

# Thiacalixarenes—A New Class of Synthetic Receptors

E. A. Shokova and V. V. Kovalev

Lomonosov Moscow State University, Vorob'evy gory, Moscow, 119992 Russia

Received May 29, 2001

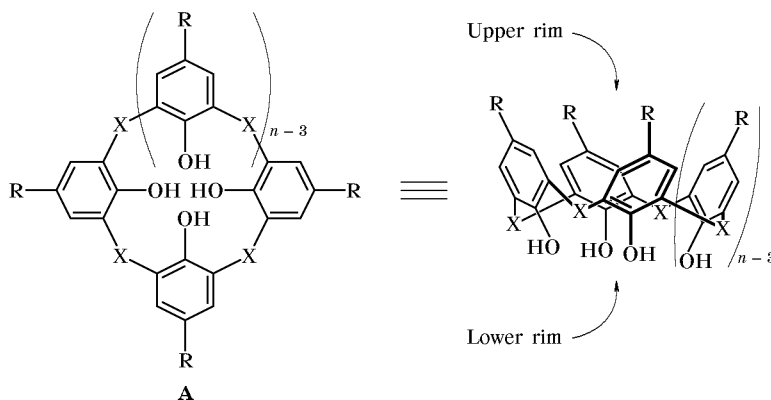
**Abstract**—The review summarizes and analyzes published data on the synthesis, modification, and complexing properties of sulfur-bridged analogs of calixarenes, which constitute a new class of metacyclophanes.

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## 1. INTRODUCTION

Since 1870s the organic chemistry was replenished with a new, very rapidly developing field of study which was called *supramolecular chemistry* [1]. This term was introduced by J.-M. Lehn in order to describe the chemistry of organized entities of the highest complexity (supramolecules) which are formed via association of two or more chemical species brought together via intermolecular forces

(noncovalent interactions). The structure and properties of supramolecules differ from those of their components (or subunits); therefore, development of supramolecular chemistry implies creation of unusual molecules possessing new exciting properties [2]. The design of supramolecules includes two principal processes, molecular recognition and self-assembly. Molecular recognition is a process where some host (or receptor) molecules selectively bind other molecules (guest or substrate) to give a well-structured



X = CH<sub>2</sub>, S; n = 4–8.

system through intermolecular forces. Creation of new molecular receptors is one of the most important problems in organic chemistry.

In terms of the above stated, very promising are calix[*n*]arenes **A** ( $X = \text{CH}_2$ ,  $n = 4, 6, 8$ ). The chemistry of calixarenes extensively develops during the last two decades [3–6]. Advantageously, calixarene molecules possess a hydrophobic aromatic cavity and there exists the possibility for modification of the upper and lower rims through introduction of appropriate functional groups. Therefore, there are wide prospects in using such compounds as selective complexing agents and carrier compounds, as well as for simulation of the main functions of biochemical processes, specifically molecular recognition, membrane transfer, and enzymatic catalysis. Calixarenes are often referred to as the third generation of host molecules [7] and macrocycles with almost unlimited potential [6]. The ease of the synthesis and modification of calixarenes sets them apart from such host compounds as crown ethers and cyclodextrins.

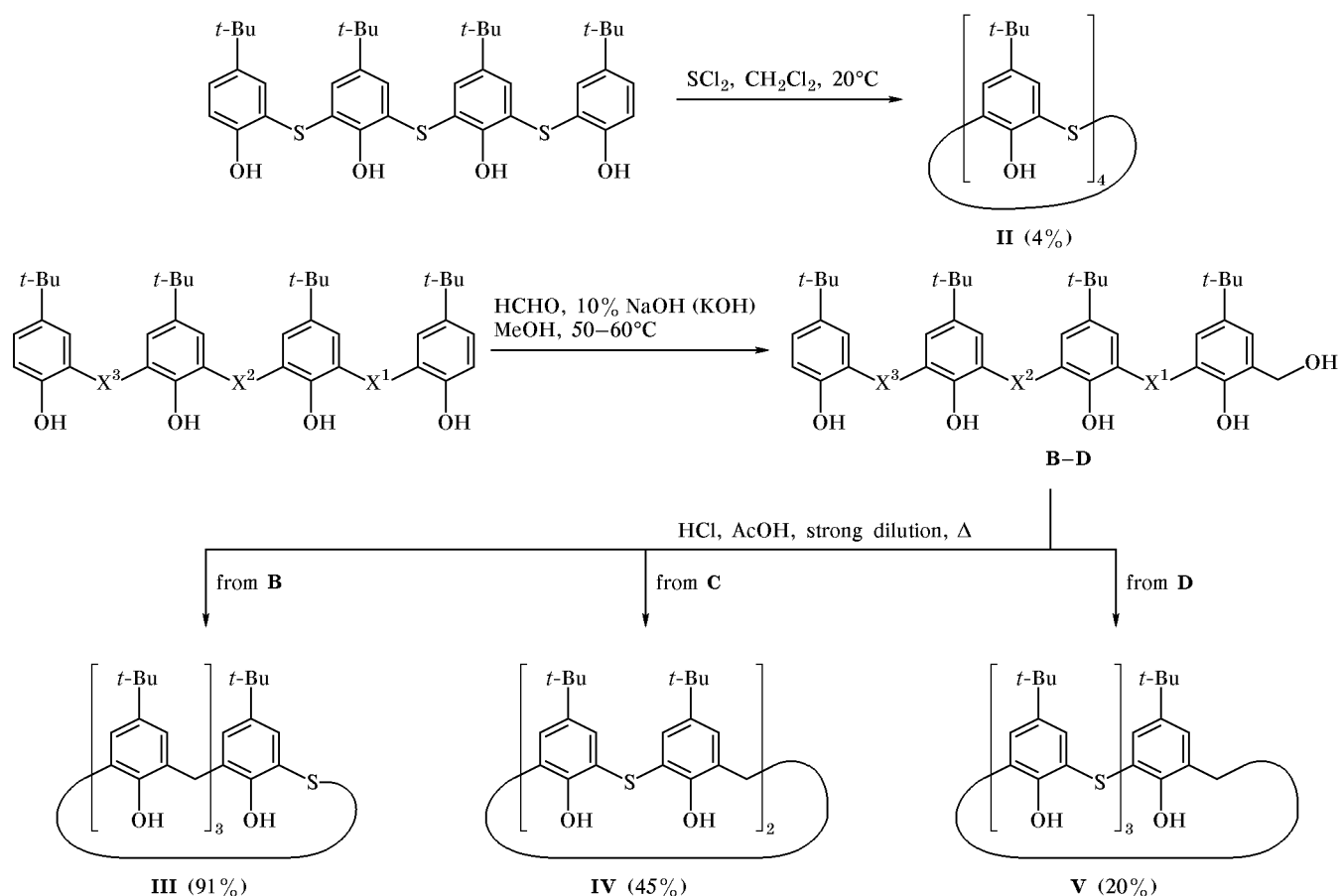
In the last 5 years, publications have appeared on a new family of calixarenes, thiacalixarenes **A**, in which the methylene bridges between the aromatic fragments are replaced by sulfur atoms ( $X = \text{S}$ ,  $n = 4, 5, 6$ ) [8, 9]. The C–S bonds (1.77 Å) [10] are longer than C–C (1.54 Å) [11]; therefore, the calixarene cavity becomes larger; the sulfide bridges are not only additional centers for coordination but also the sites of further functionalization. Undoubtedly, these features should strongly affect the receptor properties of thiacalixarenes.

The goal of the present review is to collect, systematize, and analyze published data on the synthesis, possible modifications, and receptor properties of calixarenes.

## 2. SYNTHESIS OF THIACALIXARENES

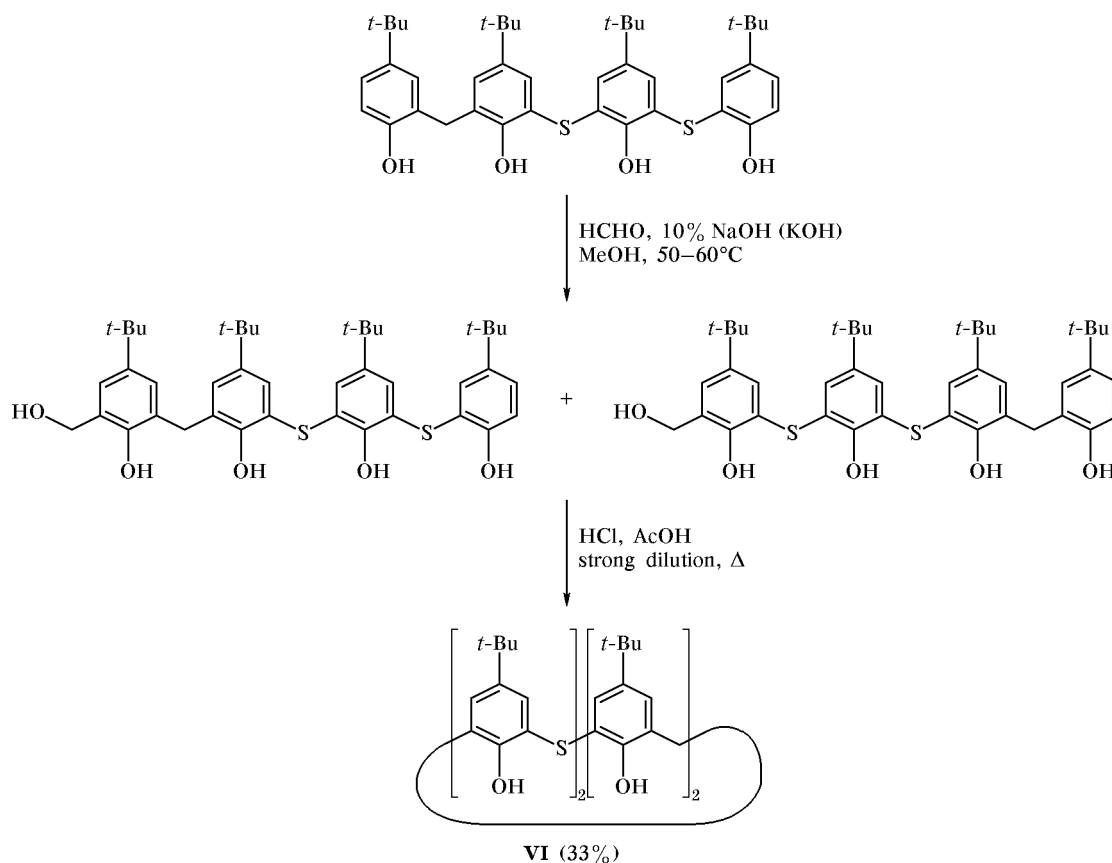
In 1993, Sone *et al.* [12] were the first to report on the synthesis of a new kind of calixarenes, analogs of *p*-*tert*-butylcalix[4]arene (**I**), in which one to four

Scheme 1.



**B**,  $X^1 = X^3 = \text{CH}_2$ ,  $X^2 = \text{S}$  (21%); **C**,  $X^1 = X^3 = \text{S}$ ,  $X^2 = \text{CH}_2$  (48%); **D**,  $X^1 = X^2 = X^3 = \text{S}$  (44%).

Scheme 2.

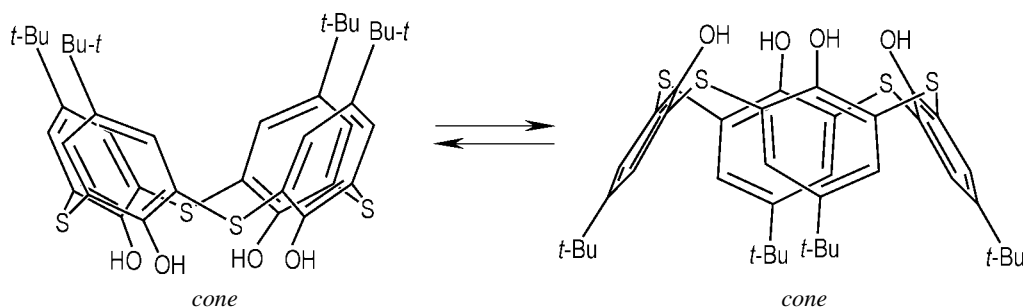


methylene bridges were replaced by sulfide moieties (compounds **II–VI**). The results of this study were published in 1997 [13]. Thiacalix[4]arenes **II–VI** were synthesized by acid cyclization of the corresponding acyclic tetramers (Schemes 1, 2).

The initial sulfur-bridged analogs of *p*-*tert*-butylphenol–formaldehyde oligomers were prepared from *p*-*tert*-butylphenol by a multistep procedure [14], and the yield of final thiacalixarene was often very poor, which strongly limited the preparative potential of this method.

Examination of the IR spectra of compounds **II–VI** [13] indicated formation of circular hydrogen bonds which are responsible to a considerable extent for their existence in the *cone* conformation, as in the case of classical *p*-*tert*-butylcalix[4]arene (**I**). Replacement of the methylene bridges by sulfide makes the hydrogen bonds weaker, presumably due to increased size of the macrocyclic ring. In the IR spectra of thiacalixarenes **II–VI** the OH vibration band appears in the region 3170–3300  $\text{cm}^{-1}$ , whereas the corresponding band in the spectrum of **I** is located at 3160  $\text{cm}^{-1}$ .

Scheme 3.



According to the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of thiacalixarenes **II–VI** in  $\text{CDCl}_3$ , the neighboring benzene rings are oriented *syn* and there exists conformational inversion *cone–cone* (Scheme 3). Comparison of the coalescence temperatures for compound **II** ( $T_c$  17°C) and classical calixarene **I** ( $T_c$  58°C) [13] suggests greater conformational lability of the former.

In 1997, Kumagai *et al.* [15] proposed a convenient one-step procedure for the synthesis of *p-tert*-butylthiacalix[4]arene **II** by heating of a mixture of *p-tert*-butylphenol, sulfur, and sodium hydroxide in tetraethylene glycol dimethyl ether at 230°C. The yield of **II** was 54%. The reaction was accompanied by formation of a complex mixture of sulfur-containing phenol oligomers and *p-tert*-butylthiacalix[5]- and -[6]arenes **VII** and **VIII** as by-products (Scheme 4). The yields of the latter were not given, and only their spectral parameters were reported. Apart from NaOH, lithium, potassium, and cesium hydroxides were tried as catalysts in the synthesis of compound **II** [15, 16]. The best results were obtained with NaOH. In the presence of LiOH, the yield of **II** was 28%, and the reactions with KOH and CsOH resulted in formation of complex mixtures containing a lot of phenol condensation products and almost no thiacalixarene **II**. Later on, thiacalix[6]arene **VIII** was isolated in 0.8% yield from the reaction mixture obtained in the presence of CsOH [17]. According to the authors [17], the predominant formation of compound **II** (rather than **VII** or **VIII**) indicates its greater thermodynamic stability and/or template effect of  $\text{Na}^+$  ions in the stabilization of intermediate or the product [15–17]. *p*-(1,1,3,3-Tetramethylbutyl)phenol was also brought into an analogous reaction with sulfur and alkali [16];

the yield of the corresponding *p*-(1,1,3,3-tetramethylbutyl)thiacalix[4]arene (**IX**) was 14% (Scheme 4). Thus thiacalixarene **II** is now almost the only preparatively accessible compound of this series.

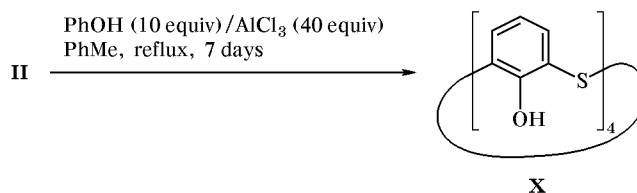
### 3. FUNCTIONALIZATION OF THIALICALIXARENES

New thiacalixarene-based synthetic receptors can be obtained by introduction of appropriate functional groups. Such modification may involve the upper and lower rims of the molecule, as well as the bridging sulfur atoms.

#### 3.1. Upper-Rim Modification

In 1998, Akdas *et al.* [18] effected *de-tert*-butylation of thiacalixarene **II** to obtain 51% of thiacalix[4]arene (**X**). The reaction was carried out by prolonged heating of compound **II** in boiling toluene in the presence of  $\text{AlCl}_3$  and phenol (Scheme 5).

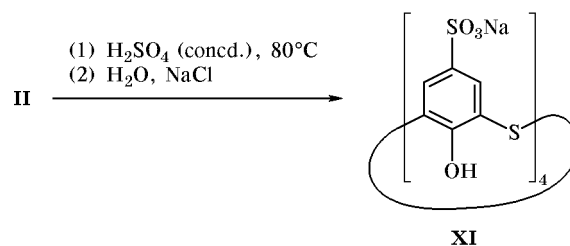
Scheme 5.



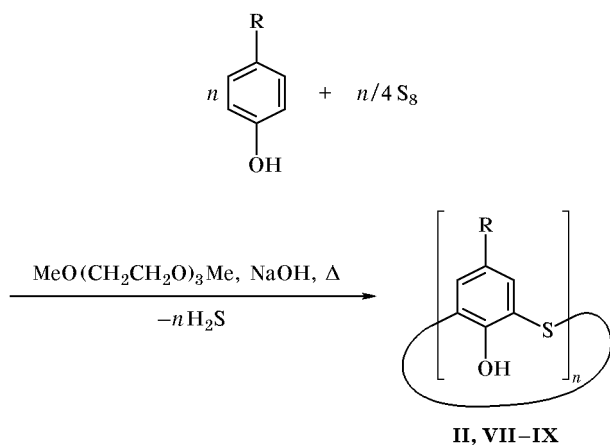
X-Ray diffraction study of a single crystal of compound **X** [9, 18] showed that its molecules exist in the *cone* conformation with a distance of 2.64 Å between the neighboring oxygen atoms, which indicates formation of intramolecular hydrogen bonds. Molecules of **X** in crystal give rise to three-dimensional units via self-inclusion; these units are stabilized by edge-to-face interactions between the aromatic rings [18].

Direct sulfonation of thiacalixarene **II** [19] by the procedure developed for calixarenes [20] gave water-soluble tetrasulfonate **XI** in 63% yield (Scheme 6).

Scheme 6.



Scheme 4.



**II**, R = *t*-Bu,  $n = 4$ ; **VII**, R = *t*-Bu,  $n = 5$ ; **VIII**, R = *t*-Bu,  $n = 6$ ; **IX**, R =  $\text{CMe}_2\text{CH}_2\text{CMe}_2\text{CH}_3$ ,  $n = 4$ .

As far as we know, the above two reactions conclude the data on the upper-rim modification of thiacalixarenes.

### 3.2. Lower-Rim Modification

Exhaustive alkylation of the lower-rim hydroxy groups in thiacalixarene **II** was accomplished by heating compound **II** with methyl iodide in a boiling THF–DMF mixture (1:9) in the presence of NaH [21]. As a result, 73% of tetramethyl ether **XII** was obtained. When the reaction was performed in boiling acetone in the presence of  $K_2CO_3$  [10, 22], the yield of **XII** was raised to 91%. Lhoták *et al.* [10] studied the effect of alkali metal carbonates on the yield of tetrapropyl ether **XIII** in acetone. In the presence of  $Cs_2CO_3$ ,  $K_2CO_3$ , and  $Na_2CO_3$ , the yield of **XIII** was 70, 65, and 0%, respectively. The alkylation in acetonitrile with potassium carbonate as a base afforded 50% of compound **XIII**. The reaction is general: by reaction of thiacalixarenes **II** and **X** with various alkylating agents the corresponding tetraethers **XII–XX** were obtained in 45–92% yield (Scheme 7).

According to the  $^1H$  NMR data, compounds **XIII–XV**, **XIX**, and **XX** exist at  $-80$  to  $100^\circ C$  as a single conformer, 1,3-*alternate* [10]. The authors assumed that the formation of only one conformer of the tetraalkyl derivative is explained in terms of the size of the alkyl groups which are insufficiently bulky to restrict rotation of the benzene rings; on the other hand, the 1,3-*alternate* conformation is the most stable from the

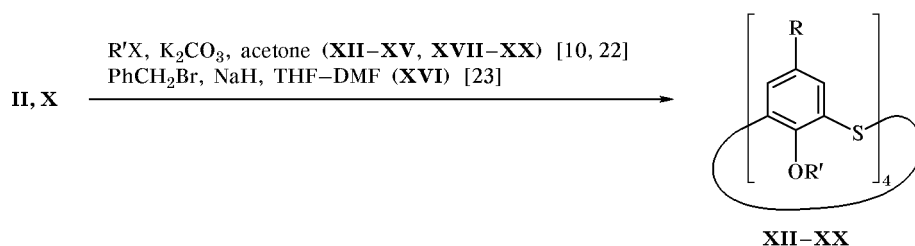
thermodynamic viewpoint.  $^1H$  NOE Diff experiment with ether **XIV** revealed interaction between  $CH_2$  protons of the alkyl groups and aromatic protons, which confirms the 1,3-*alternate* structure in  $CDCl_3$ .

Using  $^1H$  and  $^{13}C$  NMR spectroscopy, Lang *et al.* [24] found that tetraethyl ether **XVIII** in  $CDCl_3$  at  $30^\circ C$  exists as an equilibrium mixture of three conformers: *partial cone* (*paco*), 1,3-*alternate* (1,3-*alt*), and *cone* at a ratio of 56:26:17 (Scheme 8). The corresponding equilibrium constants are  $K_{ap} = 2.2$  and  $K_{pc} = 0.30$ . The existence of such an equilibrium indicates greater conformational lability of tetraethyl ether **XVIII** as compared to *p*-H- and *p*-*tert*-butylcalix[4]arene tetraethyl ethers for which only *paco* conformers were found at room temperature [25, 26].

X-Ray analysis of single crystals of compounds **XIII**, **XIV**, and **XVIII** [10, 21] showed that all these ethers in crystal occur as 1,3-*alt* conformers. It should be noted that orientation of the oppositely located phenolic fragments considerably deviates from coplanar, in contrast to the 1,3-*alt* conformer of classical calix[4]arene. The diameter of the internal cavity in thiacalixarene molecule is appreciably larger than in the corresponding calix[4]arene. The distances between the two distal and two proximal sulfur atoms are 7.8 and 5.5 Å, respectively; the distances between the corresponding  $CH_2$  groups in the 1,3-*alt* conformer of calix[4]arene are 7.1 and 5.0 Å [27].

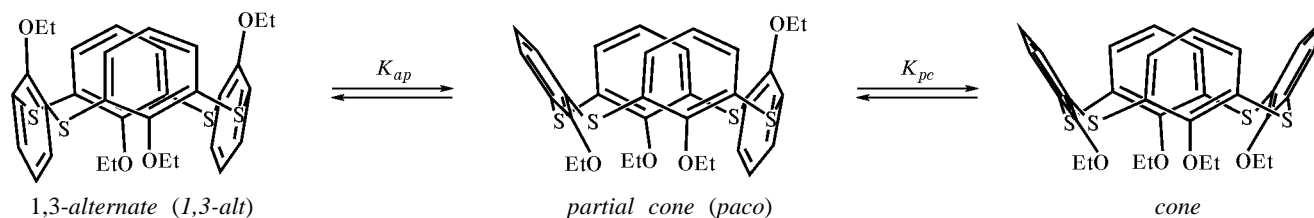
Attempts to effect alkylation of thiacalixarene **II** under the conditions typical of alkylation of calixarene

Scheme 7.



**XII**, R = *t*-Bu, R' = Me; **XIII**, R = *t*-Bu, R' = Pr; **XIV**, R = *t*-Bu, R' = Et; **XV**, R = *t*-Bu, R' = Bu; **XVI**, R = *t*-Bu, R' =  $CH_2Ph$ ; **XVII**, R = H, R' = Me; **XVIII**, R = H, R' = Et; **XIX**, R = H, R' = Pr; **XX**, R = H, R' = Bu.

Scheme 8.



**Table 1.** Reaction of thiacalixarene **II** with ethyl bromoacetate

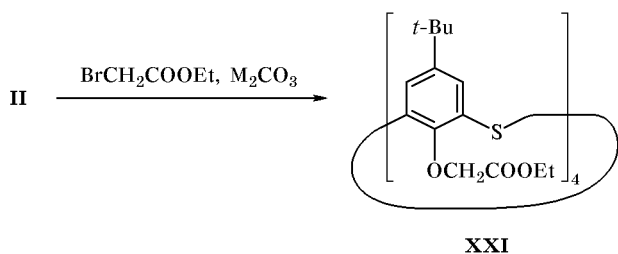
Base	Solvent	Temperature, °C	Time, h	Yield, %	Conformer fractions, %		
					<i>cone</i>	<i>paco</i>	1,3- <i>alt</i>
Li <sub>2</sub> CO <sub>3</sub> <sup>a</sup>	DMF	60	34	0	0	0	0
Na <sub>2</sub> CO <sub>3</sub>	DMF	60	16	81	26	65	9
K <sub>2</sub> CO <sub>3</sub>	DMF	60	6	95	13	63	24
Cs <sub>2</sub> CO <sub>3</sub>	DMF	60	2	85	6	34	60
Li <sub>2</sub> CO <sub>3</sub> <sup>a</sup>	Acetone	<sup>b</sup>	46	0	0	0	0
Na <sub>2</sub> CO <sub>3</sub>	Acetone	<sup>b</sup>	36	85	91	9	0
K <sub>2</sub> CO <sub>3</sub>	Acetone	<sup>b</sup>	28	95	24	61	15
Cs <sub>2</sub> CO <sub>3</sub>	Acetone	<sup>b</sup>	4	96	3	16	81

<sup>a</sup> A mixture (~1:1) of di- tri-*O*-ethoxycarbonylmethyl derivatives was obtained in ~40% yield.

<sup>b</sup> Under reflux.

**I** (DMF, NaH, excess PrI) were unsuccessful: after 48 h at room temperature, the initial compound was recovered from the reaction mixture. Heating of the reactants in THF–DMF (5:1) for 5 days under reflux resulted in formation of only trace amounts of alkylation products. The propylation of **II** in DMF at 90°C (24 h) resulted in formation of a complex mixture which contained the initial compound, and tetrapropyl derivative **XIII** was isolated in 18% yield [10]. The reaction of thiacalixarene **II** with benzyl bromide in the presence of NaH in THF–DMF (9:1) gave tetra-benzyl ether **XVI** as a mixture of conformers: *cone* (48%), *paco* (16%), and 1,3-*alt* (4%). The conformers can readily be separated by chromatography [23].

Exhaustive O-alkylation of the hydroxy groups in **II** was accomplished by treatment of the substrate with ethyl bromoacetate in DMF or acetone in the presence of alkali metal carbonates (Scheme 9) [28]. Table 1 contains the overall yields of product **XXI** and its conformational compositions, depending on the reaction conditions.

**Scheme 9.**

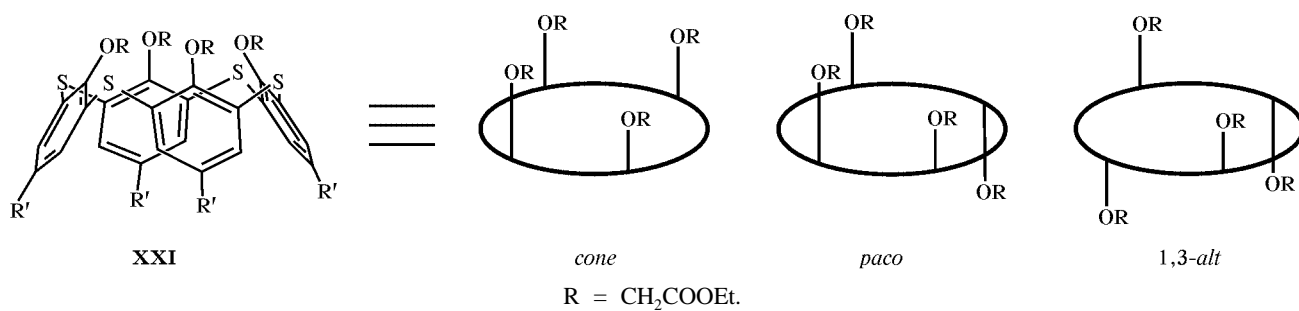
In the presence of Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, and Cs<sub>2</sub>CO<sub>3</sub>, the yield of compound **XXI** is 81–96%, while with Li<sub>2</sub>CO<sub>3</sub> as a base no tetraester **XXI** is formed at all.

The alkylation gives three of the four possible conformers: *cone*, *paco*, and 1,3-*alt* [28] (Scheme 10). Here, the alkali metal cation in the carbonate base strongly affects the conformer ratio. The authors believe that template effect is the main factor controlling the process, as in the O-alkylation of *tert*-butylcalix[4]arene [29]. In DMF with Na<sub>2</sub>CO<sub>3</sub> or K<sub>2</sub>CO<sub>3</sub> as a base, the *paco* conformer prevails in the mixture, whereas Cs<sub>2</sub>CO<sub>3</sub> favors formation of the 1,3-*alt* conformer. The selectivity of the process increases in going to acetone as solvent: in the presence of Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, and Cs<sub>2</sub>CO<sub>3</sub>, derivative **XXI** was isolated as *cone*, *paco*, and 1,3-*alt* conformers, respectively, in 77, 58, and 78% yield. A probable reason for the increased template effect in acetone is tighter coordination of the metal cation in the intermediates shown in Fig. 1 [28].

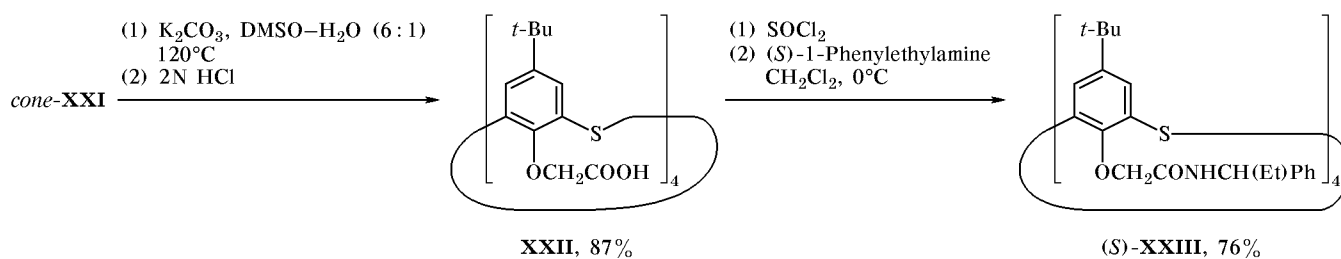
The syntheses described in [28] were reproduced, and three conformers of **XXI** were isolated: *cone*, *paco*, and 1,3-*alt*; their structure was unambiguously proved by X-ray analysis of single crystals [9, 30]. Hydrolysis of tetraester **XXI** with alcoholic alkali gave the corresponding acid **XXII** [31], the conformation of the initial ester being retained: *cone*-**XXII** was obtained from *cone*-**XXI**, and 1,3-*alt*-**XXII**, from 1,3-*alt*-**XXI**. These data suggest that the CH<sub>2</sub>COOH group is sufficiently large to hamper rotation of the benzene ring through the thiacalixarene cavity.

Thiacalixarene **XXI** was used as starting compound in the synthesis of *p-tret*-butylthiacalix[4]arene with a chiral substituent on the lower rim, (*S*)-**XXIII** [32] (Scheme 11). Lower-rim modification was also performed with thiacalixarene **X** having no substituents in the *para*-positions of the benzene rings [33] (Scheme 12). The reactions were carried out in the

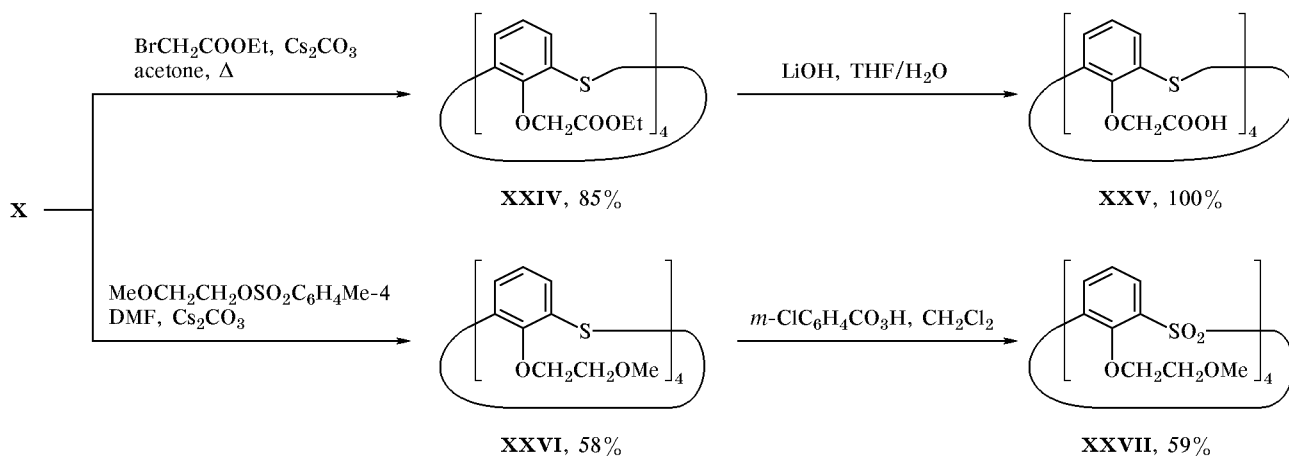
Scheme 10.



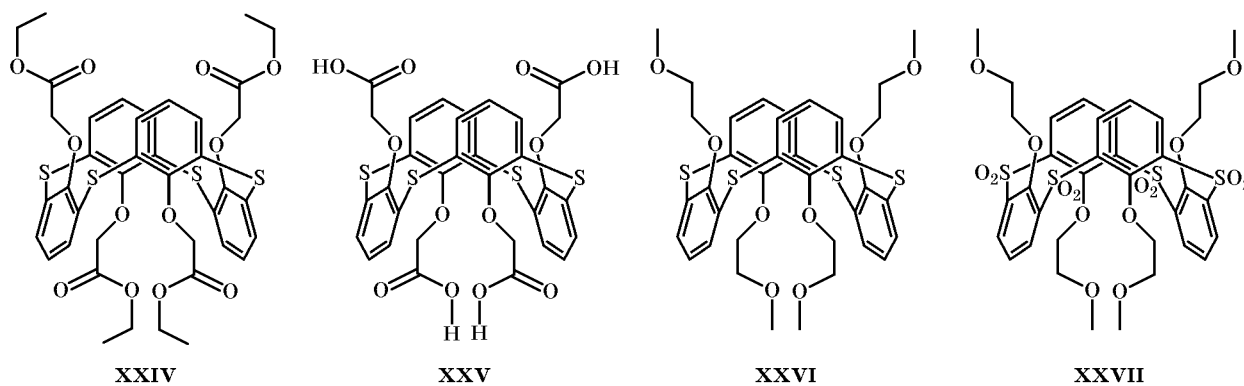
Scheme 11.

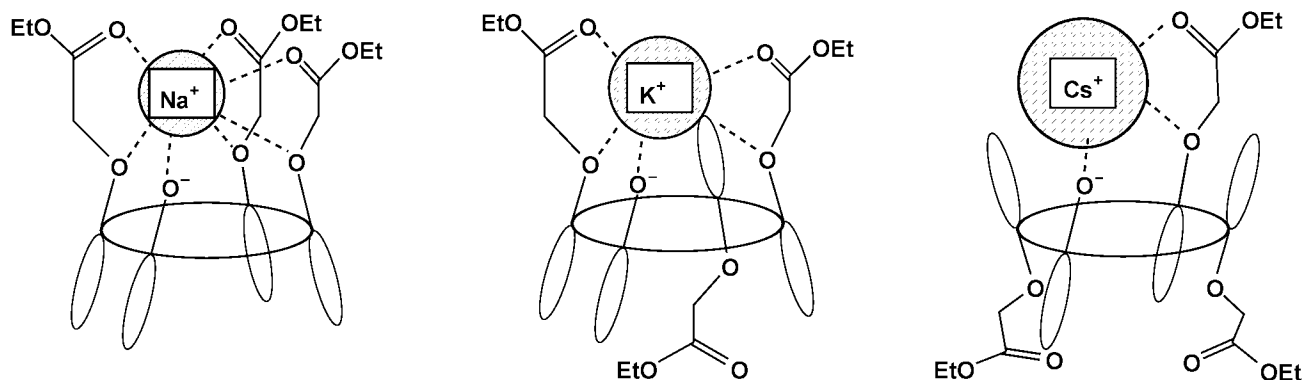


Scheme 12.



Scheme 13.



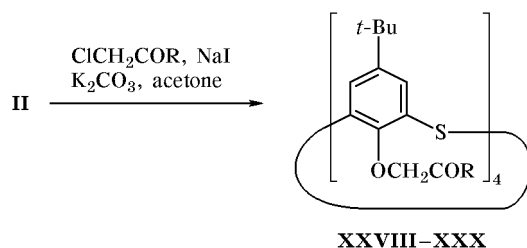


**Fig. 1.** Possible modes of metal ion coordination at tri-*O*-alkyl-substituted intermediates, leading to formation of ester **XXI** as *cone*, *paco*, and 1,3-*alt* conformers.

presence of  $\text{Cs}_2\text{CO}_3$ , and the substituting groups were sufficiently large to ensure formation of compounds **XXIV–XXVII** as 1,3-*alt* conformers (Scheme 13). Their structure was unambiguously proved by the X-ray diffraction data. Crystal lattices of compounds **XXIV**, **XXVI**, and **XXVII** contain no solvent molecules, while a unit cell of tetraacid **XXV** includes two crystallographically different calixarene molecules, two molecules of water, and one methanol molecule (the single crystal was obtained from a methanol–water mixture).

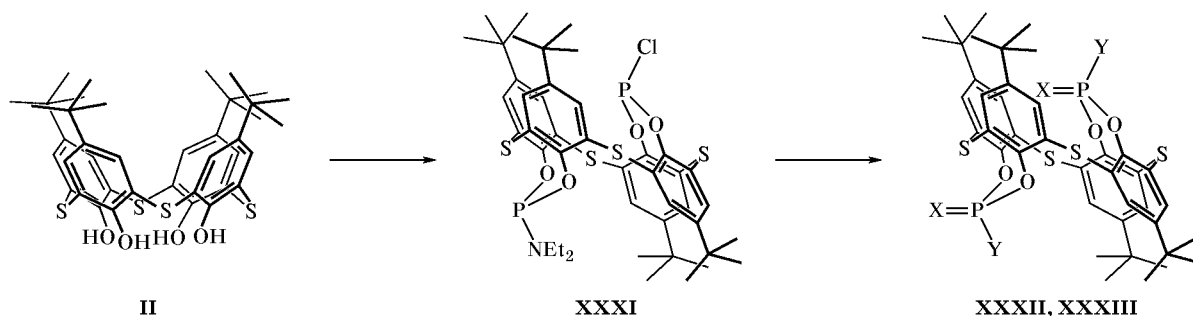
Thiacalixarene **II** was treated with chloromethyl ketones to obtain compounds **XXVIII** and **XXIX** having carbonyl-containing groups on the lower rim [34] (Scheme 14). The reactions were carried out in acetone in the presence of NaI and  $\text{K}_2\text{CO}_3$ . Tetra-*O*-carbamoylmethyl calixarene **XXX** was synthesized by reaction of compound **II** with  $\alpha$ -chloro-*N,N*-diethylacetamide under analogous conditions [34]. In all cases, only one conformer was formed. Its structure as 1,3-*alt* was determined by X-ray analysis of a single crystal.

**Scheme 14.**



**XXVIII**, R = Me (yield 53%); **XXIX**, R = Ph (15%); **XXX**, R =  $\text{NEt}_2$  (41%).

**Scheme 15.**



**XXXII**, X = lone electron pair, Y =  $\text{NEt}_2$ ; **XXXIII**, X = O, Y = Cl.



Antipin *et al.* [35] reported on the lower-rim phosphorylation of thiacalixarene **II**. The substrate was treated with  $\text{PCl}_3$  in toluene in the presence of triethylamine to obtain cyclic P(III) ester **XXXI** which, on attempted isolation, decomposed to give initial thiacalixarene **II** and unidentified products. Thus the phosphorylation product turned out to be less stable to hydrolysis than its analog derived from calixarene **I** [36]; the authors explained its hydrolytic instability by P–S interaction. Addition of diethylamine to the reaction mixture containing compound **XXXI** leads to formation of 68% of the corresponding cyclic phosphoramidite **XXXII** [37] (Scheme 15). When the reaction of **II** with phosphorus(III) chloride was carried out in *p*-bromotoluene in the absence of a base, a 2:1 complex of chlorophosphate **XXXIII** with *p*-bromotoluene was obtained in 46% yield. Its formation implies fast oxidation of primary phosphorylation product **XXXI** on exposure to air.

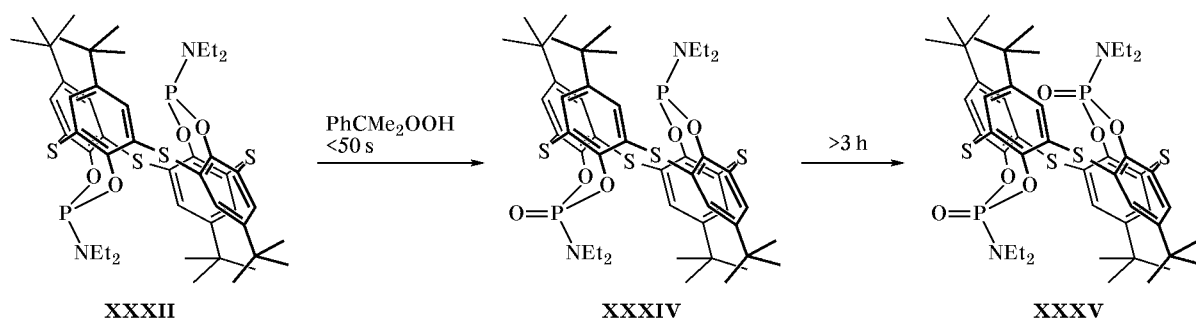
Using  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{31}\text{P}$ , and  $^{15}\text{N}$  NMR spectroscopy, diamide **XXXII** was found to exist as 1,2-*alt* con-

former having two magnetically nonequivalent phosphorus atoms [37] (phosphorus derivatives of classical calixarene **I** usually have *cone* conformation [38]). Study of the temperature dependence of the  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra of **XXXII** in the range from  $-80$  to  $120^\circ\text{C}$  revealed no conformational transformations.

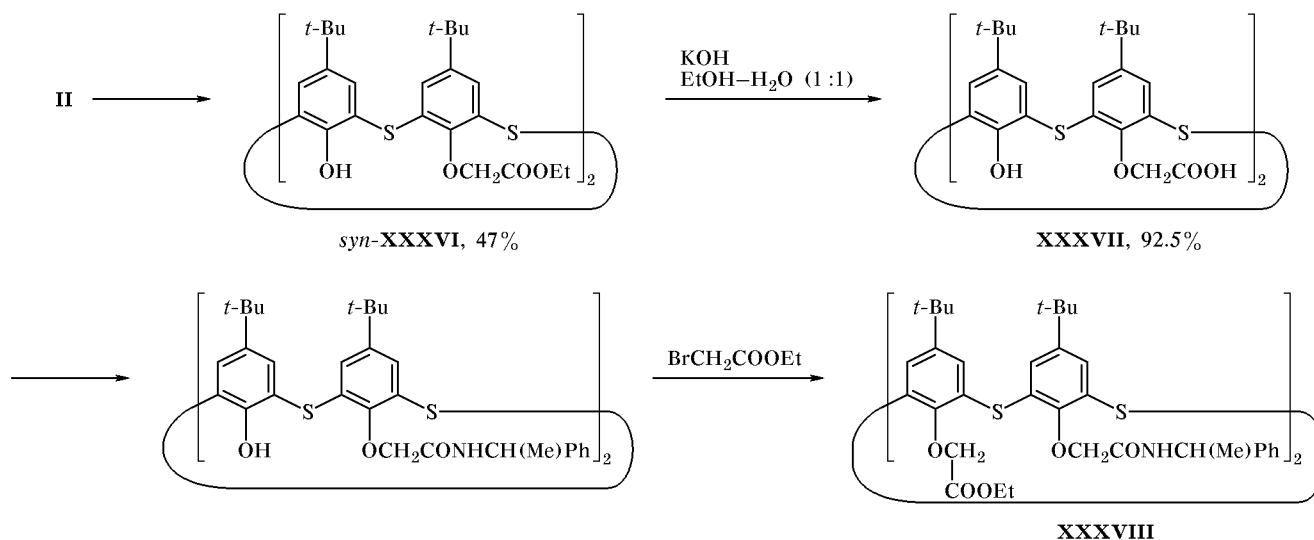
The phosphorus atoms in **XXXII** are characterized by different environments, and they behave differently in the oxidation with  $\alpha,\alpha$ -dimethylbenzyl hydroperoxide [37]: The  $\text{P}^1$  atom (unshielded) undergoes complete oxidation to amidophosphate **XXXIV** within 50 s, whereas oxidation of both phosphorus atoms with formation of bis-amidophosphate **XXXV** requires 3 h (Scheme 16).

The structure of **XXXIII** was studied by spectral methods [35] and X-ray diffraction of a single crystal. The results showed that molecule **XXXIII** in solution, as well as in crystal, adopts a flattened 1,2-*alt* conformation where two opposite benzene rings are almost coplanar to the principal molecular plane which passes through the sulfur atoms. The distance

Scheme 16.



Scheme 17.

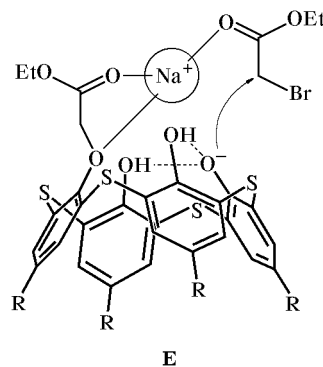


between the chlorine atom and the benzene ring plane is 3.22 Å, which implies  $\pi$ - $p$ -electron interaction between these moieties.

Apart from exhaustive alkylation of the lower-rim hydroxy groups in thiacalix[4]arenes, the possibility of effecting selective O-alkylation was examined [31]. By heating compound **II** with ethyl bromoacetate in the presence of  $\text{Na}_2\text{CO}_3$  (molar reactant ratio 1:2:1) in acetone under reflux, 47% of the corresponding *syn*-di-O-alkyl derivative **XXXVI** was obtained. The ester and hydroxy groups in molecule **XXXVI** are located at the same side of the plane passing through the sulfur atoms. The *syn*-arrangement of the ester groups was confirmed by further modification of compound **XXXVI** (Scheme 17). The authors noted [31] (with reference to unpublished results) that *syn*-**XXXVIII** was obtained as a result of such transformations. Under the conditions of synthesis of compound **XXXVI**, calixarene **I** also gives rise to the corresponding distal *syn*-diester [39, 40]; this means that the nature of the bridging group ( $\text{CH}_2$  or S) in calixarene does not affect the dialkylation process.

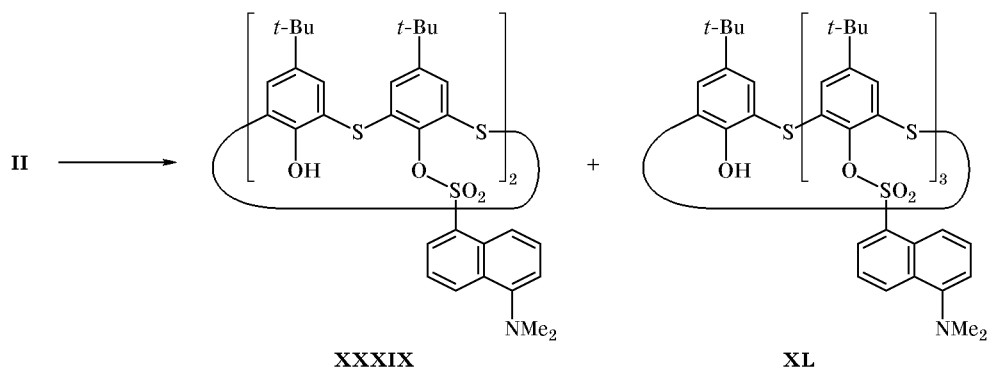
Selective formation of *syn*-diester **XXXVI** may be explained as follows: coordination of the hydroxy and phenoxide oxygen atoms to  $\text{Na}^+$  ion in the primary monoalkylated product strongly restricts conformational mobility of the molecule; as a result, sodium

carbonate as a weak base is capable of abstracting a proton only from the distal phenolic hydroxy group to give the most stable anion (from the steric and electronic viewpoints) which is stabilized by two contiguous hydrogen bonds (intermediate **E**) [31].

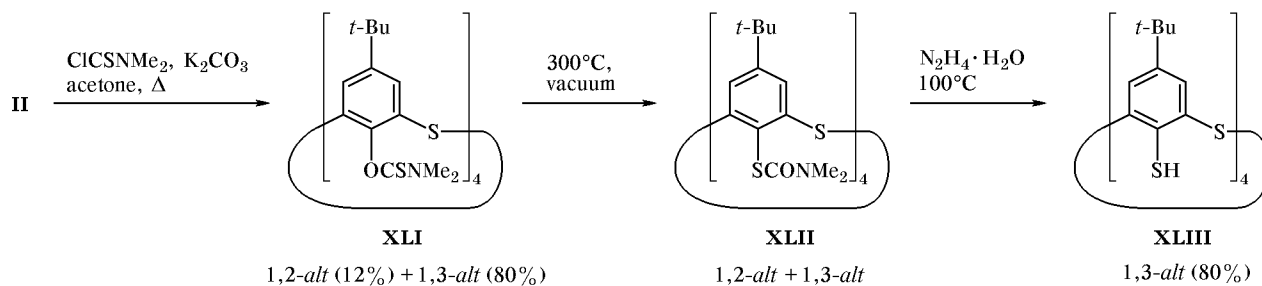


Narita *et al.* [41] reported that the reaction of thiacalixarene **II** with 5-dimethylamino-1-naphthalene-sulfonyl chloride (dansyl chloride) in the presence of NaH gives a mixture of four compounds, the major products being di- and tridansyl derivatives **XXXIX** and **XL**, respectively (Scheme 18). Neither reaction conditions nor product yields were given. *p*-*tert*-Butyl-tetramercaptotetrathiacalix[4]arene (**XLIII**) having eight sulfur atoms was synthesized from compound **II**

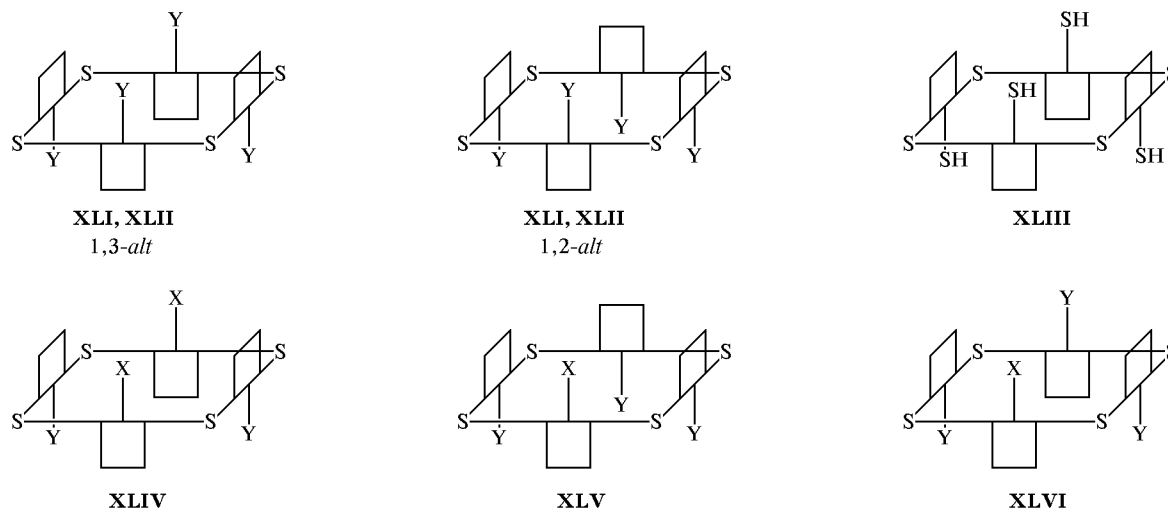
Scheme 18.



Scheme 19.

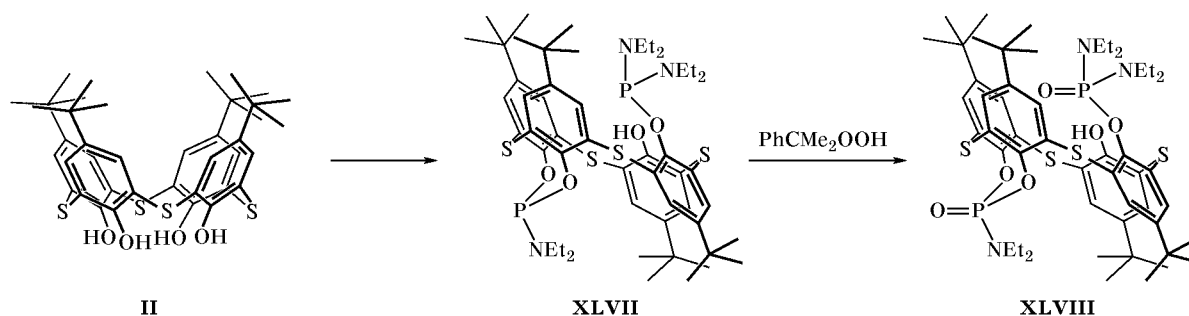


Scheme 20.



**XLI, XLIV–XLVI**, Y = OC(S)NMe<sub>2</sub>; **XLII**, Y = SC(O)NMe<sub>2</sub>; **XLIV–XLVI**, X = OH.

Scheme 21.



via transformation of the hydroxy groups into SH [42] (Scheme 19). The structure of 1,2-*alt*-**XLI** was established by X-ray analysis, and of 1,3-*alt*-**XLI**, by two-dimensional NMR spectroscopy. However, no specific data were given. The X-ray diffraction data for compound **XLIII** unambiguously indicate that it exists in crystal as 1,3-*alt* conformer, in which the opposite aromatic rings are almost coplanar and the average C–SH distances are equal to 1.78 and 1.76 Å [42].

The reaction of thiacalixarene **II** with dimethyl-(thiocarbamoyl) chloride is strongly influenced by the nature of alkali metal carbonate used as a base: in the presence of Li<sub>2</sub>CO<sub>3</sub>, 30% of disubstituted derivative **XLIV** and 5% of trisubstituted compound **XLV** are formed; sodium carbonate gives rise to 30% of **XLIV** and 3% of **XLVI**. Tetrasubstituted derivative **XLI** is formed in the presence of K<sub>2</sub>CO<sub>3</sub> and Cs<sub>2</sub>CO<sub>3</sub>: 12% of the product has 1,2-*alt* conformation, and 80% is 1,3-*alt* conformer. Scheme 20 shows graphical representations of molecules **XLI–XLVI**.

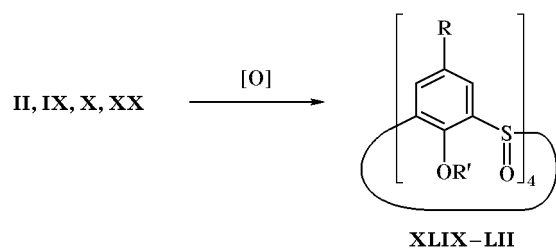
Weber *et al.* [37] demonstrated the possibility for selective lower-rim phosphorylation of thiacalixarene **II**: its reaction with P(NEt<sub>2</sub>)<sub>3</sub> in toluene gave 45% of unsymmetrical phosphorus-containing thiacalixarene **XLVII** which was completely oxidized in one minute to phosphorus(V) amide **XLVIII** by treatment with  $\alpha,\alpha$ -dimethylbenzyl hydroperoxide. The bridging sulfur atoms were not involved. According to the <sup>1</sup>H, <sup>13</sup>C, <sup>31</sup>P, and <sup>15</sup>N NMR data, molecule **XLVII** has a 1,2-*alt* conformation (Scheme 21).

### 3.3. Oxidation of Sulfide Bridges

Mild oxidation of thiacalixarenes **II** and **IX** with NaBO<sub>3</sub>·4H<sub>2</sub>O (molar ratio 1:4.3) in a mixture of chloroform with acetic acid gives tetrasulfoxides **XLIX** and **L** in ~31 and ~35% yield, respectively [43, 44]. Under analogous conditions, 82% of sulfinyl derivative **LI** was obtained from tetrabenzyl ether *cone*-**XX** [23] (Scheme 22). The benzyl protection in

**LI** can be removed by heating in boiling acetic acid. Mislin *et al.* [45] reported on the synthesis of two tetrasulfinyl calix[4]arenes **XLIX** and **LII** by oxidation of compounds **II** and **X** with hydrogen peroxide in glacial acetic acid and with *m*-chloroperoxybenzoic acid in methylene chloride. The yields of **XLIX** and **LII** were 28 and 20%, respectively. No reaction conditions were given in [45].

Scheme 22.



**XLIX**, R = *t*-Bu, R' = H; **L**, R = CMe<sub>2</sub>CH<sub>2</sub>CMe<sub>2</sub>CH<sub>3</sub>, R' = H; **LI**, R = *t*-Bu, R' = CH<sub>2</sub>Ph; **LII**, R = R' = H.

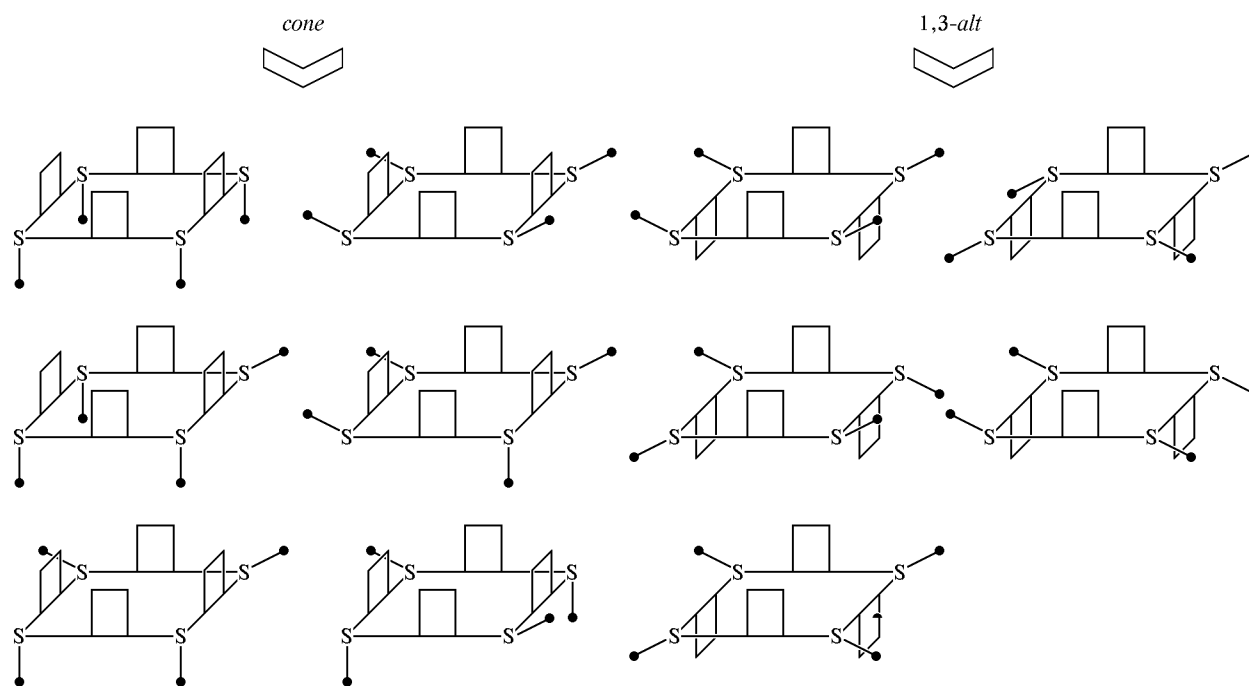
In addition to possible “classical” *cone*, *paco*, and 1,2- and 1,3-*alt* conformations, tetrasulfinylcalix[4]arenes **XLIX** and **LII** give rise to a large number of conformers with different orientations of the oxygen atoms and lone electron pairs on the sulfur atoms [44]. For instance, 6 *cone*, 16 *paco*, 15 1,2-*alt*, and 5 1,3-*alt* conformers are possible (Scheme 23). When sulfoxide groups are located between two *syn*-oriented benzene

rings (*cone*, *paco*, and 1,2-*alt* conformers), the oxygen atoms and lone electron pairs can occupy either equatorial (*e*) or axial (*a*) positions. In the 1,3-*alt* conformer, the oxygen atoms and sulfur lone electron pairs are pseudoequatorial.

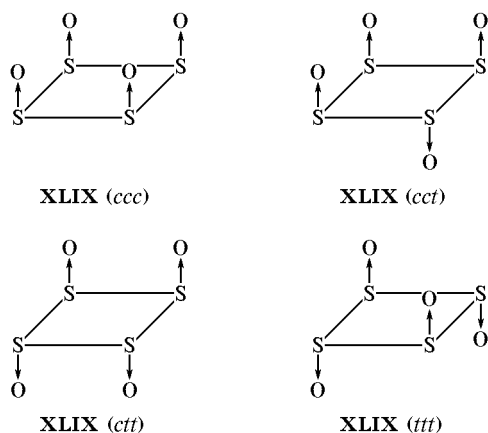
The steric configurations of tetrasulfinyl derivatives **XLIX** and **LII** were determined by X-ray analysis of single crystals [9, 45]. The two compounds in crystal exist as 1,3-*alt* conformers. All sulfoxide oxygen atoms are located above and below the plane formed by the sulfur atoms (*aeae*). This structure is stabilized by four strong hydrogen bonds OH...OS with an average length of 2.65 (**LII**) and 2.67 Å (**XLIX**). The crystal lattices of compounds **XLIX** and **LII** are different. Molecules **LII** gives rise to a 3D structure due to strong stacking interaction with participation of all four aromatic moieties in a unit cell: the distance between the centers of aromatic rings is 3.49 Å. Sulfinyl derivative **XLIX** contains bulky *tert*-butyl groups which make formation of an analogous lattice impossible.

Direct oxidation of thiacalixarenes **II** and **IX** gives only one (of the four possible) stereoisomer of sulfoxides **XLIX** and **L** [43, 44], namely *ttt*-**XLIX** and *ttt*-**L** (Scheme 24). In Scheme 24, “*c*” (*cis*) and “*t*” (*trans*) denote the position of the sulfoxide oxygen atom with respect to the plane passing through the sulfur atoms [23]. Sulfinylcalix[4]arene **XLIX** with *cis,cis,cis* configuration of the sulfoxide groups was

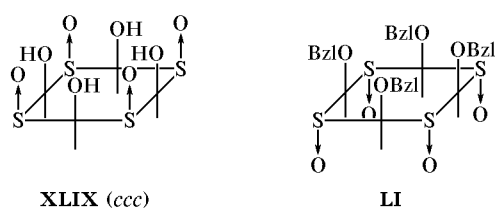
Scheme 23.



Scheme 24.

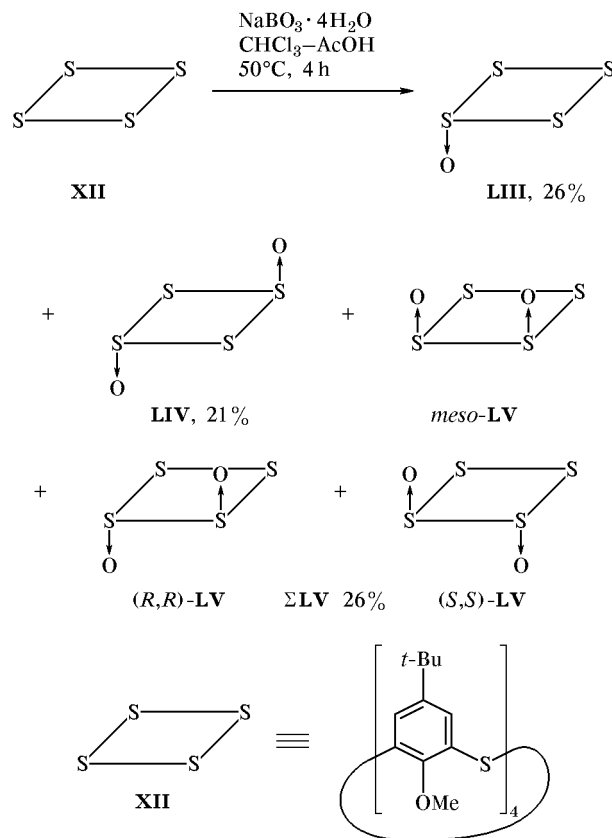


purposefully synthesized by Morohashi *et al.* [23]. Thiacalix[4]arene was preliminarily fixed in the *cone* conformation by benzylation of the hydroxy groups; subsequent oxidation of the bridging sulfur atoms and removal of the benzyl protection gave the target product. Its structure was studied by IR and  $^1\text{H}$  NMR spectroscopy (no single crystal suitable for X-ray analysis was obtained) [23], and the results were compared with those obtained previously for *ttt*-**XLIX** [43]. The authors concluded that the product has a *cone* conformation with the SO groups located *syn* with respect to the phenolic hydroxy groups. According to the X-ray diffraction data for tetra-*O*-benzyl derivative **LI**, the sulfoxide and benzyl groups are arranged *anti*.

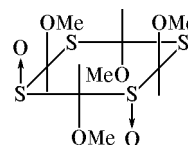


A new approach to chiral thiacalix[4]arenes, which is based on oxidation of two proximal epithio groups to chiral sulfinyl groups in tetramethyl ether **XII** (rather than on introduction of a chiral substituent), was reported in [22] (Scheme 25). The reaction gave a mixture of mono- (**LIII**) and two disulfinyl (**LIV** and **LV**) derivatives which were separated. Using  $^1\text{H}$  NMR spectroscopy, it was found that the distal SO groups in **LIV** are arranged *trans* and that bis-sulfoxide **LV** is a mixture of two enantiomers and *meso* form at a ratio of 1:4. The stereoisomers of **LV** were separated by HPLC using a chiral stationary phase. As a result, both optically pure enantiomers (+)-**LV** and (-)-**LV** were isolated,  $[\alpha]_{\text{D}}^{24} = 49.3^\circ$ .

Scheme 25.

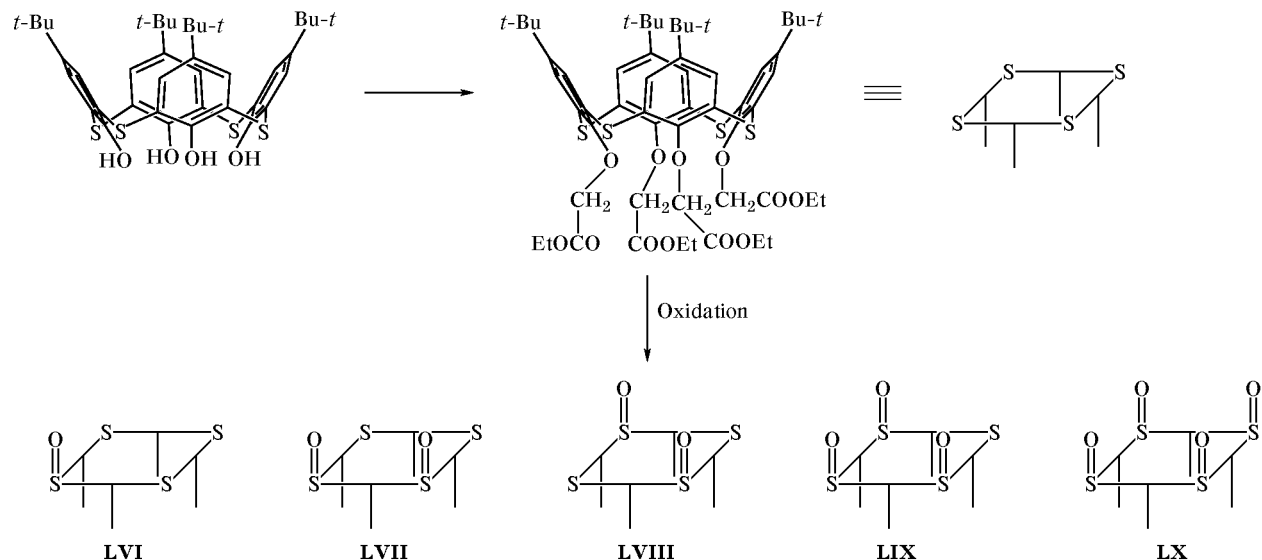


Neither epimerization nor racemization was observed on treatment of (+)-**LV** with 2M hydrochloric acid in CHCl<sub>3</sub> at room temperature. The absolute configuration of (+)-**LV** was determined by X-ray analysis. The compound was found to have the (*S,S*)-1,3-*alt* structure with *trans*-oriented neighboring SO groups.

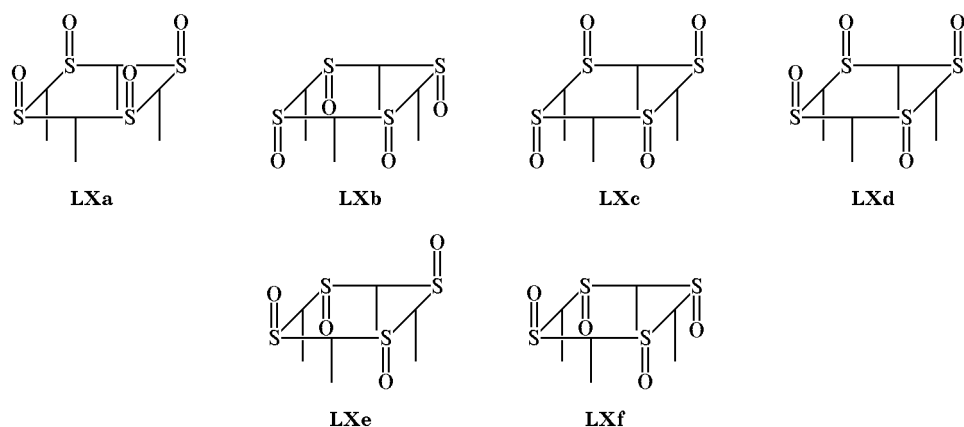


Regio- and stereoselective oxidation of tetra-*O*-ethoxycarbonylmethyl thiacalix[4]arene derivative **XXI** was reported in [46]. Tetrasulfinyl compound **LX** was formed in almost quantitative yield (93% of the isolated product) when hydrogen peroxide in acetic acid or 100% nitric acid in methylene chloride was used as oxidant at room temperature. In the synthesis of partially oxidized derivatives **LVI**–**LIX**, mixtures of products were always formed, which required chromatographic separation. Monosulfoxide **XVI** was obtained in the maximal yield (54%) with the use of 5 equiv of pyridinium chlorochromate in

Scheme 26.



Scheme 27.

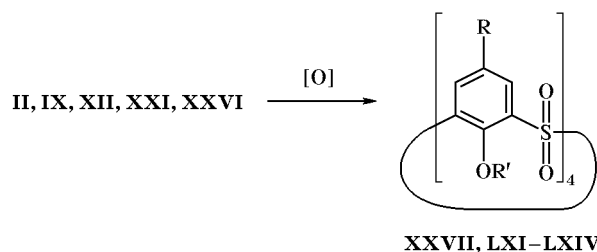


$\text{CH}_2\text{Cl}_2$ . The reaction with 15 equiv of the oxidant gave a mixture of mono- and two bis-sulfoxides, from which 28% of **LVII** and 24% of **LVIII** were isolated. Tris-sulfoxide **LIX** was formed in 26% yield by oxidation with 100%  $\text{HNO}_3$  in  $\text{CH}_2\text{Cl}_2$ -AcOH at room temperature (Scheme 26). Tetrasulfinyl derivative **LX** in the *cone* conformation gives rise to six diastereoisomers **LXa**-**LXf** differing by relative orientations of the sulfoxide oxygen atoms and lower-rim substituents (Scheme 27).

Thiacalixarenes **II** and **IX** having free hydroxy groups on the lower rim and tetraethers **XII** and **XXVI** were oxidized to the corresponding tetrasulfones [21, 43, 44]. The oxidation of **II** and **IX** was effected with 10 equiv of  $\text{Na}_3\text{BO}_3 \cdot 4\text{H}_2\text{O}$  in a mixture of chloroform and acetic acid [43, 44] or with 30% hydrogen peroxide in glacial acetic acid [21, 43].

Compounds **XII**, **XXI**, and **XXVI** were oxidized with *m*-chloroperoxybenzoic acid in chloroform or 1,2-dichloroethane [21, 33, 46] (Scheme 28).

Scheme 28.

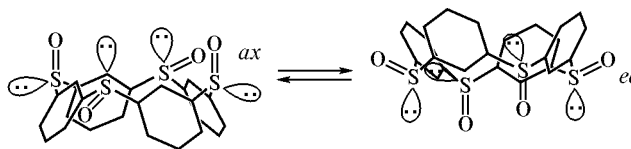


**XXVII**, R = H, R' =  $\text{CH}_2\text{CH}_2\text{OMe}$ , yield 59% [33]; **LXI**, R = *t*-Bu, R' = H, 90% [43], 59% [21]; **LXII**, R =  $\text{CMe}_2\text{CH}_2\text{CMe}_2\text{CH}_3$ , R' = H, 80% [43, 44]; **LXIII**, R = *t*-Bu, R' = Me, 88% [21]; **LXIV**, R = *t*-Bu, R' =  $\text{OCH}_2\text{CO}_2\text{Et}$  [46].

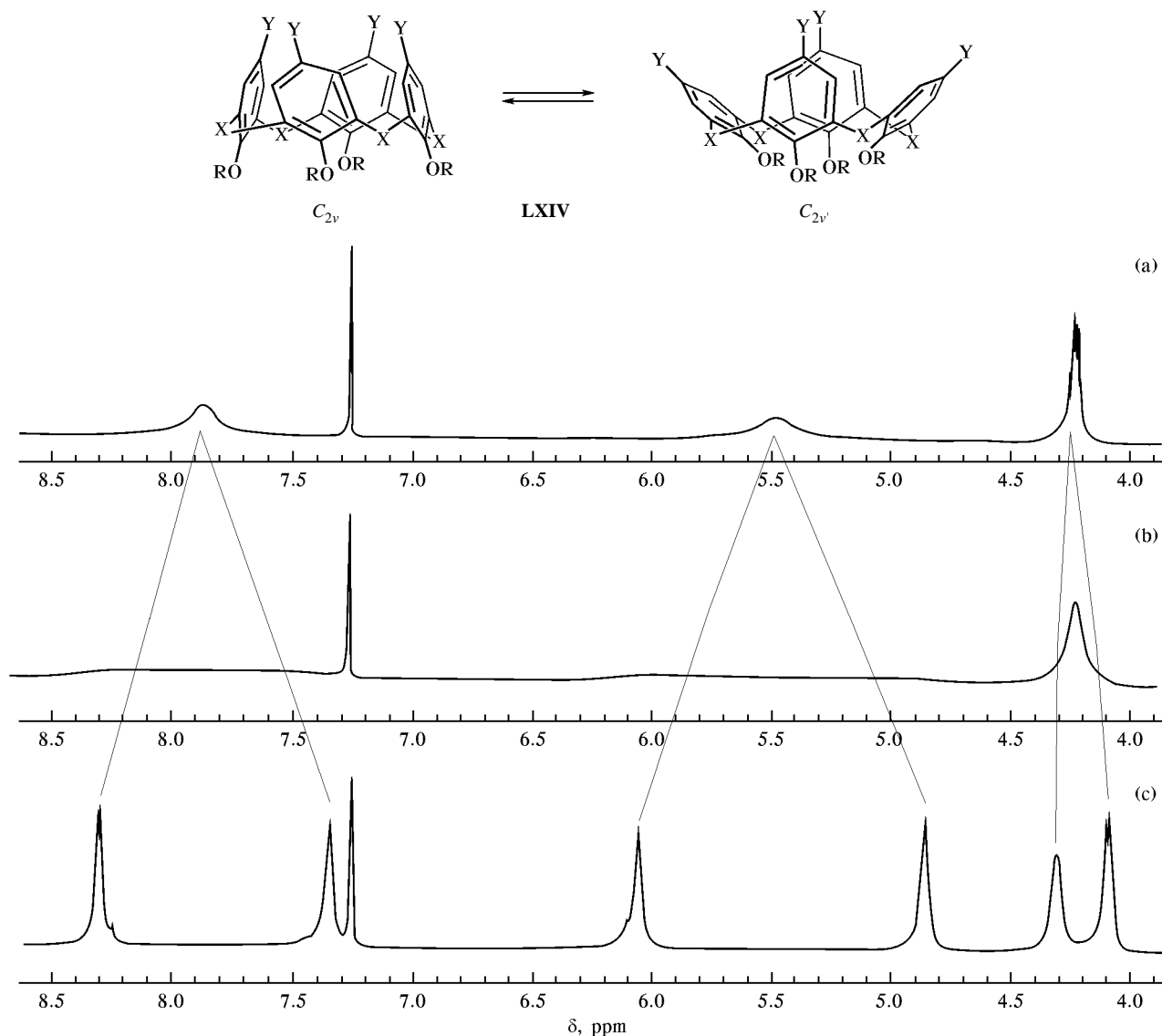
Removal of methyl protection from tetrasulfone **LXIII** by treatment with a large amount of  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  yields 30% of sulfone **LXI** [21]. Study of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of tetrasulfoxide **XLIX** and tetrasulfones **LXI** and **LXII** [43] showed that all these compounds have a *cone* conformation. The chemical shifts of two *ipso*-carbon atoms in **XLIX** suggest axial orientation of one pair of the distal SO groups, while the remaining SO groups are equatorial. On the other hand, the aromatic protons in **XLIX** appear in the  $^1\text{H}$  NMR spectrum as a singlet due to fast inversion of the molecule (Scheme 28).  $^1\text{H}$  NMR study of the structure of tetrasulfone **LXIV** [46] revealed conformational inversion like *pinched cone–pinched cone*

of its molecule (Fig. 2) with a coalescence temperature  $T_c$  of 273 K.

Scheme 28.



According to the X-ray diffraction data [9, 21], tetrasulfone **LXI** and tetramethyl ether **LIII** exist as 1,3-*alt* conformers in which the oxygen atoms on the sulfur are oriented outward. The average C–S bond



**Fig. 2.**  $^1\text{H}$  NMR spectra of tetrasulfone **LXIV** ( $\text{X} = \text{SO}_2$ ,  $\text{Y} = t\text{-Bu}$ ,  $\text{X} = \text{CH}_2\text{COOEt}$ ) at (a) 298 K, (b) 273 K, and (c) 233 K (conformational inversion like *pinched cone–pinched cone*).

length in molecules **LI** and **LXIII** is  $\sim 1.77$  Å, and the average distance between the two contiguous sulfur atoms is  $\sim 5.52$  Å. Intra- and intermolecular hydrogen bonds, involving the hydroxy and sulfonyl groups, give rise to a 3D crystal lattice of compound **LXI**.

#### 4. RECEPTOR PROPERTIES OF THIALICALIXARENES

##### 4.1. Host–Guest Complexes

Even in the first communication on the synthesis of thialicalixarenes [13] it was noted that compounds **II–VI** give host–guest complexes with a number of

organic molecules (Table 2) and that replacement of the methylene bridging groups by sulfide moieties increases the complexing power.

Thialicalixarene **II** was reported [15, 16] to form 1:1 host–guest complexes with chloroform, cyclohexane, methylcyclohexane, 1,4-dioxane, decalin, carbon tetrachloride, benzene, and triethylene glycol dimethyl ether. These complexes do not lose guest molecule on keeping for more than 2 h under reduced pressure (2–4 mm) at room temperature. With 1,2-dichloroethane and acetone, 1:2 and 3:2 complexes are formed, respectively. The structure of host–guest complexes of thialicalixarene **II** with  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ , and

**Table 2.** Crystalline host–guest complexes of thialicalixarenes **II–VI** with organic compounds

Guest	<b>I</b>	<b>II</b>	<b>III</b>	<b>IV</b>	<b>V</b>	<b>VI</b>
Benzene	1:1	2:1	1:1	2:1	2:1	1:1
Toluene	1:1		1:1		<sup>a</sup>	2:1
<i>o</i> -Xylene	1:1	<sup>b</sup>	2:1	<sup>a</sup>	<sup>b</sup>	<sup>a</sup>
Acetone	1:2		2:1	2:1		1:2
Methanol	<sup>c</sup>	<sup>b</sup>	<sup>b</sup>	<sup>b</sup>	<sup>b</sup>	<sup>b</sup>
Dioxane	1:2	1:1	1:1	1:1	1:1	1:1
Methylene chloride	1:1	2:1	2:1	2:1	2:1	1:1
1,2-Dichloroethane	1:1	2:1	2:1	2:1	2:1	1:1
1,2-Dibromoethane	1:1	<sup>b</sup>	2:1	2:1	2:1	1:1

<sup>a</sup> The guest–host ratio was not clear.

<sup>b</sup> No host–guest complex was formed.

<sup>c</sup> The ratio was not determined because of the low solubility of the host compound.

**Table 3.** Composition of host–guest complexes formed by thialicalixarenes **II** and **VIII** and organic compounds

Solvent	<b>II</b> <sup>a</sup>		<b>VIII</b>		Solvent	<b>II</b> <sup>a</sup>		<b>VIII</b>	
	solvent concentration, <sup>b</sup> mol %	H:G <sup>c</sup>	solvent concentration, <sup>b</sup> mol %	H:G <sup>c</sup>		solvent concentration, <sup>b</sup> mol %	H:G <sup>c</sup>	solvent concentration, <sup>b</sup> mol %	H:G <sup>c</sup>
Acetone	41	3:2	46	1:1	Aniline	22	<sup>d</sup>	76	1:3
Chloroform	50 <sup>e</sup>	1:1	58	2:3	1,4-Dioxane	51	1:1	52	1:1
Benzene	53	1:1	52	1:1	Octane	7	<sup>d</sup>	38	2:1
1,2-Dichloroethane	64	1:2	50	1:1	<i>m</i> -Xylene	7	<sup>d</sup>	51	1:1
Toluene	34	2:1	53	1:1	<i>o</i> -Xylene	7	<sup>d</sup>	48	1:1
Ethylbenzene	0	<sup>f</sup>	50	1:1	<i>p</i> -Xylene	6	<sup>d</sup>	66	1:2
Cyclohexane	45	1:1	58	1:1	Decalin	48	1:1	50	1:1

<sup>a</sup> Data of [16].

<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy (400 MHz).

<sup>c</sup> Host–guest ratio.

<sup>d</sup> The host–guest ratio was not clear.

<sup>e</sup> Estimated from the elemental analysis data.

<sup>f</sup> No host–guest complex was formed.



MeOH was studied by the X-ray diffraction method [9, 18]. In all these complexes, the thiacalixarene molecule has a *cone* conformation, and the guest molecule penetrates deep into the host cavity; CH<sub>2</sub>Cl<sub>2</sub> and CHCl<sub>3</sub> molecules, as well as *p*-*tert*-butyl groups in the thiacalixarene molecule, are disordered. The average distance between the two adjacent oxygen atoms is 2.85 Å, which suggests formation of intramolecular hydrogen bonds stabilizing the *cone* conformation (the corresponding distance in classical calixarene **I** is ~2.70 Å [47]). Interesting results were obtained while studying the structure of a 1:2 complex of **II** with 1,2-dichloroethane [16]. Mutual conformational variations of the guest and host molecules were observed upon formation of a stable crystal. Calixarene **II** still retains its *cone* conformation due to hydrogen bonds between the four hydroxy groups. The conformation of the guest molecule in crystal changes from *anti* to *gauche*. Here, host-induced guest deformation is observed instead of usual guest-induced host deformation.

Although thiacalixarene **VIII** having six phenolic fragments was isolated in a negligible yield (0.8%) [17], the authors made an attempt to examine its complexing properties (Table 3). Compound **VIII** was found to possess a stronger complexing ability toward various guest molecules, as compared to thiacalix[4]-arene **II**. According to the X-ray diffraction data, the host molecule in the complex **VIII**-CH<sub>2</sub>Cl<sub>2</sub> adopts a *distorted cone* conformation stabilized by two H-bond rings, each including three phenolic hydroxy groups [17].

Iki *et al.* [19] examined the complex formation properties of water-soluble tetrasulfonate **XI** toward a series of chlorinated hydrocarbons. The ligand turned out to be capable of distinguishing both size and shape of the guest molecule. Compound **XI** gives a 1:2 complex with CH<sub>2</sub>Cl<sub>2</sub> and 1:1 complexes with CHCl<sub>3</sub>, 1,2-dichloroethane, 1,1,2-trichloroethane, and 1,1,2,2-tetrachloroethane, whereas no complexes of **XI** with 1,1,1-trichloroethane and trichloroethylene were obtained.

#### 4.2. Complex Formation with Metal Cations

Tables 4 and 5 contain the results of studying complex formation of thiacalixarenes **II** and **IX** with alkali, alkaline-earth, and transition metal cations by the extraction technique (from aqueous solution to chloroform) [43, 48]. The best results were obtained with transition metals: at pH 8.0 Co<sup>2+</sup>, Ni<sup>2+</sup>, and Zn<sup>2+</sup> ions are extracted almost quantitatively; the most efficient extraction of Cu<sup>2+</sup> ions (99%) was observed

**Table 4.** Extraction (%) of alkali and alkaline-earth metal ions with thiacalixarene **II** at different pH values <sup>a</sup>

pH	Li <sup>+</sup>	Na <sup>+</sup>	K <sup>+</sup>	Rb <sup>+</sup>	Mg <sup>2+</sup>
2.2	18	12	4	8	4
5.5	15	9	32	18	7
8.0	14		25	0	6

<sup>a</sup> At pH 2.2, 6% of Cs<sup>+</sup> ions is extracted; Ca<sup>2+</sup> and Ba<sup>2+</sup> ions are not extracted under the examined conditions.

**Table 5.** Extraction (%) of transition metal ions with calixarene **I** and thiacalixarenes **II** and **IX**<sup>a</sup>

Ligand	pH	Co <sup>2+</sup>	Ni <sup>2+</sup>	Cu <sup>2+</sup>	Zn <sup>2+</sup>
<b>I</b>	8.0	5	1	1	6
	8.0 <sup>b</sup>	10	4	6	23
<b>II</b>	2.2	0	0	3	
	5.5	0	2	50	
	8.0	99	97	69 <sup>c</sup>	99
<b>IX</b>	8.0	99	96	89	99

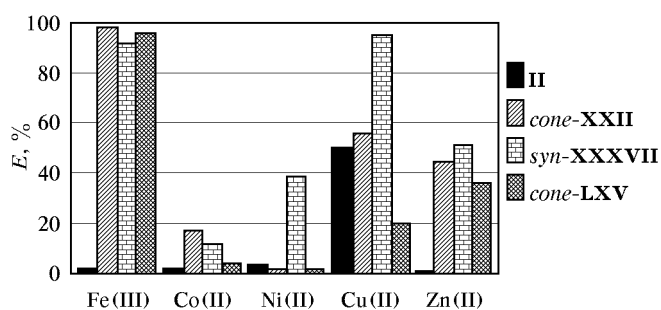
<sup>a</sup> At pH 8.0, 35% of Mn<sup>2+</sup> ions is extracted.

<sup>b</sup> In the presence of pyridine (*c* = 0.01 M).

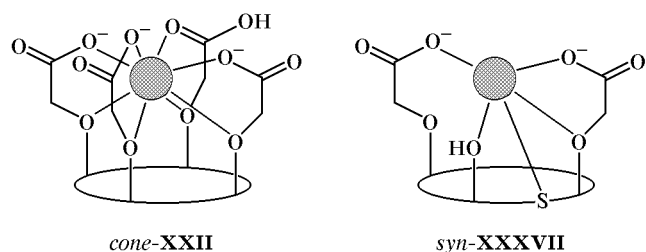
<sup>c</sup> 99% at pH 7.0.

at pH 7.0. The complexes thus formed have a composition of 1:1. <sup>1</sup>H and <sup>13</sup>C NMR study of the Zn<sup>2+</sup> complex showed that the sulfide bridges in thiacalixarene **II** are sufficiently flexible for the molecule to adopt a conformation optimal for coordination of transition metal ions, which is impossible for classical calixarene **I** [48].

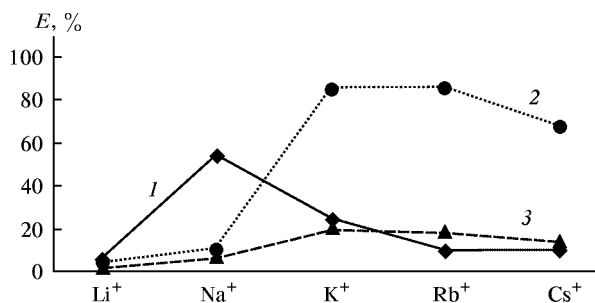
Later on, the same authors examined complex formation of transition metal ions with thiacalixarenes having carboxy groups on the lower rim: tetrakis(carboxymethyl) derivative *cone*-**XXII** and bis(carboxymethyl) derivative *syn*-**XXXVII** [31]. For comparison,



**Fig. 3.** Extraction (%) of transition metal ions with calixarenes **II**, *cone*-**XXII**, *syn*-**XXXVII**, and *cone*-**LXV** at pH 5.5.



**Fig. 4.** A probable scheme of binding of metal ions with thiacalixarenes *cone-XXII* and *syn-XXXVII*.

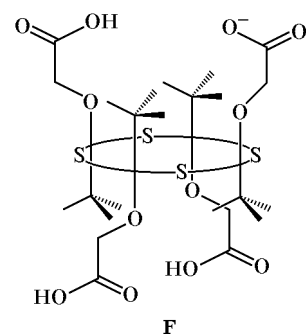


**Fig. 5.** Extraction (%) of alkali metal ions with (1) *cone*, (2) 1,3-*alt*, and (3) *paco* conformers of thiacalixarene **XXI**.

thiacalixarene **II** and tetrakis(carboxymethyl)calixarene *cone-LXV* were studied. The results are shown in Fig. 3. No extraction of transition metal ions with 1,3-*alt-XXII* was observed under the same conditions. It was presumed [31] that four carboxymethyl groups in *cone-XXII* and two carboxymethyl groups and bridging sulfur atom in *syn-XXXVII* are involved in coordination (Fig. 4). The contribution of sulfide bridges increases in going to softer metal ions [49].

A probable reason for the lack of metal ion extraction with 1,3-*alt-XXII* may be steric hindrances created by the *p-tert*-butylphenyl groups which hamper metal coordination at the carboxy groups (see structure **F** below).

The complexing ability of tetra-*O*-ethoxycarbonylmethyl thiacalixarene **XXI** toward alkali metal cations



was studied in [28] by the extraction technique where the resulting metal complexes are transferred to the organic phase as ion pairs with picrate anion. Figure 5 illustrates the efficiency of extraction with *cone*, *paco*, and 1,3-*alt* conformers of thiacalixarene **XXI**. It is seen that *cone-XXI* extracts  $\text{Na}^+$  ions most efficiently, *paco-XXI* prefers  $\text{K}^+$ , and 1,3-*alt-XXI* is effective toward  $\text{Rb}^+$ ,  $\text{K}^+$ , and  $\text{Cs}^+$  ions (in the decreasing order). These data indicate that the size of the cavity formed by peripheric ethoxycarbonylmethyl groups increases in the series: *cone-XXI* < *paco-XXI* < 1,3-*alt-XXI*. The selectivity of *cone-XXI* for alkali metal cations is somewhat higher than the selectivity of the corresponding methylene-bridged calixarene. The composition of the *cone-XXI* complex with  $\text{Na}^+$  was determined as 1:1, and its stability constant was estimated at  $102.85 \text{ mol}^{-1} \text{ l}^{-1}$  (in  $\text{CDCl}_3\text{-CD}_3\text{OD}$ , 1:1, by volume).

The ability of 1,3-*alt* conformers of thiacalixarenes **XXVIII**, **XXIX**, and **XXX** (which have four ketone or four amide groups on the lower rim) to recognize alkali, alkaline-earth, and transition metal cations was studied by extraction of the corresponding picrates from aqueous solution to methylene chloride [34] (Table 6); for comparison, the data for extraction of the same cations with hydroxy-containing thiacalixarenes **II** and **X** are given. Amido derivative **XXX** showed a considerable complexing ability with respect to all the examined metal cations, especially toward

**Table 6.** Extraction (%) of metal ions with thiacalixarenes **II**, **X**, and **XXVIII-XXX** at pH 4.0

Comp. no.	$\text{Li}^+$	$\text{Na}^+$	$\text{K}^+$	$\text{Rb}^+$	$\text{Cs}^+$	$\text{Ca}^{2+}$	$\text{Ba}^{2+}$	$\text{Mg}^{2+}$	$\text{Al}^{3+}$	$\text{Pb}^{2+}$	$\text{Fe}^{3+}$	$\text{Ni}^{2+}$	$\text{Cu}^{2+}$	$\text{Ag}^+$
<b>II</b>	2.8	1.4	2	1	1	2.4	1.6	0.8	1.1	0.4	4.5	0	1.8	6.6
<b>X</b>	0.8	0.7	0.8	0.7	1.4	0.7	0.3	2.7	3.3	3.6	5.5	3.3	3.9	8.3
<b>XXVIII</b>	1.1	1.4	0.6	0.6	0.6	1	0.6	0.9	0	1	2.5	1.4	1.3	2.4
<b>XXIX</b>	1.2	2.8	8.6	8.3	3.2	2.4	2.8	3.1	3.9	3.1	8.2	2.7	3.6	35.3
<b>XXX</b>	22.9	55	80.1	78	56.4	29.8	24.1	39.7	42.8	32.6	50.9	32.7	40.5	95.9

**Table 7.** Extraction (%) of metal ions with calixarenes **IX**, **L**, **LXII**, and **LXVII**<sup>a</sup>

Soft and moderately hard metal ions													
Comp. no.	Mn <sup>2+</sup> pH 8.0	Fe <sup>2+</sup> pH 6.8	Co <sup>2+</sup>	Ni <sup>2+</sup> pH 8.0	Cu <sup>2+</sup>	Zn <sup>2+</sup>	Pd <sup>2+</sup> <sup>b</sup>	Ag <sup>+</sup> pH 5.9	Cd <sup>2+</sup> pH 8.4	Au <sup>3+</sup> <sup>c</sup>	Hg <sup>2+</sup> pH 7.9	Pb <sup>2+</sup> pH 6.3	Bi <sup>3+</sup> pH 8.4
<b>IX</b>	80	37	98	99	91	100	73	99	98	31	100	89	42
<b>L</b>	56	100	99	64	10 <sup>d</sup>	79	92	<sup>e</sup>	14 <sup>d</sup>	38	0	89 <sup>f</sup>	78 <sup>f</sup>
<b>LXII</b>	72 <sup>g</sup>	90 <sup>g</sup>	9	2	4	10	15	<sup>e</sup>	4	12	0	0 <sup>f</sup>	26 <sup>e</sup>
<b>LXVII</b>	6	12	2	0	6	6	14	6	<sup>d</sup>	21	0	3	<sup>d</sup>

Hard metal ions											
Comp. no.	Mg <sup>2+</sup>	Ca <sup>2+</sup>	Sr <sup>2+</sup> pH 9.8	Ba <sup>2+</sup>	Y <sup>3+</sup> pH 6.0	Pr <sup>2+</sup> pH 6.3	Eu <sup>2+</sup>	Ti <sup>4+</sup> pH 2.2	Zr <sup>2+</sup> pH 1.4	Hf <sup>4+</sup>	
<b>IX</b>	0	2	0	0	5	3	0	4	22	0	
<b>L</b>	55	69	10 <sup>d</sup>	9 <sup>d</sup>	98	100	100	99	100	100	
<b>LXII</b>	56	100	95	80	44	100	100	75	99	99	
<b>LXVII</b>	0	6	0	0	9	0	0	3	21	0	

Ions extracted only by calixarene <b>L</b>										
Comp. no.	Be <sup>2+</sup> pH 5.3	Sc <sup>3+</sup> pH 2.8	V <sup>5+</sup>	Nb <sup>5+</sup> pH 4.8	Ta <sup>5+</sup>	Ru <sup>3+</sup> pH 3.3	Al <sup>3+</sup> pH 3.5	Ga <sup>3+</sup> pH 3.0	In <sup>3+</sup> pH 4.9	
<b>IX</b>	0	2	2	13	5	5	8	0	0	
<b>L</b>	100	100	41	85	1	68	100	97	42	
<b>LXII</b>	0	10	5	12	2	0	7	0	5	
<b>LXVII</b>	0	8	0	8	5	3	3	9	<sup>e</sup>	

Ions which are not extracted by calixarenes <b>IX</b> , <b>L</b> , <b>LXII</b> , and <b>LXVII</b>											
Comp. no.	Li <sup>+</sup>	Na <sup>+</sup>	K <sup>+</sup> pH 9.7	Rb <sup>+</sup>	Cs <sup>+</sup>	Cr <sup>3+</sup> pH 5.1	Mo <sup>6+</sup> pH 5.0	Rh <sup>3+</sup> pH 5.9	Pt <sup>2+</sup> pH 9.9	Tl <sup>+</sup> pH 5.7	Sb <sup>3+</sup> pH 9.7
<b>IX</b>	0	1	0	1	7	3	0	2	1	3	3
<b>L</b>	17	23	0	1	12	8	0	9	3	2	0
<b>LXII</b>	18	4	0	0	14	8	0	5	4	2	0
<b>LXVII</b>	0	2	0	0	7	9	0	6	9	0	0

<sup>a</sup> Zero values mean that the extraction efficiency is lower than 0.4%.<sup>b</sup> In a 0.05 M solution of HNO<sub>3</sub>.<sup>c</sup> In a 1.0 M solution of HNO<sub>3</sub>.<sup>d</sup> Metal ions were extracted with a 2 × 10<sup>-3</sup> M solution of calixarene **L**: Cu<sup>2+</sup>, 81% at pH 4.8; Cd<sup>2+</sup>, 44% at pH 8.3; Sr<sup>2+</sup>, 90% at pH 10.6; Ba<sup>2+</sup>, 85% at pH 10.6.<sup>e</sup> The concentration of metal ions in water was not measured because of precipitation of a solid with unknown composition.<sup>f</sup> Tetramethylammonium nitrate was added to the aqueous phase instead of Me<sub>4</sub>NCl.<sup>g</sup> M<sup>2+</sup> ions can be oxidized to M<sup>3+</sup> upon complex formation with calixarene **LXII** with a high extraction efficiency.

**Table 8.** Periodic tables of metal ions extractable ( $E > 30\%$ ) with *p-tert*-octyltetrahiacalix[4]arene (**IX**) and its analogs having SO (**L**) and SO<sub>2</sub> bridges (**LXII**)<sup>a</sup>

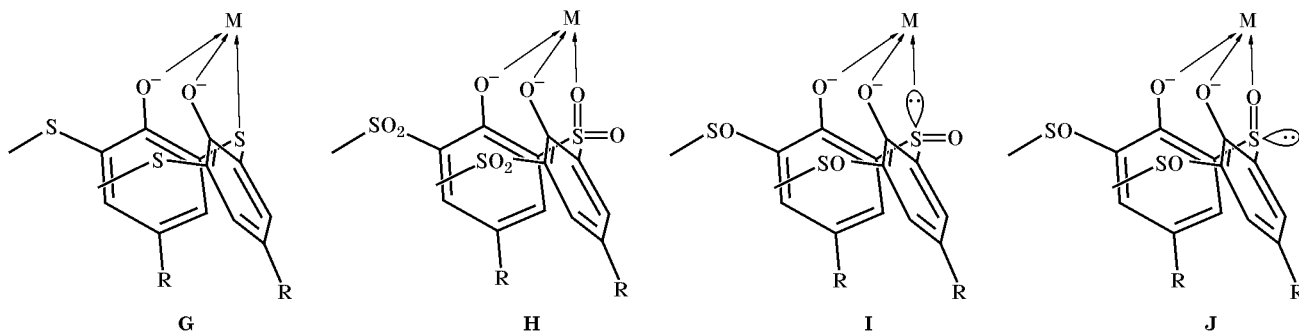
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18															
1			IX																														
2	Li	Be																															
3	Na	Mg																										Al					
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga																				
5	Rb	Sr	Y	Zr	Nb	Mo		Ru	Rh	Pd	Ag	Cd	In		Sb																		
6	Cs	Ba	Ln	Hf	Ta					Pt	Au	Hg	Tl	Pb	Bi																		
7																																	

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18															
1			L																														
2	Li	Be																															
3	Na	Mg																										Al					
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga																				
5	Rb	Sr	Y	Zr	Nb	Mo		Ru	Rh	Pd	Ag	Cd	In		Sb																		
6	Cs	Ba	Ln	Hf	Ta					Pt	Au	Hg	Tl	Pb	Bi																		
7																																	

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18															
1			LXII																														
2	Li	Be																															
3	Na	Mg																										Al					
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga																				
5	Rb	Sr	Y	Zr	Nb	Mo		Ru	Rh	Pd	Ag	Cd	In		Sb																		
6	Cs	Ba	Ln	Hf	Ta					Pt	Au	Hg	Tl	Pb	Bi																		
7																																	

<sup>a</sup> **M** stands for extractable, and **M**, for unextractable metal ions.

Scheme 29.



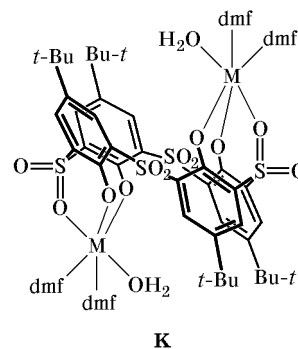
$K^+$ ,  $Rb^+$ , and  $Ag^+$  ions. The corresponding methylene-bridged analog **LXVI** efficiently extracts  $Na^+$ ,  $K^+$ ,  $Ca^{2+}$ , and  $Ba^{2+}$  ions [50]. Probably, this is explained by different conformations of the ligands: the classical calixarene exists in solution as *cone* conformer. Discrepancies in the data on the extraction ability of thiacalixarene **II**, reported in [34, 43, 48], may be due to differences in the experimental conditions.

Systematic study of the complexing properties of thiacalixarenes **II** and **IX** and their sulfinyl (**XLIX**, **L**) and sulfonyl (**LXII**) derivatives toward a wide series of metal cations was performed in 1998–2001 [43, 44]. The results were compared with those obtained for classical calixarenes **I** and **LXVII**. Apart from *p*-*tert*-butylcalixarenes **II** and **XLIX**, *p*-*tert*-octyl derivatives **IX**, **L**, **LXII**, and **LXVII** were examined. The latter are better soluble in organic solvents, which is an important factor in the transfer of metal cations from aqueous phase to chloroform solution. The results of these studies are summarized in Tables 7 and 8.

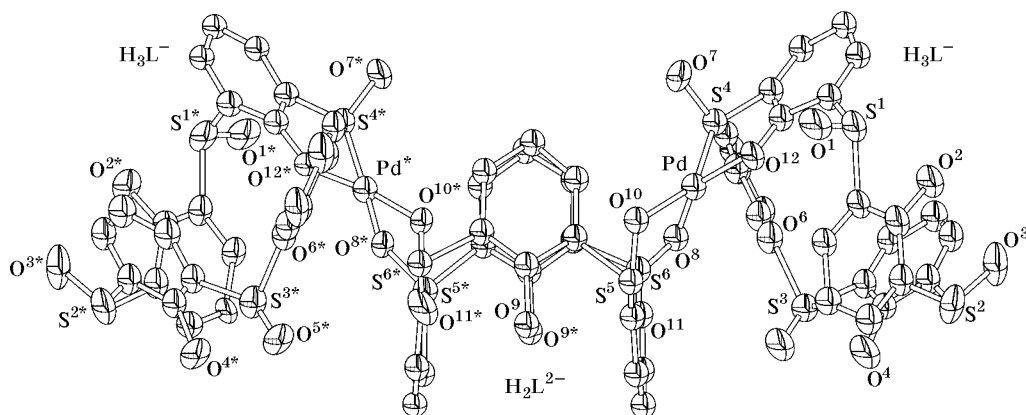
The selectivity of complex formation with metal ions is controlled by the degree of oxidation of the bridging sulfur atoms. This may be explained in terms of the concept of hard and soft acids and bases [49]. The high ability of thiacalixarenes **II** and **IX** to bind transition metal ions [43, 44, 48] is assumed to originate from the presence of sulfide sulfur atoms; lone electron pair on one of these, together with two phenoxide groups, is capable of participating in coordination with metal ion, giving rise to five-membered chelate structure **G** (Scheme 29). In going to sulfonyl derivative **LXII** which lack lone electron pairs on the sulfur atoms, binding properties toward transition metal ions disappear, but a strong affinity for hard alkaline-earth metals and lanthanides is observed, presumably due to participation of the sulfonyl oxygen atom (structure **H** in Scheme 29). In this respect, the behavior of sulfinylcalixarenes **XLIX** and **L** is very interesting. These compounds form complexes with both transition and alkaline-earth metal ions; depend-

ing on the metal, either the sulfur atom (soft metal ions) or the sulfoxide oxygen atom (hard metal ions) is involved in the coordination (structures **I** and **J** in Scheme 29) [49].

In 2001, complexes of sulfinylcalixarene **XLIX** with  $Pd^{2+}$  ions [51] and of sulfonylcalixarene **LXI** with  $Co^{2+}$  and  $Ni^{2+}$  ions [52] were obtained. The structure of these complexes was studied by X-ray analysis of single crystals. The complexes were synthesized in nonaqueous media in the presence of bases:  $Pd^{2+}$  and  $Co^{2+}$  complexes were obtained in the presence of acetate ion, and acetylacetonate ion was used as a base in the synthesis of  $Ni^{2+}$  complex. The structures of the  $Co^{2+}$  and  $Ni^{2+}$  complexes with calixarene **LXI** are identical to that shown below (structure **K**): each contains two metal ions, ligand tetra-anion  $L^{4-}$  in the 1,2-*alt* conformation, two coordination water molecules, and four molecules of DMF, which was used as solvent for recrystallization [52].



The mode of metal coordination in the above complexes is similar to that typical of tridentate dinucleating ligands: two phenoxide oxygen atoms and sulfonyl oxygen atom are involved. Such coordination mode was previously unknown for complexes with  $Co^{2+}$  and  $Ni^{2+}$  ions. The shortest Me–O distance is that with the phenoxy oxygen atoms, and the longest, with the sulfonyl oxygen atom. On the whole,  $L^{4-}$  acts as

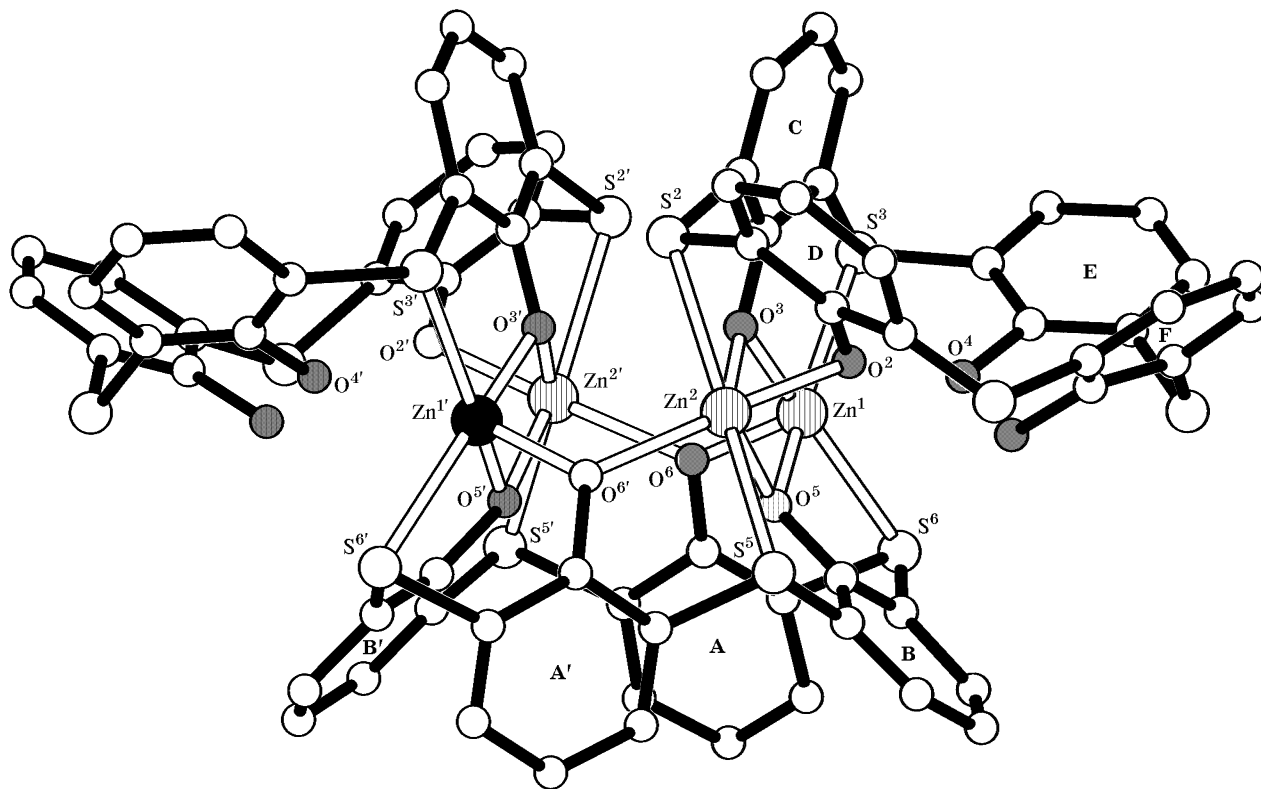


**Fig. 6.** Molecular structure of the complex of sulfinylcalixarene **XLIX** with  $\text{Pd}^{2+}$  ions (*tert*-butyl groups and hydrogen atoms are not shown).

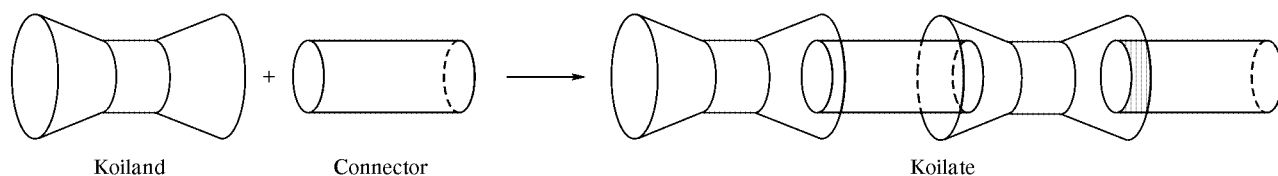
a bis-tridentate dinucleating ligand, and two metal ions in the complex are arranged *anti* with respect to each other (the ligand itself has a 1,2-*alt* conformation).

The complex of sulfinylcalixarene **XLIX** with  $\text{Pd}^{2+}$  ions consists of one  $\text{H}_2\text{L}^{2-}$  dianion and two  $\text{H}_3\text{L}^-$  monoanions which are bound through their rims by two  $\text{Pd}^{2+}$  ions. The complex has a symmetry axis

which passes through the center of the  $\text{H}_2\text{L}^{2-}$  cavity [51] (Fig. 6). The  $\text{H}_2\text{L}^{2-}$  moiety in the complex has an 1,3-*alt* conformation, and the  $\text{H}_3\text{L}^-$  fragments are *paco* conformers. The distal aromatic rings in  $\text{H}_2\text{L}^{2-}$  are equivalent, while all aromatic rings in  $\text{H}_3\text{L}^-$  are nonequivalent. Two modes of metal coordination to the sulfinyl groups are observed: in  $\text{H}_2\text{L}^{2-}$ , the coor-



**Fig. 7.** Molecular structure of the complex of thiacalixarene **II** with zinc(II) ions (*tert*-butyl groups and hydrogen atoms are not shown).

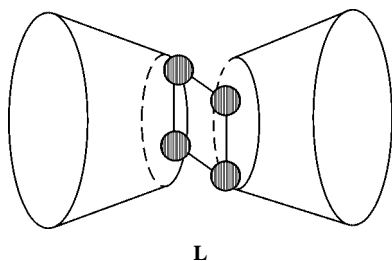


**Fig. 8.** Schemes of formation of a centrosymmetrical koilate from a centrosymmetric koiland and connector.

dination entity includes the sulfoxide and aroxide  $\text{ArO}^-$  groups which give rise to 6-membered ring, whereas with  $\text{H}_3\text{L}^-$  5-membered ring is formed.

Interesting data were obtained while studying the structure of  $\text{Zn}^{2+}$  [53] and  $\text{Cu}^{2+}$  [9, 54] complexes with thiacalixarene **II** [ $\text{H}_4\text{L}$ ] by the X-ray diffraction method. In both cases, the metal is linked to the phenoxide oxygen atoms and bridging sulfur atoms. The zinc complex has the composition  $[\text{Zn}_4\text{L}(\text{H}_2\text{L})_2]$ ; it includes one  $\text{L}^{4-}$  fragment and two  $\text{H}_2\text{L}^{2-}$  fragments in the *cone* conformation, which are linked through the lower rim by four  $\text{Zn}^{2+}$  ions (Fig. 7). Depending on the fragment involved in the coordination ( $\text{L}^{4-}$  or  $\text{H}_2\text{L}^{2-}$ ), two kinds of coordination environment of the metal ion can occur in crystal.

The  $\text{Cu}^{2+}$  complex  $[\text{Cu}_4(\text{C}_{40}\text{H}_{44}\text{O}_4\text{S}_4)_2 \cdot 2\text{CH}_2\text{Cl}_2] \cdot \text{CH}_2\text{Cl}_2$  [9, 54] is a cluster including four copper(II) ions which are located at the vertices of almost regular square arranged between two completely deprotonated calixarene fragments having a *cone* conformation (structure **L**):

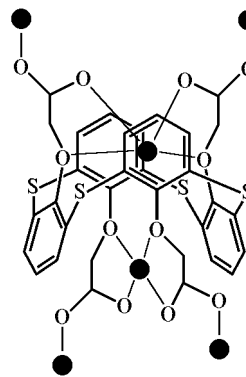


As a result, a ditopic (or divergent) receptor is formed, where the molecular cavities are oriented in the opposite directions at an angle of  $180^\circ$ . Copper(II) ions are coordinated at not only four phenoxy oxygen atoms but also at two bridging sulfur atoms. Just the latter factor is responsible for the failure to obtain an analogous complex with calixarene **I** [54]. The copper complex of thiacalixarene **II** is paramagnetic. This complex is an example of a koiland structure [47, 55]. It gives a dinuclear inclusion complex with two  $\text{CH}_2\text{Cl}_2$  molecules, each penetrating deep into the corresponding calixarene cavity. The X-ray diffraction data for the complexes of thiacalixarene **II** with  $\text{Zn}^{2+}$

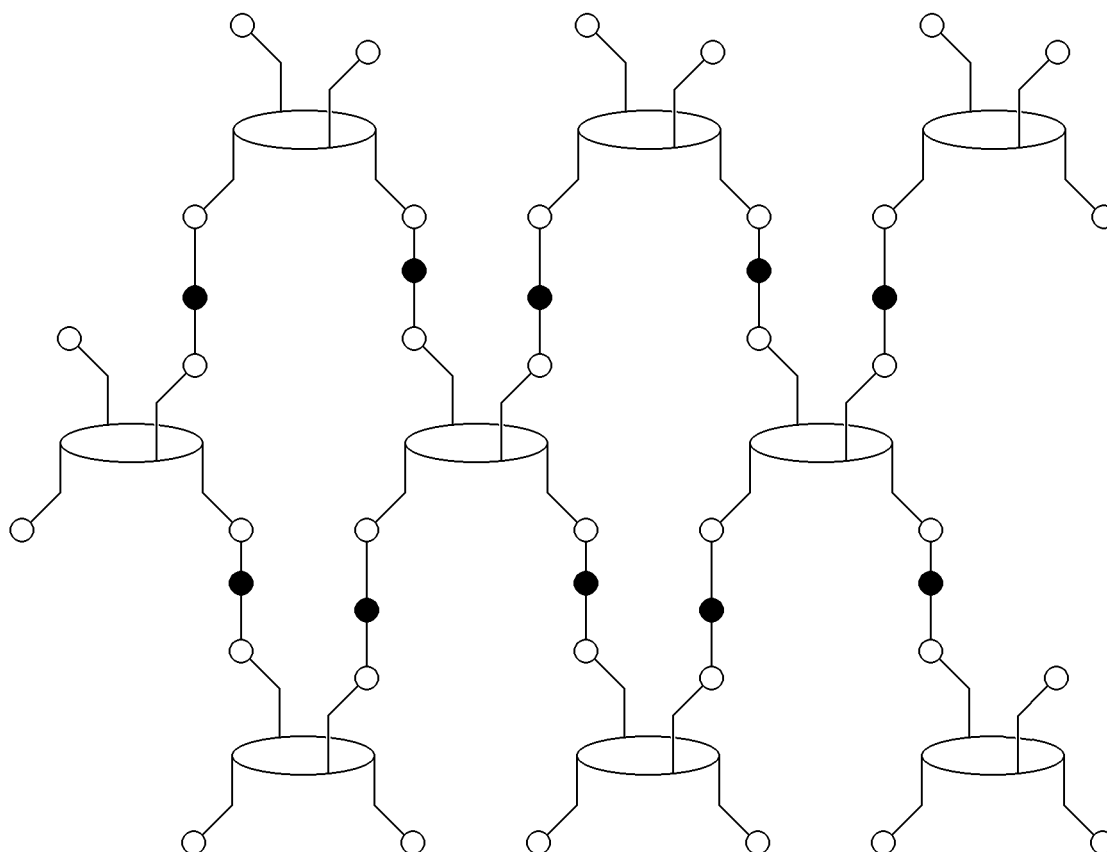
and  $\text{Co}^{2+}$  cations [9, 56] confirmed the formation of koilands in these cases: two calixarene units in the complexes are fused through three metal ions. The modes of coordination of  $\text{Co}^{2+}$  and  $\text{Zn}^{2+}$  ions are different [56]. All  $\text{Co}^{2+}$  ions in the complex may be regarded as six-coordinate, whereas in the zinc complex only two  $\text{Zn}^{2+}$  ions are six-coordinate, and the coordination number of the third zinc atom is 5. As in the copper complex, calixarene cavities of the complexes with  $\text{Co}^{2+}$  and  $\text{Zn}^{2+}$  capture solvent molecules.

The synthesis of dimeric thiacalixarene complexes with transition metal ions opens the way to molecular magnetics or koilates which are polymeric species linked through noncovalent bonds [9] (Fig. 8).

Akdas *et al.* [57] studied the complexing ability of tetracarboxylate thiacalixarene derivative **XXV** toward  $\text{Ag}^+$  ions. It was shown that its completely deprotonated form in the 1,3-*alt* conformation possesses 16 heteroatoms (12 oxygen atoms and 4 sulfur atoms capable of coordinating metal ions) and two coordination poles. One of the latter is located above, and the other, below the principal molecular plane, forming an angle of  $90^\circ$ . Each pole consists of two carboxy and two ester moieties. Taking into account that the carboxy group is separated from the ether oxygen atom by  $\text{CH}_2$  unit, the ether oxygen atom and one oxygen atom of the ester group can be arranged *syn*, giving rise to a chelate structure with metal ion. As a result, a discrete dinuclear complex of **XXV** with

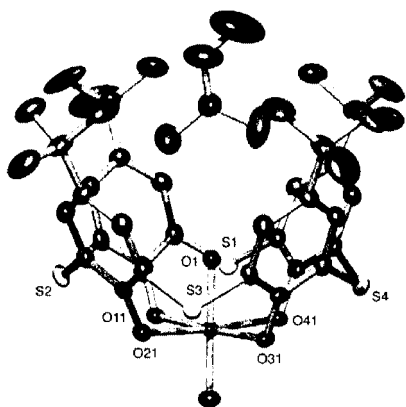


**Fig. 9.** A scheme of binding of  $\text{Ag}^+$  ions (●) with completely deprotonated ligand **XXV**.



**Fig. 10.** Schematic representation of the 2D-coordination network formed by binding of the dinuclear complexes  $[L^4(Ag^+)_2]^{2-}$  with silver cations (●).

$Ag^+$  is formed (Fig. 9). The remaining ester oxygen atoms are arranged in a divergent fashion, so that the complex can act as a tetrakis monodentate metallatecton which forms 2D-coordination networks [58] via binding dinuclear  $[L^4(Ag^+)_2]^{2-}$  complexes with silver cations through  $Ag-O$  bonds (Fig. 10).



**Fig. 11.** Structure of the complex  $[UO_2\{(II-4H)(DMF)\}] \cdot 2DMF$ .

Just recently, Asfari *et al.* [59] reported on the structures of previously unknown complexes formed by  $UO_2^{2+}$  ion with classical *para*-unsubstituted calix[4]arene and *p-tert*-butyltetrathiacalix[4]arene (**II**). The molecular structure of the complexes was shown to strongly change with variation of the ligand structure. The complex of *para*-unsubstituted calix[4]arene with  $UO_2^{2+}$  consists of one neutral ligand molecule and two its monoanions which are linked through the uranyl fragment. Thiacalixarene **II** gives two solvate complexes,  $[UO_2\{(II-4H)(DMF)\}] \cdot 2DMF$  and  $[UO_2\{(II-4H)(MeCN)\}] \cdot 1.7DMSO$ ; the structure of the first of these is shown in Fig. 11.

The above data indicate that increase in the size of the macroring due to replacement of the  $CH_2$  bridge by sulfide moiety (0.5 Å per edge) is sufficient to accommodate  $UO_2^{2+}$  ion. The latter is bound by four deprotonated phenolic hydroxy groups. The ligand molecule adopts a *flattened cone* conformation, and its cavity is occupied by DMF (or MeCN) molecule.

The geometry of the uranium coordination entity is almost the same as in the dinuclear complex of  $UO_2^{2+}$  ion with *p-tert*-butylcalix[6]arene [60]: it approaches

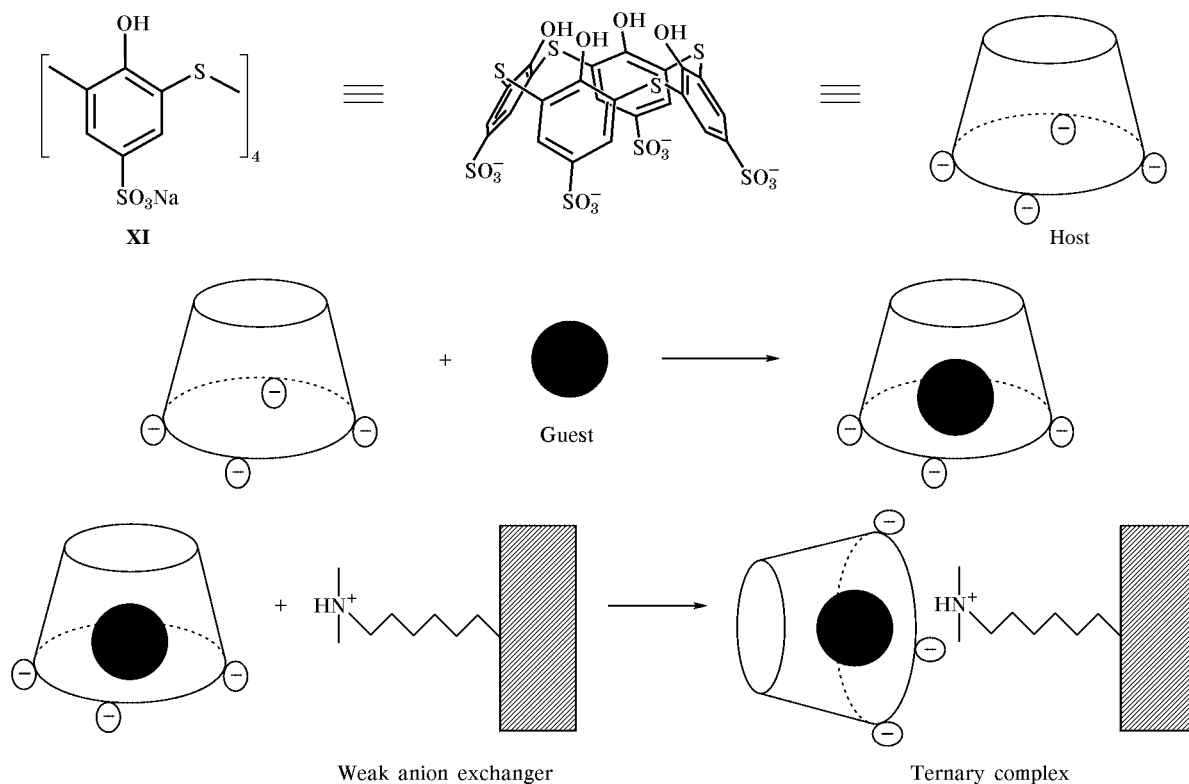


almost regular octahedral configuration, as in  $\text{UO}_2(\text{OR})_4$ . Insertion of one oxygen atom of the  $\text{UO}_2^{2+}$  fragment into the calixarene cavity does not hamper penetration of solvent molecules thereto. The  $\text{UO}_2^{2+}$ -O bonds are considerably shorter than in the corresponding complex with calix[4]arene.

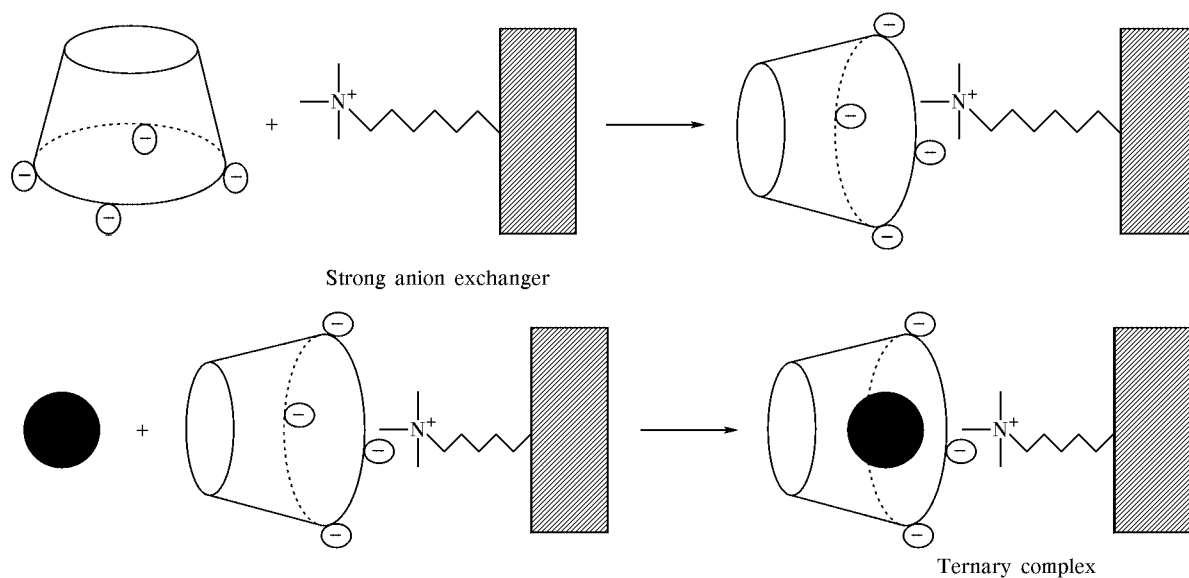
#### 4.3. Possible Practical Applications

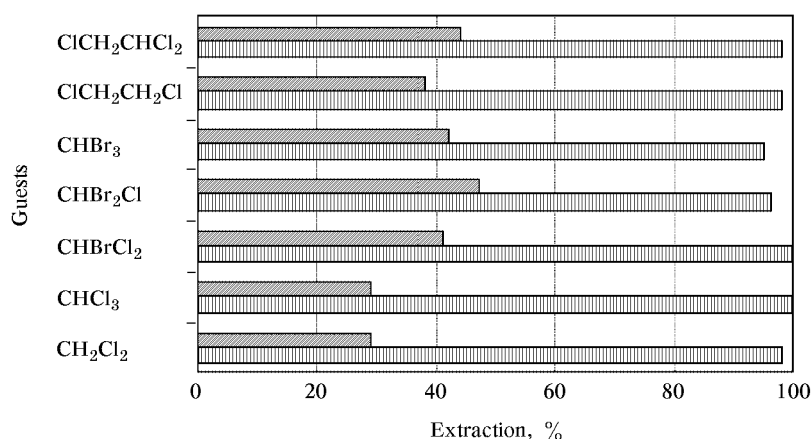
The complexing ability of water-soluble thiacalix-[4]arenesulfonate **XI** were utilized in purification of water from organohalogen compounds ( $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ ,  $\text{CHCl}_2\text{Br}$ ,  $\text{CHClBr}_2$ ,  $\text{CHBr}_3$ ,  $\text{ClCH}_2\text{CH}_2\text{Cl}$ ,

Scheme 30.



Scheme 31.





**Fig. 12.** Extraction of halogen-containing organic compounds (guests) from water according to Scheme 31 (dark areas) and in the absence of thiacalixarene **XI** (dashed areas).

and  $\text{Cl}_2\text{CHCH}_2\text{Cl}$ ) [61]. Two methods for removal of halogen derivatives from water were tried, which were based on the formation of ternary complexes with ligand **XI** and Amberlite IRA-93  $\text{ZU}^-$  anion exchanger containing dimethylamino groups (in the first case) and Amberlite IRA-900 containing trimethylammonio groups (in the second; Schemes 30 and 31, respectively). The results presented in Fig. 12 and Table 9 show that thiacalixarene derivative **XI** ensures almost complete removal from water of  $\text{CH}_2\text{Cl}_2$  and  $\text{CHCl}_3$  (99.99%) and more than 99.9% efficiency in the removal of the other halogen derivatives.

Water-soluble di- and tridansyl thiacalixarenes **XXXIX** and **XV** were used for the first time in the determination of metal cations in aqueous solutions by fluorescence spectroscopy [41]. The highest sensitivity was observed for  $\text{Cd}^{2+}$  ions. The sensitivity of compounds **XXXIX** and **XV** for metal cations decreases in the series:  $\text{Cd}^{2+} > \text{Al}^{3+} > \text{Cr}^{3+} > \text{Zn}^{2+} > \text{Cu}^{2+}$ . In all cases, didansyl derivative **XXXIX** was more sensitive

than **XV**. Apart from metal cations, some neutral molecules were examined as guests: borneol, geraniol, (–)-menthol, cyclohexanol, cyclooctanol, and 1-adamantanecarboxylic acid. Except for geraniol, all these guests are reliably determined in the presence of thiacalixarenes **XXXIX** and **XV**.

Chiral amide (*S*)-**XXIII** was used as a stationary phase for capillary gas-chromatographic separation of racemic amino acids, alcohols, and amines [32]. For comparison, analogous experiments were performed with the corresponding derivative of methylene-bridged calixarene **LXVIII**. The results showed that sulfur-bridged derivative (*S*)-**XXIII** is characterized by good chemo- and enantioselectivity for all the examined racemic samples, whereas no enantioselectivity was observed with compound **LXVIII**. The authors concluded that thiacalixarene derivatives may be convenient materials for preparation of chiral stationary phases for gas-chromatographic separation of enantiomers.

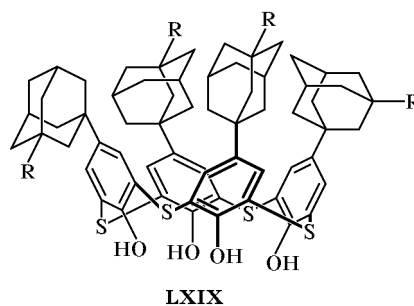
**Table 9.** Extraction of halogen-containing organic compounds (guests) from water according to Scheme 30<sup>a</sup>

Guest	$c_0$ , mg/ml	$c_f$ , mg/ml	Extraction, %
$\text{CH}_2\text{Cl}_2$	170	$6.58 \times 10^{-3}$	99.99613
$\text{CHCl}_3$	239	$1.23 \times 10^{-2}$	99.99485
$\text{CHBrCl}_2$	328	$3.44 \times 10^{-2}$	99.9895
$\text{CHBr}_2\text{Cl}$	417	$2.33 \times 10^{-1}$	99.9441
$\text{CHBr}_3$	508	$4.60 \times 10^{-1}$	99.9094
$\text{CH}_2\text{ClCH}_2\text{Cl}$	198	$4.08 \times 10^{-2}$	99.9794
$\text{CH}_2\text{ClCHCl}_2$	267	$1.35 \times 10^{-1}$	99.9495

<sup>a</sup> The initial ( $c_0$ ) and final ( $c_f$ ) concentrations of organohalogen compounds are given.

## 5. CONCLUSION

The data given in the present review indicate that a new class of macrocyclic compounds, namely thiacalix[4]arenes has confidently come into the chemical



world. The state of the chemistry of these compounds is now at the start of development, but even the first results suggest exclusive prospects in using their derivatives, specifically the possibility for creation on their basis of unique highly efficient and selective receptors. To conclude, we believe it necessary to report that we have synthesized a new type of thiacalixarene derivatives, *p*-tetrakis(3-*R*-1-adamantyl)-tetrathiocalix[4]arenes **LXIX** [62]. Study of their properties is now in progress.

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