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A new approach to inherent chirality through the N/S ratio and/or the position in mixed heterocalix[4]arenes†

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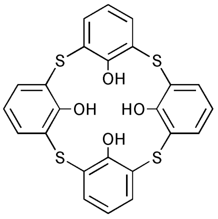
Fine control of the N/S ratio and/or the position of the bridged heteroatoms in mixed heterocalix[4]arenes leads to a new approach to generate inherent chiral scaffolds and represents a new challenge to fine-tune cooperative properties.

The access to chiral calix[4]arenes continues to spur active investigations due to the remarkable properties of this class of receptors in supramolecular chemistry.[1] These calixarenes—bearing chiral residues on the phenyl ring(s)—have been described and widely used in enantioselective recognition or asymmetric catalysis.[2] The non-planarity of calixarenes offers the possibility to prepare inherently chiral systems by introduction of achiral residues suitably disposed in order to generate an asymmetric array. The term "inherent chirality" was first introduced by Böhmer *et al.*[4a] to indicate chiral calixarenes which belong to the C_1 group of symmetry. To this end, two general strategies have been employed: (i) by asymmetric modification of the bridges[3a,b] or the aromatic rings[3c–h] (*i.e.* substitution reaction), and (ii) by cyclizing an aromatic monomer lacking an internal plane of symmetry.[4] A new approach that would allow an efficient, controlled and easier introduction of "inherent chirality" is obviously of considerable interest in order to enlarge the scope of this family of compounds.

Previous works reported that introduction of heteroatoms as bridging units can impart novel properties and functionalities[5] (*e.g.* size, conformational freedom, host–guest complexation) in comparison with the methylene linkages found in "classical" calix[*n*]arenes.



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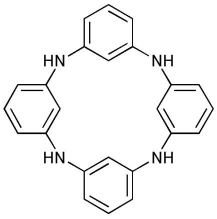

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For instance, thiacalix[4]arenes **1** have received great attention from the supramolecular community mainly due to their synthetic availability, engendering a wide range of uncommon properties.[5d] More recently, azacalix[4]arenes[6] **2** have become a focus of interest because of the presence of nitrogen bridges, which should allow not only direct interactions with guest species, but also the introduction of coordinating functions on the bridge that might be used for complexation[6i] (in the following sections, the term "heterocalixarenes" is used to indicate nitrogen or sulfur bridged calix[4]arene analogues with a $[1_4]$metacyclophane skeleton).

Curiously, the preparation of related mixed heterocalix[4]arenes which combine aza- and thia-bridges is hitherto unknown whereas the possible marriage of concomitant properties of both classes in a single molecule appears very attractive. More specifically, the possibility to readily control the N/S ratio and/or the position of the heteroatoms in these molecular frameworks represents a new challenge to fine-tune the cooperative properties and to gain a better insight into the structure–property relationships. Among them, the access to heterocalix[4]arenes with "inherent chirality" generated by the nature of the bridge would then become possible. Herein, we report the high yield stepwise fragment coupling synthesis of unprecedented mixed N,S-bridged heterocalix[4]arenes. This metal-free preparation allowed a fine control of the N/S ratio and of their position on the molecular scaffold which enabled the first "inherent chirality" that originated from the bridge (*i.e.* not by the substituent of the bridge).

Our group and others have recently shown that nucleophilic aromatic substitutions (S_NAr) are effective reactions to provide heterocalix[4]arenes in good yields[6] in contrast to the palladium catalyzed coupling reactions.[7] Accordingly, the syntheses of related N,S-mixed systems were carried out through an iterative pathway from readily available starting compounds according to a puzzle-based construction. The synthesis of the target compounds **8–10** is depicted in Scheme 1. Intermediate **4** was first prepared as described in the literature[6d] and then further reacted, in the presence of NaH, with 3-aminothiophenol (1 equiv.) giving the unsymmetrical triaryl **6** as a yellow solid in 94% yield. It is noteworthy that the reaction could be also performed without the addition of

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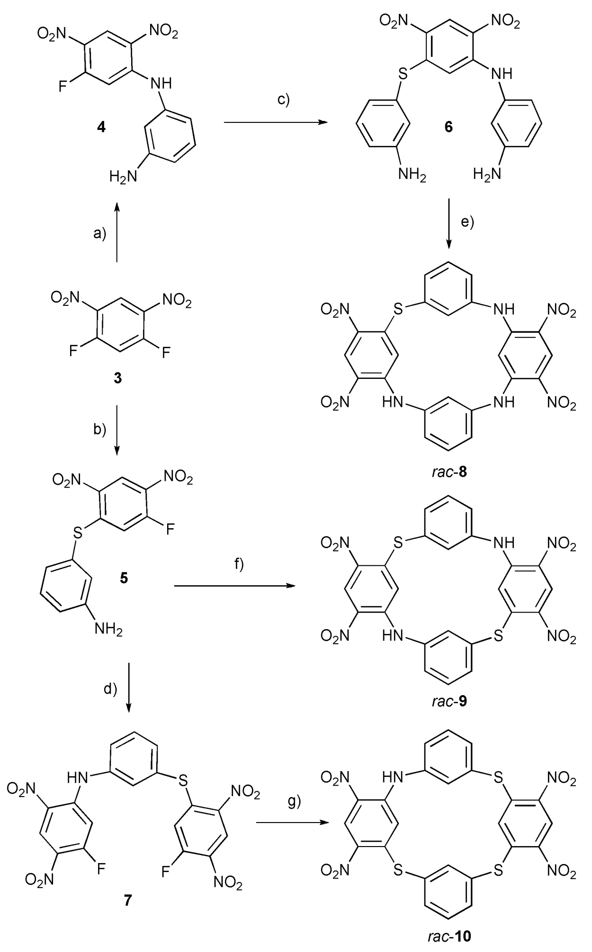

Scheme 1 Synthetic route for the preparation of the mixed heterocalix[4]arenes **8–10**. (a) 1,3-Diaminobenzene, ethanol, 0 °C, 3 hours, 86%;[6d] (b) 3-aminothiophenol, ethanol, 0 °C, 2 hours, 71%; (c) 3-aminothiophenol, NaH, THF, 0 °C to rt, 3 hours 94%; (d) **3**, THF, 0 °C, 1 hour, then rt, overnight, 61%; (e) **3**, CH_3CN, reflux, overnight 80%; (f) CH_3CN, reflux, overnight, 52%; (g) 3-mercaptothiophenol, NaH, THF 0 °C to rt, 3 hours, 71%.

base with nearly the same yield. Similarly, intermediate **5** was prepared by condensation of **3** and 3-aminothiophenol (1 equiv.) in EtOH in 71% yield. Subsequent reaction of **5** with **3** affords the precursor **7** after purification by column chromatography (61% yield). The macrocyclization step was achieved by condensation of the intermediate **6** with **3** in refluxing MeCN in the presence of $N(iPr)_2Et$. The precipitate obtained was then isolated by filtration and carefully washed with hot water and ethanol affording the heterocalix[4]arene **8** in 80% yield. Macrocycle **9** was obtained in 52% *via* self-condensation in refluxing MeCN in the presence of $N(iPr)_2Et$. Lastly, macrocycle **10** was synthesized by reacting the difluorotriaryl intermediate **7** with 3-mercapto-thiophenol (1 equiv.) in the presence of NaH in THF from 0 °C to room temperature for 3 hours. As already pointed out, the formation of the macrocycles does not require high dilution conditions due to the preorganization of the intermediates, which prevent the formation of polymers ($C \approx 4 \times 10^{-2}$ mol l^{-1}).[3f,6d] Interestingly, this preorganization is not only controlled by N–H···O_2N intramolecular H-bonds—as already shown for azacalix[4]arenes[6h]—but also by electrostatic interactions[8] between the sulfur atom (δ^+, due to its conjugation with the dinitrobenzene ring) and the oxygen atom (δ^-, in the adjacent NO_2 group) in the case of sulfur-bridged intermediates **5–7**.

Macrocycles **8–10** were fully characterized by X-ray diffraction in the case of **8** and **9**. Their structure determination indicates a 1,3-alternate conformation in which all the bridging nitrogen atoms conjugate with the dinitrobenzene rings rather than the two other phenyl rings because of the electron-withdrawing nature of the NO_2 groups.[9] As a result, the two C–N bond lengths in the C–N(H)–C moieties are not equivalent [for instance, C(2)–N(3) = 1.399(9) *vs.* C(23)–N(3) = 1.469(8) Å in **8** and C(11)–N(1) = 1.458(4) *vs.* C(2)–N(1a) = 1.384(4) Å in **9** (Fig. 1 and 2)]. Interestingly, the C(13)–N(1) bond distance in **8** is strongly elongated compared with C(15)–N(2) (1.486(10) *vs.* 1.393(9) Å). This observation can be explained by geometric constraints due to the presence of one sulfur bridge which induces a lengthening of the bonds in the C(11)–N(1)–C(13) moieties (the C–S bond distances are much longer than the C–N bonds). The angles around the bridging nitrogen are mainly about 120°. These data suggest a sp^2 character which induces a quasi-planar geometry of the bridges (the nitrogens are pyramidal in azacalix[4]arenes without NO_2 substituents).[6f]

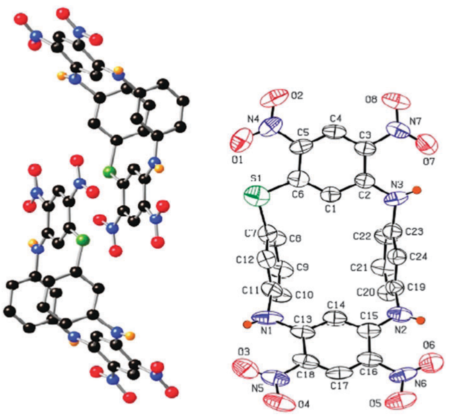

Fig. 1 Crystal structure of the racemate **8** and ORTEP diagram of one of the enantiomers (red: O; blue: N; green: S; black: C; orange: H).

Importantly, the presence of two different heteroatoms allows fine-tuning of the shape and size of the molecular plane defined by the four bridges. For instance, **9** has a shape and cavity whose dimensions (5.185 × 5.180 Å) are very close to those of a lozenge whereas **8** revealed a rectangle molecular plane (5.200 × 4.941 Å) (Fig. 1 and 2).

Examination of the non-covalent intramolecular interactions in **8** and **9** revealed the presence of H-bonds between the oxygen atoms of the NO_2 groups and the N–H protons of the bridges ($2.013 < d(N–H\cdots O_2N) < 2.022$ Å). The presence of electrostatic interactions between the oxygen and sulfur atoms was clear from the S···O_2N distances ($2.539 < d(S\cdots O_2N) < 2.624$ Å) which are significantly shorter than the sum of the van der Waals radii of sulfur and oxygen (3.25 Å) (Fig. 1 and 2).

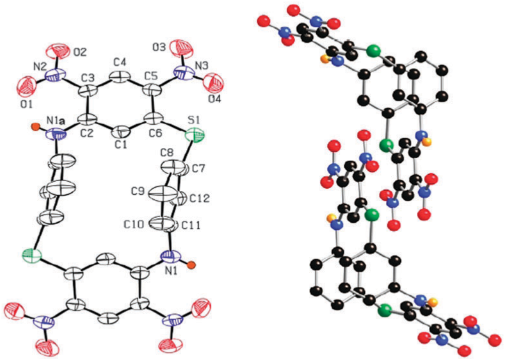

Fig. 2 Crystal structure of the racemate **9** and ORTEP diagram of one of the enantiomers (red: O; blue: N; green: S; black: C; orange: H).

Macrocycles **8–10** are obtained in a racemic form due to the enantiomerization process which occurs at room temperature. The high conformation mobility of the above heterocalixarenes is most likely due to the lack of steric hindrance and OH groups (H-bonds); both are key factors to stabilize the conformation in classical calixarenes. In addition, the sp^2 character of the bridges seems to be not sufficient to prevent the inversion of the aromatic rings. The X-ray analyses of **8** and **9** clearly established an aggregate of the two enantiomers leading to a heterochiral racemic crystal (1 : 1 ratio) in which the enantiomers pack in a dense, ordered array. In both cases, compounds **9** and **8** were arranged in a herringbone packing with strong π–π stacking ($3.438 < d(\text{C}\cdots\text{C}) < 3.890$ Å) (Fig. 1 and 2). In the lattice packing, the racemate consists of alternating layers of each enantiomer. Within each layer, all molecules have the same orientation with respect to the crystal axes (*i.e.* there are only two orientations with which a molecule might add to the lattice during crystallisation) (see ESI†, Fig. S1). In addition, building block **9** forms 3D-supramolecular channels—assembled through C–H···O and C–H···N and interactions—that might be used for complexation of guests (see ESI†, Fig. S2).

In conclusion, a stepwise fragment coupling strategy has allowed the access to the first mixed N/S heterocalix[4]arenes. The synthetic pathway turned out to be crucial to generate inherent chiral properties originating from the bridge by a ready control of the N/S ratio and/or the heteroatom position. Although, inherently chiral derivatives have been obtained in their racemic form, derivatizations of the starting materials should allow the synthesis of resolvable enantiomers (for instance by introduction on the phenyl rings of steric hindered and/or hydrogen bonding substituents). Additionally, this new class of calixarenes (**8–10**) offers the possible concomitant properties of the thiacalixarenes **1**[5d] (regio, stereo or chemoselective oxidation of the sulfur bridge) and the aza[5f–g,6] analogues **2** (as host and/or robust high spin stable polyradicals), that should open new perspectives in calixarene chemistry owing to the presence of hard and soft heteroatoms around the same cavity.

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