Synthesis and structures of [(4-pyridylmethyl)oxy]tetrathiacalix[4]arenes derived from *O*-alkylation of tetrathiacalix[4]arene with 4-(chloromethyl)pyridine

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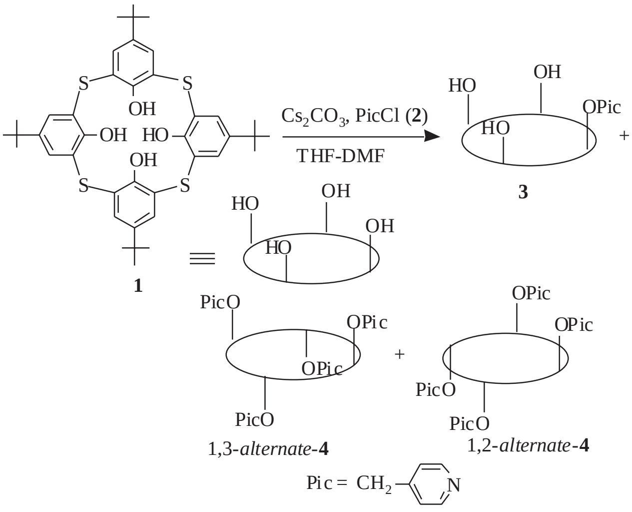
O-Alkylation of the flexible tetrathiacalix[4]arenes **1** with 4-(chloromethyl)pyridine in the presence of Cs_2CO_3 gave tetra-*O*-alkylated products with 1,3-alternate and 1,2-alternate conformation.

Keywords: thiacalix[4]arene, alkylation, conformation, template effect

Calixarene and related macrocycles have received considerable attention for their host-guest chemistry as ionophoric receptors[1] and potential enzyme mimics in biology.[2] Chemical modification of calixarene represents an effective and versatile way of producing receptors with highly selective cation binding properties. Even minor changes in the regioselective functionalisation or conformation of the chemically modified calixarene can be associated with drastic changes in the complexation properties.

Recently, we have reported that *O*-alkylation of tetrathiacalix[4]arene carried out with 2-(chloromethyl) pyridine in the presence of Cs_2CO_3 furnished exclusively the formation of the tetra-substituted products with 1,3-alternate and 1,2-alternate conformations in the ratio of 91:9.[3] Tetrakis [(2-pyridylmethyl)oxy]thiacalix[4]arenes derived from thiacalix[4]arene show strong Ag^+ ion affinity. ^1H NMR Titration with $AgSO_3CF_3$ clearly demonstrated that a 1:1 complex is formed with retention of the original symmetry. Interestingly, the conformational changes of the pyridine moiety from the original outward nitrogen to the inside orientation toward the cyclophane cavity was observed in the process of Ag^+ complexation. On the other hand, Reinhoudt and coworkers[4] also reported the well-defined hydrogen-bonded calix[4]arene duplex between tetrakis [(4-pyridyl-methyl)oxy]calix[4]arene and calix[4]arene tetracarboxylic acid. Independently, Shinkai and coworkers have extended this kind of upper-rim functionalisation to larger calixarenes such as tetrakis[(3-pyridylmethyl)oxy]calix[4] arene.[5] Thus there is substantial interest in investigating the synthesis and structures of tetrakis[(4-pyridylmethyl)oxy] thiacalix[4]arenes with cone and 1,3-alternate conformation, in which the former compounds are supposed to have the property to construct the hydrogen-bonded C_4 symmetrical calix[4]arene duplex with calix[4]arene tetracarboxylic acid.

In this paper we describe the metal template effect on *O*-alkylation of tetrathiacalix[4]arene with 4-(chloromethyl)pyridine to afford tetrakis[(4-pyridylmethyl) oxy]thiacalix[4]arenes with 1,2- and 1,3-alternate conformations and studies of their conformations in solution.



Scheme 1

Results and discussion

Like calix[4]arene, complete *O*-alkylation of the OH groups of tetrathiacalix[4]arene may produce all the four possible isomers at most, each of which should be conformationally stable in the cone, 1,2-alternate, partial-cone, and 1,3-alternate conformations. In fact *O*-alkylation of the flexible macrocycle **1**[6] with 4-(chloromethyl)pyridine **2** in the presence of K_2CO_3 under DMF-THF reflux gave only the monoalkylated compound **3** in 62% yield along with recovery of the starting compound in 14% yield. Exhaustive alkylation of thiacalix[4]arene was attained to afford 1,3-*alternate*-**4** and 1,2-*alternate*-**4** in 73 and 14% yields, respectively, when using the caesium carbonate as the base, whereas other possible isomers were not observed in tetra-*O*-alkylated product. However, in the case of NaH and Na_2CO_3 as bases under the same reaction conditions only the recovery of the starting compound **1** resulted.

In general, stereochemical assignments of calix[4]arenes with pendant pyridine groups followed unambiguously from distinctive ^1H NMR spectroscopic patterns of the bridge methylene protons[7] and OCH_2Py protons, arising from the substitution pattern at the lower rim and from the conforma-

Table 1 *O*-Substitution reaction of thiacalix[4]arene **1** with 4-(chloromethyl)pyridine **2**

		Distribution(%)^{a,b}			
Run	Base	**3**	1,3-*alternate*-**4**	1,2-*alternate*-**4**	Recovered **1**
1	NaH	0	0	0	100 (92)
2	Na_2CO_3	0	0	0	100 (90)
3	K_2CO_3	80 (62)	0	0	20 (14)
4	Cs_2CO_3	0	81 (73)	19 (14)	0

^{a}Determined by ^1H NMR spectra. ^{b}Isolated yields are shown in parentheses.

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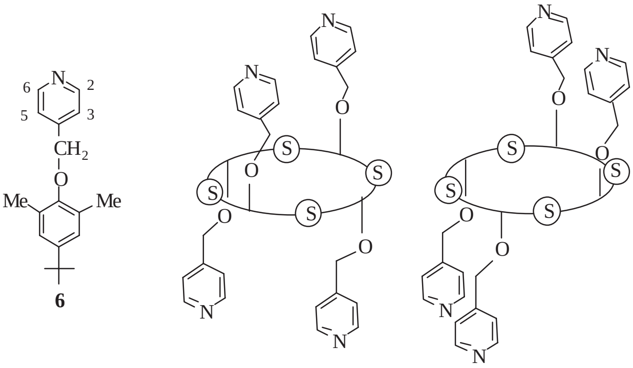


6

1,3-*alternate*-**4**

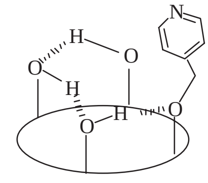
1,2-*alternate*-**4**

Fig. 1 Reference compound **6** and orientation of the pyridine N atoms in 1,3- and 1,2-*alternate*-**4**.

Table 2 Chemical shift of pyridine protons in 1,3- and 1,2-*alternate*-**4** and reference compound **6**[a]

	Chemical shift, δ ppm[b]	
Compd.	$H_{3,5}$	$H_{2,6}$
6	7.41	8.62
1,3-*alternate*-**4**	6.95	8.42
(Δδ)	(-0.46)	(-0.20)
1,2-*alternate*-**4**	6.52	8.11
(Δδ)	(-0.89)	(-0.51)

[a]Δδ values are the difference of the chemical shift between 1,2-, 1,3-*alternate*-**4** and reference compound **6** in $CDCl_3$ at 27 °C.
[b]A minus sign (–) denotes a shift to higher magnatic field.



3

Fig. 2 Intrmolecular hydrogen bonding of **3**.

tion. For example, in tetra-*O*-alkylated calix[4]arenes, the Ar*CH*$_2$Ar show one pair of doublets in the cone conformer, two pairs of doublets in the partial-cone conformer, and one singlet in the 1,3-alternate conformer. Furthermore, the O*CH*$_2$Py protons also display one singlet in the cone and 1,3-alternate conformers, while in the partial cone conformer, they give rise to two singlets and one pair of doublets (diastereotopic oxymethylenes) in the ratio 1:1:2. Unfortunately, because of the lack of bridge methylene protons, it is difficult to judge the conformation of thiacalix[4]arene derivatives from the proton NMR patterns. While similar methods were also applicable to the conformational determination through the *tert*-butyl protons, O*CH*$_2$Py protons and aromatic protons, as well as the combination of these proton patterns. It was reported that in both the calix[4]arene and thiacalix[4]arene bearing ester functional groups, the chemical shift of the butyl protons in the cone conformation was at upper field than that of those in the 1,3-alternate conformation,[8] whereas, in the calix[4]arene bearing pyridine groups, the chemical shift of the *t*-butyl protons in the cone conformation was at lower field than that of those in 1,3-alternate conformation. Similar to the case of 2-pyridylation, there are only 1,3-alternate and 1,2-alternate conformers obtained from the *O*-alkylation of thiacalix[4]arene **1** with 4-(chloromethyl)pyridine when using caesium carbonate as the base. Compared to (benzyloxy)calix[4]arene,[3,9] the same ^1H NMR patterns and close chemical shift values of protons were observed in the 1,3-alternate and 1,2-alternate conformers of the 4-pyridyl derivative. For example, in the case of 4-pyridylthiacalix[4]arene derivatives, there were singlet peaks for *t*-butyl protons, O*CH*$_2$Py protons and aromatic protons for the 1,3-*alternate*-**4** conformer at δ 0.87, 5.16, and 7.11 ppm, respectively. On the other hand for the other conformer, singlet peaks for *t*-butyl protons and O*CH*$_2$Py protons at δ 1.16 and 4.67 ppm respectively and a pair of doublet peaks for the aromatic protons at δ 7.33 and 7.76 ppm with 2.4 Hz coupling constant were also strongly in agreement with the 1,2-alternate conformation of [(4-pyridylmethyl)oxy]thiacalix[4]arene.

The ^1H NMR spectrum pattern of 1,3-*alternate*-**4** indicates a C_4-symmetrical structure. Interestingly, the hetero aromatic protons of the pyridine rings of 1,3-*alternate*-**4** are exposed to the ring current shielding effect[10] operated by the opposing pyridine ring between the diaryl thiaether linkages, and resonate at higher fields with respect to those of the reference compound **6**, which was prepared by *O*-alkylation of 4-*t*-butyl-2,6-dimethylphenol **5** with 4-(chloromethyl)pyridine in the presence of NaH. The magnitude of this shielding, computed as the difference between pertinent pyridine protons of 1,3-*alternate*-**4**, 1,2-*alternate*-**4** and reference compound **6**, increases significantly for the $H_{2,6}$ and $H_{3,5}$ protons (Table 2). The remarkable shielding effect experienced by $H_{3,5}$ (–0.46 ppm) protons of the pyridine suggest that these protons are located in much closer to the opposing pyridine ring than $H_{2,6}$ protons, due to the electron repulsion among the nitrogen atoms in the pyridine rings between the diaryl thiaether linkages. Thus, nitrogens in all of the pyridine rings were orientated outwards against the thiacalixarene cavity as shown in Fig. 1. It was also found that higher up-field shifts were observed in the pyridine protons ($\Delta\delta_{3,5}$= –0.89 and $\Delta\delta_{2,6}$= –0.51 ppm) due to the shorter distance between the 1, 2-proximal positions.

In contrast, the ^1H NMR spectrum of **3** shows resonances for the butyl protons at δ 1.17, 1.18 and 1.21 ppm as singlets in the ratio of 1:2:1, for the methylene protons at δ 5.33 as a singlet, and for the aromatic protons at δ 7.57 and 7.61 ppm (*J* = 2.4 Hz) as a doublet indicating a mono-*O*-substituted structure. Although these signals for the ^1H NMR spectrum could correspond to cone, 1,3-alternate or partial-cone conformer, the IR spectrum of diol **3** shows the absorption of the hydroxyl stretching vibration around 3362 cm^{-1}. The ^1H NMR spectrum (in $CDCl_3$) exhibits the signal for hydroxyl groups around δ = 7.56 and 8.80 ppm in the ratio of 1:2. Although the ν_{OH} and δ_{OH} values in triol **3** show a slightly lower-frequency and up-field shift compared to those of parent compound **1** (ν_{OH} = 3254 cm^{-1} and δ_{OH} = 9.35 ppm), a weaker hydrogen bond does exist than that in the corresponding calix[4]arene. Interestingly, as the temperature of the ^1H NMR sample in $CDCl_3$ was decreased the chemical shifts of the hydroxy groups shifted to lower fields (δ = 8.01 and 9.28 ppm at –50 °C). This finding suggests increased intramolecular hydrogen bonding. Therefore, mono[(4-pyridylmethyl)oxy]thiacalix[4]arene **3** might adopt a cone conformation due to the intramolecular hydrogen bonding between the three hydroxy groups and the alkoxy. Thus hydroxy groups and alkoxy groups can be held strongly on the same side of the thiacalix[4]arene **3**.

Several research groups have reported monoalkylation of calix[4]arenes via direct *O*-alkylation methods using reagents such as 3,5-dinitrobenzoyl chloride[11a] or alkyl halides in the presence of bis(butyltin)oxide. [11b] However, selective monoalkylation of thiacalix[[4]arenes has not yet been established. As mentioned previously, we have accidentally succeeded, for the first time in observing monoalkylation of a thiacalix[4]arene with 4-(chloromethyl)pyridine in 62% yield. The present regioselective reaction of single hydroxy group in thiacalix[4]arenes could be in particular important for the construction of larger molecules using thiacalix[4]arenes as building units like calix[4]arenes.[11]

In conclusion, an interesting result was obtained by introduction of 4-picolyl groups on to the hydroxy groups of tetraol **1**. We have demonstrated for the first time that *O*-alkylation of the flexible macrocycle **1** with 4-(chloromethyl)pyridine gave tetra-*O*-alkylated products with 1,3-alternate and 1,2-alternate conformations which could have promising complexation properties and interesting stereochemistry. While to date only two stereoisomers have been obtained, variation of the alkylation conditions and reagents could lead to other derivatives, which will serve as interesting building blocks for larger potential host molecules. Further studies of the structural and chemical properties of **3** and **4** are in progress.

Experimental

^{1}H NMR spectra were recorded at 300 MHz on a Nippon Denshi JEOL FT-370 NMR spectrometer in deuteriochloroform with Me4Si as an internal reference. IR spectra were measured as KBr pellets on a Nippon Denshi JIR-AQ2OM spectrometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct-inlet system. Elemental analyses were performed by Yanaco MT-5.

Materials: 5,11,17,23-Tetra-*t*-butyl-2,8,14,20-tetrathiacalix[4]arene-25,26,27,28-tetraol **1** was prepared from *p-t*-butylphenol according to the reported procedure.[6]

Alkylation of **1** *with 4-(chloromethyl)pyridine* **2** *in the presence of* K_2CO_3: A mixture of **1** (300 mg, 0.41 mmol) and K_2CO_3 (1.26 g, 4.92 mmol) in dry tetrahydrofuran (THF) (8 cm^3) was heated at reflux for 1 h under N_2. Then a solution of 4-(chloromethyl)pyridine **2** (4.92 mmol) [prepared by neutralisation of 4-(chloromethyl)pyridine hydrochloride (807 mg, 4.92 mmol) in DMF (8 cm^3) with a solution of triethylamine (0.68 cm^3, 4.92 mmol) in THF (8 cm^3) at room temperature] was added and the mixture heated at reflux for an additional 20 h. After cooling the reaction mixture to room temperature, it was acidified with 1 M HCl (10 cm^3) and extracted with CH_2Cl_2 (100 cm^3 × 2). The combined extracts were washed with water (50 cm^3 × 2), dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil. The residue was washed with methanol to give a mixture of mono-*O*-alkylated product and the starting compound **1** as a colourless precipitate. The precipitate was washed with ether (5 cm^3) to give mono-*O*-alkylated product **3** (200 mg, 62%) as a colourless solid. Recrystallisation from MeOH: $CHCl_3$ (3:1) gave **3** as a colourless prisms.

5,11,17,23-Tetra-t-butyl-26,27,28-trihydroxy-25-[(4-pyridylmethyl) oxy]-2,8,14,20-tetrathiacalix[4]arene, **3**: m.p. 224–227 °C; ν_{max} (KBr)/cm^{-1}: 3362, 2957, 2857, 1464, 1259, 1027, 884,760; δ_H ($CDCl_3$): 1.17 (9 H, s, *t*Bu), 1.18 (18 H, s, *t*Bu), 1.21 (9 H, s, *t*Bu), 5.33 (2 H, s, ArO*CH$_2$)*, 7.56 (1 H, s, *OH*), 7.57 (2 H, d, *J* = 2.4, Ar–*H*), 7.59 (4 H, s, Ar–H), 7.61 (2 H, d, *J* = 2.4, Ar–*H*), 7.65 (2 H, d, *J* = 5.7, Py–*H*), 8.67 (2 H, d, *J* = 5.7, Py–*H*), 8.80 (2 H, broad s, *OH*); *m/z*: 812 (M$^+$). Anal. calcd. for $C_{46}H_{53}O_4NS_4$ (812.18): C, 68.0; H, 6.6; N, 1.7. Found: C, 67.9; H, 6.8; N,1.75.

Alkylation of **1** *with 4-(chloromethyl)pyridine* **2** *in the presence of* Cs_2CO_3: A mixture of **1** (300 mg, 0.41 mmol) and Cs_2CO_3 (1.6 g, 4.92 mmol) in dry tetrahydrofuran (THF) (4 cm^3) was heated at reflux for 1 h under N_2. Then a solution of 4-(chloromethyl)pyridine **2** (4.92 mmol) [prepared by neutralisation of 4-(chloromethyl)pyridine hydrochloride (807 mg, 4.92 mmol) in DMF (8 cm^3) with a solution of triethylamine (0.68 cm^3, 4.92 mmol) in THF (8 ml) at room temperature] was added and the mixture heated at reflux for an additional 20 h. After cooling the reaction mixture to room temperature, it was acidified with 1 M HCl (10 cm^3) and extracted with CH_2Cl_2 (100 cm^3 × 2). The combined extracts were washed with water (50 cm^3 × 2), dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil. The residue was washed with methanol to give a mixture of tetra-*O*-alkylated products as a colourless precipitate. The precipitate was washed with ether (5 cm^3) to give 1,2-*alternate*-**4** (62 mg, 14%) as a colourless solid. The ethereal filtrate was concentrated to give 1,3-*alternate*-**4** (325 mg, 73%) as a colourless solid. Recrystallisation from MeOH:$CHCl_3$ (3:1) gave 1,2-*alternate*-**4** and 1,3-*alternate* -**4** as a colourless prisms, respectively.

1,3-*alternate*-25,26,27,28-Tetra[(4-pyridylmethyl)oxy]-5,11,17, 23-tetra-*t*-butyl-2,8,14,20-tetrathiacalix[4]arene, 1,3-*alternate*-**4**. 1,3-*alternate*-**4** was obtained as colourless prisms [MeOH:$CHCl_3$ (3:1)]; m.p. 285–287 °C; ν_{max} (KBr)/cm^{-1}: 2963, 2872, 1605, 1437, 1413, 1379, 1021, 794; δ_H ($CDCl_3$): 0.87 (36 H, s, *t*-Bu), 5.16 (8 H, s, ArO*CH$_2$)*, 6.95 (8 H, d, *J* = 5.9, Py–*H$_{3,5}$)*, 7.11 (8 H, s, Ar–*H*), 8.42 (8 H, d, *J* = 5.9, Py–*H$_{2,6}$)*; *m/z*: 1084 (M$^+$). Anal. calcd. for $C_{64}H_{68}O_4N_4S_4$ (1085.51): C, 70.8; H, 6.3; N, 5.2. Found: C, 70.6; H, 6.5; N, 4.9.

The splitting pattern in ^{1}H NMR shows that the isolated compound is 1,3-*alternate*-**4**.

1,2-*alternate*-25,26,27,28-Tetra[(4-pyridylmethyl)oxy]-5, 11,17,23-tetra-*t*-butyl-2,8,14,20-tetrathiacalix[4]arene, 1,2-*alternate*-**4**. 1,2-*alternate*-**4** was obtained as colourless prisms [MeOH:$CHCl_3$ (3:1)]; m.p. >300 °C; ν_{max} (KBr)/cm^{-1}: 2963, 2870, 1605, 1473, 1456, 1436, 1413, 1270, 804, 797; δ_H ($CDCl_3$): 1.16 (36 H, s, *t*Bu), 4.67 (8 H, s, ArO*CH$_2$)*, 6.52 (8 H, d, *J* = 5.9, Py–*H$_{3,5}$)*, 7.33 (4 H, d, *J* = 2.4, Ar–*H*), 7.76 (4 H, d, *J* = 2.4, Ar–*H*), 8.11 (8 H, d, *J* = 5.9, Py–*H$_{2,6}$)*; *m/z*: 1084 (M$^+$). Anal. calcd. for $C_{64}H_{68}O_4N_4S_4$ (1085.51): C, 70.8; H, 6.3; N, 5.2. Found: C, 71.0; H, 6.4; N, 4.9.

The splitting pattern in ^{1}H NMR shows that the isolated compound is 1,2-*alternate*-**4**.

Preparation of 4-t-butyl-2,6-dimethyl[(4-pyridylmethyl)oxy]benzene **6**: A mixture of 4-*t*-butyl-2,6-dimethylphenol (400 mg, 2.25 mmol) and NaH (580 mg, 14.5 mmol, 60%) in dry THF (20 cm^3) was heated at reflux for 1 h under N_2. Then a solution of 4-(chloromethyl)pyridine (14.5 mmol) [prepared by neutralization of 4-(chloromethyl)pyridine hydrochloride (1.92 g, 14.5 mmol) in DMF (15 cm^3) with a solution of triethylamine (2.02 cm^3, 14.52 mmol) in THF (25 cm^3) at room temperature] was added and the mixture heated at reflux for an additional 17 h. After cooling the reaction mixture to room temperature, it was acidified with 1 M HCl (10 cm^3) and extracted with CH_2Cl_2 (100 cm^3 × 2). The combined extracts were washed with water (50 cm^3 × 2), dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil. The residue was chromatographed on silica gel with methanol as an eluent to give the title compound **6** (380 mg, 63%) as a colourless oil; δ_H ($CDCl_3$) 1.30 (9 H, s, *t*Bu), 2.28 (6 H, s, Me), 4.82 (2 H, s, O*CH$_2$*Py), 7.05 (2 H, s, Ar–*H*), 7.41 (2 H, d, *J* = 5.9, Py–*H$_{3,5}$)* and 8.62 (2 H, d, *J* = 5.9, Py–*H$_{2,6}$)*; *m/z* 269 (M$^+$). Anal. calcd for $C_{18}H_{23}NO$ (389.5): C, 80.3; H, 8.6; N 5.2. Found: C, 80.55; H, 8.5; N, 4.9.

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