Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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To cite this Article Morikawa, Osamu , Miyashiro, Makoto , Yamaguchi, Hiroshi , Kobayashi, Kazuhiro and Konishi, Hisatoshi(1999) 'Synthesis of Calix[4]resorcinarenes Bearing Thioether Functionality at the Extraannular Positions', Supramolecular Chemistry, 11: 1, 67 — 72
To link to this Article: DOI: 10.1080/10610279908048717
URL: http://dx.doi.org/10.1080/10610279908048717

SUPRAMOLECULAR CHEMISTRY, Vol. 11, pp. 67-72
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Synthesis of Calix[4]resorcinarenes Bearing Thioether Functionality at the Extraannular Positions

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(Received 12 August 1998; In final form 20 May 1999)

The reactions of calix[4]resorcinarene 1 with thiols and formaldehyde in the presence of triethylamine gave tetrakis(thiomethylated)calix[4]resorcinarenes 3 in good yield. ^{1}H NMR characterization shows that in $CDCl_3$ solution these compounds exist in a cone conformation. The presence of a circular hydrogen bonding network consisting of two types of intramolecular hydrogen bondings, OH···S and OH···OH, is indicated based on IR spectroscopy.

Keywords: Calixresorcinarene, hydrogen bonding, thiomethylation, calixarene

INTRODUCTION

Calixarenes and calixresorcinarenes are cavity-containing macrocyclic compounds and are widely employed as useful supramolecular frameworks [1-3]. Recently, there has been growing interest in the calix[4]arenes having a thioether functionality in supramolecular chemistry because of their application as receptors for transition metals [4, 5], heavy metal extractants [6, 7], cation selective electrodes [8, 9] and chemically modified field effect transistors (CHEMFETs) [10].

We have been interested in the utilization of calix[4]resorcinarenes [11, 12] because of their remarkably easy availability. The objective of this study is to prepare calix[4]resorcinarenes bearing thioether functions. Such compounds may be prepared by chemical reactions involving the phenolic hydroxyl groups or the 2-position of the resorcinol nuclei. Due to the presence of two electron-donating hydroxyl groups, resorcinols are smoothly attacked by electrophiles. Indeed, several functionalized calix[4]resorcinarenes have been prepared by aromatic substitutions, such as diazo-coupling [13], bromination [12, 14], and aminomethylation [15, 16]. Since some electron-rich aromatic compounds react with thiols and formaldehyde in the presence of triethylamine to give thiomethylated products [17], we expected that the thiomethylation would readily proceed at the 2-position of the resorcinol nuclei of the calix[4]-resorcinarenes [18].

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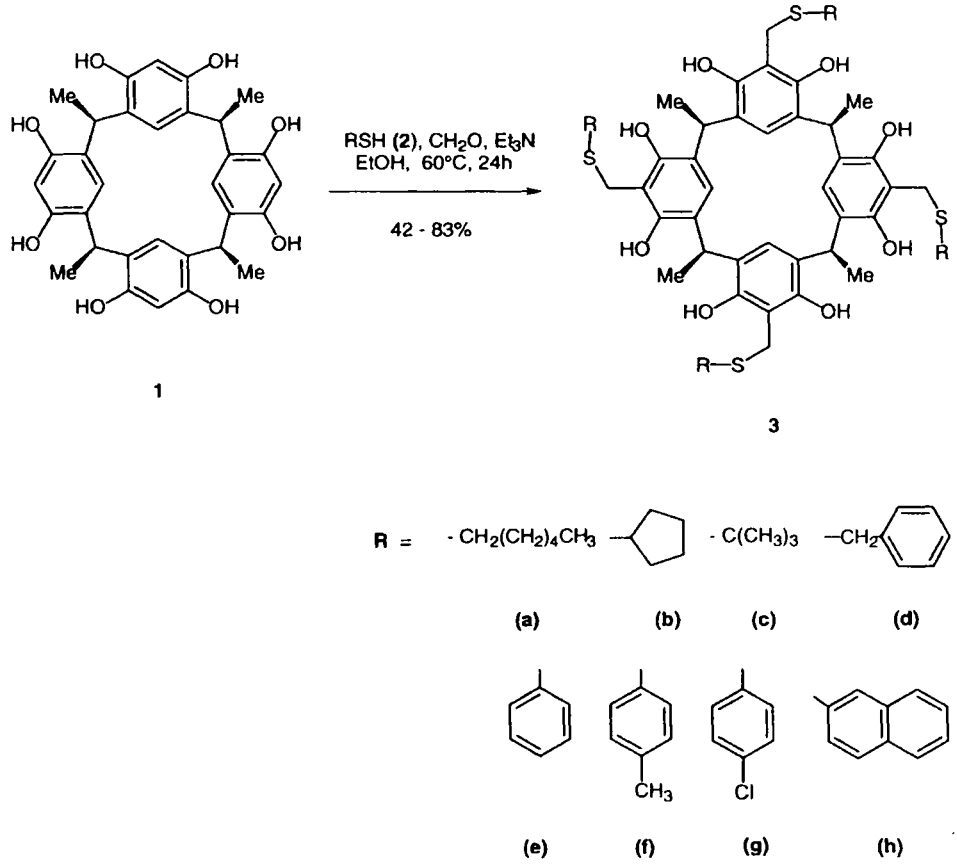
RESULTS AND DISCUSSION

The reactions of calix[4]resorcinarene (**1**) with thiols **2a-h** and 37% aqueous formaldehyde in the presence of triethylamine yielded tetrakis (thiomethylated) products (**3**) in moderate to good yields. In addition, we have also found that the thiomethylation proceeded in acetic acid [18]. However, in most cases, the reactions in acetic acid gave somewhat lower yields. Therefore, we did not investigate the acid catalyzed reaction in detail.



Structures for the tetrakis(thiomethylated) products were established based on their ^1H and ^{13}C NMR spectroscopy. The simplicity of the spectra suggests a high symmetry for the products. In the ^1H NMR spectra, the SCH_2 groups of the alkylthiomethyl derivatives **3a-d** appear as a singlet at 3.8–3.9 ppm. On the other hand, the corresponding singlets for the arylthiomethyl derivatives **3e-h** appear at 4.2–4.3 ppm. In the ^{13}C NMR spectra, these methylene carbons resonate at 23–26 ppm for the alkylthiomethyl derivatives and at 29–30 ppm for the arylthiomethyl derivatives.

The preferred conformations of calix[4]resorcinarenes are predicted by the chemical shifts of the aromatic protons at the intraannular positions. These thiomethylated cyclic tetramers, in $CDCl_3$, showed a singlet at $\delta = 7.2-7.3$ for the intraannular protons. This observation strongly indicates that the cyclophanes exist in the cone conformation in this solvent.

The low field shift of the OH protons ($\delta = 7.0-7.9$) suggests a hydrogen bonding interaction between the OH—OH and OH—S. This hydrogen

bonding interaction is also indicated by the infrared spectrum. In CCl_4 solution, the octylthiomethyl derivative **3a** showed two types of hydrogen bonded stretching vibrations at 3382 and 3198 cm^{-1}. The latter is assigned to the hydrogen bonded (OH···S) vibration (Fig. 1). The intramolecular OH—OH hydrogen bonding stabilizes the cone conformation. Furthermore, the intramolecular OH···S hydrogen bonding is expected to reduce the conformational freedom of the substituents at the 2-position of the resorcinol ring, thereby forming a deep hydrophobic cavity. Thus, these spectral features suggest the presence of a circular hydrogen bonding network as shown in Figure 2 [16, 19]. However, only one signal for the OH protons in the ^1H NMR spectrum of **3a** was observed at $-50°C$. Although the signals in the spectrum were slightly broadened, the conformational freezing to the C_4 structure could not be achieved in $CDCl_3$ at this temperature.

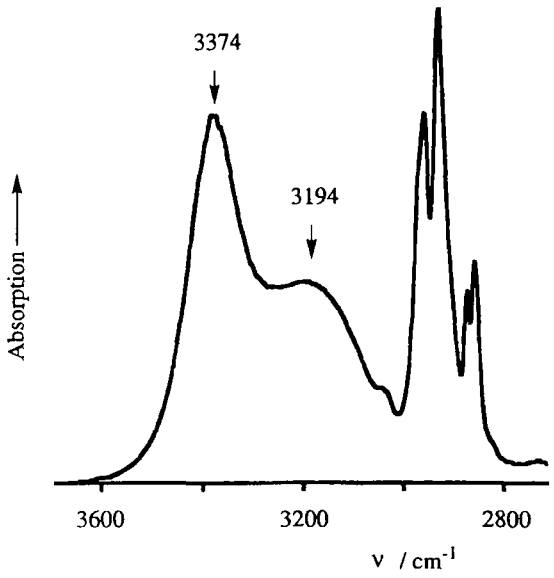


FIGURE 1 The infrared spectrum of **2a** in CCl_4 solution.

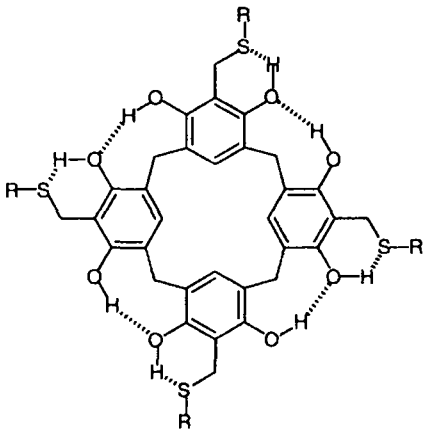


FIGURE 2 A circular hydrogen bonding network.

CONCLUSION

The tetrakis(thiomethylated) calix[4]resorcinarenes described here, except for **3g**, are soluble in the common organic solvents such as ethanol, acetone, chloroform and toluene. These macrocycles can be useful as artificial receptors in various organic solvents.

EXPERIMENTAL

Melting points are uncorrected and were obtained using a MEL-Temp apparatus (Laboratory Devices). The ^1H and ^{13}C NMR spectra were recorded on a JEOL GX-270 spectrometer, and the chemical shifts are reported as δ values. The ^1H NMR spectra are referenced to tetramethylsilane, and the ^{13}C NMR spectra are referenced to either $CDCl_3$ (77.0) or pyridine-d_5 (149.8). Infrared spectra were taken using a Perkin-Elmer 1610 spectrophotometer. All solvents were purified by standard procedures. Other chemicals were of reagent grade, and were used without further purification. Calix[4]-resorcinarene **1** was prepared as described in the literature [20]. Microanalytical samples were dried for at least 8 h at 80°C at reduced pressure. Analyses were performed at the Microanalysis Center of Kyoto University.

5,11,17,23-Tetrakis[(hexylthio)methyl]-calix[4]resorcinarene (3a)

A mixture of calix[4]resorcinarene **1** (545 mg, 1.0 mmol), hexanethiol (590 mg, 5.0 mmol), triethylamine (0.70 mL, 5.0 mmol) and 37% aqueous formaldehyde (0.96 mL, 12 mmol) in ethanol/$CHCl_3$ (1 : 1 v/v, 20 mL) was heated at 60°C under Ar for 24 h. H_2O was added (100 mL) and the mixture was extracted with EtOAc (2 × 50 mL). The organic layer was washed with 5% HCl, and dried (Na_2SO_4). The solvent was removed under reduced pressure on a rotary evaporator. The resulting residue was recrystallized from hexane to yield **3a** as a white solid; yield 742 mg (70%); mp 71–73°C. Anal. Calcd for $C_{60}H_{88}O_8S_4$: C, 67.63; H, 8.32; S, 12.04. Found: C, 67.69; H, 8.29; S, 12.21. IR (KBr) ν = 3384, 2926, 1608, 1472, 1298, 1236, 1092 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 0.834 (t, 12 H, J = 6.9 Hz, CH_3), 1.20–1.58 (m, 32H, $(CH_2)_4$), 1.746 (d, 12H, J = 7.4 Hz, bridge CH_3), 2.380 (t, 8 H, J = 7.4 Hz, CH_2 $C\underline{H}_2S$), 3.851 (s, 8H, SCH_2Ar), 4.589 (q, 4H, J = 7.4 Hz, bridge CH), 7.301 (s, 4H, ArH) 7.933 (s, 8H, OH). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 14.0 (q), 20.1 (q), 22.5 (t), 25.8 (t, SCH_2), 28.1 (d), 28.3 (t), 29.0 (t), 31.0(t), 31.3(t), 110.1 (s), 122.3 (d), 125.7 (s), 150.1 (s).

5,11,17,23-Tetrakis[(cyclopentylthio)-methyl]calix[4]resorcinarene (3b)

The same procedure as for **3a** was followed, starting from **1** (545 mg, 1.0 mmol), cyclopentanethiol (520 mg, 5.1 mmol), triethylamine (0.70 mL, 5.0 mmol) and 37% aqueous formaldehyde (0.96 mL, 12 mmol). The crude product was purified by reprecipitation from EtOAc/hexane to give **3b** as a white solid; yield 797 mg (80%); mp 207°C (dec). Anal. Calcd for $C_{56}H_{72}O_8S_4 \cdot C_3H_6O$: C, 66.89; H, 7.42; S, 12.10. Found: C, 66.66; H, 7.43; S, 11.81. IR (KBr) ν = 3395, 3142, 2957, 2868, 1607, 1472, 1236, 1091 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.19–1.27 (m, 32H, cyclopentyl CH_2), 1.747 (d, 12H, J = 6.9 Hz, bridge CH_3), 2.93 (m, 4H, cyclopentyl CH), 3.876 (s, 8H, SCH_2Ar), 4.593(q, 4H, J = 6.9 Hz, bridgeCH), 7.291 (s, 4H, ArH), 7.994 (s, 8H, OH). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 20.1 (q), 24.8 (t), 26.1 (t, SCH_2), 28.3 (d), 33.4 (t), 42.2 (d), 110.2 (s), 122.2(d), 125.7 (s), 150.0(s).

5,11,17,23-Tetrakis[[(1,1-dimethylethyl)thio]-methyl]calix[4]resorcinarene (3c)

The same procedure as for **3a** was followed, starting from **1** (545 mg, 1.0 mmol), 2-methyl-2-propanethiol (450 mg, 5.0 mmol), triethylamine (0.70 mL, 5.0 mmol) and 37% aqueous formaldehyde (0.96 mL, 12 mmol). The residue was recrystallized from ethanol to afford **2c** as colorless needles; yield 400 mg, (42%); mp 210°C (dec). Anal. Calcd for $C_{52}H_{72}O_8S_4$: C, 65.51; H, 7.61; S, 13.45. Found: C, 65.22; H, 7.60; S, 13.50. IR(KBr)ν = 3362, 2966, 1610, 1473, 1238, 1161 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.335 (s, 36H, $C(CH_3)_3$), 1.707 (d, 12H, J = 6.9 Hz, bridge CH_3), 3.903 (s, 8H, SCH_2Ar), 4.574 (q, 4H, J = 6.9 Hz, bridge CH), 7.257 (s, 4H, ArH), 7.821 (s, 8H, OH). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 19.9 (q), 22.9 (t, SCH_2), 27.8 (d), 30.5 (q), 43.8 (s), 110.1 (s), 121.9 (d), 125.7 (s), 149.1 (s).

5,11,17,23-Tetrakis[(benzylthio)methyl]-calix[4]resorcinarene (3d)

The same procedure as for **3a** was followed, starting from **1** (545 mg, 1.0 mmol), benzenemethanethiol (635 mg, 5.1 mmol), triethylamine (0.70 mL, 5.0 mmol) and 37% aqueous formaldehyde (0.96 mL, 12 mmol). The crude product was purified by reprecipitation from EtOAc solution by hexane to give **3d** as a white solid; yield 890 mg (82%): mp 175°C (dec). Anal. Calcd for $C_{64}H_{64}O_8S_4$: C, 70.56; H, 5.92; S, 11.77. Found C, 70.52; H, 6.09; S, 11.72. IR (KBr) ν = 3322, 2967, 1605, 1471, 1295, 1235, 1094, 698 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 1.738 (d, 12H, J = 7.3 Hz, CH_3), 3.558 (s, 8H, $PhCH_2S$), 3.841 (s,8H, SCH_2), 4.550 (q, 4H, J = 7.3 Hz, CH), 7.28–7.02 (m, 24H, ArH), 7.732 (s, 8H, OH). ^{13}C NMR

(67.8 MHz, $CDCl_3$): δ = 20.1 (q), 26.1 (t, SCH_2), 28.0 (d), 35.7 (t, $PhCH_2S$), 109.8 (s), 122.4 (d), 125.7 (s), 127.1 (d), 128.4 (d), 128.7 (d), 137.5 (s), 149.9 (s).

5, 11, 17, 23-Tetrakis[(phenylthio)methyl]-calix[4]resorcinarene (3e)

The same procedure as for **3a** was followed, starting from **1** (545 mg, 1.0 mmol), thiophenol (560 mg, 5.1 mmol), triethylamine (0.70 mL, 5.0 mmol) and 37% aqueous formaldehyde (0.96 mL, 12 mmol). The crude product was triturated with acetone to afford a white solid, which was recrystallized from toluene to yield **2e**; yield 739 mg (71%); mp 160–162°C (dec). Anal. Calcd for $C_{60}H_{56}O_8S_4$: C, 69.74; H, 5.46; S, 12.41. Found: C, 69.74; H, 5.48; S, 12.69. IR (KBr) ν = 3351, 1604, 1472, 1377, 733, 687 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.688 (d, 12H, J = 7.3 Hz, bridge CH_3), 4.250 (s, 8H, SCH_2Ar), 4.532 (q, 4H, J = 7.3 Hz, bridge CH), 6.96–7.28 (m, 24H, ArH), 7.403 (s, 8H, OH). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 20.1 (q), 28.0 (d), 29.3 (t, SCH_2), 110.0 (s), 122.7 (d), 125.9 (s), 127.1 (d), 128.8(d), 130.6 (d), 133.7 (s), 149.7 (s).

5, 11, 17, 23-Tetrakis[[(4-methylphenyl)thio]-methyl]calix[4]resorcinarene (3f)

The same procedure as for **3a** was followed, starting from **1** (545 mg, 1.0 mmol), 4-methythiophenol (620 mg, 5.0 mmol), triethylamine (0.70 mL, 5.0 mmol) and 37% aqueous formaldehyde (0.96 mL, 12 mmol). The crude product was recrystallized from EtOH/H_2O to yield **3f**; yield 705 mg (65%); mp 174°C (dec). Anal. Calcd for $C_{64}H_{64}O_8S_4$: C, 70.56; H, 5.92; S, 11.77. Found: C, 70.82; H, 5.90; S, 11.97. IR (KBr) ν = 3343, 1604, 1472, 1209, 1094, 802 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.698 (d, 12H, J = 7.3 Hz, bridge CH_3), 2.230 (s, 12H, $ArCH_3$), 4.213 (s, 8H, SCH_2Ar), 4.547 (q, 4H, J = 7.3 Hz, bridge CH), 7.0–7.1 (m, 8H, ArH), 7.2–7.3 (m, 12H, ArH), 7.475 (s, 8H, OH). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 20.1 (q), 20.9 (q), 28.0 (d), 29.7 (t, SCH_2), 110.1 (s), 122.5 (d), 125.9 (s), 129.7(d), 130.3 (s), 130.5 (d), 137.2 (s), 149.6 (s).

5, 11, 17, 23-Tetrakis[[(4-chlorophenyl)-thio]methyl]calix[4]resorcinarene (3g)

The same procedure as for **3a** was followed, starting from **1** (545 mg, 1.0 mmol), 4-chlorothiophenol (735 mg, 5.1 mmol), triethylamine (0.70 mL, 5.0 mmol) and 37% aqueous formaldehyde (0.96 mL, 12 mmol). The precipitate that formed during the reaction was collected by suction, and triturated with cold EtOH to give pure **3g**. An analytical sample was recrystallized from methanol; yield 888 mg (83%); mp 163°C (dec). Anal. Calcd for $C_{60}H_{52}O_8S_4Cl_4 \bullet H_2O$: C, 60.60; H, 4.58; S, 10.78. Found: C, 60.82; H, 4.57; S, 10.97. IR (KBr) ν = 3350, 2969, 1605, 1475, 1093, 1011, 813 cm^{-1}. ^1H NMR (270 MHz, pyridine-d_5): δ = 1.927 (d, 12H, J = 7.3 Hz, bridge CH_3), 4.572 (s, 8H, SCH_2Ar), 5.156 (q, 4H, J = 7.3 Hz, bridge CH), 7.16–7.29 (AA'BB', 16H, 4-chlorophenyl), 7.804 (s, 4H, Ar-H). ^{13}C NMR (67.8 MHz, pyridine-d_5): δ = 20.3 (q), 29.4 (t, SCH_2), 29.9 (d), 113.5 (s), 123.6 (d), 127.5 (s), 129.1 (d), 129.8 (d), 130.9 (s), 138.3 (s), 151.2 (s).

5, 11, 17, 23-Tetrakis[(2-naphthalenylthio)-methyl]calix[4]resorcinarene (3h)

The same procedure as for **3a** was followed, starting from **1** (545 mg, 1.0 mmol), 2-naphthalenethiol (800 mg, 5.0 mmol), triethylamine (0.70 mL, 5.0 mmol) and formaldehyde (0.96 mL, 12 mmol). The crude product was recrystallized from acetone/EtOH to give **3h** as white needles; yield 526 mg (43%); mp 140°C (dec.) Anal. Calcd for $C_{74}H_{64}O_8S_4 \bullet C_3H_6O$: C, 73.46; H, 5.46; S, 9.93. Found: C, 73.39; H, 5.50; S, 10.13.

IR (KBr) ν = 3396, 3051, 2966, 1608, 1474, 1235, 812, 743 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.705 (d, 12H, J = 7.3 Hz, bridge CH_3), 4.333 (s, 8H, SCH_2Ar), 4.604 (q, 4H, J = 7.3 Hz, bridge CH), 7.030 (bs, 8H, OH), 7.253 (4H, s, ArH), 7.33–7.75 (m, 28H, ArH). ^{13}C NMR (67.8 MHz,

$CDCl_3$): δ = 20.0 (q), 28.1 (d), 28.8 (t, SCH_2), 109.9 (s), 122.7 (d), 126.0 (s and d, 2C), 126.5 (d), 127.2 (d), 127.6 (d), 128.3 (d), 128.4(d), 131.4(s), 132.1(s), 133.6(s), 149.7 (s).

Acknowledgment

This research was partially supported by a Grant-in-Aid for Scientific Research, No. 07651060, from the Ministry of Education, Science, Sports and Culture.

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