Enantioselective Deacylation of Long Chain *p*-Nitrophenyl *N*-Acylphenylalanates by *N*-(*N*-Dodecanoyl-L-histidyl)-L-leucine and a Cationic Chiral Surfactant

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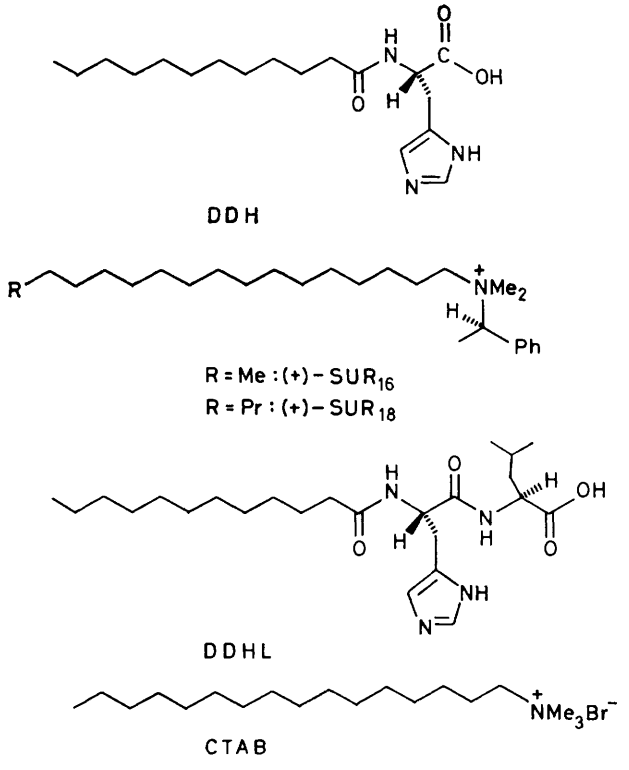
Summary Enhanced enantioselectivity (k_{cat}^{L}/k_{cat}^{D} 5·5—5·7) was observed in the deacylation of $H[CH_2]_{n-1}$—$CONHCH(CH_2Ph)CO_2C_6H_4NO_2$-*p* possessing long acyl chains (n 10—16) by comicelles of *N*-(*N*-dodecanoyl-L-histidyl)-L-leucine and (*R*)-(+)-*N*-α-methylbenzyl-*NN*-dimethyloctadecylammonium bromide.

ALTHOUGH the enantioselective deacylation of *N*-protected amino acid esters by functionalized surfactants, including amino acid groups,[1-3] or by mixed micelles of *N*-acyl-L-histidine and hexadecyltrimethylammonium bromide[4-6] has recently been documented, there has been no report of the enhancement of enantioselectivity in the micellar-catalysed deacylation of amino acid esters possessing a relatively long acyl chain by dipeptide-type nucleophiles and cationic chiral surfactants. We describe an example of such an enhanced selectivity which was observed in the deacylation of *p*-nitrophenyl *N*-acylphenylalanates, $H[CH_2]_{n-1}$—$CONHCH(CH_2Ph)CO_2C_6H_4NO_2$-*p* ($S_n$; *n* 2—16), by five different comicellar systems: (A) *N*-dodecanoyl-L-histidine (DDH) and (*R*)-(+)-*N*-α-methylbenzyl-*NN*-dimethylhexadecylammonium bromide [(+)-SUR_{16}]; (B) DDH and (*R*)-(+)-*N*-α-methylbenzyl-*NN*-dimethyloctadecylammonium bromide [(+)-SUR_{18}]; (C) *N*-(*N*-dodecanoyl-L-histidyl)-L-leucine (DDHL) and (+)-SUR_{16}; (D) DDHL and hexadecyltrimethylammonium bromide (CTAB); and (E) DDHL and (+)-SUR_{18}.

The rate constants for these reactions, with and without the nucleophile (k_{ψ} and $k_{surfact}$, respectively), were obtained from good pseudo-first-order deacylation rates followed by spectrophotometric determination of *p*-nitrophenolate (400 nm) at 25 °C (pH 7·61), and the apparent catalytic rate constant (k_{cat}) was taken as the average value obtained from more than three reactions repeated under identical conditions. In the deacylation of S_{10} (5×10^{-5} M) by (A) or (B) {[DDH] 9×10^{-5} M and [(+)-SUR_m, (*m* 16 or 18)] ($0{\cdot}45$—$4{\cdot}5$) $\times 10^{-3}$ M} at 25 °C (pH 7·61), the stereoselectivity (k^{L}_{cat}/k^{D}_{cat}) fell in the range of 2·2—4·4 or 2·9—3·2, respectively, and the highest selectivity was obtained with $2{\cdot}5 \times 10^{-3}$ M SUR_{16} or $1{\cdot}8 \times 10^{-3}$ M SUR_{18}. Therefore, the fixed surfactant concentrations ($2{\cdot}5 \times 10^{-3}$ M for (+)-SUR_{16} or CTAB and $1{\cdot}8 \times 10^{-3}$ M for (+)-SUR_{18}) were used in the deacylation of 5×10^{-5} M S_n (*n* 2—16) by 9×10^{-5} M DDH (or DDHL).



The structural effects of surfactants on the stereoselective comicellar catalysis were first recognized in the deacylation of S_n (*n* 2—16) by comicelles of (C) and (D). The Figure indicates that (C) gave appreciably higher deacylation rates for S_n (*n* 2—16) and higher stereoselectivity for the long chain S_n (*n* 10—16) than (D). The lengthening of the acyl chain in S_n from *n* 10 to *n* 16 increased the deacylation rate and had little effect on the selectivity in the case of (C), but it decreased both the rate and the selectivity in the case of (D). It can be deduced, therefore, that the hydrophobicity of the α-methylbenzyl group at the polar head of the chiral surfactant in the comicelle (C) plays an important role in the enhancement of both the deacylation rate and the selectivity.

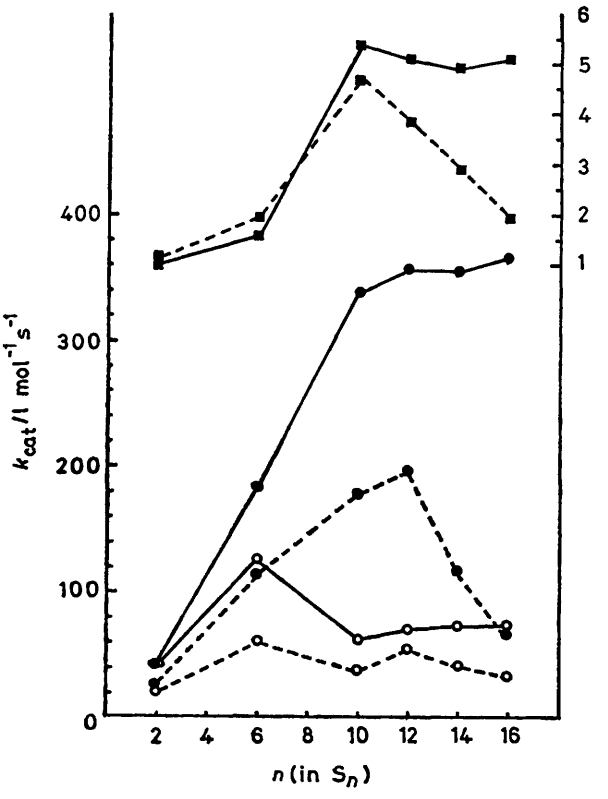


FIGURE. Effects of surfactant structure and acyl chain length. (Reaction conditions are the same as in the Table except [surfactant] = $2{\cdot}5 \times 10^{-3}$ M.) Solid line: comicelles (C). Dotted line: comicelles (D) ○: D-S_n, ●: L-S_n, ■: k^{L}_{cat}/k^{D}_{cat}.

The Table shows the difference between the stereoselective catalysis of (B) and of (E). The rate increased with increasing chain length up to *n* 14 or *n* 12 in the L-S_n deacylation by (E) or (B), respectively, while it increased up to *n* 6 in the D-S_n deacylation by (B) or (E). The rate enhancement of

TABLE. Effects of acyl chain length[a]

	k_{cat}/l mol^{-1} s^{-1}		
n(in S_n)	L	D	k^{L}_{cat}/k^{D}_{cat}
2	33(93)	34(59)	1·0(1·6)
6	186(338)	71(199)	2·6(1·7)
10	286(341)	52(113)	5·5(3·0)
12	332(370)	58(102)	5·7(3·6)
14	346(350)	61(119)	5·7(2·9)
16	334(429)	61(129)	5·5(3·3)

[a] Tris buffer (0·08 M) containing 0·08 M KCl at 25 °C (pH 7·61) in 10% (v/v) Me CN–H_2O; [nucleophile] 9×10^{-5} M, [S_n] 5×10^{-5}M, and [surfactant] $1{\cdot}8 \times 10^{-3}$ M. Values in parentheses are for the S_n deacylation by (B).

L-S_n deacylation induced by changing the chain length from *n* 2 to *n* 10—16 was about 10-fold for (E) or 4-fold for (B), while it was only about 2-fold for the D-S_n deacylation by (B) or (E). It is also noteworthy that the rate of D-S_n (*n* 2—16) deacylation by (E) was about one half that by (B), while the rate of L-S_n (*n* 10—16) deacylation by (E) was almost the same as that by (B). Therefore, the enantioselectivity was enhanced in the S_n (*n* 10—16) deacylation,

and the extent of the selectivity enhancement was more marked in the reaction with (E) than that with (B). Since the stereoselective efficiency of (+)-SUR_{16} *per se* was negligibly small ($k^{L}_{surfact}/k^{D}_{surfact}$ 1·00—1·08), the structural difference between the nucleophiles resulted in a different extent of selectivity enhancement. In this sense, the L-leucine unit of the dipeptide-type nucleophile might contribute to an increase in the enantioselectivity of the S_n (n 10—16) deacylation, partly through steric hindrance against the incorporation of D-S_n (n 6—12) by the comicelles, and partly through the hydrophobic interaction with L-S_n (n 10—16).

Finally, the stereoselective process of this comicellar catalysis is discussed in terms of the binding constants (K_b) obtained for the deacylation of S_{10} by (A) {[DDH] (3·6—9·0) × 10^{-5} M, [(+)-SUR_{16}] (1·0—2·5) × 10^{-3} M, and [DDH]/[(+)-SUR_{16}] 0·036} at 25 °C (pH 7·61). The K_b/N (N is the aggregation number) and k values, obtained in the usual way,[7] for the following simplified micellar reactions [equations (1) and (2)] were 677 l mol^{-1} for L-S_{10} (1418 l mol^{-1} for D-S_{10}) and 2·92 min^{-1} for L-S_{10} (1·23 min^{-1} for D-S_{10}), respectively.

$$S_{10} + M \overset{K_b}{\rightleftharpoons} MS_{10} \overset{k}{\longrightarrow} P \quad (1)$$

$$S_{10} \overset{k'}{\longrightarrow} P \quad (2)$$

M = Comicelles of (A); MS_{10} = Substrate complex; P = *p*-Nitrophenol.

Since the *p*-nitrophenyl unit of L-S_{10} closely approaches the imidazolyl group of the nucleophile (the same unit is well separated from the nucleophilic part) *via* hydrophobic interaction between the phenyl (substrate) and imidazolyl (nucleophile) groups and/or *via* inter-amide bonding,[1] the L-enantiomer is more easily hydrolysed by the nucleophilic imidazolyl group (there is no imidazolide anion catalysis in this reaction) than the D-enantiomer, even though the steric hindrance of the L-enantiomer against substrate incorporation by the comicelles is larger than that of the D-enantiomer.

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