# Oxygen and I

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## Abstract

Oxygen is a remarkable element and without it in its triplet, more stable state, complex life on earth would not be possible. The singlet carbon–hydrogen bond does not react readily with oxygen because of the spin barrier. Nature has, however, solved this problem by using iron based enzymes either of the heme-type (porphyrin ligand) or of the non-heme type. The $P_{450}$ enzymes are illustrative of the first kind. Methane monooxygenase (MMO) is a good example of the second type. Recent work on the selective functionalization of saturated hydrocarbons has provided a system which, like MMO, has a $\mu$-oxo-di-iron center with obligatory carboxylate complexation. In this system, two manifolds, $Fe^{II}-Fe^{IV}$ and $Fe^{III}-Fe^{V}$ provide two different processes for the selective conversion of saturated hydrocarbons into ketones.

As World War II began in 1939, I started my graduate studies at Imperial College in London. My subject was the synthesis of vinyl chloride, intended to be a contribution to the War effort. During studies on the pyrolysis of ethylene dichloride, a marked variation in rate was seen. Eventually, I realized that the ethylene dichloride must be free of ethylene chlorohydrin (a radical inhibitor) and that the apparatus needed a controlled air leak. In fact, I had discovered my first oxygen based radical chain reaction. The decomposition of ethylene dichloride to vinyl chloride and HCl, when it is initiated by oxygen, is a long chain radical reaction [1,2]. I have already discussed how the reaction of oxygen with ketonic anions (another radical chain reaction) eventually became an important industrial process for the $17\alpha$-hydroxylation of $16\beta$-methylcorticosteroids [2]. This was another ac-

cidental discovery resulting from the degradation of limonin, the first limonoid to have its structure elucidated [2]. Also accidental was the amazing capacity of certain Lewis acids to catalyze the addition of triplet oxygen to 1,4-cyclohexadienes to furnish the corresponding endo-peroxides. This reaction, formally forbidden by the concept of spin correlation, nevertheless takes place rapidly at low temperatures [2].

Gif Chemistry [3] was not an accidental discovery. It was a planned reconstitution of the world as it was 3 billion years ago when the blue–green algae first began to make oxygen. The conception was that the arrival of oxygen would have permitted a bioorganic reaction in which the oxidation of metallic iron, eventually to rust, could be correlated with the oxidation of saturated hydrocarbons to oxygenated derivatives. We added also hydrogen sulfide, to repro-
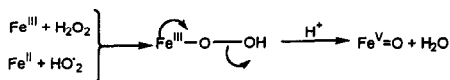
Scheme 1.

duce the 3 billion year atmosphere, and some acetic acid to react with the iron powder. The solvent was pyridine since water does not dissolve saturated hydrocarbons. Although the concept was naive, the selective oxidation of saturated hydrocarbons to ketones took place in a yield superior to other procedures.

After several years of diligent study, we concluded (Scheme 1) that an $Fe^{III}$–OOH could be formed in two different ways. Following $P_{450}$ convention, evolution to $Fe^V$=O can be postulated. The reactivity of the postulated oxenoid species is unusual as secondary positions are selectively substituted to afford, as isolated products, ketones. A careful study of intermediates showed that two (**A** and **B**) could be detected [4]. Intermediate **B** was firmly established in the Gif solvent pyridine–acetic acid to be a hydroperoxide which fragmented to ketone [5]. For several reasons, intermediate **A** has been formulated as an iron–carbon bonded species.

In principle, **A** could be a free carbon radical, but it does not respond to a number of tests for a free carbon radical. The formation of the oxygen derived ($^{18}O_2$ experiments) hydroperoxide is, at first sight, compatible with a carbon radical reaction. However, experiments with $PPh_3$ and with $P(OMe)_3$ are not in agreement with hydroperoxyl radicals as intermediates.

In fact, $Fe^{III}$ + $H_2O_2$ in pyridine is an inefficient source of hydroxyl radicals. Pyridine is, of course, a good trap for carbon and hydroxyl radicals and genuine hydroxyl radicals do indeed afford 2- and 4- hydroxypyridine. However, in Gif Chemistry, the major products from pyridine are 2- and 3-hydroxypyridine in minor amount [6].

From consideration of the formation of tertiary, but not secondary radicals, in the oxidation of adamantane, we concluded that it was reasonable to postulate an iron–carbon bond at both the secondary and tertiary positions. In the latter, the feeble carbon–iron bond by fission gave carbon radicals, whilst the secondary carbon–iron bond was relatively stable [7]. Since the chemistry takes place in the $Fe^{III}$ to $Fe^V$ valence states, it is convenient to refer to this as the $Fe^{III}$–$Fe^V$ manifold.

The reaction between $Fe^{III}$ and $H_2O_2$ to furnish $Fe^V$=O and then $Fe^V$–$CHR_2$ (from the hydrocarbon $H_2CR_2$) leads eventually to oxidation of ketone. In the presence of a large excess of chloride ion, there is no formation at all of the corresponding chloride $ClCHR_2$. However, if triphenylphosphine is added before the addition of $H_2O_2$, the formation of ketone is replaced completely by the production of chloride [8]. This reaction is due to the reduction of $Fe^{III}$ to $Fe^{II}$ by $PPh_3$ and $H_2O_2$. This reduction reaction deserves further study because the reduction of $Fe^{III}$ by $PPh_3$ alone is very slow. The ability to distinguish between $Fe^{II}$ and $Fe^{III}$ by titration played an important role in understanding the $Cl$–$CHR_2$ formation (titrated according to [9]). The alkyl chloride formation takes place in the $Fe^{II}$–$Fe^{IV}$ manifold.

The differentiation between the two manifolds is of fundamental importance. In the $Fe^{II}$–$Fe^{IV}$ manifold, an $Fe^{II}$ is oxidized by $H_2O_2$ to an $Fe^{IV}$ oxenoid which reacts with saturated hydrocarbons selectively at secondary positions to give an $Fe^{IV}$–$CHR_2$ bond. This is unstable and breaks down into a $CHR_2$ radical and $Fe^{III}$ (Scheme 2). In the presence of excess chloride ion, some $Cl$–$Fe^{III}$ species will be present. Carbon radicals react rapidly with chloride bonded to $Fe^{III}$ to furnish alkyl chloride and $Fe^{II}$ [10]. If this reaction is carried out in the absence of chloride ion and oxygen, then the same hydro-
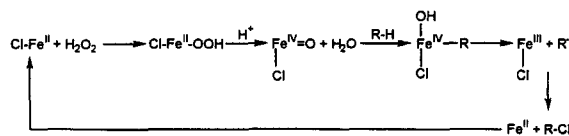


Scheme 2.

carbon species is formed from which the radicals generated can be recognized by capture by pyridine to give 2- and 4-substituted pyridines. Of course, the 2-substituted isomers are approximately two times their 4-substituted congeners.

When $Fe^{II}$ in pyridine–acetic acid solution containing chloride anion in excess in the presence of (say) cyclohexane is treated with $H_2O_2$ in portions, there is at first a fast formation of cyclohexyl chloride. After a short period of time, chloride formation stops and a slower ketonization of the hydrocarbon replaces it. At the time when chloride formation ceases, all the $Fe^{II}$ has been oxidized to $Fe^{III}$ and remains $Fe^{III}$ for the rest of the experiment. If a second portion of $Fe^{II}$ is added, rapid chloride formation recommences. The ketonization reaction is slow and there is accumulated $H_2O_2$ to permit this rapid reaction. Again, as soon as all the $Fe^{II}$ has been oxidized to $Fe^{III}$, the slow ketonization process replaces the chloride reaction. This is an experiment of fundamental importance because during the ketonization reaction, there is always an excess of $Cl–Fe^{III}$. So if no chloride is formed, no carbon radicals are present. Of course, the blank experiment to show that cyclohexyl chloride is perfectly stable under the experimental conditions was carried out.

In the $Fe^{II}$ oxidation to $Fe^{IV}$ by $H_2O_2$, there are two postulated oxidation states ($Fe^{II}$ and $Fe^{IV}$) which by a simple transfer of one electron could become $2Fe^{III}$. If this were true, then the reaction of $Fe^{II}$ with $H_2O_2$ would give the same chemistry as the reaction of $Fe^{III}$ with $H_2O_2$. Fortunately, this is not the case. The species from $Fe^{II} + H_2O_2$ leads us rapidly to $Fe^{III}$ and carbon radicals, whose reactivity is familiar from many earlier experiments outside of Gif Chemistry. The reaction of $Fe^{III}$ with $H_2O_2$ in pyridine–acetic acid affords a species which reacts selectively with saturated hydrocarbons at secondary positions to give eventually ketones without carbon radical formation. It is remarkable that the two reagents that we postulate, $Fe^{IV}=O$ and $Fe^{V}=O$, have the same selectivity for adamantane ($C^2/C^3$ = about 1.0) and the

same K.I.E. (perdeuterocyclohexane versus protiocyclohexane) of 2.0. However, the reactivity after the initial hydrocarbon substitution remains completely different both in rate and in product. The above discussion on chloride formation also pertains to a number of other anions in the $Fe^{II}–Fe^{IV}$ $H_2O_2$ manifold [11].

It has already been emphasized that in the $Fe^{III}–H_2O_2$ reactions in pyridine–acetic acid in the presence of chloride anion alkyl chlorides are never formed. However, when the $Fe^{III}–Fe^{V}$ manifold is attained by the reaction of $Fe^{II}$ with superoxide, the chemistry that follows in the $Fe^{III}–Fe^{V}$ manifold clearly does *not* involve any hydrogen peroxide. If hydrogen peroxide were present, it would react at once with the $Fe^{II}$, which is the state of most of the iron in the presence of $Zn^0$ or a cathode. In the presence of chloride anion, the $Fe^{II} + H_2O_2$ in the $Fe^{II}–Fe^{IV}$ manifold should produce chloride. In fact, we have never seen alkyl chloride formed in the reactions which depend on $Fe^{II}$ + superoxide.

It was gratifying that addition of $H_2O_2$ to a $Zn^0–Fe^{II}$-superoxide reaction immediately produced copious amounts of alkyl chloride to replace the slower ketonization process normally observed. We have again studied the electrochemical oxidation system and have confirmed that $Fe^{II}$ is kept as $Fe^{II}$, that $O_2$ is reduced to superoxide and that addition of $H_2O_2$ diverts the reaction to the formation of alkyl chloride instead of ketone [12].

Since the début of Gif Chemistry, pyridine–acetic acid has been used as a solvent. Early experiments [13] showed that a tri-iron acetate complex of mixed valency could be isolated and shown to have good catalytic acid. However, the reported structure of MMO showed that the $Fe_2$ active site had one or two carboxylate bridges just as in the complex we had studied [13]. We decided, therefore, to examine the exact status of carboxylate bridging in Gif Chemistry.

When an $Fe^{III}$ species such as $Fe^{III}Cl_3$ is dissolved in pyridine and hydrogen peroxide is added, there is a rapid and quantitative forma-

tion of oxygen (catalase reaction) both in the absence and in the presence of an excess of saturated hydrocarbon. However, if picolinic acid is added, the formation of oxygen diminishes and production of ketone (Gif Chemistry) becomes paramount. After 2 equivs. of picolinic acid are added, there is little formation of oxygen and ketone is the sole product.

Acetic acid, as two equivalents, gives little ketone, but 1 picolinic acid + 1 acetic acid per iron gives significant ketone formation. Of many other carboxylic acids studied, isoquinoline-1-carboxylic acid is even better than picolinic acid. Isomers of picolinic acid such as nicotinic acid do not make ketone. We conclude that a pyridine ring (or like congener) with a carboxylic acid in the 2-position and no substituent (except, perhaps, a carboxylic acid) in the 6-position provides maximum ketone formation. The efficiency of the reactions with respect to hydrogen peroxide can be as high as 80% depending on the hydrocarbon–pyridine ratio. Clearly then, carboxylate bridging is of major importance to Gif Chemistry.

The addition of picolinic acid to $FeCl_3$ in pyridine produces the active species for the ketonization reaction. It does not, however, define the number of picolinic acids complexed to the $Fe^{III}$. We have developed a quantitative $^{13}C$-NMR spectroscopy for the precise analysis of the picolinic acid complexes in pyridine solution. The principle of the method is that picolinic acid residues bonded to $Fe^{III}$ will have their carbon nuclei so relaxed that no signal will be seen. However, those picolinic acids which are free in solution will have their signals relaxed enough by the $Fe^{III}$ present that they can then be quantitated using an internal standard ($CCl_3$–$CCl_3$).

Using this technique, we were able to show that exactly two picolinic acids were bonded to $Fe^{III}$ and that the two extra that had been added were free in solution. The addition of oxalic acid displaced the two picolinic acids from the $Fe^{III}$. We had previously shown that oxalic acid bonds very strongly to $Fe^{III}$ and displaces all

other carboxylic ligands. Thus, we could now see all four of the picolinic acids free in solution [14].

Similar experiments were carried out with isoquinoline-1-carboxylic acid with the same results. The isomeric quinoline-2-carboxylic acid had no capacity to make ketone with $Fe^{III}$, but did make oxygen quantitatively. We examined the complexation of the quinoline-2-carboxylic acid (2 equiv.) with $Fe^{III}$ and it did, indeed, bind (2 equiv. per $Fe^{III}$). However, the binding was not strong and it was displaced from the $Fe^{III}$ by 2 equiv. of isoquinoline-1-carboxylic acid. This work clarifies with precision the nature of $Fe^{III}$ complexes in solution.

For the $Fe^{III}$–$Fe^V$ manifold, no change in product distribution was detected whether an experiment was run under argon or oxygen. Ketone was always found to be the only product in similar amounts. In contrast, the $Fe^{II}$–$Fe^{IV}$ manifold showed more sensitivity towards the reaction conditions. Under an $O_2$ stream, the ferrous iron was rapidly oxidized to ferric iron, which thereafter entered the $Fe^{III}$–$Fe^V$ manifold and produced ketone. Under an argon stream however in the absence of chloride anion, the carbon radical once formed reacts with the solvent, pyridine, yielding the 2- and 4-pyridine coupled products, as is characteristic for a free carbon centered radical.

In contrast, as already mentioned above, in the presence of chloride anion and a carboxylate ligand $Fe^{II}$ + $H_2O_2$ in pyridine yields alkyl chlorides exclusively and no ketone at all. Except in the presence of $PPh_3$ (see discussion above), the $Fe^{III}$ + $H_2O_2$ system and acetic acid never produce alkyl chlorides, but ketone (major) and alcohol (minor). Even more of a surprise was when we treated the $Fe^{III}$ + $H_2O_2$ system with an argon stream.

Thus, using 4 equiv. of picolinic acid per $Fe^{III}$ in pyridine (33 ml), a stream of argon was passed whilst 4 mmol of $H_2O_2$ was added at 0°C. Cyclooctane (20 mmol) was present from the beginning. This produced ketone (0.88 mmol) and cyclo-octyl chloride (1.0 mmol). The

formation of chloride was completely unexpected. The result was readily reproduced and shown to correlate with the reduction of $Fe^{III}$ to $Fe^{II}$. Hence the formation of a major amount of chloride. A simple $Fe^{III}$ salt, without any carboxylate grouping, such as $Fe^{III}Cl_3$ is not reduced by passage of any amount of argon and does not produce any alkyl chloride (and only traces of ketone) in the presence of saturated hydrocarbon and $H_2O_2$. We propose a simple equilibrium as follows:

$$2Fe^{III} + H_2O_2 \rightarrow Fe^{III}-O-O-Fe^{III} \rightleftharpoons 2Fe^{II} + O_2$$
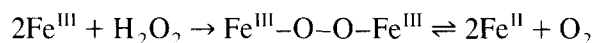
Normally, the postulated equilibrium is far to the left. However, the passage of argon sweeps out the oxygen and drives the equilibrium to the right. The amount of oxygen produced has been determined [15] by a manganese based analytical procedure. We consider this to be evidence in favor of a $\mu$-oxo-dimer species, as in MMO [13] with one or more peroxyl bridges attached as well as carboxylate bridging from one picolinic acid per $Fe^{III}$. A second molecule of picolinic acid per iron with normal complexing is also postulated [16].

Two important publications on the MMO mechanism have recently been published. The work of Lippard, Newcomb and their colleagues [17] has shown that free carbon radicals are not involved in the mechanism. The elegant experiments of Floss and his colleagues [18] have shown that a particulate form of MMO hydroxylates with perfect retention of configuration. Although indirect, these two sets of experiments are in agreement with our hypothesis of an iron–carbon bonded intermediate.

## Acknowledgements

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