QUATERNARY HETEROARENIUM ALDOXIMES AS CATALYSTS FOR CLEAVAGE OF PHOSPHATE ESTERS

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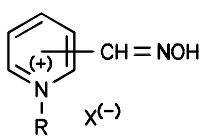
1-Methyl- (*Ia – Id*) and 1-dodecyl-2-, 3- and 4-hydroxyiminomethylpyridinium salts (*Ie – Ih*), as well as 1-methyl- (*IIa*) and 1-dodecyl-3-hydroxyiminomethylpyridazinium salts (*IIb*, *IIc*), were synthesized as catalysts for hydrolytic cleavage of organophosphates. The activities of the prepared catalysts were evaluated by measuring rate constants of hydrolysis of 4-nitrophenyl diphenyl phosphate (PNPDPP) under conditions of a pseudo-first-order reaction. The observed reactivity of pyridinium aldoximes *Ia – Ih* towards PNPDPP in neutral or slightly basic aqueous solutions (pH 7.2 and 7.8) depends on the acidity of the hydroxyimino group. The cleavage of PNPDPP is strongly accelerated in solutions of 1-dodecylhydroxyiminomethylpyridinium salts *Ie – Ih* above their critical micellar concentration (CMC). Considerable effect on the velocity of PNPDPP cleavage was observed when quaternary pyridinium aldoximes *Ie – Ih* were comicellized with inert cationic tenside hexadecyltrimethylammonium bromide (CTAB). 1-Dodecyl-3-hydroxyiminomethylpyridazinium salts *IIb* and *IIc* were unstable in aqueous solutions under the above-mentioned conditions.

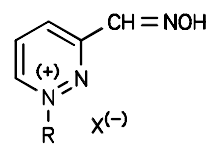
A great number of phosphonic and phosphoric acid derivatives react readily with hydroxy groups, forming relatively stable phosphonates and phosphates. This reaction is responsible for the extreme toxicity of many organophosphorus compounds (both neurotoxic chemical weapons as Sarin, Soman, VX, etc., and agrochemicals as Paraoxon, Parathion etc.) which irreversibly block the serine hydroxy group in acetylcholinesterase by phosphorylation. The problem of safe and efficient decontamination of areas affected by these toxic compounds has been under investigation for decades[1]. The simplest way how to decompose the above-mentioned reactive phosphates and phosphonates is their alkaline hydrolysis. Great effort has been exerted on finding systems capable of efficient hydrolysis of phosphates and phosphonates even under mild conditions i.e. in almost neutral water solutions at ambient temperature. Promising results were obtained with aqueous solutions of

cationic tensides. Their accelerating effect on alkaline hydrolysis of esters has been known since the end of the sixties[2]. The observed rate enhancement is caused by general micellar catalysis, i.e. by the ability of micelles to bring together both a lipophilic organic substrate and an ionic reagent (nucleophilic hydroxide anion). The hydrolytic activity of cationic tensides is increased in cases when a nucleophilic group (e.g. hydroxy[2,3], hydroperoxy[4], mercapto[3], amino[3] etc.) is bound in the proximity of the positively charged atom. These groups in the so-called functional cationic tensides are activated by the electron withdrawing effect of the polar head group and can be easily deprotonated to form powerful nucleophile attacking the ester bond.

Quaternary pyridinium aldoximes are efficient nucleophiles for cleavage of phosphates, the best known of them being 1-methyl-2-hydroxyiminomethylpyridinium iodide[5,6] (*Ia*). This reagent and many other related compounds[7] have been used for reactivation of acetylcholinesterase. For this reason the functional cationic tensides, derived from oxime *Ia* and from its positional isomers *Ib* and *Ic* by replacing the *N*-methyl group with a hydrophobic alkyl chain, were expected to be very powerful agents for the cleavage of phosphates. The hydrolytic activity of 1-dodecyl-3-hydroxyiminomethylpyridinium[8] (*Ig*), 1-dodecyl-4-hydroxyiminomethylpyridinium[9,10] (*Ih*) and 1-hexadecyl-2-hydroxyiminomethylpyridinium[10] (*Ii*) bromides towards phosphate esters has been reported. Since the above-mentioned results were obtained with different substrates at different pH values (mostly higher than 8), it was



	position	R	X
Ia	2-	Me	I
Ib	3-	Me	I
Ic	4-	Me	I
Id	4-	Me	Br
Ie	2-	$C_{12}H_{25}$	I
If	2-	$C_{12}H_{25}$	Br
Ig	3-	$C_{12}H_{25}$	Br
Ih	4-	$C_{12}H_{25}$	Br
Ii	2-	$C_{16}H_{33}$	Br



	R	X
IIa	Me	I
IIb	$C_{12}H_{25}$	I
IIc	$C_{12}H_{25}$	Br

impossible to compare the activity of the amphiphilic pyridinium aldoximes at neutral conditions, suitable for practical applications. For this reason, in the present study we have compared the reactivity of all isomeric 1-alkyl-hydroxyiminomethylpyridinium salts *Ia – Ih* towards 4-nitrophenyl diphenyl phosphate (PNPDPP) as a model substrate under neutral (pH 7.2) and slightly basic (pH 7.8) conditions. We have also tried to modify the hydrolytic activity of the aldoximes by introduction of another ring heteroatom. As an example we chose 1-alkyl-3-hydroxyiminomethylpyridazinium salts *II*. No data have been available about the influence of an inert cationic tenside on the velocity of pyridinium aldoximes-catalyzed cleavage of PNPDPP. Therefore we have also studied kinetics of this cleavage in comicellar systems with cetyltrimethylammonium bromide (CTAB).

EXPERIMENTAL

Temperature data are 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. Elemental analyses were performed on a Perkin–Elmer 240 analyzer. TLC analyses were carried out on prepared glass plates coated with 0.3 mm layer of Kieselgel G, activity 6 according to Stahl (Merck Laboratory Chemicals), detection by 1% solution of cerium sulfate in 10% sulfuric acid followed by carbonization.

Chemicals. 2-, 3- and 4-Pyridinealdoxime (purum) and dodecyl bromide (purum) were obtained from Fluka. Dodecyl iodide[11], 4-nitrophenyl diphenyl phosphate[12] (PNPDPP) and 3-pyridazinecarboxaldehyde[13,14] *III* were synthesized and purified by published methods. Cetyltrimethylammonium bromide (purum, Lachema Brno) was twice recrystallized from ethanol–ether. Methyl iodide (purum) and tris(hydroxymethyl)methylamine, Tris (analytical grade) were Lachema Brno products.

3-Pyridazinealdoxime (*IV*)

A saturated solution of hydroxylamine hydrochloride (4.87 g, 70 mmol) and potassium carbonate (12.2 g, 89 mmol) in water was added to a solution of crude aldehyde *III* (5.00 g, 46.3 mmol) in ethanol (150 ml). After standing overnight in a refrigerator, the deposited white crystals were recrystallized from ethanol. Yield of oxime *IV* 5.06 g (89%), m.p. 142 – 143 °C. For $C_5H_5N_3O$ (123.1) calculated: 48.78% C, 4.09% H, 34.13% N; found: 49.10% C, 4.21% H, 33.95% N. ^{1}H NMR spectrum ($CDCl_3$): 7.74 dd, 1 H, *J*(5,4) = 8.7, *J*(5,6) = 4.9 (H-5); 8.04 d, 1 H, *J*(5,4) = 8.5 (H-4); 8.36 s, 1 H (CH=N); 9.22 d, 1 H, *J*(5,6) = 4.9 (H-6).

Preparation of Quaternary Salts

A) A solution of the pyridinealdoxime (3.00 g, 24.6 mmol) and alkyl halide (37 mmol) in ethanol (50 ml) was refluxed until the starting oxime disappeared (TLC in chloroform–methanol 100 : 5). The reaction mixture was cooled to room temperature, the crystalline crude product was collected and recrystallized from ethanol.

B) Pyridinealdoxime (3.00 g, 24.6 mmol) and alkyl halide (37 mmol) in acetonitrile (100 ml) were heated at 110 – 120 °C in a sealed tube for 8 h. Crude products, obtained by evaporation of solvent under reduced pressure, were recrystallized from ethanol.

Conversion of Quaternary Iodides to Bromides

A column packed with Amberlite IRA-400 (OH^- form) was carefully washed with methanol. The quaternary iodide was dissolved in methanol and applied on the column. The resulting solution of the quaternary hydroxide was neutralized with 48% hydrobromic acid to pH 7. Evaporation of the solvent under reduced pressure and recrystallization yielded the desired bromide.

1-Methyl-2-hydroxyiminomethylpyridinium Iodide (*Ia*)

Prepared by method *A*. The reaction was complete after 6 h. Yield 5.27 g (81%), m.p. 230 – 232 °C (reported[15] m.p. 224 – 225 °C). ^{1}H NMR spectrum ($(CD_3)_2SO$): 4.38 s, 3 H (CH_3); 8.10 m, 1 H (H-5); 8.41 d, 1 H, *J*(4,3) = 8.1 (H-3); 8.56 m, 1 H (H-4); 8.69 s, 1 H (CH=N); 9.03 d, 1 H, *J*(5,6) = 6.1 (H-6); 13.11 s (OH). pK_a = 7.92 (7.88 – 7.97); reported[16] 8.0.

1-Methyl-3-hydroxyiminomethylpyridinium Iodide (*Ib*)

Prepared by method *A*. The reaction was complete after 4 h. Yield 4.28 g (66%), m.p. 153 – 158 °C (reported[15] m.p. 154 – 155 °C). ^{1}H NMR spectrum ($(CD_3)_2SO$): 4.39 s, 3 H (CH_3); 8.14 dd, 1 H, *J*(4,5) = 8.1, *J*(6,5) = 6.1 (H-5); 8.36 s, 1 H (CH=N); 8.70 d, *J*(5,4) = 8.1 (H-4); 8.95 d, 1 H, *J*(5,6) = 6.0 (H-6); 9.18 s, 1 H (H-2). pK_a = 9.27 (9.22 – 9.32); reported[16] 9.2.

1-Methyl-4-hydroxyiminomethylpyridinium Iodide (*Ic*)

Prepared by method *A*. The reaction was complete after 4 h. Yield 5.57 g (86%), m.p. 178 – 181 °C (reported[15] m.p. 181 – 183 °C). ^{1}H NMR spectrum ($(CD_3)_2SO$): 4.35 s, 3 H (CH_3); 8.22 d, 2 H, *J*(2,6,3,5) = 6.6 (H-3,H-5); 8.45 s, 1 H (CH=N); 8.95 d, 2 H, *J*(3,5,2,6) = 6.5 (H-2,H-6). pK_a = 8.60 (8.51 – 8.70); reported[16] 8.6.

1-Methyl-4-hydroxyiminomethylpyridinium Bromide (*Id*)

Prepared from iodide *Ic* (2.00 g, 7.6 mmol) by anion exchange. The crude product was recrystallized from ethanol. Yield 1.12 g (68%), m.p. 215 – 218 °C. For $C_7H_9BrN_2O$ (217.0) calculated: 38.73% C, 4.18% H, 36.81% Br, 12.91% N; found: 39.00% C, 4.44% H, 37.31% Br, 10.99% N. ^{1}H NMR spectrum ($(CD_3)_2SO$): 4.38 s, 3 H (CH_3); 8.25 d, 2 H, *J*(2,6,3,5) = 6.7 (H-3,H-5); 8.48 s, 1 H (CH=N); 9.05 d, 2 H, *J*(3,5,2,6) = 6.6 (H-2,H-6); 12.77 s (OH).

1-Dodecyl-2-hydroxyiminomethylpyridinium Iodide (*Ie*)

A solution of 2-pyridinealdoxime (5.00 g, 40.9 mmol) and dodecyl iodide (15.00 g, 50.6 mmol) in acetonitrile (120 ml) was stirred at 40 °C for 100 h. The solvent was removed under reduced pressure. Column chromatography (silica gel, chloroform–methanol–NH_4OH 100 : 10 : 1) of the residue afforded 1.94 g (39%) of unreacted 2-pyridinealdoxime and 3.17 g of crude product. Recrystallization from acetone gave 2.28 g (13%) of iodide *IVa*, m.p. 127 – 130 °C (reported[16] m.p. 159 – 160 °C). For $C_{18}H_{31}IN_2O$ (418.4) calculated: 51.68% C, 7.47% H, 6.70% N; found: 51.71% C, 7.63% H, 7.00% N. ^{1}H NMR spectrum ($CDCl_3$): 0.88 t, 3 H, *J*(12′,11′) = 7.1 (CH_3); 1.33 bs, 16 H ($(CH_2)_8$); 1.49 m, 2 H (**CH**$_2$CH$_2$CH$_2$N); 1.92 qi, 2 H, *J*(3′,1′,2′) = 7.0 (**CH**$_2$CH$_2$N); 4.78 t, 2 H, *J*(2′,1′) = 7.0 (CH_2N); 4.95 s, 1 H (OH); 7.84 m, 1 H (H-5); 8.36 m, 1 H (H-4); 8.52 s, 1 H (CH=N); 8.55 d, 1 H, *J*(4,3) = 8.4 (H-3); 8.96 d, 1 H, *J*(5,6) = 6.0 (H-6). pK_a = 8.20 (8.13 – 8.27).

1-Dodecyl-2-hydroxyiminomethylpyridinium Bromide (*If*)

Prepared from iodide *Ie* (0.600 g, 1.43 mmol) by anion exchange. The crude product was recrystallized from acetone–ether. Yield 0.298 g (56%), m.p. 163 – 167 °C. For $C_{18}H_{31}BrN_2O$ (371.4) calculated: 58.22% C, 8.41% H, 21.52% Br, 7.54% N; found: 56.11% C, 8.37% H, 20.68% Br, 7.21% N. ^{1}H NMR spectrum ($CDCl_3$): 0.87 t, 3 H, J(11′,12′) = 6.8 (CH_3); 1.24 bs, 16 H ((CH_2)$_8$); 1.40 m, 2 H (**CH**$_2$$CH_2$$CH_2$N); 1.93 m, 2 H (**CH**$_2$$CH_2$N); 4.94 t, 2 H, J(2′,1′) = 6.2 (CH_2N); 8.02 m, 1 H (H-5); 8.40 d, 1 H, J(4,3) = 7.6 (H-3); 8.66 m, 1 H (H-4); 8.69 s, 1 H (CH=N); 9.14 d, 1 H, J(5,6) = 5.0 (H-6).

1-Dodecyl-3-hydroxyiminomethylpyridinium Bromide (*Ig*)

Prepared by method *B*. Yield 3.41 g (37%), m.p. 138 – 139 °C (reported[17] m.p. 141 – 143 °C). ^{1}H NMR spectrum ($CDCl_3$): 0.87 t, 3 H, J(11′,12′) = 7.0 (CH_3); 1.31 bs, 18 H ((CH_2)$_9$); 2.07 m, 2 H (**CH**$_2$$CH_2$N); 4.86 t, 2 H, J(2′,1′) = 7.2 (CH_2N); 8.18 dd, 1 H, J(6,5) = 6.2, J(4,5) = 8.0 (H-5); 8.33 s, 1 H (CH=N); 8.68 d, 1 H, J(5,4) = 8.2 (H-4); 9.05 d, 1 H, J(5,6) = 6.0 (H-6); 9.50 s, 1 H (H-2); 11.13 s, 1 H (OH). pK_a = 9.01 (8.92 – 9.12).

1-Dodecyl-4-hydroxyiminomethylpyridinium Bromide (*Ih*)

Prepared by method *B*. Yield 5.36 g (59%), m.p. 131 – 132 °C (reported[9] m.p. 129 – 130 °C). ^{1}H NMR spectrum ($CDCl_3$): 0.88 t, 3 H, J(11′,12′) = 7.1 (CH_3); 1.36 bs, 18 H ((CH_2)$_9$); 2.05 m, 2 H (**CH**$_2$$CH_2$N); 4.84 t, 2 H, J(2′,1′) = 7.2 (CH_2N); 8.21 d, 2 H, J(2,6,3,5) = 6.6 (H-3,H-5); 8.36 s, 1 H (CH=N); 9.16 d, 2 H, J(3,5,2,6) = 6.6 (H-2,H-6); 11.70 s, 1 H (OH). pK_a = 8.29 (8.24 – 8.34).

1-Methyl-3-hydroxyiminomethylpyridazinium Iodide (*IIa*)

A solution of oxime *IV* (1.00 g, 8.1 mmol) and methyl iodide (2.32 g, 16.3 mmol) in ethanol (100 ml) was stirred at room temperature for 30 h. Removal of the solvent under reduced pressure and recrystallization from ethanol afforded 0.90 g (42%) of yellow crystals, m.p. 194 – 196 °C. For $C_6H_8IN_3O$ (265.1) calculated: 27.19% C, 3.04% H, 47.88% I, 15.85% N; found: 27.74% C, 3.19% H, 49.69% I, 13.63% N. ^{1}H NMR spectrum ((CD_3)$_2$SO): 4.59 s, 3 H (CH_3); 8.38 s, 1 H (CH=N); 8.70 dd, 1 H, J(4,5) = 8.7, J(6,5) = 5.6 (H-5); 8.81 d, 1 H, J(5,4) = 8.5 (H-4); 9.87 d, J(5,6) = 5.5 (H-6); 12.95 s, 1 H (OH). pK_a = 8.48 (8.41 – 8.56).

1-Dodecyl-3-hydroxyiminomethylpyridazinium Iodide (*IIb*)

A solution of oxime *IV* (2.00 g, 16.2 mmol) and dodecyl iodide (6.40 g, 21.6 mmol) in acetonitrile (100 ml) was stirred at 50 °C for 30 h. Evaporation the solvent and recrystallization from ethanol–ether gave 1.83 g (27%) of yellow crystals, m.p. 142 – 149 °C. For $C_{17}H_{30}IN_3O$ (419.4) calculated: 48.69% C, 7.21% H, 30.26% I, 10.02% N; found: 49.04% C, 7.45% H, 31.60% I, 9.90% N. ^{1}H NMR spectrum ((CD_3)$_2$SO): 0.85 t, 3 H, J(11′,12′) = 6.8 (CH_3); 1.21 bs, 16 H ((CH_2)$_8$); 1.31 m, 2 H (**CH**$_2$$CH_2$$CH_2$N); 2.00 m, 2 H (**CH**$_2$$CH_2$N); 4.81 t, 2 H, J(2′,1′) = 7.3 (CH_2N); 8.38 s, 1 H (CH=N); 8.67 dd, 1 H, J(6,5) = 5.7, J(4,5) = 8.7 Hz (H-5); 8.82 d, 1 H, J(5,4) = 8.7 (H-4); 9.97 d, 1 H, J(5,6) = 5.7 (H-6); 13.00 s, 1 H (OH). pK_a = 8.32 (8.27 – 8.37).

1-Dodecyl-3-hydroxyiminomethylpyridazinium Bromide (*IIc*)

Prepared from iodide *IIb* (0.500 g, 1.19 mmol) by anion exchange. The crude product was recrystallized from acetone–ether. Yield 0.315 g (71%), m.p. 180 – 183 °C. For $C_{17}H_{30}BrN_3O$

(372.4) calculated: 54.84% C, 8.12% H, 21.46% Br, 11.29% N; found: 53.64% C, 7.82% H, 20.96% Br, 10.83% N.

Determination of pK_a

The pK_a values of the oximes *Ia* – *Ih* and *IIa* – *IIc* (vide supra) were determined spectrophotometrically using the standard procedure[18]. The oximes were titrated with sodium hydroxide in 2.0 . 10^{-3} M CTAB at constant ionic strength *I* 0.15 mol kg^{-1} at 25 °C. The pK_a values were calculated from Eq. (*1*) using the absorbance–pH dependences at two wavelengths (at the maxima of the =NOH and $=NO^-$ forms). The confidence intervals at the significance level $\alpha = 0.05$ are given in parentheses.

$$pK_a = pH_{obs} + \log \frac{|A_{max} - A_{obs}|}{|A_{obs} - A_{min}|} \qquad (1)$$

Kinetic Measurements

Solutions of the reactants were prepared in 0.04 M tris(hydroxymethyl)methylamine–HBr buffers, pH 7.2 or 7.8. No changes in pH were observed during the kinetic runs. The reactions were followed on a spectrophotometer Shimadzu UV2100 or Specord M40 equipped with a thermostated cell at 25.0 ± 0.1 °C. The reactions were initiated by injection of 1.0 . 10^{-3} M solution of PNPDPP in acetonitrile into the spectrophotometric cell containing 2 ml of buffered solution of the catalyst (10 μl in the case of oximes *Ia* – *Ic* and oxime *IIa* or 20 μl in the case of oximes *Ie* – *Ih* and *IIb* or in the kinetic runs in which CTAB was present; the resulting concentrations of the substrate were 5.0 . 10^{-6} mol l^{-1} and 1.0 . 10^{-5} mol l^{-1}, respectively). The concentration of the *p*-nitrophenoxide ion was monitored at 400 nm. The rections 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. The fit error of the rate constant did not exceed 5% in any case.

RESULTS AND DISCUSSION

All the quaternary salts were prepared by alkylation of the corresponding aldoximes with alkyl halides; in the case of less reactive 2-pyridinealdoxime and 3-pyridazinealdoxime (*IV*) dodecyl iodide had to be used. According to NMR spectra, all the obtained products were pure geometric isomers; however, only in the case of the oximes *Ia* and *Ic* the configuration at the C=N bond could be assigned as (*E*), according to the published melting point data[19,20]. The difference between the published[16] and found melting point of the quaternary aldoxime *Ie* indicated that our product had the opposite configuration. 3-Pyridazinealdoxime (*IV*) was synthesized starting from furfuryl acetate using the transformation of 2,5-dihydro-2,5-dimethoxyfuran to pyridazine ring[13]. Considering the low solubility of cetyltrimethylammonium iodide in water all quaternary iodides had to be converted into bromides when the kinetic measurements were performed in comicelles with CTAB. This conversion was carried out on anion exchangers.

To evaluate and compare the ability of the prepared quaternary heteroarenium aldoximes to destroy phosphates in neutral or slightly basic solutions, the apparent rate constants k_{obs} for the PNPDPP cleavage (Scheme 1) under pseudo-first-order conditions ([oxime] >> [PNPDPP]) were determined. All kinetic measurements were perfomed at 25 °C at two pH values (7.2 and 7.8), both in homomicelles and in comicelles with non-functional cationic tenside cetyltrimethylammonium bromide. The reactions were followed by quantitative determination of the liberated 4-nitrophenoxide ion. The concentration interval in which the cleavage was studied was limited either by the solubility of the aldoxime or by the velocity of the reaction (for reactions with $k_{obs} > 0.5\ s^{-1}$ a stopped-flow equipment is necessary). We did not take into account the contribution of alkaline hydrolysis: under conditions of the measurements its rate constant was of the order $10^{-7} - 10^{-6}$ (see ref.[21]), i.e. much less than the observed rate constants in the presence of our aldoximes. Also the difference between the rate constants in micellar and bulk water phase and the distribution of substrate and catalyst between these phases[22] were neglected.

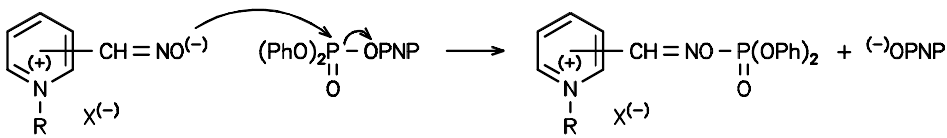
The accelerating effect of quaternary aldoximes *Ia – Ic* and *IIa* on the cleavage of PNPDPP is evident from the pseudo-first-order rate constant k_{obs} vs concentration plots (Fig. 1).

To compare the nucleophilicity of the anions formed from compounds *Ia – Ic* and *IIa*, it is necessary to derive the plot of k_{obs} vs $[A^-]$ (where $[A^-]$ stands for concentration of the oximate anion) from the data in Fig. 1. The slopes of these plots represent the formal second-order rate constants k_2 of the cleavage, revealing thus the nucleophilicity of the oximate anions. The $[A^-]$ values were calculated using Eq. (*2*) and the k_2 values were obtained from the k_{obs} vs $[A^-]$ plots by linear regression

$$[A^-] = \frac{c_{ox} K_a}{[H^+] + K_a} \quad , \qquad (2)$$

where c_{ox} is analytical concentration of the oxime and K_a is dissociation constant of the oxime.

The comparison of apparent reactivities of oximes *Ia – Ic* and *IIa* at given pH (dk_{obs}/dc_{ox} values) with their nucleophilicities (represented by k_2 values) is shown in



SCHEME 1

Table I. It is not surprising that the order of apparent reactivities of the pyridinium aldoximes is reverse to that of the nucleophilicities: the more the electron-withdrawing effect of the pyridinium nitrogen increases the acidity of the hydroxyimino group, the more it reduces the nucleophilicity of the resulting anion. Another way how to assess nucleophilicity of the pyridinium aldoxime anions could be comparison of the pseudo-first-order rate constants of the PNPDPP cleavage measured at pH values higher than pK_a; this method was used by Lion[10] and revealed the same order of nucleophilicity. However, the principal factor determining the observed high reactivity of oximes towards phosphates at neutral or slightly basic conditions is the acidity of the hydroxyimino group. A question may arise in connection with the existence of the two isomers of aldoximes: which of these two isomers is more reactive? We suppose that in solutions the equilibration to the thermodynamically more stable isomer proceeds easily after deprotonation of the hydroxyimino group, and for this reason the observed reactivity of both isomers should be the same. This assumption is supported by the fact that the less stable isomers of the quaternary oximes *Ia – Ic* slowly turn to the more stable ones at ambient temperature even in the solid state[15].

The order of reactivity of the amphiphilic 1-dodecylpyridinium aldoximes *Ie – Ig* under neutral conditions (pH 7.2) towards PNPDPP is the same as of their 1-methyl analogs. In all cases, the pseudo-first-order rate constant–concentration plots are

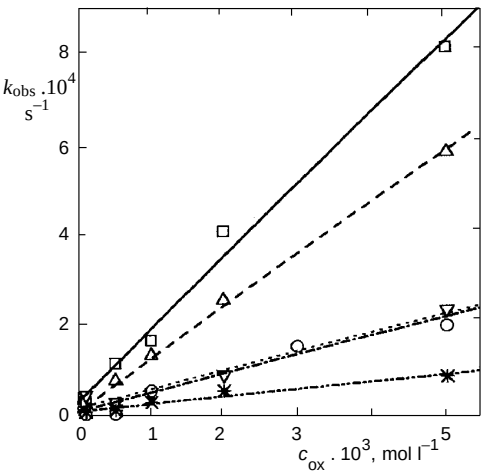


FIG. 1

Plots of pseudo-first-order rate constants of PNPDPP cleavage vs concentration for oximes *Ia – Id* and *IIa* in 5.0 mM CTAB at pH 7.2 (0.04 M Tris-HBr buffer) and 25 °C. ❒ *Ia*, ∇ *Ib*, Δ *Ic*, ❍ *IIa*, * *Id*

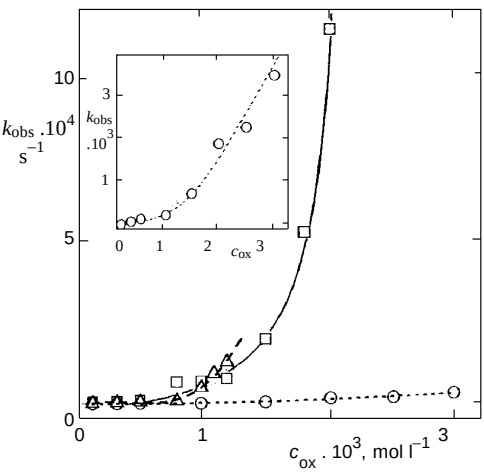


FIG. 2

Plots of pseudo-first-order rate constants of PNPDPP cleavage vs concentration for oximes *Ie*, *Ig* and *Ih* at pH 7.2 (0.04 M Tris-HBr buffer) and 25 °C. ❒ *Ie*, ❍ *Ig*, Δ *Ih*

markedly curved (Fig. 2). In the region of the curvature, cationic micelles of the amphiphilic pyridinium aldoximes begin to form micelles and consequently the rate of the cleavage dramatically increases due to the micellar catalysis. The rate profiles of cleavage at slightly alkaline conditions (pH 7.8) are similar (Fig. 3). Their pseudo-first-order rate constants are higher than those obtained at pH 7.2; this demonstrates repeatedly that oximate anion is the active species in the phosphate cleavage. We were not able to evaluate the efficiency of the pyridazinium aldoximes *IIb* and *IIc*. These quaternary salts were unstable and decomposed under the reaction conditions, most probably via nucleophilic attack by hydroxide anion at the positively charged heteroaromatic nucleus. Similar instability of the amphiphilic pyridazinium compounds was also observed by other authors[23].

TABLE I
Comparison of apparent activity (dk_{obs}/dc) with nucleophilicity (k_2) of oximes *Ia – Ic* and *IIa*

Compound	K_a mol l^{-1}	dk_{obs}/dc_{ox} l mol s^{-1}	$k_2 = dk_{obs}/d[A^-]$ l mol s^{-1}
Ia	$1.20 . 10^{-8}$	$1.6 . 10^{-1}$	$9.9 . 10^{-1}$
Ib	$5.37 . 10^{-10}$	$4.4 . 10^{-2,a}$	5.2^a
Id	$2.51 . 10^{-9}$	$1.1 . 10^{-1}$	3.0
IIa	$3.31 . 10^{-9}$	$4.1 . 10^{-2}$	$6.8 . 10^{-1}$

[a] The distant value of k_{obs} at c_{ox} $1.0 . 10^{-4}$ mol l^{-1} was neglected.

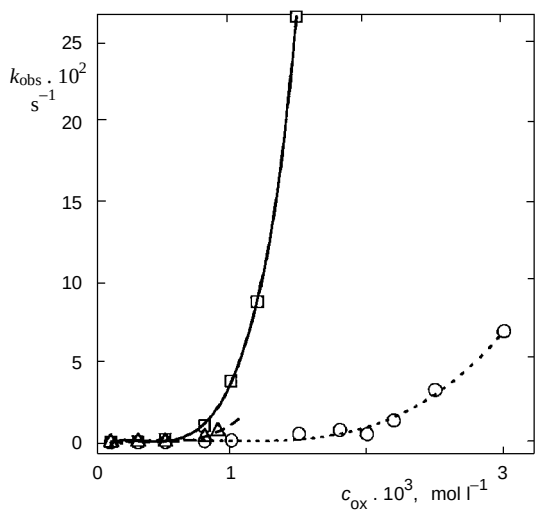


FIG. 3
Plots of pseudo-first-order rate constants of PNPDPP cleavage vs concentration for oximes *Ie*, *Ig* and *Ih* at pH 7.8 (0.04 M Tris-HBr buffer) and 25 °C. ❒ *Ie*, ❍ *Ig*, Δ *Ih*

The velocity of the PNPDPP cleavage, catalyzed by amphiphilic aldoximes *If – Ih*, increased dramatically in comicelles with inert cationic tenside CTAB. The dependences of the rate constants of the cleavage on the molar fraction of pyridinium aldoximes in a mixture with CTAB at constant total molar concentration of tensides (kinetic versions of Job's plots) are depicted in Fig. 4. In the presence of 10 – 30 mole % of CTAB the increase of the observed rate constants was approximately one order of magnitude. We have no plausible explanation for this phenomenon. Most probably, changes in the structure of cationic micelles causing changes in effective concentration of the reactants are responsible for the observed synergism.

On the other hand, PNPDPP cleavage by non-micellar 1-methylpyridinium aldoximes was inhibited by CTAB as was shown in the case of compound *Id* (see Fig. 1). This fact can be explained by "extraction" of the lipophilic substrate PNPDPP into the micelles while the hydrophilic 1-methylpyridinium aldoxime remains in the bulk water phase.

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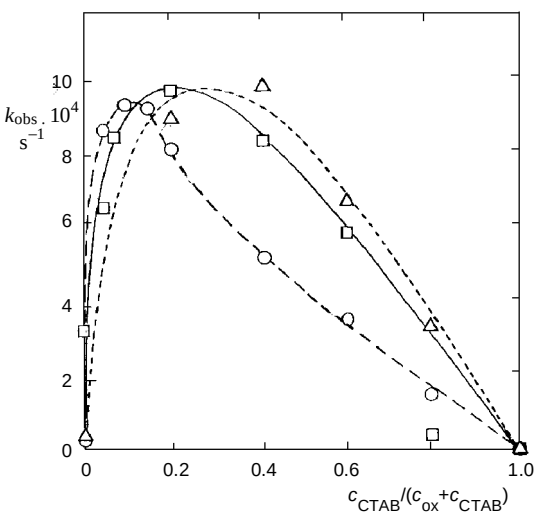

FIG. 4
Dependences of the pseudo-first-order rate constants on the molar fraction of the oximes *If*, *Ig* and *Ih* in CTAB at pH 7.2 (0.04 M Tris-HBr buffer) and 25 °C. ❑ *If*, [CTAB] + [oxime] = 2.0 . 10^{-3} mol l^{-1}; ❍ *Ig*, [CTAB] + [oxime] = 3.0 . 10^{-3} mol l^{-1}; Δ *Ih*, [CTAB] + [oxime] = 1.0 . 10^{-3} mol l^{-1}

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