The Micelle-promoted Selective Hydrolysis of Anionic and Nonionic Ester Substrates by Hydroxamic Acids and Histidine Derivatives

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The hydrolyses of anionic 3-nitro-4-acyloxybenzoic acid (S_2^-–S_{16}^-) and nonionic p-nitrophenyl carboxylate (S_2—S_{16}) substrates catalyzed by hydroxamic acids (C_6—C_{12}) and histidine derivatives (AcetHis and LauHis) were performed with and without alkyltrimethylammonium (DTAC, CTAB, and OTAC) surfactants at pH 7.45. The present reaction was characterized by the selectively efficient hydrolysis of the same substrate of S_6^- or S_{10} by the comicellar C_m (m=8, 10, or 12)–CTAB (or OTAC) or LauHis–CTAB (or OTAC) catalysts. Relevant factors to such a selective hydrolysis of a specific substrate by the comicellar catalysts were discussed by taking notice of the electrostatic-charge-attraction force, steric hindrance, and hydrophobic interaction. The investigation of the binding constants in the present micellar reaction system demonstrated the importance of an appropriate hydrophobic interaction between a substrate and micelles for the selective rate enhacement of ester-hydrolysis.

The contribution of hydrophobic (apolar) forces and micellar effects to the rate enhancement of enzyme-model reactions has recently received considerable attention, especially in connection with the hydrolysis of ester substrates by synthetic catalysts involving the hydroxamate group (a model of the Ser-195 part in chymotrypsin),[1-11] imidazolyl group (a model of the His-57 part in chymotrypsin),[12-24] both of them (bifunctional catalysts),[6,25-27] or with N-alkyl-amines,[28-30] amino acids,[31] polyelectrolytes,[32] surfactants,[33-38] and surfactants having imidazole derivatives.[39-43] The magnitude of the hydrophobic interaction between a substrate and a catalyst is well kown to be directly dependent on their apolar alkyl-chain lengths and on the micellar effects of the species participating in the reaction. In this regard, the micellar effects of catalysts, surfactants, and/or substrates on the rate enhancement of ester-hydrolyses have no yet been treated systematically by changing the hydrophobic alkyl-chain length in the above species, even though the micellar effects on the ester-hydrolyses have been discussed in many of the ealier investigations.[44]

NO₂

HOOC-⟨◯⟩-OCO(CH₂)ₙ₋₁-H

S_n^- (n=2, 4, 6, 10, 12, and 16)

NO₂-⟨◯⟩-OCO(CH₂)ₙ₋₁-H

S_n (n=2, 4, 6, 10, 12, and 16)

H-(CH₂)ₘ₋₁-CONHOH

C_m (m=6, 8, 10, and 12)

RCONHCH(CO₂H)CH₂-⟨imidazole ring⟩

AcetHis (R = CH₃) and LauHis (R = C₁₁H₂₃)

CH₃(CH₂)₁₁Ṅ(CH₃)₃Cl⁻   CH₃(CH₂)₁₅Ṅ(CH₃)₃Br⁻
DTAC   CTAB

CH₃(CH₂)₁₇Ṅ(CH₃)₃Cl⁻
OTAC

The present work has been undertaken in an attempt to investigate how the systematic change in hydrophobic chain lengths in substrates, catalysts, and surfactants influences the hydrolyses of anionic 3-nitro-4-acyloxy-benzoic acids (S_n^-) and nonionic p-nitrophenyl carboxylates (S_n) by hydroxamic acids (C_m) or L-histidine derivatives (AcetHis and LauHis) with and without cationic-surfactant (DTAC, CTAB, or OTAC) micelles.

Experimental

Material.   3-Nitro-4-acyloxybenzoic acids (S_2^-—S_{16}^-) were prepared in accordance with the method of Overberger *et al.*[18] Satisfactory elementary analyses were obtained for S_n^- (n=2—16), and those for new compounds are shown below: S_4^-: mp 113—114 °C. Found: C, 52.47; H, 4.25; N, 5.64%. Calcd: C, 52.17; H, 4.35; N, 5.53%. S_6^-: mp 75.0—76.0 °C. Found: C, 54.86; H, 5.29; N, 4.94%. Calcd: C, 55.51; H, 5.38; N, 4.98%. S_{10}^-: mp 70.1—72.0 °C. Found: C, 60.29; H, 6.79; N, 4.10%. Calcd: C, 60.52; H, 6.87; N, 4.15%. S_{12}^-: mp 87.1—89.0 °C. Found: C, 65.24; H, 8.21; N, 3.66%. Calcd: C, 65.53; H, 8.37; N, 3.32%.

p-Nitrophenyl acetate (S_2) was prepared by the acylation of p-nitrophenol with acetic anhydride, while the other p-nitrophenyl carboxylates (S_2—S_{12}) were obtained by the condensation of the corresponding acid chloride with p-nitrophenol. p-Nitrophenyl hexadecanoate (S_{16}) was commercially available and was used without further purification, because the elementary analysis of S_{16} gave satisfactory results. The results of the elementary analyses of synthetic S_n (n= 2—12) were as follows: S_2: Found: C, 52.85; H, 3.66; N, 7.65%. Calcd: C, 53.00; H, 3.86; N,7.74%. S_4: Found: C, 57.74; H, 5.32; N, 6.90%. Calcd: C, 57.50; H, 5.32; N, 6.72%. S_6: Found: C, 60.75; H,6.37; N, 5.90%. Calcd: C, 60.90; H, 6.32; N, 5.93%. S_{10}: Found: C, 65.65; H, 7.77; N, 4.68%. Calcd: C, 65.50; H, 7.85; N, 4.78%. S_{12}: Found: C, 67.71; H, 8.69; N, 4.41%. Calcd: C, 67.26; H, 8.47; N, 4.36%.

$N^α$-Lauroyl-L-histidine (LauHis) was obtained by the reaction of L-histidine and lauroyl chloride:[14] mp 162 °C (lit,[31] mp 160—161 °C). Found: C, 64.03; H, 9.27; N, 12.11%. Calcd: C, 64.06; H, 9.26; N, 12.45%. The $N^α$-acetyl-L-histidine (AcetHis) used in the present work was supplied by the Sigma Chemical Company.

The hydroxamic acids (C_6—C_{12}) were prepared from H-(CH₂)ₘ₋₁-CO₂C₂H₅ (m=6—12) and hydroxylamine, and
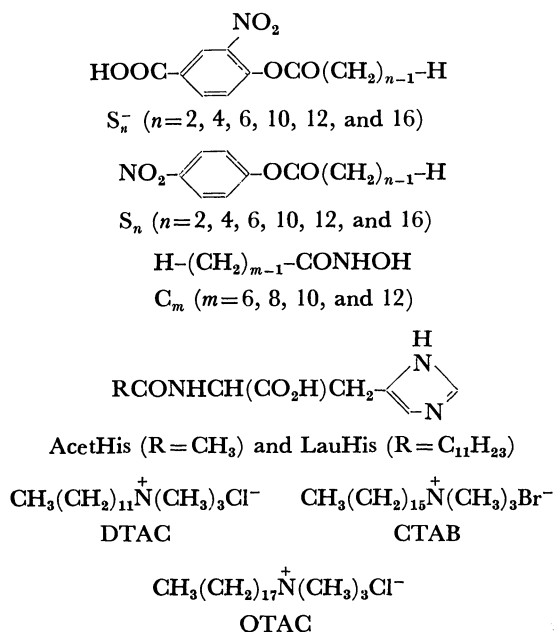
satisfactory elementary analyses were obtained: C_6: mp 45—47 °C. Found: C, 55.53; H, 9.78; N, 10.40%. Calcd: C, 54.94; H, 9.99; N, 10.68%. C_8: mp 75.6—77.2 °C. Found: C, 60.55; H, 10.52; N, 8.58%. Calcd: C, 60.34; H, 10.76; N, 8.80%. C_{10}: mp 85.9—86.7 °C. Found: C, 64.96; H, 11.10; N, 7.41%. Calcd C, 64.13; H, 11.30; N, 7.48%. C_{12}: mp 96—97 °C. Found: C, 67.13; H, 11.53; N, 6.26%. Calcd for: C, 66.98; H, 11.63; N, 6.51%.

Commercially available dodecyltrimethylammonium chloride (DTAC), hexadecyltrimethylammonium bromide (CTAB), and octadecyltrimethylammonium chloride (OTAC) were recrystallized from an anhydrous ethanol–ether mixture.

Hydrolysis. The hydrolyses of anionic S_n^- and nonionic S_n substrates ((2—5) × 10^{-5} M; 1 M=1 mol dm^{-3}) by the C_m and LauHis (and/or AcetHis) catalysts ((1—5) × 10^{-4} M) with or without a surfactant of DTAC (3.3× 10^{-2} M), CTAB (5× 10^{-3} M), or OTAC (5× 10^{-3} M) were carried out at 31.0 °C, pH 7.45, in a 0.083 M tris(hydroxymethyl)aminomethane buffer (Tris) involving 0.083 M KCl (μ=0.083) in 10%(v/v) CH_3CN-H_2O; the reactions were followed spectrophotometrically by means of the phenolate-anion formation at 410 nm (for S_n^-) and 400 nm (for S_n). In the above procedure, the concentrations of the surfactants are higher than their critical micelle concentrations (CMC).

Determination of Critical Micelle Concentration (CMC). The CMC values for the substrates (S_n^-), the catalysts (C_m or LauHis), or the surfactants were measured by means of the usual conductivity method; a remarkable change in the conductivities of the above species upon an increase in their concentrations was found in the cases of S_n^- (n=12 and 16), C_m (m=8, 10, and 12), and all of the surfactants (DTAC, CTAB, and OTAC) employed for the present work. The CMC values obtained under the present reaction conditions are summarized below: S_{12}^-=(1—3) × 10^{-4} M, S_{16}^-=2 × 10^{-5} M, C_8=1 × 10^{-4} M, C_{10}=(1.3—2.0) × 10^{-5} M, C_{12}=1 × 10^{-5} M, LauHis=5 × 10^{-5} M, DTAC=1.5 × 10^{-2} M, CTAB=1 × 10^{-3} M, and OTAC=1.3 × 10^{-4} M at 31 °C, pH 7.45, in a 0.083 M Tris–KCl buffer in 10%(v/v) CH_3CN-H_2O.

Results and Discussion

Pseudo-first-order Hydrolysis. The hydrolysis of the S_n^- or S_n (n=2—16) substrates by the C_m (m=6—12) or LauHis (and/or AcetHis) catalysts, with and without the surfactants, obeys the usual pseudo-first-order rate law, which is substantiated by the linear relationship between log $(A_\infty - A_t)$ and the reaction time (t), where A_∞ and A_t denote the absorbances of the phenolate anion formed at an infinite time and at t respectively. The second-order rate constant (k_{cat}) for the deacylation of the ester substrates was evaluated as an average value obtained from the reactions repeated three times under identical conditions:

$$k_{cat} = (k_{total} - k_{spont})/[Cat]_0,$$

where k_{total} and k_{spont} (less than 5% of the k_{total}[45]) indicate, respectively, the first-order rate constant for the S_n^- (or S_n) hydrolysis with or without the catalyst, and where $[Cat]_0$ indicates the initial catalyst concentration. The catalytic efficiency of mixed catalysts was, then, compared on the basis of the k_{cat} values obtained at a fixed surfactant concentration (DTAC= 3.3 × 10^{-2} M, CTAB=5 × 10^{-3} M, and OTAC=5 × 10^{-3} M).

Hydrolysis of Anionic S_n^- by C_m. The effects of

the hydrophobic acyl- or alkyl-chain lengths of substrates, catalysts, or surfactants on the ester-hydrolysis reaction will first be discussed by comparing the rate constants obtained in the S_n^- (n=2—16) hydrolysis by C_m (m=6—12) with or without the surfactant (DTAC, CTAB, or OTAC); since the pK_a values of the hydroxamic acids (C_m) tested are around 9.5,[46] the hydrolyzing activity of the C_m catalyst is weaker in a neutral region (pH≈7) than in a basic solution.

In the absence of the surfactant micelles, an increase in the alkyl-chain length in the C_m catalyst from m=6 to m=10 results in a monotonous rate-enhancement for the S_n^- (n=2—16) hydrolysis because of the increase in the hydrophobic interaction between S_n^- and C_m; such a rate enhancement came to be especially great when the catalyst was changed from C_{10} to C_{12}.

On the other hand, the change in the acyl-chain length of the substrates also influenced the rate of S_n^- (n=2—16) hydrolysis by C_m (m=6—12). The increase in the acyl-chain length in S_n^- (n=2—16) for the S_n^- hydrolysis by C_6, which has no CMC, retarded the hydrolysis rate monotonously, probably because of the steric hindrance of the long acyl chain (in S_n^-);[18,19] this trend was also observed in the cases of the S_n^- (n=2—6) hydrolysis by the C_m (m=8—12) catalysts. However, in the hydrolysis of S_n^- (n=10—16), which possesses a relatively long acyl-chain length, by the C_{10} and C_{12} (especially by C_{12}), the contribution of the hydrophobic forces to the hydrolysis acceleration can be recognized (Table 1).

TABLE 1. k_{cat}(M^{-1} s^{-1}) VALUES FOR THE HYDROLYSES OF S_n^- BY C_m AT pH 7.45

Catalyst	S_2^-	S_4^-	S_6^-	S_{10}^-	S_{12}^-	S_{16}^-
C_6	0.88	0.27	0.27	0.26	0.21	0.0
C_6+DTAC	1.83	0.46	0.44	0.39	0.37	0.34
C_6+CTAB	2.30	0.82	0.80	0.70	0.67	0.54
C_6+OTAC	2.15	0.67	0.93	0.66	0.70	0.52
C_8	0.99	0.29	0.30	0.41	0.32	0.00₃
C_8+DTAC	4.30	1.45	1.32	1.07	1.01	1.00
C_8+CTAB	13.6	5.59	5.91	4.76	4.03	3.28
C_8+OTAC	13.7	6.13	6.28	4.96	4.30	3.85
C_{10}	0.94	0.37	0.39	0.47	0.42	0.56
C_{10}+DTAC	6.22	2.57	2.53	2.44	2.54	2.21
C_{10}+CTAB	41.5	21.4	31.4	20.6	14.5	17.6
C_{10}+OTAC	11.7	6.80	8.77	5.91	6.94	4.48
C_{12}	4.91	1.98	0.82	2.27	4.15	7.73
C_{12}+DTAC	5.82	2.37	2.56	1.77	1.77	2.26
C_{12}+CTAB	33.6	19.3	20.0	16.8	13.8	5.10
C_{12}+OTAC	52.3	21.9	26.5	23.8	21.3	15.8

In the presence of the surfactant micelles, the comicellar catalysis was recognized in the S_n^- (n=2—16) hydrolysis, which was fairly much accelerated by condensing the anionic S_n^- substrates on the cationic micelles through electrostatic and hydrophobic forces. In this respect, the extent of the rate acceleration by the surfactant micelles, which was the most remarkable in the S_n^- (n=2—16) hydrolysis by the mixed micelles of the C_m (m=10 or 12)–CTAB (or OTAC) system,
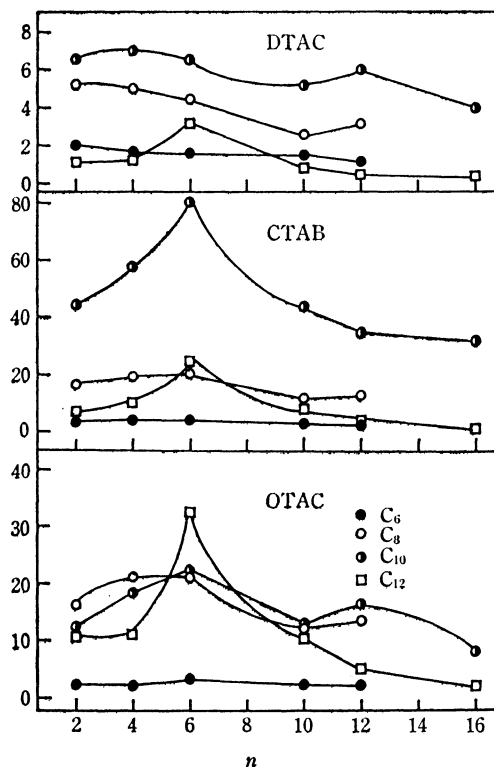
Fig. 1. Dependence of r value on the acyl chain length (n) in S_n^-.

TABLE 2. $k_{cat}(M^{-1} s^{-1})$ VALUES FOR THE HYDROLYSES OF S_n^-(or S_n) BY AcetHis AND LauHis

Catalyst	S_2^-	S_4^-	S_6^-	S_{10}^-	S_{12}^-	S_{16}^-
AcetHis	0.45	0.41	0.34	0.23	0.35	0.06
	(0.12)	(0.20)	(0.23)	(0.17)	(0.17)	(0.02)
AcetHis+ DTAC	0.18	0.05	0.03	0.03	0.02	0.07
AcetHis+ CTAB	0.27	0.05	0.03	0.01	0.02	0.07
	(0.11)	(0.08)	(0.04)	(0.01)	(0.01)	(0.01)
AcetHis+ OTAC	0.24	0.06	0.01	0.01	0.02	0.06
LauHis	0.73	0.47	0.59	1.49	1.99	3.47
	(0.58)	(1.02)	(0.91)	(1.64)	(2.36)	(10.3)
LauHis+ DTAC	3.31	2.37	2.52	2.27	2.48	2.62
	(2.10)	(2.20)	(2.03)	(2.42)	(2.57)	(2.92)
LauHis+ CTAB	6.40	6.00	7.14	6.00	5.59	5.45
	(3.65)	(4.99)	(6.08)	(9.76)	(9.54)	(6.64)
LauHis+ OTAC	5.20	4.83	5.07	4.49	3.98	3.73
	(3.27)	(5.19)	(8.03)	(9.51)	(9.31)	(9.20)

The values in parentheses are those for the S_n hydrolyses.

was not monotonously increased by lengthening the hydrophobic acyl or alkyl chain in the catalyst, substrate, or surfactant (Table 1). Here, we can notice the magnitude of the micellar influence of the surfactant on the hydrolysis acceleration, which can be measured by the ratio (r) of the k_{cat} value in the presence of the surfactant to that in its absence, and the dependence of the r value on the acyl-chain length in S_n^- is shown in Fig. 1. As Fig. 1 indicates, a remarkable enhancement of the hydrolysis rate by the comicellar catalyst was realized in the S_6^- hydrolysis by C_{10}–CTAB or C_{12}–OTAC; that is, the hydrolyzing activities of C_{10} and C_{12} in the S_6^- hydrolysis are elevated by the respective surfactants (CTAB and OTAC) to $ca.$ 80 and 32 times as great as those of C_{10} and C_{12} themselves. Such a selective enhancement of S_6^- hydrolysis by the above comicellar catalysts has also been observed in the S_n^- hydrolysis at pH 9.06.[10] The efficient activities of the mixed micelles of C_m (m=8, 10, and 12) –CTAB (or OTAC) for the selective enhancement in the hydrolysis of the same specific substrate (S_6^-) might result from the cooperative forces appearing in the following factors, in view of the fact that the alkyl-chain lengths in CTAB and OTAC are not so very different: (a) a favorable arrangement of the active nucleophilic group in C_m on the micellar surface for selectively accelerating the hydrolysis of a substrate possessing an appropriate acyl chain length and/or (b) a balance between the steric hindrance and the hydrophobic forces of the acyl-chain length (in S_n^-) in the condensation of S_n^- by the comicellar catalysts. Since the C_{10}–CTAB (or C_{12}–OTAC) catalyst showed great activity for the rate
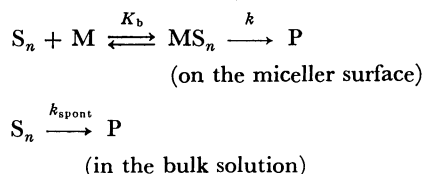
enhancement in all the hydrolyses of S_n^-, the latter factor (b) seems to play a predominant role in such a selective enhancement of S_6^- hydrolysis.

Hydrolysis of S_n^- and S_n by AcetHis and LauHis. In order to investigate the effects of different substrates and catalysts on the above-mentioned selective hydrolysis acceleration, the hydrolyses of the anionic S_n^- and nonionic S_n (n=2—16) substrates by an AcetHis (with no CMC) or micellar LauHis catalyst were performed with or without surfactants.

Although the relatively small activity of AcetHis, as compared with that of LauHis, was considerably diminished by the addition of the surfactant (DTAC, CTAB, or OTAC), the micellar or comicellar catalysis for the hydrolysis acceleration was also recognized in the S_n^- (or S_n) hydrolysis by a LauHis or LauHis-surfactant system (Table 2). The LauHis catalyst hydrolyzed both kinds of substrates (S_n^- and S_n) more easily, as the hydrophobic acyl-chain length in the substrates varied from n=4 in S_n^- (or n=6 in S_n) to n=16 through the hydrophobic forces. The extent of the change in the hydrolysis rates by lengthening the acyl chain in S_n (or S_n^-) is different between LauHis–DTAC and LauHis–CTAB (or OTAC); that is, the former comicellar catalyst increases the rate of S_n or S_n^- (n=10—16) hydrolyses monotonously, in parallel with the increase in the acyl-chain length (n), but the latter one results in a rate decrease in the S_n (n=10—16) or S_n^- (n=6—16) hydrolyses. Such a difference in catalysis between LauHis–DTAC and LauHis–CTAB (or OTAC) is also reflected in the following observations: the latter catalyst brought about a rate enhancement for the hydrolysis of anionic S_6^- and nonionic S_{10} selectively (this is probably due to the force expressed by the (b) factor mentioned before, even though such a selective rate enhancement was not realized by the former one. At any rate, it is worthy of notice that the same selective rate enhancement of S_n^- (especially S_6^-) hydrolysis by LauHis–CTAB and C_{10}–CTAB catalysts was observed in spite of the different functional groups between LauHis and C_{10}.

Binding Constants for the Selective Hydrolysis of S_n.

The present selective hydrolysis of a substrate possessing an appropriate acyl-chain length by the comicellar catalysts will be briefly discussed by taking notice of the binding constants obtained for the present hydrolyses of S_n ($n=2$, 6, 10, and 16) by the LauHis–OTAC comicelles at pH 7.45. The present micellar reactions can be given the following steps:

$$S_n + M \underset{}{\overset{K_b}{\rightleftharpoons}} MS_n \xrightarrow{k} P$$

(on the miceller surface)

$$S_n \xrightarrow{k_{spont}} P$$

(in the bulk solution)

where M=comicelles of LauHis–OTAC; MS_n=micelle-substrate complex; P=p-nitrophenol; K_b=binding constant.
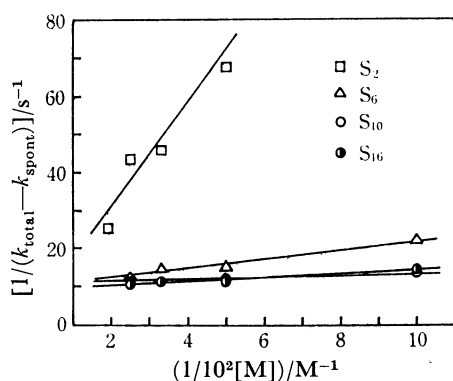

Fig. 2. Linear relationships between the reciprocal values of (k_{total}—k_{spont}) and [M] in the hydrolyses of S_n by LauHis in the presence of OTAC.

In the present study, the experiments were carried out under the following conditions: [OTAC]≫CMC, and [OTAC]>[LauHis]>[S_n], at 31 °C, pH 7.45, in a 0.083 M Tris–KCl buffer in 10%(v/v) CH_3CN–H_2O. The linear relationships between the reciprocal value of (k_{total}—k_{spont}) and [M] ([M]=[OTAC]+[LauHis]—[OTAC]$_{CMC}$; [OTAC]$_{CMC}$ is 1.3×10^{-4} M) were obtained as is indicated in Fig. 2. The K_b/N and k values were, then, evaluated from the following equation according to the previous techniques:[31,34]

$$1/(k_{total}-k_{spont}) = N/K_b(k-k_{spont})[M] + 1/(k-k_{spont})$$

where N=aggregation number.

In estimating the K_b/N and k values listed in Table 3, the monotonous increase in the former value with an increase in the acyl-chain length in S_n from $n=2$ to $n=16$ suggests that the formation of MS_n by the condensation of S_n by the comicelles is favored in the hydrolysis of S_n with a longer hydrophobic acyl-chain

Table 3. Estimated constants for the binding system in the hydrolysis of S_n by a comicellar catalyst (LauHis+OTAC)

	S_2	S_6	S_{10}	S_{16}
(K_b/N)M^{-1}	52.8	811	1829	2772
k/min^{-1}	0.149	0.100	0.106	0.099

length. However, no appreciable change in the k value with an increase in the acyl-chain length in S_n was observed.

It may be deduced, therefore, that the selective S_{10} hydrolysis by the LauHis+OTAC comicelles cannot be explained well by only the binding constant, and the present selective hydrolysis of a specific substrate with an appropriate acyl chain can be understood as a result of the approximation effect which makes the nucleophile and the substrate come close to each other.

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45) In the case of the S_n^- (or S_n) hydrolysis by AcetHis with or without the surfactant, the k_{spont} value comes to be about 20% of the k_{total} value because of the low activity of AcetHis.

46) See Refs. 3 and 7. In our experiments, the pH dependence of the k_{cat} value in the C_m ($m=6$—12)-CTAB (or OTAC) system indicated a pK_a value of *ca.* 9 for the C_m catalysts.