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Role of Water and *p*-Fluorobenzoic Acid in Mn(II)T(*p*-Cl)PP Catalyzed Aerobic Oxidation of *p*-Fluorotoluene

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A solvent-free manganoporphyrin-catalyzed oxidation of *p*-fluorotoluene was developed, using oxygen as a clean and cheap oxidant. The parameters that have relationship with conversion were investigated. The conversion of *p*-fluorotoluene was found to be depend on the stability of catalytic environment. Water and *p*-fluorobenzoic acid were the final oxidation products of *p*-fluorotoluene, would inhibit the activity of catalyst. The conversion would be increased from 7.0 to 16.5 %, by the dehydration of acetic anhydride.

Key Words: *p*-Fluorotoluene, Manganoporphyrin, Water, *p*-Fluorobenzoic acid.

INTRODUCTION

The oxidation derivates of *p*-fluorotoluene play important roles in the field of medicine manufacture, such as paroxetine, rosuvastatin, mosapride citrate[1-3], *etc*.

Nowadays, these oxidation derivates are synthesized by the chlorination of *p*-fluorotoluene followed by hydrolysis in industry. However, the corrosion of reactors and the serious environment threat have become the major drawbacks[4]. During the past decades, metalloporphyrins have been widely used as cytochrome P-450 models catalyzing the oxidation of various substrates in association with a wide variety of oxygen donors such as iodosylarenes[5], sodium periodate[6], hydrogen peroxide[7], *etc*.

However, because of the inertness of saturated hydrocarbon, few reports are available for the oxidation of toluene using molecular oxygen as oxidant[8-10]. Furthermore, the electrophilic reactivity of high valence metalloporphyrin could be decreased due to the electron-withdrawing effect of fluorine atom.

Guo and co-workers have demonstrated a solvent-free biomimetic oxidation system to the aerobic oxidate of toluene, which used simple metalloporphyrin without any co-reductants[8]. However, the application of this method in industry is hindered due to the low conversion. Although the catalysts can be recycled by supported metalloporphyrins on different carriers[9,10], the conversion of toluene was limited to 10 %. Thus, the development of a efficiency procedure for such transformation remains a highly desired goal for organic chemists. Herein, we report the Mn(II)T(*p*-Cl)PP-catalyzed biomimetic oxidation of *p*-fluorotoluene using oxygen. This work may

provide a better understanding of the catalytic behavier of metalloporphyrin in oxidation reaction.

EXPERIMENTAL

Gas chromatography analysis was performed on a Fuli-9790 chromatograph equipped with a 30 m × 0.25 mm × 0.25 μm SE54 capillary column and a flame ionization detector. MS spectra were measured on a Shimadzu GCMSQP2010. *p*-Fluorotoluene was distilled and analyzed by GC before use. Mn(II)T(*p*-Cl)PP was synthesized and purified according to documented procedures[11]. Other reagents and solvents were all analytical grade.

25 mL of *p*-fluorotoluene and a measured amount of Mn(II)T(*p*-Cl)PP were charged into a 100 mL autoclave reactor with nitrogen at 0.85 MPa. The reaction mixture was heated to 180 ℃ under magnetic stirring. The oxygen was injected to replace the nitrogen three times and then charged to 0.85 MPa. The loss of pressure was recorded every hour and the system was recharged to 0.85 MPa. After the loss of pressure was less than 0.01 MPa per hour, the mixture was cooled, neutralized by 1 mol/L NaOH. *p*-Fluorobenzoic acid was obtained by filtering the water phase neutralized by 1 mol/L HCl. The organic phase was identified by GC-MS and quantified by GC using chlorobenzene as the internal standard. GC analysis was carried out as follows: nitrogen was used as the carrier gas, at the flow rate of 30 mL/min; the column temperature was 120 ℃; the injector temperature was 200 ℃; and the detector temperature was 200 ℃.

RESULTS AND DISCUSSION

The oxidation of *p*-fluorotoluene by Mn(II)T(*p*-Cl)PP is shown in **Scheme-I**. The main oxidation products were

p-fluorobenzaldehyde and *p*-fluorobenzoic acid and only trace *p*-fluorobenzyl alcohol could be detected by GC-MS. The blank experiment confirmed that *p*-fluorotoluene could not be oxidized in the absence of Mn(II)T(*p*-Cl)PP.
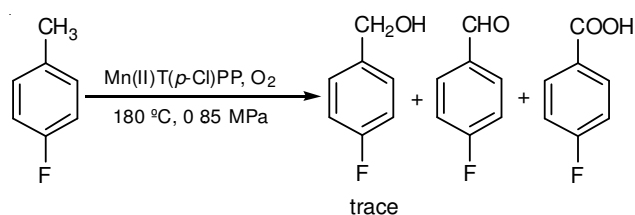
Scheme-I: Oxidation of *p*-fluorotoluene catalyzed by Mn(II)T(*p*-Cl)PP

Effect of temperature on oxidation reaction: The effects of reaction temperatures on the conversion of *p*-fluorotoluene and the product selectivity are shown in Table-1.

TABLE-1
EFFECT OF TEMPERATURE ON OXIDATION REACTION

| Temperature (ºC) | Selectivity (%) | | Conversion (%) |
	p-Fluorobenzal-dehyde	*p*-Fluoroben-zoic acid	
150	-	-	-
160	86.8	13.2	1.7
170	54.1	45.9	3.6
180	24.2	75.8	7.0
190	16.6	83.4	5.3

p-Fluorotoluene, 25 mL; catalyst, 0.8 mg (4.0×10^{-5} mol/L), pressure: 0.85 MPa

As can be seen from Table-1, the reaction could not take place below 150 ºC and the conversion increased until the temperature is elevated to180 ºC. Compared with the reported optimum reaction temperature of toluene in 160 ºC[8], the optimum temperature of *p*-fluorotoluene is much higher. This is at least partly due to the electron-withdrawing effect of fluorine atom. However, because metalloporphyrin is easily oxidized by oxygen under high temperature[9], the improvement of conversion should be resolved by other pathways.

Effect of the amount of catalyst on oxidation reaction: The effects of the amount of catalyst on the the conversion of *p*-fluorotoluene and the product selectivity are listed in Table -2.

TABLE-2
EFFECT OF THE AMOUNT OF CATALYST ON OXIDATION REACTION

| Catalyst (mol/L) | Selectivity (%) | | Conversion (%) |
	p-Fluorobenzal-dehyde	*p*-Fluorobenzoic acid	
1.0×10^{-5}	32.5	67.5	1.5
2.0×10^{-5}	30.3	69.7	2.8
4.0×10^{-5}	24.2	75.8	7.0
6.0×10^{-5}	32.9	67.1	6.2
8.0×10^{-5}	36.7	63.3	4.5

p-Fluorotoluene, 25 mL; temperature, 180 ºC; pressure, 0.85MPa

The results indicate that the conversion of *p*-fluorotoluene increases significantly with the increasment of catalyst loading from 1.0×10^{-5} to 4.0×10^{-5} mol/L. But the conversion decreases with the further increasment of catalyst. This phenomenon is contrary to supported metalloporphyrins[12]. A probable reason

is that superfluous catalyst in homogeneous system would collide with each other and convert to inactive dimer[13].

Effect of water on oxidation reaction: It is well known that the hydroxylation of methyl group in biological systems *via* a free radical pathway[14]. As a free radical inhibitor, water would quench the reaction. In present case, the oxidation reaction could not run by adding 3 wt % of water. To further understand of this phenomenon, we studied the oxidation of *p*-fluorotoluene in the presence of acetic anhydride, as shown in **Scheme-II**. The main oxidation products were *p*-fluoro-benzaldehyde, *p*-fluorobenzoic acid and *p*-fluorobenzyl acetate. The curves of pressure variations are shown in Fig. 1 and the effects of the amount of acetic anhydride on the conversion of *p*-fluorotoluene and the product selectivity are shown in Table-3.
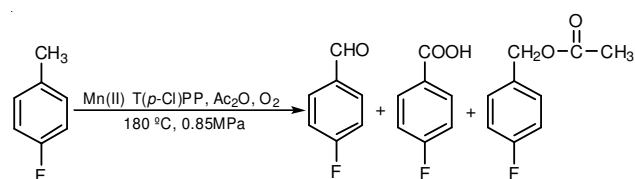
Scheme-II: Oxidation of *p*-fluorotoluene in the presence of acetic anhydride catalyzed by Mn(II)T(*p*-Cl)PP
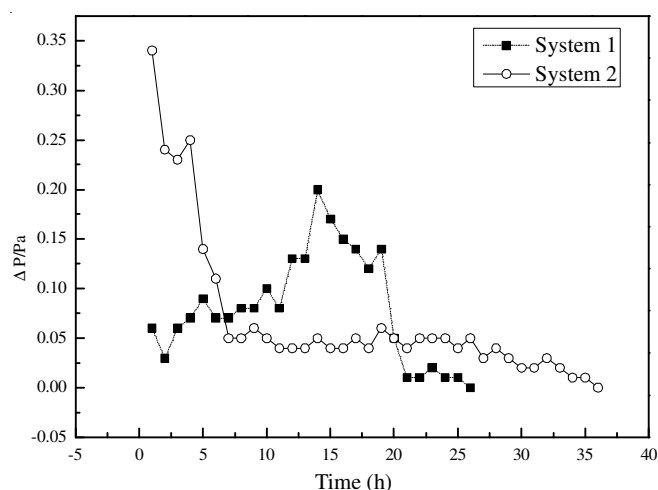

Fig. 1.   Curves of pressure variations in different oxidation systems. System 1: *p*-fluorotoluene, 25 mL; catalyst, 0.8 mg, temperature, 180 ºC; pressure, 0.85 MPa, System 2: *p*-fluorotoluene, 25 mL; acetic anhydride, 4.4 g; catalyst, 0.8 mg; temperature, 180 ºC; pressure, 0.85 MPa

TABLE-3
EFFECT OF THE AMOUNT OF ACETIC ANHYDRIDE ON OXIDATION REACTION

| Acetic anhydride (wt %) | Selectivity (%) | | | Conversion (%) |
	p-Fluorobenz-aldehyde	*p*-Fluoroben-zoic acid	*p*-Fluorobenzyl acetate	
0	24.2	75.8	-	7.0
10	17.8	71.8	10.6	13.1
15	18.3	68.9	12.8	16.5
20	17.1	67.8	15.2	5.4
50	18.0	65.7	16.3	3.2

p-Fluorotoluene, 25 mL; catalyst, 0.8 mg, temperature, 180 ºC; pressure, 0.85 MPa

The results indicate that *p*-fluorobenzyl alcohol can be protected by esterification with acetic anhydride and the conversion increases significantly with the increase of the amount of acetic anhydride from 0 to 15 wt %, because of the dehydration effect of acetic anhydride. However, the conversion decreases with further increase of acetic anhydride.

As can be seen from Fig. 1, in the oxidation system with acetic anhydride, the rate of oxygen consumption decreases rapidly in the initial 5 h, which is quite different to another system. This means that, although the conversion could be increased by removing water from the reaction system, there is still some fact inhibit the oxidation reaction. Owning to strong coordination effect, acetate could be used as an axial ligand and attached to metalloporphyrin[15]. However, the excessive axial ligand would decrease the catalytic activity of metalloporphyrin[16]. Hence, it is supposed that *p*-fluorobenzoic acid also played the same role as acetate in the oxidation reaction.

Effect of *p*-fluorobenzoic acid on oxidation reaction: The effects of the amount of *p*-fluorobenzoic acid on the conversion of *p*-fluorotoluene and the product selectivity are listed in Table-4.

TABLE-4
EFFECT OF THE AMOUNT OF *p*-FLUOROBENZOIC
ACID ON OXIDATION REACTION

p-Fluorobenzoic acid (g)	Selectivity (%)		Conversion (%)
	p-Fluorobenz-aldehyde	*p*-Fluoro-benzoic acid	
0.5	31.7	68.3	5.7
1.0	32.4	67.6	3.6
1.5	34.1	65.9	1.2
2.0	39.6	60.4	0.7
2.5	41.3	58.7	0.5

p-Fluorotoluene, 25 mL; catalyst, 0.8 mg, temperature, 180 ºC; pressure, 0.85 MPa

As can be seen from Table-4, the conversion decreases with increase of the amount of *p*-fluorobenzoic acid. The oxidation reaction is nearly terminated when the amount of *p*-fluorobenzoic acid is up to 0.08 g/mL. This observation supported the aforementioned supposition.

Conclusion

This work studies the application of metalloporphyrin for the oxidation of *p*-fluorotoluene without any solvent or co-reductants. Water and *p*-fluorobenzoic acid, which are the final oxidation products of *p*-fluorotoluene would inhibit the catalytic activity of metalloporphyrine. Hence, not only the improvement of the structure of metalloporphyrin but also stablility of catalytic system should be considered.

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