Chiral Reaction Field for Highly Stereoselective Hydrolysis of Enantiomeric Esters

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Chiral co-aggregates provide an effective and remarkably stereoselective reaction field for the hydrolytic cleavage of enantiomeric esters by dipeptide catalysts.

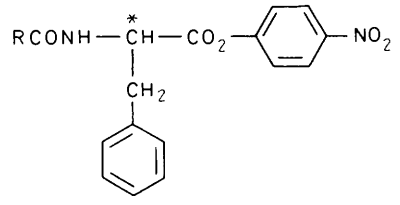
In previous papers,[1,2] we observed that comicelles of optically active *N*-acylhistidine or dipeptide derivatives, and cationic surfactants are effective stereoselective catalysts for the cleavage of enantiomeric esters. Recently, Ueoka[3] and others[4] demonstrated high stereoselective deacylation behaviour in the catalytic hydrolysis of long chain enantiomeric esters by di- or tri-peptide catalysts in the presence of vesicular and co-aggregate surfactant systems. Moreover, Ohkubo[5] found high stereoselectivity of short-chain esters in the catalytic vesicular system at low ionic strength. These results strongly suggest that the stereoselective hydrolysis in surfactant aggregates is easily controlled by changing the reaction field, *e.g.* changing the composition of the aggregates, the ionic strength, the amino acid sequence in peptide catalysts, and the reaction temperature.

Accordingly, a chiral vesicular surfactant and its co-aggregate system could provide a good reaction field for stereoselective hydrolysis of enantiomeric esters. This study led to very highly stereoselective hydrolysis of short-chain, as well as long-chain, *N*-acyl amino acid *p*-nitrophenyl esters (**1**)

Table 1. Rate constants and stereoselectivity for the hydrolysis of D(L)-(**1a** and **b**) by (**2a** and **b**) in the presence of chiral surfactant (**3**) and CTAB.[a]

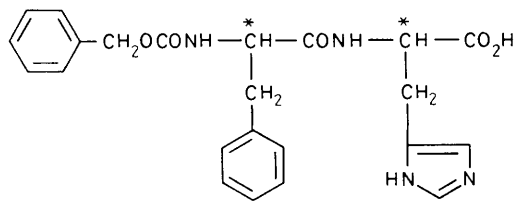
		k_c/mol^{-1} dm^3 s^{-1}					
		(**1a**)			(**1b**)		
Surfactant	Catalyst	L	D	L/D(D/L)	L	D	L/D(D/L)
(**3**)	(**2a**)	487	3.8	130	612	74	8.3
	(**2b**)	12.8	534	42	92	494	5.4
CTAB	(**2a**)	622	34.2	18	617	62	10
	(**2b**)	34.5	600	17	65	599	9.2

[a] With pH 7.30, Tris buffer (0.02 M), 25 °C, [(**1a** or **b**)] = 0.8—1.0 × 10^{-5} M, [(**2a** or **b**)] = 1.00 × 10^{-4} M, [(**3**)] = 1.00 × 10^{-3} M, [CTAB] = 2.00 × 10^{-3} M. The k_c values have maximum errors of ±5%.



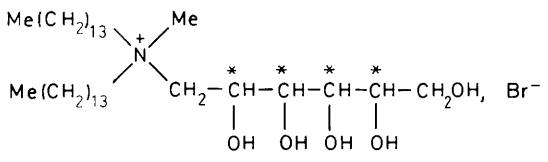
(**1**)

a; R = Me
b; R = $Me(CH_2)_{10}$



(**2**)

a; (*Z*)-L-Phe-L-His
b; (*Z*)-D-Phe-D-His



(**3**) $2C_{14}$Glu

by the simple optically active catalyst, *N*-benzyloxycarbonylphenylalanylhistidine (**2**), in the chiral surfactant (**3**), derived from *N*-methyl-D-glucamine, and co-aggregate systems with CTAB [$Me(CH_2)_{15}\overset{+}{N}Me_3Br^-$]. This is a good example of controlling the stereoselectivity in the chiral reaction field.

The hydrolyses of the substrates were examined under the conditions of [surfactant] > [catalyst] > [substrate], at pH 7.30, Tris buffer (0.02 M), and 25 °C. The pseudo-first-order rate constant k_ψ was determined by monitoring the release of the *p*-nitrophenolate ion at 400 nm. The catalytic rate constant, k_c, was calculated from the following equation, $k_c = (k_\psi - k_{surfactant})/[catalyst]$, where $k_{surfactant}$ refers to the spontaneous hydrolysis in the presence of surfactant.

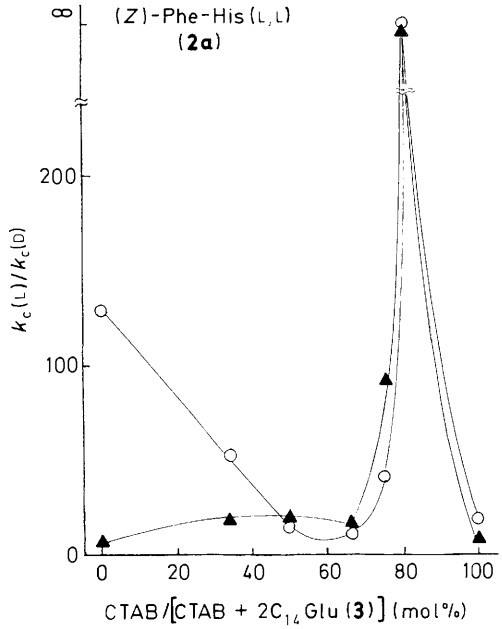


Figure 1. Stereoselectivity, k_c(L)/k_c(D), for the hydrolysis of D(L)-(**1a** and **b**) by (**2a**) *vs.* co-aggregate composition at 25 °C and pH 7.30 (0.02 M Tris buffer). *Conditions*: pH 7.30, Tris–HCl buffer, 25 °C, [(**3**)] = 1.00 × 10^{-3} M, [(**2a**)] = 1.00 × 10^{-4} M, [(**1a** and **b**)] = 0.8—1.0 × 10^{-5} M. ○ = (**1a**); ▲ = (**1b**).

Table 1 summarizes the catalytic rate constants and stereoselectivities (L/D or D/L) for cleavage of two enantiomeric substrates (**1**) by optically active dipeptide catalysts (**2a** and **b**) in the presence of the chiral surfactant (**3**) and CTAB alone. It was found that L,L-catalyst (or D,D-catalyst) stereoselectively hydrolyses the L-enantiomer (or D-enantiomer) of both substrates in all cases. This indicates that the stereoselective control is mainly determined by catalytic acyl transfer to the optically active imidazole group of the catalyst. However, the rate and stereoselectivity for the hydrolysis of both enantiomeric substrates show remarkable dependency on both catalytic systems. Reactions with L,L-(**2a**) and D,D-(**2b**) in micellar CTAB produce the same rate difference between both D- and L-substrate in opposite direction within experimental error. On the other hand, a comparison of L,L-(**2a**) and D,D-(**2b**) in vesicular (**3**) shows apparently different rate and stereoselectivity in the hydrolysis of both enantiomers. Thus, reaction of the short chain substrate (**1a**) with L,L-(**2a**) in vesicular (**3**) gives the largest stereoselectivity.

The effect of composition of the co-aggregates [(**3**) and CTAB] on the stereoselectivity was then studied. Figure 1

shows the stereoselectivity for the hydrolysis of D(L)-(**1a** and **b**) by (**2a**) *vs.* co-aggregate composition. The following observations derive from Figure 1. Firstly, the stereoselectivity in the vesicular system of (**3**) is dramatically affected by adding CTAB, it increases to a maximum then decreases as the composition of CTAB in the co-aggregate system increases. Secondly, the optimum stereoselectivities are observed on the co-aggregates composed of 80% CTAB and 20% (**3**) with both short chain and long chain substrates, respectively.

The above results strongly suggest that to achieve high stereoselectivity it is important for the chiral groups to be positioned near the polar head region of the surfactant, where the catalyst and substrate are incorporated into the surface of these co-aggregates, leading to an effective orientation between the reactants. In fact, the chiral surfactant plays an important role in the stereoselective reaction field, where the catalyst is very stable and capable of conforming to optimally fit one of the enantiomers. In addition, the stereoselectivities on the hydrolysis of both enantiomeric esters with the dipeptide catalyst increase to a maximum and then decrease as the composition of vesicular surfactant decreases. This suggests the importance of the combination of specific interactions such as steric, hydrophobic, and hydrogen bonding in this reaction field. In fact, adjusting the hydrophobic microenvironment to the optimum fit of the catalysts and substrates by changing the composition of the co-aggregates would induce the high stereoselectivity.

In conclusion, the present study demonstrates an interesting kinetic aspect which clearly shows the presence of the enzyme characteristics of stereoselectivity in chiral co-aggregate systems. Experiments are now being carried out in order to investigate the mechanisms which will clarify the stereochemical features in these reaction fields.

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