

Review

# Radical and non-radical chemistry of the Fenton-like systems in the presence of organic substrates

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## Abstract

The review deals with the chemistry concerning the processes of mild and selective oxidation of alkanes and cycloalkanes by using synthetic iron complexes as catalytic systems. These cover a number of coordinated species of iron ions including the so-called Gif systems up to the polydentated Que's models, aimed to mimic or emulate the non-haem enzymatic oxidation of alkanes. Special attention is paid to the mechanisms proposed by the various Authors and to the arguments set out for and against the free-radical interpretation to account for the activation of the C–H bonds.

The schemes of the free-radical chemistry of Fenton reagents in the presence of organic substrates are quoted as a reference basis for the discussion. © 2001 Elsevier Science B.V. All rights reserved.

*Keywords:* C–H bond; Fenton; Gif; Hydroxyl radical; Iron; Ketonization; Ligands; Oxidation

## 1. Introduction

The oxidation of organic substances catalyzed by transition metal ions is a topic of great interest in both industrial and biological chemistry. Iron in the most usual rest states  $\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$  is involved in a number of enzymes which utilize  $\text{O}_2$  or one of its partially reduced forms, e.g.  $\text{H}_2\text{O}_2$ , as the primary oxidant. To be catalytic the interchange between the redox

states of the metal ion must drive the conversion of the substrate by using up the oxidant, the fraction of which that has entered into the products providing a measure of the efficiency of the system. The mechanisms involved may be quite complex and not always clearly established in all their details. A number of specialistic reviews have dealt with the importance of Fenton-like reactions in biological systems [1,2].

The present article intends to review recent work dealing with the functionalization of saturated hydrocarbons by using synthetic iron complexes as non-haem catalytic systems. These include the Gif chemistry developed by Barton et al., the schemes of the oxygenated Fenton chemistry elaborated by Sawyer and coworkers, and the synthetic models investigated by the group of Que.

Since the mechanisms proposed by the Authors cited are circumstantially based on a non-radical

*Abbreviations:* AcOH, acetic acid; Ad, adamantyl; Bu, butyl; DETAPAC, diethylenetriaminopentaacetic acid; DMSO, dimethylsulfoxide; EDTA, ethylenediaminetetraacetic acid; Eq, equivalent; Eq., equation; KIE, kinetic isotope effect; L, ligand; Me, methyl; MMO, methane monooxygenase; PA, picolinic acid (2-pyridinecarboxylic acid); Pic, picolinate anion; Py, pyridine; Py-, pyridyl; TBHP, *tert*-butylhydroperoxide; TPA, Tris(2-pyridinemethyl)amine; Salen, *N,N*-ethylenebis(salicylideneaminato) ligand  
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chemistry, special attention is paid to the arguments set out for and against the more traditional free-radical interpretation. Accordingly, the schemes of the free-radical chemistry of the Fenton reagents are briefly quoted as a reference basis for the discussion.

A critical reexamination of the matter covering most of the work up to 1995 has been published by Perkins [3]. His review, together with Barton's responses [4], is commended for a thorough appraisal of some controversial aspects that have not been dealt with in this paper.

The present review is divided into three main sections, linked by the aim to understand how the chemical potential of the peroxidic O–O bond may be exploited by redox iron couples to introduce oxygen into inert C–H bonds under very mild conditions.

The 1st section, devoted to the Fenton reaction, starts with the known principles that control the role of its components in the activation of easily oxidizable substrates. The next paragraph deals with the functionalization of saturated hydrocarbons and the different approaches to this difficult task. The success obtained with the use of suitable ligands, complexes and solvents unavoidably entails the question of the real oxygenated species responsible for the activation of the C–H bond: O-radicals or iron–oxo intermediates? This matter is dealt with in the third paragraph which introduces to the so-called Gif chemistry.

The 2nd section is mainly concerned with the Fe<sup>III</sup>/ROOH (or H<sub>2</sub>O<sub>2</sub>) systems. Again, the first paragraph gives a short account of the free-radical view on the formation of ketones and alcohols obtained from cycloalkanes. The subsequent paragraphs deal

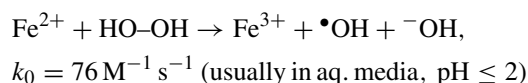
with the following topics:

- Pyridine: a not-inert solvent in free-radical processes, with main reference to the adamantane functionalization.
- Objections to the Barton's interpretation of the Gif chemistry.
- The Gif chemistry according to GoAgg<sup>III</sup> as the most representative system.
- The reappraisal of adamantane functionalization.
- The Sawyer's variant for the mechanisms of the oxygenated Fenton chemistry.
- The mono- and dinuclear Que's catalytic systems.

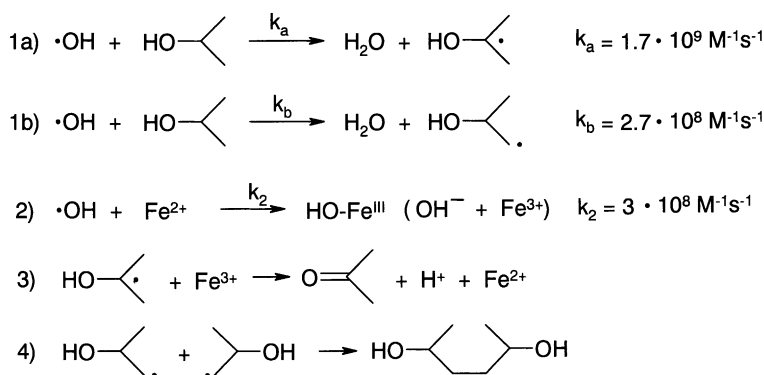
Finally, 3rd section reports on the evidence of the heterolytic cleavage of the peroxidic O–O bond in some important enzymatic systems together with the concluding remarks.

### 1.1. The Fenton reaction

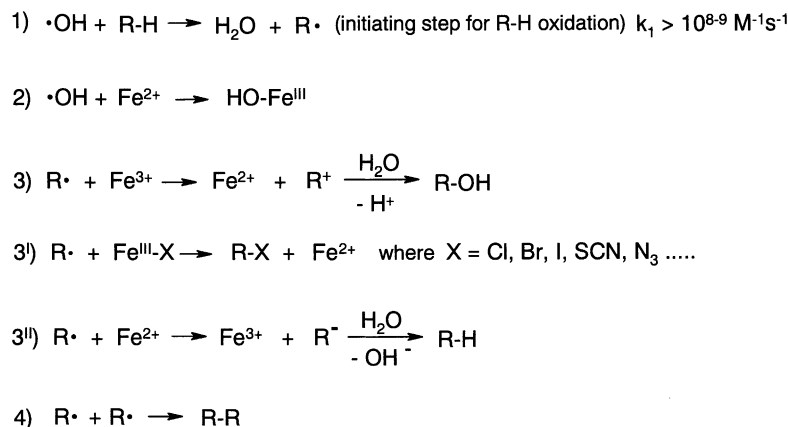
The most reactive of all oxygen-centered radicals is •OH that can be easily produced through a redox process known as the Fenton reaction and generally written as follows:



The rate constants of this and the following steps in Scheme 1 are those quoted by Walling [5,6] at 30°. Some authors prefer the value of 41 M<sup>-1</sup>s<sup>-1</sup> at 20°C for *k*<sub>0</sub>. Both values of *k*<sub>0</sub> originate from a common source and were determined in aqueous perchloric



Scheme 1.



Scheme 2.

acid, at  $[\text{H}_2\text{O}_2] < [\text{Fe}^{2+}]$ , and in the absence of  $\text{O}_2$ , to minimize side reactions [7].

The scope of the Fenton reaction may be extended by using other low-valency, transition-metal ions and/or replacing  $\text{H}_2\text{O}_2$  with  $\text{R-O-OH}$ , which will produce the corresponding alkoxy radical (Fenton-type reaction). A review of the kinetics and mechanisms of the  $\text{H}_2\text{O}_2$  decomposition by complexes of  $\text{Cu}^{\text{I}}$ ,  $\text{Cu}^{\text{II}}$ ,  $\text{Co}^{\text{II}}$ ,  $\text{Fe}^{\text{II}}$ ,  $\text{Fe}^{\text{III}}$ ,  $\text{Mn}^{\text{II}}$ ,  $\text{Mn}^{\text{III}}$ ,  $\text{Ru}^{\text{III}}$ ,  $\text{Ru}^{\text{IV}}$ ,  $\text{V}^{\text{V}}$  and  $\text{Ti}^{\text{IV}}$  has been published very recently [8].

However, in the following, the elements of the original Fenton reaction will be implicitly intended, unless otherwise specified. The roman superscripts are meant to indicate the formal oxidation state of the metal, as distinct from the charge of the ion.

In the presence of an organic substrate, the hydroxyl radical and both iron ions enter into a series of consecutive reactions that lead to its oxidation. An example of the complexity of these reactions may be given when the organic substance is an easily oxidizable substrate, such as *i*-Pr-OH (see Scheme 1, taken from [5,6]). The fast reactions of type 1) produce two different hydroxyalkyl radicals: the tertiary one, which is stabilized by the adjoining alcoholic function, and the primary one in the ratio 7.2:1. The former, however, is rapidly oxidized by  $\text{Fe}^{3+}$  while enough of the latter, even if more unstable, is accumulated to give termination products in step 4).

In more general cases, when the organic substrate is a generic chain-saturated aliphatic compound  $\text{R-H}$ , its fate is mainly governed by the nature of  $\text{R}\cdot$  produced

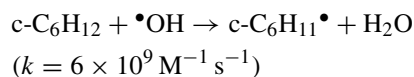
by the fast H-abstraction 1), which competes with step 2) (see Scheme 2).

If  $\text{R}\cdot$  is a tertiary radical, or adjacent to any group capable of stabilizing a positive charge, it allows the starting oxidation state of iron to be re-established by an electron-transfer reaction of type 3), which is followed by the alkyl hydroxylation. Another interesting reaction capable of functionalizing suitable substrates by halides or pseudo-halides has been reported as a ligand-mediated electron transfer, briefly called ligand-transfer, reaction 3<sup>I</sup>) [9]. However, this reaction is not so effective for the direct alkyl hydroxylation ( $\text{X} = \text{OH}, \text{H}_2\text{O}$ ) as it is with cupric ions [6] and in an acid medium is probably negligible. If  $\text{R}\cdot$  is a carbonyl-conjugated radical (or adjacent to any group capable of stabilizing a carbanion), the process is stopped by a one-electron reduction 3<sup>II</sup>). Finally, if  $\text{R}\cdot$  is a primary or secondary alkyl radical, it terminates the chain by the dimerization reaction 4).

On the other hand, in the presence of  $\text{O}_2$ , either deliberately added or produced at relatively high concentrations of  $\text{H}_2\text{O}_2$ , alkyl radicals will afford peroxy radicals, which may produce stable products through various termination reactions. Although rather inert with unactivated C-H bonds, the alkylperoxy radicals may also be reduced, by more than one route, to hydroperoxides and these then to alkoxy radicals, which abstract H from C-H bonds more selectively than  $\cdot\text{OH}$  radicals do (see Fig. 1). If  $\text{R-OH}$  is a secondary alcohol it may be easily oxidized to ketone according to Scheme 1.



for the same kind of reaction with a series of alkanes and cycloalkanes, with no reference to the identity of the products. The values were then quoted, after calibration with the rate  $\bullet\text{OH} + \text{EtOH}$  ( $k = 1.8 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ ), by Buxton et al. [16]. According to these references cyclohexane, a typical hydrocarbon used as model substrate in the functionalization studies, reacts with hydroxyl radicals produced by the Fenton reaction with the following specific rate:



One of the arguments used to raise doubts on the formation of hydroxyl radicals by Fenton's reagents is that, when they are produced by radiolysis, dimers are obtained (bicyclohexyl in the absence of  $\text{O}_2$  and  $\text{c-C}_6\text{H}_{11}\text{-O-O-c-C}_6\text{H}_{11}$  in its presence), while Fenton's reagents yield stable oxygenated products. This argument is too facile. Actually, if not carried out in suitable organic solvents, the simple Fenton reaction is not a very effective one to carry out the oxidation of cyclohexane and the yield of the main products, cyclohexanol and cyclohexanone, is marginal with respect to the amount of  $\text{H}_2\text{O}_2$  used [19]. The main progress in the activation of iron salts for the functionalization of saturated hydrocarbons stems from the introduction of the couple pyridine/acetic acid (Py/AcOH) as solvent. At first, the catalytic system was composed of  $\text{Fe}^{\text{II}}$  or  $\text{Fe}^{\text{III}}$ , which were assumed to act as AcOH-complexes, together with Zn powder as reducing agent and  $\text{O}_2$  as oxidant [20,21]. Later on, the reducing agent was done away with and the typical oxidant was  $\text{H}_2\text{O}_2$  or *tert*-butylhydroperoxide (TBHP), with or without  $\text{O}_2$ . These systems became the object of intense research, in various independent laboratories with the intent to discover their detailed mechanisms. An important result of these efforts was the high efficiency and selectivity with which the methylenic groups ( $>\text{CH}_2$ ) were oxidized to ketones ( $>\text{C}=\text{O}$ ) when the iron was introduced as the  $\text{Fe}^{\text{II}}$ bis(picolinato) complex. For instance, on treatment with a catalytic amount of this complex and a high ratio of  $\text{H}_2\text{O}_2/\text{Fe}^{\text{II}}$  in Py/AcOH (2:1), cyclohexane was converted to cyclohexanone with a high efficiency with respect to the consumed  $\text{H}_2\text{O}_2$  and an even higher selectivity (see Table 1). Under these conditions the ketone was shown not to

Table 1  
Influence of the solvent on the efficiency and selectivity of iron-catalyzed ketonization of cyclohexane by  $\text{H}_2\text{O}_2^{\text{a}}$

Solvent	Efficiency (%)	Products	
		c-C <sub>6</sub> H <sub>10</sub> =O (%)	c-C <sub>6</sub> H <sub>11</sub> -OH (%)
Py	6	93	7
Py/AcOH	72	93	7
MeCN	9	40	60
MeCN/AcOH	11	73	27

<sup>a</sup> Conditions: cyclohexane, 1 M;  $\text{Fe}^{\text{II}}(\text{Pic})_2$ , 3.5 mM;  $\text{H}_2\text{O}_2$ , 56 mM. Reprinted with permission from C. Sheu et al., J. Am. Chem. Soc. 112 (1990) 1936. © 1990 American Chemical Society.

derive from the alcohol as intermediate [22]. Replacement of the Py/AcOH solvent system with acetonitrile was found to reduce the efficiency and eliminate the selectivity for ketone formation. Moreover, the use of equimolar amounts of  $\text{H}_2\text{O}_2$  and  $\text{Fe}^{\text{II}}$ -complex in both solvent types appeared to produce results typical of a Fenton chemistry (see Table 2). Addition of Ph–Se–Se–Ph, as a radical trapping agent, brought down the efficiency and afforded Ph–Se–c-C<sub>6</sub>H<sub>11</sub> in high yield, providing good evidence that, under these conditions, alkyl radicals were formed [23].

Instead, with high ratios  $\text{H}_2\text{O}_2/\text{Fe}^{\text{II}}$ bis(picolinato) in Py/AcOH, the major reaction pathway was postulated to involve a concerted selective process, mediated by an activated iron complex, as responsible for the direct ketonization of the cycloalkane [22].

In addition to the product profile, a criterion utilized to invoke a redox oxidizing species, was the quantification of the kinetic isotopic effect (KIE). Briefly, the latter has been measured as the ratio between the yield of oxidized products arising from  $\text{R}_\text{H}\text{-H}$  and that of the analogous ones generated from perdeuterated  $\text{R}_\text{D}\text{-D}$  when a 1:1 mixture of  $\text{R}_\text{H}\text{-H}$  and  $\text{R}_\text{D}\text{-D}$  was treated with the oxygenated reactive species. The value of KIE is expected to be higher than 1 (2 to 6–7) only if the breakage of the C–H (and C–D) bond occurs in a rate-determining step. Let us consider this type of reaction as it may take place with a generic species  $\bullet\text{X}$

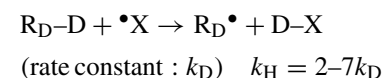
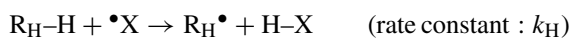


Table 2  
Effect of the Ratio  $\text{Fe}^{\text{II}}/\text{H}_2\text{O}_2$  on the Selectivity of iron-catalyzed oxidation of cyclohexane by  $\text{H}_2\text{O}_2$  in Py/AcOH ( $[\text{c-C}_6\text{H}_{12}] = 1 \text{ M}$ )<sup>a</sup>

Molarity		Efficiency (%)	Products			
$[\text{Fe}(\text{Pic})_2]$ (mM)	$[\text{H}_2\text{O}_2]$ (mM)		c-C <sub>6</sub> H <sub>10</sub> =O	c-C <sub>6</sub> H <sub>11</sub> -OH	c-C <sub>6</sub> H <sub>11</sub> -Py	(c-C <sub>6</sub> H <sub>11</sub> ) <sub>2</sub>
19	19	79	14	0	77	9
9	9	85	34	0	63	3
3.3	56	72	94	6	0	0

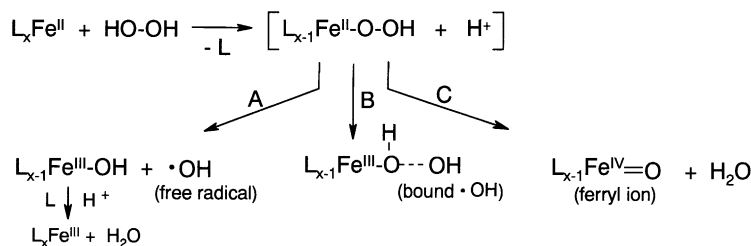
<sup>a</sup> Reprinted with permission from C. Sheu et al., J. Am. Chem. Soc. 111 (1989) 8030. © 1989 American Chemical Society.

If  $\bullet\text{X}$  is a free hydroxyl radical produced in a slow step, the reaction (with RH: cyclohexane) in non-aromatic solvents is so fast as to occur at almost every collision (rate near to the diffusion limit). In this case there is little, if any, chance to observe a difference between the yield of products arising from  $\text{R}_\text{H}\bullet$  and from  $\text{R}_\text{D}\bullet$ , respectively. This statement is correct provided that no further H- (or D-) abstraction is involved in the conversion of the hydrocarbon (see Fig. 1). With this restriction, if in the redox systems KIE ( $\text{R}_\text{H}\text{-H}/\text{R}_\text{D}\text{-D}$ ) is substantially  $> 1$ , one may suspect that not all hydroxyl radicals are produced in the free state and that other more selective species are involved. Experiments of this type, carried out on various substrates showed, in fact, kinetic isotope effects larger than expected for reactions initiated by hydroxyl radicals. Taken together with other arguments, they seemed to reinforce the idea that, in addition to the known complexities of the redox systems, the Fenton reaction must be more complicated than what it would appear to be from the simple equation written at the beginning [15,24]. Before examining how the results with the new catalytic systems have been interpreted, a more general view of the first-formed species originated from the Fenton reaction merits to be considered.

### 1.3. The nature of the transient species

According to some authors and depending on the nature of ligands, solvents and substrate to oxidize, the reaction of  $\text{Fe}^{\text{II}}$  with  $\text{H}_2\text{O}_2$  is supposed to give rise to at least three different reactive species. These are tentatively regarded as having a common origin in the nucleophilic attack of  $\text{HO-OH}$  to  $\text{Fe}^{\text{II}}$  which may evolve along one of the three following paths A, B and C (see Scheme 3, adapted from [25]).

Path A is the one traditionally ascribed to the Fenton reaction. In the presence of a saturated hydrocarbon ( $>\text{CH}_2$ ), it is expected to give products originated from the reaction  $>\text{CH}_2 + \bullet\text{OH} \rightarrow >\text{CH}\bullet + \text{H}_2\text{O}$ , which should occur with a KIE ( $k_{\text{R-H}}/k_{\text{R-D}}$ ) near to unity, similar to those obtained when  $\bullet\text{OH}$  is originated photochemically or by pulse radiolysis. Conditions which closely conform to these results have been reported for  $\text{Fe}^{\text{II}}/\text{H}_2\text{O}_2$  in aqueous solution at pH 2, where cyclohexane is oxidized with a KIE ( $k_{\text{R-H}}/k_{\text{R-D}}$ ) = 1.1–1.2 [18]. In pyridine/AcOH the Fenton system  $\text{Fe}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}/\text{H}_2\text{O}_2$  converted cyclohexane to cyclohexylpyridines or, in the presence of free-radical trapping agents, to the corresponding cyclohexyl derivatives with a KIE ( $k_{\text{R-H}}/k_{\text{R-D}}$ ) =



Scheme 3.

$1.6 \pm 0.1$ . A similar value was obtained when  $\bullet\text{OH}$  was generated by photolysis of *N*-hydroxy-2-thiopyridone in the same solvent. The slightly higher value with respect to the KIE observed in water was attributed to possible complexation of the hydroxyl radical with pyridine [24].

Path B appears to be the most reliable route in aqueous media when  $\text{Fe}^{\text{II}}$  is coordinated by strong chelators, such as EDTA (ethylenediaminetetraacetic acid) and DETAPAC (diethylenetriaminopentaacetic acid). Apparently it is also involved in the substrate oxidation when the ligands to  $\text{Fe}^{\text{II}}$  are phosphate ions (pH 7.4). On the basis of evidence by EPR spin-trapping and competitive kinetics, the extent to which  $\bullet\text{OH}$  is not free, but bound in some complex, has been reported to depend on the ligand, increasing in the order:  $\text{Fe}^{\text{II}}\text{-ADP} < \text{Fe}^{\text{II}}\text{-phosphate} = \text{Fe}^{\text{II}}\text{-EDTA} < \text{Fe}^{\text{II}}\text{-DETAPAC}$  [25].

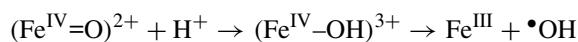
The oxidation products may differ from those observed with radiolytic  $\bullet\text{OH}$  because the reactivity of the complex with the substrate is controlled by different transition states. The process is expected to afford freely diffusing alkyl radicals with a kinetic isotope effect  $> 1$ . Most of the values calculated for the ketonization of cyclohexane in organic solvents showed KIE ranging from 2.1 to 2.5 [26,27].

A route similar to path B (or C) was proposed for the reaction of bis(1,10-phenanthroline)copper(I) ion,  $\text{Cu}(\text{Phen})_2^+$ , with  $\text{H}_2\text{O}_2$ . The observed kinetics of this reaction were interpreted in terms of a mechanism involving the formation of a mixed complex, tentatively formulated either as  $(\text{Phen})\text{Cu}^{\text{II}}(\text{OH}^-, \bullet\text{OH})$  or  $(\text{Phen})\text{Cu}^{\text{III}}(\text{-OH})_2$ . This intermediate appeared to react with added *i*-Pr-OH at a specific rate lower by at least four orders of magnitude than the rate constant of authentic  $\bullet\text{OH}$  [28].

Path C is required to take into account the possible formation of a high-valency iron species, typically pro-

duced by ferro-porphyrins. Circumstantial evidence that it may be present even in non-haem aqueous solutions at pH 7.4 has been reported in the same study cited above [25]. Other authors provided evidence that the reaction of ferrous complexes with  $\text{H}_2\text{O}_2$  at neutral pH produce transient intermediates with the oxidation state  $\text{Fe}^{\text{IV}}$  [10,29].

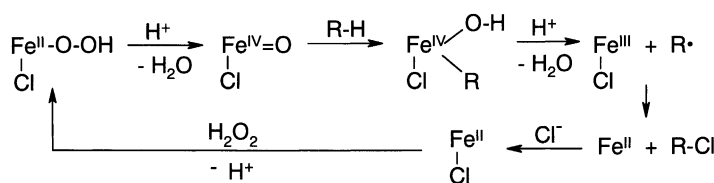
In simple acid aqueous media, the high-valency species, here postulated as ferryl ion, is unstable and would give out the hydroxyl radical easily



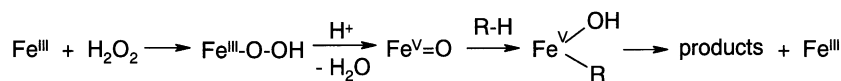
However, with suitable solvents or ligands, the oxidation state  $\text{Fe}^{\text{IV}}$  may be sufficiently stabilized to act as a key oxidizing species. Thus, the intermediacy of a ferryl ion has been suggested to account for the regio- and stereoselective hydroxylation of cyclohexanol by  $\text{Fe}^{\text{II}}/\text{H}_2\text{O}_2$  in MeCN to give the *cis*-1,3-diol. Here coordination by the metal ion of  $\text{Fe}^{\text{IV}}=\text{O}$  with the preexisting OH must assist the directed H-abstraction and the introduction of the second OH according to a rebound mechanism [30]. Incidentally, this study showed that, under the same conditions, the cyclohexane hydroxylation occurred with a kinetic isotope effect of only 1.18. At the same time it pointed out the dramatic difference in the nature of Fenton's reagents as a function of the solvent.

In the oxidation of cycloalkanes with  $\text{Fe}^{\text{II}}/\text{H}_2\text{O}_2$  in the presence of excess of  $\text{Cl}^-$  and with Py/AcOH as solvent, the ferryl ion has been proposed as the key intermediate to account for the evident formation of cycloalkyl radicals while the participation of hydroxyl radicals was excluded. The following scheme was formulated [31–33] (see Scheme 4).

With other ligands of  $\text{Fe}^{\text{II}}$  [for instance  $\text{Fe}^{\text{II}}(\text{OPPh}_3)_4$ ]  $\text{H}_2\text{O}_2$  in MeCN produces substantial amounts of cyclohexanol from *c*- $\text{C}_6\text{H}_{12}$  according to

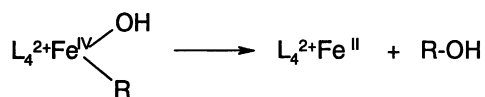


Scheme 4.



Scheme 5.

a mechanism postulated as a direct elimination from the intermediate  $\text{Fe}^{\text{IV}}$ -complex [26].



As anticipated above, interesting applications of the redox systems  $\text{Fe}^{2+}/\text{Fe}^{3+}/\text{H}_2\text{O}_2$  (and other metal ions/oxidants) have been elaborated for the oxidation of saturated hydrocarbons in solvents of very low acidity, such as pyridine/acetic acid, where the hydrocarbon is functionalized by a selective oxidation of a methylene group to ketone according to schemes that simulate the catalysis of the haemoporphyrins. The chemistry of these systems has been titled “Gif chemistry” as it was studied and first developed at Gif sur Ivette by Barton and his co-workers [34].

Most of his catalytic systems start with  $\text{Fe}^{\text{III}}$  and his main assumption is that in these cases the reaction follows a scheme parallel to that written above for  $\text{Fe}^{\text{II}}$  to give a perferryl ion, which is reminiscent of the species active in cytochrome P-450 (Scheme 5).

## 2. The systems $\text{Fe}^{\text{III}}/\text{ROOH}$ (or $\text{H}_2\text{O}_2$ )

According to Barton’s statement and supposing to start with a ferrous salt in Py/AcOH and in the presence of picolinic acid (PA), as soon as all  $\text{Fe}^{\text{II}}$  has been oxidized to  $\text{Fe}^{\text{III}}$ , the reaction halts the C-free-radical mechanism of Scheme 4 in virtue of the hypothetical appearance of oxenoid species, such as  $(\text{Pic})_2\text{Fe}^{\text{III}}\text{-O-O-Fe}^{\text{V}}\text{(=O)(Pic)}_2$ , capable of directly inserting the O atom in C–H bonds (Pic: picolinate anion) (see Fig. 2) [32].

Although very well argued, the non-radical interpretation of the Gif systems has not been unanimously accepted and various papers have been published to question the need of calling into play oxenoid intermediates and to show how the results can be explained by the free-radical redox chains [35,36]. A critical

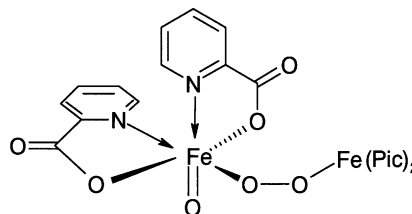


Fig. 2. The species regarded as capable of oxidizing  $>\text{CH}_2$  to  $>\text{C=O}$ .

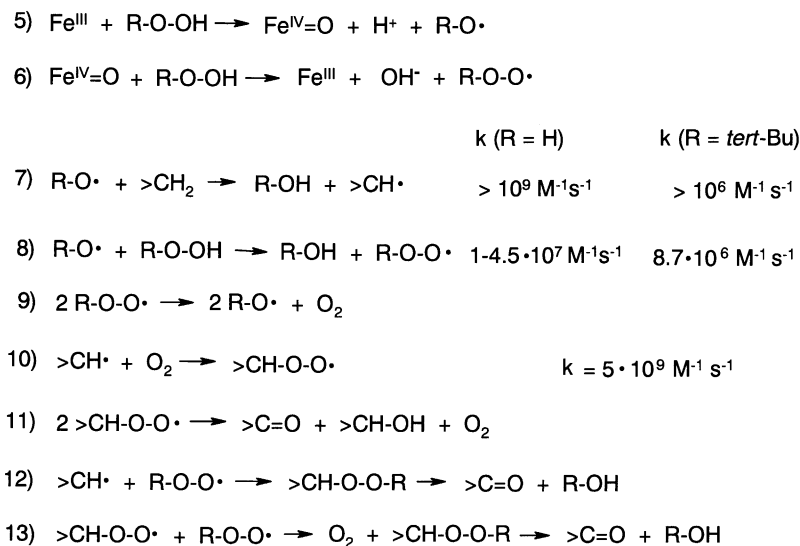
reexamination of the matter covering all work up to 1995 has been published by Perkins [3].

To understand the main reasons of the contrast it is necessary to enter into further details starting by examining how the “normal” free radical model conceives the impact of a cycloalkane ( $\text{c-C}_n\text{H}_{2n}$ ) with the redox system initiated by  $\text{Fe}^{\text{III}}$  in contact with a hydroperoxide  $\text{R-O-OH}$ . The generic form of the latter covers both  $\text{H}_2\text{O}_2$  ( $\text{R} = \text{H}$ ) and the various alkylhydroperoxides which are often used as primary oxidants.

### 2.1. The free radical view

According to the scheme adopted by Snelgrove et al. [37] for the conditions of the Gif system based on  $\text{Fe}^{\text{III}}/\text{ROOH}$ ,  $\text{Fe}^{\text{III}}$  is supposed to slowly decompose the hydroperoxide to produce “oxyl” as well as “peroxyl” radicals in a redox cycle (see Scheme 6) by reactions 5 and 6). These equations account for an alternative to the original Haber–Weiss cycle with  $\text{R-O-O}^\bullet + \text{Fe}^{\text{II}}$  directly produced by  $\text{Fe}^{\text{III}} + \text{R-O-OH}$ , and  $\text{RO}^\bullet$  resulting from a Fenton-type reaction [5]. While the “oxyl” radicals initiate the chain by H-abstraction with the hydrocarbon (reaction 7), the “peroxyl” radicals produce  $\text{O}_2$  (reaction 9), which adds to the alkyl radicals with a diffusion-controlled rate (reaction 10). This reaction is important because most of the oxygenated products of the hydrocarbon are expected to derive from these new alkylhydroperoxyl radicals, mainly by termination-disproportionation reactions (reactions 11–13).





Scheme 6.

According to Scheme 6, the yield of the oxygenated products (ketone + alcohol) must depend on whether the reaction is carried out in the presence of  $\text{O}_2$  or under Ar purge to sweep out  $\text{O}_2$  as soon as it is formed. Under the last-mentioned conditions other reactions will prevail. As for the role of pyridine in the efficiency of Gif chemistry, Minisci et al. suggested the following favorable effects it could exert in some steps of the oxidation of cycloalkanes: (a) an easier oxidation of  $\text{Fe}^{\text{III}}$ - to  $\text{Fe}^{\text{IV}}$ -complexes (Eq. (5)), promoted by an increased electron availability through coordination with Py; (b) a lowering of the rate of H abstraction from the starting hydroperoxide (Eq. 8), due to its strong hydrogen bonds with Py; (c) a facilitated oxidation of alkyl radicals by  $\text{Fe}^{\text{IV}}$  with ROO as a ligand (first part of Eq. (12), visualised as a sort of ligand transfer which regenerates  $\text{Fe}^{\text{III}}$ ); (d) a Py-catalyzed decomposition of secondary hydroperoxides, or mixed peroxides, to ketones (second part of Eq. (12)) [9,36,38].

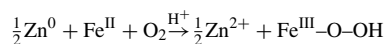
## 2.2. Pyridine, a not-inert solvent

It must be remarked that, in addition to its catalytic role, pyridine, under free-radical conditions, is not inert. As a free base it reacts rapidly with  $\cdot\text{OH}$  to give hydroxylated pyridines and bipyridyls. For a better insight see refer. [3]. Protonated pyridine

undergoes fast reactions with alkyl radicals to give 2- and 4-(alkyl)-Py [39–41] (Fig. 3).

A peculiar difference in the rate of this alkylation has been detected recently by the Minisci's group between *tert*- and *sec*-adamantyl radicals, the former resulting more reactive by two orders of magnitude than the latter [41]. The result was ascribed to the enhanced nucleophilic character of 1-Ad $\cdot$  with a lower reversibility of its addition to pyridinium than that of 2-Ad $\cdot$ . The rearomatization of the radical adduct may occur either by electron transfer ( $-\text{H}^+$ ) or by H-transfer and so the overall rate largely depends on the oxidation system. These findings may have important implications when adamantane is subjected to oxidation under Gif conditions. In their early Gif experiments carried out with  $\text{Zn}^0/\text{Fe}^{\text{II}}/\text{O}_2$ <sup>1</sup> as catalyst and adamantane as substrate, Barton et al. had

<sup>1</sup> This system, called Gif<sup>IV</sup>, was based on Zn dust, as a source of electrons, in contact with a solution of  $\text{Fe}^{2+}$  in Py. When AcOH was added to dissolve the Zn, the following reaction took place, in the presence of air, making the system catalytic in iron:



The system was, therefore, equivalent to other Gif systems (as for example GoAgg<sup>II/III</sup>), but avoided the use of  $\text{H}_2\text{O}_2$  which would have been rapidly decomposed by the reducing agents.

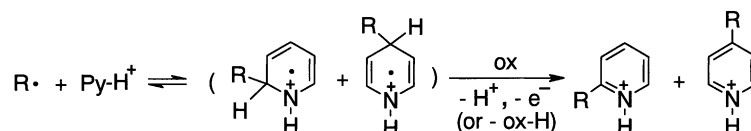


Fig. 3. Alkylation of protonated Py carried out either by an electron-transfer (ox=Fe<sup>III</sup>) or by a H-transfer (ox: oxygenated radical).

observed a much higher yield of adamantan-2-one than of adamantan-1-ol. The result was assumed to imply that the secondary C–H bonds were, per H, more reactive than the tertiary ones [20]. Subsequently, under conditions of low oxygen pressure (4% O<sub>2</sub> in N<sub>2</sub>), the presence of 2- and 4-(1-adamantyl)pyridines was detected in the products while *sec*-adamantylpyridines were almost absent. This seemed to suggest that only *tert*-adamantyl radicals were produced under Gif conditions. In fact, when the two isomeric adamantyl radicals were generated by photolysis in Py/AcOH and under the same O<sub>2</sub> pressure, both were found to afford oxygenated and pyridine-coupled products in a more equilibrate ratio between them [21]. The Gif results were then interpreted by Barton on the basis of a difference between the 1-Ad–Fe and the 2-Ad–Fe bonds in their strength: the former, presumed to be much weaker, was assumed to undergo spontaneous fragmentation to *tert*-adamantyl radicals while the latter was proposed to induce the functionalization of the secondary position by a non-radical mechanism [21]. Now, in the light of the recent quantification of the peculiar difference between *tert*- and *sec*-adamantyl radicals in their coupling rate with Py–H<sup>+</sup>, the entire matter must be reappraised, as anticipated by Perkins [3]. In fact, if a traditional free-radical mechanism is assumed to be operating under Gif conditions, the *sec*-adamantyl radicals might well be much more extensively trapped by O<sub>2</sub> than the tertiary ones, which are more efficiently trapped in coupled products with pyridine. The mechanism of adamantane oxidation will be reexamined in a later paragraph after full aspects of Gif chemistry have been presented.

### 2.3. Objections to the Barton's interpretation of the Gif chemistry

In more general terms, various authors rejected Barton's interpretation for some of the Gif systems on the basis of the following facts and comments:

1. Using H<sub>2</sub><sup>16</sup>O<sub>2</sub>/Fe<sup>III</sup> in Py:AcOH = 10:1 under an atmosphere of <sup>18</sup>O<sub>2</sub>, Knight and Perkins [42] showed that cyclodecane was oxidized to cyclodecanone incorporating ca. 50% <sup>18</sup>O into the product. This finding appeared to be more compatible with a free-radical autooxidation than with the iron–oxo mechanism. At the time of the experiment, the latter was in fact supposed to imply an origin of the ketonic oxygen from H<sub>2</sub>O<sub>2</sub>.
2. Using *tert*-Bu–O–OH (TBHP)/Fe(NO<sub>3</sub>)<sub>3</sub> in Py:AcOH (10:1) at 60° and in the presence of LiCl, Minisci and coworkers reproduced a Barton's experiment in which cyclohexane had been converted to chlorocyclohexane. Barton had interpreted the result as due to an attack of Cl<sup>–</sup> to the Fe<sup>V</sup>–CH< intermediate [43]. But the Minisci's group showed that, when electron-rich alkenes were added to the system, β-chloroalkyl *tert*-butyl ethers were obtained in competition with chlorocyclohexane (Fig. 4). This reaction is known to occur by addition of the alkoxy radical to the alkene, followed by a chloride transfer. So the results provided strong evidence that under these conditions both *tert*-Bu–O• and cyclohexyl radicals were produced [35,38].

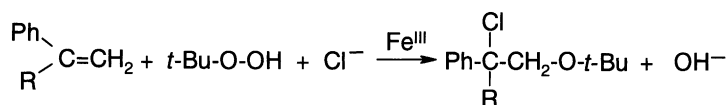


Fig. 4. Oxyalkylation of alkenes by *t*-Bu–O–OH/Fe<sup>III</sup> in the presence of Cl<sup>–</sup>.

3. Using TBHP under Gif conditions ( $\text{Fe}^{\text{III}}:\text{PA} = 1:2$  in  $\text{Py}:\text{AcOH} = 10:1$ ), Snelgrove et al. reproduced the oxidation of cyclooctane obtaining the corresponding ketone, together with minor amounts of the alcohol and small quantities of 2-cyclooctylpyridine. They showed that, when the reaction was repeated under an Ar atmosphere, the coupling products were increased while the yield of the ketone was lowered by 40 %. Replacement of TBHP with other hydroperoxides, such as  $\text{Ar}-\text{CH}_2\text{C}(\text{CH}_3)_2-\text{O}-\text{OH}$ , as mechanistic probes, afforded substantial amounts of oxidation products which could only derive from the  $\beta$ -scission of the alkoxy radicals  $\text{Ar}-\text{CH}_2\text{C}(\text{CH}_3)_2-\text{O}^\bullet$  [37].
4. The use of some hypersensitive cyclopropane probes as substrates under various Gif conditions proved unequivocally the formation of diffusively free radicals [44].

Barton acknowledged the free-radical chemistry of all systems in which TBHP or other tertiary alkyl hydroperoxides were involved, but reaffirmed, till the end of his life, his immutable belief in the non-radical nature of the Gif chemistry. This was then particularly represented by the  $\text{Fe}^{\text{III}}/\text{H}_2\text{O}_2$  systems, where, according to his view, the so-called manifold  $\text{Fe}^{\text{III}}-\text{Fe}^{\text{V}}$  was operating. The most significant of these systems, designated “GoAgg<sup>III</sup>”, will be considered in the next section. It involves a  $\text{Fe}^{\text{III}}$  complex in which two picolinate ligands and one pyridine are bound to each iron center, as deduced from  $^{13}\text{C}$  NMR studies [33].

#### 2.4. The Gif chemistry according to GoAgg<sup>III</sup> ( $\text{Fe}^{\text{III}}/\text{PA}/\text{H}_2\text{O}_2$ in $\text{Py}:\text{AcOH} = 10:1$ )

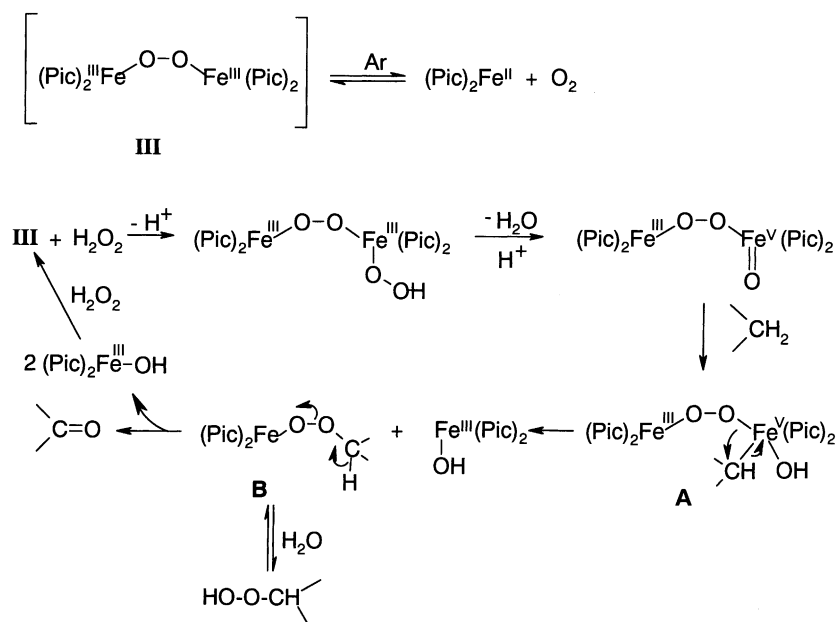
The detailed mechanism of this system may be tentatively summarized on the basis of the following remarks, which have been revised and adjusted in a large number of papers.

Addition of PA (10 mmol) to  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  (5 mmol) in  $\text{Py}/\text{AcOH}$  and cyclohexane was found to induce the formation of a complex which was isolated and characterized by X-ray crystallography as the ionic couple  $[\text{Py}-\text{H} \cdots \text{Py}]^+ [(\text{Pic})_2\text{Fe}^{\text{III}}\text{Cl}_2]^-$  (I). An important step in the rationalization of the Gif chemistry was the use of  $^{13}\text{C}$  NMR spectroscopy to demonstrate the ligand environment of two picolinate anions in the pyridine solution, which was consistent with the

solid state structure of I even when a larger excess of PA was added to the solution. Addition of  $\text{H}_2\text{O}_2$  then instantly produced a transient, purple intermediate, the decay of which was correlated to the ketonization of cycloalkanes. The structure of a cyclic peroxy anion  $[(\text{Pic})_2\text{Fe}^{\text{III}}\text{O}_2]^-$  (II) was proposed for the purple complex, which was found to disappear at a temperature-dependent rate ( $t_{1/2} = 120$  min at  $0^\circ\text{C}$ ;  $t_{1/2} = 5$  min at  $20^\circ\text{C}$ ) [31]. However, when isolated from  $\text{H}_2\text{O}_2$ , the purple complex did not oxidize saturated hydrocarbons. So it was necessary to postulate the conversion to further, hypothetical, iron species that would be responsible for the activation of both the oxygen and the hydrocarbon. In later papers, the purple complex was then replaced by the hypothetical peroxy-dimer species  $[(\text{Pic})_2\text{Fe}^{\text{III}}-\text{O}-\text{O}-\text{Fe}^{\text{III}}(\text{Pic})_2]$  (III) [32]. This suggestion was made on the analogy of the methane monooxygenase (see later on) and was circumstantially supported by the apparent easiness with which it could rationalize all experimental facts.

The dimer III was in fact regarded as the key intermediate that, with a second equivalent of  $\text{H}_2\text{O}_2$ , would give the oxenoid species capable of ketonizing the cycloalkane according to the cyclic sequence depicted in Scheme 7.

To justify the incorporation of O from  $^{18}\text{O}_2$  in the product, the peroxy-dimer III was assumed to exchange with  $\text{O}_2$  in a reversible reaction. This was consistent with the observation that, under a vigorous stream of argon, the functionalization of cyclooctane by  $\text{Fe}^{\text{III}}/\text{PA}/\text{H}_2\text{O}_2$  in pyridine showed a behavior typical of the  $\text{Fe}^{\text{II}}-\text{Fe}^{\text{IV}}$  manifold affording cyclooctylchloride and cyclooctanone. As soon as the Ar stream was replaced by  $\text{O}_2$ , the chlorination was arrested and only the usual ketonization was taking place (see Table 3). Moreover the peculiarity of PA became evident when cyclohexane was functionalized in the presence of trapping reagents, such as  $\text{CBrCl}_3$  or  $\text{Ph}_2\text{S}$ , in pyridine (see Table 4): without PA, only  $\text{O}_2$  was produced in presence of  $\text{CBrCl}_3$  while diphenylsulfoxide was the main product in presence of  $\text{Ph}_2\text{S}$ . When four equivalents of PA were added per mole of  $\text{Fe}^{\text{III}}$ , the results dramatically changed with the formation of cyclohexylbromide (in presence of  $\text{CBrCl}_3$ ) and of cyclohexanone (and virtually no sulfoxide) in presence of  $\text{Ph}_2\text{S}$ . To accommodate these results the peroxy-dimer III was proposed as the



Scheme 7.

Table 3

The importance of O<sub>2</sub> in Gif chemistry for the ketonization of cyclooctane (20 mmol) by H<sub>2</sub>O<sub>2</sub> (4 mmol), catalyzed by FeCl<sub>3</sub>·6H<sub>2</sub>O (1 mmol) + PA (4 mmol) in pyridine<sup>a</sup>

Entry	Conditions	Products	
		c-C <sub>8</sub> H <sub>14</sub> =O (mmol)	c-C <sub>8</sub> H <sub>15</sub> -Cl (mmol)
1	Under constant Ar stream	0.88	1.00
2	Under Ar stream for 2 h, then O <sub>2</sub> stream overnight	0.43, 1.31	0.33, 0.33
3	Under static atmosphere	1.28	0

<sup>a</sup> From D.H.R. Barton et al., J. Chem. Soc. Perkin Trans. 2 (1996) 1031. Reproduced by permission of the Royal Society of Chemistry.

Table 4

Chemioselectivity of the Gif chemistry in presence of the trapping reagents CBrCl<sub>3</sub> and Ph<sub>2</sub>S: the effect of PA in driving the functionalization of c-C<sub>6</sub>H<sub>12</sub> towards the formation of c-C<sub>6</sub>H<sub>11</sub>-Br (in presence of CBrCl<sub>3</sub>) or c-C<sub>6</sub>H<sub>10</sub>=O in presence of Ph<sub>2</sub>S<sup>a</sup>

Entry	Trapping reagent	PA	Products				
			c-C <sub>6</sub> H <sub>11</sub> -Br	c-C <sub>6</sub> H <sub>10</sub> =O	Ph <sub>2</sub> S=O	CO <sub>2</sub>	O <sub>2</sub>
1	CBrCl <sub>3</sub>	Absent	–	–	–	–	1.65
2	CBrCl <sub>3</sub>	Present	1.43	–	–	1.33	–
3	Ph <sub>2</sub> S	Absent	–	0.10	2.05	–	0.71
4	Ph <sub>2</sub> S	Present	–	1.57	0.08	–	0.05

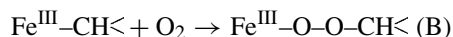
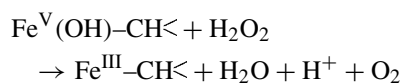
<sup>a</sup> Conditions: c-C<sub>6</sub>H<sub>12</sub>, 20 mmol; H<sub>2</sub>O<sub>2</sub>, 4 mmol; FeCl<sub>3</sub>·6H<sub>2</sub>O, 1 mmol; PA, 4 mmol when applied. From D.H.R. Barton, B. Hu, Pure & Appl. Chem. 69 (1997) 1941. Reproduced by permission of the I.U.P.A.C.

intermediate species trapped by the brominating agent, but unaffected by the sulfide [45].

So,  $\text{H}_2\text{O}_2$  would play, according to this scheme, two different roles: the first is in the formation of the oxenoid species  $\text{Fe}^{\text{V}}\text{-O}$  capable of activating the hydrocarbon to give intermediate A; the second one is in the usual production of  $\text{O}_2$  induced by  $\text{Fe}^{\text{III}}$ . After exchange with air, the oxygen atoms re-enter in the successive step to give intermediate B.

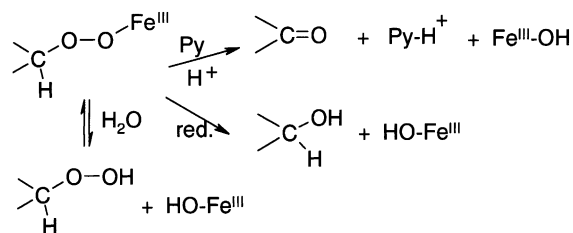
The distinction between A and B was imposed by the peculiar finding that, when  $\text{Fe}^{\text{III}}/\text{H}_2\text{O}_2$  was replaced by the analogous system  $\text{Fe}^{\text{II}}/\text{Zn}^0/\text{O}_2$ , suitable reducing agents, such as  $\text{Ph-Se-Se-Ph}$  or  $\text{Ph-S-S-Ph}$ , were able to partly trap the secondary alkyl moiety of the cycloalkane affording  $>\text{CH-Se-Ph}$  or  $>\text{CH-S-Ph}$ , respectively. In principle, this could have been compatible with a C-centered radical. However, the activated species of the hydrocarbon did not respond as expected to an excess of strong, free-radical quenchers, such as  $\text{Ph-SeH}$  or  $\text{Ph-SH}$ , so ruling out the possibility that A was a C-centered secondary radical. Exceptions may admittedly occur when the alkyl moiety is a hypersensitive cyclopropanemethyl group, or a tertiary adamantyl group, which can leave the iron complex A as a free radical. Similar experiments in the presence of  $\text{P}(\text{OMe})_3$  ruled out the alternative that A was an O-centered radical. Accordingly, a  $\sigma\text{-C-iron}$  bond was proposed for the intermediate A [46].

At first, the fact that the oxygen in the products was not directly originated from  $\text{H}_2\text{O}_2$  had been explained by assuming for the intermediate A a mononuclear carbon- $\text{Fe}^{\text{V}}\text{-OH}$  species, able to undergo a two-electron reduction by  $\text{H}_2\text{O}_2$ , followed by insertion of  $\text{O}_2$  into the resulting carbon- $\text{Fe}^{\text{III}}$  bond:



Further studies brought to adopt as more consonant with the experimental facts the dinuclear pathway up to the intermediate A.

The nature of B has been the object of different hypotheses aimed to account also for another significant observation brought to light again by  $^{13}\text{C}$  NMR spectroscopy: in the course of the cyclohexane oxidation reaction, and using oxalic acid to stop it after short times, cyclohexyl hydroperoxide was detected. It rose



Scheme 8.

to a maximum with time, and then slowly disappeared in favor of cyclohexanone and cyclohexanol. Addition of water enhanced the conversion of the substrate to the ketone and the corresponding alcohol lowering the ratio of the former to the latter [46].

According to the final version shown in Scheme 7, intermediate B is seen as the common precursor of both the ketone (main product) and the alcohol (see Scheme 8).

The non-radical nature of the Gif chemistry, at least for the  $\text{GoAgg}^{\text{III}}$  system, was additionally supported by the following observations.

1. The functionalization of hydrocarbons, when carried out under different Gif conditions, e.g.  $\text{Fe}^{\text{II}}/\text{H}_2\text{O}_2$  (Scheme 4) and  $\text{Fe}^{\text{III}}/\text{H}_2\text{O}_2$  (Schemes 5 and 7), showed the same  $\text{KIE}_{(\text{R-H})/(\text{R-D})}$  of 2.2 ( $\pm 0.1$ ) (see Table 5). This suggested that a similar reactive species had to be involved in the cleavage of the C-H bond as a crucial step for both the manifolds. According to the schemes adopted, the cleavage must, in fact, be preliminary to alkyl radical formation, when  $\text{Fe}^{\text{II}}$  is operating, and to a ligand coupling reaction, when starting with  $\text{Fe}^{\text{III}}$ . In any case the hydrocarbon activation could not be ascribed to a H-abstraction by  $\bullet\text{OH}$ , which, when produced photolytically or by radiolysis, gave lower values of KIE [24]. In a more recent paper, evidence was reported that the slow step in ketonization followed the formation of A (see Scheme 7), which was, in fact, easily quenched by addition of  $\text{LiI}$  to give alkyl iodide in competition with the elimination pathway to ketone [47]. While these findings lend support to the existence of A as an intermediate C-iron species, at the same time they appear to weaken the meaning of the kinetic isotope effect.
2. Genuine  $\bullet\text{OH}$ , produced by photolysis of *N*-hydroxy-2-thiopyridone in  $\text{Py}/\text{AcOH}$ , afforded

Table 5

Comparison of the kinetic isotopic effect (KIE) measured for the oxidation of *c*-C<sub>6</sub>H<sub>12</sub>/*c*-C<sub>6</sub>D<sub>12</sub>, catalyzed by Fe<sup>II</sup>- or Fe<sup>III</sup>-complexes + excess H<sub>2</sub>O<sub>2</sub>, with that measured for the Fenton reaction (Fe<sup>II</sup>/H<sub>2</sub>O<sub>2</sub> (1:1) in H<sub>2</sub>O, pH 2)

System	KIE (product)	Reference
Fe <sup>II</sup> (Pic) <sub>2</sub> /H <sub>2</sub> O <sub>2</sub> in Py/AcOH (2:1)	2.5 (Ketone)	[27]
Fe <sup>II</sup> (Pic) <sub>2</sub> /H <sub>2</sub> O <sub>2</sub> , O <sub>2</sub> in Py/AcOH (2:1)	2.1 (Ketone)	[27]
FeCl <sub>3</sub> ·6H <sub>2</sub> O/H <sub>2</sub> O <sub>2</sub> in Py/AcOH (10:1)	2.2 (Ketone)	[24]
FeCl <sub>3</sub> ·6H <sub>2</sub> O + PA/H <sub>2</sub> O <sub>2</sub> in Py/AcOH (10:1)	2.1 (Ketone)	[24]
Fenton	1.1 (Substrate loss)	[18]

2- and 4-hydroxypyridines accompanied by comparable amounts of 2,2'-, 4,4'- and 2,4'-dipyridines. However, in Gif chemistry, under GoAgg<sup>III</sup> conditions and in the absence of the hydrocarbon, quantification of Py-oxidation derivatives showed 3-hydroxy-Py to be the major product (but see also [3]). Moreover, in the presence of cyclohexane, no cyclohexylpyridines were detected when the experiment was run under either argon or oxygen. Coupling products with Py (2- and 4-cyclohexyl-Py) were only detected when the manifold Fe<sup>II</sup>-Fe<sup>IV</sup> was involved [31–33].

- Competitive experiments with various cycloalkanes showed an order of reactivity very different from that expected if a free radical mechanism was at work. For example, a recent paper showed that, when the oxidation of a mixture of cyclohexane and cyclooctane was carried out under free-radical conditions, the reactivity of cyclooctane (normalized per H number) was two to three times greater than that of cyclohexane. The converse occurred when the reaction was carried out under Gif conditions: here cyclooctane was somewhat less reactive than cyclohexane supporting the contention that formation of an iron–carbon bond formation is the crucial step [48].
- When a mixture of cyclohexanol and cyclooctane was oxidized under free-radical conditions (Fe<sup>III</sup>/TBHP) the results (normalized per H number) showed that the alcohol was far more reactive than the alkane. When the experiment was repeated under Gif conditions (Fe<sup>III</sup>/H<sub>2</sub>O<sub>2</sub>/PA) the ratio of reactivity was by far lower. This confirmed previous findings that saturated hydrocarbons could be oxidized under Gif conditions in the presence of alcohols, which underwent no significant oxidation and supported the thesis that •OH was not involved

as the main oxidant [49]. Actually, an evident paradox of the Gif catalytic systems, often cited by Barton, is that saturated hydrocarbons can be oxidized at a faster rate than that of easy-to-oxidize compounds. Reagents, such as H<sub>2</sub>S, Ph<sub>2</sub>S, PPh<sub>3</sub> and P(OMe)<sub>3</sub> in fact do not inhibit the reaction.

- The Cu<sup>I</sup>/H<sub>2</sub>O<sub>2</sub> and Cu<sup>II</sup>/H<sub>2</sub>O<sub>2</sub> systems have also been tested with the use of pyridine and various other ligands for the functionalization of saturated hydrocarbons. Although they shared some features typical of the Gif chemistry, their efficiency was much lower. In most cases, in fact, the generation of O<sub>2</sub> was prevailing over the ketonization [50].

In conclusion, the system GoAgg<sup>III</sup> provides a rapid catalytic functionalization of hydrocarbons with selective oxidation of secondary positions to give ketones as the main products. Both tertiary and primary C–H bonds are oxidized less efficiently. The process apparently does not involve free radicals and the bond formation between O and C is assumed to originate from a C–iron–peroxo intermediate A that undergoes unimolecular elimination to hydroperoxide-precursor B, whose fragmentation finally gives the oxygenated product(s).

### 2.5. The reappraisal of the adamantane functionalization

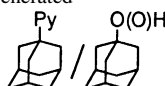
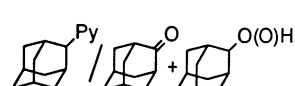
The puzzling point of the Barton's mechanism is the central role ascribed to the transient Fe<sup>V</sup>=O species, the direct evidence of which is lacking. From the other hand, even the traditional free-radical mechanism based on Scheme 6 rests on insufficient experimental evidence to explain the Gif chemistry. The question has been faced out in a most recent study by Kiani et al., who reexamined the oxygenation of

adamantane by  $\text{H}_2\text{O}_2$  in  $\text{Py}/\text{AcOH}$  starting with well-defined iron–picolinate complexes [51]. These included the ferrous compound  $[\text{Fe}^{\text{II}}(\text{Pic})_2(\text{Py})_2]$  and the ferric complexes  $[\text{Fe}^{\text{III}}(\text{Pic})_3] \cdot 0.5 \text{ Py}$ ,  $[\text{Fe}^{\text{III}}_2\text{O}(\text{Pic})_4(\text{Py})_2]$  and  $[\text{Fe}^{\text{III}}_2(\mu\text{-OH})_2(\text{Pic})_4]$ . The catalytic reactions were carried out under  $\text{N}_2$  (or  $\text{Ar}$ ) as well as under various partial pressures of  $\text{O}_2$ . The product profile was found not to change significantly with the initial state of the metal. With both  $\text{Fe}^{\text{II}}$  and  $\text{Fe}^{\text{III}}$  complexes, the ratio between the oxygenated products (adamantan-2-one, adamantan-2-ol as minor product, and adamantan-1-ol) and the coupling products with pyridine was strictly depending on  $\text{O}_2$  pressure, as expected. But, unlike in the Barton's experiments, with most of the iron complexes measurable amounts of *sec*-adamantylpyridines were detected, besides the corresponding tertiary coupled products, both under  $\text{N}_2$  and in the presence of a low pressure of  $\text{O}_2$  (4%  $\text{O}_2$  in  $\text{N}_2$ ). This fact and the ratio of the overall selectivity *tert*/*sec*, which was found to increase from 2.2 to 4.5 with increasing partial pressure of  $\text{O}_2$ , appeared to be consistent with the generation of both tertiary and secondary adamantyl radicals, both being subjected to competition between  $\text{O}_2$  and protonated pyridine as trapping agents. An useful indicator to check the consistency of the free-radical mechanism was the different partition of the two positions of adamantane between coupling products with pyridine and

oxygenated products. Under a partial pressure of 4%  $\text{O}_2$  in  $\text{N}_2$ , this was equal to 2.3 for *tert*( $\text{Ad-OH}/\text{Ad-py}$ ) and 0.09–0.10 for *sec*( $[\text{Ad=O} + \text{Ad-OH}]/\text{Ad-Py}$ ) with both  $\text{Fe}^{\text{II}}$  and  $\text{Fe}^{\text{III}}$  catalytic systems. For the sake of clearness, the results with the complex  $[\text{Fe}(\text{Pic})_3] \cdot 0.5 \text{ Py}$  are reproduced in Table 6 (entry 3) and compared with those of Barton et al. (entries 1A and 1B). When considering these data, it must be remarked that the ferric complex used by Stavropoulos and coworkers [51] differs from those of  $\text{GoAgg}^{\text{III}}$  and  $\text{Gif}^{\text{IV}}$ . In particular, the authentic complex of  $\text{Fe}^{\text{III}}$  with three moles of picolinate anion as ligands had been stated by Barton et al. to manifest a somewhat different behavior with respect to the typical  $\text{Fe}^{\text{III}}$ bis(picolinato) complex used in  $\text{GoAgg}^{\text{III}}$  [32]. Anyhow, the partition values of entry 3 differ remarkably from those measured by Barton et al., particularly in their early  $\text{Gif}^{\text{IV}}$  experiments, but are closely similar to the corresponding ratios observed when authentic *tert*- and *sec*-adamantyl radicals were generated via photolysis of suitable adamantyl esters in  $\text{Py}/\text{AcOH}$  (entry 4). These tests actually reproduced the control series of experiments originally used by Barton (entry 2) with analogous intent, but with the notable difference that now the metal complexes had been added to the reaction mixture to mimic their redox properties (see conditions, entry 4). So, the model emerging from this study was consistent with

Table 6

The partition of tertiary and secondary positions of adamantane between oxygenated and  $\text{Py}$ -coupled products under different conditions of  $\text{Gif}$  chemistry and when authentic *tert*- and *sec*-adamantyl radicals are generated<sup>a</sup>

Conditions		 <i>tert</i> [ $\text{AdPy}/\text{Ad(O)}^{\text{b}}$ ]	 <i>sec</i> [ $\text{Ad-Py}/\text{Ad(O)}^{\text{b}}$ ]	Reference
1	Adamantane oxidation			
1A	$\text{Gif}^{\text{IVc}}$ , under 4% $\text{O}_2$ in $\text{N}_2$	38	0.01	[21]
1B	$\text{GoAgg}^{\text{III d}}$ , under 4% $\text{O}_2$ in $\text{N}_2$	1.65	0	[31]
2	<i>tert</i> - or <i>sec</i> -Ad radicals generated in $\text{Py}/\text{AcOH}$ under 4% $\text{O}_2$ in $\text{N}_2$	1.36	0.24	[21]
3	Adamantane oxidation $[\text{Fe}^{\text{III}}(\text{Pic})_3] \cdot 0.5 \text{ Py}/\text{H}_2\text{O}_2$ in $\text{Py}/\text{AcOH}$ , under 4% $\text{O}_2$ in $\text{N}_2$	2.30	0.09	[51]
4	<i>tert</i> - or <i>sec</i> -Ad radicals generated in the same solution as entry 3 but without $\text{H}_2\text{O}_2$	2.29	0.08	[51]

<sup>a</sup> By photolysis of *tert*- or *sec*-adamantanecarboxylic esters of *N*-hydroxy-2-thiopyridone.

<sup>b</sup> Include hydroperoxides in experiments of entry 2.

<sup>c</sup>  $\text{Zn}^0/\text{Fe}^{\text{II}}/\text{O}_2$  in  $\text{Py}/\text{AcOH}$ .

<sup>d</sup>  $\text{Fe}^{\text{III}}/2\text{PA}/\text{H}_2\text{O}_2$  in  $\text{Py}/\text{AcOH}$ .

the production of an oxidizing radical changing from an indiscriminate H-abstrating species, under inert atmosphere, to a more selective alkoxy radical under increasing O<sub>2</sub> pressure. Evidence for the unselective species being the hydroxyl radical was provided by carrying out the catalytic oxidation of DMSO with the ferrous complex under strictly inert atmosphere. The nature of the products (methanesulfinic acid and picolines) showed that hydroxyl radicals were produced and afforded methyl radicals according to the known reaction

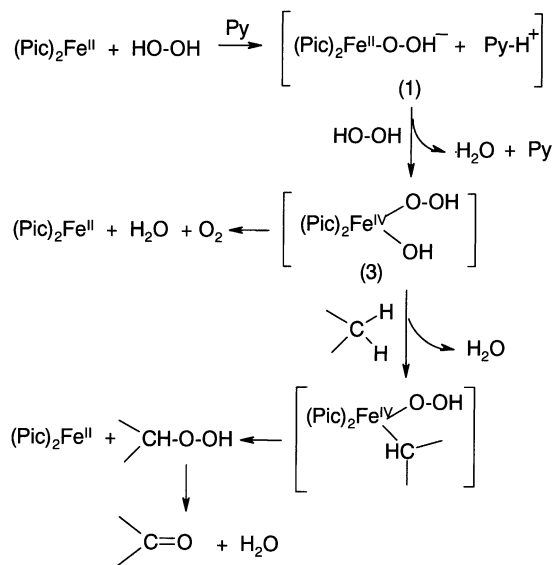
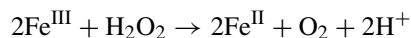


This reaction was in fact progressively inhibited by addition of increasing amounts of ethanol which afforded hydroxyethyl-pyridines, in agreement with the expected formation of secondary and primary hydroxyethyl radicals. Similar results were obtained with other iron complexes bearing trifluoroacetate ions and pyridine as ligands [52].

In conclusion, these studies provide persuasive evidence that Gif oxygenations of adamantane may proceed through free-radical pathways even if the role of pyridine in promoting so high ketonization of methylene groups needs to be more thoroughly justified.

### 2.6. The Sawyer's variant in the interpretation of the Gif chemistry

Originally, the catalytic systems based on Fe<sup>II</sup>bis-(picolinato) have also been thoroughly investigated in Py/AcOH and other solvents by Sawyer and coworkers. Their interpretation of the related mechanisms differs in some relevant details from that given by Barton and postulates other transient, hypothetical intermediates to account for the reactivity of the substrates in the so-called oxygenated Fenton chemistry [15,22,23,26]. With notable attention to the bond dissociation energies, they first observed that, when a large excess of H<sub>2</sub>O<sub>2</sub> is added to the iron complexes in Py/AcOH (in an optimized molar ratio 2:1), the reactivity of the substrates is independent of the valency of the metal ion. For instance, if the starting state of iron is Fe<sup>III</sup>, the initial events are supposed to cause its reduction by H<sub>2</sub>O<sub>2</sub>



Scheme 9.

Then a main common pathway follows, as shown in Scheme 9.

The free energy of the Fe–OH bond in species (3) was estimated to be  $-\Delta G_{\text{BF}} = 15 \text{ kcal mol}^{-1}$ . Since the bond energy H–OH is  $-\Delta G_{\text{BF}} = 111 \text{ kcal mol}^{-1}$ , the ability of the latent form of  $\bullet\text{OH}$  in (3) to abstract H from an alkane depends on whether or not the energy gain in making H<sub>2</sub>O ( $\Delta G = -111 + 15 = -96 \text{ kcal mol}^{-1}$ ) will balance the dissociation energy of the C–H bond to be cleaved. The latter is known to have the following enthalpic values

$$\Delta H_{\text{DBE}}(\text{CH}_3\text{-H}) = 104 \text{ kcal mol}^{-1}$$

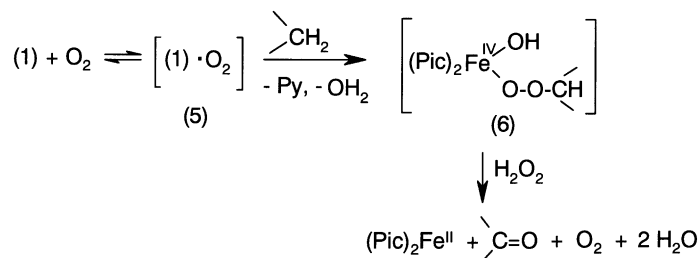
$$\Delta H_{\text{DBE}}(\text{R-CH}_2\text{-H}) \approx 100 \text{ kcal mol}^{-1}$$

$$\Delta H_{\text{DBE}}(\text{R}_2\text{CH-H}) \approx 96 \text{ kcal mol}^{-1}$$

$$\Delta H_{\text{DBE}}(\text{R}_3\text{C-H}) \approx 93 \text{ kcal mol}^{-1}$$

So, unlike the really free, extremely reactive  $\bullet\text{OH}$  radical, the bound OH should react with the methylenic group of cyclohexane ( $\Delta H_{\text{DBE}} = 95.5 \text{ kcal mol}^{-1}$ ) or any other secondary or tertiary C–H, but not with methyl groups and with methane [26]. This is in agreement with the experimental facts. In subsequent papers the Fenton intermediate (1) was postulated to react with an excess of O<sub>2</sub> to give a dioxygen adduct, (1) $\bullet\text{O}_2$ , as the steady-state

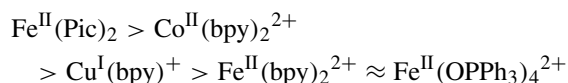




Scheme 10.

oxygenating species. The following sequence was then added for the ketonization of cyclohexane taking place with a KIE 2.1 (see Scheme 10) [27].

Schemes based on these intermediates have been included in a general model extended to other metals in their reduced state. The reactivities were found to depend on the metal, the ligand and the solvent. The efficiencies of the bipyridine (bpy) complexes of  $\text{Co}^{\text{II}}$  and  $\text{Cu}^{\text{I}}$  were compared with those of three complexes of  $\text{Fe}^{\text{II}}$  for the ketonization of cyclohexane by  $\text{H}_2\text{O}_2$ . The following order of efficiency was found [53]:



The complex of  $\text{Mn}^{\text{III}}$  with the Schiff base of ethylenediamine with 2 mol of salicylaldehyde,  $(\text{salen})\text{Mn}^{\text{III}}\text{OAc}$ , was ineffective when associated to  $\text{H}_2\text{O}_2$  for the oxidation of cyclohexane. However, it was the most efficient catalyst when tested with TBHP in MeCN for the oxidation of cyclohexene to 2-cyclohexen-1-one. When the solvent was replaced by Py/AcOH (2:1), the overall efficiency was reduced but the oxygenated Mn-Fenton-type system converted the cycloalkene to epoxide, alcohol and ketone, in approximately equal amounts [54].

An earlier work by Srinivasan et al. had clearly shown an unambiguous case of radical/non-radical dichotomy in the oxidation of cyclohexene by TBHP, catalyzed by a salt of  $(5,5'\text{-dinitrosalen})\text{Mn}^{\text{III}}$  in acetonitrile solution and in presence of pyridine, or imidazole, as cocatalyst. Two concurrent pathways were taking place: a free-radical chain produced allylic peroxidation and a non-radical route, based on the interconversion  $\text{Mn}^{\text{III}} \rightarrow \text{Mn}^{\text{V}}=\text{O}$ , was responsible for the epoxidation. The former pathway was

quenched by a hindered phenol while the latter was unaffected by the free-radical scavenger and was clearly promoted by pyridine or imidazole [55].

In a report summarizing their works, where iron complexes had been used with various R-OOH in various organic solvents, Sawyer et al. stated that “Fenton’s reagents do not produce free  $\bullet\text{OH}$  or free carbon radicals” [27]. This generalization was differently commented by several authors [56–58]. Walling cited a number of processes whose products would be inexplicable without the intermediacy of free-radicals. Among these is the well-known initiation of vinyl polymerization by Fenton-type reagents. In principle, he does not exclude a priori that the first-formed intermediate between the peroxide and  $\text{Fe}^{\text{II}}$  might undergo an internal two-electron oxidation to give a ferryl species as the real oxidant in non-enzymatic reactions. At the same time, however, he is quite uneasy about the need to take into account this or other types of complexes to the exclusion of the free radical pathway [56]. His feeling is clearly expressed, in a non-polemic sense, by a previous statement that “formulation of complexes to explain reaction and kinetic data is a great temptation, but, especially when not independently demonstrated, has little more intellectual justification than invoking malignant spirits” [5]. The Ingold’s group showed, inter alia, that using the same catalysts utilized in some of Sawyer’s experiments (e.g.  $\text{FeCl}_3$  in  $\text{CH}_3\text{-CN}$ ;  $\text{Fe}^{\text{II}}(\text{pic})_2$  in Py/AcOH; common oxidant: a *tert*-alkyl hydroperoxide), the autoxidation of ethylbenzene was inhibited by the addition of free-radical scavengers, such as the commercial antioxidant 2,6-*di*-*tert*-Bu-4-methylphenol (BHT). This was an unequivocal proof that Fenton’s reagents may involve a free-radical chemistry [57]. Circumstantial comments on the dispute were expressed by

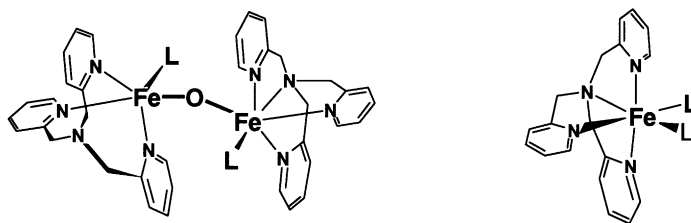


Fig. 5. The structure of typical dinuclear and mononuclear Que's catalysts.

Goldstein and Meyerstein, who added several ways through which a substrate may undergo a one-electron oxidation without the intervention of  $\bullet\text{OH}$  [58].

### 2.6.1. Que's catalytic systems

Other catalytic systems have been studied by Que's group as possible non-haem synthetic surrogates of monooxygenases. These were based on a number of complexes of Fe with polidentate amines, such as tris(2-pyridylmethyl)amine (TPA), and other ligands (L), in combination with TBHP, or  $\text{H}_2\text{O}_2$ , as the primary oxidant in  $\text{CH}_3\text{CN}$  as solvent. Typical catalysts included mononuclear  $[\text{Fe}^{\text{III}}(\text{TPA})(\text{L})_2]^{n+} \text{X}_n^-$  as well as ( $\mu$ -oxo) dinuclear complexes  $[\text{Fe}^{\text{III}}_2\text{O}(\text{TPA})_2(\text{L})_2]^{n+} \text{X}_n^-$ , (where L = OH, OAc,  $\text{H}_2\text{O}$ , Cl, Br, ...), characterized by structures of the type (shown by Fig. 5) [59–61].

Considerable efforts afforded spectroscopic evidence that transient high-valent species of iron could be produced by treatment of these complexes with  $\text{H}_2\text{O}_2$  at low temperature. Although these analyses were done on intermediates produced by  $\text{H}_2\text{O}_2$ , the experiments of hydrocarbon functionalization were carried out with TBHP to facilitate the task of determining the fate of the decomposed hydroperoxide. Using the alkyl hydroperoxide in large excess, cyclohexane was generally converted into the corresponding alcohol and ketone, typically in a ratio  $\text{ol/one} \leq 1$ , together with sizable amounts of the

mixed cyclohexyl-*tert*-Bu-peroxide. The mechanism tentatively proposed by the authors for the hydrocarbon hydroxylation assumed the intermediate formation of a metal-peroxide  $\text{L-Fe}^{\text{III}}\text{-O-O-tert-Bu}$  and a high-valent iron-oxo species ( $\text{Fe}^{\text{V}}=\text{O}$ ) derived from that by heterolysis of the O–O bond. The reaction of the iron-oxo species with the hydrocarbon could afford an alkyl radical. The latter was then supposed to react by an oxygen-rebound mechanism (in the solvent cage) with the concomitantly produced ferryl species to give the alcohol or with other trapping agents to give the other observed products (see Fig. 6) [60].

This interpretation was challenged by Ingold's group on the basis of the following arguments [62]:

1. The alcohol-to-ketone ratio and the presence of the mixed peroxide in the products were indicative of termination reactions involving peroxy radicals according to the traditional scheme of autooxidation (see Scheme 6).
2. A suitable Ar purge significantly inhibited the yield of oxidized products.
3. The use of the mechanistic probe  $\text{Ph-CH}_2\text{-C}(\text{CH}_3)_2\text{-O-OH}$  in place of *tert*-Bu-O-OH prevented the oxidation of the cycloalkane.

To overcome these objections, Que et al. published the results of several experiments carried out in an atmosphere of  $^{18}\text{O}_2$  or under Ar. The first interesting results were obtained by using the ( $\mu$ -oxo)-diiron

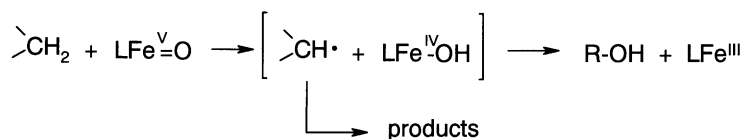
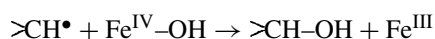


Fig. 6. Mechanism postulated for the alcohol formation by Que's group.

complex  $[\text{Fe}^{\text{III}}_2\text{O}(\text{TPA})_2(\text{H}_2\text{O})_2]^{4+}$  as a catalyst in the presence of a large excess of the cycloalkane (usually *c*- $\text{C}_6\text{H}_{12}$ , replaced by cyclooctane in the experiment with Ar purge). The amount of *tert*-butyl hydroperoxide, typically used in the proportion of 150 equivalents per mol of catalyst, was progressively reduced, in a series of virtually oxygen-free runs, to 1 equivalent and was carefully delivered into the solution during the reaction in such a way as to minimize the amount of  $\text{O}_2$  possibly generated by *tert*- $\text{Bu-O-O}^\bullet$  radicals. Under these conditions, as soon as the relative amount of the hydroperoxide was limited to less than 20 eq, the cycloalkanol was obtained as the exclusive oxidation product. In the runs carried out under  $^{18}\text{O}_2$  with 200 eq of *tert*- $\text{BuOOH}$  no label was incorporated in the mixed cycloalkyl-*tert*-butyl peroxide and only a partial incorporation was detected in the alcohol and ketone. These results suggested that part of the oxygenated products had been formed by routes totally independent of  $\text{O}_2$  and part by the autooxidation chain. In particular, the exclusive formation of the alcohol when  $\text{O}_2$  was minimized proved the participation of a metal-based oxidant as responsible for the cycloalkane hydroxylation. The mechanism originally proposed seemed to be reinforced [63]. But the last word had not yet been said. After a sophisticated re-analysis of the reaction the authors of both groups were able to demonstrate that freely diffusing *tert*-butoxyl radicals were generated by the catalyst in contact with *tert*- $\text{Bu-O-OH}$  and were responsible for the functionalization of the cycloalkane according to the usual free-radical chemistry. Nevertheless, they agreed that, when  $\text{O}_2$  was not available, the cycloalkyl radicals could only react with species like  $\text{Fe}^{\text{IV}}\text{-OH}$  (or  $\text{Fe}^{\text{III}}\text{-OH}$ ) by simple ligand transfer to give the alcohol [64]



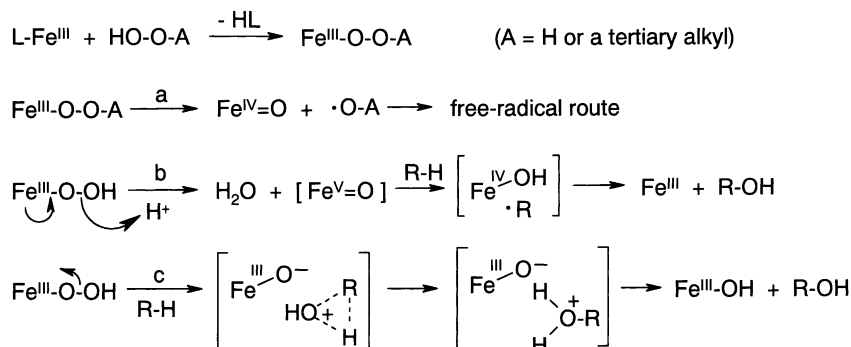
A different pattern of reactivity appeared to take place when mononuclear complexes of the type  $[\text{Fe}(\text{TPA})(\text{MeCN})_2](\text{ClO}_4)_2$ , and analogues with other tetra- and pentadentate pyridylmethylamine bases as ligands, were used in combination with an excess of  $\text{H}_2\text{O}_2$ . With these catalysts cyclohexane in MeCN was mainly oxidized to cyclohexanol either under Ar or in air. More importantly, tertiary alcohols were produced from *cis*- and *trans*-1,2-dimethylcyclohexane, and epoxides from alkenes, all with total retention of the stereochemistry. These results clearly excluded

a free-radical chain autooxidation pathway [65]. Transient species were isolated from these catalytic systems, at low temperatures, as purple low-spin  $\text{Fe}^{\text{III}}\text{-O-OH}$  complexes. Their Raman spectra have been interpreted as evidence that the O–O bond was weakened by the low-spin center while the  $\text{Fe}^{\text{III}}\text{-O}$  was probably strengthened [66]. Moreover, the deprotonation of one of these intermediates showed the reversible formation of a cyclic peroxo  $[\text{Fe}^{\text{III}}\text{O}_2]^+$  species, characterized by Raman spectroscopy and unreactive towards alkanes as substrates [67]. The goal of defining the most plausible oxidant species was further pursued by addition of an excess of  $\text{H}_2\ ^{18}\text{O}$  to  $\text{H}_2\text{O}_2$  in the experiments of *cis*-1,2-dimethylcyclohexane hydroxylation carried out with a tetradentate-ligated iron complex. The analysis showed that incorporation of  $^{18}\text{O}$  into the resulting *cis*-alcohol had taken place affording evidence that the oxidant responsible for the stereospecific hydroxylation can undergo oxygen exchange with water. Since solvent exchange was stated to cannot occur with the  $\text{LFe}^{\text{III}}\text{-O-OH}$  intermediate, the ultimate oxidant was inferred to derive from the latter by heterolysis of the O–O bond and formation of the so far elusive  $\text{LFe}^{\text{V}}\text{=O}$  [68]. A suitable mechanism by which high-valent iron–oxo species may exchange with water has been recently elucidated [69].

### 2.6.2. Concluding remarks

Important pieces of evidence support the formation of C-centered free-radicals when an organic substrate is faced with the traditional Fenton reaction. However, the variety of conditions under which this reaction can be carried out leaves room for conjectures about the nature of the first-formed, transient, oxidizing species. So this seems destined to remain a controversial question.

With regard to most of the works here reviewed, the dualism between radical and non-radical chemistry of the iron–redox systems may then be limited to the systems based on  $\text{Fe}^{\text{III}}$  as the starting state of iron. Its comprehension may be facilitated with the help of the simplified Scheme 11, where the nature of the ligands is not indicated. It is generally accepted that the first impact between the hydroperoxide and the ferric ion may result in a nucleophilic displacement of a loosely bound ligand. The resulting metal peroxide,  $\text{Fe}^{\text{III}}\text{-O-O-A}$ , has two main possibilities for the cleavage of the O–O bond: the homolytic breakage



Scheme 11.

(a), which starts off the free-radical route, or an heterolytic decomposition, which, in turn, may formally occur either by route (b) to afford the oxenoid species  $\text{Fe}^{\text{V}}\text{=O}$  or by route (c) to make available an incipient species  $^{\oplus}\text{OH}$ .

For the sake of uniformity with the enzymatic systems described later, in routes (b) and (c) the peroxy-intermediate will be assumed to be an iron-hydroperoxide, capable of inserting an O-atom into the C–H bond of a generic hydrocarbon R–H.

If the ligands and the microenvironment do not play a cooperative role in the O–O cleavage, this may be assumed to be homolytic, being favored by the weakness of the bond in the order *tert*-BuO–OFe > HO–OFe.

The heterolytic route (b) is generally assumed to be facilitated by suitable ligands capable of stabilizing by resonance the hypervalent state of the iron–oxo species. A typical case is encountered in the ubiquitous family of the cytochromes P-450. These are haem-proteins, which act as monooxygenases by using two electrons and a molecule of  $\text{O}_2$  to insert one of its atoms into non-activated C–H bonds reducing the other one to  $\text{H}_2\text{O}$ , protons being made available from the microenvironment [70]. In this case route (b) has met consensus as the most plausible way to accommodate the O-atom insertion by an electrophilic species, formally depicted by the resonance structure  $\text{Fe}^{\text{V}}\text{=O}$  which may be stabilized as an oxo–iron(IV) porphyrin radical. This is assumed to abstract a H atom from the substrate and promptly donate the hydroxyl group by a rebound mechanism. However, in the last decade the intimate features of this hydroxylation have been thoroughly investigated with the

use of mechanistic probes as substrates able to distinguish between radical and cationic transient intermediates. In one of the most recent of these studies, Newcombe et al. obtained evidence that the transition states involved in the oxygen insertion into the C–H bond bear the feature of both radical (but not freely diffusing radical) and cationic species. The former were consistent with the above mentioned iron–oxo abstraction-rebound mechanism (route b), while the latter implied the insertion of the elements of  $^{\oplus}\text{OH}$  into the C–H bond to produce a temporarily-protonated alcohol (route c). The balance between the two pathways was apparently depending on the proteic structures of the P-450 as suggested by the different rearrangements of the probe-transient intermediates when a highly conserved, suitably positioned threonine was replaced by alanine [71]. The authors arrived to postulate a unified view of the P-450-catalyzed hydroxylation by assuming the occurrence of both routes (b) and (c) of Scheme 11 as different transition states developed by two distinct electrophilic oxidants, both effecting hydroxylation via O-insertion processes. The substrate activation via a cationic species may add a new key to understand the Fenton oxygenated chemistry.

On the other hand, the haem complex is not the only form of iron capable of catalysing these reactions. A peculiar non-haem, iron-based hydroxylase is the component of methane monooxygenase (MMO) which is capable of converting methane to methanol. The active site of this enzyme contains a diiron(III)-center where the two ferric ions are bridged by hydroxide and carboxylate ligands and are further coordinated by glutamates, histidines and water [72]. A key, transient

intermediate in the catalytic cycle of MMO has been characterized by spectroscopic comparisons with synthetic high-valent Que's models and termed compound Q. It appears to contain a bridged bis- $\mu$ -oxo-diiron(IV) species, which is thought to derive from the diferric center via a peroxo-complex  $\text{Fe}^{\text{III}}\text{-O-O-Fe}^{\text{III}}$  [73–75]. Experimental facts and theoretical calculations suggest that a plausible mechanism for the alkane activation by the high-valent species may imply an almost concerted addition of C–H across an iron–oxo group.

The merit of the works here reviewed is in the effort spent to emulate the monooxygenases by non-haem, simple, synthetic systems. This is obviously a difficult task and the proof of the mechanisms really involved demands an even greater deal of sophisticated methods of investigation.

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