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Enantioselective Hydrolysis of an α-Amino Acid Ester in Sugar-Derived Surfactant Micelles

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Abstract: *p*-Nitrophenyl ester of D-phenylalanine hydrogen bromide was hydrolyzed much faster than that of the corresponding L-isomer in the micelles formed with sugar-derived surfactants such as *N*-dodecylmaltobionamide. The enantioselectivity was largely affected by the alkyl chain length as well as the structure of the sugar part of the surfactant.

Keywords: enantioselection; carbohydrates; surfactants; micellar systems

Over the past few decades, the enantioselective micellar catalysis has attracted much attention because of its usefulness as a model for enzyme catalysis. In most of such studies, the enantioselectivity has been attained by a combination of chiral nucleophiles and achiral surfactant micelles [1-7]. On the other hand, only a few studies have been reported on the enantioselective reaction in a simpler system which contains only chiral surfactant micelles [8-12]. In particular, there is no report on enantioselective reaction systems consisting of only the micelles formed with sugar-derived surfactants possessing no additional chiral center other than those from the parent sugar. Such enantioselective micellar systems consisting of sugar surfactants alone would be useful not only as a new enzyme model but also for elucidating the functions of sugar chains of the cell surface. In this letter, we wish to report the first enantioselective hydrolysis of an α-amino acid ester in the micelles formed with the sugar-derived surfactants.

Substrates *p*-nitrophenyl *N*-(benzyloxycarbonyl)-D- or L-phenylalaninate **1** and *p*-nitrophenyl ester of D- or L-phenylalanine hydrogen bromide **2** were prepared according to previously reported methods [13]. Sugar-amide surfactants **3**, **4**, and **5** were prepared by the reactions of sugar lactones with alkylamine or alkyldiamine [14,15]. Their critical micelle concentrations (cmcs), which were determined by the dye method using pinacyanol chloride as a dye probe [16], at 20 °C, are as follows: **3a**: 1.8 mM, **3b**: 0.20 mM, **3c**: 4.2×10^{-2} mM, **3d**:

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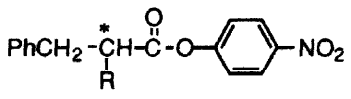
0.19 mM, **4**: 1.9 mM, **5**: 0.15 mM. Dodecyl β-D-maltoside **6** (cmc = 0.16 mM)[17] and Triton X-100 (cmc = 0.33 mM) [18] as a reference surfactant were purchased from commercial sources. The hydrolysis was carried out at 25 °C, pH 7.2 in 0.05 M potassium dihydrogenphosphate buffer solution which contains 5.0 x 10^{-5} M chiral substrate, 0.1 M LiCl, and 3 vol.% acetonitrile. Hydrolysis of the substrates was spectrophotometrically monitored by measuring absorbance of the released *p*-nitrophenolate ion at 400 nm to determine the reaction rates. Each experiment was repeated at least three times to ensure the reproducibility (± 10%).

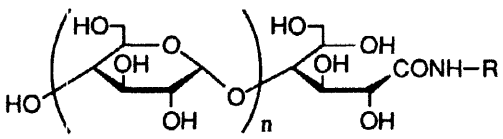
Substrate



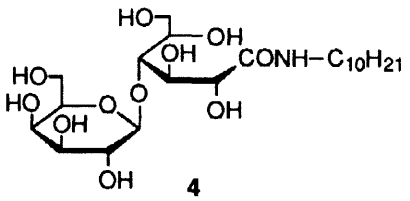
D- or L-**1** : R = NH–C(=O)–OCH_2Ph

D- or L-**2** : R = NH_3^+ Br^-

Surfactant



3a : R = $C_{10}H_{21}$, n = 1 **3b** : R = $C_{12}H_{25}$, n = 1
3c : R = $C_{14}H_{29}$, n = 1 **3d** : R = $C_{12}H_{25}$, n = 2



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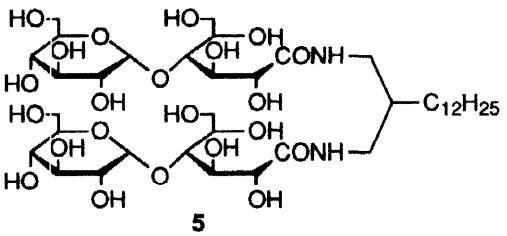

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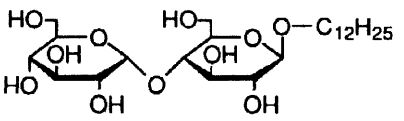

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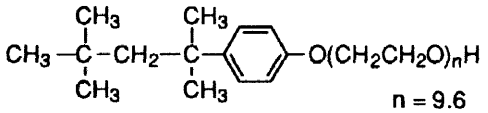

n = 9.6

Triton X-100

Table 1 shows the observed pseudo-first-order rate constants for the hydrolysis of the substrates **1** and **2** in the absence (entries 1 and 8) and the presence of sugar-derived surfactant micelles (entries 2-6 and 9-18), together with the results using Triton X-100 micelles (entries 7 and 19). The rates of hydrolysis of D- and L-**1** were somewhat increased by the sugar-amide surfactant micelles (entries 2-5), while they were markedly decreased by dodecyl β-D-maltoside **6** (entry 6) and Triton X-100 (entry 7) micelles. In these cases, no enantioselectivity for the hydrolysis was observed. These results are in accordance with our expectation based on the locus of solubilization of **1** in these surfactant micelles. The less polar substrate **1** would be solubilized in the hydrophobic cores of the dodecyl β-D-maltoside **6** and Triton X-100 micelles, so that the nucleophilic attack by water molecules or hydroxide ions from the aqueous bulk phase is largely retarded. On the other hand, in the cases of sugar-amide surfactants **3** and **4**, **1** is most likely solubilized near the hydrophilic layer of the micelles through the hydrogen bonding between the amide hydrogen of the surfactant and the carbonyl group of the

Table 1
Kinetic data[a] for hydrolysis of 1 and 2

		Surfactant		k_{obs}[b]($10^{-3}s^{-1}$)		Enantioselectivity
Entry	Substrate	Concentration (mM)		D-Substrate	L-Substrate	D/L
1	**1**	None		1.4	1.4	1.0
2	**1**	**3a**	5.0	1.5	1.5	1.0
3	**1**	**3b**	5.0	2.7	2.7	1.0
4	**1**	**3d**	5.0	5.0	4.9	1.0
5	**1**	**4**	5.0	2.4	2.4	1.0
6	**1**	**6**	5.0	0.061	0.061	1.0
7	**1**	Triton X-100	5.0	0.038	0.038	1.0
8	**2**	None		7.5	7.5	1.0
9	**2**	**3a**	5.0	28	15	1.9
10	**2**	**3b**	2.5	32	12	2.7
11	**2**	**3b**	5.0	39	12	3.3
12	**2**	**3b**	10	44	12	3.7
13	**2**	**3b**	20	51	14	3.6
14	**2**	**3c**	5.0	33	11	3.0
15	**2**	**3d**	5.0	39	12	3.3
16	**2**	**4**	5.0	9.8	9.3	1.1
17	**2**	**5**	5.0	46	19	2.4
18	**2**	**6**	5.0	10	7.9	1.3
19	**2**	Triton X-100	5.0	11	11	1.0

[a][substrate] = 5.0×10^{-5} M.
[b]Observed pseudo-first-order rate constant.

solubilized substrate. At this site, the nucleophilic attack by both the sugar hydroxyl groups of the surfactant and the water molecules (or hydroxide ions) may have occurred, giving rise to the acceleration of the hydrolysis of **1**. However, no enantioselectivity was observed in those systems, suggesting that **1** does not approach the chiral sugar head groups closely enough, and thus it is necessary to locate the substrate closer to the chiral sugar head groups for the enantioselective hydrolysis with the sugar surfactant micelles to occur. On the basis of this hypothesis, D- and L-**2** bearing an intensively hydrophilic ammonium group, which should be located between the hydrophilic head groups of the micelles, were chosen as the substrate. Surprisingly, in all the cases using the sugar surfactant micelles, D-**2** was hydrolyzed faster than L-**2** (entries 9-18). Among the surfactant micelles examined in this work, the highest enantioselectivity was attained with *N*-dodecylmaltobionamide **3b** or *N*-dodecylmaltotrionamide **3d** micelles. Concerning the monomaltobionamide-type surfactants **3**, the increase of the alkyl chain length from C10 to C12 remarkably increased the enantioselectivity, whereas the change from C12 to C14 slightly lowered it (entries 9, 11, and 14). Entries 10-13 showed that the enantioselectivity increased with the increase of concentration of surfactant **3b** in the range of 2.5 to10 mM, but decreased slightly with the increase from 10 to 20 mM. Below

the cmc (0.2 mM), **3b** showed no enantioselectivity (for example, $k_{obs(D)} = k_{obs(L)} = 8.7 \times 10^{-3}\ s^{-1}$ at 0.10 mM), indicating that the existence of the micelles is essential for the enantioselective hydrolysis of **2**. The comparison of entries 11 and 17 showed that the increase of the number of the hydrophilic branches having the same sugar units enhanced the hydrolysis rates of both D- and L-substrates but decreased the enantioselectivity. The increase of the sugar chain length had no effect on either the hydrolysis rate or the enantioselectivity (entries 11 and 15). Interestingly, large differences in both the hydrolysis rate and the enantioselectivity between **3a** and **4**, which have different terminal sugar residues, were observed. Furthermore, only a slight enantioselectivity was observed in the case of dodecyl β-D-maltoside **6** micelles even for **2**, in contrast to dodecyl maltobinamide **3b** micelles. These results indicate that the enantioselectivity for hydrolysis of **2** depends largely on the structure of the sugar moiety of the surfactant as well as the presence of amide linkage. The enantioselectivity in these micellar systems can be explained by considering the selective nucleophilic attack on the D-substrate and/or selective stabilization of the resulting intermediate by sugar hydroxyl groups in the micelle, similarly to the previous cases in which the enantioselective hydrolysis of the *p*-nitrophenyl esters was carried out using the micellar systems formed with the chiral surfactants bearing hydroxyl groups, such as D-ephedrinium derivative [8] and sodium deoxycholate [10]. Work on the detailed mechanism of the enantioselective hydrolysis in these systems and the development of a sugar surfactant micellar system with higher enantioselectivity is now in progress.

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