BIOORGANIC CHEMISTRY 13, 88–97 (1985)

Catalytic Action of Comicelles Containing Imidazolyl and Hydroxyl Groups in the Hydrolysis of Enantiomeric Esters

YASUJI IHARA[1]

Yamaguchi Women's University, 3-2-1 Sakurabatake, Yamaguchi 753, Japan

AND

YOSHIHARU KIMURA, MAMORU NANGO, AND NOBUHIKO KUROKI

Department of Applied Chemistry, University of Osaka Prefecture, Sakai, Osaka 591, Japan

Received August 10, 1984

The rate constants for hydrolysis of the enantiomers of amino acid *p*-nitrophenyl esters catalyzed by bifunctional comicellar catalysts containing the imidazolyl and hydroxyl groups have been determined at pH 7.30, 0.02 M phosphate buffer, and 25°C. The kinetic analysis suggests a reaction scheme which involves acylation followed by deacylation at the imidazolyl group. Although no appreciable cooperative catalytic efficiencies are observed between the bifunctional groups in the acylation step, it is found that the deacylation rates are thus accelerated by surfactant hydroxyl groups, and some of the stereoselective acyl transfer reaction occurs from the imidazolyl to the hydroxyl group in optically active comicellar systems.

INTRODUCTION

Proteolytic enzymes such as α-chymotrypsin exhibit a characteristic stereoselectivity as well as high reactivity in their catalytic actions toward their various substrates (*1*). Recently, several studies on bifunctional micellar catalysis have been investigated as models of esterolytic enzymes for the hydrolysis of nonspecific substrates such as *p*-nitrophenyl acetate (*2–4*).

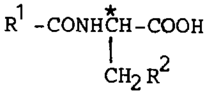
In the course of our study on stereoselective micellar catalysis (*5–8*), we found that comicelles of optically active *N*-acylhistidine or dipeptide derivatives containing histidyl residues and cationic surfactants are effective stereoselective catalysts for the hydrolysis of enantiomeric esters. A mechanism was suggested for the stereoselective catalysis involving acylation of the optically active histidyl residue.

The present study describes the results of kinetic analysis of bifunctional comicellar catalysts containing the imidazolyl and hydroxyl groups for the hydrolysis of enantiomeric amino acid *p*-nitrophenyl esters (**II**). The catalysts used in this

---

[1] To whom correspondence should be addressed.

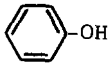
0045-2068/85 $3.00

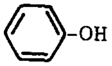


$$R^1\text{-CONH}\underset{\textstyle CH_2R^2}{\overset{*}{C}}H\text{-COOH}$$

(I)

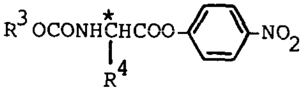
a; $R^1 = CH_3(CH_2)_8$, $R^2 =$ 

b; $R^1 = CH_3(CH_2)_8$, $R^2 =$ 

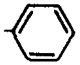
c; $R^1 = CH_3$, $R^2 =$ 

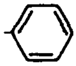
d; $R^1 = CH_3(CH_2)_8$, $R^2 =$ OH

e; $R^1 = CH_3(CH_2)_8$, $R^2 =$ 



(II)

a; $R^3 = CH_3$, $R^4 = CH_2$- 

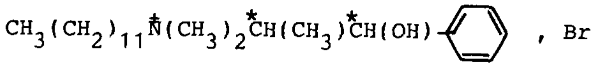
b, $R^3 = CH_2$-  , $R^4 = CH_3$

$CH_3(CH_2)_{15}\text{-}\overset{+}{N}(CH_3)_2\text{-X},\quad Br$

(III)

a; $X = CH_3$ (CTABr)

b; $X = CH_2CH_2OH$



(IV)

experiment are *N*-decanoyl-L-histidine (**Ia**) (which has an imidazolyl group) and *N*-acyl-L-tyrosine (**Ib,c**) (which has a hydroxyl group), or surfactants (**IIIb,IV**) containing a hydroxyl group.

EXPERIMENTAL PROCEDURES

Materials. *N*-Decanoyl-L-tyrosine, *N*-decanoyl-L-serine, and *N*-decanoyl-L-phenylalanine were prepared and purified by standard methods (*9*). *N*-Acetyl-L-tyrosine was purchased from the Sigma Chemical Company and was used without further purification. Other materials have been described elsewhere (*5–7*).

Kinetic measurements. Reactions were generally monitored on an Hitachi 200 spectrophotometer or a Simazu 140 spectrophotometer with a thermostated cell holder at 25°C. In the general procedure, a solution (25 μl) of substrate in acetonitrile was added to a buffer solution (3.00 ml) containing the catalyst and surfactant at the desired concentrations. The formation of *p*-nitrophenolate ion and the decay of acylated intermediate were followed spectrophotometrically at 400 nm (or 410 nm) and 245 nm (or 255 nm), respectively. Pseudo-first-order rate constants were obtained from plots of $\log(A_\infty - A_t)$ versus time (t) by use of the least-squares method. Correlation coefficients were >0.999. Details of kinetic techniques and conditions may be found under Results and Discussion.

RESULTS AND DISCUSSION

*Catalytic Action of N-Acylamino Acid (**I**) in CTABr (**IIIa**) Micelles*

Kinetic studies were performed at pH 7.30, 0.02 M phosphate buffer, and 25°C. Under the conditions [surfactant] > [catalyst] > [substrate], pseudo-first-order rate constants (k_ψ) were evaluated by monitoring the release of *p*-nitrophenoxide ion spectrophotometrically at 400 nm. The catalytic hydrolysis of **IIa** were first examined by varying the concentration of *N*-acylamino acid (**I**) at fixed [CTABr] of 6.00×10^{-3} M. Examples of the observed pseudo-first-order rate constants, k_ψ, versus concentration of **I** are shown in Fig. 1. This figure indicates that **Ia** and **Ib** accelerate the rate of hydrolysis of **IIa** and that **Ic** causes a small increase in the reaction rate. However, **Id** and **Ie** tend to decrease the catalytic activity under comparable conditions. In general, ionization of the carboxy group of **I** partially neutralizes the positively charged CTABr head groups. This factor reduces the catalytic potential in micellar systems.

For *N*-acyltyrosine (**Ib,c**) the catalytic second-order rate constants (k_c) were obtained from the linear slope in a graph of the observed pseudo-first-order rate constants versus initial catalyst concentration. The k_c values for enantiomeric substrates (**II**) at pH 7.30 are shown in Table 1, together with the results at pH 9.00 and previous results for **Ia**. As shown in Table 1, no enhanced stereoselectivity is evident for *N*-acyltyrosine (**Ib,c**) compared to **Ia.** These results indicate that the stereoselectivity depends on the active site of optically active catalysts. The unenhanced stereoselectivity in the hydrolysis of **II** by **Ib,c** is attributable to the fact that the reaction takes place at the hydroxyl group, which is far from the asymmetric center.

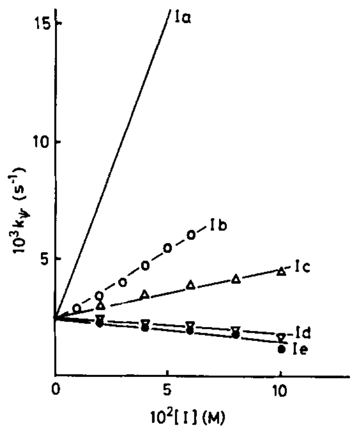


FIG. 1. Pseudo-first-order rate constants (k_ψ) for the hydrolysis of L-**IIa** as a function of the concentration of **I** in the presence of CTABr (**IIIa**) micelles at pH 7.30, 0.02 M phosphate buffer, 25°C, [**IIIa**] = 6.00×10^{-3} M, and [**IIa**] = 1.0×10^{-5} M. All of amino acids in the catalyst are of the L form.

*Catalytic Effect of **Ia** and **Ib** and c in the Presence of Micellar **IIIa***

In order to investigate the effect of the combination of imidazolyl and hydroxyl groups on the hydrolysis of **II**, kinetic studies were carried out at fixed concentrations of one catalyst (catalyst A, see Table 2) and varying concentrations of the other catalyst (catalyst B) at pH 7.30, 0.02 M phosphate buffer, and 25°C in the presence of micellar **IIIa**. The k_c values were also obtained from the slopes of straight lines of k_ψ values against catalyst concentration, and are listed in Table 2. As shown in Table 2, the comicellar catalysts have no cooperative effect on the rate of hydrolysis of **II** at neutral conditions. Some reactions were also examined

TABLE 1

CATALYTIC RATE CONSTANTS FOR THE HYDROLYSIS OF **II** IN THE PRESENCE OF CTABr MICELLES[a]

	k_c (M^{-1} s^{-1})					
	IIa			**IIb**		
Catalyst	L	D	L/D	L	D	L/D
Ia	314	145	2.17	572	231	2.52
Ib	6.37(521)	5.58(519)	1.14(1.00)	9.82(917)	9.96(746)	0.99(1.23)
Ic	1.87(123)	1.88(121)	1.00(1.02)	2.42(159)	2.73(191)	0.89(0.83)

[a] At pH 7.30, 0.02 M phosphate buffer, and 25°C in the presence of 6.00×10^{-3} M CTABr, [catalyst] = $0.50\text{–}6.0 \times 10^{-4}$ M and [substrate] = 1.0×10^{-5} M. All of the amino acids in the catalyst are of the L form. The k_c values are calculated by least-squares and generally have coefficients >0.98. The values in parentheses are at pH 9.00, 0.02 M borate buffer.

TABLE 2

CATALYTIC RATE CONSTANTS FOR THE HYDROLYSIS OF **II** IN THE PRESENCE OF COMICELLAR BIFUNCTIONAL CATALYSTS[a]

		k_c (M^{-1} s^{-1})					
		IIa			**IIb**		
Catalyst A	Catalyst B	L	D	L/D	L	D	L/D
None	**Ib**	6.37	5.58	1.14	9.82	9.96	0.99
Ia (1.00×10^{-4} M)	**Ib**	5.30	4.83	1.10	9.19	9.17	1.00
None[b]	**Ia**	314	145	2.17	572	231	2.51
Ib (1.00×10^{-4} M)[b]	**Ia**	300	132	2.27	583	221	2.63

[a] At pH 7.30, 0.02 M phosphate buffer, and 25°C in the presence of 6.00×10^{-3} M CTABr, [catalyst B (**Ib**)] = $0.50\text{–}6.0 \times 10^{-4}$ M and [**II**] = 1.0×10^{-5} M. All of the amino acids in the catalyst are of the L form. The k_c values are calculated by least-squares and generally have coefficients >0.98.

[b] [catalyst B (**Ia**)] = $0.5\text{–}6.0 \times 10^{-4}$ M.

at higher pH's, 8–10; however, no appreciable cooperative interaction was observed even at higher pH values.

*Catalytic Effect of **Ia** in the Presence of Optically Active Surfactant (**IV**) Containing a Hydroxyl Group*

Figure 2 shows pH–rate constant profiles for hydrolysis of **IIb** in the presence of surfactant micelles (**IIIa**,**IV**). The rate constants were determined at fixed surfactant concentrations of 2.00×10^{-3} M **IIIa** and 6.00×10^{-3} M **IV**, respectively,

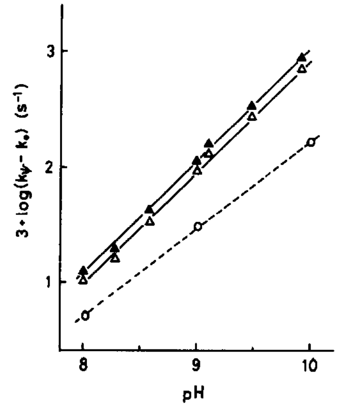


FIG. 2. pH–rate constant profiles for hydrolysis of **IIb** in the presence of surfactants at 25°C, μ = 0.05 (KCl), buffer: 0.02 M phosphate or borate (pH < 9), 0.02 M carbonate (pH > 9). (—) **IV**, (▲) D-**IIb**, (△) L-**IIb**; (----) **IIIa**, (○) D (or L)-**IIb**. [**IV**] = 6.00×10^{-3} M, [**IIIa**] = 2.00×10^{-3} M, [**IIb**] = 1.0×10^{-5} M.

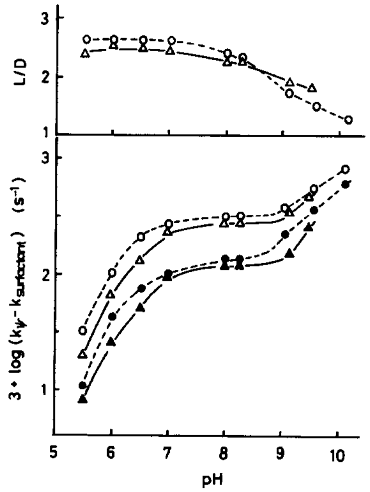


FIG. 3. pH–rate constants profiles for hydrolysis of **IIb** as catalyzed by **Ia** in the presence of surfactant micelles at 25°C, $\mu = 0.05$ (KCl), buffer: 0.04 M acetate (pH < 6), 0.02 M phosphate (6 < pH < 9), 0.02 M carbonate (pH > 9). (—) L-**Ia**–**IV**, (▲) D-**IIb**, (△) L-**IIb**; (– – –) L-**Ia**–**IIIa**, (●) D-**IIb**, (○) L-**IIb**. [L-**Ia**]/[**IV**] = $6.00 \times 10^{-4}/6.00 \times 10^{-3}$ M; [L-**Ia**]/[**IIIa**] = $2.00 \times 10^{-4}/2.00 \times 10^{-3}$ M; [**IIb**] = 1.0×10^{-5} M.

because plateau values of k_ψ were generally encountered. In pH range 8–10, **IV**, which was derived from (*l*)-ephedrine, was a more effective catalyst than **IIIa**. The reaction thus accelerates with micellar **IV**. This result suggests that the hydroxyl function of the ephedrinum head group is responsible for the augmented catalysis. It could assist ester hydrolysis either by H bonding to the ester's carbonyl oxygen, or by acting by itself as a nucleophile as described by Bunton (*10*). Optically active surfactant (**IV**) also shows slightly different catalytic efficiencies in the hydrolysis of the enantiomeric substrates, and D substrate is more reactive than L substrate. Figure 3 shows the pH–rate constant profiles for the hydrolysis of **IIb** as catalyzed by **Ia** in the presence of surfactant micelles. The rate constants were determined at fixed catalyst/surfactant concentrations of $2.00 \times 10^{-4}/2.00 \times 10^{-3}$ M [**Ia**]/[**IIIa**], and $6.00 \times 10^{-4}/6.00 \times 10^{-3}$ M [**Ia**]/[**IV**], respectively, because plateau values of k_ψ were generally encountered. The pH dependence of $(k_\psi - k_{\text{surfactant}})$ in the **Ia**–**IV** system was compared with that in the **Ia**–**IIIa** system. The $\log(k_\psi - k_{\text{surfactant}})$ profiles indicate that the micellar **IV** system is slightly less reactive than the micellar **IIIa** system, even in the high pH region, over the pH range studied. This suggests that no appreciable cooperative catalytic efficiencies are observed between the imidazolyl and the hydroxyl groups in the comicellar **Ia**–**IV** system. Furthermore, the stereoselective effects of the optically active substrate in the comicellar **Ia**–**IV** system are similar to those found in the comicellar **Ia**–**IIIa** system; L substrates react more rapidly than D substrates. These results indicate that the stereoselective catalytic effects of comicellar **IV** and **IIIa** are essentially the same and are mainly determined by reactivity of the imidazolyl group of **Ia** as described in the previous papers (*5*–*7*). It is also shown in Fig. 3 that

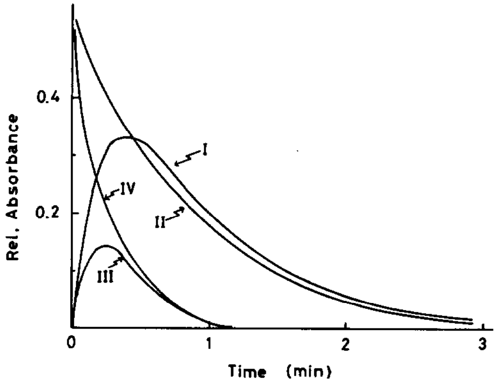


FIG. 4. Relative absorbances during reaction of **IIa** with L-**Ia** in the presence of **IIIa** (curve I at 245 nm; curve II at 255 nm) and **IIIb** (curve III at 245 nm; curve IV at 255 nm).

the decrease in stereoselectivity on increase of pH is due to the high reactivity of anionic imidazole moiety.

Deacylation Behavior

Although only the acylation process was followed in the previous section, we can clearly observe the formation and decay of an acylimidazole intermediate[2] spectrophotometrically at 245 nm. The reaction trace at 245 nm is shown in Fig. 4 (curves I and III). The reactions of **II** with **Ia** in the presence of **IIIa** or **IIIb** show different spectra–time behavior. The trace of **IIIb** (curve III) indicates a slow acylation followed by a rapid hydroxyl-mediated deacylation. This kinetic behavior has also been confirmed by several workers (*2*, *4*).

This catalytic process can be described by

$$C_{\mathrm{Im}} + \mathrm{AcONp} \xrightarrow{k_a} \begin{array}{c}\mathrm{Ac} - C_{\mathrm{Im}} \\ + \\ p\text{-nitrophenol,}\end{array} \xrightarrow{k_d} C_{\mathrm{Im}} + \mathrm{AcOH} \qquad [1]$$

where C_{Im} designates the imidazole catalyst, AcONp is the substrate, Ac-C_{Im} is the acylated intermediate, and k_a and k_d represent the rate constants for acylation and deacylation processes, respectively. The hydrolysis of the substrates was examined under single turnover conditions, [surfactant] > [catalyst] > [substrate], at pH 7.30, 0.02 M phosphate buffer, and 25°C.

The acylation rate constant (k_a) was determined by monitoring the release of *p*-nitrophenolate ion spectrophotometrically at 410 nm. The deacylation rate constant (k_d) was directly measured spectrophotometrically by following the slow decrease in absorption at 245 nm (Fig. 4, curve I) in the case of slower deacyla-

---

[2] An attempt was made to prepare the acylated intermediate under anhydrous conditions. Thus, **Ia** in *N*,*N*-dimethylformamide was treated with the *N*-hydroxysuccinimide ester of *N*-benzyloxycarbonyl-L-phenylalanine and two equivalents of triethylamine. The resulting solution was syringed into a buffered micellar solution at pH 7.3 and the uv spectrum was recorded immediately. The acylated intermediate was observed at $\lambda_{\max} = 260$ nm, using the previously hydrolyzed solution as a reference [Y. Ihara, Y. Kimura, M. Nango, and N. Kuroki (1982) *Makromol. Chem. Rapid Commun.* **3,** 521].

TABLE 3

RATE CONSTANTS OF ACYLATION AND DEACYLATION IN THE HYDROLYSIS OF **IIa** IN THE PRESENCE OF SURFACTANTS[a]

Surfactant	Catalyst **Ia** Configuration	10^2k_a (s^{-1})			10^2k_d (s^{-1})		
		L	D	L/D	L	D	L/D
IIIa	L	31.6	15.2	2.08	3.45	2.46	1.40
	D	14.5	30.1	2.08[b]	2.59	3.47	1.34[b]
IIIb	L	28.5	13.3	2.14	16.0	10.7	1.50
IV	L	21.4	11.7	1.83	4.92	4.21	1.17
	D	10.5	20.7	1.97[b]	3.61	6.28	1.74[b]

[a] At pH 7.30, 0.02 M phosphate buffer, and 25°C, [surfactant] = 5.00×10^{-3} M, [**Ia**] = 1.00×10^{-3} M, and [**IIa**] = 1.0×10^{-4} M. From three or more independent experiments, we estimate that the rate constants are reproducible to ±4%.

[b] The rate constants ratios are D/L.

tion. For the faster deacylation reactions, the rates were followed by decreases in absorption near the isosbestic point[3] for the acylation reactions (Fig. 4, curves II and IV). In both cases, the kinetics were first order and good least-squares rate constants were obtained ($r > 0.999$).

Table 3 summarizes the results of hydrolysis of **IIa** by **Ia** in the presense of surfactant micelles (**IIIa,b,** and **IV**). The deacylation of **IIa** in micellar **IIIb**, which contains an hydroxy function at the polar head, is four to five times faster than that in micellar **IIIa** although the acylation rates are essentially the same. This additional enhancement can be ascribed to intermolecular acyl transfer from imidazolyl to the hydroxy group. This observation has been made in several laboratories (*2, 4*). A more interesting result in Table 3 is the stereoselective acyl transfer in the presence of optically active surfactant (**IV**) which contains a hydroxyl group. The deacylation in micellar **IV** is about 1.4–1.8 times faster than that in micellar **IIIa**, although slower than that in micellar **IIIb**. Reactions with D-**Ia** and L-**Ia** in micellar **IIIa** produce the same deacylation difference between D and L substrates in the opposite direction within experimental error. However, a comparison of D-**Ia** and L-**Ia** in micellar **IV** shows apparently different deacylation processes in the hydrolysis of D and L enantiomers, implying that some of the stereoselective acyl transfer reaction occurs from the imidazole to the hydroxyl group in optically active comicellar systems. These results thus suggest that the stereoselective deacylation involves interactions between geometry of the acyl intermediate and that of micellar **IV**, and that the acyl intermediate formed from D-**Ia** and D-**IIa** is then optimally positioned for attack by the hydroxyl function from **IV** in the micellar phase and results in a larger deacylation rate.

Tables 4 and 5 summarize the rate constants for acylation and deacylation of **IIa**

---

[3] An isosbestic point for the acylation reactions was observed at 250–260 nm from repetitive scans and/or successive time scanning with several wavelengths in the kinetic analysis. In the case of the slower reactions, the deacylation rate constants were calculated from absorbances at 245 nm, near the isosbestic point, and agree within experimental error.

TABLE 4

RATE CONSTANTS FOR THE HYDROLYSIS OF **IIa** IN THE PRESENCE OF COMICELLAR CATALYTIC SYSTEMS[a]

Catalytic Systems	10^2k_a (s^{-1})			10^2k_d (s^{-1})			Rel. k_d(L)
	L	D	L/D	L	D	L/D	
Ia	16.8	8.03	2.09	2.62	1.95	1.34	1
Ia/Ib	15.1	7.43	2.03	4.62	3.62	1.28	1.76
Ia/Ic	14.4	7.10	2.03	3.39	2.49	1.36	1.29
Ia/Id	14.6	6.87	2.13	2.38	1.72	1.38	0.91
Ia/Ie	15.1	7.09	2.13	2.29	1.65	1.39	0.87

[a] At pH 7.30, 0.02 M phosphate buffer, and 25°C, [**IIIa**] = 1.00×10^{-2} M, [**Ia**] = 1.00×10^{-3} M, [**Ib–e**] = 1.0×10^{-3} M, and [**IIa**] = 1.0×10^{-4} M. All of the amino acids in the catalyst are of the L form. From three or more independent experiments, we estimate that the rate constants are reproducible to ±4%.

and **b** by four catalytic systems in the presence of micellar **IIIa**. From Tables 4 and 5 it is apparent that the deacylation is slower than the acylation in all cases. The stereoselectivities show that L substrates hydrolyze more rapidly than their D enantiomers, and larger stereoselectivities are observed for acylation process than for deacylation process. Although the acylation rate constants are almost independent of the four catalytic systems used, the deacylation rate constants apparently enhance in the presence of the catalysts, **Ib** and **c**. This deacylation enhancement can also be ascribed to intermolecular acyl transfer from the imidazolyl to the phenolic hydroxyl groups. We have not found appreciable stereoselective acyl transfer reaction in these systems. In our previous papers (7), we suggested that the carboxylate ion of **Ia** enhanced the reactivity of the imidazolyl group in the

TABLE 5

RATE CONSTANTS FOR THE HYDROLYSIS OF **IIb** IN THE PRESENCE OF COMICELLAR CATALYTIC SYSTEMS[a]

Catalytic Systems	10^2k_a (s^{-1})			10^2k_d (s^{-1})			Rel. k_d(L)
	L	D	L/D	L	D	L/D	
Ia	30.1	12.0	2.51	4.81	3.17	1.52	1
Ia/Ib	29.8	11.4	2.61	8.32	5.09	1.63	1.73
Ia/Id	27.7	11.0	2.52	4.37	3.19	1.37	0.91
Ia/Ie	27.1	10.7	2.53	4.01	2.96	1.35	0.83

[a] At pH 7.30, 0.02 M phosphate buffer, and 25°C, [**IIIa**] = 1.00×10^{-2} M, [**Ia**] = 1.00×10^{-3} M, [**Ib–e**] = 1.0×10^{-3} M, and [**IIb**] = 1.0×10^{-4} M. All of the amino acids in the catalyst are of the L form. From three or more independent experiments, we estimate that the rate constants are reproducible to ±4%.

micellar system. Although deacylation enhancements in the present catalytic systems are relatively small, this mode of action should be of considerable interest in connection with studies on enzyme reaction. We have also demonstrated the examples of micellar catalysis with triad of catalytic groups in the hydrolysis of *p*-nitrophenyl carboxylates (*11*).

REFERENCES

1. Bender, M. L. (1971) Mechanism of Homogeneous Catalysis from Protons to Proteins, Wiley, New York.
2. (a) Moss, R. A., Nahas, R. C., and Ramaswami, S. (1977) *J. Amer. Chem. Soc.* **99,** 627; Mittal., K. L. ed. (1977) Micellization, Solubilization, and Microemulsions, p. 603, Plenum, New York; (b) Tonellato, U. (1977) *J. Chem. Soc. Perkin Trans. 2,* 821.
3. (a) Sunamoto, J., Okamoto, H., Kondo, H., and Murakami, Y. (1975) *Tetrahedron Lett.,* 2761; (b) Kunitake, T., Okahata, Y., and Sakamoto, T. (1975) *Chem. Lett.,* 459; (1976) *J. Amer. Chem. Soc.* **98,** 7799.
4. (a) Tagaki, W., Kobayashi, S., and Fukushima, D. (1977) *J. Chem. Soc. Chem. Commun.,* 29; (b) Tagaki, W., Fukushima, D., Eiki, T., and Yano, Y. (1979) *J. Org. Chem.* **44,** 555.
5. Ihara, Y. (1978) *J. Chem. Soc. Chem. Commun.,* 984; (1980) *J. Chem. Soc. Perkin Trans. 2,* 1483.
6. Ihara, Y., and Hosako, R. (1982) *Bull. Chem. Soc. Japan* **55,** 1979.
7. Ihara, Y., Hosako, R., Nango, M., and Kuroki, N. (1980) *J. Chem. Soc. Chem. Commun.,* 393; (1983) *J. Chem. Soc. Perkin Trans. 2,* 5.
8. (a) Ihara, Y., Kunikiyo, T., Kunimasa, M., Nango, M., and Kuroki, N. (1981) *Chem. Lett.* 667; (b) Ihara, Y., Kunikiyo, N., Kunimasa, T., Kimura, Y., Nango, M., and Kuroki, N. (1983) *J. Chem. Soc. Perkin Trans. 2,* 1741.
9. (a) Inoue, T., Nomura, K., and Kimizuka, H. (1976) *Bull. Chem. Soc. Japan* **49,** 719; (b) Heitmann, P. (1968) *Eur. J. Biochem.* **3,** 346; (c) Heitmann, P., Hsung-Bublitz, R., and Zunft, H. J. (1974) *Tetrahedron* **30,** 4137.
10. (a) Bunton, C. A., Robinson, L., and Stam, M. F. (1971) *Tetrahedron Lett.,* 121; (b) (1970) *J. Amer. Chem. Soc.* **92,** 7379.
11. Ihara, Y., Nango, M., Kimura, Y., and Kuroki, N. (1983) *J. Amer. Chem. Soc.* **105,** 1252.