Stereoselective Reaction of *p*-Nitrophenyl *N*-Acyl-phenylalanines with *N*-Acyl-L-histidine in Mixed Micelles

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Summary Mixed micelles of the *N*-acyl-L-histidine (I) and the cationic surfactant (III) are effective stereoselective catalysts for deacylation of the *p*-nitrophenyl *N*-acyl-phenylalanines (II); increasing the chain length of the acyl group of (I) increases both the reaction rates and the enantiomer rate ratio.

THERE has been little study of stereochemical effects in micelle-catalysed reactions; stereospecific ester-catalysed hydrolysis occurred in the presence of optically active functional micelles[1,2] but no appreciable specificity was observed in the presence of simple optically active surfactants[3] and functionalized surfactants containing amino acid groups at the polar head.[4,5]

This study describes the stereoselective behaviour of optically active mixed micelles when used as catalysts for cleavage of the enantiomeric substrates (II).

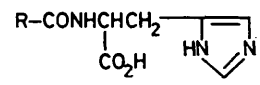
Reaction rates were followed by the spectrophotometric determination of *p*-nitrophenolate (400 nm) at 25 °C, pH 7·30. From the slope of the linear part of a plot of the observed rate constants (k_ψ) against the concentration of (I) in a $2{\cdot}00 \times 10^{-3}$ M aqueous solution of (III), the apparent catalytic rate constants (k_c) in Table 1 were evaluated.

TABLE 1. Apparent catalytic rate constants k_c in the presence of mixed micelles[a]

	k_c l mol^{-1} s^{-1}		
	L	D	k_c(L)/k_c(D)
(Ia)	2·75	1·96	1·4
(Ib)	174	101	1·7
(Ic)	1730 (877)	690 (403)	2·5 (2·2)
(Id)	2740	985	2·8
(Ic)[b]	(1·02)	(0·805)	(1·3)

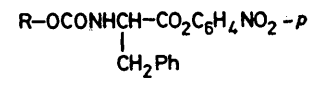
[a] In $2{\cdot}00 \times 10^{-3}$ M (III), at pH 7·30, 0·02 M phosphate buffer, 25 °C, [(IIa)] = $1{\cdot}0 \times 10^{-5}$ M, unless specified otherwise. Values in parentheses are for (IIb). The k_c values are calculated by least-squares and generally have correlation coefficients >0·98. [b] In the absence of surfactants.

The results show that the mixed micelles of (I) and the cationic surfactant (III) catalyse stereoselective deacylation of the enantiomers (II). L-(II) is consistently more reactive than D-(II). Increase in chain length of the acyl group of (I) increases both the reaction rates and the enantiomer rate ratio. Similar kinetic behaviour was observed



(I)

a; R = Me
b; R = Ph
c; R = $Me[CH_2]_8$
d; R = $Me[CH_2]_{16}$



(II)

a; R = $PhCH_2$
b; R = Me

$Me[CH_2]_{15}{}^+NMe_3Br^-$

(III)

on comparison of the *N*-acyl groups of (IIa) and (IIb) in mixed micelles of (Ic) and (III). The hydrophobicity of the acyl part is an important requirement for a high degree of stereochemical control of the enantiomeric substrates (II).

TABLE 2. Rate constants ($k_\psi - k_{surfactant}$) on variation of surfactant concentrations[a]

10^3[(III)]/M	$10^2(k_\psi - k_{surfactant})$ s^{-1}		
	L	D	Ratio (L/D)
1·00	65·3 (26·4)	28·6 (12·0)	2·3 (2·2)
2·00	33·7 (17·7)	14·2 (8·08)	2·4 (2·2)
4·00	16·2 (9·42)	6·48 (4·44)	2·5 (2·1)
6·00	11·1 (5·98)	4·39 (2·58)	2·5 (2·3)
8·00	8·16 (4·36)	3·48 (2·05)	2·3 (2·1)

[a] In $2{\cdot}00 \times 10^{-4}$ M (Ic) at pH 7·30, 0·02 M phosphate buffer, 25 °C, [(IIa)] = $1{\cdot}0 \times 10^{-5}$ M. The values in parentheses are for (IIb).

The catalytic properties of (Ic) were measured with various concentrations of the surfactant (III), and are shown in Table 2 with the apparent rate constants (k_{ψ} — $k_{surfactant}$) for the reaction of (II). At higher ratios the rates decrease but the enantiomer rate ratio is almost unchanged when (Ic) is diluted with (III). These results demonstrate that the stereochemical control is mainly determined by attack of the optically active imidazole group of (I). Gitler *et al.*[6] found that the hydrolysis of common *p*-nitrophenyl esters catalysed by mixed micelles of *N*-myristoryl-L-histidine and (III) involves nucleophilic transacylation and rate determining formation of an acylimidazole. There is probably no stereoselective discrimination due to interactions requiring micellar chirality of simple optically active surfactants.

In these experiments, normal saturation type kinetics were observed on variation of the mixed micelle concentrations above the c.m.c. at a constant ratio of (III) to (I). Treatment† of the data from the reaction of mixed micelles of (Ic) and (III) with (IIb) at a constant ratio [molar ratio of (Ic) to (III) 1 : 5] gives values of k_m (L) = 0·424 s^{-1}, and k_m (D) = 0·206 s^{-1}, $k_m(L)/k_m(D)$ = 2·1. The dissociation constants are $K(L) = 6{\cdot}38 \times 10^{-4}$ M, and $K(D) = 6{\cdot}47 \times 10^{-4}$ M. Correlation coefficients are >0·98. These results suggest that this selectivity is a consequence of differences in the free energies of the transition state complexes between the *N*-acyl-L-histidines (I) and the enantiomeric substrates (II) in mixed micelles, as described by Brown and Bunton[2] for an optically active surfactant derived from L-histidine methyl ester.

In conclusion, the present study demonstrates that the stereoselectivity in mixed micelles is mainly determined by nucleophilic acylation of the optically active imidazole group of (I) and is associated with incorporation of (I) into the surface of the micelles leading to an effective interaction between catalyst and substrate.

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† Under conditions [(III)] > [(Ic)] > [(IIb)] using the following kinetic scheme:

$$S + M \overset{K}{\rightleftharpoons} MS \overset{k_m}{\rightarrow} \text{products}; \quad S \overset{k_o}{\rightarrow} \text{products},$$

where S and M are substrate (IIb) and total mixed micelle [(Ic) + (III)], respectively. This scheme differs from that proposed by Gitler *et al.* (ref. 6) because the dissociation constants changed appreciably with the nature of (I). For example, see T. Inoue, K. Nomura, and H. Kimizuka, *Bull. Chem. Soc. Japan*, 1976, **49**, 719.

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