A Fast Access to Non-Symmetrically Substituted 1,3-Alternate Conformers of Calix[4]arenes

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A simple and direct protocol is reported for the synthesis of the first non-symmetrically substituted 1,3-alternate conformers of calix[4]arenes by selective mono-deacylation of a tribenzoyl precursor under basic conditions, followed by dialkylation.

Introduction

Calixarenes[1] constitute one of the leading building blocks in supramolecular chemistry[2] and are of widespread use for the preparation of anion receptors,[3] molecular capsules[4] and catalysts.[5] Since the molecular shapes of the calixarenes strongly influence their properties, full control of the conformation behaviour during their synthesis is essential.

Stable conformations of calix[4]arenes can be obtained by a proper restriction of the "through-the-annulus" rotation by *O*-alkylation or acylation/aroylation of the phenol OH groups. On the other hand, the use of different cations in the base-assisted *O*-functionalization has greatly contributed to the selective formation of calix[4]arenes in the cone,[6] partial cone (*paco*),[7] 1,2-alternate (1,2-*alt*), and 1,3-alternate (1,3-*alt*) conformations.[8] In the latter case, both rims of the calixarene macrocycle usually bear identical groups, though hetero-substitution of both rims can be achieved starting from di- or tri-*O*-alkylated precursors in a multi-step process.[9] Thus, a direct procedure for the synthesis of 1,3-alternate conformers carrying distinct groups at the phenol rings, as well as a simple procedure for their isolation, would be greatly beneficial for the construction of systems with adjacent, complementary features such as catalytic groups or binding sites for molecular recognition. Here we report that this can be easily achieved from tribenzoylcalix[4]arenes as starting compounds (Figure 1).

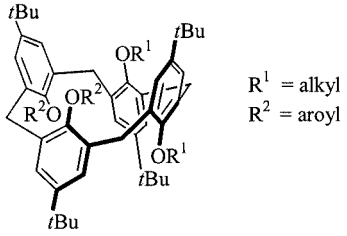

Figure 1. Schematic structure of non-symmetrically substituted 1,3-alternate calix[4]arenes

Results and Discussion

We have previously shown that the *paco* tribenzoyl derivative **1**[10] is a good precursor for the synthesis of *paco* 1,2-*anti*-heterodisubstituted calix[4]arenes carrying an alkyl and a benzoyl group; these products were isolated in a one-pot, two-step sequence.[11] The process involves an in situ alkylation with simultaneous partial deacylation. However, the use of a less reactive alkyl halide, such as propyl bromide, produced a more complex mixture of mono-*O*-propyl derivatives and, interestingly, a minor amount (5%) of the non-alkylated calix[4]arene **2**. This compound, containing two vicinal, *anti* oriented benzoyl groups, constitutes an interesting building block for supramolecular studies.[11a,12]

In order to optimize the yield of **2**, we first studied the influence of the reaction conditions on the product distribution. Our earlier studies concerned an initial mixing of all reactants, giving mono-alkylated products. When calixarene **1** was stirred for 15 min with an excess of sodium

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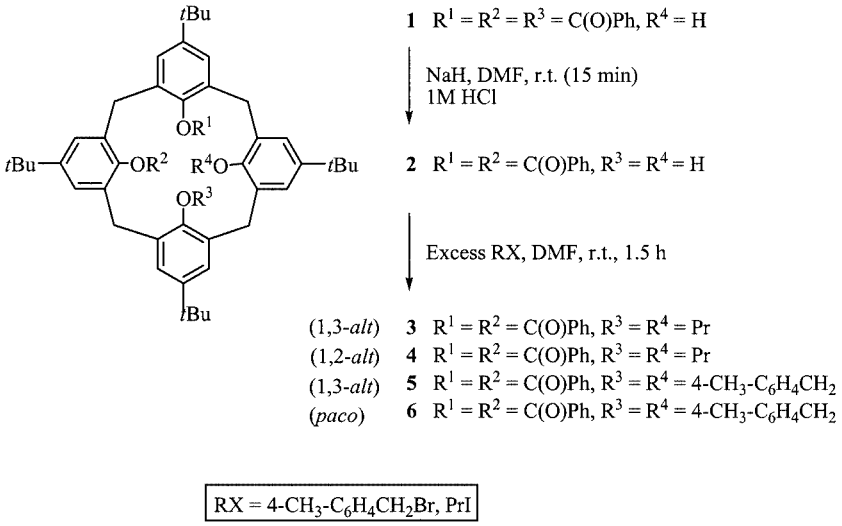

Scheme 1. Synthesis of compounds **2**−**6** from the *paco* precursor **1**

hydride (DMF, room temperature, Scheme 1) in the absence of alkylating reagent, and subsequently quenched with cold 1 M HCl, the yield of **2** improved to 52% after crystallization. Longer mixing times (i.e. 2 hours) resulted in fully deacylated calix[4]arene **1** with **2** only present in minor amounts.

Propyl iodide (excess, neat) was therefore added to in situ prepared **2** after 15 min stirring (vide supra).[13] The crude product was triturated with MeOH at room temperature and a solid material was obtained in 70% yield. An almost pure single, symmetrical compound was detected in the ^{1}H NMR spectrum (500 MHz). Two methylene CH_2 groups emerge as two well-resolved doublets at δ = 3.89 and 3.69 ppm, whereas the other two CH_2 groups appear as singlet peaks at δ = 3.91 and 3.66 ppm, respectively. The $^{13}C\{^1H\}$ spectrum displays a set of three signals for these CH_2 groups at δ = 39.8, 39.1 and 38.3 ppm, respectively, in a 1:2:1 intensity ratio.[14] These spectroscopic data account for a 1,3-alternate conformation for **3** which, interestingly, carries on both rims a propyl as well as a benzoyl group. 2D NMR spectroscopy (NOESY and COSY, 500 MHz) was additionally carried out for further structural assignment. In particular, the ^{1}H NOESY spectrum shows through-space interactions between the propyl fragment and the benzoyl group on each rim (see Figure 2).

A minor amount (3%) of an isomer of **3** was isolated from the mother liquor of the reaction (**4**, Scheme 1). Although the NMR spectra for both species are quite similar, the most striking differences were found for the CH_2 and propyl resonances. The protons of the propyl OCH_2 groups proved to be diastereotopic and give rise to two doublet-of-triplet patterns in the ^{1}H NMR spectrum, whereas the $^{13}C\{^1H\}$ NMR spectrum shows, as for **3**, three distinct signals for the methylene groups at δ = 40.0, 38.6 and 30.6 ppm, respectively.[14] These data are in agreement with a 1,2-alternate conformation for isomer **4**, which was further corroborated by 2D NMR techniques.

Other alkylating agents produced analogous results. Thus, use of 4-methylbenzyl bromide afforded calixarene **5** in 28% yield, after work up. The NMR spectra of **5** is closely related to that of **3**. The mother liquor of the trituration step also contained an isomer of **5** but in a much higher amount and in a *paco* conformation (compound **6**, 39% yield). The latter assignment was straightforward since both the ^{1}H and $^{13}C\{^1H\}$ NMR spectra indicate a fully asymmetric species, as illustrated by the magnetic inequivalence of all CH_2, OCH_2, $ArCH_3$ and *t*Bu groups. Furthermore, MALDI-TOF MS analysis provided decisive evidence for the presence of a dialkylated species.

The starting point for the formation of **3**−**6** was the in situ prepared precursor **2** that contains two free phenol positions. Obviously, lower rim "through-the-annulus" rotation of the phenol groups[12] gives access to a predefined number of possible dialkylated conformers. Remarkably, in the case of alkylation with propyl iodide almost exclusive formation of 1,3-*alt* **3** was observed, whereas treatment with 4-methylbenzyl bromide gave a significantly lower yield of the 1,3-*alt* product **5** and the *paco* isomer **6** was, in this case, isolated as the major component. These differences can be explained in terms of reactivity rather than steric hindrance of the alkyl iodide as compared to the aryl bromide.[15] The results seem to indicate that the alkylation procedure of in situ prepared **2** follows a preferred route — first an *anti*-alkylation of one of the proximal positions followed by *syn*/*anti* introduction of the second alkyl unit to afford non-symmetrical 1,3-*alt* or *paco* calix[4]arenes.

In conclusion, we have discovered a quick and accessible method[16] for the preparation of non-symmetrically substituted 1,3-alternate isomers of calix[4]arenes by alkylation of the readily available tribenzoyl precursor **1**. Therefore, new pathways could be open towards the construction of tailor-made supramolecular architectures based on calixarene scaffolds with two complementary groups (i.e. functionalized aryl/aroyl groups) directly placed in close prox-

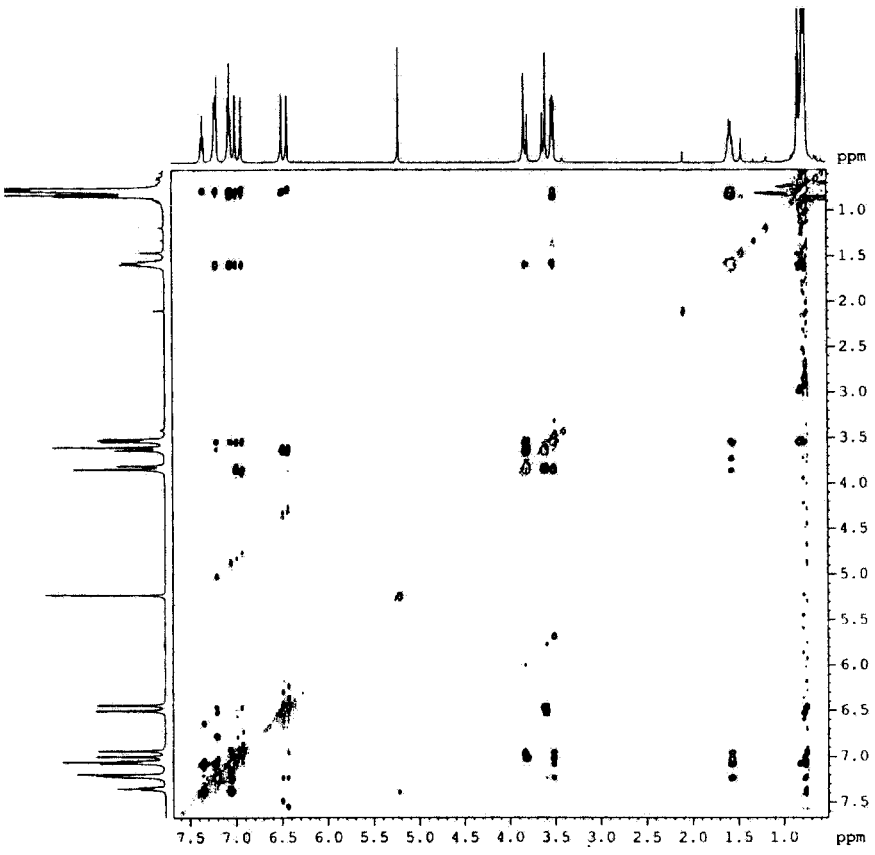

Figure 2. NOESY spectrum for compound **3**

imity and on the same rim of the calixarene. In particular, development of new catalytic systems that comprise catalytic centers flanked by groups with recognition abilities could be of widespread interest. Our future studies will be focused on a further development of this protocol with a focus on supramolecular synthesis.

Experimental Section

All air-sensitive manipulations were carried out under an argon atmosphere. Standard chemicals were purchased from Acros or Aldrich and used as received. 25,26,27-Tris(benzoyloxy)-5,11,17,23-tetrakis(1,1-dimethylethyl)-28-hydroxycalix[4]arene (**1**; symmetric partial cone isomer) was prepared according to a previously reported method.[11a] NMR spectroscopic experiments [^{1}H,^{13}C{^{1}H}, DEPT, COSY (H,H), HETCOR (C,H) and NOESY] were carried out at 298 K on Bruker AMX 300 or 500 MHz spectrometers and reported chemical shifts (δ) are externally referenced to $SiMe_4$ and given in ppm. MS measurements (MALDI-TOF method) were performed on a REFLEX spectrometer. Elemental analyses were performed on a LECO CHN 932 micro-analyser. Reported melting points were measured in open capillaries and are uncorrected.

25,26-Bis(benzoyloxy)-5,11,17,23-tetrakis(1,1-dimethylethyl)-27,28-dihydroxycalix[4]arene (2): A mixture of tribenzoylcalix[4]arene **1** (0.40 g, 0.42 mmol) and NaH (0.53 g, 13.3 mmol) in DMF (12 mL) was stirred for 20 min, after which it was quenched by addition of an excess of cold 1 M HCl. CH_2Cl_2 (100 mL) was then added to the resultant two-phase mixture and the organic layer was separated, washed with H_2O (2 × 100 mL), dried over $MgSO_4$ and filtered. After concentration under reduced pressure, the oily product was triturated with MeOH to yield a white microcrystalline solid. Yield: 0.19 g (52%). M.p. (crystals) 266−267 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 [s, 18 H, $C(CH_3)_3$], 1.07 [s, 18 H, $C(CH_3)_3$], 3.86 (s, 2 H, CH_2), 3.89 (s, 2 H, CH_2), 3.90 (s, 2 H, CH_2), 3.95 (s, 2 H, CH_2), 6.77 (s, 2 H, ArH), 6.92 (s, 2 H, ArH), 7.04−6.93 (br. m, 8 H, benzoyl-$H_{ortho+meta}$), 7.07 (s, 2 H, ArH), 7.17 (s, 2 H, ArH), 7.31 (s, 1 H, OH), 7.34 (t, *J* unresolved, 2 H, benzoyl-H_{para}), 7.72 (s, 1 H, OH) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 30.8, 31.3 [2 × $C(CH_3)_3$], 32.4 (CH_2), 33.8, 33.9 [2 × $C(CH_3)_3$], 38.9 (CH_2), 125.2, 125.6, 126.1, 126.3, 126.9, 127.9, 128.2, 128.3, 129.8, 131.5, 132.5, 132.8, 143.3, 144.2, 148.5, 149.0 (ArC, ArCH), 163.6 [ArC(O)] ppm. MS (MALDI-TOF, ditranol + KI): *m*/*z* = 857.4 $[M + H]^+$, 879.4 $[M + Na]^+$, 895.4 $[M + K]^+$. $C_{58}H_{64}O_6 \cdot 1/2H_2O$ (856.4): calcd. C 80.43, H 7.56; found C 80.52, H 7.70.

Alkylation with Propyl Iodide: A mixture of **1** (0.37 g, 0.39 mmol) and NaH (0.54 g, 13.5 mmol) in dry DMF (12 mL) was stirred at room temp. for 15 min, and propyl iodide (1.0 mL, 10.3 mmol) was then added. Stirring was continued for 1.5 h and then the reaction mixture was poured into cold 1 M HCl (100 mL). The product was extracted with CH_2Cl_2 (100 mL) and washed with H_2O (100 mL), dried over $MgSO_4$, filtered and concentrated. Finally, the yellow oil obtained was triturated with MeOH to yield highly pure **3** as a white solid as the first fraction. A second fraction (white solid) was obtained by cooling/concentration of the mother liquor and gave compound **4** as major component. Pure **4** could be isolated as white needles by crystallization from CH_2Cl_2/MeOH.

1,3-*alt*-25,26-Bis(benzoyloxy)-5,11,17,23-tetrakis(1,1-dimethylethyl)-27,28-bis(propyloxy)calix[4]arene (3): Yield: 0.25 g (70%). M.p. > 310 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 [s, 18 H, $C(CH_3)_3$], 0.85 [s, 18 H, $C(CH_3)_3$], 0.90 (t, ^3J = 7.5 Hz, 6 H, CH_2CH_3), 1.64 (m, 4 H, CH_2CH_3), 3.59 (m, 4 H, OCH_2), 3.66 (s, 2 H, CH_2), 3.69 (d, ^2J unresolved due to overlap with singlet at δ = 3.66 ppm, 2 H, CH_2), 3.89 (d, ^2J unresolved due to overlap with singlet at δ = 3.91 ppm, 2 H, CH_2), 3.91 (s, 2 H, CH_2), 6.50 (d, ^4J = 2.3 Hz, 2 H, ArH), 6.56 (d, ^4J = 2.1 Hz, 2 H, ArH), 7.00 (d, ^4J = 2.2 Hz, 2 H, ArH), 7.06 (d, ^4J = 2.0 Hz, 2 H, ArH), 7.12 (t, ^3J = 7.7 Hz, 4 H, benzoyl-H_{meta}), 7.28 (d, ^3J = 7.2 Hz, 4 H, benzoyl-H_{ortho}), 7.41 (t, ^3J = 7.5 Hz, 2 H, benzoyl-H_{para}) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 9.9 (CH_2CH_3), 23.6 (CH_2CH_3), 31.0 [(2 × $C(CH_3)_3$], 33.5, 33.8 [2 × $C(CH_3)_3$], 38.3, 39.1, 39.8 (3 × CH_2, ratio 1:2:1), 73.6 (OCH_2), 125.4, 126.0, 126.1, 126.7, 128.2, 129.1, 130.8, 132.1, 132.3, 132.6, 133.2, 133.40, 144.1, 146.2, 146.9, 155.0 (ArC, ArCH), 164.5 [ArC(O)] ppm. MS (MALDI-TOF, ditranol + KI): *m*/*z* = 941.6 [M + H]$^+$, 963.6 [M + Na]$^+$, 979.6 [M + K]$^+$. $C_{64}H_{76}O_6{\cdot}CH_2Cl_2$ (940.6): calcd. C 76.08, H 7.66; found C 76.62, H 8.08.

1,2-*alt*-25,26-Bis(benzoyloxy)-5,11,17,23-tetrakis(1,1-dimethylethyl)-27,28-bis(propyloxy)calix[4]arene (4): Yield: 9.3 mg (3%). M.p. > 310 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.26 (t, ^3J = 7.4 Hz, 6 H, $CH_2CH_2CH_3$), 0.67−0.58 (m, 2 H, $CH_2CH_2CH_3$), 0.84−0.75 (m, 2 H, $CH_2CH_2CH_3$), 0.93 [s, 18 H, $C(CH_3)_3$], 1.49 [s, 18 H, $C(CH_3)_3$], 2.97 (dt, apparent ^3J = 5.4, ^2J = 10.6 Hz, 2 H, $CH_2CH_2CH_3$), 3.08 (dt, apparent ^3J = 5.3, ^2J = 10.4 Hz, 2 H, $CH_2CH_2CH_3$), 3.37 (d, ^2J = 12.8 Hz, 2 H, CH_2), 3.90 (s, 2 H, CH_2), 3.99 (s, 2 H, CH_2), 4.11 (d, ^2J = 12.7 Hz, 2 H, CH_2), 6.76 (d, ^4J = 2.1 Hz, 2 H, ArH), 7.05 (dt, ^3J = 7.8, ^4J = 0.7 Hz, 4 H, benzoyl-H_{meta}), 7.10 (br. d, ^3J = 7.7 Hz, 4 H, benzoyl-H_{ortho}), 7.16 (d, ^4J = 2.3 Hz, 2 H, ArH), 7.35 (dt, ^3J = 7.3, ^4J = 1.2 Hz, 2 H, benzoyl-H_{para}), 7.37 (d, ^4J = 2.4 Hz, 2 H, ArH), 7.46 (d, ^4J = 2.4 Hz, 2 H, ArH) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 9.5 ($CH_2CH_2CH_3$), 22.2 ($CH_2CH_2CH_3$), 30.6 (CH_2), 30.0, 31.6 [2 × $C(CH_3)_3$], 33.8, 34.2 [2 × $C(CH_3)_3$], 38.6, 40.0 (2 × CH_2), 75.2 ($CH_2CH_2CH_3$), 124.6, 125.5, 125.7, 127.2, 127.8, 128.9, 130.7, 131.5, 131.9, 132.9, 133.4, 133.8, 143.9, 144.9, 147.9, 154.3 (ArC, ArCH), 165.0 [ArC(O)] ppm. MS (MALDI-TOF, ditranol + KI): *m*/*z* = 941.6 [M + H]$^+$, 963.5 [M + Na]$^+$, 979.5 [M + K]$^+$. $C_{64}H_{76}O_6{\cdot}1/2CH_2Cl_2$ (940.6): calcd. C 78.75, H 7.89; found C 78.36, H 8.01.

Alkylation with 4-Methylbenzyl Bromide: DMF (12 mL) was added to a solid mixture of **1** (0.38 g, 0.40 mmol), NaH (0.59 g, 14.8 mmol) and 4-methylbenzyl bromide (0.37 g, 2.00 mmol). The resultant mixture was stirred for 1.5 h, quenched with excess cold 1 M HCl and worked up as reported for compounds **3** and **4** to afford two fractions of product as white solids. The first fraction contained virtually pure **5** whereas the second fraction consisted of highly pure **6**. Analytically pure materials were obtained by crystallization from a mixture of CH_2Cl_2 and MeOH.

1,3-*alt*-25,26-Bis(benzoyloxy)-5,11,17,23-tetrakis(1,1-dimethylethyl)-27,28-bis(4-methylbenzyloxy)calix[4]arene (5): Yield: 117.0 mg (28%). M.p. (crystals) 271−272 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 [s, 18 H, $C(CH_3)_3$], 0.88 [s, 18 H, $C(CH_3)_3$], 2.44 (s, 6 H, $ArCH_3$), 3.27 (s, 2 H, CH_2), 3.38 (d, ^2J = 16.5 Hz, 2 H, CH_2), 3.55 (d, ^2J = 16.5 Hz, 2 H, CH_2), 3.72 (s, 2 H, CH_2), 4.71 (s, 4 H, $ArCH_2$), 6.50 (d, ^4J = 2.4 Hz, 2 H, ArH), 6.58 (d, ^4J = 2.1 Hz, 2 H, ArH), 6.89 (d, ^4J = 2.4 Hz, 2 H, ArH), 6.94 (d, ^4J = 2.1 Hz, 2 H, ArH), 7.03 (d, ^3J = 8.0 Hz, 4 H, ArH), 7.15 (d, ^3J = 7.7 Hz, 4 H, ArH), 7.17 (t, ^3J = 7.8 Hz, ^4J not resolved, 4 H, benzoyl-H_{meta}), 7.28 (br. d, ^3J = 7.2 Hz, 4 H, benzoyl-H_{ortho}), 7.43 (dt, ^3J = 7.4, ^4J = 1.2 Hz, 2 H, benzoyl-H_{para}) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 21.4 ($ArCH_3$), 30.9, 31.0 [2 × $C(CH_3)_3$], 33.5, 33.7 [2 × $C(CH_3)_3$], 38.3, 39.0, 39.4 (3 × CH_2, ratio 1:2:1), 73.5 ($ArCH_2$), 125.2, 125.8, 126.0, 126.7, 128.1, 128.7, 129.1, 130.3, 130.9, 131.8, 132.4, 132.9, 133.0, 133.9, 134.5, 138.2, 144.5, 146.1, 147.1, 153.4 (ArC, ArCH), 164.2 [ArC(O)] ppm. MS (MALDI-TOF, ditranol + KI): *m*/*z* = 1013.3 [M − toluene + K]$^+$, 1065.5 [M + H]$^+$, 1103.5 [M + K]$^+$. $C_{74}H_{80}O_6{\cdot}H_2O$ (1064.5): calcd. C 82.03, H 7.63; found C 81.64, H 7.93.

***paco*-25,26-Bis(benzoyloxy)-5,11,17,23-tetrakis(1,1-dimethylethyl)-27,28-bis(4-methylbenzyloxy)calix[4]arene (6):** Yield: 166.1 mg (39%). M.p. (crystals) 265−266 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.68 [s, 9 H, $C(CH_3)_3$], 0.74 [s, 9 H, $C(CH_3)_3$], 0.99 [s, 9 H, $C(CH_3)_3$], 1.44 [s, 9 H, $C(CH_3)_3$], 2.26 (s, 3 H, $ArCH_3$), 2.47 (s, 3 H, $ArCH_3$), 2.71 (d, ^2J = 12.7 Hz, 1 H, CH_2), 3.05 (d, ^2J = 12.2 Hz, 1 H, CH_2), 3.44 (d, ^2J = 12.6 Hz, 1 H, CH_2), 3.74 (m, 3 H, CH_2), 3.85 (d, ^2J = 17.1 Hz, 1 H, CH_2), 4.31 (pseudo t, apparent ^2J = 13.2 Hz, 2 H, tolyl-CH_2), 4.58 (d, ^2J = 11.6 Hz, 1 H, CH_2), 4.93 (d, ^2J = 11.5 Hz, 1 H, tolyl-CH_2), 5.00 (d, ^2J = 11.5 Hz, 1 H, tolyl-CH_2), 6.07 (d, ^3J = 7.9 Hz, 2 H, ArH), 6.40−6.17 (br. m, 2 H, benzoyl-H_{meta}), 6.47 (d, apparent ^4J = 3.5 Hz, 2 H, ArH), 6.70−6.59 (br. m, 2 H, benzoyl-H_{ortho}), 6.80 (d, *J* unresolved, 1 H, ArH), 6.81 (d, ^3J = 8.0 Hz, 2 H, ArH), 6.94 (d, *J* unresolved, 1 H, ArH), 6.97 (d, ^4J = 2.2 Hz, 1 H, ArH), 7.10 (t, ^3J = 7.4 Hz, 1 H, benzoyl-H_{para}), 7.15 (m, 2 H, ArH), 7.22 (d, ^3J = 7.9 Hz, 2 H, ArH), 7.28 (d, ^3J = 7.9 Hz, 2 H, ArH), 7.31 (m, 1 H, ArH), 7.35 (t, ^3J = 7.8 Hz, 2 H, benzoyl-H_{meta}), 7.60 (t, ^3J = 7.5 Hz, 1 H, benzoyl-H_{para}), 8.14 (d, ^3J = 7.3 Hz, 2 H, benzoyl-H_{ortho}) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 21.1, 21.4 (2 × $ArCH_3$), 30.7, 30.8, 31.1 [3 × $C(CH_3)_3$], 31.4, 31.5 (2 × CH_2), 31.7 [$C(CH_3)_3$], 33.4, 33.6, 33.7, 34.4 [4 × $C(CH_3)_3$], 38.7, 39.4 (2 × CH_2), 76.4, 76.6 (2 × tolyl-CH_2), 124.1, 124.9, 125.2, 125.5, 125.8, 125.9, 126.3, 127.8, 128.2, 128.3, 128.5, 129.0, 129.5, 129.9, 130.0, 130.9, 131.4, 131.6, 131.7, 131.8, 132.4, 132.7, 132.8, 133.6, 133.7, 134.72, 134.74, 135.6, 135.7, 137.4, 138.1, 144.4, 145.3, 145.5, 146.1, 147.4, 147.5, 151.4, 152.6 (ArC, ArCH), 163.4, 165.3 [2 × ArC(O)] ppm. MS (MALDI-TOF, ditranol + KI): *m*/*z* = 997.4 [M − toluene + Na]$^+$, 1013.3 [M − toluene + K]$^+$, 1087.5 [M + Na]$^+$, 1103.4 [M + K]$^+$. $C_{74}H_{80}O_6{\cdot}1/2H_2O$ (1064.5): calcd. C 82.72, H 7.60; found C 82.37, H 7.94.

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[16] It has to be emphasized that only a single trituration step with MeOH was needed to separate the different calixarene conformers from the crude mixture.

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