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Kinetic Studies on the Reaction of Iron(III) with D-penicillamine in Acidic Solution¹

Hung-Jae Park, Yung-Hee Oh Kim², Jung-Ae Shim, and Sung-Nak Choi*

Department of Chemistry, Pusan National University, Pusan 609-735. Received October 28, 1992

Anaerobic oxidation of D-penicillamine by Fe(III) in acidic solution has been studied kinetically by the use of stopped-flow system. The reaction is biphasic with a rapid complexation of 1 : 1 complex, Fepen⁺ (pen = D-penicillamine dianion) which is then internally reduced to Fe(II) and disulfide. Rates of both the complexation and the redox process are pH dependent and also are affected by the presence of chloride ion. Different from the reaction of Cu(II) with D-penicillamine, partially oxidized mixed-valence complex is not formed even transiently in this reaction.

Introduction

D-penicillamine [HS(CH₃)₂CCH(NH₂)COOH, H₂pen], one of the sulfur-containing amino acids, has been used as a medi-

cial chelating agent and the oral administration of the D-penicillamine to patients with Wilson's disease promotes the urinary excretion of excess copper ions.³ Because of the physiological relevance, considerable emphasis has been placed

on the redox reaction of copper(II) with D-penicillamine.⁴⁻¹⁰ This reaction is very complicated and it is well known that the type and the amount of reaction products produced in the reaction depend on experimental conditions.^{9,10}

Iron(III) metal ion is also prevalent in the biological system and it is quite interesting to study the redox process between Fe(III) and D-penicillamine since the Fe(III)-Fe(II) redox couple also plays important roles in the biological system as the Cu(II)-Cu(I) redox couple does. However the reaction of Fe(III) with D-penicillamine is expected to be more perplexing since Fe(III) ion is hydrolyzed in the aqueous solution.^{11,12} Especially in the presence of complexing anion, such as the chloride, the hydrolysis of Fe³⁺ or of FeCl₃ is very complicated giving chloro, and hydroxy species.³ This study of anaerobic oxidation of D-penicillamine by Fe(III) was undertaken for three reasons: firstly, to extend our previous studies on the redox reaction between metal ion and D-penicillamine,^{9,10} secondly, to study on the effects of the pH and the anion on the rate of redox process to provide further insight into the intimate mechanism of this reaction; thirdly, to compare the kinetics of Fe(III) oxidation of D-penicillamine with that of cysteine previously reported.^{14,15}

Experimental

Materials. Hexaaquoferric chloride, FeCl₂·6H₂O, and D-penicillamine were purchased from Fluka, Co. and used without further purification. Fe(ClO₄)₃ was prepared from the reaction of FeCl₃ and perchloric acid; FeCl₃ was dissolved in the perchloric acid and heated to remove HCl gas. After the solution failed to produce a visible precipitation in a choride test with silver ion, two successive crystallization from the concentrated perchloric acid were done.

Kinetic Measurements. All kinetic measurements were carried out on a Union Giken BA-401 stopped-flow spectrophotometer equipped with an RA-451 data processor.

The stopped-flow spectrophotometer was fitted with thermostatted cell holders connected to an external circulating water bath. The kinetics of the formation and decay of transient "blue" colored intermediate were studied by following the absorbance change at 585 nm.

Total ionic strength was maintained with NaClO₄ or KCl depending on the type of Fe(III) salt used. Pseudo-first order conditions were maintained by using twenty five-fold or more excess of D-penicillamine over iron(III) for each run.

The pH employed was measured directly after each kinetic run. All the preparative work was carried out in the nitrogen-filled glove-bag, and the reaction solutions were transferred to the stopped-flow apparatus in sealed syringes.

Results and Discussion

When Fe(III) ion in the form of FeCl₃ or Fe(ClO₄)₃ and D-penicillamine in acidic aqueous solution were mixed and stopped in a flow system, a very rapid increase followed by a slow decrease in absorbance at 595 nm was exhibited as shown in Figure 1.

The principal observation at the initial stage of the reaction was the formation of "blue" transient. The strong absorption at 595 nm is considered to be arisen from the charge transfer [S(σ)→Fe(III)] and the increase in absorbance at

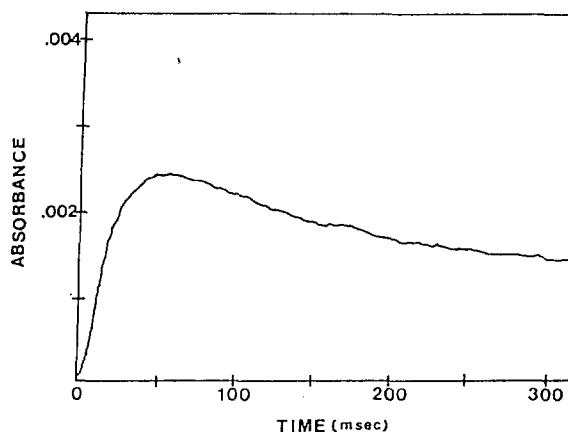
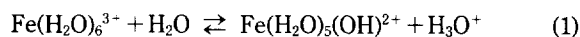
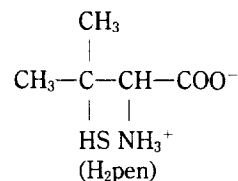


Figure 1. Typical absorbance vs. time observed at 595 nm for the reaction between Fe(III) and D-penicillamine.

595 nm is attributed to the formation of blue transient *via* Fe(III)-S bonding. The maximal absorbance change observed as a function of <D-penicillamine>/<Fe(III)> ratio exhibits a sharp peak at the ratio of one, indicating that the stoichiometry for the formation of this blue transient is one Fe(III) for one D-penicillamine.

The D-penicillamine ligand present in the acidic aqueous solution over the pH range of this study is fully protonated as shown below and the Fe(III) ion is in the forms of Fe(H₂O)₆³⁺ and Fe(H₂O)₅(OH)²⁺ in equilibrium.



$$K_1 = [\text{Fe}(\text{H}_2\text{O})_5(\text{OH})^{2+}] [\text{H}_3\text{O}^+] / [\text{Fe}(\text{H}_2\text{O})_6^{3+}]$$

In our experimental condition, Fe(H₂O)₅(OH)²⁺ is one of predominant Fe(III) species in the equilibrium system and Fe(H₂O)₅(OH)²⁺ is expected to be substitutionally more labile than Fe(H₂O)₆³⁺ since the water exchange rate of Fe(H₂O)₅(OH)²⁺ is greater than that of Fe(H₂O)₆³⁺.¹⁶ So, the stoichiometry of the formation of blue transient can be described by Eq. (2), and the rate of reaction can be expressed by Eq. (3). From now on, the coordinated water will be omitted in expression of complex ions for convenience.



$$\begin{aligned} \text{Rate} &= d[\text{blue intermediate}]/dt \\ &= k_1 [\text{H}_2\text{pen}] [\text{Fe}(\text{H}_2\text{O})_5(\text{OH})^{2+}] \end{aligned} \quad (3)$$

If we rearrange the rate law in terms of total Fe(III) concentration, [Fe(III)]_T ([Fe(III)]_T = [Fe³⁺] + [Fe(OH)²⁺]), the rate expression is rearranged to Eq. (4).

$$\text{Rate} = k_1 K_1 [\text{H}_2\text{pen}] [\text{Fe}(\text{III})]_T / ([\text{H}^+] + K_1) \quad (4)$$

The rate increases as the concentration of D-penicillamine increases at a given pH, total iron concentration and temperature conditions. When pseudo-first order condition is

Table 1. Observed and Calculated Rate Constants for the Formation of Blue Intermediate, Fepen⁺, from the Reaction of Fe(ClO₄)₃ and D-penicillamine (I=0.1 M, and [Fe(III)]=5.00×10⁻⁴ M)

pH	T (°C)	[H ₂ pen]×10 ²	k _{obs} (sec ⁻¹)	k _{cal} (sec ⁻¹)
1.88	15	1.50	1.35	1.23
		3.00	2.20	2.27
		4.50	3.10	3.31
		6.00	4.51	4.35
	25	1.50	3.92	3.30
		3.00	6.38	6.84
		4.50	9.45	10.4
		6.00	14.7	13.9
	35	1.50	10.3	9.44
		3.00	18.7	19.9
		4.50	30.1	30.3
		6.00	41.3	40.8
15	1.50	2.81	2.54	
	3.00	5.49	5.98	
	4.50	9.58	9.41	
	6.00	12.9	12.8	
2.05	25	1.50	8.92	7.45
		3.00	17.7	19.5
		4.50	30.9	31.6
		6.00	44.8	43.7
35	1.50	21.7	19.00	
	3.00	47.9	50.9	
	4.50	80.8	82.8	
	6.00	117	115	
15	1.50	5.75	4.83	
	3.00	13.8	14.6	
	4.50	23.0	24.3	
	6.00	35.1	34.0	
2.43	25	1.50	17.6	15.1
		3.00	38.2	41.2
		4.50	65.9	67.4
		6.00	95.6	93.6
35	1.50	44.5	39.6	
	3.00	97.6	103	
	4.50	164	167	
	6.00	235	231	
15	1.50	10.3	8.24	
	3.00	21.8	22.2	
	4.50	30.9	36.2	
	6.00	53.9	50.2	
2.83	25	1.50	29.1	29.1
		3.00	61.7	65.2
		4.50	108	101
		6.00	134	137
		0.60	31.0	29.0
		1.50	64.7	74.1

35	3.00	157	149	
	4.50	230	225	
	6.00	294	300	
15	0.60	9.55	8.33	
	1.50	17.8	18.7	
	3.00	34.3	36.1	
	4.50	55.5	53.5	
3.22	25	0.60	23.2	20.4
		1.50	44.2	45.1
		3.00	82.0	86.2
		4.50	128	127
35	25	0.60	49.8	53.1
		1.50	95.7	102
		3.00	195	184
		4.50	276	266
35	25	0.60	337	348
		1.50	337	348
		3.00	337	348
		4.50	337	348

Table 2. Observed and Calculated Rate Constants for the Formation of Blue Intermediate, Fepen⁺, from the Reaction of Fe(ClO₃)₃ and D-penicillamine (I=0.10 M, and [FeCl₃]=5.00×10⁻⁴ M)

pH	T (°C)	[H ₂ pen]×10 ²	k _{obs} (sec ⁻¹)	k _{cal} (sec ⁻¹)
2.1	25	3.00	87.73	86.71
2.4	∕	∕	97.95	104.2
2.5	∕	∕	107.1	108.7
2.6	∕	∕	112.1	112.8
2.7	∕	∕	118.0	115.8
2.9	∕	∕	126.6	121.0

held with respect to [H₂pen], the rate can be described by Eq. (5) with k_{1obs} being expressed by Eq. (6).

$$\text{Rate} = k_{1obs}[\text{Fe(III)}]_T \quad (5)$$

$$k_{1obs} = k_1 K_1 [\text{H}_2\text{pen}] / ([\text{H}^+] + K_1) \quad (6)$$

The rate constants for the formation of blue transient were obtained from the absorbance data obtained at 595 nm. Since the final absorbance value A_∞ of reaction curve can not be assumed, Guggenheim plot should be made for obtaining rate constant, k_{1obs}. When total iron concentration and ligand concentration are maintained constant, the observed rate constant also increases as the pH increases. Experimental results are summarized in Tables 1 and 2.

The Eq. (6) can be rearranged to Eq. (7).

$$[\text{H}_2\text{pen}] / k_{1obs} = (1/k_1) + (1/k_1 K_1) [\text{H}^+] \quad (7)$$

Plots of [H₂pen]/k_{1obs} vs. [H⁺] exhibit straight lines as shown in Figure 2.

The blue intermediate initially formed slowly decomposes to produce Fe(II) and D-penicillamine disulfide (Hpen-penH) as described by Eq. (8).



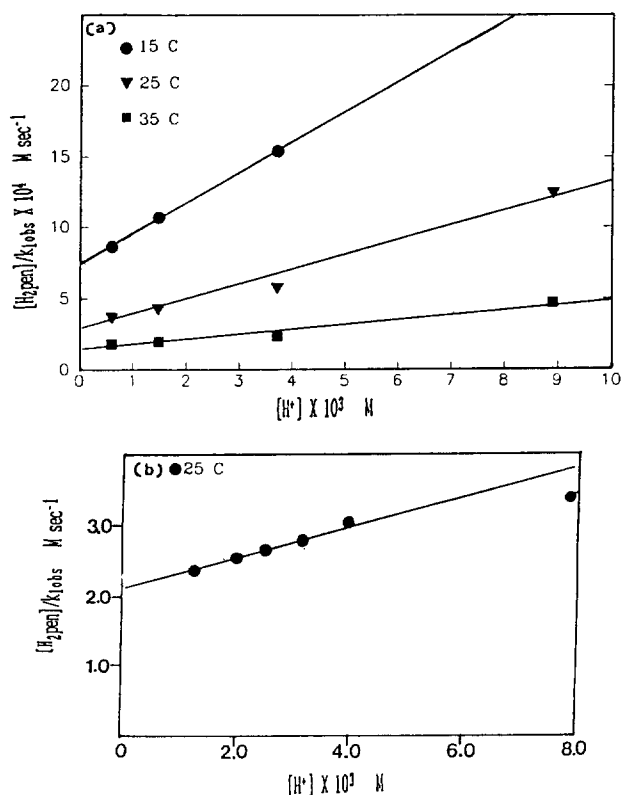


Figure 2. Plots of $[H_2pen]/k_{obs}$ vs. $[H^+]$ for the formation of $Fe(pen)^+$ from the reaction between (a) $Fe(ClO_4)_3$ and D-penicillamine and between (b) $FeCl_3$ and D-penicillamine

Table 3. Rate Data and Activation Parameters for the Formation of Blue Intermediate from the Reaction of $Fe(ClO_4)_3$ and D-Penicillamine

T (°C)	$k_1 \times 10^{-3}$ ($M^{-1}sec^{-1}$)	pK	ΔH^\ddagger (kcal/mol)	ΔS^\ddagger (eu)
15	1.4 (± 0.1)			
25	4.1 (± 0.5)	2.7 (± 0.2)	14 (± 2)	3.5 (± 0.2)
35	7.3 (± 0.1)			

The white D-penicillamine disulfide formed was isolated and characterized; the isolated disulfide also reacts with Cu(II) to exhibit characteristic blue color of Cu(II)-D-penicillamine disulfide complex.⁹

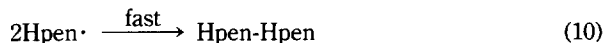
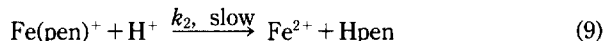
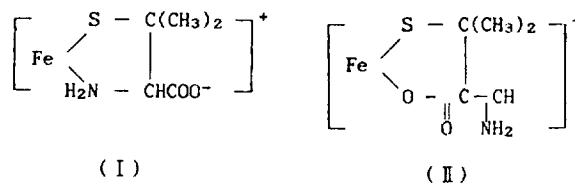
Values of rate constants for the decay process, k_{2obs} , were obtained directly from the decay part of each curve and listed in Tables 4 and 5. Plots of $\log(A_t - A_\infty)$ vs. time were linear at least for 4 half-times for most run. The decay process is also acid-dependent and the rate increases as the pH increases. Once formed blue intermediate undergoes an internal redox reaction through the Fe(III)-coordinating sulfur bond. During this process, protonation of the donor atom of the ligand, either nitrogen of amino group or oxygen of carboxyl group, seems to occur to help the coordinated ligand radical to be dissociated from the reduced metal center. The dissociated ligand radical then dimerizes rapidly to form disulfide, Hpen-penH. The presumable structure of $Fe(pen)^+$ and its decay mechanism are postulated as below.

Table 4. Observed and Calculated Rate Constants for the Reduction of Blue Transient Intermediate, $Fepen^+ + H^+ \rightarrow Fe^{2+} + 1/2 Hpen-penH$ in the Perchlorate medium ($I=0.10$, $T=25^\circ C$ and Iron(III) perchlorate is used as Fe(III) source)

pH	$k_{2obs} \times 10^2$ sec^{-1}	$[H_2pen] \times 10/k_{2obs}$ mol/dm^3	$[H_2pen] \times 10/k_{2obs}$ (mol/dm^3)
1.54	1.29	23.30	22.70
1.66	1.75	17.10	17.40
1.92	3.92	7.65	8.46
2.17	5.70	5.26	5.38
2.28	6.54	4.59	4.68
2.47	10.60	2.83	3.26
2.70	11.70	2.56	2.20
2.90	14.00	2.14	1.63
2.97	16.40	1.83	1.48
3.05	18.00	1.67	1.34

Table 5. Observed and Calculated Rate Constants for the Reduction of Blue Transient Intermediate, $Fepen^+ + H^+ \rightarrow Fe^{2+} + 1/2 Hpen-penH$ in the Chloride Medium ($I=0.10$, $T=25^\circ C$ and Iron(III)chloride is used as Fe(III) Source)

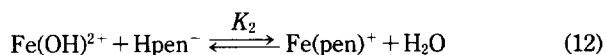
pH	$k_{2obs} \times 10^2$ sec^{-1}	$[H_2pen] \times 10/k_{2obs}$ mol/dm^3	$[H_2pen] \times 10/k_{2obs}$ (mol/dm^3)
2.07	15.1	19.9	21.6
2.42	17.2	17.4	15.1
2.79	22.1	13.6	12.4
2.88	23.0	13.1	12.0
3.04	25.7	11.7	11.5
3.06	27.6	10.9	11.4
3.16	37.6	8.0	11.2



The rate law of the decay process can be described by Eq. (11).

$$-d[Fe(pen)^+]/dt = k_2[Fe(pen)^+][H^+] \quad (11)$$

To rearrange the rate law in terms of $[Fe(III)]_T$ and $[Hpen^-]$, Eqs. (12) and (14) are considered and the equilibrium constants are expressed by Eqs. (13) and (15).



$$K_2 = [Fe(pen)^+]/[Fe(OH)^{2+}][Hpen^-] \quad (13)$$



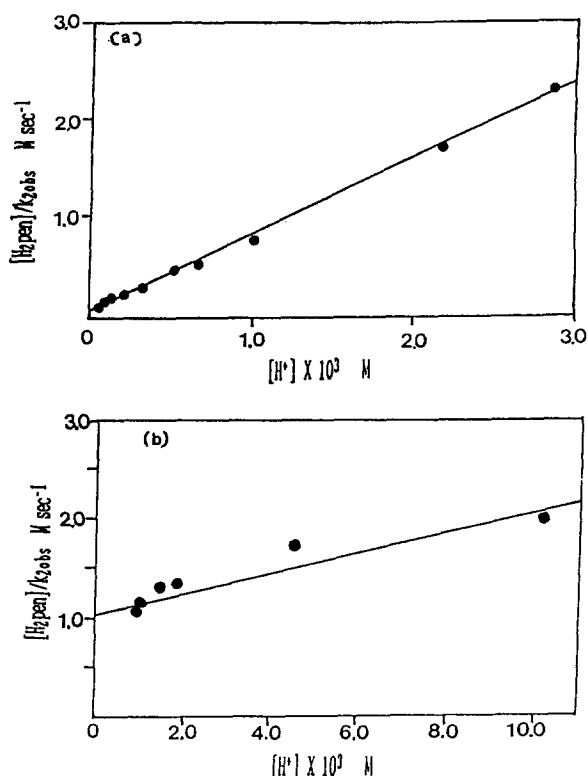


Figure 3. Plots of $[H_2pen]/k_{2obs}$ vs. $[H^+]$ for the formation of $Fe(pen)^+$ from the reaction between (a) $Fe(ClO_4)_3$ and D-penicillamine and between (b) $FeCl_3$ and D-penicillamine

$$K_3 = \frac{[H^+][Hpen^-]}{[H_2pen]} \quad (15)$$

The rate law can be further rearranged to the following expression.

$$-d[Fe(pen)^+]/dt = \frac{k_2 K_1 K_2 K_3 [H_2pen][Fe(III)]_7 (1/[H^+] + K_1)}{1 + K_1} \quad (16)$$

Since $[H_2pen]$ is at least ten times greater than $[Fe(III)]_7$, the reaction is first order with respect to $[Fe(III)]_7$.

$$\text{Rate} = k_{2obs}[Fe(III)]_7 \quad (17)$$

$$k_{2obs} = K_2 K_1 K_2 K_3 [H_2pen] (1/[H^+] + K_1) \quad (18)$$

If we arrange Eqs. (18), (19) is obtained.

$$[H_2pen]/k_{2obs} = (1/k_2 K_1 K_2 K_3) [H^+] + 1/(k_2 K_2 K_3) \quad (19)$$

Figure 3 shows plots of $[H_2pen]/k_{2obs}$ vs. $[H^+]$ for the decay process in the absence and in the presence of the chloride ion.

The equilibrium constant for the hydrolysis of $Fe(III)$, K_1 and rate constant k_1 could be obtained from a line slope and an intercept of Eq. (7) and the experimental results are summarized in Table 3. Also, K_1 can be calculated from a slope and intercept of Eq. (19). For the reaction of $Fe(ClO_4)_3$ with D-penicillamine, the pK_1 value calculated by the use of either Eq. (7) or (8) is 2.7 ± 0.2 , which is in good agreement with the reported value.¹²

These results strongly indicate that reaction mechanism postulated above is consistent with our experimental results. However, in the presence of chloride ion, *i.e.*, when $FeCl_3$ is used as $Fe(III)$ source, the pK_1 value of 1.8 was obtained.

This value is much smaller than the reported value of 2.7.

This result may indicate that the mechanism described by Eqs. (2), (9), and (10) is not valid for the oxidation of D-penicillamine by $Fe(III)$ in the presence of complexing anion such as chlorid ion. It is quite interesting to compare our experimental results with those of the reaction of $FeCl_3$ with unsubstituted cysteine¹⁴; both reactions exhibit same acid dependency and seem to proceed *via* similar reaction mechanism. The rate of the formation of transient intermediate for the reaction of $FeCl_3$ with D-penicillamine is faster than that for the reaction between $FeCl_3$ and cysteine at the same experimental condition.

However, the rate of internal redox process of transient intermediate (see Eq. (9)) is slower for $Fe(III)$ -D-penicillamine complex and transient 1:1 $Fe(III)$ -D-penicillamine complex is more stable than the corresponding cysteine complex. This may be due to the larger oxidation potential of D-penicillamine. Oxidation potentials of D-penicillamine and cysteine are -0.53 V and -0.45 V respectively in the similar pH conditions.^{17,18}

It has been reported that $Cu(I)$ -D-penicillamine complex is more stable than $Cu(I)$ -cysteine complex and the excretion of $Cu(II)$ with D-penicillamine is due to the stability difference of $Cu(I)$ -amino acids.⁹ The stability of metal-sulfur bonding in sulfur containing amino acid complexes is definitely related to the reducing ability of amino acid. It is well expected that the stability of metal-sulfur bonding is also greatly influenced by the magnitude of reduction potential of metal ion. We attempted to identify the formation of partially reduced metal complexes *i.e.*, the mixed valence complex, but failed. In the reaction of $Cu(II)$ with D-penicillamine, mixed-valence complex, $[Cu(II)_8Cu(I)_6(pen)_{12}Cl]^{-5}$ is produced,⁷ but in the reaction of $Fe(III)$ with D-penicillamine, the complex with mixed-valence state is not found and $Fe(III)$ is fully reduced to $Fe(II)$. This may be due to the difference in oxidizing power of $Fe(III)$ and $Cu(II)$ ions. Standard reduction potential for $Fe(III) \rightarrow Fe(II) + e$ is 0.77 V and that for $Cu(II) \rightarrow Cu(I) + e$ is 0.15 V.¹⁹

The presence of chloride ion increases the reaction rates of the formation and decay of transient intermediate, $Fe(pen)^+$. When $FeCl_3$, instead of $Fe(ClO_4)_3$ is used as $Fe(III)$ source, the rates of formation and decay of $Fe(pen)^+$ increase.

The increased reaction rates seems to be ascribed to the complexing ability of chloride ion. The chloride ion reacts with $Fe(III)$ species easily to form chloro complex such as $FeCl^{2+}$.¹²

The reduced charge on the $Fe(III)$ upon formation of chloro complex will increase the water exchange rate, which, in turn, enhance the rate of formation of $Fe(pen)^+$.

As mentioned earlier, the reaction mechanism described by Eq. (2), (9), and (10) is valid only in the absence of chloride ion. But in the presence of chloride ion, another reaction path way for the formation of transient intermediate seems to exist in addition to the pathway described by Eq. (2).



Reaction pathway described by Eq. (20) accounts for the increased rate for the formation of blue intermediate in the presence of chloride ion. Further investigation on the effect of complexing anion such as chloride ion on the anaerobic oxidation of sulfur containing amino acid by $Fe(III)$ is under

study.

Acknowledgement. This work has been supported by BSRI program (91-307), Ministry of Education, Korea.

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1. In writing the formula for an aqueous ion, we will omit coordinated water molecules except for Eq. (1).
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Ruthenium Complex Catalyzed Synthesis of 2-Substituted Benzoxazoles from *o*-Aminophenol and Alcohol with Spontaneous Hydrogen Evolution

Keun-Tae Huh*

Department of Materials Science and Engineering, Kyungsoong University, Pusan 608-736

Sang Chul Shim

Department of Industrial Chemistry, Kyungpook National University, Taegu 702-701

Received April 16, 1993

o-Aminophenols react with alcohols in the presence of a catalytic amount of ruthenium catalyst at 180°C to give 2-substituted benzoxazole in good yield. The yields of 2-substituted benzoxazoles were affected by the yield of N-alkylation compound from *o*-aminophenol and alcohol as starting materials. During the reaction, a stoichiometric amount of hydrogen was spontaneously evolved into the gas phase.

Introduction

Synthesis of benzoxazole derivatives from readily available starting materials have recently received some attention¹. The synthesis of benzoxazoles often carried out by heating the *o*-aminophenol with the carboxylic acid or its derivatives, such as the acid chloride, anhydride, an ester, amide or nitrile².

We have recently developed ruthenium complex catalyzed N-methylation³, N-alkylation^{4,5}, N-heterocyclization of amines⁶⁻⁸, where the ruthenium complex efficiently activates alcohol functionalities to give nitrogen compounds.

Here we report synthesis of 2-substituted benzoxazoles, using transition metal complexes as a catalyst. The ruthenium complex catalyzed reaction between *o*-aminophenol and alcohols to give the corresponding 2-substituted benzoxazo-

les.

Results and Discussion

o-Aminophenol (**1**) reacts with alcohol (**2**) in the presence of a catalytic amount of a ruthenium complex to give 2-substituted benzoxazoles (**3**) in good yield (Eq. 1).

