Calcd for $C_{15}H_{13}Cl_2NO_2S$: C, 52.64; H, 3.82; N, 4.09. Found: C, 52.38; H, 3.34; N, 3.88.

**2-(Ethylthio)-6-chloro-4-(3-(trifluoromethyl)phenyl)-1,4-dihydropyridine-3,5-dicarboxaldehyde (9d, R$^1$ = Et):** eluant, hexane–ethyl acetate (7:3); 77% yield; solid foam; IR (KBr) 3200, 2705, 1657, 1612 cm$^{-1}$; UV 248, 269, 360, 450 nm ($\epsilon$ 14 100, 12 300, 5880, 3470); $^1$H NMR (300) $\delta$ 1.31 (t, 3 H, $J$ = 7.4 Hz), 2.83–2.98 (m, 2 H), 7.36–7.54 (m, 4 H), 9.85 (s, 1 H), 10.10 (s, 1 H). Anal. Calcd for $C_{16}H_{13}ClF_3NO_2S$: C, 51.13; H, 3.48; N, 3.72. Found: C, 51.19; H, 3.83; N, 3.72.

**2,6-Bis(phenylthio)-4-(3-(trifluoromethyl)phenyl)-1,4-dihydropyridine-3,5-dicarboxaldehyde (10d, R$^1$ = Ph).** Thiophenol (0.25 mL, 0.24 g, 2.2 mmol) dissolved in dry THF (5 mL) was added dropwise to a stirred suspension of sodium hydride (0.210 g, 2.2 mmol; 50% in mineral oil) in the same solvent (5 mL) maintained in a dry nitrogen atmosphere. After 10 min, a solution of **4d** (0.350 g, 1 mmol) in THF (5 mL) was added, and the solution was stirred for 3 h. The reaction mixture was worked up as described above for the mono(ethylthio)compounds. The crude product was purified by column chromatography on silica gel (20 g) using hexane–ethyl acetate (3:1) as the eluant. The bis(phenylthio) compound was obtained as a yellow solid (0.348 g, 75% yield) which, after crystallization from dichloromethane–hexane, had mp 144–145 °C: IR 3441, 1651, 1633, 1597 cm$^{-1}$; $^1$H NMR (300) $\delta$ 5.34 (s, 1 H), 7.18–7.56 (m, 14 H), 10.08 (s, 2 H). Anal. Calcd for $C_{26}H_{18}F_3O_2S_2$: C, 62.76; H, 3.64; N, 2.81. Found: C, 62.56; H, 4.01: N, 2.52.

**Acknowledgment.** We are grateful to Dr. Najam Sharif, Institute of Pharmacology, for measuring the binding constants of the 1,4-dihydropyridine derivatives to rat cerebral cortex. We also thank Janice Nelson for carrying out the variable temperature experiments on compound **3e**.

**Registry No.** **1a**, 14149-31-6; **1b**, 113675-65-3; **1c**, 5893-43-6; **1d**, 129215-95-8; **1e**, 1121-89-7; **3a**, 129215-96-9; **3b**, 129215-97-0; **3c**, 129215-98-1; **3d**, 129215-99-2; **3e**, 129216-00-8; **4a**, 129216-01-9; **4b**, 129216-02-0; **4c**, 129216-03-1; **4d**, 129216-04-2; **4e**, 81305-72-8; **5d**, 129216-05-3; **5e**, 81319-42-8; **6**, 57147-25-8; **7**, 129216-06-4; **8**, 129216-07-5; **9b** (R$^1$ = Et), 129216-08-6; **9d** (R$^1$ = Et), 129216-09-7; **10d** (R$^1$ = Ph), 129216-10-0; **11**, 454-89-7; **12**, 93098-26-1; **13**, 129216-11-1; **14**, 129216-12-2; $CH_2(CO_2Et)_2$, 105-53-3; ethanethiol, 75-08-1; thiophenol, 108-98-5.

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# Studies on Thermodynamics for Hydrolysis. 3. Isokinetic Temperature Related to Molecular Location of Reactants in Coaggregates

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The isokinetic (enthalpy–entropy) relationship defined by the linear equation for organic reactions has been discussed in detail by Leffler.[1] About 100 organic reactions have been classified on the basis of the correlation between the isokinetic temperature ($\beta$) and the average value of the experimental temperature ($\bar{T}$).

We have attempted to clarify the interrelation between the $\beta$ value and the reaction field for the hydrolytic cleavages of $p$-nitrophenyl esters. In the course of our study on isokinetic discrimination in relation to the $\beta$ value the following interesting results were obtained: (a) In the hydrolysis of various phenyl esters catalyzed by L-histidine derivatives and hydroxamic acids, the correlation between $\beta$ and $\bar{T}$ could be grouped into $\beta > \bar{T}$ for the micellar system, $\beta < \bar{T}$ for the vesicular system, and $\beta \gg \bar{T}$ for the macromolecular system.[2,3] (b) The enantioselective hydrolysis of the long-chain substrate was governed by the entropy of activation, and this was different from the enthalpy-driven hydrolysis of the short-chain substrates.[4] (c) The entropy-driven vesicular systems were changed to be enthalpy driven by the addition of cholesterol[5,6] or micellar surfactants.[6,7]

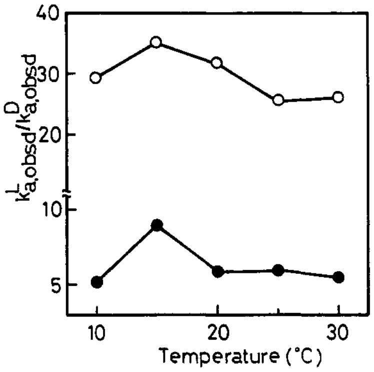

**Figure 1.** Temperature dependence of enantioselectivity for the hydrolysis of D(L)-$S_{12}$ catalyzed by Z-PheHisLeu (○) and MyrHisLeu (●) in the coaggregate composed of 59 mol % $2C_{14}Br$/41 mol % CTAB at pH 7.6 (0.2 M Tris-KCl buffer) in 3% (v/v) $CH_3CN$-$H_2O$; [catalyst] = 2 × 10$^{-4}$ M, [substrate] = 1 × 10$^{-5}$ M, [$2C_{14}Br$] = 1 × 10$^{-3}$ M, [CTAB] = 7 × 10$^{-4}$ M.

In this paper, we demonstrate the discrimination of the reaction field of micelles, vesicles, and coaggregates composed of 59 mol % ditetradecyldimethylammonium bromide (**4**, $2C_{14}Br$)/41 mol % hexadecyltrimethylammonium bromide (**5**, CTAB) on the basis of $\beta$ in the enantioselective hydrolysis of $p$-nitrophenyl $N$-(benzyloxycarbonyl)-D(L)-phenylalaninates (**1a**, D(L)-ZS) and $N$-dodecanoyl-D(L)-phenylalaninates (**1b**, D(L)-$S_{12}$) catalyzed by L-histidine derivatives ($N$-(benzyloxycarbonyl)-L-phenylalanyl-L-histidyl-L-leucine (**2a**, Z-PheHisLeu), $N$-(benzyloxycarbonyl)-L-phenylalanyl-L-histidine (**2b**, Z-PheHis), $N$-tetradecanoyl-L-histidyl-L-leucine (**3a**, MyrHisLeu), and $N$-tetradecanoyl-L-histidine (**3b**, MyrHis)). Moreover, the interrelation between the $\beta$ values and the molecular location of catalysts in the coaggregates composed of 59 mol % $2C_{14}Br$/41 mol % CTAB will be discussed.

## Results and Discussion

**Temperature Dependence of Enantioselectivity.** The morphology of the coaggregates composed of 59 mol % $2C_{14}Br$/41 mol % CTAB was found to be spherical single- and double-walled vesicles by electron microscopy and light-scattering measurements.[8] The temperature dependence of enantioselectivity (reflected in $k^{L}_{a,obsd}/k^{D}_{a,obsd}$) for the hydrolysis of D(L)-$S_{12}$ catalyzed by Z-PheHisLeu and MyrHisLeu in the coaggregates is shown in Figure 1. It is noteworthy that the pronounced maxima

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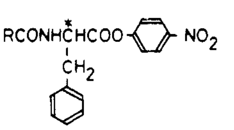
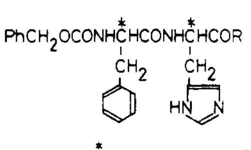
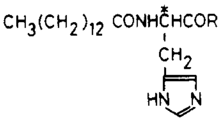


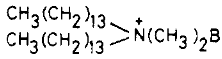
1a: R = PhCH$_2$O (D(L)-ZS)
b: R = CH$_3$(CH$_2$)$_{10}$ (D(L)-S$_{12}$)



2a: R = NHC*H(CH$_2$CH(CH$_3$)$_2$)COOH (Z-PheHisLeu)
b: R = OH (Z-PheHis)



3a: R = NHC*H(CH$_2$CH(CH$_3$)$_2$)COOH (MyrHisLeu)
b: R = OH (MyrHis)



$$\begin{matrix}CH_3(CH_2)_{13} \\ CH_3(CH_2)_{13}\end{matrix} > \overset{+}{N}(CH_3)_2Br^-$$

4 (2C$_{14}$Br)

$CH_3(CH_2)_{15}\overset{+}{N}(CH_3)_3Br^-$

5 (CTAB)

of enantioselectivity were observed ($k^L_{a,obsd}/k^D_{a,obsd}$ = 37 and 9 in the case of Z-PheHisLeu and MyrHisLeu, respectively) at 15 °C. On the other hand, the crystalline gel-liquid crystalline phase transition temperature ($T_c$) of the 59 mol % 2C$_{14}$Br/41 mol % CTAB coaggregates in the 0.2 M Tris-KCl buffer solution was determined to be 14 °C by using a differential scanning calorimetry (DSC). That is, the optimum temperature for the enhancement of enantioselectivity was in good harmony with the phase-transition temperature of the reaction field.

Figure 2 shows the temperature dependence of enantioselectivity for the hydrolysis of D(L)-S$_{12}$ catalyzed by Z-PheHisLeu and MyrHisLeu[9] in the 2C$_{14}$Br vesicular systems. Interestingly, the optimum temperature (25–30 °C) for the highest enantioselectivity in both catalytic systems ($k^L_{a,obsd}/k^D_{a,obsd}$ = 27 at 30 °C and 11 at 25 °C in the 2C$_{14}$Br + Z-PheHisLeu and 2C$_{14}$Br + MyrHisLeu systems, respectively) was observed to be somewhat higher than the $T_c$ (16 °C)[10] of the 2C$_{14}$Br vesicles. It is obvious from Figures 1 and 2 that the enhancement of enantioselectivity for the hydrolysis of enantiomeric substrates should be more sensitive to $T_c$ of the coaggregates composed of 59 mol % 2C$_{14}$Br/41 mol % CTAB as compared with that of 2C$_{14}$Br vesicles.

**Isokinetic Temperatures.** The activation parameters ($\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$) were calculated according to eq 1.

$$\Delta G^{\ddagger} = 2.303RT(kT/hk_{a,obsd}) = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \qquad (1)$$

where $k$ and $h$ stand for the Boltzmann and Plank constants, respectively. The linear relationships between the free energy of activation ($\Delta G^{\ddagger}$) and the absolute temperature ($T$) obtained in this study are shown in Figure 3.

Isokinetic relationships appear to hold for the hydrolysis of D(L)-ZS and D(L)-S$_{12}$ in the coaggregates composed of 59 mol % 2C$_{14}$Br/41 mol % CTAB. For example, Figure 3 also shows the linear relationship between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the hydrolysis of D(L)-ZS and D(L)-S$_{12}$ catalyzed by MyrHis. The correlation coefficients in the relationships between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were estimated to be more than 0.99 for the hydrolysis in all the catalytic systems employed. The isokinetic temperature ($\beta$) was evaluated by eq 2.[1]

$$\Delta H^{\ddagger} = \Delta H_0^{\ddagger} + \beta\Delta S^{\ddagger} \qquad (2)$$

where $\Delta H_0^{\ddagger}$ is simply the intercept of $\Delta H^{\ddagger}$ corresponding to $\Delta S^{\ddagger}$ = 0. The $T_c$ of 2C$_{14}$Br vesicles and coaggregates composed of 59 mol % 2C$_{14}$Br/41 mol % CTAB was determined to be 16 and 14 °C, respectively, by DSC. Here, we would like to discuss the hydrophobic microenvironment of the reaction field in relation to the $\beta$ value on the basis of $k_{a,obsd}$ values for the hydrolysis in the liquid-crystalline states, that is, at temperatures above the $T_c$ values. The $\beta$ values obtained are summarized in Table I.

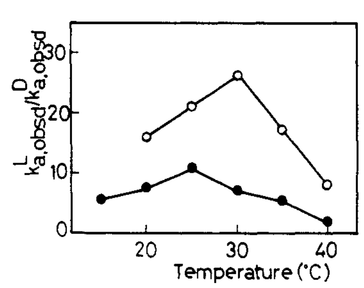


**Figure 2.** Temperature dependence of enantioselectivity for the hydrolysis of D(L)-S$_{12}$ catalyzed by Z-PheHisLeu (○) and MyrHisLeu (●) in the 2C$_{14}$Br vesicular systems at pH 7.6 (0.2 M Tris-KCl buffer) in 3% (v/v) CH$_3$CN-H$_2$O; [catalyst] = 3 × 10$^{-5}$ M, [substrate] = 1 × 10$^{-5}$ M, [2C$_{14}$Br] = 1 × 10$^{-3}$ M.

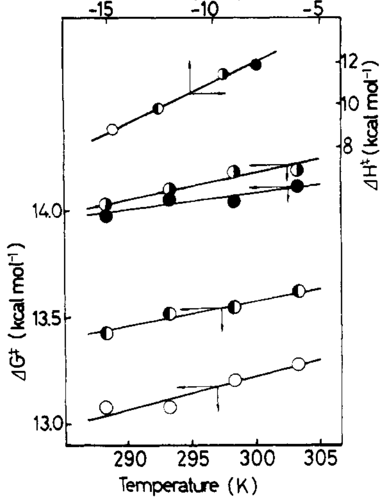


**Figure 3.** Linear correlations between $\Delta G^{\ddagger}$ and absolute temperature and isokinetic relationship for the hydrolysis of L-S$_{12}$ (○), D-S$_{12}$ (●), L-ZS (◐), and D-ZS (◑) catalyzed by MyrHis in the coaggregate composed of 59 mol % 2C$_{14}$Br/41 mol % CTAB.

**Table I. Isokinetic Temperature**[a]

| catalytic system | | $\beta$, K | $\bar{T}$, K |
|---|---|---|---|
| 2C$_{14}$Br | Z-PheHisLeu | 352 ± 1 | 306 |
| | MyrHisLeu[b] | 287 ± 2 | 303 |
| 59 mol % 2C$_{14}$Br | Z-PheHisLeu | 443 ± 20 | 296 |
| 41 mol % CTAB | Z-PheHis | 426 ± 13 | 296 |
| | MyrHis | 440 ± 9 | 296 |
| | MyrHisLeu | 384 ± 4 | 296 |
| CTAB | Z-PheHisLeu | 419 ± 19 | 298 |
| | MyrHis[b] | 363 ± 14 | 300 |

[a] The error limits were obtained by the standard error treatment. Conditions: pH 7.6, 0.2 M Tris-KCl buffer, 3% (v/v) CH$_3$CN-H$_2$O. [b] See ref 6.

It is known that hydrophobic interactions are mainly entropy driven while lyophobic ones are mainly enthalpy driven.[11,12] On the basis of the $\beta$ value in connection with $\bar{T}$ (average value of experimental temperature), it can be presumed that the hydrolysis catalyzed by MyrHisLeu in the 2C$_{14}$Br vesicular system may be governed by the en-

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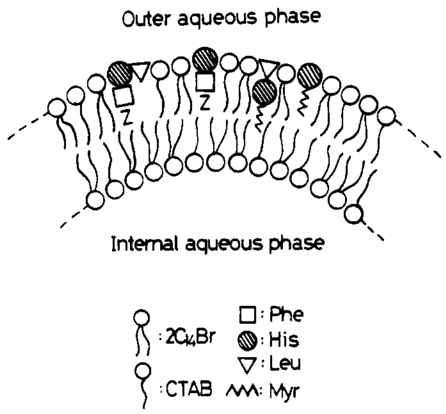

**Figure 4.** Schematic representation of molecular location of reactants in the coaggregates composed of 59 mol % $2C_{14}Br$/41 mol % CTAB.

tropy of activation, that is, $\bar{T}$ (303 K) exceeded $\beta$ (287 K). On the other hand, the hydrolysis in the coaggregates composed of 59 mol % $2C_{14}Br$/41 mol % CTAB may be governed by the enthalpy of activation, that is, $\beta$ (384–443 K) exceeded $\bar{T}$ (296 K). These results suggest that the hydrophobic microenvironment of the coaggregates composed of 59 mol % $2C_{14}Br$/41 mol % CTAB might be softer than that of the pure $2C_{14}Br$ vesicles.

Furthermore, interestingly, the correlation between $\beta$ and $\bar{T}$ was $\beta > \bar{T}$ and $\beta \gg \bar{T}$ for the catalytic system of MyrHisLeu and the others (Z-PheHisLeu, Z-PheHis, and MyrHis), respectively. This difference in $\beta$ values between the catalysts of MyrHisLeu and the others would be attributed to the difference in the location of a His unit (an active site) in the catalysts. The location of catalysts including a His unit in the coaggregates can be drawn schematically as shown in Figure 4. It is deduced that the location of a His unit in MyrHisLeu would be deeper from the surface of coaggregates than that in Z-PheHisLeu, Z-PheHis, or MyrHis. Thus, the first examples of physicochemical discrimination of the molecular location in the reaction field on the basis of isokinetic parameters were proposed.

In conclusion, (a) the pronounced maximum of enantioselectivity was attained at $T_c$ for the hydrolysis of the long-chain substrates (D(L)-$S_{12}$) in the coaggregates composed of 59 mol % $2C_{14}Br$/41 mol % CTAB; (b) on the basis of the $\beta$ value, the hydrophobic microenvironment of coaggregates composed of 59 mol % $2C_{14}Br$/41 mol % CTAB was suggested to be fairly soft, and furthermore, the location of a His unit in the catalysts employed could be established to depend on the catalysts' frameworks.

## Experimental Section

**Materials.** *p*-Nitrophenyl *N*-(benzyloxycarbonyl)-D(L)-phenylalaninate (D(L)-ZS (**1a**)), *p*-nitrophenyl *N*-dodecanoyl-D-(L)-phenylalaninate (D(L)-$S_{12}$ (**1b**)), *N*-tetradecanoyl-L-histidyl-L-leucine (MyrHisLeu (**3a**)), *N*-tetradecanoyl-L-histidine (MyrHis (**3b**)), and ditetradecyldimethylammonium bromide ($2C_{14}Br$ (**4**)) were prepared by the reported procedure.[8] *N*-(Benzyloxycarbonyl)-L-phenylalanyl-L-histidine (Z-PheHis (**2b**)) was prepared by reactions of *N*-hydroxysuccinimide esters of *N*-(benzyloxycarbonyl)-L-phenylalanine with histidine.[13] *N*-(Benzyloxycarbonyl)-L-phenylalanyl-L-histidyl-L-leucine (Z-PheHisLeu (**2a**)) was obtained from Bachem and was used without purification. Commercially available hexadecyltrimethylammonium bromide (CTAB (**5**)) was recrystallized from an anhydrous ethanol–ether mixture.

**Kinetic Measurements.** Rates of *p*-nitrophenol liberation from *p*-nitrophenyl esters were measured at 400 nm with a Hitachi 150-20 UV spectrophotometer. The reaction obeyed the usual pseudo-first-order rate law, and the apparent second-order rate constant ($k_{a,obsd}$) for the hydrolysis of an ester substrate was evaluated by eq 3. where $k_t$ and $k_s$ refer, respectively, to the

$$k_{a,obsd} = (k_t - k_s)/[\text{nucleophile}]_0 \qquad (3)$$

oberved first-order rate constants for the hydrolytic cleavage (hydrolysis) of D(L)-ZS and D(L)-$S_{12}$ with and without an nucleophile and $[\text{nucleophile}]_0$ indicates the initial nucleophile concentration.

The clear stock solutions were prepared by dissolving both nucleophile and surfactant in Tris-KCl buffer with sonication (Braun Sonic Model B 3200 apparatus, 90 W) at 50 °C for 1 h.

**Acknowledgment.** We thank Messrs. Kenji Fujiwara and Hironobu Hirasa for their technical assistance.

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# Use of Zinc Borohydride as an Efficient and Highly Selective Reducing Agent. Selective Reduction of Ketones and Conjugated Aldehydes over Conjugated Enones

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Selective reduction of one carbonyl group in the presence of other such groups with a minimum of damage to the sensitive portions of a molecule is an important synthetic operation.[1] This frequent requirement has stimulated considerable interest, leading to the development of new reagents and new methods for such selective reductions.[2] The selectivity is generally achieved by the use of modified hydride reagents which are formed by the replacement of hydride with sterically bulky substituents or electron-withdrawing groups in order to discriminate between the structural or electronic environments of the carbonyl groups.[1,2] We describe herein a convenient and efficient methodology for the selective reduction of saturated ketones and conjugated aldehydes over conjugated enones using zinc borohydride without any modification. Although zinc borohydride has been used for the specific reduction of carbonyl groups in a number of cases,[3] to the

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