Acid-base properties and nucleophilicity of *o*-aminomethylphenols in aqueous micellar solutions and microemulsions

A. B. Mirgorodskaya, N. S. Erzikova, L. A. Kudryavtseva, and A. I. Konovalov*

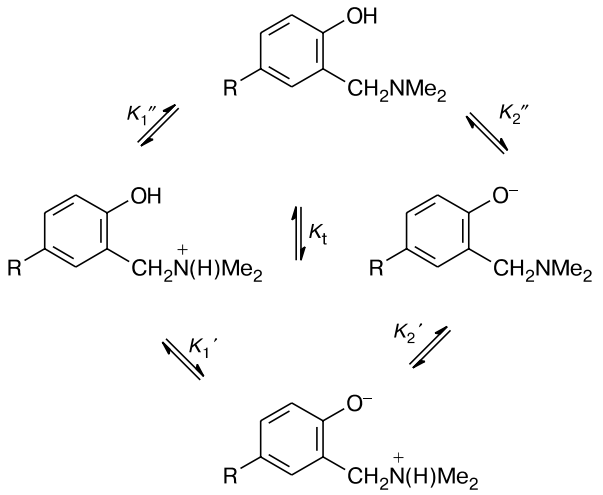
A. E. Arbuzov Institute of Organic and Physical Chemistry,
Kazan Research Center, Russian Academy of Sciences,
8 ul. Akad. Arbuzova, 420088 Kazan, Russian Federation.
Fax: +7 (843 2) 73 2253. E-mail: mirgorod@iopc.knc.ru

The pK_a values and constants of tautomeric equilibrium of several *o*-aminomethylphenols with different hydrophilic—lipophilic ability were measured in aqueous micellar solutions and in direct microemulsions based on cetyltrimethylammonium bromide. The kinetics of hydrolysis of *p*-nitrophenyl acetate at different pH and concentrations of aminomethylphenol and surfactant was studied.

Key words: micelles, microemulsions, *o*-aminomethylphenols, acid-base properties, tautomerism, *p*-nitrophenyl acetate, kinetics.

In highly organized media based on surfactants, the interface sorbs selectively particles participating in acid-base equilibria. The sorption shifts pK of solubilized substances relative to the values in molecular solutions and changes their reactivity.[1—6] The effect depends on the surfactant nature, the structure of a microaggregate and its surface potential, and the properties of the substance under study. The presence of two ionogenic groups of different nature in *o*-aminomethylphenols (AMPs) creates a complicated system of acid-base equilibria with proton transfer involving the formation of zwitterions (Scheme 1) and pre-determines their reactivity in chemical reactions.[7,8]

Scheme 1



In the present work, to reveal specific features of the effect of microdispersion media on the reaction behavior of AMPs, we studied their acid-base properties and nucleophilicity in systems based on cetyltrimethylammonium bromide (CTAB) and decaoxyethylated oleyl alcohol (Brij-97). The AMPs with different hydrophilic—lipophilic ability were used: R = H (AMP-1), Me (AMP-2), and *iso*-C_9H_{19} (AMP-3). The kinetics of hydrolysis of *p*-nitrophenyl acetate (PNPA) in the presence of these compounds was studied in molecular solutions and aqueous micellar systems, and direct microemulsions with varying pH and concentrations of the reactants and surfactants.

Experimental

Commercial CTAB and Brij-97 (Sigma) containing ~99% of the major substance were used; AMPs were synthesized and purified according to Ref. 9, and PNPA was recrystallized using standard procedures. Aqueous systems with a surfactant concentration of 0—0.015 mol L^{-1} and microemulsions containing a surfactant (9.4 g), butanol (9.4 g), hexane (2.0 g), and water (79.2 g) (volume fraction of water 0.74) were used as media.

The pK_1 and pK_2 values were determined by the potentiometric titration of AMPs and the corresponding phenoxides (C_{AMP} = 0.005—0.01 mol L^{-1}) with a 0.1 M solution of HCl using a pH-340 instrument. The values averaged over results of three experiments were used, the reproducibility being ±0.05 logarithmic units. Spectra of AMPs were recorded on a Specord UV—Vis spectrophotometer in 1-cm quartz cells in the wavelength range from 250 to 400 nm. Molar absorptivities (ε) were determined from the absorbance values, which were measured at the absorption maxima of the anionic and zwitterionic forms. The changes in ε for AMP-2 at different pH in different media are presented in Table 1 as an example.

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Table 1. Molar absorption coefficients of AMP-2 in different media

Water		Micellar solution (C_{CTAB} = 5 mmol L^{-1})		Microemulsion based on CTAB	
pH	ε (302 nm)	pH	ε (306 nm)	pH	ε (305 nm)
13.0	3400	13.0	3270	13.0	3600
12.4	3310	11.0	3050	12.5	3350
12.0	3200	10.5	2750	12.0	2800
11.5	3000	10.0	2300	11.5	1750
11.0	2830	9.4	1800	11.0	1050
10.5	2700	9.0	1400	10.5	500

The reaction kinetics was studied in freshly prepared microdispersion media by spectrophotometry on a Specord UV—Vis instrument at 25 °C under the pseudo-first reaction conditions. The reaction progress was monitored by a change in the absorbance of solutions at the wavelength 400 nm (formation of *p*-nitrophenoxide anion); the initial concentration of the substrate being $5 \cdot 10^{-5}$ mol L^{-1}, and conversion more than 90%. The apparent pseudo-first order rate constants (k_{app}) were determined from the plot $\log(D_\infty - D_t) = -0.434k_{app}t + \text{const}$, where D_t and D_∞ are the absorbancies of solutions at the moment t and after reaction completion, respectively. The k_{app} values were calculated by the least-squares method.

The formation of the hydrolysis product in microdispersion media was confirmed by the yield of the reaction products in experiment with an equimolar amount of PNPA and AMP. The concentration of acetic acid that formed was measured by potentiometric titration, and that of *p*-nitrophenol was measured spectrophotometrically. Equal amounts of these substances were found to form in the reaction. For instance, in a 0.01 *M* solution of CTAB at a concentration of AMP-1 and PNPA of 0.008 mol L^{-1}, in 10 min after the beginning of the reaction the concentrations of acetic acid and *p*-nitrophenol were 0.0033 and 0.0036 mol L^{-1}, respectively, whereas after 30 min the concentrations were 0.0056 and 0.0055 mol L^{-1}.

Results and Discussion

The pK_a values characterizing the proton addition (pK_1) and abstraction (pK_2) for the AMPs under study were determined by potentiometric titration. The acid-base properties of these compounds are virtually the same in the absence of a surfactant in molecular solutions (Table 2). A different situation is observed in CTAB-based micellar solutions, where changes in pK_a show the effect of selective sorption of ionic forms of the AMPs by the positively charged micellar surface. The pK_1 values of water-soluble AMP-1 and AMP-2 in the presence of the surfactants change almost similarly (see Table 2). The pK_2 value that characterizes proton abstraction changes more remarkably ($\Delta pK = 0.5$—1.1). For AMP-3 in a micellar solution of CTAB, the pK_2 values are close to pK_2 of the hydrophilic homologs, whereas pK_1 are substantially lower. Probably, the shift of pK_a for AMP-3 is determined by contributions of both electrostatic and hydrophobic interactions of a micelle and each AMP form involved in acid-base equilibrium.

In a CTAB-based microemulsion, differences in the acid-base properties of the AMPs are aligned. This can be due to a decrease in the role of electrostatic interactions in these systems compared to micellar solutions: for direct CTAB micelles the surface potential (ψ) is 120—140 mV,[10,11] whereas for oil—water microemulsions based on this surfactant ψ ≈ 30 mV.[12,13] The systems based on nonionic surfactants for which ψ ≈ 0 have no contribution of electrostatic interactions, and the pK_a value is affected by the hydrophobic effect, which is most significant for AMP-3 (see Table 2).

According to the earlier proposed procedure,[14] we calculated the constant of tautomeric equilibrium (K_t) for the AMPs by the equation

$$K_t = \frac{[\mathbf{B}]}{[\mathbf{A}]} = \frac{\varepsilon_m([H^+]^2 + K_1[H^+] + K_1K_2) - \varepsilon_m(\mathbf{C})K_1K_2 - \varepsilon_m(\mathbf{A})K_1[H^+]}{\varepsilon_m([H^+]^2 + K_1[H^+] + K_1K_2) - \varepsilon_m(\mathbf{C})K_1K_2 - \varepsilon_m(\mathbf{C})K_1[H^+]}$$

using combined data of potentiometric titration and UV spectroscopy when the molar absorption coefficients (ε_m) were measured at constant pH of the medium.

The UV spectra in a range of 290—310 nm contains no absorption of the cationic (**D**) and neutral (**A**) forms of the AMPs, *i.e.*, $\varepsilon_m(\mathbf{A}) = 0$. In this region, the molar ab-

Table 2. Constants of acid-base and tautomeric equilibria of AMPs in different media (C_{AMP} = 2.5 mmol L^{-1})

Medium	AMP-1			AMP-2			AMP-3		
	pK_1	pK_2	K_t	pK_1	pK_2	K_t	pK_1	pK_2	K_t
Water	8.45	10.90	2.5	8.75	11.40	3.5	—	—	—
Water—ethanol (1 : 1)*	8.20	11.60	~0	8.45	11.75	~0	8.20	11.65	~0
ЦТАБ (0.01 mol L^{-1})	8.24	10.45	1.1	8.60	10.25	1.3	6.50	10.0	0.3
Microemulsion (CTAB)	8.30	11.0	~0	8.1	11.45	~0	7.20	11.65	~0
Brij-97 (0.01 mol L^{-1})	8.4	10.95	~1	8.7	11.3	1.4	6.4	10.8	~0

* In these media, the pH value in the half-neutralization point detected with a pH-meter was accepted as pK_a. This effective value makes it possible to compare the properties of AMPs depending on their structure within the same system; however, in this case, it is incorrect to discuss the effect of the medium on pK_a.

sorption coefficients of their anionic (**C**) and zwitterionic (**B**) species are equal.

The data obtained (see Table 2) show that for the AMPs the K_t value decreases on going from aqueous to micellar solutions. This indicates preferential solubilization of the neutral AMP form by micelles compared to the zwitterionic form. In a microemulsion, as well as in an aqueous-alcohol solution, equilibrium is virtually shifted completely to the neutral form; the AMPs are located in a microdroplet regardless of the hydrophobic properties. Probably, the AMPs nonionized by the external effect of acid or alkali are located in a microregion with a lower polarity, which is the interphase layer and, the more so, the core of the microaggregate, rather than in the aqueous volume phase. The medium is insufficiently polar to favor intramolecular proton transfer and zwitterion formation. We observed[15] the same effect of the medium on AMP tautomerism in acetonitrile—water solutions with a variable ratio of the components.

According to published data,[14] the partial constants of acid-base equilibria can be calculated for the media where zwitterionic AMP forms are formed

$$K_1 = K_1' + K_1''; \; K_2 = K_2'K_2''/(K_2' + K_2'');$$
$$K_1' = K_1K_t/(1 + K_t); \; K_1'' = K_1/(1+ K_t);$$
$$K_2' = K_2(1 + K_t)/K_t; \; K_2'' = K_2(1 + K_t).$$

Based on analysis of the partial constants (Table 3), we can conclude a relative ability of different forms of AMP-1 and AMP-2 to solubilization by CTAB micelles. The ability increases in the order: cation ≈ zwitterion < neutral molecule < anion. Considerable differences between the partial constants of AMP-3 and the corresponding values for its water-soluble analogs indicate a strong effect of hydrophobic interactions on the physicochemical properties of this compound in micellar solutions. The ratio of the AMP forms in solutions should affect the reactivity of these compounds, in particular, their nucleophilicity during interaction with PNPA.

Table 3. Partial constants of acid-base equilibria of AMPs in water and aqueous micellar solutions of surfactants*

AMP	Medium	pK_1'	pK_1''	pK_2'	pK_2''
AMP-1	Water	8.6	9.0	10.75	10.36
	CTAB	8.62	8.65	10.12	10.06
	Brij-97	8.7	8.7	10.65	10.65
AMP-2	Water	8.86	9.40	11.29	10.74
	CTAB	8.85	8.96	10.0	9.90
	Brij-97	8.95	9.05	10.8	10.65
AMP-3	CTAB	7.14	6.62	9.37	9.9

* $C_{CTAB} = 0.01$ mol L^{-1}; $C_{Brij\text{-}97} = 0.01$ mol L^{-1}.

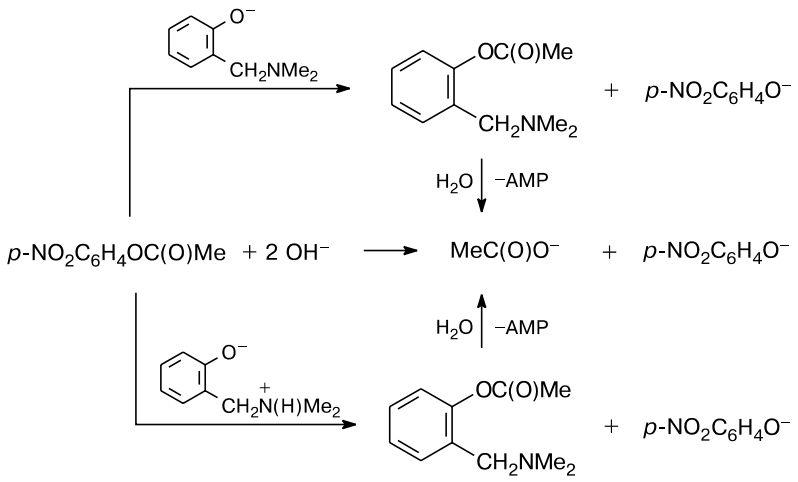
It is known[16,17] that the zwitterionic and anionic AMP forms are reactive in nucleophilic substitution reactions. The anionic form exists at high pH and, in this case, the hydroxide ion competes with AMP. The neutral form also manifests nucleophilicity due to the formation of an intramolecular hydrogen bond resulting in an increase in the electron density on the oxygen atom.

A possible general mechanism of the reaction is shown in Scheme 2.

In the case of AMPs, intermediate products of transesterification of PNPA are rapidly hydrolyzed due to intramolecular catalysis with the aminomethyl group, which was confirmed by the yields of acetic acid and *p*-nitrophenol in the reaction. Unlike simple phenols forming rather stable transesterification products,[8,18] these compounds are characterized by hydrolysis catalyzed *via* the nucleophilic mechanism at the concerted action of the amino group and phenolic hydroxyl group.

Under the conditions of changing pH of the medium, the regions of existence of different AMP forms are deter-

Scheme 2



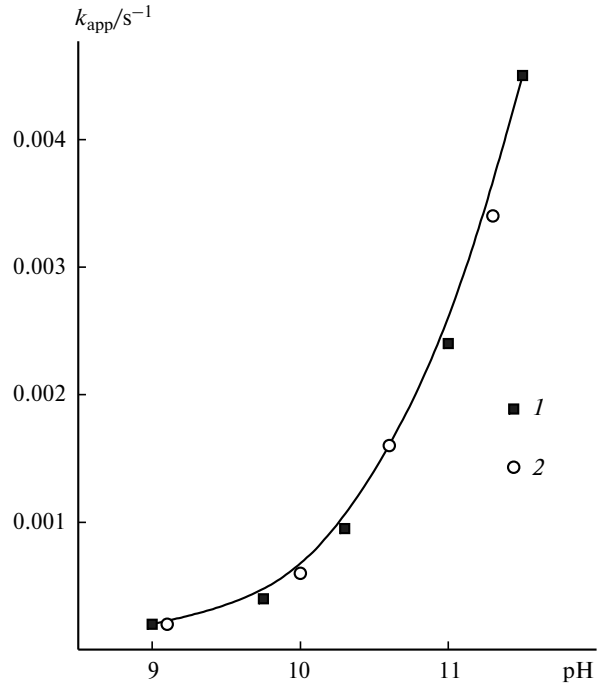


Fig. 1. Effect of pH on the apparent rate constant of PNPA hydrolysis in an aqueous-alcohol (1 : 1) solution in the presence of AMP-3 (*1*) and AMP-2 (*2*); C_{AMP} = 2.5 mmol L^{-1}, 25 °C.

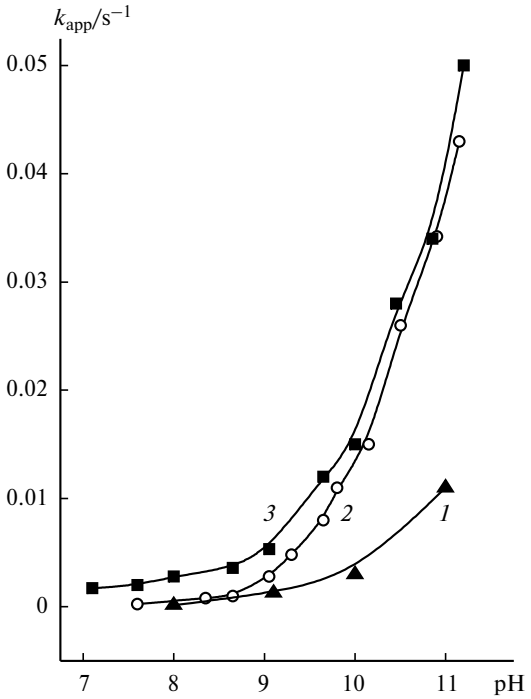


Fig. 2. Effect of pH on the apparent rate constant of PNPA hydrolysis in a micellar solution of CTAB (0.01 mol L^{-1}) in the absence of AMP (*1*) and in the presence of AMP-2 (*2*) and AMP-3 (*3*); C_{AMP} = 2.5 mmol L^{-1}, 25 °C.

mined by the pK_a values, which is reflected by their reaction behavior. In the absence of surfactants in molecular solutions, for instance, in an aqueous-alcohol medium, the acid-base properties of the AMPs under study are virtually the same (see Table 2). An aqueous-alcohol medium manifests no substantial differences in their interaction with PNPA: the plots of the apparent reaction rate constant (k_{app}) *vs.* pH in alkaline and weakly alkaline media for AMP-2 and AMP-3 are described by the single curve (Fig. 1).

A different pattern is seen when studying the properties of the AMPs in micellar systems based on cationic surfactants. The plots of the apparent rate constant for the reactions of the AMPs with PNPA *vs.* pH of the medium for AMP-2 and AMP-3 in a micellar solution of CTAB (0.01 mol L^{-1}) at 25 °C are shown in Fig. 2. According to pK_1 at pH of the medium <7.5, AMP-2 is almost completely transformed into the inactive cationic form and the k_{app} value coincides with that for substrate hydrolysis (see Fig. 1); AMP-3 is rather reactive under these conditions. The difference in k_{app} for the both AMPs decreases gradually with an increase in pH and accumulation of the reactive forms. At high pH in the region where the compounds under study exist predominantly in the anionic form, their reactivities toward PNPA are close.

When studying the kinetics of the reaction of the AMPs with PNPA with changing CTAB concentration at constant pH (data obtained at pH 10.0 are presented as an example in Fig. 3), much higher k_{app} values were revealed

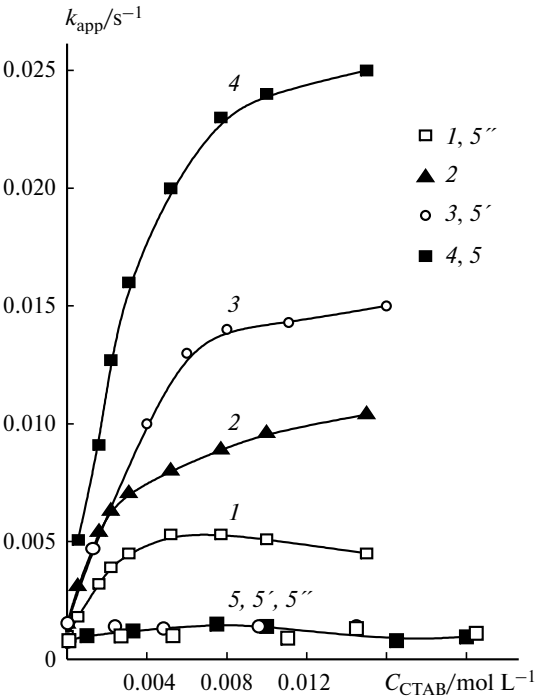


Fig. 3. Apparent rate constant of PNPA hydrolysis at pH = 10.0 as a function of the CTAB concentration in the absence of AMP (*1*) and in the presence of AMP-1 (*2*), AMP-2 (*3*), and AMP-3 (*4*) and as a function of the Brij-97 concentration in the absence of AMP (*5*) and in the presence of AMP-1 (*5′*) and AMP-3 (*5″*); C_{AMP} = 2 mmol L^{-1}, 25 °C.

for AMP-3 compared to other AMPs, which can be a consequence of high affinity of this compound to the micellar pseudo-phase and a possibility of forming mixed aggregates.

Quantitative characteristics that reflect the interaction of the substrate with a micelle can be obtained by analysis of the experimental kinetic data in the framework of the pseudo-phase model of micellar catalysis using the equation[19]

$$k_{app} = (k_m K_s C_{det} + k_0)/(1 + K_s C_{det}),$$

where C_{det} is the surfactant concentration corrected to the critical micelle concentration (CMC); k_0 and k_m are the rate constants in the aqueous medium and micellar phase, respectively; K_s is the binding constant of the substrate.

As can be seen from the results obtained in Table 4, an increase in the concentration of the anionic AMP form in a micellar solution of CTAB facilitates micelle formation decreasing the CMC, decreases binding of PNPA with a micelle, and enhances the micellar catalytic effect. The higher effect (up to 23 times) is observed for AMP-3, which can be due to the content of the anionic form for this compound at pH 10.0 exceeding those for AMP-1 and AMP-2 (see Tables 2 and 3). A small fraction of the anionic AMP form in solutions of Brij-97 results in the situation when at pH 10.0 no differences between AMP-1 and AMP-3 are seen and the main direction of ester bond cleavage is alkaline hydrolysis in solutions (see Fig. 3). Thus, the micellar catalytic effect of PNPA hydrolysis in the presence of the AMPs is related first of all to the influence of the medium on the acid-base properties of AMP.

In the case of CTAB-based microemulsions at $pH < (pK_1 + pK_2)/2$, the neutral AMP form is reactive in the reactions with PNPA. With an increase in the basicity of the system, the more reactive anionic form is accumulated and k_{app} increases (Fig. 4). The plot of k_{app} *vs.* AMP concentration at constant pH in microemulsions is linear (Fig. 5). Based on these data and taking into account pK_1

Table 4. Parameters of micelle-catalyzed PNPA hydrolysis in weakly alkaline solutions of CTAB in the presence of AMPs (C = 2 mmol L^{-1}, 25 °C)

Nucleophile	pH*	k_m/s^{-1}	K_s /L mol^{-1}	CMC /mol L^{-1}	k_m/k_0**
AMP-1	9.2	0.0035	780	0.0007	4
	10.0	0.011	450	0.00012	7
AMP-2	9.2	0.004	750	0.0007	5
	10.0	0.017	300	0.00011	11
AMP-3	9.2	0.007	650	0.0004	10
	10.0	0.035	250	0.00010	23

* To maintain pH, a buffer solution of sodium tetraborate (0.05 mol L^{-1}, pH 9.2) was used as a basis, adding a 0.1 *M* solution of sodium hydroxide and monitoring the pH value with a pH-meter.

** The k_m/k_0 ratio is a measure of the micellar catalytic effect.

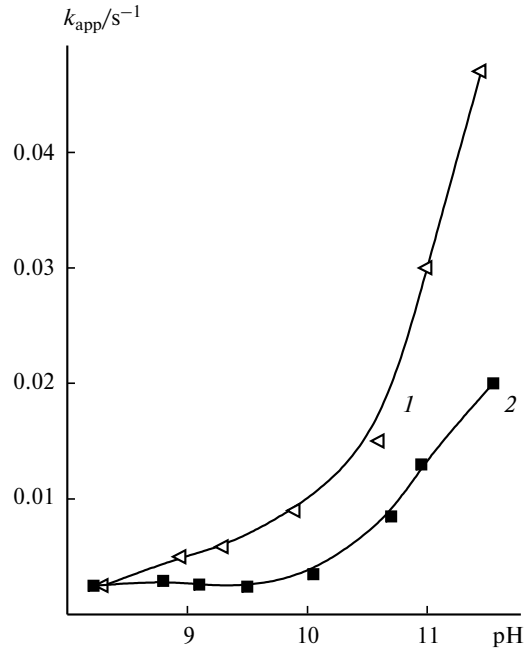


Fig. 4. Effect of pH on the apparent rate constant of PNPA hydrolysis in a direct CTAB-based microemulsion in the presence of AMP-1 (*1*) and AMP-3 (*2*); C_{AMP} = 0.05 mol L^{-1}, 25 °C.

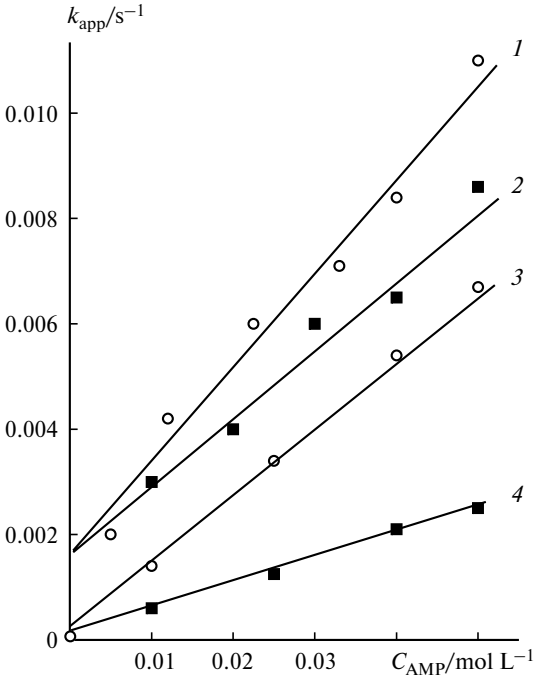


Fig. 5. Apparent rate constant of PNPA hydrolysis as a function of the AMP concentration in a direct CTAB-based microemulsion: AMP-2 (*1*) and AMP-3 (*2*) at pH = 10.6; AMP-2 (*3*) and AMP-3 (*4*) at pH = 10.0.

Table 5. Second-order rate constants of PNPA hydrolysis in the presence of the neutral and anionic AMP forms in the CTAB-based microemulsion (volume fraction of water 0.74) at 25 °C

Compound	Form	k_2/L mol^{-1} s^{-1}
AMP-1	Neutral	0.1
	Anionic	1.2
AMP-3	Neutral	0.05
	Anionic	0.8

and pK_2 of the compound under study and the alkaline hydrolysis rate constant (k_0), which is determined as a section cut on the ordinate of the $k_{app} = f(C_{AMP})$ plot, we determined the second-order rate constants for the neutral and anionic forms of the AMPs (Table 5).

The obtained data show that the nucleophilicity of the anionic AMP form is approximately an order of magnitude higher than that of the neutral form. In the microemulsion under study (unlike micellar solutions), the hydrophobic AMPs are less reactive than the hydrophilic AMPs. This is probably due to the fact that a considerable volume of the oil phase in microemulsions provides more possibilities for localization of reactants than micelles do. A hydrophobic compound can immerse into the oil phase. This shifts the zone of reactant interaction to the region of lower polarity exerting an unfavorable effect on the reaction rates.

Thus, using as an example hydrolysis of esters of carboxylic acids in the presence of the AMPs in surfactant-based microdispersion media, one can monitor a combination of possibilities of homogeneous bifunctional and micellar catalysis. The specific reaction behavior of the AMPs is due to the presence of two nonionogenic groups of different nature, which creates a complicated system of acid-base equilibria of proton transfer including the formation of zwitterions and provides prerequisites for the concerted effect of the functional groups similar to the effect of active centers in enzymes. Selective sorption of the ionic AMP forms by the positively charged interface is the main reason for the catalytic effect of microdispersion media on PNPA hydrolysis in the presence of the AMPs.

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