QUATERNARY KETOXIMES - NEW PERSPECTIVE COMPOUNDS FOR HYDROLYSIS OF TOXIC ORGANOPHOSPHATES

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Summary

Micellar systems made of amphiphilic quaternary pyridinium and quinolinium ketoximes readily hydrolyze 4-nitrophenyl diphenyl phosphate and/or 1-(1-naphtylazo)napht-2-yl diphenyl phosphate, simulants of toxic organophosphates. Reactivity of these functional surfactants towards phosphates depends strongly on the position of their nucleophilic oxime function relative to micellar surface.

Key words: Micelles; Pyridinium salts; Quinolinium salts; Ketoximes; Phosphates; Hydrolysis; Kinetics.

Fast and efficient decontamination of the surface from neurotoxic organophosphorous compounds of the type G, i.e. methylfluorophosphonic acid esters (sarin, soman, cyclosin etc.) represents still a great challenge for organic chemists. One of the possible solutions of this problem is to employ micellar systems containing surfactants or metallo-surfactants possessing a nucleophilic function in their molecule. A great number of such systems has been designed and studied within the past three decades (1-3).

Anion formed by deprotonation of oxime group seems to be one of the most powerfull nucleophiles readily attacking phosphorus atom in phosphates and phosphonates. Thus, acetylcholinesterase (AChE) inhibited by phosphorylation or phosphonylation is reactivated by pyridinium aldoxime reactivators like 2-PAM, trimedoxime, toxogonine, HI-6, and others (4, 5, 6). Replacing the methyl group for a hydrophobic alkyl chain in 2-PAM and its positional isomers leads to functional cationic surfactants (Fig. 1). A series of these compounds have been described as hydrolytic catalysts for organophosphates (7, 8, 9). High reactivity of pyridinium oximes is a result of the following properties of these compounds: (i) acidity of their hydroxyimino group ($7.9 < pK_a < 9.5$) affording relatively high concentration of the nucleophilic oximate even at neutral conditions, (ii) high nucleophilicity of oximate anion as a consequence of the α-effect of the adjacent nitrogen (4, 10).

In our laboratory, quaternary pyridinium ketoximes 1 and 2 were prepared as potential agents for destruction of toxic organophosphates. These amphiphilic ketoximes represent two series of isomeric cationic surfactants, which differ only in the position of their nucleophilic hydroxyimino group relative to micellar surface, as shown in the idealized picture (Fig. 2). Therefore, we considered quaternary pyridinium ketoximes 1 and 2 as suitable compounds for studying the influence of the relative position of the polar head group, nucleophilic function and hydrophobic alkyl chain on hydrolytic efficiency of functional surfactants. Until now, low attention has been paid to this problem in the literature (11, 12).

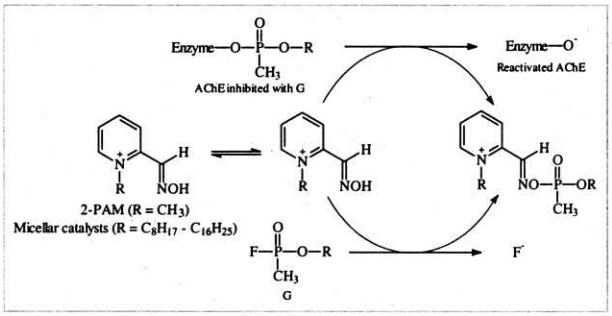
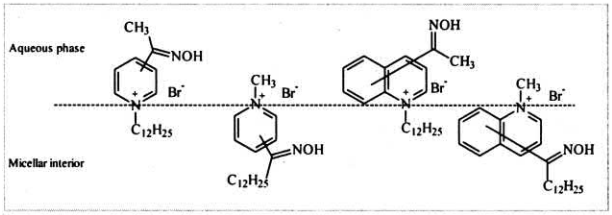


Fig. 1: Cleavage of phosphonates with quaternary pyridinium aldoximes



	position		position		position		position
1a	2-	**2a**	2-	**3a**	4-	**4a**	4-
1b	3-	**2b**	3-				
1c	4-	**2c**	4-				

Fig. 2: Location of quaternary ketoximes at micellar/water interface.

Reactivity of homomicelles made of different pyridinium ketoximes towards 4-nitrophenyl diphenyl phosphate (PNPDPP; a simulant of toxic organophosphates) is shown in Figure 3 using compounds 1c, 2a and 2c (13). Ketoximes 1a, 1b and 2b were not involved; we were not able to prepare salt 1a and in the case of 3-substituted salts 1b and 2b, anomalous absorbance *vs* time plots were obtained when PNPDPP was hydrolyzed in their micelles (14). Remarkable difference in the reactivity of isomeric compounds 1 and 2 can be a consequence of different aggregation ability of these surfactants. Indeed, critical micelle concentrations of ketoximes 2 are lower than that of 1c. Nevertheless, there exists another plausible explanation: lipophilic substrates are solubilized in micellar interior, and therefore, the probability of their attack by nucleophilic function should be higher in the case of salts 2. Moreover lost of the solvation cover in micellar interior should increase the reactivity of the oximate anion.

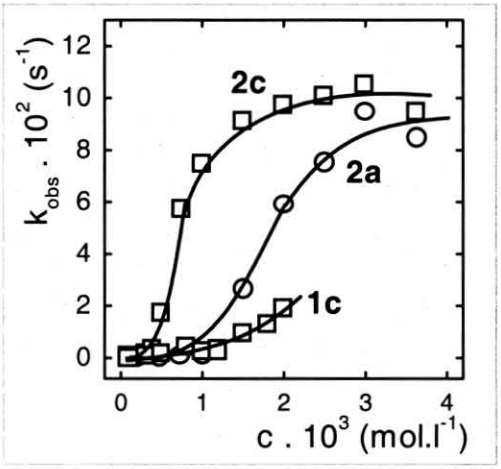


Fig. 3. Rate constant k_{obs} of the PNPDPP hydrolysis vs surfactant concentration. Conditions: 25 °C, pH 7.2 (0.05 M HEPES buffer and 0.04 M Tris-HBr buffer for ketoximes 2 and 1c, respectively)

To confirm that the observed phenomenon was not only a consequence of appreciable decrease of critical micelle concentration we have performed hydrolyses of PNPDPP in co-micelles with "inert" cationic surfactant cetyltrimethylammonium bromide (CTAB) thus ensuring comparable conditions for all the investigated surfactants (15). On the first sight, the results seem to be disappointing since the rate constant k_{obs} *vs* concentration c_{oxime} profiles (Fig. 4a) are almost the same in both cases. Nevertheless, one must have in his mind that acidity of compound **1c** (pK_a = 9.3) is higher by a factor of four than that of the compound **2c** (pK_a = 9.9). Thus, almost the same efficiency was achieved at approximately quater concentration of the nucleophilic oximate anion in the case of the surfactant **2c**. The apparent second-order rate constants $(k_2)_{app}$ values obtained as a slope of the pseudo-first order rate constant k_{obs} of the PNPDPP cleavage *vs* oximate anions concentration $c_{oximate}$ plots (Fig. 4b) give an unambiguous evidence of higher reactivity of the anion formed from the surfactant **2c** (Table I).

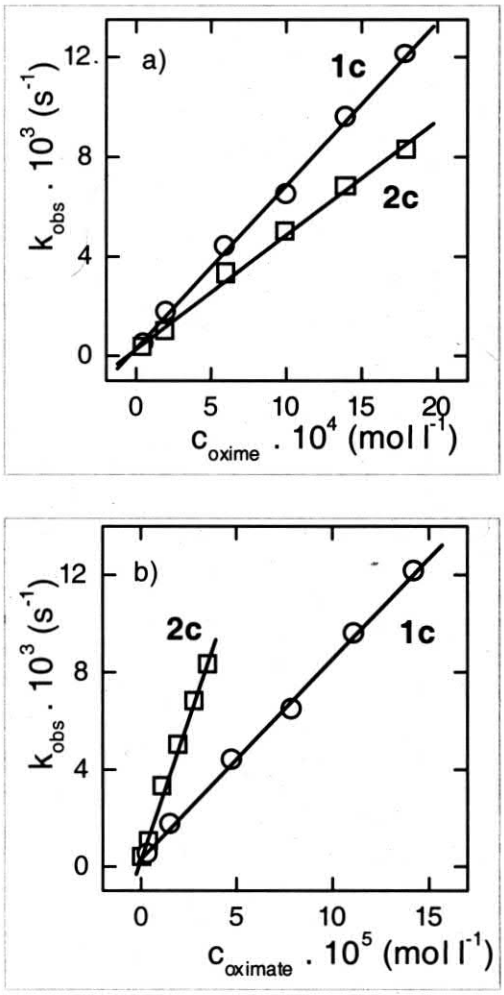
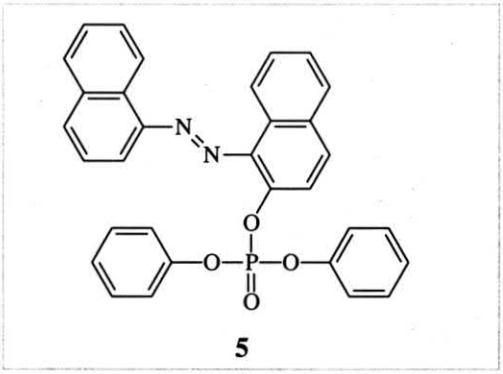


Fig. 4. Rate constant of PNPDPP cleavage in comicelles with CTAB (0.01 M) vs concentration of oxime (a) and oximate (b) plots. Conditions: t = 25 °C, pH 7.2 (0.05 M HEPES buffer).

Analogously, isomeric quinolinium ketoximes **3a** and **4a** were involved in the study of the influence of the nucleophilic group position on the reactivity of quaternary ketoximes. PNPDPP could not be used in the investigation of hydrolytic efficiency of chinolinium salts due to their strong absorption in the range used for spectrophotometric monitoring of PNPDPP hydrolysis (λ = 400 nm). Therefore 1-(1-naphtylazo)napht-2-yl diphenyl phosphate (**5**, NANDPP) releasing 1-(1-naphtylazo)napht-2-oxide

anion with maximum absorption at 532 nm, was designed and synthesized for this study. Reactivity of quinolinium salts **3a** and **4a** towards NANDPP is shown in Table I using apparent second-order rate constants of the reaction of oximates with substrate. For comparison, the reactivities of pyridinium salts **1c** and **2c** towards NANDPP are added. It is evident that quinolinium salt **4a** and pyridinium salt **2c** with hydroxyimino group located beneath the micellar surface are more reactive (in accord with the hypothesis) than their isomers.



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Further research will be oriented on quinolinium and isoquinolinium salts substituted in benzene ring in order to enlarge the distance between oxime group and quaternary nitrogen thus enabling deeper penetration of nucleophilic oxime group into micellar phase.

Table I

Apparent secon-order rate constants for PNPDPP and/or NANDPP hydrolysis with quaternary pyridinium and quinolinium ketoximes.

	$(k_2)_{app}$ (l mol^{-1} s^{-1})	
	PNPDPP	NANDPP
1c	824	11
2c	2310	82
3a	-	16
4a	-	29

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