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Unprecedented Cyclizations of Calix[4]arenes with Glycols under the Mitsunobu Protocol, Part 2.[1] O,O-and O,S-Bridged Calixarenes

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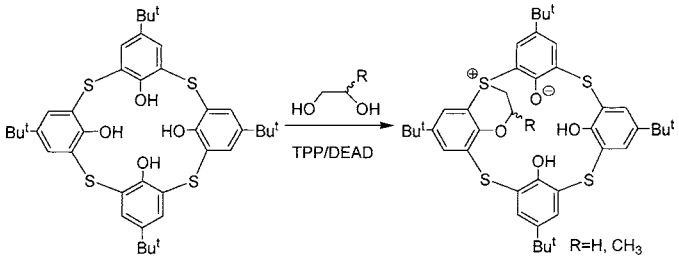
ABSTRACT



Cycloalkylations of *p-tert*-butylcalix[4]arene (CA) and *p-tert*-butylthiacalix[4]arene (TCA) with various aliphatic glycols were performed under the Mitsunobu protocol using the DEAD/TPP system. CA gave 1,3-dialkylated diols, while C_2–C_{10} glycols gave 1,2- and 1,3-bridged calixarenes. The reaction of TCA with C_2 diols afforded sulfonium phenoxide betaines via O,S-cyclization, which is the first example for the alkylation of the sulfide bridge.

In the first part of this series, the unexpectedly selective diametrical ring closure of thiacalix[4]arene (TCA) and calix[4]arene (CA) with oligoethylene glycols under the Mitsunobu conditions was reported.[1] With the aid of this simple and mild method, 1,3-calix[4]crown-4,5 and 1,3-calix[4]-crown-6 derivatives **I** (X = all CH_2 or all S, n = 1−3) (Figure 1) were accessible in yields of 40−60%, which are comparable with those of the classical templated procedures. The results obtained with glycol homologues suggested that the intra vs intermolecular reaction was mainly controlled by the chain lengths and partly by the cavity size of calixarenes (TCA > CA). The role of the latter was reflected by the reactions performed with the short-chained diethylene glycol and the long-chained pentaethylene glycol, respectively. While the former resulted in proximal bridging with CA (**II**) and 1,3-intermolecular coupling with TCA (**III**), the latter gave 1,3-calix[4]crown-6 derivative with TCA (**I**, X = S, n = 3) and failed to cyclize with CA (Figure 1).[1]

However, the unusual selectivity of a templateless reaction raised the question: is there any role of the podand-armed intermediate formed after the first coupling in governing the reaction to the preferred direction of cyclization? To have deeper insight into the nature of this valuable reaction, a series of aliphatic diols have been tested. Among them, the chain lengths of 1,6-, 1,8-, and 1,10-alkylene glycols are comparable to those of the di-, tri-, and tetraethylene glycols formerly investigated.[1]

The reactions were performed in toluene using a series of commercial glycols (1,2-ethanediol **1**, 1,3-propanediol **2**, (±)-1,2-propanediol **3**, 1,4-butanediol **4**, *cis*-buten-2-1,4-diol **5**, 1,6-hexanediol **6**, 1,8-octanediol **7**, and 1,10-decanediol **8**)

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(1) Csokai, V.; Grün, A.; Bitter, I. *Tetrahedron Lett.* **2003**, *44*, 4681−4684.

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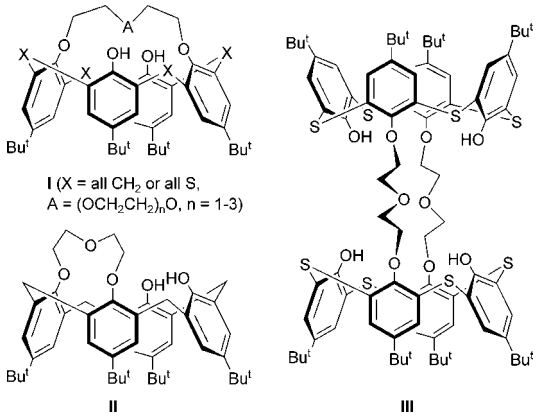
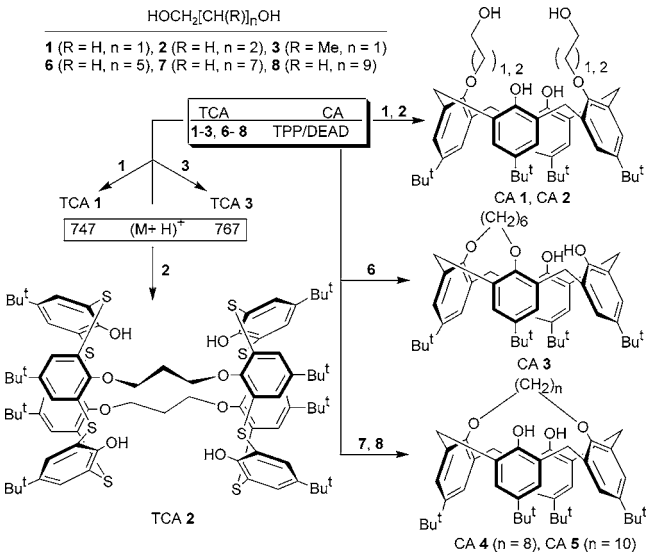


Figure 1. Survey of products obtained in the reaction of CA and TCA with oligoethylene glycols.[1]

and coupled with CA or TCA in the presence of triphenylphosphine (TPP)/diethyl azodicarboxylate (DEAD)[2] under two different conditions: (1) with the molar ratio of CA, TCA:(glycol/TPP/DEAD) = 1:(1.5/3/3) at room temperature and (2) with the molar ratio of CA, TCA:(glycol/TPP/DEAD) = 1: (4/7/7) at 110 °C (Scheme 1).

Scheme 1



The starting CA was consumed within 30 min at room temperature (TCA required 30 min of heating). The common features of all reactions were as follows: (a) neither CA nor TCA gave any reactions with C_4-diols **4** and **5**, presumably due to the fast ring closure of this diol to THF or dihydrofuran, and (b) the reactions did not proceed further in any cases when a large excess of reagents had been used at an elevated temperature. However, the outcome of the reactions was totally different.

(2) Caution! DEAD may explode if exposed to shock, friction, or heating.

CA gave no cyclic products with the short-chained 1,2-ethanediol **1** and 1,3-propanediol **2**; instead, dialkylation took place, affording diols CA**1** and CA**2**. Proximal ring closure was found with 1,6-hexanediol **6** leading to CA**3**, accordingly as diethylene glycol, which furnished 1,2-calixcrown-3 **II**.[1] Similar comparison between the chain length and the bridging site could be drawn with 1,8-octanediol **7** and triethylene glycol or 1,10-decanediol **8** and tetraethylene glycol, respectively. Each of them has a sufficiently long chain to bridge the distal OH groups resulting in the formation of 1,3-capped calix[4]arenes.

These results, in accordance with our former observations, clearly show that CA prefers intramolecular reactions with 1,*n*-diols from C_5 to C_{10} (including oligoethylene glycols) and the position of bridging is primarily controlled by the chain length.

The Mitsunobu reaction of TCA with aliphatic diols does not allow similarly straightforward conclusions to be drawn. On use of glycols **6**−**8**, an unseparable mixture of products was formed and we did not succeed in isolating any compounds related to 1:1 or 2:2 coupling. However, 1,3-propane-diol **2** gave the dimer TCA**2**, which was precipitated from the solution in essentially pure form but in very low yield (8%), and we failed to separate any other thiacalixarene derivative from the reaction mixture. Considering the ^{1}H chemical shifts, the dimer appears in a *cone* conformation where the bridged aromatic rings are parallel (Bu^t, 0.70; ArH, 6.91 ppm), whereas the phenol units are flattened (Bu^t, 1.29; ArH, 7.51 ppm).[3] Nevertheless, the insignificant amount of dimer TCA**2** indicates that intermolecular 2:2 coupling is restricted by decreasing the chain length, and probably different intramolecular reactions are favored. This conclusion is in accord with the results reported for the base-promoted alkylation of TCA with 1,3-dibromopropane, which led to the respective tetrakis(3-bromopropyl)ether, whereas 1,2-dibromoethane effected double bridging of the adjacent OH groups.[4] In light of this report, an intramolecular ring closure was expected when TCA was treated with 1,2-diols **1** and **3** (with the latter, the aim for study was the different reactivity of the primary and secondary OH groups[5]).

Actually, the FAB-MS spectra of products TCA**1** and TCA**3** obtained in yields of 40−50% gave molecular peaks 747 and 761 $(M + H)^+$, which were in accord with the insertion of one ethylene and one propylene moiety, respectively. However, the expected proximally O,O-bridged structure was not supported at all by the NMR spectra.

Akdas et al. reported the ^{1}H and ^{13}C chemical shifts of a doubly O-capped TCA comprised of two proximal ethylene fragments, which displayed two O*C*H$_2$ signals at 67.3 and 72.4 ppm in the ^{13}C spectrum.[4] For compound TCA**1**, the respective bridging carbon atoms resonated at 63.7 and 33.9 ppm. While the former shift obviously can be assigned to an OCH$_2$ group, the latter was supposed to belong to a methylene attached to a sulfur atom. Thorough NMR

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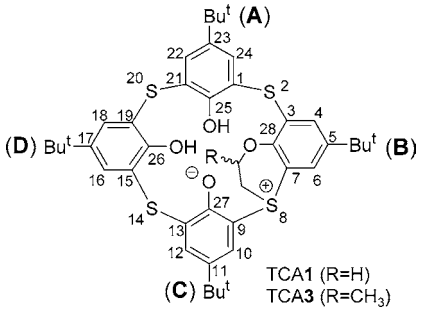
(4) Akdas, H.; Bringel, L.; Bulach, V.; Graf, E.; Hosseini, M. W.; De Cian, A. *Tetrahedron Lett.* **2002**, *43*, 8975−8979.

(5) Hughes, D. L. *Org. React.* **1992**, *42*, 335−656.

investigation, including COSY, DEPT, HSQC, HMBC, one- and two-dimensional NOESY, and ROESY, measurements were made to elucidate this unexpected structure (Table 1).

Table 1. Complete ^{1}H and ^{13}C NMR Assignment of TCA1



^{1}H NMR data (δ, ppm)[a]					
4	**6**	**10**	**12**	**16**	**18**
6.88	6.29	7.43	7.94	7.54	7.47
22	**24**	Bu^t(**A**)	Bu^t(**B**)	Bu^t(**C**)	Bu^t(**D**)
7.65	7.67	1.34	0.47	1.29	1.19
CH_2O		CH_2S^+	OH(**25**)		
4.69; 5.43		3.95; 5.50	10.85		
^{13}C NMR data (δ, ppm)[a]					
1	**3**	**4**	**5**	**6**	**7**
123.8	129.5	134.9	145.5	122.3	108.3
9	**10**	**11**	**12**	**13**	**15**
103.7	131.8	136.4	140.8	129.0	122.1
16	**17**	**18**	**19**	**21**	**22**
136.6	141.4	136.3	121.6	122.9	134.2
23	**24**	**25**	**26**	**27**	**28**
141.9	134.6	156.7	161.1	166.5	153.7
CH_2O	Bu^t(**A**)	Bu^t(**B**)	Bu^t(**C**)	Bu^t(**D**)	CH_2S^+
63.7	31.7 34.3	30.2 33.8	31.5 34.12	31.6 34.09	31.6

[a] Bold labels **A**−**D** denote the position of signals.

In the HMBC spectra, correlations were detected between the methylene protons (3.95, 5.50 ppm) attached to the carbon atom with a chemical shift of δ 33.9 ppm and between two quaternary aromatic carbon atoms at δ 103.7 and 108.3 ppm. Analogous correlations were observed with compound TCA**3**, which can only be explained by the still unprecedented alkylation of the adjacent bridging epithio group affording a benzoxathiin ring. If this supposition is true, then the sulfur atom in TCA**1** and TCA**3** should be positively charged. Comparing the ^{13}C substituent effects of the *S*-alkyl vs S^+(alkyl)$_2$ groups,[6,7] a 12−14 ppm upfield shift can be expected in the C_{ipso} positions. Actually, similar upfield values can be observed with TCA**1** if the signals of the other aromatic *ipso* carbon atoms attached to the sulfide bridge (C-1, C-15, C-19, and C-21: 121−123 ppm) are compared with those adjacent to the sulfonium unit (C-7 and C-9). The next step of the assignment was the differentiation between the signals at 103.7 and 108.3 ppm. The HMBC connectivities of the aromatic proton signal at 6.29 ppm (d, $J = 2$ Hz) to the carbon atoms at 108.3, 153.7, and 33.8 ppm proved that all of them are located in the same *p-tert*-butylphenyl moiety. The coupling of the quaternary carbon signal at 33.8 ppm to the CH_3 protons revealed the extremely low ^{1}H chemical shift (0.47 ppm) of the corresponding *p-tert*-butyl group. The other quaternary aromatic carbon atom at 103.7 ppm is located in the neighboring *p-tert*-butylphenyl moiety. The assignment of all ^{1}H and ^{13}C signals of this unit was achieved in a manner similar to that described above. It is worth mentioning that the 166.5 ppm chemical shift of the carbon atom substituted by oxygen are extremely deshielded compared with the OH-substituted positions. At the same time, the carbon attached to the *p-tert*-butyl group (136.4 ppm) in the same building block is shielded. It is known that the ^{13}C substituent effect of the phenolate vs phenol results in 12.7 ppm downfield shift in the ipso position and a 6.3 ppm upfield shift in the para position.[8] This evidence supports the presence of a phenolate counterion, i.e., compounds TCA**1** and also TCA**3** exist in the unique O,S-cyclic sulfonium phenoxide betaine form[9] possessing inherent chirality.[10] TCA**3** has an additional asymmetric center in the benzoxathiin ring, which should lead to two diastereoisomers with respect to the position of the methyl group. The one series of signals in the spectra of TCA**3** is indicative of a single diastereomer (see later).

To reveal the effects of the phenolate moiety on the ^{13}C chemical shifts and to obtain further chemical evidence for this unprecedented structure, TCA**3** was converted into the corresponding perchlorate salt. As expected, the signal of the phenolate C_{ipso}-27 shifted from 166.5 to 154.4 ppm, whereas the C_{para}-11 moved in the opposite direction from 135.9 up to 145.9 ppm (Table 2).

Additional evidence for the sulfonium structure was provided by the ^{13}C NMR spectra of the closely related models 2,2′-dihydroxy-5,5′-dichlorodiphenylsulfide and its *S*-methyl-sulfonium tetrafluoroborate salt (prepared from the commercially available sulfide by MeI and $AgBF_4$ in DCM

(6) Olah, G. A.; Westerman, P. W.; Forsyth, D. A. *J. Am. Chem. Soc.* **1975**, *97*, 3419−3427.

(7) Ricci, A.; Bernardi, F.; Danieli, R.; Macciantelli, D.; Ridd, J. H. *Tetrahedron* **1978**, *34*, 193−196.

(8) Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tabellen zur Strukturaufklarung Organischer Verbindungen*; Springer-Verlag: Berlin, 1981; p C120.

(9) Some sulfonium phenoxide betaines were described by: Schwalm, R.; Bug, R.; Dai, G.-S.; Fritz, P. M.; Reinhardt, M.; Schneider, S.; Schnabel, W. *J. Chem. Soc., Perkin Trans. 2* **1991**, *11*, 1803−1808. Cyclic sulfonium salts are reviewed: Dittmer, D. C.; Patwardhan, B. H. In *The Chemistry of Sulphonium Group*; Stirling, C. J. M., Ed.; John Wiley and Sons: Chichester, 1981; Part 2, Chapter 1, pp 387−521.

(10) Preliminary experiments for the separation of the racemates by chiral HPLC (Chiralpack AD, Chiracell OD) were unsuccessful. On addition of (*R*)-1-(9-anthryl-2,2,2-trifluoroethanol (Pirkle reagent) to the $CDCl_3$ solution of TCA**3**, the proton signals were doubled in 1:1 ratio, providing evidence for the presence of racemate (see Supporting Information).

Table 2. Complete ^{1}H and ^{13}C NMR Assignment of TCA**3**·$HClO_4$ Salt

^{1}H NMR data (δ, ppm)[a]					
4	**6**	**10**	**12**	**16**	**18**
7.29	6.94	8.03	7.96	7.32	7.57
22	**24**	Bu^t(**A**)	Bu^t(**B**)	Bu^t(**C**)	Bu^t(**D**)
7.73	7.70	1.31	0.90	1.34	1.12
CHO	CH_3	CH_2S^+			
4.52	1.22	4.01; 4.26			
^{13}C NMR data (δ, ppm)[a]					
1	**3**	**4**	**5**	**6**	**7**
120.5	126.2	134.9	146.0	126.0	110.1
9	**10**	**11**	**12**	**13**	**15**
103.4	132.8	145.9	138.9	126.0	117.3
16	**17**	**18**	**19**	**21**	**22**
136.1	145.9	136.3	120.8	121.0	1354.2
23	**24**	**25**	**26**	**27**	**28**
144.8	134.5	153.6	154.6	154.4	153.7
CHO	Bu^t(**A**)	Bu^t(**B**)	Bu^t(**C**)	Bu^t(**D**)	CH_2S^+
68.4	31.2 34.3	30.5 34.2	30.6 34.8	31.1 34.2	41.1

[a] Bold labels **A**−**D** denote the position of signals.

at rt). The signal of the aromatic ipso carbon atoms attached to the sulfide appears at 120.7 ppm, which is shifted to 109.6 in the sulfonium salt, while the Me−S^+ group resonates at 24.0 ppm. These chemical shifts, compared with those of TCA**3**·$HClO_4$, also support the undoubtedly unique sulfonium structure. The salt appears to adopt a flattened *cone* conformation in which the O-alkylated phenyl group; the opposite aromatic ring is almost parallel, and the two others are flattened, as reflected by the characteristic ^{1}H chemical shifts of the $(CH_3)_3C$ groups (0.90 and 1.12 ppm vs 1.31 and 1.34 ppm).[3] Further proof for the conic conformation is the appearance of strong NOESY responses between the four proton pairs of the neighboring aromatic groups.

Interestingly, the betaines were found to occupy a *paco* conformation, since NOESY proximities were detected between the O-alkylated aromatic nucleus and its two neighbors only (Figure 2). In addition, the lack of NOE responses between the Me and H-22, H-24 protons in TCA**3** allows one to conclude that the methyl group is oriented out of the cavity. X-ray crystallography would give unambiguous evidence for the structure, but until now, we could not succeed in preparing suitable crystals.

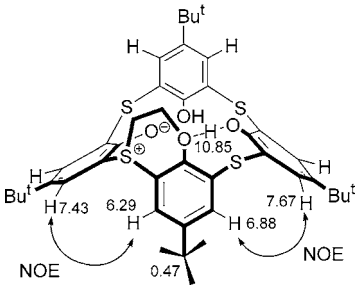


Figure 2. Stereoview of TCA**1** on the basis of the NOESY proximities.

The mechanism of the O,S-cycloalkylation reaction has not been investigated, but it presumably starts with O-alkylation by the glycol affording an *O*-(2-hydroxy-ethoxy)-intermediate, the chain of which is not sufficiently long to cyclize with the adjacent phenolic OH. Instead, the nucleophilic sulfur is attacked[11] resulting in a sulfonium betaine comprising a phenoxide counteranion. This pathway cannot give any explanation for the structural anomaly of TCA**3**, i.e., for the position of the Me group on the benzoxathiin ring. If the higher reactivity of the primary vs secondary alcohols in the Mitsunobu reaction is considered,[1,5] the Me group should reside on the carbon atom attached to the sulfonium moiety. Since the yield was moderate and the side-products were not isolated, we assume that both alcoholic parts of 1,2-propanediol **3** were competitively involved in the O-alkylation. However, the sulfur atom could not be alkylated by the sterically hindred secondary electrophilic site, and after all, this intermediate was lost during workup.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0359315

(11) For the S-alkylation of thioureas by Mitsunobu reaction, see: Kim, T. H.; Cha, M. H. *Tetrahedron Lett.* **1999**, *40*, 3125−3128.