Synthesis and complexation behaviour of tetrakis[(*N,N*-diethylamino-carbonyl)methoxy]tetrahomodioxacalix[4]arene

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O-Alkylation of the flexible tetrahomodioxacalix[4]arene **1** with *N,N*-diethylchloroacetamide in the presence of NaH, K_2CO_3 or Cs_2CO_3 gave only one pure stereoisomer, 1,4-*alternate*-**2**, while other possible isomers were not observed.

Keywords: macrocycles, homocalixarenes, *O*-alkylation, template effect, conformations, metal cation complexation, ionophores

Calix[n]arenes have attracted great attention as ionophoric receptors[1] and potential enzyme mimics[2] in host–guest chemistry. In calix[4]arenes there exist four possible conformational isomers: cone, partial-cone, 1,2-alternate and 1,3-alternate, but the previous functionalised calix[4]arene-based ionophores have exclusively dealt with the cone and partial cone conformational isomers. Thus, Shinkai *et al.* have reported the preparation and ionophoric properties of four conformers of tetra–*tert*-butyltetrakis[(ethoxycarbonyl) methoxy]calix[4]arene.[3] Cone and partial-cone conformers are obtained by the metal template effect using sodium and cesium ions, respectively, but the 1,2-alternate and 1,3-alternate conformers were synthesised by the protection–deprotection method.[4] They also found that the cone conformer shows a selectivity for sodium ion[3a] and the other conformers show a selectivity for potassium ion.[4a] In particular, metal complexation studies of the 1,2-alternate conformer are very limited because of the extreme difficulty in synthesis of 1,2-alternate conformer.[5] Therefore, it has been very difficult to obtain sufficient amounts of the above compound to investigate its chemical behaviour. On the other hand, quite recently, Masci *et al.* reported[6] the synthesis of tetraester derivatives of tetrahydroxy[3.1.3.1]MCP (tetrahomodioxacalix [4]arene) with 1,4-alternate conformation and complexation with quaternary ammonium ions. Here, we considered whether the reaction of tetrahomodioxacalix[4]arene and *N,N*-dialkylchloroacetamide would give the 1,4-alternate conformer of the tetraamide derivatives as a major product attributable to the template effect during the *O*-alkylation process because the amide derivatives of calix[4]arene interact with metal cations more strongly than the ester derivative.[7] We now describe the convenient preparation and metal complexation properties of dibenzylether-bridged calix[4]arene tetraamide with 1,4-alternate conformation, which is supposed to have encapsulated ionophilic cavity.

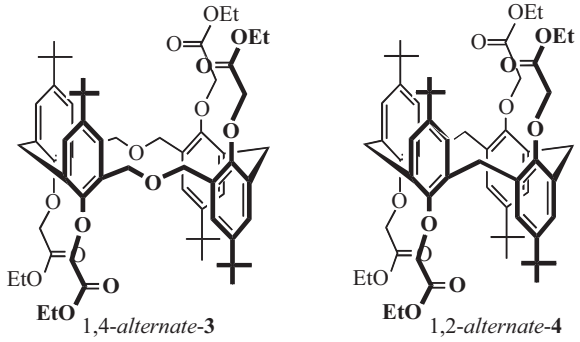
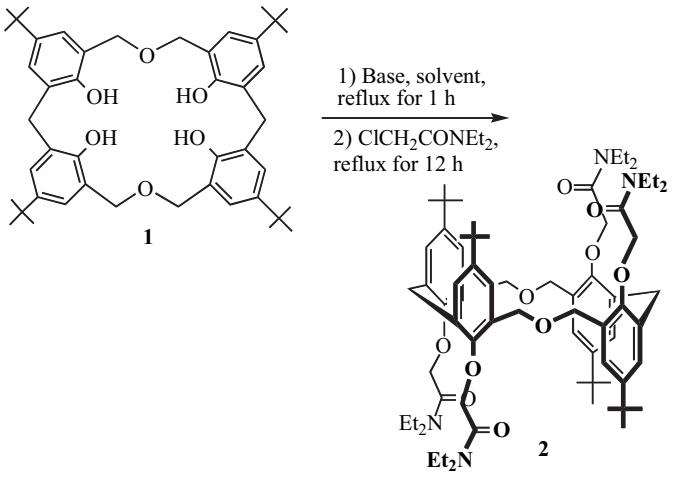


Fig. 1 Structures of 1,4-*alternate*-**3** and 1,2-*alternate*-**4**.

Results and discussion

Introduction of larger alkyl groups on the phenolic oxygens of calix[4]arenes led to a situation where the OR groups within a cyclophane ring cannot pass each other by oxygen-through-the-annulus rotation. Although there exist four possible conformational isomers in calix[4]arenes: cone, partial-cone, 1,2-alternate and 1,3-alternate, five different conformational isomers of which 1,4-alternate is newly counted, due to the dibenzylether bridges in tetrahomodioxacalix[4]arenes.[8] In contrast to four possible conformations in calix[4]arenes,[1] the conformational isomerism in the present system is slightly more complicated. However, there were a few reports concerning the introduction of substituents to the hydroxyl groups of tetrahomodioxacalix[4]arenes.[6,9]



Scheme 1

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O-Alkylation of the flexible macrocycle **1** with *N, N*-diethylchloroacetamide in the presence of NaH under THF reflux gave only one pure stereoisomer **2** in 70% yield. Other possible isomers were not observed. An attempted *O*-alkylation of **1** with *N,N*-diethylchloroacetamide in the presence of Na_2CO_3 led to a mixture of intractable compounds and the recovery of the starting compound in spite of the condition of large excess of Na_2CO_3. When K_2CO_3 or Cs_2CO_3 was used as a base, only tetrasubstituted product **2** was obtained in 76 and 81% yields, respectively. Only when the template metal ion can hold the amide group(s) and the oxide group(s) on the different side of the dibenzyl ether bridges of the tetrahomodioxacalix[4] arene is the conformation immobilised to the thermodynamically stable 1,4-alternate conformer.

The ^{1}H NMR spectrum of **2** shows a singlet for the *tert*-butyl protons and a pair of doublets with equal intensity for the aromatic protons. Furthermore, the resonance for the Ar*CH*$_2$Ar methylene protons appeared as a pair of doublets (δ 3.37 and 4.96, J_{AB} = 13.2 Hz), corresponding to a symmetric structure (C_{2v}-symmetry). It was also found that the methylene carbons for the Ar*CH*$_2$Ar are observed at δ 31.55 ppm, which strongly suggests two benzene rings adopt the syn arrangement different from those for anti arrangement of calix[4]arenes (δ 37–40 ppm).[10] On consideration of the ^{1}H NMR spectrum, there are two possible structures for **2**, cone or 1,4-alternate structure. However, the resonance for the methylene protons for the O*CH*$_2$OCONEt$_2$ appeared as a pair of doublets at upper-field (δ 4.52 and 4.98, J_{AB} = 14.1 Hz), due to the different environment and the ring current effect arising from the inverted calix benzene ring.[11] These observations strongly suggest that compound **2** adopts 1,4-alternate conformation but not cone conformation.

It is already known that the cone-conformer of a calix[4]arene tetraethyl ester shows Na^+ selectivity whereas the partial-cone-conformer of calix[4]arene tetraethyl ester shows K^+ selectivity.[1] Interestingly, much higher Li^+, Na^+, K^+ and Cs^+ affinities of 1,4-*alternate*-tetrahomodioxacalix [4]arene tetrakis(diethyl) amide 1,4-*alternate*-**2** than that of the corresponding 1,4-*alternate*-tetrahomodioxacalix[4] arene tetraethyl ester 1,4-*alternate*-**3** were observed in spite of both adopting the same conformation. The two-phase solvent extraction data also indicated that tetrakis(diethyl) amide 1,4-*alternate*-**2** (extraction%: 92.6%) shows stronger Ag^+ affinity than that for the corresponding tetraethyl ester 1,4-*alternate*-**3** (extraction%: <1.0%)[9] as well as the 18-crown-6 (extraction%: 65.0%)[12] although no significant selectivity for metal was observed under the present experimental conditions. These results can be easily explained by the much larger inner ionophilic cavity of tetrahomodioxacalix[4]arene tetrakis(diethyl) amide than that of 1,2-*alternate*-calix[4]arene tetraethyl ester 1,2-*alternate*-**4** due to the introduction of two dibenzyl ether bridges into the two methylene bridges of calix[4]arene skeleton as well as the increased electron density charge in the carbonyl oxygen attributable to the electron-donating ability of the amino group through conjugation.

Shinkai *et al.* reported that the 1,3-alternate conformer of calix[4]arene tetraethyl ester can form both 1 : 1 and 2 : 1 metal/calixarene complex and the two metal binding sites display negative allostericity by ^{1}H NMR titration experiment.[4a] In the present systems, due to the existence of two metal binding sites there are several possibilities for metal complexation mode. Thus, a 1 : 1 and a 2:1 metal complexation of 1,4-alternate conformer of tetrakis(diethyl) amide **2** might be possible. As shown in Fig. 2, the Job plots of compound 1,4-*alternate*-**2** were carried out in the H_2O/CH_2Cl_2 phases. The percent extractions reach a maximum at 0.5 mole fraction when the 1,4-*alternate*-**2** and silver cation was changed systematically. This fact clearly indicates that Ag^+ forms 1 : 1 complex with 1,4-*alternate*-**2**.

It was also found that the chemical shifts of the Ar*CH*$_2$Ar and Ar*CH*$_2$O*CH*$_2$Ar methylene protons of tetrakis(diethyl) amide 1,4-*alternate*-**2** were altered by titration with $AgSO_3CF_3$ in $CDCl_3$-CD_3OD (1 : 1 v/v): *i.e.*, 1 : 1 mixture of 1,4-*alternate*-**2** and $AgSO_3CF_3$ showed a completely different ^{1}H NMR spectrum with sharp lines becoming evident for these protons. Interestingly, the chemical shifts of a pair of doublets for the Ar*CH*$_2$O*CH*$_2$Ar methylene protons changed dramatically [an upfield shift for H_{eq} (equatorial) at δ 4.19 ppm and a downfield shift for H_{ax} (axial) at δ 4.92 ppm] in comparison to those in the metal free spectrum [δ 4.44 (H_{eq}) and 4.68 (H_{ax}), J_{AB} 14.1 Hz]. In addition to this observation, the signals for the aromatic protons slightly shifted to downfield and the phenoxy methylene protons and the methylene protons of Ar*CH*$_2$Ar also showed different chemical shifts, respectively. The ^{1}H NMR titration experiment also clearly indicates a 1 : 1 stoichiometry for the $AgSO_3CF_3$ complex with 1,4-*alternate*-**2**, since all signals remain essentially unchanged after the tetrakis(diethyl) amide 1,4-*alternate*-**2**/$AgSO_3CF_3$ ratio has reached a value of unity. These findings might be attributable to the conformational changes of the binding site in the process of metal complexation. No changes arising from the formation of two sets of non-equivalent aromatic protons and two sets of non-equivalent *tert*-butyl protons due to the contribution of the asymmetric metal cation complexation on the one side of tetrakis(diethyl) amide 1,4-*alternate*-**2** were observed. These results strongly suggest that the original C_{2v}-symmetry might remain after the complete metal cation complexation as shown in Fig. 3. It is also proposed that the rate of an intramolecular hopping between two possible metal-binding sites might be faster than the NMR time scale at room temperature. In spite of lowering the temperature to –50°C in CD_2Cl_2, no clear evidence for the intramolecular hopping behaviour was obtained as with biscalix[4]arenes.[13] Thus this result strongly suggests that the Ag^+ ion might exist in the capsule-like complexation mode.

More detail examination of the chemical shift change in the ^{1}H NMR titration experiment of tetrakis(diethyl) amide 1,4-*alternate*-**2** with $AgSO_3CF_3$ suggests that Ag^+ should be bound to the ionophoric cavity, which is composed of four phenolic oxygens, four oxygens of carbonyl groups and two benzylether oxygens because the different chemical shifts were observed for the neighbouring methylene protons of ArO*CH*$_2$CONEt$_2$ (Δδ –0.03 and –0.43 ppm), Ar*CH*$_2$O*CH*$_2$Ar [Δδ +0.24 (H_{eq}) and –0.25 (H_{ax}) ppm] and the large downfield

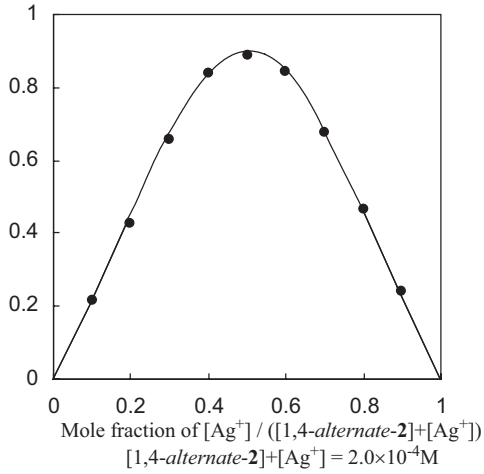

Fig. 2 Job plots of the extractions of Ag^+ with host 1,4-*alternate*-**2**.

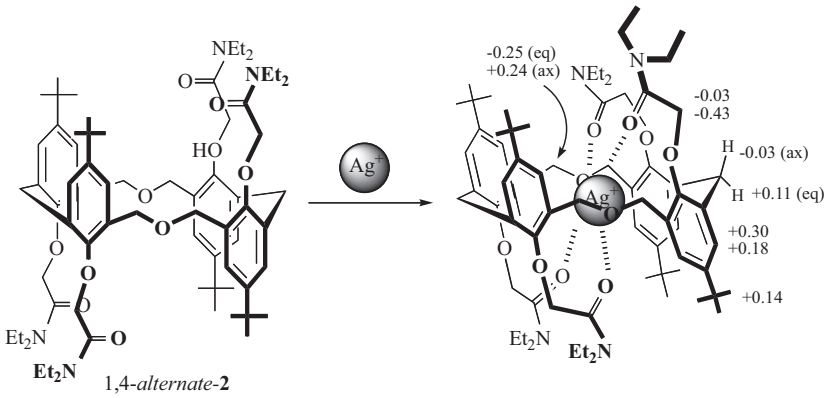

Fig. 3. Metal complexation mode of tetrakis(diethyl) amide 1,4-*alternate*-**2**. Chemical shift changes of 1,4-*alternate*-**2** induced in the presence of $AgSO_3CF_3$ in $CDCl_3$/[D_4]methanol (1:1 v/v) at 27°C; [1,4-*alternate*-**2**] = 5.0×10^{-4} M, [$AgSO_3CF_3$] = 5.0×10^{-4} M; (+) denotes the down-field shift and (–) denotes the up-field shift.

shifts were observed for the aromatic protons (Δδ from +0.18 to +0.30 ppm). The chemical shift difference, Δδ between H_{ax} and H_{eq} of the ArCH_2Ar methylene protons in calix[4]arene serves as a measure of the flattening.[14] $\Delta\delta_H$ decreases from δ 1.59 ppm to 1.45 ppm in 1,4-*alternate*-**2** in the binding of Ag^+. These findings imply that 1,4-*alternate*-**2** slightly flattens when Ag^+ is complexed because Ag^+ was encapsulated into the cavity formed by four aromatic rings and amide groups. Further experiments on these metal complexations are currently in progress in our laboratory.

Conclusions

O-Alkylation of the flexible macrocycle tetrahomodioxacalix[4]arene **1** with *N,N*-diethylchloroacetamide in the presence of NaH, K_2CO_3 or Cs_2CO_3 gave only one pure stereoisomer, 1,4-alternate conformer **2**, while other possible isomers were not observed.

The two-phase solvent extraction data indicated that tetrakis(diethyl) amide 1,4-*alternate*-**2** shows a strong affinity to alkali metal cations and Ag^+ as comparable with that for the 18-crown-6 and the extractabilities are much higher than that for calix[4]arene tetraethyl ester 1,2-*alternate*-**4** and the corresponding tetrahomodioxacalix[4]arene tetraethyl ester 1,4-*alternate*-**3**. However, no significant high ion selectivity for alkali metal cations was observed in tetrakis(diethyl) amide 1,4-*alternate*-**2**. ^{1}H NMR Titration of tetrakis(diethyl) amide 1,4-*alternate*-**2** with $AgSO_3CF_3$ clearly demonstrates that a 1:1 complex is formed with retention of the original symmetry to be conformationally frozen on the NMR time scale. The two oxygens on the dibenzyl ether bridges might play a significant role on the complexation of 1,4-*alternate*-**2** with metal cations. While up to now only one stereoisomer has been obtained, variation of the alkylation conditions and reagents could lead to the derivatives with cone-conformation, which will serve as interesting building blocks for larger potential host molecule.

Experimental

^{1}H NMR spectra were recorded at 300 MHz on a Nippon Denshi JEOL FT-300 NMR spectrometer in deuteriochloroform with Me_4Si 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.

Materials

7,13,21,27-Tetra-*tert*-butyl-29,30,31,32-tetrahydroxy-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arene **1** was prepared according to the literature.[15]

Alkylation of **1** *with N,N-diethylchloroacetamide in the presence of NaH to afford 1,4-alternate-7,13,21,27-tetra-tert-butyl-29,30,31,32-tetrakis[(N,N-diethylaminocarbonyl)methoxy]-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arene (1,4-alternate-***2***)*

A mixture of **1** (300 mg, 0.42 mmol) and NaH (340 mg, 8.4 mmol) in dry tetrahydrofuran (20 cm^3) was heated at reflux for 1 h under N_2. Then *N,N*-diethylchloroacetamide (1.26 g, 8.4 mmol) was added and the mixture heated at reflux for an additional 12 h. After cooling the reaction mixture to room temperature, it was poured into ice-water (30 cm^3) and extracted with CH_2Cl_2 (2×30 cm^3). The CH_2Cl_2 extract was washed with water, dried with Na_2SO_4 and concentrated to give a yellow oil, which was then distilled under the reduced pressure to remove the excess unreacted *N,N*-diethylchloroacetamide using a Kugelrohr apparatus. The residue was treated with methanol (10 cm^3) affording 342 mg (70%) of 1,4-*alternate*-**2** as colourless solid. Recrystallisation from $CHCl_3$/methanol (3: 1 v/v) gave 1,4-*alternate*-**2** as colourless prisms; m.p. 172–173.5°C; ν_{max} (KBr)/cm^{-1} 1662 (C=O); δ_H ($CDCl_3$) 1.07 (36H, s, *t*Bu), 1.15–1.20 (24H, m, NCH_2CH_3), 3.30–3.40 (16H, m, NCH_2CH_3), 3.37 (2H, d, J = 13.2 Hz, ArCH_2Ar, H_{eq}), 4.44 (4H, d, J = 11.9 Hz, ArCH_2OCH_2Ar, H_{eq}), 4.52 (4H, d, J = 14.1 Hz, ArOCH_2CO), 4.68 (4H, d, J = 11.9 Hz, J = 11.9 Hz, ArCH_2OCH_2Ar, H_{ax}), 4.96 (2H, d, J = 13.2 Hz, ArCH_2Ar,H_{ax}), 4.98 (4H, d, J = 14.1 Hz, ArOCH_2CO), 6.91 (4H, d, J = 2.3 Hz, Ar–*H*), 6.99 (4H, d, J = 2.3 Hz, Ar-*H*); δ_C ($CDCl_3$) 13.05, 14.31, 31.33, 31.55 ($ArCH_2Ar$), 34.01, 39.90 (NCH_2), 41.02, 67.28, 72.58, 125.26, 127.28, 130.55, 133.33, 145.88, 154.03, 168.25 (C=O); *m/z*: 1161.8 (M^+); *Found*: C, 72.0; H, 9.10; N, 4.99. *Calcd.* for $C_{70}H_{104}N_4O_{10}$ (1161.63): C, 72.38; H, 9.02; N, 4.82%.

Table 1 Extraction of alkali metal picrates by tetrahomodioxacalix[4]arene tetrakis(diethyl) amide 1,4-*alternate*-**2** in CH_2Cl_2[a]

Ionophore	Extractability/%				
	Li^+	Na^+	K^+	Cs^+	Ag^+
1,4-*alternate*-**2**	82.7	80.6	80.9	86.2	92.6
1,4-*alternate*-**3**	2.1	3.0	16.2	12.6	<1.0
18-Crown-6	8.7	23.1	77.9	62.9	65.0

[a]Extraction conditions; 2.0×10^{-4} M of ionophore in CH_2Cl_2; 2.0×10^{-4} M of picric acid in 0.1 M of alkaline hydroxide at 25°C. Ionophore solution (5.0 cm^3) was shaken for 2 h with picrate solution (5.0 cm^3) and % extraction was measured by the absorbance of picrate in CH_2Cl_2. Experimental error was ±2%.

Alkylation of **1** *with N,N-diethylchloroacetamide in the presence of alkali metal carbonate to afford 1,4-alternate-***2***: Typical procedure*
A mixture of **1** (400 mg, 0.567 mmol) and cesium carbonate (3.70 g, 11.4 mmol) in dry acetone (36 cm^3) was heated at reflux for 1 h under N_2. Then *N,N*-diethylchloroacetamide (2.35 g, 14.2 mmol) was added and the mixture heated at reflux for an additional 12 h. After cooling to room temperature, the mixture was filtered. The filtrate was concentrated to give a yellow oil, which was then distilled under reduced pressure to remove the excess unreacted *N,N*-diethylchloroacetamide using a Kugelrohr apparatus. The residue was treated with methanol (10 cm^3) and the precipitate was filtered to give 482.2 mg (81%) of 1,4-*alternate*-**2** as a colourless solid.

Picrate extraction measurements
Metal picrates (2.5×10^{-4} M) were prepared *in situ* by dissolving the metal hydroxide (0.01 mol) in 2.5×10^{-4} M picric acid (100 cm^3); triply distilled water was used for all aqueous solutions. Two-phase solvent extraction was carried out between water (5 cm^3, [alkali picrate] = 2.5×10^{-4} M) and CH_2Cl_2 (5 cm^3, [ionophore] = 2.5×10^{-4} M). The two-phase mixture was shaken in a stoppered flask for 2 h at 25°C. We confirmed that this period is sufficient to attain the distribution equilibrium. This was repeated three times, and the solutions were left standing until phase separation was complete. The extractability was determined spectrophotochemically from the decrease in the absorbance of the picrate ion in the aqueous phase as described by Pedersen.[16]

^1H NMR complexation experiment
To a $CDCl_3$ solution (5×10^{-4} M) of 1,4-*alternate*-tetrakis(diethyl) amide 1,4-*alternate*-**2** in the NMR tube was added a CD_3OD solution (5×10^{-4} M) of $AgSO_3CF_3$. The spectrum was registered after addition and the temperature of NMR probe kept constant at 27°C.

*1,4-alternate-***2***-$AgSO_3CF_3$ complex*: δ_H ($CDCl_3$: CD_3OD 1 : 1 v/v): 1.21 (36H, s, *t*Bu), 1.10–1.30 (24H, m, NCH_2CH_3), 3.15–3.70 (16H, m, NCH_2CH_3), 3.48 (2H, d, J = 13.2 Hz, $ArCH_2Ar$, H_{eq}), 4.19 (4H, d, J = 11.9 Hz, $ArCH_2OCH_2Ar$, H_{eq}), 4.50–4.61 (8H, m, $ArOCH_2CO$), 4.92 (4H, d, J = 11.9 Hz, J = 11.9 Hz, $ArCH_2OCH_2Ar$, H_{ax}), 4.93 (2H, d, J = 13.2 Hz, $ArCH_2Ar$, H_{ax}), 7.09 (4H, d, J = 2.3 Hz, Ar-*H*), 7.29 (4H, d, J = 2.3 Hz, Ar-*H*).

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