield as chloride (formed in the absence of quinone). The intermediate hydroquinone radical reduces any Fe^{III} to Fe^{II} thus maintaining the radical chemistry. TEMPO traps carbon radicals at diffusion-control rates. In an Fe^{II}-H_2O_2 reaction, in the presence of TEMPO, regardless of whether Cl^- was present or not, the only product detected was the cyclohexyl TEMPO adduct.[20] Although TEMPO oxidizes Fe^{II} to Fe^{III}, the formation of the carbon radical and trapping by TEMPO were faster than the oxidation to Fe^{III}. Cyclohexyl bromide was formed in the presence of $CBrCl_3$, no chloride or cyclohexyl pyridine coupling products were formed. This shows that $CBrCl_3$ was a better carbon radical trap than Cl^- or pyridine. Furthermore, the by-product formed in this reaction is Cl_3CCCl_3 which is different to that formed in the Fe^{III}-H_2O_2 bromination - CO_2. This again suggests different mechanisms should be operative in the Fe^{II}-H_2O_2 and Fe^{III}-H_2O_2 systems.
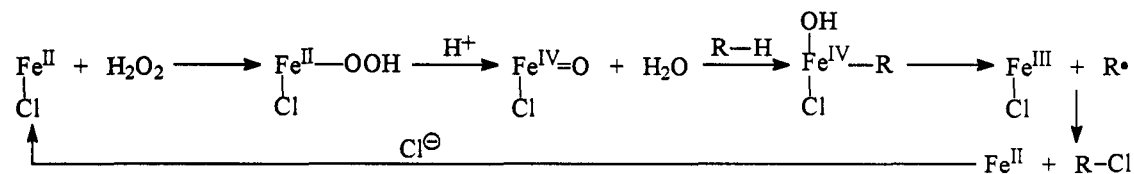
These results clearly prove that carbon-centered radicals are involved in the Fe^{II}-H_2O_2 system. Then we have to answer the question " Is this Gif Fe^{II}-H_2O_2 system the same as Fenton chemistry? ". After careful investigation, we concluded that Fenton chemistry was not involved in this Gif Fe^{II}-H_2O_2 system.[21]

Generally, Fenton chemistry [22,23] takes place only in strongly acidic aqueous medium (pH 2), while the Gif Fe^{II}-H_2O_2 reactions were first carried out in a buffered solvent system, pyridine-acetic acid ~ 10:1 (pH ≈ 5.5). Some general characteristics of Fenton chemistry are: (1) The generation of hydroxyl radical, equation [1], is the slow step;[22] (2) Since hydroxyl radicals are very reactive species, the kinetic isotope effect is approximately 1 (k_H/k_D ≈ 1.0);[24] (3) Aromatic compounds are easily hydroxylated, thus benzene forms phenol and toluene gives cresols; (4) Pyridine is attacked by hydroxyl radicals at the 2- and 4-positions to yield 2- and 4-hydroxylpyridine.

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^- + HO\bullet \qquad k_1 = 76 \text{ mol}^{-1}\text{ s}^{-1} \qquad [1]$$

As mentioned above, unlike Fenton reactions, Gif Fe^{II}-H_2O_2 reactions are extremely fast, a half-life of much less than 30 seconds ($T_{1/2}$ << 30 s) was observed even at -20 °C. The kinetic isotope effect was measured using equal amounts of cyclohexane (C_6H_{12}) and cyclohexane-d_{12} (C_6D_{12}) to give k_H/k_D = 2.1 ($C_6H_{11}Cl/C_6D_{11}Cl$), which is actually identical to that of the Fe^{III}-H_2O_2 system. This was evidence against hydroxyl radical being the hydrocarbon activating species. In addition, when benzene or diphenyl was used as the substrate, only trace phenolic products were detected. Under similar conditions, 3-hydroxylpyridine was produced as the major product for pyridine (ratio for hydroxypyridines was: 3-:2-:4- = 7.4:3.0:1.0).[21c] This was again different to that obtained with the hydroxyl radical mechanism.

In conclusion, free hydroxyl radicals, thus Fenton chemistry, can be ruled out as being responsible for hydrocarbon activation. Therefore, an Fe^{II}-Fe^{IV} manifold was proposed to be operating instead (Scheme 2); while the normal Gif Fe^{III}-H_2O_2 chemistry was referred to as the Fe^{III}-Fe^{V} manifold.

$$Fe^{II}\text{---}Cl + H_2O_2 \longrightarrow Fe^{II}\text{---OOH(Cl)} \xrightarrow{H^+} Fe^{IV}\text{=O(Cl)} + H_2O \xrightarrow{R\text{---}H} \overset{OH}{Fe^{IV}\text{---}R(Cl)} \longrightarrow Fe^{III}(Cl) + R\bullet$$

Scheme 2

If Fe^{II} is used in the presence of excess chloride ion in the H_2O_2-pyridine-acetic acid-cyclohexane oxidation system (portionwise addition of H_2O_2), cyclohexyl chloride is rapidly formed.[18,25] An important contribution to the sequel came from the ability to distinguish by titration between Fe^{II} and Fe^{III}.[16]

As soon as all the Fe^{II} has been converted to Fe^{III} the mechanism changes from radical (R• + 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, while the amount of alkyl chloride remains constant, even after an overnight reaction.

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.[25] 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} and H_2O_2 is important.

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

THE IMPORTANCE OF CARBOXYLIC ACIDS

The various Gif systems discussed so far were normally carried out in a pyridine-acetic acid solvent mixture (usually 10:1 ratio). The tradition of using acetic acid as co-solvent came from the Gif^{IV} system, in which an acid was needed to provide a proton source to dissolve the Zn powder. This tradition was routinely followed in the Gif systems developed later, although Zn powder was not used as a reagent any more. However, despite the intensive studies that had been carried out on Gif chemistry, little was known about the real role of the carboxylic acid and its participation in the hydrocarbon oxidation mechanism. More recently, studies on the role of carboxylic acids and the Fe^{III}-catalyzed H_2O_2 dismutation (Catalase activity) revolutionized our thinking on the mechanism of hydrocarbon oxidation by Gif systems, although the basic catalytic pathway (hydrocarbon $\rightarrow$ alkyl hydroperoxide $\rightarrow$ ketone and alcohol) did not change.

It was a surprise to discover that only a very small amount of cyclohexane was oxidized to cyclohexanone in the GoAgg^{II} system (FeCl$_3$ + H_2O_2) in the absence of acetic acid. Careful study showed that in this case oxygen (O_2) was formed almost quantitatively with respect to the H_2O_2 used. This oxygen formation reaction actually was the same as the catalase enzyme catalyzed H_2O_2 dismutation, therefore we called it a model catalase reaction.

Carboxylic acids were also essential in the Gif Fe^{II}-H_2O_2 system. We carried out an experiment very similar to that discussed above, which started with Fe(ClO$_4$)$_2$, LiCl, cyclohexane and adding H_2O_2 portionwise, but this time in pure pyridine, without any acetic acid.[25] In contrast to cyclohexyl chloride followed by cyclohexanone found in the previous experiment, this time we did not observe any chloride and only a very small amount of cyclohexanone. The first equivalent of H_2O_2 simply oxidized Fe^{II} to Fe^{III} and then formed minor amount of O_2 (from the remaining H_2O_2). Each equivalent of H_2O_2 added later just formed almost quantitative of O_2 in the presence of Fe^{III}.

In order to study the role of other carboxylic acids, the original Gif systems had to be simplified by leaving out the acetic acid. Since picolinic acid had shown a remarkable rate increasing effect on the Fe^{III}-H_2O_2 system, we first studied the competition between the catalase reaction (oxygen formation) and Gif activity (ketonization) by using various amounts of picolinic acid relative to the Fe^{III} used. Preliminary studies had shown that four equivalents of hydrogen peroxide gave the most efficient ketonization, hence the large excess of oxidant used in the earlier studies was not necessary anymore.

The results clearly demonstrated that increasing the ratio of picolinic acid to Fe^{III} from 0 to 2 equivalents had a significant impact on the product distribution. The amount of oxygen formed decreased from almost quantitative to almost none while ketone increased from less than 10% to be the sole major product. Thus, the 2 equivalents of picolinic acid to Fe^{III} ratio was an important point: The formation of oxygen was almost completely suppressed. The most efficient formation of ketone was obtained with 4 equivalents picolinic acid to Fe^{III}. Further increasing the amount of picolinic acid did not increase the efficiency of ketone formation. On the contrary, using 10 equivalents of picolinic acid actually slightly decreased the formation of ketone. Therefore, a system with Fe^{III}/picolinic acid/H_2O_2 = 1:4:4 was optimum for oxidation of saturated hydrocarbons by the Fe^{III}-H_2O_2 systems.

After demonstrating the essential effect of picolinic acid for the hydrocarbon activation by Gif type systems, it was of interest to test some other carboxylic acids (especially N-containing heteroaromatics) and to study the structural necessities for these acids in hydrocarbon oxidation.

Generally, simple carboxylic acids, such as acetic acid, pivalic acid and benzoic acid failed to activate the hydrocarbon to a significant extent. In these cases, the catalase reaction was by far dominant over the Gif oxidation. Among the N-containing heteroaromatic carboxylic acids, pyridine-2,6-dicarboxylic acid (dipicolinic acid), isoquinoline-1-carboxylic acid and isoquinoline-3-carboxylic acid produced similar amounts of ketone as did picolinic acid. In the presence of pyrazine-2-carboxylic acid or pyrazine-2,3-dicarboxylic acid, the ketone was also the major product although the efficiencies were slightly lower. These acids had a common structural feature, that is the carboxylic acid function was α to the aromatic N-atom. When the carboxylic acid function was β to the aromatic N-atom, like in the cases of nicotinic acid, quinoline-3-carboxylic acid and quinoline-8-carboxylic acid, the ketone became the minor product again. The explanation was quite obvious: With a carboxylic acid functionality α to the N-atom, both the acid and

N-atom could conveniently chelate with the iron atom, while this could not be achieved when the two were β to each other. Interestingly, when the quinaldic acid was used, even though it contained the carboxylic acid functionality α to the N-atom, only a quantitative amount of oxygen was formed. This was probably due to the aromatic ring α to N-atom blocking the N-atom from chelating freely with the iron. Furthermore, its *N*-oxide did show a significant hydrocarbon oxidation. In addition, picolinic acid *N*-oxide produced the same amount of ketone as did picolinic acid itself. In conclusion, a carboxylic acid function α to the aromatic N-atom was the structural prerequisite for the ketonization of saturated hydrocarbons. The known complex (1),[13a] whose structure was determined by X-ray crystallography, also exhibited the same characteristics as the successful ketonization systems just described.

The importance of a carboxylic acid such as picolinic acid (PA) becomes even more clear in the presence of $CBrCl_3$ or Ph_2S; and the results are shown in Table 1:

Table 1 Chemoselectivity study in the presence or absence of picolinic acid

Entry	FeCl$_3$ (mmol) [a]	Trapping reagents	H$_2$O$_2$ (mmol)	Products without Picolinic acid (mmol)	Products with Picolinic acid (mmol)	Efficiency (%) [c]
1	1	CBrCl$_3$	4	R-Br (n.d.), R=O (n.d.),[b] CO$_2$ (n.d.), O$_2$ (1.65)	R-Br (1.43), R=O (n.d.), CO$_2$ (1.33), O$_2$ (n.d.)	83/36
2	3	CBrCl$_3$	1.5	R-Br (0.08), R=O (n.d.), CO$_2$ (n.d.), O$_2$ (0.67)	R-Br (1.26), R=O (n.d.), CO$_2$ (0.99), O$_2$ (n.d.)	95/84
3	1	Ph$_2$S	4	R=O (0.10), Ph$_2$SO (2.05), O$_2$ (0.71)	R=O (1.57), Ph$_2$SO (0.08), O$_2$ (0.05)	92/83
4	3	Ph$_2$S	1.5	R=O (n.d.), Ph$_2$SO (1.05), O$_2$ (0.23)	R=O (0.21), Ph$_2$SO (n.d.), O$_2$ (0.11)	100/43

[a] FeCl$_3$·6H$_2$O, trapping reagents (10 mmol) and cyclohexane (20 mmol) in pyridine (33 mL); 4 equivalents of picolinic acid with respect to the Fe^{III} was used when applied. [b] n.d. = not detected. [c] Efficiencies are calculated as one equivalent of H$_2$O$_2$ is needed for the formation of one equivalent of alkyl bromide and Ph$_2$SO, while two equivalents of H$_2$O$_2$ for one equivalent of O$_2$ and ketone. CO$_2$ was not counted into the efficiencies. The first % refers to the no picolinic acid reactions. The second refers to reactions in presence of picolinic acid.

Using CBrCl$_3$, in the absence of picolinic acid, no alkyl bromide was formed at all. Instead only oxygen was produced. However, in the presence of PA, 1.43 mmol of R-Br was produced, accompanied by 1.33 mmol of carbon dioxide (entry 1). Entry 2 provides an understanding of the amounts of H$_2$O$_2$ needed to calculate the efficiencies. Using only half an equivalent of hydrogen peroxide (1.5 mmol) with respect to the iron (3 mmol) still produced 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 behavior of Ph$_2$S. In contrast to CBrCl$_3$, the absence of picolinic acid allowed conventional formation of diphenyl sulfoxide, and the saturated hydrocarbon was not affected significantly (ratio of sulfoxide to ketone = 20 : 1). However, in the presence of picolinic acid, the chemoselectivity changed dramatically, and ketone was the product formed (ratio of sulfoxide to ketone = 1 : 20). Entry 4 reveals that for the formation of one equivalent diphenyl sulfoxide one equivalent of hydrogen peroxide was necessary. Furthermore, here the presence of picolinic acid lead to a clear decrease in efficiency compared to the corresponding experiment in entry 2. No diphenyl sulfoxide, but only small amounts of O$_2$ and ketone were 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$_3$ very efficiently. What is this species?

Informative results were obtained when the Fe^{III} + PA + H$_2$O$_2$ reactions were carried out under argon. Unlike in the Fe^{II}-Fe^{IV} manifold or the Fe^{III} + H$_2$O$_2$ reactions in pyridine-acetic acid, no change in product distribution was detected whether an Fe^{III} + PA + H$_2$O$_2$ experiment was run under argon or oxygen. Ketone was always found to be the only product in similar amounts. Even more of a surprise was, that as we treated the Fe^{III} + PA + H$_2$O$_2$ system with a vigorous argon stream, as shown in Table 2. Suddenly alkyl chloride formation was observed, accompanied with ketonization and Fe^{II} formation (typically 15 %). The removed oxygen was quantified by Winkler's method and shown to be always less than half of the amount of chloride formed. This fact plus the fact that both reactions are relatively slow (T$_{1/2}$ ≈ 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 3.

Table 2 Hydrocarbon oxidation under argon or vacuum with Gif Fe^{III}-H_2O_2 systems

Entry	System [a]	Products (mmol)		Efficiency (%)
		C_8H_{14}=O	C_8H_{15}-Cl	
1	Fe^{III} + picolinic acid, Argon	0.88	1.00	94
2	Fe^{III} + picolinic acid, Vacuum	0.53	0.55	54
3[b]	Fe^{III} + picolinic acid, Argon then O_2	(0.43) 1.31	(0.33) 0.33	82
4	[(Pic)$_2$FeCl$_2$]⁻ [Pyr$_2$H]⁺ (1), Argon	0.51	0.65	58
5[c]	Fe(Pic)$_3$, Argon	0.65	0.06	40
6	Fe^{III} + isoquinoline-1-carboxylic acid, Argon	0.33	0.72	53

[a] Unless otherwise specified, FeCl$_3$•6H$_2$O (1 mmol), carboxylic acid (4 mmol), cyclooctane (20 mmol), H$_2$O$_2$ (4 mmol) and pyridine (33 mL) were used in each experiment. These experiments were carried out under vigorous argon stream or under vacuum (2 mm Hg). [b] 2 h argon stream then oxygen stream; ( ) shows the amount of products after 2 h. [c] 0.09 mmol of cyclooctanol was formed.

It is important to mention, that the oxygen loss of (2) is completely reversible, as Table 2, entry 3 shows: When flushing the reaction after 2 h argon stream with oxygen, alkyl chloride formation stops and the ketone formation carries on. Interestingly, complex (1) exhibited again the same characteristics as the FeCl$_3$ / PA system (entry 4), and in contrast, Fe(pic)$_3$ (pic = picolinate) did not yield significant amounts of alkyl chloride (entry 5), even though the reaction mixture was loaded with Cl⁻. This result prompted us to examine the ligand environment of these systems.
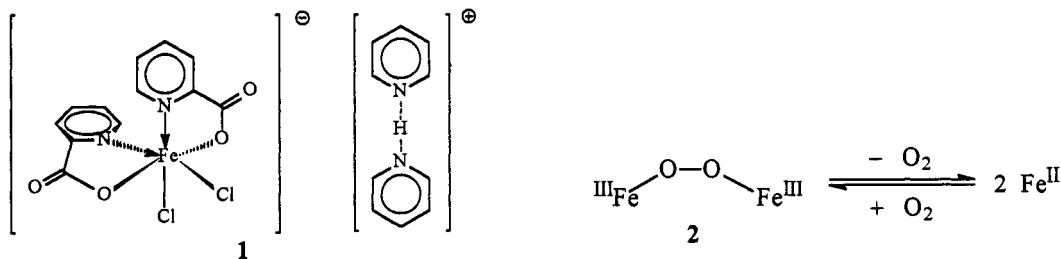
Scheme 3

DETERMINATION OF LIGAND ENVIRONMENT OF GIF CATALYSTS USING QUANTITATIVE ^{13}C-NMR[26]

Quantitative ^{13}C-NMR has been widely used in polymer and protein chemistry.[27] However, the application of a metal center as both hydrocarbon activating catalyst and paramagnetic relaxation reagent is still an unexplored field.

The study was started from a complex with known structure. Thus, the known complex (1) was prepared and redissolved in pyridine and submitted to a ^{13}C-NMR experiment. As expected, no picolinic acid signals were visible, even after 50,000 transients. From previous investigations, it was known that oxalic acid formed a tightly bound complex with Fe^{III} and did not allow hydrogen peroxide to reach the iron core, thereby completely inhibiting Gif oxidation. Hence, the addition of excess of oxalic acid would completely remove other ligands on the iron, including the picolinates. So they could become visible in the ^{13}C-NMR. In fact, we were not only able to see these free picolinic acids, but also quantify them. Two equivalents of picolinic acid free in the solution were detected using an internal standard of hexachloroethane. This correlated exactly with the X-ray structure of this complex. This determination demonstrated the effectiveness of this quantification technique.

After confirming the quantification results using a complex with known composition, we moved on to study the Fe^{III}/ligand combinations with unknown compositions in solution. Picolinic acid was first examined. Interestingly, with three or four equivalents of picolinic acid in solution, there were only two equivalents of acid complexed to the iron, while the other one or two equivalents of acid were free in the solution. This revealed that the corresponding trisubstituted iron complex, $Fe(pic)_3$, was not formed in pyridine solution. When we submitted the authentic $Fe(pic)_3$ to ^{13}C-NMR study, we did not observe any free acid in the solution. That meant that all three equivalents of picolinic acid were still on the iron. Thus, it was understandable that the hydrocarbon oxidation using $Fe(pic)_3$ and $FeCl_3 \cdot 6H_2O$ + three picolinic acid might be different, because they differ in their starting compositions in pyridine solution. Of course, upon addition of an excess of oxalic acid, all previously coordinated acids were liberated and could be measured in solution. Like picolinic acid, isoquinoline-1-carboxylic acid gave similar results. With four equivalents of isoquinoline-1-carboxylic acid to one equivalent of Fe^{III}, only two equivalents of acid were bound to the iron and the other two equivalents were free in the solution. Addition of oxalic acid displaced the two equivalents of acid on the iron, therefore four equivalents of isoquinoline-1-carboxylic acid could be detected in the solution. Interestingly, the same result was obtained for dipicolinic acid, *i.e.* two equivalents of dipicolinic acid were bound on the iron.

This quantification technique is a good method to study strongly coordinated ligands. On the other hand, when using quinaldic acid as the ligand, the limitation of this method appeared. Quinaldic acid contains an aromatic ring α to the N-atom which might block the N-atom from chelation with iron; therefore it did not give any hydrocarbon oxidation in pure pyridine. This characteristic was also reflected in the ^{13}C-NMR quantification. When two equivalents of quinaldic acid (again with respect to Fe^{III}) were added to the solution, both of them were found on the iron. However, the addition of one equivalent of isoquinoline-1-carboxylic acid (a strongly coordinated ligand) did not give the expected quantification results. We expected to see one equivalent of quinaldic acid to be replaced with one equivalent of isoquinoline-1-carboxylic acid, therefore we should have seen one equivalent of quinaldic acid in the solution. Indeed, we observed that some quinaldic acid was displaced and became visible in the ^{13}C-NMR, but we could not quantify the amount. Addition of the second equivalent of isoquinoline-1-carboxylic acid resulted in accurate quantification of quinaldic acid, *i.e.* two equivalent of quinaldic acid could be determined to be free in the solution. These results revealed that in the presence of only one equivalent of isoquinoline-1-carboxylic acid, quinaldic acid could still occupy a free coordination place on the iron. Therefore, there existed an equilibrium between the coordinated and non-coordinated acids. After adding the second equivalent of isoquinoline-1-carboxylic acid, these free coordination sites were completely occupied by the isoquinoline-1-carboxylic acid. Thus quinaldic acid was totally displaced into the solution; thus it could not bind with the iron in the first coordination sphere. The relaxation time of its nuclei were now only influenced by the paramagnetic spin density though space in solution, but not effected by direct interaction with the iron. As a consequence, quinaldic acid could again be quantified.

This quantification technique was also useful in studying the influence of side products formed in the Gif reactions. Previously, we were concerned about side products such as hydroxypyridines which could bind with iron and thus change its characteristics and the oxidation mechanism. Therefore, we wanted to determine if these hydroxypyridines were complexed to the iron by this quantitative ^{13}C-NMR technique. 2-Hydroxypyridine was chosen because it was expected to form the strongest complex with iron in these isomers. We observed that in the presence of three equivalents of picolinic acid, the addition of three equivalents of 2-hydroxypyridine did not change anything. Two equivalents of picolinic acid were still on the iron, one in the solution; while all three equivalents of 2-hydroxypyridine were free in the solution. Therefore, we proved that 2-hydroxypyridine did not chelate with iron in the presence of picolinic acid.

We discovered earlier that in the presence of one equivalent of picolinic acid, the addition of four equivalents of acetic acid increased the formation of ketone; while in the presence of two equivalents of picolinic acid, addition of acetic acid did not change anything. To further understand this, we submitted these systems to the quantitative ^{13}C-NMR study. We found that in the presence of one equivalent of picolinic acid and four equivalents of acetic acid with respect to Fe^{III}, not only the picolinic acid was on the iron, one equivalent of acetic acid was on the iron as well. There were only three equivalents of acetic acid in the solution. On the other hand, in the presence of two equivalents of picolinic acid and four equivalents of acetic acid, only the picolinic acid was on the iron, while all the four equivalents of acetic acid were free in the solution. Therefore, in this system the iron catalyst was indeed the same as that formed in the absence of acetic acid. Hence, the reason that similar results were obtained in the presence of two

equivalents of picolinic acid with or without acetic acid became obvious. Interestingly, even a large excess of acetic acid (twenty equivalents) did not displace any picolinic acid. This again suggested that picolinic acid was a much better ligand than acetic acid. Of course, the addition of oxalic acid displaced all other ligands so that both picolinic acid and acetic acid were free in the solution.

Finally, we followed the Gif reactions (with H_2O_2) by this quantitative ^{13}C-NMR technique. We found that addition of H_2O_2 did not displace the picolinic acid, regardless of whether the reaction was carried out in the presence or absence of hydrocarbon. Also, no liberation of ligands was observed during any stage of the reaction. This result did not change even if four equivalents of H_2O_2 were used.
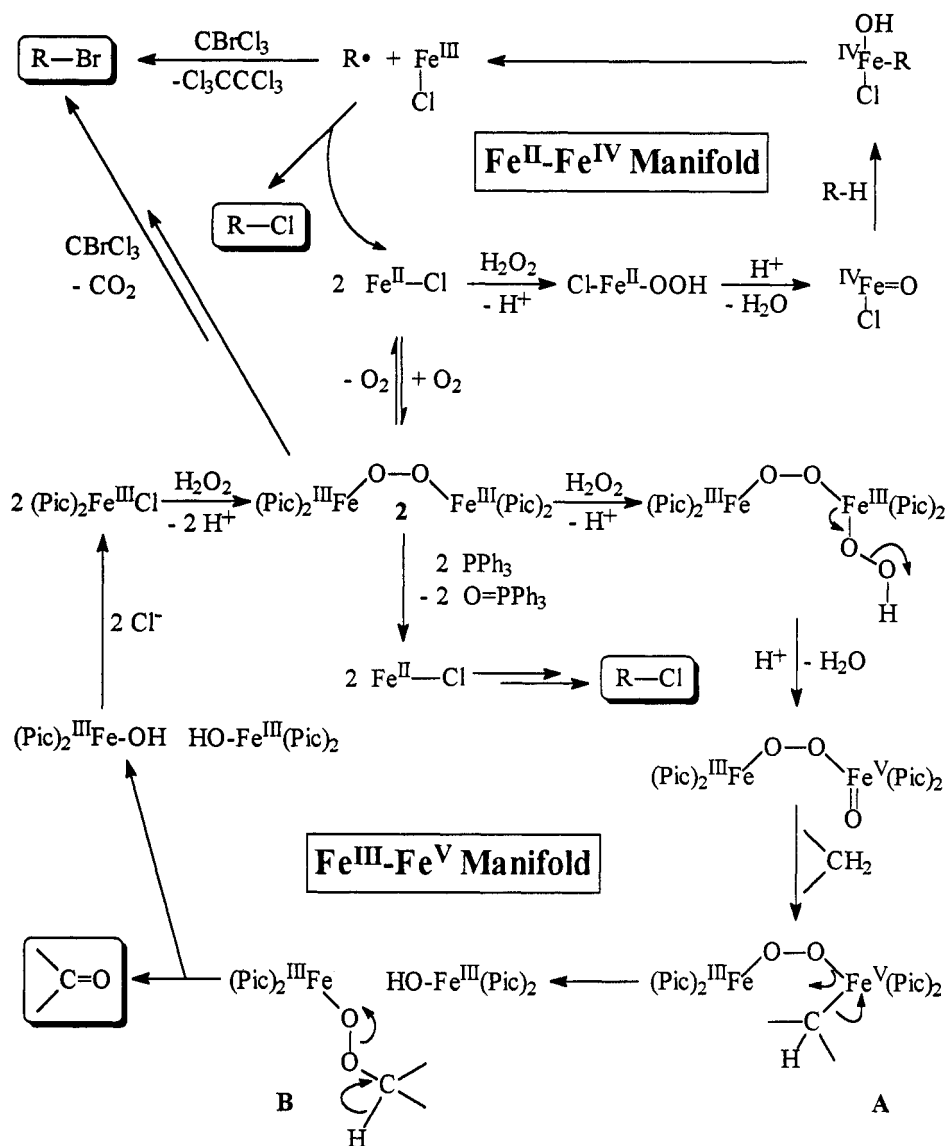
Scheme 4

CONCLUSIONS

All the results together can be put in a comprehensive mechanistic proposal (Scheme 4) which explains all data accumulated on Gif Chemistry to this day.

(2) 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 and H_2O_2 reduce **(2)**, yielding Fe^{II} and Ph_3PO.[28] Under air, the normal Fe^{III}-Fe^{V} manifold prevails, yielding ketone.

Due to the NMR results, for the first time we are able to determine the ligands on the iron. Note that the decomposition of intermediate **B** can be postulated with 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 4.

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