Improved Synthesis and Conformational Analysis of an A,D-1,10-Phenanthroline-Bridged Calix[6]arene[‡]

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The synthesis of the A,D-1,10-phenanthroline-bridged calix[6]arene **3** is improved by applying a new strategy for the synthesis of the important intermediate 2,9-bis(bromomethyl)-1,10-phenanthroline (**2**) and variation of the bridging conditions. Crystals were obtained from two different solvent systems. Two structures were determined by X-ray studies. Both analyses reveal a rare conformation for A,D-bridged calix[6]arenes (*uduuuu*). Calculations with different methods were performed for this and other relevant conformers, and revealed various local minima. The *uduuuu* conformation also explains the molecular asymmetry evident in low-temperature NMR spectra of metal complexes of **3**.

Introduction

Calixarenes are the "supramolecular chemist's benzene ring" because the well-defined conformations of calixarenes allow the chemist to selectively place functional groups in space, as *ortho*-, *meta*- or *para*-substitution of a benzene ring does in the plane.[1] For this reason the conformations of calixarenes, especially calix[4]arenes, have been studied in detail.[1–5] In contrast to calix[4]arenes, the larger calix[*n*]arenes are conformationally much more labile, which may be one reason why more than 80% of the calixarene literature deals with calix[4]arenes.

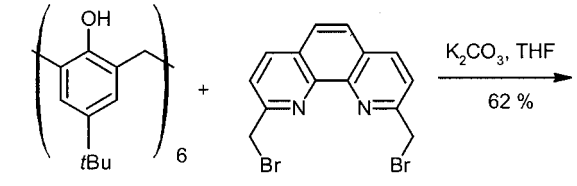
When larger calix[*n*]arenes are bridged, however, the number of conformations is drastically reduced. Several classes of A,D-bridged calix[6]arenes have been synthesised in the past decade:[6,7]

– with flexible bridges such as polymethylene or polyether chains

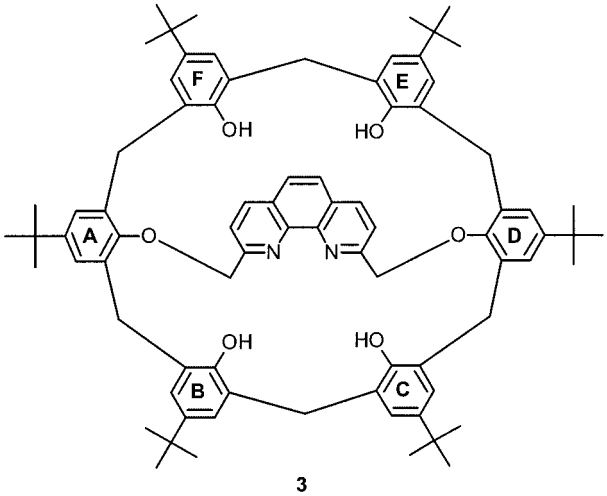
– with xylylene or pyridine-2,6-dimethylene bridges

– with a 1,10-phenanthroline-2,9-dimethylene bridge.

In the last case, calix[6]arene (**1**) was treated with 2,9-bis(bromomethyl)-1,10-phenanthroline (**2**) under basic conditions. Various methods for the synthesis of **2** are known,[8–10] but unrestricted access to the dibromide **2** is limited by either poor yields or too many synthetic steps (up to four) with intermediates which proved hard to purify. In the past, the dibromide **2** has been synthesised[11,12] in three steps with a maximum yield of 35%. We managed to improve the synthesis of the bridging reagent **2** to 60% yield in only two steps while additionally avoiding polar, notoriously sparingly soluble compounds, by varying a literature method for the bromination of bipyridines.[13] 2,9-Dimethyl-1,10-phenanthroline (**4**; neocuproine) was doubly deprotonated with three equivalents of LDA per methyl group (due to the presence of unremovable water in the purchased neocuproine). The resulting dianion was then



1 **2**



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[‡] Concave Reagents, 43. Part 42: M. Abbass, C. Kühl, C. Manthey, A. Müller, U. Lüning, *Collect Czech. Chem. Commun.* **2004**, *69*, 1325–1344.

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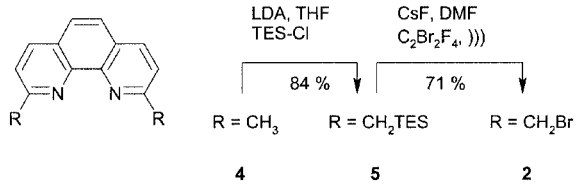
quenched with chlorotriethylsilane (TES-Cl) to give the disilylated intermediate **5** in 84% yield. The silyl groups were then exchanged for bromine by treatment with dibromotetrafluororethane and caesium fluoride in DMF while applying ultrasound. After only 2 h, 71% of the bisbromide **2** could be isolated.



The yield of the bridging of calix[6]arene (**1**) with **2** could also be improved by using potassium carbonate as base; a yield of up to 62% of **3** could be achieved. Compound **3** is a valuable ligand for metal-ion-catalysed reactions. In the copper(I)-catalysed cyclopropanation of alkenes, **3** leads to the thermodynamically less stable *syn* products.[14] Mechanistic studies and theoretical investigations[15] suggest that a bent conformer of the complex is responsible for this *syn* selectivity.

In order to investigate the conformation of the 1,10-phenanthroline-bridged calix[6]arene **3**,[16] it was crystallised from two solvent systems and low-temperature single-crystal X-ray structure determinations were carried out. Interestingly, two distinct different structures were found for **3** when obtained from acetonitrile/chloroform or pyridine in the presence of adventitious water (see Figure 1 and Figure 2).

Both crystals of the A,D-bridged calix[6]arene **3** show a new[17] conformation for bridged calix[6]arenes: one *p-tert*-butylphenol ring is inverted and the OH group points *down*, not *up*, as usually found for other bridged calixarenes, especially when carrying free OH groups.[18] A comparison of the X-ray structures of **3** with the conformations of other bridged calix[6]arenes reveals striking differences.

Conformations of bridged calix[6]arenes have already been investigated by different methods for a number of compounds. If the bridge itself is flexible, only a very short bridge like a diethylene glycol unit[19] leads to a strained conformation with the oxygen atoms of the bridgehead aryl rings in *in*-positions. Other conformers have been found for calix[6]arenes with stiffer bridges.

Calix[6]arenes with xylylene and pyridinedimethylene bridges adopt the same general geometry. Several such compounds have been investigated by calculations[20,21] and a 2′-bromoxylylene-bridged calix[6]arene **6** (X = Br) has been crystallised from chloroform by Goto, Okazaki et al.[21] The X-ray structure and various calculations differ in the fine structures (especially the orientation of the methylene groups between rings B and C, and E and F; see Figure 3), but all investigations have the following aspects in common:

– All oxygen atoms are on the same side of the calixarene macrocycle.

– The bridgehead aryl rings A and D are bent inwards, leading to an *iuuiuu*[22] conformation.

– The bridge is tilted. The plane of the pyridine or xylylene ring and the plane of the calix[6]arene macrocycle are not orthogonal to one another. The NMR spectra at room temperature, however, are in agreement with such a struc-

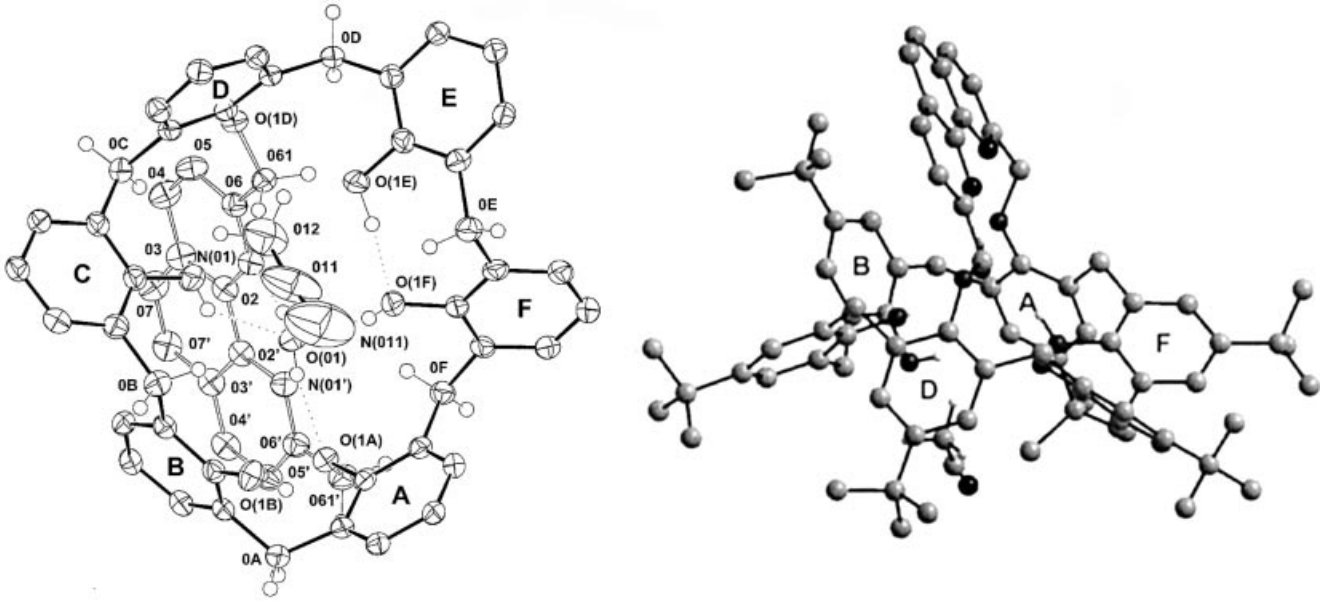


Figure 1. Structure of A,D-1,10-phenanthroline-2,9-bismethylene-bridged calix[6]arene **3** crystallised from acetonitrile/chloroform/water as determined by X-ray analysis. Left: View from below through the calixarene cavity. The *tert*-butyl groups and lattice solvent molecules have been omitted for clarity (50% displacement ellipsoids are shown for C, N and O). Right: Side-view along the A,D-axis. The inverted ring B is clearly visible.

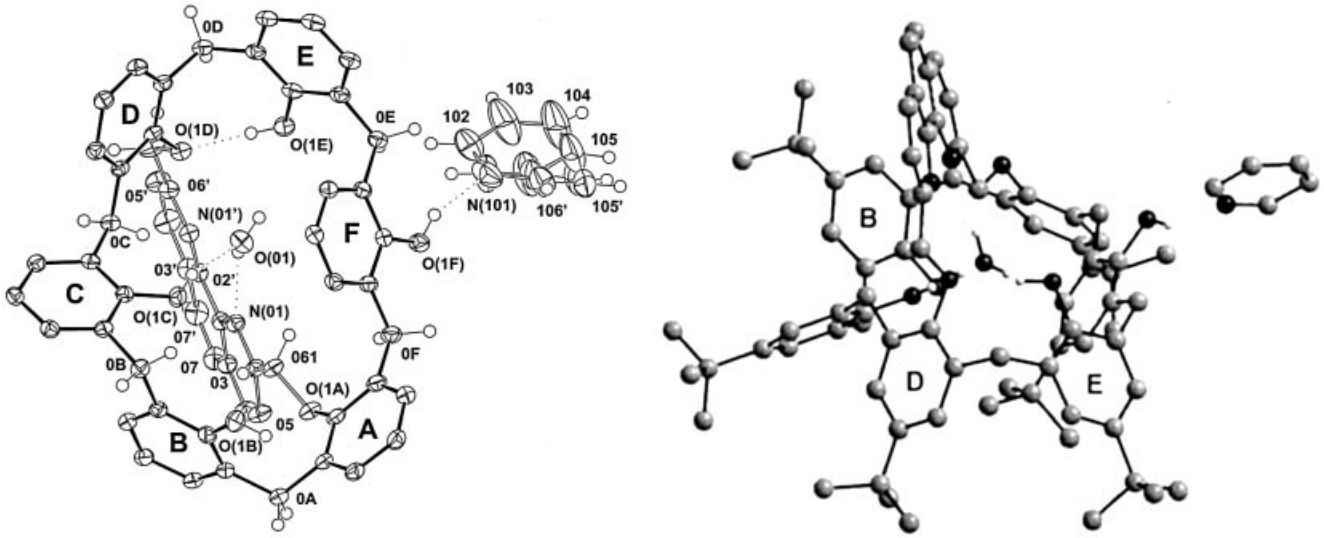


Figure 2. Structure of A,D-1,10-phenanthroline-2,9-bismethylene-bridged calix[6]arene **3** crystallised from pyridine/water as determined by X-ray analysis. Left: View from below through the calixarene cavity. The *tert*-butyl groups and lattice solvent molecules have been omitted for clarity (50% displacement ellipsoids are shown for C, N and O). Right: Side-view along the A,D-axis. The inverted ring B is clearly visible.

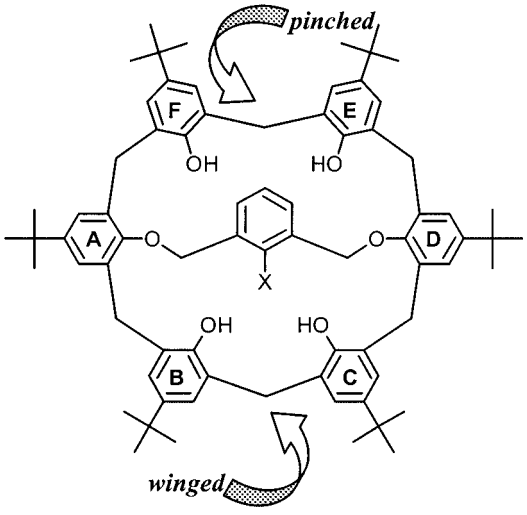


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Figure 3.A,D-xylylene-bridged calix[6]arenes **6** may exist in different conformations concerning the orientation of the methylene groups between the rings B and C, and E and F, respectively. If a CH_2 group points outward, the orientation is called *winged* (*w*), if it points inward, it is called *pinched* (*p*). Here, the *pw* conformation is shown.

ture, which is the time-average of the two conceivable tilted conformers.

– Although the bridge is bent to one side (towards the B and C rings and away from the E and F rings) it still bridges the gap between the A and D rings symmetrically. The bi-macrocycle therefore still possesses a mirror plane (through the methylene groups between the rings B and C, and E and F, respectively, and through the nitrogen atom of the pyridine (or the 2-position of the xylyl unit).

Comparison of the X-ray structure of **3** obtained from acetonitrile/chloroform with the structurally very similar xylyl- and pyridine-bridged analogues reveals some unanticipated differences:

– Not all oxygen atoms are located on the same side of the calix[6]arene macrocycle. Ring B[23] adopts a *down* orientation.

– The bridgehead rings are not forced into an *in* position. The overall conformation is *uduuuu*.

– The altered orientation of the aryl rings also causes a different orientation of the connecting methylene groups. Rather than *in* and *out*,[22] the methylene groups now also adopt *up* and *down* orientations.

– The bridge is still tilted but the centre of the bridge has moved towards ring A. In contrast to the xylylene-bridged calix[6]arene **6** (X = Br), **3** does not possess a mirror plane.

When **3** was crystallised from pyridine, a co-crystal formed which is stabilized by a hydrogen bridge between the OH group of ring F and the pyridine nitrogen atom (see Figure 2). This results in a flip of this aryl ring. The phenol group is now pointing *out*, but remarkably the overall *uduuuu* conformation is conserved. Again, the centre of the bridge is moved along the axis between ring A and D, but in this crystal it is now closer to ring D than to ring A.[23]

The difference between the 1,10-phenanthroline-bridged calix[6]arene **3** and the other bridged calix[6]arenes such as **6** led us to carry out a computational comparison of some of the different possible conformations. Five different starting geometries were chosen and optimised with four different methods: a semi-empirical method (PM3), a DFT method (BP86/SVP) and two force-field calculations [MM3* considering (GB/SA $CHCl_3$) or ignoring chloroform as solvent] (Table 1). In addition to the two conformations found in the crystal structures (solvent molecules omitted), all-*up* conformations, as found for other A,D-

Table 1. Relative energies [kJ mol^{-1}] of different conformers of the 1,10-phenanthroline-bridged calix[6]arene **3**. The geometry optimisation calculations used different starting geometries and utilized four different methods

Starting conformation	PM3	MM3*	*MM3** (GB/SA $CHCl_3$)	BP86/SVP
uduuuu ($CHCl_3/CH_3CN/H_2O$)	28.3	4.4	0.3	22.1
uduuuu (py/H_2O)	15.7	3.4	0.0	25.5
all-*up ww*[a]	0.0	0.0	17.4	9.9
all-*up pw*[a]	9.5	4.2	4.2	5.6
all-*up pp*[a]	25.6	18.0	2.9	0.0

[a] *ww*, *pw*, *pp* (*winged*/*winged*, *pinched*/*winged*, *pinched*/*pinched*); see also Figure 3.

bridged calix[6]arenes, were taken as starting points. Three substructures were considered which differ in the orientation of the two methylene groups between rings B and C, and E and F, respectively: *winged*/*winged*, *pinched*/*winged*, and *pinched*/*pinched* {as found for the bromoxylylene-bridged calix[6]arene **6** (X = Br)[21]}.

The results are puzzling as there is no distinct, most-stable conformation. Depending on the method chosen, other conformers are the most stable ones, but, more interestingly, almost all structures differ by less than 20 kJ mol^{-1}. Therefore, the new *uduuuu* conformer must also be taken into account when discussing the structure of A,D-bridged calix[6]arenes with remaining free OH groups. It may also explain some unexpected results in the low-temperature NMR spectra of the copper(I) complexesof **3**. The spectra of the free ligand **3** and the complex Cu^+·**3** at higher temperatures show only one signal for the *tert*-butyl groups in positions B, C, E and F. The high symmetry of these spectra at elevated temperatures suggests an equilibrium between conformers that are rapidly interconverting on the NMR timescale. At lower temperatures, as the motion of the molecules becomes slower, line broadening in the case of the free ligand, and separation of signals in the case of the copper(I) complex, was observed (Figure 4).

The asymmetry of the NMR spectrum of the copper(I) complex may be interpreted in terms of a conformer in which the 1,10-phenanthroline bridge is tilted, as discussed for the xylylene-bridged compounds. However, the number of signals observed for the copper(I) complex indicates an even higher degree of asymmetry, and an interaction of one of the phenol groups with the copper ion was suggested.[24]

A quick flip of the bridge from the rings B and C to the rings E and F and back, and a quick rocking from A to D and back results in an averaged structure with a high symmetry, as found in the room-temperature spectrum: only the *tert*-butyl groups of the bridgeheads and those of the other four phenol rings can be distinguished from one another. With declining temperature, one or both of these processes will slow down, eventually being slower than the NMR timescale. If the rocking becomes slow whilst the flipping remains quick, the *tert*-butyl group of A would be different from D, and B and F would be different from C and E. If, in contrast, the flipping becomes slow and the rocking is still quick, three signals of equal intensity would be expected (A and D, B and C, and E and F). If both processes become slow or one of the phenols inverts, as seen in the X-ray analyses, all six *tert*-butyl groups would be different.

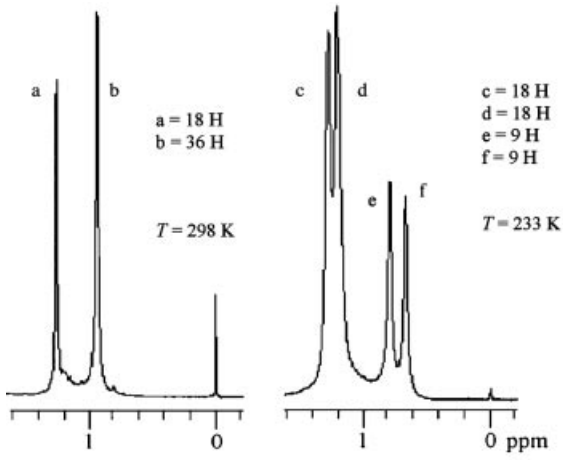

Figure 4.Part of the NMR spectra (500 MHz, CD_2Cl_2/CD_3CN = 10:1) ofthe copper(I) complex (ca. 1.5 equivalents of $[(CH_3CN)_4Cu]PF_6$) of the A,D-1,10-phenanthroline-bridged calix[6]arene **3** at 298 K (left) and at 233 K (right). At room temperature, only the *tert*-butyl groups of the alkylated rings A and D (signal a) are separated from the other four groups (signal b). At 233 K, the *tert*-butyl signals split into four groups, with an intensity distribution of 2:2:1:1 (signals c, d, e and f).

Consequently, up to six signals could be detected, although there is also a chance that the signals are isochronous.

The existence of more than two separate *tert*-butyl signals agrees with a "frozen" structure, and, at first glance, would argue for a slow rocking and a quick flip. However, in the complex with copper(I), the flip should be more hindered by a complexed copper ion than the rocking. Therefore, a copper(I)-stabilized form of the *uduuuu* conformer, as found in the X-ray study of the metal-free ligand **3**, is not unlikely if one assumes that some signals of the *tert*-butyl groups have the same chemical shift by chance. The exact structure of the complex, however, cannot be proven by these experiments, although these results suggest that the new *uduuuu* conformer must also be taken into account when discussing structures of bridged calix[6]arenes.[25]

Experimental Section

General Remarks: All reactions requiring dry solvents were carried out using standard Schlenk techniques under an argon atmosphere. Dry solvents were purchased or obtained by drying with suitable desiccants: DMF (Fluka) and tetrahydrofuran were distilled from lithium aluminium hydride. The following reagents are commer-

cially available and were used without further purification: chlorotriethylsilane (Acros), lithium diisopropylamide (Fluka, 2 M solution in tetrahydrofuran/heptane/ethylbenzene), neocuproine (2,9-dimethyl-1,10-phenanthroline, **4**; Chempur). *tert*-Butylcalix[6]arene (**1**) was synthesised according to a literature procedure.[26] Flash chromatography was carried out on silica (Macherey–Nagel, 0.04–0.063 mesh). All products were characterised by ^{1}H NMR and IR spectroscopy and mass spectrometry. The new compound was further characterised by ^{13}C NMR spectroscopy and elemental analysis. NMR spectra were recorded on Bruker AM 300 (300 MHz) or Bruker DRX 500 (500 MHz) spectrometers with tetramethylsilane as internal standard. IR spectra were obtained with a Perkin–Elmer 1600 Series Fourier Transform spectrometer. Mass spectra were recorded on a Finnigan MAT 8230. The elemental analyses was carried out on a HEKAtech GmbH EA3000CHNS.

2,9-Bis[(triethylsilyl)methyl]-1,10-phenanthroline (5): A solution of neocuproine (**4**; 1.04 g, 5.00 mmol) in dry tetrahydrofuran (20 mL) was cooled to 0 °C under argon. A 2 M solution of lithium diisopropylamide (15.0 mL, 30.0 mmol) was added quickly, the cooling was removed and the reaction mixture was stirred for 1 h at room temperature. Chlorotriethylsilane (1.72 mL, 10.2 mmol) was added and the solution was stirred for another 30 min at room temperature. The reaction was quenched by addition of water (20 mL) while cooling. The organic layer was separated and the aqueous layer was extracted with tetrahydrofuran (2 × 35 mL). The combined organic layer was washed with saturated brine (40 mL), dried with sodium sulfate and the solvent was removed in vacuo. The crude product was purified by flash chromatography (silica deactivated with cyclohexane/triethylamine (5:1); eluent: cyclohexane/ethyl acetate/triethylamine, 100:10:1), to give 1.83 g (84%) of **5**, m.p. 34 °C. IR (KBr): $\tilde{\nu}$ = 2950 cm^{-1} (aliph. C–H), 1589 (arom. C=C), 1489 (aliph. C–H), 849, 750, 731 (arom. C–H). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, J = 8.5 Hz, 2 H, Phen-$H^{4,7}$), 7.59 (s, 2 H, Phen-$H^{5,6}$), 7.28 (d, J = 8.5 Hz, 2 H, Phen-$H^{3,8}$), 2.77 (s, 4 H, CH_2), 0.90 (t, J = 8.2 Hz, 18 H, CH_2CH_3), 0.61 (q, J = 8.2 Hz, 12 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$):δ = 162.0 (Phen-$C^{2,9}$), 145.6 (Phen-$C^{10a,b}$), 135.4 (Phen-$C^{4,7}$), 125.8 (Phen-$C^{4a,6a}$), 124.5 (Phen-$C^{3,8}$), 122.5 (Phen-$C^{5,6}$), 26.8 (Phen-CH_2), 7.3 (Si-CH_2CH_3), 3.3 (Si-CH_2CH_3) ppm. MS (EI, 70 eV): m/z (%) = 436 (38) [M$^+$], 407 (100) [M$^+$ – Et]. $C_{26}H_{40}N_2Si_2$·0.1C_6H_5Et[27] (447.41): calcd. C 71.95, H 9.27, N 6.26; found C 71.89, H 9.41, N 6.04. Due to the sensitivity of the product to heat and acidic conditions it was stored under argon at –18 °C.

2,9-Bis(bromomethyl)-1,10-phenanthroline (2): 2,9-Bis[(triethylsilyl)-methyl]-1,10-phenanthroline (**5**; 1.31 g, 3.00 mmol) was dissolved in dry DMF (15 mL) under argon. Dibromotetrafluoroethane (7.79 g, 30.0 mmol) and caesium fluoride (1.81 g, 12.0 mmol, previously dried for 2 h at 100 °C in vacuo) were added and the reaction mixture was sonicated for 2 h. Unreacted dibromotetrafluoroethane was removed in vacuo. The residue was cooled to 0 °C and water (25 mL) was added while stirring vigorously. The precipitate was filtered off and dried in vacuo. The crude product was purified by flash chromatography (silica; eluent: dichloromethane/ethyl acetate/ethanol, 20:4:1), to give 780 mg (71%) of **2**, m.p. 171 °C (dec.). The obtained spectra were in accordance with those reported previously.[11]

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,40,41-tetrahydroxy-39,42-bis[2,9-(1,10-phenanthroline)diylbis(methylenoxy)]calix[6]arene (3): Under nitrogen, *p*-*tert*-butylcalix[6]arene (**1**; 2.42 g, 2.49 mmol) and potassium carbonate (8.00 g, 58.0 mmol) were stirred under reflux in a mixture of dry THF (250 mL) and dry DMF (25 mL). After 30 min, the mixture was allowed to cool to room temperature and a solution of 2,9-bis(bromomethyl)-1,10-phenanthroline (**2**; 1.00 g, 2.74 mmol) in tetrahydrofuran (50 mL) was added dropwise within 30 min. The mixture was stirred for 15 h. The yellow turbid solution was neutralised with 1 M hydrochloric acid and the solvents were removed in vacuo. The residue was dissolved in dichloromethane (100 mL), the organic layer washed with sodium hydrogencarbonate solution (30 mL) and water (2 × 30 mL) and the aqueous layer was extracted with dichloromethane (30 mL). The combined organic layer was dried with magnesium sulfate and the solvent removed in vacuo. The crude product was purified by column chromatography (silica; eluent: cyclohexane/ethyl acetate, 1:1) and recrystallised from dichloromethane/acetonitrile to yield 1.82 g (62%) of **3**. Identity and purity were verified by ^{1}H NMR spectroscopy.[16]

X-ray Analyses of 3: Full spheres of CCD area-detector diffractometer data were measured (Bruker AXS instrument, ω-scans, monochromatic Mo-K_α radiation, λ = 0.71073 Å; $T \approx$ 153 K) yielding $N_{t(otal)}$ reflections, merging to N unique (R_{int} quoted) after "empirical"/multiscan absorption correction, N_0 with $F > 4\sigma(F)$ being used in the large-block, least-squares refinement [non-hydrogen atom thermal parameters refined; (x, y, z, $U_{iso})_H$ treatment as specified; reflection weights: $[\sigma^2(F) + 0.0004\,F^2]^{-1}$; solvent residues modelled as specified].

3, Recrystallised from Acetonitrile/Chloroform: [(H_2O)·**3**·(CH_3CN)]·$CHCl_3$·1.5CH_3CN = $C_{86}H_{102.5}Cl_3N_{4.5}O_7$, M_r = 1417.7. Monoclinic, $C2/c$, a = 34.290(2), b = 26.038(2), c = 19.752(1) Å, β = 111.686(1)°, V = 16387 Å^3. D_c (Z = 8) = 1.149 g cm^{-3}. μ_{Mo} = 1.66 mm^{-1}; specimen 0.45 × 0.35 × 0.22 mm; $T_{min,max}$ = 0.81, 0.96. $2\theta_{max}$ = 75°; N_t = 80 008, N = 14 396 (R_{int} = 0.038), N_0 = 10 334; R = 0.069, R_w = 0.082; $|\Delta\rho_{max}|$ = 1.39(2) e Å^{-3}. (x, y, z, $U_{iso})_H$ were constrained at estimates throughout, except those for the hydroxylic hydrogen atoms, which were refined. *tert*-Butyl 54 was modelled as rotationally disordered about its pendent bond over two sets of sites, with occupancies of 0.5. The non-included solvent molecules were also modelled as disordered.

3, Recrystallised from Pyridine: [(H_2O)·**3**·(py)]·0.5 py = $C_{87.5}H_{101.5}N_{3.5}O_7$, M_r = 1314.3. Triclinic, $P\bar{1}$, a = 13.083(2), b = 13.919(2), c = 22.641(3) Å, α = 75.265(3)°, β = 80.051(3)°, γ = 73.451(3)°, V = 3800 Å^3. D_c (Z = 2) = 1.149 g cm^{-3}. μ_{Mo} = 0.072 mm^{-1}; specimen 0.65 × 0.25 × 0.15 mm; $T_{min,max}$ = 0.85, 0.96. $2\theta_{max}$ = 68°; N_t = 78 279, N = 19 988 (R_{int} = 0.037), N_0 = 14233; R = 0.051, R_w = 0.059; $|\Delta\rho_{max}|$ = 0.58(3) e Å^{-3}. (x, y, z, $U_{iso})_H$ were refined in the substrate (and associated water) molecule except in *tert*-butyl 44, which was modelled as rotationally disordered about its pendent bond over two sets of sites, with occupancies 0.5; (x, y, z, $U_{iso})_H$ were constrained at estimates for the other entities. Pyridine py(1) was modelled as disordered about its nitrogen atom, lattice py(2) being disordered about a crystallographic inversion centre located at its centroid.

CCDC-262029 and -262030 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Computations: All calculations were performed with an AMD-Athlon processor running under a Suse Linux 7.1 distribution. To preserve as much information as possible from the original X-ray structure analysis, both *uduuuu* geometries (see Figure 1 and Figure 2) were chosen as starting conformations (after removal of solvent molecules) for a semi-empirical PM3optimisation using the Gaussian 98 program.[28] To allow a comparison with other conformations, three idealised all-*up* conformations (*pp*, *pw*, *ww*) were generated (with the aid of the Hyperchem software package[29] and

ACD/ChemSketch[30]) and were also PM3 optimised. The geometries gained from these PM3 calculations were then used for the following density-functional and force-field calculations. The density-functional calculations were carried out at the BP86/SDD level, using the RI (resolution of identity) approximation[31,32] as implemented in TURBOMOLE.[33] The molecular mechanics calculations were carried out with the MacroModel software package (version 7.1)[34] using the MM3* force field (with and without use of the solvent option for chloroform).

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