Syntheses and Catalytic Actions of Self-Micelle-Forming Hydrolase Models

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Hydrolase model catalysts, *N*-alkyl-N^{α}-[2-(D-polyhydroxypentyl)-3-acetyl-4-thiazolidinylcarbonyl]-L-histidinamide (acyclic-type catalyst) and *N*-(*N*-alkanoyl-L-histidyl)-β-D-glucosamine (cyclic-type catalyst), which easily form micelles in water by themselves, have been designed and the stereostructural effects of sugar moieties examined on stereoselective hydrolyses of *p*-nitrophenyl *N*-benzyloxycarbonyl-L-(or D-)phenylalaninates. An acyclic-type catalyst is D-selective, while a cyclic-type catalyst is L-selective. The stereorecognition of acyclic-type catalysts was found to be performed by a sugar moiety, rather than the histidyl type. Comparisons of the activities of three acyclic-type catalysts having different sugar moieties show that a mannose-derived catalyst is the most stereoselective. Judging from kinetic data, it is concluded that the configuration of OH on C-3 of the sugar moiety takes a significant part in the stereorecognition of a catalyst.

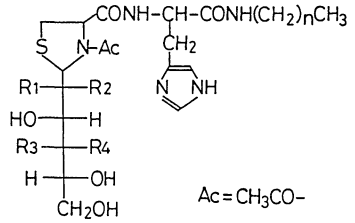
Within these years, a great number of enzyme models have been designed and examined in biomimetic reactions, some of which have been reported to be excellent models for reaction selectivities.[1] In hydrolase models, for example, a catalytic action closely similar to hydrolase was observed in stereoselective hydrolyses of *p*-nitrophenyl *N*-acyl-L-(or D-)phenylalaninates using a tripeptide-type catalyst.[2,3] The tripeptide slightly catalyzes the hydrolysis by itself, but develops a latent hydrolysis ability, and dramatically exhibits high stereorecognition when it is used together with surfactants which provide a sutable reaction environment.

Hydrolase models which do not require any surfactant, on the other hand, have also been reported. Cyclodextrin[4] and polyethylenimine[5] are representative of the models. Other type of enzyme models belonging to this category include catalysts having self-micelle or vesicle-forming abilities.[6-10] Such models have recently been modified so as to recognize the chiralities of substrates;[11-16] then, peptide lipid models were designed and proposed.[17-20] Models comprising an amino acid backbone with a polar head moiety and a hydrophobic hydrocarbon group are capable of forming vesicles in water and exhibit excellent catalysis in the stereoselective hydrolyses of chiral substrates. Such synthetic peptide lipids are characterized by their similarity to enzymes, with respect to both their structures and functions.

We also reported that glycopeptide-type hydrolase models, *N*-stearoyl-N^{α}-[*o*-[(D-glucosylimino)methyl]-benzylidene]-L-histidinamide and *N*-(*N*-stearoyl-L-histidyl)-β-D-glucosamine, are active catalysts in the hydrolyses of *p*-nitrophenyl *N*-*Z*-L-(or D-)phenylalanine[22] (in this paper, *Z* indicates a benzyloxycarbonyl group). These models can form micelles by themselves. The present paper describes the stereostructural effect of sugar moieties in glycopeptide-type catalysts: catalysts which contain various thiazolidine derivatives such as sugar moiety, *N*-alkyl-N^{α}-[2-(D-polyhydroxypentyl)-3-acetyl-4-thiazolidinylcarbonyl]-L-histidinamide (**1**) (acyclic-type catalyst), are discussed regarding the stereoselective hydrolysis of *p*-nitrophenyl *Z*-L-(or D-)phenylalaninate (**4**). Two kinds of cyclic glucosamine derivatives, *N*-(*N*-alkanoyl-L-histidyl)-β-D-glucosamine (**3**) (cyclic-type catalyst) are also discussed regarding their use as catalysts.

Experimental

Syntheses of Catalysts. Acyclic-type catalysts, *N*-dodecyl- and *N*-octadecyl-N^{α}-[2-(D-*gluco*-, *manno*-, and *galacto*-pentahydroxypentyl)-3-acetyl-4-thiazolidinylcarbonyl]-L-histidinamide (**1**), were prepared as follows:



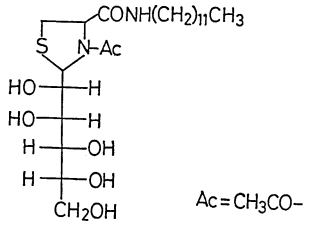
(**1**)

(**1-a**) Glucose-derived catalysts: R_1=R_3=H, R_2=R_4=OH
n=11 acyclic Glu·His·Lau Amine
n=17 acyclic Glu·His·Ste Amine
(**1-b**) Mannose-derived catalysts: R_1=R_4=OH, R_2=R_3=H
n=3 acyclic Man·His·But Amine
n=11 acyclic Man·His·Lau Amine
n=17 acyclic Man·His·Ste Amine
(**1-c**) Galactose-derived catalysts: R_1=R_4=H, R_2=R_3=OH
n=11 acyclic Gal·His·Lau Amine
n=17 acyclic Gal·His·Ste Amine

The *N*-alkyl-N^{α}-[2-(D-*gluco*-, *manno*-, and *galacto*-pentahydroxypentyl-3-acetyl-4-thiazolidinecarbonyl]-L-histidinamide: 2-(D-*gluco*-, *manno*-, and *galacto*-pentahydroxypentyl)-3-acetyl-4-thiazolidinecarboxylic acid (1.23×10^{-3} mol) were prepared in accordance with the method by Rezso et al.[21] and *N*-alkyl-L-histidinamide[22] (1.23×10^{-3} mol) were dissolved in 100 ml of chloroform; dicyclohexylcarbodiimide (DCC) (1.85×10^{-3} mol) was added with stirring at ice-bath temperature. After one hour, the reaction mixture was

warmed up to room temperature and stirred for 24 hours. After filtering off *N,N'*-dicyclohexylurea the solvent was removed under vacuum. The resulting residue was washed successively with 1 mol dm^{-3} HCl, 4% $NaHCO_3$, and water. It was then dissolved in and allowed to react with 50 ml of a 1 mol dm^{-3} solution of $NaOCH_3$ in methanol at ice-bath temperature for 3 hours. The reaction mixture was neutralized with 1 mol dm^{-3} HCl. The solution was evaporated, and the residue was recrystallized from acetone- petroleum ether (1 : 7 by volume).

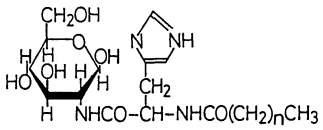
2-(D-*manno*-Pentahydroxypentyl)-3-acetyl-4-dodecylcarbamoylthiazolidine (**2**) (acyclic Man · Lau Amine) was prepared by the reaction of 2-(D-*manno*-Pentahydroxypentyl)-3-acetyl-4-thiazolidinecarboxylic acid with dodecylamine, according to a similar method:



(**2**)

acyclic Man · Lau Amine

Cyclic-type catalysts, *N*-[*N*-(lauroyl and stearoyl)-L-histidyl]-*β*-D-glucosamine (**3**), were prepared as described in a preceding paper.[22]

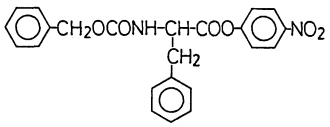


(**3**)

n=10 cyclic Glu · His · Lau Acid
n=16 cyclic Glu · His · Ste Acid

Elemental analyses and physical data of the catalysts are summarized in Table 1.

Substrates. Chiral substrates, *p*-nitrophenyl *N*-*Z*-L-(and D-)phenylalaninates (**4**), were obtained by the reaction of *Z*-L-(or D-)phenylalaninate with *p*-nitrophenol in the presence of DCC.[23]



(**4**)

Measurements of Critical Micelle Concentrations (cmc). The critical micelle concentration of a catalyst was determined by monitoring the turbidity of solutions of the catalyst in Tris buffer (pH 8.0, 0.083 mol dm^{-3}) over a wide range of concentrations.[22]

Procedure and Kinetic Measurements. The hydrolysis of a chiral substrate was carried out using a glycopeptide-type catalyst (5.67×10^{-3} mol) in Tris buffer (pH 8.0, 0.083 mol dm^{-3}) containing KCl (0.083 mol dm^{-3}) in the absence or presence of hexadecyltrimethylammonium bromide (CTAB) (5.67×10^{-4} mol dm^{-3}) at 20 °C. A micelle system of the catalyst was prepared by sonication, using a SUG 2820 sonicater at 20 °C. A reaction was caused to start by the addition of a substrate to the micelle system.

The reaction obeyed the usual pseudo-first-order rate law until it was substantially completed. The second-order rate constant (k_2) was calculated according to

$$k_2=(k_{obsd}-k_{spont})/[\text{catalyst}]_o, \quad (1)$$

where k_{obsd} and k_{spont} are first-order rate constants in the presence and absence of a catalyst, respectively, and $[\text{catalyst}]_o$ represents the initial concentration of the catalyst, regardless of whether the catalyst forms micelles or not. In this paper, therefore, the concentration of a catalyst is defined in terms moles of the catalyst charged initially.

The binding constant (K_b) and the rate constant (k_{cat}) were calculated using Eq. 2, derived form the following Michaelis-Menten mechanism, which is reasonably applicable to the reactions in this study:

$$\text{Catalyst}+\text{Substrate}\overset{K_b}{\rightleftarrows}\text{Complex}\overset{k_{cat}}{\rightarrow}\text{Product}+\text{Catalyst}$$

$$k_{spont}$$

$$\frac{1}{(k_{obsd}-k_{spont})}=\frac{1}{K_b(k_{cat}-k_{spont})}\times\frac{1}{[\text{catalyst}]_o}+\frac{1}{(k_{cat}-k_{spont})} \quad (2)$$

where k_{obsd}, k_{spont}, and k_{cat} are rate constants of corresponding steps.

Table 1. Syntheses of Catalysts

Catalyst	Yield	Mp	$[\alpha]_D^{20}$	Carbon (%)		Hydrogen (%)		Nitrogen (%)	
	%	°C	(c 0.1, MeOH)	Calcd	Found	Calcd	Found	Calcd	Found
Acyclic Glu · His · Lau Amine	15.7	82—84	−72.2	55.32	54.93	8.11	8.59	11.13	11.34
Acyclic Man · His · Lau Amine	35.5	102—103	−83.2	55.32	54.84	8.11	8.57	11.13	11.42
Acyclic Gal · His · Lau Amine	17.8	94—95	−79.6	55.32	55.19	8.11	8.00	11.13	11.51
Acyclic Glu · His · Ste Amine	29.3	111—112	−21.1	58.90	59.02	8.84	8.46	9.82	10.28
Acyclic Man · His · Ste Amine	56.7	118—119	−35.3	58.90	58.78	8.84	8.53	9.82	11.99
Acyclic Gal · His · Ste Amine	25.4	156—157	−47.8	58.90	58.81	8.84	8.62	9.82	9.90
Acyclic Man · His · But Amine	59.4	126—127	−18.3	48.55	48.18	7.13	7.36	13.49	13.11
Acyclic Man · Lau · Amine	68.2	52—53	+28.6	53.33	52.90	8.69	8.20	5.66	5.85
Cyclic Glu · His · Lau Acid	35.2	152—153	+53.1	57.83	58.22	8.43	7.98	11.24	11.79
Cyclic Glu · His · Ste Acid	21.5	102—103	+115.8	61.86	61.45	9.28	9.56	9.62	9.81

Results and Discussion

Critical Micelle Concentrations (cmc) of Catalysts. Inherent cmc values could be obtained for all glycopeptide-type catalysts synthesized (Table 2). The cmc of an acyclic-type catalyst was generally lower than that of a cyclic-type catalyst. Since a cmc value is dependent mainly on the balance between the hydrophilic moiety of a sugar and the hydrophobic moiety of a long alkyl chain of a catalysts, catalysts having hydrophobic chains of the same carbon number show approximately the same cmc value. It was also found that an acyclic-type catalyst tends to form micelles more easily in comparison with a cyclic type.

Stereoselective hydrolyses of chiral substrates in this study were carried out at a catalyst concentration of 5.67×10^{-4} mol dm^{-3} (unless otherwise indicated), which is above the critical micelle concentration.

Effect of Micelle Formation on Catalytic Activities. The effect of the catalyst concentration on catalytic activities was examined using a mannose-derived catalyst (acyclic Man·His·Lau Amine) in stereoselective hydrolyses of the substrates. As shown in Fig. 1, the k_2 value for the L-substrate was almost constant over a range of catalyst concentration of 2×10^{-6}—2×10^{-5} mol dm^{-3}. On the contrary, the k_2 value for the D-substrate increased with an increase in the catalyst concentration; this was especially and did abruptly so around the cmc of the catalyst (1.06×10^{-5} mol dm^{-3}). As a result, the stereoselectivity (k_2^D/k_2^L) increased by about four times at a catalyst concentration just above the cmc. This result well suggests that the formation of micelles is also very important for enhancing catalytic activities for the self-micelle-forming catalysts examined in this study.

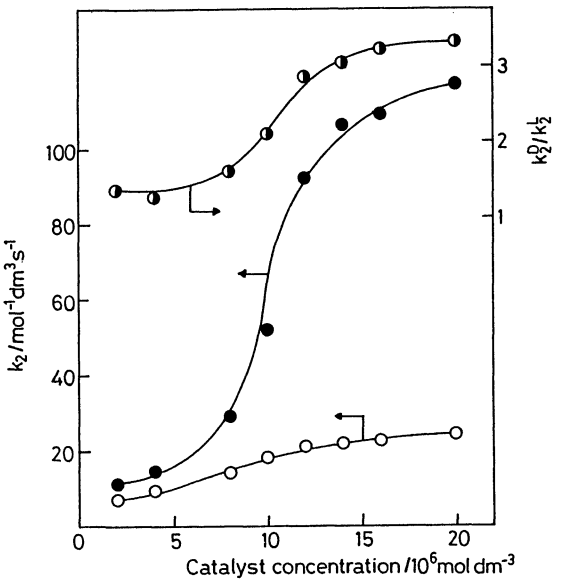


Fig. 1. Effect of catalyst concentration on catalytic activities of acyclic-Man·His·Lau Amine.
●: D-substrate, ○: L-substrate, ◑: k_2^D/k_2^L.

Table 2. Critical Micelle Coincentration (cmc) Values at 20 °C

Catalyst	cmc/mol dm^{-3}
Acyclic Glu·His·Lau Amine	1.10×10^{-5}
Acyclic Man·His·Lau Amine	1.06×10^{-5}
Acyclic Gal·His·Lau Amine	1.08×10^{-5}
Acyclic Glu·His·Ste Amine	9.92×10^{-5}
Acyclic Man·His·Ste Amine	9.01×10^{-5}
Acyclic Gal·His·Ste Amine	9.89×10^{-5}
Acyclic Man·His·But Amine	—
Acyclic Man·Lau Amine	1.03×10^{-5}
Cyclic Glu·His·Lau Acid	3.05×10^{-4}
Cyclic Glu·His·Ste Acid	2.69×10^{-4}

Effect of Hydrophobic Moieties. Second-order rate constants (k_2) and stereoselectivities (k_2^D/k_2^L) are listed in Table 3. The k_2 values of catalysts having a hydrophobic C_{18}-chain, in general, were higher than those having a C_{12}-chain, regardless of the acyclic- and cyclic-type catalysts. A similar phenomenon, that is an increase in the k_2 value with the extension of an acyl chain, was also reported[24] by Ihara, who carried out stereoselective hydrolyses of the substrates by

Table 3. Second-Order Rate Constants and Stereoselectivities at 20 °C

Catalyst	k_2/mol^{-1} dm^3 s^{-1}		k_2^D/k_2^L	k_2^L/k_2^D
	L	D		
Acyclic Glu·His·Lau Amine	74.40	162.00	2.18	
Acyclic Man·His·Lau Amine	24.60	121.80	4.95	
Acyclic Gal·His·Lau Amine	68.45	175.19	2.56	
Acyclic Glu·His·Ste Amine	157.49	247.31	1.57	
Acyclic Man·His·Ste Amine	92.22	225.75	2.45	
Acyclic Gal·His·Ste Amine	127.41	233.53	1.83	
Acyclic Man·His·But Amine	1.34	1.29		1.04
Acyclic Man·Lau Amine	12.49	56.32	4.51	
Cyclic Glu·His·Lau Acid	31.74	4.19		7.58
Cyclic Glu·His·Ste Acid	35.90	4.59		7.82
CTAB+*N*-Lau·His Amine	181.50	101.10		1.08
CTAB+*N*-Ste·His Amine	116.20	68.10		1.71

In 0.083 mol dm^{-3} Tris KCl buffer (pH 8.0), catalyst concentration=5.67×10^{-3} mol dm^{-3}.

micelle catalysts consisting of hexadecyltrimetylammonium bromide (CTAB) and various *N*-alkanoyl-L-histidine. From Table 3, it was also noted that the k_2 values obtained using an acyclic- type catalyst were comparable to those using a micelle catalyst consisting of a combination of *N*-alkyl-L-histidinamide and CTAB.[22] This means that the acyclic-type catalyst, especially having a hydrophobic C_{18}-chain, which can form micelle by itself, provides an excellent reaction environment, similar to that of CTAB. However, opposite results were obtained with respect to stereoselectivities: The acyclic-type catalyst with a C_{18}-chain was less stereoselective than that with a C_{12}-chain.

The acyclic-type catalyst, acyclic Man·His·But Amine, which did not form micelles by itself (Table 2), gave considerably lower k_2 values compared to those of acyclic-type catalysts having longer alkyl chains.

In addition, the acyclic Man·His·But Amine only sightly exhibited a stereorecognition of chiral substrates. It is clear, therefore, that the formation of micelles by the catalyst, itself, effectively enhances the catalytic activities.

Effect of Sugar Moieties. A stereostructural effect of sugar moieties of catalysts was examined on the hydrolyses of chiral substrates. As shown in the Table 3, both the hydrolytic rate and the stereoselectivity were directly influenced by the kinds of sugar moieties. The k_2 value for an acyclic-type catalyst, in general, was higher than that of a cyclic type-catalyst, probably due to the fact that an acyclic-type catalyst is inclined to form micelles more easily than a cyclic-type one, as reflected by the cmc values (Table 2). In order to discuss in greater detail the influence of micelle environments on catalytic action, hydrolyses catalyzed by either acyclic- or cyclic-type catalysts also were carried out in the presence of CTAB as an additional surfactant. The resulting second-order rate constants (k_2) and stereoselectivities (k_2^D/k_2^L) are summarized in Table 4. For acyclic-type catalysts, the addition of CTAB seemed to affect less remarkably the k_2 values, although it decreased the k_2^D values with a sight increase in the k_2^L values. Both the k_2^L and k_2^D values for cyclic-type catalysts, however, increased considerably in the presence of CTAB. This fact well coincides with the result mentioned in the previous paragraph, and suggests that a weaker micelle-forming ability of a cyclic-type catalyst is assisted by CTAB, resulting in the formation of an effective reaction environment.

The stereostructure of sugar moieties was also found to affect the stereoselectivity. It is clear from Table 3 that an acyclic-type catalyst is more D-selective, while a cyclic-type catalyst is more L-selective. This fact suggests that the stereoselectivity defends on the stereostructure of sugar moietes, but cannot always deny the participation of the histidyl moiety in stereorecognition.

Table 3 also compares the second-order rate constants for acyclic-type catalysts with or without the histidyl moiety (acyclic Man·His·Lau Amine or acyclic Man·Lau Amine respectively). Though the latter had a lower activity than the former, the stereoselectivity of acyclic Man·Lau Amine was almost equal to that of acyclic Man·His·Lau Amine. Thus, it may be said that a sugar moiety is responsible for stereorecognition, rather than the histidyl moiety.

Table 5 shows the binding constants (K_b) and the catalytic rate constants (k_{cat}). For catalysts having the

Table 4. Second-Order Rate Constants and Stereoselectivities in the Presence of CTAB at 20 °C

Catalyst	k_2/mol^{-1} dm^3 s^{-1}		k_2^D/k_2^L	k_2^L/k_2^D
	L	D		
Acyclic Glu·His·Lau Amine	128.7	160.5	1.25	
Acyclic Glu·His·Ste Amine	180.2	200.9	1.11	
Cyclic Glu·His·Lau Acid	157.6	141.3		1.12
Cyclic Glu·His·Ste Acid	130.1	121.7		1.07

In 0.083 mol dm^{-3} Tris KCl buffer (pH 8.0), catalyst concentration=5.67×10^{-5} mol dm^{-3}, CTAB concentration=5.67×10^{-3} mol dm^{-3}.

Table 5. Binding Constants and Catalytic Rate Constants

Catalyst	$10^4K_b^L$	$10^4k_{cat}^L$	$10^4K_b^D$	$10^4k_{cat}^D$	K_b^D/K_b^L	k_{cat}^D/k_{cat}^L
	mol^{-1} dm^3	s^{-1}	mol^{-1} dm^3	s^{-1}		
Acyclic Glu·His·Lau Amine	10.38	18.52	20.74	20.18	2.00	1.09
Acyclic Man·His·Lau Amine	4.21	15.66	19.58	17.84	4.65	1.14
Acyclic Gal·His·Lau Amine	8.14	21.37	17.15	23.28	2.11	1.09
Acyclic Glu·His·Ste Amine	7.58	25.16	10.11	28.51	1.33	1.13
Acyclic Man·His·Ste Amine	6.25	31.25	16.67	33.34	2.67	1.07
Acyclic Gal·His·Ste Amine	7.96	27.52	12.66	28.63	1.59	1.04

In 0.083 mol dm^{-3} Tris KCl buffer (pH 8.0), substrate concentration=5.67×10^{-6} mol dm^{-3}.

same hydrophobic group, the ratios of the binding constants, (K_b^D/K_b^L), remarkably depend on the kinds of catalysts, compared with those of the catalytic rate constants, (k_{cat}^D/k_{cat}^L), which are almost unity. This aspect is considered to be one of the special features of the catalysts designed in this study, considering that a stereorecognition of catalysts synthesized so far[25] can be observed in the last product-forming step. When the ratios (K_b^D/K_b^L) are compared with the k_2^D/k_2^L values shown in Table 3, both ratios are found to have good correlation. These results strongly indicate that stereorecognition is performed on a substrate captured into the micelle formed by the catalyst itself.

Effect of Hydroxyl Groups of Sugar Moiety. As discussed above, stereorecognition is in close relation with the acyclic or cyclic configuration of a sugar moiety. A cyclic-type catalyst having a rather rigid configuration of the moiety seems to give higher stereorecognition (Table 3).

A comparison of stereoselectivities among three acyclic-type catalysts can make the effect of the configuration of hydroxyl groups clearer. Using these catalysts, the D-selectivity was obtained, regardless of the kinds of catalysts. This result suggests that the OH configuration on C-3 common to three catalysts is the key point to D-selectivity. In these three catalysts, however, the mannose-derived catalyst was most stereoselective, and the glucose- and galactose-derived catalysts exhibited approxmately the same stereoselectivity. Therefore, the hydroxyl group on C-2 in sugar moieties may also play an important role in D-stereorecognition. In other words, the configuration of OH on C-2, being in the cis-position to OH on C-3, promotes D-selectivity. On the contrary, the OH on C-2 in the trans-position diminishes the D-selectivity of the OH on C-3. In this respect, the mannose-derived catalyst is considered to have the most preferable configuration of hydroxyl groups to stereoselective capture of a substrate into the catalyst micelles.

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