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Pentakis–Amidothiacalix[4]arene Stereoisomers: Synthesis and Effect of Central Core Conformation on Their Aggregation Properties

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New monosubstituted pentakisthiacalix[4]arenes in three different configurations (cone, partial cone and 1,3-alternate) were synthesized and their structure and composition were characterized by a number of physical methods including ^{1}H, ^{13}C, IR spectroscopy and mass spectrometry. The spatial structure was confirmed by two-dimensional ^{1}H-^{1}H NMR spectroscopy. It was shown that nano-sized aggregates with silver cation were formed only in the case of multicalixarene with a cone configuration of the central core.

Keywords: Thiacalix[4]arene, multithiacalix[4]arene, synthesis, aggregates, silver cation.

Стереоизомеры пентакис–амидотиакаликс[4]аренов: синтез и влияние конформации центрального ядра на агрегационные свойства

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Синтезированы пентакистиакаликс[4]арены в трех конфигурациях – конус, частичный конус, 1,3-альтернат. Структура и состав полученных макроциклов были охарактеризованы с помощью ряда физико-химических методов, включающих ^{1}H, ^{13}C, ИК спектроскопии и масс спектрометрии и элементным анализом. Пространственная структура синтезированных полимакроциклов была охарактеризована с помощью двумерной ^{1}H-^{1}H спектроскопии. Было показано, что наноразмерные агрегаты в присутствии катиона серебра образуются только в случае мультикаликсаренов, центральное ядро которых находится в конфигурации конус.

Ключевые слова: Тиакаликс[4]арен, мультитиакаликс[4]арен, синтез, агрегаты, катион серебра.

Introduction

To date, the development of polyfunctional nanoscale (1-10 nm) synthetic receptors for recognizing large substrates like nucleic acids and proteins is one of the most extensively studied areas of supramolecular chemistrys. Supromolecular self-assembly is one of the procedures employed for the development of polyfunctional nanoscale receptors.[1-6] Thiacalixarene is a readily available macrocyclic platform with great potential for further functionalization.[7-16] The ability to partial functionalization of the macrocycle[17-19] as well as the existence of different spatial isomers make thiacalixarenes essential blocks in the synthesis of self-assembled supramolecular systems, *e.g*., one-dimensional fibres[20] (supramolecular polymers), two-dimensional sheets[21,22] (vesicles or self-assembled monolayers on surfaces) and three-dimensional solids (metal-organic frameworks).[23]

Besides supramolecular polymerization[20] realized with thiacalixarenes and calixarenes via various endoreceptoric/exoreceptoric binding motifs, the possibility of development of new structures by combination of various cyclophane-based binding sites, *i.e*., multicyclophanes where the central core and peripheral groups have different recognition patterns, is of great interest. It is known that the coordination of *d*-metal cations by thiacalixarene derivatives is achieved by the sulphur bridge atoms and depends on the spatial orientation of the thiacalixarene functional groups.[24] Moreover, the presence of large substituents in the macrocycle structure can also affect the supramolecular self-assembly of macrocycle derivatives.[25]

In order to develop multicalixarenes, we have chosen easily available *p-tert-butyl*-thiacalix[4]arene tetraacid derivatives in *cone* **1**, *partial cone* **2** and *1,3-alternate* **3** configuration as the central core and monoaminothicalixarenes **4** and **9** containing hydroxyl and benzyl groups as the peripheral fragments. Different configuration of the central core allows regulation of the spatial orientation of the thiacalixarene units in the multicalixarene. Hydroxyl and benzyl groups were selected in order to determine the effect of steric factors on the coordination properties of multicalixarenes towards *d*-metal cations.

Thus, we have synthesized multithiacalixarenes containing hydroxyl and benzyl fragments in *cone, partial cone* and *1,3-alternate* configuration. The interaction of the synthesized multithiacalixarenes in the presence of silver cations was studied using DLS.

Experimental

General

^{1}H NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer and ^{13}C and 2D NOESY NMR spectra were obtained on impulse spectrometer Bruker Avance II (125 MHz and 500 MHz respectively). Chemical shifts were determined relative to the signals of residual protons of deuterated solvent ($CDCl_3$). The concentration of the sample solutions was 3–5 %.

Attenuated total internal reflectance IR spectra were recorded with Spectrum 400 (Perkin Elmer) Fourier spectrometer.

Elemental analysis was performed with Perkin Elmer 2400 Series II instrument.

The mass spectra were obtained on Bruker Ultraflex III MALDI-TOF instrument using 1,8,9-trihydroxyanthracene or 4-nitroaniline matrices.

Melting points were determined using the Boetius Block apparatus.

Additional control of the purity of compounds and monitoring of the reaction was carried out by thin-layer chromatography using Silica G, 200 μm plates, UV 254.

*General procedure for the preparation of pentakis-amidothiacalix[4]arenes **5**-**7***. In the round bottom flask equipped with magnetic stirrer and reflux condenser with calcium chloride tube, 0.57 g (0.59 mmol) of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(hydroxycarbonyl)methoxy]thiacalix[4]arene in a certain configuracion (*cone*-**1**, *partial cone*-**2**, *1,3-alternate*-**3**) were mixed with 10.0 ml (0.14 mol) of thionyl chloride, and the mixture was refluxed for 1.5 hours. After that, thionyl chloride was evaporated at reduced pressure, the residue was dried over 2 hours at the reduce pressure. Next, the resulting tetrachloride was dissolved in 20 ml of dichloromethane and transferred to a dropping funnel. Then 2.00 g (2.62 mmol) of 5,11,17,23-tetra-*tert*-butyl-25,26,27-trihydroxy-28-[2'-aminethoxy]-thiacalix[4]arene, 0.5 ml (3.6 mmol) of triethylamine and 30 ml of dichloromethane were placed in a three-necked round bottom flask. The solution of tetrachloride was dropwise added to the flask under stirring and cooling in ice. Resulting solution was left overnight at room temperature. Then white precipitate (triethylamine hydrochloride) was filtered off and the solution was extracted three times with distilled water. After separating organic layer, dichloromethane was evaporated on a rotary evaporator. The white residue was poured in 30 ml of methanol and heated to reflux with stirring. The precipitate (pentathiacalixarene) was filtered off and dried under reduced pressure over P_2O_5.

*Pentakis-amidothiacalix[4]arene cone **(5)***. Yield 1.20 g (51 %). M.p. 201 °C. ^{1}H NMR ($CDCl_3$) δ_H ppm: 0.61 br.s (36H, $(CH_3)_3C$); 1.04 s (36H, $(CH_3)_3C$); 1.15 s (36H, $(CH_3)_3C$); 1.25 s (72H, $(CH_3)_3C$); 4.08 br.s (8H, -O-CH_2-C(O)); 4.86 br.s (8H, -O-CH_2-CH_2-NH); 5.14 br.s (8H, -O-CH_2-CH_2); 6.77 br.s (8H, Ar-H); 7.23 br.s (8H, Ar-H); 7.46 s (8H, Ar-H); 7.51 dd (16H, Ar-H, ^4J=2.5 Hz); 7.57 dd (16H, Ar-H, ^4J=2.5 Hz); 8.84 s (4H, NH). ^{13}C NMR ($CDCl_3$) δ_C ppm: 7.90, 9.09, 30.48, 31.19, 31.43, 31.50, 34.01, 45.97, 52.93, 74.74, 121.52, 121.91, 128.64, 130.38, 130.53, 134.06, 134.57, 135.16, 136.12, 136.22, 141.57, 146.38, 157.04, 158.38, 169.37. IR ν cm^{-1}: 3325 (NH); 1669 (C(O)-NH); 1551 (C(O)-NH). Mass-spectrum (MALDI-TOF): calculated *m/z*=3937.7, found *m/z*=3960.1 (M+Na$^+$). Calculated ($C_{216}H_{260}N_4O_{24}S_{20}$): C, 65.89%; H, 6.66%; N, 1.42%; S, 16.28%; found: C, 65.89%; H, 5.95; N, 1.91%; S, 15.24%.

*Pentakis-amidothiacalix[4]arene partial cone **(6)***. Yield 0.89 g (38 %). M.p. 165 °C. ^{1}H NMR ($CDCl_3$) δ_H ppm: 0.38 br.s (9H, $(CH_3)_3C$); 0.45 br.s (9H, $(CH_3)_3C$); 0.56 br.s (18H, $(CH_3)_3C$); 1.05 s (18H, $(CH_3)_3C$); 1.15 s (9H, $(CH_3)_3C$); 1.18 s (36H, $(CH_3)_3C$); 1.29 s (36H, $(CH_3)_3C$); 1.31 s (36H, $(CH_3)_3C$); 1.37 s (9H, $(CH_3)_3C$); 3.46 m (2H, -O-CH_2-CH_2-NH); 3.93 m (4H, -O-CH_2-CH_2-NH); 4.01 m (4H, -O-CH_2-CH_2-NH); 4.50 dd (2H, -O-CH_2-C(O)); 4.82 m (4H, -O-CH_2-CH_2-NH); 4.90-5.11 m (8H, -O-CH_2-CH_2-NH); 6.41 br.s (2H, Ar-H); 6.52 br.s (2H, Ar-H); 6.67 br.s (4H, Ar-H); 7.03 dd (2H, Ar-H, ^4J=2.5 Hz); 7.45-7.62 m (36H, Ar-H); 7.92 s (2H, Ar-H,); 8.69 s (3H, NH); 9.08 s (1H, NH). ^{13}C NMR ($CDCl_3$) δ_C ppm: 7.89, 8.91, 30.39, 30.34, 30.49, 31.16, 31.28, 31.42, 31.45, 31.50, 31.53, 34.04, 34.30, 40.01, 45.85, 73.83, 121.77, 121.90, 122.08, 123.64, 124.18, 126.42, 126.77, 128.27, 128.51, 130.26, 130.43, 130.92, 131.19, 133.39, 133.87, 134.57, 135.01, 135.16, 136.38, 136.52, 139.99, 141.19, 141.64, 141.88, 145.23, 146.21, 146.64, 147.08, 155.44, 155.73, 156.60, 156.69, 156.77, 156.93, 157.47, 158.09, 159.31, 168.69, 169.34, 169.52. IR ν cm^{-1}: 3319 (NH); 1675 (C(O)-NH); 1539 (C(O)-NH). Mass-spectrum (MALDI-TOF): calculated *m/z*=3937.7, found *m/z*=3960.1 (M+Na$^+$).

Pentakis-amidothiacalix[4]arene 1,3-alternate (***7***). Yield 0.85 g (35 %). M.p. 178 °C. ^{1}H NMR ($CDCl_3$) δ_H ppm: 1.18 s (36H, $(CH_3)_3C$); 1.20 s (36H, $(CH_3)_3C$); 1.21 s (72H, $(CH_3)_3C$); 1.31 s (36H, $(CH_3)_3C$); 4.01 s (8H, -O-CH_2-C(O)); 4.18 m (8H, -O-CH_2-CH_2-NH); 4.54 t (8H, -O-CH_2-CH_2, $^3J_{HH}$=5.6 Hz); 7.50-7.61 m (40H, Ar-H); 8.67 s (4H, NH); 9.28 s (8H, OH); 9.46 s (4H, OH). ^{13}C NMR ($CDCl_3$) δ_C ppm: 31.08, 31.29, 31.34, 31.39, 34.08, 34.17, 34.36, 34.48, 39.55, 120.18, 120.83, 120.87, 128.61, 128.72, 132.58, 135.96, 136.07, 136.29, 136.41, 136.94, 143.49, 143.86, 147.17, 149.30, 156.25, 156.66, 157.66, 169.22. IR ν cm^{-1}: 3354 (NH); 1675 (C(O)-NH); 1528 (C(O)-NH). Mass-spectrum (MALDI-TOF): calculated *m/z* = 3937.7, found *m/z* = 3960.5 (M+Na$^+$). Calculated ($C_{216}H_{260}N_4O_{24}S_{20}$): C, 65.89%; H, 6.66%; N, 1.42%; S, 16.28%; found: C, 67.46%; H, 6.01; N, 2.12%; S, 15.32%.

*5,11,17,23-Tetra-tert-butyl-25,26,27-tribenzoxy-28-[2'-(N-phthalimide)ethoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate-**9**)*. In the round bottom flask equipped with magnetic stirrer and reflux condenser, 1 g (1.12 mmol) of 5,11,17,23-tetra-*tert*-butyl-25,26,27-trihydroxy-28-[2'-(*N*-phthalimide)ethoxy]-2,8,14,20-tetrathiacalix[4]arene was mixed with 2.91 g (8.94 mmol) of dry cesium carbonate and 50 ml of acetone. 2.1 ml (17.88 mmol) of benzyl bromide were added to this suspension. The reaction mixture was stirred at reflux temperature for 16 hours. After cooling the reaction mixture, the solvent was evaporated under reduced pressure, dry residue was dissolved in chloroform and washed with 2 M HCl and distilled water. The organic layer was separated, dried over 3 Å molecular sieves. The solvent was removed on a rotary evaporator under reduced pressure. The residue was washed with 50 ml of methanol. Yield of tetrathiacalix[4]arene **9** in *1,3-alternate* configuration was 0.95 g (73 %). M.p. 213 °C. ^{1}H NMR ($CDCl_3$) δ_H ppm: 0.80 s (9H, $(CH_3)_3C$); 0.83 s (9H, $(CH_3)_3C$); 0.98 s (18H, $(CH_3)_3C$); 3.97 m (2H, CH_2-NPhth); 4.23 m (2H,CH_2-CH_2-O-); 5.07-5.14 m (6H, O-CH_2-Ph); 6.66 m (2H, Ar-H); 6.95-7.17 m (15H, Ar-H); 7.08 s (2H, Ar-H); 7.11 s (2H, Ar-H); 7.66 m (2H, Ar-H); 7.75-7.91 m (4H, Ar-H). NMR ^{1}H-^{1}H NOESY ($CDCl_3$) δ_H ppm: H$^{4''b}$/H$^{7''}$, H$^{3'}$/H$^{7''}$, H$^{3''}$/H$^{7''}$, H$^{4''b}$/H$^{7'}$, H^7/H$^{7'}$, H^8/H$^{7''}$, H^3/H$^{7'''}$, H^{4b}/H$^{7'''}$. ^{13}C NMR ($CDCl_3$) δ_C ppm: 28.56; 30.33; 30.98; 31.22; 33.89; 33.98; 36.98; 65.43; 67.03; 125.28; 125.91; 126.19; 126.56; 127.19; 127.60; 128.67; 130.90; 145.15; 154.94; 160.61. IR ν cm^{-1}: 1667 (C(O)-), 1120 (Ar-H). Mass-spectrum (MALDI-TOF): calculated *m/z* = 1088.5, found *m/z* = 1089.6 (M+H). Calculated ($C_{66}H_{73}NO_5S_4$): C, 72.82%; H, 6.76%; N, 1.29%; S, 11.78%; found: C, 73.01%; H, 6.93%; N, 1.33%; S, 11.85%.

*5,11,17,23-Tetra-tert-butyl-25,26,27-tribenzoxy-28-[2'-aminethoxy]-2,8,14,20-tetrathiacalix[4]arene (**10**)*. In the round bottom flask equiped with magnetic stirrer and reflux condenser, 1 g (0.86 mmol) of 5,11,17,23-tetra-*tert*-butyl-25,26,27-tribenzoxy-28-[2'-(*N*-phthalimide)ethoxy]-2,8,14,20-tetrathiacalix[4]arene **9**, 1.07 ml (21.49 mmol) of hydrazine hydrate, 25 ml of tetrahydrofurane and 25 ml of ethanol were mixed. The reaction mixture was refluxed for 15 hours. After cooling the reaction mixture, the solvent was evaporated under reduced pressure; dry residue was dissolved in chloroform and threefold extracted with distilled water. Organic layer was separated, dried over 3 Å molecular sieves. The solvent was removed on a rotary evaporator under reduced pressure. The residue was washed with 50 ml of methanol. Yield of thiacalix[4]arene **10** is 0.84 g (95 %). M.p. 170 °C. ^{1}H NMR ($CDCl_3$) δ_H ppm: 0.83 s (9H, $(CH_3)_3C$); 0.84 s (9H, $(CH_3)_3C$); 1.02 s (18H, $(CH_3)_3C$); 2.70 m (2H, CH_2-NH_2); 4.10 m (2H,CH_2-CH_2-O-); 5.06-5.12 m (6H, O- CH_2-Ph); 6.78 m (2H, Ar-H); 6.91-7.25 m (15H, Ar-H); 7.11 s (2H, Ar-H); 7.12 s (2H, Ar-H); 7.35 m (2H, Ar-H). ^{13}C NMR ($CDCl_3$) δ_C ppm: 30.69, 30.73, 30.76, 30.80, 31.01, 69.89, 70.70, 71.03, 124.83, 125.88, 126.80, 126.93, 127.23, 127.57, 127.93, 128.03, 128.07, 128.35, 128.41, 128.70, 128.81, 129.06, 129.18, 129.26, 130.35, 137.37, 137.50, 137.83, 146.22, 146.47, 146.55, 156.46, 156.51. IR ν cm^{-1}: 3740 (OH), 3655 (OH), 3374, 3317 (NH). Mass-spectrum (MALDI-TOF): calculated *m/z*=1033.4, found *m/z* = 1034.4 (M+H). Calculated ($C_{63}H_{71}NO_4S_4$): C, 73.14%; H, 6.92%; N, 1.35%; S, 12.40%; found: C, 73.23%; H, 6.98%; N, 1.25%; S, 12.32%.

*General procedure for the preparation of pentakis-amido-thiacalix[4]arenes **11-13***. In the round bottom flask equipped with magnetic stirrer and reflux condenser with calcium chloride tube, 0.57 g (0.59 mmol) of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(hydroxycarbonyl)methoxy]thiacalix[4]arene in a certain configuration (*cone*-**1**, *partial cone*-**2**, *1,3-alternate*-**3**) and 10.0 ml (0.14 mol) of thionyl chloride were mixed, the mixture was refluxed for 1.5 hour. Then the thionyl chloride was evaporated at reduced pressure, the residue was dried over 2 hours at reduce pressure. Next, the resulting tetrachloride was dissolved in 20 ml of dichloromethane and transferred to a dropping funnel. 2.73 g (2.62 mmol) of 5,11,17,23-tetra-*tert*-butyl-25,26,27-tribenzoxy-28-[2'-aminethoxy]-2,8,14,20-tetrathiacalix[4]arene **10**, 0.5 ml (3.6 mmol) of triethylamine and 30 ml of dichloromethane were placed in a three-necked round bottom flask. Then the solution of tetrachloride was dropwise added to the mixture under stirring and cooling in an ice. Then the resulting solution was left overnight at room temperature. White precipitate (triethylamine hydrochloride) was filtered off and the solution extracted three times with distilled water. After separating the organic layer, dichloromethane was evaporated on a rotary evaporator. Multicalixarenes **11-13** were obtained using gravity chromatography (dichloromethane:acetone 1:3).

*Pentakis-amidothiacalix[4]arene cone (**11**)*. Yield 2.60 g (87 %). M.p. 181 °C. ^{1}H NMR ($CDCl_3$) δ_H ppm: 0.78 s (36H, $(CH_3)_3C$); 0.85 s (36H, $(CH_3)_3C$); 0.87 s (72H, $(CH_3)_3C$); 1.08 s (36H, $(CH_3)_3C$); 3.74 m (8H, -O-CH_2-CH_2-NH); 4.27 t (8H, -O-CH_2-C(O), $^3J_{HH}$=6.6 Hz); 4.84 s (8H, -O-CH_2-C(O)); 5.08-5.11 m (24H, Bn-CH_2), 6.63-7.62 m (100 H, Ar-H); 8.24 s (4H, NH). ^{13}C NMR ($CDCl_3$) δ_C ppm: 30.68, 30.82, 30.96, 31.13, 31.16, 33.99, 68.77, 70.68, 71.08, 125.01, 126.31, 126.73, 127.20, 127.27, 127.80, 128.04, 128.16, 128.22, 128.62, 128.68, 129.23, 130.03, 130.20, 134.33, 137.79, 137.91, 145.31, 146.21, 146.26, 146.79, 147.09, 147.36, 156.16, 156.98, 157.38, 157.98, 168.08. IR ν cm^{-1}: 3333 (NH); 1684 (C(O)-NH); 1527 (C(O)-NH). Mass-spectrum (MALDI-TOF): calculated *m/z*=5024.3, found *m/z* = 5025.5 (M+H$^+$). Calculated ($C_{300}H_{332}N_4O_{24}S_{20}$): C, 71.79%; H, 6.67%; N, 1.12%; S, 12.78%; found: C, 72.20%; H, 6.88%; N, 1.17%; S, 13.34%.

*Pentakis-amidothiacalix[4]arene partial cone (**12**)*. Yield 2.7 g (90 %). M.p. 240 °C. ^{1}H NMR ($CDCl_3$) δ_H ppm: 0.79 s (18H, $(CH_3)_3C$); 0.82 s (9H, $(CH_3)_3C$); 0.85 s (18H, $(CH_3)_3C$); 0.86 s (36H, $(CH_3)_3C$); 0.91 s (18H, $(CH_3)_3C$); 0.92 s (18H, $(CH_3)_3C$); 0.93 s (18H, $(CH_3)_3C$); 1.03 s (18H, $(CH_3)_3C$); 1.26 s (9H, $(CH_3)_3C$); 1.32 s (9H, $(CH_3)_3C$); 1.45 s (9H, $(CH_3)_3C$); 3.57-4.87 m (24H, -CH_2-); 5.07 m (16H, -O-CH_2Bn); 5.13 s (8H, -O-CH_2Bn); 6.68-7.80 m (100H, Ar-H); 7.93 s (1H, NH); 8.30 s (2H, NH); 8.38 s (1H, NH). ^{13}C NMR ($CDCl_3$) δ_C ppm: 30.32. 30.78, 30.81, 30.94, 31.01, 31.10, 31.25, 31.43, 68.88, 69.26, 69.42, 71.02, 71.32, 74.69, 124.98, 125.29, 125.59, 125.80, 126.24, 126.80, 127.11, 127.17, 127.22, 127.33, 127.83, 127.88, 128.06, 128.32, 128.52, 128.56, 128.70, 129.28, 129.44, 129.55, 129.63, 129.81, 130.26, 132.98, 134.90, 135.20, 136.79, 137.62, 137.73, 137.95, 138.02, 145.31, 145.73, 146.07, 146.28, 146.33, 146.40, 146.90, 156.28, 156.32, 156.35, 156.86, 156.90, 156.99, 157.08, 157.17, 158.46, 167.87. IR ν cm^{-1}: 3319 (NH); 1681 (C(O)-NH); 1526 (C(O)-NH). Mass-spectrum (MALDI-TOF): calculated *m/z*=5015.7 found *m/z*=5038.2 (M+Na$^+$). Calculated ($C_{300}H_{332}N_4O_{24}S_{20}$): C, 71.79%; H, 6.67%; N, 1.12%; S, 12.78 %; found: C, 72.05%; H, 6.95%; N, 1.15%; S, 12.85%.

*Pentakis-amidothiacalix[4]arene 1,3-alternate (**13**)*. Yield 2.78 g (93 %). M.p. 210 °C. ^{1}H NMR ($CDCl_3$) δ_H ppm: 0.81 s (36H, $(CH_3)_3C$); 0.87 s (36H, $(CH_3)_3C$); 0.93 s (72H, $(CH_3)_3C$); 1.10 s (36H, $(CH_3)_3C$); 3.65 m (8H, -O-CH_2-CH_2-NH); 4.09 s (8H, -O-CH_2-C(O)); 4.26 t (8H, -O-CH_2-C(O), $^3J_{HH}$=7.0 Hz); 5.06-5.16 m (24H, Bn-CH_2), 6.72-7.52 m (100H, Ar-H); 8.17 s (4H, NH). ^{13}C NMR ($CDCl_3$) δ_C ppm: 12.62, 13.78, 24.55, 24.86, 25.26, 25.52, 26.14, 29.27, 31.09, 31.33, 33.70, 34.50, 38.14, 39.38, 65.24,

66.70, 119.37, 120.11, 126.60, 127.26, 127.65, 127.86, 128.14, 128.33, 128.43, 146.32, 147.19, 155.33, 156.24, 157.12. IR ν cm^{-1}: 3335 (NH); 1680 (C(O)-NH); 1523 (C(O)-NH). Mass-spectrum (MALDI-TOF): calculated *m/z* = 5024.3, found *m/z* = 5025.5 ($M+H^+$). Calculated ($C_{300}H_{332}N_4O_{24}S_{20}$): C, 71.79%; H, 6.67%; N, 1.12%; S, 12.78 %; found: C, 72.26%; H, 6.90%; N, 1.21%; S, 12.92%.

Dynamic light-scattering (DLS). The particle size was determined using the Zetasizer Nano ZS instrument at 20 °C in CH_2Cl_2. The instrument contains the 4 mW He–Ne laser operating at the wavelength of 633 nm and incorporates non-invasive backscatter optics (NIBS). The measurements were performed at the detection angle of 173 and the measurement position within the quartz cuvette was automatically determined by the software. The solutions of the systems investigated were prepared by addition of a metal nitrate to 10 ml of $1 \cdot 10^{-5}$ M solution of thiacalixarene derivatives in CH_2Cl_2, (HPLC grade). The mixture was mechanically shaken for 2 hours and then magnetically stirred in thermostated water bath at 20 °C for 1 hour. The final concentration of metal nitrates in 10 ml CH_2Cl_2, (HPLC grade) was equal to $1 \cdot 10^{-4}$ M. Three independent experiments were carried out for each combination of a ligand and metal nitrate.

Results and Discussion

Thiacalix[4]arene derivatives are generally polyfunctional reagents. In this regard, synthesis of multicalix[4] arenes, usually leads to mixtures of products or to low yields of the compound desired. To synthesize multicalixarenes, various reaction procedures such as O-alkylation,[26] cross-coupling of an olefin and alkynyl derivatives,[27-29] as well as linking calixarene units by forming amide and ester bond[30-32] have been described.

We have specified for the interaction of primary amines with acid chlorides. To be able to control the spatial arrangement of the terminal units in the central core of pentakiscalixarene, we selected the tetra acid of thiacalix[4]arene in *cone*, *partial cone* and *1,3-alterntat* configurations. Monosubstituted thiacalix[4]arene **4** containing three hydroxyl groups was selected as a terminal fragment. Previously, our research group,[33] showed that monoamine **4** could exist in the *cone* or *partial cone* conformation depending on the temperature. Thus, to avoid the formation of byproducts, the synthesis was carried out at low temperature (Scheme 1).

Pentakiscalixarenes **5-7** were obtained from the reaction mixture with 35–51 % yields. Poor yields are due to side reaction involving the acylation of phenolic hydroxyl groups of calixarene **4.** Attempts of chromatographic separation of the compounds **5-7** using different eluents did not lead to satisfactory results. Probably, the presence of phenolic hydroxyl groups in the macrocycle leads to considerable complication during the chromatographic separation of the target macrocycles **5-7**. Multicalixarenes **5-7** were obtained by repeated recrystallization from methanol.

To introduce bulky non-coordinating groups in the terminal calixarene units so as to prevent complexation with silver cation, we have synthesized monoamine based thiacalixarene, wherein the phenolic hydroxyls was substituted with benzyl moieties. Moreover, it is known that benzyl moieties are convenient protecting groups for phenolic and alcoholic hydroxyl groups.[34] Mild conditions for debenzylation in combination with high yields of protection reaction of hydroxyl groups makes benzyl group well appropriate for the synthesis of protected monoamine based the macrocycles **5-7** with high yields.

The reaction between the monophthalemide **8** previously obtained in our group[33] and benzyl bromide in the presence of cesium carbonate in acetone resulted in the macrocycle **9** with 73 % yield (Scheme 2). It should be noted that according to two-dimensional NMR ^1H-^1H data, macrocycle **9** exists in the *1,3-alternate* conformation. Hydrazinolysis of the macrocycle **9** resulted in amine **10** with 95 % yield.

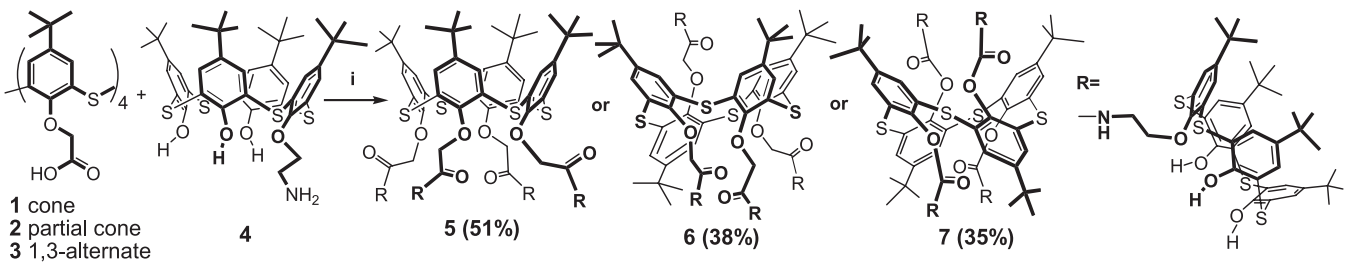
For synthesis of pentakis-calixarenes containing benzyl moieties, the amine **10** reacted with tetrasubstituted thiacalixarene carboxylic groups in *cone, partial cone* and *1,3-alternate* configuration (Scheme 3). Synthesis was carried out under cooling to reduce the possibility of side reactions.

The reaction progress was monitored by IR and ^1H NMR spectroscopy. Table 1 shows the characteristic band values for the stretching vibrations of the amide group in the compounds **5-7** and **11-13**. As could be seen from Table 1, the amide protons in the multicalixarenes **5-7** and **11-13** are in the associated form.

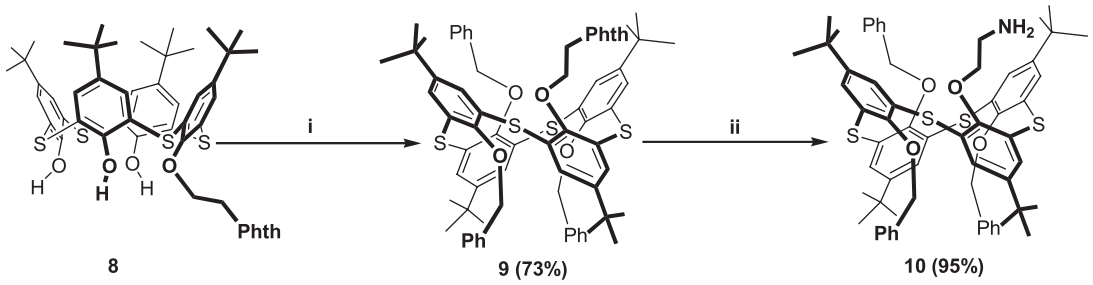
Table 1. The values of valence vibrations for macrocycle **5-7** and **11-13** in the IR spectra.

Compound	ν (-C(O)NH-), cm^{-1}	ν (-C(O)-), cm^{-1}
5	3325, 3047	1669
6	3319, 3052	1675
7	3354, 3053	1675
11	3333, 3060	1684
12	3319, 3062	1681
13	3335, 3061	1680

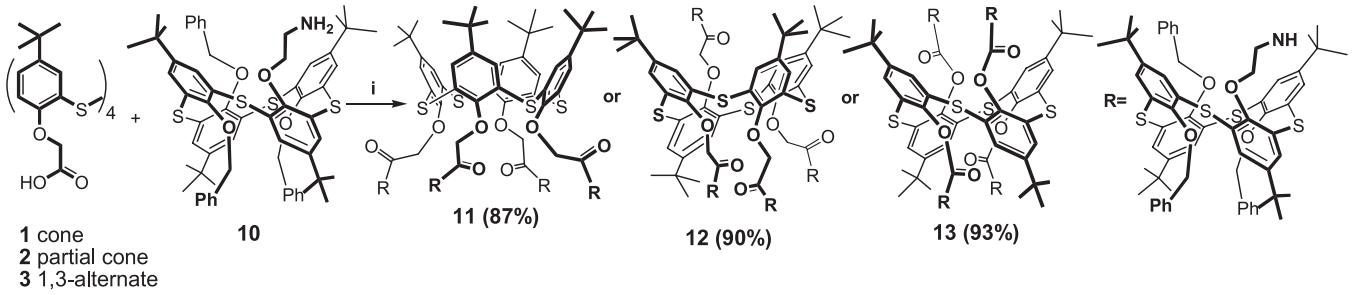
Pentakis-calix[4]arenes **11-13** were finally isolated in good yields by preparative chromatography on silica gel (dichloromethane-acetone 3:1 as an eluent). The structure



Scheme 1. Reagents and conditions: i, 1) $SOCl_2$, 2) RH, CH_2Cl_2/NEt_3.



Scheme 2. Reagents and conditions: i, BnBr, Cs_2CO_3, acetone; ii, $NH_2NH_2 \cdot H_2O$, EtOH/THF.



Scheme 3. Reagents and conditions: i, 1) $SOCl_2$ 2) RH, CH_2Cl_2/NEt_3.

and composition of the macrocycles synthesized were characterized by a number of physical-chemical methods including ^1H and ^{13}C NMR, two-dimensional NOESY ^1H-^1H spectroscopy, IR spectroscopy, MALDI-TOF mass spectrometry and elemental analysis.

Figure 1 shows the ^1H NMR spectrum of multicalixarene **6** as an example**.** The complicated character of signals for the *tert*-butyl, oxymethylene and aromatic protons indicates low symmetry in structure of the compound **6**. Analysis of the chemical shifts, multiplicity and intensity of the proton signals suggests that the structure of the resulting compound corresponds to the pentakis-calixarene **6**.

Figure 2 shows the ^1H NMR spectrum of compound **12** in which the type and intensity of the proton signals are fully

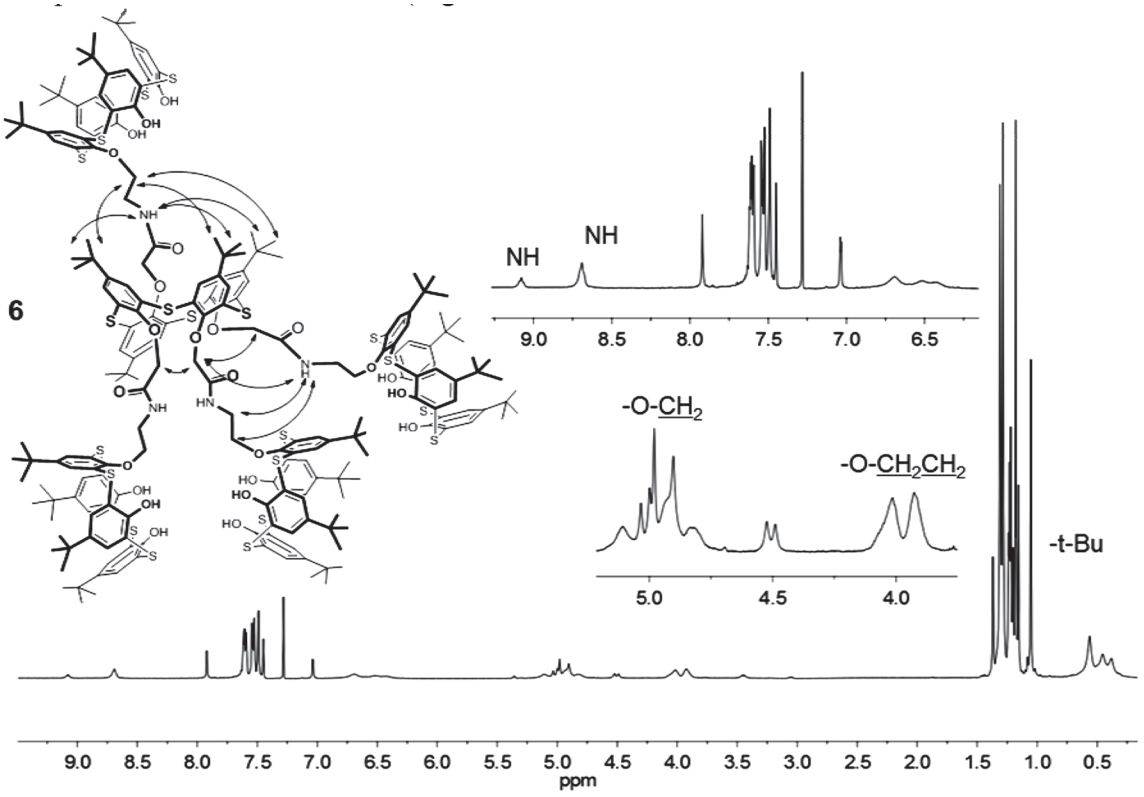


Figure 1. ^1H NMR spectrum of compound **6** ($CDCl_3$, at 25 °C, 400 MHz).

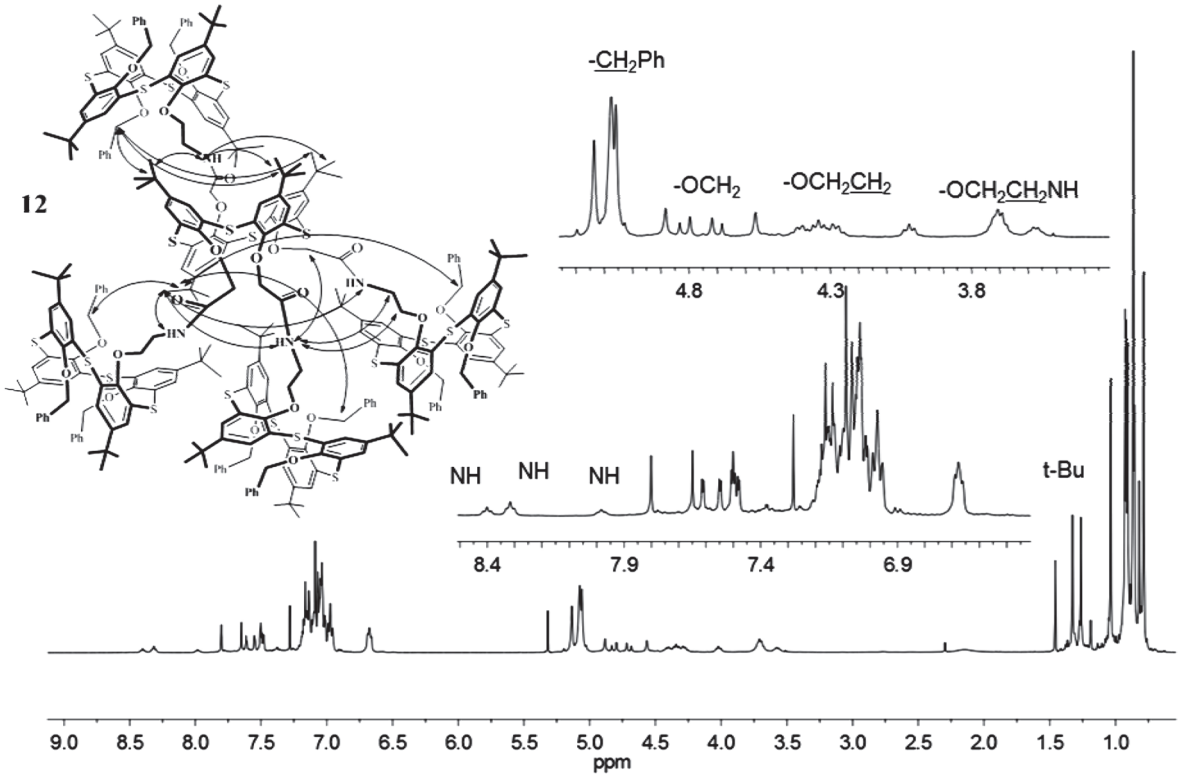


Figure 2. ^{1}H NMR spectrum of compound **12** ($CDCl_3$, at 25 °C, 400 MHz).

consistent with the proposed structure of the compound **12**. To conclusively establish the structures of multicalixarenes, two-dimensional NOESY ^{1}H-^{1}H experiment was carried out (Figures 3 and 4 show the spectra of the macrocycles **6** and **12** respectively). Cross-peaks between *tert*-butyl, amido and oxymethylene fragments clearly indicate that multicalixarenes **6** and **12** exist in the *partial cone* configuration.

*Aggregation Study of p-tert-Butylmultithiacalix[4] arenes **5-7** and **11-13** by DLS Method*

Thiacalixarene derivatives are known to be able to form supramolecular aggregates with cations of *s*-, *p*-, and *d*-elements.[4,5] Previously, our research group demonstrated supramolecular self-assembling of pentathiacalixarene bearing nitrile fragments with Ag^+, Cu^{2+}, Co^{2+}, Ni^{2+}, Fe^{3+} cations into nanoscale aggregates. It should be noted that aggregate formation was observed for all three configurations of thiacalixarene.[31] For the realization of supramolecular self-assembly of the multicalixarenes synthesized, we have investigated interaction of multicyclophanes **5-7** and **11-13** with a number of cations of *d*-elements (Ag^+, Cu^{2+}, Co^{2+}, Ni^{2+}, Fe^{3+}). From all the multicalixarenes synthesized, only macrocycles of **5** and **11** in *cone* configuration form supramolecular aggregates with silver cation in dichloromethane with average hydrodynamic diameter 180 and 201 nm, respectively (Table 2). The formation of colloidal aggregates was observed only for multicyclophanes **5** and **11** in *cone* configuration. Probably, this might be due to higher steric accessibility of bridging sulfur atoms of a core and of peripheral thiacalixarene units necessary for coordination of silver cation.[4,5]

Despite the fact that multicyclophanes **5-7** and **11-13** synthesized have different functional groups (hydroxyl and benzyl moieties), the formation of supramolecular aggregates has occurred exclusively in case of the compounds **5** and **11**. This indicates that aggregation of the multicalixarenes **5-7** and **11-13** with silver cation depends on the configuration of the central core of multicalixarenes.

Table 2. The size of aggregates (hydrodynamic diameters, average value, d_1, d_2 (nm), and peak area intensity, S_1, S_2 (%), for peaks 1, 2, respectively) obtained with *p-tert*-butyl thiacalix[4]arene **5** and **11**, $AgNO_3$ in CH_2Cl_2 (HPLC), and polydispersity index (PDI).

Compound	d_1, nm/S_1, %	d_2, nm/S_2, %	PDI
5	188.4±6.08/ 100	–	0.13±0.02
11	210.7±2.57/ 95.6±2.1	4566±186.6/ 4.8±2.1	0.25±0.03

Conclusion

We have developed method for the synthesis of multicalixarenes based on the interaction of amino derivatives with carboxylic acid derivatives of thiacalixarene. New monosubstituted pentakis-thiacalix[4]arenes in three different configurations, *cone, partial cone* and *1,3-alternate,* were synthesized. The structure and composition of the

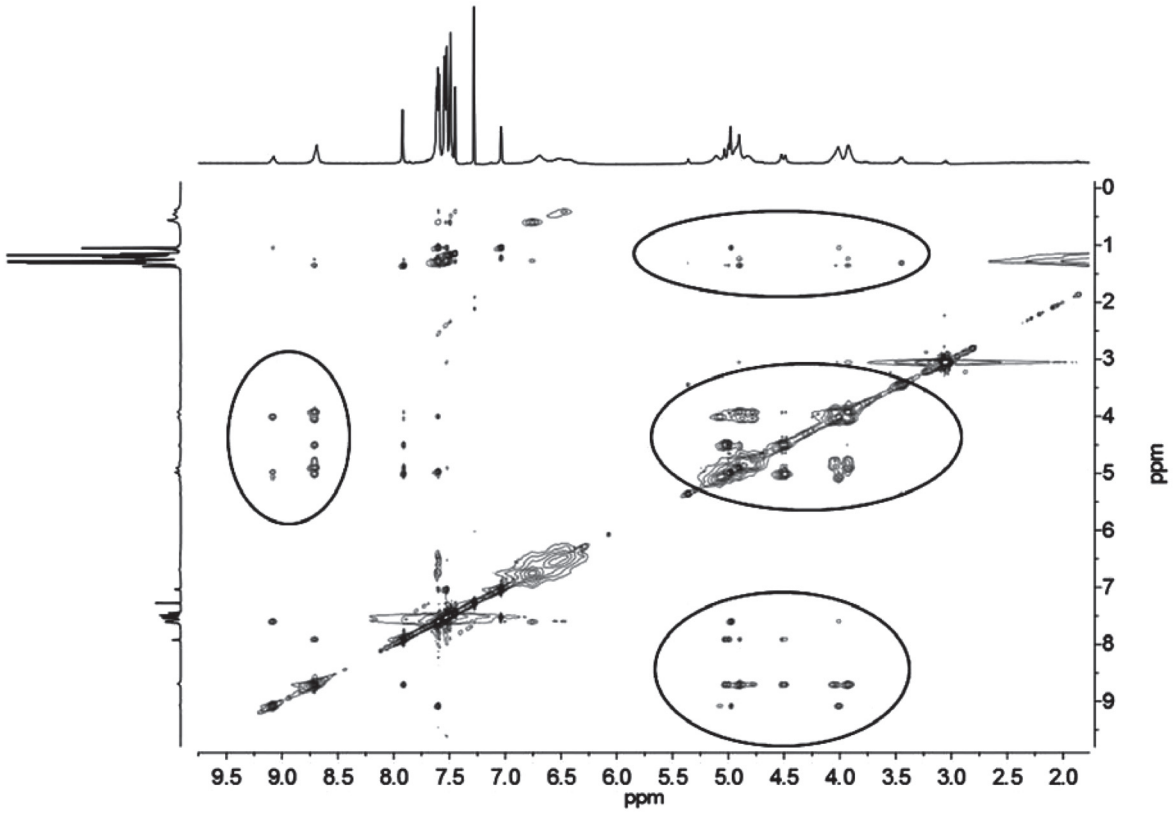


Figure 3. NOESY ^{1}H-^{1}H NMR spectrum of compound **6** ($CDCl_3$, at 25 °C, 400 MHz).

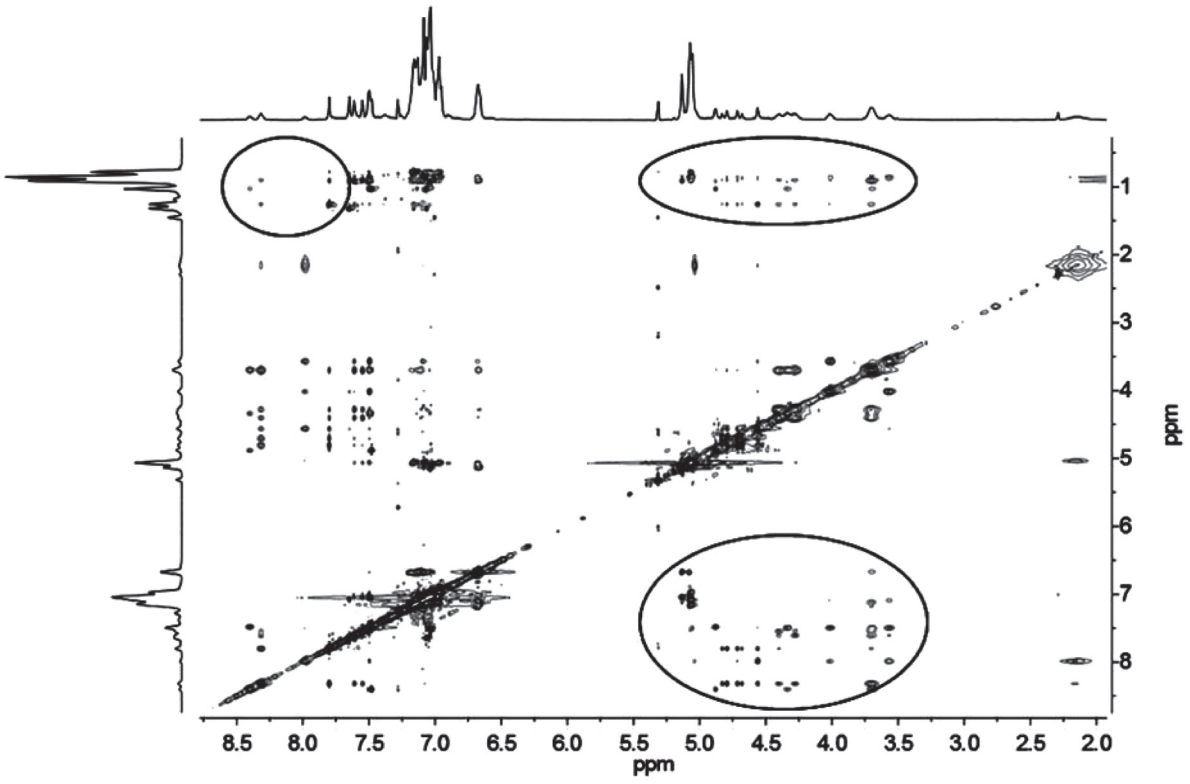


Figure 4. NOESY ^{1}H-^{1}H NMR spectrum of compound **12** ($CDCl_3$, 25 °C, 400 MHz).

polymacrocycles obtained were characterized by a number of physical methods including ^{1}H, ^{13}C, IR spectroscopy and mass spectrometry. The spatial structure was confirmed by two-dimensional ^{1}H-^{1}H NMR spectroscopy. It has been shown that nano-sized aggregates with silver cation formed only in the case of multicalixarene with a *cone* central core configuration.

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