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Mono–, 1,3-Di– and Tetrasubstituted *p-tert*-Butylthiacalix[4]arenes Containing Phthalimide Groups: Synthesis and Functionalization with Ester, Amide, Hydrazide and Amino Groups

Andrey V. Galukhin,[a] Evgeny N. Zaikov,[a] Igor S. Antipin,[a] Alexander I. Konovalov,[a] and Ivan I. Stoikov[a,b@]

[a]*Kazan (Volga Region) Federal University, A.M.Butlerov Chemical Institute, 420008 Kazan, Russian Federation*
[b]*Kazan Institute of Biochemistry and Biophysics, Russian Academy of Sciences, 420111 Kazan, Russian Federation.*
[@]*Corresponding author E-mail: ivan.stoikov@mail.ru*

A number of new p-tert-butylthiacalix[4]arene derivatives in the cone and 1,3-alternate configuration, containing binding sites for alkali metal cations and the phthalimide group were synthesized. The complexation properties of the synthesized macrocycles with alkali metals and silver cations were studied by picrate extraction. As it was shown, the introduction of the phthalimide group in the p-tert-butylthiacalix[4]arenes tetrasubstituted at the lower rim with ester and amide groups significantly influences the selectivity of the extraction of the alkali metal cations.

Keywords: Thiacalix[4]arene, picrate extraction, recognition of cations, phthalimide group.

Моно–, 1,3-ди– и тетразамещенные *п-трет*-бутилтиакаликс[4]–арены, содержащие фталимидные группы: синтез и функционализация сложноэфирными, амидными, гидразидными и аминогруппами

А. В. Галухин,[a] Е. Н. Зайков,[a] И. С. Антипин,[a] А. И. Коновалов,[a] И. И. Стойков[a,b@]

[a]*Казанский (Приволжский) федеральный университет, Химический институт им. А.М. Бутлерова, 420008 Казань, Россия*
[b]*ФГБУН Казанский институт биохимии и биофизики РАН, 420111 Казань, Россия*
[@]*E-mail: ivan.stoikov@mail.ru*

Синтезирована серия новых производных п-трет-бутилтиакаликс[4]арена в конфигурации конус и 1,3-альтернат, содержащих участки связывания катионов щелочных металлов и фталимидную группу. Методом пикратной экстракции изучены комплексообразующие свойства синтезированных макроциклов по отношению к катионам щелочных металлов и серебра. Установлено, что введение в тетразамещенные по нижнему ободу п-трет-бутилтиакаликс[4]арены со сложноэфирными и амидными группами фталимидной группы существенно изменяет селективность экстракции катионов щелочных металлов.

Ключевые слова: Тиакаликс[4]арен, пикратная экстракция, распознавание катионов, фталимидная группа.

Introduction

Calixarenes and thiacalixarenes are a convenient synthetic platform for the design of the different types of host molecules.[1,2] The molecular recognition ability of thiacalixarene derivatives towards cations and anions, the possibility to oxidize the bridging sulphur atoms of the macrocycle, and the conformational diversity can be counted among the attractive features of thiacalixarenes.[3-5] The size of the thiacalixarene macrocycle cavity is determined by the weak circular hydrogen bonds. This leads to normalization of the subsequent dissociation constant values of the macrocycle phenolic groups and hence makes it difficult to selectively obtain partially substituted derivatives.[4,5]

The phthalimide group is suitable for further functionalization of the lower rim of the substituted *p-tert*-butylthiacalix[4]arenes.[6-10] The aim of this work was to develop the method for the selective synthesis of mono-, 1,3-di- and tetrasubstituted *p-tert*-butylthiacalix[4]arenes containing phthalimide groups in the *cone* conformation as precursors of new synthetic receptors for metal cations. In this paper, we have obtained a number of thiacalix[4]arene derivatives containing the phthalimide group in addition to the tertiary amides and esters. Also, the products of complete and partial hydrolysis of the phthalimide group were characterized. It was shown that the introduction of the phthalimide group in the lower rim of *p-tert*-butylthiacalix[4] arenes tetrasubstituted by ester and amide groups significantly influences the efficiency and selectivity of extraction for alkali metal cations.

Experimental

Melting points were determined using Boetius Block apparatus. Most chemicals were purchased from Aldrich and used as received without additional purification. Organic solvents were purified by standard procedures. The ^{1}H and ^{13}C NMR spectra were recorded with 300 MHz Varian XL-300 spectrometer. IR spectra (KBr pellets or nujol) were recorded with Vector 22 (Bruker) IR spectrometer. ESI and MALDI-TOF mass spectra were recorded with Bruker Esquire MS. Elemental analysis was performed with Perkin–Elmer 2400 Series II instruments.

The compounds **2**, **3**, **7** were synthesized as described earlier.[10]

*General procedure of the synthesis of the compounds **4**, **5***. A mixture of 1.00 g (1.39 mmol) of *p-tert*-butylthacalix[4]arene **1**, 2.89 g (10.80 mmol) of *N*-(3-bromopropyl)phthalimide, 1.14 g (10.80 mmol) of sodium carbonate were refluxed in 60 ml of dry acetonitrile for 50 (compound **5**) or 100 (compound **4**) hrs. 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-25,26,27,28-tetrakis(3'-(N-phthalimide)propoxy)-2,8,14,20-tetrathiacalix[4]arene (cone), **4***. White powder. 53 %, mp. 253-255 °C. Found: C 68.72, H 5.42, N 3.86, S 9.02 %. $C_{84}H_{84}N_4O_{12}S_4$. Calculated: C 68.64, H 5.76, N 3.81, S 8.72. *m/z* (MALDI-TOF): 1469.1 [(M+H)$^+$], 1491.1 [(M+Na)$^+$], 1507.0 [(M+K)$^+$]. IR (nujol) ν_{max} cm^{-1}: 1268, 1709, 1771. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.71-7.78 (8H, m, Ar^{Pht}), 7.57-7.64 (8H, m, Ar^{Pht}), 7.25 (8H, s, Ar-H), 4.32 (8H, t *J* = 7.7 Hz, O-CH_2), 3.99 (8H, t *J* = 6.8 Hz, N-C*H*$_2$), 2.39 (8H, m, CH_2-C*H*$_2$-CH_2), 1.06 (36H, s, $(CH_3)_3$C). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 168.1, 159.0, 146.1, 134.1, 133.7, 132.5, 130.1, 123.2, 73.9, 35.9, 34.2, 31.3, 29.6. Spectrum ^{1}H-^{1}H NOESY: H^{4b} / H^3, H^7 / H^8, H^8 / H^9.

*5,11,17,23-Tetra-tert-butyl-25,27-dihydroxy-26,28-bis(3'-(N-phthalimide)propoxy)-2,8,14,20-tetrathiacalix[4]arene (cone), **5***. White powder. 79 %, mp. 215-217 °C. Found: C 67.52, H 6.31, N 2.40, S 11.42. $C_{62}H_{66}N_2O_8S_4$. Calculated: C 67.98, H 6.07, N 2.56, S 11.71. *m/z* (MALDI-TOF): 1117.5 [(M+Na)$^+$], 1133.5 [(M+K)$^+$]. IR (nujol) ν_{max} cm^{-1}: 1266, 1713, 1773, 3383. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.75-7.90 (4H, m, Ar^{Pht}), 7.72 (2H, s, OH), 7.59 (4H, s, Ar^2-H), 7.56-7.61 (4H, m, Ar^{Pht}), 6.89 (4H, s, Ar^1-H), 4.65 (4H, t *J* = 6.8 Hz, O-CH_2), 4.04 (4H, t *J* = 7.1 Hz, N-C*H*$_2$), 2.50 (4H, m, CH_2-C*H*$_2$-CH_2), 1.32 (18H, s, $(CH_3)_3$C), 0.76 (18H, s, $(CH_3)_3$C). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm:168.3, 156.1, 155.7, 147.8, 142.5, 134.2, 133.5, 132.7, 132.3, 128.8, 123.0, 122.1, 73.1, 35.5, 34.1, 34.0, 31.5, 30.7. Spectrum ^{1}H-^{1}H NOESY: H$^{4'b}$ / H$^{3'}$, H^{4b} / H^3, H$^{3'}$ / H^5, H$^{7'}$ / H^7, H$^{7'}$ / H^8, H$^{7'}$ / H^9.

*General procedure of the synthesis of the compounds **6**, **8**, **9***. A mixture of 1.00 g (1.12 mmol) of compound **2**, 6.72 mmol of ethylbromoacetate or *N*,*N*-diethylchloroacetamide, 6.72 mmol of carbonate of appropriate alkali metal was refluxed in 60 ml of dry acetone for 15-60 hrs. 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 MS 3 Å, and the solvent was evaporated. The residue was crystallized from ethanol.

*5,11,17,23-Tetra-tert-butyl-25,26,27-tri[(ethoxycarbonyl)-methoxy]-28-[2'-(N-phthalimide)ethoxy]-2,8,14,20-tetrathiacalix[4]arene (cone), **6***. White powder. 71 %, mp. 166 °C. Found: C 64.98, H 6.59, N 1.12, S 11.36. $C_{62}H_{75}NO_{12}S_4$. Calculated: C 64.61, H 6.38, N 1.22, S 11.13. *m/z* (ESI): 1151.5 [M$^+$]. IR (nujol) ν_{max} cm^{-1}: 1267, 1712, 1768. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.80-7.85 (2H, m, Ar^{Pht}), 7.68-7.73 (2H, m, Ar^{Pht}), 7.52 (2H, s, Ar^3-H), 7.51 (2H, s, Ar^2-H), 7.07 (2H, d *J* = 2.6 Hz, Ar^1-H), 7.04 (2H, d *J* = 2.6 Hz, Ar^1-H), 5.32 (2H, s, O-CH_2-CO), 5.06 (4H, d *J* =15.8 Hz, O-CH_2-CO), 4.45-4.55 (4H, m, N-C*H*$_2$-C*H*$_2$), 4.17 (4H, q *J* = 7.1 Hz, O-C*H*$_2$-CH_3), 4.14 (2H, q*J* = 7.1 Hz, O-C*H*$_2$-CH_3), 1.23 (6H, t, J = 7.1 Hz, O-CH_2-C*H*$_3$), 1.18 (3H, t *J* = 7.1 Hz, O-CH_2-C*H*$_3$), 1.22 (9H, s, $(CH_3)_3$C), 1.21 (9H, s, $(CH_3)_3$C), 0.93 (18H, s, $(CH_3)_3$C). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 169.7, 169.5, 168.1, 159.0, 158.2, 156.9, 146.8, 146.2, 146.1, 134.8, 134.7, 133.7, 133.2, 133.1, 132.3, 130.6, 129.6, 129.0, 128.7, 123.0, 71.7, 70.4 , 70.3, 60.7, 60.4, 37.7, 34.2, 34.1, 33.9, 31.3, 31.2, 30.9, 14.1, 14.0. Spectrum ^{1}H-^{1}H NOESY: H^{4b} / H$^{4'b}$, H$^{4'b}$ / H^{4+b}, H^7 / H$^{7'}$, H$^{7'}$ / H^8, H$^{7'}$ / H^{7+}, H$^{3'}$ / H^5, H$^{5'}$ / H^{3+}.

*5,11,17,23-Tetra-tert-butyl-25,26,27-tris(N,N-diethylcarbomoyl)-28-[2'-(N-phthalimide)ethoxy]-2,8,14,20-tetrathiacalix[4]arene (cone), **8***. White powder. 69 %, mp. 161 °C. Found: C 66.55, H 7.48, N 4.63, S 10.49. $C_{68}H_{88}N_4O_9S_4$ Calculated: C 66.20, H 7.19, N 4.54, S 10.39. *m/z* (MALDI-TOF): 1233.4 [(M+H)$^+$], 1255.5 [(M+Na)$^+$], 1271.5 [(M+K)$^+$]. IR (nujol) ν_{max} cm^{-1}: 1265, 1659, 1715, 1773. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.77-7.83 (2H, m, Ar^{Pht}), 7.68-7.73 (2H, m, Ar^{Pht}), 7.64 (2H, s, Ar^3-H), 7.61 (2H, s, Ar^2-H), 6.97 (2H, d *J* = 2.6 Hz, Ar^1-H), 6.92 (2H, d *J* = 2.6 Hz, Ar^1-H), 6.92 (2H, d *J* = 2.6 Hz, Ar^1-H), 5.68 (2H, s, O-CH_2-CO), 5.10 (2H, d *J* = 13.5 Hz, O-CH_2-CO), 4.91 (2H, d *J* = 13.5 Hz, O-CH_2-CO), 4.65-4.75 (2H, m, O-CH_2), 3.43-3.53 (2H, m, N-CH_2), 3.60 (2H, q *J* = 6.9 Hz, NC*H*$_2$$CH_3$), 3.49 (4H, q *J* = 6.9 Hz, NC*H*$_2$$CH_3$), 3.30 (4H, q *J* = 6.9 Hz, NC*H*$_2$$CH_3$), 3.24 (2H, q *J* = 6.9 Hz, NC*H*$_2$$CH_3$), 1.28 (9H, s, $(CH_3)_3$C), 1.28 (9H, s, $(CH_3)_3$C), 1.22 (3H, t *J* = 6.9 Hz, NCH$_2$C*H*$_3$), 1.15 (6H, t *J* = 6.9 Hz, NCH$_2$C*H*$_3$), 1.07 (6H, t *J* = 6.9 Hz, NCH$_2$C*H*$_3$), 1.04 (3H, t *J* = 6.9 Hz, NCH$_2$C*H*$_3$), 0.86 (18H, s, $(CH_3)_3$C). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm:168.0, 167.9, 167.0, 158.9, 158.6, 157.1, 146.5, 145.9, 145.1, 135.9, 134.6, 133.6, 132.9, 132.2, 131.1, 129.3, 128.7, 128.4, 122.8, 73.3, 69.9, 69.5, 41.5, 41.4, 40.0, 39.6, 37.7, 34.3, 34.1, 33.8, 31.4, 31.3, 30.9, 14.4, 14.2, 13.0. Spectrum ^{1}H-^{1}H NOESY: H^{4b} / H$^{3'}$, H$^{4'b}$ / H^5, H$^{4'b}$ / H^{3+}, H$^{7'}$ / H^{7+}, H$^{7'}$ / H^7, H$^{7'}$ / H^8, H^7 / H^{7+}, H^8 / H^{7+}.

*5,11,17,23-Tetra-tert-butyl-25,26,27-tri[(ethoxycarbonyl)-methoxy]-28-[2'-(N-phthalimide)ethoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate), **9***. White powder. 60 %, mp. 247 °C.

Found: C 66.40, H 7.35, N 4.81, S 10.20 %. $C_{68}H_{88}N_4O_9S_4$. Calculated: C 66.20, H 7.19, N 4.54, S 10.39. *m/z* (MALDI-TOF): 1256.0 [(M+Na)$^+$]. IR (nujol) ν_{max} cm^{-1}: 1266, 1648, 1672, 1719, 1774. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.83-7.88 (2H, m, Ar^{Pht}), 7.69-7.74 (2H, m, Ar^{Pht}), 7.66 (2H, d *J* = 2.6 Hz, Ar^2-H), 7.61 (2H, s, Ar^3-H), 7.52 (2H, d *J* = 2.6 Hz, Ar^2-H), 7.46 (2H, s, Ar^1-H), 4.84 (2H, d *J* = 12.6 Hz, O-CH_2-CO), 4.66 (2H, s, O-CH_2-CO), 4.57 (2H, d *J* = 12.6 Hz, O-CH_2-CO), 4.12-4.21 (2H, m, O-CH_2), 3.90-3.98 (2H, m, N-CH_2), 3.42 (2H, q *J* = 6.9 Hz, NCH_2CH$_3$), 3.37 (4H, q *J* = 6.9 Hz, NCH_2CH$_3$), 3.31 (2H, q *J* = 6.9 Hz, NCH_2CH$_3$), 3.21 (4H, q *J* = 6.9 Hz, NCH_2CH$_3$), 1.29 (18H, s, $(CH_3)_3$C), 1.25 (9H, s, $(CH_3)_3$C), 1.25 (9H, s, $(CH_3)_3$C), 1.24-1.32 (3H, m, NCH$_2$CH_3), 1.15 (6H, t *J* =6.9 Hz, NCH$_2$CH_3), 1.00 (6H, t *J* = 6.9 Hz, NCH$_2$CH_3), 0.80 (3H, t *J* = 6.9 Hz, NCH$_2$CH_3). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm:167.8, 166.5, 157.8, 157.7, 157.5, 146.1, 145.9, 145.8, 134.0, 133.9, 132.5, 133.3, 132.2, 132.1, 128.8, 128.0, 127.8, 127.6, 123.2, 70.3, 68.7, 66.6, 41.4, 39.9, 37.1, 34.3, 34.2, 31.3, 31.2, 14.5, 13.0. Spectrum ^{1}H-^{1}H NOESY: H^5 / H$^{7'}$, H^{3+} / H$^{7'}$, H$^{5'}$/ H^{7+}, H$^{3'}$ / H^7, H$^{3'}$ / H^8.

General procedure of the synthesis of compounds ***10-13***. A mixture of 1.00 g appropriate compound **2-5**, hydrazine hydrate (1 ml, 20 mmol) refluxed in 30 ml of ethanol for 30 h. The solvent was evaporated in vacuo. The residue was dissolved in 50 ml of $CHCl_3$ and mixed with H_2O (40 ml). The organic phase was dried over Na_2SO_4, and the solvent was evaporated.

5,11,17,23-Tetra-tert-butyl-25,26,27-trihydroxy-28-(2'-aminoethoxy)-2,8,14,20-tetrathiacalix[4]arene (cone), ***10***. White powder. 80 %, mp. 185-186 °C. Found: C 66.18, H 7.26, N 1.96, S 16.56. $C_{42}H_{53}NO_4S_4$ Calculated: C 66.02, H 6.99, N 1.83, S 16.78. *m/z* (ESI): 764.1 [(M+H)$^+$]. IR (nujol) ν_{max} cm^{-1}: 1264, 2252-2725, 3394. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.53 (4H, s, Ar^3-H), 7.49 (2H, s, Ar^2-H), 6.80 (2H, s, Ar^1-H), 4.70 (2H, br.s, O-CH_2), 3.73 (2H, br.s, N-CH_2), 1.26 (18H, s, $(CH_3)_3$C), 1.16 (9H, s, $(CH_3)_3$C), 0.64 (9H, s, $(CH_3)_3$C). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm:157.0, 155.7, 147.7, 142.1, 136.4, 135.1, 134.4, 131.1, 129.8, 123.4, 123.1, 122.3, 41.7, 34.2, 33.9, 33.8, 31.6, 31.6, 30.1, 2.1. Spectrum ^{1}H-^{1}H NOESY: H$^{3'}$ / H^5, H^{4+b} / H$^{5'}$.

5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis(3'-aminopropoxy)-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate), ***11***. White powder. 90 %, mp. 258-260 °C. Found: C 65.51, H 8.30, N 5.91, S 13.70 %. $C_{52}H_{76}N_4O_4S_4$. Calculated: C 65.78, H 8.07, N 5.90, S 13.51. *m/z* (ESI): 949.5 [(M+H)$^+$]. IR (nujol) ν_{max} cm^{-1}: 1265, 3385. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.35 (8H, s, Ar-H), . 3.91 (8H, t *J* = 6.8 Hz, O-CH_2), 2.46 (8H, t *J* = 7.3 Hz, N-CH_2), 1.29 (36H, s, $(CH_3)_3$C), 1.24 (8H, m, CH_2-CH_2-CH_2). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 157.0145.5, 128.1, 127.7, 67.0, 39.3, 34.2, 33.1, 31.3. Spectrum ^{1}H-^{1}H NOESY: H^{4b} / H^7, H^{4b} / H^8, H^{4b} / H^9, H^3 / H^7, H^3/ H^8, H^3 / H^9.

5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetrakis(3'-aminopropoxy)-2,8,14,20-tetrathiacalix[4]arene (cone), ***12***. White powder. 93 %, mp. 100-102 °C. Found: C 65.23, H 8.17, N 5.87, S 13.67 %. $C_{52}H_{76}N_4O_4S_4$. Calculated: C 65.78, H 8.07, N 5.90, S 13.51. *m/z* (ESI): 949.5 [(M+H)$^+$]. IR (nujol) ν_{max} cm^{-1}: 1265, 3385. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.27 (8H, s, Ar-H), 3.91 (8H, t *J* = 6.7 Hz, O-CH_2), 2.97 (8H, t *J* = 7.0 Hz, N-CH_2), 2.07 (8H, m, CH_2-CH_2-CH_2). 1.08 (36H, s, $(CH_3)_3$C). Spectrum ^{1}H-^{1}H NOESY: H^{4b} / H^3, H^7 / H^8, H^8 / H^9, H^7 / H^9.

5,11,17,23-Tetra-tert-butyl-25,27-dihydroxy-26,28-bis(3'-aminopropoxy)-2,8,14,20-tetrathiacalix[4]arene (cone), ***13***. White powder. 95 %. Found: C 66.4, H 7.61, N 3.40, S 14.62 %. Calculated: C 66.15, H 7.48, N, 3.35, S 15.36. *m/z* (MALDI-TOF): 857.4 [(M+Na)$^+$]. IR (nujol) ν_{max} cm^{-1}: 1266, 1713, 1773, 3383. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.66 (4H, s, Ar^2-H), 7.00 (4H, s, Ar^1-H), 4.56 (4H, t *J* = 5.7 Hz, O-CH_2), 3.12 (4H, t *J* = 6.4 Hz, N-CH_2), 2.10 (4H, m, CH_2-CH_2-CH_2), 1.33 (18H, s, $(CH_3)_3$C), 0.81 (18H, s, $(CH_3)_3$C). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 156.4, 156.0, 148.2, 134.4, 133.3, 129.0, 122.1, 73.8, 39.0, 34.3, 34.2, 33.7, 31.6, 30.9. Spectrum ^{1}H-^{1}H NOESY: H$^{4'b}$ / H$^{3'}$, H^{4b} / H^3, H^{4b} / H$^{3'}$, H$^{4'b}$ / H^5, H^7 / H^8, H^8 / H^9.

General procedure of the synthesis of the compounds ***14***, ***15***. A mixture of 1.00 g of the appropriate compound **6** or **7** and 1 ml (20 mmol) of hydrazine hydrate was refluxed in the mixture of 30 ml THF and 30 ml ethanol for 20 hrs. The solvent was evaporated and white powder was washed from water.

5,11,17,23-Tetra-tert-butyl-25,26,27-tri[(hydrozidocarbonyl)methoxy]-28-[2'-aminoethoxy]-2,8,14,20-tetrathiacalix[4]arene (cone), ***14***. White powder. 86 %, mp. 296-297 °C. Found: C 58.83, H 6.76, N 10.23, S 13.03 %. $C_{48}H_{65}N_7O_7S_4$. Calculated: C 58.81, H 6.68, N 10.00, S 13.08. *m/z* (MALDI-TOF): 980.9 [(M+H)$^+$], 1003.0 [(M+Na)$^+$]. IR (nujol) ν_{max} cm^{-1}: 1271, 1683, 1695, 3355. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 9.08 (2H, br.s, N*H*NH$_2$), 7.97 (1H, br.s, N*H*NH$_2$), 7.81 (2H, s, Ar^3-H), 7.80 (2H, s, Ar^2-H), 6.86 (2H, d *J* = 2.4 Hz, Ar^1-H), 6.83 (2H, d *J* = 2.4 Hz, Ar^1-H), 4.79 (2H, s, O-CH_2-CO), 4.71 (2H, d *J* = 14.4 Hz, O-CH_2-CO), 4.53 (2H, t *J* = 5.9 Hz, O-CH_2), 4.22 (2H, d *J* = 14.4 Hz, O-CH_2-CO), 3.88-3.97 (2H, m, N-CH_2), 1.37 (9H, s, $(CH_3)_3$C), 1.36 (9H, s, $(CH_3)_3$C), 0.82 (18H, s, $(CH_3)_3$C). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 169.5, 167.9, 159.1, 156.9, 155.7, 148.8, 148.0, 147.8,. 136.5, 136.4, 133.2, 132.7, 130.33, 130.3, 128.4, 128.0, 75.3, 72.7, 69.8, 38.8, 34.7, 34.6, 34.0, 31.4, 31.3, 30.7.

5,11,17,23-Tetra-tert-butyl-25,26,27-tri[(hydrozidocarbonyl)methoxy]-28-[2'-aminoethoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate), ***15***. White powder. 67 %, mp. 243 °C. Found: C 58.86, H 6.40, N 10.27, S 13.07. $C_{48}H_{65}N_7O_7S_4$. Calculated: C 58.81, H 6.68, N 10.00, S 13.08. *m/z* (MALDI-TOF): 980.6 [(M+H)$^+$], 1002.6 [(M+Na)$^+$]. IR (nujol) ν_{max} cm^{-1}: 1267, 1682, 3323, 3416. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.46 (2H, s, Ar^3-H), 7.42 (2H, d *J* = 2.6 Hz, Ar^1-H), 7.39-7.42 (2H, br.s, N*H*NH$_2$), 7.36 (2H, s, Ar^2-H), 7.32 (2H, d *J* = 2.6 Hz, Ar^1-H), 6.01(1H, s, N*H*NH$_2$), 4.58 (4H, s, O-CH_2-CO), 4.50 (2H, s, O-CH_2-CO), 4.18 (2H, t *J* = 5.5 Hz, O-CH_2), 3.56 (4H, s, NH$_2$), 2.76 (2H, t *J* = 5.5 Hz, N-CH_2), 1.27 (9H, s, $(CH_3)_3$C), 1.26 (18H, s, $(CH_3)_3$C), 1.25 (9H, s, $(CH_3)_3$C). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 168.2, 166.9, 157.2, 154.6, 153.5, 148.3, 147.5, 129.5, 128.6, 127.9, 127.8, 127.5, 127.3, 127.0, 74.2, 68.3, 65.7, 41.9, 34.6, 34.5, 34.4, 31.4, 31.2.

Complex of 5,11,17,23-Tetra-tert-butyl-25,26,27-tri[(hydrozidocarbonyl)methoxy]-28-[2'-aminoethoxy]-2,8,14,20-tetrathiacalix[4]arene with KBr (cone), ***16***. A mixture of 1.00 g (0.81 mmol) of the compound ***8***, 1 ml (20 mmol) of hydrazine hydrate was refluxed in the mixture 10 ml ethanol and 10 ml THF for 3 hrs. After cooling the solvent was evaporated in vacuo. The residue was dissolved in 50 ml of $CHCl_3$ and mixed with H_2O (50 ml). The organic phase was dried over MS 3 Å, and then refluxed with KBr for 1 h. Then KBr was filtered and solvent was evaporated in vacuo. Pale yellow powder. 92 %, mp. 125 °C. Found: C 58.32, H 7.05, Br 6,34, N 4.43, S 10.34 %. $C_{60}H_{86}BrKN_4O_7S_4$. Calculated: C 58.94, H 7.09, Br 6.54, N 4.58, S 10.49. *m/z* (MALDI-TOF): 1125.9 [(M+Na)$^+$]. IR (nujol) ν_{max} cm^{-1}: 1267, 1645. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 8.36 (2H, br. s, NH$_2$), 7.82 (2H, s, Ar^3-H), 7.76 (2H, s, Ar^2-H), 7.04 (2H, d *J* = 2.6 Hz, Ar^1-H), 6.95 (2H, d *J* = 2.6 Hz, Ar^1-H), 5.15 (2H, s, O-CH_2-CO), 4.72 (4H, d *J* = 12.9 Hz, O-CH_2-CO), 3.84 (2H, t *J* = 5.1 Hz, OCH_2CH$_2$), 3.87-3.97 (2H, m, NCH_2CH$_2$), 3.46 (4H, q *J* = 7.1 Hz, NCH_2CH$_3$), 3.37 (2H, q *J* = 7.1 Hz, NCH_2CH$_3$), 3.25 (4H, q *J* = 7.1 Hz, NCH_2CH$_3$), 3.17 (2H, q *J* = 7.1 Hz, NCH_2CH$_3$), 1.35 (9H, s, $(CH_3)_3$C), 1.34 (9H, s, $(CH_3)_3$C), 1.23 (6H, t *J* = 7.1 Hz, NCH$_2$CH_3), 1.19 (6H, t *J* = 7.1 Hz, NCH$_2$CH_3), 1.12 (3H, t *J* = 7.1 Hz, NCH$_2$CH_3), 1.06 (3H, t *J* = 7.1 Hz, NCH$_2$CH_3), 0.85 (18H, s, $(CH_3)_3$C). Spectrum ^{1}H-^{1}H NOESY: H^{4b} / H$^{3'}$, H$^{4'b}$ / H^{3+}, H^5 / H$^{3'}$, H$^{5'}$ / H^{3+}, H$^{7'}$/ H^7, H$^{7'}$ / H^8, H$^{7'}$ / H^{7+}.

5,11,17,23-Tetra-tert-butyl-25,26,27-tri[(hydrozidocarbonyl)methoxy]-28-[2'-aminoethoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate), ***17***. A mixture of 1.00 g (0.81 mmol) of compound ***9***, 1 ml (20 mmol) of the hydrazine hydrate was refluxed in the mixture of 10 ml ethanol and 10 ml THF for 3 hrs. After cooling the solvent was evaporated in vacuo. The residue was dissolved in 50 ml of $CHCl_3$ and mixed with H_2O (50 ml). The organic phase was dried over MS 3 Å and then solvent was evaporated in vacuo. White

powder. 98 %, mp. 105-106 °C. Found: C 65.32, H 7.93, N 5.33, S 11.51 %. $C_{60}H_{86}N_4O_7S_4$. Calculated: C 65.30, H 7.85, N 5.08, S 11.62. *m/z* (MALDI-TOF): 1103.6 [(M+H)$^+$], 1125.5 [(M+Na)$^+$]. IR (nujol) ν_{max} cm^{-1}: 1265, 1648, 1678. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.56 (2H, s, Ar^3-H), 7.46 (2H, s, Ar^2-H), 7.45 (2H, d *J* = 2.6 Hz, Ar^1-H), 7.39 (2H, d *J* = 2.6 Hz, Ar^1-H), 4.77 (2H, d *J* = 12.9 Hz, O-CH_2-CO), 4.63 (2H, s, O-CH_2-CO), 4.58 (2H, d *J* = 12.9 Hz, O-CH_2-CO), 3.84 (2H, t *J* = 5.6 Hz, OCH_2CH_2), 3.36 (6H, q *J* = 6.6 Hz, NCH_2CH_3), 3.26 (2H, q *J* =6.6 Hz, NCH_2CH_3), 3.17 (4H, q *J* = 6.6 Hz, NCH_2CH_3), 2.64 (2H, t *J* = 5.6 Hz, NCH_2CH_3), 1.26 (9H, s, $(CH_3)_3$C), 1.25 (27H, s, $(CH_3)_3$C), 1.13 (9H, t *J* = 6.6 Hz, NCH_2CH_3), 0.98 (6H, t *J* = 6.6 Hz, NCH_2CH_3), 0.91 (3H, t *J* = 6.6 Hz, NCH_2CH_3). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm:166.5, 166.2, 157.7, 157.4, 156.9, 145.9, 145.7, 145.6, 132.9, 131.5, 131.2, 130.5, 128.8, 127.66, 127.63, 127.5, 69.4, 68.1, 41.9, 41.25, 41.16, 39.8, 39.7, 34.1, 31.2, 31.15, 31.13, 14.4, 14.3, 12.9. Spectrum ^{1}H-^{1}H NOESY: H^5 / H$^{7'}$, H^{3+} / H$^{7'}$, H$^{3'}$/ H^{7}, H$^{3'}$ / H^{8}, H$^{5'}$ / H^{7+}.

*General procedure of the synthesis of compounds **18** and **19**.* 1.00 g (0.87 mmol) of compound **6** or **7** in 30 ml THF was added solution 0.55 g (13.05 mmol) of $LiOH·H_2O$ in 30 ml of water. Then reaction mixture was refluxed for 50 hrs. After cooling 10 ml of 2 M HCl was dropwise added. THF was evaporated and white solid was filtered from water and then was crystallized from ethanol.

*5,11,17,23-Tetra-tert-butyl-25,26,27-tri[(hydroxycarbonyl)-methoxy]-28-[2'-aminoethoxy]-2,8,14,20-tetrathiacalix[4]arene (cone), **18**.* White powder. 81 %, mp. 210-212 °C. Found: C 61.25, H 6.60, N 1.37, S 16.89 %. $C_{48}H_{59}NO_{10}S_4$. Calculated: C 61.45, H 6.34, N 1.49, S 17.05. *m/z* (MALDI-TOF): 938.4 [(M+H)$^+$], 976.4 [(M+K)$^+$]. IR (nujol) ν_{max} cm^{-1}: 1270, 1742, 2252-2750, 3165. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 8.02 (2H, br.s, NH_2), 7.86 (2H, s, Ar^3-H), 7.79 (2H, s, Ar^2-H), 7.09 (2H, d *J* = 2.4 Hz, Ar^1-H), 7.03 (2H, d *J* = 2.4 Hz, Ar^1-H), 5.23 (2H, s, O-CH_2-CO), 4.70 (2H, br.s, O-CH_2), 4.52 (4H, s, O-CH_2-CO), 3.98 (2H, br.s, N-CH_2), 1.36 (9H, s, $(CH_3)_3$C), 1.35 (9H, s, $(CH_3)_3$C), 0.87 (18H, s, $(CH_3)_3$C). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 170.6, 170.5, 159.5, 158.8, 154.7, 147.8, 147.3, 147.2, 133.0, 132.7, 130.2, 129.1, 128.2, 128.2, 73.2, 72.5, 69.8, 34.1, 34.0, 33.6, 31.0, 30.9, 30.9, 30.3. Spectrum ^{1}H-^{1}H NOESY: H^{4b} / H$^{3'}$, H$^{4'b}$ / H^{3+}, H^{7} / H$^{7'}$, H^{8} / H$^{7'}$, H$^{7'}$/ H^{7+}.

*5,11,17,23-Tetra-tert-butyl-25,26,27-tri[(hydroxycarbonyl)-methoxy]-28-[2'-aminoethoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate), **19**.* White powder. 80 %, mp. 234-235 °C. Found: C 61.97, H 5.47, N 1.57, S 11.70 %. $C_{56}H_{63}NO_{13}S_4$. Calculated: C 61.91, H 5.85, N 1.29, S 11.80. *m/z* (MALDI-TOF): 1108.9 [(M+Na)$^+$], 1124.8 [(M+K)$^+$]. IR (nujol) ν_{max} cm^{-1}: 1267, 1719, 1746, 1763, 1783, 3173, 3396, 3463. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 7.87-7.92 (1H, m, N*H*CO), 7.32-7.52 (2H, m, Ar^4-H), 7.59 (2H, d *J* = 2.6 Hz, Ar^2-H), 7.37 (2H, s, Ar^3-H), 7.30 (2H, d *J* = 2.6 Hz, Ar^2-H), 7.26 (2H, s, Ar^1-H), 4.98 (3H, br.s, OH), 4.62 (2H, d *J* = 15.3 Hz, O-CH_2-CO), 4.48 (2H, d *J* = 15.3 Hz, O-CH_2-CO), 4.46 (2H, s, O-CH_2-CO), 4.24 (2H, t *J* = 7.1 Hz, O-CH_2), 3.47 (2H, m, N-CH_2), 1.24 (18H, s, $(CH_3)_3$C), 1.22 (9H, s, $(CH_3)_3$C), 1.22 (9H, s, $(CH_3)_3$C). ^{13}C NMR (([D_6]DMSO$_3$, 298 K) δ_C ppm: 169.2, 169.2, 169.0, 167.9, 157.8, 156.7, 156.6, 146.2, 146.0, 138.9, 133.3, 132.5, 132.3, 132.2, 131.7, 130.4, 129.5, 129.3, 128.1, 127.9, 127.8, 127.5, 127.5, 68.1, 68.0, 67.8, 38.6, 34.1, 34.1, 34.0, 31.1, 31.0, 30.9. Spectrum ^{1}H-^{1}H NOESY: H^{4b} / H$^{7'}$, H^{5} / H$^{7'}$, H^{3+} / H$^{7'}$, H$^{7'}$ / H^{4+b}, H$^{4'b}$/ H^{8}, H$^{3'}$ / H^{8}.

Materials and general methods. The studies of the receptor abilities of the thiacalix[4]arene derivatives **3-8** were carried out in CH_2Cl_2 (analytical grade). UV-Vis spectra were recorded on the Perkin Elmer spectrophotometer Lambda 35.

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 concentrations of alkali metals and Ag$^+$ were 0.1 M and 0.016 M, correspondingly. Aqueous picrate solution (3 ml, $2.32·10^{-4}$ M) and dichloromethane or chloroform solution of ligand (3 ml, $2.5·10^{-3}$ M) were stirred for 0.5 hrs and then kept for 1 h for phase separation at 25 °C. The absorbance of the aqueous phase before (A_0) and after (A_i) extraction 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 replications, the estimated relative standard deviation was less than ±3 %.

General method for determination of the stability constant log K and stoichiometry of the complexes. A solution of metal nitrate in methanol ($1.5·10^{-2}$ M $AgNO_3$, $6·10^{-3}$ M KNO_3) was added to $1·10^{-5}$ M solution of the ligand in dichloromethane. The cation concentration in the final solution varied in the range 10^{-6}-10^{-3} M. The stability constant log*K* and stoichiometry of the complexes were determined from the plot of log(Δ*A*/e[L]) *vs*. log[M].

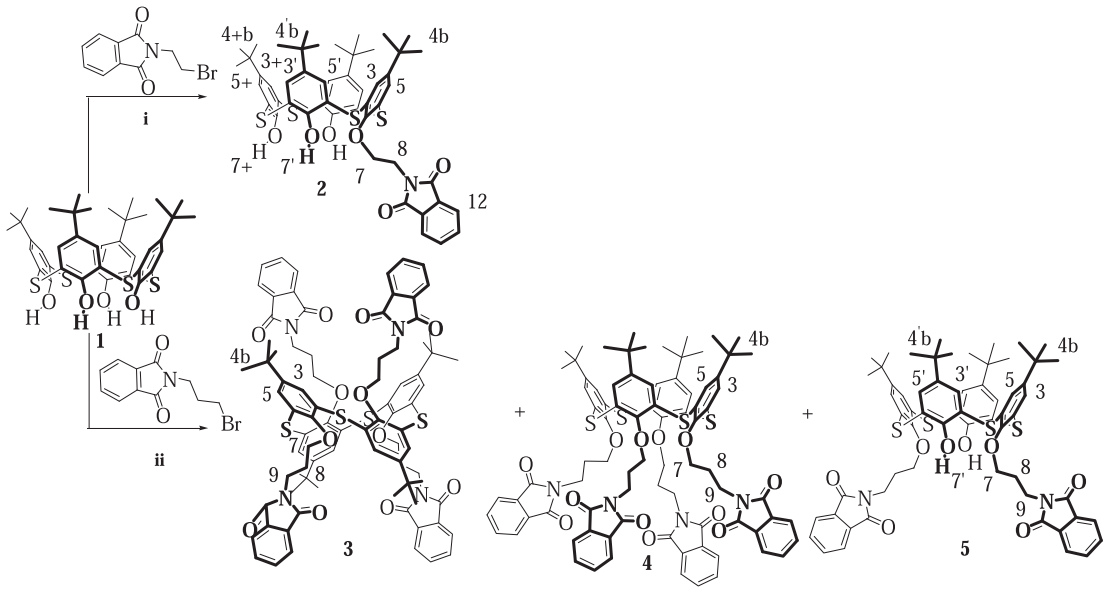
General method of dynamic light scattering (DLS). The particle size was determined with a Zetasizer Nano ZS instrument. The conditions of experiment: solvent CH_2Cl_2 (HPLC), temperature 25 °C, 4 mW He–Ne laser operating at a wavelength of 633 nm. The solutions to be investigated were prepared by addition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

Results and Discussion

Synthesis

In order to obtain partially substituted thiacalixarenes, the reagents with sufficiently bulky groups capable to form hydrogen bonds with the free hydroxyl groups of the thiacalix[4]arene have been specified. *N*-(2-Bromoethyl)-phthalimide and *N*-(3-bromopropyl)phthalimide which differ by the number of methylene groups between the reacting and the phthalimide fragments were used as alkylating agents. The presence of the phthalimide group located close to the reaction centre of the alkylating agent will be effective for obtaining substituted derivatives. Acetone and acetonitrile were applied as solvents for the alkylation of the macrocycle **1**. The nature of alkali metal cation (Na^+, K^+, Cs^+) and the reaction time (20-100 hrs.) were varied. As it was determined, depending on the nature of the alkylating agent (*N*-(2-bromoethyl)phthalimide and *N*-(3-bromopropyl)phthalimide), the solvent, base and reaction time, *p-tert*-butylthiacalix[4]arene derivatives **2-5** with different numbers of the phthalimide groups could be obtained with high yields.

It was observed that irrespective of the reaction conditions, the interaction of *p-tert*-butylthiacalix[4]arene **1** with *N*-(2-bromoethyl)phthalimide resulted in the formation of the monosubstituted product **2** in the *cone* conformation. The use of 2-20 fold excess of the alkylating agent did not result in the formation of the products of either partially or tetrasubstituted *p-tert*-butylthiacalix[4]arenes. The formation of compound **2** was probably due to two factors, *i.e.* the use of a bulky substituent (phthalimide group) shielding the phenolic groups of the macrocycle, and due to the intramolecular hydrogen bonds between the carbonyl groups of the heterocycle and the phenolic hydroxyl groups of the thiacalix[4]arene. Possibly, the intramolecular hydrogen bonds (OH···O=C) fix the bulky substituent in position preventing next molecule of the alkylating agent from



Scheme 1. Reagents and conditions: (i) Na_2CO_3, acetone, reflux; (ii) M_2CO_3 (M = Na, K, Cs), acetone or CH_3CN, reflux (see Table 1).

approaching the reaction center. Thus, the reactivity of *N*-(2-bromoethyl)phthalimide is not enough for further alkylation of the macrocycle.[10]

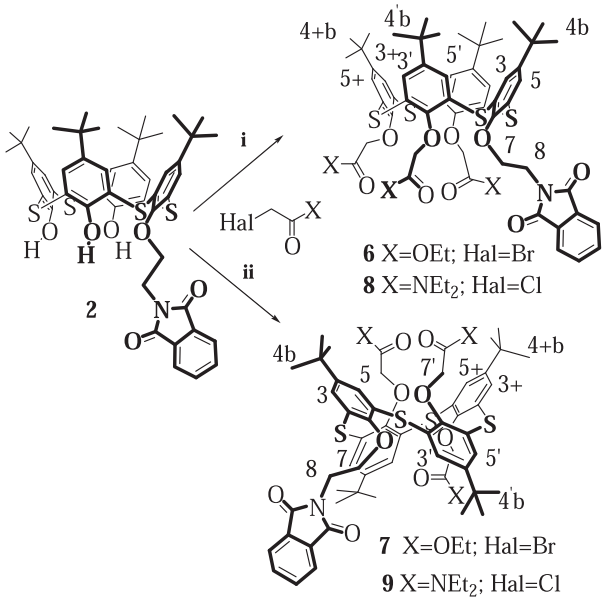
In the case of *N*-(3-bromopropyl)phthalimide and *p-tert*-butylthiacalix[4]arene **1** (Scheme 1), the compound **3** in *1,3-alternate* configuration was the main product regardless of the ratio of reactants. From the literature,[3-5] it could be concluded that the reactions with alkyl halides easily resulted in the formation of the *1,3-alternate* thiacalix[4] arene stereoisomer with no respect of the template effect of an alkali metal cation. However, the interaction of *N*-(3-bromopropyl)phthalimide with macrocycle **1** in acetonitrile in the presence of sodium carbonate resulted in the 1,3-disubstituted derivative of thiacalix[4]arene **5** with a 29 % yield. When the reaction took place in the presence of sodium iodide, the yield of the product **5** increased to 72 %. Prolongation of the synthesis to 100 hrs. resulted in a good yield of the tetrasubstituted derivative **4** in the *cone* configuration. The products formed in the reaction and their yields are presented in Table 1.

Table 1. Alkylation of compound **2** by the bromoalkylphthalimide: product yields.

Cation	*N*-(2-bromoethyl)-phthalimide	*N*-(3-bromopropyl)-phthalimide
	Acetone	
Na^+	No reaction	No reaction
K^+	**2** (54 %)	**3** (51 %)
Cs^+	**2** (71 %)	**3** (70 %)
	Acetonitrile	
Na^+	No reaction	**4** (53 %, T=100 hrs) **5** (72 %, T=60 hrs)
K^+	**2** (33 %)	**3** (50 %)
Cs^+	**2** (70 %)	**3** (72 %)

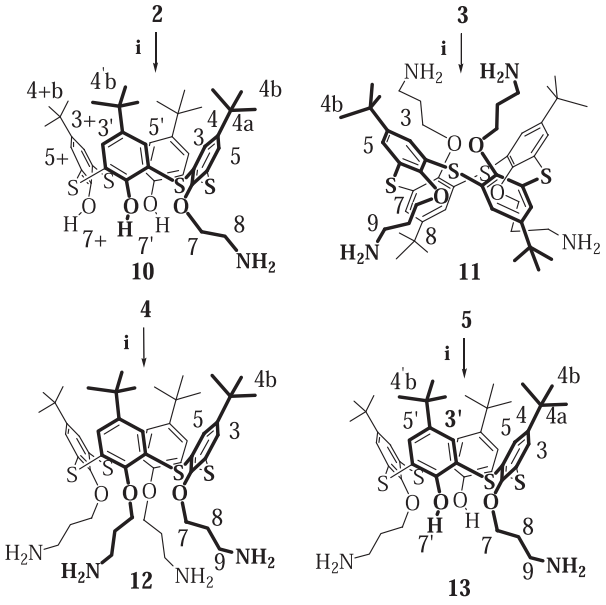
In order to obtain differently substituted derivatives of *p-tert*-butylthiacalix[4]arene containing a protected amine group in addition to the binding sites for alkali metal cations, the reaction of *p-tert*-butylthiacalix[4]arene **2** with ethyl bromoacetate and *N*,*N*-diethylchloroacetamide in acetone was studied. It is known that *p-tert*-butylthiacalix[4]arenes containing ester and tertiary amide groups are quite effective extractants for alkali metal cations.[11]

Tertiary amide fragment, in turn, is resistant to hydrolysis and hydrazinolysis. In carrying out the reactions, the nature of the template cation (Na^+, K^+, Cs^+) and the synthesis duration (15-60 hrs.) were varied (see Scheme 2).



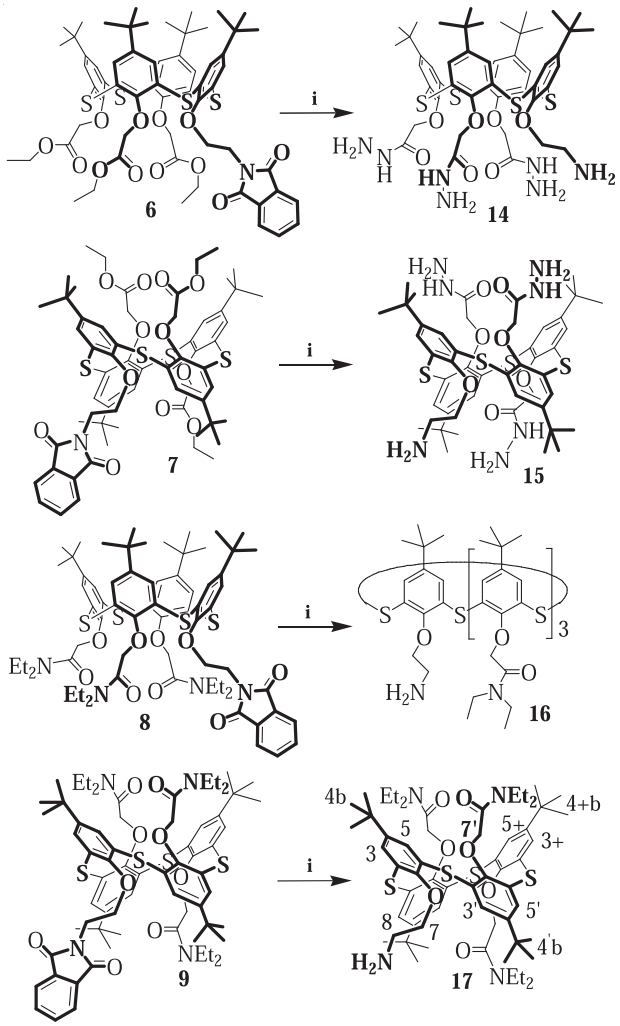
Scheme 2. Reagents and conditions: (i) M_2CO_3 (M=Na, K), acetone, reflux; (ii) M_2CO_3 (M=K, Cs), acetone, reflux.

Further, the hydrazinolysis of the phthalimide group was studied (see Scheme 3) to obtain amines as convenient precursors for the subsequent functionalization of the macrocycles. The corresponding amines **10-13** were obtained in high yields (80-95%). Using 2D NMR spectroscopy NOESY ^{1}H-^{1}H, it was shown that the removal of the phthalimide groups of the macrocycle did not lead to changes in conformation.



Scheme 3. Reagents and conditions: (i) $H_2NNH_2 \cdot H_2O$.

To remove the phthalimide protection in the presence of the other functional groups (esters and tertiary amides), hydrazinolysis of the phthalimide group in compounds **6-9** was studied (see Scheme 4). In the case of the ester derivatives **6** and **7**, the hydrazinolysis of both the phthalimide and ester groups occurred as expected and resulted in the products **14** and **15**. In the case of the *N*,*N*-diethylacetamide derivative, for the compound **9** in the *1,3-alternate* configuration, the hydrazinolysis led to the corresponding amine **17**.



Scheme 4. Reagents and conditions: (i) $H_2NNH_2 \cdot H_2O$.

Using 2D NMR spectroscopy NOESY ^{1}H-^{1}H, it was shown that the configuration of the macrocycles **6**, **7** and **9** did not change in the course of the reaction. In contrast, the hydrazinolysis of the *N*,*N*-diethylacetamide derivative in the *cone* configuration **8** resulted in a mixture of the conformational isomers of the *p-tert*-butylthiacalix[4]arene **16** (Figure 1).

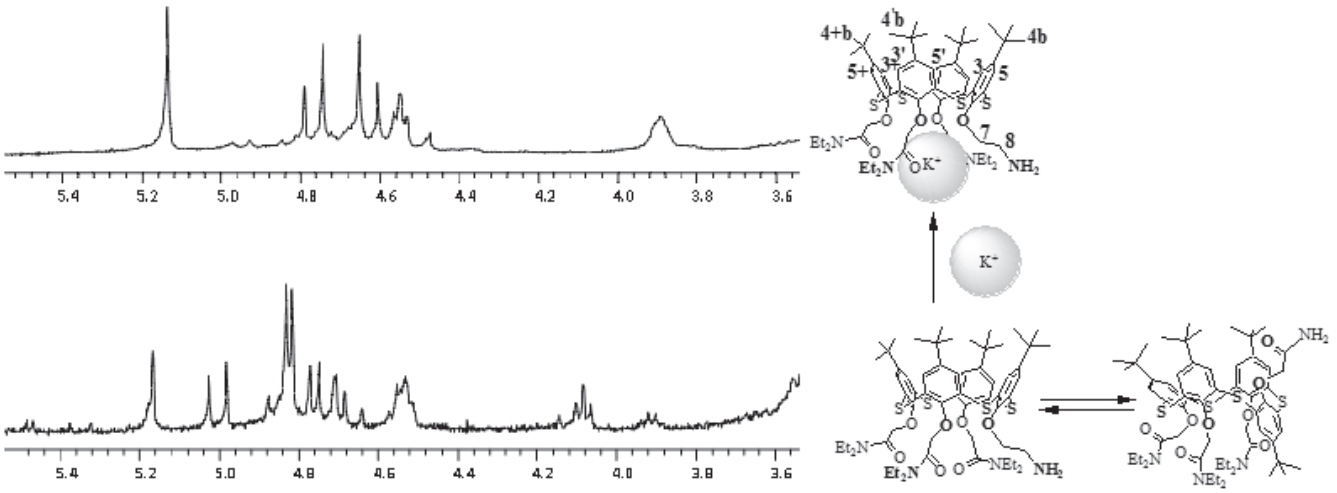


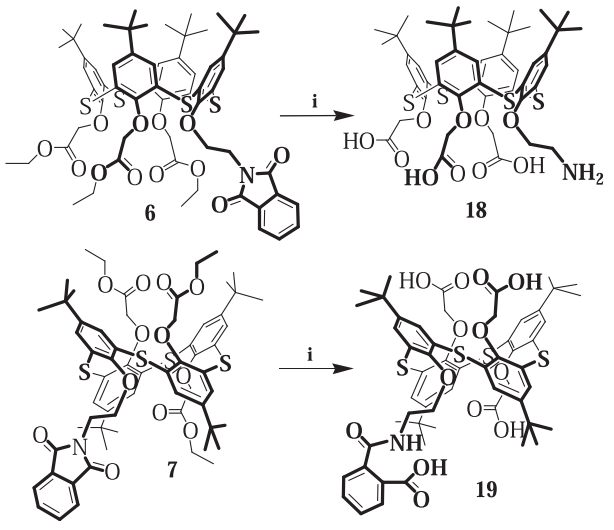
Figure 1. ^{1}H NMR spectra of compound **16** before (bottom) and after (top) refluxing with KBr.

On the basis of ^{1}H NMR spectroscopy, we propose that a mixture of conformational isomers is formed during the reaction. This is possibly due to the fact that the 2-aminoethoxyl fragments flip around the ring of the macrocycle resulting in the formation of the *partial cone* configuration. This is unusual for the *p-tert*-butylthiacalix[4]arenes. Commonly in the chemistry of calixarenes it is stated that the substituents with the chain of not less than three carbon atoms (*e.g.*, propyl) at the lower rim of the macrocycle rigidly fix the configuration of the macrocycle so that conformational transitions seem impossible. From the literature, there is an example of the conformational transition involving *p-tert*-butylthiacalix[4]arene derivative containing cyanomethoxyl groups at the lower rim of the macrocycle in the reduction of the nitrile group.[6]

From [4,5] it is evident that the *N*,*N*-diethylacetamide derivatives of *p-tert*-butylthiacalix[4]arene effectively form complexes with alkali metal cations. Also, various stereoisomers of the tetrasubstituted derivatives of the thiacalix[4]arene containing *N*,*N*-diethylacetamide fragments at the lower rim are produced by the template effect of metal cations.[11] Thus, it can be proposed that heating the mixture of conformers obtained in the presence of an alkali metal salt would shift the conformational equilibrium toward one of the configurations. Potassium bromide was used in the experiments. Figure 1 shows a section of the ^{1}H NMR spectrum (the region of oxymethyl protons of acetamide and ethylamine fragments) of the compound **16** before (bottom) and after (top) refluxing with KBr. From 2D NMR spectroscopy NOESY ^{1}H-^{1}H, the configuration of the complex involving the macrocycle **16** and KBr was determined as a *cone*.

The phthalimide protecting group was removed by alkaline hydrolysis of triesters based on *p-tert*-butylthiacalix[4]arenes **6** and **7** in the presence of monohydrate of the lithium hydroxide in a THF/water system (Scheme 5).

In the case of the compound **6**, the hydrolysis predictably affected both ester and phthalimide groups. The amino acid **18** was the reaction product. In the case of the triester **7** in the *1,3-alternate* configuration, the ester fragments were hydrolyzed fully but the phthalimide group only partially to give the product **19**. Refluxing the reaction mixture for a week only resulted in increase of the yield of amide **19** but did not promote the hydrolysis of the amide fragment. In accordance to literature data,[13] it can be assumed that the presence of the bulky *tert*-butyl groups near the reaction center hinders the amide bond hydrolysis.



Scheme 5. Reagents and conditions: (i) LiOH, H_2O, THF.

Study of Complexation Properties

To assess the ability of thiacalix[4]arenes with a phthalimide fragment to recognize single charged metal cations (alkali metals and silver), liquid picrate extraction was performed in the mutually saturated water-dichloromethane system.[14] The compounds **2-7** contain different kinds of the binding site, *i.e.* carbonyl groups of the phthalimide fragments, the alkoxy and ester groups capable to bind 'hard' ions, *e.g.*, alkali metal cations, and the π-system of the heterocycle interacting with the 'soft' cations of transition metals such as Ag^+. The compound **3** is insoluble in dichloromethane, hence the extraction was carried out in chloroform. The degree of extraction (*E*, %) of alkali metals and Ag^+ ions are shown in Table 2.

Table 2. Percent of extraction (*E*, %) of alkali metal and silver cations. Extraction conditions: [L] = $2.5\cdot10^{-3}$ M, [MPic] = $2.32\cdot10^{-4}$ M.

Compound	Li^+	Na^+	K^+	Cs^+	Ag^+
2	8	6	5	<4	100
3*	<4	<4	<4	10	4
4	<4	<4	<4	<4	<4
5	<4	<4	<4	<4	38
6	<4	8	13	<4	65
7	8	13	69	40	84
8	93	98	81	26	-**
9	43	100	100	98	-**
20[14]	5	54	23	8	62
21[14]	5	7	85	66	81
22[11]	62	78	80	45	-
23[11]	89	99	94	99	-

* - $CHCl_3$

** - extraction of picric acid

It was observed that the phthalimide derivatives of the thiacalixarene **2-5** did not extract the alkali metal cations under the studied conditions. Meanwhile the monosubstituted product **2** effectively bonded Ag^+. The low extraction ability of macrocycles **2-5** toward the cations of alkali metals is probably due to the weaker affinity of the carbonyl group of the phthalimide fragment toward the alkali metal cations against that of the other *p-tert*-butylthiacalix[4]arene derivatives containing a carbonyl group.[11,14-16]

The complexation properties of the *p-tert*-butylthiacalix[4]arene based tetraesters and tetraamides **20-23** described in literature were compared with those of the macrocycles **6-9** synthesized in this work, which differ by substituents in the lower rim (Table 2). As it was shown, substitution of one ester fragment by a phthalimide group led to the change in the extraction properties of esters **6** and **7**.

In the case of compound **7** in the *1,3-alternate* configuration, the efficiency of binding of the cations decreased while the selectivity of K^+ cation extraction against that of Cs^+ increased. A general decrease in the complexation properties of thiacalixarene **6** in the *cone* configuration against that of the tetraester based *p-tert*-butylthiacalix[4]arene **20** was observed. In the case of tetraamides **22** and **23**, replacing one *N*,*N*-diethylacetamide by a phthalimide fragment increased sensitivity of the receptors **8** and **9** to the cation size. Thus, an increase in the selectivity of extraction of ion pairs Cs^+/Li^+ was shown.

To quantify the ability of the *p-tert*-butylthiacalix[4]arene derivatives to recognize single charged metal cations, the stability constants and stoichiometry of the complexes with a highest degree of extraction (**2** + Ag^+, **7** + Ag^+, **7** + K^+) were determined by photometric titration (Table 3).

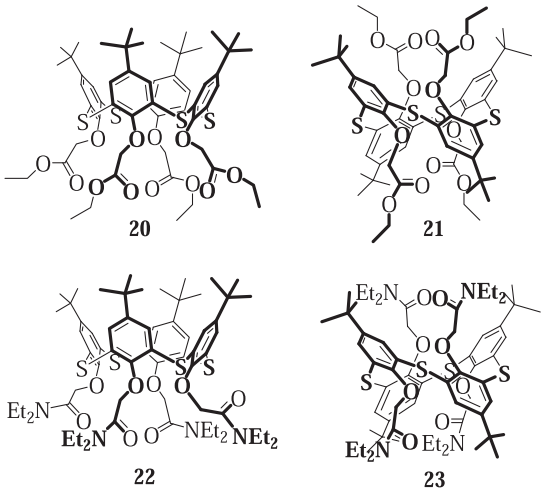


Table 3. The logarithms of the stability constant log*K* and stoichiometry *n* of the complexes.

Complex	*n*	log*K*
2+$AgNO_3$	1.06	4.30
7+$AgNO_3$	1.16	3.71
7+KNO_3	0.49	3.22

The stoichiometry of the complexes of the compounds **2** and **7** with Ag^+ cations is almost equal to 1:1. From the literature it is known that thiacalix[4]arenes can form 1:1 nanoscale aggregates with the silver cations via 'soft' bridging sulphur atoms,[17-21] so the formation of such complex in the case of compounds **2** and **7** can be assumed.

The formation of supramolecular associates of the macrocycle **2** with the silver cations (diameter 147 nm) was confirmed by the dynamic light scattering. The result obtained confirms the hypothesis that the aggregates similar to those described in literature are formed (Figure 2).[17-21]

An unusual stoichiometry was observed for the complex of the compound **7** with K^+ cation. Two molecules of the receptor **7** bind one metal cation. This might be due to the negative allosteric effect. Binding of a metal cation alters the spatial arrangement of the thiacalixarene functional groups and makes it difficult for an additional metal cation to bind to another side of the macrocycle. Meanwhile the presence of the bulky phthalimide fragment in thiacalix[4]arene **7**, which converges in space with the *tert*-butyl groups led to pre-organization of the ligand binding sites for a second macrocycle molecule to take part in a more stronger binding of K^+.

Conclusion

We have proposed and realized an approach to the synthesis of the mono-, 1,3-di- and tetrasubstituted at the lower rim *p-tert*-butylthiacalix[4]arenes with phthalimide fragments. A number of new *p-tert*-butylthiacalix[4]arene derivatives in the *cone* and *1,3-alternate* conformation containing phthalimides, amines, esters, tertiary amides, carboxyl and hydrazide groups on the lower rim of the macrocycle have been synthesized. The complexation properties of the synthesized receptors toward alkali metal and silver cations were studied by picrate extraction. It was shown that introduction of the phthalimide fragment in the *p-tert*-butylthiacalix[4]arene tetrasubstituted at the lower rim significantly affected the selectivity of the extraction of alkali metal cations.

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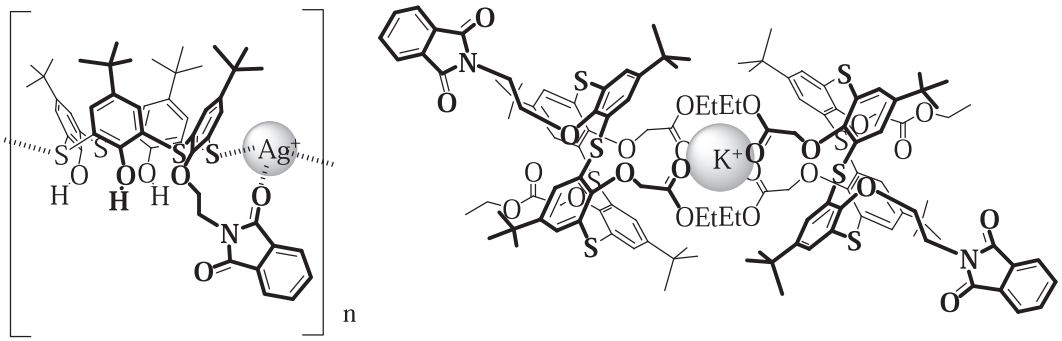

Figure 2. The structures proposed for the complexes of macrocycles **2** and **7** with the silver and potassium cations.

References

1. Atwood J.L., Steed J.W. *Organic Nanostructures*. Weinheim: Wiley-VCH, **2008**. 352 p.
2. Gutsche C.D. *Calixarenes - An Introduction, 2nd Edition*. Cambridge: RSC, **2008**. 290 p.
3. Iki N., Miyano S. *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, *41*, 99-105.
4. Lhotak P. Eur. *J. Org. Chem.* **2004**, *71*, 1675-1692.
5. Morohashi N., Narumi F., Iki N., Hattori T., Miyano S. *Chem. Rev.* **2006**, *106*, 5291-5316.
6. Bhalla V., Kumar M., Hattori T., Miyano S. *Tetrahedron* **2004**, *60*, 5881-5887.
7. Bitter I., Csokai V. *Tetrahedron Lett.* **2003**, *44*, 2261-2265.
8. Bhalla V., Babu N., Kumar M., Hattori T., Miyano S. *Tetrahedron Lett.* **2007**, *48*, 1581-1585.
9. Kumar M., Dhir A., Bhalla V. *Tetrahedron* **2009**, *65*, 7510-7515.
10. Stoikov I.I., Galukhin A.V., Zaikov E.N., Antipin I.S. *Mend. Comm.* **2009**, *19*, 193-195.
11. Solov'eva S.E., Gruner M., Omran A.O., Gubaidullin A.T., Litvinov I.A., Habicher W.D., Antipin I.S., Konovalov A.I. *Izv. Akad. Nauk, Ser. Khim.* **2005**, *9*, 2041-2049 (in Russ.).
12. Asfari Z., Bohmer V., Harrowfield J. M., Vicens J., Saadioui M.M. *Calixarenes 2001*. Dordrecht: Kluwer Academic Publisher, 2001. 683 p.
13. Štastny V., Stibor I., Dvorakova H., Lhotak P. *Tetrahedron* **2004**, *60*, 3383-3391.
14. Stoikov I.I., Omran O.A., Solovieva S.E., Latypov S.K., Enikeev K.M., Gubaidullin A.T., Antipin I.S., Konovalov A.I. *Tetrahedron* **2003**, *59*, 1469-1476.
15. Iki N., Narumi F., Fujimoto T., Morohashi N., Miyano S. *J. Chem. Soc., Perkin Trans*. **1998**, *2*, 2745-2750.
16. Gafiullina L.I., Vershinina I.S., Stoikov I.I., Antipin I.S., Konovalov A.I. *J. Struct. Chem.* **2005**, *46*, 22-27.
17. Stoikov I.I., Yushkova E.A., Zhukov A.Yu., Zharov I., Antipin I.S., Konovalov A.I. *Tetrahedron* **2008**, *64*, 7112-7121.
18. Stoikov I.I., Yushkova E.A., Zhukov A.Yu., Zharov I., Antipin I.S., Konovalov A.I. *Tetrahedron* **2008**, *64*, 7489-7497.
19. Yushkova E.A., Stoikov I.I. *Langmuir* **2009**, *25*, 4919-4928.
20. Stoikov I.I., Yushkova E.A., Zharov I., Antipin I.S., Konovalov A.I. *Tetrahedron* **2009**, *65*, 7109-7114.
21. Stoikov I.I., Yushkova E.A., Bukharaev A.A., Biziaev D.A., Ziganshina S.A., Zharov I. *J. Phys. Chem. C* **2009**, *113*, 15838-15844.

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