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Synthesis of New Cu(II)-Chelating Ligand Amphiphiles and Their Esterolytic Properties in Cationic Micelles

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Four new tetradentate 2,6-disubstituted pyridine and tridentate 2-substituted pyridine ligands were synthesized. Two of these compounds possessed a metal ion binding subunit in the form of a 2,6-disubstituted-4-*N*,*N*′-dimethylamine pyridine moiety. Cu^{2+}-complexes of these ligands incorporated in cetyltrimethylammonium bromide (CTABr) micelles speeded the cleavage of *p*-nitrophenyldiphenyl phosphate and *p*-nitrophenyl hexanoate at pH 7.6. On the basis of a kinetic version of Job plot analysis, a 1:1 ligand/Cu^{2+} stoichiometry was found to be the most active species. In CTABr micelles, the pK_a values for the Cu^{2+}-coordinated hydroxyl or pendant $-CH_2OH$ in these ligands were between 7.8 and 7.9. The metallomicellar systems displayed catalytic (turnover) behavior in the presence of excess substrates.

Introduction

To achieve ester hydrolysis near physiological pH, metal-complexing amphiphiles demonstrate impressive results.[1,2] These are also interesting biomimetic models of hydrolytic metalloenzymes.[3] Coordination of the nucleophilic side chains or water molecules to the metal ion enhances their acidity, facilitating deprotanation near physiological pH and thereby accelerating reaction with electrophilic substrates, e.g., ester or phosphates. Several reports have been published describing esterolytic abilities of metal-chelating bidentate and tridentate amphiphiles.[4,5a] However, nothing is known about the amphiphiles derived from tetradentate ligands.

Earlier we reported catalytic ester hydrolysis by monoperoxyphthalates in various surfactant aggregates.[5b] We also examined the catalytic esterolytic properties of synthetic amphiphiles bearing 4-(dialkylamino) pyridine in micellar or microemulsion media.[6] Herein we introduce tetradentate ligand amphiphiles, **1** and **2**, that contain 2-CH_2OH and 4-*N*,*N*-dimethylamino substituents on the pyridine moiety, and two tridentate ligands **3** and **4** that are devoid of 2-CH_2OH and 4-*N*,*N*-dimethylamino units. The synthesis and characterization of the new ligands and their Cu^{2+}-complexes, the results of the kinetic studies at pH 7.6 under pseudo-first-order conditions for the *p*-nitrophenyl diphenyl phosphate (PNPDPP) and *p*-nitrophenyl hexanoate (PNPH) hydrolyses in cationic micelles, and the reactivities in the presence of excess substrates are presented here.

Results and Discussion

The syntheses of **1** and **2** (Scheme 1) were achieved in a few steps from chelimidic acid. The dimethyl 4-chloropyridine-2,6-dicarboxylate, **5**, was hydrolyzed to the diacid and converted to 4-*N*,*N*-dimethylamino derivative upon treatment with aqueous $(CH_3)_2NH$ solution in a pressure tube at 160 °C for ∼24 h. This was then converted to the corresponding dimethyl ester, **6**, in 70% yield by treatment with $SOCl_2$ in MeOH, and **6** was then partially reduced with $NaBH_4$ to methyl-6-hydroxymethyl-4-*N*,*N*-(dimethylamino)pyridine-2-carboxylate (91%). This was oxidized with 1 equiv of MnO_2 to give the monoaldehyde, **7**, in 88% yield. Condensation of **7** with 2-picolylamine to a Schiff base, followed by its reduction with $NaBH_4$, furnished the amine, **8**, in 71% yield. Michael addition of methyl acrylate to **8** gave **9a**, in 60% yield. Saponification of **9a** gave the acid, **9**, in 67% yield. Coupling of *n*-octadecylamine with **9** in $CHCl_3$ at room temperature in the presence of DCC gave **1**, in ∼47% yield. The synthesis of **2** began with the preparation of **10**. This was synthesized in overall 73% yield via Schiff base formation from **7** and $Me_2NCH_2CH_2NH_2$ followed by reduction with $NaBH_4$. Reflux of **10** with

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(1) (a) Scrimin, P.; Tecilla, P.; Moss, R. A.; Bracken, K. *J. Am. Chem. Soc.* **1998**, *120*, 1179. (b) Weijnen, J. G. J.; Koudijs, A.; Engbersen, J. F. J. *J. Org. Chem.* **1992**, *57*, 7258.

(2) (a) Bracken, K.; Moss, R. A.; Ragunathan, K. G. *J. Am. Chem. Soc.* **1997**, *119*, 9323. (b) Menger, F. M.; Gan, L. H.; Johnson, E.; Durst, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 2800. (c) Gellman, S. H.; Petter, R.; Breslow, R. *J. Am. Chem. Soc.* **1986**, *108*, 2388.

(3) (a) Claudia, S.; Rossi, P.; Felluga, F.; Formaggio, F.; Palumbo, M.; Tecilla, P.; Toniolo, C.; Scrimin, P. *J. Am. Chem. Soc.* **2001**, *123*, 3169. (b) Yamada, K.; Takahashi, Y.; Yamamura, H.; Araki, S.; Saito, K.; Kawai, M. *Chem. Commun.* **2000**, 1315. (c) Yan, J.; Breslow, R. *Tetrahedron Lett.* **2000**, *41*, 2059. (d) Kriste, A. G.; Vizitiu, D.; Thatcher, R. J. *Chem. Commun.* **1996**, 913.

(4) (a) Scrimin, P.; Tecilla, P.; Tonellato, U. *J. Org. Chem.* **1994**, *59*, 4194. (b) Scrimin, P.; Tecilla, P.; Tonellato, U.; Vendrame, T. *J. Org. Chem.* **1989**, *54*, 5988.

(5) (a) Bhattacharya, S.; Snehalatha, K.; George, S. K. *J. Org. Chem.* **1998**, *63*, 27. (b) Bhattacharya, S.; Snehalatha, K. *J. Org. Chem.* **1997**, *62*, 2198.

(6) (a) Bhattacharya, S.; Snehalatha, K. *Langmuir* **1995**, *11*, 4653. (b) Bhattacharya, S.; Snehalatha, K. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2021. (c) Bhattacharya, S.; Snehalatha, K. *Langmuir* **1997**, *13*, 378.

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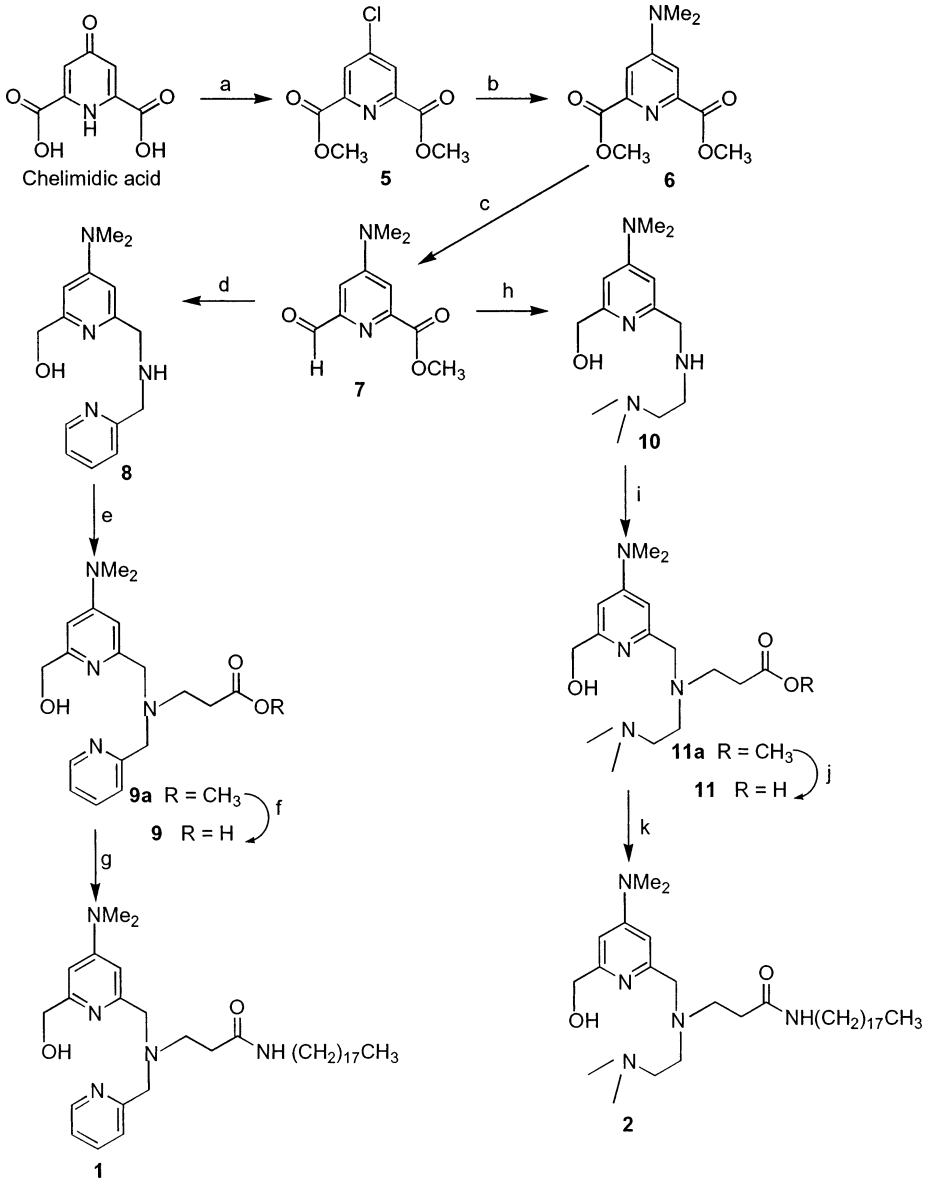
SCHEME 1[a]



[a] Reagents and Conditions: (a) PCl_5, CCl_4, 120 °C; then dry MeOH, reflux 54%; then 1 M NaOH, 80 °C; aq HCl; (b) Me_2NH, 120 °C, aq H_2SO_4, 43%; then $SOCl_2$, MeOH, −10 °C; reflux, 83%; (c) (i) $NaBH_4$ (1 equiv), CH_2Cl_2−MeOH, 0 °C (30 min), rt (5 h), 91%; (ii) MnO_2, CH_2Cl_2, rt, 88%; (d) 2-picolylamine, dry MeOH, 0 °C, 1 h; then $NaBH_4$, rt, 5 h, 71%; (e) methyl acrylate, reflux, 8 h, 60%; (f) MeOH, NaOH, reflux, 1 h, 67%; (g) *n*-$C_{18}H_{37}NH_2$, DCC, dry $CHCl_3$, rt, 12 h, 47%; (h) $Me_2NCH_2CH_2NH_2$, dry MeOH, 0 °C, 1 h; then $NaBH_4$, rt, 5 h, 72%; (i) methyl acrylate, MeOH, reflux, 8 h, 47%; (j) MeOH, NaOH, reflux, 1 h, 90%; (k) *n*-$C_{18}H_{37}NH_2$, DCC, dry $CHCl_3$, rt, 24 h, 70%.

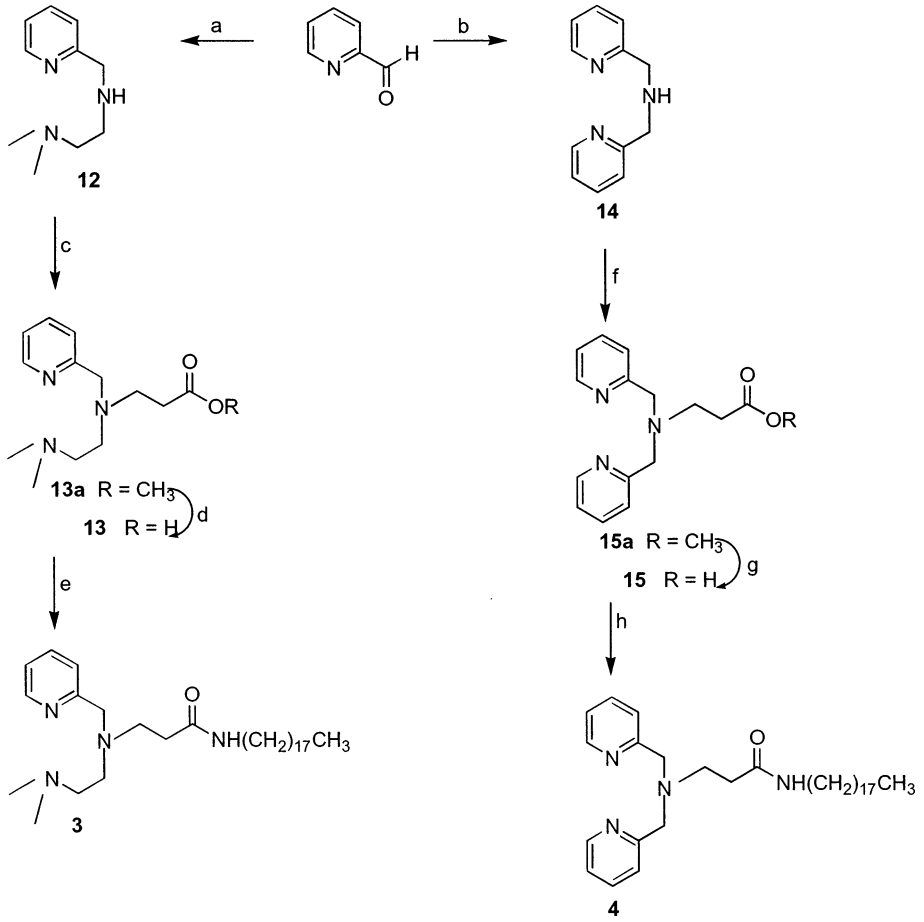
methyl acrylate followed by hydrolysis gave **11**. Reaction of **11** with *n*-octadecylamine in the presence of DCC in $CHCl_3$ afforded **2**, in 70% yield (Scheme 1).

The synthesis of **4** began via coupling of 2-pyridylmethylamine with pyridine-2-carboxaldehyde in MeOH. The Schiff base was reduced with $NaBH_4$ to furnish **14** in 72% yield; **14** upon refluxing with methyl acrylate gave **15a** in ∼77% yield. Saponification of the ester, **15a**, gave the acid, **15**, in 66% yield. Coupling of *n*-octadecylamine with **15** using DCC in $CHCl_3$ gave 70% of **4** (Scheme 2). Similar sequence of reactions was followed for the synthesis of **3**, which started with imination of pyridine-2-carboxaldehyde with *N*,*N*-dimethylethylenediamine. The imine was reduced with $NaBH_4$ to furnish **12** (47%). Reaction of **12** with methylacrylate under reflux followed by saponification gave the acid, **13** (54%). A DCC-mediated coupling of **13** with *n*-octadecylamine gave the ligand, **3**, in ca. 33% yield.

Metal Complexation and Stoichiometry. The ligands **1**−**4** were sparingly soluble in water. The corresponding metal complexes with Co^{2+}, Ni^{2+}, Cu^{2+}, or Zn^{2+} ions required >50 vol % MeOH to keep them in solution in water. However, ligands formed stable solutions when solubilized in cetyltrimethylammonium bromide (CTABr) micelles. Cu^{2+}-complexes of ligands **1**−**4** were generated in situ in CTABr (5×10^{-3} M) micelles prepared in HEPES buffer, pH 7.6 by adding the required amount of $CuCl_2$ solution. Initial experiments suggested that only Cu^{2+}-complexes of **1**−**4** in CTABr micelles were capable of speeding the substrate hydrolysis rates (see below).

A 1:1 complex of **3** and Cu^{2+} gave λ_{max} at ∼667 nm in a CTABr micellar solution. Similarly λ_{max} at ∼680 nm

SCHEME 2[a]



[a] Reagents and conditions: (a) $Me_2NCH_2CH_2NH_2$, dry MeOH, rt, 2 h; then $NaBH_4$, rt, 6 h, 47%; (b) 2-picolylamine, dry MeOH, rt, 1 h; then $NaBH_4$, rt, 3 h, 72%; (c) methyl acrylate, dry MeOH, 12 h, 61%; (d) MeOH, NaOH, reflux, 0.5 h, 54%; (e) *n*-$C_{18}H_{37}NH_2$, DCC, dry $CHCl_3$, rt, 12 h, 33%; (f) methyl acrylate, dry MeOH, reflux, 10 h, 77%; (g) MeOH, NaOH, reflux, 1 h, 66%; (h) *n*-$C_{18}H_{37}NH_2$, DCC, dry $CHCl_3$, rt, 15 h, 70%.

was observed for 1:1 Cu^{2+}-complex of the ligand **4**. The corresponding λ_{max} values for **1** and **2** were 601 and ~650 nm, respectively (Supporting Information, Table S1). The UV−vis absorption spectra of the Cu^{2+}-complexes due to **1**−**4** in micelles are consistent with the formation of four coordinated species, with weak axial interactions. The presence of a single *d*-*d* band in each of these spectra with Cu^{2+}-complexes of **1**−**4** support such conclusions.[7]

To ascertain the nature of the Cu^{2+}-complexes of ligands in solution, we utilized the kinetic version of a Job's plot.[8] A 1:1 stoichiometry for the complexes, ligand:Cu^{2+}, led to the kinetically most efficient formulation in the case of the cleavages of PNPDPP with both tetradentate and tridentate amphiphiles in CTABr micelles at 25 °C, in 0.05 M HEPES buffer (pH 7.6). The cases of ligand **3** and **4** have been illustrated (Supporting Information, Figure S1a) The structures of Cu^{2+}-complexes bis(pyridylmethyl)amine based ligands are already known.[9] The reported stoichiometry of ligand:Cu = 1:1 is also consistent with the present experimental results.

Energy minimized structures for Cu^{2+}-complexes of **1**−**4** are shown in Figure S2 (Supporting Information). The central Cu^{2+} ion utilizes the $-CH_2OH$ group at the 2-position of 4-*N*,*N*-(dimethylamino)pyridine (DMAP)-based ligands **1** and **2** in a distorted square pyramidal geometry. An additional ligating site on Cu^{2+} is occupied by a water molecule in micellar solution. Each tridentate ligand **3** or **4** utilizes two water molecules to satisfy the coordination site of the Cu^{2+} ion.

pK_a Determinations. A pH−rate constant profile was obtained for reactions of substrate PNPH or PNPDPP with catalyst **2**·Cu^{2+} in CTABr comicelles. Buffers used were MES (pH = 6.5−6.9), HEPES (pH = 6.9−7.7), and EPPS (pH = 7.7−8.6) each at 10 mM concentration. A plot of log k_ψ vs pH (Figure S1b, Supporting Information) gave sharp breaks at pH ~7.9 for both the substrates, which was taken as the systemic pK_a of the hydroxyl bound to the Cu^{2+} ion under the given micellar conditions. Similar studies with **1**·Cu^{2+} in CTABr micelles also yielded a pK_a value ~7.9. A pK_a value of 7.7 reported[10] for metallomicellar catalysts based on Cu^{2+}-coordinated 2-hydromethyl pyridine subunits is consistent with our data.

(7) (a) Casell, L.; Carugo, O.; Gullotti, M.; Doldi, S.; Frassoni, M. *Inorg. Chem.* **1996**, *35*, 1101. (b) Hathaway, J. B. *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon: New York, 1987; Vol. 5, p 533.

(8) Job, P. *Ann. Chim. (Rome)* **1928**, *113*, 9.

(9) Young, M. J.; Wahnon, D.; Hynes, R. C.; Chin, J. *J. Am. Chem. Soc.* **1995**, *117*, 9441.

(10) Scrimin, P.; Tecilla, P.; Tonellato, U. *J. Org. Chem.* **1991**, *56*, 161.

TABLE 1. Metallomicellar Cleavages of PNPH and PNPDPP under Pseudo-First-Order Conditions[a]

catalytic ligand	pK_a[b] [% ionization]	PNPH $10^3\ k_\psi$ (s^{-1})	PNPH k_{rel}[c]	PNPDPP $10^3\ k_\psi$ (s^{-1})	PNPDPP k_{rel}[c]
none[d]		0.04	1	0.06	1
1	7.9 [33.4]	2.13	53.3	1.97	32.8
2	7.9 [33.4]	1.62	40.5	0.68	11.3
3	7.8 [38.7]	0.1	2.5	0.33	5.5
4	7.8 [38.7]	0.18	4.5	0.32	5.3

[a] Conditions: 0.05 M HEPES buffer, 0.1 M KCl, pH 7.6; 25 ± 0.1 °C, 0.3 vol % CH_3CN. [ligand] = 5×10^{-4} M, [Cu^{2+}] = 5×10^{-4} M, [CTABr] = 5×10^{-3} M. [b] See text for discussion of pK_a values. Values in brackets are % ionizations at pH 7.6. [c] $k_{rel} = k_\psi/k_{CTABr}$, [d] [cat.] = 0, i.e., without ligands, [CTABr] = 1×10^{-2} M, [$CuCl_2$] = 5×10^{-4} M.

The pH−rate constant profiles for **3** and **4** showed sharp inflections at pH ∼7.8 with either ligand under above condition. Young et al. reported[9] the presence of one titratable proton with pK_a value of ∼8.8 in the corresponding nonamphiphilic Cu^{2+}-bis(pyridylmethyl)-amine complexes, which was assigned to be due to the Cu^{2+}-bound water molecule. Water bound to micellized Cu^{2+}-complexes of **3** and **4** should have an even lower pK_a owing to the highly cationic stern layer wherein the water resides. The release of a proton from Cu-$^+OH_2$ would also be facilitated in a low dielectric constant (∼36) environment known to exist at the micellar surface.[11] Similar pK_a lowering with other nucleophilic systems has also been reported in cationic micelles.[4,9] A pK_a value of ∼7.8 for the deprotonation of the OH bound to **4**·Cu^{2+}-complexes should also originate from effects related to micellization.

Kinetic Studies. The ester cleaving abilities of the ligands **1**−**4** were first examined in CTABr micellar media at pH 7.6 in the absence of any Cu^{2+} ions. Solubilization of **1**, **3**, or **4** in CTABr micelles did not accelerate the substrate hydrolysis rates. The pseudo-first-order rate constants were in fact found to be slightly lower than the rates of hydrolysis in CTABr micelles alone in the absence of ligands. Only ligand **2** displayed ∼7 times greater activity in the cleavage of PNPH in CTABr micelles (Table S2, Supporting Information). Each of **1**−**4** when included in CTABr micelles, however, showed enhanced rate for the cleavage of PNPDPP. The observed modest rate enhancement with **2** in CTABr for both PNPH and PNPDPP hydrolysis reactions is probably due to the involvement of the "supernucleophilic" DMAP moiety in **2**. It is not apparent why **1**/CTABr comicelles were as ineffective as its tridentate ligand counterparts **3** and **4**. It is possible that in the absence of metal ions, the presence of substituents at either 2- or 2- and 6- positions in the DMAP moiety suppresses the esterolytic efficiency of these catalysts, presumably because of steric crowding near the nucleophilic pyridine nitrogen.

Cleavage in the Presence of Cu^{2+} Ions. The Cu^{2+}-complexes of the ligands were prepared in situ in CTABr micelles, and the resulting comicelles were tested for substrate hydrolysis. In Table 1, we collect the values of k_ψ^{obs} for the cleavages of both PNPH and PNPDPP by each Cu^{2+}-complex of ligands **1**−**4** at specified ligand and CTABr concentrations. Catalyst **1**·Cu^{2+} was found to be ∼21 and ∼12 times more efficient in promoting the hydrolysis of PNPH over **3**·Cu^{2+} and **4**·Cu^{2+}, respectively. Similarly, in the case of PNPDPP hydrolysis, catalysts **3**·Cu^{2+} and **4**·Cu^{2+} were ∼6 times inferior to catalyst **1**·Cu^{2+}. The catalyst **2**·Cu^{2+} also exhibited superior rates of substrate cleavage compared to **3**·Cu^{2+} and **4**·Cu^{2+}.

TABLE 2. Kinetic and Thermodynamic Parameters for Cleavage of PNPH or PNPDPP by Comicelles of Either 1·Cu^{2+} or 4·Cu^{2+} with CTABr[a]

ligand	substrate	[CTABr]/[ligand	$10^4\ k_{lim}$ (s^{-1})	K_b (M^{-1})	$10^3\ k_2$ ($M^{-1}\ s^{-1}$)
1	PNPH	30	20.3	6757	67.46
1	PNPDPP	30	12.7	2119	42.21
1	PNPDPP	20	26.7	6849	59.16
1	PNPDPP	10	44.4	7246	49.19
4	PNPH	20	1.85	7042	3.54
4	PNPDPP	30	2.1	2155	6.02
4	PNPDPP	20	4.0	3154	7.65
4	PNPDPP	10	4.58	3389	4.38

[a] Kinetic runs were performed at pH 7.6, with ligand concentrations of 0.1, 0.25, 0.5, 0.75, and 1 mmol and equivalent amount of Cu^{2+} and different molar ratios of CTABr as shown.

A more rigorous analysis of the rate data at pH 7.6 in CTABr comicelles was obtained for two types of catalytic systems, **1**·Cu^{2+} and **4**·Cu^{2+}. For this, kinetic studies were performed with solutions containing increasing amounts of complexes **1**·Cu^{2+} or **4**·$Cu^{2+}$and CTABr with molar ratios relative to the complexes of 30, 20, and 10, using either PNPH or PNPDPP as substrates. The corresponding rate−concentration profiles show saturation behavior (Figure S3, Supporting Information). Analysis of the curves by fitting the k_ψ vs [ligand] data using the Michaelis−Menten type equation[12] allows the estimation of (i) the rate constants, k_{lim} expected for the substrate being fully bound to the aggregates, and (ii) the apparent binding constants (K_b) for PNPH or PNPDPP in different comicelles. Both in the case of **1** and **4**, K_b as well as k_{lim} values increase as the ratio [CTABr]/[ligand] decreases. Selected data are given in Table 2.

The second-order rate constants for these reactions in micellar pseudophase, k_2, were calculated[13] using the equation, $k_2 = k_{lim} \cdot V_M \cdot [D^t]_m/[D^f]_m(1 + [H^+]/K_a)$, where $[D^t]_m$ is the total concentration of the micellized surfactant, $[D^f]_m$ is the concentration of the Cu^{2+}-complexed amphiphile, and K_a is the dissociation constant for the complexed ligand. We have used a V_M value of 0.37 $dm^3\ mol^{-1}$ for CTABr micelles.[13b] The term $[D^t]_m/[D^f]_m$ takes into account the dilution of the reactive Cu^{2+}-complex in the CTABr comicelle, and the term $(1 + [H^+]/K_a)$ denotes the fraction of the dissociated ligand. Comparison of k_2 values in Table 2 also confirms better reactivity of **1** over **4** for both PNPH and PNPDPP.

Turnover Experiments. To test whether different Cu^{2+}-complexes of ligands exhibit catalytic turnover under comicellar conditions, kinetic runs in the presence of excess substrates were performed. At pH 7.6 and 25 °C, using [ligand] = 1.25×10^{-5} M, [$CuCl_2$] = 1.25×10^{-5}

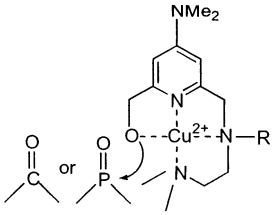
(11) Mukherjee, P.; Ray, A. *J. Phys. Chem.* **1966**, *70*, 2144.

(12) (a) Fornasier, R.; Tonellato, U. *J. Chem. Soc., Faraday Trans.* **1980**, *76*, 1301. (b) Bunton, C. A.; Savelli, G. *Adv. Phy. Org. Chem.* **1986**, *22*, 213.

(13) (a) Scrimin, P.; Tecilla, P.; Tonellato, U.; Bunton, C. A. *Colloids Surf., A* **1998**, *144*, 71. (b) Mancin, F.; Tecilla, P.; Tonellato, U. *Langmuir* **2000**, *16*, 227.

M, and [CTABr] = 1×10^{-3} M, we observed a quantitative release of *p*-nitrophenoxide with no evidence of "burst" kinetics, using up to a 4-fold excess of either PNPH or PNPDPP over the catalyst. Kinetic profiles with **1** or **4** obtained in the presence of 4-fold excess PNPDPP are shown (Figure S1c). These results provide clear evidence of turnover with both types catalysts (**1** or **4**) and substrates (PNPH or PNPDPP). Control experiments showed that *p*-nitrophenoxide released during esterolysis did not practically affect the rate of cleavage. This is in accordance with observation reported earlier.[10]

Taken together these data clearly show that the Cu^{2+}-complexes of **1** and **2** featuring a pendant $-CH_2OH$ coordinating unit are more effective as catalysts than **3** and **4**, both of which lacked the $-CH_2OH$ group in their Cu^{2+}-complexation sites. Assuming that Cu^{2+} is strongly bound to all of the ligands in CTABr comicelles, the esterolysis reaction most likely proceeds via a nucleophilic attack of a $-CH_2OH$ bound to the Cu^{2+} ion on to the hydrophobic substrate confined in the micellar assembly. Within such an assembly, a hydroxide may



Micelle-bound

compete with the ligand (dissociated) $-CH_2OH$ group for a nucleophilic attack to the carbonyl or phosphoryl centers of PNPH or PNPDPP, respectively. The involvement of the $-CH_2OH$ group of the ligand is favored as the result of entropic reasons and also owing to its higher apparent acidity.[14] The stronger reactivity of **1** or **2** over **3** or **4** may in part be attributed to the higher nucleophilicity of the Cu^{2+}-bound $-CH_2O^-$ moiety relative to the metal-bound hydroxy group. Thus with ligands **1** and **2**, a "complex" of the type shown below appears as the most effective system leading to the cleavage of PNPH or PNPDPP on the basis of the following evidence: the 1:1 stoichiometry, the same apparent pK_a for both types of substrates indicating Cu^{2+} activated $-CH_2OH$ as the nucleophilic function, the absence of inhibition due to the liberated *p*-nitrophenoxide in the turnover experiments, and hence, the lack of competition for the complexation to the Cu^{2+} ion.

However, with either **1**·Cu^{2+} or **2**·Cu^{2+}, transfer of the acyl or phosphoryl group from the substrate to the $-CH_2OH$ was not observed in the presence of excess substrates. Although there is no buildup of a transacylated or phosphorylated intermediate (no "burst" kinetics) during the reaction involving excess substrate, this does not exclude their rapid formation and hydrolysis assisted by Cu^{2+}-bound hydroxy group. Indeed lack of transacylation or phosphorylation of the $-CH_2OH$ by the substrates such as PNPH or PNPDPP was also observed with Cu^{2+}-complex of 6-(dodecylamino)methyl-2-hydroxymethyl pyridine in micellar media where the involvement of Cu^{2+}-bound $-CH_2OH$ was proven.[10]

(14) Petitfaux, C. *Ann. Chim.* **1973**, *14*, (8), 33.

Experimental Section

Melting points are uncorrected. Description of analytical instruments have been reported.[6] All buffers were made in Millipore water. All chemicals were purchased from best known commercial sources. Solvents were dried and freshly distilled as required. PNPDPP was synthesized and purified according to literature method.[15c] Energy minimizations were performed using Insight II program version 97.5 (Biosym. Technology) on a Silicon Graphics Octane workstation.

Synthesis. Compounds **9** and **14** were synthesized using procedures as described earlier.[5a,15]

2-Hydroxymethyl-4-*N*,*N*-(dimethylamino)pyridine-6-aminomethyl-*N*′2-pyridylmethylamine (8). To a solution of 0.21 g (1 mmol) of **7** in dry MeOH (8 mL) was added 0.11 g of picolylamine (1 mmol) with continuous stirring under nitrogen for 3 h. Next, 0.38 g of $NaBH_4$ (10 mmol) was added, and the mixture was stirred for another 12 h. Excess $NaBH_4$ was quenched with dilute HCl until neutral. The mixture was concentrated and extracted using $CHCl_3$. The solution was concentrated, and the residue was purified by chromatography over neutral alumina column using MeOH/$CHCl_3$ (2:98). The pure product was isolated as a gummy solid in 70% yield. ^{1}H NMR: ($CDCl_3$, 90 MHz) δ 3.1(s, 6H), 4.0 (s, 4H), 4.7 (s, 2H), 4.9 (s, 1H), 5.1 (s, 1H), 6.5 (d, 2H), 7.2 (t, 1H), 7.4 (d, 1H), 7.7 (t, 1H), 8.5 (d, 1H). EI-MS: 271 (M^+, 18%), 180 (40%), 166 (100%), 93(13%).

2-Hydroxymethyl-4-*N*,*N*-(dimethylamino)pyridine-6-aminomethyl-*N*′-2-pyridylmethylamine-*N*′-(3-methyl propionate) (9a). A mixture of 0.19 g (0.69 mmol) of **8** and 0.6 g of methyl acrylate (0.7 mmol) in dry MeOH was refluxed for 8 h. Excess methyl acrylate and MeOH were evaporated, and the crude compound was purified by chromatography on silica gel using MeOH/$CHCl_3$ (5:95). The pure compound was isolated as a gum in 60% yield. IR: (neat) 1720 cm^{-1}. ^{1}H NMR: ($CDCl_3$, 90 MHz) δ 2.5 (t, 2H), 3.0 (t, 2H), 3.1 (s, 6H), 3.6 (s, 3H), 3.9 (d, 4H), 4.8 (s, 2H), 5.7 (m, 1H), 6.7 (d, 2H), 7.2 (t, 1H), 7.4 (d, 1H), 7.7 (t, 1H), 8.6 (d, 1H). EI-MS: 358 (M^+, 2%), 194 (21%), 180 (40%), 166 (100%), 93 (26%).

2-Hydroxymethyl-4-*N*,*N*-(dimethylamino)pyridine-6-aminomethyl-*N*′-2-pyridylmethylamine-*N*′-(3-propionic acid) (9). To a solution of 0.18 g (0.5 mmol) of **9a** in 5 mL of MeOH was added 0.04 g (1 mmol) of NaOH, and the mixture refluxed for 1 h. This was cooled to 0 °C and neutralized with dilute HCl, excess MeOH was evaporated, and the residue was purified by column chromatography using MeOH/$CHCl_3$ (1:4). The purified compound was isolated as a low melting solid in 67% yield. IR: (neat) 3400, 1705 cm^{-1}. ^{1}H NMR: ($CDCl_3$, 90 MHz) δ 2.5 (t, 2H), 3.0 (t, 2H), 3.2 (s, 6H), 4.0 (d, 4H), 4.8 (t, 1H), 4.9 (s, 2H), 6.4 (d, 2H), 7.4 (m, 3H), 8.5 (t, 1H). Anal. Calcd for $C_{18}H_{24}N_4O_3 \cdot H_2O$: C, 59.65; H, 7.23; N, 15.46. Found: C, 60.02; H, 7.5; N, 15.12.

2-Hydroxymethyl-4-*N*,*N*-(dimethylamino)pyridine-6-aminomethyl-*N*′-2-pyridylmethylamine-*N*′-(3-octadecyl propionamide) (1). To a stirred solution of 0.5 g (1.45 mmol) of **9** and 0.59 g (2.86 mmol) of DCC in dry $CHCl_3$ (20 mL) was added 0.39 g of *n*-octadecylamine, and the mixture was stirred for 12 h. This was then filtered, the filtrate was evaporated, and the crude compound was purified by column chromatography on silica gel using MeOH/$CHCl_3$ (8:92). The pure compound was isolated in 47% yield. IR: (neat) 1630 cm^{-1}. ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.8 (t, 3H), 1.1 (s, 32H), 1.47 (t, 2H), 2.6 (t, 2H), 3.0 (t, 2H), 3.2 (s, 6H), 4.0 (s, 4H), 4.8 (s, 2H), 6.5 (d, 1H), 6.6 (d, 1H), 7.2 (t, 1H), 7.4 (d, 1H), 7.6 (t, 1H), 7.9 (br t, 1H), 8.6 (d, 1H). EI-MS, 595 (M^+, 5%), 503 (20%), 180 (100%), 166 (100%). Anal. Calcd for $C_{36}H_{61}N_5O_2$: C, 72.56; H, 10.32; N, 11.75. Found: C, 72.73; H, 10.1; N, 11.93.

(15) (a) Larsen, S.; Michelsen, K.; Pederson, E. *Acta Chem. Scand.* **1986**, *40*, 63. (b) Gultneh, Y.; Ahvazi, B.; Khan, A. R.; Butcher, R. J.; Tuchagues, J. P. *Inorg. Chem.* **1995**, *34*, 3633. (c) Gulik, W. M.; Geske, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 2928.

2-Hydroxymethyl-4-*N*,*N*-(dimethylamino)pyridine-6-aminomethyl-*N*′-2-*N*,*N*-dimethylaminoethylamine (10). A mixture of 0.21 g of (1 mmol) of **7** and 0.088 g (1 mmol) of *N*,*N*-dimethylethylenediamine was taken in 5 mL of dry MeOH and stirred for 2 h. To this was added 0.19 g of $NaBH_4$ (5 mmol), and the mixture was stirred for another 5 h. Excess $NaBH_4$ was quenched by dilute HCl at 0 °C. MeOH was evaporated, and the residue extracted with $CHCl_3$, concentrated, and purified by column chromatography (silica gel) using MeOH/$CHCl_3$ (15:85). The pure product was isolated as a yellow gum in 73% yield. IR: (neat) 3310 cm^{-1}. ^1H NMR: ($CDCl_3$, 90 MHz) δ 2.2 (s, 6H), 2.5 (t, 2H), 2.7 (t, 2H), 3.0 (s, 6H), 3.8 (s, 2H), 4.6 (s, 2H), 6.4 (d, 1H), 6.5 (d, 1H). EI-MS: 252 (M^+, 10%), 208 (20%), 194 (50%), 181 (100%).

2-Hydroxymethyl-4-*N*,*N*-(dimethylamino)pyridine-6-aminomethyl-*N*′-2-*N*,*N*-dimethylaminoethane-*N*′-(3-methyl propionate) (11a). Compound **11a** was synthesized analogously as described under the synthesis of **9a**. Chromatography on silica gel using MeOH/$CHCl_3$ (5:95) afforded the pure product as a yellow viscous liquid in 58% yield. IR: (neat) 1730 cm^{-1}. ^1H NMR: ($CDCl_3$, 90 MHz) δ 2.3 (s, 6H), 2.5 (m, 8H), 3.0 (s, 6H), 3.6 (d, 3H), 3.9 (s, 2H), 4.6 (s, 2H), 6.4 (s, 1H), 6.6 (s, 1H).

2-Hydroxymethyl-4-*N*,*N*-(dimethylamino)pyridine-6-aminomethyl-*N*′-2-*N*,*N*-dimethylaminoethane-*N*′-(3-propionic acid) (11). Compound **11** was synthesized using procedure a similar to that used for **9**. Purification was achieved using chromatography on silica gel with MeOH/$CHCl_3$ (15:85). Pure compound was isolated in 90% yield. IR: (neat) 1700 cm^{-1}. ^1H NMR: ($CDCl_3$, 90 MHz) δ 2.3 (s, 6H), 2.6 (m, 8H), 3.0 (s, 6H), 4.0 (s, 2H), 4.6 (s, 2H), 6.7 (s, 2H). Anal. Calcd for $C_{16}H_{28}N_4O_3 \cdot H_2O$: C, 56.12; H, 8.83; N, 16.36. Found: C, 56.51; H, 9.17; N, 15.99.

2-Hydroxymethyl-4-*N*,*N*-(dimethylamino)pyridine-6-aminomethyl-*N*′-2-*N*,*N*-dimethylaminoethane-*N*′-(3-octadecyl propionamide) (2). To 60 mg (0.185 mmol) of **11** in dry $CHCl_3$ (5 mL) was added 76 mg of DCC (0.37 mmol), and the mixture was stirred for 10 min at room temperature. Next, 0.5 g (0.185 mmol) of *n*-octadecylamine was added, and the mixture was stirred for 12 h, filtered, concentrated, and purified by chromatography on silica gel with MeOH/$CHCl_3$ (1:9) to afford a solid in 70% yield. IR: (neat) 1630 cm^{-1}. ^1H NMR: ($CDCl_3$, 200 MHz) δ 0.87 (t, 3H), 1.24 (s, 32H), 1.46 (t, 2H), 2.42 (t, 2H), 2.7 (t, 6H), 2.89−3.11 (m, 6H), 3.17 (s, 6H), 3.78 (s, 2H), 4.67 (s, 2H), 6.54 (s, 1H), 6.56 (s, 1H), 7.62 (br t, 1H). EI-MS: 575 (M^+, 5%), 194 (100%), 182 (40%). Anal. Calcd for $C_{34}H_{65}N_5O_2$: C, 70.91; H, 11.38; N, 12.16. Found: C, 70.6; H, 11.03; N, 12.41.

***N*-(3-Methylpropionate)-bis(2-pyridylmethyl)amine (15a).** Compound **15a** was prepared following a method described for the synthesis of **9a**. Chromatography on silica gel using MeOH/$CHCl_3$ (2:98) furnished a yellow oil (0.49 g, 77%). IR: (neat) 1730 cm^{-1}. ^1H NMR: ($CDCl_3$, 90 MHz) δ 2.5 (t, 2H), 2.8 (t, 2H), 3.6 (s, 3H), 4.8 (s, 4H), 7.2 (t, 2H), 7.4 (d, 2H), 7.6 (t, 2H), 8.5 (d, 2H). EI-MS: *m*/*z* 285 (M^+, 15%), 93 (100%), 193 (90%). This was isolated as hydrochloride and was recrystallized from EtOAc/hexane to afford a colorless solid as a trihydrochloride salt. Anal. Calcd for $C_{16}H_{19}N_3O_2.3HCl$: C, 48.68; H, 5.62; N, 10.65. Found: C, 48.69; H, 5.25; N, 11.03.

***N*-(3-Propionicacid)bis(2-pyridylmethyl)amine (15).** Compound **15** was synthesized using a procedure described for the synthesis of **9**. Final purification was achieved with column chromatography (silica gel) using MeOH/$CHCl_3$ (15:85) to give a hygroscopic solid (0.16 g, 66%), mp 104−105 °C. IR: (Nujol) 3350, 1710 cm^{-1}. ^1H NMR: ($CDCl_3$, 90 MHz) δ 2.6 (t, 2H), 3.0 (t, 2H), 4.0 (s, 4H), 7.2 (t, 2H), 7.4 (t, 2H), 7.7 (t, 2H), 8.6 (d, 2H). EI-MS: *m*/*z* 271 (M^+, 25%), 93 (100%), 212 (42%), 193(40%). Anal. Calcd for $C_{15}H_{17}N_3O_2 \cdot H_2O$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.35; H, 6.18; N, 14.86.

***N*-(3-Octadecylpropanamido)bis(2-pyridylmethyl)-amine (4).** To a solution of 0.2 g (0.74 mmol) of **15** in 10 mL of dry $CHCl_3$ was added 0.3 g (1.5 mmol) of DCC, and the mixture was stirred at room temperature for 10 min. Next, 0.2 g (0.74 mmol) of *n*-octadecylamine was added to this, and the resulting mixture was stirred for 15 h. Then the solvent from the reaction mixture was evaporated, and the residue was chromatographed on silica gel using MeOH/$CHCl_3$ (5:95). Evaporation of the fractions gave pure compound gave a hygroscopic, white solid (0.27 g, 70%), mp ∼50 °C. IR: (Nujol) 3250, 1640 cm^{-1}. ^1H NMR: ($CDCl_3$, 200 MHz) δ 0.8 (t, 3H), 1.2 (s, 32H), 2.4 (t, 2H), 2.8 (t, 2H), 3.2 (m, 2H), 3.9 (s, 4H), 7.1 (t, 2H), 7.4 (d, 2H), 7.6 (t, 2H), 8.2 (m, 1H), 8.6 (d, 2H). EI-MS: *m*/*z* 522 (M^+, 10%) Anal. Calcd for $C_{33}H_{54}N_4O \cdot 1.5H_2O$: C, 72.08; H, 10.45; N, 10.19. Found: C, 72.02; H, 10.61; N, 9.94.

***N*-(*N*′,*N*′-Dimethylaminoethyl)(2-pyridylmethyl)-amine (12).** To a solution of 1.07 g (10 mmol) of 2-pyridine carboxaldehyde in 5 mL of dry MeOH was added 0.88 g (10 mmol) of *N*,*N*-dimethylethylenediamine, and the mixture was stirred at room temperature for 2 h. The mixture was cooled to 0 °C, and 1.89 g (50 mmol) of $NaBH_4$ was added and stirred for 6 h. Then the reaction mixture was neutralized with dilute HCl and evaporated to dryness. The residue was extracted with $CHCl_3$ and concentrated to afford a crude product, which was purified by column chromatography on silica gel using MeOH/$CHCl_3$ (8:92) to obtain **7** as a yellow oil (0.85 g, 47%). IR: (neat) 3340 cm^{-1}. ^1H NMR: ($CDCl_3$, 90 MHz) δ 2.2 (s, 6H), 2.5 (t, 2H), 2.7 (t, 2H), 2.9 (s, 1H), 3.9 (s, 2H), 7.1 (t, 1H), 7.4 (d, 1H), 7.7 (t, 1H), 8.5 (d, 1H). EI-MS: *m*/*z* 179 (M^+, 3%), 58 (100%), 121 (85%), 71 (43%), 92 (30%).

***N*-(3-Methylproionate)(*N*′,*N*′-Dimethylaminoethyl)(2-pyridylmethyl)amine (13a).** Compound **13a** was synthesized using a procedure described for the synthesis of **9a**. Chromatography on silica gel using MeOH/$CHCl_3$ (1:9) afforded pure product as an oil (0.38 g, 60%). IR: (neat) 1720 cm^{-1}. ^1H NMR: ($CDCl_3$, 90 MHz) δ 2.2 (s, 6H), 2.5 (m, 4H), 2.8 (m, 4H), 3.6 (s, 3H), 3.8 (s, 2H), 7.2 (t, 1H), 7.4 (d, 1H), 7.7 (t, 1H), 8.5 (d, 1H). EI-MS: *m*/*z* 265 (M^+, 25%), 207 (100%), 58 (55%), 175 (43%), 92 (43%).

***N*-(3-Propionic acid)(*N*′,*N*′-dimethylaminoethyl)(2-pyridylmethyl)amine (13)** Compound **13** was prepared following the synthetic procedure of **9**. Purification was achieved by column chromatography on silica gel using MeOH/$CHCl_3$ (1:3). The pure compound was isolated as a solid (0.076 g, 54%). IR: (neat) 3400, 1710 cm^{-1}. ^1H NMR: ($CDCl_3$, 90 MHz) δ 2.5−2.6 (br *m*, 6H), 2.8 (s, 6H), 3.2 (t, 2H), 3.8 (s, 2H), 7.2 (t, 1H), 7.5 (d, 1H), 7.6 (t, 1H), 8.2 (d, 1H). EI-MS: *m*/*z* 251 (M^+, 8%), 58 (100%), 193 (62%), 92 (42%), 121 (40%). Anal. Calcd for $C_{13}H_{21}N_3O_2 \cdot H_2O$: C, 57.97; H, 8.61; N, 15.6. Found: C, 58.2; H, 9.0; N, 15.27.

***N*-(3-Octadecylpropanamido)(*N*′,*N*′-dimethylamino-ethyl)(2-pyridylmethyl)amine (3).** A mixture of 0.13 g of **13** (0.52 mmol) and 0.207 g (1 mmol) of DCC was taken in 10 mL of dry $CHCl_3$, and the mixture was briefly stirred. Next, 0.139 g (0.52 mmol) of *n*-octadecylamine was added, and the mixture was stirred for 16 h. Then $CHCl_3$ was stripped from the mixture to leave a residue purified by chromatography (silica gel) using MeOH/$CHCl_3$ (8:92). The pure compound was isolated as a gum (0.086 g, 33%). IR: (neat) 3250, 1640 cm^{-1}. ^1H NMR: ($CDCl_3$, 90 MHz) δ 0.87 (t, 3H), 1.25 (s, 32H), 2.44 (t, 2H), 2.5 (s, 6H), 2.8 (m, 6H), 3.2 (t, 2H), 3.8 (s, 2H), 7.2 (t, 1H), 7.4 (d, 1H), 7.7 (t, 1H), 7.8 (m, 1H), 8.5 (d, 1H). HR-MS: calcd for $C_{31}H_{58}N_4O$ 506.4611, found 506.4635. Anal. Calcd for $C_{13}H_{58}N_4O$: C, 74.05; H, 11.63; N, 11.14. Found: C, 74.3; H, 11.41; N, 11.52.

Kinetic Measurements. Solutions of ligands and additives (CTABr) were prepared in 0.05 M HEPES buffer (μ = 0.1 KCl). The metallomicelles were generated in situ by the addition of an appropriate amount of a given metal salt solution to the cuvette. The solution was carefully stirred, and the reaction was initiated by injection of 15 μL of stock solution of PNPH or PNPDPP in CH_3CN. Substrate hydrolysis was followed

spectrophotometrically at 25 ± 0.1 °C by measuring the absorbance at 400 nm for the release of *p*-nitrophenoxide ion as a function of time. Esterolysis followed pseudo-first-order kinetics when a large excess of catalyst (5×10^{-4} M) was employed over substrate (2.5×10^{-5} M). The rate constants were obtained by nonlinear regression analysis of the absorbance vs time data.[6a]

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Supporting Information Available: Computer-generated energy minimized structures of Cu^{2+}-complexes of **1**−**4**; kinetic version of Job's plot, log k_ψ vs pH profile, excess substrate cleavage, and kinetic experiments at different molar ratios of L/Cu^{2+}/CTABr profiles; UV−vis spectral data for Cu^{2+}-complexes of ligands **1**−**4** in CTABr micelles and kinetic parameters for micellar cleavages of PNPH and PNPDPP. This material is available free of charge via the Internet at http://pubs.acs.org.

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