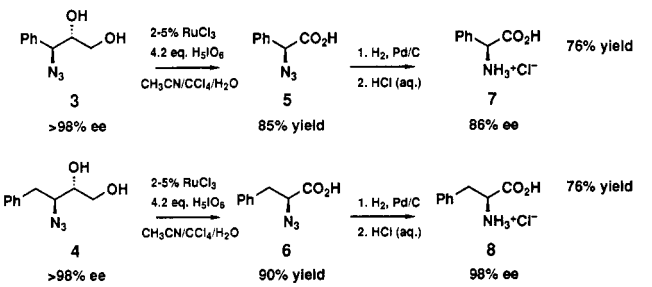
Scheme II



thermore, entry 8 shows that $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ is powerful enough to achieve neopentyl substitution,[13] overriding the strong C-2 preference of the substrate. Similarly, the presence of electron-withdrawing groups at C-3 also decreases C-3 selectivity (entry 12). Regioselective ring opening at C-3 was possible with $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ (entry 13), although use of this reagent with a nitrogen analogue was not as successful (entry 14). Treatment of *cis*-2,3-epoxy alcohols with $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ gave the corresponding azido diols with no selectivity (entry 15) or slight C-2 selectivity (entries 16, 17).[14]

While the origin of the enhanced rate and C-3 selectivity is not completely understood, coordination of the epoxy alcohol to the metal center in a bidentate manner is believed to play an important role.[15,16] This hypothesis is consistent with the observation that the benzyl ether of 1 is completely consumed only after 5 h at 75 °C. The yield is quite low, due to opening by other nucleophiles present in the reaction (one of which is isopropoxide), but interestingly, no product of C-2 azide opening was detected.

At the outset of this study, we observed that the azide ring opening proceeds at room temperature in less than 5 min in a number of solvents.[17] It was found that regioselectivity increased with temperature in ether and benzene for a number of substrates. For example, epoxy alcohol **2** is opened with a regioselectivity of 11.6:1 in benzene at room temperature; at 75 °C, the C-3:C-2 selectivity increases to 27:1. Thus, thermally labile substrates may be opened with good regioselectivity in benzene or ether at room temperature, but we recommend performing the reaction at elevated temperatures to obtain the maximum selectivity.[18]

The 3-azido 1,2-diols obtained from homochiral epoxy alcohols[19] have many potential uses; in particular they are readily transformed in two steps to the corresponding α-amino acids (Scheme II). RuO_4 oxidation of the 1,2-diol,[20-23] followed by reduction of the azide by catalytic hydrogenation,[24] affords the α-amino acids **7** and **8** in good yields. The enantiomeric excess of the products was determined by chiral stationary phase HPLC of the methyl ester 3,5-dinitrobenzamide derivatives.[25] Such analysis reveals that there is no significant loss in optical purity in the transformation of **4** but a substantial loss of percent ee in the transformation of **3**. Chiral lanthanide shift reagent ^1H NMR experiments[26] on the methyl ester of the intermediate azido acid **5** confirms that the loss of stereochemical integrity occurs during the oxidation, undoubtedly at the aldehyde stage.[27] The poor enantiomeric excess realized for L-phenylglycine **7** is therefore probably a consequence of the presence of an electron-withdrawing phenyl group at the α-carbon. Thus this methodology should be most suitable for the asymmetric synthesis of amino acids that lack electron-withdrawing groups at the α-position.

Acknowledgment. We are grateful to the National Science Foundation (Grant CHE-8308355) and to Merck and Co. for generous support of this work. M.C. thanks the Natural Science and Engineering Research Council of Canada (NSERC) for a postdoctoral fellowship.

Supplementary Material Available: Selected experimental details and spectroscopic data for the transformations described herein, including a procedure for preparation of $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ on a 5-g scale (12 pages). Ordering information is given on any current masthead page.

(13) For an example in which the trans diaxial opening rule is violated to avoid neopentyl substitution, see: Sirat, H. M.; Wallis, J. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2885.

(14) Similar results were observed in the $Ti(O\text{-}i\text{-}Pr)_4$-mediated nucleophilic openings of *cis*-2,3-epoxy alcohols (M. Caron, unpublished results.).

(15) (a) See ref 1, especially footnote 21. (b) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.

(16) There is a favorable change in $T\Delta S^*$ of about 5 kcal mol^{-1} for reduction in the kinetic order by one; this corresponds to an increase in rate of approximately 10^3 at 25 °C (Bruice, T. C.; Benkovic, S. J. *J. Am. Chem. Soc.* **1964**, *86*, 418).

(17) Reaction solvents must be aprotic and dry, and ether and benzene gave the best yields and selectivities. Acetonitrile, pentane, and 1,2-dimethoxyethane gave lower selectivity and/or side products, and THF was partially decomposed by the reagent.

(18) The enhanced regioselectivity at higher temperatures might be due to the dissociation of an oligomeric form of $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ into a lesser aggregate or monomer exhibiting higher C-3 selectivity. This hypothesis is supported by the observation that, for a number of substrates, when the concentration of reagent is raised above 0.2 M, the regioselectivity of the opening reaction decreases.

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(21) α-Azido acids prepared in this manner decompose gradually on standing; their lability is due to the presence of trace amounts of low-valent ruthenium. We therefore recommend immediate reduction to the amino acid.

(22) Oxidation of mixtures of azido diols derived from **2** highly enriched in the C-3 regioisomer (>20:1) affords essentially pure azido acid **6**; the products of oxidation of the minor regioisomer cannot be detected.

(23) We recommend the use of periodic acid (H_5IO_6) in place of $NaIO_4$ for the stoichiometric oxidant (see ref 15b).

(24) (a) Augustine, R. L. *Catalytic Hydrogenation*; Marcel Dekker: New York, 1965; p 95. (b) Rylander, P. N. *Catalytic Hydrogenation over Platinum Metals*; Academic: New York, 1967; p 494. (c) Moore, A. T.; Rydon, H. N. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 586.

(25) Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 352.

(26) (a) Fraser, R. R. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 1, Chapter 9, p 173. (b) McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038.

(27) (a) α-Azido aldehydes are especially susceptible to epimerization (see Kuzuhara, H.; Emoto, S. *Tetrahedron Lett.* **1975**, 1853 and references cited therein). (b) No substantial loss of ee accompanies catalytic hydrogenation of α-azido acids (see Zaloom, J.; Roberts, D. C. *J. Org. Chem.* **1981**, *46*, 5173).

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Highly Enantioselective Solvolyses of L- and D-Phenylalanine *p*-Nitrophenyl Esters by an L-Histidyl Dipeptide in Surfactant Coaggregates Formed by Cholesterol-Containing Amphiphiles

Summary: Highly enantioselective catalysis ($k_{cat}(L)/k_{cat}(D)$ = 98.2) was observed in the solvolyses of *N*-dodecanoyl-L- and -D-phenylalanine *p*-nitrophenyl esters (**2**-L and **2**-D)

by *N*-(benzyloxycarbonyl)-L-phenylalanyl-L-histidine methyl ester (**1**) in the coaggregate systems containing [[(cholesteryloxy)carbonyl]methyl][2-(isobutyryloxy)-ethyl]dimethylammonium bromide (CHODABA, 58 molar %) and cetyldimethylethylammonium bromide (CDEAB, 42 molar %). In the above composition, the inhibition effect by the catalyst was exhibited in the solvolysis of the D isomer of the substrates at higher pH values, 8.0 and 9.0.

Sir: High enantioselectivity is always encountered in the actions of natural enzymes, regardless of enzyme class or reaction type. Many efforts have been made by many research groups for many years in the search for the model systems in which high enantioselective catalysis can be observed, particularly those systems mimetic to proteolytic enzymes.[1] In the course of our investigation on the solvolytic reactions of active esters by high and low molecular weight imidazole derivatives,[2] we have found a system in which high enantioselective catalysis was displayed by a histidyl dipeptide. The present system features the solvolyses of L- and D-phenylalanine *p*-nitrophenyl esters by an L-histidyl dipeptide in the presence of amphiphile coaggregates composed of cholesteryl derivatives and other surfactants. In this system enantioselectivity (k_{cat}(L)/k_{cat}(D)) in the order of 100 was observed. We now describe the system and present the kinetic data we have obtained in the initial phase of the work.

The optically active catalyst employed was *N*-(benzyloxycarbonyl)-L-phenylalanyl-L-histidine methyl ester (**1**) and the substrates solvolyzed were *N*-dodecanoyl-L- and -D-phenylalanine *p*-nitrophenyl esters (**2**-L and **2**-D). The characteristic chiral surfactants we used in the present system were cationic cholesterol-containing amphiphiles, [[(cholesteryloxy)carbonyl]methyl][2-(isobutyryloxy)-ethyl]dimethylammonium bromide (CHODABA)[3] and [[(cholesteryloxy)carbonyl]decanyl][2-(isobutyloyloxy)-ethyl]dimethylammonium bromide (CHODABU).[4] We also used [[[(1-methyl-1,3,5,6-norcholestatetraen-3-yl)-oxy]carbonyl]methyl][2-(isobutyryloxy)ethyl]dimethylammonium chloride (ACHODABA)[5] to observe any possible effect of the presence of an aromatic function in the surfactant. To form coaggregates a simple well-known surfactant, cetyldimethylethylammonium bromide (CDEAB) was adopted. It was expected that these coaggregates provide solvolytic matrices of pertinent hydrophobicity with proper fluidity for substrate absorption and which also maintain a tight chiral microenvironment for enantioselective catalysis.

Table I. Enantioselectivity and Rate Constants of Solvolyses[a] of 2-L and 2-D by L-Histidine Dipeptide 1 in Coaggregate Systems Formed by CDEAB and Different Steroid Surfactants

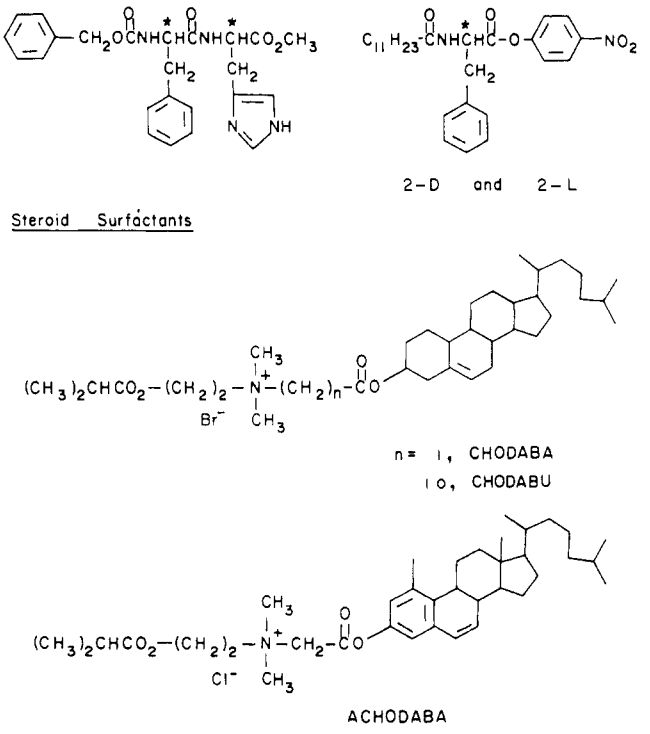
% steroid surfactant in the coaggregate	k_{cat}, M s^{-1}		
	2-L	**2**-D	k_{cat}(L)/k_{cat}(D)
ACHODABA (50 molar %)	106.7	5.3	15.6
CHODABA (50 molar %)	146.7	1.7	86.4
CHODABU (50 molar %)	162.1	19.0	8.5

[a] At 20 °C, pH 7.4 in 0.02 M Tris-buffer (0.02 M KCl), 3% (v/v) dioxane–water, [substrate] = 1.00 × 10^{-5} M, [catalyst] = 1.32 × 10^{-4} M, [steroid surfactant] = 6.67 × 10^{-4} M. The rate constants were reproducible within an accuracy of ±3.5%.

Table II. Rate Constants of Solvolyses[a] of 2-L and 2-D by L-Histidyl Dipeptide 1 in Coaggregates Composed of CHODABA and CDEAB

CDEAB/(CDEAB+-CHODABA) (molar %)	k_{cat}, M s^{-1}		
	2-D	**2**-L	k_{cat}(L)/k_{cat}(D)
0	0.66	11.5	17.4
24	1.26	45.0	35.7
42	1.30	127.7	98.2
50	1.70	146.8	86.4
66	2.50	83.0	33.2

[a] At 20 °C, pH 7.4, 0.02 M Tris-buffer (0.02 M KCl), 3 % (v/v) dioxane–water, [substrate] = 1.00 × 10^{-5} M, [catalyst] = 1.32 × 10^{-4} M, [CHODABA] = 6.67 × 10^{-4} M. The rate constants were reproducible within an accuracy of ±4%.



In the first series of solvolyses, substrates **2**-D or **2**-L were solvolyzed by L-histidyl dipeptide **1** in the presence of cationic coaggregates formed by cosonication of CDEAB (50 molar %) and chiral steroid surfactants (50 molar %) in Tris-buffer (pH 7.40) solution (Table I).

The kinetic data in Table I show that lengthening of the acyl chain of the cholesterol-based surfactant from n = 1 (CHODABA) to n = 10 (CHODABU) brought about an increase in the deacylation rate (k_{cat})[6] of the solvolysis, but

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(3) (a) CHODABA was synthesized according to the method described previously:[3b] mp 192–193 °C; R_f 0.57 (with chloroform–methanol, 3:1); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 5.45 (m, 1 H, CH_2CH=C), 5.10 (s, 2 H, $OCOCH_2N^+$), 4.63 (t, 2 H, OCH_2), 4.46 (t, 2 H, CH_2N^+), 4.7–4.3 (br m, 1 H, OCH), 3.65 (s, 6 H, $(CH_3)_2N^+$), 2.25–0.65 (br m, 50 H, residue). (b) Cho, I.; Chung, K.-C. *Macromolecules* **1984**, *17*, 2935–2937.

(4) Mp 138–140 °C; R_f 0.57 (with chloroform–methanol, 3:1) ^{1}H NMR ($CDCl_3$, Me_4Si) δ 5.42 (m, 1 H, CH_2CH=C), 4.63 (t, 2 H, OCH_2), 4.46 (t, 2 H, CH_2N^+), 4.7–4.3 (br m, 1 H, OCH), 3.50 (s, 10 H, $(CH_3)_2N^+(CH_2)$-(CH_2)), 2.25–0.65 (br m, 68 H, residue).

(5) (a) ACHODABA was synthesized by reaction of 1-methyl-3-hydroxy-19-nor-1,3,5,6-cholestatetraene[5b] with chloroacetyl chloride in ether/pyridine (8 h, 25 °C), followed by quaternization with [(*N*,*N*-dimethylamino)ethyl]isobutylate (24 h, 80 °C, neat): mp 174–175 °C; R_f 0.37 (with chloroform–methanol, 3:1) ^{1}H NMR ($CDCl_3$, Me_4Si) δ 6.67 (s, 2 H, benzene ring), 6.52–5.80 (q, 2 H, CH=CH), 5.60 (s, 2 H, $OCOCH_2N^+$), 4.9–4.2 (br m, 4 H, $O(CH_2)_2N^+$), 3.81 (s, 6 H, $(CH_3)_2N^+$), 2.42 (s, 3 H, CH_3C), 2.0–0.71 (br m, 39 H, residue). (b) Rome, J.; Djerassi, C.; Rosenkranz, G. *J. Org. Chem.* **1950**, *15*, 896–900.

Table III. Enantioselectivity and Rate Constants of Solvolyses[a] of 2-L and 2-D by L-Histidine Dipeptide 1 in Coaggregate Systems Formed by CDEAB (42 molar %) and CHODABA (58 molar %) at Different pH Values

pH	no catalyst 10^3k_{blank}, s^{-1}	10^3k_{mead}(L), s^{-1}	10^3k_{mead}(D), s^{-1}	k_{cat}, $M\ s^{-1}$ 2-L	k_{cat}, $M\ s^{-1}$ 2-D	$k_{cat}(L)/k_{cat}(D)$
7.4	1.9	18.4	2.6	125.0	5.3	23.4
8.0	9.3	26.0	8.4	126.1	−6.8	*b*
9.0	23.0	41.2	14.0	138.0	−68.2	*b*

[a] At 10 °C in 0.02 M Tris-buffer (0.02 M KCl), 3 % (v/v) dioxane–water, [substrate] = 1.00×10^{-5} M, [catalyst] = 1.32×10^{-4} M, [CHODABA] = 6.67×10^{-4} M. [b] Rate retardation for 2D substrate was observed. The rate constants were reproducible within an accuracy of ±3.5%.

the enantioselectivity was low. Particularly noteworthy is the case of the coaggregate system consisting of 50 molar % CHODABA and 50 molar % CDEAB, in which the best enantioselective solvolysis was observed, viz., $k_{cat}(L)/k_{cat}(D)$ = 86.4. Another surfactant ACHODABA, which has an aromatized A ring in the chemical structure, failed to contribute to any significant degree in the enhancement of enantioselectivity.

The above results indicate that to achieve high enantioselective catalysis it is important for the chiral cholesteryl group to be positioned near the polar region of the surfactant where catalytic solvolyses are supposed to take place.

We have also performed the solvolyses of **2**-D or **2**-L by L-histidyl dipeptide **1** in the coaggregate systems of different compositions of CHODABA and CDEAB, as shown in Table II. In response to increased addition of CDEAB, the enantioselectivity was enhanced sharply from 17.4 observed in the presence of vesicle-forming CHODABA alone to 98.2 in the coaggregates containing 42 molar % CDEAB and 58 molar % CHODABA. However, the selectivity decreased with further addition of CDEAB.

When the above solvolyses were carried out in 15 vol % dioxane, the enantioselectivity disappeared completely, presumely due to the complete disarray of the surfactant aggregate system. Electron micrographs show that CHODABA/CDEAB coaggregates actually lose vesicular structures and take on a different morphology, which is not clear on electron micrographs when the coaggregate contains more than 35 molar % CDEAB.

This result is somewhat puzzling to us at the present time. However, it seems to be clear that the kind of morphology of the coaggregate in which high enantioselectivity was observed should be such that the substrate as well as the catalyst can be absorbed into the coaggregate at a proper rate and while the hydrophobic environment is maintained by a certain array formation by the surfactants.

We have further examined the enantioselective solvolysis of **2**-D or **2**-L at different pH values in the above coaggregate system (42 molar % CDEAB/58 molar % CHODABA). The results are presented in Table III.

In Table III it is notable that as pH values of the solvolytic solution are raised, the blank rates increased significantly, probably due to the increased local concentration of hydroxide ion at the periphery of surfactant coaggregates. The catalytic activity (k_{cat}) for the **2**-L remained about same with a slight increase at pH 9.0. The most interesting to observe was, however, that inhibition effect was exhibited by catalyst in the case of the solvolysis of **2**-D at pH 8.0 and 9.0. The values of k_{mead}(D) were actually smaller than those of the blank rates and k_{cat}(D) values were negative.[1c]

We assume that this inhibition by the catalyst is due to the increased portion of imidazole anion,[7] which acts as the counterion of positive ion of surfactant polar heads, thus reducing the local concentration of hydroxide ion at the periphery (Stern layer) of the surfactant coaggregates. This situation should be same in the case of solvolysis of **2**-L. However, the stereochemistry of the intermediate complex (transition state) between catalyst and **2**-L substrate is such that neutral and anionic imidazoles act as attacking nucleophiles, showing yet high k_{cat} values. Obviously, this is not occurring in the case of solvolysis of **2**-D.

The detailed mechanism and stereochemical pictures are not yet clear to us at the present time, and for the more plausible explanation other model systems are now under investigations.

(6) Kinetic data were treated as pseudo-first-order by the least-squares method ($r > 0.99$). The slope (k_{mead}) was corrected by substracting the blank rate to obtain the observed rate constant k_{obsd}. The second-order rate constant k_{cat} was then calculated by dividing k_{obsd} by the catalyst concentration. Thus obtained k_{cat} values are to be called apparent catalytic constants. $k_{cat} = k_{obsd}/[cat.]$.

(7) The pK_a values of imidazole of histidine are as follows: pK_1 = 6.04, pK_2 = 9.33.

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Synthetic Studies of the Nargenicins. Introduction of the C_{14}–C_{19} Side Chain by Diastereoselective [2,3] Wittig Rearrangement of a Tertiary Allylic Ether

Summary: The stereocontrolled [2,3] Wittig rearrangement of a tertiary allylic ether is employed to establish the remotely functionalized C_{14}–C_{19} macrolide fragment of an advanced intermediate related to the nargenicin macrolides.

Sir: The nargenicins[1] constitute a small family of macrolide antibiotics that have attracted synthetic attention as a result of their novel structure and activity against drug-resistant microorganisms.[2] Recently, we reported the first total synthesis of a naturally occurring nargenicin, 18-deoxynargenicin A_1 (**1b**).[3] A key step in our route to **1b** was the addition of an optically active fragment cor-

(1) Nargenicin A_1: Celmer, W. D.; Chmurny, G. N.; Moppett, C. E.; Ware, R. S.; Watts, P. C.; Whipple, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 4203. Nodusmicin: Whaley, H. A.; Chidester, C. G.; Mizsak, S. A.; Wnuk, R. J. *Tetrahedron Lett.* **1980**, *21*, 3659. 18-Deoxynargenicin A_1: Whaley, H. A.; Coates, J. H., Abstract #187 from the 21st Interscience Conference of Antimicrobial Agents and Chemotherapy, November 4, 1981.

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(3) Plata, D. J.; J. Kallmerten, J. *J. Am. Chem. Soc.* **1988**, *110*, 4041.

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