Russian Journal of General Chemistry, Vol. 72, No. 8, 2002, pp. 1261–1265. Translated from Zhurnal Obshchei Khimii, Vol. 72, No. 8, 2002, pp. 1343–1348.
Original Russian Text Copyright © 2002 by Mirgorodskaya, Kudryavtseva.

Nucleophilic Substitution in Carboxylic Esters in Oil-In-Water Microemulsions

A. B. Mirgorodskaya and L. A. Kudryavtseva

Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center,
Russian Academy of Sciences, Kazan, Tatarstan, Russia

Received August 9, 2000

Abstract—In hydrolysis and aminolysis of *p*-nitrophenyl esters of carboxylic acids in oil-in-water microemulsions on the basis of surfactants of various nature, a complex mechanism of the effect of the medium is operative, including shift of acid–base equilibria in the nucleophile. The rate constants of the processes studied are quantitatively related to the surface potential of the microdroplet. Varied hydrophobicity of the nucleophile and substrate changes the site of the reaction act and the relative contributions of aminolysis and hydrolysis.

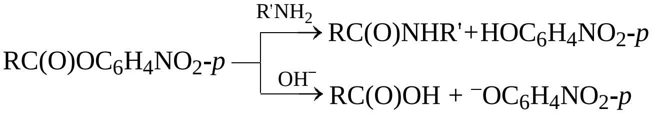
Surfactant microemulsions are thermodynamically stable, self-organized, and macroscopically uniform dispersions with aqueous and hydrocarbon phases, stabilized by surfactants and cosurfactants [1]. The high solubilizing ability and the exceptionally developed interface providing effective contact between reagents with different solubilities in the aqueous and organic phases explain the interest in such systems as microreactors for various chemical processes [2–4].

Knowledge of factors determining the rate and direction of processes in microemulsions is very important, allowing one to forecast and plan results of scientific research and favoring purposeful search for new catalytic systems. These problems are closely related to enzymology, since most enzyme processes occur in highly organized systems, such as cell membranes and subcellular particles. Microemulsions can serve as a convenient model for studying *in vitro* processes in living cells [5].

The present work is a continuation and development of our research into the catalytic properties of oil-in-water microemulsions in nucleophilic substitution reactions [6]. Its aim is to study the properties of oil-in-water microemulsions on the basis of surfactants of various nature and to gain insight into the effect of these systems on hydrolysis and aminolysis of carboxylic esters.

As the reaction medium for nucleophilic substitutions in carboxylic esters we chose microemulsions with equal volumes of the disperse phases but differently charged microdroplet surfaces. Varied nature of surfactants forming microemulsions should affect the physicochemical properties and reactivity of reagents, as well as the rate and mechanism of chemical processes.

Chemical processes in surfactant oil-in-water microemulsions generally occur either on the surface of or inside the microdroplet. By varying the hydrophobicity of reagents, one can affect the site of their localization and also their partners by the reaction act, which can be exemplified by hydrolytic cleavage of *p*-nitrophenyl carboxylates in microemulsions in the presence of primary aliphatic amines. In aqueous solutions, this process generally occurs by two directions: aminolysis (major reaction) and alkaline hydrolysis (side reaction).



$$\mathrm{RC(O)OC_6H_4NO_2\text{-}}p \begin{array}{l} \xrightarrow{\mathrm{R'NH_2}} \mathrm{RC(O)NHR'+HOC_6H_4NO_2\text{-}}p \\ \xrightarrow{\mathrm{OH^-}} \mathrm{RC(O)OH} + {}^{-}\mathrm{OC_6H_4NO_2\text{-}}p \end{array}$$

To estimate the relative contributions of these two processes in microemulsions, we at first considered alkaline hydrolysis of *p*-nitrophenyl esters in the absence of amines. It should be noted that the kinetic dependences of this process on the nature of microemulsion-forming surfactants, the hydrophobicity of substrate, the pH and temperature of reaction medium are of interest in their own.

The apparent hydrolysis rate constants ($k_{1,o}$) of *p*-nitrophenyl acetate (**I**) and *p*-nitrophenyl caprylate (**II**) in microemulsions on the basis of cetyltrimethylammonium bromide (**III**), cetylpyridinium bromide (**IV**), dodecylpyridinium bromide (**V**), cetylpyridinium chloride (**VI**), Brij-97 (**VII**), and sodium dodecyl sulfate (**VIII**) at pH 9.35 are listed in Table 1. In the microemulsions studied (fraction of the disperse

Table 1. Apparent hydrolysis rate constants of compounds **I** and **II** in surfactant oil-in-water microemulsions (pH 9.35)[a]

Surfactant	I			II	
	T, °C	$k_{1,o}$, s^{-1}	φ, mV	T, °C	$k_{1,o}$, s^{-1}
III	25	0.00091	30.2	25	0.00026
III	33	0.00195		33	0.00053
III	41	0.00350		41	0.0010
III	43	0.00387		43	0.0011
IV	25	0.00110	35.1	25	0.00037
V	25	0.00150	43.1	25	0.0007
VI	25	0.00102	33.2	25	0.00034
VII[b]	25	0.00028	0	25	0.000041
VII	31	0.00053			
VII	37	0.00070			
VII	43	0.00096			
VIII	25	0.000123	–21.1	25	0.000025
VIII	32	0.00020		34	0.000051
VIII	43	0.00046		41	0.000113
VIII	51	0.00085		47	0.00015

[a] The $k_{1,o}$ values in aqueous solutions at pH 9.35 are 0.00032, 0.0062, 0.0126, and 0.015 s^{-1} at 25, 32, 47, and 51°C, respectively, for compound **I** and 0.000045, 0.000080, and 0.00019 s^{-1} at 25, 35, and 47°C, respectively, for compound **II**.

[b] At higher temperatures, addition of compound **II** to the microemulsion on the basis of surfactant **VII** induces phase separation.

phase ψ 0.13), microdroplet formation involves, along with a surfactant (5.05 wt%), a hydrocarbon (hexane, 1.97 wt%) that forms a nonpolar nucleus, and a cosurfactant (1-butanol, 5.05 wt%). As follows from the oil–water partition constants {10.8 (**I**) and 95.9 (**II**) [4]}, substrate is almost completely localized inside microdroplet. As the volume phase we used aqueous sodium tetraborate [c 0.05 M (pH 9.35)]. The resulting data suggest electrostatic interactions: concentration of hydroxide ion at a positively charged microdroplet surface (cationic surfactants) accelerates hydrolysis of esters **I** and **II** compared with aqueous solution at the same pH, a negatively charged surface (anionic surfactants) slows down the reaction, and microemulsions on the basis of nonionogenic surfactants has almost no rate effect. Therewith, the effects of the medium, measured by the ratio of the apparent rate constants in microemulsions and in water $k_{1,o}$(me)/$k_{1,o}$(water), are slightly better pronounced with ester **II** compared with ester **I**, probably, on account of different localizations of these substrates in the surface layer of the microdroplet. The same reason is responsible for the higher sensitivity of compound **II**, compared with compound **I**, to the chain length and the nature of surfactant head group and counterion (Table 1). It should be noted that acetate **I** undergoes a more facile hydrolysis than caprylate **II** both in all the microemulsions studied and in molecular aqueous solutions. In this respect microemulsions considerably differ from micellar systems, where the micellar catalytic effect with ester **I** is weak, while with ester **II** it is strong and results in reactivity reversal of these two substrates [7].

The kinetic effect of microemulsions can be divided into two contributions: (1) nonelectrostatic which relates to hydrophobic interactions with reagent and is commonly modeled by the effect of nonionogenic surfactants and (2) electrostatic which relates to interaction of hydroxide ion with a charged microdroplet surface [8].

$$\ln k'_{2,\psi} = \ln k''_{2,\psi} + \bar{e}\varphi/k_BT.$$

Here $\bar{e}$ is the electronic charge, φ is the effective surface potential, k_B is Boltzmann's constant, T is the absolute temperature, and $k'_{2,\psi}$ and $k''_{2,\psi}$ are the second-order rate costants, determined in microemulsions on the basis of ionogenic surfactants and a nonionogenic surfactant, corrected for the phase volume. At the same ψ value, the $k_{2,\psi}$ value for two microemulsions under comparison can be replaced by $k_{1,o}$. In our case, for the nonionogenic surfactant we used compound **VII**.

The effective surface potentials (φ) in microemulsions on the basis of ionogenic surfactants, estimated by the above equation from the kinetic data for alkaline hydrolysis of ester **I**, proved to be 50–100 mV lower in absolute value than those in micellar solutions of the same compounds [9–11] (Table 1). This is explained by the presence in the surface layer of the microdroplet of the neutral 1-butanol molecules.

The example of the microemulsion on the basis of surfactant **III** was used to trace the effect of the pH of the medium of the apparent hydrolysis rate constant of esters **I** and **II** (Fig. 1). It will be remembered that the listed pH values are formal and thus unsuitable for estimating the true nucleophile concentration and the second-order rate constants of alkaline hydrolysis.

Cetylamine added to the reaction mixture localizes in the microdroplet and competes with hydroxide in the nucleophilic attack on the substrate ester bond. The contribution of aminolysis increases and becomes dominating as the amine concentration increases and the pH of the medium decreases. The high solubilizing ability of microemulsions allows such amine concentrations to be attained that alkaline hydrolysis of *p*-nitrophenyl esters is suppressed completely. The dependences of the apparent rate constants of aminolysis (k_{app}) on amine concentration in various microemulsions in the concentration range studied (to 0.05 M) are linear both with compound **I** and with compound **II** (Fig. 2). It should be borne in mind that acid–base equilibria in surfactant solutions are shifted due to selective solubilizing ability of microaggregates with respect to neutral and ionized forms of compounds. This shift is primarily determined by the surface potential of the microdroplet and results in that, at the same pH of surfactant microemulsions, the fraction of the neutral form of the amine (α) increases in cationic surfactant solutions and decreases in anionic surfactant solutions. The shift of pK_a can contribute much into the catalytic effect by changing the concentration of the neutral (reactive) form of the amine.

From the dependences of the apparent rate constants of cleavage of the *p*-nitrophenyl esters on amine concentration (c_{am}) by the equation $k_{2,am} = (k_{app} - k_{1,o})/\alpha c_{am}$ we estimated the volume-averaged second-order aminolysis rate constants ($k_{2,am}$) (Table 2). On an example of reaction of ester **I** with cetylamine one can see that the $k_{2,am}$ values in microemulsions depend on the sign of the surface potential of the microdroplet, being slightly lower that the k_2 value for this reaction in water and much higher that that in hexane (Table 2). These findings suggest that aminolysis of acetate **I** takes place in a fairly polar region of microemulsions, i.e., at the interface. The hydrophobic caprylate **II** is likely to react with cetylamine in the oil phase, and, therefore, its $k_{2,am}$ values are almost independent on the nature of the microemulsion-forming surfactant. It should be noted that the apparent rate constants of aminolysis in microemulsions on the basis of cationic and anionic surfactants vary 30 times with ester **I** and 50 times with ester **II**, whereas the $k_{2,am}$ values, 7 and 1.5 times with esters **I** and **II**, respectively. These results provide evidence for the assumption that the main factor controlling the rate of this reaction is shift of the pK_a of the amine, i.e. the amount of its reactive form.

When analyzing the kinetic data for cleavage of *p*-nitrophenyl esters in the presence of butylamine, one should take into account that the latter is fairly hydrophilic and is partition between the aqueous and oil phases. Butylamine is a strong base and, therefore, regardless of the fact that microemulsions on the basis of cationic surfactants reduce the pK_a values of amines, in a buffer solution at pH 9.35 the fraction of its neutral form is low (α 0.13), which adversely affects experimental accuracy. We determined the rate constant of reactions of butylamine with esters **I** and **II** in the microemulsion on the basis of surfactant **III** at various pHs. With account for the contribution of alkaline hydrolysis and for the α values, we estimated

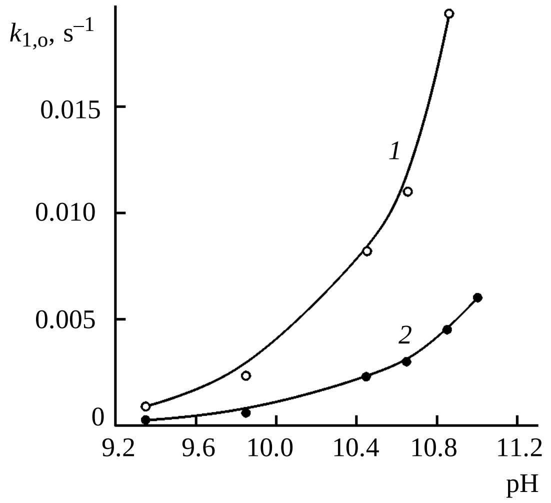


Fig. 1. Hydrolysis rate constants ($k_{1,o}$) of (*1*) *p*-nitrophenyl acetate and (*2*) *p*-nitrophenyl caprylate vs. pH of the medium in the microemulsion on the basis of surfactant **III** (25°C).

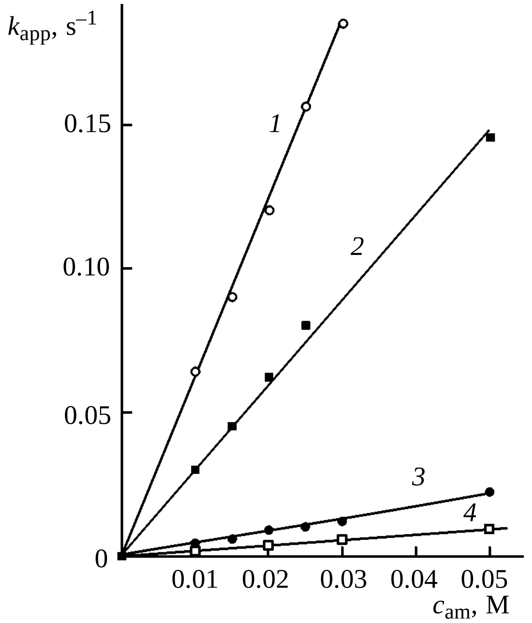


Fig. 2. Apparent rate constants (k_{app}) of cleavage of ester **I** in the microemulsions on the basis of surfactants (*1*) **III**, (*2*) **VII**, (*4*) **VIII** and (*3*) of ester **II** in the microemulsion on the basis of surfactant **III** vs. concentration of cetylamine (25°C).

Table 2. Apparent rate constants for cleavage of the ester bonds in compounds **I** and **II** in surfactant oil-in-water microemulsions in the presence of amines (pH 9.35)[a]

Surfactant	α	**I**			**II**		
		T, °C	k_{app}, s^{-1} (c_{am} 0.01 M)	$k_{2,am}$, $l\ mol^{-1}\ s^{-1}$	T, °C	k_{app}, s^{-1} (c_{am} 0.025 M)	$k_{2,am}$, $l\ mol^{-1}\ s^{-1}$
			Cetylamine				
III	0.95	25	0.064	6.64	25	0.010	0.42
III		33	0.080	8.22	33	0.0126	0.53
III		41	0.094	9.52	41	0.0160	0.67
III		48	0.11	11.2	48	0.0230	0.92
IV	0.93	25	0.05	5.0	25	0.0101	0.43
V	0.98	25	0.059	5.75	25	0.0092	0.37
VI	0.95	25	0.051	5.2	25	0.010	0.42
VII	0.80	25	0.036	4.50	25	0.014	0.70
VII		31	0.448	5.60			
VII		34	0.052	6.45			
VIII	0.2	25	0.0018	0.84	25	0.00185	0.365
VIII		34	0.0030	1.38	32	0.0025	0.450
VIII		41	0.0038	1.67	43	0.0031	0.612
VIII		51	0.00502	2.09	51	0.0046	0.886
			Butylamine[b]				
III	0.15	25	0.0079	4.60	25	0.005	0.64

[a] The k_2 values for the reaction of ester **I** with cetylamine in hexane are 0.022, 0.023, and 0.021 $l\ mol^{-1}\ s^{-1}$ at 23, 27, and 37°C, respectively. [b] The $k_{2,am}$ value was calculated taking into account that at amine concentrations of 0.01 and 0.025 M the pHs of the microemulsion are 9.55 (α 0.15) and 10.0 (α 0.25), respectively.

second-order rate constants for aminolysis of esters **I** and **II**, which proved to be close to the k_2 values with cetylamine. These results gives us grounds to state that aminolysis with butylamine occurs in the disperse phase. The contribution of volume aminolysis into the overall reaction rate appears to be small. The reaction rates depend on the concentrations of the nucleophile and substrate in the same phase rather than on the hydrophobicity of the amines.

Kinetic studies on cleavage of ester bonds in microemulsions in the presence of cetylamine allowed us to estimate activation parameters for hydrolysis and aminolysis of esters **I** and **II** (Tale 3). The activation energies (E_a) and preexponential terms ($\log A$) are apparent and depend on the thermodynamic parameters of intermediate equilibrium processes. Hydrolysis of *p*-nitrophenyl esters in microemulsions is characterized by high activation energies which only slightly depend of surfactant nature and are slightly higher than the E_a values in water (Table 3). It is known that aminolysis processes have low activation energies [12]. The E_a value for the reaction of cetylamine with ester **I** in hexane, we estimated with data in Table 2, too, is close to zero. In microemulsions, the activation energy for aminolysis in much higher than zero but much lower than for hydrolysis. This result is probably explained by temperature- and reagent-induced structural changes in microemulsions, by the character of distribution of their components between the aqueous and nonaqueous phases, as well as with possible changes in reaction mechanisms. Thus, at the same pH, the contribution of alkaline hydrolysis in ester cleavage increases with increasing temperature. Consequently, in oil-in-water microemulsions, temperature (along with hydroxide and amine concentration) may prove an important parameter controlling the amide : acid ratio in the final reaction products.

To conclude, in oil-in-water microemulsions on the basis of surfactants of various nature, a complex mechanism of the effect of the medium on nucleophilic substitution in carboxylic esters is operative, including shift of acid–base equilibria in the nucleophile. The hydrolysis rate constants of esters are quantitatively related to the surface potential of the microdroplet, and this process can serve as a probe for estimating the latter parameter. By varying the hydrophobicity of the nucleophile and substrate, one can change the site of the reaction act and control the

Table 3. Activation parameters of cleavage of ester bonds in compounds **I** and **II** in surfactant oil-in-water microemulsions in the absence and in the presence of cetylamine

Surfactant	**I**			**II**		
	E_a,[a] kJ/mol (hydrolysis)	E_a, kJ/mol (aminolysis)	log A (aminolysis)	E_a,[a] kJ/mol (hydrolysis)	E_a, kJ/mol (aminolysis)	log A (aminolysis)
III	63.19	17.27	3.93	63.49	24.99	3.99
VII	52.01	29.63	5.84	–	–	–
VIII	59.84	29.0	6.93	67.28	26.63	4.21

[a] The log A value could not be estimated because of the lack of second-order rate constants for hydrolysis; the E_a values for this process in aqueous solutions at pH 9.35 are 45.86 (ester **I**) and 52.06 kJ/mol (ester **II**).

relative contributions of the competing processes. Therewith, in microemulsions, like in molecular solutions, acetate **I** undergoes a more facile cleavage than caprylate **II**, i.e. no reactivity reversal of these esters is observed, by contrast to what happens in micellar systems on the basis of the same surfactants. Temperature, along with nucleophile concentrations, determines the fractions of amides and acids formed by ester cleavage.

EXPERIMENTAL

The solvents, amines, and *p*-nitrophenyl carboxylic esters were purified by conventional procedures. The samples of ionogenic surfactants were twice reprecipitated from ethanol with diethyl ether.

Kinetic measurements were performed spectrophotometrically on a Specord UV-Vis instrument in temperature-controlled cells, following the optical density at 400 nm (formation of *p*-nitrophenolate anion). The initial concentration of the substrate was 5×10^{-5} M, conversion >90%.

The apparent pseudo-first-order rate constants (k_{app}) were determined from the dependence log $(D_\infty - D_\tau) = -0.434k_{app}\tau$ + const (D_τ and D_∞ are the optical densities of solutions at time τ and after reaction completion). The k_{app} values were calculated by the least-squares method.

The fractions of the neutral forms of amines at a given pH were found by potentiometric titration with 0.1 N hydrochloric acid using a pH-340 pH meter in microemulsions with an aqueous volume phase.

ACKNOWLEDGMENTS

The work was financially supported by the Russian Foundation for Basic Research (project no. 99-03-32 037a).

REFERENCES

1. *Mikroemul'sii: struktura i dinamika* (Microemulsions: Structure and Dynamics), Friberg, S.E. and Botorel, P., Eds., Moscow: Mir, 1990.
2. Schwuger, M.J., Stichdom, K., and Schomacker, R., *Chem. Rev.*, 1995, vol. 95. no. 4. p. 849.
3. Menger, F.M. and Elrington, A.R., *J. Am. Chem. Soc.*, 1991, vol. 113, no. 25. p. 9621.
4. Bhattacharya, S. and Senhalatha, K., *J. Chem. Soc., Perkin Trans. 2,* 1996, no. 9. p. 2021.
5. Martinek, K., Levashov, A.V., Khmel'nitskii, Yu.L., and Klyachko N.L., in *Fiziko-khimicheskie problemy fermentativnogo kataliza* (Physicochemical Problems of Enzyme Catalysis), Moscow: Nauka, 1984, p. 18.
6. Mirgorodskaya, A.B. and Kudryavtseva, L.A., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 1998, no. 2, p. 272.
7. *Micellization, Solubilization, and Microemulsions*, Mittal, K., Ed., New York: Plenum, 1977.
8. Mackay, R.A. and Hermansky, C., *J. Phys. Chem.*, 1981, vol. 85, no. 6. p. 739.
9. Mirgorodskaya, A.B., Kudryavtseva, L.A., Zakharova, L.Ya., and Bel'skii, V.E., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 1998, no. 7, p. 1333.
10. Bohmer, M.R., Koopal, L.K., and Lyklema, J., *J. Phys. Chem.*, 1991, vol. 95, no. 23, p. 9569.
11. Mchedlov-Petrosyan, N.O., Loginova, L.P., and Kleshchevnikova, V.N., *Zh. Fiz. Khim.*, 1993, vol. 67, no. 8, p. 1649.
12. Bel'skii, V.E., Valeeva, F.G., and Kudryavtseva, L.A., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 1998, no. 7, p. 1339.