Synthesis of "calixarene-like" *N*,*N*-ditosyldiaza[3.3](1,4)-naphthalenophanes†

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A series of new tetrahomodiazacalix[2]naphthalenes, containing 2,3-dialkoxy-substituted naphthalene units, have been synthesized and some of their properties are reported. All of the newly-synthesized macrocycles were highly symmetrical and conformationally rigid and revealed "calixarene-like" 1,3- alternate type structures.

Introduction

There are several examples of homoazacalixarenes such as **1a–4** (Fig. 1) which have been reported by various research groups.[1–11] These compounds belong to a class of macrocyclic-ring expanded calixarenes in which the methylene bridges are partly, or completely, replaced by $-CH_2NRCH_2-$ groups (R = H, alkyl, benzyl, tosyl, *etc.*). Such homoazacalixarenes are of considerable interest because they have been shown to be moderate receptors for various guests such as alkali-metal ions,[2] UO_2^{2+},[2,3] Zn^{2+},[4] Co^{3+},[4] Nd^{3+},[5] Yb^{3+},[6] ammonium anion[7] and various fluorescent molecules.[8,9] In general, these homoaza calixarene analogues were prepared *via* Schiff base intermediates,[10] or *via* *N*-alkylation of the corresponding precursors.[1–9,11]

To date, however, there have been no reports dealing with analogous homoazacalixnaphthalenes and/or their derivatives. In order to expand the known class of homoheterobridged isocalixnaphthalenes beyond the known homoxa- (**5** and **6**)[12] and homothia- (**7** and **8**)[13] analogues, the synthesis of the analogous *N*-substituted homoazaisocalixnaphthalenes **9a–d** were undertaken (Fig. 2). Notably, CPK models suggested that the *N*-tosyl side-arm substituents could efficiently reduce the flexibility of compounds **9a–d** and that these newly-synthesized calixnaphthalenes **9a–d** might serve as potentially useful receptors for binding studies with neutral or ionic guest species.

Results and discussion

In order to synthesize the target homoazaisocalixnaphthalenes **9a–d** and **10a–d**, we first attempted to employ the Schiff-base approach involving the condensation between dialdehyde **15** or **16**, with 1,4-bis(aminomethyl)-2,3-dimethoxynaphthalene **19a**. These precursors were derived from 2,3-dihydroxynaphthalene (**11**) as shown below in Schemes 1 and 2, respectively.

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PCC-mediated oxidation of 1,4-bis(hydroxymethyl)-2,3-dimethoxynaphthalene (**14**)[12] derived *via* a three-step sequence from 2,3-dihydroxynaphthalene (**11**) afforded pure dialdehyde **15** in near-quantitative yields (Scheme 1). By comparison, the direct diformylation of 2,3-dimethoxynaphthalene (**12a**) *via* a dilithiation reaction[14,15] afforded **15** in only at best, 10% yields. Demethylation of intermediate **15** with BBr_3 in DCM at room temperature gave dialdehyde **16** in 73–100% yields (Scheme 1). Our procedure proved to be more reproducible[16] than that described by Reinhoudt.[17] Application of the Skattebøl formylation procedure,[18] failed to give **16** directly from **11**.

The bis(methylamino) intermediates **19a–d** were synthesized from the corresponding bis(bromomethyl)naphthalenes **13a–d** *via* two-step Gabriel reactions (Scheme 2). Firstly, treatment of each of the 2,3-dialkoxynaphthalenes **13a–d** with potassium phthalimide (**17**) in refluxing DMF afforded the corresponding 1,4-bis(*N*-phthalimidomethyl)-2,3-dialkoxynaphthalenes **18a–d**, each in high yields (70–93%). Subsequent treatment of each of **18a–d** in the presence of hydrazine in refluxing methanol produced the corresponding products **19a–d** in 65–100% yields. In the case of **18b**, using ethanol as solvent resulted in a lower yield (63%) of **19** than that obtained with methanol which was quantitative.

The Schiff-base approach was then first attempted using Kuhnert's procedure without using a cationic template (Scheme 3).[15] However, none of the desired product was obtained either at ambient temperature, or upon heating at reflux for different reaction times, solutions of dialdehyde **15** and bis(aminomethyl)naphthalene **19a** in either DCM, acetonitrile[19] or benzene. Employing MacLachlan's acetonitrile–chloroform conditions[20] gave an unidentified resinous mixture which was not soluble in most of the common organic solvents and could not be characterized.

The condensation of 1,4-diformyl-2,3-dihydroxynaphthalene (**16**) and 1,4-bis(aminomethyl)-2,3-dimethoxynaphthalene (**19a**) (Scheme 3) was also attempted in several solvent conditions (CH_2Cl_2,[15] CH_3CN,[19] 1 : 1 CH_3CN–$CHCl_3$,[16b,20,21] or 1 : 1 MeOH–CH_3CN[17]). In all cases, solutions of **16** were either added dropwise, to solutions of **19a** in the same solvent, or *vice versa*, or using a two-syringe pump in order to add both reactant solutions at the same rate. These reactions were conducted at either room temperature (3–14 d) or at reflux

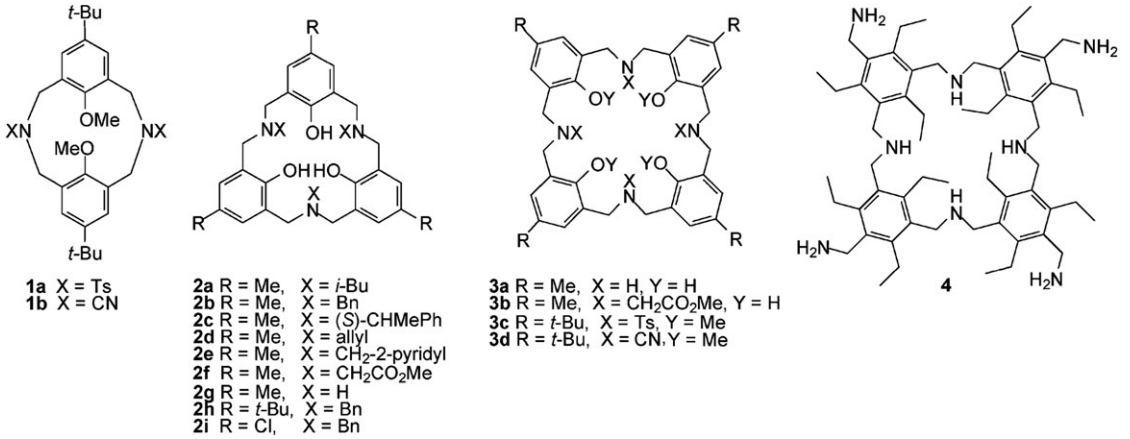


Fig. 1

(2–4 h). Under the conditions employed, the starting materials were completely consumed. The products however were not soluble in the common organic solvents and thus could not be characterized. Similarly, attempts using $Ba(CF_3SO_2)_2$ or $Ba(SCN)_2$ as the source of the Ba^{2+} template to prepare the Schiff bases **20** or **21**, following Reinhoudt's protocol,[17] in a variety of solvents (CH_2Cl_2,[15] CH_3CN,[19] 1 : 1 CH_3CN–$CHCl_3$,[16b,20,21] 1 : 1 MeOH–CH_3CN[17]) at either room temperature (1–3 d) or reflux temperatures (1–4 h), gave brown or orange precipitates which were not soluble in most common organic solvents and could not be characterized. No further attempts were therefore carried out using this Schiff-base approach.

An alternate approach using Anslyn's procedure[9] in which 1,4-bis(bromomethyl)-2,3-diethoxynaphthalene (**13b**)[12] was added to the mixture of 1,4-bis(aminomethyl)-2,3-dimethoxynaphthalene (**19b**) and TEA in DCM at room temperature (Scheme 4) also gave only an intractable resinous mixture. The expected cyclization, therefore, failed to form desired cyclic products, *e.g.* **22b** and **23b**.

"Calixarene-like" *N,N*-ditosyldiaza[3.3](1,4)-naphthalenophanes 9a–d

Since both Anslyn's procedure and the Schiff base approach failed to give the desired precursors for **9a–d** and/or **10a–d**, a different strategy (Scheme 5) involving coupling of 1,4-bis(bromomethyl)-2,3-dialkoxynaphthalenes (**13a–d**) and 1,4-bis(*p*-tolylsulfonylaminomethyl)-2,3-dialkoxynaphthalenes (**24a–d**) was evaluated.[22] The attempted ditosylation of **19a–d** by TsCl (Scheme 5) under various conditions using organic bases such as TEA–THF,[22] pyridine–THF or DCM,[23] or neat TEA–pyridine[23] however failed to produce any of the desired products **24a–d**. Nevertheless, when Hart's protocol[24] using a two-phase system consisting of aqueous NaOH and DCM was employed, compounds **24a–d** were produced in 73–83% yields.

The coupling reactions between intermediates **13a–d** and **24a–d**, respectively, in DMF in the presence of Cs_2CO_3 however, surprisingly produced **9a–d** as the only products (Scheme 5). None of the expected [2 + 2], coupling products *e.g.* **10a–d** (or higher), as were observed previously in the synthesis of homooxa-**5a–d** or homothiocalixnaphthalenes **7a–d**, were formed. Examination of CPK models suggested that due to steric strain, the desired [2 + 2] coupling products **10a–d** were expected to be more favorably formed over the [1 + 1] products, namely *N,N*-ditosyldiaza[3.3](1,4)naphthaleneophanes (**9a–d**). Nevertheless, (+)-APCI MS analysis all showed the correct molecular ion peaks of **9a–d**, respectively, at *m*/*z* 767.0, 823.3, 879.5, and 935.4 with 100% relative intensities.

All of these newly-synthesized macrocyclic compounds **9a–d** had relatively simple ambient-temperature ^{1}H NMR spectra which indicated that they were highly symmetrical. The bridging methylene groups of **9a–d** were slightly more shielded in the following order: **9a** > **9b** > **9c** > **9d**. Noticeably, the ^{1}H NMR spectra for compounds **9a–d** all revealed AB-type doublets of doublets for their bridging methylene groups, at δ 4.19 and 5.29 ppm; 4.13 and 5.24 ppm; 4.11 and 5.23 ppm; and 4.09 and 5.23 ppm, respectively, thus indicating that compounds **9a–d** are conformationally rigid. This observation is consistent with other [3.3](1,4)naphthaleneophanes.[25]

The formation of **9a** was confirmed by its X-ray structure (Fig. 3).[26] The X-ray structure of **9c** was also obtained, but only for reference, because of its much lower refinement,[27]

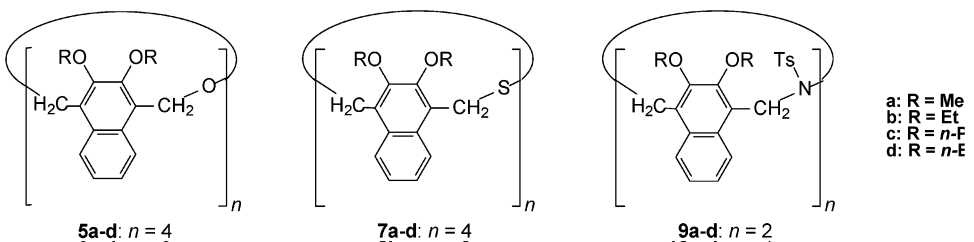
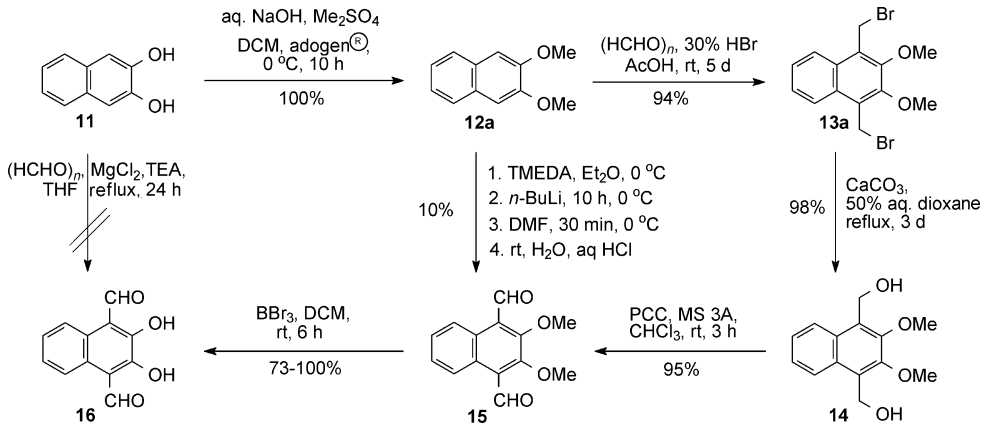
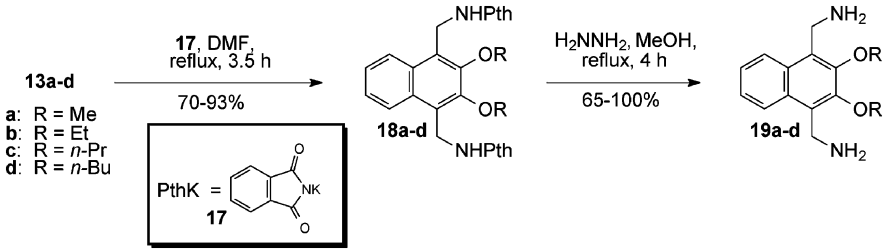


Fig. 2



Scheme 1



Scheme 2

although for both **9a** and **9c**, molecular mechanics calculations[28] suggested the same "1,3-alternate"-type conformers[29] as minimum energy conformers (see Fig. 3).

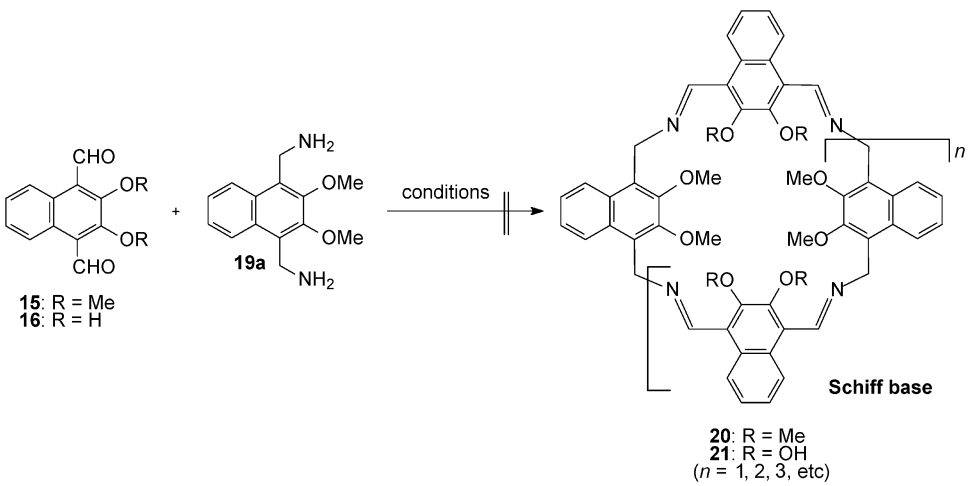
Pappalardo and co-workers[30] previously found that the coupling reaction between 1,4-bis(chloromethyl)-2,3,5,6-tetramethylbenzene (**25**) and monosodium *p*-toluenesulfonamide (**26**) also formed only the [1 + 1] coupling product, **27**. This product was formed in 15% yield along with the substitution product 1,4-bis(tosylaminomethyl)durene (**28**) in 36% yield (Scheme 6).

Complexation with C_{60}- or C_{70}-fullerene guests

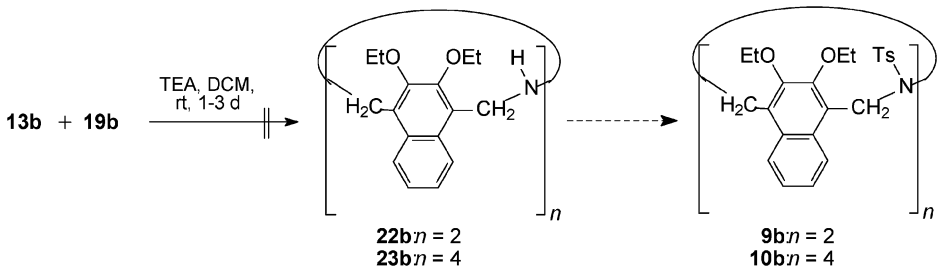
Molecular mechanics simulations suggested that both C_{60}- or C_{70}-fullerene could potentially form inclusion complexes with **9a–d**. Disappointingly, however, complexation tests with these compounds and C_{60} and C_{70} in either toluene, or carbon disulfide solutions, as monitored by both colour changes or by complexation-induced chemical shifts in their ^{1}H NMR spectra, failed to reveal any evidence for any such complexation.

Conclusions

In summary, both the *N*-alkylation and cyclic Schiff base approaches failed to afford the desired precursors for synthesis of homoazaisocalixnaphthalenes **9a–d** and **10a–d** but instead give resinous intractable products or no reaction. The coupling between 1,4-bis(*p*-tolylsulfonylaminomethyl)-2,3-dialkoxynaphthalenes (**13a–d**) and 1,4-bis(bromomethyl)-2,3-dialkoxynaphthalenes (**24a–d**), respectively, gave a series



Scheme 3



Scheme 4

of new corresponding *N*,*N*-ditosyldiaza[3.3](1,4)naphthaleneophanes (**9a–d**) (or "tetrahomodiazaisocalix[2]naphthalenes"), respectively, in reasonable yields (29–48%) for such macrocyclizations. The ^{1}H NMR spectra of all of the macrocycles obtained showed clearly that they were highly symmetrical and also conformationally rigid and thus could provide a new series of pre-organized molecular scaffolds. The X-ray crystal structures of **9a** and **9c** also revealed that the 1,3-alternate conformations are most likely the dominant ones.

Complexation studies to evaluate the binding properties of these new tetrahomodiazaisocalix[2]naphthalenes with neutral fullerene guests failed to reveal any such binding. Nevertheless, an extensive study employing various metal and transition-metal ions[4–6,31] will be undertaken and if any significant binding properties are observed these will reported upon in due course.

Experimental

1,4-Diformyl-2,3-dimethoxynaphthalene (15)

Procedure 1: oxidation of 1,4-bis(hydroxylmethyl)-2,3-dimethoxynaphthalene (14). To a stirred suspension of PCC (1.86 g, 3.72 mmol) and 3 Å molecular sieves (2.8 g) in $CHCl_3$ (30 mL) at room temperature was added a solution of **14**[12] (0.51 g, 2.0 mmol) in $CHCl_3$ (100 mL). The reaction mixture was stirred for a further 3 h, filtered through a Florisil® pad, and then the residue was washed with $CHCl_3$ (3 × 30 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. After the solvent was removed under reduced pressure, the crude product was purified by chromatography (1 : 9 EtOAc–hexane) to yield **15** (0.46 g, 92%) as a yellow solid: mp 100–101 °C (acetone–hexane) (lit.[16b] 101–102 °C); ^{1}H NMR δ 4.11 (s, 6H), 7.60–7.62 (m, 2H), 9.02–9.04 (m, 2H), 10.8 (s, 2H); ^{13}C NMR δ 63.2, 125.1, 128.2, 128.8, 129.0, 158.4, 192.2; GCMS *m*/*z* (%) 244 (M^+, 85), 229 (30), 169 (65), 102 (100).

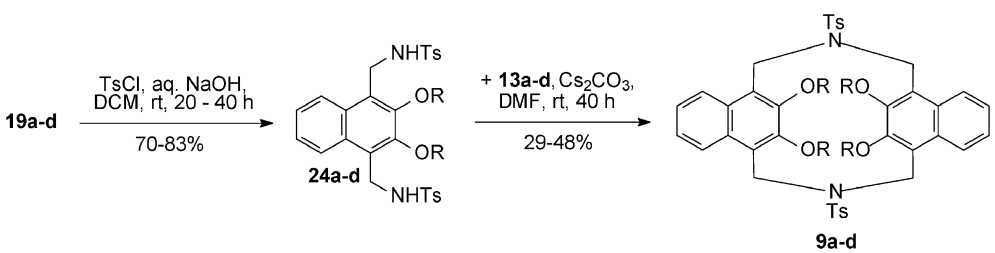
Procedure 2: Direct diformylation of 2,3-dimethoxynaphthalene (12a). To a stirred solution of **12a** (0.75 g, 4.00 mmol) and TMEDA (3.0 mL, 20 mmol) in anhydrous Et_2O (25 mL) at 0 °C was added dropwise 1.6 M *n*-BuLi in hexane (13 mL, 20 mmol), and the reaction mixture was then heated at reflux for a further 10 h and cooled to room temperature. To the reaction mixture DMF (1.6 mL, 20 mmol) was added dropwise, and the mixture was stirred for a further 30 min. Cool water (20 mL) was added to the mixture, followed by aqueous 3 M HCl (4.0 mL). The mixture was extracted with Et_2O (3 × 40 mL). The organic layers were combined, washed with brine (1 × 40 mL), dried over $MgSO_4$ and filtered. After the solvent was removed under reduced pressure, the resulting residue was purified by chromatography (2 : 98 EtOAc–hexane) to yield **15** (0.10 g, 10%) having identical characterization data to those obtained from procedure 1.

1,4-Diformyl-2,3-dihydroxynaphthalene (16)

To a stirred solution of **15** (1.12 g, 4.50 mmol) in dry DCM (45 mL) was added dropwise a solution of BBr_3 (1.7 mL, 18 mmol) in dry DCM (17 mL) over 1 h. The reaction mixture was stirred for a further 5 h, and cold water (100 mL) was then added at 0 °C. The mixture was acidified with aqueous 6 M HCl until pH reached 1–2, extracted with $CHCl_3$ (3 × 60 mL), dried over anhydrous $MgSO_4$ and filtered. After the solvent was removed under reduced pressure, the residue was dried over night on a vacuum pump to yield crude product (0.99 g, 100%), which was purified by chromatography (2 : 8 EtOAc–hexane) to yield **16** (0.72 g, 73%) as a yellow solid: mp 205 °C (decomp.) [lit.[16b] >180 °C (decomp.)]; ^{1}H NMR δ 7.58–7.60 (m, 2H), 8.39–8.41 (m, 2H), 10.9 (s, 2H), 13.0 (s, 2H, disappears upon D_2O addition); ^{13}C NMR δ 115.6, 120.2, 126.4, 127.0, 155.2, 194.6; GCMS *m*/*z* (%) 216 (M^+, 100), 188 (100).

1,4-Bis(*N*-phthalimidomethyl)-2,3-dimethoxynaphthalene (18a). General procedure

To a stirred solution of crude **13a** (3.74 g, 10.0 mmol) in DMF (100 mL), was added potassium phthalimide (**17**) (4.07 g,



Scheme 5

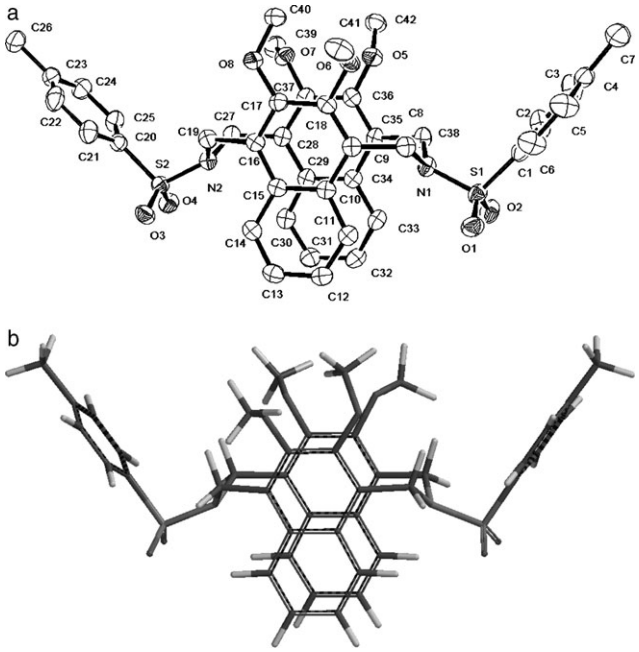


Fig. 3 ORTEP representation of **9a** (top) showing its "1,3-alternate" conformation (solvent molecules were removed for clarity) identical with its computer-generated lowest energy conformer (bottom).

22.0 mmol). The reaction mixture was heated at reflux (153–160 °C) with stirring for 3.5 h, cooled to room temperature and then poured into cold water (500 mL). The resulting precipitate was filtered and dried at 60 °C to afford crude product (4.20 g, 83%) as a light yellow powder, which was purified by chromatography (5 : 95 EtOAc–DCM) to yield **18a** (3.34 g, 66%) as also a light yellow powder: mp 270–272 °C; ^{1}H NMR δ 4.09 (s, 6H), 5.37 (s, 4H), 7.37–7.39 (m, 2H), 7.64–7.66 (m, 4H), 7.77–7.78 (m, 4H), 8.06–8.08 (m, 2H); ^{13}C NMR δ 33.8, 61.0, 123.4, 124.0, 124.4, 125.7, 129.5, 132.2, 134.1, 152.0, 168.4; (+)-APCI MS m/z (%) 507.0 (M^+, 40), 360.1 (100), calc.: 506.51 for $C_{30}H_{22}N_2O_6$.

1,4-Bis(*N*-phthalimidomethyl)-2,3-diethoxynaphthalene (18b)

Using the general procedure for **18a**, the reaction of the crude **13b** (2.81 g, 6.99 mmol) and **17** (2.76 g, 14.9 mmol) gave the crude product (3.11 g, 83%) as a light yellow powder, which was purified by chromatography (3 : 7 EtOAc–hexane) to yield **18b** (2.94 g, 79%) as a colourless powder: mp 238–240 °C; ^{1}H NMR δ 1.46 (t, J = 7.1 Hz, 6H), 4.34 (q, J = 7.1 Hz, 4H), 5.38 (s, 4H), 7.36–7.38 (m, 2H), 7.64–7.65 (m, 4H), 7.76–7.78 (m, 4H), 8.03–8.05 (m, 2H); ^{13}C NMR δ 16.0, 34.1, 69.4, 123.3, 124.1, 124.3, 125.6, 129.5, 132.2, 134.0, 151.3, 168.3; (+)-APCI MS m/z (%) 535.1 (M^+, 70), 388.1 (100), calc.: 534.37 for $C_{32}H_{26}N_2O_6$.

1,4-Bis(*N*-phthalimidomethyl)-2,3-di-*n*-propoxynaphthalene (18c)

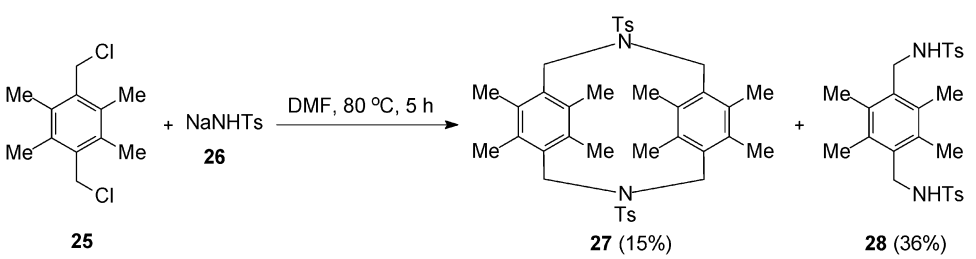
Using the general procedure for **18a**, the reaction of the crude **13c** (3.44 g, 8.00 mmol) and **17** (3.16 g, 17.1 mmol) gave crude product (4.20 g, 93%) as a yellow powder, which was purified by chromatography (DCM) to yield **18c** (3.12 g, 69%) as a light yellow powder: mp 193–195 °C; ^{1}H NMR δ 1.07 (t, J = 7.5 Hz, 6H), 1.87–1.94 (m, 4H), 4.24 (t, J = 6.5 Hz, 4H), 5.39 (s, 4H), 7.34–7.35 (m, 2H), 7.64–7.66 (m, 4H), 7.76–7.78 (m, 4H), 7.99–8.01 (m, 2H); ^{13}C NMR δ 10.8, 23.8, 34.1, 75.3, 123.4, 124.0, 124.3, 125.5, 129.5, 132.2, 134.0, 151.5, 168.3; (+)-APCI MS m/z (%) 563.1 (M^+, 40), 416.1 (100), calc.: 562.62 for $C_{34}H_{30}N_2O_6$.

1,4-Bis(*N*-phthalimidomethyl)-2,3-di-*n*-butoxynaphthalene (18d)

Using the general procedure for **18a**, the reaction of the crude **13d** (5.50 g, 12.0 mmol) and **17** (4.89 g, 26.4 mmol) gave crude product (6.77 g, 95%) as a yellow powder, which was purified by chromatography (DCM) to yield **18d** (4.96 g, 70%) as a light yellow powder: mp 184–185 °C; ^{1}H NMR δ 0.99 (t, J = 7.4 Hz, 6H), 1.49–1.57 (m, 4H), 1.83–1.89 (m, 4H), 4.28 (t, J = 6.7 Hz, 4H), 5.38 (s, 4H), 7.33–7.35 (m, 2H), 7.63–7.65 (m, 4H), 7.76–7.77 (m, 4H), 7.99–8.00 (m, 2H); ^{13}C NMR δ 14.3, 19.6, 32.7, 34.0, 73.7, 123.4, 124.0, 124.3, 125.5, 129.5, 132.2, 134.0, 151.6, 168.3; (+)-APCI MS m/z (%) 591.1 (M^+, 70), 444.2 (100), calc.: 590.68 for $C_{36}H_{34}N_2O_6$.

1,4-Bis(aminomethyl)-2,3-dimethoxynaphthalene (19a). General procedure

The suspension of **18a** (3.04 g, 6.00 mmol) and hydrate hydrazine (2.4 mL, 48 mmol) in MeOH (85 mL) was heated at reflux with stirring for 4 h. After the solvent was removed under reduced pressure, the residue was dissolved in distilled water (50 mL) and extracted with $CHCl_3$ (3 × 50 mL). The organic layers were combined, washed with distilled water (2 × 50 mL), brine (1 × 50 mL), dried over anhydrous $MgSO_4$ and filtered. After the solvent was removed under reduced pressure, the residue was dried overnight on a vacuum pump, to yield **19a** (1.29 g, 88%) as a yellow oily liquid: ^{1}H NMR δ 1.59 (s, br, 4H, disappears upon D_2O addition), 3.96 (s, 6H), 4.29 (s, 4H), 7.47–7.50 (m, 2H), 8.05–8.07 (m, 2H); ^{13}C NMR δ 36.7, 61.5, 124.1, 125.6, 130.0, 130.9, 150.0; GCMS m/z (%) 246 (M^+, 45), 202 (95), 171 (70), 128 (60), 115 (100).



Scheme 6

1,4-Bis(aminomethyl)-2,3-diethoxynaphthalene (19b)

Procedure 1. Using the general procedure for **19a**, the reaction of **18b** (3.21 g, 6.00 mmol) and H_2NNH_2 (2.4 mL, 48 mmol) gave **19b** (1.65 g, 100%) as a yellow oily liquid: ^{1}H NMR δ 1.46 (t, J = 7.1 Hz, 6H), 1.54 (s, br, 4H, disappears upon D_2O addition), 4.14 (q, J = 7.0 Hz, 4H), 4.30 (s, 4H), 7.47–7.49 (m, 2H), 8.05–8.07 (m, 2H); ^{13}C NMR δ 16.1, 37.0, 69.9, 124.2, 125.5, 130.0, 131.1, 149.2; GCMS m/z (%) 274 (M^+, 45), 257 (20), 201 (100), 184 (40), 115 (100).

Procedure 2. Using 95% EtOH as solvent instead of MeOH afforded **19b** (63%) having identical characterization data to those obtained by procedure 1.

1,4-Bis(aminomethyl)-2,3-di-*n*-propoxynaphthalene (19c)

Using the general procedure for **19a**, the reaction of **18c** (2.25 g, 4.00 mmol) and H_2NNH_2 (1.6 mL, 32 mmol) gave **19c** (1.21 g, 100%) as a yellow semisolid: mp 50–51 °C; ^{1}H NMR δ 1.10 (t, J = 7.3, 6H), 1.59 (s, br, 4H, disappears upon D_2O addition), 1.84–1.91 (m, 4H), 4.02 (t, J = 6.8 Hz, 4H), 4.29 (s, 4H), 7.47–7.49 (m, 2H), 8.05–8.07 (m, 2H); ^{13}C NMR δ 10.8, 23.9, 37.0, 76.1, 124.2, 125.5, 130.0, 131.1, 149.5; GCMS m/z (%) 302 (M^+, 60), 257 (20), 226 (60), 215 (100), 200 (63), 184 (45), 128 (50), 115 (60).

1,4-Bis(aminomethyl)-2,3-di-*n*-butoxynaphthalene (19d)

Using the general procedure for **19a**, the reaction of **18d** (2.95 g, 5.00 mmol) and H_2NNH_2 (2.0 mL, 40 mmol) gave **19d** (1.08 g, 65%) as a light yellow liquid: ^{1}H NMR δ 1.01 (t, J = 7.4 Hz, 6H), 1.51 (s, br, 4H, disappears upon D_2O addition), 1.53–1.60 (m, 4H), 1.80–1.86 (m, 4H), 4.06 (t, J = 6.7 Hz, 4H), 4.29 (s, 4H), 7.47–7.49 (m, 2H), 8.06–8.08 (m, 2H); ^{13}C NMR δ 14.2, 19.6, 32.8, 37.0, 74.4, 124.3, 125.5, 130.0, 131.1, 149.5; GCMS m/z (%) 330 (M^+, 60), 285 (20), 240 (84), 229 (100), 184 (65), 128 (67), 115 (60).

2,3-Diethoxy-1,4-bis(*p*-tolylsulfonylaminomethyl)naphthalene (24a). General procedure

To a stirred solution of **19a** (0.25 g, 1.0 mmol) in DCM (1 mL) at room temperature was added an aqueous solution of 0.2 M NaOH (10 mL, 2.00 mmol). The reaction mixture was stirred at room temperature a further 10 min, and a solution of TsCl (0.39 g, 2.00 mmol) in DCM (9 mL) was added dropwise over 20 min. The reaction mixture was stirred for another 20 h, and water (100 mL) was added to the mixture. The resulting precipitate was filtered off, washed several times with DCM and dried at 50 °C to afford **24a** (0.44 g, 80%) as a light yellow powder: mp >257 °C (decomp.); ^{1}H NMR δ 2.42 (s, 6H), 3.65 (s, 6H), 4.32 (d, J = 5.3 Hz, 4H), 7.43 (d, J = 8.0 Hz, 4H), 7.46–7.48 (m, 2H), 7.76 (d, J = 8.7 Hz, 4H), 7.80 (t, J = 5.4 Hz, 2H, disappears upon D_2O addition), 7.95–7.97 (m, 2H); ^{13}C NMR δ 21.0, 37.1, 60.8, 124.4, 124.5, 125.4, 126.7, 129.3, 129.6, 137.0, 142.7, 150.3; (−)-APCI MS m/z (%) 553.0 (M^+, 100), calc.: 554.67 for $C_{28}H_{30}N_2O_6S_2$.

2,3-Diethoxy-1,4-bis(*p*-tolylsulfonylaminomethyl)naphthalene (24b). General procedure

To a stirred solution of **19b** (1.75 g, 6.37 mmol) in DCM (2.0 mL) at room temperature was added an aqueous solution of 0.3 M NaOH (63.0 mL, 19.0 mmol). The reaction mixture was stirred for another 10 min, and a solution of TsCl (3.65 g, 19.1 mmol) in DCM (75 mL) was added dropwise over 30 min at room temperature. The reaction mixture was stirred for a further 40 h. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). The organic layers were combined, washed with water (2 × 50 mL), brine (1 × 50 mL), dried over $MgSO_4$ and filtered. After the solvent was removed under reduced pressure, the resulting residue was purified by chromatography (2 : 98 EtOAc–DCM) to yield **24b** (2.88 g, 77%) as a colourless powder: mp 210–211 °C; ^{1}H NMR δ 1.23 (t, J = 7.0 Hz, 6H) 2.41 (s, 6H), 3.89–3.94 (q, J = 7.1 Hz, 4H), 4.51 (d, J = 5.3 Hz, 4H), 4.64 (t, J = 4.8 Hz, 2 H, disappears upon D_2O addition) 7.23 (d, J = 8.0 Hz, 4H), 7.40–7.42 (m, 2H), 7.72 (d, J = 7.7 Hz, 4H) 7.77–7.79 (m, 2H); ^{13}C NMR δ 15.9, 21.7, 38.6, 70.0, 124.0, 125.2, 126.4, 127.5, 129.6, 129.8, 136.7, 143.7, 149.9; (−)-APCI MS m/z (%) 581.1 ([M − 1]$^-$, 100), calc.: 582.7 for $C_{30}H_{34}N_2O_6S_2$.

2,3-Di-*n*-propoxy-1,4-bis(*p*-tolylsulfonylaminomethyl)-naphthalene (24c)

Using the general procedure for **24b**, the crude product from the reaction of **19c** (0.50 g, 1.65 mmol) with TsCl (0.94 g, 2.0 mmol) was purified by chromatography (2 : 98 EtOAc–DCM) to yield **24c** (0.83 g, 83%) as a colourless powder: mp 199–200 °C; ^{1}H NMR δ 0.91 (t, J = 7.2 Hz, 6H), 1.58–1.65 (m, 4H), 2.41 (s, 6H), 3.78 (t, J = 6.7 Hz, 4H), 4.51 (d, J = 5.5 Hz, 4H), 4.62 (t, J = 5.8 Hz, 2H, disappears upon D_2O addition), 7.22 (d, J = 8.1 Hz, 4H), 7.41–7.43 (m, 2H), 7.72 (d, J = 8.1 Hz, 4H), 7.79–7.81 (m, 2H); ^{13}C NMR δ 10.6, 21.7, 23.6, 38.5, 76.1, 124.0, 125.0, 126.4, 127.5, 129.6, 129.8, 136.7, 143.7, 150.1; (−)-APCI MS m/z (%) 609.1 ([M − 1$^-$], 100), calc.: 610.8 for $C_{32}H_{38}N_2O_6S_2$.

2,3-Di-*n*-butoxy-1,4-bis(*p*-tolylsulfonylaminomethyl)-naphthalene (24d)

Using the general procedure for **24b**, the crude product from the reaction of **19d** (0.83 g, 2.5 mmol) with TsCl (0.30 g, 7.5 mmol) was purified by chromatography (5 : 95 EtOAc–DCM) to yield **24d** (1.17 g, 73%) as a colourless powder: mp 190–192 °C; ^{1}H NMR δ 0.92 (t, J = 7.4 Hz, 6H), 1.30–1.37 (m, 4H), 1.54–1.60 (m, 5H, overlap with HOD signal), 2.41 (s, 6H), 3.82 (t, J = 6.8 Hz, 4H), 4.50 (d, J = 6.4 Hz, 4H), 4.63 (t, J = 5.9 Hz, 2H, disappears upon D_2O addition), 7.23 (d, J = 8.5 Hz, 4H), 7.41–7.43 (m, 2H), 7.72 (d, J = 8.6 Hz, 4H), 7.81–7.83 (m, 2H); ^{13}C NMR δ 14.2, 19.4, 21.7, 32.5, 38.6, 74.4, 124.0, 125.0, 126.4, 127.5, 129.6, 129.8, 136.7, 143.6, 150.1; (−)-APCI MS m/z (%) 637.2 ([M − 1]$^-$, 100), calc.: 638.2 for $C_{34}H_{42}N_2O_6S_2$.

Bis(*N*-tosylamide)azaisocalix[2]-2,3-dimethoxynaphthalene (9a). General procedure

To a suspension of Cs_2CO_3 (0.36 g, 1.1 mmol) in dry DMF (5 mL) was added dropwise a solution of **13a** (187 mg,

0.500 mmol) and **24a** (277 mg, 0.500 mmol) in dry DMF (15 mL) at room temperature over 5 h using a syringe pump. The reaction mixture was stirred for a further 40 h at room temperature. After the solvent was removed under reduced pressure, to the resulting residue was added distilled water (30 mL), and the mixture was extracted with $CHCl_3$ (3 × 30 mL). The organic layer was combined, washed with distilled water (2 × 40 mL) and brine (1 × 40 mL), dried over $MgSO_4$ and filtered. After the solvent was removed under reduced pressure, the residue was purified by chromatography (DCM) to yield **9a** (0.14 g, 37%) as a light yellow powder: mp >290 °C ($CHCl_3$–acetone) (decomp.); ^{1}H NMR δ 2.56 (s, 3H), 3.64 (s, 6H), 4.19 (d, J = 13.5 Hz, 2H), 5.29 (d, J = 13.5 Hz, 2H), 7.01–7.03 (m, 2H), 7.49 (d, J = 7.5 Hz, 2H), 7.94 (d, J = 7.5 Hz, 2H), 8.05–8.08 (m, 2H); ^{13}C NMR δ 21.9, 45.9, 63.1, 123.0, 125.3, 125.4, 128.1, 130.3, 130.5, 134.5, 144.1, 150.0; (+)-APCI MS m/z (%) 767.0 (M^+, 100), calc.: 766.9 for $C_{42}H_{42}N_2O_8S_2$.

Bis(*N*-tosylamide)azaisocalix[2]-2,3-diethoxynaphthalene (9b)

Using the general procedure for **9a**, the coupling reaction between **13b** (0.20 g, 0.50 mmol) and **24b** (0.29 g, 0.50 mmol) gave the crude product, which was purified by chromatography (DCM) to yield **9b** (0.12 g, 29%) as a light yellow powder: mp >260 °C ($CHCl_3$–acetone) (decomp.); ^{1}H NMR δ 1.18 (t, J = 7.3 Hz, 6H), 2.55 (s, 3H), 3.69–3.75 (m, 2H), 3.87–3.92 (m, 2H), 4.13 (d, J = 13.5 Hz, 2H), 5.24 (d, J = 13.5 Hz, 2H), 8.99–7.00 (m, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.93 (d, J = 8.0 Hz, 2H), 7.99–8.01 (m, 2H); ^{13}C NMR δ 15.7, 21.9, 46.4, 70.6, 122.8, 125.0, 125.3, 128.1, 130.0, 130.3, 134.1, 144.0, 148.9; (+)-APCI MS m/z (%) 823.3 (M^+, 100), calc.: 823.0 for $C_{46}H_{50}N_2O_8S_2$.

Bis(*N*-tosylamide)azaisocalix[2]-2,3-dipropoxynaphthalene (9c)

Using the general procedure for **9a**, the coupling reaction between **13c** (0.21 mg, 0.50 mmol) and **24c** (0.31 g, 0.50 mmol) gave the crude product, which was purified by chromatography (DCM) to give **9c** (0.21 g, 48%) as a colourless powder: mp >280 °C ($CHCl_3$–CH_3CN) (decomp.); ^{1}H NMR δ 0.88 (t, J = 7.5 Hz, 6H), 1.55–1.65 (m, 4H), 2.53 (s, 3H), 3.50–3.55 (m, 2H), 3.79–3.83 (m, 2H), 4.11 (d, J = 13.4 Hz, 2H), 5.23 (d, J = 13.4 Hz, 2H), 6.99–7.01 (m, 2H), 7.47 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.1 Hz, 2H), 7.97–7.99 (m, 2H); ^{13}C NMR δ 10.7, 21.8, 23.7, 46.3, 76.6, 122.7, 125.0, 125.3, 128.0, 129.9, 130.3, 133.8, 143.9, 149.0; (+)-APCI MS m/z (%) 879.5 (M^+, 100), calc.: 879.1 for $C_{50}H_{58}N_2O_8S_2$.

Bis(*N*-tosylamide)azaisocalix[2]-2,3-dibutoxynaphthalene (9d)

Using the general procedure for **9a**, the coupling reaction between **13d** (0.23 g, 0.50 mmol) and **24d** (0.32 g, 0.50 mmol) gave the crude product, which was purified by chromatography (1 : 9 EtOAc–hexane) to yield **9d** (0.15 g, 31%) as a colourless powder: mp >290 °C ($CHCl_3$–CH_3CN) (decomp.); ^{1}H NMR δ 0.89 (t, J = 7.3 Hz, 6H), 1.26–1.34 (m, 2H), 1.36–1.43 (m, 2H) 1.47–1.52 (m, 2H), 1.55–1.62 (m, 2H), 2.54 (s, 3H), 3.52–3.57 (m, 2H), 3.81–3.85 (m, 2H), 4.09 (d, J = 13.3 Hz, 2H), 5.23 (d, J = 13.7 Hz, 2H), 6.99–7.01 (m, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.92 (d, J = 7.9 Hz, 2H), 7.98–8.00 (m, 2H); ^{13}C NMR δ 14.2, 19.6, 21.8, 32.7, 46.3, 74.8, 122.7, 125.0, 125.3, 128.0, 130.0, 130.3, 133.8, 143.8, 149.1; (+)-APCI MS m/z (%) 935.4 (M^+, 100), calc.: 935.3 for $C_{54}H_{66}N_2O_8S_2$.

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26. *X-Ray crystallographic data* for **9a**: $C_{45.50}H_{45.50}Cl_{10.50}N_2O_8S_2$, M_r = 1184.75, primitive triclinic cell, $P\bar{1}$ (no. 2), a = 12.9568(11), b = 14.4422(14), c = 15.5453(12) Å, α = 92.4503(16), β = 103.0694(12), γ = 112.024(2)°, V = 2600.5(4) Å^3, Z = 2; 31 107 independent reflections, 13 377 were observed ($I > 2\sigma(I)$), R_1 = 0.0795, wR_2 = 0.2094 (observed), R_1 = 0.0860, wR_2 = 0.2094 (all reflections). CCDC reference number 673893. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b717797f.
27. The X-ray crystal structure of **9c** was also obtained but with a very low refinement (mainly due to the disorder inherent in the propyl groups), with two extra crossing C–C bonds in its structure.
28. Computer-assisted molecular modeling were conducted using Spartan'04, V1.0.3, from Wavefunction, Inc., Irvine, CA, USA. Calculations at the MP3 level of theory were conducted o the optimized geometry of the host and/or complexes which were obtained through molecular mechanics (MMFF94) conformational searches.
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