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LIGHT-MEDIATED OXIDATION OF ALCOHOLS AND MANDELATE BY FLAVIN-METAL COMPLEXES

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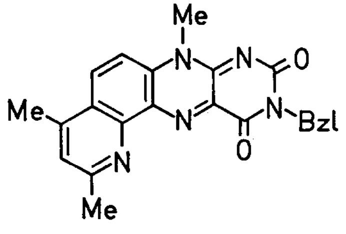
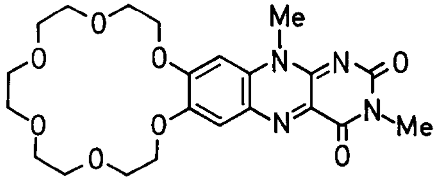
New flavins with metal affinity, (1) and (2) were applied to photo-oxidation of alcohols and mandelate. (1) rapidly photo-oxidized alcohols in the presence of Mg(II) and Zn(II): the rate augmentation corresponds to 16-18 fold. (2) could photo-oxidize $PhCH(OH)COO^-K^+$ but only slightly $PhCH(OH)COO^-NMe_4{}^+$: the rate difference amounts to 110-fold. Thus, the photo-oxidizability of these modified flavins can be markedly improved through complexation with metal ions.

Flavin and $NAD(P)^+$ coenzymes are versatile redox "catalysts" in many biological systems. In the past, biomimetic studies to apply these coenzymes to mediate redox reactions in nonenzymatic systems have been of much concern. In particular, flavin coenzymes and their analogues have been expected to be useful as "recycle oxidation catalysts", because the reduced forms can be readily converted to the oxidized forms by molecular oxygen(i.e., a ping-pong mechanism).[1-4] Meanwhile, it is known that photo-excited flavins act as electron-acceptors to oxidize phenols, amines, etc.[5-7] but are not electron-deficient enough to oxidize alcohols. We have found that the oxidizability of ground-state flavins is efficiently improved through complexation with certain metal ions.[8,9] One may thus expect that the oxidizability of photo-excited flavin-metal complexes should be further improved. In order to examine the above hypothesis, we have synthesized a metal-coordinative flavin (1) (2,4,7-trimethyl-10-benzylquino[8,7-g]pteridine-9,11(7H,10H)-dione) and a crown ether flavin mimic (2)(3,10-dimethyl-1',4',7',10',13',16'-hexaoxaclo-octadec-2'-eno[2',3'-i]isoalloxazine.[9,10] We used 3-methyl-10-ethyliso-alloxazine (3) as a reference flavin.



(1)



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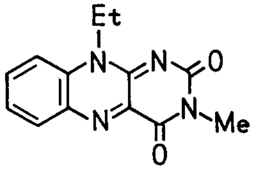

(3)

It is known that flavin derivatives can associated with Mg(II) in acetonitrile, the association constants being about 10^2 M^{-1}.[7,11,12] We have found from the spectral studies that (1) strongly binds to heavy metal ions. The absorption maximum of (1) in acetonitrile (444 nm) shifted to 454, 466, and 468 nm in the presence of $Mg(ClO_4)$, $Zn(ClO_4)_2 \cdot 6H_2O$, and $Cd(ClO_4)_2 \cdot 6H_2O$, respectively. Continuous variation plots indicated that these complexes consist of a 1:1 (1)/metal ratio. From the concentration dependence we estimated the association constants (K_c) to be 37, 1.40×10^5, and 2.50×10^5 M^{-1} for Mg(II), Zn(II), and Cd(II), respectively. The K_c of (1) for Mg(II) is greater only 2.3 times than that of (3) (16 M^{-1}). On the other hand, those of (1) for Zn(II) and Cd(II) are enhanced by 2.7×10^3 and 4.0×10^3 fold, respectively, compared with those of (3) (51 and 60 M^{-1}). The finding suggests that the phenanthroline-like moiety incorporated as an additional ligation-site markedly enhances the affinity for relatively "soft" metal ions.

The absorption spectra of (1) and (3) were unaffected by the addition of $KClO_4$. In contrast, the absorption maximum of (2) in acetonitrile (459 nm) shifted to 455 nm with decrease in the molar absorption coefficient (6300→5900 cm^{-1} M^{-1}). This is due to the association between K^+ and the crown ether moiety in (2). The K_c was estimated to be 2.50×10^4 M^{-1}.

Light-mediated oxidation was carried out anaerobically in a thermostated

Table 1. Pseudo-first-order rate constants (k_1') for photo-oxidation of benzyl alcohol by (1) and (3)[a]

Flavin	Metal (conc. mM)	$10^2 \cdot k_1'/\text{min}^{-1}$
(1)	none	0.85
(1)	$Mg(ClO_4)_2$ (5.11)	13.5
(1)	$Zn(ClO_4)_2$ (0.02)	13.3
(1)	$Zn(ClO_4)_2$ (0.101)	14.9
(3)	none	0.58
(3)	$Mg(ClO_4)_2$ (5.11)	2.20
(3)	$Zn(ClO_4)_2$ (0.02)	1.55
(3)	$Zn(ClO_4)_2$ (0.101)	4.00

[a] 30 °C, [flavin] = 2.00×10^{-5} M, [benzyl alcohol] = 0.200 M, acetonitrile.

(30 °C) water bath using a Thunberg cuvette and a 17-W fluorescent lamp. The distance between the cuvette and the lamp was 10 cm. The oxidation of benzyl alcohol in acetonitrile was followed spectrophotometrically by monitoring the disappearance of the absorption maximum of flavins (1) and (3). The absorption maxima disappeared slowly even in the absence of metal ions. Addition of $Mg(ClO_4)_2$ and $Zn(ClO_4)_2 \cdot 6H_2O$ induced a rapid decrease in the absorption maxima, and the time-dependence was apparently approximated (for up to two half-lives) by the first-order equation. Introduction of O_2 into the final solution regenerated oxidized (1) or (3) quantitatively. The pseudo-first-order rate constants (k_1') thus obtained are summarized in Table 1, and the typical [Zn(II)] dependence is illustrated in Figure 1.

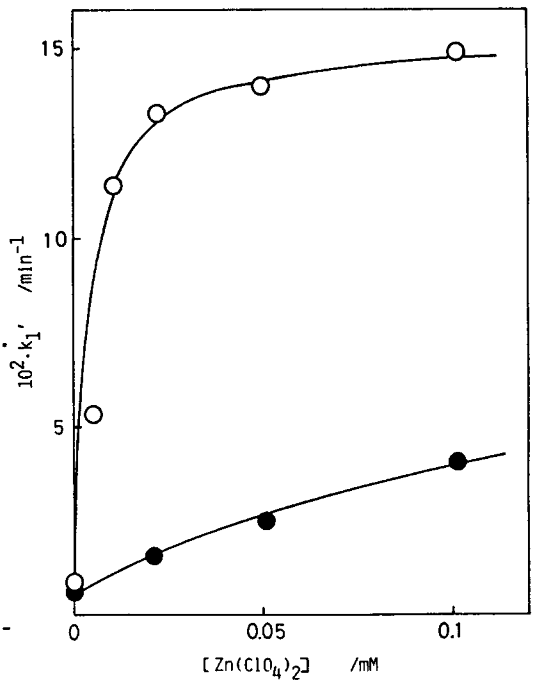

Figure 1. Photo-oxidation of benzyl alcohol by (1) (○) or (3) (●). [benzyl alcohol]=0.200 M, [flavin]= 2.00×10^{-5} M, acetonitrile.

The k_1' values for (1) and (3) in the absence of metal ions were comparable each other. The k_1' for (1) increased efficiently with increasing Zn(II) concentration and reached a maximum value at around 1×10^{-4} M. The maximum k_1' (0.15 min^{-1}) is greater by 17.6-fold than that in the absence of metal ions. Similar rate increase was observed for (3), but the rate augmentation was much smaller (6.9-fold). As the K_c for (1) + Zn(II) estimated from the plot in Figure 1 (2.6×10^5 M^{-1} in MeCN containing 0.2 M $PhCH_2OH$) is close to that estimated by the spectroscopic method (1.40×10^5 M^{-1} in pure MeCN), one may conclude that the rate acceleration is ascribed to electron-deficiency of the isoalloxazine ring enhanced by the metal-(1) interaction. Under aerobic conditions, 20 h photoirradiation of this solution ([(1)]=9.50×10^{-4} M, [$PhCH_2OH$]=0.483 M, [Zn(II)]=4.6 mM) gave 6150% of benzaldehyde (base on (1)). We also found that the (1)-Zn(II) complex can photo-oxidize 1-phenylethanol, cyclohexanol, 1-butanol, etc.

(3) (2.00×10^{-5} M) in acetonitrile was photo-reduced by potassium mandelate and tetramethylammonium mandelate (2.47×10^{-3} M): the k_1' at 30 °C being 3.6×10^{-2} and 9.7×10^{-2} min^{-1}, respectively. Addition of monobenzo-18-crown-6 (2.10×10^{-5} M) slightly enhanced the rate constant for potassium mandelate (4.7×10^{-2} min^{-1}). On the other hand, photo-oxidation of tetramethylammonium mandelate by (2) proceeded very slowly ($k_1'=1.4 \times 10^{-3}$ min^{-1}). The low oxidizability of (2) is compatible with its inability to photo-oxidize

alcohols. Probably, the crown ring acts as an electron-donating "substituent", leading to deactivation of the isoalloxazine ring. Interestingly, we have found that photo-oxidation of potassium mandelate occurred very rapidly, the rate constant (0.155 min^{-1}) being greater by 110-fold than that for photo-oxidation of tetramethylammonium counterpart. The result clearly demonstrates that (2) exhibits a specific reactivity toward K^+ salt species. Presumably, potassium mandelate and (2) form a preequilibrium complex owing to the K^+-crown interaction followed by pseudo-intramolecular photo-oxidation. In addition, we have found that (2) can photo-oxidize potassium salts of amino acids very rapidly.

In conclusion, the present study suggests that flavins are activated as photo-oxidation catalysts in the presence of certain metal ions. In particular, modified flavins we used herein can act as excellent photo-oxidation catalysts because of the electron-deficient nature caused by metal-flavin interactions.

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