calix-Tris-Tröger's bases – a new cavitand family†

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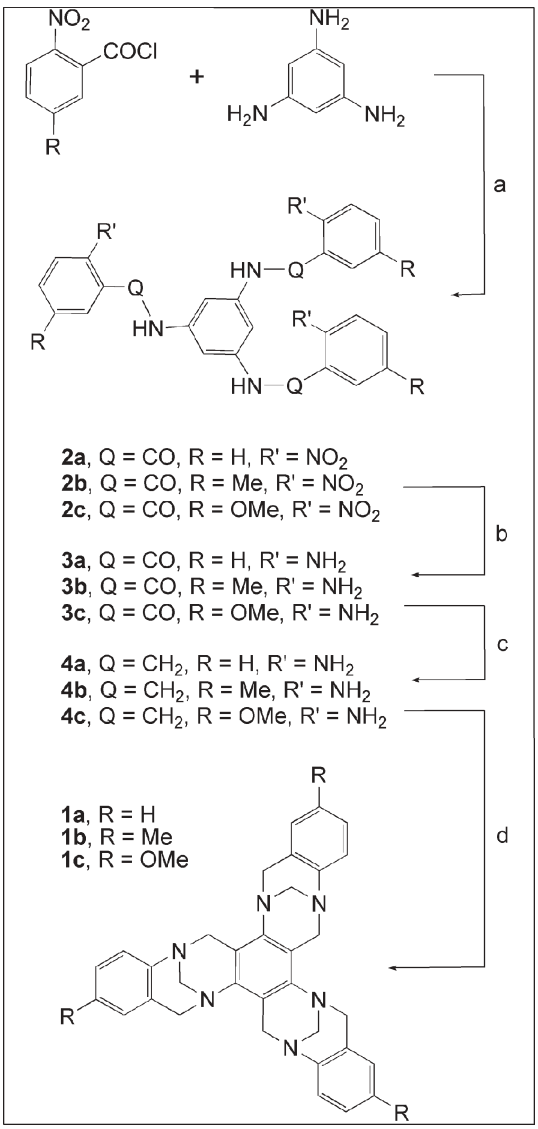
The first members of a new cavitand family, represented by calix-shaped tris Tröger's base diastereoisomers, are prepared *via* step-by-step synthesis as well as one-pot mixed troegeration.

Tröger's base (TB, 2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine) is a structural motif known to almost every chemist. The compound was first described[1] by Tröger in 1887, its structure correctly suggested by Spielman in 1935,[2] and its enantiomers first separated[3] by Prelog in 1944. Since then TB derivatives have become a touchstone of chiral separation performance and a textbook example of chiral nitrogen. At the end of the 20th century, TB derivatives, as was reviewed recently,[4] were being used as building blocks for receptor preparations. The 21st century has brought more new dimensionality for TB derivatives with the discovery of oligoTB; the finding that an aromatic part of one TB can be an aromatic part of another TB.[5–7]

We have recently published that it is even possible to annelate all three TB units (1,5-diazabicyclo[3.3.1]nonane) to a single benzene ring (Scheme 1), thus creating a trisTB.[6a] TrisTB derivatives **1** can form two diastereoisomers, the calix-like one (*calix*-trisTB, Fig. 1 and 2) and the throne-like one (*throne*-trisTB, Fig. 3 and 4). Up until now *calix*-trisTB has never been isolated or observed by spectroscopy, steric hindrance being the unwritten reason. However we found that *calix*-trisTB can be obtained by the isomerization of *throne*-trisTB under acidic conditions, and isolated as a stable compound after fast alkalization. This finding makes the trisTB derivatives **1** unique cavitands, differing from known cavitands (*e.g.* calixarenes, cyclodextrins, resorcinarenes, cyclotriveratrylene, cucurbiturils *etc.*)[8,9] in their ability to switch from calix to throne isomers in acidic pH. Additionally, Lenev *et al.* have recently shown[10] than the "conformational" stability of TB derivatives under acidic conditions can be set-up by suitable substituents, which could be a very useful function for drug delivery systems.

TrisTBs **1** were prepared according to the four-step amide protocol (Scheme 1).[6a] The acylation of 1,3,5-triaminobenzene by chlorides of 2-nitrobenzoic acids produced nitroamides **2**. Then catalytic reduction of the nitro groups of **2** produced aminoamides **3**, which were reduced by $LiAlH_4$ to their corresponding hexaamines **4**. The final troegeration (treatment with formaldehyde equivalent, *e.g.* paraformaldehyde, under acidic conditions, *e.g.* in TFA) of hexaamines **4** resulted in the targeted trisTBs **1**. However we found that the troegeration of hexaamine **4a** does not produce the corresponding trisTB **1a**, which is obviously due to the *para* position to the amine group being free (R = H). This corresponds with the fact that aniline TB derivatives give very low or zero yields.[6a,11] Fortunately when the position was blocked by a suitable moiety the yield increased significantly.[6c] Thus the troegeration of hexaamine **4b** (R = Me) gave 8% preparative



Scheme 1 Preparation of trisTB. *Reagents and conditions*: (a) pyridine, 12 h, RT; (b) H_2, Pd/C; (c) $LiAlH_4$; (d) $(CH_2O)_n$, TFA, **1a** (0%), **1b** (8%, overall 3%), **1c** (18%, overall 6%).

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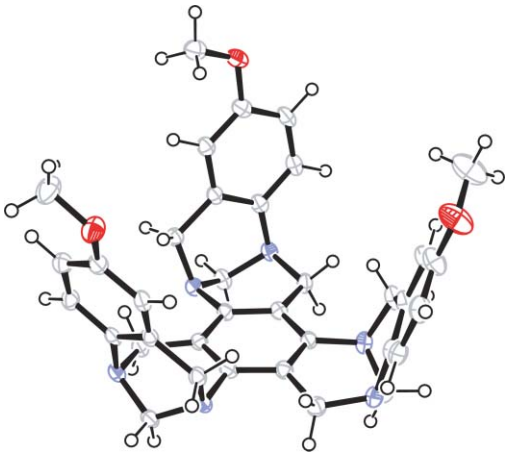

Fig. 1 ORTEP style plot of compound *calix*-**1c**. Thermal ellipsoids are drawn at 50% probability level.

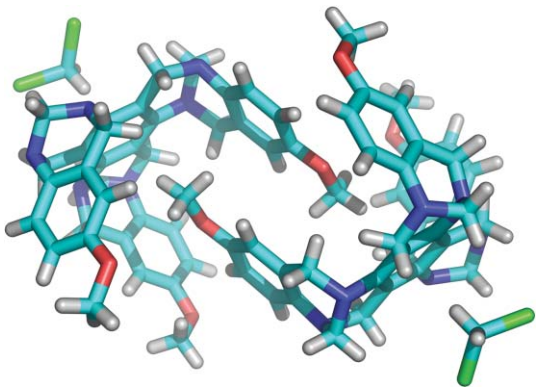

Fig. 2 Part of *calix*-**1c** crystal packing showing intertwining of two enantiomeric molecules, and CH_2Cl_2 position.

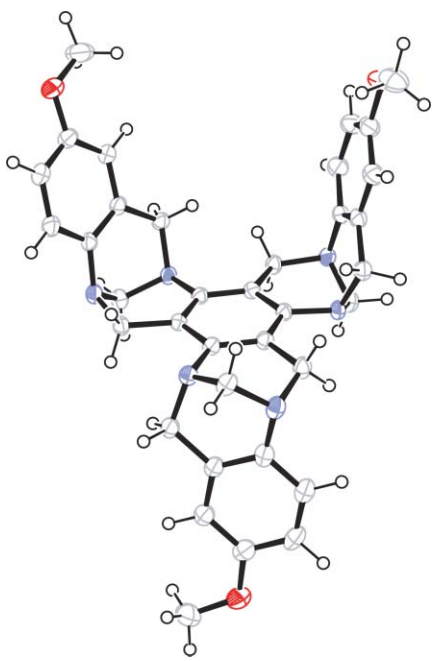

Fig. 3 ORTEP style plot of compound *throne*-**1c**. Thermal ellipsoids are drawn at 50% probability level.

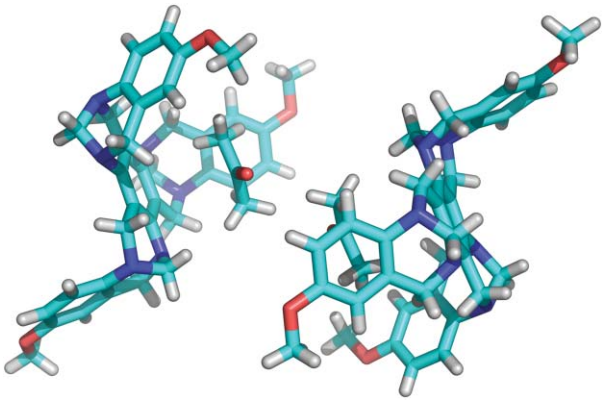

Fig. 4 Spacial arrangement of two enantiomeric molecules of *throne*-**1c** forming a nano-capsule containing two acetone molecules.

yield (3% overall yield) of the expected trisTB **1b**, and the troegeration of hexaamine **4c** (R = OMe) produced 18% preparative yield (6% overall yield) of the corresponding trisTB **1c**. The low yields of the troegerations should be tolerated, because, in total, 12 new bonds are formed in one reaction step, which means that "yield per bond formed" is higher than 80%.

In addition, we have recently published[6b] our success with oligo-troegeration, the mixed troegeration of amine and diamine, which resulted in the corresponding oligoTB derivatives. Therefore we tried one-pot preparation of trisTB **1b** by the mixed troegeration of 1,3,5-triaminobenzene and *p*-toluidine (TFA, paraformaldehyde, 60 °C, overnight). The expected trisTB **1b** was formed and isolated in 2% yield. The fact that, in this case, 18 new bonds are formed in one reaction step makes the yield excellent (80% yield per bond formed). However, the preparation of trisTB **1c** by this one-pot arrangement failed.

In both the trisTB **1b** and trisTB **1c** preparations only the throne-like diastereoisomers were isolated, which is probably due to the very low yields of the calix-like diastereoisomers. When the *throne*-**1b** or *throne*-**1c** was treated in TFA, diastereoisomerisation took place even at room temperature, within a few minutes. In both cases (**1b** and **1c**), the ratio of *throne*-trisTB to *calix*-trisTB at equilibrium was 97 : 3. The calix-like diastereoisomers *calix*-**1b** and *calix*-**1c** were isolated by chromatography, and fully identified. In the case of trisTB **1c**, single crystals of both diastereoisomers were obtained, X-ray diffraction confirming their structures.‡ Our *calix*-**1c** (Fig. 1) and *throne*-**1c** (Fig. 3) are the first examples of X-ray data for trisTB derivatives.

X-Ray structure determination proved that *calix*-**1c** is racemic and cavity shaped. Probably the first thing to consider concerning a new cavitand molecule is its volume. Unfortunately general rules for the calculation of cavity volume do not exist, therefore, to have some idea, we estimated the volume from the X-ray atom coordinates. The volume of the cavity was approximated from the truncated cone, wherein the lower rim is defined by the circle intersecting the nitrogen atoms (d_1 = 0.65 nm), and the upper rim is defined by the circle intersecting the oxygen atoms (d_2 = 0.98 nm), and the depth defined as the distance between the oxygen atoms' centroid and the nitrogen atoms' centroid (h = 0.55 nm). With the measurements reduced using van der Waals diameters, the calculated volume was approximately 0.078 nm^3, which means that the volume of the *calix*-**1c** cavity was around

44% of an α-cyclodextrin cavity[9] (0.174 nm^3). The cavity's potential to bind is demonstrated by the crystal packing (Fig. 2), in which two molecules are intertwined with each other; one methoxy group of one molecule being inside the cavity of the second molecule, and *vice versa*. Conversely, the crystal methylene chloride is outside the cavity, wherein its hydrogen is bound to the center of the central benzene unit.

As in the case of *calix*-**1c**, the X-ray structure of *throne*-**1c** displayed both enantiomers. Single-crystal packing showed that two molecules formed a cavity consisting of two acetone molecules (Fig. 4). The volume of this cavity was estimated using a cuboid (1.10 × 0.91 × 1.06 nm), which, after correction with a van der Waals diameter (0.16 nm), gave a cavity volume of approximately 0.63 nm^3.

In summary, we herein present the first members of a new cavitand family, the inherently chiral and calix-like oligoTB derivatives. They are destined to become building blocks for the construction of molecular reactors and capsules. In addition, the ability of the TB unit to isomerize under acidic conditions means that *calix*-oligoTB derivatives offer potential extra functionality, *e.g.* for drug delivery systems. The cavity of the presented trisTB derivatives, the smallest member of this cavitand family, is suitable, *e.g.* for methoxy group inclusion as was observed in the solid state (Fig. 2). Finally, we have demonstrated the new three-component condensation reaction, which leads to formation of 18 new bonds at once. Our future research will target *calix*-oligoTB derivatives with deeper sidewalls and larger cavities, in particular focusing on the implementation of the central-reagent approach we recently developed for the preparation of bisTB derivatives.[6e]

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