METALLOMICELLAR HYDROLYTIC CATALYSTS CONTAINING LIGAND SURFACTANTS DERIVED FROM ALKYL PYRIDIN-2-YL KETOXIME

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Dedicated to Professor Jaromir Plesek on the occasion of his 70th birthday.

N-Hexyl- (**2a**), *N*-octyl- (**2b**), *N*-decyl- (**2c**) and *N*-dodecyl-*N*-[2-(hydroxyimino)-2-(pyridin-2-yl)-ethyl]dimethylammonium (**2d**) nitrates were synthesized as water-soluble cationic ligand surfactants. Three types of micellar catalytic systems employing salts **2** were prepared: homomicellar water solutions of salts **2**, comicellar solutions of salts **2** with an inert cationic tenside hexadecyltrimethylammonium bromide (CTAB) and comicellar systems consisting of complexes of ligand surfactants **2** with transition metal ions (Co(II), Ni(II), Cu(II) and Zn(II)) and CTAB. Hydrolytic efficiency of all micellar and metallomicellar systems was tested by measuring the kinetics of the model substrate cleavage under pseudo-first-order reaction conditions. Of the above-mentioned catalysts, comicellar systems of salts **2** comicellized with CTAB were most efficient. In all cases, with the exception of Zn(II), coordination of a metal ion decreased the hydrolytic efficiency of salts **2**.
Key words: Ester hydrolysis; Ligand surfactant; Micellar catalysis; Pyridine derivatives.

Catalytic effect of micellar systems on hydrolytic reactions has been studied for several decades[1]. So far, a great number of different types of functional tensides have been designed and studied as hydrolytic catalysts, many of them exhibiting impressive efficiency[2]. Among them, amphiphilic transition metal ion complexes possessing hydrophobic alkyl chain in molecule have been of considerable interest during the last decade[3]. These compounds can be considered as "metallotensides" with a cationic metal ion polar head group. Several "metallomicelles" formed either by aggregation of "metallotensides" (ref.[3c]) or by their co-aggregation with an inert cationic tenside, such as cetyltrimethylammonium bromide (CTAB), have been reported to mimic the function of hydrolytic metalloenzymes, *e.g.* carboxypeptidase A (ref.[4]) and alkaline phosphatases[5]. They bring together the lipophilic substrate with the nucleophilic function of the cata-

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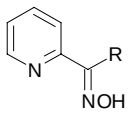
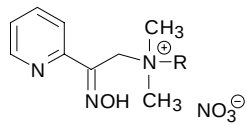
lyst activated by its coordination to the metal ion. Activation of the electrophilic center by the metal ion has been also suggested[3a,3c,3f].

In our previous communication[6] we described powerful hydrolytic metallocatalysts containing Ni(II) complexes of lipophilic alkyl pyridin-2-yl ketoximes **1** comicellized with CTAB. These catalysts efficiently cleaved alkanoates in the span of several pH units, starting from pH 4 up to pH 9. However, solubility of ligands **1** in micellar solutions of CTAB was poor, thus limiting the efficiency of the prepared catalysts. This led us to modify the structure of alkyl pyridin-2-yl ketoximes **1** by introducing a solubilizing quaternary ammonium group into the side alkyl chain. In the present communication we describe the synthesis of alkyl(dimethyl)[2-(hydroxyimino)-2-(pyridin-2-yl)ethyl]-ammonium salts **2**.



	R
1a	octyl
1b	dodecyl
1c	tridecyl



	R
2a	hexyl
2b	octyl
2c	decyl
2d	dodecyl

Quaternary salts **2** can be considered as cationic "ligand surfactants", *i.e.* cationic tensides containing chelating *N,N′*-donor grouping in their molecule. The quaternary salts **2** were expected to be soluble both in CTAB and in pure water forming thus comicellar and homomicellar systems. The hydrolytic efficiency of micellar systems containing surfactants **2** and their complexes with several transition metal ions (Co(II), Ni(II), Cu(II) and Zn(II)) was tested in the cleavage of 4-nitrophenyl hexanoate (PNPH), 4-nitrophenyl diphenyl phosphate (PNPDPP) and 4-nitrophenyl picolinate (PNPP) as model substrates.

EXPERIMENTAL

Temperature data were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM 400 spectrometer (400 MHz). Chemical shifts are given in ppm relative to tetramethylsilane as internal standard, coupling constants *J* in Hz. IR spectra were recorded on a Nicolet 740 FT-IR spectrometer. Bands are given in cm^{-1}. Elemental analyses were performed on a Perkin–Elmer 240 analyzer. TLC analyses were carried out on glass plates Kieselgel 60 F254 or on DC Alufolien, Kieselgel 60 F254 (Merck Laboratory Chemicals). Column chromatography was performed on Kieselgel 60 H (Merck Laboratory Chemicals).

Chemicals: Hexyl-, octyl-, decyl- and dodecylamine, formaldehyde and formic acid (purum) were obtained from Fluka. 2-Acetylpyridine (purum) and hexadecyltrimethylammonium bromide (p.a.) were purchased by Merck. 2-(Morpholin-1-yl)ethanesulfonic acid (MES), *N*-(2-hydroxyethyl)piperazine-*N*′-(2-ethanesulfonic acid) (HEPES), *N*-(2-hydroxyethyl)piperazine-*N*′-(3-propanesulfonic acid) (EPPS), 2-(cyclohexylamino)ethanesulfonic acid (CHES), 3-(cyclohexylamino)-1-propanesulfonic acid (CAPS), 4-nitrophenyl hexanoate (PNPH), 4-nitrophenyl pyridine-2-carboxylate (PNPP) (all p.a.) were products of Sigma. Bromine (purum) was obtained from Reachim. 4-Nitrophenyl diphenyl phosphate (PNPDPP) was synthesized and purified by published method[7].

2-(Bromoacetyl)pyridinium Bromide

A solution of bromine (8.5 ml, 0.165 mol) in CCl_4 (30 ml) was added dropwise to the refluxing solution of 2-acetylpyridine (20 g, 0.165 mol) in CCl_4 (370 ml). After 2 h the resulting yellow crystals were filtrered off, washed with acetone and dried in dessicator. Yield 34.8 g (75%), m.p. 203–207 °C (reported[8] 204–208 °C). ^{1}H NMR spectrum (CD_3OD): 3.88 m, 2 H (CH_2Br); 8.16 ddd, 1 H, *J*(5,4) = 8.2, *J*(5,6) = 5.9, *J*(5,3) = 1.3 (H-5); 8.30 dt, 1 H, *J*(3,4) = 8.2, *J*(3,5) = *J*(3,6) = 1.0 (H-3); 8.75 td, 1 H, *J*(4,5) = *J*(4,3) = 7.8, *J*(4,6) = 1.6 (H-4); 8.83 ddd, 1 H, *J*(6,5) = 5.8, *J*(6,4) = 1.5, *J*(6,3) = 0.7 (H-6).

Alkyl(dimethyl)amines **3**

Alkyl(dimethyl)amines **3** were prepared by Eschweiler–Clark methylation of corresponding alkylamines with formaldehyde and formic acid[9]. The obtained products were purified by distillation.

Hexyl(dimethyl)amine (**3a**)

Yield 135.1 g (55%), b.p. 146 °C (reported[10] 143–144 °C). ^{1}H NMR spectrum ($CDCl_3$): 0.87 t, 3 H, *J*(6′,5′) = 6.9 (CH_3); 1.28 m, 6 H ((CH_2)$_3$); 1.44 qi, 2 H, *J*(2′,3′) = *J*(2′,1′) = 7.3 (C**H**$_2$CH$_2$N); 2.20 s, 6 H ((CH_3)$_2$N); 2.22 t, 2 H, *J*(2′,1′) = 7.4 (CH_2N).

Dimethyl(octyl)amine (**3b**)

Yield 88.6 g (38%), b.p. 97–99 °C/4.7 kPa (reported[10] 79–80 °C/2.1 kPa). ^{1}H NMR spectrum ($CDCl_3$): 0.88 t, 3 H, *J*(8′,7′) = 6.9 (CH_3); 1.29 m, 10 H ((CH_2)$_5$); 1.45 qi, 2 H, *J*(2′,3′) = *J*(2′,1′) = 7.0 (C**H**$_2$CH$_2$N); 2.21 s, 6 H ((CH_3)$_2$N); 2.23 t, 2 H, *J*(2′,1′) = 7.4 (CH_2N).

Decyl(dimethyl)amine (**3c**)

Yield 178.5 g (74%), b.p. 80–83 °C/0.2 kPa (reported[10] 62 °C/0.1 kPa). ^{1}H NMR spectrum ($CDCl_3$): 0.88 t, 3 H, *J*(10′,9′) = 7.0 (CH_3); 1.26 m, 14 H ((CH_2)$_7$); 1.45 qi, 2 H, *J*(2′,3′) = *J*(2′,1′) = 7.2 (C**H**$_2$CH$_2$N); 2.21 s, 6 H ((CH_3)$_2$N); 2.23 t, 2 H, *J*(2′,1′) = 7.4 (CH_2N).

Dodecyl(dimethyl)amine (**3d**)

Yield 184.9 g (53%), b.p. 108–110 °C/0.1 kPa (reported[11] 111–114 °C/0.3 kPa). ^{1}H NMR spectrum ($CDCl_3$): 0.88 t, 3 H, *J*(12′,11′) = 7.1 (CH_3); 1.26 m, 18 H ((CH_2)$_9$); 1.45 q, 2 H, *J*(2′,3′) = *J*(2′,1′) = 7.3 (C**H**$_2$CH$_2$N); 2.21 s, 6 H ((CH_3)$_2$N); 2.23 t, 2 H, *J*(2′,1′) = 7.4 (CH_2N).

Alkyl(dimethyl)[2-oxo-2-(pyridin-2-yl)ethyl]ammonium Bromides **4**. General Procedure

2-(Bromoacetyl)pyridine (5.1 g, 26 mmol) was prepared from its hydrobromide (7 g, 35 mmol) by reaction with saturated aqueous potassium carbonate (3.5 g, 25 mmol). The liberated base was extracted into ether (4 × 20 ml) and the solvent was removed by evaporation under reduced pressure. This procedure was carried out as fast as possible. Freshly prepared crude 2-(bromoacetyl)pyridine was dissolved in ethanol (50 ml) and alkyl(dimethyl)amine (31 mmol) was added. After 4 days standing at room temperature the solvent was evaporated and the resulting crude product was recrystallized from ethanol–ether.

Hexyl(dimethyl)[2-oxo-2-(pyridin-2-yl)ethyl]ammonium Bromide (**4a**)

Yield 3.6 g (56%), m.p. 164–165 °C. For $C_{15}H_{25}BrN_2O$ (329.3) calculated: 54.71% C, 7.65% H, 8.51% N; found: 55.00% C, 8.04% H, 8.23% N. ^{1}H NMR spectrum ($CDCl_3$): 0.87 t, 3 H, J(6′,5′) = 7.2 (CH_3); 1.30 m, 6 H ((CH_2)$_3$); 1.75 m, 2 H (C**H**$_2$CH$_2$N$^+$); 3.80 s, 6 H ((CH_3)$_2$N$^+$); 3.91 t, 2 H, J(2′,1′) = 8.5 (CH_2N^+); 5.78 s, 2 H (CH_2C=O); 7.59 ddd, 1 H, J(5,4) = 7.6, J(5,6) = 4.8, J(5,3) = 1.2 (H-5); 7.91 td, 1 H, J(4,3) = J(4,5) = 7.8, J(4,6) = 1.7 (H-4); 8.04 dt, 1 H, J(3,4) = 7.9, J(3,5) = J(3,6) = 1.0 (H-3); 8.68 ddd, 1 H, J(6,5) = 4.7, J(6,4) = 1.6, J(6,3) = 0.9 (H-6). IR spectrum (KBr): 2 927 ($CH_3(CH_2)_n$), 1 706 (C=O).

Dimethyl(octyl)[2-oxo-2-(pyridin-2-yl)ethyl]ammonium Bromide (**4b**)

Yield 3.7 g (41%), m.p. 163.5–164.5 °C. For $C_{17}H_{29}BrN_2O$ (357.3) calculated: 57.14% C, 8.18% H, 7.84% N; found: 56.85% C, 8.18% H, 7.59% N. ^{1}H NMR spectrum ($CDCl_3$): 0.87 t, 3 H, J(8′,7′) = 7.0 (CH_3); 1.26 m, 10 H ((CH_2)$_5$); 1.60 m, 2 H (C**H**$_2$CH$_2$N$^+$); 3.74 s, 6 H ((CH_3)$_2$N$^+$); 3.88 t, 2 H, J(2′,1′) = 8.1 (CH_2N^+); 5.78 s, 2 H (CH_2C=O); 7.60 ddd, 1 H, J(5,4) = 7.6, J(5,6) = 4.7, J(5,3) = 1.2 (H-5); 7.93 td, 1 H, J(4,3) = J(4,5) = 7.8, J(4,6) = 1.7 (H-4); 8.05 dt, 1 H, J(3,4) = 7.9, J(3,5) = J(3,6) = 1.1 (H-3); 8.69 ddd, 1 H, J(6,5) = 4.7, J(6,4) = 1.7, J(6,3) = 0.9 (H-6). IR spectrum (KBr): 2 925 ($CH_3(CH_2)_n$), 1 708 (C=O).

Decyl(dimethyl)[2-oxo-2-(pyridin-2-yl)ethyl]ammonium Bromide (**4c**)

Yield 4.3 g (49%), m.p. 150–151 °C. For $C_{19}H_{33}BrN_2O$ (385.4) calculated: 59.22% C, 8.63% H, 7.27% N; found: 58.99% C, 8.78% H, 7.22% N. ^{1}H NMR spectrum ($CDCl_3$): 0.88 t, 3 H, J(10′,9′) = 6.7 (CH_3); 1.24 m, 14 H ((CH_2)$_7$); 1.61 m, 2 H (C**H**$_2$CH$_2$N$^+$); 3.76 s, 6 H ((CH_3)$_2$N$^+$); 3.88 t, 2 H, J(2′,1′) = 8.6 (CH_2N^+); 5.78 s, 2 H (CH_2C=O); 7.60 ddd, 1 H, J(5,4) = 7.6, J(5,6) = 4.8, J(5,3) = 1.2 (H-5); 7.92 td, 1 H, J(4,3) = J(4,5) = 7.8, J(4,6) = 1.7 (H-4); 8.05 dt, 1 H, J(3,4) = 7.9, J(3,5) = J(3,6) = 1.0 (H-3); 8.69 ddd, 1 H, J(6,5) = 4.7, J(6,4) = 1.6, J(6,3) = 0.9 (H-6). IR spectrum (KBr): 2 924 ($CH_3(CH_2)_n$), 1 709 (C=O).

Dodecyl(dimethyl)[2-oxo-2-(pyridin-2-yl)ethyl]ammonium Bromide (**4d**)

Yield 5.0 g (56%), m.p. 140–142 °C. For $C_{21}H_{37}BrN_2O$ (413.4) calculated: 61.01% C, 9.02% H, 6.78% N; found: 60.98% C, 9.48% H, 6.42% N. ^{1}H NMR spectrum ($CDCl_3$): 0.88 t, 3 H, J(12′,11′) = 7.06 (CH_3); 1.24 m, 18 H ((CH_2)$_9$); 1.65 m, 2 H ($CH_2CH_2N^+$); 3.77 s, 6 H ((CH_3)$_2$N$^+$); 3.89 t, 2 H, J(2′,1′) = 8.59 (CH_2N^+); 5.78 s, 2 H (CH_2C=O); 7.60 ddd, 1 H, J(5,4) = 7.61, J(5,6) = 4.75, J(5,3) = 1.22 (H-5); 7.92 td, 1 H, J(4,3) = J(4,5) = 7.77, J(4,6) = 1.69 (H-4); 8.05 dt, 1 H, J(3,4) = 7.86, J(3,5) = J(3,6) = 1.07 (H-3); 8.69 ddd, 1 H, J(6,5) = 4.72, J(6,4) = 1.63, J(6,3) = 0.90 (H-6). IR spectrum (KBr): 2 925 ($CH_3(CH_2)_n$), 1 708 (C=O).

Alkyl(dimethyl)[2-hydroxyimino-2-(pyridin-2-yl)ethyl]ammonium Nitrates **2**. General Procedure

Ketone **4** (10 mmol) and hydroxylamine hydrochloride (1.7 g, 20 mmol) were stirred in pyridine (8 ml) and ethanol (8 ml) at 65 °C for 25 h. Then, the solvents were evaporated under reduced pressure and the residue purified by column chromatography (chloroform–methanol–acetone–water 15 : 5 : 5 : 1). The obtained salts were converted to nitrates by anion exchange on Amberlite IRA 400 (OH^- form, solvent ethanol) and neutralization with diluted nitric acid (1 : 1). Pure products were obtained by repeated crystallization from ethyl acetate.

Hexyl[(2-hydroxyimino)-2-(pyridin-2-yl)ethyl]dimethylammonium Nitrate (**2a**)

Yield 0.5 g (15%), m.p. 95–96 °C. For $C_{15}H_{26}N_4O_4$ (326.4) calculated: 55.20% C, 8.03% H, 17.17% N; found: 55.50% C, 8.29% H, 17.42% N. ^{1}H NMR spectrum ($CDCl_3$): 0.88 t, 3 H, J(6′,5′) = 6.7 (CH_3); 1.32 m, 6 H ((CH_2)$_3$); 1.88 m, 2 H ($CH_2CH_2N^+$); 3.18 s, 6 H ((CH_3)$_2N^+$); 3.46 t, 2 H, J(2′,1′) = 8.0 (CH_2N^+); 4.83 s, 2 H (CH_2C=NOH); 7.30 dd, 1 H, J(5,4) = 8.0, J(5,6) = 5.0 (H-5); 7.74 t, 1 H, J(4,5) = J(4,3) = 7.5 (H-4); 8.09 d, 1 H, J(3,4) = 8.1 (H-3); 8.53 d, 1 H, J(6,5) = 4.2 (H-6); 13.59 s, 1 H (OH). IR spectrum (KBr): 2 924 ($CH_3(CH_2)_n$), 1 618 (C=NOH). pK_a = 9.3.

[2-Hydroxyimino-2-(pyridin-2-yl)ethyl]dimethyl(octyl)ammonium Nitrate (**2b**)

Yield 0.6 g (18%), m.p. 96–98 °C. For $C_{17}H_{30}N_4O_4$ (354.5) calculated: 57.61% C, 8.53% H, 15.81% N; found: 57.54% C, 8.89% H, 15.55% N. ^{1}H NMR spectrum ($CDCl_3$): 0.87 t, 3 H, J(8′,7′) = 6.9 (CH_3); 1.26 m, 10 H ((CH_2)$_5$); 1.88 m, 2 H (C**H**$_2CH_2N^+$); 3.18 s, 6 H ((CH_3)$_2N^+$); 3.45 t, 2 H, J(2′,1′) = 6.8 (CH_2N^+); 4.81 s, 2 H (C**H**$_2$C=NOH); 7.28 ddd, 1 H, J(5,4) = 7.6, J(5,6) = 5.0, J(5,3) = 1.1 (H-5); 7.69 td, 1 H, J(4,5) = J(4,3) = 7.7, J(4,6) = 1.8 (H-4); 8.05 d, 1 H, J(3,4) = 8.1 (H-3); 8.51 ddd, 1 H, J(6,5) = 4.8, J(6,4) = 1.7, J(6,3) = 1.1 (H-6); 13.50 s, 1 H (OH). IR spectrum (KBr): 2 927 ($CH_3(CH_2)_n$), 1 618 (C=NOH). pK_a = 9.3.

Decyl[2-hydroxyimino-2-(pyridin-2-yl)ethyl]dimethylammonium Nitrate (**2c**)

Yield 0.5 g (13%), m.p. 82–84 °C. For $C_{19}H_{34}N_4O_4$ (385.5) calculated: 59.66% C, 8.96% H, 14.65% N; found: 59.33% C, 9.08% H, 14.45% N. ^{1}H NMR spectrum ($CDCl_3$): 0.88 t, 3 H, J(10′,9′) = 6.6 (CH_3); 1.25 m, 14 H ((CH_2)$_7$); 1.88 m, 2 H (C**H**$_2CH_2N^+$); 3.18 s, 6 H ((CH_3)$_2N^+$); 3.46 t, 2 H, J(2′,1′) = 7.9 (CH_2N^+); 4.82 s, 2 H (C**H**$_2$C=NOH); 7.28 d, 1 H, J(5,4) = 7.3 (H-5); 7.70 t, 1 H, J(4,5) = J(4,3) = 8.0 (H-4); 8.08 d, 1 H, J(3,4) = 8.0 (H-3); 8.52 d, 1 H, J(6,5) = 4.1 (H-6); 13.57 s, 1 H (OH). IR spectrum (KBr): 2 926 ($CH_3(CH_2)_n$), 1 621 (C=NOH). pK_a = 9.3.

Dodecyl[2-hydroxyimino-2-(pyridin-2-yl)ethyl]dimethylammonium Nitrate (**2d**)

Yield 0.5 g (11%), m.p. 74–76 °C. For $C_{21}H_{38}N_4O_4$ (410.6) calculated: 61.44% C, 9.33% H, 13.65% N; found: 61.64% C, 9.18% H, 13.42% N. ^{1}H NMR spectrum ($CDCl_3$): 0.88 t, 3 H, J(12′,11′) = 7.0 (CH_3); 1.25 m, 18 H ((CH_2)$_9$); 1.88 m, 2 H (C**H**$_2CH_2N^+$); 3.18 s, 6 H ((CH_3)$_2N^+$); 3.45 t, 2 H, J(2′,1′) = 8.6 (CH_2N^+); 4.81 s, 2 H (C**H**$_2$C=NOH); 7.28 d, 1 H, J(5,4) = 7.5 (H-5); 7.70 t, 1 H, J(4,5) = J(4,3) = 7.7 (H-4); 8.08 d, 1 H, J(3,4) = 8.0 (H-3); 8.52 d, 1 H, J(6,5) = 4.6 (H-6); 13.55 s, 1 H (OH). IR spectrum (KBr): 2 922 ($CH_3(CH_2)_n$), 1 618 (C=NOH). pK_a = 9.4.

pK_a Determination

pK_a values were determined spectrophotometrically at two wavelengths (maxima of the =NOH and $=NO^-$ form, respectively). The pH values of oxime solutions were adjusted with 0.05 M buffers

(HEPES, EPPS, CHES, CAPS) ranging from pH 7.2 up to 11.1. The pK_a values were obtained by nonlinear regression analysis of the absorbance *vs* pH data using software package Enzfitter (Leatherbarrow R. J.: Enzfitter. Elsevier, Amsterdam 1987).

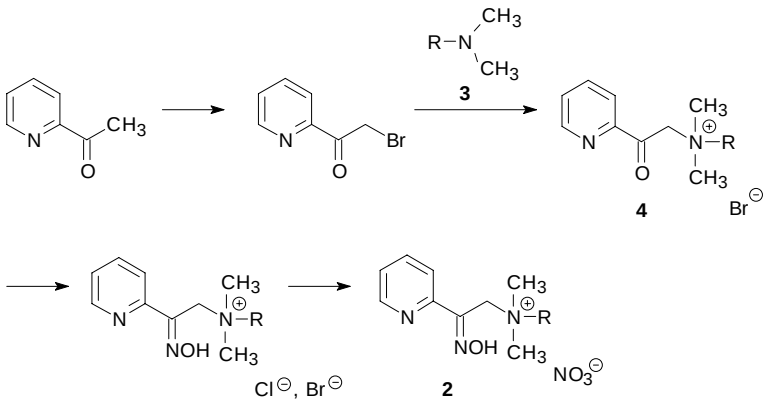
Kinetic Measurements

Solutions of the reactants were prepared in 0.05 M MES buffer (pH 6.3). No changes in pH were observed during the kinetic runs. The reactions were followed on a spectrophotometer HP 8452A (diode array, Hewlett–Packard) equipped with a thermostatted multicell transport cell holder HP 89075C at 25.0 ± 0.1 °C. The reactions were initiated by injection of the $2.0 \cdot 10^{-3}$ mol l^{-1} solution of the substrate (PNPDPP, PNPH or PNPP) in acetonitrile into the spectrophotometric cell containing 2 ml of the buffered solution of the catalyst. The volume of the added substrate solution was 4 μl when the concentration of catalyst were below $3 \cdot 10^{-3}$ mol l^{-1} or 20 μl in all other cases, the resulting concentrations of the substrate being $4 \cdot 10^{-6}$ mol l^{-1} and $2 \cdot 10^{-5}$ mol l^{-1}, respectively. The concentration of the 4-nitrophenoxide ion was monitored at 400 nm. The reactions invariably followed the first-order kinetics up to 90% conversion. The rate constants were obtained by nonlinear regression analysis of the absorbance *vs* time data using the software package Enzfitter. The fit error of the rate constant did not exceed 2% in the case of PNPDPP and 5% in the other cases.

RESULTS AND DISCUSSION

Syntheses of the Ligand Surfactants **2**

Ketoximes **2** were synthesized starting from 2-acetylpyridine as outlined in Scheme 1. Its bromination followed by quaternization with alkyl(dimethyl)amines **3** afforded alkyl(dimethyl)[2-oxo-2-(pyridin-2-yl)ethyl]ammonium bromides **4** in good yields. On the other hand, transformation of ketones **4** proceeded very slowly and the desired oximes **2** were obtained in relatively low yields. Similar results were reported by Kunitake[12] in the synthesis of a structurally related surfactant dodecyl[2-hydroxyimino-2-phenylethyl]dimethylammonium bromide.



SCHEME 1

Since both bromides and chlorides might occur as counterions in the prepared oximes, the crude products were subjected to anion exchange as indicated in Scheme 1. Nitrate was chosen as a counterion for its low coordination ability.

Kinetic Studies

Three model substrates were used for testing the hydrolytic efficiency of micellar and metallomicellar systems prepared from ligand surfactants **2**. 4-Nitrophenyl diphenyl phosphate (PNPDPP) was employed as a model of toxic organophosphorus compounds[3c]. 4-Nitrophenyl hexanoate (PNPH) and 4-nitrophenyl pyridine-2-carboxylate (PNPP) were chosen as representatives of carboxylates, the latter as a substrate possessing the ability to coordinate itself as a ligand to metal ions in metallocatalysts[3a,3d]. All the kinetic experiments were performed under pseudo-first-order conditions, $c_{cat} >> c_{subst}$, with monitoring the appearance of 4-nitrophenoxide ion at 400 nm, at 25 °C in 0.05 M MES buffer (pH 6.3). These experimental conditions allowed direct comparison of our results with those reported in previous studies[3e,6].

In the first series of experiments, hydrolytic efficiency of the prepared salts **2** was tested in comicelles with CTAB (salts **2b–2d**) and homomicelles (salt **2d**). In all cases, the comicelles of ligand surfactants **2** with CTAB were much more efficient than analogous comicellar system of the ligand **1c** (ref.[6]) at the same conditions (Tables I–III). Since the nucleophile attacking the ester function is oximate anion, the remarkable increase in hydrolytic activity of salts **2** compared to ligand **1c** can be explained by increased acidity of their hydroxyimino groups. pK_a of the ligand **1c** was 11.8 (ref.[13]) while pK_a of salts **2** was close to 9.3 due to the electron-withdrawing effect of the quaternary nitrogen. The hydrolytic efficiency of salts **2** comicellized in CTAB increased with the length of the hydrophobic alkyl chain.

In our previous paper[6] we reported acceleration of the PNPH hydrolysis by a factor of 20 as a result of fourfold decrease of the c_{CTAB}/c_{1a} molar ratio. This fact demonstrated that both the substrate and the catalyst were tightly bound in micelles due to the hydrophobic forces; consequently, high concentrations of the reactants were achieved in a small micellar volume. On the other hand, the observed rate constant k_{obs} of the PNPH cleavage in the presence of the comicellar system **2b**–CTAB was almost unaffected by a change of the $c_{CTAB}/c_{\mathbf{2b}}$ molar ratio, thus revealing that a significant part of the salt **2a** remained in non-aggregated form in bulk water phase without the kinetic benefit of micellar catalysis. At low concentrations of CTAB, the reactivity of the catalyst was limited by the amount of micelles present in the solution and by the partition of the salt **2b** between micellar and bulk water phase. At high concentrations of CTAB, salt **2b** was diluted in the micellar phase by the inert cationic tenside. As a result, the k_{obs} *vs* $c_{CTAB}/c_{\mathbf{2b}}$ plot was a flat curve with a maximum at $c_{CTAB}/c_{\mathbf{2b}} \approx 20$ (Fig. 1). Comicelles of the more lipophilic salt **2d** and CTAB were more reactive at the same

TABLE I
Hydrolytic activity[a] of ligands **2** and their complexes towards PNPDPP

Cation	**2b**		**2c**		**2d**		**1c** (ref.[6b])	
	k_{obs}, s^{-1}	k_{obs}/k_{CTAB}	k_{obs}, s^{-1}	k_{obs}/k_{CTAB}	k_{obs}, s^{-1}	k_{obs}/k_{CTAB}	k_{obs}, s^{-1}	k_{obs}/k_{CTAB}
–	$2.58 . 10^{-4}$	4.4	$1.33 . 10^{-3}$	23	$3.30 . 10^{-3}$	56	$8.20 . 10^{-5}$	1.4
Co(II)	$6.78 . 10^{-5}$	1.2	$8.00 . 10^{-5}$	1.4	$8.25 . 10^{-5}$	1.4	$8.02 . 10^{-5}$	1.4
Ni(II)	$9.26 . 10^{-5}$	1.6	$2.01 . 10^{-4}$	3.4	$2.39 . 10^{-4}$	4.1	$1.84 . 10^{-4}$	3.1
Cu(II)	$7.75 . 10^{-5}$	1.3	$3.87 . 10^{-4}$	6.6	$4.80 . 10^{-4}$	8.1	$2.09 . 10^{-4}$	3.5
Zn(II)	$2.43 . 10^{-4}$	4.1	$1.22 . 10^{-3}$	21	$3.18 . 10^{-3}$	54	$7.51 . 10^{-5}$	1.3

[a] Conditions: [ligand] = [metal] = $4 . 10^{-4}$ mol l^{-1}, [CTAB] = $8 . 10^{-3}$ mol l^{-1}, 0.05 M MES buffer, pH 6.3, 25 °C; $k_{CTAB} = 5.90 . 10^{-5}$ s^{-1} (rate constant in pure CTAB).

TABLE II
Hydrolytic activity[a] of ligands **2** and their complexes towards PNPH

Cation	**2b**		**2c**		**2d**		**1c** (ref.[6b])	
	k_{obs}, s^{-1}	k_{obs}/k_{CTAB}	k_{obs}, s^{-1}	k_{obs}/k_{CTAB}	k_{obs}, s^{-1}	k_{obs}/k_{CTAB}	k_{obs}, s^{-1}	k_{obs}/k_{CTAB}
–	$2.04 . 10^{-3}$	540	$1.19 . 10^{-2}$	3 200	$3.48 . 10^{-2}$	9 300	$6.82 . 10^{-5}$	18
Co(II)	$3.14 . 10^{-5}$	8.4	$3.53 . 10^{-4}$	94	$9.17 . 10^{-4}$	240	$6.64 . 10^{-6}$	1.7
Ni(II)	$2.39 . 10^{-4}$	64	$1.75 . 10^{-3}$	470	$2.24 . 10^{-3}$	600	$3.03 . 10^{-3}$	810
Cu(II)	$2.75 . 10^{-5}$	7.3	$3.30 . 10^{-4}$	88	$4.43 . 10^{-4}$	120	$4.44 . 10^{-5}$	12
Zn(II)	$1.86 . 10^{-3}$	500	$1.13 . 10^{-2}$	3 000	$3.35 . 10^{-2}$	8 900	$7.86 . 10^{-4}$	210

[a] Conditions: [ligand] = [metal] = $4 . 10^{-4}$ mol l^{-1}, [CTAB] = $8 . 10^{-3}$ mol l^{-1}, 0.05 M MES buffer, pH 6.3, 25 °C; $k_{CTAB} = 3.75 . 10^{-6}$ s^{-1} (rate constant in pure CTAB).

conditions and an expected monotonic k_{obs} *vs* $c_{CTAB}/c_{\mathbf{2d}}$ plot was obtained (Fig. 1). The lower gradient in comparison with ligand **1a** indicated higher hydrophilicity of the salt **2d**.

In the absence of the comicellizing tenside CTAB, the reactivity of the octylammonium salt **2b** was poor and the k_{obs} *vs* *c* plot gave evidence that no aggregates were formed in the solution (Fig. 2). A rate profile characteristic of a spontaneous aggregation and micellar catalysis was observed in the case of the most lipophilic dodecylammonium salt **2d** (Fig. 2); the critical micelle concentration (CMC) estimated from this plot was approximatelly $3 \cdot 10^{-3}$ mol l^{-1}. PNPDPP was the only substrate the cleavage of which we were able to follow in homomicellar solutions of the salt **2d**. The hydrolysis of both PNPH and PNPP under above mentioned conditions (pH 6.3, 25 °C) was too fast ($\tau_{1/2} < 2$ s).

Preparation of metallomicellar systems and basic evaluation of their hydrolytic efficiency was carried out as described in previous studies[3d,3e]. Metal ions were added in proper amount to comicellar solutions of ligand **2** and CTAB. The formation of complexes was monitored spectrophotometrically by appearance of new bands in UV spectra (Table IV). Interestingly, while Cu(II) complexes were formed immediately after the addition of $Cu(NO_3)_2$ to comicellar solutions of ligand surfactants **2**, formation of Co(II) complexes was completed approximately after 5 s and complexation of Ni(II) took more than 1 min. The UV/VIS spectra gave no evidence of the formation of Zn(II) complexes.

Kinetics of complexation in homogeneous and micellar solutions can be different as was demonstrated by Tondre *et al.*[14] in the case of coordination of Cu(II) and Ni(II) to 6-[(alkylamino)methyl]-2-(hydroxymethyl)pyridines and 7-(4-ethyl-1-methyloctyl)quinolin-8-ol comicellized with CTAB. The authors explained the decrease in the rate of complex formation by electrostatic repulsion of metal ions by the positive surface

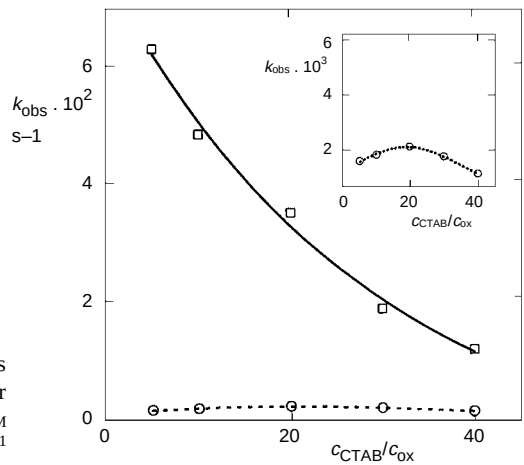


FIG. 1
Plots of pseudo-first-order rate constants of PNPH cleavage *vs* c_{CTAB}/c_{ox} ratio for oximes **2b** (❍) and **2d** (❒) at pH 6.3 (0.05 M MES buffer) and 25 °C, $c_{ox} = 4 \cdot 10^{-4}$ mol l^{-1}

charge of cationic micelles. We do not expect that the dependence of complexation velocity on the type of metal ion can be explained by electrostatic repulsions due to the surface charge of micelles. So far, we have not found any plausible explanation for this phenomenon.

The results of the preliminary kinetic screening of the hydrolytic efficiency of the metallomicellar catalysts prepared from ligand surfactants **2** are summarized in Tables I–III. Relative values k_{obs}/k_{CTAB} showing the rate enhancement of the PNPDPP and PNPH hydrolysis in the presence of metallomicellar systems compared to the reaction running in CTAB are given as well (Tables I and II). Since the transition metal ions themselves

TABLE III
Hydrolytic activity[a] of the ligand **2d** and its complexes towards PNPP

Cation	k_M, s^{-1}(ref.[6b])	**2d**		**1c** (ref.[6b])	
		k_{obs}, s^{-1}	k_{obs}/k_M	k_{obs}, s^{-1}	k_{obs}/k_M
–	–	$5.98 . 10^{-2}$	–	$3.15 . 10^{-4}$	–
Co(II)	$9.64 . 10^{-5}$	$3.68 . 10^{-3}$	38	$3.22 . 10^{-4}$	3.3
Ni(II)	$3.92 . 10^{-4}$	$2.67 . 10^{-2}$	68	$1.12 . 10^{-2}$	29
Cu(II)	$2.63 . 10^{-2}$	$1.95 . 10^{-1}$	7.4	$1.83 . 10^{-2}$	0.7
Zn(II)	$7.07 . 10^{-5}$	$6.82 . 10^{-2}$	970	$1.31 .10^{-3}$	19

[a] Conditions: [ligand] = [metal] = $4 . 10^{-4}$ mol l^{-1}, [CTAB] = $8 . 10^{-3}$ mol l^{-1}, 0.05 M MES buffer, pH 6.3, 25 °C.

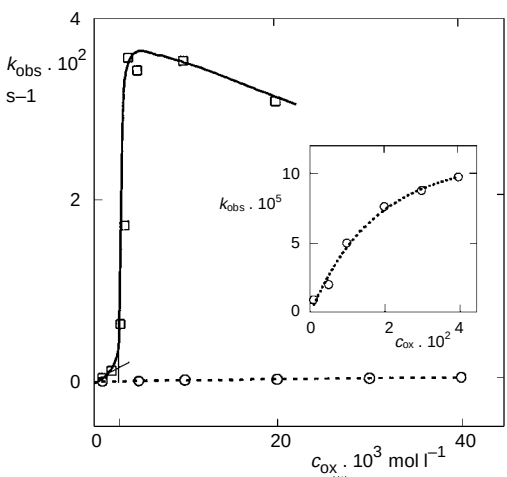


FIG. 2
Plots of pseudo-first-order rate constants of PNPDPP cleavage *vs* concentration for oximes **2b** (○) and **2d** (❒) at pH 6.3 (0.05 M MES buffer) and 25 °C.

as Lewis acids accelerate the hydrolysis of PNPP by electrophilic catalysis[3a], the catalytic effect of the metallomicellar systems is expressed as k_{obs}/k_M where k_M stands for the pseudo-first-order rate constant of the PNPP cleavage in the presence of a metal ion (Table III). Surprisingly, in all cases with an exception of Zn(II), the presence of metal ions decreased the reactivity of salts **2** towards the model substrates. The fact that the hydrolytic efficiency of ligand surfactants **2** was almost unaffected by the presence of Zn(II) was in accordance with the UV/VIS spectral data giving no evidence of some complex formation (Table IV).

To our best knowledge, metallomicellar systems based on complexes of salts **2** are the first known example of deactivation of the nucleophilic function by its coordination to metal ion.

The generally accepted mechanism of the activation of nucleophilic functions in hydrolytic metalloenzymes and their models is outlined in Scheme 2. Coordination to a metal ion increases the acidity of the ligand (in many cases by several orders of magnitude[15]) and consequently the concentration of the nucleophile.

On the other hand, the coordination to a metal ion must decrease the nucleophilicity of the deprotonated ligand. Apparently, the observed reactivity of the hydrolytic metallocatalyst is the result of these contradictory effects of the coordination. In the hitherto published studies[3,6] only the activating effect of the metal ions has been mentioned. This is not surprising since the acidity of the ligands so far investigated has been too low, with the pK_a values ranging approximately from 12 (hydroxyimino group in alkyl pyridin-2-yl ketoximes[13]) to 15 (primary or secondary hydroxy group in pyridinyl[3d,3e] or imidazolyl[3a,3f,3g] ligands) and the hydrolytic activity of the micellar and metallomicellar systems has been tested mostly under mild conditions close to physiological pH. Under these conditions, the ligands (regardless whether coordinated or non-coordinated) have been far from the fully deprotonated state in which the differences in the

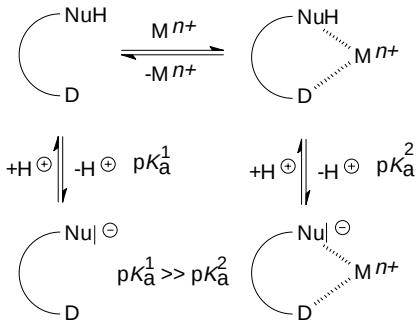
TABLE IV
UV spectra of the ligands **2** and their complexes[a]

Cation	λ_{max}, nm
–	270
Co(II)	348
Ni(II)	324
Cu(II)	328
Zn(II)	270

[a] Conditions: [ligand] = 1 . 10^{-4} mol l^{-1}, [metal] = 2 . 10^{-3} mol l^{-1}, [CTAB] = 8 . 10^{-3} mol l^{-1}, 0.05 M MES buffer, pH 6.3.

nucleophilicity of the free and coordinated ligand could be observed (in micellar and similar aggregated systems where the reactions proceed mainly at the interface of the bulk water phase and micellar pseudophase, second order rate constant k_2 derived formally as a quotient of k_{obs} and analytical concentration of the catalyst has no real physical sense).

Contrary to all other ligands so far investigated, the decrease in the nucleophilicity of the ligand surfactants **2** by their coordination to metal ions was the dominating effect. This fact can be explained by the relatively high acidity of salts **2** diminishing the significance of the ligand activation according to Scheme 2.



SCHEME 2

Conclusions

Reactivity of the transition metal ion complexes of alkyl(dimethyl)[2-hydroxyimino-2-(pyridin-2-yl)ethyl]ammonium salts **2** prepared as water soluble ligand surfactants pointed out that metal ions influenced the efficiency of the hydrolytic metallocatalysts in two contradictory ways. Until now, solely the activating effect of metal ions due to the increase of the ligand acidity has been taken into account while the decrease of the ligand anion nucleophilicity has been ignored. Apparently, the design of new and more effective metallomicellar hydrolytic catalysts will require optimization of the above mentioned effects based on the results of detailed investigation of the coordination processes.

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