Reviews

The Fe^{II}—Fe^{IV} and Fe^{III}—Fe^{V} manifolds in an expanded world of Gif chemistry*

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The Gif systems for the selective functionalization of saturated hydrocarbons based on the reactions of superoxide with Fe^{II} and of hydrogen peroxide with Fe^{III} are described. Both systems are relatively efficient, but not nearly so efficient as the electrochemical system developed in collaboration with Prof. G. Balavoine and Dr. Aurore Gref (Université de Paris-Sud-Orsay, France). All of the systems afford mainly ketones. This is an unusual selectivity, which implies a non-radical mechanism. It has been proven for the Fe^{III}—H_2O_2 system that the activation of the Fe^{III} is independent of the formation of ketone, which involves a hydroperoxide (derived from oxygen) as an intermediate. This intermediate controls the formation of ketone and of secondary alcohol. The addition of a number of trapping reagents such as $BrCCl_3$ diverts the reaction from oxygenation to bromide formation. Although $BrCCl_3$ is indeed a good trap for carbon radicals, the pattern of selectivity across a range of saturated hydrocarbons is completely different for Gif chemistry when compared with normal radical bromination. The chemistry is explained in terms of an Fe^{V} oxenoid species that inserts itself into secondary C—H bonds (a compromise between bond strength and steric hindrance). This gives an Fe^{V} intermediate **A** with an iron—carbon bond, which is probably rapidly reduced to the Fe^{III} state by hydrogen peroxide. Then oxygen is inserted into the Fe^{III}—C bond. Hydrolysis affords the isolateable intermediate hydroperoxide (intermediate **B**). A system based on *tert*-butyl hydroperoxide (TBHP) is described. This is similar to the above Gif systems, but the kinetic isotope effect is very different and the selectivity for adamantane substitution is different. However, Fe^{III} is activated by TBHP to an Fe^{V} oxenoid which, after reaction with a hydrocarbon, reacts with oxygen to give a hydroperoxide. So the pattern of intermediates **A** and **B** is maintained with TBHP. Radical chemistry is involved in some of the reactions that involve ionic coupling to saturated hydrocarbons. The importance of the Fe^{II}—Fe^{IV} manifold in providing a mechanism that permits the selective functionalization of saturated hydrocarbons by ionic trapping with chloride, azide, and other anions is made manifest. Comparison is made with the Fe^{III}—Fe^{V} manifold where ionic trapping is never seen. Traditional Fenton chemistry (hydroxyl radical formation) is not operative here, but the trapping does involve the formation of carbon radicals. These react very efficiently with anions bonded to Fe^{III}.

Key words: saturated hydrocarbons, selective functionalization; Fe^{II}-superoxide and Fe^{III}—H_2O_2 systems; electrochemical functionalization of cycloalkanes.

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* D. R. H. Barton is a Nobel Prize winner in chemistry in 1969. Since 1994, he is a foreign member of the Russian Academy of Sciences.

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Introduction

There is universal acceptance that the selective functionalization of saturated hydrocarbons is a research challenge of major proportions. Although paraffins are, as their name implies, usually considered to be inert, Nature has solved the problem of their functionalization using complexes of iron and, to a lesser extent of copper. The iron complexes are either heme based, as in the ubiquitous P_{450} enzymes, or non-heme based, as in the vitally important proline-4-hydroxylase and in the fascinating enzyme, methane monooxygenase. These enzymes contain one Fe^{III}, or two Fe^{III} atoms linked by an oxo bridge, respectively. Although the protein in these enzymes is responsible for their chemo- and stereo-selectivity, the activation of iron should also be taken into account. Models of P_{450} enzymes have been known for decades and the work of J. T. Groves is particularly noteworthy in this respect. Models of non-heme iron enzymes are much less familiar and, until our publications on Gif type chemistry, were not efficient.[1]

The use of superoxides and of hydrogen peroxide

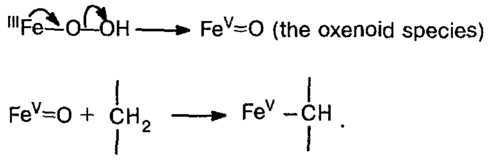
Our work started with the assumption that when, 3 billion years ago, the blue-green algae started to make oxygen, oxidation of iron by unicellular forms of life, accompanied by the oxidation of saturated hydrocarbons, also began. It is agreed that after 1 billion years of life under reductive conditions, the world was full of saturated hydrocarbons, Fe^{II} compounds, and metallic iron, as well as an abundance of hydrogen sulfide, since life was using the reduction of sulfate to sulfide as an energy source.

So our first experiment to test our hypothesis was the oxidation of adamantane in pyridine with some acetic acid in the presence of iron powder, hydrogen sulfide, and oxygen. Surprisingly, a major amount of adamantanone was formed and there was only minor formation of the tertiary alcohol. Later, we obtained the same results when we replaced the iron powder with zinc powder and added a catalytic amount of an Fe^{II} salt. This showed the unusual power of the iron species formed to make ketones as principal products.

During systematic studies on adamantane oxidation, we examined the effect of reducing oxygen pressure. We were surprised to find that lowering the oxygen pressure increased the selectivity for adamantanone formation. We defined selectivity as the C^2/C^3 ratio, where C^2 is the total quantity of products at the secondary carbon atom (mmol) and C^3 is the total quantity of products at the tertiary carbon atom (mmol). At the secondary position, only ketone and alcohol are formed. The reaction at the tertiary position at reduced oxygen pressures gave 2- and 4-*tert*-adamantyl-substituted pyridines and *tert*-adamantanol. When all of the secondary and tertiary products were taken into consideration, then C^2/C^3 was about 1.0 and was pressure invariant. Conversely, the C^2/C^3 for oxygen radical reactions is about 0.1. By application of Ockam's razor, we concluded that the reactions at secondary and tertiary positions involve the same intermediate. We postulated that this was formed by insertion of an Fe^V oxenoid species into the C—H bond. In the case of the secondary carbon atom, the Fe—C bond was stable, but at the tertiary position, the weaker Fe—C bond fragmented into radicals, which coupled with pyridine in the ordinary way. The appropriate blank experiments were carried out to show that secondary radicals, had they been formed at the lower oxygen pressures, would have been captured by the solvent pyridine.[2] Potassium superoxide reacted with Fe^{II} under argon to give an iron species that also gave an adamantane selectivity of about 1.0.

In addition, a similar behavior was observed for the system based on Fe^{III} and H_2O_2. We can summarize the results in the following way:

$$Fe^{II} + {}^{\bullet}O_2^{-} + H^{\oplus} \text{ or } Fe^{III} + H_2O_2 \longrightarrow Fe^{III}\text{—O—OH}$$



$$^{III}Fe\text{—O—OH} \longrightarrow Fe^V{=}O \text{ (the oxenoid species)}$$

$$Fe^V{=}O + \overset{|}{\underset{|}{C}}H_2 \longrightarrow Fe^V-\overset{|}{\underset{|}{C}}H\ .$$

The H_2O_2 system is very convenient to use and, since it is homogeneous, it lends itself to ^{13}C NMR studies. Using singly labeled cyclohexane, we could show that an intermediate was formed between cyclohexane and cyclohexanone. By comparison with an authentic specimen and by isolation, this was shown to be cyclohexyl hydroperoxide. The reaction, at room temperature had a half-life of about 2 hours and so was easy to follow by NMR spectroscopy.

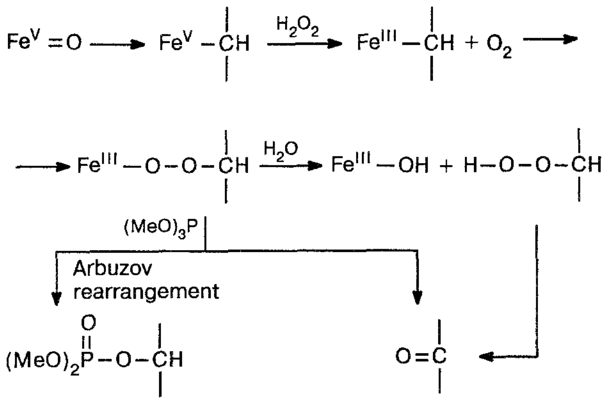
Further evidence for an intermediate hydroperoxide was found in Zn^0—Fe^{II}-superoxide experiments when triphenylphosphine was added before the formation of the superoxide. This did not change the total amount of oxidation products (ketone + alcohol), but did dramatically change the ketone to alcohol ratio in favor of alcohol. It is well known that PPh_3 rapidly reduces hydroperoxides to alcohols. Furthermore when trimethyl phosphite is used instead of PPh_3, the products of the reaction are phosphate and ketone.[3] Trimethyl phosphite is a reagent that reduces hydroperoxides at once to alcohols. To better understand the role of trimethyl phosphite in this reaction, we should find out how hydroperoxides are formed.

Using the Fe^{III}—H_2O_2 system, this question can be answered. If we accept that Fe^{III} is oxidized to the Fe^V oxenoid, then we can also understand how this is reduced back again to Fe^{III} and O_2 by a second molecule of H_2O_2. Using $^{18}O_2$ labeled oxygen, we can show that the oxygen that appears in the hydroperoxide is indeed formed from molecular oxygen and not from hydrogen peroxide. Does this mean that we have a conventional autoxidation process? The trimethyl phosphite reaction mentioned above precludes this possibility. Hydroperoxyl and alkoxyl radicals are reduced very efficiently by trimethyl phosphite to furnish alkyl radicals. We have indeed confirmed that this is so under Gif conditions. Therefore, the reaction with trimethyl phosphite which forms phosphate (see above) precludes the intermediacy of a hydroperoxyl radical. We propose that the reaction may occur according to the following mechanism (Scheme 1).

The key step here is the insertion of oxygen into the Fe^{III}—C bond for which there is precedent in porphyrin chemistry.[4]

Further study of the reactions in the Fe^{III}—H_2O_2 system showed that bromotrichloromethane and its congeners afford bromination instead of oxidation. The selectivity is the same as in the oxidation reaction and does not follow a typical radical bromination pattern.[5]

Scheme 1



Scheme 2 shows relative reactivities of a series of hydrocarbons (normalized per hydrogen) for radical bromination and for Gif type Fe^{III}—picolinic acid (PA)—H_2O_2 bromination. In each case, the C—H bond reactivity in cyclohexane is set at 1.0. The two sets of numbers are completely different. Cyclohexane is the most active hydrocarbon in Gif bromination and the least active in radical bromination. The data were accumulated by competing the hydrocarbons mixed together in pairs. This avoids the possibility that radical chain reactions might be different in two separate experiments carried out under nominally the same conditions in different flasks.

The same conclusion could be drawn from a comparison of the relative reactivities of the brominating reagents in radical bromination (Table 1) and in Gif bromination (Table 2).

For the relative rates of radical bromination, a competition was set up between the reagents, one by one, and thiophenol. Cyclohexyl radicals were generated by photolysis of the cyclohexylcarboxylic ester of *N*-hydroxy-2-thiopyridone, so one measures the ratio between cyclohexane (formed by the transfer of the thiophenol hydrogen atom) and the cyclohexyl bromide formed with participation of the reagent studied. For the Gif chemistry competitive oxidation to cyclohexanone was compared to bromination in the Fe^{III}—PA—H_2O_2—brominating agent system. In all cases of Gif bromination, the other product was CO_2 rather than hydrogen bromide, which is normally seen in radical bromination chemistry. All of the results show clearly that Gif bromination and radical bromination are completely different processes.

Another good test for either of the processes in question is bromination of cyclohexyl bromide. When

Scheme 2

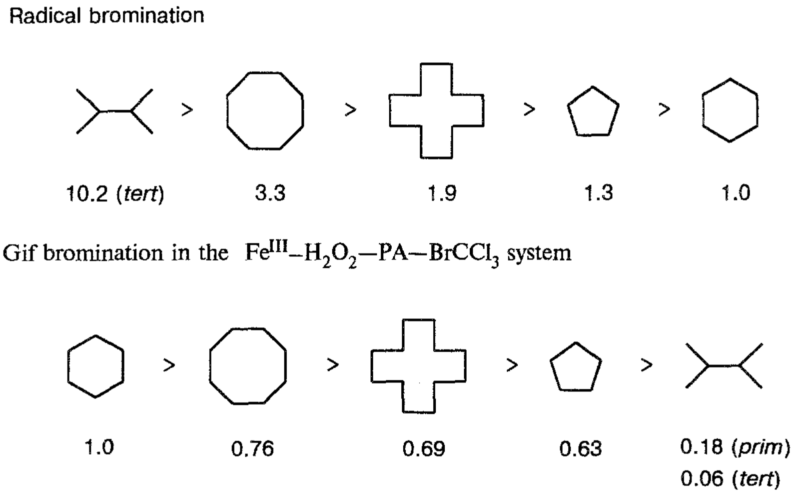
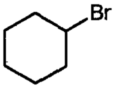
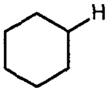


Table 1. Relative rates for radical bromination

(reagents: R—Br =

, R—H =

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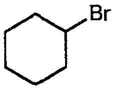
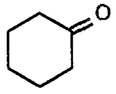
Entry	Halogenating reagent	Yield /mmol		$\frac{R-Br}{R-H}$	Total products /mmol
		R—H	R—Br		
1	CBr_4	0.065	0.133	2.05	0.198
2	CBr_2Cl_2	0.108	0.093	0.86	0.201
3	$CBrCl_3$	0.099	0.072	0.73	0.171
4	$(CBrCl_2)_2$	0.124	0.072	0.58	0.196
5	CBr_2F_2	0.120	0.005	0.01	0.125

Table 2. Relative rates for Gif bromination

(reagents: R—Br =

, R=O =

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Entry	Halogenating reagent	Yield /mmol		$\frac{R-Br}{R=O}$	Total products /mmol
		R—Br	R=O		
1	$CBrCl_3$	0.024	0.686	28.6	0.710
2	$(CBrCl_2)_2$	0.031	0.529	17.1	0.560
3	CBr_4	0.070	0.396	5.6	0.466
4	CBr_2Cl_2	0.300	0.418	1.4	0.718
5	CBr_2F_2*	0.352	0.079	0.2	0.431

* Reaction carried out at 0 °C due to the volatility of CBr_2F_2. Reaction time: 48 h.

radical bromination is involved, *trans*-1,2-dibromocyclohexane is the major product (Skell-Walling effect). Again, with Gif bromination, completely different results are seen (Table 3).

Our results for the radical bromination of cyclohexyl bromide are largely in agreement with the literature and completely different from the results of Gif bromination. A major equatorial preference is seen in that much more *cis* (diequatorial) than *trans* (equatorial, axial) 1,2-dibromide is formed, whereas for the 1,4-dibromination, much more *trans* (diequatorial) than *cis* (equatorial, axial) dibromide is seen. Insertion of the Fe^V oxenoid is subject to steric hindrance and hence, equatorial insertion followed by ligand coupling of bromide with retention of configuration would be expected in agreement with the results.

Less extensive data are at present available for the oxidation of cycloalkanes to ketones.[6] The results presented below (Scheme 3) are also expressed per C—H bond and cyclohexane is taken as 1.0. Again the hydrocarbons were competed against each other in pairs.

The order is approximately the same as for the Fe^{III}—PA—H_2O_2 bromination, but of course, the ligands are very different.

The oxidation of saturated hydrocarbons at the cathode of an electrochemical cell (Fe^{II} + superoxide) is a superior procedure from the viewpoint of electronic yield. An extensive study[7] carried out in collaboration with Prof. G. Balavoine, Dr. Aurore Gref, and other colleagues at the Université de Paris-Sud gave results that are partially summarized in Table 4. The electronic yield represents the proportion of the electrons appearing in the final product that come from the zinc in the Zn^0—Fe^{II}—O_2 system, or from the cathode. The electrochemical system is far superior from this point of view and it is also more selective. The electrochemical system uses trifluoroacetic acid, instead of acetic acid. The protonation of pyridine provides the cations necessary for the conductance of the current.

In any case, the selectivity of the electrochemical system confirms the preferential attack on secondary carbon atoms, which we have seen during extensive studies of oxidation.

The present position for the theory of Gif chemistry is summarized in Scheme 4.

It is now clear that two intermediates can be discerned in Gif chemistry, **A** and **B**. **B** has been thoroughly characterized as the hydroperoxide that is the precursor of the ketone and of the alcohol. There is evidence (trimethyl phosphite effect) that the hydroperoxide is formed *via* a form bound to iron. Intermediate **A** is not a carbon radical since it does not react with pyridine even when all the oxygen is removed by a vacuum. Its reactivity towards bromotrichloromethane is very different from standard radical bromination. The postulated Fe—C bond is still the best hypothesis for **A**.

It is established that the activation of the iron does lead to an attack on the hydrocarbon and that oxygen

Scheme 3

Gif oxidation in the Fe^{III}—H_2O_2 system

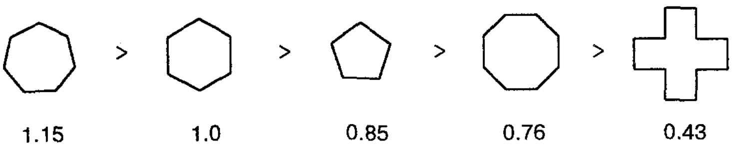
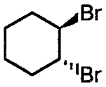
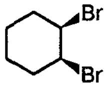
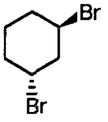
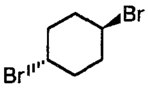
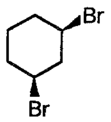
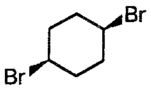


Table 3. Comparison of the distribution (%) of dibromocyclohexanes for a radical chain bromination and for a Fe^{III}—PA—H_2O_2 bromination reaction

Entry						
1[a]	94.0	3.5[b]	0.9	0.5	0.5	0.5
2[c]	7.7	—[d]	1.9	45.2	27.9	17.3
3[e]	41.0	14.0	0.8	21.0	16.0	7.2
4[f]	33.0	25.0	7.0	15.0	13.0	7.0

[a] Values for radical chain bromination. The conversion was 20 %. [b] 1,1-Dibromocyclohexane and *cis*-1,2-dibromocyclohexane could not be distinguished. [c] Values obtained for bromination with cyclohexyl bromide in the Fe^{III}—PA—H_2O_2 system. [d] Not detected. [e] A mixture of cyclohexyl bromide (1.0 mmol) and $CBrCl_3$ (4.0 mmol) was irradiated in a photoreactor with four 3000 Å light tubes under Ar at 35—38 °C for 22 h. [f] Radical reaction initiated by $(PhCOO)_2$ in pyridine in the presence of AcOH.

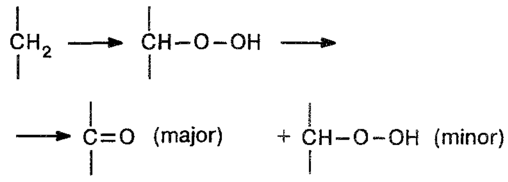
Table 4. The yields in the chemical and electrochemical oxidation of hydrocarbons

Hydrocarbon	Electronic yield (%)	
	Chemical	Electrochemical
Methylcyclopentane	3.6	20
cis-Decaline	34	50
trans-Decaline	16	42
Adamantane	3	12

from gaseous oxygen is introduced in a second step. This contrasts to the theory of P_{450} oxidation, where the activation of the iron leads to attack on the hydrocarbon and then to hydroxylation. Recent work in our laboratory has confirmed this theory experimentally.

Use of *t*-butyl hydroperoxide (TBHP)

The use of TBHP introduces a new dimension to Gif chemistry. As with Fe^{III}—H_2O_2, the addition of picolinic acid (PA) greatly speeds up the reaction to give mainly ketone. In general, the TBHP reactions are slower than their superoxide or hydrogen peroxide congeners already discussed. Whilst the TBHP is essential for the activation of the Fe^{III}, the products of the reaction are the corresponding hydroperoxide formed, as with the H_2O_2 chemistry, from oxygen. Using cyclooctane at room temperature, it was possible to isolate and completely characterize the intermediate cyclooctyl hydroperoxide. Using labeled $^{18}O_2$, this hydroperoxide was analyzed as its trimethylsilyl derivative by mass spectrometry. The ratio between $C_{18}H_{15}{}^{16}O—{}^{16}O—SiMe_3$ and $C_8H_{15}{}^{18}O—{}^{18}O—SiMe_3$ was about 1 : 4, showing that some of the oxygen came from the slow decomposition of TBHP to give oxygen induced by Fe^{III} (blank experiments). Thus, the pathway for TBHP is exactly the same as for Fe^{II} + superoxide or Fe^{III} + H_2O_2, *viz.*:



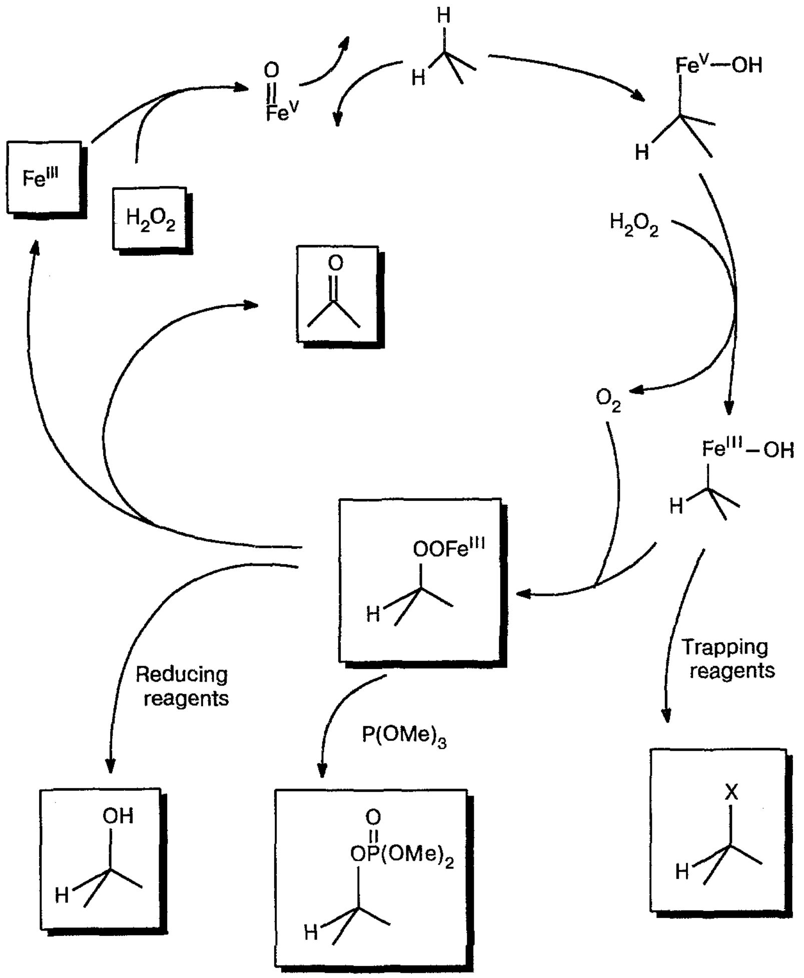
The same reaction pathway was demonstrated for the solvent acetonitrile, although here the alcohol is the main product.[8—11]

With TBHP, it is easy to remove the oxygen as it is formed by passing a slow current of argon. The main products formed were cyclooctene (minor) and cyclooctyl *tert*-butyl mixed peroxide (major). We consider that these products arise from the postulated intermediate containing a Fe^{V}—C bond by 1,2-elimination to give cyclooctene and Fe^{III}, or by ligand coupling of bound TBHP to give the mixed peroxide and Fe^{III}.

In addition to the relatively slow rate, reactions of TBHP exhibit the kinetic isotope effect, which is about 8±0.3 for cyclohexane with respect to perdeuterocyclohexane at room temperature. This value differs markedly from the corresponding value for H_2O_2 (2.2±0.1). Also, the selectivity for adamantane oxidation is different, having C^2/C^3 about 0.5.

A study of the oxidation of benzylic methylene groups using TBHP has shown that two mechanisms are available for the formation of ketones.[12] One is oxygen dependent, the other not. The first is analogous to the formation of cyclooctanone from cyclooctane. The second involves the mixed peroxide, analogous to the conversion of cyclooctane into mixed peroxide as described above. The cyclooctyl mixed peroxide is stable under the

Scheme 4



reaction conditions, but the corresponding benzylic mixed peroxides readily decompose into ketones.

When saturated hydrocarbons are oxidized with $Fe^{III}—H_2O_2$ or $Fe^{III}—PA—H_2O_2$ in the presence of chloride or azide ions, the corresponding chlorides or azides are not observed even *in vacuo*. However in TBHP oxidations, the use of $FeCl_3$ and, in particular, the addition of chloride anion gave chlorinated derivative in up to quantitative yield with respect to TBHP. Azide, thiocyanate, and other anions also reacted smoothly to yield the corresponding products.

We had interpreted these anionic coupling reactions as ligand coupling on an Fe^V species to which both a carbon and a (say) chloride are bonded.[10,11] This would furnish the observed chloride and Fe^{III}.

Minisci and Fontana[13] have recently offered an alternative explanation in which an Fe^{II} species (of undefined origin) reacts with TBPH in the Fenton manner to generate a *tert*-butoxide radical, which then reacts with the hydrocarbon to make a carbon radical, which then reacts with the anion attached to Fe^{III} and so makes the corresponding organic derivative and reforms Fe^{II}. In any case, we do have a very efficient method for turning saturated hydrocarbons into their monochloro derivatives.[14]

The formation of the dibromides on bromination of cyclohexyl dibromide is a valuable indicator of mechanism (see above). Bromination using bromide ion and TBHP gave, as sole product, the *trans*-1,2-dibromide, which hence is formed by a radical mechanism. However, bromination with $BrCCl_3$ gave a different pattern with little formation of the *trans*-1,2-dibromide, and must have a non-radical mechanism.

Prof. D. T. Sawyer and his colleagues have made important contributions to Gif chemistry. In addition to optimization studies, they have confirmed that the $Fe^{III}—H_2O_2$ system produces ketones selectively.[15—18]

Prof. U. Schuchardt and his colleagues[19,20] have made a thorough study of the conversion of cyclohexane to cyclohexanone under various Gif systems. The reaction can be optimized to an excellent level of efficiency. We also note the related work by Prof. Patin.[21,22]

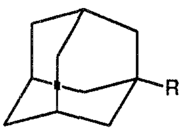
The Fe^{II}—Fe^{IV} manifold

As already alluded to, chlorides and bromides can be formed by CCl_4 and $BrCCl_3$ trapping, respectively, in the Fe^{III}—H_2O_2 system, but are never seen by a reaction with chloride or bromide anions.[5] Formation of chloride is possible however if PPh_3 is added to a Fe^{III}—H_2O_2 system containing chloride ion.[23] In contrast, chlorides are readily and efficiently formed[10,24] by Fe^{III}—*tert*-butyl hydroperoxide (TBHP) oxidation of saturated hydrocarbons at 60 °C (half-life ≈ 110 min) when chloride ion is present. Likewise azo compounds, thiocyanates, cyano derivatives, and even nitro compounds (from nitrite anion) are easily prepared.[11] We found finally that Fe^{II}—H_2O_2 is at the origin of chloride formation in the aforementioned systems. Hydroxyl radicals are not involved (traditional Fenton chemistry) while *tert*-butoxy radicals are at least in part responsible for hydrocarbon activation with TBHP in the presence of Fe^{II}.

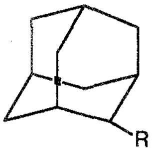
The Fe^{II}—Fe^{IV} and Fe^{III}—Fe^{V} manifolds

During recent systematic studies of the chloride formation in the Fe^{III}—H_2O_2—PPh_3 system we had occasion to add ferrous chloride. This resulted in the immediate formation of large amounts of alkyl chloride. Thus, we have suggested that triphenylphosphine reduces a Fe^{III} complex to Fe^{II} and the latter valent state of iron is responsible for the formation of chloride. That such a reduction is possible was confirmed by titration experiments, which showed that Fe^{III} μ-oxo dimers (believed to be the initial species formed in solution) are slowly transformed to Fe^{II} and triphenylphosphine oxide. With this result in hand we then turned our attention to the Fe^{II}—Fe^{IV} manifold. There were also some helpful comments from Prof. F. Minisci (Milan) (*vide supra*).

Table 5 shows the reactivity of adamantane towards the Fe^{II}—H_2O_2 and Fe^{II}—TBHP systems. Addition of chloride ions (Entries *2* and *4*) to the Fe^{II}—H_2O_2 system not only significantly increases the amount of reaction but also results in a dramatic increase in the C^2/C^3 ratio. The activation of adamantane is thus catalyst dependent, *i.e.*, it cannot be due to the formation of hydroxyl radicals (Fenton chemistry) as in this case, the C^2/C^3 ratio would remain constant. Support for carbon radicals in the Fe^{II} system came from experiments similar to those in Table 5. When $Fe^{II}(ClO_4)_2$ and cyclohexane (40 mmol) were used, 1.07 mmol of chloride was formed. When 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) was added, chloride formation was suppressed completely in favor of formation of 1.06 mmol of cyclohexyl TEMPO adduct. This suggests that the alkyl chloride is not formed *via* ligand coupling. Furthermore, the distribution of products (**1—6**) given in Table 5 is indicative of carbon radical chemistry. Since the tertiary adamantyl radical is highly reactive, (it is pyramidal, *i.e.*, "primary-like")[25] it reacts preferentially with the solvent (protonated pyridine) while the secondary adamantyl radical is of greater stability, (planar)[25] and reacts with the Fe^{III}—Cl species to produce Fe^{II} and alkyl chloride. Such coupling is of course known.[26] For Entries *2* and *4* the initial process must be Fe^{IV} oxenoid insertion followed by iron—carbon bond radical fragmentation.



1—3



4—6

R = 2-pyridyl (**1**, **4**); 4-pyridyl (**2**, **5**); Cl (**3**, **6**)

Table 5. The reactivity and selectivity of adamantane based on the Fe^{II}—H_2O_2 and Fe^{II}—TBHP systems[a]

Entry	System[b]	Products /mmol	Yield /mmol	C^2/C^3 [c]
1	*A*	**1** (0.06), **2** (0.05), **4** (0.02)	0.13	0.18
2	*A* + + LiCl (9 mmol)	**1** (0.10), **2** (0.04), **3** (0.05), **6** (0.20)	0.39	1.05
3[d]	*A* + + PA (6 mmol)	**1** (0.06), **2** (0.04), **4** (0.03)	0.13	0.30
4	*A* + + LiCl (9 mmol)+ + PA (6 mmol)	**1** (0.08), **2** (0.03), **3** (0.01), **6** (0.17)	0.29	1.42
5	*B*	**1** (0.57), **2** (0.18), **4** (0.15), **5** (0.04)	0.94	0.25
6	*B* + + LiCl (9 mmol)	**1** (0.42), **2** (0.13), **3** (0.22), **4** (0.01), **5** (0.01), **6** (0.36)	1.15	0.49
7[d]	*B* + + PA (6 mmol)	**1** (0.43), **2** (0.11), **4** (0.11), **5** (0.02)	0.67	0.24
8	*B* + + LiCl (9 mmol)+ + PA (6 mmol)	**1** (0.43), **2** (0.15), **3** (0.05), **4** (0.02), **5** (0.01), **6** (0.32)	0.98	0.55
9	*C*	**1** (1.14), **2** (0.62), **4** (0.38), **5** (0.11)	2.25	0.28

[a] All products were identified by GC (comparison with authentic samples), GC-MS, and NMR. [b] Conditions: *A*. $Fe(ClO_4)_2 \cdot 6\ H_2O$, 3 mmol; adamantane, 10 mmol; H_2O_2 (30 %), 3 mmol; pyridine/AcOH (10 : 1), 33 mL; 25 °C under argon for 3 h. *B*. As in *A*, but TBHP (3 mmol) was employed instead of H_2O_2. *C*. Adamantane, 10 mmol; di-*tert*-butyl peroxalate, 10 mmol; pyridine, 33 mL, 40 °C under argon for 3 h, see text. [c] The C^2/C^3 ratio is defined as the total secondary products divided by total tertiary products. [d] PA refers to picolinic acid.

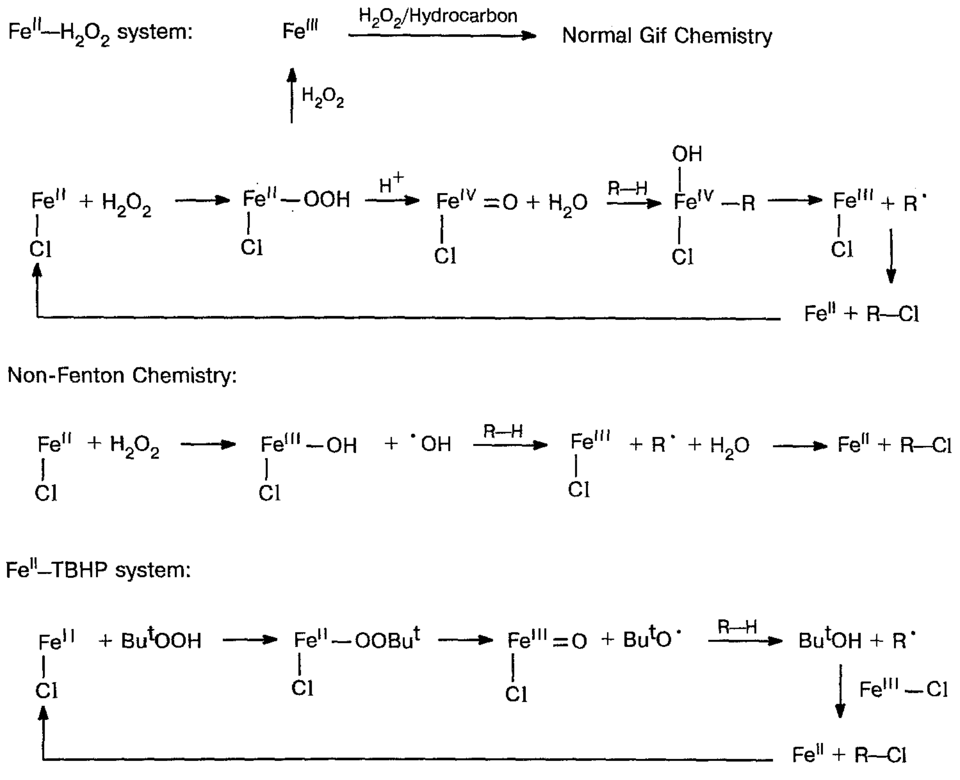
Additional evidence indicating that the activation process is not due to formation of hydroxyl radicals came when excess benzene was added to the reaction mixture. No phenol was produced. Likewise, functionalization of toluene gave benzyl chloride and benzyl alcohol (and its acetate), and no cresols. Also the formation of highly reactive hydroxyl radicals in traditional Fenton chemistry is reflected in $k_H/k_D = 1.0$ (see Ref. 27). The $Fe^{II}—H_2O_2$ system described here is very fast ($t_{1/2}$ <<< 30 s) and has $k_H/k_D = 2.1$. The latter is in agreement with the assumption that the insertion of an Fe^{IV} oxenoid species (as in related Gif systems[28]) precedes the radical formation. Recent literature supports this conclusion.[29]

The Fe^{II}—TBHP system has completely different characteristics. (a) The reaction is slower ($t_{1/2} \approx 3$ min at −20 °C); (b) $k_H/k_D = 8.0$; (c) the yield of products in this system is higher (Entries *5—8*), while the C^2/C^3 ratio is lower (0.24—0.55). Although in this case, the formation of alkyl radicals could not be confirmed by trapping with TEMPO, (Fe^{II} converts TEMPO to the parent hydroxylamine on the Fe^{II}—TBHP time scale), the product distributions shown in Table 5 are again indicative of the intermediacy of secondary and tertiary adamantyl radicals.[25] When *tert*-butoxy radicals were generated at 40 °C in pyridine by decomposition of preformed di-*tert*-butyl peroxalate[30] under argon in the presence of adamantane, all of the adamantyl radicals were captured by pyridine with a C^2/C^3 selectivity of 0.28 (Entry *9*). The same ratio was seen in the presence of oxygen.

The species responsible for alkane activation in the Fe^{II}—TBHP chlorination system was further identified by evaluating the relative reactivities of the primary, secondary, and tertiary C—H bonds in this system by employing equal amounts of cyclohexane and 2,3-dimethylbutane at 0 °C. After statistical correction, the relative reactivities of the primary, secondary, and tertiary CH bonds were found to be: 0.03, 1.0, and 2.9, respectively, in close agreement with those determined for genuine *tert*-butoxy radicals, *i.e.*, 0.1 : 1.0 : 4.4 at 40 °C.[31] Our results along with those outlined by Minisci[13,14] clearly suggest that the activation of hydrocarbons by the Fe^{II}—TBHP system is a result of efficient formation of *tert*-butoxy radicals. The formation of chloride in the Fe^{III}—TBHP system can therefore be rationalized as resulting from the Fe^{II}—TBHP manifold. It was previously determined that the C^2/C^3 adamantane ratio in the Fe^{III} experiments was 0.55[10] and k_H/k_D was 8.0. Again these criteria are identical with the Fe^{II}—TBHP experiments described herein. It is possible that the Fe^{II}—TBHP cycle is initiated by the reduction of Fe^{III} to Fe^{II} at 60 °C. This is, however, a minor reaction because of the slow rate of chloride formation.

The difference in chemical behavior between the Fe^{II} and $Fe^{III}—H_2O_2$ systems is highlighted by the

Scheme 5



following experiment. When cyclohexane and $Fe^{II}(ClO_4)_2$ were treated with a 10-fold excess (with respect to Fe^{II}) of H_2O_2 (3 mmol every 15 min at 0 °C) in the presence of excess chloride ion in a similar way to the experiments described in Table 5, facile chloride formation was observed only while the system contained Fe^{II} (titration).[32] However as soon as all the Fe^{II} had been oxidized to Fe^{III} (2 additions of H_2O_2), addition of further aliquots of H_2O_2 resulted in the relatively slow formation of ketone with very little additional chloride. The mechanism therefore changed from a radical mechanism (in the presence of Fe^{II}) to one involving the Fe^{III}—Fe^{V} non-radical manifold. Comprehensive mechanistic details for the Fe^{II}—H_2O_2 system have revealed further that two catalytic cycles are operative. The first cycle produces chloride *via* the reaction of an Fe^{IV} oxenoid with the hydrocarbon followed by subsequent reaction of the alkyl radical with the liganded chloride on Fe^{III} to reform Fe^{II}. The stoichiometry of this cycle is 1 : 1 : 1 with respect to Fe^{II}, H_2O_2, and the chloride formed. Slow addition of H_2O_2 therefore affords quantitatively alkyl chloride and Fe^{II}. The fact that alkyl chloride can be obtained in quantitative efficiency with respect to H_2O_2 employed clearly rules out the possibility that hydroxyl radicals are involved in the activation process. The competing cycle results from the further reaction of Fe^{IV} oxenoid with H_2O_2 to quantitatively produce Fe^{III}. Further addition of H_2O_2 therefore leads to Gif oxidation chemistry with no chloride formation. From the above results we conclude that hydrocarbon activation and alkyl chloride formation in the Fe^{II}—H_2O_2 and Fe^{II}—TBHP systems occur according to the following mechanism (Scheme 5).

Finally, the addition of thiocyanate or azide ions to the Fe^{II}—H_2O_2 or Fe^{II}—TBHP systems also produced substantial quantities of monosubstituted derivatives that are apparently formed in a similar manner. Such behavior is of course in sharp contrast with the traditional thinking for Fenton chemistry, *i.e.*, that the hydrocarbon is activated by hydroxyl radical abstraction. We consider that the results now reported are a proof that Gif Fe^{III}—H_2O_2 chemistry is not radical chemistry.

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References

1. D. H. R. Barton, M. J. Gastiger, and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 1983, 41.
2. D. H. R. Barton, F. Halley, N. Ozbalik, M. Schmitt, E. Young, and G. Balavoine, *J. Am. Chem. Soc.*, 1989, **111**, 7144.
3. D. H. R. Barton, S. D. Bévière, and D. Doller, *Tetrahedron Lett.*, 1991, **32**, 4671.
4. D. H. R. Barton, S. D. Bévière, W. Chavasiri, E. Csuhai, D. Doller, and W.-G. Liu, *J. Am. Chem. Soc.*, 1992, **114**, 2147.
5. D. H. R. Barton, E. Csuhai, and D. Doller, *Tetrahedron*, 1992, **48**, 9195.
6. D. H. R. Barton, S. D. Bévière, W. Chavasiri, E. Csuhai, and D. Doller, *Tetrahedron*, 1992, **48**, 2895.
7. G. Balavoine, D. H. R. Barton, J. Boivin, A. Gref, P. Le Coupanec, N. Ozbalik, J. A. X. Pestana, and H. Rivière, *Tetrahedron*, 1988, **44**, 1091.
8. D. H. R. Barton, S. D. Bévière, W. Chavasiri, D. Doller, and B. Hu, *Tetrahedron Lett.*, 1992, **33**, 5473.
9. D. H. R. Barton and W. Chavasiri, *Tetrahedron*, 1994, **50**, 19.
10. D. H. R. Barton, S. D. Bévière, and W. Chavasiri, *Tetrahedron*, 1994, **50**, 31.
11. D. H. R. Barton and W. Chavasiri, *Tetrahedron*, 1994, **50**, 47.
12. D. H. R. Barton and T.-L. Wang, *Tetrahedron*, 1994, **50**, 1011.
13. F. Minisci and F. Fontana, *Tetrahedron Lett.*, 1994, **35**, 1427.
14. F. Minisci, F. Fontana, S. Araneo, and F. Recupeno, *Tetrahedron Lett.*, 1994 (in press).
15. C. Sheu, A. Sobkowiak, L. Zhang, N. Ozbalik, D. H. R. Barton, and D. T. Sawyer, *J. Am. Chem. Soc.*, 1989, **111**, 8030.
16. C. Sheu, S. A. Richert, P. Cofré, B. Ross, Jr. A. Sobkowiak, D. T. Sawyer, and J. R. Kanofsky, *J. Am. Chem. Soc.*, 1990, **112**, 1936.
17. C. Sheu and D. T. Sawyer, *J. Am. Chem. Soc.*, 1990, **112**, 8212.
18. H.-C. Tung, C. Kang, and D. T. Sawyer, *J. Am. Chem. Soc.*, 1992, **114**, 3445.
19. U. Schuchardt, W. A. Carvalho, and E. V. Spinacé, *Synlett*, 1993, 713.
20. U. Schuchardt, C. E. Z. Krähembühl, and W. A. Carvalho, *New J. Chem.*, 1991, **15**, 955.
21. T. Briffaud, C. Larpent, and H. Patin, *J. Chem. Soc., Chem. Commun.*, 1990, 1193.
22. C. Larpent and H. Patin, *J. Mol. Catal.*, 1992, **72**, 315.
23. D. H. R. Barton and S. D. Bévière, *Tetrahedron Lett.*, 1993, **34**, 5689.
24. D. H. R. Barton, S. D. Bévière, W. Chavasiri, D. Doller, and B. Hu, *Tetrahedron Lett.*, 1993, **34**, 1871.
25. G. H. Kruppa and J. L. Beauchamp, *J. Am. Chem. Soc.*, 1986, **108**, 2162; J. C. Walton, *Chem. Soc. Rev.*, 1992, 105; I. Tabushi, J. Hamuro, and R. Oda, *J. Am. Chem. Soc.*, 1967, **89**, 7127.
26. J. K. Kochi, *Free Radicals*, John Wiley and Sons, Inc., New York, 1973.
27. D. T. Sawyer, C. Kang, A. Llobet, and C. Redman, *J. Am. Chem. Soc.*, 1993, **115**, 5817 (and references therein).
28. D. H. R. Barton and D. Doller, *Acc. Chem. Res.*, 1992, **25**, 504.
29. I. Yamazaki and L. H. Piette, *J. Am. Chem. Soc.*, 1991, **113**, 7588.
30. P. D. Bartlett, E. P. Benzing, and R. E. Pincock, *J. Am. Chem. Soc.*, 1960, **82**, 1762.
31. W. A. Pryor, D. L. Fuller, and J. P. Stanley, *J. Am. Chem. Soc.*, 1972, **94**, 1632.
32. L. J. Clark, *Anal. Chem.*, 1962, **34**, 348.

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