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Reactions of calix[4]resorcinolarene anions with esters of carboxylic acids in H_2O—DMF solvent

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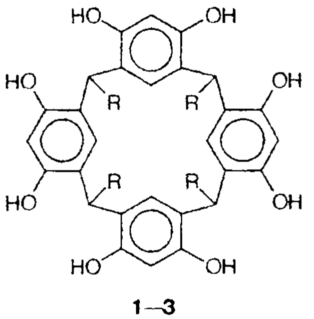
Reactions of calix[4]resorcinolarene anions with *para*-nitrophenyl carboxylates in the H_2O—DMF medium were studied. The kinetics of this process was measured by optical spectroscopy and potentiometric titration: the step of formation of acylated calixarene and the subsequent step of its hydrolysis were detected. Self-association of long-chain calixarenes into micelles decreases their reactivity with respect to that of the monomers.

Key words: calix[4]resorcinolarenes, esters of carboxylic acids, nucleophilic substitution, kinetics, micelle formation.

The interest in the chemistry of calixarenes is largely due to their unique ability to take part in "host—guest" type interactions and to serve as a convenient model of enzymes. Studies of these compounds as analogs of hydrolases and esterases are documented.[1—3]

In the investigations of the reactivity of calix[4]resorcinolarenes, considerable attention is paid to the nucleophilic activity of these compounds in the transfer of acyl and phosphoryl groups.[4—10] Studies of the kinetics of hydrolysis of esters of carboxylic[3,7,8] and phosphorus-containing[9,10] acids revealed a catalytic influence of calixarenes, which accelerated the reaction several-fold. The effect of dissociation or self-association of calixarenes on their nucleophilic reactivity virtually has not been discussed in the literature.

In this work, we study the reactivity of the anionic forms of calix[4]resorcinolarenes **1—3**, which act as nucleophiles in the cleavage of carboxylates **4—6** in H_2O—DMF solvent.



1—3

$R'COOC_6H_4NO_2$-*p*

4—6

R = Me (**1**), C_9H_{19} (**2**), $C_{11}H_{23}$ (**3**)
R' = Me (**4**), Pr (**5**), C_7H_{15} (**6**)

In order to elucidate the influence of reagent hydrophobicity on the course of the reaction, we used calixarenes with different radicals R and various *p*-nitrophenyl carboxylates, namely, acetate, butyrate, and caprylate.

Experimental

Calix[4]resorcinolarenes **1—3** were synthesized by a known procedure[11] as isomers with the *cis*-orientation of substituents R in the bowl-shaped conformation of the phenyl groups. The stereoisomeric homogeneity of the compounds obtained was checked using ^1H NMR spectra. The calixarenes were deprotonated to di- and tetraanions by adding four or eight equivalents of NaOH. Solutions for kinetic measurements were stored preliminarily for 24 h.

The kinetics of the reaction of anions **1—3** with carboxylates in H_2O—DMF solvent was studied by spectrophotometry on a Specord UV-VIS instrument in cells maintained at a constant temperature (±0.5 °C). The process was monitored based on variation of the optical density of solutions at 400 nm (the formation of the *p*-nitrophenoxide anion). The initial substrate concentration was $5 \cdot 10^{-5}$ mol L^{-1}, and the degree of conversion was ~90%. The observed pseudo-first-order rate constants (k_{obs}) were determined from the dependence $\log(D_\infty - D_\tau) = -0.434k_{obs}\tau + \text{const}$ (D_τ and D_∞ are the optical density of solutions at instant τ and after completion of the reaction, respectively). The k_{obs} values were calculated by the least-squares method and the second-order rate constants ($k_2{}'$) were found from the linear variation of k_{obs} *vs* calixarene concentration.

The amount of caprylic acid formed upon cleavage of acid **6** in the presence of anions of **1** at equal concentrations of the calixarene and the substrate (0.01 mol L^{-1}) was determined by potentiometric titration. The second-order rate constant was calculated from the equation $k_2{}'' = C_\tau/\tau C_\infty(C_\infty - C_\tau)$ (C_τ and C_∞ are the acid concentrations by instant τ and after the reaction has been completed, respectively[12]).

The surface tension of solutions was determined by the ring detachment method using a du Noüy tensiometer.[13]

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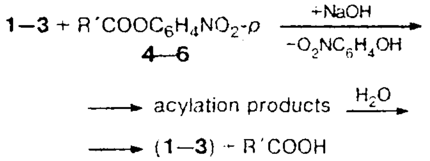
Results and Discussion

The reaction of *p*-nitrophenyl carboxylates with calixarene anions is nucleophilic substitution at the carbonyl group accompanied by liberation of the *p*-nitrophenoxide (PNP) anion (step I). The acylation products thus formed decompose in aqueous solutions *via* hydrolysis to give the corresponding carboxylic acid and the initial calixarene (step II).



$$\mathbf{1{-}3} + \underset{\mathbf{4{-}6}}{\mathrm{R'COOC_6H_4NO_2}\text{-}p} \xrightarrow[-\mathrm{O_2NC_6H_4OH}]{+\mathrm{NaOH}} \text{acylation products} \xrightarrow{\mathrm{H_2O}} (\mathbf{1{-}3}) + \mathrm{R'COOH}$$

This scheme was confirmed in relation to the reaction of anions of **1** with ester **6** taken in equivalent amounts by monitoring the yield of PNP and caprylic acid. The increase of the acid concentration with time during the reaction was detected by potentiometry. Dissociation of macrocyclic calixarenes occurs stepwise with abstraction of one, two, four, or eight protons.[11] When the [calixarene] : [alkali] ratio is 1 : 8, which corresponds to the region of existence of the calixarene tetraanion,[14] the second-order rate constant for the hydrolysis of the acylation products (k_2'') is equal to 0.12 L mol^{-1} s^{-1} (H_2O—30% (v/v) DMF, 25 °C). The rates of evolution of caprylic acid depend on the degree of deprotonation of calixarene; the k_2'' value found for the dianion is 0.034 L mol^{-1} s^{-1}.

The $k_{obs} = f(C_{calix})$ dependences were found by spectrophotometry for reactions of the tetraanion derived from **1** with all of the substrates in an aqueous solution containing 30% (v/v) DMF under pseudo-first-order conditions. These plots are linear for $C_{calix} <$ 0.002 mol L^{-1}; this made it possible to estimate the second-order rate constants for the calixarene acylation step (k_2'). At 25 °C, they are equal to 96, 25, and 17 L mol^{-1} s^{-1} for esters **4**, **5**, and **6**, respectively. The k_2' values that we determined for the reaction of the resorcinol monoanion with esters **4** and **6** under the same conditions are 25 and 4.8 L mol^{-1} s^{-1}, *i.e.*, they are ~4-fold lower than that for the reaction of the tetraanion of **1** with the same substrates. This suggests that the nucleophilic activity of calixarenes is proportional to the number of anionic sites. The $k_{obs} = f(C_{NaOH})$ plots for step I of the reaction of calixarenes **1** and **2** with substrate **4** reflect the special features of their dissociation; the patterns of the plots are similar to those reported previously.[9] They have a plateau in the region where calixarenes exist as tetraanions.

It is noteworthy that the k_2' value for the reaction of the tetraanion of **1** with substrate **6** is ~2 orders of magnitude greater than k_2''. Thus, the intermediate is accumulated during the reaction.

It is known that at a certain concentration in an aqueous solution containing 30% DMF, the tetraanions of **1** can form nonmicellar "head-to-head" aggregates,[14] which are less nucleophilic in the reactions with phosphorus-containing esters than the monomers. This manifests itself as a substantial decrease in the observed rate constant of the process after a critical concentration of association for calixarene has been attained.[9,10] However, in the case of hydrolysis of carboxylic acid esters in the concentration range of **1** studied, no decrease in the reactivity is observed and the $k_{obs} = f(C_{calix})$ plot is linear.

The measurement of the electrical conductivity as a function of the concentration of tetraanion **1** in the H_2O—30% (v/v) DMF solvent in the presence of carboxylic acid esters also supports the assumption that these compounds prevent association. No characteristic inflection point at $6 \cdot 10^{-4}$ mol L^{-1}, defined as the critical concentration of association of **1**, is observed on this plot upon the addition of substrate **4** ($C = 5 \cdot 10^{-5}$ mol L^{-1}).

Note that in an aqueous solution containing 80% DMF, nonmicellar associates are formed at lower concentrations of calixarenes[14]; however, no formation of associates is detected in the reactions with carboxylates. When the tetraanion of **1** reacts with substrate **4**, $k_2' =$ 36 L mol^{-1} s^{-1} (25 °C).

These results indicate that carboxylic acid esters prevent aggregation of calixarenes. Unlike bulky and low-polarity esters of phosphorus acids, carboxylates might be accumulated near the outer rim of the calixarene due to electrostatic interaction, thus preventing the formation of "head-to-head" associates. The orientation of the substrate near the active sites of calixarene should diminish the activation parameters of the reaction. Thus the reaction of ester **6** with the tetraanion of **1** is

Table 1. Activation parameters of the reactions of the **1** tetraanion and resorcinol monoanion with ester **6** in water—30% (v/v) DMF

Compound	k'_2*/L mol^{-1} s^{-1}				$\Delta H^{\#}$ /kJ mol^{-1}	$\Delta S^{\#}$ /kJ K^{-1} mol^{-1}
	15 °C	25 °C	35 °C	45 °C		
Tetraanion of **1**	11.8	17.2	22.1	27.3	20.56±1.65	−210.18±16.82
Resorcinol monoanion**	2.9	4.8	6.3	7.7	26.22±2.18	−201.95±18.17

* The error in determination of k_2 does not exceed 4%.

** Determined in solution at pH = pK_1 + 1 ≈ 10.6.

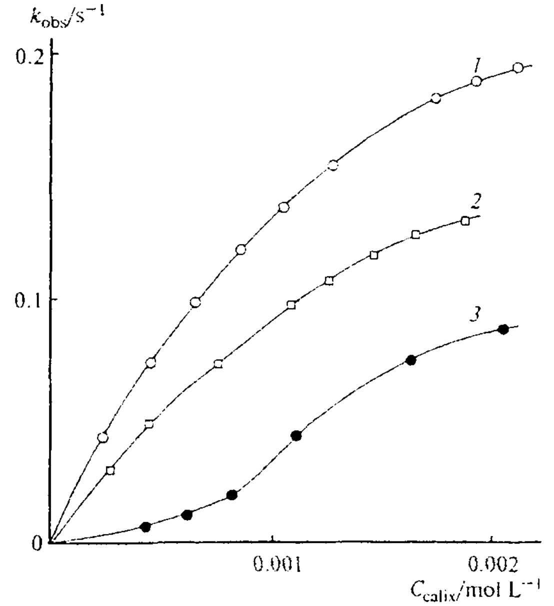


Fig. 1. Dependence of k_{obs} for the cleavage of ester **4** on the concentration of the anions of hydrophobic calixarenes (H_2O—30% (v/v) DMF, 25 °C): calixarene **2** (*1*), calixarene **3** (*2*), [calixarene] : [NaOH] = 1 : 8; calixarene **2** (*3*), [calixarene] : [NaOH] = 1 : 4.

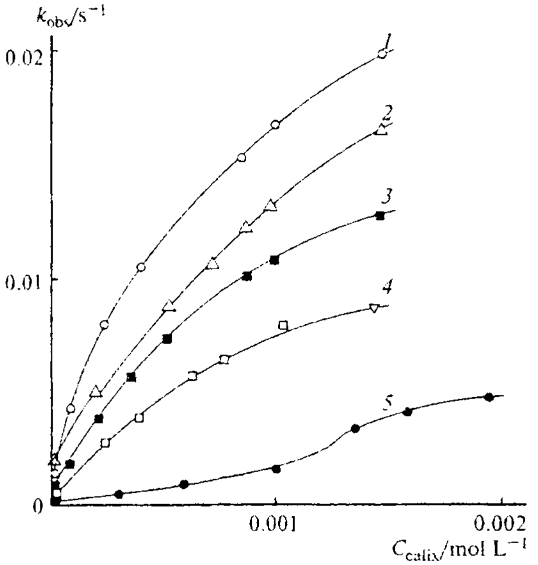


Fig. 2. Effect of the temperature on the variation of k_{obs} for the cleavage of esters (**5**, **6**) *vs* concentration of the calixarene (**2**, **3**) anions (H_2O— 30% (v/v) DMF): ester **6**, calixarene **3** tetraanion, 35 (*1*), 25 (*3*), 17 (*4*) °C; ester **5**, calixarene **3** tetraanion, 25 °C (*2*); ester **6**, calixarene **2** dianion, 25 °C (*5*).

characterized by smaller activation enthalpy ($\Delta H^{\neq}$) and entropy ($\Delta S^{\neq}$) than the reaction of the same ester with the resorcinol monoanion (Table 1).

Calixarenes **2** and **3** are prone to hydrophobic interactions giving micellar aggregates[9,10]; this influences the rates of reactions. The shapes of the kinetic curves for the observed rate constants for the cleavage of esters **4**—**6** in an aqueous solution containing 30% DMF based on the concentration of nucleophiles **2** and **3** are typical of micelle-catalyzed processes (Figs. 1 and 2). The experimental data were processed in terms of a pseudo-phase model[15] using the equation relating k_{obs} to the parameters of processes in the micellar phase

$$k_{obs} = \frac{k_m K_{bond} C_{det} + k_0}{1 + K_{bond} C_{det}}, \qquad (1)$$

where C_{det} is the detergent concentration reduced by the critical micelle concentration (CMC), k_0 and k_m are the rate constants in the absence of a detergent and in the micellar phase, and K_{bond} is the constant for binding of the substrate.

The results are presented in Table 2. The CMC values reflect the ability of compounds **2** and **3** to form micelles at very low concentrations. The accumulation of the negative charge on the outer rim of calixarene

Table 2. Micellar parameters for the interaction of calixarenes **2** and **3** with carboxylates **4**—**6** in the H_2O—30% (v/v) DMF solvent[a]

Calix-arene	[calixarene]: [alkali]	Substrate	T /°C	$k_0 \cdot 10^3$	$k_m \cdot 10^2$	CMC · 10^4 /mol L^{-1}	K_{bond} /mol^{-1} L	k_m/k_0
				s^{-1}				
2	1 : 8	**4**	25	2.0	34.3	0.2, 0.6[b]	700	170
2	1 : 4	**4**	25	2.0	12.1	2.7	260	60
2	1 : 4	**6**	25	0.44	0.59	3.8, 8.5[b]	650	12
3	1 : 8	**4**	25	2.0	27.0	0.5	610	135
3	1 : 8	**5**	25	1.0	2.30	0.2	1200	23
3	1 : 8	**6**	17	0.20	1.14[c]	0.55	1687	57
3	1 : 8	**6**	25	0.44	1.56[c]	0.11	1700	35
3	1 : 8	**6**	35	0.80	2.45[c]	0.125	1785	30

[a] Results of calculations of the concentration dependences given in Figs. 1 and 2 by Eq. (1); correlation coefficient 0.990—0.999. [b] Determined from the data of measuring the surface tension. [c] Calculated from the k_m temperature dependence: $\Delta H^{\neq}$ = 29.17±2.33 kJ mol^{-1}, $\Delta S^{\neq}$ = −181.46±16.33 J K^{-1} mol^{-1}.

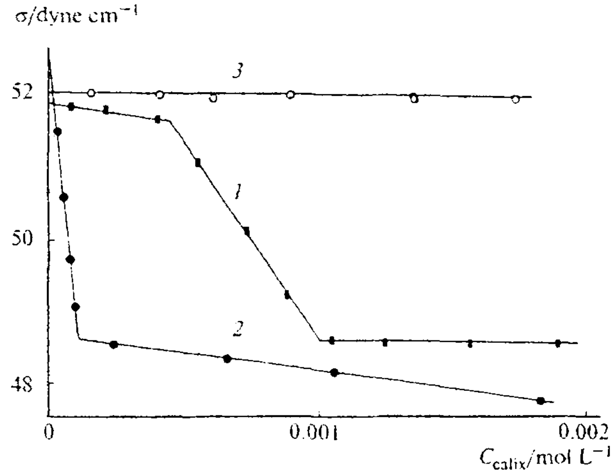


Fig. 3. Effect of the content of calixarene on the surface tension in solutions (H_2O—30% (v/v) DMF, 20 °C): calixarene **2** ([calixarene] : [NaOH] = 1 : 4) (*1*); calixarene **2** (*2*) and calixarene **3** (*3*) ([calixarene] : [NaOH] = 1 : 8).

decreases the CMC and increases binding of the substrate. In addition, the binding constants increase with enhancement of the substrate hydrophobicity, whereas the micellar effect simultaneously decreases. Apparently, localization of hydrophobic esters in the hydrocarbon part of the micelle leads to their separation from the nucleophilic center, which results in substrate specificity. The fact that the activation energy found from the temperature dependence for the reaction of the tetraanion of **3** with ester **6** (see Table 2, Fig. 2) is higher than that calculated for the reaction of **1** with the same substrate (see Table 1) also does not contradict the assumption that micelle formation has an unfavorable effect on the process in question.

The calculated CMC values for calixarene **2** (for calixarene to NaOH ratios of 1 : 4 and 1 : 8) are in good agreement with our data obtained in the surface tension measurements (Fig. 3, see Table 2). Regarding calixarene **3**, the surface tension does not change as the calixarene concentration in the solution increases. This type of behavior is observed for micelle-forming calixarenes with low aggregation numbers (down to monomicelles).[16]

Thus, the reaction of calix[4]resorcinolarene anions with esters of carboxylic acids in the H_2O—DMF solvent yields in the first step acylated calixarene, which is then hydrolyzed, while the initial calixarene is recovered. The reactivity of calixarene depends on the number of anionic sites in it. Carboxylic acid esters prevent the formation of "head-to-head" type dimers typical of the anions of **1**. Long-chain calixarenes self-associated into functional micelles have lower nucleophilic activities than the monomeric forms.

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