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Synthesis of (thia)calix[4]arene oligomers: towards calixarene-based dendrimers

Václav Šťastný,[a] Ivan Stibor,[a] Hana Dvořáková[b] and Pavel Lhoták[a,*]

[a]*Department of Organic Chemistry, Prague Institute of Chemical Technology, Technicka 5, 166 28 Prague 6, Czech Republic*
[b]*Laboratory of NMR Spectroscopy, Institute of Chemical Technology, Technicka 5, 166 28 Prague 6, Czech Republic*

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Abstract—Thiacalix[4]arenes bearing two or four carboxylic functions on the lower rim served as starting compounds for the synthesis of novel calixarene oligomers connected by amidic functions. The cone conformers react smoothly with four molecules of 5-amino-calix[4]arene to yield the corresponding pentakis-calixarenes. On the other hand, because steric hindrance, the 1,3-alternate condenses only with two molecules leading thus to *tris*-calixarene, possessing a novel type of inherent chirality based on the 25,26-substitution pattern. The title compounds, which connect together 'classical' calixarene and thiacalixarene building blocks, represent a first step towards calixarene-based dendritic structures.
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1. Introduction

The overall shape of hyperbranched polymers or dendritic structures[1] can be controlled by using an appropriate multivalent core. The geometry of this core determines the direction of branching while the number of its functional groups controls the number of branches. The chemistry of calix[*n*]arenes and thiacalix[n]arenes offers us broad variations in the structural and geometrical features of calixarene derivatives, making the calixarenes ideal candidates for the core moieties of dendrimers. The shape of the core can be changed depending on the conformation used. Particularly, we can control the size (calix[4]arene, calix[6]arene, calix[8]arene), the multiplicity of functionality (e.g., number of hydroxyl groups could be from 4 to 8) and the conformation of molecules (Fig. 1).

Thiacalixarene[2] **1** has appeared recently as a novel member of the well-known calixarene[3] family. The presence of four sulfur atoms results in many novel features[4] compared with 'classical' calixarenes, such as different complexation ability with sulfur contribution, easy chemical modification (oxidation) of bridges, different size and different conformational behaviour of this novel macrocycle. Hence, thiacalix[4]arene exhibits a broad range of interesting functions, which make this compound a good candidate for many applications in supramolecular chemistry.

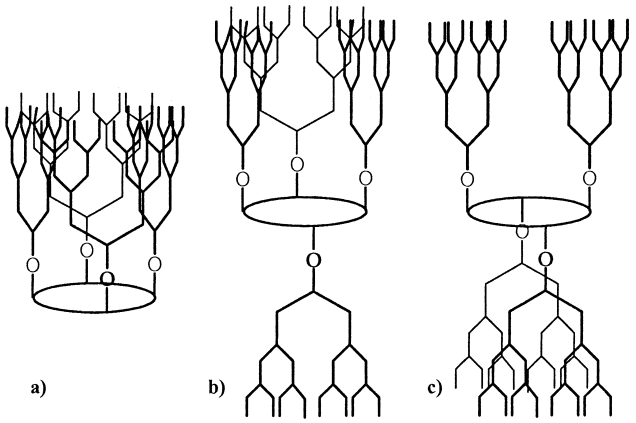

Figure 1. Dendritic structures based on the various calix[4]arene conformations (schematically): (a) *cone*, (b) *partial cone*, (c) *1,3-alternate*.

Tetraalkylation of the phenolic functions (lower rim) is a common procedure for the shaping of the thiacalixarene skeleton.[3] Recently, several groups[5] have studied the conformational preferences during the alkylation reaction of thiacalixarenes **1** and **2** with ethyl bromoacetate in acetone. It was found that thiacalixarenes exhibit a pronounced template effect, and the conformer distribution depends strictly on the reaction conditions used. Thus, using different bases M_2CO_3 (M=Na^+, K^+ and Cs^+), the reaction yields selectively the corresponding tetraacetates in various conformations (cone, partial cone, 1,3-alternate). As the products are readily isolable in multi-gram amounts without chromatographic purification, the tetraacetates represent suitable building blocks for the construction of more sophisticated molecules.

Keywords: Calixarenes; Dendrimers; Conformational analysis.
* Corresponding author. Tel.: +420-2-2435-4280; fax: +420-2-2435-4288; e-mail address: lhotakp@vscht.cz

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In this paper we report on the first example of systems combining both types of building blocks (classical calix[4]-arenes and thiacalix[4]arenes) within one molecule. These oligocalixarenes are preorganised in defined conformations and could be potentially used as the core molecules for the construction of various dendritic[6] structures.

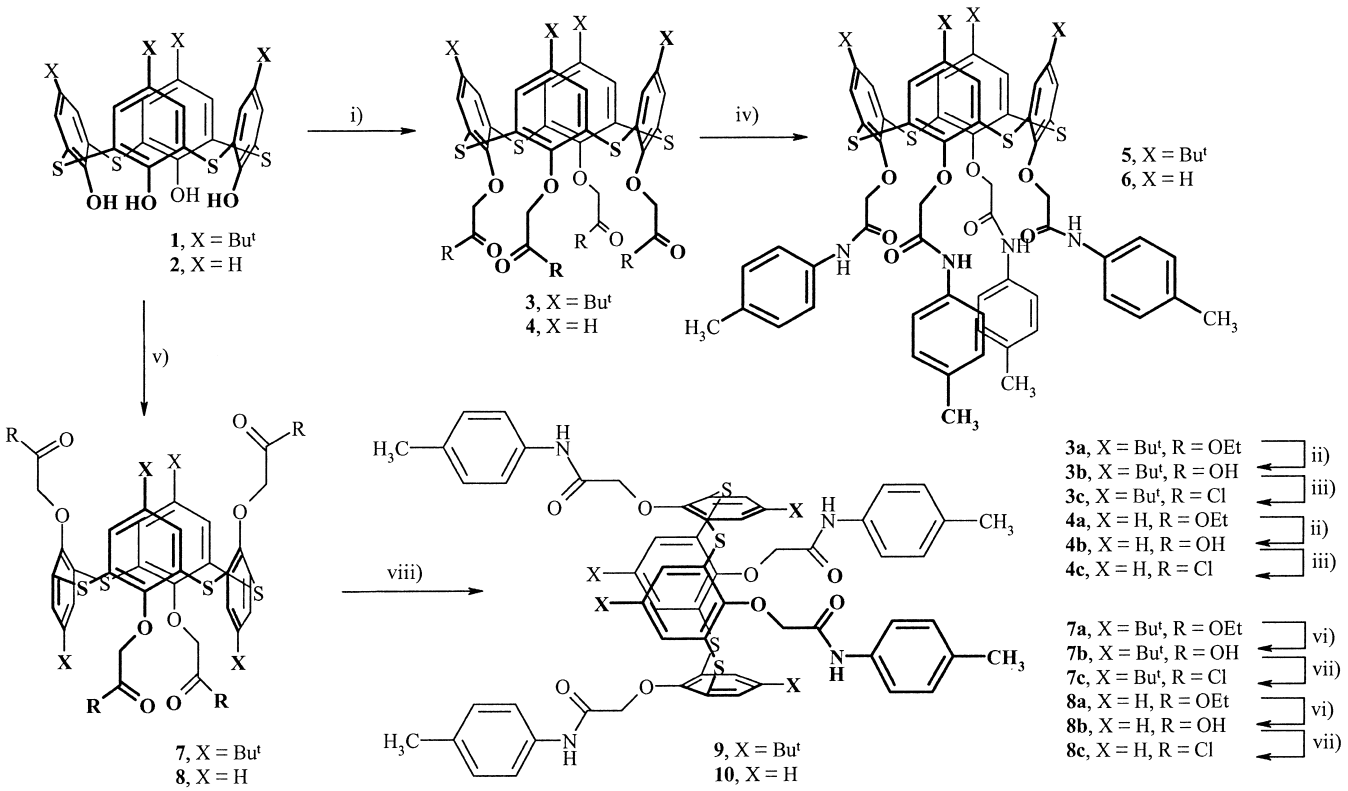
2. Results and discussion

2.1. Synthesis of conjugates

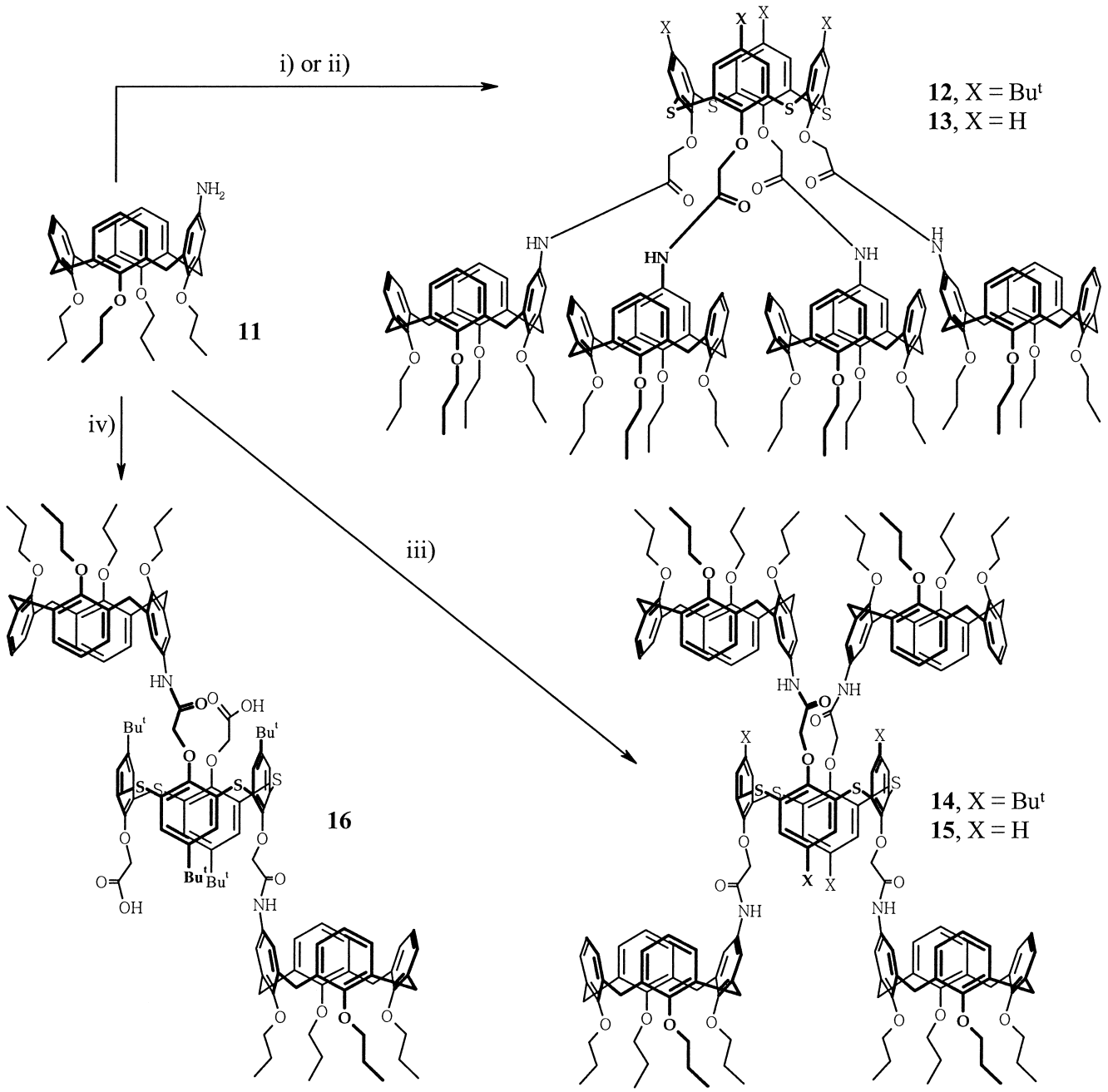
The synthesis started from parent thiacalixarenes **1** and **2**, which were transformed into the corresponding tetraacetates by alkylation with ethyl bromoacetate in refluxing acetone using Na_2CO_3 (**3a**, 75%; **4a**, 55% yield) or Cs_2CO_3 (**7a**, 68%; **8a**, 48% yield) as a base. These esters were hydrolysed with NaOH in aqueous ethanol under reflux to yield tetracarboxylic acids **3b**, **4b**, **7b**, and **8b** in quantitative yields. Before coupling with the corresponding amino-calix[4]arene, we tested the general applicability of the synthetic methods in the thiacalixarene series using a model aromatic amine (4-aminotoluene). Two methods were selected for the screening: (i) a direct reaction of carboxylic acids with 4-aminotoluene using dicyclohexylcarbodiimide as a coupling agent, and (ii) reaction of the corresponding acyl chlorides with 4-aminotoluene (Scheme 1).

The reactions with DCC/4-aminotoluene were carried out in dichloromethane solution. The coupling accomplished with 5 equiv. of DCC led to a complicated mixture of several products corresponding to the incomplete reaction (mixture of mono- to tetra-amides). Surprisingly, using an excess of DCC (10, 20, and 40 equiv.) did not significantly improve the outcome. The plausible explanation could be based on steric reasons: the DCC is too bulky for the activation of all four carboxylic functions at the same time. Hence, we focused on the second method. The preparation of acid chlorides was accomplished by stirring the starting acids with an excess of oxalyl chloride in CCl_4 under reflux. The crude acid chlorides **3c**, **4c**, **7c**, and **8c** were obtained in almost quantitative yield and used without purification in the next step due to their presumed instability. Subsequent condensation with 4-aminotoluene (5 equiv., dichloromethane or THF, rt) in the presence of Et_3N gave the corresponding tetraamides both in the *cone* **5** (88%), **6** (41%), and in the *1,3-alternate* **9** (71%), and **10** (20%) conformations (Scheme 1).

Similar reaction conditions were applied for the synthesis of oligocalixarenes combining within the molecule both common building blocks: 'classical' calixarene and thia-calixarene. Thus, monoamino derivative **11** immobilised in the *cone* conformation, reacted smoothly with central *cone* acid tetrachloride moieties **3c** and **4c** to give the corresponding pentakis-calixarenes **12** and **13** in 25 and 52% yields, respectively. On the other hand, the reaction of chlorides **7c** and **8c** revealed that steric hindrance of the central *1,3-alternate* unit plays a key role in the condensation. While the corresponding pentakis-calixarene **15** was obtained in 11% yield after preparative TLC of a very complicated reaction mixture, the similar product **14** bearing *tert*-butyl groups on the upper rim of the *1,3-alternate* core was not isolated at all. Instead, *tris*-calixarene **16** was obtained in 21% yield



Scheme 1. (i) $BrCH_2COOEt/Na_2CO_3$, acetone, reflux (**3a**, 75%; **4a**, 55%); (ii) NaOH, EtOH/water, reflux (**3b**, 99%; **4b**, 99%); (iii) oxalyl chloride/CCl_4, reflux (**3c**, **4c**, quant.); (iv) 4-aminotoluene/Et_3N/CH_2Cl_2, rt (**5**, 88%; **6**, 41%); (v) $BrCH_2COOEt/Cs_2CO_3$, acetone, reflux (**7a**, 68%; **8a**, 48%); (vi) NaOH, EtOH/water, reflux (**7b**, 99%; **8b**, 99%); (vii) oxalyl chloride/CCl_4, reflux (**7c**, **8c**, quant.); (iv) 4-aminotoluene/Et_3N/CH_2Cl_2, rt (**9**, 71%; **10**, 20%).



Scheme 2. (i) **3c**/Et_3N/CH_2Cl_2, rt (**12**, 25%); (ii) **4c**/Et_3N/CH_2Cl_2, rt (**13**, 52%); (iii) **8c**/Et_3N/CH_2Cl_2, rt (**15**, 11%); (iv) **7c**/Et_3N/CH_2Cl_2, rt (**16**, 21%).

(Scheme 2). It is obvious, that the presence of bulky groups on the upper rim prevents the complete condensation of both acid chlorides at the same side of the molecule. The acid tetrachloride can react only with two amines **11** leading thus to derivative **16** after quenching of the reaction mixture. This compound represents a novel type of inherent[7] chirality in the calixarene family. The symmetry of *1,3-alternate* structure is broken by a 25,26-substitution pattern which gives rise to a chiral derivative never described in calixarene literature.[8] Unfortunately, all our attempts to separate the racemate using chiral HPLC columns (Chiralpack, Wheelk-O) failed.

2.2. Structure assignments and NMR study

The structures of the novel tetraamides were proved using a combination of ^{1}H NMR spectroscopy and mass spectroscopy (ESI-MS or FAB MS). As the synthesis started from the conformationally immobilised compounds of known structures, proved by one-dimensional DPFGSE-NOE experiments,[9] the conformation assignment of products was not necessary. Thus, the ^{1}H NMR spectrum of derivative **15** (Fig. 2) reflects several characteristic features of both thiacalix[4]arene and calix[4]arene systems: (i) the presence of two doublets due to the equatorial protons of $Ar-CH_2-Ar$ bridging groups (3.08 and 3.12 ppm) with the geminal coupling constant of 13.2 Hz being clear evidence for a mono-substituted *cone* conformation (coming from amine units); (ii) the presence of two singlets of amidic NH and bridging $-CO-CH_2-$ groups at 8.28 and 4.81 ppm, respectively; (iii) typical doublet of aromatic protons (*meta*) of thiacalixarene part (7.51 ppm, J=7.7 Hz), all in accordance with proposed S_4 symmetry of the whole system. The

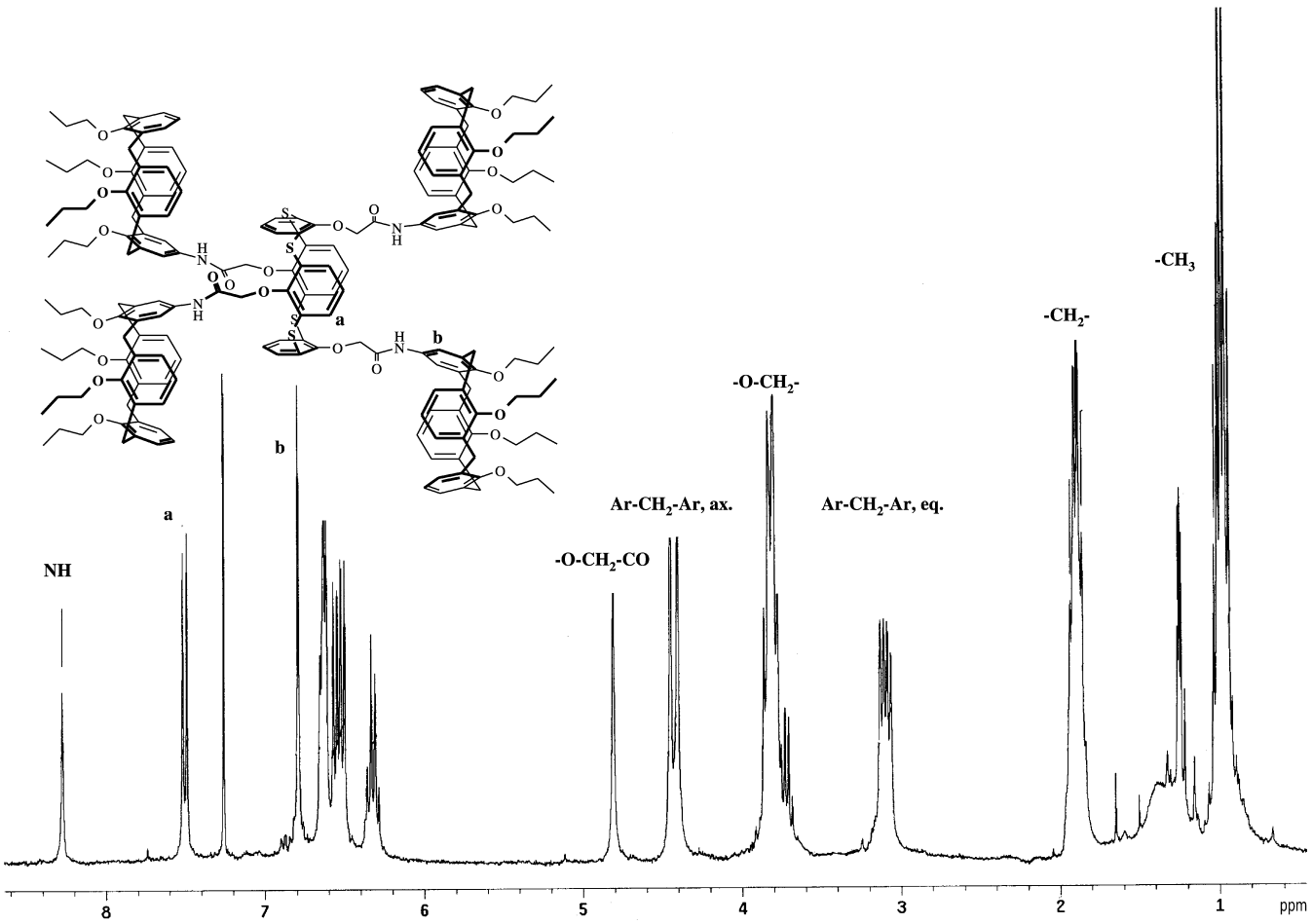


Figure 2. ^{1}H NMR spectrum of pentakis-calixarene **15** (300 MHz, $CDCl_3$, 298 K).

FAB MS spectrum shows the two most intense signals at *m*/*z*=3090.7 and 2440.3 corresponding to the molecular peak $[M+1]^+$ and to the fragment without one calix-CO–CH_2– moiety, respectively.

Interesting behaviour was found in the case of tetraamides **6** and **13** possessing a central thiacalix[4]arene moiety in the *cone* conformation without *tert*-butyl groups on the upper rim. The ^{1}H NMR spectrum of **6** measured in $CDCl_3$ at room temperature showed duplicate multiplicity with a substantial line broadening indicating a dynamic process ascribed to the *pinched cone*–*pinched cone* interconversion (Fig. 3). It is known, that the C_{4v} symmetry usually observed in the NMR spectra of classical calix[4]arene *cone* derivatives is a time-averaged signal due to fast chemical exchange between the two conformers with lower C_{2v} symmetry.[3] While the coalescence phenomenon of this interconversion in tetraalkylated classical calix[4]arenes is usually observable only at very low temperatures,[10] the situation in the thiacalixarene series is notably different. As we have shown in our previous study,[11] this phenomenon in

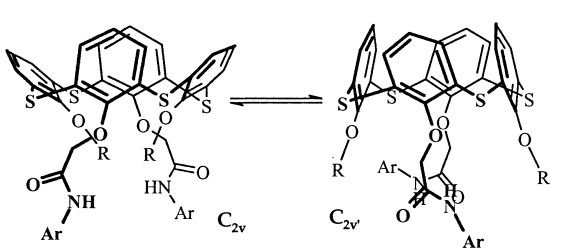


Figure 3. *Pinched cone*–*pinched cone* interconversion of **6**.

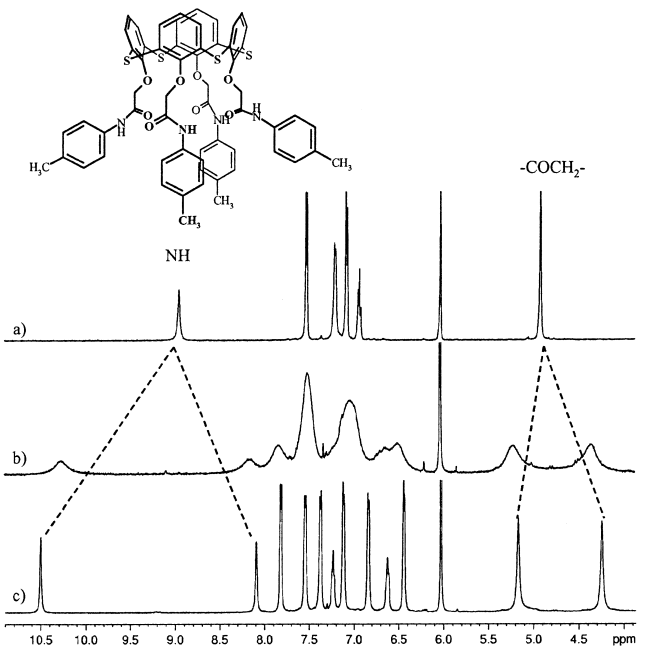


Figure 4. The partial ^{1}H NMR spectra of **6** (500 MHz, $CDCl_2CDCl_2$): measured at (a) 398 K; (b) 308 K; (c) 248 K.

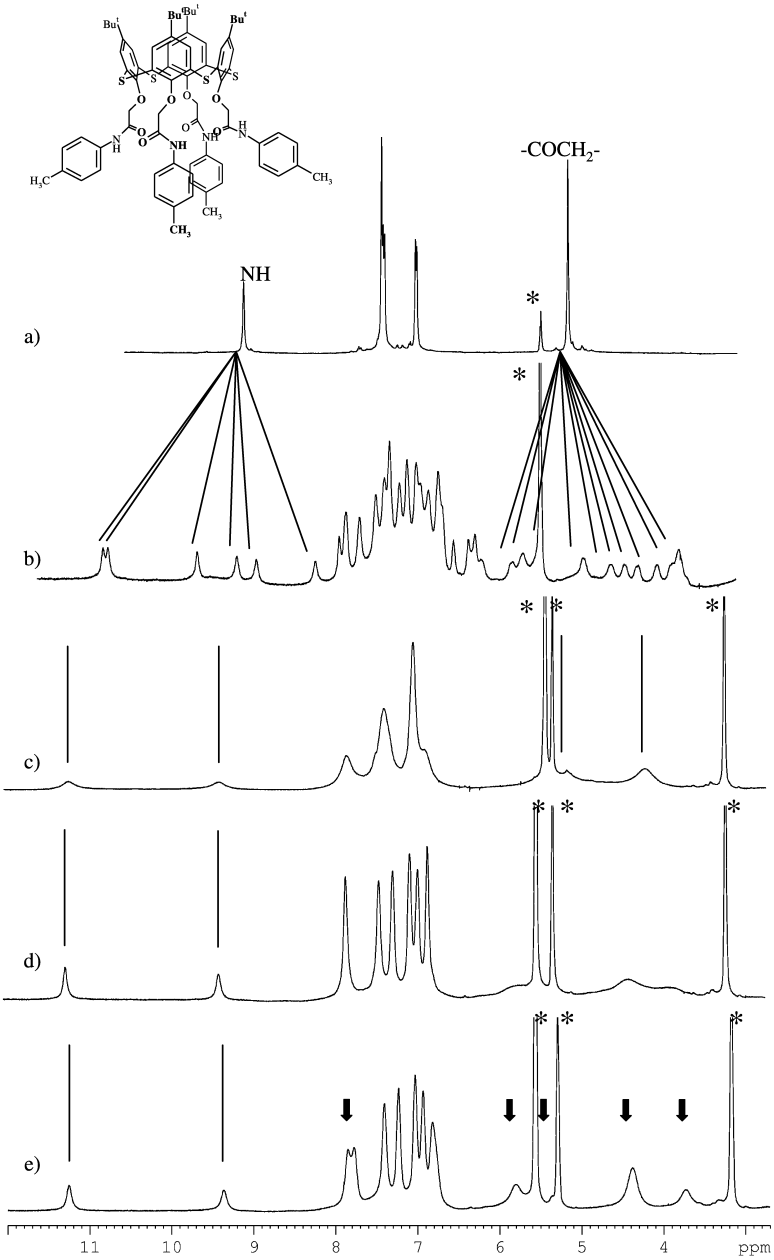


Figure 5. The partial ^{1}H NMR spectra of **5** (500 MHz, a,b=CD_2Cl_2; c,d,e=CD_2Cl_2/CD_3OD=4:1v/v): measured at (a) 298 K; (b) 203 K; (c) 203 K; (d) 183 K; (e) 173 K; *denotes the solvents.

the thiacalix[4]arene series exhibits much higher coalescence temperatures if compared with classical calixarenes.

The conformational behaviour of tetraamide derivative **6** was studied in the range of 213–398 K using $CDCl_2CDCl_2$ as a solvent. As shown in Figure 4, a simple set of signals corresponding to C_{4v} symmetry (e.g., singlets at δ=9.11 ppm (NH) and 4.92 ppm (–$COCH_2$–)) appeared at 398 K because of fast chemical exchange of C_{2v} conformers. Subsequent lowering the temperature led to the appearance of new signals, already well visible at ambient temperature, and corresponding to the presence of two conformers having C_{2v} symmetry (Fig. 4(b)).

The coalescence temperature T_c of the above exchange process was used to calculate the activation free energy of the process by means of the Eq. 1 (where R is the universal gas constant, $\Delta\nu$ is the chemical shift difference of the exchanging signals at zero rate of chemical exchange).

$$\Delta G_0^{\#} = RT_c[22.96 + \ln(T_c/\Delta\nu)] \quad (1)$$

The activation free energy $\Delta G_0^{\#}$=60.5 kJ mol^{-1} ($\pm$1 kJ mol^{-1}) computed from independent signals (Δ_{NH}=1206 Hz, T_c=333 K; Δ_{-COCH_2-}=462 Hz, T_c=323 K) and the corresponding coalescence temperatures are the highest ever observed in the thiacalixarene series. As the coalescence temperature of –CO–CH_2– groups in starting tetraester **4a** (T_c=263 K) is much lower, the substitution pattern on the lower rim obviously plays an important role in the overall energy barrier of this process. On the other hand, the activation free energy $\Delta G_0^{\#}$ of derivative **13** was found to be essentially the same as that of **6**. It indicates that the presence of four calix[4]arene units in

the amidic part of the molecule has almost no influence on the dynamics of the whole system.

The temperature-dependent NMR study on derivative **5** revealed a dramatic influence of the *tert*-butyl groups on the dynamic behavior of thiacalixarenes. The spectra measured in $CDCl_2CDCl_2$ corresponded to C_{4v} symmetry in the whole temperature range with considerable line broadening at the lowest temperatures (≈213 K) indicating additional motion. Surprisingly, the low temperature ^1H NMR in CD_2Cl_2 reflected unexpected asymmetry of the system. Figure 5(a) and (b) shows the situation where the originally simple spectrum (room temp.) gradually becomes very complicated at 203 K. Obviously, the singlet of the OCH_2- group at 4.95 ppm is split into at least eight new signals at low temperature, and the same tendency is well observable for all other signals. As the exact assignment of spectrum is extremely difficult we can only speculate that this phenomenon corresponds to the formation of asymmetric hydrogen bonding array(s) on the lower rim (amidic functions), probably with simultaneous appearance of the *pinched cone* interconversion. This assumption is further supported by the fact that addition of CD_3OD into the sample leads to the interruption of hydrogen bonds array and to the reappearance of proposed C_2 symmetry at lower temperature (Fig. 5(c)). The coalescence temperature (213 K) corresponds to the activation free energy $\Delta G_0^{\#}=38\pm1$ kJ mol^{-1} as computed from the NH signals. While the NH signals (2 singlets) and the aromatic part of spectrum (6 signals) exactly reflect the proposed C_2 symmetry at −90 °C (Fig. 5(d)), the CH_2 region surprisingly reveals another coalescence phenomenon. This is clearly apparent at −100 °C (Fig. 5(e)) where several novel signals appeared if compared with original C_2 symmetry (designated by arrows).

As the *cone* tetraacetates are known[12] for their complexation ability towards alkali metal cations, we tested the influence of sodium cation on the dynamic behaviour of compounds **5** and **6**. As expected, the addition of 2 equiv. of Kobayashi reagent (tetrakis[3,5-bis(trifluoromethyl)-phenyl]boron sodium) led to the formation of 1:1 complexes with tetraamides **5** and **6**. As a consequence, only the spectra reflecting the C_{4v} symmetry of the complex formed were observable in CD_2Cl_2 with no indications of intra/intermolecular hydrogen bonding or *pinched cone–pinched cone* interconversion down to 40 °C.

In conclusion, we have shown that thiacalix[4]arene tetraacetates can be used as a starting point in the synthesis of multiple calixarenes connecting together 'classical' calixarene and thiacalixarene building blocks. These compounds, representing a first step towards calixarene-based dendritic structures, exhibit interesting dynamic behaviour because of multiple hydrogen bonding interactions.

3. Experimental

3.1. General

Melting points were determined on a Boetius block (Carl Zeiss Jena, Germany) and are not corrected. The IR spectra were measured on an FT-IR spectrometer Nicolet 740 in $CHCl_3$ and/or in KBr. ^1H NMR spectra were recorded on a Varian Gemini 300 spectrometer, the temperature dependant spectra were recorded on a Bruker AMX3 400 and Bruker DRX 500 Avance spectrometers using tetramethylsilane as an internal standard. Dichloromethane and CCl_4 used for the reaction were dried with CaH_2 and P_2O_5, respectively, and stored over molecular sieves. The purity of the substances and the courses of reactions were monitored by TLC using TLC aluminium sheets with Silica gel 60 F_{254} (Merck). Preparative TLC chromatography was carried out on 20×20 cm glass plates covered by Silica gel 60 GF_{254} (Merck).

Starting esters **3a**, **4a**, **7a** and **8a** were prepared according to known procedures[12] by the reaction of **1** and **2** with ethyl bromoacetate in boiling acetone in the presence of Na_2CO_3 or Cs_2CO_3.

It is known that the elemental analyses of the calixarene derivatives are sometimes ambiguous.[13] The EA usually resulted in *C* values 1–3% lower than the calculated values. There are two possible and widely accepted explanations: (i) cavity-possessing compounds contain the molecules of solvents/reagents which are extremely difficult to eliminate; (ii) the incomplete combustion of these high-melting compounds under the standardized conditions of the elemental analysis. We believe that the structures of the calixarenes are sufficiently documented by the spectral evidence or by the subsequent chemical transformations.

3.1.1. Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis(carboxymethoxy)-2,8,14,20-tetrathia-calix[4]arene (*cone*) 3b. Tetraester **3a** (2.0 g, 1,88 mmol) was dissolved in 150 ml of EtOH and a solution of NaOH (1.5 g, 37.5 mmol) in 10 ml of distilled water was added. The reaction mixture was stirred for 6 days at reflux. Ethanol was then removed on vacuum evaporator, the residue was dissolved in water and acidified by 1 M HCl. The white precipitate was collected by filtration and dried in vacuum to yield the title compound in quantitative yield. Mp 333–334 °C (lit.[14] mp 293.4–294.8 °C). ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.40 (s, 8H, H-arom), 5.03 (s, 8H, $-O-CH_2-CO-$), 1.12 (s, 36H, Bu^t). IR (KBr) ν_{max} (cm^{-1}): 1758 (C=O), 3462 (O–H). MS-ESI *m*/*z*=975.1 $[M+Na]^+$.

3.1.2. Synthesis of 25,26,27,28-tetrakis(carboxymethoxy)-2,8,14,20-tetrathiacalix[4]arene (*cone*) 4b. The preparation was analogous to that described for **3b**, quantitative yield of white precipitate. Mp 287–288 °C. ^1H NMR (DMSO-d_6, 300 MHz) δ: 6.93 (bs, 8H, H-arom), 6.84 (t, 4H, H-arom, *J*=7.14 Hz), 5.04 (s, 8H, $-O-CH_2-CO$). IR (KBr) ν_{max} (cm^{-1}): 1738 (C=O). EA Calcd for $C_{32}H_{24}O_{12}S_4$: C, 52.74; H, 3.32; S, 17.60. Found: C, 52.82; H, 3.52; S, 17.12.

3.1.3. Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-(carboxymethoxy)-2,8,14,20-tetrathia-calix[4]arene (*1,3-alternate*) 7b. The preparation was analogous to that described for **3b**, quantitative yield of white precipitate. Mp 325–326 °C (lit.[15] 325–327 °C). ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.39 (s, 8H, H-arom), 4.66 (s,

8H, –O–CH_2–CO–), 1.25 (s, 36H, Bu^t). IR (KBr) ν_{max} (cm^{-1}): 1695 (C=O). MS-ESI *m/z*=975.1 $[M+Na]^+$.

3.1.4. Synthesis of 25,26,27,28-tetrakis(carboxymethoxy)-2,8,14,20-tetrathiacalix[4]arene (*1,3-alternate*) 8b. The preparation was analogous to that described for **3b**, quantitative yield of white precipitate. Mp 309–310 °C (lit.[16] 290 °C (decomp.)). ^1H NMR (DMSO-d_6, 300 MHz) δ: 7.60 (d, 8H, H-arom, *J*=7.69 Hz), 6.81 (t, 4H, H-arom, *J*=7.14 Hz), 4.53 (s, 8H, –O–CH_2–CO–). IR (KBr) ν_{max} (cm^{-1}): 1743 (C=O). MS-ESI *m/z*=751.0 $[M+Na]^+$.

3.2. Synthesis of model compounds

3.2.1. Preparation of acid chloride. A mixture of tetraacid (76 μmol) and $(COCl)_2$ (0.13 ml; 1.52 mmol) in 5 ml of anhydrous CCl_4 was stirred under reflux for 3 h (**3c**) to 3 days (**8c**). The end of reaction was indicated by the formation of the clear yellowish solution. The solvent and the residual oxalyl chloride were distilled off, the residue was treated with anhydrous CH_2Cl_2 (5 ml) and the solvent was again evaporated under reduced pressure. The resulting solid was then dried in a vacuum (5 Torr) for 2 h to yield the corresponding acyl chlorides **3c**, **4c**, **7c**, and **8c** in almost quantitative yield. These reactive intermediates were used in the next step without subsequent characterisation and purification.

3.2.2. Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(4-methylphenyl)carbamoyl-methoxy]-2,8,14,20-tetrathiacalix[4]arene (*cone*) 5. A solution of 4-aminotoluene (0.11 g, 1.05 mmol) in 5 ml of dry DCM was added dropwise at room temperature to a stirred solution of tetrachloride **3c** (0.215 g, 0.21 mmol) and Et_3N (0.3 ml, 2.1 mmol) in 5 ml of dry DCM. The reaction mixture was stirred overnight and the solvent was removed in a reduced pressure. The residue was dissolved in $CHCl_3$ (30 ml) and washed with 1 M HCl and then with water. The separated organic layer was dried over $MgSO_4$. The volume of solution was reduced to 5 ml and product (190 mg, 88%) was obtained by precipitation with methanol as beige solid with mp 272–273 °C ($CHCl_3$–MeOH). ^1H NMR ($CDCl_3$, 300 MHz) δ: 9.28 (s, 4H, –NH), 7.43 (d, 8H, H-arom, *J*=8.2 Hz), 7.38 (s, 8H, H-arom), 6.97 (d, 8H, H-arom, *J*=8.2 Hz), 4.95 (s, 8H, –O–CH_2–CO–), 2.24 (s, 12H, Ar-CH_3), 1.13 (s, 36H, Bu^t). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3307 (N–H), 1678 (C=O). EA Calcd for $C_{76}H_{84}N_4O_8S_4$: C, 69.69; H, 6.46; N, 4.28; S, 9.79. Found: C, 70.41; H, 6.75; N, 4.32; S, 10.23.

3.2.3. Synthesis of 25,26,27,28-tetrakis[(4-methyl-phenyl)-carbamoylmethoxy]-2,8,14,20-tetrathia-calix[4]-arene (*cone*) 6. The reaction was carried out analogously to the procedure described for **5** using tetrachloride **4c** as starting compound. The crude product was purified by preparative TLC chromatography on silica gel using $CHCl_3$–acetone (10:1) mixture to yield derivative **6** (41%) as a white powder with mp 289–290 °C. ^1H NMR ($CDCl_2$–$CDCl_2$, 135 °C, 500 MHz) δ (ppm): 9.11 (s, 4H, –NH), 7.52 (d, 8H, *J*=7.2 Hz, H-arom), 7.20 (brd, 8H, H-arom), 7.07 (d, 8H, *J*=7.3 Hz, H-arom), 6.92 (t, 4H, H-arom), 4.92 (s, 8H, –O–CH_2–CO–), 2.32 (s, 12H, Ar-CH_3). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3409, 3314 (N–H), 1680 (C=O). MS-ESI *m/z*=1107.2 $[M+Na]^+$.

3.2.4. Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(4-methylphenyl)carbamoyl-methoxy]-2,8,14,20-tetrathiacalix[4]arene (*1,3-alternate*) 9. The reaction was carried out analogously to the procedure described for **5** using tetrachloride **7c** as starting compound. The crude product was purified by precipitation from $CHCl_3$/methanol mixture to yield derivative **9** (71%) as a white powder with mp 295–296 °C ($CHCl_3$–MeOH). ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.45 (s, 4H, –NH), 7.47 (s, 8H, H-arom), 7.40 (d, 8H, *J*=8.2 Hz, H-arom), 7.15 (d, 8H, *J*=8.8 Hz, H-arom), 4.86 (s, 8H, –O–CH_2–CO–), 2.32 (s, 12H, Ar-CH_3), 0.70 (s, 36H, Bu^t). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3394, 3283 (N–H), 1679 (C=O). EA Calcd for $C_{76}H_{84}N_4O_8S_4$: C, 69.69; H, 6.46; N, 4.28; S, 9.79; C, 69.66; H, 6.55; N, 3.78; S, 10.19.

3.2.5. Synthesis of 25,26,27,28-tetrakis[(4-methyl-phenyl)-carbamoylmethoxy]-2,8,14,20-tetrathia-calix[4]-arene (*1,3-alternate*) 10. The reaction was carried out analogously to the procedure described for **5** using tetrachloride **8c** as starting compound. The crude product was purified by preparative TLC chromatography on silica gel using $CHCl_3$ as eluent to yield derivative **10** (20%) as a beige solid with mp 256–257 °C ($CHCl_3$–MeOH). ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.22 (s, 4H, –NH), 7.53 (d, 8H, *J*=7.7 Hz, H-arom), 7.28 (d, 8H, *J*=8.8 Hz, H-arom), 7.17 (d, 8H, *J*=8.2 Hz, H-arom), 6.56 (t, 4H, *J*=7.7 Hz, H-arom), 4.95 (s, 8H, –O–CH_2–CO–), 2.35 (s, 12H, Ar-CH_3). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3388, 3298 (N–H), 1686 (C=O). MS-ESI *m/z*=1107.2 $[M+Na]^+$.

3.2.6. Synthesis of pentakis-calixarene 12. A solution of aminocalixarene **11** (75 mg, 0.123 mmol) in 3 ml of dry CH_2Cl_2 was added at room temperature under a nitrogen atmosphere to a stirred solution of tetrachloride **3c** (24.6 mg, 0.024 mmol) and Et_3N (0.1 ml, 0.72 mmol) in 3 ml of dry CH_2Cl_2. The reaction mixture was stirred for 22 h and the solvent was distilled off. The residue was dissolved in $CHCl_3$ (20 ml) and thoroughly washed with 1 M HCl. The organic layer was separated and the aqueous layer was extracted twice with small amount of $CHCl_3$. The collected organic layers were dried over $MgSO_4$ end evaporated to dryness. The residue was purified by repeated preparative TLC on silica gel using $CHCl_3$–ethyl acetate=250:1 and petroleum-ether–$CHCl_3$=5:1 mixtures as eluents. The title compound was obtained as yellowish powder (20 mg, 25%) with mp 195–196 °C ($CHCl_3$–MeOH). ^1H NMR ($CDCl_3$, 300 MHz) δ: 9.12 (s, 4H, –NH), 7.39 (s, 8H, H-arom), 7.06 (s, 8H, H-arom), 6.66–6.38 (m, 36H, H-arom), 4.98 (s, 8H, –O–CH_2–CO–), 4.41, 4,30 (2d, 16H, *J*=13.5 Hz, Ar-CH_2-Ar ax.), 3.84–3.73 (m, 32H, –O–CH_2–CH_2–), 3.09, 3.01 (2d, 16H, *J*=13.2 Hz, Ar-CH_2-Ar eq.), 1.90–1.80 (m, 32H, –CH_2–CH_3), 1.14 (s, 36H, Bu^t), 1.20–0.90 (m, 48H, –CH_2–CH_3). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3308 (N–H), 1678 (C=O). MS-ESI *m/z*=3335.2 $[M+Na]^+$, 1679,5 $[M+2Na]^{2+}$.

3.2.7. Synthesis of pentakis-calixarene 13. Reaction was carried out analogously to the procedure described for **12** using tetrachloride **4c** as starting compound. The product

was obtained as a beige solid (52%) after preparative TLC chromatography on silica gel using $CHCl_3$ as an eluent. Mp 197–199 °C ($CHCl_3$–MeOH). ^1H NMR ($CDCl_2$–$CDCl_2$, 135 °C, 500 MHz) δ: 8.58 (s, 4H, –NH), 6.84 (s, 8H, H-arom), 6.24–6.52 (m, 36H, H-arom), 4.68 (s, 8H, –O–CH_2–CO–), 4.34, 4.26 (2d, 16H, J=13.5 Hz, Ar-CH_2-Ar ax.), 3.71 (m, 32H, O–CH_2–CH_2–), 3.00, 2.92 (2d, 16H, J=13.2 Hz, Ar-CH_2-Ar eq.), 1.85–1.95 (m, 32H, –CH_2–CH_3), 0.80–1.00 (m, 48H, –CH_2–CH_3). IR ($CHCl_3$) ν_{max} (cm^{-1}): (N–H), (C=O). MS-ESI (CH_3CN) m/z=3111 $[M+Na]^+$, 1567 $[M+2Na]^{2+}$.

3.2.8. Synthesis of pentakis-calixarene 15. The reaction was carried out analogously to the procedure described for **12** using tetrachloride **8c** as starting compound. The product was obtained as a white solid (11%) after repeated preparative TLC chromatography on silica gel using $CHCl_3$ and then petroleum-ether–ethyl acetate=10:1 as an eluent. Mp 214–216 °C ($CHCl_3$–MeOH). ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.28 (s, 4H, –NH), 7,51 (d, 8H, J=7.7 Hz, H-arom), 6.79 (s, 8H, H-arom), 6.65–6.50 and 6.32 (2m, 40H, H-arom), 4.81 (s, 8H, –O–CH_2–CO–), 4.43 (d, 16H, J=13.2 Hz, Ar-CH_2-Ar ax.), 3.86–3.71 (m, 32H, O–CH_2–CH_2–), 3.12, 3.08 (2d, 16H, J=13.2 Hz, Ar-CH_2-Ar eq.), 1.90 (m, 32H, –O–CH_2–CH_2–), 0.99 (m, 48H, CH_2–CH_3). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3399, 3288 (N–H), 1677 (C=O). MS-FAB m/z (int.%)=3090.7 (100%) $[MH]^+$, 2440.3 (98%) $[M-(calix\text{-}CO\text{-}CH_2\text{-})]^+$.

3.2.9. Synthesis of *tris*-calixarene 16. Reaction was carried out analogously to the procedure described for **12** using tetrachloride **7c** as starting compound. The product was obtained as a white solid (21%) after several times repeated preparative TLC chromatography on silica gel ($CHCl_3$–acetone=50:1, petroleum-ether–ethyl acetate=5:2). Mp 206–208 °C ($CHCl_3$–MeOH). ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.60 (s, 2H, –NH), 7.70 (d, 2H, J=2.8 Hz, H-arom), 7.54 (d, 2H, J=2.2 Hz, H-arom), 7.33 (d, 2H, J=2.2 Hz, H-arom), 7.19 (d, 2H, J=2.2 Hz, H-arom), 6.80 (d, 4H, J=7.7 Hz, H-arom), 6.59 (t, 2H, J=7.4 Hz, H-arom), 6.44–6.39 (m, 16H, H-arom), 4.71, 4.58, 4.37, 4.22 (4d, 8H, –O–CH_2–CO–), 4.46, 4.42 (2d, 8H, Ar-CH_2-Ar), 3,95–3,71 (m, 16H, O–CH_2–CH_2–), 3.17, 3.13 (2d, 8H, Ar-CH_2-Ar), 1.88 (m, 16H, –CH_2–CH_3), 1.20, 1,13 (2s, 36H, Bu^t), 1.09–0.92 (m, 24H, CH_2–CH_3). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3451, 3387, 3302 (N–H), 1786 (C=O). MS-FAB m/z=2131.5 $[M^+]$.

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