Syntheses and Conformations of Tetrahomodioxacalix[4]arene Tetraamides and Tetrathioamides

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Abstract: A series of tetrahomodioxacalix[4]arene tetraamides and tetrathioamides with four *p*-phenyl groups on their upper rim were synthesized. From the ^{1}H and ^{13}C NMR and crystal structure, *N*-butylamido homooxacalix[4]arene (**4**) was found to be in the 1,3-alternate conformation and has intramolecular hydrogen bonding between N−H and facing oxygen atoms of the carbonyl O═C group. This hydrogen bonding decreased the metal ion complex ability. Transformation of the 1,3-alternate *N*-butylamido (**4**) into *N*-butylthioamido homooxacalix[4]arene (**5**) using Lawesson's reagent gave a conformational change to the C-1,2-alternate.

Calixarenes have been of interest both as complexation hosts for ions and molecules and as frameworks for elaborating more complex structures.[1−3] Homooxacalix[4]arenes, which contain extra oxygen atoms in the macrocyclic ring, however, have received relatively little attention, mainly because they can be synthesized only in rather low overall yields.[4−6] There have only been limited studies of the solution conformations, solid-state structures, and complexation properties of homooxacalix[4]arenes.[7−10] Masci and co-worker[11] reported that the main conformation of tetrahomodioxa-*p*-*tert*-butylcalix[4]arene tetramethyl ether is C-1,2-alternate on the basis of temperature-dependent NMR spectral analysis. Recently, we reported that C-1,2-alternate tetrahomodioxacalix[4]arene tetraamide (**2**) selectively encapsulates Pb^{2+} over alkali, alkaline earth, ammonium, and transition metal ions with formation of a 1:1 complex. In the solid-state structure, the Pb^{2+} is bound to the carbonyl oxygens of two adjacent amide substituents and an aryl-alkyl ether oxygen of one of them.[12] In this paper, we report the synthesis of a series of tetrahomodioxa-*p*-phenylcalix[4]arene tetraamides and tetrathioamides and their two-phase picrate extraction for metal cations.

The synthetic routes for homooxacalix[4]amides (**2** and **4**) and homooxacalix[4]thioamides **3** and **5** are described in Scheme 1. Reaction of **1** having a flexible conformation with *N*,*N*-diethyl chloroacetamide gave **2**, which is in the C-1,2-alternate conformation.[12] In an earlier paper, we chose to designate one of the conformers of a tetrahomodioxacalix[4]arene as a 1,4-alternate.[12] On further reflection, however, we have decided that it would be preferable to retain the 1,2-alternate designation for this conformer and to differentiate between the two possible 1,2-alternate conformers in the following manner: the 1,2-alternate conformer in which the adjacent syn aryl moieties are joined by a CH_2 group is designated as the C-1,2-alternate, while the 1,2-alternate conformer in which the adjacent syn aryl moieties are joined by a CH_2-OCH_2 moiety is designated as the COC-1,2-alternate. Each conformation can be identified by ^{1}H and ^{13}C NMR spectroscopy. Using Lawesson's reagent, we obtained **3**, which retained the C-1,2-alternate conformation as proved by NMR spectroscopy. In the 600 MHz ^{1}H NMR spectrum, the methylene protons of the ArCH_2Ar bridge for **3** showed two AB doublets at δ 4.56 and 3.57 ($\Delta\nu$ = 596.28 Hz) with a geminal coupling constant of 13.5 Hz. An AB pattern for the dimethylenoxy protons of ArCH_2-OCH_2Ar appeared at δ 4.74 and 4.31 ($\Delta\nu$ = 262.38 Hz) with a geminal coupling constant of 12.09 Hz. Another AB pattern for the methylene protons of ArOCH_2CSNEt$_2$ appeared at δ 4.97 and 4.45 ($\Delta\nu$ = 312.18 Hz) with a geminal coupling constant of 12.3 Hz. The ^{13}C NMR spectrum showed a single peak from a carbonyl carbon, one peak at 67.38 ppm for the ArCH_2O bridge methyleneoxy carbons, and one peak at 30.89 ppm for the ArCH_2Ar bridge carbons implying that two adjacent benzene rings are in a syn orientation. So, **3** is in the stable C-1,2-alternate conformation.

Interestingly, reaction of **1** with *N*-butyl chloroacetamide instead of *N*,*N*-diethyl chloroacetamide provided **4**, but corresponding NMR patterns were quite different

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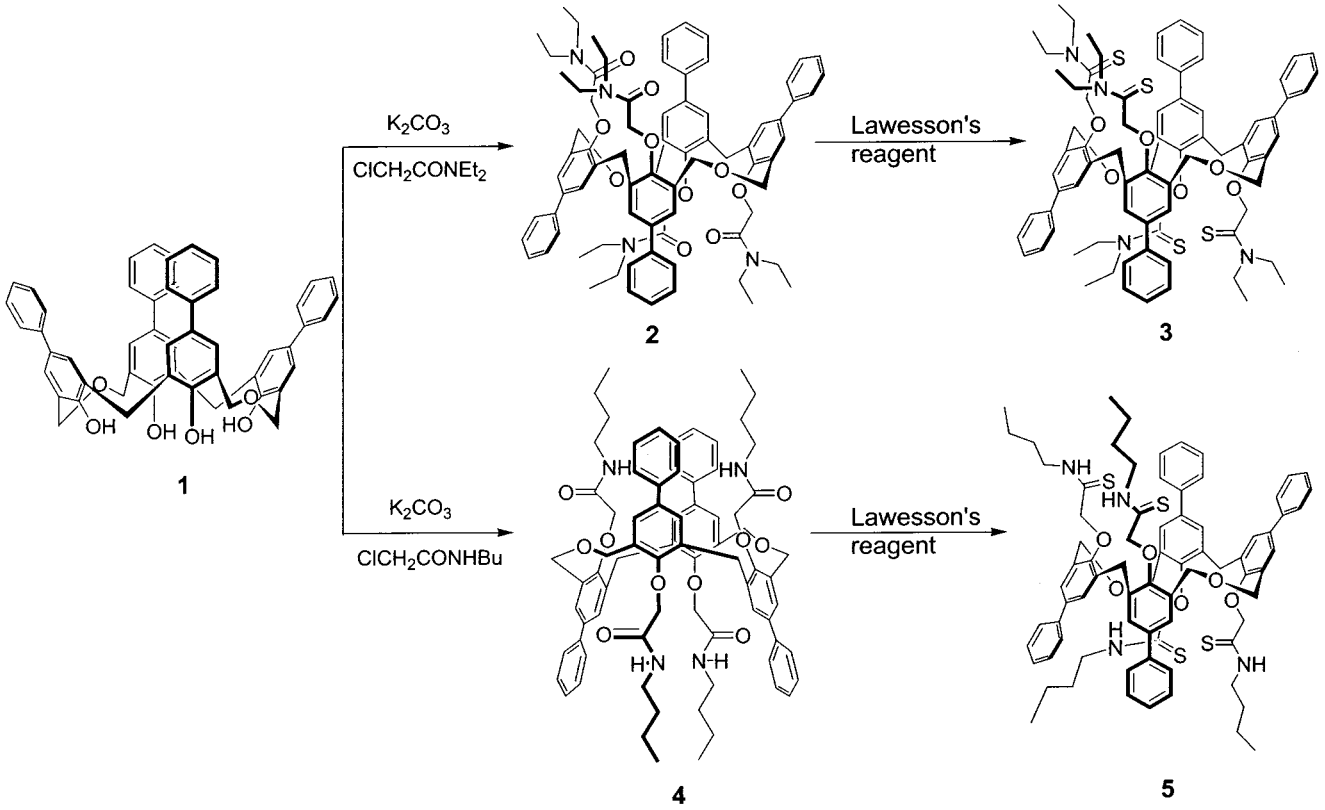
Scheme 1. Synthetic Routes for 2−5



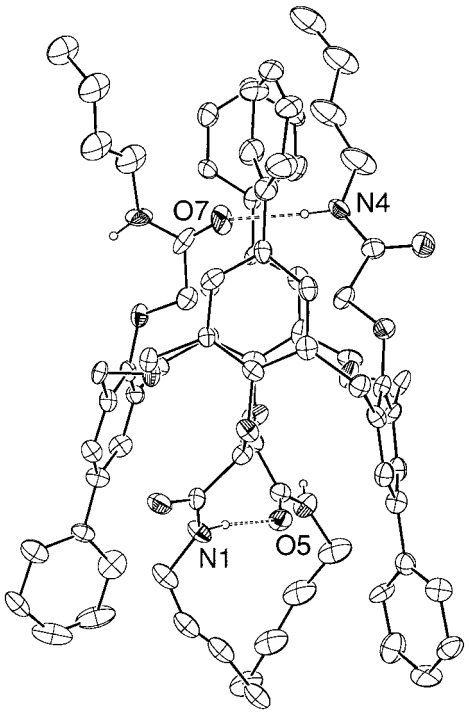


Figure 1. ORTEP drawing of **4**.

from those of **2**. A singlet at δ 4.01 in the ^{1}H NMR spectrum and a singlet at 38.9 ppm in the ^{13}C NMR spectrum indicated that **4** is in the 1,3-alternate conformation. No other conformations were observed. The X-ray crystal structure of **4** is also a positive proof for the 1,3-alternate conformation as shown in Figure 1. In the crystal structure, distances for N(1)H···O(5) and N(4)H···O(7) were found to be 2.08 and 2.01 Å, respectively. Angles of N(1)−H−O(5) and N(4)−H−O(7) are 169.8 and 176.8°, respectively, indicating that there are intramolecular hydrogen bondings between amide N−H and the facing oxygen atom of C═O. Using TLC to monitor the synthesis of **4**, we found that after 6 h the product was a mixture of the 1,3- and C-1,2-alternate conformers. After 12 h, however, the product was entirely the 1,3-alternate conformer, suggesting that the C-1,2-alternate conformer is the initially formed product that then changes to the 1,3-alternate conformer, which is more stable as a result of intramolecular H-bonding. More interestingly, during the preparation of thioamide **5** using Lawesson's reagent, the conformation changed to C-1,2-alternate again. In the ^{1}H NMR spectrum, the methylene protons of the ArCH_2-Ar bridge for **5** showed two AB doublets at δ 4.81 and 3.59 ($\Delta\nu$ = 730.38 Hz) with a geminal coupling constant of 15.8 Hz. An AB pattern for the dimethylenoxy protons of ArCH_2OCH_2Ar appeared at δ 4.78 and 4.08 ($\Delta\nu$ = 417.12 Hz) with a geminal coupling constant of 15.36 Hz. Another AB pattern for the methylene protons of ArOCH_2-$CSNHC_4H_9$ appeared at δ 4.76 and 4.60 ($\Delta\nu$ = 93.54 Hz) with a geminal coupling constant of 10.62 Hz. The ^{13}C NMR spectrum showed one peak at 31.88 ppm for the ArCH_2Ar bridge carbons. On the basis of the NMR spectra, one can assign the C-1,2-alternate conformation to **5**. In contrast to **4**, the thioamide **5** is less strongly intramolecularly H-bonded, with the result that the C-1,2-alternate conformer does not convert to the 1,3-alternate conformer.

To prove the conformational change of **4** when it forms from **1**, we carried out an amination of the C-1,2-alternate homooxacalix-tetraethyl ester **6** as shown in Scheme 2. Stirring the reaction mixture of **6** and butylamine for 6 h gave **4** as a mixture of 1,3- and C-1,2-alternate conformers with 55 and 45% yields, respectively. In a 24 h

Scheme 2. Synthetic Routes for 4 from Homooxacalix[4]arene Tetraethyl Ester 6

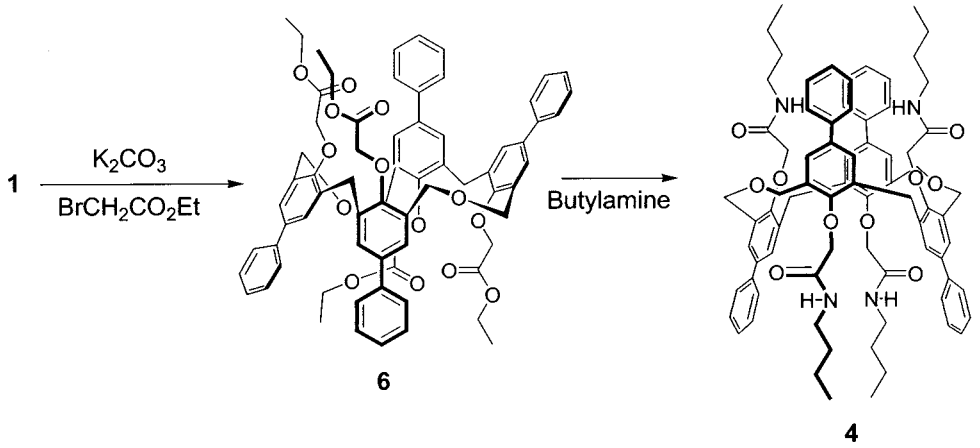


Table 1. Extractability (%) of 2−5 for Cations in Picrate Extraction

	extractability (%)[a] for cations							
ligand	Na^+	K^+	Rb^+	Cs^+	NH_4^+	Ag^+	Pb^{2+}	Sr^{2+}
2	0	0.16	2.16	1.01	3.97	14.49	86.55	9.50
3	4.03	6.51	5.04	5.65	3.58	158.64	4.89	6.22
4	0	0	0	3.47	0	4.36	0	0
5	7.70	2.69	3.82	2.40	7.78	179.04	7.90	9.55

[a] Extractability = (metal ion concentration extracted into organic layer)/(ligand concentration used) × 100.

reaction, the conformation completely changed to 1,3-alternate as observed in Scheme 1 as well. This is also ascribed to the intramolecualr H-bonding between the N-H and the facing oxygen atom of C=O in the 1,3-alternate conformation. To investigate the conformational change of **6** itself at high temperatures, ethanol solution of **6** was refluxed for 7 days, but no conformational changes were observed at all.

It has been noted that for calix[4]arene ester and amide derivatives, the latter are stronger metal ion complexing agents.[13,14] To obtain insight into the metal ion affinity of homooxacalixarene-based ligands, extractabilities toward metal ions by **2**−**5** were determined by the metal picrate extraction method. The results are listed in Table 1. The C-1,2-alternate tetrahomodioxacalix[4]arene tetraamide (**2**) selectively binds Pb^{2+} over other cations with formation of a 1:1 complex.[12] However, the binding ability of **4** for all the cations remarkably decreased. This is obviously because the 1,3-alternate conformation driven by stable intramolecular H-bonding gives an unsuitable binding site for the cations. C-1,2-Alternate thioamide derivatives **3** and **5** showed Ag^+ ion selectivity due to the sulfur atoms of the carbonyl group. In the case of Ag^+ ion, the complex ratio of **3**·Ag^+ to **5**·Ag^+ was found to be 1:2 by mass spectral analysis. This is the reason 100% extractability was obtained in the case of **3** and **5**. The *N*-butylamide group seems to be less hindered for silver ion than the *N*,*N*-diethylamide group, resulting in higher extractability with **5**.

In conclusion, a series of tetrahomodioxacalix[4]arene tetraamides and tetrathioamides with four *p*-phenyl groups on their upper rim were synthesized. From the ^1H and ^{13}C NMR and crystal structure, *N*-butylamido (**4**) is shown to be in the 1,3-alternate conformation and there is intramolecular hydrogen bonding between N-H and the facing oxygen atoms of the carbonyl O=C group. This hydrogen bonding decreases the metal ion complex ability. Transformation of *N*-butylamido homooxacalix[4]arene (**4**) into *N*-butylthioamido homooxacalix[4]arene (**5**) caused a conformational change from 1,3-alternate to C-1,2-alternate. One can conclude that *N*,*N*-dialkylamido and the corresponding thioamido homooxacalix[4]arene exist as an C-1,2-alternate conformation, while *N*-monoalkylamido homooxacalix[4]arene favors the 1,3-alternate conformation due to intramolecular H-bonding.

Experimental Section

Unless otherwise noted, reagents were obtained from commercial suppliers and used without further purification. Melting points were taken in evacuated and sealed capillary tubes. IR spectra were determined as KBr pellets and are available in Supporting Information. Chemical shifts are recorded in parts per million relative to TMS as an internal standard.

Compounds **1**,[7] **2**,[12] and **6**[13−15] were prepared from adaptation of the reported procedures.

Syntheses: 7,13,21,27-Tetraphenyl-29,30,31,32-tetrakis-(diethylthiocarbamoyl)methoxy-2,3-16,17-tetrahomo-3,17-dioxacalix[4]arene (3). To a solution of **2** (504 mg, 0.41 mmol) in dry toluene (20 mL) was added 0.37 g (0.91 mmol) of Lawesson's reagent. The mixture was heated for 20 h at 90 °C. Solvent was removed in vacuo, and the residue was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with water, dried over $MgSO_4$, and evaporated in vacuo. The residue was triturated with MeOH to give 501 mg (94.5%) of the **5** as a pale yellow, crystalline solid with mp 255 °C. Anal. Calcd for $C_{78}H_{88}O_6N_4S_4$: C, 71.74; H, 6.79. Found: C, 71.56; H, 6.70.

7,13,21,27-Tetraphenyl-29,30,31,32-tetrakis(butylcarbamoyl)methoxy-2,3-16,17-tetrahomo-3,17-dioxacalix[4]-arene (4). The procedure was the same as that for **2**: yield 45%; crystalline solid with mp 240 °C. Anal. Calcd for $C_{78}H_{88}O_{10}N_4$: C, 75.46; H, 7.14. Found: C, 75.40; H, 7.05.

Amination (4) from 6 (See Scheme 2). To a solution of **6** (500 mg, 0.44 mmol) in absolute ethanol (25 mL) was added 8 mL of *n*-butylamine under an Ar atmosphere. The mixture was refluxed for 7 days. Solvent was evaporated in vacuo, and the residue was triturated with MeOH to give 470 mg (85.8%) of **4** as colorless crystals.

7,13,21,27-Tetraphenyl-29,30,31,32-tetrakis(butylthiocarbamoyl)methoxy-2,3-16,17-tetrahomo-3,17-dioxacalix-[4]arene (5). The procedure was the same as that for **3**: yield 76.2%; colorless crystalline solid; mp 238 °C dec. Anal. Calcd for $C_{78}H_{88}O_{10}N_4$: C, 75.46; H, 7.14. Found: C, 75.42; H, 7.05.

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Metal Picrate Extraction. Metal picrates were prepared by reaction of picric acid with the appropriate metal carbonate.[16,17] To determine the extractability of the ligand for a metal picrate, an aqueous solution (2.0 mL) containing 0.20 mM metal picrate and a chloroform solution (2.0 mL) of the extractant (0.10 mM) were shaken for 30 min at 25 °C. The concentration of picrate anion extracted from the aqueous phase into the organic layer was determined by UV spectrophotometry (λ_{max} = 373 nm). Three independent experiments were carried out for each combination of ligand and metal picrate. The extractability values listed in Table 1 are averages.

Solid-State Structure. Yellow crystals of **4** were obtained by slow evaporation of the solvent of a solution of **4** in CH_3CN-MeOH. A crystal of 0.3 × 0.3 × 0.1 mm was mounted and aligned on a diffractometer.[18−20] The final X-ray data are given in Table S1 (Supporting Information).

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Supporting Information Available: An additional Table S1 and Data S1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

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