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Pentakis-thiacalix[4]arenes with nitrile fragments: receptor properties toward cations of some *s*- and *d*-metals and self-assembly of nanoscale aggregates

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Pentakis-thiacalix[4]arenes containing thiacalix[4]arene fragments in *cone*, *partial cone* and *1,3-alternate* conformations as their central core have been obtained. Their interaction with cations of *s*- and *d*-metals gives supramolecular assemblies whose composition depends on the conformation of pentakis-thiacalix[4]arenes and the nature of the 'guests'.

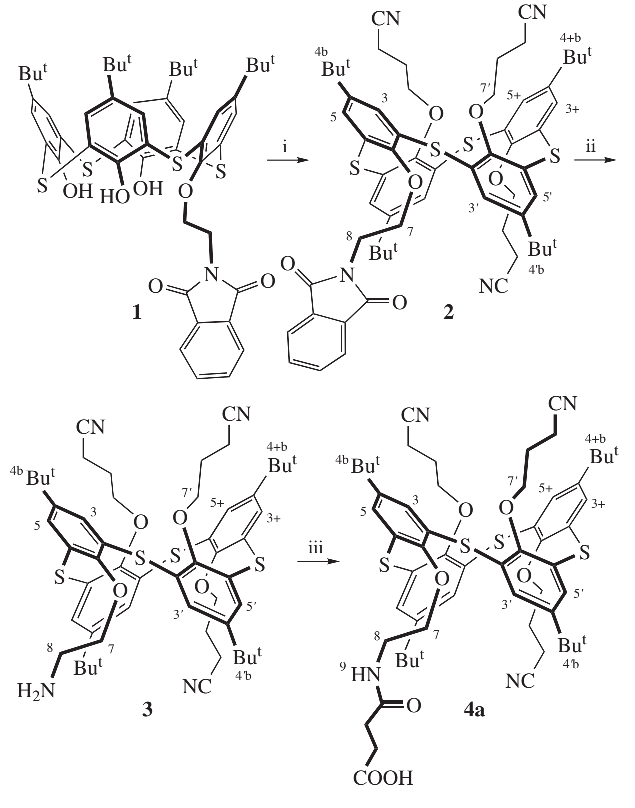
Organic nanoscale structures are widely used to create materials able to molecular recognition of targeted substrates.[1,2] Calixarenes have proved to be promising synthetic building blocks for the design of selective 'host' molecules.[3–8] Combining multiple calixarene fragments in one structure yields multifunctional nanoscale receptors able to recognize ion pairs,[9,10] surface of biomacromolecules and also, to transfer them through cell membranes.[11] Nitrile group is one of topical due to its synthetic potential and complexation properties.[12,13] Polymers containing nitrile groups are used in lithium-ion batteries as electrodes.[14,15] For thiacalix[4]arenes tetrasubstituted at the lower rim, three conformational isomers of the macrocycle (*cone*, *partial cone*, *1,3-alternate*) are easily synthesized.[16,17]

In this regard we studied the block synthesis of nitrile-containing pentakis-thiacalix[4]arenes in which the central core is formed by thiacalix[4]arene fragments in *cone*, *partial cone* and *1,3-alternate* conformations.

Previously we have shown[18,19] that variation of the length of a spacer linking the phthalimide fragment and leaving group in bromoalkylphthalimides makes it possible to vary the number of phthalimide groups at the lower rim of thiacalix[4]arene. Monosubstituted derivative **1** containing the phthalimide fragment[18] was selected as starting compound for the synthesis of the terminal fragment precursor of pentakis-thiacalix[4]arenes. The target compound **4a** was obtained by alkylation of the monosubstituted macrocycle **1** with 4-chlorobutyronitrile followed by removing the phthaloyl protection with hydrazine hydrate and amine acylation with succinic anhydride (Scheme 1).†

Conformations of thiacalix[4]arenes **2**–**4** were established by two-dimensional ^{1}H–^{1}H NMR NOESY spectroscopy. The presence of cross-peaks between spatially close protons of *tert*-butyl groups and the substituents at the lower rim of the macrocycle clearly indicates that they possess *1,3-alternate* conformation.

Recently, it was found that thiacalix[4]arene derivatives containing aminoethylidene fragments exist in solution as a mixture of conformers[19] due to twisting of the fragment through the macrocyclic ring. Using ^{1}H NMR spectroscopy, it was shown that macrocycle **3** exists as a single conformer at room temperature. Acylation of the amine group of **3** with succinic anhydride at room temperature does not lead to the formation of products related to other conformations. However, raising temperature (35 °C or higher) results in a mixture of conformational isomers of *1,3-alternate* and *partial cone* in the ratio 82 : 18 (Scheme 2). In the ^{1}H NMR spectrum of such reaction mixture, the proton signals of the *partial cone* conformer **4b** are clearly observed (see Figure S1, Online Supplementary Materials).



Scheme 1 *Reagents and conditions*: i, 4-chlorobutyronitrile, K_2CO_3, acetone; ii, $N_2H_4{\cdot}H_2O$, THF–EtOH; (iii) succinic anhydride, CH_2Cl_2, 0 °C.

We selected thiacalix[4]arene based tetraethanolamide stereoisomers **5**–**7** (Scheme 3) as the central core of pentakis-thiacalix[4]arenes because they can be easily synthesized from corresponding tetraesters.[20] In addition, they contain primary hydroxy groups available for further functionalization. The condensation between thiacalix[4]arenes **4a** and **5**–**7** was performed using dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP).[21]

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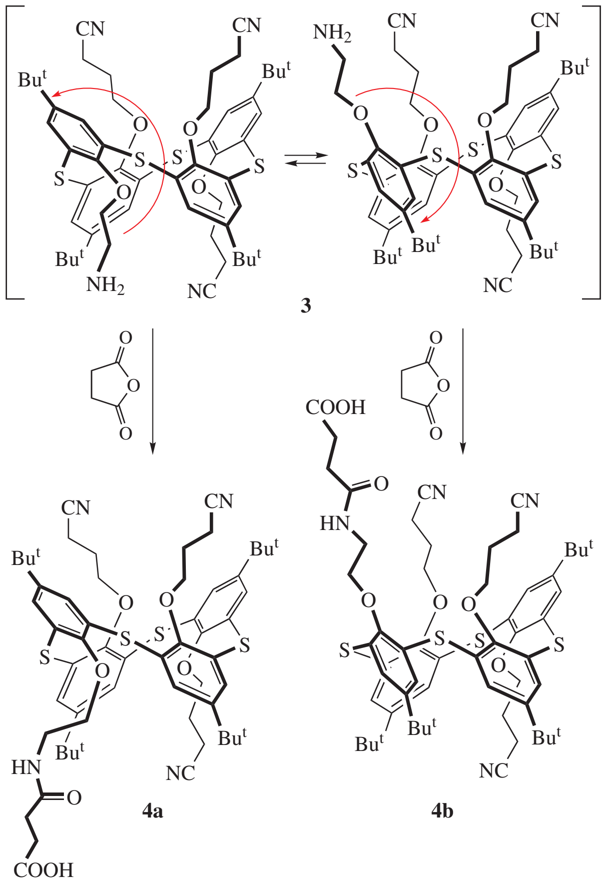
† For synthetic procedures and characteristics of compounds **2**, **3**, **4a**, **8**–**10**, see Online Supplementary Materials.



Scheme 2 Formation of conformers **4a** and **4b** at 35 °C.

The rate of such condensation was found to be dependent on the conformation of the central core **5–7** (TLC control). In case of the *cone* conformation, the reaction proceeded within 48 h, for *partial cone* within 80 h and for the *1,3-alternate* within 125 h. This might have been owing to an increase in steric hindrance between the hydroxyl and *tert*-butyl groups in the *partial cone* and *1,3-alternate* conformations.

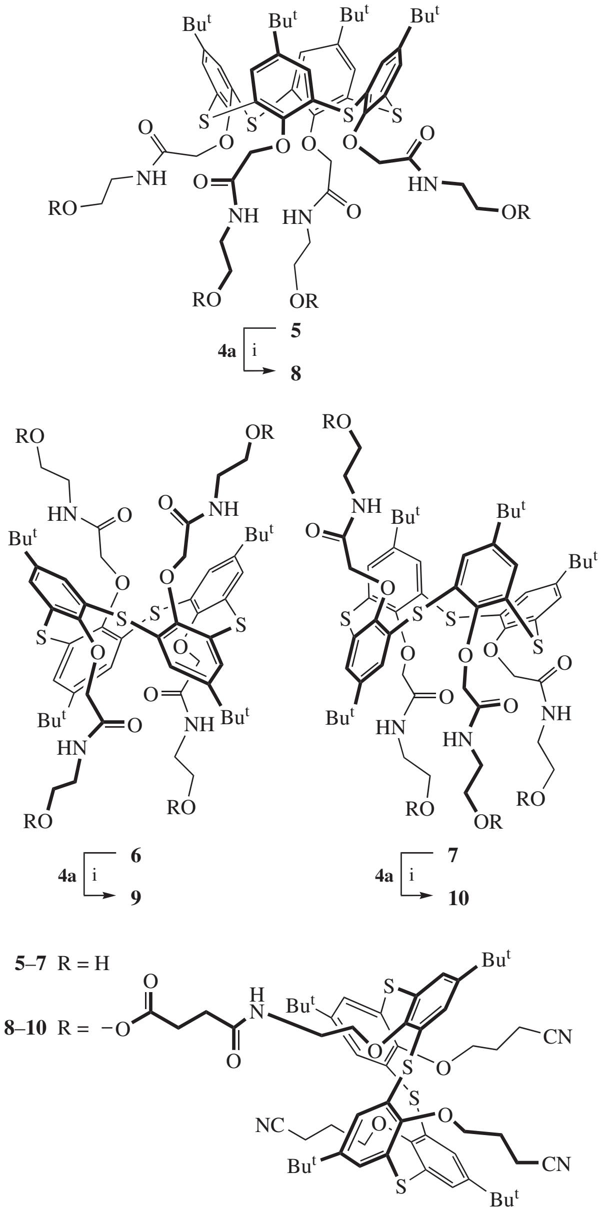
The structure and composition of compounds **8–10**† were confirmed by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The MALDI mass spectra of pentakis-thiacalix[4]arenes **8–10** include the peak 5354.4 *m/z*, corresponding to their molecular ion peak with potassium cations $(M + K^+)$. Acetophenone and *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile were used as a matrix.

Tetrasubstituted at the lower rim thiacalix[4]arenes containing amide,[22] ester[23] and ketone[24] groups effectively interact with alkali metal cations. The study of the complexation properties towards cations of *d*-elements with different coordination geometry by *p*-*tert*-butylthiacalix[4]arenes *via* soft donor atoms of nitrogen and sulfur, is of significant interest. This is mostly due to the possibility of formation of 'host–guest' complexes[25,26] or supramolecular aggregates[27–29] depending on the mode of substrate coordination. Spectrophotometric (UV) titration‡ in CH_2Cl_2/MeOH was carried out to quantify the molecular recognition of cations of some *s*- and *d*-elements by the macrocycles **4a** and **8–10**. Thus measured stability constants and the stoichiometry of the cation–macrocycle complex formed in the organic phase are given in Table 1. In the case of macrocycle **4a**, the stoichiometry of all the complexes was 1:1. This assumes that the interaction occurs only on one side of a macrocyclic platform regardless of the cation size and its coordination geometry. Note that the efficiency of interaction of the synthesized macrocycles with substrates increased by an order of magnitude in direction from the mono- and divalent cations of lithium, silver(I), copper(II) and nickel(III) ions to the trivalent iron(III) and cobalt(III) ions. Obviously, lithium cation is coordinated by the most 'hard' carboxy group. This is confirmed by the absence of interaction with lithium nitrate in the case of pentakis-thiacalix[4]arenes **8–10**. It is well known that the interaction of thiacalix[4]arenes with silver is achieved through the coordination with the bridging sulfur atoms and the formation of extended associates.[30,31] Thus,

Table 1 Logarithms of the association constants ($\log K_{ass}$) and stoichiometry ('host' : 'guest') of the complexes (1 : 1) of macrocycles **4a**, **8–10** with metal nitrates.

Metal nitrate	4a	8	9	10
$LiNO_3$	4.53±0.23	—	—	—
$AgNO_3$	4.18±0.17	2.69±0.32	2.94±0.12	2.87±0.22
$Ni(NO_3)_2$	4.36±0.12	4.20±0.15	4.71±0.14	4.72±0.14[a]
$Cu(NO_3)_2$	4.44±0.11	4.99±0.15	5.62±0.18[a]	4.51±0.20
$Co(NO_3)_3$	5.88±0.17	5.30±0.17[a]	4.33±0.16	5.33±0.14[a]
$Fe(NO_3)_3$	5.71±0.09	5.50±0.13[a]	4.65±0.07	4.73±0.10

[a] Stoichiometry of 3:2 ('host' : 'guest').



Scheme 3 *Reagents and conditions*: i, DCC, DMAP, CH_2Cl_2.

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‡ For details of UV titration and DLS, see Online Supplementary Materials.

Table 2 Size of aggregates (hydrodynamic particle size d_1, d_2), the peak areas (S_1, S_2) of particle size distribution (intensity) in CH_2Cl_2 and polydispersity index (PDI).

System	d_1/nm	S_1 (%)	d_2/nm	S_2 (%)	PDI
4a + $LiNO_3$	144.1±13.9	100	—	—	0.12±0.06
4a + $AgNO_3$	147.2±6.7	100	—	—	0.38±0.02
4a + $Ni(NO_3)_2$	—	—	—	—	—
4a + $Cu(NO_3)_2$	347.5±33.5	100	—	—	0.38±0.02
4a + $Co(NO_3)_3$	409.5±71.8	100	—	—	0.32±0.07
4a + $Fe(NO_3)_3$	325.3±59.4	100	—	—	0.23±0.02
8 + $AgNO_3$	81.5±4.4	100	-	—	0.13±0.05
8 + $Ni(NO_3)_2$	188.4±37.7	94.2	4228.4±457.8	5.8	0.25±0.08
8 + $Cu(NO_3)_2$	—	—	—	—	—
8 + $Co(NO_3)_3$	266.4±19.1	100	—	—	0.22±0.08
8 + $Fe(NO_3)_3$	334.5±45.3	100	—	—	0.23±0.05
9 + $AgNO_3$	143.2±10.4	100	—	—	0.21±0.01
9 + $Ni(NO_3)_2$	312.6±46.4	88.0	4109.7±262.2	12.0	0.31±0.08
9 + $Cu(NO_3)_2$	313.3±6.7	100	—	—	0.15±0.06
9 + $Co(NO_3)_3$	221.1±21.3	100	—	—	0.26±0.05
9 + $Fe(NO_3)_3$	193.3±24.3	89.7	3870.6±396.0	10.3	0.32±0.03
10 + $AgNO_3$	72.1±5.8	100	—	—	0.14±0.02
10 + $Ni(NO_3)_2$	—	—	—	—	—
10 + $Cu(NO_3)_2$	297.9±17.1	100	—	—	0.28±0.02
10 + $Co(NO_3)_3$	267.4±42.4	88.8	4154.9±317.1	11.2	0.29±0.05
10 + $Fe(NO_3)_3$	177.3±32.1	96.2	4633.5±182.1	3.8	0.28±0.05

the decrease in efficiency of complexation with silver nitrate by two orders of magnitude in the transition from the macrocycle **4a** to multi(thia)calixarenes **8–10** indicates a decrease in steric availability of bridging sulfur atoms.

Increasing the number of binding sites (in the series **4a**, **8–10**) did not lead to any significant change in the efficiency of interaction with di- and trivalent cations of *d*-metals. The absence of a single trend in the changes in the efficiency of interaction and observed stoichiometry of the cation–macrocycle complexes makes it possible to conclude that the recognition can be complicated by the ability of these systems to form aggregates.

Therefore, the ability of compounds to self-assemble into supramolecular aggregates in the presence of metal nitrates was studied by dynamic light scattering (DLS).[‡] It was found that *p-tert*-butylthiacalix[4]arenes **4a**, **8–10** form supramolecular associates with the investigated nitrates of *s*- and *d*-elements (Table 2). An increase in the hydrodynamic particle size from mono- to two- and trivalent metal cations was observed only for the macrocycle **8** in the *cone* conformation. In the case of the stereoisomers *partial cone* **10** and *1,3-alternate* **9**, a different characteristic trend of increasing hydrodynamic diameter of the particles was found. The comparison of data in Tables 1 and 2 shows that the complexes of macrocycles with the highest stability constant correspond to associates with the largest size, while the least stable complexes form the smallest associates. Note that the lowest particle size was established for nanoscale associates based on silver nitrate.

To conclude, a series of nitrile-containing pentakis-thiacalix[4]arenes was synthesized. Using DLS and electron spectroscopy, series of patterns in supramolecular nanoscale aggregate formation by the synthesized *p-tert*-butylthiacalix[4]arenes with a number of cations of *s*- and *d*-elements in the organic phase was established. Increasing the number of binding sites of the pentakis-thiacalix[4]arenes studied reduces the efficiency of interaction with lithium and silver nitrates. Formation of supramolecular assemblies with cations of *s*- and *d*-elements depends on the configuration of pentakis-thiacalix[4]arenes and the nature of the 'guests'.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.07.005.

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