

## TUNING OF THE CAVITY OF WATER-SOLUBLE THIALICALIX[4]ARENE FOR THE CONTROL OF INCLUSION ABILITY TOWARD WATER-MISCIBLE ORGANIC MOLECULES

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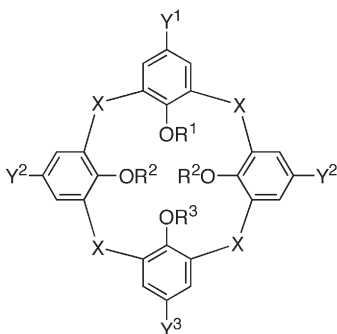
*Dedicated to Professor Ivan Stibor on the occasion of his 60th birthday in recognition of his outstanding contributions to the area of supramolecular chemistry.*

Inclusion abilities of water-soluble thiacalix[4]arenetetrasulfonate (**3**) and mono-*O*-carboxymethylated derivatives **5** and **6** toward water-miscible organic molecules such as alcohols, ketones, and nitriles in water were investigated by <sup>1</sup>H NMR. The limit chemical shift change of the guest upon inclusion in the host suggested that the hosts regioselectively encapsulate the guests from the side of aliphatic moiety. Large guests such as pentan-1-ol showed folding of the alkyl chain to be included inside the cavity. On the other hand, mono-*O*-substituted **6** included a guest molecule less deep in the cavity than **3** did. Binding constants (*K*) of **3** toward guest molecules increased with hydrophobicity of the guest, suggesting that hydrophobic effect plays a main role for the complexation. On the contrary, mono-*O*-carboxymethyl derivatives **5** and **6** showed the opposite dependency of stability on hydrophobicity; higher affinities toward less hydrophobic guests. Among the guests examined, the smallest entities such as CH<sub>3</sub>OH and CH<sub>3</sub>CN were best included in **5** with the highest binding constant ever reported (*K* > 10<sup>2</sup> M<sup>-1</sup>). It was concluded that introduction of the carboxymethyl group into one of the phenolic OH of thiacalix[4]arene led to tuning of the cavity shape for stereospecific inclusion of small guests. The tuning of cavity by the *O*-alkylation was actually confirmed by X-ray crystal analysis of a complex of **5** with diethyl ketone.

**Keywords:** Calixarenes; Thiacalixarenes; Inclusion; Alcohols; Ketones; Hydrophobic interactions; Molecular recognition; NMR spectroscopy; X-ray diffraction.

Thiacalix[4]arenes (e.g. **1**)<sup>1</sup>, in which methylene bridges of calix[4]arenes (e.g. **2**) are replaced with sulfides, have revealed themselves to be not a simple substitute for the “classical” **2** but a new molecular scaffold with intrin-

sic characteristic features originating from the bridging sulfur<sup>2</sup>. For example, coordination to metal ions by the ligation of sulfide moiety is one of the distinctive features of thiacalix[4]arenes, which is not attainable by methylene-bridged **2**<sup>3</sup>. Furthermore, water-soluble thiacalix[4]arene **3** is able to include a wide variety of molecules ranging from halomethanes<sup>4</sup> to substituted benzenes in the hydrophobic cavity<sup>5</sup>. Recently, it has been shown that thiacalix[4]arene **3** forms inclusion complexes with water-miscible molecules such as alcohols, ketones, cyclic ethers, DMF, and DMSO<sup>6</sup>. These complexes can be precipitated by salting out, retaining the guest molecule in the cavity. In general, the content of the guest in **3**-guest complexes was approximately 100 mole %, which is higher than that obtained by calix[4]arenetetrasulfonate (**4**)-guest complexes. This may be ascribed to the enlarged cavity of thiacalix scaffold (ca. 15%<sup>1b</sup>) due to -S- linkage instead of -CH<sub>2</sub>- linkage of **4**. Exceptions were inclusion of small guest molecules such as methanol and acetonitrile, where these were better included by calix **4** than thiacalix **3**. This seems to suggest that fitting of the cavity size of a host with the bulk of a guest plays an important role in



<b>1</b>	X = S	R <sup>1-3</sup> = H	Y <sup>1-3</sup> = Bu <sup>+</sup>
<b>2</b>	X = CH <sub>2</sub>	R <sup>1-3</sup> = H	Y <sup>1-3</sup> = Bu <sup>+</sup>
<b>3</b>	X = S	R <sup>1-3</sup> = H	Y <sup>1-3</sup> = SO <sub>3</sub> <sup>-</sup>
<b>4</b>	X = CH <sub>2</sub>	R <sup>1-3</sup> = H	Y <sup>1-3</sup> = SO <sub>3</sub> <sup>-</sup>
<b>5</b>	X = S	R <sup>1</sup> = CH <sub>2</sub> COOH, R <sup>2,3</sup> = H	Y <sup>1</sup> = Bu <sup>+</sup> , Y <sup>2,3</sup> = SO <sub>3</sub> <sup>-</sup>
<b>6</b>	X = S	R <sup>1</sup> = CH <sub>2</sub> COOH, R <sup>2,3</sup> = H	Y <sup>1</sup> = H, Y <sup>2,3</sup> = SO <sub>3</sub> <sup>-</sup>
<b>7</b>	X = S	R <sup>1-3</sup> = CH <sub>2</sub> COOEt	Y <sup>1-3</sup> = Bu <sup>+</sup>
<b>8</b>	X = S	R <sup>1,3</sup> = CH <sub>2</sub> COOEt, R <sup>2</sup> = H	Y <sup>1-3</sup> = Bu <sup>+</sup>
<b>9</b>	X = S	R <sup>1</sup> = CH <sub>2</sub> COOEt, R <sup>2,3</sup> = H	Y <sup>1-3</sup> = Bu <sup>+</sup>
<b>10</b>	X = S	R <sup>1</sup> = CH <sub>2</sub> COOH, R <sup>2,3</sup> = H	Y <sup>1-3</sup> = SO <sub>3</sub> <sup>-</sup>
<b>11</b>	X = S	R <sup>1-3</sup> = H	Y <sup>1-3</sup> = H
<b>12</b>	X = S	R <sup>1</sup> = CH <sub>2</sub> COOEt, R <sup>2,3</sup> = H	Y <sup>1-3</sup> = H
<b>13</b>	X = S	R <sup>1-3</sup> = CH <sub>2</sub> COOH	Y <sup>1-3</sup> = SO <sub>3</sub> <sup>-</sup>
<b>14</b>	X = S	R <sup>1-3</sup> = CH <sub>2</sub> COOH	Y <sup>1-3</sup> = Bu <sup>+</sup>
<b>15</b>	X = CH <sub>2</sub>	R <sup>1-3</sup> = CH <sub>2</sub> COOH	Y <sup>1-3</sup> = H
<b>16</b>	X = CH <sub>2</sub>	R <sup>1-3</sup> = CH <sub>2</sub> COO <sup>-</sup>	Y <sup>1-3</sup> = SO <sub>3</sub> <sup>-</sup>

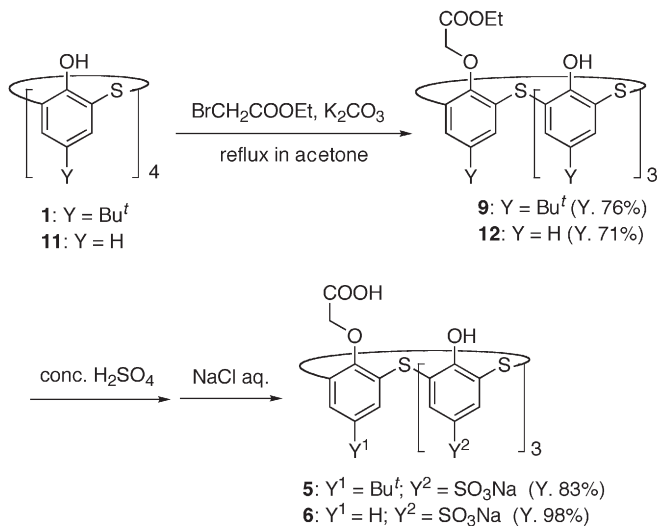
Thiacalix[4]arenes and calix[4]arenes

the encapsulation. To construct a cavity of a smaller available space for the complexation, herein we designed mono-*O*-carboxymethylated thiacalix[4]arenes **5**, **6** with the intention of tuning the cavity shape and/or size as well as suppression of ring inversion due to the steric repulsion between the substituent and the distal phenyl group. The inclusion behaviors of mono-*O*-alkylated derivatives **5** and **6** were compared with that of parent host **3** to obtain suggestive information concerning the complexation mechanism and the effect of the mono-*O*-alkylation on the complexation behavior.

## RESULTS AND DISCUSSION

### Synthesis

Previously, we reported that tetra- (**7**)<sup>7</sup> and 1,3-di-*O*-alkylthiacalix[4]arenes **8**<sup>8</sup> can selectively be obtained by the controlled alkylation of *p*-*tert*-butylthiacalix[4]arene (**1**) with BrCH<sub>2</sub>COOEt. Herein we were pleased to find that the use of 1.1 equivalent of BrCH<sub>2</sub>COOEt for **1** afforded mono-*O*-alkylated **9** in a satisfactory yield (Scheme 1). The direct sulfonation protocol for **1** to **3** was employed in the sulfonation of mono-*O*-ether **9** but without heating; treatment of **9** with concentrated H<sub>2</sub>SO<sub>4</sub> at ambient temperature gave sulfonate **5** in 83% yield with concomitant hydrolysis of ethyl es-



SCHEME 1

Synthesis of water-soluble mono-*O*-alkylthiacalix[4]arenes (**5** and **6**)

ter moiety to carboxyl group. Notably, the sulfonation took place at the three, instead of four, para positions with one *tert*-butyl group remaining intact at Y<sup>1</sup>, the position of which was confirmed by X-ray crystallographic analysis (*vide infra*).

In an attempted synthesis of tetra-*p*-sulfonated **10**, we applied the same protocol to de-*tert*-butylated analogue<sup>9</sup> **11** consisting of mono-*O*-alkylation followed by sulfonation. The monoalkylation of **11** proceeded smoothly to give **12** in a comparable yield to **9**. The direct sulfonation, however, resulted in obtaining trisubstituted **6** in 98% yield, in which sulfonation took place exclusively at the para positions of the unsubstituted phenolic OH. The regioselectivity suggests stronger electron-donating effect of OH group than the one of carboxymethoxy group.

Further attempts at complete introduction of four sulfonate groups to **9** and **12** by sulfonation at elevated temperature, 80 °C, resulted in obtaining only trisulfonated **5** and **6** in lower yields. Furthermore, treatment of tetra-*O*-alkylated **7** with concentrated H<sub>2</sub>SO<sub>4</sub> resulted in hydrolysis of the ethyl ester moiety to carboxyl group to give **14** quantitatively without indication of the formation of detectable amount of tetrasulfonate **13**. This sharply contrasts with the sulfonation of *O*-alkyl derivatives of conventional calix[4]arene **15** by concentrated H<sub>2</sub>SO<sub>4</sub>, where sulfonation takes places at all the four para positions to give **16**<sup>10</sup>. The difference in the reactivity might be attributed to the electron density of aromatic rings: Thiacalixarenes have more electron-deficient  $\pi$  systems<sup>11</sup> due to a resonance-like interaction of vacant 3d orbital of sulfide linkages with the  $\pi$  orbital of adjacent aromatic rings to delocalize negative charges<sup>12</sup>. Therefore, decrease in the electron density of aromatic ring by introduction of ethoxycarbonylmethyl group at the phenolic OH further reduced the reactivity toward the electrophile, SO<sub>3</sub>, resulting in selective sulfonation at the para position of free phenolic groups in thiacalixarenes **9** and **12**. On the other hand, the benzene ring of conventional calix[4]arene is still electron rich even after tetra-*O*-etherification (to **15**) to keep reactivity with the electrophile.

### NMR Investigations

<sup>1</sup>H NMR spectra of the free hosts (**5** and **6**) per se showed no change in the <sup>1</sup>H resonance signals in the concentration range of 1–50 mmol/l, suggesting that selfassociation or micelle formation of the hosts could be ruled out within the range. The inclusion abilities of **3**, **5** and **6** toward water-miscible compounds such as alcohols, ketones, and nitriles were investi-

gated by NMR titration of a host against a fixed amount of guest in  $D_2O$  solution (pD = 7.3 adjusted by 0.1 M phosphate buffer). In all combinations of the host–guest system, the host to guest stoichiometry of the inclusion complex was confirmed to be 1:1 by Job's plot. Therefore the inclusion equilibrium is written as



where H, G, and H·G are free host, free guest, and 1:1 host–guest complex, respectively. In all cases, the guest protons were observed as a single resonance due to fast exchange between free guest (G) and complexed one (H·G) on the NMR time scale. Upon titrating with **3** and **6**, the resonance signals of guests showed distinctive upfield shifts, suggesting that inclusion complexes were formed in which a guest was encapsulated into the cavity of the host to be shielded. For example, the changes of chemical shifts,  $\Delta\delta$ , of  $n\text{-C}_3\text{H}_7\text{OH}$  upon addition of **3** are shown in Fig. 1, where

$$\Delta\delta = \delta_{G,\text{obsd}} - \delta_{G,\text{free}} \quad (2)$$

and negative value of  $\Delta\delta$  means an upfield shift of resonance signals. Estimation of the association constants ( $K$ ) and limit chemical shift changes ( $\Delta\delta_{\text{lim}}$ ) of the guest were performed through non-linear least square fitting of  $\Delta\delta$  vs  $[H]_{\text{Total}}$  curve<sup>13</sup>. Here,

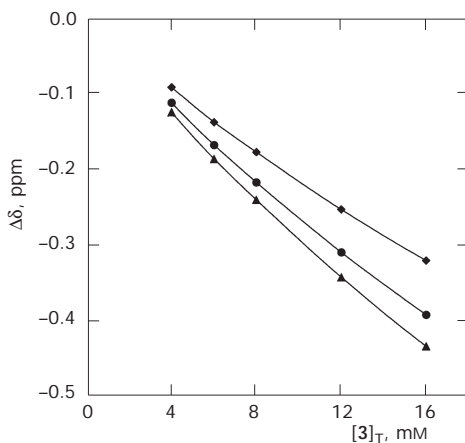


FIG. 1

Chemical shift changes ( $\Delta\delta$ ) of  $n\text{-C}_3\text{H}_7\text{OH}$  versus  $[3]_T$  in  $D_2O$  at pD = 7.3, 300 K. ◆  $\text{CH}_2\text{OH}$ , ●  $\text{CH}_2$ , ▲  $\text{CH}_3$

$$K = \frac{[H \cdot G]}{[H][G]} \quad (3)$$

$$\Delta\delta_{\text{lim}} = \delta_{\text{G, in H-G complex}} - \delta_{\text{G, free}} \quad (4)$$

The estimated values of  $\Delta\delta_{\text{lim}}$  and  $\log K$  are shown in Tables I and II, respectively. In the case of inclusion by **5**,  $\Delta\delta$  values were so small ( $-0.02$  to  $-0.3$  ppm) that interpretation of the  $\Delta\delta_{\text{lim}}$  values among guest protons and species is not attempted.

TABLE I  
The limit  $^1\text{H}$  NMR chemical shift change ( $\Delta\delta_{\text{lim}}$ ) of water-miscible molecules in the complexation with **3** and **6**

Guest	<b>3</b>					<b>6</b>				
	H <sub>a</sub>	H <sub>b</sub>	H <sub>c</sub>	H <sub>d</sub>	H <sub>e</sub>	H <sub>a</sub>	H <sub>b</sub>	H <sub>c</sub>	H <sub>d</sub>	H <sub>e</sub>
<sup>a</sup> CH <sub>3</sub> OH	-0.22					-0.08				
<sup>a</sup> <sup>b</sup> CH <sub>3</sub> CH <sub>2</sub> OH	-1.60	-1.38				-0.28	-0.26			
<sup>a</sup> <sup>b</sup> <sup>c</sup> CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> OH	-2.40	-2.19	-1.77			-0.67	-0.56	-0.51		
<sup>a</sup> <sup>b</sup> <sup>c</sup> <sup>d</sup> CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	-2.26	-2.07	-1.80	-1.35		-0.86	-1.09	-0.76	-0.53	
<sup>a</sup> <sup>b</sup> <sup>c</sup> <sup>d</sup> <sup>e</sup> CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	-1.69	-2.07	-1.41	-1.28	-0.89	-2.25	<sup>a</sup>	<sup>a</sup>	<sup>a</sup>	-2.25
<sup>a</sup> <sup>b</sup> CH <sub>3</sub> CH(OH)CH <sub>3</sub>	-2.07	-1.72				-0.34	-0.23			
<sup>a</sup> <sup>b</sup> <sup>c</sup> <sup>d</sup> CH <sub>3</sub> CH <sub>2</sub> CH(OH)CH <sub>3</sub>	-1.77	-1.73	-1.43	-1.50		-0.75	-0.86	-0.76	-0.68	
<sup>a</sup> CH <sub>3</sub> COCH <sub>3</sub>	-1.90					-0.32				
<sup>a</sup> <sup>b</sup> <sup>c</sup> CH <sub>3</sub> CH <sub>2</sub> COCH <sub>3</sub>	-1.80	-2.30	-1.77			-1.45	-1.81	-1.13		
<sup>a</sup> <sup>b</sup> CH <sub>3</sub> CH <sub>2</sub> COCH <sub>2</sub> CH <sub>3</sub>	-1.29	-1.98				-0.96	-1.80			
<sup>a</sup> CH <sub>3</sub> CN	-2.42					-0.24				
<sup>a</sup> <sup>b</sup> CH <sub>3</sub> CH <sub>2</sub> CN	-2.29	-2.51				-0.65	-0.76			
<sup>a</sup> <sup>b</sup> <sup>c</sup> CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CN	-2.01	-2.11	-2.11			-1.26	-1.31	-1.39		

<sup>a</sup> The limit chemical shift change could not be estimated due to overlap of the absorption signals.

### Orientation of the Included Guests

In the complexation of **3** with *n*-alkyl alcohols except *n*-C<sub>5</sub>H<sub>11</sub>OH, the protons on the terminal CH<sub>3</sub> (at *a*) exhibited the largest  $|\Delta\delta_{\text{lim}}|$  values, whereas the protons on CH<sub>2</sub> groups exhibited gradual decrease in the value depending on the position from methyl side (*b*) to OH side (*c*, *d*, ...) (Table I). This clearly indicates that the guests were regioselectively encapsulated into the cavity through aliphatic chain rather than OH group (Scheme 2a), which may be partly due to the hydrophobic interaction between the nonpolar cavity of **3** and aliphatic group of the guest and also due to polar OH group preferring the bulk water phase to be hydrated. In the *n*-C<sub>5</sub>H<sub>11</sub>OH system, on the other hand,  $|\Delta\delta_{\text{lim}}|$  values decreased in the order  $H_b > H_a > H_c > H_d > H_e$ , indicating that CH<sub>2</sub> proton at *b* is included more deep in the cavity than terminal CH<sub>3</sub> group. In this case, the depth of the cavity of **3** might not be sufficient to accommodate *n*-pentyl group with linear (or more precisely,

TABLE II

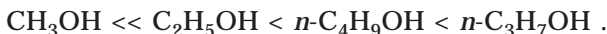
Association constants ( $K$ , M<sup>-1</sup>) in the complexation of **3**, **5** and **6** with water-miscible molecules, and partition coefficient of a guest between octan-1-ol and water (log  $P_o$ )

Guest	log $K$			log $P_o$ <sup>a</sup>
	<b>3</b>	<b>5</b>	<b>6</b>	
CH <sub>3</sub> OH	0.65	2.16	1.48	-0.82
C <sub>2</sub> H <sub>5</sub> OH	0.88	1.90	0.94	-0.32
<i>n</i> -C <sub>3</sub> H <sub>7</sub> OH	1.15	1.66	0.85	0.34
<i>n</i> -C <sub>4</sub> H <sub>9</sub> OH	1.48	1.39	0.78	0.88
<i>n</i> -C <sub>5</sub> H <sub>11</sub> OH	1.77	1.19	0.61	1.40
CH <sub>3</sub> CH(OH)CH <sub>3</sub>	1.00	2.08	1.17	0.06
CH <sub>3</sub> CH(OH)C <sub>2</sub> H <sub>5</sub>	1.41	1.76	0.90	0.83
CH <sub>3</sub> COCH <sub>3</sub>	1.10	1.93	1.40	-0.24
CH <sub>3</sub> COC <sub>2</sub> H <sub>5</sub>	1.39	1.85	0.93	0.29
C <sub>2</sub> H <sub>5</sub> COC <sub>2</sub> H <sub>5</sub>	1.70	1.70	0.87	
CH <sub>3</sub> CN	0.87	2.31	1.22	-0.34
C <sub>2</sub> H <sub>5</sub> CN	1.20	2.07	0.97	0.16
<i>n</i> -C <sub>3</sub> H <sub>7</sub> CN	1.66	1.78	0.87	

<sup>a</sup> Lit.<sup>15</sup>

zigzag) conformation, which seemed to adopt V-shaped one folding at the *b* methylene group.

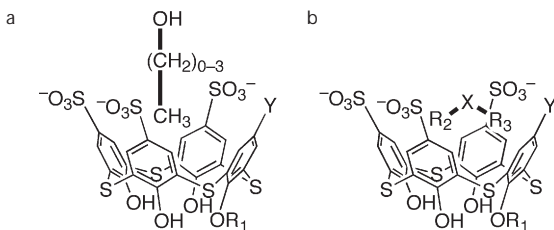
Although the terminal  $\text{CH}_3$  is commonly shown to be included more deeply in the cavity than  $\text{CH}_2$  moieties except the case of pentan-1-ol, the  $|\Delta\delta_{\text{lim}}|$  value for terminal  $\text{CH}_3$  differs among the *n*-alkyl alcohols in the order:



This suggests that *n*- $\text{C}_3\text{H}_7\text{OH}$  is nearly the right size for thiacalix[4]arene **3** to accommodate the methyl terminal at the aromatic center. Also, the methyl moiety of smaller *n*-alkyl alcohols is not able to penetrate into the cavity, which may be attributed to the solvation of OH group with bulk water and displacement of the guest outside the cavity. This should lead to the smaller association constants of the relevant guests with **3** (vide infra). On the other hand, butan-1-ol as its straight form must penetrate deeper into the cavity to form the most stable complex, forcing the methyl moiety to locate away from the aromatic center to have smaller  $|\Delta\delta_{\text{lim}}|$  value.

The  $|\Delta\delta_{\text{lim}}|$  values of branched alcohols in the complexes of **3** decreased in the order  $H_a > H_b$  for isopropyl alcohol and  $H_a \geq H_b > H_d \geq H_c$  for *sec*-butyl alcohol, respectively (Table I). Since  $\text{CH}(\text{OH})$  proton is least shielded in each case, it might be conceivable that both aliphatic chains of the guests are encapsulated into the cavity and OH group points away from the cavity of **3** as illustrated in Scheme 2b.

In the complexation of ketones with **3**, the difference in the  $|\Delta\delta_{\text{lim}}|$  values of  $\text{CH}_3\text{COC}_2\text{H}_5$  and  $\text{C}_2\text{H}_5\text{COC}_2\text{H}_5$  was distinctly in the order  $H_b > H_a \geq H_c$  and  $H_b > H_a$  (Table I), respectively. This indicates that  $\text{CH}_2$  group rather than terminal methyl group is most deeply included into the cavity, while the carbonyl group directs outwards the cavity. The inclusion manner is



SCHEME 2

Binding manner of hosts toward *n*-alkyl alcohols (a) and branched alcohols and ketones (b).  $\text{R}^1 = \text{H}$  or  $\text{CH}_2\text{COOH}$ ;  $\text{R}^2$ ,  $\text{R}^3 = \text{CH}_3$  or  $\text{CH}_3\text{CH}_2$ ;  $\text{X} = \text{CH}(\text{OH})$  or  $\text{C}=\text{O}$



consistent with the one of diethyl ketone in **5** as evidenced by crystallographic analysis (vide infra). In case of acetone, inclusion from both sides of aliphatic chains has already been shown by X-ray crystallography<sup>6</sup>. On the whole, it is concluded that a guest tends to orient the aliphatic chain(s) to hydrophobic cavity of **3** rather than to bulk water. This is also supported by the fact that a longer group is more deeply included than a shorter one in the complexation of  $\text{CH}_3\text{COC}_2\text{H}_5$  and  $\text{CH}_3\text{CH}(\text{OH})\text{C}_2\text{H}_5$  bearing aliphatic chains of different lengths (Table I).

Nitriles exhibited large  $|\Delta\delta_{\text{lim}}|$  values comparable to alcohols. Judging from the dependence of the  $|\Delta\delta_{\text{lim}}|$  value on the position, the methylene (at *b*) of propionitrile should be accommodated more deeply in the cavity than terminal methyl (at *a*). This may be because of the electron-withdrawing nature of the CN group, which should induce positive charge on the methylene hydrogen to interact with  $\pi$ -basic cavity of **3** (i.e., CH- $\pi$  interaction)<sup>14</sup>. In the case of butanenitrile, the difference in  $|\Delta\delta_{\text{lim}}|$  value among the positions (*a*-*c*) is so subtle that there seems no regioselectivity in the inclusion manner. This may be due to the competition between CH- $\sigma$  interaction to prefer the inclusion from *c* position and hydrophobic interaction to prefer inclusion from *a* position.

In the case of inclusion by mono-*O*-functionalized **6**, the estimated  $|\Delta\delta_{\text{lim}}|$  values for almost all the guests are smaller than those obtained for **3** (Table I), indicating that **6** has a narrower cavity and includes the guest more shallowly than **3** does. However, the dependence of  $|\Delta\delta_{\text{lim}}|$  values on the position of guest followed the same tendency as shown by the case of host **3**. Exceptions were found in inclusion of *n*- and *sec*-butyl alcohols by **6**: In the case of butan-1-ol,  $|\Delta\delta_{\text{lim}}|$  values decreased in the order of  $H_b > H_a > H_c > H_d$ , indicating that  $\text{CH}_2$  protons ( $H_b$ ) pointed into the cavity more deeply than terminal  $\text{CH}_3$  group ( $H_a$ ) did with the folding of butan-1-ol at *b*. This is another evidence that the available space of the cavity of **6** for the inclusion is smaller than that of **3**, considering the fact that unsubstituted **3** was able to accommodate butan-1-ol without folding of the conformation.

In the case of inclusion of *sec*-butyl alcohol by **6**, terminal  $\text{CH}_3$  group (at *a*) of the ethyl group points more outside the cavity than  $\text{CH}_2$  protons (at *b*), and CH (at *c*) moiety is more shielded than adjacent  $\text{CH}_3$  group (at *d*). Moreover, the difference between each  $|\Delta\delta_{\text{lim}}|$  value is small, suggesting that penetration of *sec*-butyl alcohol into the cavity of **6** is far shallower than that of *n*-butyl counterpart. The observation is in contrast with that of the complexation with **3**, in which **3** can accommodate both methyl and ethyl groups of  $\text{CH}_3\text{CH}(\text{OH})\text{C}_2\text{H}_5$  in the cavity. In conclusion, the mono-

*O*-alkylation of thiacalix[4]arene tuned the cavity to be narrower to provide guest molecules more constrained space.

### Inclusion Abilities

Table II shows the binding constants ( $K$ ) of each host toward water-miscible guest molecules. The parent compound **3** showed larger  $K$  values toward *n*-alkyl alcohols as the aliphatic chain becomes longer. A similar tendency was observed in the complexation with other guest species such as branched alkyl alcohols, ketones, and nitriles. It is apparent that the  $\log K$  value depends on hydrophobicity of the guest molecules. This is clearly demonstrated by the correlation between  $\log K$  value and partition coefficient of a guest between octan-1-ol and water ( $P_o$ )<sup>15</sup>, which is a measure of hydrophobicity (Fig. 2, solid line:  $R^2 = 0.9225$ ). The good correlation suggests that hydrophobic effect<sup>16</sup> plays a predominant role in the formation of the inclusion complexes of **3** in water. In addition, when limited to alcoholic guest systems the correlation led to a higher value of  $R^2 = 0.9893$  as shown by dashed line in Fig. 2.

In contrast to parent **3**, mono-*O*-substituted hosts **5** and **6** showed the opposite affinities toward guest molecules depending on the size (Table II). In each class of guest species, **5** and **6** showed higher affinity towards smaller molecules. In particular, the complexation abilities of **5** and **6** toward

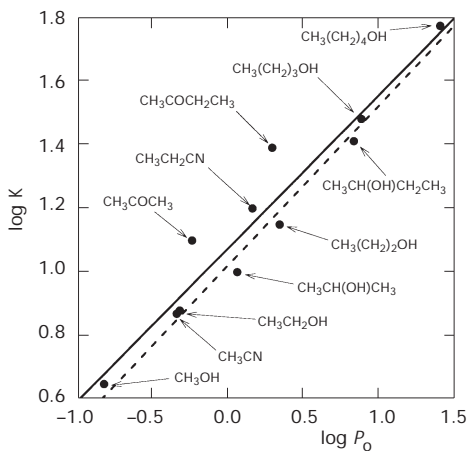


FIG. 2

The correlation between binding constant ( $K$ ) of **3** with water-miscible guest molecules versus partition constant ( $P_o$ ) of guest between water–octan-1-ol phases at pD = 7.3. Solid line: for all guest species;  $R^2 = 0.9225$ . Dashed line: for alcohols only;  $R^2 = 0.9893$

$\text{CH}_3\text{OH}$  were large:  $K = 10^{2.16}$  and  $10^{1.48} \text{ M}^{-1}$ , respectively. To the best of our knowledge, these are the first examples of host molecule having binding constant  $K$  toward  $\text{CH}_3\text{OH}$  in water more than  $10 \text{ M}^{-1}$ <sup>17</sup>. The correlation between  $\log K$  and  $\log P_o$  values for inclusion systems of *n*-alkyl alcohols with **5** and **6** as well as with **3** (Fig. 3) clearly shows that the stability of the complex of **5** and **6** decreased as aliphatic chain of the guest elongated. The right-slanting relationship between  $\log K$  and  $\log P_o$  suggests that mono-*O*-alkylated hosts **5** and **6** provide guest molecules with highly constrained cavity, which is most suitable for small guests such as methanol and acetonitrile. For larger guests, only methyl group could be accommodated in the narrow cavity, while the rest of aliphatic group of the guest is exposed to the polar water phase leading to smaller  $\log K$  because of the situation that is not preferred for entropy reasons. Thus, it may be concluded that introduction of a  $\text{CH}_2\text{COOH}$  group at one of phenolic OH group of thiacalix[4]-arene affected the conformation to restrict the available hydrophobic space, which is rather adequate for the complexation of the smallest molecules among those examined. This agrees with the conclusion derived from the  $|\Delta\delta_{\text{lim}}|$  values (vide supra). In addition, Stibor et al. suggested that suppression of ring inversion of conventional calix[4]arenes by partial modification with bulky group at the lower rim can enhance the complexation abilities toward  $\text{CH}_3\text{CN}$  and its derivatives in apolar solvent<sup>18</sup>.

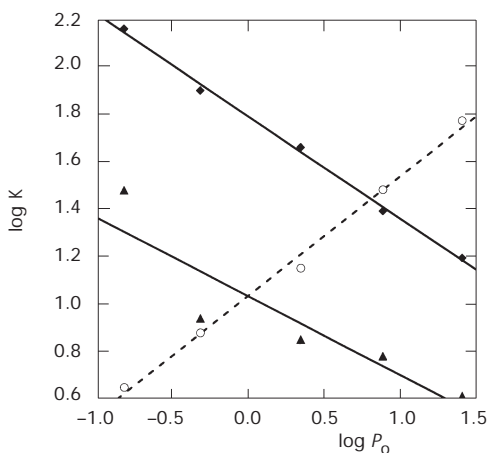


FIG. 3

The correlation between binding constant ( $K$ ) of mono-*O*-alkylated **5** and **6** with *n*-alkyl alcohols versus partition constant ( $P_o$ ) of the guest between water–octan-1-ol phases at  $\text{pD} = 7.3$ . Solid lines are linear correlation curves for hosts **5** ( $R^2 = 0.9972$ ) and **6** ( $R^2 = 0.8193$ ). Dashed line represents correlation for host **3** ( $R^2 = 0.9940$ ). ○ Host **3**, ◆ host **5**, ▲ host **6**

As can be seen from the two separate solid lines in Fig. 3, **5** has higher inclusion ability ( $\Delta \log K \approx 0.6\text{--}0.8$ ) toward all guests than that of **6**, indicating that the presence of *tert*-butyl group substantially enhanced the complexation ability. This suggests that *tert*-butyl group acts as a fence together with three sulfo groups to surround a guest molecule (vide infra).

### *X-ray Crystallographic Analysis of the Complex of 5 with Diethyl Ketone*

To obtain more concrete view of how the guest is included in the host, X-ray crystallographic analysis of the complex of **5** with diethyl ketone was carried out (Fig. 4). Apparently, host **5** adopts cone conformation to include diethyl ketone in its cavity having extended fence consisting of three sulfo and one *tert*-butyl groups. The guest diethyl ketone has W-shaped carbon chain placing the carbonyl oxygen outside from the cavity. The scrutiny of the complex structure revealed that the conformation of host is intermediate of cone and pinched cone: The torsion angles ( $\theta$ ) of distal aromatic rings are  $32.4^\circ$  and  $97.6^\circ$ , where the aromatic ring bearing  $\text{CH}_2\text{COOH}$  and the distal one lie inward<sup>19</sup>. It should be noted that tetra-*O*-substituted thiacalix[4]arenes such as **7** (having  $\theta = -10$  and  $100^\circ$ ) and tetra-*O*-benzyl ether ( $\theta = 0$  and  $85^\circ$ ) adopt pinched cone conformation, where the cavity is not large enough to accommodate guest molecules<sup>7,20</sup>. On the other hand, *p*-*tert*-butylthiacalix[4]arene (**1**) adopting cone conformations with exact or

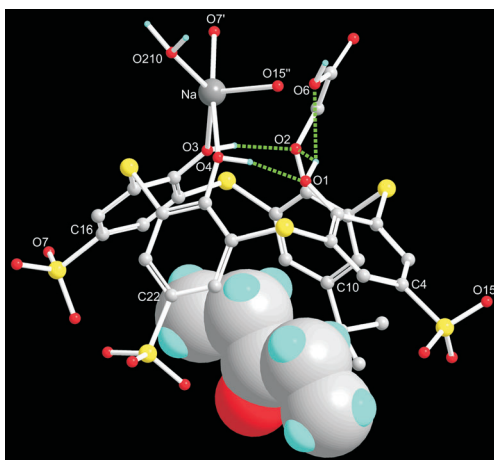


FIG. 4

Crystallographic structure of **5** including diethyl ketone. Hydrogen attached to phenyl rings and *p*-*tert*-butyl group are omitted for clarity. Diethyl ketone is depicted by space filling model. Hydrogen bondings are drawn as green broken lines

approximate  $C_4$  symmetry included a guest molecule in the cavity<sup>1b,9a</sup>. Characterized as intermediate of cone and pinched cone, present mono-*O*-substituted thiacalix[4]arene **5** can provide somewhat reduced but exact space to accommodate small guest molecules.

The structure of host **5** seems to be stabilized by intramolecular hydrogen bonds (depicted as green broken lines in Fig. 4) and coordination to a  $\text{Na}^+$  ion. The hydrogen bonds are rather complicated; there observed are four sets of  $\text{O}-\text{H}\cdots\text{O}$  type hydrogen bonding, the dimensions of which are summarized in Table III together with one of circular array of  $\text{O}-\text{H}\cdots\text{O}$  intramolecular hydrogen bonding of thiacalix[4]arene<sup>1b</sup> **1**. Judging from the dis-

TABLE III

Interatomic distances and bond angles of  $\text{O}-\text{H}\cdots\text{O}$  type intramolecular hydrogen bonding in the mono-*O*-substituted thiacalix[4]arene **5**

	Interatomic distance, Å			Bond angle, ° $\text{O}-\text{H}\cdots\text{O}$
	$\text{O}\cdots\text{O}$	$\text{O}-\text{H}$	$\text{H}\cdots\text{O}$	
$\text{O3}-\text{H22}\cdots\text{O2}$	2.649	0.973	1.760	150.0
$\text{O4}-\text{H23}\cdots\text{O1}$	2.867	0.938	2.264	121.5
$\text{O1}-\text{H21}\cdots\text{O2}$	3.125	0.877	2.452	134.0
$\text{O1}-\text{H21}\cdots\text{O6}$	3.077	0.877	2.328	143.5
$\text{O}-\text{H}\cdots\text{O}$ for <b>1</b> <sup>a</sup>	2.784	0.8	2.1	146

<sup>a</sup> See lit.<sup>1b</sup> cf. Hosseini reported that the average value of the  $\text{O}\cdots\text{O}$  distance for **1** including dichloromethane, chloroform, and methanol is 2.85 Å. See lit.<sup>9a</sup>

TABLE IV

Selected bond lengths (Å) and angles (°) for  $\text{Na}^+$  coordination center

$\text{Na3}-\text{O3}$	2.594(4)	$\text{Na3}-\text{O4}$	2.338(4)
$\text{Na3}-\text{O7}'$	2.289(4)	$\text{Na3}-\text{O15}''$	2.527(4)
$\text{Na3}-\text{O210}$	2.274(4)		
$\text{O3}-\text{Na3}-\text{O4}$	88.0(1)	$\text{O3}-\text{Na3}-\text{O7}'$	88.1(1)
$\text{O3}-\text{Na3}-\text{O15}''$	127.1(1)	$\text{O3}-\text{Na3}-\text{O210}$	146.2(1)
$\text{O4}-\text{Na3}-\text{O7}'$	173.0(1)	$\text{O4}-\text{Na3}-\text{O15}''$	66.1(1)
$\text{O4}-\text{Na3}-\text{O210}$	90.3(1)	$\text{O7}'-\text{Na3}-\text{O15}''$	112.0(1)
$\text{O7}'-\text{Na3}-\text{O210}$	96.2(2)	$\text{O15}''-\text{Na3}-\text{O210}$	82.2(1)

tance and angle, O3–H22...O2 hydrogen bonding is much stronger than that in thiactalix[4]arene **1**, while O4–H23...O1 hydrogen bonding is rather weaker. Notably, O1–H21 forms bifurcated hydrogen bonds with phenolic O2 and carboxyl O6. In terms of coordination to Na<sup>+</sup> ion, the host acts as a bidentate ligand to one of the counter Na<sup>+</sup> ions (Na3) by two phenolic OH (O3 and O4), while the carboxy O6 does not seem to coordinate (Na3...O6 distance: 3.152 Å). In addition, the Na3 center is coordinated by two oxygen atoms of SO<sub>3</sub><sup>–</sup> groups (O7' and O15'') of the other two neighboring hosts **5** and also by one water molecule (O210), constructing distorted trigonal bipyramidal arrangement (Fig. 4, Table IV).

## CONCLUSION

We have compared the inclusion behaviors of water-soluble thiactalix[4]-arene **3**, and the mono-*O*-carboxymethyl derivatives **5** and **6** toward water-miscible organic molecules. In general, the guest molecule orients the aliphatic chain(s) into the cavity of the host rather than into the bulk water due to hydrophobicity of the group. Guest molecules as large as pentan-1-ol showed folding of the hydrophobic chain to avoid polar water phase to be shielded by the cavity. Importantly, the mono-*O*-alkylation of thiactalix[4]-arene was shown to be able to tune the cavity conformation to restrict the space, which is rather suitable for inclusion of the smallest class of molecules such as methanol with high stability.

## EXPERIMENTAL

Melting points were taken using a Yamato MP-21 apparatus and are uncorrected. Microanalyses were carried out in the Microanalytical Laboratory of the Institute of Multidisciplinary Research for Advanced Materials, Tohoku University. Merck silica gel 60GF<sub>254</sub> was used for TLC. <sup>1</sup>H NMR spectra (δ, ppm; J, Hz) were measured on a Bruker DPX-400 spectrometer operated at 400 MHz. IR spectra were obtained with a Shimadzu IR-460. Mass spectra were recorded with a JEOL JMS-GC mate GC-MS system.

### Preparation of Mono-*O*-alkylated Thiactalixarenes **9** and **12**. General Procedure

A mixture of thiactalix[4]arene (**1** or **11**; 5 mmol), K<sub>2</sub>CO<sub>3</sub> (20 mmol), and ethyl bromoacetate (5 mmol) in dry acetone (200 ml) was heated at reflux for 18 h under nitrogen. After the solvent was removed under reduced pressure, the residue was treated with 2 M HCl (100 ml) and extracted with CHCl<sub>3</sub> (100 ml). After the organic layer was dried over MgSO<sub>4</sub>, the solvent was removed to give crude product. Recrystallization from CHCl<sub>3</sub>–CH<sub>3</sub>CN afforded mono-*O*-alkylated derivative (**9** or **12**).

*5,11,17,23-Tetra-tert-butyl-25-[(ethoxycarbonyl)methoxy]-26,27,28-trihydroxy-2,8,14,20-tetra-thiactalix[4]arene (9)*. Colorless needles, yield 76.3%, m.p. 314–316 °C. IR (KBr): 1753 (C=O),

3337 (OH).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.18 (s, 9 H, *t*-Bu); 1.21 (s, 18 H, *t*-Bu); 1.23 (s, 9 H, *t*-Bu); 1.44 (t, 3 H,  $J = 7.2$ , Et); 4.45 (q, 2 H,  $J = 7.2$ , Et); 5.22 (s, 2 H,  $\text{OCH}_2\text{CO}$ ); 7.57 (d, 2 H,  $J = 2.4$ , ArH); 7.62 (d, 2 H,  $J = 2.4$ , ArH); 7.62 (s, 2 H, ArH); 7.63 (s, 2 H, ArH); 9.26 (s, 2 H, OH); 9.61 (s, 1 H, OH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 14.3, 61.7 (Et); 31.0, 31.3, 34.1, 34.1, 34.4, 35.4 (*t*-Bu); 72.2 ( $\text{OCH}_2\text{CO}$ ); 119.6, 120.4, 120.7, 120.8, 128.2, 136.0, 136.2, 136.8, 143.6, 143.87, 149.1, 156.3, 156.8, 157.7 (Ar); 169.2 (C=O). FAB-MS:  $m/z$  807 ( $\text{M}^+$ ). For  $\text{C}_{44}\text{H}_{54}\text{O}_6\text{S}_4$  (807.2) calculated: 65.47% C, 6.74% H, 15.89% S; found: 65.40% C, 6.49% H, 15.65% S.

**25-[(*E*-ethoxycarbonyl)methoxy]-26,27,28-trihydroxy-2,8,14,20-tetrathiacalix[4]arene (12).** Colorless needles, yield 71.3%, m.p. 228–230 °C. IR (KBr): 1751 (C=O), 3281 (OH).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.43 (t, 3 H,  $J = 7.2$ , Et); 4.43 (q, 2 H,  $J = 7.2$ , Et); 5.18 (s, 2 H,  $\text{OCH}_2\text{CO}$ ); 6.68 (t, 1 H,  $J = 7.7$ , ArH); 6.69 (t, 1 H,  $J = 7.7$ , ArH); 6.92 (t, 2 H,  $J = 7.7$ , ArH); 7.52–7.59 (m, 8 H, ArH); 9.03 (s, 2 H, OH); 9.12 (s, 1 H, OH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 14.2, 61.8 (Et); 72.3 ( $\text{OCH}_2\text{CO}$ ); 120.7, 120.9, 121.0, 121.1, 121.2, 126.1, 128.9, 138.5, 138.6, 138.7, 139.3, 158.2, 158.9, 160.0 (Ar); 169.2 (C=O). FAB-MS:  $m/z$  583 ( $\text{M}^+$ ). For  $\text{C}_{28}\text{H}_{22}\text{O}_6\text{S}_4$  (582.7) calculated: 57.61% C, 3.81% H, 22.01% S; found: 57.38% C, 3.83% H, 22.13% S.

### Preparation of Trisulfonates **5** and **6**. General Procedure

A suspension of mono-*O*-alkylated thiactalix[4]arene (**9** or **12**; 6 mmol) in concentrated  $\text{H}_2\text{SO}_4$  (50 ml) was stirred at ambient temperature for 18 h. After quenching with ice-water, the precipitate was filtered off. To the solution of the trisulfonic acid was added saturated aqueous NaCl to salt out the sodium salt. Recrystallization from water afforded trisulfonated derivative (**5** or **6**).

**Trisodium 5-*tert*-butyl-25-(carboxymethoxy)-26,27,28-trihydroxy-2,8,14,20-tetrathiacalix-4]arene-11,17,23-trisulfonate (5).** Colorless needles, yield 83.3%, m.p. > 338.5 °C (decomp.). IR (KBr): 1719 (C=O), 3387 (OH).  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ): 0.61 (s, 9 H, *t*-Bu); 4.94 (s, 2 H,  $\text{OCH}_2\text{CO}$ ); 6.84 (s, 2 H, ArH); 7.77 (s, 2 H, ArH); 8.09 (d, 2 H,  $J = 2.1$ , ArH); 8.13 (d, 2 H,  $J = 2.1$ , ArH).  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ ): 30.2, 34.0 (*t*-Bu); 70.8 ( $\text{OCH}_2\text{CO}$ ); 119.7, 121.1, 122.6, 123.4, 128.5, 131.6, 134.8, 135.3, 135.4, 136.0, 150.2, 154.6, 159.8, 161.4 (Ar); 173.3 (C=O). FAB-MS (negative):  $m/z$  916 ( $\text{M}^-$ ). For  $\text{C}_{30}\text{H}_{23}\text{Na}_3\text{O}_{15}\text{S}_7 \cdot 3\text{H}_2\text{O}$  (971.0) calculated: 37.11% C, 3.01% H, 23.12% S; found: 37.26% C, 3.20% H, 22.95% S.

**Trisodium 25-(carboxymethoxy)-26,27,28-trihydroxy-2,8,14,20-tetrathiacalix[4]arene-11,17,23-trisulfonate (6).** Colorless needles, yield 98.6%, m.p. > 262.5 °C (decomp.). IR (KBr): 1720 (C=O), 3279 (OH).  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ): 4.89 (s, 2 H,  $\text{OCH}_2\text{CO}$ ); 6.70 (bs, 1 H, ArH); 6.87 (bs, 2 H, ArH); 7.45 (s, 2 H, ArH); 8.12 (d, 2 H,  $J = 2.3$ , ArH); 8.16 (d, 2 H,  $J = 2.3$ , ArH).  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ ): 71.4 ( $\text{OCH}_2\text{CO}$ ); 119.7, 121.0, 122.3, 122.5, 127.5, 134.0, 134.9, 135.2, 135.4, 135.8, 136.2, 157.1, 159.0, 159.6 (Ar); 172.6 (C=O). FAB-MS (negative):  $m/z$  860 ( $\text{M}^-$ ). For  $\text{C}_{26}\text{H}_{15}\text{Na}_3\text{O}_{15}\text{S}_7 \cdot 3.5\text{H}_2\text{O}$  (860.8) calculated: 33.80% C, 2.40% H, 24.30% S; found: 33.79% C, 2.69% H, 24.37% S.

### NMR Titration

All experiments were performed in  $\text{D}_2\text{O}$  solution adjusted at pD = 7.3 with 0.1 M  $\text{H}_3\text{PO}_4^-$  NaOD buffer at 300 K. Chemical shifts ( $\delta$ ) were externally referenced to 2,2-dimethyl-2-silapentane-5-sulfonate in order to avoid any possible interaction of the reference with the hosts or the guests. The guest concentration was kept constant at 0.2 mmol/l and the host concentration was varied in the range:  $[\text{Host}]_{\text{T}} = 0\text{--}16$  mmol/l. Association constants ( $\log K$ ) were calculated using a non-linear curve fit of the observed chemical shifts of guest mole-

cule<sup>13</sup>. The averaged value for relevant protons are presented in Table II. All experiments were repeated at three times. Standard deviations are within 10%.

### X-ray Crystallographic Analysis of the Diethyl Ketone Complex of 5

Single crystals of the diethyl ketone complex of **5** were obtained by slow diffusion of diethyl ketone into the water solution of **5**. Crystal data for  $C_{35}H_{45}Na_3O_{27}S_7$ ,  $M = 1191.11$  g/mol, triclinic system, space group  $P1$  (No. 2),  $a = 9.998(4)$  Å,  $b = 16.216(6)$  Å,  $c = 16.663(7)$  Å,  $\alpha = 94.899(6)^\circ$ ,  $\beta = 102.410(7)^\circ$ ,  $\gamma = 96.101(6)^\circ$ ,  $V = 2607(1)$  Å<sup>3</sup>,  $Z = 2$ ,  $D_{\text{calc}} = 1.517$  g/cm<sup>3</sup>,  $\mu(\text{MoK}\alpha) = 4.12$  cm<sup>-1</sup>, crystal dimensions  $0.3 \times 0.2 \times 0.15$  mm, colorless prisms. Data were measured at 223 K on a Rigaku/MSC mercury CCD diffractometer with graphite monochromated MoK $\alpha$  radiation ( $\lambda = 0.71070$  Å). The structure was solved by direct methods (SIR92) and are anisotropically refined by fullmatrix least-squares on  $F$  to final  $R = 0.041$  and  $R_w = 0.047$  using 5986 independent reflections ( $I > 4.00\sigma(I)$ ,  $2\theta < 55.0^\circ$ ), GOF = 1.27. Hydrogen atoms were found from the expected geometry; they are not refined. Lorentz polarization-absorption correction was used.

CCDC 226817 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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14. cf. It has been revealed that 1,1,2-trichloroethane is included into thiacalix[4]arene (**3**) from one of methyl groups which has 2 chlorine atoms rather than 1 chlorine. This suggests that CH- $\pi$  take places between  $\pi$ -electron rich cavity and more positively charged hydrogen atom of  $\text{CHCl}_2$  rather than that of  $\text{CH}_2\text{Cl}$ <sup>4</sup>. Also, presense of CH- $\pi$  interaction is suggested by X-ray structure of a complex of thiacalix[4]arene **1** including 1,2-dichloroethane pointing the C-H hydrogen to benzene ring<sup>1</sup>.
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