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The effect of metal salts on the oxidation reaction of (acetylphenyl)ferrocenes

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Abstract: The effect of metal salts on the oxidation reaction of (acetylphenyl)ferrocenes was determined. For the *p*- and *m*-isomers, the effect was accelerated, but for the *o*-isomer, the effect was suppressed. This suppressing effect was related to the chelate ring containing the substrate and the metal ion.

Keywords: Ferrocene derivatives; oxidation reaction; metal salt; chelate effect.

1. Introduction

The oxidation reaction of ferrocenes is one of the typical reactions of ferrocenes. Ferrocene is very stable in air and the oxidation from Fe(II) to Fe(III) is not easy. However, under acidic conditions, it is easily oxidized by air and is converted to ferrocenium ion. The reaction mechanism is shown in Figure 1. Based on this mechanism, ferrocene is converted to ferrocenonium ion by the coordination of a proton to the Fe atom followed by abstraction of the hydrogen atom to form ferrocenium ion. [1-3] The oxidation of ferrocenes to ferrocenium ion was very important for the interpretation of its biological activity,[4] for example antitumor activity, [5,6] and synthesis of the bio-related compounds.[7-11]
For ferrocene derivative, which has a substituent, the oxidation reaction rate is mainly influenced by the electron densities of the intramolecular Fe atom determined by the electronic effect of the substituents. As an example, for the oxidation reaction of (*p*-substituted phenyl)ferrocenes, a linear relationship was recognized between the rate constants and the Hammett's substituent constants; the reaction rate was mainly dominated by the electronic effect of the substituents. However, for the corresponding *o*-derivatives, the rate was influenced not only by the electronic effect, but also by steric effects.[12]
The steric effects shown by these derivatives are as followings:[12]
(i) The interaction of the substituent with the intramolecular Fe atom (the depression-effect for the oxidation reaction)
For (*o*-methyl and *o*-hydroxyphenyl)ferrocenes, the *o*-substituents take an end conformation due to the CH-d type interaction or OH-d type hydrogen bond between the substituents and intramolecular Fe atom. The electron densities of Fe atom are decreased by these interactions so that the oxidation reactivities are lower than the corresponding *p*-isomers.

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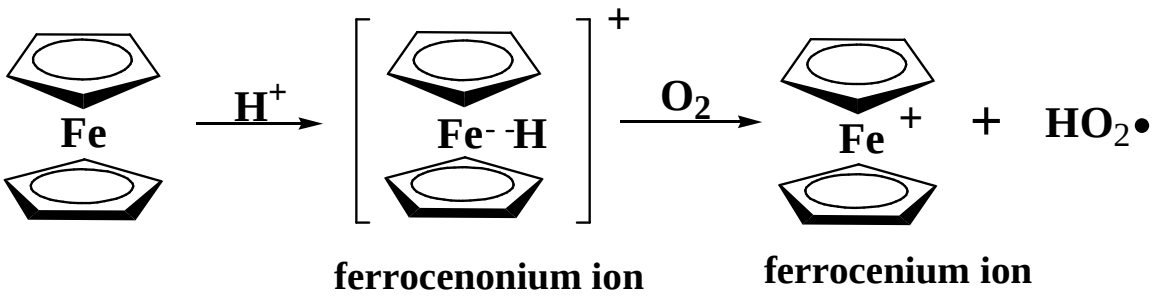

Figure 1. Oxidation mechanism of ferrocene

(ii) The chelate effect (the oxidation reaction accelerated effect)
For (*o*-acetyl, *o*-methoxycarbonyl, and *o*-methoxyphenyl)ferrocenes, coordination of the catalytic proton can occur with the carbonyl or ethereal oxygen. The proton is transferred to the Fe atom by formation of a chelate ring as shown in Fig. 2. Due to this chelate effect, the oxidation reactions of these *o*-isomers are accelerated when compared to the corresponding *p*-isomers.

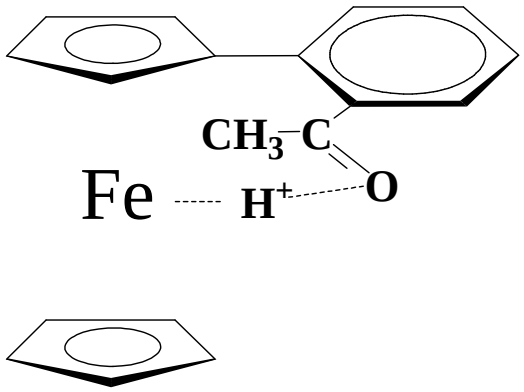

Figure 2. Plausible conformation of (*o*-acetylphenyl)ferrocene in acidic conditions

Furthermore, for 1,1'- bis(*o*-acetyl- or (methoxycarbonyl)phenyl)ferrocenes, the accelerating effect disappeared. This was attributed to a proton transfer between the two carbonyl oxygens.[13]

In this way, for (*o*-substituted phenyl)ferrocenes, the characteristic oxidation reaction occurs by these specific steric effects around the *o*-substituents.

2. Results and discussion

2.1. The effect of metal salts on the oxidation reaction of (acetylphenyl) ferrocenes

To discuss the influence of the metal salts on the oxidation reaction, the oxidation reactions of (acetyl phenyl)ferrocenes and phenylferrocene were carried out. The rate constants of these reactions are summarized in Table 1. Based on these results, for (*p*- and *m*-acetylphenyl)ferrocenes and phenylferrocene, the reactivities in the presence of the salts were higher than those in the absence of the salts. On the other hand, for (*o*-acetylphenyl)ferrocene, the reactivities in the presence of the salts were lower than those in the absence of the salts; the salts lowered the reactivity of (*o*-acetylphenyl)ferrocene. The influence by the number of charges of the metal ions was "$M^{2+} > M^{3+}$" regardless of the position of the acetyl group.

Table 1. The rate constants of (substituted phenyl)ferrocenes in the presence of metal salts

Entry	X	$k \times 10^5/s^{-1}$					
		none	$MgCl_2$[a]	$CaCl_2$[a]	$SrCl_2$[a]	$AlCl_3$[a]	YCl_3[a]
1	H	3.00	7.19	8.03	6.62	4.47	5.46
2	*p*-acetyl	1.30	2.82	2.54	2.47	1.89	2.38
3	*m*-acetyl	2.80	5.09	5.59	4.68	2.75	3.09
4	*o*-acetyl	7.50	4.80	5.20	4.70	2.30	2.20

a (substituted phenyl)ferrocenes : metal salt = 1:1

2.2. The oxidation reactivity of (p- and m-acetylphenyl) ferrocenes

As mentioned in section 2.1, the oxidation reactivities of (*p*- and *m*-acetylphenyl)ferrocenes increased by the addition of the metal salts.

To examine the effect of the metal ions, the oxidation reactions with phenol or salicylic acid were carried out. As a result, the oxidation reactivity of (*p*-acetylphenyl) ferrocene increased (Table 2). The accelerated effect by the metal salts would be due to either the metal ions or chloride ion. The result in which the oxidation reactivity increased by salicylic acid having a cation binding ability indicated that metal ions have a suppressing effect, while chloride ion has an accelerating one.

It is well known that ferrocene is decomposed by nucleophilic reagents to form the Fe^{3+} ion.[14,15] Therefore, chloride ion, which is a weak nucleophile, would decompose the ferrocene nucleus. To confirm this supposition, the experiments to detect Fe^{2+} and Fe^{3+} ions by 1,10-phenanthroline and potassium thiocyanate, respectively, were done. As the results, Fe^{2+} and Fe^{3+} ions were confirmed when the reaction solution became blue, that is to say, ferrocenium ion was formed. These results indicate that ferrocene is oxidized by the Fe^{3+} ion formed from the ferrocene nucleus.

That is, the metal ion suppresses the oxidation reaction, but chloride ion accelerates the reaction. For (*p*- and *m*-acetylphenyl)ferrocenes, the oxidation reactivities would become higher by the metal salts as the final result of these suppressing and accelerating effects.

Table 2. The rate constants of (*p*-acetylphenyl)ferrocenes in the presence of some additives

Entry	X	metal salt[a]	additive [a]	$k \times 10^5/s^{-1}$
1	*p*-acetyl	$MgCl_2$	none	2.82
2	*p*-acetyl	$MgCl_2$	phenol	4.43
3	*p*-acetyl	$MgCl_2$	salicylic acid	6.13
4	*p*-acetyl	$MgCl_2$	(*o*-acetylphenyl)ferrocene	5.67
6	*o*-acetyl	$MgCl_2$	none	4.80
5	*o*-acetyl	$MgCl_2$	(*p*-acetylphenyl)ferrocene	4.63

a : (substituted phenyl)ferrocenes : metal salt : adduct = 1:1:1

2.3. The oxidation reactivity of (o-acetylphenyl)ferrocenes

The oxidation reaction of (*o*-acetylphenyl)ferrocene was suppressed by the metal salts as mentioned in section 2.1.

The oxidation reaction of (*p*-acetylphenyl)ferrocene mentioned in section 2.2 was carried out in the presence of (*o*-acetylphenyl)ferrocene instead of salicylic acid. As a result, the reaction of (*p*-acetylphenyl)ferrocene was accelerated as well as with salicylic acid. Furthermore, the reactivity of (*o*-acetylphenyl)ferrocene was similar to that with no additives. These results show that (*o*-acetylphenyl)ferrocene has the cation binding ability with the same degree as salicylic acid, therefore it forms a chelate ring with the metal ions (Fig. 3). The metal ion would cause the crowded conformation around the intramolecular Fe atom, which interferes with the approach of catalytic proton or Fe^{3+} ion. Moreover, the reaction rate with M^{3+} was faster than with M^{2+}. This would be due to the high charge density on the ion surface for easy formation of the chelate ring.

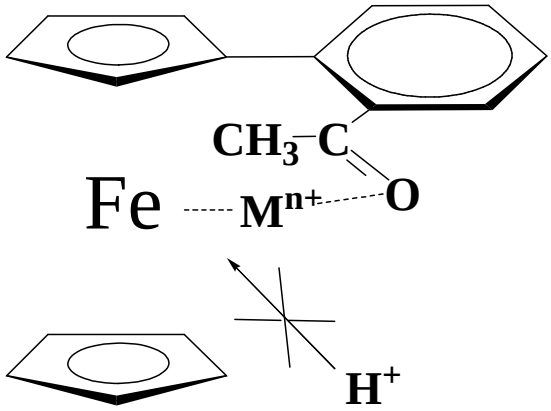

Figure 3. Plausible conformation of (*o*-acetylphenyl)ferrocene in the presence of metal ion

For (*o*-acetylphenyl)ferrocene, the accelerating effect by chloride ion should exist. However, the remarkable suppressing effect by formation of the chelate ring suppresses the accelerating effect: Overall, the oxidation reaction of (*o*-acetylphenyl)ferrocene was suppressed**.**

3. Experimental

3.1. Syntheses

(Substituted phenyl)ferrocenes were synthesized from ferrocene based on a previously reported procedure.[16]

3.2. Measurements of oxidation reactivity

The oxidation reactions were carried out using trichloroacetic acid as the catalyst at 40℃. The mixed solvent was ethanol: dioxane (9:1). The metal salts included $MgCl_2$, $CaCl_2$, $SrCl_2$, $AlCl_3$, and YCl_3. The conversion was measured by analyzing the amounts of unreacted ferrocenes by HPLC. The rate constants were calculated as a pseudo-first order reaction regarding the ferrocene derivative.

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