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Mendeleev Commun., 2009, **19**, 193–195
Mendeleev Communications

Synthesis and complexation properties of 1,3-*alternate* stereoisomers of *p-tert*-butylthiacalix[4]arenes tetrasubstituted at the lower rim by the phthalimide group

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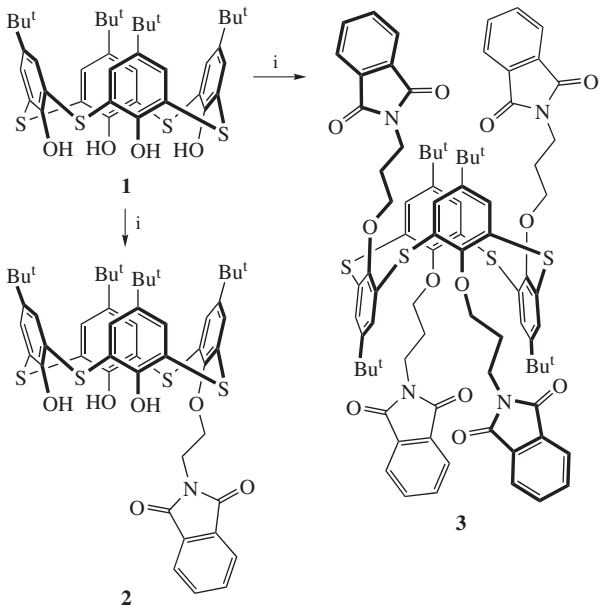
DOI: 10.1016/j.mencom.2009.07.006

Thiacalix[4]arenes containing the phthalimide group were synthesized and their extraction ability toward monocharged cations (alkali metals and Ag^+) was investigated.

Calixarene derivatives[1] hold a unique position among extractants and complexing agents used in mixture analysis and separation.[2] Calix- and thiacalixarenes are widely used as a building macrocyclic platform for designing synthetic receptors toward metal cations.[2] Macrocycles modified by ester fragments can recognize alkali metal cations due to coordination of an ion with carbonyl and ester oxygen atoms of the substituents.[3] In alkylation of *p-tert*-butylthiacalix[4]arene **1**[4] by compounds pocessing carbonyl group performed in the presence of alkali metal carbonates, a cation template effect was observed.[5–8] It resulted in selective formation of tetrasubstituted derivatives of thiacalix[4]arene in three conformations (*cone*, *partial cone* and 1,3-*alternate*) in high yield. The 1,3-*alternate* stereoisomer, which shows allosteric effect in metal cation binding, is of special interest.[9] For the synthesis of macrocycles with controlled (switchable) binding sites of metal cations,[10] there is a need in development of novel approaches to the design of tetrasubstituted thiacalix[4]arenes with various groups in a certain conformation. In this respect, the synthesis of monosubstituted at the lower rim *p-tert*-butylthiacalix[4]arene **1** and its further alkylation by ethyl bromoacetate in the presence of cesium cation as a template for the formation of 1,3-*alternate* stereoisomer has been investigated. *N*-(3-Bromopropyl)phthalimide and *N*-(2-bromoethyl)phthalimide were used as alkylating agents. The number of methylene groups between the reacting group and phthalimide fragment acting as a bulky substituent was varied (Scheme 1).



Scheme 1 *Reagents and conditions*: i, 8 equiv. of *N*-(bromoalkyl)phthalimide, 8 equiv. of M_2CO_3 (M = Na, K, Cs), acetone, reflux.

The interaction of **1** with *N*-(3-bromopropyl)phthalimide and *N*-(2-bromoethyl)phthalimide in acetone was studied. The nature of the base (M_2CO_3, M = Na, K or Cs) and the time of reaction (24–72 h) were varied in the alkylation process. However, only two compounds were isolated from the reaction mixture, *i.e.* monosubstituted macrocycle **2** in *cone* conformation in case of *N*-(2-bromoethyl)phthalimide and tetrasubstituted product **3** in 1,3-*alternate* conformation for *N*-(3-bromopropyl)-phthalimide. The yields of the reaction products are presented in Table 1. The structures of compounds **2** and **3** (Scheme 1) were characterized by physical methods.†

The conformation of macrocycle **2** as *cone* and that of compound **3** as 1,3-*alternate* were established by 2D NMR NOESY ^1H–^1H spectroscopy.

† *General procedure for synthesis of compounds* **2** *and* **3**. A mixture of 1.00 g (1.39 mmol) of *p-tert*-butylthiacalix[4]arene **1**, 11.12 mmol of *N*-(3-bromopropyl)phthalimide or *N*-(2-bromoethyl)phthalimide, and 3.62 g (11.12 mmol) of cesium carbonate were refluxed in 60 ml of dry acetone for 24 h. The solvent was evaporated *in vacuo*. The residue was dissolved in 40 ml of $CHCl_3$ and mixed with 2 M HCl aqueous solution (40 ml). The organic phase was dried over Na_2SO_4, and the solvent was evaporated. The residue was crystallized from Et_2O.

5,11,17,23-Tetra-tert-*butyl-25,26,27-trihydroxy-28-[2'-(*N*-phthalimido)-ethoxy]-2,8,14,20-tetrathiacalix[4]arene* **2**. White powder, yield: 0.81 g (65%), mp 126 °C.

5,11,17,23-Tetra-tert-*butyl-25,26,27,28-tetrakis-[3'-(*N*-phthalimido)-propoxy]-2,8,14,20-tetrathiacalix[4]arene* **3**. White powder, yield: 1.39 g (68%), mp 254 °C.

5,11,17,23-Tetra-tert-*butyl-25,26,27-tris[(ethoxycarbonyl)methoxy]-28-[2'-(*N*-phthalimido)ethoxy]-2,8,14,20-tetrathiacalix[4]arene* **4**. A mixture of 1.00 g (1.12 mmol) of monosubstituted compound **2**, 0.75 ml (6.72 mmol) of ethyl bromoacetate, and 2.20 g (6.72 mmol) of cesium carbonate were refluxed in 60 ml of dry acetone for 15 h. The solvent was evaporated *in vacuo*. The residue was dissolved in 40 ml of $CHCl_3$ and mixed with 2 M HCl aqueous solution (40 ml), the organic phase was dried over Na_2SO_4, and the solvent was evaporated. A pure product was obtained by recrystallization from ethanol. White powder, yield 0.91 g (71%), mp 245 °C.

For spectral characteristics and elemental analyses of compounds **2**–**4**, see Online Supplementary Materials.

Table 1 Yields of alkylation of *p-tert*-butylthiacalix[4]arene by *N*-(bromoalkyl)phthalimides.

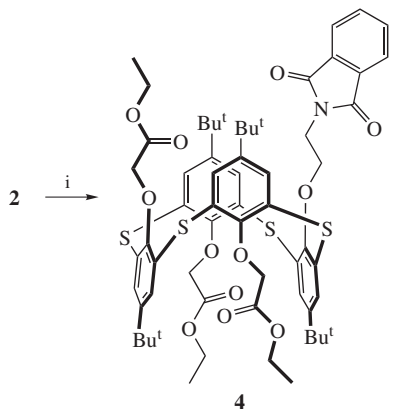
Base	Alkylating agents	
	N-(2-bromoethyl)-phthalimide	*N*-(3-bromopropyl)-phthalimide
Na_2CO_3	no reaction	no reaction
K_2CO_3	54% (compound **2**)	51% (compound **3**)
Cs_2CO_3	65% (compound **2**)	70% (compound **3**)

Thus, in the case of *N*-(2-bromoethyl)phthalimide contained ethylene bridge, *p-tert*-butylthiacalix[4]arene **2** monosubstituted at the lower rim was obtained. It is interesting that the use of 2–8-fold excesses of alkylation agent against macrocycle **1** did not lead to formation of other partially or tetrasubstituted products. Obviously, the formation of compound **2** is related to two factors: (i) bulky substituent (phthalimide fragment) able to shield phenolic groups of the macrocycle and (ii) intramolecular hydrogen bonds between carbonyl groups of the heterocycle and hydroxyl protons of thiacalix[4]arene. Probably, intramolecular hydrogen bonds (OH···O=C) fix a bulky substituent in the position that complicates the access of other molecules of alkylation agent to the reaction centre, whereas the reactivity of *N*-(2-bromoethyl)phthalimide is insufficient for further alkylation of the macrocycle.

Increasing the number of methylene fragments in *N*-(3-bromopropyl)phthalimide between the reaction centre and heterocycle leads to formation of tetrasubstituted product **3** in 1,3-*alternate* conformation in the alkylation reaction of compound **1** irrespective of the ratio of reagents. The same is specific for alkylhalogenides in the absence of the template effect.[12]

To obtain 1,3-*alternate* stereoisomer, alkylation of monosubstituted thiacalix[4]arene **2** by ethyl bromoacetate in the presence of cesium carbonate was performed (Scheme 2). Compound **4** was isolated in 71% yield. The formation of the full alkylation product is probably related to high reactivity of ethyl bromoacetate and cesium carbonate, competition between intramolecular and intermolecular hydrogen bonds resulting in decrease of the steric barrier in alkylation reaction. The conformation of macrocycle **4** was established by 2D NMR NOESY ^{1}H–^{1}H spectroscopy as 1,3-*alternate*.

To estimate the ability of synthesized compounds to recognize monocharged metal cations (alkali metals and silver), liquid picrate extraction[6] in the mutually saturated water–dichloromethane system was carried out.‡ In compounds **2**–**4**, various binding sites are presented, *i.e.*, carbonyl groups of phthalimide moieties, alkoxy and ester groups able to bind rigid ions like alkali metals, and π-system of heterocycle able to interact with soft transition metal cations like Ag^+. Compound **3** is insoluble in dichloromethane,[6] therefore, the extraction in chloroform



Scheme 2 *Reagents and conditions*: i, 6 equiv. of $BrCH_2COOEt$, 8 equiv. of Cs_2CO_3, acetone, reflux.

Table 2 Percent of extraction (*%E*) of alkali metal and silver cations. Extraction conditions: [L] = 2.5×10^{-3} mol dm^{-3}, [MPic] = 2.32×10^{-4} mol dm^{-3}.

Compound	Li^+	Na^+	K^+	Cs^+	Ag^+
2	8	6	5	< 4	100
3[a]	< 4	< 4	< 4	10	4
4	8	13	69	40	84
5a	5[9]	54[9]	23[9]	8[9]	62
5b	< 4[9]	5[9]	20[9]	8[9]	47
5c	5[9]	7[9]	85[9]	66[9]	81

[a]Chloroform extraction.

solution was conducted.[7] Percent of extraction (*%E*) of alkali metals and ion Ag^+ are presented in Table 2.

The phthalimide derivatives of thiacalix[4]arene **2** and **3** did not extract alkali metal cations under conditions studied. Meanwhile, monosubstituted product **2** showed effective binding of Ag^+. Weak extraction ability of macrocycle **3** toward alkali metal and silver cations can be due to inconsistency of the geometry of thiacalixarene binding sites and the size of the ions studied. In 1,3-*alternate* **3**, the interaction of unshared electron pairs of oxygen atoms with metal cations becomes impossible due to steric hindrance of spatially closed *tert*-butyl and phthalimide groups. This prevents ions binding.

It is interesting to compare the properties of tetraesters of *p-tert*-butylthiacalix[4]arene **5a**–**c**[8] (Figure 1) and those of triester **4** in 1,3-*alternate* conformation, differed from each other by one substituent. As was shown, the replacement of one ester fragment by phthalimide group changed the extraction properties. In case of compound **4** and **5c** in 1,3-*alternate* conformations (Table 2), the change of substitution nature increases the selectivity of extraction in the cation pair K^+/Cs^+.

To quantitatively estimate the ability of *p-tert*-butylthiacalix[4]arene derivatives to recognize monocharged metal cations, stability constants and complex stoichiometry were determined with UV titration‡ under conditions given maximum percent of extraction (**2** + Ag^+, **4** + Ag^+, **4** + K^+) (Table 3).

The stoichiometry of the complexes of compounds **2** and **4** with Ag^+ was found to be about 1:1. It is known[13,14] that thiacalix[4]arenes form 1:1 complexes with the participation of bridged sulfur atoms and carbonyl groups. The same type of

‡ *General method for picrate extraction.* Solutions of metal picrates were prepared from aqueous picric acid solution and aqueous solution of metal hydroxide (LiOH, NaOH, KOH or CsOH) or $AgNO_3$; final concentration of alkali metals was 0.1 mol dm^{-3}, and that of Ag^+ was 0.016 mol dm^{-3}. Aqueous picrate solution (3 ml, 2.32×10^{-4} mol dm^{-3}) and dichloromethane or chloroform solution of ligand (3 ml, 2.5×10^{-3} mol dm^{-3}) were stirred for 0.5 h and then kept for 1 h for phase separation at 25 °C. Absorbance of the aqueous phase before (A_0) and after extraction (A_i) was measured at 355 nm. The percentage of cation extracted (*%E*) was calculated as the ratio $100(A_0 - A_i)/A_0$. The values presented resulted from three parallel runs, estimated standard deviation was less than ±3%.

General method for determination of stability constant log *K and stoichiometry of the complexes*. A solution of metal nitrate in methanol (1.5×10^{-2} mol dm^{-3} of $AgNO_3$, 6×10^{-3} mol dm^{-3} of KNO_3) was added to 10^{-5} M solution of ligand in dichloromethane. The cation concentration in the final solution varied in the range 10^{-6}–10^{-3} mol dm^{-3}. The stability constant log *K* and stoichiometry of the complexes were determined from the plot of $\log(\Delta A/\varepsilon[L])$ *vs.* $\log[M]$.[14]

General method of dynamic light scattering (DLS). The particle sizes were determined with a Zetasizer Nano ZS instrument. The conditions of experiment: solvent CH_2Cl_2 (HPLC), temperature 25 °C, 4 mW He–Ne laser operating at a wavelength of 633 nm. The systems of investigated solutions were prepared by addition of metal nitrate (2.32×10^{-4} mol dm^{-3}) to 10 ml of 2.5×10^{-3} M solution of thiacalixarene derivatives in CH_2Cl_2 (HPLC). Then the mixtures were mechanically shaken for 3 h and after the measurements were carried out. Estimated standard deviation of method of dynamic light scattering for measurement of particle sizes was less than ±2%. During determination of the hydrodynamic size of particles, three independent experiments were carried out for each system.

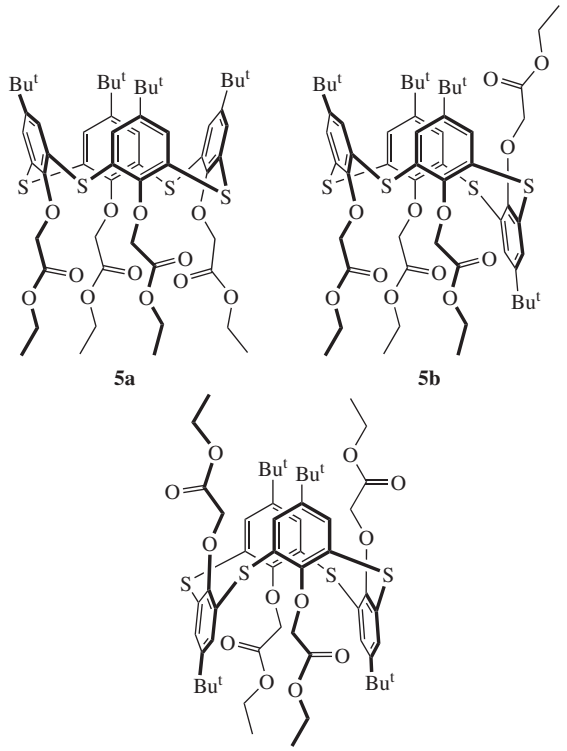


Figure 1 Structures of tetraesters based on *p-tert*-butylthiacalix[4]arene in *cone* (**5a**), *partial cone* (**5b**) and 1,3-*alternate* (**5c**) conformations.

complexes can be assumed for compounds **2** and **4**. Unusual stoichiometry of the complex of compound **4** with the cation K^+ was observed: two receptor molecules participate in the substrate binding. Such a stoichiometry of the complex can be due to a negative allosteric effect. The binding of one metal cation changes the spatial location of thiacalixarene functional groups. This complicates the binding of the second metal cation on another side of the macrocycle.[6] Meanwhile, the inclusion of a bulky phthalimide fragment into thiacalix[4]arene results in preorganization of the binding sites of the ligand. This provides the participation of the second macrocycle molecule in stronger K^+ binding. The formation of nanoscaled aggregates of macrocycle **2** with silver cation (diameter of 147.5±5.6 nm) and the absence of nanoparticles in case of potassium cation was confirmed by dynamic light scattering (DLC).[13,‡]

Thus, new thiacalix[4]arene derivatives **2**–**4** containing phthalimide groups at the lower rim of the macrocycle were synthesized. The extraction ability of the compounds synthesized toward monocharged alkali metal and silver cations was investigated. The replacement of one ester fragment by the phthalimide group increases the selectivity of extraction in the cation pair K^+/Cs^+.

This work was supported by the Russian Foundation for Basic Research (project no. 08-03-91106-CRDF), and CRDF (RUC1-2910-KA-07).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2009.07.006.

Table 3 Stability constants log *K* and stoichiometry *n* of the complexes.

Complex	*n*	log *K*
Ag^+ + **2**	1.06	4.30
Ag^+ + **4**	1.16	3.71
K^+ + **4**	0.49	3.22

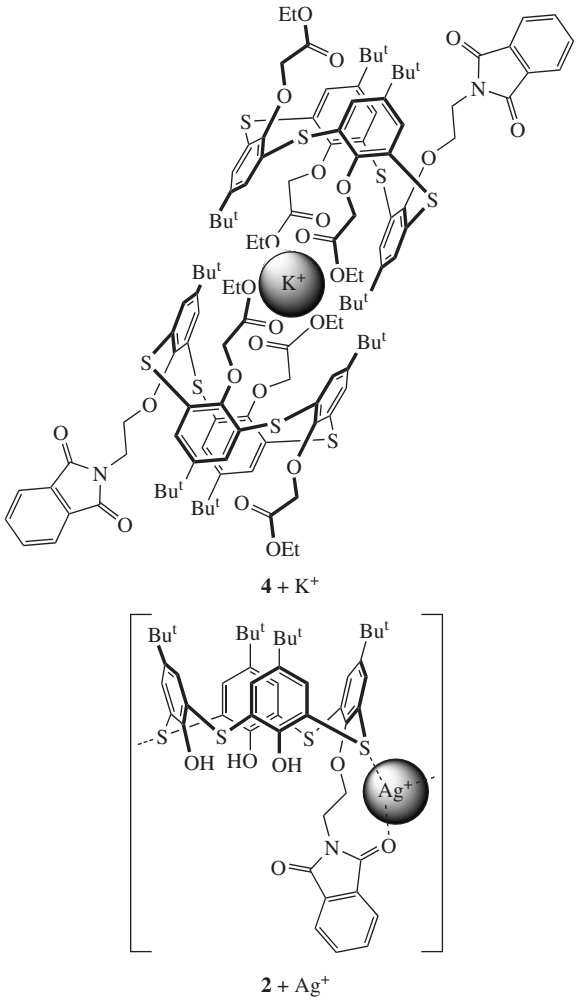


Figure 2 Possible structures of the complexes of *p-tert*-butyl thiacalix[4]arenes with metal cations.

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Received: 12th December 2008; Com. 08/3250