Functional Micellar Catalysis. Part 8.[1] Catalysis of the Hydrolysis of *p*-Nitrophenyl Picolinate by Metal-chelating Micelles containing Copper(II) or Zinc(II)

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The kinetic analysis of the esterolysis of *p*-nitrophenyl picolinate in neutral aqueous solutions of Cu^{2+} and Zn^{2+} in the presence of co-micelles made up of cetyltrimethylammonium bromide and either 6-(myristoylamido)methylpyridine-2-carboxylic acid (**1**) or 6-(myristoylamido)methyl-2-hydroxymethylpyridine (**2**) is reported. The results strongly indicate the formation of reactive micellar ternary complexes composed of metal ion, (**1**) or (**2**), and the substrate. The higher reactivity observed with co-micelles of (**2**) than that with those of (**1**) suggests that the metal ion in the ternary complex with (**2**) acts as a template for an intracomplex nucleophilic attack of the activated hydroxy function of (**2**) on the carbonyl of *p*-nitrophenyl picolinate.

Micelles of functionalized surfactants have been extensively investigated mainly as esterolytic reagents.[2,3] Their mode of action involves hydrophobic binding of the substrate and interaction between the reactive functions covalently bound to the surfactant and the substrate. Analogies have been drawn between enzymatic and micellar reactions and, although their validity may be questioned, they are supported by the observation of quite remarkable accelerations[4–6] in the esterolysis of activated substrates in the presence of functionalized micelles.

Metallomicelles made up of functionalized surfactants capable of effective chelation of metal ions appear as an obvious step towards more versatile systems which may mimic hydrolytic metalloenzymes.[7] Very few examples of this type of system have been so far reported. Melhado and Gutsche[8] described the kinetic effects, albeit modest, in the hydrolysis of acetylphosphate of micellar 5-alkyltriethylenetriamines with divalent ions, suggesting the formation of mixed metal ion–tetramine–substrate chelates. More recently, Tagaki and his co-workers[9] investigated the reactivity of co-micelles of cetyltrimethylammonium bromide (CTABr) and *N*-dodecyl-2-hydroxymethylimidazole with Zn^{2+} in the hydrolysis of *p*-nitrophenyl picolinate (*p*NPP); the accelerations observed have been explained assuming the formation of a reactive mixed chelate in which the activated hydroxy function bound to the imidazole moiety acts as a nucleophile. The kinetic benefits arising from the formation of ternary (functionalized ligand, metal ion, and substrate) complexes have been reported[10,11] for a number of simple non-micellar systems in the hydrolysis of *p*NPP or ATP.

Following early attempts[12] to devise soluble metallomicelles we have synthesized compounds (**1**) and (**2**) which are good candidates as strong chelating agents and investigated their esterolytic reactivity toward *p*NPP (**3**) in co-micelles with CTABr (**4**) in the presence of Cu^{2+} and Zn^{2+}. We here report on the results of the kinetic analysis of this system which strongly suggests the formation of micellar mixed chelates and in the case of (**2**) the nucleophilic action of the hydroxy function bound to the pyridine moeity in the esterolytic process.

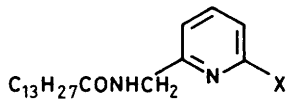
Results and Discussion

Synthesis and Properties of the Ligands.—Both surfactant ligands (**1**) and (**2**) were obtained from pyridine-2,6-dicarboxylic acid diethyl ester. To synthesize (**1**), the diester was partially reduced[13] to 6-hydroxymethylpyridine-2-carboxylic acid ethyl ester which was then converted into the corresponding 6-chloromethyl, 6-aminomethyl, and 6-(myristoylamido)methyl derivatives; the latter was finally hydrolysed [to (**1**)]. To obtain (**2**), the diester was reduced to 2,6-dihydroxymethylpyridine which was converted into the 6-bromomethyl-[14] 6-aminomethyl-, and 6-(myristoylamido)methyl-2-hydroxymethylpyridine (**2**).

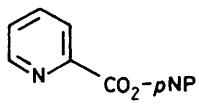
Table 1. Apparent stability constants, K_M/l mol^{-1}, for metal-ion complexes, pH 7.35, 25 °C

	Ligands		
	(1)[a]	(2)[a]	*p*NPP
Cu^{2+}	$>1 \times 10^6$	$(2.0 \pm 0.5) \times 10^4$	$(5 \pm 1) \times 10^3$
Zn^{2+}	$(4 \pm 2) \times 10^4$		

[a] For co-micelles with CTABr; see text.



(**1**) X = CO_2H
(**2**) X = CH_2OH



(**3**)

$C_{16}H_{33}\overset{+}{N}(CH_3)_3\ Br^-$
(**4**)

Compounds (**1**) and (**2**) are very weakly soluble ($< 1 \times 10^{-5}$M) in water. Clear stable solutions of (**1**) up to 1.5×10^{-3}M and of (**2**) up to 5×10^{-4}M can be obtained in the presence of 1×10^{-2}M-CTABr at room temperature. In a 0.02M-*N*-methylmorpholine buffer, pH 7.35 at 25 °C, where most of the kinetic measurements were carried out, the c.m.c. of micelles of CTABr and co-micelles of (**1**) and (**2**) was found to be 0.9—1×10^{-4}M either from surface tension measurements or from the rate–concentration profiles. In the same buffer solution, from changes in the u.v. absorbance[15] of co-micellar (**1**) and (**2**) (using a molar ration CTABr:ligand = 20) in the presence of increasing amounts of Cu^{2+} or Zn^{2+} the apparent stability constants of the complexes shown in Table 1 could be estimated. In the case of Zn^{2+} the relatively small changes in absorbance allowed us to obtain only approximate values for (**1**) and unreliable values with (**2**). The apparent stability constants thus evaluated are approximately one order of magnitude lower than

those measured [16] for picolinic acid or 2-hydroxymethylpyridine and indicate that the chelating ability of the 2-substituted pyridine moiety of (1) or (2), although predictably lower,[2,15] is not dramatically altered by the 6-substituent and by electrostatic effects in the micellar cationic pseudophase.

Hydrolysis of p*NPP in the Absence of Metal Ions.*—In the above cited buffer, pH 7.35, the rate of hydrolysis of *p*NPP is normally accelerated by CTABr micelles or co-micelles. We did not observe any significant difference in the rate–concentration profiles between homo-micelles and co-micelles containing (1) and (2): this indicates that the above co-micellized compounds are virtually inert as esterolytic reagents. Treatment of the kinetic raw data obtained by keeping [*p*NPP] ≪ [CTABr], following established procedure,[2,17] allowed an estimate of the association constant of *p*NPP to micellar or co-micellar surfactants, $K_m = 60 \pm 5$ l mol^{-1}, and a limiting (saturation) rate constant for the hydrolysis of the substrate fully aggregated to micelles, $k_m = 1.2 \times 10^{-3}$ s^{-1} (a limiting acceleration factor of 15 over the spontaneious hydrolysis).

Hydrolysis of p*NPP in the Presence of Metal Ions.*—The hydrolysis of *p*NPP is quite remarkably accelerated by Cu^{2+}. At pH 7.35, with [Cu^{2+}] 1×10^{-4}M, the apparent pseudo-first-order rate constant, k_ψ, is 1 200 times larger than that in the absence of metal ion. The rate–[Cu^{2+}] profile shows a downward curvature indicating a trend toward saturation. Due to turbidity or precipitation, saturation conditions could not be reached; besides, in the range [Cu^{2+}] 2.5—4 $\times 10^{-4}$M, although the solutions were clear, kinetic data were not satisfactorily reproducible. From data obtained for [Cu^{2+}] 0.5—3 $\times 10^{-4}$M and [*p*NPP] 5—9 $\times 10^{-6}$M, the apparent stability constant of the *p*NPP complex with Cu^{2+}, K_M, shown in Table 1, was evaluated by means of the relationship [18] $k_\psi = (k_M K_M[M])/(1 + K_M[M])$. By the same means, the limiting rate constant for the complex between *p*NPP and Cu^{2+} was evaluated $k_M = 0.28 \pm 0.03$ s^{-1}.

The effect of Zn^{2+} on the hydrolysis of *p*NPP is much smaller than that of Cu^{2+}. Being [Zn^{2+}] $= 1 \times 10^{-4}$M the increase of k_ψ is only three-fold relative to that in the absence of metal ion. The rate–[Zn^{2+}] profile up to [Zn^{2+}] 1.4×10^{-3}M does not show any appreciable curvature and indicates that the stability constant for the complex with *p*NPP is very small.

Hydrolysis of p*NPP in the Presence of Metal Ion and Co-micellized* (1) *and* (2).—When the hydrolysis is carried out in the same buffer solution in the presence of metal ion and co-micelles of (1) or (2), the kinetic effects are, predictably, complicated.

Table 2 shows indicative k_ψ values measured for very dilute solutions of metal ions and co-micellized ligands. These data clearly show, besides the much larger catalytic effects of Cu^{2+} than those of Zn^{2+}, that both (1) and (2) in the presence of Cu^{2+} and (2) with Zn^{2+} enhance the rate of esterolysis, (2) being more effective than (1).

The rate–[ligands] profiles obtained for [Cu^{2+}] 8.5×10^{-5}M in excess over [ligands] are shown in Figure 1 and also illustrate the greater effectiveness of (2) relative to (1). In the case of co-

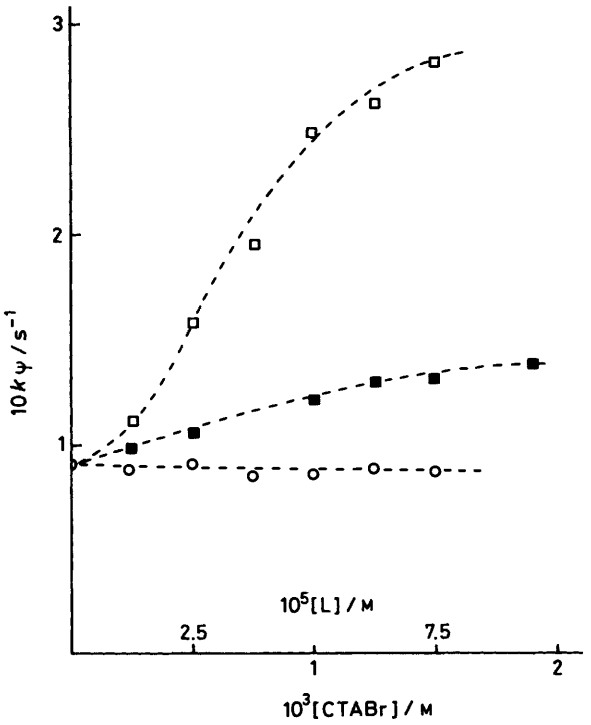


Figure 1. Rate–concentration profiles for [Cu^{2+}] 8.5×10^{-5}M. ○, CTABr only, L absent; ■, L = (1); □, L = (2), [CTABr]:[L] = 20

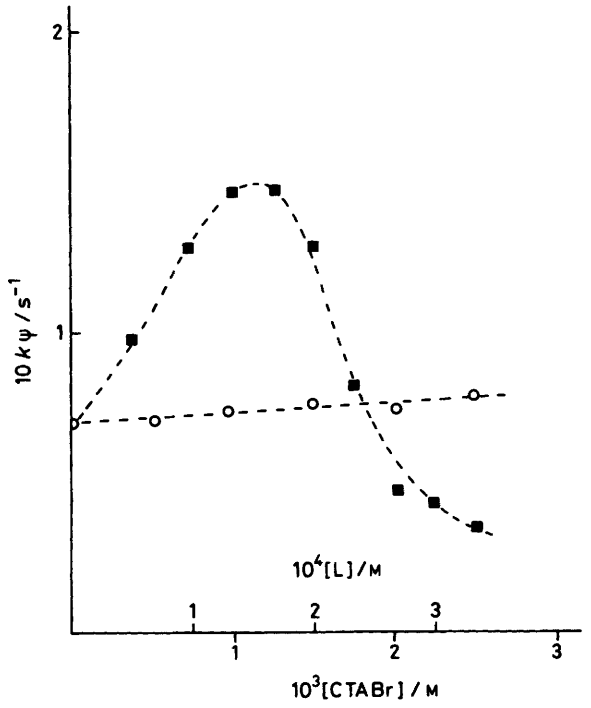


Figure 2. Rate–concentration profiles for [Cu^{2+}] 6.5×10^{-5}M. ○, CTABr only; ■, L = (1), [CTABr]:[L] = 7.5

Table 2. Observed rate constants, $10^4 k_\psi$/s^{-1}, for the esterolysis of *p*NPP,[a] pH 7.35

	M^{2+}[b]		
Ligand	None	Cu	Zn
None	0.8	850	2.5
None + CTABr[c]	2.0	780	2.3
(1)[c,d]	1.9	1 100	2.2
(2)[c,d]	2.0	2 600	5.5

[a] [*p*NPP] 7×10^{-6}M. [b] [M^{2+}] 8.5×10^{-5}M. [c] [CTABr] 1.5×10^{-3}M. [d] [(1)] or [(2)] 7.5×10^{-5}M.

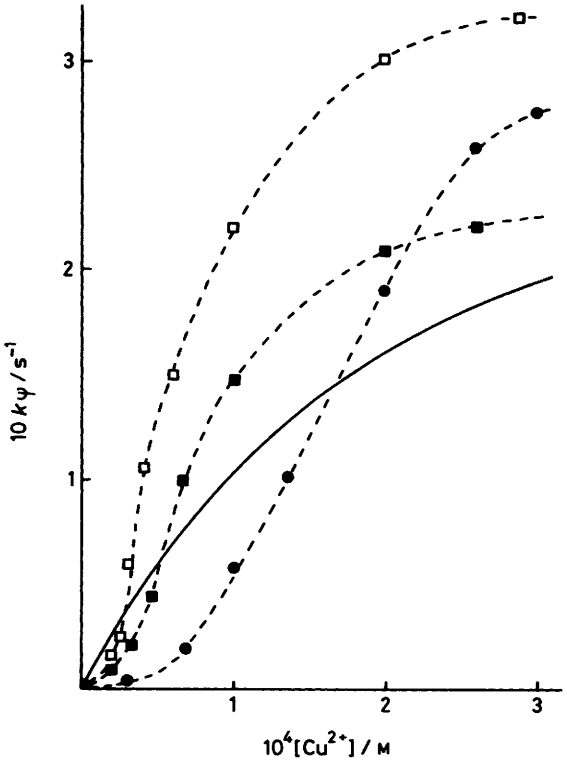


Figure 3. Rate–concentration profiles: [CTABr] 1.5×10^{-3}M in each case: ■, [(1)] 7.4×10^{-5}M; ●, [(1)] 1.98×10^{-4}M; □, [(2)] 7.4×10^{-5}M. The solid line refers to the hydrolysis of *p*NPP without other additives

micelles of (1) the rate–[ligand] profiles display an increase in rate when $[(1)] \leqslant [Cu^{2+}]$ and then a decrease when $[(1)] > [Cu^{2+}]$ as shown in Figure 2. Under the same conditions, using co-micelles of (2) no decrease in rate was observed with increasing [ligand]. It may be noticed from Figures 1 and 2 that addition of CTABr alone does not sensibly affect the rate of esterolysis. Figure 3 shows the rate–$[Cu^{2+}]$ profiles at a given concentrations of (1) or (2): a rather pronounced inhibition is exerted by (1) when $[Cu^{2+}] < [(1)]$ and then a kinetic benefit is apparent. A similar trend is also manifest in the case of (2) although the inhibiting effect is much less pronounced than in the case of (1).

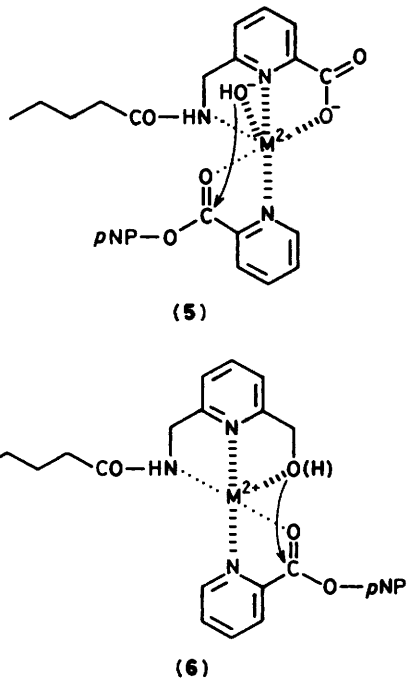
The same type of analysis with Zn^{2+} was not carried out in much detail since the kinetic effects are rather limited. The main difference between Zn^{2+} and Cu^{2+} concerns the effect of co-micelles of (1); these always exert a modest retarding effect in the presence of molar excess of Zn^{2+} relative to the esterolysis carried out in the presence of the metal ion alone.

The kinetic effects reported above, complicated as they appear, can be explained assuming the operation of the processes in the Scheme where S, M, L, and D are the substrate, the metal ion, the ligand, and the surfactant(s) component of the micelles or co-micelles, the subscript m indicates micellar status, S·M, L·M are binary complexes with the metal ion, L·M·S a ternary complex, and $(S \cdot D)_m$ is the micellar aggregate including S. Only the esterolysis of S·M and $(S \cdot M \cdot L)_m$ are indicated as 'productive' thus disregarding spontaneous or micellar (metal ion absent) hydroysis as minor (see above) contributors to the overall rate.

In the case of (1) and Cu^{2+}, K_L is very large, likely more than three orders of magnitude larger than K_M (see Table 1) so that Cu^{2+} is virtually all bound to L_m when $[(1)] > [M]$. Under these conditions, the substrate distributes itself between the large fraction of micelles not containing metal ion and the small fraction of those containing Cu^{2+}, only the latter ones being productive: the overall effect of co-micelles of (1) is then to decrease the apparent rate relative to that in the absence of (1).* When $[Cu^{2+}] > [L_m]$, S may react *via* both processes (1) and (4) in the Scheme, the latter being more effective than the former.

In the case of (2) and Cu^{2+}, K_L is not so large and the relative inhibition due to sequestering of metal ion into the co-micelles when $[L_m] > [M]$ is less pronounced than in the case of (1). On the other hand, this provides further arguments for the high effectiveness of process (4), *i.e.*, for the high reactivity of the micellar ternary complex with (2) compared with that with (1).

Unfortunately, the low solubility of ligands and metal ions prevent us from performing a more quantitative analysis of the system and the evaluation of all parameters involved in the Scheme.



$$S + M \rightleftharpoons S \cdot M \xrightarrow{k_M} P \quad (1)$$

$$S + D_m \overset{K_M}{\rightleftharpoons} (S \cdot D)_m \quad (2)$$

$$M + L_m \overset{K_L}{\rightleftharpoons} (M \cdot L)_m \quad (3)$$

$$S + (L \cdot M)_m \overset{K_T}{\rightleftharpoons} (L \cdot M \cdot S)_m \xrightarrow{k_T} P \quad (4)$$

Scheme.

The kinetic benefits of the ternary complexes involving (1) and (2) may arise from the reactivity of structures (5) and (6). In the case of (5) an activated hydroxide ion, probably co-ordinated to the metal ion but possibly external, is indicated as the nucleophile.[11a,b,19] In the case of (6), furthermore, the

* As suggested by a referee, the rate reduction for $[(1)] > [Cu^{2+}]$ could be due to the formation of ternary complexes $[L_2 \cdot M]_m$, inactive towards *p*NPP, which withhold L·M for the productive step (4) of the Scheme. This cannot be ruled out although the formation of $L_2 \cdot M$ appears unlikely to play a major role in dilute co-micelles ([CTABr]:[L] = 20) such as those used for the profiles of Figure 3.

activated hydroxy function bound to the pyridine moiety of (2) is involved[10,11] as a very effective species in a nucleophilic attack which would lead to a transesterification process.

Using [*p*NPP] ≫ [(2)] ≃ [Cu^{2+}], 'burst' kinetics,[17,20] carried out to verify the transesterification hypothesis, were indeed observed but they were largely artifacts. The slowdown of *p*-nitrophenol release observed after the apparent 'burst' was due to the formation of picolinic acid which, being a very strong chelating agent,[16] removes Cu^{2+} ions from the co-micelles containing (2).

In summary, the present results provide evidence of the formation of metallomicelles and suggest that their catalytic activity in hydrolytic or acyl-transfer process, at least with *p*NPP, is due to the formation of micellar mixed chelates. The potential catalytic activity of the systems could not be fully exploited due to the very low solubility of (1) and (2) and the use of co-micelles with large [CTABr]:[ligand] ratios. Further research aimed to synthesize soluble surfactant analogues of (2) and capable to give metallo-homo-micelles is in progress in this laboratory.

Experimental

Cetyltrimethylammonium bromide, (4), $CuCl_2$, and $ZnCl_2$ were reagent grade commercial products. Metal ion stock solutions were titrated against EDTA following standard procedures.[21] *p*-Nitrophenyl picolinate (3), m.p. 143—145 °C (lit.,[11a] 144—146 °C), 6-hydroxymethylpyridine-2-carboxylic acid ethyl ester, m.p. 95—96 °C (lit.,[13] 95—97 °C), and 2-bromomethyl-2-hydroxymethylpyridine, m.p. 75—78 °C (decomp.) [lit.,[14] 74 78 °C (decomp.)] were prepared according to the literature.

All glass containers were washed with dilute EDTA solutions and then repeatedly washed with bidistilled water before using them with metal ion solutions. ^{1}H N.m.r. spectra were recorded on WP 200 SY or WP 60 Fourier transform Bruker instruments; u.v. and visible absorption measurements were made on a Varian–Cary 219 or a Perkin-Elmer Lambda 5 spectrophotometer equipped with a thermostatted cell holder.

6-Chloromethylpyridine-2-carboxylic Acid Ethyl Ester.—6-Hydroxymethylpyridine-2-carboxylic acid ethyl ester (5.05 g, 30.4 mmol) was dissolved in $SOCl_2$ (10 ml) at 0 °C with stirring. After 1 h, the solution was allowed to reach room temperature and the excess of $SOCl_2$ removed under reduced pressure without heating. Toluene (10 ml) was added to the oily residue, the solution extracted (2 × 10 ml) with a cold 1M-$NaHCO_3$ solution, and dried. Evaporation of the solvent afforded the oily *product* (5.8 g, 96%), $\delta_H(CDCl_3)$ 0.5 (3 H, t, *J* 7 Hz), 3.55 (2 H, q, *J* 7 Hz), 4.6 (2 H, s), and 7.2—7.9 (3 H, m); *m/z* 201 (M^+, 0.69%) 199 (2.07), 155 (14), and 127 (100).

6-Methylaminopyridine-2-carboxylic Acid Ethyl Ester.—The above chloride (29.1 mmol), dissolved in anhydrous DMF (10 ml), was slowly added to a DMF solution of sodium phthalimide (29.5 mmol). After stirring for 2 h at room temperature, the reduction mixture was centrifuged, the solvent removed under reduced pressure, and the residue dissolved in $CHCl_3$. The resulting solution was washed with 0.2M-NaOH (2 × 100 ml) then with H_2O, and dried. Removal of the solvent yielded a solid residue (7.9 g) which was dissolved in warm ethanol (500 ml). Hydrazine (50 mmol) was added and the mixture refluxed until disappearance (t.l.c.) of the starting material. The mixture was then filtered and the solvent evaporated to a small volume. Additions of ethyl ether gave a precipitate which was filtered off; evaporation of the solvent yielded the *product* as an oil (2.2 g, 45%), δ_H ($CDCl_3$) 1.45 (3 H, t), 2.0 (2 H, br, s), 4.08 (2 H, s), 4.48 (2 H, q), and 7.42—8.08 (3 H, m).

6-(Myristoylamido)methylpyridine-2-carboxylic Acid.—To the above amino derivative (11.6 mmol) dissolved in $CHCl_3$ containing triethylamine (11.7 mmol) was slowly added an equimolar amount of myristoyl chloride. After disappearance of the amine (ninhydrin test) the solution was washed with $NaHCO_3$ solution, repeatedly with H_2O, and dried. Evaporation of the solvent afforded a residue which was purified by chromatography on a silica gel column using ethyl acetate–chloroform as eluant. The product, *6-(myristoylamido)methylpyridine-2-carboxylic acid ethyl ester* (2.76 g, 61%), $\delta_H(CDCl_3)$ 0.85 (3 H, t) 1.1 (20 H, m), 1.42 (3 H, t), 1.67 (2 H, br, m), 2.25 (2 H, t), 4.48 (2 H, q), 4.65 (2 H, d), 6.7 (1 H, br, s), and 7.5—8.1 (3 H, m), was dissolved in dioxane (110 ml)–1M-NaOH (27 ml). After hydrolysis of the ester was complete (t.l.c.), HCl was added (pH *ca.* 3) and the solvent evaporated. The residue was crystallized from methanol to give the *product* (1.54 g, 60%), m.p. 138—140 °C (Found: C, 69.75; H, 9.45; N, 7.7. $C_{21}H_{34}N_2O_3$ requires C, 69.75; H, 9.2; N, 7.75%); $\nu_{max.}$(KBr) 3 325, 1 760, and 1 645 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 0.85 (3 H, br, t), 1.23 (20 H, m), 1.55 (2 H, br, m), 2.18 (2 H, t), 4.3 (2 H, d), 7.45—7.92 (3 H, m), and 8.5 (1 H, br, t).

6-Aminomethyl-2-hydroxymethylpyridine.—6-Bromomethyl-2-hydroxymethylpyridine (1.25 g, 6.18 mmol) in anhydrous DMF (10 ml) was added dropwise to a solution of sodium phthalimide (6.2 mmol) in dry DMF (50 ml). The solution was then kept at 40 °C for 5 h under stirring and then cooled at room temperature. Water (50 ml) was added and the solution extracted with CH_2Cl_2 (3 × 40 ml). The organic layer was dried, the solvent removed, and the solid residue washed with light petroleum (b.p. 40—60 °C). This material (1.38 g) was dissolved in ethanol (70 ml) and hydrazine (6.5 mmol) was added. The solution was refluxed for 4 h and filtered. Evaporation of the solvent afforded a residue which was treated with 0.1M-HCl (60 ml). After filtration the aqueous solution was extracted with $CHCl_3$ (30 ml). The aqueous layer was then neutralized with $NaHCO_3$ and continuously extracted with $CHCl_3$. Evaporation of $CHCl_3$ yielded the *product* (0.5 g, 59%) as an oil, b.p. 170 °C at 0.1 mmHg (bulb-to-bulb) (Found: C, 60.5; H, 7.1; N, 20.0. $C_7H_{10}N_2O$ requires C, 60.9; H, 7.25; N, 20.3%); $\delta_H(CDCl_3)$ 2.8 (3 H, br, s), 3.95 (2 H, s), 4.80 (2 H, s), 7.15 (1 H, d, *J* 4 Hz), 7.17 (1 H, d, *J* 4 Hz), and 7.80 (1 H, d, *J* 4 Hz).

6-(Myristoylamido)methyl-2-hydroxymethylpyridine (2).—6-Aminomethyl-2-hydroxymethylpyridine (0.20 g, 1.45 mmol) was dissolved in $CHCl_3$ (40 ml) containing triethylamine (1.5 mmol). Myristoyl chloride (1.5 mmol) in $CHCl_3$ (7 ml) was then added dropwise at 0 °C with stirring. The solution was allowed to warm to room temperature and extracted with saturated $NaHCO_3$ solution (2 × 30 ml) and with water (3 × 30 ml). The organic layer was dried and stripped of solvent. The crude residue was crystallized from ethyl ether–light petroleum (b.p. 40—60 °C) as the *product*, m.p. 98—100 °C (Found: C, 72.25; H, 10.5; N, 8.05. $C_{21}H_{36}N_2O_2$ requires C, 72.4; H, 10.4; N, 8.05%); $\nu_{max.}$(KBr) 3 313, 3 219, and 1 647 cm^{-1}; $\delta_H(CDCl_3)$ 0.89 (3 H, t), 1.4 (20 H, m), 1.65 (2 H, m), 2.26 (2 H, t), 4.6 (2 H, d), 4.8 (2 H, s), 6.58 (1 H, br), and 7.2—7.8 (3 H, m).

pK_a *Spectrophotometric Measurements.*—Absorbances were measured at 25 °C for aqueous buffer solutions containing (1) or (2) (1 × 10^{-4}M) and CTABr (2 × 10^{-3}M) and metal ion of varying concentrations. The blank cell contained an aqueous buffer solution of the metal ion of the same concentration. The ratios of complexed to uncomplexed ligands were obtained from changes in optical density at 270 (1) and 265 (2) nm.

Kinetic Measurements.—The appearance of *p*-nitrophenol was monitored at 400 nm. The kinetic run was initiated by

injecting a 20 μl portion of *p*NPP in CH_3CN into a cuvette containing 2 ml of the proper buffered solution thermostatted at 25 °C. The observed rate constants were related in the case of micellar solutions, in the absence of metal ions, by the equation $k_\psi = (k_o + k_m[D]_m)/(1 + K_m[D]_m)$, to the k_m and K_m parameters defined above, to $[D]_m$ the concentration of micellar surfactants, and to k_o, the k_ψ value in the absence of micelles.

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