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Conformationally Selective Synthesis of Mononitrocalix[4]arene in *Cone* or *Partial Cone*

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Abstract Nitro-substituted calixarenes in a *cone* and a *partial cone* conformation were prepared selectively using distinct synthetic routes. The selective nitration of tris- or penta- substituted phenols of calix[4]arene or calix[6]arene provided mononitrocalix[*n*]arenes (n = 4, 6). Subsequent addition of ethylene glycol (EG) moieties to mononitrocalix[4]arene provided tetraEGylcalix[4]arene in locked *partial cone* conformation. By an alternative route – initial addition of EG moieties to the non-derivatized calix[4]arene followed by the uncontrolled nitration – provided mononitro- and dinitro-tetraEGylcalix[4]arenes locked in the *cone* conformation. These nitrocalix[4]arenes with locked *cone* or *partial cone* conformation are useful building blocks for further assembly of supramolecular systems, especially in the area of material sciences.

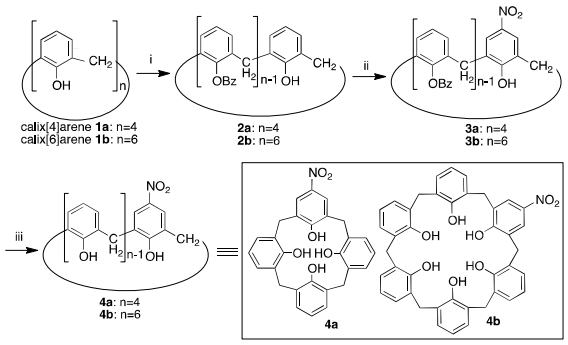
Keywords: calixarenes • conformation • NMR

Introduction

Calixarenes are macrocyclic compounds composed of phenolic units linked together by methylene groups at the 2- and 6-positions. They have a defined structure with an upper rim, a lower rim, and a central annulus. Their sizes can vary from four to eight, and sometimes 20 phenolic units and they

can present different conformations that arise from the rotation of the methylene groups through the annulus. Due to their unique physicochemical properties, calixarenes have found a wide variety of applications including ion-transport membranes,[1,2] chemosensors,[3,4] catalysts,[5,6] and enzyme mimetics.[7] They also play an important role in research towards drug discovery. Calixarenes in a *cone* conformation belong to a family of macrocyclic host compounds together with crown ethers, cyclodextrins, porphyrins, and cavitands.[8-11] They present specific structures and properties such as (1) cavities with suitable sizes for ion and small molecule inclusion, (2) variable conformation, (3) formation of complexes with larger molecules, (4) formation of ditopic ligands with binding sites at the upper and lower rims, and (5) the capability of combining ligands for the formation of molecular sensors, vectors, and switches. These features are desirable for constructing new molecular platforms for the design and development of new materials and drugs.

In the field of supramolecular chemistry including host-guest complexation, calixarenes play an important role. In the calixarene supramolecular systems, a guest and a calixarene host can form a complex by non-covalent intermolecular interactions such as hydrogen bonding, ion pairing, ion-π, CH–π dispersion, and π-π interactions. Compared to other host compounds, the conformation of the calixarene annulus is not always locked; therefore, it is very important to develop a convenient synthetic approach for their specific derivatization suitable for each conformation. In addition, to construct functionalized calixarene derivatives covalently connected to other functional moieties, mono- and di-substituted calixarenes are important building blocks.



Scheme 1 Synthesis of mononitrocalix[*n*]arene **4a** (n = 4) and **4b** (n = 6) *via* tris- and penta-*O*-benzoylcalix[n]arenes **2a** (n = 4) and **2b** (n = 6). *Reaction conditions*: i) BzCl (8.1 equiv), pyridine, 0 °C – rt, 1 h for **1b** (83%); BzCl (7.4 equiv), pyridine, 0 °C – rt, 5 h for **2b** (30%); ii) 65% HNO_3 (1.3 equiv), CH_2Cl_2/AcOH, rt, 1 h, **3a** (47%); 65% HNO_3 (2.5 equiv) for **3b** (20%); iii) NaOH, THF/EtOH/H_2O, reflux, 17 h, **4a** (56%); 24 h, **4b** (48%).

Preparation of mono-substituted calix[4]arene derivatives has already been intensively studied.[12-14] One useful approach includes a selective mono-nitration of the aromatic tri-*O*-benzoylcalix[4]arene[15-18] by taking advantage of the different reactivities of the aromatic carbon at the *para*-position of the OH group with or without benzoyl groups.[19] In the present study, this strategy was used to prepare mononitrocalix[*n*]arenes **4a** and **4b** (n = 4, 6) starting from calixarenes **1a** and **1b** through their tris- and pentabenzoyl derivatives **2a** and **2b** (Scheme 1). Subsequent attachment of ethylene glycol (EG) moieties to the OH groups of **4a** and **4b** provided respectively tetra-ethyoxyethyl (tetra-EGyl) derivative locked exclusively in the *partial cone* conformation (**5a** in Fig. 3) and hexa-EGyl derivatives, which remained flexible. An alternative

route with initial addition of EG groups to calix[4]arene **1a** and subsequent non-controlled nitration provided derivatives **5a'** and **9** (Fig. 4) locked into the *cone* conformation.

Results and Discussion

*Benzoyl esterification of calix[n]arenes **1a** and **1b** (n = 4 and 6)*

In order to carry out a selective nitration, it was necessary to have one activated aryl carbon in *para* position to the phenol group. With that in mind, the initial step involved a selective tri-*O*-benzoylation of calix[4]arene **1a** (Scheme 1).[15,19] In good agreement to previous reports, tri-*O*-benzoylcalix[4]arene **2a** was obtained efficiently (73% yield), using pyridine as a base, from **1a** as a single product. This tris esterification was successful even in the presence of an excess amount of benzoyl chloride (8.1 equiv) [1] and no tetra-adduct was obtained. In a similar manner, calix[6]arene **1b** was subjected to the reaction with benzoyl chloride with the same amount (8.1 equiv) as in case of **1a** but provided a large amount of hexa-adduct in addition to the desired penta-adduct **2b**. This was due to the less hindered and more flexible structure of calix[6]arene with larger cavity. Optimized reaction conditions with 7.4 equiv of benzoyl chloride in the presence of pyridine afforded penta-*O*-benzoylcalix[6]arene **2b** in 30% yield.

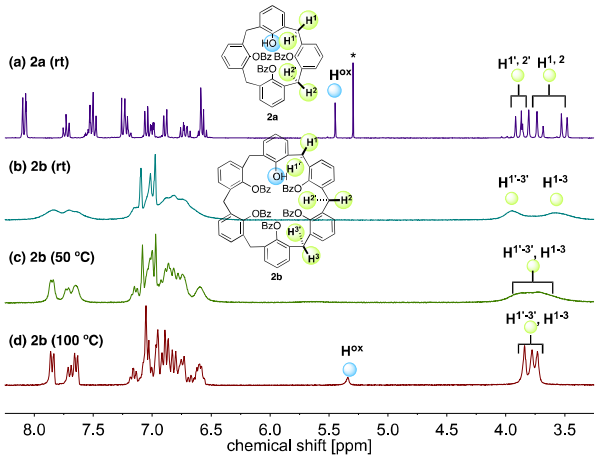


Figure 1. ^{1}H-NMR spectra of **2a** at rt (a) and of **2b** at rt (b), 50 °C (c), and 100 °C (d) in toluene-d_8 (*: residue of a solvent).

The ^{1}H-NMR spectrum of tri-*O*-benzoylcalix[4]arene **2a** (Figure 1a) indicated that the conformation of the cavity was locked into the *partial cone* based on the chemical shift patterns of the bridging methylenes ($H^{1,2}$, $H^{1',2'}$) in comparison to the reported values.[20] Furthermore, DFT calculations for the ^{1}H-NMR chemical shift estimation of the bridging methylene protons suggested that the recorded ^{1}H-NMR chemical shift values were in a better agreement to the calculated values for the *partial cone* rather than for the *cone* conformation (Table 1).

[1] Tetra-benzoylester of calix[4]arene can be prepared in the presence of AlCl3 without providing any Friedel-Craft acylation product.

Table 1. Observed and calculated ^{1}H-NMR chemical shifts of the bridging protons of **2a**.

	^{1}H-NMR chemical shift [ppm]			
	$H^{2'}(1)/(2)$	$H^{1'}(1)/(2)$	$H^{1}(1)/(2)$	$H^{2}(1)/(2)$
experimentally measured[a]	3.89	3.83	3.71	3.50
calculated for *cone*[b]	3.7/4.5	4.2/4.1	3.4/3.5	3.5/3.4
calculated for *partial cone*[b]	3.7/4.5	4.2/4.1	3.4/3.5	3.5/3.4

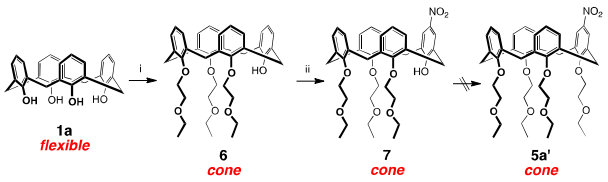
[a]In $CDCl_3$. [b]Geometry optimization: B3LYP/6-31G*; shift calculation: B3LYP/6-31+G(d,p) in implicit $CDCl_3$; scaling parameters: slope: -1.0472, intercept: 31.6874 (http://cheshirenmr.info).

As shown in Fig. 1b, the ^{1}H-NMR peaks of penta-*O*-benzoylcalix[6]arene **2b** were very broad at room temperature in toluene-d_8, in contrast to the ones of tri-*O*-benzoylcalix[4]arene **2a** (Figure 1a).[21] This indicated that **2b** had a flexible conformation and the conformational exchange was in the intermediate regime of NMR time scale. Upon increasing the temperature to 100 °C, the ^{1}H-NMR peaks of **2b** in toluene-d_8 became sharper due to the faster conformational interchange (Figure 1c, d). Similar conformational flexibility was also observed in the nitro derivative of calix[6]arene **3b**, which was obtained by subsequent nitration as described below.

*Selective mono-nitration of tri-O-benzoylcalix[4]arene **2a**, penta-O-benzoylcalix[6]arene **2b**, and triEGylcalix[4]arene **6***

As expected, nitration of tri- and penta-*O*-benzoylcalix[n]arene **2a** and **2b** (n = 4, 6) using 65% HNO_3 and AcOH successfully provided mono-nitro derivative **3a** and **3b** in a selective manner and in reasonable yields (47% and 20% respectively) (Scheme 1). Compounds **3a** and **3b** were subsequently subjected to deprotection of the phenol groups by base to provide nitrocalixarenes **4a** and **4b**. The conformations of **4a** and **4b** with free phenolic groups in the lower rim are not locked, as shown by the ^{1}H-NMR with broad peaks of the bridging methylene protons observed at around 3.5 - 4.2 ppm (Figures 3f and S17).

For an alternative but similar approach to the selective mononitration, calix[4]arene derivative **6** having three phenol OH groups EGylated (instead of Bz) was synthesized (Scheme 2). It was expected that this strategy would show the following advantages: (1) triEGylcalix[4]arene **6** could produce mononitro derivative **7** selectively, and (2) there would not be the need for the subsequent deprotection of the phenolic OH, so that the conformation of the calix[4]arene would be kept as *cone*. Taking advantage of the previously reported study on the metal-template alkoxylation of tetra-*t*-butylcalix[4]arene in *cone* conformation,[22] a selective tri-EGylation of **1a** was achieved in the presence of barium hydroxide and barium oxide and in DMF providing tris-EGyl derivative **6** in 80% yield (scheme 2). The conformation of **6** was confirmed to be *cone* based on the ^{1}H-NMR chemical shift of the bridging methylenes as described below.



Scheme 2 Tris EGylation of calix[4]arene and subsequent mononitration. *Reaction conditions:* i) $C_2H_5OC_2H_4Br$ (20 equiv), $Ba(OH)_2 \bullet 8H_2O$, BaO, DMF, rt - 80 °C, on, 80%; ii) 65% HNO_3 (1.2 equiv), DCM/AcOH (3:1), rt, 1.5 h, 52%. Last step of EGylation was not successful even using excess amount of $C_2H_5OC_2H_4Br$ or $C_2H_5OC_2H_4OTs$.

The ^{1}H-NMR of tris-EGylated derivative **6** showed two distinct types of bridging methylene protons (Figure 2c, the axial protons ($H^{1,2ax}$) at 4.58 and 4.98 ppm and the equatorial protons ($H^{1,2eq}$) at 3.35 and 3.26 ppm), indicating clearly that **6** is in *cone* conformation. As described in the previous section, the corresponding methylene protons of **2a** were observed in closer chemical shift range ($H^{2ax,2eq}$ and $H^{1,1'}$ in Figure 2a) corresponding to the *partial cone* conformation.[2] In addition, ^{13}C-NMR chemical shifts of the bridging methylenes of **2a** and **3a** in *partial cone* conformation were 37.5, 32.5 ppm and 37.4, 32.6 ppm, respectively, while the ones of **6** and **7** were 30.9, 30.8 ppm and 30.8, 30.7 ppm, which corresponded to the *cone* conformation. Taken together, these results show that the tris addition of EG to calix[4]arene afforded **6** in a *cone* conformation, while the tris addition of benzoyl group provided **2a** in a *partial cone* conformation.[3] Selective nitration of **6** – at the most activated aryl ring bearing a free phenol group – was successfully carried out in a mixture of HNO_3 and AcOH to provide mononitrocalix[4]arene **7** (Scheme 2, 52% yield).

The ^{1}H-NMR spectra of **3a** and **7** clearly confirmed successful mono-nitration of **2a** and **6** by the appearance of a singlet at around 8 ppm corresponding to the protons in the *ortho*-position to the nitro group (H^{m1} in Fig. 2b, d). Simultaneously, the OH protons (H^{ox}) shifted to lower field in both **3a** (from 5.4 (in **2a**) to 6.3 ppm) and **7** (from 5.0 (in **6**) to 6.9 ppm) being correlated to a decrease of pKa of phenolic OH due to the nitration in *para*-position (p*K*a of phenol and nitrophenol are about 10 and 7 respectively). The conformation of nitro derivative **7** was confirmed to be *cone* by ^{1}H-NMR with two distinct types of bridging methylene protons ($H^{1,2ax}$ at 4.49 and 4.59 ppm and $H^{1,2eq}$ at 3.21 and 3.15 ppm) observed in a similar pattern to **6** but with a slight change of chemical shift (Figgure 2d). This result indicated that **7** was also in a *cone* conformation with a small conformational change from **6** in the cavity, possibly due to the bulky nitro group in **7**. A similar situation was observed in the nitro derivative **3a,** in comparison to **2a** (Figure 2a, b).

[2] Also ^{1}H NMR of a standard cone calix[4]arene **8**, with distinct two types of bridging methylene protons (H^{ax} at 4.50 ppm and H^{eq} at 3.15 ppm), can be referred (Figure 3e).

[3] ^{13}C-NMR chemical shift of bridging methylenes of **2a** and **6** were respectively 37.5, 32.4 ppm (Figure S2) and 30.9, 30.8 ppm (Figure S30).

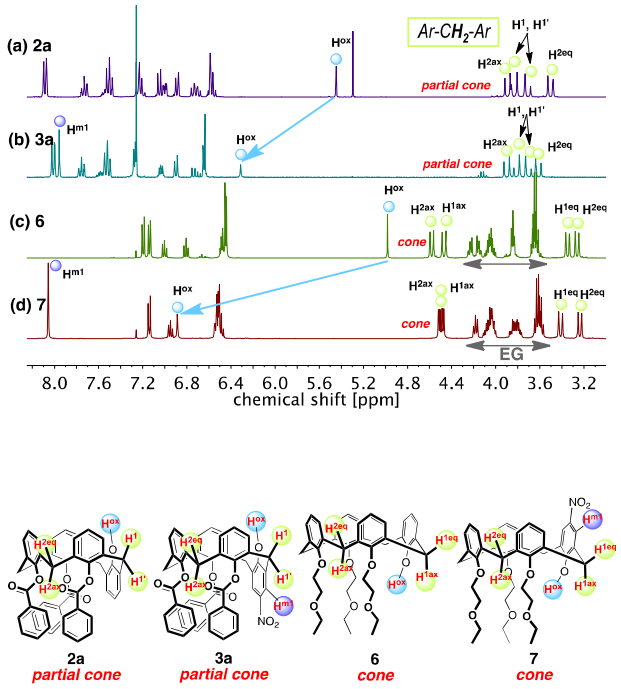


Figure 2. Comparison of ^{1}H-NMR spectra of tri-substituted calix[4]arenes **2a** (a), **3a** (b), **6** (c) and **7** (d) in $CDCl_3$ and their chemical structures. The chemical shifts of CH_2 protons in equatorial ($H^{1\text{-}2eq}$) and axial position ($H^{1\text{-}2ax}$) were more apart in the presence of the EG groups (**6** and **7**), indicating that compounds **6** and **7** have distinct *cone* conformations.

Unfortunately, as shown in Scheme 2, further EGylation of the remaining last OH in **7** was not successful. The *cone* mononitro-tetraEGylcalix[4]arene **5a'** was not obtained in the presence of NaH and 1-bromoethoxyethane in DMF even at elevated temperatures (0 to 80 °C) for longer reaction time using a high excess (50 equiv) of the 1-bromoethoxyethane. Additional attempt using 1-tosylethoxyethane with extended reaction time was not successful. Taken together, the reported fact that calixarene **1a** can be converted to tetraEGylcalix[4]arene **8** efficiently (see also Fig. 3a in the following section), the reactivity difference in the phenolic groups of **6**[4] and **7** may be explained that phenolic OH with *para*-substituted nitro group is less nucleophilic although initial deprotonation step can occur easier due to it's lower pKa. In addition, a slight conformational change in the cavity due to the nitro group could impact the steric hindrance of the phenol affecting the reaction kinetics, taken together the fact that tetraEGylation of calix[4]arene **1a** and nitrocalix[4]arene **4a** were both successful as described in the following section.

*EGylation of calix[4]arenes **1a** and **4a***

As described above, EGylation of the phenols in the lower rim can lock the conformation of calix[4]arene cavity to restrict the interconversion. For this reason, EGylation of the flexible mononitrocalix[4]arene **4a** was carried out in the presence of NaH at 85 ºC to afford

[4] Since tetraEGylcalix[4]arene **8** was obtained from **1a** efficiently, it was speculated that additional EGylation of **7** to provide **5a'** was possible.

tetraEGylcalix[4]arene **5a** (Figure 3b). As a standard reaction, flexible calix[4]arene **1a** was subjected to the same EGylation condition. As previously reported, the reaction of **1a** provided tetra-EGylated compound **8** in only the *cone* conformation, owing to the Na^+ coordinating in the lower rim of the cavity (Figure 3a).[5]

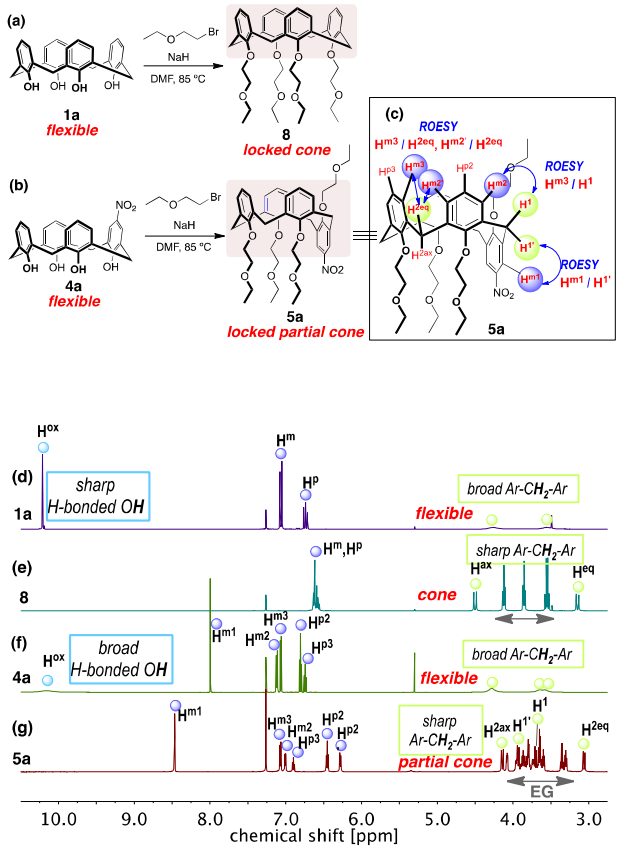


Figure 3. (a-c) Tetra EGylation of **1a** (a) and **4a** (b), and conformational determination of **5a** by ROESY measurement (c). While unsubstituted **1a** provided **8** with locked *cone* conformation, mono-nitro derivative **4a** provided **5a** in locked *partial cone* conformation. *Reagents and conditions:* (a) $TsOC_2H_4OC_2H_5$, NaH, DMF, 85 °C, overnight, 55%, (b) $BrOC_2H_4OC_2H_5$, NaH, DMF, 85 °C, 4 days, 12%. (d-g) ^1H NMR spectra of **1a** (d), **8** (e), **4a** (f), and **5a** (g) in $CDCl_3$. The broadening of bridging methylene protons in **1a** and **4a** indicated that their cavities are in flexible conformation, which was locked by the addition of EG groups as suggested from the sharper peaks of bridging protons (Ar-CH_2-Ar) of **8** and **5a**. The patterns of these protons (H^{ax} and H^{eq}) of **8** and **5a** indicated that they are in *cone* and *partial cone* conformations respectively, which was further confirmed by ROESY measurement in case of **5a** (c).

As indicated by broad peaks for the bridging methylene protons (H^{ax} and H^{eq}) in ^1H-NMR, mononitrocalix[4]arene **4a** had a flexible conformation (Figure 3f) similar to **1a** (Figure 3d). On the other hand, the phenolic protons of both **1a** and **4a** were observed in > 10 ppm area corresponding to the region for H-bonded OH groups. The OH signals of **4a** were much broader than the ones of **1a**, which has less flexibility with stronger H-bonding. As previously reported, after EGylation of **1a**, the methylene bridging protons of **8** became sharper with two distinct

[5] We also carried out hexa-EGylation of **1b** and **4b**, but obtained hexa adducts of calix[6]arenes remained flexible in $CDCl_3$.

doublets, which corresponded to the axial (H^{ax}, 4.50 ppm) and equatorial (H^{eq}, 3.15 ppm) methylene protons confirming the successful lock to *cone* conformation of the cavity (Figure 3c). This *cone* shape of **8** was also confirmed by ^{13}C-NMR with the appearance of a single peak at 30.9 ppm corresponding to the bridging methylene carbons, which are in accordance to the literature.[22]

Similarly, tetra-EGylated product **5a** was obtained as a single conformer from flexible **4a**. Detailed ^{1}H, ^{13}C NMR[6] and ROESY analyses confirmed that compound **5a** was in a *partial cone* conformation (Figures 3c, S23-28). Considering the fact that calix[4]arene **1a** provided **8** in a *cone* conformation, we speculated that **4a** did not have preferred *cone* shape due to its rather bulky NO_2 group, which simultaneously weakened the H-bonds of the phenolic protons. This was also indicated by the broadening of ^{1}H NMR peak corresponding to the OH groups in **4a** that appeared in H-bonding OH region at ≥ 10 ppm (Figure 3f).

*Mononitrocalix[4]arene **5a'** in cone conformation*

For the preparation of mononitro-tetraEGylcalix[4]arene in *cone* conformation, tetraEGylcalix[4]arene **8** with a pre-locked *cone* conformation was subjected to the non-controlled nitration to provide mononitro- and dinitro-tetraEGylcalix[4]arenes **5a'** and **9** both in *cone* conformation (Fig. 4a). The conformations of the obtained products **5a'** and **9** were confirmed to be *cone* by ^{1}H-NMR by the two distinct types of bridging methylenes (Fig. 4c, d). The chemical shift of bridging methylenes (H^{d}, H^{u}) of **8**, **5a'** and **9** showed only slight difference, indicating that their conformations of the cavity parts were all similar showing little effect of the nitro groups in the upper rim.

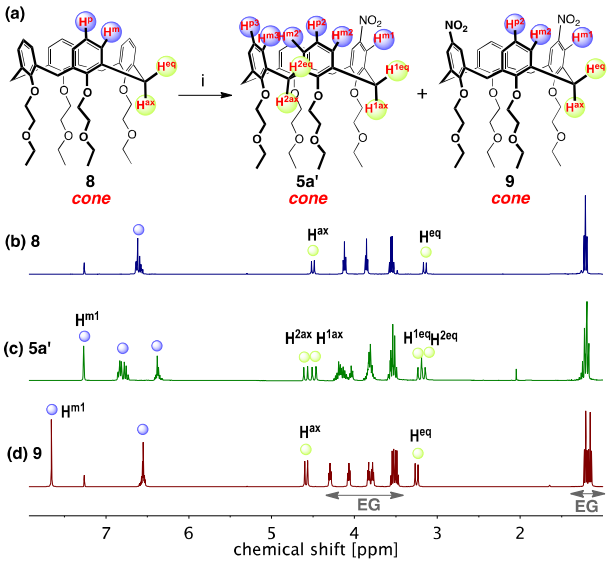


Figure 4. (a) Non-controlled nitration of calix[4]arene **8** with pre-locked *cone* conformation to form mononitro-and dinitro-tetraEGylcalix[4]arenes **5a'** and **9** and (b-d) their ^{1}H-NMR of **8**, **5a'**, and **9** in $CDCl_3$. *Reagents and condition:* i) HNO_3 (65%, 23 equiv), DCM/AcOH, rt, 3 h, 28% (**5a'**) and 38% (**9**). There is little effect by the NO_2 substitution in the upper rim on the conformation of cavity as indicated chemical shifts of bridging methylene protons (H^{ax} and H^{eq}) of **8**, **5a'**, and **9** in a similar range.

[6] ^{13}C-NMR chemical shifts of bridging methylenes of **5a** were 34.4 and 30.4 ppm (Figure S24).

Effect of EG groups in lower rim on the conformation of calix[4]arene cavity

As described above, EGylation of OH groups can lock the conformation of calix[4]arenes. However, the hexaEGylation at the lower rim of calix[6]arenes **1b** and **4b** possessing larger cavities was not successful locking in their conformation, as confirmed by the broad peaks of their bridging methylene protons in ^{1}H-NMR (data are not shown). To see the effect of EGylation on the cavity conformation of calix[4]arenes, we compared ^{1}H-NMR signals of bridging methylene protons of EGylated calix[4]arenes with different numbers of EG groups in the lower rim (Figure 5). As indicated in Figure 5b, the conformation of calix[4]arene **10** with just one EG group was locked to *cone* conformation, which was additionally confirmed by ^{13}C-NMR peaks of bridging methylenes (31.9 and 31.2 ppm). Consequently, the three phenolic protons (H^{ox}) of **10** were observed in H-bonded OH region (> 9 ppm), while one phenol OH in *cone*-tri-EG-calix[4]arene **6** was observed at around 5 ppm in non-H-bonding region. The ^{1}H-NMR chemical shifts of the bridging methylene protons, especially equatorial protons (H^{ex}) of mono-, tris-, and tetraEGylcalix[4]arenes **10**, **6**, and **8**, shifted to upper field upon increasing the numbers of EGs, presumably by reflecting the different shapes of their *cone* cavities (Figures 5 and S51).

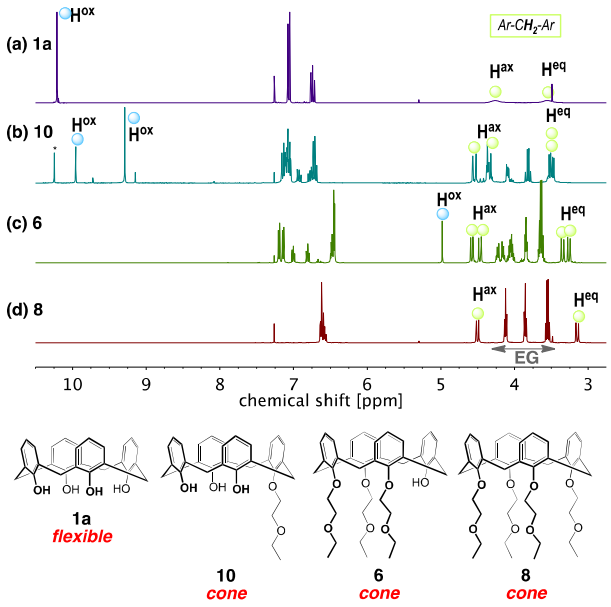


Figure 5 (a-d) ^{1}H-NMR spectra of EGylated calix[4]arene derivatives **1a** (a), **10** (b), **6** (c), and **8** (d) in $CDCl_3$. The change in the chemical shift of the methylene bridging protons (Ar-CH_2-Ar) by the addition of EG groups indicated that addition of EG in the lower rim affects the conformation of the *cone* cavity.

Conclusions

Mono-nitro calix[4]arene derivatives in both locked *partial cone* and locked *cone* conformations were successfully prepared by two different synthetic approaches. While EGylation of calix[4]arene provided tetra-EGylated product in a *cone* conformation, the same reaction of mononitro calix[4]arene provided the one in *partial cone* conformation. Even single EGylation

was efficient to lock the conformation of calix[4]arenes but not in the case of calix[6]arenes. Tetra EGylated calix[4]arene was subjected to the non-controlled nitration to provide mono- and di-nitro calix[4]arene derivatives in *cone* conformation.

Experimental Section

General

NMR spectra were recorded on a Varian Mercury-vx 300 spectrometer (Varian, UK), a Brucker Magnet System 400 Mhz/54 mm spectrometer (Brucker BioSpin, Fällanden, CH) and, a Brucker Avance III 600 spectrometer (Brucker BioSpin AG, Fällanden, CH). IR spectra were recorded on a JASCO FT/IR-4100 (JASCO, Tokyo, JPN). Mass Spectrometry was performed on a Brucker Maxis (Brucker Daltonics GmbH, Bremen, D). HPLC analysis were carried out using a JASCO PU-2080 intelligent HPLC pump, solvent mixing module MX-2080-31, PDA detector MD-2018 Plus (JASCO, Tokyo, JPN). Melting points were measured on a Büchi Melting Point B-545 (Büchi Labortechnik AG, Flawil, CH). All solvents were purchased from Sigma-Aldrich Chemie GmbH (Steinheim, D). Sodium hydroxide, hydrochloric acid and pyridine (distilled in calcium hydride) were purchased from Fluka Chemie GmbH (Buchs, CH). Acetic acid and nitric acid were purchased from Merck KGaA (Darmstadt, D). Calixarenes and Benzoyl chloride were purchased from Acros Organics (Geel, BE) and, 2-bromoethyl ethyl ether from ABCR GmbH (Karlsruhe, D).

25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene (2a). To a solution of calix[4]arene **1a** (0.935 g, 2.20 mmol) in anhydrous pyridine (11 mL), benzoyl chloride (2.07 mL, 2.5050 g, 17.81 mmol) was added at 0 ºC (ice bath). The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm slowly to room temperature over another 1 h. Then water (70 mL) was added to produce the insoluble material, which was filtered off and washed with methanol. The white precipitate was then recrystallized from MeOH-$CHCl_3$ (1:2) to yield small colorless crystals **2a** (1.34 g, Y = 82%); mp 274-275 °C; IR 3541 cm^{-1} (OH), 1727 cm^{-1} (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$, RT) δ (ppm) 3.4-3.9 (m, 8H), 5.4 (s, OH), 6.5-8.1 (m, 36H); ^{13}C-NMR (100 MHz, $CDCl_3$, RT) δ (ppm) 32.4, 37.5, 119.8, 125.2, 126.0, 127.8, 127.9, 128.1, 129.2, 129.5, 130.3, 130.7, 130.8, 131.3, 132.6, 132.9, 133.2, 133.5, 138.8, 146.7, 148.3, 152.8, 163.9, 164.5; HR-ESI-MS(+) $[M+H]^+$ calcd. for $C_{49}H_{37}O_7^{+\bullet}$ 737.2534 *m/z,* found 737.2531 *m/z*.

37,38,39,40,41-pentabenzoyloxy-42-hydroxy-calix[6]arene (2b). To a stirred solution of calix[6]arene (2.5 g, 3.93 mmol) in dry pyridine (30 mL) was added benzoyl chloride (3.4 mL, 29.04 mmol) at 0 °C under nitrogen atmosphere. After 1 h, the reaction mixture was allowed to warm up to room temperature and it was stirred for another 4 hours. The reaction was quenched with an aqueous HCl solution (2 M, 150 mL) and the precipitate was filtered. The precipitated was further washed with an aqueous NaOH solution (2 M), water and methanol in order to afford pentabenzoylcalix[6]arene **2b** as colorless crystals (1.37 g, 30%); ^{1}H-NMR (300 MHz, toluene, 100 °C) δ (ppm) 3.8 (s, 4H), 3.9 (s, 4H), 3.95 (s, 4H), 5.4 (s, 1H), 6.6-7.3 (m, 34H), 7.7-8.0 (m, 9H); HRMALDI-TOF(+) (3-HPA) $[M+Na]^+$ calcd for $C_{57}H_{56}NaO_{11}^+$ 1179.37 *m/z,* found 1179.373 *m/z*, $[M+K]^+$ calcd for $C_{57}H_{56}KO_{11}^+$ 1195.35 *m/z,* found 1196.349 *m/z*..

5-nitro-25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene (3a). HNO_3 (65%, 17.46 µL) was added to a stirred solution of **2a** (100 mg, 0.136 mmol) in a mixture of CH_2Cl_2 (2 mL) and AcOH (0.67 mL) at room temperature. The reaction mixture stirred for 1 h and was then quenched with water (10 mL). The organic layer was washed twice with water (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and purified by a silica gel flash column chromatography to give **3a** as a yellow solid (50 mg, 47%); mp 270-272 °C (dec.); IR [cm^{-1}] 3497m (O-H), 2924m, 1729s (C=O), 1601w, 1519m, 1451m, 1337m (NO_2), 1265s, 1169m, 1061m, 1024m, 755m 708s; ^{1}H NMR (300 MHz, $CDCl_3$, RT) δ_H: 3.5-3.9 (m, 8H), 6.35 (s, OH) 6.5-8.0 (m, 26H), 7.9 (s, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$, RT) δ_C 32.6, 37.4, 125.0, 125.3, 126.3, 127.9, 128.0, 128.3, 128.4, 128.8, 129.3, 130.6, 130.9, 131.0, 131.2, 131.3, 133.3, 133.5, 133.8, 134.1, 140.4, 146.9, 148.3, 158.6, 163.8, 164.2; HRMS (MALDI TOF (–)) (matris: 3-HPA) *m/z* calcd for $C_{49}H_{34}NO_9^-$: 780.2234, found: 780.2239 $[M-H]^-$.

5-nitro-37,38,39,40,41-pentabenzoyloxy-42-hydroxy-calix[6]arene (3b). HNO_3 (65%, 10 µL) was added to a solution of **2b** (67.7 mg, 0.0585 mmol) in CH_2Cl_2 (0.9 mL) and AcOH (0.3 mL) and stirred at room temperature for 1 h. Then, the reaction mixture was quenched with water, and the organic layer was washed twice with water and dried over $MgSO_4$. The solvent was removed under reduce pressure and the residue was purified by a silica gel flash column chromatography (Hexane/$CHCl_3$/EtOAc 8:4:2) followed by a semi-prep HPLC (10% of EtOAc in *n*-hexane-toluene (2:1)) to give **3b** as a pale yellow solid (13.6 mg, 20%); ^{1}H-NMR (300 MHz, toluene, 100 °C) δ (ppm) 3.7 (s, 4H), 3.8 (s, 4H), 3.9 (s, 4H), 6.3 (s, 1H), 6.6-7.3 (m, 31), 7.7-8.0 (m, 11), 7.9 (s, 2H). HRMALDI-TOF(+) (matrix: 3-HPA) $[M+Na]^+$ calcd for $C_{77}H_{55}NNaO_{13}^+$ 1224.3571 *m/z*, found 1224.357 *m/z*, $[M+K]^+$ cacld for $C_{77}H_{55}NKO_{13}^+$ 1240.3310 *m/z*, found 1240.334 *m/z.*

5-nitro-25,26,27,28-hydroxycalix[4]arene (4a). NaOH (3.0 g, 75 mmol) was added to a solution of **3a** (797 mg, 1.02 mmol) in a mixture of THF (50 mL), EtOH (30 mL), and water (20 mL). The reaction mixture was heated at 85 °C overnight. After the solvents were removed under reduced pressure, the residue was acidified with 2M HCl (60 mL), and the precipitate was collected by filtration and dried overnight at 60 °C. The crude mixture was purified by a silica gel flash column chromatography (dry loading, Haxena/$CHCl_3$ 19:1 to 7:1) to give **4a** as a pale yellow solid (267 mg, 56%); mp 244-246 °C (dec.); IR (KBr) [cm^{-1}] 3414s (O-H), 2929m, 1617m, 1521w, 1466s, 1450s, 1406w, 1340m (NO_2), 1282m, 1259m, 1211m, 1098m, 1025m, 756m; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.61 (brd, 4H, *J* 46.1 Hz, CH_2), 4.28 (bs, 4H, CH_2), 6.74 (dd app t, 1H, *J* 7.6 Hz, HAr), 6.81 (dd app t, 2H, *J* 7.6 Hz, HAr), 7.06 (d, 2H, *J* 7.6 Hz, HAr), 7.12 (dq, 4H, J 1.7 and 7.6 Hz, HAr), 8.00 (s, 2H, HAr), 10.15 (brs, 4H, OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 31.5 (CH_2), 31.6 (CH_2), 122.5 (CHAr), 122.7 (CHAr), 124.7 (CHAr), 126.5 (CAr), 127.8 (CAr), 128.5 (CAr), 129.0 (CHAr), 129.0 (CHAr), 129.3 (CAr), 129.6 (CHAr), 141.9 (CAr), 148.4 (CAr), 148.5 (CAr); HRMS (ESI+) *m/z* 470.1598 calcd for $C_{28}H_{24}NO_6^+$, found: 470.1598 $[M+H]^+$.

5-nitro-37,38,39,40,41,42-hydroxycalix[6]arene (4b). To a stirred solution of **3b** (56 mg, 0.046 mmol) in a mixture of THF (2.5 mL), EtOH (1.5 mL), and water (1 mL), NaOH (0.24 g) was added at room temperature. The reaction mixture was allowed to stir overnight at 85 °C. The solvents were removed under reduced pressure and the residue was acidified with an aq. sol. HCl (2 M). The precipitate was filtered and the residue was purified by flash column chromatography (DCM/hexane: 1:1 to 4:1) to afford **4b** as a yellowish solid (15 mg, 48%); δ_H (600 MHz, $CDCl_3$): 3.90 (brs, 12H, CH_2), 6.73-7.21 (m, 15H, HAr), 7.96 (brs, 2H, HAr), 10.20 (brs,

2H, OH), 10.28 (brs, 2H, OH), 11.33 (brs, 1H, OH). δ_C (150 MHz, $CDCl_3$): 32.1 (CH_2), 32.2 (CH_2), 121.9 (CHAr), 122.2 (CHAr), 122.5 (CHAr), 125.3 (CHAr), 125.8 (CAr), 127.2 (CAr), 127.4 (CAr), 127.7 (CAr), 128.4 (CAr), 129.6 (CHAr), 129.8 (CHAr), 129.8 (CHAr), 130.2 (CHAr), 141.8 (CAr), 149.3 (CAr), 149.4 (CAr), 149.6 (CAr), 155.9 (CAr); HRMALDI-TOF(−) (3-HPA) $[M-H]^-$ calcd for $C_{42}H_{34}NO_8^-$ 680.2284 *m/z,* found 680.2281 *m/z*.

5-nitro-25,26,27,28-tetra(ethoxyethoxy)calix[4]arene (*partial cone* 5a). To a solution of **4a** (90 mg, 0.191 mmol) in a mixture of THF (4.6 mL) and DMF **(**15.0 mL), NaH (92 mg, 3.83 mmol) and 2-bromoethyl ethyl ether (0.646 mL, 5.73 mmol) were added and the reaction mixture was refluxed (85 °C) for 4 days. THF was removed under reduced pressure and the excess of NaH was destroyed by addition of water. The mixture was neutralized with 2M HCl and the product was extracted with dichloromethane. The organic layer was washed twice with water and dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a brown oily residue, which was purified by a silica gel flash column chromatography which was followed by semi-prep HPLC to give **5a** as a white solid (17.26 mg, 12%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.1 (t, *J* = 7.0 Hz, 1H), 1.2-1.4 (m, 9H), 3.0 (d, *J* = 13.4 Hz, 1H), 3.2-3.4 (m, 4H), 3.5-4.0 (m, 22H), 4.0-4.1 (m, 2H), 4.15 (d, *J* = 13.3 Hz, 1H), 6.3 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.45 (t, *J* = 7.6 Hz, 1H), 6.9 (t, *J* = 7.4 Hz, 1H), 7.0 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.05 (d, *J* = 7.4 Hz, 1H), 8.4 (s, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$, rt) δ (ppm) 15.20, 15.5, 30.4, 34.4, 65.7, 66.7, 66.8, 69.1, 69.6, 69.8, 71.7, 72.6, 73.9, 122A, 122.3, 126.1, 128.9 (2 carbons), 131.3, 133.7, 135.5, 136.5, 134.6, 142.6, 154.9, 157.3, 162.7; HRMALDI-TOF(+) (3-HPA) $[M+Na]^+$ calcd for $C_{44}H_{55}NaO_{10}^+$ 780.3724 *m/z*, found 780.3713 *m/z,* $[M+K]^+$ calcd for $C_{44}H_{55}KO_{10}^+$ 796.3463 *m/z,* found 796.3457 *m/z*.

25,26,27-tris(ethoxyethoxy)calix[4]arene (6). To a stirred solution of calix[4]arene **1a** (1.93 g, 4.10 mmol) in dry DMF (100 mL) was added barium hydroxide octahydrate (3.88 g, 12.30 mmol) and barium oxide (3.29 g, 19.3 mmol, 90%) at room temperature under nitrogen atmosphere. After 2 h, the temperature was increased to 80 °C and the reaction mixture was allowed to stir overnight. The solvent was evaporated and the oil residue was dissolved in DCM (100 mL). The organic layer was washed with water (4x100 mL) and the combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. The oil residue was purified by flash column chromatography (hexane/ethyl acetate 9:1) to afford tri-EGylatedcalix[4]arene **6** as a colorless solid (2.11 g, 80%); □□ (400 MHz, $CDCl_3$): 1.27 (t, 3H, *J* 7.0 Hz, CH_3), 1.28 (t, 6H, *J* 7.0 Hz, CH_3), 3.26 (d, 2H, *J* 13.3 Hz, CH_2), 3.35 (d, 2H, *J* 13.7 Hz, CH_2), 3.64 (q, 4H, *J* 7.0 Hz, O*CH*$_2$CH$_3$), 3.65 (q, 2H, *J* 7.0 Hz, O*CH*$_2$CH$_3$), 3.83-3.86 (m, 4H, OCH$_2$*CH*$_2$O), 4.00-4.10 (m, 4H, O*CH*$_2$CH$_2$O), 4.13-4.17 (m, 2H, OCH$_2$*CH*$_2$O), 4.21-4.25 (m, 4H, O*CH*$_2$CH$_2$O), 4.47 (d, 2H, *J* 13.7 Hz, CH_2), 4.58 (d, 2H, *J* 13.3 Hz, CH_2), 4.98 (s, 1H, OH), 6.44-6.50 (m, 6H, HAr), 6.81 (dd apt t, 1H, *J* 7.5 Hz, HAr), 7.00 (dd apt t, 1H, *J* 7.5 Hz, HAr), 7.14 (d, 2H, *J* 7.5 Hz, HAr), 7.20 (d, 1H, *J* 7.5 Hz, HAr); □$_C$ (100 MHz, $CDCl_3$): 15.3 (CH_3), 15.6 (CH_3), 30.1 (CH_2), 31.0 (CH_2), 66.4 (O*CH*$_2$CH$_3$), 66.7 (O*CH*$_2$CH$_3$), 69.2 (OCH$_2$*CH*$_2$O), 69.4 (OCH$_2$*CH*$_2$O), 71.9 (O*CH*$_2$CH$_2$O), 74.6 (O*CH*$_2$CH$_2$O), 119.2 (CHAr), 123.1 (CHAr), 123.3 (CHAr), 127.9 (CHAr), 128.1 (CHAr), 128.5 (CHAr), 129.2 (CHAr), 130.7 (CAr), 132.8 (CAr), 133.6 (CAr), 137.0 (CAr), 153.4 (CAr), 154.1 (CAr), 156.7 (CAr); HRMS (ESI): m/z calculated for $C_{40}H_{52}NO_7$ $[M+NH_4]^+$ 658.3738, found 658.3732.

5-nitro-26,27,28-tris(ethoxyethoxy)calix[4]arene (7). To a solution of tripEylatedgcalix[4]arene **6** (185 mg, 0.29 mmol) in a mixture of DCM/AcOH 3:1 (10 mL) was added dropwise fuming HNO_3 (15 µL, 0.34 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to warm up to room temperature. After 1.5 h water (3x10 mL)

was added to the reaction mixture and it was extracted with CH_2Cl_2 (2x10 mL). The organic layer was then washed with aq solution K_2CO_3 (5%) until pH 7. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/ethyl acetate 0.5:9.5 to 9:1) to give the product as a yellowish solid (103 mg, 52%). δ_H (400 MHz, $CDCl_3$): 1.58 (t, 3H, *J* 7.0 Hz, CH_3), 1.59 (t, 6H, *J* 7.0 Hz, CH_3), 3.58 (d, 2H, *J* 13.1 Hz, CH_2), 3.75 (d, 2H, *J* 13.9 Hz, CH_2), 3.94 (q, 2H, *J* 7.0 Hz, O*CH*$_2$CH$_3$), 3.96 (q, 4H, *J* 7.0 Hz, O*CH*$_2$CH$_3$), 4.11-4.12 (m, 4H, OCH$_2$*CH*$_2$O), 4.34-4.45 (m, 4H, O*CH*$_2$CH$_2$O), 4.34-4.45 (m, 2H, OCH$_2$*CH*$_2$O), 4.50-4.54 (m, 2H, O*CH*$_2$CH$_2$O), 4.83 (d, 2H, *J* 13.8 Hz, CH_2), 4.84 (d, 2H, *J* 13.1 Hz, CH_2), 6.81-6.89 (m, 6H, HAr), 7.23 (s, 1H, OH), 7.29 (dd apt t, 1H, *J* 7.5 Hz, HAr), 7.48 (d, 2H, *J* 7.5 Hz, HAr), 8.40 (s, 2H, HAr). δ_C (100 MHz, $CDCl_3$): 15.2 (CH_3), 15.5 (CH_3), 30.7 (CH_2), 30.8 (CH_2), 66.4 (O*CH*$_2$CH$_3$), 66.7 (O*CH*$_2$CH$_3$), 69.1 (OCH$_2$*CH*$_2$O), 69.3 (OCH$_2$*CH*$_2$O), 71.9 (O*CH*$_2$CH$_2$O), 74.9 (O*CH*$_2$CH$_2$O), 123.3 (CHAr), 123.7 (CHAr), 124.5 (CHAr), 127.8 (CHAr), 128.9 (CHAr), 129.1(CHAr), 129.7 (CAr), 131.2 (CAr), 134.0 (CAr), 136.5 (CAr), 139.6, (CAr), 153.9 (CAr), 156.3 (CAr), 159.7 (CAr). HRMS (ESI): m/z calculated for $C_{40}H_{51}N_2O_9$ $[M+NH_4]^+$ 703.3589, found 703.3581.

25,26,27,28-tetra(ethoxyethoxy)calix[4]arene (8). Calix[4]arene **1a** (2.54 g, 5.41 mmol) was dissolved in dry DMF (76 mL) and cooled down to 0 °C. Sodium hydride (2.16 g of a 60% dispersion in oil, 54.1 mmol) was added portionwise and the reaction mixture was stirred for 30 min under nitrogen atmosphere. 2-ethoxyethyl 4-methylbenzenesulfonate (6.44 g, 0.10 mmol) was then added portionwise and the reaction mixture was allowed to warm up to room temperature during 1.5 h. After that time the reaction warmed up to 80 °C and stirred overnight. The reaction was quenched with water (100 mL) and the solvents were evaporated. The residue was dissolved in DCM (100 mL) and washed with an aq. sat. solution of NH_4Cl (100 mL). The organic layer was separated and washed 2x with water, dried over $MgSO_4$ and concentrated under reduced pressure. The obtained oil was treated with cold methanol and the tetrapegcalix[4]arene **8** was obtained by crystallization as a white solid (2.13 g, 55%); δ_H (400 MHz, $CDCl_3$): 1.21 (t, 12 H, *J* 7.0 Hz, CH_3), 3.15 (d, 4H, *J* 13.4 Hz, CH_2), 3.55 (q, 8H, *J* 7.0 Hz, O*CH*$_2$CH$_3$), 3.85 (t, 8H, *J* 5.8 Hz, OCH$_2$*CH*$_2$O/H3), 4.12 (t, 8H, *J* 5.8 Hz, O*CH*$_2$CH$_2$O/H2), 4.50 (d, 4H, *J* 13.4 Hz, CH_2), 6.56-6.64 (m, 12 H, HAr); δ_C (100 MHz, $CDCl_3$): 15.3 (CH_3), 30.9 (CH_2), 66.4 (CH_2/C5), 69.7 (CH_2/C3), 73.1 (CH_2/C2), 122.2 (CHAr, C4'), 128.2 (CHAr, C3'), 135.0 (CAr/C2'), 156.3 (CAr/C1').

5-nitro-25,26,27,28-tetra(ethoxyethoxy)calix[4]arene (*cone* 5b) and 5,x-dinitro-25,26,27,28-tetra(ethoxyethoxy)calix[4]arene (9). To a solution of tetra-EGylated calix[4]arene **8** (1g, 1.40 mmol) in a mixture of CH_2Cl_2/acetic acid 17:1 (50 mL) was added nitric acid (5 mL, 70 mmol, 65% solution in water) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 2 h at 0 °C and 1 h at room temperature. It was observed that the color of the reaction mixture changed as it warmed up, from pink to black. Water (100 mL) was added to the reaction mixture and it was extracted with CH_2Cl_2 (2x100 mL). The organic layer was then washed with an aq. solution K_2CO_3 (5%) until pH 7. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by a silica gel flash column chromatography (hexane/ethyl acetate 9:1 to 7:3) to afford mononitrocalix[4]arene **5a'** as a white solid (292 mg, 27.5%) and 450 mg of dinitrocalix[4]arene **9** which was further recrystallised in ethyl acetate/hexane; **5a'**: δ_H (300 MHz, $CDCl_3$): 1.17-1.25 (m, 12 H, CH_3), 3.15 (d, 2H, *J* 13.3 Hz, CH_2), 3.21 (d, 2H, *J* 13.3 Hz, CH_2), 3.49-3.59 (m, 8H, O*CH*$_2$CH$_3$), 3.75-3.87 (m, 8H, OCH$_2$*CH*$_2$O), 4.02-4.23 (m, 8H, O*CH*$_2$CH$_2$O), 4.49

(d, 2H, *J* 13.6 Hz, CH_2), 4.59 (d, 2H, *J* 13.6 Hz, CH_2), 6.33-6.40 (m, 3H, HAr), 6.73-6.86 (m, 6H, HAr), 7.27 (s, 2H, HAr); δ_C (75 MHz, $CDCl_3$): 15.3 (CH_3), 15.3 (CH_3), 30.9 (CH_2), 31.0 (CH_2), 62.3 (CH_2), 66.4 (CH_2), 66.4 (CH_2), 69.7 (CH_2), 69.7 (CH_2), 69.7 (CH_2), 73.0 (CH_2), 73.4 (CH_2), 74.0 (CH_2), 122.0 (CHAr), 122.6 (CHAr), 123.3 (CHAr), 128.0 (CHAr), 128.3 (CHAr), 129.2 (CHAr), 134.3 (CAr), 134.5 (CAr), 136.0 (CAr), 136.3 (CAr), 142.6 (CAr), 155.7 (CAr), 156.9 (CAr), 161.6 (CAr); HRMS (ESI): *m/z* calculated for $C_{44}H_{59}N_2O_{10}$ $[M+NH_4]^+$ 775.4164, found 775.4156; **9**: δ_H (400 MHz, $CDCl_3$): 1.16 (t, 6 H, *J* 7.0 Hz, CH_3), 1.21 (t, 6 H, *J* 7.0 Hz, CH_3), 3.25 (d, 4H, *J* 13.7 Hz, CH_2), 3.49 (q, 8H, *J* 7.0 Hz, OCH_2CH_3), 3.54 (q, 8H, *J* 7.0 Hz, OCH_2CH_3), 3.78 (t, 4H, *J* 5.2 Hz, OCH_2CH_2O), 3.83 (t, 4H, *J* 5.1 Hz, OCH_2CH_2O), 4.07 (t, 4H, *J* 5.2 Hz, OCH_2CH_2O), 4.30 (t, 8H, *J* 5.1 Hz, OCH_2CH_2O), 4.58 (d, 4H, *J* 13.7 Hz, CH_2), 6.53-6.59 (m, 6 H, HAr), 7.66 (s, 4H, HAr); δ_C (100 MHz, $CDCl_3$): 15.3 (CH_3), 15.3 (CH_3), 30.9 (CH_2), 66.3 (CH_2), 66.4 (CH_2), 69.5 (CH_2), 69.8 (CH_2), 73.6 (CH_2), 73.6 (CH_2), 123.1 (CHAr), 123.7 (CHAr), 128.6 (CHAr), 133.3 (CAr), 136.9 (CAr), 142.5 (CAr), 155.6 (CAr), 162.6 (CAr); HRMS (ESI): *m/z* calculated for $C_{44}H_{58}N_3O_{12}$ $[M+NH_4]^+$ 820.4015, found 820.4009.

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

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Author Contribution Statement

A.R.S.N.R, S.A and *Y.Y*. designed the experiments and *A.R.S.N.R* and *M.A* conducted the experiments of synthesis and characterization. *A.R.S.N.R* and *YY* carried out the data analysis and wrote the manuscript.

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