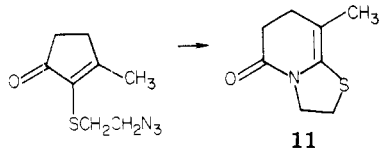
1c. Both 2a and 3a are formed from the azido enone corresponding to 1c in yields nearly identical with those of 1c, indicating that the *gem*-dimethyl group in 1c has no effect on product distribution.

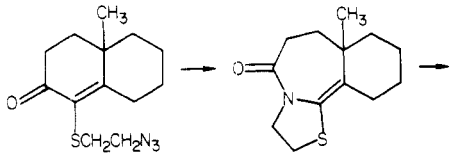
Cyclopentenone 10 undergoes rearrangement to dihydropyridone 11 in 93% yield. Thus, ring contraction of 10 to a cyclobutanone does not compete with ring expanstion to 11 (eq 2).



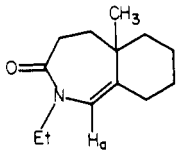
10 11 (2)

In contrast to 1c, we have found that thermolysis of fused-ring azidocyclohexenones results only in products of ring expansion. Thus, octalone 12 cleanly gives 13 (eq 3) in 70% isolated yield: mass spectrum (electron impact) m/e 237; IR ($CHCl_3$) 6.03 μm. Desulfurization of 13 gives 14 [^1H NMR ($CDCl_3$) for H_a δ 5.55 (1 H, s, weak allylic coupling)].

The exclusive formation of 13 at the expense of ring-contracted 16 may be a result of a preferred orientation for azide–olefin cycloaddition to give triazoline 15, rather

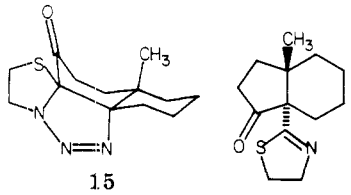


12 13



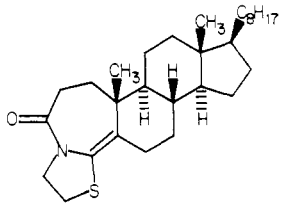
14 (3)

than that with a cis-fused decalone ring system. Carbonyl migration with expulsion of N_2 from 15 would be expected to produce a ring-contracted compound with a relatively strained trans ring fusion, e.g., 16. We intend to test this supposition in future experiments.



15 16

Finally, we note that 4β,5β-epoxycholestan-3-one[14] can be converted to steroid derivative 17 (mp 99–101 °C) in 64% overall yield, suggesting that this methodology will be useful in the construction of a variety of *A*-aza-*A*-homosteroid analogues.[15]



17

Acknowledgment. This work was supported by the National Institutes of Health (Grant GM 26568).

Supplementary Material Available: Complete experimental details (9 pages). Ordering information is given on any current masthead page.

Arthur G. Schultz,* Ramanathan Ravichandran
Department of Chemistry
Rensselaer Polytechnic Institute
Troy, New York 12181
Received August 5, 1980

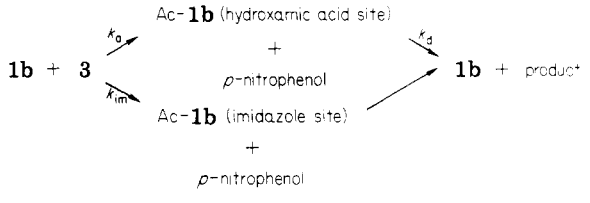
Stereoselective Micellar Bifunctional Catalysis

Summary: The catalytic effect in the hydrolysis of enantiomeric amino acid ester derivatives by an optically active bifunctional catalyst containing the hydroxamic acid and imidazole groups shows high reactivities and pH dependence of stereoselectivity in the presence of CTABr.

Sir: Proteolytic enzymes exhibit a characteristic stereospecificity as well as structural specificity in their catalytic actions toward their various substrates. Optically active micellar catalysts are being increasingly studied as models to gain further insight of stereospecific properties in enzymic reactions.[1-10] In our previous papers,[11,12] it has been shown that mixed micelles of *N*-acyl-L-histidine and the cationic surfactant are effective stereoselective catalysts for cleavage of the enantiomeric substrates.

Recently, it has been reported that micellar bifunctional

Scheme I



Ac-1b = acylated intermediate

(1) C. A. Bunton, L. Robinson, and M. F. Stam, *Tetrahedron Lett.*, 121 (1971).
(2) J. M. Brown and C. A. Bunton, *J. Chem. Soc., Chem. Commun.*, 969 (1974).
(3) R. A. Moss and W. L. Sunshine, *J. Org. Chem.*, **39**, 1083 (1974).
(4) R. A. Moss, T. J. Lukas, and R. C. Nahas, *Tetrahedron Lett.*, 3531 (1977).
(5) R. A. Moss, R. C. Nahas, and T. J. Lukas, *Tetrahedron Lett.*, 507 (1978).
(6) J. Koga, M. Shoshi, and N. Kuroki, *Nippon Kagaku Kaishi*, 1179 (1978).
(7) K. Yamada, H. Shosenji, and H. Ihara, *Chem. Lett.*, 491 (1979).
(8) K. Yamada, H. Shosenji, H. Ihara, and Y. Otsubo, *Tetrahedon Lett.*, 2529 (1979).
(9) R. Ueoka, T. Terao, and K. Ohkubo, *Noppon Kagaku Kaishi*, 462 (1980).
(10) H. Ihara, S. Ono, H. Shosenji, and K. Yamada, *J. Org. Chem.*, **45**, 1623 (1980).
(11) Y. Ihara, *J. Chem. Soc., Chem. Commun.*, 984 (1978).
(12) Y. Ihara, *J. Chem. Soc., Perkin Trans. 2*, in press.

(14) H. B. Henbest and W. R. Jackson, *J. Chem. Soc. C*, 2459 (1967).
(15) Compound 17 can be desulfurized in 96% yield to give *N*-ethyl-3a-aza-*A*-homocholest-4-en-3-one [mp 111–112° C (hexane)]. This compound gave UV and IR spectra completely analogous to those reported for the *N*-methyl derivative; see D. H. R. Barton, M. J. Day, R. H. Hesse, and M. M. Pechet, *J. Chem. Soc., Perkin Trans. 1*, 1764 (1975). The *N*-methyl derivative is prepared by rearrangement of 3-(methylimino)-cholest-4-ene *N*-oxide.

0022-3263/80/1945-5009$01.00/0

Table I. Apparent Catalytic Rate Constants in Mixed Micellar System[a]

	k_c, M^{-1} s^{-1}								
	3a			3b			3c		
catalyst	L	D	L/D	L	D	L/D	L	D	L/D
1a[b]	572	231	2.51	281	140	2.01	314	145	2.17
1b	2880	2060	1.40	2350	1920	1.22	2230	1610	1.39
2	1530	1770	0.86	1630	1670	0.98	1450	1810	0.80

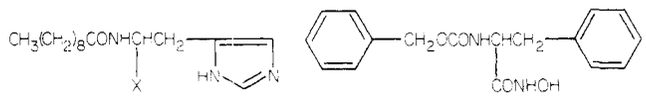
[a] At pH 7.30, 0.02 M phosphate buffer, 35 °C, 0.83 v/v % CH_3CN-H_2O, [CTABr] = 6.00×10^{-3} M, [catalyst] = $(0.40\text{–}5.33) \times 10^{-4}$ M, [substrate] = $(0.5\text{–}1.0) \times 10^{-5}$ M. The k_c values are calculated by least squares and generally have correlation coefficients >0.99. [b] From ref 12.

Table II. Kinetic Analysis under Burst Conditions[a]

substrate		k_a, M^{-1} s^{-1}	k_{im}, M^{-1} s^{-1}	$10^3 k_d$, s^{-1}
3a	L	2460	560	~0
	D	1900	380	~3
3c	L	1520	307	~0
	D	1250	186	~2

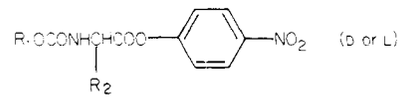
[a] At pH 7.30, 0.02 M phosphate buffer, 25 °C, 0.83 v/v % CH_3CN-H_2O, [CTABr] = 6.00×10^{-3} M, [1b] = 1.15×10^{-5} M, [substrate] = $(0.960\text{–}1.11) \times 10^{-4}$ M. The kinetic treatment is that of Kunitake and has been used by others.[13-16]

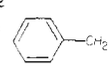
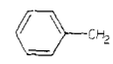
catalsyts which contain the hydroxamate and imidazole functions show remarkably high reactivities toward *p*-nitrophenyl acetate.[13,14] Therefore, it is thought interesting to examine the catalytic action of an optically active bifunctional catalsyt in a micellar system. In this communication, we describe an interesting kinetic property for cleavage of enantiomeric *N*-acylamino acid *p*-nitrophenyl esters (**3**) in a optically active bifunctionalized mixed micellar system formed from *N*-decanoyl-L-histidinehydroxamic acid (**1b**) and cetyltrimethylammonium bromide (CTABr), and the results are compared with those of *N*-decanoyl-L-histidine (**1a**) and *N*-[(benzyloxy)-carbonyl]-L-phenylalaninehydroxamic acid (**2**) in CTABr.



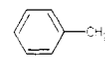
1a, X = COOH
b, X = CONHOH

2



3a, R_1 =  ; R_2 = 

b, R_1 =  ; R_2 = CH_3

c, R_1 = CH_3; R_2 = 

Pseudo-first-order rate constants (k_ψ) for cleavage of the substrate were determined by monitoring the release of *p*-nitrophenol spectrophotometrically at 25 °C under conditions [substrate] < [catalyst] < [CTABr]. In all cases there exists the expected linear relation between the rate and the catalyst concentration. From the slope of k_ψ against catalyst concentration at a fixed [CTABr] of 6.00 $\times 10^{-3}$ M, the apparent second-order rate constants (k_c) in Table I are evaluated. We also examined some experiments at different CTABr concentrations. The k_c values decreased with increased CTABr concentrations, but the $k_c(L)/k_c(D)$ ratio did not depend on the CTABr to catalyst ratio.

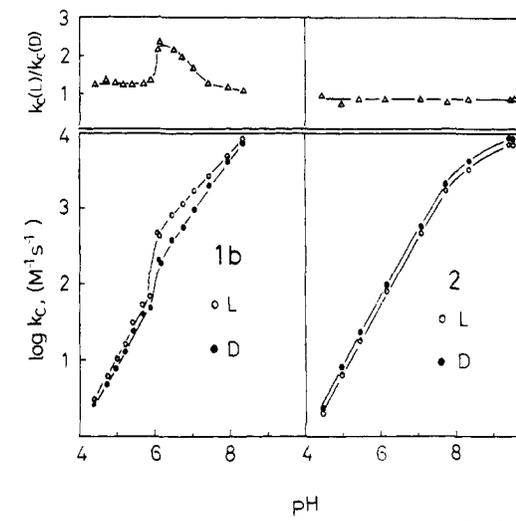
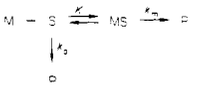


Figure 1. pH–rate profiles for reactions of **3a** with **1b** and **2** in CTABr at 25 °C, μ = 0.05 (KCl), buffer 0.04 M acetate (pH <6), 0.02 M phosphate (9 > pH > 6), and 0.02 M carbonate (pH >9), [CTABr] = 6.00×10^{-3} M, [**1b** or **2**] = $(0.60\text{–}1.20) \times 10^{-4}$ M, [**3a**] = $(0.5\text{–}1.0) \times 10^{-5}$ M. From the three or more reactions, we estimate that the rate constants are reproducible to ±4%.

As shown in Table I, the reactivity of the bifunctional catalyst **1b** is generally larger than those of **1a** and **2**. The catalysts containing the hydroxamic acid groups, **1b** and **2**, are 3–15 times more reactive than **1a**. The pK_a values of the hydroxamic acid groups determined by the spectrophotomeric titration are 8.45 for **1b** and 8.36 for **2**, respectively (3.00×10^{-4} M **1b** or **2** in 6.00×10^{-3} M CTABr, μ = 0.05, KCl). Therefore, the large enhanced reactivities of **1b** and **2** are apparently due to the formation of the hydroxamate anion. On the other hand, the stereoselective behavior shows that the L substrate is more reactive than the D substrate with **1a** and **1b**, but **2** is slightly more reactive with the D substrate. The stereoselective rate ratio of **1a** is 2.0–2.5; however, **1b** reduced the stereoselectivity to 1.2–1.4.[17] These results also suggest that the reaction of **1b** occurs mostly at the hydroxamic acid site.

(13) T. Kunitake, Y. Okahata, and T. Sakamoto, *Chem. Lett.*, 459 (1975).
(14) T. Kunitake, Y. Okahata, and T. Sakamoto, *J. Am. Chem. Soc.*, **98**, 7799 (1976).
(15) M. L. Bender and T. H. Marshall, *J. Am. Chem. Soc.*, **90**, 201 (1968).
(16) C. A. Bunton and Y. Ihara, *J. Org. Chem.*, **42**, 2865 (1977).

(17) At constant **1b** to CTABr ratio, the k_ψ values are fitted to the following kinetic scheme:



where M and S are the total mixed micelle (**1b** + CTABr) and the substrate, respectively. The kinetic treatment for reaction of **3a** with **1b** in CTABr at pH 7.30, 0.02 M phosphate (molar ratio of **1b** to CTABr 1:10), gives values of $k_m(L)$ = 1.47 s^{-1}, $k_m(D)$ = 1.08 s^{-1}, and $k_m(L)/k_m(D)$ = 1.36. The dissociation constants are $K(L) = 7.13 \times 10^{-4}$ M, and $K(D) = 8.82 \times 10^{-4}$ M.

(18) Yamaguchi Women's University.

The reaction of **1b** was examined in CTABr, using excess substrate so that there was a rapid evolution of *p*-nitrophenol followed by a slow reaction as the acylated intermediate was hydrolyzed to regenerate the catalyst (Scheme I). The kinetic analysis under burst conditions shows that the catalytic efficiency of **1b** mainly depends on acylation process at pH 7.30 (Table II).

Figure 1 shows the pH–rate profiles for the reactions of **3a** with **1b** and **2** in the presence of CTABr. The log k_c–pH profiles in Figure 1 indicate that the catalytic action of **1b** involves both of the imidazole and hydroxamic acid groups over the pH range studied. It is noteworthy that the stereoselective behavior of **1b** corresponds to a bell-shaped curve with the maximum at near pH 6.2. This behavior is quite different from that of **2** (the stereoselectivity does not depend on pH). The above observation indicates that at lower pH (<7) the stereoselectivity of **1b** is determined by the reactivity of the imidazole group rather than that of the hydroxamic acid group. However, at higher pH (>7), the reaction occurs mostly at the hydroxamic acid site as mentioned above.

The present study demonstrates an interesting kinetic property of the optically active bifunctional catalyst toward the enantiomeric amino acid ester derivatives in the presence of CTABr, and a mechanism is suggested for the stereselective behavior involving acylation of the optically active imidazole and hydroxamic acid functions because the stereoselectivity depends on pH. A detailed study of the mechanisms involving the deacylation process is a future problem.

Registry No. **1a**, 55258-10-1; **1b**, 75232-98-3; **2**, 73048-81-4; L-**3a**, 2578-84-9; D-**3a**, 2578-85-0; DL-**3a**, 2578-86-1; L-**3b**, 1168-87-2; D-**3b**, 30960-00-0; DL-**3b**, 4108-17-2; L-**3c**, 1456-03-7; D-**3c**, 1243-60-3; DL-**3c**, 70148-11-7; CTABr, 57-09-0.

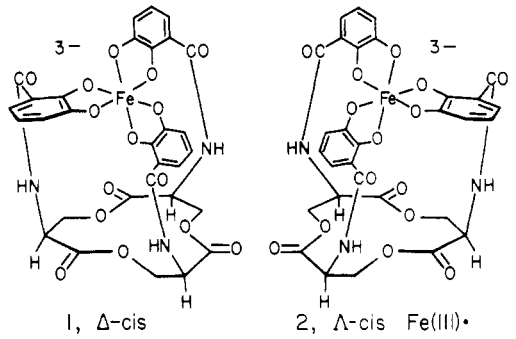
Yasuji Ihara,*[18] Mamoru Nango, Nobuhiko Kuroki
Yamauchi Women's University
3-2-1 Sakurabatake, Yamaguchi 753, Japan
Department of Applied Chemistry
University of Osaka Prefecture
Sakai, Osaka 591, Japan
Received July 7, 1980

Syntheses of Enterobactin and Enantioenterobactin

Summary: Enterobactin, the siderophore (iron-binding ionophore) of the enteric bacteria has been synthesized from L-serine; the antipode of the natural product, enantioenterobactin, synthesized from D-serine, displays the unnatural Λ-cis configuration of the metal center in its Fe(III) complex.

Sir: Microbes have evolved specialized ligands or siderophores[1] for the acquisition and transport of insoluble Fe(III) [$K_{sp}(Fe(OH)_3) \simeq 10^{-38}$][2] into the cell. Three distinct mechanisms for siderophore-mediated iron transport, differing in the details of entry and release of iron, have been recognized.[1]

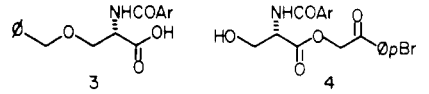
Enterobactin,[3] the cyclic trimer of *N*-(2,3-dihydroxybenzoyl)-L-serine (see antipode **15**), is a siderophore which is overproduced by *E. coli* and related enteric bacteria under low iron stress. The catechol-based siderophore forms a ferric complex, **1**, of exceptional stability (K_f = 10^{52}).[4] The transport of **1**, mediated by a membrane receptor protein,[5] is followed by hydrolysis of the 12-membered, serine-derived trilactone and release of iron.[1]



1, Δ-cis Fe(III)•enterobactin — **2**, Λ-cis Fe(III)•enantioenterobactin

Fe(III)–enterobactin exists predominantly as the Δ-cis complex **1**,[6] the configuration of the L-seryl ester platform favoring the Δ helicity of the iron–catecholate center. It has been assumed that the chirality of **1** may play a key role in the recognition, binding, and transport of the complex into the bacterial cell. Herein we report the syntheses of enantioenterobactin (D-serylenterobactin) **15** (Scheme I; cf. Λ-cis complex **2**) and of the naturally occuring antipode, enterobactin (see Δ-cis complex **1**). Details of membrane receptor binding and transport studies in *E. coli* with synthetic enterobactin and its antipode (**15**) will appear elsewhere.[7]

We have evaluated two fundamentally different approaches to enterobactin and its antipode (**15**). The first entails the coupling of differentially protected *N*-[2,3-bis(benzyloxy)benzoyl]serine monomers, e.g., **3**[8] and **4**.[8]



3 **4**

Ar = 2,3-bis(benzyloxy)phenyl

The second utilizes urethane protection for the monomer amino groups (e.g., see Scheme I) and introduces the *N*-benzoyl ligands only after cyclization of the seryl ester platform. Inherent to the second approach is urethane deprotection and subsequent N-acylation of three amino groups in the cyclic triester of L- or D-serine (cf. **13** in Scheme I). The propensity for *O*- to *N*-acyl shifts in *O*-acylserine derivatives,[9] e.g., **13**, poses a potential risk late in the synthetic sequence for the urethane approach. Consequently, we initially weighed the risk inherent to any *N*-benzoyl monomer approach, viz., racemization of an activated ester (e.g., from **3**) during coupling.

A survey of coupling methods revealed dicyclohexylcarbodiimide/*N*-hydroxybenzotriazole (DCC/HOBt)[10] to be the most satisfactory for the coupling of monomers **3**

(1) Raymond, K. N.; Carrano, C. J. *Acc. Chem. Res.* **1979**, *12*, 183 and references therein.
(2) Linke, W. F. "Solubilities. Inorganic and Metal-Organic Compounds", 4th ed.; Van Nostrand: Princeton, NJ, 1958; Vol. 1, p 1039.
(3) (a) Pollock, J. R.; Neilands, J. B. *Biochem. Biophys. Res. Commun.* **1970**, *38*, 989. (b) O'Brien, I. G.; Gibson, F. *Biochim. Biophys. Acta* **1970**, *215*, 393.
(4) Harris, W. R.; Carrano, C. J.; Cooper, S. R.; Sofen, S. R.; Avdeef, A. E.; McArdle, J. V.; Raymond, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 6097.
(5) Hollifield, W. C., Jr.; Neilands, J. B. *Biochemistry* **1978**, *17*, 1922.
(6) (a) McArdle, J. V.; Sofen, S. R.; Cooper, S. R.; Raymond, K. N. *Inorg. Chem.* **1978**, *17*, 3075. (b) Isied, S. S.; Kuo, G.; Raymond, K. N. *J. Am. Chem. Soc.* **1976**, *98*, 1763.
(7) Neilands, J. B.; Erickson, T. J.; Rastetter, W. H., submitted for publication in *J. Biol. Chem.*
(8) Satisfactory spectral data (^{1}H NMR, IR, and mass spectra) were obtained for this compound.
(9) Schröder, E.; Lübke, K. "The Peptides"; Academic Press: New York, 1965; Vol. 1, pp 213–214.
(10) (a) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788. (b) Klausner, Y.; Chorev, M. *J. Chem. Soc., Chem. Commun.* **1975**, 973. (c) Chorev, M.; Knobler, Y.; Klausner, Y. *J. Chem. Res. (S)* **1977**, 202. (d) Weber, U. *Z. Naturforsch., B.* **1976**, *31*, 1157. (e) Young, G. T. "Proceedings of the 12th European Peptide Symposium"; Hanson, H., Jakubke, H., Eds.; North-Holland Publishing Co.: Amsterdam, 1973; p 132.

0022-3263/80/1945-5011$01.00/0