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MICELLAR-CATALYZED HYDROLYSIS OF ORGANOPHOSPHORUS COMPOUNDS. O-*n*-ALKYL-*p*-NITROPHENYLMETHYLPHOSPHONATES IN THE HEXADECYLTRIMETHYLAMMONIUM BROMIDE—HEXANOL—WATER SYSTEM

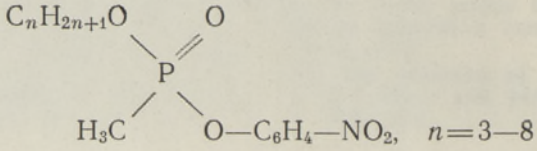
(Presented by E. Lippmaa)

The hydrolysis of many important organophosphorus compounds has been extensively studied in solutions [1], but there are no reports of this reaction in micelles. Our interest in the antichymotrypsin activity of organophosphorus inhibitors (OPI) in liquid-crystalline (LC) mesophases has promoted us to study the basic hydrolysis of organophosphorus compounds in micellar solution (Mi) and LC phases of a well-defined system, hexadecyltrimethylammonium bromide (CTABr)—hexanol—H_2O [2–6]. The related reaction, hydrolysis of *p*-nitrophenyl dodecanoate in the different phases of the CTABr—hexanol—water system was investigated in [2, 7]. Our previous results in the α-chymotrypsin-catalyzed hydrolysis of *p*-nitrophenyl acetate (not a specific substrate for α-chymotrypsin) in the micellar and LC phases of the CTABr—hexanol—water system provided information on the effects of controlled phase-dependent rate changes in the enzymatic reaction [8].

Alkaline hydrolysis of OPI has been studied as a model reaction for investigations of the antichymotrypsin activity of organophosphorus compounds in micellar and LC phases of the CTABr—hexanol—water system. Basic hydrolysis of organophosphorus compounds is considered to be a nucleophilic substitution reaction at the phosphorus atom (S_N2P-reaction) (cf. ref. [1]). Cationic CTABr micelles catalyze the hydrolysis of aryl phosphate triester [9] and *bis*-*p*-nitrophenylphenylphosphonate (cf. ref. [10]). CTABr enhances 260-fold the rate of the hydrolysis of *bis*-*p*-nitrophenylphenylphosphonate (cf. ref. [10]). The reaction rate of *p*-nitrophenyldiphenylphosphate with OH^- was increased approximately 11 times [9], but basic hydrolysis of *p*-nitrophenylphenylphosphonate is changed only 1.26-fold in micellar CTABr (cf. ref. [10]). The reaction rate enhancements are explained by a marked decrease in the hydrolysis activation entropy by CTABr [10].

Experimental

Alkaline hydrolysis of homologous O-*n*-alkyl-*p*-nitrophenylmethylphosphonates [11]



has been measured. Doubly distilled H_2O, distilled 1-hexanol and CTABr (p. a., Merck, Germany) were used. 1,4-dioxane (Sojuzchim, USSR, Reagent Grade) was refluxed over sodium for several hours and finally distilled through a column, bp. 100—101 °C. Ethanol was purified and absolutized by the standard method [12]. Samples of LC phases were prepared by mixing three components — buffer solution, 1-hexanol and CTABr — which were left to stand for 48 h at 25°. The formation of LC phases was controlled with a polarizing microscope.

Ethanol or dioxane solutions of OPI were added to micellar or LC phases, and the hydrolytic reaction rates of esters were observed by measuring the absorption (OD_t) of *p*-nitrophenolate ions (at 400 nm) at 25° as a function of time by means of the Cary 1501 spectrophotometer with a thermostat cell compartment (0—0.1 and 0—1.0 absorbance slide wires were used). When the reaction was complete, the absorption (OD_∞) was determined from the absorption *versus* time curve after a sufficiently long time. The results were analyzed as first-order kinetics by a NIC-1085 computer which displayed ($OD_\infty - OD_t$) in a logarithmic scale against *t*. The slope of the line afforded the pseudo-first-order rate constant k_{obs}. The conditions were always chosen in such a way that pseudo-first-order kinetics could be applied. The concentration of OPI varied between 10^{-5} and 10^{-4} M. The rate constants for the alkaline hydrolysis in LC phases were determined by the method of Guggenheim [13].

Results and discussion

Reaction rates were determined in aqueous solutions and in two quite different, micellar and LC lamellar neat phases. In the reaction of hydroxide ions in the presence of CTABr, there is no direct way of measuring the OH^- concentration in the micelles. The situation is even worse in buffered solutions, because there is no indication of how the pH of the buffer is affected by the micelle. It was previously shown in [14] that addition of CTABr to hydrophilic buffer solutions changes the pH if the buffer is very dilute and the CTABr concentration is below or near its critical micelle concentration (CMC). Changes in pH are negligible if relatively high concentrations ($\geqslant 0.02$ M) of .hydrophilic buffers are used. In the present study we have determined the reaction rate in 0.2 M phosphate buffer above the CMC of the surfactant. The CMC of CTABr in aqueous solutions is $0.99 \cdot 10^{-3}$ (cf. ref. [6]). All our measurements were made above this concentration. Alkaline hydrolysis of OPI in 0.007 NaOH (pH 11.50) was used as a reference reaction. k^0_{obs} is defined as an experimental rate constant in aqueous solutions and k^{MI}_{obs}, k^{LC}_{obs} as an experimental rate constant in the presence of CTABr. Each rate constant is the mean of at least three runs and the precision is estimated to be $\pm 5\%$ in aqueous solutions, $\pm 10\%$ in micellar solutions and $\pm 30\%$ in LC phases.

The basic hydrolysis rate constants of phosphonates in aqueous solutions are given in Table 1. Calculated k_{OH^-} for the alkaline hydrolysis of OPI are in a fair agreement with literature data [1]. No dependence of k^0_{obs} upon the hydrocarbon chain length of OPI was found.

Table 2 gives the values of k_{obs} for OPI in micellar phases with different compositions. Comparison of the catalytic effect of CTABr for various phosphonates shows that the effect increases with the lengthening of the hydrocarbon chain. The values of k^{MI}_{obs} reveal a slight dependence upon the hexanol—CTABr ratio. The reaction rate increases with the

Table 1

The pseudo-first-order rate constants k^0_{obs} and the second-order rate constants k_{OH^-} for the alkaline hydrolysis of OPI (in 0.007 M NaOH, 25 °C, pH 11.50)

R	k_{obs}, min^{-1}	k_{OH^-}, $M^{-1} \cdot min^{-1}$	
		measured by us	taken from [1]
n-C_3H_7	0.230±0.003	32.9±1.0	33.0±0.4
n-C_4H_9	0.210±0.001	30.0±1.2	32.0±0.3
n-C_5H_{11}	0.220±0.002	31.4±1.1	33.0±1.1
n-C_6H_{13}	0.200±0.005	28.6±1.4	
n-C_7H_{15}	0.200±0.003	28.6±1.6	
n-C_8H_{17}	0.170±0.006	24.3±2.1	

Table 2

Values of k^{Mi}_{obs} for the alkaline hydrolysis of O-alkyl-*p*-nitrophenylmethylphosphonates in micellar phases (25 °C, 0.2 M phosphate buffer, pH 10.50, 0.1 vol.% ethanol)

Micellar phases, wt.%			$(RO)(CH_3)P(O)OC_6H_4NO_2$-*p*					
Buffer	CTABr	Hexanol	k^{Mi}_{obs}, min^{-1}					
			n-C_3H_7	n-C_4H_9	n-C_5H_{11}	n-C_6H_{13}	n-C_7H_{15}	n-C_8H_{17}
99.96	0.04	—	0.142	0.199	0.256	0.289	0.289	0.252
99.91	0.09	—	0.154	0.215	0.277	0.312	0.313	0.273
99.85	0.09	0.06	0.180	0.243	0.304	0.305	0.333	0.353
99.78	0.18	0.04	0.154	0.212	0.271	0.285	0.333	0.353
98.50	0.9	0.6	0.178	0.240	0.300	0.300	0.330	0.360
96.26	3.74	—	0.12	0.16	0.21	0.22	0.22	0.21
91.00	9.00	—	0.05	0.08	0.10	0.11	0.11	0.10

Table 3

Values of k^{LC}_{obs} for the alkaline hydrolysis of O-alkyl-*p*-nitrophenylmethylphosphonates in LC phases (25 °C, 0.2 M phosphate buffer, pH 10.50)

LC lamellar phases, wt.%			$(RO)(CH_3)P(O)OC_6H_4NO_2$-*p*					
Buffer	CTABr	Hexanol	k^{LC}_{obs}, min^{-1}					
			n-C_3H_7	n-C_4H_9	n-C_5H_{11}	n-C_6H_{13}	n-C_7H_{15}	n-C_8H_{17}
85	9	6	0.10	0.11	0.12	0.13	0.14	0.16
80	12	8	0.08	0.09	0.10	0.11	0.12	0.14
[99.85	0.09	0.06]*	0.178	0.240	0.300	0.300	0.330	0.360
$k^{Mi}_{obs}/k^{LC}_{obs}$, %			178	218	250	230	236	218

* Micellar phase, see Table 2.

hexanol—CTABr ratio. At the same hexanol—CTABr ratio the reaction rate is the same. At a higher CTABr concentration (9%) the reaction rate dropped a little.

Table 3 gives the k^{LC}_{obs} for the OPI in the LC lamellar phases. In

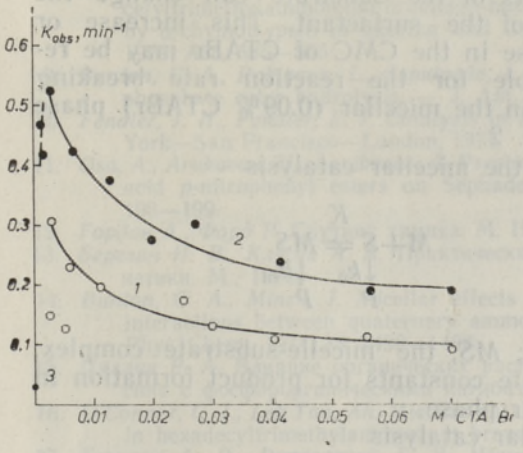


Fig. 1. Micellar catalyzed reactions of O-hexyl-*p*-nitrophenylmethylphosphonate (0.2 M phosphate buffer, pH 10.70, 25 °C): *1* — solutions containing 0.1 vol.% ethanol; *2* — solutions containing 1 vol.% dioxane. 3 — k^0_{obs} =0.024 min^{-1} (measured in 0.01 M NaOH and calculated to pH 10.70).

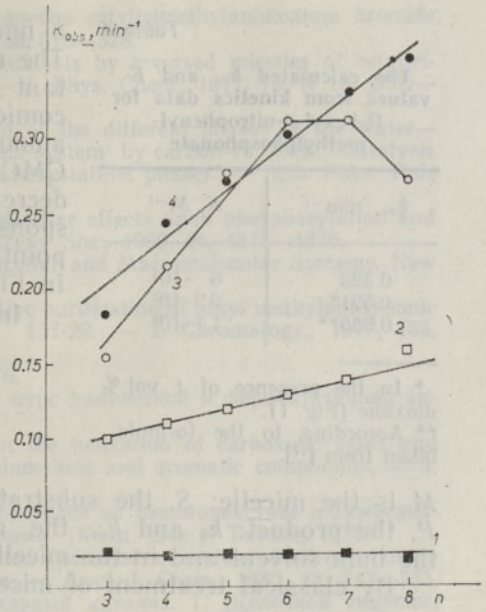


Fig. 2. k_{obs} *versus* n plots for $(C_nH_{2n+1}O)P(O)CH_3—C_6H_4—NO_2—p$. In solutions without CTABr: measured in 0.007 M NaOH and calculated to pH 10.50 — *1*; in LC phases — *2*; in micellar phases: with CTABr — *3*; with CTABr and hexanol — *4*.

general, the effect of structural changes of OPI on the reaction rates of hydrolysis in LC phases is, as expected, negligible.

Micellar effects of CTABr on the basic hydrolysis of OPI with $n=6$ are illustrated by Fig. 1. CTABr increases the rate of hydrolysis by a factor of 10. It is interesting to note, though more difficult to interpret, that 1 vol.% dioxane enhances the micellar catalysis of both steps about two-fold. At higher detergent concentration the catalysis became progressively less pronounced. However, a number of other micellar-catalyzed reactions between anion and neutral molecules exhibit similar rate maxima (cf. ref. [10]). It is highly probable that these rate maxima represent a saturation of the substrate by cationic micelles.

Thus, the maximum rate acceleration occurs in the region of catalyst concentration, at which the bulk of the substrate is incorporated into the micelles, and the additional detergent (i.e., the micelles) simply solubilizes the nucleophile in the Stern layer, thereby rendering it inactive.

A comparison of the catalytic effects for the various phosphonates shows that the CTABr effect in micellar and LC phases increases as the hydrocarbon chain of phosphonates is lengthened (Fig. 2). Micellar activity curves had a breaking point at $n=6$. It is interesting to note that an analogous dependence of the inhibitory activity on the length of the normal alkyl chain of OPI indicated maximum activity at $n=6$ for α-chymotrypsin [15]. In micellar catalysis the hydrophobic substances are solubilized in the interior of the micelle with the hydrophobic chain oriented between the detergent carbon chains, so that the functional group is located near the surface. It is conceivable, however, that deep penetration of the phosphonate into the micelle could result in an environment in which the phosphorus atom is either not suitably oriented for

Table 4

The calculated k_m and K values from kinetics data for O-hexyl-*p*-nitrophenylmethylphosphonate

k_m, min^{-1}	K, M^{-1}
0.323	$6 \cdot 10^5$
0.591*	$2.2 \cdot 10^5$
0.330**	$1.1 \cdot 10^4$

* In the presence of 1 vol.% dioxane (Fig. 1).
** According to the formula taken from [17].

a nucleophilic attack or it is just buried. The reactants may interact with the surfactant to form submicellar aggregates or comicelles. In [16] it is shown that trace amounts of the substrate can change the CMC of the surfactant. This increase or decrease in the CMC of CTABr may be responsible for the reaction rate breaking point in the micellar (0.09% CTABr) phase in Fig. 2.

In the micellar catalysis

$$\begin{array}{ccc} & \overset{K}{} & \\ M + S & \rightleftharpoons & MS \\ \downarrow k_0 & & \downarrow k_m \\ P & & P \end{array}$$

M is the micelle; S, the substrate; MS, the micelle-substrate complex; P, the product; k_0 and k_m, the rate constants for product formation in the bulk solvent and in the micellar phase.

By classical treatment of micellar catalysis

$$\frac{1}{k_0 - k_f} = \frac{1}{k_0 - k_m} + \frac{1}{k_0 - k_m} \cdot \frac{N}{K(C_D - CMC)}, \qquad (1)$$

where C_D is the total concentration of the detergent; N, the aggregation number; k_f, the observed rate constant for the product formation. In the calculations we have used the value of CMC 0.001 M (cf. ref. [7]) and the value of $N=61$ for the aggregation number [10]. A plot of the left-hand side of Eq. (1) *versus* $\frac{1}{C_D - CMC}$ allows for the calculation of k_m and K. The calculated k_m and K values from kinetics data are presented in Table 4. The calculated k_m value compares well with the experimental value of 0.312 min^{-1}.

Conclusions

Comparison of the reaction rates of the alkaline hydrolysis of OPI in aqueous, micellar and LC phases reveals a catalytic effect of CTABr, caused by micelle formation. The reaction rates of hydrolysis of OPI are about the same in micellar and LC lamellar phases. In micellar catalysis a pronounced dependence of reaction rates upon the length of the alkyl chain of O-alkyl-*p*-nitrophenylmethylphosphonates is observed. This new effect is likely to be caused by changes in the micelle formation (the CMC value).

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FOSFORORGAANILISTE ÜHENDITE HÜDROLÜÜSI MITSELLAARNE KATALÜÜS. O-*n*-ALKÜÜL-*p*-NITROFENÜÜLMETÜÜLFOSFONAATIDE HÜDROLÜÜS SÜSTEEMIS HEKSADETSÜÜLTRIMETÜÜLAMMOONIUMBROMIID—*n*-HEKSANOOL—H_2O

On esitatud andmed fosfonaatide $C_nH_{2n+1}OP(O)CH_3OC_6H_4—NO_2—p$ ($n=3—8$) hüdrolüüsi kohta mitsellaarses ja vedela kristalli keskkonnas süsteemis heksadetsüültrimetüülammooniumbromiid—*n*-heksanool—H_2O. Katsete põhjal on konstateeritud, et mitsellid kiirendavad maksimaalselt O-heksüülmetüül-*p*-nitrofenüülfosfonaadi hüdrolüüsi (ca 10 korda). Üldiselt on fosfonaatide hüdrolüüsi kiirus mõlemas keskkonnas sama suurusjärku.

Эне КИЙРЕНД

МИЦЕЛЛЯРНЫЙ КАТАЛИЗ ГИДРОЛИЗА ФОСФОРОРГАНИЧЕСКИХ СОЕДИНЕНИЙ. О-*н*-АЛКИЛ-О′-*п*-НИТРОФЕНИЛМЕТИЛФОСФОНАТЫ В СИСТЕМЕ ГЕКСАДЕЦИЛТРИМЕТИЛАММОНИЙБРОМИД—*н*-ГЕКСИЛОВЫЙ СПИРТ—ВОДА

Щелочной гидролиз О-*н*-алкил-*п*-нитрофенилметилфосфонатов ($n=3—8$) значительно ускоряется в мицеллярной фазе системы гексадецилтриметиламмонийбромид—*н*-гексиловый спирт—вода. Найдены константы скорости щелочного гидролиза фосфонатов в мицеллярной и жидкокристаллических фазах системы детергент—*н*-гексиловый спирт—вода.