Synthesis and Structure of a Bridged Calix[6]arene with a Sulfenic Acid Functionality in the Cavity

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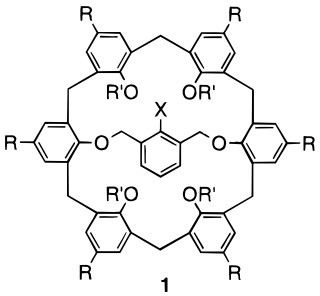
Recently, increasing attention is being paid to concave reagents,[1] that is, cavity-shaped molecules with an inwardly-directed functionality embedded in the concave position, which are modeled on the environment of the active sites of enzymes. Calixarenes have been widely utilized as a versatile building block in supramolecular chemistry,[2] and incorporation of a concave functionality into their cavity would open up a new mode of application of this class of macrocycles. However, they are at a disadvantage in that the functionalities in their upper and lower rims tend to diverge away from the substrates held within the cavity.

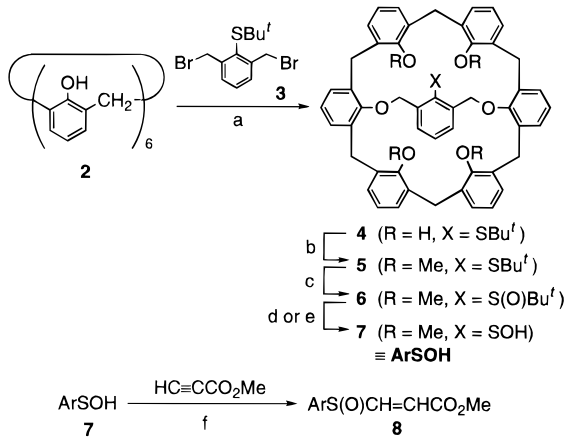
As a strategy for introducing an inwardly-directed functional group into the cavity of a calix[6]arene, we have designed bridged calix[6]arenes represented by a general formula **1** and previously reported the photolysis



1

of an azide bearing this framework.[3,4] While the cavities of calixarenes have so far been utilized mostly as a complexing site,[5] that of **1** is expected to work also as a reaction field for the functionality and regulate its reactivities in a unique fashion. In the course of our study on macrobicyclic cyclophanes, we have found that their bowl-shaped framework is of great use for the stabilization of a reactive species such as a sulfenic acid

Scheme 1[a]



[a] Reagent: (a) KOH, THF−DMF, 92%; (b) KH, CH_3I, THF−DMF, 82%; (c) *m*-CPBA, CH_2Cl_2, 81%; (d) toluene, 80 °C, 4 h, 97%; (e) in the solid state, 150 °C (bath temp), 60 s, 76%; (f) $CDCl_3$, 50 °C, 16 h, 86%.

(RSOH),[6] which is known to play important roles in some enzymatic reactions but to be usually very unstable because of its quite easy self-condensation to the corresponding thiosulfinate.[7,8] If a sulfenic acid functionality is incorporated into the cavity of **1**, it would provide a good probe to investigate how the bridged calixarene framework can regulate the reactivity of an intracavity functional group. In this paper, we report the synthesis and crystal structure of a bridged calix[6]arene bearing a sulfenic acid functionality in the cavity.[9]

As the method of generating a sulfenic acid, thermolysis of a *tert*-butyl sulfoxide was employed because it can be carried out under mild conditions.[10] The reaction of calix[6]arene **2** and sulfide **3** in the presence of KOH gave sulfide **4** in a high yield of 92% (Scheme 1).[11] Methylation of **4** with KH and methyl iodide afforded a tetramethyl ether **5**. Sulfoxide **6** was readily obtained by oxidation of **5** with *m*-CPBA as a mixture of two inseparable conformational isomers (ca. 10:3 ratio by ^{1}H NMR). Thermolysis of sulfoxide **6** was carried out in solution or in the solid state, and in either case sulfenic acid **7** was obtained as stable colorless crystals in good yields (97% in toluene, 80 °C, 4 h; 76% in the solid state, 160 °C, 60 s).[12,13]

The ^{1}H NMR spectrum of **7** ($CDCl_2CDCl_2$)[11] showed quite broadened signals at room temperature, which were

(1) (a) Lüning, U. *Liebigs Ann. Chem.* **1987**, 949−955. (b) Lüning, U. *Top. Curr. Chem.* **1995**, *175*, 57−99 and references therein.

(2) (a) Gutsche, C. D. In *Calixarenes*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1989. (b) Vicens, J., Böhmer, V., Eds. *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Kluwer Academic Publishers: Dordrecht, 1991. (c) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713−745.

(3) Tokitoh, N.; Saiki, T.; Okazaki, R. *J. Chem. Soc., Chem. Commun.* **1995**, 1899−1900.

(4) Very recently, Lüning et al. reported the concave pyridines bearing a framework similar to **1**: Ross, H.; Lüning, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2555−2557.

(5) For other examples of bridged or capped calix[6]arenes, see: (a) Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3160−3166. (b) Kanamathareddy, S.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 6572−6579. (c) Otsuka, H.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 1542−1547. (d) Araki, K.; Akao, K.; Otsuka, H.; Nakashima, K.; Inokuchi, F.; Shinkai, S. *Chem. Lett.* **1994**, 1251−1254. (e) Takeshita, M.; Nishio, S.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 4032−4034. (f) Janssen, R. G.; Verboom, W.; van Duynhoven, J. P. M.; van Velzen, E. J. J.; Reinhoudt, D. N. *Tetrahedron Lett.* **1994**, *35*, 6555−6558. (g) Casnati, A.; Jacopozzi, P.; Pochini, A.; Ugozzoli, F.; Cacciapaglia, R.; Mandolini, L.; Ungaro, R. *Tetrahedron* **1995**, *51*, 591−598.

(6) Goto, K.; Tokitoh, N.; Okazaki, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1124−1126.

(7) For reviews on the chemistry of sulfenic acids, see: Hogg, D. R. In *The Chemistry of Sulfenic Acids and Their Derivatives*; Patai, S., Ed.; John Wiley & Sons: New York, 1990; pp 361−402. Kice, J. L. *Adv. Phys. Org. Chem.* **1980**, *17*, 65−181.

(8) For leading references on the biological reactions of sulfenic acids, see: (a) Allison, W. S. *Acc. Chem. Res.* **1976**, *9*, 293−299. (b) Claiborne, A.; Miller, H.; Parsonage, D.; Ross, R. P. *FASEB J.* **1993**, *7*, 1483−1490.

(9) A part of this work has been presented in 12th Symposium on Fundamental Organic Chemistry, Fukuoka, Japan, Oct 15−17, 1994, 2P36.

(10) Davis, F. A.; Jenkins, L. A.; Billmers, R. L. *J. Org. Chem.* **1986**, *51*, 1033−1040.

(11) Experimental details for the synthesis of **3**−**11**, their spectral and analytical data, and the variable-temperature ^{1}H NMR spectra of **7** (25−120 °C) are described in the supporting information.

(12) Monitoring of the thermolysis in toluene-d_8 at 80 °C for 4 h in a sealed tube indicated that both conformers of **6** disappeared at a similar rate.

(13) **7**: colorless crystals, mp 182 °C dec; HRMS(FAB) *m*/*z* calcd for $C_{54}H_{50}O_7S$ 842.3277, found 842.3245; ν_{OH} (CH_2Cl_2) 3479 (m) and 3282 (m) cm^{-1}. For the ^{1}H NMR data, see the supporting information.

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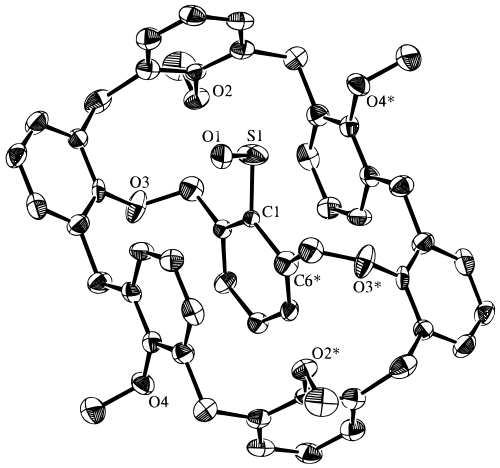
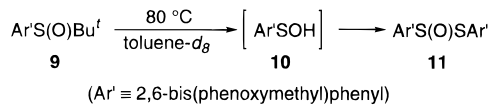


Figure 1. ORTEP drawing of **7** (one of two disordered molecules) with thermal ellipsoid plot (30% probability).

sharpened at high temperatures. At 120 °C were observed a singlet at δ 3.56 for OMe protons, two pairs of doublets for $ArCH_2Ar$ methylenes (ratio 1:2), a singlet at δ 4.59 for $ArCH_2O$ methylenes, and a singlet at δ 2.39 which is most likely assigned to the hydroxyl proton of SOH.[14] The signal broadening at room temperature indicates that the conformational interconversion of the calix[6]arene macrocycle is considerably restrained by the *m*-xylenyl bridge. Recently, it has been reported that bridging at two or three positions reduces the conformational flexibility of calix[6]arenes effectively.[5] In compound **7**, the *m*-xylenyl bridge not only introduces the functional group but also rigidifies its structure. At 120 °C, the four nonbridged anisolic rings appear equivalent, which can be explained in terms of their rapid flipping motion through the annulus. The geminal coupling of $ArCH_2Ar$ protons indicates that there is no complete inversion of the calix[6]arene with the central aromatic ring passing through the annulus even at temperatures as high as 120 °C.

The structure of **7** was finally determined by X-ray crystallographic analysis (Figure 1).[15] This is the first X-ray analysis of an arenesulfenic acid[16] as well as of a calix[6]arene bridged by an aromatic unit. It has been found that **7** is solvated by one molecule of toluene and its conformation is the (**u**,u,d,d,d,u)[17] 1,2,3-alternate, which has been proposed for several bridged calix[6]arenes[5b,g] but has not been established by X-ray crystallography. As expected, the SOH functionality is directed into the cavity and shielded by the parent macrocycle, enjoying a situation apparently unfavorable for self-condensation. The central aromatic ring is arranged almost parallel to two of the nonbridged rings at a distance of ca. 3.5 Å. Unfortunately, the disordering at the bridging *m*-xylene unit has made it difficult to discuss the detailed structural parameters of the benzenesulfenic acid moiety at present.[18]

Scheme 2



(Ar' ≡ 2,6-bis(phenoxymethyl)phenyl)

The reaction of **7** with methyl propiolate in $CDCl_3$ at 50 °C afforded sulfoxide **8** (86%), although it took 16 h to be completed probably due to the strong shielding by the calix[6]arene macrocycle.

Sulfenic acid **7** has remarkable stability both in the crystalline state and in solution. Heating of **7** even at 80 °C for 4 h in $CDCl_3$ or toluene-d_8 resulted in only slight decomposition. In order to clarify the stabilizing effect of the calixarene framework, a control experiment was carried out using sulfoxide **9** which does not have macrocyclic structure (Scheme 2). Although ^{1}H NMR monitoring of the thermolysis of **9** at 80 °C in toluene-d_8 indicated the formation of sulfenic acid **10** along with its self-condensation product **11**,[19] only thiosulfinate **11** was obtained after silica gel chromatography (98%). These results clearly demonstrate that in the case of **7** encapsulation of the sulfenic acid functionality within the cavity of calix[6]arene effectively prevents its self-condensation, thus rendering it stable enough to be isolated.

In summary, the bridged calix[6]arene **1**, which can fix a functionality in such a way that it points into the cavity, presents a new mode of functionalization of calixarenes to furnish them with unprecedented properties. A variety of highly functionalized macrocycles would be developed by modifying its upper and lower rims and by making the most of its potential complexing ability. Investigations including the synthesis of a water-soluble derivative of **7** are currently in progress.

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Supporting Information Available: Synthetic procedures and spectral and analytical data for the new compounds **3**−**11** and variable-temperature ^{1}H NMR spectra of **7** (11 pages).

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(14) The confirmation of the assignment of the hydroxyl proton by a D_2O exchange experiment was unsuccessful because the signal at δ 2.39 appears only at high temperatures above ca. 100 °C, where, in the presence of water, some decomposition of **7** was observed.

(15) Crystallographic data for **7**·C_7H_8: $C_{61}H_{58}O_7S$, FW = 935.18, triclinic, space group $P\bar{1}$, a = 11.487(3) Å, b = 13.776(4) Å, c = 7.915(1) Å, α = 90.19(2)°, β = 89.89(2)°, γ = 105.29(2)°, V = 1208.2(5) Å^3, Z = 1, D_{calcd} = 1.285 g/cm^3, μ = 1.24 cm^{-1}. The intensity data were collected on a Rigaku AFC7R diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.710 69 Å), and the structure was solved by direct methods and expanded using Fourier techniques. The bridging *m*-xylene moiety including the SOH group exhibited inversional disorder with regard to the center of symmetry, while the structure of calix[6]arene moiety was found common to both of the disordered molecules. Some non-hydrogen atoms were refined anisotropically, while the rest were refined isotropically. Hydrogen atoms except for those of the SOH group and the solvent were included but not refined. The final cycle of full-matrix least-squares refinement was based on 1948 observed reflections [$I > 3.00\sigma(I)$] and 336 variable parameters with R (Rw) = 0.117 (0.135). The author has deposited atomic coordinates for **7** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(16) For X-ray analysis of an alkanesulfenic acid, two examples have been reported: (a) Kato, K. *Acta Crystallogr., Sect. B.* **1972**, *28*, 55−59. (b) Tripolt, R.; Belaj, F.; Nachbaur, E. *Z. Naturforsch., Sect. B* **1993**, *48*, 1212−1222. The X-ray structure of 9-triptycenesulfenic acid has also been determined, although not published: Nakamura, N. Private communication.

(17) For the conformational notations, see ref 5b.

(18) The preliminary results for the bond lengths (Å), bond angles (deg), and torsion angle (deg) around the sulfenic acid group: S(1)−O(1),1.58(3); S(1)−C(1), 1.75(3); O(1)−S(1)−C(1), 107(1); C(6)*−C(1)−S(1)−O(1), 72(2).

(19) The generation of **10** was confirmed by a trapping experiment with methyl propiolate.