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Synthesis of a calix[4]crown modified with germanium-containing side chains

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A germacalix-crown, 25,27-bis[1-(3-trimethylgermylpropyl)oxy]calix[4]arene-crown-6, 1,3-alternate (1a), and its carbon analog, 25,27-bis-[1-(4,4-dimethylpentyl)oxy]calix[4]arene-crown-6, 1,3-alternate (1b), were prepared and their structures were confirmed by elemental analysis and ^{1}H and ^{13}C NMR spectroscopy. A cation transport test indicated that both compounds exhibited much the same cation transport ability, so that the role of the germanium moiety in capturing and transporting counteranions is not yet clear. Copyright © 2005 John Wiley & Sons, Ltd.

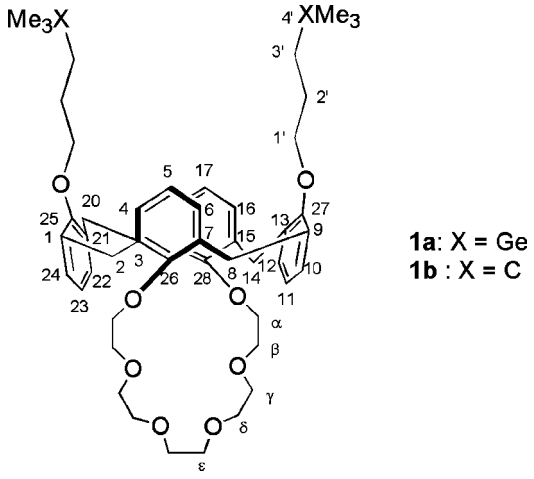
KEYWORDS: calix-crown; calixarene; heteroditopic host; organogermanium compound; ^{1}H NMR spectra; ^{13}C NMR spectra; cation transport; H-tube test

INTRODUCTION

In previous communications, we reported attempts to prepare a new type of heteroditopic host where a germanium-containing side chain will act as a host of an anion, and prepared a series of calix[4]arenes modified with germanium-containing side chains at the upper[1,2] or lower rim.[3] Unfortunately, all these calixarenes failed to show any appreciable cation transport property, indicating that the structure designed, i.e. a calixarene with germanium-containing side chains at upper or lower rim, cannot meet the requirement for an effective heteroditopic host.

Since it was already established that the germanium moiety could act as a host for anions,[4,5] we concluded that calix[4]arenes themselves are not nucleophilic enough to capture cations, particularly when bulky side chains tend to block the cavity. Since a calix-crown is a much stronger host for cations,[6,7] modification of this type of compound with germanium-containing side chains might give an efficient heteroditopic host.

We thought that a germacalix-crown, 25,27-bis[1-(3-trimethylgermylpropyl)oxy]calix[4]arene-crown-6, 1,3-alternate (**1a**), might be a good candidate for the heteroditopic host. Compared with germacalixarenes prepared previously, **1a** has a stronger site for the capture of cations. Furthermore, the site for capture of anions is separated from the cation, and this structure is in line with that reported by Gielen and co-workers.[8,9]



1a: X = Ge
1b : X = C

In this paper, the synthesis and the structure elucidation of **1a**, and the carbon analog, 25,27-bis-[1-(4,4-dimethylpentyl)oxy]calix[4]arene-crown-6, 1,3-alternate (**1b**), together with their cation capture/transport ability will be described.

RESULTS AND DISCUSSION

Synthesis

The synthesis of **1** was conveniently achieved by the method of the synthesis of calix[4]arene-crown-6 reported

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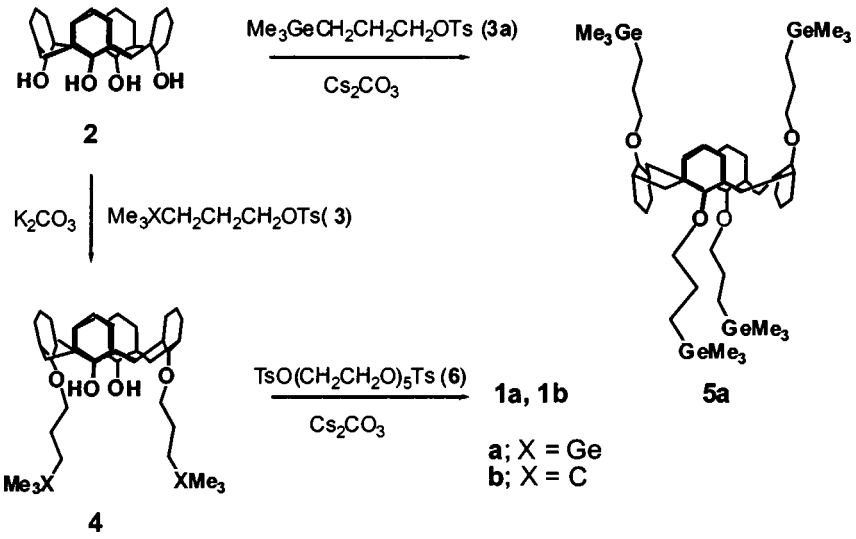

Scheme 1.

by Reinhoudt and co-workers[6] and of calix[4]arene-crown-4 reported by Yamamoto and Shinkai.[7]

Thus, 25,26,27,28-tetrahydroxycalix[4]arene (**2**) was caused to react with 1-(3-trimethylgermylpropyl) *p*-toluenesulfonate (tosylate) (**3a**) or 1-(4,4-dimethylpentyl) tosylate (**3b**) in the presence of K_2CO_3 to afford 25,27-bis[(3-trimethylgermylpropyl)oxy]-26,28-dihydroxycalix[4]arene (**4a**) or 25,27-bis[1-(4,4-dimethylpentyl)oxy]-26,28-dihydroxycalix[4]arene (**4b**). The reaction between **4a** or **4b** and pentaethylene glycol ditosylate (**6**) in the presence of Cs_2CO_3 conveniently afforded the target molecules **1a** and **1b** respectively. The synthesis procedure is summarized in Scheme 1.

It must be added that the reaction between **2** and **3a** in the presence of Cs_2CO_3, rather than K_2CO_3, afforded the tetraether, 25,26,27,28-tetrakis[1-(3-trimethylgermylpropyl) oxy]calix[4]arene (**5a**).

The 1,3-alternate conformation of **1** was confirmed from the NMR data, which will be described later.

Characterization

For **1a** and **1b** to act as an effective heteroditopic host, it is essential that these compounds are in the 1,3-alternate conformation so that the cation-capturing site (i.e. crown) and the anion-capturing site (i.e. germanium moiety) are appropriately separated. Reinhoudt and co-workers[6] reported that the ^{1}H NMR spectra of calix[4]arene in the 1,3-alternate conformation exhibit a singlet around δ 3.8 for the bridging methylene protons and δ 38 for the bridging methylene carbon.

The corresponding bridging methylene protons of **1a** and **1b** appear as a slightly broad singlet at δ 3.8 and the corresponding carbon atoms appear at δ 37.9, which is in good agreement with the chemical shifts reported for 1,3-alternate calix[4]arenes.

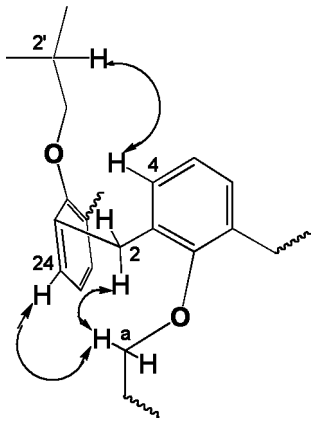

Figure 1. Confirmation of 1,3-alternate conformation by NOESY measurements.

The ^{1}H and ^{13}C NMR resonances of **1a, 1b, 4a, 4b** and **5a** are listed in Table 1.

The assignment was based on H–H COSY, H–C COSY, HMBC and NOESY measurements. The correlation observed in NOESY spectra establishes the 1,3-alternate conformation. Thus, correlations were observed between one of the α protons and one of the H2 protons, between one of the α protons and H24, and one of the H2′ protons and H4, as are shown in Figure 1.

Cation transport experiment

Cation transport experiments of the prepared calixarenes **1a** and **1b** were carried out using an H-tube test (Figure 2).[10–13]

A chloroform solution of the host was added to the bottom of the H-tube and aqueous nitrate solution (100 mmol dm^{-3}) of Na^+, K^+, Rb^+ and Cs^+ was added to the right arm of the H-tube (source phase). Pure H_2O was added to the left

Table 1. ^{1}H and ^{13}C NMR chemical shifts of **1a**, **1b**, **4a**, **4b** and **5a**[a,b]

	1a	**1b**	**4a** (cone)	**4b** (cone)	**5a** (1,3-alternate)
2	3.8 (37.9)	3.76s (37.9)	3.37d, (31.5) 4.34d	3.37d, (31.4) 4.33d	3.64s (36.7)
1(21)	−(134.1)	−(134.1)	−(133.3)	−(133.2)	−(133.7)
24(22)	7.08d (129.7)	7.09d (129.7)	6.89t (128.8)	6.87t (128.8)	6.99d (129.7)
23	6.83t (122.1)	6.83t (122.1)	6.71d (125.1)	6.70d (125.1)	6.67t (121.4)
25	−(156.8)	−(156.9)	−(152.2)	−(152.3)	−(156.5)
3(7)	−(133.8)	−(133.8)	−(128.2)	−(128.2)	equal to 1 (21)
4(6)	7.01d (129.8)	7.01d (129.9)	7.01t (128.4)	7.06d (128.4)	equal to 24 (22)
5	6.76t (122.0)	6.76t (122.0)	6.65m (118.9)	6.66t (118.8)	equal to 23
26	−(156.5)	−(156.4)	−(153.4)	−(153.5)	equal to 25
OH	−(−)	−(−)	8.01s (−)	7.95s (−)	−(−)
α	3.59t (69.97 or 67.95)	3.60t (70.03)	—	—	—
β	3.42t (69.97 or 67.95)	3.44t (69.99)	—	—	—
γ	3.48m (71.0)	3.46m (71.0)	—	—	—
δ	3.66m (71.8)	3.66m (71.23)	—	—	—
ε	3.71s (71.22.)	3.71s (71.21.)	—	—	—
1′	3.41t (73.0)	3.42m (71.3)	3.96t (79.3)	3.96t (77.9)	3.50t (74.2)
2′	1.34m (24.7)	1.30m (24.5)	2.10m (25.5)	2.01m (25.4)	1.61m (25.6)
3′	0.53m (12.2)	1.07m (39.8)	0.93m (12.5)	1.47m (40.0)	0.66m (12.5)
4′	−(Ge)	−(30.1)	(Ge)	−(30.3)	(Ge)
Me	0.15s (−2.2)	0.90s (29.5)	0.19s (−2.2)	0.99s (29.5)	0.17s (−2.3)

[a] Values in parentheses are for ^{13}C data.
[b] Dashes indicate no relevant nuclei at this position.

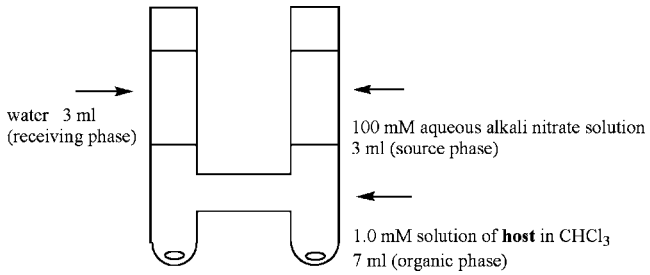

Figure 2. Cation transport measurement by H-tube method.

arm of the H-tube (receiving phase). A small magnetic bar was placed in the bottom of each arm and the solutions were stirred. The whole apparatus was kept at 25 °C for 24 h. The amount of cations in the receiving arm was measured by atomic absorption spectroscopy. A blank test was also performed, where no host was dissolved in the organic layer. The results are summarized in Table 2.

We expected that the transportation of cations (Na^+, K^+, Rb^+) by **1a** is more effective as compared with that by **1b**. There was not much difference between cation transport ability of **1a** and **1b**, which will probably to due to the insufficient Lewis acidity of germanium atoms in **1a**. It will be necessary to enhance the Lewis acidity of the germanium atom by introducing strong electron-withdrawing groups on it.

As for Cs^+ is concerned, large values were found for both **1a** and **1b**. Much the same result was reported for calix-crowns

Table 2. Cation concentration in receiving phase ($\times 10^{-6}$ mol l^{-1})[a]

	1a			**1b**		
	c	c_e	c_0	c	c_e	c_0
Na^+	8.2	68.7	60.5	18.7	67.4	48.7
K^+	4.3	13.8	9.5	9.4	19.4	10.0
Rb^+	84.2	82.1	2.7	85.3	85.7	0.4
Cs^+	1310.8	1315.5	4.7	1930.7	1934.8	4.1

[a] c: concentration of the transported ion, defined as $c = c_e - c_0$; c_e: concentration of the ion in the receiving phase with **1** in the organic phase; c_0: concentration of the ion in the receiving phase without **1** in the organic phase.

prepared by Reinhouldt *et al*.[6] In this particular case, the larger values seem to obscure whether there is a meaningful difference or not.

CONCLUSION

When we started the synthesis of calix-crown modified with germanium-containing moieties, we expected that the cation transport ability of the calix-crown part will be enhanced by the assistance of the germanium moiety which could be a host for counteranions. This was not, however, the case. One possible reason for this will be due to the weakness of

Lewis acidity of germanium atoms in **1a**. One or more methyl groups on germanium should be replaced by a stronger electron acceptor such as halogens. Studies along this line is under progress in this laboratory.

EXPERIMENTAL

^{1}H NMR spectra were determined by JEOL ECP 500 spectrometer operating at 500 MHz, and the chemical shifts were reported in δ (ppm) with tetramethylsilane (TMS) as the internal standard. ^{13}C NMR spectra were determined with the same spectrometer operating at 125 MHz and the chemical shifts were reported in δ (ppm) with TMS as the internal standard. Elemental analyses were carried out at the Microanalytical Laboratory, Department of Chemistry, Faculty of Science, the University of Tokyo. Atomic absorption spectra were determined with the aid of Hitachi 12–8100 polarized Zeeman atomic absorption spectrometer.

Synthesis

*3-Trimethylgermyl-1-propyl tosylate (**3a**)*

The reduction of 3-trimethylgermyl-1-propanoic acid[11] by $LiAlH_4$ afforded 3-trimethylgermyl-1-propanol; b.p.: 180–182 °C; lit.[14] b.p.: 182 °C. To this, alcohol (10.7 g; 0.061 mol) in pyridine (25.5 g, 0.322 mol) was added dropwise in 1 h under an ice–salt bath. Stirring was continued for 6 h. Water (50 ml) was added and the solution was made acidic by concentrated hydrochloric acid (36%) under ice cooling. The organic layer was extracted twice with diethyl ether (200 and 100 ml), which was combined and dried over $MgSO_4$. The diethyl ether was evaporated and the residue was purified by column chromatography (silica gel; $CHCl_3$) to afford 16.15 g of colorless liquid. Yield: 98.7%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80, 7.79, 7.35, and 7.34 (AA′BB′, 4H, ArH), 3.98 (t, 2H, C*H*$_2$OTs), 2.45 (s, 3H, ArC*H*$_3$), 1.68 (m, 2H, CH$_2$C*H*$_2$CH$_2$OTs), 0.62 (m, 2H, C*H*$_2$CH$_2$CH$_2$OTs), 0.08 (s, 9H, Me). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.6, 133.4, 129.8, 127.9 (Ar), 72.9 (CH_2OTs), 24.7 ($CH_2CH_2CH_2$OTs), 21.6 (Ar*Me*), 11.9 ($CH_2CH_2CH_2$OTs), −2.6 (Ge*Me*$_3$).

*4,4-Dimethyl-1-pentyl tosylate (**3b**)*

4,4-Dimethyl-1-pentanoic acid[15] (4.02 g, 30.9 mmol) in diethyl ether (50 ml) was added to a suspension of $LiAlH_4$ (1.74 g, 37.7 mmol) in diethyl ether (50 ml) so that gentle reflux took place. The mixture was stirred for 5.5 h at room temperature. Water was added and the organic layer was separated, washed with water (25 ml) and saturated NaCl (25 ml) and dried over anhydrous Na_2SO_4. The residue (3.14 g) after removing the solvent was distilled under reduced pressure (13.4 kPa, 104 °C) to afford 2.34 g of 4,4-dimethyl-1-pentanol as a colorless liquid. Yield: 65.5%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.62 (t, 2H, C*H*$_2$OH), 1.54 (m, 2H, CH$_2$C*H*$_2$CH$_2$OH), 1.21 (m, 2H, C*H*$_2$CH$_2$CH$_2$OH), 0.89 (s, 9H, Me). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 63.9 (CH_2OH), 39.9 ($CH_2CH_2CH_2$OH), 30.1 (CCH_3), 29.3 (Me), 28.0 ($CH_2CH_2CH_2$OH). Lit.:[16] 3.77 (2, t, OC*H*$_2$), 1.27 and 1.58 (4, m, C*H*$_2$C*H*$_2$CMe$_3$), 0.93 (9, s, Me). The synthesis of this compound was previously reported, but our procedure is much simpler than that of the literature.[16]

To a pyridine solution (7.14 g, 90.3 mmol) of 4,4-dimethyl-1-pentanol (2.19 g, 18.9 mmol), tosyl chloride (4.57 g, 24.0 mmol) was added so that the temperature was maintained below 2 °C. Stirring was continued for another 6 h. The solid was filtered off, washed with diethyl ether, and the organic layer was combined. The organic layer was made acidic by adding H_2O (20 ml) and aqueous HCl (3.6%, 50 ml). The mixture was extracted with diethyl ether, which was washed by H_2O (25 ml) and saturated NaCl. The aqueous layer was further extracted with diethyl ether three times (25 ml × 3) and the combined diethyl ether layer was dried over anhydrous $MgSO_4$. By removing the solvent, 5.76 g of pale yellow liquid was obtained, which was purified by column chromatography (silica gel; benzene:hexane = 1 : 1) to give 4.02 g of **3b**. Yield: 78.8%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80, 7.78, 7.35, and 7.33 (AA′BB′, 4H, ArH), 4.00 (t, 2H, C*H*$_2$OTs), 2.45 (s, 3H, ArC*H*$_3$), 1.60 (m, 2H, CH$_2$C*H*$_2$CH$_2$OTs), 1.15 (m, 2H, C*H*$_2$CH$_2$CH$_2$OTs), 0.83 (s, 9H, Me). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.6, 133.3, 129.8, 127.9 (Ar), 71.5 (CH_2OTs), 39.4 ($CH_2CH_2CH_2$OTs), 30.0 (C*Me*$_3$), 29.1 (C*Me*$_3$), 24.3 ($CH_2CH_2CH_2$OTs), 21.6 (Ar*Me*). Lit.:[16] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75, 7.31 (4H, ArH), 3.98 (t, 2H, C*H*$_2$OTs), 2.39 (s, 3H, ArC*H*$_3$), 1.53 and 1.12 (m, 4H, C*H*$_2$C*H*$_2$CH$_2$OTs), 0.78 (s, 9H, Me).

*25,27-Dihydroxy-26,28-bis[1-(3-trimethylgermylpropyl)oxy]calix[4]arene (**4a**)*

A mixture of 25,26,27,28-tetrahydroxycalix[4]arene (**2**) (0.79 g, 1.86 mmol), **3a** (1.35 g, 4.08 mmol) and K_2CO_3 (0.32 g, 2.32 mmol) in CH_3CN (50 ml) was refluxed for 3 days under nitrogen. After the solvent was removed, $CHCl_3$ (100 ml) was added, and the undissolved material was filtered off. The organic layer was washed successively with H_2O(25 ml × 2) and saturated aqueous NaCl (25 ml), and dried over Na_2SO_4. The solvent was removed, and the residue was recrystallized from CH_2Cl_2–EtOH to give 0.70 g of colorless crystals. The sample for analysis was further recrystallized from CH_2Cl_2–2-propanol. Yield: 51%; m.p.: 182–184.5 °C. Anal. Found: C, 64.66, H, 7.05. Calc. for $C_{40}H_{52}Ge_2O_4$: C, 64.75; H, 7.06%.

*25,26,27,28-Tetrakis[1-(3-trimethylgermylpropyl)oxy]calix[4]arene (**5a**)*

A mixture of **2** (0.51 g, 1.20 mmol), **3a** (0.88 g, 2.66 mmol) and Cs_2CO_3 (1.06 g, 3.25 mmol) in CH_3CN (80 ml) was treated in a manner similar with the synthesis of **4a**, and the crude product was recrystallized from $CHCl_3$–CH_3OH to give 0.078 g of white crystals. Yield: 10.7%; m.p.: 213–216 °C (0.115 g).

*25,27-Bis[1-(3-trimethylgermylpropyl)oxy]calix[4]arene-crown-6, 1,3-alternate (**1a**)*

A mixture of **4a** (2.53 g, 0.4 mmol), pentaethyleneglycol ditosylate) **6** (2.31 g, 4.2 mmol) and Cs_2CO_3 (4.6 g, 14.1 mmol)

in CH_3CN (400 ml) was refluxed for 25 h under nitrogen. The solvent was removed *in vacuo* and $CHCl_3$ (250 ml) was added to the residue. The mixture washed with aqueous HCl (10%, 100 ml), H_2O(50 ml × 2), and dried over $MgSO_4$. The solid remaining after the removal of the solvent was purified by column chromatography (solvent: benzene/ethyl acetate (1 : 2)) to afford 1.02 g of colorless solid which was recrystallized from MeCN. Yield: 31.7%. m.p.: 117–119 °C. Anal. Found: C, 63.51; H, 7.48. Calc. for $C_{50}H_{70}Ge_2O_8$: C, 63.60; H, 7.47%.

*25,27-Dihydroxy-26,28-bis[1-(4,4-dimethylpentyl) oxy]calix[4]arene (**4b**)*

A mixture of **2** (1.04 g, 2.45 mmol), **3b** (1.44 g, 5.33 mmol) and K_2CO_3 (0.47 g, 3.40 mmol) in CH_3CN (60 ml) was refluxed for 19 h under nitrogen. After the solid material was filtered off, $CHCl_3$ (100 ml) was added, and the organic layer washed with aqueous HCl (3.6%, 25 ml × 2) and saturated aqueous NaCl (25 ml), and dried over $MgSO_4$. The solvent was removed, and the residue was recrystallized from CH_2Cl_2–EtOH to give 0.70 g of colorless crystals. Recrystallization of the solid product from 2-propanol gave 0.70 g of colorless crystals. Yield: 46%; m.p.: 209–212 °C. Anal. Found: C, 81.04; H, 8.49. Calc. for $C_{42}H_{52}O_4$: C, 81.25; H, 8.44%.

*25,27-bis-[1-(4,4-dimethylpentyl)oxy]calix[4] arene-crown-6, 1,3-alternate (**1b**)*

A mixture of **4a** (1.48 g, 2.4 mmol), **6** (1.52 g, 2.8 mmol) and Cs_2CO_3 (3.29 g, 10.1 mmol) in CH_3CN (400 ml) was refluxed for 26 h under nitrogen. After the solvent was removed *in vacuo*, $CHCl_3$ (150 ml) was added, and the mixture was washed with aqueous HCl (10%, 80 ml × 2) and H_2O(50 ml × 2), and dried over $MgSO_4$. The residue was purified with column chromatography (solvent: benzene, then benzene/ethyl acetate (1 : 2)) to afford 1.2 g of colorless powder, which was recrystallized from MeCN. Yield: 61.2%; m.p.: 128–131 °C. Anal. Found: C, 75.78; H, 8.56. Calc. for $C_{52}H_{70}O_8$: C, 75.88; H, 8.57%.

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