Bolaform and Classical Cationic Metallomicelles as Catalysts of the Cleavage of *p*-Nitrophenyl Picolinate

Roberto Fornasier, Paolo Scrimin,* Paolo Tecilla, and Umberto Tonellato*

Contribution from the Dipartimento di Chimica Organica and Centro CNR Meccanismi di Reazioni Organiche, Università di Padova, via Marzolo 1, 35131 Padova, Italy.
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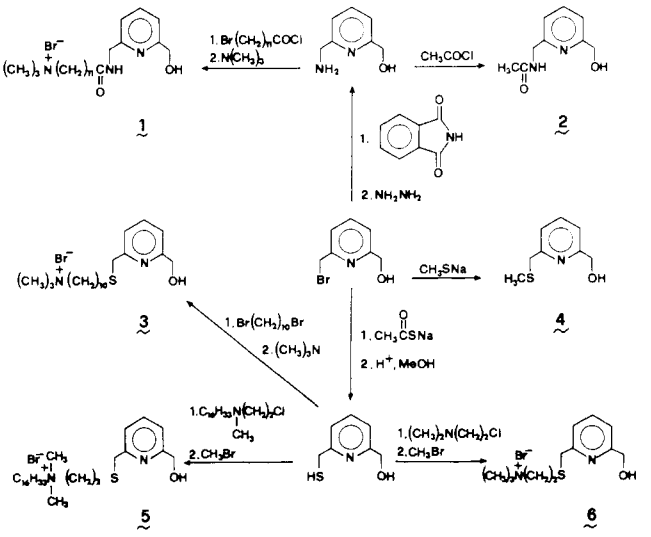
Abstract: Bolaform micelles made of ligand surfactants 6-((((12-(trimethylammonio)-*n*-dodecanoyl)amino)methyl)-2-(hydroxymethyl)pyridine bromide (**1**) or 6-((((10-(trimethylammonio)-*n*-decyl)thio)methyl)-2-(hydroxymethyl)pyridine bromide (**3**) in the presence of Cu(II) or Zn(II) ions are good catalysts of the hydrolysis of *p*-nitrophenyl picolinate (PNPP). In the presence of 4.6×10^{-4} M Cu(II) at pH = 6.25 and 25 °C, 2×10^{-3} M **1** and **3** cleave PNPP with kinetic advantages of 7.6×10^5 and 1.6×10^6, respectively, over the uncatalyzed hydrolysis of the substrate. Classical micelles made of surfactant 6-(((2-(*n*-hexadecyldimethylammonio)ethyl)thio)methyl)-2-(hydroxymethyl)pyridine bromide (**5**) are less efficient ligands for Cu(II) or Zn(II) ions and poorer catalysts of the cleavage of PNPP than **1** or **3** due to the proximity and hence to the electrostatic repulsion between the ammonium group and the metal ion coordination site. The critical feature of the catalytic process is, quite likely, the formation of a ternary complex (**8**) involving ligand, metal ion, and substrate. The (deprotonated) hydroxyl bound to the pyridine moiety of the catalyst in the ternary complex acts as a nucleophile leading to a transacylation intermediate that undergoes a rapid, metal ion assisted hydrolysis "turning over" the catalyst. In all cases the micellar systems are better catalysts than the corresponding neutral nonmicellar models. This indicates that concentration effects coupled with a more facile acid dissociation of the hydroxyl and, possibly, with an enhanced electrophilicity of the metal ion in the aggregates largely offset the adverse electrostatic interactions between the metal ions and the positively charged micellar surface.

The active site of carboxypeptidase A (CPA), a hydrolytic metalloenzyme,[1] has been well defined by X-ray crystallographic analysis,[2] which shows the presence of the coordinated Zn(II) (His-69, His-196, and Glu-72) and of the carboxyl group of Glu-270. Though, at least under special conditions, the participation of Glu-270 as a nucleophile (mixed-anhydride mechanism) has been proved,[3] nucleophilic attack by Zn(II)-coordinated hydroxide ion has been also suggested as a possible mechanism.[4] Indeed, several studies on model compounds have shown that divalent metal cation coordinated water molecules[4,5] or hydroxyl groups[6] may behave as good nucleophiles even at pH close to neutrality because of a decrease of their apparent pK_a by as much as 6 units.[4,6a]

Among the above-mentioned biomimetic models of metalloenzymes there are a few reports in the literature of more complex systems in which a ligand subunit is bound to a receptor molecule or to a micellar system. Thus, Breslow and Overman[7] reported on an α-cyclodextrin functionalized with a Ni(II)-chelated nucleophilic group that is effective in promoting the cleavage of *p*-nitrophenyl acetate. More recently, Murakami and his associates[8] synthesized a bis(imidazole) functionalized cyclophane that, in the presence of Cu(II), accelerated the cleavage of *p*-nitrophenyl dodecanoate. On the other hand, Gutsche prepared metal-chelating micelles[9a] and comicelles[9b] which he tested as catalysts in the cleavage of acetyl phosphate. Tagaki and his co-workers reported on lipophilic ligand molecules in comicellar systems showing good catalytic properties in the cleavage of *p*-nitrophenyl picolinate (PNPP).[10] Accelerated PNPP cleavage has also been observed with micelles made of *N*-aminimides functionalized with a Zn(II) ligand.[11] Recently, Menger reported remarkable accelerations in phosphate ester cleavages by Cu(II) metallomicelles.[12]

Nevertheless a full account on the kinetic effects by homometallomicelles in ester cleavage processes is still lacking in the chemical literature. Following our previous studies on the catalytic effects on PNPP hydrolysis by metal-chelating comicelle,[13] we

Scheme I



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(8) Murakami, Y.; Aoyame, Y.; Kida, M. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1665.
(9) (a) Melhado, L. L.; Gutsche, C. D. *J. Am. Chem. Soc.* **1978**, *100*, 1850. (b) Mei, G. C.; Gutsche, C. D. *Ibid.* **1985**, *107*, 7964.
(10) Tagaki, W.; Ogino, K. *Top. Curr. Chem.* **1985**, *128*, 144 and references therein.
(11) Kuwamura, T.; Yono, Y.; Inokuma, S.; Takenouchi, Y.; Tokue, H. *Chem. Lett.* **1986**, 1519.
(12) Menger, F. M.; Gan, L. H.; Johnson, E.; Durst, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 2800.

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here report the results[14] on the ligand-functionalized, cationic amphiphiles **1**, **3**, and **5**. Comparison of their behavior with that of neutral ligands **2** and **4** and cationic **6** provided additional insight into the mechanism of the catalytic process. The substrate of choice was PNPP since, being also a ligand, it was expected to stress the catalytic effects related to the coordination to the metal cations.

Results

Synthesis and Properties of the Ligands. Surfactants **1**, **3**, and **5** and models **2**, **4**, and **6** were all synthesized from 2-(bromomethyl)-6-(hydroxymethyl)pyridine[15] as a common precursor as outlined in Scheme I. Compounds **1** and **2** were obtained by Gabriel reaction followed by acylation with acetyl chloride (**2**) or ω-bromododecyl chloride and quaternization with trimethylamine (**1**). Model compound **4** was synthesized by reaction of 2-(bromomethyl)-6-(hydroxymethyl)pyridine with sodium thiomethoxide. Surfactant **3** was obtained in four steps: synthesis of the 2-(hydroxymethyl)-6-(mercaptomethyl)pyridine, reaction of the latter with excess 1,10-dibromodecane, and quaternization with trimethylamine. For the synthesis of **5** and **6** the starting material was first converted to 2-(hydroxymethyl)-6-(mercaptomethyl)pyridine and then reacted with *n*-hexadecylmethyl(2-chloroethyl)amine (**5**) or dimethyl(2-chloroethyl)amine (**6**) and eventually with methyl bromide.

All surfactants **1**, **3**, and **5** are reasonably soluble in water and form micellar aggregates. Cmc values have been obtained in pure water by surface tension measurements (3.5×10^{-4} M for **1**, 4×10^{-4} M for **3**, and 1.8×10^{-5} M for **5**; see Figure S1 of the Supplementary Material) and from the rate vs concentration profiles in the buffer system used (1.2×10^{-4} M for **1**, 2.0×10^{-4} M for **3**, and 5×10^{-5} M for **5**). No significant changes of the cmc are apparent from the kinetic profiles upon metal ion complexation.

Following the addition of Cu(II), the aqueous solutions of ligands **3**–**6** (containing a thioether function) show a clearly resolved absorption band around 320 nm. This band does not appear in the case of ligands **1** and **2** and may be classified as the "blue band" due to a $S(\sigma) \rightarrow d_{x^2-y^2}(Cu)$ transition, according to Bosnick and his co-workers.[16] The intensity of the blue bands under similar conditions ([ligand] = 3.3×10^{-4}, $[Cu^{2+}] = 1.33 \times 10^{-3}$ M) is remarkably greater in the case of **3** and **4** than in that of **5** and **6** (A = 0.66, 0.67 and 0.045, 0.048, respectively), thus suggesting a quite different chelating ability in the two sets of thioether ligands. Qualitatively this is also supported by the fact that ligands **3** and **4** are saturated by Cu(II) at relatively low [Cu(II)]/[ligand] ratios. Such a saturation is not attained for ligands **5** and **6** even at very high ratios (>10).

Kinetic Studies. Kinetic experiments were performed in 2-(*N*-morpholino)ethanesulfonate (MES) buffer (pH = 6.25) in the case of Cu(II) and 2,6-lutidine (pH = 7.25) in the case of Zn(II).

In the absence of divalent metal cations surfactants **1** and **3**, above the cmc, slightly increase the rate of cleavage of PNPP. This effect is predictable since it is well-known that cationic micelles increase the rate of hydrolysis of activated esters.[17a] A much lower rate increase was also observed in the presence of the neutral models **2** and **4**.

In the presence of added Cu(II) or Zn(II) cations and *without* other additives the rate of hydrolysis of PNPP increases by at least 2 (Zn(II))[18] or 4 (Cu(II))[18] orders of magnitude. The effect of these metal ions on the hydrolysis of PNPP has been thoroughly investigated by Fife and his associates[19] after early reports by Sigman and Jorgensen.[6a] On addition of micellar surfactants **1** and **3** the rate of cleavage is further increased so that the overall rate acceleration exerted by surfactants and metal cations amounts to ca. 3 (Zn(II))[18] or 6 (Cu(II))[18] orders of magnitude. Models **2** and **4** show also a rate acceleration effect, albeit smaller than that of their surfactant siblings. The rate effect due to addition of micellar **5** is quite small and that of its model **6** is virtually negligible. For these reasons we report the effects due to these last two ligands only at a single Cu(II) concentration.

The tridimensional rate profiles showing all combined effects are reported in Figures 1 and 2 for surfactant **1**. The analogous

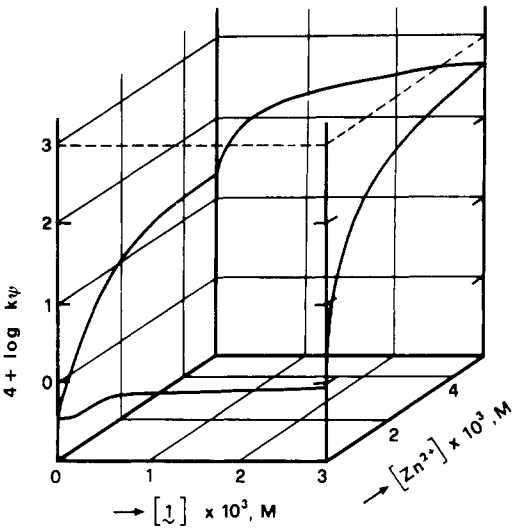

Figure 1. Tridimensional representation of the changes of the observed rate constant, k_ψ, for the cleavage of PNPP as a function of Zn(II) and catalyst **1** concentrations. (2,6-lutidine buffer, pH = 7.25, 25 °C).

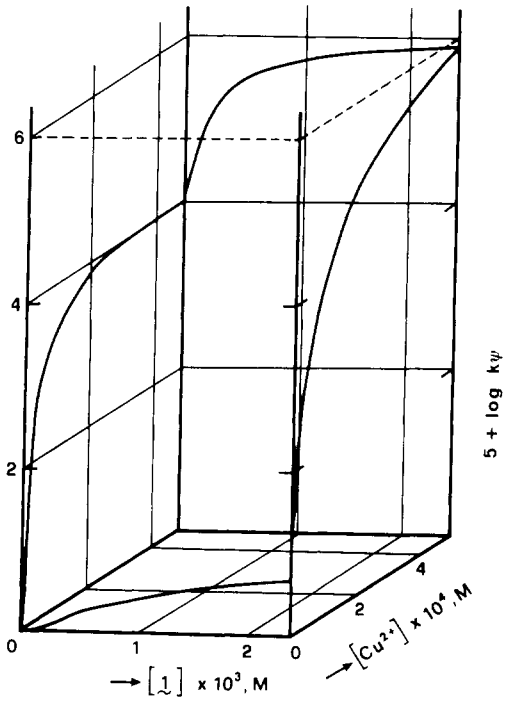

Figure 2. Tridimensional representation of the changes of the observed rate constant, k_ψ, for the cleavage of PNPP as a function of Cu(II) and catalyst **1** concentrations. (MES buffer, pH = 6.25, 25 °C).

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(16) Amundsen, A. R.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6730.

(17) (a) Fendler, J. H.; Fendler, E. J. *Catalysis in Micellar and Macromolecular Systems*; Academic: New York, 1975; pp 104–102. (b) Ibid., pp 194–206.

(18) See Table I for conditions.

(19) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 1041 and references therein.

Table I. Observed Rate Constants, k_ψ (s^{-1}), for the Cleavage of PNPP[a]

cat.[b]	metal[b]	k_ψ, s^{-1}	k_ψ/k_0
none	none	9.7×10^{-6},[c] 2.8×10^{-5}[d]	1, 1
none	Zn	2.8×10^{-3}	100
none	Cu	1.4×10^{-1}	14433
1	none	2.8×10^{-5},[c] 5.5×10^{-5}[d]	2.9, 2.1
1	Zn	3.0×10^{-2}	1071
1	Cu	7.4	762886
2	none	1.1×10^{-5},[c] 3.5×10^{-5}[d]	1.1, 1.2
2	Zn	1.4×10^{-2}	500
2	Cu	1.4	144330
3	none	1.8×10^{-5},[c] 5.0×10^{-5}[d]	1.8, 1.8
3	Zn[e]	1.1×10^{-2}	393
3	Cu	15.5	1597938
4	none	1.0×10^{-5},[c] 3.9×10^{-5}[d]	1, 1.4
4	Zn[e]	4.6×10^{-3}	164
4	Cu	1.3	129897
5	Cu	7.6×10^{-1}	78350
6	Cu	2.7×10^{-1}	27835

[a] At 25 °C and 0.05 M MES buffer (pH = 6.25) for Cu(II) or 0.05 M 2,6-lutidine buffer (pH = 7.25) for Zn(II). [b] Concentration is 5×10^{-3} M for Zn(II) and 4.6×10^{-4} for Cu(II) unless otherwise stated. Catalyst concentration is 2.0×10^{-3} M in all cases. [c] pH = 6.25. [d] pH = 7.25. [e] [Zn(II)] = 3.7×10^{-3} M.

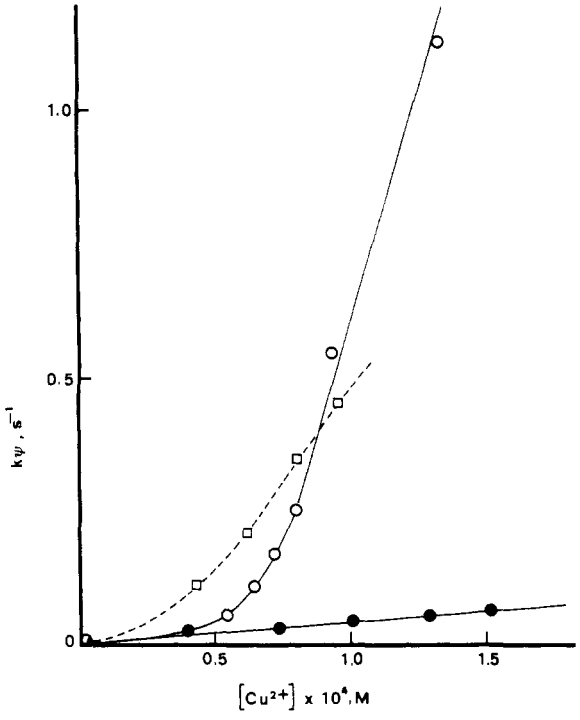


Figure 3. Observed rate constant, k_ψ, for the cleavage of PNPP in MES buffer at pH = 6.25 as a function of Cu(II) concentration in the presence of different catalysts at very high [catalyst]/[Cu(II)] ratios: (●) no catalyst added; (○) [**1**] = 2.9×10^{-3} M; (□), [**2**] = 2.9×10^{-3} M.

profiles for surfactant **3** are quite similar, the system being only slightly more efficient than that with **1**.

Tables S1–S7 of the Supplementary Material present the observed rate constants for the cleavage of PNPP as functions of metal(II), **1**, **2**, **3**, **4**, **5**, and **6** concentrations. Table I summarizes the maximum effects obtained under the different conditions for the various catalysts. These k_{max} values underestimate the maximum catalytic effects since saturation conditions (i.e., ligands completely saturated with metal and substrate) were not experimentally accessible. Figure 3 presents the rate profiles observed for surfactant **1** and model **2**, keeping constant their concentrations and increasing the Cu(II) concentration when [**1**] ≫ [Cu(II)] or [**2**] ≫ [Cu(II)]. Both curves show an inflection, suggesting a lower catalytic effect under these extreme conditions. The effect is apparently more important for surfactant **1** than for the neutral model **2**. An almost superimposable trend is observed for **3** and **4**. This kind of behavior is not observed in the presence of Zn(II).

Table II. Transacylation (k_ψ) and Turnover (k_{turn}) Rate Constants Observed for Catalysts **3** and **4**[a]

run	cat. (10^4concn, M)	$10^2 k_\psi$, s^{-1}	$10^2 k_{turn}$, s^{-1}
1	**3** (0)		(5)[b]
2	**3** (3.8)	310	0.35[c]
3	**4** (0)		8.5
4	**4** (3.8)	46	0.60,[c] 0.65[d]

[a] Conditions: 0.05 M MES, pH = 6.25, 25 °C; [Cu(II)] = 1.37×10^{-4} M. [b] Estimated figure assuming the same inhibition observed for catalyst **4**. [c] For the slow process in the cleavage of PNPP (see text). [d] For the hydrolysis of **7b**.

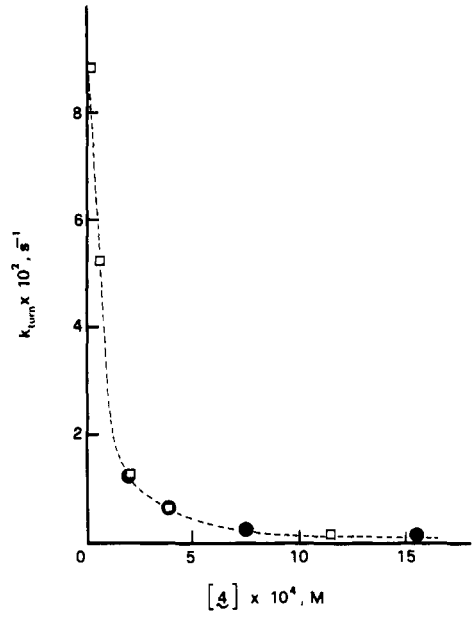
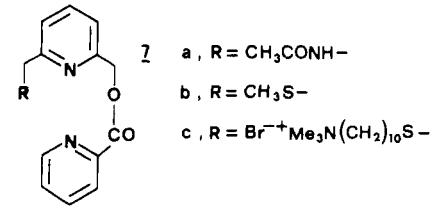


Figure 4. Observed "turnover" rate constant, k_{turn}, as a function of catalyst **4** concentration (MES buffer, pH = 6.25, [Cu(II)] = 1.37×10^{-4} M); (●) slow process in the cleavage of PNPP; (□) cleavage of **7b**.

Turnover Experiments. In a preliminary communication[14] we reported that catalyst model **2** in the presence of Zn(II) and PNPP undergoes a transesterification process leading to intermediate **7a**, which eventually undergoes hydrolysis to give picolinic acid and **2**. Thus, it was important to evaluate the "turnover" capacity of the present catalysts.



This is usually evaluated by the kinetic method described by Bender et al.[20] According to this method an excess substrate (PNPP in our case) is used. When the deacylation of the intermediate is the rate-determining step in the hydrolytic process, the catalyst is rapidly acylated, releasing a burst of *p*-nitrophenol (PNP) stoichiometrically equivalent to the amount of catalyst. After that, the release of PNP should be linear with time and related to the regeneration of catalyst ("turnover"). From the slope of the steady-state portion of the kinetic run, the turnover rate may be evaluated. Although both **1** and **3** present a "burst kinetic" behavior, the real turnover rate can hardly be evaluated with precision because (a) PNPP hydrolysis is catalyzed by the metal also *without* any added catalyst, (b) the released picolinic acid binds strongly to the metal ion and, therefore, quenches the

(20) Bender, M. L.; Kezdy, F. J.; Wadler, F. C. *J. Chem. Educ.* **1967**, *44*, 84.

catalytic process under study, and (c) conditions where [Cu(II)] ≫ [PNPP] ≫ [ligand] cannot be attained due to the limited solubility of Cu(II) ion.

Luckily enough, this problem could be solved for the Cu(II)-catalyzed process in a different way. In fact, during the kinetic experiments with the thioether catalysts **3** and **4** (under the conditions reported in Table II and Figure 4) we observed that the increase of the absorbance at 317 nm due to the release of PNP was followed by a slower kinetic process detectable by the decrease of the absorbance at the same wavelength. We correlated this decrease of absorbance with the competition for Cu(II) between catalyst **3** or **4** and picolinic acid generated during the turnover process. Indeed, for solutions containing the above ligands, in the presence of Cu(II), the blue band at ca. 320 nm decreases on addition of picolinic acid, and it disappears when the [picolinic acid]/[ligand] ratio is ca. 2 (Figure S2 of the Supplementary Material).

Accordingly, by monitoring the decrease of absorbance at 320 nm, it became possible to evaluate the turnover rate constant. For practical reasons this analysis has been done in detail for catalyst **4**. In the same kinetic run we found it more convenient to follow the first, faster, process at 400 nm (PNP released) and then switch the wavelength setting to 320 nm and follow at this wavelength the second, slower, process. These data are reported in Figure 4 as a function of increasing concentrations of catalyst **4** and at a fixed Cu(II) concentration.

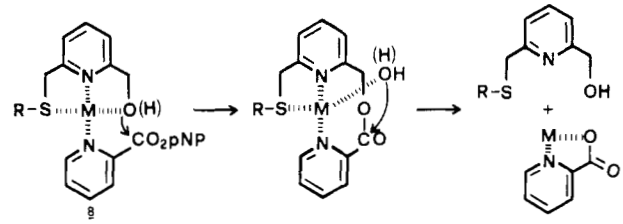
A clear-cut demonstration that the slower process is due to the hydrolytic cleavage of the intermediate **7** is given by the fact that the independently synthesized transacylation product **7b** reacts, under the same conditions, at the same rate observed for the second, slower, process in the cleavage of PNPP in the presence of ligand **4** (squares of Figure 4). This turnover rate depends on the catalyst concentration and decreases on increasing the concentration of **4** to reach a plateau region. In Table II the rates of turnover of surfactant **3** and model **4** at a fixed Cu(II) concentration ([Cu(II)] = 1.37×10^{-4} M) are compared with the rates of the transacylation process, k_ψ, observed for the same catalysts.

Discussion

By all available evidence, ligands **1** and **3**, in spite of the short alkyl chain, form micellar aggregates capable of effectively chelating Zn(II) or Cu(II) ions. In acidic solution or in the presence of the metal ions, they have ionic head groups at the two extreme positions of the paraffinic chain and may therefore be classified as bolaform electrolytes.[21] Ligand **5** is a classical cationic functionalized surfactant, bearing a quaternary ammonium group placed in the proximity of the ligand subunit.

Comparison of the intensity of the blue band in the case of thioether ligands **3**–**6** indicates that the chelating ability of **3** toward Cu(II) ions, also in micelles, is comparable to that of the "neutral" model **4** and is considerably greater (by a factor >10 under similar conditions) than that of **5** and **6**. Thus, apparently, electrostatic factors are of importance when the ammonium nitrogen is structurally close to the pyridino moiety chelating a metal ion and not when it is loosely placed at the surface of micelles as in the case of aggregates of the bolaforms **1** and **3**. Although these indications should be confirmed by a precise determination of the binding constants for all ligands, the spectroscopic indications are substantiated by the kinetic results. Micellar **3** and **1** as well are very effective catalysts whereas, under similar conditions, micelles of **5** are less reactive (again by a factor larger than 10) in the cleavage of PNPP. The lower reactivity may thus be related to a lesser ability of **5** of chelating the metal ion which activates the hydroxy function (see below). On the other hand, aggregates of **1** and **3** are more effective than the corresponding nonsurfactant neutral models **2** and **4**, respectively. Apparently, the hydrophobic binding of the PNPP substrate (the K_b in the case of CTABr micelles is ca. 60 M^{-1})[13] is sufficiently large to offset the adverse electrostatic effect of the positively charged micellar surface.

Scheme II



A solution containing the ligands here investigated, the metal ions, and the reacting substrate is a quite complicated system. From the changes observed in the blue band of thioether ligand **3** and particularly **4**, depending on the relative concentration of the components, the formation of binary complexes L·M, S·M, and P^1·M and ternary homo- and heterogeneous complexes L_2·M, $P^1{}_2$·M, L·M·S, and P·M·S is apparently involved (where S, M, L, P^1, and P are the substrate, the metal ion, the ligand, the transacylation product, and picolinic acid, respectively). When the ratio [Cu(II)]:[L] is not very large, i.e., in most of the experimental conditions used in this work, due also to the low solubility of the metal ion, ternary complexes play a major role.

It is apparent that the catalytic behavior of the ligands here investigated is due to the formation of the ternary complex **8** (ligand–metal ion–substrate). As indicated in Scheme II, the cleavage of the substrate occurs via a pseudointramolecular attack of the hydroxy function[22] on the carbonyl carbon of the ester to give *p*-nitrophenol and the intermediate transacylation product **7**. On the basis of available literature data,[6,23] the apparent pK_a of the hydroxyl group may be estimated to be in the range 7–8 and, therefore, at the pHs used, a significant fraction of the alcoholic function within the complex **8** is expected to be dissociated. Moreover, the metal ion may activate the carbonyl group for a nucleophilic attack as has been suggested for the metal ion mediated hydrolysis of picolinate esters[19,24] occurring via the formation of a binary substrate–metal ion complex.

The efficient hydrolysis of the transacylation intermediate **7** was not unexpected on the basis also of recent studies by Fife and his co-workers[24] on the metal ion catalyzed cleavage of similar derivatives. In this process, as indicated in Scheme II, a Cu(II)-coordinated water molecule (or, more likely, a hydroxide ion) is assumed to be the effective nucleophile, although other kinetically indistinguishable mechanistic pathways are possible. The rate of hydrolysis of **7** and hence the turnover in the presence of **4** (or **3**) decrease with increasing concentration of the catalysts to reach a minimum in a plateau region (see Figure 4). This may indicate that a different reactive species, possibly a ternary complex such as **4**–Cu(II)–**7**, less effective than the binary complex Cu(II)–**7** may intervene in the hydrolysis of **7** at moderately high ligand concentration.

At variance with the transacylation process, the hydrolysis of **7** and hence the turnover are slightly faster for the model system **4** than for the corresponding micellar one **3**. This is somewhat surprising since electrostatic factors should favor the dissociation of the coordinated water to hydroxide ion and hence speed up the hydrolysis in the case of micelles. A possible explanation may be found in the larger availability of water, and consequently in a larger hydration of the metal ion, in the case of the model than in that of the micellar system.

The formation of other ternary complexes is of relevance for the reactivity of the system under extreme conditions. Thus, the inflection observed in the rate profiles of Figure 3 at very low

(21) (a) Fuoss, R. M.; Edelson, D. J. *J. Am. Chem. Soc.* **1951**, *73*, 269. (b) Menger, F. M.; Wrenn, S. *J. Phys. Chem.* **1974**, *78*, 1387.

(22) This is also true for catalysts **1** and **2** where the possibly deprotonated amide moiety could compete with the hydroxyl for the substrate. In fact the transacylation product **7a**[14a] was the only intermediate detected in the catalytic process.

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[Cu(II)]:[L] ratios is likely to be due to the formation of nonproductive ternary L_2–M complexes which subtract the metal ion for the formation of the productive complex **8**. Such inflection is more pronounced in the micellar system of **1** or **3** due to the very high local concentration of surfactant ligands. Nonproductive ternary complexes involving two molecules of picolinic acid are also at work when the substrate concentration is large as indicated by the results of the partly artifactual "burst" experiments and by the "titration measurements" carried out by adding picolinic acid to a solution of Cu(II) and **3** or **4** (see Figure S2 of the Supplementary Material).

Conclusion

The catalytic effectiveness of micellar **1** and **3** as compared to that of the corresponding nonsurfactant uncharged model **2** and **4** may be ascribed to (a) hydrophobic factors that bring the substrate in a small volume together with ligands and metal ions, (b) the enhanced electrophilicity of divalent metal ions toward micellar-bound substrates,[12] and (c) the "local" pH at the micellar surface, which is higher[17b] than that in the bulk phase and may favor the acid dissociation of the hydroxy groups in the reactive ternary complex, **8**.

It is worth mentioning here that preliminary experiments suggest that the catalysts described here require substrates that are able to form complexes with divalent metal cations like PNPP and esters of natural amino acids.[25] A correct geometry is also necessary, and no catalytic effects are observed with nicotinate or isonicotinate esters. Nonligand substrates like *p*-nitrophenyl acetate or hexanoate are not cleaved at appreciably accelerated rates even by micellized **1** or **3**. This behavior has been observed also for other metallomicelles.[26] Apparently, in these cases a micellar-bound substrate does not approach the active site of the ligand functionalized surfactants with the correct geometry for the occurrence of the catalytic process. The mobility of the substrate in the micellar environment far exceeds that in which the metal ion acts as a template, like in **8**, to say nothing of that in the hydrophobic pocket of the enzyme.

The design of a more effective artificial enzyme apparently requires a receptor molecule in which the mode of complexation forces the substrate in close proximity to the reactive center. Work is in progress in our laboratory aimed at the synthesis of such a more sophisticated metalloenzyme model.

Experimental Section

General Methods. Melting points are uncorrected. NMR spectra were measured with Bruker WP 200 SY or WP 60 spectrometers operating respectively at 200 and 60 MHz, and chemical shifts are reported relative to internal Me_4Si. UV spectra were recorded with Perkin-Elmer Lambda 5 or Varian Cary 219 spectrometers equipped with a thermostated cell holder. Surface tension measurements were performed with a Kruss type 8451 tensiometer. Microanalyses were performed by the Laboratorio di microanalisi of our department.

Materials. $Cu(NO_3)_2$ and $Zn(NO_3)_2$ were analytical grade commercial products. Metal ion stock solutions were titrated against EDTA following standard procedures.[27] PNPP[6a] and 6-(bromomethyl)-2-(hydroxymethyl)pyridine[15] were prepared and purified by literature methods. 6-(Aminomethyl)-2-(hydroxymethyl)pyridine was obtained according to the procedure previously described.[13]

6-(((12-(Trimethylammonio)-*n*-dodecanoyl)amino)methyl)-2-(hydroxymethyl)pyridine Bromide (1). To a solution of 6-(aminomethyl)-2-(hydroxymethyl)pyridine (497 mg, 3.6 mmol) and triethylamine (0.53 mL, 3.8 mmol) in freshly distilled $CHCl_3$ (10 mL) was added, dropwise, 12-bromododecanoyl chloride (1.07 g, 3.6 mmol) dissolved in 5 mL of $CHCl_3$. After the addition was complete, the solution was further stirred (3 h) and extracted with H_2O (2 × 10 mL), a saturated solution of $NaHCO_3$ (2 × 10 mL), and finally again with H_2O (2 × 10 mL). The dried $CHCl_3$ solution (Na_2SO_4) was evaporated to one-third of its volume. Upon addition of *n*-pentane a white precipitate was obtained (1.18 g, 82% yield), mp 82–83 °C, which was identified as 6-(((12-bromo-*n*-dodecanoyl)amino)methyl)-2-(hydroxymethyl)pyridine: NMR δ_{CDCl_3} 1.3 (m, 14 H, $(CH_2)_7$), 1.62 (m, 2 H, CH_2CH_2CO), 2.8 (m, 2 H, CH_2CH_2Br), 2.3 (t, 2 H, CH_2CO), 3.4 (t, 2 H, CH_2Br), 4.6 (d, 2 H, NCH_2Py), 4.8 (s, 2 H, OCH_2Py), 6.5 (br t, 1 H, NH), 7.25 (dd, 2 H, Py H3 and H5), 7.75 (t, 1 H, Py H4).

This material was dissolved in 30 mL of a 30% solution of trimethylamine in methanol and kept at 30 °C for 12 h in a sealed vial. Evaporation of the solvent afforded a sticky solid, which was purified by column chromatography (Al_2O_3, MeOH). Analytically pure **1** was obtained as a white solid, mp 80–82 °C (1.08 g, 80% yield): NMR $\delta_{Me_2SO-d_6}$ 1.26 (m, 14 H, $(CH_2)_7$), 1.53 (m, 2 H, CH_2CH_2CO), 1.66 (m, 2 H, CH_2CH_2N), 2.17 (t, J = 7.17 Hz, 2 H, CH_2CO), 3.02 (s, 9 H, $(CH_3)_3N$), 3.24 (m, 2 H, CH_2N), 4.31 (d, J = 6.10 Hz, 2 H, NCH_2Py), 4.53 (s, 2 H, OCH_2Py), 7.11 (d, J = 7.63 Hz, 1 H, Py H5), 7.33 (d, J = 7.63, 1 H, Py H3), 7.76 (t, J = 7.73 Hz, 1 H, Py H4), 8.45 (br t, 1 H, NH).

Anal. Calcd for $C_{22}H_{40}N_3O_2Br$: C, 57.63; H, 8.79; N, 9.16. Found: C, 57.27; H, 8.60; N, 9.33.

6-((Acetylamino)methyl)-2-(hydroxymethyl)pyridine (2). To a solution of 6-(aminomethyl)-2-(hydroxymethyl)pyridine (340 mg, 2.5 mmol) and triethylamine (263 mg, 2.6 mmol) in freshly distilled $CHCl_3$ (10 mL) was added dropwise acetyl chloride (204 mg, 2.6 mmol) dissolved in 5 mL of $CHCl_3$. Stirring was continued for an additional 2 h after completion of the addition. Workup of the reaction mixture afforded after flash chromatography and crystallization from chloroform/*n*-pentane analytically pure **2** as a white solid, mp 99–100 °C (342 mg, 76% yield): NMR δ_{CDCl_3} 2.07 (s, 3 H, CH_3), 2.92 (br s, 1 H, OH), 4.56 (d, J = 5.5 Hz, 2 H, NCH_2), 4.76 (s, 2 H, OCH_2), 6.53 (br t, 1 H, NH), 7.06–7.87 (m, 3 H, Py).

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.54. Found: C, 59.73; H, 6.64; N, 15.40.

6-(((10-(Trimethylammonio)-*n*-decyl)thio)methyl)-2-(hydroxymethyl)pyridine Bromide (3). To a stirred suspension of thiolacetic acid (430 mg, 5.6 mmol) and triethylamine (570 mg, 5.6 mmol) in THF (50 mL) was added at once 6-(bromomethyl)-2-(hydroxymethyl)pyridine (1.08 g, 5.3 mmol), and the slurry was refluxed for 2 h. After cooling to room temperature the reaction mixture was filtered off with suction and the solvent rotary evaporated. The oily crude 6-((acetylthio)-methyl)-2-(hydroxymethyl)pyridine (1 g, 95% yield) was not further purified: NMR δ_{CDCl_3} 2.45 (s, 3 H, CH_3), 4.31 (s, 2 H, SCH_2), 4.7 (s, 2 H, OCH_2), 7.1–7.75 (m, 3 H, Py).

This material was dissolved in 26 mL of a 0.4 M solution of HCl in dry methanol and refluxed under a nitrogen atmosphere for 6 h. The solvent was evaporated, and the crude 6-(mercaptomethyl)-2-(hydroxymethyl)pyridine hydrochloride was crystallized from chloroform with the addition of a few drops of *n*-pentane. The material is very hygroscopic and must be kept in a nitrogen atmosphere to avoid oxidation: NMR δ_{D_2O} (reference HDO = 4.8) 4.1 (s, 2 H, SCH_2), 4.9 (s, 2 H, OCH_2), 7.8–8.4 (m, 3 H, Py).

Anal. Calcd for $C_7H_{10}ClNOS$: C, 43.90; H, 5.20; N, 7.31. Found: C, 43.54; H, 5.28; N, 7.24.

1,10-Dibromo-*n*-decane (1.8 g, 6 mmol) was dissolved in 60 mL of dry DMF containing 1.1 g of anhydrous K_2CO_3. The slurry was vigorously stirred and heated to 60 °C; then 6-(mercaptomethyl)-2-(hydroxymethyl)pyridine hydrochloride (440 mg, 2.3 mmol) dissolved in 60 mL of dry DMF was added during 4 h. After the addition was complete, the mixture was further stirred for 3 h at 60 °C, cooled to room temperature, and left overnight. DMF was then removed under reduced pressure, and the oily material was washed with water (2 × 10 mL) and purified by column chromatography (SiO_2, ethyl acetate/chloroform, 2:5). Evaporation of the proper fractions afforded 6-(((10-bromo-*n*-decyl)thio)-methyl)-2-(hydroxymethyl)pyridine as a colorless solid (628 mg, 73% yield): NMR δ_{CDCl_3} 1.3 (m, 12 H, $(CH_2)_6$), 1.57 (m, 2 H, CH_2CH_2S), 1.85 (m, 2 H, CH_2CH_2Br), 2.49 (t, 2 H, CH_2S), 3.40 (t, 2 H, CH_2Br), 3.83 (s, 2 H, SCH_2Py), 4.74 (s, 2 H, OCH_2), 7.12 (d, 1 H, Py H5).

Anal. Calcd for $C_{17}H_{28}BrNOS$: C, 54.54; H, 7.54; N, 3.74. Found: C, 54.34; H, 7.80; N, 3.72.

The bromide (500 mg, 1.3 mmol) was dissolved in a 33% solution of trimethylamine in methanol and kept at 50 °C overnight in a sealed vial. Evaporation of the solvent afforded crude **3** as a pale yellow solid. Analytically pure **3** was obtained after flash chromatography on Al_2O_3 (MeOH), mp 70–73 °C (504 mg, 87% yield): NMR δ_{CD_3OD} 1.34, 1.42 (2 m, 12 H, $(CH_2)_6$), 1.57 (m, 2 H, CH_2CH_2S), 1.82 (m, 2 H, CH_2CH_2N), 2.51 (t, J = 7.32 Hz, 2 H, CH_2S), 3.16 (s, 9 H, $N(CH_3)_3$), 3.37 (partly hidden behind solvent) (t, 2 H, CH_2N), 3.84 (s, 2 H, SCH_2Py), 4.71 (s, OCH_2Py), 7.39 (d, J = 7.93 Hz, 2 H, Py H5), 7.46 (d, J = 7.93 Hz, 1 H, Py H3), 7.84 (t, J = 7.93 Hz, 1 H, Py H4).

Anal. Calcd for $C_{20}H_{37}ON_2SBr$: C, 55.42; H, 8.60; N, 6.46. Found: C, 55.30; H, 8.78; N, 6.28.

6-((Methylthio)methyl)-2-(hydroxymethyl)pyridine (4). 6-(Bromomethyl)-2-(hydroxymethyl)pyridine (1.2 g, 5.9 mmol) was dissolved in

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10 mL of dry THF and added dropwise to a suspension of sodium thiomethoxide (0.55 g, 7.8 mmol) in 30 mL of dry THF. After completion of the addition, the slurry was refluxed for 2 h, cooled to room temperature, and filtered off and the THF was rotary evaporated. The crude material was distilled (bulb to bulb, 125 °C, 0.01 mmHg) to give 810 mg (80% yield) of product **4** as a pale yellow oil: NMR δ_{CDCl_3} 2.10 (s, 3 H, CH_3), 3.85 (s, 2 H, SCH_2), 4.75 (s, 2 H, OCH_2), 7.1–7.9 (m, 3 H, Py).

Anal. Calcd for $C_8H_{11}NOS$: C, 56.77; H, 6.55; N, 8.28. Found: C, 56.30; H, 6.61; N, 8.03.

6-(((2-(*n*-Hexadecyldimethylammonio)ethyl)thio)methyl)-2-(hydroxymethyl)pyridine Bromide (5). Methyl(2-hydroxyethyl)-*n*-hexadecylamine[28] (2.0 g, 6.7 mmol) was dissolved in 50 mL of thionyl chloride and stirred for 48 h at room temperature. Thionyl chloride was then evaporated under reduced pressure, and the solid residue was washed twice with toluene. The crude *n*-hexadecylmethyl(2-chloroethyl)amine hydrochloride thus obtained, mp 119–122 °C (2.25 g, 95% yield), was not further purified: NMR δ_{CDCl_3} 0.89 (br t, 3 H, $(CH_2)_{15}CH_3$), 1.28 (m, 26 H, $(CH_2)_{13}$), 1.84 (m, 2 H, $(CH_2)_{13}CH_2CH_2N$), 2.83 (s, 3 H, NCH_3), 2.92–3.55 (m, 4 H, NCH_2CH_2Cl and $NCH_2(CH_2)_{14}$), 4.06 (br t, 2 H, CH_2Cl).

This product (942 mg, 2.7 mmol) was dissolved in 60 mL of dry DMF and added dropwise to a suspension of anhydrous K_2CO_3 (1.65 g) and 6-(mercaptomethyl)-2-(hydroxymethyl)pyridine hydrochloride (1.02 g, 5.3 mmol) in 100 mL of dry DMF kept at 40 °C under a nitrogen atmosphere. After the addition was complete (3 h), the reaction mixture was further stirred at 40 °C for 24 h. The DMF was then removed under reduced pressure, and the residual brown solid was dissolved in water and extracted with $CHCl_3$ (3 × 100 mL). The dried (Na_2SO_4) organic layer was filtered and stripped of the solvent. The crude material was chromatographed (SiO_2, $CHCl_3$/MeOH 20:1) to afford 6-(((2-*n*-hexadecylmethylamino)ethyl)thio)methyl)-2-(hydroxymethyl)pyridine as a white solid (520 mg, 44% yield): NMR δ_{CDCl_3} 0.89 (br t, 3 H, CH_3-$(CH_2)_{15}$), 1.28 (m, 26 H, $(CH_2)_{13}$), 1.45 (m, 2 H, $(CH_2)_{13}CH_2CH_2N$), 2.21 (s, 3 H, CH_3N), 2.34 (t, 2 H, CH_2CH_2S), 2.60 (m, 4 H, NCH_2CH_2S and $NCH_2(CH_2)_{14}$), 3.91 (s, 2 H, SCH_2Py), 4.79 (s, 2 H, OCH_2Py), 7.17 and 7.35 (2 d, J = 7.5 Hz, 2 H, Py H3 and H5), 7.72 (t, J = 7.5 Hz, 1 H, Py H4).

A solution of the above derivative (360 mg, 0.82 mmol) in 25 mL of dry CH_3OH was placed in a screw-top pressure tube and cooled to −78 °C. After the addition of 0.25 mL of CH_3Br (4.4 mmol), the tube was sealed and kept at room temperature for 48 h. The solvent was then evaporated and the crude solid obtained was crystallized from acetone/ethyl ether to afford 377 mg (86% yield) of analytically pure **5**, mp 100–102 °C: NMR δ_{CDCl_3} 0.90 (br t, 3 H, $(CH_2)_{15}CH_3$), 1.29 (m, 26 H, $(CH_2)_{13}$), 1.70 (m, 2 H, $(CH_2)_{13}CH_2CH_2$), 2.97 (m, 2 H, NCH_2CH_2S), 3.41 (s, 6 H, $N(CH_3)_2$), 3.54 (m, 2 H, $NH_2(CH_2)_{14}$), 3.85 (m, 2 H, NCH_2CH_2S), 4.07 (s, 2 H, SCH_2Py), 4.84 (s, 2 H, $HOCH_2Py$), 7.12 and 7.51 (2 d, J = 7.63 Hz, 2 H, Py H3 and H5), 7.82 (t, J = 7.63 Hz, 1 H, Py H4).

Anal. Calcd for $C_{25}H_{51}BrN_2OS$: C, 61.00; H, 9.67; N, 5.27. Found: C, 60.90; H, 9.91; N, 5.14.

6-(((2-(Trimethylammonio)ethyl)thio)methyl)-2-(hydroxymethyl)-pyridine Bromide (6). To 50 mL of thionyl chloride cooled at 0 °C was slowly added 2-(dimethylamino)ethanol (2 g, 22.5 mmol). After the addition, stirring was continued at room temperature for 12 h. The thionyl chloride was then evaporated under reduced pressure, and the residue was washed twice with toluene to give 2.97 g (92% yield) of dimethyl(2-chloroethyl)amine hydrochloride, mp 201–203 °C (lit.[29] mp 201.5–203 °C), which was not further purified: NMR δ_{CD_3OD} 3.0 (s, 6 H, $N(CH_3)_2$), 3.62 (t, J = 5.0 Hz, 2 H, NCH_2), 4.02 (t, J = 5.0 Hz, 2 H, CH_2Cl).

This tertiary amine hydrochloride (0.35 g, 2.4 mmol) was dissolved in 70 mL of dry DMF and added dropwise under a nitrogen atmosphere to a suspension of dry K_2CO_3 (1.66 g) and 6-(mercaptomethyl)-2-(hydroxymethyl)pyridine hydrochloride (920 mg, 4.8 mmol) in 100 mL of dry DMF heated at 45 °C. After completion of the addition (2.5 h), stirring was continued at 45 °C for an additional 24 h. After the mixture cooled to room temperature, DMF was evaporated under reduced pressure and the residue was taken up in water (50 mL) and extracted with $CHCl_3$ (3 × 100 mL). The $CHCl_3$ solution was dried and rotary evaporated. The crude material obtained was chromatographed (SiO_2, $CHCl_3$/MeOH, 9:1) to give 520 mg (94% yield) of pure 6-(((2-(dimethylamino)ethyl)thio)methyl)-2-(hydroxymethyl)pyridine as a yellow oil: NMR δ_{CDCl_3} 2.25 (s, 6 H, $N(CH_3)_2$), 2.56 (m, 4 H, NCH_2CH_2S), 3.86 (s, 2 H, SCH_2Py), 4.73 (s, 2 H, OCH_2Py), 7.11 and 7.29 (2 d, J = 7.50 Hz, 2 H, Py H3 and H5), 7.65 (t, J = 7.50 Hz, 1 H, Py H4).

A solution of this material (250 mg, 1.1 mmol) in dry methanol was placed in a screw-top pressure tube and cooled to −78 °C. Methyl bromide (0.63 mL, 11 mmol) was then added, the tube was sealed, and the reaction mixture was stirred for 48 h at room temperature. Evaporation of the solvent gave compound **6** as a pale yellow sticky solid (340 mg, 96% yield): NMR $\delta_{1:1CDCl_3/CD_3OD}$ 2.91 (m, 2 H, NCH_2CH_2S), 3.18 (s, 9 H, $N(CH_3)_3$), 3.66 (m, 2 H, NCH_2CH_2S), 3.99 (s, 2 H, SCH_2Py), 4.76 (s, 2 H, $HOCH_2Py$), 7.51 and 7.52 (2 d, J = 7.63 Hz, 2 H, Py H3 and H5), 7.93 (t, J = 7.63, 1 H, Py H4).

As a consequence of the high hygroscopicity of this compound, no satisfactory elemental analysis could be obtained.

6-((Methylthio)methyl)-2-((2-pyridylcarboxy)methyl)pyridine (7b). Picolinic acid (192 mg, 1.6 mmol) and dicyclohexylcarbodiimide (322 mg, 1.6 mmol) were dissolved in dry pyridine (8 mL). Ligand **4** (264 mg, 1.6 mmol) was then added and the reaction mixture was stirred for 20 h at room temperature. The precipitate formed was then filtered with suction, and the pyridine was evaporated to dryness. The crude material was next purified by column chromatography (SiO_2, $CHCl_3$). Crystallization from ethyl ether/*n*-pentane afforded analytically pure **7b**, mp 68–70 °C (120 mg, 28% yield): NMR δ_{CDCl_3} 2.1 (s, 3 H, CH_3), 3.8 (s, 2 H, SCH_2), 5.6 (s, 2 H, OCH_2), 7.2–8.9 (m, 7 H, 2 Py).

Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21. Found: C, 60.99; H, 5.23; N, 10.29.

Kinetic Studies. Solutions were prepared in MES buffer (0.05 M, pH = 6.25) or 2,6-lutidine buffer (0.05 M, pH = 7.25). Slower reactions were followed on Perkin-Elmer Lambda 5 or Varian Cary 219 spectrophotometers. Faster reactions were followed on a Gilford 2400 spectrophotometer equipped with a Hi-Tech stopped-flow accessory and a Hewlett-Packard 1201A oscilloscope. Reaction temperature was maintained at 25 ± 0.1 °C. Release of *p*-nitrophenol was followed at 317 nm in the case of ligands **1** and **2** and at 400 nm (*p*-nitrophenoxide) in the case of ligands **3**–**6**. Each kinetic run was initiated by injecting a 20–40-μL portion of substrate (1×10^{-3} M in CH_3CN) into the cuvette containing 2 mL of the buffer solution. Rate constants were obtained by linear plots of log $(A_0 - A_t)$ vs time. Correlation coefficients were 0.998 or better. At very low metal ion concentrations a slight deviation from linearity (inhibition) was observed in the very last part of the kinetic run due to subtraction of the metal by released picolinic acid. All the results are reported in Table I and Tables S1–S7 of the Supplementary Material.

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Registry No. 1, 117161-48-5; **2**, 105243-75-2; **3**, 117146-04-0; **4**, 117146-06-2; **5**, 117146-05-1; **6**, 117146-07-3; **7b**, 117146-14-2; Cu(II), 15158-11-9; Zn(II), 23713-49-7; *p*-nitrophenyl picolinate, 24690-42-4; 6-(aminomethyl)-2-(hydroxymethyl)pyridine, 50501-31-0; 12-bromodecanoyl chloride, 61658-00-2; thiolacetic acid, 507-09-5; 6-(bromomethyl)-2-(hydroxymethyl)pyridine, 40054-01-1; 6-[(acetylthio)methyl]-2-(hydroxymethyl)pyridine, 117146-08-4; 6-(mercaptomethyl)-2-(hydroxymethyl)pyridine hydrochloride, 117146-09-5; 1,10-dibromo-*n*-decane, 4101-68-2; 6-(((10-bromo-*n*-decyl)thio)methyl)-2-(hydroxymethyl)pyridine, 117146-10-8; sodium thiomethoxide, 5188-07-8; methyl(2-hydroxyethyl)-*n*-hexadecylamine, 7089-36-3; *n*-hexadecylmethyl(2-chloroethyl)amine hydrochloride, 117146-11-9; 6-(((2-(*n*-hexadecylmethylamino)ethyl)thio)methyl)-2-(hydroxymethyl)-pyridine, 117146-12-0; 2-(dimethylamino)ethanol, 108-01-0; dimethyl(2-chloroethyl)amine hydrochloride, 4584-46-7; 6-(((2-(dimethylamino)ethyl)thio)methyl)-2-(hydroxymethyl)pyridine, 117146-13-1; picolinic acid, 98-98-6; 6-(((12-bromo-*n*-dodecanoyl)amino)methyl)-2-(hydroxymethyl)pyridine, 105243-74-1.

Supplementary Material Available: Figure S1 reporting the surface tension versus concentration profiles for surfactants **1**, **3**, and **5**, Figure S2 reporting the change of absorbance of **3**·Cu(II) and **4**·Cu(II) complexes at 320 nm on addition of picolinic acid, and Tables S1–S7 reporting the observed rate constants as a function of the various catalyst and metal concentrations (10 pages). Ordering information is given on any current masthead page.

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