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Synthesis of *p*-*tert*-butylthiacalix[*n*]arenes (*n*=4, 6, and 8) from a sulfur-bridged acyclic dimer of *p*-*tert*-butylphenol

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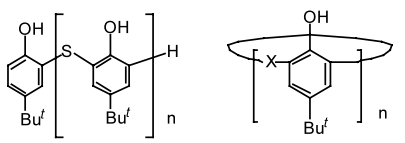
Abstract—The one-step method for the synthesis of *p*-*tert*-butylthiacalix[*n*]arenes **TCnA**s (*n*=4 and 6) by reacting *p*-*tert*-butylphenol **1** with elemental sulfur in the presence of a base was advantageously replaced by a two-step procedure in which a sulfur-bridged linear dimer of **1** was prepared first to use as the starting material for the cyclo-condensation with sulfur to greatly improve the yields of **TC4A** (83%) and **TC6A** (5.3%). The present dimer method allowed the isolation of **TC8A** in an appreciable amount (4.3%) for the first time. © 2002 Elsevier Science Ltd. All rights reserved.

Calix[*n*]arenes (e.g. **CnA**s) are nowadays the most important molecular platform for the construction of synthetic receptors towards ions as well as neutral molecules.[1] This is mainly due to the ready availability of the parent macrocyclic molecular framework in substantial amounts by one-pot condensation of *p*-alkylphenols with formaldehyde, in which proper choice of the established reaction conditions can provide preferentially a particular macrocycle of the component phenol units ranging from *n*=4 to 8.[2,3] Another possible modification of the calix skeleton may involve replacement of the methylene bridges between the phenol units by heteroatoms bearing lone pair electrons of donor ability such as nitrogen, oxygen, sulfur, and the like; this replacement, however, had been one of the most difficult synthetic tasks in calixarene chemistry.[4]



1: n=0
2: n=1

TC4A: X=S; n = 4
TC6A: X=S; n = 6
TC8A: X=S; n = 8
CnAs: X=CH_2; n=4~8

In 1997, we reported a practical method for the synthesis of thiacalix[4]arenes (e.g. **TC4A**), in which methylene bridges are replaced by epithio bonds, by reacting *p*-alkylphenols with elemental sulfur using NaOH as a base catalyst (54% yield for **TC4A**).[5] Since then, there has been increasing interest among us[6] and others[7] in the chemistry of these new members of the calixarene family. With the progress of work it has been revealed that **TC4A** class compounds are not a simple substitute for the conventional **C4A** counterparts, but that the presence of the sulfur moiety provides the former various intrinsic characteristics which cannot be attained by the latter.[8] In this context, preparation of the larger ring analogues **TCnA**s (*n*>4) has been a major concern from the early stage of our investigation on thiacalixarenes. However, even after considerable efforts directed towards scrutinizing reaction variables involving base catalysts, reaction temperature and time, and ratios of the reactants, the one-pot protocol by reacting *p*-*tert*-butylphenol (**1**) with elemental sulfur gave **TC6A** in only 0.8% yield at best by using CsOH rather than NaOH as the base.[9]

In the next step, we turned our attention from the one-pot method to a two-step process by starting from a sulfur-bridged dimer of phenol **1**, 2,2′-thiobis(4-*tert*-butylphenol) **2**, in the hope of a better chance to form larger cyclic oligomers (vide infra).[10] Herein, we report preliminary results obtained in our endeavor along this line, showing that NaOH-promoted reaction of **2** with sulfur can actually provide an alternative method for the synthesis of **TC4A** and **TC6A** in largely improved yields.[11] Also, reported is the first synthesis of **TC8A** in appreciable amounts by the dimer method.[12]

Keywords: calixarenes; thiacalixarenes; sulfide.

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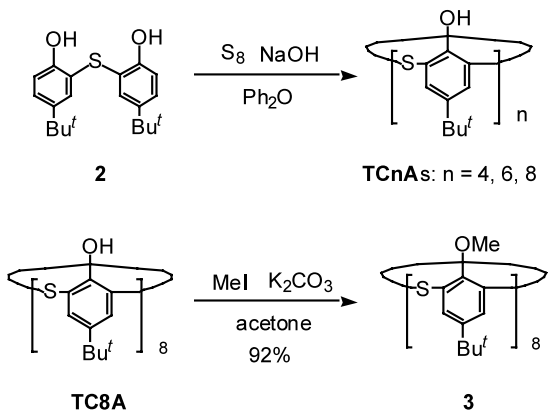
The starting dimer **2** was readily obtainable in good yield (75%) by treating phenol **1** with SCl_2 in dry $CHCl_3$ according to the literature procedure.[13] Generally, the base-catalyzed reactions of **2** with sulfur are carried out in diphenyl ether using NaOH as the base in a round-bottomed flask equipped with a magnetic stirbar and a distillation head to let out low-boiling materials such as water evolved during the reaction (Scheme 1).[14] After heat treatment of the reactants as indicated in Table 1, the reaction mixtures were shown by HPLC to contain a complex mixture of many oligomers of phenol **1** bridged by sulfur, among which were cyclic oligomers **TCnA**s including $n=4$, 6, and 8. Although the mixtures were almost intractable by chromatography on silica gel or alumina, we were pleased to know that CH_3CN dissolved the acyclic oligomers preferentially from the mixtures, leaving the cyclic **TCnA**s as a white precipitate. It was also found that these **TCnA**s were, in turn, conveniently separable by preferential precipitation by using a combination of solvents including $CHCl_3$, CH_2Cl_2, and acetone.

As can be seen from the data in Table 1, the dimer method gave **TC4A** in yields as high as 83% (run 3). Although the one-pot procedure starting from phenol **1** gave **TC4A** in a good yield for this type of cyclo-oligomerization reaction (54%), tedious column chromatography was necessary to secure the yield.[5] Furthermore, the yield of **TC6A** was substantially improved (5.3%, run 4) over that attained by the one-pot procedure.[9] Therefore, considering the ready availability of the starting **2** and no need of column separation, the present two-step procedure may be a good alternative synthesis of **TCnA**s ($n=4$ and 6) to the previous one-pot method.



Scheme 1. Syntheses of **TCnA**s and **3**.

It should also be noted here that the present procedure allowed the first isolation of **TC8A** (4.3%) by slightly tuning the reaction variables (run 1). The identity of the cyclo-octamer was confirmed by spectral data including ^1H NMR, IR, and FAB-MS (m/z 1440, M^+) and elemental analysis.[14] The ^1H NMR spectrum of **TC8A** in $CDCl_3$ is quite similar to that of **TCnA**s ($n=4$, 6) showing only singlet peaks for *tert*-butyl (δ 1.22, 76H), phenyl (δ 7.56, 16H) and hydroxy protons (δ 8.68, 8H), respectively, indicating that it should rapidly convert between the stable conformers in solution at ambient temperature as the smaller ring members of $n=4$ and 6 do. Although the crystal structure of **TC8A** itself has not yet been elucidated, its treatment with CH_3I/K_2CO_3 in acetone gave the octamethyl ether **3** in 92% yield (Scheme 1).[15] Slow diffusion of CH_3CN into a solution of **3** in $CHCl_3$ afforded single crystals as colorless prisms suitable for X-ray structure analysis to show that it adopts 1,2,3,4-alternate like conformation encapsulating two molecules of CH_3CN in the cavity (Fig. 1).[16]

The idea of using dimer **2** as the starting material for cyclo-oligomerization with sulfur came from the HPLC assay of the time-course of the reaction of **1**, S_8, and NaOH.[5] It was found that heating a mixture of the reactants at 170°C caused reaction between phenol **1** and sulfur to form a complex mixture of acyclic oligomers of the phenol **1** joined by sulfide (-S-) as well as polysulfide ($-S_x-$) linkages at the *o*,*o*′-positions, the composition of which was highly dependent on the reaction variables such as heating rate and reactant

Table 1. Reaction conditions and the yields of **TCnA**s

Run	Reaction conditions		Yields (%)[b]		
	2:S:NaOH[a]	Heating time	**TC4A**	**TC6A**	**TC8A**
1	1:2:1	130°C: 2 h 170°C: 2 h 230°C: 3 h	48	0	4.3
2	1:2:1	130°C: 2 h 170°C: 5 h 230°C: 3 h	82	1.1	0.1
3	1:2:1	130°C: 2 h 170°C: 5 h 230°C: 5 h	83	0	0
4	1:2:1.5	130°C: 2 h 170°C: 5 h 230°C: 3 h	39	5.3	0

[a] Mol:g-atom:mol.
[b] Isolated yield based on **2**.

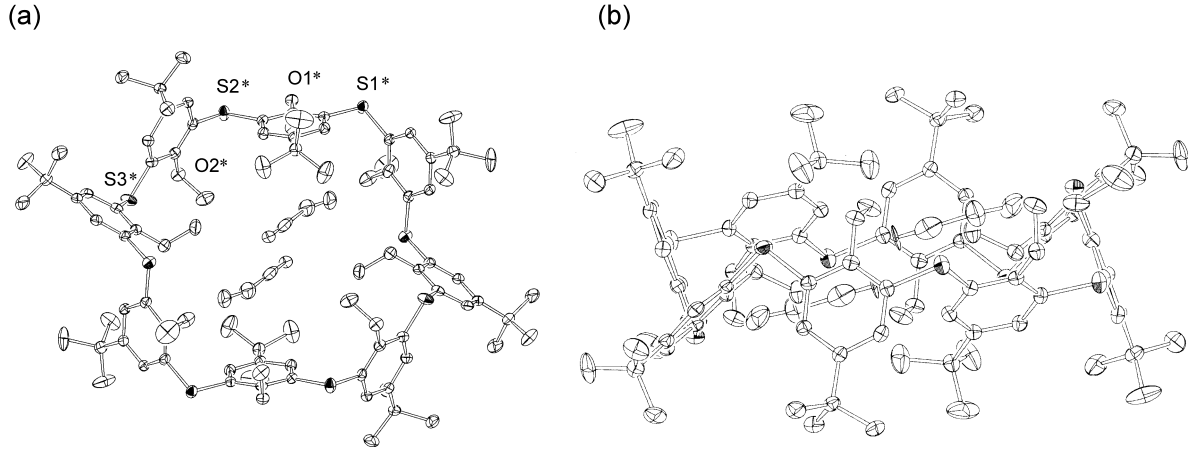


Figure 1. Molecular structure of $2CH_3CN$ complex of **3**. (a) Top view; (b) side view.

ratios. After 2 h heating at 170°C of a 1:1:1 mixture of **1**/sulfur/NaOH, HPLC peaks corresponding to linear oligomers containing up to 10 phenol units were detected. Then, heating the mixture up to 230°C brought about appearance of a peak identical to that of cyclic tetramer **TC4A**, occasionally accompanying a small peak of **TC6A** depending on the reaction conditions. It was observed that the latter peak increased to a maximum and then disappeared with the progress of the reaction, while that of the former gradually increased to reach a plateau. These observations strongly suggest that **TC6A** is a kinetic product while **TC4A** is thermodynamically more stable under the reaction conditions. Actually, control experiments proved that **TC6A** as well as **TC8A** were thermally convertible to **TC4A** under the corresponding basic conditions, as the methylene-bridged counterparts **CnA**s ($n=6$ and 8) were also amenable to thermal transformation to **C4A**.[2a] Although detailed mechanism of the present cyclo-oligomerization reaction must await further investigation, it may be conceivable that isolation of **TCnA**s ($n=6$ and 8) is attainable only when suitable acyclic oligomers which can cyclize to **TCnA**s accumulate in substantial quantities and then they are timely heated to a temperature to promote the cyclization while keeping the reaction time short enough to let them survive the ring degradation. It may be said that these subtle conditions were partly attained by shortening the heating time at 230°C by using the dimer **2** as the starting material to allow the isolation of **TCnA**s ($n=6$ and 8) in appreciable yields.

In conclusion, we have shown here that the NaOH-catalyzed reaction of an acyclic dimer of *p*-*tert*-butylphenol **2** with elemental sulfur in Ph_2O provides an improved method for the synthesis of **TCnA** ($n=4$ and 6) as well as the first synthesis of **TC8A** by slightly controlling the reaction conditions.

Acknowledgements

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14. In a typical run (run 2 in Table 1), a mixture of **2** (10.0 g, 30.0 mmol), S_8 (1.96 g, 60.0 mg-atom), and NaOH (1.24 g, 30.0 mmol) in diphenyl ether (30 ml) was heated with stirring to 130°C and kept at this temperature for 2 h, then at 170°C for 5 h, and finally at 230°C for 3 h under nitrogen atmosphere. The reaction mixture was cooled to ambient temperature, to which were added $CHCl_3$ and 1 M H_2SO_4. After $CHCl_3$ was removed from the organic phase under reduced pressure, dilution of the residue with CH_3CN caused precipitation of a white solid comprising **TCnA** where $n=4$, 6, and 8 as evidenced by HPLC. To the precipitate, in turn, was added CH_2Cl_2 to dissolve **TC6A** and **TC8A**, leaving **TC4A** as the insoluble part (7.96 g, 73% yield). From the CH_2Cl_2–soluble part were recovered **TC6A** (0.12 g, 1.1%) as the less soluble component by addition of $CHCl_3$, and then **TC8A** (13 mg, 0.1%) as the more soluble one. Acetone was added to the resultant solution to give additional **TC4A** (0.96 g). The combined yield of **TC4A** was 8.92 g (81.6%). All spectral data of **TC4A** and **TC6A** coincided with those of previous reports. See: Refs. 5 and 9. **TC8A**: mp 304–307°C; IR (KBr): 3327 (OH), 2963 (CH) cm^{-1}; FAB-MS m/z 1440 (M^+, 100%); ^1H NMR ($CDCl_3$) δ 8.68 (s, 8H, OH), 7.56 (s, 16H, Ar), 1.22 (s, 72H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 154.9, 144.3, 134.8, 120.4 (Ar), 34.2 ($\underline{C}(CH_3)_3$), 31.3 ($C(\underline{C}H_3)_3$). Anal. calcd for $C_{80}H_{96}O_8S_8$: C, 66.63; H, 6.71; S, 17.79. Found: C, 66.76; H, 6.59; S, 18.09.
15. A mixture of **TC8A** (51.8 mg, 0.04 mmol), MeI (204.3 mg, 1.4 mmol), and K_2CO_3 (50.0 mg, 0.4 mmol) in dry acetone (30 ml) was stirred and refluxed for 2.5 days under N_2 atmosphere. The reaction mixture was cooled to ambient temperature and the solvent was removed under reduced pressure. To the resultant material was added $CHCl_3$, and then insoluble material was removed by filtration. Recrystallization from $CHCl_3$–CH_3CN afforded **3** as colorless prisms (51.7 mg, 91.5%). mp 320–323°C; FAB-MS m/z 1554 ($[M+1]^+$, 100%); ^1H NMR ($CDCl_3$) δ 7.05 (s, 16H, Ar), 3.75 (s, 24H, OMe), 1.08 (s, 72H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 155.3, 147.8, 129.1, 129.0 (Ar), 60.5 (s, OMe), 34.4 ($\underline{C}(CH_3)_3$), 31.1 ($C(\underline{C}H_3)_3$). Anal. calcd for $C_{88}H_{112}O_8S_8 \cdot H_2O$: C, 67.22; H, 7.31. Found: C, 67.42; H, 7.15.
16. Crystal data: $C_{88}H_{112}O_8S_8 \cdot 2\ CH_3CN$, $M=1636.43$, colorless, sizes $=0.15\times0.2\times0.2$ mm, triclinic, $a=10.900(2)$, $b=13.560(1)$, $c=15.780(1)$ Å, $\alpha=85.250(4)$, $\beta=82.180(5)$, $\gamma=74.440(1)°$, $V=2222.3450$ Å^3, Mo Kα radiation ($\lambda=0.71070$ Å), space group $P1$ ($\#2$), $Z=1$, $D_{calcd}=1.223$ g/cm^3, $T=220$ K, μ(Mo Kα) $=2.56$ cm^{-1}, data collection using Rigaku/MSC mercury CCD diffractometer, number of measured reflections $=17310$ ($2\theta<55.0°$), independent reflections $=8654$ ($R_{int}=0.022$), a symmetry-related absorption correction, final $R=0.050$, $R_w=0.055$ for 5025 observed reflections ($I_o>3\sigma(I_o)$), GOF $=1.36$. The CH_3CN molecules are included in the mole ratio of 1:2 (host:guest) in the crystal, which disordered in two parts, respectively. Further details of the X-ray analysis are available on request from the Director of the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK.