Conformational Control of Calix[6]arenes Through Multiple Bridges

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The synthesis of the A,D-*m*-xylylene-bridged B,C,E,F-tetra-*O*-alkylcalix[6]arenes **1b–c** and the A,D-B,C;E,F-triply bridged calix[6]arenes **2a–c** is described. The cone conformation of the new bridged calix[6]arenes has been established by a full set of 1D/2D ^{1}H and ^{13}C NMR techniques. These compounds are substantially more rigid than calix[6]arene analogues with an A,D-*p*-xylylene bridge, and the resulting cavities are better defined. Molecular mechanics optimization of triply bridged calix[6]arenes **2b** and **2c** resulted in structures fully consistent with the NMR spectra.

Introduction

The design of platforms, cavities or capsules based on calixarenes for molecular recognition or self-assembly requires efficient control over the conformational flexibility of these cyclic phenol oligomers.[1] Although the conformation is restricted for *O*-alkylcalix[4]arenes with groups larger than ethyl,[2] this is not the case for the wider calix[6]-arenes, since rotation of the rings can also take place by the introduction of the *para*-substituent (i.e. *tert*-butyl) through the cavity.[3] Stable cone shapes can occasionally be obtained, as in the cases of 1,3,5-tri-*O*-methyl derivatives, in which the alkyl groups partly occupy the cavity and are stabilized by CH–π interactions with the aromatic rings,[3b,4] or of mono-*O*-benzyl derivatives, in which the remaining hydrogen-bonded network arising from the five unsubstituted phenols hampers both the *tert*-butyl and the *O*-benzyl groups in freely crossing the annulus.[5]

Otherwise, the obvious strategy for restricting the conformations of calix[6]arenes is based on bridging the phenol rings through suitable spacers. One of the most commonly employed covalent bridges involves a linkage between two opposite phenol rings A and D[6] through suitable spacers, such as *m*-xylylene,[7] 2,6-lutidinediyl,[8] *p*-xylylene,[9,10] 9,10-anthrylene,[9] or 1,10-phenanthroline-2,9-bis(methylene).[11–13] The *p*-xylylene spacer is too long to keep the A and D rings comfortably in a *syn* orientation and a twist of the bridge across the annulus upon *O*-methylation has been reported by Gutsche.[9] In the cases of the better adjusted *m*-xylylene or 2,6-lutidinediyl spacers, the relative orientation of the remaining four rings depends on their *O*-substitution. While free OH groups give rise to cone shapes, due to hydrogen bond formation, OMe moieties are flexible,[14] and several conformations have been reported for OEt[7b] and OBn derivatives.[7a,15a] To provide a permanent cavity, other groups or bridges have to be incorporated in rings B, C, E and F in order to restrict the conformation further. Although only three examples of triply bridged calix[6]-arenes have been reported so far,[10,15] none of them uses *m*-xylylene for the central A,D bridge.

Here we report the synthesis and the conformational study of novel A,D-*m*-xylylene-bridged calix[6]arenes **1b–c** and the first examples of the triply bridged compounds **2a–c** (Figure 1).

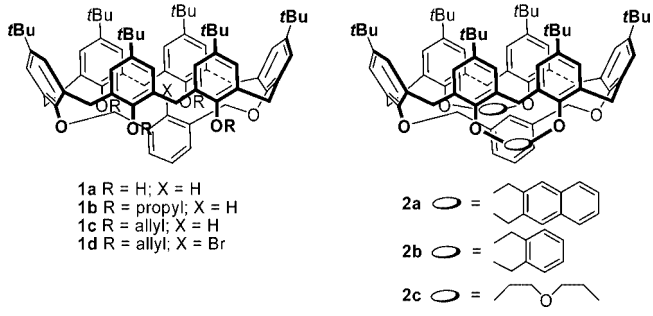

Figure 1. Monobridged compounds **1a–d** and triply bridged compounds **2a–c**.

Results and Discussion

The syntheses of compounds **1b–c** and **2a–c** were achieved in one step by alkylation of the already reported A,D-*m*-xylylene-bridged *tert*-butylcalix[6]arene **1a** (obtained in 90% yield)[16] in the presence of NaH. The yields

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for compounds **1b** and **1c** were 71% and 64%, respectively (overall yields from *p*-*tert*-butylcalix[6]arene were 64% and 57%, respectively), but additional bridge formation to afford compounds **2a**–**c** [with α,α′-dibromo-*o*-xylene, 2,3-bis(bromomethyl)naphthalene[17] or diethyleneglycol ditosylate, respectively] proved more difficult and required high-dilution conditions (22–49% yields; overall yields from *p*-*tert*-butylcalix[6]arene were 20%, 44% and 43% for **2a**–**c**, respectively). Attempts to introduce five-carbon hydrocarbon chains (by treatment with 1,5-dibromo- or 1,5-diiodopentane) failed, probably because of a template effect by the cation in the case of the crown ether and a more preorganized structure in the cyclizations with aromatic derivatives.

The conformations of the new bridged calix[6]arenes were established by a full set of 1D and 2D ^{1}H or ^{13}C NMR techniques. Two AB systems in 1:2 ratios were observed for the $ArCH_2Ar$ protons in all cases, in agreement with the two symmetry planes arising from the bridging at opposite rings. The carbon signals for these methylene groups appear in the δ = 28–32 ppm range, typical of *syn*-oriented phenol rings, so the macrocycles display cone conformations in all cases.[18a] No significant changes for the ^{1}H NMR methylene patterns were observed in the 403–183 K range.

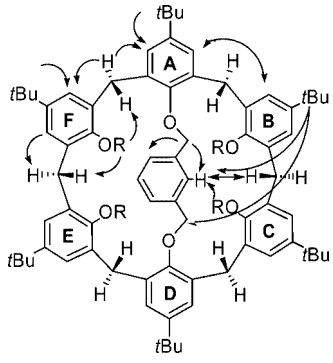

Figure 2. NOESY and ROESY contacts observed for compounds **1b**–**c** and **2a**–**c**.

The common cone conformation was further confirmed by the expected contacts observed in the NOESY and ROESY experiments (Figure 2). Additional contacts between the *tert*-butyl groups (B, C, E and F), and some of the protons at the central bridge (i.e. one aromatic proton and the benzyl CH_2 protons) indicate that at least one of these groups is sequentially folded inside the cavity. The contacts with the benzyl groups also point to an orientation of these bridging CH_2 protons towards the cavity. Indeed, these protons are abnormally shielded, appearing at $\delta \approx$ 4.2 ppm (monobridged compounds **1b** and **1c**) and at $\delta \approx$ 4.4 ppm (triply bridged **2a**–**c**), in sharp contrast with the chemical shifts observed for the 9,10-anthrylene (δ = 5.9 ppm) and *p*-xylylene (δ = 5.1 ppm) A,D-bridged analogues, in which the benzyl CH_2 protons are thus oriented *out* in solution, similarly to their behaviour in the solid state.[9,10]

Monobridged compounds **1b** and **1c** were also found to be single cone conformers. In contrast with the homologous derivative with OMe groups,[14] the cone–cone inversion of compounds **1b**–**c** is slow on the NMR timescale, even at 403 K. Remarkably, the related bromo derivative **1d** has been reported by Goto to exist as a mixture of cone and 1,2,3-alternate conformers.[7b] To rule out the possible influence of the base employed during the synthesis in the final conformational outcome, compound **1c** was synthesized under the same conditions as described by Goto for **1d** (Cs_2CO_3, DMF). Since cone conformations again resulted, it is likely that the different conformation of **1d** arises from the presence of the bromine atom.

The benzyl protons of the outer bridges in **2a** and **2b** appear as AB systems (δ = 5.02 and 4.92 ppm for **2a**, δ = 4.86 and 4.77 ppm for **2b**), the doublets appearing only ca. 0.1 ppm apart, which might indicate that they are in rather similar chemical environments. These results differ signifi-

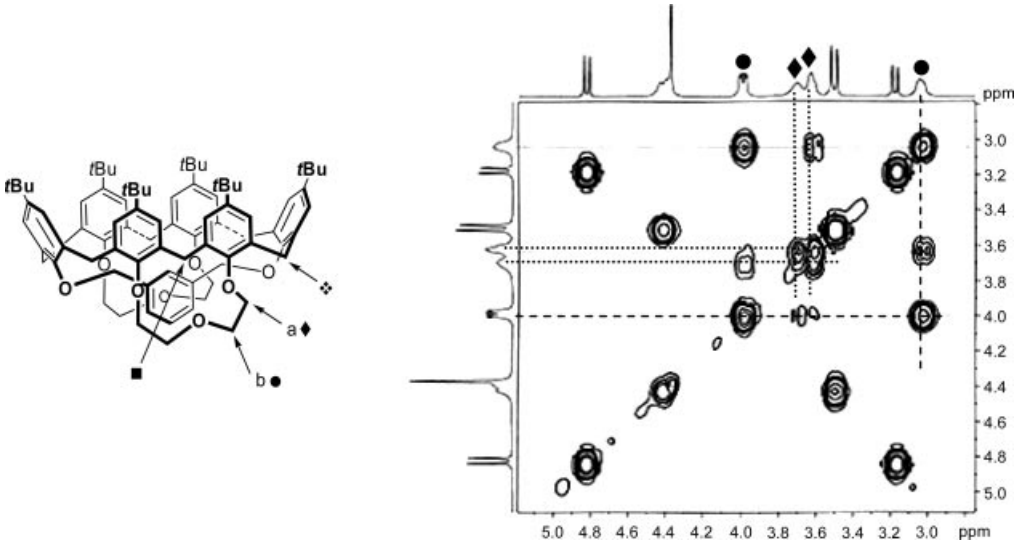

Figure 3. COSY experiment on **2c** ($C_2D_2Cl_4$, 500 MHz, 323 K).

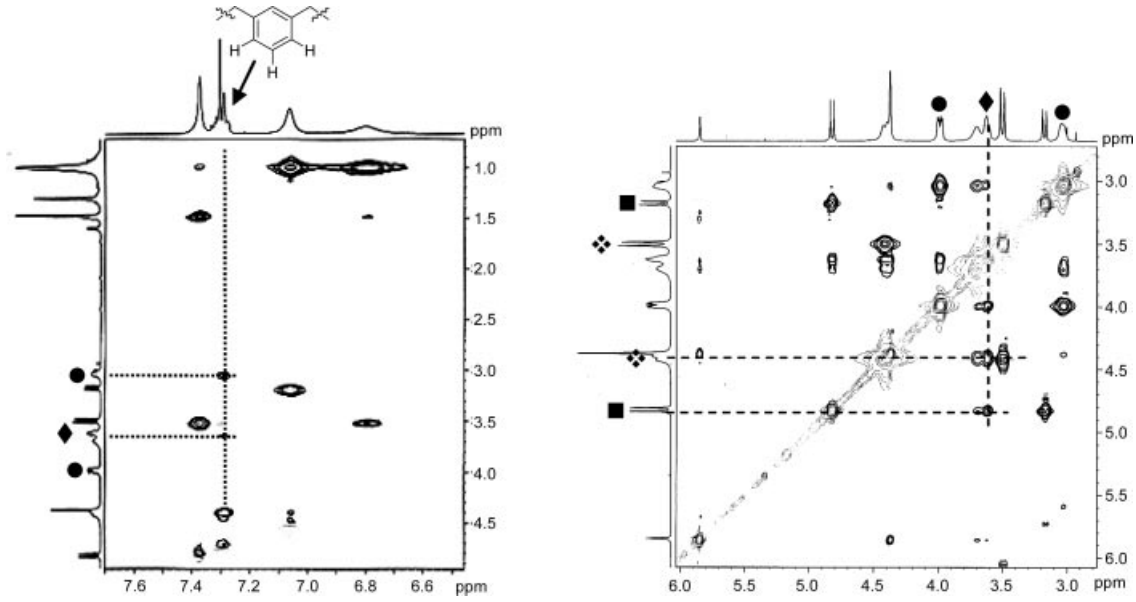

Figure 4. NOESY experiment on **2c** ($CDCl_3$, 500 MHz, 300 K; symbols are as in Figure 3).

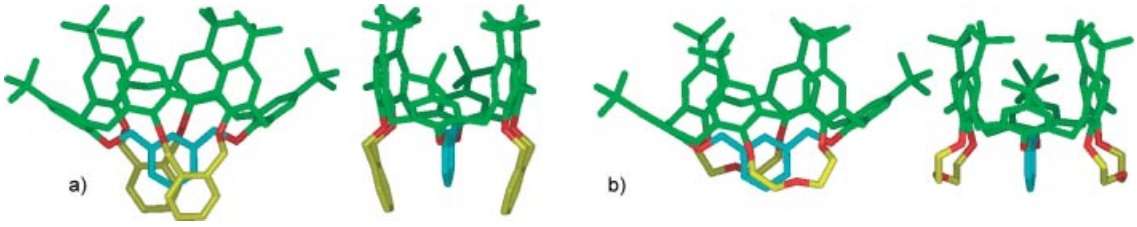

Figure 5. Two side views of optimized structures for triply bridged calix[6]arenes: a) **2b** and b) **2c**.

cantly from those found for the *p*-xylylene-bridged analogue described by Nam, showing a pair of doublets 0.6 ppm apart (i.e., in rather different chemical environments), which could be explained by the higher flexibility of the *p*-substituted bridge.[10]

In compound **2c**, possessing two oxybis(ethylene) B,C; E,F outer bridges, the effect produced by the central aromatic *m*-xylylene ring is remarkable. At room temperature each methylene proton of the bridge appears as an independent, well differentiated, broad signal, which becomes defined as a multiplet as the temperature is raised, probably due to an almost locked conformation of the whole chain. 2D NMR experiments were employed for the unambiguous assignments of these signals (Figures 3 and 4).

Methylene protons *a* and *b* were unambiguously assigned by COSY experiments ($C_2D_2Cl_4$, 500 MHz, 323 K, Figure 3); NOESY experiments revealed that the aromatic protons of the *m*-xylylene bridge displayed a weak contact with protons *a* ($\delta \approx 3.5$ ppm) and a stronger one with one of the protons *b* ($\delta = 2.98$ ppm), indicating that this proton is facing the aromatic surface. On the other hand, only protons *a* have NOE contacts with the axial protons of calixarene methylene groups, the one at the molecular symmetry plane showing the strongest effect (Figure 4).

Optimization of triply bridged calix[6]arenes **2b** and **2c** in cone conformations by molecular mechanics gave structures fully consistent with the NMR spectra described above (Figure 5). In particular, the structure obtained for **2c** is in good agreement with the finding that only one of the protons *b* is shielded (i.e., the central oxygen atom points away from the aromatic electron cloud). In each case the central bridge lies almost perpendicular to the main plane of the macrocycle, stacked between the adjacent bridges. Rings A and D become winged, while the remaining rings adopt an almost cylindrical shape.

Conclusions

In conclusion, alkylation of A,D-*m*-xylylene-bridged calix[6]arenes with medium-sized alkyl groups (such as propyl or allyl) or bridging of the neighbouring remaining rings (B,C; E,F) by aromatic or aliphatic chains gives rise to cone-shaped compounds substantially more rigid than calix[6]arene analogues with a *p*-xylylene bridge. The resulting cavities are better defined, and could thus be useful for molecular recognition of sizeable guests, such as quaternary ammonium salts or, upon appropriate functionalization, as building blocks for the molecular assembly of more complex structures and cavities.

Experimental Section

General: Unless otherwise reported, all reactions were carried out under dry argon. Solvents were freshly distilled and dried by standard methods before use. All chemicals were used as purchased. Melting points are uncorrected and were measured in open capillaries. ^1H and $^{13}C\{^1H\}$ NMR experiments were recorded with a Bruker DRX 500 spectrometer at 500 (125) MHz. Chemical shifts (δ) are expressed in ppm relative to the solvent residual peak. MALDI-TOF mass spectra were registered with a REFLEX spectrometer. Elemental analyses were determined with a LECO CHN 932 microanalyser. Compounds **1a**[16] and 2,3-bis(bromomethyl)naphthalene[17] were synthesized by literature procedures.

Molecular Modelling: The INSIGHT-II/Discover packages were used for the calculations of the structures of compounds **2b** and **2c**. Standard potentials and atomic charges, as provided by the cvff force field, were employed without modifications. Calculations were performed in vacuo, with a dielectric constant $\varepsilon = 1$, and the initial structure was slowly relaxed by 300 steepest descent iterations, followed by full optimization with enough conjugate gradient iterations to reach an energy RMS gradient of less than 0.001 kcal mol^{-1} Å^{-1}.

General Procedures for Tetra-*O*-alkylation of A,D-*m*-Xylylenedioxycalix[6]arenes with Mono- and Dialkylating Agents. Method A: A suspension of **1a** and NaH (60% in a dispersion oil, 2 equiv. per OH) in dry DMF (10^{-2} M) was heated at 70 °C under argon for 30 min, and the appropriate alkylating agent (1.2 equiv. per OH) was then added. The reaction mixture was stirred at 70 °C for 2–3 d. The mixture was quenched with an excess of 30% NH_4OH, stirred for an additional 30 min and concentrated in vacuo. The residue was dissolved in $CHCl_3$ and washed with HCl (1 N) and water. The organic phase was dried ($MgSO_4$) and concentrated, and the remaining oil was triturated with MeOH, filtered and triturated again with $CHCl_3$/MeOH. **Method B:** A mixture of **1a** and Cs_2CO_3 (3 equiv. per OH) in dry DMF (2×10^{-2} M) was heated at 70 °C under argon for 30 min. The appropriate alkylating agent (1.5 equiv. per OH) was then added and the reaction mixture was stirred at 70 °C for 2–3 d. The mixture was quenched with an excess of 30% NH_4OH, and worked up as in Method A. **Method C:** A suspension of **1a** and NaH (60% in a dispersion oil, 2 equiv. per OH) in dry DMF (5.5×10^{-3} M) was heated at 70 °C under argon for 30 min, and a solution of the appropriate alkylating agent (0.55 equiv. per OH) in dry DMF (0.1 M) was slowly added. The reaction mixture was stirred at 70 °C for 2–3 d, quenched with an excess of 30% NH_4OH, stirred additionally for 30 min and concentrated in vacuo. The residue was dissolved in $CHCl_3$ and washed with HCl (1 N) and brine. The organic phase was dried ($MgSO_4$) and concentrated, and the remaining oil was triturated with $CHCl_3$/MeOH and purified by column chromatography.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,40,41-tetrapropoxy-39,42-(*m*-xylylenedioxy)calix[6]arene (1b): This compound was obtained by Method A, from **1a** (0.2 g, 0.186 mmol), NaH (59.5 mg, 1.487 mmol) and 1-iodopropane (0.082 mL, 0.837 mmol) in DMF (20 mL). Yield: 167 mg (71%). M.p. 280–285 °C. ^1H NMR (500 MHz, $CDCl_3$, 298 K): δ = 0.84 [t, $^3J_{H,H}$ = 7.4 Hz, 12 H, $O(CH_2)_2$-CH_3], 0.92 [s, 36 H, $C(CH_3)_3$], 1.45 [s, 18 H, $C(CH_3)_3$], 1.43 (m, 4 H, OCH_2–CH_2Me), 1.57 (m, 4 H, OCH_2–CH_2Me), 3.24 (d, $^2J_{H,H}$ = 14.2 Hz, 2 H, $ArCH_2Ar$), 3.44 (m, 8 H, $ArCH_2Ar$, OCH_2Et), 3.54 (m, 4 H, OCH_2Et), 4.20 (s, 4 H, $ArCH_2$-*m*-xylylene), 4.37 (d, $^2J_{H,H}$ = 14.2 Hz, 2 H, $ArCH_2Ar$), 4.51 (d, $^2J_{H,H}$ = 15.4 Hz, 4 H, $ArCH_2Ar$), 5.31 (s, 1 H, $ArH_{xylylene}$), 6.82 (s, 4 H, ArH), 6.89 (s, 4 H, ArH), 7.16 (s, 3 H, $ArH_{xylylene}$), 7.35 (s, 4 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, DEPT, 298 K): δ = 10.5 [$O(CH_2)_2$-CH_3], 23.4 (OCH_2–CH_2Me), 28.5, 30.2 ($ArCH_2Ar$), 31.3, 31.7 [$C(CH_3)_3$], 34.0, 34.3 [$C(CH_3)_3$], 71.7 ($ArCH_2$-*m*-xylylene), 74.7 (OCH_2Et), 122.2, 122.6, 124.1, 125.1, 126.6, 128.0 (ArH), 132.8, 133.5, 138.2, 144.9, 145.8, 152.2, 152.8 (Ar) ppm. MS (MALDI-TOF): *m*/*z* = 1265.8 [*M* + Na]$^+$. $C_{86}H_{114}O_6 \cdot 1/2CHCl_3$ (1301.8): calcd. C 79.70, H 8.85; found C 80.09, H 9.02.

37,38,40,41-Tetraallyloxy-5,11,17,23,29,35-hexa-*tert*-butyl-39,42-(*m*-xylylenedioxy)calix[6]arene (1c): The compound was obtained by Methods A and B, from **1a** (0.1 g, 0.093 mmol), NaH (59.5 mg, 0.744 mmol, Method A) or Cs_2CO_3 (363.5 mg, 1.115 mmol, Method B) and allyl bromide (0.064 mL, 0.409 mmol, Method A; 0.048 mL, 0.558 mmol, Method B) in dry THF (10 mL) or dry DMF (5 mL), respectively, for 2 d. Yield: 75 mg (64%, Method A) and 63 mg (55%, Method B). M.p. 190 °C (dec.). ^1H NMR (500 MHz, $CDCl_3$, 298 K): δ = 0.92 [s, 36 H, $C(CH_3)_3$], 1.43 [s, 18 H, $C(CH_3)_3$], 3.25 (d, $^2J_{H,H}$ = 14.2 Hz, 2 H, $ArCH_2Ar$), 3.43 (d, $^2J_{H,H}$ = 15.4 Hz, 4 H, $ArCH_2Ar$), 3.99 (dd, $^3J_{H,H}$ = 5.0, $^2J_{H,H}$ = 13.2 Hz, 4 H, OCH_2–CH), 4.13 (dd, $^3J_{H,H}$ = 5.0, $^2J_{H,H}$ = 13.2 Hz, 4 H, OCH_2–CH), 4.24 (s, 4 H, $ArCH_2$-*m*-xylylene), 4.34 (d, $^2J_{H,H}$ = 14.2 Hz, 2 H, $ArCH_2Ar$), 4.43 (d, $^2J_{H,H}$ = 15.4 Hz, 4 H, $ArCH_2Ar$), 5.02 (dd, $^2J_{H,H}$ = 1.9, $^3J_{H,H}$ = 10.4 Hz, 4 H, CH_2=), 5.15 (dd, $^2J_{H,H}$ = 1.8, $^3J_{H,H}$ = 17.3 Hz, 4 H, CH_2=), 5.50 (s, 1 H, $ArH_{xylylene}$), 5.73 (m, 4 H, CH=), 6.82 (d, $^4J_{H,H}$ = 1.9 Hz, 4 H, ArH), 6.91 (d, $^4J_{H,H}$ = 2.2 Hz, 4 H, ArH), 7.18 (s, 3 H, $ArH_{xylylene}$), 7.33 (s, 4 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, DEPT, 298 K): δ = 28.8, 30.4 ($ArCH_2Ar$), 31.3, 31.7 [$C(CH_3)_3$], 34.1, 34.3 [$C(CH_3)_3$], 71.8 ($ArCH_2$-*m*-xylylene), 74.0 (OCH_2–CH), 115.6 (CH_2=), 121.7, 122.8, 124.3, 125.1, 126.7, 127.9 (ArH), 132.7, 132.9, 133.5 (Ar), 134.8 (CH=), 138.3, 145.3, 146.0, 152.0, 152.8 (Ar) ppm. MS (MALDI-TOF): *m*/*z* = 1257.8 [*M* + Na]$^+$. $C_{86}H_{106}O_6 \cdot 1/2CHCl_3 \cdot 1/2H_2O$ (1303.7): calcd. C 79.64, H 8.31; found C 79.80, H 8.75.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38;40,41-bis[naphthalene-2,3-diylbis(methyleneoxy)]-39,42-(*m*-xylylenedioxy)calix[6]arene (2a): The compound was obtained by Method C, from **1a** (0.2 g, 0.186 mmol), NaH (59.5 mg, 1.488 mmol) in DMF (34 mL) and 2,3-bis(bromomethyl)naphthalene (0.108 g, 0.409 mmol) in dry DMF (5 mL), column chromatography (hexane/EtOAc, 97.5:2.5). Yield: 56 mg (22%). M.p. 246 °C (dec.). ^1H NMR (500 MHz, $CDCl_3$, 298 K): δ = 0.97 [s, 36 H, $C(CH_3)_3$], 1.46 [s, 18 H, $C(CH_3)_3$], 3.00 (d, $^2J_{H,H}$ = 13.9 Hz, 2 H, $ArCH_2Ar$), 3.64 (d, $^2J_{H,H}$ = 15.1 Hz, 4 H, $ArCH_2Ar$), 4.24 (d, $^2J_{H,H}$ = 13.9 Hz, 2 H, $ArCH_2Ar$), 4.39 (s, 4 H, $ArCH_2$-*m*-xylylene), 4.57 (d, $^2J_{H,H}$ = 15.1 Hz, 4 H, $ArCH_2Ar$), 4.92 (d, $^2J_{H,H}$ = 11.7 Hz, 4 H, $ArOCH_2$-naphthalene), 5.02 (d, $^2J_{H,H}$ = 11.7 Hz, 4 H, $ArOCH_2$-naphthalene), 6.23 (s, 1 H, $ArH_{xylylene}$), 6.87 (d, $^4J_{H,H}$ = 2.2 Hz, 4 H, ArH), 6.87 (m, 1 H, $ArH_{xylylene}$), 6.90 (d, $^4J_{H,H}$ = 2.2 Hz, 4 H, ArH), 6.96 (d, $^4J_{H,H}$ = 7.2 Hz, 2 H, $ArH_{xylylene}$), 7.43 (m, 8 H, $ArH_{naphthalene}$, ArH), 7.61 (s, 4 H, $ArH_{naphthalene}$), 7.74 (m, 4 H, $ArH_{naphthalene}$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, DEPT, 298 K): δ = 30.6 ($ArCH_2Ar$), 31.3, 31.8 [$C(CH_3)_3$], 31.9 ($ArCH_2Ar$), 34.0, 34.4 [$C(CH_3)_3$], 71.8 ($ArCH_2$-*m*-xylylene), 75.1 ($ArCH_2$-naphthalene), 122.2, 122.7, 124.7, 125.3, 126.2, 127.0, 127.5, 127.6, 129.4 (ArH), 132.8, 133.4, 133.7, 133.8, 134.8, 138.8, 145.7, 146.4, 152.2, 153.0 (Ar) ppm. MS (MALDI-TOF) *m*/*z* = 1401.8 [*M* + Na]$^+$. $C_{98}H_{106}O_6 \cdot 3H_2O$ (1433.9): calcd. C 82.09, H 7.87; found C 82.49, H 8.09.

5,11,17,23,29,35-Hexa-*tert*-butyl-39,42-(*m*-xylylenedioxy)-37,38;40,41-bis(*o*-xylylenedioxy)calix[6]arene (2b): The compound was obtained by Method C, from **1a** (0.2 g, 0.186 mmol), NaH (59.5 mg, 1.488 mmol) in dry DMF (34 mL) and α,α′-dibromo-*o*-xylene (0.108 mg, 0.409 mmol) in dry DMF (4 mL), column chromatography (hexane/$CHCl_3$, 4:6). Yield: 116.7 mg (49%). M.p.

230 °C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 0.96 [s, 36 H, $C(CH_3)_3$], 1.44 [s, 18 H, $C(CH_3)_3$], 3.02 (d, $^2J_{H,H}$ = 13.8 Hz, 2 H, $ArCH_2Ar$), 3.57 (d, $^2J_{H,H}$ = 15.0 Hz, 4 H, $ArCH_2Ar$), 4.22 (d, $^2J_{H,H}$ = 13.8 Hz, 2 H, $ArCH_2Ar$), 4.39 (s, 4 H, $ArCH_2$-*m*-xylylene), 4.50 (d, $^2J_{H,H}$ = 15.0 Hz, 4 H, $ArCH_2Ar$), 4.86 (d, $^2J_{H,H}$ = 11.8 Hz, 4 H, $ArCH_2$-*o*-xylylene), 4.77 (d, $^2J_{H,H}$ = 11.8 Hz, 4 H, $ArCH_2$-*o*-xylylene), 6.19 (s, 1 H, $ArH_{m\text{–xylylene}}$), 6.82 (d, $^4J_{H,H}$ = 1.7 Hz, 4 H, ArH), 6.92 (d, $^4J_{H,H}$ = 2.2 Hz, 4 H, ArH), 6.95 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H, $ArH_{m\text{–xylylene}}$), 7.08 (d, $^3J_{H,H}$ = 7.2 Hz, 2 H, $ArH_{m\text{–xylylene}}$), 7.12 (m, 4 H, $ArH_{o\text{–xylylene}}$), 7.19 (m, 4 H, $ArH_{o\text{–xylylene}}$), 7.38 (s, 4 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 30.5, 31.5 ($ArCH_2Ar$), 31.2, 31.8 [$C(CH_3)_3$], 34.0, 34.4 [$C(CH_3)_3$], 71.7 ($ArCH_2$-*m*-xylylene), 75.1 ($ArCH_2$-*o*-xylylene), 122.1, 122.6, 124.6, 125.2, 127.1, 127.6, 127.8, 130.1 (ArH), 133.4, 133.6, 133.7, 136.7, 138.8, 145.6, 146.3, 152.2, 153.0 (Ar) ppm. MS (MALDI-TOF): *m*/*z* = 1279.8 [*M* + H]$^+$, 1301.8 [*M* + Na]$^+$, 1317.7 [*M* + K]$^+$. $C_{90}H_{102}O_6 \cdot H_2O$ (1297.8): calcd. C 83.29, H 8.08; found C 83.00, H 8.22.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38;40,41-bis(1,4,7-trioxaheptane-1,7-diyl)-39,42-(*m*-xylylenedioxy)calix[6]arene (2c): A mixture of **1a** (0.2 g, 0.186 mmol) and NaH (52.0 mg, 1.302 mmol) in DMF (68 mL) was heated at 50 °C under argon for 10 min, and 3-oxapentane-1,5-diyl bis(*p*-tosylate) (169.6 mg, 0.409 mmol) in dry DMF (6.5 mL) was then added slowly. The reaction mixture was heated at 50 °C for 4 d. The mixture was quenched with an excess of methanol and HCl (1 N), stirred additionally for 30 min, and the solid was filtered and triturated with MeOH. The resulting solid was purified by column chromatography (CH_2Cl_2/1% *i*PrOH). Yield: 107.5 mg (48%). M.p. 210 °C (dec.). ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 403 K): δ = 0.96 [s, 36 H, $C(CH_3)_3$], 1.42 [s, 18 H, $C(CH_3)_3$], 2.98 (m, 4 H, CH_2OCH_2, protons *b* in text), 3.08 (d, $^2J_{H,H}$ = 14.1 Hz, 2 H, $ArCH_2Ar$), 3.43 (d, $^2J_{H,H}$ = 15.1 Hz, 4 H, $ArCH_2Ar$), 3.58 (m, 4 H, $ArOCH_2$, protons *a* in text), 3.67 (m, 4 H, $ArOCH_2$, protons *a* in text), 3.69 (m, 4 H, CH_2OCH_2, protons *b* in text), 4.36 (s, 4 H, $ArCH_2$-*m*-xylylene), 4.38 (d, $^2J_{H,H}$ = 15.0 Hz, 4 H, $ArCH_2Ar$), 4.82 (d, $^2J_{H,H}$ = 14.1 Hz, 2 H, $ArCH_2Ar$), 5.90 (s, 1 H, $ArH_{xylylene}$), 6.76 (d, $^4J_{H,H}$ = 1.9 Hz, 4 H, ArH), 7.00 (d, $^4J_{H,H}$ = 2.2 Hz, 4 H, ArH), 7.23 (s, 3 H, $ArH_{xylylene}$), 7.30 (s, 4 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, DEPT, 298 K): δ = 27.7, 29.7 ($ArCH_2Ar$), 31.3, 31.7 [$C(CH_3)_3$], 34.1, 34.3 [$C(CH_3)_3$], 71.5, 72.8, 73.5 (CH_2O), 122.1, 122.7, 124.2, 125.5, 126.9, 127.8 (ArH), 133.1, 133.3, 133.7, 139.4, 145.6, 146.5, 151.1, 152.8 (Ar) ppm. MS (MALDI-TOF): *m*/*z* = 1237.8 [*M* + Na]$^+$, 1253.8 [*M* + K]$^+$. $C_{82}H_{102}O_8 \cdot H_2O$ (1233.7): calcd. C 79.83, H 8.50; found C 79.67, H 8.74.

Supporting Information (see also footnote on the first page of this article): Variable-temperature (403–188 K) experiments, and ROESY and NOESY spectra of compounds **1b**–**c** and **2a**–**c**.

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