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Synthesis and Metal-Binding Properties of Oligo-Calixarenes. An Approach towards the Calix[4]arene-Based Dendrimers

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Abstract. A series of bis-calix[4]arene derivatives **4a-h** (cone conformation) linked through the phenolic oxygens with the help of a single aliphatic chain (lower rim-lower rim connection) was obtained in high yields (50-80%) by alkylation of 25, 26, 27-tripropoxy-28-hydroxycalix[4]arenes **2a**, **2b** with 0.5 equiv. of Br-$(CH_2)_n$-Br in the presence of NaH. The same reaction with excess dibromides yielded corresponding bromoalkyl derivatives **3a-c** which were used for construction of oligo-calix[4]arenes (bis, tris, pentakis) - a new family of calix[4]arene derivatives representing the first step on the way towards the calixarene-based dendrimers. The metal complexation behavior of newly prepared compounds was investigated with the help of ^{1}H NMR spectroscopy.

INTRODUCTION

Calixarenes[1-3] are cyclic oligomers from the class of [1$_n$]metacyclophanes readily accessible by condensation of phenols and formaldehyde under basic conditions. Owing to the possibility of their easy synthetic modifications in a selective manner, they have been used in supramolecular chemistry as building blocks for larger and more sophisticated molecular systems.[4,5] Most attention has been paid to calix[4]arene derivatives which can serve as selective receptors for binding of ions[6] or neutral molecules [7]

Several papers appeared recently[8] which deal with construction of new double-calix[4]arene-based derivatives, exhibiting very interesting phenomena such as "metal-vibration" and "metal-hopping" between suitably designed binding places. That is why the design and synthesis of some higher members of oligo-calixarene's family seem to be very interesting, because they can offer us multifunctional spaces for complexation of metals (other cations) or for inclusion of suitable neutral molecules. Last but not least, the synthesis of oligo-calixarenes can be the first step on the way to the calixarene-based dendrimers,[9] where we can assume interesting properties (allosteric effects, cooperative guest-bindings, *etc.*).

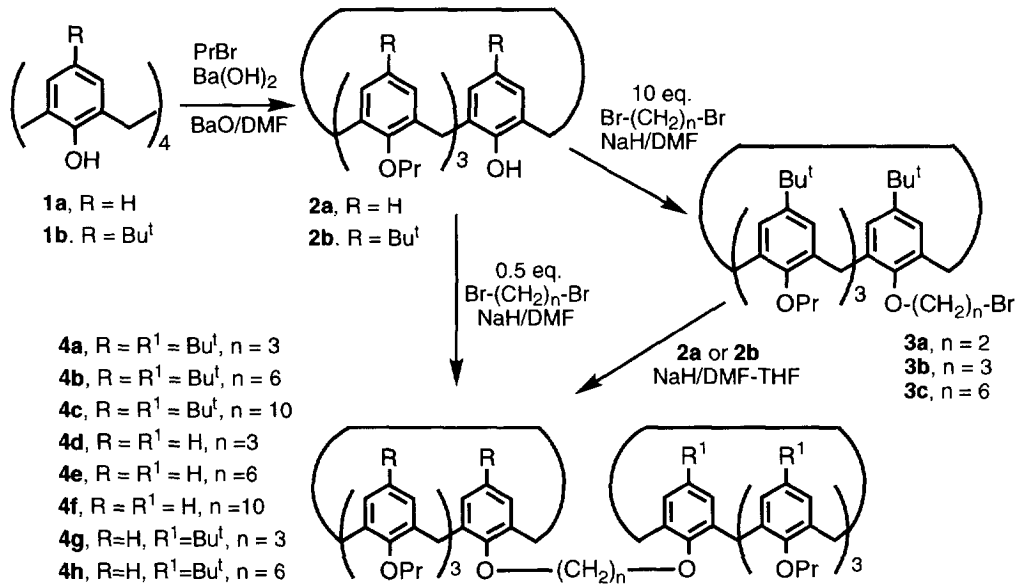
The easiest way how to link two or more calix[4]arene units together seems to be direct connection of oxygen atoms on the lower rim by simple aliphatic chains: i.e. "lower rim-lower rim" connection.[5] Such arrangement we can achieve by the reaction of suitably substituted calix[4]arene derivatives with dialkylation agent (for instance, Br-$(CH_2)_n$-Br). The drawback of this strategy is the possibility of ambiguous intra- versus intermolecular reactions in case of some calixarene derivatives. Therefore, such type of reaction is useful only for the preparation of bis-calixarenes from trialkylated starting compounds where intramolecular bis-alkylation is made impossible.

Another approach comprises the usage of a calixarene monobromoalkyl derivative as simple alkylation agent. Such a derivative should show an unambiguous behavior in Williamson-type alkylations (multiple intra- or/and intermolecular reactions are impossible in this case). We can simply use this derivative for alkylation of selected calix[4]arene derivatives to prepare "lower rim-lower rim" connected oligomers. In this case pentakis-calix[4]arenes seem to be a dead-line of this method from a practical viewpoint.

RESULTS AND DISCUSSION

SYNTHESIS OF COMPOUNDS

The starting monobromoalkyl derivatives **3a-c** were prepared by the reaction of appropriate tripropyl-substituted calix[4]arene **2b** with 10 equivalents of a,w-dibromoalkanes in DMF at elevated temperature and in the presence of NaH. Under these reaction conditions only proposed products were isolated (51%, 81%, and 76% yields, respectively) and there was no evidence for the presence of theoretically possible bis-calixarenes **4a-c** in the reaction mixture. The formation of monobromoalkyl derivatives can be clearly follows from their ^{1}H NMR spectral data, which give the typical splitting pattern for nonsymmetrically substituted calixarene derivatives (see later).

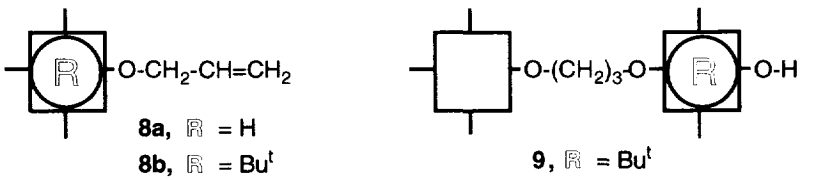


Scheme 1. Preparation of bis-calix[4]arenes

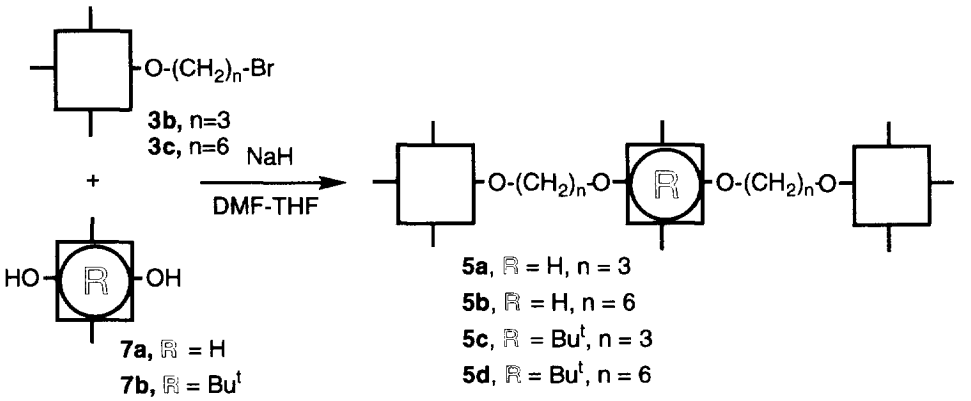
Monobromo derivatives **3a-c** represent the key intermediates for the preparation of higher members of oligo-calixarene family. To check their alkylation ability in Williamson-type reactions we carried out several experiments from which we found that the usage of THF-DMF mixture and NaH as a base possesses the best results. By the reaction of tripropyl derivative **2a** with monobromide **3b** or **3c** we obtained the bis-calixarene derivative **4g** or **4h**, respectively, in good yields. To our best knowledge these compounds represent the first example of connection of *tert*-butylated and de-*tert*-butylated calix[4]arene units in one molecule. The sole byproduct found in the reaction mixture was monoallyl derivative **8b**, which is the product of b-elimination

reaction of the starting -O-CH_2-CH_2-CH_2-Br group (**3b**). No such elimination was observed in case of longer spacer **3c**. Derivative **3a** with a shortest C_2 spacer chain did not react at all with compound **2b**, probably owing to the steric hindrance in the reaction intermediate (according to the CPK models).

The symmetrical bis-calix[4]arenes **4a-e** were prepared either by the reaction of monobromoalkyl derivatives **3b,c** with appropriate tripropoxy derivative (in case of **4a,** 35% yield) or by direct reaction of tripropoxy derivatives **2a**, **2b** with 0.5 equivalent of a,w-dibromides. While in case of *tert*-butyl substituted bis-calixarenes **4a-c** the yields of reactions are surprisingly high (70-86%), derivatives **4d-f** were prepared only in medium yields (33-51%). Again, from the reaction mixture of **4d** the substantial amount of allyl derivative **8a** was isolated. 1,2-Dibromoethane did not react with **2b** under these reaction conditions.



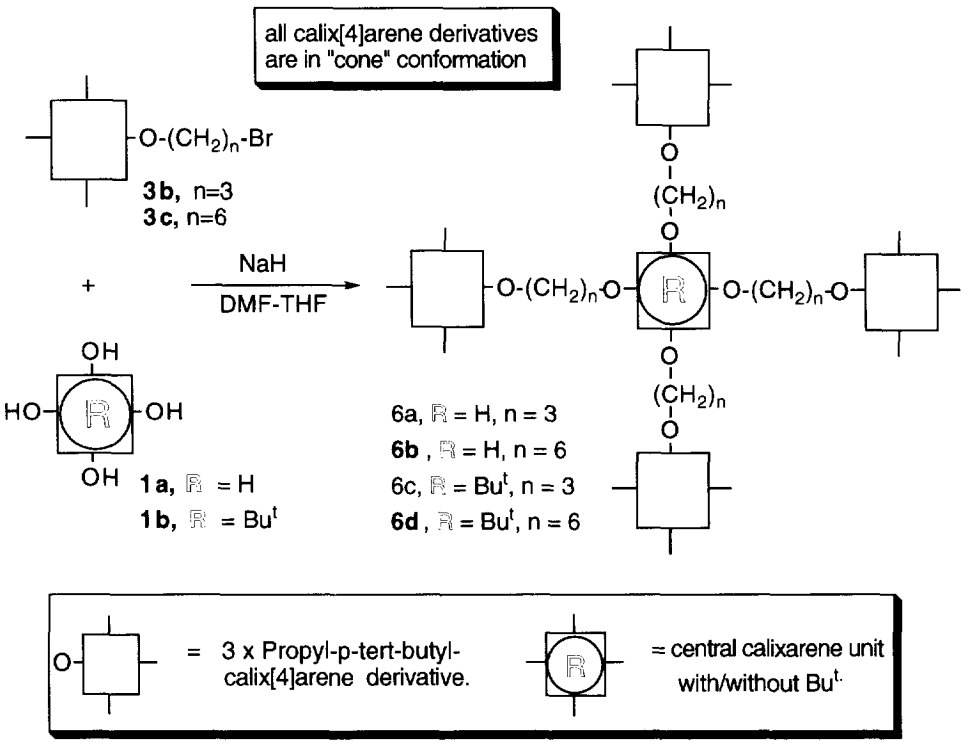
Tris-calix[4]arenes **5a-d** were prepared (Scheme 2) in 27 - 53% yields by the reaction of dipropoxy derivatives **7a**, **7b** with NaH (5 eq.) and bromoalkyl calix[4]arenes **3b**, **3c** (5 eq.) in a DMF-THF mixture at room temperature. Especially in case where the bromopropoxy derivative **3b** was used, the isolation of pure



Scheme 2. Preparation of tris-calix[4]arenes

products **5a** and **5c** was extremely difficult due to the presence of allyl derivative **8b** and excess of starting bromide in the reaction mixture. Several times repeated preparative TLC on SiO_2 (hexane-$CHCl_3$) was the only useful purification tool in such case. If the reaction of **3b** with **7b** was decomposed after 1 day stirring at room temperature, compound **9** (representing the reaction intermediate) was isolated. The structure was proved by FAB-MS, where the molecular ion of m/e 1548 clearly shows the introduction of one calixarene units into starting dihydroxy derivative **7b**.

The pentakis-calix[4]arenes **6b** and **6d** were prepared (Scheme 3) by alkylation of starting **1a** or **1b** with 8 equivalents of bromide **3c** in 38 and 7% yields, respectively. The reaction yield in case of derivative **6d** is substantially low. Such phenomena may be caused by steric hindrance between coming calixarene units and *tert*-butyl groups at upper rim of the central unit. We did not succeed in preparation of derivatives **6a** and **6c**, where the rate of alkylation is probably lower than the rate of the elimination reaction and allyl derivative **8b** was the only isolable product.



Scheme 3. Preparation of pentakis-calix[4]arenes

^{1}H NMR SPECTRA OF OLIGO-CALIX[4]ARENES

The ^{1}H NMR spectra of newly prepared calixarene derivatives possess some characteristic features and we can classify them into 3 subregions. First region (0.8-2.5 ppm) consists of the signals of terminal CH_3-, internal -CH_2-, and Bu^t groups. Especially, the splitting pattern of *tert*-butyl groups can be efficiently used for judging of symmetry assignable to each structure. Second region (3.1-4.50 ppm) contains doublets of equatorial and axial hydrogens of Ar-CH_2-Ar methylene groups together with -O-CH_2- groups of alkyl chains. While in case of shorter C_3 spacer between calixarene units we can observe isolated doublets for H-3,4,8,9 (see **4a** and **4d**), introduction of longer C_6 and C_{10} spacers (**4b**,**4c**,**4e**, and **4f**) results in simplification of these signals into two doublets due to the greater "symmetry" of molecules (we can imagine that compound **4b** or **4e** consists of two wholly symmetrical tetrapropoxycalix[4]arene subunits). Third region is formed by aromatic protons and

usually is useless for assigning the molecular structure due to the fact that several different hydrogens give the same signal. The spectra of tris-calixarene derivatives **5a-d** and unsymmetrical biscalixarenes **4g**, **4h** are very complicated owing to their lower symmetry, but the proposed splitting pattern and integral intensity ratios of appropriate signals are still satisfactorily observable (see Figure 1). On the other hand, ^{1}H NMR spectra of pentakis-calixarenes are very simple (Figure 2).

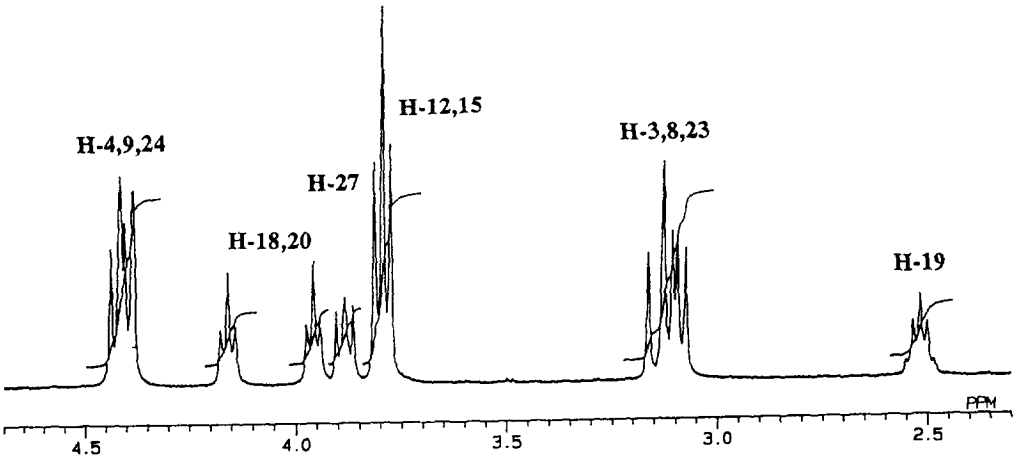


Figure 1. Partial ^{1}H NMR spectrum of **5a** (400 MHz, $CDCl_3$, 30 °C)

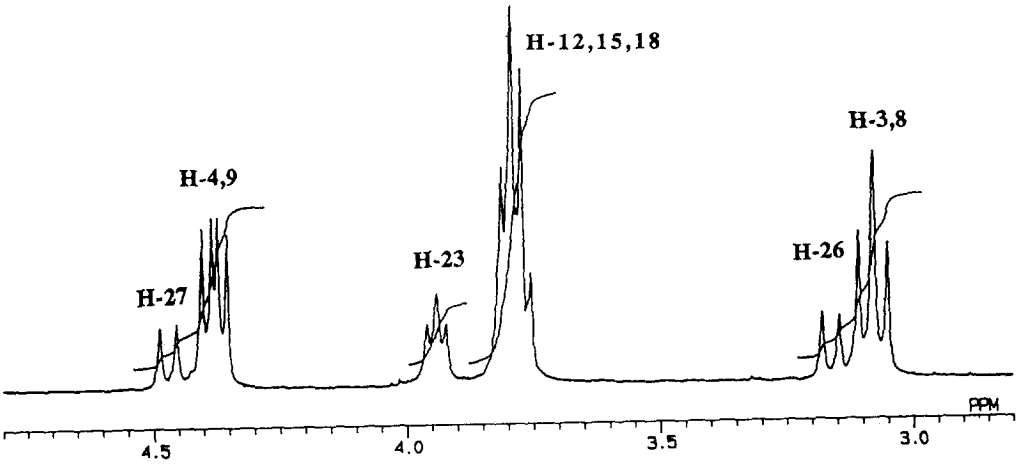
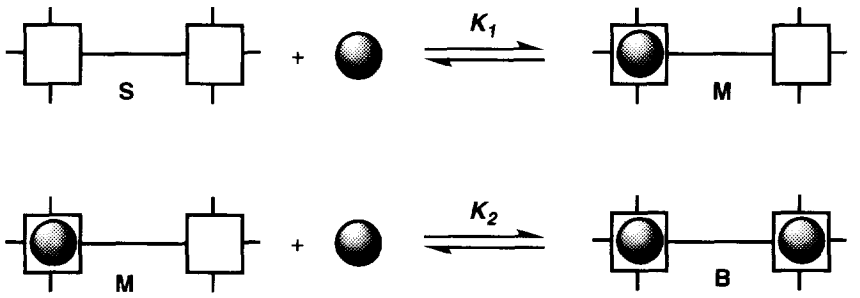


Figure 2. Partial ^{1}H NMR spectrum of **6b** (400 MHz, $CDCl_3$, 30 °C)

COMPLEXATION ABILITY OF NEW COMPOUNDS

The complexation behavior of newly prepared bis-calixarene derivatives **4a-g** in the presence of several monovalent and divalent metal cations was studied with the help of ^{1}H NMR. While there is no visible change of the spectrum in the presence of Ag^+, K^+, Cs^+, Rb^+, and Mg^{2+} cations, the addition of 1 equivalent of $LiClO_4$ caused a dramatic change of the spectrum ($CDCl_3$:CD_3CN=4:1 v/v, room temperature) and the signals of monocomplex (M), biscomplex (B), and free ligand (S) species appeared. Association constants K_1 and K_2 were calculated directly from the ratios of B, M, S, that were determined from the integral intensity of appropriate signals (see Figure 3).



$$K_1 = \frac{M}{Li \times S} = \frac{c_M}{(c_{Li(0)} - c_M - 2c_B) \times c_S}$$

$$K_2 = \frac{B}{Li \times M} = \frac{c_B}{(c_{Li(0)} - c_M - 2c_B) \times c_M}$$

$c_{Li(0)}$ ..... initial conc. of Li^+

c_M, c_B, c_S .... conc. determined by NMR

Figure 3. Association constants for $LiClO_4$ complexes

Table 1. Association constants of $LiClO_4$ - calixarene system ($CDCl_3$-CD_3CN=4:1, room temperature)

Compound	log K_1	log K_2
4xPr *tert*-butylcalix[4]arene (cone)	3.72	
4a	3.81	3.66
4b	3.67	3.38
4xPr calix[4]arene (cone)	2.62	-
4d	2.42	2.41

From the table above we can derive several conclusions: a) *Tert*-butylated calix[4]arene derivatives act as a much better "catcher" of Li^+ cation than the same derivatives without *tert*-butyl groups (compare **4a** and **4d**). b) Association constants are unexpectedly high if we compare them with those already measured for similar (alkylated monocalixarenes) systems. Ikeda *et al.*[11] reported for 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrapropoxycalix[4]arene association constant <1 ($CDCl_3$-CD_3OD=4:1 v/v, -50 °C). Such difference is caused

by the usage of acetonitrile instead of methanol as cosolvent, in which competitive complexation (solvation) of Li^+ cations is substantially suppressed. c) K_1 is significantly higher than K_2 (at least in *tert*-butylated derivatives). d) Since all complexes are stable under measurement conditions, we can simply observe separated signals for complexed and uncomplexed species. The similar complexation constants for $NaClO_4$ could not be evaluated due to the extensive line broadening.

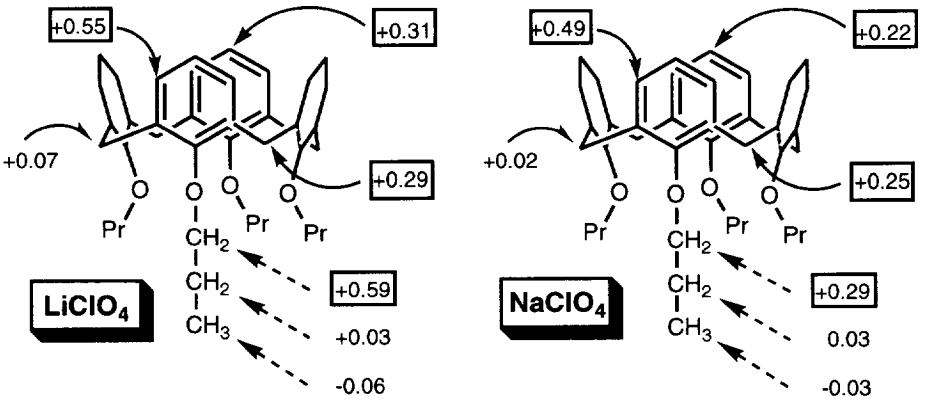


Figure 4. Chemical shift changes induced by $MClO_4$ addition in $CDCl_3$-CD_3CN=4:1 v/v at 30 °C (calculated as a difference between signals of complexed and uncomplexed species.). (+) denotes the down-field shift, whereas (-) denotes the up-field shift.

Figure 4 shows the chemical shift changes caused by addition of $MClO_4$ to 25,26,27,28-tetrapropoxycalix[4]arene used as a model compound in $CDCl_3$-CD_3CN solution at room temperature. It was reported previously[10] that *"tetramethyl derivative can bind Li^+ cation to the lower rim cavity with the help of four oxygen atoms. In contrast, such a metal-binding ability was not observed for tetrapropyl derivative"*. However, we demonstrated here, if the competitive complexation of cation by solvent is suppressed (CD_3OD was changed by CD_3CN) strong complexation takes place even in such derivatives and we can observe high induced chemical shifts for the aromatic protons. Such shifts could be explained by cation - p-basic cavity[10,11] interactions. Nevertheless, it is difficult to believe that such binding mode could operate in case of Na^+ and Li^+ cations which are known as typical "hard" cations, while aromatic cavity represents "soft" base. That is why we suppose that cations are bound by oxygene lone pairs indeed, but they are pushed deeper into the cavity by influence of relatively bulky propyl groups. Of course such a phenomenon is better visible in case of Na^+ (see Figure 4) due to its greater ionic radius. Bis-calixarenes **4d-f** possess similar values of induced chemical shifts, therefore we can simply suppose the same binding mode.

As far as higher members of oligo-calixarene family are concerned, the ^1H NMR spectra of tris-derivatives **5a**, **5b**, and **7b** were measured in the presence of $LiClO_4$. The only evident result is that these derivatives can also bind Li^+ cations (up to number of calix[4]arene units in molecule) and association constants K_1 - K_X are comparable with those already measured for simpler derivatives. Such poor results are caused by high complexity of the measured system in which we can theoretically find signals of (in case of tris-calixarenes)

6 species. Obviously, NMR spectra of these derivatives are very complicated and actually illegible and "unassignable". That is why we were not able to evaluate corresponding constants.

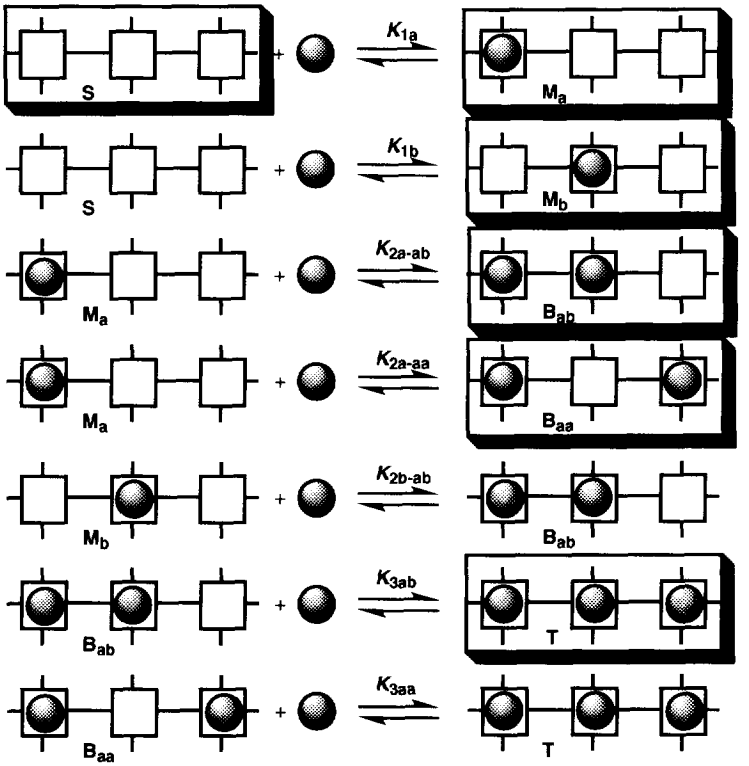


Figure 5. Theoretical equilibria in tris-calixarene - $LiClO_4$ system

CONCLUSIONS

Monobromoalkyl derivatives of calix[4]arene were prepared and used for the introduction of calix[4]arene moiety into other molecules. Such procedure represents a new and very simple strategy for the synthesis of oligo-calix[4]arenes with defined structure. Several examples representing the first step on the way towards calix[4]arene-based dendrimers (bis-, tris, pentakis-derivatives) have been prepared. This approach has enabled us to prepare symmetrical bis-calixarenes but also unsymmetrical derivatives for the first time. We believe that the introduction of other functional groups instead n-propoxy groups would be useful for the preparation of more attractive compounds in near future.

EXPERIMENTAL

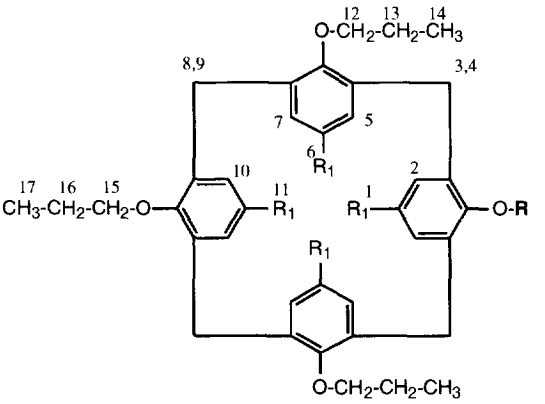
Melting points were determined on a Micro Melting Point Apparatus Yanaco MP-500D and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-250P and JEOL-GSX 400 spectrometers in $CDCl_3$ with TMS as internal standard. Mass spectra were obtained with a Hitachi M-2500 spectrometer. Possitive-ion fast-atom-bombardement (FAB) spectra were measured with m-nitrobenzyl alcohol as a matrix. IR spectra were recorded with a Jasco A-100 spectrophotometer. Preparative thin layer chromatography was performed on glass plates (20 x 20 cm) coated by *Silica gel* 60 GF_{254} (Merck). All reaction were carried out under a nitrogen atmosphere.

Compounds **2a**, **2b**, **7a**, **7b** were prepared according to the known procedures.[12]

25-(2-Bromoethoxy)-5,11,17,23-tetra-*tert*-butyl-26,27,28-tripropoxycalix[4]arene (3a). NaH (0.03 g, 0.75 mmol) was added to a suspension of calix[4]arene **2b** (0.5 g, 0.645 mmol) in 15 ml of DMF and the reaction mixture was stirred at 55 °C for 1h until clear solution was obtained. Then 1.21 g of Br-CH_2-CH_2-Br (6.45 mmol, 10 eq.) was added and the mixture was stirred for 15 h at the same temperature. After evaporation of the solvent the residue was submitted to column chromatography (SiO_2, $CHCl_3$-hexane=1:3) to yield 0.10 g of starting compound and 0.23 g of **3a** (51% based on reacted material), m.p. 247.5-248.5 °C (EtOH-AcOEt). ^{1}H NMR spectrum (250 MHz, $CDCl_3$) d 0.85 (s, 18H, H-6); 0.97 (t, 3H, J=7.5 Hz, H-17); 1.07 (t, 6H, J=7.5 Hz, H-14); 1.30 (s, 9H, H-1 or 11); 1.30 (s, 9H, H-11 or 1); 1.95 (m, 6H, H-13,16); 3.14 (d, 4H, J=12.5 Hz, H-3, 8); 3.67 (t, 4H, J=7.7 Hz, H-12, 13); 3.95 (t, 2H, J=7.7 Hz, H-15); 4.20 (m, 4H, H-18, 19); 4.29 (d, 2H, J=12.9 Hz, H-4 or 9), 4.43 (d, 2H, J=12.3 Hz, H9 or 4); 6.44 (m, 2H, H-arom), 6.54 (m, 2H, H-arom); 7.07 (s, 4H, H-arom). EA calcd. for $C_{55}H_{77}O_4Br$: C, 74.87; H, 8.82. Found: C, 75.05; H, 8.80.

25-(3-Bromopropoxy)-5,11,17,23-tetra-*tert*-butyl-26,27,28-tripropoxycalix[4]arene (3b). The similar procedure as **3a** using **2b** and 1,3-dibromopropane. Stirred 48 h at 55-60 °C, 81% yield, m.p. 223.5-226 °C (EtOH-AcOt). ^{1}H NMR spectrum (250 MHz, $CDCl_3$) d 0.98 (s, 18H, H-6); 0.99 (s, 9H, H-14, 17); 1.17 (s, 9H, 1 or 11); 1.18 (s, 9H, 11 or 1); 1.97 (m, 6H, H-13, 16); 2.65 (quint., 2H, J=6.9 Hz, H-19); 3.12 (d, 2H, J=12.5 Hz, H-3 or 8); 3.14 (d, 2H, J=12.5 Hz, H-8 or 3); 3.69 (t, 2H, J=6.7 Hz, H-15); 3.76 (t, 4H, J=7.4 Hz, H-12); 3.88 (t 2H, J=7.8 Hz, H-18); 4.01 (t, 2H, J=6.9 Hz, H-20); 4.35 (d, 2H, J=12.5 Hz, H-4 or 9); 4.42 (d, 2H, J=12.5 Hz, H-9 or 4); 6.66 (m, 4H, H-arom); 6.88 (m, 4H, H-arom). EA calcd. for $C_{56}H_{79}O_4Br$: C, 75.04; H, 8.90. Found: C, 75.52; H, 8.91.

25-(6-Bromohexyloxy)-5,11,17,23-tetra-*tert*-butyl-26,27,28-tripropoxycalix[4]arene (3c). The same procedure as **3a** using **2b** and 1,6-dibromohexane. Stirred 72 h at 55 °C, 76%, m.p. 85-88 °C (AcOEt-MeOH). ^{1}H NMR spectrum (250 MHz, $CDCl_3$) d 0.98 (m, 9H, H-14,17); 1.06 (s, 18H), 1.09 (s, 18H, H-1, 6, 11), 1.45 (m, 4H, H-20,21); 2.00 (m, 10H, H-13, 16, 19, 22); 3.11 (d, 4H, J=12.5 Hz, H-3, 8); 3.44 (t, 2H, J=6.8 Hz, H-23); 3.81 (m, 8H, H-12, 15, 18); 4.39 (d, 2H, J=12.3 Hz, H-4 or 9); 4.41 (d, 2H, J=12.5 Hz, H-9 or 4); 6.76 (s, 4H, H-arom); 6.79 (s, 4H, H-arom). EA calcd. for $C_{59}H_{85}O_4Br$: C, 75.52; H, 9.15. Found: C, 75.43; H, 9.09.



18 19
R_1= Bu^t **3a** = -CH_2-CH_2-Br

18 19 20
3b = -CH_2-CH_2-CH_2-Br

18 19 20 21 22 23
3c = -CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-Br

18 19 20
8b = -CH_2-CH=CH_2

18 19 20
R_1=H **8a** = -CH_2-CH=CH_2

Figure 6. The numbering system of ^{1}H NMR spectra

Preparation of bis-calix[4]arene 4a *(by bisalkylation)*. NaH (0.03 g, 0.75 mmol) was added to a suspension of tripropoxy derivative **2b** (0.5 g, 0.645 mmol) in 15 ml of DMF and the reaction mixture was stirred at 50-55 °C for 1h. Then 0.065 g of Br-CH_2-CH_2-CH_2-Br (0.323 mmol, 0.5 eq.) was added and the mixture was stirred for 24 h at the same temperature. After evaporation of the solvent the residue was dissolved in $CHCl_3$, washed with 1N HCl and dried over $MgSO_4$. The crude product was purified by column chromatography (SiO_2, $CHCl_3$-hexane=1:3) to give 0.36 g **4a** (70%), m.p. 181.5-185 °C, then again solidifies and melts once more at 266-269 °C. (EtOH-AcOEt). ^{1}H NMR spectrum (250 MHz, $CDCl_3$) d 0.91 (m, 18H, H-14, 17); 0.99 (s, 18H, H-1 or 11); 1.00 (s, 18H, H-11 or 1); 1.16 (s, 36H, H-6); 2.00 (m, 12H, H-13, 16); 2.50 (m, 2H, H-19); 3.11 (d, 8H, J=12.3 Hz, H-3, 8); 3.73 (t, 4H, J=7.6 Hz, H-15); 3.84 (t, 8H, J=8.3 Hz, H-12); 4.11 (t, 4H, J=7.1 Hz, H-18); 4.40 (d, 4H, J=12.4 Hz, H-4 or 9); 4.42 (d, 4H, J=12.5 Hz, H-9 or 4); 6.65 (s, 4H, H-arom); 6.67 (s, 4H, H-arom); 6.87 (s, 8H, H-arom). EA calcd. for $C_{109}H_{152}O_8$: C, 82.30; H, 9.65. Found: C, 82.39; H, 9.62.

Bis-calix[4]arene 4b. The same procedure as **4a** using **2b** and 1,6-dibromohexane. Stirred 72 h at 55 °C, isolated by simple crystallization, 76%, m.p. 261.5-264 °C (AcOt-EtOH). ^{1}H NMR spectrum (250 MHz, $CDCl_3$) d 1.00 (m, 12H, H-14,17); 1.06 (s, 36H), 1.10 (s, 36H, H-1, 6, 11); 1.50 (m, 4H, H-20); 2.04 (m, 16H, H-13, 16, 19); 3.12 (d, 8H, J=11.9 Hz, H-3, 8); 3.83 (m, 16H, H-12, 15, 18); 4.42 (d, 8H, J=11.7 Hz, H-4,9); 6.75 (s, 8H, H-arom); 6.80 (s, 8H, H-arom).EA calcd. for $C_{112}H_{158}O_8$: C, 82.39; H, 9.77. Found: C, 82.35; H, 9.69.

Bis-calix[4]arene 4c. Prepared analogously to **4b** using **2b** and 1,10-dibromodecane, 86%, m.p. 241-244 °C (EtOH-AcOEt). ^{1}H NMR spectrum (250 MHz, $CDCl_3$) d 1.00 (t, 18H, J=7.5 Hz, H-14, 17); 1.08 (s, 72H, H-1, 6, 11); 1.40 (brs, 12H, H-20, 21, 22); 2.03 (m, 16H, H-13, 16, 19); 3.11 (d, 8H, J=12.6 Hz, H-3, 8); 3.81 (m, 16H, H-12, 15, 18); 4.41 (d, 8H, J=12.5 Hz, H-4, 9); 6.77 (s, 8H, H-arom); 6.78 (s, 8H, H-arom). EA calcd. for $C_{116}H_{166}O_8$: C, 82.49; H, 9.93. Found: C, 82.43; H, 9.89.

Preparation of bis-calix[4]arene 4d. *Procedure A:* NaH (0.03 g, 0.75 mmol) was added to a suspension of tripropyl calix[4]arene **2a** (0.35 g, 0.645 mmol) in 10 ml of DMF and the reaction mixture was stirred at room temp. for 30 min. Then 0.065 g of Br-CH_2-CH_2-CH_2-Br (0.323 mmol, 0.5 eq.) was added and the mixture was stirred for another 3 days. After precipitation with 1N HCl the solid was filtered, and purified by preparative TLC to yield 0.12 g of allyl derivative **8a**, 0.10 g of starting **2a**, and 0.07 g of **4d** (26% based on reacted material), m.p. 202.5-205 °C ($CHCl_3$-MeOH). ^{1}H NMR spectrum (250 MHz, $CDCl_3$) d 0.91 (t, 12H, J=7.5 Hz, H-14); 0.99 (t, 6H, J=7.5 Hz, H-17); 1.90 (m, 12H, H-13,16); 2.48 (m, 2H, H-19); 3.11 (d, 4H, J=13.6 Hz, H-3 or 8); 3.14 (d, 4H, J=13.5 Hz, H-8 or 3); 3.83 (m, 12H, H-12, 15); 4.11 (t, 4H, H-18); 4.39 (d, 4H, J=13.5 Hz, H-4 or 9); 4.42 (d, 4H, J=13.5 Hz, H-9 or 4); 6.47 s, 6.50 s, 6.68 m (H24, H-arom). EA calcd. for $C_{77}H_{88}O_8$: C, 81.00; H, 7.79. Found: C, 80.65; H, 7.69.

Procedure B: The same as procedure A, stirred at 55 °C, 33% yield of **4d**.

25-(allyloxy)-26,27,28-tripropoxycalix[4]arene (8a). Yield 32%. M.p. 186-189 °C (AcOEt-$CHCl_3$). ^{1}H NMR spectrum (250 MHz, $CDCl_3$) d 0.95 (t, 3H, J=7.4 Hz, H-17); 1.03 (t, 6H, J=7.4 Hz, H-14); 1.91 (m, 6H, H-13, 16); 3.15 (d, 4H, J=13.1 Hz, H-3,8); 3.77 (t, 4H, J=7.2 Hz, H-12); 3.92 (t, 2H, J=7.2 Hz, H-15); 4.40 (d, 2H, J=13.1 Hz, H-4 or 9); 4.45 (d, 2H, J=13.1Hz, H-9 or 4); 4.50 (d, 2H, J=6.5 Hz, H-18); 5.16 (m, 2H, H-20a,b); 6.41 (m, 5H, H-19 + H arom); 6.80 (m, 4H, H-arom). EA calcd. for $C_{40}H_{46}O_4$: C, 81.31; H, 7.86. Found: C, 81.26; H, 7.92.

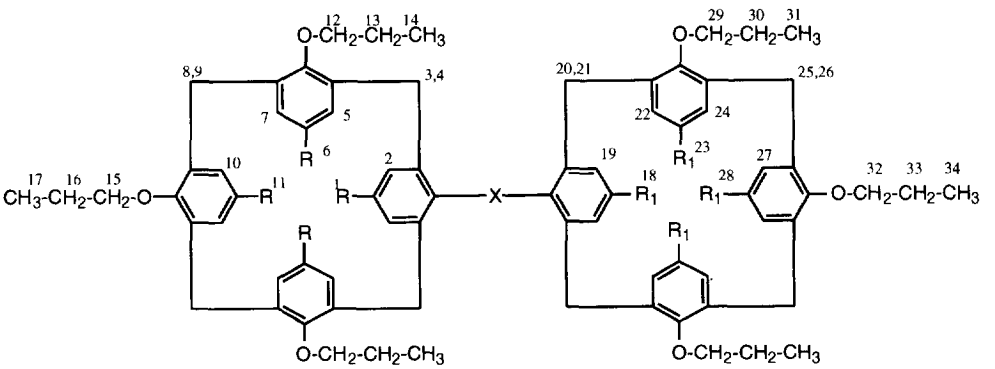
Bis-calix[4]arene 4e. The same procedure as **4d** using **2a** and 1,6-dibromopropane (procedure A), 51%, m.p. 205-208 °C ($CHCl_3$-MeOH). ^{1}H NMR spectrum (250 MHz, $CDCl_3$) d 0.98 (t, 18H, J=7.4 Hz, H-14, 17); 1.47 (m, 4H, H-20); 1.92 (m, 16H, H-13, 16, 19); 3.15 (d, 8H, J=13.4 Hz, H-3, 8); 3.84 (m, 16H, H-12, 15, 18); 4.44 (d, 8H, J=13.3 Hz, H-4, 9); 6.60 (brs, 24H, H-arom). EA calcd. for $C_{80}H_{94}O_8$: C, 81.17; H, 8.02. Found: C, 81.18; H, 7.84.

Bis-calix[4]arene 4f. The same procedure as **4d** using **2a** and 1,10-dibromodecane (procedure A), 51%, m.p. 101-106 °C ($CHCl_3$-MeOH). ^{1}H NMR spectrum (250 MHz, $CDCl_3$) d 0.98 (t, 18H, J=7.4 Hz, H-14, 17); 1.37 (m, 12H, H-20, 21, 22); 1.90 (m, 16H, H-13, 16, 19); 3.15 (d, 8H, J=13.5 Hz, H-3, 8); 3.84 (m, 16H, H-12, 15, 18); 4.44 (d, 8H, J=13.2 Hz, H-4, 9); 6.60 (m, 24H, H-arom). EA calcd. for $C_{84}H_{102}O_8$: C, 81.37; H, 8.31. Found: C, 81.39; H, 8.28.

Preparation of bis-calix[4]arene 4a *(by monoalkylation).* The mixture of 0.22 g of **2b** (0.279 mmol) and 0.012 g of NaH (2.6 eq.) in 10 ml DMF-THF mixture (1:1 v/v) was stirred for 40 min and then 0.50 g of **3b** (0.558 mmol) was added as one portion. After stirring for 72 h at room temp. reaction mixture was poured into 1N HCl and extracted with $CHCl_3$. Organic layer was then washed with water, dried with $MgSO_4$ and evaporated. The crude product was purified by column chromatography (SiO_2, hexane:$CHCl_3$=4:1) to give 0.16 g of **4a** (35%), which was identical with product obtained by direct bisalkylation of **2b**.

Bis-calix[4]arene 4g. Similar procedure as **4a** using **3b** and **2a** as starting compounds. Stirred 5.5 days, 0.13 g (35% yield), m.p. 254.5-257 °C. ^{1}H NMR spectrum (400 MHz, CDCl3) d 0.85 (t, 6H, J=7.3 Hz, H-14 or 31); 0.95 (t, 6H, J=7.6 Hz, H-31 or 14); 1.00 (m, 6H, H-17, 34); 1.05 (s, 9H, H-1 or 11); 1.07 (s, 9H, H-11 or 1); 1.08 (s, 18H, H-6); 1.89 (m, 6H, H-30, 33); 2.01 (m, 6H, H-13, 16); 2.53 (m, 2H, H-36); 3.12 (m, 8H, H-3, 8, 20, 25); 3.75 (t, 4H, J=7.2 Hz, H-12 or 29); 3.80 (t, 4H, J=7.3 Hz, H-29 or 12); 3.87 (m, H-15, 32); 4.02 (t, 2H, J=6.8 Hz, H-35 or 37); 4.15 (t, 2H, J=7.0 Hz, H-37 or 35); 4.42 (m, 8H, H-4, 9, 21, 26); 6.36 (m, 6H, H-arom); 6.76 (m, 14H, H-arom). EA calcd. for $C_{93}H_{120}O_8$: C, 81.76; H, 8.87. Found: C, 81.93; H, 8.99.

Bis-calix[4]arene 4h. Similar procedure as **4a** using **3c** and **2a**. Stirred 5.5 days, 0.24 g (78% yield), m.p. 207-210 °C (AcOEt-MetOH). ^{1}H NMR spectrum (400 MHz, CDCl3) d 0.99 (t, 18H, J=7.3 Hz, H-14, 17, 31, 34); 1.08 (s, 36H, H-1, 6, 11); 1.48 (m, 4H, H-37, 38); 1.93 (m, 8H, H-30, 33, 39); 2.02 (m, 8H, H-13, 16, 36); 3.11 (d, 4H, J=12.5 Hz, H-3, 8); 3.15 (d, 4H, J=13.4 Hz, H-20, 25); 3.84 (m, 16H, H-12, 15, 29, 32, 35, 40); 4.41 (d, 4H,J=12.5 Hz, H-4, 9); 4.45 (d, 2H, J=13.4 Hz, H-21 or 26); 4.46 (d, 2H, J=13.4 Hz, H-26 or 21); 6.59 (m, 12H, H-18, 19, 22-24, 27, 28); 6.77 (s, 8H, H-2, 5, 7, 10). EA calcd. for $C_{96}H_{126}O_8$: C, 81.87; H, 9.04. Found: C, 81.93; H, 8.99.



4a, R=R$_1$=Bu^t 18 19 -CH$_2$-CH$_2$-CH$_2$-
4d, R=R$_1$=H

4b, R=R$_1$=Bu^t 18 19 20 -CH$_2$-CH$_2$-CH$_2$-(CH$_2$)$_3$-
4e, R=R$_1$=H

4c, R=R$_1$=Bu^t 18 19 20 21 22 -CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-(CH$_2$)$_5$-
4f, R=R$_1$=H

4g, R=Bu^t, R$_1$=H 35 36 37 -CH$_2$-CH$_2$-CH$_2$-

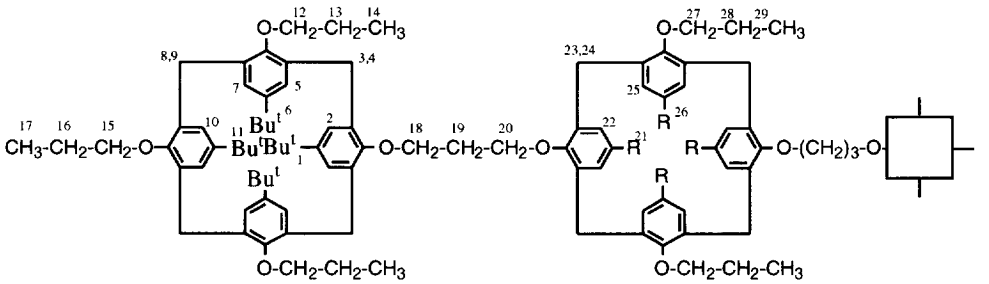
4h, R=Bu^t, R$_1$=H 35 36 37 38 39 40 -CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-

Figure 7. The numbering system of ^{1}H NMR spectra

Preparation of tris-calix[4]arene 5a. The mixture of 57 mg of **7a** (0.112 mmol) and 21 mg of NaH (0.558 mmol) in 20 ml DMF-THF mixture (1:1 v/v) was stirred for 30 min and then 0.50 g of **3b** (0.558 mmol) was added as one portion. After stirring for 3 days at room temp. reaction mixture was poured into 1N HCl, precipitate filtered, and purified by preparative TLC. During several times repeated procedure, fractions with

slightly higher Rf than product (unreacted **3b**, allyl derivative) were carefully removed until only one spot remained. Pure compound was then crystallized from acetone to yield 125 mg of **5a** (53%), m.p. 183-186 °C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) d 0.73 (t, 6H, J=7.6 Hz, H-29); 0.95 (t, 12H, J=7.3 Hz, H-14); 0.97 (t, 6H, J=7.6 Hz, H-17); 1.06 (s, 54H, H-6, 1 or 11); 1.08 (s, 18H, H-11 or 1); 1.85 (m, 4H, H-28); 2.00 (m, 12H, H-13, 16); 2.51 (quint., 4H, J=7.7 Hz, H-19); 3.09 (d, 4H, J=12.5 Hz, H-3 or 8), 3.11 (d, 4H, J=13.1 Hz, H-8 or 3), 3.14 (d, 4H, J=14.7 Hz, H-23); 3.79 (t, 12H, J=7.6 Hz, H-12,15); 3.88 (t, 4H, J=8.2 Hz, H-27); 3.95 (t, 4H, J=6.3 Hz, H-18 or 20); 4.16 (t, 4H, J=7.0 Hz, H-20 or 18); 4.40 (d, 4H, J=12.2 Hz, H-4 or 9,); 4.40 (d, 4H, 12.5 Hz, H-9 or 4); 4.42 (d, 4H, J=13.4 Hz, H-24); 6.18 (d, 4H, J=7.6 Hz, H-22); 6.30 (t, 2H, J=7.3 Hz, H-21); 6.74 (s, 4H, H-2); 6.77 (s, 12H, H-5, 7, 10); 6.83 (t, 2H, J=7.3 Hz, H-26); 6.98 (d, 4H, J=7.6 Hz, H-25). EA calcd. for $C_{146}H_{192}O_{12}$: C, 81.96; H, 9.06. Found: C, 81.79; H, 9.01.

Tris-calix[4]arene 5c. The same as **5a** using **7b** and **3b** as starting compounds, stirred 5 days, isolated 0.16 g of allyl derivative **8b** and 0.076 g of product **5c** (29%), m.p. 254-57 °C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) d 0.83 (t, 6H, J=7.7 Hz, H-17 or 29); 0.90 (t, 12H, J=7.5 Hz, H-14); 0.91 (s, 18H, H-Bu^t); 0.99 (t, 6H, J=7.7 Hz, H-29 or 17); 1.00 (s, 18H, H-Bu^t); 1.01 (s, 18H, H-Bu^t); 1.14 (s, 36H, H-6); 1.23 (s, 18H, H-Bu^t); 2.00 (m, 16H, H-13, 16, 28), 2.45 (m, 4H, H-19); 3.10 (d, 12H, J=12.6 Hz, H-3, 8, 23); 3.74 (t, 4H, J=7.7 Hz, H-15 or 27); 3.83 (t, 8H, J=7.8 Hz, H-12); 3.86 (t, 4H, J=7.9 Hz, H-27 or 15); 4.01 (t, 4H, J=6.6 Hz, H-18 or 20); 4.09 (t, 4H, J=6.6 Hz, H-20 or 18); 4.39 (d, 4H, J=12.4 Hz); 4.40 (d, 4H, J=12.4 Hz); 4.41 (d, 4H, J=12.4 Hz, H-4, 9, 24); 6.55 (s, 4H, H-arom); 6.66 (s, 4H, H-arom); 6.68 (s, 4H, H-arom); 6.85 (s, 8H, H-arom); 6.97 (s, 4H, H-arom). EA calcd. for $C_{162}H_{224}O_{12}$: C, 82.32; H,9.55. Found: C, 82.17, H, 9.58.



5a R = H

5c R = Bu^t

Figure 8. The numbering system of ^{1}H NMR spectra

25-allyloxy-5,11,17,23-tetra-*tert*-butyl-26,27,28-tripropoxycalix[4]arene (8b). Yield 29%. M.p. 226.5-228 °C (AcOEt), ^{1}H NMR spectrum (250 MHz, $CDCl_3$) d 0.99 (m, 9H, H-14,17); 1.00 (s, 18H, H-6); 1.15 (s, 9H, H-1 or 11); 1.16 (s, 9H, H-11 or 1); 1.97 (m, 6H, H-13, 16); 3.11 (d, 4H, J=12.5 Hz, H-3, 8); 3.76 (t, 4H, J=7.7 Hz, H-12); 3.85 (t, 2H, J=7.7 Hz, H-15); 4.39 (d, 2H, J=12.5 Hz, H-4 or 9); 4.41 (d, 2H, J=12.5 Hz, H-9 or 4); 4.51 (d, 2H, J=6.5 Hz, H-18); 5.19 (m, 2H, H-20a,b); 6.47 (m, 1H, H-19); 6.67 (s, 4H), 6.87 (s, 2H), 6.88 (s, 2H, H-arom). EA calcd. for $C_{56}H_{78}O_4$: C, 82.49; H,9.66. Found: C, 81.91; H, 9.59.

Tris-calix[4]arene 5b. Analogously to **5a** using **7a** and **3c**, stirred 5 days, 0.091 g of product (37%), m.p. 222-225 °C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) d 0.97 (m, 26H, H-14, 17, 32); 1.04 (s, 18H, H-1 or 11); 1.05 (s, 18H, H-11 or 1); 1.10 (s, 36H, H-6); 1.54 (brs, 8H, H-21,22); 2.00 (m, 24H, H-13, 16, 19, 22, 31); 3.10 (d, 4H, J=12.5 Hz, H-3 or 8); 3.11 (d, 4H, J=12.5 Hz, H-8 or 3); 3.15 (d, 4H, J=13.4 Hz, H-26); 3.85 (m, 24H, H-12, 15, 18, 23, 30); 4.40 (d, 8H, J=13.4 Hz, H-4,9); 4.45 (d, 4H, J=13.1 Hz, H-27); 6.42 (m, 4H, H-arom); 6.73 (m, 10H, H-arom); 6.80 (m, 12H, H-arom.). EA calcd. for $C_{152}H_{204}O_{12}$: C, 82.10; H, 9.27. Found: C, 81.80; H, 9.24.

Tris-calix[4]arene 5d. Similarly to **5a** using **7b** and **3c**, stirred 4 days, 0.130 g of product (47%), m.p. 145-155 °C (very broad). ^{1}H NMR spectrum (400 MHz, $CDCl_3$) d 0.98 (m, 24H, H-14, 17, 32); 0.99 (s, 18H); 1.05 (s, 18H); 1.06 (s, 18H); 1.09 (s, 36H, H-6); 1.17 (s, 18H); 1.53 (m, 8H, H-20, 21); 2.00 (m, 24H, H-13, 16, 19, 22, 31); 3.10 (d, 8H, J=12.5 Hz); 3.12 (d, 4H, J=12.5 Hz, H-3, 8, 26); 3.82 (m, 24H, H-12, 15, 18, 23, 30); 4.41 (d, 8H, J=12.5 Hz), 4.43 (d, 4H, J=12.5 Hz, H-4, 9, 27); 6.66 (s, 4H, H-arom); 6.74 (s, 4H, H-arom); 6.75 (s, 4H, H-arom); 6.79 (s, 8H, H-arom); 6.89 (s, 4H, H-arom). EA calcd.for $C_{168}H_{236}O_{12}$: C, 82.42; H, 9.74. Found: C, 81.96; H, 9.63.

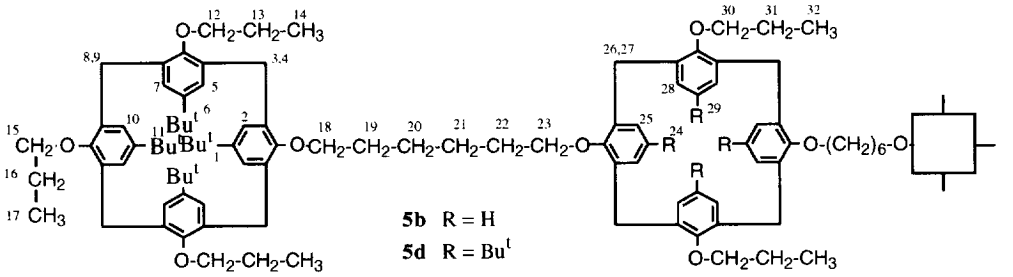


Figure 9. The numbering system of ^{1}H NMR spectra

Preparation of pentakis-calix[4]arene 6b. The mixture of **1a** (0.030 g, 0.071 mmol) and 0.022 mg of NaH (0.554 mmol, 8 eq.) in 20 ml DMF-THF mixture (1:1 v/v) was stirred for 30 min and then 0.52 g of **3c** (0.554 mmol, 8 eq.) was added. Reaction mixture was then stirred for 7 days at room temp., poured into 1N HCl, the precipitate filtered, and purified by repeated preparative TLC. Pure compound was then dissolved in CH_2Cl_2 and precipitated with MeOH to yield 101 mg of **6b** (38%), m.p. 145-50 °C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) d 0.94 (t, 24H, J=7.3 Hz, H-14); 0.97 (t, 12H, J=7.3 Hz, H-17); 1.02 (s, 36H, H-1 or 11); 1.04 (s, 36H, H-11 or 1); 1.10 (s, 72H, H-6); 1.46 (brs, 16H, H-20, 21); 1.99 (m, 40H, H-13, 16, 19, 22); 3.06 (d, 8H, J=11.9 Hz, H-3 or 8); 3.08 (d, 8H, J=11.6 Hz, H-8 or 3); 3.16 (d, 8H, J=13.4 Hz, H-26); 3.78 (m, 32H, H-12, 15, 18); 3.94 (t, 8H, J=7.2 Hz, H-23); 4.37 (d, 8H, J=12.5 Hz, H-4 or 9); 4.39 (d, 8H, J=12.5 Hz, H-9 or 4); 4.47 (d, 4H, J=13.1 Hz, H-27); 6.58 (m, 12H, H-24, 25); 6.70 (s, 8H, H-arom); 6.72 (s, 8H, H-arom); 6.79 (s, 16H, H-arom). EA calcd. for $C_{264}H_{360}O_{20}$: C, 82.26; H, 9.43. Found: C, 82.16; H, 9.38.

Pentakis-calix[4]arene 6d. Analogously to **6b** using **1b** and **3c** as starting compounds, isolated 17 mg of product (7% yield). M.p. 160-165 °C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) d 0.94 (t, 24H, J=7.33 Hz, H-14);0.97 (t, 12H, J=7.33 Hz, H-17); 1.02 (s, 36H, H-1 or 11); 1.04 (s, 36H, H-11 or 1); 1.08 (s, 36H, H-24); 1.09 (s, 72H, H-6); 1.50 (m, 16H, H-20, 21); 2.00 (m, 40H, H-13, 16, 19, 22); 3.07 (d, 8H, J=12.5 Hz, H-3 or 8); 3.08 (d, 8H, J=12.6 Hz, H-8 or 3); 3.12 (d, 4H, J=12.6 Hz, H-26); 3.79 (m, 32H, H-12, 15, 18); 3.93 (t, 8H, J=7.3 Hz, H-23); 4.38 (d, 8H, J=12.5 Hz, H-4 or 9); 4.39 (d, 8H, J=12.5 Hz, H-9 or 4); 4.44 (d, 4H, J=12.5 Hz, H-27); 6.70 (s, 8H, H-arom); 6.73 (s, 8H, H-arom); 6.78 (s, 8H, H-25); 6.79 (s, 16H, H-arom).

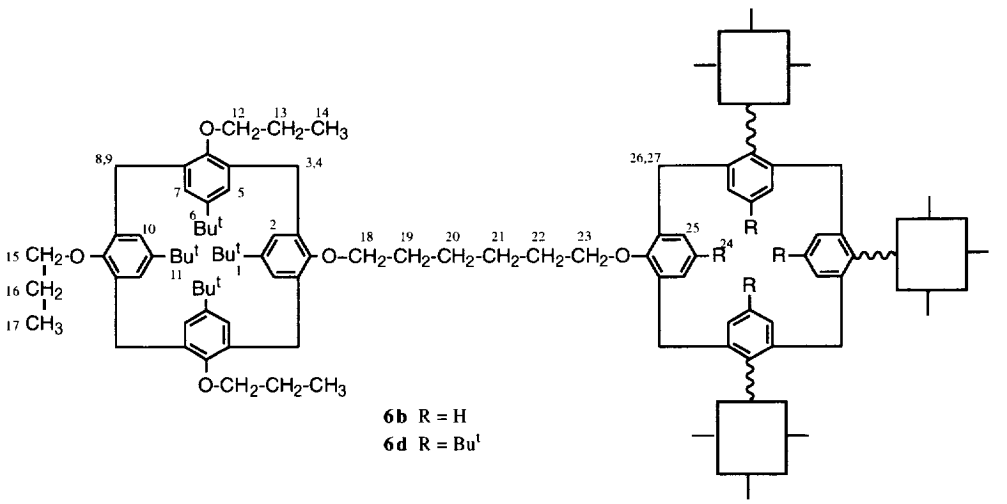


Figure 10. The numbering system of ^{1}H NMR spectra

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