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Genesis of thiacalixarenes: a one-pot highly efficient synthesis of TC4A

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Abstract

This Letter reports the results of our studies towards the synthesis of thiacalixarenes. In an effort to develop an efficient and inexpensive synthetic methodology for thiacalixarenes, several trials were conducted to study the effect of base/template, solvents, catalyst, phenol substitutions and temperature profile. Microwave synthesis was also tested to reduce the overall time for the reaction. Based on the results of these investigations, a detailed reaction mechanism is proposed and an optimized synthetic procedure for *p-tert*-butylthiacalix[4]arene is demonstrated.

Keywords: Thiacalixarene; Dimer–trimer–tetramer; Oligomers; Mechanism; Microwave; LC–MS

1. Introduction

Supramolecular hosts, especially calixarenes and congeners, have offered promising results as convenient platforms for the elaboration of sophisticated complexing systems, especially for molecular and ionic recognition.[1,2] Thiacalixarenes,[3,4] sulfur-bridged cyclic oligo-phenols, have been one of the most studied supramolecules in recent times. However, contrary to calixarenes, thiacalixarenes are not so trivial to synthesize, and apart from a few direct synthetic methods,[5–10] little has been reported concerning their synthesis, thus their chemistry is still an enigma.

Thiacalixarene chemistry dates back to 1997, with the first report of *p-tert*-butylthiacalix[4]arene (TC4A), achieved through a stepwise procedure in 4% yield by Sone et al.[11] In the same year, Miyano and co-workers[5] reported a facile procedure which involved heating a mixture of *p-tert*-butylphenol, elemental sulfur (S_8) and NaOH in tetraethylene glycol dimethyl ether to afford TC4A, accompanied by the traces of TC5A and TC6A. The latter have also reported a high yield synthetic procedure[6,7] starting from the sulfur-bridged dimer of *p-tert*-butylphenol, yielding predominantly TC4A with TC6A and TC8A in synthetically useful yields. Thiacalix[4]arenes prepared from *p-tert*-octylphenol,[8] *p*-admantylphenol[9] and biphenyl-4-ol[10] have also been reported. Further, an intuitive strategy has been put forward for the synthesis of TC8A[12] by the terephthalate-induced cyclization of a mixture of acyclic oligomers (obtained by reacting a mixture of *p-tert*-butylphenol and sulfur in ethylene glycol/diphenyl ether in the presence of CaO). Recently, the same strategy has been extended to improve the yields of TC4A, TC6A and TC8A, using different organic acids as templates.[13] Though more than 200 publications have appeared on thiacalixarenes and their derivatives, most of the synthetic efforts have been devoted towards the modifications of TC4A only. The mechanism of thiacalixarene synthesis has not been explained on a conventional basis as yet. In this Letter, we report a detailed mechanism for the synthesis of thiacalixarenes from acyclic precursors. An optimized one-pot high yield synthesis of TC4A has also been demonstrated following the postulated mechanism.

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2. Strategy

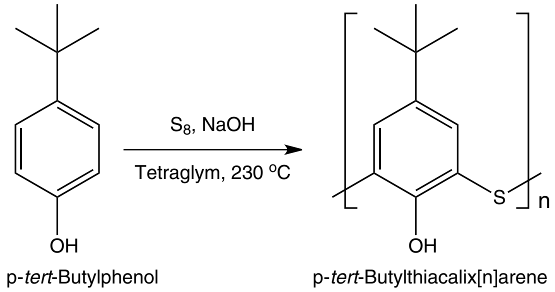
The motive of this investigation was to study thiacalixarene synthesis exhaustively by varying different reaction parameters with respect to the standard synthesis protocol (Scheme 1) devised by Miyano and co-workers[5] with a view to attain an insight into the reaction mechanism so that the reaction parameters can be tweaked to achieve desirable outcomes.

3. Template effect

The template effect for alkali metals has already been investigated in the previous publications;[5,6] however, no effort has been made to study the reactions using alkaline earth metal oxides/hydroxides as base/template. Reactions were performed with various alkaline earth metal (Ca, Mg and Ba) oxides and hydroxides. In all the cases, the traces of TC4A were detected by LC–MS but no isolable material was obtained. In the cases where 1:1 combinations of metal hydroxides with NaOH were used, the effect of NaOH was dominant. In all the cases, the dimer and other oligomers were isolable in varying yields. The results are tabulated in Table 1 (see Supplementary data).

4. Effect of solvent, temperature and catalyst

Thiacalixarene synthesis has been reported in either tetraglym[4] or diphenyl ether[5,7,9,10] as they are better heat exchangers and practically inert with respect to the sulfurization process. To explore the possibility of lower temperature synthesis, other solvents were studied, namely toluene and xylene. Further, ring closure reactions with sulfur have been known to be catalyzed by iodine, especially in phenothiazenes.[14] Thus, reactions were attempted with a catalytic amount of iodine (1% of phenol) with a view to compensate for the decreased reaction temperature. Reactions in both these solvents proved to be essentially straightforward with definite product – the dimer, but no detectable oligomerization was observed. The reactions were never complete, and even after reflux for 48 h, the reaction mixture contained a considerable amount of unchanged phenol. Also, the presence of iodine seemed to have no effect on the reaction whatsoever. The results are tabulated in Table 2 (see Supplementary data).



Scheme 1. Standard synthesis protocol to prepare thiacalix[*n*]arenes.

5. Effect of substitutions on phenols

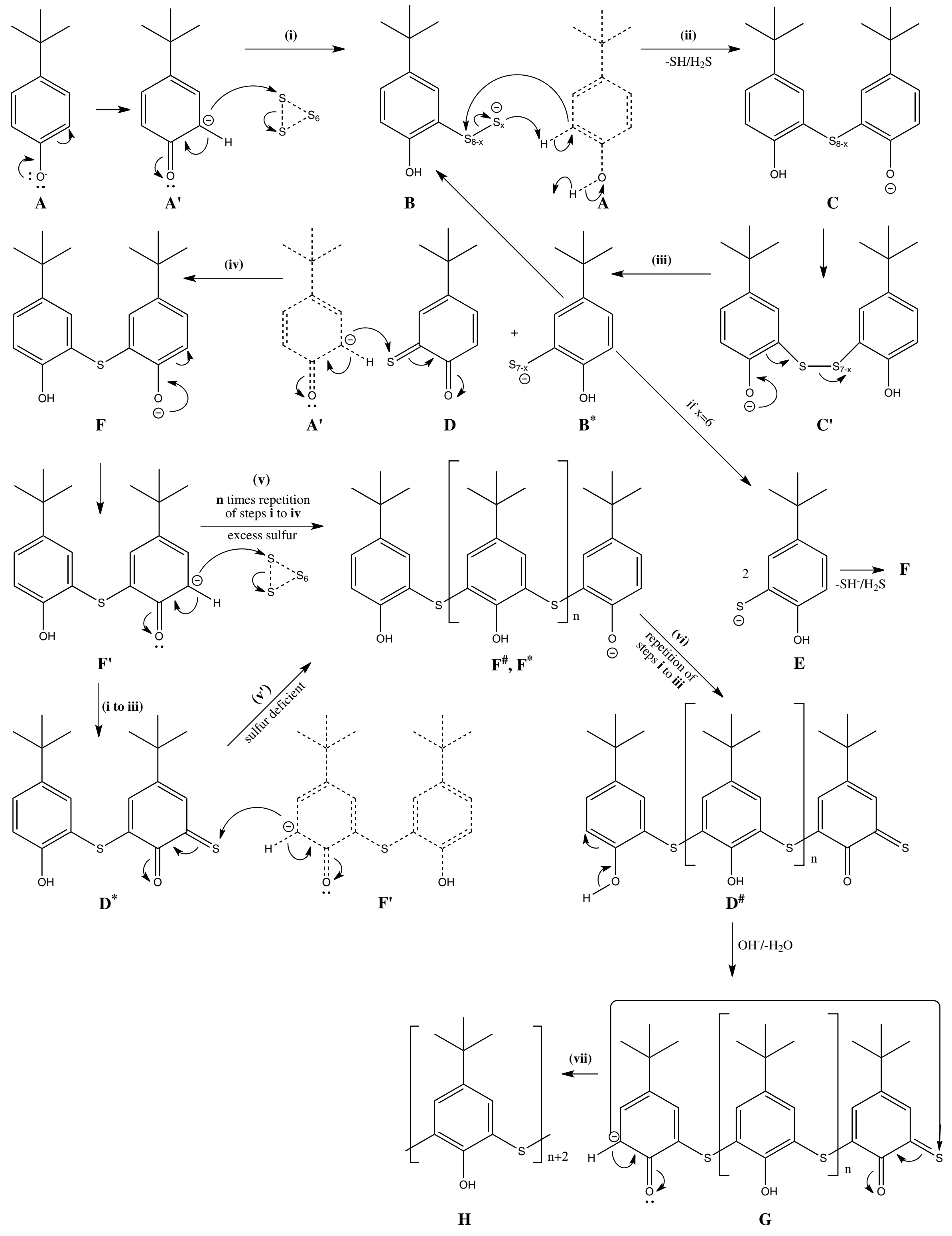
The sulfurization of substituted phenols[15] has been described previously, in light of which, several attempts were given to synthesize thiacalixarenes from other phenol derivatives like *p*-cresol, *p*-acetamidophenol, bis-phenol and *p*-*tert*-butylanisole. Unsuccessful attempts with thiophenol[16] have already been reported earlier. In our present study, non-uniform products were obtained in all the cases. In some cases, the formation of dimers and oligomers was observed. Details are given in Table 3 (see Supplementary data). Also noteworthy is the attempt where the phenol was replaced with resorcinol in the standard procedure, with a view to prepare thiaresorcinarene; however, the reaction mixture turned out to be a non-uniform mixture of acyclic oligomers.

6. Microwave synthesis

Microwave-assisted synthetic[17] procedures have the reputation of enhanced speed, reproducibility and scalability. With a view to reduce the reaction time, traditional heating was replaced with microwave irradiation. In practice, the reaction mixture in diphenyl ether was allowed to react with constant stirring under microwave-assisted heating (Biotage Advancer Microwave oven from Biotage AB, Sweden). The reaction profile was set to impart heating at a uniform rate from ambient temperature to 230 °C, at different heating rates ranging from 0.5 to 4.0 °C/s. The results are tabulated in Table 4 (see Supplementary data). However, under the conditions tested, not even the traces of thiacalixarene were found, and the single product isolated was the dimer in very poor yield.

7. Interpretation of the results

From the outcomes of these experiments the following generalizations can be made. (a) The successful sulfurization in all the cases with various base/catalysts suggests that the presence of NaOH is only required for the template effect. (b) A study of solvent effect reveals that oligomerization requires high temperatures and diphenyl ether is the most appropriate solvent. (c) Any reaction mechanism based on or similar to iodine catalysis is ruled out. (d) The presence of water retards the rate of reaction but does not affect the yield. (e) Failures with other *p*-substituted phenols indicate that an optimally activating group such as *p*-*tert*-butyl is prerequisite (it should also be noted that other reported syntheses with *p*-*tert*-octyl, *p*-admantyl and *p*-phenyl groups were successful only due to their close resemblance with the *tert*-butyl group). (f) Failure with *p*-*tert*-butylanisole indicated that a free phenolic –OH is required, that is, some keto intermediate (from keto–enol tautomerism) must be involved in the reaction. Although resorcinol has free –OH groups, it does not cyclize because of its inability to participate constructively in templation. (g) Microwave synthesis does indicate sulfurization but no oligomerization, which suggests that it is a time-driven process. (h) In all the cases, only the traces of mercaptophenols (i.e., with free –SH groups) were detected



Scheme 2. Reaction mechanism for the synthesis of *p*-*tert*-butylthiacalixarene. Though the reaction involves electrophilic aromatic substitution, electrophile S_8 is a neutral species, thus the mechanism is described by conventional electron 'pushing' (attack on electrophile and accompanying resonance stabilization) depicted by curved arrows. (′, $*$ and # indicate resonance equivalent, next homolog and higher homolog, respectively). The scheme depicts the most probable pathway accounting for most of the possible entities taking part or being produced during the reaction. Entities with dashed (- - -) bonds are new entries in respective steps, that is, other than the products of the previous steps. $n > 1$; $0 < x < 8$.

(0.1–0.3% based on LC–MS) suggesting that they are highly reactive species under the specified reaction conditions. (i) In all the attempts, only a cyclic tetramer was detected by LC–MS analysis reconfirming the fact that thiacalix[4]arene is a thermodynamic product.[2] This is also the reason why attempts to synthesize thiaresorcinarene under standard conditions were unsuccessful because, unlike calixarenes, resorcinarenes are kinetic products.[18]

8. Mechanism of the reaction

The above interpretations give some insight into the reaction mechanism, which in combination with the previously reported[19,20] mechanism of sulfurization of phenols can give a complete picture of the reaction mechanism for thiacalixarene synthesis. Scheme 2, which presents the probable pathway for the formation of TCnA from *p*-*tert*-butylphenol is an extension of the sulfurization process with respect to the present investigation. The mechanism can be summarized in the following steps. (i) The reaction is basically aromatic electrophilic substitution, initiated by the deprotonation of phenol giving resonance-stabilized phenolate ion **A**. Its keto tautomer (**A**′) attacks S_8 through the *ortho*-position giving a phenol poly-sulfide ion **B**. (ii) Species **B** attacks a phenol to give poly-sulfide bis-phenolate ion **C**. During this process a simple condensation occurs, whereby H_2S_x is removed, which is generally H_2S. (iii) The unstable entity **C**′ (due to a labile S–S bond) fragments into *o*-thioquinonoid **D** and another phenol poly-sulfide ion **B**. The fate of $\mathbf{B}^*$ is the same as **B** (as $\mathbf{B}^*$ is a homolog of **B**) and enters into the loop (i.e., repeats step ii again) until it becomes *o*-mercapto-phenolate **E**, which dimerizes to give *mono*-sulfide bis-phenolate **F**. (iv) The *o*-thioquinonoid **D** is attacked by **A**′ to give *mono*-sulfide bis-phenolate ion **F** (dimer), the fate of which depends upon the phenol/sulfur ratio.[19,20] (v) When the reaction mixture contains excess sulfur, the mono-sulfide bis-phenolate ion **F**′ again attacks a fresh S_8 and goes through steps (i)–(iii) repeatedly (*n* times) yielding acyclic epithio-bridged oligomer $\mathbf{F}^{\#}$ (with $n+2$ phenol units). The oligomerization continues until a thermodynamically stable chain is formed, that is, capable of delocalizing effectively the negative charge or until it is cyclized. (v′) In the case of sulfur deficiency (i.e., excess phenol), bis-phenolate ion **F**′ attacks *o*-thioquinonoid $\mathbf{D}^*$ (the homolog of **D** having 2 phenol units) to give tetramer $\mathbf{F}^*$ (with $n = 2$). (vi) $\mathbf{F}^{\#}/\mathbf{F}^*$ undergo steps (i)–(iii) to give *o*-thioquinonoid species $\mathbf{D}^{\#}$, which is deprotonated to give **G**. (vii) The species **G** is special in a sense that it contains both *o*-thioquinonoid and phenolate parts at two terminals of the chain. **G** orients itself to co-ordinate a Na^+ ion and, in a process called templation, is preorganized in a geometry appropriate for cyclization. The cyclization step is essentially step (iii) which is described before, involving the attack of the phenolate ion on the *o*-thioquinonoid, but in an intramolecular fashion to give the final product, *p*-*tert*-butylthiacalixarene **H**.

9. Process optimization for the synthesis of TC4A

In light of the above results and with the enhanced understanding of the reaction mechanism, a one-pot procedure for the synthesis of TC4A was devised by optimizing the standard procedure. Optimization was achieved by in situ formation of a sulfur-bridged dimer and its quantitative conversion into a tetramer without the considerable formation of other oligomers through appropriate temperature control and sulfur deficiency. In practice, in the first stage of the reaction, only half of the requisite amount of sulfur was added, along with a gradual increase of temperature upto 160 °C. This resulted in a predominant formation of a sulfur-bridged dimer (and also a reduction in decomposition of the reactants by avoiding higher temperatures, initially). In the second stage, the remaining sulfur was added to allow further oligomerization and cyclization. Prolonged heating (230 °C) during the second stage ensured the conversion of higher TCnAs into TC4A as a single product. However insignificant the optimizations may seem, they allowed us to isolate *p*-*tert*-butylthiacalix[4]arene in yields as high as 74%[21] via an inexpensive and reproducible procedure.[22] Consistency of the optimized procedure with the proposed theory was established through LC–MS analysis of the reaction mixture and plotting the component distribution against the reaction progress (Fig. 1). As can be observed, at the end of the first stage of heating, ca. 70% of the initial amount of phenol had been converted into the dimer with ca. 10% each of unchanged phenol and the trimer. Also, no significant amounts of higher oligomers were present at this stage. In the second stage, preferential conversion into the tetramer was observed with the minimal formation of the trimer. After ca. 5 h, the tetramer starts to cyclize giving TC4A. Finally, the residual sulfurized phenols and higher TCnAs are converted into TC4A during the last hour of the reaction. The results revealed the quantitative conversion of phenol into dimer and tetramer throughout the reaction, signifying the success of our strategy in limiting excessive side reactions.

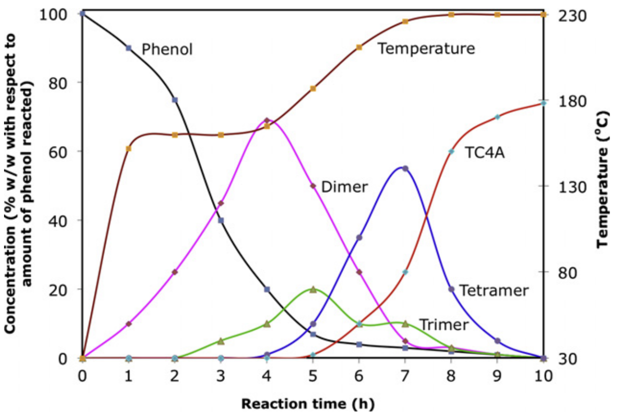


Fig. 1. Changes in concentration of reaction intermediates and product (TC4A) with time for the optimized process by LC–MS.

In conclusion, a mechanism for the synthesis of thiacalixarene has been proposed, which may give better understanding of the reaction and serve as a guide for further research. Also, the synthesis of TC4A is optimized considering the above mentioned approach. Further efforts to explore the chemistry of thiacalixarenes with reference to the postulated model are being undertaken in our lab.

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Supplementary data

Experimental details (synthesis, isolation and instrumentation). Table 1 (template effect); Table 2 (effect of solvent and catalyst); Table 3 (Effect of substitution on phenol); Table 4 (microwave synthesis), Table 5 (elemental analysis and MS data). Scheme 3 (proposed fragmentation pathway for TC4A), Fig. 2 (mass spectra of TC4A); Fig. 3 (^{1}H NMR of TC4A). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.052.

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22. A mixture of *p-tert*-butyl phenol (64.5 g, 0.43 mol), elemental sulfur S_8 (14 g, 0.44 mol), and NaOH (8.9 g, 0.22 mol) in super-dry diphenyl ether (100 ml) was stirred for 15 min, heated gradually to 160 °C over a period of 1 h and kept at this temperature for further 3 h. Then, the temperature of the reaction mixture was brought down to 80 °C and additional sulfur (14 g, 0.44 mol) was added carefully. The temperature was raised to 230 °C over a period of 3 h and maintained for further 3 h. The reaction was continuously monitored by TLC (hexane:chloroform, 1:1(v/v)). The resulting dark brown reaction mixture was cooled to ambient temperature and diluted with 250 ml cold acetonitrile. The precipitates thus produced were of *p-tert*-butylthiacalix[4]arene and were collected by filtration over a sintered glass funnel (preferably G2), and washed with 1 M HCl to remove any traces of alkali. Further purification was achieved by recrystallization from chloroform. The yield obtained was 74%.