Catalysis of Amide Hydrolysis due to Micelles Containing Imidazole and Hydroxy Functional Groups

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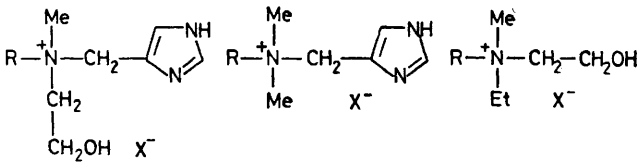
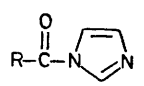
Summary Catalysis due to bifunctional 'chymotrypsin model' micelles implies a change in the effective nucleophilic site from the imidazole to the hydroxy function on going from the hydrolysis of esters to that of amides.

PREVIOUSLY,[1] micelles of cationic surfactants containing both an imidazole ring and a hydroxy-group (**1**) or one of these groups (**2**) and (**3**) were described as effective catalysts in the hydrolysis of esters. In the pH range 7—9 the imidazole ring is a much better micellar function than the hydroxy-group in promoting the hydrolysis of *p*-nitrophenyl acetate (PNPA) and hexanoate (PNPH) and the observed order of catalytic effectiveness is (**1**) ≥ (**2**) ≫ (**3**). The mechanistic mode of catalysis by bifunctional micelles composed of either (**1**) or a 1 : 1 mixture of (**2**) and (**3**) was suggested[1b,2] to involve *N*-acylation of the imidazole ring followed by a rapid intramicellar intermolecular acyl transfer to the hydroxy group: an unusual ester → amide → ester chemical sequence.

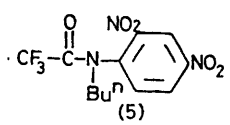


(1) (2) (3)

R = $C_{16}H_{33}$; (1) and (2), $X^- = Cl^-$; (3) $X^- = Br^-$



(4)
a, R = Me
b, R = C_5H_{11}



(5)

We have extended the study of micellar catalysis due to (**1**)—(**3**) to the hydrolysis of some reactive amides:[3] the acylimidazoles (**4a**) and (**4b**) and *N*-(n-butyl)-2,4-dinitrotrifluoroacetanilide (**5**). With these substrates, the order of catalytic effectiveness is (**3**) ≥ (**1**) ≫ (**2**) and the nucleophilic site of bifunctional micelles is, from kinetic evidence, the hydroxy group.

Such a change in catalytic abilities is better illustrated by the data in the Table and by the rate–[surfactant] profiles in the Figure. Micellar effects on amide hydrolysis are strongly dependent on the type of buffer used and its concentration.[4] Thus, at pH 8·4 values of k_c/l mol^{-1} s^{-1} and $k_{\psi max}/k_{buffer}$[5] for the hydrolysis of (**5**) in the presence of (**3**) are 910 and 1500 in borate buffer (conditions as in the Table) and 95 and 200 in Tris-buffer (conditions as in the Figure). However, in each case, whereas micellar (**3**) and

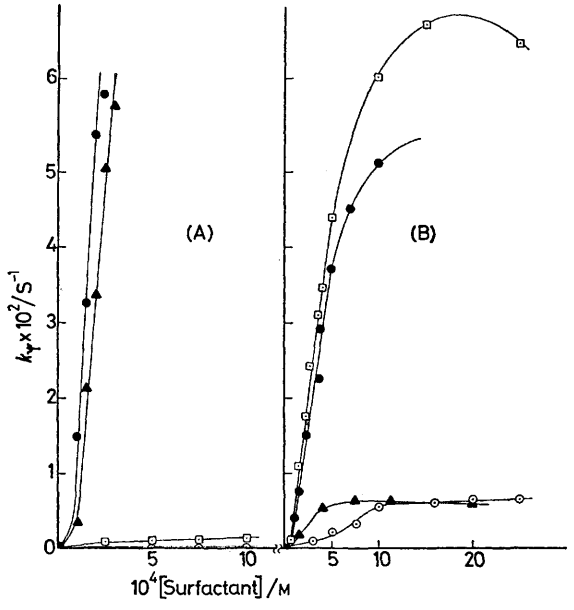


FIGURE. Rate–[surfactant] profiles for the hydrolysis of: (A) PNPH and (B) the anilide (**5**) in Tris-buffer (*I* 0·05M), pH 8·4, 25 °C. ● (**1**), △ (**2**), □ (**3**), and ○ CTABr.

(**1**) are effective functional catalysts, (**2**) behaves virtually as a non-functional surfactant like cetyltrimethylammonium bromide (CTABr) (see Figure).

The change in nucleophilic abilities of the two functions indicates a shift in the rate-limiting step of the general mechanism[4] involving carbonyl attack by the anionic[1,2,6] form of the micellar function —YH (equation 1). In the case of esters (LH = *p*-nitrophenol) the release of L$^-$ from (**6**) is faster than its formation. In the case of amides having much poorer leaving groups L, the opposite is true and the $k_2:k_{-1}$ ratio becomes smaller on going from the hydroxy to the imidazole function. In the limiting case of

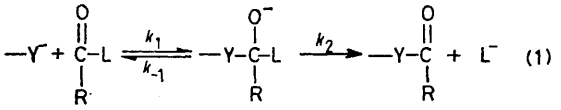
TABLE

Apparent catalytic rate constants,[a] k_c/l mol^{-1} s^{-1}, for the hydrolysis of the esters PNPA and PNPH and the amides (**4a**), (**4b**), and (**5**) in 0·02M-borate buffer, pH 8·4, at 25 °C.

	PNPA	PNPH	(**4a**)	(**4b**)	(**5**)
(**1**)	22	640	7·8	31	510
(**2**)	11	390	—[b]	—[b]	*ca.* 40[b]
(**3**)	0·32	7	13·5	95	910

[a] Calculated as described (see ref. 1) from the slope of the plot-$k\psi$ *vs.* [surfactant] above the 'kinetic' critical micellar concentration. The $k\psi$ values for amides were obtained from spectral changes monitored at 243, 247, and 368 nm for (**4a**), (**4b**), and (**5**), respectively. [b] The value is too close to that of CTABr to be meaningful: see text.

(**2**) and acylimidazoles (**4**) both —Y and L of (**6**) are imidazolyl residues. However, —Y is a weaker base than L by *ca.* 3 p*K* units, as previously reported;[1] thus, the $k_2:k_{-1}$ value must be correspondingly low and the nucleophilic catalysis virtually absent as observed.



(**6**)

The present results, while providing experimental support for a two-step mechanistic hypothesis for the bifunctional micellar catalysis of ester hydrolysis, point to the flexibility of these bifunctional micelles. Although co-operative catalysis is absent, the two functional groups are used in the micellar pseudo-phase in an effective and complementary way depending on the substrate.

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[3] A rather unexplored field; see V. Gani, C. Lapinte, and P. Viout, *Tetrahedron Letters*, 1973, 4435 and ref. 5, p. 166.
[4] Acid–base catalysis of micellar reactions is under investigation. See, for the hydrolysis in non-micellar solutions: D. G. Oakenfull, K. Salvesen, and W. P. Jencks, *J. Amer. Chem. Soc.*, 1971, **93**, 188; R. L. Schowen, C. R. Hopper, and C. M. Bazikian, *ibid.*, 1972, **94**, 3095; R. M. Pollack and T. C. Dumsha, *ibid.*, 1975, **97**, 377, and references therein.
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