Macrocyclic aromatic tetrasulfonamides with a stable cone conformation†

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Received (in Columbia, MO, USA) 17th March 2005, Accepted 2nd June 2005
First published as an Advance Article on the web 28th June 2005
DOI: 10.1039/b503921e

Aromatic tetrasulfonamide macrocycles carrying alkoxy side chains adopt a stable cone conformation in both the solid state and solution.

Numerous unnatural macrocylic structures have been prepared and studied. For example, many macrocyclic compounds with internal cavities, such as cyclophanes, calixarenes, and resorcinarenes, have acted as receptors for organic molecules.[1–4] These macrocycles usually possess several interconvertible conformations.[2b,5] Strategies to "freeze" these conformations could lead to hosts with better-defined cavities that bind guest molecules with enhanced specificity and strength.[6] In addition to being effective hosts, macrocycles with a stable conformation could also provide scaffolds for the presentation of chemical functionality, leading to efficient catalysts and precise control of intermolecular assembly.[7] We would like to report here the one-step preparation and characterization of a class of aromatic tetrasulfonamide macrocycles that possess a stable cone conformation with an internal cavity.

In recent years, folding aromatic oligoamides with rigidified backbones have been reported.[8–10] We have developed a class of backbone-rigidified aromatic oligoamides by incorporating a localized, three-center H-bond, which leads to folding oligomers with a crescent or helical conformation.[11] We recently started to extend this backbone-rigidification strategy to the design of folded aromatic oligosulfonamides, as shown by **1**. The three-center H-bond, consisting of a five- and a six-membered H-bonded ring, should act to rigidify the backbone of the corresponding oligosulfonamide. Stepwise preparation of the oligosulfonamide should lead to oligomers with crescent or helical conformations. In a parallel effort, a one-step preparation of folded polysulfonamide based on the same folding principle was also attempted by treating benzenedisulfonyl chlorides **2** with diamine **3** (Scheme 1). This reaction could result in one of two outcomes: the formation of polysulfonamides or the one-step generation of macrocyclic sulfonamides. The latter possibility is likely based on recently discovered examples of the one-step formation of aromatic oligoamide macrocycles.[12,13]

Benzenedisulfonyl chloride **2a** (1.97 mmol) and diamine **3** (2.19 mmol), each dissolved in CH_2Cl_2 (15 mL), were added concomitantly to a flask containing Et_3N (4.38 mmol) at −12 °C. The mixture was stirred until it gradually warmed up to room temperature (4–6 h), and was then heated under reflux for 12 h, after which the reaction was quenched by addition of acetyl chloride followed by methanol. After removing solvent and other volatile fractions, the remaining solid residue was examined by MALDI-TOF, which failed to reveal peaks corresponding to high molecular weight polymers. Instead, two rather strong peaks appeared at *m*/*z* 995 and 1011 (Fig. 1a), corresponding to the four-residue macrocycle **4a** (Scheme 1) plus a sodium ion and a potassium ion. By washing the solid residue with methanol, acetone, THF, and then recrystallizing from DMF, pure **4a** was

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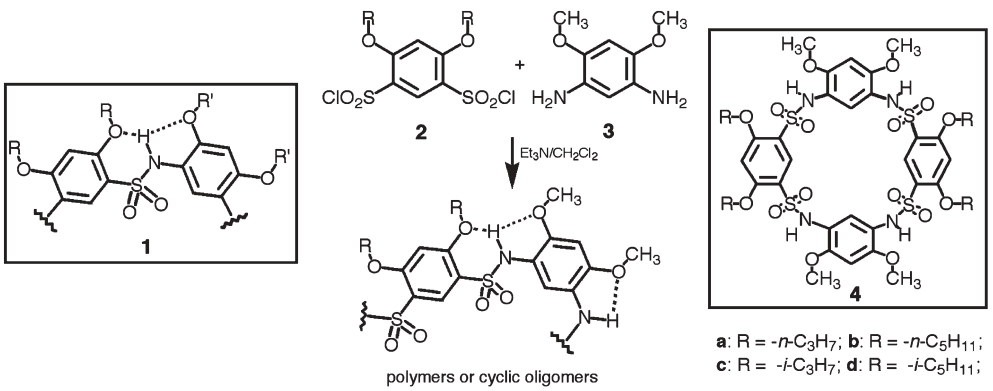
† Electronic supplementary information (ESI) available: Experimental procedures; 1D, 2D and variable-temperature NMR spectra; MALDI spectra. See http://dx.doi.org/10.1039/b503921e



Scheme 1

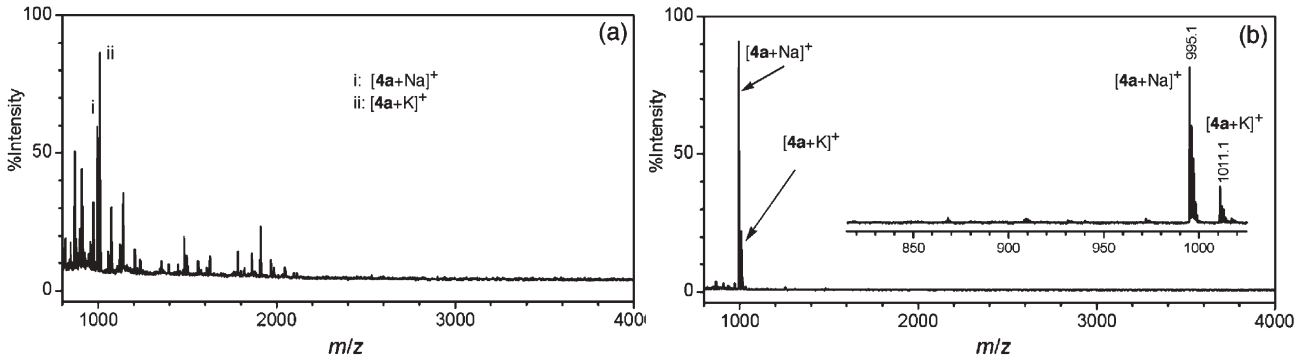


Fig. 1 MALDI-TOF spectra of (a) untreated non-volatile residue from the reaction of **2a** and **3**; (b) purified **4a**.

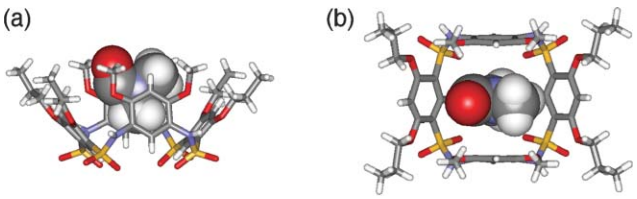


Fig. 2 Structure of **4a** in the crystal: (a) side view, (b) top view. The DMF molecule found in the cavity is shown by a space-filling model.

obtained in 38% as a white solid (Fig. 1b). Repeating the above steps gave macrocycles **4b–d** in yields ranging from 44% to 51%.†

Crystals of compound **4a** were obtained by cooling from DMF and the X-ray structure is shown in Fig. 2.‡ In the solid state, **4a** adopts a cone conformation similar to that observed for calix[4]arene.[2b] This cone conformation has a *C*2 axis and contains a cavity surrounded by four aromatic residues. In this conformation the two diamine residues are parallel to the *C*2 axis of the molecules and thus to each other, while a dihedral angle of ~90° exists between the two benzenedisulfonyl residues. The alkoxy side chains of the four residues are attached to the wider rim of the molecule and the four sulfonamide groups define the narrower rim. In the crystal structure of **4a**, the expected intramolecular H-bonds between each of the sulfonanamide NH protons and the two flanking ether oxygens do not exist (average NH···O distances = 2.62 and 2.85 Å). In fact, all four N–H groups point away from the center of the cavity.

In the crystal structure of **4a**, a DMF molecule is sandwiched between the two diamine residues. This suggests that other guest molecules could also be complexed in the cavity of **4**.

To probe if the same cone conformation also exists in solution, variable-temperature 1D ^{1}H NMR experiments were performed

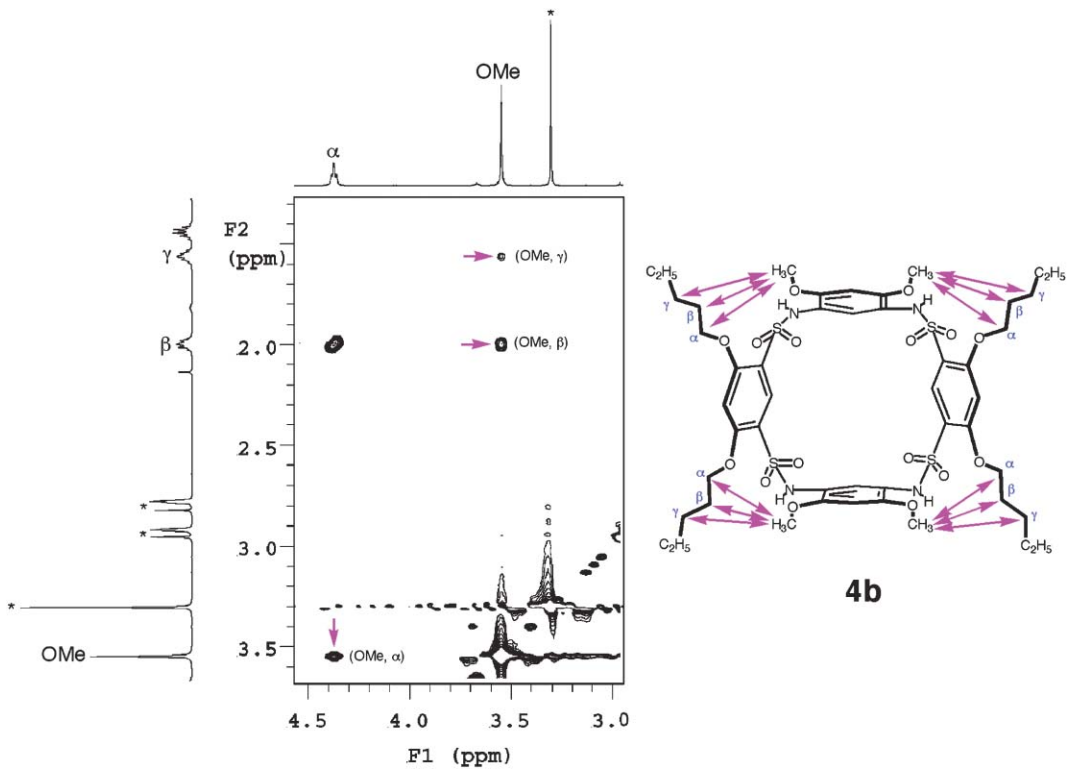


Fig. 3 NOESY spectrum of **4b** (500 MHz, 2 mM in 1 : 1 DMF-d_7–$CDCl_2CDCl_2$, 294 K, mixing time = 0.35 s). *Solvent peak.

with the more soluble **4b** in DMF-d_7. From –20 °C to 60 °C in DMF-d_7, there was a small downfield shift (~0.06 ppm) for all aromatic and alkyl protons. This indicates that any change of **4b** from one conformation to another through the annulus of the molecule is unlikely. In contrast, a significant downfiled shift of 0.53 ppm for the NH protons was observed within the same temperature range, suggesting that the NH groups are exposed to solvent. This is consistent with the non-H-bonded, exposed NH groups revealed by the crystal structure of **4a**.

A two-dimensional NMR (NOESY) study provided the most diagnostic evidence for the cone conformation adopted by **4b** in solution. As shown in Fig. 3, three NOEs corresponding to the contacts between the methoxy (OMe) protons and protons α, β, and γ of the pentyl group were clearly detected. These NOEs are fully consistent with the cone conformation as revealed by the crystal structure of **4a**. No NOEs corresponding to other alternative conformations were present.

The adoption of the stable cone conformations by macrocyles **4a** and **4b**, and most likely by other analogous macrocycles of this series such as **4c–d**, can be easily understood by the interaction between the sulfonamide oxygens and the oxygens of the alkoxy side chains. Simple molecular modeling† showed that an alternative conformation of macrocycles **4**, corresponding to the partial cone conformation of calix-[4]-arene that involves "up" and "down" arrangements of the benzene rings, would require the sulfonamide oxygens to be placed in close proximity with the alkoxy oxygens (1.8–2.5 Å), which is highly unfavorable due to the repulsion between the lone pairs carried on these oxygen atoms.

Thus, the observed cone conformation of macrocycles **4** is the result of repulsive interaction between the side chains and sulfonamide backbone. This may provide a new strategy for designing cyclic and non-cyclic oligosulfonamides that adopt stable conformations. Macrocycles **4**, with their stable conformation, internal cavity, and well-positioned side chains, should serve as a new platform for designing hosts, and as building blocks for constructing larger structures.

This work was supported by the Thans-Century Training Program Foundation for the Talents, Ministry of Education of China (to L.H.), and by the US National Institute of Health (R01GM63223 to B.G.).

Notes and references

‡ *Crystal data* for **4a**: $C_{49}H_{73}N_7O_{19}S_4$, M = 1192.38, monoclinic, space group $C2$, a = 32.684(3), b = 20.741(2), c = 8.9393(9) Å, α = 90, β = 95.263(2), γ = 90°, U = 6034.4(10) Å^3, Z = 4, μ(Mo-Kα) = 0.231 mm^{-1}, 20841 reflections measured (10243 unique, R_{int} = 0.0351). The final w$R(F^2)$ was 0.1729 (all data). CCDC 266730. See http://dx.doi.org/10.1039/b503921e for crystallographic data in CIF or other electronic format.

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