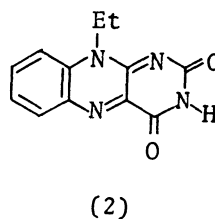
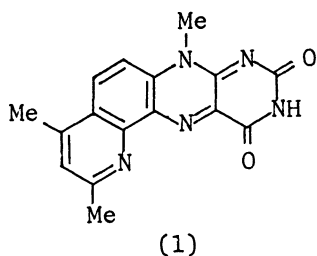


FLAVIN-Zr<sup>4+</sup> COMPLEX AS OXIDATION CATALYST

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A new metal-coordinative flavin, 2,4-dimethylpyrido[5,6-h](10-methyl)-isoalloxazine was synthesized. The complex with Zr<sup>4+</sup> acted as an efficient catalyst for the oxidation of alcohols and ascorbic acid under mild reaction conditions.

Flavin coenzymes serve as electron carriers to and from iron-sulfur proteins, molybdenum(xanthine oxidase), and heme proteins, and the interactions between flavins and metal ions thus have drawn considerable attention. However, the model investigations of the flavin-metal interactions have been very limited.<sup>1-4)</sup> This is solely ascribable to the poor affinity of flavin molecules for metal ions. As an attempt to gain an insight into the interaction from a viewpoint of model studies, we have synthesized a metal-coordinative flavin, 2,4-dimethylpyrido[5,6-h](10-methyl)isoalloxazine (1)<sup>5)</sup> and have found that the complex with Zr<sup>4+</sup> acts as an efficient oxidation catalyst.



The uv-visible absorption spectrum of (1) ( $\lambda_{\max}(\epsilon)$  in methanol, 258 nm (27270), 317 nm (14280), and 437 nm (8910)) dramatically changed on the addition of ZrCl<sub>4</sub>: the absorption bands were totally enhanced in all wavelength region ( $\lambda_{\max}(\epsilon)$  in methanol at [(1)] =  $1.72 \times 10^{-5}$  M and [ZrCl<sub>4</sub>] =  $3.30 \times 10^{-5}$  M, 263 nm (53060), 328 nm (27810), and 434 nm (13810)). The finding is contrasting to the fact that the spectrum of a conventional flavin analogue, 10-ethylisoalloxazine (2) is not affected at all by the addition of ZrCl<sub>4</sub>. The metal chelation of Ag<sup>+</sup> or Ru<sup>2+</sup> with conventional flavin analogues, which occurs at 4-C=O and 5-N position of isoalloxazine rings, results in a new absorption band in longer wavelength region.<sup>2,4)</sup> Since the spectrum of the (1)-Zr<sup>4+</sup> complex did not give such a new absorption band in longer wavelength region, we believe that Zr<sup>4+</sup> interacts with (1) at its 5-N and 6-N position.

The oxidation activity of the (1)-Zr<sup>4+</sup> complex was estimated spectrophotometrically by following the disappearance of the absorption band (434 nm) of the oxidized form. The spectrum of the oxidized form was completely regenerated by bubbling molecular oxygen into the final reaction mixture, suggesting that the system would act as a recycle oxidation system. The apparent second-order rate constants ( $k_2 = v_{\text{obs}}/[(1)][\text{substrate}]$ ), which were determined from the initial stipes, are summarized in Table 1.

The examination of Table 1 reveals that neither (1) nor (2) is able to oxidize alcohols, whereas in the presence of ZrCl<sub>4</sub> alcohols are oxidized by (1) but not by (2). It is worth while mentioning that the reaction conditions are very mild (30°C, no base). The novel catalytic behavior of the (1)-Zr<sup>4+</sup> complex is ascribable to the Zr<sup>4+</sup>-induced extreme electron-deficiency of (1). The product analysis (solvent acetonitrile, one day, 50°C), in which the products were isolated as 2,4-dinitrophenylhydrazone derivatives, showed that benzyl alcohol and cyclohexanol are oxidized quantitatively to the corresponding carbonyl compounds under anaerobic conditions, while the yields of carbonyl compounds under aerobic conditions amount to 10<sup>3</sup>-10<sup>4</sup>% (depending on the rate of an O<sub>2</sub> stream).<sup>6)</sup> The finding clearly establishes that the (1)-Zr<sup>4+</sup> complex acts as an efficient recycle oxidation catalyst for alcohols.

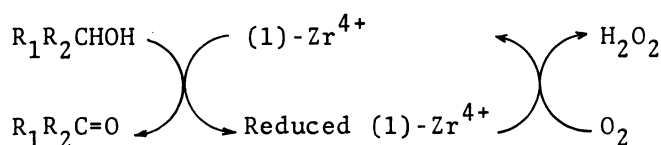


Table 1. Second-order rate constants for the oxidation of alcohols and ascorbic acid by (1) and (2)

Substrate (conc. mM)	$k_2$ (M <sup>-1</sup> s <sup>-1</sup> )			
	(1)	(1) + Zr <sup>4+</sup>	(2)	(2) + Zr <sup>4+</sup>
Benzyl alcohol (290) <sup>a)</sup>	0	$1.56 \times 10^{-4}$	0	0
Cyclohexanol (570) <sup>a)</sup>	0	$1.86 \times 10^{-4}$	0	0
Ethanol (1100) <sup>a)</sup>	0	$\sim 10^{-6}$	0	0
Ascorbic acid (14) <sup>b)</sup>	$2.3 \times 10^{-4}$	$1.84 \times 10^{-2}$	0	$6.3 \times 10^{-4}$

a) 30°C, N<sub>2</sub>, CH<sub>3</sub>CN, [(1)] = [(2)] =  $1.50 \times 10^{-5}$  M, [ZrCl<sub>4</sub>] =  $2.30 \times 10^{-4}$  M.

b) 30°C, N<sub>2</sub>, 95 vol% EtOH, [(1)] = [(2)] =  $1.40 \times 10^{-5}$  M, [DBU] = 0.140 M, [ZrCl<sub>4</sub>] =  $2.20 \times 10^{-4}$  M.

Table 1 also shows that the (1)-Zr<sup>4+</sup> complex rapidly oxidizes ascorbic acid. In the presence of excess DBU, ascorbic acid was oxidized by (1) but not by (2). This indicates that the isoalloxazine ring of (1) is more electron-deficient than (2). The absorption spectra showed that (1) forms the complex with Zr<sup>4+</sup> even in the presence of DBU and ascorbic acid. When ZrCl<sub>4</sub> was added to the reaction system, the rate constant for (1) was enhanced by a factor of 80 in comparison to that in the absence of ZrCl<sub>4</sub>. We found, however, that the addition of ZrCl<sub>4</sub> also accelerates the oxidation by (2) although the rate constant is smaller by a factor of 29 than that for (1) + Zr<sup>4+</sup>. It is not clear, therefore, whether the facile oxidation of ascorbic acid by (1) + Zr<sup>4+</sup> is solely ascribed to the electron-deficiency of the isoalloxazine ring.

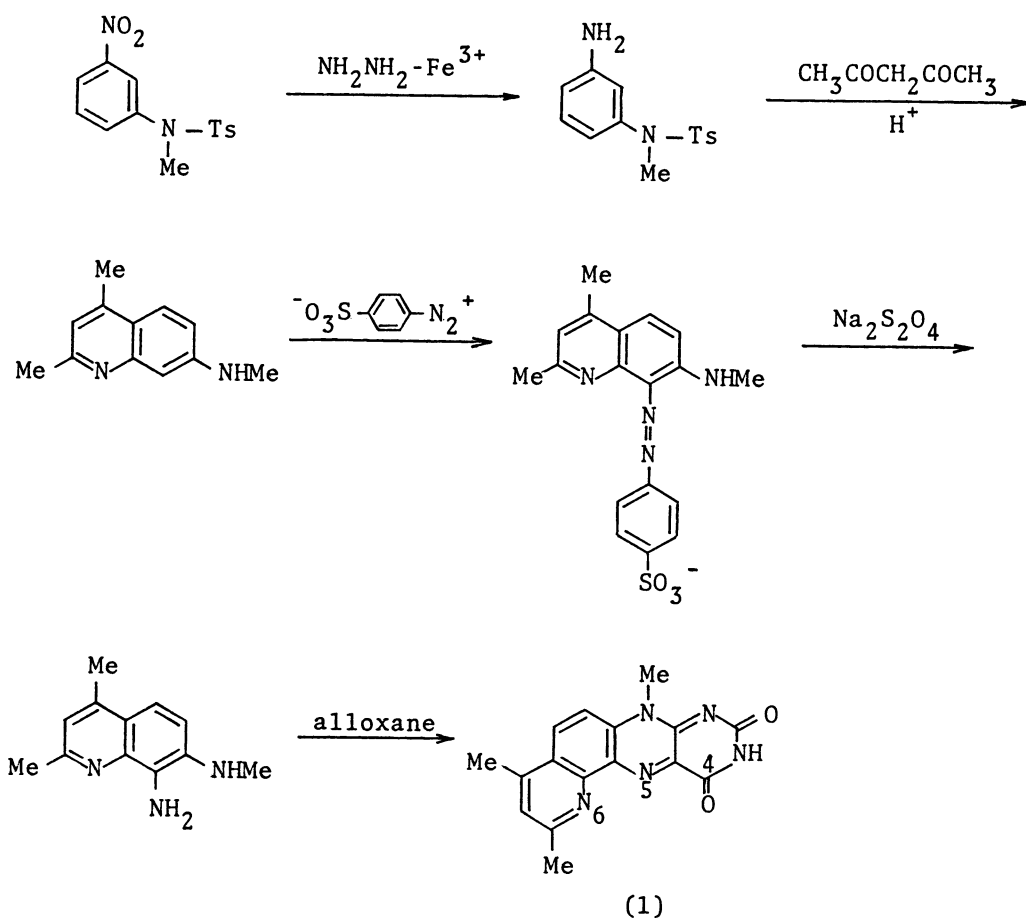
It is known that many electron-deficient organic molecules (e.g., azodicarboxylic acid diesters, 2,3-dichloro-5,6-dicyanobenzoquinone, etc.) serve as oxidation reagents for alcohols.<sup>7-11</sup> Because of the insensitivity of the reduced forms to molecular oxygen, however, few of them are able to catalyze the oxidation in a recycle manner. In the (1)-Zr<sup>4+</sup> complex, the oxidation ability of (1) is enhanced by the Zr<sup>4+</sup>-coordination without loss of the sensitivity of reduced (1) to molecular oxygen. Therefore, the most noteworthy characteristic of the (1)-Zr<sup>4+</sup> as an organic reagent would be its recycle oxidation behavior. Also significant is the fact that the absorption spectrum of (1) changes sensitively in the presence of metal ions. The spectral data would be important to understand the interactions between flavin coenzymes and metal ions in enzymatic systems.

Further investigations on the influence of various metal ions on the spectrum and the reactivity of (1) are now continued in this laboratory.

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- 5) (1) was synthesized according to the following reaction scheme (Ts = tosylate) and identified by mass spectrum, IR, and elemental analysis: mp > 293°C.



- 6) Reaction conditions:  $[(1)] = 3.00 \times 10^{-5}$  M,  $[\text{ZrCl}_4] = 3 \times 10^{-4}$  M, [alcohol] = 10 vol% in acetonitrile, 50°C, under  $\text{O}_2$ -current (when aerobic) or in the  $\text{N}_2$ -substituted ampoule (when anaerobic).
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