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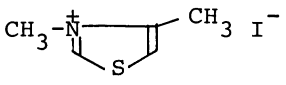
OXIDATION OF ALDEHYDES BY THIAZOLIUM IONS AND FLAVIN IN A CATIONIC MICELLE

Yumihiko YANO, Yutaka HOSHINO, and Waichiro TAGAKI
Department of Chemistry, Faculty of Technology, Gunma University,
Kiryu, Gunma 376

The reactions of aldehydes with thiazolium ions and flavin were investigated in the presence of CTABr micelle. The reactions were found to be facilitated by a cationic micelle.

Very recently, we have shown that 2-(α-hydroxybenzyl)thiazolium ion (active aldehyde) is readily oxidized by 3-methyllumiflavin(Eqs. 2 and 3).1) We also reported that a micelle forming thiazolium ion was an efficient catalyst for acyloin condensation in aqueous solution,2) in which the above active aldehyde is involved as a key intermediate.3) As a rational extension, it is of interest to examine the reaction of aldehydes with thiazolium ions and flavin. This may be a good model of flavin pyruvate oxidase, which catalyzes the oxidative decarboxylation of pyruvate to give acetate and CO_2.4) Meanwhile, Shinkai et al. have reported a detailed study of the oxidation of aldehydes with cyanide ion and flavin in a cationic micelle.5)

In this paper, we describe the kinetics of oxidation of aldehydes with 3-methyllumiflavin under micellar conditions, employing the following thiazolium salts as the catalysts.



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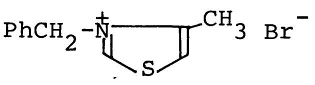

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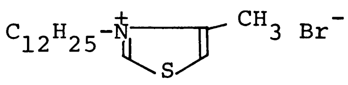

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As reported previously,1) the reactions were followed by monitoring the decrease of absorption of flavin (6.9×10^{-5}M) at 443 nm under anaerobic conditions at pH 8.76 (0.1 M carbonate, $\mu = 0.11$, 25°C). The effect of surfactant CTABr was examined by employing benzaldehyde as a substrate. In the absence of CTABr, flavin was not reduced under the conditions of [PhCHO] = 2×10^{-3}M and the catalysts (**1**, **2** or **3**) = 1×10^{-3}M.6) However, in the presence of CTABr (8×10^{-3}M, a micellar condition), flavin reduction occurred and the observed zero-order rate constants (v_{obsd}) were 3.3×10^{-8}, 6.6×10^{-8}, and 8.0×10^{-6}M min^{-1} for **1**, **2**, and **3**, respectively. The relative rates are 1 : 2 : 250. A large rate enhancement for **3** may be accounted for by high local concentration of hydroxide ion and PhCHO on cationic **3** - CTABr co-micellar surface. In fact, the hydrogen at 2-carbon of a micelle forming thiazolium ion (**3**) is shown to exchange with the hydrogen of solvent water 16 times faster than that of a non-micelle forming thiazolium ion (**1**).[7)] Meanwhile, flavin exists in a bulk water, not in micellar phase, since the absorption spectra of flavin [443 nm(ε = 12,000 $M^{-1}cm^{-1}$, 368 nm(ε = 10,000$M^{-1}cm^{-1}$)] in water were exactly the same as those in the presence of CTABr (8 x 10^{-3}M). In organic solvents such as EtOH and $CHCl_3$, the absorption at 368 nm was found to shift to shorter wave length [345 nm(ε = 9,000 $M^{-1}cm^{-1}$)]. Thus the oxidation seems to occur at the micelle-water interface.

The values of v_{obsd} were found to be first order with respect to each of PhCHO and thiazolium ion (**3**) concentration in the presence of CTABr (Figs. 1 and 2).

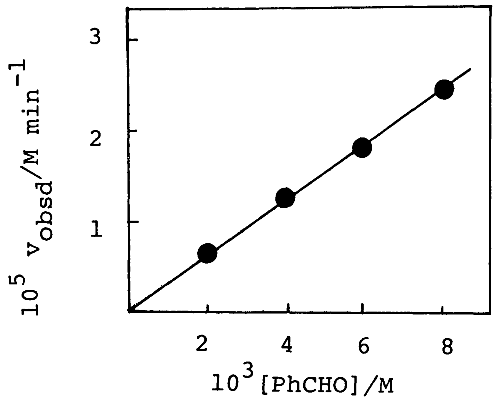


Fig. 1. v_{obsd} vs. [PhCHO]. [CTABr]= 4 x 10^{-3}M, [**3**] = 1 x 10^{-3}M.

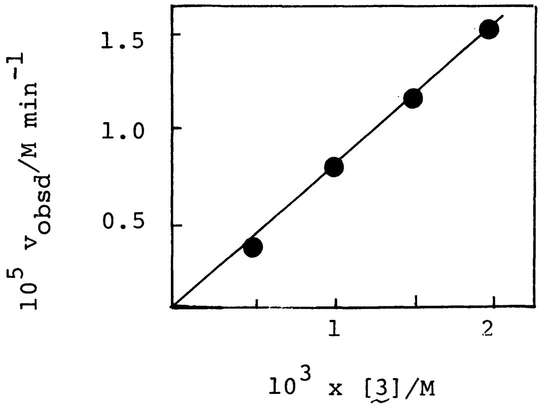
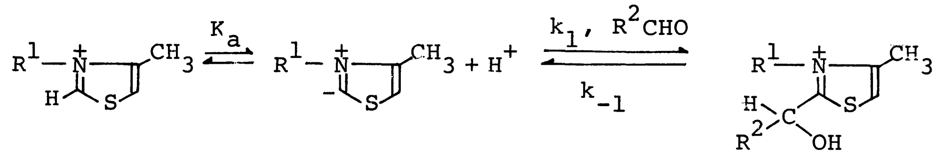
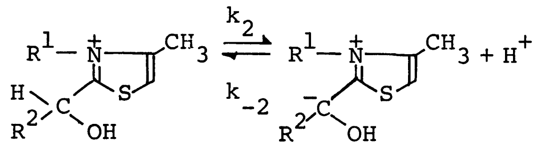


Fig. 2. v_{obsd} vs. [**3**]. [CTABr]= 8 x 10^{-3}M, [PhCHO] = 2 x 10^{-3}M.

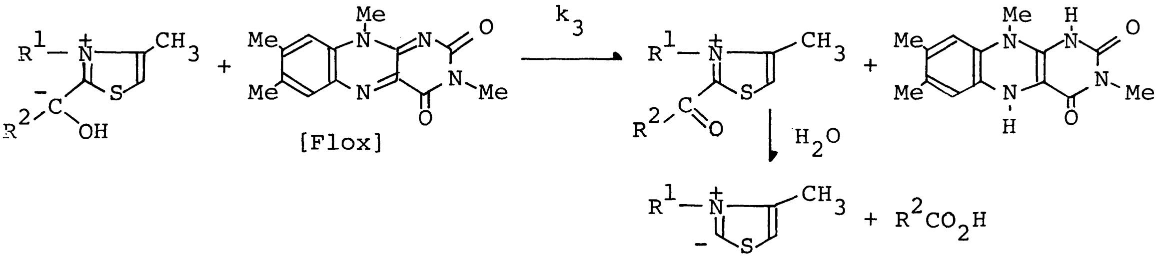
These results together with zero-order dependency on flavin are in accord with the following reaction scheme (Eqs. 1 - 3) and kinetic equations (Eqs. 4 - 6).



(1)



(2)



(3)

$$-\frac{d(\mathrm{Flox})}{dt} = \frac{k_1k_2k_3K_a[T][R^2CHO][Flox]}{k_{-1}(K_a/[H^+] + 1)(k_{-2}[H^+] + k_3[Flox])} \qquad (4)^{8)}$$

$$k_{-2}[H^+] \ll k_3[Flox], \quad K_a/[H^+] \ll 1 \qquad (5)^{9)}$$

$$v_{obsd} = \frac{k_1k_2K_a}{k_{-1}}[T][R^2CHO] \qquad (6)$$

Namely, Eq. 6 indicates that the rate is first order with respect to thiazolium ion and aldehyde. In Eqs. 4 and 6, [T] and [R^2CHO] represent total concentrations of thiazolium ion and aldehyde, respectively.

Oxidation of other aldehydes were also examined under micellar conditions. The results are shown in the Table. Aromatic and hydrophobic aliphatic aldehydes are very reactive as observed in acyloin condensation of aldehydes catalyzed by **3** in aqueous solution.2)

Table. The second-order rate constants$^{a)}$

R^2CHO	$k_1k_2K_a/k_{-1}$ $M^{-1}\,min^{-1}$	k_{rel}
R^2=CH_3CH_2-	0.009$^{b)}$	1
$CH_3(CH_2)_5$-	1.08	120
Ph-	3.18	350

a) [CTABr] = [R^2CHO] = 4 x 10^{-3}M, [**3**] = 1 x 10^{-3}M

b) v_{obsd} was calculated from the initial slope.

Meanwhile, 2-acylthiazolium ions are known to undergo a rapid hydrolysis in aqueous alkaline solution,10) and the reduced 1,4-dihydroflavins are also known to be easily oxidized by O_2 to starting flavins.11) Thus, one may expect that thiazolium ion and flavin can act as catalysts for oxidation of aldehydes under aerobic conditions. This possibility was examined as follows. A mixture of

PhCHO (0.1 g, 0.94 mmol), **2** (0.02 g, 0.094 mmol), flavin (0.02 g, 0.083 mmol), and Et_3N (0.05 g, 0.5 mmol) in EtOH (20 ml) was stirred for 24 h at room temperature under aerobic conditions. After work up, $PhCO_2Et$ (0.1 g) was obtained by distillation (71 %).12)

References and Notes

1) Y. Yano, Y. Tamura, Y. Hoshino, and W. Tagaki, Bull. Chem. Soc. Jpn., 53, No. 8 (1980).

2) W. Tagaki and H. Hara, J. Chem. Soc., Chem. Commun., 1973, 891.

3) R. Breslow, J. Am. Chem. Soc., 80, 3719 (1958); Ann. New York Acad. Sci., 98, 445 (1962).

4) L. P. Hager, J. Biol. Chem., 229, 251 (1957); Bacterial Proc., 1958, 109.

5) S. Shinkai, T. Ide, and O. Manabe, Chem. Lett., 1978, 583; S. Shinkai, T. Yamashita, Y. Kusano, T. Ide, and O. Manabe, J. Am. Chem. Soc., 102, 2335 (1980); Furthermore, Shinkai et al. have also investigated the essentially same reactions as those described here (The 41th Annual Meeting of the Chemical Society of Japan, Osaka, April (1980), Abstract II, p. 885).

6) The CMC of **3** is 3.3×10^{-3}M(ref. 2). When 8×10^{-3}M of **3** was used, the reaction occurred without CTABr ($v_{obsd} = 1.83 \times 10^{-4}$ M min^{-1}).

7) Y. Yano, Y. Tamura, and W. Tagaki, Bull. Chem. Soc. Jpn., 53, 740 (1980).

8) This equation was derived by the assumption of steady state concentration for α-hydroxy carbanion (Eqs. 2 and 3).

9) $K_a = 10^{-20}$; J. Crosby and G. E. Lienhard, J. Am. Chem. Soc., 92, 5707 (1970).

10) T. C. Bruice and N. G. Kundu, J. Am. Chem. Soc., 88, 4097 (1966); G. E. Lienhard, ibid., 88, 5642 (1966).

11) T. C. Bruice, "Progress in Bioorganic Chemistry," ed by E. T. Kaiser and F. J. Kezdy, John Wiley & Sons, New York (1976), vol. 4, p. 1.

12) In aqueous buffer solution (pH 8.23, 0.5 M phosphate) by using **3**, a mixture of $PhCO_2H$ and benzoin was detected (TLC).

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