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Synthesis of hybrid calix[6]arenes having both methylene and epithio bridging groups

Naoya Morohashi,* Tomohiro Ishiwata, Kazuaki Ito and Yoshihiro Ohba*

Department of Chemistry and Chemical Engineering, Faculty of Engineering, Yamagata University, 4-3-16, Jonan, Yonezawa, Yamagata 992-8510, Japan

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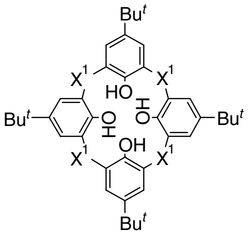
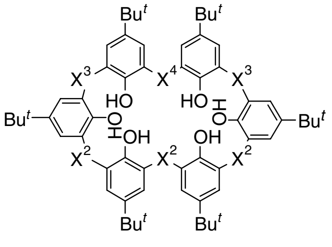
Abstract—Mono-, tri-, and tetra-thiacalix[6]arene were obtained by acid-catalyzed condensation of the corresponding tetramer and dimer derivatives of *p-tert*-butylphenol bridged by methylene or sulfur. Replacement of CH_2 by sulfur has significant effect on the properties of calix[6]arene such as the strength of intramolecular hydrogen bonding, inclusion ability toward organic molecules, and conformation properties.

Calixarenes are an extensively utilized molecular scaffold for synthetic receptors in supramolecular and molecular recognition chemistry.[1] This is mainly due to the availability of the basic macrocycles in substantial quantities from base-catalyzed condensation of *p*-alkylphenols with formaldehyde, in which proper choice of the established reaction conditions can provide preferentially particular macrocycles of the component phenol units ranging from $n = 4$ to 8.[2] The macrocycles are, in turn, amenable to various modifications at the hydroxyl groups (lower rim) and/or at the *para* positions (upper rim) of the phenolic units to bring about various functions.[1] Although modification of the bridging methylene groups or their replacement with heteroatoms is a highly intriguing method to alter the properties of the class compounds, there have been only few attempts because of the synthetic difficulties.

So, our interest was focused on the modification of the methylene moiety by changing to another group such as carbonyl, sulfur, or amino acids.[3] For example, we reported the replacement of any of the four bridging methylene groups of calix[4]arene by epithio groups via the stepwise joining of the component phenol units by methylene or epithio bonds followed by ultimate cyclization of the resulting acyclic tetramer.[4] Furthermore, replacement of all of the original methylene bridges between the aromatic units in calixarenes by sulfur atoms has been reported recently, leading to thiacalix[4]arenes (**TC4A**).[5] Since then, interest in the development of **TC4A** has been increasing because of their unique properties.[6] While many studies of **TC4A** have been reported, there have been only few for calix[6 or 8]arene having bridging sulfur groups due to the synthetic difficulties.[7]



C4A: $X^1 = CH_2$
TC4A: $X^1 = S$



C6A: $X^2 = X^3 = X^4 = CH_2$
1: $X^2 = X^3 = CH_2$, $X^4 = S$
2: $X^2 = S$, $X^3 = X^4 = CH_2$
3: $X^2 = S$, $X^3 = CH_2$, $X^4 = S$
TC6A: $X^2 = X^3 = X^4 = S$

Herein, we report the synthesis of novel hybrid calix[6]arenes **1**–**3**, in which part of the CH_2 group of calix[6]arene is replaced by sulfur, by acid-catalyzed condensation between bis(hydroxymethyl) dimer and tetramer of *p-tert*-butylphenol bridged by methylene or

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* Corresponding authors. Tel.: +81-238-26-3096; fax: +81-238-26-3413 (N.M.); tel.: +81-238-26-3095; fax: +81-238-26-3413 (Y.O.); e-mail addresses: n-moro@yz.yamagata-u.ac.jp; ohba@yz.yamagta-u.ac.jp

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sulfur. In order to investigate the effect of bridging sulfur groups on ability of calix[6]arenes as host molecules, physical properties and inclusion properties toward organic molecules of **1**–**3** were compared with those of **C6A** and **TC6A**.

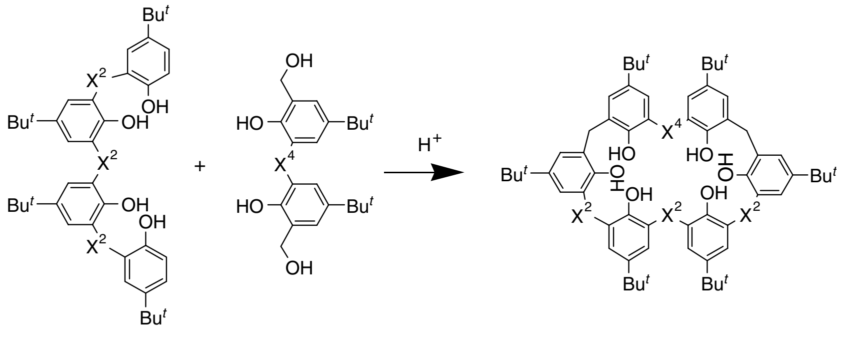
The sulfur-bridged and methylene-bridged analogs of *p*-*tert*-butylphenol (**4a**–**b** and **5a**–**b**), precursor for calix[6]arene, were prepared according to the literature procedure.[8] The reaction of the *p*-*tert*-phenol with SCl_2 in CH_2Cl_2 gave phenol–sulfur dimers followed by reaction with SCl_2 to yield all sulfur-bridged tetramer (**4b**). Bis(hydroxymehtyl) methylene- and sulfur-bridged *p*-*tert*-butylphenol dimer (**5a** and **5b**) were prepared by a bishydroxymethylation of the corresponding methylene- and sulfur-bridged phenol dimer, respectively. The tetramers (**4a**) have been synthesized by the condensation of *p*-*tert*-butylphenol with **5a**.

The condensation reactions of phenol dimer derivatives and phenol tetramer are summarized in Table 1.[9] The reaction of methylene-bridged phenol tetramer (**4a**) and bis(hydroxymethyl) sulfur-bridged phenol dimer (**5b**) in the presence of HCl in acetic acid under the highly diluted and refluxed conditions gave an insoluble product in both methanol and hexane (entry 1). The identity of the obtained product is confirmed by FAB-MS (m/z 1027 (M^+)) and ^1H NMR spectrum (500 MHz, $CDCl_3$, 296 K), which showed three singlets of *tert*-butyl protons at 1.23, 1.24, and 1.25 (each 18H), indicating the presence of three unequivalent phenol moieties in the compounds. This promised the formation of 1:1 cycloadduct of **4a** and **5b**, that is monothiacalix[6]arene (**1**). In this reaction, the formation of polymeric products was confirmed. Furthermore, the yield of **1** was improved to 34% by the reaction in the presence of *p*-TsOH in benzene under highly diluted and refluxed conditions (entry 2). This indicated that mild conditions could prevent the formation of polymeric products. In a similar manner, the condensation reactions of **4b** and **5a** gave one of trithiacalix[6]arene (**2**) in 44% yield (entry 4). Furthermore, one of tetrathiacalix[6]arene (**3**) could be obtained in 26% yield by the reaction of **4b** and **5b** (entry 6). The identity of the obtained cyclohexamers was confirmed by spectral data including ^1H NMR, IR, and FAB-MS.

One particularly distinctive feature of the calixarenes is the unusually low frequency of stretching vibration of the OH group in IR spectra and downfield shift of OH resonance of the ^1H NMR spectra, because of the strong intramolecular hydrogen bonding. In order to investigate the effect of bridging sulfur groups on intramolecular hydrogen bonding, IR spectra and OH resonance of ^1H NMR of **1**–**3** were compared with those of **C6A** and **TC6A** (Table 2). It may be said that the hydrogen bondings comprising a cyclic array of the phenolic OH groups exist in **1**–**3**. Interestingly, the IR spectra of **1**–**3** and **TC6A** display OH stretching bands in the 3183–3279 cm^{-1} region, while **C6A** shows the band at 3157 cm^{-1}; the bands move to higher frequency with increasing number of the sulfur bridge. Likewise, each sulfur bridge shifts the OH proton resonance to the higher field. These results suggested that replacement of the CH_2 group with sulfur weakens the hydrogen bonding, probably as a result of increasing cavity size of the calix[6]arene.

Table 3 lists the inclusion behavior of **C6A**, **TC6A**, and **1**–**3** studied by recrystallization from guest solvents.[10] It is noteworthy that synthesized calix[6]arenes have different inclusion properties compared with **C6A** and

Table 1. Condensation reaction between **4** and **5** to produce hybrid calix[6]arenes **1**–**3**



4a: $X^2 = CH_2$,
4b: X = S

5a: $X^4 = CH_2$,
5b: $X^4 = S$

1: $X^2 = CH_2$, $X^4 = S$
2: $X^2 = S$, $X^4 = CH_2$
3: $X^2 = X^4 = S$

Entry	Tetramer	Dimer	Time (h)	Procedure[9]	Product (yield, %)
1	**4a**	**5b**	18	A	**1** (12)
2			33	B	**1** (34)
3	**4b**	**5a**	59	A	**2** (12)
4			22	B	**2** (44)
5	**4b**	**5b**	28	A	**3** (10)
6			15	B	**3** (26)

Table 2. Spectroscopic data of OH group of calix[6]arenes

Calix[6]arene	IR: ν_{OH} (cm^{-1})[a]	^{1}H NMR: δ_{OH} (ppm)[d]
C6A	3157	10.5
1	3183	10.42, 10.24
2	3226	10.14, 9.97, 9.81
3	3273	9.67, 9.76, 9.90
TC6A[b]	3279[c]	9.18

[a] Solution of calix[6]arenes (5 mM) in $CHCl_3$–CS_2 (3:2) were used.
[b] Data of Ref. 7a.
[c] In KBr.
[d] In $CDCl_3$ at 296 K.

Table 3. The host versus guest (H:G) ratio in the inclusion complex formed with calix[6]arenes

Guest (G)	Host (H)				
	C6A	**1**	**2**	**3**	**TC6A**
Toluene	1:1	1:1	2:1	1:1	1:1
o-Xylene	1:1	1:1	1:1	1:1	1:1
m-Xylene	1:1	2:3	2:1	1:1	1:1
p-Xylene	1:1	1:1	3:1	2:3	1:2

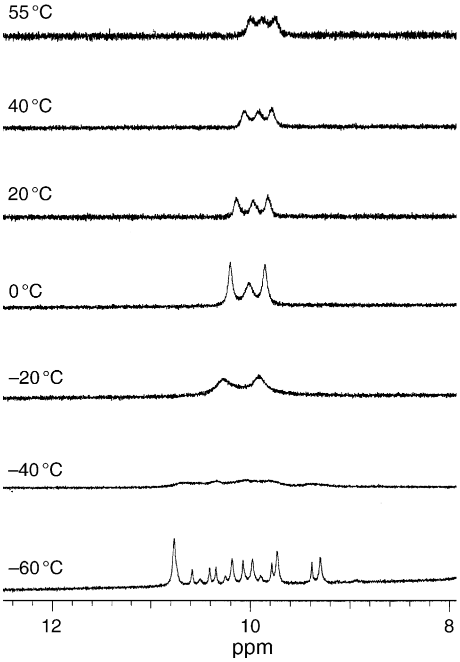
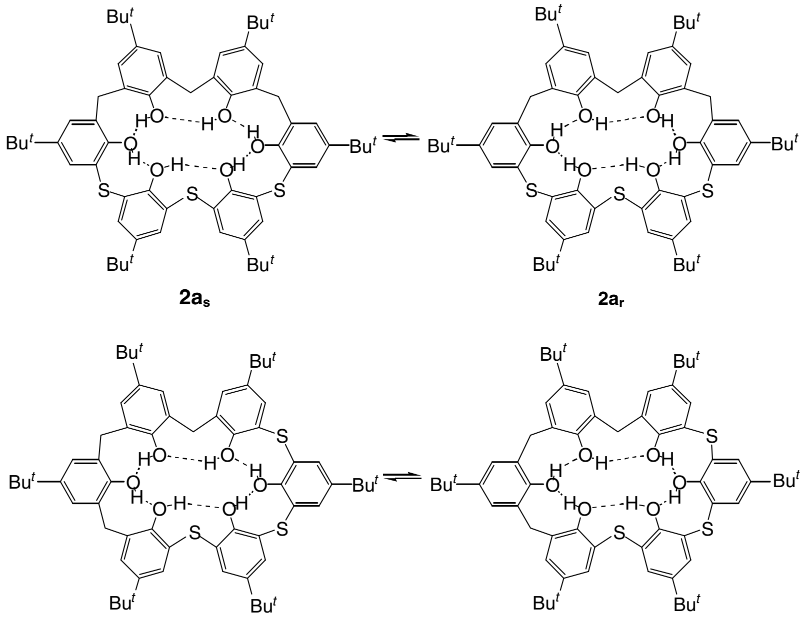


Figure 1. Partial ^{1}H NMR spectra of the OH protons in **2** in $CDCl_3$ at variable temperatures at 500 MHz.

TC6A, in which guests were included mostly in 1:1 manner. Particularly, in the case of trithiacalix[6]arene **2**, the stoichiometric ratios with isomeric xylenes range from 1:1 to 3:1. This result suggested that **2** should form different crystalline inclusion complex according to isomer of xylene. Furthermore, the inclusion selectivity of **2** for xylene isomers was examined. Recrystallization of **2** from 1:1:1 mixture of *o*-, *m*-, and *p*-xylene afford 1:1 (host:guest) complex, in which the ratio of isomers was 68:12:20 (*o*:*m*:*p*), indicating that **2** includes preferentially *o*-xylene among xylene isomers. This selectively could not be observed in the case of **C6A**, **1**, and **3**. Interestingly, **2** and **3** have poor solubility in various solvents except toluene, xylene, and CS_2, whereas **C6A**, **1**, and **TC6A** can be solved in most solvents such as $CHCl_3$, CH_2Cl_2, and benzene. We realized that the replacement of CH_2 with sulfur has also significant effect on not only inclusion properties but also solubility of calix[6]arenes.



2a$_s$ **2a**$_r$

2b$_s$ **2b**$_r$

Figure 2. Possible structure of trithiacalix[6]arene **2** adopting pinched cone conformation. The term r and s represent clockwise and counterclockwise hydrogen bonding array, respectively.

In order to clarify the reason for appearance of the above-mentioned inclusion properties, the conformational properties of trithiacalix[6]arene **2** were investigated by using variable temperature ^{1}H NMR experiments. The OH signals of **2** were observed as three broad singlets, 9.81, 9.97, and 10.14 (each 2H), at ambient temperature. Cooling the temperature to −60 °C, OH signals of **2** gave many singlet peaks of different intensity (Fig. 1). In contrast, the methylene signals of **2** resulted in signal broading at low temperature, but did not split even at −60 °C in $CHCl_3$. It is well known that in both the crystal state and solution, **C6A** adopts pinched cone conformation, in which two methylene groups locate inward from the cavity and OH groups form circular intramolecular hydrogen bonding to produce three unequivalent phenol moieties.[11] Actually, OH resonance on the ^{1}H NMR spectrum of **C6A** changes from one singlet at 20 °C to three singlets at −60 °C due to the freezing of inversion of conformation and switching of the hydrogen bondings array. So, our result suggested that **2** adopts several stable conformation at low temperature due to the decrease of molecular symmetry by introducing sulfur groups. This is explicable by the following hypothesis. If **2** adopt pinched cone conformation as stable conformation same as **C6A**, there are two possible conformer (**2a** and **2b**) due to the arrangement of bridging atoms respect to two bridging groups locating inward from the cavity (Fig. 2). Furthermore, it is clear that two unequivalent array of hydrogen bonding (**2b**$_r$ and **2b**$_s$) exist in dissymmetry conformation **2b**, whereas **2a**$_r$ and **2a**$_s$ are equal because of symmetry. The existence of these conformer of **2** should cause complex ^{1}H NMR spectrum at low temperature. This interesting nonuniformity may be the reason why **2** have strange inclusion properties among calix[6]arenes.

In conclusion, condensation reaction between bis(hydroxymethyl) dimer of *p-tert*-butylphenol and tetramer of *p-tert*-butylphenol could afford new hybrid calix[6]arene, in which part of the CH_2 group of calix[6]arene is replaced by an epithio group. The replacement of CH_2 with sulfur has significant effect on conformational properties, strength of intramolecular hydrogen bonding, and inclusion property of calix[6]arene.

Acknowledgements

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9. Procedure A: Both a solution of **4** (0.2 mmol) in acetic acid (50 mmol) and a solution of **5** (0.2 mmol) were added dropwise slowly to refluxing acetic acid (110 mL) containing concd HCl (4 mL). Concd HCl (4 mL) was added to reaction mixture every 4 h. The mixture was stirred under reflux until loss of substrate, which was monitored by TLC. The acetic acid was evaporated to dryness. The solid residue was triturated well with MeOH and hexane to give pure product.

   Procedure B: Both a solution of **4** (0.2 mmol) in benzene (50 mL) and a solution of **5** (0.2 mmol) in benzene were added dropwise to refluxing benzene (80 mL) containing *p*-toluenesulfonic acid (catalytic amount). The mixture was stirred under reflux; the water produced during the reaction was removed by azeotropic distillation using a Dean–Stark condenser. The benzene was evaporated to dryness. The solid residue was triturated well with MeOH and hexane to give pure product.

   Compound **1**: mp > 300 °C; IR (cm^{-1}, KBr): 3149 (OH), 2962 (CH); ^{1}H NMR (500 MHz, $CDCl_3$): 1.23 (s, 18H, $C(CH_3)_3$), 1.24 (s, 18H, $C(CH_3)_3$), 1.27 (s, 18H, $C(CH_3)_3$), 3.89 (br, 10H, CH_2), 7.12–7.53 (m, 12H, ArH), 10.24 (s, 4H, OH), 10.42 (s, 2H, OH); FAB-MS (*m/z*): 991(M^+).

   Compound **2**: mp > 300 °C; IR (cm^{-1}, KBr): 3205 (OH), 2962 (CH); ^{1}H NMR (500 MHz, $CDCl_3$): 1.23 (s, 18H, $C(CH_3)_3$), 1.24 (s, 18H, $C(CH_3)_3$), 1.25 (s, 18H, $C(CH_3)_3$), 3.95 (br, 6H, CH_2), 7.14–7.65 (m, 12H, ArH), 9.81 (s, 2H, OH), 9.97 (s, 2H, OH), 10.14 (s, 2H, OH); FAB-MS (*m/z*): 1027 (M^+).

   Compound **3**: mp > 300 °C; IR (cm^{-1}, KBr): 3239 (OH), 2962 (CH); ^{1}H NMR (500 MHz, $CDCl_3$): 1.23 (s, 18H, $C(CH_3)_3$), 1.26 (s, 18H, $C(CH_3)_3$), 3.95 (br, 4H, CH_2), 7.22–7.62 (m, 12H, ArH), 9.67 (s, 2H, OH), 9.76 (s, 2H, OH), 9.90 (s, 2H, OH); FAB-MS (*m/z*): 1044 (M^+).
10. Host calix[6]arenes was added to guest solvent being heated at the boiling point until it was saturated. The solution was then allowed to cool to rt to recrystallize. The precipitated crystals were filtered off, dried in vacuo (2–4 mmHg) at rt for 1 h, and then subjected to ^{1}H NMR to determine the content of the guest molecules in the crystal.
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