Micellar Effects upon the Acid Hydrolysis of *N*-Acylimidazoles [1]

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The acid-catalysed hydrolysis of various *N*-acylimidazoles has been studied in the presence of anionic [sodium dodecyl sulphate (NaLS)] and cationic [cetyltrimethylammonium bromide (CTABr)] surfactants. For the hydrolysis of the *N*-lauroyl derivative, CTABr causes a rate decrease on increasing the pH in the range where the observed rate constants level off in water, whereas NaLS does not affect the slope of the rate profile in the same pH range.

The hydrolysis of *N*-acylimidazoles has been widely studied in connection with the importance of the imidazole nucleus for acyl transfer and hydrolysis in biochemical systems.[2] The rates of hydrolysis of *N*-acetylimidazole are strongly dependent on the pH of the solution and the pH–rate profile is complex. The rate of hydrolysis increases sharply above and below pH 7. Below pH 4 the rate becomes almost constant up to an acid concentration of 1M. This behaviour demonstrates that in the plateau region, pH 0—3, *N*-acetylimidazole is completely protonated and the cation undergoes bimolecular attack by water.[2a]

Further investigations based on the proton inventory technique have shown that the pH-independent water-catalysed hydrolysis of *N*-acetylimidazolium ion probably involves a transition-state structure composed of two water molecules with three protons contributing to the isotope effect.[3]

Our study concerns the influence of the addition of surfactants, about the critical micelle concentration (c.m.c.), on the water-catalysed hydrolysis of a series of N-COR imidazoles with R of increasing hydrophobicity (R = Me, Et, Bu^n, n-heptyl, n-undecyl).

Results and Discussion

Binding of Substrate to the Micelles.—Both anionic and cationic surfactants give a rate inhibition and typical results for sodium dodecyl sulphate (NaLS) are shown in Tables 1 and 2. We used the observed inhibitions to calculate the binding constant, K_S, of the substrate to the micellized surfactants. Following Scheme 1 the binding constants, K_S, are given by equation (1), where the subscript W denotes the

$$K_S = [SD_n]/[S_W]([D] - \text{c.m.c.}) \quad (1)$$

$$k_\psi = \{k_W' + k_M' K_S([D] - \text{c.m.c.})\}/\{1 + K_S([D] - \text{c.m.c.})\} \quad (2)$$

$$1/(k_W' - k_\psi) = 1/(k_W' - k_M') + 1/(k_W' - k_M')K_S([D] - \text{c.m.c.}) \quad (3)$$

substrate S in the aqueous pseudophase and the amount of monomer is assumed to be given by the c.m.c. The relation between k_ψ and the micellized surfactant D_n is shown by equation (2) where k_W' and k_M' are, respectively, the first-order rate constants in the aqueous and micellar pseudophase. Rearrangement of equation (2) gives (3);[4] by plotting $1/(k_W' - k_\psi)$ against $1/([D] - \text{c.m.c.})$ it is possible to calculate k_M', k_W', and K_S. This plot is sensitive to the c.m.c. value, but there is considerable inhibition at concentrations below the c.m.c. in water. This behaviour has been ascribed to interactions between the surfactants and solutes which induce micellization or formation of submicellar aggregates.[5] As previously shown this problem can be treated both by assuming the c.m.c. value is an adjustable parameter or by assuming k_M' *ca.* 0.[6]

Table 1. Inhibition of hydrolysis of *N*-octanoylimidazole by NaLS [a]

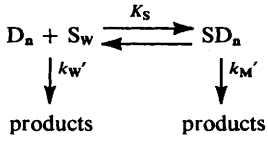
10^3[NaLS]/M	$10^2 k_\psi$/s^{-1}
	3.90
0.8	3.68
1.0	2.20
1.5	1.79
3.0	1.28
4.0	1.21
8.0	1.19
10.0	1.17
80.0	0.92

[a] At 25.0 °C, 0.01M-HCl.

Table 2. Inhibition of hydrolysis of *N*-lauroylimidazole by NaLS [a]

10^3[NaLS]/M	$10^3 k_\psi$/s^{-1}
	45.00 [b]
4	26.50
6	21.01
8	18.60
10	16.46
13	13.60
16	11.80
20	10.40
30	9.35
40	9.30
50	8.20

[a] At 25.0 °C, 0.01M-HCl. [b] Value extrapolated from k_ψ obtained in MeCN–H_2O mixtures (see text).



Scheme 1.

Inhibition of Hydrolysis by Cetyltrimethylammonium Bromide (CTABr).—Cationic micelles of CTABr inhibit the hydrolysis reaction, the extent of inhibition being strongly related to the size of the hydrocarbon chain attached to the carbonyl group (Table 3). The experimental data for the

Table 3. Rates of hydrolysis of N-COR imidazoles in water and in the presence of CTABr and NaLS [a]

R	H_2O	CTABr 4×10^{-2}M	NaLS 8×10^{-2}M
Me	5.1	5.1	2.1
Et	5.9	5.6	1.8
Bu^n	3.9	3.7	1.0
Heptyl	3.9	2.4	1.0
Undecyl	4.5 [b]	0.3	0.8

[a] Values of $10^2 k_\psi/s^{-1}$, at 25.0 °C and 0.01M-HCl. [b] Value extrapolated from k_ψ obtained in MeCN–H_2O mixtures (see text).

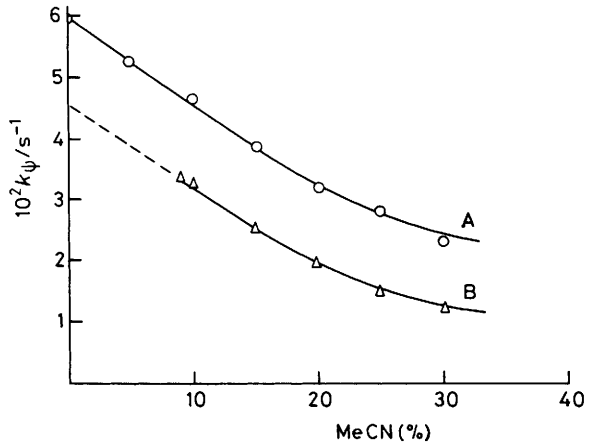


Figure 1. Plot of k_ψ *versus* % MeCN in 0.01M-HCl for: A, *N*-propionylimidazole; B, *N*-lauroylimidazole

hydrolysis of *N*-lauroylimidazole fit equation (3) and K_S 1 850 l mol^{-1} and $k_W' - k_M'$ 4.35 × 10^{-2} s^{-1}. The K_S value is approximate since the concentration of mixed unreactive counterions changes with CTABr concentration and this change could produce variations in the properties of micelles.[7] However, the results clearly show, as expected, that the substrate is strongly bound to CTABr micelles.

Inhibition of Hydrolysis by NaLS.—The anionic micelle NaLS inhibits the hydrolysis reactions of *N*-acyl derivatives, the extent of inhibition being approximately independent of the hydrophobic character of the hydrocarbon chain (Table 3). The experimental data given for *N*-octanoyl and *N*-lauroylimidazole at [H$^+$] 0.01M, K_S 1 339 and 2 311 l mol^{-1}, respectively, showing that in both cases association between the substrate and micelles is very strong.

The $k_W' - k_M'$ values for the two substrates are, respectively, 2.89 × 10^{-2} and 3.61 × 10^{-2} s^{-1} showing, as expected, that the contribution of the k_M' values is very small.

Micellar Effects on pH–Rate Profiles.—The rates of hydrolysis of N-COR imidazoles, measured at [H$^+$] 10^{-1}, 10^{-2}, and 10^{-3}M without any added salt, have been found to be substantially constant and the numerical values at [H$^+$] 10^{-2}M are in Table 3. The figure for R = n-undecyl is extrapolated from the k_ψ values obtained in MeCN–H_2O mixtures, since the compound is very sparingly soluble in water. A plot of k_ψ against the percentage of MeCN is almost linear up to 20% MeCN and the effect of MeCN is the same for different R groups as shown in Figure 1. The similarity of the values obtained for different lengths of the chain in R and the same dependence on the medium effect suggest that the micro-

Table 4. Rates of hydrolysis of *N*-lauroylimidazole in water in the presence of CTABr and NaLS [a]

[HCl]/M	$[H_2O]$/M	CTABr 4×10^{-2}M	NaLS 8×10^{-2}M
1		1.23	
0.5		1.25	
0.1	4.5	1.22	0.77
0.01	4.5	0.21	0.81
0.001	4.5	0.04	0.86

[a] Values of $10^2 k_\psi/s^{-1}$, at different concentrations of HCl.

environment of the reaction centre is not very much influenced by the hydrophobicity of the alkyl chain in R.

The rates of hydrolysis of all the substrates in the presence of NaLS show the typical behaviour for inhibitory effects in micelles. The values in Table 3 at 8×10^{-2}M-NaLS and at 4×10^{-2}M-CTABr in 0.01M-HCl represent a minimum in the plot of k_ψ *versus* [surfactant]. The rates of hydrolysis in the presence of CTABr show that the hydrolysis of N-COR imidazoles when R = Me, Et, and Bu^n is unaffected by the presence of the cationic surfactant, while an inhibitory effect is acting for R = n-heptyl and strong inhibition is found for R = n-undecyl (*N*-lauroylimidazole). CTABr does not affect the rate of hydrolysis of short-chain N-COR imidazoles suggesting that in this case the contribution to the overall reaction is due to the aqueous pseudophase.

These compounds, at least in the protonated form, are not very much solubilized in CTABr micelles. Furthermore the strong inhibition in the rate shown by *N*-lauroylimidazole suggests much solubilization of this compound due to the presence of the long alkyl chain.

A 'forced' solubilization can lead in this case to deeper penetration of the interior of micelles and consequently causes a change in the apparent pK_a value of the protonated form of the substrate (*N*-lauroylimidazole) which is responsible for the observed kinetic behaviour. To test this point we measured the rates of hydrolysis of different *N*-acylimidazoles at different CTABr and NaLS concentrations and at different acid concentrations.

The observed rate inhibition at the same CTABr or NaLS concentration in the [H$^+$] range studied ([H$^+$] = 10^{-3}—1M) is reported in Table 4. A plot of log k_ψ *versus* analytical pH_a shows the dependence on −log[H$^+$] of log k_ψ for *N*-lauroylimidazole at constant concentration of NaLS and CTABr and in the absence of surfactant compared with the reaction in water of *N*-acetylimidazole (Figure 2). While in the presence of NaLS, *N*-lauroylimidazole shows a [H$^+$]-independent region for all [H$^+$] studied, in the presence of CTABr the profile seems to be very similar to those of *N*-lauroyl- and *N*-acetyl-imidazole in water with slope of about unity, the main difference being the relative position of the plots with respect to the −log[H$^+$] axis.

Jencks and Carriuolo have previously shown [2a] that below pH 4 the rate of hydrolysis of *N*-acetylimidazole in water approaches a plateau and remains almost constant up to [H$^+$] 1M. This fact suggests that in this pH range the substrate becomes completely converted into its conjugate acid so that a further increase in the acid concentration does not increase the concentration of reactive *N*-acetylimidazolium cation, *i.e.* the rate becomes independent of pH. From these data it is possible to estimate the pK_a of *N*-acetylimidazole as 3.6 and to calculate the rate law for the kinetic process in Scheme 2 as in equation (4). Following the same equation we calculated an apparent

$$k_\psi = k_1 K/(K + [H^+]) + k_2[H^+]/(K + [H^+]) \quad (4)$$

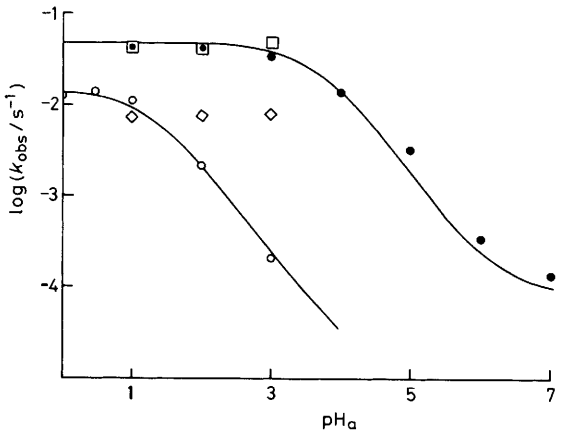
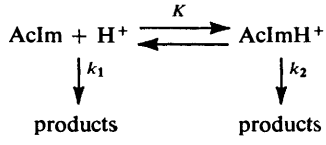


Figure 2. Plot of log k_ψ *versus* pH$_a$ (the apparent pH in the micelle) for: ●, *N*-acetylimidazole in water; □, *N*-lauroylimidazole in water; ◇, *N*-lauroylimidazole in NaLS; ○, *N*-lauroylimidazole in CTABr



Scheme 2

pK_a' of 1.22 for *N*-lauroylimidazole in CTABr which is at least two orders of magnitude lower than that of *N*-acetylimidazole in water. The apparent pK_a of indicators has been shown to be increased by cationic and decreased by anionic micelles.[6] From considerations of Figure 2 we can ascribe the different behaviour to the different influence of CTABr and NaLS on the rate profile. The plateau region in the presence of NaLS is in the same range as in water and perhaps it will extend to lower [H$^+$], since anionic micelles favour the equilibrium toward the protonated form of *N*-lauroylimidazole, which is the reactive form in water-catalysed hydrolysis. On the other hand the protonation of *N*-lauroylimidazole is less favourable in the presence of CTABr and therefore the plateau region must be shifted to higher [H$^+$].

Micellar Effects on Other 'Water-catalysed' Reactions.—So far few reports on micellar effects on water-catalysed reactions have appeared.

First, the rate of the pH-independent hydrolysis of long-chain alkyl sulphates is not influenced when these substrates undergo micellization. Since this reaction involves attack of water on the sulphate ester, it was suggested that the water activity is not very different from that in the water bulk phase.[7]

Second, the rate of attack of water on triphenylmethyl cationic dyes is unchanged by the presence of micelles of NaLS, CTABr, and Igepal.[8]

Third, the rate of the pH-independent hydrolysis of *p*-nitrophenyl carbonate involving a transition state with two molecules of water is only slightly affected by the presence of ionic micelles.[9]

Finally, the rate of the pH-independent hydrolysis of *N*-trifluoroacetylpyrrolidone is unaffected by addition of NaLS and CTABr.[10]

These observations are consistent with the results showing that the extent of hydration of the C=O group of 3-formyl-*N*-tetradecylpyridinium bromide is not very different in both *N*-tetradecyltrimethylammonium bromide and NaLS solutions and in water[11] and that the extent of hydration of counterions incorporated into the Stern layer of various micelles is about the same as that for the same ions in the bulk aqueous phase.[12]

These results suggest that the activity of water in the micellar pseudophase of ionic micelles is not very different from that in water. However, it is not possible, in our opinion, to obtain information from these results on water penetration in micellar aggregates, mainly because we do not know what is the location of the substrates in the micellar pseudophase.

Conclusion

The observed inhibition on the rate of hydrolysis of the fully micellar bounded *N*-lauroyl derivative in the presence of CTABr can be interpreted in terms of the apparent pK_a shift due both to the decreased concentration of hydrogen ions in the Stern layer and to the stabilization of the unprotonated form of the substrate by head groups of the cationic micelles. Anionic micelles of NaLS, favouring the equilibrium towards the imidazolium cation, show the same pattern as in water. The lower reactivity with respect to water probably reflects the sensitivity of the reaction to the medium effect. Overall results are in agreement with the hypothesis that water activity in the micellar pseudophase is similar to that in the bulk solution.

Experimental

Materials.—*N*-Acetylimidazole was prepared following the method previously described[13] and purified by recrystallization from anhydrous benzene. *N*-Propionyl-, *N*-valeryl-, and *N*-octanoyl-imidazole were prepared and purified by the method of Staab.[14] *N*-Lauroylimidazole was prepared from imidazole (0.68 g, 0.001 mol) dissolved in reagent grade $CHCl_3$ (10 ml) and lauroyl chloride (1.1 g, 0.005 mol) added dropwise to the magnetically stirred solution kept at 10 °C for 12 h. The resulting suspension was filtered, the filtrate evaporated, and the residual material was purified by recrystallization from ethyl acetate in 90% yield, m.p. 69.5—70.5 °C (lit.,[14] 69.5—70.5 °C). CTABr and NaLS were purified by methods already described.[15]

Kinetics.—Hydrolyses were followed spectrophotometrically at 25 °C at the following wavelengths: *N*-acetylimidazole, 245 nm; *N*-propionylimidazole, 250 nm; *N*-valerylimidazole, 250 nm; *N*-octanoylimidazole, 240 nm; *N*-lauroylimidazole, 240 nm; the substrate concentrations were 10^{-4}—10^{-5}M. Pseudo-first-order rate constants, k_ψ s^{-1}, were calculated by the least-squares treatment by means of an Olivetti P6060 desk computer.

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