# Tetra-urea calix[4]arenes 1,3-bridged at the narrow rim†

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The synthesis of special tetra-urea calix[4]arene derivatives is described. Two propyl ether groups in 1,3-position and a 5-iodo-isophthalamide bridge connecting two aminopropylether residues in 2,4-position at the narrow rim keep the molecule fixed in the cone conformation. The aryl urea residues are substituted by decyloxy groups in *p*-position to increase the solubility in apolar solvents, while the iodo substituent allows further functionalization. Two single crystal X-ray structures of **3** and **4** show a strongly pinched cone conformation in which the bridged phenol units are bent outwards, while the phenol units bearing the propyl ether groups are nearly parallel. The molecules are flexible enough, however, to form hydrogen bonded dimeric capsules in apolar solvents. Their (time averaged) $D_2$ conformation is confirmed by $^1$H NMR spectroscopy.

## Introduction

Calix[4]arenes substituted at their wide rim by four (aryl) urea groups form dimeric capsules in aprotic, apolar solvents.[1] The two calixarenes, turned by 45° around their common axis relative to each other, are held together by a seam of intermolecular hydrogen bonds between the urea functions.

The stability of these dimers has been characterized in various ways.[2] Association constants cannot be obtained from equilibrium concentrations due to their extreme values. Kinetic studies under high dilution (0.05–0.5 μM) by fluorescence resonance energy transfer (FRET) gave association and dissociation rates from which association constants (up to $K_A = 10^9$ $M^{-1}$) have been derived.[3] Rates for the guest exchange against the solvent have been used to characterize the (kinetic) stability with respect to the structure of the capsule, the included guest and to the solvent.[4]

The rapid development of atomic force microscopy (AFM) makes it possible meanwhile to study the mechanical strength of covalent bonds within a molecule or even of weaker forces between molecules. We recently described such AFM studies with dimers of tetra-urea calix[4]arenes.[5] In these experiments the stretching forces were applied between two ether functions (one per each calixarene of the capsular dimer). The corresponding tetra-urea calix[4]arenes with ***one*** functionalized ether group at the narrow rim are readily prepared, although a multistep synthesis is required.[6] Geometrically, however, this attachment has some fundamental disadvantages. The pulling forces are not exerted "colinear" with the molecular axis and there are two "regioisomeric" possibilities for the attack. The stretching of a single capsule may involve two adjacent or two remote phenolic units in the two calix[4]arenes.[7]

From this point of view, an attachment in the middle of a bow connecting the phenolic oxygens in 1,3-position would be better. With this background we started the synthesis of tetra-urea calix[4]arenes bridged by a handle based on 5-iodo-isophthalic acid, where the iodo atom should allow further functionalization by Suzuki or Sonogashira cross-coupling and the attachment *e.g.* to the cantilever of an AFM tip.

## Syntheses

The synthesis requires the independent acylation of two amino functions attached in 1,3-position at the narrow rim *via* propylether linkers, and the acylation of the four amino groups at the wide rim to introduce the four urea groups. Starting with the known 1,3-phthalimido derivative **1**,[8] in which the calix[4]arene is fixed already in the cone-conformation by the four ether residues, two pathways may be envisaged for the synthesis of the target tetra-urea calix[4]arene **11** (Fig. 1). They differ mainly by the moment where the iodo-isophthalimide bridge is introduced. This macrocyclization may be carried out before or after the introduction of the urea functions.

The first strategy involves hydrazinolysis of **1** to diamine **2** (75% yield) and subsequent acylation under high dilution conditions by 5-iodo-isophthalic acid dichloride in dichloromethane solution in the presence of *i*-$Pr_2$EtN as base.[9] The bridged product **3** was isolated with 14% yield after purification by column chromatography. *ipso*-Nitration of the compound **3** gave the hardly soluble tetranitro compound **4**. The structure of calixarenes **3** and **4** was confirmed by X-ray analysis. The low yield in the bridging step and the separation difficulties of the product mixture derived from compound **4** after hydrogenation forced us, however, to try the second strategy.

The di-*N*-phthalimidopropyl calixarene **1** was *ipso*-nitrated as published[8] and the phthalimido groups were cleaved from compound **5** by reflux with hydrazine–ethanol to produce the corresponding diamine **6** in 87% yield. (The acylation of **6** by 5-iodo-isophthalic acid dichloride has been attempted, however, the cyclic diamide **4** could not be isolated from the reaction mixture.)

The diamine **6** was *N*-Boc-protected to produce compound **7** (98% yield). The replacement of the phthalimide by the Boc protective group in steps (i) and (iv) is necessary, since urea

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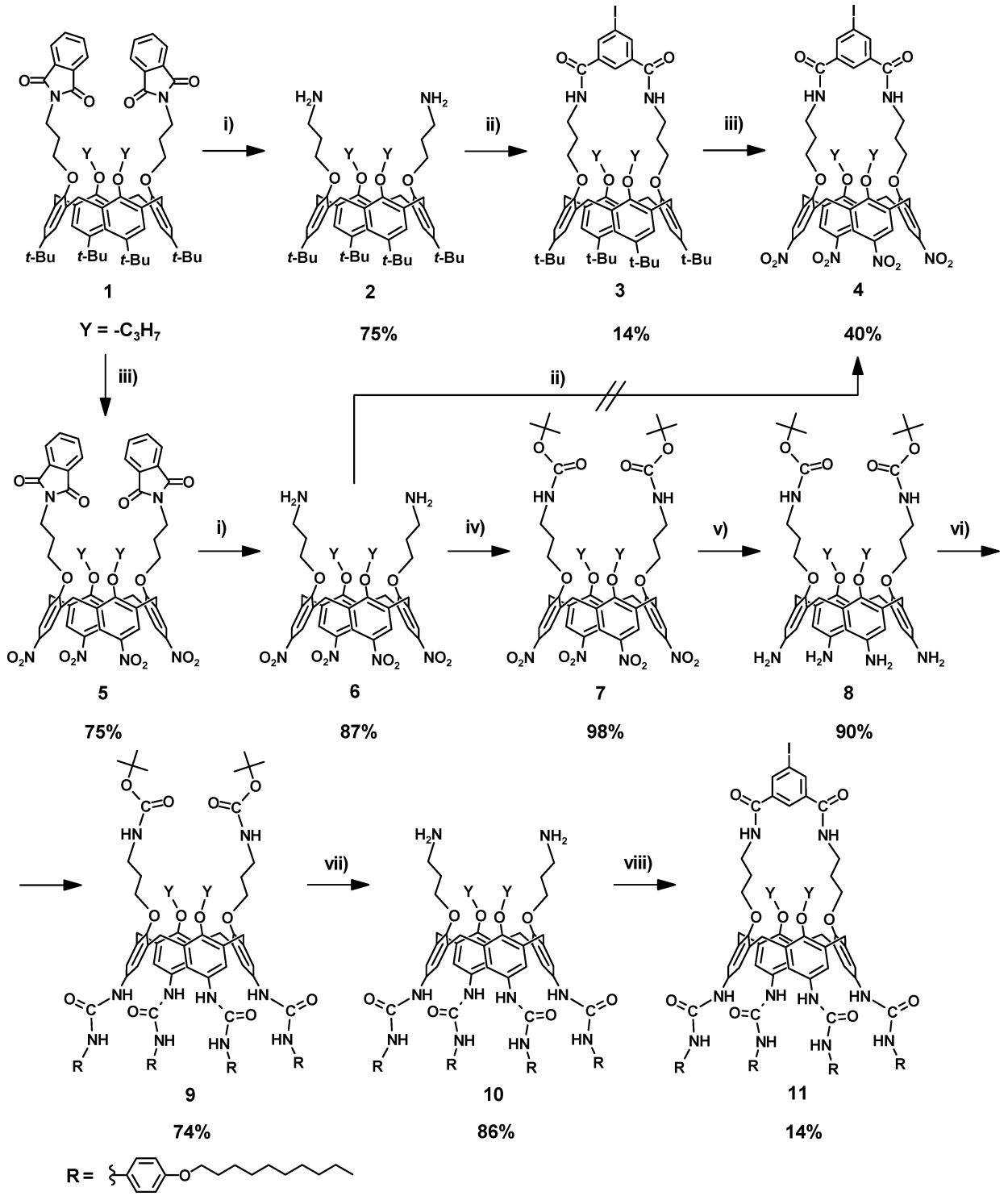


**Fig. 1** (i) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux; (ii) 5-iodo-isophthalic acid dichloride, *i*-$Pr_2EtN$, $CH_2Cl_2$; (iii) $HNO_3$–HOAc, $CH_2Cl_2$; (iv) $Boc_2O$, THF; (v) $H_2$, Raney-Ni, toluene; (vi) *p*-nitrophenyl urethane of *p*-*n*-decyloxyaniline, *i*-$Pr_2EtN$, THF; (vii) $CF_3COOH$, $CH_2Cl_2$; (viii) 5-iodo-isophthalic acid, *i*-$Pr_2EtN$, PyBOP, DMF.

groups could be destroyed under the conditions necessary for the phthalimide-cleavage. The resulting tetranitro **7** was hydrogenated in toluene using Raney-Ni as catalyst (90%) and the tetraamine **8** was acylated by *p*-nitrophenyl urethane of *p*-*n*-decyloxyaniline (74%).

The Boc-groups were cleaved from tetra-urea **9** by trifluoroacetic acid (86%) and the diamino tetra-urea **10** was acylated by 5-iodo-isophthalic acid in the presence of PyBOP in DMF to produce compound **11**, isolated in 14% yield, after purification by column chromatography.

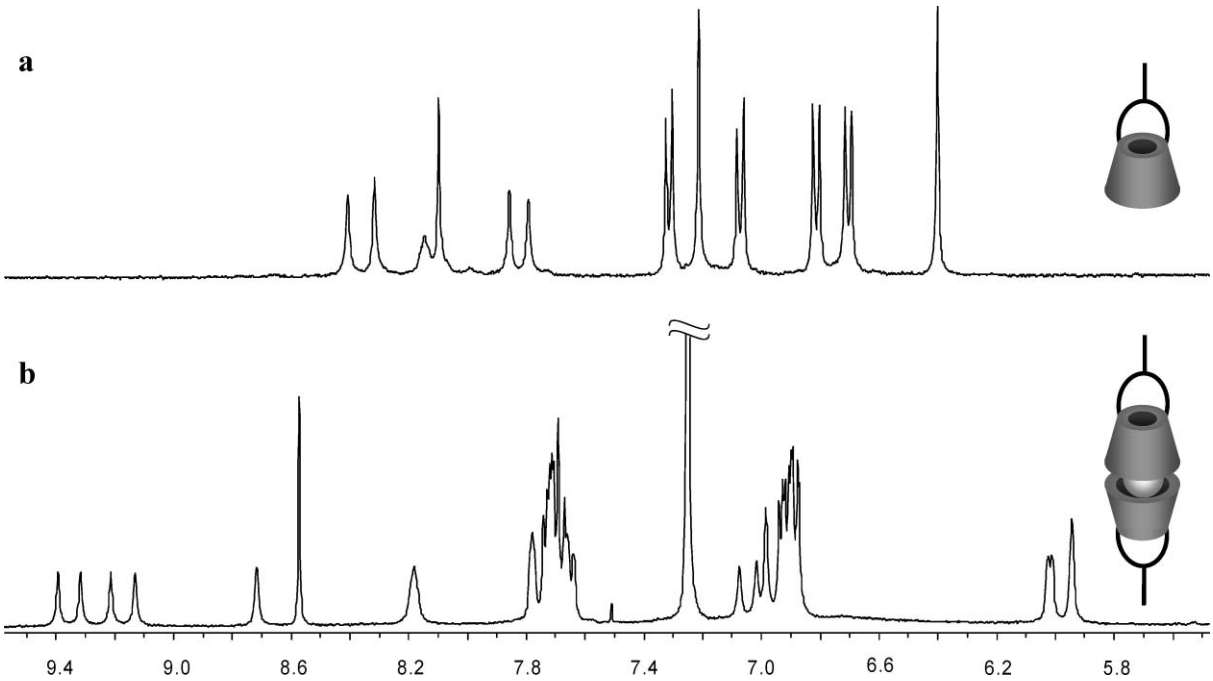


**Fig. 2** Parts of $^1$H NMR spectra of calixarene **11** (a) in DMSO-$d_6$, rt; (b) in $CDCl_3$, rt.

## Self-organization of narrow rim-bridged tetra-urea

In polar solvents like DMSO, tetra-urea **11** displays a $^1$H NMR spectrum corresponding to a $C_{2v}$ symmetrical molecule (Fig. 2a): two singlets at 6.43 and 7.24 ppm for the aryl protons of the calixarene skeleton; two pairs of doublets at 6.73, 6.84, 7.10 and 7.34 ppm for the aryl protons adjacent to the urea functions; four singlets at 7.82, 8.17, 8.34 and 8.43 ppm in the ratio 1 : 1 : 1 : 1 for NH protons of the urea groups; two triplets at 3.90 and 3.83 ppm for –$OCH_2$– protons of the decyloxy groups attached to the phenyl rings adjacent to urea groups.

The splitting of the signals for –$OCH_2$– protons of decyloxy groups together with the large difference in shifts of the signals for the aromatic protons (for singlets of calixarene skeleton $\Delta\delta =$ 0.81 ppm) and for protons of the urea groups suggest a *pinched cone* conformation of the molecule (compare also the crystal structures of compounds **3** and **4**). This is the typical conformation for tetraethers of calix[4]arenes, which exist in solution in equilibrium between two pinched cone conformations.

The formation of hydrogen bonded, dimeric capsules requires a $C_4$-symmetrical conformation of the two tetra-urea calix[4]arenes. If the energy gain of their $C_{2v}$-symmetrical pinched cone conformation is too large, the formation of dimers may be impossible. However, in apolar solvents the bridged **11** forms capsule-like dimers similarly to normal "open chain" tetra-ureas. This calix[4]arene can be classified as a tetra-urea of the ABAB-type.[7] Such a dimer has $D_2$ symmetry and is chiral only due to the arrangement of the two achiral calixarenes. This type of chirality may be referred to as *supramolecular chirality.* It is worth noting that the directionality of the hydrogen bonded belt does not create additional stereoisomers, but just reduces the symmetry of the capsule to $C_2$.

In its $^1$H NMR-spectrum the $C_2$ symmetry of the assembly is reflected by an additional splitting of the signals (Fig. 2b): four singlets in the ratio 1 : 1 : 1 : 1 for downfield shifted NH protons of the urea groups (9.39, 9.31, 9.21 and 9.13 ppm); four pairs of *m*-coupled doublets for protons of the aryl groups of the calixarene skeleton, among them four doublets shifted upfield (6.03, 6.01 and two signals overlapped at 5.94 ppm) and four doublets shifted downfield (two signals overlapped at 8.18 ppm and two signals overlapped at 7.78 ppm).

## Crystal structures

Single crystals for the bridged compounds **3** and **4** were obtained by slow evaporation of their solutions in methylene chloride–ethylacetate–methanol and THF–methanol, respectively. In spite of their structural difference (unpolar *t*-butyl *vs.* polar nitro groups) and the different (and different amount of) solvent included in the crystal lattice, the molecular conformations of both compounds are rather similar.

Fig. 3 shows both molecules from two different perspectives. Typical data (distances and angles) are collected in Table 1. In both cases the molecule is found in a strongly pinched cone conformation. The phenolic units I and III of the calix[4]arene which are connected by the isophthalamide bridge are strongly bent outwards and nearly perpendicular to each other in molecule **3**. In compound **4** they include an angle (79.5°) distinctly lower than 90°. The non connected propylphenylether units (II/IV) are nearly parallel in **3** (including an angle of 5.4°), while both are bent inwards in **4**, with an interplanar angle of 14.4°. For further details see Fig. 3, 4 and Table 2.

The iodo-isophthalyl fragment is practically planar in both structures and oriented perpendicular (89.62°) to the reference plane in **3**. In **4**, however, it is considerably inclined by nearly 18°, most probably due to "packing effects". No strain occurs in the –O–C–C–C– chains connecting the bridge to the metacyclophane skeleton, since all torsion angles are in the range of 177.5–180.0°.

 

**Table 1** Comparison of typical crystal data of compounds **3** and **4**

| Compound | **3** (t-Bu) | **4** ($NO_2$) |
|---|---|---|
| Distance/Å | | |
| O1–O2 | 3.334 | 3.189 |
| O2–O3 | 3.247 | 3.612 |
| O3–O4 | 3.211 | 3.018 |
| O4–O1 | 3.187 | 3.633 |
| O1[a]–O3[a] | 3.597 | 3.682 |
| O2–O4 | 5.373 | 5.632 |
| C15[b]–C35[b] | 9.454 | 9.848 |
| C25[b]–C45[b] | 5.606 | 4.544 |
| $C_{BP}$–RP | 6.582 | 6.553 |
| $C_{BP}$–O2 | 6.018 | 6.192 |
| $C_{BP}$–O4 | 5.712 | 5.763 |
| $O_{(water)}$–$N_{(amide)}$ | 3.062/3.063 | 3.127/3.127 |
| $O_{(water)}$–$C_{BP}$ | 3.131 | 3.256 |
| $O_{(water)}$–RP | 4.024 | 4.057 |
| $O_{(water)}$–BP | 1.178 | 1.217 |
| Angles/° | | |
| RP–Ar1 | 133.8 | 136.6 |
| RP–Ar3 | 135.1 | 143. 9 |
| Ar1–Ar3 | 88.88 | 79.48 |
| RP–Ar2 | 88.16[c] | 84.01[c] |
| RP–Ar4 | 97.26 | 81.70[c] |
| Ar2–Ar4 | 5.43 | 14.40 |
| RP–BP | 89.62 | 72.29 |

[a] Oxygens connected by the bridge. [b] C-atoms in *p*-position of the calixarene rings Ar1 to Ar4. [c] Values <90° indicate that the aromatic ring is bent into the cavity. RP = reference plane (defined by the methylene bridge carbons). BP = bow plane (defined by 6 aromatic carbons).

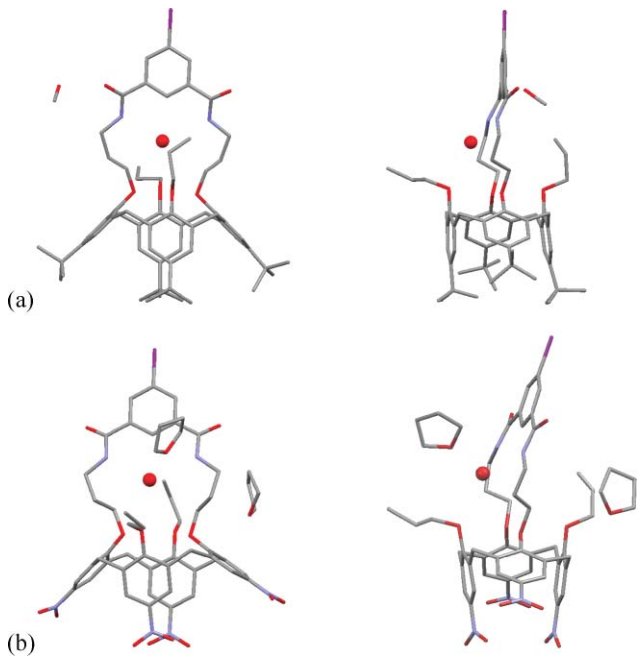


**Fig. 3** The molecular conformation of **3** (a) and of **4** (b) found in the crystal structure of **3**·$H_2O$·MeOH and **4**·$H_2O$·2THF, respectively, seen from two directions.

Both crystals were obtained from non aqueous solvent mixtures, although not under strictly anhydrous conditions. Nevertheless, one molecule of water is incorporated in both cases, which is hydrogen bonded by both NH-groups. Therefore the distance between the water oxygen and both amide nitrogens is identical, 3.063 Å for **3** and 3.127 Å for **4**. For both structures the distance

**Table 2** Summary of crystallographic data

| Compound | **3** (t-Bu) | **4** ($NO_2$) |
|---|---|---|
| | $C_{64}H_{83}IN_2O_6$·$CH_3OH$·$H_2O$ | $C_{48}H_{47}IN_6O_{14}$·$2C_4H_8O$·$H_2O$ |
| M | 1153.28 | 1221.04 |
| T, K | 173 | 173 |
| Crystal system | Orthorhombic | Monoclinic |
| Space group | $P\,2_12_12_1$ | $P\,2_1/n$ |
| *a*, Å | 11.2099(5) | 13.2687(5) |
| *b*, Å | 15.8759(6) | 13.5843(4) |
| *c*, Å | 35.5340(15) | 31.5174(12) |
| $\alpha$, ° | 90 | 90 |
| $\beta$, ° | 90 | 94.788(3) |
| $\gamma$, ° | 90 | 90 |
| *V*, Å$^3$ | 6323.9(5) | 5661.1(3) |
| *Z* | 4 | 4 |
| Reflections | 35791 | 58800 |
| Unique reflections | 11121 | 10402 |
| Final *R* indices [$I > 2\sigma(I)$], *R*1, w*R*2 | 0.0387, 0.1059 | 0.0352, 0.0918 |
| *R* indices (all data), *R*1, w*R*2 | 0.0411, 0.1082 | 0.0429, 0.0952 |
| CCDC deposition number | 706486 | 706487 |

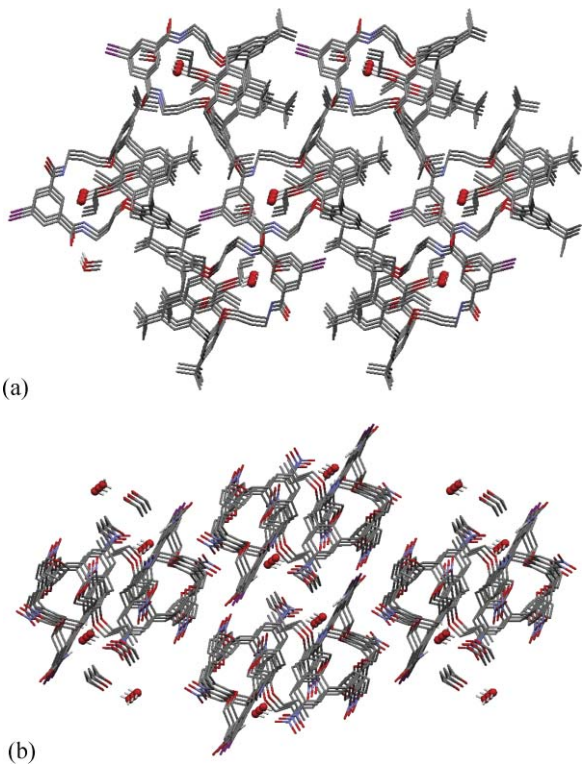


**Fig. 4** Packing of the molecules **3** seen along the a-axis (a) and of the molecules **4** seen along the b-axis (b).

to the reference plane (defined by the methylene bridge carbon atoms of the calix[4]arene skeleton) is also very similar, 4.025 Å for **3** and 4.057 Å for **4**, and the same is true for the distance to the isophthalyl plane (1.178 Å and 1.217 Å). Obviously this water molecule occupies the same place, filling a gap in the crystal lattice, which otherwise cannot be formed. Since both crystals were grown from methanol containing solvent mixtures, it may be concluded that the methanol molecule is already too large to be incorporated here.

## Experimental

$^1$H NMR spectra were recorded on a Bruker DRX400 Avance instrument (at 400 MHz). FD and ESI mass spectra were measured on a Finnigan MAT 8230 spectrometer and a Micromass Q-ToF Ultima3 instrument, respectively. Melting points are uncorrected. Tetra-*tert*-butyl- and tetranitrocalix[4]arene 1,3-dipropyl-2,4-diphthalimidopropyl ethers **2** and **5** were prepared as described.[8]

### Calix[4]arene 3

5-Iodo-isophthalic acid (0.178 g, 0.608 mmol) and oxalyl chloride (0.435 g, 3.42 mmol) were mixed in toluene (10 ml), 1 drop of DMF was added and the reaction mixture was stirred for 4 h at 60 °C. Then it was cooled to room temperature, the liquid was decanted and the solvent was completely removed by evaporation in vacuum leaving an oil which slowly crystallized in the fridge.[10] The product was dissolved in dichloromethane (200 ml). A solution of calixarene diamine **2** (0.515 g, 0.608 mmol) and *i*-Pr$_2$EtN (0.236 g, 1.82 mmol) in dichloromethane (200 ml) was prepared. Both solutions were added dropwise with stirring to dichloromethane (150 ml). After 24 h the solvent was evaporated and the residue was passed through the column (silica, THF–$CH_2Cl_2$, 1 : 30) to yield the product (0.093 g, 14%) as a white powder; mp >290 °C (decomp.); $\delta_H$ ($CDCl_3$) 8.53 (2 H, s, Ar-*H*), 8.50 (1 H, s, Ar-*H*), 7.58 (2 H, s, N-*H*), 7.13 (4 H, s, Ar-*H*), 6.58 (4 H, s, Ar-*H*), 4.38 (4 H, d, $^2J_{HH}$ 12.3 Hz, Ar-C$H_2$-Ar), 4.33 (4 H, br.t, $^3J_{HH}$ 7.3 Hz, -O-C$H_2$-), 3.68 (4 H, t, $^3J_{HH}$ 7.5 Hz, -O-C$H_2$-), 3.57–3.49 (4 H, m, -NH-C$H_2$-), 3.18 (4 H, d, $^2J_{HH}$ 12.3 Hz, Ar-C$H_2$-Ar), 2.25–2.13 (4 H, m, -NH-CH$_2$-C$H_2$-), 1.89–1.79 (4 H, m, -O-CH$_2$-C$H_2$-), 1.32 (18 H, s, -C$H_3$), 0.88 (6 H, t, $^3J_{HH}$ 7.3 Hz, -C$H_3$), 0.83 (18 H, s, -C$H_3$); MS (FD): *m/z* 1103.3 (M$^+$, 100%), required 1103.3.

### Calix[4]arene 4

Glacial acetic acid (1.0 ml) and fuming nitric acid (1.6 ml) were added to a solution of the bridged calixarene **3** (0.132 g, 0.120 mmol) in dichloromethane (25 ml). The mixture was stirred for 2 h, then quenched by the addition of water. A precipitate was formed and the water layer was decanted. The suspension in dichloromethane was washed additionally with water (3 × 100 ml). Finally, the solvent was evaporated from the suspension and the residue was dried by azeotropic distillation of added toluene. Recrystallization of the residue in dichloromethane gave the product (0.050 g, 39%) as yellowish powder; mp >240 °C (decomp.); $\delta_H$ (DMSO-d$_6$) 8.45 (4 H, s, Ar-*H*), 8.21 (2 H, s, N-*H*), 8.12 (2 H, s, Ar-*H*), 8.07 (1 H, s, Ar-*H*), 6.89 (4 H, s, Ar-*H*), 4.55–4.42 (4 H, m, -O-C$H_2$-), 4.35 (4 H, d, $^2J_{HH}$ 13.6 Hz, Ar-C$H_2$-Ar), 3.76–3.59 (8 H, m, -O-C$H_2$-, Ar-C$H_2$-Ar), 3.43–3.33 (4 H, m, -NH-C$H_2$-), 1.87–1.73 (4 H, m, -NH-CH$_2$-C$H_2$-), 1.67–1.54 (4 H, m, -O-CH$_2$-C$H_2$-), 0.74 (6 H, t, $^3J_{HH}$ 7.3 Hz, -C$H_3$).

### Calix[4]arene 6

Hydrazine hydrate (60 ml) was added to a stirred suspension of calix[4]arene **5** (7.47 g, 7.03 mmol) in ethanol (240 ml). The reaction mixture was refluxed for 2 hours, then cooled to room temperature and left for 2 hours in the fridge. The precipitate was filtered off, washed with ethanol (2 × 50 ml) and dried (in high vacuum) to give the product as a 1 : 1 complex with ethanol (4.85 g, 86%) as yellow powder which was used for the next step; mp >165 °C (decomp.); $\delta_H$ (DMSO-d$_6$) 7.79 (4 H, s, Ar-*H*), 7.51 (4 H, s, Ar-*H*), 4.39 (4 H, d, $^2J_{HH}$ 13.7 Hz, Ar-C$H_2$-Ar), 4.04 (4 H, t, $^3J_{HH}$ 6.8 Hz, -O-C$H_2$-), 3.99 (4 H, t, $^3J_{HH}$ 7.3 Hz, -O-C$H_2$-), 3.69 (4 H, d, $^2J_{HH}$ 13.7 Hz, Ar-C$H_2$-Ar), 3.54–2.92 (10 H, m, -O-C$H_2$-CH$_3$, N-$H_2$), 2.71 (4 H, t $^3J_{HH}$ 6.6 Hz, NH$_2$-C$H_2$-,), 1.98–1.78 (8 H, m, -NH-CH$_2$-C$H_2$-, -O-CH$_2$-C$H_2$-), 1.05 (3 H, t, $^3J_{HH}$ 7.1 Hz, -C$H_3$), 0.96 (6 H, t, $^3J_{HH}$ 7.3 Hz, -C$H_3$); for a sample obtained by evaporation from acetone: $\delta_H$ (DMSO-d$_6$) 7.95 (4 H, s, Ar-*H*), 7.38 (4 H, s, Ar-*H*), 4.36 (4 H, d, $^2J_{HH}$ 13.9 Hz, Ar-C$H_2$-Ar), 4.28–3.38 (10 H, m, -N-$H_2$, -O-C$H_2$-), 3.70 (4 H, d, $^2J_{HH}$ 13.9 Hz, Ar-C$H_2$-Ar), 2.88 (4 H, t, $^3J_{HH}$ 7.1 Hz, NH$_2$-C$H_2$-), 2.04 (4 H, m, -C$H_2$), 1.91–1.78 (4 H, m, -C$H_2$), 0.93 (6 H, t, $^3J_{HH}$ 8.1 Hz, -C$H_3$); MS (ESI): *m/z* 803.4 (M + H$^+$, 100%), required 803.8.

### Calix[4]arene 7

Boc anhydride (1.07 g, 4.91 mmol) was added to a solution of calix[4]arene **6**·ethanol (1.89 g, 2.23 mmol) in THF (30 ml) and the reaction mixture was stirred at rt for 12 h. Then the solvent was evaporated and the oily residue was reprecipitated from dichloromethane–hexane to give the pure product (2.19 g, 98%) as white powder; mp >125 °C (decomp.); $\delta_H$ (DMSO-d$_6$) 7.78 (4 H, s, Ar-*H*), 7.50 (4 H, s, Ar-*H*), 6.92 (2 H, br.t, N-*H*), 4.37 (4 H, d, $^2J_{HH}$ 13.7 Hz, Ar-C$H_2$-Ar), 4.00 (4 H, t, $^3J_{HH}$ 7.6 Hz, -O-C$H_2$-), 3.95 (4 H, t, $^3J_{HH}$ 6.6 Hz, -O-C$H_2$-), 3.68 (4 H, d, $^2J_{HH}$ 14.2 Hz, Ar-C$H_2$-Ar), 3.18–3.05 (4 H, m, NH-C$H_2$-), 2.04–1.92 (4 H, m, -NH-CH$_2$-C$H_2$-), 1.92–1.79 (4 H, m, -O-CH$_2$-C$H_2$-), 1.37 (18 H, s, -C$H_3$), 0.94 (6 H, t, $^3J_{HH}$ 7.3 Hz, -C$H_3$).

### Calix[4]arene 8

A solution of calix[4]arene **7** (1.86 g, 1.85 mmol) in toluene (100 ml) was vigorously stirred under hydrogen at rt in the presence of a catalytic amount of Raney-Ni for 5–6 hours (the conversion was controlled by TLC). Then the catalyst was filtered off and the solvent was removed in vacuum. The oily residue was reprecipitated from chloroform–hexane to give the tetraamino product (1.49 g, 90%) in appropriate purity as white powder; mp >125 °C (decomp.); $\delta_H$ (DMSO-d$_6$) 6.78 (2 H, br.t, N-*H*), 5.97 (4 H, s, Ar-*H*), 5.92 (4 H, s, Ar-*H*), 4.34–4.03 (12 H, m, N-$H_2$, Ar-C$H_2$-Ar), 3.80–3.53 (8 H, m, -O-C$H_2$-), 3.13–2.96 (4 H, m, NH-C$H_2$-), 2.77 (4 H, d, $^2J_{HH}$ 12.7 Hz, Ar-C$H_2$-Ar), 2.12–1.70 (8 H, m, -NH-CH$_2$-C$H_2$-, -O-CH$_2$-C$H_2$-), 1.38 (18 H, s, -C$H_3$), 0.89 (6 H, t, $^3J_{HH}$ 7.3 Hz, -C$H_3$); $\delta_H$ ($CDCl_3$) 6.22 (4 H, s, Ar-*H*), 5.87 (4 H, s, Ar-*H*), 5.00 (2 H, br.s, N-*H*), 4.24 (4 H, d, $^2J_{HH}$ 13.3 Hz, Ar-C$H_2$-Ar), 3.84 (4 H, t, -O-C$H_2$-), 3.63 (4 H, br.t, -O-C$H_2$-), 3.28–3.10 (4 H, m, NH-C$H_2$-), 2.77 (12 H, m, N-$H_2$, Ar-C$H_2$-Ar), 2.06 (4 H, br.s, -NH-CH$_2$-C$H_2$-), 1.90–1.69 (4 H, m, -O-CH$_2$-C$H_2$-), 1.44 (18 H, s, -C$H_3$), 0.95 (6 H, t, $^3J_{HH}$ 7.3 Hz, -C$H_3$); MS (FD): *m/z* 882.7 (M$^+$, 100%), required 883.1.

### Calix[4]arene 9

A solution of tetraamine **8** (0.515 g, 0.580 mmol) and *i*-Pr$_2$EtN (0.315 g, 2.44 mmol) in THF (10 ml) was added to the solution of N-(*p*-decyloxyphenyl) *p*-nitrophenyl carbamate (1.02 g, 2.44 mmol) in THF (10 ml). The reaction mixture was stirred at

 

rt for 12 h, acetonitrile (60 ml) was added, and the stirring was continued for further 12 h. During this time a solid precipitated which was filtered off and washed thoroughly with acetonitrile to give the product (0.856 g, 74%) as a beige powder; mp >170 °C (decomp.); $\delta_H$ (DMSO-$d_6$) 8.26–7.95 (8 H, m, N-*H*), 7.31–7.12 (8 H, m, Ar-*H*), 6.95–6.64 (18 H, m, N-*H*, Ar-*H*), 4.32 (4 H, d, $^2J_{HH}$ 12.2 Hz, Ar-C*H*$_2$-Ar), 3.99–3.65 (16 H, m, -O-C*H*$_2$-), 3.18–2.97 (8 H, m, -NH-C*H*$_2$-, Ar-C*H*$_2$-Ar), 2.05 (4 H, m, -NH-CH$_2$-C*H*$_2$-), 1.98–1.82 (4 H, m, -C*H*$_2$-), 1.74–1.57 (8 H, m, -O-CH$_2$-C*H*$_2$-), 1.49–1.13 (74 H, m, -C*H*$_3$, -C*H*$_2$-), 0.95 (6 H, t, $^3J_{HH}$ 7.3 Hz, -C*H*$_3$), 0.85 (12 H, br.t, -C*H*$_3$); MS (ESI): *m/z* 2007.4 (M + Na$^+$, 69%), required 2007.7.

### Calix[4]arene 10

Trifluoroacetic acid (3 ml) was added to a solution of tetra-urea **9** (0.303 g, 0.153 mmol) in dichloromethane (10 ml) and the mixture was stirred at rt for 2 h. Then the solvent was removed in vacuum and the salt was dissolved in dichloromethane and washed with an aqueous solution of sodium hydrocarbonate. The diamine was extracted with dichloromethane, the solution was dried ($MgSO_4$) and finally the solvent was removed under reduced pressure. The oily residue was triturated with methanol; the solid was filtered off and washed thoroughly with methanol to give the product (0.236 g, 86%) as beige powder; mp >205 °C (decomp.); $\delta_H$ (DMSO-$d_6$) 8.30 (2 H, s, N-*H*), 8.23 (4 H, s, N-*H*), 8.13 (2 H, s, N-*H*), 7.23 (4 H, d, $^3J_{HH}$ 8.5 Hz, Ar-*H*), 7.19 (4 H, d, $^3J_{HH}$ 8.5 Hz, Ar-*H*), 6.90–6.63 (16 H, m, Ar-*H*), 4.31 (4 H, d, $^2J_{HH}$ 12.3 Hz, Ar-C*H*$_2$-Ar), 3.99–3.72 (16 H, m, -O-C*H*$_2$-), 3.08 (4 H, d, $^2J_{HH}$ 12.6 Hz, Ar-C*H*$_2$-Ar), 2.82 (4 H, br.t, NH$_2$-C*H*$_2$-), 2.03 (4 H, m, -NH-CH$_2$-C*H*$_2$-), 1.98–1.82 (4 H, m, -C*H*$_2$-), 1.74–1.57 (8 H, m, -O-CH$_2$-C*H*$_2$-), 1.46–1.13 (56 H, m, -C*H*$_2$-), 0.95 (6 H, t, $^3J_{HH}$ 7.2 Hz, -C*H*$_3$), 0.84 (12 H, br.t, -C*H*$_3$); MS (ESI): *m/z* 1785.2 (M + H$^+$, 100%), required 1785.5.

### Calix[4]arene 11

Trifluoroacetic acid (4 ml) was added to a solution of tetra-urea **9** (0.170 g, 0.0856 mmol) in dichloromethane (10 ml) and the reaction mixture was stirred at rt for 2 h. The solvent was removed in vacuum and the salt was dissolved in THF (10 ml). An excess of $Et_3N$ (1 ml) was added to convert the salt into the appropriate amine **10**, and the solvent was evaporated to dryness. The residual amine was dissolved in DMF (100 ml). 5-Iodo-isophthalic acid (0.025 g, 0.086 mmol) was mixed with PyBOP (0.089 g, 0.17 mmol) in DMF (100 ml) and the mixture was stirred for 20 min under nitrogen. Both solutions were simultaneously added dropwise with stirring to 50 ml DMF. The reaction mixture was stirred under nitrogen for a further 24 h, the solvent was removed under reduced pressure and water (100 ml) was added to the residue to precipitate the products. The precipitate was filtered off, washed with water and methanol. The target product (0.025 g, 14%) was isolated by column chromatography (silica, THF–hexane, 1 : 2, followed by 3 : 4) as white powder; mp >220 °C (decomp.); $\delta_H$ (DMSO-$d_6$) 8.43 (2 H, s, N-*H*), 8.43 (2 H, s, N-*H*), 8.34 (2 H, s, N-*H*), 8.17 (2 H, br.t, N-*H*), 8.12 (3 H, s, Ar-*H*), 7.88 (2 H, s, N-*H*), 7.82 (2 H, s, N-*H*), 7.34 (4 H, d, $^3J_{HH}$ 8.9 Hz, Ar-*H*), 7.24 (4 H, s, Ar-*H*), 7.10 (4 H, d, $^3J_{HH}$ 9.2 Hz, Ar-*H*), 6.84 (4 H, d, $^3J_{HH}$ 9.2 Hz, Ar-*H*), 6.73 (4 H, d, $^3J_{HH}$ 8.9 Hz, Ar-*H*), 6.43 (4 H, s, Ar-*H*), 4.47–4.22 (8 H, m, $^2J_{HH}$ 12.6 Hz, -O-C*H*$_2$-, Ar-C*H*$_2$-Ar), 3.90 (4 H, t, $^3J_{HH}$ 6.3 Hz, -O-C*H*$_2$-), 3.83 (4 H, t, $^3J_{HH}$ 6.5 Hz, -O-C*H*$_2$-), 3.54 (4 H, t, $^3J_{HH}$ 7.3 Hz, -O-C*H*$_2$-), 3.46–3.35 (4 H, m, -NH-C*H*$_2$-), 3.08 (4 H, d, $^2J_{HH}$ 11.9 Hz, Ar-C*H*$_2$-Ar), 2.02–1.88 (4 H, m, -NH-CH$_2$-C*H*$_2$-), 1.74–1.53 (12 H, m, -O-CH$_2$-C*H*$_2$-), 1.46–1.12 (56 H, m, -C*H*$_2$-), 0.92–0.77 (12 H, m, -C*H*$_3$), 0.67 (6 H, t, $^3J_{HH}$ 7.5 Hz, -C*H*$_3$); MS (ESI): *m/z* 2063.2 (M + Na$^+$, 100%), required 2063.5; 1043.1 (M + 2Na$^+$, 36%), required 1043.1.

### Single-crystal X-ray diffraction

Data were collected on a STOE-IPDS-II two-circle diffractometer employing graphite-monochromated MoK$\alpha$ radiation (0.71073 Å). Data reduction was performed with the X-AREA software.[11] An empirical absorption correction was done with the PLATON program.[12] Structures were solved by direct methods with SHELXS-90[13] and refined by full-matrix least-squares techniques with SHELXL-97.[13]

All non-H atoms were refined with anisotropic displacement parameters. Hydrogen atoms bonded were included at calculated positions and allowed to ride on their parent atoms. The H atoms bonded to N and O in **4** were freely refined. The two propyl groups and the THF molecule in **4** are disordered over two positions with a ratio of the site occupation factors of 0.54(1)/0.46(1), 0.59(2)/0.41(2) and 0.62(2)/0.38(2), respectively. The absolute structure of **3** has been determined by the Flack-parameter $x = -0.01(1)$.

## Conclusions and outlook

We have developed a multistep synthesis for tetra-urea calix[4]arenes, in which two opposite phenolic units are connected by a macrocyclic ether bridge containing a 5-iodo-isophthalamide structure. Although the single molecules assume the expected pinched cone conformation they readily form hydrogen bonded dimers in apolar solvents. The symmetrically placed iodo atom may be converted to further functions to allow attachment to a cantilever in an AFM setup. Thus, the mechanical strength of the hydrogen bonded belt of such dimers may be measured, using symmetrical stretching forces. This will improve former experiments where the stretching of the dimer occurred between single ether residues in a necessarily non symmetric way.[5] We are presently trying to improve the yield of the single reaction steps, especially for the cyclisation.

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