Concave reagents. Part 27.[1] Steric requirements of intraannular substituents in A,D-bridged calix[6]arenes

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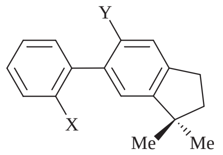
A series of A,D-*m*-xylylene bridged calix[6]arenes 5 carrying substituents of different size in 2-position of the bridge have been investigated by dynamic NMR spectroscopy and by force field methods. Molecular mechanics calculations indicate a bean shaped conformation as the global energy minimum in which the calixarene scaffold adopts a half-pinched/half-winged arrangement.

Introduction

Hindered rotations about single bonds have been the subject of numerous studies.[2,3] The influence of the steric requirements of substituents on the height of rotational barriers for a particular system has been intensively studied by dynamic NMR spectroscopy (DNMR). Thus in biphenyls **1**, Sternhell and co-workers[4] found increasing barriers to rotation along the aryl aryl bond for the following substituents: CN < OCH_3 < NO_2 ≈ CO_2Me < Cl < NH_2 ≈ CH_3 < Br < I. But in other systems, other sequences have been observed, especially for CH_3, Br and Cl.[5] Clearly, these results cannot be easily transferred to sterically more demanding systems.[6]



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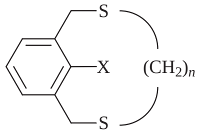

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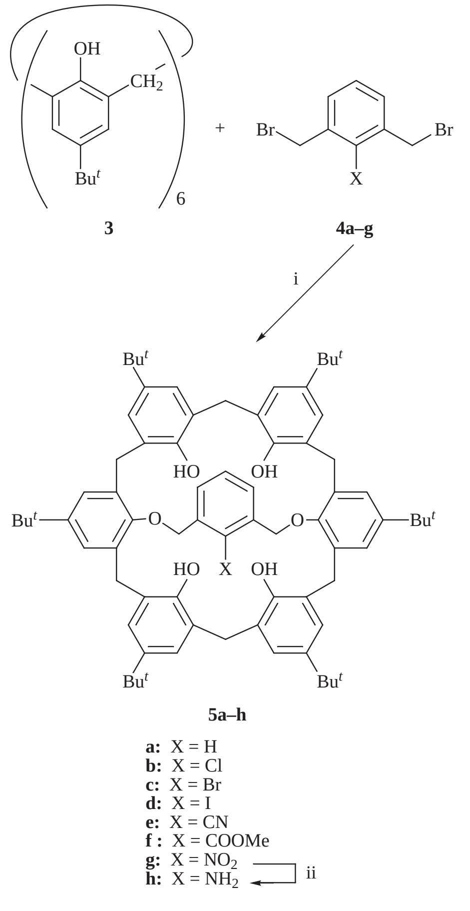
More detailed information about the spatial requirements of substituents can be derived from DNMR studies on the ansa compounds **2**. In these macrocycles the whole substituent at the 2-position interacts with the ansa chain so that the effective bulk of the entire substituent can be estimated:[7] NH_2 < NO_2 ≈ Cl < CH_3 < CN ≈ Br ≈ OCH_3 < I < CO_2Me (the particular sequence of CN, Br and OCH_3 depends on the ring size of **2**).

A similar spatial situation for substituents X occurs in the A,D-bridged‡ tetrahydroxycalix[6]arenes **5** (Scheme 1) which have been described recently by Shinkai,[8] Okazaki[9] and our own group.[10] In these compounds, the substituent X of the bridge is located in a concave environment which makes these compounds good candidates for concave reagents.[11] Concave reagents are bimacrocyclic compounds carrying a functional group, for instance an acid or a base, in the concave position. Due to the concave shielding of the functional group they are able to increase selectivities in model reactions.[11] For this purpose we have already synthesized the pyridine **6** whose nitrogen atom points into the calixarene cavity.[12]



Scheme 1 *Reagents and conditions*: i, NaH, THF–DMF; ii, $Fe(CO)_5$, NaOH, Aliquat 336[10]

In fact, the bridge of compound **6** is in a fast flipping motion. The differences in symmetry between compound **6** and other already known A,D-bridged calix[6]arenes[8–10] can be explained by different orientations of the bridge (see Fig. 1), but it has been found independently by Okazaki and our group that introduction of bulkier substituents at the bridge can result in restriction of this motion.[9b,10]

Since we are interested[11] in further bimacrocyclic calix[6]arenes with diversely functionalized bridges it is necessary to know in detail the spatial requirements of substituents as well as the conformational preferences of this particular molecular system.

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‡ A,D-Bridging is defined as the connection of two opposite phenol rings of a calix[6]arene. The alternative term, 1,4-bridging does not correspond to the numbering of the calix[6]arene oxygen atoms (37–42).

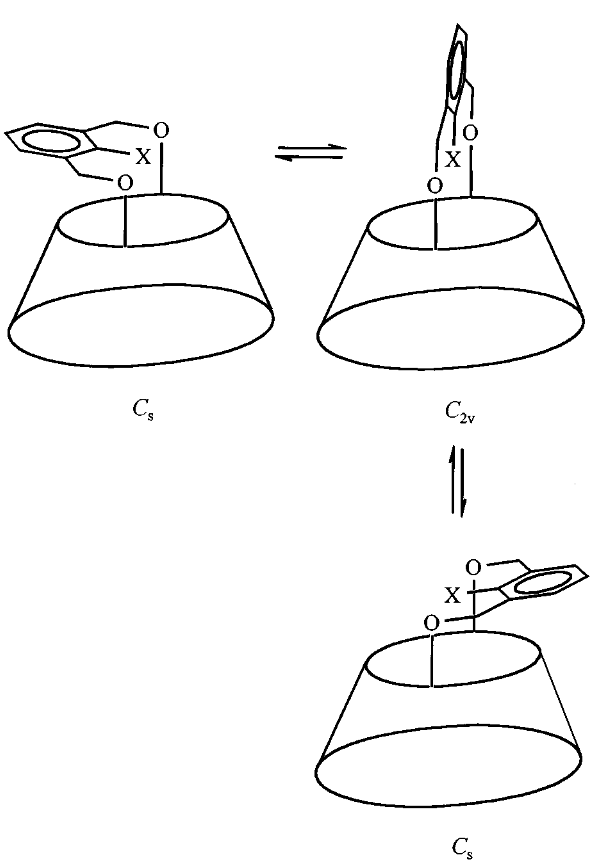
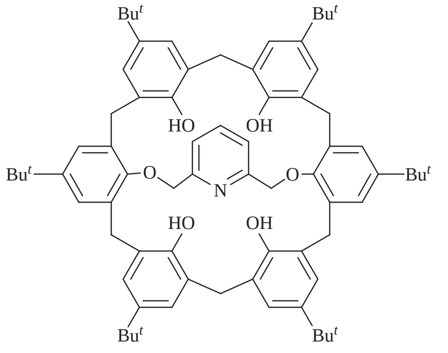


Fig. 1 C_s and C_{2v} conformations for a (**u**,u,u,u,u,u)-A,D-bridged calix[6]arene



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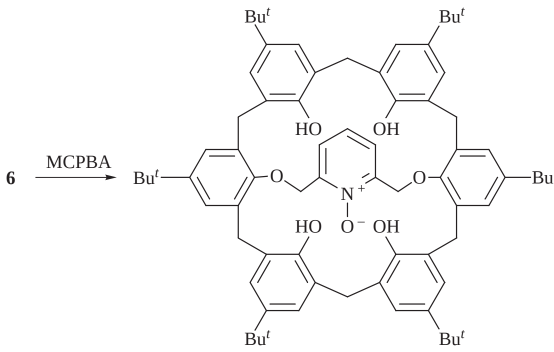
Results and discussion

The syntheses of A,D-bridged tetrahydroxycalix[6]arenes **5a**, **5c**, **5g–h** and **6** have been described previously.[8,9b,10,12a] The new compounds **5b** and **5d–f** were prepared in an approved manner without high dilution from *p*-*tert*-butylcalix[6]arene (**3**) and the appropriate bis(bromomethyl)benzene **4** in the presence of sodium hydride in refluxing THF–DMF. Yields were between 57 and 80%. The pyridine *N*-oxide **7** was obtained in 75% yield by oxidation of pyridine **6** using MCPBA.

Like its precursor **6** the *N*-oxide **7** adopts a C_{2v} symmetrical (**u**,u,u,u,u,u) conformation.[13] The ^{1}H NMR spectrum features two singlets arising from the *tert*-butyl hydrogen atoms (2:1 ratio), two pairs of AB doublets (2:1 ratio) for the diarylmethylene hydrogen atoms, one singlet for the oxymethylene groups of the bridge, and one singlet for the hydroxy groups. By contrast with this, the spectra of the chloride **5b** and the cyanide **5e** show pronounced line broadenings in the methylene region. Upon heating, sharp signals are observed and the spectra are very similar to the spectrum of pyridine *N*-oxide **7** at room temperature. On the other hand, sharp signals are also observed at temperatures below 0 °C, but there are three singlets for the *tert*-butyl hydrogen atoms (1:1:1 ratio), four pairs of AB doublets (2:2:1:1 ratio) in the diarylmethylene region, two doublets for the oxymethylene groups of the bridge (1:1 ratio), and two singlets (1:1 ratio) for the hydroxy groups. The spectrum indicates a C_s symmetrical structure for the chloride **5b** and the cyanide **5e** at low temperatures. A similar behaviour was observed in the case of the nitro compound **5g**[10] and the aryl bromide **5c**.[9b] In the case of the iodide **5d**, the C_s symmetrical structure is already apparent from the ^{1}H NMR spectrum at room temperature. But upon heating, coalescences of the signals are observed until finally above 80 °C the simpler spectrum of the C_{2v} symmetrical structure is obtained.



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The differences in symmetry of the calixarenes **5** can be explained by different orientations of the bridge (see Fig. 1). If the substituent X points into the centre of the cavity the resulting bimacrocycle possesses a C_{2v} symmetry while a bent bridge lowers the symmetry to C_s. Because the bridge can be bent to both sides there are two possible C_s symmetrical conformers which can be interconverted by a flipping of the bridge in the course of which the functional group passes the rim of the calixarene cavity. At low temperatures or with very large substituents, this process is slow on the NMR timescale leading to an observed C_s symmetry. With small substituents or at high temperatures, the flipping of the bridge becomes faster, and only the average C_{2v} symmetry is found.

The spectra of the ester **5f** differ from those of the other calixarenes **5**. At room temperature two conformers are observed in a ratio of 87:13. Although many signals of the two isomers overlap, all the clearly separated signals are in accordance with (**u**,u,u,u,u,u)-conformations with C_s symmetry as in the iodide **5d** for both the major and the minor isomer of the ester **5f**. At elevated temperatures, coalescence occurs from which an activation enthalpy of $\Delta G^\ddagger = 16.4$ kcal mol^{-1} for the interconversion of the two isomers can be calculated. But this process is not the flipping of the bridge which was observed for the other compounds because a C_{2v} symmetrical conformer could not be observed in the investigated temperature range. The major and minor conformer of **5f** presumably possess different orientations of the ester group in a C_s symmetrical conformation which interconvert at elevated temperatures. Molecular mechanics calculations (see below) indicate that the observed large chemical shift differences of the methyl protons may result from the inclusion of the ester group inside the calixarene cavity in the winged conformation while it adopts an outside orientation in both the pinched and the half-pinched/half-winged conformation. However, the calculations seem to overestimate attractive van der Waals interactions between the methyl group and the aromatic rings in the winged structure (see Table 2).

The free enthalpy of activation $\Delta G^\ddagger$ for the motion of the bridge can be determined from the coalescence temperature of the *tert*-butyl and the hydroxy resonances. These values are summarized in Table 1.

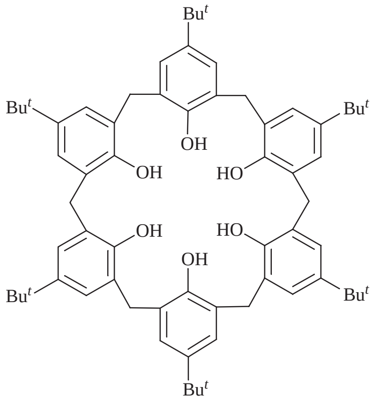
Table 1 Free enthalpies of activation $\Delta G^{\ddagger}$ for the flipping of the bridge in A,D-bridged calix[6]arenes calculated from DNMR coalescence data

	Solvent	NMR freq./ MHz	X	Coalescence of Bu^t T_c/K	$\Delta\nu$/Hz	$\Delta G^{\ddagger}$/kcal mol^{-1}	Coalescence of OH T_c/K	$\Delta\nu$/Hz	$\Delta G^{\ddagger}$/kcal mol^{-1}
5a	CD_2Cl_2	200	H			<11.4[a]			<11.4[a]
5g	CD_2Cl_2	300	NO_2	270	17.36	13.8	*ca.* 288[b]	181.47	*ca.* 13.4
5e	CD_2Cl_2	200	CN	292	10.65	15.2	284	5.26	15.2
5b	CD_2Cl_2	200	Cl	295	10.82	15.4	292	8.55	15.4
5c	$C_2D_2Cl_4$	200	Br	305	7.40	15.8[c]	316	35.84	16.2[c]
5d	$C_2D_2Cl_4$	200	I	333	6.85	17.8	358	45.50	17.8
5f	$C_2D_2Cl_4$	200	COOMe			>18.9[d]			>18.9[d]

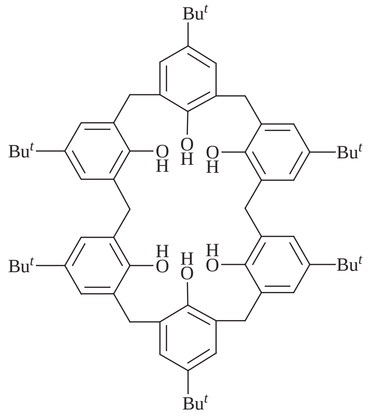
[a] No coalescence until −44 °C (solubility limit). [b] Coalescence between 283 K and room temp. [c] 16 kcal mol^{-1} in ref. 9(*b*). [d] No coalescence for the flipping of the bridge until 80 °C.

Molecular mechanics calculations

Calix[6]arenes in the (**u**,u,u,u,u,u) arrangement[14] may adopt two extreme conformations which have been referred to as 'pinched' and 'winged' cone.[15,16] They differ in the position of the methylene carbon atoms relative to the cavity formed by the aromatic rings. In the winged conformation all six bridging methylene groups point outwards from the macrocyclic annulus while in the pinched conformation two opposite methylene carbon atoms point inwards. Very recently, Reinhoudt and co-workers[16] reported molecular mechanics calculations on the hexahydroxycalix[6]arene and they obtained the pinched cone conformation as the global minimum whereas the winged cone represented a local minimum on the energy hypersurface. In contrast, Molins *et al.*[15a] reported a winged cone conformation for a calix[6]arene with alternating *tert*-butyl and chlorine substituents at the upper rim on the basis of NMR experiments and restrained molecular dynamics simulations.



winged



pinched

In the case of the A,D-bridged calix[6]arenes **5**–**7** the bridging substituent may lead to a change in the conformational preferences. We have therefore explored the energy hypersurface of compounds **5a**–**e**, **5h** and **6** using the stochastic search method[17] implemented in the MM3[18] program. The energies of stable conformers are summarized in Table 2.

Table 2 MM3 calculated steric energies of the stable cone conformers of A,D-bridged calix[6]arenes (in kcal mol^{-1}). Energy differences to the lowest energy conformation are given in parentheses

	Half pinched/ half winged	Pinched	Winged
5a	39.2 (0.0)	42.2 (3.0)	42.7 (3.5)
5b	39.0 (0.0)	41.6 (2.6)	41.8 (2.8)
5c	38.6 (0.0)	40.6 (2.0)	42.0 (3.4)
5d	37.4 (0.0)	39.2 (1.8)	42.7 (5.3)
5e	37.4 (0.0)	40.3 (2.9)	40.2 (2.8)
5f	41.7 (4.9)	42.1 (5.3)	36.8 (0.0)
5h	42.3 (0.0)	46.1 (3.8)	44.4 (2.1)
6	50.4 (0.0)	53.7 (3.3)	54.7 (4.3)

Interestingly, neither the pinched nor the winged cone conformation represents the global minimum found for the compounds under study.[19] In the lowest energy structures a single methylene group points inside the calix[6]arene annulus, thus representing a 'half-winged'/'half-pinched' structure[20] of approximate C_s symmetry as exemplified for **5c** in Fig. 2. The bridge adopts a lateral position as suggested by the low temperature NMR studies and the substituent in the 2-position of the bridge points towards the pinched cone subunit. This conformation is approximately 1.8–5.3 kcal mol^{-1} more stable than the pinched and winged cone structures. The stabilisation may be attributed to favourable van der Waals interactions particularly between the OH groups of the winged cone subunit and the aromatic ring of the bridge. This assumption is supported by calculations on conformers with an inverted orientation of the bridge which are about 3–6 kcal mol^{-1} less stable.

Conclusions

The conformations of A,D-bridged calix[6]arenes could be studied in detail by DNMR measurements and MM3 calculations. The conformation with the lowest energy (i) possesses a (**u**,u,u,u,u,u) conformation (cone), (ii) has a bent bridge which flips between the two possible orientations. The inversion times depend on the size of the substituent in the 2-position of the bridge. (iii) Molecular mechanics calculations suggest that in the conformation with a bent bridge, the calix[6]arene macrocycle adopts a half-pinched/half-winged conformation. During the inversion process between the two stable C_s conformations, not only must the bridge flip from one side to the other but also the pinched methylene groups must move into the winged orientation and *vice versa*. Therefore the activation enthalpies calculated from the DNMR experiments reflect the highest barrier of these three processes.

The sequence of the activation barriers for different substituents X in **5** differs from the order found for **1** and **2**. This may be explained by the varying shapes for the substituents: the cyano

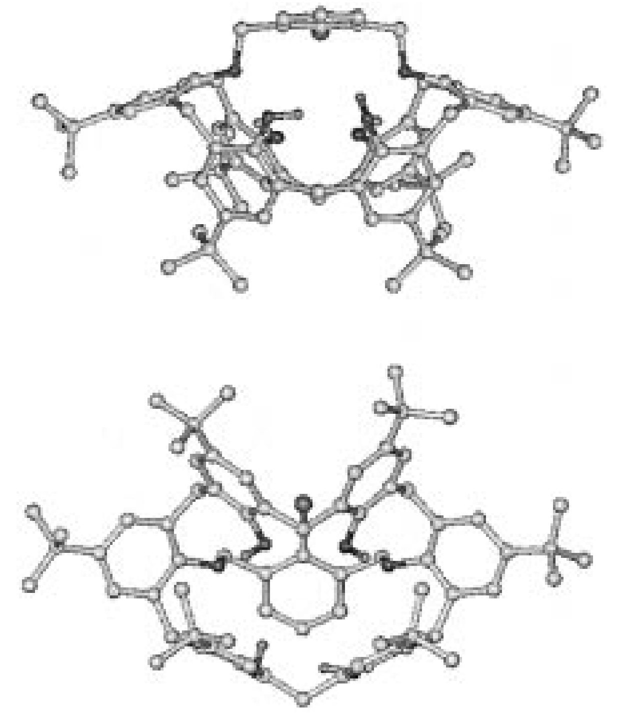


Fig. 2 Side view and view into the cavity of the lowest energy conformer of the bromide **5c**. Hydrogen atoms bonded to carbon atoms are omitted for clarity. The view into the cavity can be called the top-view (view from the upper rim of a calixarene into the bridged cavity) but also can be considered as the view from below (if the bridged calixarene is viewed as a concave reagent, as shown here).

group is linear (**5e**), nitro and amino groups are close to planar (**5g**,**h**), while the halogens are spherical (**5b**–**d**). For these dimensional differences, the bimacrocyclic structures **5** are much more sensitive than for instance a linear biphenyl **1**.

Experimental

Melting points were determined with a Büchi melting point apparatus. IR spectra were recorded on Perkin-Elmer 1600 Series and Paragon spectrometers. Variable-temperature ^{1}H NMR spectra were recorded on Bruker AC 200 and AM 300 spectrometers. For analytical purposes, ^{1}H NMR spectra were recorded on the same instruments. All coupling constants are given in Hz and chemical shifts on the δ scale in ppm. EI mass spectra (70 eV) were recorded on Finnigan MAT 8230 and MAT 8200 spectrometers.

THF was freshly distilled from LiAlH$_4$–triphenylmethane. DMF (<0.01% H$_2$O) was purchased from Fluka.

Preparation of pyridine *N*-oxide 7

A solution of MCPBA (80–90%; 65 mg, *ca.* 320 μmol) was added to a solution of pyridine **6**^{12a} (270 mg, 251 μmol) in dichloromethane (5 cm^3) at 0 °C. After a few minutes a pale sludge precipitated. The mixture was then stirred for another 6–10 h and the course of the reaction was followed by TLC. After addition of dichloromethane (5 cm^3) the mixture was washed twice with dilute aqueous sodium carbonate. The organic layer was dried and evaporated under reduced pressure. After purification by column chromatography [silica, dichloromethane–methanol (50 : 1)], the product was dissolved in dichloromethane and precipitated with methanol to give the *N*-oxide **7** (206 mg, 75%) as a colourless solid; R_f (dichloromethane–methanol, 50 : 1) 0.65; mp 231–233 °C (decomp.) (Found: C, 80.1; H, 8.4; N, 1.3. $C_{73}H_{89}NO_6$ requires C, 80.3; H, 8.2; N, 1.3%); ν_{max}(KBr)/cm^{-1} 3384, 2959, 1482 and 1362; δ_H(200 MHz, CDCl$_3$) 1.16 (18 H, s, Bu^t), 1.26 (36 H, s, Bu^t), 3.38 (2 H, d, *J* 13.9, ArCH_2Ar), 3.57 (4 H, d, *J* 14.6, ArCH_2Ar), 3.95 (2 H, d, *J* 13.9, ArCH_2Ar), 4.39 (4 H, d, *J* 14.6, ArCH_2Ar), 5.52 (4 H, s, OCH$_2$), 7.04 (4 H, s, ArH), 7.08 (8 H, m$_c$, ArH), 7.34 (1 H, t, *J* 7.8, Py ArH), 7.63 (2 H, d, *J* 7.8, Py ArH) and 8.09 (4 H, s, OH); *m*/*z* (EI) 1091 (M$^+$, 3%), 1073 (100, M$^+$ − H$_2$O).

Preparation of A,D-bridged calix[6]arenes 5. General procedure Under nitrogen, *p*-*tert*-butylcalix[6]arene **3**^{21} (1.95 g, 2.00 mmol) was added to a suspension of sodium hydride (60%; 0.50 g, *ca.* 12.5 mmol) in THF–DMF (180 cm^3–20 cm^3). While the mixture was heated to reflux, a solution containing the appropriate dibromide **4** in THF–DMF (45 cm^3–5 cm^3) was added dropwise. Heating was continued for 18 h and then the mixture was cooled and quenched by careful addition of methanol (10 cm^3). Water (100 cm^3) and chloroform (150 cm^3) were added. The organic layer was separated, dried with MgSO$_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica using dichloromethane as eluent to yield the product **5** as a colourless solid; R_f (dichloromethane) >0.90.

Chloride 5b. Synthesized according to the general procedure with all quantities doubled: (3.40 g, 77%) from *p*-*tert*-butylcalix[6]arene **3** (3.90 g, 4.01 mmol) and 1,3-bis(bromomethyl)-2-chlorobenzene **4b**^{22} (1.31 g, 4.39 mmol); mp 230–233 °C (decomp.) (Found: C, 79.3; H, 8.0. $C_{74}H_{89}ClO_6\cdot0.5H_2O$ requires C, 79.4; H, 8.1%); ν_{max}(KBr)/cm^{-1} 3386, 2957, 1482 and 1362; δ_H(200 MHz, CD$_2$Cl$_2$; 273 K) 1.17, 1.23 and 1.29 [3 × (18 H, s, Bu^t)], 3.21 (2 H, m$_c$, ArCH_2Ar), 3.56 (4 H, m$_c$, ArCH_2Ar), 3.89 (1 H, d, *J* 13.4, ArCH_2Ar), 4.09 (3 H, m$_c$, ArCH_2Ar), 4.68–4.75 (4 H, m, ArCH_2Ar and OCH$_2$), 5.88 (2 H, d, *J* 9.8, OCH$_2$), 7.00 (2 H, d, *J* 2.2, ArH), 7.07–7.18 (8 H, m, ArH), 7.20 (2 H, d, *J* 2.2, ArH), 7.30 (1 H, t, *J* 7.6, bridge ArH), 7.57 (2 H, d, *J* 7.6, ArH) and 8.51 and 8.55 [3 × (2 H, s, OH)]; δ_H(300 MHz; C$_2$D$_2$Cl$_4$; 363 K) 1.27 (18 H, s, Bu^t), 1.34 (36 H, s, Bu^t), 3.39 (2 H, d, *J* 13.3, ArCH_2Ar), 3.59 (4 H, d, *J* 13.0, ArCH_2Ar), 4.02 (2 H, d, *J* 13.3, ArCH_2Ar), 4.54 (4 H, d, *J* 13.0, ArCH_2Ar), 5.36 (4 H, s, OCH$_2$), 7.08 (4 H, d, *J* 2.4, ArH), 7.15–7.20 (8 H, m, ArH), 7.37 (1 H, A_2B, *J* 7.5, bridge ArH), 7.60 (2 H, $A_2\mathrm{B}$, *J* 7.5, bridge ArH) and 8.66 (4 H, s, OH); *m*/*z* (EI) 1108 (M$^+$, 100%).

Iodide 5d. Synthesized according to the general procedure: (1.76 g, 73%) from *p*-*tert*-butylcalix[6]arene **3** (1.95 g, 2.00 mmol) and 1,3-bis(bromomethyl)-2-iodobenzene **4d**^{23} (858 mg, 2.20 mmol); mp 257–258 °C (decomp.) (Found: C, 73.2; H, 7.4. $C_{74}H_{89}IO_6\cdot0.5H_2O$ requires C, 73.4; H, 7.5%); ν_{max}(KBr)/cm^{-1} 3421, 2960, 1482 and 1362; δ_H(200 MHz; CD$_2$Cl$_2$; 293 K) 1.19, 1.25 and 1.30 [3 × (18 H, s, Bu^t)], 1.54 (<6 H, br s, H$_2$O), 3.18 and 3.26 [2 × (1 H, d, *J* 13.4 and 13.7, ArCH_2Ar)], 3.52–3.65 (4 H, m, ArCH_2Ar), 3.88 and 4.05 [2 × (1 H, d, *J* 13.7 and 13.4, ArCH_2Ar)], 4.21 (2 H, d, *J* 12.9, ArCH_2Ar), 4.89 (2 H, d, *J* 9.9, OCH$_2$), 5.04 (2 H, d, *J* 13.4, ArCH_2Ar), 5.84 (2 H, d, *J* 9.9, OCH$_2$), 7.01 (2 H, d, *J* 2.4, ArH), 7.15 (6 H, m, ArH), 7.16 and 7.21 [2 × (2 H, d, *J* 2.4, ArH)], 7.38 (1 H, $A\mathrm{B}_2$, *J* 7.3, bridge ArH), 7.58 (2 H, m, $\mathrm{A}B_2$, *J* 7.3, bridge ArH) and 8.39 and 8.45 [2 × (2 H, s, OH)]; δ_H(200 MHz; C$_2$D$_2$Cl$_4$; 362 K) 1.27 (18 H, s, Bu^t), 1.34 (36 H, s, Bu^t), 3.27 (2 H, d, *J* 13.9, ArCH_2Ar), 3.60 (4 H, d, *J* 13.2, ArCH_2Ar), 4.02 (2 H, d, *J* 13.9, ArCH_2Ar), 4.74 (4 H, m$_c$, ArCH_2Ar), 5.40 (4 H, br s, OCH$_2$), 7.08 (4 H, d, *J* 2.4, ArH), 7.17 (8 H, m$_c$, ArH), 7.42 (1 H, $A\mathrm{B}_2$, *J* 7.3, bridge ArH), 7.57 (2 H, $\mathrm{A}B_2$, *J* 7.3, ArH) and 8.50 (4 H, s, OH); *m*/*z* (EI) 1201 (M$^+$, 100%).

Nitrile 5e. Synthesized according to the general procedure: (1.76 g, 80%) from *p*-*tert*-butylcalix[6]arene **3** (1.95 g, 2.00 mmol) and 2,6-bis(bromomethyl)benzonitrile **4e**^{24} (636 mg, 2.20 mmol); mp 248–250 °C (decomp.) (Found: C, 81.2; H, 8.1; N, 1.25. $C_{75}H_{89}NO_6\cdot0.5H_2O$ requires C, 81.2; H, 8.2; N, 1.3%); ν_{max}(KBr)/cm^{-1} 3366, 2955, 2225, 1482 and 1362; δ_H(200 MHz; CD$_2$Cl$_2$; 273 K) 1.17, 1.23 and 1.29 [3 × (18 H, s, Bu^t)], 3.21 (2 H, m$_c$, ArCH_2Ar), 3.55 and 3.60 [2 × (2 H, d, *J* 12.8 and 13.3, ArCH_2Ar)], 3.91 (1 H, d, *J* 13.4, ArCH_2Ar), 4.03 (2 H, d, *J* 12.8, ArCH_2Ar), 4.07 (1 H, d, *J* 13.7, ArCH_2Ar), 4.76 (2 H, d, *J* 13.3, ArCH_2Ar), 4.80 and 5.92 [2 × (2 H, d, *J* 10.3, OCH$_2$)], 7.01

(2 H, d, *J* 2.2, ArH), 7.08–7.15 (8 H, m, ArH), 7.17 (2 H, d, *J* 2.2, ArH), 7.97 (3 H, s, bridge ArH) and 8.39 and 8.42 [2 × (2 H, s, OH)]; δ_H(200 MHz; $C_2D_2Cl_4$; 353 K) 1.27 (18 H, s, Bu^t), 1.34 (36 H, s, Bu^t), 3.30 (2 H, d, *J* 13.5, $ArCH_2Ar$), 3.60 (4 H, d, *J* 13.2, $ArCH_2Ar$), 4.05 (2 H, d, *J* 13.5, $ArCH_2Ar$), 4.54 (4 H, d, *J* 13.2, $ArCH_2Ar$), 5.42 (4 H, s, OCH_2), 7.08 and 7.16 [2 × (4 H, d, *J* 2.4, ArH)], 7.20 (4 H, s, ArH), 7.70 (3 H, s, ArH) and 8.51 (4 H, s, OH); *m*/*z* (EI) 1100 (M^+, 100%).

Methyl ester 5f. Synthesized according to the general procedure: (1.30 g, 57%) from *p-tert*-butylcalix[6]arene **3** (1.95 g, 2.00 mmol) and methyl 2,6-bis(bromomethyl)benzoate **4f**[25] (708 mg, 2.20 mmol); mp 222–224 °C (Found: C, 80.4; H, 8.3. $C_{76}H_{92}NO_8$ requires C, 80.5; H, 8.2%); ν_{max}(KBr)/cm^{-1} 3300, 2959, 1718, 1484 and 1362; δ_H(300 MHz; $CDCl_3$; 273 K; main conformer) 1.19, 1.23 and 1.28 [3 × (18 H, s, Bu^t)], 1.56 (<6 H, br s, H_2O), 3.17 and 3.24 [2 × (1 H, d, *J* 13.7 and 13.6, $ArCH_2Ar$)], 3.52 and 3.54 [2 × (2 H, d, *J* 12.9 and 13.2, $ArCH_2Ar$)], 3.66 (3 H, s, OCH_3), 3.90 and 4.06 [2 × (1 H, d, *J* 13.7 and 13.6, $ArCH_2Ar$)], 4.28 and 4.65 [2 × (2 H, d, *J* 12.9 and 13.2, $ArCH_2Ar$)], 4.75 and 6.13 [2 × (2 H, d, *J* 9.4, OCH_2)], 6.99, 7.07 and 7.08 [3 × (2 H, d, *J* 2.4, ArH)], 7.12–7.14 (6 H, m, ArH), 7.52 (1 H, t, *J* 7.4, bridge ArH), 7.66 (2 H, d, *J* 7.4, bridge ArH) and 8.62 and 9.25 [2 × (2 H, s, O*H*]; δ_H(300 MHz; $CDCl_3$; 273 K; minor conformer, selected signals) 0.73 (3 H, s, OCH_3), 0.87, 0.97 and 1.41 [3 × (18 H, s, Bu^t)]; *m*/*z* (EI) 1133 (M^+, 70%), 1101 (100, $M^+ - CH_4O$).

Force field calculations

All calculations were performed using the default MM3(94) force field running on SGI Indigo2 workstations. In order to locate minima on the energy hypersurface, a conformational search using the stochastic search subroutine of MM3 was performed, starting from the (**u**,u,u,u,u,u) cone conformation. This approach moves atoms randomly and the resulting structure is energetically minimised. Since in MM3 the full-matrix Newton–Raphson minimisation scheme is limited to 120 atoms, the block-diagonal Newton–Raphson method was applied. Missing torsional parameters [atom types 2–1–6–2 corresponding to C(sp^2)–C(sp^3)–O(sp^3)–C(sp^2)] were generated using the MM3 parameter estimator and used without further modification. The default values for the input parameters of the stochastic search were employed except for the number of pushes which was set to 10 000.

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