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Synthesis, structure and binding properties of a series of dissymmetric resorcin[4]arene-based cavitands

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ABSTRACT

The synthesis of four new dissymmetric cavitands is reported. These deep-walled receptors are constructed from a resorcin[4]arene scaffold bearing anti-disposed quinoxaline substituents, with either *N*-haloalkyl-diazaphthalimide (**1**), dinitrophenyl (**2**) or diaminophenyl (**3**) moieties as the other wall components. The structure and inclusion properties of **1** and **2** have been probed in solution by NMR spectroscopy and notably in the solid-state by X-ray crystallography. The diazaphthalimide-based compounds **1** crystallise as 1:1 host-guest complexes with chloroform, with the resorcin[4]arene scaffolds adopting pinched cone conformations. Conversely, the dinitrophenyl-variant **2** features a more open, symmetric structure in the solid-state and co-crystallises with two acetone molecules within the central cavity. Preliminary binding experiments in mesitylene-d_{12} at 303 K demonstrate **1** ($K_{app} = 5 \times 10^2$ M^{-1}) and **2** ($K_{app} = 2 \times 10^2$ M^{-1}) are effective hosts for cyclohexane guest molecules in the absence of competitive solvent inclusion.

1. Introduction

The strong and selective binding of guests within well-defined hosts continues to be one of the principal themes of supramolecular chemistry.[1–3] Hosts have ranged from relatively simple ion-binding compounds such as cryptands and the ubiquitous crown ethers, to more elaborate interlocked systems that utilise a range of intermolecular interactions to efficiently complex neutral, cationic or anionic guests.[4,5] Cavitands represent an important class of concave, container-shaped host that are capable of strong and discriminatory binding,[6] often employing size and shape complementarity,[7] in addition to hydro- and solvophobic effects.[8] Amongst a variety of naturally occurring and synthetic examples, resorcin[4]arenes have emerged as versatile scaffolds for the construction of cavitands.[8–10]

In seminal work exemplifying the versatility of resorcin[4]arene scaffolds, Cram and co-workers reported the encapsulation of (otherwise unstable) cyclobutadiene within bis-resorcin[4]arene hemicarcerand **A** (Fig. 1).[11] Guest uptake in this case was modulated through the fluxional nature of the vessel. The solvophobic cavities of extended resorcin[4]arene cavitands **B** have been exploited by Rebek as templates for macrocyclisation reactions.[12] Through utilisation of the hydrophobicity of the internal cavity the authors were able to effect selective lactam formation. Subsequent work by Ballester extended this approach to organometallic transformations, in this case the hydrogenation of a rhodium norbornene complex within **C**.[13] Resorcin[4]arene-based systems, in particular deep tetra-walled cavitands have also been used extensively in molecular recognition. For instance, disubstituted **D** has been shown to bind steroidal molecules through a combination of hydrogen-bonding and CH-π interactions.[14] The related dialkyne bridged tetrasubsituted receptor **E** prepared by Diederich displays a strong affinity for cyclohexane in mesitylene-d_{12}; binding is facilitated through multiple synergistic CH-π interactions and augmented by solvophobic effects.[15]

In the context of developing the chemistry of molecular receptors based on resorcin[4]arene scaffolds, in this paper we report the synthesis of four novel well-defined resorcin[4]arene-based cavitands, their characterisation in the solid-state and preliminary cyclohexane binding experiments.

2. Results and discussion

The field of resorcin[4]arene-based cavitands is largely dominated by symmetrical species bearing identical “walls”. In this work

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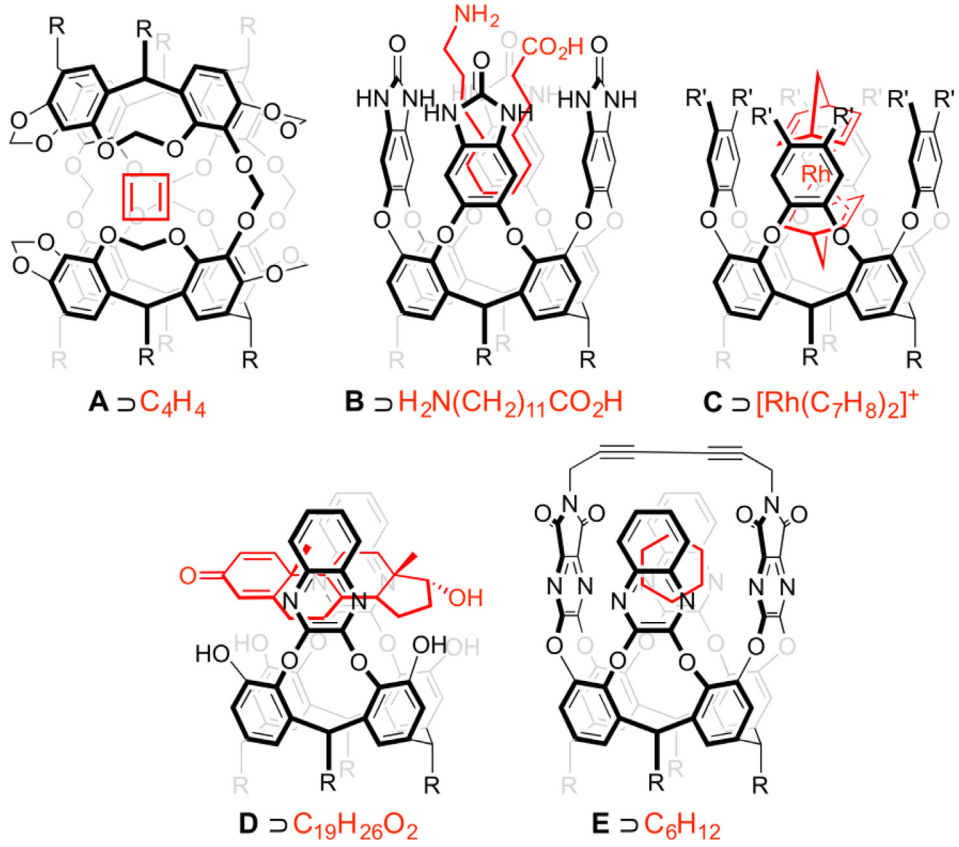

Fig. 1. Resorcin[4]arene-based host-guest systems.

we targeted the preparation of a series of new dissymmetric cavitands utilising the well-known quinoxaline moiety and varying the identity of the other substituents. With a view to potential late stage functionalisation we chose to incorporate *N*-haloalkyl-diazaphthalimide (**1**), dinitrophenyl (**2**) and diaminophenyl (**3**) walls via a convergent synthetic route involving the common diquinoxaline substituted resorcin[4]arene **4** (Fig. 2). The preparation of **4** was achieved in three steps using literature protocols (full details in ESI)[16–18] and we have been able to determine its solid-state structure using X-ray diffraction (*vide infra*).

Reacting **4**, 1,2-difluoro-4,5-dinitrobenzene[19] and five equivalents of triethylamine for 36 h in DMF at 70 °C resulted in the formation of **2**, which was obtained in moderate yield following recrystallization from acetone (51%; Fig. 2). Cavitands **1** were prepared in a similar manner although, due to the greater susceptibility of the imide-based precursors **5** (prepared from 2,3-dichlorodiazaphthalic anhydride[20]) to nucleophiles, *N*,*N*-diisopropylethylamine (DiPEA) and milder reaction conditions (36 h, DMF at 40 °C) were employed. The resulting products were obtained as analytically pure materials following chromatographic purification (**1a**, 47%; **1b**, 59%). Cavitand **2** was subsequently reduced to afford **3** in high yield (93%) by reduction of the nitro substituents using Raney-nickel under 1 atm. of hydrogen. The structures of all four new macromolecular compounds were fully established in solution using a combination of NMR spectroscopy and high resolution ESI-MS; the NMR spectra at 298 K of the cavitands exhibited time-averaged C_{2v} symmetry, resulting from well-known vase type conformations in the solution state.[21,22] The solid-state structures of this class of dissymmetric cavitand, however, remains largely unexplored and we sought to investigate these further.[23,24] In addition to **4**, single crystal samples of **1a**, **1b** and **2** were obtained and analysed by X-ray crystallography (Fig. 3 – 6). Unfortunately, we have so far been unable to grow suitable crystals of **3** for analysis.

Crystals of **4** were obtained from slow evaporation of an acetone solution and the data collected at 200 K, rather than routine 150 K, due to poor crystal stability in the cryostream of the diffractometer (Fig. 4).[25] Contrasting the parent tetra quinoxaline substituted resorcin[4]arene, which forms well-defined host-guest complexes,[26–28] **4** demonstrates self-inclusion in the solid-state. This interaction is presumably mediated via aromatic donor-acceptor (π-π) interactions and is quantified through close intermolecular interactions between two parallel (∠0.0(4)°) quinoxaline substituents on adjacent molecules in the extend solid-state structure (4.336(4) Å separation). Quantified through deviation of the ratio of opposing centroid distances ($ROCD_{Res}$ = 1.079(2), Fig. 3) from unity, the resorcin[4]arene scaffold is slightly distorted away from an ideal C_{4v} towards 'pinched cone' C_{2v} symmetry. Other salient features include the adoption of hydrogen bonding interactions between the unfunctionalised hydroxyl substituents (2.722(5) and 2.746(5) Å) and the presence of two acetone solvates, one that approaches the lower-rim of the resorcin[4]arene ($Me_2CO\cdots HC$ ca. 3.8 Å). Similar phenomena are observed for **D** (R = undecyl).[14]

Single crystals of **1a** and **1b** were obtained through diffusion of hexane into chloroform solutions of the hosts. The compounds are essentially isostructural in the solid-state, with both displaying discrete inclusion of chloroform (**1a** shown in Fig. 5). The intra-quinoxaline distances (Cnt_{Quin}–Cnt_{Quin}) of the cavitands are comparable (**1a**, 9.307(4); **1b**, 9.329(6) Å), and larger than the corresponding intra-diazaphthalimide distances (Cnt_{Ar}–Cnt_{Ar} = 8.447(4), **1a**; 8.451(6), **1b**). This disparity is associated with a pinched conformation of the resorcin[4]arene, as

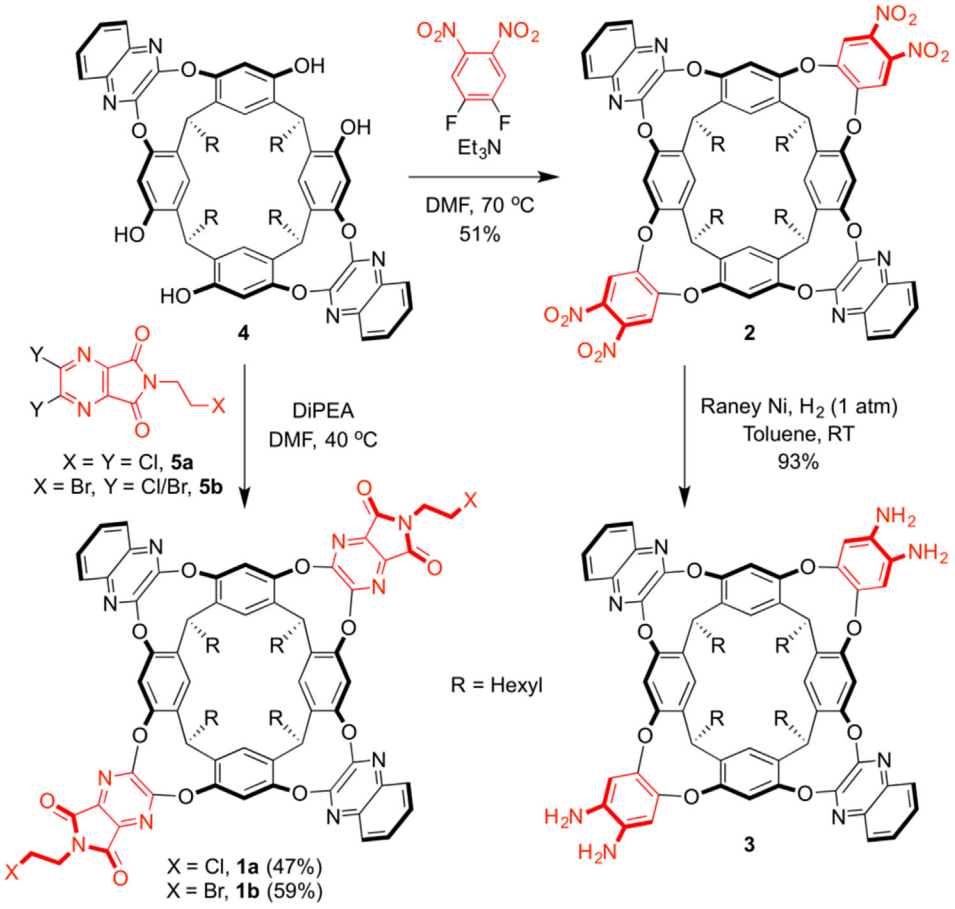

Fig. 2. Synthesis of cavitands **1**–**3**.

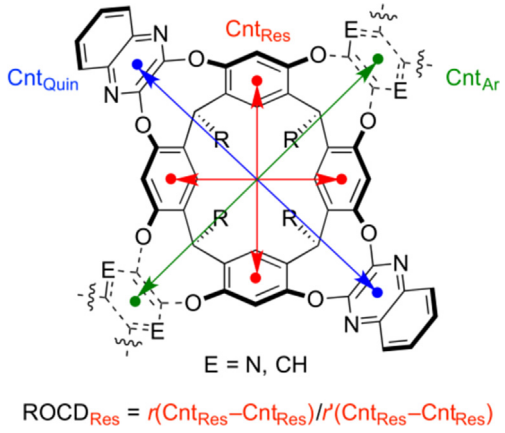

Fig. 3. Metrics used to assess the conformations of **1**, **2** and **4** in the solid-state.

indicated by values of $ROCD_{Res} > 1$ (1.112(1), **1a**; 1.105(2), **1b**), and accounted for by the relatively flat nature of the $CHCl_3$ guest in a psuedo spherical, but flexible binding cavity.[29,30]

Crystals of **2** suitable for analysis by X-ray diffraction were obtained through recrystallization from acetone (Fig. 6). Interestingly, two molecules of acetone are bound within the receptor in a head-to-tail arrangement (CO···CO = 3.571(8) Å). The most deeply bound acetone appears to be orientated to maximise CH-π interactions with the more electron rich quinoxaline walls (ca. 3.6 vs. 4.2 Å), while the other is presumably influenced by a combination of CH-π and hydrogen bonding interactions with the host. In comparison to **1**, the solid-state structure of **2** is more symmetrical, with Cnt_{Quin}–Cnt_{Quin} = 9.240(4) Å ≈ Cnt_{Ar}–Cnt_{Ar} = 9.214(4) Å and $ROCD_{Res}$ ≈ 1 [1.010(1)], consistent with the larger combined guest volume. Acetone solvate is also present on the periphery of the receptor cavity, including one that as for **4** approaches the lower-rim of the resorcin[4]arene ($Me_2CO\cdots HC$ ca. 3.7 Å).

In order to investigate the inclusion properties of the new cavitands in solution, we targeted the binding of cyclohexane in (carefully dried) mesitylene-d_{12} – which is too large to occupy the central cavity – based on related literature precedents (i.e. **E**).[15,29] Binding experiments were performed using isolated, vacuum dried samples of **1** and **2**; unfortunately tetraamino cavitand **3** was not sufficiently soluble in this non-polar aromatic solvent. Encapsulation of cyclohexane was apparent in each case by the appearance of a characteristically low frequency cyclohexane resonance at *ca.* δ −3 ppm by ^{1}H NMR spectroscopy, arising from CH-π interactions and consistent with slow host-guest exchange, but fast chair-chair interconversion on the NMR timescale.[15] Association constants (K_{app}) were estimated for 1:1 stoichiometric binding[15,29] of cyclohexane by **1**–**2** through integration of ^{1}H NMR data at 303 K (Table 1). The resulting values for **1a** and **1b** are equivalent within error ($K_{app} = 5 \times 10^2$ M^{-1}), which is unsurprising given the hosts structural similarity, but an order of magnitude lower than dialkyne-bridged receptor **E** (R = hexyl) under similar conditions ($K_{app} = 3.6 \times 10^3$ M^{-1} at 298 K).[15] This difference can be attributed to the greater preorganisation of **E**, in which the two of the imide-based walls are tethered together. In comparison, the tetranitro **2** exhibits further diminished binding of cyclohexane (2×10^2 M^{-1}),

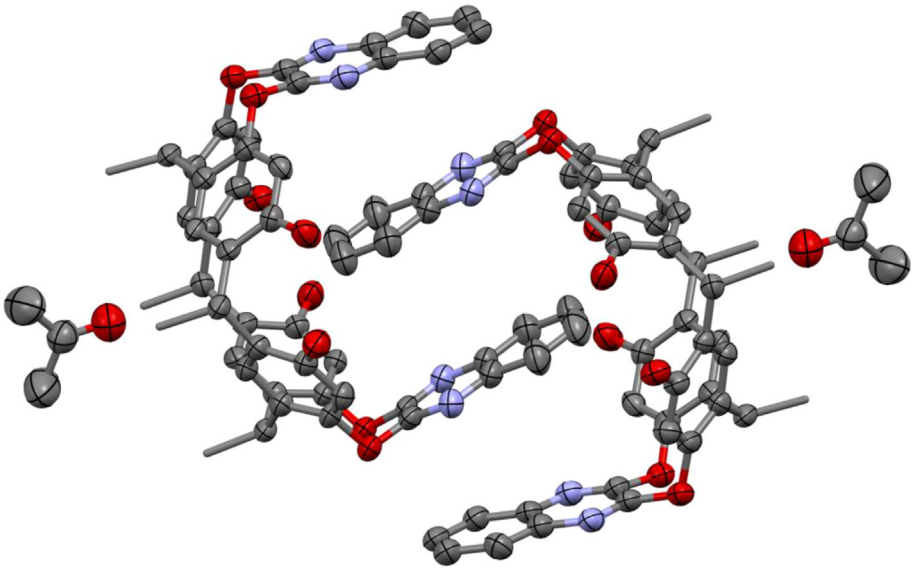

Fig. 4. Solid-state structure of **4**. H-atoms, one unique acetone solvate, and alkyl chains omitted for clarity; ellipsoids plotted at the 50% probability level.

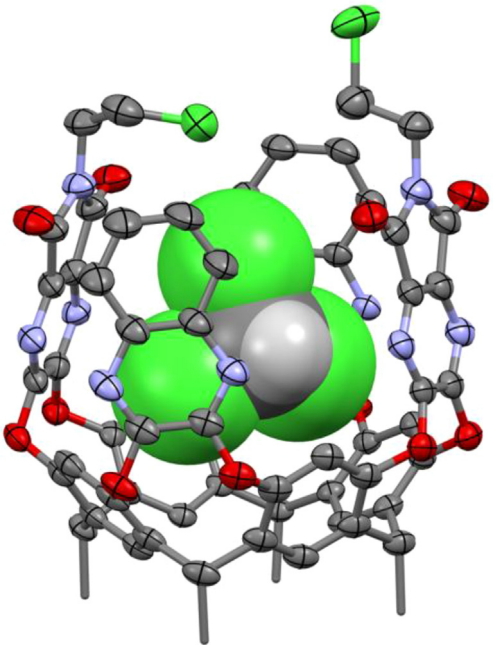

Fig. 5. Solid-state structure of **1a**⊃$CHCl_3$. Host H-atoms, disordered components, and alkyl chains omitted for clarity; ellipsoids plotted at the 50% probability level, guest in space-fill.

presumably due to the more electron-deficient nature of the dinitrophenyl walls.

For comparison to these data obtained in mesitylene-d_{12} and the solid-state structures, the ability of **1a** and **2** to bind cyclohexane in $CDCl_3$ and $(CD_3)_2CO$ was also assessed. In the presence of 50 equivalents of the hydrocarbon guest no competitive binding could be detected for either host in $CDCl_3$, while only weak binding was observed in $(CD_3)_2CO$ at 303 K (both $K_{app} = 3\ M^{-1}$). In the latter case, the ability to even detect host-guest formation, albeit two orders of magnitude lower than in mesitylene-d_{12}, is presumably a consequence of entropic effects associated with the 1:2 binding stoichiometry of acetone inferred from the solid-state structure of **2**.

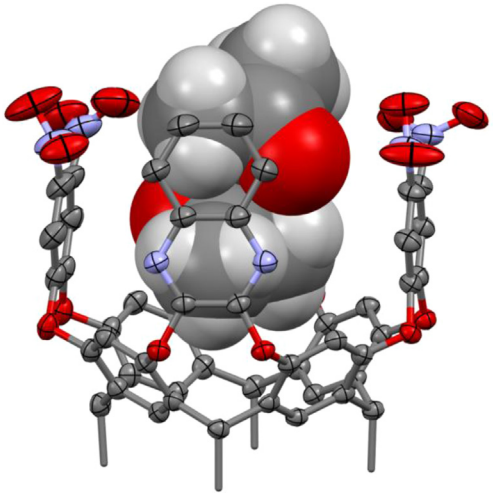

Fig. 6. Solid-state structure of **2**⊃2($OCMe_2$). Host H-atoms, exo-cavity solvate, and alkyl chains omitted for clarity; ellipsoids plotted at the 50% probability level, guests in space-fill.

Table 1
Association constants for the encapsulation of cyclohexane by **1** − **3** (mesitylene-d_{12}, 303 K).[a]

Host cavitand	Association constant (K_{app})/M^{-1}
1a	5×10^2
1b	5×10^2
2	2×10^2
3	Not soluble

[a] Estimated by integration of ^1H NMR data.

3. Conclusion

We have described the synthesis, structure and binding properties of four novel dissymmetric resorcin[4]arene-based receptors. These cavitands feature anti-disposed quinoxaline substituents, with either *N*-haloalkyl-diazaphthalimide (**1**), dinitrophenyl (**2**) or diaminophenyl (**3**) moieties as the other components; functionality

which may make them amenable to further derivatisation. The structure and inclusion properties of **1** and **2** have been probed in solution by NMR spectroscopy and notably in the solid-state by X-ray crystallography. Diazaphthalimide-based cavitands **1** crystallise as 1:1 host-guest complexes with chloroform, with the resorcin[4]arene scaffolds adopting pinched cone conformations. Conversely, the dinitrophenyl-variant **2** features a more open, symmetric structure in the solid-state and co-crystallises with two acetone molecules within the central cavity. Preliminary binding experiments in mesitylene-d_{12} at 303 K demonstrate **1** ($K_{app} = 5 \times 10^2\ M^{-1}$) and **2** ($K_{app} = 2 \times 10^2\ M^{-1}$) are effective hosts for cyclohexane guest molecules in the absence of competitive solvent inclusion.

4. Experimental

4.1. General procedures

All manipulations were performed under an atmosphere of nitrogen, using Schlenk unless otherwise stated. Glassware was oven dried at 150 °C overnight and flamed under vacuum prior to use. Anhydrous solvents were purchased from ACROS or Aldrich and stored under nitrogen. CD_2Cl_2 was dried over thoroughly vacuum-dried 3 Å molecular sieves and stored under argon. Mesitylene-d_{12} was dried over molten sodium at 100 °C, vacuum distilled and stored under argon. NMR binding studies were performed using HPLC grade cyclohexane, which was used without further purification. Diquinoxaline substituted resorcin[4]arene **4** was prepared from commercially available starting materials in three steps using literature protocols (detailed in the ESI)[16–18] 1,2-difluoro-4,5-dinitrobenzene[19] and 2,3-dichlorodiazaphthalic anhydride[20] were synthesised using literature protocols. All other solvents and reagents are commercial products and were used as received. NMR spectra were recorded on Bruker AV-250, DPX-400, AV-400, AV-500, AVIIIHD-500 spectrometers at 298 K unless otherwise stated. Coupling constants are quoted in Hertz. Microanalyses were performed by Stephen Boyer at London Metropolitan University. Low-resolution mass spectrometry was performed on an Agilent 6130B and high-resolution analyses were performed on a Bruker MaXis II spectrometer.

4.2. Preparation of new compounds

4.2.1. Cavitand *1a*

To a solution of **5a** (78 mg, 27.8 μmol) and **4** (100 mg, 9.3 μmol) in dry DMF (5 mL) was added DiPEA (81 μL, 46.4 μmol). The reaction was then stirred at 40 °C for 36 h. The solvent was removed *in vacuo* and subsequently co-evaporated with toluene (3 × 2 mL). The crude material was purified by gradient column chromatography (SiO_2; CH_2Cl_2/EtOAc 100:0 → 97.5:2.5) to afford analytically pure **1a** as a white solid. Yield = 65 mg (47%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 4H, ArH), 7.92–7.97 (m, 4H, ArH), 7.45–7.49 (m, 4H, ArH), 7.23 (s, 4H, ArH), 5.65 (t, $^3J_{HH}$ = 8.1, 2H, ArCH), 5.52 (t, $^3J_{HH}$ = 8.1, 2H, ArCH), 4.05 (t, $^3J_{HH}$ = 6.1, 4H, CH_2), 3.60 (t, $^3J_{HH}$ = 6.1, 4H, CH_2), 2.21–2.31 (m, 8H, $CHCH_2$), 1.30–1.52 (m, 32H, CH_2), 0.93 (t, $^3J_{HH}$ = 6.9, 6H, CH_3), 0.92 (t, $^3J_{HH}$ = 6.9, 6H, CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$): δ 162.3, 158.5, 153.1, 152.2, 152.1, 141.5, 139.8, 136.8, 135.6, 129.6, 128.4, 123.8, 118.8, 40.3, 39.9, 34.4, 32.7, 32.4, 32.0, 29.5, 29.5, 28.1, 22.8, 14.2. **HR ESI-MS** positive ion: 1515.5246 *m/z* $[M+Na]^+$ (calc. 1515.5236). **Anal.** Calcd for $C_{84}H_{80}Cl_2N_{10}O_{12}$ (1492.52 g mol^{-1}): C, 67.60; H, 5.40; N, 9.38. Found: C, 67.43; H, 5.30; N, 9.27.

4.2.2. Cavitand *1b*

To a solution of **5b** (100 mg, ca. 31 μmol) and **4** (111 mg, 10.2 μmol) in dry DMF (5 mL) was added DiPEA (91 μL, 51.2 μmol). The reaction was then stirred at 40 °C for 36 h. The solvent was removed *in vacuo* and subsequently co-evaporated with toluene (3 × 2 mL). The crude material was purified by gradient column chromatography (SiO_2; CH_2Cl_2/EtOAc 100:0 → 95:5) to afford analytically pure **1b** as a white solid. Yield = 95 mg (59%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 4H, ArH), 7.92–7.94 (m, 4H, ArH), 7.45–7.49 (m, 4H, ArH), 7.23 (s, 4H, ArH), 5.65 (t, $^3J_{HH}$ = 8.0, 2H, ArCH), 5.53 (t, $^3J_{HH}$ = 8.4, 2H, ArCH), 4.12 (t, $^3J_{HH}$ = 6.3, 4H, CH_2), 3.46 (t, $^3J_{HH}$ = 6.3, 4H, CH_2), 2.21–2.31 (m, 8H, $CHCH_2$), 1.25–1.50 (m, 32H, CH_2), 0.90–0.95 (m, 12H, CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$): δ 162.2, 158.5, 153.1, 152.2, 141.5, 139.8, 136.8, 135.6, 129.7, 128.4, 123.8, 118.8, 39.8, 34.4, 32.7, 32.4, 32.0, 29.5, 29.5, 28.1, 27.8, 22.8, 14.2. **HR ESI-MS** positive ion: 1603.4086 *m/z* $[M+Na]^+$ (calc. 1603.4212). **Anal**. Calcd for $C_{84}H_{80}Br_2N_{10}O_{12}$ (1581.43 g mol^{-1}): C, 63.80; H, 5.10; N, 8.86. Found: C, 63.83; H, 5.01; N, 8.80.

4.2.3. Cavitand *2*

To a solution of **4** (100 mg, 9.3 μmol) and 1,2-difluoro-4,5-dinitrobenzene (60 mg, 29.4 μmol) in dry DMF (5 mL) was added Et_3N (87 μL, 48.9 μmol). The reaction was then stirred at 70 °C for 36 h. The solvent was removed *in vacuo* and the subsequently co-evaporated with toluene (3 × 2 mL). The crude material was dissolved in a minimum of hot acetone and cooled to 4 °C. The solid was filtered and washed with cold acetone to afford analytically pure **2** as an off white solid. Yield = 66 mg (51%).

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.89 (br. s, 4H, ArH), 7.81–7.83 (m, 4H, ArH), 7.64–7.67 (m, 4H, ArH), 7.54 (br. s, 4H, ArH), 7.11 (br. s, 4H, ArH), 5.11 (br.s, 4H, ArCH), 2.10–2.26 (m, 12H, $CHCH_2$), 1.22–1.47 (m, 32H, CH_2), 0.84–0.96 (m, 12H, CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$): δ 153.0, 150.2, 139.4, 133.1, 130.4, 127.6, 32.2, 31.9, 31.8, 31.1, 29.3, 29.3, 27.6, 22.8, 22.7, 14.2. The remaining resonances could not be unambitiously assigned. **HR ESI-MS** positive ion: 1427.5134 *m/z* $[M+Na]^+$ (calc. 1427.5271). **Anal**. Calcd for $C_{80}H_{76}N_8O_{16}$ (1404.54 g mol^{-1}): C, 68.36; H, 5.45; N, 7.97. Found: C, 68.15; H, 5.26; N, 7.81.

4.2.4. Cavitand *3*

A suspension of **2** (600 mg, 0.427 mmol) and Raney-Ni (*ca.* 60 mg) in toluene (100 mL) was placed under an atmosphere of H_2 (*ca.* 1 atm.) and stirred at ambient temperature for 18 h. The solution was filtered, washing the residue with toluene (2 × 20 mL), and the solvent removed *in vacuo* from the combined organic fractions to afford analytically pure **3** as an off white solid. Yield = 493 mg (93%).

^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.86–7.90 (m, 4H, ArH), 7.67 (br. s, 4H, ArH), 7.60–7.64 (m, 4H, ArH), 7.25 (br. s, 4H, ArH), 6.57 (s, 4H, ArH), 5.59 (br. s, 4H, ArCH), 2.97 (br. s, 8H, NH_2), 2.28–2.36 (m, 4H, CH_2), 2.12–2.21 (m, 4H, $CHCH_2$), 1.24–1.54 (m, 32H, CH_2), 0.89–0.95 (m, 12H, CH_3). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2): δ 156.9, 152.6, 140.3, 136.6, 135.5, 132.7, 130.1, 128.1, 124.0, 118.3, 111.7, 35.0, 34.0, 32.5, 32.4, 29.9, 28.6, 28.5, 23.3, 14.4. The remaining resonances could not be unambitiously assigned. **HR ESI-MS** positive ion: 1285.6487 *m/z* $[M+H]^+$ (calc. 1285.6485). **Anal**. Calcd for $C_{80.5}H_{85}N_8O_8$ (1328.07 g mol^{-1}): C, 72.80; H, 6.45; N, 8.44. Found: C, 72.88; H, 6.36; N, 8.19.

4.2.5. Chloroethyl-diazaphthalimide *5a*

Under air, a test tube was charged with 2,3-dichlorodiazaphthalic anhydride (410 mg, 1.872 mmol) and 2-chloroethylamine hydrochloride (223 mg, 1.919 mmol). Acetic anhydride (400 μL) was added and the reaction sealed and heated to 120 °C for 30 min. The reaction was cooled to ambient temperature and diluted with H_2O (2 mL). The crude solid was filtered and washed with H_2O (2 × 5 mL) and then purified by eluting through a

plug (SiO_2; CH_2Cl_2) to afford analytically pure **5a** as a white solid. Yield = 391 mg (75%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.18 (t, $^3J_{HH}$ = 6.1, 2H, CH_2), 3.83 (t, $^3J_{HH}$ = 6.1, 2H, CH_2). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$): δ 161.9, 154.1, 143.4, 40.5, 40.4. **HR ESI-MS** positive ion: 333.9521 *m/z* $[M + Na + MeOH]^+$ (calc. 333.9523). **Anal.** Calcd for $C_8H_4Cl_3N_3O_2$ (280.49 g mol^{-1}): C, 34.26; H, 1.44; N, 14.98. Found: C, 34.33; H, 1.38; N, 14.96.

4.2.6. Bromoethyl-diazaphthalimide **5b**

Under air, a test tube was charged with 2,3-dichlorodiazaphthalic anhydride (400 mg, 1.826 mmol) and 2-bromoethylamine hydrobromide (384 mg, 1.872 mmol). Acetic anhydride (400 μL) was added and the reaction sealed and heated to 120 °C for 30 min. The reaction was cooled to ambient temperature and diluted with H_2O (2 mL). The crude solid was filtered and washed with H_2O (2 × 5 mL) and purified by eluting through a plug (SiO_2; CH_2Cl_2) to obtain the product as a mixed halo compound, which was used without further purification. Yield = 417 mg. Compound **5b** was obtained as an approximately 1:1 mixture of the dichloro- and bromochloro- diazaphthalimide as a result of the ammonium counter anion becoming partially exchanged into the pyrazine ring. Attempts to prevent this halide exchange using excess NH_4Cl yielded significant amounts of inseparable **5a** as a side-product. Nevertheless, **5b** was reacted on as the mixed halide species with no significant impact on the subsequent synthesis of **1b** (*vide supra*).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24 (t, $^3J_{HH}$ = 6.4, 2H, CH_2), 4.23 (t, $^3J_{HH}$ = 6.4, 2H, CH_2), 3.67 (t, $^3J_{HH}$ = 6.4, 2H, CH_2), 3.66 (t, $^3J_{HH}$ = 6.4, 2H, CH_2). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$): δ 162.0, 161.9, 161.8, 161.8, 156.4, 154.1, 150.3, 147.4, 143.9, 143.7, 143.7, 143.4, 40.2, 40.2, 27.7, 27.7. **HR ESI-MS** positive ion: 379.9013 *m/z* $[C_8H_4BrCl_2N_3O_2+Na + MeOH]^+$ (calc. 379.8995), 423.8489 *m/z* $[C_8H_4Br_2ClN_3O_2+Na + MeOH]^+$ (calc. 423.8492). **Anal.** Calcd for $C_8H_4Br_{1.5}Cl_{1.5}N_3O_2$ (347.17 g mol^{-1}): C, 27.68; H, 1.16; N, 12.10. Found: C, 28.34; H, 0.92; N, 11.26; error <0.9%.

4.3. Binding studies

4.3.1. General protocol in mesitylene-d_{12}

For investigation of host-guest formation, 1000 μL of a 2 mM solution of host was made up in mesitylene-d_{12}; 500 μL was transferred to an NMR tube and cyclohexane was added as a stock solution in mesitylene-d_{12} (1 equiv., 10.0 μL, 0.1 M). The system was thoroughly mixed and allowed to equilibrate for ten minutes before data acquisition. ^{1}H NMR spectra were recorded on a Bruker AV-500 spectrometer at 303 K using a one second relaxation delay. Association constants (K_{app} = [Host⊃C_6H_{12}]/[Host][C_6H_{12}]) were estimated by integration of the combined host and host-guest complex C$\underline{H}_3$ resonances (*a*) against those of the bound guest resonances (*b*), *viz.* $K_{app} = [Host]_0^{-1} \cdot b \cdot (a-b)^{-2}$. Reflecting a combined error of *ca.* 25% (approximated by propagation of errors based on 5% error for each integration), values of K_{app} are only reported to 1 significant figure. Integrated spectra are provided in the ESI.

4.3.2. General protocol in $CDCl_3$ and $(CD_3)_2CO$

For investigation of host-guest formation, 1000 μL of a 2 mM solution of host was made up in the deuterated solvent; 500 μL of this solution was transferred to an NMR tube and cyclohexane (50 equiv., 5.4 μL) added. The system was thoroughly mixed and allowed to equilibrate for ten minutes before acquisition of the spectrum. ^{1}H NMR spectra were recorded on a Bruker AV-500 spectrometer at 303 K using a one second relaxation delay. Association constants (K_{app} = [Host⊃C_6H_{12}]/[Host][C_6H_{12}]) were estimated by integration of the combined host and host-guest complex C$\underline{H}_3$ resonances (*a*) against those of the bound guest resonances (*b*), *viz.* $K_{app} = [Host]_0^{-1} \cdot b \cdot (a-b)^{-2}$. Reflecting a combined error of *ca.* 17% (approximated by propagation of errors based on 5% error for each integration), values of K_{app} are only reported to 1 significant figure. Integrated spectra are provided in the ESI.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.06.023.

References

1. Spence GT, Beer PD. *Acc Chem Res*. 2013;46:571.
2. Mutihac L, Lee JH, Kim JS, Vicens J. *Chem Soc Rev*. 2011;40:2777.
3. Rebek JJ. *Chem Commun*. 2000:637.
4. Langton MJ, Beer PD. *Acc Chem Res*. 2014;47:1935.
5. Bao XF, Isaacsohn I, Drew AF, Smithrud DB. *J Org Chem*. 2007;72:3988.
6. Pinalli R, Brancatelli G, Pedrini A, et al. *J Am Chem Soc*. 2016;138:8569.
7. Yamanaka M, Kobayashi K. *Asian J Org Chem*. 2013;2:276.
8. Jordan JH, Gibb BC. *Chem Soc Rev*. 2015;44:547.
9. Gangemi CMA, Pappalardo A, Sfrazzetto GT. *Curr Org Chem*. 2015;19:2281.
10. Pinalli R, Suman M, Dalcanale E. *Eur J Org Chem*. 2004:451.
11. Cram DJ, Tanner ME, Thomas R. *Angew Chem Int Ed*. 1991;30:1024.
12. Mosca S, Yu Y, Gavette JV, Zhang KD, Rebek JJ. *J Am Chem Soc*. 2015;137:14582.
13. Korom S, Martin E, Serapian SA, Bo C, Ballester P. *J Am Chem Soc*. 2016;138:2273.
14. Cacciarini M, Azov VA, Seiler P, Kunzer H, Diederich F. *Chem Commun*. 2005;42:5269.
15. Gottschalk T, Jaun B, Diederich F. *Angew Chem Int Ed*. 2007;46:260.
16. Kass JP, Slasor LA, Zambrano CH, Dueno EE. *Org Prep Proced Int*. 2006;38:480.
17. Castro PP, Zhao G, Masangkay GA, Hernandez C, Gutierrez-Tunstad LM. *Org Lett*. 2004;6:333.
18. Dalcanale E, Soncini P, Bacchilega G, Ugozzoli F. *J Chem Soc, Chem Commun*. 1989:500.
19. Knighton RC, Chaplin AB. *Chemspider Synth*; 2015. http://cssp.chemspider.com/783.
20. Körner SK, Tucci FC, Rudkevich DM, Heinz T, Rebek JJ. *Chem Eur J*. 2000;6:187.
21. Moran JR, Karbach S, Cram DJ. *J Am Chem Soc*. 1982;104:5826.
22. Azov VA, Beeby A, Cacciarini M, et al. *Adv Funct Mater*. 2009;16:147.
23. Hornung J, Fankhauser D, Shirtcliff LD, Praetorius A, Schweizer WB, Diederich F. *Chem Eur J*. 2011;17:12362.
24. Pochorovski I, Breiten B, Schweizer WB, Diederich F. *Chem Eur J*. 2010;16:12590.
25. Despite repeated attempts, even at 200 K, only a partial data set could be obtained (78%).
26. Pinalli R, Barboza T, Bianchi F, Massera C, Ugozzoli F, Dalcanale E. *Supramol Chem*. 2013;25:682.
27. Soncini P, Bonsignore S, Dalcanale E, Ugozzoli F. *J Org Chem*. 1992;57:4608.
28. Moran JR, Ericson JL, Dalcanale E, Bryant JA, Knobler CB, Cram DJ. *J Am Chem Soc*. 1991;113:5707.
29. Gottschalk T, Jarowski PD, Diederich F. *Tetrahedron*. 2008;64:8307.
30. Kvasnica M, Purse BW. *New J Chem*. 2010;34:1097.