On The Mechanism of Gif Reactions

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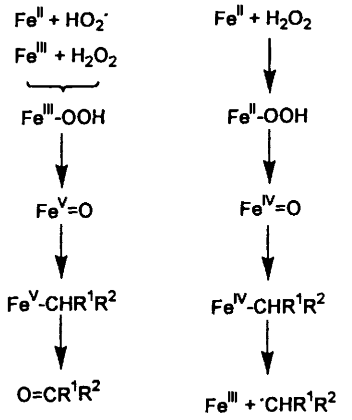
The foregoing review article[1] makes extensive reference to Gif chemistry and involves the role that oxygen and carbon radicals may play in this phenomenon. In brief, Gif chemistry permits the conversion of saturated hydrocarbons into ketones at room temperature under nearly neutral conditions. There is also a surprising chemoselectivity where saturated hydrocarbons are more reactive than would be expected. Thus, ketones were originally[2] formed in the presence of H_2S, normally much more easily oxidized.

Over the years, our theory, which originally was an hypothesis, has evolved to explain all the facts that we have observed. Other suggestions about mechanism are always welcome, but they must explain *all* of the facts and not just a small selection of data.

From the beginning it has been important to distinguish between oxygen- and carbon-radicals and mechanisms which do not involve radicals. Fortunately, great progress has been made in the last two years in distinguishing the role of radicals in Gif chemistry from that important mechanism where they are not involved.

Amongst many indications which are mechanistically helpful we would underline the following techniques. (*i*) The coupling of carbon radicals to pyridine as pioneered by Hey[3] and later by Minisci.[4] This technique has always proved reliable. (*ii*) The reaction of carbon radicals with chloride bonded to Fe^{III} to afford R−Cl and Fe^{II}. This well known reaction[5] has played an important role in distinguishing between Fe^{II} and Fe^{III} chemistry. Finally, we would emphasize the importance of distinguishing between Fe^{II} and Fe^{III} by simple chemical titration.[6]



Scheme 1

In Gif chemistry, we recognize that Fe^{II} activated by superoxide and Fe^{III} activated by nucleophilic displacement by H_2O_2 afford the same Fe^{III}−OOH species (Scheme 1). Postulated evolution to an Fe^V oxenoid species and reaction with a saturated hydrocarbon $CH_2R^1R^2$ affords an Fe^V species with an Fe^V−carbon bond. Eventually this affords ketones selectively, showing preferred insertion into secondary C−H bonds.

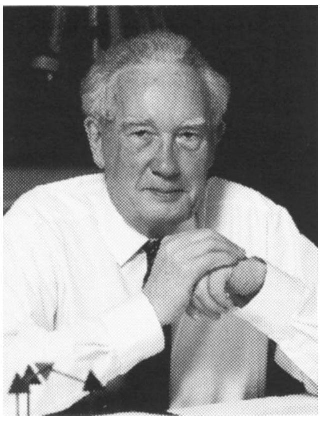
A second route to activation is provided by the nucleophilic displacement of H_2O_2 on Fe^{II} to furnish Fe^{II}−OOH from which an Fe^{IV} oxenoid species results. This shows similar reactivity towards saturated hydrocarbons and affords an Fe^{IV} species which rapidly breaks down to Fe^{III} and a carbon radical (Scheme 1). We have good evidence that hydroxyl radicals are *not* involved in Gif chemistry in pyridine.[7] Indeed hydroxyl radical attack could not explain the selectivity for secondary attack nor the fact that all systems have the same kinetic isotope effect of 2.1 (cyclohexane *vs*. perdeuteriocyclohexane) and the same selectivity for adamantane functionalization. This is always close to 1.0 for C^2/C^3 where C^2 represents the sum (in mmol) of all secondary products and C^3 is the same for all tertiary products. For *tert* -butoxyl radicals, in pyridine, the C^2/C^3 is 0.3. This is a new value determined with care and not a quotation from the literature.[8]

In Scheme 1 we now distinguish two manifolds: Fe^{III}–Fe^V, the non-radical producing manifold and Fe^{II}–Fe^{IV}, the radical manifold.[8] In principle, electron transfer between valence states could remove these differentiations. Fortunately, the chemistry of Fe^{II} + H_2O_2 is completely different from that of Fe^{III} + H_2O_2. Also, the Fe^{II} or Fe^{III} + equivalent H_2O_2 in both manifolds can be varied widely without any change in efficiency. So electron transfer here is not a fast process.

The conclusion that iron–carbon bonds were involved in Gif chemistry came from early studies[9] on the oxidation of adamantane using a superoxide +Fe^{II} system (Zn^0 as reductant) in pyridine–acetic acid. On reducing the oxygen pressure coupling of the tertiary position to pyridine was detected, but not at the secondary position. Later work showed[10] that genuine secondary radicals from adamantane showed the same competitive reaction as did genuine tertiary radicals. Hence, there was a difference which was most easily explained (Occam's Razor) by the formation of iron–carbon bonds at both positions. In the tertiary case the bond was so weak that spontaneous fragmentation to carbon radicals took place.

It has not been easy to detect iron–carbon bonds in Gif systems. They may be present in low concentrations. The best evidence comes from recent work by Newcomb[11] who has shown that a number of hyperactive traps do show the presence of radicals in Gif

Professor (Sir) Derek H. R. Barton was born on September 8, 1918 in Gravesend, Kent. His first academic appointments (1945–1949) were as Lecturer in Inorganic and then Physical Chemistry at Imperial College. After a stint at Harvard (1949–1950), which produced eventually (1969) a Nobel Prize, he was appointed Reader at Birkbeck College, then Professor, and in 1954 was elected FRS. After two years (1955–1957) as Regius Professor in Glasgow, he returned to Imperial College (1957–1978) as, eventually, Hofmann Professor of Organic Chemistry. His career became more interesting when he was appointed as 'Directeur de l'Institut de Chimie des Substances Naturelles', a large CNRS Laboratory in Gif-sur-Yvette, France. In 1986, he became a European retirement refugee at Texas A&M University where he is currently very happy as Dow Professor of Chemical Invention. He was elected an Honorary member of the National Academy in 1970 and received the Priestley Award of the American Chemical Society in 1995. His experience of working in three countries spanning two continents is probably unique. As he has commented before, 'the older you are the harder you have to work because the time left to work is diminishing.' His current schedule of 3:00 a.m. to 8:00 p.m., seven days a week is probably at his limit, pending transfer to another, celestial laboratory where perhaps you can work 24 hours a day forever! Imagine what the literature must be like!



oxidation If iron–carbon bond formation precedes further chemistry, then the structural driving force for the rearrangement may well weaken the iron–carbon bond to the point where it dissociates to give radicals

In the discussion of Professor Perkins as to whether cyclohexanol or cyclohexyl hydroperoxide is the precursor of the ketone, we have studied the rate of oxidation of cyclohexanol It is very slow in the Fe^{II}–Zn^0-pyridine–acetic acid system, but somewhat faster with the Fe^{III}–H_2O_2 procedure There is, however, good evidence that the main source of the ketone, as long as pyridine–acetic acid is the solvent, is the hydroperoxide [12] Professor Perkins suggests that the hydroperoxide, by reaction with Fe^{II}, is the source of the cyclohexyloxyl radical and hence of the alcohol He has overlooked the study that we made[12] to show that with $Fe^{II}Cl_2$ in pyridine–acetic acid cyclohexyl hydroperoxide is converted rapidly (2 min) and *quantitatively* into cyclohexanone No cyclohexanol is formed

In the Fe^{II}–Zn^0 system the addition of increasing amounts of triphenylphosphine changes formation of ketone to formation of alcohol However, the *total* of *ketone* + *alcohol* is *constant* over a wide range of Ph_3P concentration [12] This important experiment shows that alkoxyl and alkylperoxyl radicals are not present, that the activated iron species reacts faster with the hydrocarbon than with Ph_3P and that the activation to give hydroperoxide, which was then reduced to alcohol, was constant Similar studies were made with quenching experiments (benzenethiol with or without oxalic acid) In the Fe^{III}–H_2O_2 series a ^{13}NMR experiment proved that the hydroperoxide preceded the ketone Quenching experiments with oxalic acid demonstrated that ketone came mainly from hydroperoxide and not from alcohol

After reference to this work Professor Perkins comments on some difficulty in reproducing oxidation results obtained using hydrogen peroxide In fact, there are many articles by Sawyer on the H_2O_2–pyridine–acetic acid system, in one of which we were co-authors [13 14] There was no difficulty in obtaining reproducible results The same applies to the extensive work of Professor Ulf Schuchardt and his colleagues [15] This work on the oxidation of cyclohexane has examined in depth the Fe^{II}–Zn^0–pyridine acetic system and the Fe^{III}–H_2O_2 system with various ligands The results are always as good as ours and sometimes better with respect to yield In a comparison of iron and ruthenium chemistry,[16] work on the repetition of the Fe^{II}–Zn^0 process gave a turnover number of 1000, similar to our own results [9] A communication from Geletii[17] using H_2O_2–Fe^{III} in pyridine–acetic acid reported that cyclohexanone was formed by a non-radical reaction and not *via* cyclohexanol Similar results were obtained with Cu^{II} salts An interesting study of cyclohexane oxidation to cyclohexanone using the Fe^{III}–H_2O_2–pyridine–acetic acid system has been reported [18] The various variables were analysed including the kinetics There was no difficulty in repeating the Gif-type chemistry by these authors

We have detected one factor that can influence yield in H_2O_2 experiments Some, but not all, metal syringes catalyse the decomposition of H_2O_2 to oxygen and water This is usually obvious from the oxygen bubbles However, it would be normal practice to carry out the blank experiment to make sure that the H_2O_2 drawn into the syringe is, in fact, delivered intact into a solution of the solvent actually being used

The non-existence of hydroxyl radicals in pyridine has already been commented upon earlier It is suggested by Professor Perkins that hydroxylated pyridines would be oxidized by H_2O_2–Fe^{III} In pyridine as solvent all the hydroxy-pyridines are recovered intact [19] Of course, the 2- and 4-hydroxypyridines are really amides, so oxidation would not be expected

With regard to the interesting reaction[20] which converts saturated hydrocarbons into dimethyl phosphates by using Fe^{II}–Zn^0 in pyridine–acetic acid in the presence of trimethyl phosphite, the following comments are relevant Trimethyl phosphite is well known to react with alkylhydroperoxyl radicals to reduce them to alkoxyl radicals which in turn are reduced to alkyl radicals A blank experiment with trimethyl phosphite, oxygen and cyclohexyl radicals was carried out in a previously cited paper [12] In the blank experiments with trimethyl phosphite, cyclohexyl hydroperoxide and Fe^{II}, approximately equal amounts of cyclohexanone, cyclohexanol and dimethylcyclohexyl phosphate were formed No cyclohexane was observed in these accurate ^{13}C studies In order for the Scheme 5 of Professor Perkins to be operative, the Fe^{III} oxidation of the intermediate radical would have to be favourable thermodynamically It is doubtful if this can be true The product of the proposed Arbusov reaction that makes the dimethylcyclohexyl phosphate has recently been identified by ^{13}C NMR It is methyl acetate and not an *N*-methylpyridinium salt [21] In any case, the initial addition of the cyclohexyloxyl radical postulated by Professor Perkins should have lead to immediate deoxygenation to afford a cyclohexyl radical (*vide supra*)

The proposal in the Scheme 6 of Professor Perkins is even less likely to explain the experimental facts As above, the addition of the cyclohexyloxyl radical to triphenylphosphine would lead at once to deoxygenation to the corresponding cyclohexyl radical Over a number of years we had carried out Gif Fe^{III}–H_2O_2 oxidation of saturated hydrocarbons to give ketones in the presence of chloride and bromide anion without seeing a trace of alkyl chloride or bromide It was, therefore, a surprise when the addition of hydrogen peroxide to $FeCl_3$ in the presence of triphenyl phosphine in pyridine–acetic acid gave smooth formation of cyclohexyl chloride instead of the ketone which was normally produced in the Fe^{III}–Fe^{V} manifold [22] Clearly the activation of the alkane was nearly as great as it was for the usual ketone formation After a helpful publication by Minisci,[23] we realized that alkyl chloride formation was due to production of Fe^{II} In fact, whilst triphenylphosphine reduces Fe^{III} to Fe^{II} only slowly, the addition of H_2O_2 produces a fast formation of Fe^{II} and of $Ph_3P{=}O$ The Fe^{II}–Fe^{IV} manifold then proceeds to activate the hydrocarbon and to make carbon radicals These combine with the chloride bonded to Fe^{III} to make the observed chloride In principle, this reaction reforms Fe^{II} However, there is another oxidation reaction with H_2O_2 which oxidizes Fe^{II} to Fe^{III} in competition with the chlorination reaction and eventually all the Fe^{II} is reconverted to Fe^{III} These reactions provide a valuable proof that the Fe^{III} + H_2O_2 reaction makes the ketone by a non-radical mechanism [8] If one adds H_2O_2 portionwise to an Fe^{II} salt in pyridine–acetic acid containing chloride ion, alkyl chloride is first formed However, as soon as all the Fe^{II} is converted into Fe^{III} (titration) chloride formation ceases and the Fe^{III}–Fe^{V} manifold more slowly produces ketone If more Fe^{II} is added, rapid alkyl chloride formation recommences, then ceases and is replace by ketonisation when all the Fe^{II} has been converted into Fe^{III} Most experiments have been done with cyclohexane We have, of course, shown by suitable blank experiments that cyclohexyl chloride is inert under the Fe^{III}–H_2O_2 oxidation conditions and is *not* the source of cyclohexanone When all the Fe^{II} has been converted to Fe^{III} there is still a large excess of chloride ion present, some of which is bonded to Fe^{III} So if the Fe^{III}–H_2O_2 system were producing carbon radicals it would still be making alkyl chloride Indeed the alkyl chloride reaction is much faster than the ketonisation process [24]

The comparison of Professor Perkins of radical bromination and Gif bromination fails to mention certain important facts Citation is made of the preliminary communication,[25] but not of the full paper [26] In the latter, mass balances are given for all the hydrocarbons that are not too volatile These are satisfactory mass balances and there is no reason to think that the very volatile hydrocarbons (cyclopentane and 2,3-dimethylbutane) would not follow the same reactions More important is the failure to mention the comparative bromination of cyclohexyl bromide Radical bromination affords 1,2-dibromides as major products, whereas in Gif bromination 1,2-dibromides are very minor and 1,4-dibromocyclohexanes are the major product This bromination in the 4-position corresponds to Schuchardt's observation[15] that the ultimate oxidation product of cyclohexanone is cyclohexane-1,4-dione

As far as *tert*-butyl hydroperoxide (TBHP) reactions are concerned, these have a kinetic isotope effect of about 7, very different from the 2 1 found for Gif chemistry It is clear that these reactions are largely radical in nature The slow formation of chloride and other congeners from cyclohexane[27] is probably due to radical chemistry produced by reduction of a small amount of Fe^{III} to Fe^{II} If the reaction is started using Fe^{II} then the derivative formation is fast[28] and we agree involves carbon radical formation by reaction with *tert*-butoxyl radicals

The contrast between H_2O_2 and TBHP chemistry finds a possible explanation in the importance of the ligands in Gif chemistry All the Gif reactions are only seen when the right kind of carboxylate ligand is present[24 29] This chemistry probably involves an $Fe^{III}-O-O-Fe^{III}$ functionality stimulated by carboxylate bridging This peroxyl function is not possible with TBHP

Finally, I would point out that if you consider the whole body of evidence, carbon radicals, when present, can be detected easily In those reactions where carbon radicals cannot be detected an alternative mechanism must be proposed Gif chemistry is a well established experimental fact But if any other theory can be advanced to explain all of the facts, we shall be happy to consider it Such a theory must explain also the Gif paradox How is it possible to generate an iron species which attacks selectively saturated hydrocarbons in the presence of PPh_3, $(MeO)_3P$, H_2S, even PhSeH *etc* , reagents which by conventional standards are much more easily oxidized? We have offered an explanation in the as yet unappreciated nature of iron–hydrogen peroxide derived species [30]

References

1 M J Perkins, *Chem Soc Rev* , 1996, 229

2 D H R Barton, M J Gastiger and W B Motherwell, *J Chem Soc Chem Commun* , 1983, 41

3 D H Hey, C J M Stirling and G H Williams, *J Chem Soc* , 1955, 3963, and references there cited

4 F Minisci and A Citterio, *Adv Free Radical Chem* , 1980, **6**, 65, F Minisci *Acc Chem Res* , 1975, **8**, 165

5 J K Kochi, in *Free Radicals*, ed J K Kochi, Wiley, New York, 1973, pp 591–683

6 L J Clark, *Anal Chem* , 1962, **34**, 348

7 D H R Barton, S D Beviere, W Chavasiri, D Doller, W G Liu and J H Reibenspies, *New J Chem* , 1992, **16**, 1019, D T Sawyer, C Kang, A Llobet and C Redman, *J Am Chem Soc* , 1993, **115**, 5817, J P Hage, A Llobet and D T Sawyer, *Bioorg Med Chem* , 1995, **3**, 1383

8 C Bardin, D H R Barton, B Hu, R Rojas Wahl and D K Taylor, *Tetrahedron Lett* , 1994, **35**, 5805

9 D H R Barton, J Boivin, W B Motherwell, N Ozbalik and K M Schwartzentruber, *Nouv J Chim* 1986, **10**, 387

10 D H R Barton, F Halley, N Ozbalik, M Schmitt, E Young and G Balavoine, *J Am Chem Soc* , 1989, **111**, 7144

11 M Newcomb, P A Simakov and S V Park, *Tetrahedron Lett* , in press

12 D H R Barton, S D Beviere, W Chavasiri, E Csuhai, D Doller and W G Liu, *J Am Chem Soc* , 1992, **114**, 2147, D H R Barton, E Csuhai, D Doller and G Balavoine *J Chem Soc Chem Commun* , 1990, 1787

13 C Sheu, A Sobkowiak, L Zhang, N Ozbalik, D H R Barton and D T Sawyer, *J Am Chem Soc* , 1989, **111**, 8030

14 C Sheu, A Sobkowiak, S Jeon and D T Sawyer, *J Am Chem Soc* , 1990, **112**, 879, C Sheu, S A Rickert, P Cofre, B Ross, A Sobkowiak, D T Sawyer and J R Kanofsky, 1990, **112**, 1936, C Sheu and D T Sawyer, 1990 **112**, 8212, and later papers from the Sawyer group

15 Summarizing article U Schuchardt, W A Carvalho and E V Spinace, *Synlett*, 1993, 713, and references there cited

16 G Powell, D T Rickens and L Khan, *J Chem Res (S)*, 1994, 506

17 Y V Geletii, V V Lavrushko and G V Lubimova, *J Chem Soc Chem Commun* , 1988, 936

18 S B Kim, K W Lee, Y J Kim and S I Hong, *Bull Korean Chem Soc* , 1994, **15**, 424, S B Kim and K W Lee, *Korean J Chem Eng* , 1995, **12**, 188, and prior references there cited

19 D H R Barton, B Hu and R U Rojas Wahl, unpublished observations

20 D H R Barton, S D Beviere and D Doller, *Tetrahedron Lett* , 1991, **32**, 4671

21 D H R Barton and D K Taylor unpublished observations

22 D H R Barton and S D Beviere, *Tetrahedron Lett* , 1993, **34**, 5689

23 F Minisci and F Fontana, *Tetrahedron Lett* , 1993, **35**, 1431

24 D H R Barton, B Hu, D K Taylor and R U Rojas Wahl, *J Chem Soc Perkin Trans 2*, 1996, 1031

25 D H R Barton, E Csuhai and D Doller, *Tetrahedron Lett* , 1992, **33**, 3413,

26 D H R Barton, E Csuhai and D Doller, *Tetrahedron*, 1992, **48**, 9195

27 D H R Barton, S D Beviere, W Chavasiri, D Doller and B Hu, *Tetrahedron Lett* , 1993, **34**, 1871, D H R Barton and W Chavasiri, *Tetrahedron*, 1994, **50**, 19, D H R Barton, S D Beviere and W Chavasiri, *Tetrahedron*, 1994, **50**, 31, D H R Barton and W Chavasiri, *Tetrahedron*, 1994, **50**, 47

28 D H R Barton, B Chabot, N C Delanghe, B Hu, V N Le Gloahec and R U Rojas Wahl, *Tetrahedron Lett* , 1995, **36**, 7007

29 D H R Barton, B Hu, D K Taylor and R U Rojas Wahl, *Tetrahedron Lett* , 1996, **37**, 1133

30 D H R Barton and D Doller, *Acc Chem Res* , 1992, **25**, 504