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The Functionalisation of Saturated Hydrocarbons. Part XXI+. The Fe(III)-Catalyzed and the Cu(II)-Catalyzed Oxidation of Saturated Hydrocarbons by Hydrogen Peroxide: A Comparative Study

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Key words: Gif Systems; Saturated Hydrocarbons, activation; Hydrogen peroxide; Iron catalysts; Copper catalysts.

Abstract: The selective functionalisation of saturated hydrocarbons catalyzed by copper or iron salts are compared. In addition to further studies on the homogeneous oxidation by Cu(II)-H_2O_2 in pyridine-acetic acid (*GoChAgg* system), we introduce a heterogeneous Gif^{III}-analog based on Cu^0 and dioxygen in pyridine-acetic acid. Both Cu-based systems display Gif-type reactivity. The intermediacy of alkyl hydroperoxides in the Cu(II)-catalyzed reaction has been proven spectroscopically (following the reaction on [1-^{13}C]-cyclohexane by ^{13}C-N.M.R. spectroscopy) and chemically (quenching the reaction with triphenylphosphine to reduce the hydroperoxide to alcohol). The same holds for the Cu^0/O_2 system, as shown by the effect of triphenylphosphine added to the reaction mixture. Thus, both reactions follow the pathway *alkane* → *alkyl hydroperoxide* → *alcohol* or *ketone*. Experiments running the GoChAgg reaction (H_2O_2-based) under an $^{18}O_2$-atmosphere showed the incorporation of $^{18}O_2$ into the hydroperoxide and the alcohol (which derives itself from the alkyl hydroperoxide). The relative reactivity of this Cu(II) system was studied for a series of cycloalkanes. The participation of another reaction intermediate (**A**) has also been demonstrated. However, some important differences are presented, that show that the chemical properties of the **Cu-A** and the **Fe-A** intermediates are different. Thus, Gif-type reactivity is metal-dependent and involves two chemically different non-radical species.

+ Part XX: Barton D.H.R.; Bévière, S.D.; Chavasiri, W.; Csuhai, É.; Doller, D, and Liu, W.-G. *J. Am. Chem. Soc.*, submitted for publication.

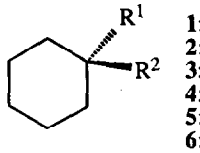
This paper is dedicated to Professor Yao-Zeng Huang, Shangai Institute of Organic Chemistry, on the occasion of his eightieth birthday.

INTRODUCTION

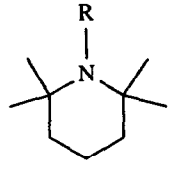
The economic and practical selective functionalisation of saturated hydrocarbons is still a major objective for the end of this century. We know that the objective can be attained because Nature does it easily at room temperature (or slightly above in mammals) using enzymes. Enzymes referred to as oxygenases are known to incorporate either one or two atoms of oxygen per mole of substrate; they are therefore divided into monooxygenases and dioxygenases, respectively. Although this process of activation of molecular oxygen seems quite general, only four types of prosthetic groups are associated with monooxygenases: heme-iron, non-heme iron, copper and flavin[1].

The activation of molecular oxygen (dioxygen, O_2) by hemoproteins and porphyrin-containing metal complexes is known in detail[2]. Thus, the P_{450} enzymes hydroxylate readily many substrates including saturated hydrocarbons. Such enzymes play a major role in biosynthetic processes which developed after the change from anaerobic to mainly aerobic life. The use of P_{450} models as well as the study of special substrates has been interpreted as radical chemistry of the Fe^{IV}=O oxenoid species, perhaps better written as Fe^{III}-O·, acting like an alkoxide radical.

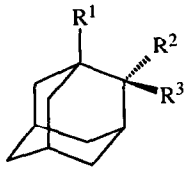
The chemistry of related processes which are mediated by non-heme iron or copper proteins and complexes is still to be developed. During the last years the isolation, purification and characterization of several non-heme iron-containing biologically active systems, especially *methane monooxygenase*[3], has encouraged an enormous effort in the field of model systems that emulate monooxygenase activity[4]. We have approached this problem developing the Gif systems[5]. The most valuable members of this family are Gif^{IV} [Fe(II) catalyst, dioxygen, Zn powder, in pyridine acetic acid], $GoAgg^{II}$ [Fe(III) catalyst, hydrogen peroxide in pyridine-acetic acid], and $GoAgg^{III}$ ($GoAgg^{II}$ + picolinic acid). Less practically important, the Gif^{III} systems involves Fe powder and dioxygen, in pyridine-acetic acid. These iron-based models are able to activate saturated hydrocarbons in quantitative yields at 10-25% conversions. Ketones are the major product of the reaction. Ketone to alcohol ratios range between 15:1 (for Gif^{IV} reactions) to 4:1 (for $GoAgg^{II}$ reactions).



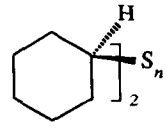
1: R^1=R^2=H
2: R^1,R^2=O
3: R^1=H; R^2=OH
4: R^1=H; R^2=OOH
5: R^1=H; R^2=$OSiMe_3$
6: R^1=H; R^2=SePh
9: R^1=H; R^2=*o*-pyridyl
10: R^1=H; R^2=*p*-pyridyl
19: R^1=H; R^2=$OP(O)(OMe)_2$



7: Tempo, R= O·
8: R=O-cyclohexyl



11: R^1=R^2=R^3=H
12: R^1=H; R^2,R^3=O
13: R^1=R^3=H; R^2=OH
14: R^1=OH; R^2=R^3=H
15: R^1=R^2=H; R^3=*o*-pyridyl
16: R^1=R^2=H; R^3=*p*-pyridyl
17: R^1=*o*-pyridyl; R^2=R^3=H
18: R^1=*p*-pyridyl; R^2=R^3=H



20: *n*=2-4

We have recently incorporated a new member into the Gif family. The GoChAgg system, employing a Cu(II) catalyst and hydrogen peroxide, has been shown to share many properties with the Fe-catalyzed process[6]. In this article we report our findings on the mechanism of this new reaction, and a comparison that permits us to distinguish it from the Fe-based systems. We also introduce a Cu^0-based system capable of activating saturated hydrocarbons, analogous to the Gif^{III} system.

RESULTS AND DISCUSSION

On the Cu(II)-catalyzed oxidation of saturated hydrocarbons by hydrogen peroxide in pyridine-acetic acid.

We have previously reported the ketonisation of saturated hydrocarbons in pyridine by hydrogen peroxide catalyzed by $Cu(ClO_4)_2.6H_2O$. Early selectivity studies on adamantane, cyclododecane, and *n*-hexane showed that this new reaction displays typical Gif-reactivity[6]. Analysis of kinetic isotope effects (k_H/k_D) and relative reactivity values for the pair cyclopentane-cyclohexane (C_5/C_6) proved that the mechanism of C-H activation is different from a hydrogen atom abstraction in both the Fe- and the Cu-catalyzed reactions[7]. In addition, alkyl hydroperoxides have been shown to be reaction intermediates in both the Fe(II)- and the Fe(III)-based oxidations[8].

Subsequently the GoChAgg system was modified by substituting $Cu(ClO_4)_2.6H_2O$ with $Cu(OAc)_2.H_2O$ and by adding acetic acid. This allows us to compare it with the iron systems in the same solvent matrix.

Continuing with our mechanistic studies on the Cu(II)-catalyzed system, the time course of the GoChAgg oxidation of [1-^{13}C]-cyclohexane (99% ^{13}C) in pyridine-d_5-acetic acid was followed by ^{13}C-NMR. The formation of [*n*-^{13}C]-cyclohexyl hydroperoxide (*n*=1-4) as a reaction intermediate was observed, together with labelled cyclohexanol. At the end of the reaction, though, *only* labelled cyclohexanone was present. Thus, the alcohol was oxidized to ketone, yielding the high ketone to alcohol ratio typical of the Cu(II)-catalyzed process[6,9]. The intermediacy of cyclohexyl hydroperoxide in the GoChAgg reaction was also demonstrated by chemical means. Instead of the usual work-up procedure, the reaction mixture was quenched with triphenylphosphine. This reduces both the hydrogen peroxide (to water) and the alkyl hydroperoxide (to the alcohol), and prevents the reaction from proceeding any further. The results are shown in Figure 1. The difference between the amount of cyclohexanol obtained after the normal work-up and that using the reductive quenching is due to the alkyl hydroperoxide present at any given time. In addition, the difference between the two curves for cyclohexanone (normal work-up and reductive quenching) shows that in the early stages of the reaction cyclohexyl hydroperoxide is the only reaction product.

To further test the participation of cyclohexyl hydroperoxide as a reaction intermediate an authentic specimen was prepared and subjected to GoChAgg conditions with and without hydrogen peroxide. These experiments gave a nearly quantitative yield of cyclohexanone and cyclohexanol in a ratio of 18.8 and 10.2, respectively. These figures are in agreement with the values for ketone/alcohol of 10-20, usually obtained for the Cu(II)-catalyzed reaction. They also prove that part of the cyclohexanol arises from reduction of the hydroperoxide, and is re-oxidized to cyclohexanone by the hydrogen peroxide under the reaction conditions.

From these findings we conclude that alkyl hydroperoxides are reaction intermediates in the Cu(II)-catalyzed oxidation at secondary positions of saturated hydrocarbons by hydrogen peroxide. Similar conclusions have been recently reported for the Fe-catalyzed processes[8,10].

Recent mechanistic investigations revealed that in the Fe-based Gif^{IV} [8b], $GoAgg^{II}$ [8b,11], and $GoAgg^{III}$ [8b] reactions the oxygen atoms in the alkyl hydroperoxide (and the alcohol) are derived from dioxygen. Thus, although hydrogen peroxide is the source of these two atoms of oxygen, it needs to be oxidized to dioxygen prior to its insertion into a putative carbon-iron bond[8b]. When the Cu(II)-catalyzed oxidation of cyclohexane was run under an atmosphere of $^{18}O_2$, the GC-MS analysis of the reaction mixture after silylation showed oxygen incorporation into the alcohol (Table 1). We have been unable to find any label on the oxygen atom in

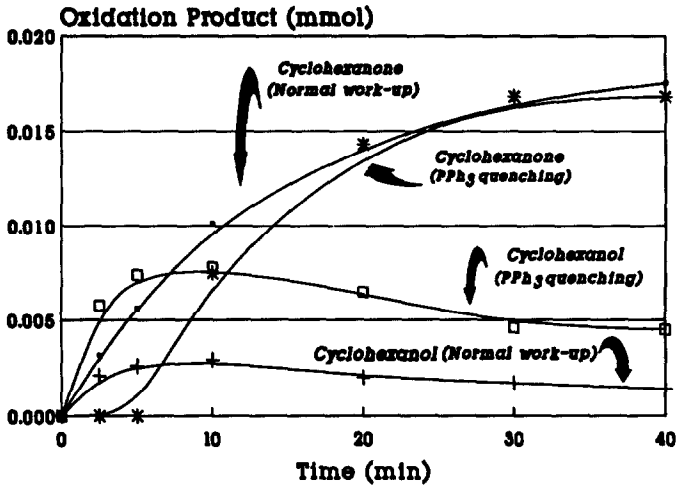


Figure 1. Comparison between the normal work-up and the triphenylphosphine quenching for the GoChAgg oxidation of cyclohexane **1**. For reaction conditions see Experimental.

Table 1. Isotopic abundance for the ion $[M\text{-}CH_3]^+$ (*m/z*=157) in trimethylsilyloxy-cyclohexane **5** (experiments with $^{18}O_2$ or $H_2{}^{18}O$)

	Ion (*m/z*)				
Experiment	157	158	159	160	161
Calculated value[1]	100	14.2	4.3	---	---
$C_6H_{11}OSiMe_3$ [2]	100	13.3	4.0	---	---
GoChAgg + $^{18}O_2$	100	15.1	27.8	3.1	---
GoChAgg + $^{18}O_2$ (PPh_3 *quenching*)	100	16.8	83.2	9.1	---
GoChAgg + $H_2{}^{18}O$	100	11.3	2.6	---	---

1. From natural isotopic abundance tables[13].
2. Prepared from an authentic specimen of cyclohexanol.

cyclohexanone. However, an indication of incorporation of dioxygen into cyclohexyl hydroperoxide was obtained by quenching the reaction mixture with triphenylphosphine and analyzing by GC-MS the incorporation of ^{18}O into the trimethylsilyl-derivative of cyclohexanol. Blank experiments in the presence of $H_2{}^{18}O$ (see Experimental) showed efficient incorporation of ^{18}O into cyclohexanone, as could be expected from a hydration-dehydration mechanism[12]. Therefore, one could expect that in the experiment run under $^{18}O_2$ the originally labelled cyclohexanone exchanged its ^{18}O atom with the $H_2{}^{16}O$ present in the reaction mixture. Again, the reaction pathway is similar to that for the Fe-catalyzed process[8]. In addition, GoChAgg reactions run under $H_2{}^{16}O$-free conditions in the presence of $H_2{}^{18}O$ did not show any incorporation of labelled oxygen into the alcohol. This rules out a reaction mechanism for the formation of alcohols involving hydroxy ligands. It also agrees with the fact that the alcohol is formed by *in situ* reduction of the alkyl hydroperoxide (Table 1).

Knowing that dioxygen is a stoichiometric reactant in the Cu(II)-catalyzed oxidation of saturated hydrocarbons by hydrogen peroxide, we examined the effect of removing the gas from the reaction mixture by running it under vacuum. In the case of the Fe(III)-catalyzed reaction, a pressure of *ca.* 40 mmHg was enough to suppress almost completely the formation of ketone[8b] (Table 2). We know that activation of the hydrocarbon under vacuum still occurs, since the first reaction intermediate (**Fe-A**) can be trapped, for instance, with Tempo[14] (**7**), affording adducts such as **8** for the case of cyclohexane. However, in the absence of any added trapping reagent, no coupling products between the alkane and pyridine were observed (**9** and **10**; GC-MS analysis). This argues for a non-radical nature for intermediate **Fe-A**, since under these conditions

Table 2. $GoAgg^{II}$ and GoChAgg reactions under reduced pressure [cyclohexane (**1**) as substrate].

System, Conditions	**2**,*mmol*	**3**, *mmol*	**8**, *mmol*
$GoAgg^{II}$, atm. pressure [1]	0.781	0.136	-----
$GoAgg^{II}$, 40 mmHg [1]	*traces*	*traces*	-----
$GoAgg^{II}$, 40 mmHg [1] + Tempo (1 mmol)	*traces*	*traces*	0.380
$GoAgg^{II}$, atm. pressure [1] + Tempo (1 mmol)	0.458	0.095	0.202
GoChAgg, atm. pressure [2]	0.564	0.039	-----
GoChAgg, 65 mmHg [2]	0.348	0.033	-----
GoChAgg, 40 mmHg [2]	0.129	0.039	-----
GoChAgg, atm. pressure [2] + Tempo (0.6 mmol)	0.564	0.038	0.022
GoChAgg, 65 mmHg [2] + Tempo (0.6 mmol)	0.330	0.051	0.029

1. Reaction conditions: cyclohexane (30 mmol), $FeCl_3.6H_2O$ (0.3 mmol), hydrogen peroxide (30%, 6 mmol) in pyridine (30 ml)-acetic acid (3 ml).
2. Reaction conditions: cyclohexane (120 mmol), $Cu(OAc)_2.H_2O$ (0.6 mmol), hydrogen peroxide (4.2 mmol), in pyridine (30 ml)-acetic acid (3 ml).

carbon radicals *do* couple at the *ortho* and *para* positions of pyridine, yielding products **9** and **10** [8b,15].

What is the effect of running the GoChAgg reaction under vacuum? In the case of the Cu(II)-catalyzed oxidation the decrease in the reaction yield is only moderate when compared to the Fe(III)-catalyzed process (Table 2). Interestingly, Tempo was inefficient as a trapping reagent *with or without* vacuum applied to the system, and even in the presence of an excess of the reagent.

With adamantane as the substrate, the amount of *tert*-adamantyl pyridine coupled products (**17** and **18**) obtained in the GoChAgg reaction was relatively small when compared with the Fe-catalyzed process (Table 3). Running the reaction under reduced pressure did not affect these results.

Table 3. $GoAgg^{II}$ and GoChAgg reactions on adamantane **11**.

System	Reaction product, *mmol*						C^2/C^3
	14	**12**	**13**	**17**	**18**	**16**	
GoChAgg [1] 1 atm.	0.065	0.045	0.004	0.001	0.002	0.001	0.74
GoChAgg [1] 10 mmHg	0.049	0.037	0.008	0.001	0.002	0.001	0.87
$GoAgg^{II}$ [2] 1 atm.	0.240	0.430	0.050	0.180	0.080	*n. d.*[3]	0.96
$GoAgg^{II}$ [2] 10 mmHg	0.010	0.030	*n. d.*[3]	0.190	0.080	*n. d.*[3]	0.09

1. Reaction conditions: Adamantane (5 mmol), $Cu(OAc)_2.H_2O$ (0.2 mmol), hydrogen peroxide (1.4 mmo l in pyridine (15 ml) - acetic acid (1 ml).
2. Reaction conditions: Adamantane (5.0 mmol), $FeCl_3.6H_2O$ (0.3 mmol), hydrogen peroxide (10.0 mmol) in pyridine (30 ml)-acetic acid (3 ml).
3. Not detected. Also no **15** was detected in any of these experiments.

These findings suggest that in the Cu(II) system the competition between dioxygen and Tempo for intermediate **A** (**Cu-A**) favors the first process rather than the second one. This contrasts with the Fe(III) system, where the opposite is valid for intermediate **Fe-A** [8b]. This supports a different nature for intermediates **Cu-A** and **Fe-A** and proves that the metal is somehow involved in the structure of the first reaction intermediate.

Another interesting aspect of Gif-type reactions is the relative reactivity order for different hydrocarbons. We have previously examined this order for the bromination reaction under $GoAgg^{II}$ conditions ($FeCl_3.6H_2O$, H_2O_2, $CBrCl_3$ in pyridine-acetic acid), and found it different from the typical radical chain bromination order ($CBrCl_3$, dibenzoyl peroxide in pyridine-acetic acid)[16]. In Table 4 are shown the relative reactivities for the oxidation under $GoAgg^{II}$ [Fe(III)-based] and GoChAgg [Cu(II)-based] conditions. They show the same pattern, disregarding of which metal is employed as catalyst.

An important characteristic of the GoChAgg reaction is related to the nature of the Cu(II)-catalyst. In many of the model systems developed so far, the active site of the catalyst added to the reaction mixture consists of two copper atoms joined by a μ-oxo bridge[17]. This refers to the structure of the catalyst before the initiation of the reaction. To gain information on the type of Cu(II) core involved in GoChAgg reactions, we carried out magnetic moment determinations through the NMR-based Evans method[18]. Cyclohexane was used as the probe substance. These experiments showed that in solution the copper catalyst has a magnetic moment of 1.90 ± 0.05 BM, typical of a not antiferromagnetically coupled octahedral copper complex (1.7-2.2 BM)[19]. When water is added to this system the formation of an antiferromagnetically coupled

Table 4. Relative reactivities for the oxidation of cycloalkanes by the $GoAgg^{II}$ and GoChAgg systems[1,2].

System	*c-C_5H_{10}*	*c-C_6H_{12}*	*c-C_7H_{14}*	*c-C_8H_{16}*	*c-$C_{12}H_{24}$*
$GoAgg^{II}$	0.85[3]	1	1.15	0.75	0.43
GoChAgg	0.80[3]	1	1.36	0.76	0.56

1. Values normalised *per* hydrogen atom and relative to cyclohexane.
2. Reaction conditions: alkane (5.0 mmol each), catalyst (0.2 mmol), hydrogen peroxide (1.4 mmol) in pyridine (10 ml)-acetic acid (1.0ml).
3. From reference 7.

Cu(II)-species is observed, as shown by the linear decrease in the magnetic moment cf the solution (Figure 2). The influence of the water on the reaction kinetics, slowing down the rate of ketonisation, agrees with the participation of a non antiferromagnetically coupled Cu(II) core as the active catalytic species in GoChAgg reactions (Figure 3). Therefore, if the catalytic core is not modified during the reaction the GoChAgg system is a model for enzymes containing this unit at the active site, such as *dopamine β-hydroxylase*[20].

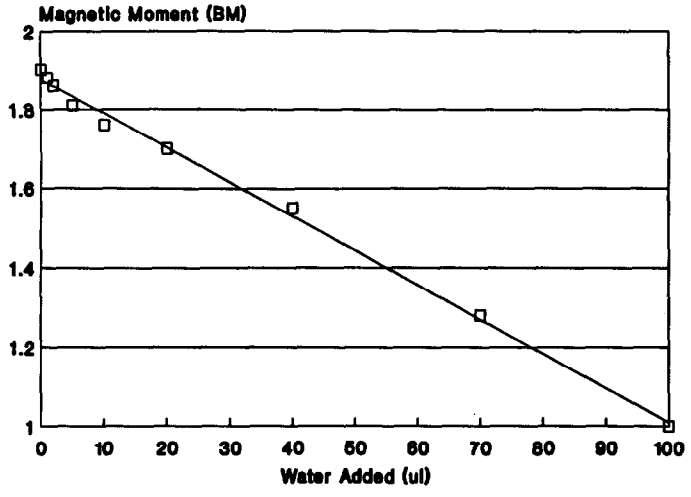


Figure 2. Variation of the magnetic moment of the Cu(II) catalyst as a function of the amount of water added to the system.

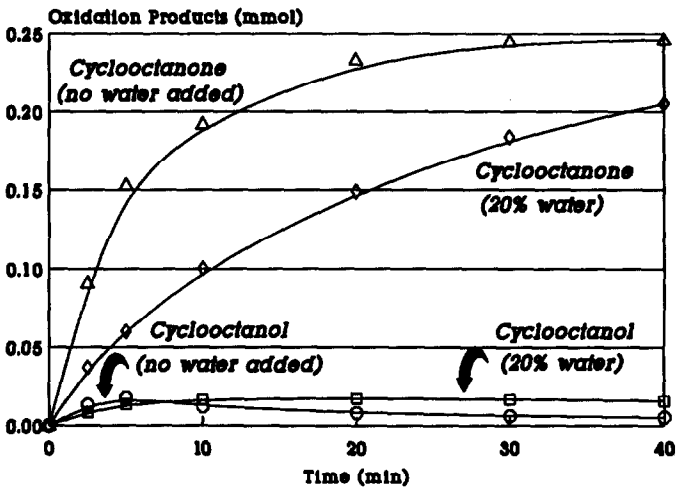


Figure 3. Effect of water on the rate of oxidation of cyclooctane by the GoChAgg reaction. For reaction conditions see Experimental.

On the oxidation of saturated hydrocarbons by Cu powder-dioxygen in pyridine-acetic acid.

By analogy with the Gif^{III} system[5] [Fe^0, dioxygen, pyridine-acetic acid solution] we studied the activation of saturated hydrocarbons coupled to the oxidation of copper powder by dioxygen (1 atm) in pyridine-acetic acid. We found that cyclohexane is efficiently oxidized to cyclohexanone and cyclohexanol. No other oxidation products were detected (Table 5). Adamantane (**11**, 5.0 mmol) was oxidized mainly to

Table 5. The oxidation of cyclohexane (**1**) by Cu powder/dioxygen in pyridine-acetic acid.

1, *mmol*	**2**, *mmol*	**3**, *mmol*	*Efficiency*, %[2]
40	0.70	0.08	7.7
80	1.18	0.16	13.4
120	1.33	0.30	16.3
160	1.83	0.52	23.5
200	1.29	0.35	16.4

1. Reaction conditions: cyclohexane (X mmol), pyridine (28 ml), acetic acid (2.3 ml), Cu powder (20 mmol) were stirred at room temperature under oxygen (balloon, 1 atm) until all the Cu was dissolved.
2. Based on Cu powder as limiting reagent.

adamantanone (**13**, 0.182 mmol), 1-adamantanol (**12**, 0.071 mmol), and 2-adamantanol (**14**, 0.020 mmol). Tertiary pyridine-coupled adamantyl derivatives **17** and **18** were found (0.034 mmol and 0.039 mmol, respectively), together with traces of 2-*ortho*-pyridyl-adamantane (**15**, 0.007 mmol). This affords a C^2/C^3 ratio of 1.45, typical of Gif-type selectivity (C^2/C^3 ratios of *ca.* 1.0 [21]) and very different from radical chain autooxidation values (C^2/C^3 *ca.* 0.15 [22]).

The effect of triphenylphosphine on the product distribution in cyclohexane oxidation by the Cu^0/O_2 system strongly supports the intermediacy of cyclohexyl hydroperoxide in the oxidation process, as it was established for the Fe(II)-, Fe(III)-, and Cu(II)-based hydrocarbon oxidations (Figure 4).

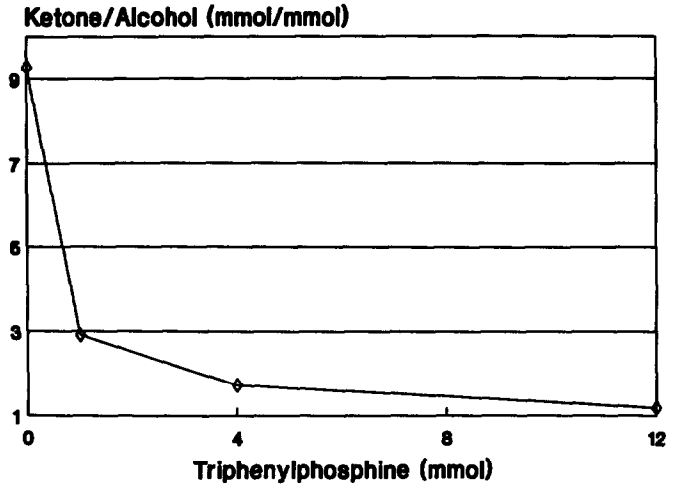


Figure 4. Effect of triphenylphosphine on the Cu^0/O_2 oxidation of cyclohexane **1**. For reaction conditions see Experimental.

One of the characteristics of Gif reactions is that by addition of an appropriate reagent the formation of ketone is diverted to different monosubstituted alkyl derivatives[5]. Thus, addition of diphenyl diselenide to a Gif^{IV} reaction on cyclohexane affords the cyclohexylphenylselenide **6** in very high yield (based on selenium)[23]. Although this reaction was also observed in the Cu/O_2 system, the reaction efficiency dropped dramatically with increasing amounts of diphenyl diselenide added (Table 6). In these experiments traces of diphenylselenide were detected, resulting from the long known reduction of diphenyl diselenide by metals[24].

Interestingly, both Cu-based systems failed to show any considerable reaction with other Gif-traps. Trimethylphosphite, which under $GoAgg^{II}$ or Gif^{IV} conditions affords the alkyl dimethyl phosphate[25] **19**, completely suppressed [Cu(II)-H_2O_2 system] or considerably diminished (0.402 mmol of cyclohexanone, 0.078 mmol of cyclohexanol with the Cu^0/O_2 system) the oxidation process, without formation of cyclohexyl dimethyl phosphate **19** (GC-MS analysis).

Sodium sulfide ($Na_2S.9H_2O$) is another reagent that traps the first reaction intermediate **A** with formation of dialkyl oligosulfides **20** in Fe-based systems[26]. In the Cu-based oxidations the oligosulfides were not obtained above the trace level, and the alkane oxidation was significantly suppressed (0.233 mmol of cyclohexanone, 0.051 mmol of cyclohexanol, 2.84% efficiency based on Cu).

Table 6. Phenylselenylation of cyclohexane by the $Cu^0/O_2/Ph_2Se_2$ system in pyridine-acetic acid.

Ph_2Se_2, *mmol*	**2**, *mmol*	**3**, *mmol*	**6**, *mmol*	*Efficiency*, %[2]
0	0.696	0.075	----	7.71
1.0	0.081	0.018	0.285	2.40
4.0	----	*traces*	0.150	0.75

1. Reaction conditions: cyclohexane (40 mmol), pyridine (28 ml), acetic acid (2.3 ml), Cu powder (20 mmol) were stirred at room temperature under oxygen (balloon, 1 atm) until all the Cu was dissolved.
2. Based on Cu powder as limiting reagent.

CONCLUSIONS

The continuation of our research on the activation of saturated hydrocarbons through transition metal activation of dioxygen or hydrogen peroxide has proven that copper [either as Cu powder or Cu(II) salts] is capable of carrying out an important part of the chemistry shown by its iron-based counterpart. Although the use of Cu^0/O_2 was reported for the oxidation of various organic substrates[27], our system is the first Cu-based non-heme model system which *efficiently* utilizes dioxygen for the activation of saturated hydrocarbons.

Although there are many common characteristics between these two model systems, there are also differences. Both systems oxidize saturated hydrocarbons to ketones following the same mechanistic pathway *alkane* → *intermediate* **A** → *alkyl hydroperoxide* → *ketone* and *alcohol*. The reactions require oxygen gas, which is the source of the two oxygen atoms in the alkyl hydroperoxide. This seems to be a *common* reaction intermediate; only one mechanistic pathway operates although two reaction products are obtained (ketone and alcohol). The ratio ketone to alcohol depends on the oxidative system chosen, and on the extent on which the alcohol is oxidized to the ketone under such conditions. The ketone is the main reaction product since pyridine is a basic solvent which facilitates the elimination of water from the hydroperoxide. In agreement with this theory, in a less basic solvent as acetonitrile ketone to alcohol ratios close to unity are obtained[4f,8b].

On the other hand, there are differences, such as the vacuum effect, the Tempo effect, the reactivity towards trimethylphosphite or sodium sulfide. These are important since they show that the nature of the metal is determinant for the reactivity of the first reaction intermediate (**Cu-A** or **Fe-A**). They prove that the metal itself participates actively in the activation process, and allow us to rule out definitively any metal-independent species, such as a free HO·-based activation[28] or a free pyridyl cation radical as a hydrocarbon-activating species[29].

By analogy with our working hypothesis for Fe-based systems, we postulate for GoChAgg oxidations the reaction mechanism shown in Figure 5. Ligands have been omitted for clarity. Transient high oxidation state copper species generated in systems closely related to ours have been postulated[30].

Hydrogen peroxide plays two different roles in the Cu(II)-catalyzed and Fe(III)-catalyzed ketonisation of saturated hydrocarbons. First, its interaction with the catalyst produces an "activated oxygen species" (represented as Cu^{IV}=O in GoChAgg systems or Fe^{V}=O in GoAgg systems). This derives from an heterolytic breakage of the O-O bond in hydrogen peroxide, and is the responsible for the activation of the hydrocarbon by generating intermediate **Cu-A** (or **Fe-A**), formally a monosubstituted alkyl derivative *of non-radical nature*. The second role of hydrogen peroxide consists in being a precursor of dioxygen, necessary for the insertion step into the carbon-copper (or carbon-iron) bond. These conclusions indicate that the oxygen atom that is finally incorporated into the alcohol or the ketone is previously transferred into the alkyl moiety as a two-atoms unit (alkyl hydroperoxide) which then is fragmented to the final product (ketone or alcohol). In

addition two equivalents of hydrogen peroxide are required, and the oxygen atom involved in the first step is different from the one that ends up in the alcohol or the ketone.

This reaction pathway is different from that accepted for the cytochrome P_{450} catalytic cycle, where only one equivalent of dioxygen (or hydrogen peroxide in the shunt mechanism) is involved and the originally activated oxygen atom is the same one that is incorporated into the alcohol[2]. Thus, if the reactivity of enzymes is truly emulated by using simplificated models, these conclusions indicate a different mechanistic pathway between heme-based and non-heme enzymes.

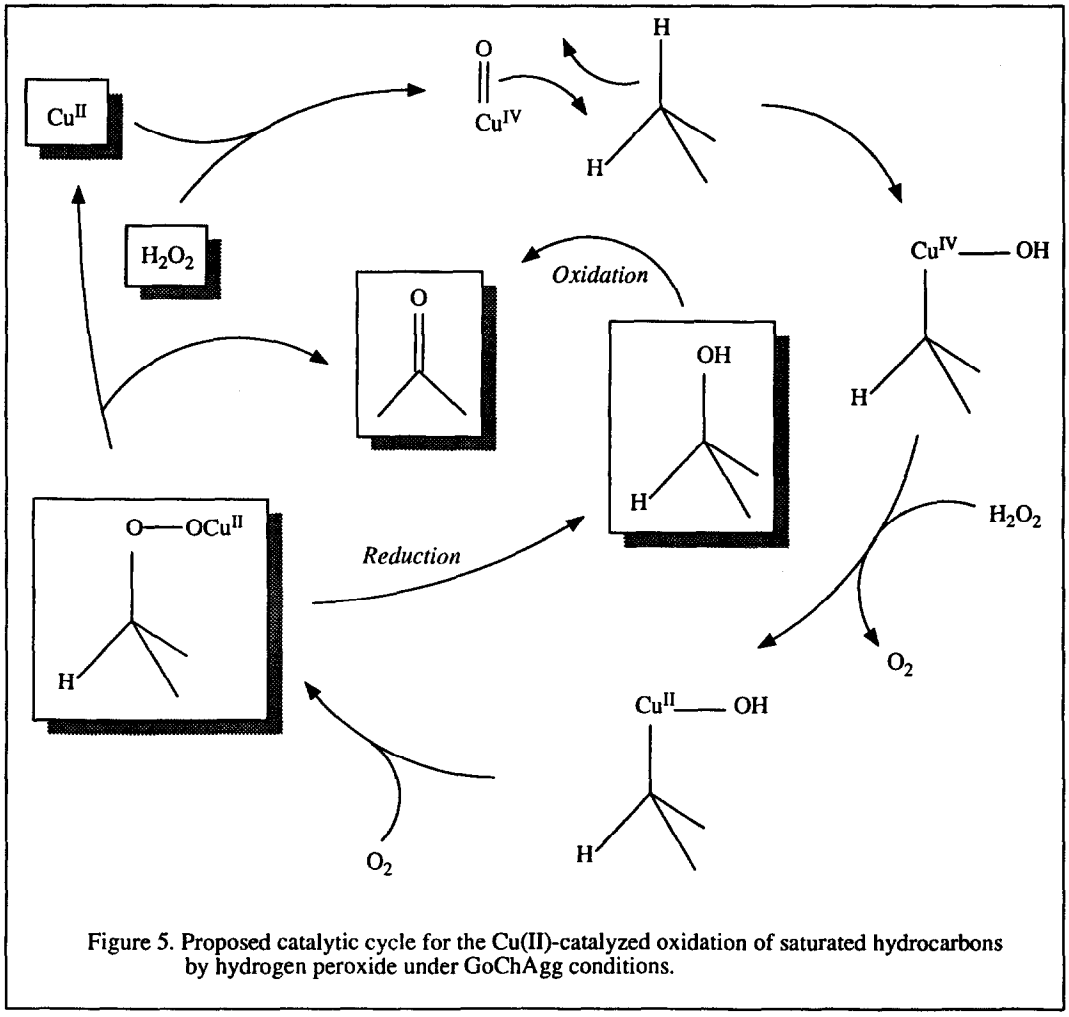


Figure 5. Proposed catalytic cycle for the Cu(II)-catalyzed oxidation of saturated hydrocarbons by hydrogen peroxide under GoChAgg conditions.

EXPERIMENTAL

Unless otherwise stated, the experimental methods (including work-up procedures and g.c. analyses) used throughout this work are as reported previously[6]. Gif^{IV} and GoAgg^{II} reactions were carried out as described elsewhere[5,15]. Mass spectrometric analyses were performed on a Hewlett-Packard 5790A Series gas chromatograph equipped with a mass-selective detector. ^{13}C-N.M.R. experiments were carried out at room temperature on a Varian XL-200 or a Gemini-200 N.M.R. spectrometer operating at 50 MHz, using 5 mm tubes. Chemical shifts are reported relative to TMS (δ=0.00 ppm).

Unless otherwise stated, all the chemicals were purchased from commercial sources and used without further purification. An authentic specimen of cyclohexylphenylselenide was prepared from cyclohexyl bromide by the $Ph_2Se_2/NaBH_4$ method[31]. The authentic samples of the *ortho-* and *para*-cyclohexylpyridines, *tert*-adamantylpyridine and *sec*-adamantylpyridine were obtained by photolysis of the corresponding *N*-hydroxy-2-thiopyridone acyl-derivative in pyridine-trifluoroacetic acid[15]. Labelled water (10.1 atom % ^{17}O, 22.9 atom % ^{18}O) was purchased from Aldrich Chemical Co. Labelled 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[32,33]. 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[34]. The adducts cyclohexyl-Tempo[35], *tert*-adamantyl-Tempo, and *sec*-Adamantyl-Tempo were prepared by photolysis of the *N*-hydroxy-pyridine-2-thione derivative of the corresponding alkylcarboxylic acid[36]. ^{1}H- and ^{13}C-NMR, mass spectra and infrared spectra were in agreement with their structures.

Magnetic moment measurements were carried out by the Evans method[18]. A solution of cyclohexane (100 µl) and acetic acid (100 µl) in pyridine-d_5 (1 ml) was prepared. Part of this solution (*ca.* 100 µl) was placed in a capillary tube and then sealed. $Cu(AcO)_2.H_2O$ (*ca.* 5 mg) was weighed in a 5 mm NMR tube and dissolved in 800 µl of the aforementioned solution. Appropriate amounts of water were added to this mixture. Molar magnetic susceptibilities were calculated by using eq. 1, where $\Delta\nu$ (Hz) is the frequency difference for cyclohexane resonance in the capillary tube and the Cu-containing solution, ν is the spectrometer frequency (200 MHz), and c is the molar concentration of copper salt. The term involving the density difference between sample and reference solution as well as the solvent contribution were omitted after being considered negligible compared with the frequency differences measured. The values of μ_{eff} were calculated from the spin-only formula, eq. 2, where χ_M is the molar susceptibility[37].

$$\chi_M = -\frac{3}{4\pi}\,\frac{\Delta\nu}{\nu}\,\frac{1000}{c} \qquad (1)$$

$$\mu_{eff} = 2.828\,(\chi_M T)^{1/2} \qquad (2)$$

^{13}C-N.M.R. experiment following the time course of the GoChAgg reaction. 80 µL of [1-^{13}C]-cyclohexane was dissolved in a mixture of pyridine-d_5(500 µL) and acetic acid (100 µL) containing *ca.* 2 mg of $Cu(OAc)_2.H_2O$ in a 5 mm N.M.R. tube, at room temperature. The reaction was initiated by addition of 50 µL of H_2O_2 (30% in water). Spectra were collected every five minutes.

Kinetic experiments quenching the GoChAgg reaction with triphenylphosphine. Cyclohexane (40 mmol), pyridine (10 ml), acetic acid (1 ml), and $Cu(OAc)_2.H_2O$ (0.2 mmol) were mixed in an erlenmeyer flask. The reaction was cooled to 0°C and initiated by dropwise addition of hydrogen peroxide (30%, 0.2 mmol). At appropriate times 1 ml aliquots were taken, to which triphenylphosphine (1 mmol) was immediately added. After overnight standing the samples were worked-up and analyzed by GC in the usual manner.

Blank experiments on cyclohexyl hydroperoxide. Cyclohexyl hydroperoxide (0.08 mmol) was added to

a solution of $Cu(AcO)_2.H_2O$ in pyridine (10 ml) and acetic acid (1 ml). The reaction mixture was stirred overnight at room temperature. Alternatively, hydrogen peroxide (1.4 mmol) was added before starting the stirring. After the usual work up, cyclohexanone (0.069 mmol or 0.0676 mmol, respectively) and cyclohexanol (0.0068 mmol or 0.036 mmol, respectively) were found.

Reaction under an $^{18}O_2$ atmosphere. $Cu(OAc)_2.H_2O$ was dissolved in a mixture of cyclohexane (40 mmol), pyridine (10 ml), and acetic acid (1 ml). The solution was frozen by cooling to -80°C and degassed by applying vacuum (40 mmHg for 10 min). Labelled dioxygen was introduced to the system until the manometer indicated 1 atm of pressure. The frozen reaction mixture was allowed to reach room temperature and hydrogen peroxide (1.4 mmol) was added to start the reaction. The solution was stirred overnight at room temperature, worked-up, concentrated (rotary evaporator), silylated (see below), and analyzed by GC and/or GC-MS.

When the GoChAgg reaction was submitted to the usual work-up (without PPh_3) cyclohexanone (0.0215 mmol) and cyclohexanol (0.0060 mmol) were obtained (total oxidation = 0.0275 mmol). For the case with PPh_3 quenching prior to the work-up the amounts were 0.0153 mmol, and 0.0122 (total oxidation = 0.0275 mmol), respectively.

GoChAgg reaction in the presence of $H_2{}^{18}O$. Urea-hydrogen peroxide (13 mg, 0.14 mmol) was stirred in a solution of anhydrous pyridine (1 mL), glacial acetic acid (0.1 mL), cyclohexane (216 µl, 2 mmol), and water (or water-^{18}O, 49 µL, 2.8 mmol) in a closed flask under argon. After stirring at 0°C for 10 min, the reaction was initiated by addition of $Cu(OAc)_2.H_2O$ (0.05 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 $NaHCO_3$ (satd. sol), water, dried ($MgSO_4$), and concentrated (rotary evaporator). The residue was analyzed by GC-MS. Under these conditions the mass spectrum of the cyclohexanone formed in the reaction showed relative peak intensities as shown in Table 7. The distribution is similar to that obtained in the presence of $H_2{}^{18}O$ in the absence of oxidant.

Table 7. Relative isotopic abundance for the molecular ion region of cyclohexanone ($H_2{}^{18}O$ experiments)

	Ion (*m/z*)			
Experiment	98	99	100	101
Calculated value[1]	100	6.9	0.5	---
Cyclohexanone[2]	100	6.8	0.6	---
GoChAgg + $H_2{}^{18}O$[3]	100	14.2	15.2	0.3
Cyclohexanone + $H_2{}^{18}O$[4]	100	12.8	17.6	---

1. From natural isotopic abundance tables [13].
2. Authentic sample.
3. Obtained from the reaction mixture.
4. Exchange experiment: cyclohexanone in pyridine-acetic acid containing $Cu(OAc)_2.H_2O$.

Analysis of the reaction mixtures by GC-MS after derivatization. The cyclohexanol was converted into the corresponding trimethylsilyl derivative (TMSCl, HMDS, Py, room temp., 5 min)[38]. By the same procedure an authentic specimen of trimethylsilyloxycyclohexane was obtained. This showed a molecular ion of medium intensity (*m/z*=127; *ca.* 25%). Therefore, the ion $[M\text{-}CH_3]^+$ (*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.

GoChAgg reaction at reduced pressure (with or without Tempo). $Cu(AcO)_2.H_2O$ (12.6 mg, 0.6 mmol) was dissolved in a mixture of pyridine (30 ml), acetic acid (3 ml), and cyclohexane (12.6 ml, 120 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 (0.6 mmol) was added. The reaction was started by addition of hydrogen peroxide (30% in water, 4.2 mmol). The reaction mixture was stirred at room temperature for 20 min. 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 pure cyclohexyl-Tempo adduct (0.029 mmol).

Effect of water on the GoChAgg oxidation rate. $Cu(OAc)_2.H_2O$ (0.4 mmol) was dissolved in pyridine (20 ml or 17 ml pyridine plus 3 ml water) containing acetic acid (2 ml) and cyclooctane (2.7 ml, 20 mmol). The reaction was initiated by the addition of hydrogen peroxide (30%, 0.28 ml, 2.8 mmol). 1 ml aliquots were taken and analyzed after the usual work up.

Typical procedure for the Cu^0/O_2 ketonisation of saturated hydrocarbons. Effect of triphenylphosphine. Cyclohexane (4.3 ml, 40 mmol) was dissolved in pyridine (28 ml). Copper powder (1.27 g, 20 mmol) was added, together with the appropriate amount of triphenylphosphine. The oxidation was initiated by addition of acetic acid (2.3 ml). The reaction mixture was stirred at room temperature until all the copper powder was dissolved (12-18 hs)

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