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A New Catalytic System for Alcohol Oxidations by Employing N-Hydroxylamine-Flavin-O_2 in a Two-Phase System

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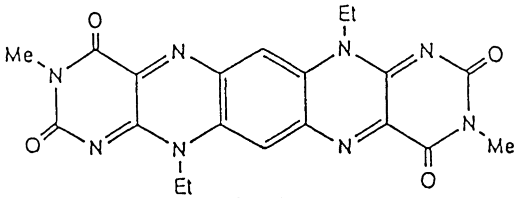
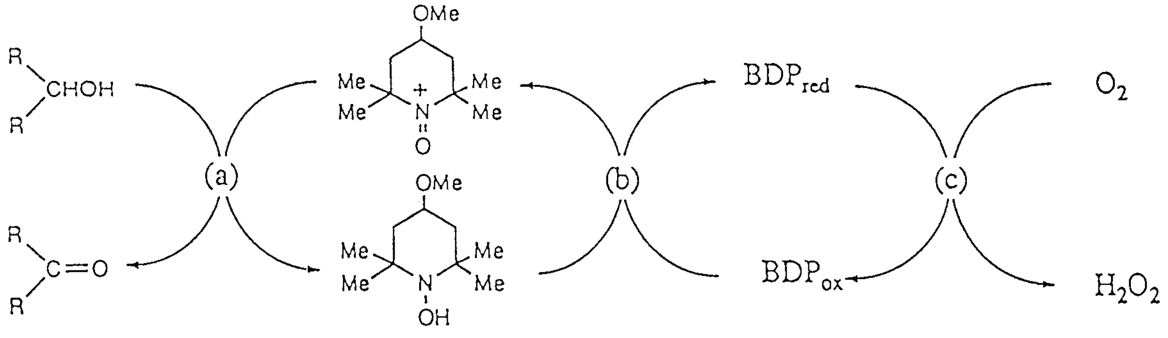
1-Hydroxyl-4-methoxy-2,2,6,6-tetramethylpiperidine (TMP) and benzo-dipteridine (BDP_{ox}) were found to act as turnover oxidation catalysts for alcohols under aerobic conditions in a two-phase system (H_2O-CH_2Cl_2). This catalytic activity was enhanced by photo-irradiation.

An oxidation-active flavin mimic is quite useful for investigations of flavin-mediated oxidations in model systems. For that purpose, we have exploited several oxidation-active flavin model compounds by chemical modification of an isoalloxazine ring.[1)] Among them, benzo-dipteridine (BDP_{ox}), which shows specific rate enhancement (ca. 10^7 folds) toward oxidations proceeding via nucleophilic attack at C(4a)-position, is a most versatile flavin mimic.[1d,2)] By employing BDP_{ox}, we have exploited the following new flavin model reactions in aqueous solutions: (i) oxidative dealkylation of N-nitrosamine derivatives (a model for metabolic activation of N-nitrosamines),[3)] (ii) oxidation of sulfite ion (an APS reductase model),[2b)] and (iii) oxidative cyclization of o-aminophenols (an isophenoxazine synthase model).[4)] It should be noted that conventional flavin model compounds are unable to oxidize these substrates under the same reaction conditions.



BDP_{ox}

During the course of our investigation to search for new model systems, we found that BDP_{ox} oxidizes N-hydroxylamines via two-electron oxidation, whereas the conventional flavin model such as 3,10-dimethylisoalloxazine does not. Thus if BDP_{ox} oxidizes TMP to afford the corresponding N-oxoaminium ion, the following catalytic cycle could be constructed (Scheme 1), since it is known that the N-oxoaminium ion oxidizes primary and secondary alcohols to give the correponding carbonyl compounds and TMP,[5)] and reduced BDP (BDP_{red}) is oxidized by O_2 to regenerate BDP_{ox}. This possibility was examined.



TMP

Scheme 1.

Prior to oxidation of alcohols by this catalytic system, each of the steps was examined independently. Meanwhile the oxidation of alcohols by N-oxoaminium ions [step (a)] has been well investigated, which can be conducted in CH_2Cl_2 or CH_2Cl_2-H_2O.$^{5)}$ Recycling systems have been also reported: N-oxyl compound-$CuCl_2$-O_2,$^{5b)}$ N-oxyl-NOCl-KBr,$^{5c)}$ and N-oxyl-$NaBrO_2$.$^{5d)}$ For step (b), the oxidation of TMP by BDP_{ox} was kinetically examined in brief to estimate the oxidation mechanism. Pseudo-first-order rate constants were determined as described previously.$^{2,3)}$ Effects of [TMP] and pH on the rates are shown in Figs. 1 and 2. These results are best explained by the following reaction scheme and rate equation.$^{6)}$ It was also confirmed that the rate in CH_2Cl_2 is faster (ca. 2 folds) than that in H_2O (pH 7.0). For step (c), the oxidation of BDP_{red} by O_2 was found to be

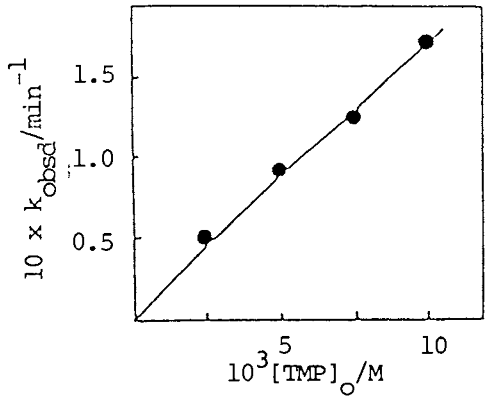


Fig. 1. Effect of $[TMP]_o$ on k_{obsd}. $[BDP_{ox}]_o = 1.0 \times 10^{-5}$ M, pH 7.46 (0.1 M phosphate, $\mu = 0.3$), N_2, 25 °C.

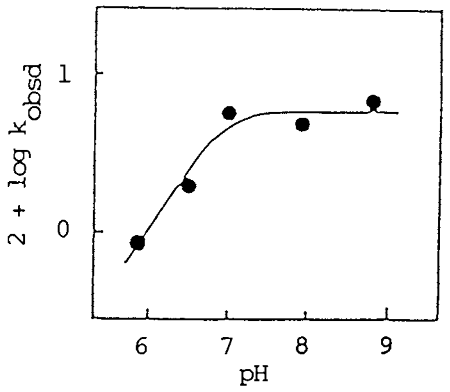


Fig. 2. Effect of pH on k_{obsd}. $[BDP_{ox}]_o = 1.0 \times 10^{-5}$ M, $[TMP]_o = 5.00 \times 10^{-3}$ M, N_2, 25 °C (1 M = 1 mol dm^{-3}).

$$TMPH^+ \overset{K_a}{\rightleftharpoons} TMP + H^+$$

$$TMP + BDP_{ox} \xrightarrow{k} BDP_{red} + {>}\overset{+}{N}{=}O$$

$$k_{obsd} = \frac{kK_a[TMP]_o}{[H^+] + K_a}$$

markedly dependent on solvents. Namely, BDP_{red} was found to be stable toward O_2 in CH_2Cl_2, whereas in an aqueous solution BDP_{ox} is immediately regenerated by O_2. In aprotic solvents, this step was found to require a proton. In fact, an addition of a proton source (N-ethylmorpholine $HClO_4$) regenerated BDP_{ox} quantitatively. However, use of acid decreases the rate of step (b) as shown in Fig. 2. Thus we adopted a two-phase system of CH_2Cl_2-H_2O, in which the oxidation of TMP by BDP_{ox} occurs in CH_2Cl_2, and BDP_{red} formed is transferred into an aqueous solution, since BDP_{red} is soluble in a slightly alkaline solution due to proton-dissociation at N(1) and N(8) positions of BDP_{red}.7)

Catalytic activity of TMP-BDP_{ox}-O_2 toward $PhCH_2OH$ was examined as follows: A mixture of CH_2Cl_2(2.5 cm^3)-H_2O(pH 8.9, 2.5 cm^3) containing small amounts of the catalysts [BDP_{ox} 0.2 mg (5.1×10^{-4}mmol), TMP 10 mg (5.3×10^{-2} mmol)] and $PhCH_2OH$ 1.2 g (11 mmol) was stirred vigorously under aerobic conditions at room temperature. Time course of PhCHO formation is shown in Fig. 3.8) It should be noted that the yields without BDP_{ox} are calculated for convenience' sake as similar as those with BDP_{ox} for direct comparison of both the systems. It was also confirmed that the yield of PhCHO increased with the increase of [BDP_{ox}]. Figure 3 indicates that (i) the catalytic system acts as a recycling catalyst, (ii) the oxidation is enhanced by photo-irradiation (60 W tungsten lamp),9) and (iii) PhCHO was formed even without BDP_{ox}, but not formed without both BDP_{ox} and TMP. Formation of PhCHO in the control experiment may be explained by formation of N-nitroxyl radical from TMP and O_2, which dispropotionates to TMP and

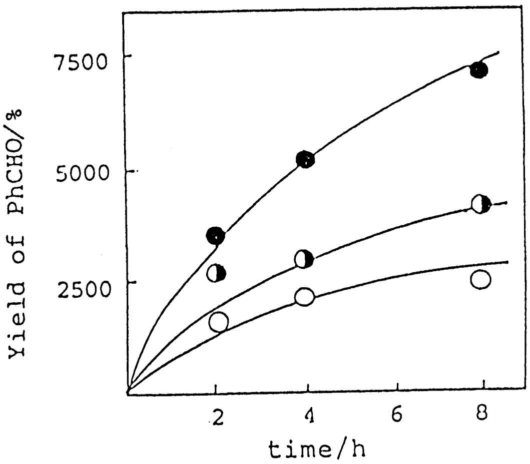
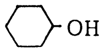


Fig. 3. Time course of PhCHO formation. ●: TMP-BDP_{ox}-O_2/hν, ◑: TMP-BDP_{ox}-O_2/dark, ○: TMP-O_2/hν.

Table 1. Yields of carbonyl compounds a)

Alcohols	Based on TMP/%	Based on BDP_{ox}/%
$PhCH_2CH_2OH$	48 (14) b)	3500
$\underset{OH}{PhCHCH_3}$	67 (17) b)	5200
$n\text{-}C_6H_{13}\underset{OH}{C}HCH_3$	87 (24) b)	6000
	77 (23) b)	5900

a) After 14 h stirring. b) Yields due to TMP-O_2/hν.

the N-oxoaminium ion.[10] Meanwhile the reaction mixture showed a blue colour of BDP_{red} throughout the reaction, suggesting that step (c) is rate-determining in the catalytic cycle. In passing, BDP_{ox} exerts a reddish colour in solution.

Since the catalytic activity of TMP-BDP_{ox}-O_2 is enhanced by photo-irradiation, the oxidations of other alcohols were examined under photo-irradiation (Table 1).[9] As shown in Table 1, the net turnover numbers of the catalytic cycle in scheme 1 are estimated to be 35-60.

The present study demonstrates a new type of turnover catalysts for alcohol oxidations coupled with the oxidation of TMP by an oxidation-active flavin model in which the catalytic activity is enhanced by photo-irradiation, although much remains to be done from the aspects of a practical synthetic method.

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6) Similar kinetic results were obtained for Me_2NOH, and formation of HCHO was confirmed spectrophotometrically by the Nash method [T. Nash, Biochem. J., 55, 416 (1953)], suggesting formation of N-oxoaminium ion as follows;

$$Me_2\overset{+}{N}{=}O \rightleftharpoons \overset{-}{C}H_2(Me)\overset{+}{N}{=}O \xrightarrow{H_2O} HOCH_2(Me)NOH \longrightarrow HCHO + MeNHOH$$

7) Ref. 2. $BDPH_2 \rightleftharpoons BDPH^- + H^+$ (pK_a 3.6), $BDPH^- \rightleftharpoons BDP^{2-} + H^+$ (pK_a 8.5)

8) Yields of carbonyl compounds were determined as 2,4-dinitrophenyl-hydrazone derivatives (Ref. 1c).

9) The distance between the lamp and the reaction vessel was 10 cm and the reaction temperature was controlled at 25 °C with a water-jaket.

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