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The Functionalization of Saturated Hydrocarbons. Part XIX+. Oxidation of Alkanes by H_2O_2 in Pyridine Catalyzed by Copper(II) Complexes. A Gif-Type Reaction.

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Abstract: The Cu^{II}-catalyzed oxidation of saturated hydrocarbons by hydrogen peroxide proceeds in pyridine-acetic acid solutions affording mainly ketones as the reaction product. The conversion of hydrocarbon is about 20-30 %. This system (called GoChAgg) shares with the Fe^{III}-catalyzed system ($GoAgg^{II}$) its unusual chemical characteristics.

INTRODUCTION

In a series of papers[1] we have developed what we call Gif systems for the oxidation of saturated hydrocarbons. All of these systems are based on an iron-containing catalyst. They involve a pyridine-acetic acid solution of the hydrocarbon, and oxygen (with Fe^{II} and Zn powder as electron source) or hydrogen peroxide (with Fe^{III}) as the ultimate oxidant. The main features of all Gif systems are: *i*) the oxidation of *sec.* C-H bonds occurs mainly to ketones, alcohols are not reaction intermediates; *ii*) the excess of alcohols or other easily oxidizable compounds does not suppress significantly the oxidation of alkanes[2]; *iii*) cyclic olefins are not epoxidized, but yield conjugated ketones[3]; *iv*) the selectivity order for C-H bonds is *sec.* > *tert.* ≥ *prim.*; *v*) *sec.* alkyl radicals are not intermediates in the activation process; the reacion proceeds smoothly, even in the presence of different radical trapping reagents (which do not interfere with the activation process but yield functionalised hydrocarbons). Other systems, based on a copper-containing catalyst were discovered as well[4,5]. The first three of those characteristics were also found for the oxidation with copper catalysis. In this paper we present the results of a detailed examination of the oxidation of saturated hydrocarbons with copper-based catalysts, showing that these systems display Gif-type reactivity. We propose to call this system GoChAgg and shall use this abbreviation below. All names of the Gif-family systems are geographically based[6], Ch comes from Chernogolovka (USSR), where this system was first discovered[4,5].

+ Part XVIII: Barton, D. H. R. and Doller, D., *Coll. Czech. Chem. Commun.*, in press.

EXPERIMENTAL

Chemicals. Unless otherwise stated all the chemicals were used as received from commercial sources. Pyridinium perchlorate was prepared by mixing equimolar amounts of pyridine and cold $HClO_4$ (10% in H_2O). The precipitated salt was filtered, washed with cold water and dried under vacuum. The authentic samples of adamantylpyridine derivatives were synthesized as described elsewhere[7].

General procedure. All reactions were conducted in an Erlenmeyer flask closed with a rubber septum, at room temperature. Unless otherwise stated the total amount of solvent used was 32.0 ml (28.0 ml Py + 5.0 ml HOAc or 32.0 ml Py). The iron or copper salt and the substrate were dissolved in the solvent, and the reaction was started by adding H_2O_2 (30% in H_2O). Although $Cu(ClO_4)_2.6H_2O$ was not completely soluble in dry pyridine, the addition of a small amount of water or H_2O_2 (in water) led to a homogeneous solution. The oxidations were considered to be complete when the reaction mixture gave a negative test for H_2O_2 (KI-starch). An aliquot of the reaction mixture was analyzed by GC after the work-up procedure (see below). All the reaction products were identified by comparison with an authentic specimen (GC and GC-MS analysis).

Work-up procedure. a) An aliquot of the reaction mixture (2.0 ml) was acidified with cold H_2SO_4 (5.0 ml, 20%). The mixture was extracted with ether (3x5 ml), the appropriate internal standard being added as an ethereal solution with the first portion of the ether. The combined ethereal extracts were washed with $NaHCO_3$ (2 ml, sat. sol.) and dried over $MgSO_4$. b) An aliquot of the reaction mixture (2.0 ml) was made alkaline by addition of NaOH (5 ml, 5% in water). The basic products were extracted with ether (2x5 ml). The work-up procedure followed as in a).

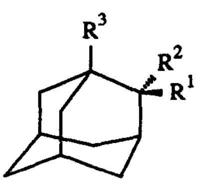
GC analysis. Gas chromatographic analyses were perfomed on a Chrompack model 439 or a Hewlett-Packard 5890 series II gas chromatograph, using a DB-5 or a DB-WAX capillary column (30 m. long, film thickness 0,25 μm for both of them, J&W Scientific). GS-MS analyses were carried out on a Hewlett-Packard 5790A gas chromatograph coupled to a Hewlett-Packard 5970 mass selective detector (70 eV, electron impact), using a methyl silicone column.

H_2O_2 was determined by iodometric analysis[8].

RESULTS AND DISCUSSION

Adamantane **1** has always been a key substrate in our studies as the C^2/C^3 ratio (defined as total oxidation products at the secondary position / total oxidation products at the tertiary position) allows one to draw conclusions on the regioselectivity of the process. An attack on any hydrogen with equal probability would give for C^2/C^3 a value of 3. When adamantane is oxidized under Gif^{IV} conditions [Zn powder, O_2(air), an Fe^{II} complex as catalyst, in pyridine-acetic acid-water as solvent] the products are adamantanone **2** (17.2%), *sec*-adamantanol **3** (1.25%), *tert*-adamantanol **4** (0.8%), and a mixture of *tert*-adamantyl pyridines **5** and **6** (total 16%), and hence C^2/C^3=1.1[9]. In oxidations by Fenton's reagent (H_2O_2: Fe^{II}, in equimolar amounts) the hydroxy radical ($HO^{\cdot}$) is accepted to be the reactive species[10]. When this reaction was carried out in a mixture of pyridine-acetic acid as the solvent, the ratio C^2/C^3 obtained was 1.7[11]. The oxidation of adamantane by H_2O_2-based reagents catalyzed by Fe^{III} (GoAgg systems) or Cu^{II} (GoChAgg systems) led to the same products as in Gif^{IV} (Table 1). The regioselectivity in these systems was the same as well, within the range of experimental error. The remarkable fact in all these reactions is that no *sec*-adamantyl pyridines **7** and **8** are found amongst the coupled products, but only those coupled at the *tertiary* position of adamantane **5** and **6**. These results show that secondary alkyl radicals are not involved in Gif-type reactions. Indeed, the reductant (Zn or Fe powder, Hg-cathode) and O_2 can be successfully replaced by H_2O_2 without loss of Gif-type selectivity, iron and copper complexes being both active catalysts. The real advantage of these H_2O_2-based systems is their homogeneity and, as a consequence, their high reproducibility.

Another very interesting substrate is *n*-hexane. The regioselectivity of its oxidation is well documented for different systems[11,12]. The ratio of oxidation products at position 1, 2 and 3 is usually very sensitive to any



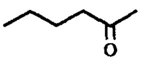
1 : R^1, R^2, R^3=H
2 : R^1,R^2=O, R^3=H
3 : R^1,R^3=H, R^2=OH
4 : R^1,R^2=H; R^3=OH
5 : R^1,R^2=H; R^3=*o*-pyridyl
6 : R^1,R^2=H; R^3=*p*-pyridyl
7 : R^1,R^3=H; R^2=*o*-pyridyl
8 : R^1,R^3=H; R^2=*p*-pyridyl

Table 1. Oxidation of Adamantane **1** (4.8 mmol) by H_2O_2 (13 mmol) in Pyridine Catalyzed by $FeCl_3.6H_2O$ (0.1 mmol) or $Cu(ClO_4)_2.6H_2O$ (0.2 mmol)

System	**2**	**3**	**4**	**5**	**6**	**7**	**8**	Σ	Σ	C^2/C^3
				mmol.10^2				mmol.10^2	%	
GoAgg^{III}	10.5	4.5	6.0	4.5	4.5	0.6	0.45	31.5	6.5	1.1
Fe^{III}, $HClO_4$ (15 mmol)	6.9	1.2	3.6	3.3	1.8	--	--	16.8	3.5	0.9
Cu^{II}, $HClO_4$ (15 mmol)	9.6	7.8	0.9	14.6	5.1	*traces*	0.3	26.1	5.4	0.7
Cu^{II}, AcOH (40 mmol)	4.2	0.9	4.5	← 0.6 →				10.2	2.1	1.0

Table 2. Oxidation of *n*-hexane (4.5 mmol) by H_2O_2 (13 mmol) in Pyridine Catalyzed by $FeCl_3.6H_2O$ (0.1 mmol) or $Cu(ClO_4)_2$.$6H_2O$ (0.2 mmol).

System	Σ	Σ	C^1 (13)	C^2 (9+11)	C^3 (10+12)	C^2/C^3	C^1/C^2
	mmol	%		%			
GoAgg^{II}	0.44	10	6.0	50	44	1.1	0.12
Fe^{III}, $HClO_4$ (15 mmol)	0.31	6.9	6.0	46	48	1.0	0.09
Cu^{II}, AcOH (40 mmol)	0.24	5.3	4.0	47	49	1.0	0.09
Cu^{II}, $HClO_4$ (15 mmol)	0.36	8.0	3.4	51	46	1.1	0.07



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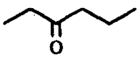

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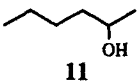

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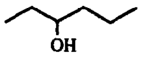

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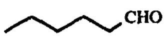

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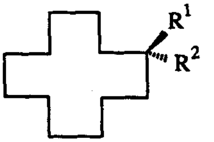
steric factors and the ratio C^2/C^3(where C^2 is defined as the amount of oxidation products at carbon 2, etc.) depends upon electronic factors. The major reaction products in this case were ketones **9** and **10**, although alcohols **11** and **12** and hexanal **13** were also detected (Table 2). Again, the regioselectivities observed for different catalysts are very similar. The low value for the ratio C^1/C^2 (<0.1) shows the absence of any significant steric hindrance on the active species, and suggests that its reactivity is related to the C-H bond energy. The value C^2/C^3, close to 1, indicates the electrophilic nature of the active species.

Cyclododecane **14** is a very convenient substrate for the study of Gif reactions, for the low volatility of the substrate itself and the oxidation products allows excellent mass balances. The main product of the oxidation in GoChAgg system is cyclododecanone **15**, cyclododecanol **16** being observed either in trace amounts or with smaller yields than in GoAgg systems. The mass balance is almost quantitative, and hence no other products are formed in the process. Cyclododecyl pyridines **17** and **18** were not found amongst the reacion products, not even in trace amounts.

We first studied the effect of different counterions (ligands) in Cu^{II} salts and the concentration of the catalyst on the reaction yield. The yield appeared not to be very sensitive to the nature of the anion and to the amount of cupric salt used (Tables 3 and 4). Cupric chloride and sulphate are poorly soluble in dry pyridine, but the solution becomes homogeneous upon addition of hydrogen peroxide. The reaction rate increases when the concentration of the catalyst is higher, but the final yield was independent of the amount of catalyst present. The rates for ketone formation and hydrogen peroxide decomposition vary in a wide range when



14 : $R^1, R^2 = H$
15 : $R^1, R^2 = O$
16 : $R^1 = H$; $R^2 = OH$
17 : $R^1 = H$; $R^2 = o$-pyridyl
18 : $R^1 = H$; $R^2 = p$-pyridyl

Table 3. Oxidation of Cyclododecane **14** (3.6 mmol) with H_2O_2 (9.5 mmol) in Pyridine Catalyzed by Copper Salts (0.3 mmol). Effect of the Counterion.

Catalyst	**14**[a]	**15** mmol	**16**	Σ mmol	Σ %	Mass Balance %
$Cu(ClO_4)_2$	3.17	0.40	*traces*	0.40	11.0	100
$Cu(OAc)_2$	3.05	0.32	*traces*	0.32	9.0	94
$CuSO_4$[b]	3.22	0.35	*traces*	0.35	9.7	100
$CuCl_2$[b]	3.15	0.42	*traces*	0.42	11.7	100

a. Recovered starting material.
b. Salt is not completely soluble in dry pyridine.

Table 4. Oxidation of Cyclododecane **14** (2.0 mmol) with H_2O_2 (19 mmol) in Pyridine Catalyzed by $Cu(ClO_4)_2.6H_2O$. Effect of the catalyst concentration.

$Cu(ClO_4)_2.6H_2O$	**14**[a]	**15** mmol	**16**	Σ mmol	Σ %	Mass Balance %
0.055	1.75	0.24	0.03	0.27	13.5[a]	101
0.150	1.54	0.29	0.02	0.31	15.5	93.0
0.300	1.65	0.35	0.02	0.37	18.5	101
0.600	1.64	0.35	0.03	0.38	19.0	101
1.400	1.62	0.32	0.05	0.37	18.5	99.5

a. Recovered starting material.

different ligands are added to the reaction mixture. The effect of picolinic acid is remarkable. Unlike the Fe^{III}-based system, where it speeds up the reaction rate up to fifty times[13], in the Cu^{II}-based system picolinic acid slows down both the oxidation rate and the hydrogen peroxide decomposition (Figure 1). The half-lives for the ketonisation process are 34 min (no ligand added), 105 min (Cu:Picolinic acid=2:1), and 25 hs (Cu:Picolinic acid=1:1).

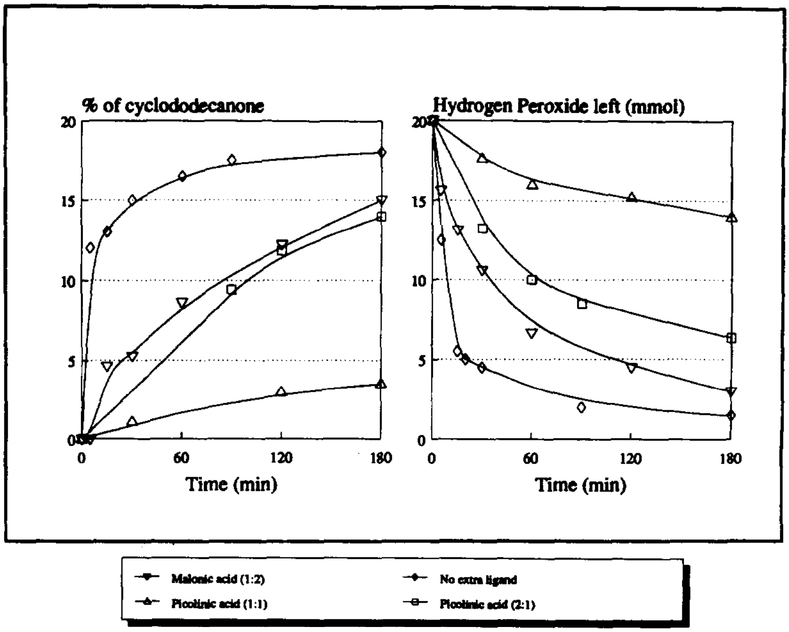


Figure 1. Kinetics of cyclododecane 14 (5.0 mmol) oxidation and hydrogen peroxide decomposition in GoChAgg systems with different ligands added (Cu:ligand ratio). Py=28.0 ml, AcOH=2.3 ml, Cu(OAc)$_2$=0.4 mmol.

The amount of ketone obtained can be easily improved by using more substrate, the conversion of hydrocarbon remaining mostly unchanged (Table 5). The conversion increases when more hydrogen peroxide is used, the yield based on the oxidant becoming worse. The selectivity of the oxidation to ketone is still very high at a conversion of about 30%, although overoxidation products (cyclododecyl diketones)[2] are seen at this conversion (Table 6).

From these data it is clear that a competitive oxidation of the substrate and the solvent (pyridine) occurs in this system. In order to improve the yield and to avoid the oxidation of the solvent, part of the pyridine was replaced by the less easily oxidizable acetonitrile (Table 7). The results indicate that at least two thirds of the pyridine could be replaced by acetonitrile without losing the Gif-type selectivity, but pyridine is essential and must be present in the system.

All original Gif systems include a carboxylic acid, mainly acetic acid, as a component of the reaction mixture. This acid plays a very important role in the process of metal powder dissolution; in the absence of acid the metal (Fe^0 or Zn^0) is stable and no oxidation occurs. The function of acetic acid in these oxidative systems has been explained through the formation of a specific solvent matrix, the ratio Py:AcOH being

Table 5. Oxidation of Cyclododecane 14 with H_2O_2 (9.5 mmol) in Pyridine Catalyzed by $Cu(ClO_4)_2.6H_2O$ (0.3 mmol). Effect of Substrate Concentration.

$[14]_0$ mmol	14[a]	15 mmol	16	Σ mmol	Σ %	Mass Balance %
0.55	0.51	0.03	--	0.03	5.9	98.0
1.10	1.02	0.08	0.01	0.08	7.3	100
2.50	2.20	0.24	0.02	0.26	10.4	98.0
4.30	3.97	0.34	0.03	0.37	8.6	101
5.80	5.17	0.55	0.05	0.60	10.3	99.0

a. Recovered starting material.

Table 6. Oxidation of Cyclododecane 14 (2.2 mmol) with H_2O_2 in Pyridine Catalyzed by $Cu(ClO_4)_2.6H_2O$ (0.3 mmol). Effect of the Amount of H_2O_2.

H_2O_2 mmol	14[a]	15 mmol	16	Σ mmol	Σ %	Mass Balance %
1.9	2.11	0.06	*traces*	0.06	2.7	98.5
3.9	2.12	0.09	*traces*	0.09	4.1	100.5
9.5	2.02	0.21	0.01	0.22	10.0	99.5
39.0	1.35	0.57	0.07	0.64	29.1	90.5[b]

a. Recovered starting material.
b. Cyclododecyl diketones are formed.

highly important[11]. Indeed, the reaction rate of the Cu^{II}-catalyzed process was very sensitive to this ratio. The GoChAgg reaction was very fast ($\tau_{1/2}$ of *ca.* 3 min.) in the absence of acetic acid. However, with a AcOH:Py ratio of 1.5 (V/V) the reaction was not complete after 1 day. The yield and selectivity (ketone to alcohol ratio) did not depend significantly on the amount of carboxylic acid present (Table 8). Moreover, when a $GoAgg^{II}$ reaction is run in the absence of AcOH the decomposition of H_2O_2 to O_2 occurs very fast, before the homogenization of the mixture (during the addition of hydrogen peroxide) could take place. Then, the yield of the ketonisation process seems to decrease in the absence of AcOH. However, when the concentration of the catalyst is decreased, and hence the rate of H_2O_2 decomposition is lower, one could observe the weak dependence of the oxidation yield on AcOH in the $GoAgg^{II}$ system.

The strong dependence of the reaction rate on the amount of AcOH can be explained by postulating the formation in the reaction mixture of different complexes between Fe^{III} and Cl^-, Py, AcO^-, and H_2O, with comparable stability, whose nature (and hence the catalytic activity of the whole system) varies with the amount of AcOH. This explanation is supported by the weak influence of the amount of AcOH on the $GoAgg^{III}$ reaction rate, where picolinate is the strongest ligand available in solution (Table 9). Nevertheless, the oxidation yield is practically constant in a wide range of Py:AcOH ratios, suggesting that the reaction leading to hydrocarbon oxidation is not too sensitive to its variation.

The carboxylic acid might be needed not only as a ligand for the assembling of the catalyst active towards hydrocarbon oxidation, but also could supply the protons which would be important in the formation

Table 7. Oxidation of Cyclododecane 14 (0.9 mmol) in Pyridine-Acetonitrile Mixtures. H_2O_2=4.3 mmol; $Cu(ClO_4)_2.6H_2O$=0.03 mmol; $HClO_4$=2.5 mmol.

Py	CH_3CN	Py/ CH_3CN	Py/14	14[a]	15	16	Σ	Σ	Mass Balance
ml (mmol)	ml (mmol)	mol/mol	mol/mol		mmol		mmol	%	%
11.0 (136)	0 (0.0)	---	151	0.77	0.13	0.02	0.15	16.7	102
8.5 (105)	2.5 (48)	2.2	117	0.75	0.15	0.02	0.17	18.9	102
6.0 (74)	5.0 (96)	0.8	82	0.72	0.18	0.02	0.20	22.2	102
3.5 (43)	7.5 (144)	0.3	48	0.71	0.20	0.02	0.22	24.4	103
1.0 (12)	10.0 (192)	0.06	13[b]	0.67	0.20	0.04	0.24	26.7	101

a. Recovered starting material.
b. Cyclododecane was not completely soluble in the reaction mixture.

Table 8. Oxidation of Cyclododecane 14 (2.0 mmol) in GoChAgg System for Differents Py/AcOH Ratios. $Cu(ClO_4)_2.6H_2O$=0.3 mmol.

AcOH	Py	14[a]	15	16	Σ	Σ	Mass Balance
ml	ml		mmol		mmol	%	%
0	33.0	1.88	0.18	0.03	0.21	10.5	104
1.0	32.0	1.95	0.20	0.03	0.23	11.5	109
2.0	31.0	1.82	0.21	0.03	0.24	12.0	103
5.0	28.0	1.82	0.22	0.03	0.25	12.5	103
11.0	22.0	b	0.20	0.02	0.22	11.0	b
20.0	13.0	b	0.13	0.02	0.15	7.5[c]	b

a. Recovered starting material.
b. not determined.
c. The reaction is not complete after 1 day.

Table 9. Oxidation of Cyclododecane 14 (2.0 mmol) in $GoAgg^{III}$ System for Differents Py/AcOH Ratios. $FeCl_3.6H_2O$=1.0 mmol, Picolinic Acid=1.0 mmol. Reaction Time=1 Day.

AcOH	Py	14[a]	15	16	Σ	Σ	Mass Balance
ml	ml		mmol		mmol	%	%
0.0	33.0	1.38	0.36	0.06	0.42	21.0	91
1.0	32.0	1.45	0.35	0.08	0.43	21.5	94
2.0	31.0	1.52	0.35	0.07	0.42	21.0	97
5.0	28.0	1.51	0.37	0.07	0.44	22.0	98
11.0	22.0	1.59	0.30	0.07	0.37	18.5	98
20.0	13.0	1.68	0.22	*traces*	0.22	11.0	98

a. Recovered starting material.

of the reactive species. Therefore, we have studied the GoChAgg oxidation at different concentrations of Py.$HClO_4$, a very strong acid in pyridine (Table 10). The reaction rate went down with increasing amounts of acid, the yield and selectivity remaining constant, as in the case of acetic acid. These facts could be explained considering that in the absence of any rather strong acid, a significant part of hydrogen peroxide in pyridine exists as the more reactive HO_2^- anion. This anion is protonated by acids and the total rate of the process decreases. This smooth dependence of the rate of H_2O_2 decomposition on the acidity was observed in $GoAgg^{III}$ system.

Table 10. Oxidation of Cyclododecane 14 (1.94 mmol) in GoChAgg System. Effect of the Amount of Py.$HClO_4$. H_2O_2=19 mmol; $Cu(ClO_4)_2.6H_2O$=0.3 mmol.

Py.$HClO_4$	14[a]	15	16	Σ	Σ	Mass Balance
mmol		mmol		mmol	%	%
0.0	1.59	0.34	0.02	0.36	18.0	95.0
1.0	1.51	0.42	0.03	0.45	22.5	101
2.0	1.50	0.38	0.03	0.41	20.5	98.5
4.0	1.46	0.38	0.03	0.41	20.5	97.0
6.0	1.48	0.37	0.03	0.40	20.0	97.0
8.0	1.35	0.34	0.02	0.36	18.0	88.0[b]

a. Recovered starting material.
b. The reaction mixture was not homogeneous.

In regular experiments hydrogen peroxide is used as a 30% aqueous solution, and water itself could play an important role in this chemistry since μ-oxo dimeric species are postulated as active catalysts for the ketonisation process[14]. In all the systems studied in this work hydrogen peroxide is decomposed to water, so that it is experimentally difficult to get rid of it completely. In order to study the effect of the water content in our systems we used a small amount of practically 100% H_2O_2. Interestingly, we found different patterns for $GoAgg^{III}$ and GoChAgg systems (Figure 2). In the presence of an iron complex the reaction yield did not depend on the amount of water added, although a small influence is seen in the ratio ketone to alcohol[6]. With the copper complex the yield increased significantly with the addition of water. This fact was rather important for GoChAgg system because regularly the oxidation yield was about twice lower than in GoAgg, and it could reach a higher value if the proper amount of water is added. There is no reasonable explanation of this observed fact yet, although more water might be necessary for the formation of a μ-oxo dimeric active species in the case of copper-catalysts than for iron-catalysts.

CONCLUSIONS

The experiments carried out so far have shown that the Cu^{II}-catalyzed oxidation of saturated hydrocarbons by H_2O_2 shares many of the unusual chemical properties of the Fe^{III}-catalyzed process. The main reaction product are ketones, and the reaction yields are comparable. The regioselectivity of both processes seems to be the same (*sec.* > *tert.* ≥ *prim.*). Both reaction rates are very sensitive towards the influence of ligands, although the effect of one ligand is not necessarily the same in both systems (*e.g.* picolinic acid).

Water has a different effect in GoAgg reactions than in GoChAgg reactions. In the former system, there is a small, but detectable and reproducible, decrease in the ketone to alcohol ratio, without much change in the total oxidation yield. For the latter, a remarkable increase in the reaction yield was observed, but still no alcohol was formed.

The similarities between Cu^{II} and Fe^{III} chemistries and their relationship with many enzymatic catalytic oxidations[15] suggest mechanistic studies to be carried out in order to gain a deeper understanding of the subject.

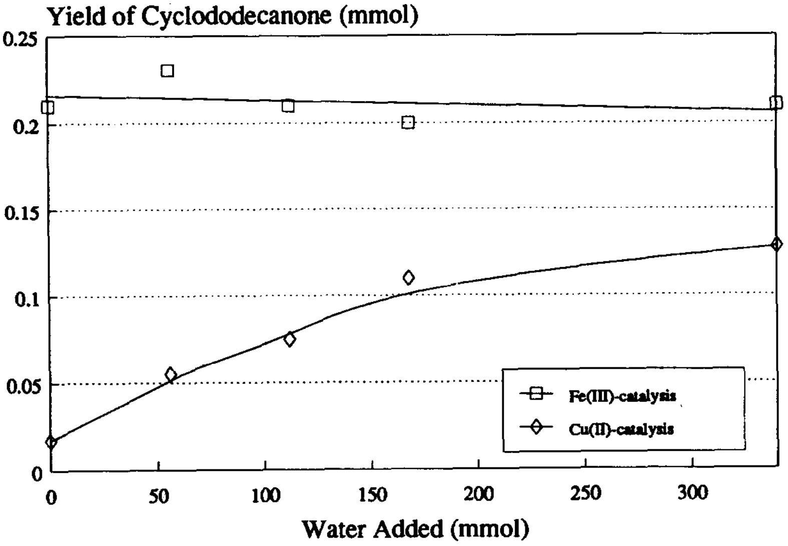


Figure 2. Effect of water added to GoAgg^{III} (Fe^{III}-catalyzed) and GoChAgg (Cu^{II}-catalyzed) reactions on the yield of cyclododecane oxidation by H_2O_2 (>98%, 5.9 mmol).
GoAgg^{III}: Py=28.0 ml, AcOH=5.0 ml, $FeCl_3.6H_2O$=0.2 mmol, picolinic acid=0.6 mmol, 14=1.81 mmol.
GoChAgg: Py=33.0 ml, $Cu(AcO)_2$=0.3 mmol, 14=2.19 mmol.

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