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SYNTHESIS AND STRUCTURE OF THIACALIX[4]ARENE DERIVATIVES BEARING THIADIAZOLE FUNCTIONAL GROUPS AT LOWER RIMS

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Abstract - The *p-tert*-butylthiacalix[4]arene (**1**) was firstly alkylated with 1, 3-dibromopropane and 1,4-dibromobutane to give thiacalix[4]arene derivatives (**2a** and **2b**) in the presence of potassium carbonate, respectively. A series of *p-tert*-butylthiacalix[4]arene derivatives (**3a**, **3b**, **4a**, **4b**) which append thiadiazole groups at the lower rims were easily synthesized in good yields by the reaction of tetrabromoalkoxythiacalix[4]arene intermediates **2** with 2-mercaptothiadiazole compounds in the presence of potassium carbonate. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, elemental analysis and X-ray diffraction on single crystals of **2b**, **3b**.

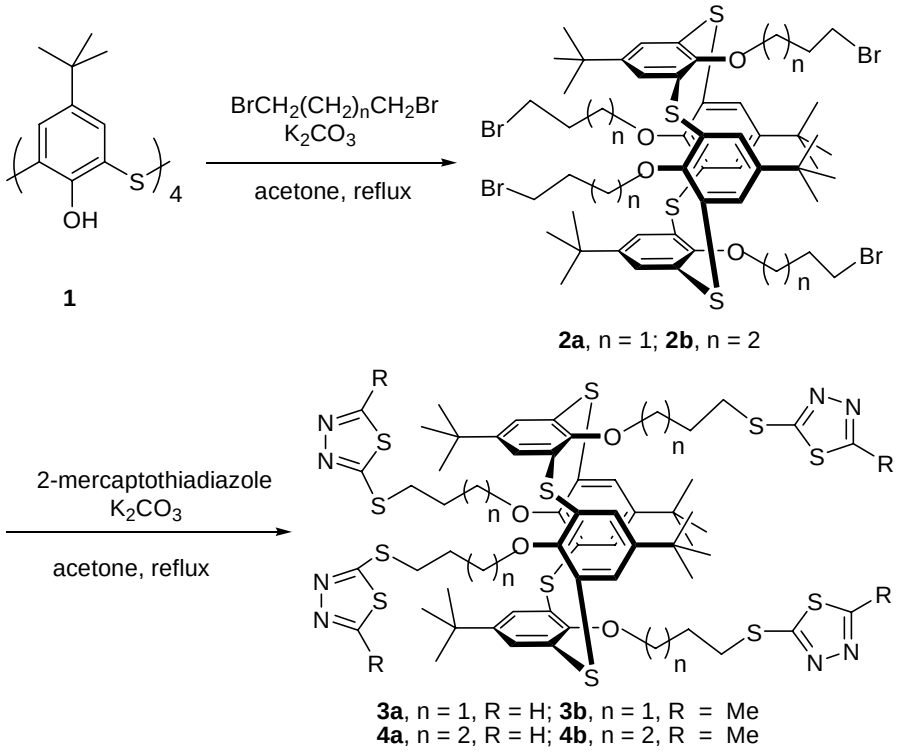
INTRODUCTION

By the virtue of their versatility and utility in supramolecular chemistry as host molecules, calixarenes have been taken as "macrocycles with almost unlimited possibility",[1] which mostly result from the ease in the synthesis of the basic platform and ready modification at the lower and upper rims as well as the functional developments in molecular recognition and assembly.[2-5] Although replacement of the CH_2 linkage by heteroatoms such as N, O, and S had been a challenge in the calixarene,[6] the synthetic difficulty postponed the emergence of heteroatom-bridged calixarenes to explore the interesting properties expected. It is in 1997 that Miyano *et al.* first reported the viable synthetic routes to thiacalixarenes,[7] since then thiacalixarenes have attracted considerable interest as an alternative to "classic" calixarenes by providing sites for functionalization not only on the aromatic rings but also on

the bridging sulfur atoms. Further, thiacalixarenes possess additional coordination sites and the cavity dimensions are increased compared with analogous calixarenes.[8,9] Unlike calix[4]arenes, thiacalix[4]arenes show affinity for transition metal ions because the sulfur atoms in the calixarene framework take part in the metal ion complexation.[10,11] As we know, calixarene possessing thiadiazole groups on lower rims have shown important recognition ability for metal ions and analytical application to ISE, metal-ion complexing agents and so on.[12] More recently, many heterocyclic groups such as pyridyl, bipyridl have been introduced into the thiacalixarene framework.[13,14] Thiadiazoles and their derivatives have been widely studied for analytical and industrial applications such as bioactive compounds, metal chelating agents, lubricant additives like corrosion inhibitors and antiwear agents, cross-linkers or polymers, and as components of cathode material battery systems.[15-18]

During our ongoing research on calixarene chemistry, we launched the program for constructing novel thiacalixarene bearing thiadiazole groups in order to enhance their cation selectivities. In this paper we focus on the synthesis of thiacalix[4]arene derivatives possessing thiadiazole groups at the lower rims and their conformational behavior by the combination of NMR spectroscopy and single crystal X-ray diffraction.

RESULTS AND DISCUSSION



Scheme 1

Design and synthesis

Tetraalkylation of the lower rims in thiacalix[4]arene **1** represents an usual procedure for tuning the thiacalixarene framework.[19-22] In this text, the synthetic routine is straight way as shown in Scheme 1. The alkylation of **1** with 10-fold excess of α, ω-dibromoalkyl in the presence of K_2CO_3 in refluxing acetone gave the expected tetrabromothiacalix[4]arene **2a**, **2b** smoothly in satisfactory yields. The target compounds **3a**, **3b** and **4a**, **4b** were easily obtained by the reaction of **2a** or **2b** and 2-mercaptothiadiazole derivatives in presence of K_2CO_3 in higher yields, respectively.

Conformation analysis

It has been well-known that the conformations of classic calix[4]arene derivatives can conveniently be assigned by use of the ^{1}H NMR resonance pattern of the methylene groups linking the phenol nuclei.[23] However, it is not easy to assign the conformations of thiacalixarene because of the absence of the probing methylene moiety. For the conformations of thiacalix[4]arene, theoretically, partialcone and 1,2-alternative among the possible four conformers can be deduced from their ^{1}H NMR resonances of the *tert*-butyl and aromatic protons, respectively. On the contrary, the distinction between the cone and 1,3-alternate conformers is very different in solution, because ^{1}H NMR spectra of these two conformers appear the same resonance pattern for the Bu^t and Ar-H protons. Lhoták *et al.* [19] reported that it was possible to distinguish between these cone and 1,3-alternate isomers by the ^{1}H NOE Diff experiment. Subsequently, Lhoták *et al.* [21] reported that the tetraalkylation of thiacalix[4]arene **1** using a bulky alkyl halide (such as 1-iodopropane (PrI)) was carried out by the procedure of PrI/K_2CO_3 in refluxing acetone to immobilize a main 1,3-alternate conformer. Practically, the alkylation of **1**, carried out using α, ω-dibromoalkyl in the presence of K_2CO_3 in refluxing acetone, lead to the main 1,3-alternate conformer **2a** and **2b** detected by TLC, ^{1}H NMR as well as X-ray diffraction. The tetrabromo derivatives **2a** and **2b** in 1,3-alternate conformer are preferentially kept the corresponding configure in thiacalix[4]arene derivatives **3a, 3b** and **4a, 4b**. Indeed, their ^{1}H NMR spectra are extremely simple and show the presence of one conformer under measurement conditions. Also, the 1,3-alternate conformation of **2b,3b** were unequivocally confirmed by X-ray crystallography.

X-Ray structure

In order to gain more information about conformational properties, single crystals of two compounds (**2b** and **3b**) have been obtained by the slow evaporation of chloroform-methanol solution at rt and studied by

X-ray diffraction methods. Obviously, both two derivatives adopt the 1,3-alternate conformation in the solid state. (See Figures **1**, and **2**)

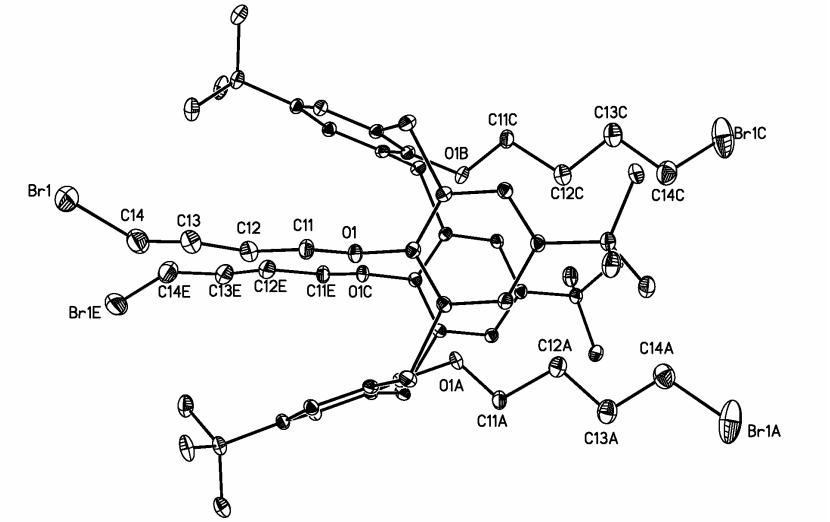


Figure 1. The structure of compound **2b** (hydrogen atoms were deleted for clarity)

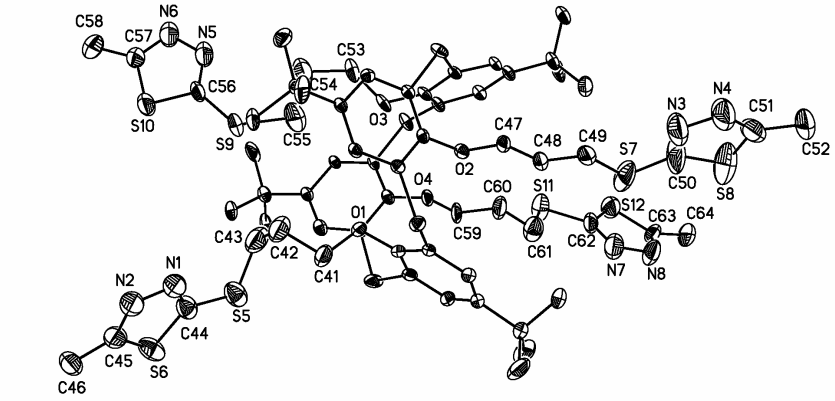


Figure 2. The structure of compound **3b** (each chloroform and methanol solvent molecules as well as all hydrogen atoms were deleted for clarity)

EXPERIMENTAL

All reactions were carried out under nitrogen atmosphere. All dry solvents were prepared according to standard procedures. Melting points are uncorrected and were determined using a Boetius Block apparatus (China). ^{1}H NMR spectra were recorded at Bruker DPX 400 MHz. Elemental analyses were measured on Carlo-Erba 1106 instruments. All samples were dried in the desiccator over P_2O_5 under vacuum (1 torr) at 80 ˚C for 8 h. Mass spectra were measured using ESI technique on Bruker Esquire 3000 spectrometer. IR spectra were measured on an FT-IR spectrometer Nicolet Avata 350 in KBr. The purity of the substances and the courses of reactions were monitored by TLC using TLC glass sheets with silica gel. X-Ray crystallographic data for **2b, 3b**, were obtained using a Bruker SMART APEX II CCD

diffractometer equipped with graphite monochromated Mo *K*α radiation (λ = 0.71073 Å) at 291 K. The structure was solved by direct methods using SHELXS-97 and refined using SHELXL-97 by full-matrix least-squares methods on F^2.[24,25] Hydrogen atoms were located from expected geometry and were isotropically refined by riding model. All non-hydrogen atoms were refined anisotropically except those of the disordered fragments. The φ-ω scan was used for absorption correction.

Synthesis of *p-tert*-butyltetrabromoalkylthiacalix[4]arene (general procedure)

A mixture of *p-tert*-butylthiacalix[4]arene (2.00 g, 2.78 mmol), dibromoalkane (55.00 mmol), K_2CO_3 (1.92 g, 13.9 mmol) in dry acetone (150 mL) was refluxed under N_2 at 80 ˚C. After the solution was cooled at rt, the solvent was evaporated under reduced pressure and the residue was resolved in $CHCl_3$ (100 mL). The mixture was washed with water (4×100 mL) and the organic layer was dried with Na_2SO_4 and evaporated to dryness under reduced pressure. It was recrystallized by $CHCl_3$/MeOH (1/3), and the pure compound was obtained as white solid.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetra(3-bromepropoxy)-2,8,14,20-tetrathiacalix[4]arene 2a. The reaction time was 40 h. Yield : 72 %. Mp > 270 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.35 (s, 8 H, ArH), 3.97 (t, *J* = 6.8 Hz, 8 H, -O$\underline{CH_2}CH_2$-); 3.07 (t, *J* = 7.1 Hz, 8 H, Br$\underline{CH_2}CH_2$-); 1.54 (t, *J* = 7.3 Hz; 8 H; -$CH_2\underline{CH_2}CH_2$-);1.34 (s, 36 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ: 156.3; 146.5; 128.2; 127.3; 67.1 (OCH_2); 34.5 (CCH_3); 32.3; 31.4; 30.5. MS/ESI: m/z: calculated :1205.0; found: 1227.1 $(M+Na-H)^+$; Anal. Calcd for $C_{52}H_{68}O_4Br_4S_4$: C ,51.83 ; H, 5.69; S ,10.64. Found: C, 52.72; H, 5.93; S, 10.45.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetra(4-brominebutoxy)-2,8,14,20-tetrathiacalix[4]arene 2b. The reaction time was 36 h. Yield: 47 %. Mp > 270 ˚C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ: 7.34 (s, 8 H, ArH); 3.85 (t, *J* = 7.7 Hz, 8 H, -O$\underline{CH_2}CH_2$-); 3.27 (t, *J* = 6.9 Hz, 8 H, -$CH_2\underline{CH_2}$Br-); 1.70 (t, *J* = 7.4 Hz, 8 H, -$OCH_2\underline{CH_2}$-); 1.26 (t, *J* = 9.4 Hz, 8 H, -$\underline{CH_2}CH_2$Br-); 1.29 (s, 36 H ,$C(CH_3)_3$). ^{13}C NMR ($CDCl_3$,, 125 MHz): δ: 157.1, 145.8, 128.3, 128.0, 68.2, 34.3, 33.1, 31.5, 29.3, 27.8; IR(KBr) ν: 2961, 2869 1637, 1617, 1383,1263, 1090, 877, 764, 621. MS/ESI: m/z: calculated:1261.1; found: 1283.1 $(M+Na-H)^+$. Anal. Calcd for $C_{56}H_{76}O_4S_4Br_4$: C, 53.34; H, 6.07; S,10.17. Found: C, 53.12; H, 6.02; S, 10.09.

Synthesis of *p-tert*-butylthiacalix[4]arene bearing thiadiazole groups (general procedure)

A mixture of *p-tert*-butyltetrabromoalkyoxythiacalix[4]arene (0.17 mmol), 2-mercaptothiadiazole compound (1.32 mmol), and K_2CO_3 (0.23 g, 1.65 mmol) in dry acetone (60 mL) was refluxed under N_2 at 62 ˚C. After the solution was cooled at rt, the solution was evaporated under reduced pressure and the

residue was resolved in $CHCl_3$ (50 mL). the mixture was washed with water (4×50 mL) and the organic layer was dried with Na_2SO_4 overnight and evaporated to dryness under reduced pressure. Recrystallized by $CHCl_3$/MeOH, the pure compound was obtained as white solid.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetra{3-[(thiadiazol-2-yl)sulfanyl]propoxy}-2,8,14,20-tetrathiacalix[4]arene 3a. The reaction time was 33.5 h**.** Yield: 89%. Mp 260.2-261.6 ˚C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ: 9.00 (s, 4 H, CH); 7.35 (s, 8 H, ArH); 4.01 (t, J = 7.0 Hz, 8 H, -O$\underline{CH_2}CH_2$-); 3.16 (t, J = 7.3 Hz, 8 H, -$CH_2\underline{CH_2}$S-); 1.55 (t, J = 7.2 Hz, 8 H, -$OCH_2\underline{CH_2}CH_2$S-); 1.25 (s, 36 H, -$C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ: 165.6, 156.5, 151.2, 146.4, 128.2, 127.5, 67.0, 34.4, 31.3, 30.8, 29.7, 28.6. IR (KBr) ν: 2960, 2868., 1637, 1617, 1566, 1442., 1383, 1265, 1062, 616. MS/ESI m/z: calculated:1352.2. found:1375.2 $(M+Na)^+$; Anal. Calcd for $C_{60}H_{72}O_4S_{12}N_8$: C, 53.25; H, 5.37; N, 8.28; S, 28.37. Found: C, 53.18; H, 5.12; N, 8.09; S, 28.30.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetra{3-[(5-methylthiadiazol-2-yl)sulfanyl]propoxy}-2,8,14, 20-tetrathiacalix[4]arene 3b. The reaction time was 21 h. Yield**:** 76%. Mp 266.3-267.4 ˚C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ: 7.34 (s, 8 H, ArH); 3.98 (t, J = 6.7 Hz, 8 H, -O$\underline{CH_2}CH_2$-); 3.08(t, J = 7.1 Hz, 8 H, -$CH_2\underline{CH_2}$S-); 2.74 (s, 12 H, -CH_3); 1.50 (t, J = 6.9 Hz, 8 H, -$CH_2\underline{CH_2}CH_2$-); 1.25 (s, 36 H, -$C(CH_3)_3$). ^{13}C NMR: ($CDCl_3$, 125 MHz): δ: 165.4, 164.9, 156.5, 146.4, 128.2, 127.5, 67.1, 34.4, 31.4, 30.7, 28.6, 15.7; IR(KBr) ν: 2960, 2867 1568, 1442, 1383, 1265, 1011, 874, 763. MS/ESI: m/z: calculated:1408.3. found: 1431.3 (M+Na)$^+$; Anal. Calcd for $C_{64}H_{80}O_4S_{12}N_8$: C, 54.53; H, 5.73; N, 7.95; S, 27.24. Found: C, 54.38; H, 5.64; N, 7.86; S, 27.11.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetra{4-[(thiadiazol-2-yl)sulfanyl]butoxy}-2,8,14,20-tetrathiacalix[4]arene 4a. The reaction time was 48 h**.** Yield: 69%. Mp 239.9-240.4 ˚C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ: 9.00 (s, 4 H); 7.35 (s, 8 H, ArH,); 3.89 (t, J = 7.8 Hz, 8 H, -O$\underline{CH_2}CH_2$-); 3.28 (t, J = 7.3 Hz, 8 H, -$CH_2\underline{CH_2}$S-); 1.71 (t, J = 7.5 Hz, 8 H, -$OCH_2\underline{CH_2}$-); 1.32 (t, J = 7.6 Hz, 8 H, -$\underline{CH_2}CH_2$S-); 1.27 (s, -$C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ: 165.7, 157.0, 151.2, 145.7 128.2, 128.1, 68.3, 34.3, 34.0, 31.4, 28.2, 25.4. MS/ESI: m/z: calculated: 1408.3. found: 1431.3$(M+Na)^+$. IR(KBr) ν: 2959, 2868, 1633, 1567, 1444, 1374, 1266, 1059, 877, 618. Anal. Calcd for $C_{64}H_{80}O_4S_{12}N_8$: C, 54.53; H, 5.73; N, 7.95; S, 27.24. Found: C, 54.46; H, 5.68; N, 7.88; S, 27.13.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetra{4-[(5-methylthiadiazol-2-yl)suifanyl]butoxy}-2,8,14,20-tetrathiacalix[4]arene 4b. The reaction time was 38 h. Yield: 74%. Mp 225.8-226.5 ˚C. ^{1}H NMR

($CDCl_3$, 400 MHz): δ: 7.83 (s, 8 H, ArH); 3.87 (t, J=7.8 Hz, 8 H, -O$\underline{CH_2}CH_2$-); 3.20 (t, J = 7.3 Hz, 8 H, -$CH_2\underline{CH_2}$S-); 2.73 (s, 12 H, -CH_3); 1.67 (t, J = 7.4 Hz, 8 H, -O$\underline{CH_2}CH_2$-); 1.27 (s, 36 H, -$C(CH)_3$); 1.29(t, J = 12.0 Hz, 8 H,-$\underline{CH_2}CH_2$S-). ^{13}C NMR ($CDCl_3$, 125 MHz): δ: 165.3, 164.9, 157.1, 145.7, 128.2, 128.2, 68.4, 34.3, 33.9, 31.5, 29.7, 28.2, 25.5, 15.7. MS/ESI: m/z: calculated: 1466.2; found: 1489.2 $(M+Na)^+$. IR (KBr) ν: 2943, 2867, 1633, 1568, 1442, 1382, 1263, 1089, 1033, 880, 765, 615. Anal. Calcd for $C_{68}H_{88}O_4S_{12}N_8$: C, 55.72; H, 6.06; N, 7.65; S, 26.20. Found: C, 55.45; H, 5.98; N, 7.38; S, 25.86.

Crystallographic study

X-Ray data for **2b**: $C_{56}H_{76}Br_4O_4S_4$, M = 1261.05 g/mol, tetragonal system, space group I4(1)/a, a = 19.3664(12) Å, b = 19.3664(12) Å, c = 16.012(2) Å, $\alpha = \beta = \gamma = 90°$, V = 6005.6(9) Å^3, Z = 4, D_c = 1.395 g/cm^3, μ = 2.861 mm^{-1}, F(000) = 2592, crystal dimensions of 0.22 x 0.19 x 0.13 mm. The final refinement gave R = 0.0818 and Rw = 0.1964 using 2798 independent reflections (θ_{max} = 25.50, 179 parameters). The maximum and minimum difference peaks and holes are 0.850 and -0.654 e·Å^{-3}, respectively. Some atoms of four bromoalkoxy chains were found disordered and were modeled with two positions and occupation factors. Some constraints on bond lengths and angles were applied on the disordered fragments. Crystallographic data were deposited in CSD under CCDC registration number 642371.

X-Ray data for **3b**: $C_{64}H_{80}N_8O_5S_{12}\cdot CHCl_3\cdot CH_3OH$, M = 1561.49 g/cm^3, triclinic system, space group p-1, a = 15.431(11) Å, b = 16.177(11) Å, c = 17.917(12) Å, α = 112.719(10)º, β = 93.557(11)º, γ = 90.380(11)º, V = 4115(5) Å^3, Z = 2, Dc = 1.260 g/cm^3, μ = 0.464 mm^{-1}, F(000) = 1640, crystal dimensions of 0.38 x 0.27 x 0.24 mm. The final refinement gave R = 0.1589 and Rw = 0.3578 using 20075 independent reflections (θ_{max} = 28.62, 865 parameters). The maximum and minimum difference peaks and holes are 1.121 and -0.563 e·Å^{-3}, respectively. Crystallographic data were deposited in CSD under CCDC registration number 642373.

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