The effect of self-association on the reactivity of calix[4]resorcinolarene anions with respect to esters of phosphorus acids

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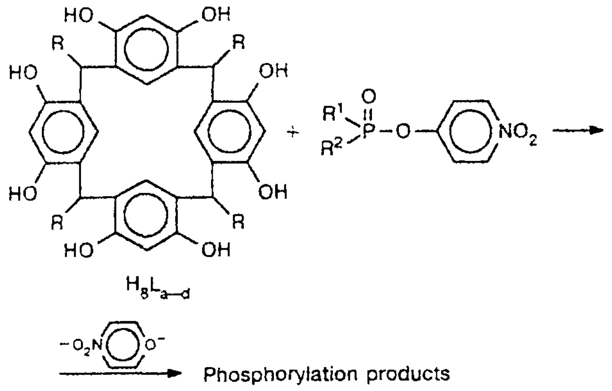
The kinetics of reactions of amphiphilic anions derived from calix[4]resorcinolarenes and their aggregates with *p*-nitrophenyl esters of phosphorus acids were studied by spectrophotometry. The effect of hydrophobicity of the substituent R and of the composition of aqueous dimethylformamide solvent (30, 50, 80% (v/v) DMF) on these processes was investigated.

Key words: kinetics; self-association; micelle formation, calix[4]resorcinolarenes, esters of phosphorus acids.

It is known[1,2] that in alkaline media, calix[4]resorcinolarenes (H_8L) form tetraanions ($[H_4L]^{4-}$), which contain nucleophilic centers located on the hydrophilic "upper rim," a hydrophobic cavity formed by aromatic rings, and, in some cases, hydrophobic substituents R. The tetraanions are stabilized in a cone-shaped conformation owing to intramolecular hydrogen bonds.[3] It has been found by conductometry[2] that in aqueous solutions containing 50 or 80% (v/v) DMF, the $[H_4L]^{4-}$ anions are aggregated. The formation of aggregates from amphiphilic water-soluble calixarenes and the critical concentration of aggregation (CCA) depend on a number of factors, including hydrophobicity (the lengths of the hydrocarbon radicals and the size of the cavity), and the conformation of the calixarene.[4,5] Calix[4]resorcinolarenes served as the basis for the synthesis of numerous compounds containing various functional groups;[6] however, virtually no data on the reactivity of calix[4]resorcinolarenes or their derivatives or on the influence of self-organization of these compounds in solution on their reactivity can be found in the literature.[7]

The purpose of this work is to study the reactivity of amphiphilic calix[4]resorcinolarene anions and their aggregates with respect to *p*-nitrophenyl ethyl chloromethylphosphonate (1) and *p*-nitrophenyl diphenyl phosphate (2) in DMF—H_2O solutions and to elucidate the effects of the hydrophobicity of radical R and the composition of the mixed solvent on these processes.



R = Me(H_8L_a), *n*-C_7H_{15} (H_8L_b), *n*-C_9H_{19} (H_8L_c), *n*-$C_{11}H_{23}$ (H_8L_d)
1: R^1 = —CH_2Cl, R^2 = —OEt
2: R^1 = R^2 = —OPh

Experimental

Compounds H_8L_{a-d} were synthesized by the known procedure;[8] the purity of the products was checked by TLC. The stereoisomeric homogeneity of the product, characterized by the *cis*-orientation of all the aliphatic chains R at the C atoms linking the aryl groups together, was checked based on the ^1H NMR spectra. The kinetics of the reactions of H_8L-derived anions with substrates **1** and **2** in solutions containing 30, 50, and 80 % (v/v) DMF were studied under pseudo-monomolecular conditions ($C_{1,2} = 4 \cdot 10^{-1}$ mol L^{-1}) at 20 °C and at pH 10.7 by spectrophotometry using a Specord UV/VIS spectrophotometer based on the increase in the optical density due to the *p*-nitrophenoxide formed. The yield of *p*-nitrophenoxide was ~85%. Deprotonation of H_8L to $[H_4L]^{4-}$ and to $[L]^{8-}$ was accomplished by adding 8 and 20 (or 30) equivalents of NaOH, respectively. The observed rate constants (k_{obs}) were calculated from a first-order equation, while the constants of bonding of the substrate (K_{bond}), critical micelle concentrations (CMC), and the rate constants for the reactions involving micelles (k_m) were found from the equation reported previously[9] using the least-squares method.

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Results and Discussion

Figure 1 shows the plot $k_{obs} = f(C_{NaOH})$ for the reaction of substrates **1** and **2** with H_8L_b at a constant concentration of the substrates, equal to $4 \cdot 10^{-4}$ mol L^{-1}, in 50% (v/v) aqueous DMF. This plot made it possible to elucidate more precisely the ratios of the reactants needed for the formation of $[H_4L]^{4-}$ and $[L]^{8-}$ and the regions of their existence. It can be seen from Fig. 1 that the curves for substrates **1** and **2** contain two plateaus each. One of them corresponds to the existence of $[H_4L]^{4-}$, and the other is related to the existence of $[L]^{8-}$, which is in agreement with the data published previously.[1,3] The k_{obs} value for the second plateau is ~2 times larger than that for the first one; therefore, it can be concluded that starting from a 10-fold excess of NaOH with respect to H_8L, the $[H_4L]^{4-}$ ions present in the solution are further deprotonated up to the $[L]^{8-}$ ions, the possibility of whose existence has been demonstrated previously.[3]

The dependences of k_{obs} on the concentration of $[H_4L]^{4-}$ and $[L]^{8-}$ for substrates **1** and **2** in 30 and 50% (v/v) DMF are shown in Figs. 2. and 3. The curves (Fig. 2, *1—7* and Fig. 3, *1*, *2*) contained two sections, a straight section and a descending section, and then flatten out, indicating binding of the substrates. The concentration of H_8L at which k_{obs} sharply decreases corresponds to the CCA and varies from $\sim 1 \cdot 10^{-3}$ to $8 \cdot 10^{-4}$ mol L^{-1} for $[H_4L]^{4-}$ and $[L]^{8-}$ in a solution containing 50% (v/v) DMF or is equal to $\sim 8 \cdot 10^{-4}$ mol L^{-1} in the case of $[H_4L]^{4-}$ in 30% (v/v) DMF. The CCA values for $[H_4L]^{4-}$ found from the kinetic data coincide with those determined by the conductometric method. Since an increase in the hydrophobicity of R has no effect on the reactivity of these aggregates, the electrostatic interactions of $[H_4L]^{4-}$ with Na^+ and the hydrogen bonds in the "upper rim" ("head-to-head" aggregates) act, apparently, as the driving force for their formation. Dimeric aggregates of this type have been reported previously.[10] The complex formation should decrease the negative charge in the resulting supramolecular aggregates and, hence, they are less reactive than the monomeric forms. In addition, the lower reactivity of the aggregates can be explained by the fact that the nucleophilic centers in them are less accessible to the substrates and also by the change in the microenvironment of the reagents.

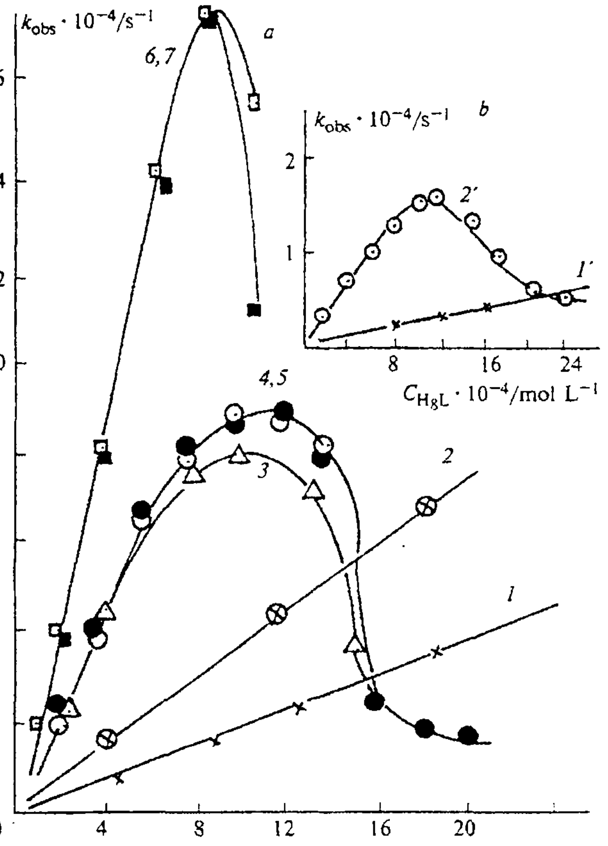

Fig. 2. *a*, Dependence of the observed rate constant (k_{obs}) for the reaction of substrate **1** with $[H_4L_a]^{4-}$ (*3*), $[H_4L_b]^{4-}$ (*4*), $[H_4L_c]^{4-}$ (*5*) (H_8L : NaOH = 1 : 8), L_8^{8-} (H_8L_b : NaOH = 1 : 20) (*6*), H_8L_b : NaOH = 1 : 30 (*7*), HL_c^- (*1*) and L_c^{2-} (*2*) on their concentration; *b*, dependence of k_{obs} for the reaction of **2** on the concentration of $[H_4L_b]^{4-}$ (*2'*) and $[HL_c]^-$ (*1'*) (50% (v/v) DMF, 25 °C).

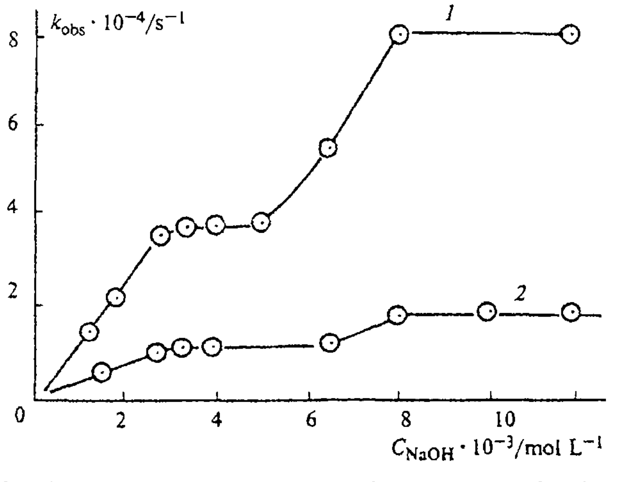

Fig. 1. Dependence of the observed rate constant for the reaction of substrate **1** (*1*) and **2** (*2*) with H_8L_b ($4 \cdot 10^{-4}$ mol L^{-1}) on the concentration of NaOH (50% (v/v) DMF, 25 °C).

The straight sections in the concentration dependences shown in Figs. 2 and 3 refer to the region of existence of monomeric $[HL]^{4-}$ and $[L]^{8-}$. The concentration plots for the reactions of **1** and **2** with the $[HL_c]^-$ anion derived from 4-hexylresorcinol (see Figs. 2 and 3) and with the $[H_4L_f]^-$ anion derived from resorcinol (see Fig. 3) are straight lines up to a concentration of 0.01 mol L^{-1}. Comparison of the bimolecular rate constants (k/mol^{-1} L s^{-1}), calculated from the linear sections for the reaction with substrate **1** (see Fig. 2) and equal to 2.0 for $[L_b]^{8-}$, 1.0 for $[H_4L]^{4-}$, and 0.23 for $[HL_c]^-$,

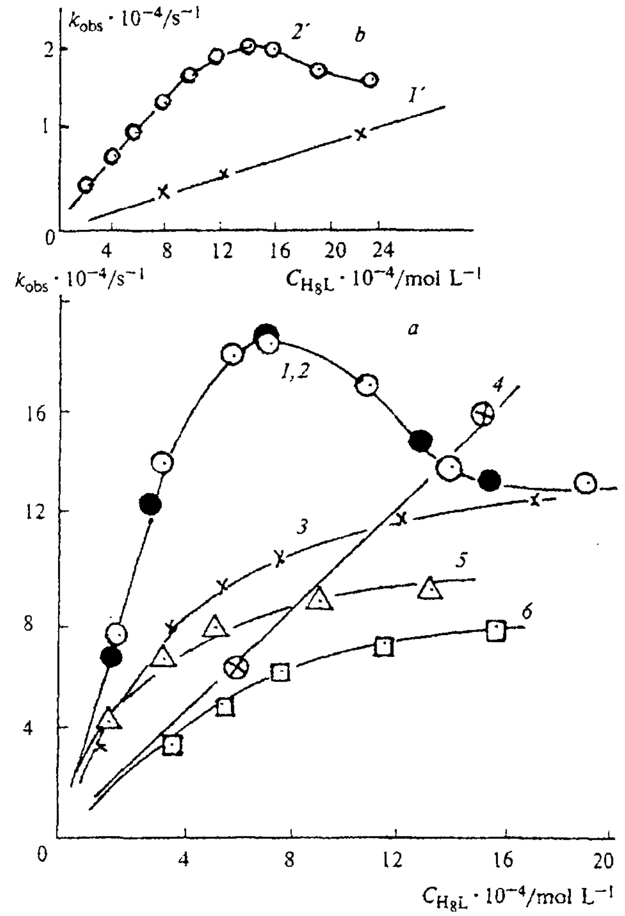

Fig. 3. *a*, Dependence of the observed rate constant (k_{obs}) for the reaction of substrate **1** with $[H_4L_a]^{4-}$ (*1*), $[H_4L_b]^{4-}$ (*2*), $[H_4L_c]^{4-}$ (*3*), $[H_4L_d]^{4-}$ (*5*), $[HL_e]^{-}$ (*6*), and $[HL_f]^{-}$ (*4*) on their concentrations; *b*, dependence of k_{obs} for the reaction of **2** on the concentration of $[H_4L_c]^{4-}$ (*2′*) and $[HL_f]^{-}$ (*1′*) (30% (v/v) DMF, 25 °C).

suggests that the reactivity of the monomeric anions formed from H_8L (in the concentration range up to the CCA) is determined only by their nucleophilic centers, whereas the presence of the hydrophobic cavity in $[HL]^{4-}$ or the change in the hydrophobicity of R have no effect on it. The bimolecular rate constants for the tetra- and octaanions are ~4 and 8 times greater than that for the anion derived from 4-hexylresorcinol. For the reaction of **2** with $[H_4L_b]^{4-}$ and with $[HL_e]^{-}$, the *k* values are equal to 0.15 and 0.035 L (mol s)$^{-1}$ (see Fig. 3). In 30% (v/v) DMF, the *k* value for $[HL_{a,b}]^{4-}$ is 4.0 and that for $[HL_f]^{-}$ is 1.0 L (mol s)$^{-1}$. Thus, we determined by kinetic measurements the range of existence of the monomeric forms in these media; in some cases, this is needed for the use of these compounds, for example, as receptors of biogenic amines;[11] however, as can be seen from the above-presented data, $[H_4L]^{4-}$ and $[L]^{8-}$, unlike their aggregates, do not bind substrates **1** and **2** (do not undergo "guest-host" interactions), which is in agreement with the results obtained previously.[12,13]

Table 1. Parameters of the micelle-catalyzed reaction of substrate **1** with the anions in 30% (v/v) DMF

Anion	$k_m \cdot 10^{-3}$ /s^{-1}	CMC /mol L^{-1}	K_{bond} /L mol^{-1}
$[H_4L_c]^{4-}$	1.7	$6.02 \cdot 10^{-5}$	2120
$[H_4L_d]^{4-}$	1.29	$2.16 \cdot 10^{-5}$	2400
$[HL]^{-}$	0.997	$1.96 \cdot 10^{-4}$	2600

The kinetics observed in 30% (v/v) DMF are more complicated than those in 50% (v/v) DMF (see Fig. 3 and 2): further increase in the hydrophobicity of R in $[H_4L]^{4-}$ (R = C_9H_{19} and $C_{11}H_{23}$) results in the flattening-out of the kinetic curves (see Fig. 3), typical of enzymatic or micelle-catalyzed reactions in which a substrate is bound; this suggests the formation of micelle type aggregates. A similar kinetic curve is also observed for $[HL_e]^{-}$ (see Fig. 3). The formation of micelles by amphiphilic calixarenes with a "cone" conformation[5] and by long-chain phenoxides has been reported in the literature.[14] We considered these processes in terms of the pseudo-phase model of micellar catalysis[9] and calculated the CMC, K_{bond}, and k_m (Table 1) from the kinetic equation proposed previously.[9]

$$k_{obs} = k_{H_2O} + k_m K_{bond} C_{surfactant}/1 + K_{bond} C_{surfactant},$$

where k_{H_2O} is the rate constant of the reaction in the aqueous phase, and $C_{surfactant}$ is the concentration of calix[4]resorcinolarene anions. The CMC value found by the surface tension method for $[H_4L_c]^{4-}$ amounts to $1 \cdot 10^{-4}$ mol L^{-1}, which is in good agreement with the CMC determined by the kinetic method. The CMC values for the micellar aggregates are comparable with those reported in the literature for water-soluble amphiphilic calix[4]arenes[4] and range from $2.5 \cdot 10^{-3}$ to $5.5 \cdot 10^{-7}$ mol L^{-1}, depending on the structure, type of the charge, and the length of the hydrocarbon radical. It can be seen from Fig. 3 that the $[H_4L]^{4-}$ ions, self-associated into functional micelles, are less reactive than the corresponding monomeric forms, *i.e.*, the formation of these associates inhibits the reaction studied. It can be suggested that this is due to the fact that the substrate is separated from the nucleophilic centers, because it is located in a position that is "inconvenient" for the interaction, for example, between the benzene rings of the neighboring cones of the calixarenes aggregated in a micelle. Examples of blocking of the substrate in the hydrophobic cavity of an inhibitor are known.[15] It is noteworthy that k_m for $[H_4L_{c,d}]^{4-}$ in the reaction with **1** is close to k_{obs} in the plateau for the "head-to-head" aggregates formed from the $[HL_{a,b}]^{4-}$ anions. Apparently, the microenvironments of the substrate in these two cases are similar: the process occurs either on the surface of an anionic micelle in the Stern layer or in the layer between the negatively charged "rims" of $[H_4L]^{4-}$ forming the aggregate.

The shape of the kinetic curves (flattening out) in 80% (v/v) DMF (Fig. 4), together with the conducto-

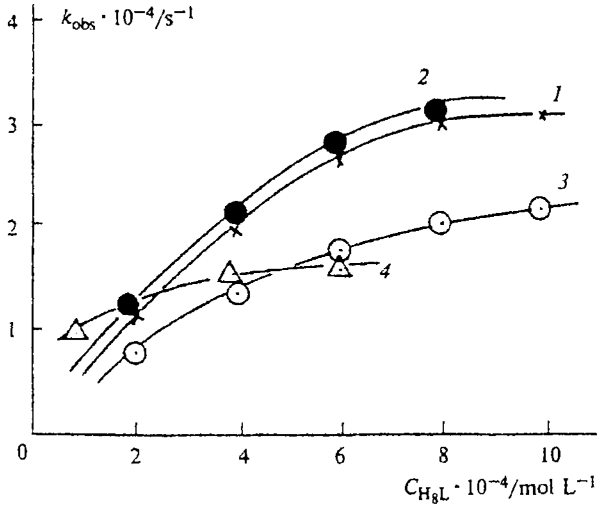

Fig. 4. Dependence of the observed rate constant (k_{obs}) for the reaction of substrate **1** $[H_4L_a]^{4-}$ (*1*), $[H_4L_b]^{4-}$ (*2*), $[H_4L_c]^{4-}$ (*3*), $[H_4L_d]^{4-}$ (*4*) on their concentrations (30% (v/v) DMF, 25 °C).

Table 2. Parameters of the reaction of substrate **1** with the anions in 80% (v/v) DMF

Anion	$k'(k_m) \cdot 10^{-4}$ /s^{-1}	CCA $\cdot 10^{-5}$(CMC) /mol L^{-1}	K_{bond} /L mol^{-1}
$[H_4L_a]^{4-}$	4.4	6.3	2160
$[H_4L_b]^{4-}$	4.5	5.2	2660
$[H_4L_c]^{4-}$	4.5	2.2	1015

metric data,[2] make it possible to claim that in this medium, $[H_4L]^{4-}$ also forms two types of aggregates binding the substrate. Since the CCA for $[H_4L_b]^{4-}$ in 80% (v/v) DMF is lower than that in 50% DMF,[2] the formation of "head-to-head" dimeric aggregates that bind the substrate at low concentrations of $[H_4L_a]^{4-}$, $[H_4L_b]^{4-}$ makes it possible to obtain the kinetic curve for the reaction of the aggregates with substrate **1** and to calculate the parameters of this reaction, namely, CCA, K_{bond}, and the rate constants k' with these aggregates (Table 2). The reactions of compound **1** with the aggregates formed from $[H_4L_a]^{4-}$ and $[H_4L_b]^{4-}$ occur at almost identical rates. As in the medium containing 30% (v/v) DMF, an increase in the length of R in $[H_4L_c]^{4-}$ and $[H_4L_d]^{4-}$ leads to a decrease in the k_{obs} values; this may be due to the formation of micelle type aggregates (see Fig. 4).

It can be seen from the data listed in Table 2 that k_m in 80% (v/v) DMF is markedly lower than that in 30% DMF (see Table 1). It should also be noted that for $[HL_e]^-$ in 30% (v/v) DMF, k = 4.0 L (mol s)$^{-1}$ and for $[HL_f]^-$ in 50% (v/v) DMF, it is 1.0 L (mol s)$^{-1}$. An increase in the amount of the bipolar aprotic solvent (DMF) results in a decrease in the rate of these reactions. This is apparently due to the fact that in these solvents, the degree of solvation of big polarizable anions increases, and the anions derived from H_8L belong to this type.[16]

Thus, in all the media studied here, except for 50% (v/v) DMF, in addition to "head-to-head" type aggregates, micellar aggregates are formed. The absence of micelles in 50% DMF can be attributed to the sharp increase in the viscosity of the medium, which hampers migration of molecules in this solvent compared to that in 30% or 80% DMF.[17] Unlike the monomeric forms of the anions, aggregates of both types are receptors of substrates **1** and **2**, and the reactivity of the aggregated anions is lower than the reactivities of the monomers.

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