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FUNCTIONALISATION OF SATURATED HYDROCARBONS. PART XVI[1]. CHEMOSELECTIVE OXIDATION

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Summary. Cyclododecane is efficiently oxidised under Gif^{IV} and $GoAgg^{II}$ conditions to give over 25% of cyclododecanone with some cyclododecanol. The addition in equimolar amounts of ethanol, isopropanol, ethylene glycol, diisopropyl ether, biphenyl, anisole, diphenyl sulfide, methyl benzoate and dimethylacetamide have little effect on the oxidation. Thiophenols have a minor effect, but *t*-butyl thiol and dimethylaniline reduce oxidation to a major extent. In all cases, the mass balances are satisfactory. Overoxidation of cyclododecanone affords cyclododecane-1,3-, 1,4-, 1,5- and 1,6-diones. The major dione is 1,4- followed by 1,6-.

The first practical Gif-type systems[2] were Gif^{III} (Fe° + catalyst + pyridine-acetic acid + oxygen) and Gif^{IV} (Fe^{II} or Fe^{III} catalyst + pyridine-acetic acid + Zn° and oxygen). The more efficient Gif-Orsay system replaces the Zn° in Gif^{IV} by the cathode of an electrochemical cell. $GoAgg^{I}$ uses stoichiometric Fe^{II} + KO_2 in pyridine-acetic acid under argon, whilst $GoAgg^{II}$ involves catalytic Fe^{III} + H_2O_2 in pyridine-acetic acid.[3] In all these systems, the acetic acid can be replaced by other carboxylic acids. All five systems seem to be based on the same ^{V}Fe oxenoid species which oxidises saturated hydrocarbons selectively to ketones and shows the unusual reactivity order sec. > tert. ≥ prim. for hydrocarbon substitution.[4]

Studies with adamantane provide evidence that the tertiary position is oxidised by a radical mechanism, but the secondary position is not.[3,4] Based on this and other observations, it was postulated that the ^{V}Fe oxenoid species affords firstly an iron-carbon bonded species which, when the iron-carbon bond is tertiary, may dissociate into radicals but in the secondary case, evolves into ketones.

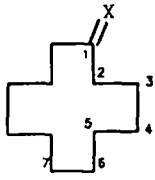
A comparison between the reactivity of radicals generated from the acyl derivatives of *N*-hydroxy-2-thiopyridone[5] and the application of the Gif^{IV} system to the appropriate hydrocarbon has confirmed the original conclusion.[6]

Nevertheless, a number of reagents, like diphenyl diselenide,[7] which are well known to react with radicals, also capture an intermediate in the

Gif^{III} and Gif^{IV} type reactions.

Another way to explore the chemoselectivity of these reactions is to oxidise selected saturated hydrocarbons in the presence of other substances well known to be more reactive towards radicals. In the case of radical intermediates, the saturated hydrocarbon should be oxidised less efficiently than the competitive additive.

A convenient hydrocarbon for this purpose was cyclododecane **1**. This is sufficiently non-volatile so that a good mass balance can be obtained with respect to the hydrocarbon and its oxidation products cyclododecanone **2** and cyclododecanol **3**.



1 X = H,H

2 X = O

3 X = H, OH

Table 1

1 mmol	n[a]	1 % recovered	2 %	3 %	2/3	Mass Balance
5	1	89	12.9	0.1	129	102
	2	76.8	21.5	0.72	30	99
	3	72	29.3	1.5	20	103
	4	63.8	32.1	3.3	9.7	99
10	1	84.7	11.9	0.3	40	97
	2	81.3	14.3	1.5	9.5	97
	3	78.6	17.4	2.0	8.7	98

[a]n is the number of additions of zinc powder and acetic acid that were made.

We started with Gif^{IV} and obtained the results recorded in Table 1. With 5 mmol and with 10 mmol of hydrocarbon and with repeated additions of Zn° and acetic acid, the hydrocarbon was smoothly oxidised to ketone with minor formation of alcohol. In each case, the mass balance was satisfactory.

Table 2

5 mmol **1** + co-substrate (mmol)	Recovered **1** %	**2** %	**3** %	Ketone / Alcohol	Mass Balance
(0)	76.5	21.5	0.7	31	99
EtOH (5.0)	72.0	21.4	1.5	14	95
$(CH_3)_2CHOH$ (5.0)	69.6	21.2	1.5	14	92.3
$(CH_2OH)_2$ (5.0)	68.4	22.2	3.3	6.7	94
$(CHMe_2)_2O$ (5.0) (oxygen under baloon)	79.8	20.4	1.3	16	102
Ph_2 (5.0)	69.8	21.8	1.2	18	93
PhOMe (5.0)	72.9	22.4	1.7	13	97
NEt_3 (5.0)	75.9	17.5	<1	>18	93.4
$PhCO_2Me$ (5.0)	68.5	22.1	<1	>22	90.6
CH_3CONMe_2 (5.0)	75.1	23.1	<1	>23	98.2
$(PhCMeOH)_2$ (5.0)	78.4	18.6	2.6	7.2	99.6
$PhNMe_2$ (1.0)	66.6	18.8	6.5	2.9	92
$PhNMe_2$ (2.0)	68.0	13.8	7.8	1.8	90
$PhNMe_2$ (5.0)	92.5	4.2	0	>>4.2	96.7
Ph_2S (5.0)	74.6	24.6	<1	>25	99
PhSH (0.5)	71.0	21.7	5.0	4.3	98
PhSH (2.0)	76.0	21.5	8.2	2.6	106
PhSH (5.0)	77.2	15.6	9.5	1.6	102
$o\text{-}OMeC_6H_4SH$ (5.0)	76.3	11.8	8.5	1.4	96.6
t-BuSH (5.0)	93.1	6.8	<1	>6.8	100

We now compared the standard oxidation above with that observed when the substrate was mixed with a series of compounds normally regarded as being more easily oxidised (Table 2). Thus, equimolecular ethanol, isopropanol and ethylene glycol had no effect on the oxidation of **1**.

We determined the conversion of the isopropanol (5 mmol) to acetone. In the presence of the hydrocarbon 14% of acetone was formed and 24% cyclododecane was oxidised. In the absence of **1** the conversion to acetone was 24%. The acetone was determined by 2,4-dinitrophenylhydrazone formation (double traps) and the appropriate isolation blank.

In a further experiment with 50 mmol of isopropanol and 5 mmol cyclododecane, 5.7% of acetone resulted as well as 13.7% of cyclododecanone and a trace of the corresponding alcohol.

Clearly, cyclododecanone is oxidised more easily than isopropanol, a very surprising result based on conventional knowledge. For the ethylene glycol experiment, 98% was recovered unchanged. So here the hydrocarbon is oxidised much faster.

A more sensitive test of selectivity was Gif^{IV} oxidation of cyclododecane in the presence of diisopropyl ether (Table 2). Again the yield of oxidation products was little changed even though the ether is readily autoxidised and has a weak C-H bond.

As a test of a possible electron transfer mechanism, we then examined the effect of biphenyl, anisole and triethylamine on the rate of oxidation. Biphenyl (97% recovery) and anisole had no significant effect on the oxidation process but triethylamine reduced the yield slightly. Methyl benzoate, dimethylacetamide and 2,3-diphenylbutane-2,3-diol also had little or no effect on the oxidation. The last named compound produced 5.6% of acetophenone.

N,N-Dimethylaniline is an easily oxidised compound.[8] Addition of an equimolar amount of this did reduce the oxidation of cyclododecane to only 4.2% of cyclododecanone. However, only 1 mmol of dimethylaniline had little effect on the cyclododecane oxidation, but there was 15% oxidation of dimethylaniline to *N*-formyl-*N*-methylaniline. For 2 mmol of dimethylaniline the total oxidation products were not changed greatly but the dimethylaniline was oxidised to the *N*-formyl derivative (20% of 2 mmols). On the 5 mmol scale, the *N*-formyl derivative was the principal oxidation product (19% of 5 mmol).

The results in Table 2 so far reported are incompatible with attack by an oxygen based radical or with a strongly electrophilic species (electron transfer). Further interesting results were obtained by addition of sulfur compounds. One of our original unusual observations[4] was that adamantane was oxidised in the usual way even in the presence of diphenyl sulfide. We have now repeated this experiment using cyclododecane and paying attention to the mass balance. The results in Table 2 show that diphenyl sulfide slightly increases the amount of oxidation of cyclododecane without itself being consumed (103% recovery). Thiophenol had little effect on the total

Table 3

5 mmol 1 + co-substrate (mmol)	Recovered 1 %	2 %	3 %	Ketone / Alcohol	H_2O_2 in Products %	Mass Balance
(0)	67.2	26	5.7	4.6	23	99
EtOH (5.0)	77	24.1	4.2	5.7	21	105
$(CH_3)_2CHOH$ (5.0)	75	23.4	5.3	4.4	21	104
$(CH_2OH)_2$ (5.0)	72.2	21.0	3.4	6.2	18	97
$(CHMe_2)O$ (5.0)	71	22.8	4.3	5.3	20	98
Ph_2 (5.0)	67	20.1	4.1	4.9	18	91
PhOMe (5.0)	72.9	21.1	4.8	4.4	19	99
NEt_3 (5.0)	80.7	11.4	3.7	3.1	11	96
$PhCO_2Me$ (5.0)	66.5	23.4	4.3	5.4	20	94
CH_3CONMe_2 (5.0)	71.2	21.2	3.6	5.9	18	96
$(PhCMeOH)_2$ (5.0)	69.5	22.8	4.4	5.2	20	97
$PhNMe_2$ (5.0)	83.6	9.7	8.0	1.2	11	101
Ph_2S (5.0)	70.4	23.2	5.6	4.1	21	99
PhSH (0.5)	78.4	15.0	4.7	3.2	14	98
o-$OMeC_6H_4SH$ (0.5)	71.2	13.7	6.6	2.1	14	92
t-BuSH (0.5)	86.4	10.9	2.3	4.7	10	100

oxidation, but it changed the ketone/alcohol ratio in favor of alcohol. Most of the thiophenol (72%) was recovered unchanged, but 8% of diphenyldisulfide was detected. When the thiophenol was reduced to 2 mmol, oxidation again proceeded normally, as did the reaction when only 0.5 mmol of thiophenol was added.

We also examined the effect of 2-methoxythiophenol with very similar results (Table 2). The 2-methoxythiophenol was largely (76%) converted to the corresponding disulfide with some unchanged 2-methoxythiophenol. It is again remarkable that the oxidation of the saturated hydrocarbon cyclododecane proceeds normally, except for a change in the ketone/alcohol ratio, even in the presence of easily oxidised thiophenols.

A larger inhibitory effect was shown by t-butyl mercaptan (Table 2). Here only ketone was produced in 7% yield and the hydrocarbon was recovered unchanged (93%). Thiophenols are more easily oxidised than ordinary thiols so this result is also unexpected.

Similar studies (Table 3) were then carried out using GoAgg^{II} system. Again ethanol, isopropanol and ethylene glycol did not effect the oxidation very much. Using 5 mmol of isopropanol, 26% was oxidised to acetone but when 5 mmol of cyclododecane was added (Table 3) the acetone formed (16%) was less than the nearly 29% oxidation of the cyclododecane. Again, diisopropyl ether and biphenyl had little effect on the oxidation. The latter was recovered to the extent of 95%. Anisole likewise did not change the reaction but triethylamine reduced the oxidation significantly. As before, methyl benzoate, dimethylacetamide and $(PhCMeOH)_2$ had no effect.

Dimethylaniline had a smaller influence in the GoAgg^{II} system than in Gif^{IV} (Table 2). It gave, however, more alcohol. Diphenylsulfide had no effect on the oxidation and was recovered unchanged (96%). Thiophenol and o-methoxythiophenol reduced the oxidation by about a half, comparable to their effects with Gif^{IV} (Table 2).

We have also studied the limits to the oxidation of cyclododecane. On a 5 mmol scale, both Gif^{IV} and GoAgg^{II} permit the preparation of 25-30% of cyclododecanone with some cyclododecanol. Further oxidation produces cyclododecanediones. This was shown by studying the further oxidation of cyclododecanone. Under Gif^{IV} or GoAgg^{II} conditions, a mixture of four diketones was formed as shown by GC-MS spectrum. By synthesis (see Experimental) it was shown that the 1,3- and 1,4-diones were present. Comparison with an authentic specimen proved the presence of the 1,6-dione. Comparison of the mixed diketals, formed in the usual way, with an authentic specimen of the 1,7-dione diketal[10] did not reveal the latter to be present (<0.2%). Synthesis of the 1,2-dione showed that this was not present either. Hence the fourth dione must be the 1,5-dione. Table 4 summarizes the results.

Table 4[a]

System	1,3-dione %	1,4-dione %	1,5-dione %	1,6-dione %	Mass Balance %
Gif^{IV}	0.5	5.7	1.1	1.8	85
GoAgg^{II}	1.4	8.7	2.4	6.0	98

[a] Oxidation of 5 mmols cyclododecanone under the conditions described in the experimental part.

These four diketones were also produced in the overoxidation of cyclododecane. Nevertheless, it is possible to obtain up to 22% cyclododecanone, easily separable from cyclododecane, in a preparative run.

Experimental

General: NMR spectra were recorded with Varian XL-200E and Varian Gemini-200 spectrometers for $CDCl_3$ solutions (δ scale; TMS as internal standard). The GC-MS instrument was a Hewlett Packard 5790A gas chromotograph connected to a Hewlett Packard 5970 mass selective detector (70 eV, electron impact). Exact mass measurements were carried out with a VG Analytical 70S high resolution double-focusing magnetic sector mass spectrometer with attached VG Analytical 11/250J data system. The IR spectra were measured with a Perkin-Elmer 881 spectrometer; only the most significant absorptions are listed. Analytical GC was performed on a Chrompack 437S equipped with a FID detector using a fused silica capillary column, CP-Sil-S CB, 20 x 0.22 mm i.d. (N_2 as carrier gas). Merck silica gel 60,230-400 mesh was used for column chromatography. Melting points were determined with a Kofler hot stage apparatus and are uncorrected.

General Procedure for Gif^{IV} Reactions. A solution of cyclododecane (0.84 g; 5.0 mmol) in pyridine (28 ml) containing $FeCl_2.4H_2O$ ($2.0x10^{-2}$ g; 0.2 mmol) and zinc powder (1.31g; 20 mg-at) was placed in a 125 ml Erlenmeyer flask open to air. The reaction was started by adding glacial acetic acid (2.3 ml; 40 mmol) and the solution was stirred for 7 hrs. at room temperature.
General Procedure for GoAgg^{II} Reactions. A solution of cyclododecane (0.84 g; 5.0 mmol) and $FeCl_3.6H_2O$ (2.7×10^{-2} g; 0.1 mmol) in pyridine (28 ml)-acetic acid (2.3 ml; 40 mmol) was placed in a 125 ml Erlenmeyer flask and deaerated with nitrogen for 20 min. The reaction was started by adding 30% aqueous solution of H_2O_2 (1.5 ml; 13 mmol) and stirred overnight at room temperature.
Workup and Analysis. An aliquot (2.0 ml) taken from the homogeneous reaction mixture was chilled and acidified by slow addition of cold 20% H_2SO_4 (5 ml). The mixture was extracted (3x5 ml) with ether. The ethereal extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$ and filtered. The resulting solution was analyzed by GC and GC-MS after addition of an internal standard.

The oven temperature for GC increased from an initial temperature (1 min) of 70° to 200° at a rate of 15°/min. The retention times (min) were as follows: 1.9 for naphthalene (internal standard), 3.1 for cyclododecane, 4.4 for cyclododecanone, 4.7 for cyclododecanol, 5.0 for 1,3-dione, 5.3 for

1,4-dione, 5.4 for 1,6-dione and 5.8 for 1,5-dione.

The GC-MS obtained at 75° to 220° (15°/min) showed the molecular ion peak (m/z=196) for all the diketones detected.

Quantification of Cyclododecane and Cyclododecanone by Isolation. The GoAgg[II] oxidation of cyclododecane (5.0 mmol) was carried out as described above. To the clear brown solution, ether (30 ml) and water (10 ml) were added. The chilled mixture (ice-bath) was acidified with cold 50% H_2SO_4. After separation of layers, the aqueous phase was extracted with ether (2x30 ml), washed with water and saturated $NaHCO_3$. One-third of the dried ($MgSO_4$) ethereal extract was evaporated to dryness under reduced pressure. The crystalline residue (285 mg) was passed through a silica column (1.8 x 7.0 cm) using hexane-ether (12:1) as an eluent. The first 25 ml of the eluate gave 202 mg (72.1%) of >99% (GC) pure cyclododecane. 66.0 mg (21.5%) of 99% (GC) pure cyclododecanone was obtained from evaporation of the next 30 ml of the eluate.

The Preparation of Cyclododeanediones. 1,2- and 1,3-Cyclododecanediones were prepared according to known methods.[11]

Cyclododecene-3,12-diol. To a solution of cyclododecene (9.96 g; 60 mmol) in carbon tetrachloride (100 ml) N-bromosuccinimide (21.3 g; 120 mmol) was added. After addition of benzoylperoxide (0.5 g; 2.0 mmol) the mixture was allowed to stand at room temperature for 1 hr. then refluxed for 80 min. The succinimide formed was filtered and washed with carbon tetrachloride. The filtrate was evaporated to dryness under vacuum to give 19.9 g. of an oily residue.

GC-MS analysis showed that isomeric mixtures of the dibromides constitute about 50% of the oily residue. An acetone solution (240 ml) of this mixture was refluxed for 2 hrs. after addition of water (160 ml) and $NaHCO_3$ (25 g). Then, the acetone was evaporated and the aqueous solution was extracted (4x150 ml) with ether. The combined ether extracts were washed with water, dried ($MgSO_4$) and concentrated to about 100 ml. Keeping the concentrate refrigerated overnight resulted in deposition of white crystals which were filtered and recrystallized from methanol (630 mg; 5.4%), mp. 165.5-167°C. ^{1}H-NMR δ: 5.75 (dd,2H), 4.30 (m,2H), 1.2-1.7 (m,16H); ^{13}C-NMR δ: 133.6, 71.8, 34.8, 25.2, 24.7, 21.7; IR (nujol) ν: 3285, 3207, 1012 cm^{-1}; MS m/z (% intensity): 198 M^+ (4), 180 M^+-H_2O (5), 162 M^+-2H_2O (3), 141 (20), 113 (100), 95 (46), 82 (53), 67 (65), 57 (97), 55 (92).

Cyclododecene-3,12-dione: Cyclododecene-3,12-diol (0.2 g; 1.0 mmol) was dissolved in chloroform (25 ml) and activated MnO_2 (2.0 g; 23 mmol) was added. The mixture was stirred vigorously at room temperature for 48 hrs. then filtered through a short silica gel column which was washed with hot chloroform (20 ml). After evaporation of solvent, pale yellow crystals

separated (63 mg; 32%) were recrystallized (hexane), mp. 78.5-80°C (subl.). ^{1}H-NMR δ: 6.98 (s,2H), 2.59 (m, 4H), 1.65-1.82 (m,4H), 1.15-1.50 (m, 8H); ^{13}C-NMR δ: 204, 138, 39.3, 24.9, 24.7, 24.3; ms m/z (% intensity): 194 M^{+} (3), 166 (1.5), 135 (8), 121 (11), 107 (9), 97 (68), 93 (10), 82 (56), 69 (28), 55 (100).

Cyclododecane-1,4-dione: To a pyridine (2.0 ml) solution of cyclododecene-3,12-dione ($3x10^{-2}$ g; 0.15 mmol) zinc powder ($6.5x10^{-2}$ g; 1.0 mmol) and acetic acid (0.12 ml; 2.0 mmol) were added. The mixture was stirred at room temperature until all the zinc was consumed (43 hrs.) The solution was acidified with 20% H_2SO_4 and extracted (3x15 ml) with ether. The ethereal extracts were washed with saturated $NaHCO_3$, water and dried ($MgSO_4$). After evaporation, The residue (28 mg; 93%) was recrystallized from hexane; mp. 72-74 °C (lit[12] 78-80°C).

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2. The nomenclature used is geographical. Gif stands for Gif-sur-Yvette, the town in France where Gif[III] and Gif[IV] were invented. Gif-Orsay was a joint work involving Professor G. Balavoine and his colleagues at the Université de Paris-Sud at Orsay, the next town to Gif-sur-Yvette. GoAgg[I] and GoAgg[II] introduces work done at Texas A&M in Aggieland. These abbreviations save space.

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