Systems based on nonionic amphiphilic compounds: aggregation and catalytic properties

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The micellization properties, solubilization capability, and catalytic effect of conventional nonionic surfactants and amphiphilic compounds of oligomeric (Tyloxapol) and polymeric (Synperonic F-68, Pluronic F-127) structure were compared. The systems studied demonstrate a marked catalytic effect toward basic hydrolysis of *p*-nitrophenyl laurate, which exceeds the effect of aqueous alkali solutions by two orders of magnitude. Correlations between the solubilization capacity of aggregates and their catalytic effect were observed. The maximum efficiency was found for the Tyloxapol solution. The synergetic enhancement of the catalytic effect was observed for the mixed Tyloxapol-cetyltrimethylammonium bromide systems in the presence of small amounts of cationic surfactant.

Key words: nonionic surfactants, cationic surfactants, block copolymers, aggregation, *p*-nitrophenyl laurate, solubilizaton, hydrolysis, kinetics.

Amphiphilic compounds including surfactants and polymers are widely used in gene therapy for transportation of medicines and as the catalysts (nanoreactors) simulating the basic factors of catalytic action of enzymes.[1—4] Specific features of chemical and biochemical processes occurring in the systems based on surfactants arise from the nanoscale sizes of the reaction zone and from the developed area of the interface layer, which determine the behavior of reactants.[5—8] Structural variations in the substances forming the interface, as well as directed variation of the contributions of electrostatic, hydrophobic, and specific interactions between the surface and the reactants allow one to control the rates of chemical transformations. Mixed solutions of amphiphilic compounds are promising for controllable variation of the surface properties of aggregates. Previously,[9—12] we have shown that modification of micellar solutions of nonionic surfactants by ionic surfactant additives can be a tool for target control of the rates of ion-molecular reactions due to the change in the microscopic properties of the interface, such as the surface potential, micropolarity, *etc*. In particular, a synergetic effect in the micelle-forming and catalytic properties of the systems based on cetyltrimethylammonium bromide (CTAB) and nonionic surfactants Triton-X-100 and Brij-97 was revealed.[9] It was shown[11] that the addition of CTAB to a Triton-X-100 solution results in the formation of mixed aggregates in which an increase in the rate of basic hydrolysis of carboxylic acid esters and the acids containing four-coordinate phosphorus is observed.

The present work is devoted to the study of aggregation of biocompatible amphiphilic nonionic compounds possessing the surface activity, to estimation of their solubilization ability toward biologically active compounds, and to control of the reactivity of the latter. Particular attention is paid to the study of aggregation and catalytic activity of the mixed systems based on CTAB and Tyloxapol (nonionic amphiphile with oligomeric structure). Mixed systems based on surfactants are widely used in modern technologies;[13] therefore, information on the properties of such systems is topical. The mixed systems based on Tyloxapol have not been studied as yet. Since Tyloxapol has oligomeric structure and occupies a position between surfactants and polymers, information on this system can be of very importance for understanding the mechanism of self-organization in mixed systems based on monomeric and high-molecular amphiphiles. The catalytic effect of binary surfactant solutions and surfactant—polymer systems is poorly studied;[14—18] therefore, it is also of special interest. In addition, data on the regularities of changes in the reactivity in organized media can be used as additional tool for exploration of the properties of these systems (see, for example, Ref. 19).

In order to estimate the properties of the solution of non-classical amphiphile Tyloxapol, we compared its aggregation ability with those of traditional nonionic surfactants polyoxyethylene(10)—monooleic ether (Brij-97), polyoxyethylene(23)—monododecyl ether (Brij-35), polyoxyethylene(10)—mono-4-isooctylphenyl ether (Triton-

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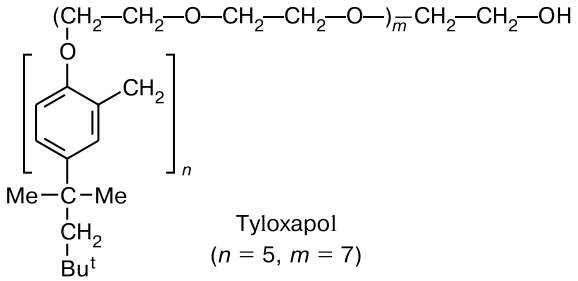
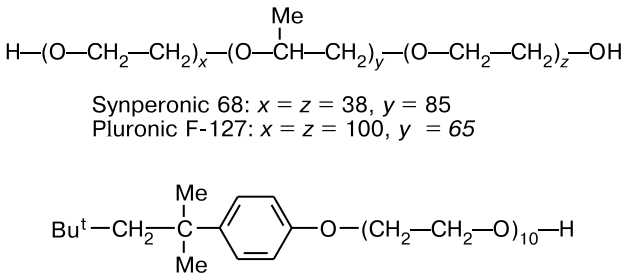


Tyloxapol
(n = 5, m = 7)



Synperonic 68: $x = z = 38$, $y = 85$
Pluronic F-127: $x = z = 100$, $y = 65$

Triton-X-100

$C_{18}H_{36}(OCH_2CH_2)_{10}OH$
Brij-97

$C_{12}H_{25}(OCH_2CH_2)_{23}OH$
Brij-35

X-100), as well as with those of macromolecular amphiphiles (poly(ethylene oxide)—poly(propylene oxide) block copolymers).

p-Nitrophenyl laurate (PNPL) was used as a probe for the study of the solubilization properties and catalytic activity of micellar systems. A general scheme of the reaction studied is as follows:

$$C_{11}H_{23}C(O)OC_6H_4NO_2 + 2\ {}^-OH \longrightarrow$$
$$\longrightarrow C_{11}H_{23}C(O)O^- + {}^-OC_6H_4NO_2 + H_2O.$$

Experimental

Commercially available surfactants (Triton-X-100, Brij-35, Brij-97, CTAB) and block copolymers (Synperonic F-68, Pluronic F-127, Tyloxapol) (Sigma), containing ~99% of the main substance were used. The molar concentrations (mol L^{-1}) of conventional nonionic surfactants are used as they were; the molar concentrations of Tyloxapol and block copolymers are given per monomer unit.

The solubilization of the micellar systems toward PNPL was determined according to the procedure involving the preparation of saturated PNPL solution, subsequent basic hydrolysis, and spectrophotometrical determination of the content of *p*-nitrophenol. For this purpose, the sample of freshly recrystallized PNPL was flushed with the solution of the surfactant studied and then vigorously stirred for 6 h at constant temperature. Then, the undissolved PNPL was separated; an aliquot was taken from the saturated solution, and a known amount of concentrated NaOH solution (2 mol L^{-1}) was added to the aliquot. The completeness of PNPL hydrolysis was confirmed by spectrophotometry until a constant optical density (A) at 400 nm (the absorption of *p*-nitrophenolate-anion). The concentration of the *p*-nitrophenolate (C_{PhO^-}) equal to the concentration of the initially solubilized PNPL was determined using the expression $C_{PhO^-} = \varepsilon AL$, where L is the width of the absorbing layer and ε is the extinction coefficient of *p*-nitrophenolate ion (18000).

The kinetics of basic hydrolysis of PNPL was studied by spectrophotometry on a Specord UV—Vis instrument at 25 °C. The course of the reaction was monitored by the change in the optical density of the solutions at 400 nm. The initial substrate concentration was $5 \cdot 10^{-5}$ mol L^{-1}, the degree of conversion was >90%. The observed pseudofirst order rate constants (k_{app}) were determined using the expression $\log(A_\infty - A_\tau) = -0.434k_{app}\tau + \text{const}$, where A_τ and A_∞ are the optical densities of the solutions at the instant τ and after completion of the reaction. The k_{app} values were calculated by the least squares method.

The kinetic data were analyzed using the equation of the pseudo-phase model[5,6] for micellar catalysis

$$k_{app} = (k_m K_S C + k_0)/(1 + K_S C), \quad (1)$$

where k_0 and k_m (s^{-1}) are the first-order rate constants in water and in the micellar phase, respectively, K_S (L mol^{-1}) is the constant of substrate binding, C is the total surfactant concentration minus the critical micelle concentration (CMC).

The data on the micellar aggregate sizes were obtained by the dynamic light scattering on a Photocor Complex spectrophotometer (He—Ne-laser, 633 nm). The details of the experimental design were described in Ref. 20. The measurement error did not exceed 4%.

The concentration of bromine ions in mixed surfactant systems was determined by a bromine-selective electrode on a I-160MI ion-meter. The electrode potential (ΔE) and the bromide-ion activity are related by the Nernst equation:

$$\Delta E = -(RT/F)\log(a_{Br}) + \text{const}, \quad (2)$$

where F is the Faraday constant. Theoretically, the slope of the ΔE — $\log(a_{Br})$ dependence is 59.2 mV equiv.$^{-1}$ at 25 °C. The potential was measured during a gradual increase in the surfactant concentration; the extent of counter-ion binding was calculated as the ratio of the concentration of bound bromide ions and the total surfactant concentration in the micelle.

The surface tension was measured by the Du Nouy ring detachment method.

Results and Discussion

Previously,[8—12] we studied aggregation of nonionic surfactants Brij-97, Brij-35, and Triton-X-100 both in individual solutions and in mixed systems with ionic surfactants by tensiometry and conductometry. The CMC of surfactants depend on their hydrophilic-lipophilic balance and decreases in the series Brij-35, Triton-X-100, Brij-97: 0.31, 0.2, and 0.017 mmol L^{-1}, respectively. At concentrations exceeding the CMC, micellar aggregates with

a mean hydrodynamic radius of 4.5—5.0 nm are formed in the solutions. The surface tension isotherms for the synthetic amphiphiles Tyloxapol and Synperonic F-68, which are structurally similar to nonionic surfactants, are shown in Fig. 1. The CMC and the effective sizes of aggregates for Tyloxapol are nearly the same as those of Triton-X-100. According to tensiometry data, micelle formation was not observed in solutions of the Synperonic F-68 block copolymer in the studied interval of concentrations, probably, due to its high hydrophilicity. The same results were obtained for Pluoronic F-127.

One could expect that the aggregation behavior in the system Tyloxapol—CTAB is analogous to that of a binary system of surfactants or of a surfactant—polymer system, because Tyloxapol, being an amphiplile, has oligomeric structure. The tensiometry data for the mixed systems Tyloxapol—CTAB at different mole fractions of CTAB (α) are demonstrated in Fig. 2. In all cases, the surface tension isotherms have two breakpoints. This character of tensiometric curves is typical of surfactant—polymer systems,[21] whereas for the binary surfactant solutions the shapes of the surface tension isotherms of individual and mixed solutions are the same and exhibit one breakpoint at the CMC. Probably, the character of Tyloxapol aggregation in mixed solutions with conventional surfactants is similar to that observed in surfactant—polymer systems due to the oligomeric structure of Tyloxapol. In this case, the first breakpoint C_{cr}^1 in the isotherms (see Fig. 2) can be attributed to the critical concentration of aggregation, characterizing the beginning of mixed aggregation in the solution, while the second breakpoint C_{cr}^2 can be attributed to the saturation concentration of the oligomeric chain by micelles. At higher concentrations, free surfactant micelles are formed in the solution.

The C_{cr}^1 values are nearly the same for all α values studied (~0.1 mmol L^{-1}) and are below the CMC of both amphiphiles. Probably, this can be considered as indirect confirmation of the mixed aggregation in the system. The C_{cr}^2 values decrease with an increase in the CTAB fraction in the system (C_{cr}^2 = 1.15, 1.07, and 0.17 mmol L^{-1} at α = 0.3, 0.5, and 0.7, respectively), which suggests the narrowing of the interval of mixed aggregation with the increase in the fraction of the cationic surfactant.

We performed a potentiometric study of the mixed systems Tyloxapol—CTAB with the use of bromine-selective electrodes. For all Tyloxapol : CTAB ratios up to a particular surfactant concentration, the dependence of ΔE on log$C$ is linear with the slope equal to 59±5 mV equiv.$^{-1}$ (see Fig. 3, inset, as an example). The concentration corresponding to the change in the slope equals C_{cr}^2. This fact, as well as the proximity of the C_{cr}^2 value to the CMC of individual CTAB solutions, poorly agrees with the assumption of the formation of mixed aggregates in the system or suggests a high extent of dissociation of CTAB

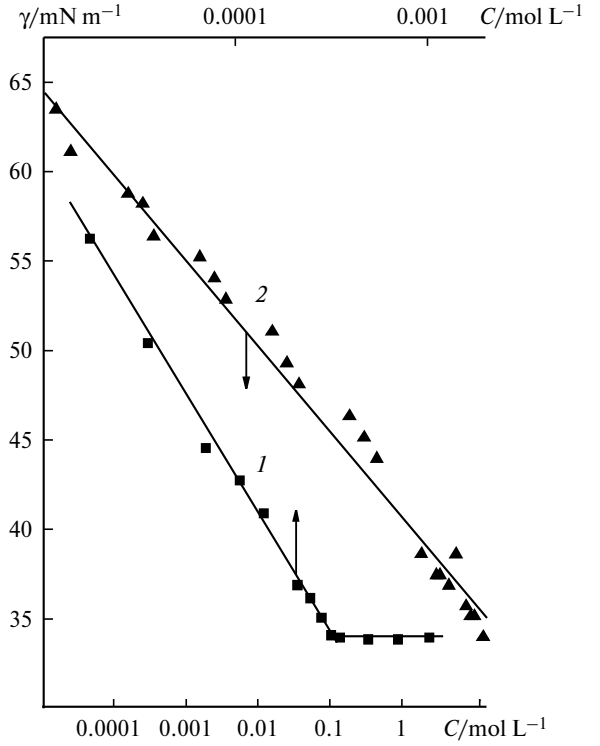


Fig. 1. Surface tension (γ) isotherms of aqueous solutions of Tyloxapol (*1*), and Synperonic F-68 (*2*) (amphiphile concentrations are given per mole unit); 25 °C. Herein and in Fig. 2 logarithmic abscissa axis is shown.

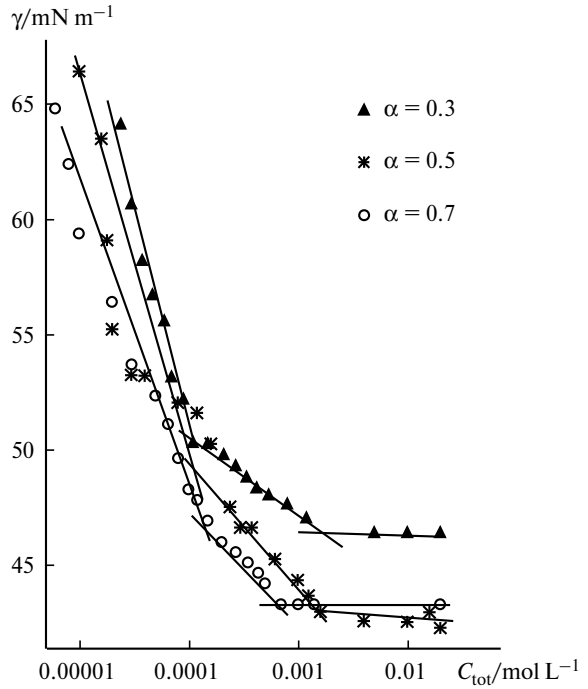


Fig. 2. Surface tension isotherms of aqueous Tyloxapol—CTAB solutions at different component ratio; 25 °C; C_{tot} is the total concentration of amphiphiles.

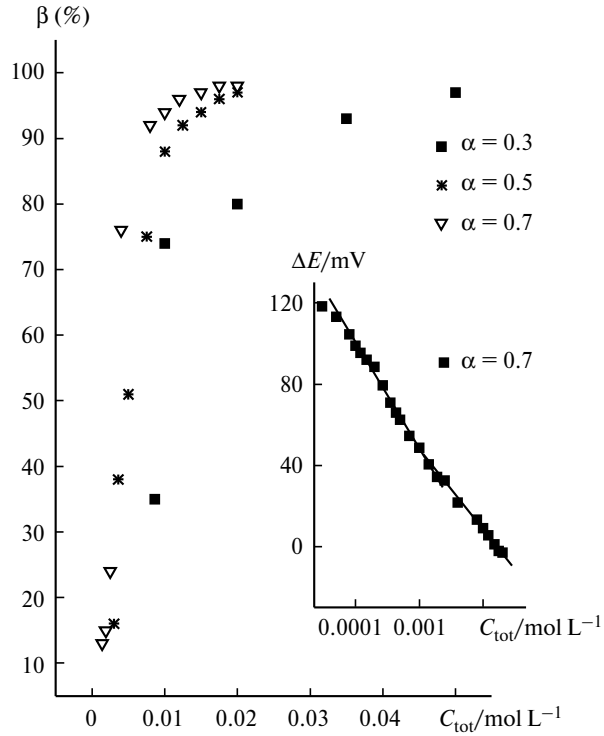


Fig. 3. The dependence of the binding extent of bromide ions (β) in the system Tyloxapol—CTAB on the total concentration (C_{tot}) of amphiphiles at different component ratio; 25 °C. Inset: the dependence of the electrode potential (ΔE) on the total concentration of amphiphiles at the CTAB : Tyloxapol ratio equal to 0.7; 25 °C; logarithmic abscissa axis is shown.

micelles bound to Tyloxapol. The binding degree of the counter ions depends on the composition of micellar systems (Fig. 3); it increases with the increase in the CTAB fraction and approaches a value of 1.0 in the plateau region at high amphiphile concentrations.

The data characterizing the solubilization action of the systems studied were obtained by spectrophotometry at the amphiphile concentration of 0.02 mol L^{-1} (see Table 1). They give evidence that block copolymers only slightly promote the increase in solubility of PNPL; this is in agreement with the results shown in Fig. 1, which confirm the lack of micelle formation in the studied region of amphiphile concentrations. Tyloxapol increases the solubility of the ester by an order of magnitude. One can assume that the ability of the systems studied to dissolve the hydrophobic substrate is determined by the correlation of the contribution of two types of interactions, *viz.*, the solubilization mechanism of PNPL binding, which assumes the formation of mixed micelles, and the sorption mechanism on the polymer surface. Estimation of the hydrolytic stability of the guest in aqueous solutions of amphiphilic compounds at concentrations of 0.02 mol L^{-1} was performed; as a result, the data on the rate of basic hydrolysis of PNPL were obtained (see Table 1).

As a rule, nonionic surfactants have little effect on the rate of ion-molecular reactions. Previously,[12] a slight retardation of basic hydrolysis of esters in solutions of nonionic amphiphiles was demonstrated. In this work, we observed acceleration of the hydrolysis of PNPL; the catalytic activity of the systems studied changes in parallel to their solubilization ability (see Table 1). The maximum effect is observed in the Tyloxapol solutions, namely, a 14-fold increase in the solubility of PNPL and a 145-fold acceleration of its hydrolysis. It is known that PNPL is prone to self-association, which is the reason for its lower reactivity (compared to non-micelle-forming homologs) in the nucleophilic substitution in the absence of surfactants. Probably, in micellar solutions the structure of these associates is changed and mixed micelles possessing higher reactivity appear.

In order to obtain systematic data on the catalytic effect of supramolecular systems, the kinetics of the reactions at different surfactant concentrations was studied (see Fig. 4) with the subsequent quantitative analysis of the concentration dependences of the observed rate constant for PNPL hydrolysis. The character of the dependences showing plateau regions at high concentration

Table 1. Solubilization of PNPL and the observed rate constant for basic hydrolysis of PNPL in water, in solutions of nonionic surfactants and block copolymers

System	$[PNPL]_m \cdot 10^{-4}$ /mol L^{-1}	$[PNPL]_m/[PNPL]_0$	k_{app}/s^{-1} (0.05 *M* NaOH)	k_{app}/k_0
Water	0.12	1	0.0002	1
Triton-X-100	3.35	28	0.010	50
Brij-35	0.42	3.5	0.008	40
Brij-97	0.82	6.8	0.016	80
Pluronic F-127	0.17	1.4	0.00078	3.9
Synperonic F-68	0.14	1.2	0.00074	3.7
Tyloxapol	1.79	15	0.029	145

Note. $[PNPL]_m$ and $[PNPL]_0$ are the maximum concentrations of PNPL, which are achieved on dissolution in solutions of amphiphiles and water, respectively. The amphiphile concentration is 0.02 mol L^{-1}, 25 °C.

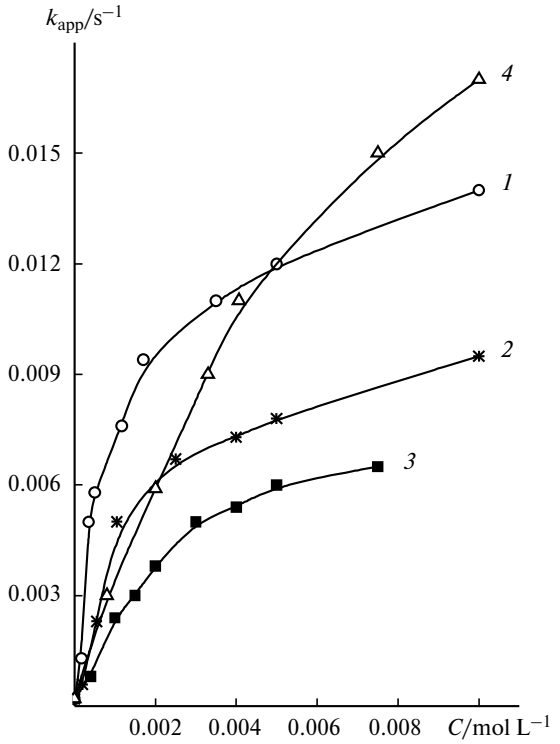


Fig. 4. The dependence of the observed rate constant (k_{app}) for basic hydrolysis of PNPL on the concentration (C) of nonionic surfactants: Brij-97 (*1*), Triton-X-100 (*2*), Brij-35 (*3*), Tyloxapol (*4*); 0.05 *M* NaOH, 25 °C.

allows one to apply the pseudophase model (1) to the kinetic data obtained and to calculate the constants of substrate binding (K_S) and the rate constants in the micellar pseudo-phase (k_m) (Table 2). It is seen from the calculations that for nonionic surfactants the increase in the binding constant is accompanied by the increase in the rate of hydrolysis. Thus, for Brij-35 one gets K_S = 370 L mol^{-1} and acceleration (compared with the rate constant in the absence of surfactants) by 45 times. For Brij-97, one gets K_S = 1100 L mol^{-1} and acceleration by ~70 times. The CMC value resulted from the kinetic and tensiometric studies are close. Much higher acceleration in the case of Tyloxapol (up to 150 times), is probably due to favorable changes in the microenvironment of PNPL when it is incorporated into aggregates based on this oligomer.

Table 2. Results of quantitative analysis of kinetic data for basic hydrolysis of PNPL in solutions of nonionic surfactants and Tyloxapol using Eq. (1) (0.05 *M* NaOH, 25 °C)

Surfactant	k_m/s^{-1}	K_S /L mol^{-1}	CMC /mol L^{-1}	k_m/k_0
Triton-X-100	0.01	890	0.00013	50
Brij-35	0.009	370	0.00033	45
Brij-97	0.014	1100	0.00005	70
Tyloxapol	0.030	140	0.0009	150

Mixed systems with cationic surfactant were studied for Tyloxapol, which is the most efficient catalyst (see Fig. 3). It was assumed that the positive charge on the surface of micelles can lead to additional concentration of hydroxide ions in the micelles and enhancement of the catalytic action of Tyloxapol. The results of kinetic studies of basic hydrolysis of laurate in the system Tyloxapol—CTAB at different component ratios are demonstrated in Fig. 5. They show that the catalytic effect of this system considerably differs from that obtained for the previously studied[10,11] binary solutions CTAB—Triton-X-100. In the CTAB—Triton-X-100 system a monotonous increase in the rate constant with an increase in the mole fraction of the cationic surfactant was observed. This agrees with the concept of formation of combined aggregates whose surface potential varies depending on the component ratio and is the rate-determining factor. For the binary system Tyloxapol—CTAB, the introduction of small amounts of the cationic surfactant (α = 0.1) results in fivefold increase in the rate of PNPL basic hydrolysis; however, even at α = 0.2 the effect of CTAB introduction virtually reaches its limiting value and increases by 6—10 times on subsequent increase in the cationic surfac-

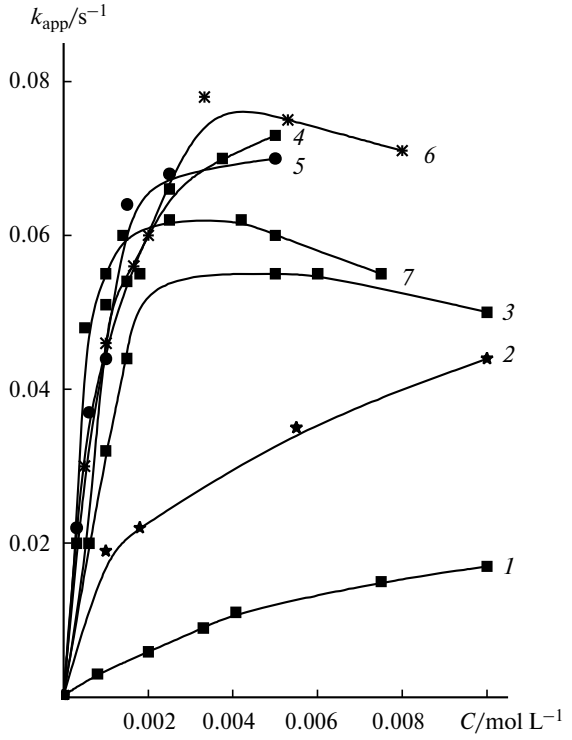


Fig. 5. The dependence of the observed rate constant for basic hydrolysis of PNPL in the system Tyloxapol—CTAB on the total concentration of amphiphiles at different mole fraction of CTAB: α = 0 (*1*), 0.1 (*2*), 0.2 (*3*), 0.3 (*4*), 0.5 (*5*), 0.7 (*6*), 1 (*7*); 0.05 *M* NaOH, 25 °C.

tant fraction to 1.0 (see Fig. 5). Probably, this is due to the observed narrowing of the region of existence of mixed aggregates, and also to stronger binding of counterions, resulting in the decrease in the surface potential with the increase of the CTAB fraction in the system. It should be noted that at $\alpha = 0.3—0.7$ the observed rate constant is higher than that in the individual Tyloxapol and CTAB systems. The demonstrated kinetic data give additional evidence of the formation of mixed aggregates, which cause the observed synergetic catalytic effect.

Thus, we obtained and characterized micellar systems based on nonionic amphiphiles with oligomeric (Tyloxapol) and polymeric (Synperonic F-68, Pluronic F-127) structure, as well as previously not studied mixed systems Tyloxapol—CTAB. The CMCs, aggregate sizes, and the extent of counterion binding of mixed systems were established. The micelle-forming properties, solubilization capability, and catalytic effect of the classical surfactants and amphiphilic high-molecular compounds were compared. In contrast to the usually observed slowing down or the lack of the influence of nonionic micelles on the rate of nucleophilic substitution, it was shown that the systems studied have a pronounced catalytic effect on the basic hydrolysis of PNPL, which exceeds two orders of magnitude. A correlation between the solubilization ability of aggregates based on nonionic amphiphiles and their catalytic effect was revealed for the first time. The highest efficiency was found for the Tyloxapol solution. For the mixed systems Tyloxapol—CTAB, synergetic enhancement of the catalytic effect upon addition of small amounts of CTAB was established.

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