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Introduction

Recently, the design of high-performance and selective ligands for the metal cations binding, which combine receptor and signal function, attracts the considerable interest of researchers; that can be valuable for the production of sensors, ion-selective electrodes, and so on. One of the promising classes of compounds with these properties are calix[4]arenes 1a and 2a with crown ether fragments (Figure 1).

These compounds have the receptor ability towards alkali and alkaline-earth metal cations and their binding selectivity mainly depends on the number of oxygen atoms in polyethylene glycol chain and calixarene stereoisomeric form. Among them very selective receptor molecules were discovered. For example, calix[4]crown-6-ether in 1,3-alternate conformation demonstrated high Cs⁺/Na⁺ selectivity (more than 30000).

Substitution of methylene bridges for sulfur atoms results in the macrocycle size increase and the formation of new receptor properties for thiacalixarene derivatives. Potentiometric sensors based on thiacalix[4]crown ethers 2b in poly(vinyl chloride) membrane electrodes have the detection limit of cesium cations less than 10⁻⁷ M; compounds 1b with pyridylmethyl substituents in 1,3-alternate conformation demonstrate the ability to switchable recognition of lithium and silver cations; 1b with methoxy and propoxy groups extract selectively potassium and rubidium cations.

Size of thiacalixarene platform is the key parameter to control the complexation ability of derivatives 2b towards alkali metal ions. The size of crown ether chain plays an important role as well.

To use the thiacalixcrowns for sensor design the presence of appropriate terminal functional groups, which can effectively interact with solid surface, is required (Figure 2). For this reason, regio- and stereoselective synthesis of thiacalix-monocrowns derivatives containing lateral omega-functionalized substituents represents an important problem.

This work is devoted to the synthesis of ω-bromoalkoxy derivatives of thiacalix-monocrown ethers in 1,3-alternate conformation was performed. The complexation ability of synthesized macrocycles towards alkali metal cations was investigated by two-phase extraction method.

Keywords: Thiacalix[4]monocrown, picrate extraction, 2D NMR, Mitsunobu reaction.
Thiacalix[4]arenes with Crown Ether Fragments

Experimental

Solvents were purified according to the known procedures. [20] Parent thiacalix[4]arene 3 was synthesized according to the procedure described earlier. [20] Oligoether glycols with the content of main substance of more than 99% (diethylene glycol of an Acros Company; triethylene glycol, Acros; and tetraethylene glycol, Alfa Aesar), triphenylphosphate (Acros, 99%), diethyl azodicarboxylate (Lancaster, 97%) were used without further purification.

IR spectra of the compounds synthesized were recorded on a Bruker Vector-22 Fourier spectrometer in the wavenumber range from 400 to 4000 cm⁻¹. Melt points of substances were determined on a BOETIUS compact heating table. Mass spectra were recorded on a MALDI-TOF Ultraflex III mass spectrometer from the solutions of deuterated solvents (CDCl₃:CD₂OD = 1:1), [21] Parent thiacalix[4]arene 3 was synthesized according to the procedure described earlier. [20] Oligoether glycols with the content of main substance of more than 99% (diethylene glycol of an Acros Company; triethylene glycol, Acros; and tetraethylene glycol, Alfa Aesar), triphenylphosphate (Acros, 99%), diethyl azodicarboxylate (Lancaster, 97%) were used without further purification. Addition of methanol gave white precipitate. After column chromatography (eluent is hexane:ethyl acetate from 10:1 to 2:1) individual products were obtained as white powders. IR spectra of the compounds synthesized were recorded on a Bruker Vector-22 Fourier spectrometer in the wavenumber range from 400 to 4000 cm⁻¹. Melt points of substances were determined on a BOETIUS compact heating table. Mass spectra were recorded on a MALDI-TOF Ultraflex III mass spectrometer from the solutions of deuterated solvents (CDCl₃:CD₂OD = 1:1), [21] Parent thiacalix[4]arene 3 was synthesized according to the procedure described earlier. [20] Oligoether glycols with the content of main substance of more than 99% (diethylene glycol of an Acros Company; triethylene glycol, Acros; and tetraethylene glycol, Alfa Aesar), triphenylphosphate (Acros, 99%), diethyl azodicarboxylate (Lancaster, 97%) were used without further purification. Addition of methanol gave white precipitate. After column chromatography (eluent is hexane:ethyl acetate from 10:1 to 2:1) individual products were obtained as white powders. 

Table 1. Ratio of yields of monosubstituted 5-7 and open-chain derivatives 8-9 under various conditions.

<table>
<thead>
<tr>
<th>Temperature, °C</th>
<th>Time, h</th>
<th>Reagents ratio Glycol:TPP:DEAD:4 ratio</th>
<th>Yield 5-7, %</th>
<th>Yield 8-9, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>m=1</td>
<td>20</td>
<td>1.5</td>
<td>43 (5a)</td>
<td>27 (8a)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>24</td>
<td>1.5:3:1</td>
<td>25 (5a)</td>
</tr>
<tr>
<td>n=1</td>
<td>20</td>
<td>2</td>
<td>60 (6a)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>3</td>
<td>1.5:1</td>
<td>32 (7a)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>3:6:1</td>
<td>36 (7a)</td>
</tr>
<tr>
<td>m=2</td>
<td>20</td>
<td>48</td>
<td>36 (7a)</td>
<td>32 (9a)</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>1.5</td>
<td>46 (5b)</td>
<td>10 (8b)</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>2</td>
<td>24:1</td>
<td>61 (6b)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>2</td>
<td>2:4:1</td>
<td>26 (7b)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>2</td>
<td>3:6:1</td>
<td>23 (7b)</td>
</tr>
</tbody>
</table>

**Results and Discussion**

Synthesis of monomeric bis-omega-bromalkoxy thiacalix[4]arenes can be performed according to two pathways (Scheme 1).

The former involves the preliminary formation of crown-ether fragment (Scheme 1, a) on a calixarene platform and further functionalization of remaining two phenolic hydroxyl groups by $\alpha,\omega$-dihaloalkanes. In the case of thiacalix[4]arenes, on the first step the formation of some by-products was observed, namely, products of 1,2-macrocyclization (Scheme 1, b), biscalixarenes(22) (Scheme 1, c), and biscrown-ether derivatives in 1,3- and 1,2-alternate conformations(23) (Scheme 1, d, e) and the target product can be obtained in rather low yield (Scheme 1, g). Other approach represents the primary synthesis of distal disubstituted calixarenes (Scheme 1, f) with further crosslinking of remaining free hydroxyl groups by oligoethylene glycols. The second way looks more preferable because the formation of bis-crown-ether derivatives (e and d) as well as 1,2-cyclization products (b and e) is principally blocked (Scheme 1). Moreover the convenient method of synthesis of thiacalix[4]arene distal derivatives in high yield was recently discovered.(21)

Starting compounds, namely, distal substituted $\omega$-bromoderivatives of thiacalix[4]arene 4a,b with the number of methylene units of 2 and 3 (Scheme 2) were synthesized according to Mitsunobu protocol(20) from corresponding bromo-substituted alcohols. Their spatial structure was elucidated from 1D NOE measurements. NOE's between protons of CH and OH groups of lower rim substituents as well as between tert-butyl protons and aromatic protons of calixarene rim are observed. Keeping in mind the symmetry of NMR spectra, we can conclude that macrocycles 4a,b adopt the cone stereoisomeric form in solution.

The formation of crown ether fragment on disubstituted derivatives 4 was performed by their reaction with a series of oligoethylene glycols, namely, di-, tri-, and tetraethylene glycols, under Mitsunobu protocol. Both target biscalixarencrowns 5-7 and their open-chain products 8, 9 were isolated from the reaction mixture by column chromatography (Scheme 3). It should be noted that the formation of such open-chain derivatives in thiacalixarene chemistry was not observed earlier. Compounds 8 and 9 can represent special interest.

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**Procedure of Extraction Studies**

Alkali metal picrates were obtained by mixing aqueous solutions of picric acid and metal hydroxide solutions, which were preliminarily titrated by 0.1 M HCl. Aqueous solutions of picrates (4 ml), which contain excess metal hydroxide, and the solutions of the compounds under study in CH$_2$Cl$_2$ (4 ml) were stirred for 60 min at ~20°C and kept for 90 min for phase separation. Initial concentrations of ligand in organic phase and metal hydroxide and picrate in aqueous phase corresponded to $[5-7]_0 = 10^{-2}$ mol/l, $[MOH]_0 = 10^{-2}$ mol/l, and $[HPic]_0 = 5.0 \times 10^{-2}$ mol/l, respectively. Optical densities of aqueous phase prior to and after extraction ($A$ and $A_0$, respectively) were determined according to UV spectroscopy on a Perkin Elmer Lambda 35 device at 355 nm Extraction percentage ($\%E$) was calculated according to the following relationship: $\%E = [(A_0 - A)/A_0] \times 100$.

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**Scheme 1.** Possible pathways of the synthesis of distally substituted thiacalix-crowns.
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because terminal OH and Br groups located on the different sides of 1,3-alternate give unique possibility to construct sophisticated structures capable of acting as multifunctional devices, for example, sensor systems.

Macrocyclization of distal derivatives has several features. We established the first example of intramolecular crosslinking of distal hydroxyl groups of thiacalix[4]arene by diethylene glycol under Mitsunobu protocol. Usually, unsubstituted thiacalix[4]arene 3 gives bis-thiacalix[4]arene 10 whereas 1,2-crosslinked product 11 is formed with calix[4]arene in analogous reaction (Scheme 4).[22]

To explain such behavior the formation of betaine intermediate 12 in 1,3-alternate stereoisomeric form has been suggested[24] (Figure 3). In this case, intramolecular crosslinking is more preferential compared to intermolecular interaction due to the steric effects, which are caused by the presence of tert-butyl groups preventing the approach of the second calixarene molecule. At the same time, the reaction with the second glycol molecule should proceed substantially easier and leads to the formation of open-chain podands 8, 9.

It is well known the yield of macrocyclization products depends on several factors. The main of them is the special

Figure 3. Possible structure of betaine intermediate 12.

Scheme 2. Synthesis of dibromoalkoxythiacalixarenes 4 by Mitsunobu reaction.

Scheme 3. Reaction of dibromoalkoxythiacalixarenes 4 with oligoethylene glycols.

and energetical complementarity of the reacting molecules. In our case, the effectiveness of the crown ether fragment formation should depend on the glycol flexibility (number of oxyethyl fragments in glycols) and thermodynamic stability of the cyclic system formed.

Analysis of Table 1 indicates that the reaction under study is extremely sensitive to the number of oxyethyl fragments in glycols. In the case of triethylene glycol, the formation of only cyclic products was observed in rather good yield (ca. 60%) and open-chain products are not observed in the reaction mixture. Involvement in the reaction of shorter or longer glycols leads to the formation of mixture of crown ether and open-chain products. So, triethylene glycol is optimal reagent for macrocyclization of distal substituted thiacalix[4]arenes.

To optimize the conditions of synthesis, an effect of temperature and reaction time on the yields of cyclic and open-chain products was estimated on the example of the reaction of dibromopropanoic derivative 4b with diethylene glycol (Table 1). The increase of temperature up to 80°C leads to decrease of the yields of the both products. It can be caused by competitive reaction of C-Br bond and triphenylphosphine being in excess with phosphonium salts formation. Reaction time increasing (from 2 to 48 hours) gives rise to increase the amount of podand in reaction mixture. It can be explained that investigated reaction is an equilibrium and gradually the more thermodynamically stable open-chain product becomes dominant. Thus, macrocyclization is kinetically controlled process, while the formation of open-chain products proceeds under thermodynamic control. Therefore, factors, which increase the rate of reaction, will provide macrocyclization. In particular, large excess of glycol, as well as triphenylphosphinediethyl azodicarboxylate (TPP/DEAD) increases the yields of thiahalixcrowns yield (Table 1).

Structure of compounds 5a, b and 8a, b was established on the basis of homo- and heteronuclear correlation NMR experiments (1D/2D DEPT, COSY, HSQC, and HMBC). Conclusions on the spatial structure are based on the estimations of NOE (1D DPPFGNOE),[25] 1H NMR spectra of the products correspond to the structure with high symmetry, that is, cone or 1,3-alternate stereoisomeric forms. However, the presence NOE between protons of methylene and tert-butyl groups and aromatic protons of thiacalixarene cycle (Figure 4) indicates unambiguously the formation of 1,3-alternate stereoisomers.

Complexation Ability of Monocrown-Thiacalixarenes

To evaluate the complexation ability of the monocrown-thiacalix[4]arenes towards alkali metal cations, the liquid extraction of their picrates in a water-dichloromethane system was performed. The results obtained are given in Table 2.

One can see thiacalix-monocrowns 5 and 6 did not demonstrate substantial binding efficiency and selectivity of alkali metal cations. It is obviously that crown ether cavity of these macrocycles is not suitable for the incorporation of any alkali metal cations. It seems that cavity size is too small for effective binding of these ions. In the case of monocrowns 7a, b formed by tetraethylene glycol the drastic changes were observed. They demonstrate not only large extraction ability towards alkali metal cations but also good selectivity relatively potassium and rubidium cations. For this reason, it was interesting to determine the effect of the nature of lateral substituents on binding properties of crown ether fragment in the compounds studied. It is well known that calixarenes are allosteric systems, where structural (including conformational) changes of macrocyclic cavity from one side may lead to the drastic changes in another one. This feature should be taken into account upon the use of these compounds as sensors on a solid surface. Immobilization on surface can cause the conformational changes in the macrocycle that can lead to the change or even loss of receptor properties.

To estimate this effect the extraction ability of some thiacalixcrown with different lateral substituents was compared. For comparison, compounds 13 and 14 bearing methyl and propyl substituents were chosen; their extraction degrees of alkali metal cations were determined earlier[18] (with an exception of sodium cation) under the same experimental conditions. It was established (Figure 5) that in a row of methyl - propyl - bromoethyl - bromopropyl, despite the changes in the sizes of substituents, no considerable changes in extraction ability were observed. Thus, substituents which are at the opposite sides from the macrocycle plane do not affect each other and no substantial changes should be expected upon immobilization of these compounds on surface.

Conclusions

Thus, novel o-bromoalkoxy-thiacalix[4]arenes 5-7 with crown ether fragments and open-chain podands 8, 9 in 1,3-alternate stereoisomeric form were synthesized under Mitsu-nobu protocol. The formation of open-chain derivatives 8-9 was not known earlier in the chemistry of calixarenes. For

Figure 4. NOE (arrows) in compounds 5a, b and 8a, b

Table 2. Extraction percentage (E, %) of alkali metal cations by monocrowns 5-7.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Cations</th>
<th>Li</th>
<th>Na</th>
<th>K</th>
<th>Rb</th>
<th>Cs</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td></td>
<td>4.9</td>
<td>7.9</td>
<td>9.1</td>
<td>7.7</td>
<td>5.6</td>
</tr>
<tr>
<td>5b</td>
<td></td>
<td>9.2</td>
<td>8.6</td>
<td>3.8</td>
<td>0</td>
<td>14.4</td>
</tr>
<tr>
<td>6a</td>
<td></td>
<td>3.6</td>
<td>0.2</td>
<td>1.1</td>
<td>6.4</td>
<td>8</td>
</tr>
<tr>
<td>6b</td>
<td></td>
<td>2.6</td>
<td>0</td>
<td>0</td>
<td>4.2</td>
<td>8</td>
</tr>
<tr>
<td>7a</td>
<td></td>
<td>0.7</td>
<td>2.9</td>
<td>53.5</td>
<td>51.4</td>
<td>22.6</td>
</tr>
<tr>
<td>7b</td>
<td></td>
<td>11.2</td>
<td>0</td>
<td>49.8</td>
<td>44.9</td>
<td>23.2</td>
</tr>
</tbody>
</table>
Figure 5. Alkali metal picrate extraction by monocrowns 7, 13, and 14.

the first time the intramolecular crosslinking of 1,3-hydroxyl groups of distally substituted thiacalix[4]arenes by the short spacer of diethylene glycol was observed. It was shown that the yields of cyclic 5-7 and open-chain products 8,9 substantially depend on the reaction conditions (temperature, time and reagents ratio). Triethylene glycol is optimal reagent for macrocyclization of distally substituted thiacalix[4]arenes. Involvement in the reaction of shorter or longer glycols leads to the formation of mixture of crown ether and open-chain products.

It was shown by the two-phase extraction method that cavity of monocrowns-5 has the highest binding ability to rubidium and potassium cations. Monocrown ethers with the smaller cavity size did not demonstrate any high selectivity and efficiency of alkali metal cations extraction.

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References


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