576 © 1981 The Chemical Society of Japan Bull. Chem. Soc. Jpn., 54, 576—580 (1981) [Vol. 54, No. 2

The Stereoselective Deacylation of Long-chain Amino Acid Esters by Comicelles of *N*-Acyl-L-histidine and Various Cationic Surfactants

Katsutoshi Ohkubo,* Kiyoshi Sugahara, Hidefumi Ohta,
Katsuro Tokuda,† and Ryuichi Ueoka†

Department of Synthetic Chemistry, Faculty of Engineering, Kumamoto University, Kumamoto 860
†*Department of Industrial Chemistry, Kumamoto Institute of Technology, Kumamoto 860*

(Received February 18, 1980)

The stereoselective deacylation of $H\text{-}(CH_2)_{\overline{n-1}}CONHCH(R)CO_2\text{-}C_6H_4NO_2\text{-}p$ ($R=CH_3$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, and $C_6H_5CH_2$; $n=2$—16) with *N*-acyl-L-histidine (acyl=octanoyl, dodecanoyl, and hexadecanoyl) and cationic surfactants ($C_mH_{2m+1}\overset{+}{N}(CH_3)_2R\ X$; $(R,X,m)=(CH_3,Br,16)$, $(C_2H_5,Br,16)$, $(C_6H_5CH_2,Cl,16)$, and $(\overset{*}{C}H(CH_3)C_6H_5,Br,$ 14—18$)$) was examined with particular reference to the structural effects of surfactants, nucleophiles, and substrates on both the deacylation rates and the stereoselectivity. The cationic surfactant, R-(+)-$C_{16}H_{33}\overset{+}{N}(CH_3)_2\overset{*}{C}H(CH_3)C_6H_5\ Br$, which possesses the hydrophobic and chiral groups near the polar head, formed the stereoselectively most effective comicelles with *N*-dodecanoyl-L-histidine. The order of stereoselectivity observed in the deacylation of the amino acid esters including the identical acyl chain length (n), phenylalanine>leucine>alanine∼valine, suggested steric effects of the substituent bound to the asymmetric carbon atom of the substrate on the stereoselectivity. The highest stereoselectivity (enantiomer rate ratio=4.4 at 25 °C under pH 7.61) was observed in the deacylation of the *N*-decanoylphenylalanine *p*-nitrophenyl ester, involving an appropriately long acyl chain.

The stereoselective micelle-catalyzed deacylation of amino acid esters has recently received considerable attention in the field of enzyme model reactions, and the deacylation of *N*-protected amino acid esters including *N*-CH_3CO, *N*-CH_3OCO, or *N*-$C_6H_5CH_2OCO$ by the amino acid-functionalized surfactants[1–5)] or by the mixed micelles of *N*-acyl-L(or D)-histidine (acyl=CH_3CO, C_6H_5CO, $C_7H_{15}CO$, $C_{11}H_{23}CO$, or $C_{17}H_{35}CO$) and hexadecyltrimethylammonium bromide(CTAB)[6–8)] has hitherto been documented at enantiomer rate ratios below or around 3.0. However, the stereoselective catalysis of mixed micelles composed of structurally different nucleophiles and surfactants in the deacylation of amino acid esters including long *N*-acyl chains has not yet been investigated systematically. Therefore, we have examined the stereoselective deacylation of amino acid esters possessing a series of *N*-acyl chain lengths by chiral micelles of *N*-acyl-L-histidine and various cationic surfactants at 25 °C (pH 7.61).

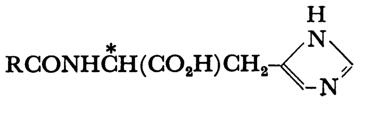
In this paper, we wish to report the structural effects of surfactants, nucleophiles, and substrates on the deacylation rate and stereoselectivity when the following compounds were used:

Substrate

$$H\text{-}(CH_2)_{\overline{n-1}}CONH\underset{\displaystyle R}{\underset{|}{C}}HCO_2C_6H_4NO_2\text{-}p$$

Phe–S_n ($R=CH_2C_6H_5$; $n=2,6,10,12,14$, and 16)
Ala–S_n ($R=CH_3$; $n=10$)
Val–S_n ($R=CH(CH_3)_2$; $n=10$)
Leu–S_n ($R=CH_2CH(CH_3)_2$; $n=10$)

Nucleophile



OctHis ($R=C_7H_{15}$)
LauHis ($R=C_{11}H_{23}$)
PalHis ($R=C_{15}H_{31}$)

Surfactant

$C_mH_{2m+1}\overset{+}{N}(CH_3)_2R\ X$

CTAB ($R=CH_3$; $X=Br$; $m=16$)
CEAB ($R=C_2H_5$; $X=Br$; $m=16$)
CBzAC ($R=CH_2C_6H_5$; $X=Cl$; $m=16$)
R-(+)-SUR_{14} ($R = C_6H_5\overset{*}{C}H(CH_3)$; $X = Br$; $m = 14$)
R-(+)-SUR_{16} ($R = C_6H_5\overset{*}{C}H(CH_3)$; $X = Br$; $m = 16$)
R-(+)-SUR_{18} ($R = C_6H_5\overset{*}{C}H(CH_3)$; $X = Br$; $m = 18$)

Experimental

N-*Acylphenylalanine* p-*Nitrophenyl Esters (Phe-S_n).* Phe–S_n ($n=2$—16) esters were prepared from *N*-benzyloxycarbonyl-D(or L)-phenylalanine by the esterification of the CO_2H group, the hydrobromination of the NH_2 group, and then the acylation of the NH_2HBr group in a way similar to the previous method.[9)] Satisfactory results of elemental analyses were obtained for Phe–S_n ($n=2$—16). L-Phe–S_2: mp 137.5—138 °C (lit,[9)] mp 140.0—140.5 °C). $[\alpha]_D^{25}$ −17.57° (*c* 2, $CHCl_3$) (lit,[9)] $[\alpha]_D^{20}$ −18.6° (*c* 2, $CHCl_3$)). Found: C, 61.96; H, 5.00; N, 8.66%. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53 %. D-Phe–S_2: mp 133.5—134.0 °C (lit,[9)] 135—137 °C). $[\alpha]_D^{25}$ +18.15° (*c* 2, $CHCl_3$) (lit,[9)] $[\alpha]_D^{20}$ +17.4° (*c* 2, $CHCl_3$)). Found: C, 62.06; H, 4.84; N, 8.66%. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53%. L-Phe–S_6: mp 113.7—114.5 °C. $[\alpha]_D^{25}$ −14.71° (*c* 2, $CHCl_3$). Found: C, 65.98; H, 6.28: N, 7.35%. Calcd for $C_{21}H_{24}O_5N_2$: C, 65.61; H, 6.29; N, 7.29%. D-Phe–S_6: mp 113.5—114.0 °C. $[\alpha]_D^{25}$ +15.02° (*c* 2, $CHCl_3$). Found: C, 65.83; H, 6.24; N, 7.25%. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29%. L-Phe–S_{10}: mp 100.0—100.5 °C $[\alpha]_D^{25}$ −13.01° (*c* 2, $CHCl_3$). Found: C, 68.29; H, 7.42; N, 6.23%. Calcd for $C_{25}H_{32}N_2O_5$: C, 68.16; H, 7.32; N, 6.36%. D-Phe–S_{10}: mp 99.5—100.0 °C, $[\alpha]_D^{25}$ +12.28° (*c* 2, $CHCl_3$). Found: C, 68.36; H, 7.50; N, 6.18%. Calcd for $C_{25}H_{32}N_2O_5$: C, 68.16; H, 7.32; N, 6.36%. L-Phe–S_{12}: mp 107.0—107.5

°C. $[\alpha]^{25}_{\mathrm{D}}$ −11.44° (*c* 2, CHCl$_3$). Found: C, 69.17; H, 7.74; N, 6.01%. Calcd for $C_{27}H_{36}N_2O_5$: C, 69.21; H, 7.74; N, 5.98%. D-Phe–S$_{12}$: mp 107.5—108.0 °C. $[\alpha]^{25}_{\mathrm{D}}$ +11.91° (*c* 2, CHCl$_3$). Found: C, 69.27; H, 7.85; N, 5.89%. Calcd for $C_{27}H_{36}N_2O_5$: C, 69.21; H, 7.74; N, 5.98%. L-Phe–S$_{14}$: mp 100.5—101.0 °C. $[\alpha]^{25}_{\mathrm{D}}$ −11.23° (*c* 2, CHCl$_3$). Found: C, 70.18; H, 8.28; N, 5.66%. Calcd for $C_{29}H_{40}N_2O_5$: C, 70.13; H, 8.12; N, 5.64%. D-Phe–S$_{14}$: mp 100.5—101.0 °C. $[\alpha]^{25}_{\mathrm{D}}$ +10.95° (*c* 2, CHCl$_3$). Found: C, 69.81; H, 8.29; N, 5.36%. Calcd for $C_{29}H_{40}N_2O_5$: C, 70.13; H, 8.12; N, 5.64%. L-Phe–S$_{16}$: mp 101.0—101.5 °C. $[\alpha]^{25}_{\mathrm{D}}$ −9.97° (*c* 2, CHCl$_3$). Found: C, 70.83; H, 8.47; N, 5.37%. Calcd for $C_{31}H_{44}N_2O_5$: C, 70.96; H, 8.45; N, 5.34%. D-Phe–S$_{16}$: mp 100.5—101.0 °C. $[\alpha]^{25}_{\mathrm{D}}$ +11.62° (*c* 2, CHCl$_3$). Found: C, 70.36; H, 8.41; N, 5.23%. Calcd for $C_{31}H_{44}N_2O_5$: C, 70.96; H, 8.45; N, 5.34%.

N-Decanoylamino Acid p-Nitrophenyl Esters (Ala–S$_{10}$, Val–S$_{10}$, and Leu–S$_{10}$). These substrates were prepared by the method used for the Phe–S$_n$ formation. L-Ala–S$_{10}$: mp 100.5—101.0 °C. Found: C, 62.57; H, 7.73; N, 7.57%. Calcd for $C_{19}H_{28}N_2O_5$: C, 62.62; H, 7.74; N, 7.69%. D-Ala–S$_{10}$: mp 101.5—102.0 °C. Found: C, 63.07; H, 7.26; N, 7.66%. Calcd for $C_{19}H_{28}N_2O_5$: C, 62.62; H, 7.74; N, 7.69%. L-Val–S$_{10}$: mp 70.5—71.0 °C. Found: C, 63.99; H, 8.46; N, 6.69%. Calcd for $C_{21}H_{32}N_2O_5$: C, 64.26; H, 8.22; N, 7.14%. D-Val–S$_{10}$: mp 71.0—71.5 °C. Found: C, 64.04; H, 8.15; N, 7.09%. Calcd for $C_{21}H_{32}N_2O_5$: C, 64.26; H, 8.22; N, 7.14%. L-Leu–S$_{10}$: mp 67.5—68.0 °C. Found: C, 65.10; H, 8.41; N, 6.91%. Calcd for $C_{22}H_{34}N_2O_5$: C, 65.00; H, 8.43; N, 6.89%. D-Leu–S$_{10}$: mp 68.0—68.5 °C. Found: C, 65.01; H, 8.54; N, 6.90%. Calcd for $C_{22}H_{34}N_2O_5$: C, 65.00; H, 8.43; N, 6.89%.

N-Acyl-L-histidine (OctHis, LauHis, and PalHis). These nucleophiles were prepared by the reaction of L-histidine and the corresponding acid chlorides.[10] Satisfactory results of elemental analyses were also obtained for these compounds. OctHis: mp 179—181 °C. Found: C, 52.97; H, 7.36; N, 13.29%. Calcd for $C_{14}H_{23}N_3O_3\cdot HCl$: C, 52.90; H, 7.61; N, 13.22%. LauHis: mp 161—162 °C (lit,[11] 160—161 °C). Found: C, 64.03; H, 9.27; N, 12.11%. Calcd for $C_{18}H_{31}N_3O_3$: C, 64.06; H, 9.27; N, 12.45%. PalHis: mp 153—155 °C. Found: C, 67.13; H, 10.18; N, 10.37%. Calcd for $C_{22}H_{39}N_3O_3$: C, 67.14; H, 9.99; N, 10.68%.

Surfactants (CTAB, CEAB, CBzAC, R-(+)-SUR$_m$ (m=14, 16, and 18)). Commercially available CTAB, CEAB, and CBzAC were used after recrystallization with absolute ethanol and diethyl ether. The chiral surfactants were prepared by the reaction of R-(+)-*N*,*N*,*α*-trimethylbenzylamine and the corresponding alkyl bromide in accordance with the previous method.[12] R-(+)-SUR$_{14}$: mp 109.0—110.0 °C. Found: C, 68.02; H, 10.55; N, 3.30%. Calcd for $C_{24}H_{44}NBr$: C, 67.57; H, 10.42; N, 3.28%. R-(+)-SUR$_{16}$: mp 110.5—112.5 °C (lit,[12] 111.5—113.0 °C). $[\alpha]^{18}_{\mathrm{D}}$ +20.44° (*c* 4, CH$_3$OH) (lit,[12] $[\alpha]^{21}_{\mathrm{D}}$ +19.82° (*c* 45, CH$_3$OH)). Found: C, 67.38; H, 10.87; N, 2.98%. Calcd for $C_{26}H_{48}NBr$: C, 68.70; H, 10.64; N, 3.22%. R-(+)-SUR$_{18}$; mp 112.0°—113.5 °C. Found: C, 68.76; H, 10.99; N, 2.84%. Calcd for $C_{28}H_{52}NBr$: C, 69.67; H, 10.88; N, 2.90%.

Deacylation. The stereoselective micelle-promoted deacylation of L or D-substrates *(5×10^{-5} mol dm^{-3}) with and* without the nucleophile (9×10^{-5} mol dm^{-3}) in the presence of the cationic surfactant ((4.5—55)$\times10^{-4}$ mol dm^{-3}) was carried out at 25 °C (pH 7.61) in a Tris buffer (0.083 mol dm^{-3}) containing KCl (0.083 mol dm^{-3}) in 10% (v/v) CH$_3$CN–H$_2$O. The above concentrations of the surfactants were higher than their critical micelle concentrations (CMC); for example, the CMC values of CTAB, CBzAC, and R-(+)-SUR$_{16}$ are 1×10^{-3},[13] 2.7×10^{-4},[12] and 2.08×10^{-4} mol dm^{-3} [12] respectively. The deacylation rate was followed by the spectrophotometric determination of *p*-nitrophenolate (400 nm). In the present experiments, the substrate deacylation by the nucleophile was not performed in the absence of the cationic surfactant because the precipitation of the substrates during the reaction was observed in the absence of the surfactant under the present conditions.

Determination of Rate Constants. The rate constants for the present reaction with and without the nucleophile (k_ψ and k_{surfact} respectively) were obtained from good pseudo-first-order deacylation rates, while the apparent catalytic rate constant (k_{cat}) was evaluated in the usual way ($k_{\mathrm{cat}}=(k_\psi-k_{\mathrm{surfact}})/[\text{nucleophile}]$).

Results and Discussion

Structural Effects of Surfactants and Nucleophiles. The structural effects of the polar head groups of the cationic surfactants (CTAB, CEAB, CBzAC, and R-(+)-SUR$_{16}$) involving the same alkyl chain length on both the deacylation rate and the stereoselectivity were first examined in the deacylation of Phe–S$_n$ (n=2, 10, and 16) with LauHis; the results of a series of experiments are shown in Table 1. In the deacylation of the short-chain substrate (Phe–S$_2$), neither the deacylation rate nor the stereoselectivity (defined by $k^{\mathrm{L}}_{\mathrm{cat}}/k^{\mathrm{D}}_{\mathrm{cat}}$) was affected remarkably by the surfactant structure. The increase in the acyl chain length of Phe–S$_n$ from n=2 to n=10, however, increased both the rate and the selectivity in all the cases by intensifying the stereoselective micellar catalysis through the substrate incorporation by the comicelles of LauHis and the surfactant. The rate increase was about 4—5 fold for the L-enantiomer, while it was about 2—3 fold for the D-enantiomer. Therefore, the nucleophilic attack of the imidazolyl group of LauHis on the susceptible carbonyl group of the substrate incorporated into the comicelles occurred more favorably in the L-Phe–S$_{10}$

Table 1. Structural effects of surfactants on deacylation rate and stereoselectivity[a)]

Surfactant	Phe–S$_n$	k_{cat}/mol^{-1} dm^3 s^{-1} L	k_{cat}/mol^{-1} dm^3 s^{-1} D	$k^{\mathrm{L}}_{\mathrm{cat}}/k^{\mathrm{D}}_{\mathrm{cat}}$
CTAB	n=2	57	35	1.6
	=10	304	108	2.8
	=16	50	31	1.6
CEAB	n=2	73	40	1.8
	=10	302	100	3.0
	=16	54	33	1.6
CBzAC	n=2	64	37	1.7
	=10	281	97	2.9
	=16	326	152	2.1
R-(+)-SUR$_{16}$	n=2	86	47	1.8
	=10	380	86	4.4
	=16	362	114	3.2

a) Tris buffer (0.083 mol dm^{-3}) containing KCl (0.083 mol dm^{-3}) at 25 °C, pH 7.61, in 10% (v/v) CH$_3$CN–H$_2$O; [LauHis]=9×10^{-5} mol dm^{-3}, [Phe–S$_n$]=5×10^{-5} mol dm^{-3}, and [Surfactant]=2.5×10^{-3} mol dm^{-3}.

TABLE 2. CONCENTRATION EFFECTS OF SURFACTANTS ON DEACYLATION RATE AND STEREOSELECTIVITY[a)]

10^4[Surfactant]	LauHis+R-(+)-SUR$_{14}$			LauHis+R-(+)-SUR$_{16}$			LauHis+R-(+)-SUR$_{18}$		
	$k_{\mathrm{cat}}/\mathrm{mol^{-1}\,dm^3\,s^{-1}}$		$k^{\mathrm{L}}_{\mathrm{cat}}/k^{\mathrm{D}}_{\mathrm{cat}}$	$k_{\mathrm{cat}}/\mathrm{mol^{-1}\,dm^3\,s^{-1}}$		$k^{\mathrm{L}}_{\mathrm{cat}}/k^{\mathrm{D}}_{\mathrm{cat}}$	$k_{\mathrm{cat}}/\mathrm{mol^{-1}\,dm^3\,s^{-1}}$		$k^{\mathrm{L}}_{\mathrm{cat}}/k^{\mathrm{D}}_{\mathrm{cat}}$
	L	D		L	D		L	D	
4.5				1227	561	2.2	1095	375	2.9
8.3	520	253	2.1						
9.0				890	303	2.9	788	261	3.0
15	509	170	3.0	596	189	3.2	548	177	3.1
18				500	161	3.1	461	144	3.2
25	351	113	3.1	380	86	4.4	355	128	2.8
35	271	86	3.2	300	80	3.8	300	108	2.8
45	223	62	3.6	267	73	3.7	228	77	3.0
55	179	52	3.4						

a) The reaction conditions are the same as in Table 1 except for the surfactant concentration. Substrate=Phe–S$_{10}$.

deacylation than in the D-Phe–S$_{10}$ deacylation. In this respect, the comicelles of LauHis and R-(+)-SUR$_{16}$ resulted in the highest deacylation rate of L-Phe–S$_{10}$ (and a slightly lower rate of D-Phe–S$_{10}$) as compared with the other comicellar systems. Since the stereoselective efficiency of R-(+)-SUR$_{16}$ *per se* was negligibly small ($k^{\mathrm{L}}_{\mathrm{surfact}}/k^{\mathrm{D}}_{\mathrm{surfact}}=1.00$—1.08), the hydrophobic and chiral α-methylbenzyl group at the polar head of R-(+)-SUR$_{16}$ might facilitate the interaction of LauHis with L-Phe–S$_{10}$. In the deacylation of Phe–S$_{16}$, the structural effects of CTAB and CEAB on the deacylation rate and the stereoselectivity were appreciably different from those of CBzAC and R-(+)-SUR$_{16}$; that is, CTAB and CEAB decreased both the rate and the stereoselectivity of Phe–S$_{16}$ remarkably as compared with those of Phe–S$_{10}$, while CBzAC and R-(+)-SUR$_{16}$ did not reduce the rate of L-Phe–S$_{16}$, but increased the rate of D-Phe–S$_{16}$ considerably. The rates of L and D-Phe–S$_{16}$ in the LauHis+CBzAC (or R-(+)-SUR$_{16}$) system were about 6—7 fold and about 3.5—5 fold with respect to those in the LauHis+CTAB (and +CEAB) systems respectively. Therefore, the hydrophobicity of the benzyl (or α-methylbenzyl) group of CBzAC (or R-(+)-SUR$_{16}$) contributes to the rate enhancement of the long-chain substrates (Phe–S$_{10}$ and Phe–S$_{16}$). It is noteworthy, with respect to the stereoselectivity, that the enantiomer-rate ratio of 4.4 for Phe–S$_{10}$ (or that of 3.2 for Phe-S$_{16}$) in the case of the LauHis+R-(+)-SUR$_{16}$ system is 1.5 times as high as the rate ratio of 2.9 for Phe–S$_{10}$ (or that of 2.1 for Phe–S$_{16}$) in the case of the LauHis+CBzAC system. This might be due not to the hydrophobicity difference in the polar-head groups of the surfactants, but to the chirality of the hydrophobic α-methylbenzyl group of R-(+)-SUR$_{16}$. It is deduced, therefore, that the comicelles consisting of chiral nucleophiles and chiral surfactants tend to enhance the stereoselectivity of the long-chain substrates, especially such substrates as Phe–S$_{10}$ which possess an appropriately long acyl chain.

The concentration effects of surfactants on the stereoselective comicellar catalysis were, then, examined in the deacylation of Phe–S$_{10}$ with LauHis and R-(+)-SUR$_m$ (m=14, 16, and 18); the experimental results are shown in Table 2. In all the comicellar systems of LauHis+R-(+)-SUR$_m$ (m=14—18), the increase in the surfactant concentration in the range of 4.5×10^{-4}—5.5×10^{-3} mol dm^{-3} with respect to 9×10^{-5} mol dm^{-3} of LauHis decreased the deacylation rate of Phe–S$_{10}$ monotonously. The stereoselectivity in the deacylation of Phe–S$_{10}$ (5×10^{-5} mol dm^{-3}) with LauHis (9×10^{-5} mol dm^{-3}) and R-(+)-SUR$_m$ (m=14—18) was also affected by the surfactant concentration; the highest enantiomer-rate ratios ($k^{\mathrm{L}}_{\mathrm{cat}}/k^{\mathrm{D}}_{\mathrm{cat}}$=3.6, 4.4, and 3.2) were obtained under the conditions of [R-(+)-SUR$_{14}$]=4.5×10^{-3} mol dm^{-3}, [R-(+)-SUR$_{16}$]=2.5×10^{-3} mol dm^{-3}, and [R-(+)-SUR$_{18}$]=1.8×10^{-3} mol dm^{-3}

TABLE 3. STRUCTURAL EFFECTS OF NUCLEOPHILES ON DEACYLATION RATE AND STEREOSELECTIVITY[a)]

System	Phe–S$_2$			Phe–S$_{10}$			Phe–S$_{16}$		
	$k_{\mathrm{cat}}/\mathrm{mol^{-1}\,dm^3\,s^{-1}}$		$k^{\mathrm{L}}_{\mathrm{cat}}/k^{\mathrm{D}}_{\mathrm{cat}}$	$k_{\mathrm{cat}}/\mathrm{mol^{-1}\,dm^3\,s^{-1}}$		$k^{\mathrm{L}}_{\mathrm{cat}}/k^{\mathrm{D}}_{\mathrm{cat}}$	$k_{\mathrm{cat}}/\mathrm{mol^{-1}\,dm^3\,s^{-1}}$		$k^{\mathrm{L}}_{\mathrm{cat}}/k^{\mathrm{D}}_{\mathrm{cat}}$
	L	D		L	D		L	D	
OctHis+R-(+)-SUR$_{16}$	17	14	1.2	41	38	1.1	59	59	1.0
LauHis+R-(+)-SUR$_{16}$	86	47	1.8	380	86	4.4	362	114	3.2
LauHis+R-(+)-SUR$_{18}$	93	59	1.6	461	144	3.2	429	129	3.3
PalHis+R-(+)-SUR$_{14}$	66	44	1.5	253	72	3.5	304	98	3.1
PalHis+R-(+)-SUR$_{16}$	111	69	1.6	469	116	4.0	511	169	3.0
PalHis+R-(+)-SUR$_{18}$	111	60	1.9	636	174	3.7	483	181	2.7

a) Tris buffer (0.083 mol dm^{-3}) containing KCl (0.083 mol dm^{-3}) at 25 °C, pH 7.61, in 10% (v/v) CH$_3$CN–H$_2$O; [OctHis]=[LauHis]=[PalHis]=9×10^{-5} mol dm^{-3}, [Substrate]=5×10^{-5} mol dm^{-3}, [R-(+)-SUR$_{14}$]=4.5×10^{-3} mol dm^{-3}, [R-(+)-SUR$_{16}$]=2.5×10^{-3} mol dm^{-3}, and [R-(+)-SUR$_{18}$]=1.8×10^{-3} mol dm^{-3}.

respectively. Therefore, the stereoselective efficiency of the comicelles of the Phe–S_{10} deacylation followed the order of LauHis+R-(+)-SUR_{16}>LauHis+R-(+)-SUR_{14}>LauHis+R-(+)-SUR_{18}. This fact might imply that the hydrophobic chain length of the nucleophile requires an appropriately long (not too short and not too long) hydrophobic chain length of the surfactant for the formation of stereoselectively effective comicelles. The effects of the hydrophobic chain length of the surfactant on the stereoselective comicellar catalysis were also recognized in the deacylation of Phe–S_n (n=2, 10, and 16) with PalHis and R-(+)-SUR_m (m= 14, 16, and 18) (see Table 3); the comicellar system of PalHis+R-(+)-SUR_{16} was rather more efficient for the stereoselective deacylation of the long-chain substrate (Phe–S_{10}) than that of PalHis+R-(+)-SUR_m (m=14 and 18).

The experimental results shown in Table 3 also indicate the effects of the hydrophobic chain length of nucleophiles on the stereoselective comicellar catalysis. In the deacylation of Phe–S_n (n=2, 10, and 16) with the nucleophile (OctHis, LauHis, or PalHis) and R-(+)-SUR_{16}, the lengthening of the alkyl chain of the nucleophile increased the deacylation rate of Phe–S_n (n=2—16) monotonously, and the enantiomer-rate ratios in the deacylation of the identical substrate followed the order of LauHis+R-(+)-SUR_{16}>PalHis+R-(+)-SUR_{16}≫OctHis+R-(+)-SUR_{16}. At any rate, among the present comicellar systems, the LauHis+R-(+)-SUR_{16} system was found to contain the most efficient comicelles for the stereoselective deacylation of Phe–S_n (n=2—16). Therefore, stereoselectively efficient comicellar systems do not require too long hydrophobic chains for the nucleophile or the surfactant. Table 3 also indicates that the comicelles of LauHis+R-(+)-SUR_m (m=16 and 18) or PalHis+R-(+)-SUR_m (m=14,16, and 18) resulted in a high stereoselectivity (k^L_{cat}/k^D_{cat}=3.2—4.4) in the deacylation of Phe–S_{10} rather than in the deacylation of Phe–S_{16} or Phe–S_2.

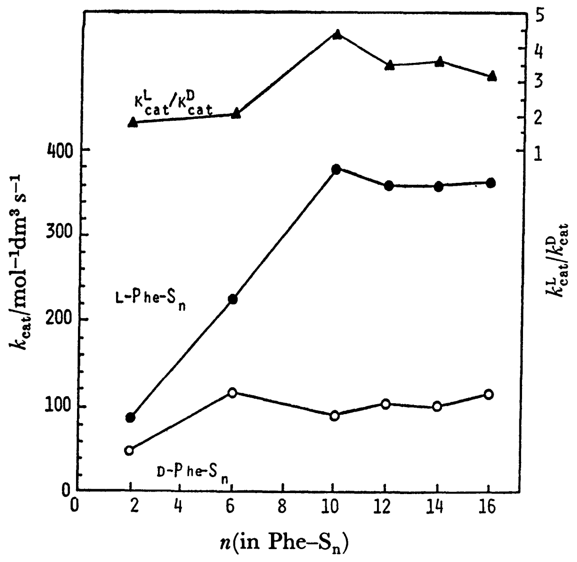


Fig. 1. Dependence of deacylation rate and stereoselectivity on the acyl chain length of Phe–S_n (The deacylation was carried out with LauHis and R-(+)-SUR_{16} under the same conditions as shown in Table 1).

Structural Effects of Substrates. Although the effects of the N-acyl chain length of the amino acid esters on the stereoselectivity have already been briefly discussed, a more detailed explanation of the structural effects of the substrates will be developed in this section. With regard to the dependence of the rates and stereoselectivity on the N-acyl chain length of a substrate in the deacylation of Phe–S_n (n=2—16) by the LauHis +R-(+)-SUR_{16} system (Fig. 1), the rate increases upon a change in the chain length (n) from n=2 to n=6 were 2.7 and 2.3 fold for the L and D-enantiomer respectively, while the stereoselectivity enhancement was very slight. However, the rate increase upon a change in the chain length from n=2 to n=10—16 was remarkable for the L-enantiomer (4.2—4.4 fold), but slight for the D-enantiomer (1.8—2.4 fold). Therefore, the stereoselectivity enhancement became larger with the increase in the chain length from n=6 to n=10—16, and the highest stereoselectivity was found in the Phe–S_{10} deacylation; that is, Phe–S_{10} incorporated into the comicelles (LauHis+R-(+)-SUR_{16}) might be exposed to the asymmetric environment of the comicelles more directly than with the other Phe–S_n substrates.

TABLE 4. STRUCTURAL EFFECTS OF SUBSTRATES ON DEACYLATION RATE AND STEREOSELECTIVITY[a)]

Substrate	k_{cat}/mol^{-1} dm^3 s^{-1} L	D	k^L_{cat}/k^D_{cat}
Ala–S_{10}	89	73	1.1
Val–S_{10}	19	16	1.2
Leu–S_{10}	221	70	3.2
Phe–S_{10}	380	86	4.4

a) The deacylation reactions were carried out by the use of the comicelles of LauHis and R-(+)-SUR_{16} under the same conditions as are shown in Table 1.

The structural effects of amino-acid esters on the stereoselectivity were also observed in the deacylation of Ala–S_{10}, Val–S_{10}, Leu–S_{10}, and Phe–S_{10} by the comicelles of LauHis+R-(+)-SUR_{16} (Table 4). The deacylation rates followed the order of L-Phe–S_{10}>L-Leu–S_{10}≫L-Ala–S_{10}≫L-Val–S_{10} for the L-enantiomers or of D-Phe–S_{10}>D-Leu–S_{10}~D-Ala–S_{10}≫D-Val–S_{10} for the D-enantiomers. The very low rates of L- and D-Val–S_{10} might be due to the steric hindrance of the isopropyl group, which is adjacent to the susceptible carbonyl group in the substrate, toward the nucleophilic attack of LauHis. In this regard, the very low rate of the N-benzyloxycarbonylvaline p-nitrophenyl ester was observed in the deacylation of N-(benzyloxycarbonyl)-amino acid esters by the L (or D)-LauHis+CTAB system.[8)] Such a steric hindrance might be reduced in the other substrates, $RCH_2CH(NHCO(CH_2)_8CH_3)$-$CO_2C_6H_4NO_2$-$p$ (R=H, $(CH_3)_2CH$, and C_6H_5); the deacylation rate increases with the increase in the bulkiness (and/or hydrophobicity) of the R group in the substrate. Table 4 also indicates that the order of the stereoselectivity. Phe–S_{10}>Leu–S_{10}>Val–S_{10}~

Ala–S_{10}, is parallel with the bulkiness (and/or hydrophobicity) of the substituent in the ester. Presumably, the bulkiness (and/or hydrophobicity) of the substrate plays an important role in the increase in the energy difference between the interaction of L-S_{10}–LauHis and D-S_{10}–LauHis in the transition state of the present deacylation.

References

1) J. M. Brown and C. A. Bunton, *J. Chem. Soc., Chem. Commun.*, **1974**, 969.

2) J. M. Brown, C. A. Bunton, and S. Diaz, *J. Chem. Soc., Chem. Commun.*, **1974**, 971.

3) R. A. Moss, T. J. Lukas, and R. C. Nahas, *Tetrahedron Lett.*, **1977**, 3851.

4) R. A. Moss, R. C. Nahas, and T. J. Lucas, *Tetrahedron Lett.*, **1978**, 507.

5) R. A. Moss, Y.-S. Lee, and T. J. Lukas, *J. Am. Chem. Soc.*, **101**, 2499 (1979).

6) Y. Ihara, *J. Chem. Soc., Chem. Commun.*, **1978**, 984.

7) K. Yamada, H. Shosenji, and H. Ihara, *Chem. Lett.*, **1979**, 491.

8) K. Yamada, H. Shosenji, H. Ihara, and Y. Otsubo, *Tetrahedron Lett.*, **1979**, 2529.

9) D. W. Ingles and J. R. Knowles, *Biochem. J.*, **104**, 369 (1967).

10) C. Gitler and A. Ochoa-Solano, *J. Am. Chem. Soc.*, **90**, 5004 (1968).

11) T. Inoue, K. Nakamura, and H. Kimizuka, *Bull. Chem. Soc. Jpn.*, **49**, 719 (1976).

12) R. A. Moss and W. L. Sunshine, *J. Org. Chem.*, **39**, 1083 (1974).

13) R. Ueoka, H. Matsuura, S. Nakahata, and K. Ohkubo, *Bull. Chem. Soc. Jpn.*, **53**, 347 (1980).