Stereoselective Micelle-promoted Ester Hydrolysis

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Summary The functional surfactant (**2**) forms micellar aggregates which promote rapid and enantioselective deacylation of *p*-nitrophenyl esters.

N-METHYLCAPROLACTAM is converted into 5-carboxyheptadecyltrimethylammonium chloride (**1**) by successive alkylation with dodecyl bromide,[1] hydrolysis, methylation, and finally acid hydrolysis.‡ The corresponding acid chloride reacts with L-histidine methyl ester giving (**2**) (33% yield after recrystallisation from CH_2Cl_2–$CHCl_3$). This is thought to be one pure diastereoisomer on the basis of its sharp m.p., 172—173°, ^{13}C n.m.r. spectrum,§ and c.d. curve [pronounced ellipticity below 200 nm, Φ 196 (H_2O) 6300; Φ 190 (H_2O) −4750, unlike L-histidine methyl ester, Φ 196 (H_2O) ⩽500].

The surfactant (**2**) in 0·02M aqueous phosphate buffer solution, pH 7·35 at 25° is a powerful catalyst for deacylation of either *R*-(−)- or *S*-(+)-*p*-nitrophenyl 2-phenylpropionate (**3**).[2] The shape of the rate constant–surfactant concentration curve clearly demonstrates that catalysis is associated with the formation of micelles, becoming marked above $[(\mathbf{2})] \geqslant 5{\cdot}5 \times 10^{-4}$M. Rate measurements over a pH range 6·38—7·51 in 0·02M phosphate buffer solutions indicate that catalytic activity requires a reactive group of $pK_a = 6{\cdot}7$, and independent spectrophotometric deter-

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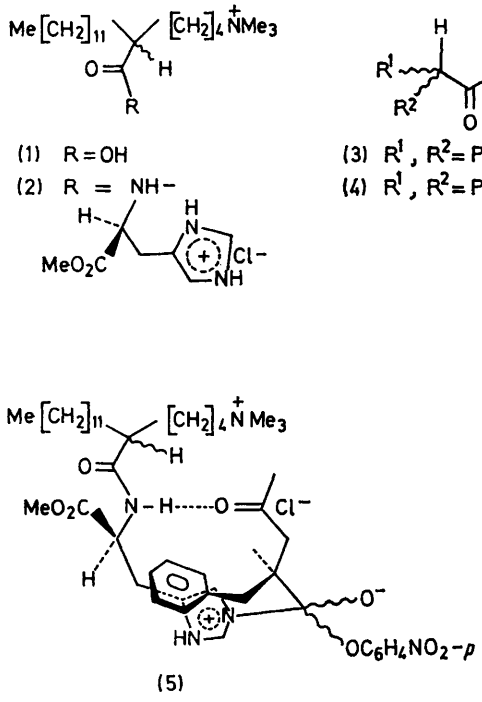
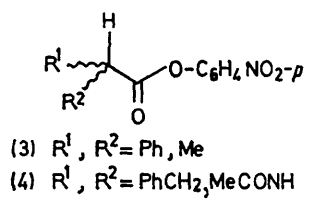
‡ Reagents: n-$C_{12}H_{25}Br$, Pr^i_2NLi, tetrahydrofuran, −80° (78%); 6N-HCl, 110° (66%); MeBr, K_2CO_3; H_2O, $CHCl_3$ (98%); 3N-HCl, slow evacuation (78%).

§ δ(D_2O; 40 °C), 179·4 (*CO_2Me), 173·4 (*CONH),[1] 134·8 (γ-C), 130·5 (ε-C), 118·5 (δ-C), 67·7 (1-C), 54·4 (NMe), 54·0 (α-C), 53·1 (CO_2Me), 47·8 (5-C), 34·3 (4-C), 33·5 (6-C), 33·1 (15-C), 30·9 (CH_2), 28·5 (7-C), 27·2 (β-C), 25·0 (3-C), 23·8 (2- and 16-C), and 15·2 (17-C) p.p.m. The residues from recrystallisation of (**2**) contain a compound with a similar, but non-identical, ^{13}C n.m.r. spectrum and very different solubilities, which has not yet been obtained pure.

mination of the pK_a of (2) above the critical micelle concentration confirms this value for the imidazole residue. At high surfactant concentrations the values of rate constant describe a plateau, consistent with an imidazole-mediated reaction, but not[3] with micelle-promoted hydroxide-ion catalysed hydrolysis. *R*-(−)-(3) is consistently more reactive than *S*-(+)-(3) in micellar hydrolysis. Treatment of the data by established procedures[4] and





(5)

making the usual simplifying assumptions gives values of k_m (*S*) = 3·23 × 10^{-2} s^{-1}, and k_m (*R*) = 3·62 × 10^{-2} s^{-1}, *i.e.* rate enhancements of 260 and 283 over the (phosphate-catalysed) reaction in the absence of (2). There is no discrimination in binding efficiency of the enantiomers for the binding constants per micelle are equal within experimental error: $K(R)/N$ = 2680,[5] $K(S)/N$ = 2640.

More substantial stereoselectivity is observed with *p*-nitrophenyl *N*-acetylphenylalanine (4) (Figure). Similar kinetic behaviour is obtained on variation of surfactant concentration, although reaction rates are an order of magnitude faster than with (3), with $k_m(R)$ = 0·129 s^{-1} and k_m (*S*) = 0·393 s^{-1}. The enantiomer reaction rate ratio of 3 : 1 is a consequence of differences in the free energies of diastereoisomeric transition states rather than micellar discrimination between enantiomeric substrates, for the micelle binding constants are $K(R)/N$ = 760 and $K(S)/N$ = 720, identical within experimental error. This selectivity is due in greater part to interactions between individual molecules of (2) and (4) rather than to interactions requiring macroscopic chirality in the micellar aggregate, because enantiomer rate ratios of 2·13 and 2·49 are observed when (2) is diluted with an 11·5 and 4·5 molar excess, respectively of cetyltrimethylammonium bromide (CTAB). The phosphate buffer plays a significant, but not crucial role in catalysis since both reaction rates and enantioselectivity are lower when hydrolysis is conducted in the absence of buffer at pH 7·2.

Hydrolysis of *p*-nitrophenyl esters catalysed by mixed micelles of CTAB and *N*-myristoyl histidine involves nucleophilic transacylation and rate-determining formation of an acylimidazole.[6] On this basis the pronounced stereoselectivity observed in the hydrolysis of (4) by (2) may be rationalised. We assume (a) that the *p*-nitrophenolate leaving-group is in a hydrophilic region at the Stern layer of the micelle, (b) that the preferred environment of the benzyl group is hydrophobic, and (c) a strong inter-amide

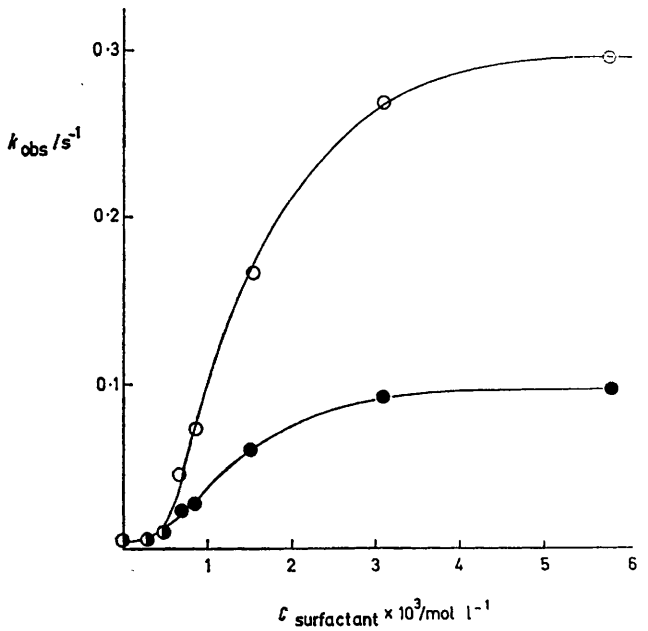


FIGURE. Variation of k_{obs} with [(2)]. Solid circles are 4-*R* points and open circles 4-*S*.

hydrogen bond is formed between reagent and substrate. This leads to a tetrahedral intermediate which when derived from the *R*-isomer (5) has severe proximity strain between the benzyl and histidine residues. The intermediate derived from *S*-(4) experiences much less unfavourable non-bonded interactions. The ability of amides to form strong intermolecular hydrogen bonds[7] must bring about the higher stereoselectivity in hydrolysis of (4) relative to (3), and also possibly the higher reactivity of the former.

In conclusion, we note several points of similarity between this proposal and the suggested origins of stereoselectivity in proteolytic enzymes,[8] despite the simplicity of our system. No clear-cut example of stereoselectivity in micelle-catalysed reactions has previously been reported,[9] and these results demonstrate the potential of functional

surfactants in catalysis. Attachment of the reactive group to the alkyl chain rather than to the head group may well be advantageous.

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