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## Breaking thiocalix[4]arene into pieces – a novel synthetic approach to higher calixarenes bearing mixed (–S–, –CH<sub>2</sub>–) bridges†

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A novel approach to calix[5–7]arenes possessing mixed (S and CH<sub>2</sub>) bridges within the skeleton is based on the reaction of thiocalix[4]arene monosulfoxide with BuLi leading to a linear phenolic tetramer in essentially quantitative yield. This key intermediate is then cyclized with suitable building blocks to give macrocyclic calixarene analogues. Compared to the traditional stepwise construction of similar systems, this procedure based on thiocalixarene cleavage represents a scalable, robust, and straightforward synthesis and enables the preparation of larger calixarenes on a gram scale. As shown by <sup>1</sup>H NMR and UV-vis titration experiments, the mixed-bridge calix[7]arene is able to recognize fullerenes C<sub>60</sub> and C<sub>70</sub>, thus showing possible applications of such systems. The structures of the mixed bridge systems were confirmed by single crystal X-ray analysis, and the behavior of novel macrocyclic skeletons in solution was studied using dynamic NMR techniques.

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### Introduction

Calix[n]arenes<sup>1</sup> are a well-established family of macrocyclic compounds due to their preorganization and easy derivatization, and are frequently used as molecular scaffolds in the design and synthesis of more complex supramolecular systems, including various receptors. The introduction of sulfur instead of methylene bridges has opened<sup>2</sup> many new possibilities, as the chemistry of so-called thiocalixarenes offers many new features compared to “classical” calixarenes.

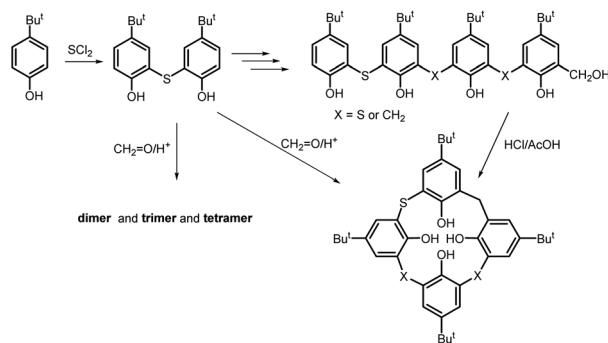
As recently documented,<sup>3</sup> the presence of heteroatoms brings about different complexation properties, novel types of chemical transformations unknown for pristine macrocycles, and different conformational preferences leading to 3D structures/conformations and/or substitution patterns which are otherwise hardly accessible for classical calixarenes. All these features make thiocalixarene an attractive platform for applications in supramolecular chemistry.

In this context, it seems interesting to study macrocycles formed by “interbreeding” the two parent systems – calixarene

and thiocalixarene. Structures having both –S– and –CH<sub>2</sub>– bridges could, on the one hand, retain some of the characteristics of the parent systems, on the other hand, exhibit new behavior compared to the originals, offering thus new applications.

While the chemistry of calixarenes and thiocalixarenes is already well-established, mixed bridge systems remain almost untouched in the literature, mainly because of their hard accessibility. For the time being, the preparation of calix[4]arene analogues bearing one, two, or three sulfur bridges using the stepwise construction of linear tetramers that were finally cyclized (Scheme 1) was reported.<sup>4</sup>

Alternative approach is based on the cyclization of bisphenolic building blocks with formaldehyde, leading to a mixture of tetrameric, hexameric, or octameric condensation products.<sup>5</sup>



Scheme 1 Various approaches to mixed (S/CH<sub>2</sub>) bridge systems.

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† Electronic supplementary information (ESI) available: Experimental procedures, full characterization of compounds 5–8 and 12–16, X-ray data for structures 6 and 7, and the complexation studies of C<sub>60</sub> and C<sub>70</sub>. CCDC 2110418 and 2110419. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra07464d



Recently, our group succeeded with simple and scalable fragment condensation synthesis<sup>6</sup> of 2,14-dithiacalix[4]arene possessing the alternating -S- and -CH<sub>2</sub>- bridges, which enabled the study of basic properties of this analogue.<sup>7</sup>

Unfortunately, the above-mentioned procedures rely on the electrophilic reaction of phenols with SCl<sub>2</sub>, which is the key reagent in all these approaches. While just a few years ago it was a common commercially available chemical sold by, *e.g.*: Aldrich company, recently, this compound became unavailable due to significant safety concerns regarding its possible use in the preparation of chemical warfare agents (sulfur mustard = yperite). Hence, as a direct consequence of the worldwide counter terrorism measures, the above approaches currently cannot be used because of the total unavailability of the starting compound.

In this contribution, we report an entirely novel approach overcoming the above-mentioned difficulties, and moreover, paving the path to so far inaccessible bigger calixarene systems having mixed bridges (S and CH<sub>2</sub>) within the basic macrocyclic skeleton.

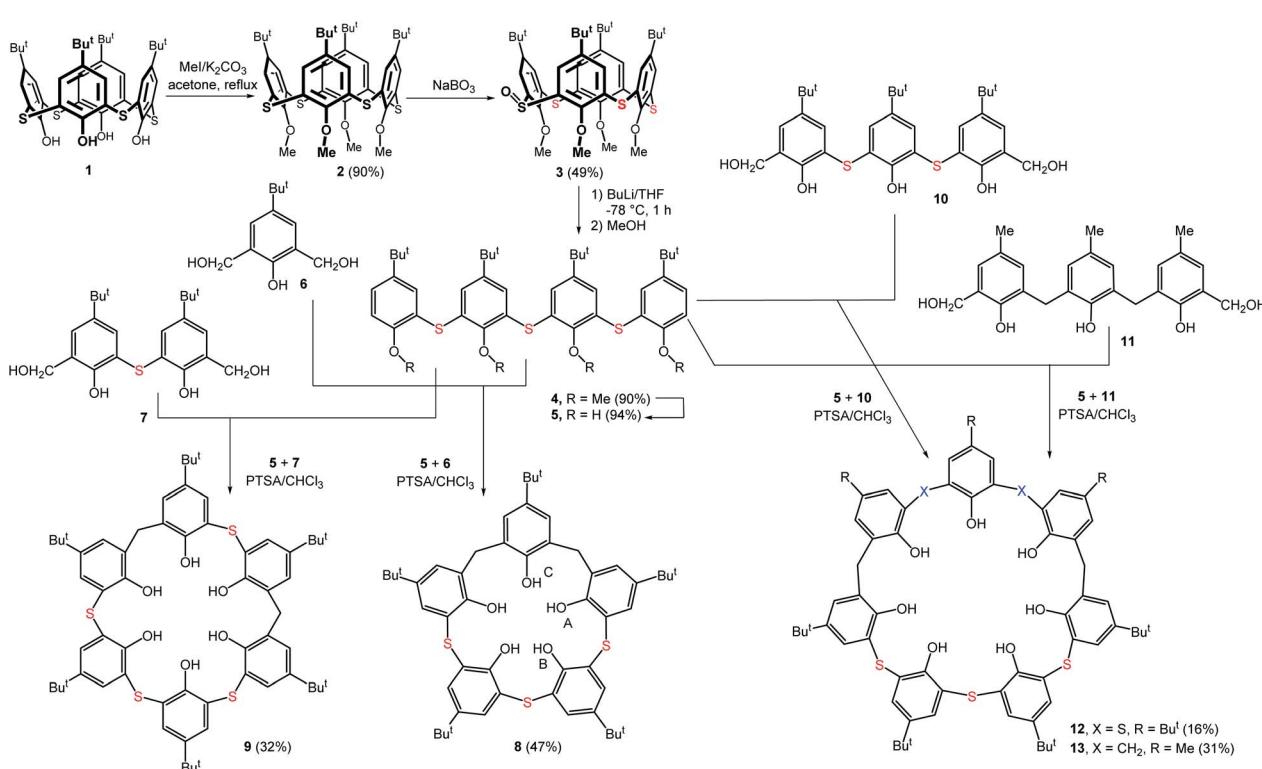
## Results and discussion

The whole synthetic procedure starts with pristine thiocalix[4]arene **1** (Scheme 2), which is easily accessible in 100 g scale using the condensation of *p*-*tert*-butylphenol and sulfur under basic conditions.<sup>2</sup> Subsequent alkylation with methyl iodide<sup>8</sup> to the corresponding methoxy derivative **2** and selective monooxidation (NaBO<sub>3</sub>) leads to monosulfoxide<sup>9</sup> **3** in good yield after column chromatography on silica gel.

The key step is based on the recently discovered unexpected reactivity of thiocalixarene monosulfoxides with organolithium compounds.<sup>10</sup> It was shown that irrespective of the conformation of the starting sulfoxide the macrocycle can be cleaved *via* a ligand exchange mechanism yielding linear thiocalixarene analogues which would be otherwise hardly obtainable. Thus, the reaction of compound **3** with an excess of *n*-BuLi (10 equiv.) in THF at -78 °C and subsequent quenching with MeOH provided a linear tetramer **4** (Scheme 2) in 90% yield and dibutyl sulfoxide as a byproduct. Methoxy derivative **4** was subjected to demethylation using BBr<sub>3</sub>, thus leading to tetraphenol **5** in excellent yield (94%). The use of Me<sub>3</sub>SiI as the dealkylation agent did not result into complete dealkylation.

In fact, tetramer **5** represents a key intermediate, which can be used for further synthesis of the mixed-bridge systems. So far, it has only been prepared *via* time-consuming stepwise procedure (as shown in Scheme 1) with very low overall yield,<sup>11</sup> which hindered the preparation of compound **5** on a gram scale. In contrast, the procedure shown in Scheme 2 allows the preparation of **5** on a large scale, and, except for sulfoxide formation step, without any chromatographic separation.

The condensation reactions of **5** with suitable building blocks were carried out in chloroform where all reactants exhibited good solubility. Thus, the reaction of **5** with 2,6-bis(hydroxymethyl)-*p*-*tert*-butylphenol **6** (ref. 12) with PTSA under high-dilution conditions led to calix[5]arene derivative **8** in 47% yield (Scheme 2). Similarly, condensation of **5** with bisphenol **7** (ref. 7) provided calix[6]arene derivative<sup>13</sup> **9** in 32% yield.



Scheme 2 Synthesis of bigger calixarenes bearing mixed bridges (S and CH<sub>2</sub>) starting from thiocalix[4]arene.



The structures of products **8** and **9** were confirmed by HRMS ESI+ analysis, which excluded the formation of higher macrocycles (e.g.: 2 + 2 products). Thus, macrocycle **8** showed the most intense signals at  $m/z$  = 887.3808 and 903.3548, which is in good agreement with the calculated values 887.3805 and 903.3538 for the  $[M + Na]^+$  and  $[M + K]^+$  ions. Similar agreement was found also for **9** (found: 1067.4417 vs. calc.: 1067.4417) for  $[M + Na]^+$  species.

The  $^1\text{H}$  NMR spectrum of **8** ( $\text{CDCl}_3$ , 298 K) reflects the expected  $C_s$  symmetry of the compound showing three singlets of OH groups A, C, and B (Scheme 2) at 8.31, 8.25, and 8.16 ppm with 2 : 1 : 2 intensity ratio, respectively (Fig. 1). The shape of the signal of the methylene bridges – singlet at 3.85 ppm – indicates a fast conformational motion of the molecule at room temperature (time averaged signal).

As shown by the dynamic NMR study (298–153 K), cooling  $\text{CD}_2\text{Cl}_2$  solution of **8** (Fig. 1) resulted in the extensive broadening of the  $\text{CH}_2$  singlet, leading finally to the disappearance at around 225 K (coalescence temperature). Further cooling resulted in the appearance of two new broad signals at 3.60 and 4.10 ppm (203 K) resembling the axial and equatorial signals for the *cone* conformer of calix[5]arene derivatives.<sup>14</sup> This phenomenon could be explained as a fast *cone* – inverted *cone* interconversion<sup>15</sup> of the two identical *cone* conformations held by hydrogen bond array on the lower rim. The corresponding activation free energy ( $\Delta G^*$ ) was calculated using Eyring equations for the rate constant  $k$ :

$$k = \frac{k_{\text{B}} T_{\text{C}}}{h} e^{-\frac{\Delta G^*}{RT_{\text{C}}}}$$

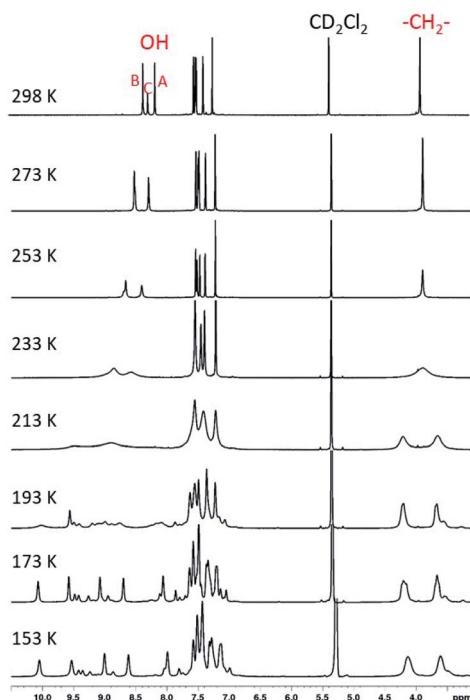


Fig. 1 The partial  $^1\text{H}$  NMR spectra of **8** (phenolic OH and  $\text{CH}_2$  area) at various temperatures ( $\text{CD}_2\text{Cl}_2$ , 500 MHz) reflecting the *cone*–*cone* interconversion and the flip-flop motion of the circular HB array on the lower rim of calixarene.

where  $k_{\text{B}}$  is the Boltzmann constant,  $T_{\text{C}}$  is the coalescence temperature,  $h$  is the Planck constant,  $R$  is the gas constant, and  $\Delta\nu$  is the chemical shift difference of the exchanging signals in the absence of chemical exchange. The value obtained (42  $\text{kJ mol}^{-1}$ ) is much smaller than that of *p*-*tert*-butylecalix[5]arene<sup>14</sup> (55.2  $\text{kJ mol}^{-1}$ ) suggesting that the presence of sulfur gives birth to a much higher conformational mobility of the resulting macrocyclic system.

Remarkably, further lowering the temperature down to 153 K led to the appearance of five different main signals of the OH groups (7.59, 8.62, 9.00, 9.54, and 10.05 ppm). This observation can be ascribed to the flip-flop motion of the circular hydrogen bond array at the lower rim of **8**. The orientation of HB array (clockwise vs. anti-clockwise) makes the system chiral, and originally equivalent signals of the OH protons (3 signals under fast exchange conditions) become inequivalent under slow exchange conditions (Fig. 1). The presence of other small peaks in the OH area of the spectrum suggests that there are probably some other minor conformations besides the *cone* in the equilibrium.

The single crystal X-ray diffraction analysis revealed that compound **8** crystallized in a triclinic crystal system, space group  $\bar{P}1$  (Fig. 2) as a complex with EtOH and  $\text{H}_2\text{O}$ . The macrocycle adopted the *cone* conformation held by two circular hydrogen bonds between phenolic OH groups ( $\text{O}-\text{H}\cdots\text{O}$  distances are 2.035 and 2.039  $\text{\AA}$ ) completed by several HBs between OH, EtOH and  $\text{H}_2\text{O}$  (from 1.863  $\text{\AA}$  for  $\text{EtO}-\text{H}\cdots\text{OH}_2$  interaction to 2.308  $\text{\AA}$  for  $\text{H}-\text{O}-\text{H}\cdots\text{OH}$  bonding). Moreover, the overall supramolecular motif is complemented by the  $\text{S}\cdots\text{O}$  (3.304  $\text{\AA}$ ) and  $\text{S}\cdots\text{H}-\text{O}$  (2.854  $\text{\AA}$ ) close contacts (Fig. 2).

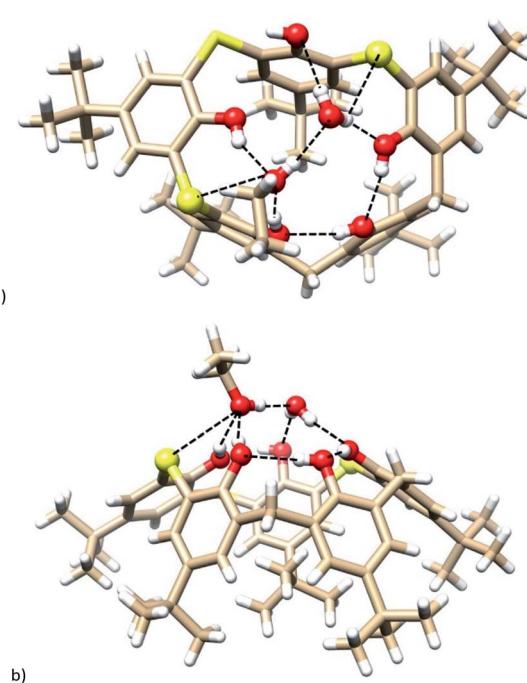


Fig. 2 Single crystal X-ray structures of compound **8**·EtOH· $\text{H}_2\text{O}$ : (a) top-view showing the array of HBs, (b) side-view (interacting atoms shown as balls for better clarity).

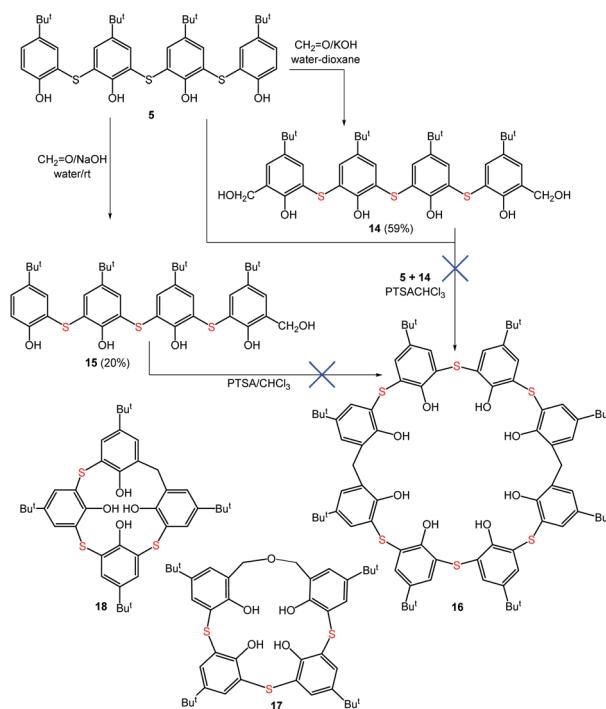


Compound **9** has crystallized in triclinic system in space group  $P\bar{1}$  as a complex with DMSO (see ESI Fig. 57†). Only half of the calix[6]arene molecule is present in the asymmetric unit, resulting in complete disorder of methylene and sulfur bridges. The solvent is disordered over two positions, with both positions held by two hydrogen bonds between OH groups and oxygen atom of DMSO with distances 1.936 Å and 2.085 Å for main positions and 2.037 Å and 2.041 Å. The remaining hydroxyl group forms intramolecular hydrogen bond with one of the solvent binding hydroxyl groups with distance of 2.075 Å.

To prepare bigger calixarenes while showing a general use of our synthetic approach, tetramer **5** was reacted with trisphenols **10** (ref. 16) and **11** (ref. 17) to provide the corresponding calix[7]arenes **12** and **13** in 16 and 31% yields, respectively (Scheme 2).

It is well known that higher calixarenes can form complexes with fullerenes based on a mutual size and shape complementarity (concave *vs.* convex).<sup>18</sup> Derivative **13** was selected for the complexation study using  $^1\text{H}$  NMR titration experiments with  $\text{C}_{60}$  fullerene in toluene- $d_8$ . The addition of  $\text{C}_{60}$  led to a reasonable change of the NMR spectrum, particularly in the aromatic range, shifting the signals towards higher field ( $\text{CIS} \approx 0.1$  ppm) as shown in ESI (Fig. 52†). To avoid the problems associated with overlapping of the aromatic signals the  $\text{CH}_2$  bridges were selected for building the binding isotherm. Surprisingly, the shape of the titration curve indicated that the stoichiometry of the complex formed did not correspond to a simple 1 : 1 model. There are two plateaus indicating the more complex behavior which was confirmed also by Job plot analysis (Fig. 3) reflecting the 2 : 1 stoichiometry ( $\text{C}_{60} : \mathbf{13}$ ).

To shed more light into the stoichiometry, we have carried out the UV-vis titration in toluene to achieve a higher  $\text{C}_{60}/\mathbf{13}$  ratio. The titration was carried out in toluene with a constant concentration of fullerene. To avoid the influence of self-absorption of **13** ( $\lambda_{\text{max}} = 290$  nm) the region of wavelengths  $>400$  nm was chosen to build the binding isotherms. Fitting procedure using program Bindfit<sup>19</sup> confirmed the 2 : 1



Scheme 3 Attempted synthesis of calix[8]arene derivative.

stoichiometry with an overall complexation constant  $\beta = 4900$  ( $K_1 \times K_2$ ). Interestingly, the same conditions used for the complexation of  $\text{C}_{70}$  resulted in the expected 1 : 1 stoichiometry with the corresponding association constant  $K = 3100$ .

We also tried to extend this methodology to even larger calix[8]arenes derivatives. Tetramer **5**, therefore, was hydroxymethylated by standard procedure<sup>4</sup> ( $\text{CH}_2=\text{O}/\text{KOH}$ ) to provide disubstituted derivative **14** in 59% yield (Scheme 3). The condensation of building blocks **5** and **14** under high dilution conditions, however, did not lead to expected product **16**, but rather, homooxacalix[4]arene **17** was isolated as the only product (95% yield) of self-condensation<sup>20</sup> of **14**. The condensation in the presence of  $\text{C}_{60}$ , to use the possible template effect of the fullerene ball, had no success as well since only **14** was isolated again as a single product. To overcome this issue, we employed mono(hydroxymethyl) compound **15** (ref. 4) (a byproduct in the preparation of **14**) as it cannot provide the homooxa product. The attempted self-dimerization of **15** resulted in the exclusive formation of calix[4]arene derivative **18** (90% yield) representing the self-(mono)condensation product.

## Conclusion

In conclusion, a novel approach to calix[5–7]arenes having mixed (S and  $\text{CH}_2$ ) bridges within the skeleton is based on the reaction of thiocalix[4]arene monosulfoxide with  $\text{BuLi}$  leading to a linear phenolic tetramer in an essentially quantitative yield. This key intermediate is then cyclized with suitable building blocks to give macrocyclic calixarene analogues. Compared to the traditional stepwise construction of similar systems, this procedure based on thiocalixarene cleavage represents

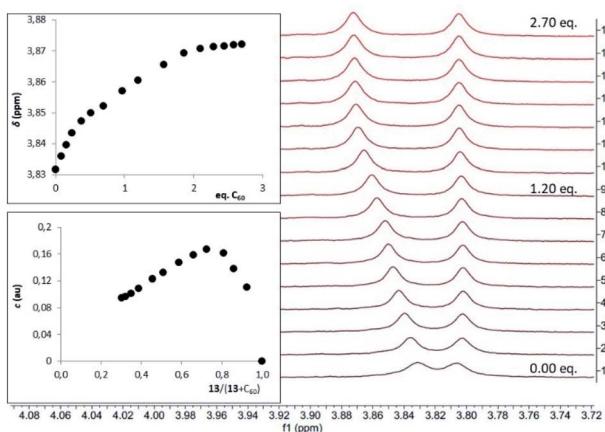


Fig. 3 The complexation induced chemical shifts of the  $\text{CH}_2$  signals in  $^1\text{H}$  NMR spectra of **13** upon addition of  $\text{C}_{60}$ . Upper inset: the corresponding titration curve (toluene- $d_8$ , 298 K, 400 MHz); lower inset: the Job plot of the same system.



a scalable, robust, and straightforward synthesis enabling the preparation of larger calixarenes in a gram scale. As shown by titration experiments the mixed-bridge calix[7]arene **13** is able to recognize fullerenes C<sub>60</sub> and C<sub>70</sub> in solution, with remarkable differences in the stoichiometry of the corresponding complexes, thus indicating possible applications of such systems.

## Experimental

### General experimental procedures

All chemicals were purchased from commercial sources, and used without further purification. Chloroform, tetrahydrofuran and dichloromethane used for the reactions were dried with CaH<sub>2</sub> or MgSO<sub>4</sub> and stored over molecular sieves. Melting points were measured on a Heitzisch Mikroskop-Polytherm A (Wagner & Munz, Germany). The IR spectra were measured on a FT-IR spectrometer Nicolet 6700 combined with an ATR cell GladiATR (PIKE). NMR spectra were recorded on Agilent 400-MR DDR2 (<sup>1</sup>H, 400 MHz; <sup>13</sup>C, 100 MHz), Bruker Avance DRX 500 (<sup>1</sup>H, 500 MHz; <sup>13</sup>C, 125 MHz), and Bruker 600 Avance III (<sup>1</sup>H, 600.1 MHz; <sup>13</sup>C, 150.9 MHz) spectrometers at 298 K. Structural assignments were made with additional information from gCOSY, gHMQC, and gHMBC experiments. The mass analyses were performed using the ESI technique on a FT-MS (LTQ Orbitrap Velos) spectrometer. Column chromatography was performed on silica gel 60 with particle sizes 0.063–0.200 mm (Merck). Radial thin layer chromatography was carried out using Chromatotron on glass disks covered by silica gel 60 PF254 containing CaSO<sub>4</sub> (Merck). Purity of the substances and courses of the reactions were monitored by TLC using TLC aluminium sheets with Silica gel 60 F254 (Merck) and analysed at 254 nm.

Compound **2** was prepared according to the described procedure.<sup>8</sup>

**Thiacalixarene monosulfoxide 3.** Thiacalixarene **2** (6.66 g, 8.56 mmol) was dissolved in 250 mL of chloroform, the same volume of AcOH was added and the mixture was heated to 60 °C. Sodium perborate tetrahydrate (1.415 g, 9.0 mmol) was slowly added and the mixture was stirred and heated at 60 °C for 4 h. The reaction mixture was cooled to rt and approx. 200 mL of 1 M HCl was poured into the flask. The crude product was extracted with chloroform (3 × 200 mL), the organic phase was then carefully washed with sodium bicarbonate solution, dried over MgSO<sub>4</sub> and evaporated to dryness. Column chromatography on silica gel with cyclohexane ethyl acetate mixture (15 : 1 v/v) as an eluent provided monosulfoxide **3** as a white powder (3.95 g, 49%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz, 298 K) δ 7.63 (bs, 2H, Ar-H), 7.56 (d, *J* = 2.3 Hz, 2H, Ar-H), 7.43 (bs, 4H, Ar-H), 3.78 (s, 6H, Ar-O-CH<sub>3</sub>), 3.46 (s, 6H, Ar-O-CH<sub>3</sub>), 1.23 (s, 36H, Ar-C(CH<sub>3</sub>)<sub>3</sub>) ppm. The data are in agreement with ref. 9.

**Linear tetramer 4.** Monosulfoxide **3** (3.90 g, 4.91 mmol) was placed in a two-neck 250 mL round-bottom flask, the flask was evacuated and filled with argon several times. Then, 150 mL of dry THF was added, the flask was cooled to -78 °C and 11 M n-BuLi (4.50 mL, 49.14 mmol) was added dropwise while the reaction mixture was stirred under Ar at -78 °C for 1 h. The

reaction was quenched carefully with methanol (10 mL) and solvent was evaporated. The residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>, organic layer was washed with water and dried over MgSO<sub>4</sub>. The product was purified using radial chromatography with CH<sub>2</sub>Cl<sub>2</sub> as an eluent. Linear tetramer **4** was obtained as a yellowish powder (3.39 g, 91%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz, 298 K) δ 7.30 (dd, *J* = 8.4, 2.5 Hz, 2H, Ar-H), 7.26 (d, *J* = 2.5 Hz, 2H, Ar-H) 6.98 (d, *J* = 2.3 Hz, 2H, Ar-H), 6.88 (d, *J* = 2.4 Hz, 2H, Ar-H), 6.86 (d, *J* = 8.3 Hz, 2H, Ar-H), 3.93 (s, 6H, Ar-O-CH<sub>3</sub>), 3.83 (s, 6H, Ar-O-CH<sub>3</sub>), 1.23 (s, 18H, Ar-C(CH<sub>3</sub>)<sub>3</sub>), 1.07 (s 18H, Ar-C(CH<sub>3</sub>)<sub>3</sub>) ppm. The data are in agreement with ref. 10.

**Linear tetraphenol 5.** Tetramer **4** (2.8 g, 4.06 mmol) was dissolved in 200 mL of dry CH<sub>2</sub>Cl<sub>2</sub> and cooled to -78 °C. 1 M BBr<sub>3</sub> (24.3 mL, 26.39 mmol) was added dropwise and the flask was warmed to rt. The mixture was stirred under argon for 2 h and quenched with satd. aqueous sodium bicarbonate (approx. 200 mL). The organic layer was separated, washed with water and dried over MgSO<sub>4</sub>. Removing of solvent provided 2.45 g of title compound **5** as a white powder (94%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz, 298 K) δ 7.79 (bs, 2H, Ar-O-H), 7.53 (d, *J* = 2.3 Hz, 2H, Ar-H), 7.36 (d, *J* = 2.4 Hz, 2H, Ar-H), 7.30 (dd, *J* = 8.6, 2.4 Hz, 2H, Ar-H), 6.92 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.24 (d, *J* = 2.4 Hz, 2H, Ar-H), 6.86 (bs, 2H, Ar-O-H), 1.26 (s, 18H, Ar-C(CH<sub>3</sub>)<sub>3</sub>), 1.14 (s, 18H, Ar-C(CH<sub>3</sub>)<sub>3</sub>) ppm. The data are in agreement with ref. 11.

**Calix[5]arene 8.** Tetramer **5** (150 mg, 0.22 mmol) and monomer **6** (45.6 mg, 0.22 mmol) were put together into a small flask fitted with septum, and the mixture was evacuated and filled with argon several times. The mixture was then dissolved in 30 mL of dry chloroform. *p*-Toluene sulfonic acid monohydrate (83 mg, 0.44 mmol) was put into a 250 mL two-neck round-bottom flask that was evacuated and filled with argon. The flask containing 70 mL of dry chloroform was heated under reflux and stirred while the mixture of starting materials was gradually added using the syringe pump with addition rate of 3 mL h<sup>-1</sup>. The next day, mixture was cooled to rt and the solvent was evaporated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (30 mL), the precipitate containing TSOH was filtered off and the residue was purified by radial chromatography (CH<sub>2</sub>Cl<sub>2</sub>) on silica gel. Calix[5]arene **8** was isolated as a pinkish powder (88 mg, 47%) m.p. > 350 °C (decomp). <sup>1</sup>H-NMR (CD<sub>2</sub>Cl<sub>2</sub>, 600 MHz, 298 K) δ 8.34 (bs, 2H, Ar-OH), 8.27 (bs, 1H, Ar-OH), 8.15 (bs, 2H, Ar-OH), 7.53 (d, *J* = 2.3 Hz, 2H, Ar-H), 7.51–7.47 (m, 4H, Ar-H), 7.38 (d, *J* = 2.3 Hz, 2H, Ar-H), 7.23 (s, 2H, Ar-H), 3.89 (s, 4H, Ar-CH<sub>2</sub>-Ar), 1.32–1.28 (m, 27H, Ar-C(CH<sub>3</sub>)<sub>3</sub>), 1.21 (s, 18H, Ar-C(CH<sub>3</sub>)<sub>3</sub>) ppm. <sup>13</sup>C-NMR (CD<sub>2</sub>Cl<sub>2</sub>, 125 MHz, 298 K) δ 154.3, 151.1, 147.6, 144.4, 144.3, 143.9, 133.3, 132.8, 131.4, 129.4, 126.3, 125.9, 120.2, 119.7, 118.9, 34.0, 34.0, 33.9, 32.1, 31.2, 31.1, 30.9 ppm. IR (ATM)  $\nu$  3370, 2955, 2867, 1570 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calcd for C<sub>52</sub>H<sub>64</sub>O<sub>5</sub>S<sub>3</sub> 887.3808 [M + Na]<sup>+</sup>, 903.3548 [M + K]<sup>+</sup>, found *m/z* 887.3803 [M + Na]<sup>+</sup>, 903.3520 [M + K]<sup>+</sup>.

**Calix[6]arene 9.** Tetramer **5** (100 mg, 0.135 mmol) and dimer **7** (45.6 mg, 0.217 mmol) were put together into a small flask fitted with septum and the mixture was evacuated and filled with argon several times. The mixture was then dissolved in 30 mL of dry chloroform. *p*-Toluene sulfonic acid monohydrate (55 mg, 0.270 mmol) was put into a 100 mL two-neck round-bottom flask that was evacuated and filled with argon. The



flask containing 30 mL of dry chloroform was heated under reflux and stirred while the mixture of starting compounds was gradually added using the syringe pump with addition rate of 2 mL h<sup>-1</sup>. The next day, mixture was cooled to rt the solvent was evaporated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (30 mL), the precipitate containing TsOH was filtered off and the residue was purified by radial chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub> : C<sub>6</sub>H<sub>12</sub> = 10 : 1 v/v). Calix[6]arene **9** was isolated as a pinkish powder (48 mg, 32%) m.p. > 350 °C (decomp). <sup>1</sup>H-NMR (CD<sub>2</sub>Cl<sub>2</sub>, 600 MHz, 298 K) δ 9.75 (s, 2H, Ar-OH), 9.57 (s, 2H, Ar-OH), 9.50 (s, 2H, Ar-OH), 7.71–7.66 (m, 4H, Ar-H), 7.61–7.56 (m, 4H, Ar-H), 7.35 (d, *J* = 2.3 Hz, 2H, Ar-H), 7.30 (d, *J* = 2.3 Hz, 2H, Ar-H), 4.00 (bs, 4H, Ar-CH<sub>2</sub>-Ar), 1.29 (s, 18H, Ar-C(CH<sub>3</sub>)<sub>3</sub>), 1.27 (s, 36H, Ar-C(CH<sub>3</sub>)<sub>3</sub>) ppm. <sup>13</sup>C-NMR (CD<sub>2</sub>Cl<sub>2</sub>, 125 MHz, 298 K) δ 155.2, 151.4, 150.9, 144.8, 144.7, 144.7, 136.0, 135.5, 132.4, 132.3, 132.0, 129.6, 129.5, 126.9, 126.8, 121.4, 120.7, 120.4, 120.3, 34.1, 34.0, 32.8, 31.1, 31.0, 30.9, 29.7, 29.7 ppm. IR (ATM) ν 3236, 2959, 2868, 1736, 1685, 1578 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calcd for C<sub>62</sub>H<sub>76</sub>O<sub>6</sub>S<sub>4</sub> 1067.4417 [M + Na]<sup>+</sup>, 1083.4156 [M + K]<sup>+</sup>, found m/z 1067.4417 [M + Na]<sup>+</sup>, 1083.4145 [M + K]<sup>+</sup>.

**Calix[7]arene 12.** *p*-Toluene sulfonic acid monohydrate (32.12 mg, 0.168 mmol) was placed in a 100 mL two-neck round-bottom flask and dissolved in 30 mL of dry chloroform with stirring under reflux. Tetramer **5** and trimer **10** (both 0.084 mmol) were dissolved together in 20 mL of dry chloroform and the mixture was added slowly into the two-neck flask *via* syringe pump with rate of 2 mL h<sup>-1</sup>. The reaction mixture was stirred and heated under reflux overnight. The next day, the mixture was cooled to rt, transferred into a separating funnel and washed with water. After drying over MgSO<sub>4</sub> the product was isolated by radial chromatography with CH<sub>2</sub>Cl<sub>2</sub> as an eluent. Calix[7]arene **12** was obtained as a white powder (16.6 mg, 16%) m.p. 149–155 °C. <sup>1</sup>H-NMR (CD<sub>2</sub>Cl<sub>2</sub>, 600 MHz, 298 K) δ 8.92 (bs, 1H, Ar-OH), 8.75 (bs, 4H, Ar-OH), 8.69 (bs, 2H, Ar-OH), 7.63 (s, 2H, Ar-H), 7.62–7.59 (m, 4H, Ar-H), 7.53 (d, *J* = 2.2 Hz, 2H, Ar-H), 7.51 (d, *J* = 2.2 Hz, 2H, Ar-H), 7.35–7.33 (m, 4H, Ar-H), 3.99 (s, 4H, Ar-CH<sub>2</sub>-Ar), 1.29–1.25 (m, 63H, Ar-C(CH<sub>3</sub>)<sub>3</sub>) ppm. <sup>13</sup>C-NMR (CD<sub>2</sub>Cl<sub>2</sub>, 150 MHz, 298 K) δ 154.5, 154.4, 151.0, 150.9, 144.8, 144.7, 144.6, 144.5, 134.4, 134.3, 134.2, 131.6, 131.5, 129.4, 129.3, 127.0, 126.9, 120.8, 120.5, 120.2, 120.1, 120.0, 34.1, 34.0, 32.4, 31.1, 31.0, 30.9, 29.7 ppm. IR (ATM) ν 3300, 2955, 2866, 1739 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calcd for C<sub>72</sub>H<sub>88</sub>O<sub>7</sub>S<sub>5</sub> 1247.5026 [M + Na]<sup>+</sup>, found m/z 1247.5031 [M + Na]<sup>+</sup>.

**Calix[7]arene 13.** *p*-Toluene sulfonic acid monohydrate (47.3 mg, 0.244 mmol) was placed in a 100 mL two-neck round-bottom flask and dissolved in 40 mL of dry chloroform with stirring under reflux. Tetramer **5** and trimer **11** (both 0.122 mmol) were dissolved together in 15 mL of dry chloroform and the mixture was added slowly into the two-neck flask *via* syringe pump with rate of 1.5 mL h<sup>-1</sup>. The reaction mixture was stirred and heated under reflux overnight. The next day, after cooling down to room temperature, the content of the flask was transferred into a separating funnel and washed with water. After drying over MgSO<sub>4</sub>, the product was isolated using radial chromatography with dichloromethane as an eluent. Calix[7]arene **13** was obtained as a yellow solid (40 mg, 31%) m.p. 199–200 °C. <sup>1</sup>H-NMR (CD<sub>2</sub>Cl<sub>2</sub>, 600 MHz, 298 K) δ 9.66 (bs, 1H, Ar-

OH), 9.54–9.47 (m, 4H, Ar-OH), 9.43 (bs, 2H, Ar-OH), 7.70–7.66 (m, 4H, Ar-H), 7.58 (d, 2H, *J* = 2.4 Hz, Ar-H), 7.38 (d, 2H, *J* = 2.4 Hz, Ar-H), 7.07–7.03 (m, 6H, Ar-H), 3.97 (bs, 4H, Ar-CH<sub>2</sub>-Ar), 3.91 (bs, 4H, Ar-CH<sub>2</sub>-Ar) 2.29 (s, 9H, Ar-CH<sub>3</sub>), 1.32 (s, 18H, Ar-C(CH<sub>3</sub>)<sub>3</sub>), 1.29 (s, 18H, Ar-C(CH<sub>3</sub>)<sub>3</sub>) ppm. <sup>13</sup>C-NMR (CD<sub>2</sub>Cl<sub>2</sub>, 150 MHz, 298 K) δ 154.7, 151.1, 147.3, 147.3, 144.0, 135.0, 135.0, 132.3, 131.2, 131.0, 129.8, 129.7, 129.6, 129.6, 129.4, 129.4, 127.9, 127.6, 127.6, 127.2, 121.4, 120.4, 120.0, 34.2, 34.1, 32.4, 31.8, 31.1, 31.1, 31.0, 30.9, 20.2, 20.2 ppm. IR (ATM) ν 3230, 2955, 2885, 1604 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calcd for C<sub>65</sub>H<sub>74</sub>O<sub>7</sub>S<sub>3</sub> 1085.4489 [M + Na]<sup>+</sup>, found m/z 1085.4488 [M + Na]<sup>+</sup>.

**Bis(hydroxymethyl) tetramer 14 and monohydroxymethyl tetramer 15.** Tetramer **5** (500 mg, 0.725 mmol) was treated with 4% KOH in water (4 mL, 3.00 mmol) while stirring and approx. 2 mL of 1,4-dioxane was added to achieve a complete dissolution of the starting materials. HCHO (35% in water, 1.15 mL) was added dropwise into the reaction mixture and the flask was stirred at 50 °C for 24 h. After cooling to rt, the mixture was quenched by 5 M HCl until acidic pH. The crude product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 5 mL) and isolated by radial chromatography using CH<sub>2</sub>Cl<sub>2</sub> : MeOH mixture (99 : 1 v/v) as an eluent. The first fraction provided compound **14** as a thick pinkish glue-like matter (324 mg, 59%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 298 K) δ 7.40–7.36 (m, 4H, Ar-H), 7.33 (d, *J* = 2.4 Hz, 2H, Ar-H), 7.15 (d, *J* = 2.4 Hz, 2H, Ar-H), 4.78 (s, 4H, Ar-CH<sub>2</sub>-OH), 1.22 (s, 18H, Ar-C(CH<sub>3</sub>)<sub>3</sub>), 1.17 (s, 18H, Ar-C(CH<sub>3</sub>)<sub>3</sub>) ppm.

Compound **15** was isolated from the second fraction (103 mg, 24%) as a yellowish glassy solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 298 K) δ 7.51 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.47 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.45 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.38 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.33 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.27 (dd, *J* = 2.4 Hz, 7.5 Hz, 1H, Ar-H), 7.20 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.11 (d, *J* = 2.4 Hz, 1H, Ar-H), 6.84 (d, *J* = 8.5 Hz, 1H, Ar-H), 4.89 (s, 2H, Ar-CH<sub>2</sub>-OH), 1.25 (s, 9H, Ar-C(CH<sub>3</sub>)<sub>3</sub>), 1.22 (s, 9H, Ar-C(CH<sub>3</sub>)<sub>3</sub>), 1.18 (s, 9H, Ar-C(CH<sub>3</sub>)<sub>3</sub>), 1.16 (s, 9H, Ar-C(CH<sub>3</sub>)<sub>3</sub>) ppm.

The data are in agreement with ref. 4.

#### Attempted synthesis of calix[8]arene **16**

**Procedure A.** A mixture of bis(hydroxymethyl) tetramer **14** (0.146 mmol, 110 mg) and tetramer **5** (0.146 mmol, 101.2 mg) dissolved in chloroform (25 mL) was added *via* syringe pump (2.5 mL h<sup>-1</sup>) into a flask containing TsOH monohydrate (2 equiv., 55.7 mg) in refluxing chloroform (100 mL). The next day, solvent was evaporated and the crude reaction mixture was separated using radial chromatography with CH<sub>2</sub>Cl<sub>2</sub> as an eluent. Homooxacalixarene **17** was isolated as a white solid (102 mg, 95% based on **14**) together with unreacted tetramer **5**.

The addition of fullerene C<sub>60</sub> (1 equiv.) into the reaction mixture as possible template did not provide any required calix[8]arene.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 298 K) δ 9.10 (s, 2H, Ar-OH), 8.46 (s, 2H, Ar-OH), 7.70 (d, *J* = 2.5 Hz, 2H, Ar-H), 7.66 (d, *J* = 2.5 Hz, 2H, Ar-H), 7.60 (d, *J* = 2.5 Hz, 2H, Ar-H), 7.10 (d, *J* = 2.5 Hz, 2H, Ar-H), 4.62 (s, 4H, Ar-CH<sub>2</sub>-O-CH<sub>2</sub>-Ar), 1.26 (s, 18H, Ar-C(CH<sub>3</sub>)<sub>3</sub>), 1.22 (s, 18H, Ar-C(CH<sub>3</sub>)<sub>3</sub>) ppm. The data are in agreement with ref. 20.



**Procedure B.** Monohydroxymethyl tetramer **15** (0.08 mmol, 58 mg) was dissolved in 10 mL of chloroform and added *via* syringe pump (1 mL h<sup>-1</sup>) into a flask containing TsOH monohydrate (2 equiv., 30.4 mg) in 100 mL of CHCl<sub>3</sub> under reflux. The next day, solvent was evaporated and the residue was separated using radial chromatography with CH<sub>2</sub>Cl<sub>2</sub> as an eluent. Calix[4]arene **18** was isolated as a white solid (51 mg, 90% yield).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 298 K)  $\delta$  9.81 (s, 2H, Ar-OH), 9.71 (s, 2H, Ar-OH), 7.64–7.60 (m, 4H, Ar-H), 7.50 (d,  $J$  = 2.4 Hz, 2H, Ar-H), 7.24 (d,  $J$  = 2.4 Hz, 2H, Ar-H), 4.24 (bs, 1H, Ar-CH<sub>2</sub>-Ar), 3.61 (bs, 1H, Ar-CH<sub>2</sub>-Ar) 1.22 (s, 18H, Ar-C(CH<sub>3</sub>)<sub>3</sub>), 1.23 (s, 18H, Ar-C(CH<sub>3</sub>)<sub>3</sub>) ppm. The data are in agreement with ref. 4.

The addition of fullerene C<sub>60</sub> (1 equiv.) into the reaction mixture as possible template did not provide any required calix[8]arene.

### X-ray crystallography

**Crystallographic data for 8.**  $M = 929.36$  g mol<sup>-1</sup>, triclinic system, space group  $P\bar{1}$ ,  $a = 13.2330$  (3) Å,  $b = 14.4941$  (4) Å,  $c = 14.6750$  (4) Å,  $\alpha = 71.9424$  (11)°,  $\beta = 82.1907$  (11)°,  $\gamma = 89.1864$  (12)°,  $Z = 2$ ,  $V = 2650.05$  (12) Å<sup>3</sup>,  $D_c = 1.165$  g cm<sup>-3</sup>,  $\mu(\text{Cu-K}\alpha) = 1.66$  mm<sup>-1</sup>, crystal dimensions of 0.21 × 0.11 × 0.09 mm. Data were collected at 200 (2) K on D8 Venture Photon CMOS diffractometer with Incoatec microfocus sealed tube Cu-K $\alpha$  radiation. The structure was solved by charge flipping methods<sup>21</sup> and anisotropically refined by full matrix least squares on  $F$  squared using the CRYSTALS<sup>22</sup> to final value  $R = 0.055$  and  $wR = 0.153$  using 9633 independent reflections ( $\Theta_{\text{max}} = 68.2^\circ$ ), 668 parameters and 94 restraints. The hydrogen atoms attached to carbon atoms were placed in calculated positions, refined with weak restraints and then refined with a riding constrains. The hydrogen atoms attached to oxygen atoms were refined with retrained geometry. The disordered functional groups positions were found in difference electron density maps and refined with restrained geometry. The occupancy was constrained to full for each functional group. MCE<sup>23</sup> was used for visualization of electron density maps. Diamond 3.0 (ref. 24) was used for molecular graphics. The structure was deposited into Cambridge Structural Database under number CCDC 2110418.†

**Crystallographic data for 9.**  $M = 1201.81$  g mol<sup>-1</sup>, triclinic system, space group  $P\bar{1}$ ,  $a = 11.1603$  (3) Å,  $b = 11.9646$  (3) Å,  $c = 13.1785$  (3) Å,  $\alpha = 81.0129$  (10)°,  $\beta = 70.9839$  (9)°,  $\gamma = 80.0849$  (10)°,  $Z = 1$ ,  $V = 1629.33$  (7) Å<sup>3</sup>,  $D_c = 1.225$  g cm<sup>-3</sup>,  $\mu(\text{Cu-K}\alpha) = 2.35$  mm<sup>-1</sup>, crystal dimensions of 0.18 × 0.15 × 0.12 mm. Data were collected at 200 (2) K on a D8 Venture Photon CMOS diffractometer with Incoatec microfocus sealed tube Cu-K $\alpha$  radiation. The structure was solved by charge flipping methods<sup>21</sup> and anisotropically refined by full matrix least squares on  $F$  squared using the CRYSTALS<sup>22</sup> to final value  $R = 0.033$  and  $wR = 0.082$  using 5978 independent reflections ( $\Theta_{\text{max}} = 68.4^\circ$ ), 440 parameters and 62 restraints. The hydrogen atoms attached to carbon atoms were placed in calculated positions, refined with weak restraints and then refined with a riding constrains. The hydrogen atoms attached to oxygen atoms were refined with retrained geometry. The disordered bridging atoms

were refined with sum of sulfur atom occupancies restrained to 2 and the occupancy of each position constrained to 1. The disordered solvent positions were located in difference electron density maps and refined with restrained geometry. The solvent occupancy was refined with the sum constrained to 1. MCE<sup>23</sup> was used for visualization of electron density maps. Diamond 3.0 (ref. 24) was used for molecular graphics. The structure was deposited into Cambridge Structural Database under number CCDC 2110418.†

### Conflicts of interest

There are no conflicts to declare.

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### Notes and references

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