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The Selective Functionalisation of Saturated Hydrocarbons. Part 41. The Use of Cu^{II}/H_2O_2 and Cu^{I}/H_2O_2 Systems in Pyridine.

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Abstract: *The Cu^{II}/H_2O_2 and Cu^{I}/H_2O_2 systems for the functionalisation of saturated hydrocarbons are presented. A mechanism is proposed.* © 1997 Elsevier Science Ltd.

INTRODUCTION

Copper as well as iron are predominantly contained in metalloenzymes that play important roles in biological dioxygen metabolism.[1] Although much effort has been devoted to mimicking heme-iron containing enzymes such as cytochrome P-450,[2] model studies for the copper containing monooxygenases such as peptidylglycine α-amidating monooxygenase, are limited to a few cases.[3] Some examples demonstrate the use of a copper catalyst in the oxidation of alkanes. In 1988, Geletii and Lubimova were the first to report the oxidation of saturated hydrocarbons in the presence of copper perchlorate in pyridine.[4] Later, Sawyer et al. described a bis(bipyridine) copper[I] complex as an activator of H_2O_2 and TBHP for the selective ketonisation of methylenic carbons, in acetonitrile/pyridine.[5] The oxidation of alkanes to the corresponding alcohols and ketones, and epoxidation of alkenes can be performed efficiently at room temperature with molecular oxygen in the presence of an aldehyde and a copper catalyst such as $Cu(OH)_2$.[6] This process has been recently optimized by the addition of crown-ether.[7]

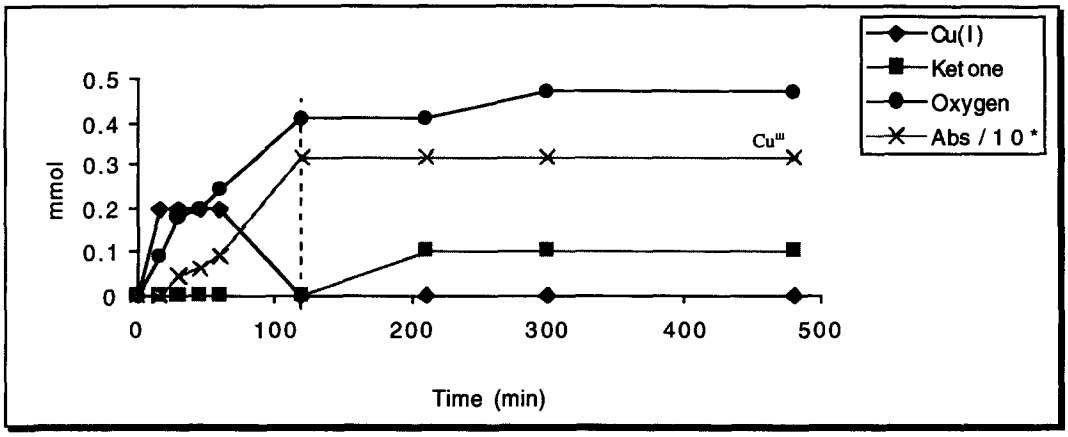
In 1991, a new member was incorporated into the Gif family: the GoChAgg system.[8] Employing a Cu^{II} catalyst and hydrogen peroxide, it was shown to share many properties with the Fe-catalyzed process.[9] In this article, we report our findings on the mechanism of this reaction by doing a comparative study of the Cu^{II}/H_2O_2 and Cu^{I}/H_2O_2 systems and on the influence of different ligands.

DISCUSSION

Mechanistic study

We have previously reported the ketonisation of saturated hydrocarbons in a pyridine/acetic acid solution.[8,9] In this study only pyridine was used as solvent. An initial kinetic study showed that the formation of ketone was dependant on the oxidation state of the copper (**Chart 1**). The Cu^{II} was first reduced to Cu^{I}. (The absorptiometric determination of Cu^{I} was performed using 2,2'-biquinoline as a chelating agent which is specific for Cu^{I}.[10]) The Cu^{I} was reoxidised to Cu^{III}. This final species was isolated and identified as Cu^{III} by iodometric titration (described later in the discussion). Most of the hydrogen peroxide was decomposed to O_2 before the oxidation of alkane to ketone. Therefore, these two processes do not seem to be competitive. Varying the amount of H_2O_2 does not change the Ketone/O_2 ratio (**Table 1**).

Chart 1: Kinetics of the parameters of the reaction using the Cu^{II}/H_2O_2 system.



Cyclohexane 10 mmol, $Cu(ClO_4)_2 6H_2O$ 0.2 mmol, H_2O_2 2 mmol, Pyridine 33 ml, 0°C to room temperature.
*The reaction mixture is diluted ten times before measuring the absorbance.

Table 1: Correlation between the amount of H_2O_2 and the amount of cyclohexanone and oxygen formed.

H_2O_2	Cyclohexanone	Oxygen	Ketone/O_2
2	0.098	0.49	0.2
4	0.195	0.91	0.21
6	0.29	1.98	0.15
8	0.38	2.12	0.18
10	0.55	3.14	0.18
14	0.78	5.28	0.15

Cyclohexane 10 mmol, $Cu(ClO_4)_2 6H_2O$ 0.2 mmol,
H_2O_2 x mmol, Pyridine 33 ml,under air, 0°C to room temperature.
All the results are in mmol.

The study of adamantane selectivity gave a ratio C_2/C_3 of 0.85 (**Table 2**). The Kinetic Isotope Effect was 2.34, therefore the main characteristics of the Gif system were respected.

Table 2: Adamantane selectivity.

1-Ad-OH	2-Ad-one	2-Ad-OH	1-Ad-Pyr	Adamantane	Mass Balance	C_2/C_3
0.40	0.32	0.046	0.03	8.79	96%	0.85

Adamantane 10 mmol, $Cu(ClO_4)_2 6H_2O$ 0.2 mmol, H_2O_2 10 mmol, Pyr 33 ml. All the results are in mmol.

Compared to the dismutation of hydrogen peroxide into oxygen and water, the functionalization of alkanes represents a minor pathway. Nevertheless we became interested in the mechanism of the formation of these oxidation products. An experiment using uv-visible measurements, revealed the appearance of a new copper species (λ=472 nm) as indicated in **Chart 1**.

The relation between cyclohexanone formation and the new copper species was demonstrated by simultaneous kinetic studies of the O_2 and cyclohexanone formation, the quantity of Cu^I, and the absorbance of the reaction mixture (**Chart 1**). The ketone formation stopped when all H_2O_2 was consumed; the addition of new portions of H_2O_2 increased the amount of cyclohexanone (**Table 3**, entries 1, 2, 3, 4, 5). After the fifth portion (**Table 3**, entry 5), oxidation power still remained, however no more ketone was being formed. When a new portion of copper salt was added, ketone formation continued (**Table 3**, entry 6).

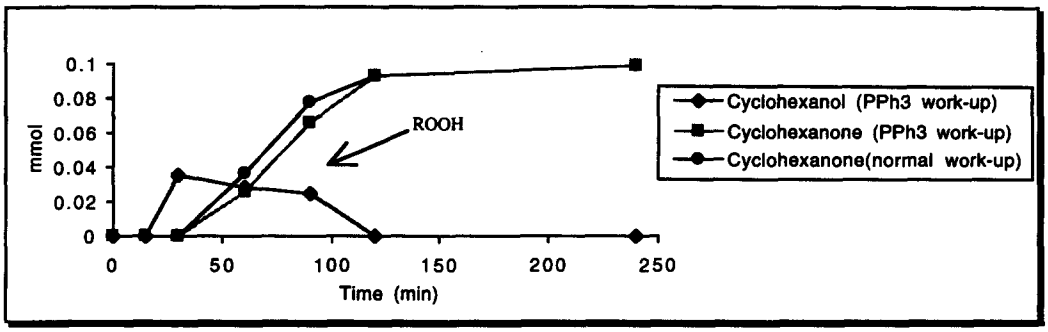
Table 3: Succesive addition of different portions of oxidant.

Entry	Addition			O_2	OP left	UV (472 nm)	MB of the step with respect to H_2O_2	Overall MB with respect to H_2O_2
1	H_2O_2 2 mmol	0.096	0.026	0.73	0	0.55	84 %	84 %
2	H_2O_2 1 mmol	0.131	0	1.05	0	0.82	72 %	79 %
3	H_2O_2 4 mmol	0.35	0	2.25	0	2.07	70 %	74 %
4	H_2O_2 6 mmol	0.58	0.024	3.74	0.485	2.68	78 %	70 %
5	H_2O_2 4 mmol	0.57	0.032	4.16	2.34	2.05	80 %	70 %
6	Cu^{II} 0.2 mmol	0.70	0	4.67	0	3.5	55 %	63 %

Cyclohexane 10 mmol, $Cu(ClO_4)_2 6H_2O$ 0.2 mmol, H_2O_2 2 mmol + different portions, Pyr 33 ml, 0°C to room temperature. OP: oxidizing power left. All the results are in mmol. MB: mass balance.

Continuing with our mechanistic studies, the intermediacy of cyclohexyl hydroperoxide in the reaction was demonstrated by chemical means. Instead of the usual work-up procedure, the reaction mixture was quenched with triphenylphosphine. This reduced both the hydrogen peroxide (into water) and the alkyl hydroperoxide (into the alcohol), and prevents the reaction from proceeding further. The results are shown in **Chart 2.** 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) showed that in the early stages of the reaction cyclohexyl hydroperoxide is the only reaction product.

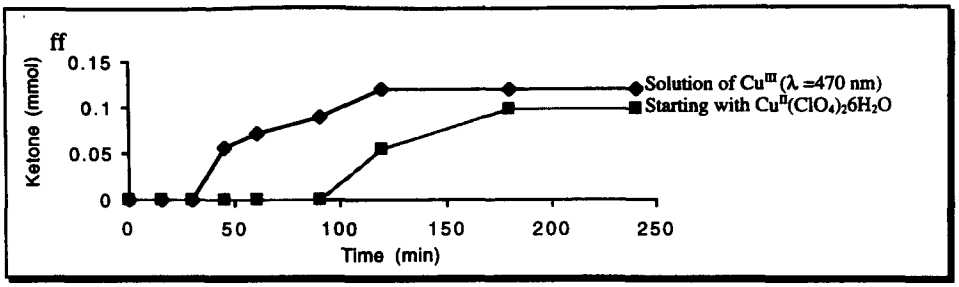
Chart 2: Cyclohexyl hydroperoxide is an intermediate.



Cyclohexane 10 mmol, $Cu(ClO_4)_2 6H_2O$ 0.2 mmol, H_2O_2 2 mmol, Pyridine 33 ml, from 0°C to room temperature.

Different methods have been examined to isolate the copper species responsible for the absorbance at 472 nm. The best way was to use silica gel column chromatography with pyridine as eluant.[11] A green solution was obtained first and identified as $Cu^{I}(Pyr)_4ClO_4$. Then an orange solution with an absorbance at 472 nm, was collected. Titration shows that it is not a Cu^{I} species. A precipitate showing the 472 nm band was obtained by adding ether at -25°C to the pyridine solution. The I.R. spectrum of this brown solid showed bands corresponding to perchlorate anion and pyridine. Reduction of a portion of this solid with hydroxylamine hydrochloride followed by determination of the amount of Cu^{I} by the standard procedure[10] gave the amount of Cu^{I} in the reduced brown solid. A simple iodometric titration of the latter, then enabled its oxidising power to be determined and thus the conclusion could be drawn that it contained Cu^{III}. A further experiment using the orange solution containing 0.2 mmol of copper was carried out. We needed to add more oxidant to observe the oxidation of cyclohexane. The reaction was faster than when we started with $Cu^{II}(ClO_4)_2 6H_2O$ (**Chart 3**).

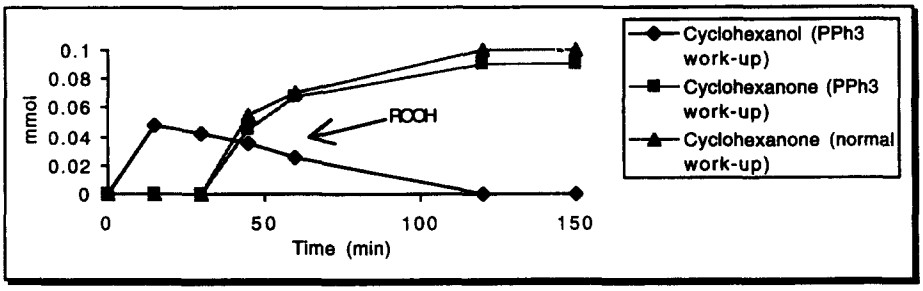
Chart 3: Kinetics of Ketone formation starting with the solution containing the active species.



Cyclohexane 10 mmol, copper 0.2 mmol, H_2O_2 2 mmol, Pyridine 33 ml, 0°C to room temperature.

From these experiments we have obtained the Cu^{III} intermediate which seems to be the active species. Moreover, slightly more cyclohexanone was formed under the same conditions as for a Cu^{II} reaction: 0.16 mmol against 0.098 mmol. Cyclohexyl hydroperoxide was still an intermediate (**Chart 4**). The addition of different salts such as LiCl, NaN_3, NaSCN, NaCN, did not result in the formation of alkyl derivatives, which makes unlikely a radical mechanism.[12]

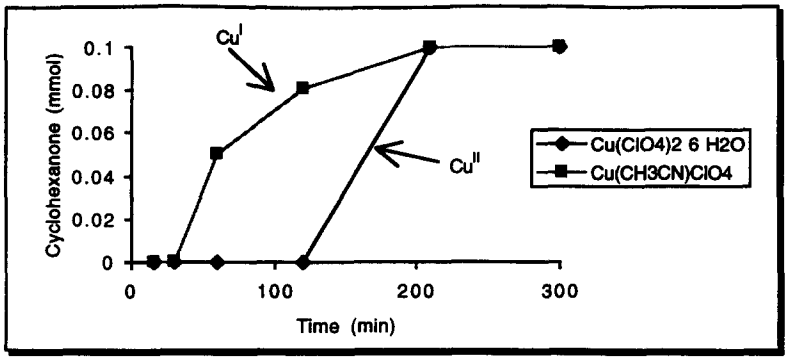
Chart 4



Cyclohexane 10 mmol, solution of Cu^{III} species (λmax= 472 nm) 0.2 mmol, H_2O_2 2 mmol, Pyridine 33 ml, from 0°C to room temperature.

Before reaching a conclusion on a probable mechanism, we studied the Cu^{I}/H_2O_2/Pyridine system. The copper^{I} complex used, $Cu(CH_3CN)_4ClO_4$ was synthesized as described in the literature and kept under argon.[13] The formation of ketone was faster when starting with Cu^{I} as a catalyst, than with Cu^{II} (**Chart 5**).

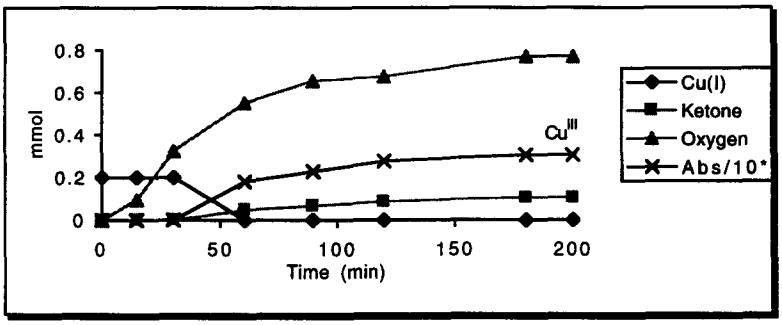
Chart 5: Kinetic comparison.



Cyclohexane 10 mmol, copper salt 0.2 mmol, H_2O_2 2 mmol, Pyridine 33 ml, under argon from 0°C to room temperature

The adamantane selectivity and the KIE were similar to the results we observed with Cu^{II}: C_2/C_3=0.97, KIE=2.36. No alkyl derivatives were formed by addition of salts NaSCN, NaN_3, LiCl. The simultaneous analysis of the absorbance (measured by spectrophotometry), the quantity of Cu^{I} (titration), oxygen and ketone formation, showed the same trend as what we observed for Cu^{II} (see **Chart 1**). However, no induction period was observed because the copper was already in the Cu^{I} oxidation state. This explains the difference in the kinetic rates between Cu^{II}/H_2O_2 and Cu^{I}/H_2O_2 systems (**Chart 5**). The oxygen was produced first; then a new copper species was formed (λ=472 nm) and then ketone formation started (**Chart 6**).

Chart 6: Kinetics of the parameters of the reaction using Cu^{I}/H_2O_2 system.



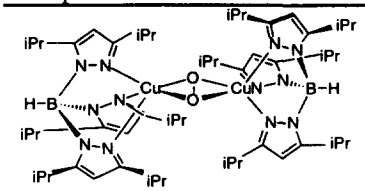
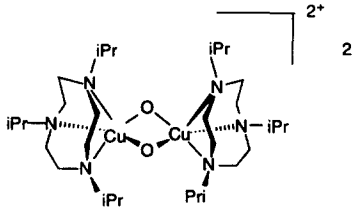
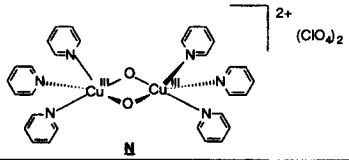
Cyclohexane 10 mmol, $Cu(CH_3CN)4ClO_4$ 0.2 mmol, H_2O_2 2 mmol, Pyridine 33 ml, 0°C to room temperature.
*The reaction mixture is diluted ten times before measuring the absorbance.

These results do not support the presence of two distinct manifolds as in iron chemistry.[14] The proposed mechanism is described in **Scheme 1**. Starting with Cu^{II}, we first need to reduce it to Cu^{I} by addition of H_2O_2 (1 H_2O_2 for 2 Cu^{II}). The yellow complex $Cu^{I}(Pyr)_4ClO_4$ formed has been identified and characterized. Then the active species responsible for the absorbance at 472 nm is formed. The exact structure is still in question. Davies already reported this species, and proposed $_n(Pyr)CuOOCu(Pyr)_n$ as a formula.[11] Davies' strongest evidence for

the existence of pyridine coordinated cuprous peroxide was his report of a characteristic peroxide band at 586 nm in the Raman spectrum. Rogic and coworkers were unable to observe this band in solution. That is why they propose that a bis oxo species is responsible for the absorbance.[15]

Following the early work by Karlin[16] on reversible O_2-binding with copper, various reversible (Cu_2O_2) species have been described.[17] The recent remarkable work by Que and Tolman[18] showed that these kinds of peroxo or bis oxo copper complexes can be characterized at -80°C {μ-peroxo complex $[(LCu)_2(\mu\text{-}O)_2](X)_2$ λ_{max}= 360 nm (ε 20000 $M^{-1}.cm^{-1}$), 510 nm (ε 1000$M^{-1}.cm^{-1}$); μ-bis-oxo complex λ_{max}= 320 nm (ε 12000 $M^{-1}.cm^{-1}$), 430 nm (ε 14000 $M^{-1}.cm^{-1}$)} (**Table 4**).

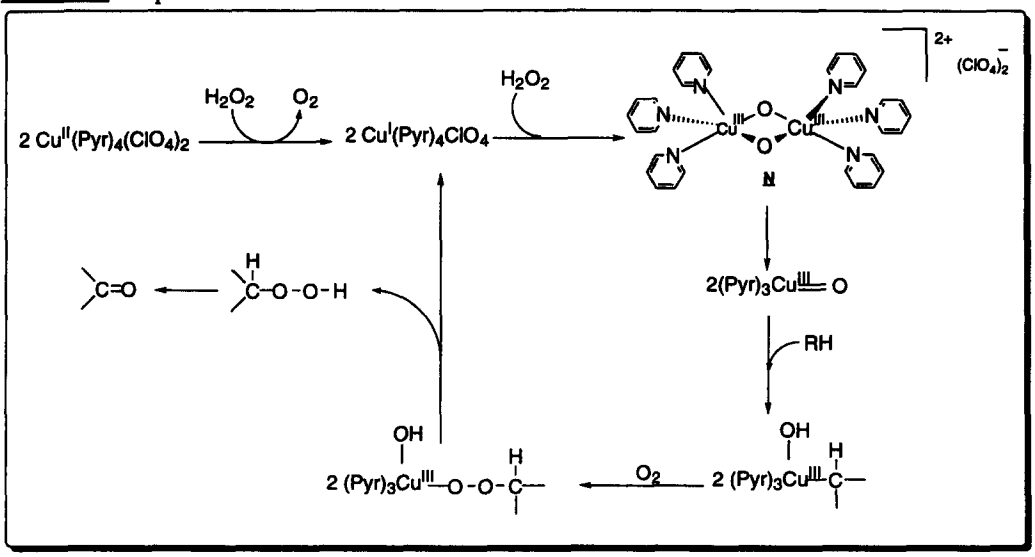
Table 4: Comparison of the characteristics of the known complexes described in the literature with our species.

Complex	Uv-Vis λ_{max} nm (ε $M^{-1}.cm^{-1}$)
	360 (20000), 510 (1000)[17,18]
	318(12000), 430 (14000)[18]
	335 (7077), 472 (3492)

When reaching a conclusion, we considered the following facts: our species is a Cu^{III} complex, its uv-visible characteristics (λ_{max}= 335 nm (ε 7077 $M^{-1}.cm^{-1}$), 472 nm (ε 3490 $M^{-1}.cm^{-1}$)) are similar to the bis oxo complex described by Que and Tollman. This complex did not react with PPh_3 neither did our complex. Therefore by analogy we propose the structure N described in **Table 4**. The next step involves a Cu^{III} oxenoid species which has already been proposed by Maumy.[19] The alkane is then activated to give a Cu^{III}-carbon bond. We have already reported good evidence for such a bond[20] based on ^{13}CO absorption and relatively good yields of carboxylic acid using CO. The presence of a higher valence state of copper was demonstrated by running the reaction in methanol to afford the methyl ester or in water to give the appropriate acid. In this earlier article[20] we had written Cu^{IV}, qualified as a formalism, for a higher oxidation state of copper. Now we can be sure that it is

Cu^{III} that is involved. In the absence of CO it is oxygen which is inserted into the copper-carbon bond in agreement with hydroperoxide formation. In the case of the iron-carbon bond, the original evidence was not as strong as for the Cu-carbon bond because the yield with carbon monoxide was lower, but easily detected. Later work[21,22] has established much more firmly the insertion of carbon monoxide into the iron-carbon bond also.

Scheme 1: Proposed mechanism



Influence of various ligands on the ratio of ketone to oxygen

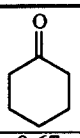
In order to optimize the formation of ketone against oxygen, we studied the influence of numerous ligands. The addition of 2 equivalents of tetramethyl-1,1,3,3-guanidine and of N-*tert*-butyl tetramethyl-1,1,3,3-guanidine inhibits the ketone formation but 5 mmol of oxygen were produced. The same result was obtained in the iron system. They are strong bases and can change the pH of the reaction mixture and thus increase the concentration of HO_2^- and increase the reaction rate.

Different carboxylic acids such as picolinic acid, 3-hydroxypicolinic acid, pyridine-2,6- dicarboxylic acid and isoquinoline-1-carboxylic, known to reduce oxygen formation in the case of the oxidation of alkane in presence of iron,[14] have been tested in the copper system. Here, unlike the results obtained in the Fe^{III} system, inhibition of both ketone and oxygen formation were seen. The formation of a stable complex between copper, the nitrogen of the aromatic ring and the carboxylic group in α position to the aromatic N-atom, avoids any coordination, and any activation, of H_2O_2 and the alkane.

No significant improvement has been noticed with the addition of many ligands such as: 2,2'-bipyridine, 2,2'-biquinoline, phenanthroline, 2,2':6',2''-terpyridine, L-cysteine, sarcosine, phthalazine, imidazole, 3-amino

pyrazine-2-methylcarboxylate, 2-amino-pyrimidine and 2-hydroxybenzoic acid (**Table 5**). The ketone and oxygen formation remain competitive. The ketone over oxygen ratio is hardly different from one to another (from 0.14 to 0.21). The active species seems to be similar in all these experiments.

Table 5: Formation of ketone and oxygen

Ligand		O_2	OP left	Ketone/O_2
2,2'-bipyridine[a]	0.67	2.99	0.21	0.22
2,2'-biquinoline[a]	0.53	2.57	0.00	0.20
phenanthroline[a]	0.58	2.50	0.70	0.23
2, 2':6', 2''-terpyridine[a]	0.52	2.23	1.05	0.23
3-amino-pyrazine-2-methylcarboxylate[b]	0.10	0.61	0.00	0.16
imidazole[b]	0.11	0.45	0.00	0.24
2-hydroxy-benzoic acid[b]	0.07	0.62	0.48	0.11
L-cysteine[b]	0.10	0.45	0.27	0.23
sarcosine[b]	0.09	0.62	0.34	0.14
2-amino-pyrimidine[b]	0.09	0.58	0.00	0.16
phthalazine[b]	0.11	0.62	0.00	0.23

a: Cyclohexane 10 mmol, $Cu(ClO_4)_2 6H_2O$ 0.2 mmol, ligand 0.4 mmol, **H_2O_2 5x2 mmol** each 15 min, Pyr 33 ml.
b: cyclohexane 10 mmol, $Cu(ClO_4)_2 6H_2O$ 0.2 mmol, ligand 0.4 mmol, **H_2O_2 2 mmol**, Pyr 33ml. All the results are in mmol.

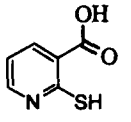
Nevertheless it is interesting to note the importance of the position of the carboxylic group relative to the aromatic N-atom. Isoquinoline-1-carboxylic acid completely inhibits the reaction (**Table 6**). Quinoline-2-carboxylic acid (quinaldic acid) shows some activity and quinoline-3-carboxylic acid is more active. In the latter case the carboxyl group is β to the aromatic nitrogen group which prevents any complex with copper to be formed. A similar relationship applies for nicotinic acid. In contrast picolinic acid forms so strong a complex that no reaction at all takes place.

Table 6 : Position of the carboxylic acid compared to the aromatic N-atom

Ligand		O_2	OP left
isoquinoline-1-carboxylic acid	0.00	0.00	1.93
quinoline-2-carboxylic acid	0.05	0.34	0.75
quinoline-3-carboxylic acid	0.10	0.72	0.14
picolinic acid	0	0	2.00
nicotinic acid	0.097	0.76	0.1

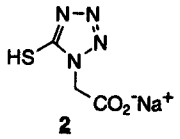
Cyclohexane 10 mmol, $Cu(ClO_4)_2 6H_2O$ 0.2 mmol, ligand 0.4 mmol, H_2O_2 2 mmol, Pyr 33 ml. All the results are in mmol.

Mercapto-2-nicotinic acid (1)and 5-mercapto-1-tetrazoleacetic acid (2) are the only two ligands, we have found, allowing a restricted amount of oxygen while the cyclohexane is oxidized to cyclohexanone (**Table 7**). The reason becomes clear when looking at the characteristics of both ligands: they present a thiol group with a carboxylic group in α position. The copper is then complexed with the sulfur atom and the carboxylic group.



1

2-mercapto-nicotinic acid



2

5-mercapto-1-tetrazole-acetic acid

Table 7: Ligand characteristics

Ligand		O_2	OP left	Ketone/O_2
5-mercapto-1-tetrazole acetic acid 2[c]	0.10	0.00	0.00	-
2-mercapto-nicotinic acid 1[c]	0.20	0.00	0.00	-
2-mercapto-nicotinic acid 1[d]	0.59	0.48	2.81	1.23
2-mercapto-pyridine[d]	0.53	1.85	0.00	0.28
2-mercapto-benzoic acid[d]	0.54	1.42	0.60	0.38

[c] Cyclohexane 10 mmol, $Cu(ClO_4)_2 6H_2O$ 0.2 mmol, ligand 1 mmol, **H_2O_2 2 mmol**, Pyr 33 ml. [d] Cyclohexane 10 mmol, $Cu(ClO_4)_2 6H_2O$ 0.2 mmol, ligand 1 mmol, **H_2O_2 10 mmol**, Pyr 33 ml. All the results are in mmol.

Comparing the results obtained with mercapto-2-nicotinic acid (1), mercapto-2-pyridine and the mercapto-2-benzoic acid, reveals the importance of a simultaneous presence, within a single ligand, of a free aromatic N-atom, a thiol group and a carboxylic group (**Table 7**).

CONCLUSION

The oxidation of saturated hydrocarbons using copper salts in pyridine is not as efficient as the corresponding iron based process. In most cases oxygen generation has priority over ketonisation of the hydrocarbons.

Evidence has been presented for the role of a Cu^{I}-Cu^{III} manifold in the formation of ketone and of oxygen. There is no evidence for a Cu^{II}-Cu^{IV} manifold and indeed Cu^{II} salts are reduced to Cu^{I} salts by hydrogen peroxide.

EXPERIMENTAL

General Procedure for Cu^{II} or Cu^{I} experiments.

The copper salt (0.2 mmol) and the cyclohexane (10 mmol) were dissolved in pyridine (33 ml). The solution was cooled down to 0°C before adding H_2O_2 (2 mmol). All yields were determined by G.-C. using a Hewlett Packard 5890 series II instrument equipped with flame ionisation detectors, with N_2 as a carrier gas. The column used for chromatography was a DB-Wax (30m X 0.32 mm, 0.25µm). In order to quantify the products, a basic work-up was made: a 1 ml aliquot of the reaction mixture was taken and poured into $NaHCO_3$ saturated solution and extracted with ether. The organic phase was dried over $MgSO_4$, filtered and analysed by G.-C. after the introduction of an appropriate standard (Naphtalene).

Quantification of Cu^{I}.[10]

A 1 ml aliquot of the reaction mixture was put in a 10 ml volumetric flask and completed with 9 ml of a solution of 2,2'-biquinoline (0.19 mmol in 250 ml of 1-pentanol). The mixture was shaked and the uv absorbance measured (ε=340, λ=516 nm).[10]

Iodometric titration of Cu^{III}.

To a degassed mixture of 5 ml of H_2O and 5 ml of acetic acid, the copper species N (1.08 µmol) and potassium iodide (0.3g) were added simultaneously. The solution was stirred under argon during 30 minutes before titration with a $Na_2S_2O_3$ solution. The amount found was 2.066 µmol; according to the theory it should have been 2.16µmol for a Cu^{III} species and 1.08µmol for a Cu^{II} species. So we concluded that N was a Cu^{III} species.

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