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The Functionalization of Saturated Hydrocarbons. Part 20.[+] Alkyl Hydroperoxides: Reaction Intermediates in the Oxidation of Saturated Hydrocarbons by Gif-Type Reactions and Mechanistic Studies on Their Formation

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Abstract: Chemical and ^{13}C and ^{2}H NMR spectroscopic evidence is presented, proving that secondary alkyl hydroperoxides are reaction intermediates in the oxidation of saturated hydrocarbons under GoAgg^{II} conditions (ferric chloride, hydrogen peroxide in pyridine–acetic acid solution). Isolation of cyclohexyl hydroperoxide from a GoAgg^{III} oxidation of cyclohexane (GoAgg^{II} + picolinic acid as catalyst) and the effect of reducing agents (such as thiophenol, benzeneselenol, diphenyl disulfide, and diphenyl diselenide) on the Gif^{IV} oxidation of cyclohexane (ferrous chloride, zinc powder, oxygen gas, in pyridine–acetic acid solution) permit a generalization of the alkyl hydroperoxide intermediacy to the whole family of Gif systems. All those reducing agents lower the ketone/alcohol ratio, with either a decrease in the total amount of hydrocarbon activation or formation of phenylseleno derivatives. Triphenylphosphine (up to 3.5 mmol) shows the same effect on the ketone/alcohol ratio, but the total amount of activation remains approximately constant and no byproduct is formed. The mechanism of formation of the alkyl hydroperoxide intermediate has been studied using $^{18}O_2$. The results indicate that the oxygen atoms in the alkyl hydroperoxide do not arise *directly* from hydrogen peroxide but from O_2, formed in situ by the well-known iron(III)-catalyzed decomposition of hydrogen peroxide. The mechanism of formation of alcohols under these conditions has been addressed as well. The results from experiments in the presence of $H_2{}^{18}O$, combined with those from the above-mentioned experiments under an $^{18}O_2$ atmosphere, proved that the oxygen atom in the alcohol does not arise from a hydroxy species but from reduction of the intermediate alkyl hydroperoxide. The participation of another reaction intermediate (prior to the alkyl hydroperoxide) has been secured. If O_2 is eliminated from the reaction mixture (running the reaction at reduced pressure) this first intermediate **A** can be trapped with Tempo. However, when the reaction was carried out at reduced pressure and in the absence of Tempo, no traces of alkylpyridine coupled products were detected. These alkylpyridines have been demonstrated to be formed when carbon radicals are generated under the same reaction conditions by photolysis of the corresponding *N*-hydroxypyridine-2-thione derivative of an alkyl carboxylic acid. This paradox can only be explained if intermediate **A** is *not* a carbon-centered radical. In a competitive experiment a ratio cyclopentyl-Tempo adduct/cyclohexyl-Tempo adduct of 0.66 was obtained. This figure differs from the values reported for typical carbon-radical competitive experiments, where cyclopentane is more reactive than cyclohexane. This further supports the nonradical nature of reaction intermediate **A**. Finally, studies with trimethyl phosphite, which affords with cyclohexane cyclohexyl dimethyl phosphate, show that cyclohexyl peroxyl radical is *not* an intermediate in the formation of the hydroperoxide as it would be if the cyclohexyl radical was reacting with oxygen.

Introduction

Despite the fact that enzymes that catalyze reactions involving dioxygen are so largely distributed in nature, the molecular mechanisms of their reactions are known in considerably less detail than those for most other biological reactions.[1] One very important approach to gaining a deeper understanding of these biological processes consists of using model compounds to emulate the enzymatic activity.[2] We have developed a family of chemical systems which allows the oxidation and functionalization of saturated hydrocarbons under mild conditions. We group them under the name Gif systems.[3] All of them involve a pyridine–acetic acid (or other carboxylic acid) solution of the hydrocarbon being oxidized, an Fe-based catalyst, an oxidant, and an electron source. The two most practical members of the Gif family are Gif^{IV} [using iron(II), oxygen (from air), and zinc dust] and GoAgg^{II} [using iron (III) and hydrogen peroxide]. This group of chemical systems is able to convert[4] saturated hydrocarbons quantitatively to ketones (and a small amount of alcohol) in conversions ranging between 20 and 30%. More surprisingly, the oxidation of the hydrocarbon takes place even in the presence of different, more easily oxidizable compounds.[5]

Gif systems were originally designed to mimic non-heme enzymatic oxidation of alkanes.[6] This group of enzymes includes methane monooxygenase,[7] prolyl 4-hydroxylase,[8] isopenicillin *N*-synthase,[9] γ-butyrobetaine hydroxylase,[10] and biologically active systems like bleomycin.[11]

As a result of our studies on the mechanism of Gif-type reactions, the process of ketonization of saturated hydrocarbons was

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[+] Part 19: Barton, D. H. R.; Csuhai, E.; Doller, D.; Geletii, Yu. V. *Tetrahedron* **1991,** *47,* 6561–6570. For a preliminary communication of this work, see: Barton, D. H. R.; Csuhai, E.; Doller, D.; Balavoine, G. *J. Chem. Soc., Chem. Commun.* **1990,** 1787–1789.

(1) Channa Reddy, C.; Hamilton, G. A.; Madyastha, K. M. In *Biological Oxidation Systems*; Academic Press: 1990; San Diego, California, Vol. I, pp xix–xx.

(2) For examples of model systems that mimic enzymatic activity, see: (a) Kurusu, Y.; Neckers, D. C. *J. Org. Chem.* **1991,** *56,* 1981–1983. (b) Kitajima, N.; Ito, M.; Fukui, H.; Moro-oka, Y. *J. Chem. Soc., Chem. Commun.* **1991,** 102–104. (c) Briffaud, T.; Larpent, C.; Patin, H. *J. Chem. Soc., Chem. Commun.* **1990,** 1193–1194. (d) Norman, R. E.; Yan, S.; Que, Jr., L.; Backes, G.; Ling, J.; Sanders-Loehr, J.; Zhang, J. H.; O'Connor, Ch. J. *J. Am. Chem. Soc.* **1990,** *112,* 1554–1562. (e) Traylor, T. G.; Xu, F. *J. Am. Chem. Soc.* **1990,** *112,* 178–186. (f) Sheu, C.; Sawyer, D. T. *J. Am. Chem. Soc.* **1990,** *112,* 8212–8213. (g) Borovik, A. S.; Hemdrich, M. P.; Holman, T. R.; Münck, E.; Papaefthymiou, V.; Que, Jr., L. *J. Am. Chem. Soc.* **1990,** *112,* 6031–6038. (h) Kitajima, N.; Fukui, H.; Moro-oka, Y. *J. Chem. Soc., Chem. Commun.* **1988,** 485–486. (i) Gorum, S. M.; Papaefthymiou, G. C.; Frankel, R. B.; Lippard, S. J. *J. Am. Chem. Soc.* **1987,** *109,* 3337–3348. (j) Murch, B. P.; Bradley, F. C.; Que, Jr., L. *J. Am. Chem. Soc.* **1986,** *108,* 5027–5028. (k) Traylor, T. G.; Lee, W. A.; Stynes, D. V. *J. Am. Chem. Soc.* **1984,** *106,* 755–764. (l) Armstrong, W. H.; Lippard, S. J. *J. Am. Chem. Soc.* **1983,** *105,* 4837–4838.

(3) For a definition of the Gif system nomenclature, see: Barton, D. H. R.; Halley, F.; Ozbalik, N.; Schmitt, M.; Young, E.; Balavoine, G. *J. Am. Chem. Soc.* **1989,** *111,* 7144–7149.

(4) Barton, D. H. R.; Ozbalik, N. Selective Functionalization of Saturated Hydrocarbons by the "Gif" and "Gif-Orsay" Systems. In *Activation and Functionalization of Alkanes*; Hill, C. L., Ed.; J. Wiley & Sons, Inc.: New York, 1989; Chapter IX, pp 281–301.

(5) Barton, D. H. R.; Csuhai, E.; Ozbalik, N. *Tetrahedron* **1990,** *46,* 3743–3752.

(6) Barton, D. H. R.; Doller, D. The Selective Functionalization of Saturated Hydrocarbons. Gif and All That. In *Dioxygen Activation and Homogeneous Catalytic Oxidation*; Simándi, L. I., Ed.; Elsevier: Amsterdam, 1991; pp 1–10.

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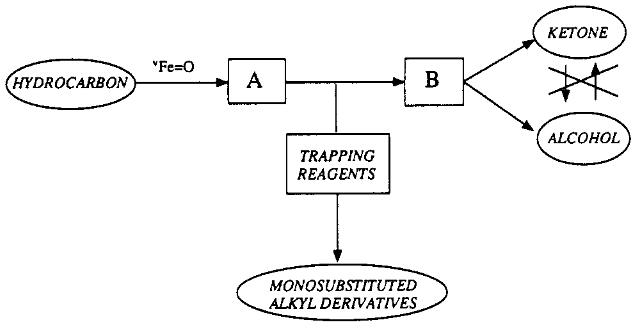
Scheme I



tentatively divided in the following steps (Scheme I): 1. Activation of the dioxygen molecule, formally as an $Fe^V{=}O$ species;[12] 2. Activation of the hydrocarbon at the monosubstituted level (intermediate **A**). In the presence of suitable reagents such as diphenyl diselenide, diphenyl disulfide, bromotrichloromethane, or sodium sulfide, **A** is trapped affording the corresponding alkyl phenyl selenide, alkyl phenyl sulfide, alkyl bromide, and dialkyl disulfide, respectively.[13-15] 3. In the absence of any trapping reagent, **A** is converted into **B**, a second reaction intermediate. **B** is subsequently transformed into either ketone or alcohol, whose ratio depends on the presence of reducing agents.

In this article we present chemical and ^{13}C and ^{2}H NMR spectroscopic evidence fully characterizing intermediate **B** as an alkyl hydroperoxide. A GoAgg^{II} reaction on [1-^{13}C]cyclohexane was followed by ^{13}C NMR. The formation of labeled cyclohexyl hydroperoxide and its transformation into labeled cyclohexanone were observed. In the case of the GoAgg^{III} reaction, the cyclohexyl hydroperoxide was isolated from the reaction mixture and identified by comparison of spectroscopic properties (^{1}H and ^{13}C NMR data) with an authentic sample. The half-life of cyclohexyl hydroperoxide in Gif^{IV} reactions is too short to allow its direct determination. However, indirect evidence was obtained by adding different reducing reagents to the reaction mixture, that transform the alkyl hydroperoxide in situ to the alcohol. Thus, we report the results from our studies on the effect of reductants on the ketone/alcohol ratio and the total hydrocarbon activation in Gif-type processes, in agreement with the intermediacy of the alkyl hydroperoxide. Triphenylphosphine has the peculiarity of changing the ketone/alcohol ratio without significantly decreasing the total amount of hydrocarbon activation. These results show that secondary alkyl hydroperoxides are common reaction intermediates for every member of the Gif family of systems for the activation of saturated hydrocarbons.

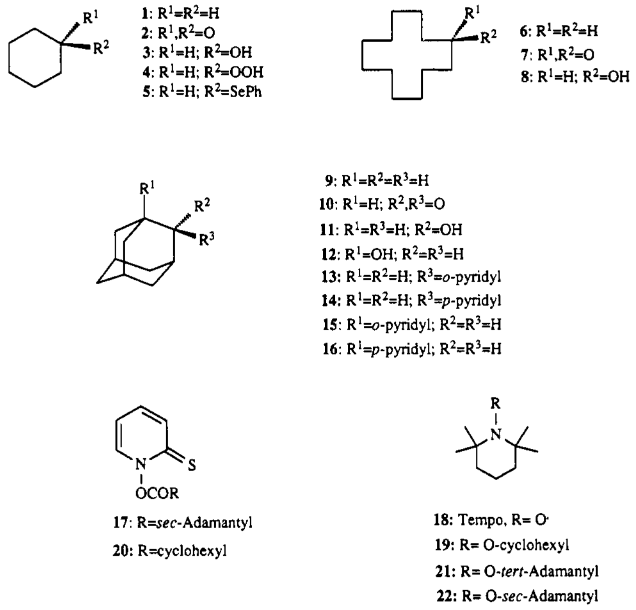


Figure 1.

Table I. Effect of Reducing Agents on Gif^{IV} Reactions[a]

reagent, mmol	ketone **2**, mmol	alcohol **3**, mmol	other products product, mmol	Σ,[b] mmol	ketone/alcohol, mmol/mmol
none	1.30	0.12		1.42	10.83
PhSH, 1.0	0.85	0.27		1.12	3.15
PhSH, 2.0	0.53	0.26		0.79	2.04
PhSH, 5.0	0.32	0.22		0.54	1.45
PhSeH, 1.0	0.93	0.52	**5**, 0.04	1.49	1.79
PhSeH, 2.0	0.54	0.53	**5**, 0.08	1.15	1.02
PhSeH, 5.0	0.35	0.36	**5**, 0.22	0.93	0.97
Ph_2S_2, 1.0	0.65	0.25		0.90	2.60
Ph_2S_2, 2.0	0.46	0.35		0.81	1.31
Ph_2S_2, 5.0	0.18	0.19		0.37	0.95
Ph_2Se_2, 1.0	0.59	0.60	**5**, 0.08	1.27	0.98
Ph_2Se_2, 2.0	0.51	0.69	**5**, 0.10	1.30	0.74
Ph_2Se_2, 5.0	0.34	0.53	**5**, 0.37	1.24	0.64

[a] Reaction conditions: cyclohexane (50.0 mmol), $FeCl_2{\cdot}4H_2O$ (0.2 mmol), Zn (20 mmol), pyridine (28.0 mL), and acetic acid (2.3 mL), under air. [b] Total yield of oxidation products.

The mechanism of formation of the alkyl hydroperoxide and the alcohol by Gif-type reactions was also addressed. Experiments running the GoAgg^{II} reaction under an atmosphere of $^{18}O_2$ afforded labeled hydroperoxide and alcohol. This proves that hydrogen peroxide is not the *direct* chemical source of the oxygen atoms in the ketone and the alcohol. Thus, the hydrogen peroxide plays two different roles in this process of oxidation of saturated hydrocarbons: the first one, the formation of an activated $Fe^V{=}O$ species, which is responsible for the activation of the hydrocarbon and the second, the production of O_2, which later on affords the alkyl hydroperoxide. Experiments were run in the presence of $H_2{}^{18}O$. The results prove that the alcohol is not formed by any kind of ligand coupling mechanism involving a hydroxy group but by reduction of the alkyl hydroperoxide. In those experiments where $H_2{}^{16}O$-free conditions were required, the solid clathrate

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(7) Woodland, M. P.; Patil, D. S.; Cammack, R.; Dalton, H. *Biochim. Biophys. Acta* **1986**, *873*, 237–242. Ericson, A.; Hedman, B.; Hodgson, K. O.; Green, J.; Dalton, H.; Bentsen, J. G.; Beer, R. H.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 2330–2332. Fox, B. G.; Froland, W. A.; Dege, J.; Lipscomb, J. D. *J. Biol. Chem.* **1989**, *264*, 10023–10033.

(8) Kivirikko, K. I.; Myllyla, R.; Pihlajaniemi, T. *FASEB* **1989**, *3*, 1609–1617.

(9) Baldwin, J. E. *J. Heterocycl. Chem.* **1990**, *27*, 71–78.

(10) Ziering, D. L.; Pascal, Jr., R. A. *J. Am. Chem. Soc.* **1990**, *112*, 834–838.

(11) Suga, A.; Sugiyama, T.; Otsuka, M.; Ohno, M.; Sugiura, Y.; Maeda, K. *Tetrahedron* **1991**, *47*, 1191–1204. Kittaka, A.; Sugano, Y.; Otsuka, M.; Ohno, M. *Tetrahedron* **1988**, *44*, 2811–2820, 2821–2833. Stubbe, J.; Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107–1136. Hecht, S. M. *Acc. Chem. Res.* **1986**, *19*, 383–390.

(12) The approach is essentially the same as accepted in cytochrome P_{450} chemistry, with the difference that there is no electron donation from the porphyrin ring to the iron atom. For evidence for the participation of $Fe^V{=}O$ species in the alkane functionalization by hydrogen peroxide catalyzed by non-heme iron centers, see: Leising, R. A.; Brennan, B. A.; Que, Jr., L.; Fox, B. G.; Münck, E. *J. Am. Chem. Soc.* **1991**, *113*, 3988–3990. For a discussion of the participation of $Fe^V{=}O$ species in the mechanism of action of cytochrome P_{450}, peroxidase, and catalase, see: Likhtenshtein, G. I. *Chemical Physics of Redox Metalloenzyme Catalysis*; Springer-Verlag: Berlin, 1988; Chapter VI, pp 123–160 and Chapter XI, pp 250–291. For spectrophotometric characterization of Fe^V species, see: Bielski, B. H. J.; Thomas, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 7761–7764. For evidence for the formation of $Fe^V{=}O$ species during the Fe^{III}-catalyzed decomposition of hydrogen peroxide, see: Kremer, M. L. *Int. J. Chem. Kinet.* **1985**, *17*, 1299–1314, and references cited therein. Cf.: Walling, C.; Goosen, A. *J. Am. Chem. Soc.* **1973**, *95*, 2987–2991, and references therein cited. For identification of a fluoroiron(V) porphyrin intermediate, see: Nanthakumar, A.; Goff, H. M. *J. Am. Chem. Soc.* **1990**, *112*, 4047–4049, and references cited therein. For a review on higher oxidation state chemistry of iron, see: Levason, W.; McAuliffe, C. A. *Coord. Chem. Rev.* **1974**, *12*, 151–184. See, also: Klemm, W. *Angew. Chem.* **1954**, *16*, 468–474. Cf.: Walling, C.; Kurz, M.; Schugar, H. J. *Inorg. Chem.* **1970**, *9*, 931–937.

(13) Barton, D. H. R.; Csuhai, E.; Doller, D.; Ozbalik, N.; Senglet, N. *Tetrahedron Lett.* **1990**, *30*, 3097–3100.

(14) Balavoine, G.; Barton, D. H. R.; Boivin, J.; Lecoupanec, P.; Lelandais, P. *New J. Chem.* **1989**, *13*, 691–700.

(15) Balavoine, G.; Barton, D. H. R.; Gref, A.; Lellouche, I. *Tetrahedron Lett.* **1991**, *32*, 2351–2354.

urea–hydrogen peroxide was used instead of anhydrous hydrogen peroxide. This avoids the preparation of the latter by a potentially dangerous reduced pressure distillation.

Attempts were made to examine the generality of the pathway *alkane → alkyl hydroperoxide → ketone or alcohol* studying other hydrogen peroxide-based systems. When the reaction was carried out in acetonitrile as solvent,[16] alkyl hydroperoxides were found to be reaction intermediates as well. Remarkably, when pure cyclohexyl hydroperoxide was submitted to the same reaction conditions in acetonitrile, it afforded a 1:1 mixture of ketone and alcohol. This value is the same as the ratio obtained from the reaction mixture, and it is in contrast with the 10:1 ratio obtained in the pyridine/acetic acid-based solvent matrix. Therefore, alkyl hydroperoxides appear to be common reaction intermediates for different types of enzymatic model systems, the ratio of ketone/alcohol in the reaction products mixture depending on the reaction solvent. Our hypothesis of alkyl hydroperoxides being reaction intermediates in the non-porphyrin enzymatic monooxygenation of saturated hydrocarbons[17] is reinforced by all these results.

Results and Discussion

Chemical Evidence: The Effect of Reducing Agents on the Ketone to Alcohol Ratio. Previous experiments running Gif reactions in the presence of dianisyltelluride gave valuable information on the existence of **B**, a common intermediate for ketone and alcohol formation. However, when more than 0.5 mmol of this reagent was added to the Gif^{IV} reaction mixture, the total amount of hydrocarbon activation diminished.[18] In search for a reducing agent which would influence the ketone/alcohol ratio without affecting the amount of hydrocarbon activation, we first studied the effect of several reducing agents on the Gif^{IV} oxidation of cyclohexane **1**. This heterogeneous superoxide version of Gif chemistry was adopted instead of the homogeneous GoAgg^{II} or GoAgg^{III} systems,[19] since these two are based on hydrogen peroxide as the ultimate oxidant. This is reduced almost instantly by any of the reducing agents chosen. The results of these experiments are shown in Table I.

In Table I the addition of 5.0 mmol of potential reducing agent is in large excess compared with the amount of oxidation seen without the addendum (1.4 mmol). Nevertheless with PhSH and Ph_2S_2 the amount of oxidation is reduced by only a half and with PhSeH and Ph_2Se_2 the total products, including the phenylcyclohexyl selenide **5**, remain constant. However, in every series there is a marked decrease in the ketone/alcohol ratio.

At this point, we were interested in the fate of diphenyl diselenide under Gif^{IV} conditions.[20] By quenching the crude reaction mixture with an excess of methyl iodide, more than 96% of the initial diphenyl diselenide was found as methyl phenyl selenide. In the corresponding blank experiment in the absence of zinc no methyl phenyl selenide was detected. This suggests that the diphenyl diselenide is reduced by the Zn powder to benzeneselenol. It is worth noting that thiophenol and benzeneselenol are both excellent traps for carbon radicals, acting as H$^{\bullet}$ transfer reagents with very fast reaction rates ($k_{PhSH} = 1.1 \times 10^8$ M^{-1} s^{-1} at 25 °C; $k_{PhSeH} = 2.0 \times 10^9$ M^{-1} s^{-1} at 20 °C).[21,22] Thus, we have again found[3] strong evidence against the participation of carbon radicals in Gif-type reactions, since they would be reduced back to the hydrocarbon by either of these reagents, and the activation process would be completely quenched if radicals were involved. These results, combined with recent kinetic isotope effect measurements,[23] strengthen the hypothesis of a hydrocarbon activation mechanism in Gif chemistry not involving carbon radicals.[6,17]

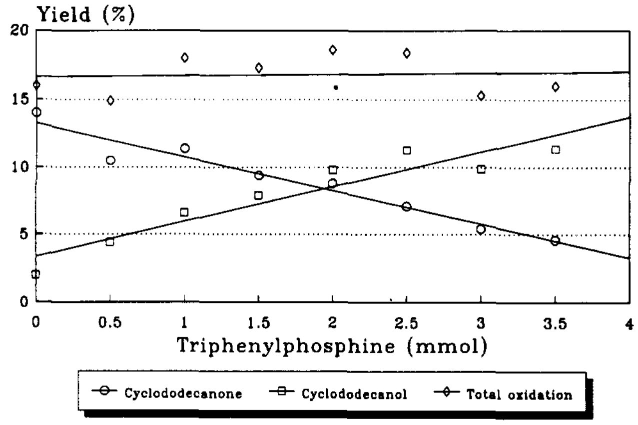

Figure 2. Variation of the amount of ketone and alcohol in the Gif^{IV} oxidation of cyclododecane (**6**, 5.0 mmol) in the presence of 0–3.5 mmol of triphenylphosphine.

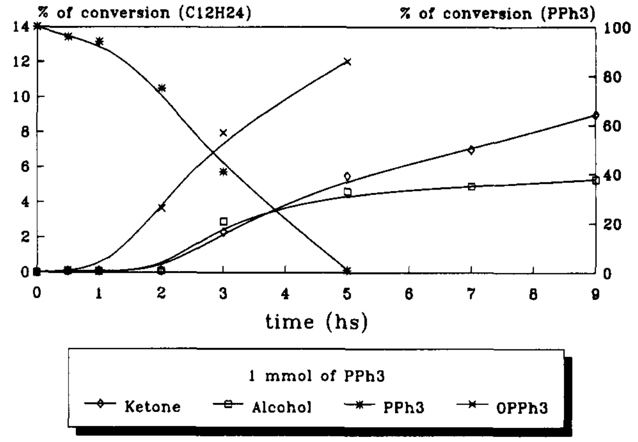

Figure 3. Kinetics of the Gif^{IV} oxidation of cyclododecane (**6**, 5.0 mmol) in the presence of triphenylphosphine (1 mmol). Experimental conditions: Zn (20.0 mmol), $FeCl_2 \cdot 4H_2O$ (0.25 mmol), pyridine (28 mL), and acetic acid (2.3 mL). The left ordinate gives the percentages of ketone and alcohol. The right ordinates gives the percentages of triphenylphosphine and triphenylphosphine oxide.

An ideal reducing agent for our mechanistic studies would have the property of changing the ketone/alcohol ratio, without affecting the activation process. Amongst the many reducing reagents tried, we found that triphenylphosphine met the required needs. The results obtained by adding up to 3.5 mmol of this reagent to a Gif^{IV} reaction on cyclododecane **6** are presented in Figure 2. It can be seen that increasing the amount of triphenylphosphine reduces the yield of cyclododecanone **7** and increases proportionally the yield of cyclododecanol **8**. The sum ketone plus alcohol remains constant.

To confirm that the usual Gif selectivity remained unchanged and that the mechanism of the reaction had not been diverted to a radical reaction triggered by triphenylphosphine, we studied the product distribution in the oxidation of adamantane **9**. For a normal Gif^{IV} reaction, in the absence of PPh_3, the ratio of sub-

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(16) For enzymatic model systems based on Fe^{III}/hydrogen peroxide in acetonitrile as solvent, see: Sugimoto, H.; Sawyer, D. T. *J. Am. Chem. Soc.* **1985**, *107*, 5712–5716. *J. Org. Chem.* **1985**, *50*, 1784–1786. Groves, J. T.; Van der Puy, M. *J. Am. Chem. Soc.* **1976**, *98*, 5290–5297.

(17) Barton, D. H. R.; Csuhai, E.; Doller, D.; Balavoine, G. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 3401–3404. Barton, D. H. R.; Csuhai, E.; Doller, D.; Balavoine, G. *J. Chem. Soc., Chem. Commun.* **1990**, 1787–1789.

(18) Barton, D. H. R.; Csuhai, E.; Ozbalik, N. *Tetrahedron Lett.* **1990**, *31*, 2817–2820.

(19) About-Jaudet, E.; Barton, D. H. R.; Csuhai, E.; Ozbalik, N. *Tetrahedron Lett.* **1990**, *31*, 1657–1660.

(20) Attempts were made to follow the fate of diphenyl diselenide by ^{77}Se NMR experiments. In $CHCl_3$ solution, PhSeH showed a sharp line at 146.0 ppm (reference Ph_2Se_2, δ = 475.0 ppm). However, in pyridine–acetic acid a broad line was observed at 283.0 ppm. We relate this behavior to the process $PhSeH + Py \rightleftarrows PhSe^- + PyH^+$, which affords a coalescent signal for the ^{77}Se nucleus. In the case of the Gif^{IV} reaction, a broad signal was observed as well. This behavior did not allow any conclusion from these NMR experiments.

(21) Franz, J. A.; Bushaw, B. A.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 268–275.

(22) Newcomb, M.; Manek, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 9662–9663.

(23) Barton, D. H. R.; Doller, D.; Geletii, Yu. V. *Tetrahedron Lett.* **1991**, *32*, 3811–3814.

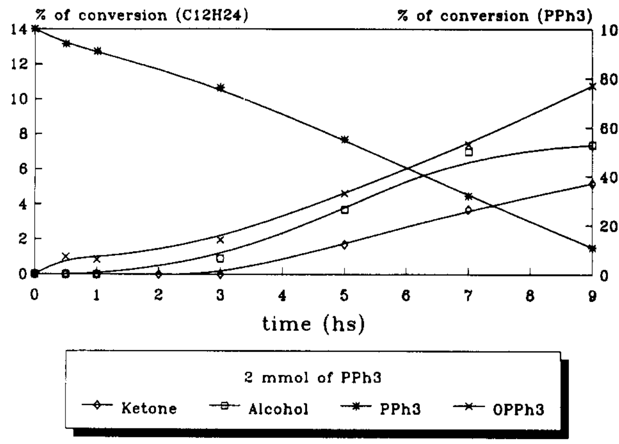

Figure 4. Kinetics for the Gif^{IV} oxidation of cyclododecane (**6**, 5.0 mmol) in the presence of triphenylphosphine (2 mmol). Experimental conditions: Zn (20.0 mmol), $FeCl_2 \cdot 4H_2O$ (0.25 mmol), pyridine (28 mL), and acetic acid (2.3 mL). The left ordinate gives the percentages of ketone and alcohol. The right ordinates gives the percentages of triphenylphosphine and triphenylphosphine oxide.

stituted products at the secondary position to substituted products at the tertiary position, C^2/C^3, usually has a value of 1.1.[14] This parameter (C^2/C^3) allows for a clear differentiation from an oxygen-based radical attack on adamantane, for which a value of 0.15 has been reported.[24] In the presence of PPh_3 (2.0 mmol), the Gif^{IV} oxidation of adamantane **9** afforded a mixture of 2-adamantanone **10** (3.7%), 2-adamantanol **11** (3.0%), 1-adamantanol **12** (1.4%), and the *o*- and *p*-pyridine coupled products **15** and **16** (3.9% and 1.4%, respectively); hence, a C^2/C^3 value of 1.0 is obtained, showing that the presence of PPh_3 in the system does not alter the typical Gif selectivity but only the ketone/alcohol ratio.

A more detailed examination of the Gif^{IV} oxidation of cyclododecane **6** in the presence of triphenylphosphine was addressed by following the reaction kinetics. The results are presented in Figures 3 and 4. Control experiments showed that only 3% of triphenylphosphine oxide was formed after 18 h under Gif^{IV} conditions *without zinc powder*. However, in the presence of zinc [*with* and *without* iron(II) catalyst], the complete conversion of triphenylphosphine to the oxide was observed. In Gif^{IV} reactions superoxide is the actual oxidant; it is produced by electron transfer from zinc to dioxygen.[3] Thus, triphenylphosphine is not only reducing the alkyl hydroperoxide to alcohol but also competing against iron(II) for superoxide. Indeed, Figures 3 and 4 show that the oxidation of triphenylphosphine and cyclododecane occur at the same time. After all the triphenylphosphine is converted to its oxide, the amount of alcohol remains constant, while the ketone increases until all the zinc is consumed (Figure 3). When, however, there is excess of triphenylphosphine (Figure 4), the amount of alcohol is always bigger than the ketone.

Figures 3 and 4 also give information on the competition between Fe(II) and the triphenylphosphine for the superoxide and on the relative rates of cleavage of the putative Fe(III)–O–OH species and of the hydroperoxide by triphenylphosphine. Thus, Figure 3 shows that 1 mmol of triphenylphosphine has disappeared after 5 h at which time 5% of alcohol (0.25 mmol) and 4% of ketone (0.2 mmol) have been produced. If we assume that the Fe(V) species with the iron–carbon bond is also reduced by the triphenylphosphine to Fe(III) prior to oxygen insertion (see later discussion concerning Figure 8), then the alcohol formation consumes 0.25 + 0.25 = 0.50 mmol of triphenylphosphine whilst ketone formation consumes another 0.2 mmol. Thus, 70% of the triphenylphosphine is involved in the oxidation process, and only 30% reacts with the superoxide or with the Fe(III)–O–OH species. Similar information is provided by Figure 4. These results show that in these experiments the alcohol is formed *only* by reduction of the intermediate **B** with triphenylphosphine.

Table II. Effect of Quenching the GoAgg^{II} Reaction with Thiophenol[a]

reaction time, h	normal workup, %			quenching with PhSH–oxalic acid, %			difference, %
	7	**8**	**7/8**	**7′**	**8′**	**7′/8′**	**8′ − 8**
1					traces		
2	traces	traces		traces	2.30		2.30
4.5	6.54	4.69	1.40	6.36	11.04	0.58	6.35
6	14.93	3.21	4.65	13.68	4.40	3.11	1.19
13	17.63	2.60	6.78	18.07	2.56	7.06	−0.04
16	21.11	4.01	5.26	22.04	4.18	5.29	0.17

[a] Reaction conditions: cyclododecane (5.0 mmol), $FeCl_3 \cdot 6H_2O$ (0.2 mmol), H_2O_2 (30%, 1.5 mL), pyridine (28.0 mL), and acetic acid (2.3 mL).

Spectroscopic Evidence: Following the Time Course of the GoAgg^{II} Reaction on [1-^{13}C]Cyclohexane by ^{13}C NMR Spectroscopy and on Cyclohexane-d_{12} by ^{2}H NMR Spectroscopy. Previous experiments in following the course of the GoAgg^{II} oxidation of substrates like cyclohexane **1** by ^{1}H NMR had encountered the difficulty of very broad lines, caused by the presence of paramagnetic Fe^{III} species in the reaction mixture. This is mainly due to the large magnetogyric ratio of the proton nucleus, which results in a high sensitivity toward paramagnetic species.[25] Since ^{13}C nuclei (and ^{2}H nuclei as well) have a smaller magnetogyric ratio than protons, we thought that the line-broadening effect of the paramagnetic iron would be diminished, and better results could be expected.

Preliminary experiments in ^{13}C NMR spectroscopy with unlabeled cyclohexane as starting material showed that ^{13}C-enriched substrate would be essential in order to achieve a satisfactory signal-to-noise ratio. Picolinic acid was not added to the system, so that the reaction rate would be slow enough to permit the detection of a relatively short-lived intermediate by ^{13}C NMR.[19]

The series of spectra obtained after addition of H_2O_2 (30% in H_2O) to a solution of [1-^{13}C]cyclohexane in Py-d_5/AcOH containing a catalytic amount of $FeCl_3 \cdot 6H_2O$ is shown in Figure 5. The formation of an intermediate characterized by four resonances at 82.64, 30.99, 26.23, and 24.11 ppm can be seen. The intensity of these four peaks initially increases with time, reaching a maximum at ca. 3.5 h after the addition of hydrogen peroxide. Afterwards, all of them disappear gradually as four new signals appear at 212.16, 42.00, 27.25, and 25.01 ppm, assigned to C-1 to C-4 of cyclohexanone, respectively.[26]

Suspecting that the monosubstituted cyclohexyl derivative could be cyclohexyl hydroperoxide **4**, an authentic specimen was prepared,[27] and its ^{13}C NMR spectrum showed perfect agreement with the four chemical shifts values found in the kinetic experiment. Thus, the intermediate was characterized as cyclohexyl hydroperoxide.

In Figure 6 the peak intensity for the C-2 resonances of cyclohexyl hydroperoxide and cyclohexanone are compared as a function of the reaction time. It can be concluded that the former is the main source of the latter in the kinetic experiment.

The following experiment was designed to prove chemically that the hydroperoxide was an intermediate. The time course of ketone and alcohol formation in a normal GoAgg^{II} reaction was compared with the results of a workup which quenched Fe^{III} reactivity (oxalic acid, see further below) and reduced (thiophenol) excess hydrogen peroxide and the hydroperoxide formed. The difference between the amount of alcohol in a "normal" workup and that in the "quench" workup would give the amount of hydroperoxide present. Indeed, the intermediacy of cyclododecyl hydroperoxide in a GoAgg^{II} reaction on cyclododecane **6** could also be confirmed.

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(24) Fossey, J.; Lefort, D.; Massoudi, M.; Nedelec, J.-Y.; Sorba, J. *Can. J. Chem.* **1985**, *63*, 678–680.

(25) Mantsch, H. H.; Saitô, H.; Smith, I. C. P. *Prog. NMR Spectrosc.* **1977**, *11*, 211–272.

(26) Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tables of Spectral Data for Structure Determination of Organic Compounds*, 2nd ed.; Springer-Verlag: Berlin, 1989; p C190.

(27) Williams, H. R.; Mosher, H. S. *J. Am. Chem. Soc.* **1954**, *76*, 2984–2987.

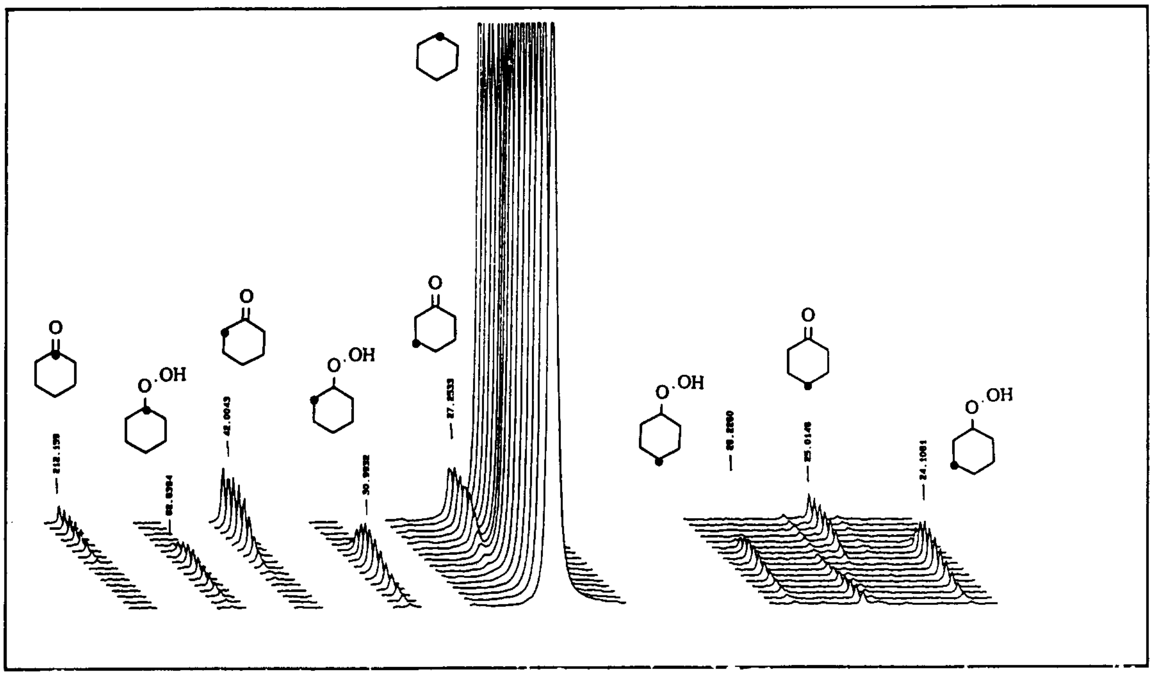

Figure 5. ^{13}C NMR experiment follwoing the time course of the $GoAgg^{II}$ oxidation of $[1\text{-}^{13}C]$cyclohexane.

Table III. Effect of Oxalic Acid on Gif^{IV} and $GoAgg^{II}$ Reactions[a]

Fe:oxalic acid (molar ratio)	Gif^{IV}, %				$GoAgg^{II}$, %			
	6 (recovered)	**7**	**8**	Σ	**6** (recovered)	**7**	**8**	Σ
no oxalic acid	84.3	12.6	2.8	99.7	78.3	18.2	3.4	99.9
1:1	84.1	13.0	traces	97.1	72.0	19.4	3.2	94.6
1:2	79.3	17.0	2.6	98.9	91.4	7.8	0.9	100.1
1:3	72.9	19.2	3.0	95.1	99.0			99.0
1:5	86.1	13.0	3.9	103.0	99.8			99.8
1:10	84.4	12.2	0.6	97.2				

[a] For reaction conditions, see Experimental Section.

The results of this kinetic study are presented in Table II. The presence of cyclododecyl hydroperoxide in solution before quenching is clearly shown.

To complement these results and confirm that cyclohexyl hydroperoxide is a real reaction intermediate, a sample of the hydroperoxide was submitted to $GoAgg^{II}$ reaction conditions (except hydrogen peroxide), and its transformation into cyclohexanone was observed (ketone to alcohol ratio 10:1).

The presence of cyclohexyl hydroperoxide as an intermediate in Gif-type ketonizations was also demonstrated by ^{2}H NMR spectroscopy. Cyclohexane-d_{12} was the substrate. In this case, the signal for the deuterium atom at C-1 of cyclohexyl hydroperoxide-d_{11} (resonating at 4.16 ppm) was first detected. Then, it decayed to cyclohexanone-d_{10}, as showed by the resonances of its deuterium atoms at C-2 and C-3 (2.32 and 1.68 ppm, respectively).

Effect of Ligands on the $GoAgg^{II}$ Reaction: Isolation of Cyclohexyl Hydroperoxide from a $GoAgg^{III}$ Reaction. Picolinic acid and congeners, when complexed to Fe^{III}, have been shown to catalyze $GoAgg^{II}$ reactions, increasing the reaction rate up to 50-fold.[19] The influence of ligands added on the reaction rate has also been demonstrated for the Cu^{II}-catalyzed process, known as the GoChAgg reaction.[28] These discoveries opened the door to a new field in Gif chemistry: the design of an *ideal* catalyst. Such a catalyst would provide the highest chemical yield, a fast reaction, and eventually would allow the isolation and characterization of reaction intermediates. So far picolinic acid is at the top of the ranking as far as reaction rates are concerned ($\tau_{1/2}$ = 6 min).[19] However, two other ligands have shown a remarkable effect on the rate of Gif-type hydrogen peroxide reactions: pyridine-2-phosphonic acid and oxalic acid. The former kills the $GoAgg^{II}$ reaction (Fe^{III}, H_2O_2) dead for a ratio ligand to iron of 3:1. Hydrogen peroxide consumption ceases as well. Upon further addition of $FeCl_3{\cdot}6H_2O$ the reaction resumes. Oxalic acid has the same effect on $GoAgg^{II}$ reactions as pyridine-2-phosphonic acid. The inhibitory effect of oxalic acid is presented in more detail in the Table III. Such effects are only seen for Fe^{III}–H_2O_2 systems and is specific for oxalic acid, since neither malonic acid, succinic acid, 3,3-dimethylglutaric acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, nor sebacic acid showed any effect on the $GoAgg^{II}$ reaction. On the contrary, oxalic acid and pyridine-2-phosphonic acid have no effect on Fe^{II}–superoxide reactions (Gif^{III} and Gif^{IV}).

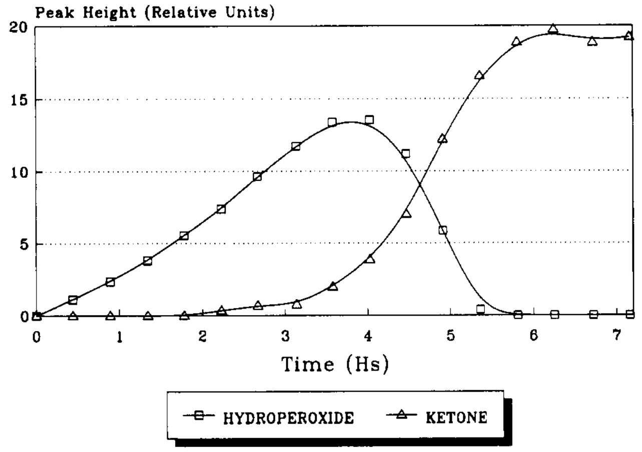

Figure 6. Comparison of the peak intensities for C-2 of both cyclohexyl hydroperoxide and cyclohexanone during the ^{13}C NMR experiment.

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(28) Barton, D. H. R.; Csuhai, E.; Doller, D.; Geletii, Yu. V. *Tetrahedron* **1991**, *47*, 6561–6570.

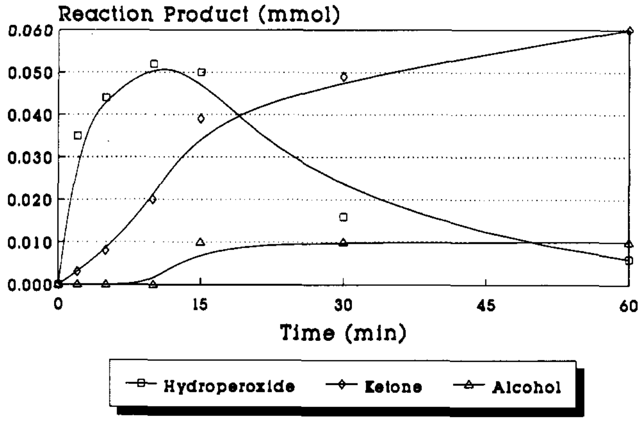

Figure 7. Kinetic analysis of the GoAgg^{III} oxidation of cyclohexane (**1**, 10 mmol) using the oxalic acid workup. Experimental conditions: $FeCl_3 \cdot 6H_2O$ (0.1 mmol), picolinic acid (0.1 mmol), H_2O_2 (2 mmol), pyridine (5 mL), and acetic acid (0.5 mL).

In order to examine if the addition of picolinic acid changed the reaction pathway, we investigated whether alkyl hydroperoxides are reaction intermediates in the GoAgg^{III} reaction or not. Using the property of oxalic acid of stopping the reaction dead, we were able to study this reaction at short reaction times. By modifying the normal workup procedure by early addition of oxalic acid, a mixture of cyclohexyl hydroperoxide, cyclohexanone, and cyclohexanol could be isolated and each component quantified by ^1H NMR spectroscopy against an internal standard. The results of this experiment are shown in Figure 7. They clearly show the role of intermediate of the alkyl hydroperoxide in the GoAgg^{III} reaction. Similar results were obtained when the GoAgg^{III} reaction was quenched with oxalic acid (to complex the Fe^{III}) and triphenylphosphine (to destroy the excess of hydrogen peroxide).

Having demonstrated the intermediacy of secondary alkyl hydroperoxides in the ketonization of aliphatic hydrocarbons by Gif-type reactions, we were encouraged to examine the catalytic activity of picolinic acid complexed to Fe^{III} on the fragmentation of the isolated hydroperoxide. Thus, the time course for the decay of the cyclohexyl hydroperoxide was followed by ^{13}C NMR spectroscopy. Indeed, picolinic acid catalyzes the transformation of the hydroperoxide to the ketone in an $FeCl_3$–pyridine–acetic acid solution, reducing the half-life of the reaction from 3 h to 40 min under these experimental conditions.

On the Mechanism of Formation of Alcohols in Gif-Type Reactions. Although the alcohols are minor reaction products of Gif-type reactions, we felt that an insight into the mechanism of its formation could give valuable information on the nature of the whole oxidation process. Having proved the intermediacy of alkyl hydroperoxides and knowing from several blank experiments that the alcohol does not originate by reduction of the ketone,[4] we considered two possible ways in which alcohols could be formed (Scheme II). The first hypothesis involved a coupling between a hydroxy and an alkyl ligand bonded to an iron species. This mechanism seemed attractive to us since ligand coupling is a rather general process in organometallic chemistry.[29] In addition, *assuming that both oxygen atoms in the alkyl hydroperoxide derive from hydrogen peroxide*, the same mechanism could be invoked to explain the formation of the hydroperoxide through a ligand coupling with a hydroperoxy ligand.

The second hypothesis was that the alcohol is formed by reduction of the alkyl hydroperoxide under the reaction conditions. In particular, the same Fe^{III}-catalyzed heterolytic fragmentation as for hydrogen peroxide could be proposed (Scheme II).

Scheme II

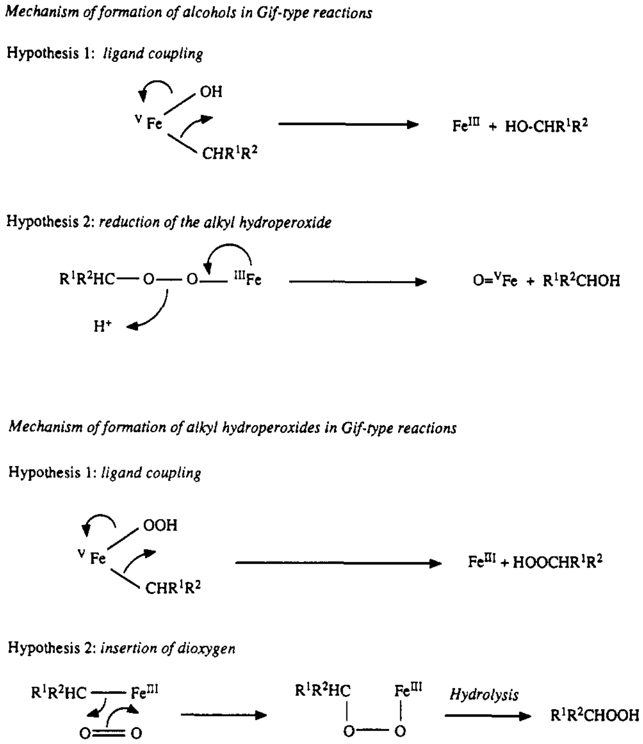

Table IV. Isotopic Abundance for the Ion $[M-CH_3]^+$ (m/z = 157) in Trimethylsilyloxycyclohexane (Experiments with $H_2{}^{18}O$)

sample	ion (m/z) 157	158	159	160
calculated value[a]	100	14.2	4.3	<0.1
blank[b]	100	14.3	4.5	
GoAgg^{III} reaction[c]	100	14.2	4.1	
$C_6H_{11}OSiMe_3$[d]	100	13.3	4.0	

[a] From natural isotopic abundance tables.[26] [b] Reaction mixture using unlabeled water. [c] Reaction mixture using $H_2{}^{17}O/H_2{}^{18}O$. [d] Prepared from an authentic specimen of cyclohexanol.

To test this theory we carried out some experiments under $H_2{}^{16}O$-free conditions in the presence of $H_2{}^{18}O$.[30] If the cyclohexanol originated by reduction of the alkyl hydroperoxide, it should not incorporate labeled oxygen into its structure. Otherwise, if the ligand-coupling mechanism were operating, the $H_2{}^{18}O$ would provide the labeled hydroxy ligand, which in turn would be incorporated into the alcohol. The corresponding blank experiments were carried out, showing that under the reaction conditions the alcohol did not incorporate ^{18}O from water by any kind of exchange process, as it could be anticipated. However, the ketone was shown to exchange its ^{16}O for ^{18}O by the well-known hydration–dehydration mechanism.[31]

So far, every experiment requiring water-free conditions had been carried out using anhydrous hydrogen peroxide, obtained by careful vacuum distillation of the commercial 50% solution in water.[32] Recently, the solid clathrate urea–hydrogen peroxide was reported as an alternative to hydrogen peroxide.[33] We thought that this crystalline clathrate would be useful for our $H_2{}^{16}O$-free experiments. Indeed, when a GoAgg^{II} reaction was carried out with urea–hydrogen peroxide the result was the same as with the aqueous hydrogen peroxide.

The results of these experiments are shown in Table IV. They indicate clearly that no incorporation of oxygen from water had taken place, weakening the hypothesis of a ligand exchange mechanism and suggesting that alcohols are formed in Gif-type

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(29) Negishi, E.-I. *Organometallics in Organic Synthesis*; Wiley: New York, 1980; Vol. 1, pp 76–77.

(30) A mixture of $H_2{}^{17}O/H_2{}^{18}O$ was used since it was the only product immediately commercially available.

(31) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper & Row: New York, 1987; Chapter 8, pp 661–735.

(32) Available from Fisher Scientific.

(33) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett.* **1990**, 533–535.

Table V. Isotopic Abundance for the Ion $[M-CH_3]^+$ (m/z = 157) in Trimethylsilyloxycyclohexane (Experiments with $^{18}O_2$)

sample	ion (m/z) 157	158	159	160	161
calculated value[a]	100	14.2	4.3		
$C_6H_{11}OSiMe_3$[d]	100	13.3	4.0		
GoAgg^{III} + $H_2{}^{16}O$[b]	100	14.3	4.5		
GoAgg^{III} + $H_2{}^{17/18}O$[c]	100	14.2	4.1		
Gif^{IV} + $^{16}O_2$	100	14.7	4.3		
Gif^{IV} + $^{18}O_2$	100	18.8	120.6	16.3	5.1

[a] From natural isotopic abundance tables.[26] [b] Reaction mixture using unlabeled water. [c] Reaction mixture using $H_2{}^{17}O/H_2{}^{18}O$. [d] Prepared from an authentic specimen of cyclohexanol.

Table VI. Isotopic Abundance for the Molecular Ion (m/z = 188) in Trimethylsilylperoxycyclohexane

sample	ion (m/z) 188	189	190	191	192	193
calculated value[a]	100	15.6	4.8	<0.1		
$C_6H_{11}OOSiMe_3$[b]	100	15.9	5.0			
GoAgg^{II} + $^{18}O_2$	100	16.4	45.5	10.1	43.6	5.9

[a] From natural isotopic abundance tables.[26] [b] Prepared from an authentic specimen of cyclohexylhydroperoxide.

reactions by reduction of the intermediate alkyl hydroperoxides.

On the Mechanism of Formation of the Alkylhydroperoxide Intermediate. Having demonstrated the participation of secondary alkyl hydroperoxides as reaction intermediates in Gif-type reactions, the next question was how this key intermediate is formed, especially regarding the origin of the two linked oxygen atoms. Considering how a GoAgg^{II} reaction is usually carried out, we visualized two different sources of oxygen: hydrogen peroxide and dioxygen [both from the air or generated by the iron(III)-catalyzed decomposition of hydrogen peroxide]. Then, it might well be that the oxygen is incorporated into the alkyl hydroperoxide from O_2 and not from hydrogen peroxide. In order to address this question, we carried out the GoAgg^{II} reaction under an atmosphere of $^{18}O_2$.

To verify the incorporation of the two oxygen atoms from $^{18}O_2$ into the hydroperoxide, the reaction was not run to completion, but the crude isolated reaction mixture was reacted with trimethylchlorosilane/hexamethyldisilazane/pyridine,[34] and the alcohol and the alkyl hydroperoxide were analyzed by gas chromatography–mass spectrometry of their trimethylsilyl (TMS) derivatives. The results obtained are shown in Tables V and VI.

The isotopic abundance pattern observed for the $[M-Me^\bullet]^+$ ion of the TMS derivative of cyclohexanol and the molecular ion region of the TMS derivative of cyclohexyl hydroperoxide show that *both* have incorporated oxygen from $^{18}O_2$ when a GoAgg^{II} reaction was performed under an atmosphere of labeled oxygen (Tables V and VI). In the case of the Gif^{IV} reaction cyclohexyl hydroperoxide could not be isolated due to the faster rate of its transformation to cyclohexanone under these reaction conditions. The TMS derivative of cyclohexanol was fully labeled, though, and some label was still detected on the cyclohexanone. Thus, oxygen gas was incorporated into both the alkyl hydroperoxide and the alcohol.

These results, when considered together with those from the experiments run in the presence of $H_2{}^{18}O$, definitively rule out a ligand coupling process involving hydrogen peroxide as the mechanism of alkyl hydroperoxide formation in Gif-type reactions. Also, they prove that the alkyl hydroperoxide is not only the intermediate for the formation of the ketone (by its Fe^{III}-catalyzed dehydration) but also the *common* reaction intermediate for the formation of the alcohol (through its reduction under the reaction conditions).

During the course of our work on the origin of the oxygen in the alcohol, we received a letter (dated June 3rd) from Prof. M. J. Perkins (New College, University of London, U.K.) with a copy of a manuscript which has just been published.[35] This reports that the hydroperoxide is indeed derived from oxygen as we have confirmed.

On the Nature of Intermediate A. Our previous knowledge[4] on Gif chemistry and all the evidence presented so far in this article show that Gif-type oxidations and radical chain autooxidation processes share certain common characteristics. Particularly, Gif-type reactions need oxygen gas in stoichiometric amounts, and, in the presence of well-known radical traps, like diphenyl diselenide, diphenyl disulfide, bromotrichloromethane, or carbon tetrachloride, the formation of ketones is diverted to the corresponding monosubstituted alkyl derivatives. In addition, Knight and Perkins were able to isolate the cyclohexyl spin adduct of deuterated 3,5-dibromo-4-nitrosobenzenesulfonic acid, pointing toward a "preponderant free-radical pathway for the (GoAgg^{II}) reaction".[35]

We have already proven[3] that when (say) secondary adamantyl radicals are generated by photolysis of the corresponding *N*-hydroxy-2-thiopyridone acyl derivative **17** under an inert atmosphere, in the absence of any better trapping reagent, they end up affording the *o*- and *p*-pyridine coupled products **13** and **14**. As the partial pressure of oxygen gas increased, so did the amount of oxygenated products **10** and **11**, with the corresponding decrease in **13** and **14**. Therefore, oxygen gas and pyridine compete for the *sec*-adamantyl radicals, and at low partial pressure of oxygen the coupling with pyridine *does* occur.

Knowing that oxygen gas is needed as a stoichiometric reagent in Gif-type processes, it was logical to think that it could be removed from the reaction mixture by running the GoAgg^{II} reaction under reduced pressure (10–40 mmHg). Then, one would expect intermediate A to follow a different reaction pathway. This simple idea works well and at the right pressure only traces, if at all, of oxidation products are formed, but intermediate A is still generated by addition of hydrogen peroxide.

We studied the influence of Tempo (**18**) on a GoAgg^{II} reaction (Table VII). Tempo has been extensively used as a carbon radical trap in organic and biological chemistry.[36] An authentic sample of the cyclohexyl-Tempo adduct **19** was prepared by photolysis of the *N*-hydroxypyridine-2-thione derivative of cyclohexanecarboxylic acid (**20**) in pyridine–acetic acid solution. When a GoAgg^{II} reaction on cyclohexane was run in the presence of Tempo and under reduced pressure (40 mmHg), the cyclohexyl-Tempo adduct was obtained in 36% yield (based on Tempo), accompanied with traces of cyclohexanone. When adamantane was used as a substrate, in the presence of Tempo and at reduced pressure (10 mmHg), both tertiary and secondary Tempo-adamantyl derivatives **21** and **22** were obtained as the major reaction products, together with some 1-adamantanol, adamantanone, and *only* tertiary pyridine-coupled products **15** and **16**. No traces of secondary adamantylpyridines **13** and **14** were detected. Therefore, intermediate A does react with Tempo.

Now, why is it that intermediate A is not a carbon radical? If A were a carbon radical, in the absence of Tempo and under reduced pressure it should behave as a carbon radical does, affording the corresponding pyridine-coupling products. However, Table VII shows that this is not the case: *only* tertiary adamantylpyridines **15** and **16** are obtained with adamantane. Clearly, the activation of saturated hydrocarbons *at secondary positions* by Gif-type reactions involves a species different from a carbon radical. This result was confirmed with cyclohexane and cyclopentane as substrates. In neither case cycloalkylpyridines were detected (GC–MS analysis).

In addition, the nonradical nature for intermediate A is supported by the following facts.

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(34) Sweeley, C. C.; Bentley, R.; Makita, M.; Wells, W. W. *J. Am. Chem. Soc.* **1963**, *85*, 2497–2507.

(35) Knight, C.; Perkins, M. J. *J. Chem. Soc., Chem. Commun.* **1991**, 925–927.

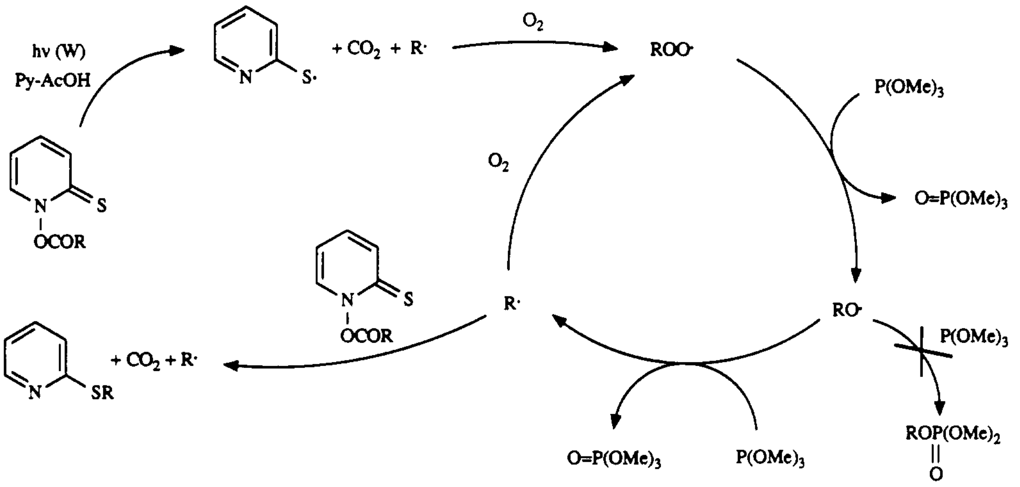
(36) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687–5698. Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1989**, *111*, 1927–1928. Chatteauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 2877–2885. Evans, C. A. *Aldrichimica Acta* **1979**, *12*, 23–29. Keana, J. F. W. *Chem. Rev.* **1978**, *78*, 37–64.

Table VII. GoAgg^{II} Reactions under Reduced Pressure[a]

	product									
reaction conditions	9[b]	10	11	12	15	16	21	22	Σ	C^2/C^3
air atmosphere	82.8	8.6	0.9	4.7	3.6	1.6			102.2	0.96
under vacuum (10 mmHg)	83.8	0.5	nd[c]	0.2	3.8	1.6			89.9	0.09
air atmosphere + Tempo (2 mmol)	81.7	3.2	0.3	2.7	1.9	0.8	1.9	3.8	96.3	1.00
under vacuum (10 mmHg) + Tempo (2 mmol)	85.3	0.5	nd	traces	2.4	1.2	1.8	5.0	96.2	1.02

[a] Percent reaction yield based on adamantane (**9**). No *sec*-adamantylpyridines (**13** and **14**) were detected. Reaction conditions: adamantane (5.0 mmol), $FeCl_3 \cdot 6H_2O$ (0.3 mmol), H_2O_2 (30%, 10 mmol), pyridine (30 mL), and acetic acid (3 mL). Reaction time: 6–7 h. [b] Unreacted starting material. [c] Not detected.

Scheme III. Radical Chain Cycle for the Photolysis of *N*-Hydroxypyridine-2-thione Derivative **20** in the Presence of $P(OMe)_3$ and O_2



1. As previously stated (see above), Gif^{IV} reactions can be carried out in the presence of PhSeH or PhSH in quantities largely in excess with respect to the amount of activated hydrocarbon. If carbon radicals were involved, they would be quenched through a H$^{\bullet}$-transfer at a very fast rate, affording the starting hydrocarbon. No activation would be observed.

2. We recently reported that alkanes are transformed to the corresponding alkyl dimethyl phosphates by treatment with trimethyl phosphite under Gif^{IV} conditions.[37] Mechanistic studies proved that the alkyl dimethyl phosphate arises from the reaction between the alkyl hydroperoxide coordinated to an iron species and trimethyl phosphite. When carbon radicals were generated in pyridine–acetic acid in the presence of trimethyl phosphite and oxygen, only traces of the corresponding alkyl dimethyl phosphate were obtained. Most of the trimethyl phosphite was converted into trimethyl phosphate as shown in Scheme III.[38] Thus, alkyl radicals react with oxygen affording alkylperoxy radicals, which in turn are reduced to alkoxy radicals by trimethyl phosphite. The alkoxy radicals further react with trimethyl phosphite regenerating alkyl radicals. Most of the alkyl radicals finally end up as 2-(alkylthio)pyridines. The catalytic effect on trimethyl phosphate formation is 425%. Therefore, trimethyl phosphite is a very efficient "oxygen-centered radical quencher", and no oxygen radical chain could be propagated in its presence.

3. The relative reactivity of cyclopentane and cyclohexane (C_5/C_6) is a useful criterion for establishing the mechanism of C–H bond cleavage.[39] For several different radical-chain reactions, carbon–hydrogen bonds in cyclopentane are more reactive than those in cyclohexane, and C_5/C_6 ratios greater than unity are obtained.[13,23,40] In Gif chemistry, however, cyclohexane is more reactive than cyclopentane.[13] In agreement with this precedent, the GoAgg^{II} competitive reaction between cyclopentane and cyclohexane in the presence of Tempo afforded a C_5/C_6 ratio of 0.66. As the reactivity of secondary carbon–hydrogen bonds in cycloalkanes has been related to the nature of the activation mechanism (e.g., carbocation, radical), the difference between the Gif value and the radical-chemistry value of C_5/C_6 agrees with the theory of a nonradical nature for intermediate **A**.

Conclusions

The extensive chemical and spectroscopic evidence presented demonstrates the participation of alkyl hydroperoxides as reaction intermediates in the ketonization of saturated hydrocarbons under Gif-type conditions. In addition, the mechanistic studies carried out using ^{18}O-enriched compounds indicate that the hydrogen peroxide is not the *direct* precursor of the oxygen atoms in the alkyl hydroperoxide. Interestingly, the hydrogen peroxide has first to be oxidized to dioxygen, which then can be incorporated into the hydroperoxide. Oxygen gas is also the source of the oxygen atom in the alcohol, which is formed by reduction of the alkyl hydroperoxide under the reaction conditions.

As far as intermediate **A** is concerned, it is clear that, should it be a carbon radical, it would give *every* test that carbon radicals give. It would not be logical to think of a carbon radical that reacts sometimes as a radical and some other times as a different species. The experiments with adamantane, cyclohexane, and cyclopentane as substrate show that intermediate **A**, from secondary positions, does *not* react with pyridine under reaction conditions where carbon radicals do react. Therefore, the nonradical nature of intermediate **A** is demonstrated. Several other experiments (influence of PhSH and PhSeH, effect of $P(OMe)_3$, C_5/C_6 ratios, and kinetic isotope effects[23]) confirm this statement.

From all this evidence, for GoAgg^{II} reactions we propose the catalytic cycle shown in Figure 8. For clarity, ligands have been omitted. This is a working hypothesis which explains every experimental fact known to date in Gif chemistry. The formation

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(37) Barton, D. H. R.; Bévière, S. D.; Doller, D. *Tetrahedron Lett.* **1991**, *32*, 4671–4674.

(38) Kochi, J. K. *Free Radicals*; Wiley: New York, 1973; Chapter 11, p 625. Ingold, K. U. *Acc. Chem. Res.* **1969**, *2*, 1–9. Plumb, J. B.; Griffin, C. E. *J. Org. Chem.* **1963**, *28*, 2908–2910. Buckler, S. A. *J. Am. Chem. Soc.* **1962**, *84*, 3093–3097. Walling, C.; Rabinowitz, R. *J. Am. Chem. Soc.* **1959**, *81*, 1243–1249.

(39) Tishchenko, N. A.; Rudakov, E. S.; Volkova, L. K. *Kinet. Katal.* **1989**, *30*, 319–325. Tishchenko, N. A.; Rudakov, E. S.; Lyubchik, S. B. *Kinet. Katal.* **1989**, *30*, 588–593.

(40) Huyser, E. S.; Schimke, H.; Burham, R. L. *J. Org. Chem.* **1963**, *28*, 2141–2143. Traynham, J. G.; Lee, Y.-S. *J. Am. Chem. Soc.* **1974**, *96*, 3590–3594.

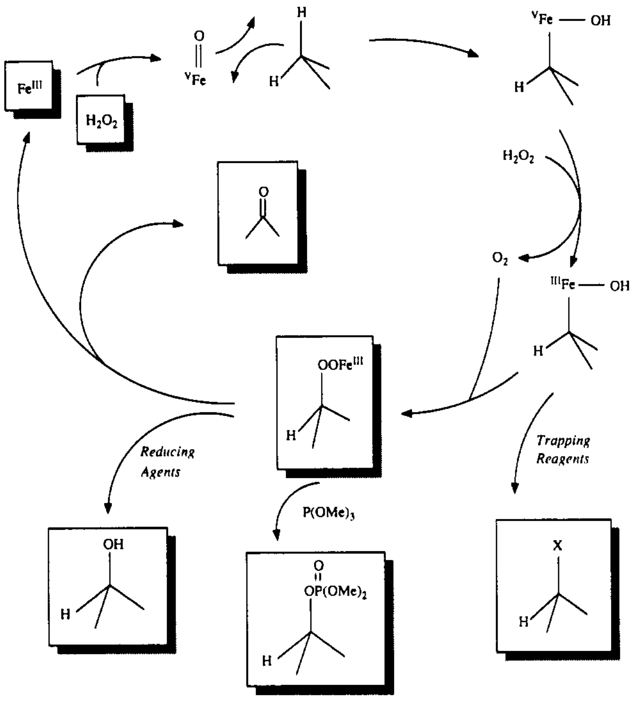

Figure 8. Proposed catalytic cycle for GoAgg^{II} reactions.

of an Fe^V=O species has considerable support.[12] Similarly, oxidative addition reactions are well-known processes in metallo-organic chemistry.[41]

There is concrete experimental support for the insertion of oxygen gas into carbon–Fe^{III} σ bonds.[42–45] The reduction of carbon–Fe^V moiety into a carbon–Fe^{III} species by hydrogen peroxide (which is oxidized to dioxygen) seems a logical step, followed by the insertion of oxygen into the iron–carbon bond as proposed in porphyrin chemistry.[42–45]

Prof. D. T. Sawyer and his colleagues have recently provided valuable evidence that confirms the selectivity of Gif-type chemistry for the secondary positions in saturated hydrocarbons. They have also developed a new system involving ferrous dipicolinate reacting with triplet oxygen.[46] Following our preliminary communication reporting the intermediacy of alkyl hydroperoxides in Gif-type reactions,[17b] other authors have reported similar results with related model systems which mimic enzymatic activity through an Fe^{III} complex and hydrogen peroxide in acetonitrile as a solvent.[47] Ourselves, we inspected briefly the $FeCl_3$–hydrogen peroxide–acetonitrile system.[46] We were able to detect cyclohexyl hydroperoxide as a reaction intermediate following the reaction by ^2H NMR experiments and isolated from the reaction mixture the pure cyclohexyl hydroperoxide, which was characterized by spectroscopic techniques and identified by comparison with an authentic standard. From all the work carried out by us and other research teams it seems that the chemistry associated with all these processes is strongly related.

The evident similarity between Gif chemistry and that of methane monooxygenase (MMO) suggsts that the chemical basis of their behavior should be related. It is interesting that MMO is a three component enzyme, constituted by a hydroxylase, a reductase, and the component B.[1,7] The question is, then, whether or not MMO, which catalyzes the oxidation of alkanes to alcohols with selectivity often similar to that shown by the Gif system, does so via an intermediate alkyl hydroperoxide, which is then transferred to a different site on the enzyme and reduced to the alcohol. The recent interesting observations of radical trapping in MMO oxidations[48] are not necessarily incompatible with the formation of an iron–carbon bond. In any case these reactions have to be quantified to establish if the "radicals" observed represent a major or minor path in the chemistry of the enzyme.

The considerable clarification that this paper brings to the mechanism of Gif chemistry does not resolve the fundamental paradox, which began in 1983, when we announced that saturated hydrocarbons could be converted to ketones in the presence of an excess of hydrogen sulfide. What kind of iron species (formally Fe^V) can it be that inserts itself into a strong C–H bond faster than into a weak S–H bond? The question is posed; the answer is awaited.

Experimental Section

General Methods. Unless otherwise stated, the experimental methods (including workup procedures and GC analyses) used throughout this work are as reported previously.[28] Gif^{IV} and GoAgg^{II} reactions were carried out as described elsewhere.[5] Mass spectrometric analyses were performed on a Hewlett-Packard 5790A series gas chromatograph equipped with a mass-selective detector. ^{13}C NMR experiments were carried out at room temperature on a Varian XL-200 or a Gemini-200 NMR spectrometer operating at 50 MHz, using 5-mm tubes. Chemical shifts are reported relative to TMS (δ = 0.00 ppm). ^2H NMR experiments were carried out at room temperature on a Varian XL-200 NMR spectrometer operating at 31 MHz, using 10-mm tubes. No lock signal was used. Chemical shifts are referenced to cyclohexane-d_{12} (δ = 1.38 ppm). ^{77}Se NMR were carried out at room temperature on the latter instrument operating at 38.2 MHz, using 10-mm tubes. Chemical shifts are referenced to diphenyl diselenide (δ = 475.0 ppm).

Triphenylphosphine and triphenylphosphine oxide were determined by HPLC on a Waters Model 600 instrument, equipped with a Waters 740 data module and a Waters Lambda-Max Model 481 UV detector operating at a fixed wavelength of 225 nm, using a Versapack C18 column (Alltech, 10μ particle size, 100 mm length × 4.6 mm diameter). Methanol–water (90:10) was the elution solvent at a flow rate of 1 mL/min, and benzoic acid was used as internal standard.

Unless otherwise stated, all the chemicals were purchased from commercial sources and used without further purification. Authentic specimens of cyclohexyl phenyl selenide and methyl phenyl selenide were prepared from cyclohexyl bromide and methyl iodide, respectively, by the $Ph_2Se_2/NaBH_4$ method.[49] Benzeneselenol was prepared according to a published procedure.[50] The authentic samples of the *o*- and *p*-cyclohexylpyridines, *tert*-adamantylpyridine, and *sec*-adamantylpyridine were obtained by photolysis of the corresponding *N*-hydroxy-2-thiopyridone acyl derivative in pyridine–trifluoroacetic acid.[3] Labeled water (10.1 atom % ^{17}O, 22.9 atom % ^{18}O) was purchased from Aldrich Chemical Co. Labeled dioxygen (25% $^{18}O_2$; 50% $^{18}O^{16}O$; 25% $^{16}O_2$) was purchased from Cambridge Isotope Laboratories.

[1-^{13}C]cyclohexane (99% ^{13}C) was prepared from cyclopentanone and $K^{13}CN$ (99% ^{13}C, Isotec Inc.) by a combination of previously reported methods.[51,52] An authentic sample of cyclohexyl hydroperoxide was obtained from cyclohexanol, by mesylation (MsCl, NEt_3, CH_2Cl_2) and substitution (H_2O_2, KOH, MeOH) as described elsewhere.[27] The adduct cyclohexyl-Tempo,[53] *tert*-adamantyl-Tempo, *sec*-adamantyl-Tempo, and cyclopentyl-Tempo were prepared by photolysis of the *N*-hydroxy-pyridine-2-thione derivative of the corresponding alkylcarboxylic acid.[54] ^1H and ^{13}C NMR, mass spectra, and infrared spectra were in agreement with their structures.

^{13}C NMR Experiment. [1-^{13}C]cyclohexane (80 μL) was dissolved in a mixture of pyridine-d_5 (500 μL) and acetic acid (100 μL) containing 5.13 mg (19.0 μmol) of $FeCl_3 \cdot 6H_2O$ in a 5-mm NMR tube, at room

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(41) Saillard, J.-Y. Theoretical Aspects of Alkane C–H Activation by Organometallics. In *Selective Hydrocarbon Activation*; Davies, J. A., Watson, P. L., Greenberg, A.; Liebman, J. F., Eds.; VCH Publishers: New York, 1990; Chapter 7.

(42) Arasasingham, R. D.; Balch, A. L.; Hart, R. L.; Latos-Grażyński, L. *J. Am. Chem. Soc.* **1990**, *112*, 7566–7571.

(43) Balch, A. L.; Hart, R. L.; Latos-Grażyński, L. *J. Am. Chem. Soc.* **1990**, *112*, 7382–7388.

(44) Arasasingham, R. D.; Balch, A. L.; Cornman, C. R.; Latos-Grażyński, L. *J. Am. Chem. Soc.* **1989**, *111*, 4357–4363.

(45) Arasasingham, R. D.; Balch, A. L.; Latos-Grażyński, L. *J. Am. Chem. Soc.* **1987**, *109*, 5846–5847.

(46) Sheu, C.; Richert, S. A.; Cofré, P.; Ross, B., Jr.; Sobkowiak, A.; Sawyer, D. T.; Konofsky, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 1936–1942.

(47) Fish, R. H.; Konings, M. S.; Oberhausen, K. J.; Fong, R. H.; Yu, W. M.; Christou, G.; Vincent, J. B.; Coggin, D. K.; Buchanan, R. M. *Inorg. Chem.* **1991**, *30*, 3002–3006.

(48) Deighton, N.; Podmore, I. D.; Symons, M. C. R.; Wilkins, P. C.; Dalton, H. *J. Chem. Soc., Chem. Commun.* **1991**, 1086.

(49) Klagman, D. L.; Griffin, T. S. *J. Am. Chem. Soc.* **1973**, *95*, 197–199.

(50) Reich, H. J.; Cohen, M. L. *J. Org. Chem.* **1979**, *44*, 3148–3151.

(51) Geiss, F.; Blech, G. *J. Labelled Compd.* **1968**, *4*, 119–127.

(52) Kabalka, G. W.; Baker, J. D., Jr. *J. Org. Chem.* **1975**, *40*, 1834–1835.

(53) Kovtun, G. A.; Aleksandrov, A. L.; Golubev, V. A. *Izvest. Akad. Nauk* **1974**, *10*, 2197–2204.

(54) Barton, D. H. R. *Aldrichimica Acta* **1990**, *23*, 3–11.

temperature. The reaction was initiated by addition of 50 μL of H_2O_2 (30% in water). Spectra were collected every 20 min.

^{2}H NMR Experiment. Cyclohexane-d_{12} (300 μL) was dissolved in a mixture of pyridine (3.0 mL) and acetic (300 μL), containing 5.40 mg (20.0 μmol) of $FeCl_3 \cdot 6H_2O$, in a 10-mm NMR tube, at room temperature. H_2O_2 (200 μL) was added to start the reaction. Spectra were collected every 10 min.

Fragmentation of Cyclohexyl Hydroperoxide under GoAgg^{II} Conditions (except for H_2O_2). Cyclohexyl hydroperoxide (200 mg) was dissolved in pyridine-d_5 (2.0 mL) and acetic acid (200 μL). An aliquot (500 μL) was placed in a 5-mm NMR tube. A solution of $FeCl_3 \cdot 6H_2O$ (2.7 mg, 10.0 μmol) in pyridine-d_5 was added to start the reaction. Spectra were recorded every 30 min.

Kinetic Experiment Quenching the GoAgg^{II} Reaction with Thiophenol. A GoAgg^{II} oxidation of cyclododecane (5.0 mmol) in pyridine (28.0 mL) and acetic acid (2.3 mL) containing $FeCl_3 \cdot 6H_2O$ (0.2 mmol) was initiated by addition of H_2O_2 (30% in H_2O, 1.5 mL). At different times an aliquot (1.0 mL) of the reaction mixture was poured into a test tube containing PhSH (2.5 mL) and oxalic acid (0.6 mmol). After 10 min the aliquot was treated as usual in the workup procedure.

Fate of Ph_2Se_2 Gif^{IV} Conditions. Cyclohexane (50 mmol), diphenyl diselenide (5.0 mmol), $FeCl_2 \cdot 4H_2O$ (0.25 mmol), and Zn powder (20 mmol) in pyridine (28.0 mL)–acetic acid (2.3 mL) were stirred under air for 1 h. Methyl iodide (20 mmol) was added. After 2 h the reaction mixture was submitted to the usual workup conditions. Gas chromatographic analysis showed 3% of diphenyl diselenide and 96% of methyl phenyl selenide. The blank experiment in the absence of zinc powder was carried out under exactly the same conditions except for leaving this reagent out of the reaction mixture. No methyl phenyl selenide was formed.

Experiments with Labeled Oxygen: GoAgg^{III} Reactions in the Presence of $H_2{}^{18}O$. Urea–hydrogen peroxide (500 mg, 5.21 mmol) was stirred in a solution of anhydrous pyridine (5 mL), glacial acetic acid (0.5 mL), cyclohexane (1.5 mL, 14 mmol), water (or water-$^{17/18}$O, 300 μL, 16.7 mmol), and picolinic acid (12.3 mg, 0.1 mmol) in a closed flask under argon. After stirring at 0 °C for 10 min, the reaction was initiated by addition of $FeCl_3 \cdot 6H_2O$ (27 mg, 0.1 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was cooled in a ice–water bath, diluted with ethyl ether, and acidified with H_2SO_4 (50%). The aqueous phase was extracted twice with ether. The organic layers were collected, washed with $NaHCO_3$ (saturated solution) and water, dried ($MgSO_4$), and concentrated (rotary evaporator). The residue was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR ($CHCl_2CHCl_2$ as internal standard), ^{13}C NMR, and GC–MS. Under these conditions the reaction yielded 0.15 mmol of cyclohexanone and 0.04 mmol of cyclohexanol, with a ketone/alcohol ratio of 4.75.

Gif^{IV} Reactions under an Atmosphere of $^{18}O_2$. In a 50-mL, two-necked, round-bottomed flask were placed zinc (0.325 g, 5.0 mmol), cyclohexane (1.0 mL, 4.6 mmol), pyridine (7.0 mL), acetic acid (0.58 mL), and $FeCl_2 \cdot 4H_2O$ (12.4 mg, 0.05 mmol). The flask was closed with a rubber septum, connected to a mercury manometer, and cooled to −45 °C (carbon tetrachloride/dry ice bath). The reaction mixture solidified. The flask was evacuated, purged with Ar, and evacuated again, and $^{16}O_2$ or $^{18}O_2$ (1 atm) was introduced in the system. The low temperature bath was removed. After melting, the reaction mixture was stirred vigorously under oxygen ($^{16}O_2$ or $^{18}O_2$) until all the zinc powder had consumed. The workup procedure was as in the GoAgg^{III} reaction.

Analysis of the Reaction Mixtures by GC–MS After Derivatization. The cyclohexanol and the cyclohexyl hydroperoxide were converted into the corresponding trimethylsilyl derivatives (TMSCl, HMDS, Py, room temperature, 5 min).[34] By the same procedure an authentic specimen of trimethylsilyloxycyclohexane was obtained. The TMS derivative of cyclohexanol showed a molecular ion of medium intensity (*m*/*z* 127; ca. 25%). Therefore, the ion $[M-CH_3]^+$ (*m*/*z* = 157) was used for the mass spectrometric analysis, since it showed peak intensities of ca. 60% of base peak. Isotopic compositions were calculated by averaging the peak intensities throughout the entire GC peak.

GoAgg^{II} Reaction at Reduced Pressure (with or without Tempo). $FeCl_3 \cdot 6H_2O$ (135 mg, 0.5 mmol) was dissolved in a mixture of pyridine (20 mL), acetic acid (2.0 mL), and cyclohexane (5.0 mL, 46 mmol) in a three-necked, round-bottomed flask connected to a manometer. The solution was cooled to 0 °C (ice–water bath). The system was evacuated to the appropriate pressure (10–40 mmHg), and (when necessary) Tempo (1.0 mmol) was added. The reaction was started by addition of hydrogen peroxide (30% in water, 10 mmol). The reaction mixture was stirred at room temperature for 6 h. The solvent was removed by distillation at reduced pressure (1 mmHg) at 30–35 °C. The residue obtained was submitted to column chromatography. Elution with ethyl ether/hexanes (1:1) afforded pured cyclohexyl-Tempo adduct (0.36 mmol, 36% yield).

Effect of Oxalic Acid on Gif^{IV} and GoAgg^{II} Reactions. The Gif^{IV} reactions were carried out on cyclododecane (5.0 mmol) using Zn powder (1.3 g), pyridine (28 mL), acetic acid (2.3 mL), and $FeCl_2 \cdot 4H_2O$ (0.25 mmol), under a balloon of oxygen, until all the Zn was consumed (16–24 h). The GoAgg^{II} reactions were run on cyclododecane (5.0 mmol) using hydrogen peroxide (1.5 mL, 15 mmol), pyridine (28 mL), acetic acid (2.3 mL), and $FeCl_3 \cdot 6H_2O$ (0.2 mmol). The reaction mixtures were stirred overnight at room temperature. Workup procedures were as reported elsewhere.[28] The results of these experiments varying the ratio Fe/oxalic acid are presented in Table III.

Effect of Pyridine-2-phosphonic Acid on Gif^{IV} and GoAgg^{II} Reactions. A Gif^{IV} reaction on cyclododecane was carried out as above, using a ratio pyridine-2-phosphonic acid/Fe of 3. The results were as follows: recovered cyclododecane (91.4%), cyclododecanone (10.5%), and cyclododecanol (1.2%) and mass balance 103.1%. For the GoAgg^{II} reaction carried out with the same ligand/iron ratio, 100% of cyclododecane was recovered.

Photolysis of *N*-Hydroxypyridine-2-thione Derivatives in the Presence of $P(OMe)_3$ and O_2. The *N*-hydroxypyridine-2-thione derivative of cyclopentyl carboxylic acid (0.2 mmol) was added to a solution of trimethyl phosphite (100 μL, 0.85 mmol) in pyridine (3 mL) and acetic acid (0.2 mL). The mixture was photolyzed under a continuous flux of O_2 (3 mL/min) at room temperature for 20 h. At the end of the reaction no cyclopentyl dimethyl phosphate was detected (GC–MS analysis). In addition, trimethyl phosphate (0.74 mmol, 87% yield) and (pyridylthio)cyclopentane (0.09 mmol, 45% yield) were detected.

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