Pergamon

Tetrahedron 54 (1998) 5805–5817

TETRAHEDRON

Tetrahedron report number 452

Gif Chemistry: The Present Situation.

Derek H.R. Barton

Texas A&M University, Chemistry Department, P.O. 300012, College Station, TX 77842-3012, USA

Received 20 January 1998

Gif Chemistry began in 1983[1] with the hypothesis that if one recreated the world as it was 3 billion years ago, when oxygen began to be produced by photosynthesis, then there might be a mechanism in which the oxidation of metallic iron was coordinated with the oxidation of saturated hydrocarbons. We selected adamantane as a convenient hydrocarbon whose limited volatility would permit a precise determination of mass balances. A convenient solvent for the hydrocarbon was pyridine[2] and because the dissolution of the iron required a complementary anion we selected acetic acid. Also included was an excess of hydrogen sulfide. We were pleasantly surprised to find that this system at room temperature gave smoothly adamantan-2-one in a yield superior to previous systems. A fact which was also surprising was that this oxidation took place in the presence of an excess of hydrogen sulfide, a compound much easier to oxidize than a saturated hydrocarbon. As an Organic Chemist, I felt that there must be something of fundamental importance in this observation.

A more practical modification of the system was the use of metallic zinc in pyridine-acetic acid using an iron catalyst.[3] Here turn-over numbers of 2,000 or more were readily attained.

The apparent selectivity of the adamantane oxidation, which strongly favoured the secondary position, did not afford a satisfactory mass balance. Further investigation revealed that the *tert*-position in adamantane was bonded to pyridine in the 2- and 4-positions, but not the secondary position.[4] We concluded that carbon radicals were being formed at the *tert*-position of adamantane, but not at the secondary position. A careful study of radical chemistry at the *sec*- and *tert*-positions of adamantane showed that coupling to pyridine was in competition with oxidation as would be expected. In Gif Chemistry at reduced oxygen pressure there was still no coupling of the secondary positions and hence no secondary radicals.[5]

From these observations came the idea of the iron-carbon bond as a precursor, in exceptional cases like the *tert*-adamantyl position, of radicals, but **not** normally involved in radical generation. Experiments on the conversion of cyclohexane to cyclohexanecarboxylic acid using CO[6] and $Fe(CO)_5 + H_2O_2$[7] gave good support to the iron-carbon bond hypothesis. Also, the iron-carbon bond can be captured by phenylselenol[8] and by iodide ion.[9] Both reagents afford comparable yields in separate quenchings.

Some years ago we summarized what was known about Gif Chemistry[10] at that time. It was recognized that the Fe^0 and Zn^0-Fe^{II} catalysis systems involved the addition reaction of Fe^{II} with superoxide and that the same intermediate could be reached by a displacement on Fe^{III} by hydrogen peroxide (Scheme 1). For convenience, we do not specify other ligands attached to the iron species, although these are, of course, essential. The hypothesis that Fe^{II} and superoxide were involved was confirmed by extensive studies using electrochemical reduction of oxygen at the cathode to furnish superoxide.[11] Apart from its enhanced efficiency, the electrochemical study shows that oxygen is

0040-4020/98/$19.00
PII: S0040-4020(98)00155-0

reduced to superoxide and that the iron species is Fe^{II} in agreement with Scheme 1.

$$Fe^{II} + \dot{O}_2H \xrightarrow{\text{Coupling}} Fe^{III}\text{-O-O-H} \xleftarrow{\text{Displacement}} Fe^{III} + H_2O_2$$

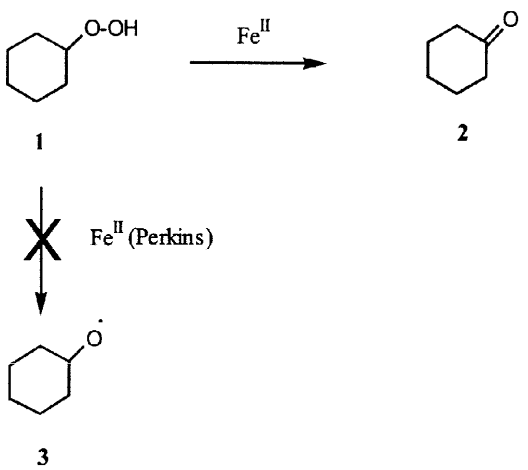
Scheme 1

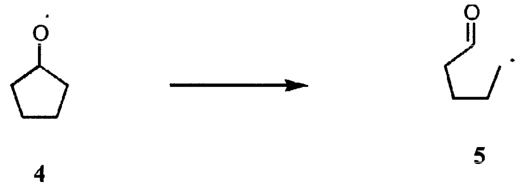
$$Fe^{III}\text{-O-O-}Fe^{III} \rightleftharpoons 2Fe^{II} + O_2$$

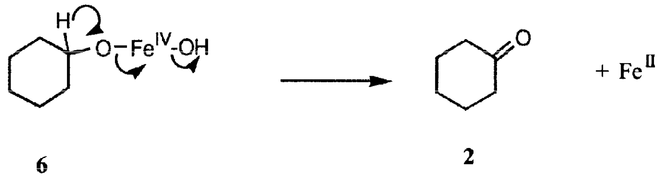
Scheme 2

In our prior review,[10] we presented the hypothesis of two intermediates A and B. A was regarded as the iron-carbon bond whose nature we have already discussed above. In the case of cyclohexane B was shown to be cyclohexyl hydroperoxide **1**. It was first characterised by ^{13}C NMR and then isolated. Under the conditions of Gif Chemistry at the time (pyridine-acetic acid), the addition of Fe^{II} gave immediately and nearly quantitatively the corresponding ketone **2**. It has been suggested by Prof. M.J. Perkins[12] that the Haber-Weiss mechanism should apply to this reaction so that the cyclohexyloxy radical **3** should be formed first. Recently [13a] we studied the reaction of three different hydroperoxides in pyridine solution towards Fe^{II}. With or without picolinic acid, cyclopentyl hydroperoxide was transformed by Fe^{II} into cyclopentanone and some cyclopentanol. The corresponding cyclopentyloxy radical is well known[13b] for its fragmentation to radical **5**. Thus pyridine, in fact, does not permit the Haber-Weiss mechanism to apply to cyclopentyl hydroperoxide. The same behaviour was seen with *n*-pentyl hydroperoxide. In contrast, the tertiary cumyl hydroperoxide ($PhCMe_2$-O-OH) did fragment into the cumyloxy radical which, by loss of a methyl radical, afforded acetophenone. On addition of 3-pentanol, the postulated cumyloxy radical was cleanly captured and acetophenone was only formed in trace amounts. 3-Pentanol had no effect on the decomposition of cyclopentyl hydroperoxide. Our interpretaion of these reactions was that an Fe^{IV} **6** intermediate was formed by insertion into the hydroperoxide. When fragmentation with loss of H^+ was possible then ionic chemistry took place. If this type of fragmentation was not possible then the normally expected radical fragmentation was observed. Titration for Fe^{II} showed that this valence state was retained during the ionic type fragmentation as theory would suggest.

The role of acetic acid in Gif Chemistry is important. However, acetic acid can be replaced by other carboxylic acids.[14] In particular, picolinate and 1,10-phenanthroline-2-carboxylate were suitable ligands.[15] A kinetic study[16] showed that picolinic acid increased the rate of oxidation fifty-fold relative to acetic acid.







As was evident from studies with 1-methylcyclohexane, 1-methylcyclopentane, *cis*-decalin, *trans*-decalin and *trans*-1,4-dimethylcyclohexane, Gif Chemistry shows an unusual selectivity for secondary position oxidation.[5, 10, 17] The normalized ratio of secondary to tertiary oxidation is about 2:1, whereas with radical autoxidation it is about 4:1 in the reverse sense of tertiary substitution being favored over secondary.[18] We have always explained these experimental facts[10] by the concept of an $Fe^V{=}O$ species which inserts itself preferentially into secondary positions. This we regard as a compromise between steric effects (tert. > sec. > prim.) and bond strength considerations (prim. > sec. > tert.).

The most remarkable aspect, however, of Gif Chemistry is that saturated hydrocarbons can be oxidized in the presence of substances like H_2S (see above), Ph_2S,[19,20] PPh_3,[21, 25] $P(OMe)_3$,[22] PhSH[23,24] and especially PhSeH,[8,25] all of which are normally far more easily oxidized than saturated hydrocarbons. As we already pointed out,[10] the iron species that attacks the hydrocarbon so efficiently does not react with the easily oxidized compounds which are listed above. The only way that we can understand this extraordinary phenomenon is that the iron species present is only activated **by contact with the saturated hydrocarbon**. Thus it is the substrate hydrocarbon which creates the iron species with which it at once reacts. We have called this[10] the 'Sleeping Beauty Effect', but one can also regard it as an extreme form of agostic interaction.

Many experiments using Fe^{II} + superoxide or Fe^{III} + H_2O_2 in the presence of excess chloride ion always gave oxidation products without formation of cycloalkyl chloride. It was, therefore, a surprise[26] when the addition of an excess of triphenylphosphine to an Fe^{III}-H_2O_2 experiment in the presence of chloride ion produced from cyclooctane cyclooctyl chloride in an amount equivalent to the ketone and alcohol normally expected. The presence of other anions such as azide and thiocyanate also gave azides and thiocyanates in the same way. At the same time experiments using *tert*-butylhydroperoxide (TBHP) at 60° in pyridine-acetic acid also produced cycloalkyl chloride and similar coupling products.[27] At first we interpreted this chemistry as a further development of Gif Chemistry. However, Minisci[28] pointed out that chloride formation and similar reactions were better explained as radical reactions.

After due consideration we recognized that this was so and identified that chloride formation was the reaction of a carbon radical with Fe^{III}-Cl. This is, in fact, a well known reaction.[29]

In the triphenylphosphine experiments[22] the Fe^{III} was reduced to Fe^{II} which then initiated radical chemistry. The reduction can be explained as **7** → **8**. However, the reaction deserves further study.

$$Fe^{III}\text{-}O\text{-}Fe^{III} + PPh_3 + 2H_2O \longrightarrow Fe^{II}\text{-}O\text{-}Fe^{II} + Ph_3P(OH)_2 + 2H^{\oplus}$$

7 **8**

As soon as we realized that there was a simple titration[30] for Fe^{II} we could initiate chloride formation using $Fe^{II} + H_2O_2$. The H_2O_2 was added in portions and, as soon as the Fe^{II} had been converted to Fe^{III}, chloride formation ceased and the normal slower reaction of ketonization replaced chloride formation. Of course the chloride remains attached to Fe^{III} and is still present during the ketonization reaction. So this phenomenon is an excellent demonstration that carbon radicals are not involved in the formation of ketone from $Fe^{III} + H_2O_2$.

The chemistry of TBHP has been studied extensively[31, 32, 33] and all authors now agree that it is simply radical chemistry based on the reactivity of the *tert*-butylperoxy- and *tert*-butyloxy-radicals. Thus the reactions of TBHP can be compared with those of Gif Chemistry and a clear distinction can be drawn.[33, 34]

The reaction of Fe^{II} with H_2O_2 has already been mentioned above. The formation of chloride is indicative of radical chemistry. However, this is not initiated by hydroxyl radicals because the selectivity for adamantane on a normalized basis is 0.35, the same as the $Fe^{III} + H_2O_2$ selectivity. We have checked carefully *tert*-butoxy radical reactivity and this, in our hands, is always, after normalization, 0.1. In the event that hydroxyl radicals were formed they should react with the solvent pyridine to afford 2- and 4-hydroxypyridine in a ratio of 2:1[35]. In fact there is little coupling to pyridine and it is 3-hydroxypyridine that is the principal product.[35, 36]

The clear differentiation in the chemistry seen with $Fe^{II} + H_2O_2$ as compared with $Fe^{III} + H_2O_2$ led us to the concept of two manifolds[37]. The $Fe^{III} + H_2O_2$ (Fe^{III}-Fe^{V}) manifold was one that we had already studied carefully. The $Fe^{II} + H_2O_2$ (Fe^{II}-Fe^{IV}) was a different conception whose exploration has been a stimulating experience.[20]

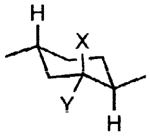
As soon as we realised[16] that picolinic acid was a superior ligand relative to acetic acid and its congeners, we undertook a systematic comparison of analogues of picolinic acid.[20] Isoquinoline-1-carboxylic acid was comparable to picolinic acid but quinaldic acid (quinoline-2-carboxylic acid) was relatively inert. Clearly, there was needed a carboxylic function next to an unhindered aromatic nitrogen in order to produce efficient oxidation. Nicotinic acid (pyridine-3-carboxylic acid) gave little oxidation, whereas isoquinoline-3-carboxylic acid showed normal oxidizing powers. Using quantitative ^{13}C NMR spectroscopy we were able to show for the first time[38] with this convenient technique that two picolinic acids were bonded to each Fe^{III}. Similarly, when most of the pyridine used in Gif Chemistry was replaced with acetonitrile and ony a limited amount of pyridine or of 4-*tert*-butylpyridine was used, it was possible to demonstrate by the same ^{13}C NMR spectroscopy that only one pyridine, or congener, was bonded[39] to Fe^{III}.

The carboxylic acids which were inefficient in the oxidation of cyclohexane to cyclohexanone converted hydrogen peroxide instead into oxygen (the catalase reaction). A separate study using $FeCl_3$ in pyridine without any carboxylic acid showed that oxygen formation was quantitative[40]. However, there was a definite intermediate, because addition of variable amounts of Ph_2S afforded $Ph_2S{=}O$. The total of oxygen (x2, because 2 H_2O_2 make 1 O_2) + $PhS{=}O$ was constant and close to the amount of H_2O_2 that was added. Hence, it was clear that H_2O_2 and Ph_2S were competing for the same species. Based on further competition with unhindered *n*-Bu_2S and hindered *t*-Bu_2S, it was concluded that an $Fe^{V}{=}O$ was formed from Fe^{III} + H_2O_2. Of course this was not the same species as is obtained with the right carboxylic acid like picolinic acid. Without the latter the addition of excess cyclohexane gives only a trace of ketone. As soon as the right carboxylic acid is added then ketonization replaces oxygen formation.

The overall conclusion that can be drawn from this work was that Gif Chemistry in either manifold required the right kind of carboxylic acid and a suitable unhindered pyridine base.

An interesting observation in our recent work was that passing a current of argon through a solution containing Fe^{III}, pyridine and picolinic acid to which H_2O_2 had been added gave, as well as the expected ketone, a significant amount of chloride. Titration for Fe^{II} showed that about 15% of the original Fe^{III} had been reduced to Fe^{II}. The obvious mechanism for this would be as shown in Scheme 2, where the stream of argon sweeps out the oxygen as it is formed. This suggests that the active species contains two Fe^{III} (or Fe^{II}) bonded to each other by carboxylate bridging. In this respect there is some analogy with the recently revealed structure of methane monoxygenase where there are two carboxylate bridges and one basic histidine on each iron.[41] In Gif Chemistry we need carboxylate bridging and pyridine, or a congener, for binding once to each iron.

So far, no mention has been made of stereoselectivity in Gif oxidation chemistry. The most convenient available hydrocarbon for this purpose[42] was *trans*-1,4-dimethylcyclohexane **9**. This is a beautifully symmetrical hydrocarbon with 8 secondary hydrogens (4 equatorial and 4 axial) as well as two tertiary hydrogens and six primary hydrogens. Oxidation of the latter was negligible. Application of the Zn^0-Fe^{II} pyridine-acetic acid system gave mainly ketone **10** with some *tert*-alcohol (normalized C^2/C^3 = 1.5). A better yield of ketone was obtained with Fe^{III} + H_2O_2 oxidation with picolinic acid (C^2/C^3 = 1.7) or without but using acetic acid (C^2/C^3 = 1.8). These reactions take place in the Fe^{III}-Fe^{V} manifold. The amount of secondary alcohol was small, but only the equatorial alcohol was formed. When the reaction using Zn^0-Fe^{II} was run in the presence of PPh_3, a reagent which reduced the intermediate hydroperoxide to alcohol, the amount of ketone **10** formed diminished in proportion to the amount of PPh_3 that was added. However, the total of ketone **10** + alcohol **11** was constant and only traces of axial alcohol **12** were seen. Noteworthy was the fact that 5mmol of PPh_3 did not reduce the overall oxidation at all, in keeping with several prior studies (*vide supra*). A similar reaction using Zn^{o}-Fe^{II} catalyst with addition of diphenyldiselenide, and hence quantitative formation of phenylseleconl as proved by methylation, gave the equatorial phenylselenide **13** and some axial derivative **14** in a ratio of 6:1 in favour of the equatorial isomer. There was no formation of tertiary phenylselenide. These results show a considerable selectivity for formation of the equatorial iron-carbon bond. Since phenylselenol is a wonderful trap for radicals,[43] this study again shows that carbon radicals are not involved.



9 X=Y=H
10 X,Y=O
11 X=H, Y=OH
12 X=OH, Y=H
13 X=H, Y=SePh
14 X=SePh, Y=H

As mentioned already the most interesting aspect of Gif Chemistry is that efficient oxidation of saturated hydrocarbons takes place in the presence of substances that are normally much easier to oxidize. The most striking of these compounds is phenylselenol.

Phenylselenol is generated using Fe^{o} or Zn^{o} + Fe^{II} catalyst and diphenyldiselenide. Methylation of an aliquot showed that the phenylselenol formation was quantitative. This shows that the phenylselenation reaction, which replaces all other oxidation products, must at the same time be quenching any carbon radicals or hydroxyl radicals that are formed. Therefore the phenylselenation reaction involves an insertion into the iron-carbon bond (*vide infra*). An alternative explanation[12] has been offered that phenylselenol is so acidic that is affords with pyridine the anion. Hence there is no phenylselenol left and the reaction is that of a carbon radical with the selenol anion. In fact, phenylselenol is a weaker acid that acetic acid. In the sequel we have added excess trifluoroacetic acid without any effect on the phenylselenation reaction. On the other hand, the addition of triethylamine and then, in a separate experiment, of a strong guanidine base reduced considerably the yield of the phenylselenation reaction. We consider that the anion theory can be dismissed.[25]

Recently we have used a convenient procedure based on tributylphosphine and diphenyldiselenide which produces phenylselenol in a homogeneous solution in a fast reaction (2min.) as measure by phosphorus NMR. Using only 1mmol of H_2O_2, 0.5mmol Ph_2Se_2 and 0.75mmol (50% excess) of tributylphosphine in acetonitrile with 15mmol of 4-*tert*-butylpyridine and 0.25mmol of $FeCl_2$ it was possible to prepare cyclohexyl phenyl selenide with 90% efficiency with respect to hydrogen peroxide[25]. This means that the hydrogen peroxide reacts with the iron preferentially to reaction with tributylphosphine or with phenylselenol. Thus the initially formed iron species is not reactive towards any of the other species present, but it does react efficiently with the saturated hydrocarbon. Again the latter creates the really reactive iron species.

Reference has already been made[21] to the effect of triphenylphosphine on the Zn^{o}-Fe^{II}-O_2 reaction. Over a range of 0 to 3.5mmol of triphenylphosphine with respect to 5mmol of cyclododecane we obtained a constant amount of ketone and alcohol. The more triphenylphosphine was added the more alcohol was produced by reduction of the intermediate hydroperoxide. Again there was no interference with the activation of the hydrocarbon.

In the first experiments on Gif Chemistry we added H_2S and this did not inhibit the oxidation. Now the removal of H_2S from natural gas is an essential and important process before combustion can take place. It is carried out on a very large scale. It occurred to me that the oxidation of H_2S to sulfur might be synergistically combined with the oxidation of a saturated hydrocarbon.[44] The ideal oxidant would be air and, of course, the right Gif type catalyst and a pyridine base would also be needed.

In the event the pyridine base normally used was replaced by the more practical solvent acetonitrile and 4-*tert*-butylpyridine (15 equiv. relative to the Fe^{II}) was added to complex with the iron. Picolinic acid (2 equivs. per Fe^{II}) was needed to complete the Gif catalyst, but an excess of picolinic acid does not effect the yield of product. The results obtained were impressive. Cyclohexane could be oxidized to cyclohexanone and cyclohexanol and with a conversion of 35% the reaction was quantitative. Furthermore under these conditions cyclohexanone was not oxidized to any other product and cyclohexanol was oxidized only very slowly to cyclohexanone. These results are far superior to the DuPont oxidation of cyclohexane using high temperature cobalt catalyzed autoxidation under pressure. Here on a 20% conversion only 4% is cyclohexanone.[45]

The reason for the success of the H_2S-oxygen experiments became clear when we realised that H_2S reduces any carbon radicals that are formed back to the parent hydrocarbon.[46] Thus adamantane shows a remarkable selectivity (normalized) of 1.0, which is three time as selective as usual. This is because the *tert*-adamantyl radicals, which are produced at the tertiary position, but **not** at the secondary position, are reduced back to adamantane by the hydrogen sulfide.

Our conclusions were confirmed by experiments with diphenyl diselenide comparable to those already discussed.[25] The addition of diphenyl diselenide with an appropriate excess of tributylphosphine to cyclohexane gave with H_2S-O_2 a mixture of ketone, alcohol, and cyclohexyl phenyl selenide. The total amount of product was the same as normally expected. Hence the reaction was not inhibited by phenylselenol and hence radical chemistry was not involved. In experiments where H_2S and H_2O_2 were used with phenylselenol excellent yields of cyclohexyl selenide were obtained; e.g. 85%. The phenylselenol was generated in the usual way from diphenyl diselenide and 50% excess of tributylphosphine. Since the rate constant[43] for the reaction of a carbon radical with phenylselenol is close to the diffusion controlled rate at $3x10^9$, whereas the rate for the reaction with diphenyl diselenide is $2.6x10^7$, it is clear that even 10-20% of the diselenide would not change the results to any significant extent.

As we have commented above, the normal course of reaction in the Fe^{II}-Fe^{IV} manifold is reaction with the saturated hydrocarbon to furnish the Fe^{IV}-CHR_2 bond that then fragments to Fe^{III} and the $^{\bullet}CHR$. This cannot apply in the cyclohexylphenyl selenide reaction because of the excess of phenylselenol. For that reason the mechanism proposed is that of ligand coupling as in $PhSeFe^{IV}$-$CHR_2 \rightarrow PhSeCHR_2 + Fe^{II}$. This mechanism may also apply in the formation of R_2CH-Cl because by adding excess of chloride ion to the phenylselenol reaction the formation of chloride is in competition with the formation of cyclohexylphenyl selenide. Again the chloride cannot be formed from a radical reaction in the presence of the phenylselenol.

It is appropriate to mention other contributions to the study of Gif Chemistry. From the point of view of cyclohexane oxidation all the various Gif systems have been applied by Schuchardt and his colleagues with precision and care. These results are the same, or sometimes better, that those that we have found.[47]

Professor D.T. Sawyer is a well known expert on oxidation. His work on anhydrous acetonitrile as a solvent is frequently cited.[48] Changing to pyridine-acetic acid as a solvent (Gif Chemistry) gave excellent results for cyclohexane oxidation.[49, 50]

A relative newcomer to Gif Chemistry is Professor P. Stavropoulos. He and his colleagues have made elegant contributions to the nature of the complexes that give rise to the oxidation process.[51] It is important that well qualified experts in organometallic chemistry contribute to a better understanding of complex phenomena.

Dr. Kyu-Wan Lee and his collaborators have also made important contributions to Gif Chemistry[52] including an interesting study on the kinetics of the reaction.[53] A further advance was the use of a catalyst supported on silica.[54] An important new direction was the development of an iron-palladium system where the palladium catalyses the formation of H_2O_2 from hydrogen and oxygen and the iron carries out Gif-type oxidation.[55]

We should also not forget the helpful criticism that we have received and continue to receive.[12] We replied appropriately because a simple radical mechanism cannot explain the majority of the chemical facts.[56] Of course, we do not forget that Professor Perkins did indentify independantly intermediate B as the hydroperoxide at the same time that we did.[57]

From all this work it is clear that Gif Chemistry is an original and efficient procedure for the selective substitution of saturated hydrocarbons which depends on a totally novel and interesting mechanism. Whether this mechanism is related to that of the enzyme methane momooxygenase remains to be seen.

The author thanks all the colleagues who have worked hard, and with enthusiasm, on Gif Chemistry. Also those who have made the work possible by essential financial contributions.

Coda

It has been suggested that a summary of the facts of Gif Chemistry, which cannot be explained by simple radical chemistry, would be welcome.

(i) The selectivity for secondary over tertiary positions already discussed above.

(ii) The formation of *tert*-radicals in the adamantane oxidation with no formation of secondary radicals. This was also presented above.

(iii) The selective oxidation of saturated hydrocarbons in the presence of reductants like H_2S and especially phenylselenol, is not compatible with radical chemistry. This is the most interesting aspect of Gif Chemistry (*vide supra*).

(iv) The relative reactivity of a series of hydrocarbons in Gif reactions and in radical reactions has been compared.[10, 58] In brief, using normalized data, cyclohexane is less reactive in radical bromination than other cyclic hydrocarbons. On the contrary it is more reactive than other cyclic hydrocarbons (except cycloheptane) in Gif oxidative bromination. Specially noteworthy is the difference between radical bromination of 1-bromocyclohexane and Gif oxidative bromination.[59] In the radical case much 1,2-dibromination is seen. In Gif oxidative bromination 45% of 1,4-*trans*-(diequatorial) dibromide, 28% of 1,3-*cis*-(diequatorial) dibromide and 17% of 1,4-*cis*-(equatorial, axial) dibromide was observed. As expected with Gif Chemistry the electrophilic reagent seeks mainly equatorial substitution as far as possible away from the original electron attracting 1-bromide substituent.

(v) In collaboration with Gilbert Balavoine we made an extensive study of Gif electrochemical oxidation, as already mentioned. This work confirmed the selectivity and showed that in pyridine, an electrochemical efficiency for the electrons of 60% was attainable. More to the point here is that oxidations in 1:1-pyridine to acetone had the same efficiency. That is to say that the hydrocarbon (50-100mmol) was oxidized more efficiently than 15ml of acetone. Even more remarkable, the presence of 15ml of isopropanol and 15ml of pyridine reduced the coulombic efficiency to only 33%. Surely any radicals would have reacted with the isopropanol and there would not have been any product from the hydrocarbon.

(vi) The limits to Gif oxidation were studied using cyclododecane. A maximum yield of cyclododecanone of 30-35% was obtained. After that further oxidation started to make cyclododecane-1,3-; 1,4-; 1,5- and 1,6-diones. There was no trace of ring fission or of attack at the 2-position as would be expected from radical chemistry.[60]

(vii) The conversion of cyclohexane to cyclohexanecarboxylic acid has been mentioned. The addition of methanol to the solvent affords the corresponding methyl ester. Consequently there must be an electrophilic leaving group of the nature $C_6H_{11}\text{-CO-Fe}^{IV} \rightarrow C_6H_{11}\text{-}CO_2Me + Fe^{II}$. Again, this is not radical chemistry or the radicals would have reacted with the methanol.

(viii) The concept of two manifolds has been presented above. In apparent contradiction radical addition to 2-methylnapthaquinone with $Fe^{II} + H_2O_2$ and $Fe^{III} + H_2O_2$ took place. In fact, the intermediate in the addition reduced Fe^{III} to Fe^{II} (titration) and the Fe^{II} chemistry, being much faster, took over from Fe^{III}. So there was not a real anomaly.[61]

(ix) When Tempo was added to the Fe^{III}-Fe^{IV} manifold it trapped carbon radicals, which should not happen with Fe^{V}-carbon bond. In fact, Tempo reduces Fe^{V} to Fe^{IV}, thus providing generation of carbon radicals. At the same time Tempo is oxidized to $\text{Tempo}^{\oplus}$ which has its own known chemical reactivity.[62]

(x) In a recent study of Gif Chemistry,[63] we found that ascorbic acid is a good ligand for iron. It keeps the iron as Fe^{II} and reduces oxygen to superoxide. In the oxidation of adamantane, the normalized selectivity was 0.7, not 0.35 as is normally seen. This shows, as expected, that most of the tertiary radicals, formed by the iron-carbon bond fragmentation, had been reduced back to adamantane. In contrast in the presence of phenylselenol, produced by Fe^{0} reduction, the oxidation of adamantane with superoxide afforded only phenylselenation in 35% conversion and quantitative yield.[64] The normalized selectivity was 0.35. Thus, the phenylselenation reaction captured the tertiary iron-carbon bond *before* fragmentation to radicals took place. Had the fragmentation taken place, then the phenylselenol would have reduced the radicals back to the hydrocarbon. Then the selectivity would have been much higher as in the ascorbic acid experiments cited above. These results cannot be explained by radical chemistry at the secondary position.

References and Notes

1. Barton, D.H.R.; Gastiger, M.J. and Motherwell, W.B. *J. Chem. Soc. Chem. Commun.* **1983**, 41.
2. Tabushi, I. and Yazaki, A. *J. Am. Chem. Soc.* **1981**, *103*, 7371.
3. Barton, D.H.R.; Boivin, J.; Ozbalik, N. and Schwartzentruber, K.M. *Tetrahedron Lett.* **1985**, *25*, 4219. See also Powell, G.; Richens, D.T. and Khan, L. *J. Chem. Res.*

(S) **1994**, 506.

4. Barton, D.H.R.; Boivin, J.; Ozbalik, N. and Schwartzentruber, K.M. *Tetrahedron Lett.* **1985**, *26*, 447.
5. Barton, D.H.R.; Halley, F.; Ozbalik, N.; Schmitt, M.; Young, E. and Balavoine, G. *J.Am Chem. Soc.* **1989**, *111*, 7144.
6. Barton, D.H.R.; Beck, A.H. and Delanghe, N.C. *Tetrahedron Lett.* **1996**, *37*, 1555.
7. Barton, D.H.R. and Delanghe, N.C. **1996**, *37*, 8137.
8. Barton, D.H.R.; Boivin, J. and LeCoupanec, P. *J. Chem. Soc. Chem. Commun.* **1987**, 1379. Balavoine, G.; Barton, D.H.R.; Boivin, J.; LeCoupanec, P. and Lelandais, P. *New J. Chem.*, **1989**, *13*, 691. Barton, D.H.R. and Chabot, B. *Tetrahedron* **1996**, *52*, 10287.
9. Barton, D.H.R.; Costas Salgueiro, M. and MacKinnon, J. *Ibid.* **1997**, *53*, 7417. Barton, D.H.R.; Li, T. and Peralez, E. *J. Chem. Soc. Perkin 2* submitted for publication.
10. Barton, D.H.R. and Doller, D. *Acc. Chem. Res.* **1992**, *25*, 504. Dr. Doller has recently applied Gif Chemistry to a study of potential drug metabolites. The major product of Gif oxidation was indeed simply related to the main metabolite of the specific drug (Doller, D.; Chackalamannil, S.; Stamford, A.; McKittrick, B and Czarniecki, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1381). It is much easier to carry out Gif chemistry than to isolate metabolites from natural sources. Often only minute amounts are available. We think that a routine application of Gif Chemistry would take little time and might shorten considerably the studies of drug metabolism.
11. Balavoine, G.; Barton, D.H.R.; Boivin, J.; Gref, A.; Ozbalik, N. and Rivière, H. *Tetrahedron Lett.* **1986**, *27*, 2849. *Idem, J. Chem. Soc. Chem. Commun.* **1986,** 1727. Balavoine, G.; Barton, D.H.R., Boivin, J.; Gref, A.; LeCoupanec, P.; Ozbalik, N.; Pestana, J.A.X. and Rivière, H. *Tetrahedron* **1988**, *44*, 1091. Balavoine, G.; Barton, D.H.R.; Boivin, J.; Gref, A.; Halley, I.; Ozbalik, N.; Pestana, J.A.X. and Rivière, H. *New J. Chem.*, **1990**, *14*, 175. Barton, D.H.R. and Sobkowiak, A. *Ibid.* **1996**, *20*, 929.
12. Perkins, M.J. *Chem. Soc. Rev.* **1996**, *25*, 229.
13. Barton D.H.R. and Launay, F. *Tetrahedron* **1997**, *53*, 14565. (b) See, for example, Robinson, C.H.; Gnoj, O.; Mitchell, A.; Oliveto, E.P. and Barton, D.H.R. *Tetrahedron* **1965**, *21*, 743.
14. Barton, D.H.R.; Hay-Motherwell, R.S. and Motherwell, W.B. *Tetrahedron Lett.* **1983**, *24*, 1979.
15. Balavoine, G.; Barton, D.H.R.; Boivin, G. and Gref, A. *Ibid.* **1990**, *31*, 659.
16. About-Jaudet, E.; Barton, D.H.R.; Csuhai, E. and Ozbalik, N. *Ibid.* **1990**, *31*, 1657.
17. Barton, D.H.R. and Chavasiri, W. *Tetrahedron* **1997**, *53*, 2997.
18. We thank Prof. Ulf Schuchardt of the University of Campinas, Brazil, for recent results on the oxidation of *cis-* and *trans*-decalin using Fe^{III} and H_2O_2 with and without picolinic acid. For *cis*-decalin the normalised ratio of secondary to tertiary oxidation was 1.8 and 2.4. For *trans*-decalin the ratios were 2.3 and 3.5.
19. Gastiger, M. Ph.D. Thesis, Université de Paris-Sud, Orsay, France, **1984**.
20. Barton, D.H.R.; Hu, B; Taylor, D.K. and Rojas Wahl, R.V. *J. Chem. Soc. Perkin Trans. 2* **1996**, 1031.
21. Barton, D.H.R; Bévière, S.D.;Chavasiri, W.;Csuhai, E.; Doller, D. and Liu W.-G. *J. Am. Chem. Soc.* **1992**, *114*, 2147.
22. Barton, D.H.R., Bévière, S.D. and Doller, D. *Tetrahedron Lett.* **1991**, *32*, 4671.

23. Balavoine, G.; Barton, D.H.R.; Gref, A. and Lellouche, I. *Tetrahedron Lett.* **1991**, *32*, 2351.
24. Balavoine, G.; Barton, D.H.R.; Gref, A. and Lellouche, I. *Tetrahedron* **1992**, *48*, 1883.
25. Barton, D.H.R.; Lalic, G. and Smith, J.A. *Tetrahedron* **1998**, in press. For other applications of tributylphosphine in selenium chemistry see Grieco, P.A.; Jaw, J.Y.; Claremon, D.A. and Nicolaou, K.C. *J. Org. Chem.* **1981**, *46* 1215.
26. Barton, D.H.R. and Bévière, S.D. *Tetrahedron Lett.* **1993**, *34*, 5689.
27. Barton, D.H.R. and Wang, T.-L. *Tetrahedron* **1994**, *50*, 1011. Barton, D.H.R. and Chavasiri, W. *Tetrahedron* **1994**, *50*, 19. Barton, D.H.R. and Chavasiri, W. *Tetrahedron* **1994**, *50*, 47. Barton, D.H.R. and Wang, T.-L. *Tetrahedron Lett.* **1994**, *35*, 1519.
28. Minisci, F. and Fontana, F. *Tetrahedron Lett.* **1994**, *35*, 1427.
29. Kochi, J.K. in Free Radicals, Kochi, J.K Ed.; John Wiley and Sons Inc., New York, **1973**.
30. Clark, L.J. *Anal. Chim.* **1962**, *34*, 348.
31. Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F.; Zhao, L. *Synlett* **1996**, 119.
32. Snelgrove, D.W.; MacFaul, P.A.; Ingold, K.U.; Wayner, D.D.M. *Tetrahedron Lett.* **1996**, *37*, 823. MacFaul, P.A.; Ingold, K.U.; Wayner, D.D.M. and Que, L. *J. Am. Chem. Soc.* **1997**, *119*, 10594. The latter article deals with TBHP chemistry using sophisticated Que ligands as well as the elegant new reagent $PhCH_2CMe_2$-O-OH. The alkoxy radical derived from the latter fragments rapidly to give benzyl radicals. We agree that the chemistry studied is radical chemistry based on monosubstituted hydroperoxide fragmentation to alkoxy radicals. It is not part of Gif Chemistry at all.
33. Barton, D.H.R. *Synlett*, **1997**, 229. Barton, D.H.R.; LeGloahec, V.N.; Patin, H. and (in part) Launay, F. *New J. Chem.* in press. Barton, D.H.R.; LeGloahec, V.N. and Patin, H. *Ibid.* in press.
34. Barton D.H.R.; Launay, F.; LeGloahec, V.N.; Li, T. and Smith, F. *Tetrahedron Lett.* **1997**, *38*, 8491. Barton, D.H.R. and LeGloahec, V.N. *Tetrahedron Lett.* submitted for publication.
35. Hage, J.P.; Llobet, A. and Sawyer, D.T. *Bioorg. and Med. Chem.* **1995**, *3*, 1383. Kang, C.; Redman, C.; Cepak, V. and Sawyer, D.T. *Ibid.*, **1993**, *1*, 125.
36. Barton, D.H.R., Bévière, S.D.; Chavasiri, W.; Doller, D.; Liu, W.G. and Riebenspies, J.H. *New J. Chem.* **1992**, *16*, 1019.
37. Bardin, C.; Barton, D.H.R.; Hu, B.; Rojas Wahl, R.U. and Taylor, D.K. *Tetrahedron Lett.* **1994**, *35*, 5805. Barton, D.H.R.; Chabot, B.M.; Delanghe, N.C.; Hu, B.; LeGloahec, V.N. and Rojas Wahl, R.V. *Ibid.* **1995**, *36*, 7007.
38. Barton, D.H.R.; Hu, B.; Rojas Wahl, R. U. and Taylor, D.K. *New J. Chem.* **1996**, *20*, 121.
39. Barton, D.H.R.; Hu, B.; Li, T. and Mackinnon, J. *Tetrahedron Lett.* **1996**, *37*, 8329.
40. Barton, D.H.R. and Hu, B. *Tetrahedron* **1996**, *52*, 10313.
41. Rosenzweig, A.C.; Frederick, C.A.; Lippard, S.J. and Nordlund, P. *Nature* **1993**, *366*, 537. Rosenzweig, A.C.; Nordlund, P.; Takahara, P.M.; Frederick, C.A. and Lippard, S.J. *Chem. Biol.* **1995**, *2*, 409. Liu, K.E.; Valentine, A.M.; Wang, D.; Huynh, B.H.; Edmondson, D.E.; Salifoglou, A. and Lippard, S.J. *J. Am. Chem. Soc.* **1995**, *117*, 10174.
42. Barton, D.H.R. and Chavasiri, W. *Tetrahedron* **1997**, *53*, 2997.

43. Newcomb, M. and Marek, M.B. *J. Am. Chem. Soc.* **1990**, *112,* 9662. Newcomb, M. *Tetrahedron* **1993**, *49*, 7417.
44. Barton, D.H.R.; Li, T. and MacKinnon, J. *J. Chem. Soc. Chem. Commun.* **1997**, 557.
45. Ingold, K.U. *Aldrichchimica Acta* **1989**, *22*, 69.
46. Barton, D.H.R. and Li, T. *J. Chem. Soc. Chem. Commun.* in press.
47. Schuchardt, U.; Krähembül, C.E.Z. and Carvalho, W.A. *New J. Chem.* **1991**, *15*, 955. Schuchardt, U.; Carvalho, W.A. and Spinacé, E.V. *Synlett* **1993**, 713. The latter article makes reference to all prior work by Prof. Schuchardt.
48. Sugimoto, H. and Sawyer, D.T. *J. Am. Chem. Soc.* **1984,** *106*, 4283. *Idem, Ibid.* **1985**, *107*, 5712.
49. Sheu, C.; Sobkowiak, A.; Zhang, L.; Ozbalik, N.; Barton, D.H.R. and Sawyer, D.T. *Ibid.* **1989**, *111*, 8030.
50. Sheu, C., Robert, S.A.; Cofré, P.; Ross Jr., B.; Sobkowiak, A.; Sawyer, D.T. and Kanofsky, J.R. *Ibid.* **1990**, *112*, 1936. Sheu, C.; Sobkowiak, A.; Jeon, S. and Sawyer, D.T. *Ibid.* **1990,** *112,* 879. Sheu, C. and Sawyer, D.T. *Ibid.* **1990**, *112*, 8212. Tung, H.-C.; Kaug, C. and Sawyer, D.T. *Ibid.* **1992**, *114*, 3445.
51. Singh, B.; Long, J.R.; Fabrizi de Biani, F.; Gatteschi, D. and Stavropoulos, P. *J. Am. Chem. Soc.* **1997**, *119*, 7030. Singh, B.; Long, J.R.; Papaefthymiou, G.C. and Stavropoulos, P. *J. Am. Chem. Soc.* **1996**, *118*, 5824.
52. Kim, S.-B.; Lee, K.-W.; Kim, Y.-J. and Hong, S.I. *Bull. Korean Chem. Soc.* **1994**, *15* 424.
53. Kim, S.-B. and Lee, K.-W. *Korean J. Chem. Eng.* **1995**, *12*, 188.
54. Lee, K.-Y.; Kim, S.-B.; Jun, K.-W. and Shim, E.-K. *New J. Chem.* **1993**, *17*, 409.
55. Jun, K.-W.; Lee, K.-W.; Shim, E.-K. and Cho, N.-S. *Applied Catalysis A. Gen.* **1993**, *96*, 269. Jun, K.-W.; Shim, E.-K.; Park, S.-E. and Lee, K.-W. *Bull. Korean Chem. Soc,* **1995**, *16,* 398. Kim, S.-B.; Jun, K.-W.; Kin, S-Bo. and Lee, K.-W. *Chem. Lett.* **1995**, 535.
56. Barton, D.H.R. *Ibid.* **1996**, 237. See also *Synlett* **1997**, 229.
57. Knight, C. and Perkins, M.J. *J. Chem. Soc. Chem. Commun.* **1991**, 925.
58. Barton, D.H.R.; Csuhai, E.; Doller, D.; Ozbalik, N. and Senglet, N. *Tetrahedron Lett.* **1990**, *31*, 3097. Barton, D.H.R.; Csuhai, E. and Doller, D. *Tetrahedron Lett.* **1992**, *33*, 3413. Barton, D.H.R.; Csuhai, E. and Doller, D. *Tetrahedron* **1992**, *48*, 9195.
59. Barton, D.H.R. Csuhai, E. and Doller, D. *Tetrahedron Lett.* **1992**, *33*, 3413. *Idem, Tetrahedron* **1992**, *48*, 9195.
60. Barton, D.H.R.; Csuhai, E. and Ozbalik, N. *Tetrahedron* **1990**, *46*, 3743.
61. Barton, D.H.R.; Chabot, B.M. and Hu, B. *Tetrahedron Lett.* **1996**, *37*, 1755.
62. Barton, D.H.R.; Chabot, B.M. and Hu, B. *Tetrahedron* **1996**, *52*, 10301.
63. Barton, D.H.R. and Delanghe, N.C. *Tetrahedron* submitted for publication.
64. Barton, D.H.R.; Boivin, J. and LeCoupanec, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1379. Balavoine, G.; Barton, D.H.R.; Boivin, J.; LeCoupanec, P. and Lelandais, P. *New J. Chem.* **1989**, *13*, 691.

Biographical sketch

Derek H. R. Barton

Professor (Sir) Derek H.R. Barton was born on September 8, 1918 in Gravesend, Kent. His first academic appointments (1945-49) were as Lecturer in Inorganic and then Physical Chemistry at Imperial College. After a stint at Harvard (1949-50), 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 (1955-57) as Regius Professor in Glasgow, he returned to Imperial College (1957-1958) 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. In addition, Professor Barton has been Chairman of The Editorial Board of Tetrahedron Publications for the last 25 years. 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.