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The Selective Functionalization of Saturated Hydrocarbons. Part 47. Investigation of the Size of the Reagent Involved in the Fe^{II}-Fe^{IV} Manifold.

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Abstract: Competition experiments between cyclohexane and various aromatic substrates have been carried out in pyridine-acetonitrile in order to ascertain the steric requirements of the Fe^{II}-H_2O_2 reagent in comparison with the Fe^{III}-H_2O_2 reagent already studied. The latter is distinctly larger and much less reactive than the former. Although these results might indicate that the Fe^{II}-H_2O_2 reagent is simply the hydroxyl radical, the chemistry observed is strictly dependent on the presence of picolinic acid. Without the latter, no significant oxidation of any substrate is observed. Hydroxyl radical formation (Fenton Chemistry) is not considered to be ligand dependent in preceding investigations. © 1998 Elsevier Science Ltd. All rights reserved.

In Part 44 of this series,[1] we investigated the size of the reagent that attacks hydrocarbons in the Fe^{III}-Fe^{V} manifold. This was done by competing the oxidation of cyclohexane with a variety of aromatic substrates in which the degree of hindrance to addition and oxidation of the aromatic ring varied over a wide range. The reagent was large as it was subject to significant steric hindrance effects.

This paper reports the same sort of study in the Fe^{II}-Fe^{IV} manifold. In this manifold, the Fe^{IV} reacts with the hydrocarbon to form the Fe^{IV} carbon bond, which then in most, but not all cases, fragments into radicals.[2] The latter react with the pyridine in a Minisci type reaction. The best evidence for the nature of this Fe^{IV} species comes from our recent studies of the phenylselenation reaction,[3] where the phenylselenol was produced by reaction of tributylphosphine (50% excess) with diphenyl diselenide. The excess of phenylselenol would quench any radicals since its reactions are nearly diffusion controlled.[4] We concluded that the phenylselenation reaction was an example of Fe^{IV} ligand coupling.

At a first glance, the Fe^{II}-Fe^{IV} manifold when it produces carbon radicals might be considered a manifestation of hydroxyl radical formation. However, the preferred selectivity for secondary positions and the phenylselenation reaction[3] are not compatible with this suggestion. Moreover, in the absence of saturated hydrocarbon, the pyridine hydroxylation pattern does not agree with the pulse radiolysis data for real hydroxyl radicals.[5,6] Similarly, the pulse radiolysis pattern for the oxidation of (say) toluene is very different (aromatic substitution) from that seen with ordinary Fenton Chemistry. Another factor that must be taken into consideration is that Gif Chemistry in both of the manifolds is highly dependent on complexation of the Fe^{II} or Fe^{III} with the right kind of ligand[2] (e.g. picolinic acid).

With these considerations in mind, we decided again to determine the size of the reagent produced from the Fe^{II} + H_2O_2 reaction just as we had done[1] for the Fe^{III} -Fe^{V} manifold reagent.

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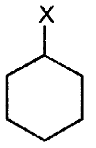
Results and Discussion.

A stoichiometric 1:1 Fe^{II}:H_2O_2 system was chosen for study since this avoids complications with Fe^{III} chemistry. A preliminary study on cyclohexane oxidation (Table 1) showed that the convenient pyridine-acetonitrile solvent system could vary considerably without altering, in a major way, the results. The amount of Fe^{II} was also determined. We opted for the ratio of 23:7 acetonitrile to pyridine for all the further experiments. The ratio of picolinic acid to Fe^{II} was kept at the theoretical value of 2. The expression ΣC_6Py refers to the total of 2- and 4-substituted pyridines produced by radical addition.

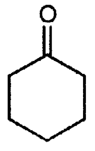
Table 1. Influence of the relative amount of Pyridine and CH_3CN on the efficiency of Fe^{II}/PA/H_2O_2 systems.

Entry	Py/CH_3CN (mL)	Fe^{II} (%)	**1**	**2**	**3**	ΣC_6Py	Eff. (%)
			(mmol)				
1	2/30	-	1.19	0.12	0.04	0.05	55
2	5/25	7	1.43	0.12	0.02	0.07	63
3	7.5/22.5	17	1.37	0.08	0.01	0.08	59
4	10/20	22	1.33	0.09	0.01	0.10	59

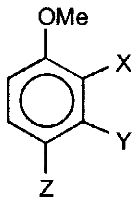
All the reactions were carried out at RT under static Ar and were analyzed 45min later. **Reaction conditions:** H_2O_2 (2.90mmol), $FeCl_2,4H_2O$ (3.0mmol), picolinic acid (6.0mmol) and cyclohexane (20.0mmol). Eff. = $[((1+\Sigma C_6Py)+2(2+3))x100]/2.90$.



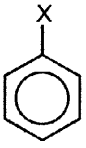
1 X=Cl
3 X=OH
7 X=H



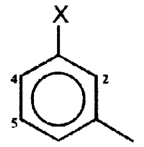
2



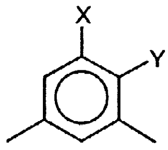
4 X=OH, Y=Z=H
5 Y=OH, X=Z=H
6 Z=OH, X=Y=H
8 X=Y=Z=H



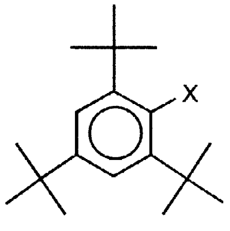
9 X=H
10 X=OH
11 X=Cl
12 X=Me
13 **12**-2-OH
14 **12**-3-OH
15 **12**-4-OH
16 X=CH$_2$Cl
17 X=CHO



18 X=Me
19 **18**-2-OH
20 **18**-4-OH
21 **18**-5-OH
22 X=CHO
23 X=CH$_2$OH



24 X=Me, Y=H
25 X=Me, Y=OH
26 X=CHO, Y=H
27 X-sidechain dimer, Y=H



28 X=H
29 X=OH

In Table 2, we show that in the absence of picolinic acid almost no oxidation took place (Entry 1). All the hydrogen peroxide was consumed to furnish 0.9mmol of oxygen, formed from Fe^{III} + H_2O_2 and the balance was used to convert Fe^{II} to Fe^{III}. The addition of one equivalent of picolinic acid per Fe^{II} (Entry 2) produced also only minor amounts of oxidation. However, the addition of two equivalents, as required to complete the bonding to Fe^{II}, gave the expected oxidation of cyclohexane in competition with oxidation of anisole (Entry 3). This is the same phenomenon that we saw in the Fe^{III} study.[1] So all the Fe^{II} reacts first with one picolinic acid, but the second picolinic acid is needed to effect oxidation.

Table 2. Influence of the Ligand/Fe^{II} Ratio on the Cyclohexane-Anisole Competitive Oxidation.

Entry	PA	X	O_2	**1**	**2**	**3**	$\sum C_6Py$	**4**	**5**	**6**	**10**
1	0[a]	ClO_4	0.90	-	0.02	0.03	-	0.02	-	-	0.02
2	3	Cl	0.11	0.04	0.12	0.04	-	0.14	-	0.12	0.01
3	6	Cl	0	0.41	0.05	0.03	0.06	0.64	-	0.35	0.03

[a] $FeCl_2,4H_2O$ was totally insoluble in the mixture of solvents used and had to be replaced by $Fe(ClO_4)_2,6H_2O$. **Reaction conditions:** $FeX_2,\alpha H_2O$ (3.00mmol); PA (6.00mmol); H_2O_2(30%) (3.00mmol); Pyridine (7.00mL); CH_3CN (23.00mL); cyclohexane (10.00mmol); anisole (40mmol) under static argon at RT (45 min). All data in Table are in mmol.

The experiments in Table 3 show that the oxidation of cyclohexane and of anisole are in competition as expected. The column Ane/Aro normalized is a reference to a summation of the cyclohexane and of the anisole oxidation products each divided by the number of hydrogens at which reaction could take place (12 for cyclohexane, 5 for anisole) and further corrected for the mole ratios of the substrates. Non-aromatic oxidation is not included in the calculations. The fact that the numbers in this column are nearly constant over a wide range of concentrations confirms that competitive oxidation is taking place.

Table 3. Competitive Oxidation of Cyclohexane-Anisole. Variation of the Substrate Ratio.

7	**8**	**1**	**2**	**3**	$\sum C_6Py$	**4**	**5**	**6**	**10**	Ane/Aro norm.
20	0	1.47	0.07	0.01	0.19	-	-	-	-	-
20	20	0.91	0.06	0.03	0.14	0.34	-	0.19	-	**0.89**
20	40	0.74	0.10	0.04	0.09	0.52	-	0.29	0.04	**0.95**
0	20	-	-	-	-	0.58	-	0.32	0.05	-
40	0	1.60	0.13	0.03	0.17	-	-	-	-	-
40	20	1.25	0.09	0.03	0.13	0.23	-	0.14	0.04	**0.76**
10	0	1.03	0.05	0.01	0.11	-	-	-	-	-
10	40	0.41	0.05	0.03	0.06	0.64	-	0.35	0.03	**0.90**

Reaction conditions: Cyclohexane/Anisole; $FeCl_2,4H_2O$ (3.00mmol); PA (6.00mmol); H_2O_2(30%) (3.00mmol); Pyridine (7.00mL); Acetonitrile (23.00mL) under static argon, at RT (5h). All data in Table are in mmol.

Table 4 contains the results which enable us to compare the size of the reagent from Fe^{II} + H_2O_2 with that already reported for Fe^{III} + H_2O_2.[1] The standard reaction (Entry 1) compares with the equivalent reaction with Fe^{III} in its efficiency.[1] The result with benzene (Entry 2) affords even less phenol than the Fe^{III}

experiment.[1] So again, the competition with benzene was not great enough for a meaningful comparison. The same applied to the competition between cyclohexane and chlorobenzene (Entry 3) where even less oxidation was observed in the aromatic partner. The electrophilic reactivity of the Fe^{II}-H_2O_2 reagent is comparable with that of the Fe^{III}-H_2O_2 reagent.[1] Again, we had to turn to anisole to secure a meaningful competition. Now there was nearly 1mmol of hydroxy-anisoles formed as compared with 0.5mmol cyclohexane derivatives (Entry 4).

Table 4. Competitive Oxidation of Various Aromatic Substrates and Cyclohexane.

Entry	Substrates (mmol)	**1** (mmol)	**2** (mmol)	**3** (mmol)	ΣC_6Py (mmol)	Aromatic Derivatives (mmol)	MB (%)	Ane/Aro norm.
1	**7** (10)	1.03	0.05	0.01	0.11	-	-	-
2	**7/9** (9.2/44.7)	- 0.64	0.10	0.02	0.06	**10** 0.20 0.11	98 -	18
3	**7/11** (9.3/39.3)	0.84	0.08	-	0.11	Traces (0.06) $C_6H_4Cl(OH)$	n.d.	**30**
4	**7/8** (9.2/36.8)	0.41	0.05	0.03	0.06	**4** 0.64 **6** 0.35 **10** 0.03	98	**0.9**
5	**7/12** (9.2/37.6)	0.45	0.08	0.01	0.05	**13** 0.16 **14** 0.02 **15** 0.06 **16** 0.03 **17** 0.05	108	**4.2**
6	**7/18** (9.2/32.7)	0.45	0.04	0.01	0.05	**19** 0.23 **20** 0.39 **21** 0.07 **22** 0.10 **23** 0.15	101	**1**
7	**7/24** (9.2/28.8)	0.32	-	-	-	**25** 0.89 **26** 0.05 **27** 0.21	96	**0.3**
8	**7/28** (9.2/4.7)	1.16	0.10	0.16	0.12	**29** 0.06 2 sidechain products	-	**2**

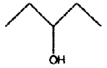
Reaction conditions: $FeCl_2,4H_2O$ (3.00mmol); PA (6.00mmol); Pyridine (7.00mL); Acetonitrile (23.00mL); H_2O_2(30%) (3.00mmol) at RT under argon for 45min. n.d. is not determined. MB--Mass balance for the aromatic derivative.

A similar ratio was seen with the Fe^{III} + H_2O_2 reagent,[1] but there was significant formation of phenyl formate in the earlier experiments.[1] A competition between cyclohexane and toluene (Entry 5) gave 0.2mmol of cresols and traces of benzaldehyde. With the Fe^{III}-H_2O_2 reagent, the amount of benzaldehyde was equal to toluene derived cresol formation. The picture with *meta*-xylene (Entry 6) was comparable with the results for toluene. The most sharply defined difference between the two reagents was seen in the competitive oxidation of cyclohexane and mesitylene (Entry 7). Here the Fe^{II}-H_2O_2 reagent gave three times as much phenolic product (0.9mmol) as cyclohexane was derivatized. Also, there was little attack on the methyl groups. This is in contrast with the Fe^{III}-H_2O_2 reagent where no phenolic derivative of mesitylene was formed at all and there was 0.34mmol of methyl group oxidation. Clearly, the Fe^{II}-H_2O_2 reagent is much less subject to steric constraints than the Fe^{III}-H_2O_2 reagent. We tested the limits of the steric requirements by using 1,3,5-tri-*t*-butyl benzene **28** as the aromatic competitor (Entry 8). Now only a trace of the phenol **29** was formed. Two side chain products were not identified, but they were readily separated from **29**. As would be expected when the aromatic substitution was diminished by steric hindrance, there was a major increase in the formation of cyclohexane derivatives.

At this point, it might be concluded that the steric hindrance data showed clearly that the Fe^{III}-H_2O_2 reagent was too bulky to be a hydroxyl radical. However, the Fe^{II}-H_2O_2 reagent might be generating hydroxyl radicals which were too bulky through solvation to react with 1,3,5-tri-*t*-butylbenzene.

In Table 5, we summarize some significant data relevant to these points. In Fenton Chemistry, it has always been considered that the important factor is Fe^{II} and not any ligands[7,8] associated with the Fe^{II}. In Table 5, we show that if Fe^{II} is present as Fe^{II} perchlorate, then no competitive oxidation between cyclohexane and anisole took place at all even though all the other factors were present including, of course, 3mmol of H_2O_2. If two easily oxidized substances (3 hydroxypentane and diphenylsulfide) are added in 10mmol amounts, then still the oxidation seen is negligible. If the reaction of Fe^{II} with H_2O_2 were generating hydroxyl radicals, then normal oxidation should have been seen.

Table 5. Effect of Additives on the Competitive Oxidation of Cyclohexane and Anisole.

Additive	1	2	3	ΣC_6Py	4	5	6	10	Ane/Aro norm.
				Without Picolinic acid					
				No Products					
 (10mmol)	- 3-pentanone:0.05	0.03	0.03	-	0.02	-	-	0.02	
Ph_2S (10mmol)	- Ph_2SO:0.03	0.05	0.03	-	0.02	-	-	0.05	
				With Picolinic acid					
-	0.41	0.05	0.03	0.06	0.64	-	0.35	0.03	**0.9**
 (10mmol)	0.32 3-pentanone:0.20	0.03	0.03	0.06	0.71	-	0.36	0.04	**0.7**
Ph_2S (10mmol)	0.32 Ph_2SO: 0.02 + Ph_2SO_2: 0.03	0.06	0.03	0.04	0.54	-	0.26	0.05	**0.9**

Reaction conditions: $FeCl_2,4H_2O$ or $Fe(ClO_4)_2,6H_2O$ [in the absence of Picolinic acid] (3.00mmol); PA (0 or 6.00mmol); Pyridine (7.00mL); Acetonitrile (23.00mL); H_2O_2(30%) (3.00mmol); cyclohexane (9.2mmol); anisole (36.8mmol) at RT, under argon, 45min.

In contrast with the two equivalents of picolinic acid added, then all returns to normal. The addition of 3-hydroxypentane disturbs slightly the usual oxidation pattern, but diphenylsulfide, as is common in Gif Chemistry,[2] has no effect. It is difficult to explain all this by a hydroxyl radical hypothesis.

Recent work has augmented the evidence against activation in the Fe^{II}-Fe^{IV} manifold by hydroxyl radicals. The phenylselenation of saturated hydrocarbons takes place in the presence of phenylselenol in the Fe^{II}-Fe^{IV} manifold.[9] Phenylselenol is a very efficient trap for radicals at a nearly diffusion controlled rate.[4] Hence, the high efficiency of oxidation that we see cannot be due to hydroxyl radicals.

Since there is general agreement that *tert.*-butyl hydroperoxide (TBHP) chemistry is simply radical chemistry,[10] it is possible to contrast these reactions with non-radical Gif Chemistry. In our first comparison,[11] we pointed out that the normalized radical reactivity of cyclooctane was 2-3 times greater than that of cyclohexane. In contrast, in Gif Chemistry, cyclohexane was 20% more reactive per hydrogen than cyclooctane. This relationship pertained in the Fe^{II}-Fe^{IV} manifold and in the Fe^{III}-Fe^{V} manifold. Hence, hydroxyl radicals cannot be the activating species for the hydrocarbon oxidation in either manifold.

Similarly, in the competitive oxidation of secondary alcohols and saturated hydrocarbons with TBHP as compared with the same competition in either manifold, the oxidation of the alcohols was about five times faster with TBHP than with either of the Gif manifolds. In fact, in the Fe^{II}-Fe^{IV} manifold, there was less oxidation of the secondary alcohol than in the Fe^{III}-Fe^{V} manifold. Hence, again hydroxyl radical oxidation is not involved.[12]

In traditional Gif Chemistry, pyridine and acetic acid were used. Clearly, the acetic acid must furnish the carboxylate bridge which is needed for the activation process. We have repeated a number of competition experiments with the following reaction conditions: $FeCl_2,4H_2O$--3.00mmol; CH_3CO_2H--3.00mL; pyridine--7.00mL; acetonitrile--20mL; H_2O_2(30%)--3.00mmol at room temperature under argon for 45min. In each case, there was close agreement between the results reported in Table 4 and the new results with acetic acid.

Comparative Experiments at Room Temperature and at -40°.

Two experiments at R.T. and at -40° (Entries 1 and 2, respectively) were carried out to establish the approximate speed of the reaction. The results are summarized in Table 6. When this experiment was repeated at -40° and the two hydrocarbons were added 15sec after the addition of the H_2O_2, the results in Entry 3 were observed. There was no change after 20 and 40mins.

This experiment shows that even at -40°, the Fe^{II} based experiment was very fast. In comparison, we have shown that for the Fe^{III}-H_2O_2 reagent, the iron-carbon bond with cyclohexane is formed very rapidly ($I^{\ominus}$ trapping), but the cyclohexanone formation (ligand coupling) has a half-life of about 45mins.[13] Clearly, the Fe^{II} and Fe^{III} experiments show a remarkable difference in rate.

Table 6. Test of the Stability of the Fe^{II}/H_2O_2 Reagent.

Entry	Temp. °C	**1**	ΣC_6Py	**25**	**26**	**27**	Ane/Aro norm.
1	R.T.	0.32	-	0.89	0.05	0.21	0.3
2	-40	0.44	0.03	1.00	0.05	0.56	0.4
3	-40	0.13	-	0.30	0.04	0.23	0.3

$FeCl_2,4H_2O$ (3mmol); picolinic acid (6mmol); pyridine (7mL); acetonitrile (23mL); cyclohexane (9.2mmol); mesitylene (28.8mmol) and H_2O_2(30%) (3.0mmol). The last was added at t=0 under argon for entries 1 and 2. (See text for entry 3).

Experimental.

For the general procedures, see Reference 1. Unless otherwise stated, typical conditions for Fe^{II}-based experiments were as follows: A 0.60g amount of $FeCl_2,4H_2O$ (3mmol) and 0.74g of picolinic acid (6mmol) were dissolved in 7mL of pyridine and 23mL of acetonitrile and stirred under a strong argon stream for 30min. The amount(s) of substrate(s) reported in the different tables were introduced under static argon atmosphere just before the dropwise addition of 30% aqueous hydrogen peroxide (0.3mL, 2.90mmol) at room temperature.

Acknowledgements.

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