MICELLAR EFFECTS ON THE ALKALINE HYDROLYSIS OF N-ALKYL-4-CYANOPYRIDINIUM IONS. AN EXAMPLE OF MICELLE-INDUCED REGIOCHEMICAL SELECTIVITY

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The rates of the reaction of N-alkyl-4-cyanopyridinium (RCP) ions [alkyl = CH_3 (MCP), $n-C_4H_9$ (BCP), $n-C_8H_{17}$ (OCP), $n-C_{12}H_{25}$ (DCP)] with OH^- ion in water are independent of chain length and RCP concentration up to 0.001 M. The ratios of the concentrations of the reaction products, N-alkyl-4-pyridone (P) and N-alkyl-4-carboxamidopyridinium (A), P/A, are similar for all substrates. In water the P/A ratios increase with pH, reaching a plateau value of ca 2 at pH $\geqslant$ 13. Added salts slightly decrease the reaction rate and do not affect the P/A ratios. In aqueous solutions, addition of dioxane increases both rates and P/A ratios. Micelles of hexadecyltrimethylammonium bromide (cetyltrimethylammonium bromide; CTAB) and 3-(N,N-dimethyl dodecyl ammonium)propane-1-sulphonate (SDP) catalyse the alkaline hydrolysis of OCP and DCP and increase the yield of pyridone with BCP, OCP and DCP. In micellar CTAB and SDP the attack of OH^- on RCP occurs almost exclusively at the 4-position of the pyridinium ring. Sodium dodecyl sulphate micelles inhibit the reaction and produce small changes in the P/A ratio. The regiochemical selectivity produced by micelles, leading to a preference for the attack of OH^- at the pyridinium ring, was rationalized in terms of the low effective dielectric constant at the micelle–water interface.

INTRODUCTION

Micelles and vesicles, supramolecular aggregates formed by amphiphiles in water, can produce major changes in reaction rates.[1] The catalytic effects of micelles in unimolecular reactions have been ascribed to, among other factors, the effective low dielectric constant in the micelle and to conformer stabilization.[1-3] The effect of micelles on bimolecular reactions is due mainly to the reagent concentration in the micelle.[1,2] Rate constants for bimolecular reactions in the micelle rarely differ from those in the aqueous phase by more than one order of magnitude.[4] However, micelles can influence not only rates but also the effects of substituents and the selectivity of organic reactions.[5-11] There are few reports of regiochemical selectivity in which the reaction site is affected on transferring the reaction from the aqueous phase to the micelle.[10,11]

We have used the reaction of OH^- attack on N-alkyl-4-cyanopyridinium ions (RCP) (Scheme 1) to probe several features of micelles and vesicles.[11,12] The site of OH^- attack on 4-cyanopyridinium compounds and, as a consequence, product distribution, is particularly sen-
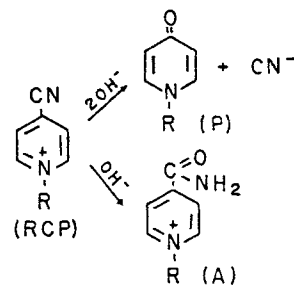
Scheme 1

sitive to the addition of positively charged micelles.[11] In this work we have extended the study of the kinetics of the reaction of RCPs with OH^-. Salt and solvent effect on the rate and product distribution of the reaction in aqueous solution were determined in order to elucidate micellar effects. The effects of positive, negative and zwitterionic micelles on the rate and product distribution of the reaction of OH^- attack on RCP were determined. The calculated second-order rate constants in the micelle were higher than those in water. These data, together with the known mechanism of the

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reaction,[13] were used to conclude that micellar effects on this reaction can be interpreted in terms of reagent concentration in the micelle and medium-induced changes in the site of OH$^-$ attack on the cyanopyridinium ion in the micelle-incorporated RCPs.

EXPERIMENTAL

5,5'-Dithiobis-p-nitrobenzoic acid (DTNB) (BDH Biochemicals) and tris(2,2'-bipyridine)ruthenium(II) dichloride hexahydrate [Ru(Bipy)$_3^{2+}$] (G. Frederick Smith) were used as received. Tetramethylammonium bromide (TMAB), obtained by neutralization of tetramethylammonium hydroxide (Merck) with HBr (Carlo Erba), were recrystallized from acetone–ethanol–water (7:2·5:5, v/v) and vacuum dried. 1,4-Dioxane (Carlo Erba) was purified and distilled over sodium. All other reagents were of analytical-reagent grade; water was deionized and doubly distilled in glass.

Sodium dodecyl sulphate (SDS) (BDH Chemicals, Gold Label) was used without further purification. Hexadecyltrimethylammonium bromide (cetyltrimethylammonium bromide; CTAB) (Merck) was purified by recrystallization (×3) in acetone–ethanol (85:15, v/v) and vacuum dried. 3-(N,N-Dimethyldodecylammonium)propane-1-sulphonate (SDP) was generously provided by Professor O. A. El-Seoud of the Institute of Chemistry, University of São Paulo. All detergents exhibited the expected critical micelle concentrations (CMC)[1,14] and SDS showed no minimum in surface tension versus concentration plots.

N-Methyl-4-cyanopyridinium (MCP) iodide was synthesized from 4-cyanopyridine (Aldrich) and methyl iodide (Aldrich).[13,15] The chloride salt of MCP was obtained from the iodide salt by treatment with (freshly prepared) silver chloride. N-Butyl- (BCP), N-octyl- (OCP) and N-dodecyl- (DCP) 4-cyanopyridinium

bromides were obtained from 4-cyanopyridine by treatment with the corresponding alkyl bromides (Aldrich).[16] The elemental analyses (C,H,N) (performed by Dr Rita Moscovici) and the equivalent molecular weights (calculated from halide titration)[17] were in accord with the expected structures (Table 1).

Cyanide concentration was determined by titration with DTNB in both the presence and absence of CTAB.[18] Determination of CN$^-$ ion with an ion-selective electrode gave the same results as those obtained using DTNB titration in the absence of detergents. CN$^-$ determinations with the ion-selective electrode in the presence of detergents were non-reproducible, except when performed with a newly acquired electrode; thus titration with DTNB was the method of choice. The determination of CN$^-$ in SDS-containing samples was performed after separation of the detergent by precipitation with barium chloride.

Fluorescence was measured with a Hitachi–Perkin-Elmer MPF-4 spectrofluorimeter (ratio mode) and absorbances with a Beckman M-25 spectrophotometer. All measurements were made at 30 ± 0.1 °C. Reported first-order rate constants are the averages of at least three separate experiments differing by no more than 5 per cent.

RESULTS

Product composition

The molar absorptivities of n-methylpyridone (ε_p) and N-methyl-4-carboxamidopyridinium ion (ε_A), the products from the hydrolysis of MCP have been determined.[13] The concentration ratio P/A of the products from MCP hydrolysis (P and A, Scheme 1) was determined from the absorbance of the reaction mixtures obtained at 265 nm after complete reaction as

Table 1. Analytical and spectral data for RCP ions and their corresponding products [amide (A) and pyridone (P), Scheme 1]

N-Alkyl-4-cyano-pyridinium ion	C, H, N(%)[a] (expected)	Molar absorptivity[b] (l mol^{-1} cm^{-1})
N-Methyl- (MCP)	55·38, 3·88, 18·7 (55·01, 3·96, 18·36)	RCP, 4750, 11 800; P, 16 660; A, 4959
N-Butyl- (BCP)	50·76, 5·67, 11·47 (49·81, 7·43, 11·61)	RCP, 4620, 13 520; P, 17 590; A, 4960
N-Octyl- (OCP)	55·32, 7·43, 9·49 (55·74, 7·42, 9·82)	RCP, 4280, 12 200; P, 16 830; A, 4850
N-Dodecyl- (DCP)	60·75, 8·30, 7·80 (61·20, 8·30 7·91)	RCP, 4380, 12 420; P, 16 410; A, 4880

[a] Elemental analyses were obtained with MCP.Cl, BCP.Br, OCP.Br and DCP.Br. Quantitative halide analyses[17] of MCP.Cl, BCP.Br, OCP.Br and DCP.Br were in agreement with reported structures.
[b] Solvent was water in all cases. Molar absorptivities for RCPs reported at 278 and 233 nm, respectively; for P and A molar absorptivities reported at 265 nm.

follows. The final concentration of A, A, was estimated using

$$A = (Abs_{265} - RCP_T \varepsilon_P)/(\varepsilon_A - \varepsilon_P) \qquad (1)$$

where Abs_{265} is the observed absorbance at 265 nm and RCP_T the initial concentration of RCP.

For the hydrolysis of MCP, where ε_P and ε_A are known (see above), the P/A ratios calculated from absorbances were identical with those calculated from CN^- measurements (relative standard deviation of 5 per cent in 20 independent determinations). For all other RCPs the final concentration of the corresponding pyridone was determined by measuring the yield of CN^- (Scheme 1). The value of ε_A was determined at low pH, where the yield of pyridone can be neglected.[13] From these data and equation (1), we obtained the corresponding values of ε_P (Table 1). The P/A ratios after complete reaction (ten half-lives) were determined for each RCP under different conditions (at least 20 different experiments). The results obtained by measuring the concentration of CN^- and those using equation (1) gave identical P/A values with a standard deviation of 5 per cent (20 determinations).

Alkaline hydrolysis of N-alkyl-4-cyanopyridinium ions in the absence of micelles

The alkaline hydrolysis of RCPs can be represented as in Scheme 2.[13]
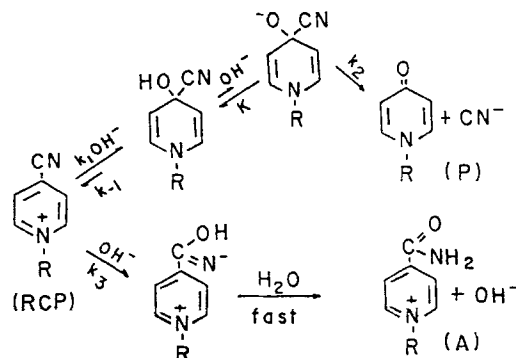
Scheme 2

In buffered solutions or in the presence of excess OH^-, and assuming a steady state for the intermediate cyanohydrins, the first-order rate constants for the

Table 2. Effect of pH on the first-order rate constant (k_ψ) and product distribution ratios (P/A) for the alkaline hydrolysis of RCP ions

pH[a]	$k_\psi(\times 10^3 \text{ s}^{-1})$[b,d]				P/A[c,d]			
	MCP	BCP	OCP	DCP	MCP	BCP	OCP	DCP
9·40	0·058	0·057	0·059	–	0·02	0·02	0·02	–
9·43				0·052				0·02
9·90			0·22				0·08	
10·00			0·28				0·10	
10·10	0·32	0·32		0·34	0·11	0·11		0·12
10·15			0·40				0·14	
10·18		0·39					0·12	
10·25	0·49			0·46	0·14			0·12
10·62	1·16	1·12	1·11	1·14	0·28	0·28	0·28	0·31
10·88			2·53				0·56	
11·10		3·39	3·39	3·40		0·49	0·54	0·60
11·12	3·43				0·44			
11·15			4·09	4·25			0·66	0·69
11·35	6·45				0·82			
11·40		6·47				0·91		
11·52	10·1	10·7		11·2	1·04	1·18		0·95
11·55			13·2				1·08	
11·85	24·7	24·5	26·3	27·9	1·35	1·73	1·42	1·53
11·95			32·2	25·0			1·23	
12·09	46·5				1·70			

[a] 0·02 M buffer; borate (pH 9·4–10·25), hydrogencarbonate (10·62), phosphate (10·8–12·09).
[b] Observed rate constant for substrates listed.
[c] P/A values obtained for substrates listed after complete reaction (ca 10 half-lives) were obtained by CN^- determination and spectral measurements (see Experimental).
[d] Substrate concentration $4·7 \times 10^{-5}$ M.

formation of the amide (k_A) and pyridone (k_P) can be described by equations (2) and (3), respectively:[13]

$$k_A = k_3[OH^-] \qquad (2)$$

$$k_P = \frac{Kk_1k_2[OH^-]^2}{k_{-1} + k_2K[OH^-]} \qquad (3)$$

The observed first-order rate constant (k_ψ) for the reaction can be represented by

$$k_\psi = k_A + k_P = \frac{k_1k_2[OH^-]^2}{k_{-1} + k_2K[OH^-]} + k_3[OH^-] \qquad (4)$$

and the P/A ratio by

$$P/A = \frac{k_1}{k_3}\left(\frac{k_2K[OH^-]}{k_{-1} + k_2K[OH^-]}\right) \qquad (5)$$

Values of k_ψ and corresponding P/A ratios for the hydrolysis of RCPs at different pHs are given in Table 2. The values of k_ψ were independent of RCP concentration up to 0.001 M substrate (not shown), demonstrating that, under the conditions used, the RCPs did not aggregate.[12d] At the same pH, the k_ψ values for all RCPs were very similar (Table 2). Thus the data describing the k_ψ–pH dependence for all RCPs fitted a linear function [equation (6)] with a correlation higher than 0.999 (Figure 1).

$$\log k_\psi = 1.072\text{pH} - 14.3 \qquad (6)$$

Using equations (2)–(5), several parameters of Scheme 2 were calculated from the data presented in Table 2. The first-order rate constant for OH^- attack on the CN group [k_A, equation (2)] can be expressed as

$$k_A = k_3[OH^-] = \frac{k_\psi}{1 + P/A} \qquad (7)$$

A value of $1.34 \pm 0.26\,l\,mol^{-1}$ was obtained for k_3 from the (linear) pH dependence of k_A (Figure 2)

[equation (7)]. Using equation (4) and the values of k_A and k_ψ, values of k_P were obtained at different $[OH^-]$. A complex plot of $\log k_p$ versus pH was obtained (Figure 2); this behaviour can be understood upon inspection of equation (3). In the limit of $k_2K \ll k_{-1}$, equation (3) reduces to

$$k_P = \frac{Kk_1k_2}{k_{-1}}\,[OH^-]^2 \qquad (8)$$

Below pH 10·2 the slope of the $\log k_P$ versus pH plot was 2·0 (Figure 2), and from the linear portion of the plot below that pH we calculated a value of $950\,s^{-1}\,l^2\,mol^{-2}$ for the constant term in equation (8). In the limit of $k_2K[OH] \gg k_{-1}$, equation (3) reduces to

$$k_P = k_1[OH^-] \qquad (9)$$

Above pH 11·5 the slope of the $\log k_P$ versus pH plot (Figure 2) was 1·0 and from this region we calculated a value of $1·8\,s^{-1}\,l\,mol^{-1}$ for k_1. k_1 was also calculated from the limiting value of the P/A ratio at high pH since, under these conditions [see equation (5)], $P/A = k_1/k_3$. Using this relationship and the previously calculated k_3 [$1·34\,l\,mol^{-1}\,s^{-1}$ from a plot of equation (7), Figure 2; see text], we obtained a value of $2·3\,s^{-1}\,l\,mol^{-1}$ for k_1, in satisfactory agreement with that calculated before [$1·8\,l\,mol^{-1}\,s^{-1}$ from a plot of equation (9); see text]. The values of k_1 and k_3, obtaining using all RCPs, are in good agreement with those obtained with MCP by Kosower and Patton.[13]
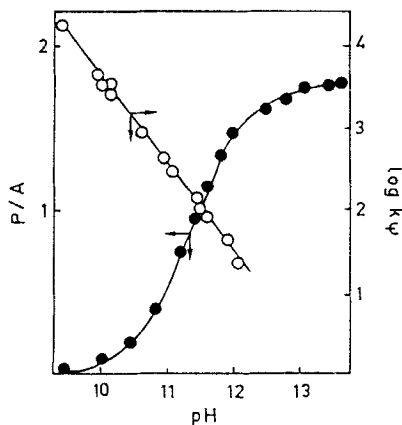

Figure 1. Effect of pH on the alkaline hydrolysis of N-alkyl-4-cyanopyridinium ions. Representative data taken from Table 2. (•) P/A ratio; (○) $\log k_\psi$
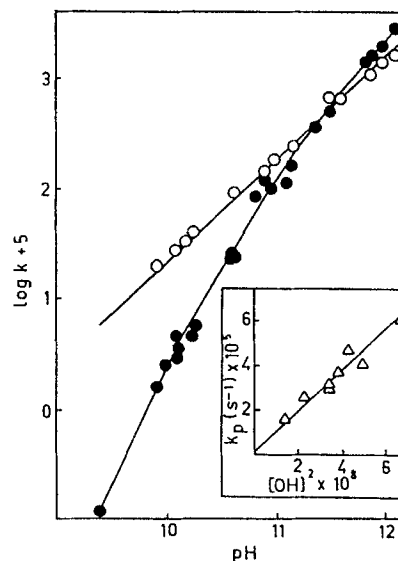

Figure 2. Effect of pH on the alkaline hydrolysis of N-alkyl-4-cyanopyridinium ions. Representative values calculated from the data in Table 2. (•) k_p; (○) k_A. Inset shows the variation of k_P with $[OH]^2$

Hence changing the size of the alkyl chain does not alter either the rate or product composition in this reaction.

Different models of ionic micelles describe the aqueous space determined by the hydrocarbon–water interface and extending to 2–3 Å from that surface as a region where the local salt concentration can reach 3 M.[1,2,4] Micelle models and experimental values also show that the micelle surface exhibits effective dielectric constants which are significantly lower than that of bulk water.[1,2,4] The effect of salts and solvent on a reaction in water can thus be informative of the type of kinetic and mechanistic effects expected on transferring the reaction from water to the (micellar) Stern layer.

Addition of salt produced a moderate decrease in the rate of hydrolysis of RCPs with no significant change in product composition (a representative example is shown in Table 3). Using equations (4) and (7) and the Brønsted–Bjerrum approximation, the extrapolated values of k_A and k_P at zero ionic strength were $1\cdot8$ and $3\cdot2\ s^{-1}\ lmol^{-1}$, respectively. The limiting value of P/A at high OH^- [equation (5)] was $1\cdot78$, in good agreement with data obtained using MCP.[13]

The effect of change in the dielectric constant on the hydrolysis of RCPs was explored using water–dioxane mixtures. The rate constants for RCP hydrolysis increased with increasing dioxane concentration (Table 4), and this effect can be accounted for by the Scatchard equation.[19] The product ratio P/A also increased with increasing dioxane concentration (Table 4). The effect of the solvent was greater with DCP. The effect of dioxane on the reaction rate can be expressed in terms of the dielectric constant, D.[19,20] Calculation of k_A and k_P in the presence of dioxane for both MCP and DCP demonstrated that k_P was more sensitive, and decreased linearly with increase in dielectric constant (Figure 3).

Table 3. Effect of tetramethylammonium bromide (TMAB) on the observed first-order rate constant (k_ψ) and the product distribution ratio (P/A) of the reaction of MCP with OH^- ion (Scheme 1)

pH[a]	[TMAB] $(M \times 10^3)$	$k_\psi (s^{-1} \times 10^2)$	P/A
12·3	—	7·9	1·53
12·3	4	7·6	1·47
12·3	10	7·1	1·43
12·3	20	6·9	1·42
12·3	40	6·7	1·39
12·3	60	6·6	1·38
12·3	80	6·2	1·45
10·9	—	0·24	0·42
10·9	4	0·18	0·43
10·9	18	0·17	0·39
10·9	30	0·17	0·42
10·9	50	0·17	0·38

[a] pH was obtained by addition of NaOH and measured with a pH electrode before and after reaction. [MCP] = 5×10^{-5} M.

Table 4. Effect of dioxane on the observed first-order rate constant (k_ψ) and product distribution ratio (P/A) for the reaction of MCP and DCP with OH^- (Scheme 1)

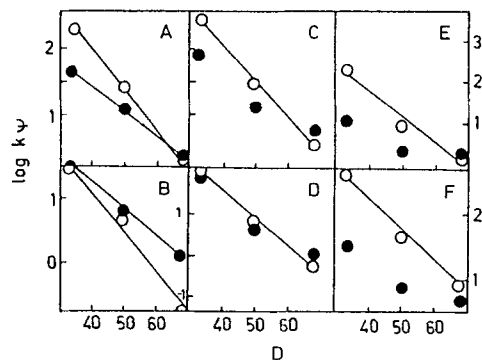| Dioxane (%, v/v)	NaOH $(M \times 10^3)$	MCP		DCP	
		k_ψ^a	P/A	k_ψ^a	P/A
10	0·6	1·9	0·4	1·6	0·5
30	0·6	10·9	0·7	10·2	1·6
50	0·6	64·1	0·9	188	1·6
10	1·0	4·05	0·7	3·3	0·9
30	1·0	39·2	2·1	11·1	3·8
50	1·0	253	5·3	18·3	14·1
10	2·0	9·73	0·7	11·5	1·6
30	2·0	43·6	2·3	55·0	6·7
50	2·0	39·9	3·5	47·3	13·3

^{a} [RCP] = 5×10^{-5} M.

Figure 3. Effect of dioxane on the alkaline hydrolysis of N-alkyl-4-cyanopyridinium ions [RCP] = 5×10^{-5} M. A, C and E, N-dodecyl-, and B, D and F, N-methyl-4-cyanopyridinium ions. (o) k_P; (•) k_A (see text). The final NaOH concentrations were 0·6 (A, B), 1·0 (C, D) and 2·0 mM (E, F). The dielectric constants (D) were calculated for solutions of 10, 30 and 50 per cent (v/v) dioxane–water

Micellar effects on the hydrolysis of N-alkyl-4-cyanopyridinium ions

Having explored the kinetics and product distribution of the alkaline hydrolysis of RCPs in aqueous solution, we analysed the effect of micelles on the reaction rates and product distribution. Quantitative analysis of micellar rate effects requires, when possible, independent measurement of the micelle–water substrate distribution.[1–4] The distribution of DCP between water and micelles was determined measuring the quenching of the fluorescence of $Ru(bipy)_3^{2+}$.[11,21] RCPs quench the fluorescence of the ruthenium complex [Figure 4(A)] and from the relative fluorescence intensity, under comparable conditions,

the concentration of free RCP can be calculated. At a fixed [DCP], the addition of CTAB produces an increase in the fluorescence intensity owing to the incorporation of DCP into the micelles [Figure 4(b)]. The incorporation of the cyanopyridinium quencher into the micelle was analysed using the following relationship:[21]

$$K_s = \frac{S_b}{S_f(C_d + S_f)} \quad (10)$$

where K_s is the incorporation constant and S_b and S_f are the analytical concentrations of the quencher bound to the micelle and free in the intermicellar compartment, respectively; C_d represents the concentration of the micellized detergent, equal to the total added (C_t) minus the critical micelle concentration (CMC). The
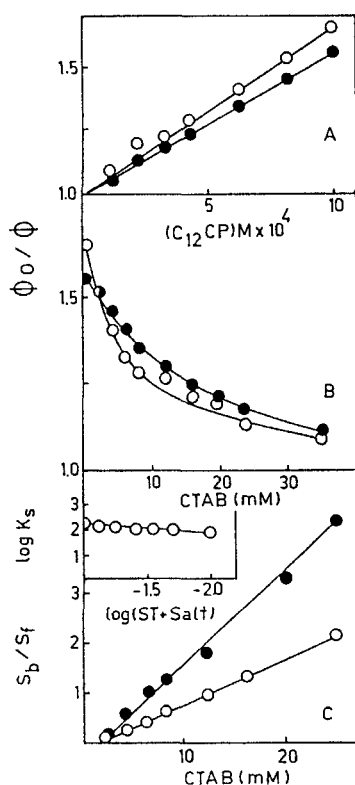
Figure 4. Effect of CTAB on the quenching of fluorescence of Ru(bipy)$_3^{2+}$ by DCP ions. Ru(bipy)$_3^{2+}$ concentration, 4×10^{-5} M; NaBr concentrations, (○) 0·01 and (●) 0·07. (A) Effect of [DCP] on the fluorescence intensity of Ru(bipy)$_3^{2-}$; (B) effect of [CTAB] on the fluorescence intensity of a solution containing 1·0 mM DCP and 4×10^{-5} M Ru(bipy)$_3^{2+}$ (see A); (C) determination of K_s from the calculated S_b/S_f ratios [see text, equation (10)]. Inset shows the variation of the DCP–CTAB association constant (K_s) with salt; ST represents the total concentration of DCP

fluorescent ruthenium complex does not incorporate in CTAB micelles,[21] so S_f was calculated from the effect of micelles on the fluorescence intensity at a fixed concentration of added DCP [Figure 4(B)].[11,21] The value of K_s for DCP, obtained from a linearized plot of equation (10) [Figure 4(C)], was 195 l mol^{-1}. The effect of ionic strength on the Stern–Volmer suppression constant (K_{sv}) was corrected for as described previously.[21] For DCP, the value of K_{sv} extrapolated to zero ionic strength (K_{sv}^0) was 387 l mol^{-1}. Taking 0·68 μs as the fluorescence lifetime of Ru(bipy)$_3^{2+}$, the calculated value of the quenching rate constant ($5·7 \times 10^8$ s^{-1} l mol^{-1}) was in the expected diffusion-controlled suppression range.[22]

CTAB micelles increased the rate of hydrolysis of DCP (Figure 5). The shape of the observed first-order rate constant (k_ψ) versus [CTAB] plot was typical of micelle-modified rate profiles for reactions between a micelle-incorporated substrate and a reactive counterion.[1,4,23] The experimental results were fitted to an ion-exchange pseudo-phase model using[23]

$$k_\psi = \frac{k_2^0 OH_f[1 + \delta(1/V)K_{OH/Br}K_s(Br_b/Br_f)]}{(1 + K_s C_d)} \quad (11)$$

where Br_b, Br_f and OH_f are the analytical concentrations of Br$^-$ and OH$^-$ ions free in the intermicellar compartment (f) and bound to the micelle (b), respectively, δ is the ratio between the second-order rate constant in water (k_2^0) and that in the micelle (k_2^m), V represents the partial molar volume of the micellized detergent (0·37 l mol^{-1} for CTAB)[3,23], K_s is the micelle–water distribution constant of the substrate and
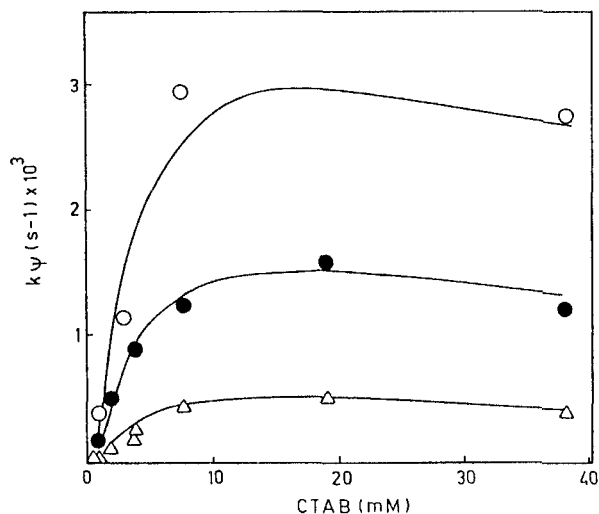
Figure 5. Effect of CTAB on the alkaline hydrolysis of DCP ions. [DCP] = 5×10^{-5} M. Borate buffer, 0·020 M, pH (○) 9·90, (●) 9·61 and (△) 9·13. Solid lines are calculated (see text)
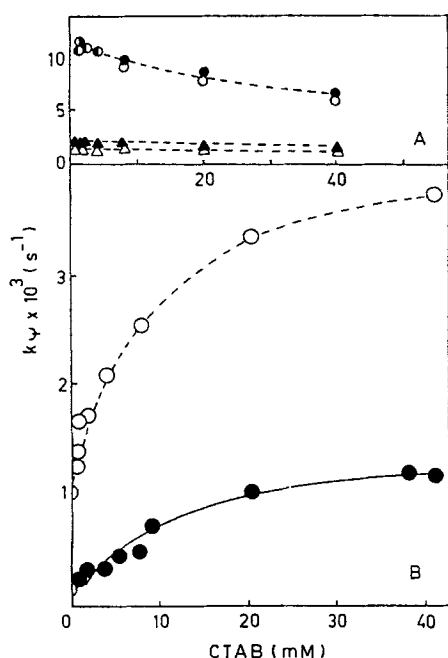
Figure 6. Effect of CTAB on the alkaline hydrolysis of OCP, BCP and MCP ions. RCP concentration $4 \cdot 7 \times 10^{-5}$ M. (A) (○) BCP; (●) MCP, $0 \cdot 02$ M phosphate buffer, pH $11 \cdot 4$; (△) BCP, (▲) MCP, $0 \cdot 02$ M hydrogencarbonate buffer, pH $10 \cdot 7$. (B) (●) OCP, $0 \cdot 02$ M borate buffer, pH $9 \cdot 85$ (solid line was calculated, see text); (○) $0 \cdot 02$ M hydrogencarbonate buffer, pH $10 \cdot 56$

$K_{OH/Br}$ is the selectivity constant for OH^-/Br^- exchange at the micellar surface ($0 \cdot 08$ in CTAB).[3,23] The conceptual foundations and mathematical and computational methodologies for fitting experimental data to equation (11) have been described in great detail.[3,23] The data in Figure 5, obtained at three different pH values, were fitted to equation (12) using a single set of two adjustable parameters. The best fit values were 35 l mol^{-1} and 14 for K_s and δ, respectively. The value of K_s obtained from the fit was different from that obtained measuring the fluorescence quenching (195 l mol^{-1}; see above). This difference may be attributed to the different properties of the system sensed by the two methods.[24] Figure 6 shows the effect of CTAB on the rate of hydrolysis of OCP, BCP and MCP. Only the results with OCP at pH $9 \cdot 85$ were fitted to equation (12); the best fit parameters were $0 \cdot 8$ and 14 for K_s and δ, respectively. Note that, with both substrates, the calculated values of the second-order rate constants in the micelle are higher than those in water, suggesting that CTAB micelles not only concentrate RCP and OH^- but also catalyse the reaction (see Ref. 2 for a discussion of the relative significance of the calculations of second-order rate constants in micelles for bimolecular reactions).

The pyridone yield increased with increasing CTAB concentration for DCP, OCP and BCP (Figure 7). Without detergent, the yield of P from RCPs at pH 9 ws 2 per cent, increasing to 50 per cent at pH $11 \cdot 4$ (Figure 1). The yield of pyridone was essentially 100 per cent for DCP with 0.002 M CTAB and 80 per cent for OCP with $0 \cdot 03$ M CTAB at pH $9 \cdot 8$. Even for BCP, where the kinetic effect of CTAB was negligible, the yield of pyridone at high detergent concentration increased by a factor of two. As demonstrated previously, CTAB did not affect the product distribution with MCP.[12a]

A zwitterionic detergent, SDP, produced a significant rate effect and, most interestingly, increased the yield of P to the same levels reached with the addition of CTAB (Table 5). Rate enhancements on biomolecular
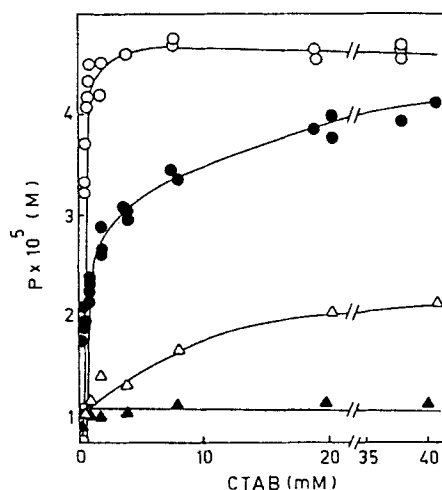

Figure 7. Effect of CTAB on the final concentration of pyridone for the alkaline hydrolysis of RCP ions. Initial concentration of RCP, $4 \cdot 5 \times 10^{-5}$ M; $0 \cdot 02$ M borate buffer, pH $9 \cdot 8$. (○) DCP; (●) OCP; (△) BCP: (▲) MCP

Table 5. Effect of SDP on the observed rate constant (k_ψ) and the product distribution ratio (P/A) for reaction of DCP[a] with OH^-

[SPD] (M $\times 10^3$)	k_ψ (s$^{-1} \times 10^3$)	P/A
$1 \cdot 0$	$2 \cdot 30$	$0 \cdot 50$
$2 \cdot 5$	$2 \cdot 30$	$0 \cdot 50$
$3 \cdot 0$	$2 \cdot 85$	$0 \cdot 74$
$4 \cdot 0$	$13 \cdot 40$	$3 \cdot 35$
$8 \cdot 0$	$20 \cdot 70$	$14 \cdot 60$
$10 \cdot 0$	$24 \cdot 10$	$19 \cdot 00$
$20 \cdot 0$	$31 \cdot 10$	$32 \cdot 00$
$40 \cdot 0$	$27 \cdot 00$	$750 \cdot 00$
$80 \cdot 0$	$20 \cdot 00$	$750 \cdot 00$

[a] in 1 mM NaOH (pH $10 \cdot 80$); [DCP] $= 6 \times 10^{-5}$ M.

Table 6. Effect of SDS on the observed rate constant (k_ψ) and the product distribution ratio (P/A) for the alkaline hydrolysis of RCP (Scheme 1)[a,b]

SDS [M]	k_ψ (s⁻¹ × 10⁴)[a]				P/A							
	MCP	BCP	OCP	DCP	MCP		BCP		OCP		DCP	
					Obs.	Calc.[c]	Obs.	Calc.[c]	Obs.	Calc.[c]	Obs.	Calc.[c]
0·01	370	14·0	—	4·5	1·45	1·46	1·43	1·20	—	—	0·30	0·12
0·02	270	9·0	9	4·4	1·40	1·33	1·70	0·90	1·00	0·17	0·42	0·12
0·05	130	36·0	9	4·6	1·50	1·14	1·90	0·50	1·00	0·17	0·38	0·12
0·08	115	32·0	8	5·3	1·40	1·01	1·80	0·50	0·80	0·17	0·42	0·15

[a] pH 12·30 in 0·02 M phosphate buffer.
[b] [RCP] = 5 × 10⁻⁵ M.
[c] Calculated from the expected P/A corresponding to the observed k_ψ (see text).

reactions by this detergent have been observed previously[25] and an analysis of the effects of SDP on the rate of hydrolysis of RCPs has been reported.[26]

The negatively charged detergent SDS strongly inhibits the rate of alkaline hydrolysis of RCPs.[27,28] The effect of SDS on the P/A ratio is presented in Table 6. In contrast with the effects of CTAB and SDP, the P/A ratios obtained after RCP hydrolysis with SDS micelles, with the exception of MCP, were lower than those obtained in water at the same intermicellar pH (compare Tables 2 and 6). However, the reaction especially for the more hydrophobic substrates, i.e. DCP, takes place exclusively at the micellar surface. The local pH of the negatively charged micellar surface is lower than that in bulk solution (even in the presence of an external buffer), since negatively charged surfaces concentrate counterions, including protons.[1,2,4,23,27,29] Hence the P/A ratio obtained in the absence of micelles at the same pH is not an adequate comparison for data obtained with a micelle-incorporated substrate. Calculation of an absolute value for pH at the micellar surface depends on several debatable assumptions.[1,23] In order to compare the experimentally obtained P/A ratios in SDS micelles with those obtained in water we assumed that the second-order rate constant for the reaction at the micellar surface is identical with that in water. This assumption has been reported repeatedly for several bimolecular reactions.[27] With this assumption, we took the observed second-order rate constant in SDS and, using the data in Table 2, calculated an expected P/A ratio (Table 6). The calculated values, with the exception of the most hydrophilic substrate (MCP), were lower than those observed, suggesting that even in a negatively charged micelle the attack of OH⁻ occurs preferentially at the pyridinium ring.

DISCUSSION

For various types of chemical reactions the second-order rate constants in micelles, calculated using several

models, differ from those in water by no more than one order of magnitude.[4] Thus, micellar rate accelerations stem primarily from substrate concentration and micellar inhibition occurs when one of the reagents is totally or partially excluded from the aggregate.[1,2,4,21] This apparent lack of micellar effects on intrinsic reactivity contrasts with the fact that the properties of many micelle-solubilized substrates are different from those in bulk aqueous solution.[1,30] In several cases, however, micelles do alter reaction products, substituent effects, mechanisms and rate-determining steps.[1,2,5]

The formation of two products on OH⁻ attack on substituted N-alkylpyridinium ions (RCP) is well established.[13,31] With RCPs our values for the product composition of reaction mixtures, obtained using two different analytical procedures, were very similar to those described for MCP.[13] Since both rates and product composition of RCPs were independent of the alkyl chain length, the reaction pathways of RCPs in aqueous solution can be considered identical. The effect of dioxane on P/A ratios can be understood qualitatively. The transition state for pyridone formation involves a species bearing less charge than that leading to the formation of carboxamidopyridinium ion and lowering the dielectric constant should favour the formation of pyridone.

Bulk properties, although not ideal, are convenient models for the rationalization of some properties of the surface of micelles.[1,2] From the effects of salts and dioxane on RCP hydrolysis, we calculated a second-order rate constant in a medium having the bulk properties of the Stern layer of an ionic micelle such as CTAB. The estimated ionic strength at the surface of a CTAB micelle was taken as 3·0 M and the dielectric constant as 32.[1,2] The second-order rate constant in such a medium (k_2^s) was calculated first correcting for the ionic strength using the Brønsted–Bjerrum equation. This value was employed to estimate k_2^s using the Scatchard equation[32] using a value of 4·5 Å as the sum of the radii of the reacting ions.[33] The calculated value of k_2^s was eight times higher than the second-

order rate constant for the alkaline hydrolysis of RCPs extrapolated to zero ionic strength.

The maximum value of the P/A ratio for RCP hydrolysis in aqueous solution is ca 2 whereas in both CTAB and SDP micelles the yield of pyridone approximates 100 per cent. Since the analytical methods employed here have an error of ca 5 per cent, the upper limit of analytically meaningful P/A ratios is 20. A decrease in the effective dielectric constant at the surface of CTAB and SDP micelles, as discussed above, could account for this large difference in product composition. Note that the overall acceleration produced by CTAB is much larger than that obtained with SDP. In part, this latter result is to be expected since CTAB micelles concentrate OH⁻ much more effectively than those of SDP.[25,26] The inhibitory effect of SDS was expected on the basis of substrate incorporation and exclusion of a large part of the OH⁻ from the micellar reaction volume.[27,28] The effect of SDS on the distribution of products, if referred to that expected on the basis of observed rates (Table 6), was small but still showed a preference for attack on the pyridinium ring for the micelle-incorporated substrate.

Micelles, being very loose and constantly fluctuating aggregates,[34] seem poorly suited to produce major changes in activation energy. In fact, most of the rate effects arise from substrate concentration.[1] However, micelles can substantially affect the nature or distribution of products in some chemical reactions.[6-11] Regioselectivity effects have been observed in the OH⁻ attack on vinylphosphonium salts where micellar incorporation results in a preferential reaction at phosphorus.[10] In the system described in this paper micelles of CTAB and SDP produced an increase in the preference for OH⁻ ion attack on the CN carbon of RCPs by at least one order of magnitude. In terms of energy requirements, small differences between two relatively large numbers such as the activation energy for competing reactions can produce dramatic effects on product composition. Even enzymes, which are very sophisticated catalysts, exert their precise mechanistic specificity by combining a large number of small energy contributions.

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