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The Selective Functionalization of Saturated Hydrocarbons. Part 44. Measurement of Size of Reagent by Variation of Steric Demands of Competing Substrates using Gif Chemistry.†

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Abstract: Cyclohexane has been co-oxidized with a number of aromatic compounds of varying steric requirements. The oxidant was hydrogen peroxide with Fe^{III}-picolinic acid in a Gif type solvent of pyridine and acetonitrile. Both the cyclohexane and the aromatic derivatives were reacting with the same iron species. From the steric requirements for the hydroxylation of the aromatic partner, it can be deduced that the iron species is of significant size. For this reason, and also because of known pulse radiolysis results, hydroxyl radicals are not involved. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Gif Chemistry began with the concept that saturated hydrocarbons might be selectively substituted by oxidation with oxygen and iron powder in pyridine-acetic acid in the presence of hydrogen sulfide.[1,2] Although this recreation of the world as it was 3 billion years ago, when the blue algae first started to make oxygen was highly speculative, it did produce a better conversion and higher selectivity for ketone formation than preceding systems. Also, the reactions at 30° or so and at a pH close to neutrality, were pleasingly similar to biogenetic conditions.

Much of the early work was done with adamantane. The apparent selectivity for ketone formation was, in fact, due to capture by pyridine of tertiary adamantyl radicals.[3] Even so, the normalized value for C^2/C^3 selectivity (per hydrogen) was 0.35, different from the typical radical reactivity of 0.1.[4] We carried out careful model experiments to show that **had carbon radicals been generated at the secondary position of adamantane, they would have been captured by pyridine under the reaction conditions.**[5] At the same time, we showed that the ratio of oxidation to pyridine radical trapping was completely different at both secondary and tertiary positions in Gif oxidations from that seen in radical reactions at the same reduced oxygen pressure.[6]

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†This paper is dedicated to Prof. Peter Welzel (Leipzig) on the occasion of his 60th birthday.

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The nature of the unusual iron species responsible for selective hydrocarbon oxidation remains an interesting challenge. We have for some years proposed that an Fe^V species is responsible for the novel chemistry observed.[5] Also, the hypothesis of the iron-carbon bond has long been maintained to explain *inter alia*, the unusual reactivity of the tertiary position in adamantane (radical formation).[5,6] **Be these considerations as they may, the electrophilic nature of the iron and its size can be explored without an exact specification** of its valence state. It was clear from the early work on the oxidation of natural products that the reagent was electrophilic in nature.[7,8] In the oxidation of cyclohexane to cyclohexanone, there was no formation of adipic acid. A second ketone function was eventually introduced to give cyclohexane-1,4-dione.[9] Similarly in the oxidation of cyclododecanone, there was no attack on the α-position and the major products were the 1,4-, 1,5- and 1,6- diones.[10] So far as the steric demands of the iron species are concerned, it is clear that, in the absence of electrophilic considerations, hindered methylene groups are less attacked than those that are unhindered.[7,11] In the steroid nucleus, the most hindered methylene at C_{11} is the least attacked.[8,12,13]

In recent years there has been some discussion about the role of radical chemistry in Gif oxidation.[14,15] We have recognized two manifolds.[16] The Fe^{III}-Fe^V manifold covers all the earlier chemistry where, with the exception of the tertiary position in adamantane, radicals were not detected. The Fe^{II}-Fe^{IV} manifold is also considered to form at first an iron-carbon bond, but this easily breaks into Fe^{III} and a carbon radical. The latter is readily trapped. All the experiments described in the present paper take place in the Fe^{III}-Fe^V manifold.

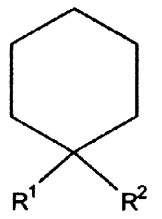
Last year in 1996, Newcomb[17] reported studies on the oxidation of his elegant hypersensitive radical probes using $Fe^{III} + H_2O_2$ and Fe^{III} + *tert*-butyl hydroperoxide. In the latter case, as we would have expected,[18] carbon radicals were formed and detected by ring opening. However, the same experiments applied in the Fe^{III}-H_2O_2 system also showed radical formation and ring opening. Since the Fe^{III}-H_2O_2 system does not give any indication of radicals, except at the tertiary positions of adamantane, this seeming paradox must be explained by the formation and then fragmentation of an iron-carbon bond.[18] In fact, we consider it good evidence for the formation of the latter.

Of more concern was the report of phenol formation in the oxidation of toluene,[19] as well as the expected side chain oxidation. In an earlier paper,[20] we reported that oxidation of diphenyl (5mmol, 95% of recovery) was not seen when 5mmol of cyclododecane were oxidized to ketone (20%) and alcohol (4%). Of course in cyclododecane, there are 24 methylenic C-H bonds whereas in the diphenyl, there are only 10 C-H bonds present.

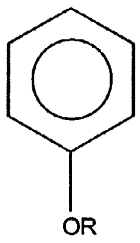
We decided that co-oxidation of cyclohexane and benzenoid hydrocarbons would provide information about the relative reactivity of the components. By variation of the relative amounts of the substrates, it would be possible to demonstrate that the same electrophilic iron species was involved. Furthermore by variation of the degree of hindrance of the benzenoid compound, it should be possible to measure the size of the electrophilic reagent. Thus, an hydroxyl radical would have little size restriction on its reactivity, whereas an Fe^V species bonded to picolinic acid should have significant bulk. So far as we are aware, this kind of experiment has not been carried out before in hydrocarbon oxidation chemistry.

In preliminary experiments, the oxidation of varying amounts of cyclohexane **1** and benzene in pyridine using picolonic acid as ligand showed that the cyclohexyl hydrogens were about 10 times more reactive than the aromatic-C-H groups after normalization per hydrogen. Of course, the aromatic -C-H groups are not activated by insertion or abstraction, but surely by addition. So, we are using a convenient formalism. From cyclohexane, mainly cyclohexanone **2** was formed and from benzene, phenol **8** was produced in accordance with the findings of Newcomb.[17] When a mixture of acetonitrile (33ml) and *t*-butylpyridine (15mmol) was used as solvent, [21] the cyclohexane C-H bonds were about 7 times more reactive than the aromatic C-H groups. Finally using acetonitrile (23ml) and pyridine (7ml), the original ratio of about 12 was seen. All the further experiments in this paper were carried out in this solvent mixture.

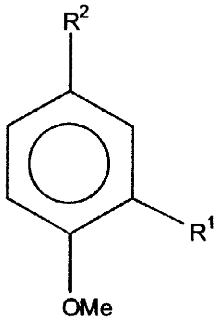
Since benzene was not very reactive, it seemed more reasonable to study anisole **3**. The results are summarized in Table 1. Oxidation of cyclohexane **1** alone (Entry 1) gave a normal amount of cyclohexanone **2** and alcohol **4**. The oxidation of anisole **3** afforded the 2-hydroxy- and 4-hydroxy-derivatives (**6** and **7**, respectively), but no 3-hydroxy-anisole was detected in any of our experiments. The amount of derivatives **6** and **7** was about one half of the oxidation products from cyclohexane.



1 $R^1=R^2=H$
2 $R^1=R^2=O$
4 $R^1=OH, R^2=H$
10 $R^1=OOH, R^2=H$



3 R=Me
5 R=CHO
8 R=H
9 $R=CH_2OH$



6 $R^1=OH, R^2=H$
7 $R^1=H, R^2=OH$

Then in Entries 2 and 3, a competition between cyclohexane and anisole oxidation was carried out. An equimolecular competition (Entry 2) gave smaller amounts of oxidation for both cyclohexane and anisole in agreement with competition for the same amount of oxidation (4mmol H_2O_2). An excess of anisole (x 2) increased **6** and **7** slightly and decreased the cyclohexane oxidation. In all the competitive oxidations, a small amount of phenyl formate **5** was detected as well as some phenol **8**. This may have come from **5** by hydrolysis or from the hydroxymethyl analogue **9** by fragmentation to phenol and formaldehyde. The former explanation seems more reasonable. The formation of **5** and **8** was normal Gif Chemistry.

The other Entries in Table 1 use different ratios of cyclohexane and anisole and show in each case the competitive oxidation. The final column in Table 1 gives a ratio of the normalized results per hydrogen for cyclohexane (Ane) oxidation versus the anisole (Aro) oxidation to phenolic products. If reactivity were independent of concentration, then these numbers should be identical. From Entries 6 and 8, it is clear that higher concentrations appear to provoke higher reactivity. Nevertheless, the differences are small enough that the same reagent must be involved in both the oxidation of cyclohexane and of anisole.

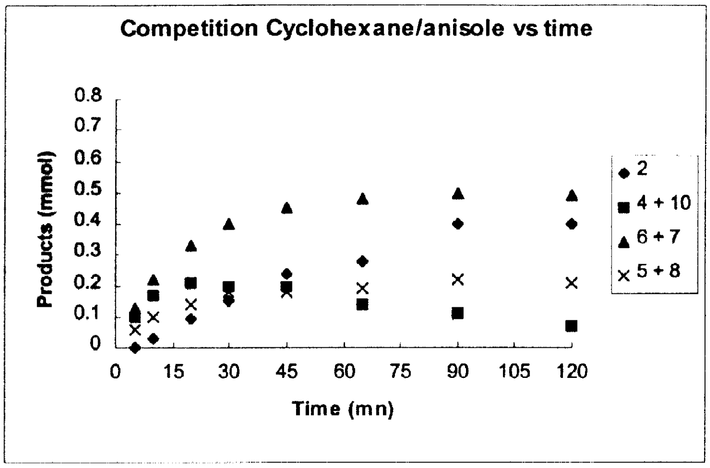
Table 1. Competition Experiments between Cyclohexane and Anisole. Variation of the substrate ratio.
(All data in mmol.)

$FeCl_3$, 6 H_2O 1.00mmol
Picolinic Acid 2.50mmol
H_2O_2 (30%) 4.00mmol
under air, at RT (5h)

Entry	RH **1**	ArH **3**	**2**	**4**	**5**	**6**	**7**	**8**	Ane/Aro norm.
1	20	0	1.20	0.08	-	-	-	-	-
2	20	20	0.72	0.10	0.08	0.14 (88)[a]	0.02 (12)	0.03	**1.80**
3	20	40	0.57	0.08	0.13	0.24 (77)	0.07 (23)	0.04	**1.50**
4	0	20	-	-	-	0.51 (76)	0.16 (24)	0.10	-
5	40	0	1.11	0.11	-	-	-	-	-
6	40	20	0.90	0.11	0.05	0.07 (88)	0.01 (12)	0.01	**2.30**
7	10	0	0.72	0.04	-	-	-	-	-
8	10	40	0.38	0.06	0.20	0.37 (82)	0.08 (18)	0.03	**1.60**

[a] Phenols distribution in %.

A kinetic study of Entry 8 (Table 1) is shown in Scheme 1. The formation of the ketone **2** from the hydroperoxide **10** is evident form the experiments quenched with triphenylphosphine. As would be expected from the same iron species throughout the normalized ratios (Ane/Aro) are 1.2(5′); 1.5(10′); 1.5(20′); 1.4(30′); 1.6(45′); 1.5(65′); 1.7(90′); 1.6 (120′).



Reaction conditions: $FeCl_3,6H_2O$: 1.00mmol; PA: 2.5mmol; Pyridine: 7.00mL; Acetonitrile: 23mL; Anisole: 40mmol; Cyclohexane: 10mmol; H_2O_2: 4.00mmol at RT under air.

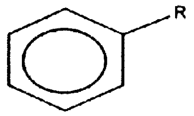
Scheme 1

Table 2. Competitive Experiments between Cyclohexane and Various Aromatic Derivatives.
(All data in mmol.)

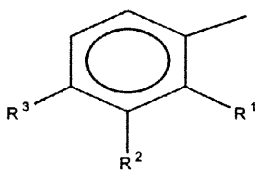
Entry	Substrates	O_2	2	4	Aromatics	Mass Balance % (M.B.)	Ane/Aro normalized
1	Benzene 40	0.41	-	-	**8** 0.30	116	-
2a	**1** 9.2 **3** 36.8	-0.17	0.38	0.06	**6** 0.37, **7** 0.08 **8** 0.03, **5** 0.20	103	1.6
2b (no PA)	**1** 9.2 **3** 36.8	1.60	0.01	0.02	Zero aromatics	105	-
3	**1** 9.2 **11** 37.6	0.20	0.45	0.04	**12** 0.12, **13** 0.03 **14** 0.05, **15** 0.23	98	4.2
4	**1** 9.2 **16** 32.7	-0.17	0.31	0.07	**17** 0.02, **18** 0.12 **19** 0.33	96	3.2
5	**1** 9.2 **20** 28.8	-0.37	0.22	0.03	**21** 0.00, **22** 0.32 **23** 0.02	94	∞

Reactions conditions: $FeCl_3,6H_2O$: 1.00mmol; picolinic acid (PA) 2.5mmol; Pyridine: 7.0mL; Acetonitrile: 23mL; H_2O_2 (30%): 4.0mmol at room temperature under air for 3hr (24hr for mesitylene).

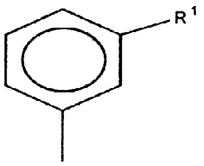
In Table 2, various aromatic molecules of increasing steric hindrance were competitively oxidized in the presence of cyclohexane. Entry 1 shows the yield of phenol **8** produced from 40mmol of benzene. The greater reactivity of anisole has been studied in Table 1 (see Entry 8). However, if the picolinic acid ligands are not added then, as shown in Entry 2b, there was almost no oxidation and certainly no phenolic products. In Entry 3, the competitive oxidation of cyclohexane and toluene **11** is reported. The three possible phenols **12**, **13** and **14** were found as well as benzaldehyde **15**. The latter, a normal Gif product, was the major compound formed. The cyclohexane oxidation was normal. More interesting was the competition with *meta*-xylene. This gave the phenol **17** and in major amount, the phenol **18**. The aldehyde **19** was, however, the principal oxidation product. Again, Gif Chemistry was dominant. The formation of **19** was responsible for the lowered yield of cyclohexanone. The competitive oxidation of cyclohexane and mesitylene was surprising. No mesitol **20** was formed and the aldehyde **22** and alcohol **23** were the only products. Even the oxidation of cyclohexane was diminished. *p*-Xylene also behaved like mesitylene and no phenolic products were detected. From these results, it is clear that the same species reacts with cyclohexane and with the aromatic substrates. From the relative reactivity of benzene and anisole, it is clearly electrophilic. In agreement, nitrobenzene and chlorobenzene were not oxidized. From the failure to give any phenolic product with mesitylene, the iron species must be bulky and certainly not like a hydroxyl radical.



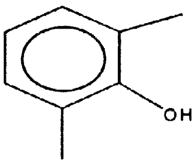
11 R=Me
15 R=CHO



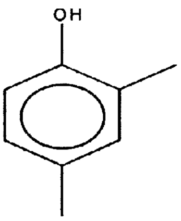
12 R^1=OH, R^2=R^3=H
13 R^2=OH, R^1=R^3=H
14 R^3=OH, R^1=R^2=H



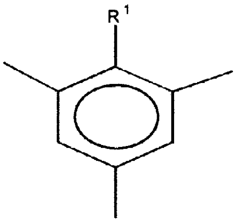
16 R^1=Me
19 R^1=CHO



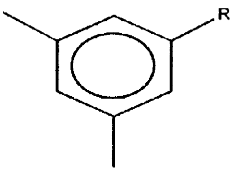
17



18



20 R^1=H
21 R^1=OH



22 R^1=CHO
23 R^1=CH_2OH

Another kind of competition that can give useful information is that with diphenyl sulfide.[22] In Table 3, a competition between cyclohexane, anisole and diphenyl sulfide has been established. The data without picolinic acid show that oxygen is formed with trace oxidation of cyclohexane and no phenol formation. In the presence of diphenyl disulfide, oxidation of the latter largely replaces the formation of oxygen as would be expected.[23] The addition of the ligand picolinic acid completely changed the picture. There was not formation of oxygen. The amounts of ketone **2** and alcohol **4** were the same with, or without, the diphenyl sulfide. The data for anisole were also very similar in both cases. However, now there was essentially no oxidation of the diphenyl sulfide.

Table 3. Competitive oxidation of Cyclohexane, Anisole and Diphenyl Sulfide.
(All data in mmol.)

Ph_2S	$^{\cdot}O_2$	**2**	**4**	**5**	**6**	**7**	**8**
			Without Picolinic Acid				
-	1.6	0.01	0.02	0	0	0	0
Ph_2S* (10mmol)	0.53	0	0.03	0	0	0	0
			With Picolinic Acid				
-	-0.17	0.38	0.06	0.20	0.37	0.08	0.03
Ph_2S** (10mmol)	-0.04	0.37	0.06	0.13	0.30	0.06	0.08

Reaction Conditions: $FeCl_3,6H_2O$: 1.00mmol; PA: 0 or 2.5; Pyridine: 7.00mL; Acetonitrile: 23.00mL; H_2O_2 (30%): 4.0mmol; Cyclohexane: 9.2mmol; Anisole: 36.8mmol at room temperature under air for 5hr. *Products--Ph_2SO 3.10 + Ph_2SO_2 0.02. **Products--Ph_2SO 0.12

The dramatic change produced by the picolinic acid encourages us to examine the effect of the ratio of picolinic acid to the Fe^{III}. Previously, we had determined[23] by quantitative ^{13}C NMR that two picolinic acids were bound to each Fe^{III}. However, it was of interest to know if 1 picolinic acid per iron would be 50% of the species with 2 ligands and 50% without the picolinic acid. In fact, one picolinic acid per Fe^{III} produced almost entirely oxygen and there was only trace oxidation of cyclohexane **2** and of anisole **3**. This further supports the conclusion that it is the same reagent that attacks both substrates.

Until recently, Gif Chemistry has been carried out in pyridine-acetic acid. It was of interest, therefore, to carry out experiments with acetic acid as the carboxylate ligand instead of picolinic acid. The results are summarized in Table 4. Entries 1 and 2 are similar to Entries 3 and 4 in Table 2. However, with mesitylene, there is formation of a small amount of mesitol. We conclude that the acetate derived reagents is somewhat smaller than the picolinate reagent, a result which is not surprising.

Table 4 Influence of the ligand to Fe^{III} on the Selectivity in Competition Experiments.
All Data in mmol.

Entry	Substrates	O_2	**2**	**4**	Aromatics	Mass Balance %	Ane/Aro normalized
1	**1** 9.2 **3** 36.8	0.43	0.27	-	**6** 0.14, **7** 0.05, **8** 0.04	105	2.7
2	**1** 9.2 **16** 32.7	0.54	0.21	0.04	**17** 0.02, **18** 0.07, **19** 0.27	106	3.3
3	**1** 9.2 **20** 28.8	0.58	0.11	0.06	**21** 0.05, **22** 0.20	100	2.7

Reaction conditions: $FeCl_2,6H_2O$: 1.00mmol; CH_3CO_2H: 3mL; Pyridine: 7.0mL; Acetonitrile: 20.0mL; H_2O_2 (30%): 4.00mmol at room temperature under air for 3hr.

The formation of chlorides and azides in Gif oxidation is characteristic of radical chemistry in the Fe^{II}-Fe^{IV} manifold.[22] Bromides can also be formed in this way, but in the Fe^{III}-Fe^{V} manifold bromides are formed by non-radical chemistry of $BrCCl_3$. Iodides are produced from iodide anion in both manifolds and are characteristic for the iron-carbon bond.[24]

We examined the competitive reaction of cyclohexane and *m*-xylene in the Fe^{III}-Fe^{V} manifold (Table 5). As expected LiBr, LiCl and NaN_3 (Entries 1, 2 and 4) gave no derivatives of either cyclohexane or *m*-xylene. The bromide ion (Entry 1) reduced oxidation of cyclohexane and no phenol derivatives could be detected. The LiCl (Entry 2) and NaN_3 (Entry 4) also gave no derivatives, but the oxidation of the substrates was normal. As before,[24] the LiI dominated the reaction and cyclohexyl iodide (X=I) was the major product (Entry 3). Counting the iodide as a reflection of cyclohexane activation the Ane/Aro ration was normal.

With $BrCCl_3$ (Entry 5), cyclohexyl bromide was a major product. The *m*-xylene was oxidized to **17** and **18** in an approximately normal ratio, but *m*-methylbenzaldehyde was the major product. The effect of an oxygen stream (Entry 6) was little different from working under air. *t*-Butanol, which is well-known[25] to give a crystalline dimer from the Fenton reagent, had no effect at all on Gif oxidation (Entry 7). Since hydroxyl radicals were not present, this result was not surprising.

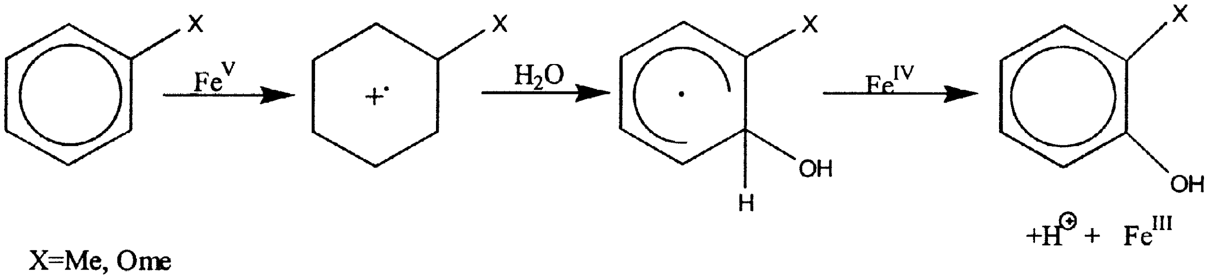
Table 5. Effect of various trapping agents on the competition between cyclohexane and *m*-xylene.

Entry	Additive	$C_6H_{11}X$	**2**	**4**	**17**	**18**	**19**	Mass Balance %	Ane/Aro Normalized
	No	-	0.31	0.07	0.02	0.12	0.33	96	**3.2**
1	LiBr (5.6mmol)	-	0.10	0.07	-	-	0.19	96	∞
2	LiCl (10.0mmol)	-	0.22	0.03	0.03	0.08	0.03	96	**2.7**
3	LiI (3.1mmol)	0.34	-	0.03	0.02	0.12	0.07	96	**3.1**
4	NaN_3 (7.9mmol)	-	0.28	0.07	0.01	0.07	0.32	93	**4.6**
5	$BrCCl_3$ (3.00mmol)	0.34	-	-	0.02	0.07	0.38	94	**4.5**
6	O_2 stream	-	0.30	-	0.02	0.11	0.41	96	**2.7**
7	*t*-BuOH[a] (5.00mmol)	-	0.33	0.04	0.02	0.12	0.27	97	**2.9**

Reaction Conditions: $FeCl_3,6H_2O$: 1.00mmol; PA: 2.5mmol; Pyridine: 7.00mL; Acetonitrile: 23.00mL; H_2O_2 (30%): 4.00mmol; Cyclohexane: 9.2mmol; *m*-xylene: 32.7mmol at room temperature under air for 3hr. [a]*Tert*-Butanol Mass Balance was 96%.

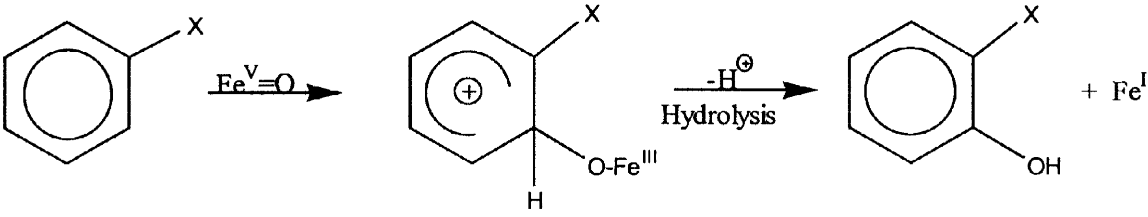
Stavropoulos *et al.*[26] and Sawyer[27] have both pointed out that pulse radiolysis of toluene gave 97% addition of hydroxyl radicals to the aromatic nucleus and only 3% attack upon the methyl group. Thus, real hydroxyl radicals are very different from Gif reactivity. In Table 2, Entry 3, the data for toluene show that the substitution on the aromatic ring is 0.20mmol, whilst the methyl group is transformed to 0.23mmol of benzaldehyde. The same considerations apply for the oxidation of *m*-xylene (Table 2, Entry 4) where phenol formation was only 0.14mmol whilst side-chain attack gave 0.33mmol of aldehyde.

The formation phenols cannot come from an oxygen insertion into an aromatic C-H as this bond strength is too great. We have considered two alternative processes. An electron transfer from the aromatic nucleus to Fe^V=O would give a radical cation (Scheme 2).



Scheme 2. The Electron Transfer Mechanism

The addition of water followed by a second electron transfer would furnish the observed product and Fe^{III}. However, this mechanism cannot be correct. When the oxidation of benzene to phenol was carried out in anhydrous pyridine with anhydrous ferric chloride and 100% hydrogen peroxide to which water (depleted almost completely of O^{17} and O^{18}) had been added, the isotope ratio in the phenol was normal. This showed that the oxygen in the phenol had come from hydrogen peroxide and not from the water that was added.



Scheme 3. The Fe^V=O Addition Mechanism.

The second mechanism shown in Scheme 3 involves addition of an Fe^V oxenoid to the benzene ring. This is compatible with the results of the water experiment described above. It also explains the electrophilic nature of the reagent and agrees with our finding that it is not small like the hydroxyl radical.

Experimental.

1. General.

Except for pyridine and acetonitrile whose purity was checked, all other solvents were redistilled. Chemicals, after verification, were used as purchased.

2. GC and GCMS instruments and techniques.

GC: all analyses were performed employing a Hewlett-Packard 5890 series II instrument, on a Chrompack Model 439 or 437S instrument with a flame ionization detector and Hewlett-Packard 3396A integrator. Prepurified N_2 was used as the carrier gas. The capillary columns used were DB-Wax (polyethylene glycol, 30m x 0.32mm, 0.25μm) and/or DB-1 (chemically bonded methyl silicone, 15m x 0.32mm, 0.25μm) from J&W Scientific. The routinely employed temperature program was: 50°C, 5min, 20°C min^{-1}, 245°C, 10min (for cyclohexane and cyclooctane). Injector and detector temperatures were 245°C and 300°C, respectively. All products had identical retention times with authentic samples. GCMS: all analyses were carried out on a Hewlett-Packard 5890A series II gas chromatograph using an HP-5971 series quadrupole mass-selective detector (40eV, electron impact). The column in the GC was an HP-5MS (cross-linked 5% Ph Me Silicone, 30m x 0.25mm, 0.25μm). The routinely employed temperature program was 50°C, 5min, 20°C min^{-1}, 10min.

3. Typical conditions and work-up procedures for catalytic oxidations.

A 0.27g amount of $FeCl_3,6H_2O$ (1mmol) and 0.31g of picolinic acid (2.5mmol) were dissolved in 7mL of pyridine and 23mL of acetonitrile. The mixture was stirred for 30min before adding the amount(s) of substrate(s) as reported in the different tables. 30% aqueous hydrogen peroxide (0.4mL, 3.9mmol) was then added dropwise to the resulting stirred solution at room temperature.

Product quantification was carried out 5 hours later as follows:
A 2mL aliquot was withdrawn and diluted into 5mL of water. The aqueous solution hence obtained was extracted with 10mL of diethyl ether and 1mL of a0.047 naphthalene solution in diethylether (internal standard). The resulting dried solution was analyzed by GC using appropriate correction factors which were determined using the same work-up procedure with synthetic mixtures of authentic samples.

The determination of the residual oxidizing power and Fe^{II} titrations were performed with 1mL aliquots following procedures already described by our group.[16]

When dioxygen formation was monitored, the reaction flask was made gastight (before adding H_2O_2) and connected to a manometric burette filled with brine saturated with oxygen prior to use.

4. Carboxylic acid quantification.

Benzoic acid: The acid was quantified as its corresponding methyl ester as follows:
A 2mL aliquot was withdrawn and diluted into 4mL of 20% H_2SO_4 at 0°C. The aqueous solution was extracted with 10mL of diethylether and 1mL of a 0.04M naphthalone solution. The resulting mixture was dried and an excess of freshly prepared diazomethane was added 10min before the analysis of the sample. The correction factor was determined using this same work-up procedure with authentic benzoic acid.

3,5-dimethylbenzoic acid: All the reaction mixture was poured into 30mL of H_2SO_4 (20%) at 0°C and the aqueous phase was extracted 3 times with diethylether. The resulting organic layers were mixed and extracted 3 times with 20% NaOH and then the aqueous phases neutralized with concentrated HCl. The carboxylic acid was then recovered by extracting twice the neutral aqueous solution with diethylether. After drying, ether was removed under reduced pressure. The residue was weighted and a known amount of 1,1,2,2 tetrachloroethane (internal standard) was added. The quantification was done in acetone d_6 using 200 MHz ^{1}HNMR.

1HNMR (acetone d_6): S 2.35 (S,6H,CH_3); 7.25 (S1H,H aro); 7.65 (S, 2H, aro).

The procedure was checked first on a synthetic mixture whose composition was similar to the reaction crude.

5. Kinetics of cyclohexane vs. anisole competitive oxidation.

A two-scale typical experiment was carried out with cyclohexane (2mL, 18.5mmol) and anisole (8mL, 73.6mmol) as described before. Each 2mL aliquot was quenched by 5mL of water and the resulting mixture extracted with 10mL of a 0.04M triphenylphosphine solution in diethylether and 1mL of the usual naphthalene solution. The organic mixture was dried and analyzed by GC.

6. Influence of the ligand on the ane/aro selectivity.

The typical procedure was slightly modified as follows: Picolinic acid was replaced by 3mL of glacial acetic acid and the volume for acetonitrile was reduced to 20mL, all other conditions remaining the same.

7. Origin of oxygen in the phenol produced by the H_2O_2/Fe^{III}/benzene reaction. Use of H_2O depleted in ^{17}O and ^{18}O.

The natural abundances of oxygen are ^{16}O – 00.76%, ^{17}O – 0.38% and ^{18}O 0.200%. The depleted water from Isotec Inc. Matheson had a minimum of 99.98% ^{16}O.

The experiments were carried out as follows: $FeCl_3$ anhydrous (1.0mmol) in freshly dried and distilled pyridine (22mL) containing picolinic acid (4mmol) and benzene (45mmol) was treated with anhydrous H_2O_2 (4.0mmol) in pyridine (8mL) in the presence of water (0.5mL) which either depleted (see above) or normal (for the blank expt.).

The anhydrous H_2O_2 in pyridine was prepared from the H_2O_2 –urea complex as follows: The complex (2.5g) was stirred with pyridine (30mL) for 15min and the heterogenous mixture was stored in a freezer for 20min. The ppt. of urea was filtered and rinsed with cold pyridine. The total volume was adjusted to 50mL. with pyridine and then contained (iodometric titration) 0.5 mmol of H_2O_2 per mL.

The blank expt. gave 0.2mmol of phenol (Fe^{II} – 18%) whilst the reaction with the ^{16}O depleted water gave 0.2mmol of phenol (Fe^{II} – 24%).

In order to obtain reliable GCMS results, we isolated the phenol. Potassium *t*-butoxide (9.0mmol) was added to each solution. The resulting solution was evaporated *in vacuo* and the solid residue was taken up in acidified water (pH<7). A blank experiment with reagent grade phenol was carried out first. The GCMS results were as follows:

	p+1	*P*+2
Commercial Phenol Blank (after being taken through the work-up procedure)	6.54	0.33
Blank expt. with ordinary water	6.60	0.32
Reaction with depleted water	6.27	0.37

The difference is not significant.[28] Hence the oxygen in phenol comes from H_2O_2 and not from water.

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