The syn and anti carbon nuclei in 7-chloronorbornane (13, X = Cl) were unambiguously distinguished by recording of the ^{13}C spectrum of *exo,exo*-2,3-dideuterio-*syn*-7-chloronorbornane (prepared as described).[77] Long-range $^3J_{^{13}C-F}$ coupling constants were employed in the analysis of 7-fluornorbornane (13, X = F) to distinguish the syn and anti positions: δ 26.52 (syn), $^3J_{^{13}C-F}$ = 1.72 Hz; δ 25.18 (anti), $^3J_{^{13}C-F}$ = 8.60 Hz. The largest coupling was assigned to the γ-*anti*-carbon in accord with the analysis of such coupling given by Schneider.[78] The syn and anti carbon nuclei in 7-iodonorbornane (13, X = I) were correlated with the assigned protons in the molecule by selective proton decoupling experiments (*exo-syn*-^1H, δ 1.95; *exo-anti*-^1H, δ 1.62; *endo-syn*- and *endo-anti*-^1H, δ 1.30; for 13, X = I) to give the results in Table I for this compound. The *syn*- and *anti*-carbons in 7-bromonorbornane (13, X = Br) differ by only 0.07 ppm (i.e., δ 27.33 and 27.26), and it was not possible to unambiguously assign these resonances.

The *exo*-2-halo-7,7-dimethylnorbornanes (18, X = Cl, Br, I) were prepared in an attempt to probe the effect of proximate δ groups. While it proved possible to assign the chemical shifts of C(1), C(2), C(3), C(4), and C(7) in these molecules by a combination of the techniques outlined above, it was not possible to unambiguously distinguish C(5) from C(6), and the assignments of these resonances in Table I were made by analogy. The *syn*- and *anti*-7-methyl groups in all of the *exo*-2-halo-7,7-dimethyl compounds differed only slightly in chemical shift, and no effort was made to distinguish between the methyl nuclei since these data were not used in the factor analysis.

Acknowledgment. At Yale this investigation was supported by Grant CHE77-24629 from the National Science Foundation and at the University of Connecticut by the donors of the Petroleum Research Fund (9456-G4), administered by the American Chemical Society. We also acknowledge the support of the Southern New England High Field NMR Facility made possible by a grant from the Biotechnology Resources Program of the National Institues of Health (RR-798). The factor analysis program was kindly made available by Professor Howrey.

Registry No. 1 (X = F), 593-53-3; 1 (X = Cl), 74-87-3; 1 (X = Br), 74-83-9; 1 (X = I), 74-88-4; 2 (X = F), 353-36-6; 2 (X = Cl), 75-00-3; 2 (X = Br), 74-96-4; 2 (X = I), 75-03-6; 3 (X = F), 460-13-9; 3 (X = Cl), 540-54-5; 3 (X = Br), 106-94-5; 3 (X = I), 107-08-4; 4 (X = F), 420-26-8; 4 (X = Cl), 75-29-6; 4 (X = Br), 75-26-3; 4 (X = I), 75-30-9; 5 (X = F), 2366-52-1; 5 (X = Cl), 109-69-3; 5 (X = Br), 109-65-9; 5 (X = I), 542-69-8; 6 (X = F), 353-61-7; 6 (X = Cl), 507-20-0; 6 (X = Br), 507-19-7; 6 (X = I), 558-17-8; 7 (X = F), 41909-29-9; 7 (X = Cl), 616-20-6; 7 (X = Br), 1809-10-5; 7 (X = I), 1809-05-8; 8 (X = F), 649-80-9; 8 (X = Cl), 994-25-2; 8 (X = Br), 73908-04-0; 8 (X = I), 75066-51-2); 9 (X = F), 666-16-0; 9 (X = Cl), 1120-57-6; 9 (X = Br), 4399-47-7; 9 (X = I), 38557-29-8; 10 (X = F), 1481-36-3; 10 (X = Cl), 930-28-9; 10 (X = Br), 137-43-9; 10 (X = I), 1556-18-9; 11 (X = F), 372-46-3; 11 (X = Cl), 542-18-7; 11 (X = Br), 108-85-0; 11 (X = I), 626-62-0; 12 (X = F), 765-92-4; 12 (X = Cl), 765-91-3; 12 (X = Br), 2534-77-2; 12 (X = I), 30983-85-8; 13 (X = F), 70279-04-8; 13 (X = Cl), 765-80-0; 13 (X = Br), 13237-88-2; 13 (X = I), 70279-05-9; 14 (X = F), 20277-22-9; 14 (X = Cl), 2064-03-1; 14 (X = Br), 7697-09-8; 14 (X = I), 931-98-6; 15 (X = F), 63160-84-9; 15 (X = Cl), 15158-55-1; 15 (X = Br), 15292-76-9; 15 (X = I), 63160-85-0; 16 (X = F), 768-92-3; 16 (X = Cl), 935-56-8; 16 (X = Br), 768-90-1; 16 (X = I), 768-93-4; 17 (X = F), 16668-83-0; 17 (X = Cl), 7346-41-0; 17 (X = Br), 7314-85-4; 17 (X = I), 18971-91-0; 18 (X = F), 70279-06-0; 18 (X = Cl), 22768-98-5; 18 (X = Br), 70279-07-1; 18 (X = I), 70279-08-2; 2-chloroacrylonitrile, 920-37-6; 1-methoxycyclohexa-1,4-diene, 2886-59-1; 1-methoxycyclohexa-1,3-diene, 2161-90-2; 1-methoxybicyclo-[2.2.2]oct-5-en-2-one, 38213-08-0; apoborene, 6541-60-2.

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Coenzyme Models. 26. Facile Oxidation of Aldehydes and α-Keto Acids by Flavin as Catalyzed by Thiazolium Ion and Cationic Micelle[1]

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The reaction sequence of acyloin condensation of aldehydes which is catalyzed by *N*-hexadecylthiazolium bromide (HxdT) in the CTAB micelle was readily diverted by added 3-methyltetra-*O*-acetylriboflavin (MeFl) to the oxidation reaction to afford carboxylic acids. Similarly, the micellized thiazolium ion plus MeFl system efficiently catalyzed the decarboxylative oxidation of aliphatic α-keto acids but scarcely catalyzed that of aromatic α-keto acids. In contrast, hydrophilic thiazolium ions such as *N*-benzylthiazolium bromide (BzlT), thiamine, and thiamine pyrophosphate (TPP) were less effective catalysts. The reactions were zero-order in MeFl and first-order in HxdT and substrates, the apparent second-order rate constants being enhanced by factors of 10^2–10^4 in comparison to those in the nonmicellar system. On the basis of the kinetic examination and the product analysis, we proposed that the reactions involve oxidative trapping by MeFl of the intermediate formed by the rate-limiting deprotonation or decarboxylation from the HxdT–substrate adducts. This means that the intermediate of the thiazolium ion catalysis (active aldehyde) serves as substrate for the flavin oxidation. This is the first nonenzymatic example for the synergistic catalysis of flavin coenzyme and TPP coenzyme. The relevance of the reactions to biological systems (in particular, to pyruvate dehydrogenase which requires FAD and TPP as cofactors) is discussed. Since the 2-acyl group of the oxidation products (2-acylthiazolium ions) is sensitive to nucleophiles, the reaction is readily applicable to synthesis of esters from aldehydes.

Recently, it was proposed that some flavin-dependent enzymes employ carbanion intermediates during the course of the oxidation of bound substrates.[2,3] In a previous publication of this series,[4] we demonstrated that the application of the concept "flavin oxidation of carbanion" to organic chemistry is very useful in exploring a new class of oxidation reactions. A successful example is seen in the

(1) Preliminary communication: Shinkai, S.; Yamashita, T.; Kusano, Y.; Manabe, O. *Tetrahedron Lett.* **1980**, 2543. A similar system has recently been communicated by: Yano et al. *Chem. Lett.* **1980**, 749. Abbreviations used in this paper are as follows: FAD, flavin adenine dinucleotide; TPP, thiamine pyrophosphate; HxdT, *N*-hexadecylthiazolium bromide; BzlT, *N*-benzylthiazolium bromide; MeFl, 3-methyltetra-*O*-acetylriboflavin; CTAB, hexadecyltrimethylammonium bromide; SDS, sodium dodecylsulfate.

(2) Bruice, T. C. *Prog. Bioorg. Chem.* **1976**, *4*, 1.
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(4) (a) Shinkai, S.; Ide, T.; Manabe, O. *Chem. Lett.* **1978**, 583. (b) Shinkai, S.; Yamashita, T.; Manabe, O. *J. Chem. Soc., Chem. Commun.* **1979**, 301. (c) Shinkai, S.; Yamshita, T.; Kusano, Y.; Ide, T.; Manabe, O. *J. Am. Chem. Soc.* **1980**, *102*, 2335.

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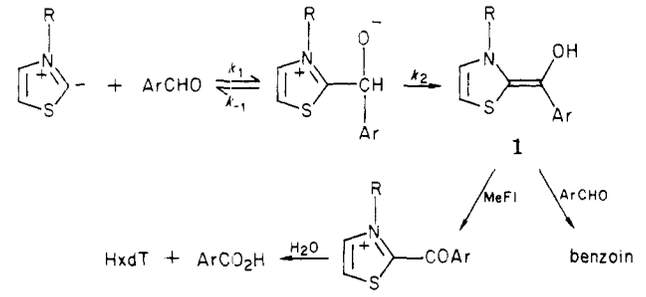
Table I. Product Analysis for the Flavin Oxidation of 4-Chlorobenzaldehyde (ArCHO)[a]

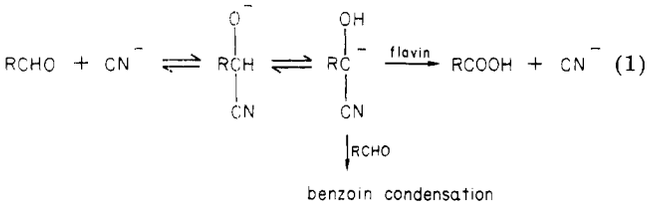
[ArCHO], mM	[HxdT], mM	[MeFl], mM	[CTAB], mM	% product		
				$ArCO_2H$	ArCH(OH)COAr	ArCOCOAr
50	0	5	0	0	0	0
50	0	0	10	1	0	0
50	1[b]	0-5	0	0	0	0
50	1	0	10	0.4	37	47
5[c]	1	5	10	63	0	0

[a] At 30 °C and pH 8.0 with 0.05 M phosphate for 1 day in the dark. [b] BzlT was used instead of HxdT. [c] At the elevated ArCHO concentrations, we could detect ArCH(OH)COAr.

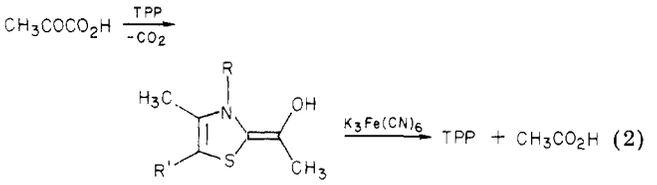
Scheme I



benzoin condensation (eq 1), the intermediary carbanion of which can be trapped oxidatively by flavin.[4]

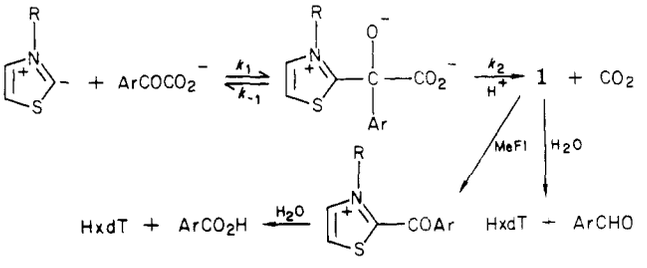


Pyruvate dehydrogenase (E.C.1.2.2.2) requires FAD and thiamine pyrophosphate (TPP) as cofactors and catalyzes the conversion of pyruvic acid to acetic acid.[5] Although the detailed reaction mechanism of pyruvate dehydrogenase is unknown, one may expect that the decarboxylated intermediate from the adduct of TPP and pyruvic acid, which is equivalent to the deprotonated intermediate from the adduct of TPP and acetaldehyde, is trapped oxidatively by FAD because the TPP catalysis is essentially analogous to the CN^- catalysis.[6] In fact, the intermediate (active aldehyde) produced by the enzyme can be oxidized by a strong electron-acceptor such as $K_3Fe(CN)_6$ (eq 2).[7]



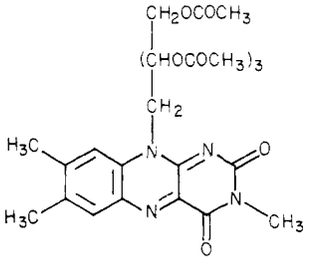
TPP itself exhibits no catalytic activity in the nonenzymatic system. It has been found, however, that the cationic micelle of thiazolium salts catalyzes the acyloin condensation of aldehydes.[8] We found that on the addition of flavin to the system, the reaction is readily diverted to the oxidation reaction, affording carboxylic acids from corresponding aldehydes and α-keto acids. This is the first example for a model system of pyruvate dehydrogenase.

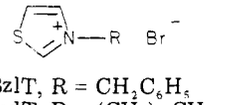
Scheme II



Results and Discussion

Flavin Oxidation of 4-Chlorobenzaldehyde. We have used 3-methyltetra-*O*-acetylriboflavin (MeFl) and *N*-hexadecyl- (HxdT) or *N*-benzylthiazolium bromide (BzlT). The product analysis for the oxidation of 4-chlorobenzaldehyde (ArCHO) is summarized in Table I. 4-Chlorobenzaldehyde was selected because of the high solubility in water in comparison to benzaldehyde.





In the nonmicellar system, neither condensation products nor oxidation products were obtained significantly, and ArCHO was recovered almost quantitatively. In the presence of HxdT and CTAB, ArCHO was converted to 4,4′-dichlorobenzoin and 4,4′-dichlorobenzil, the total yield being 84%. 4,4′-Dichlorobenzil was afforded owing to further oxidation of 4,4′-dichlorobenzoin.[4] The result is in accord with a previous finding by Tagaki and Hara[8] that the acyloin condensation occurs only in the micellized thiazolium ion solution. On the other hand, addition of MeFl strikingly suppressed the formation of condensation products, and 4-chlorobenzoic acid became a main product. These results establish that (i) the existence of micellized thiazolium ion is a primary prerequisite to the oxidation and (ii) added MeFl dramatically diverts the reaction sequence from acyloin condensation to oxidation.

On the basis of the foregoing results, we can propose Scheme I, which involves 1 as a key intermediate. It is known that 2-acylthiazolium ions are readily hydrolyzed to corresponding carboxylic acids in aqueous solution.[9,10]

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(6) Breslow, R. *J. Am. Chem. Soc.* **1957**, *79*, 1762.
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(8) Tagaki, W.; Hara, H. *J. Chem. Soc., Chem. Commun.* **1973**, 891.
(9) White, F. G.; Ingraham, L. L. *J. Am. Chem. Soc.* **1962**, *84*, 3109.

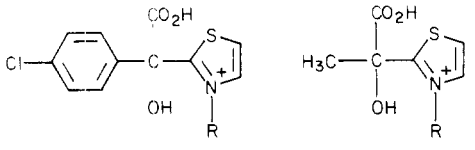
Table II. Product Analysis for the Decarboxylative Oxidation of (4-Chlorobenzoyl)formic Acid and Pyruvic Acid

substr (concn, mM)	[HxdT], mM	[MeFl], mM	[CTAB], mM	% product[g] RCO$_2$H	RCHO	RCOCO$_2$H[c]
4-ClC$_6$H$_4$COCO$_2$H[a] (5)	0	5	0	0	0	100
(5)	1[f]	5	0-10	0	0	100
(5)	1	0	10	0	3	71
(5)	1	5	10	8	1	63
CH$_3$COCO$_2$H[b] (25)	0	5	10	0	0	*d*
(25)	5[f]	5	0-10	0	0	*d*
(25)	5	0	10	0	~10[e]	*d*
(25)	5	5	10	93-100	0	*d*

[a] At 30 °C and pH 8.0 with 0.05 M phosphate for 1 day in the dark. [b] At 30 °C and pH 8.0 with 0.05 M phosphate for 36 h in the dark. [c] Recovered (4-chlorobenzoyl)formic acid. [d] The content of unreacted pyruvic acid could not be determined by GLC under the analytical conditions used to detect acetic acid, acetaldehyde, acetoin, and diacetyl. [e] The content of acetaldehyde could be determined by GLC, but the reproducibility was inferior, owing to its volatility. [f] BzlT was used instead of HxdT. [g] No RCH(OH)COR or RCOCOR was found in any case.

Decarboxylative Oxidation of (4-Chlorobenzoyl)formic Acid and Pyruvic Acid. Results of the product analysis are summarized in Table II. The importance of the micellized thiazolium ion and the diversion of the reaction sequence to the oxidation reaction are also seen in Table II. Hence, the mechanism for the decarboxylative oxidation of α-keto acids must be similar to that depicted for the oxidation of aldehydes. Aldehydes afforded in the absence of MeFl are attributed to hydrolysis of a key intermediate 1 (Scheme II). The aldehydes were left unreacted in the reaction media because of the low concentrations.

It should be noted here that in the case where (4-chlorobenzoyl)formic acid was used as substrate, the yields of both aldehyde and carboxylic acid were extremely low. We previously found that cyanide ion is able to attack the aldehyde group of 2,4-dichlorobenzaldehyde, whereas it cannot react with the keto group of (2,4-dichlorobenzoyl)formic acid owing to the steric hindrance of the adduct.[4c] This implies that the reaction center of aromatic α-keto acids is sterically crowded. The low reactivity of (4-chlorobenzoyl)formic acid is due probably to the steric hindrance of the adduct with thiazolium ion **2**. The CPK



2 **3**

model building of **2** also supports this presumption. On the other hand, the keto group of pyruvic acid smoothly reacted with thiazolium ion, as observed in the enzymatic system, owing to the reduced steric hindrance of the adduct **3**. The result clearly indicates that thiazolium ion serves as a decarboxylation catalyst for aliphatic α-keto acids but only poorly catalyzes the decarboxylation of aromatic α-keto acids. The conclusion is in line with the following kinetic results.

Kinetics of Flavin Oxidation. The kinetic measurements of the flavin oxidation were carrid out at 30 °C under anaerobic conditions (N_2). The reaction was followed spectrophotometrically by monitoring the disappearance of the absorption band of MeFl at 448 nm. The detailed reaction conditions are recorded under in the captions of Figures 1–5. Interestingly, the decrease of the 448-nm band was zero order up to, for example, 90% reaction for benzaldehyde and 60% reaction for pyruvic acid. The reaction rates were calculated from the linear, initial slopes. Introduction of oxygen into the final reaction cell regenerated MeFl quantitatively, and after several minutes the zero-order disappearance of MeFl started again (Figure 1). Hence, MeFl acts as a turnover oxidation catalyst as shown in Scheme III (i.e., Ping-Pong mechanism).

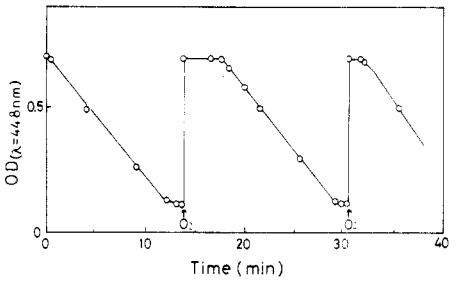


Figure 1. Time-dependence of absorbance of MeFl: [4-ClC$_6$H$_4$CHO] = 1.00×10^{-2} M, [HxdT] = 5.00×10^{-4} M, [MeFl] = 5.00×10^{-5} M, [CTAB] = 1.00×10^{-2} M, pH 7.52 with 0.02 M phosphate, 3 vol % ethanol, μ = 0.052.

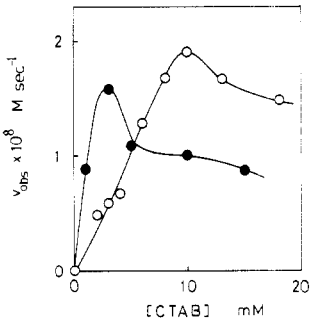
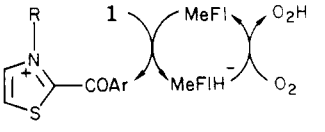


Figure 2. Plots of v_{obsd} vs. CTAB concentration: ○, [C_6H_5CHO] = 1.00×10^{-2} M, [MeFl] = 5.00×10^{-5} M, [HxdT] = 5.00×10^{-4} M, pH 7.52 with 0.02 M phosphate, μ = 0.052; ●, [CH_3COCO_2H] = 3.00×10^{2} M, [MeFl] = 5.00×10^{-5} M, [HxdT] = 1.00×10^{-3} M, pH 7.30 with 0.02 M phosphate, μ = 0.052.

Scheme III



The reaction rates (v_{obsd}) were plotted as a function of the CTAB concentration (Figure 2). BzlT was used instead of HxdT to obtain a plot at [CTAB] = 0 mM, since the HxdT solution was slightly turbid. The disappearance of MeFl was undetected at [CTAB] = 0 mM, indicating v_{obsd} to be less than 10^{-11} M s^{-1}. The v_{obsd} value increased with increasing CTAB concentration, and rate maxima resulted at about 3–10 mM CTAB. This proves that the

(10) Daigo, K.; Reed, L. J. *J. Am. Chem. Soc.* **1962**, *84*, 659.

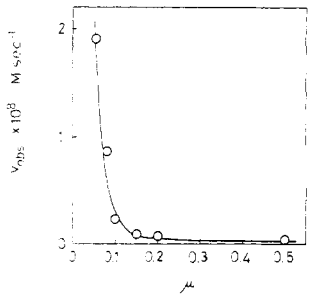


Figure 3. Effect of ionic strength on the reaction rate: $[C_6H_5CHO] = 1.00 \times 10^{-2}$ M, [MeFl] = 5.00×10^{-5} M, [HxdT] = 5.00×10^{-5} M, [CTAB] = 1.00×10^{-2} M, pH 7.52 with 0.02 M phosphate.

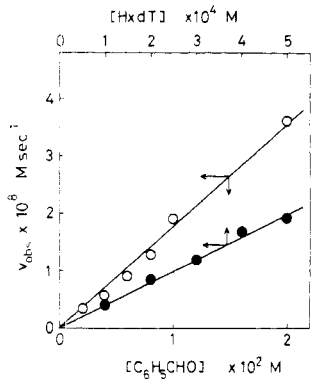


Figure 4. Plots of v_{obsd} vs. $[C_6H_5CHO]$ (○) or [HxdT] (●) for the oxidation of benzaldehyde: 3 vol % ethanol, pH 7.52 with 0.02 M phosphate, $\mu = 0.052$, [MeFl] = 5.00×10^{-5} M, [CTAB] = 1.00×10^{-2} M, $[C_6H_5CHO]$ (when kept constant) = 1.00×10^{-2} M, [HxdT] (when kept constant) = 5.00×10^{-4} M.

reactions are subject to a typical micellar catalysis.[11] The micellar effect is sensitive to ionic strength.[11] As shown in Figure 3, the reaction was markedly suppressed by enhanced ion concentration, the maximal rate suppression being $^1/_{48}$.

For specification of the reaction order, v_{obsd} values were determined as functions of the concentrations of substrates (S = benzaldehyde and pyruvic acid) and HxdT. Figures 4 and 5 prove that the rates are first-order with respect to the substrates and HxdT. As described above, the v_{obsd} is zero-order with respect to MeFl. There are several precedents for the zero-order behavior in flavin-mediated reactions,[12] the proposed mechanisms for which commonly involve the rate-limiting formation of reactive species followed by the immediate oxidation by flavin. Therefore, the deprotonation in Scheme I and the decarboxylation in Scheme II (i.e., k_2) are assigned to the rate-limiting step. The v_{obsd} is thus expressed by eq 3, where $K = k_1/k_{-1}$ and

$$v_{obsd} = \frac{k_2 K K_a [S]_0 [HxdT]_0}{[H^+] + K K_a [S]_0} \quad (3)$$

K_a is the acid-dissociation constant of thiazolium ion (10^{-20}).[13] To derive eq 3, we assumed $[H^+]/K_a \gg 1$ and $[S]_0 \gg [HxdT]_0$. Since v_{obsd} is first-order in both S and HxdT, $[H^+] \gg KK_a[S]_0$ is assumed under the present experimental conditions, and eq 3 is rewritten as eq 4.

$$v_{obsd} = \frac{k_2 K K_a [S]_0 [HxdT]_0}{[H^+]} \quad (4)$$

Hence, the apparent second-order rate constant ($k_{2,app}$) is equivalent to $k_2KK_a/[H^+]$.

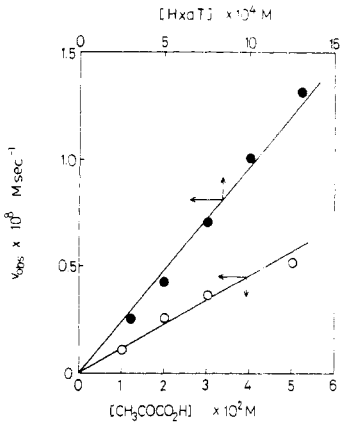


Figure 5. Plots of v_{obsd} vs. $[CH_3COCO_2H]$ (○) or [HxdT] (●) for the decarboxylative oxidation of pyruvic acid: 3 vol % ethanol, pH 7.30 with 0.02 M phosphate, $\mu = 0.052$, [MeFl] = 5.00×10^{-5} M, [CTAB] = 1.00×10^{-2} M, $[CH_3COCO_2H]$ (when kept constant) = 3.00×10^{-2} M, [HxdT] (when kept constant) = 5.00×10^{-4} M.

Table III. Apparent Second-Order Rate Constants ($10^3 k_{2,app}$, M^{-1} s^{-1}) for the Oxidation of Aldehydes and α-Keto Acids[a]

substr	surfactant		
	CTAB	Brij-35	SDS
Aldehyde[b]			
$2,4\text{-}Cl_2C_6H_3CHO$	114		
$4\text{-}ClC_6H_4CHO$	17.4		
C_6H_5CHO	3.47	0.068	~0 (<0.004)
	3.92[d]		
HCHO	0.020		
C_3H_7CHO	0.130		
$C_7H_{15}CHO$	0.738		
α-Keto Acid[c]			
$4\text{-}ClC_6H_4COCO_2H$	0.010		
CH_3COCO_2H	0.232		
	0.323[d]		

[a] The rate constants were determined, unless otherwise stated, by varying the substrate concentration while maintaining the concentration of HxdT constant. [b] At 30 °C and pH 7.52 with 0.02 M phosphate, $\mu = 0.052$, [surfactant] = 1.00×10^{-2} M, [MeFl] = 5.0×10^{-5} M, and [HxdT] = 5.00×10^{-4} M. [c] At 30 °C and pH 7.30 with 0.02 M phosphate, $\mu = 0.052$, [surfactant] = 1.00×10^{-2} M, [MeFl] = 5.0×10^{-5} M, and [HxdT] = 5.00×10^{-4} M. [d] The rate constants were determined by varying the concentration of HxdT while maintaining the substrate concentration constant: $[C_6H_5CHO] = 1.00 \times 10^{-2}$ M; $[CH_3COCO_2H] = 3.00 \times 10^{-2}$ M.

Apparent second-order rate constants are recorded in Tables III and IV. The examination of these tables reveals that (i) only the cationic CTAB micelle acts as an excellent catalyst, and nonionic (Brij-35) and anionic (SDS) micelles have little or no effect, (ii) the substrate with an electron-withdrawing substituent(s) is oxidized more rapidly, (iii) as shown for aliphatic aldehydes, the hydrophobic substrate is oxidized more rapidly, (iv) the reactivity of BzlT is suppressed by more than 2 orders of magnitude relative to that of HxdT, and (v) polyanionic TPP is more effective than thiamine. These results consistently support

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(13) The pK_a of 19.2–20.6 was proposed for the dissociation of the hydrogen atom at C-2 of the 3,4-dimethylthiazolium ion,[14a] but the lower pK_a value (12.6) was proposed for thiamine.[14b]

Table IV. Apparend Second-Order Rate Constants ($10^3 k_{2,app}$, M^{-1} s^{-1}) for the Oxidation of Aldehydes by Various Thiazolium Ions[a]

	C_6H_5CHO		4-ClC_6H_4CHO		2,4-$Cl_2C_6H_3CHO$	
thiazolium	none	CTAB	none	CTAB	none	CTAB
HxdT		3.47		17.4		114
BzlT	0	0.027				
thiamine	0	0.010				
TPP	0	0.034	0	0.123	0	0.307

[a] At 30 °C and pH 7.52 with 0.02 M phosphate, μ = 0.052, [CTAB] (if added) = 1.00×10^{-2} M, [MeFl] = 5.0×10^{-5} M, and [thiazolium ion] = 5.00×10^{-4} M.

the supposition that the reaction proceeds in the CTAB micellar phase.

The decarboxylative oxidation of (4-chlorobenzol)formic acid was extremely slow, the $k_{2,app}$ at 10 mM CTAB being about 1×10^{-5} M^{-1} s^{-1}. As described above, this is due to the steric hindrance of the adduct **2**. On the other hand, the decarboxylative oxidation of pyruvic acid occurred more easily ($k_{2,app}$ = (2–3) $\times 10^{-4}$ M^{-1} s^{-1} at 10 mM CTAB), owing to reduced steric crowding of the adduct **3**. The kinetic examination was thus performed with pyruvic acid.

Catalytic Role of the CTAB Micelle. The CTAB micelle enhances the local concentration of reactants in the micellar phase, leading to the apparent increase in the reaction rates.[11,14] However, the rate enhancement of 10^2–10^4-fold observed for the present system cannot be accounted for by the classical concentration effect. The apparent second-order rate constant $k_{2,app}$ is equivalent to $k_2KK_a/[H^+]$, so that the reaction rate is affected by the acid-dissociation constant of HxdT (K_a), the equilibrium constant for the adduct formation (K), and the rate constant for the formation of a key intermediate 1 (k_2).

There are many examples that the dissociation of acids is facilitated in a cationic micelle.[15] Tagaki and Hara,[8] who found for the first time that the micellized thiazolium ion catalyzes the acyloin condensation, attributed the excellent catalytic activity to the facile dissociation of the micellized thiazolium ion. The shift is due to the enhanced local concentration of OH^- and to the cationic electrostatic environment.[11,15] Conceivably, the pK_a of HxdT in the CTAB micelle is lowered by several pK units. According to Martinek et al.,[16] the nucleophilicity of anions bound to the cationic micelle is not reduced in spite of their lowered pK_a values. Several other groups observed that anions bound to the cationic micelle are more activated than those in bulk water.[17] We accounted for the phenomenon by the concept of "hydrophobic ion pairs" — an anion in the cationic micelle phase is activated due to desolvation.[18,19] It is thus presumed that the K value is rather enhanced or at least is not reduced.

The rate-limiting step (k_2) is the deprotonation or the decarboxylation from the adducts. In a previous study of this series, we reported that the CTAB micelle accelerates the proton abstraction from carbon acids owing to the enhanced OH^- ion concentration around the micelle surface.[20] The rate suppression by enhanced ionic strength is thus attributed to the competitive binding of anions and OH^- onto a site of the cationic head group of the surfactant. It is expected, therefore, that the k_2 term for the oxidation of aldehydes is enhanced by the CTAB micelle as long as the ionic strength of the reaction medium is suppressed. The micellar effect on decarboxylation has been well documented by Bunton et al.[21] For example, the rate of the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate is speeded up by 2 orders of magnitude in the presence of the CTAB micelle.[21] The origin of the rate enhancement was discussed by several groups and was attributed to the stabilization of the delocalized transition state and to the activation of the carboxylate ion by the hydrophobic environment of the micelles.[18,19,21] This accelerative effect can be also expected for the k_2 term of the decarboxylative oxidation of α-keto acids.

On the basis of the foregoing considerations, one may conclude that the marked rate acceleration is brought about by synergistic micelle effects on the K_a, K, and k_2 terms.

Table V. Application to Ester Synthesis in Methanol[a]

aldehyde	[BzlT], mM	[MeFl], mM	yield of ester, %
C_6H_5CHO	2	4	71
C_6H_5CHO[b]	2	2	0
$C_6H_5CHCHCHO$	2	2	23
$C_6H_5CHCHCHO$	20	2	57
$C_6H_5CHCHCHO$[b]	20	4	27
p-$C_6H_4(CHO)_2$	20	2	39
p-$C_6H_4(CHO)_2$	50	10	73

[a] At 30 °C for 48 h. The concentration of NEt_3 was 100 mM and the concentration of the aldehyde was 20 mM in all cases. [b] *tert*-Butyl alcohol was used instead of methanol.

Application to Ester Synthesis. 2-Acylthiazolium ions readily undergo hydrolysis in aqueous solution and alcoholysis in alcoholic solution.[9,10] Hence, the present finding is useful as a new method to synthesize esters from aldehydes. Several examples are shown in Table V. The products were analyzed by using GLC, and the yields were calculated on the basis of the aldehydes. It is seen from Table V that this is a convenient route to obtain methyl esters from aldehydes, but the yields of bulky *tert*-butyl esters are relatively low. Further application is currently

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under way in this laboratory.

Concluding Remark. The present study establishes that the combination of micellized thiazolium ion and flavin remarkably facilitates the oxidation of aldehydes and α-keto acids, and both cofactors act as turnover catalysts. The finding provides a useful insight into the mechanism of pyruvate dehydrogenase. Also significant is that the reaction sequence is readily diverted to the oxidation reaction, leading to exploitation of a new class of synthetic procedures.

Experimental Section

Materials. *N*-Hexadecylthiazolium bromide (HxdT) and *N*-benzylthiazolium bromide (BzlT) were prepared from thiazole and the corresponding alkyl bromides. For HxdT: mp 77–79 °C; NMR ($CDCl_3$) δ 0.88 (3 H, t, CH_3), 1.24 (28 H, m, $(CH_2)_{14}$), 4.75 (2 H, t, *N*-CH_2), 8.19 (2 H, m, 4-H and 5-H), 10.90 (1 H, m, 2-H). Anal. Calcd for $C_{19}H_{36}NSBr \cdot H_2O$: C, 55.88; H, 9.38; N, 3.43. Found: C, 55.52; H, 9.42; N, 3.38. For BzlT, mp 155–156 °C. Anal. Calcd for $C_{10}H_{10}NSBr$: C, 46.70; H, 3.94; N, 5.47. Found: C, 46.70; H, 3.93; N, 5.41.

Thiamine and TPP were kindly supplied from Kyowa Hakko Co. Ltd. and were used without further purification. Preparations of authentic samples for GLC and high-pressure LC analyses were described previously.[4c]

Methods of Flavin Oxidation and Product Analyses. An aqueous solution containing substrate, CTAB, HxdT, and MeFl was kept in the dark. The detailed reaction conditions are recorded in the tables. The solution was acidified with 1% HCl to pH 1–2. In the oxidation of aromatic substrates [4-chlorobenzaldehyde and (4-chlorobenzoyl)formic acid], the final solution was extracted with chloroform. The chloroform layer was concentrated under reduced pressure and then analyzed by using high-pressure liquid chromatography (Shimadzu LC-3). In the oxidation of pyruvic acid, the aqueous solution was directly subjected to GLC analysis (Shimadzu GC-4CM).

Kinetic Measurements. The kinetic measurements of the flavin oxidation were carried out at 30 °C under anaerobic (N_2) conditions in 3 vol % of aqueous ethanol. A Thunberg cuvette was used to provide the anaerobic reaction conditions. The detailed procedure was described previously.[4c] The progress of the reaction was monitored spectrophotometrically by following the disappearance of MeFl at 448 nm.[22]

Registry No. 4-Chlorobenzaldehyde, 104-88-1; 4-chlorobenzoic acid, 74-11-3; 4,4'-dichlorobenzoin, 4254-20-0; 4,4'-dichlorobenzil, 3457-46-3; (4-chlorobenzoyl)formic acid, 7099-88-9; pyruvic acid, 127-17-3; acetic acid, 64-19-7; acetaldehyde, 75-07-0; 2,4-dichlorobenzaldehyde, 874-42-0; benzaldehyde, 100-52-7; formaldehyde, 50-00-0; butyraldehyde, 123-72-8; octanol, 124-13-0; thiamine, 59-43-8; thiamine pyrophosphate, 582-37-6; cinnamaldehyde, 104-55-2; terephthalaldehyde, 623-27-8; methyl benzoate, 93-58-3; methyl cinnamate, 103-26-4; *tert*-butyl cinnamate, 14990-09-1; dimethyl terephthalate, 120-61-6; thiazole, 288-47-1; benzyl bromide, 100-39-0; hexadecyl bromide, 112-82-3; HxdT, 75066-49-8; MeFl, 21066-33-1; CTAB, 57-09-0; BzlT, 75066-50-1.

(22) **Note Added in Proof.** Recently a thiazolium-catalyzed ester synthesis was reported: Inoue et al. *J. Chem. Soc., Chem. Commun.* **1980**, 549.

Reaction of α-Azido Esters with Lithium Ethoxide: Synthesis of Dehydroamino Esters and α-Keto Esters

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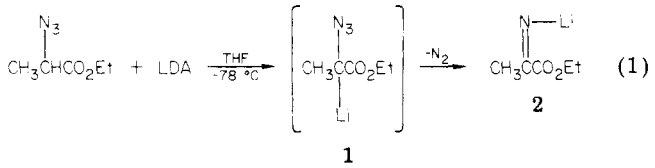
α-Azido esters **4** react with catalytic amounts of ethoxide in tetrahydrofuran/ethanol to evolve nitrogen and form dehydroamino esters **3**. Acid hydrolysis gives α-keto esters **5** in good yields.

In an attempt to prepare enolate **1**, ethyl 2-azidopropanoate was added to a solution of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at dry ice temperature. Nitrogen was evolved and the reaction mixture turned deep red. Hydrolytic workup gave an intractable tar and no GLC volatile products. Presumably, **1** is formed but spontaneously loses nitrogen to form imine anion **2**, which, in the strongly basic reaction medium, undergoes further reaction (eq 1). In agreement with this,

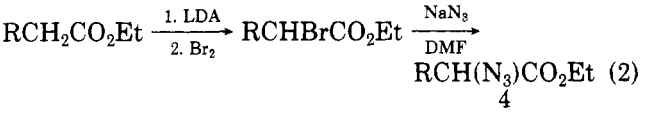


(1)

1 **2**

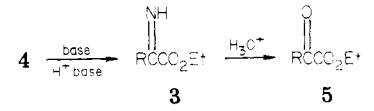
there are scattered reports in the literature of base-induced elimination of nitrogen from α-azido ketones[1] and acids[2] leading to imine-derived products. Prior to the completion of this work, Jarvis[3] described the synthesis of nitriles from α-azido sulfur compounds via presumed imine intermediates.

It seemed likely that generation of anions analogous to **2** in a protic medium would allow isolation of the corresponding dehydroamino esters **3**. Since α-azido esters **4** are readily obtained from the corresponding esters (eq 2), the overall sequence would provide a simple route to dehydroamino esters and, by hydrolysis, the corresponding α-keto esters **5** (eq 3). Accordingly, we have examined the



(2)

4



(3)

3 **5**

reaction of α-azido esters with several weak bases with the results reported here.

Results and Discussion

THF solutions containing ethyl 2-azidopropanoate (**4**, R = Me) and triethylamine did not evolve nitrogen even at reflux temperatures. Reaction of **4** (R = Me) with

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