A tri-armed sulfonamide host for selective binding of chloride

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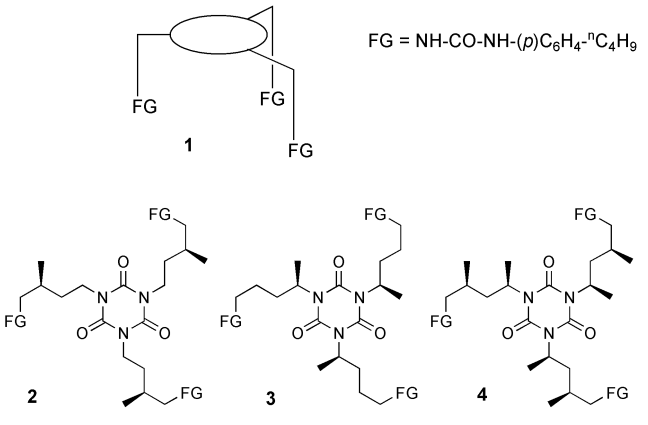
An uncharged host **6** for selective binding of chloride is described. This host features a triazine–trione platform, three short side-arms which are conformationally preorganised relative to the platform, and *p*-nitrophenylsulfonamide groups for hydrogen-bonding to anions. Host **6** binds chloride with $K \approx 150\,000\ M^{-1}$ in $CHCl_3$ and shows a chloride/nitrate selectivity of 10^2.

Introduction

Conformational preorganisation is found in many flexible natural products.[1] This feature may be advantageous for nature to strike a balance between flexibility on the one side and optimisation of binding free energy on the other side when a natural product is interacting with whatever biological partner. Conformational preorganisation has been recognised[2] ever since the pioneering investigations of Cram,[3] to affect binding constants and binding selectivities.

In our ongoing studies on conformation design[1] we became interested in directly assessing the effect of conformational preorganisation on binding constants and binding selectivities. As a test system we used tripodal hosts, of the general type **1**, bearing urea functions to complex anions,[4] such as chloride. In a preceding investigation[5] we studied a set of three tripodal hosts **2**–**4** based on a triazine–trione platform,[6] hosts which have an identical binding topology but differ in the level of conformational preorganisation, *cf.* Scheme 1.

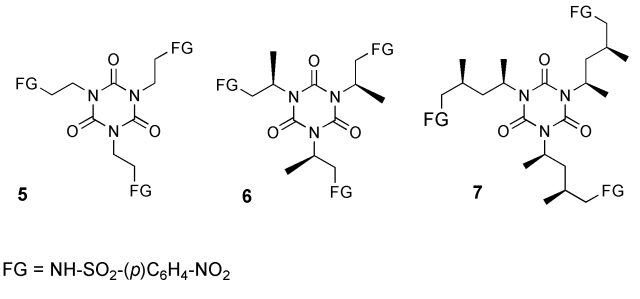


Scheme 1

We found a 2.5-fold increase in the binding constant for Bu_4N^+Cl in $CDCl_3$ on going from host **2** to host **3**. This can be attributed to a distinct arrangement of the side arms relative to the platform caused by the avoidance of $A^{1,3}$-strain in compound **3**.[7] Further conformational organisation within the side-chains itself, *i.e.* going from host **3** to **4**, did not lead to an additional increase in the binding constant for chloride. It did, however, increase the chloride/nitrate selectivity to 24 (**4**) compared to 16 for compound **3** and 4 for compound **2**. While the set of hosts **2**–**4** gave us a first insight, the effects were rather small. This led us to question our plan on two points:

Is a four-carbon length of the side-arms optimal? Long spacers, in general, will have adverse effects on binding entropies. We therefore wanted to evaluate an analogous system with shorter side-arms. Second, urea groups are often prone to self-association,[8] an effect which counteracts the binding of anions. Hence, we decided to evaluate another powerful anion-coordinating group in addition and opted for a *p*-nitrophenylsulfonamide group.[9,10]

As it is not wise to change two parameters in one stroke, we projected first host **7** which, compared to **4**, reflects only the change from urea to the *p*-nitrophenylsulfonamide group. A subsequent change to host **6** then maintains conformational preorganisation with respect to the platform, but reduces the length of the side-chain. This reduction in chain-length will moreover position the anionic guests closer to the (partially) positively charged centre of the triazine–trione platform,[11] a position which corresponds to a Bürgi–Dunitz trajectory with respect to the carbonyl groups.[12] Finally, host **5** has the same binding topology as **6**, but is devoid of any conformational preorganisation; *cf.* Scheme 2.



Scheme 2

We report here on the synthesis of these three new hosts and on their ability to bind and differentiate between the anions chloride, bromide and nitrate in solution in chloroform.

Synthesis and conformational analysis

The synthesis of host **5** started from the commercially available cyanuric acid **8**. The hydroxy functions were replaced by azido

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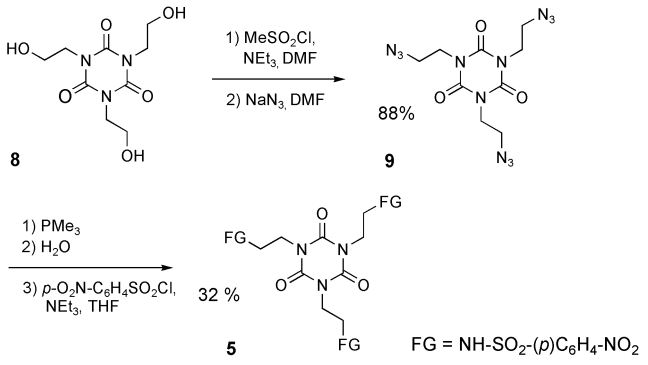
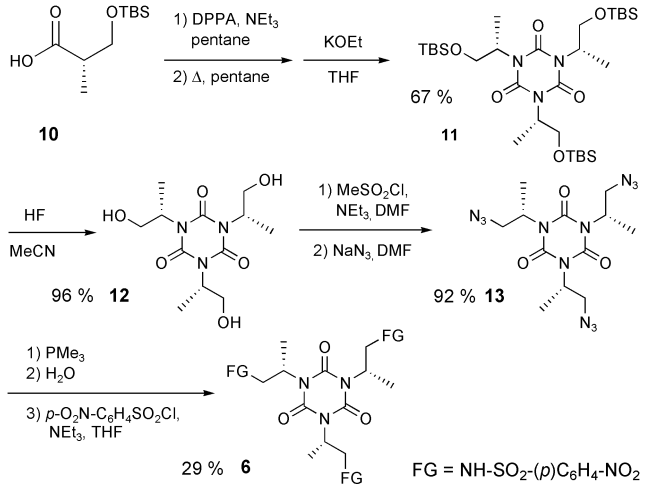
groups to give 88% of **9**. The azido groups were subsequently reduced[13] followed by direct conversion of the amino functions into sulfonamido groups (32%) as outlined in Scheme 3.



Scheme 3

Host **6** has a stereogenic centre in each of the side-chains. The intended binding studies by NMR-titration require that a single stereoisomer of the host is used, rather than a mixture of diastereomeric hosts. Hence, the synthesis of **6** had to make sure that the side-chains in **6** are homochiral to one another. This was attained by a convergent synthesis starting from the enantiomerically pure acid **10**.

The carboxylic acid **10** was subjected to a Curtius degradation and the resulting isocyanate was immediately cyclotrimerised[14] to give the triazine–trione **11**.[15] After conversion of **11** into the tris-azide **13**, further processing to the tris-sulfonamide **6** followed the steps outlined above in the preparation of **5**; *cf.* Scheme 4.

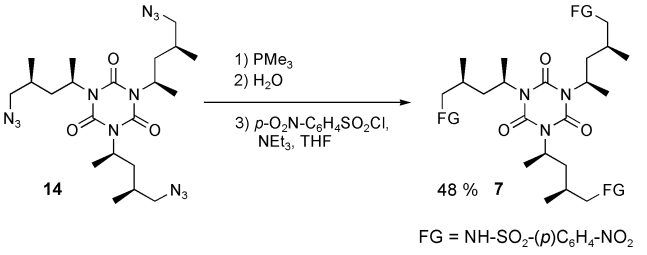


Scheme 4

Host **7** with two stereogenic centres in each of the side-chains likewise had to be prepared as a single stereoisomer. To this end we started as shown in Scheme 5 from the configurationally homogenous tris-azide **14**, an intermediate in our previous synthesis of the tris-urea **4**.[5] The conversion of **14** into the tris-sulfonamide **7** followed again the steps outlined above in the preparation of **5**.

Finally, the simple conformationally non-preorganised tren-derivative **15** was prepared as shown in Scheme 6. We wanted **15** for comparison, as tren-derived hosts frequently have been used in anion complexation.[16,17]

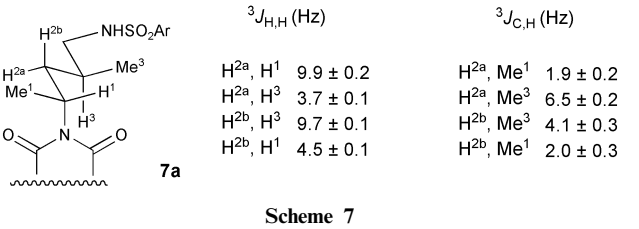
When choosing the *p*-nitrophenylsulfonamide moiety as the anion complexing group instead of the urea groups in hosts



Scheme 5

Scheme 6

2–4 we presumed that self-interaction between the sulfonamide groups would be less than between the urea moieties.[8] Whereas the urea-based host **4** showed a self-association of about 20 M^{-1} which was determined by following the ^{1}H-NMR chemical shift ($CDCl_3$) of the NH protons on dilution,[5] the NH chemical shift of the sulfonamide-based host **6** in $CDCl_3$ turned out to be concentration independent, suggesting negligible self-association of the tris-sulfonamide **6**. Such lack of self-association should then be reflected in a cleaner conformational preorganisation within the side-chains of host **7**. The anticipated[18] preferred conformation is shown as **7a** in Scheme 7.



Scheme 7

The conformational preorganisation in the side arms of compound **7** was monitored by determining $^3J_{H,H}$ and $^3J_{C,H}$ coupling constants. $^3J_{H,H}$ coupling constants of almost 10 Hz from H-1 as well as from H-3 to protons H^{2a} and H^{2b} of the methylene group indicated that there is indeed a strong conformational preference. The nature of the preferred conformation as **7a** follows from the $^3J_{C,H}$ coupling constants, which form a unique set of data: two small[19] couplings between Me^1 and the methylene protons indicated that the conformation around the C-1/C-2 bond is as shown. A large and a small $^3J_{C,H}$ coupling of the methylene protons at C-2 to Me^3 indicates that the preferred conformation around the C-2/C-3 bond is also that shown in **7a**. However, the values of 6.5 and 4.1 Hz suggest that the conformational preference at the C-2/C-3 bond may not be as high as at the C-1/C-2 bond.

Complexation studies

The binding of anions (tetrabutylammonium salts) to the hosts **5–8** was followed by monitoring the chemical shift of NH protons. Job plots (SigmaPlot2000[20]) showed that in all cases 1:1 complexes were formed. Binding constants were estimated by curve fitting with the program SigmaPlot2000.[20] Initial binding studies with the host **7** used $CDCl_3$ as solvent, in order to relate the measurements to those obtained previously[5] with host **4**. The results are compiled in Table 1.

Table 1 Binding constants for tetrabutylammonium salts in $CDCl_3$ (300 K) determined by NMR titration for the hosts **7** and **4**

	Host	
Guest	**7**	**4**
Cl^-	151 000 ± 34 200	19 500 ± 2160
Br^-	16 200 ± 1800	2260 ± 100
NO_3^-	6100 ± 140	800 ± 10

The data in Table 1 show that host **7** with the sulfonamide groups binds the anions (chloride, bromide, nitrate) about 8 times more strongly than host **4** featuring urea groups. The selectivity of hosts **7** towards the different anions remains, however, the same as that of host **4**.

The binding constants of host **7** extended into a range ($> 50\,000$ M^{-1}) in which the curvature of the NMR titration changes so sharply at the 1:1 point, that determination of the binding constants becomes rather inaccurate. This prevented a meaningful determination of the binding constant between host **6** and chloride, which was even larger. Large binding constants may, however, be determined by microcalorimetric titration.[21] With this technique we obtained the binding parameters of chloride to both hosts **7** and **6** (in $CHCl_3$) *cf.* Table 2. A direct comparison of the two methods was possible in the case of chloride binding to host **7**. The values for the binding constant (Table 1 *vs.* Table 2) are of the same magnitude but differ by a factor of about 2, which appears acceptable.[22] Microcalorimetry then indicates that host **6** indeed binds chloride even more strongly than host **7**.

Table 2 Microcalorimetrically determined parameters for complexation of tetrabutylammonium chloride by the tris-sulfonamides **6** and **7** in $CHCl_3$ at 298 K

	Host	
Parameter	**7**	**6**
K/L mol^{-1}	81 000 ± 10 000	155 000 ± 11 000
ΔG/kJ mol^{-1}	−28.1 ± 0.35	−29.7 ± 0.38
ΔH/kJ mol^{-1}	−19.6 ± 0.27	−9.4 ± 0.05
ΔS/J mol^{-1} K^{-1}	+29 ± 2.1	+68 ± 1.4

However, there are more subtle differences between the two hosts as revealed by the binding enthalpy and entropy available through microcalorimetry.[21] Complexation of chloride by a tridentate host leads to a positive complexation entropy, as solvent molecules are released from the solvation shells of the chloride anion and the host. The entropy change on complexation to the host **7** is, however, far less positive than for complexation by host **6**. This may be a consequence of reducing the rotational freedom of the longer side arms of host **7** on complexation, in line with the NMR studies above which indicated that there is still considerable rotational freedom around bonds C-2/C-3 in host **7**. Regarding enthalpy, the binding of chloride by host **6** is clearly less exothermic than binding by host **7**. This invites the speculation that the more flexible host **7** can adopt an optimal coordination geometry, whereas the more rigid host **6** is less in a position to do so. Moreover, a potential electrostatic attraction of chloride by the triazine–trione platform[11] is not reflected by the data.

Another aspect we wanted to focus on is the binding selectivity between different anions. Before addressing this, we noted that chloroform was not an optimal solvent to determine binding constants for such strongly complexing hosts as **6**. In order to determine binding selectivities, we therefore moved to a more polar solvent ($CDCl_3$/DMSO = 95:5) in which the binding constants are numerically smaller[23] (*ca.* ×0.03, *cf.* the data for host **7**). The data for the full range of hosts in the more polar mixed solvent are compiled in Table 3.

Table 3 Binding constants for tetrabutylammonium salts in $CDCl_3$/DMSO 95:5 (300 K)

	Host			
Guest	**7**	**5**	**6**	**15**
Cl^-	4170 ± 130	4870 ± 170	12 630 ± 1100	174 ± 5
Br^-	570 ± 30	1020 ± 65	425 ± 10	35 ± 5
NO_3^-	275 ± 10	380 ± 5	120 ± 10	< 10

Consider first hosts **5** (no conformational preorganisation) and **6** (conformationally preorganised) having the same binding topologies: conformational preorganisation leads to a moderate increase (×2.6) in the binding of chloride, but to decreases (×0.4) in the binding of bromide or of nitrate. Hence, conformational preorganisation accentuates binding selectivities, which becomes apparent when comparing the Cl^-/NO_3^- selectivity for **5**, which is 13; with that for **6** = 105!

The tren-derived conformationally non-preorganised host **15** has binding selectivities[17] similar to those of host **5** with conformationally non-preorganised side arms. But overall binding constants are much smaller for **15** than for **5** showing the benefits of having a rigid central platform.

Host **7**, with conformational preorganisation in the side arms, comes out pretty similar to the fully flexible host **5** regarding binding constants and selectivities, something we would not have expected. Thus, the unique position of host **6** regarding the selective binding of chloride becomes more manifest.

With compound **6** we have prepared a neutral host which complexes chloride strongly ($K \approx 1.5 \times 10^5$ M^{-1} in chloroform) and reaches a chloride/nitrate selectivity of 10^2. It compares favourably with the highly chloride-selective sulfonamide host described recently by Davis.[10] The key features of host **6** are the triazine–trione platform, short but conformationally preorganised side-arms and *p*-nitrophenylsulfonamide hydrogen bond donors.

Experimental

General remarks. All temperatures quoted are uncorrected. ^{1}H NMR, ^{13}C NMR: Bruker ARX-200, AC-300, WH-400, AMX-500. Boiling range of petroleum ether: 40–60 °C. Flash chromatography: silica gel SI 60, E. Merck KGaA, Darmstadt, 40–63 μm. pH 7 buffer: $NaH_2PO_4 \cdot 2H_2O$ (56.2 g) and $Na_2HPO_4 \cdot 4H_2O$ (213.6 g) filled up to 1 L with water.

1. 1,3,5-Tris(2-azidoethyl)-1,3,5-triazine-2,4,6-trione (9). Triethylamine (2.30 mL, 16.6 mmol) was added at 0 °C into a solution of 1,3,5-tris(2-hydroxyethyl)-1,3,5-triazine-2,4,6-trione (**8**) (1.0 g, 3.8 mmol) in DMF (100 mL). After stirring for 10 min at 0 °C methanesulfonyl chloride (1.11 mL, 14.4 mmol) was added. After continued stirring for 2.5 h the mixture was allowed to reach room temperature. Sodium azide (8.80 g, 13.5 mmol) was added and the mixture was heated for 5 d to 70 °C. Saturated aqueous $NaHCO_3$ solution (250 ml) and water (200 mL) were added. The layers were separated and the aqueous layer was extracted with ether (5 × 150 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether = 1:3 furnished the tris-azide **9** (1.12 g, 88%) as a colourless resin. M.p. 83–84 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.56 (t, J = 5.9 Hz, 6H), 4.14 (t, J = 5.9 Hz, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 41.7, 48.3, 148.6. $C_9H_{12}N_{12}O_3$ (336.3): Calcd.:

C, 32.15; H, 3.60; N 49.98; Found: C, 32.14; H, 3.57; N 49.88%.

2. 1,3,5-Tris[2-(4-nitrophenylsulfonylamido)ethyl]-1,3,5-triazine-2,4,6-trione (5). A solution of trimethylphosphine (1.0 M in THF, 2.4 mL, 2.4 mmol) was added at 0 °C into a solution of the tris-azide **9** (250 mg, 684 μmol) in THF (8.0 mL). After stirring for 5 h at room temperature water (60.0 μL, 3.28 mmol) was added. After continued stirring for 3 d triethylamine (430 μL, 3.19 mmol) and *p*-nitrophenylsulfonyl chloride (672 mg, 3.03 mmol) were added and the mixture was heated to 80 °C for 8 h. The solvents were removed *in vacuo* and the residue was purified by flash chromatography with chloroform/methanol/formic acid = 20:1:0.1 to 15:1:0.1 giving the tris-sulfonamide **5** (180 mg, 32%) as a slightly yellowish resin. M.p. 193–194 °C. ^{1}H-NMR (500 MHz, acetone-D$_6$): δ = 3.28 (t, J = 6.0 Hz, 6H), 6.10 (t, J = 6.1 Hz, 6H), 7.02 (broad s, 3H), 8.08 (d, J = 8.1 Hz, 6H), 8.40 (d, J = 8.2 Hz, 6H). ^{13}C-NMR (125 MHz, acetone-D$_6$): δ = 41.0, 42.8, 125.2, 129.0, 147.3, 149.9, 150.9. HRMS (ESI) $C_{27}H_{27}N_9O_{15}S_3$ + Na Calcd.: 836.0686; Found: 836.0716.

3. (2*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropionic acid (10). Imidazole (1.03 g, 15.1 mmol), 4-dimethylaminopyridine (160 mg, 1.31 mmol) and *tert*-butylchlorodimethylsilane (50% in toluene, 4.50 g, 14.9 mmol) were added at 0 °C into a solution of methyl (2*S*)-3-hydroxy-2-methylpropionate (1.15 g, 9.74 mmol) in dichloromethane (40 mL). After stirring for 1 h at room temperature methanol (2 mL) was added and stirring was continued for 15 min. Water (50 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (4 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was taken up in a THF/methanol/water = 2:2:1 mixture. After cooling to 0 °C aqueous NaOH solution (5M, 2.80 mL, 14.0 mmol) was added. After stirring for 16 h at room temperature saturated aqueous NH_4Cl solution (20 mL) and water (20 mL) were added. The layers were separated and the aqueous layer was extracted with ether (5 × 25 mL). The combined organic layers were washed with water (10 mL) and brine (30 mL). The combined aqueous layers were saturated with NaCl and extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with *tert*-butyl methyl ether was followed by bulb to bulb distillation of the crude product at ⩽60 °C *in vacuo* to give the acid **10** (1.39 g, 66%) as a colourless oil. $[\alpha]_D^{20}$ = +17.2 (c = 3.08, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.87 (s, 9H), 1.16 (d, J = 7.2 Hz, 3H), 2.60–2.69 (m, 1H), 3.69 (dd, J = 9.9, 5.8 Hz, 1H), 3.77 (dd, J = 7.0, 9.9 Hz, 1H), OH signal not detected. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = −5.5 (2C), 13.1, 18.2, 25.8 (3C), 42.2, 64.9, 180.4. $C_{10}H_{22}O_3Si$ (218.4): Calcd.: C, 55.00; H, 10.15; Found: C, 54.74; H, 10.38%.

4. 1,3,5-Tris[(1*S*)-2-(*tert*-butyldimethylsilyloxy)-1-methylethyl]-1,3,5-triazine-2,4,6-trione (11). Triethylamine (470 μL, 3.39 mmol) and diphenoxyphosphoryl azide (dppa, 780 μL, 3.65 mmol) were added at 0 °C into a solution of the acid **10** (712 mg, 3.26 mmol) in pentane (18 mL). The mixture was stirred for 16 h at room temperature and then for 6.5 h at 65 °C. The solution was decanted and the residue was triturated with pentane (4 × 7 mL). The combined solutions were concentrated and the residue was heated for 4 min to 70 °C. The residue was bulb to bulb distilled at ⩽50 °C *in vacuo* to give the isocyanate (532 mg) as a colourless oil which was taken up in THF (1.5 mL). KOEt (15 mg, 0.18 mmol) was added and the mixture was stirred for 20 h. The solvents were removed *in vacuo* and the residue was subjected to flash chromatography with pentane/*tert*-butyl methyl ether = 40:1 to furnish the product **11** (470 mg, 67%) as a colourless oil. $[\alpha]_D^{20}$ = +4.9 (c = 3.2, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.00 (s, 9H), 0.01 (s, 9H), 0.83 (s, 27H), 1.35 (d, J = 6.7 Hz, 9H), 3.76 (dd, J = 9.4, 6.8 Hz, 3H), 3.98 (pseudo t, J = 8.9 Hz, 3H), 4.93 (pseudo sex, J = 7.1 Hz, 3H). ^{13}C-NMR (500 MHz, $CDCl_3$): δ = −5.5 (3C), −5.4 (3C), 14.3 (3C), 18.0 (3C), 25.8 (9C), 53.2 (3C), 63.4 (3C), 149.2 (3C). $C_{30}H_{63}N_3O_6Si_3$ (645.4): Calcd.: C, 55.77; H, 9.83; N, 6.50; Found: C, 55.61; H, 9.65; N, 6.80%.

5. 1,3,5-Tris[(1*S*)-2-hydroxy-1-methylethyl]-1,3,5-triazine-2,4,6-trione (12). HF (5% in acetonitrile, 3.2 mL) was added to **11** (426 mg, 659 μmol). After stirring for 2 h saturated aqueous $NaHCO_3$ solution (5 ml) was added dropwise. The layers were separated and the aqueous layer was saturated with NaCl and extracted with ethyl acetate (6 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with ethyl acetate furnished the triol **12** (193 mg, 96%) as a colourless solid. M.p. = 192–194 °C. $[\alpha]_D^{20}$ = −3.7 (c = 1.4, acetone). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.28 (d, J = 6.9 Hz, 9H), 3.60 (dd, J = 11.6, 5.6 Hz, 3H), 4.09 (pseudo t, J = 11.6 Hz, 3H), 4.85–4.95 (m, 3H), OH signals not detected. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 13.8 (3C), 52.0 (3C), 61.9 (3C), 149.1 (3C). $C_{12}H_{21}N_3O_6$ (303.1): Calcd.: C, 47.52; H, 6.98; N, 13.85; Found: C, 47.55; H, 6.84; N, 13.90%.

6. 1,3,5-Tris[(1*S*)-2-azido-1-methylethyl]-1,3,5-triazine-2,4,6-trione (13). Triethylamine (233 μL, 1.68 mmol) was added at 0 °C into a solution of the triol **12** (115 mg, 379 μmol) in DMF (20 mL). After stirring for 10 min at 0 °C methanesulfonyl chloride (111 μL, 1.44 mmol) was added. After continued stirring for 2.5 h the mixture was allowed to reach room temperature and sodium azide (845 mg, 13.0 mmol) was added. The mixture was heated to 65 °C for 5 d. Saturated aqueous $NaHCO_3$ solution (50 mL) and water (40 mL) were added. The layers were separated and the aqueous layer was extracted with ether (5 × 30 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane/*tert*-butyl methyl ether = 4:1 furnished the tris-azide **13** (132 mg, 92%) as a colourless resin. $[\alpha]_D^{20}$ = −2.1 (c = 1.9, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.43 (d, J = 7.0 Hz, 9H), 3.46 (dd, J = 12.5, 5.7 Hz, 3H), 3.97 (dd, J = 12.5, 10.0 Hz, 3H), 4.94–5.03 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.5 (3C), 51.1 (3C), 52.5 (3C), 148.6 (3C). $C_{12}H_{18}N_{12}O_3$ (378.4): Calcd.: C, 38.09; H, 4.80; N, 44.42; Found: C, 37.91; H, 4.76; N, 44.63%.

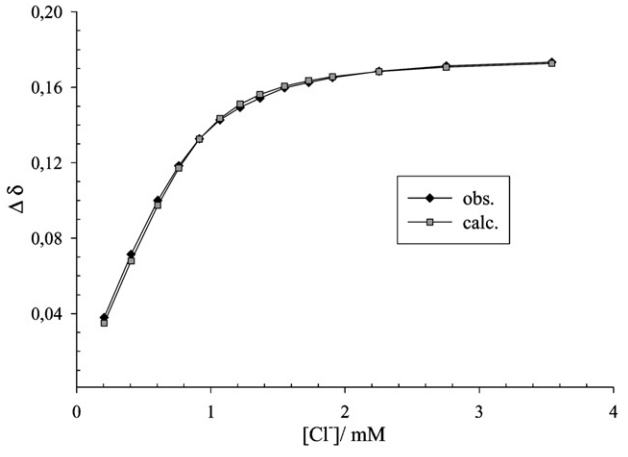
7. 1,3,5-Tris[(1*S*)-2-(4-nitrophenylsulfonamido)-1-methylethyl]-1,3,5-triazine-2,4,6-trione (6). The tris-azide **13** (47.0 mg, 124 μmol) was allowed to react as described in part 2 above. Flash chromatography of the crude product with *tert*-butyl methyl ether/dichloromethane = 4:1 furnished the tris-sulfonamide **6** (31 mg, 29%) as a slightly yellowish solid. M.p. 118–120 °C. $[\alpha]_D^{20}$ = −138 (c = 2.55, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.46 (d, J = 6.7 Hz, 9H), 3.13 (pseudo dt, J = 14.6, 5.3 Hz, 3H), 3.75 (ddd, J = 14.6, 11.3, 6.7 Hz, 3H), 5.18–5.29 (m, 3H), 6.21 (broad s, 3H), 8.05 (d, J = 8.9 Hz, 6H), 8.32 (d, J = 8.9 Hz, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.2 (3C), 44.4 (3C), 52.0 (3C), 124.5 (6C), 128.1 (6C), 145.6 (3C), 149.3 (3C), 150.2 (3C). HRMS (ESI) $C_{30}H_{33}N_9O_{15}S_3$ + Na Calcd.: 878.1156; Found: 878.1198.

8. 1,3,5-Tris[(1*R*,3*S*)-4-(4-nitrophenylsulfonamido)-1,3-dimethylbutyl]-1,3,5-triazine-2,4,6-trione (7). The tris-azide **14**[24] (207 mg, 410 μmol) was allowed to react as described in part 2 above. Flash chromatography of the crude product with *tert*-butyl methyl ether, saturated with NH_3, furnished the product **7** (195 mg, 48%) as a colourless solid. M.p. = 91–93 °C.

$[\alpha]_D^{20} = -53.1$ ($c = 1.64$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 500 MHz): $\delta = 0.96$ (d, $J = 6.6$ Hz, 9H), 1.27 (ddd, $J = 13.9$, 9.7, 4.5 Hz, 3H), 1.41–1.51 (m, 3H), 1.46 (d, $J = 7.0$ Hz, 9H), 2.37 (ddd, $J = 13.9$, 9.9, 3.7 Hz, 3H), 2.70–2.88 (m, 6H), 4.89–5.00 (m, 3 H), 5.69 (broad s, 3H), 8.07 (d, $J = 8.9$ Hz, 6H), 8.33 (d, $J = 9.0$ Hz, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): $\delta = 17.6$ (3C), 18.7 (3C), 31.7 (3C), 37.5 (3C), 49.0 (3C), 49.3 (3C), 124.4 (6C), 128.3 (6C), 145.4 (3C), 148.9 (3C), 150.0 (3C). HRMS (ESI) $C_{39}H_{51}N_9O_{15}S_3 + Na$, Calcd.: 1004.2564; Found: 1004.2543.

9. *N,N,N*-Tris[2-(4-nitrophenylsulfonamido)ethyl]amine (15). Triethylamine (1.08 mL, 7.80 mmol) and *p*-nitrophenylsulfonyl chloride (1.70 g, 7.67 mmol) were added into a solution of tris(2-aminoethyl)amine (317 mg, 2.16 mmol) in THF (10 mL). After stirring for 6 h at 80 °C and 12 h at room temperature the solvent was removed *in vacuo*. The crude product was purified by twofold flash chromatography with *tert*-butyl methyl ether/acetone = 9:1 → acetone in each case to give the tris-sulfonamide **15** (520 mg, 34%) as a slightly yellowish solid. M.p. = 180–181 °C. ^{1}H-NMR (500 MHz, DMSO-D_6): $\delta = 2.33$ (t, $J = 6.4$ Hz, 6H), 2.73 (d, $J = 6.4$ Hz, 6H), 7.77 (broad s, 3H), 8.01 (d, $J = 9.0$ Hz, 6H), 8.38 (d, $J = 9.0$ Hz, 6H). ^{13}C-NMR (125 MHz, DMSO-D_6): $\delta = 40.4$, 52.9, 124.6, 127.9, 146.1, 149.5. HRMS (ESI) $C_{24}H_{27}N_7O_{12}S_3 + H$, Calcd.: 702.0958; Found: 702.0999.

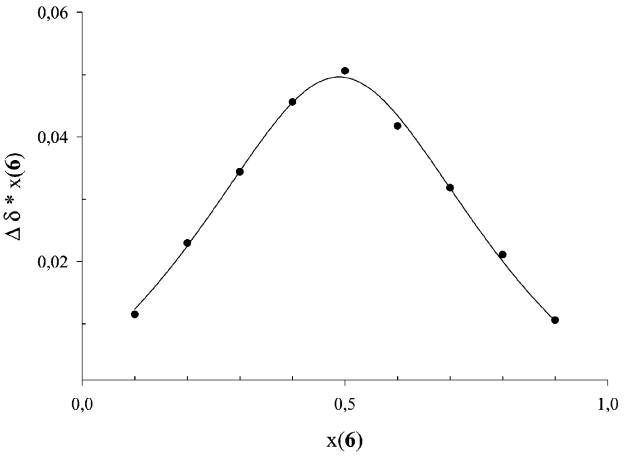
10. Complexation studies. Tetrabutylammonium salts were of >98% purity and were used as obtained from Aldrich or Merck. $CDCl_3$ and DMSO-D_6 (Aldrich or Deutero GmbH; deuterium content >99.6%) were used as obtained. A solution of the host (*ca.* 1 mM, 600 μL) was placed in an NMR tube. Spectra were recorded after injection of increments of a solution of the guest (*ca.* 25 mM). The changes upon complexation in the chemical shift ($\Delta\delta$) of either the NH-proton or of the protons of the arene moieties (or both) were recorded. A plot of $\Delta\delta$ against the concentration of the guest showed a characteristic curvature The curve was fitted with the program SIGMA Plot 2000[20] with routines to determine complexation constants for 1:1 complexes. The prevalence of 1:1 complexes was secured by Job plot experiments, in which based on the chemical shift of the free host (500 μL) $\Delta\delta$ was determined for the following host/guest combinations (host and guest having the same stock concentration; host μL/guest μL: 450/50, 400/100, 350/150, 300/200, 250/250, 200/300, 150/350, 100/400, 50/450). A plot of the product $\Delta\delta \times$ mole fraction (x) of the host against x led to a characteristic curvature, which was fitted using again SIGMA plot 2000.[20] Results from a typical experiment are reproduced in Fig. 1: A representative Job plot is reproduced in Fig. 2. Characteristic data for the microcalorimetric titration are given in Fig. 3 and Fig. 4.



Solvent	$CDCl_3$/ 5% DMSO-d_6	Σ of increments of guest solution added/μL	5, 10, 15, 19, 23, 27, 31, 35, 40, 45, 50, 60, 75, 100
$Volume_{(sample, initial)}$/μL	600		
$[Host]_{initial}$/mM	0.95		
$[Guest]_{stock}$ /mM	24.79		

NMR-signal used	NH	upfield CH_{ar}
$K_{ass\ 1:1}/M^{-1}$ (Std.Err/M^{-1})	13385 (± 743)	12630 (± 1105)

Fig. 1 NMR titration for the association of tetrabutylammonium chloride to host **6** in $CDCl_3$ at 300 K.



Solvent	$CDCl_3$	NMR-signal	CH_{ar} [u]
$Volume_{(total)}$/μL	500	**Maximum at ratio**	**0.49**
$[Host]_{stock}$ = $[Guest]_{stock}$/mM	2.00		

Fig. 2 Job plot for binding of tetrabutylammonium chloride to host **6** in $CHCl_3$.

11. Microcalorimetric titrations. The calorimetric titrations were made at 298 K using a Thermometric® titration calorimetric system (Thermometric®, Sweden). The reproducibility of the calorimeter was checked using the complexation of Ba^{2+} by 18-crown-6. A solution of tetrabutylammonium chloride (40.03 mM) in chloroform was titrated into a 1.59 mM

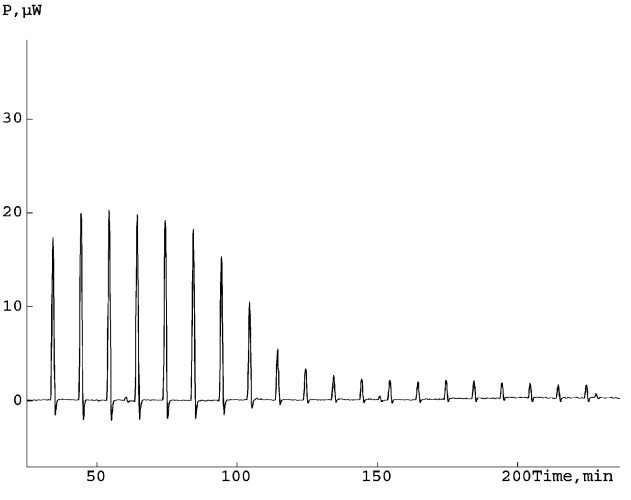


Fig. 3 Calorimetric titration of tetrabutylammonium chloride/host **6** in $CHCl_3$.

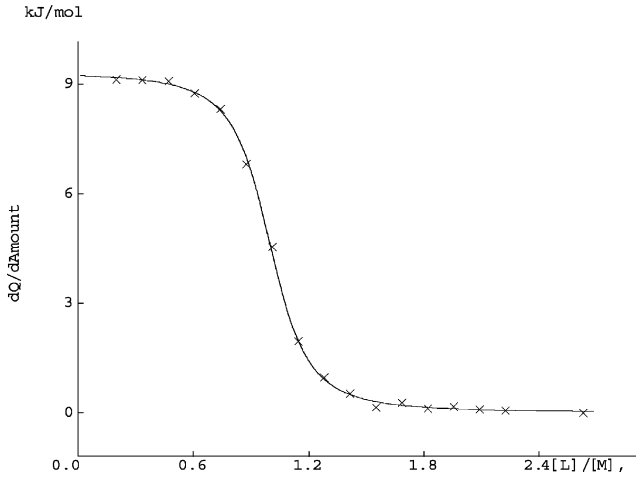


Fig. 4 Resulting binding curve (corrected for enthalpy of dilution) leading to $K_a = 154\,880 \pm 11\,370$ M^{-1}; $\Delta H = -9.38 \pm 0.05$ kJ mol^{-1}, for formation of a 1:1 complex.

solution of host **7** or a 0.82 mM solution of host **6** in chloroform. All non-chemical heat effects (*i.e.* heat of dilution) were corrected. The data obtained were analysed using the Digitam 4.1 software provided by Thermometric®.

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