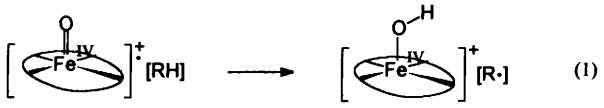
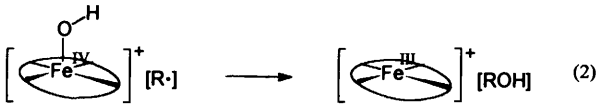
A Radical Reappraisal of Gif Reactions

M. John Perkins
Department of Chemistry, Brunel University, Uxbridge UK UB8 3PH

Selective alkane functionalisation is achievable by a variety of natural enzymic systems. Perhaps the most extensively studied of these are the cytochrome P-450 enzymes,[1] in which the active site contains an iron atom coordinated with a tetradentate porphyrin ligand. The mechanism of alkane functionalisation catalysed by P-450 enzymes has widely been accepted as involving the so-called 'oxygen rebound' mechanism,[1b] in which an iron (IV)–oxo intermediate* is generated which removes hydrogen from the hydrocarbon substrate [eqn. (1)]; the resulting alkyl radical immediately removes hydroxyl from iron to form alcohol and regenerate a low-valent iron species [eqn. (2)]. Very recent studies,[1c] depending upon the use of cyclopropylcarbinyl radical 'clocks'[2] have attempted to 'time' the rebound process.



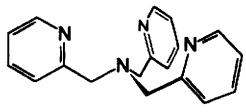
(1)



(2)

Less well studied than the P-450s, but attracting considerable attention recently, are those non-haem iron-based oxidases[3,4] in which the iron ligands are principally substituents in amino acid residues of the enzyme. These include the methane monooxygenases,[3a] which catalyse the oxidation by air of methane to methanol, isopenicillin-*N* cyclase,[3b] prolyl-4-hydroxylase,[3c] and γ-butyrobetaine hydroxylase.[3d] Uniquely amongst these, but in common with certain other redox iron enzymes, the methane monooxygenases incorporate a di-iron-containing active centre.

In addition to investigations of structure and mode of action of the non-haem iron-based enzymes, attempts have been made to replicate their selective oxidising characteristics in model experiments.[4] Among examples of these model studies is the work of Que and his colleagues who, in exploiting the tetradentate tris-(2-pyridyl methyl)amine ligand **1**, have provided direct spectroscopic evidence for the formation of an unstable binuclear species in which one iron atom is in an oxidation state greater than III.[5]



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This review focuses primarily upon another, more extensively reported, and superficially simpler set of model studies, begun in the early 1980s[6] by D. H. R. Barton and his colleagues. The essential features of these new oxidation processes, which were whimsically designated *inter alia* 'Gif' and 'GoAgg' reaction systems after the geographical locations of the investigators, are the use of an oxygen source or other oxidising agent, a reducing agent, and a (catalytic) source of ferric iron.[7] Until very recently, the solvent has invariably been a mixture of pyridine and acetic acid, in which the pyridine, present in large excess, was originally included as a simple iron-coordinating species [eqn. (3)]. In the earliest investigations the substrate was commonly cyclohexane. Predominantly, this is oxidised not to cyclohexanol, but to cyclohexanone [eqn. (4)].

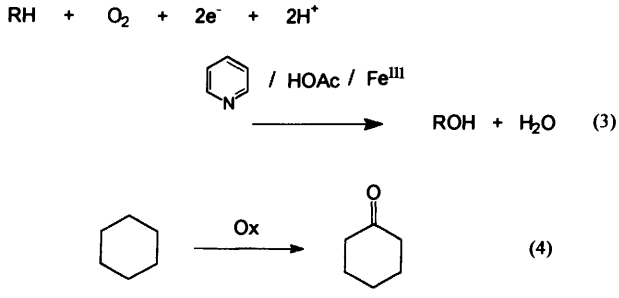


Table 1 Some 'Gif' oxidation systems[a]

Gif^{III}	Fe^0/O_2
Gif^{IV}	$Zn^0;Fe^{II}$(cat.)/O_2
Gif–Orsay	e^-(cathode);Fe^{II}(cat.)/O_2
$GoAgg^{I}$	$Fe^{II};KO_2$/argon
$GoAgg^{II}$	$Fe^{III};H_2O_2$
$GoAgg^{III}$	Fe^{III};added ligand[b]/H_2O_2
$GoAgg^{IV}$	Fe^{III};Bu^tOOH
$GoAgg^{V}$	Fe^{III};added ligand[b]/Bu^tOOH

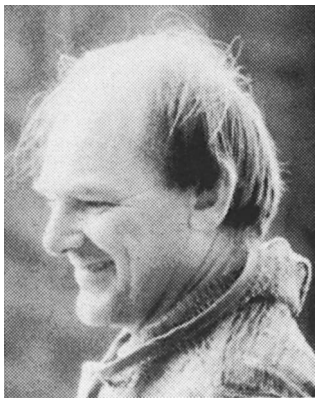
[a] All of these systems utilise pyridine–acetic acid (10 : 1 v v) as solvent, and air is not normally excluded. [b] Usually picolinic acid

Table 1 lists some of the Gif family of reaction systems, the mechanisms of each of which has been investigated to a greater or lesser extent. In one of their more recent publications, Barton and his colleagues have acknowledged that the proliferation of names for these systems is unwelcome.[8] However, 'Gif' has now come to be accepted by a number of authors to embrace many of these oxidations, as well as those variants in which other reagents are added in order to intercept intermediates. In what follows, I shall occasionally specify some of the oxidation systems using names listed in the Table.

Central to Barton's discussion of these oxidation reactions has been the conclusion that, *at least where secondary carbon is functionalised*, the results *cannot* be accommodated in terms of simple free-radical processes. The object of the present article is to

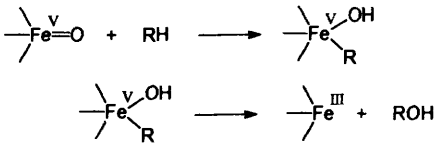
* Since, in the iron(IV) species, the porphyrin ligand is oxidised to a radical cation, the whole has sometimes been represented as incorporating iron(V)

John Perkins, Professor Emeritus in the University of London, has been Associate Professor at Brunel since taking early retirement in 1992 from the London chair which he had held for 20 years. Following his PhD with D. H. Hey he has worked principally in the area of free radicals, for which his early research was recognised with the award of a Corday-Morgan Medal by the Chemical Society. He has contributed to, and edited volumes in Wiley's Organic Reaction Mechanisms series, and is responsible for a short text, Radical Chemistry, published recently by Ellis Horwood.

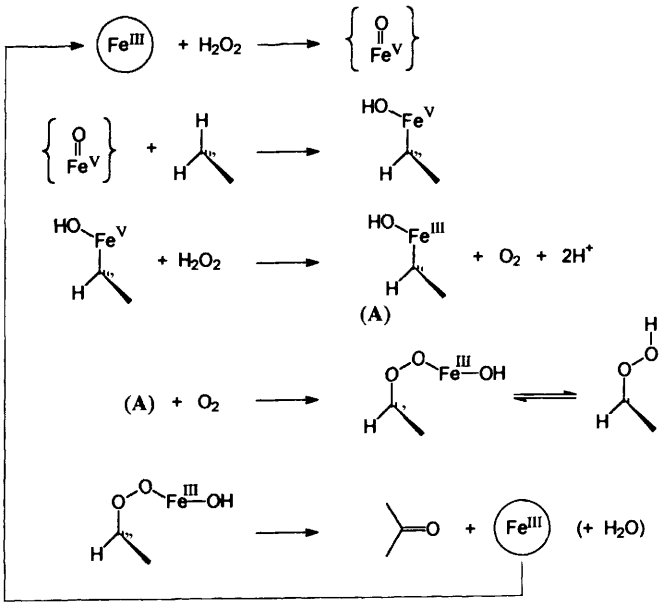


attempt to provide a critical reexamination of the arguments against radical intermediates in Gif chemistry One problem which arises in so doing is that the totality of the evidence which has culminated in a global (non-radical) mechanism embracing many of these reactions has been culled from individual systems Thus, data for, say, one of the early Gif systems has been used in explaining a GoAgg reaction The exceptions to this involve reactions listed at the foot of Table 1, in which the oxidising agent is *tert*-butyl hydroperoxide Although these represent a relatively recent development in the history of Gif chemistry, many investigators would now contend that they are better understood Nevertheless, their consideration here is deferred until towards the end of this review

The global mechanism which is currently favoured for methylene functionalisation depends on the formation of an iron(V)–oxo species which inserts into the C–H bond of the substrate, sub sequently, oxygen transfer to carbon leads to the product These essential features are outlined in Scheme 1a This is the first time in a review article that the case against an alternative free radical mechanism has been the subject of critical examination Other reviews have presented the iron–oxo mechanism[4-7] and have usually[7] accepted that the evidence against radicals is over whelming



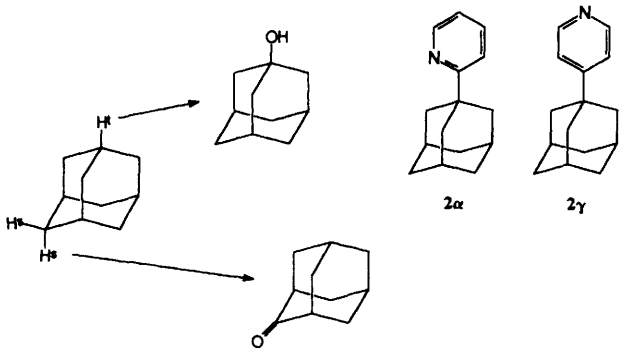
Scheme 1a



Scheme 1b

One of the earliest reasons to believe that Gif chemistry *is* quite different from established radical processes, and might indeed have some synthetic importance, was the observation that, when adamantane was the substrate for oxidation in place of cyclohexane,[6,9] there was a very much larger yield of adamantan-2-one than of adamantan-1-ol This prompted the conclusion that the secondary position of adamantane was much more reactive than the tertiary position Allowing for the statistical factor of three (there are twelve secondary hydrogens but only four tertiary hydrogens in adamantane), these early results suggested that, per hydrogen, the secondary position is *more* reactive than the tertiary by *ca* 7 1 This is in sharp contrast to familiar radical reactions of adamantane (or of almost any other aliphatic hydrocarbon), where (per hydrogen) the tertiary position is normally at least as reactive as the secondary [10] This radical selectivity is markedly dependent upon the reacting radical, with ratios (tertiary/secondary) close to unity for the most reactive radicals such as hydroxyl,[11] but rising to *ca* 20 for the relatively unreactive bromine atom

Unfortunately, however, the Gif result with adamantane was incomplete Whereas the secondary position was predominantly oxidised to ketone (with much smaller amounts of adamantan 2 ol),



it was later discovered that the tertiary position is functionalised not only by hydroxylation, but also by the adamantylation of pyridine (to give **2**α and **2**-γ) [12] When this was taken into account, the per hydrogen reactivity ratio now favoured tertiary by *ca* 3 1, firmly in the range expected of radical chemistry, although suggestive of a rather reactive abstracting radical [*†] But why should the tertiary intermediate behave so differently from the secondary? The non radical interpretation is simple, if somewhat contrived radicals *are* involved in functionalising the tertiary position, they are *not* involved in functionalising the secondary position The difference is attributed to the relative strengths of iron–carbon bonds The tertiary alkyl-to-iron bond is proposed to be so weak that it dissociates into radicals, the secondary alkyl to iron bond is considered to be suffi ciently strong that there is negligible dissociation within the life time of the intermediate [7a] This analysis seems to find support from experiments (*vide infra*) in which sources of the two isomeric adamantyl radicals, when decomposed in pyridine–acetic acid mixtures, *both* give adamantylpyridines [15] But could there be an alter native and purely radical interpretation? We shall reconsider these important results when some further aspects of Gif chemistry have been presented

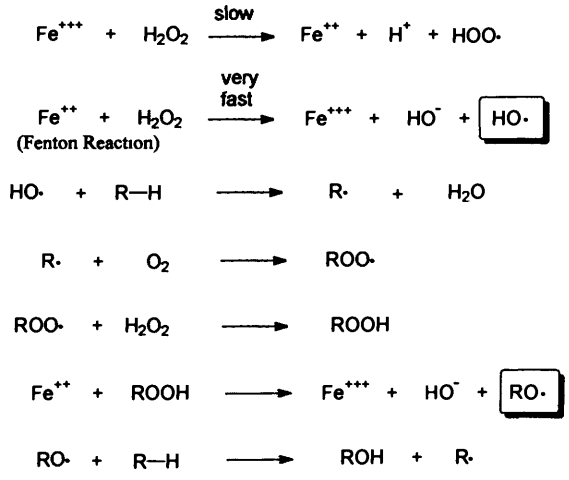
In addition to the revision of the reactivity ratios for adamantane, it also proved necessary to revise the mechanistic rationalisation for these alkane functionalisations as more information became available For example, early proposals, which invoked a binuclear iron complex similar to those of the methane monooxygenases, were modified[16] when it was discovered that, if GoAgg[11] oxidation (see Table 1) of ^{13}C-enriched cyclohexane was monitored by ^{13}C NMR spectroscopy cyclohexyl hydroperoxide was revealed as a major long-lived intermediate [16,17] The concentration of this intermediate at first grew, but then dimin ished as it was replaced by the previously reported cyclohexanone This result prompted our own short contribution[18] to this story, in which ^{18}O-incorporation experiments were carried out in order to investigate whether the oxygen of the product (and by implication that of the intermediate hydroperoxide) was derived from the hydrogen peroxide, as required by the then current mechanistic proposal, or from molecular oxygen The finding that it came substantially from molecular oxygen led us to propose that the intermediate hydroperoxide might be none other than the product of a

* It is important to be clear whether per hydrogen reactivity or simply site reactivity ratio is being presented Clearly the statistical factor is incorporated into one of these Unfortunately the early reports are not entirely self consistent in this regard In this article per hydrogen relative reactivities are used throughout unless explicitly stated otherwise

† The early work was also in error in using data which were uniquely based on aroyloxyl radicals[13] to provide a reference value for the secondary/tertiary competition ratio expected for hydrogen abstraction from adamantane by oxygen centred radicals Although this was doubly flawed in that not only does selectivity vary markedly from radical to radical but also the assumed abstraction by aroyloxyl radicals is probably contaminated by aryl radical chemistry the comparison has been perpetuated in a very recent report from the Barton group [14]

radical autoxidation.* However, when this isotope-incorporation result was corroborated in Barton's own laboratory,[17] it simply led to yet another revision of the *non-radical* mechanism, essentially to its current form,[7a,14] shown in Scheme 1b (which fleshes out Scheme 1a). In this, the observed hydroperoxide is in equilibrium with a species in which molecular oxygen has inserted into the Fe–C bond of the organo-iron intermediate (**A**).

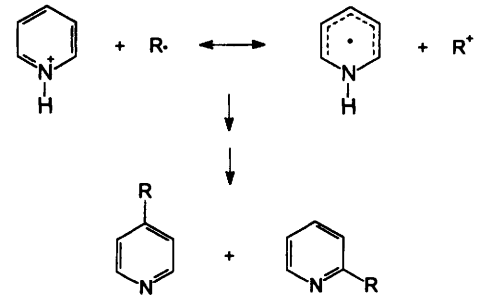
The proposal[18] of a radical autoxidation pathway presented the problem of what species could be responsible for the 3:1 selectivity in adamantane functionalisation. Our suggestion was that catalysed decomposition of hydrogen peroxide would generate hydroxyl, and catalysed decomposition of intermediate alkyl hydroperoxides would give alkoxyl radicals. Both of these radical types are known to abstract hydrogen from alkanes, the former with almost negligible selectivity,[11] the latter with a tertiary to secondary reactivity ratio of *ca.* 4—5:1.[19] Clearly, the observed ratio lies between these limits. A very similar argument can be used[18] to accommodate the modest kinetic isotope effects which have been obtained[9a] for cyclohexane *versus* [$^2H_{12}$]cyclohexane†. The essential features of the radical mechanism are outlined in Scheme 2.‡



Scheme 2

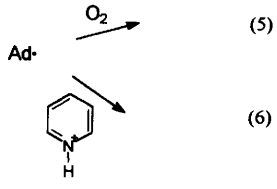
A problem with the hydroxyl–alkoxyl interpretation is that, in the cyclohexane functionalisation, the product from cyclohexyloxyl radicals would be cyclohexanol. This is reported by Barton's group to be only a minor product, and not to be oxidised *in situ* to cyclohexanone, yet in our hands, under GoAgg^{II} conditions, this transformation appeared to be efficient. We have experienced other problems of accurate reproducibility using hydrogen peroxide in these oxidations, including ones between individual investigators in this laboratory. These problems are hinted at in one published report,[20] which included *inter alia* the observation that in a GoAgg^{II} system a 15 °C temperature rise altered peroxide consumption from zero to 98%. Another possible difficulty is the fact that oxygen gas is generated *within the system*. In the absence of adequate agitation, this could result in reaction mixtures which are supersaturated with respect to oxygen. Clearly, therefore, the physical procedure may be critical in determining the relative concentrations of vital components of these reaction systems.

What, then, could be a radical interpretation of the pyridine-adamantylation results described earlier? In discussing a possible solution to this, it should first be noted that tertiary alkyl radicals are generally insufficiently reactive to alkylate simple benzenoid aromatics in significant yields. The exception to this is the alkylation of *protonated* pyridines, extensively studied by Minisci and his colleagues.[21] These reactions are characterised by the strongly facilitating influences of electron-donating substituents in the protonated pyridine, and they have been interpreted as having transition states with substantial charge-transfer character in which the alkyl radical becomes carbocation-like (Scheme 3). If this is so, then it is



Scheme 3

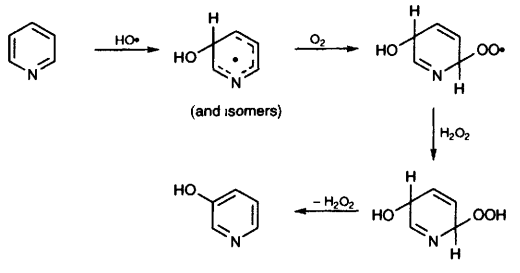
easy to see that tertiary alkylation might be facilitated to a greater extent than secondary alkylation.§ Any misgivings that this might not be the case for the *bridgehead* tertiary adamantyl system should be dispelled by the knowledge that the 1-adamantyl *cation* is more stable than its (secondary) 2-isomer.[23] Were adamantyl radicals to be generated in partially protonated pyridine which contained dissolved oxygen, we should then expect competition between alkylation of the abundant pyridinium cation, and peroxyl radical formation [eqn. (5) and (6)]. This should occur for both secondary



and tertiary radicals, but the reaction with oxygen, because it is essentially diffusion-controlled, *will have almost the same rate constant for both radicals*. On the other hand, it seems plausible, from the reasoning just presented, that the rate of reaction of the tertiary radical with the pyridinium ion might be appreciably greater than that of the secondary one, and therefore k_5/k_6 may be correspondingly greater for the tertiary radical.§ This implies that at certain oxygen concentrations tertiary adamantylation of pyridinium may compete effectively with peroxyl production whereas secondary adamantylation might be negligible.

It is actually possible to argue that Barton's results with the authentic adamantyl-radical precursors mentioned earlier tend to

* At the time of our report, we considered *in situ* reduction of molecular oxygen to H_2O_2 to be unlikely. This neglected the sequence outlined below which is a plausible source of the hydroxypyridines discussed later (see Scheme 4), but which would generate insufficient H_2O_2 to be competitive with the H_2O_2 originally present

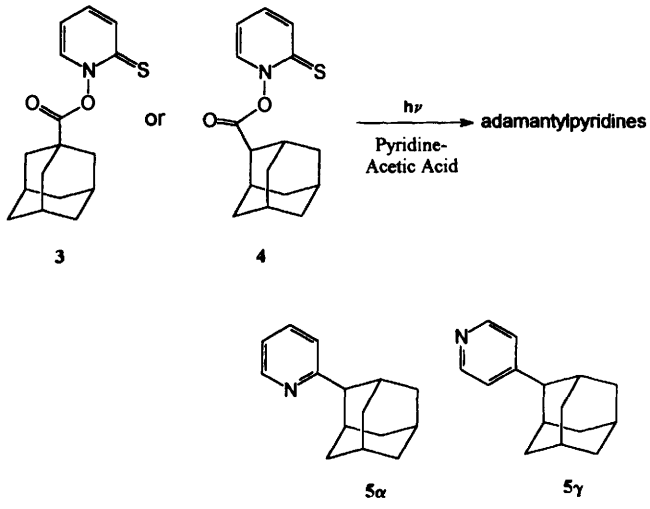


† These explanations of the adamantane reactivity pattern, and of the isotope-effect data, would appear to require that the quantitative results should be a function of the progress of reaction, since at the commencement the dominant hydrogen-abstracting species must be hydroxyl, whilst at a later stage in the reaction the more selective alkoxyl must assume much greater importance. This does not appear to have been tested.

‡ In our experiments, in which a GoAgg^{II} oxidation of cyclodecane was carried out under an atmosphere of $^{18}O_2$, the ^{18}O-incorporation into ketone was *ca* 50%. It should be noted, however, that $^{16}O_2$ is available from termination reactions involving the peroxyl radicals in Scheme 2 (or by oxidation of HOO·). Indeed (in isotopically normal experiments) the ketone yield was little affected by changing from an air atmosphere to one of N_2. Only with a brisk N_2 purge was ketone formation almost eliminated.

§ Absolute rate data for reaction of alkyl radicals with protonated pyridine are few. Whilst butyl and *tert*-butyl radicals were reported to react at roughly the same rate,[22] the *tert*-butyl data were complicated by reversibility, and a marked steric factor was evident. Therefore extrapolation to the adamantane radicals is difficult.

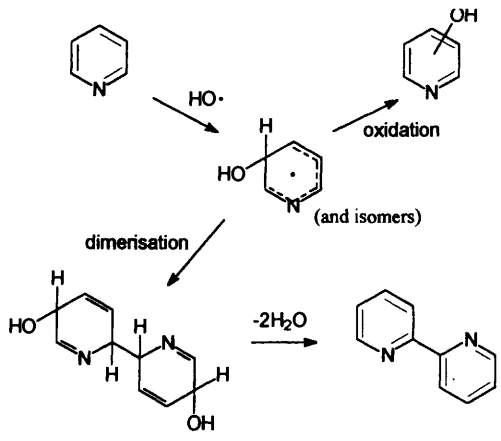
support the above interpretation. *N*-Acyloxypyridine-2-thiones **3** and **4** were the precursors used in these experiments;[15] in the



absence of oxygen, both gave adamantylpyridines, but as each reaction was repeated with increasing concentrations of molecular oxygen present, the pyridine adamantylation products were replaced by adamantane oxidation products. However, whilst the 2-adamantylpyridines (**5**α and **5**γ) from **4** were virtually eliminated by oxygen concentrations corresponding approximately to GoAgg^{II} conditions, the same oxygen concentrations reduced the yield of 1-adamantylpyridines (**2**α and **2**γ) from **3** by only *ca.* 50%.* Furthermore, Barton has very recently reported[14] a model *radical* experiment in which butoxyl radicals, generated by di-*tert*-butyl peroxyoxalate decomposition in a pyridine solution of adamantane containing HCl (from the oxalyl chloride used *in situ* to prepare the peroxide) and under oxygen, yielded the **2** isomers, but apparently not the **5** isomers!†

In the GoAgg^{II} system, a key point of controversy, of much wider significance than in Gif chemistry alone, is whether or not an iron(III) system can catalyse the production of hydroxyl radicals from hydrogen peroxide (the Haber–Weiss reaction). That it can has been argued by Walling,[24] and is now widely accepted in a biological context. The manner whereby this is thought to happen involves a slow reaction which generates iron(II) followed by a very rapid Fenton-type reaction in which the iron(II) is re-oxidised (Scheme 2). A probe for participation of hydroxyl radicals in biological systems is the pattern of hydroxylation of added aromatic amino acids, such as phenylalanine.[25] Added to the GoAgg^{II} system, phenylalanine does indeed show this pattern.[18]

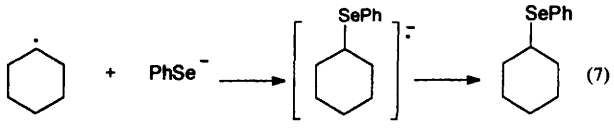
The chemistry of hydroxyl radicals has been extensively studied, especially by pulse-radiolysis techniques, which have yielded a large number of rate constants for hydroxyl radical attack on organic molecules.[11] It can be deduced from these that if some 50% of the GoAgg^{II} oxidation of cyclohexane is initiated by hydroxyl radicals, then there should be a significant amount of hydroxylation of the solvent. In fact, the rate of reaction with most monocyclic aromatic compounds appears to be at least an order of magnitude slower than that with cyclohexane, so that reaction with cyclohexane will not be swamped by the large excess of pyridine. Are hydroxypyridines formed? Not only is the answer 'yes', but they are accompanied by bipyridyls,[26] expected products of pyridine hydroxylation by the mechanism outlined in Scheme 4. The picture is further complicated by the instability of the hydroxypyridines under the reaction conditions: one possible fate may involve



Scheme 4

oxidation by iron(III).‡ This would presumably constitute an alternative route to iron(II), and it is interesting that the reaction appears to have an induction period. This is evident in the initial slow build-up of hydroperoxide in cyclohexane oxidation.[17]

Especially in more recent work, the Gif systems have been extended by incorporating a variety of additional reagents, and the results obtained have been construed as affording further evidence against the possibility of radical pathways. One of the earliest of these variations incorporated diphenyl diselenide into a Gif^{IV} oxidation of cyclohexane.[12,17,27] The product was no longer cyclohexanone; instead, cyclohexyl phenyl selenide was obtained. However, it was reported that under the reaction conditions the diselenide was reduced to benzeneselenol (which could be intercepted by methyl iodide, giving methyl phenyl selenide). Since benzeneselenol was known to reduce secondary alkyl radicals to alkane with a rate constant approaching the diffusion limit,[28] it was concluded that cyclohexyl radicals could not be involved. Unfortunately, this rationalisation appears to have overlooked the high acidity of benzeneselenol, which exceeds that of acetic acid [pK_a(PhSeH)<5;[29] pK_a(H_2Se) = 3.73], so that the predominant species in the pyridine solvent must have been the conjugate base, $PhSe^-$. Indeed, in the presence of zinc salts, it seems likely that it may be coordinated to zinc. Reaction of alkyl radicals with the benzeneselenolate anion would be expected to give the observed products, in a reaction which finds a close parallel in S_{RN} processes [eqn. (7)].



The less acidic benzenethiol is not deprotonated under comparable conditions, and addition of it, or of diphenyl disulfide (which is also reduced), lowers the yields of oxygenation products, but no alkyl phenyl sulfide is formed.[18] In these cases, the simple radical interpretation is that the thiol is intercepting alkyl radical to regenerate alkane.§

A subsequent modification, with results which again could apparently not be explained in terms of radical intermediates, involved the Gif^{IV} oxidation of cyclohexane in the presence of trimethyl phosphite. The unexpected product of this reaction was cyclohexyl dimethyl phosphate.[30a] A 'control' experiment emphasised in subsequent reviews of this work showed that cyclohexyl hydroperoxide is quite rapidly reduced to cyclohexanol by trimethyl phosphite, the latter being oxidised to trimethyl phosphate. But a key element may be seen to be absent from this control, namely

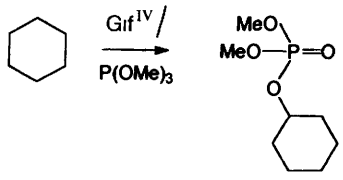
* Clearly, these results suggest that the rate of reaction of 1-adamantyl radicals with protonated pyridine is indeed greater than that of the corresponding reaction with 2-adamantyl. Indeed, based on reasonable assumptions regarding the concentration of oxygen in Barton's experiments, it is possible to argue that the 1-adamantyl rate is approximately one order of magnitude greater than that published for *tert*-butyl (see footnote § on previous page).

† Though it should be recorded that secondary-alkylpyridines were detected in a similar experiment with cyclooctane as substrate.

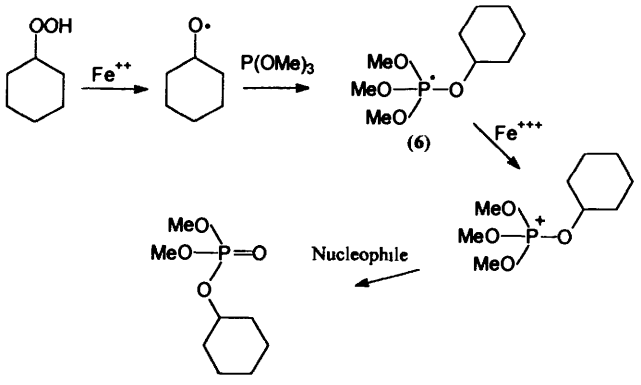
‡ Iron(III) is also a plausible candidate for the oxidant in Scheme 4 (but see footnote * on previous page).

§ This diminution in yield is very close to that calculated taking known rate constants for reaction of secondary alkyl radicals with oxygen and with PhSH, and making a reasonable assumption regarding the oxygen concentration in the reaction mixture (M. Newcomb, personal communication).

iron A wholly plausible reaction sequence in the *presence* of iron salts is set out in Scheme 5 Iron(II)-catalysed decomposition of the



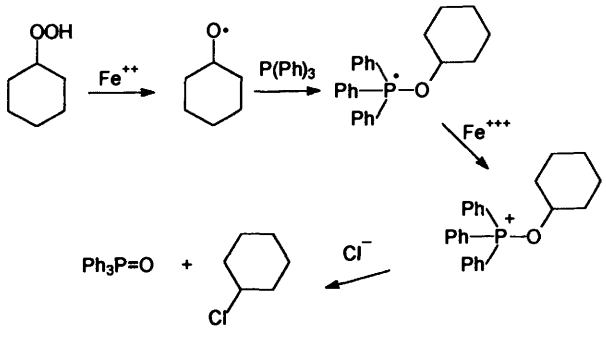
Radical Interpretation



Scheme 5

hydroperoxide would generate cyclohexyloxyl radicals Since alkoxyl radicals are known to add to phosphite to generate phosphoranyl radicals, it seems reasonable to suppose that the tetraalkoxyphosphoranyl radical **6** would be formed and that this would be particularly susceptible to one-electron oxidation, there is ample precedent for S_N2 displacement (in this case of one of the small methyl groups) on the resulting tetraalkoxyphosphonium ion Critical to the evaluation of this reinterpretation is the determination of the relevant rate constants for destruction of the hydroperoxide, and an estimate of the iron(II) concentration, but it is interesting that in the original work an additional control experiment, generally neglected in subsequent discussion, was carried out in the presence of an iron salt *Under these conditions, the mixed phosphate was indeed produced* [30a]

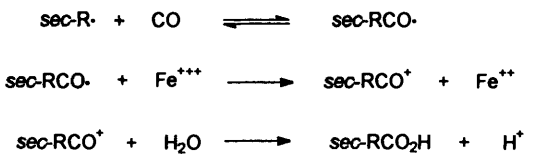
A parallel rationalisation is available for the formation of chlorocyclohexane when triphenylphosphine is added [30b] (Scheme 6)



Scheme 6

A thorough discussion of a reaction proceeding *via* a similar mechanism, *i e* one which also involves one-electron oxidation of an alkoxyphosphoranyl radical followed by nucleophilic displacement of alkyl from the resulting alkoxyphosphonium ion, was given recently by Kampmeier and Nalli [31]

The presence of carbon monoxide in a cyclohexane oxidation gives cyclohexanecarboxylic acid, interpreted as arising by carbon monoxide insertion into the alkyliron intermediate [32] In radical chemistry, cyclohexylcarbonyl radicals might be expected to decarbonylate, but there is in fact precedent in the literature for a process



Scheme 7

such as that outlined in Scheme 7, in which the acyl radical, formed *reversibly*, is intercepted by one-electron oxidation [33]

In all of these modifications, the radical mechanism assumes that the alkyl radical intermediate is intercepted by the added reagent, whereas the iron–oxo mechanism assumes that it is the intermediate iron alkyl (**A** in Scheme 1b) which is diverted to product One strategy which could perhaps allow these mechanisms to be differentiated would be *competitive* interception of the intermediate using systems for which the competition for alkyl radicals is well established Such competition was investigated for a number of systems in which the product was alkyl halide

Two different types of competitive study were carried out with halogen donors [8 34] One of these followed the strategy outlined above, with a single cycloalkane and two different halogen donors The other, which produced some particularly dramatic results, examined the competitive halogenation of two different hydrocarbons Arguably, these series of experiments provide some of the most compelling evidence *against* radical participation in the Gif oxidations For example, when judged by the bromination yields, using bromotrichloromethane as halogen donor, cyclohexane has a per hydrogen reactivity greater than that of any other cycloalkane examined, *and significantly greater than the reactivity of tertiary hydrogen in 2,3-dimethylbutane* [C_6H_{11}–H/$Me_2CHC(Me)_2$–H = 10 2] The dimethylbutane result seems particularly damaging to the radical argument, in view of the earlier comments on relative reactivities of tertiary and secondary hydrogens The apparently lower reactivity of, *e g* cyclopentane when compared with cyclohexane is also out of line with radical behaviour, where radical reactivities can be analysed in terms of relative strain factors in the sp^3 cycloalkane and the derived sp^2 cycloalkyl radical Perhaps these results deal a fatal blow to the case for radicals However, there was apparently no attempt to obtain a total product balance in these experiments It is not impossible that the concentration of bromotrichloromethane was at such a level that it competed effectively with oxygen for secondary alkyl radicals, *but that it was insufficient entirely to suppress reaction of the tertiary 2,3-dimethyl-2-butyl radicals with protonated pyridine* These tertiary radicals would be expected to be intercepted more slowly by the $BrCCl_3$, but would be particularly reactive with respect to protonated pyridine The result might then be the observed depletion in the bromination yield Many other inconsistencies with behaviour expected of radical chemistry are claimed for relative reactivities for halogenation Space does not permit a full discussion of these, though it must be pointed out that relative substrate reactivities depend on the halogen-abstracting species For example, if bromination by $BrCCl_3$ added to Gif systems is not a chain process, reactivity patterns may be quite different from those found when the chain carrier is $\cdot CCl_3$ (although this would not, of course, explain the low tertiary reactivity found with dimethylbutane)

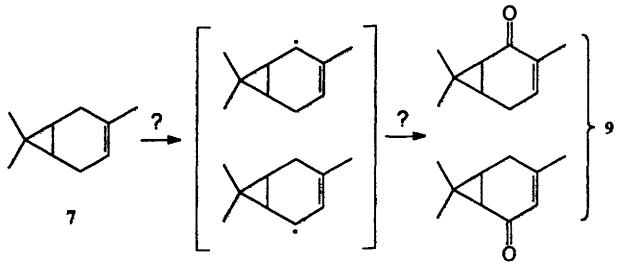
It was noted earlier that Barton's group had accepted that the functionalisation of the 1-position of adamantane in Gif reactions *does* involve radicals Presumably the same is accepted as applying to the functionalisation of the tertiary sites in dimethylbutane The greater reactivity of cyclohexane is then attributed to the intervention of the non-radical mechanism, in which the cyclohexyliron intermediate (**A** in Scheme 1b) is formed relatively rapidly, and is then intercepted by $BrCCl_3$

One possible approach to resolving the question of whether or not the alkyl fragment in Gif oxidations has a discrete existence as a radical might be to employ the 'free-radical clock' method [2] For this, a suitable substrate must be found which, if oxidised to a radical, would then undergo rapid, unimolecular and characteristically radical rearrangement, competitively with inter-

molecular trapping. Among the best alkyl-radical clocks are cyclopropylcarbinyl radicals which rearrange more or less rapidly to allylcarbinyl, depending upon the substituents present [eqn. (8)]. The fastest of these rearrangements occur on a timescale


(8)

approaching that of molecular vibrations. When devising an experiment designed to use this approach, it is essential to ensure not only that the rearrangement is sufficiently rapid, but also that ionic or other non-radical pathways cannot result in formation of the expected rearrangement products. Thus, when 3-carene **7** was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subjected to Gif oxidation,[35] the products included **9**. However, the most likely derived radicals **8** are allylic, and probably, as with α-cyclopropylbenzyl radicals, cyclopropane ring-opening is thermodynamically unfavourable. Whilst radical autoxidation of **7** is known to give ring-opened products, it seems likely that the ring-opening involved cationic rearrangement of the initial products.[36] More recently, Newcomb's group have subjected the GoAgg^{III} system to scrutiny with 1-methyl-2-phenylcyclopropane; no products of oxidation at the methyl group were isolated which had *not* rearranged.[37*] In this case, the free (2-phenylcyclopropyl)carbinyl radical is known to undergo very rapid rearrangement ($k = 3 \times 10^{11}$ s^{-1}),[28] yet, in marked contrast, when the same hydrocarbon was oxidised using a methane monooxygenase preparation, the only products of the enzyme-catalysed oxidation at the methyl were unrearranged![38]

Finally, we turn our attention to the recent work in which GoAgg systems have been modified by the replacement of hydrogen peroxide by *tert*-butyl hydroperoxide (see Table 1).[8,39] An interesting distinction between these and the earlier H_2O_2 systems is that the cycloalkane substrate may be functionalised by reactions in which the alkyl intermediate is captured by an added nucleophile. For example, when the catalytic iron salt in cyclohexane oxidation is iron(III) chloride, a significant product is chlorocyclohexane.[39] Similarly, with added nucleophiles such as azide or thiocyanate, the corresponding cyclohexyl derivatives are formed. Although initially perceived by Barton as an extension of the methane monooxygenase biomimetic process, this has been interpreted by Minisci in terms of a well-established mechanism involving ligand-transfer oxidation of cyclohexyl radicals [eqn. (9)].[40] Evidence for alkyl-


(9)

radical intermediates came from their interception by added quinoline, the protonated form of which is more reactive towards alkylation than is protonated pyridine. The cyclohexyl radicals from cyclohexane oxidation, as well as the methyl radicals from butoxyl fragmentation, were trapped as alkylquinolines. Indeed, in the absence of a halide counter-ion, cyclohexyl*pyridines* were found. Minisci's interpretation was immediately challenged;[41] one argument was that during cyclohexane oxidation in the presence of both halide and a stable nitroxide, halogenation of cyclohexane predominated over radical trapping by nitroxide, but when, instead, a typical alkyl radical precursor was used, the diffusion-controlled reaction of the alkyl radical with the nitroxide completely masked any reaction with the nucleophilic iron(III) halide. Barton also pointed out a distinction between the experimental techniques of the two laboratories. This is that in the Italian work somewhat higher temperatures are employed, under which conditions alkyl–iron intermediates would be more prone to dissociate into radicals.

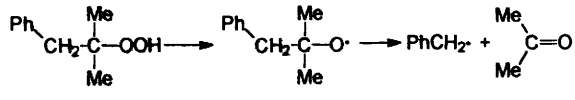
Minisci's group also noted that butoxyl radicals may be intercepted by nucleophilic alkenes, *e.g.* styrene, added to the system, followed by ligand-transfer oxidation of the resulting adduct radicals.[42]

Whilst the alkyl hydroperoxide systems have the advantage that reaction of possible alkoxyl radical intermediates with pyridine solvent would be negligible (in contrast to hydroxyl), *in situ* formation of molecular oxygen cannot be excluded, since hydrogen abstraction from the hydroperoxide could form peroxyl radicals; dimerisation of these is a well documented source of O_2.

In addressing Minisci's mechanistic proposals, which depend essentially upon iron(II)-promoted decomposition of hydroperoxide (*cf.* Scheme 2), Barton has investigated reactions in which hydrocarbon oxidation by H_2O_2 or *tert*-butyl hydroperoxide is promoted in pyridine–acetic acid by added iron(II) salts, and has now accepted that hydrocarbon activation in the Bu^{t}OOH systems involving *either* iron(II) *or* iron(III) does involve butoxyl radicals. On the other hand, he has proposed that with iron(II) and H_2O_2 an iron(IV)–oxo intermediate is the active species which abstracts hydrogen, but that this does also give free alkyl radicals.[43]

It is, of course, pertinent to note that, if the *tert*-butyl hydroperoxide chemistry with iron(III) is accepted as radical, then it might be difficult to refute radical character at least for a part of the GoAgg reactions with hydrogen peroxide, *i.e.* that part which occurs *subsequent to formation of intermediate alkyl hydroperoxide*.

I have emphasised here the work deriving directly from Barton's original observations. Discussion of complementary approaches to alkane functionalisation, such as those of Que[6,44] and of Sawyer[45] and their colleagues, have been almost completely neglected, as has work in which the iron is successfully replaced by other transition metals.[4,46] Both Que and Sawyer have argued that mechanisms similar to that of Scheme 1b are operating in their experiments, and have presented evidence for the formation of high-valent iron species; but evidence that these are directly involved in alkane activation is less compelling, and has begun to be questioned in recent publications.[47] In one of these, a relatively well-controlled system originating in Que's laboratory was selected for experimental scrutiny. This employed *tert*-butyl hydroperoxide as oxidant, acetonitrile as solvent, and a tris-(2-pyridylmethyl)amine **1** iron complex as catalyst. When the *tert*-butyl hydroperoxide was replaced by 2-methyl-1-phenyl-2-propyl hydroperoxide **10**, high


10

yields of products arising *via* benzyl radicals were formed, strongly suggestive of the intermediacy of alkoxyl radicals which, in this case, rapidly fragment. It was argued that if the mechanism advanced by Que, involving an iron–oxo intermediate and by-passing radicals, were operative, then there should be no significant difference between the reactions with the two hydroperoxides.* The report concluded by suggesting 'that each claim for alkyl hydroperoxide-derived high-valent metal–oxo species as oxidising agents should at least be checked using 2-methyl-1-phenyl-2-propyl hydroperoxide as a mechanistic probe.'[47a]

Interestingly, in one recent case in which a metal–oxo species *does* appear to react as an 'oxyl' radical, its reactivity was very much lower, and its selectivity correspondingly greater, than are those of *tert*-butoxyl: the metal–oxo species in question is chromyl chloride.[48] Where measurements have been made, the enzyme systems are also more selective.

* The possibility that this result might be interpreted in terms of cationic ring-opening of an initially formed cyclopropylmethanol was excluded when authentic (2-phenylcyclopropyl)methanol gave no rearrangement product under GoAgg^{III} conditions and was largely (90%) recovered unchanged.[37]

* At present, the possibility that a small amount of radical fragmentation might redirect the overall process cannot be dismissed.

A final point may be made by further reference the P-450 mechanism One, at one time puzzling, feature was the absence of any significant kinetic isotope effect in competition between oxidation by the enzyme of deuteriated and undeuteriated substrates There is, however, a marked intramolecular isotope effect when partially deuteriated substrates are oxidised [1b] This difference can easily be rationalised if the rate-limiting step is transfer of the hydrocarbon substrate into the binding pocket of the active site within the enzyme structure * And, of course, it is within the constraints of this site that the oxygen rebound occurs so rapidly Without those constraints, the radical organic chemist might anticipate some contribution from geminate recombination within the solvent cage if an iron–oxo species were to abstract hydrogen in a simple chemical model, but would expect also that the majority of any radicals formed would diffuse away from their site of formation This simple picture may not always apply in organometallic instances, relatively efficient cage recombination has been reported in some systems where there is no greater constraint than the solvent cage of a non-viscous solvent [50] This may add a further dimension to Gif chemistry

In conclusion, it has been the purpose of this short review to evaluate some of the evidence against radicals in the continually broadening spectrum of Gif chemistry (where the solvent system chosen for much of the early work has probably played a uniquely complicating role), and to argue that a radical interpretation of much of the data, for at least some of these oxidation systems, remains a tenable alternative to that favoured in other review articles [7] Inevitably, space restrictions have precluded comprehensive reporting, and well-informed readers will recognise a certain selectivity, designed to establish the view that the case against radicals is unproven Nevertheless, it is seldom, in recent chemistry, that so much experimental information may seem capable of more than one explanation, and this adds a particular savour to the Gif problem Not infrequently, when this situation has prevailed during earlier scientific investigations, the truth has been found to comprise elements of both of the conflicting analyses Mechanistic hypothesis undoubtedly has a major role to play in addressing the problem – but investigators are bound to consider all possible interpretations of their results, and should not overlook the fact that, as scientists, 'we are dedicated to the discovery of truth '[51]

Note added in proof Since this review was submitted, a summary of the work of the Milan group on the use of *tert*-butyl hydroperoxide as a Gif oxidant has been published (F Minisci, F Fontana, S Araneo, F Recupero and Lihua Zhao, *Synlett*, 1996, 119), as have the results of Newcomb *et al* on the use of cyclopropylcarbinyl radical clocks to investigate GoAgg[III] system (M Newcomb, P A Simakov and S -U Park, *Tetrahedron Lett* , 1996, **37**, 819) In the latter work, further evidence is adduced for the occurrence of aromatic hydroxylation in these reactions Other significant publications include the following D W Snelgrove, P A MacFaul, K U Ingold and D D M Wayner, *Tetrahedron Lett* , 1996, **37**, 823, D H R Barton, Bin Hu, D K Taylor and R U Rojas-Wahl, *Tetrahedron Lett* , 1996, **37**, 1133, J Kim, R G Harrison, C Kim and L Que, *J Am Chem Soc* , 1996, **118**, 4373, D T Sawyer, A Sobkowiak and T Matsushita, *Acc Chem Res* , 1996, **29**, 407

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The interesting question arises here as to what *intramolecular* isotope effect would be expected for a diffusion controlled hydrogen abstraction in a mobile solvent *e g* by hydroxyl radicals from $C_6H_6D_6$ Apparently experimental data do not exist The value of unity noted earlier was obtained by comparing liquid phase rate data for C_6H_{12} and for C_6D_{12} This was appropriate for comparison with the Gif experiments There are however gas phase data for hydrogen abstraction from alkanes by HO which not only give a kinetic isotope effect of *ca* 2 *but also show a threefold preference (at 294 K) for abstraction of tertiary rather than secondary hydrogen* [49]

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