## Casting heteracalixarenes from calixarene templates: a unique synthetic strategy<sup>†</sup>

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A simple, intuitive and modular strategy to synthesize higher heteracalixarene (in particular thiacalixarene) homologs using respective calixarene templates has been developed and demonstrated.

Heteracalixarenes (HCnAs, n = 4-8 represents number of phenyl units in the macrocycle), the hetero-atom bridged metacyclophanes, have earned significant interest in the last decade by virtue of their structural similarities with calixarenes  $2_n$  (CnAs), but with much superior complexing abilities.<sup>1</sup> The main hurdle in the development of heteracalixarene chemistry is their synthesis, especially of higher HCnAs, which are not generally easily accessible.<sup>2</sup> In this communication, we demonstrate an intuitive strategy to synthesize various thiacalixarene homologs  $1_n$  (TCnAs—sulfur bridged heteracalixarenes), *via* respective calixarene templates.

Since the first practicable synthesis of TCnAs,<sup>3</sup> there have been very few successful reports on the subject.<sup>4</sup> Recently, we have investigated microwave assisted reactions, yielding  $1_{5-8}$  in minor yields.<sup>5</sup> No reports of the synthesis of **1**<sub>5-8</sub> (especially for  $1_5$  and  $1_7$ ) in substantial yields are available so far. To understand the problem in hand in its correct perspective, it would be appropriate to briefly review the chemistry of thiacalixarene synthesis. As has been reported earlier, the template effect is not so pronounced in the case of TCnA synthesis, as compared to CnAs.<sup>1,3</sup> In case of CnA synthesis, the number of aromatic units in the product macrocycle depends largely on the template ion used as base catalyst.<sup>6</sup> In the presence of NaOH, the predominant product is  $2_4$ , while, if KOH is used, the product is a mixture of  $2_6$  and  $2_8$ . Further, odd membered CnAs (2<sub>5</sub>, 2<sub>7</sub>) are achievable as by-products in synthetically useful yields, which is not the case with TCnAs, where such products are generally obtained in trace amounts. The reason is the stringent thermodynamic requirements for the cyclization of acyclic oligo-phenolsulfide intermediates whose fate depends upon their thermodynamic stability, and hence they end up as  $1_4$ —the most thermodynamically stable product amongst all TCnAs.<sup>3</sup> This was further evident from our recent investigations of thiacalixarene synthesis protocol.<sup>2,5</sup> Though significant success was achieved in the synthesis of higher TCnAs  $(1_{5-8})$ , the optimized methods required much more

rigorous maintenance of reaction conditions, and thus were not viable for large scale synthesis.

One way to prepare higher TCnAs in good yields is to search for better templates (a partly successful approach).<sup>4</sup> However, a more appropriate approach would be to pre-organize individual phenol units according to required geometry and then add sulfur bridges between them, thereby removing the possibility of uncontrollable oligomerization completely. Pre-organizing many phenol units may seem a daunting task at first, which may not be possible practically except *via* templation or, better, true complexation. However, if the movement of the phenol units is restricted within certain limits, it may essentially serve the same purpose. In practice, the restriction was imposed upon the phenol units by anchoring them covalently on fixed scaffolds, namely, calixarenes, and thus were brought into a state of pre-organization.

It was also required by this strategy that, after anchoring the phenol units to the calixarene scaffold, the calix should retain/ acquire a cone conformation, otherwise cyclization (via complete sulfurization) to form a macrocycle would be impossible. Two pathways were employed to anchor phenol units on a calixarene scaffold (Scheme 1). The first approach was to append an ethyl chloride chain on  $2_n$  (Route A—by reacting with 1-chloro-2-bromoethane) and react p-tert-butylphenol with the available chloride of  $3_n$ . While successful in case of  $2_4$  and partly for  $2_5$ , the approach failed to secure the *cone* conformation in case of higher CnAs ( $2_{6-8}$ ) due to the small size of the appended chain, which was unable to restrict the flip-flop motion of the calix-framework,<sup>6</sup> and hence a mixture of conformers was obtained, separable only through tedious column chromatography. The second approach was to utilize the template effect of CnAs towards alkali metal ions and directly attach pre-formatted Ph-O-Et- chains on CnAs (Route B-by reaction with 6). This approach was greatly successful on a wide range for  $2_{4-7}$ , and partly for  $2_8$ . Beyond  $2_8$ , the cavity size becomes too large and hence, the restriction of the flip-flop motion of the calixarene-framework becomes too tough to accomplish.

Having pre-organized the phenol units, the next step would be to add sulfur bridges between the appended phenol units. However, the traditional 'elemental sulfur—NaOH—heating' method (C in Scheme 1) would not work satisfactorily in this case, the reason being that the sulfurization process involves a keto intermediate,<sup>2</sup> which in turn requires a free phenolic –OH, not available in  $4_n$ . Indeed, direct sulfurization of  $4_n$ with this approach yielded a very small amount of completely sulfurized products  $5_n$ , along with a diverse consortium of mono sulfurized to poly sulfurized products, as detected by UPLC-MS analysis of the reaction mixture after completion of

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Scheme 1 Calix[n]arene templated synthesis of thiacalix[n]arenes.

the reaction. Though  $5_n$  were detected in the reaction mixture, it was not possible to isolate them, and hence a better method was required for sulfurization. An already known sulfurization technique is the one using SCl<sub>2</sub> (D in Scheme 1), which incidentally was used for the first synthesis of  $1_4$  in a step-wise manner.<sup>7</sup> In present case, sulfurization of  $4_n$  with SCl<sub>2</sub> gave excellent results in all the cases, and CnA–TCnA pseudo dimers  $5_n$  were obtained in good yields.<sup>8</sup> The <sup>1</sup>H NMR spectra of all variants  $5_{4-8}$  showed similar unrestrained structures.<sup>9</sup>

The final step to achieve the TCnA derivatives was exhaustive halo-dealkoxylation<sup>10</sup> of  $5_n$  in aqueous ethanol using LiI, to cleave the ether linkages between two macrocycles  $(1_n \text{ and } 2_n)$ , followed by their chromatographic separation or fractional crystallization (based on differential solubility). As can be inferred from the data listed in Table 1, all TCnA variants have been achieved in very good yields, and though being a multi-step synthesis, satisfactory overall yields promise its application on relatively larger scales. Further, the CnA templates may be recuperated with high overall % recovery ranging from *ca*. 60–75%.

The present strategy, *viz.* pre-organization of individual aromatic units with the help of other similar assembly and subsequent cyclization to produce pseudo dimers, is modular in the sense that it can be applied to synthesize other supramolecular assemblies of the calix family in numerous ways.<sup>11</sup> For instance, the strategy can be extended (a) to prepare various heteracalixarenes, with hetero-atom bridges other than sulfur, by employing different reagents for cyclization of appended phenol units, (b) to synthesize TCnA derivatives with various *para*-substitutions (for which cyclization is not possible *via* direct sulfurization), as long as they are sufficiently activating to permit *meta*-substitution. It may be noticed that **5** possesses a

**Table 1** % yields of products  $(\mathbf{X}_n)$  in individual steps (as per Scheme 1)

| n                  | Intermediates/products (X) |   |                 |             |
|--------------------|----------------------------|---|-----------------|-------------|
|                    | $3^{a}$                    | $4 \ (\mathbf{A}/\mathbf{B})^{a,b}$       | 5               | 1           |
| 4                  | 86                         | 76/82                                     | 62              | 85          |
| 5                  | 42                         | 70/78                                     | 58              | 84          |
| 6                  |                            | /70                                       | 57              | 79          |
| 7                  | _                          | —/59                                      | 54              | 73          |
| 8                  |                            | —/37                                      | 32              | 64          |
| <sup>a</sup> Isola | ted yields of cor          | <i>w</i> conformer only. <sup>b</sup> Acc | ording to Route | es A and B. |

carcerand type structure, and thus, this approach can be employed to produce some more exciting carcerands as well.

In conclusion, an alternative approach to synthesize higher heteracalixarenes, in particular thiacalixarenes, has been developed and demonstrated successfully. Further, the carcerand like intermediates (pseudo-dimers) achieved in this fashion have dimensions on the nano scale, and are promising candidates for supramolecular nano-tubes, which will be further explored in due course to fulfil a variety of purposes already described in the nano-sciences.

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