would be to realize that phosphate transforms part of the ImpN into another activated form of nucleotides, i.e., the nucleoside diphosphate. Even though less activated than the imidazolides, they may, under the proper conditions, also polymerize and lead to polynucleotide synthesis.

Acknowledgment. This research was supported by Grant No NCA 2-474 from the Exobiology Program of the National Aeronautics and Space Administration. We thank Dr. S. Chang from the Planetary Biology Branch of the NASA/Ames Research Center and Prof. C. F. Bernasconi from the Chemistry Department of the University of California at Santa Cruz for providing facilities and for discussions.

Registry No. MES, 4432-31-9; ImpG, 69281-33-0; ImpC, 69673-09-2; GDP, 146-91-8; 2-MeImpG, 80242-42-8; $H_2PO_4^-$, 14066-20-7; HPO_4^{2-}, 14066-19-4; acetic acid, 64-19-7; 2-methylimidazole, 693-98-1.

Enhanced Enantioselectivity of an Enzymatic Reaction by the Sulfur Functional Group. A Simple Preparation of Optically Active β-Hydroxy Nitriles Using a Lipase[1]

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Received May 30, 1990

The enantioselectivity of a lipase-catalyzed hydrolysis was improved by varying the acyl residue into the sulfur functional one, i.e. the β-(phenylthio)- or β-(methylthio)acetoxy group, from acetate or valerate to realize satisfactory resolution of β-hydroxy nitriles using lipase P (*Pseudomonas* sp.).

Introduction

Optically active β-hydroxy nitriles are expected to be useful chiral building blocks for asymmetric synthesis because the cyano group is a functional precursor group of amino and carbonyl groups.[2] Therefore, it is desired to establish a simple method to supply chiral β-hydroxy nitriles that have certain elementary skeletons.[3,4] We have studied the preparation of those compounds using a biocatalytic system such as baker's yeast reduction of the corresponding β-keto nitriles.[5] In these studies, we have encountered a serious problem that limited the number of substrates which could be reduced to the alcohols by bakers' yeast. To obtain various optically active β-hydroxy nitriles, the resolution method using lipases was established for study because these enzymes are stable, cheap, and have broad substrate specificity and stereospecificity.[6] We have tested several kinds of commercially available lipases using 3-(valeroyloxy)butyronitrile as a substrate. However, it has been found that all of the lipases tested lack the capability to resolve the butyronitrile. This shortcoming was generally solved by the discovery of new enzymes with the desired stereochemical features.[6i,j] However, if alternative strategies could be developed for improving enantioselectivity, especially by a chemical modification of the substrate, the usefulness of the biocatalyst could be extended.

In this paper, we describe a simple method of enhancing the enantioselectivity of a lipase-catalyzed hydrolysis by proper modification of the substrates.[1]

Results and Discussion

In 1981, Ohno et al.[7] first reported that the enantioselectivity of pig liver esterase catalyzed hydrolysis of dimethyl β-aminoglutarate was drastically improved by the modification of the substrate, i.e. acylation of the β-amino group. Several reports have been published describing a method of enhancing the stereoselectivity of the enzyme-catalyzed hydrolysis especially by the modification of the substrates.[8] The fact that the enantioselectivity depends on the structure of the acid component of the esters[8a] envisioned us to survey the ester which has a good specificity to a lipase. To determine the combination of the substrates and the lipase to ensure satisfactory results, several kinds of lipases have been tested during 3-hydroxy nitriles as substrates (eq 1).

To a suspension of the substrate, 1, in 0.1 M phosphate buffer (pH 7.2) was added the lipase (50 wt % of the substrate), which was stirred at 40 °C. Progress of the reaction was monitored by silica gel thin-layer chromatography (TLC). The reaction was stopped when the spots due to the ester and the alcohol became the same size. The reaction mixture was extracted with ethyl acetate and separated by silica gel TLC with the conversion ratio being determined by ^1H NMR analysis. Optical purity of the hydrolyzed alcohol, 2, was determined by ^1H NMR analysis

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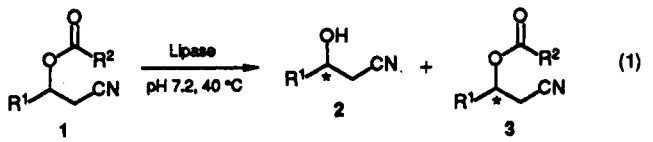

(1)

1,3	R^1	R^2
a	CH_3	CH_3
b	CH_3	n-C_3H_7
c	CH_3	n-C_4H_9
d	CH_3	CH_2SMe
e	CH_3	CH_2SBu
f	CH_3	CH_2SPh
g	CH_3	CH_2SO_2Me
h	CH_3	CH_2OMe
i	CH_3	CH_2OPh
j	CH_3	CH_2Cl
k	Ph	CH_2SPh
l	Ph	CH_2SMe
m	Ph	n-C_4H_9
n	$PhCH_2CH_2$	CH_2SPh
o	$PhCH_2CH_2$	n-C_4H_9
p	PHCH=CH	CH_2SPh
q	PHCH=CH	n-C_4H_9
r	$PhthNCH_2$	CH_3
s	$PhthNCH_2$	CH_2SPh
t	$PhthNCH_2$	CH_2SMe

1	R^1
a	CH_3
b	Ph
c	$PhCH_2CH_2$
d	PhCH=CH
e	$PhthNCH_2$

of the corresponding (+)-α-methoxy-α-phenyl-α-(trifluoromethyl)acetate (MTPA ester).[9] The results are summarized in Table I. Preliminary experiments involving the hydrolysis of 3-acetoxybutyronitrile (**1a**) revealed that lipase P (Amano, *Pseudomonas* sp.) was more promising than any other of the nine enzymes tested. In these reactions, lipase from *Aspergillus niger* (A and A-6), *Candida* sp. (MY and M10), *Rhizopus* sp. (F-AP15 and Newlase F), Porcine pancreatin (PPL), and Hog pancreatin (F) were not stereospecific. As can be seen in Table I, it was noticed that the enantioselectivity of the hydrolysis was influenced strongly by the structure of the ester part and that the highest (E)[10] value of the hydrolysis was obtained when 3-[(methylthio)acetoxy] nitrile, **1d**, was subjected to the reaction (entry 4). Activated esters such as methylsulfonyl or chloroacetoxy esters did not give satisfactory results (entries 7 and 10). To determine whether this effect was a general occurrence, the resolution experiments of **1a** were tested using various lipases. From the results it was discovered that this effect was particularly specific for lipase P, with no enhancement of the enantioselectivity for lipases MY, M10, F-AP15, pancreatin F, and Newlase F.

To determine the scope and limitation of this method and to improve the stereoselectivity of the lipase-catalyzed hydrolysis, several nitriles (Table II) were tested. With aromatic substrates (entries 2–5), the (phenylthio)acetoxy group was better than the (methylthio)acetoxy group. With aliphatic nitriles such as 3-hydroxyheptanenitrile (R^1 = n-C_4H_9) and 3-hydroxynonanenitrile (R^1 = n-C_8H_{17}), lipase P was not stereospecific even if they were subjected to the reaction of (methylthio)- or (phenylthio)acetoxy esters. Consequently, it seemed that this enzymatic hydrolysis promised to give satisfactory results especially with esters of (±)-3-hydroxy nitriles which involve an aromatic substituent. For the resolution of (±)-**1s** (entry 5), the results were not satisfactory, but the ee rose easily by recrystallization from ethyl acetate, giving optically pure **2e** and **1s**, both of which were applied to the synthesis of new copper(II) complexes as a model of active sites of copper protein.[11]

Several reports have been published describing that the sulfur functional group of substrates played an important role for stereorecognition in an enzymatic reaction in microbes such as bakers' yeast.[12] However, it is not clear as to what factors caused this phenomenon of enhancing the stereoselectivity of lipase P by the sulfur functional group. Considering the broad substrate specificity of the lipase, the present method of improving the enantioselectivity by changing the acyl residue is recommended to be used as an efficient method that provides optically active cyano alcohols.

Experimental Section

General Procedures. Wakogel C-300 and Wakogel B5F were used for flash column chromatography and thin-layer chromatogrphy (TLC), respectively. Melting points are uncorrected.

(±)-3-Phenyl-3-hydroxypropionitrile (2b). To a solution of 10 mmol of lithium diisopropylamide (LDA) in 14 mL of THF was added a solution of acetonitrile (1.20 g, 12 mmol) in 5 mL of THF at −78 °C, and the solution was stirred for 2 h to produce a white viscous mixture, then a THF (3 mL) solution of benzaldehyde (1.07 g, 10 mmol) was added dropwise using a syringe. After the addition was completed the mixture was stirred for 1 h at the same temperature. The reaction was quenched using 2 M HCl, extracted with ethyl acetate, dried, and evaporated. Distillation of the crude product gave **2b** (2.00 g, 10 mmol) as a light yellow oil in 80% yield: bp 120 °C (0.5 mmHg) (Kugelrohr); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 2.70 (3 H, d, J = 6.15 Hz), 3.10 (1H, br s, OH), 4.97 (1 H, dt, J_1 = 6.15 Hz, J_2 = 3.77 Hz), 7.4 (5 H, br s); ^{13}C NMR (50 MHz, δ, $CDCl_3$) 27.76, 69.73, 117.40, 125.44, 128.60, 128.75, 140.93; IR (neat) 3400, 3050, 3030, 2920, 2250 (CN), 1500, 1450, 1410, 1060, 940, 870, 750, and 650 cm^{-1}. Anal. Calcd for C_9H_9ON: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.41; H, 6.16; N, 9.45. Hydroxy nitriles **2c** and **2d** were obtained by the same method as previously described.

(±)-5-Phenyl-3-hydroxypentanenitrile (2c): bp 130 °C (1.5 mmHg) (Kugelrohr); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.8–2.0 (2 H, m), 2.53 (1 H, d, J = 6.21 Hz), 2.54 (1 H, d, J = 5.07 Hz), 2.6–2.9 (2 H, m), 2.70 (1 H, br s, OH), 3.95–4.00 (1 H, m), 7.2–7.5 (5 H, m); ^{13}C NMR (50 MHz, δ, $CDCl_3$) 26.17, 31.50, 37.84, 66.74, 117.72, 126.13, 128.19, 128.31, 128.50, 128.62, and 140.69 ppm; IR (neat) 3470, 3050, 2930, 2150 (CN), 1730, 1600, 1500, 1080, 930, 850, 750, and 690 cm^{-1}. Anal. Calcd for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.48; H, 7.54; N, 7.81.

(±)-5-Phenyl-3-hydroxy-4-pentenenitrile (2d): bp 170 °C (0.25 mmHg) (Kugelrohr); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 2.65 (3 H, dd, J_1 = 6.22, J_2 = 1.28 Hz), 2.9 (1 H, br s, OH), 4.61 (1 H, q, J = 5.97 Hz), 6.22 (1 H, dd, J_1 = 15.9, J_2 = 6.62 Hz), 6.69 (1 H, d, J = 15.86 Hz), 7.2–7.4 (5 H, m); ^{13}C NMR (50 MHz, δ, $CDCl_3$) 26.25, 68.49, 117.32, 126.69, 128.02, 128.33, 128.65, 132.73, 135.52; IR (neat) 3400, 3050, 2920, 2250 (CN), 1660, 1620, 1490, 1450, 1410, 1110, 1040, 970, 850, 750, and 690 cm^{-1}. Anal. Calcd for $C_{11}H_{11}ON$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.32; H, 6.50; N, 7.89.

(±)-*N*-(3-Cyano-2-hydroxypropyl)phthalimide (2e). To a solution of 3.66 g (56 mmol) of potassium cyanide in 45 mL of methanol was added a methanol solution (100 mL) of 12.0 g (50.6 mmol) of *N*-(3-chloro-2-hydroxypropyl)phthalimide[13] under argon, and the solution was refluxed for 2 h. When the spot of chloride had disappeared, the reaction mixture was cooled to room temperature. A brown solid, which was obtained from the reaction mixture after removing methanol by evaporation, was dissolved in ethyl acetate and washed with brine three times. The organic layer was dried, evaporated, giving a white solid. This was recrystallized from ethyl acetate to give white needles of **2e** in 89% yield (10.72 g, 45.1 mmol): mp 104 °C; R_f 0.1, hexane/ethyl acetate (1:1); ^{1}H NMR (100 MHz, δ, $CDCl_3$) 2.6 (2 H, d, J = 5.8 Hz), 3.0 (1, H, brs, OH), 4.0 (2 H, d, J = 6.2 Hz), 4.3–4.4 (1 H, m), 7.9–8.1 (4 H, m); ^{13}C NMR (50 MHz, δ, $CDCl_3$) 24.04, 43.06, 66.53, 116.70, 123.74, 131.61, 134.51, and 168.76 ppm; IR (KBr disk) 3450, 2920, 2900, 2870, 2200 (CN), 1760, 1700, 1450, 1310, 1030, 885, 710, 700, and 680 cm^{-1}. Anal. Calcd for $C_{12}H_{10}O_3N_2$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.70; H, 4.68; N, 11.86.

(±)-3-[(Methylthio)acetoxy]butyronitrile (1d). To a solution of 3-hydroxybutyronitrile[4c] (426 mg, 5.0 mmol) in CH_2Cl_2 (10 mL) and pyridine (1.1 mL) was added a CH_2Cl_2 solution (3 mL) of (methylthio)acetyl chloride (748 mg, 6.0 mmol) at 0 °C.

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Table I. Kinetic Resolution of Various Esters of 3-Hydroxybutyronitrile (2a) Using Lipase P (*Pseudomonas* sp.)

	1			2a				
entry	compd	R^2	time, h	% ee[b]	% Y	$[\alpha]^{21}_D$ in EtOH	config	(E)[a]
1	**a**	CH_3	6	61 (45)	45	+3.1° (*c* 1.1)	*R*	7
2	**b**	*n*-C_3H_7	19	18 (51)	51	+0.8° (*c* 2.0)	*R*	2
3	**c**	*n*-C_4H_9	35	35 (58)	58	+1.9° (*c* 1.0)	*R*	3
4	**d**	CH_2SMe	6	84 (44)	37	+4.1° (*c* 3.0)[c]	*R*	29
5	**e**	CH_2SBu	7	66 (56)	52	+3.2° (*c* 1.1)	*R*	13
6	**f**	CH_2SPh	10	51 (56)	56	+2.6° (*c* 1.2)	*R*	6
7	**g**	CH_2SO_2Me	12	3 (22)	19	+0.2° (*c* 1.2)	*R*	1
8	**h**	CH_2OMe	19	70 (54)	54	+3.5° (*c* 1.0)	*R*	14
9	**i**	CH_2OPh	16	69 (45)	45	+3.8° (*c* 1.0)	*R*	10
10	**j**	CH_2Cl	20	53 (48)	32	+2.5° (*c* 1.5)	*R*	6

[a] $(E) = \ln[(1 - c)(1 - ee2)]/\ln[(1 - c)(1 + ee3)]$, where $c = ee3/(ee2 + ee3)$. See ref 10. [b] Percent conversion in parentheses. [c] $[\alpha]^{23}_D$ −89.3° (*c* 2.30, H_2O), lit.[3] −10.08° (*R*).

Table II. Kinetic Resolution of Ester 1 by the Hydrolysis Using Lipase P

	1			2				3				
entry	compd	R^1	R^2	compd	% ee[a]	% Y	$[\alpha]_D$[b]	compd	% ee[a]	% Y	$[\alpha]_D$[b]	(E)[10]
1	**d**	CH_3	CH_2SMe	**a**	84 (44)	45	+4.1° (*R*)	**d**	>98% ee (64)	35	−34.4° (*S*)	29
2	**k**	Ph	CH_2SPh	**b**	94 (46)	43	+58.0° (*R*)	**k**	>98% ee (65)	35	−79.0° (*S*)	74 (8)[b] (18)[c]
3	**n**	$PhCH_2CH_2$	CH_2SPh	**c**	88 (45)	34	−23.5° (*S*)	**n**	>98% ee (68)	32	+17.0° (*R*)	36 (1)[b]
4	**p**	PhCH=CH	CH_2SPh	**d**	95 (40)	39	+8.1° (*R*)	**p**	>98% ee (60)	38	−91.0° (*S*)	55 (6)[b]
5	**s**	$PhthNCH_2$[d]	CH_2SPh	**e**	78 (23)	23	−15.0°[e] (*R*)	**s**	80% ee (66)	30	−26.3°[e] (*S*)	10 (1)[c] (6)[f]

[a] Percent conversion in parentheses. [b] In EtOH, *c* ca. 1. [b] Result from pentanoate; $R^2 = n\text{-}C_4H_9$. [c] Result from (methylthio)acetate; $R^2 = CH_2SMe$. [d] (*N*-Phthalimidoylamino)methyl. [e] In THF. [f] Result from acetate, $R^2 = Me$.

The solution was stirred at room temperature for 2 h. Workup and distilation of the crude product gave **1d** (745 mg, 4.3 mmol) in 86% yield: bp 110 °C (1.5 mmHg) (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$) 1.44 (3 H, d, J = 6.37 Hz), 2.22 (3 H, s), 2.66 (1 H, d, J = 5.35 Hz), 2.70 (1 H, d, J = 5.37 Hz), 3.19 (2 H, s) 5.1–5.18 (1 H, m); ^{13}C NMR (50 MHz, δ, $CDCl_3$) 16.38, 19.16, 24.35, 35.55, 66.46, 116.05, and 169.42 ppm; IR (neat) 3450, 2950, 2250 (CN), 1730, 1420, 1260, 960, 750, and 680 cm^{-1}.

(±)-3-Acetoxybutyronitrile (1a): R_f 0.5, hexane/ethyl acetate (3:1); bp 75 °C (20 mmHg) (Kugelrohr); ^1H NMR (100 MHz, δ, $CDCl_3$) 1.4 (3 H, d, J = 6.8 Hz), 2.1 (3 H, s), 2.6 (2 H, dd, J_1 = 3.1 Hz, J_2 = 1.0 Hz), 4.9–5.2 (1 H, m); IR (neat) 2200 (CN) and 1740 (CO) cm^{-1}.

(±)-3-(Butanoyloxy)butyronitrile (1b): R_f 0.5, hexane/ethyl acetate (1:1); bp 100 °C (3.0 mmHg) (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$) 0.90 (3 H, t, J = 7.36 Hz), 1.35 (3 H, d, J = 6.40 Hz), 1.61 (2 H, tq, J_1 = 7.46 Hz, J_2 = 7.52 Hz), 2.26 (2 H, t, J = 7.52 Hz), 2.55 (1 H, dd, J_1 = 5.31 Hz, J_2 = 16.9 Hz), 2.65 (1 H, dd, J_1 = 5.31 Hz, J_2 = 16.8 Hz), 4.95–5.15 (1 H, m); IR (neat) 2950, 2230 (CN), 1740, 1260, 1130, and 1120 cm^{-1}.

(±)-3-(Pentanoyloxy)butyronitrile (1c): R_f 0.5, hexane/ethyl acetate (3:1); bp 100 °C (2.5 mmHg) (Kugelrohr); ^1H NMR (100 MHz, δ, $CDCl_3$) 1.0 (3 H, t, J = 7.8 Hz), 1.4 (3 H, d, J = 7.1 Hz), 1.8 (2 H, q, J = 7.8 Hz), 2.3 (2 H, t, J = 7.8 Hz), 2.7 (2 H, dd, J_1 = 5.8 Hz, J_2 = 2.1 Hz), 5.0–5.2 (1 H, m); IR (neat) 2950, 2230 (CN), 1740, 1260, and 1130 cm^{-1}.

(±)-3-[(Butylthio)acetoxy]butyronitrile (1e): bp 160 °C (2.5 mmHg) (Kugelrohr); ^1H NMR (100 MHz, δ, $CDCl_3$) 0.9 (3 H, t, J = 7.3 Hz), 1.0–1.8 (4 H, m), 1.5 (3 H, d, J = 6.8 Hz), 2.4–2.7 (4 H, m), 3.2 (2 H, s), 5.1–5.3 (1 H, m); IR (neat) 2970, 2940, 2880, 2250 (CN), 1740, 1480, 1270, 970, and 750 cm^{-1}.

(±)-3-[(Phenylthio)acetoxy]butyronitrile (1f): R_f 0.6, hexane/ethyl acetate (2:1); bp 150 °C (1.0 mmHg) (Kugelrohr); ^1H NMR (100 MHz, δ, $CDCl_3$) 1.3 (3 H, d, J = 6.8 Hz), 2.6 (2 H, d, J = 6.2 Hz), 3.7 (2 H, s), 5.0–5.2 (1 H, m), 7.4–7.7 (5 H, m); IR (neat) 3000, 2250 (CN), 1740, 1580, 1490, 1440, 1270, 1130, 970, 740, and 690 cm^{-1}.

(±)-3-[(Methylsulfonyl)acetoxy]butyronitrile (1g). To a solution of **1d** (173 mg, 1.0 mmol) in acetic acid (1.6 mL) was added hydrogen peroxide (35%, 2.2 mL), and the mixture was refluxed for 1 h. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated. Purification of TLC gave **1g** in 11% yield (22.5 mg, 0.11 mmol) as a coloress oil and the starting material recovered in 17% yield (29.1 mg): R_f 0.2, hexane/ethyl acetate (1:1); ^1H NMR (100 MHz, δ, $CDCl_3$) 1.5 (3 H, d, J = 6.8 Hz), 2.8 (2 H, dd, J_1 = 6.5 Hz, J_2 = 2.6 Hz), 3.2 (3 H, s), 4.1 (2 H, s), 5.2–5.5 (1 H, m); IR (neat) 3550, 2940, 2240 (CN), 1740, 1460, 1050, 980, 910, and 800 cm^{-1}.

(±)-3-(Methoxyacetoxy)butyronitrile (1h): bp 125 °C (0.5 mmHg) (Kugelrohr); ^1H NMR (100 MHz, δ, $CDCl_3$) 1.5 (3 H, d, J = 6.8 Hz), 2.7 (2 H, dd, J_1 = 6.5 Hz, J_2 = 2.6 Hz), 3.3 (3 H, s), 4.0 (2 H, s), 5.12–5.3 (1 H, m); IR (neat) 3000, 2950, 2825, 2250 (CN), 1760, 1120, and 950 cm^{-1}.

(±)-3-(Phenoxyacetoxy)butyronitrile (1i): R_f 0.9, hexane/ethyl acetate (1:1); bp 170 °C (1.3 mmHg) (Kugelrohr); ^1H NMR (100 MHz, δ, $CDCl_3$) 1.5 (3 H, d, J = 6.6 Hz), 2.7 (2 H, dd, J_1 = 6.6, J_2 = 2.6 Hz), 4.8 (2 H, s), 5.1–5.5 (1 H, m), 7.0–7.2 (3 H, m), 7.4–7.7 (2 H, m); IR (neat) 3080, 3060, 3000, 2950, 2250 (CN), 1760, 1600, 1500, 1200, 1090, 750, and 700 cm^{-1}.

(±)-3-(Chloroacetoxy)butyronitrile (1j): R_f 0.5, hexane/ethyl acetate (3:1); bp 112 °C (24 mmHg) (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$) 1.45 (3 H, d, J = 6.35 Hz), 2.58–2.80 (2 H, m), 4.08 (2 H, s), 5.1–5.3 (1 H, m); IR (neat) 3000, 2250 (CN), 1750, 1410, 1390, 1180, 1050, 970, and 700 cm^{-1}.

(±)-3-[(Phenylthio)acetoxy]-3-phenylpropionitrile (1k): R_f 0.5, hexane/ethyl acetate (3:1); bp 150 °C (1.0 mmHg) (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$) 2.83 (2 H, d, J = 6.28 Hz), 3.70 (2 H, s), 5.95 (1 H, t, J = 5.97 Hz), 7.2–7.6 (10 H, m); ^{13}C NMR (50 MHz, δ, $CDCl_3$) 25.39, 36.58, 71.50, 126.14, 127.31, 128.94, 129.14, 130.36, and 155.69 ppm; IR (neat) 3050, 2950, 2920, 2230 (CN), 1740, 1580, 1480, 1440, 1260, 1130, 1120, 1100, 740, and 700 cm^{-1}.

(±)-3-[(Phenylthio)acetoxy]-5-phenylpentanenitrile (1n): R_f 0.8, hexane/ethyl acetate (3:2); bp 165 °C (1.0 mmHg) (Kugelrohr); ^1H NMR (100 MHz, δ, $CDCl_3$) 1.8–2.2 (2 H, m), 2.4–2.8 (4 H, m), 3.7 (2 H, s), 4.9–5.1 (1 H, m), 7.1–7.5 (10 H, m); ^{13}C NMR (50 MHz, δ, $CDCl_3$) 22.89, 31.12, 34.55, 36.34, 69.16, 115.87, 126.37, 127.24, 128.27, 128.60, 129.18, 129.99, 134.36, 139.91, and 169.09 ppm; IR (neat) 3050, 2950, 2250 (CN), 1750, 1580, 1490, 1450, 1260, 1030, 960, and 850 cm^{-1}.

(±)-3-[(Phenylthio)acetoxy]-5-phenyl-4-pentenenitrile (1p): R_f 0.3, hexane/ethyl acetate (3:1); bp 175 °C (1.5 mmHg) (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$) 2.71 (2 H, dd, J_1 = 5.56 Hz, J_2 = 0.65 Hz), 3.68 (2 H, s), 5.79 (1 H, dq, J_1 = 5.61 Hz, J_2 = 0.95 Hz), 6.38 (1 H, dd, J_1 = 15.84 Hz, J_2 = 8.38 Hz), 6.75 (1 H, dd, J_1 = 15.9 Hz, J_2 = 0.90 Hz), 7.1–7.4 (10 H, m); ^{13}C NMR (50 MHz, δ, $CDCl_3$) 23.83, 36.67, 70.42, 115.74, 122.74, 126.92, 127.37, 128.60, 128.69, 128.82, 128.96, 129.00, 129.14, 130.48, 134.18, 135.02, 135.76, and 168.55 ppm; IR (neat) 3050, 2925, 2240 (CN), 1730, 1580, 1260, 1120, 960, 740, and 650 cm^{-1}.

(±)-*N*-[3-Cyano-2-[(phenylthio)acetoxy]propyl]phthalimide (1s): mp 179 °C; R_f 0.5, hexane/ethyl acetate (2:3); ^1H

NMR (100 MHz, δ, $CDCl_3$) 2.6 (2 H, d, J = 5.8 Hz), 3.6 (2 H, s), 3.9 (2 H, d, J = 6.2 Hz), 5.1-5.2 (1 H, m), 7.0-7.4 (5 H, m), 7.7-7.9 (4 H, m); ^{13}C NMR (50 MHz, δ, $CDCl_3$) 21.08, 36.20, 39.47, 67.72, 115.39, 123.63, 127.00, 129.03, 129.81, 131.58, 134.36, 167.93, and 168.82 ppm; IR (KBr disk) 3060, 2950, 2250, 1780, 1710, 1400, 1270, 1120, 895, 715, 690 cm^{-1}.

Lipase Resolution. A solution of nitrile **1d** (100 mg, 0.578 mmol) in 0.1 M phosphate buffer (pH 7.2, 3.0 mL) and acetone (0.1 mL) was incubated with lipase P (50 mg) at 40 °C for 3 h. The mixture was extracted with ethyl acetate and separated by silica gel TLC. The optical purity of the alcohols produced and the remaining ester, which was converted into the alcohol by LAH reduction, were determined by the ^1H NMR analysis of the corresponding (+)-MTPA esters, respectively. To hydrolyze the (phenylthio)acetoxy group of **1s**, only the enzymatic reaction using lipase MY (*Candida* sp.) was successful.

Absolute Stereochemistry of 2b, 2c, 2d, and 2e. Authentic (*R*)-(-)-epoxystyrene was converted to (*S*)-3-hydroxy-3-phenylpropionitrile via reaction with KCN.[4c] The product had $[\alpha]^{25}_D$ -45.3° (*c* 1.91, EtOH, 94% ee) and had the reverse optical rotation as **2b**. Therefore, **2b**, which was produced by lipase-catalyzed hydrolysis of **1k**, was established to have the *R* configuration. Authentic (*S*)-(+)-epichlorohydrin (>98% ee) was converted to (*S*)-1-chloro-4-phenyl-2-butanol via reaction with $PhCH_2MgBr$ (THF solution) at -40 °C in the presence of 10 mol % of CuI,[14] and then the chloride was treated with KCN in MeOH to produce (*S*)-3-hydroxy-5-phenylpentanenitrile; $[\alpha]^{25}_D$ -19.7° (*c* 1.45, EtOH, 96% ee). Consequently, **2c**, which was produced by lipase-catalyzed hydrolysis of **1n**, was established to have the *S* configuration. The absolute configuration assignment of **2d** and **2e** was performed by the ^1H NMR analysis of the corresponding (+)-MTPA esters using reference products (*R*)-**2a**, (*R*)-**2b**, (*S*)-**2c**, and (*S*)-**4**. From the diastereomeric differences in chemical shifts made by the methoxy group in (+)-MTPA esters, the configuration was theorized. Since the signal due to the methoxy group of the (+)-MTPA ester of the racemic **2e** split into two peaks (δ 3.58 and 3.49) in the ^1H NMR spectra, the enantiomeric excess of **2e** was calculated by comparison with the intensity of the two peaks. The absolute configuration of **2e**, which was produced by lipase-catalyzed hydrolysis of **1s**, was presumed as *R* of 78% ee because this ratio was just the same tendency of the chemical shift of the methoxy group of the (+)-MTPA ester of 75% ee of (*S*)-*N*-[3-(phenylthio)-2-hydroxypropyl]phthalimide (**4**). Following the same method described as above, the absolute configuration of **2d** was presumed as *R*.

(2*S*)-*N*-[3-(Phenylthio)-2-hydroxypropyl]phthalimide (4). A solution containing 105 mg (0.7 mmol) of phtalimide and (*S*)-glycydyl sulfide[14] (100 mg, 0.61 mmol, 75% ee) in 5 mL of DMF was heated at 140-150 °C for 3 h under argon. The reaction mixture was cooled to room temperature and dissolved in ethyl acetate. The organic layer was washed with water and dried. Evaporation and purification using silica gel TLC (Wako gel B5-F, hexane/ethyl acetate, 2:1), gave **4** (40 mg, 0.143 mmol, 23%): $[\alpha]^{21}_D$ -3.4° (*c* 2.0, THF); R_f 0.5, hexane/ethyl acetate (2:1); mp 38-40 °C; ^1H NMR (100 MHz, δ, $CDCl_3$) 2.9 (2 H, dd, J_1 = 16.8 Hz, J_2 = 8.4 Hz), 3.9-4.1 (3 H, $RNCH_2CHOH$, m), 7.0-8.0 (9 H, m); ^{13}C NMR (50 MHz, δ, $CDCl_3$) 39.54, 42.83, 68.64, 123.41, 123.59, 123.98, 126.85, 129,12, 130.36, 131.86, 132.60, 134.16, 134.24, 134.30, 134.91, 167.95, and 168.70 ppm; IR (KBr disk) 3450, 3200, 2950, 1780, 1710, 1470, 1310, 1050, 790, 710, and 690 cm^{-1}.

(+)-MTPA Ester of (2*S*)-4: ^1H NMR (200 MHz, δ, $CDCl_3$) 3.10 (1 H, dd, J_1 = 7.0 Hz, J_2 = 14.17 Hz), 3.24 (1 H, dd, J_1 = 6.0 Hz, J_2 = 14.18 Hz), 3.44 (O*Me*, d, J = 1.14 Hz), 3.53 (O*Me*, d, J = 1.2 Hz), 4.12 (1 H, dd, J_1 = 7.30 Hz, J_2 = 14.5 Hz), 5.44-5.56 (1 H, m), 7.19-7.90 (14 H, m). The ratio of the peak intensity of two signals due to the methoxy group at δ 3.44 and 3.53 was 87.6 to 12.4

Acknowledgment. We are grateful to Professor Masanori Utaka of the Faculty of Engineering of Okayama University for the helpful discussions throughout this work. We are also grateful to Mr. Eiichiro Amano of the Faculty of Engineering for elemental analyses and the SC-NMR Laboratory of Okayama University for the NMR measurements. We thank Amano Pharmaceutical Co., Ltd., for providing lipases.

Supplementary Material Available: ^1H NMR of compounds **1a-t**, **4**, and the (+)-MTPA ester of (*S*)-**4** and ^{13}C NMR of compounds **1a-t** and **4** (29 pages). Ordering information is given on any current masthead page.

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Lipophilic Derivatives of [2.2.1]- and [2.2.2]Cryptands: Thermodynamics of Micellization of Their Alkali and Alkaline Earth Cryptates[1]

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Received February 27, 1990

Critical micelle concentrations (cmc's) were measured at several temperatures in the range 8-32 °C for previously unknown 2-*n*-$C_{14}H_{29}$-[2.2.1], cryptand **1**, in the presence of 1 equiv of either Na^+ or Ca^{2+}. Thermodynamic parameters for micelle formation by the complexes were assessed by using the cmc dependence on temperature, $\Delta H°_{mic}$, which was found to be 3.5 kJ/mol (0.84 kcal/mol) for Na^+·**1**, (cmc at 26 °C = 0.092 mM), and 8.4 kJ/mol (2.0 kcal/mol) for Ca^{2+}·**2** (cmc at 26 °C = 0.583 mM). $\Delta S°_{mic}$ was 0.09 kJ/mol K for both complexes. The overall micellization process is entropy driven (large $T\Delta S°$) while the major difference between the two complexes is of enthalpic origin. These results are compared to the ones observed for the K^+ and Ba^{2+} complexes of known 2-*n*-$C_{14}H_{29}$-[2.2.2]cryptand. These observations help quantitate the problem of micellar surface charge.

Introduction

The effect of surface charge on micellar structure, aggregation number, and stability is a subject of considerable current interest and debate. Theoretical, as well as experimental, models have been developed to explain charge effects on amphiphile head groups and the counteranions associated with them in micelles.[2] Macrocyclic polyethers

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(1) Portions of this work were presented in preliminary form at the Fifth International Symposium on Inclusion Phenomena and Molecular Recognition (Orange Beach, Alabama, Sept 1988).

0022-3263/91/1956-1524$02.50/0