Tetrahedron Vol. 48, No. 9, pp. 1557-1566, 1992
Printed in Great Britain

0040-4020/92 $3.00+.00
Pergamon Press plc

Air Oxidation of *p*-Substituted Benzoin to the Corresponding Benzil Catalyzed by Fe(II)-Cysteine Peptide Complexes

Wei-Yin Sun, Norikazu Ueyama and Akira Nakamura*

Department of Macromolecular Science, Faculty of Science, Osaka University, Toyonaka, Osaka 560, Japan

(*Received in Japan* 15 *November* 1991)

Key Words: Fe(II)-cysteine peptide complexes; catalytic reaction; air oxidation; benzoin; benzil.

Abstract: *The Fe(II)-cysteine-containing peptide complexes were found to exhibit catalytic activity for air oxidation of benzoin to benzil and methyl DL-mandelate to methyl benzoylformate. In the presence of* $[Fe(Z\text{-}\mathbf{cys}\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$*, the rates of catalytic air-oxidation of p-substituted benzoin indicate a trend,* $Br > H > CH_3 > MeO$*, and the isotope effect* k_H/k_D *was 3.4. The result indicates that the methine hydrogen of benzoin is released as a proton in the rate determining step. Furthermore, solvent effect was found, in a non-polar solvent, e.g. 1,2-dimethoxyethane (DME), a chelating bidentate cys-peptide complex,* $[Fe(Z\text{-}\mathbf{cys}\text{-}Pro\text{-}Leu\text{-}\mathbf{cys}\text{-}Gly\text{-}Val\text{-}OMe)_2]^{2-}$ *shows higher catalytic activity than that of a non-chelating cys-peptide complex,* $[Fe(Z\text{-}\mathbf{cys}\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$*. This is explained by the contribution of intramolecular NH---S hydrogen bonds since such hydrogen bonds stabilize the Fe(III) state which is the active species during the oxidation.*

INTRODUCTION

Catalytic oxidation of organic substrates by iron thiolate complex is of interest as a simple model of metalloenzyme. For example, iron-sulfur proteins such as rubredoxin and ferredoxin, are known to involve in a wide range of reactions including electron and proton transport. The active center of rubredoxin and ferredoxin consists of a FeS_4 core and a Fe_4S_4 cluster, respectively.[1] It has been reported that rubredoxin from *Pseudomonas oleovorans* is involved in fatty acid oxidation and hydrocarbon ω-hydroxylation reactions.[2] Many iron-thiolate complexes were synthesized as models of these native proteins both in structural and reactivity aspect.[3-5] The studies of catalytic reactivity of Fe_4S_4 cluster have been carried out to reveal two redox pairs, *i.e.* $[Fe_4S_4(SR)_4]^{2-/-}$ and $[Fe_4S_4(SR)_4]^{3-/2-}$.[6-8] However, only a few similar reactions utilizing mononuclear iron-thiolate complexes have been reported.[9,10] Recently, we have reported the catalytic air oxidation of benzoin and *p*-substituted benzhydrol in the presence of $[Fe(SPh)_4]^{2-}$.[11] This

work was extended to the cysteine-containing oligopeptide-Fe(II) complexes as catalysts and the results are presented in this paper.

A series of Fe(II)-cys peptide complexes have been synthesized and their spectral and electrochemical properties were studied.[4,12] For example, the redox potentials of $[Fe(Z\text{-}\mathbf{cys}\text{-}Pro\text{-}Leu\text{-}\mathbf{cys}\text{-}OMe)_2]^{2-}$ and $[Fe(Z\text{-}\mathbf{cys}\text{-}Pro\text{-}Leu\text{-}\mathbf{cys}\text{-}Gly\text{-}Val\text{-}OMe)_2]^{2-}$ were -0.54 and -0.46 V vs SCE in acetonitrile, respectively. However, in a non-polar solvent, *e.g.* DME, $[Fe(Z\text{-}\mathbf{cys}\text{-}Pro\text{-}Leu\text{-}\mathbf{cys}\text{-}OMe)_2]^{2-}$ gives a redox potential at -0.59 V vs SCE which is a negative shifted value compared to that in CH_3CN, while $[Fe(Z\text{-}\mathbf{cys}\text{-}Pro\text{-}Leu\text{-}\mathbf{cys}\text{-}Gly\text{-}Val\text{-}OMe)_2]^{2-}$ exhibits a positively shifted redox potential at -0.35 V vs SCE. This difference was explained by the formation of hydrogen bond of Val-NH---S-cys(2) in $[Fe(Z\text{-}\mathbf{cys}(1)\text{-}Pro\text{-}Leu\text{-}\mathbf{cys}(2)\text{-}Gly\text{-}Val\text{-}OMe)_2]^{2-}$.[12] Such hydrogen bonds have been suggested to exist in native rubredoxin and ferredoxin from X-ray analysis. The study of model complexes has revealed that the NH---S hydrogen bonds play an important role in regulating the Fe(II)/Fe(III) redox potential.[4,5c] The sequences of Cys-Pro-Leu-Cys and Cys-Pro-Val-Cys exist in *Clostridium pasteurianum* and *Desulfovibrio gigas* rubredoxin, respectively,[13] and the catalytic reactivity of their Fe(II) complexes was considered to be similar since they gave very similar spectral properties as described in the previous paper.[12] We thus use the Fe(II) complexes of Z-Cys-Gly-Val-OMe, Z-Cys-Pro-Val-Cys-OMe and Z-Cys-Pro-Leu-Cys-Gly-Val-OMe in this study to clarify the role of hydrogen bond in the present catalytic reaction. The mechanism of α-CH bond cleavage in the oxidation of benzoin is studied by the *p*-substituent effect and kinetic deuterium effect.

RESULTS

Formation of Fe(III) Species from One-Electron Air-Oxidation of $[Fe^{II}(Z\text{-}\mathbf{cys}\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$

Air oxidation of $[Fe^{II}(Z\text{-}\mathbf{cys}\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$ was investigated by the absorption and CD spectra. As shown in Figure 1, an absorption maximum at 315 nm (6400) was observed for the complex in deaerated DMF solution which is very similar to that in acetonitrile (316 nm (5300)). When air was bubbled to the solution, the spectrum changed to the one given in broken line immediately and new absorption maxima at 345 nm (8600) and 482 nm (4700) appeared. The ligand-to-metal charge transfer (LMCT) absorptions of Fe(III)/oligopeptide complexes were reported to appear at 350 and 490 nm,[17] *e.g.* $[Fe^{III}(Z\text{-}\mathbf{cys}\text{-}Pro\text{-}Leu\text{-}\mathbf{cys}\text{-}OMe)_2]^{-}$, 355 nm (6600) and 490 nm (4700), $[Fe^{III}(Z\text{-}Ala\text{-}\mathbf{cys}\text{-}OMe)_4]^{-}$, 348 nm (4400) and 495 nm (2700) in dimethyl sulfoxide. The oxidized rubredoxin also has such absorption maxima at 353 nm (9600), 380 nm (10800), 493 nm (9200) and 560 nm(4400) (Table 1).[18] The change of the CD spectra during air-oxidation of $[Fe^{II}(Z\text{-}\mathbf{cys}\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$ in DMF is shown in the bottom of Figure 1. The spectrum of Fe(II) state is given in solid line. The spectrum in DMF, 318 nm (-2.0) and 340 nm (0.8), is also similar to that in CH_3CN as reported previously.[12] New peaks at 315 nm (-3.2), 423 nm (1.6), 485 nm (-1.8), 555 nm (0.5) and 650 nm (-0.2) were observed after 3 min of bubbling air. The CD spectra of the Fe(III) peptide complexes and oxidized rubredoxin also exhibit many peaks at the LMCT region.[17,18] From the data in Table 1, a complex, $[Fe^{III}(Z\text{-}\mathbf{cys}\text{-}Gly\text{-}Val\text{-}OMe)_4]^{-}$, was confirmed to be formed in situ which gave a similar spectral pattern to those of chelate-peptide Fe(III) complex and oxidized rubredoxin. A non-chelate peptide Fe(III) complex, *e.g.* $[Fe^{III}(Z\text{-}Ala\text{-}\mathbf{cys}\text{-}OMe)_4]^{-}$ was reported to exhibit a different CD spectrum from those of chelated peptide Fe(III) complex and oxidized rubredoxin.[17]

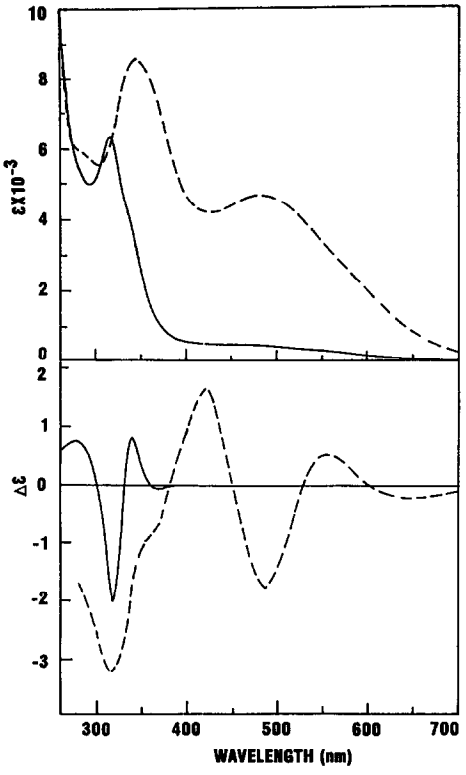


Figure 1. Absorption (top) and CD (bottom) spectra of $[Fe(Z\text{-cys-Gly-Val-OMe})_4]^{2-}$ in DMF under an argon atmosphere (——) and after bubbling air (---).

Table 1 UV-vis and CD spectral data of Fe(III) complex and oxidized rubredoxin

Complex	Solvent	UV-vis[a]	CD[b]
$[Fe^{III}$(Z-cys-Pro-Leu-cys-OMe)$_2]^-$ [c]	Me_2SO	355 (6600), 490 (4700)	350 (5.5), 385 (-0.6), 428 (3.2), 494 (-5.0), 562 (1.4), 640 (-0.5)
Oxidized rubredoxin[d]	H_2O	353 (9600), 380 (10800), 493 (9200), 560 (4400)	344 (-6.2), 412 (10.8), 440 (14.3), 500 (-20.7), 564 (20.8), 637 (-6.9)

[a] In nm (ε, $M^{-1}cm^{-1}$). [b] In nm ($\Delta\varepsilon$, $M^{-1}cm^{-1}$). [c] From reference 17b. [d] From reference 18.

Catalytic Air-Oxidation of p-Substituted Benzoin and Methyl DL-Mandelate

Fe(II)/thiolate and selenolate complexes have been found to be catalytically active for oxidation of α-phenyl-substituted alcohols.[11] $[Fe^{II}(Z\text{-cys-Gly-Val-OMe})_4]^{2-}$ was employed as a catalyst in the air oxidation of *p*-substituted benzoin and methyl *DL*-mandelate. The results are listed in Table 2. All these catalytic

reactions were carried out in DMF at 25 °C and in the presence of 5% molar amount of the catalyst. The formation of oxidized products was examined by ^{13}C-NMR spectroscopy. Methyl benzoylformate formed in 3 h in 18% yield (catalytic yield, 360%). 55% (catalytic yield, 1100%) of benzoin was oxidized to benzil in 20 h. A similar result was reported for the air oxidation of benzoin catalyzed by $[Fe(SPh)_4]^{2-}$ under the same reaction conditions (catalytic yield of benzil was 1100% in 15 h).[11] While in the case of $[Mn(SPh)_4]^{2-}$, catalytic yield of 900% was obtained in the air oxidation of benzoin in DMF at 20 °C in 50 h.[19] Thus the cysteine-containing oligopeptide Fe(II) complexes as well as simple Fe(II) thiolate complex were found to have higher catalytic activity than $[Mn(SPh)_4]^{2-}$.

α-C-Deuterated benzoin was used to study the isotope effect in the air-oxidation of benzoin. The ratio of [α-C-deuteriobenzoin]/ $[Fe^{2+}]$ was 20. At the initial stage of the reaction, the isotope effect k_H/k_D was 3.4 in DMF at 25 °C. Similar values were reported for catalytic oxidation of benzoin in the presence of $[Ni(O_2CCH_3)_2]$,[20] $[Fe_4S_4(tipbt)_4]^{2-}$ (tipbt = 2,4,6-triisopropylbenzenethiolate) cluster[7] and $[Fe(SPh)_4]^{2-}$.[11] The observed k_H/k_D value indicates that the rate-determining step involves cleavage of the α-C-H bond of benzoin.

Table 2 Catalytic air oxidation of organic substrates in the presence of $[Fe(Z\text{-}cys\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$ in DMF at 25 °C

Substrate	Product	Time, h	Yield (%)
Methyl *DL*-mandelate	Methyl benzoylformate	3	18
4,4'-Dibromobenzoin	4,4'-Dibromobenzil	20	60
Benzoin	Benzil	20	55
4,4'-Dimethylbenzoin	4,4'-Dimethylbenzil	20	29
4,4'-Dimethoxybenzoin	4,4'-Dimethoxybenzil	20	25

Reaction conditions: [Substrates] = 20 mM, [Catalyst] = 1 mM.

In the presence of $[Fe^{II}(Z\text{-}cys\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$, the yield of the corresponding benzil during the air oxidation of 4,4'-dibromobenzoin, benzoin, 4,4'-dimethylbenzoin and 4,4'-dimethoxybenzoin gave in a order: 4-Br, 60% > H, 55% > 4-CH_3, 29% > 4-MeO, 25% (Table 2). This *p*-substituent effect is the same as ones catalyzed by $[Ni(O_2CCH_3)_2]$ and Fe_4S_4 cluster *etc.* The electron-withdrawing group, *e.g.* 4-Br, accelerates the oxidation but the electron-donating substituents as 4-CH_3, 4-MeO, work opposite. This means that the intermediate of the reaction is likely involved in a carbanion. Considering the kinetic deuterium effect mentioned above, cleavage of the α-C-H bond of benzoin in the rate-determining step releases a proton.

Catalytic Oxidation of Benzoin by p-Benzoquinone and Pyridine N-Oxide

Instead of oxygen, *p*-benzoquinone and pyridine *N*-oxide were used as oxidants in the catalytic oxidation of benzoin in the presence of $[Fe^{II}(Z\text{-}cys\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$. The results were summarized in Figure 2. In the *p*-benzoquinone oxidation of benzoin, the conversion of *p*-benzoquinone to hydroquinone was monitored by ^1H-NMR spectra in acetonitrile-d_3 as reported for the reaction catalyzed by Fe_4S_4 cluster.[7]

In the case of air-oxidation, the initial rate of the reaction is the fastest and deactivation is also rapid. On the contrary, when the *p*-benzoquinone and pyridine *N*-oxide were used as oxidants, the reactions run gently although it is somewhat slower than that of air-oxidation at the initial stage as shown in Figure 2. In 10 h, the yield of benzil was in order of pyridine *N*-oxide, 58%, *p*-benzoquinone, 56% and air, 48%. The reaction oxidized by pyridine *N*-oxide perhaps progressed in a different mechanism which requires further study. Both of the reactions using air and *p*-benzoquinone as oxidants indicated the Fe(III) complex to be the active species as reported previously.[11]

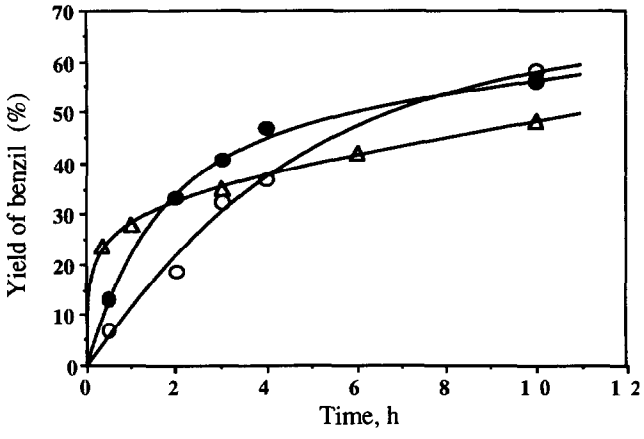


Figure 2. Time course for catalytic air (Δ), *p*-benzoquinone (●) and pyridine *N*-oxide (○) oxidation of benzoin in the presence of $[Fe(Z\text{-}cys\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$. Reaction conditions: [benzoin] = 20 mM; $[Fe(Z\text{-}cys\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$ = 1 mM; [*p*-benzoquinone] = [pyridine *N*-oxide] = 20 mM, in DMF at 25 °C.

Catalytic Air-Oxidation of Benzoin in the Presence of $[Fe(Z\text{-}cys\text{-}Pro\text{-}Val\text{-}cys\text{-}OMe)_2]^{2-}$, $[Fe(Z\text{-}cys\text{-}Pro\text{-}Leu\text{-}cys\text{-}Gly\text{-}Val\text{-}OMe)_2]^{2-}$, $[FeBr_4]^{2-}$ *and* $FeBr_2$

Catalytic air-oxidation of benzoin was carried out with the catalysts in the title. Fe(II) complexes coordinated by chelating ligand Z-Cys-Pro-Val-Cys-OMe and Z-Cys-Pro-Leu-Cys-Gly-Val-OMe were used for comparison to that of nonchelating ligand complex $[Fe(Z\text{-}cys\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$. In order to compare the catalytic reactivity of Fe(II)-thiolate complexes, the reactions using $[FeBr_4]^{2-}$ or $FeBr_2$ as catalyst were also carried out in the same reaction conditions (in DMF at 25 °C and [Benzoin]/[catalyst] = 20). The results are listed in Table 3. Only 14% and 18% of benzil was formed in the air oxidation of benzoin catalyzed by $FeBr_2$ and $[FeBr_4]^{2-}$ in 4 h, respectively. About 2-folds of benzil were produced by the reactions catalyzed by Fe(II)/peptide complexes in the same reaction time. Furthermore, no remarkable difference was observed between the Fe(II) complexes with chelating and non-chelating peptide ligands. This indicates that the cysteine thiolate ligands were possibly preserved during the catalytic cycle.

Table 3 Catalytic air oxidation of benzoin to benzil in the presence of Fe(II) complexes in DMF at 25 °C

Complexes	Yield of benzil (%)
$FeBr_2$	14
$(Et_4N)_2[FeBr_4]$	18
$(Et_4N)_2$[Fe(Z-cys-Gly-Val-OMe)$_4$]	38
$(Et_4N)_2$[Fe(Z-cys-Pro-Val-cys-OMe)$_2$]	30
$(Et_4N)_2$[Fe(Z-cys-Pro-Leu-cys-Gly-Val-OMe)$_2$]	36

Reaction conditions: [Benzoin] = 20 mM, [Catalyst] = 1 mM, reaction time, 4 h.

Solvent Effect

Since the redox potential of [Fe(Z-cys-Pro-Leu-cys-Gly-Val-OMe)$_2$]$^{2-}$ was solvent dependent as reported previously.[12] The catalytic air-oxidation was examined in two different solvents, DMF and DME. For comparison, the reaction catalyzed by [Fe(Z-cys-Gly-Val-OMe)$_4$]$^{2-}$ was also performed in the same solvents. Figure 3 shows the effect of solvent on the catalytic oxidation. In the case of [Fe(Z-cys-Pro-Leu-cys-Gly-Val-OMe)$_2$]$^{2-}$, the catalyst is more effective in DME than that in DMF while an opposite trend is observed in the case of [Fe(Z-cys-Gly-Val-OMe)$_4$]$^{2-}$.

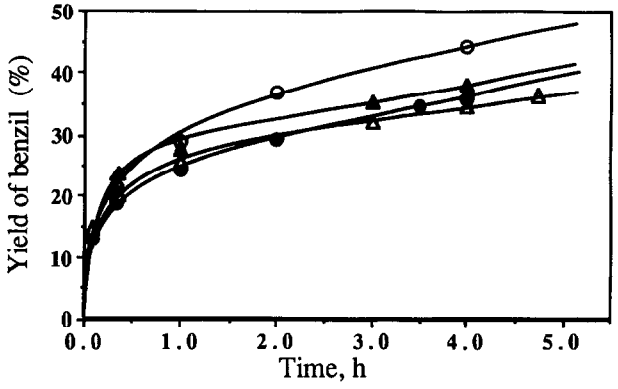


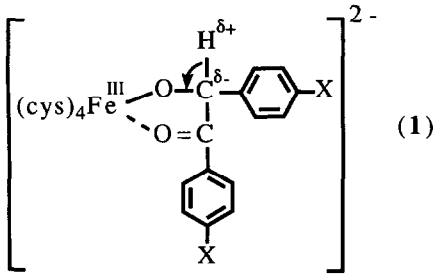
Figure 3. Time course for catalytic air oxidation of benzoin in the presence of [Fe(Z-cys-Gly-Val-OMe)$_4$]$^{2-}$ in DMF (▲) and in DME (Δ); in the presence of [Fe(Z-cys-Pro-Leu-cys-Gly-Val-OMe)$_2$]$^{2-}$ in DMF (●) and in DME (○). Reaction conditions: [benzoin] = 20 mM; [Fe(Z-cys-Gly-Val-OMe)$_4$]$^{2-}$ = [Fe(Z-cys-Pro-Leu-cys-Gly-Val-OMe)$_2$]$^{2-}$ = 1 mM, at 25 °C.

The solvent properties, *e.g.* relative permittivity (DMF, ε_r = 36.7, DME, ε_r = 7.2) and protophilia, were considered to influence the oxidation significantly. It is believed that the catalytic oxidation of benzoin was accelerated in a solvent with higher permittivity as DMF, because of an ionic intermediate. In addition, the greater donor number of solvent, namely more protophilic, induces more effective proton transfer. The

donor numbers of DMF and DME are 26.6 and 20, respectively.[21] Therefore, from these two aspects, the catalytic activity is expected to be generally higher in DMF than that in DME. For example, the *p*-benzoquinone oxidation of benzoin catalyzed by a variety Fe_4S_4 clusters was reported more favorable in DMF than that in DME.[7] The air oxidation of benzoin in DMF and DME was in the same order in the presence of $[Fe(Z\text{-cys-Gly-Val-OMe})_4]^{2-}$. However, when the chelating peptide Fe(II) complex $[Fe(Z\text{-cys-Pro-Leu-cys-Gly-Val-OMe})_2]^{2-}$ was used as catalyst, the order of reaction was DME > DMF. This is explained by the contribution of NH---S hydrogen bond which can stabilize the oxidized state in the chelating peptide complex as discussed later.

DISCUSSION

The air oxidation of cys-containing peptide/Fe(II) complex gives the corresponding Fe(III) species which is confirmed by UV-vis and CD spectra as shown in Figure 1. The Fe(III) species can also be produced by oxidation reaction of Fe(II) complex with *p*-benzoquinone as reported previously.[11] These Fe(III) species were considered to be catalytically active in the oxidation of benzoin and methyl *DL*-mandelate. No absorption spectral change was observed when the benzoin was added to a solution of Fe(II) complex. Thus, it is clear that Fe(II)-peptide complex does not react with benzoin. All the present catalytic oxidation reactions require addition of a suitable oxidant, *i.e.* air or *p*-benzoquinone or pyridine *N*-oxide. The solution turned to brown immediately by addition of the oxidant and the oxidized product, *e.g.* benzil, was detected. Benzoin coordinates to the Fe(III) ion through oxygen atoms of the hydroxy group and the ketone group to form, perhaps, a six-coordinated Fe(III) complex. Coordination of benzoin to the catalyst has been reported for catalytic air oxidation by Mo(VI) complexes.[22] A structure of proposed intermediate(**1**) is shown below.



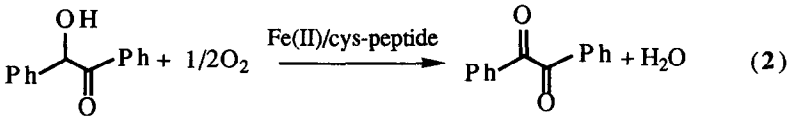
(**1**)

In the following step, one-electron oxidation of benzoin occurs and the iron(III) is reduced to the original Fe(II) state. Another one-electron oxidation is considered to occur rapidly in the same way and leads to benzil. The cleavage of the C-C bond of benzoin was not found. A more detailed mechanism is under study and will be reported elsewhere.

The coordination of substrate to the metal ion was also proposed for the oxidation of benzoin catalyzed by Ni(II)[20] and by Fe_4S_4 cluster.[7] An octahedral intermediate has been considered for the case of nickel(II) acetate and the electron-transfer was considered to occur between benzoin and Ni(II).[20] Since the catalytic activity of non-chelating peptide-Fe(II) complex is similar to that of chelating ones (Table 3), benzoin is

considered to coordinate to iron ion without dissociation of the thiolate ligand and further study on this point is required. The observed *p*-substituent effect implies that α-H of benzoin is released as a proton ($H^{\delta+}$) while the α-carbon is left as a carbanion ($C^{\delta-}$) (**1**).

In the air oxidation of benzoin, the rate at initial stage was very rapid (see Figure 2). About 25% of benzoin was oxidized to benzil in 20 min and then the catalyst deactivated gradually. 2.5% of benzoin was consumed in the stoichiometric reaction with the catalyst since the content of catalyst was 5% and two equivalents of one-electron-oxidized $[Fe^{III}$(Z-**cys**-Gly-Val-OMe)$_4]^-$ are involved in the oxidation of benzoin. As shown in equation (**2**):



(**2**)

Equation (**2**) indicates that one equivalent of benzoin is oxidized with the formation of one equivalent of water. Therefore, ten equivalents of water were produced while the yield of benzil was 25% in 20 min. These water molecules will partially decompose the iron complex and the deactivation of catalyst was observed. In the *p*-benzoquinone oxidation of benzoin, the deactivation of catalyst occurs more slowly since there is no water formed, the slower deactivation was considered to be caused by the acidic product, hydroquinone.

The above mentioned solvent effect indicates that the NH---S hydrogen bond plays an important role not only in iron(II) complex but also in its oxidized state. The hydrogen bond of Val-NH---S-cys(2) in $[Fe^{II}$(Z-**cys**(**1**)-Pro-Leu-**cys**(**2**)-Gly-Val-OMe)$_2]^{2-}$ was reported stronger in a non-polar solvent as DME than in a polar solvent as DMF.[12] This difference also appeared in Fe(III) state which is considered to be an active species. The X-ray analysis of oxidized *D. gigas* rubredoxin has suggested the existence of NH---S hydrogen bonds.[23] The importance of hydrogen bonds has been proposed for the stability of the oxidized state (Fe^{3+}) and the positive shift of redox potential in the native rubredoxin.[23,24] Such NH---S hydrogen bonds were also found for $[Fe_2S_2]^{2+}$/peptide complexes which the iron ions are in 3+ state.[25] It is known that the strength of NH---S hydrogen bond is controlled by the polarity of the solvent. Therefore, $[Fe^{III}$(Z-**cys**-Pro-Leu-**cys**-Gly-Val-OMe)$_2]^-$ is more stable in DME than that in DMF. The catalytic reaction in the presence of $[Fe^{II}$(Z-**cys**-Pro-Leu-**cys**-Gly-Val-OMe)$_2]^{2-}$ is more favorable in DME than in DMF. On the contrary, in the case of $[Fe$(Z-**cys**-Gly-Val-OMe)$_4]^{2-}$, since there is no strong NH---S hydrogen bond as reported in the previously paper,[12] the catalytic reactivity was controlled by the properties of solvent, *i.e.* permittivity and protophilia *vide supra*.

From this study, it is clear that the intramolecular NH---S hydrogen bond plays an important role in simple model complexes as well as in the electron transfer oxidation process of native iron-sulfur proteins.

EXPERIMENTAL

Materials — Anhydrous iron(II) bromide was obtained from Morton Thiokol, Inc. and used without further purification. $(Et_4N)_2[FeBr_4]$ was prepared according to the literature.[14] Substrates, *e.g.*, methyl *DL*-mandelate was purchased from Tokyo Kasei Co. Ltd. Benzoin was from Wako Pure Chemical Industries and

purified by recrystallization. 4,4'-Dimethylbenzoin, 4,4'-dimethoxybenzoin and 4,4'-dibromobenzil were obtained from Aldrich Chemical Co. 4,4'-Dibromobenzoin was synthesized by reduction of the corresponding benzil using a method reported in the literature.[15] α-C-deuterated benzoin was prepared by a literature method.[16] All operations except for air oxidation reactions and spectral measurements were carried out under inert gas atmosphere. *N,N'*-dimethylformamide (DMF), 1,2-dimethoxyethane (DME) and all other solvents were purified by distillation.

Syntheses of Fe(II)/Cysteine-Containing Oligopeptide Complexes — These complexes were synthesized by the ligand-exchange reaction method reported previously.[4] An acetonitrile solution of $(Et_4N)_2[Fe(S\text{-}t\text{-}Bu)_4]$ was added to a THF solution of SH-free peptide Z-Cys-Gly-Val-OMe, Z-Cys-Pro-Val-Cys-OMe or Z-Cys-Pro-Leu-Cys-Gly-Val-OMe. The mixture was stirred for 20 min at room temperature and purified by standard procedure.

Typical Procedure for Catalytic Air Oxidation of Benzoin — A solution of $[Fe(Z\text{-}\mathbf{cys}\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$ (4.03 mg, 2 X 10^{-6} mol) in DMF (1 ml) was added to a solution of benzoin (8.49 mg, 4 X 10^{-5} mol) in DMF (1 ml) and stirred at 25 °C. The reaction was started by bubbling air into the mixture. After a given period, a part of the reaction mixture was taken out and added to a mixture of diethyl ether and water (2 : 1) to extract benzil and unreacted benzoin to the diethyl ether layer. The percentage of benzil formed was determined by HPLC with a COSMOSIL 5C18-AR column (150 mm X 4.6 mm inside diameter). The results are shown in Table 2.

The catalytic air oxidation of α-C-deuterated benzoin in the presence of $[Fe(Z\text{-}\mathbf{cys}\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$ was carried out in the same way.

Catalytic Air Oxidation of Methyl *DL*-Mandelate in the Presence of $[Fe(Z\text{-}\mathbf{cys}\text{-}\mathbf{Gly}\text{-}\mathbf{Val}\text{-}\mathbf{OMe})_4]^{2-}$ — This reaction was also carried out in DMF at 25 °C. $[Fe(Z\text{-}\mathbf{cys}\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$ (4.03 mg, 2 X 10^{-6} mol) in DMF (1 ml) and methyl *DL*-mandelate (6.65 mg, 4 X 10^{-5} mol) in DMF (1 ml) were mixed and the reaction was started by bubbling air into the mixture. The product of the reaction was examined by HPLC to find methyl benzoylformate (see Table 2).

Catalytic Oxidation of Benzoin by *p*-Benzoquinone and Pyridine *N*-Oxide — A DMF (0.5 ml) solution of $[Fe(Z\text{-}\mathbf{cys}\text{-}Gly\text{-}Val\text{-}OMe)_4]^{2-}$ (4.03 mg, 2 X 10^{-6} mol) was added to a DMF (0.5 ml) solution of benzoin (8.49 mg, 4 X 10^{-5} mol) at 25 °C. The mixture was stirred vigorously and the reaction was started by addition of a DMF (1 ml) solution of *p*-benzoquinone (4.32 mg, 4 X 10^{-5} mol) or pyridine *N*-oxide (3.80 mg, 4 X 10^{-5} mol). After a prescribed reaction time, the product was extracted with diethyl ether and analyzed by HPLC.

Physical Measurements — Absorption spectra were recorded on a JASCO Ubest-30 spectrophotometer in visible region. Circular dichroism (CD) spectra were measured on a JASCO J-40 spectropolarimeter, using a 1 mm cell. The sample concentrations were 1.0 mM. Absorbance and CD transition were given in units of $M^{-1}cm^{-1}$. 400 MHz ^1H-NMR and 100 MHz ^{13}C-NMR spectral measurements were performed on a JEOL GSX400 FT NMR spectrometer.

REFERENCES

1. a) Jensen, L. H. *Iron-Sulfur Proteins*; Lovenberg, W. Ed.; Academic Press: New York, 1973, Vol.

II, p164. b) Carter, Jr., C. W. *Iron-Sulfur Proteins*; Lovenberg, W. Ed.; Academic Press: New York, 1973, Vol. III, p157.

2. Peterson, J. A.; Kusunose, M.; Kusunose, E. and Coon, M. J. *J. Biol. Chem.*, **1967,** 242, 4334.
3. a) Hagen, K. S.; Watson, A. D. and Holm, R. H. *J. Am. Chem. Soc.*, **1983,** 105, 3905. b) Hagen, K. S.; Reynolds, J. G. and Holm, R. H. *J. Am. Chem. Soc.*, **1981,** 103, 4054. c) Lane, R. W.; Ibers, J. A.; Frankel, R. B.; Papaefthymiou, G. C. and Holm, R. H. *J. Am. Chem. Soc.*, **1977,** 99, 84.
4. a) Ueyama, N.; Nakata, M.; Fuji, M.; Terakawa, T. and Nakamura, A. *Inorg. Chem.*, **1985,** 24, 2190. b) Sun, W. Y.; Ueyama, N. and Nakamura, A. *Inorg. Chem.*, **1991,** 30, 4026.
5. a) Hill, C. L.; Renaud, J.; Holm, R. H. and Mortenson, L. E. *J. Am. Chem. Soc.*, **1977,** 99, 2549. b) Que, Jr., L.; Anglin, J. R.; Bobrik, M. A.; Davison, A. and Holm, R. H. *J. Am. Chem. Soc.*, **1974,** 96, 6042. c) Ueyama, N.; Terakawa, T.; Nakata, M. and Nakamura, A. *J. Am. Chem. Soc.*, **1983,** 105, 7098.
6. Ueyama, N.; Sugawara, T.; Kajiwara, A. and Nakamura, A. *J. Chem. Soc., Chem. Commun.*, **1986,** 434.
7. Sugawara, T.; Ueyama, N. and Nakamura, A. *J. Chem. Soc., Dalton. Trans*, **1991,** 249.
8. a) Inoue, H.; Fujimoto, N. and Imoto, E. *J. Chem. Soc., Chem. Commun.*, **1977,** 412. b) Tano, K. and Schrauzer, G. N. *J. Am. Chem. Soc.*, **1975,** 97, 5404. c) Schrauzer, G. N.; Robinson, P. R.; Moorhead, E. L. and Vickrey, T. M. *J. Am. Chem. Soc.*, **1976,** 98, 2815. d) Odell, B. and Geary, P. J. *J. Chem. Soc., Dalton. Trans*, **1984,** 29.
9. Yanada, K.; Nagano, T. and Hirobe, M. *Tetrahedron Lett.*, **1986,** 27, 5113.
10. Yanada, K.; Nagano, T. and Hirobe, M. *Chem. Pharm. Bull.*, **1988,** 36, 535.
11. Sun, W. Y.; Ueyama, N. and Nakamura, A. *J. Mol. Catal.*, in press.
12. Ueyama, N.; Sun, W. Y. and Nakamura, A. *J. Am. Chem. Soc.*, in press.
13. Watenpaugh, K. D.; Sieker, L. C. and Jensen, L. H. *J. Mol. Biol.*, **1979,** 131, 509.
14. Gill, N. S. and Taylor, F. B. *Inorg. Synth.*, **1967,** 9, 136.
15. Harris, A. R. and Mason, T. J. *Synth. Commun.*, **1989,** 19, 529.
16. Bachmann, W. E. *J. Am. Chem. Soc.*, **1934,** 56, 963.
17. a) Ueyama, N.; Nakata, M. and Nakamura, A. *Bull, Chem. Soc. Jpn.*, **1981,** 54, 1727. b) Nakata, M.; Ueyama, N.; Terakawa, T. and Nakamura, A. *Bull, Chem. Soc. Jpn.*, **1983,** 56, 3647.
18. Eaton, W. A.; Lovenberg, W. *Iron-Sulfur Proteins*; Lovenberg, W. Ed.; Academic Press: New York, 1973, Vol. II, p131.
19. Kajiwara, A.; Ueyama, N. and Nakamura, A. *Catal. Lett.*, **1989,** 3, 25.
20. Hammond, G. S. and Wu, C.-H. S. *J. Am. Chem. Soc.*, **1973,** 95, 8215.
21. Gutmann, V. *The Donor-Acceptor Approach to Molecular Interactions*, Plenum, New York, 1978.
22. Ueyama, N.; Kamabuchi, K. and Nakamura, A. *J. Chem. Soc., Dalton. Trans*, **1985,** 635.
23. Frey, M.; Sieker, L.; Payan, F.; Haser, R.; Bruschi, M.; Pepe, G. and LeGall, J. *J. Mol. Biol.*, **1987,** 197, 525.
24. Ueyama, N.; Sugawara, T.; Tatsumi, K. and Nakamura, A. *Inorg. Chem.*, **1987,** 26, 1978.
25. Unpublished data.