



The Functionalization of Saturated Hydrocarbons. Part 39.[†] Further Evidence for the Role of the Iron-Carbon Bond in Gif Chemistry

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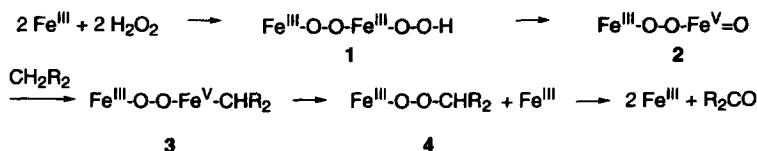
Abstract: The functionalization of saturated hydrocarbons utilizing the Gif oxidation system is considered to occur via an intermediate containing an Fe-C bond. Iodine and iodide ion have been found to capture efficiently the Fe-C bond to give the corresponding alkyl iodide in both the Fe^{II}-Fe^{IV} and Fe^{III}-Fe^V manifolds. This trapping of the Fe-C bond in both manifolds is shown to be non-radical in nature. © 1997 Elsevier Science Ltd.

INTRODUCTION

In Gif Chemistry¹ we have delineated² two manifolds: Fe^{II}-Fe^{IV} and Fe^{III}-Fe^V. In both manifolds there is preferential attack at secondary positions of saturated hydrocarbons to furnish ketones. The K.I.E. (kinetic isotope effect) for both manifolds is identical. For reasons summarized earlier^{1,2}, in both manifolds the formation of an iron-carbon bond has been postulated. In the Fe^{II}-Fe^{IV} manifold, the Fe^{IV}-CHR₂ bond cleaves to Fe^{III} and a CHR₂ radical, which shows typical radical chemistry. In the Fe^{III}-Fe^V manifold, the Fe^V-CHR₂ bond does not, except in special cases, cleave into Fe^{IV} and carbon radicals. The chemistry that follows is non-radical and depends on whether the solvent is pyridine-acetic acid (10:1) or simply pyridine. In the latter case the ligands on the Fe^{III} are critical. Gif Chemistry is only seen in the presence of carboxylic acids with an α-nitrogen like picolinic acid². By NMR studies we have shown³ that two picolinic acid ligands must be bonded per Fe^{III}. Recent work on the replacement of pyridine by other solvents such as acetonitrile has demonstrated that either pyridine or appropriately substituted pyridines are also essential ligands on Fe^{III}. Again from NMR studies⁴ it was shown that there is one pyridine ligated per Fe^{III}.

All this evidence characterizes well the nature of the active Fe^{III} complex. However, it does not provide conclusive proof of the iron-carbon bond which, in the Fe^{III}-Fe^V manifold, must be relatively stable. The current hypothesis for ketone formation in pyridine is shown in **Scheme 1**. For simplification we have omitted all ligands other than those involved directly with the chemistry.

Scheme 1.



[†] Part 38. D.H.R. Barton and B.M. Chabot, *Tetrahedron*, 1997, 53, 511. Part 39 is dedicated with admiration to Professor Dieter Seebach on the occasion of his sixtieth birthday.

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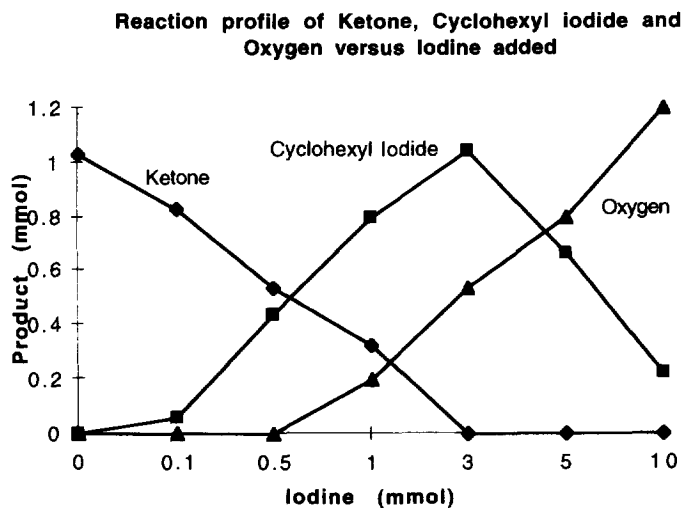
The hypothesis includes the formation of **1** and the transformation of the terminal hydroperoxide into an Fe^{V} oxenoid **2** which reacts selectively at the secondary position in a hydrocarbon to give **3** with the Fe^{V} carbon bond. Ligand coupling is proposed for the formation of peroxide **4**. This species is known to fragment into Fe^{III} and ketone.

Positive evidence⁵ for the Fe^{V} -carbon or Fe^{III} -carbon bond is difficult to obtain. There is strong evidence that it is not a carbon radical. We decided to search for more solid evidence. In principle, the reaction of iodine with an iron-carbon bond should give (if the polarization is I^+ and I^-) R_2CHI and $\text{Fe}^{\text{V}}\text{-I}$ or $\text{Fe}^{\text{III}}\text{-I}$ depending on the valence state of the iron.

RESULTS AND DISCUSSION

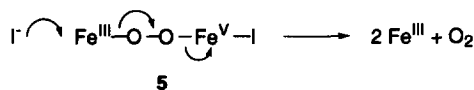
In the first experiments (Figure 1) we began with normal Gif oxidation of cyclohexane to cyclohexanone (about 1 mmol). Addition of iodine diminished the formation of ketone and replaced it with iodide formation. With 3 mmol of iodine, ketone formation was completely suppressed with only cyclohexyl iodide being formed along with a small amount of 2-iodopyridine. In addition, oxygen formation began from 1 mmol of iodine onwards. When 10 mmol of iodine were present oxygen formation largely replaced iodide formation. As is well known in volumetric analysis, iodine does not react with H_2O_2 to form oxygen. We have confirmed this for pyridine as solvent.

Figure 1.



In principle the reaction of **3** with iodine should furnish the observed iodide and an $\text{Fe}^{\text{V}}\text{-I}$ species as in **5**. We suspect that this is the source of the oxygen as shown in Scheme 2.

Scheme 2.



In order to test for carbon radicals we added a large excess of lithium chloride (**Table 1**). With either 1 or 5 mmol of iodine there was no indication of cyclohexyl chloride formation or of coupling to pyridine which are indicative of a radical mechanism in Gif systems.

Table 1. Reaction of the Fe^{III} / Iodine System in the Presence of Lithium Chloride

Iodine (mmol)	$\text{C}_6\text{H}_{10}=\text{O}$ (mmol)	$\text{C}_6\text{H}_{11}\text{I}$ (mmol)	$\text{C}_6\text{H}_{11}\text{Cl}$ (mmol)	2-I-pyr (mmol)
1	0.41	0.47	0	0.10
5	0	0.68	0	0

$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (1 mmol), Picolinic acid (4 mmol), Cyclohexane (20 mmol), Iodine (x mmol), LiCl (10 mmol), Pyridine (33 mL) and HOOH (4 x 1 mmol each 10 min).

Another convenient test for carbon radicals is to compete cyclohexane (only secondary hydrogens) with 2,3-dimethylbutane (only primary and tertiary hydrogens). The addition of up to 20 mmol of 2,3-dimethylbutane had little effect on iodide formation (**Table 2**).

Table 2. Competition Reaction Between Cyclohexane and 2,3-Dimethylbutane in the Fe^{III} / I_2 System

2,3-Dimethyl-butane (mmol)	$\text{C}_6\text{H}_{11}\text{I}$ (mmol)	2,3-Dimethyl-butane-2-ol (mmol)	2-I-pyr (mmol)
0	0.55	n.d.	0.22
10	0.45	n.d.	0.18
20	0.47	n.d.	0.19
40	0.27	n.d.	0.03

$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (1 mmol), Picolinic acid (4 mmol), Cyclohexane (20 mmol), Iodine (3 mmol), Pyridine (33 mL) and HOOH (4 x 1 mmol each 10 min).

It is interesting to compare the effects of addition of iodide ion with those of iodine itself (**Table 3**). Some chloride was formed (with small amounts of iodide) but not beyond 0.2 mmol of LiI. Addition of 2 or 5 mmols of iodide afforded more than 1 mmol of cyclohexyl iodide as well as 0.25 mmol of 2-iodopyridine. 4-Iodopyridine was not formed.

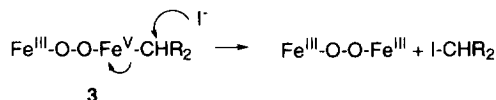
Table 3. Effect of LiI on the Formation of Cyclohexyl Iodide in the Fe^{III} System

LiI (mmol)	$\text{C}_6\text{H}_{10}=\text{O}$ (mmol)	$\text{C}_6\text{H}_{11}\text{I}$ (mmol)	$\text{C}_6\text{H}_{11}\text{Cl}$ (mmol)	$\text{C}_6\text{H}_{11}\text{OH}$ (mmol)	2-I-pyr (mmol)
0.2	0.56	0.12	0.10	0.01	0.05
0.5	0.52	0.26	0	0	0.10
0.8	0.35	0.26	0	0	0.14
2	0	1.16	0	0	0.25
5	0	1.08	0	0	0.24

$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (1 mmol), Picolinic acid (4 mmol), Cyclohexane (20 mmol), LiI (x mmol), Pyridine (33 mL) and HOOH (4 x 1 mmol each 10 min). Reactions were carried out at 0°C under argon.

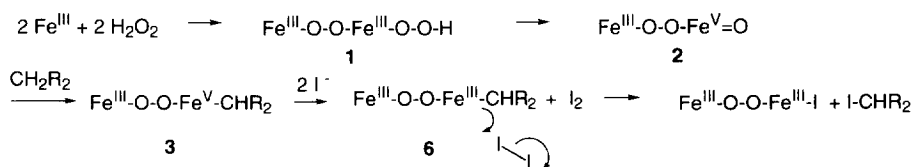
The simplest interpretation of the effect of iodide anion is shown in **Scheme 3**. However, this would not explain the relative inefficiency of the reaction.

Scheme 3.



Both iodine and lithium iodide give similar results suggesting that both react through a common intermediate, the Fe-C bond. Upon quenching the oxidation reaction, substantial amounts of cyclohexyl iodide were formed. It is also important to realize that the kinetic isotope effect (K.I.E.) of 1.95 is the same as that of ketone formation². Therefore, the hydrocarbon activation⁶ in both types of reactions are equivalent to each other. We also investigated the possibility of other nucleophiles being able to react with the Fe-C bond. With the addition of lithium bromide no cyclohexyl bromide was observed. However, when the above reaction was carried out in the presence of LiBr and iodine, both cyclohexyl bromide (0.36 mmol) and cyclohexyl iodide (0.47 mmol) were formed. The possibility that the cyclohexyl bromide was formed from bromide ion in the Fe^{III}-Fe^V manifold is shown not to be the case in the former experiment, whereas the mixed halide of I-Br resulting from the reaction of iodine and bromide ion gave a mixture of both the cyclohexyl halides. Cyanide ion was also tried as an alternative nucleophile. No cyclohexyl cyanide was formed. One can conclude therefore that in the Fe^{III}-Fe^V manifold, since good nucleophiles such as bromide and cyanide do not attack the Fe-C bond to give the corresponding cyclohexyl bromide or cyanide, the formation of cyclohexyl iodide must be generated *via* an alternative mechanism (**Scheme 4**).

Scheme 4.



The formation of cyclohexyl iodide can be explained by the oxidation of iodide to iodine. This reaction does not occur if the hydrocarbon is not present. Thus, the hydrocarbon is acting as an activator of the complex. To prove if the iodide ion is reducing the Fe^V species to Fe^{III}, removal of the iodine as it is formed *in situ* would reduce the amount of cyclohexyl iodide obtained as product. When oxidation of the hydrocarbon was carried out in the presence of sodium thiosulfate and lithium iodide, the amount of cyclohexyl iodide was reduced by 50%.

A kinetic profile of the rate of formation of cyclohexyl iodide was performed (**Table 4**).

Table 4. Rate of Formation of Cyclohexyl Iodide in the $\text{Fe}^{\text{III}}/\text{I}$ System

Time (mins)	$\text{C}_6\text{H}_{11}\text{I}$ (mmol)	2-I-pyr (mmol)	$\text{C}_6\text{H}_{10}=\text{O}$ (mmol)
15	0.76	0.14	0
30	0.91	0.17	0
60	1.07	0.20	0
90	1.14	0.22	0.02
120	1.17	0.23	0.04
180	1.22	0.24	0.05
900	1.22	0.24	0.05

$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (1 mmol), Picolinic acid (4 mmol), Cyclohexane (20 mmol), LiI (2 mmol), Pyridine (33 mL) and HOOH (4 mmol). The reactions was carried out at 0°C under argon.

The half-life of cyclohexyl iodide was found to be less than 15 minutes. However, by varying the concentrations of the reactants, we were able to determine the half-life more accurately and to demonstrate its dependence on the amount of iodide ion in solution (Table 5).

Table 5. Measurement of $t_{1/2}$ by Modifying the Concentration of Reactants in the $\text{Fe}^{\text{III}}/\text{I}$ System

HOOH (mmol)	LiI (mmol)	Cyclohexane (mmol)	$t_{1/2}$ (mins)
4	4	20	<5
4	2	20	<15
2	4	20	<5
2	2	20	<5
4	4	10	<5
4	2	10	10-15
1	4	20	<<2
2	4	20	<<2
1	1	20	<2
1	0.4	20	5
1	0.5	20	4
1	0.6	20	5

$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (1 mmol), Picolinic acid (2 mmol), Cyclohexane (10 or 20 mmol), LiI (x mmol), Pyridine (33 mL) and HOOH (y mmol). Reactions were carried out at 0°C under argon.

In all cases, the half-life was measured by the formation of cyclohexyl iodide. The half-life of iodide formation decreases as the overall iodide ion concentration is increased. The above analysis shows an approximate first order dependence. The rate of reaction is also faster with respect to the normal ketone formation, where the half-life is on the order of 30 mins. Neither the selectivity nor the K.I.E. was affected by the addition of lithium iodide, therefore the change in speed of the reaction must be the result of a more efficient interception of the $\text{Fe}^{\text{V}}\text{-C}$ bond.

As in the case of iodine, radical involvement is a possibility. When the reaction was carried out in the presence of LiCl (20 mmol) and LiI (10 mmol), only cyclohexyl iodide (1.0 mmol) was formed with a little 2-Iodopyridine (0.21 mmol). No cyclohexyl chloride was observed. A reaction was performed with $\text{FeCl}_3/\text{LiCl}$ in the presence of a carbon radical (carbon radicals can be readily generated from thiohydroxamate esters). A quantitative yield of the alkyl chloride was obtained. Therefore a radical mechanism can be eliminated. The absence of radicals can also be confirmed by the C2/C3 ratio (2° carbons to 3° carbons) of adamantane when used as a substrate. The substitution pattern of the adamantane products in the presence of iodine would be a clear indication of the pathway of the

reaction (*i.e.* radical or non-radical). The C2/C3 ratio of the adamantane products was determined as 1.12 — a clear indication that the pathway is non-radical. The radical substitution pattern is 0.3.

Valuable information about the nature and the rate of formation of intermediates in Gif chemistry can be obtained by using the Fe^{III} species in a non-catalytic manner. Recent work by Russian colleagues⁷, as well as our own studies on the Fe^{III} -catalyzed reaction of H_2O_2 with triphenylphosphine and trimethyl phosphite⁸, have shown that the reaction of H_2O_2 with Fe^{III} is very fast. The same applies for the catalase reaction where carboxylate ligands are not added.⁸

In theory, two equivalents of H_2O_2 are needed to make 1 mol of ketone. Thus, if only 1 H_2O_2 per Fe^{III} species (ligated to picolinic acid) is added, either a new single iron species will be formed or one half of the two-iron ketonization reagent will result. We present in the sequel that it is the latter reaction which is in agreement with the experimental facts. Knowing that the reaction of one Fe^{III} with one H_2O_2 is an almost instantaneous reaction, the stability of the iron complex can be studied by monitoring the disappearance of oxidation power. As shown in **Table 6**, in the absence of hydrocarbon, the iron species has a half-life of approximately 50 minutes at 0°C. This is in agreement with earlier unpublished work⁹.

Table 6. Measurement of $t_{1/2}$ of the $\text{Fe}^{\text{V}}=\text{O}$ Oxenoid Species

Time (mins)	5	15	30	45	60	75
Oxidant (mmol)	0.93	0.84	0.69	0.54	0.45	0.30

$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (1 mmol) was added to solution of Picolinic acid (4 mmol) and Pyridine (33 mL). HOOH (1 mmol) was added slowly to the reaction mixture at 0°C under argon.

We could now determine the rate of reaction of the iron species with the hydrocarbon. The reagent was prepared using 4 mmol of FeCl_3 for one H_2O_2 . After 30 minutes at 0°C (**Table 7**), an excess of hydrocarbon was added. Slow ketonization took place with a half-life of about 45 minutes at 0°C. However, if excess of iodide was added after a short interval (15 mins), a relatively large amount of iodide was formed. Allowing two H_2O_2 for ketonization and one H_2O_2 for iodide formation (iron-carbon bond reaction), the total of ketone and iodide was constant over the 90 minutes required to complete the reaction.

Table 7. Measurement of Stability of the $\text{Fe}^{\text{V}}=\text{O}$ Oxenoid Species Towards Ketone/Iodide Formation

Time (mins)	Ketone (mmol)	Iodide (mmol)
15	0.03	0.25
30	0.07	0.15
45	0.06	0.15
60	0.08	0.12
90	0.11	0.07
120	0.11	0.07

$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (4 mmol), Picolinic acid (8 mmol), Cyclohexane (20 mmol), Pyridine (33 mL) and HOOH (1 mmol). The reaction was carried out at 0°C under argon. After 30 mins, cyclohexane (20 mmol) was added. At varying times, 2 mL of the reaction mixture was quenched with 2 mL of a solution containing LiI (4 mmol) in pyridine (33 mL) at 0°C and stirred for a further 10 mins. The reaction was then quenched with 2 mL of 10% $\text{Na}_2\text{S}_2\text{O}_3$ in H_2O .

From our previous work^{1,2}, we have always argued that the hydrocarbon creates the reagent with which it reacts ("Sleeping Beauty Effect"). Now we could test this hypothesis (**Table 8**). The experiment described in **Table 6**

was repeated, but the hydrocarbon was added 5 minutes after the formation of the reagent. After varying times, aliquots were quenched with excess iodide ion and then analysed.

Table 8. Measurement of the Stability of Fe^{v} -Carbon Species Towards Ketone/Iodide Formation

Time (mins)	$\text{C}_6\text{H}_{10}=\text{O}$ (mmol)	$\text{C}_6\text{H}_{11}\text{I}$ (mmol)	2-I-Pyr (mmol)
2	0	0.45	0.18
5	0.03	0.34	0.10
8	0.11	0.38	0.12
17	0.07	0.36	0.11
30	0.10	0.29	0.09
45	0.13	0.25	0.08
90	0.21	0.11	0.04
120	0.27	0	0
180	0.29	0	0

$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (4 mmol), Picolinic acid (8 mmol), Cyclohexane (20 mmol), Pyridine (33 mL) and HOOH (2 mmol). The reaction was carried out at 0°C under argon. After 5 mins, cyclohexane (20 mmol) was added. At varying times, 2 mL of the reaction mixture was quenched with a 2 mL solution containing LiI (4 mmol) in pyridine (33 mL) at 0°C and stirred for a further 10 mins. The reaction was then quenched with 2 mL of 10% $\text{Na}_2\text{S}_2\text{O}_3$ in H_2O .

The fact that iodide quenching and ketone formation together are of equal efficiency from 2 minutes to 3 hours proves that the species formed from the iron oxidation reagent and hydrocarbon has a long life and cannot therefore be a carbon radical. We have, of course, proven this thoroughly in the past^{1,2}. This new proof should convince even the most ardent of our radical critics.

A similar study was also carried out with BrCCl_3 , an efficient brominating reagent, varying the time at which the hydrocarbon was added to the reaction mixture followed by quenching aliquots of this solution at different time periods by addition to BrCCl_3 solution (Table 9). The reagent was prepared using 4 mmol of FeCl_3 and 1 mmol H_2O_2 . After either 10 or 30 minutes at 0°C (Table 9), an excess of hydrocarbon was added. Slow ketonization took place with a half-life of approximately 55 minutes at 0°C . Again, if excess of BrCCl_3 was added after a short interval (2-30 mins), a relatively large amount of bromide was formed. Allowing two H_2O_2 for ketonization and one H_2O_2 for bromide formation (iron-carbon bond reaction) the total amount of ketone and bromide was reasonably constant.

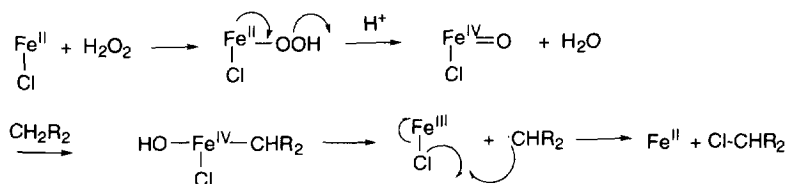
Table 9. Quenching of the $\text{Fe}^{\text{V}}=\text{O}$ Oxenoid Species with BrCCl_3

Hydrocarbon time (mins)	BrCCl_3 quench time (mins)	Bromide (mmol)	Ketone (mmol)
10	2	0.33	0.01
10	15	0.26	0.05
10	30	0.25	0.07
10	720	0.00	0.19
30	2	0.22	0.02
30	15	0.18	0.06
30	30	0.11	0.08
30	720	0.00	0.17

$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (4 mmol), Picolinic acid (8 mmol), Pyridine (33 mL) and HOOH (1 mmol). The reaction was carried out at 0°C under argon. After 10 or 30 mins, Cyclohexane (20 mmol) was added. At varying times, 2 mL of the reaction mixture was quenched with a solution of BrCCl_3 (10 mmol) in Pyridine (16 mL) at 0°C and stirred for a further 10 mins. The reaction was then quenched with 2 mL of 10% $\text{Na}_2\text{S}_2\text{O}_3$ in H_2O .

It has been shown in Gif chemistry that two manifolds exist in which the mechanistic pathway towards selective functionalization of hydrocarbons can vary between a non-radical pathway ($\text{Fe}^{\text{III}}\text{-Fe}^{\text{V}}$) and a radical pathway ($\text{Fe}^{\text{II}}\text{-Fe}^{\text{IV}}$). In both these manifolds the activation of the hydrocarbon is very similar as shown by their identical K.I.E. It is not until the Fe-C bond is formed in either manifold that this similarity parts. In the $\text{Fe}^{\text{III}}\text{-Fe}^{\text{V}}$ mechanistic pathway (**Scheme 1**), the activated hydrocarbon complex rearranges *via* ligand coupling to give ketone. It is also shown experimentally that the activated hydrocarbon complex can be intercepted to give, for example, an alkyl halide. In the $\text{Fe}^{\text{II}}\text{-Fe}^{\text{IV}}$ manifold the activated hydrocarbon complex undergoes homolytic cleavage to give a radical (**Scheme 5**).

Scheme 5.



Since the trapping of the Fe-C bond in the $\text{Fe}^{\text{III}}\text{-Fe}^{\text{V}}$ manifold was found to be a very facile process, we decided to investigate the possible capture of the Fe-C bond in the $\text{Fe}^{\text{II}}\text{-Fe}^{\text{IV}}$ manifold. The attack of the reagent on the Fe-C bond in the $\text{Fe}^{\text{III}}\text{-Fe}^{\text{V}}$ manifold is several orders of magnitude faster than ligand coupling to give the corresponding ketone. The question is whether or not a similar type of approach would work for the radical $\text{Fe}^{\text{II}}\text{-Fe}^{\text{IV}}$ manifold, *i.e.* whether trapping of the $\text{Fe}^{\text{IV}}\text{-C}$ bond is faster than that of homolytic cleavage to give the radical products. Normal conditions for activation of the hydrocarbon with Fe^{II} were carried out in the presence of a varying amount of LiI . The results are summarized in **Table 10**.

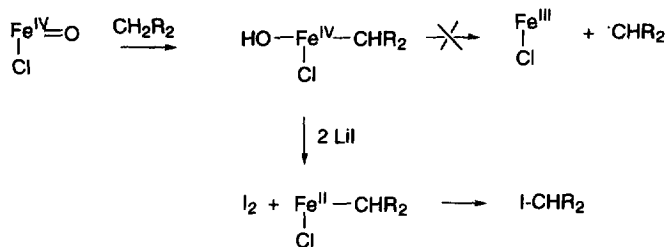
Table 10. Reaction of the Fe^{II} System in the Presence of LiI

LiI (mmol)	Cl (mmol)	I (mmol)	Cy-2-py (mmol)	2-I-pyr (mmol)	Cy-4-pyr (mmol)
0.2	0.90	0.10	0.27	0.06	0.14
0.5	0.71	0.27	0.23	0.13	0.12
1	0.50	0.60	0.16	0.17	0.08
4	tr.	1.02	0.03	0.23	0.02

FeCl₂·4H₂O (1 mmol), Picolinic acid (4 mmol), Cyclohexane (20 mmol), LiI (x mmol), LiCl (10 mmol), Pyridine (33 mL) and HOOH (4 mmol). The reaction was carried out at 0°C under argon.

Addition of LiI (0.2 mmol) to the system gave the characteristic distribution of products seen in the Fe^{II}-Fe^{IV} radical manifold. Cyclohexyl chloride (0.90 mmol) is the major product along with the radical coupling 2- and 4-products in 0.27 mmol and 0.14 mmol yield, respectively. When the amount of LiI is increased to 1 and then to 4 mmol, both the chloride and the coupling products decrease substantially. At the same time, the amount of cyclohexyl iodide increases to the point where if 4 mmol of LiI is added, no radical products are produced. Only cyclohexyl iodide (1.02 mmol) and 2-iodopyridine (0.23 mmol) were formed. This distribution of products mirrors exactly that of the Fe^{III}-Fe^V manifold. As the iodide concentration increases, the radical pathway is shut off as the Fe^{IV}-C bond is trapped with the iodide (**Scheme 6**).

Scheme 6.



Again, the formation of cyclohexyl iodide can be explained by the oxidation of iodide to iodine. A blank experiment was carried out in the absence of hydrocarbon. No iodine was detected after 2h. Therefore the hydrocarbon was acting as an activator of the complex. To prove if the iodide ion was reducing the Fe^{IV} to Fe^{II}, removal of the iodine as it was formed *in situ* would reduce the amount of cyclohexyl iodide being formed as product. However, it would increase the amount of cyclohexyl chloride derived by the radical coupling. Oxidation of the hydrocarbon was carried out in the presence of thiosulfate (1-20 mmol) and lithium iodide (2 mmol). The amount of cyclohexyl iodide was reduced from 0.33 mmol to 0.23 mmol and at the same time cyclohexyl chloride increased from 0.44 mmol to 0.69 mmol. Further evidence which points towards a non radical pathway was one experiment which examined the competition between different halides. A mixture of LiCl (10 mmol) and LiBr (10 mmol) was subjected to normal oxidation conditions in the Fe^{II}-Fe^{IV} manifold starting with Fe^{II}. After completion of the reaction, cyclohexyl chloride (0.45 mmol) and cyclohexyl bromide (0.12 mmol) were formed. The conclusion was that in the presence of cyclohexyl radicals, chloride was better formed than bromide. Again this

showed that the previous analysis within the $\text{Fe}^{\text{III}}\text{-Fe}^{\text{V}}$ manifold that no carbon radicals were present was valid. It also suggested that the coupling of cyclohexyl radicals with iodide should be worse than bromide and that the coupling between cyclohexyl radicals and $\text{Fe}^{\text{III}}\text{-I}$ does not exist. Finally, as in the previous section, adamantane can be used as a probe to determine whether radicals are involved in the formation of the cyclohexyl iodide. The C2/C3 ratio of adamantane products was found to be 1.16 in the presence of iodine, again a clear indication that the formation of cyclohexyl iodide does not form *via* a radical coupling process.

The kinetics of the reaction in the $\text{Fe}^{\text{II}}\text{-Fe}^{\text{IV}}$ manifold containing LiI were also examined (**Table 11**).

Table 11. Reaction Kinetics of Fe^{II} in the Presence of LiI

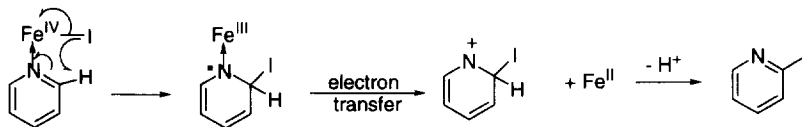
Time (mins)	Cl	I	Cy-o-pyr	2-I-pyr	Cy-p-pyr
3	0.32	0.65	0.11	0.15	0.06
6	0.23	0.72	0.11	0.17	0.06
10	0.35	0.78	0.10	0.18	0.05
15	0.32	0.78	0.10	0.18	0.05
31	0.32	0.85	0.11	0.20	0.06
45	0.32	0.85	0.11	0.20	0.06
720	0.33	0.85	0.11	0.20	0.06

$\text{FeCl}_2 \cdot 6\text{H}_2\text{O}$ (1 mmol), Picolinic acid (3 mmol), Cyclohexane (20 mmol), LiI (2 mmol), Pyridine (33 mL) and HOOH (4 mmol). The reaction was carried out at 0°C under argon.

The half-life of the reaction was found to be much less than 3 minutes. This is similar to that of the $\text{Fe}^{\text{III}}\text{-Fe}^{\text{V}}$ study containing iodide. It is clear from the above table that the insertion of iodide into the hydrocarbon is substantially faster than the competing radical coupling pathway with 0.65 mmol of cyclohexyl iodide and only 0.32 mmol of cyclohexyl chloride being formed. This proves, along with the evidence from the mixed halide experiment, that the iodide is coupled to the cyclohexyl ring in a non-radical manner. Thus it is evidence of the existence of an Fe-C bond which is captured with a reagent such as iodide.

In both the $\text{Fe}^{\text{II}}\text{-Fe}^{\text{IV}}$ and the $\text{Fe}^{\text{III}}\text{-Fe}^{\text{V}}$ manifolds the reaction with iodide ion produced a side product — 2-iodopyridine. It is postulated that this side product is a result of ligand coupling between an Fe-I bond and the solvent (pyridine) which is also complexed to the iron center *via* an electron transfer mechanism (**Scheme 8**). A similar formation of 2-phenylselenopyridine was seen in the phenylselenation of saturated hydrocarbons.¹⁰

Scheme 7.



CONCLUSIONS

The Fe-C bond in both the $\text{Fe}^{\text{II}}\text{-Fe}^{\text{IV}}$ and the $\text{Fe}^{\text{III}}\text{-Fe}^{\text{V}}$ manifolds can be efficiently trapped by the addition of an external reagent such as iodide ion. In the $\text{Fe}^{\text{III}}\text{-Fe}^{\text{V}}$ manifold the capturing of the Fe-C bond is much faster than ligand coupling to form ketone. This trapping has been shown to be of a non-radical nature by the chloride ion test

and by the absence of typical products from a radical pathway (*e.g.* pyridine coupling products). In the $\text{Fe}^{\text{II}}\text{-Fe}^{\text{IV}}$ manifold, capturing of the Fe-C bond with iodide is faster than homolytic cleavage to give radical by-products. In both manifolds the C2/C3 ratio of adamantane oxidation also confirms the hypothesis that the trapping of the Fe-C bond is not radical in nature. These results substantiate our hypothesis that a rapidly formed Fe^{V} oxenoid species exists and that it is fairly stable. This species reacts rapidly with saturated hydrocarbons to give another species which has the properties of an iron-carbon bond. A further important conclusion is that the slow step in Gif ketonization chemistry comes after the formation of the iron-carbon bond. The reaction of the hydrocarbon with the activated iron species is relatively fast.

CODA

Helpful referees have pointed out that in the $\text{Fe}^{\text{II}}\text{-Fe}^{\text{IV}}$ and the $\text{Fe}^{\text{III}}\text{-Fe}^{\text{V}}$ manifolds the μ -oxo bridging units should render the valence states as $\text{Fe}^{\text{III}}\text{-Fe}^{\text{III}}$ and $\text{Fe}^{\text{IV}}\text{-Fe}^{\text{IV}}$, respectively. We agree that this is another paradox. Fortunately, experimentally the two manifolds are clearly differentiated. One explanation could be that the Fe^{IV} and Fe^{V} oxenoids are really Fe^{II} and Fe^{III} cyclic peroxides. Further experimental work is needed.

EXPERIMENTAL

Gas chromatography analysis was performed on a Hewlett-Packard 5890 series II instrument equipped with flame ionization detector and a Hewlett-Packard 3396A integrator. Purified nitrogen was used as the carrier gas. The columns used were DB-WAX (30 m, 0.32 mm i.d., 25 μm film thickness), DB-5 (30 m, 0.32 mm i.d., 25 μm film thickness) or DB-1 (15 m, 0.32 mm i.d., 25 μm film thickness) capillary columns from J&W Scientific. Gas chromatography-mass spectrometry (GC-MS) analysis was carried out on a Hewlett-Packard 5890 series II gas chromatograph coupled with a Hewlett-Packard 5971 series quadrupole mass-selective detector (40 eV, electron impact). Helium was used as the carrier gas. The column used in the GC-MS was a HP-5MS (30 m, 0.25 mm i.d., 0.25 μm film thickness). Chemicals were purchased from Aldrich Chemical Co., except for pyridine (E. Merck), MgSO_4 , and H_2O_2 (Fisher). H_2O_2 was used as 30% in H_2O . The peroxide content was checked regularly by titration.

General procedures:

Typical neutral work-up: An aliquot (1 mL) was taken from the reaction mixture and added to diethyl ether (10 mL). Naphthalene in diethyl ether (1 mL, 0.08M) was then added to this mixture. The ether solution was then washed with H_2O (5 mL) and the organic extract was dried over MgSO_4 . The products were analyzed by gas chromatography.

Determination of the residual oxidizing power: An aliquot (1 mL) was added to water (5 mL) and acetic acid (5 mL) containing KI (0.5 g). After standing at room temperature in a closed flask for 10 minutes, the I_2 formed was titrated with a $\text{Na}_2\text{S}_2\text{O}_3$ (40 mM) solution with starch as indicator.

Measurement of the amount of O_2 formed: The reaction system was gas-tight and connected to a manometric burette filled with brine solution which was saturated with oxygen prior to usage. The volume of O_2 gas evolved from the Gif reactions was measured.

Typical $\text{Fe}^{\text{III}}\text{-H}_2\text{O}_2$ experiment: $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (1 mmol) and picolinic acid (4 mmol) were dissolved in pyridine (33 mL). Either LiI (2 mmol) or iodine (2 mmol) was added. Cyclohexane (20 mmol) was then added and the resulting mixture was cooled to 0°C . Reactions were typically carried out under an argon atmosphere. When

quantification of oxygen was necessary, argon was replaced with an oxygen atmosphere. H_2O_2 was added (4 x 1 mmol each 10 mins) to the reaction mixture and stirred for typically 12h. The products formed were quantified by the standard work-up procedure.

Typical $\text{Fe}^{\text{II}}\text{-H}_2\text{O}_2$ experiment: $\text{FeCl}_2\cdot 4\text{H}_2\text{O}$ (1 mmol) and picolinic acid (4 mmol) were dissolved in pyridine (33 mL). Either LiI (2 mmol) or iodine (2 mmol) was added. Cyclohexane (20 mmol) was then added and the resulting mixture was cooled to 0°C . Reactions were typically carried out under an argon atmosphere. When quantification of oxygen was necessary, argon was replaced with an oxygen atmosphere. H_2O_2 was added (4 x 1 mmol each 10 mins) to the reaction mixture and stirred for typically 12h. The products formed were quantified by the standard work-up procedure.

Generation of carbon radicals: A solution of $\text{FeCl}_3\cdot 6\text{H}_2\text{O}$ (1 mmol), LiCl (10 mmol), and cyclohexyl thiohydroxamate ester (1 mmol) in THF (25 mL) at room temperature was photolyzed with a 250W tungsten lamp for 30 mins. Cyclohexyl chloride was formed quantitatively (0.99 mmol) as determined by g.c. analysis.

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REFERENCES

1. D.H.R. Barton and D. Doller, *Acc. Chem. Res.*, **1992**, 25, 504; H-C Tung, C. Kang and D.T. Sawyer, *J. Am. Chem. Soc.*, **1992**, 114, 3445; U. Schuchardt, W.A. Carvalho and E.V. Spinace, *Synlett*, **1993**, 713; K-W Lee, K-W. Jun and E.K. Shim, *New J. Chem.*, **1993**, 17, 409; T. Briffaud, C. Larpent and H. Patin, *J. Chem. Soc., Chem. Commun.*, **1993**, 17, 409; L.I. Simandi, ed., *Dioxygen Activation and Homogeneous Catalytic Oxidation*, Elsevier Science, 1991; W Ando and Y. Moro-Oka, eds., *The Role of Oxygen in Chemistry and Biochemistry*, Elsevier Science, 1988.
2. D.H.R. Barton, B. Hu, D.K. Taylor and R.U. Rojas-Wahl, *J. Chem. Soc., Perkin Trans. 2*, **1996**, 1031.
3. D.H.R. Barton, B.Hu, R.U. Rojas-Wahl and D.K. Taylor, *New J. Chem.*, **1996**, 20, 121.
4. D.H.R. Barton, B.Hu, T. Li and J. MacKinnon, *Tetrahedron Lett.*, **1996**, 37, 8329.
5. T.J. McMurray and J.T. Groves in *Cytochrome P-450*, Plenum Press, ed. P.R. Ortiz de Montellano, New York, 1986, pp 1-28.
6. J.A. Davies, P.L. Watson, J.F. Liebman and A. Greenberg, eds., *Selective Hydrocarbon Activation: Principles and Progress*, VCH Publishers, Inc., New York, 1990; C.L. Hill, ed., *Activation and Functionalization of Alkanes*, ed., John Wiley & Sons, New York, 1989; D.H.R. Barton, D.T. Sawyer and A.E. Martell, eds., *The Activation of Dioxygen and Homogeneous Catalytic Oxidation*, Plenum press, New York, London, 1993.
7. A.P. Soboler, D.E. Babushkin, A.A. Shibin and E.P. Talsi, *J. Mol. Cat. A. Chemical*, **1996**, 112, 253.
8. D.H.R. Barton, D.R. Hill and B. Hu, *Tetrahedron Lett.*, **1997**, 38, 1711.
9. D.H.R. Barton, E. Csuhai, D. Doller and G. Balavoine, *J. Chem. Soc., Chem. Commun.*, **1990**, 1787.
10. D.H.R. Barton and B.M. Chabot, *Tetrahedron*, **1996**, 52, 10287.