The Selective Functionalization of Saturated Hydrocarbons: Gif Chemistry

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Life existed on Earth under anaerobic conditions long before the blue-green algae started to make oxygen. Under reducing conditions the atmosphere was full of hydrocarbons, especially methane, whose oxidation contributed to keep the oxygen concentration at a low level.[1] But how did this oxidation happen? There was hydrogen sulfide, from reduction of sulfate; the abundant element iron was present as metallic iron (cf. bog iron) and in the seas as Fe(II). A form of life took advantage of the new aerobic conditions to oxidize the iron to Fe(III) and deposit it as pure ferric oxide in vast mountain ranges in Australia and Brazil. This new form of life would have obtained far more energy from coupling the oxidation of iron and hydrocarbons together than from just making ferric oxide. The hydrocarbon oxidation product (CO₂) would have left no geological trace. Although this reasoning was naive, it was the starting point for a new chapter in selective hydrocarbon activation chemistry that would be known as Gif chemistry.

The Gif and Gif–Orsay Period

Historically, according to logical thinking, to adamantane (1) (Figure 1) in pyridine containing hydrogen sulfide was added iron powder and an equivalent amount of acetic acid (to dissolve the iron), and the suspension was stirred under air. The iron powder, aided by a surface effect of the hydrogen sulfide, dissolved and the adamantane was oxidized to mainly adamantanone (2) with a 10-, then 20-, and finally 30-fold increase in yield over experiments with Fe(II) alone. The first significant Gif system (Gif^III) had been invented.[2] Later, we showed that the reaction could be made catalytic in iron (up to 2000 turnovers) by using metallic zinc as a source of electrons (Gif^IV). Hydrogen sulfide was not needed for Gif^IV, nor for Gif^III if the temperature was raised to 30–40 °C to start the reaction. From the beginning, carbon radicals were not thought to play a major role as they are quenched efficiently by hydrogen atom transfer from the S–H bond.

Derek Barton graduated from Imperial College, London, in 1940. He obtained a Ph.D. in 1942. After two years in military intelligence work and one year in industry he returned to Imperial College to teach inorganic and physical chemistry. After Harvard, Birkbeck College, and Glasgow he returned to Imperial College from 1957 to 1978 as professor of organic chemistry. He was Director of the Natural Products Institute at Gif-sur-Yvette from 1978 until taking up his present appointment in 1986. He shared the Nobel prize in chemistry in 1969 for the concept of conformational analysis.

Darío Doller was born and raised in Buenos Aires, Argentina. He received his chemical education from the Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, graduating as Licenciado en Química in 1983. He earned a Ph.D. degree in 1989, for his work in the steroid field under the guidance of Prof. Eduardo G. Gros. Shortly afterward, he joined the Gif team at Texas A&M University, working together with Prof. Barton. He is continuing his professional career at the Rohm and Haas Company.
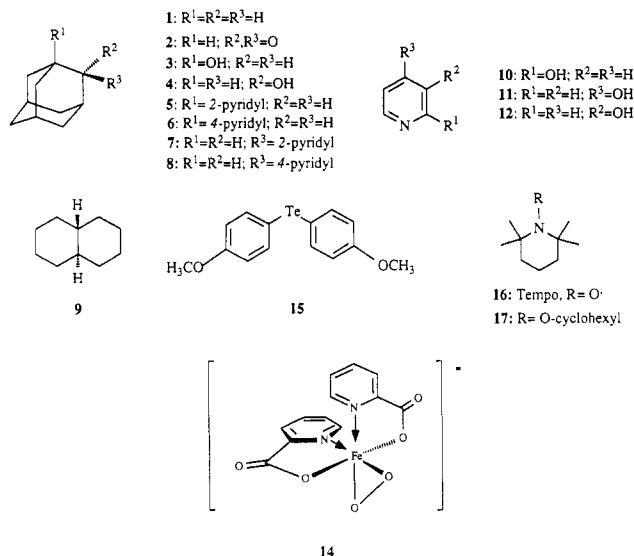

Figure 1.

The characteristics of Gif chemistry were uncovered during the first experiments. Why did we choose adamantane (1) as the substrate? The reasons for this were its non-volatility, which would make good mass balances feasible, and its symmetry, which simplifies the problem of product identification. In addition, adamantane is a nice mechanistic probe. It has 12 equivalent secondary C–H bonds and four equivalent tertiary C–H bonds. If all of them had the same reactivity toward a certain chemical process, a normalized ratio $C^2/C^3 = 3$ should be obtained for the quotient between the oxidation products at the secondary position and those at the tertiary position. However, it is a well-known fact that chemical reactions do show regioselectivity, and that tertiary, secondary, and primary C–H bonds, in general, behave in a different fashion. Typical C^2/C^3 ratios for radical reactions on adamantane are between 0.05 and 0.15, reflecting the lower bond energy of the tertiary C–H bond with respect to the secondary C–H bond. For radical chain reactions it is well established that the reactivity order is tertiary C–H > secondary C–H > primary C–H.[3]

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Gif Chemistry

Acc. Chem. Res., Vol. 25, No. 11, 1992 **505**

Table I. The Nomenclature of Gif Chemistry[a]

system	catalyst	electron source	oxidant
Gif[III]	Fe(II)	Fe[0]	O_2
Gif[IV]	Fe(II)	Zn[0]	O_2
GO	Fe(II)	cathode	O_2
GoAgg[I]	Fe(II)		KO_2/Ar
GoAgg[II]	Fe(III)		H_2O_2
GoAgg[III]	Fe(III)/picolinic acid		H_2O_2
GoChAgg	Cu(II)		H_2O_2
Cu[0]/O_2	Cu(I)?	Cu[0]	O_2

[a] The nomenclature of the Gif systems is geographically based: G stands for Gif-sur-Yvette, O is for Orsay, Agg is for Aggieland, Texas A&M, and Ch is for Chernogolovka, Russia.

What were the C^2/C^3 values obtained during our first Gif experiments? Surprisingly, values as high as 22 were obtained, seeming to show that under Gif-type conditions the secondary C–H bonds in adamantane are more reactive than the tertiary C–H bonds. This also suggested that the chemistry involved in the hydrocarbon activation process was different from carbon radical chemistry.

Under Gif[IV] conditions, as we decreased the partial pressure of oxygen, the reaction seemed to become more and more selective for adamantanone. However, a more exhaustive examination of the reaction mixture showed that, in addition to the expected oxidation products (adamantanone (2), 1-adamantanol (3), and 2-adamantanol (4)), the products derived from coupling of adamantane *only* at the tertiary position to pyridine (on both the 2 and 4 positions, 5 and 6, respectively) were produced. When these two new products are taken into account, the ratio C^2/C^3 decreased to 1.1, still much higher than typical values for radical reactions.[4]

The radical coupling chemistry of nitrogen heterocycles had been thoroughly studied by Prof. Minisci, especially the coupling of tertiary and secondary alkyl radicals with substituted pyridines.[5] We were interested in the reaction between *tert*- and *sec*-adamantyl radicals and pyridine. On the basis of the *N*-hydroxy-2(1*H*)-thiopyridone methodology, we proved that when genuine carbon radicals were generated by photolysis of the appropriate precursor, they afforded the pyridine-coupled products 5–8.[6] Thus, if both *tert*- and *sec*-adamantyl radicals *do couple* with pyridine, why under Gif reaction conditions did we observe *only* the *tert*-adamantylpyridine coupled products and none of the *sec*-adamantylpyridines? Clearly *sec*-adamantyl radicals are not present in the reaction mixture but *tert*-adamantyl radicals are. Further evidence against the intermediacy of secondary carbon radicals will be presented later on.

After these first attempts, Gif chemistry moved forward, and different systems were developed, all of them with the same chemical peculiarities. The nomenclature is geographically based and is explained in Table I.

An electrochemical version of the Gif system was developed at Orsay, France.[7] Hence, it became known as the GO system. In this, the electron source was a
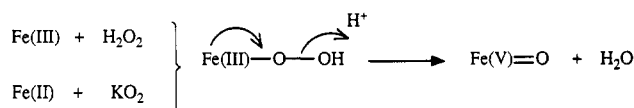
Scheme I

cathode in an electrochemical cell under a stream of oxygen. The solvent system was unchanged. Coulombic yields were as high as 60%, and oxidation yields attained nearly 20%. The GO system showed the same chemical characteristics as its chemical congeners. The non-radical nature of the activation step was further manifested when *trans*-decalin (9) was used as a substrate, affording a C^2/C^3 value of 36, in sharp contrast with the value of 0.14 obtained for the cobalt-catalyzed radical autoxidation reaction.[8]

The GoAgg Period

After the move to Texas A&M University, in Aggieland, a new chapter of Gif chemistry began: the GoAgg system (the origin of the name is rather obvious!). The first system developed was GoAgg[I]. Fe(II) and superoxide (as KO_2) in pyridine/acetic acid under an argon atmosphere were able to emulate the peculiar properties of the Fe(II)/Zn[0]/O_2 system (Gif[IV]). However, the reaction was only theoretically important since it was not of preparative value.[9]

Instead, the GoAgg[II] system was much more important. Fe(III) and hydrogen peroxide in pyridine/acetic acid also showed the characteristics of Gif-type reactions. However, now up to 30% of hydrocarbon activation could be achieved at quantitative yields. Prof. Schuchardt and co-workers have reported GoAgg[II] reaction efficiencies as high as 91% based on H_2O_2.[10] In addition, the reaction proceeded smoothly in a homogeneous solution, which made mechanistic studies much simpler. One inconvenience of the GoAgg[II] reaction was its relatively slow rate. The discovery that catalytic amounts of picolinic acid and congeners decrease the reaction half-life from 4–6 h to 5–10 min gave rise to the GoAgg[III] system (GoAgg[II] plus a ligand, generally picolinic acid).[11]

Fe(II) + O_2^- and Fe(III) + O_2^{2-} are able to carry out the same chemistry. A logical rationale for this is that they interact heterolytically, forming the same Fe[V]=O species (Scheme I). What is this Fe[V]=O species? Well, this is similar to the high-oxidation-state iron species accepted in cytochrome P-450 (CP-450) chemistry as a reaction intermediate. The difference is that in Gif chemistry there is no porphyrin ligand around the iron to transfer one electron and reduce it to Fe(IV), as is the case in the heme-based CP-450 systems.[12] Evidence for the intermediacy of Fe(V) species in several iron-based model systems that catalyze the dismutation of H_2O_2 into H_2O and O_2 or the activation of saturated

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506 *Acc. Chem. Res., Vol. 25, No. 11, 1992*

Barton and Doller

hydrocarbons in different Fe-based systems has been acquired by other research teams.[13] We prefer this rationale rather than the one based on hydroxyl radicals (Fenton chemistry).[14] Why? Just because neither carbon (except for *tert*-adamantyl) nor hydroxyl radicals could be detected under Gif-type conditions. And because when genuine carbon and hydroxyl radicals are generated under Gif-type conditions, their fate is dramatically different from the typical chemical characteristics of Gif systems (see below). For instance, photolytically generated hydroxyl radicals behave as weak nucleophiles by reacting with pyridine, affording 2-hydroxypyridine (**10**) and 4-hydroxypyridine (**11**). Instead, the major hydroxypyridine detected under GoAgg[II] or GoAgg[III] conditions is 3-hydroxypyridine (**12**) showing the weakly electrophilic characteristics of the oxidizing species responsible for Gif chemistry.[15] In this respect, pyridine plays a very important role: the trapping of any trace of hydroxyl radicals that could have been formed by Fenton-type processes and would trigger a chain radical reaction.

A Little Biochemistry

At the same time as we were developing the chemistry of the Gif systems, important research was being carried out in the biochemical field, related to the enzymatic oxidation of nonactivated C–H bonds. In addition to the iron-heme-based CP-450 group of enzymes, a new group of iron-based enzymes was very intensely studied, with the peculiarity of lacking the heme group within their structures: the non-heme metalloenzymes.[16] Studies on the active sites of these enzymes showed that iron could be found in two different states. On one hand, dinuclear μ-oxo diiron centers are structural components of methane monooxygenase (MMO), ribonucleotide reductase, hemerythrin, and the purple acid phosphatases. On the other hand, several other non-heme iron-based biological systems contain a single-iron core. This group includes γ-butyrobetaine hydroxylase, proline hydroxylase, isopenicillin N-synthase, and bleomycin.

The case of MMO, which catalyzes the oxidation of methane to methanol, deserves special attention. MMO

Figure 2. Structure of complex **13**.

seems to be a catholic enzyme, being able to oxidize a large variety of hydrocarbons, a few of them with a selectivity paralleling that found in Gif-type reactions, particularly for adamantane.[17,18] Thus, we could ask the question, What kind of non-heme enzymes is Gif chemistry emulating?

The answer to this question came from NMR experiments studying the magnetic properties of the iron catalyst and their variation upon titration with picolinic acid. μ-Oxo diiron systems are able to show antiferromagnetic coupling. This interaction between the two closely situated iron atoms produces a decrease in the magnetic moment of the catalyst. On the other hand, high-spin single-iron complexes possess a d^5 configuration and are characterized by a magnetic moment of ca. 5.9 μ_B. The magnetic moment of the iron catalyst in the absence of picolinic acid was significantly lower than 5.9 μ_B (between 4.4 and 4.9 μ_B, depending on the system), suggesting that part of the iron was involved in antiferromagnetic coupling. Indeed, upon addition of water, a further decrease in the magnetic moment of the catalyst could be observed. However, stepwise addition of picolinic acid produced a continuous increase in the magnetic moment of the catalyst up to a value in agreement with a high-spin single-iron core. The same conclusion could be obtained through nuclear relaxativity measurements. Finally, the complex was isolated from the reaction mixture and characterized by X-ray crystallography as the previously unknown **13** (Figure 2). Solid-state magnetic moment determination for complex **13** was in agreement

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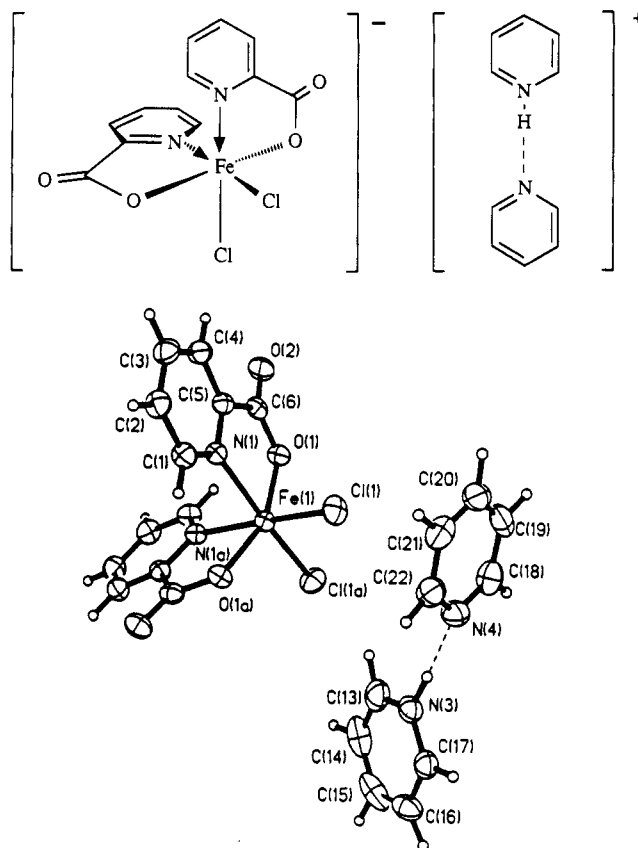
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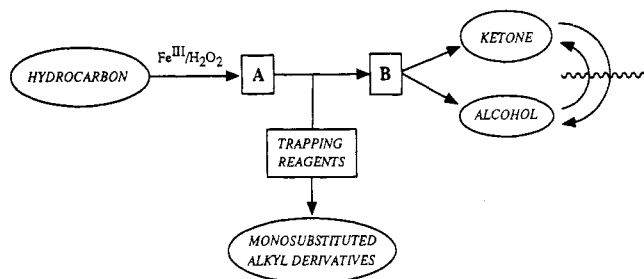
Figure 3.

Figure 4. Effect of increasing amounts of PPh_3 on the ketone/alcohol ratio from a Gif^{IV} reaction: O, cyclododecanone; □, cyclododecanol; ◊, total oxidation.

Figure 5. Kinetic analysis for a Gif^{IV} reaction in the presence of 1 mmol of PPh_3: ◊, ketone; □, alcohol; △, PPh_3; O, O=PPh_3.

with the solution-state value. Thus, the $GoAgg^{III}$ reaction is a model for non-heme single-iron enzymes.

What happens to complex **13** upon addition of hydrogen peroxide to start a $GoAgg^{III}$ reaction? Recent studies have permitted us to detect the intermediacy of a purple complex. Its formation and decay could be correlated with the timing for ketone and alcohol formation.[18] On the basis of similar $Fe(III)-H_2O_2$ complexes whose structure has recently been elucidated,[19] we propose for the purple complex the structure **14**.

Another consequence of these studies was that the Gif oxidation can be carried out in solvents different from pyridine *as long as the pH is adjusted to the appropriate value* (pH ca. 6.0 ± 0.4). In fact, Prof. H. Patin has been able to oxidize saturated hydrocarbons by Gif-type reactions in aqueous systems (microemulsions of water in oil).[20]

The Two-Intermediates Theory

One of the unknown features of Gif chemistry was the mechanism of the ketonization reaction. A mechanistic scheme could be depicted as in Figure 3. Ketones are not reduced to alcohols under the reaction conditions; neither are alcohols converted to ketones in amounts compatible with the ketone/alcohol ratio typical of Gif chemistry. This suggested that a common reaction intermediate B was responsible for the formation of both ketone and alcohol. Also, addition of different trapping reagents diverts the formation of ketone to the appropriate monosubstituted alkyl derivative: $CBrCl_3$ affords the alkyl bromide in quantitative yield at 30% conversion, Ph_2Se_2 produces a quantitative (in Se) yield of the (phenylseleno)cycloalkane, and sodium sulfide gives a good yield of dialkyl oligosulfide. All these results suggest the participation of another reaction intermediate A prior to B, which is trapped by all those reagents. How to explain such a complex reaction picture?

The first clue on the existence of intermediate B came from experiments running Gif^{IV} reactions in the presence of the reducing agent dianisyl telluride (**15**).[21] When added in excess compared to the amount of hydrocarbon being oxidized, An_2Te did not greatly deplete the total amount of hydrocarbon activation (ketone plus alcohol), but did decrease the ketone/alcohol ratio. Similarly, other reducing agents (such as PhSH and PPh_3) show the same effect on Gif^{IV}-type oxidations: changing the ketone/alcohol ratio while keeping constant the total amount of hydrocarbon activation. This effect is
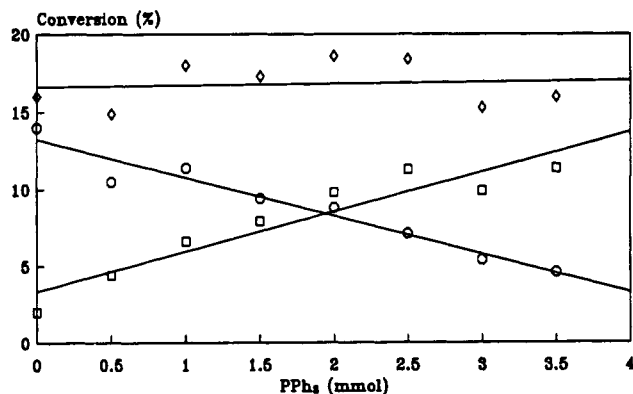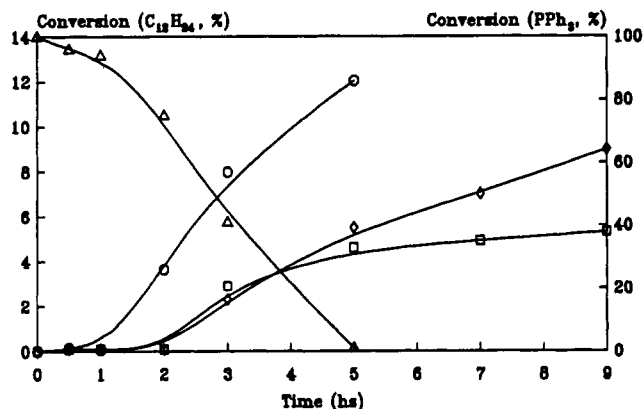
dramatic for the case of PPh_3 (Figure 4). These results have been confirmed by Dr. K. W. Lee and co-workers.[22] However, an even more interesting observation was made when following the kinetics of the Gif^{IV} oxidation of cyclododecane in the presence of PPh_3 (1.0 mmol, Figure 5). Actually, the easily oxidizable phosphine and the hard-to-oxidize saturated hydrocarbon are being oxidized at the same time! They are competing for the same reactive intermediate (formally the Fe^V=O species).

What is the nature of this intermediate B, common precursor to ketone and alcohol? ^{13}C-NMR experiments following the time course of a $GoAgg^{II}$ reaction on [1-^{13}C]cyclohexane revealed the answer (Figure 6). The formation of a reaction intermediate was observed, characterized by four different resonances. This intermediate decayed later on, affording the four resonances of evenly labeled [^{13}C]cyclohexanone. The intermediate was identified as cyclohexyl hydroperoxide by comparison with an authentic specimen. When it was resubmitted to $GoAgg^{II}$ conditions, its transformation into cyclohexanone and cyclohexanol was verified, in a ratio in agreement with the typical ratio of $GoAgg^{II}$ reactions. Later, cyclododecyl hydroperoxide was isolated from a $GoAgg^{III}$ reaction on cyclododecane. This was done by quenching the reaction with oxalic acid, which stops the $GoAgg^{III}$ reaction dead when it is added in a ratio 3/1 with respect to iron. Thus, the existence and structure of intermediate B have been confirmed. The same reaction pathway was verified

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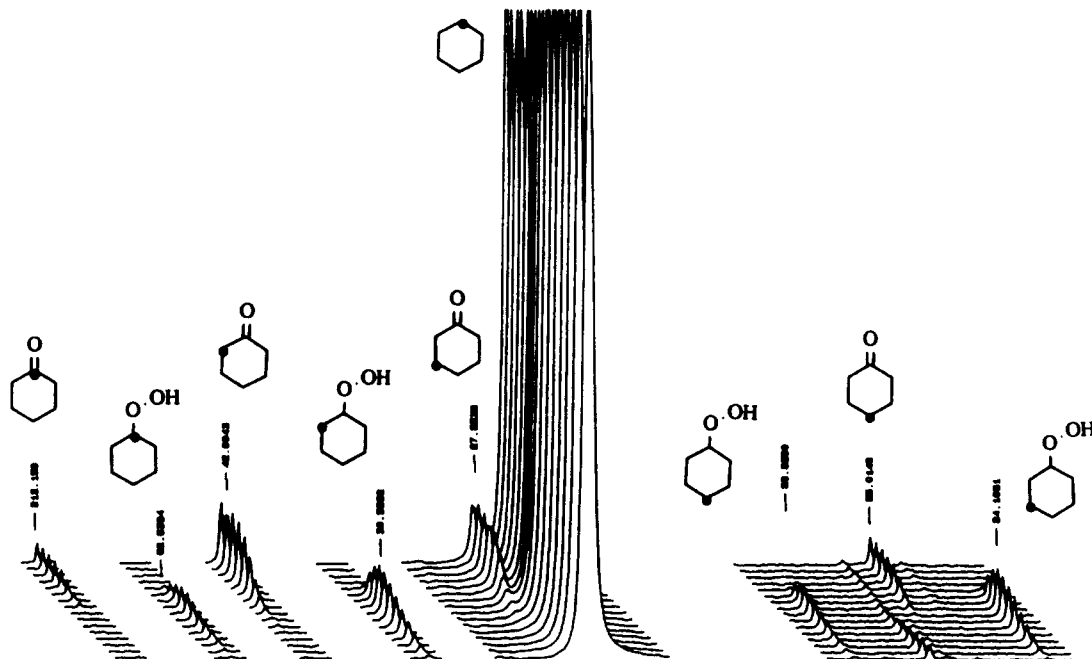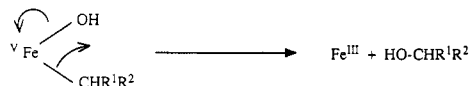
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Figure 6. ^{13}C-NMR experiment following the time course of the GoAgg^{II} reaction on [1-^{13}C]cyclohexane.

Mechanism of formation of alcohols in Gif-type reactions
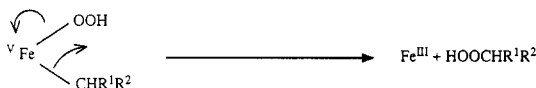
Hypothesis 1: *ligand coupling*

$$Fe^{III} + HO\text{-}CHR^1R^2$$

Hypothesis 2: *reduction of the alkyl hydroperoxide*

$$O=^VFe + R^1R^2CHOH$$

Mechanism of formation of alkyl hydroperoxides in Gif-type reactions

Hypothesis 1: *ligand coupling*

$$Fe^{III} + HOOCHR^1R^2$$

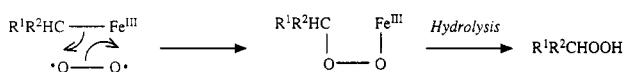Hypothesis 2: *insertion of dioxygen*

$$R^1R^2CHOOH$$

Figure 7. Hypotheses for the formation of alcohol and alkyl hydroperoxide under Gif-type reaction conditions.

with different substrates and working with other members of the Gif family.[23]

How Is This Alkyl Hydroperoxide Made?

Knowing that an alkyl hydroperoxide was involved as a reaction intermediate in the ketonization reaction of methylene groups in saturated hydrocarbons, we posed the question on the mechanism of its formation: basically, on the origin of the oxygen atoms of the hydroperoxide and the alcohol. We considered two different hypotheses (Figure 7). The answer to this question came from experiments in the presence of $^{18}O_2$ and $H_2^{18}O$ and was quite surprising: the two oxygen

atoms in the alkyl hydroperoxide came from O_2 and not *directly* from H_2O_2! This was, of course, anticipated for the Gif^{IV} reaction, but was unexpected for the hydrogen peroxide-based GoAgg^{II} reaction. Also, the oxygen atom in the alcohol comes from O_2 and not from H_2O. These results disprove the ligand-coupling mechanism. However, they show that the pathway followed by the hydrocarbon in Gif-type reactions is quite simple and common for both reaction products: hydrocarbon → alkyl hydroperoxide → ketone or alcohol.

Identification of A: The Fate of Carbon Radicals under Gif-Type Conditions

From the mechanistic studies described thus far, there is one clear point: Gif chemistry and chain radical autoxidation reactions share certain common characteristics. Their reaction pathways involve a reaction intermediate (A). Intermediate A reacts with stoichiometric amounts of O_2, affording an alkyl hydroperoxide (intermediate B). In the presence of suitable reagents such as Ph_2Se_2, Ph_2S_2, $CBrCl_3$, or CCl_4, well-known for carbon radical trapping, the formation of the alkyl hydroperoxide is diverted toward the corresponding monosubstituted alkyl derivative (phenyl selenide, phenyl sulfide, bromide, or chloride, respectively). Also, Prof. Perkins and co-workers were able to isolate the cyclohexyl spin adduct of deuterated 3,5-dibromo-4-nitrosobenzenesulfonic acid and suggested a "preponderant free-radical pathway for the (GoAgg^{II}) reaction".[24] Then, why is it that intermediate A in Gif chemistry is not a carbon radical?

The answer is simple: should A be a carbon radical, it would behave as such for every aspect of the chemistry displayed by carbon radicals. To test if this were true, we decided to generate genuine carbon radicals under Gif-type conditions in the presence of different "radical traps" and observe the fate of the carbon radicals thus formed. Alkyl radicals were smoothly generated at room temperature by photolysis of the appropriate

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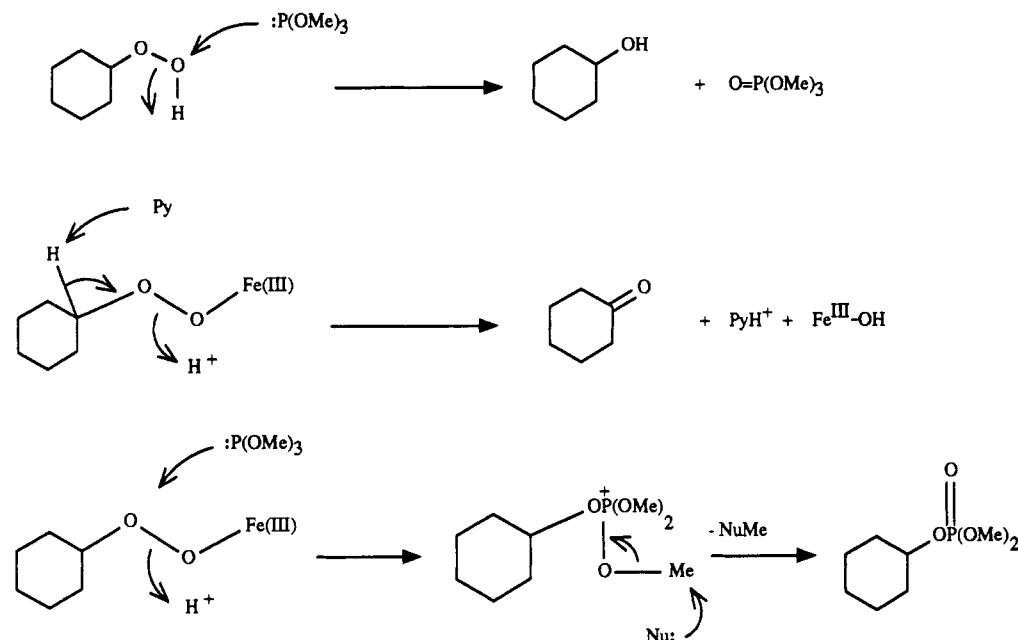(24) Knight, C.; Perkins, M. J. *J. Chem. Soc., Chem. Commun.* **1991**, 925–927.

Figure 8. Fate of cyclohexyl hydroperoxide in the presence of $P(OMe)_3$ and/or iron salts.

N-hydroxy-2(1H)-thiopyridone derivative of an alkane carboxylic acid.[25] Then, they were submitted to the following experiments.

1. Effect of PhSeH. When diphenyl diselenide is added to a Gif[IV] oxidation, some of the hydrocarbon oxidation is replaced by phenylselenation.[4,26] There is also, of course, a major reduction in the ketone/alcohol ratio. Since there is an excess of metallic zinc, one can wonder if the diphenyl diselenide is reduced to benzene selenol under the reaction conditions. By quenching a working reaction mixture with excess methyl iodide, we found that 96% of the initial diselenide was converted to methyl phenyl selenide. Thus, the reagent is benzene selenol, not diphenyl diselenide. Now benzene selenol quenches carbon radicals at a diffusion-controlled rate of 2×10^9 M^{-1} s^{-1} at 20 °C,[27] so any carbon radicals formed would be reduced back to hydrocarbon at once.

2. Effect of P(OMe)₃. As a part of our mechanistic studies on reaction intermediate B (the alkyl hydroperoxide), we examined the effect of different reducing agents on Gif-type reactions. Logically, one would expect that reducing agents (such as PPh₃, see above) would intercept the hydroperoxide and convert it into the alcohol. However, a related reducing agent, the easily oxidizable P(OMe)₃, gave us another piece of mechanistic information. When P(OMe)₃ was added to a Gif[IV] reaction on cyclohexane, mainly ketone and a new product were obtained. This was identified as cyclohexyl dimethyl phosphate.[28]

How is the alkyl dimethyl phosphate formed? NMR experiments showed that cyclohexyl hydroperoxide is reduced instantly and quantitatively to cyclohexanol by P(OMe)₃ in pyridine/acetic acid. Also, a catalytic amount of an iron salt in the same solvent mixture converts quantitatively the cyclohexyl hydroperoxide to cyclohexanone. However, when P(OMe)₃ *and* a

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(26) Barton, D. H. R.; Boivin, J.; Le Coupanec, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1379–1380.
(27) Newcomb, M.; Manek, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 9662–9663.
(28) Barton, D. H. R.; Bévière, S. D.; Doller, D. *Tetrahedron Lett.* **1991**, *32*, 4671–4674.

catalytic amount of an iron salt react in pyridine/acetic acid with cyclohexyl hydroperoxide, a mixture of ketone, alcohol, and the alkyl dimethyl phosphate is obtained. These results suggest that coordination of the alkyl hydroperoxide with iron changes the reactivity of the R–O–O–H moiety, setting up the right environment for the formation of the alkyl dimethyl phosphate (Figure 8).

We also examined the possibility of setting up a radical chain autoxidation reaction in the presence of O₂ and P(OMe)₃. Again, genuine cyclohexyl and cyclopentyl radicals were generated through the thione methodology and reacted in the presence of O₂ and P(OMe)₃. Carbon radicals react with oxygen to give peroxyl radicals R–O–O•. This type of radical is well-known to react with trialkyl phosphites to furnish alkoxy radicals and trialkyl phosphates. The alkoxy radicals in turn react in the same way to give trialkyl phosphate with re-formation of the original alkyl radical. In fact, this reaction is a way of converting trialkyl phosphite catalytically to trialkyl phosphate. In agreement, we have found that carbon radicals generated in pyridine/acetic acid and cyclohexane in the presence of trimethyl phosphite and oxygen do not afford cyclohexyl dimethyl phosphate, but give an excess of trimethyl phosphate (425%). The chemistry involved is summarized in Figure 9.

3. Running the GoAgg[II] Reaction under Reduced Pressure. Reaction with Tempo. Additional evidence regarding the non-carbon radical nature of intermediate A was established by running GoAgg[II] experiments under reduced pressure (10–40 mmHg). Of course, Fe(III) reacts with H₂O₂ to furnish oxygen, but the reduced pressure removes this so that only traces of ketone and alcohol are formed. Tempo (**16**) is an excellent trap for carbon radicals. An example of trapping by Tempo of the cyclohexyl radical was observed in the photolysis of the N-hydroxy-2(1H)-thiopyridone derivative of cyclohexanecarboxylic acid to give the adduct **17** in reasonable yield. When a GoAgg[II] reaction with cyclohexane was run under reduced pressure in the presence of Tempo, adduct **17**
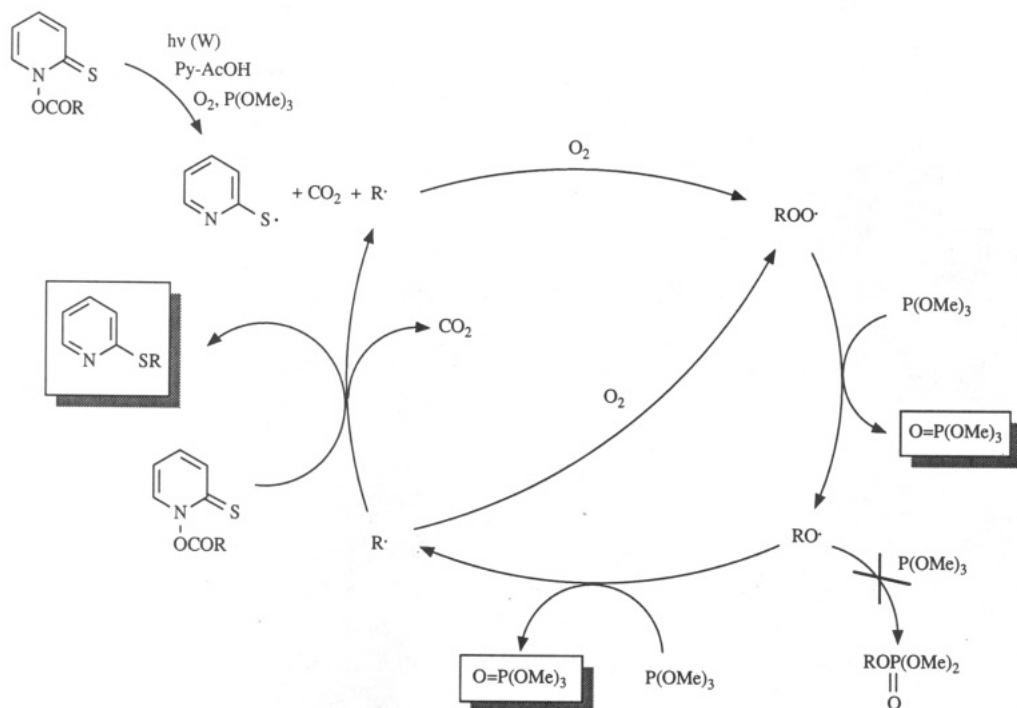
Figure 9. Radical chain cycle for the photolysis of the cyclohexanecarboxylic acid derivative of *N*-hydroxy-2(1*H*)-thiopyridone in the presence of trimethyl phosphite and oxygen.

was formed in approximately the same amount as ketone would have been formed in a normal reaction without reduced pressure. However, if no Tempo was added, no oxidation products were formed under reduced pressure; and no matter how much hydrogen peroxide was added or for how long the reaction was run, there was no formation of cyclohexylpyridines. The appropriate blank experiments have always confirmed that cyclohexyl radicals, in the absence of oxygen, are efficiently trapped by the solvent pyridine. Hence, Tempo cannot be trapping carbon radicals. It must be trapping the iron–carbon bond. The same experiments were carried out on cyclopentane with similar results. If CBrCl₃ is added instead of Tempo, the alkyl bromide is formed in a yield comparable to that of normal oxidation products. Again, there is no coupling to pyridine.

All these vacuum experiments were carried out with double dry ice traps. The first trap contained a little pyridine and hydrocarbon, which was added to the main reaction mixture before workup. The second (control) trap contained nothing.

4. Alkane Bromination under Gif-Type Conditions. The chain free radical halogenation of saturated hydrocarbons is a well-studied process in organic chemistry. Gif chemistry is able to carry out the same transformation through a different route. Indeed, when CBrCl₃ is added to a GoAgg^{III} reaction, the formation of ketone and alcohol is almost completely diverted toward the production of alkyl bromide. What kind of mechanism does this reaction follow? To examine the possibility of a carbon radical reaction intermediate, we compared the bromination of saturated hydrocarbons under typical radical chain conditions and under GoAgg conditions. We looked upon two aspects of these processes: the selectivity from the point of view of the

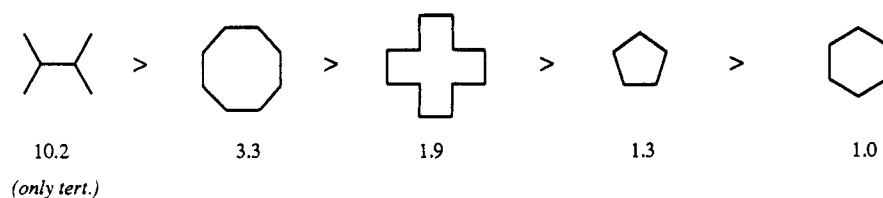hydrocarbon and from the point of view of the brominating reagent.[29]

The hydrocarbon selectivity for a radical chain bromination with CBrCl₃ was studied for a series of saturated hydrocarbons. The order found is shown in Figure 10. It is clearly seen that the two processes show a different selectivity. The stability of all the reaction products under the reaction conditions was demonstrated by the appropriate blank experiments.

We also tested several halogenating reagents and compared their efficiency as traps for carbon radicals. We carried out experiments having genuine carbon radicals competing between the halogenating species and thiophenol (which converts carbon radicals into alkanes). This resulted in an order of reactivity of brominating traps that is in agreement with the scarce data in the literature. On the other hand, the efficiency of the brominating reagent as a trap of intermediate A was measured as the alkyl bromide/ketone ratio. The results are summarized in Figure 11. If intermediate A were a carbon radical, one would expect to find the same order of efficiency in both experiments. Again, the results are not compatible with a carbon radical structure for intermediate A.

5. Effect of CO. Under an atmosphere of CO and O₂ (1/1), with Cu⁰ or Fe⁰ being employed as electron source, the ketonization of saturated hydrocarbons (c-C_nH_{2n}) is partially diverted toward the formation of the corresponding carboxylic acid (c-C_nH_{2n-1}COOH). Again, experiments with carbon radicals competing for O₂ and CO showed that the oxygenation process is much more favorable, in agreement with literature reports. Mechanistic studies support a reaction pathway involving the insertion of CO into a carbon–metal bond, according to Figure 12.[30]

(29) Barton, D. H. R.; Csuhai, E.; Doller, D. *Tetrahedron Lett.* **1992**, *33*, 3413–3416.

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Gif Chemistry

Acc. Chem. Res., Vol. 25, No. 11, 1992 **511**

Radical bromination with CBrCl₃ (normalized)

10.2   3.3   1.9   1.3   1.0

(only tert.)

Bromination with CBrCl₃ under GoAgg^{III} conditions (normalized)

tert. 0.18   0.63   0.69   0.76   1.0
prim. 0.06
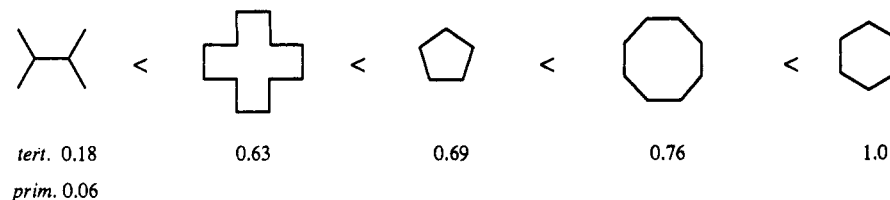
Figure 10. Comparison between the bromination of different saturated hydrocarbons with CBrCl₃ under radical and GoAgg^{III} conditions.

Reactivity order as brominating reagents under chain radical reaction conditions.
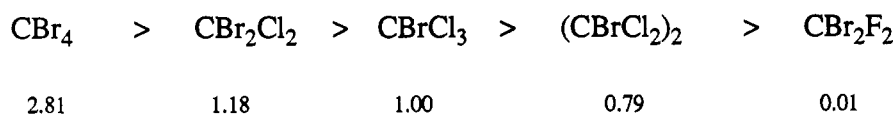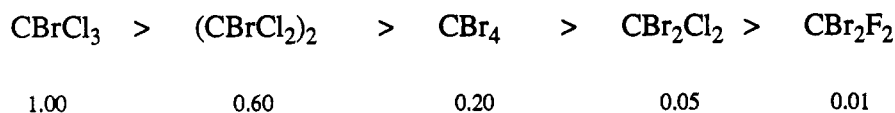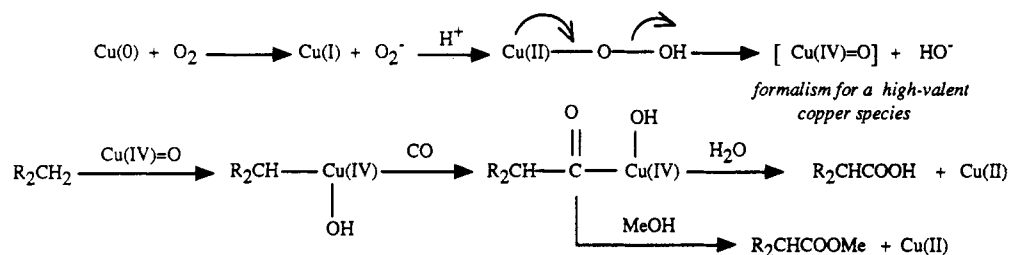
$$CBr_4 \quad > \quad CBr_2Cl_2 \quad > \quad CBrCl_3 \quad > \quad (CBrCl_2)_2 \quad > \quad CBr_2F_2$$

2.81   1.18   1.00   0.79   0.01

Reactivity order as brominating reagents in GoAgg^{III} reactions.

$$CBrCl_3 \quad > \quad (CBrCl_2)_2 \quad > \quad CBr_4 \quad > \quad CBr_2Cl_2 \quad > \quad CBr_2F_2$$

1.00   0.60   0.20   0.05   0.01

Figure 11. Comparison among different brominating reagents under chain radical and GoAgg^{III} conditions.

Figure 12. Proposed reaction mechanism for the carboxylation of saturated hydrocarbons under Gif-type reaction conditions.

Conclusion

From all this evidence it is clear that, in our mechanistic scheme, reaction intermediate A could not be a carbon radical. What is A, then? We propose for GoAgg^{II} reactions the mechanism shown in Figure 13. As usual, ligands around the iron atom have been omitted for clarity. We consider this a logical pathway which explains all the facts of Gif chemistry known up to the present. The formation of Fe^V=O species by reaction between Fe(III) salts and H₂O₂ has been recently reported.[13] As stated before, this species is equivalent to that widely accepted in CP-450 chemistry. The reduction of R₃CFe^V to R₃CFe^{III} is an accepted part of the mechanism of dismutation of hydrogen peroxide to water and oxygen catalyzed by catalase. The insertion of dioxygen into carbon–Fe(III) porphyrinic derivatives is also well documented in the literature.[31]

The Gif Paradox and the Sleeping Beauty

The Gif paradox, clear from our experiments, is that we oxidize saturated hydrocarbons to ketones at a faster rate than we transform other easy-to-oxidize compounds. H₂S, Ph₂S, PPh₃, and P(OMe)₃ do not inhibit the reaction. Furthermore, secondary alcohols, acetone, diisopropyl ether, biphenyl, etc., all compounds which are agreed to be more easily oxidized than saturated hydrocarbons, do not interfere when added in amounts equal to the amount of oxidation. How can all this be possible?

Before any attempt is made at answering this question, there is additional relevant information to be taken into account. A few years ago, Prof. Shilov and

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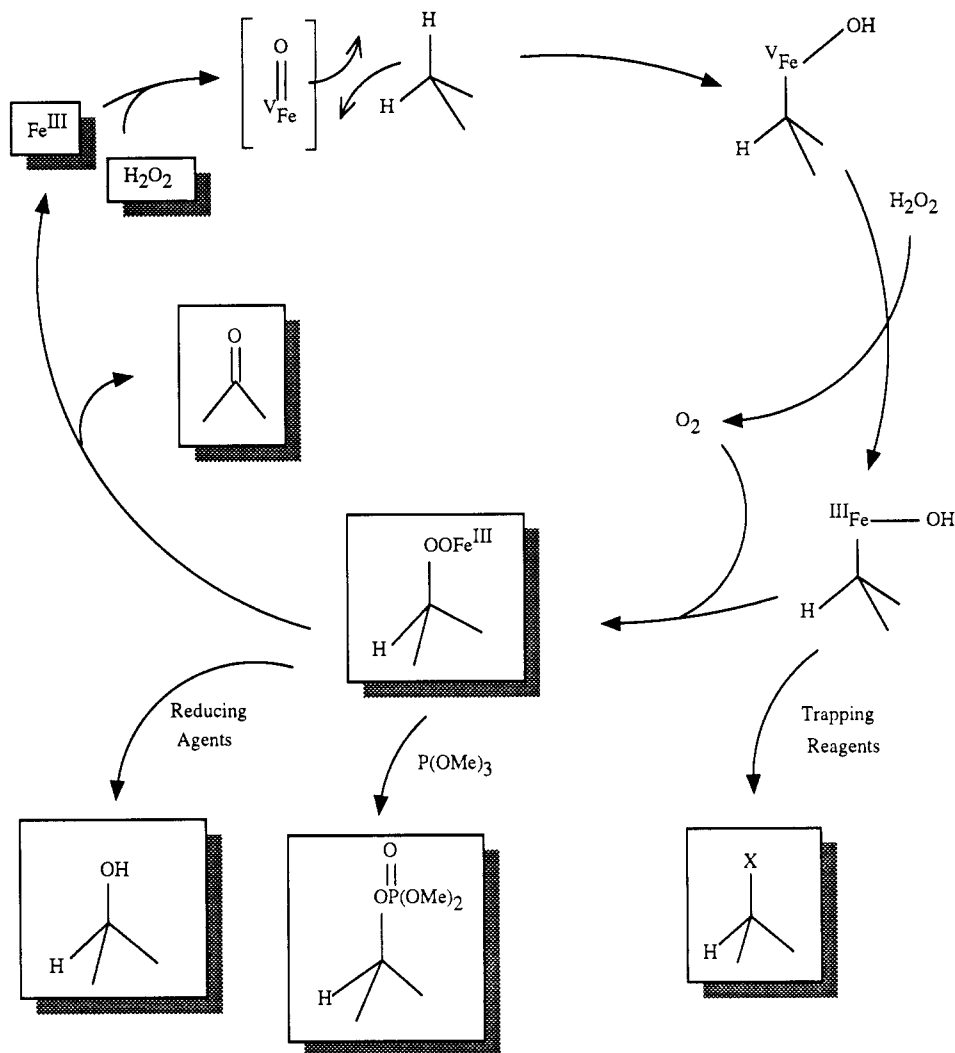
Figure 13. Proposed catalytic cycle for GoAgg^{II} reactions.

Dr. Geletii studied the activation of saturated hydrocarbons by copper metal coupled to dioxygen reduction.[32] Inspired by this pioneering work, Geletii proposed the GoChAgg system (Table I), in which under Cu(II) catalysis in pyridine/acetic acid solution saturated hydrocarbons are oxidized to ketones.[32] Besides sharing a few important characteristics of the Gif family, the differences between the Cu(II)-based and the Fe(III)-based systems are a manifestation of the metal dependence of the chemistry associated with the hydrocarbon activation process.[33]

The only way that we can explain these results is by a hypothesis that the reagent that oxidizes the hydrocarbon is present in a dormant form (Sleeping Beauty) until it collides with the saturated hydrocarbon (the Prince) and reacts with a saturated C–H bond (the kiss) to form the real reagent, which immediately gives the iron–carbon bond (intermediate A). So, the hydrocarbon on contact with the iron species activates and reacts with the activated iron species without separation. The hydrocarbon should be inducing in the (formally) Fe^V=O species a change that makes possible such an unusual reaction. There is evidence in the

literature for this sort of agostic interaction between nonactivated carbon–hydrogen bonds and organometallic species.[34]

Of course, Gif chemistry challenges us with some still unanswered questions. These will surely become clear in the near future, no doubt just to face us with even more sophisticated dilemmas to be solved. However, we hope that in this instance we have proven that chemists should devote more of their efforts to the discovery and invention of new chemical processes, which seem to be there, dormant, waiting for us to bring them to life.

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