Synthesis and complexation properties of carbonyl-containing thiacalix[4]arenes

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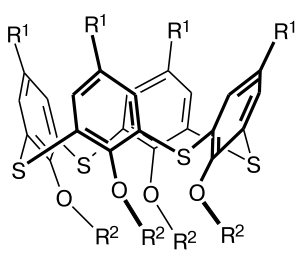
Stereoisomers of thiacalix[4]arenes unsubstituted at the upper rim and containing four carbonyl fragments have been synthesized for the first time. Their structures were studied by 1D and 2D NMR spectroscopy, IR spectroscopy, and mass spectrometry. The complexation properties of the macrocycles toward alkaline metal cations were estimated by the picrate extraction method. The absence of the preorganization effect in the case of the thiacalixarenes unsubstituted at the upper rim is the main reason for the sharp decrease in their extraction ability.

Key words: thiacalix[4]arenes, template synthesis, NMR spectroscopy, extraction, preorganization, alkaline metals.

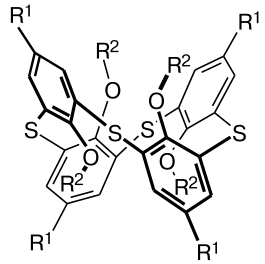
Calix- and thiacalix[4]arenes **1**—**6** are three-dimensional structures with distinctly pronounced molecular cavities.[1—4] They contain active reaction centers, which makes it possible to modify the upper and lower rims for the creation of preorganized receptor structures. Additional possibilities for the design of molecular receptors are due to the existence of several stereoisomeric forms of the calix[4]arene platforms: *cone*, *partial cone*, and *1,3-* and *1,2-alternates*. Therefore, they find growing use in various areas of supramolecular chemistry.[2—6] Tetraesters **3**,[7—9] phenylcarbonyl derivatives **4** (see Refs 10 and 11), and tetraamides **5** (see Refs 10, 12, and 13) based on *p-tert*-butylthiacalix[4]arene **1** in different conformations have been synthesized earlier. It was found that the efficiency and selectivity of extraction were affected by both the spacial structure (macrocycle conformation) and the nature of substituents at the lower rim.

Data on the influence of the *tert*-butyl group at the upper rim on the complexation properties of the thiacalix[4]arenes substituted at the lower rim are presently lacking. At the first glance, this effect should be negligible, because the *tert*-butyl groups possess weak electron-donating properties and are arranged rather far from the complexation centers on the lower rim. However, it should be mentioned that the calixarenes are allosteric molecular systems[14—17] in which even minor structural changes at one side of the macrocycle can result in a substantial steric reorganization of the binding sites localized at another side.

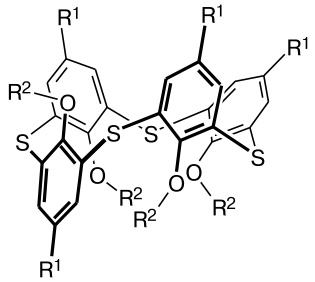
In this connection, in the present work we synthesized tetrasubstituted at the lower rim derivatives **7**—**9** based on unsubstituted at the upper rim thiacalix[4]arene **2** (R^1 = H). In order to obtain different stereoisomeric forms (*cone*, *partial cone*, and *1,3-alternate*), we used the



Cone



1,3-Alternate



Partial cone

Compound	R^1	R^2	Compound	R^1	R^2
1	Bu^t	H	**6**	H	CH_2COOEt
2	H	H	**7**	H	$CH_2C(O)Ph$
3	Bu^t	CH_2COOEt	**8**	H	$CH_2C(O)NEt_2$
4	Bu^t	$CH_2C(O)Ph$	**9**	H	$CH_2C(O)NBu_2$
5	Bu^t	$CH_2C(O)NEt_2$			

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template effect of an alkaline metal cation, which has earlier been applied successfully to the functionalization of *p-tert*-butylthiacalix[4]arene (**1**) derivatives.[11—13]

Results and Discussion

It is found for the reactions of thiacalix[4]arene **2** with *N*,*N*-diethylbromoacetamide and α-bromoacetophenone in acetone that alkaline metal carbonates used as bases exert a substantial effect on the stereochemical result of the reactions, although the stereoselectivity of the process is lower, as a rule, compared to that of *tert*-butyl analog **1**. The high stereoselectivity of these reactions was observed for sodium and cesium carbonates: the *cone* stereoisomers of compounds **7** and **8** are formed in the presence of sodium carbonates in 66 and 59% yield, respectively, and the *1,3-alternate* stereoisomers of the same compounds in the presence of cesium carbonates are formed in 64 and 69% yield, respectively. When potassium carbonate was used, the *1,3-alternate* stereoisomers of compounds **7** and **8** were isolated from the reaction mixture in 45 and 50% yield, respectively.

Due to the absence of methylene bridges in a thiacalixarene molecule (the NMR signals of their protons are usually used for the identification of the conformation of classical calix[4]arene derivatives),[1] it is nontrivial problem to establish the spatial structure of the thiacalix[4]arene derivatives: the ^{1}H and ^{13}C NMR spectra of the macrocycles in the symmetric *cone* and *1,3-alternate* conformations resemble each other by the number and multiplicity of the signals. The structures of macrocycles **7—9** were completely determined by 2D NMR spectroscopy (2D COSY, HSQC, and HMBC).[18,19]

The spatial structures of macrocycles **7** and **8** were ultimately determined by an analysis of the nuclear Overhauser effects (NOE). All experiments on NOE measurement were carried out in a rotating coordinate system. For example, the NOE on the protons at the C(7) atom, *N*-ethyl substituent, and aromatic ring is observed in the 1D ROESY spectrum[20] of compound **8** by the excitation of the proton at the C(1) atom (Fig. 1, *a*, curve *1*). A similar pattern is observed by the excitation of the protons of the C(7)H_2 methylene group (see Fig. 1, *a*, curve *2*) and *N*-ethyl fragments (see Fig. 1, *a*, curves *3* and *4*). The observed effects indicate that these groups of protons spatially are not far from each other, suggesting unambiguously that this compound exists in the *1,3-alternate* stereoisomeric form (see Fig. 1, *b*).

In the ^{1}H NMR spectra of the *cone* stereoisomers of compounds **7** and **8** at room temperature, the majority of signals are strongly broadened, indicating the conformational exchange, whose rate is intermediate in the ^{1}H NMR time scale. The attempts to obtain the spectra under the fast exchange conditions by the temperature raising (to 323 K) were unsuccessful. This evidences that the chemical shifts of the corresponding exchangeable protons differ strongly by the equilibrium components (conformers). The observed pattern could be a result of the equilibrium *pinched cone—cone—pinched cone* (Fig. 2), which has previously been found for similar structures.[21]

The low-temperature NMR experiments completely confirmed this hypothesis. With a temperature decrease compound **7** exhibits the strong broadening and then splitting of the signals (Fig. 3), and the spectrum under

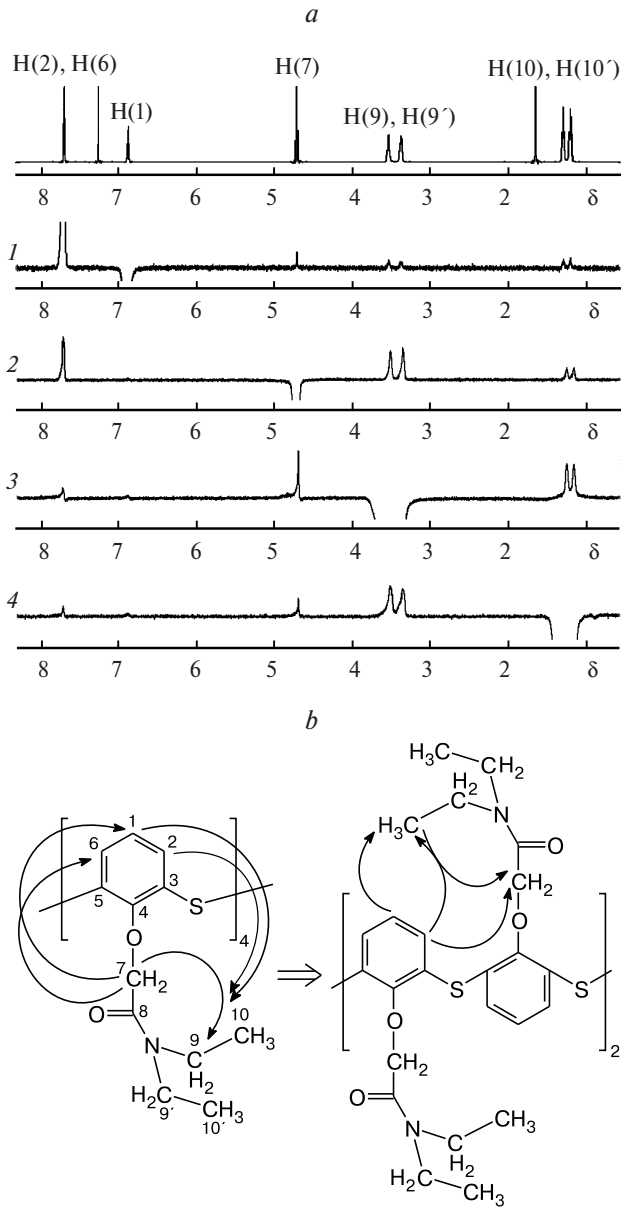

Fig. 1. 1D ROESY spectra (*a*) and the main NOE values (*b*) for compound **8** ($CDCl_3$, 20 °C). The spectra correspond to the excitation of protons at the C(1) (*1*), C(7) (*2*), C(9) and C(9´) (*3*), and C(10) and C(10´) (*4*) atoms.

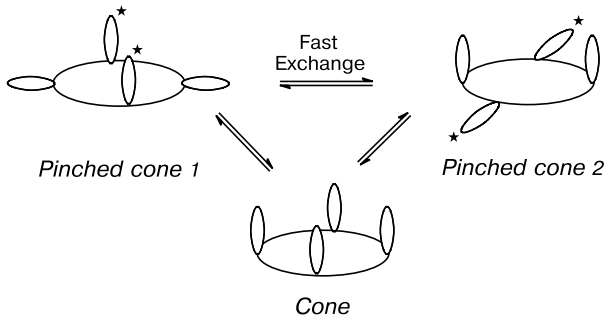

Fig. 2. Interconversion between the *pinched cone* conformations in compounds **7** and **8**.

the slow exchange conditions is observed at 243 K. The ^{1}H NMR spectrum contains two sets of signals (see Fig. 3) corresponding to a lower C_{2v} symmetry of the *pinched cone* conformation. All signals in each half of this structure were unambiguously assigned on the basis of the 1D/2D homo- and heterocorrelation experiments. The combined use of the NOESY and ROESY methods made it possible to differentiate the NOE due to the chemical exchange and to identify the spectral components of the exchange.

Theoretical calculations of chemical shifts of protons are a reliable tool in an analysis of spacial structures of compounds bearing anisotropic groups. Therefore, the shielding effects of the protons of the calixarene platform were calculated for compound **7**. Geometry optimization (MM2 method)[22—24] in the *cone* conformation gives the structure with the C_{2v} symmetry (Fig. 4) in which the protons of the adjacent aromatic rings of the calixarene rim exist in different magnetic environments.

This agrees qualitatively with the ^{1}H NMR spectral data at low temperatures in which the chemical shifts of the corresponding signals of all adjacent groups differ strongly. Moreover, the calculated shielding effects for the protons of the calixarene rim (in the framework of the circular current model on the geometry optimized by the MM2 method)[25—27] agree with those observed for the corresponding protons at the quantitative level (Fig. 5).

An analysis of the full lineshapes (WinDNMR v.7.1.6 program)[28] made it possible to determine the rate constant for the exchange between the forms *pinched cone 1* and *pinched cone 2* in the 223—273 K temperature range. The activation parameters of this process in $CDCl_3$ were determined by the Eyring equation[29,30]: $\Delta H^{\neq} = 10.6$ kcal mol^{-1}, $\Delta S^{\neq} = -8.4$ cal mol^{-1} deg^{-1}, and $\Delta G^{\neq}_{303} = 13.1$ kcal mol^{-1}. The latter value is well consistent with the data obtained earlier for the tetra-*O*-propyl and tetra-*O*-ethyl derivatives of thiacalix[4]arene **2** (see Ref. 21) in the same solvent: $\Delta G^{\neq}_{303} = 13.3$ and 11.9 kcal mol^{-1}, respectively.

It should be mentioned that the activation energies of the interconversion of the thiacalix[4]arene derivatives are unexpectedly high compared to analogous parameters for the classical calixarenes. For instance, for the tetra-*O*-propyl calix[4]arene derivative under the comparable conditions, $\Delta G^{\neq}_{303}$ is lower than 9.8 kcal mol^{-1}.[21] The higher activation energies of the interconversion for the larger macrocyclic ring of the thiacalix[4]arene derivatives compared to the activation energies of the calix[4]arenes are possibly caused by the stabilization of the C_{2v} forms in the

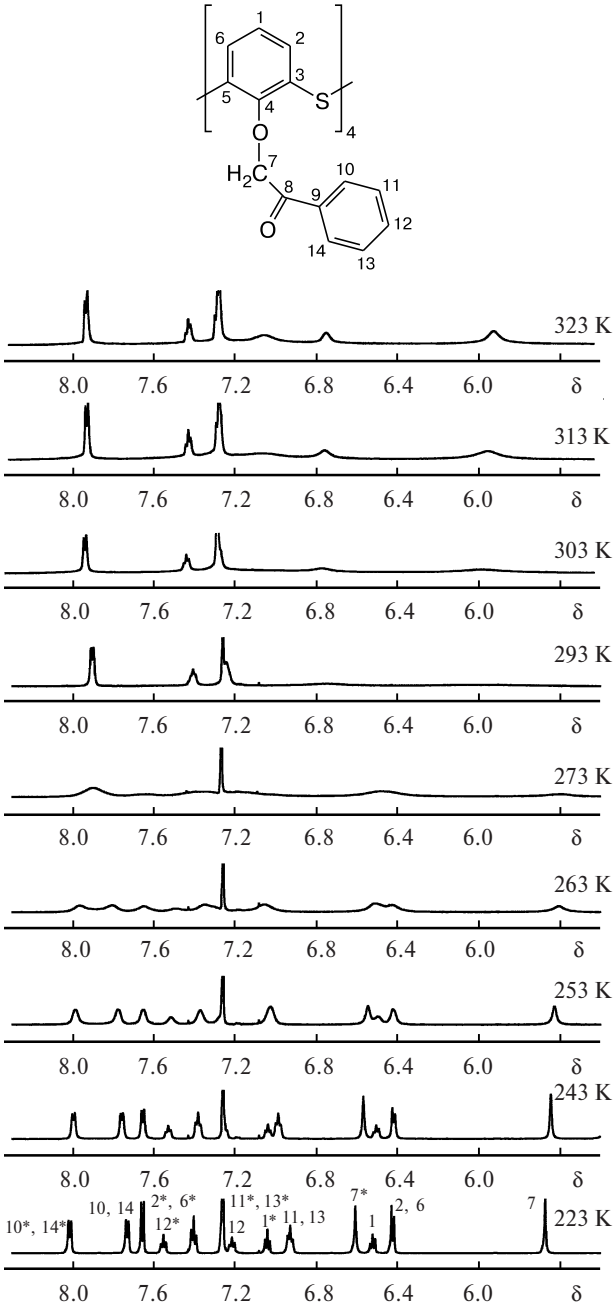

Fig. 3. Temperature dependence of the ^{1}H NMR spectra of compound **7** in the *cone* conformation in $CDCl_3$ (the numbers of protons with asterisks designate the equivalent groups in the *pinched cone* conformation).

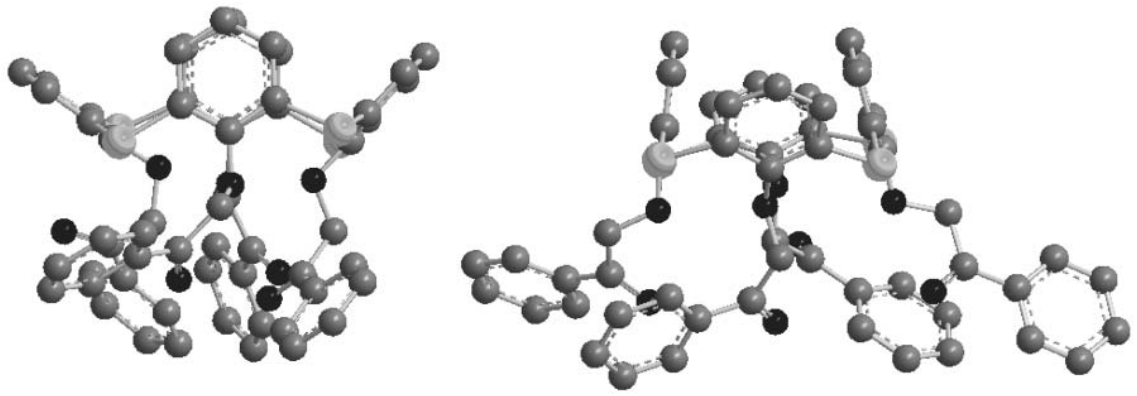

Fig. 4. Optimized by the MM2 method geometry of compound **7** in the *cone* conformation: side view from two sides.

case of the thiacalixarenes due to the conjugation of the bridging sulfur atoms with the aromatic rings. The higher stability of the *pinched cone* conformation in the case of the unsubstituted at the upper rim thiacalix[4]arenes is indirectly specified by the fact that starting thiacalix[4]arene **2** in the crystalline state also has the C_{2v} symmetry according to the IR spectroscopic[31,32] and X-ray diffraction[8] data.

This behavior principally differs from that of the *tert*-butyl derivatives. According to the 2D NMR spectroscopy (weak cross-peaks of structurally equivalent protons), the fast chemical exchange, *viz.*, interconversion of the C_{2v}—C_{2v}' forms (293 K), occurs in amide **5** bearing the *tert*-butyl group.[12] Crystalline macrocycle **1** with the *tert*-butyl substituents in the *para*-position in crystalline phase is characterized by the *cone* conformation with

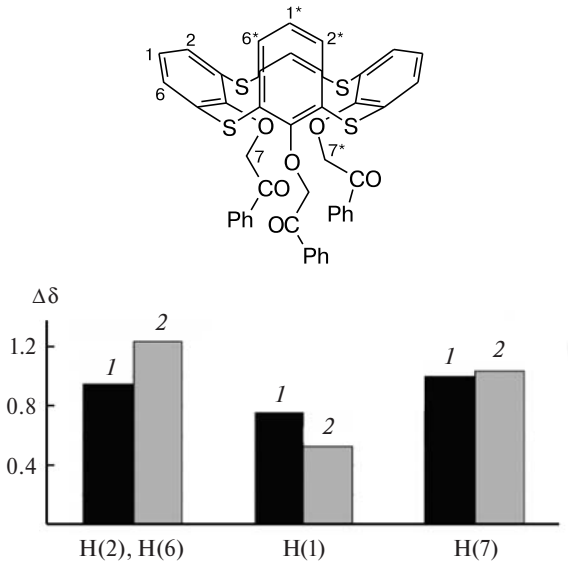

Fig. 5. Comparison of the theoretical[25—27] (*1*) and experimental (*2*) differences in the chemical shifts (Δδ) for protons in the adjacent fragments of thiacalix[4]arene **7** in the *pinched cone* conformation ($\Delta\delta_i = \delta_i - \delta_{i^*}$).

the C_{4v} symmetry.[8,31,32] These regularities are the same in the classical analogs of compounds **1** and **2**.[31,32]

The aforesaid indicates that the steric arrangement of substituents at the lower rim of thiacalixarenes unsubstituted at the upper rim or bearing the *tert*-butyl group at this rim should substantially be different; therefore, their complexation ability will also differ. This is indicated by the data on extraction of alkaline metal cations by tetraesters of the classical calix[4]arenes with both the substituted and free upper rim,[33] and the macrocycles bearing the *tert*-butyl groups at the upper rim exhibit the better extraction properties. The selectivity remains unchanged: the classical analogs of compounds **3** and **6** in the *cone* conformation preferentially extract the sodium cation, and the same analogs in the *1,3-alternate* conformation preferentially extract the potassium cation. There are no similar data on tetraamides and tetraphenylcarbonyl derivatives of the classical calix[4]arenes.

In order to estimate the ability of new thiacalix[4]arene derivatives **7** and **8** to bind alkaline metal ions, the liquid extraction of their picrates (in a mutually saturated water—dichloromethane system) was studied. The data on the extraction of the alkaline metal cations by compounds **6**—**9** and literature data[7,11,13] on the extraction of these cations by *tert*-butyl analogs **3**—**5** under comparable conditions are presented in Table 1.

In all cases, the extraction ability of the macrocyclic ligands decreases substantially upon the removal of the *tert*-butyl group from the upper rim (see Table 1). The decreasing the extraction ability depends on the macrocycle conformation. For the stereoisomers in the *cone* conformation, the effect of *tert*-butyl group removal turned out to be much greater than that for the stereoisomers in the *1,3-alternate* conformation. For instance, macrocycles **6** and **7** in the *cone* conformation almost completely lost the ability to extract alkaline metal cations. The selectivity of binding changes simultaneously with the efficiency. The ester (**3**) and phenylcarbonyl (**4**) derivatives in the *1,3-alternate* conformation extract the potassium cation most efficiently, whereas macrocy-

Table 1. Degree of extraction (*E*) of alkaline metal picrates by derivatives **3**—**9**[a]

Compound	Conformation	*E*(%)				Reference
		Li^+	Na^+	K^+	Cs^+	
3	*1,3-Alternate*	5	9	84	67	7
	Cone	5	54	25	7	7
4	*1,3-Alternate*	19	33	99	76	11
	Cone	12	85	46	10	11
5[b]	*1,3-Alternate*	100 (89)	100 (99)	100 (94)	100 (99)	13
	Cone	100 (62)	100 (78)	100 (80)	100 (45)	13
6	*1,3-Alternate*	0	3	11	34	—[c]
	Cone	0	8	0	7	
7	*1,3-Alternate*	3	7	15	39	—[c]
	Cone	0	0	14	0	
8	*1,3-Alternate*	11	81	98	96	—[c]
	Cone	95	70	23	14	
9	*1,3-Alternate*	10	76	98	96	—[c]

[a] The initial concentrations of ligands **3**—**9** in the organic phase ($[L]_0$), metal hydroxide ($[MOH]_0$) in the aqueous phase, and picric acid ($[HPic]_0$) in the aqueous phase were $2.5 \cdot 10^{-3}$, 0.1, and $2.5 \cdot 0^{-4}$ mol L^{-1}, respectively.
[b] The data for $[\mathbf{5}]_0 = 3.5 \cdot 10^{-4}$ mol L^{-1}, $[MOH]_0 = 7.0 \cdot 10^{-5}$ mol L^{-1}, and $[HPic]_0 = 5.0 \cdot 10^{-5}$ mol L^{-1} are given in parentheses.
[c] Data of this work.

cles **6** and **7** in the same conformation have a very weak extraction ability toward small alkaline metal cations but rather efficiently extract the cesium cation and manifest a good selectivity with respect to this cation.

As in the case of the above-considered ester and phenylcarbonyl derivatives, the efficiency and selectivity change substantially for amides **5** and **8** in the both conformations (Fig. 6, *a*, *b*). In addition, under the conditions used for the extraction of compound **8**, *tert*-butyl derivative **5** extracts the alkaline metal cations so efficiently that the concentrations of both the ligand and metal ions should be decreased to estimate the selectivity of extraction (see Table 1 and Fig. 6, *a*). As a whole, the better ability to bind amide derivatives **5** and **8** is due to the fact that the amides are stronger electron donating groups than ester and phenylcarbonyl substituents of derivatives **3**, **4**, **6**, and **7**.

It turned out that amide **8** in the *cone* conformation with the unsubstituted upper rim is selective to the lithium cation, whereas its *tert*-butyl analog (tetraamide **5**) preferentially binds the sodium and potassium cations, although its selectivity with respect to other alkaline metal cations is not so high. From this point of view, the extraction behavior of tetraamide **8** in the *cone* conformation is remarkable: the extraction ability of the macrocycle decreases with an increase in the cation size. Taking into account the substantially higher energy of lithium cation transfer from the aqueous to organic phase in the series of alkaline metal cations,[34] one can speak about the creation of the highly efficient complexation agent to the lithium cation.

A different pattern is observed for the *1,3-alternate* stereoisomers. Macrocycle **5** is characterized by the absence of selectivity toward the alkaline metal cations (see Fig. 6, *b*), while the removal of the *tert*-butyl group from the upper rim produces selectivity. However, unlike compound **8** in the *cone* conformation, an inverse dependence is observed in this case: the extraction ability increases with an increase in the cation size.

The observed differences in the extraction ability of macrocycles **5** and **8** can be caused by several factors, first of all, by a decrease in the lipophilicity of the ligand due to the removal of four hydrophobic *tert*-butyl substituents from the upper rim. Therefore, we synthesized *N*,*N*-dibutylamide derivative **9** in the *1,3-alternate* conformation, whose lipophilicity is approximately equal

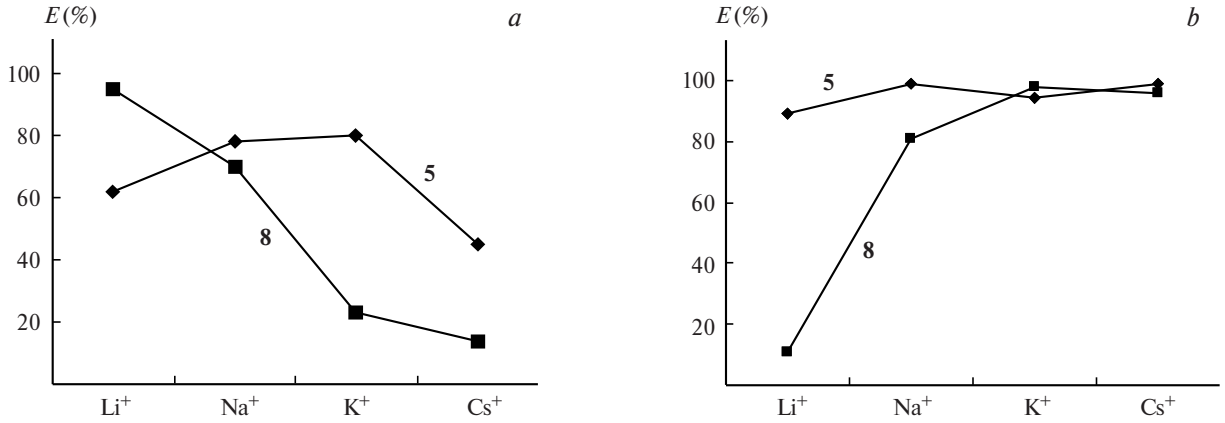

Fig. 6. Dependences of the degree of extraction (*E*) of the alkaline metal cations by compounds **5** (see Ref. 13) and **8** in the *cone* (*a*) and *1,3-alternate* (*b*) conformations. Extraction conditions: $[\mathbf{5}]_0 = 3.5 \cdot 10^{-4}$ mol L^{-1}, $[MOH]_0 = 7.0 \cdot 10^{-5}$ mol L^{-1}, $[HPic]_0 = 5.0 \cdot 10^{-5}$ mol L^{-1}; $[\mathbf{8}]_0 = 2.5 \cdot 10^{-3}$ mol L^{-1}, $[MOH]_0 = 0.1$ mol L^{-1}, and $[HPic]_0 = 2.5 \cdot 10^{-4}$ mol L^{-1}.

to that of macrocycle **5**.[35] The data on the extraction of the alkaline metal cations by compounds **8** and **9** are presented in Table 1. It is seen that more lipophilic amide **9** extracts the alkaline metal cations nearly in the same way as compound **8**. Thus, the lipophilicity of the macrocycles exerts no decisive effect on the observed change in the extraction ability upon the removal of the *tert*-butyl group from the upper rim.

Another possible reason for serious differences in the complexation ability can be the effect of ligand preorganization. We succeeded to obtain a single crystal of tetraamide **8** in the *1,3-alternate* conformation by crystallization from acetonitrile and studied it by X-ray diffraction analysis. The comparison of these and earlier[13] obtained data on the structure of compound **5** showed that the steric structures of the free ligands differed strongly (Fig. 7).

The *tert*-butyl groups of ligand **5** preorganized the cavity for cation incorporation: the distance between the oxygen atoms of the carbonyl groups at one part of the macrocycle is 6.65 Å, the distance between the phenoxylic oxygen atoms is 5.66 Å, and the distance between the benzene rings at the opposite part of the macrocycle is 5.65 Å, *i.e.*, the aromatic rings are parallel. In the absence of *tert*-butyl groups, the aromatic rings in compound **8** are brought together and the amide groups move apart: the distance between the oxygen atoms of the carbonyl groups at one part of the macrocycle is 8.14 Å, the distance between the phenoxylic oxygen atoms is 6.48 Å, and the distance between the benzene rings at the opposite part of the macrocycle is 3.9 Å. The data presented convincingly prove that macrocycle **8**, unlike macrocycle **5**, is not sterically preorganized for the interaction with the cation, and an additional energy should be consumed during the complexation process to reorganize the binding sites of the ligand. Therefore, the absence of the preorganization effect in the case of the thiacalixarenes unsubstituted at the upper rim is the main reason for their lower extraction ability.

Thus, new derivatives of the unsubstituted at the upper rim thiacalix[4]arenes **7—9** in the *cone* and *1,3-alternate* conformations have been synthesized for the first time and characterized. The study of the extraction properties of the synthesized compounds by the picrate method showed that the removal of the *tert*-butyl groups decreases the extraction ability of the macrocycles, and the selectivity can either increase or decrease depending on the stereoisomer nature. Amide **8** is a less efficient but more selective extragent compared to analogous *p-tert*-butyl thiacalix[4]arene derivative **5**. Compound **8** in the *cone* conformation is a new efficient and selective extragent for the Li^+ cation, and compounds **6** and **7** in the *1,3-alternate* conformation are selective extragents of the cesium cation. An increase in the lipophilicity of compound **9** in the absence of *tert*-butyl groups at the upper rim exerts no effect on the extraction of the alkaline metal cations. It is most likely that the main factor of the lower extraction ability of the thiacalixarenes unsubstituted at the upper rim is the absence of the preorganization effect of macrocyclic platform.

Experimental

Solvents were purified prior to use according to known procedures.[36]

1D and 2D NMR spectra (DEPT, NOESY, 2D COSY, 2D HSQC, and 2D HMBC) in $CDCl_3$ were recorded on a Bruker Avance-600 spectrometer (600.13 (^{1}H) and 150.92 MHz (^{13}C)); residual signals of $CHCl_3$ (δ_H 7.26) and $CDCl_3$ (δ_C 77.16)[37] were used as internal standards; the NOE values in the laboratory and rotating coordinates were measured by the 1D DPFGSE method.[20] A VT-2200 temperature unit was used for low-temperature NMR experiments. The temperature was calibrated for a methanol sample using a standard procedure. Prior to experiment the samples were kept in a sensor for 15 min to achieve the temperature equilibrium.

The MM2 calculations (force constants)[22—24] were performed using the CS Chem3D Ultra 6.0 program (CambridgeSoft Corp.). The shielding effects were calculated (in the framework of the circular

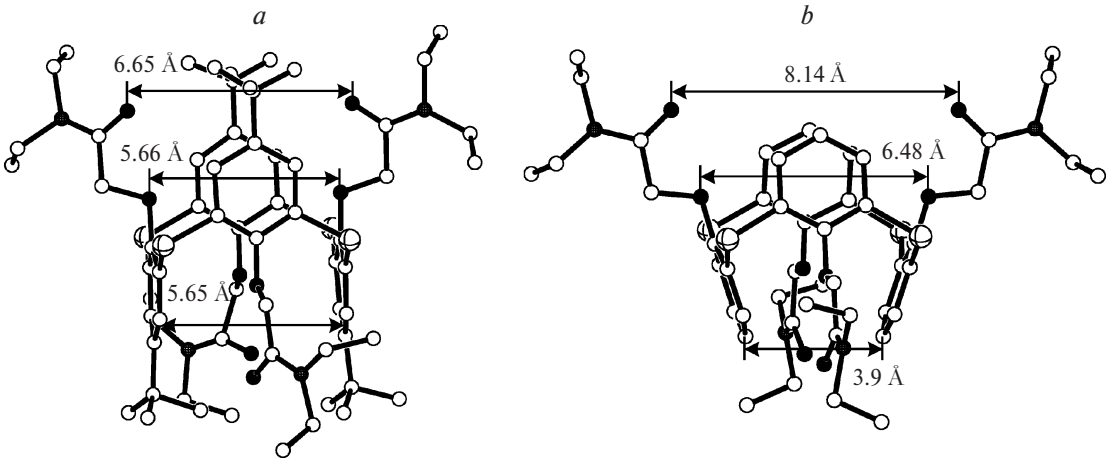

Fig. 7. Crystal structures of ligands **5** (*a*) and **8** (*b*) in the *1,3-alternate* conformation according to the X-ray diffraction data.

current model)[25—27] by the Shield program. In the presence of chemical exchange, the full lineshape was calculated by the WinDNMR v.7.1.6 program.[28] The activation parameters were calculated by the Eyring equation.[29,30]

IR spectra were recorded on a Bruker Vector 2-2 FT-IR spectrometer (resolution ability 1 cm^{-1}, accumulation 64 scans) in KBr pellets in the 400—4000 cm^{-1} interval. Mass spectra were obtained on a MALDI-TOF Dynamo Finnigan mass spectrometer. 1,8,9-Trihydroxyanthracene or *p*-nitroaniline was used as the matrix. UV spectra were recorded on a UV-VIS Spectrometer Lambda 35 instrument (Perkin—Elmer).

Elemental analysis was performed on a Perkin—Elmer PE 2400 series 2 CHNS/O analyzer. Melting points of the substances were determined on a Boetius small-scale heating stage with an RNMK 05 visual device. The purity of the substances was monitored by TLC on Silufol UV 254 plates (developed by the UV light of a VL-6.LC lamp (6W-254 nm tube) and, in several cases, by iodine vapors).

The compounds were studied at the NMR Division of the Federal Collective Spectral Analytical Center for the Physicochemical Investigation of Structure, Properties, and Composition of Substances and Materials and the Federal Center for Physicochemical Investigation of Substances and Materials (State Contracts of the Ministry of Education and Science of the Russian Federation 02.451.11.7036 and 02.451.11.7019).

α-Bromoacetophenone[38] and thiacalix[4]arene **2** [39] were synthesized by known procedures. 25,26,27,28-Tetrakis[(ethoxycarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene (**6**) in the *cone* and *1,3-alternate* conformations were synthesized using a described procedure.[9]

Synthesis of 25,26,27,28-tetrakis[(phenylcarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene stereoisomers (7) (general procedure). A mixture of thiacalix[4]arene **2** (1.0 g, 2.0 mmol), α-bromoacetophenone (3.98 g, 20 mmol), and anhydrous alkaline metal carbonate (20 mmol) in anhydrous acetone (50 mL) was refluxed for 31 h under argon atmosphere. The reaction course was monitored by TLC. Then the reaction mixture was treated using different methods depending on the base used.

Base Na_2CO_3. Dilute hydrochloric acid (50 mL) and chloroform (100 mL) were added to the precipitate that was filtered from the reaction mixture, the layers were separated, the organic layer was washed with water to pH 7 and dried over $MgSO_4$, and chloroform was removed to a minimum volume (~10 mL). The precipitate formed was filtered off and washed with a minor amount of chloroform, and target product **7** in the *cone* conformation was isolated. The yield was 1.18 g (61%), R_f 0.66 (acetone—hexane (1 : 1) as eluent). The product (0.09 g, 5%) was additionally isolated from the acetone filtrate.

Base K_2CO_3. The MALDI-TOF mass spectrum of the reaction mixture, *m/z*: 991 $[M + Na]^+$ (tetrasubstituted derivative). According to the TLC data, the reaction mixture contained two products: with R_f 0.30 (presumably, the *partial cone* stereoisomer) and R_f 0.18 (*1,3-alternate*) (chloroform as eluent); no starting thiacalix[4]arene was found.

The reaction mixture was filtered, and the filtrate was concentrated on an oil pump to a small volume. The precipitate formed was filtered off and washed with diethyl ether. The solvent from the filtrate was removed until a viscous resin-like residue was formed to which diethyl ether was added. The precipitate formed was filtered off, dissolved in dichloromethane (20 mL), treated with dilute HCl, washed with water to pH 7, and dried over $MgSO_4$. The mixture was concentrated to a volume of 5 mL, the precipitate formed was filtered off and washed with methanol, and target product **7** in the *1,3-alternate* conformation was isolated. The yield was 0.88 g (45%), R_f 0.18 (chloroform as eluent).

Base Cs_2CO_3. The reaction mixture was filtered, and the precipitate was washed with acetone (75 mL). The solvent from the joined acetone filtrates was removed to dryness, and diethyl ether (75 mL) was added to the solid residue. Then the precipitate was filtered off and washed several times by diethyl ether. A small amount of chloroform was added to the precipitate. The non-dissolved portion was filtered off, and target product **7** in the *1,3-alternate* conformation was isolated. The yield was 1.23 g (64%).

Compound 7, *cone* conformation. White powder, m.p. >350 °C. Found (%): C, 69.34; H, 4.10; S, 13.12. $C_{56}H_{40}O_8S_4$. Calculated (%): C, 69.42; H, 4.13; S, 13.22. IR, ν/cm^{-1}: 1704 (C=O), 3056 (CH). ^1H NMR (313 K), δ: 5.9 (br.s, 8 H, OCH_2); 6.7 (br.s, 4 H, H(1)); 7.0 (br.s, 8 H, H(2), H(6)); 7.2 (br.s, 8 H, H(11), H(13)); 7.4 (t, 4 H, H(12), J = 7.5 Hz); 7.9 (d, 8 H, H(10), H(14), J = 7.5 Hz). ^{13}C NMR (223 K), δ: 74.1, 75.2 (C(7)), 123.0, 126.2 (C(1)), 126.8, 127.9 (C(10), C(14)), 128.3, 128.7 (C(11), C(13)), 130.7, 131.6 (C(5), C(3)), 133.4, 133.7 (C(12)), 131.8, 137.6 (C(6), C(2)), 155.2, 159.7 (C(4)), 193.6, 195.2 (C(8)). MALDI-TOF MS, *m/z*: 991 $[M + Na]^+$.

Compound 7, *1,3-alternate* conformation. White powder, m.p. >350 °C. Found (%): C, 69.34; H, 4.19; S, 13.24. $C_{56}H_{40}O_8S_4$. Calculated (%): C, 69.42; H, 4.13; S, 13.22. IR, ν/cm^{-1}: 1705 (C=O), 3058 (CH). ^1H NMR, δ: 5.36 (s, 8 H, OCH_2); 6.80 (t, 4 H, *p*-H arom., J = 7.0 Hz); 7.52 (t, 8 H, *m*-H arom., J = 8.0 Hz + d, 8 H, *m*-H arom., J = 7.0 Hz); 7.63 (t, 4 H, *p*-H arom., J = 8.0 Hz); 8.00 (d, 8 H, *o*-H arom., J = 8.0 Hz). MALDI-TOF MS, *m/z*: 1101 $[M + Cs]^+$.

Synthesis of 25,26,27,28-tetrakis[(*N*,*N*-diethylcarbamoyl)-methoxy]-2,8,14,20-tetrathiacalix[4]arene stereoisomers (8) (general procedure). A mixture of thiacalix[4]arene **2** (1.00 g, 2.0 mmol), *N*,*N*-diethylbromoacetamide (5.7 mL, 40 mmol), and anhydrous metal carbonate (20 mmol) in anhydrous acetone (50 mL) was refluxed for 48 h under argon atmosphere. The reaction course was monitored by TLC. Then the reaction mixture was treated using different methods depending on the base used.

Base Na_2CO_3. The reaction mixture was poured into water and extracted with chloroform (~350 mL), and the extract was treated with dilute hydrochloric acid, washed with water to pH 7, and dried over $MgSO_4$. Chloroform was removed *in vacuo*. An excess of the starting $BrCH_2CONEt_2$ was removed in vacuum of an oil pump (bath temperature 130 °C) nearly to dryness, and the residue (resin-like mass) was subjected to column chromatography on silica gel 60 (Lancaster, 220—440 mesh, for column chromatography, chloroform—hexane (1 : 2) mixture as eluent). Target product **8** in the *cone* conformation was isolated. The yield was 1.10 g (59%), R_f 0.87 (acetone—hexane (1 : 1) as eluent).

Base K_2CO_3. The MALDI-TOF mass spectrum of the reaction mixture, *m/z*: 951 $[M + H]^+$, 973 $[M + Na]^+$, 989 $[M + K]^+$ (tetrasubstituted products). According to the TLC data (acetone—hexane (1 : 1.5) as eluent), the reaction mixture contained two products with R_f 0.24 and 0.51 (presumably, the *partial cone* stereoisomer). The precipitate was filtered off from the reaction mixture and washed with acetone. The filtrate was evaporated on a rotary evaporator until a viscous resin-like residue was formed (bath temperature 32 °C). Colorless crystals that formed were filtered off, washed with diethyl ether, and recrystallized from acetoni-

trile, and product **8** in the *1,3-alternate* conformation was isolated. The yield was 0.95 g (50%).

Base Cs_2CO_3. The reaction mixture was cooled to room temperature, water was added, and the mixture was treated with dilute hydrochloric acid. The mixture was extracted with chloroform (250 mL), and the organic layer was washed with water to pH 7 and dried over $MgSO_4$. Chloroform was removed on a rotary evaporator (bath temperature 30 °C). An excess of $BrCH_2CONEt_2$ was removed in vacuum of a rotary evaporator (bath temperature >200 °C) almost to dryness. After cooling to room temperature, diethyl ether was added to the solid residue. The precipitate was filtered off, washed with diethyl ether (~30 mL), and recrystallized from acetonitrile, and target product **8** in the *1,3-alternate* conformation was isolated. The yield was 1.3 g (69%), R_f 0.24 (acetone—hexane (1 : 1.5) as eluent).

Compound 8, *cone* conformation. Yellowish powder, m.p. 295 °C. Found (%): C, 60.34; H, 6.31; N, 5.75; S, 13.42. $C_{48}H_{60}N_4O_8S_4$. Calculated (%): C, 60.76; H, 6.33; N, 5.91; S, 13.50. IR, ν/cm^{-1}: 1672 (C=O), 2957 (CH). ^{1}H NMR, δ: 0.84, 0.88 (both t, 12 H each, CH_3, J = 4.7 Hz); 3.38, 3.55 (both br.s, 8 H each, NCH_2); 5.22 (br.s, 8 H, OCH_2); 6.63 (t, 4 H, *p*-H arom., J = 5.2 Hz); 7.51 (d, 8 H, *m*-H arom., J = 5.1 Hz). MALDI-TOF MS, *m/z*: 973 $[M + Na]^+$.

Compound 8, *1,3-alternate* conformation. White crystals, m.p. 243 °C. Found (%): C, 60.71; H, 6.23; N, 5.82; S, 13.30. $C_{48}H_{60}N_4O_8S_4$. Calculated (%): C, 60.76; H, 6.33; N, 5.91; S, 13.50. IR, ν/cm^{-1}: 1660 (C=O), 2960 (CH). ^{1}H NMR, δ: 1.17, 1.26 (both t, 12 H each, CH_3, J = 6.8 Hz); 3.35, 3.52 (both q, 8 H each, NCH_2, J = 6.8 Hz); 4.68 (s, 8 H, OCH_2); 6.87 (t, 4 H, *p*-H arom., J = 7.6 Hz); 7.70 (d, 8 H, *m*-H arom., J = 7.6 Hz). ^{13}C NMR, δ: 13.09 (C(10)), 14.50 (C(10′)), 40.19 (C(9)), 41.56 (C(9′)), 71.05 (C(7)), 123.85 (C(1)), 128.8 (C(3), C(5)), 138.62 (C(2), C(6)), 160.9 (C(4)), 166.72 (C(8)). MALDI-TOF MS, *m/z*: 952 $[M + H]^+$, 973 $[M + Na]^+$, 989 $[M + K]^+$, 1083 $[M + Cs]^+$.

25,26,27,28-Tetrakis[(*N*,*N*-dibutylcarbamoyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene (9), *1,3-alternate* conformation. A mixture of calix[4]arene **2** (0.363 g, 0.72 mmol), Cs_2CO_3 (2.36 g, 7.24 mmol), and $BrCH_2CONBu_2$ (3.62 g, 14.48 mmol) in anhydrous acetone (20 mL) was stirred for 60 h under argon atmosphere at the boiling point of acetone. The completeness of the reaction was monitored by TLC and MALDI-TOF mass spectrometry. After the end of the reaction, water was added to the reaction mixture, which was extracted with chloroform (250 mL), the organic layer was dried over $MgSO_4$, and the solvent was removed until a viscous resin-like residue was formed and subjected to column chromatography on silica gel 60 (Lancaster, 220—440 mesh for column chromatography, chloroform as eluent). The crystals, formed after solvent excess was removed from the main fraction, were washed with acetonitrile, and target product **9** in the *1,3-alternate* conformation was obtained. The yield was 0.42 g (58%), white needle-like crystals, m.p. >350 °C, R_f 0.23 (chloroform as eluent). Found (%): C, 65.55; H, 7.97; N, 4.70; S, 10.93. $C_{64}H_{92}N_4O_8S_4$. Calculated (%): C, 65.53; H, 7.85; N, 4.78; S, 10.92. IR, ν/cm^{-1}: 1660 (C=O), 3055 (CH). ^{1}H NMR, δ: 0.92—1.00 (m, 24 H, CH_3); 1.33, 1.43 (both m, 16 H each, CH_2CH_2); 3.33, 3.46 (both t, 8 H each, NCH_2, J = 7.5 Hz); 4.69 (s, 8 H, OCH_2); 6.86 (t, 4 H, *p*-H arom., J = 7.6 Hz); 7.76 (d, 8 H, *m*-H arom., J = 7.6 Hz). MALDI-TOF MS, *m/z*: 1173 $[M + H]^+$.

Extraction studies. Picric acid (HPic), LiOH, NaOH, KOH, and CsOH (all reagent grade) were used. Dichloromethane (reagent grade) was purified by a standard method.[36] Alkaline metal picrates were prepared by the dissolution of weighed samples of picric acid in aqueous solutions of metal hydroxides (MOH), which were pretitrated with a 0.1 *M* solution of hydrochloric acid.

A solution of ligands **6**—**9** in dichloromethane was added to 5 mL of an aqueous solution of MOH (C = 0.1 mol L^{-1}) and HPic ($C = 2.5 \cdot 10^{-4}$ mol L^{-1}). The biphase system was stirred for 30 min in a closed flask on a magnetic stirrer (IKA-WERKE RO 15 power) and then left to stay for 90 min for phase separation. Absorbances of the aqueous phase before and after extraction (A_0 and A_i, respectively) were determined at 355 nm.[40,41] The extraction percentage (E) was calculated by the equation

$$E = [(A_0 - A_i)/A_0] \cdot 100.$$

Experiments on extraction were carried out for the initial concentration of ligands **3**—**9** equal to $2.5 \cdot 10^{-3}$ mol L^{-1} and for $[\mathbf{5}]_0 = 3.5 \cdot 10^{-4}$ mol L^{-1}.

X-ray diffraction analysis of compound **8** in the *1,3-alternate* conformation was performed on an Enraf-Nonius CAD-4 four-circle automated diffractometer. The crystals of compound **8** ($C_{48}H_{60}N_4O_8S_4$) were tetragonal, at 20 °C $a = b$ = 16.829(4) Å, c = 17.889(6) Å, V = 5066(2) Å^3, Z = 4, d_{calc} = 1.24 g cm^{-3}, space group $I4_1/a$. The unit cell parameters and intensities of 5370 reflections, 1518 of which had $I \geq 2\sigma$, were measured at 20 °C (Cu-Kα radiation, λ(Cu-Kα) = 1.54184 Å, graphite monochromator, ω/2θ scan mode, θ = 74.14°). No decrease in the intensities of three control reflections was observed during the experiment, and an absorption correction was applied (μ(Cu) = 2.16 mm^{-1}). The crystal structure was solved by a direct method using the SIR program,[42] and non-hydrogen atoms were refined in the full-matrix anisotropic approximation for F^2 using the SHELXL program.[43] The coordinates of hydrogen atoms were calculated on the basis of stereochemical criteria and refined by the corresponding riding models. The final values of the R factors were R = 0.0561, R_w = 0.1471 for 1518 reflections with $I^2 \geq 2\sigma$; R = 0.1060, R_w = 0.1752 for all reflections. The fitting parameter for F^2 was 1.022. All calculations were performed by the MolEN[44] and WINGX[45] programs, and the figures of molecules were drawn using the PLATON program.[46] The X-ray diffraction data for compound **8** were deposited with the Cambridge Structure Data Collection (CCDC no. 665 719).

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