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ARTICLE

meta-Bridged Calix[4]arenes with Methylene Moiety Possessing In/Out Stereochemistry of Substituents

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meta-Substituted organomercury calix[4]arenes and their corresponding iodo derivatives have been used for lithiation followed by a reaction with various aldehydes or ketones. The resulting diastereomers were in some cases separable using simple column chromatography. Subsequent intramolecular Friedel–Crafts alkylation led to calix[4]arenes with additional methylene bridge bearing two different substituents with in/out (relative to the cavity) stereochemistry. Our results indicate that the stereochemistry of the final cyclised product does not depend on the structure /stereochemistry of the starting compound, but rather it is influenced by the stability of products. The relationship between the position of these substituents and the complexation properties was demonstrated by ^{1}H NMR titration experiments with *N*-methylpyridinium iodide.

Introduction

Calix[n]arenes[1], a well-known family of macrocyclic host molecules, are widely studied in supramolecular chemistry due to their inexpensive one-pot synthesis, the easy modifications and the well-defined and tuneable 3D shape of their cavity. These properties make calix[4]arenes an ideal starting platform for the synthesis of more sophisticated supramolecular systems that can be used as receptors in the host-guest chemistry.

Over the years, there have been many attempts at altering the rigidity, and consequently, the complexation properties of calixarenes by introducing additional bridges to the calixarene's skeleton.[2] The most common method uses selective alkylation of the free hydroxy groups at the lower rim of a calixarene with the appropriate substituents (Fig. 1a).[3] Another strategy is based on a connection of the unsubstituted *para* positions of phenolic units at the upper rim (Fig. 1b).[4] In this context, we recently reported another approach based on a direct connection (via a single-bond-bridge) between the *meta*-positions of neighbouring aromatic subunits (Fig. 1c).[5] This was enabled using the *meta*-substituted organomercury derivative obtained by electrophilic aromatic mercuration of starting calix[4]arene.[6]

The previously reported *meta*-bridged derivative[7] (carbonyl bridge, Fig. 1d) prepared by intramolecular Friedel-Crafts acylation of the corresponding carboxylic acid, was subjected to nucleophilic addition of organometallic compounds. As shown by X-ray the addition occurred selectively from the outside of the cavity providing tertiary alcohols with the OH group pointing towards the cavity (Fig. 1e). Interestingly, all our attempts to prepare bridged calixarenes with the reversed orientation of the substituents (OH vs R) have failed. Very recently, we reported a different synthetic approach based on the intramolecular Friedel-Crafts alkylation of calixarenes with substituted hydroxymethyl groups at the *meta* positions.[8] As a result, the calix[4]arenes containing two identical substituents on the methylene bridge (Fig. 1f) were obtained.

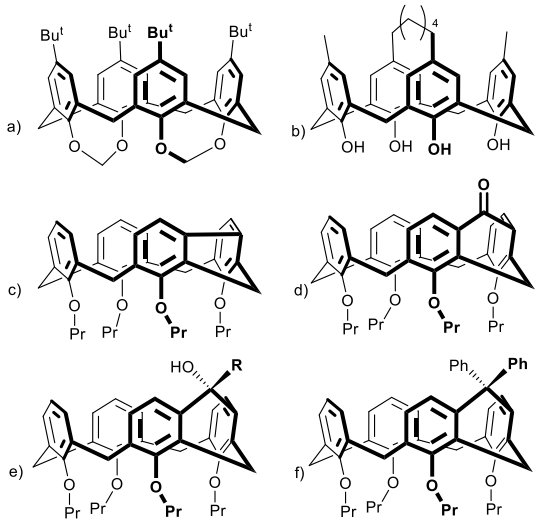

Figure 1. Examples of different approaches for the intramolecular bridged calix[4]arenes.

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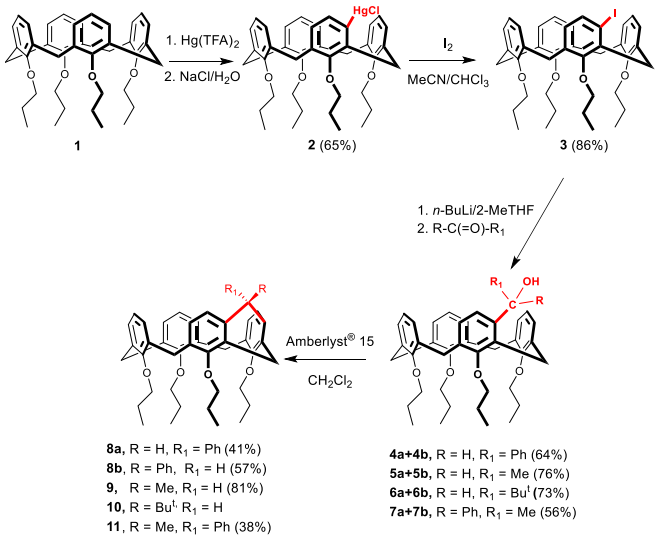
In this paper, we report on our continuous synthetic effort to synthesise *meta* bridged calix[4]arenes with unsymmetrically substituted methylene bridges prepared via intramolecular Friedel–Crafts alkylation.

Results and discussion

The first step of the synthesis was introducing HgCl group into the *meta* position of calix[4]arene **1** according to a recently published procedure[6] using $Hg(TFA)_2$ as a mercuration agent. The desired *meta*-substituted calixarene **2** was isolated in 65% yield. Subsequent reaction with iodine in $MeCN/CHCl_3$ mixture provided corresponding iodo derivative **3** in 86% yield. To introduce variously substituted hydroxymethyl groups, calixarene **3** was treated with *n*-BuLi in dry 2-Me THF at -78 °C followed by a reaction with various aldehydes and ketones. As a result, we obtained diastereomeric mixtures of derivatives **4**, **5**, **6** and **7** in 64%, 76%, 73% and 56% overall yields, respectively. Surprisingly, in the case of product **6** (reaction with pivalaldehyde) we managed to separate both diastereomers using simple column chromatography on silica gel to obtain diastereomers **6a** and **6b** in 22% and 51% yields, respectively. Similarly, we obtained single diastereomers **4a** and **4b** (benzaldehyde adduct) in 41% and 23% yields, respectively. In all the remaining cases, the separation was complicated and therefore, calixarenes **5** (acetaldehyde) and **7** (acetophenone) were isolated only as mixtures of diastereomers.



Scheme 1. Synthesis of unsymmetrically bridged calix[4]arenes.

The exact structure of diastereomers **6a** and **6b** was revealed by the single crystal X-ray analysis. Derivative **6a** crystallized in the orthorhombic system, space group $Pca2_1$. Derivative **6b** prefered the monoclinic system, space group $P2_1/n$. Both of them were in the form of a racemic mixture. As shown in Figure 2, it is evident that in the solid state calixarenes **6a** and **6b** are fixed in only one *pinched cone* conformation, where the bulk *tert*-butyl group is located on the aromatic ring pointing outside from the cavity. Obviously, this is the result of minimising undesirable steric hindrance of bulky *meta* substituents. Unfortunately, we were unable to grow suitable single crystals in the case of diastereomers **4a** and **4b**, hence, their stereochemistry remained unknown.

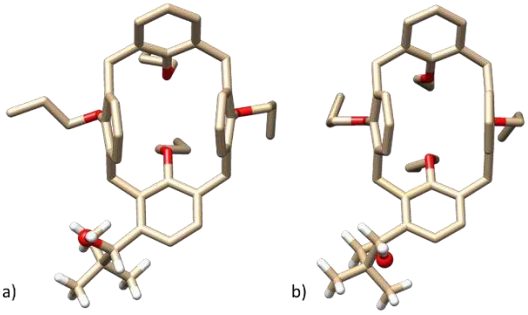


Figure 2. X-ray structures (hydrogens partly omitted for better clarity) of: a) **6a**-top view; b) **6b**-top view.

The intramolecular Friedel-Crafts reaction of **4a** was carried out using Amberlyst® 15 as an acidic catalyst in dichloromethane under reflux. The crude reaction mixture contained two main products **8a (R = H, R_1 = Ph)** and **8b (R = Ph, R_1 = H)**, which were isolated using preparative TLC (silica gel) in 41% and 57% yields, respectively. To demonstrate whether the ratio of these two products could be influenced by the structure of starting compound, the diastereomer **4b** was used as a starting material for the intramolecular cyclization under identical reaction conditions. However, the analysis of reaction mixture showed an almost identical ratio of the products. Moreover, the same result was obtained when a mixture of unseparated diastereomers **4a/4b** was used for cyclization. All these observations indicate that the stereochemistry of the final cyclised product does not depend on the structure /stereochemistry of the starting compound, but rather, it is influenced by the stability of products. In other words, the benzylic type of carbocation, which is formed from starting hydroxymethyl derivative, can adopt a structure (via planar arrangement) that better corresponds to the requirements of the final macrocycle.

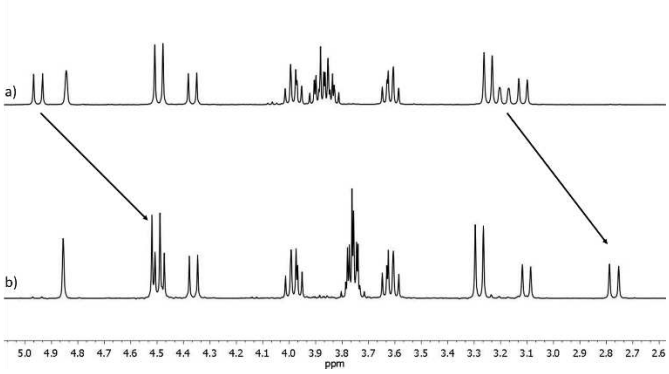


Figure 3. ^1H NMR spectra (400 MHz, $CDCl_3$, 298 K) of Ar-CH_2-Ar region of compound: a) **8a**; b) **8b**.

To determine the stereochemistry of cyclised structures, derivatives **8a** and **8b** were analysed using ^1H NMR techniques. The spectrum of **8a** showed six doublets at 4.95, 4.50, 4.37, 3.25, 3.18 and 3.12 ppm in the 1:2:1:2:1:1 ratio with typical

geminal coupling constants approx. 12-13 Hz corresponding to the Ar-CH_2-Ar bridges. The observed splitting pattern was in agreement with the expected C_S symmetry of the product. Moreover, we observed a singlet of a hydrogen atom on a newly formed methylene bridge (4.84 ppm). Surprisingly, in the case of calixarene **8b**, this signal has an almost identical chemical shift (4.86 ppm). However, there was a significant upfield shift (Fig. 3) of the signals from the CH_2 moiety under a newly formed bridge (4.95 and 3.18 ppm for **8a**, 4.49 and 2.77 ppm for **8b**) with slightly larger geminal coupling constants J = 14.1 Hz. This clearly suggested that in the case of derivative **8b** the CH_2 group is reasonably shielded by the close phenyl moiety pointing outside from the calixarene cavity. This observation was in good agreement with previously reported calixarenes bearing OH and Ph group on methylene bridge (Fig. 1e), even though in that case the shielding was even more striking resulting in the upfield shift to 2.59 ppm.[7]

The final unambiguous structural evidence was obtained by a single crystal X-ray crystallography. Calixarene **8a** crystallized in the triclinic system with *P*-1 space group, while calixarene **8b** crystallized in the trigonal system, *R*-3 space group (Fig. 4). From both structures it was evident that the shape of the calixarene cavity is significantly distorted by the presence of the additional bridge. In the case of derivative **8a,** the length of the short diagonal (the C···C distance of two opposite methylene bridges) was 6.618 Å, while the longer diagonal was 7.583 Å. Almost identical geometry parameters were found for derivative **8b**.

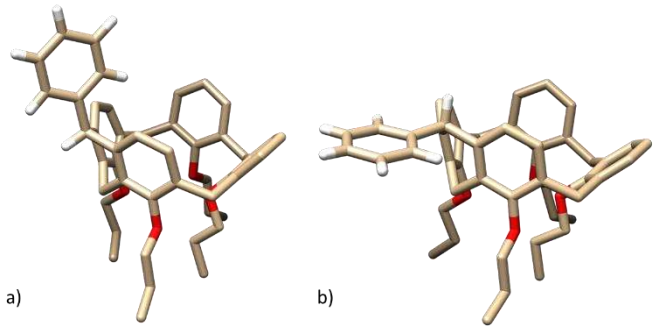


Figure 4. X-ray structures (hydrogens partly omitted for better clarity) of compounds: a) **8a** (in isomer); b) **8b** (out isomer).

The intramolecular cyclization of the remaining derivatives was performed under identical reaction conditions (DCM/Amberlyst® 15/ reflux). Surprisingly, the reaction of a diastereomeric mixture of **5a**/**5b** led to a single product **9 (R = Me)** in 81% yield. Similarly, macrocyclisation of the acetophenone adducts **7a**/**7b** resulted in the isolation of a single product **11 (R = Me, R_1 = Ph)** in 38% yield. The reaction of **6a** or **6b** led to the very complicated reaction mixture (probably, as a consequence of carbocation rearrangement) from which we were unable to isolate the expected product **10 (R = Bu^t)**.

The stereochemistry of product **9** was determined by the X-ray analysis (monoclinic system, space group $P2_1/c$) which clearly showed that methyl group on a newly formed methylene bridge is pointing towards the calixarene cavity (Fig. 5). The other possible product, where the methyl would be oriented outside, was not observed probably because of steric repulsion with the equatorial hydrogen from the proximal Ar-CH_2-Ar bridge. As we could not obtain suitable crystals of derivative **11**, the structure was determined using NMR techniques. Again, we observed a significant upfield shift of one methylene bridge (2.45 ppm, J = 14.5 Hz) suggesting a strong shielding by the phenyl unit in close proximity. At the same time, this observation is also in good agreement with the structures of **8** and **9**. The phenyl ring can be located in the outside position (see the structure of **8b**) while the methyl group is too bulky for this location and must be pointing inside the cavity (compare the structure of **9**).

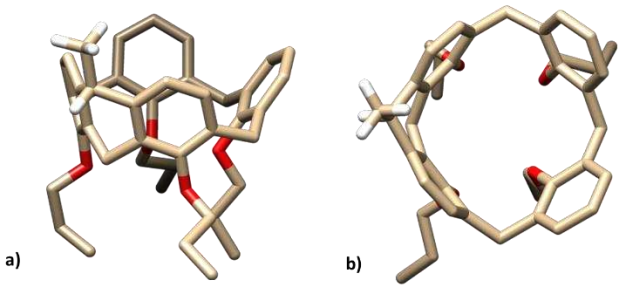


Figure 5. X-ray structure of **9** (hydrogens partly omitted for clarity): a) side view, b) top view.

Having two different diastereomers **8a** and **8b** available, we were further interested if the position of the substituent on the methylene bridge could influence the complexation properties of these calix[4]arenes, as the rigidified cavities could complex cations and neutral compounds using CH–π and/or cation–π interactions. For this purpose, we carried out a ^{1}H NMR titration experiments with calixarenes **8a** and **8b** as a host molecule and *N*-methylpyridinium iodide (NMPI) as a guest in 1,2-$C_2D_2Cl_4$.[9]

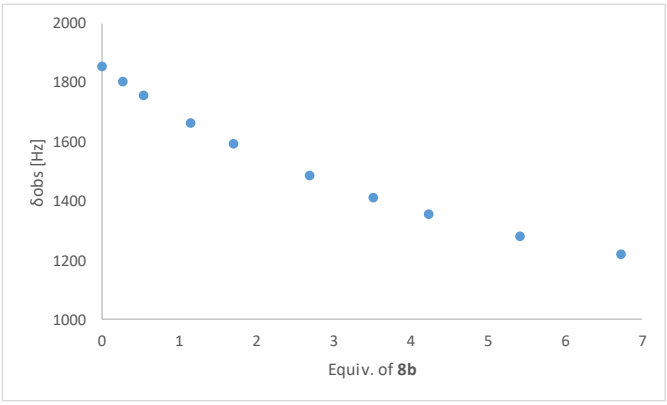


Figure 6. ^{1}H NMR titration curve of **8b** with *N*-methylpyridinium iodide (NMPI) ($C_2D_2Cl_4$, 298 K, 400 MHz).

The complexation occurred under fast-exchange conditions and the aliquots of the host were gradually added to the NMR tube to achieve different calixarene/guest ratios (1:0-7), ensuring constant guest concentration during the ^{1}H NMR experiment. The titration curves (Fig. 6) were constructed from the CIS (complexation induced

shift) values of the methyl group of NMPI. The values of the complexation constants were determined by analyzing the binding isotherms for the 1:1 stoichiometry (using the online application Bindfit).[10,11] The complexation constants for receptors **8a** and **8b** were 24.2 ± 0.2 M^{-1} and 62.3 ± 0.5 M^{-1}, respectively.[12] These findings clearly demonstrate the significant impact of the position of the substituent on the methylene bridge on the overall complexation properties. The lower binding constant for derivative **8a** could be ascribed to the fact that calixarene cavity is at least partly blocked by rotating phenyl moiety. The value of the binding constant for the derivative **8b** was comparable with that of the previously reported derivative bearing unsubstituted methylene bridge (K = 74 ± 1 M^{-1} for NMPI in 1,2-$C_2D_2Cl_4$).[8]

CONCLUSION

A novel *meta*-bridged calix[4]arenes with additional methylene bridge bearing two different substituents were prepared using intramolecular Friedel–Crafts alkylation. In some cases, two products differing in the position of substituents were obtained. The position of these substituents could be determined either by X-ray analysis or by NMR techniques. The influence of the orientation of the substituents on the complexation properties was demonstrated by ^{1}H NMR titration experiments with *N*-methylpyridinium iodide (NMPI).

Experimental

General Experimental Procedures

All chemicals were purchased from commercial sources and used without further purification. Chloroform, acetonitrile and dichloromethane used for the reactions were dried with CaH_2 or $MgSO_4$ and stored over molecular sieves. Melting points were measured on Heiztisch Mikroskop-Polytherm A (Wagner & Munz, Germany). The IR spectra were measured on FT-IR spectrometer Nicolet 740 in KBr transmission mode. NMR spectra were recorded on spectrometers Agilent 400-MR DDR2 (^{1}H: 400 MHz, ^{13}C: 100 MHz) and Bruker Avance DRX 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz). Chemical shifts (δ) are expressed in parts per million and are referenced to the residual peak of solvent or TMS as an internal standard, coupling constants (*J*) are in Hertz. The mass analyses were performed using ESI technique on a FT-MS (LTQ Orbitrap Velos) spectrometer. Purity of the substances and courses of the reactions were monitored by TLC using TLC aluminum sheets with Silica gel 60 F_{254} (Merck) and analyzed at 254 or 365 nm. Preparative TLC chromatography was carried out on a Chromatotron (Harrison Research) with plates covered by Silica gel 60 GF_{254} (Merck).

General procedure for the lithiation and subsequent reaction with aldehydes/ketones

Calixarene **3** was added to an oven-dried Schlenk flask and put under a high vacuum. After 30 minutes, the flask was filled several times with argon and dry THF (20 mL) was added through the septum. The solution was cooled down to -78 °C and stirred for 10 minutes. *n*-Butyllithium (hexane, 1.6M) was added drop-wise to the flask. The solution was stirred for 10 minutes at -78 °C and then 20 minutes at room temperature. The mixture was cooled down again to -78 °C and aldehyde was added. After 20 minutes, the solution was allowed to reach room temperature. The reaction was quenched by the addition of water. The mixture was extracted with dichloromethane, the organic layers were separated, washed with water, dried over $MgSO_4$ and evaporated to dryness. The products were further purified by a preparative TLC.

Procedures for the synthesis of compounds 4a and 4b

Compounds **4a** and **4b** were prepared according to general procedure using calixarene **3** (0.120 g, 0.17 mmol), *n*-BuLi (0.21 mL, 0.34 mmol) and dry benzaldehyde (0.043 mL, 0.42 mmol). The products were separated using preparative TLC (hexane:CH_2Cl_2 1:1). Calixarene **4a** (0.048 g, 41%, mp: <40 °C) and calixarene **4b** (0.027 g, 23%, mp: 62-64 °C) were both obtained as white powders.

4-(1-Hydroxybenzyl)-25,26,27,28-tetrapropoxycalix[4]arene 4a

^{1}H NMR ($CDCl_3$, 400 MHz, 293 K): δ = 7.40-7.26 (m, 5H, Ar-**H**), 7.00-6.84 (m, 3H, Ar-**H**), 6.76 (t, 1H, *J*= 7.4 Hz, Ar-**H**), 6.60 (d, 1H, *J*=7.8 Hz, Ar-**H**), 6.39-6.17 (m, 6H, Ar-**H**), 6.05 (bs, 1H, **OH**), 4.52-4.40 (m, 4H, Ar-**CH_2**-Ar), 4.04-3.69 (m, 10H, O-**CH_2** + Ar-**CH_2**-Ar), 3.22-3.10 (m, 3H, Ar-**CH_2**-Ar), 2.05-1.84 (m, 8H, O-CH_2-**CH_2**), 1.11-1.03 (m, 6H, O-CH_2-CH_2-**CH_3**), 0.98-0.89 (m, 6H, O-CH_2-CH_2-**CH_3**) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 293 K): δ = 155.9, 155.7, 143.3, 140.6, 136.5, 134.0, 133.9, 133.6, 128.6, 128.4, 128.2, 127.7, 127.6 (2x), 127.4, 127.2, 126.8, 122.1, 122.0, 121.7, 121.6, 120.9, 76.9, 76.7, 76.6, 76.4, 73.3, 31.2 (2x), 31.0, 30.9, 23.4, 23.2, 23.1 (2x), 10.1 (2x), 10.0 (2x) ppm. (Some carbons were not visible) IR (KBr): *v* 3382.8, 1454.6 cm^{-1}. HRMS (ESI^+): $C_{47}H_{54}O_5$ calcd for 721.38635 $[M+Na]^+$, 737.36028 $[M+K]^+$; found: 721.38666 $[M+Na]^+$, 737.35999 $[M+K]^+$.

4-(1-Hydroxybenzyl)-25,26,27,28-tetrapropoxycalix[4]arene 4b

^{1}H NMR ($CDCl_3$, 400 MHz, 293 K): δ = 7.40-7.20 (m, 4H, Ar-**H**), 6.93-6.80 (m, 4H, Ar-**H**), 6.80-6.71 (m, 1H, Ar-**H**), 6.46-6.31 (m, 5H, Ar-**H**), 6.15 (s, 1H, **CH**-OH), 4.46 (d, 2H, *J*= 13.3 Hz, Ar-**CH_2**-Ar), 4.45 (d, 1H, *J*= 13.7 Hz, Ar-**CH_2**-Ar), 4.35 (d, 1H, *J*= 14.5 Hz, Ar-**CH_2**-Ar), 3.99-3.68 (m, 8H, O-**CH_2**), 3.53 (d, 1H, *J*= 14.5 Hz, Ar-**CH_2**-Ar), 3.21-3.10 (m, 3H, Ar-**CH_2**-Ar), 2.03-1.78 (m, 8H, O-CH_2-**CH_2**), 1.07-0.97 (m, 6H, O-CH_2-CH_2-**CH_3**), 0.97-0.90 (m, 6H, O-CH_2-CH_2-**CH_3**) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 293 K): δ = 157.5, 157.4, 156.0, 155.9, 144.1, 140.3, 136.3, 136.1, 135.1, 134.5, 134.4, 134.2, 133.9 (2x), 128.6, 128.5, 128.3, 128.2, 127.8 (2x), 127.7, 127.1, 127.0, 126.6, 126.4, 122.2, 122.0, 121.9, 121.0, 76.9, 76.7, 76.6, 76.4, 72.5, 31.2, 31.0, 30.9, 29.7, 23.4, 23.3, 23.1 (2x), 10.4 (2x), 10.1 (2x) ppm. IR (KBr): *v* 3388.5, 1453.9 cm^{-1}. HRMS (ESI^+): $C_{47}H_{54}O_5$ calcd for 721.38635 $[M+Na]^+$, 737.36028 $[M+K]^+$; found: 721.38741 $[M+Na]^+$, 737.36016 $[M+K]^+$.

4-(1-Hydroxyethyl)-25,26,27,28-tetrapropoxycalix[4]arene 5a and 5b

Compounds **5a** and **5b** were prepared according to general procedure using calixarene **3** (0.100 g, 0.14 mmol), *n*-BuLi (0.26 mL, 0.42 mmol) and dry acetaldehyde (0.025 mL, 0.45mmol). The products were purified using preparative TLC (hexane:ethyl acetate 4:1). However, due to the very complicated separation products were isolated as a mixture of diastereomers (0.067 g, 76%, white powder).

HRMS (ESI$^+$): $C_{47}H_{54}O_5$ calcd for 659.37070 $[M+Na]^+$, 675.34463 $[M+K]^+$; found: 659.37074 $[M+Na]^+$, 675.34355 $[M+K]^+$.

Procedures for the synthesis of compounds 6a and 6b

Compounds **6a** and **6b** were prepared according to general procedure using calixarene **3** (0.090 g, 0.13 mmol), *n*-BuLi (0.16 mL, 0.25 mmol) and dry pivaldehyde (0.035 mL, 0.31 mmol). The products were separated using preparative TLC (hexane: ethyl acetate 4:1). Calixarene **6a** (0.019 g, 22%, mp: 149-152 °C) and calixarene **6b** (0.043 g, 51%, mp: 167-168 °C) were both obtained as white powders.

4-(1-Hydroxy-2,2-dimethylpropyl)-25,26,27,28-tetrapropoxycalix[4]arene 6a

The NMR signals of this diastereomer were not well resolved at r.t. ^{1}H NMR ($CDCl_3$, 500.1 MHz, 323 K): δ = 7.03-6.95 (m, 2H, Ar-**H**), 6.94 (d, 1H, *J*= 7.9 Hz, Ar-**H**), 6.80 (t, 1H, *J*= 7.3 Hz, Ar-**H**), 6.74 (d, 1H, *J*= 7.9 Hz, Ar-**H**), 6.19 (t, 1H, *J*= 7.3 Hz, Ar-**H**), 6.12-6.02 (m, 3H, Ar-**H**), 5.96-5.86 (m, 2H, Ar-**H**), 4.61 (s, 1H, C**H**-OH), 4.39 (d, 2H, *J*= 13.4 Hz, Ar-**CH$_2$**-Ar), 4.35 (d, 1H, *J*= 13.7 Hz, Ar-**CH$_2$**-Ar), 4.16 (d, 1H, *J*= 14.0 Hz, Ar-**CH$_2$**-Ar), 4.02 (d, 1H, *J*= 14.0 Hz, Ar-**CH$_2$**-Ar), 3.97-3.82 (m, 4H, O-**CH$_2$**), 3.71-3.56 (m, 4H, O-**CH$_2$**), 3.07 (d, 1H, *J*= 13.4 Hz, Ar-**CH$_2$**-Ar), 3.06 (d, 2H, *J*= 13.4 Hz, Ar-**CH$_2$**-Ar), 1.97-1.72 (m, 8H, O-CH$_2$-**CH$_2$**),), 1.02 (t, 6H, *J*= 7.6 Hz, O-CH$_2$-CH$_2$-**CH$_3$**), 0.93 (s, 9H, C-**CH$_3$**), 0.85-0.78 (m, 6H, O-CH$_2$-CH$_2$-**CH$_3$**) ppm. ^{13}C NMR ($CDCl_3$, 125.8 MHz, 323 K): δ = 159.2, 158.2, 155.5, 155.3, 138.3, 137.3, 136.9, 136.7, 135.6, 134.8, 133.4, 133.2 (2x), 129.0, 128.7, 127.6, 127.5, 127.2, 126.9 (2x), 123.4, 122.2, 122.1, 121.6, 76.8, 76.5, 76.3 (2x), 36.8, 31.2, 31.0, 30.9, 30.8, 27.1, 27.0, 23.5, 23.4, 23.0, 22.8, 10.8 (2x), 9.9 (2x) ppm. IR (KBr): *v* 3383.2, 1454.6 cm^{-1}. HRMS (ESI$^+$): $C_{43}H_{54}O_5$ calcd for 673.38635 $[M+Na]^+$, 689.36028 $[M+K]^+$; found: 673.38600 $[M+Na]^+$, 689.35888 $[M+K^+]^+$.

4-(1-Hydroxy-2,2-dimethylpropyl)-25,26,27,28-tetrapropoxycalix[4]arene 6b

^{1}H NMR ($CDCl_3$, 400 MHz, 293 K): δ = 7.15 (d, 1H, *J*= 7.8 Hz, Ar-**H**), 7.10-7.03 (m, 3H, Ar-**H**), 6.89 (t, 1H, *J*= 7.4 Hz, Ar-**H**), 6.29-6.08 (m, 5H, Ar-**H**), 6.00-5.95 (m, 1H, Ar-**H**), 4.96 (s, 1H, C**H**-OH), 4.44 (d, 2H, *J*= 13.3 Hz, Ar-**CH$_2$**-Ar), 4.44 (d, 1H, *J*= 13.3 Hz, Ar-**CH$_2$**-Ar), 4.28 (d, 1H, *J*= 14.1 Hz, Ar-**CH$_2$**-Ar), 4.06-3.87 (m, 4H, O-**CH$_2$**), 3.81-3.62 (m, 4H, O-**CH$_2$**), 3.56 (d, 1H, *J*= 14.5 Hz, Ar-**CH$_2$**-Ar), 3.15 (d, 1H, *J*= 13.7 Hz, Ar-**CH$_2$**-Ar), 3.14 (d, 2H, *J*= 13.7 Hz, Ar-**CH$_2$**-Ar), 2.10-1.81 (m, 8H, O-CH$_2$-**CH$_2$**),), 1.10 (t, 6H, *J*= 7.4 Hz, O-CH$_2$-CH$_2$-**CH$_3$**), 1.00 (s, 9H, C-**CH$_3$**), 0.94-0.87 (m, 6H, O-CH$_2$-CH$_2$-**CH$_3$**) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 293 K): δ = 157.9, 157.6, 155.2, 155.1, 139.3, 137.0 (2x), 135.4, 135.1, 133.4 (2x), 133.3, 133.1, 128.8, 128.7, 128.0, 127.4 (2x), 127.3, 127.1, 122.1, 122.0, 121.7, 120.9, 77.4, 76.9, 76.6, 76.5, 76.4, 36.8, 31.2, 31.1, 31.0, 30.7, 26.1, 25.7, 23.5, 23.4, 23.0 (2x), 10.8 (2x), 9.3 (2x) ppm. IR (KBr): *v* 3416.4, 1455.1 cm^{-1}. HRMS (ESI$^+$): $C_{43}H_{54}O_5$ calcd for 673.38635 $[M+Na]^+$, 689.36028 $[M+K]^+$; found: 673.38600 $[M+Na]^+$, 689.35888 $[M+K]^+$.

4-(1-Hydroxy-1-phenylethyl)-25,26,27,28-tetrapropoxycalix[4]arene 7a+7b

Compounds **7a** and **7b** were prepared according to general procedure using calixarene **3** (0.100 g, 0.14 mmol), *n*-BuLi (0.26 mL, 0.42 mmol) and dry acetophenone (0.055 mL, 0.45 mmol). The products were purified using preparative TLC (hexane:ethyl acetate 20:1). However, due to the very complicated separation products were isolated as a mixture of diastereomers (0.055 g, 56%, white powder).

HRMS (ESI$^+$): $C_{48}H_{56}O_5$ calcd for 730.44660 $[M+H]^+$, 735.40200 $[M+Na]^+$, 751.37593 $[M+K]^+$; found: 730.44762 $[M+H]^+$, 735,40240 $[M+Na]^+$, 751.37503 $[M+K]^+$.

General procedure for the intramolecular Friedel-Crafts alkylation

Calixarene was dissolved in dry CH_2Cl_2 (15 mL). Amberlyst® 15 was added and the solution was stirred at 40 °C. The course of the reaction was monitored by the TLC. After the signal of the starting compound disappeared, the saturated solution of $NaHCO_3$ was added. The mixture was extracted with dichloromethane, the organic layers were separated, washed with water, dried over $MgSO_4$ and evaporated to dryness.

Procedures for the synthesis of compounds 8a and 8b

Compounds **8a** and **8b** were prepared according to general procedure using calixarene **4a** (0.040 g, 0.057 mmol) and Amberlyst® 15 (0.010 g). The products were separated using preparative TLC (hexane: ethyl acetate 20:1). Calixarene **8a** (0.016 g, 41%, mp: 195-197 °C) and calixarene **8b** (0.022 g, 57%, mp: 163-164 °C) were both obtained as white powders.

6,10-(*endo*-Phenyl)methylene-bridged-25,26,27,28-tetrapropoxycalix[4]arene 8a

^{1}H NMR ($CDCl_3$, 400 MHz, 293 K): δ = 7.43-7.29 (m, 3H, Ar-**H**), 7.25 (d, 2H, *J*= 8.2 Hz, Ar-**H**), 6.98-6.90 (m, 4H, Ar-**H**), 6.71 (t, 2H, *J*= 7.4 Hz, Ar-**H**), 6.64 (d, 2H, *J*= 7.8 Hz, Ar-**H**), 6.30 (d, 2H, *J*= 7.8 Hz, Ar-**H**), 4.95 (d, 1H, *J*= 13.3 Hz, Ar-**CH$_2$**-Ar), 4.84 (s, 1H, **CH**-Ph$_3$), 4.50 (d, 2H, *J*= 12.1 Hz, Ar-**CH$_2$**-Ar), 4.37 (d, 1H, *J*= 12.9 Hz, Ar-**CH$_2$**-Ar), 4.04-3.94 (m, 2H, O-**CH$_2$**), 3.93-3.80 (m, 4H, O-**CH$_2$**), 3.66-3.57 (m, 2H, O-**CH$_2$**), 3.25 (d, 2H, *J*= 12.1 Hz, Ar-**CH$_2$**-Ar), 3.18 (d, 1H, *J*= 13.7 Hz, Ar-**CH$_2$**-Ar), 3.12 (d, 1H, *J*= 12.5 Hz, Ar-**CH$_2$**-Ar), 2.25-2.12 (m, 4H, O-CH$_2$-**CH$_2$**), 2.04-1.83 (m, 4H, O-CH$_2$-**CH$_2$**), 1.19 (t, 6H, *J*= 7.4 Hz, O-CH$_2$-CH$_2$-**CH$_3$**), 1.02 (t, 6H, *J*= 7.4 Hz, O-CH$_2$-CH$_2$-**CH$_3$**) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 293 K): δ = 156.0, 154.8, 143.2, 137.4, 136.3, 134.7, 132.4, 132.0, 130.7, 128.9, 128.2, 127.9, 126.9, 125.9, 122.7, 119.4, 77.3, 76.7, 51.5, 31.5, 29.3, 24.5, 23.6, 22.9, 11.0, 10.1. IR (KBr): *v* 1456.0 cm^{-1}. HRMS (ESI$^+$): $C_{47}H_{52}O_4$ calcd for 703.37578 $[M+Na]^+$, 719.34972 $[M+K]^+$; found: 703.37655 $[M+Na]^+$, 719.34938 $[M+K]^+$.

6,10-(*exo*-Phenyl)methylene-bridged-25,26,27,28-tetrapropoxycalix[4]arene 8b

^{1}H NMR ($CDCl_3$, 400 MHz, 293 K): δ = 7.30-7.15 (m, 5H, Ar-**H**), 7.03-6.94 (m, 4H, Ar-**H**), 6.80-6.69 (m, 6H, Ar-**H**), 4.86 (s, 1H, **CH**-Ph$_3$), 4.51 (d, 2H, *J*= 12.5 Hz, Ar-**CH$_2$**-Ar), 4.49 (d, 1H, *J*= 14.1 Hz, Ar-**CH$_2$**-Ar), 4.36 (d, 1H, *J*= 12.5 Hz, Ar-**CH$_2$**-Ar), 4.03-3.94 (m, 2H, O-**CH$_2$**), 3.82-3.71 (m, 4H, O-**CH$_2$**), 3.66-3.57 (m, 2H, O-**CH$_2$**), 3.28 (d, 2H, *J*= 12.1 Hz, Ar-**CH$_2$**-Ar), 3.10 (d, 1H, *J*= 12.5 Hz, Ar-**CH$_2$**-Ar), 2.77 (d, 1H, *J*= 14.1 Hz, Ar-**CH$_2$**-Ar), 2.21-2.05 (m, 4H, O-CH$_2$-**CH$_2$**), 1.94-1.75 (m, 4H, O-CH$_2$-**CH$_2$**), 1.12 (t, 6H, *J*= 7.4 Hz, O-CH$_2$-CH$_2$-**CH$_3$**), 0.98 (t, 6H, *J*= 7.4 Hz, O-CH$_2$-CH$_2$-**CH$_3$**) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 293 K): δ = 156.0, 155.8, 142.5, 141.7, 136.6, 134.6, 133.9, 131.2, 128.9, 128.1, 127.8, 127.7, 126.8, 125.7, 123.5, 122.8, 77.2, 76.7, 53.9, 31.5, 29.1, 24.4, 23.5, 22.9, 10.9, 10.1 ppm. IR (KBr): *v* 1456.8 cm^{-1}. HRMS (ESI$^+$): $C_{47}H_{52}O_4$

Table 1. Crystallographic Data

	6a	6b	8a	8b	9
formula	$C_{45}H_{58}O_5$	$C_{45}H_{58}O_5$	$C_{47}H_{52}O_4$	$C_{47}H_{52}O_4$	$C_{42}H_{50}O_4$
formula *wt*	678.95	678.95	680.93	680.93	618.86
color	colourless	colourless	colourless	colourless	colourless
cryst morphology	block	block	prism	prism	platelet
cryst size (mm³)	0.38x0.16x0.13	0.60x0.39x0.39	0.43x0.31x0.16	0.80x0.10x0.08	0.44x0.32x0.05
radiation	Cu Kα	Cu Kα	Cu Kα	Cu Kα	Cu Kα
wavelength (Å)	1.54178	1.54178	1.54178	1.54180	1.54178
cryst system	orthorhombic	monoclinic	triclinic	trigonal	monoclinic
space group	$Pca2_1$	$P2_1/n$	P-1	R-3	$P2_1/c$
***a* (Å)**	20.9267 (5)	11.8255 (2)	11.9163 (3)	40.2679 (7)	21.9174 (4)
***b* (Å)**	14.4964 (3)	26.0677 (6)	12.3039 (3)	40.2679 (7)	18.1166 (4)
***c* (Å)**	26.1402 (7)	12.7656 (3)	13.9877 (3)	13.0215 (2)	18.3273 (4)
α (°)	90	90	94.2680 (7)	90	90
β (°)	90	95.1043 (7)	103.0367 (6)	90	104.5755 (9)
γ (°)	90	90	100.6984 (6)	120	90
volume (Å³)	7929.9 (3)	3919.56 (15)	1948.71 (8)	18285.5 (5)	7043.0 (3)
Z	8	4	2	18	8
Density (g/mL)	1.137	1.150	1.160	1.113	1.167
μ (1/mm)	0.56	0.57	0.56	0.54	0.57
***F*(000)**	2944	1472	732	6588	2672
θ(min, max)	3.1, 68.6	3.4, 68.4	3.3, 68.5	2.2; 68.4	2.1, 68.5
no. unique reflns	14459	7182	7144	7459	12849
no. obs. reflns	13893	6890	6992	6993	11220
no. of params	1132	489	461	512	887
$h_{min,\ max}$	-25, 25	-14, 14	-14, 14	-48, 23	-26, 26
$k_{min,\ max}$	-17, 17	-31, 31	-13, 14	0, 48	-21, 21
$l_{min,\ max}$	-31, 31	-15, 15	-16, 16	0, 15	-22, 21
$R_{\_all}$, $wR2_{\_all}$	0.0845, 0.1907	0.0480, 0.1140	0.0381, 0.0886	0.0584, 0.1373	0.0646, 0.1196
$R_{\_obs}$, $wR2_{\_obs}$	0.0819, 0.1896	0.0465, 0.1125	0.0374, 0.0885	0.0545, 0.1334	0.0549, 0.1135
$\Delta\rho_{min}$, $\Delta\rho_{max}$ (e Å^{-3})	-0.52, 0.40	-0.42, 0.40	-0.16, 0.21	-0.26, 0.51	-0.37, 0.63
GOF	1.00	0.98	1.00	0.98	0.92
CCDC number	1842830	1842831	1842832	1842833	1842834

calcd for 703.37578 $[M+Na]^+$, 719.34972 $[M+K]^+$; found: 703.37643 $[M+Na]^+$, 719.34915 $[M+K]^+$.

6,10-(*endo*-Methyl)methylene-bridged-25,26,27,28-tetrapropoxycalix[4]arene 9

Compound **9** was prepared according to general procedure using a mixture of calixarene **5a+5b** (0.061 g, 0.098 mmol) and Amberlyst® 15 (0.015 g). The product was purified using preparative TLC (hexane: dichloromethane 1:1). Calixarene **9** (0.048 g, 81%, mp: 167-169 °C) was obtained as white powder. ^{1}H NMR ($CDCl_3$, 400 MHz, 293 K): δ = 7.00-6.92 (m, 4H, Ar-**H**), 6.75-6.68 (m, 4H, Ar-**H**), 6.56 (d, 2H, *J*= 7.8 Hz, Ar-**H**), 4.81 (d, 1H, *J*= 13.3 Hz, Ar-**CH$_2$**-Ar), 4.49 (d, 2H, *J*= 12.5 Hz, Ar-**CH$_2$**-Ar), 4.36 (d, 1H, *J*= 12.5 Hz, Ar-**CH$_2$**-Ar), 4.05-3.95 (m, 2H, O-**CH$_2$**), 3.94-3.79 (m, 4H, O-**CH$_2$**), 3.73-3.58 (m, 3H, O-**CH$_2$** + C**H**-CH_3), 3.26 (d, 2H, *J*= 12.1 Hz, Ar-**CH$_2$**-Ar), 3.17-3.06 (m, 2H, Ar-**CH$_2$**-Ar), 2.27-2.08 (m, 4H, O-CH_2-**CH$_2$**), 2.03-1.84 (m, 4H, O-CH_2-**CH$_2$**), 1.57 (d, 3H, *J*= 6.7 Hz, CH-**CH$_3$**), 1.20 (t, 6H, *J*= 7.4 Hz, O-CH_2-CH_2-**CH$_3$**), 1.02 (t, 6H, *J*= 7.4 Hz, O-CH_2-CH_2-**CH$_3$**) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 293 K): δ = 155.9, 154.7, 144.6, 136.7, 134.7, 133.5, 130.6, 128.8, 128.1, 126.4, 122.8, 117.3, 77.3, 76.7, 36.8, 31.4, 29.2, 24.6, 23.6, 22.9, 12.5, 10.9, 10.1 ppm. IR (KBr): *v* 1456.2 cm^{-1}. HRMS (ESI$^+$): $C_{42}H_{50}O_4$ calcd for 636.40474 $[M+NH_4]^+$, 641.36013 $[M+Na]^+$, 657.33407 $[M+K]^+$; found: 636.40537 $[M+NH_4]^+$, 641.36037 $[M+Na]^+$, 657.33359 $[M+K]^+$.

6,10-(*exo*-Phenyl-*endo*-methyl)methylene-bridged-25,26,27,28-tetrapropoxycalix[4]arene 11

Compound **11** was prepared according to general procedure using a mixture of calixarene **7a+7b** (0.043 g, 0.060 mmol) and Amberlyst® 15 (0.010 g). The product was purified using preparative TLC (hexane: DCM 1:1). Calixarene **11** (0.016 g, 38%, mp: 44-46 °C) was obtained as a white product. ^{1}H NMR ($CDCl_3$, 400 MHz, 293 K): δ = 7.21-7.13 (m, 5H, Ar-**H**), 6.99 (dd, 2H, *J*= 7.4, 1.6 Hz, Ar-**H**), 6.95 (dd, 2H, *J*= 7.4, 1.6 Hz, Ar-**H**), 6.84 (d, 2H, *J*= 8.2 Hz, Ar-**H**), 6.78 (d, 2H, *J*= 8.2 Hz, Ar-**H**), 6.71 (t, 2H, *J*= 7.4 Hz, Ar-**H**), 4.49 (d, 2H, *J*= 12.1 Hz, Ar-**CH$_2$**-Ar), 4.48 (d, 1H, *J*= 14.1 Hz, Ar-**CH$_2$**-Ar), 4.35 (d, 1H, *J*= 12.5 Hz, Ar-**CH$_2$**-Ar), 4.01-3.92 (m, 2H, O-**CH$_2$**), 3.69 (t, 4H, *J*= 7.0 Hz, O-**CH$_2$**), 3.64-3.56 (m, 2H, O-**CH$_2$**), 3.28 (d, 2H, *J*= 12.1 Hz, Ar-**CH$_2$**-Ar), 3.10 (d, 1H, *J*= 12.5 Hz, Ar-**CH$_2$**-Ar), 2.45 (d, 1H, *J*= 14.5 Hz, Ar-**CH$_2$**-Ar), 2.18-2.06 (m, 4H, O-CH_2-**CH$_2$**), 1.90-1.75 (m, 4H, O-CH_2-**CH$_2$**), 1.73 (s, 3H, C-**CH$_3$**), 1.08 (t, 6H, *J*= 7.4 Hz, O-CH_2-CH_2-**CH$_3$**), 0.97 (t, 6H, *J*= 7.8 Hz, O-CH_2-CH_2-**CH$_3$**) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 293 K): δ = 156.0, 155.5, 146.4, 145.6, 136.6, 134.7, 134.3, 130.9, 128.8, 128.2, 127.6, 126.7, 126.1,

125.4, 122.8, 119.6, 77.1, 76.6, 50.8, 31.4, 29.2, 24.9, 23.5, 22.9, 10.8, 10.0 ppm. IR (KBr): ν 1456.2cm^{-1}. HRMS (ESI$^+$): $C_{48}H_{54}O_4$ calcd for 712.43604 $[M+NH_4]^+$, 717.39143 $[M+Na]^+$, 733.36537 $[M+K]^+$; found: 712.43728 $[M+NH_4]^+$, 717.39192 $[M+Na]^+$, 733.36470 $[M+K]^+$.

X-ray crystallography

The crystallographic data were collected at 180 (2) K on a D8 Venture Photon CMOS diffractometer with Incoatec microfocus sealed tube Cu-Kα radiation. The data reduction, scaling and absorption correction were done using Apex3 software.[13] The structures were solved by charge flipping methods[14] and anisotropically refined by full matrix least squares on F squared using the CRYSTALS suite of programs.[15] The disordered functional groups were refined with restrained geometry and constrained sum of occupancies. The MCE software[16] was used for visualization of residual electron density maps. The structure **8b** contained severely disordered solvent molecules. Regardless the effort reasonable solvent model couldn't be produced; therefore it was removed from the structure model using PLATON squeeze.[17] The structures were deposited into Cambridge Structural Database. For further information about the data collection and refinement see Table 1.

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Notes and references

(1) For selected books on calixarenes and their applications, see: (a) *Calixarenes and Beyond*; P. Neri, J. L. Sessler and M. X. Wang, Eds.; Springer: Cham, Switzerland, 2016. (b) C. D. Gutsche, *Calixarenes: An Introduction*, 2nd ed., Royal Society of Chemistry: Cambridge, U.K., 2008. (c) *Calixarenes in the Nanoworld*; J. Vicens, J. Harrowfield and L. Backlouti, Eds.; Springer: Dordrecht, The Netherlands, 2007. (d) *Calixarenes 2001*; Z. Asfari, V. Böhmer, J. Harrowfield and J. Vicens, Eds.; Kluwer: Dordrecht, The Netherlands, 2001. (e) *Calixarenes in Action*; L. Mandolini and R. Ungaro, Eds.; Imperial College Press: London, 2000.

(2) (a) L. Baklouti, J. Harrowfield, B. Pulpoka and J. Vicens, *Mini-Rev. Med. Chem.* 2006, **3**, 355; (b) D. A. Tan and M. Mocerino, In *Calixarenes and Beyond*; P. Neri, J. L. Sessler and M. X. Wang, Eds.; Springer: Cham, Switzerland, 2016; p 235.

(3) (a) P. Neri, G. Ferguson, J. F. Gallagher and S. Pappalardo, *Tetrahedron Lett.* 1992, **33**, 7403; (b) C. Alfieri, E. Dradi, A. Pochini, R. Ungaro and G. D. Andreetti, *J. Chem. Soc., Chem. Commun.* 1983, 1075; (c) A. Casnati, A. Pochini, R. Ungaro, F. Ugozzoli, F. Arnaud, S. Fanni, M.-J. Schwing, R. J. M. Egberink, F. de Jong and D. N. Reinhoudt, *J. Am. Chem. Soc.* 1995, **117**, 2767.

(4) (a) H. Goldmann, W. Vogt, E. Paulus and V. Boehmer, *J. Am. Chem. Soc.* 1988, **110**, 6811; (b) V. Bohmer, H. Goldmann, W. Vogt, E. F. Paulus, F. L. Tobiason and M. J. Thielman, *J. Chem. Soc., Perkin Trans. 2* 1990, 1769; (c) A. Dondoni, A. Marra, M. C. Scherrmann, A. Casnati, F. Sansone and R. Ungaro, *Chem. Eur. J.* 1997, **3**, 1774. (c) O. Struck, J. P. M. van Duynhoven, W. Verboom, S. Harkema and D. N. Reinhoudt, *Chem. Commun*. 1996, 1517.

(5) (a) K. Flidrova, P. Slavik, V. Eigner, H. Dvorakova and P. Lhotak, *Chem. Commun.* 2013, **49**, 6749; (b) P. Slavik, M. Kohout, S. Bohm, V. Eigner and P. Lhotak, *Chem Comm.* 2016, **52**, 2366, (c) P. Slavik, M. Kohout, S. Bohm, V. Eigner and P. Lhotak, *Tetrahedron Lett.* 2017, **58**, 1846.

(6) P. Slavik, M. Dudic, K. Flidrova, J. Sykora, I. Cisarova, S. Bohm and P. Lhotak, *Org. Lett.* 2012, **14**, 3628.

(7) P. Slavik, V. Eigner and P. Lhotak, *Org. Lett.* 2015, **17**, 2788.

(8) P. Slavik, H. Dvorakova, V. Eigner and P. Lhotak, *New J. Chem.* 2017, **41**, 14738.

(9) For selected reviews of cation−π complexes of calixarenes, see: W. J. Abraham, *Inclusion Phenom. Mol. Recognit. Chem.* 2002, **43**, 159.

(10) The binding constants were calculated using the Bindfit application (freely available at http://supramolecular.org). The complexation curves gave the best fits using 1:1 stoichiometry.

(11) For the determination of association constants and the stoichiometry of the complexes from titration experiments in supramolecular chemistry, see: (a) P. Thordarson, *Chem. Soc. Rev.* 2011, **40**, 1305. (b) F. Ulatowski, K. Dabrowa, T. Balakier and J. Jurczak, *J. Org. Chem.* 2016, **81**, 1746. (c) D. B. Hibbert and P. Thordarson, *Chem. Commun.* 2016, **52**, 12792.

(12) The results of the calculations can be found at http://app.supramolecular.org/bindfit/view/624d0507-82a2-4d44-a98d-599234bd99dc for **8a** and at http://app.supramolecular.org/bindfit/view/ac408c2a-c25e-4ffe-99a1-5bc6f487926b for **8b**.

(13) Bruker (2015). APEX3, SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.

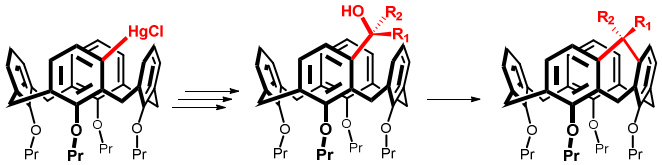
(14) L. Palatinus and G. Chapuis, *J. Appl. Cryst.* 2007, **40**, 786.

(15) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout and D. J. Watkin, *J. Appl. Cryst.* 2003, **36**, 1487.

(16) J. Rohlicek and M. Husak, *J. Appl. Cryst.* 2007, **40**, 600.

(17) A. L. Spek, *Acta Cryst.* 2009, **D65**, 148.

TOC graphic



Calix[4]arenes possessing two different substituents on an additional methylene bridge were prepared and the relationship between the in/out position of these substituents and the complexation properties was studied.