Functionalization of Saturated Hydrocarbons. Part 4.[1] The Gif System for Selective Oxidation using Molecular Oxygen

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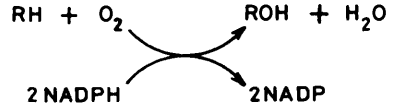
Various systems for the selective oxidation of saturated hydrocarbons have been developed. These are based on the idea of an iron catalyst which is reduced by electron transfer and oxidized by molecular oxygen simultaneously in the presence of a source of protons. Four modifications of this system (the Gif system) have been devised of which the best (Gif IV) consists of an iron catalyst with metallic zinc as the reductant, acetic acid as the proton source and pyridine as the solvent. At room temperature, using oxygen or air, saturated hydrocarbons are oxidized selectively to ketones in isolated yields superior to those reported for comparable model systems.

The direct functionalization of saturated hydrocarbons usually requires drastic conditions (*i.e.* high temperature, high pressure, strongly electrophilic or radical reagents) and gives mixtures of products including polyfunctionalized compounds.[2] The oxidation of saturated hydrocarbons under mild conditions is an intellectually stimulating and industrially important objective of current relevance. Many biological systems are able to hydroxylate non-activated carbon hydrogen bonds. Of particular interest are the mono-oxygenases of which cytochrome P450 (Cp450) constitutes the most studied group and consists of a family of isozymes which are active in the oxidation of numerous drugs, xenobiotics and endogenous compounds.[3,4] Among these transformations, the hydroxylation of saturated hydrocarbons according to Equation (1) represents an



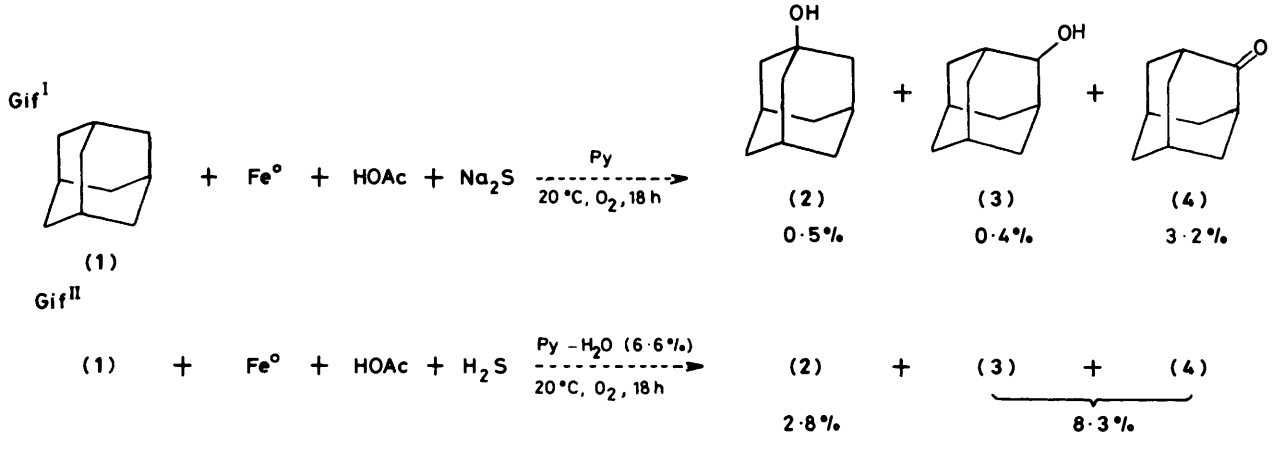
(1)

attractive model for smooth oxygenations. *In vitro*, hydroxylation occurs mainly at tertiary and non-hindered secondary positions.

The active site of these enzymes comprises an iron porphyrin in which the metal has a thiolate (from a cysteine residue) and a histidine as ligands.[3d] The catalytic cycle is beginning to be understood in detail.[3a,d] One of the less clear steps is, in fact, the insertion of one oxygen into the C–H bonds of the substrate. Nevertheless, the actual data[3c,5,6] strongly support a Fe^{V}=O species, probably acting as an hydrogen abstractor giving a discrete carbon radical. The same preferred species has been recently postulated in catalytic oxygen transfer by Fe–bleomycin complex[7] which displays a reactivity similar to that of Cp450.

Many systems, more or less biomimetic, based on the use of a transition metal cation (Fe, Co, Rh, Mn, Cr, V) as catalyst have been developed in the past decade for the oxidation of hydrocarbons,[8,9] notably the results obtained by Groves, Mansuy, Meunier, Mimoun, Tabushi, Udenfriend, Ullrich, and their co-workers. In spite of intensive studies these model systems have to date given poor yields when based on percentage of oxidation of the hydrocarbon. Moreover, in many instances, the important problem of activation of molecular oxygen is bypassed and alternative sources such as iodosobenzene, hydroperoxides, hypochlorite, *etc.* are used.

In preliminary communications[10,11] we described what we call the 'Gif system'. This consists of molecular oxygen, acetic acid (or other acid) in pyridine as solvent, iron powder as a source of electrons and of iron catalyst, and sodium sulphide (Gif I) or hydrogen sulphide (Gif II) which could form an iron–sulphur bond (as in Cp450). The combination of all these reagents, each of which is essential to reaction, permits the oxidation, at room temperature, of adamantane (1) with yields much superior to those observed in other models using



Scheme 1.

molecular oxygen (Scheme 1). It is of importance to note that oxidation occurs preferentially at the secondary position giving mainly the ketone (4). Here we report in more detail the study and improvement of this original system.

Results and Discussion

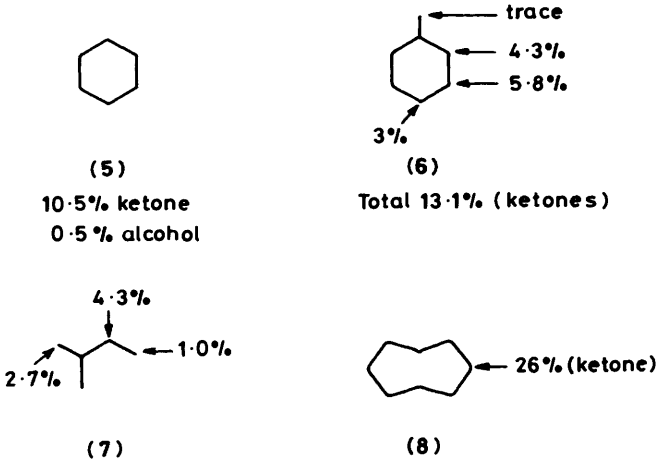
In order to evaluate the regioselectivity of the oxidation, adamantane (1), a spherically symmetrical hydrocarbon was chosen as the substrate. We defined a ratio C^2/C^3 as:

$$C^2/C^3 = \frac{\%\ \text{adamantan-2-ol} + \%\ \text{adamantanone}}{\%\ \text{adamantan-1-ol}}$$

A statistical attack on the carbon–hydrogen bonds would give a C^2/C^3 value of 3. A radical or electrophilic process would lead to a $C^2/C^3 < 3$. We have determined the C^2/C^3 value of a typical radical autoxidation of adamantane (1) initiated with benzoyl peroxide, to be 0.8, in agreement with the scanty literature data[12] and in the same order of magnitude as previous hydroxylating systems.[8a] The parameters of this Gif^{II} system were studied in detail with the aim of improving the yield and, if possible, the selectivity.

Preliminary experiments[10,13a] demonstrated that an acid is necessary. Systematic variation of the nature of the acid in the Gif^{II} system showed that acetic and tartaric acids gave good yields of oxidized products. Malonic, mucic and citric acid also gave close to 30% oxidation. The results were given in a preliminary communication.[11]

In the Gif^{II} system other representative saturated hydrocarbons (5)—(8) were oxidized,[11] the results are summarized in Scheme 2.



Scheme 2.

It is noteworthy that in all cases ketones are the major products and that the pattern of carbonyl site selectivity in 2-methylbutane (7) and methylcyclohexane (6) is different from that observed *in vivo* for Cp450 hydroxylation of the same substrates.[3c] No trace of tertiary alcohols could be detected in the oxidation of compounds (6) and (7). These alcohols are, of course, stable to the reaction conditions.

It was possible that the yield of oxidation was limited by the amount of one or more of the components of the system. A series of control experiments in which additional portions of reagents (H_2S, Fe^0, HOAc, H_2O) were added during the course of the reaction showed that, in the case of adamantane (1), the total yield and the selectivity remained close to the reference values. In like fashion, the use of mixtures of solvents (*i.e.* pyridine containing increasing proportions of acetone) showed that pyridine cannot be diluted or replaced by another solvent without a decrease in both yield and selectivity.[10]

It has already been shown that in the absence of a sulphur or selenium compound such as hydrogen sulphide, sodium sulphide, sulphur or selenium, no oxidation takes place.[10] The observations that catalytic amounts of hydrogen sulphide or a simple heating of the reaction mixture at 30—40 °C permit the reaction clearly demonstrates that H_2S is not a reductant in the Gif^{II} system and that formation of an Fe–S bond is not essential to the oxidation process. It is thought that the role of hydrogen sulphide is to activate the iron surface towards attack by the acid. The Gif system now becomes Gif^{III} (Equation (2).

$$\text{Gif}^{III}\ \text{R-H} + \text{Fe}^0 + \text{HOAc} \xrightarrow[\text{O}_2,\ 40\ ^\circ\text{C}]{\text{Py-H}_2\text{O}\ 6.6\%} \qquad (2)$$

Isolation and Demonstration of the Catalytic Activity of a Trinuclear Organoiron Carboxylate Cluster.—One can speculate that in the Gif^{III} system iron powder serves not only as a reducing agent, but also as the precursor of a cationic iron complex. In like fashion one can envisage that the organic acid could also function in a dual role, not only as a proton source, but also, in the form of its corresponding carboxylate ion, as a ligand for iron. If iron powder is treated with HOAc under oxygen in aqueous pyridine, a brown mixture results which, after removal of the unchanged iron powder by filtration, addition of adamantane, acetic acid, and reducing agent (iron powder, zinc, cobalt, nickel, or stannous chloride) gives under oxygen, an oxidation comparable to the original Gif^{III} system in both yield and selectivity.

Similarly, when iron powder is treated with acetic acid in pyridine under argon the resulting mixture, after removal of the unchanged iron by filtration, and addition of zinc and adamantane (1), with oxygen, leads to oxidation (Table 1).

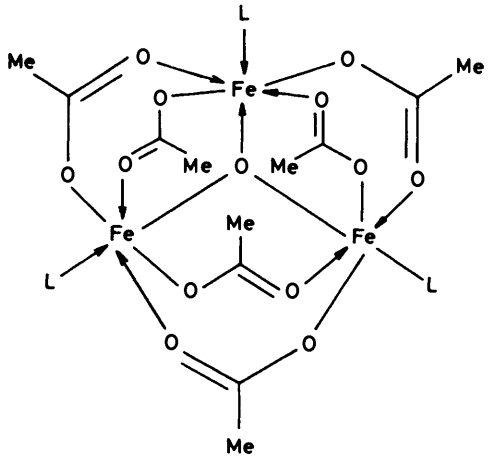
Clearly the oxidation proceeds *via* a soluble iron complex. It has been possible to isolate from the reaction of iron powder with acetic acid and aqueous pyridine in air a black crystalline compound. Analytical, mass spectral, and titration data served to establish the constitution of $Fe^{II}Fe^{III}_2O(OAc)_6(py)_{3.5}$. Such a complex has in fact been described in the literature.[14] It is formed by ligand exchange in pyridine of the corresponding aquo complex.[15] The latter, in turn, is readily prepared in 70% yield by reaction of ferrous chloride with calcium acetate in aqueous acetic acid. On the basis of a detailed examination of the magnetic and spectroscopic properties, and the *X*-ray analysis of an isostructural manganese analogue the trinuclear iron cluster carboxylate structure (9) can be formulated[16] (Figure).

The isolation of the crystalline cluster (9a) enabled us to test the hypothesis that this species could function as a catalyst in the presence of acetic acid, pyridine and a reducing agent (Zn) in the oxidation of hydrocarbons with dioxygen. The results collected in Table 2 show that even for low concentrations with

Table 1. *Reagents:* i, Pyridine–water (6.6%), H_2S, Argon, 30 °C, 20 h; ii, filtration; iii, O_2, 30 °C, 22 h

$$\text{Fe}^0 + \text{HOAc} \xrightarrow[\text{ii}]{\text{i}} + (\text{Y}) \xrightarrow{\text{iii}} (2) + (3) + (4)$$

Y	Unchanged (1) %	(2) %	(3) + (4) %	C^2/C^3
(1)	86	0.7	0.75	1
(1) + Zn	84	1.25	5.5	4.4



(9) a; L = Py
b; L = H_2O

Figure.

Table 2.

(1) (2 mmol) + (9a) + HOAc (40 mmol) + Zn (20 mmol) $\xrightarrow[O_2,\ 30\ °C,\ 18\ h]{Py\ (28\ ml)}$ (2) + (3) + (4)

(9a) (10^{-3} mmol)	(2) %	(3) %	(4) %	Total %	C^2/C^3	Turn-over[a]
300	1.45	2.3	6	9.75	5.7	0.65
18	1.4	2	8.2	11.6	7.3	12.9
3	0.5	1.75	5.5	7.75	14.5	51.7
0.8	0.7	3.4	5.6	9.7	12.8	242
0.2	1.4	5.8	6	13.2	8.4	1 320
0.054	0.7	4.6	3.8	9.1	12	3 370

[a] Turn-over is mol oxidized products/mol catalyst.

that of the cluster (**9a**), except for the manganese analogue which was found to be inactive. It is important to note that, for the first time, under our conditions, iron salen and iron porphyrins are able to oxidize hydrocarbons with dioxygen to the corresponding alcohols and ketones with relatively good yields.

Table 3.

(1) (2 mmol) + Zn (20 mmol) + HOAC (40 mmol) + catalyst $\xrightarrow[O_2,\ 30\ °C,\ 18\ h]{Py\text{–}H_2O\ (6.6\%)}$ (2) + (3) + (4)

Catalyst (10^{-3} mmol)	(1) % recovered	(2) %	(3) %	(4) %	C^2/C^3	Turn-over[a]
$FeCl_2{\cdot}4H_2O$ (5)	72	0.5	6.8		13.6	30
$FeSO_4{\cdot}7H_2O$ (10.8)	75	0.8	4.1	4.3	10.5	17
$Fe(NO_3)_3{\cdot}9H_2O$ (2.5)	72	0.7	3.7	4.5	11.7	71
(**9b**) (4)	59	0.9	3.6	7.1	11.9	58
$[Fe(salen)]_2O$ (80)	66	1.2	7.4		6.2	2.15
$[Fe(tpp)]_2O$ (70)	77	0.6	4.9		8.2	1.6
Fe(tpp)OAc (5)	61	1.7	1	11.7	7.5	57.5
(**10a**) (3.3)	74	0.25	5.5		22	35
(**10b**) (3)	68	0.6	7.6		12.7	54.5
(**10c**) (2.7)	72	0.3	2.4	4.1	22	50.5
(**10d**) (1.4 or 12)	90					
(**10e**) (2.7)	68	0.7	2.4	8	14.8	82

[a] Turn-over is mol oxidized products/mol catalyst.

respect to the substrate, the iron cluster (**9a**) in Gif^{IV} system [(Equation (3)] allows oxidation of adamantane (**1**) in yields

$$Gif^{IV}\ R\text{-}H + (9a) + HOAc + Zn \xrightarrow[O_2,\ 40\ °C]{Pyr.} \quad (3)$$

comparable to those obtained with the Gif^{III} system (yield 16.3%, $C^2/C^3 = 2.4$)[13b] and even better selectivity for the secondary position.

For comparison we have replaced the trinuclear cluster (**9a**) in our system by simple inorganic iron salts, iron tetraphenylporphyrin, iron salen* μ-oxo complex and mixed complexes $M_2^{III}M'^{II}O(OAc)_6{\cdot}6H_2O$[17] [(**10a**; M = Fe, M′ = Ni), (**10b**; M = Fe, M′ = Zn), (**10c**; M = Fe, M′ = Co), (**10d**; M = Mn, M′ = Mn), (**10e**; M = M′ = Ru^{III})]. The results given in Table 3 show that the reactivity of these catalysts is comparable to

It is conceivable that the same iron-containing catalyst could be formed from any of the transition metal compounds where iron is involved. However, the question of the 'real' active species in all these oxidations remains to be demonstrated and is discussed further in the next part of this series.

In order to gain more insight into the kinetics of the oxidation process, the rate of formation of the oxygenated products (**2**)—(**4**) was followed by g.l.c. analysis of 1 ml aliquots taken from the reaction mixture [see Experimental part, procedure (iv), treatment (*f*)]. The conclusions were that half of the ketone (**4**) was produced within 35 min, half the secondary alcohol (**3**) within 45 min, and half of the tertiary alcohol (**2**) within 50 min. After complete consumption of zinc (*ca.* 6—8 h) no further

* salen = *N*,*N*′-ethylenebis(salicylideneaminato).

Table 4.

$$(5) + Fe^0 + HOAc \xrightarrow[O_2,\ 30\ °C,\ ca.\ 20\ h]{Py\text{–}H_2O\ (6.6\%)}$$

Cyclohexane (5) (mmol)	Fe^0 (mmol)	HOAc (mmol)	Yield (%) Cyclohexanol	Yield (%) Cyclohexanone	Total oxidized products (mmol)
1.9[a]	55.5	137	2.2	7.8	0.185
5.6[a]	55.5	121	1.8	7.4[c]	0.515
9.26[a]	18.6	38.5	0.55	6.4	0.645
9.26[a]	93.1	192.5	1.1	3.5	0.425
18.57[a]	93.1	192.5	1.1	2.8	0.72
27.86[a]	55.7	114.6	1.4	5.7[c]	1.98
46.43[a]	55.7	114.6	1.1	3.6	2.18
13.93[b]	55.7	119	1.6	16.5[c]	2.52
27.86[b]	55.7	119	1	10.5[c]	3.20
46.43[b]	92.7	184	2.5	4.5[c]	3.25

[a] Reaction under static pressure of O_2 (1 atm). [b] Reaction under flux of O_2. [c] Isolated as its DNP derivative.

Table 5.

$$(5) + (9a) + Zn + HOAc \xrightarrow[20\ °C,\ 4\ h,\ air]{Py\text{–}H_2O\ (6.6\%)\ (30\ ml)}$$

(mmol) 7×10^{-3} 20 40

(5) (mmol)	Cyclohexanol (%)	Cyclohexanone %	Total oxidized products (mmol)	Turn-over
2.3	0.80	21	0.50	71
4.6	0.80	17.70	0.85	121

oxidation took place and the oxidized products (2)—(4) were shown to be stable in the reaction mixture.

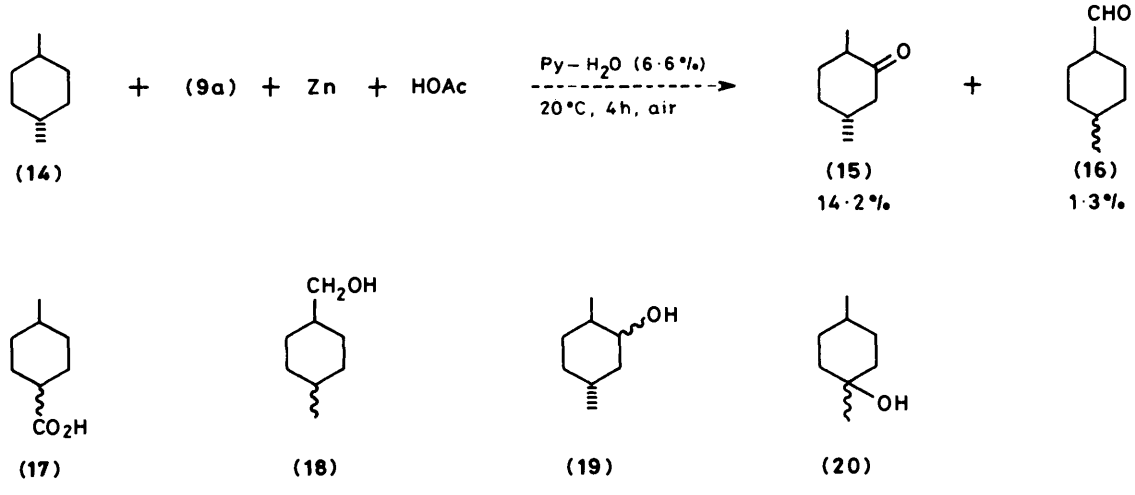
The principal characteristics of the Gif system for the oxidation of saturated hydrocarbons are high yields of oxidation products (relative to those reported in the literature for similar models) and a preponderence of oxygenated products at secondary positions, ketones being the major products. These observations led us to examine the scope of this method on other representative substrates.

Cyclohexane (5) was oxidized by the Gif^{III} and Gif^{IV} systems. The results reported in Tables 4 and 5 show that in both cases the ketone is the major product. For high concentrations of the substrate the Gif^{III} system oxidized up to 3.25 mmol of cyclohexane (5). Similarly cyclo-octane (8) and cyclododecane (11) gave, under the Gif^{IV} conditions, the corresponding ketones (12) and (13) with yields of 19.5 and 24% respectively [Equations (4) and (5)]. Only traces of the secondary alcohols were detected.

$$\underset{\substack{(8)\\ 2.0\ mmol}}{\text{Cyclo-octane}} + (9a) + Zn + HOAc \xrightarrow[\text{flux of } O_2,\ 40\ °C,\ 17h]{Py\text{–}H_2O\ (6.6\%)} \underset{(12)\ 19.5\%}{\text{Cyclo-octanone}} \quad (4)$$

$$\underset{\substack{(11)\\ 2.0\ mmol}}{\text{Cyclododecane}} + (9a) + Zn + HOAc \longrightarrow \underset{(13)\ 24\%}{\text{Cyclododecanone}} \quad (5)$$

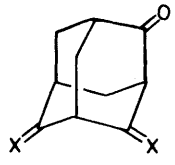
trans-1,4-Dimethylcyclohexane (14), a simple and symmetrical hydrocarbon, which possesses primary, secondary, and tertiary positions, was chosen as a suitable substrate to evaluate the selectivity of the oxidation process. The only oxidation products observed were the ketone (15) and the aldehyde (16) (Scheme 3). Special attention was given to the other possible oxidation products [acids and primary, secondary, or tertiary alcohols, compounds (17)—(20)]. None of these could be detected by g.l.c. (by co-injection with authentic samples). This confirms that our system possesses a high regioselectivity which



Scheme 3.

differs from that observed in the case of Cp450 and previous models.

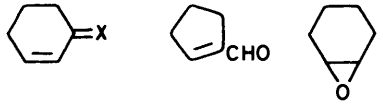
A striking observation about the reactivity of the Gif system is that it permits selective *mono*-oxygenation of the substrates. Therefore, cyclohexanol and adamantanone (**4**) were examined as substrates in the oxidation. In the case of cyclohexanol, only 14% of cyclohexanone was formed under Gif^{IV} conditions. Using the same system, adamantanone (**4**) yielded a mixture of the diketones (**21**) (7.9%) and (**22**) (2.3%). These results indicate that secondary alcohols are not the main precursors of the ketones and that over-oxidation of compound (**1**) to diketones [(**21**) + (**22**) 0.9% in the oxidation of adamantane (**1**) under Gif^{IV} conditions] cannot explain the observed mass balance. Likewise, in the oxidation of cyclohexane and cyclo-octane, for example, it has been shown that the diacids (**23**) and (**24**) under Gif^{III} conditions are not formed. Such acids are, of course, stable under these conditions.



(**21**) X = O, Y = H_2
(**22**) X = H_2, Y = O

$HO_2C(CH_2)_nCO_2H$

(**23**) *n* = 4
(**24**) *n* = 6



(**25**) X = H (**27**) (**28**) (**29**) (**30**) (**31**)

The same trends (*i.e.* selective mono-oxygenation) are observed in more complex molecules such as steroids.[1] Olefinic compounds are always considered to be more readily oxidizable than saturated hydrocarbons and under Gif^{III} conditions, cyclohexene (**25**) led to a mixture of cyclohexenone (**26**) (1.1%) and cyclopentenecarbaldehyde (**27**) (1.3%), products derived from a classical autoxidation reaction.[18] No cyclohexene oxide (**28**) (stable under these conditions) was detected, a result which again distinguishes our system from more biomimetic systems.[6b,19] It is of interest that similar iron cluster complexes that we find active in a reduced form, were reported to epoxidize alkenes using dioxygen *without* the presence of a reductant.[9c]

In a similar fashion, diphenyl sulphide (**29**) was not oxidized by the Gif^{III} and Gif^{IV} systems;[20] less than 1% of diphenyl sulphoxide (**30**) and diphenyl sulphone (**31**) were formed. It has, of course, been shown that diphenyl sulphoxide (**30**) is not reduced under these conditions.[21]

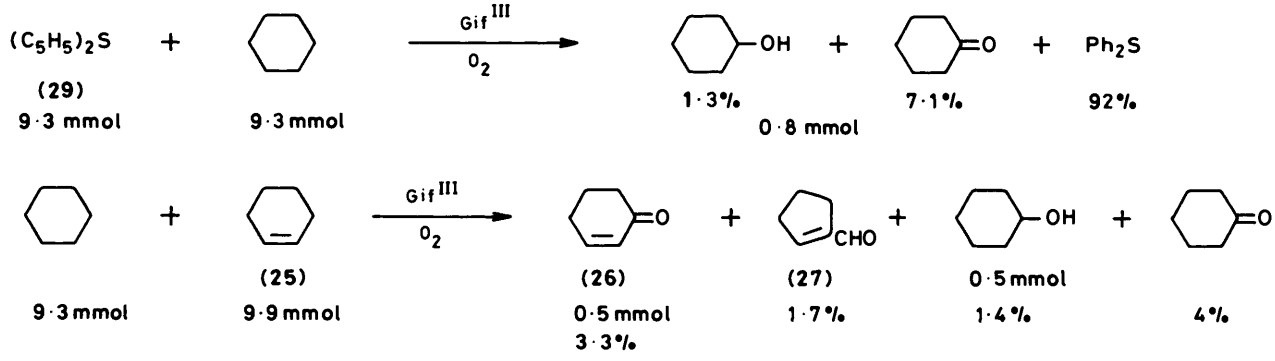
Competitive oxidations (Scheme 4) clearly indicate that, even in the presence of usually readily oxidizable substrates, saturated hydrocarbons are still oxidized in good yields.

Indubitably we are dealing with an original, relatively high yielding, regio- and chemo-selective system for the oxidation of saturated hydrocarbons.[22] A more detailed study and mechanistic hypothesis on the Gif^{IV} system will be presented in a subsequent paper.[23]

Experimental

M.p.s were determined with a Reichert apparatus. ^1H N.m.r. spectra were recorded on a Varian EM 360 (60 MHz) or Bruker (400 MHz) instrument using [^2H]chloroform as solvent and tetramethylsilane as an internal standard. I.r. spectra were recorded on a Perkin-Elmer 257 instrument. Mass spectra were recorded on AEI MS 9 and MS 50 instruments. U.v. spectra were measured on a Jobin-Yvon Duospec 203 spectrophotometer. Analytical g.l.c. employed a Girdel series 330 gas chromatograph with 140 cm 5% SE 30, 150 cm OV17 (3%), or 400 cm OV17 (5%) columns according to the following conditions:

(i) For the oxidation of adamantane (**1**). Column OV17, 3%, 150 cm, temperature program 90—140 °C (2 °C min^{-1}); R_t (s): adamantane 223, naphthalene (internal standard) 529, adamantan-1-ol 730, adamantan-2-ol 904, adamantanone 1 005. (ii) For the oxidation of cyclo-octane. Same as (i), R_t (s): cyclo-octanol + cyclo-octanone 400, naphthalene (internal standard) 503. (iii) For the oxidation of cyclododecane. Column OV17, 3%, 150 cm, temperature program 125—150 °C (2 °C min^{-1}); R_t (s): cyclododecane 272, adamantanone (internal standard) 465, cyclododecanone 765, cyclododecanol 837. (iv) For the oxidation of cyclohexane. Column OV17, 5%, 400 cm, temperature program 90—145 °C (2 °C min^{-1}); R_t (s): cyclohexanol 731, cyclohexanone 873, adamantane (internal standard) 1 250. (v) For the oxidation of *trans*-1,4-dimethylcyclohexane. Column OV17, 5%, 400 cm, temperature program 130—190 °C (2 °C min^{-1}); R_t (s): *trans*-2,5-dimethylcyclohexanone 1 330, 4-methylcyclohexanecarbaldehyde 1 240; internal standard: cyclododecane. (vi) For the oxidation of cyclohexene.



Scheme 4.

Column OV17, 5%, 400 cm, temperature program 120—190 °C (2 °C min^{-1}); retention times (s): cyclohexene 370, cyclohex-2-enol 620, cyclohex-2-enone 860, cyclopentenecarbaldehyde 660; internal standard: toluene. For all hydrocarbons analysed: carrier gas N_2, pressure 1 bar, detector temperature 250 °C, injector temperature 250 °C.

All the reagents and solvents used were commercial analytical grade unless otherwise stated. Peroxidic titrations were performed as described in the literature.[24] Oxidations of hydrocarbons with the Gif systems were carried out in 125 ml Erlenmeyer flask with magnetic stirring unless otherwise stated.

Typical Procedures for Gif Oxidation.—(i) *Gif*^{I} *system.* The hydrocarbon (2 mmol), sodium sulphide·$9H_2O$ (2 mmol), the solvent [(pyridine (30 ml)–HOAc (1.15 ml)], and iron powder (1.07 g, 19.2 mmol) were placed in a 125 ml conical flask and stirred under the static pressure of an oxygen filled balloon at room temperature for 18 h. Treatment of the crude reaction mixture according to (*a*) (see below) afforded the oxidation products which were analysed by g.l.c.

(ii) *Gif*^{II} *system.* The same procedure as (i) except that sodium sulphide was replaced by a solution of hydrogen sulphide (90 μmol) dissolved in pyridine.

(iii) *Gif*^{III} *system.* The hydrocarbon (2 mmol), solvent [pyridine (28 ml), acetic acid (2.3 ml), water (2 ml)] and iron powder (1.07 g, 19.2 mmol) were placed in a 125 ml conical flask and stirred under a static pressure of oxygen, provided by a balloon, at 30—40 °C for 18 h. Treatment of the crude reaction mixture according to (*a*) (see below) afforded the oxidation products which were analysed by g.l.c.

(iv) *Gif*^{IV} *system.* The hydrocarbon (2 mmol), the solvent [pyridine (28 ml)–acetic acid (2.3 ml), with or without water (1.85 ml)], iron catalyst (7 μmol), and zinc powder (1.31 g, 20 mmol) were placed in a 125 ml conical flask and stirred at room temperature for 18 h under a static pressure of oxygen, provided by a balloon, or under a flow of air or oxygen blown over the surface of the reaction mixture, or simply with flask open to the air. Treatment of the crude reaction mixture according to (*a*)—(*c*) (see below) afforded the oxidation products which were analysed by g.l.c.

Different treatments of the crude reaction mixture were used throughout our studies: (*a*) Aqueous sodium hydroxide (20 ml; 10%, v/v) were added to the reaction mixture. The aqueous layer was extracted with three portions of pentane (100 ml × 3). The combined organic extracts were washed with water, and with saturated cupric sulphate, dried ($MgSO_4$), and evaporated under reduced pressure at 20 °C. Samples were taken up in ether for g.l.c. analysis.

(*b*) Water (20 ml) was added to the reaction mixture. The aqueous layer was extracted with ether (3 × 100 ml). The combined organic extracts were washed with water, with 1M-HCl, and with brine, dried over $MgSO_4$ and evaporated under reduced pressure at 20 °C. The residue was taken up in ether for g.l.c. analysis.

(*c*) The same treatment as in (*b*) except that the organic extracts were concentrated to a volume of *ca.* 10 ml. This volume was then adjusted to 25 ml by the addition of ether. The internal standard was added to an aliquot (5 ml) and the resulting solution analysed by g.l.c.

(*d*) Water (15 ml) and ether (15 ml) were added to the ice-cooled reaction mixture. After acidification with dilute, ice-cooled aqueous H_2SO_4 (25%, v/v) the mixture was extracted with ether (4 × 65 ml). The combined organic extracts were washed with dilute sulphuric acid (90 ml; 5% v/v), with aqueous sodium hydroxide (30 ml; 20 g l^{-1}), with aqueous sodium hydrogen carbonate (30 ml; 50 g l^{-1}), and with brine, dried over $MgSO_4$ and concentrated under reduced pressure at 20 °C to a volume of *ca.* 10 ml and then analysed as in (*c*).

Table 6.

Treatment	% Recovery (1)	(2)	(3)	(4)
(*b*)	91	82	90	80
(*d*)	85	89	79	81
(*e*)		78	68	94
(*f*)		83	93	94

In the case of cyclohexane as substrate, the organic extracts, after drying ($MgSO_4$), were adjusted to a volume of 250 ml. The internal standard was added to an aliquot (50 ml) and the resulting solution analysed by g.l.c.

(*e*) To an aliquot (1 ml) of the crude reaction mixture, ether (5.0 ml) and the internal standard were added. After centrifugation, the supernatant was analysed by g.l.c.

(*f*) Same procedure as in (*e*) except that the aliquot was acidified with concentrated sulphuric acid (0.6 ml). The percentage recovery in the oxidation of adamantane (**1**) was determined for work-up procedures (*b*)—(*f*) (see Table 6) by dissolving a synthetic mixture of (**1**), (**2**), (**3**), and (**4**) in pyridine–HOAc.

Autoxidation of Adamantane (**1**).—A solution of adamantane (**1**) (272 mg, 2 mmol) in aqueous pyridine (6.6% v/v; 30 ml) and acetic acid (2.3 ml, 20 mmol) was heated at 80 °C for 24 h under a flow of oxygen. Benzoyl peroxide (3 × 60 mg, 3 × 0.1 mmol) was added at the beginning of the reaction and after 2 and 4 h. After cooling to 40 °C, zinc powder (1.31 g, 20 mmol) was added and the stirring was continued for 1 h. Work-up procedure (*d*) and g.l.c. analysis gave compounds (**2**) (0.85%), (**3**) (0.30%), and (**4**) (0.35%).

Isolation and Catalytic Activity of the Iron Cluster (**9a**).—Iron powder (1.08 g, 19.3 mmol) was added to a mixture of pyridine (28 ml), water (2 ml), and acetic acid (2.1 ml, 37 mmol). After 16 h under a static pressure of oxygen (1 atm) at 30 °C, unchanged iron powder (5%) was filtered off and a black crystalline precipitate was collected (3.6 g), $\nu_{max.}$(Nujol) 2 950, 2 850, 1 610, 1 450, and 1 415 cm^{-1}; *m/z* 652 $[Fe_4O(OAc)_7]$, 593 $[Fe_4O(OAc)_6]$, 550 $[Fe_4O_2(OAc)_5]$, 537 $[Fe_3O(OAc)_6]$, 491 $[Fe_4O_2(OAc)_4]$, 478 $[Fe_3O(OAc)_5]$, 432 $[Fe_4O_2(OAc)_3]$, 419 $[Fe_3O(OAc)_4]$, 360 $[Fe_3O(OAc)_3]$, 305 $[Fe_2O(OAc)_3]$, 289 $[Fe_2(OAc)_3]$, 174 $[Fe(OAc)_2]$, 159 $[Fe(OAc)(CO_2)]$, 132 [Fe(OH)(OAc)], and 115 [FeOAc] (Found: C, 43.75; H, 4.55; N, 6.05. Calc. for $[Fe_3O(O_2CCH_3)_6(C_6H_5N)_3]_2C_6H_5N$: C, 43.49; H, 4.39; N, 6.02); titration of Fe^{II} with $KMnO_4$: 0.127 mmol, calculated 0.123 mmol.

Preparation of the Aquo Complex $[Fe_3O(OAc)_6]\cdot 3H_2O$ (**9b**).—This compound was prepared according to the literature,[14,15] $\nu_{max.}$(Nujol) 3 350, 2 900, 2 850, 1 595, and 1 410 cm^{-1}; *m/z* 652 $[Fe_4O(OAc)_7]$, 609 $[Fe_4O_2(OAc)_6]$, 593 $[Fe_4O(OAc)_6]$, 550 $[Fe_4O_2(OAc)_5]$, 537 $[Fe_3O(OAc)_6]$, 491 $[Fe_4O_2(OAc)_4]$, 478 $[Fe_3O(OAc)_5]$, 419 $[Fe_3O(OAc)_4]$, 360 $[Fe_3O(OAc)_3]$, 304 $[Fe_2O(OAc)_3]$, 288 $[Fe_2(OAc)_3]$, 174 $[Fe(OAc)_2]$, 159 $[Fe(OAc)(CO_2)]$, 132 [FeOH(OAc)], and 115 [Fe(OAc)] (Found: C, 24.0; H, 4.45. Calc. for $[Fe_3O(OAc)_6]\cdot 3H_2O$: C, 24.35; H, 4.09).

Preparation of the Cluster (**9a**).—This compound was prepared by ligand exchange from the complex (**9b**) according to the literature,[14] $\nu_{max.}$(Nujol) 2 900, 2 850, 1 600, and 1 440 cm^{-1}; *m/z* 842 $[Fe_5O_2(OAc)_9]$, 783 $[Fe_5O_2(OAc)_8]$, 740 $[Fe_5O_3(OAc)_7]$, 668 $[Fe_4O_2(OAc)_7]$, 652 $[Fe_4O(OAc)_7]$, 609

Table 7.

Complex (9a) μmol	Unchanged (1) %	(2) %	(3) %	(4) %	Total yield (%)	C^2/C^3
310	65	1.45	2.30	6.0	9.75	5.7
70	74	1.20	2.50	6.9	10.6	7.8
37	71	1.30	2.20	8.1	11.6	7.9
18	66	1.40	2.0	8.2	11.6	7.3

$[Fe_4O_2(OAc)_6]$, 593 $[Fe_4O(OAc)_6]$, 550 $[Fe_4O_2(OAc)_5]$, 537 $[Fe_3O(OAc)_6]$, 491 $[Fe_4O_2(OAc)_4]$, 478 $[Fe_3O(OAc)_5]$, 419 $[Fe_3O(OAc)_4]$, 360 $[Fe_3O(OAc)_3]$, 305 $[Fe_2O(OAc)_3]$, 289 $[Fe_2(OAc)_3]$, 174 $[Fe(OAc)_2]$, 159 $[Fe(OAc)(CO_2)]$, 132 [Fe(OH)(OAc)], and 115 [Fe(OAc)] (Found: C, 43.75; H, 4.55; N, 6.1. Calc. for $[Fe_3O(O_2CCH_3)_6(C_6H_5N)_3]_2C_6H_5N$: C, 43.49; H, 4.39; N, 6.02%).

Catalytic Activity of the Isolated Cluster (**9a**).—The complex isolated from the reaction of iron powder with pyridine and acetic acid (see above) was used in the oxidation of adamantane (**1**) under Gif^{IV} conditions [static pressure of oxygen (1 atm); 30 °C, 24 h; work-up procedure (*b*)], results are given in Table 7.

Catalytic Activity of the Synthetic Cluster (**9a**).—The complex prepared by ligand exchange from (**9b**) (see above) was used in the oxidation of adamantane (**1**) under Gif^{IV} conditions [static pressure of oxygen (1 atm); 30 °C, 18 h, work-up procedure (*b*)], results are given in Table 2.

Oxidation of Cyclohexane (**5**) *by the* Gif^{III} *System.*—Cyclohexane was purified by washing with concentrated sulphuric acid, water, aqueous sodium hydrogen carbonate, and brine. The organic layer was dried ($MgSO_4$) and distilled from sodium. Oxidation of various amounts of cyclohexane (**5**) under Gif^{III} conditions [30 °C, 20 h, static pressure of oxygen (1 atm) or flux of oxygen (0.2 ml s^{-1}), work-up procedure (*b*)] gave the results shown in Table 4.

Oxidation of Cyclohexane (**5**), *Cyclo-octane* (**8**), *Cyclododecane* (**11**) *and* trans-1,4-*Dimethylcyclohexane* (**14**) *by the* Gif^{IV} *System.*—Cyclo-octane was purified as for cyclohexane (see above). Cyclohexane was oxidized according to method (iv) [pyridine–water (6.6% v/v), air, 20 °C, 4 h]. Work-up procedure (*f*) gave the results indicated in Table 5.

Cyclo-octane (**8**) was oxidized according to method (iv) [pyridine–water (6.6% v/v), 40 °C, flow of oxygen (*ca.* 30 ml min^{-1}), 17 h]. Work-up procedure (*b*) gave 19.5% of cyclo-octanone with traces of cyclo-octanol (g.l.c. analysis). Reaction of the ethereal extract with 2,4-dinitrophenylhydrazine[25] gave the DNP derivative of cyclo-octanone (13.7% after chromatography) identical with an authentic sample.

Cyclododecane (**11**) was oxidized according to method (iv) [pyridine, 20 °C, air, 17 h]. Work-up procedure (*d*) and g.l.c. analysis gave cyclododecanone (24%) and cyclododecanol (3%).

trans-1,4-Dimethylcyclohexane (**14**) was oxidized according to method (iv) [pyridine–water (6.6% v/v), air, 20 °C, 4 h] work-up procedure (*f*) to give *trans*-2,5-dimethylcyclohexanone (**15**) (14.2%) and 4-methylcyclohexanecarbaldehyde (**16**) (1.3%) (g.l.c. analysis) identified by co-injection with authentic samples (see below). Compounds (**17**)—(**20**) and 1,4-dimethylcyclohexene were not detected by the same technique. DNP derivatives of (**15**) and (**16**), prepared[25] from the ethereal extract and separated by preparative t.l.c., were identical with authentic specimens (see below).

Preparation of Authentic Samples.—trans-2,5-*Dimethylcyclohexanone* (**15**). To a solution of di-isopropylamine (16.19 g, 0.16 mol) in dry THF (160 ml) at −78 °C under argon atomosphere, butyl-lithium (1.6M; 100 ml) was added. After a few min at 0 °C, the solution was cooled to −78 °C and 2-methylcyclohexanone (17.92 g, 0.16 mol) was slowly added. The reaction was allowed to warm to 0 °C and after 10 min at this temperature was recooled to −78 °C. Bromine (25.6 g, 0.16 mmol) was then added dropwise. Two min after the end of the addition, the mixture was poured into saturated sodium hydrogen carbonate (200 ml) and extracted with ether (3 × 100 ml). The combined organic layers were successively washed with water (100 ml), saturated sodium hydrogen sulphite (100 ml), and brine. After the extract had been dried ($MgSO_4$) the solvent was removed under reduced pressure to give a yellow oil which was subsequently used without purification. To a suspension of LiBr (8.8 g, 0.1 mmol) and Li_2CO_3 (27.5 g, 0.37 mol) in DMF (160 ml) at 130 °C under argon, was slowly added a solution of the above oily residue in DMF (20 ml). After 2 h at 130 °C, the reaction mixture was cooled to 20 °C, poured into saturated sodium hydrogen carbonate (150 ml) and extracted with ether (3 × 100 ml). The combined organic extracts were washed with water (150 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a brown oily residue (19.17 g). An aliquot (4.03 g) was purified by silica gel column chromatography. Elution with hexane–ether (9:1 v/v) gave 6-methylcyclohex-2-enone (1.98 g, 53%),[26a] $\nu_{max.}$(film) 2 930, 2 870, 1 680, 1 455, and 1 220 cm^{-1}; δ($CDCl_3$) 7.27 (1 H, m), 6.27 (1 H, m), 2.79—1.03 (8 H), and 1.17 (3 H, d, Me).

To a suspension of cuprous iodide (8.61 g, 44 mmol) in dry ether (160 ml) at 0 °C under argon, was added methyl-lithium [105 ml, 87 mmol of a 0.83M-solution in ether, prepared from lithium and methyl iodide]. To this mixture, a solution of 6-methylcyclohex-2-enone (1.58 g, 14 mmol) in dry ether (100 ml) was added over 20 min. Stirring was continued for 3 h at 0 °C, when the mixture was poured into a saturated solution of ammonium chloride and extracted with ether (3 × 75 ml). The combined organic extracts were washed with water (100 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting yellow oil was dissolved in methanol (40 ml) saturated with potassium carbonate and heated at 40 °C for 16 h. After evaporation of the solvent under reduced pressure the residue was taken up in ether and potassium carbonate was filtered off. Evaporation of the ether gave an oil which was purified by silica gel column chromatography [pentane–ether, 4:1 v/v)]. 2,5-Dimethylcyclohexanone (**15**) was obtained as a mixture of *trans*/*cis* isomers (*ca.* 9:1 by g.l.c.) (1.21 g, 61%), $\nu_{max.}$(film) 2 920, 2 870, 1 710, 1 450, and 1 210 cm^{-1}; δ($CDCl_3$) 2.6—0.8 (CH and CH_2), and 1.15—0.85 (Me).

2,5-*Dimethylcyclohexanol* (**19**). To a mixture of sodium borohydride (51 mg, 1.3 mmol) in anhydrous methanol (5 ml), was added the ketone (**15**) (170 mg, 1.3 mmol). After 2 h at 20 °C the reaction mixture was diluted with ether and poured into water. The aqueous layer was extracted with ether (3 × 20 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography. Elution with pentane–ether (6:4 v/v) gave *trans*-2,5-dimethylcyclohexanol (1,2 *cis*)[26] (**19a**) (78 mg, 45%); $\nu_{max.}$(film) 3 400, 2 925, 1 455, 1 000, and 980 cm^{-1}; δ($CDCl_3$) 4.0—3.88 (1 H, m, C*H*OH) and 2.1—0.7 (15 H); *m*/*z* 110 ($M^+ - H_2O$), 71 and 55 and *trans*-2,5-dimethylcyclohexanol (1,2 *trans*) (**19b**) (62 mg, 36%); $\nu_{max.}$(film) 3 450, 2 925, 1 450, 1 058, 1 030, and 1 015 cm^{-1}; δ($CDCl_3$) 3.5—3.0 (1 H, m, C*H*OH), 2.29—0.72 (15 H), and 1.65 (1 H, s, OH); *m*/*z* 110 ($M^+ - H_2O$), 71, and 55.

4-*Hydroxymethylmethylcyclohexane* (**18**). Toluene-*p*-sulphonyl chloride (9.62 g, 50 mmol) was added to an ice cooled solution of 4-bis(hydroxymethyl)cyclohexane [commercial mixture of *cis*- and *trans*-isomers (7.29 g, 50 mmol)], in anhydrous pyridine (25 ml). The reaction mixture was left for 36 h at 20 °C,

and was then diluted with ether and poured into water. The aqueous layer was extracted with ether (3 × 100 ml). The combined ethereal extracts were washed successively with water (150 ml), dilute hydrochloric acid (1M; 150 ml), water (150 ml), and finally with saturated sodium hydrogen carbonate (150 ml). After drying ($MgSO_4$), the solvent was removed under reduced pressure to give an oily residue (9.12 g, 61%); δ($CDCl_3$) 7.92 (2 H, d), 7.40 (2 H, d), 3.85 (2 H, m), 3.45 (2 H, m), 2.50 (3 H, s), and 2.0—0.70 (11 H). To a suspension of $LiAlH_4$ (1.77 g, 46 mmol) in dry THF (30 ml) was added a solution of the above mono-toluene-*p*-sulphonate (7.20 g, 24 mmol) in THF (30 ml). The reaction mixture was refluxed for 4 h. After the reaction had been cooled, water (1.77 ml), dilute sodium hydroxide (1.77 ml; 15%) and water (1.77 ml) were successively added. After filtration, the solvent was removed under reduced pressure. Distillation of the crude residue gave the alcohol (**18**)[26] (1.61 g, 52%); b.p. 97—98 °C/30 mmHg; $\nu_{max.}$(film) 3 325, 2 950, 2 850, 1 445, 1 060, 1 040, and 1 000 cm^{-1}; δ($CDCl_3$) 3.53 (2 H, m), 2.0—0.8 (14 H), 1.75 (1 H, OH), and 0.92 (3 H, Me).

4-*Methylcyclohexanecarbaldehyde* (**16**). To a solution of oxalyl chloride (1 ml, 1 mmol) in dry CH_2Cl_2 (25 ml) at −60 °C was added a solution of Me_2SO (1.7 ml, 22 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred for 2 min when a solution of the alcohol (**18**) (1.28 g, 10 mmol) in CH_2Cl_2 (10 ml) was added. After 15 min, triethylamine (7 ml) was added and the reaction mixture was allowed to warm to room temperature. After addition of water, the crude reaction mixture was extracted with CH_2Cl_2 (3 × 75 ml). The combined organic extracts were washed with water (100 ml), brine (100 ml) and dried ($MgSO_4$). After removal of the solvent the residue was purified by column chromatography [pentane–ether (4:3 v/v)] to give the aldehyde (**16**) (0.98 g, 78%); $\nu_{max.}$($CHCl_3$) 2 850, 2 700, 1 715, 1 705, 1 440, 935, and 910 cm^{-1}; δ($CDCl_3$) 9.95 (1 H, m, CHO) and 2.5—0.8 (13 H). The DNP derivative was prepared according to the standard method,[25] m.p. 184—186 °C (lit.,[26a,b] 183—184 °C).

4-*Methylcyclohexanecarboxylic Acid* (**17**). Pyridinium dichromate[27] (1.6 g, 4.06 mmol) was added to a solution of the alcohol (**18**) (148 mg, 1.16 mol) in dry DMF (5 ml). The reaction mixture was stirred for 14 h at 20 °C and then poured into water (50 ml). Extraction with ether (4 × 50 ml) and work-up gave the acid (**17**)[26a,b] (0.155 g, 94%), $\nu_{max.}$(film) 3 100, 2 900, 1 705, 1 440, and 1 200 cm^{-1}; *m/z* 142 ($M^{+\cdot}$), 97, and 56.

1,4-*Dimethylcyclohexanol.* (**20**). To a suspension of magnesium (6.08 g, 0.25 mol) in dry ether (13 ml) was slowly added a solution of methyl iodide (35.5 g, 0.25 mol) in ether (75 ml). The reaction mixture was refluxed for 2 h and filtered. To half of the resulting solution (0.12 mol of methyl magnesium iodide) at 3 °C was added a solution of 4-methylcyclohexanone (11.2 g, 0.1 mol) in dry ether (75 ml). The temperature was allowed to rise slowly to 20 °C and the stirring was continued for 16 h. The crude reaction mixture was poured into saturated aqueous ammonium chloride and extracted with ether (2 × 75 ml). After the usual work-up a white crystalline residue was obtained (3.2 g, 25%). N.m.r. and g.l.c. analysis showed that this material was essentially the tertiary alcohol (**20**)[26a] contaminated by traces of 4-methylcyclohexanone, $\nu_{max.}$(film) 3 450, 2 950, 2 860, 1 460, 1 440, and 1 380 cm^{-1}; δ($CDCl_3$) 2.4—0.9 (10 H), 1.29 (3 H, s, 1-Me), and 1.05 (3 H, s, 4-Me).

Dehydration of 1,4-*Dimethylcyclohexanol* (**20**).—A solution of the title compound (**20**) (128 mg, 1 mmol) and toluene-*p*-sulphonic acid (19 mg, 0.1 mmol) in benzene (15 ml) was refluxed for 2 h in a Dean-Stark apparatus. The crude reaction mixture was poured into saturated aqueous sodium hydrogen carbonate. After the usual work-up, the solvent was carefully removed under reduced pressure at 20 °C. G.l.c. analysis showed that the starting material had disappeared with formation of 1,4-dimethylcyclohexene,[26] $\nu_{max.}$(film) 2 900, 1 450, and 1 370 cm^{-1}; δ($CDCl_3$) 5.30 (1 H, m, C=CH) and 2.43—0.82 (13 H).

Stability of 1,4-*Dimethylcyclohexanol* (**20**) *under Gif Conditions.*—The title compound (**20**) was treated under the Gif^{IV} conditions in the absence of iron-catalyst (**9a**) [pyridine–water (6.6% v/v), 20 °C, air, 4 h]. After treatment (*e*), g.l.c. analysis indicated that 85% of the starting material had been recovered and no trace of 1,4-dimethylcyclohexene was observed.

Oxidation of Adamantanone (**4**) *by the* Gif^{IV} *System.*—A mixture of adamantanone (**4**) (1.50 g, 10 mmol), iron catalyst (**9a**) (25 mg), zinc (6.5 g, 0.1 mol), pyridine (150 ml) and acetic acid (13 ml, 0.21 mol) was stirred at 30 °C under a static pressure of oxygen provided by a balloon for 12 h. Work-up procedure (*b*) afforded a residue which was subjected to silica gel column chromatography. Elution with chloroform containing increasing proportions of ether gave successively adamantanone (**4**) (1.15 g, 77%), adamantan-2,4-dione (**21**)[28] (100 mg, 6.1%) and adamantane-2,6-dione (**22**)[29] (50 mg, 3%) which were authenticated by g.l.c. (co-injection with authentic samples). Direct analysis of the crude reaction mixture by g.l.c. gave the diones (**21**) (7.9%) and (**22**) (2.3%).

Oxidation of Cyclohexene (**25**) *by the* Gif^{III} *System.*—Cyclohexene was purified by washing several times with an acidic solution of ferrous sulphate, with water, and finally with brine. After drying ($MgSO_4$), cyclohexene was passed through an alumina (grade I) column and twice distilled from sodium.

A mixture of purified cyclohexene (**25**) (4.1 g, 50 mmol), iron powder (5.58 g, 0.1 mmol), acetic acid (12 ml, 0.2 mol), pyridine (28 ml), and water (2 ml) was stirred for 9 h at 40 °C under a flow of oxygen. Work-up procedure (*b*) gave a crude mixture which was separated by preparative t.l.c. Two compounds were isolated: cyclohex-2-enone (**26**), δ($CDCl_3$) 6.97 (1 H, m, J_1 10 Hz, J_2 4 Hz), 5.97 (1 H, d, *J* 10 Hz), 2.37 (4 H, m), and 2.0 (2 H, m); and cyclopent-1-enecarbaldehyde (**27**), δ($CDCl_3$) 9.7 (1 H, s), 6.81 (1 H, m), 2.6 (4 H, m), and 2.0 (2 H, m). The structure of these two compounds was confirmed by comparison with authentic samples (n.m.r., g.l.c.), [cyclopent-1-enecarbaldehyde was prepared according to the lit.,[30]]. Yields of compounds (**26**) (1.1%) and (**27**) (1.3%) were determined by g.l.c. of the crude ethereal extract. No cyclohexeneoxide (**28**), stable under Gif^{III} conditions, could be detected.

Oxidation of Diphenyl Sulphide (**29**) *by the* Gif^{III} *System.*—Diphenyl sulphide (1 ml, 6 mmol) was oxidized under Gif^{III} conditions [pyridine (28 ml), water (2 ml), iron powder (3.03 g, 54 mmol), acetic acid (6.2 ml, 108 mmol), 23 h, 30 °C, static pressure of oxygen (1 atm)]. Work-up procedure (*b*) gave a crude mixture which was separated by silica gel column chromatography: diphenyl sulphide (**29**) (98%) and diphenyl sulphoxide (**30**) and diphenyl sulphone (**31**) (less than 1%) were recovered. Authentic samples of (**30**) and (**31**) were prepared according to refs. 31 and 32.

Attempted Reduction of Diphenyl Sulphoxide (**30**) *by the* Gif^{III} *System in the Absence of Oxygen.*—To a mixture of degassed pyridine (14 ml) and water (1 ml), diphenyl sulphoxide (1.27 mmol), iron powder (25 mmol) and acetic acid (50 mmol) were added. After 25 h at 30 °C under a nitrogen atmosphere the reaction mixture was treated as in (*b*). The residue was purified by preparative t.l.c. to give diphenyl sulphoxide (**30**) (60%, m.p. 66—68 °C, lit.,[31] 69—71 °C) and diphenyl sulphide (**29**) (less than 1%).

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