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The Importance of Pyridine Complexation on Selective Oxidation within the Fe(III)-Fe(V) Manifold in Gif Chemistry.

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Abstract: Acetonitrile is an efficient solvent for Gif ketonisation chemistry in the presence of pyridine based amines. Pyridine bases constitute an important role in the Fe^{III} complex. Efficient ketonisation proceeds with as little as 15 mmol of base per mmol of Fe^{III}.

The selective oxidation of saturated hydrocarbons into functionalized molecules under mild conditions remains a topic of current relevance[1]. Recent studies have shown that the presence of certain carboxylate ligands[2] such as picolinic acid, in both the Fe^{II}-Fe^{IV} and the Fe^{III}-Fe^{V} manifolds[3] in pyridine is necessary for efficient Gif oxidation to take place. Traditionally, Gif chemistry has been carried out in pyridine. Sawyer and co-workers were the first group to study the Fe^{II} and the Fe^{III} systems in acetonitrile[4] in which they concluded that the replacement of a AcOH/pyridine system with acetonitrile reduces the reaction efficiency and eliminates selectivity[5]. We now re-examine Gif chemistry in acetonitrile and in particular examine the importance of pyridine and pyridine bases in the Gif system.

A series of experiments was carried out with $FeCl_3.6H_2O$ and picolinic acid in pyridine/acetonitrile mixtures to quantify the effect of an increasing amount of acetonitrile on the efficiency of the oxidation of cyclohexane. The results are summarized in Table 1.

Table 1. Gif Oxidation of Cyclohexane to Cyclohexanone in Acetonitrile/Pyridine

Entry	Pyridine (ml)	Acetonitrile (ml)	Ketone (mmol)	Alcohol (mmol)	Oxygen (mmol)	Efficiency (%)
1	33	0	1.20	0	0.05	63
2	25	8	1.29	0.05	0.23	79
3	16.5	16.5	1.29	0	0.23	76
4	8	25	1.18	0	0.43	81
5	3	30	1.18	0.11	0.46	88
6	1	32	0.98	0.19	0.45	81
7	0	33	0	0	0.07	4

Reactions were carried out with 1 mmol $FeCl_3.6H_2O$, 4 mmol picolinic acid, 20 mmol cyclohexane and 33 ml of solvent. To a homogeneous solution was added 4 mmol H_2O_2 and stirred for 16 h. Reactions were carried out at room temperature under air. The reaction flask was made gastight and connected to a manometric burette filled with brine, saturated with oxygen. %eff. = 2 x [R=O + ROH+ O_2]/$4H_2O_2$.

When all the pyridine is replaced by acetonitrile there was no formation of ketone or alcohol. Only traces of oxygen were formed. In pure pyridine the usual ketonisation was observed. The addition of acetonitrile up to 50% gave a small increase in the ketone formed. In fact even when there was only 3% of pyridine the formation of oxidation products was the same as for pure pyridine. This is important with respect to the industrialisation of Gif oxidation. For example, (see below) using 15 mmol of 4-t-butylpyridine, at the end of the conversion simple distillation affords separable unreacted cyclohexane, acetonitrile, cyclohexanone and cyclohexanol.The cycle can then be repeated.

Several pyridine based compounds were selected as possible alternatives to pyridine itself. The alternate pyridine bases were then used in the Gif oxidation of cyclohexane. The results are summarized in Table 2.

Table 2. Effect of Various Pyridine Bases on Ketone Formation in the Gif Fe^{III}-Fe^{V} Manifold

Entry	Bases[a]	Ketone (mmol)	Alcohol (mmol)	Oxygen (mmol)	Efficiency (%)
1	pyridine	0.49	0.3	0.2	49
2	3-methylpyridine	0.75	0.33	0.51	79
3	4-methylpyridine	0.75	0.25	0.42	71
4	2,4,6-trimethylpyridine	0.35	0.28	0.25	44
5	2,6-di-t-Bu-4-methylpyridine	0	0	0.11	5
6	isoquinoline	0.51	0.23	0.31	52
7	quinoline	0.40	0.29	0.16	42
8	2,2-bipyridyl	0	0	0.20	10
9	pyridine-N-oxide	0	0	0.21	10
10	4-nitropyridine-N-oxide	0	0	0.20	10
11	3-bromopyridine	0.09	0.07	0.25	19

Reactions were carried out with 1 mmol $FeCl_3.6H_20$, 4 mmol picolinic acid, 20 mmol cyclohexane and 33 ml of acetonitrile. (a) 10 mmol of pyridine derived base were added. To the homogeneous solution was added 4 mmol H_2O_2 (30%) The reaction was stirred for 16h. at room temperature under air. The reaction flask was made gastight and connected to a manometric burette filled with brine, saturated with oxygen. %eff. = 2 x $[R{=}O + ROH + O_2]/4H_2O_2$.

3- and 4-Methyl pyridine were found to be efficient bases forming 0.75 mmol of ketone. When the position α to the nitrogen atom was substituted as in entry 4, the efficiency of formation of ketone decreases. When the α substituent becomes too large (entry 5) ketone formation is supressed completely. Quinoline bases were also tested (entry 7) with only a moderate amount of ketone being formed. Pyridine-N-oxide bases (entries 9 and 10) were tested with no ketone being formed. 4-t-Butylpyridine was also tested and found to be the most practical base with respect to

easily separable oxidation products with a satisfactory yield. Those results are summarized in Table 3.

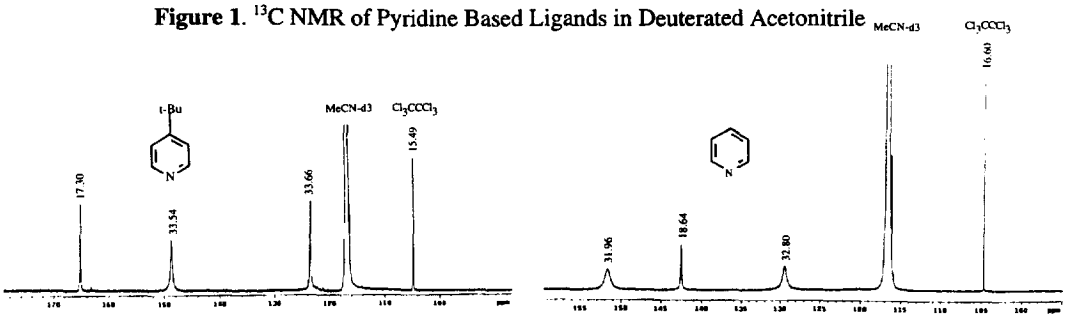
Table 3. Efficiency of 4-t-Butylpyridine as a Ligand in the Acetonitrile Solvent System

4-t-Butylpyridine (mmol)	Ketone (mmol)	Alcohol (mmol)	Oxygen (mmol)	Efficiency (mmol)
1	0.06	0.06	0.22	17
2	0.29	0.28	0.20	39
5	0.53	0.38	0.20	56
10	0.72	0.28	0.21	61
15	0.97	0.16	0.21	67
24.7	1.03	0.22	0.22	74

Reactions were carried out with 1 mmol $FeCl_3.6H_2O$, 4 mmol picolinic acid, 20 mmol cyclohexane and 33 ml of acetonitrile. x mmol of 4-t-Butylpyridine was added. To a homogeneous solution was added 4 mmol H_2O_2 and stirred for 16 h. Reactions were carried out at room temperature under air. The reaction flask was made gastight and connected to a manometric burette filled with brine, saturated with oxygen. %eff. = 2 x [R=O + ROH + O_2]/4H_2O_2.

Although the addition of 1 mmol of 4-t-butylpyridine per Fe^{III} did not produce much ketone, there was a major increase up to the normal oxidation products at 10-15 mmol per Fe^{III}. That such small amounts of the pyridine base had a major effect on ketonisation suggested that it was acting as a ligand. The quantitative use of ^{13}C NMR[6] confirmed this hypothesis. Previously the carboxylate ligands on the Fe^{III} were quantified. The same principle can be applied to the pyridine bases. The results are shown in Figure 1.

Figure 1. ^{13}C NMR of Pyridine Based Ligands in Deuterated Acetonitrile



0.055 mmol $FeCl_3.6H_2O$, 0.11 mmol Picolinic acid, 0.22 mmol pyridine ligand and 0.08 mmol Cl_3CCCl_3 in 1.0 mL MeCN-d3. Experiments were carried out at room temperature using a Varian Unity 500 equipped with a broad band probe. Hexachloroethane was used as internal standard. Integral values are shown above baseline.
equiv. of ligand in solution = (integral pyr/integralCl_3CCCl_3) x 2/5 x 0.08/0.055.

In this system the paramagnetic Fe^{III} reduces the relaxation times of the nuclei suppressing the NOE effect thereby allowing for quantitative analysis of the ^{13}C signals. Only the molecules

which are not bound to the iron are observed. It is known that in solution and in the solid state that two equivalents of picolinic acid bind strongly to the Fe^{III} centre. $Fe^{III}Cl_3$, picolinic acid and hexachloroethane (internal standard) were added to MeCN-d_3. To this solution was added 4 eq of the respective pyridine ligand. After 50000 transients no picolinic acid was detected (as expected). Only the free pyridine ligand which remained off the iron center was visible (signals downfield from solvent) and subsequently quantified. In the case of 4-t-butylpyridine one equivalent of the ligand was determined to be coordinated to the iron center with three equivalents free in solution. When pyridine itself was used, again one equivalent was found to be coordinated to the iron center (Fig. 1). When 2,6-di-t-butyl-4-methylpyridine was used as a ligand it was found that the bulky ligand remained in solution with no coordination to the iron center. This result is exactly what one would expect since using the bulky amine results in no ketonization of the hydrocarbon (Table 2, entry 5). To confirm the amount of pyridine base we have in solution an excess of oxalic acid was added. Four equivalents of the pyridine base are observed as well as picolinic acid. We can now confirm for the first time the primary role of the pyridine in Gif chemistry as a ligand to the Fe^{III} catalyst.

In summary, we have shown that acetonitrile is a very effective solvent in Gif chemistry oxidations providing that a pyridine base in an adequate amount is present in solution. We have also shown that a variety of pyridine bases can be used to replace pyridine especially 4-t-butylpyridine. Finally, we have determined the major role that the pyridine ligand plays in solution by quantifying the ligand environment by ^{13}C NMR.

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