Tetrahedron Letters,Vol.25,No.13,pp 1363-1366,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

ISOKINETIC DISCRIMINATION OF ARTIFICIAL MEMBRANE SYSTEMS IN THE ENANTIOSELECTIVE HYDROLYSIS

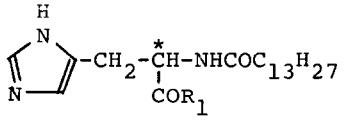
Ryuichi Ueoka*, Yōko Matsumoto, Toshiro Nagamatsu, and Syoichi Hirohata

Department of Industrial Chemistry, Kumamoto Institute of Technology, Kumamoto 860, Japan

Summary: The enantioselectivity was markedly enhanced by addition of cholesterol and micelles for the deacylation of p-nitrophenyl N-dodecanoyl-D(L)-phenylalaninates catalyzed by L-histidine derivatives in artificial membrane systems and this would be attributed to the change of hydrophobic microenvironments on the basis of the isokinetic temperature (β) in connection with $\bar{T}$ (average of experimental temperature)

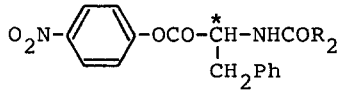
The isokinetic relationships for the reaction systems have been studied in detail by Leffler.[1] Very recently, the authors have attempted to classify into three catalytic systems (micellar, bilayer, or macromolecular system) on the basis of the isokinetic temperature (β) for the hydrolysis of various phenyl esters catalyzed by L-histidine derivatives and hydroxamic acids.[2,3]

In this paper, we wish to demonstrate the interrelation between the reaction field of artificial membrane systems and the β value in the enantioselective deacylation of p-nitrophenyl N-acyl-D(or L)-phenylalaninates (D(or L)-S_n; n=2 and 12) and N-benzyloxycarbonyl-D(L)-phenylalaninates (D(L)-ZS) by the bilayer catalytic systems of L-histidine derivatives (N-tetradecanoyl-L-histidine (MyrHis) and N-tetradecanoyl-L-histidyl-L-leucine (MyrHisLeu)) and bilayer surfactants (didodecyldimethylammonium bromide ($2C_{12}$) and ditetradecyldimethylammonium bromide ($2C_{14}$)) with and without the other compositions (cholesterol (Chol) and hexadecyltrimethylammonium bromide (CTAB)).



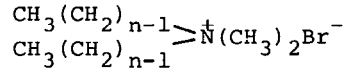
MyrHis (R_1=OH)

MyrHisLeu (R_1=NHCHCH$_2$CH(CH$_3$)$_2$, COOH)

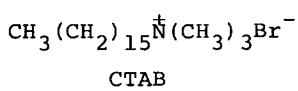


D(L)-ZS (R_2=PhCH$_2$O), D(L)-S_2 (R_2=CH$_3$)

D(L)-S_{12} (R_2=CH$_3$(CH$_2$)$_{11}$)



$2C_{12}$ (n=12), $2C_{14}$ (n=14)



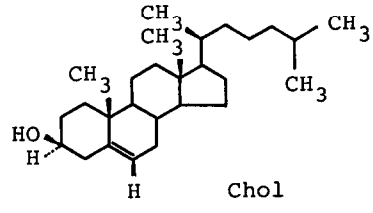
CTAB

Table 1 The Deacylation Rates ($k_{a,obsd}$, $sec^{-1}M^{-1}$) and Stereoselectivity ($k^{L}_{a,obsd}/k^{D}_{a,obsd}$) at pH 7.6 and 25 °C[a)]

Catalytic system	L-S_2	D-S_2	L/D	L-S_{12}	D-S_{12}	L/D
MyrHis + $2C_{12}$	340	130	2.6	1500	380	3.9
MyrHis + $2C_{12}$ + Chol	-	-	-	2100	410	5.1
MyrHis + $2C_{12}$ + CTAB	110	52	2.1	680	100	6.8
MyrHisLeu + $2C_{12}$	67	50	1.3	670	130	5.2
MyrHisLeu + $2C_{12}$ + Chol	-	-	-	1200	160	7.5
MyrHisLeu + $2C_{12}$ + CTAB	80	55	1.5	960	76	13
MyrHis + $2C_{14}$	-	-	-	1800	340	5.3
MyrHisLeu + $2C_{14}$	130	95	1.4	560	50	11
MyrHisLeu + $2C_{14}$ + CTAB	43	25	1.7	560	36	16
MyrHis + CTAB	130	70	1.9	740	190	3.9
MyrHis + CTAB +Chol	-	-	-	750	170	4.4
MyrHisLeu + CTAB	48	29	1.7	280	30	9.3

a) 0.083 M Tris buffer (0.083 M KCl), 3 %(v/v) CH_3CN-H_2O, [Sub]=$1x10^{-5}$ M, [MyrHis]=$5x10^{-5}$ M, [MyrHisLeu]=$3x10^{-5}$ M, [$2C_{12}$]=[$2C_{14}$]=$1x10^{-3}$ M, [CTAB]=$3x10^{-3}$ M, [Chol]=$(1.5 - 2.2)x10^{-4}$ M.

The catalytic efficiency (reflected in the rate constant, $k_{a,obsd}$)[4] and the stereoselectivity (reflected in $k^{L}_{a,obsd}/k^{D}_{a,obsd}$) for the deacylation of S_n (n=2 and 12) catalyzed by MyrHis or MyrHisLeu are summarized in Table 1. The noteworthy aspects are as follows: (a) The hydrophobic acyl chain in the S_{12} substrate is of great importance to the enhancement of rate constants and enantioselectivity; With respect to the enantioselective deacylation of the long-chain substrate (S_{12}), (b) the L-histidine derivative including two amino acid parts (L-histidine and L-leucine) elevated the enantioselectivity more and reduced the catalytic efficiency more when compared with that including only L-histidine part; (c) the values of $k_{a,obsd}$ and $k^{L}_{a,obsd}/k^{D}_{a,obsd}$ were enhanced by addition of cholesterol in the bilayer catalytic systems of MyrHis + $2C_{12}$ and MyrHisLeu + $2C_{12}$, though no effect was observed in the micellar catalytic system of MyrHis + CTAB; (d) the enantioselectivity was markedly enhanced by adding micelles (CTAB) to the bilayer catalytic systems, and it is especially



Chol

notable that the high enantioselectivity ($k^{L}_{a,obsd}/k^{D}_{a,obsd}$ = 13 and 16) was attained in the catalytic systems of MyrHisLeu + $2C_{12}$ + CTAB and MyrHisLeu + $2C_{14}$ + CTAB, respectively.

The activation parameters ($\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$) were evaluated using Equation (1) on the basis of the rate constants ($k_{a,obsd}$): $\Delta G^{\ddagger} = 2.303RT\log(kT/hk_{a,obsd}) = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$, (1) where k and h stand for Boltzmann and Planck constants, respectively Furthermore, the β values have been determined by plotting $\Delta H^{\ddagger}$ against $\Delta S^{\ddagger}$ according to Equation (2) and are summarized in Table 2. $\Delta H^{\ddagger} = \Delta H^{\ddagger}_{0} + \beta\Delta S^{\ddagger}$, (2) where $\Delta H^{\ddagger}_{0}$ is simply the intercept of $\Delta H^{\ddagger}$ corresponding to $\Delta S^{\ddagger} = 0$.

Table 2 Isokinetic Temperature (β)[a)]

Catalytic system	β (K)[b)]	$\bar{T}$ (K)[c)]	$\beta-\bar{T}$ (K)
MyrHis + $2C_{12}$	269 ± 8	296	-27 ± 8
MyrHis + $2C_{12}$ + Chol	332 ± 8	298	+34 ± 8
MyrHis + $2C_{12}$ + CTAB	302 ±11	300	+2 ±11
MyrHisLeu + $2C_{12}$	252 ± 9	296	-44 ± 9
MyrHisLeu + $2C_{14}$	287 ± 2	308	-21 ± 2
MyrHis + CTAB	363 ±14	300	+63 ±14
MyrHis + CTAB + Chol	325 ±12	298	+27 ±12
L-histidine derivatives + $2C_{12}$[d)]	275 ± 4	303	-28 ± 4
L-histidine derivatives + micellar surfactants[d)]	320 ± 2	303	+17 ± 2

a) The reaction conditions are the same to those as described in Table 1. The D(L)-S_n (n=2 and 12) and D(L)-ZS substrates were employed in this study
b) The error limits were obtained by the standard error treatment.
c) Average value of experimental temperatures.
d) See Ref. 3.

It is known that hydrophobic interactions are mainly entropy driven while lyophobic ones are mainly enthalpy driven.[5,6] On the basis of the β value in connection with $\bar{T}$, it is acceptable that the bilayer (liquid crystalline)[7] catalytic systems tend to be governed by the entropy of activation, that is, $\bar{T}$ exceeded ($\beta - \bar{T} = -21 \sim -44$), though the comicellar catalytic systems tend to be governed by the enthalpy of activation ($\beta - \bar{T} = +17 \sim +63$). These results suggest that the stereoselective deacylation in the liquid-crystalline bilayer systems would

proceed through a stronger hydrophobic interaction between reactants. Interesting to note is that, however, the β value in the bilayer catalytic system of MyrHis + $2C_{12}$ is elevated markedly by addition of cholesterol. The enhancement of catalytic efficiency and stereoselectivity would be attributed the change of membrane fluidity resulting from addition of cholesterol, because the catalytic system of MyrHis + $2C_{12}$ + Chol is enthalpy driven ($\beta - \bar{T} = +34 \pm 8$ K). It is also noteworthy that the addition of CTAB to the bilayer catalytic system of MyrHis + $2C_{12}$ elevated the β value, that is, the β value (302 $\pm$11 K) in the system of MyrHis + $2C_{12}$ + CTAB is larger than that (269 $\pm$ 8 K) in the bilayer system of MyrHis + $2C_{12}$ and is smaller than that (363 $\pm$14 K) in the micellar system of MyrHis + CTAB. This result suggests that the CTAB micelles change the hydrophobicity of the membrane matrix and that the systems of MyrHisLeu + $2C_{12}$ + CTAB and MyrHisLeu + $2C_{14}$ + CTAB might present an appropriately strong (not too strong and not too small) hydrophobic environment for the greater enhancement of enantioselectivity.

REFERENCES

1. J. E. Leffler, J. Org. Chem., 20, 1202 (1955).
2. R. Ueoka, Y. Matsumoto, Y. Furuya, and M. Shiraishi, Nippon Kagaku Kaishi, 1983, 1412.
3. Y. Matsumoto and R. Ueoka, Bull. Chem. Soc. Jpn., 56, 3370 (1983).
4. The apparent second-order rate constants ($k_{a,obsd}$) were evaluated from $(k_t - k_s)/[Cat]_0$, where k_t and k_s denote the first-order rate constants with and without nucleophile, respectively.
5. G. Nemethy. Angew. Chem., Int. Ed. Engl., 6, 195 (1967); Ann. N. Y. Acad. Sci., 155, 492 (1969).
6. C. G. Overberger, R. C. Glowaky, and P. -H. Vandewyer, J. Am. Chem. Soc., 95, 6008 (1973).
7. The reactions in the bilayer catalytic systems were carried out above the phase transition (crystalline-liquid crystalline) temperature (T_c). The T_c values were determined to be 5-10 °C and 16 °C for the aqueous solutions of $2C_{12}$ and $2C_{14}$, respectively, by using a differential scanning calorimeter described in Y. Okahata, S. Tanamachi, and T. Kunitake, Nippon Kagaku Kaishi, 1980, 442.

(Received in Japan 3 December 1983)