



## Synthesis, structure and complexing properties of new calix[4](aza)crowns

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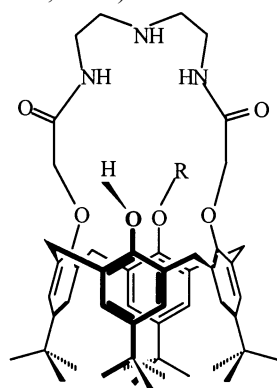
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Received 22 November 2000; accepted 22 December 2000

**Abstract**—The synthesis of calix[4](aza)crowns capped by one ‘tren’ or doubly capped by two azacrowns is described. The crystal structure of the tripodal ‘tren’ is given. Complexing properties towards  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Zn}^{2+}$  and  $\text{Cu}^{2+}$  are described. Conclusions are drawn on the role of functional groups and molecular topology in the complexation behavior of calix[4](aza)crowns. © 2001 Published by Elsevier Science Ltd.

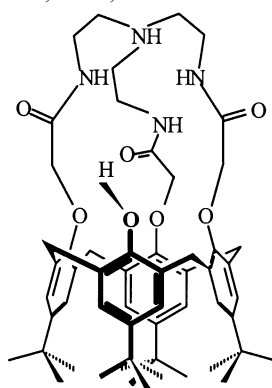
Calix[4](aza)crowns refer to molecules combining calix[4]arene elements and aza crown units. They are constructed with NH-ethylene chains attached to the phenolic oxygen atoms of the calix via acetamido functions which may also serve as linking functions and chelating groups. The first 1,3-calix[4](aza)crowns were prepared by reaction of either calix dimethyl ester or calix diacid chloride with the appropriate diamine  $\text{NH}_2\text{-R-NH}_2$  and were shown to complex divalent ( $\text{Be}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Sr}^{2+}$ ,  $\text{Ba}^{2+}$ ) and trivalent ( $\text{Sc}^{3+}$ ,  $\text{Y}^{3+}$ ,  $\text{In}^{3+}$ ,

$\text{Gd}^{3+}$ ,  $\text{Bi}^{3+}$ ) metal cations.<sup>1</sup> Regioselective alkylations of the two remaining phenolic OH and NH groups of 1,3-calix[4](aza)crowns afforded new derivatives with labile protons.<sup>2,3</sup> However, no complexation studies were reported.<sup>2,3</sup> Related methylated calix[4](aza)crowns were obtained by bridging appropriate 1,3-dimethoxy-2,4-dimethylester calix derivative.<sup>4</sup> Only the fully methylated derivative with  $2\text{OCH}_3$  and  $1\text{NCH}_3$  was shown to complex  $\text{Co}^{2+}$  and  $\text{Cu}^{2+}$  as their picrates, while the related compounds presenting labile-H pro-

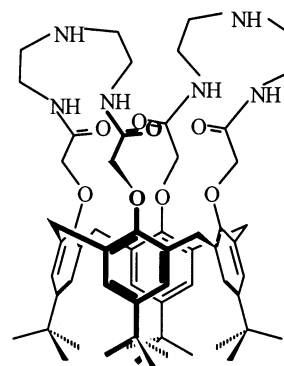


3, 4

3 (R = H), 4 (R =  $\text{CH}_2\text{CO}_2\text{Me}$ )



5



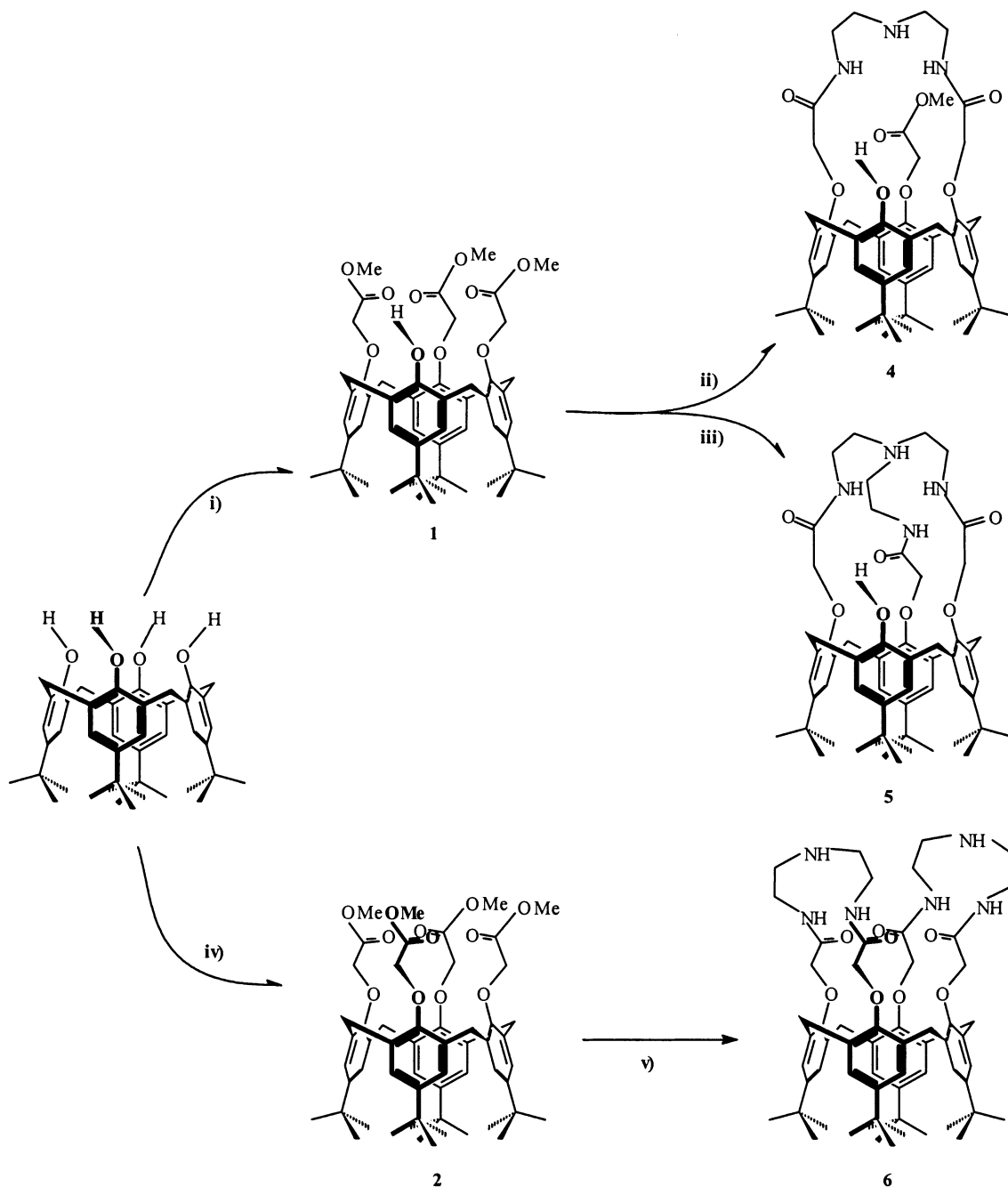
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tons were observed to extract picric acid.<sup>4</sup> An alternative route to calix[4](aza)crowns consisted of a preliminary amidation of *syn* 1,2- and 1,3-diethyl ester calix[4]-arenes with various alkanoamines followed by chlorination of the terminal OH groups and double intramolecular ring closure leading to 1,2;3,4-calix[4]bis(aza)-crowns in cone conformation and doubly bridged with aza crowns.<sup>5</sup> Recently, tetraethyl ester calix[4]arene was treated with ethylene diamine to yield the corresponding 1,2;3,4-calix[4]bis(aza)crown in cone conformation.<sup>6</sup>

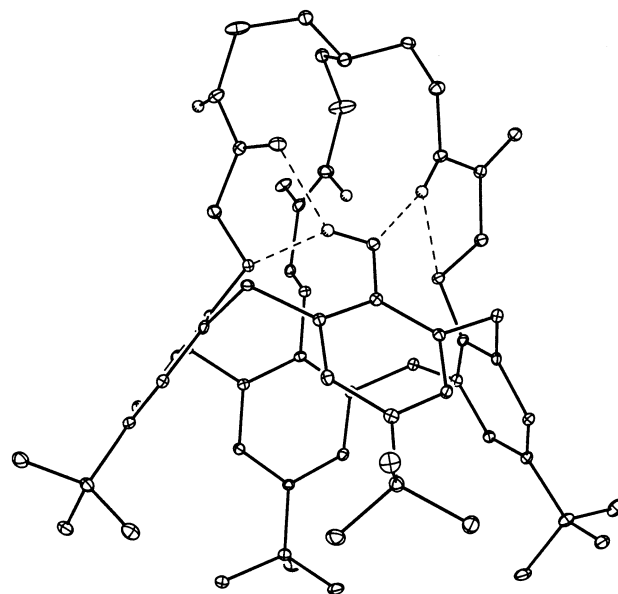
The present work was aimed at preparing calix[4]-(aza)crowns **4–6** to compare their complexing behavior to the already known calix[4](aza)crown **3**.<sup>1</sup> **4** is related to **3** by the presence of a  $\text{CH}_2\text{CO}_2\text{CH}_3$  arm on one OH function. **5** is a vaulted molecule similar to a tripodal-‘tren’ type capped benzo crown *p*-*tert*-butylcalix[4]-arene already published by us.<sup>7</sup> Calix[4]bis(aza)crown **6** is a 1,2;3,4-calix[4]bis(aza)crown doubly bridged by triethylene diamido chains.

The synthetic approach is depicted in Scheme 1.



**Scheme 1.** (i)  $\text{BrCH}_2\text{CO}_2\text{CH}_3/\text{K}_2\text{CO}_3/\text{acetone}$ , reflux; (ii)  $(\text{H}_2\text{NCH}_2\text{CH}_2)_2\text{NH}/\text{methanol-toluene}$ , reflux; (iii)  $(\text{H}_2\text{NCH}_2\text{CH}_2)_3\text{N}/\text{methanol-toluene}$ , reflux; (iv)  $\text{BrCH}_2\text{CO}_2\text{CH}_3/\text{K}_2\text{CO}_3/\text{acetonitrile}$ , reflux; (v)  $(\text{H}_2\text{NCH}_2\text{CH}_2)_2\text{NH}/\text{methanol-toluene}$ , reflux.

The synthesis of **4** began by preliminary preparation of intermediate trimethyl ester **1**, which was prepared by reaction of *p*-*tert*-butyl calix[4]arene with 3.4 equiv. of methyl bromo acetate and 3 equiv. of potassium carbonate with reflux for 3.5 days. The reaction was monitored by TLC and we were able to produce **1** in good yield.<sup>8</sup> FAB(+)MS and elemental analysis were in agreement with the proposed structure. The cone conformation of **1** was deduced from its <sup>1</sup>H NMR spectra: two AB systems were found at 4.91 and 3.26 ppm and 4.33 and 3.26 ppm with  $J=13.0$  Hz characteristic of ArCH<sub>2</sub>Ar of the calix unit. Three singlets were observed at 0.87, 1.28 and 1.29 ppm in an integration ratio of 1:1:2 for the *tert*-butyl groups showing that the molecule presents a symmetry plane. Then **1** was refluxed with 3 equiv. of triethylene diamine in 1:1 methanol:toluene for 24 h. Expected 1,3-calix[4]*mono*(aza)crown **4** substituted by one CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub> on the OH groups was produced in 23% yield. That the diamination really did occur was shown by FAB(+)MS spectrometry and elemental analysis. The 1,3-capping and the cone conformation of **4** were deduced from <sup>1</sup>H NMR data. Two AB systems were observed at 4.68 and 3.30 ppm and 4.19 and 3.29 ppm with  $J=13.0$  Hz for the ArCH<sub>2</sub>Ar. Three singlets in 1:1:2 integration ratio were detected at 1.37, 1.36 and 0.84 ppm for the *tert*-butyl groups indicative of a symmetry plane. In order to obtain the 1,3-capped calix[4]*mono*(aza)crown with two lateral CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub> we have run a similar reaction with tetramethyl ester **2**. In fact we obtained the 1,2;3,4-calix[4]bis(aza)crown **6**. The 1,2;3,4 double capping was deduced from the similitude in the aromatic region between the <sup>1</sup>H NMR spectrum of **6** and related calix[4]bis(aza)crown<sup>6</sup> with two ethylene diamines as bridges. In addition we found two AB systems with same integration ratio at 4.56 and 3.36 ppm and 4.17 and 3.24 ppm with  $J=13.0$  Hz were also observed for the ArCH<sub>2</sub>Ar of the calix unit. Another AB system was observed at 4.73 and 4.39 ppm with  $J=15.5$  Hz for the ArOCH<sub>2</sub>CONH. We concluded that the presence of the fourth CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub> prevents the 1,3-capping by steric hindrance and enforces the 1,2- and 3,4-bridgings into **6**. In a previous paper<sup>7</sup> we have published the capping of a calix[4]arene by a tripodal-amino *dome*. We decided therefore to react **1** with tris(2-aminoethyl)amine. In similar conditions tripodal-amine calix[4] (aza)crown **5** was obtained. The capping of **1** by triple amidation was confirmed by FAB(+)MS spectrometry and elemental analysis. The cone conformation of **5** was deduced from its <sup>1</sup>H NMR in CDCl<sub>3</sub>. Two sets of doublets with the same integration ratio at 3.38 and 4.10 ppm and 3.48 and 4.34 ppm both with  $J=13.0$  Hz were observed corresponding to two AB systems for ArCH<sub>2</sub>Ar of the calix[4] unit. One AB system was also observed for the two lateral ArOCH<sub>2</sub> with two doublets at 4.24 and 4.64 ppm with  $J=16.0$  Hz, while one singlet is observed for the central ArOCH<sub>2</sub>. The integration ratio of these signals was 2:1. The same integration ratio was observed on the two triplets of the CONH functions. This molecular arrangement was confirmed by X-ray crystallography.



**Figure 1.** View of the molecular unit in **7**. Hydrogen bonds in dashed lines. Protons of phenolic, ammonium and hydroxylic groups only are represented as small spheres of arbitrary radii. Only the main component of disordered groups is represented. Symmetry code: ' = 1-*x*, -*y*, -*z*.

The crystal structure of compound **5**·2CH<sub>3</sub>OH·CH<sub>2</sub>Cl<sub>2</sub> (**7**) is represented in Fig. 1.<sup>9</sup> Both intra- and intermolecular hydrogen bonds are present. The two intramolecular bonds are bifurcated, the first pair between the phenolic proton and the two oxygen atoms of one of the arms, and the second pair between the amide proton and two oxygen atoms bound to the calixarene. The intermolecular hydrogen bonds link another amide group to two successive methanol molecules, the second one being hydrogen bonded to an amide oxygen atom from a neighboring molecule. The dihedral angles between the aromatic rings and the mean plane defined by the methylenic carbon atoms are 56.3(1), 71.9(1), 58.5(1) and 64.8(1)°. A dichloromethane molecule is included in the calixarene cavity.

Preliminary complexation studies of **5** and **6** with transition metal picrates (Co(Pic)<sub>2</sub>, Ni(Pic)<sub>2</sub>, and Zn(Pic)<sub>2</sub>) were realized by means of <sup>1</sup>H NMR. <sup>1</sup>H NMR spectra were recorded after 4 weeks reaction between solid metal picrates and a chloroform solution of free ligands. The spectrum of **5** was not affected, while **6** gave unreadable spectra. We tentatively attributed a broad singlet for the eight picrate protons ( $H_{pic}$ ). According to reference 1, we investigated FAB(+)MS experiments on the resulting mixtures. Signals were found at  $m/z=2062.8$  (**6**+2Co<sup>2+</sup>+4 picrates+H<sub>2</sub>O-H<sup>+</sup>),  $m/z=2084.5$  (**6**+2 Ni<sup>2+</sup>+4 picrates+2H<sub>2</sub>O+3H<sup>+</sup>) and  $m/z=2064.7$  (**6**+2Zn<sup>2+</sup>+4 picrates+2H<sup>+</sup>). We also noticed the loss of one metal with  $m/z=1991.6$ , 1990.7 and 1992.7, respectively. Comparing with the corresponding calixarene bearing one (aza)crown bridge **3** which does not complex these transition metal cations but extracts the picric acid,<sup>4</sup> we assumed that the complexation of these cations by **6** is due to a cooperative effect between the two (aza)crown bridges and/or the different topology of

the bridging and/or the absence of the labile phenolic protons. The results presented in this work from us<sup>4</sup> and others<sup>10</sup> seem to indicate that the presence of phenolic OH on the calix and NH group in the bridge allows the extraction of picric acid, while the extraction of the metal cations requires the presence of four acetamide groups. We could not interpret <sup>1</sup>H NMR and FAB(+)MS spectra obtained with Cu(Pic)<sub>2</sub> and **5** and **6**.

Future work will be directed towards (a) determining the binding properties of calix[4](aza)crowns to find selectivities, (b) synthesizing new calix[4](aza)crowns to understand the mechanism of complexation with metal cations and (c) testing their ability to act as anion receptors.

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- General.** Melting points (mps), capillaries, N<sub>2</sub>, Büchi 500. Chromatography on SiO<sub>2</sub> column Kieselgel Merck (Art. 11567). TLC plates silica gel 60 F<sub>254</sub> Merck. <sup>1</sup>H NMR in CDCl<sub>3</sub>, Bruker SY200 ( $\delta$  in ppm). FAB(+)MS, VG-Analytical ZAB HF. Elemental analyses at the Service de Microanalyse of the Institut de Chimie de Strasbourg.
- Preparation of trimethyl ester-*p*-tert-butyl calix[4]arene (1).** *p*-tert-Butylcalix[4]arene (20.00 g; 30.91 mmol) and K<sub>2</sub>CO<sub>3</sub> (5.233 g; 37.89 mmol) in acetone (1400 mL) were stirred for 1 h at rt under N<sub>2</sub>. Then, BrCH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub> (11.391 g; 74.45 mmol) was added. After refluxing for 24 h, additional K<sub>2</sub>CO<sub>3</sub> (6.410 g; 46.41 mmol) and BrCH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub> (4.729 g; 30.91 mmol) were added. After 3.5 days, the solvents were evaporated to dryness. The crude mixture was solubilized in CH<sub>2</sub>Cl<sub>2</sub> and acidified (aqueous HCl, pH 2). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the residue precipitated in CH<sub>3</sub>OH to give **1** as white crystals. Mp 118–119°C. *R*<sub>f</sub>=0.59 (95/5 dichloromethane–acetone). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) 7.07 (s, 2H, Ar*H*<sub>meta</sub>), 7.01 (s, 2H, Ar*H*<sub>meta</sub>), 6.68 (s, 1H, ArOH), 6.59 (broad s, 4H, Ar*H*<sub>meta</sub>), 5.11 (s, 2H, ArOCH<sub>2</sub>), 4.91 (d, *J*=13.0 Hz, 2H, ArCH<sub>2</sub>Ar), 4.68 (d, *J*=15.5 Hz, 2H, ArOCH<sub>2</sub>), 4.40 (d, *J*=15.5 Hz, 2H, ArOCH<sub>2</sub>), 4.33 (d, *J*=13.0 Hz, 2H, ArCH<sub>2</sub>Ar), 3.82 (s, 6H, OCH<sub>3</sub>), 3.71 (s, 3H, OCH<sub>3</sub>), 3.26 (d, *J*=13.0 Hz, 4H, ArCH<sub>2</sub>Ar), 1.29 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.28 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 0.87 (s, 18H, C(CH<sub>3</sub>)<sub>3</sub>). FAB(+) MS, *m/z* 864.3 (M<sup>+</sup>). Anal. calcd for C<sub>53</sub>H<sub>68</sub>O<sub>10</sub>: C, 73.58; H, 7.92. Found C, 73.75; H, 7.99. Yield 54%. **Preparation of monomethyl ester 1,3-calix[4](aza)monocrown (4).** Compound **1** (0.370 g; 0.38 mmol), ethylene triamine (0.113 g; 1.19 mmol) in 1:1 methanol:toluene (60 mL) were refluxed for 24 h. After removing the solvents, the crude mixture was precipitated with methanol to give **5** (0.079; 0.08 mmol) as a white solid. Mp 187–188°C. *R*<sub>f</sub>=0.34 (50/50 acetic acid–acetonitrile). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) 7.99 (t, *J*=5.0 Hz, 2H, CONH), 7.19 (s, 2H, Ar*H*<sub>meta</sub>), 7.15 (s, 2H, Ar*H*<sub>meta</sub>), 6.58 (d, *J*=2.0 Hz, 2H, Ar*H*<sub>meta</sub>), 6.56 (d, *J*=2.0 Hz, 2H, Ar*H*<sub>meta</sub>), 5.01 (s, 2H, ArOCH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 4.69 (s, 1H, ArOH), 4.68 (d, *J*=13.0 Hz, 2H, ArCH<sub>2</sub>Ar), 4.63 (d, *J*=15.0 Hz, 2H, ArOCH<sub>2</sub>CONH), 4.19 (d, *J*=13.0 Hz, 2H, ArCH<sub>2</sub>Ar), 4.13 (d, *J*=15.0 Hz, 2H, ArOCH<sub>2</sub>CONH), 3.72 (s, 3H, OCH<sub>3</sub>), 3.44–3.40 (m, 4H, CH<sub>2</sub>NHCO), 3.30 (d, *J*=13.0 Hz, 2H, ArCH<sub>2</sub>Ar), 3.29 (d, *J*=13.0 Hz, 2H, ArCH<sub>2</sub>Ar), 2.92 (t, *J*=5.0 Hz, 4H, CH<sub>2</sub>NH), 1.59 (broad s, 1H, NH), 1.37 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.36 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 0.84 (s, 18H, C(CH<sub>3</sub>)<sub>3</sub>). FAB(+)MS, *m/z* 904.5 (M<sup>+</sup>). Anal. calcd for C<sub>55</sub>H<sub>73</sub>N<sub>3</sub>O<sub>8</sub>: C, 70.69; H, 8.44. Found C, 70.75; H, 8.49. Yield 23%. **Preparation of tripodal-amine-*p*-tert-butyl-calix[4](aza)-crown (5).** **1** (0.456 g; 0.53 mmol), tris(2-aminoethyl)-amine (0.078 g; 0.53 mmol) in 1:1 methanol:toluene (80 mL) were reflux for 38 h. Then, a second crop of tris(2-aminoethyl)amine (0.076 g; 0.53 mmol) was added with methanol (5 mL). The mixture was refluxed for additional 73 h. After removing the solvents, the crude mixture was precipitated with methanol to afford **5** (0.241 g; 0.26 mmol) as a white solid. Mp>270°C. *R*<sub>f</sub>=0.74 (acetone). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 8.26 (t, *J*=5.5 Hz, 2H, NH), 8.01 (t, *J*=5.5 Hz, 1H, NH), 7.20 (s, 2H, Ar*H*<sub>meta</sub>), 7.12 (s, 2H, Ar*H*<sub>meta</sub>), 6.81 (d, *J*=2.5 Hz, 2H, Ar*H*<sub>meta</sub>), 6.66 (d, *J*=2.5 Hz, 2H, Ar*H*<sub>meta</sub>), 5.29 (s, 1H, ArOH), 4.64 (d, *J*=16.0 Hz, 2H, ArOCH<sub>2</sub>), 4.45 (s, 2H, ArOCH<sub>2</sub>), 4.34 (d, *J*=13.0 Hz, 2H, ArCH<sub>2</sub>Ar), 4.24 (d, *J*=16.0 Hz, 2H, ArOCH<sub>2</sub>), 4.10 (d, *J*=13.0 Hz, 2H, ArCH<sub>2</sub>Ar), 3.48 (d, *J*=13.0 Hz, 2H, ArCH<sub>2</sub>Ar), 3.38–3.48 (m, 6H, CH<sub>2</sub>-CONH), 3.38 (d, *J*=13.0 Hz, 2H, ArCH<sub>2</sub>Ar), 3.00–2.90 (m, 2H, CH<sub>2</sub>-CONH), 2.75–2.62 (m, 4H, CH<sub>2</sub>-CONH), 1.32 (s, 18H, C(CH<sub>3</sub>)<sub>3</sub>), 0.87 (s, 18H, C(CH<sub>3</sub>)<sub>3</sub>). FAB(+)MS, *m/z* 915.6 (M<sup>+</sup>). Anal. calcd for C<sub>56</sub>H<sub>74</sub>N<sub>4</sub>O<sub>7</sub>·0.5CH<sub>2</sub>Cl<sub>2</sub>·CH<sub>3</sub>OH: C, 69.27; H, 8.12. Found C, 69.10; H, 8.13. Yield 50%. **Preparation of 1,2,3,4-calix[4]bis(aza)crown (6).** Compound **2** (3.754 g; 3.93 mmol), triethylene diamine (0.739 g; 7.17 mmol) in 1:1 methanol:toluene (400 mL) were refluxed for 6 days. After removing the solvents, the crude mixture was precipitated with methanol to afford **6** (0.699 g; 0.68 mmol) as a white solid. Mp>270°C. *R*<sub>f</sub>=0.27 (acetic acid:acetonitrile:water 4:4:1). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 7.46 (broad t, *J*=2.5 Hz, 4H, NH), 6.89 (s, 4H, Ar*H*<sub>meta</sub>), 6.87 (s, 4H, Ar*H*<sub>meta</sub>), 4.73 (d, *J*=15.5 Hz, 4H, ArOCH<sub>2</sub>), 4.56 (d, *J*=13.0 Hz, 2H, ArCH<sub>2</sub>Ar), 4.39 (d, *J*=15.5 Hz, 4H, ArOCH<sub>2</sub>), 4.17 (d, *J*=13.0 Hz, 2H, ArCH<sub>2</sub>Ar), 3.48–3.65 (m, 8H, CH<sub>2</sub>-NHCO), 3.36 (d, *J*=13.0 Hz, 2H, ArCH<sub>2</sub>Ar), 3.24 (d, *J*=13.0 Hz, 2H, ArCH<sub>2</sub>Ar), 2.92 (t, *J*=2.5 Hz, 8H, CH<sub>2</sub>NHCH<sub>2</sub>), 1.77 (broad s, 2H, NH), 1.09 (s, 36H, C(CH<sub>3</sub>)<sub>3</sub>). FAB(+)MS,

$m/z$  1015.6 (M+H)<sup>+</sup>. Anal. calcd for C<sub>60</sub>H<sub>82</sub>N<sub>6</sub>O<sub>8</sub>·CH<sub>3</sub>OH: C, 69.95; H, 8.28. Found C, 69.82; H, 7.69. Yield 18%.

9. **Crystal structure.** The data were collected on a Nonius Kappa-CCD area detector diffractometer using graphite-monochromated Mo K $\alpha$  radiation (0.71073 Å). The crystal, which was highly unstable out of its mother-solution, was introduced in a Lindemann glass capillary with a protecting 'Paratone' oil (Exxon Chemical Ltd.) coating. The protons bound to phenolic oxygen and amine nitrogen atoms and the hydroxylic protons of the methanol molecules were introduced as found on the Fourier difference maps, whereas all other hydrogen atoms were introduced at calculated positions. All hydrogen atoms were treated as riding atoms with a displacement parameter equal to 1.2 (OH, NH, CH, CH<sub>2</sub>) or 1.5 (CH<sub>3</sub>) times that of the parent atom. All non-hydrogen atoms were refined anisotropically, except the disordered ones and the carbon atom of the dichloromethane molecule, which was not stable on refinement. Two carbon atoms of the bridges were found disordered over two sites and refined with occupation factors constrained to sum to unity. Two of those positions are too close to each other and the occupation factors have been chosen so as to take into account the impossibility of them to both being occupied in the same molecule. Final  $R_1=0.080$  for 9511 ( $R_{\text{int}}=0.099$ ) reflections and 676 parameters. Crystal data have been deposited with the Cambridge Crystallographic Data Centre. **Crystal data for 5·2CH<sub>3</sub>OH·CH<sub>2</sub>Cl<sub>2</sub> (7):** C<sub>59</sub>H<sub>84</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>9</sub>;  $M=1064.20$ , triclinic, space group  $P\bar{1}$ ,  $a=12.0599(9)$ ,  $b=12.351(2)$ ,  $c=19.855(3)$  Å,  $\alpha=77.707(4)$ ,  $\beta=79.147(8)$ ,  $\gamma=86.083(7)^\circ$ ,  $V=2836.8(6)$  Å<sup>3</sup>,  $Z=2$ ,  $D_c=1.246$  g cm<sup>-3</sup>,  $\mu=0.173$  mm<sup>-1</sup>,  $F(000)=1144$ ,  $T=110(2)$  K.
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