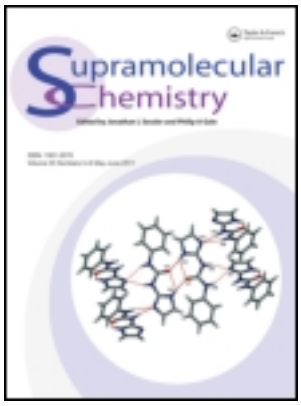

Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsch20

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Available online: 28 Nov 2011

To cite this article: Martin Havlík, Bohumil Dolenský, Jiří Kessler, Ivana Císařová & Vladimír Král (2012): A new synthetic strategy to prepare throne and calix diastereoisomers of parallel tris-Tröger's bases, Supramolecular Chemistry, 24:2, 127-134

To link to this article: http://dx.doi.org/10.1080/10610278.2011.632822

Supramolecular Chemistry
Vol. 24, No. 2, February 2012, 127–134

A new synthetic strategy to prepare throne and calix diastereoisomers of parallel tris-Tröger's bases

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(*Received 30 June 2011; final version received 13 October 2011*)

The calix diastereoisomers of the parallel tris-Tröger's base (tris-TB) derivatives were suggested as potential cavitands in 2002, and the first members of this cavitand family were introduced in 2007. The synthetic strategy enabling the preparation of naphthalene and anthracene derivatives of parallel tris-TBs, i.e. preparation without any reduction step, is introduced. Naphthalene *calix*-tris-TB derivative having a cavity volume of about 0.113 nm^3 (65% of α-CD cavity) is prepared by isomerisation in various acid conditions.

Keywords: parallel tris-Tröger's base; diastereoisomerisation; cavitand

Introduction

More than 120 years ago, Tröger prepared an unknown compound with basic character, today known as Tröger's base (TB) (*1*). TB derivatives are compounds containing two aromatic systems annelated by 1,5-diazabicyclo[3.3.1]nonane (TB unit). The molecular features of TB derivatives (C2 symmetry, concave V-shape and chirality) predestine them to be building blocks for molecular architecture (*2*). We have recently published a new type of cavitand based on parallel tris-TB derivatives (*3*).

Parallel tris-TBs include three TB units annelated to a single arene (e.g. benzene). These compounds have two diastereoisomers: non-cavity *throne*-tris-TB and *calix*-tris-TB having a cavity compartment (Figure 1). Tris-TB diastereoisomers can be interconverted to each other in acid medium; thus, the cavity can be created or disposed by a change in pH. This unique property differes *calix*-tris-TBs from other known cavitands, such as cyclodextrins, calixarenes, resorcinarenes, cucurbiturils and so on (*4*).

At present, we introduce a new synthetic method for the preparation of tris-TBs derivative from naphthalene and anthracene, their isomerisation under various acid conditions and a molecular modelling study of *calix*-tris-TB cavitands.

Results and discussion

Preparation

We established the preparation of parallel tris-TB derivatives **1** based on the synthetic protocol, which were successful in the preparation of bis-Tröger's (bis-TB) derivatives (*5*). The key to the success is the preparation of hexaamine intermediate **2** without using any reduction step, since it is expected to be unstable in reduction condition (*5a*).

The preparation starts from mesitylene (Scheme 1). Nitration of mesitylene followed by reduction gave triamine **5** (*6*). The following reaction of triamine **5** with di-*tert*-butyl dicarbonate (Boc_2O) provided triamine **4**. The radical bromination gave the key tribromide **3** in 61%. It is worth mentioning that two atropoisomers (symmetric and unsymmetric) were observed in ^{1}H NMR spectra of both triamine **4** and tribromide **3**, wherein the averaged spectrum is observed above 50°C.

We also tried an alternative way for preparing tribromide **3**. Triamine **4** was treated with Boc_2O (4-dimethylaminopyridine – DMAP as catalyst is required) to form fully protected triamine **7**. The following radical bromination of triamine **7** gave tribromide **8**. Tribromide **3** was obtained by partial deprotection of tribromide **8** by the treatment with trifluoroacetic acid (TFA). This latter synthetic method gave lower overall yield (44%), but isolation and purification of product are easier and more suitable for upscaling.

The treatment of tribromide **3** with arylamines (Scheme 2) in the presence of K_2CO_3 produced hexaamines **2** (41% yield of **2a** and 20% yield of **2b**). Slightly better yields were obtained by the reaction without K_2CO_3 (50% yield of **2a** and 34% yield of **2b**). Surprisingly, analogous treatment of tribromide **8** with arylamines gave no corresponding hexaamines; the steric restraint of *tert*-butoxycarbonyl groups could be the reason. Using stronger base and higher temperature gave a mixture of unidentified compounds.

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ISSN 1061-0278 print/ISSN 1029-0478 online

http://dx.doi.org/10.1080/10610278.2011.632822
http://www.tandfonline.com

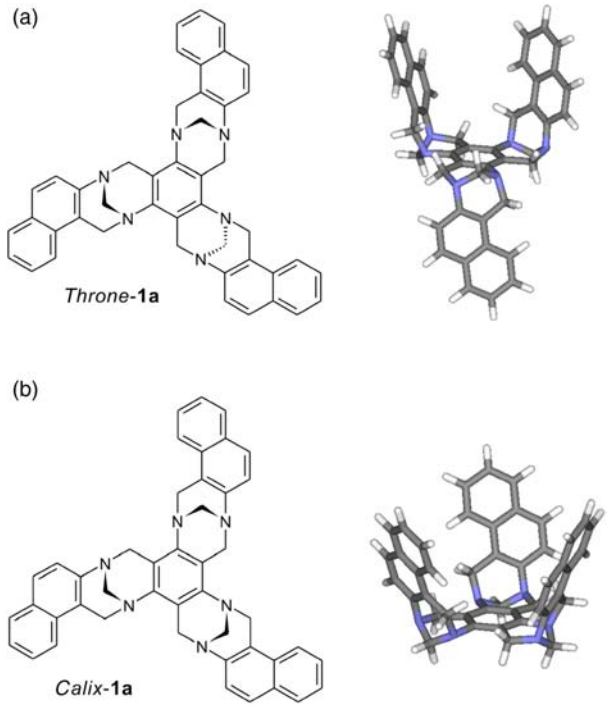


Figure 1. Diastereoisomers of tris-TB **1a**. (a) the structure and optimised geometry of *throne*-**1a** and (b) the structure and optimised geometry of *calix*-**1a.**

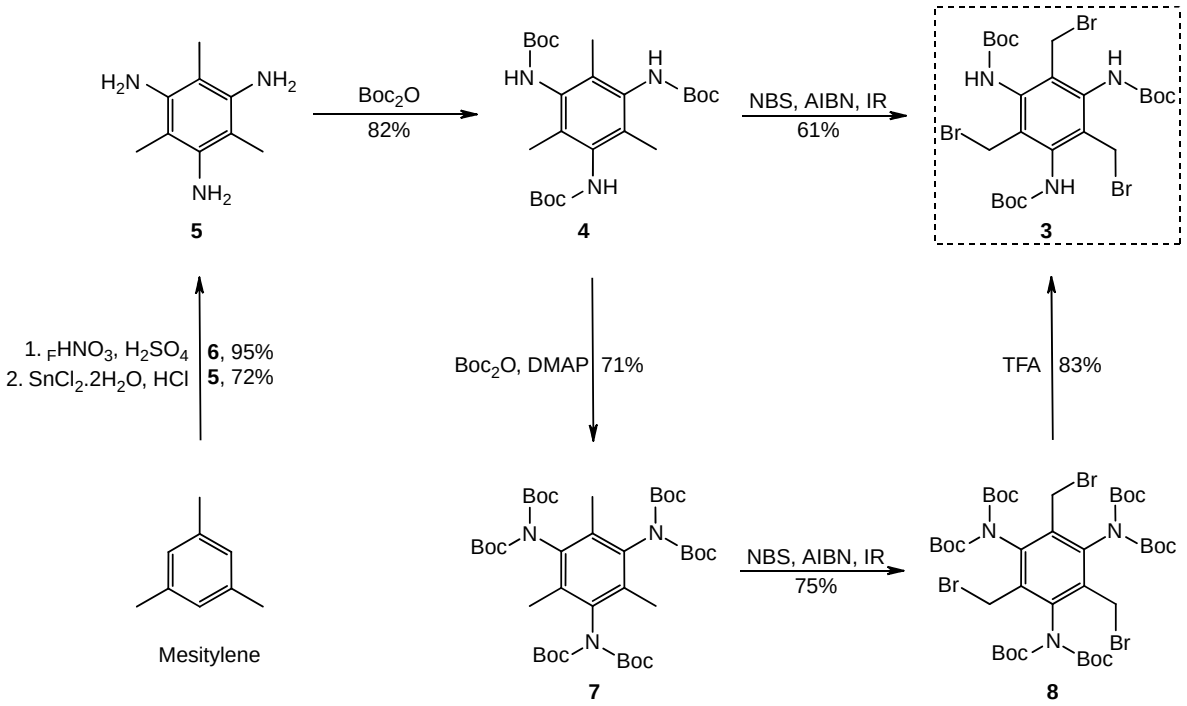
The final treatment of hexaamines **2** with paraformaldehyde in TFA produced corresponding tris-TBs **1** (Scheme 2). Tris-TB **1a** was formed in excellent 88% yield. On the other hand, tris-TB **1b** is formed in only 26% yield, and is followed by several unidentified compounds. As was expected, formation of only *throne*-tris-TBs was observed (*3*).

Suitable single crystal of *throne*-**1a** for single-crystal X-ray diffraction was obtained by crystallisation from the mixture of dichloromethane and methanol (Figure 2 left). The crystal packing uncovered short contacts between two molecules of *throne*-**1a** (Figure 2 right). The naphthalene plane of one molecule is coplanar with the naphthalene plane of the second molecule (π-π interaction, distance of planes is 0.35 nm); in addition, a naphthalene hydrogen atom of one molecule interacts with central benzene of the second molecule (CH-π interaction, distance is 0.25 nm).

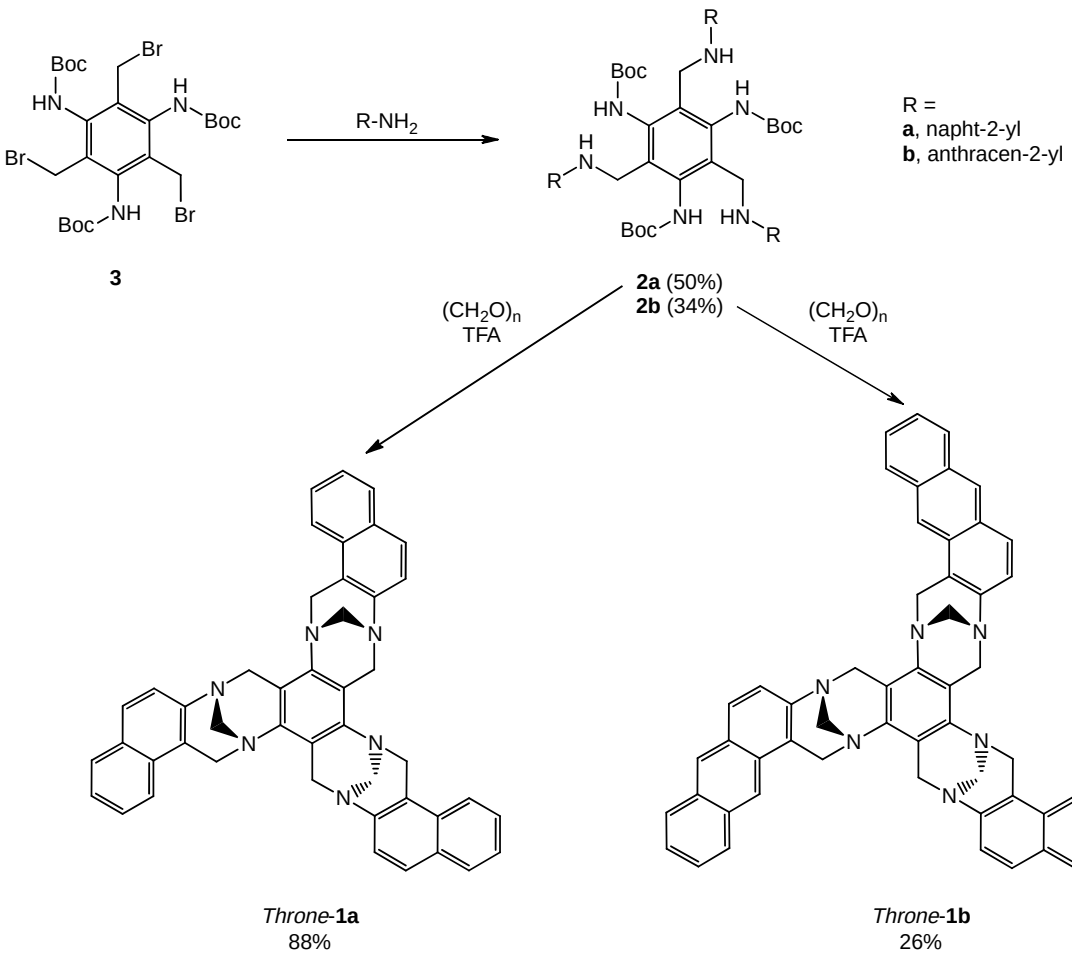
Diastereoisomerisation study

There are only a few studies dealing with diastereoisomerisation of oligo-TB derivatives (*7*). A significant effect of HCl was observed on the equilibrium ratio of diastereoisomers. The presence of HCl or NH_4Cl increases yields of cavity-like diastereoisomers in case of both bis-TBs and linear tris-TBs. It was assumed that there is an interaction between chloride anion and both aromatic sidewalls of oligo-TBs. We therefore examined an effect of anions in the acid medium on the *throne*-**1a** : *calix*-**1a** ratio.

The diastereoisomerisation study (Scheme 3) was performed at 60°C with *throne*-**1a**, wherein neat TFA, or 1:1 mixture of TFA with 35% aq. HCl, 48% aq. HBr, 57%



Scheme 1. Preparation of tribromide **3**.



Scheme 2. Synthesis of tris-TB **1a** and **1b**.

aq. HI, or 85% aq. H_3PO_4 was used. TFA was used to maintain the solubility of *throne*-**1a**. The ratio of diastereoisomers was followed by HPLC analysis (Table 1). In all cases, the equilibrium was reached in 4 days. The treatment in TFA with 57% aq. HI led to *throne*-**1a** decomposition. For preparative scale, diastereoisomerisation of *throne*-**1a** in the mixture of TFA and 48% aq. HBr was chosen. In accordance with the previous study, *calix*-**1a** was obtained in 4% yield.

Molecular modelling

Finally, we tried to estimate a cavity volume of *calix*-**1a**, *calix*-**1b** and *calix*-**9** (a benzene tris-TB derivative). The molecular geometry of calix diastereoisomers was optimised on DFT-level using B3LYP functional with 6–31 g** basis set and dispersion correction (*8*). The cavity of calix diastereoisomers was approximated by a truncated cone, whose top radius was determined as a radius of the

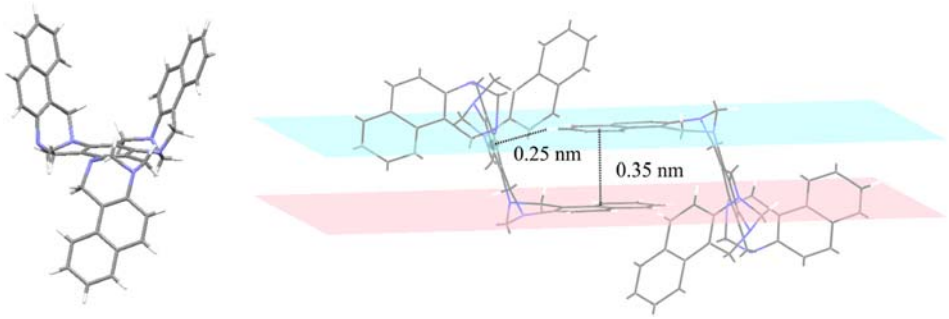
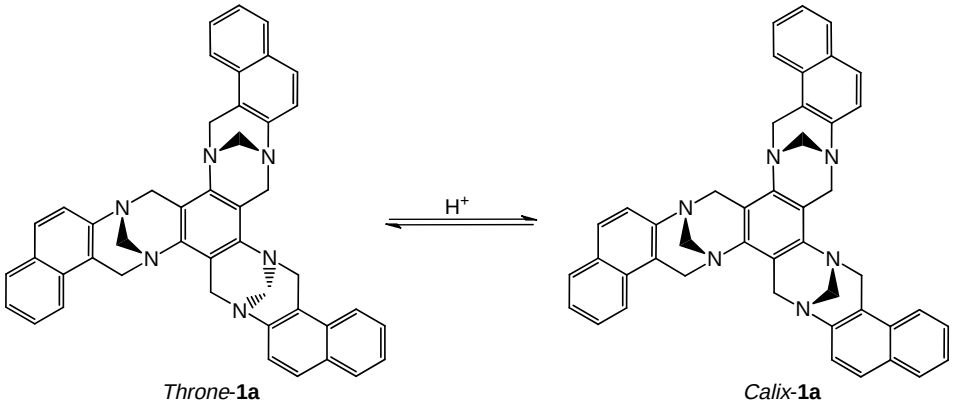


Figure 2. The X-ray crystal structure of *throne*-**1a** (left), short contacts between two molecules of *throne*-**1a** (right).



Scheme 3. Diastereoisomerisation of tris-TB **1a**.

described circle defined by the upper carbon atoms of the cavity sidewalls. The cone height was measured as a distance between the plane of bottom benzene and the plane of the upper carbon atoms of the cavity sidewalls (Figure 3). All the measurements were lowered by 0.16 nm (a van der Waals radius) and the volume was calculated (Table 2). The cavity volume of *calix*-**1a** is 65% of α-CD cavity, whereas *calix*-**1b** cavity is 124% of α-CD and 82% of β-CD.

Conclusion

In conclusion, we presented a new synthetic method for the preparation of tris-TB derivatives resulting in naphthalene *throne*-**1a** in 88% yield and anthracene *throne*-**1b** in 26% yield. We found a slight influence of the used acid on the diastereoisomerisation ratio of *calix*-**1a** and *throne*-**1a**. We isolated a new cavitand, *calix*-**1a**, having a cavity volume of about 0.113 nm^3 (65% of α-CD cavity). We demonstrated that tris-TB cavitands having a deep-wall cavity can be prepared.

Experimental part

Measurements and materials

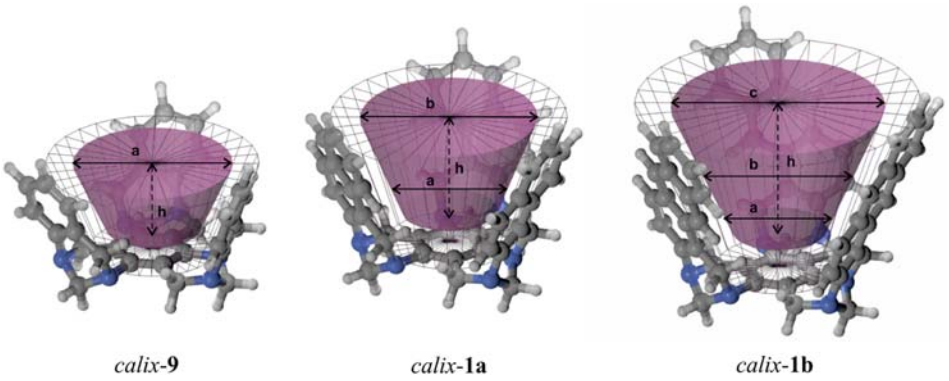
All chemicals were purchased from Sigma-Aldrich Co. and TCI Europe N. V. and used without further purification. NMR spectra were recorded on Varian Gemini 300 HC (300.077 MHz for ^1H and 75.460 MHz for ^{13}C) at room temperature (23–25°C) in $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) are presented in ppm and, coupling constants (*J*) in Hz. The program MestReNova v. 6.02 was used for workup of NMR spectra. Mass spectra were obtained by electrospray ionisation (ESI^+) with a VG Analytical ZAB-EQ spectrometer. HPLC (LC 5000 HPLC) was used for the determination of ratio of diastereoisomers of tris-TB **1a**. The program Gaussian 09 was used for the quantum chemical calculations of molecules. The UCSF Chimera v. 1.5.3 was used to generate 3D model of molecules, and this model was processed in Blender 2.5 to obtain cavity visualisation. Silica (32–63 D, 60 Å) was used for column chromatography.

Preparations of triamines 4 and 7

Mesitylene (8.6 g, 71.6 mmol) was added to the nitration mixture (42 ml of sulphuric acid and 21 ml of fuming nitric acid), and the reaction mixture was stirred and kept under 0°C in water cooling bath for 2 h. The reaction mixture was then poured onto ice. Precipitated solid was filtered off, washed with water and methanol and dried *in vacuo* to obtain 17.4 g (95.3%) of 1,3,5-trinitromesitylene (**6**). Compound **6** (3.0 g, 11.8 mmol) was treated with $SnCl_2 \cdot 2H_2O$ (31.8 g, 140.9 mmol) in concentrated HCl (300 ml) at 105°C for 5 h. The solution was carefully alkalinised at 0°C by concentrated aq. NH_3 and extracted with dichloromethane. The organic parts were extracted by water, dried over Na_2SO_4 and evaporated to dryness *in vacuo* to obtain 1.4 g (72.1%) of triamine **5**. Triamine **5** (2.0 g, 12.1 mmol)

Table 1. Results of isomerisation study of tris-TB **1a**.

60°C	Ratio of diastereoisomers depending on the time of *throne*-**1a** : *calix*-**1a**					
Acid medium	2 h	4 h	6 h	24 h	4 days	7 days
TFA	99.7 : 0.3	99.3 : 0.7	98.7 : 1.3	98.0 : 2.0	97.9 : 2.1	97.9 : 2.1
TFA : HCl	99.8 : 0.2	99.6 : 0.4	98.7 : 1.3	98.4 : 1.6	97.2 : 2.7	97.4 : 2.6
TFA : HBr	99.7 : 0.3	99.3 : 0.7	98.6 : 1.4	97.0 : 3.0	96.4 : 3.6	96.4 : 3.6
TFA : H_3PO_4	99.5 : 0.5	99.2 : 0.8	97.8 : 2.2	97.1 : 2.9	96.4 : 3.6	96.3 : 3.7



calix-**9** *calix*-**1a** *calix*-**1b**

Figure 3. Optimised geometry of *calix*-tris-TB derivatives. The calculated cavity volume is indicated by a purple cone.

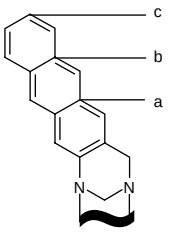
was treated with Boc_2O (10.6 g, 48.6 mmol) in THF (100 ml) at reflux for 2 days. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was separated by column chromatography (dichloromethane/methanol 95:5) to obtain 4.6 g (81.6%) of triamine **4**. Triamine **4** (3.0 g, 6.4 mmol) was treated with Boc_2O (6.3 g, 28.9 mmol) and DMAP (37.0 mg, 0.3 mmol) in THF (150 ml) at reflux for overnight. The reaction mixture was evaporated to dryness *in vacuo* and triamine **7** was obtained and purified by crystallisation from dichloromethane/petrol ether 3.5 g (70.9%). *1,3,5-trinitromesitylene* (**6**): ^{1}H NMR ($CDCl_3$): δ2.27 (9H, s). ^{13}C APT NMR ($CDCl_3$): δ150.51 (C), 124.50 (C), 13.34 (CH_3). *2,4,6-trimethylbenzene-1,3,5-triamine* (**5**): ^{1}H NMR (DMSO-d_6): δ3.94 (6H, bs), 1.79 (9H, s). ^{13}C APT NMR (DMSO-d_6): δ141.45 (C), 95.83 (C), 11.07 (CH_3). *N^1,N^3,N^5-tris(tert-butoxycarbonyl)-2,4,6-trimethylbenzene-1,3,5-triamine* (**4**): ^{1}H NMR ($CDCl_3$, 50°C): δ5.83 (3H, bs), 2.17 (9H, s), 1.48 (27H, s). ^{13}C APT NMR ($CDCl_3$): δ153.98 (C), 133.50 (C), 132.32 (C), 79.85 (C), 28.48 (CH_3), 14.02 (CH_3). HR-MS (ESI^+) for $C_{24}H_{39}N_3O_6Na$ $[M + Na]^+$ calculated: 488.2731, found: 488.2724. *N^1,N^1,N^3,N^3,N^5,N^5-hexakis(tert-butoxycarbonyl)-2,4,6-trimethylbenzene-1,3,5-triamine* (**7**): ^{1}H NMR ($CDCl_3$): δ2.02 (9H, s), 1.39 (54H, s). ^{13}C APT NMR ($CDCl_3$): δ151.17 (C), 135.80 (C), 133.85 (C), 82.37 (C), 28.04 (CH_3), 13.20 (CH_3). HR-MS (ESI^+) for $C_{39}H_{63}N_3O_{12}Na$ $[M + Na]^+$ calculated: 788.4304, found: 788.4285.

Preparations of tribromides 3 and 8

*2,4,6-Tris(bromomethyl)-N^1,N^3,N^5-tris(tert-butoxycarbonyl)-2,4,6-trimethylbenzene-1,3,5-triamine (**3**)*

Procedure I. Triamine **4** (0.25 g, 0.54 mmol) was treated with *N*-bromosuccinimide (NBS, 0.35 g, 1.97 mmol) and α,α′-azo-bis-isobutyronitrile (AIBN, 0.03 g) in CCl_4 (60 ml) under irradiation by the IR lamp for 5 h. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was separated by column chromatography (dichloromethane/diethylether 3:1) to obtain 0.23 g (61.0%) of tribromide **3**. ^{1}H NMR (DMSO-d_6, 50°C): δ8.86 (3H, bs), 4.56 (6H, s), 1.46 (27H, s). ^{13}C APT NMR (DMSO-d_6): δ153.69 (C), 137.37 (C), 133.41 (C), 79.18 (C), 28.21 (CH_3), 25.75 (CH_2). HRMS (ESI^+): for $C_{24}H_{36}Br_3N_3O_6Na$ $[M + Na]^+$ calculated: 727.9985, 724.0026, 722.0046, found: 727.9978, 724.0022, 722.0046.

Table 2. Cavity parameters for *calix*-tris-TBs and cyclodextrins (**4a**).



	calix-**9**	*calix*-**1a**	*calix*-**1b**	α-CD	β-CD	γ-CD
a [nm]	0.63	0.65	0.65	0.47–0.53	0.60–0.65	0.75–0.83
b [nm]	–	0.74	0.74			
c [nm]	–	–	0.89			
h [nm]	0.26	0.45	0.64	0.79	0.79	0.79
V [nm^3]	0.053	0.113	0.215	0.174	0.262	0.427

Procedure II. Tribromide **8** (0.50 g, 0.50 mmol) was dissolved in dichloromethane (250 ml) and TFA (1 ml) was added. The reaction mixture was monitored by TLC analysis (toluene:ethyl acetate 5:1). The reaction mixture was alkalinised by concentrated aq. NH_3 (1 ml) in water (250 ml). The organic part was extracted by water, dried over Na_2SO_4 and dried *in vacuo*. Tribromide **3** was obtained and purified by crystallisation from THF/petrol ether 0.29 g (82.8%).

*2,4,6-Tris(bromomethyl)-N^1,N^1,N^3,N^3,N^5,N^5-hexakis(tert-butoxycarbonyl)-2,4,6-trimethylbenzene-1,3,5-triamine (**8**)*

Triamine **7** (0.50 g, 0.65 mmol) was treated with N-bromosuccinimide (NBS, 0.42 g, 2.36 mmol) and α,α′-azo-bis-isobutyronitrile (AIBN, 0.03 g) in CCl_4 (60 ml) under irradiation by an IR lamp for 5 h. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was separated by column chromatography (dichloromethane/diethylether 25:1) to obtain 0.49 g (74.9%) of tribromide **8**. ^{1}H NMR ($CDCl_3$): δ4.33 (6H, s), 1.45 (54H, s). ^{13}C APT NMR ($CDCl_3$): δ150.20 (C), 139.40 (C), 135.23 (C), 84.14 (C), 28.08 (CH_3), 23.38 (CH_2). HR-MS (ESI^+): for $C_{39}H_{60}Br_3N_3O_{12}Na$ $[M + Na]^+$ calculated: 1024.1599, 1026.1578, 1027.1612, found: 1024.1598, 1026.1577, 1027.1598.

Preparation of hexaamines 2

Procedure I

*N^1,N^3,N^5-tris(tert-butoxycarbonyl)-2,4,6-tris((naphthalen-2-ylamino)methyl)benzene-1,3,5-triamine (**2a**)*. Tribromide **3** (250 mg, 356 μmol) was treated with 2-aminonaphthalene (310 mg, 2165 μmol) and K_2CO_3 (110 mg, 796 μmol) in 40 ml of DMF at 50°C for 2 h. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was separated by column chromatography (toluene:ethyl acetate 5:1) to obtain 130 mg (41.1%) of hexaamine **2a**. ^{1}H NMR ($CDCl_3$): δ7.73 (3H, d, $J = 7.5$), 7.70 (3H, d, $J = 8.8$), 7.69 (3H, d, $J = 7.5$), 7.49 (3H, bs), 7.42 (3H, dt, $J = 7.5$, $J = 1.2$), 7.27 (3H, dt, $J = 7.5$, $J = 1.2$), 7.12 (3H, d, $J = 2.2$), 7.05 (3H, dd, $J = 8.8$, $J = 2.2$), 4.60 (3H, bs), 4.34 (6H, s), 1.37 (27H, s). ^{13}C APT NMR ($CDCl_3$): δ155.36 (C), 146.52 (C), 137.17 (C), 135.08 (C), 129.90 (C), 129.04 (CH), 128.53 (C), 127.79 (CH), 126.49 (CH), 126.36 (CH), 122.85 (CH), 119.21 (CH), 107.48 (CH), 81.04 (C), 44.03 (CH_2), 28.31 (CH_3). HR-MS (ESI^+) for $C_{54}H_{61}N_6O_6$ $[M + H]^+$ calculated: 889.4647, found: 889.4636.

*N^1,N^3,N^5-tris(tert-butoxycarbonyl)-2,4,6-tris((anthracen-2-ylamino)methyl)benzene-1,3,5-triamine (**2b**)*. Tribromide **3** (250 g, 356 μmol) was treated with 2-aminoanthracene (420 mg, 2173 μmol) and K_2CO_3 (110 mg, 796 μmol) in 40 ml of DMF at 50°C for 2 h. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was separated by column chromatography (toluene:ethyl acetate 5:1) to obtain 74 mg (20.0%) of hexaamine **2b**. ^{1}H NMR ($CDCl_3$): δ8.29 (3H, s), 8.19 (3H, s), 7.94 (3H, d, $J = 7.1$), 7.91 (3H, d, $J = 7.1$), 7.83 (3H, d, $J = 8.9$), 7.47 – 7.30 (9H, m), 7.16 (3H, bs), 7.05 (3H, d, $J = 8.9$), 4.65 (3H, bs), 4.39 (6H, s), 1.34 (27H, s). ^{13}C APT NMR ($CDCl_3$): δ155.44 (C), 145.70 (C), 137.23 (C), 133.43 (C), 132.54 (C), 130.35 (C), 129.98 (C), 129.47 (CH), 128.37 (CH), 128.11 (C), 127.62 (CH), 126.31 (CH), 125.52 (CH), 124.07 (CH), 123.24 (CH), 121.10 (CH), 104.36 (CH), 81.20 (C), 43.50 (CH_2), 28.26 (CH_3). HR-MS (ESI^+) for $C_{66}H_{67}N_6O_6$ $[M + H]^+$ calculated: 1039.5117, found: 1039.5149.

Procedure II

*N^1,N^3,N^5-tris(tert-butoxycarbonyl)-2,4,6-tris((naphthalen-2-ylamino)methyl)benzene-1,3,5-triamine (**2a**)*. Tribromide **3** (350 mg, 498 μmol) was treated with 2-aminonaphthalene (430 mg, 3003 μmol) in 50 ml of THF at 50°C for 5 h. The reaction mixture was alkalinised by concentrated aq. NH_3 (1 ml) in water (250 ml). Chloroform (50 ml) was added, organic part was extracted by water, dried over Na_2SO_4, evaporated to dryness *in vacuo* and the residue was separated by column chromatography (toluene:ethyl acetate 5:1) to obtain 222 mg (50.1%) of hexaamine **2a**.

*N^1,N^3,N^5-tris(tert-butoxycarbonyl)-2,4,6-tris((anthracen-2-ylamino)methyl)benzene-1,3,5-triamine (**2b**)*. Tribromide **3** (350 g, 498 μmol) was treated with 2-aminoanthracene (580 mg, 3001 μmol) in 50 ml of THF at 50°C for 5 h. The reaction mixture was alkalinised by concentrated aq. NH_3 (1 ml) in water (250 ml). Chloroform (50 ml) was added, organic part was extracted by water, dried over Na_2SO_4, evaporated to dryness *in vacuo* and the residue was separated by column chromatography (toluene:ethyl acetate 5:1) to obtain 176 mg (34.0%) of hexaamine **2b**.

Preparation of tris-TB 1

Throne-**1a**. Hexaamine **2a** (100 mg, 112 μmol) was dissolved in 10 ml of TFA, and 64 mg of paraformaldehyde (1332 μmol of CH_2O equiv.) was added. The reaction mixture was stirred at room temperature for overnight. The reaction mixture was diluted with ice water, alkalinised by concentrated aq. NH_3 and extracted with dichloromethane. The organic parts were extracted by water, dried over Na_2SO_4, evaporated to dryness *in vacuo* and the residue was separated by column chromatography (toluene:acetone 3:1) to obtain 65 mg (87.5%) of *throne*-**1a**. ^{1}H NMR ($CDCl_3$): δ7.88–7.18 (18H, m), 4.90–4.51 (9H, m), 4.42–3.92 (9H, m). ^{13}C APT NMR ($CDCl_3$): δ145.49 (C), 145.37 (C), 145.10 (C), 144.71 (C), 144.67 (C), 144.50

(C), 131.48 (C), 131.32 (C), 131.00 (C), 130.93 (C), 130.87 (C), 130.71 (C), 128.79 (CH), 128.63 (CH), 128.53 (CH), 127.96 (CH), 127.94 (CH), 127.79 (CH), 126.63 (CH), 126.53 (CH), 126.35 (CH), 125.12 (CH), 124.90 (CH), 124.83 (CH), 124.73 (CH), 124.64 (CH), 124.14 (CH), 121.41 (C), 121.35 (C), 121.33 (C), 121.20 (CH), 121.14 (CH), 120.78 (CH), 119.13 (C), 118.32 (C), 118.20 (C), 66.90 (CH_2), 66.85 (CH_2), 66.68 (CH_2), 55.31 (CH_2), 54.22 (CH_2), 54.18 (CH_2), 53.94 (CH_2), 53.03 (CH_2), 53.01 (CH_2). HR-MS (ESI^+) for $C_{45}H_{37}N_6$ $[M + H]^+$ calculated: 661.3074, found: 661.3077.

Calix-**1a**. *Throne*-**1a** (100 mg, 151 μmol) was dissolved in acid mixture (5 ml of TFA and 5 ml of HBr). The reaction mixture was stirred at 60°C for 5 days. The reaction mixture was diluted with ice water, alkalinised by concentrated aq. NH_3 and extracted with dichloromethane. The organic parts were extracted by water, dried over Na_2SO_4, evaporated to dryness *in vacuo* and the residue was separated by column chromatography (toluene:acetone 3:1) to obtain 4.0 mg (4.0%) of *calix*-**1a** and 94.8 mg (94.8%) of starting *throne*-**1a**. ^1H NMR ($CDCl_3$): δ7.63 (3H, d, $J = 8.8$), 7.59 (3H, dd, $J = 7.9$, $J = 1.4$), 7.38 (3H, d, $J = 8.8$), 7.33 (3H, dd, $J = 8.3$, $J = 1.3$), 7.29-7.15 (6H, m), 4.82 (3H, d, $J = 17.5$), 4.80 (3H, d, $J = 16.8$), 4.58 (3H, d, $J = 17.5$), 4.36 (3H, d, $J = 12.8$), 4.32 (3H, d, $J = 12.8$), 3.99 (3H, d, $J = 16.8$). ^{13}C APT NMR ($CDCl_3$): δ145.41 (C), 144.80 (C), 131.22 (C), 130.98 (C), 128.53 (CH), 127.98 (CH), 126.38 (CH), 124.63 (CH), 124.30 (CH), 121.20 (C), 120.98 (CH), 120.55 (C), 66.47 (CH_2), 55.17 (CH_2), 53.15 (CH_2). HRMS (ESI^+) for $C_{45}H_{37}N_6$ $[M + H]^+$ calculated: 661.3074, found: 661.3081.

Throne-**1b**. Hexaamine **2b** (55 mg, 53 μmol) was dissolved in 10 ml of TFA, and 30 mg of paraformaldehyde (624 μmol of CH_2O equiv.) was added. The reaction mixture was stirred at room temperature for overnight. The reaction mixture was diluted with ice water, alkalinised by concentrated aq. NH_3 and extracted with dichloromethane. The organic parts were extracted by water, dried over Na_2SO_4, evaporated to dryness *in vacuo* and the residue was separated by column chromatography (toluene:acetone 3:1) to obtain 11 mg (25.6%) of *throne*-**1b**. ^1H NMR ($CDCl_3$): δ8.35 (1H, s), 8.21–7.19 (23H, m), 5.01–4.56 (9H, m), 4.50–4.04 (9H, m). ^{13}C APT NMR ($CDCl_3$): δ144.87 (C), 144.79 (C), 144.77 (C), 144.72 (C), 144.45 (C), 144.29 (C), 132.07 (C), 131.91 (2 × C), 130.92 (C), 130.75 (C), 130.71 (C), 129.93 (2 × C), 129.76 (C), 129.59 (2 × C), 129.55 (C), 128.38 (2 × CH), 128.20 (2 × CH), 128.14 (CH), 128.08 (CH), 128.02 (2 × CH), 127.95 (CH), 127.29 (CH), 127.19 (CH), 126.97 (CH), 125.92 (CH), 125.71 (CH), 125.64 (CH), 125.37 (CH), 125.18 (CH), 125.09 (CH), 124.99 (CH), 124.95 (CH), 124.35 (CH), 120.45 (C), 120.42 (C), 120.39 (C), 119.12 (CH), 119.10 (C), 119.06 (CH), 118.87 (CH), 118.34 (C), 118.32 (C), 67.11 (CH_2), 67.01 (CH_2), 66.81 (CH_2), 54.71 (CH_2), 54.20 (CH_2), 53.37 (CH_2), 53.55 (CH_2), 53.33 (CH_2), 53.24 (CH_2). HR-MS (ESI^+) for $C_{57}H_{43}N_6$ $[M + H]^+$ calculated: 811.3544., found: 811.3541.

X-ray crystallographic analysis of **throne-*1a***

Suitable single crystal of *throne*-**1a** for single-crystal X-ray diffraction was obtained by crystallisation from the mixture of dichloromethane and methanol. The intensity data were collected using a Bruker APEX-II CCD diffractometer. Crystal data: $C_{45}H_{36}N_6{\cdot}2(CH_2Cl_2)$, $M_r = 830.65$, crystal size: $0.58 \times 0.45 \times 0.37$ mm, colourless prism, triclinic, space group: *P*-1 (No. 2), $a = 10.2949$ (5) Å, $b = 13.8180$ (7) Å, $c = 15.2560$ (7) Å, $\alpha = 110.341$ (2)°, $\beta = 102.153$ (2)°, $\gamma = 94.045$ (2)°, $V = 1964.70$ (16) $Å^3$, $Z = 2$, $F_{000} = 864$, $D_x = 1.404$ mg m^{-3}, $\lambda = 0.71073$ Å [Mo, Kα], $\theta = 2.2–27.5°$, $\mu = 0.35$ mm^{-1}, $T = 150$ (2) K. Data collection and refinement details: 66073 measured reflections, 9025 independent reflections, $R_{int} = 0.030$, 7147 reflections with $I > 2\sigma(I)$, $\theta_{max} = 27.5°$, $\theta_{min} = 1.5°$, $R[F^2 > 2\sigma(F^2)] = 0.057$, $wR(F^2) = 0.167$, $w = 1/[\sigma^2(F_o^2) + (0.091P)^2 + 1.2586P]$ where $P = (F_o^2 + 2F_c^2)/3$, $S = 1.07$, $(\Delta/\sigma)_{max} = 0.002$, $\Delta\rho_{max} = 0.84$ $eÅ^{-3}$, $\Delta\rho_{min} = -0.86$ $eÅ^{-3}$. The contributions of the disordered second molecule of dichloromethane were removed from the diffraction data with PLATON/SQUEEZE procedure to improve the precision of the main molecule (*9*). The number of electrons removed from the voids was estimated as 97, which corresponds to the two molecules of dichloromethane in the unit cell. Crystallographic data for the structural analysis have been deposited at the Cambridge Crystallographic Data Centre (CCDC No. 847361). These data can be obtained free of charge from the director, CCDC (http://www.ccdc.cam.ac.uk/conts/retrieving.html).

Diastereoisomerisation studies of tris-TB 1a

Throne-**1a** (5.0 mg, 7.6 μmol) was dissolved in 5 ml of acid. The reaction mixture was stirred at 60°C for 7 days and samples (0.2 ml) were obtained in time intervals. The sample was alkalinised by concentrated aq. NH_3 and extracted with dichloromethane. The organic parts were dried over Na_2SO_4 and analysed by HPLC. The ratios of diastereoisomers of tris-TB **1a** and conditions (acid, reaction time) are listed in Table 1.

Supplementary data

Supplementary data (^1H and ^{13}C APT NMR spectra) for all presented compounds can be found in the online version.

Acknowledgement

This work was supported by the Grant Agency of the Czech Republic (P207/11/P121).

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