Mechanism of the selective functionalization of saturated hydrocarbons by Gif systems: Relationship with methane monooxygenase

(adamantane/selectivity)

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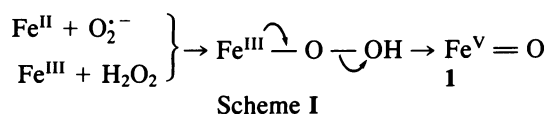Contributed by Derek H. R. Barton, February 6, 1990

ABSTRACT Two intermediates, A and B, have been identified in the selective oxidation of saturated hydrocarbons to ketones by Gif-type systems. Intermediate A has been characterized as an Fe^V species with a secondary iron σ-bond to carbon; it is captured by four different reagents or transformed into the second intermediate, B, which hydrolyzes to form a secondary alcohol. A μ-oxo Fe_2^{III} dimer is proposed as a basis for Gif-type reactivity. If the first iron is involved in the synthesis of intermediate A, the second is used to oxidize intermediate B intramolecularly to a ketal, which on hydrolysis yields a ketone. The enzyme methane monooxygenase shows a remarkable similarity to Gif-type systems in its selective hydrocarbon oxidation, particularly in the case of adamantane.

There are two well-known mechanisms for the selective oxidation of saturated hydrocarbons. The first is the Fenton reaction of H_2O_2 with Fe^{II}, which leads to the production of hydroxyl radicals (1). The second mechanism is the iron-based porphyrin system of the P450 enzymes. In porphyrin models, based on this system, alkoxy radical-like chemistry is clearly seen (2). Thus, saturated hydrocarbons are attacked with a selectivity normal to radical reactions (tertiary>secondary>primary), sulfides are oxidized to sulfoxides, and olefins are epoxidized (3, 4).

The family of Gif systems for the selective substitution of saturated hydrocarbons has very different reactivity from any prior process (5, 6). We first define (7) the systems: GifIII consists of iron powder suspended in pyridine-acetic acid with oxygen as oxidant. GifIV is similar but has an Fe^{II} catalyst with suspended zinc dust as a source of electrons and again oxygen is the oxidant. The Gif-Orsay (Go) electrochemical system replaces the zinc dust in GifIV by the cathode of an electrochemical cell. This system has a good coulombic yield (up to 50%). More recently, three new systems have been added: GoAggI, GoAggII, and GoAggIII. The GoAggI system consists of pyridine-acetic acid with stoichiometric Fe^{II} and KO_2 under argon. The GoAggII system is the same except that the oxidant is hydrogen peroxide and the catalyst is $FeCl_3$ or other Fe^{III} salt.

As will be described in more detail later, the addition of picolinic acid and its congeners has a major effect on the rate of oxidation of saturated hydrocarbons while preserving the characteristic Gif selectivity. The system using Fe^{III} plus H_2O_2 in the presence of picolinic acid or other special ligand is now referred to as GoAggIII. The names are geographical: G is for Gif-sur-Yvette, O is for Orsay, and Agg is for "Aggieland," where the last three systems were developed.

In brief, all six of these systems show the same behavior toward saturated hydrocarbons, oxidizing them selectively to ketones. The selectivity order, secondary>tertiary≥primary, differs greatly from that for radical reactions (tertiary>secondary>primary). Also, saturated cyclic hydrocarbons are oxidized in preference to secondary alcohols and to easily autoxidized ethers. To explain these and other unusual observations, we propose that $Fe^{II} + O_2^{\cdot-}$ is generated in GifIII, GifIV, and Go. In GoAggI these two reagents are naturally present. In GoAggII and GoAggIII, Fe^{III} plus H_2O_2 gives the same iron species. This formalism (Scheme I) is the same as that used in arguments about the mechanism of P450 oxidation (2, 8).
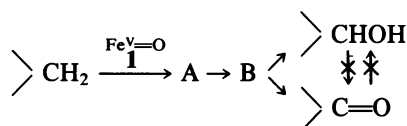
$$\left.\begin{array}{l} Fe^{II} + O_2^{\cdot-} \\ Fe^{III} + H_2O_2 \end{array}\right\} \rightarrow Fe^{III}\!\!-\!O\!-\!OH \rightarrow Fe^V = O$$
$$\text{1}$$

Scheme I

There the porphyrin ring redistributes the electrons and most experts write $Fe^{IV} = O(\cdot)$, but the equivalent $Fe^{III} — O\cdot(\cdot)$ might be more in keeping with the radical nature of the oxidizing species.

In the Go, GoAggI, GoAggII, and GoAggIII systems it is clear that pyridine is not being reduced to dipyridyls or other pyridine-derived species. The role of the pyridine is to act as a ligand and to prevent hydroxyl radical-induced autooxidation chains.

With certain hydrocarbons (adamantane, cis- and trans-decalins, and the steroid side chain) radicals have been detected but only at tertiary positions, not at secondary positions. In adamantane, tertiary radicals can be detected by competitive attack on oxygen and on pyridine. The reduction of oxygen pressure increases the amount of attack of the tertiary radicals on the pyridine. However, the selectivity (C^2/C^3, where C^2 = total of secondary oxidation products and C^3 = total oxidation and pyridine-coupled products) is always constant. Coupling at the secondary position is not seen. When the secondary coupled product is prepared by a rational synthesis, it is completely stable under the reaction conditions. Indeed, secondary radicals, when generated by photolysis of the acyl derivatives of N-hydroxy-2-thiopyridone, show competitive partitioning between oxygen and pyridine as would be expected (7).

From the abnormal selectivity it is clear that the $Fe^V = O$ reagent does not behave like a radical. We have detected two intermediates between the saturated hydrocarbon and the derived ketone. Scheme II summarizes the relationship be-

Abbreviation: MMO, methane monooxygenase.
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tween the starting material, the products, and the intermediates A and B.

Scheme II

Intermediate A can be transformed to ketone (with some alcohol) or can be captured by various reagents [(PhSe)$_2$, (PhS)$_2$, CHBr$_3$, CCl$_4$] to furnish $>$CHSePh, $>$CHSPh, $>$CHBr, and $>$CHCl, respectively. These reagents would normally be considered characteristic of capture of carbon radicals. However, the systems do not respond to another test, for radicals capture by the solvent pyridine. When carbon radicals are generated under Gif-type conditions, they are, indeed, captured by pyridine (7). Also, if Fenton-type chemistry (Fe^{II} + H$_2$O$_2$ + H$^+$ → Fe^{III} + H$_2$O + OH$^·$) is deliberately produced in the presence of cyclohexane, cyclohexyl radicals are generated and readily captured to give 2- and 4-cyclohexylpyridines (9). Carbon radicals are readily quenched by the —SH bond. However, relatively large amounts of H$_2$S can be added without affecting the oxidation, so carbon radicals cannot be present (10, 11).

We have always considered (12) that intermediate A contains an Fe—C bond, now viewed as an Fe^V$<$$^{OH}_{CH<}$ species (6). The four reagents (13) that captured intermediate A (see above) all have weak bonds, which, we consider, permit insertion into the Fe—C bond. The role of an Fe—C bond in the biosynthesis of β-lactam antibiotics was proposed independently by J. E. Baldwin (14). E. J. Corey (15) also suggested that soybean oxygenase oxidation involves an Fe—C bond in the enzymatic mechanism.

Evidence for the second intermediate comes from the discovery of conditions that divert GifIV from producing ketone to producing secondary alcohol. In early studies it was shown that ketone and alcohol were not interconverted under Gif conditions (Scheme II). Now dianisyl telluride (An$_2$Te) is a very efficient reagent for transforming hydroperoxides to the corresponding alcohols by an ionic reduction mechanism not involving oxygen radicals (16). Addition of An$_2$Te to a GifIV oxidation of adamantane 2 reduces the formation of ketone 3 and increases the amount of alcohol 4 (Table 1, Formulae 1).
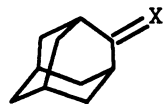

2   X - H, H

3   X - O

4   X - H, OH

Formulae 1

Because 1.0 mmol of An$_2$Te is already a 2-fold excess over the oxidation products, it is clear that ketone is formed in two steps. The first step is diminished by a large excess of reductant, but the second step is much more sensitive to An$_2$Te. The alcohol, therefore, arises from the hydrolysis of an intermediate B, which is normally largely transformed into ketone.

There has been intense activity recently in the study of nonporphyrinic iron-containing enzymes (17). The fascinating enzyme (18–20) methane monooxygenase (MMO) has in the resting state at the hydroxylation site a μ-oxo Fe$_2^{III}$ group, which has been thoroughly characterized (21–23). The active site of this enzyme and of a number of congeners of different enzymatic function have been modeled recently by μ-oxo iron dimer structures (24–28).

This, and other prior considerations (29), led us to a revised working hypothesis to explain the unusual chemistry of Gif-type systems. Our hypothesis is summarized in Scheme III.
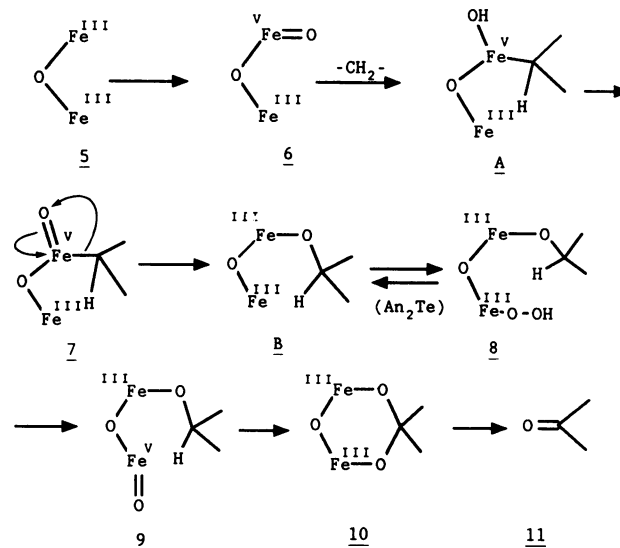
Scheme III

For clarity of exposition, we have omitted all the ligands. The ligands are important because the addition of picolinic acid changes a GoAggII system to GoAggIII and, depending on the quantity of ligand added, can increase the oxidation rate 50-fold (30). Other analogues of picolinic acid, like pyridine-2,4-dicarboxylic acid and pyrazine-2-carboxylic acid, are as effective in speeding up the reaction.

Thus, the Fe^{III} μ-oxo dimer 5 is oxidized to the Fe^V oxo species 6; this inserts into the C—H bond to give intermediate A. By elimination of a ligand from intermediate A, another Fe^V species 7 can be formed. We then postulate an unusual rearrangement (see species 7), which is surely thermodynamically sound because it changes Fe^V to Fe^{III} and transforms a weak Fe–C bond into a strong Fe—O bond. This change gives intermediate B. If intermediate B is further oxidized by hydrogen peroxide, it will yield species 8. Interception of species 8 by An$_2$Te would give back intermediate B. On the other hand, evolution to species 9, Fe—C bond formation as in intermediate A, and rearrangement as in species 7 would afford species 10. This is a ketal and on hydrolysis it would give the ketone 11 and the resting Fe^{III} species 5.

Critics object to the change from species 6 to intermediate A as being an unprecedented insertion process. However, the Gif oxidation systems are unprecedented in any case.

Fe^V=O species could be written as Fe^{IV}—O$^·$, which might permit O—H bond formation slightly in advance of Fe—C bond formation. However, the very unusual Gif selectivity is better explained by insertion.

This hypothesis explains all the facts that have been accumulated about Gif chemistry. A recent publication by Green and Dalton (31) raises the discussion to a higher plane. These authors have shown that, with certain discrepancies, the major product of MMO oxidation of several saturated

Table 1. Effect of dianisyl telluride on the ketone/alcohol ratio

An$_2$Te, mM	Ketone 3*, %	Alcohol 4*, %	Total, %	Ketone 3/ alcohol 4	Ketone 3 + alcohol 4/An$_2$Te
0	16.5	2.9	19.4	5.70	
0.5	7.7	9.7	17.4	0.79	0.70
1.0	4.7	9.1	13.8	0.51	0.28
2.0	3.6	6.6	10.2	0.54	0.10

GifIV conditions with 2 mmol of adamantane 2 were used.
*Ketone 3 is adamantan-2-one 3; alcohol 4 is adamantan-2-ol.

hydrocarbons is the secondary alcohol—that is to say, Gif selectivity with hydrolysis at the intermediate B stage.

When an enzyme has a specific substrate that reacts in a chemoselective manner, the products are determined by the protein conformation and not by any intermolecular chemo-selectivity, so little can be deduced about mechanism based on the products. MMO is an unusual enzyme because it oxidizes a range of substrates from methane to adamantane. It is, therefore, more likely to have a large cavity in which normal intermolecular selectivity might be seen. In this case, products would give information about mechanism.

We have frequently used adamantane 2 functionalization as an indication of mechanism. Alkoxy radical attack gives a selectivity (C^2/C^3 where C^2 equals total of secondary products and C^3 equals total of tertiary products) of 0.15 (32). P450 models, which also have alkoxy radical-like behavior, give an even smaller number (33).

The GifIV selectivity for oxidation of adamantane, taking into account tertiary-radical coupling to pyridine, is 1.15. The other reagents that capture the Fe—C bond have a similar selectivity as do GoAggI and GoAggII for overall oxidation (Table 2). Green and Dalton (31) significantly observed that MMO oxidizes adamantane to the secondary and tertiary alcohols with a C^2/C^3 selectivity of 1.0, exactly the Gif-type selectivity. Such a coincidence can hardly be chance. There is a large published literature on adamantane chemistry and the only prior selectivity for secondary positions is the Gif phenomenon.

Why does MMO stop at intermediate B in Scheme III? This may be a question of differential liganding of the two iron centers such that the conversion of intermediate B to species 8 and 9 is slow or a reductant may reduce species 8 back to intermediate B, as in our Gif-type experiments. This question will be clarified when the MMO enzyme has been completely characterized.

We have also addressed the question of the capacity of Gif-type systems to oxidize low molecular weight hydrocarbons (methane to *n*-butane). Oxidation of *n*-butane under GoAggIII conditions at 2 atm (1 atm = 101.3 kPa) pressure gave methylethyl ketone as the only product in 17% yield with respect to H$_2$O$_2$. Similarly, propane at 7 atm pressure gave only acetone in 13% yield (relative to H$_2$O$_2$).

Table 2. Selectivity in adamantane functionalization

System	Adamantane selectivity, C^2/C^3	Ref.
GifIV oxidation (overall)	1.15	5
GoAggI oxidation (overall)	1.0	7
GoAggII oxidation (overall)	0.8	7
GifIII phenylselenation (PhSe)$_2$	1.1	13
GifIII phenylsulfuration (PhS)$_2$	1.2	13
GifIII bromination (CHBr$_3$)	1.15	13
GifIII chlorination (CCL$_4$)	1.05	13
MMO	1.0	31

C^2, total of secondary oxidation products; C^3, total oxidation and pyridine-coupled products. Ref., reference.

Under GoAggIII oxidation conditions with a pressure of 48 atm of carbon monoxide, cyclohexane gave a small but significant amount of cyclohexanecarboxylic acid as well as cyclohexanone and some cyclohexanol. A GifIV experiment on cyclohexane at 58 atm of a 1:1 mixture of oxygen and carbon monoxide also afforded a significant amount of cyclohexanecarboxylic acid. This is further evidence for the postulated Fe—C bond.

Our colleague, D. T. Sawyer (of this Department), was provided with a copy of our article (6) on the GoAggI and GoAggII systems in October 1988. Using ferrous picolinate, oxidized *in situ* by hydrogen peroxide to the ferric state, he confirmed the peculiar Gif selectivity for a number of hydrocarbons (34); his enthusiasm (35) for Gif-type chemistry is welcome.

Although priority is an important question in scientific work, it is a sobering thought that, in fact, God has a priority of ≈2.5 billion years in inventing the fascinating MMO mechanism.

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