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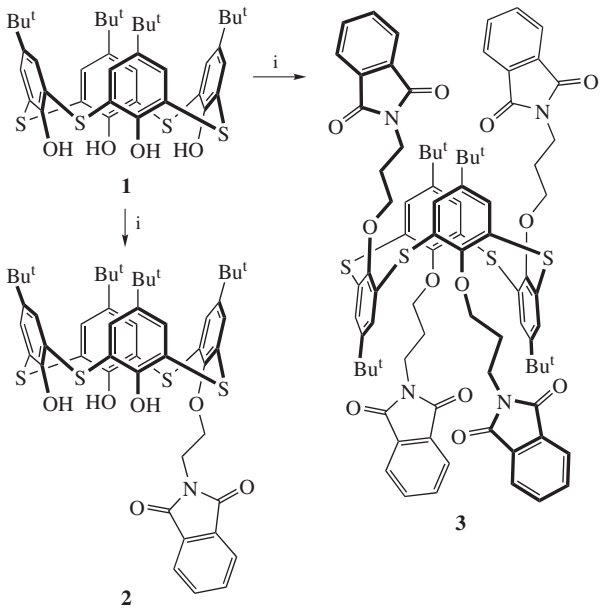
Thiacalix[4]arenes containing the phthalimide group were synthesized and their extraction ability toward monocharged cations (alkali metals and Ag^+) was investigated.

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.