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The Gif Paradox

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ABSTRACT
This Account summarizes research work on the structural aspects and functional features encountered in all major branches of the Gif family of hydrocarbon-oxidizing reagents. Despite assertions by the inventor of Gif chemistry, D. H. R. Barton, to the effect that nonradical pathways could better explain the behavior of Gif systems, detailed experimental investigations provide compelling evidence to support the preponderance of oxygen- and carbon-centered radical chemistry.

Introduction

> "It would seem perhaps to be better, indeed necessary, that in the sake of preserving the truth, we have to do away even with what we keep most at heart, since, after all, we are philosophers; both are dear, but we have a sacred duty to place truth first." —Aristotle, *Nicomachean Ethics* 1096a14

In January 1983, a communication by Derek H. R. Barton[1] disclosed "a new procedure for the oxidation of saturated hydrocarbons", centered on a reagent composed of metallic iron and hydrogen sulfide dissolved in pyridine/acetic acid (10:1 v/v) in the presence of a small amount of water. Two observations were considered to support the novel nature of this system: first, the oxygenation of adamantane afforded 1-adamantanol and a mixture of 2-adamantanol and adamantanone, at yields signifying an unusually high selectivity for the secondary C−H position; and, second, the oxygenation of the hydrocarbon was uninhibited by the presence of such an easily oxidizable substrate as hydrogen sulfide. The latter observation, subsequently extended to include a host of similar substances (Ph_2S, PPh_3, $P(OMe)_3$, PhSH, PhSeH), has been known to constitute the "Gif paradox".[2]

An article by I. Tabushi and co-workers,[3] published in 1980, described a dioxygen-dependent system for the oxidation of adamantane mediated by $[Fe(salen)]_2O$ in the presence of 2-mercaptoethanol in pyridine. The oxygenation afforded 1-adamantanol, 2-adamantanol, and adamantanone. Notable was the high selectivity for the oxygenation of the secondary position ($3°/2° = 0.94$ (normalized)), and the preponderance of 2-adamantanol over adamantanone (2-ol/one = 3.2; Gif chemistry[2] usually gives the reverse preference), in contrast to product profiles derived from autoxidation of adamantane ($3°/2° = 2.4−5.5$; 2-ol/one ≈ 1). In autobiographical pages, Barton[4] summarized attempts to follow up on Tabushi's leads as follows: "We repeated the work of Tabushi, as well as many comparable experiments, always with miserable results. One day, I was reading a general article about the primitive world with its reducing atmosphere. It occured to me that most of the iron in the primitive world must have been metallic iron. The major iron ore deposits are, after all, supposed to have been produced by biological oxidative processes. I asked Michel Gästiger, who was doing the work, to add some iron powder (and acetic acid) to the Tabushi system. The result was a dramatic improvement in the percentage of oxidation (an increase of five- or tenfold!)". From these initial attempts in 1980 at Gif-sur-Yvette, and until Barton's death in 1998, "Gif chemistry" was vigorously pursued by Barton's group through several metamorphoses of the original system. This activity resulted in a stream of publications: 46 articles were presented in a thematic series on "the selective functionalization of saturated hydrocarbons", while another 60 articles, expounding on Gif-related chemistry, were published as independent contributions.

Summarized in Table 1 are different branches of the family of Gif reagents in chronological order. In all systems explored, the precatalyst is derived from a readily available source of iron or copper. Both oxidizing and reducing equivalents are necessary, and those are provided in Gif chemistry either by dioxygen combined with a reducing agent or via a reduced form of dioxygen. The most practical oxygenation system in the former category is supported by a heterogeneous mixture of $Fe_{cat}/O_2/Zn$ (Gif^{IV}); this system affords turnover numbers in excess of 2000.[14] The latter category is best represented by $GoAgg^{III}$-type homogeneous combinations of $FeCl_3/H_2O_2/PicH$ (PicH = 2-picolinic acid). Picolinic acid is known to enhance the rate of Gif oxygenations 50-fold over acetic acid.[10] The presence of a carboxylic acid is necessary for hydrocarbon oxidation, otherwise solely disproportionation of H_2O_2 is observed.[15] Pyridine is a decisive component for obtaining the good turnover numbers and the unusually high one/2-ol ratios (≈3−10) observed in Gif oxygenations. It can be replaced by a more practical solvent, such as acetonitrile, but a minimum amount of a coordinatively unhindered pyridine (>10 equiv over catalyst) is always essential for turnover.[16]

With some important exceptions, Barton[17] maintained that the peculiar selectivity of the Gif reaction, as well as data from related control experiments and diagnostic product profiles, are best accounted for by a mechanistic

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Table 1. Gif Oxygenation Systems in Chronological Order of Development

system	precatalyst	oxidant	reductant	solvent[c]	ref
Gif$^{\text{I}}$	none added[a]	O_2	Fe^0/Na_2S	py/AcOH (10:1 v/v)	1
Gif$^{\text{II}}$	none added[a]	O_2	Fe^0/H_2S	py/AcOH/H_2O (6.6%)	1, 5
Gif$^{\text{III}}$	none added[a]	O_2	Fe^0	py/AcOH/H_2O (6.6%) 40 °C	6
Gif$^{\text{IV}}$	$Fe^{\text{II/III}}$[b]	O_2	Zn	py/AcOH/H_2O[d] (6.6%)	6
GO	$Fe^{\text{II/III}}$[b]	O_2	Hg cathode	py/CF_3COOH	7
GoAgg$^{\text{I}}$	Fe^{II}	KO_2[e]		py/AcOH	8
GoAgg$^{\text{II}}$	Fe^{III}[f]	H_2O_2 (30%)[g]		py/AcOH	8, 9
GoAgg$^{\text{III}}$	Fe^{III}[f]/PicH (1:3)	H_2O_2 (30%)[g]		py/AcOH (or py)	10
GoChAgg$^{\text{I}}$	Cu^{II}	H_2O_2 (30%)[g]		py/AcOH (or py)	11
GoChAgg$^{\text{II}}$	none added[a]	O_2	Cu^0	py/AcOH	12
GoAgg$^{\text{IV}}$[h]	Fe^{III}[i]	*t*-BuOOH (90%)[g]		py/AcOH, 60 °C	13
GoAgg$^{\text{V}}$[h]	Fe^{III}[i]/PicH (1:3)	*t*-BuOOH (90%)[g]		py/AcOH, 60 °C	13

[a] Although no compound is added, the zerovalent metal partially dissolves in solution. [b] Usually $[Fe_3O(OAc)_6(py)_3]\cdot 0.5py$. [c] At room temperature, unless otherwise noted. [d] Addition of H_2O is optional. [e] Under inert gas (Ar, N_2). [f] Usually $FeCl_3\cdot 6H_2O$. [g] Under inert gas or O_2. [h] Later expelled from the Gif family.[13] [i] Usually $Fe(NO_3)_3\cdot 9H_2O$.

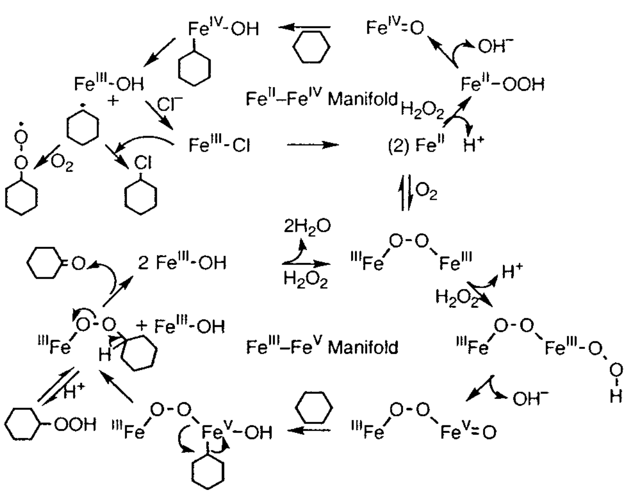
pathway featuring metal-bound oxidants and intermediates, rather than diffusively free oxygen- and carbon-centered radicals. The present Account details research work that provides compelling evidence that "radical" chemistry pervades all major Gif oxygenation systems. This conclusion has been reached by examining branches of the Gif family in an order reverse to their development.

Irrespective of the mechanistic ambiguities, Gif chemistry attracted interest for industrial applications, especially in relation to the conversion of cyclohexane or cyclododecane to the corresponding ketone and alcohol. The one/2-ol mixture is an important feedstock for further catalytic oxidation to adipic acid or 1,12-dodecanedioic acid, both of which are key precursors in the DuPont Nylon manufacturing process. Major limitations of the Gif reaction are (i) the relatively slow reaction rate (0.267 M solutions of one/2-ol with 100% selectivity achieved in 1 h, versus 0.3 M at 80% selectivity in 40 min for the industrial autoxidation process); (ii) the sizable amount of catalyst needed and its quick precipitation/deactivation to form particulate iron oxides/hydroxides; and (iii) the dependence on pyridine, an expensive and toxic solvent.[18]

The Gif Reaction: Nonradical or Radical Mechanism?

Barton's Mechanism. The alleged selectivity for the oxygenation of secondary bonds in Gif chemistry (*sec* > *tert* ≫ *prim*) and the modest KIE values (≈2 for ketone) have been interpreted by Barton[2] via a mechanism (Scheme 1) featuring a high-valent $Fe^{V}{=}O$ oxidant performing [2+2]-type concerted addition to C−H bonds. The preference for *sec*-C−H activation then arises as a compromise between bond strength and steric encumbrance, while the KIE values reflect the side-on C−H approach in the transition state. The resulting organometallic species is subsequently converted to ketone (major product) and alcohol (minor reduction product) via initial formation of alkylhydroperoxide.[19] The oxygen content of ROOH in cyclodecane oxygenation experiments was shown by Perkins[20] (confirmed by Barton[19] for cyclohexane) to be derived from dioxygen. This result alone strongly suggests the possibility of radical chemistry interference ($R^{\bullet} + O_2 \rightarrow ROO^{\bullet}$). Informed by diagnostic alkyl-radical trapping tests,[9] which were perceived to exclude $R^{\bullet}/ROO^{\bullet}$ involvement, Barton's mechanism featured metal-bound R−/ROO− moieties.

Scheme 1



In addition to this "nonradical $Fe^{\text{III}}/Fe^{\text{V}}$ manifold" arising from Fe^{III}/H_2O_2 chemistry, Barton had also recognized the existence of a "radical $Fe^{\text{II}}/Fe^{\text{IV}}$ manifold" generated from circumstantial Fe^{II}/H_2O_2 interactions.[15,17] The latter does not generate $HO^{\bullet}$ radicals (Fenton chemistry) but a high-valent $Fe^{\text{IV}}{=}O$ oxidant that behaves similarly to the $Fe^{\text{V}}{=}O$ unit of the nonradical manifold, save for the presumed collapse of the resulting $Fe^{\text{IV}}{-}C$ moiety to afford alkyl radicals. The corresponding $Fe^{\text{V}}{-}R$ bond is assumed to dissociate only in exceptional cases (most notably when R = *tert*-adamantyl). Allegedly, the two manifolds can interconvert via reversible dioxygen activation. The distinction between the two manifolds was largely based on experiments[15] indicating rapid formation of alkyl chlorides ($R^{\bullet} + Fe^{\text{III}}{-}Cl \rightarrow R{-}Cl + Fe^{\text{II}}$) in the presence of $Fe(II)/H_2O_2$. Once all Fe(II) had been oxidized to Fe(III), generation of RCl ceased, and the slow ketonization process took over.

Reappraisal of Gif/*t*-BuOOH Systems. In a reinvestigation of GoAgg$^{\text{IV}}$ and GoAgg$^{\text{V}}$ systems, Minisci[21] was first to recognize that these *t*-BuOOH-based reagents provide unmistakable evidence of *t*-BuO$^{\bullet}$/*t*-BuOO$^{\bullet}$ involvement. Minisci's mechanism for Gif/*t*-BuOOH systems is a Haber−Weiss−Walling radical chain, resulting in selectivities dictated by the predominance of *t*-BuO$^{\bullet}$ over *t*-BuOO$^{\bullet}$, owing to the resistance of the H-bonded *t*-BuOOH to undergo H-atom abstraction.[22] Similar conclusions have also been reached by Ingold and Wayner,[23] who have employed GoAgg^V systems supported by diagnostic alkylhydroperoxides. Barton's reexamination[13] of the Gif/*t*-BuOOH systems concurred that *t*-BuO$^\bullet$/*t*-BuOO$^\bullet$ radicals were generated via decomposition of *t*-BuOOH by Fe(II)/Fe(III).

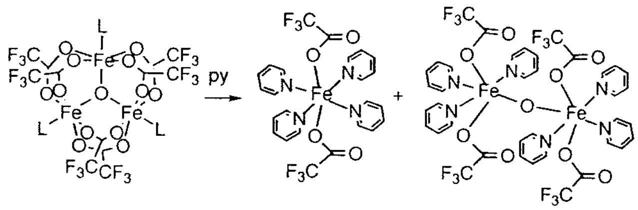
Minisci's work with *t*-BuOOH-supported P-450 mimics[22] confirmed that employment of *t*-BuOOH introduces a substantial *t*-BuO$^\bullet$/*t*-BuOO$^\bullet$ radical component. Therefore, *t*-BuOOH-based systems are not necessarily faithful mechanistic indicators to report on reagents supported by H_2O_2 or O_2.

Gif/H_2O_2 Systems. (i) Evidence for the Generation of Diffusively Free Substrate Radicals. Prior to our work, only a handful of experimental results were available to address the mechanistic ambiguities of Gif/H_2O_2 systems. Most prominent was an elegant study by M. Newcomb,[24] which succeeded in highlighting crucial differences in the mechanism of a GoAgg^{III} reagent and the biological oxygenases P-450 and sMMO. By employing ultrafast cyclopropane radical probe substrates, Newcomb's results strongly supported the notion that the Gif system generated diffusively free substrate-centered radicals. In contrast, the enzymatic processes generated transient (<100 fs) carbon-centered radicals, participating as a component of the transition state. Barton[17] speculated that the long-lived probe radicals were the result of the exceptional cleavage of a precursor Fe^V–R bond, similar to that encountered with the tertiary positions of adamantane. A brief report by Perkins[20] provided an early indication that GoAgg^{II} oxidation of cyclohexane involves participation not only of cyclohexyl radicals (spin-trapped and detected by EPR) but also of hydroxyl radicals (determined by virtue of para-hydroxylation of phenylalanine). An influential review by Perkins[25] pointed out several inconsistencies in Barton's mechanistic analysis.

In view of the emerging mechanistic controversy at the time, we chose to employ mainstream Gif systems and common substrates that were used by Barton in support of a "nonradical" mechanism. We followed a two-step approach: first, we investigated whether diffusively free, carbon-centered radicals were entirely dictating the observed product profile; and second, we inquired whether free oxygen-centered radicals (HO$^\bullet$, RO$^\bullet$), rather than metal-bound oxidants, were responsible for abstracting H atoms from alkanes.

(ii) Iron Trifluoroacetate/H_2O_2 Systems. The first Gif-type reagents that alerted us to the possibility that not only the tertiary but also the secondary C–H sites of adamantane may be activated via H-atom abstraction to generate adamantyl radicals were Fe$_{cat}$/H_2O_2 systems in py/TFA (10:1 v/v).[26] A convenient entry to suitable iron precatalysts is achieved by dissociation of the mixed-valent $[Fe_3O(O_2CCF_3)_6(L)_3]$ (L = H_2O (**1**), DMSO (**2**)) in pyridine to afford *trans*-$[Fe^{II}(O_2CCF_3)_2(py)_4]$ (**3**) and $[Fe^{III}_2O(O_2CCF_3)_4(py)_6]$ (**4**) (Scheme 2).

Scheme 2

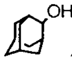
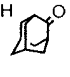
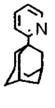
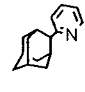
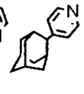


L = H_2O (**1**)
L = DMSO (**2**)

3

4

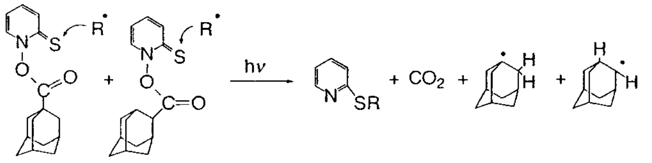
Table 2. Product Profile of Adamantane Oxidation[a] by H_2O_2 Mediated by 3 or 4, and via Authentic Adamantyl Radicals[a]

System	Products (mmol)							3°/2°
								
3/Ar	0.001	nd	0.004	0.124	0.085	0.132	0.124	2.4
3/O_2(4%)	0.003	0.016	0.117	0.120	0.077	0.018	0.018	3.5
3/O_2	0.034	0.027	0.143	0.128	0.078	0.001	0.001	4.2
4/Ar	0.001	0.002	0.036	0.100	0.065	0.057	0.057	3.3
4/O_2(4%)	0.003	0.011	0.095	0.088	0.059	0.010	0.011	3.5
4/O_2	0.025	0.015	0.098	0.091	0.056	0.001	nd	4.5
3/O_2(4%)[b]	0.002	tr	0.027	0.029	0.032	0.002	0.003	

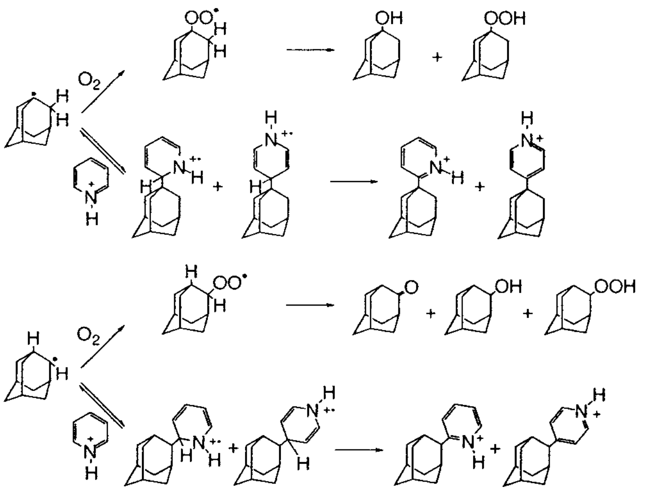
[a] See text for conditions. [b] Photolysis of Barton's PTOC esters.

The most striking and hitherto unexpected result in Gif oxygenations of adamantane (Table 2) was an important addition to the product profile. The usual partitioning of products includes oxo adamantanes (1-ol, 2-ol, 2-one) and, as Barton had recognized with some delay, *tert*-adamantylpyridines arising from coupling of *tert*-adamantyl radicals with protonated pyridine (positions 2 and 4).[27] For the first time, *sec*-adamantylpyridines were also observed in comparable yields. The alleged absence of *sec*-adamantylpyridines from Gif product profiles has been a historic argument in Barton's defense[19] of a predominantly nonradical mechanism for the activation of *sec*-C–H bonds in adamantane oxidations. It is also important to note that both Fe(II) (**3**)/H_2O_2 and Fe(III) (**4**)/H_2O_2 systems provide *sec*-adamantylpyridines, suggesting that a clear distinction between the proposed two manifolds cannot be readily made. However, in both cases the active oxidant is most likely generated through Fe(II)/H_2O_2 chemistry, as moderately air-stable Fe(II) sites can be easily formed by Fe(III) (**4**)/H_2O_2 combinations in py/TFA. Another notable trend in the product profile is the shift toward increased formation of oxo products at the expense of pyridine-coupled products (most conspicuously for the secondary position) with increasing partial pressure of O_2. This is accompanied by a progressive increase in the *tert*/*sec* selectivity values. The former observation suggests that dioxygen and pyridine compete for capturing *tert*- and *sec*-adamantyl radicals, as subsequently confirmed in control experiments. The latter result is consistent with progres-

Scheme 3



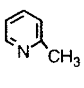
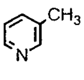
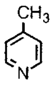
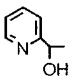
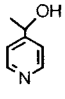
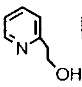
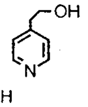
Scheme 4



sive interference of a more selective oxidant upon increasing O_2 pressures.

To explore whether the observed product profiles were largely derived from trapping of *tert*- and, most importantly, *sec*-adamantyl radicals by dioxygen and protonated pyridine, we turned our attention to a control experiment[9] that has been central to Barton's argument in favor of a nonradical mechanism for the activation of *sec*-C−H positions of alkanes. In Barton's experiment, authentic *tert*- and *sec*-adamantyl radicals, generated by photolysis of the corresponding Barton PTOC esters in py/AcOH under 4% O_2 (Scheme 3), were allowed to partition between protonated pyridine, O_2, and the 2-pyridylthiyl moiety of Barton's esters. While both *tert*- and *sec*-adamantyl radicals are captured by O_2 at diffusion-controlled rates, the rate constant for the *reversible* addition of the highly nucleophilic *tert*-adamantyl radicals to protonated pyridine has been evaluated[27] to be larger, by 2 orders of magnitude, than that for *sec*-adamantyl radicals (Scheme 4). The so-obtained adamantylpyridinium radicals are highly reducing and rapidly rearomatize to the final adamantylpyridines. Barton's experiment furnished a value of 0.74 for the ratio of oxygen trapped over pyridine-coupled *tert*-adamantyl radicals and one of 4.3 for the *sec*-adamantyl radicals. In contrast, the corresponding Gif^{IV}-type ($FeCl_2/Zn/O_2$ (4%)) oxidation of adamantane afforded a ratio of 0.03 for the tertiary positions and one of 94 for the secondary sites. The predominance of *tert*-adamantylpyridines in the Gif experiment clearly established the case of radical activation for the *tert*-C−H position, and the discrepancy of values by comparison to the control experiment was attributed to the preferential coupling of *tert*-adamantyl radicals to *metal-bound* pyridine.[9] On the other hand, the miniscule amounts of *sec*-adamantylpyridines observed in the Gif oxidation versus those of the control experiment were interpreted as a clear indication of a nonradical mechanism for the secondary position. Minisci[27] has hypothesized that the discrepancy may arise due to the reductive environment of the Gif^{IV} solutions that disfavors the irreversible rearomatization step; thus, by virtue of the most reversible *sec*-adamantyl radical addition to pyridinium, dioxygen is allowed to compete effectively for capturing *sec*-adamantyl radicals.

Table 3. Product Profile of DMSO/EtOH Oxidations by H_2O_2 Mediated by 3 under Ar

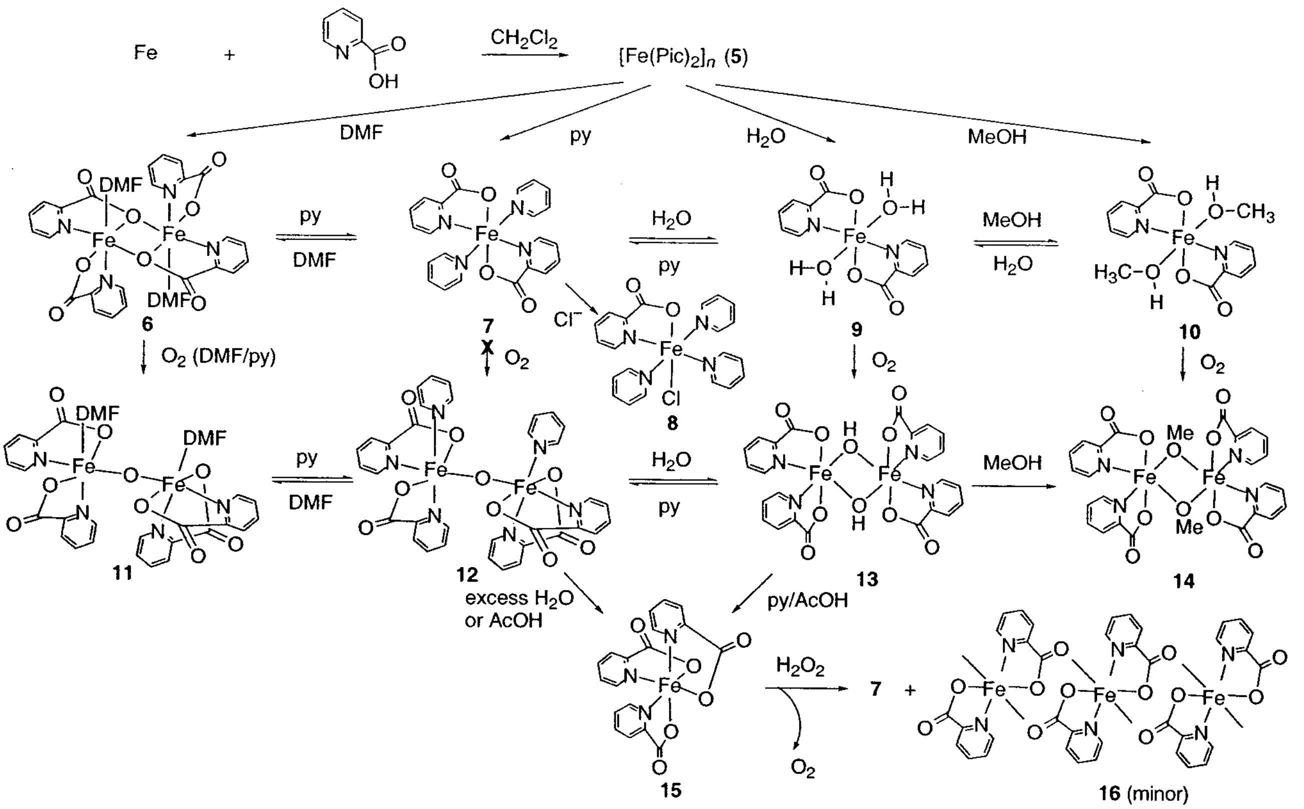
Entry	Products (mmol)							k_{EtOH}/k_{DMSO}
								
1[a]	0.198	0.026	0.099					
2[b]	0.154	0.016	0.078	0.026	0.011	0.003	0.002	0.29
3[c]	0.179	0.020	0.090	0.092	0.038	0.013	0.005	0.36
4[d]	0.118	0.016	0.059	0.080	0.029	0.009	0.004	0.32

[a] DMSO (5 mmol). [b] DMSO/EtOH (5:3). [c] DMSO/EtOH (5:7). [d] DMSO/EtOH (5:10).

We have revisited this control experiment by generating *tert*- and *sec*-adamantyl radicals via photolysis of the appropriate Barton PTOC esters in py/TFA (10:1 v/v) under O_2 (4%). In contrast to Barton's experiment, precatalyst **3** was added to the solution to better mimic the conditions of the Gif reaction. This is necessary, as iron ions can be involved in redox reactions with alkyl radicals, thus affecting the product profile of the competition experiment. The ratio of oxo- versus pyridine-trapped adamantyl products is found to be 0.03 for the tertiary and 5.4 for the secondary position. The Gif reaction (**3**/H_2O_2) under comparable conditions provides the corresponding values of 0.02 and 3.7. These values are in good agreement and establish that the entire product profile of adamantane oxidation is fully consistent with partitioning of adamantyl radicals between dioxygen and protonated pyridine.

The highly specific addition reaction of HO• radicals to DMSO (eq 1) was employed, along with the competitive H-atom abstraction from EtOH (eq 2), to investigate whether the competition kinetics support HO• radical involvement. The analysis was accomplished by trapping the alkyl radicals generated in eqs 1 and 2 with py/$[pyNH]^+$. A constant stream of Ar was applied to avoid capturing of alkyl radicals by O_2. The diffusion-controlled oxidation of α-hydroxyethyl radicals by Fe(III) (eq 3) can interfere, but the low iron concentrations and the preponderance of TFA-stabilized Fe(II) sites minimize the importance of this reaction. In the presence of DMSO, all possible methylpyridines (picolines) were observed (Table 3), resulting from the addition of the highly reactive methyl radical to py/$[pyNH]^+$. Traces of methylated bipyridines were also observed by GC−MS. Upon addition of increasing amounts of EtOH, both α- and *β*-hydroxyethylpyridines were obtained in increasing relative amounts versus those of methylpyridines, denoting competition

Scheme 5



between EtOH and DMSO. An average $k_{\mathrm{EtOH}}/k_{\mathrm{DMSO}}$ value of 0.32(4), extracted from the ratio of methylpyridines over hydroxyethylpyridines and the initial concentrations of DMSO and EtOH, is consistent with the expected ratio of rate constants ($k_{\mathrm{EtOH}}/k_{\mathrm{DMSO}} = 0.29$) for radiolytic HO• attack on EtOH/DMSO.

$$\mathrm{Me_2S{=}O + HO^{\bullet} \rightarrow MeS({=}O)OH + Me^{\bullet}} \qquad (1)$$

$$\mathrm{CH_3CH_2OH + HO^{\bullet} \rightarrow H_2O + {}^{\bullet}CH_2CH_2OH\ (13.2\%) + CH_3{}^{\bullet}CHOH\ (84.3\%) + CH_3CH_2O^{\bullet}\ (2.5\%)} \qquad (2)$$

$$\mathrm{Fe^{III} + CH_3{}^{\bullet}CHOH \rightarrow Fe^{II} + H^+ + CH_3CHO} \qquad (3)$$

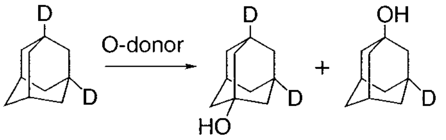
(iii) Iron Picolinate/H_2O_2 Systems. GoAgg$^{\mathrm{III}}$-type oxygenation reagents constitute the most efficient and commonly used Gif systems in mechanistic studies. Scheme 5 summarizes pertinent Fe(II) and Fe(III) picolinate precursors along with relevant interconversions.[28] Oxidations of adamantane by H_2O_2 were performed in the presence of ferrous and ferric precatalysts. In the presence of [Fe$^{\mathrm{II}}$(Pic)$_2$(py)$_2$], both *tert*- and *sec*-adamantylpyridines were again observed to dominate the product profile,[28] in amounts diminishing with increasing partial pressures of O_2, most prominently for the secondary position. Notable is also the concomitant increase in *tert*/*sec* selectivity values with increasing dioxygen pressure. Addition of excess Zn under N_2 minimizes the amounts of oxo adamantyl products in favor of pyridine-coupled products. Zinc is expected to slowly scavenge O_2 or act via rapid reduction of Fe(III) sites, thus minimizing dioxygen generated from Fe(III)/H_2O_2 interactions. On the other hand, the *tert*/*sec* selectivity (≈4.6) observed in the presence of Zn is one of the highest obtained, indicating that Zn may quench HO• more efficiently than RO• radicals.

Similar trends are observed for oxidations of adamantane by H_2O_2 in the presence of [Fe(Pic)$_3$] or [Fe$^{\mathrm{III}}_2$O(Pic)$_4$(py)$_2$]. Again, *sec*-adamantylpyridines are readily detected under N_2,[28] albeit in suppressed amounts by comparison to the oxo adamantyl products, most likely due to internal generation of oxygen. Two instructive examples of adamantane oxygenations in which *sec*-adamantylpyridines are barely detected, even under inert atmosphere, are those mediated by [Fe$^{\mathrm{III}}_2$(μ-OH)$_2$(Pic)$_4$] and FeCl$_3$. Careful inspection of the product profile indicates that an unusually high amount of 2-ol versus 2-one is observed in the former case, while the latter example features two new products not previously detected in Barton's work,[15] namely 1-chloro-adamantane and 2-chloro-adamantane. Indeed, the absence of *sec*-adamantylpyridines is fully compensated for by the presence of 2-ol or 2-Cl-Ad. The chlorinated product can be readily attributed to the diffusion-controlled Cl-atom abstraction from Fe$^{\mathrm{III}}$−Cl units by alkyl radicals (eq 4). A similar reaction may account for −OH abstraction from Fe$^{\mathrm{III}}$−OH moieties.

$$\mathrm{Fe^{III}{-}Cl + Ad^{\bullet} \rightarrow Fe^{II} + Ad{-}Cl} \qquad (4)$$

Competition kinetics confirmed that the observed product profiles are dictated by partition of *tert*- and *sec*-adamantyl radicals between dioxygen (4%) and protonated pyridine.[28] Competitive capturing of adamantyl radicals

Scheme 6



was also studied under pure O_2, but this time in the presence of the superior alkyl-radical trap TEMPO (0.15 M). Both 1-Ad-TEMPO and 2-Ad-TEMPO were detected and quantified by GC and GC−MS. In the presence of $[Fe^{II}(Pic)_2(py)_2]$, authentic *tert*- and *sec*-adamantyl radicals partition between TEMPO and O_2 in py/AcOH to afford values of *tert*-Ad-TEMPO/Ad(O) (0.56) and *sec*-Ad-TEMPO/Ad(O) (0.46) that correspond closely to values obtained from Gif oxidation of adamantane under identical conditions (*tert*-Ad-TEMPO/Ad(O) = 0.52; *sec*-Ad-TEMPO/Ad(O) = 0.44). Good correspondence of partition values has also been documented in the presence of $[Fe(Pic)_3]$. These results confirm that carbon-centered radicals are generated under all conditions, irrespective of O_2 partial pressures and the presence of Fe(II) or Fe(III).

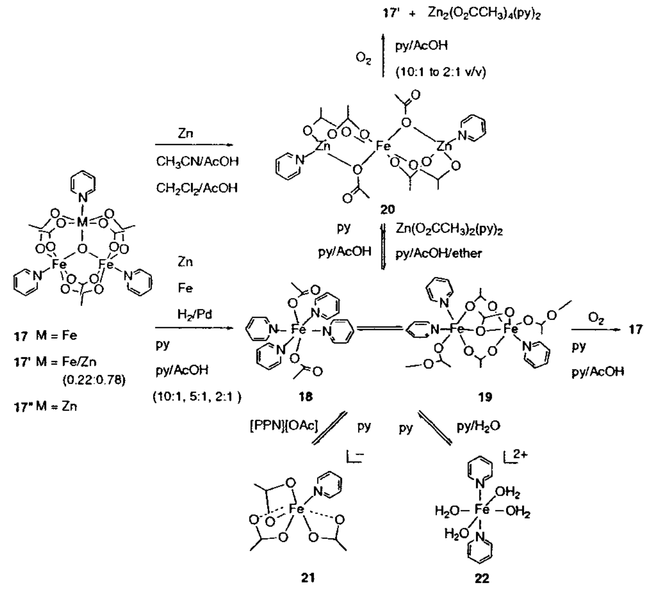
Several lines of evidence support the contention that hydroxyl radicals are the major H-atom-abstracting entities generated by these iron picolinate reagents. Using adamantane-1,3-d_2 (Scheme 6) as the substrate[28] of a Gif system composed of $[Fe(Pic)_2(py)_2]/H_2O_2$, we obtain a primary KIE value of 1.06(6) under N_2 and 1.73(2) under O_2(4%) for oxidation to 1-adamantanol. The value close to unity is consistent with the known kinetics of hydroxyl radicals, while the larger value obtained under 4% O_2 probably reflects the interference of a more selective, H(D)-abstracting agent, most likely 1-adamantyloxyl radicals. A measured intermolecular KIE value of 1.46(3) for the oxygenation of adamantane/adamantane-d_{16} to 2-adamantanol by the same oxidation system would suggest that the contribution from a secondary KIE can be as large as 1.4. This sizable value is consistent with H-atom abstraction, rather than insertion to or hydride abstraction from a C−H bond.

More direct evidence for the involvement of hydroxyl radicals is obtained from the competitive reaction of $HO^{\bullet}$ with DMSO/EtOH, enabling a rough evaluation of k_{EtOH}/k_{DMSO} (0.34(3)) and $k_{CH_3CH_2OH}/k_{CH_3CH_2OH}$ (7.3(4)), in reasonable agreement with known hydroxyl radical kinetics. The generation of methyl radicals from the addition reaction of $HO^{\bullet}$ to DMSO has also been documented via the thermodynamically driven iodine-atom abstraction from 1-Ad-I by the very reactive $Me^{\bullet}$ to generate the more nucleophilic 1-$Ad^{\bullet}$ radical (eq 5). When the amount of 1-Ad-I is adjusted so that picolines are no longer observed, the only products obtained are the two *tert*-adamantylpyridines and traces of 1-adamantanol.

$$Me^{\bullet} + 1\text{-Ad-I} \rightarrow Me\text{-I} + 1\text{-Ad}^{\bullet} \qquad (5)$$

Gif/O_2/Zn Systems. (i) Iron and Ruthenium Acetate Reagents. These systems were scrutinized with the intention of exploring claims[15] that they are structurally and functionally related to the activity of the di-iron site of sMMO. To identify structural motifs that were likely to be favored in py/AcOH solutions, we explored stoichiometric reductions (Zn, Fe, H_2/Pd) of commonly used Gif^{IV} catalyst precursors (Scheme 7).[29] The most important finding of this study is that reduction of $[Fe_3O(O_2CCH_3)_6(py)_3]$ leads to generation of two dioxygen-sensitive ferrous species: monomeric *trans*-$[Fe(O_2CCH_3)_2(py)_4]$ (**18**) and polymeric $[Fe_2(O_2CCH_3)_4(py)_3]_n$ (**19**) consisting of dinuclear block units. The latter species shows noteworthy structural analogies, albeit divergent electromagnetic properties, to the diferrous site (H_{red}) of sMMO.[30]

Scheme 7



Despite these structural analogies, the *tert*/*sec* selectivities and KIE values obtained in Gif^{IV} oxidations betray a less selective oxidant than the presumed high-valent, iron-oxo units operating in oxygenations by sMMO or P-450. On the other hand, a handful of product profiles did not seem at the time consistent with the presence of $HO^{\bullet}$ radicals as the *sole active oxidant* in Gif^{IV} oxygenations. In retrospect, this is only true inasmuch as the role of the more selective, substrate-centered alkoxyl radicals is accentuated due to the dioxygen dependence of the Gif^{IV} systems. As noted above, Zn may have a similar effect by preferentially quenching $HO^{\bullet}$ rather than $RO^{\bullet}$ radicals. Those selected product profiles which seemed to diminish the importance of $HO^{\bullet}$ radicals need eventually to be reconciled with the action of oxygen-centered radicals.

A frequently cited[29] anomaly is the alleged inferiority of *sec*-alcohols as substrates by comparison to the parent alkanes. Based on *normalized* data,[31] competition for the oxidation of 2-ol/ane by Gif/*t*-BuOOH and Gif/H_2O_2 systems favors the alcohol in all cases. The 2-ol/ane ratio is higher by a factor of 4−5 for Gif/*t*-BuOOH systems than that for Gif/H_2O_2 oxidations. This important observation was interpreted by Barton[31] as confirming the difference between *t*-$BuO^{\bullet}$ radical chemistry (Gif/*t*-BuOOH) and nonradical oxidations (Gif/H_2O_2). However, it is most consistent with the difference in reactivity/selectivity between *t*-$BuO^{\bullet}$ and $HO^{\bullet}$ radicals.

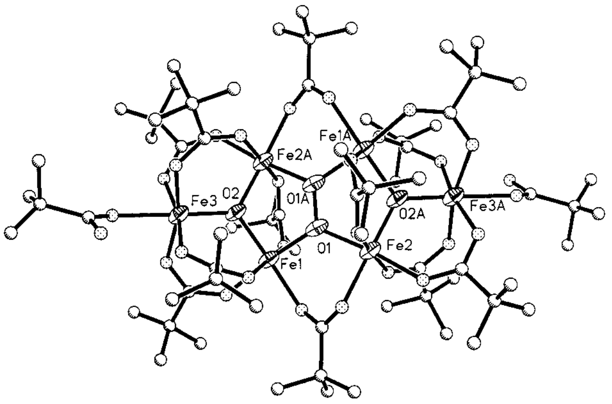


FIGURE 1.

A comparative study of Gif^{IV} type solutions, based on identical iron and ruthenium reagents ($[M_3O(O_2CCH_3)_6(py)_3]$), has revealed a close relationship between in situ generation of the reduced $[M^{II}(O_2CCH_3)_2(py)_4]$ and ketone formation. As indicated by an arsenal of physicochemical techniques (cyclic voltammetry, ^{1}H NMR, UV−vis) implemented in Richens's laboratory,[32] oxygenation of cyclohexane by the system $Ru_{cat}/O_2/Zn$ produces cyclohexanol much earlier in the course of the reaction than that by the iron-based system, while generation of cyclohexanone becomes more prominent at later stages, in strict correspondence to the slower rates observed for the assembly of the Ru(II) versus the Fe(II) sites. These results underscore the importance of M(II)/ROOH systems in the decomposition of the intermediate *sec*-alkylhydroperoxide largely to ketone. The bulk of alcohol is formed via the facile reduction of ROOH by Zn dust. Therefore, the one/2-ol ratio is dictated by competition between M(II) and Zn toward decomposition of ROOH.

(ii) Iron Pivalate Reagents. Further reappraisal of the mechanistic intricacies surrounding O_2/Zn-suported Gif systems has been undertaken with the assistance of iron pivalate reagents.[33a] Compounds $[Fe^{II}(O_2CCMe_3)_2(py)_4]$, $[Fe_3O(O_2CCMe_3)_6(py)_3]$, and $[Fe_3O(O_2CCMe_3)_6(py)_3](Cl)$ mediate oxygenation of adamantane in py/PivH (10:1) to afford the usual oxo and pyridine-coupled adamantyl products.[33b] The product profile largely favors the oxo products at the expense of adamantylpyridines, not only because of the obligatory presence of O_2 but also due to the limited protonation of pyridine by the weak acid PivH. As a result, these pivalate-based systems afford 1-adamantanol, rather than adamantanone, as the major product. Otherwise, the product profile is still dictated by partitioning of *sec*- and *tert*-adamantyl radicals between O_2 and protonated pyridine, as evidenced via control experiments involving authentic radicals.

Hydrogen peroxide supports generation of only substoichiometric yields of adamantane oxidation products, probably due to formation of unreactive ferric sites. Most interestingly, $[Fe_3O(O_2CCMe_3)_6(py)_3]^+$ reacts with H_2O_2 to furnish a hexairon(III) η^2,μ_4-peroxo species of stoichiometry $[Fe_6(O_2)(O)_2(O_2CCMe_3)_{12}(L)_2]$ ($L = Me_3CCO_2H$, py),[33a] whose structure (Figure 1) is identical to that of $[Fe_6(O_2)(O)_2(O_2CPh)_{12}(H_2O)_2]$, previously documented by Lippard and co-workers.[34] Stoichiometric reactions of these peroxo species with *cis*-stilbene and adamantane show that only low yields of products are obtained under prolonged heating. The *tert*/*sec* selectivity obtained in the oxidation of adamantane (≈8) differs from that encountered in typical catalytic oxidations (*tert*/*sec* = 3−5). Furthermore, oxidations of adamantane by H_2O_2 in the presence of catalytic amounts of the peroxo species afford trace amounts of products. Therefore, this class of peroxo complexes does not dictate the outcome of typical Gif oxygenations.

Finally, to evaluate the role of substrate-centered alkylhydroperoxides as contributing H-atom-abstracting agents in Gif chemistry, we attempted oxygenations of adamantane by 1-AdOOH in the presence of $[Fe^{II}(O_2CCMe_3)_2(py)_4]$ or $[Fe_3O(O_2CCMe_3)_6(py)_3]$. Under a stream of inert gas, the product profile is composed exclusively of the now familiar *tert*- and *sec*-adamantylpyridines. The *tert*/*sec* selectivity obtained (≈9) is consistent with alkoxyl radical involvement. In contrast, employment of 2-AdOOH does not afford products of adamantane oxidation but leads exclusively to decomposition of the alkylhydroperoxide to ketone and alcohol (minor product). It has been suggested[28] that a 1,2-H atom shift may competitively transform 2-AdO$^\bullet$ to a carbon-centered radical (2-Ad$^\bullet$−OH).

Returning to the "Gif paradox" mentioned at the outset, we note that the concept would have been valid provided that a selective oxidant, such as an iron-oxo unit, had been involved. However, when indiscriminate oxygen-centered radicals prevail, the paradox can be resolved if the quantitative aspects of the kinetics pertaining to the attack of these radicals on various substrates are carefully taken into consideration. Some examples are given in this Account, and others have been contemplated in a review by Perkins.[25]

Conclusions

Gif oxygenation systems have been exhaustively studied by employing all major versions developed by Barton and co-workers. First, Gif/*t*-BuOOH systems have been conclusively shown to operate via H-atom-abstracting *tert*-alkoxyl radicals. The case of *sec*-ROOH-supported Gif systems is more uncertain, because these reagents tend to be unproductive as H-atom-abstracting agents, presumably due to competitive decomposition of the intermediate *sec*-alkoxyl radicals. Furthermore, Gif/H_2O_2 reagents have been found to generate product profiles consistent with the presence of diffusively free substrate-centered radicals. These results apply to both Fe(II) and Fe(III) precatalysts, and further hold true for various partial pressures of O_2, thus directly refuting the dioxygen-dependent, double-manifold mechanism. The role of hydroxyl radicals as the major H-atom-abstracting agent has also been securely documented in Gif/H_2O_2 chemistry. Finally, Gif/O_2/Zn systems display functional features that are in agreement with preponderant radical chemistry. The true nature of these systems is somewhat disguised by the obligatory use of O_2, which conceals the presence of *sec*-alkyl radicals and implicates the more selective alkoxyl radicals. The product profile is also influenced by the presence of Zn, which reduces *sec*-ROOH to the corresponding alcohol, in competition with M(II)-dependent decomposition of *sec*-ROOH to ketone.

The combined studies of several research groups have culminated in substantial clarification of the intricacies surrounding Gif-type alkane oxygenation systems, leading to the recognition of the preponderant role of oxygen- and carbon-centered radicals.

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