Catalytic activity of aminomethylated calix[4]resorsinolarene aggregates in hydrolysis of esters of phosphorus acids

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The reaction kinetics of aminomethylated calix[4]resorcinolarenes (AMC) with *p*-nitrophenyl esters of phosphorus acids (EPA) in a water—DMF solution (30 vol.% DMF) was studied by spectrophotometry and ^{31}P NMR spectroscopy in the presence and absence of the nonionic surfactant Triton X-100. The AMC form aggregates of micellar and nonmicellar types and are the catalysts for EPA hydrolysis. The catalytic activity of the aggregates depends on their structure, pH of the medium, and the nature of the solvent.

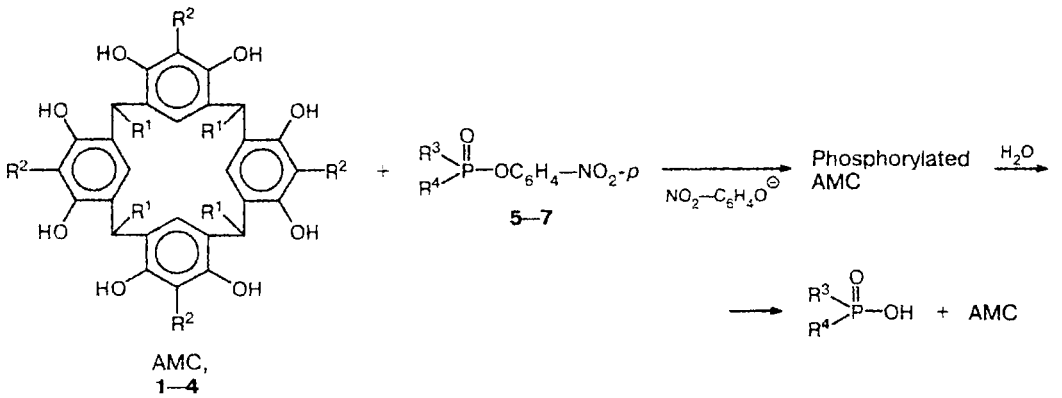
Key words: kinetics, micelles, aggregates, surfactants, aminomethylated calix[4]resorcinolarenes, esters of phosphorus acids, hydrolysis.

Calix[*n*]arenes ($n = 4—8$)[1,2] containing various functional groups at the "bottom" and "upper" rims of the cavity formed by aromatic rings are "*endo*-receptors"[3] and models of enzymes.[4—8] At the same time, amphiphilic water-soluble calix[*n*]arenes possess the properties of surfactants. They are self-organized to form, depending on the conformation, aggregates of micellar and lamellar types[9] and, similarly to natural detergents, are readily incorporated in micelles and bilayers formed by other amphiphilic substances.[10] However, the catalytic activity of aggregates of calix[*n*]arenes and, in particular, calix[4]resorcinolarenes is poorly studied.[11—13]

The purpose of this work is to study the reactivity of the aggregates of aminomethylated calix[4]resorcinolarenes (AMC, **1—4**) in the reaction with 4-nitrophenyl bis(chloromethyl)phosphinate (**5**), 4-nitrophenyl chloromethylethylphosphonate (**6**), and 4-nitrophenyl diphenylphosphate (**7**) in aqueous DMF (30 vol.% DMF) in the absence and presence of the nonionic surfactant Triton X-100.

We have previously shown that in water—alcohol solutions the reactions of AMC[13] and 2-aminomethylphenols (AMP),[14] which are the structural units of AMC, with esters of phosphorus acids (EPA) proceed in two stages: the first stage produces phosphorylated AMP or AMC, which then are hydrolyzed to the corresponding acids, *i.e.*, AMP and AMC are the catalysts for EPA hydrolysis and model the action of esterases. According to the data of spectrophotometry and ^{31}P NMR spectroscopy, the reactions of AMC with EPA in aqueous DMF studied in this work also proceed in two stages by Scheme 1.

Scheme 1



1: R^1 = Me, R^2 = CH_2NMe_2 **3**: R^1 = $C_{11}H_{23}$, R^2 = CH_2NMe_2 **5**: R^3 = R^4 = CH_2Cl **7**: R^3 = R^4 = OPh
2: R^1 = C_9H_{19}, R^2 = CH_2NMe_2 **4**: R^1 = Me, R^2 = CH_2NEt_2 **6**: R^3 = CH_2Cl, R^4 = OEt

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Experimental

Compounds **1**—**4** [15] and substrates **5**—**7** [16,17] were synthesized by known procedures. Stoichiometric uniformity of the AMC corresponding to the product with the *cis*-orientation of all aliphatic chains R^1 at the C atoms linking aryl groups was monitored by the ^1H NMR spectra; their physicochemical properties are presented in our previous work.[13] The kinetics of the reactions of compounds **1**—**4** and AMP with substrates **5**—**7** were studied by spectrophotometry (the first stage) and ^{31}P NMR (the second stage) under conditions of pseudo-first order with respect to AMC and AMP, whose concentrations by at least an order of magnitude exceeded the concentrations of EPA. The formation of *p*-nitrophenoxide (λ = 400 nm) was monitored spectrophotometrically on a Specord UV-Vis spectrophotometer at 25 °C, pH 8.0 and 10.9, $C^0_{5,6} = 5 \cdot 10^{-5}$ mol L^{-1}. ^{31}P NMR spectra were recorded on a Bruker MSL-400 instrument with a working frequency of 161.97 MHz at 308 K. The chemical shifts are presented relative to 85% H_3PO_4. The observed rate constants (k_{obs}) were calculated by a first-order equation. Using data of the functions $k_{obs} = f(C_{AMC,AMP,Surf})$, the bonding constants of the substrates (K_{bond}), the critical micelle concentrations (*CMC*), and the rate constants of reactions of the aggregates (the rate constants in the micellar phase (k_m)) were determined. With this purpose, we used the equation for the calculation of the kinetic curves, which reached a plateau, taking into account the partition of the substrate between the bulk and micellar phase[18]:

$$k_{obs} = \frac{k_{H_2O} + k_m K_{bond} C_{Surf}}{1 + K_{bond} C_{Surf}} \quad (1)$$

Here k_{H_2O} (s^{-1}) is the rate constant of the reaction in the water—DMF phase; C_{Surf} (mol L^{-1}) is the concentration of AMC, AMP, or Triton X-100 corrected for *CMC*. The surface tension of solutions was measured on a tensiometer by the method of ring detachment, and the electroconductivity of solutions was measured on a CDM-2d conductometer.

Results and Discussion

The plots of k_{obs} for the reaction of **5** with AMC **1**—**3** and 2-dimethylaminomethyl-4-isononylphenol (**8**) *vs.* their final concentrations ($4 \cdot 10^{-4}$—$3 \cdot 10^{-3}$ mol L^{-1}) in a 30% (vol.) solution of DMF at pH 8.0 have a nonlinear character and reach a plateau (the Michaelis function) (Fig. 1), which indicates the formation of aggregates that bind the substrate. To increase the solubility of AMC, the reactions were carried out in the presence of the nonionic surfactant Triton X-100 ($5 \cdot 10^{-3}$ mol L^{-1}), which possesses a high solubilizing capability with respect to macrocyclic compounds.[19]

It is known[20] that Triton X-100 forms micellar aggregates also in water—dimethylformamide solutions. To reveal the influence of this surfactant on the reactivity of AMC, we studied the function $k_{obs} = f(C_{Surf})$ for the reaction of **5** with **2** (30 vol.% DMF, $C_{AMC} = 4 \cdot 10^{-4}$ mol L^{-1}, pH 8.0), whose shape is unusual for the systems containing the nonionic surfactant and nucleophile. It was found that for the concentrations of Triton X-100 from $1 \cdot 10^{-3}$ to $1.3 \cdot 10^{-2}$ mol L^{-1} the k_{obs} value is constant and equal to $1.8 \cdot 10^{-2}$ s^{-1}, *i.e.*, Triton X-100

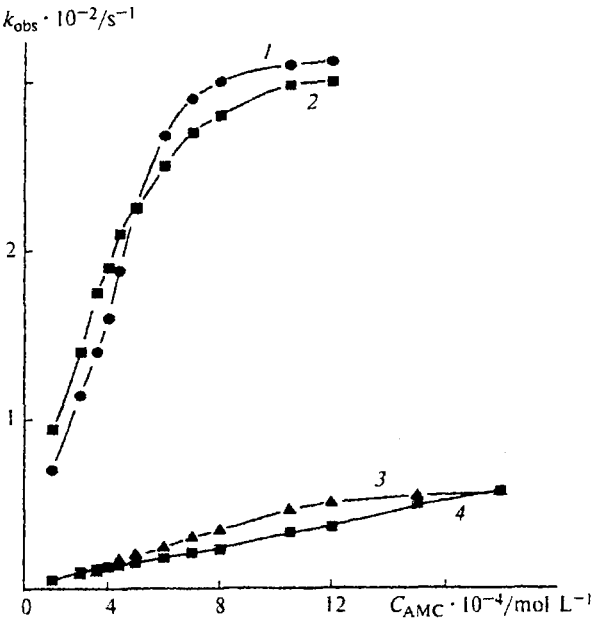

Fig. 1. Observed rate constants of the reaction (k_{obs}) of substrate **5** with compounds **1** (*1*), **2** (*2*), **3** (*3*), and **8** (*4*) as functions of their concentration in a 30% (vol.) aqueous solution of DMF, pH 8.0, C_{Surf} = 0.005 mol L^{-1}, 25 °C.

in a concentration of $5 \cdot 10^{-3}$ mol L^{-1} does not affect the reactivity of AMC. In the region of surfactant concentrations from $2 \cdot 10^{-2}$ to $5 \cdot 10^{-2}$ mol L^{-1}, k_{obs} is $1.2 \cdot 10^{-2}$ s^{-1}. The k_{obs} value decreases in this system, most likely, because of the formation of mixed aggregates or structural rearrangements of Triton X-100 micelles, which occur, as is known,[21] after a surfactant concentration of $1 \cdot 10^{-2}$ mol L^{-1} was achieved. The measurement of the electroconductivity of solutions at different concentrations of Triton X-100 (C_{AMC} = $4 \cdot 10^{-4}$ mol L^{-1}, 30 vol.% DMF) showed an inflection point (*CMC*) at a concentration of the surfactant equal to $1.5 \cdot 10^{-2}$ mol L^{-1}. By contrast, the plot $k_{obs} = f(C_{Surf})$ for the reactions of **5** with **8** and 2-dimethylaminomethylphenol (**9**) (30 vol.% DMF, C_{AMP} = $6 \cdot 10^{-3}$ mol L^{-1}, pH 8.0) is typical of micelle-catalyzed reactions (*CMC* = $2.6 \cdot 10^{-4}$ and $1.05 \cdot 10^{-3}$ mol L^{-1}, K_{bond} = 69 and 65 L mol^{-1}, k_m = $1.6 \cdot 10^{-1}$ and $5 \cdot 10^{-2}$ s^{-1}, respectively).

As seen in Fig. 1, the reactivity of AMC depends on the hydrophobicity of R^1. This is probably explained by the different types of aggregates that formed. Taking into account that AMC exists in a solution in a cone-like conformation,[22] we may assume that **2** and **3** form in a solution aggregates of micellar type with hydrophobic radicals ($R^1 = C_9H_{19}$, $C_{11}H_{23}$)[9] or are incorporated into Triton X-100 micelles similarly to mixed micelles.[23] Using Eq. (1), we found the parameters of the micelle-catalyzed reactions of **5** with **2**, **3**, and **8** (Table 1).

Comparison of the parameters of the reactions catalyzed by AMC (*CMC* = $4 \cdot 10^{-5}$—$7.6 \cdot 10^{-5}$ mol L^{-1},

Table 1. Parameters of the reaction[a] of substrate **5** (pH 10.9) with AMC **2**—**4**, AMP **8**, and calix[4]resorcinolarene tetraanion **11**

Compound	*CMC*[b] /mol L^{-1}	k_m /s^{-1}	K_{bond} /L mol^{-1}
2	$4 \cdot 10^{-5}$	$7.1 \cdot 10^{-2}$	940
3	$7.6 \cdot 10^{-5}$	$6.3 \cdot 10^{-2}$	1200
8	$1.0 \cdot 10^{-4}$	$2.8 \cdot 10^{-2}$	140
4	$1.4 \cdot 10^{-4}$	$7.2 \cdot 10^{-3}$	440
2[c]	$2.0 \cdot 10^{-5}$	$4.4 \cdot 10^{-3}$	1570
11[c]	$6.0 \cdot 10^{-5}$	$1.7 \cdot 10^{-3}$	2120
2[d]	$1.8 \cdot 10^{-5}$	$5 \cdot 10^{-4}$	5370

[a] pH 8.0, Triton X-100, 30 vol.% DMF, 25 °C. [b] The *CMC* values determined by the surface tension method in the absence of Triton X-100 at pH 8 and 25 °C are $5 \cdot 10^{-5}$ mol L^{-1} for **2** and $1 \cdot 10^{-4}$ mol L^{-1} for **3**. [c] Reaction with substrate **6** (pH 10.9, Triton X-100, 30 vol.% DMF, 25 °C). [d] See Ref. 13.

K_{bond} = 1200—940 L mol^{-1}) and AMP micelles (*CMC* = $1 \cdot 10^{-4}$ mol L^{-1}, K_{bond} = 140 L mol^{-1}) (see Table 1) shows that the AMC micelles are formed much more easily and bind the substrates much more strongly, and their catalytic activity is 2.5-fold higher than that for AMP micelles. The function $k_{obs} = f(C_{AMP})$ for reaction of **5** with **9**, which has no hydrophobic group, is linear in the region of the studied concentrations of $6 \cdot 10^{-4}$—$3 \cdot 10^{-3}$ mol L^{-1}; the bimolecular constant of this reaction is 1.7 L mol^{-1} s^{-1}. Unlike **9**, the kinetic curve for the reaction of **5** with AMC **1** (R^1 = Me) reaches a plateau, *i.e.*, macrocyclic calixarene **1** forms aggregates that bind the substrate. In this case, aggregates are probably formed due to the intermolecular hydrogen bonds between the functional groups of AMC and Triton X-100. These aggregates are formed at concentrations an order of magnitude higher than those for AMC micelles. They bind the substrate more weakly and are ~10 times less reactive (see Table 1). The K_{bond} and *CMC* values for these aggregates almost coincide with similar parameters for the AMC aggregates that are formed in a water—isopropyl alcohol mixture (pH 9.0).[13]

The study of the plot $k_{obs} = f(pH)$ (Fig. 2) for the reactions of **5** with **2** and **4** showed that the shift of pK_a to a more acidic region due to micelle formation is responsible for the high reactivity of micellar aggregates of **2** as compared to that of aggregates of **4**. In the case of AMC **2**, this results in the appearance of reactive anionic species already at sufficiently low pH.

In the absence of a surfactant, at a ratio of AMC : NaOH of 1 : 8 (pH 10.9), we also obtained the nonlinear functions $k_{obs} = f(C_{AMC})$ for the reactions of **2** and **4** with **6** (Fig. 3). In this case, we observed kinetic curves of two types: the Michaelis function for the reactions of micellar aggregates of AMC **2** (see Fig. 3 and Table 1) and the extreme function of AMC **4**. Similar behavior of calixarene tetraanions with R^1 = Me, R^2 = H (**10**) and the hydrophobic substituent R^1 = C_9H_{19}, R^2 = H (**11**) has been described by us previously[11,12]; these results are presented in Fig. 3 for comparison. The calixarene tetraanions with R^1 = CH_3—C_6H_{13}, which form "head-to-head" aggregates when kinetic aggregation is achieved,[24] had an extreme kinetic profile. In the case of **4**, the kinetic curve drops at a concentration of $6 \cdot 10^{-4}$ mol L^{-1}, which coincides

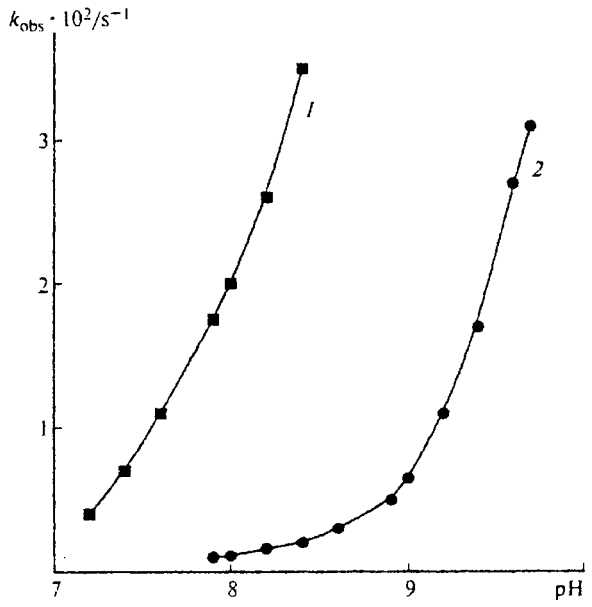

Fig. 2. Observed rate constants of the reaction (k_{obs}) of compounds **5** with **2** (*1*) and **4** (*2*) ($C_{AMC} = 4 \cdot 10^{-4}$ mol L^{-1}) as functions of the pH of their 30% (vol.) aqueous solutions of DMF at C_{Surf} = 0.005 mol L^{-1}, 25 °C.

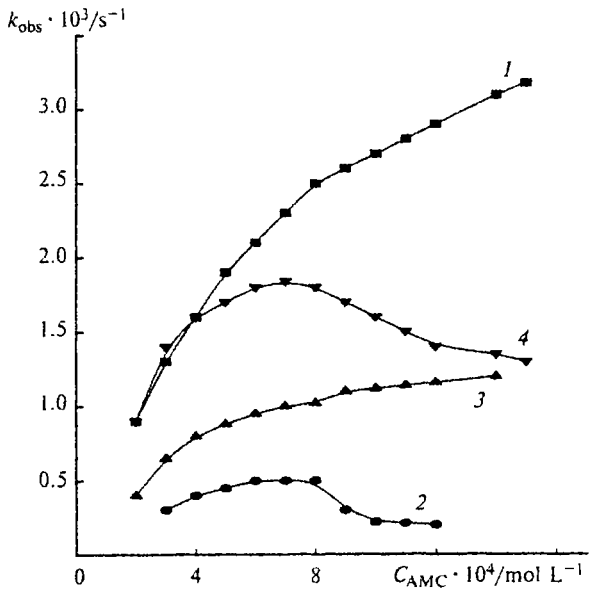

Fig. 3. Observed rate constants (k_{obs}) of the reaction of compound **6** with **2** (*1*), **4** (*2*), and calix[4]resorcinolarene-tetraanions **11** (*3*) and **10** (*4*) as functions of their concentrations at pH 10.9, 25 °C.

with the inflection in the plot of the electroconductivity of solutions *vs* the concentration of **4** determined by the conductometric method under identical conditions. The *CMC* values for **2** and **3** in DMF (30 vol.%) at pH 8 and 10.9 in the absence of Triton X-100, which were obtained by the measurement of the surface tension of the solutions, well coincide with the kinetic data (see Table 1).

The reactivity of the micellar aggregates of AMC at pH 10.9 in the absence of a surfactant is much higher than that of the nonmicellar aggregates. As seen in Table 1 and Fig. 3, the catalytic activity of the functional AMC micelles is almost threefold higher than that for **11**. The K_{bond} and *CMC* values for the micellar aggregates **2**, **3**, and **11** formed in the presence and absence of the surfactant are approximately the same and have an order of 10^3 and 10^{-5}, respectively. Their values are comparable to similar parameters of the AMC micelles in a water—isopropyl alcohol mixture[13] at pH 10.9. The reactivity of the micellar aggregates of AMC in a water—DMF mixture is an order of magnitude higher than that for a water—isopropyl alcohol mixture (see Table 1).

The kinetics of the reactions of compounds **1**—**3** and **9** with substrate **7** in a water—DMF mixture (30 vol.% DMF) was also studied by ^{31}P NMR, which made it possible to calculate the rate constants of the second stage of the reaction. The study of the kinetics of the reaction of **9** ($C_9 = 1.4 \cdot 10^{-1}$ mol L^{-1}) with **7** ($C_7 = 2 \cdot 10^{-3}$ mol L^{-1}) in a water—DMF mixture at pH 9 showed that a phosphorylated intermediate (−18.8 ppm) and diphenyl phosphate (**12**) (−11.2 ppm) are formed, similarly to that described previously,[25] along with the disappearance of the chemical shift (^{31}P δ) of substrate **7** (−19.5 ppm). However, unlike water—alcohol media, the intermediate is virtually not accumulated in the solution. The k_{obs} values of the decomposition of substrate **7** and the formation of **12** are very close and equal to $3 \cdot 10^{-3}$ and $2 \cdot 10^{-3}$ s^{-1}, respectively. This tendency is enhanced for AMC, for which at pH 8 and 9 only the second reaction step (the hydrolysis of the intermediate (−18.6 ppm) and the formation of **12** (−11.2 ppm)) was detected. The changes in the intensities of the ^{31}P NMR signals in time for the reaction of **2** ($C_2 = 1.5 \cdot 10^{-2}$ mol L^{-1}) with substrate **7** ($C_7 = 2 \cdot 10^{-3}$ mol L^{-1}) at pH 8 are presented in Fig. 4 as an example. The observed rate constants of the decomposition of phosphorylated AMC and the formation of **12** calculated by a first-order equation are $1.1 \cdot 10^{-3}$ s^{-1} ($r = 0.993$) and $0.94 \cdot 10^{-3}$ s^{-1} ($r = 0.998$) at pH 8, whereas at pH 9 in the presence of Triton X-100, they amount to $4.3 \cdot 10^{-3}$ and $3.9 \cdot 10^{-3}$ s^{-1}, respectively. The k_{obs} values for the hydrolysis of **7** and the formation of **12** in a borate buffer (30 vol.% DMF, pH 9.2) are equal and amount to $7 \cdot 10^{-4}$ s^{-1}. The phosphorylated AMC are much less stable than the phosphorylated calix[4]resorcinolarenes and AMP. The kinetic data obtained by ^{31}P NMR for substrate **7** show that the hydrolysis of phosphorylated compound **2** ($k_{obs} = 4.3 \cdot 10^{-3}$ s^{-1})

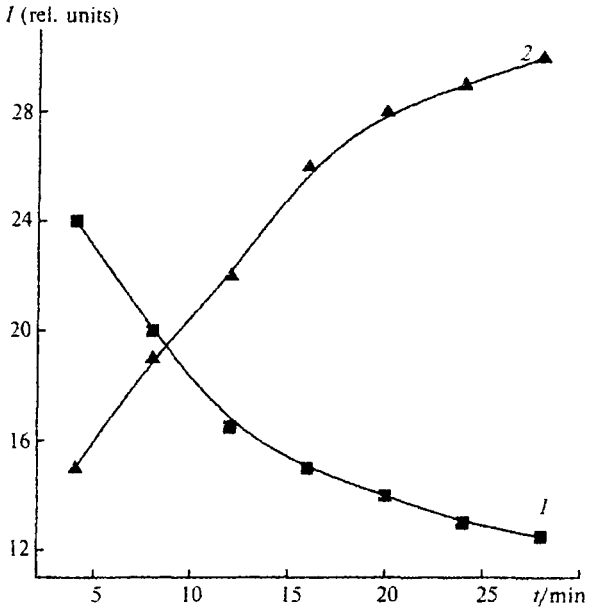

Fig. 4. Changes in the intensities of the ^{31}P NMR signals during the reaction of **2** ($C_2 = 1.5 \cdot 10^{-2}$ mol L^{-1}) with **7** ($C_7 = 2 \cdot 10^{-3}$ mol L^{-1}) in a 30% (vol.) water—dimethylformamide solution at pH 8, 35 °C. Chemical shifts ^{31}P NMR, δ: −18.6 (*1*), −11.2 (*2*).

proceeds by an order of magnitude more rapidly than that of **11** ($k_{obs} = 4.4 \cdot 10^{-4}$ s^{-1}) and 20-fold more rapidly than that for phosphorylated aggregate **9** ($k_{obs} = 2 \cdot 10^{-4}$ s^{-1}), *i.e.*, the intramolecular catalysis of the hydrolysis of the phosphorylated macrocycles is much more efficient than the hydrolysis of their structural units.[25]

Thus, the study of the reactivity of AMC in reactions with EPA in a water—DMF mixture (30 vol.% DMF) showed that AMC that form aggregates of the micellar and nonmicellar types more efficiently catalyze EPA hydrolysis than their structural units AMP. The catalytic activity of the AMC aggregates depends on their structure, pH of the medium, and solvent nature.

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References

1. *Host-Guest Complex Chemistry Macrocycles*, Ed. F. Vogtle and E. Weber, Springer Verlag, Berlin—Heidelberg—New York—Tokyo, 1985.
2. D. J. Cram and J. M. Cram, *Container Molecules and Their Guests, Monographs in Supramolecular Chemistry*, The Royal Society of Chemistry, University of Birmingham, UK, 1994, 192 pp.
3. J.-M. Lehn, *Supramolekulyarnaya khimiya — masshtaby i perspektivy. Molekuly—supermolekuly—molekulyarnye ustroistva* [*Supramolecular Chemistry: Scales and Challenges.*

Molecules—Supermolecules—Molecular Devices], Znanie, Moscow, 1989, 48 pp. (Russ. Transl.).
4. S. Shinkai, S. Mori, H. Koreishi, T. Tsubaki, and O. Manabe, *J. Am. Chem. Soc.*, 1986, **108**, 2409.
5. C. D. Gutsche and I. Alam, *Tetrahedron*, 1988, **44**, 4689.
6. N. Pirrincioglu, F. Zaman, and A. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2561.
7. R. Cacciapaglia, A. Casnati, L. Mandolini, and R. Ungaro, *J. Am. Chem. Soc.*, 1992, **114**, 10956.
8. P. Molenveld, S. Kapsabelis, J. F. J. Embersen, and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1997, **119**, 2948.
9. S. Arimori, T. Nagasaki, and S. Shinkai, *J. Chem. Soc., Perkin Trans. 2*, 1995, 679.
10. N. Kimizuka, T. Wakiama, A. Yanagi, S. Shinkai, and T. Kunitake, *Bull. Chem. Soc. Jpn.*, 1996, 69, 3681.
11. I. S. Ryzhkina, L. A. Kudryavtseva, E. Kh. Kazakova, A. R. Burilov, and A. I. Konovalov, *Mendeleev Commun.*, 1997, No. 3, 88.
12. I. S. Ryzhkina, L. A. Kudryavtseva, A. R. Burilov, E. Kh. Kazakova, and A. I. Konovalov, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 275 [*Russ. Chem. Bull.*, 1998, **47**, 269 (Engl. Transl.)].
13. I. S. Ryzhkina, L. A. Kudryavtseva, A. R. Mustafina, Yu. E. Morozova, E. Kh. Kazakova, K. M. Enikeev, and A. I. Konovalov, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 456 [*Russ. Chem. Bull.*, 1999, **48**, 453 (Engl. Transl.)].
14. I. S. Ryzhkina, L. A. Kudryavtseva, V. E. Bel'skii, I. E. Ismaev, V. I. Morozov, A. V. Il'yasov, and B. E. Ivanov, *Zh. Obshch. Khim.*, 1990, **60**, 820 [*J. Gen. Chem. USSR*, 1990, **60** (Engl. Transl.)].
15. Y. Matsuskita and T. Matsui, *Tetrahedron Lett.*, 1993, **34**, 7433.
16. V. E. Bel'skii, L. A. Kudryavtseva, O. M. Il'ina, and B. E. Ivanov, *Zh. Obshch. Khim.*, 1979, **49**, 2470 [*J. Gen. Chem. USSR*, 1979, **49** (Engl. Transl.)].
17. C. A. Bunton, S. J. Farher, and E. J. Fendler, *J. Org. Chem.*, 1968, **35**, 29.
18. *Advances in Physical Organic Chemistry*, Ed. V. Gold, Academic Press, London—New York, 1970, **8**.
19. K. Kano, Y. Ueno, and S. Hashimoto, *J. Phys. Chem.*, 1985, **89**, 3161.
20. M. Tuncay, G. Afun, and G. Hisarli, *Abstrs. 35th IUPAC Congr.*, August 14—19, 1995, **I**, Sec. 1—3, Istambul, P083.
21. L. A. Bulavin, V. M. Garamus, T. V. Karmazin, and S. P. Shtan'ko, *Kolloidn. Zh.*, 1995, **57**, 902 [*Colloid J.*, 1995, **57** (Engl. Transl.)].
22. F. Kh. Karataeva, A. I. Rakhmatullin, A. V. Aganov, Yu. E. Morozova, and E. Kh. Kazakova, *Zh. Obshch. Khim.*, 1998, **68**, 837 [*Russ. J. Gen. Chem.*, 1998, **68** (Engl. Transl.)].
23. M. S. Westwell, B. Bardsley, R. J. Dancer, A. C. Try, and D. H. Williams, *J. Chem. Soc., Chem. Commun.*, 1996, 589.
24. A. R. Mustafina, R. R. Galimov, L. V. Ermolaeva, N. N. Sarvarova, A. R. Burilov, and V. S. Reznik, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 1117 [*Russ. Chem. Bull.*, 1996, **45**, 1111 (Engl. Transl.)].
25. I. S. Ryzhkina, R. A. Shagidullina, L. A. Kudryavtseva, I. E. Ismaev, and B. E. Ivanov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 242 [*Russ. Chem. Bull.*, 1994, **43**, 219 (Engl. Transl.)].

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